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Catalytic Castagnoli–Cushman reaction-based synthesis of tetrahydroisoquinolone–glutarimide dyads and their evaluation as potential cereblon ligands

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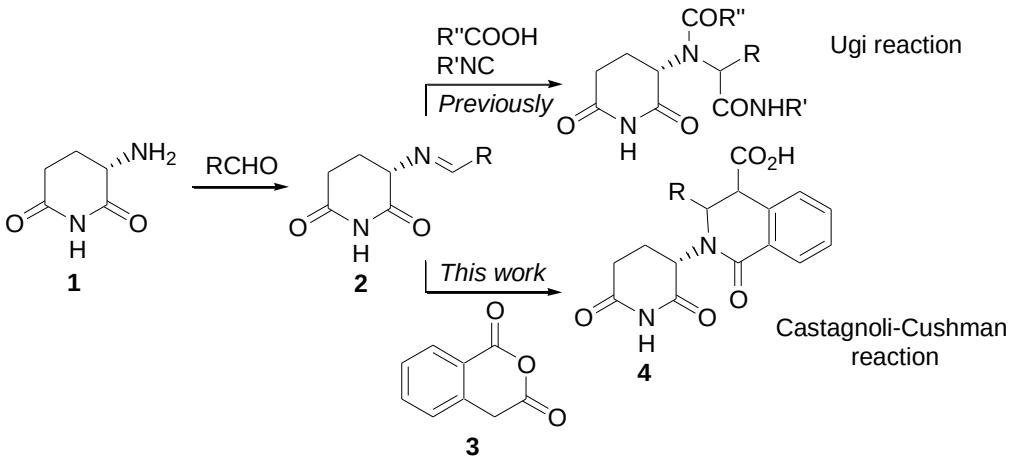


Scheme S1 Synthesis and multicomponent reactions of imines of α-aminoglutarimide **1**

Table S1. Optimization of reaction conditions 2a + 3a → 4a

Entry	Reagent	Solvent	*T*/°C	Loading, equiv.			Yield of **4a**, %
				imine **2a**	HPA **3a**	Reagent	
1	BF_3*Et_2O	DCM	~20	1	1	1	n.d
2	BF_3*Et_2O	DCE	80	1	1	0.1	n.d
3	BF_3*Et_2O	DCE	80	1	1	1	n.d
4	BF_3*Et_2O	DCE	50	1	1	0.1	n.d
5	DiPEA	DCM	~20	1	1	1	n.d
6	$Sc(OTf)_3$	DMSO-d_6	~20	1	1	0.2	traces
7	-	-	110	1	1	-	n.d
8	-	-	80	1	1	-	n.d
9	NEt_3	MeCN	80	1	1	0.1	n.d
10	DiPEA	MeCN	80	1	1	1	n.d
11	-	PhMe	110	1	1	-	n.d
12	$Sc(OTf)_3$	DMSO-d_6	~20	1	1.2	0.05	33*
13	$Yb(OTf)_3$	DMSO-d_6	~20	1	1.2	0.05	34*
14	$In(OTf)_3$	DMSO-d_6	~20	1	1.2	0.05	44*
15	$In(OTf)_3$	DMSO-d_6	~20	21	21	0.025	34*
16	$In(OTf)_3$	DMSO-d_6	~20	1	2	0.05	50*
17	$In(OTf)_3$	DMSO-d_6	~20	2	1	0.05	59*
18	$In(OTf)_3$	DMSO-d_6	80	1	1.2	0.05	39*
19	$Zn(OTf)_2$	DMSO-d_6	~20	1	1	0.05	traces
20	$Cu(OTf)_2$	DMSO-d_6	~20	1	1	0.05	traces

all reactions were carried out for 16 hours

* Isolated yield

Crystal structure of compound *cis*-4a

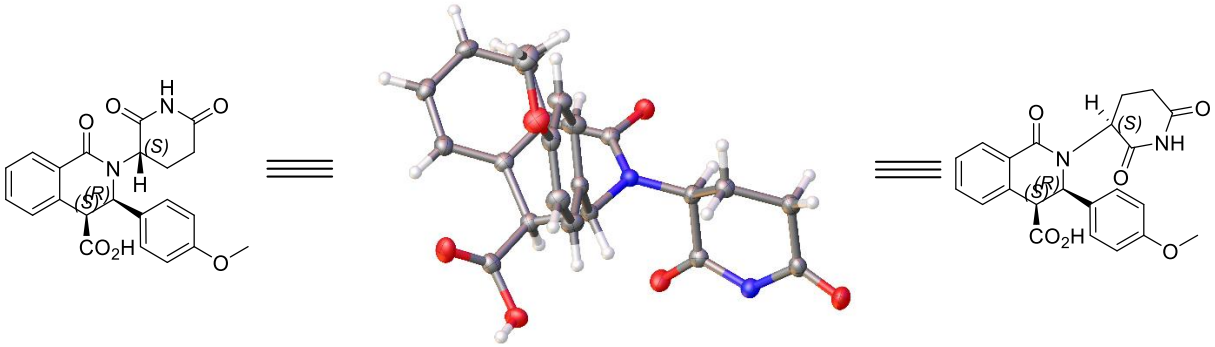
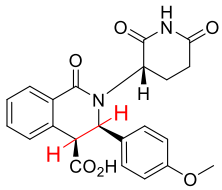
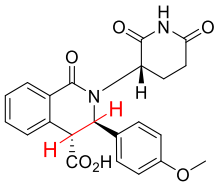
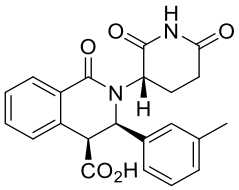
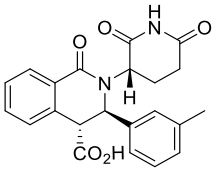
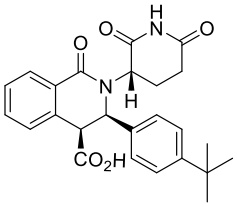
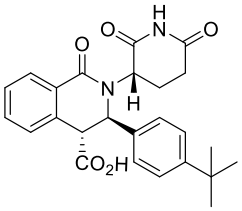
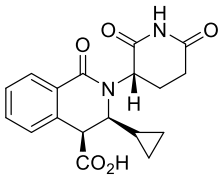
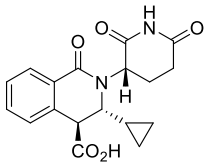
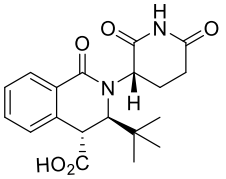
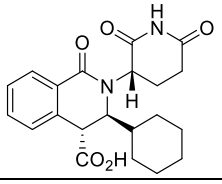
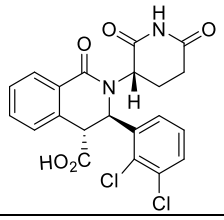
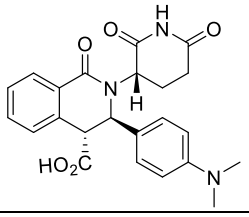
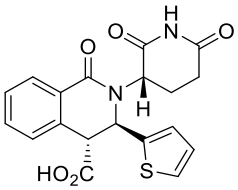
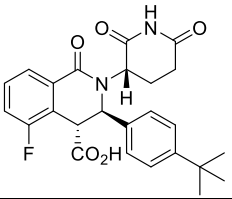
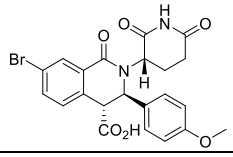
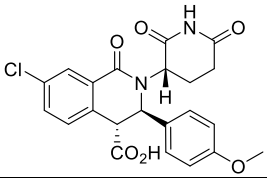
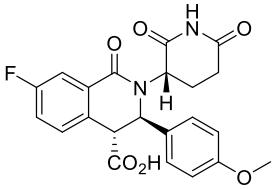


Figure S1. Crystal structure of compound ***cis*-4a**

Table S2. Structures of compound *cis*-**4** and *trans*-**4** and their selected ^{1}H NMR data (chemical shifts and coupling constants) corresponding to signals of vicinal CH protons from lactam ring (red color)

cis-Isomers **4**			*trans*-Isomers **4**		
no.	Structure	*J*/Hz	no.	Structure	*J*/Hz
a		5.08 (d, *J* = 5.7 Hz, 1H), 4.76 (d, *J* = 5.7 Hz, 1H	**a**		5.33 (s, 1H), 3.98 (s, 1H)
b		5.07 (d, *J* = 5.7 Hz, 1H), 4.79 (d, *J* = 5.7 Hz, 1H)	**b**		5.36 (s, 1H), 3.95 (s, 1H)
c		5.11 (d, *J* = 5.8 Hz, 1H), 4.79 (d, *J* = 5.8 Hz, 1H)	**c**		5.37 (s, 1H), 4.00 (s, 1H)
d		5.98 (br.s, 1H), 4.52 (br.s, 1H)	**d**		4.00 (s, 1H), 3.36 (dd, *J* = 9.9, 1.6 Hz, 1H)
			e		4.17 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.93 (s, 1H)
			f		4.16 (dd, *J* = 11.4, 5.5 Hz, 1H), 3.91 (d, *J* = 4.6 Hz, 1H)

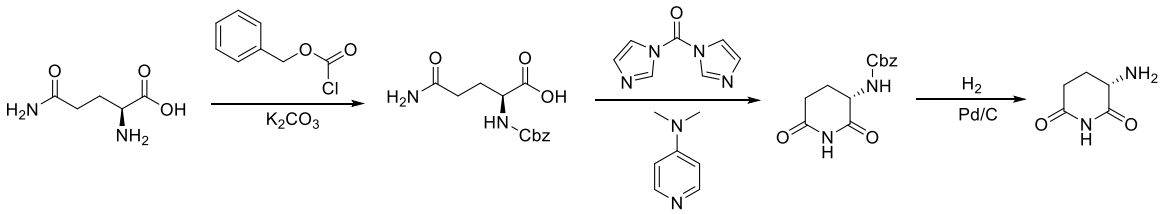
			g		5.71 (s, 1H), 4.15 (s, 1H)
			h		5.27 (s, 1H), 4.01 (s, 1H)
			i		5.63 (s, 1H), 4.13 (s, 1H)
			j		5.46 (s, 1H), 4.17 (s, 1H)
			k		5.35 (d, *J* = 1.5 Hz, 1H), 4.11 (d, *J* = 1.5 Hz, 1H)
			l		5.37 (s, 1H), 4.14 (s, 1H)
			m		5.35 (d, *J* = 1.5 Hz, 1H), 4.10 (d, *J* = 1.5 Hz, 1H)

Experimental part. Synthesis

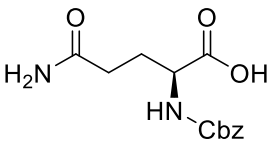
General information

NMR spectra were acquired with 400 MHz Bruker Avance III spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ or DMSO-d_6 and were referenced to residual solvent proton signals (δ_H = 7.26 and 2.50, respectively) and solvent carbon signals (δ_C = 77.16 and 39.52, respectively). Mass spectra were acquired with HRMS-ESI-qTOF spectrometer Nexera LCMS-9030 or MaXis II Bruker Daltonic GmbH (electrospray ionization mode, positive ions detection). Flash column chromatography on silica (Merck, 230-400 mesh) was performed with Biotage Isolera Prime instrument. TLC was performed on aluminium-backed pre-coated plates (0.25 mm) with silica gel 60 F254 with a suitable solvent system and was visualized using UV fluorescence. Preparative HPLC was carried out on compact preparative system ECOM ECS28P00, equipped with spectrophotometric detector or Shimadzu LC-20AP. Column: YMC-Pack SIL-06, 5 μm, 250×20 mm or Agilent Zorbax prepHT XDB-C18, 5 μm, 21.2×150 mm.

Synthesis of compound S3, general scheme

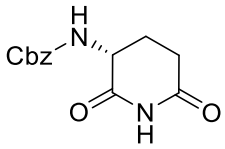


(S)-((Benzyloxy)carbonyl)glutamine (S1)



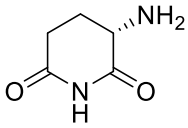
According to the described procedure,[S1] a stirred solution of L-glutamine (40.2 g, 275 mmol) in H_2O (275 mL) was treated with K_2CO_3 (57 g, 413 mmol). The reaction mixture was cooled to 0°C followed by slow addition of benzyl chloroformate (49 mL, 344 mmol). After stirring at room temperature overnight, the reaction mixture was extracted with EtOAc (3×200 mL) and the pH of the aqueous layer was adjusted to 1-2 with concentrated HCl under cooling with ice and then left in the refrigerator overnight to complete crystallization. Then the mixture was filtered and the solid was washed with water. The resulting white powder was dried at 80°C. Yield 55.4 g, 77%. The product was used in the next step without characterization.

Benzyl (S)-(2,6-dioxopiperidin-3-yl)carbamate (S2)



To a mixture of ((benzyloxy)carbonyl)glutamine (10 g, 35.6 mmol) and *N*,*N*-dimethylpyridin-4-amine (0.131 g, 1.07 mmol) in absolute THF placed in a round-bottom flask (100mL), 1,1'-carbonyldiimidazole (6.07 g, 37.46 mmol) was added (gas evolution!). The reaction mixture was refluxed for 14 h, then concentrated *in vacuo*, diluted with brine (100 mL) and stirred for 40 minutes. Then the mixture was filtered, the solid was washed with water (2×40 mL) and dried *in vacuo.* The residue was purified by column chromatography on silica gel with a linear gradient of MeOH in DCM (5−75%) to provide pure title compound. Yield 5.04 g, 54%. NMR data are in accordance with the literature.[S2]

(S)-3-Aminopiperidine-2,6-dione (S3)

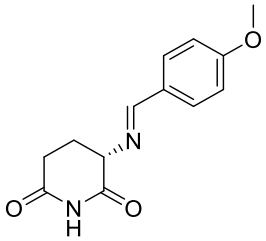


Preparation from benzyl (2,6-dioxopiperidin-3-yl)carbamate and NMR data in accordance with[S3].

General procedure for preparation of imines and their analytical data:

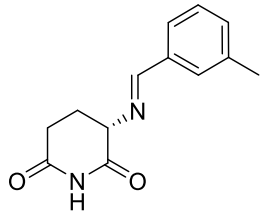
In a round-bottom flask equipped with a magnetic stir bar, 3-aminopiperidine-2,6-dione (1eq; 0.8-3.9 mmol, freshly prepared) and magnesium sulfate (1.5 eq) were mixed in dry methanol (0.2 M). Then the corresponding aldehyde (1.01 eq, 0.8-4.1 mmol) was added. After stirring for 16 h at room temperature, the mixture was concentrated *in vacuo* at 30°C and dissolved in chloroform. The solution was filtered through celite and the solvent was evaporated at 30°C. The resulting solid or oil was ground with a hexane/Et_2O mixture (5%), filtered and dried *in vacuo* at 30°C to provide pure compounds **2a-i**.

(S)-3-((4-Methoxybenzylidene)amino)piperidine-2,6-dione (2a)



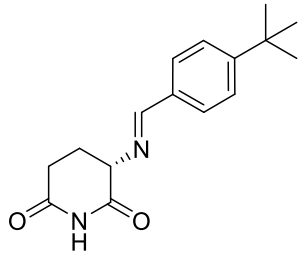
Yield 808 mg, 91%; light green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.08 (t, *J* = 5.1 Hz, 1H), 3.84 (s, 3H), 3.06 (dt, *J* = 17.5, 7.3 Hz, 1H), 2.64 (dt, *J* = 17.3, 5.5 Hz, 1H), 2.21 (q, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 171.5, 164.6, 162.5, 130.4, 128.5, 114.2, 68.1, 55.5, 29.0, 26.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2O_3^+$ 247.1077; Found 247.1083.

(S)-3-((3-Methylbenzylidene)amino)piperidine-2,6-dione (2b)



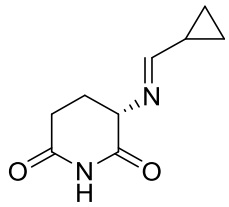
Yield 158 mg, 88%; green solid. ^{1}H NMR (400 MHz, $CDCl_3$). δ 8.41 (s, 1H), 8.18 (s, 1H), 7.62 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.40 – 7.12 (m, 2H), 4.13 (t, *J* = 5.2 Hz, 1H), 3.08 (dt, *J* = 17.6, 7.3 Hz, 1H), 2.66 (dt, *J* = 17.6, 5.8 Hz, 1H), 2.39 (s, 3H), 2.25 (q, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$). δ 172.6, 171.2, 165.7, 138.6, 135.4, 132.6, 129.0, 128.7, 126.4, 68.3, 29.0, 26.4, 21.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2O_2^+$ 231.1128; Found 231.1138.

(S)-3-((4-(Tert-butyl)benzylidene)amino)piperidine-2,6-dione (2c)



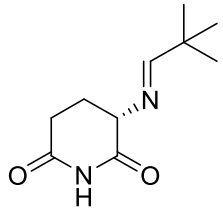
Yield 366 mg, 86%; grey solid. ^{1}H NMR (400 MHz, $CDCl_3$). δ 8.42 (s, 1H), 8.17 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 4.12 (t, *J* = 4.9 Hz, 1H), 3.08 (dt, *J* = 17.3, 7.3 Hz, 1H), 2.65 (dt, *J* = 17.6, 5.6 Hz, 1H), 2.23 (q, *J* = 5.6 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$). δ 172.7, 171.2, 165.2, 155.3, 132.9, 128.6, 125.8, 68.2, 35.1, 31.3, 29.0, 26.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}N_2O_2^+$ 273.1598; Found 273.1597.

(S)-3-((Cyclopropylmethylene)amino)piperidine-2,6-dione (2d)



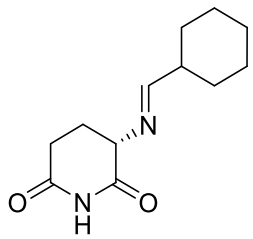
The product was used in the next step without characterization.

(S)-3-((2,2-Dimethylpropylidene)amino)piperidine-2,6-dione (2e)



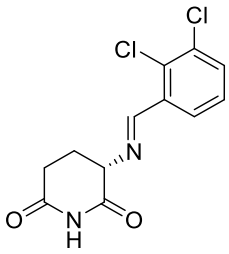
The product was used in the next step without characterization.

(S)-3-((Cyclohexylmethylene)amino)piperidine-2,6-dione (2f)



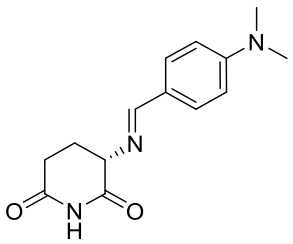
The product was used in the next step without characterization.

(S)-3-((2,3-Dichlorobenzylidene)amino)piperidine-2,6-dione (2g)



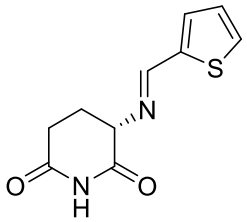
Yield 400 mg, 72%; blue solid. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 10.76 (s, 1H), 8.77 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 2.80 (dt, *J* = 17.2, 6.0 Hz, 1H), 2.58 (dt, *J* = 17.3, 6.7 Hz, 1H), 2.16 (q, *J* = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6). δ 171.7, 170.1, 159.9, 133.4, 131.9, 131.8, 131.5, 126.5, 125.7, 67.1, 28.2, 25.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{11}Cl_2N_2O_2^+$ 285.0192; Found 285.0207.

(S)-3-((4-(Dimethylamino)benzylidene)amino)piperidine-2,6-dione (2h)



Yield 360 mg, 89%; beige solid. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6). δ 10.73 (s, 1H), 8.20 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 3.99 (dd, *J* = 7.1, 4.8 Hz, 1H), 2.97 (s, 6H), 2.76 (m, *J* = 17.2, 7.4, 5.5 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.08 (pt, *J* = 7.9, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6). δ 172.9, 172.1, 163.7, 151.9, 129.5, 123.1, 111.0, 110.7, 67.7, 29.0, 26.1 HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{17}N_3O_2Na^+$ 282.1213; Found 282.1219.

(S)-3-((Thiophen-2-ylmethylene)amino)piperidine-2,6-dione (2i)



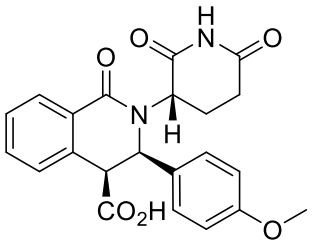
Yield 327 mg, 75%; brown oil. ^{1}H NMR (400 MHz, $CDCl_3$). δ 8.54 (s, 1H), 7.89 (s, 1H), 7.46 (m, *J* = 4.6 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.14 – 7.01 (m, 1H), 4.18-4.02 (m, 1H), 3.05 (dt, *J* = 14.8, 7.2 Hz, 1H), 2.65 (dt, *J* = 17.4, 5.4 Hz, 1H), 2.25 (q, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$). δ 172.7, 171.1, 158.5, 141.5, 132.4, 130.4, 127.7, 67.6, 28.9, 26.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{11}N_2O_2S^+$ 223.0536; Found 223.0526.

Procedures for preparation of lactams:

General procedure for preparation of lactams *cis*-4a-d, *trans*-4d-f and their analytical data:

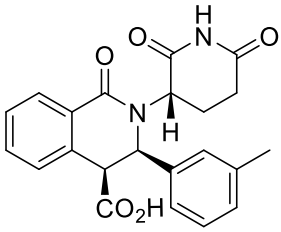
In a screw-cap vial equipped with a magnetic stir bar homophthalic anhydride **3** (1 eq, 0.19-0.28 mmol) and the corresponding imine **2** (a) (2 eq, 0.38-0.55 mmol) were mixed in dry DMSO (0.4-0.6M, 0.5 mL). Then indium(III) trifluoromethanesulfonate (5% mol., 0.01-0.02 mmol) was added. The resulting mixture was placed in a pre-heated to 30°C metal heating block. After 2h the mixture was purified by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of MeCN in 20 min; 45 °C; 12 mL/min) to provide pure products.

(3R,4S)-2-((S)-2,6-Dioxopiperidin-3-yl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (cis-4a)



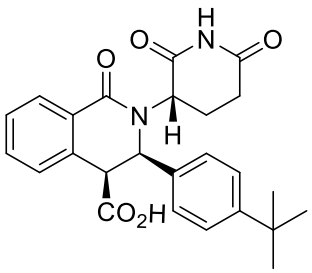
Yield 49 mg, 59%, *dr* >20:1, white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 10.61 (s, 1H), 8.01 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.52 (td, *J* = 7.6, 1.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.04 – 6.92 (m, 2H), 6.74 – 6.66 (m, 2H), 5.14 (d, *J* = 11.1 Hz, 1H), 5.08 (d, *J* = 5.8 Hz, 1H), 4.76 (d, *J* = 5.7 Hz, 1H), 3.67 (s, 3H), 2.77 – 2.61 (m, 1H), 2.49 – 2.41 (m, 1H), 2.22 – 2.05 (m, 1H), 1.76 – 1.52 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 170.9, 170.4, 163.4, 159.5, 134.3, 132.5, 129.9, 129.7, 129.6, 128.3, 127.8, 127.8, 113.8, 60.1, 56.7, 55.5, 49.4, 31.7, 22.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for 409.1394 $C_{22}H_{20}N_2O_6^+$; Found 409.1400.

(3R,4S)-2-((S)-2,6-Dioxopiperidin-3-yl)-1-oxo-3-(m-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (cis-4b)



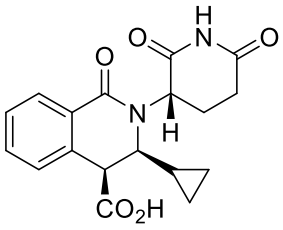
Yield 30 mg, 35%, *dr* >20:1, white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 10.62 (s, 1H), 8.02 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.09 – 6.94 (m, 2H), 6.90 (s, 1H), 6.82 (d, *J* = 7.1 Hz, 1H), 5.19 (d, *J* = 12.9 Hz, 1H), 5.07 (d, *J* = 5.8 Hz, 1H), 4.79 (d, *J* = 5.7 Hz, 1H), 2.76 – 2.60 (m, 1H), 2.48 – 2.40 (m, 1H), 2.15 (s, 3H), 2.13 – 2.06 (m, 1H), 1.73 – 1.49 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 172.0, 170.2, 169.6, 162.7, 137.1, 136.3, 133.4, 131.7, 128.9, 128.4, 128.1, 127.4, 127.3, 127.0, 126.9, 124.6, 59.7, 55.9, 48.6, 30.8, 21.8, 20.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{20}N_2O_5Na^+$ 415.1264; Found 415.1272.

(3R,4S)-3-(4-(tert-Butyl)phenyl)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (cis-4c)



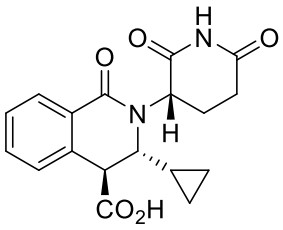
Yield 34 mg, 42%, *dr* >20:1, purple solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.94 (s, 1H), 10.84 (s, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 5.11 (d, *J* = 5.8 Hz, 1H), 4.79 (d, *J* = 5.8 Hz, 1H), 2.70 (ddd, *J* = 17.7, 13.6, 5.2 Hz, 1H), 2.43 (d, *J* = 17.0 Hz, 1H), 2.13 (d, *J* = 9.2 Hz, 1H), 1.58 (br.s, 1H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 172.9, 172.7, 169.4, 162.1, 149.5, 132.0, 129.6, 129.2, 128.1, 127.6, 127.2, 126.6, 124.7, 124.4, 62.2, 58.7, 48.8, 34.1, 31.0, 30.6, 21.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{26}N_2O_5Na^+$ 457.1734; Found 457.1730.

(3S,4S)-3-Cyclopropyl-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (cis-4**d)***



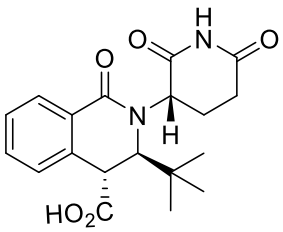
Yield 5 mg, 5%, *dr* >20:1, purple solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.62 (s, 1H), 10.70 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 4.52 (s, 1H), 2.77 – 2.60 (m, 2H), 2.43 (s, 1H), 1.89 (s, 2H), 1.06 (s, 1H), 0.77 (d, *J* = 7.8 Hz, 2H), 0.58 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 173.0, 172.3, 167.6, 166.2, 132.2, 131.6, 130.3, 127.7, 67.2, 30.8, 26.8, 24.1, 11.9, 8.0, HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{18}N_2O_5Na^+$ 365.1108; Found 365.1109.

(3R,4S)-3-Cyclopropyl-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4**d***)



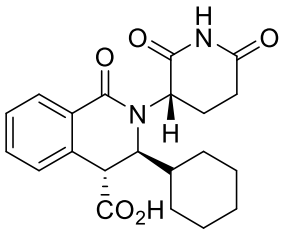
Isolated along with *cis*-**4d** from the same experiment. Yield 7 mg, 7%, *dr* >20:1, purple solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.76 (s, 1H), 10.67 (s, 1H), 7.83 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.55 (td, *J* = 7.5, 1.5 Hz, 1H), 7.50 – 7.42 (m, 2H), 4.60 – 4.37 (m, 1H), 4.00 (s, 1H), 3.58 (s, 1H), 3.36 (dd, *J* = 9.9, 1.6 Hz, 1H), 2.82 – 2.62 (m, 2H), 2.57 (m, *J* = 2.9 Hz, 1H), 2.11 – 2.01 (m, 1H), 0.68 (ddd, *J* = 17.9, 8.0, 3.7 Hz, 2H), 0.50 (dt, *J* = 9.2, 5.7 Hz, 1H), 0.42 (dt, *J* = 9.2, 4.8 Hz, 1H), 0.21 (dq, *J* = 10.3, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 172.7, 171.8, 169.5, 161.6, 135.1, 131.8, 129.9, 128.6, 127.5, 126.9, 65.4, 59.2, 49.0, 31.1, 26.8, 22.4, 15.6, 5.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{18}N_2O_5Na^+$ 365.1108; Found 365.1107.

(3R,4R)-3-(tert-Butyl)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4**e′)***



Yield 5 mg, 6%, *dr* >20:1, white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 13.29 (s, 1H), 10.62 (s, 1H), 7.64 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 – 7.32 (m, 2H), 4.17 (dd, *J* = 11.5, 5.5 Hz, 1H), 4.03 (s, 1H), 3.93 (s, 1H), 2.74 – 2.60 (m, 1H), 2.48 – 2.39 (m, 1H), 2.24 (qd, *J* = 14.1, 13.4, 4.2 Hz, 1H), 2.05 (s, 1H), 0.82 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 173.3, 172.9, 169.8, 162.7, 137.1, 131.5, 129.7, 128.5, 127.1, 126.1, 68.4, 60.9, 45.7, 37.1, 30.6, 27.3, 20.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{22}N_2O_5Na^+$ 381.1421; Found 381.1419.

(3S,4R)-3-Cyclohexyl-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4f)

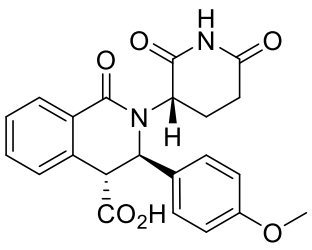


Yield 10 mg, 12%, *dr* >20:1, a white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.85 (s, 1H), 10.68 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.46 – 7.30 (m, 2H), 4.16 (dd, *J* = 11.4, 5.5 Hz, 1H), 4.04 (s, 1H), 3.91 (d, *J* = 4.6 Hz, 1H), 2.65 (ddd, *J* = 16.7, 13.8, 5.3 Hz, 1H), 2.53 (s, 1H), 2.41 (qd, *J* = 12.8, 4.3 Hz, 1H), 2.05 – 1.89 (m, 1H), 1.79 – 1.59 (m, 3H), 1.49 (d, *J* = 12.3 Hz, 2H), 1.42 (d, *J* = 12.3 Hz, 1H), 1.18 (td, *J* = 18.9, 15.9, 7.4 Hz, 2H), 0.96 (h, *J* = 12.8 Hz, 2H), 0.43 (qd, *J* = 12.2, 3.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 173.4, 173.1, 170.3, 161.7, 136.1, 131.9, 129.1, 128.9, 127.4, 126.4, 65.0, 59.7, 44.5, 41.4, 30.8, 29.0, 28.3, 26.1, 26.1, 25.8, 21.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{24}N_2O_5Na^+$ 407.1577; Found 407.1584.

General procedure for preparation of lactams *trans*-4a-m and their analytical data:

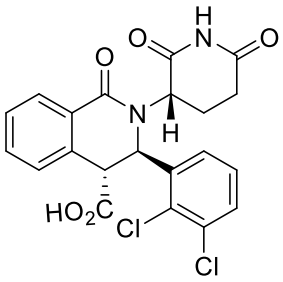
In a screw-cap vial equipped with a magnetic stir bar homophthalic anhydride **3** (1 eq, 0.1-0.2 mmol) and the corresponding imine **2** (2 eq, 0.2-0.4 mmol) were mixed in dry DMSO (0.4 M, 0.5 mL). Then indium(III) trifluoromethanesulfonate (5% mol., 0.01 mmol) was added. The resulting mixture was placed in a pre-heated to 30°C metal heating block. After 2 h at this temperature the reaction mixture was placed in a pre-heated to 80°C metal heating block. After 1-6 days the mixture was purified by RP-HPLC (ACN-water + 0.1% TFA; gradient 5-60% of ACN in 40 min, then 60-95% of ACN in 20 min; 45 °C; 12 mL/min) to provide pure products. For compound *trans*-**4a** K_2CO_3 (1.5 eq., 42 mg, 0.305 mmol) was added before heating to 80°C. In the case of compounds *trans*-**4a**,**l**-**n** heating took 1 day, for *trans*-**4g** - 2 days, *trans*-**4d** - 6 days, *trans*-**4k** - 4 days.

(3R,4R)-2-((S)-2,6-Dioxopiperidin-3-yl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4a)



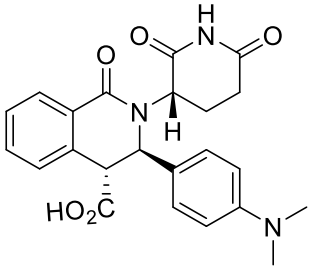
Yield 10 mg, 20%, *dr* >20:1, brown solid. ^{1}H NMR (500 MHz, DMSO-d_6). δ 12.96 (s, 1H), 10.65 (s, 1H), 7.80 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.40 (dtd, *J* = 18.6, 7.4, 1.3 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 6.9 Hz, 1H), 6.80 – 6.69 (m, 2H), 5.33 (s, 1H), 4.17 (s, 1H), 3.98 (s, 1H), 3.71 – 3.65 (m, 1H), 3.66 (s, 3H), 2.65 – 2.57 (m, 1H), 2.39 – 2.30 (m, 1H), 2.09 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$). δ 172.9, 171.9, 169.4, 162.1, 158.5, 134.5, 131.8, 131.0, 129.5, 129.2, 128.0, 127.6, 126.5, 113.4, 61.7, 54.9, 40.4, 40.1, 30.6, 21.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{20}N_2O_6Na^+$ 431.1214; Found 431.1210.

(3R,4R)-3-(2,3-Dichlorophenyl)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4g)



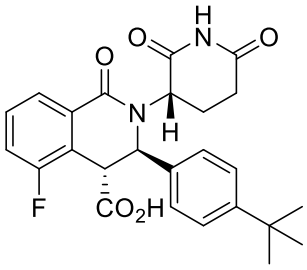
Yield 10 mg, 23%, *dr* >20:1, purple solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 13.15 (s, 1H), 10.72 (s, 1H), 7.93 – 7.73 (m, 1H), 7.60 – 7.49 (m, 1H), 7.48 – 7.41 (m, 2H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 5.71 (s, 1H), 4.26 (s, 1H), 4.15 (s, 1H), 2.71 – 2.57 (m, 1H), 2.40 – 2.23 (m, 1H), 2.17 – 1.93 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6). δ 186.5, 172.8, 169.5, 162.4, 132.2, 131.9, 130.0, 129.8, 129.8, 129.5, 128.6, 128.4, 128.4, 127.9, 127.4, 126.6, 45.6, 40.4, 40.1, 30.6, 21.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{16}Cl_2N_2O_5Na^+$ 469.0328; Found 469.0340.

(3R,4R)-3-(4-(Dimethylamino)phenyl)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4h)



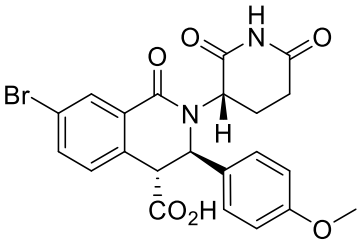
Yield 20 mg, 25%, *dr* >20:1, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.96 (s, 1H), 10.66 (s, 1H), 7.82 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.42 (pd, *J* = 7.4, 1.7 Hz, 2H), 7.26 – 7.09 (m, 3H), 6.67 (d, *J* = 6.1 Hz, 2H), 5.27 (s, 1H), 4.22 (s, 1H), 4.01 (s, 1H), 2.84 (s, 6H), 2.63 (ddd, *J* = 17.5, 13.0, 4.9 Hz, 1H), 2.47 (t, *J* = 3.7 Hz, 1H), 2.40 – 2.20 (m, 1H), 2.04 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6). δ 173.4, 172.6, 169.9, 162.6, 158.6, 134.2, 132.3, 129.9, 129.8, 128.3, 128.0, 127.1, 121.2, 117.8, 115.5, 112.9, 62.0, 52.2, 31.1, 22.1. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{23}N_3O_5Na^+$ 444.1530; Found 444.533.

(3R,4R)-3-(4-(tert-Butyl)phenyl)-2-((S)-2,6-dioxopiperidin-3-yl)-5-fluoro-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-4j)



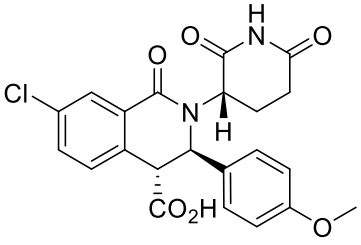
Yield 27 mg, 31%, *dr* >20:1, purple solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 13.70 (s, 1H), 10.70 (s, 1H), 7.68 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.44 (td, *J* = 8.0, 5.3 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.28 – 7.22 (m, 2H), 5.46 (s, 1H), 4.27 (s, 1H), 4.17 (s, 1H), 2.61 (ddd, *J* = 16.8, 13.3, 5.3 Hz, 1H), 2.48 – 2.43 (m, 1H), 2.29 (qd, *J* = 12.5, 3.7 Hz, 1H), 2.07 (s, 1H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 172.8, 170.8, 169.3, 161.2 (d, *J* = 3.0 Hz), 159.2 (d, *J* = 246.1 Hz), 149.7, 135.8, 131.2 (d, *J* = 3.4 Hz), 129.3 (d, *J* = 7.8 Hz), 126.4, 124.9, 122.7 (d, *J* = 2.7 Hz), 121.6 (d, *J* = 15.8 Hz), 118.8 (d, *J* = 21.4 Hz), 61.8, 58.7, 45.9, 42.1, 34.1, 31.0, 30.6, 21.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{25}FN_2O_5Na^+$ 475.1640; Found 475.1649.

***(3R,4R)-7-Bromo-2-((S)-2,6-dioxopiperidin-3-yl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-*4k**)**



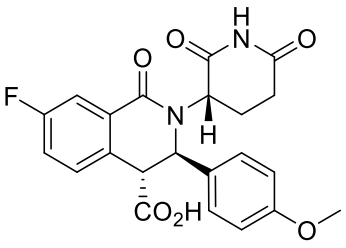
Yield 11 mg, 23%, *dr* >20:1, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 10.70 (s, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.65 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.82 – 6.77 (m, 2H), 5.35 (s, 1H), 4.30 (s, 1H), 4.11 (d, *J* = 1.5 Hz, 1H), 3.67 (s, 3H), 2.63 (ddd, *J* = 18.0, 13.3, 5.2 Hz, 1H), 2.48 – 2.45 (m, 1H), 2.29 (qd, *J* = 14.8, 13.6, 5.1 Hz, 1H), 2.07 – 1.99 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 172.8, 171.5, 169.3, 160.9, 158.6, 139.1, 134.6, 131.9, 131.2, 128.9, 128.0, 120.8, 113.5, 113.3, 61.8, 55.0, 51.5, 30.6, 21.5, 1.2. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{19}BrN_2O_6Na^+$ 509.0319; Found 509.0320.

***(3R,4R)-7-Chloro-2-((S)-2,6-dioxopiperidin-3-yl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-*4l**)**



Yield 7 mg, 16%, *dr* >20:1, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 13.10 (s, 1H), 10.71 (s, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.85 – 6.75 (m, 2H), 5.37 (s, 1H), 4.31 (s, 1H), 4.14 (s, 1H), 3.68 (s, 3H), 2.64 (ddd, *J* = 17.9, 13.2, 5.2 Hz, 1H), 2.48 (m, 1H), 2.31 (qd, *J* = 12.7, 4.4 Hz, 1H), 2.08 – 1.99 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6). δ 172.8, 171.6, 169.3, 161.0, 158.6, 139.1, 132.7, 131.8, 131.7, 131.0, 128.0, 126.1, 113.5, 113.3, 61.8, 61.6, 55.0, 51.1, 30.6, 21.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{19}ClN_2O_6Na^+$ 465.0824; Found 465.0838.

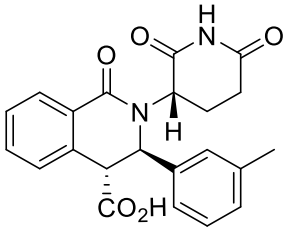
***(3R,4R)-2-((S)-2,6-Dioxopiperidin-3-yl)-7-fluoro-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-*4m**)**



Yield 22 mg, 51%, dr >20:1, brown solid. ^{1}H NMR (500 MHz, DMSO-d_6). δ 13.09 (s, 1H), 10.71 (s, 1H), 7.54 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.81 – 6.76 (m, 2H), 5.35 (s, 1H), 4.36 – 4.20 (m, 1H), 4.10 (d, *J* = 1.5 Hz, 1H), 3.66 (s, 3H), 2.68 – 2.59 (m, 1H), 2.49 – 2.46 (m, 1H), 2.30 (qd, *J* = 12.7, 4.4 Hz, 1H), 2.06 – 2.00 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6). δ 172.8, 171.9, 169.3, 161.6 (d, *J* = 244.6 Hz), 161.1, 158.6, 157.8 (d, *J* = 31.8Hz), 131.9 (d, *J* = 7.9 Hz), 131.3 (d, *J* = 7.4 Hz), 130.0 (d, *J* = 3.0 Hz), 128.0, 119.0 (d, *J* = 21.8 Hz), 113.5, 112.9 (d, *J* = 23.5 Hz), 61.6, 58.4, 55.0, 50.9, 30.6, 21.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{19}FN_2O_6Na^+$ 449.1119; Found 449.1108.

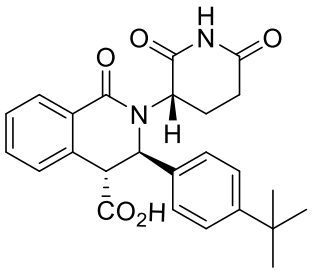
Procedures for preparation of *lactams trans*-4b,c,i:

***(3R,4R)-2-((S)-2,6-Dioxopiperidin-3-yl)-1-oxo-3-(m-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans*-4b**)



In a screw-cap vial equipped with a magnetic stir bar homophthalic anhydride **3a** (35.2 mg, 0.21 mmol) and the corresponding imine **2** (2 eq, 100 mg, 0.43 mmol) were mixed in dry DMSO (0.4M, 0.5 mL). Then indium(III) trifluoromethanesulfonate (5% mol., 0.01 mmol) was added. The resulting mixture was placed in a pre-heated to 30°C metal heating block. After 2 h at this temperature, the reaction mixture was placed in a pre-heated to 80°C metal heating block. After 1-6 days, the mixture was purified by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of MeCN in 20 min; 45 °C; 12 mL/min) to provide pure compound **4b** (30 mg). After two weeks in DMSO-d_6 pure compound *cis*-**4b** began to transform into the *trans*-isomer. This mixture was purified by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of ACN in 20 min; 45 °C; 12 mL/min) and pure fraction was placed in a pre-heated to 80°C metal heating block. After 10 days the solvent was removed by freeze-drying and the title compound was obtained pure 30 mg, 37% with *dr* >20:1 as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 13.37 (s, 1H), 10.63 (s, 1H), 7.83 – 7.73 (m, 1H), 7.37 (m, *J* = 7.0 Hz, 2H), 7.24 (s, 1H), 7.15 (dd, *J* = 13.2, 7.4 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 5.36 (s, 1H), 4.12 (s, 1H), 3.95 (s, 1H), 2.61 (ddt, *J* = 17.5, 13.0, 6.5 Hz, 1H), 2.47 – 2.43 (m, 1H), 2.41 – 2.25 (m, 1H), 2.19 (s, 3H), 2.13 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 172.9, 172.0, 169.5, 162.2, 139.5, 137.0, 134.7, 131.6, 129.4, 129.1, 127.8, 127.8, 127.5, 127.3, 126.4, 123.8, 62.4, 58.6, 52.4, 30.6, 21.5, 21.0. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{20}N_2O_5Na^+$ 415.1264; Found 415.1272.

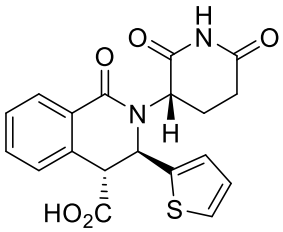
***(3R,4R)-3-(4-(tert-Butyl)phenyl)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans*-4c**)



After 4 days, pure compound *cis*-**4c** in DMSO-d_6 began to transform into the *trans*-isomer. This mixture was purified by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of MeCN in 20 min; 45 °C; 12 mL/min) and pure fraction in DMSO-d_6 was placed in a pre-heated to 80°C metal heating block. After 1 day the solvent was removed by freeze-drying to obtain pure compound 10.3 mg 41% with *dr* >20:1 as a purple solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 13.12 (s, 1H), 10.63 (s, 1H), 7.81 (dd, *J* = 7.3, 1.5 Hz, 2H), 7.39 (m, *J* = 7.4, 1.5 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.17 (m, 2H), 5.37 (s, 1H),

4.13 (d, *J* = 5.4 Hz, 1H), 4.00 (s, 1H), 2.60 (ddd, *J* = 17.6, 13.1, 5.1 Hz, 1H), 2.41 – 2.25 (m, 1H), 2.13 (s, 1H), 1.27 – 1.21 (m, 1H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 172.9, 172.2, 169.4, 162.1, 149.5, 136.2, 131.7, 131.6, 129.6, 129.2, 127.6, 126.6, 126.4, 124.8, 62.1, 58.7, 52.0, 34.1, 31.0, 30.6, 21.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{26}N_2O_5Na^+$ 457.1734; Found 457.1730.

(3R,4R)-2-((S)-2,6-Dioxopiperidin-3-yl)-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (trans-*4i**)



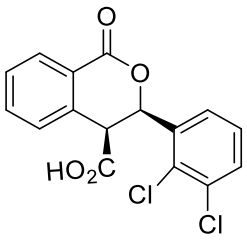
In a screw-cap vial equipped with a magnetic stir bar homophthalic anhydride **3a** (35.2 mg, 0.21 mmol) and the 3-((thiophen-2-ylmethylene)amino)piperidine-2,6-dione **2i** (2 eq, 100 mg, 0.43 mmol) were mixed in dry DMSO (0.4M, 0.5 mL). Then indium(III) trifluoromethanesulfonate (5% mol., 0.01 mmol) was added. The resulting mixture was placed in a pre-heated to 30°C metal heating block. After 2 h at this temperature the reaction mixture was placed in a pre-heated to 80°C metal heating block. After 1-6 days the mixture was purified by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of MeCN in 20 min; 45 °C; 12 mL/min) to provide pure *cis*-**4i** (10 mg, 12%). After 7 days in DMSO-d_6 pure compound *cis*-**4i** began to transform into the *trans*-isomer. This mixture in DMSO-d_6 was placed in a pre-heated to 80°C metal heating block. After 1 day the solvent was removed by freeze-drying to obtain pure compound 10 mg, 100% with *dr* ~ 6.7:1 as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6). δ 10.65 (s, 1H), 7.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 6.82 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.63 (s, 1H), 4.35 (dd, *J* = 10.5, 4.2 Hz, 1H), 4.13 (s, 1H), 2.64 (ddd, *J* = 17.6, 13.2, 5.2 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.42 – 2.23 (m, 1H), 2.17 – 1.94 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6). δ 172.9, 171.4, 169.3, 161.6, 142.9, 134.8, 131.9, 129.8, 128.9, 127.7, 126.7, 126.5, 126.0, 125.6, 59.3, 58.6, 42.1, 30.7, 21.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{16}N_2O_5SNa^+$ 407.0672; Found 407.0681.

General procedure for preparation of lactones *cis/trans*-5 and their analytical data:

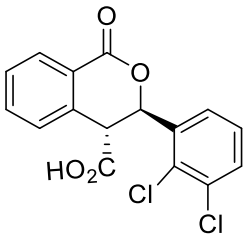
In a screw-cap vial equipped with a magnetic stir bar homophthalic anhydride **3a** (1 eq, 28.4 mg, 0.175 mmol) and imine **2g** (2 eq, 100 mg, 0.35 mmol) were mixed in dry DMSO (0.35M, 0.5 mL). The resulting mixture was placed in a pre-heated to 30°C metal heating block. After 2 h at this temperature the reaction mixture was separated by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of MeCN in 20 min; 45 °C; 12 mL/min) to provide pure compounds.

(3R,4S)-3-(2,3-Dichlorophenyl)-1-oxoisochromane-4-carboxylic acid (cis-5)



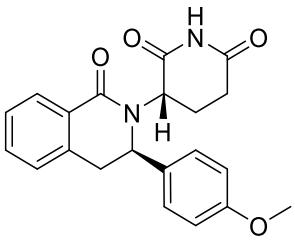
Yield 16 mg, 28%, *dr* >20:1, white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.94 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.71 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.33 (d, *J* = 6.2 Hz, 1H), 4.65 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 170.0, 162.5, 136.7, 135.6, 134.1, 132.3, 131.5, 130.6, 130.1, 129.1, 128.3, 128.0, 127.5, 126.6, 76.9, 46.9. HRMS (ESI) m/z: $[M+H]^-$ Calcd for $C_{16}H_9Cl_2O_4^-$ 334.9883; Found 334.9881.

(3R,4R)-3-(2,3-Dichlorophenyl)-1-oxoisochromane-4-carboxylic acid (trans-5)



Yield 11 mg, 19%, *dr* >20:1, white solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 12.62 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 6.21 (d, *J* = 3.4 Hz, 1H), 4.38 (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6). δ 167.1, 166.5, 136.4, 136.1, 132.2, 131.5, 131.5, 131.0, 130.5, 129.6, 129.5, 128.7, 127.6, 127.2, 76.1, 46.5. HRMS (ESI) m/z: $[M+H]^-$ Calcd for $C_{16}H_9Cl_2O_4^-$ 334.9883; Found 334.9895.

(S)-3-((R)-3-(4-Methoxyphenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (6)



In a screw-cap vial equipped with a magnetic stir bar homophthalic anhydride **3a** (1 eq, 32.9 mg, 0.203 mmol) and imine **2a** (2 eq, 100 mg, 0.406 mmol) were mixed in dry DMSO (0.4M, 0.5 mL). Then indium(III) trifluoromethanesulfonate (5% mol., 5.7 mg, 0.01 mmol) was added. The resulting mixture was placed in a pre-heated to 30°C metal heating block. After 2 h at this temperature, K_2CO_3 (1.5 eq., 42 mg, 0.305 mmol) was added to the reaction mixture and this was placed in a pre-heated to 150°C metal heating block. After 16 h, the mixture was purified by RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-60% of MeCN in 40 min, then 60-95% of MeCN in 20 min; 45 °C; 12 mL/min) to provide pure compound **6** (4 mg, 10%) with *dr* >20:1 as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6). δ 10.86 (s, 1H), 7.89 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.40 (td, *J* = 7.4, 1.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 3H), 6.77 – 6.72 (m, 2H), 4.92 (d, *J* = 5.2 Hz, 1H), 3.67 – 3.59 (m, 4H), 2.97 (dd, *J* = 15.7, 2.3 Hz, 1H), 2.73 (ddd, *J* = 18.4, 13.6, 5.5 Hz, 1H), 2.45 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.06 – 1.90 (m, 1H), 1.79 – 1.68 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6). δ 172.7, 170.5, 163.5, 158.2, 136.0, 132.9,

132.1, 129.4, 127.9, 127.7, 127.4, 127.0, 126.9, 113.9, 113.5, 55.0, 54.9, 36.3, 31.0, 22.0, 21.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{20}N_2O_4Na^+$ 387.1315; Found 387.1313.

Experimental part. Biological studies

Cell culture. Multiple myeloma cell line KMS-12-PE were purchased from the DSMZ. MM1.S, NALM-6 and WIL2-S cell were purchased from the ATCC. The cells were maintained in RPMI-1640 (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 UI mL^{-1}), streptomycin (100 µg mL^{-1}) and GlutaMax (2 mM, Gibco, UK). All cells line cultivation under a humidified atmosphere of 95% air/5% CO_2 at 37 °C. The number of viable cells was determined by trypan blue exclusion.

MTT assay. All examined cells were diluted with growth medium to a final concentration of 3.0×10^5 cells per mL. Aliquots of 15×10^3 cells in 50 µL were placed in individual wells of white 96-well multiplates (Nunc, USA). In triplicate wells, test compounds were added, initially starting at a concentration of 100 µM, then diluted to achieve a final concentration of 50 µM for testing. Dimethyl sulfoxide (DMSO, Sigma, USA) was used as a control at a final concentration of 0.1%. The plates were incubated for 72 hours at 37 °C in a 5% CO_2 atmosphere. Following incubation, 100 µL of CellTiter-Glo® One Solution (Promega, USA) was added to each well. The plates were then shaken for 10 minutes. Luminescence was measured using a GloMax Multi+ microplate reader (Promega, USA). Cytotoxicity of each compound was evaluated in three separate experiments.

Microscale Thermophoresis assay

For affinity measurements we used a previously described competitive MST assay[4]. Compounds were dissolved in DMSO, diluted 1:1 in a 16-point dilution series and subsequently the complete series was diluted in H_2O. The resulting dilution series were mixed 1:1 with a protein reporter stock to final concentrations of 500 µM compound (highest concentration), 10 µM *h*TBD, 200 nM BODIPY-uracil and 0.5% DMSO. MST measurements were carried out with the Monolith NT.115, equipped with a Nano BLUE detector, at 20% excitation power, medium MST power and 25 °C. Resulting MST traces were evaluated at an MST on-time of 20 s. The corresponding normalized fluorescence counts of dublicates were baseline corrected (ΔF_{norm}) to the mean response of the lowest ligand concentration and analyzed using GraphPad Prism 9. IC_{50} values were obtained from a non-linear, 4 parameters fit of the Hill equation. The reported error corresponds to a symmetric 95% confidence interval of the IC_{50}. K_i values were calculated as reported previously[5]. The lower 95% confidence interval was converted to a theoretical K_i. This theoretical K_i was subtracted from the K_i, resulting in the final error of the K_i.

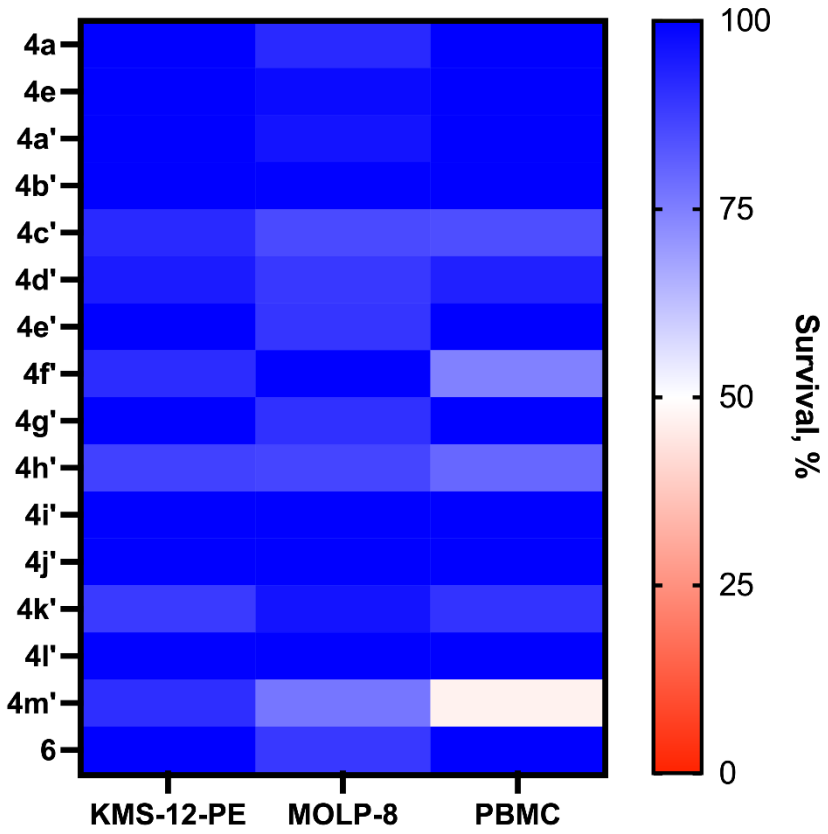
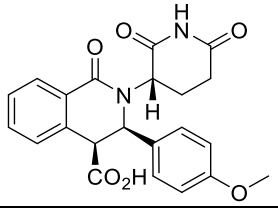
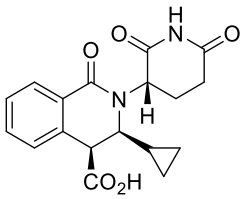
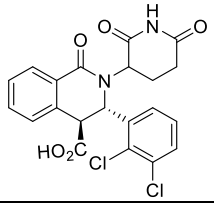
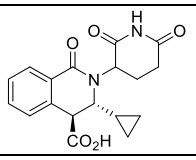
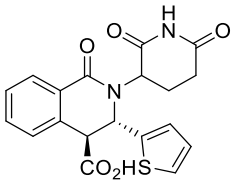
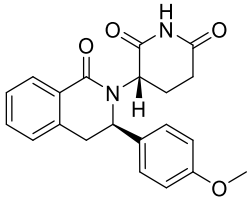
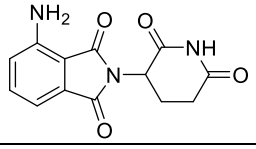


Figure S2. Cytotoxicity profile of the synthesized compounds against the KMS-12-PE and MOLP-8 cell lines

Table S3. CRBN binding data of compounds *cis*-**4a,d,** *trans*-**4d,g,i** and **6.** Data for Thalidomide shown for reference.[S4]

Compound	Structure	IC_{50}, µM	K_i, µM
***cis*-4a**		51.38 ± 8.86	23.32 ± 4.61
***cis*-4d**		221.90 ± 248.9	106.81 ± 129.45
***trans*-4g**		216.3 ± 130.75	109.09 ± 68.00
***trans*-4d**		187.2 ± 46.3	94.0 ± 24.1
***trans*-4i**		243.8 ± 149.0	123.4 ± 77.5
6		39.6 ± 4.7	17.2 ± 2.4
Thalidomide		22.9 ± 1.6	8.5 ± 0.8

References

S1. G. He, K. Wang, Q. Zhang and Z. Xie, *Patent CN103242215* (*A*), 2013.

S2. A. Shoji, M. Kuwahara, H. Ozaki and H. Sawai, *J, Am. Chem. Soc.*, 2007, **129**, 1456; https://doi.org/10.1021/ja067098n.

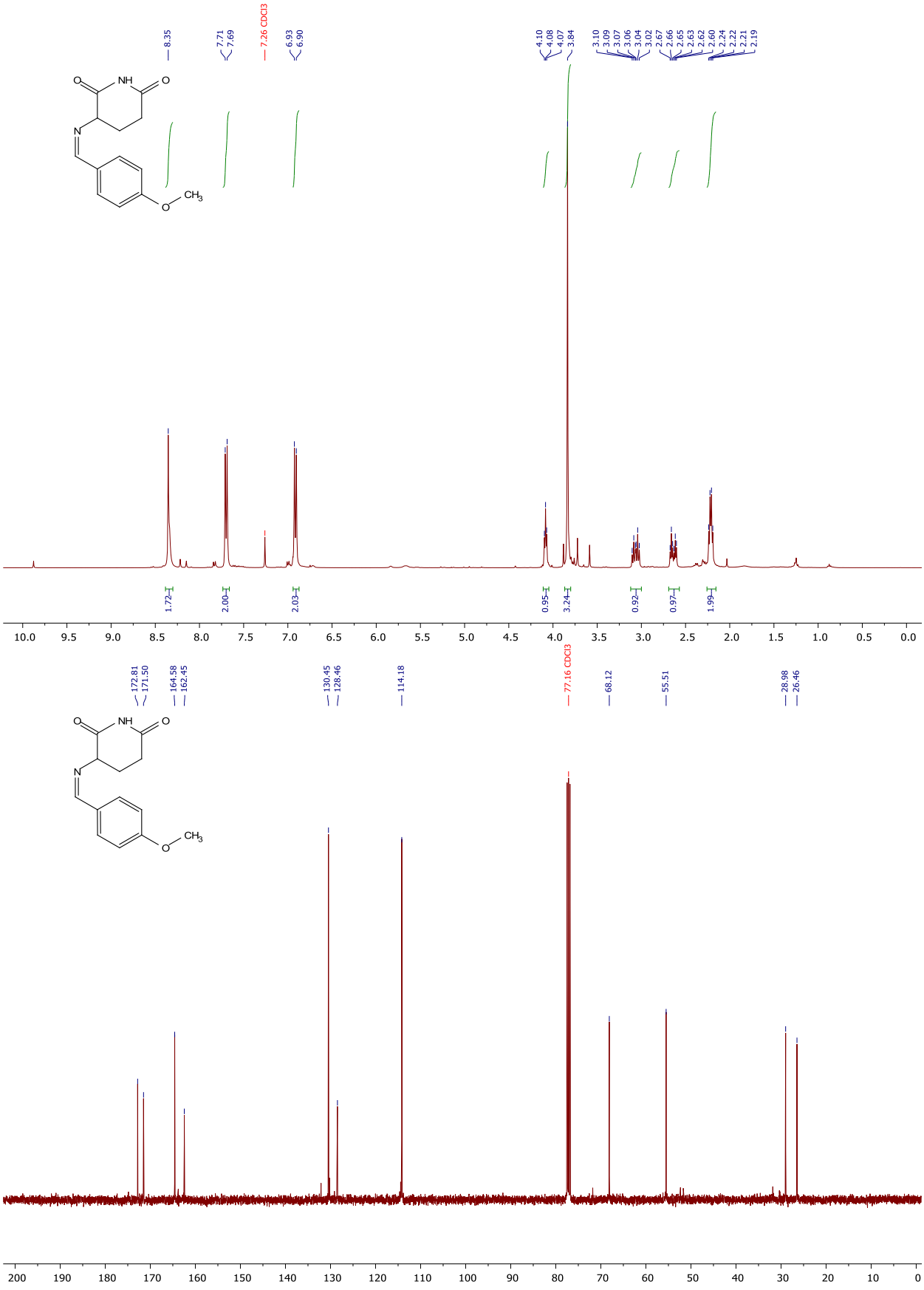
S3. E. S. Khazanova and S. Yu. Nogai, *Patent RU2730858C1*, 2020.

S4. S. Maiwald, C. Heim, B. Hernandez Alvarez and M. D. Hartmann, *ACS Med. Chem. Lett.*, 2021, **12**, 74; https://doi.org/10.1021/acsmedchemlett.0c00440.

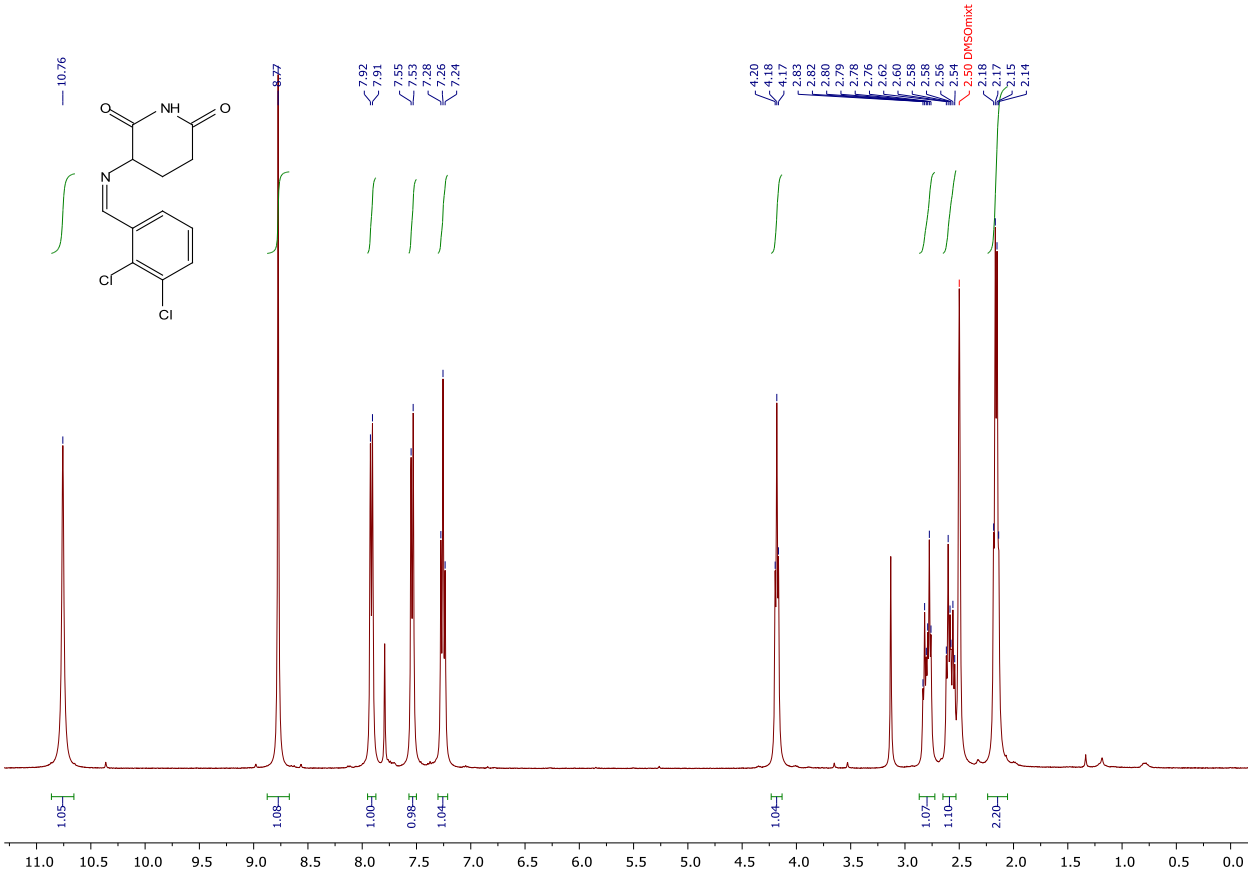
S5. Z. Nikolovska-Coleska, R. Wang, X. Fang, H. Pan, Y. Tomita, P. Li, P. P. Roller, K. Krajewski, N. G. Saito, J. A. Stuckey and S. Wang, *Anal. Biochem.*, 2004, **332**, 261; https://doi.org/10.1016/j.ab.2004.05.055.

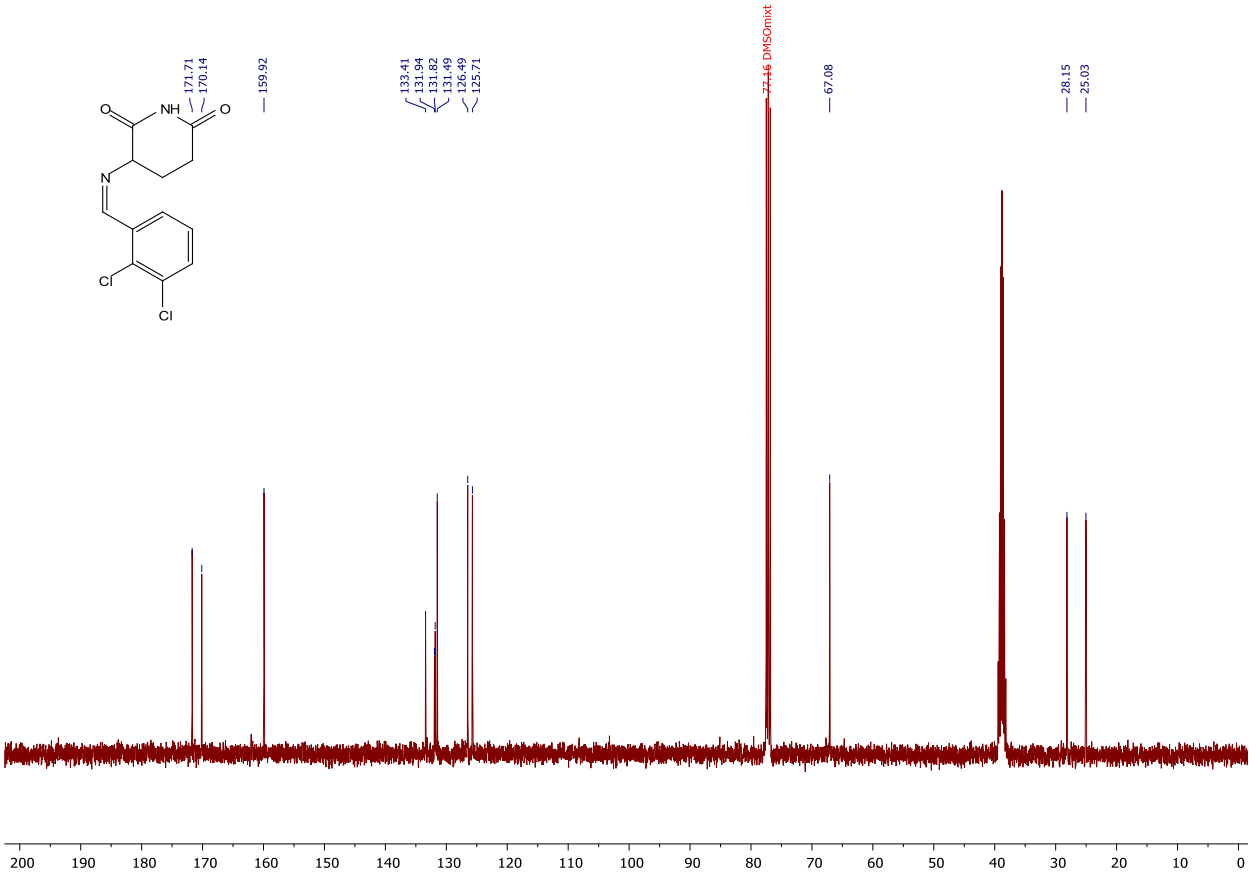
Copies of ^{1}H and ^{13}C NMR spectra

^{1}H and ^{13}C NMR spectra of compound ***2a***

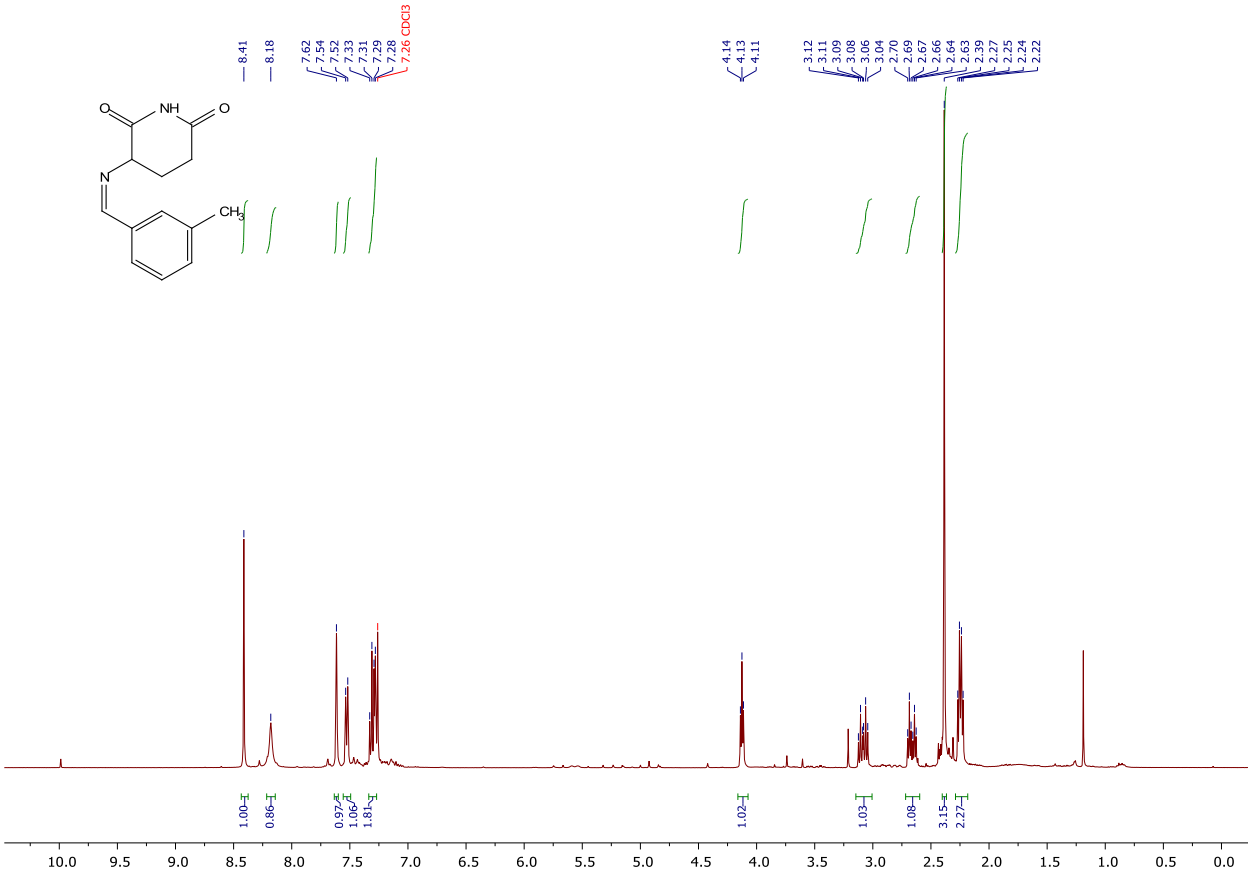


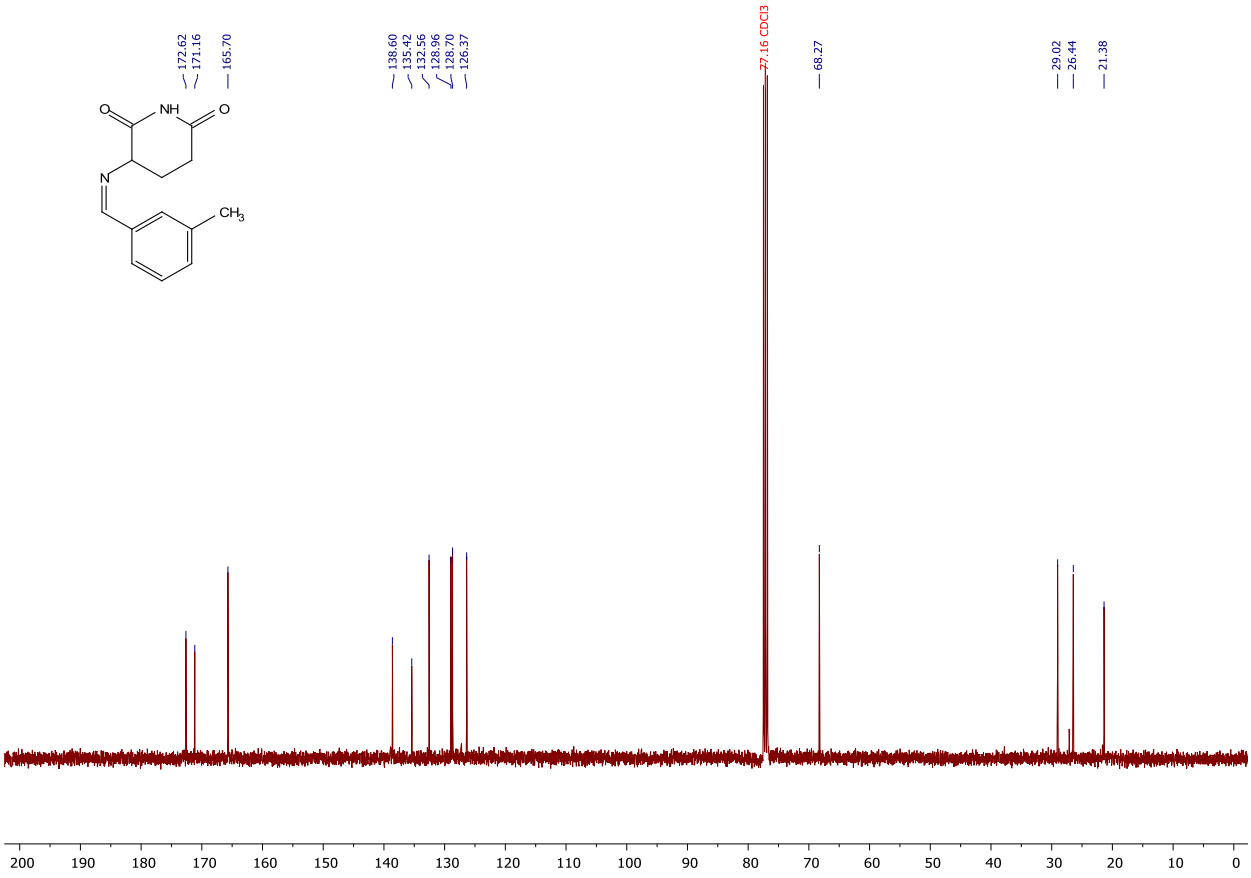
^{1}H and ^{13}C NMR spectra of compound ***2g***



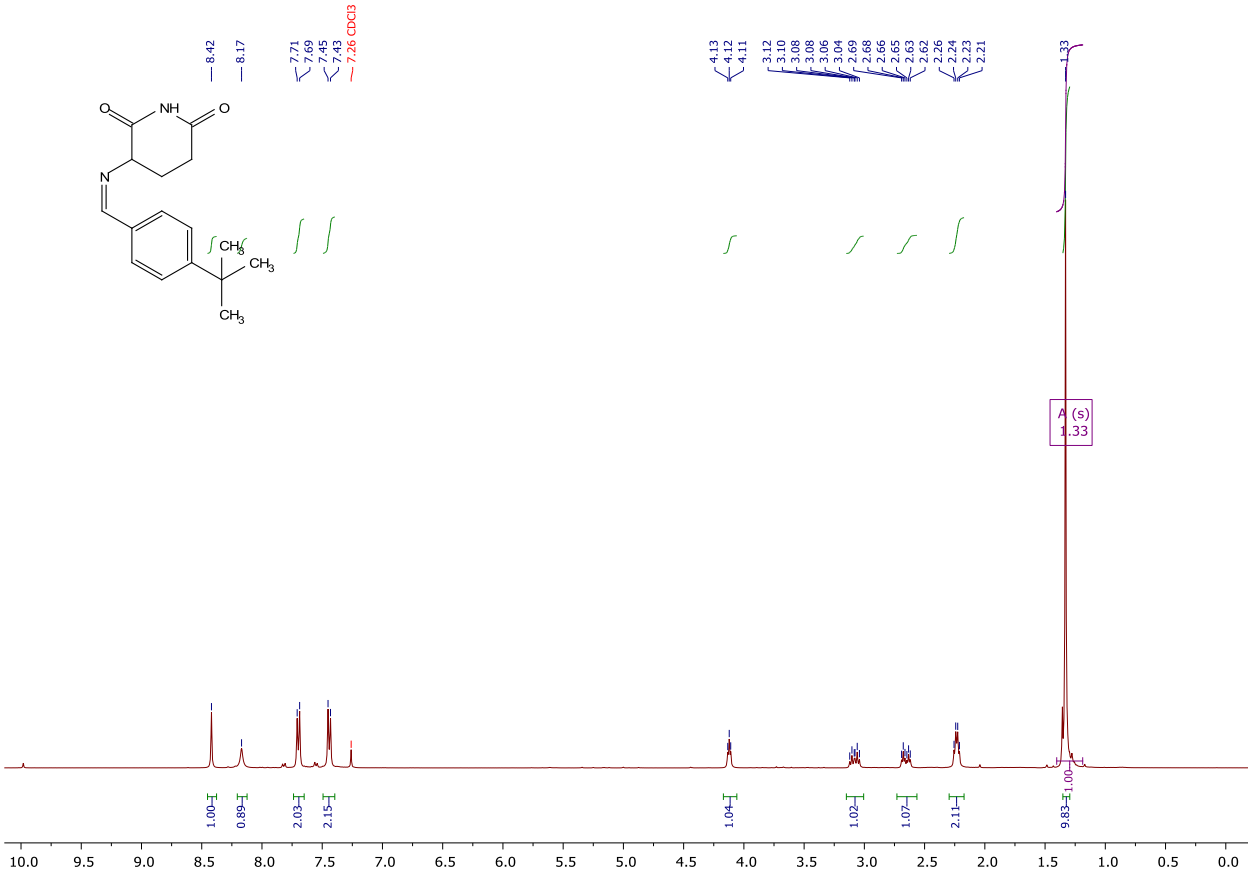


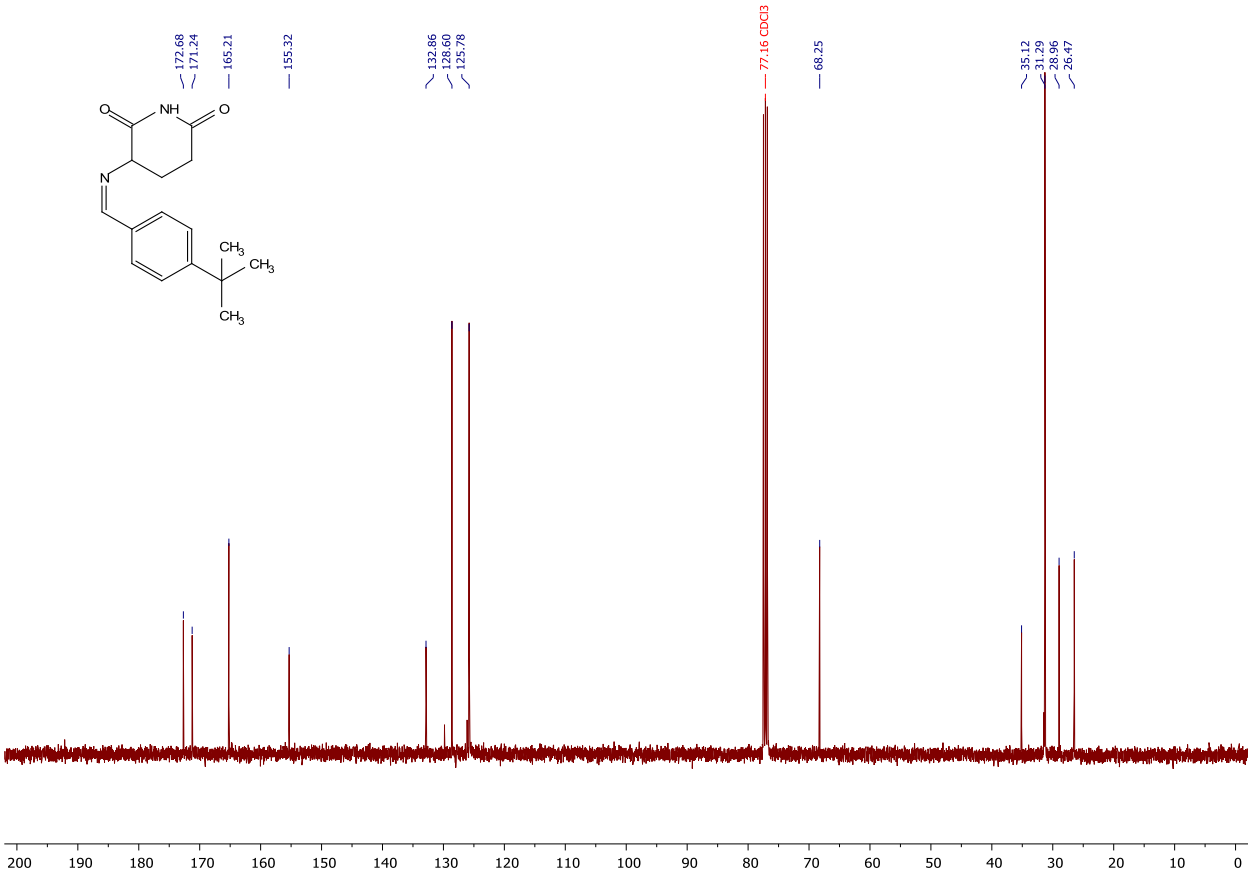
^{1}H and ^{13}C NMR spectra of compound ***2b***



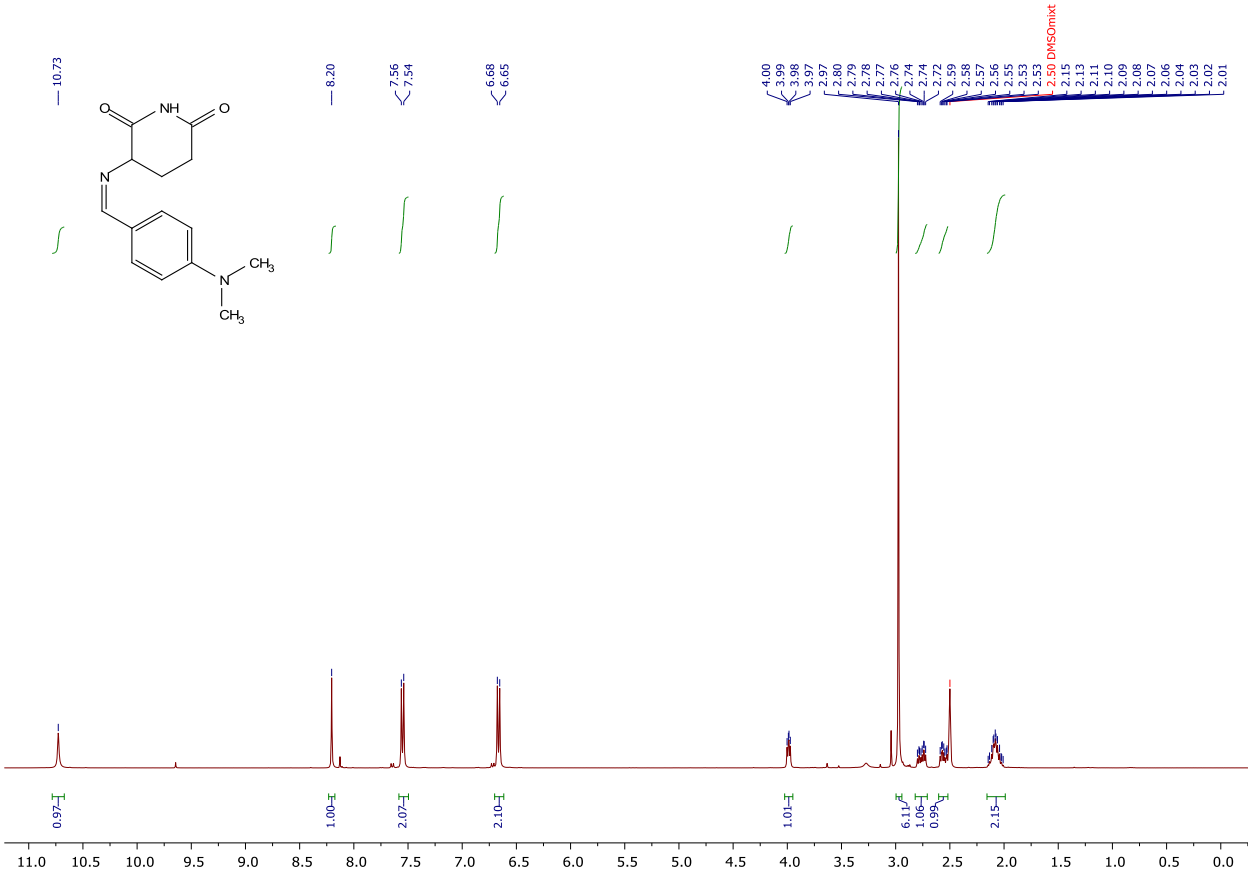


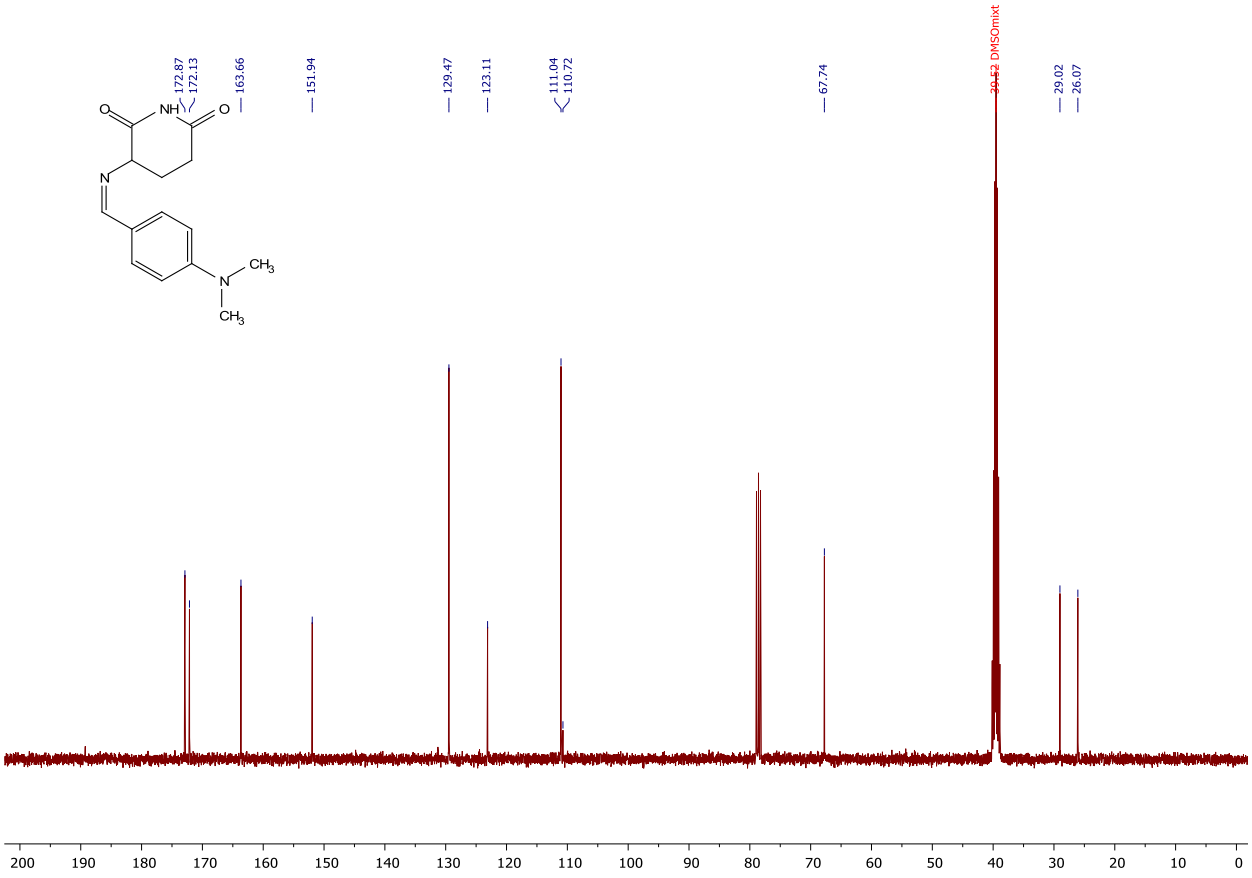
^{1}H and ^{13}C NMR spectra of compound ***2c***



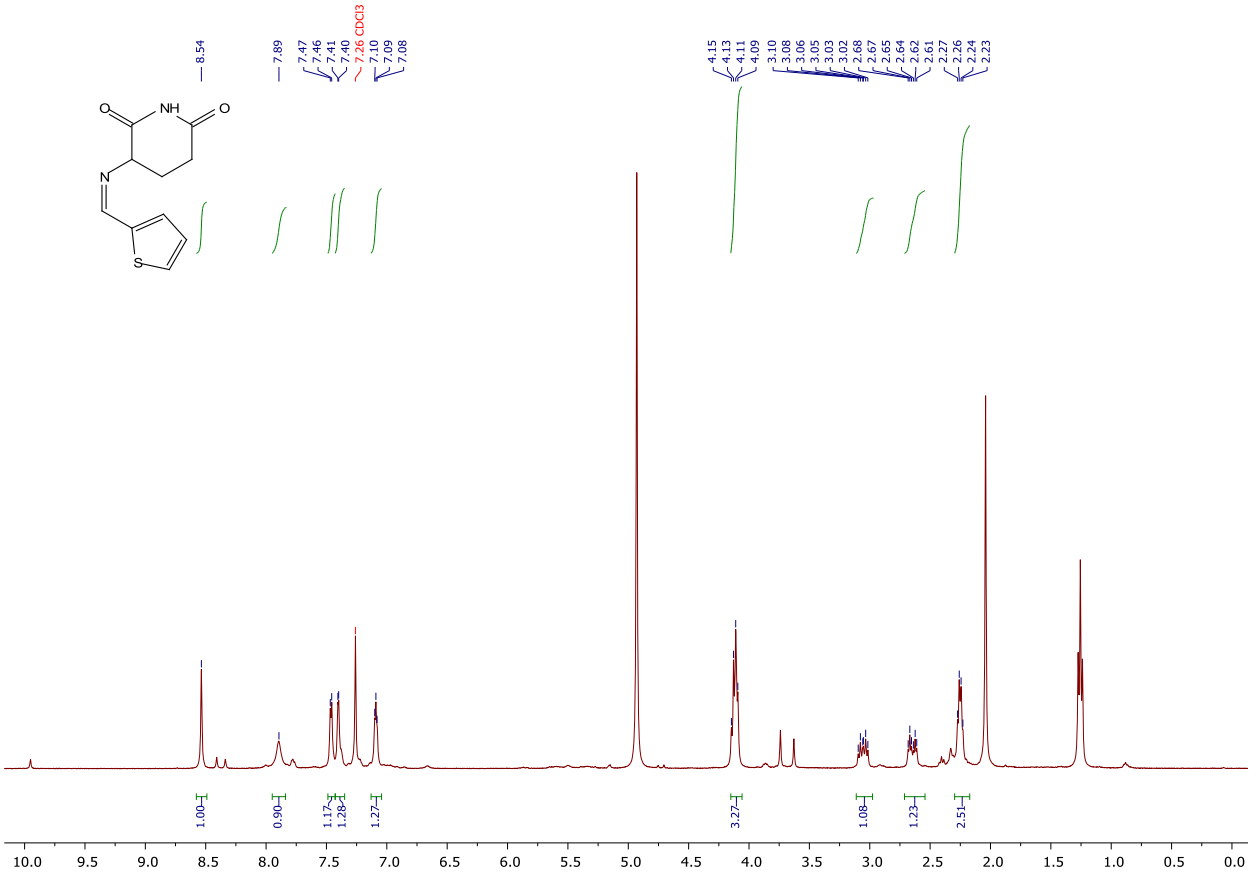


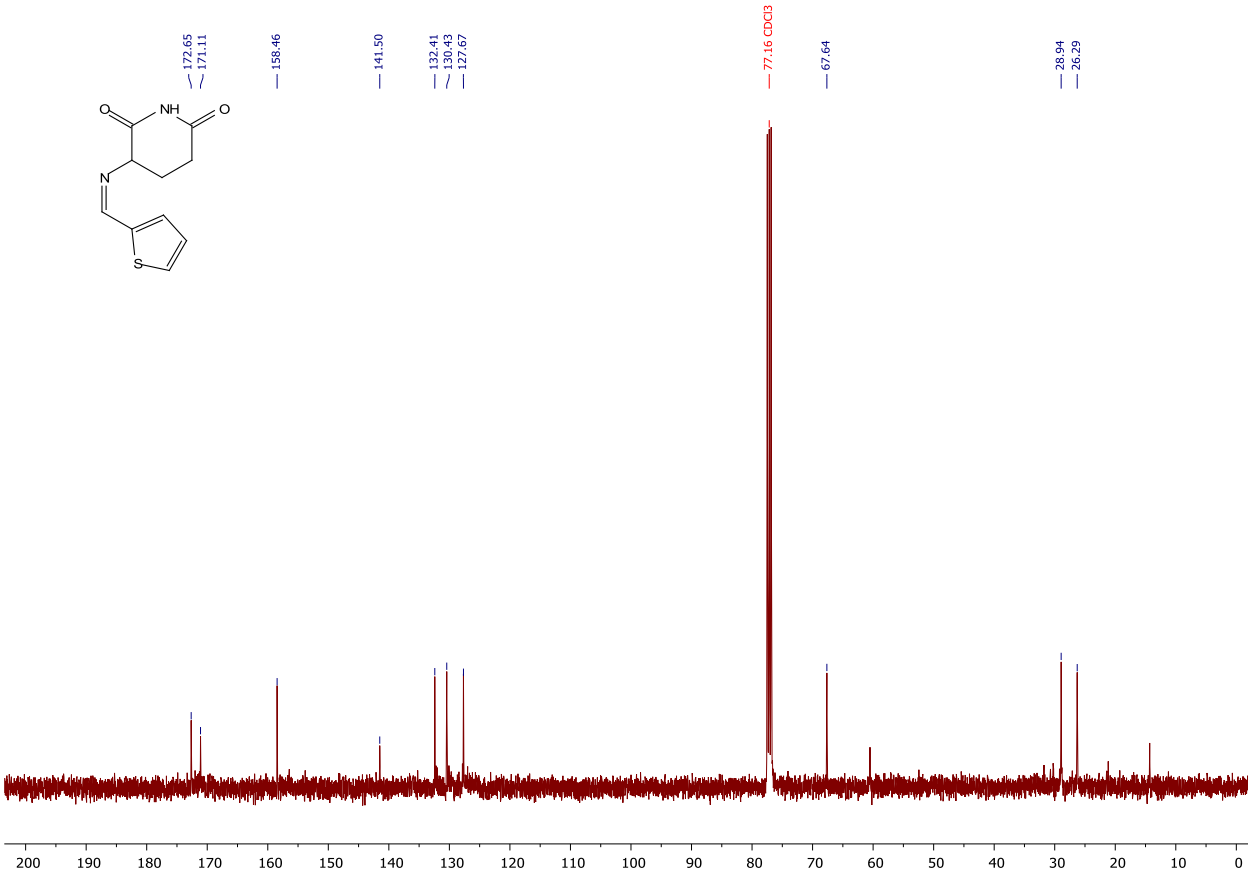
^{1}H and ^{13}C NMR spectra of compound ***2h***



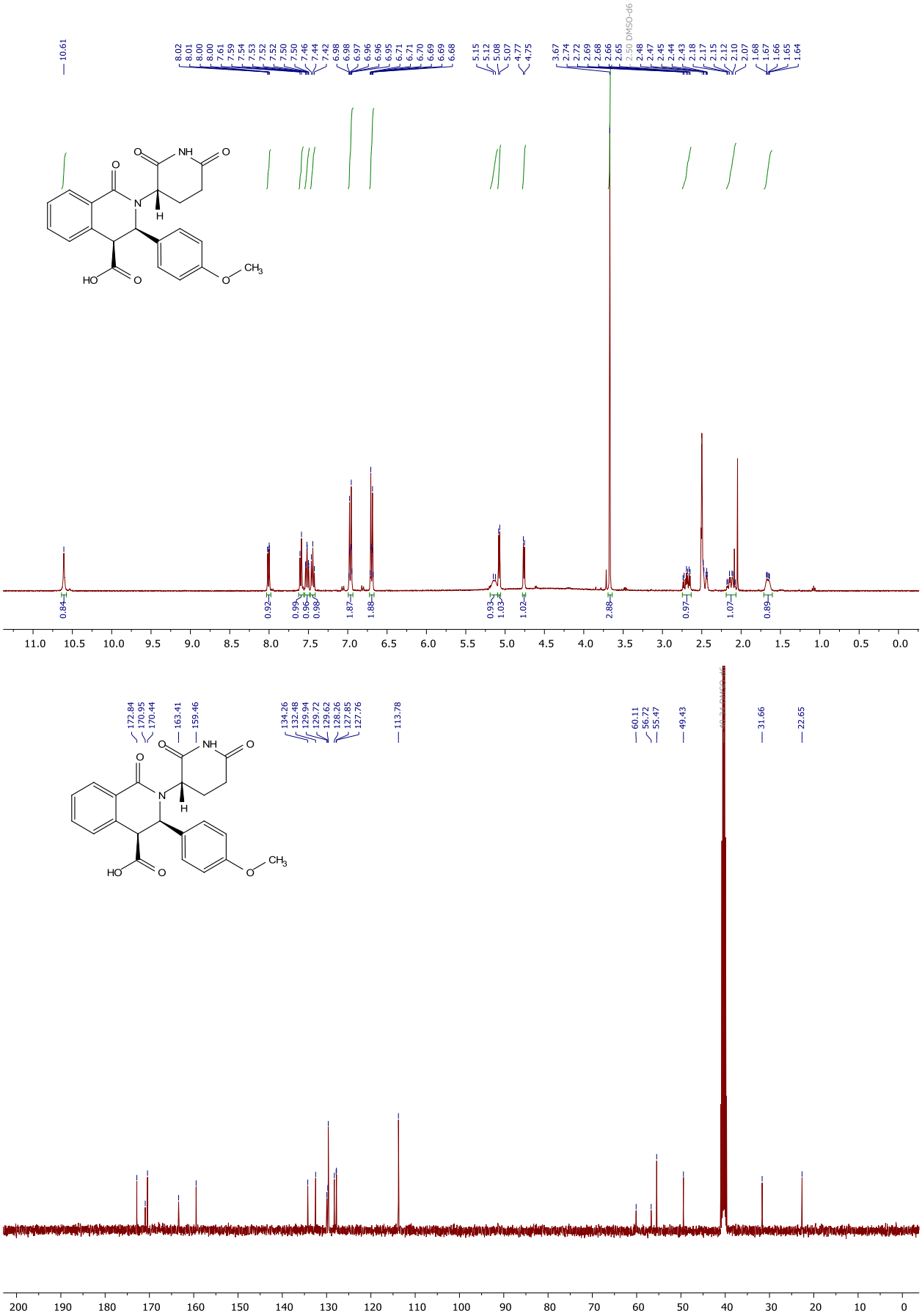


^{1}H and ^{13}C NMR spectra of compound ***2i***

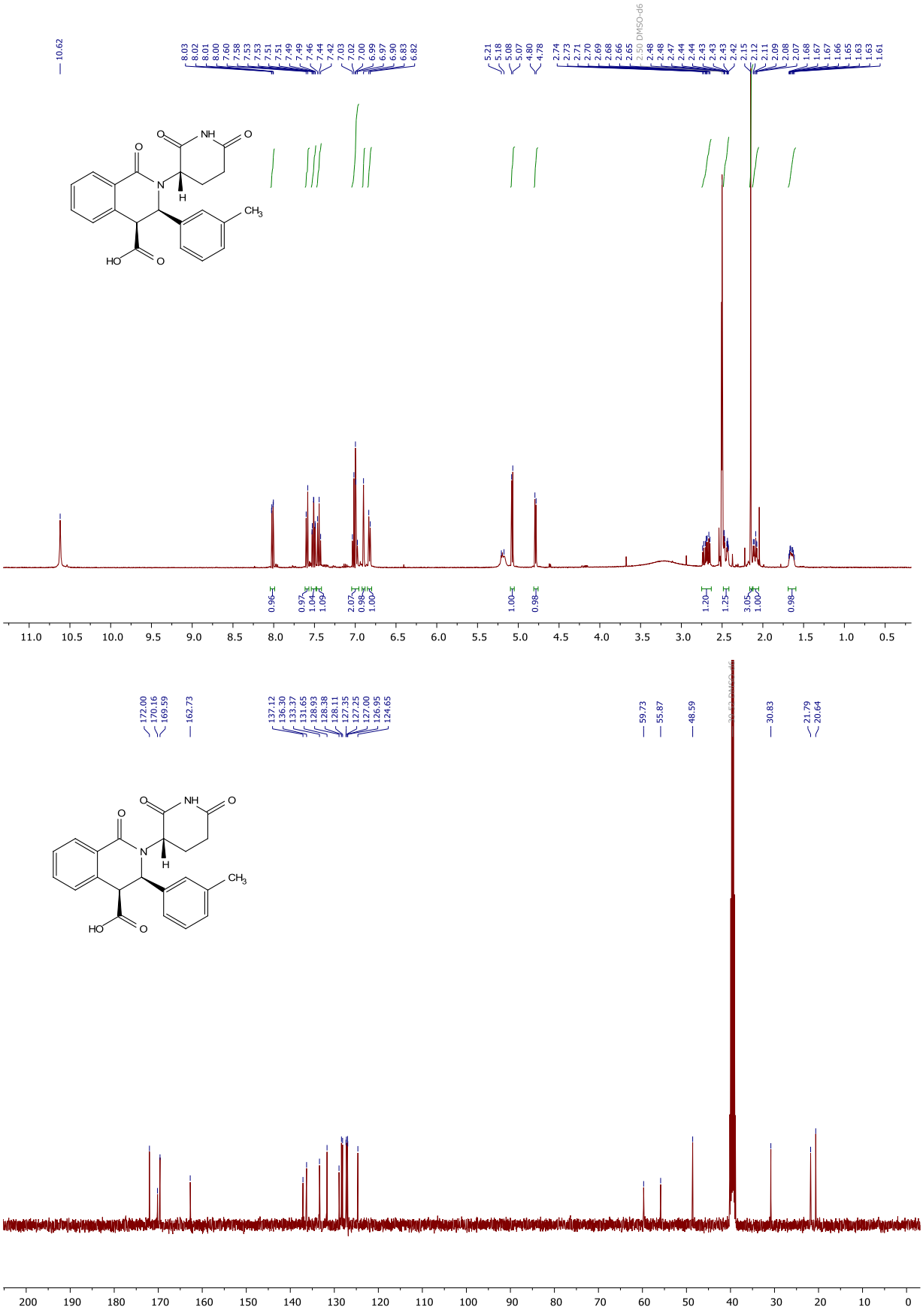




^{1}H and ^{13}C NMR spectra of compound *cis*-***4a***



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



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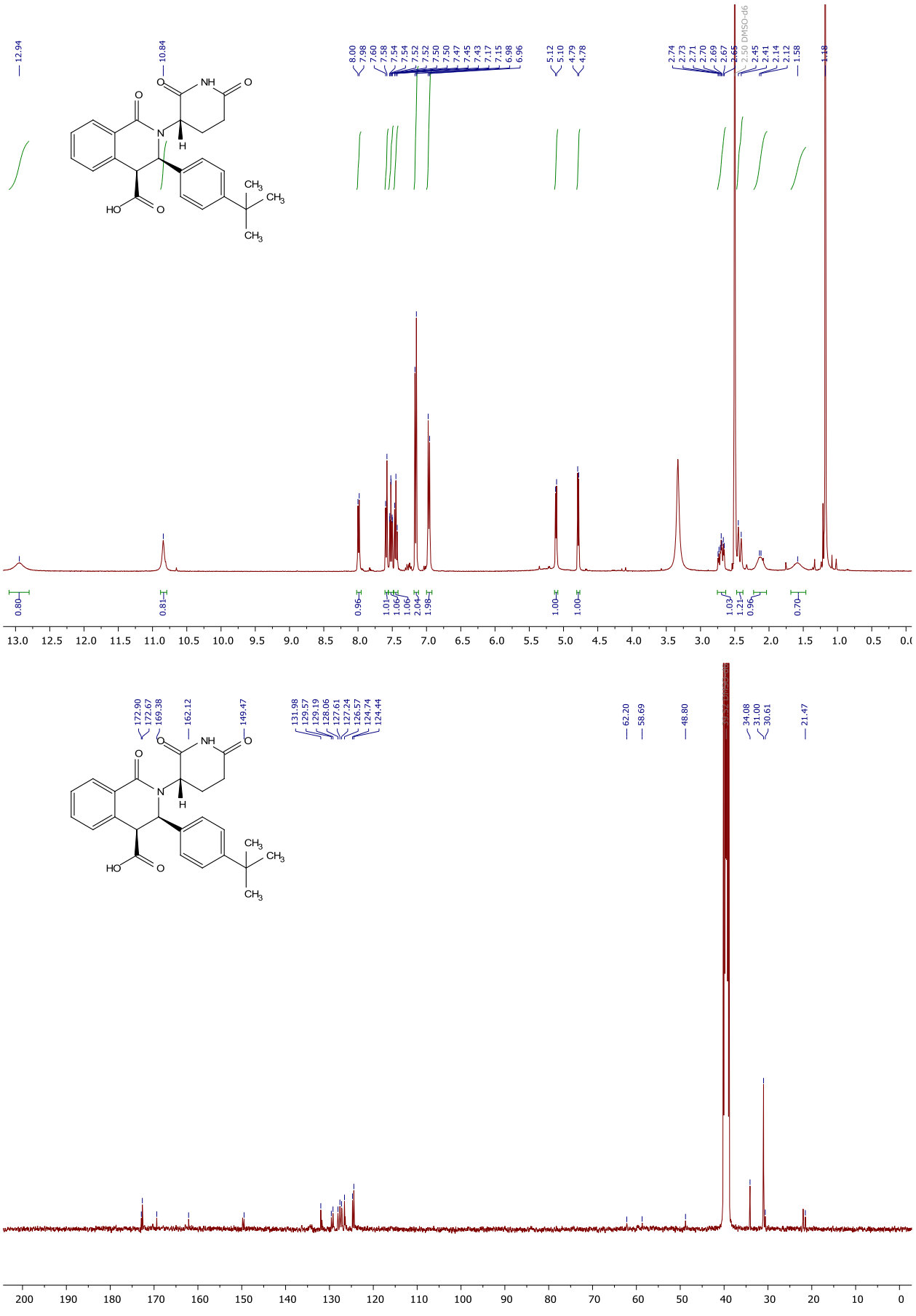
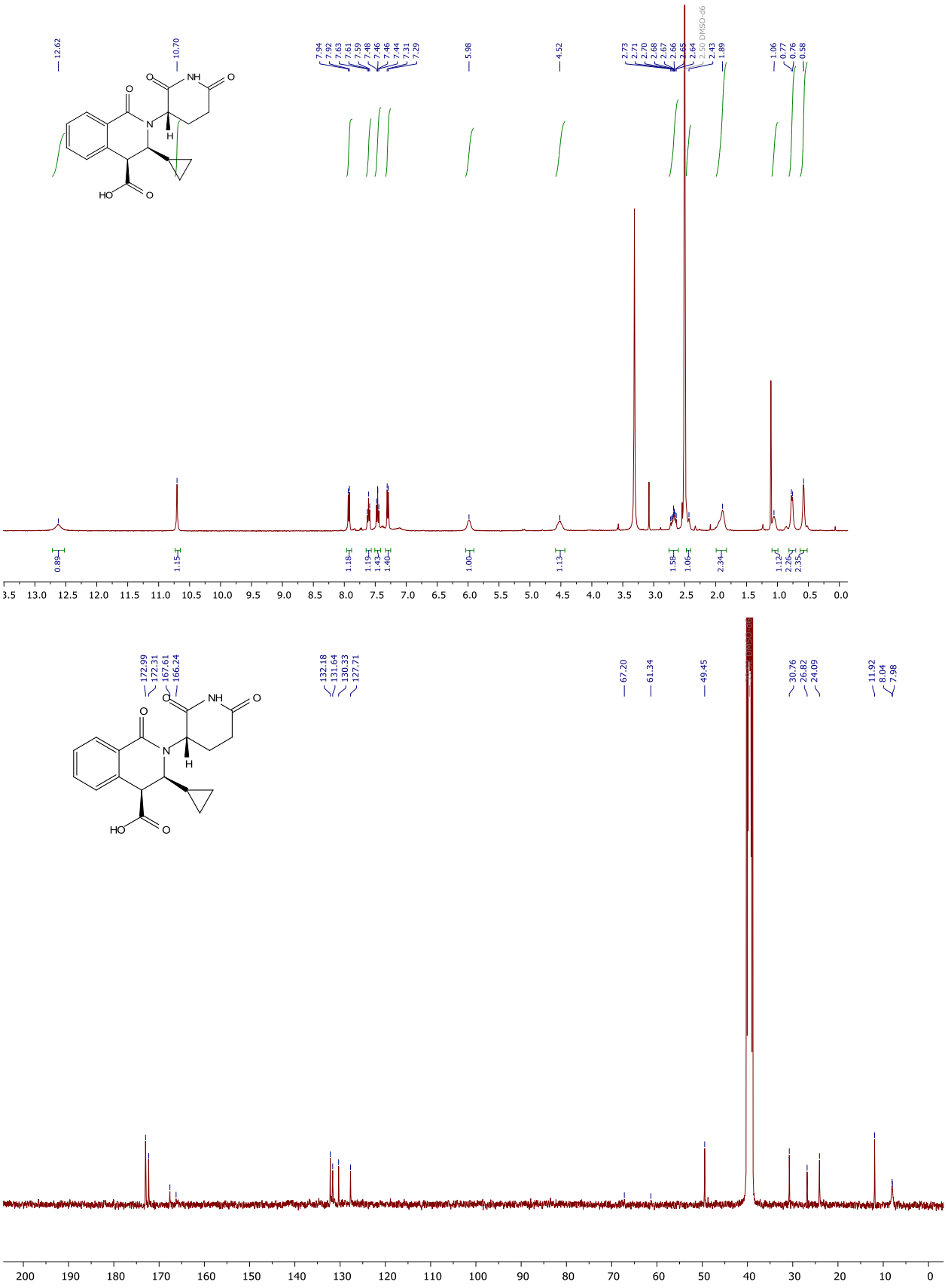
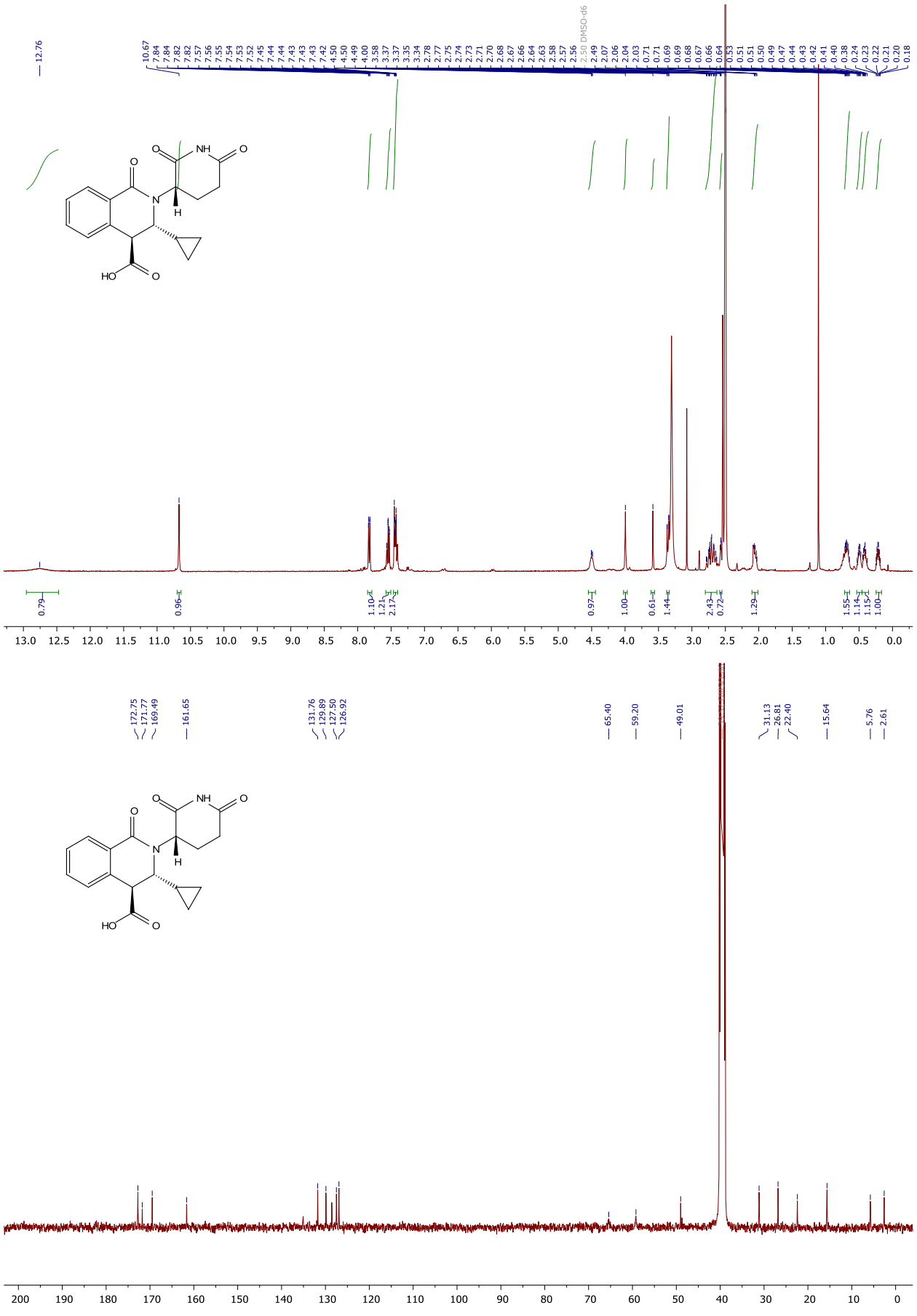


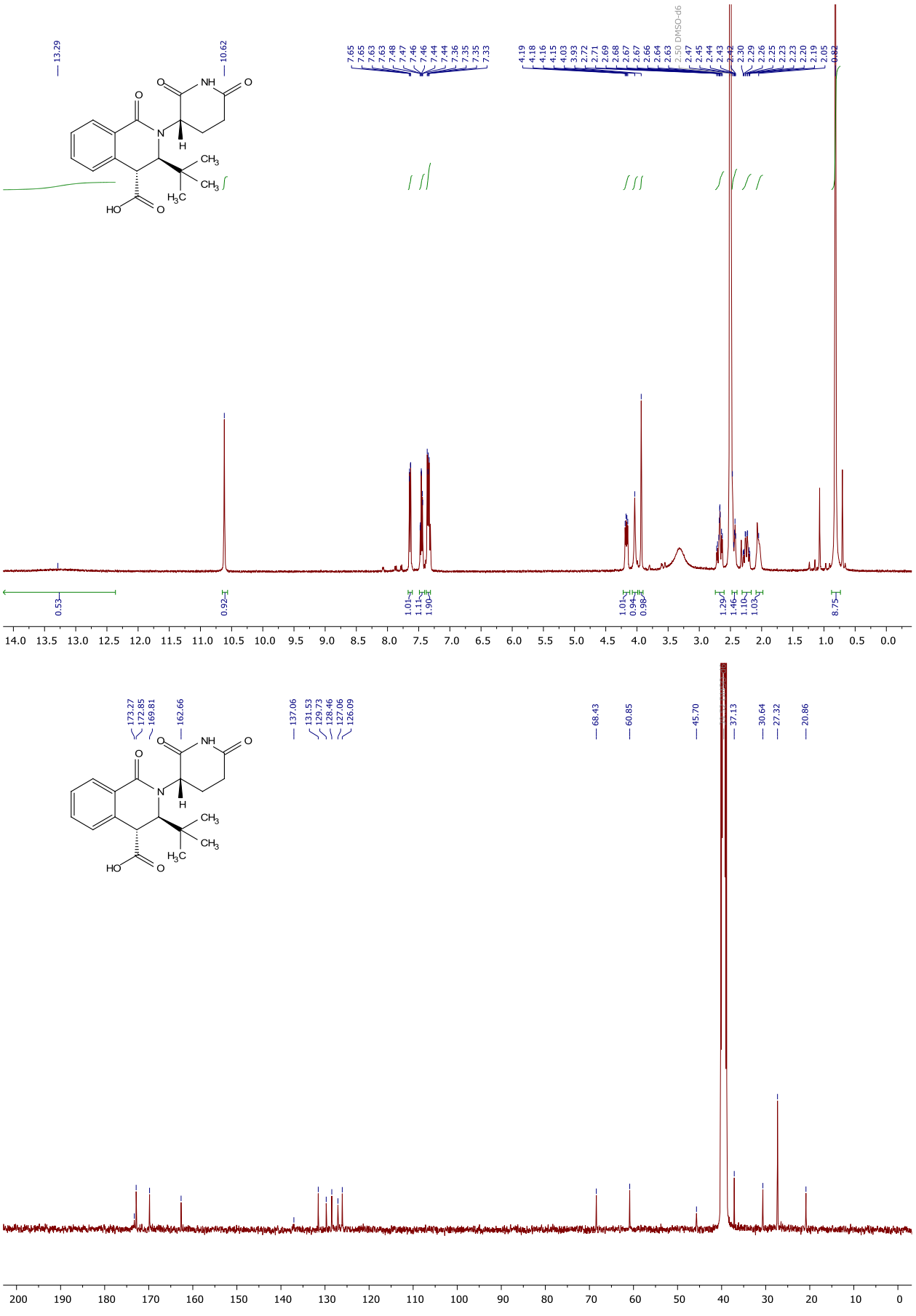
^{1}H and ^{13}C NMR spectra of compound *cis*-***4d***



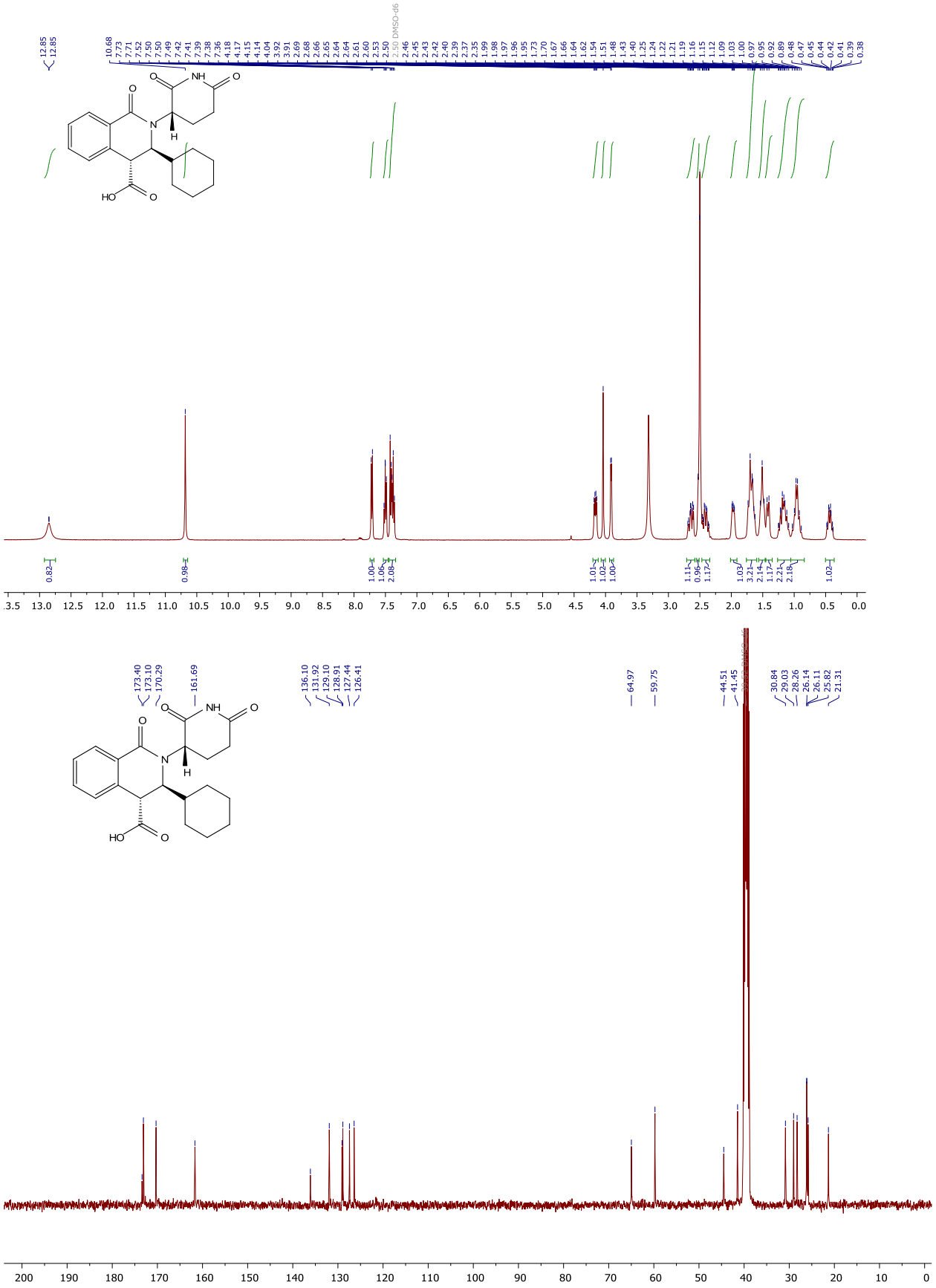
^{1}H and ^{13}C NMR spectra of compound *trans-**4e***



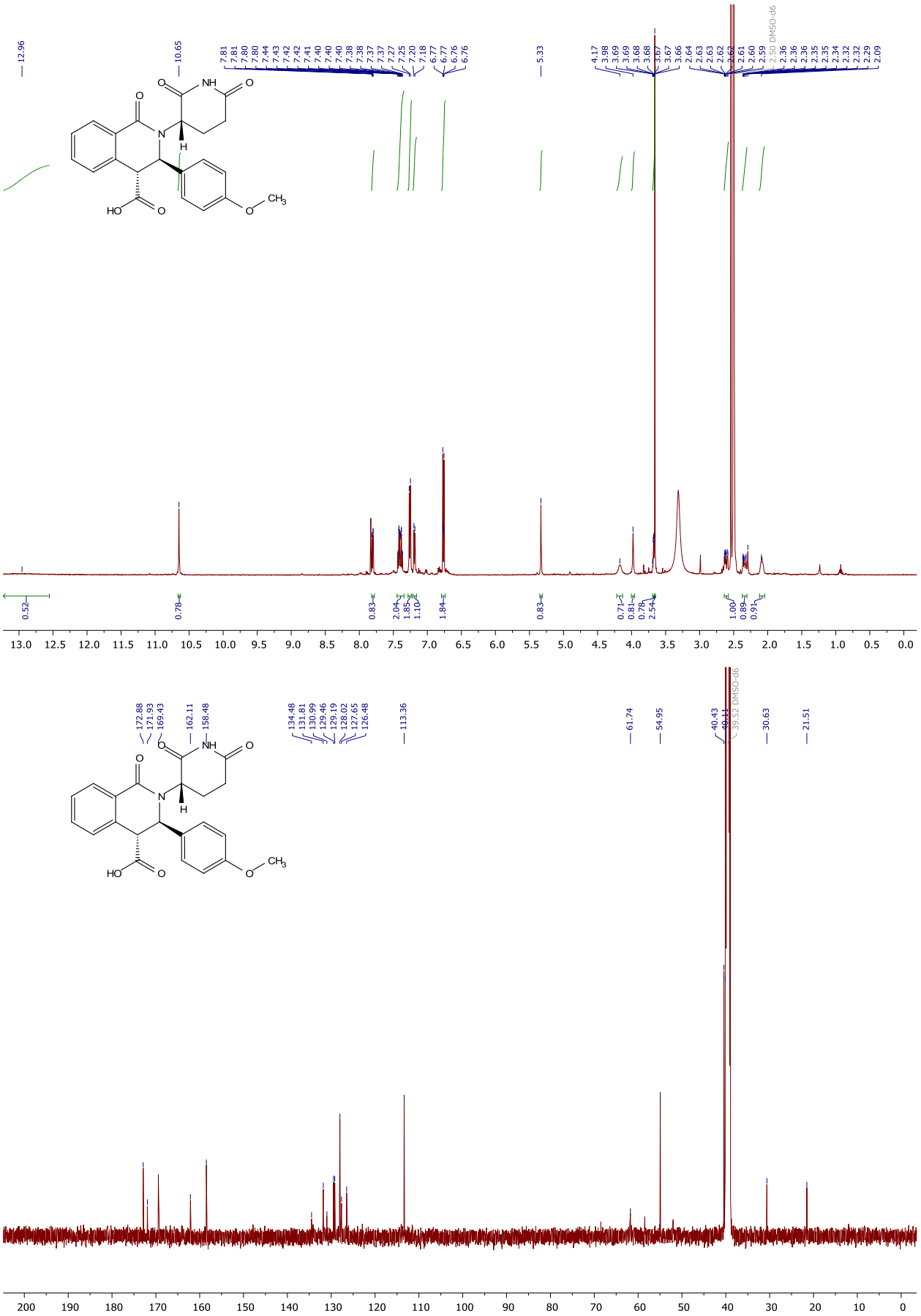
^{1}H and ^{13}C NMR spectra of compound *trans*-***4e***



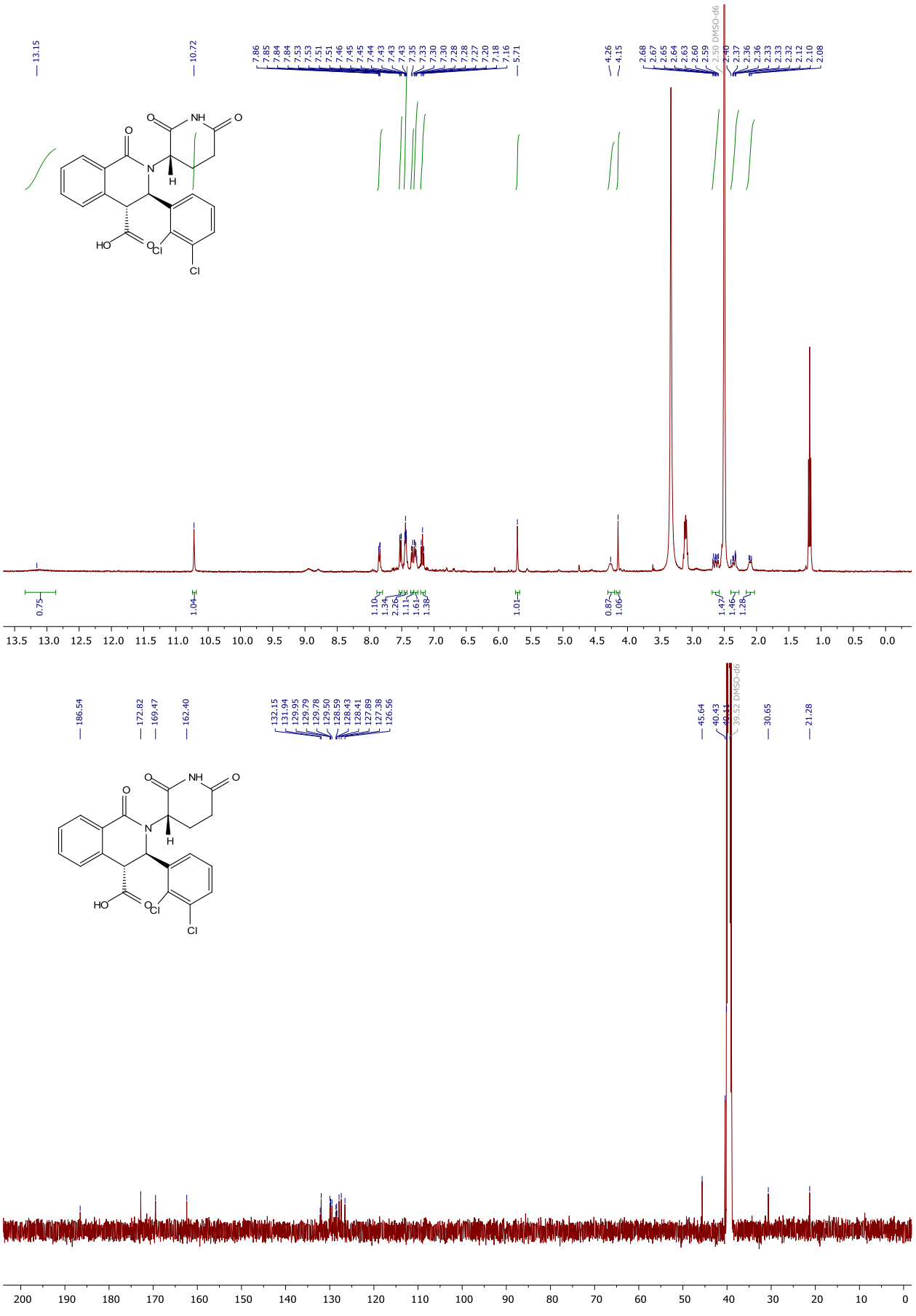
^{1}H and ^{13}C NMR spectra of compound *trans-**4f***



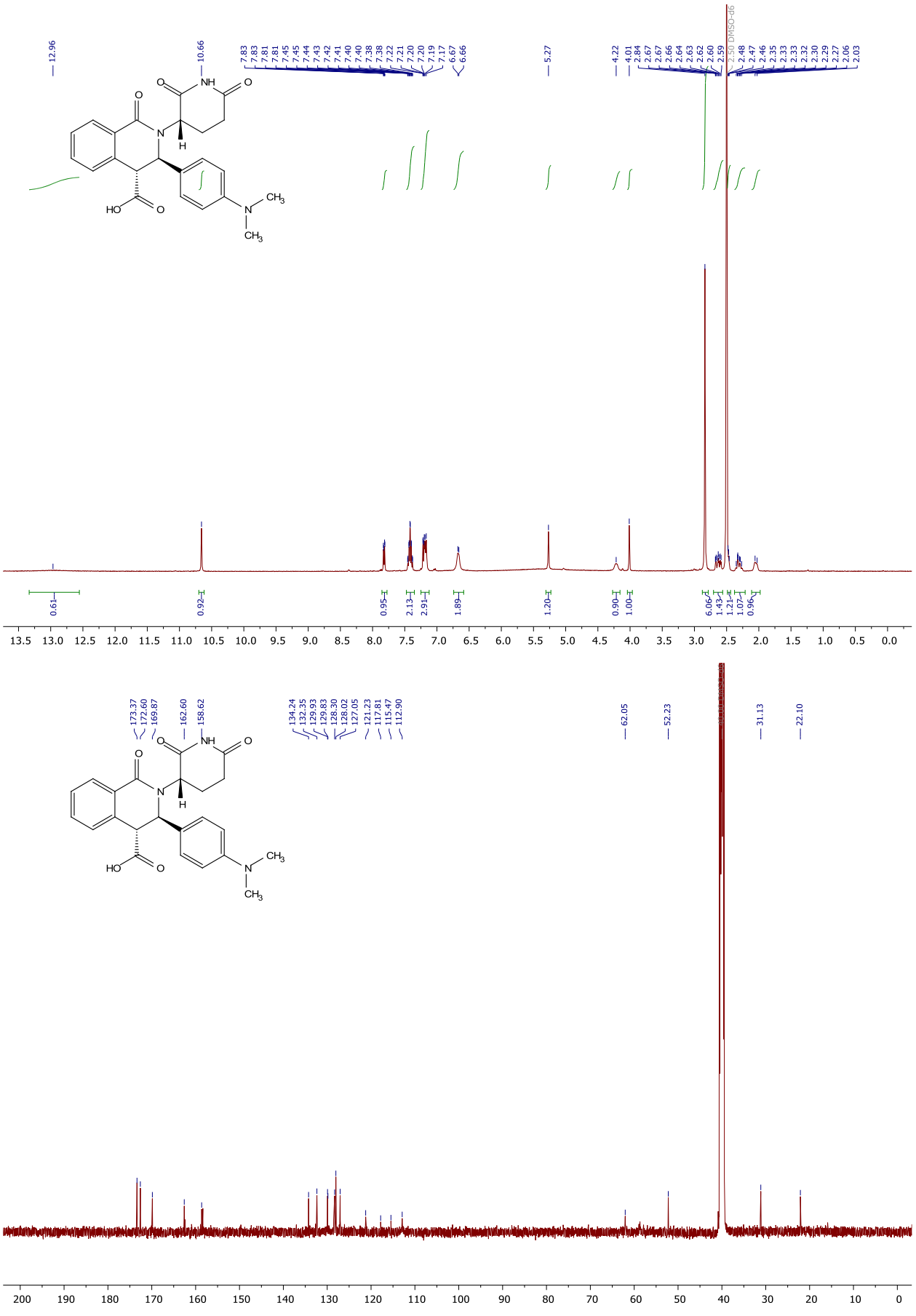
^{1}H and ^{13}C NMR spectra of compound *trans-**4a***



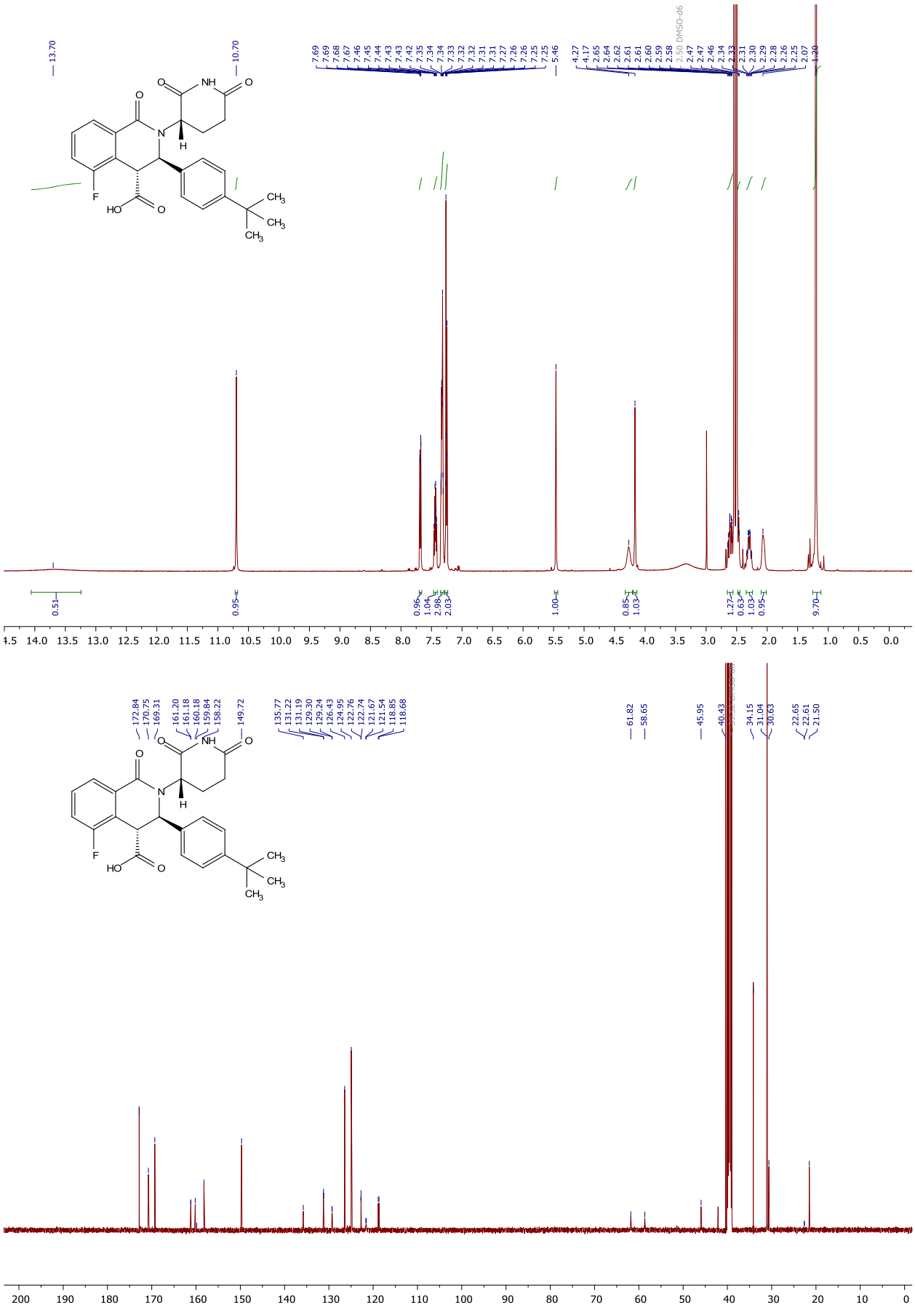
^{1}H and ^{13}C NMR spectra of compound *trans-**4g***



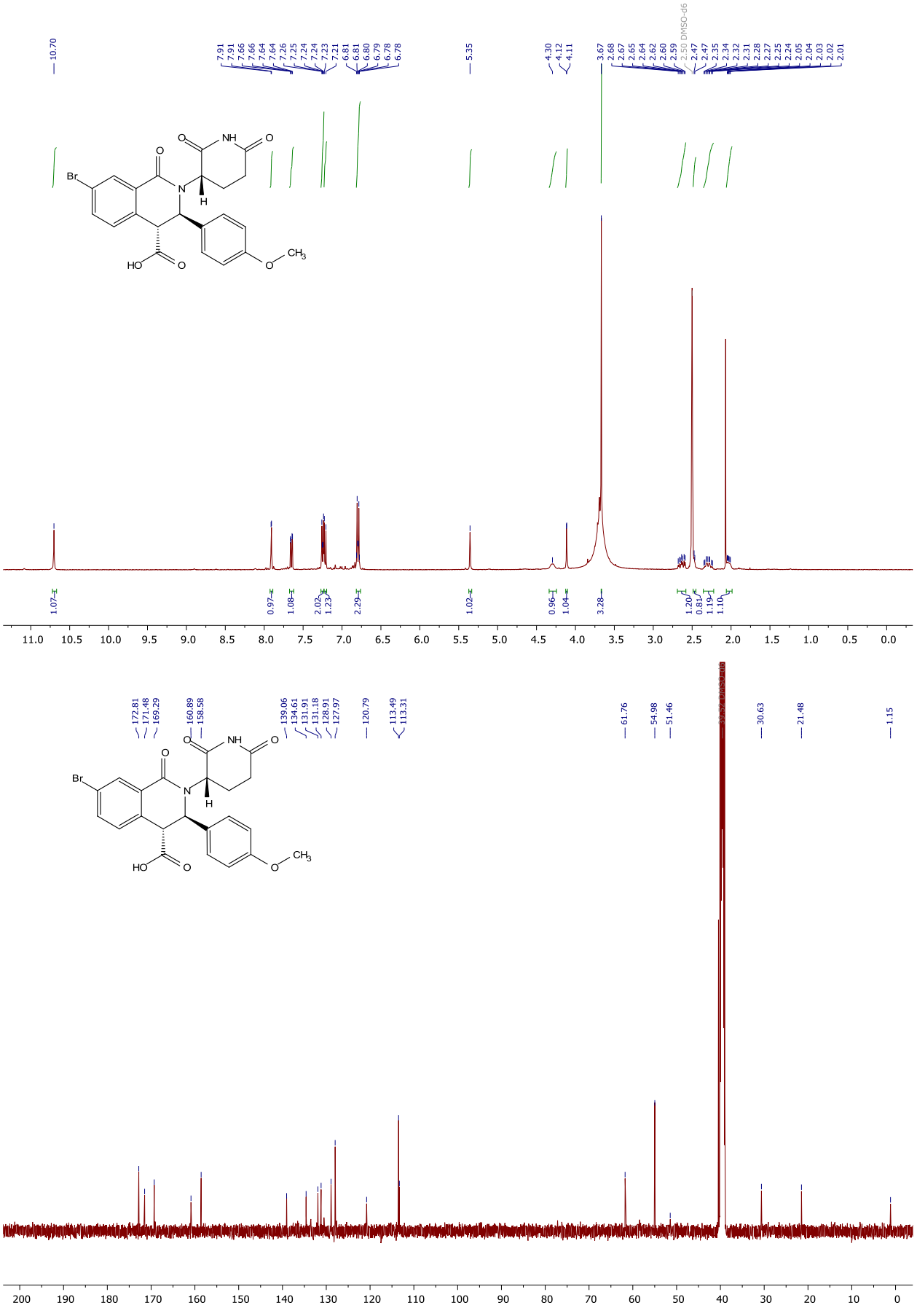
^{1}H and ^{13}C NMR spectra of compound *trans-**4h***



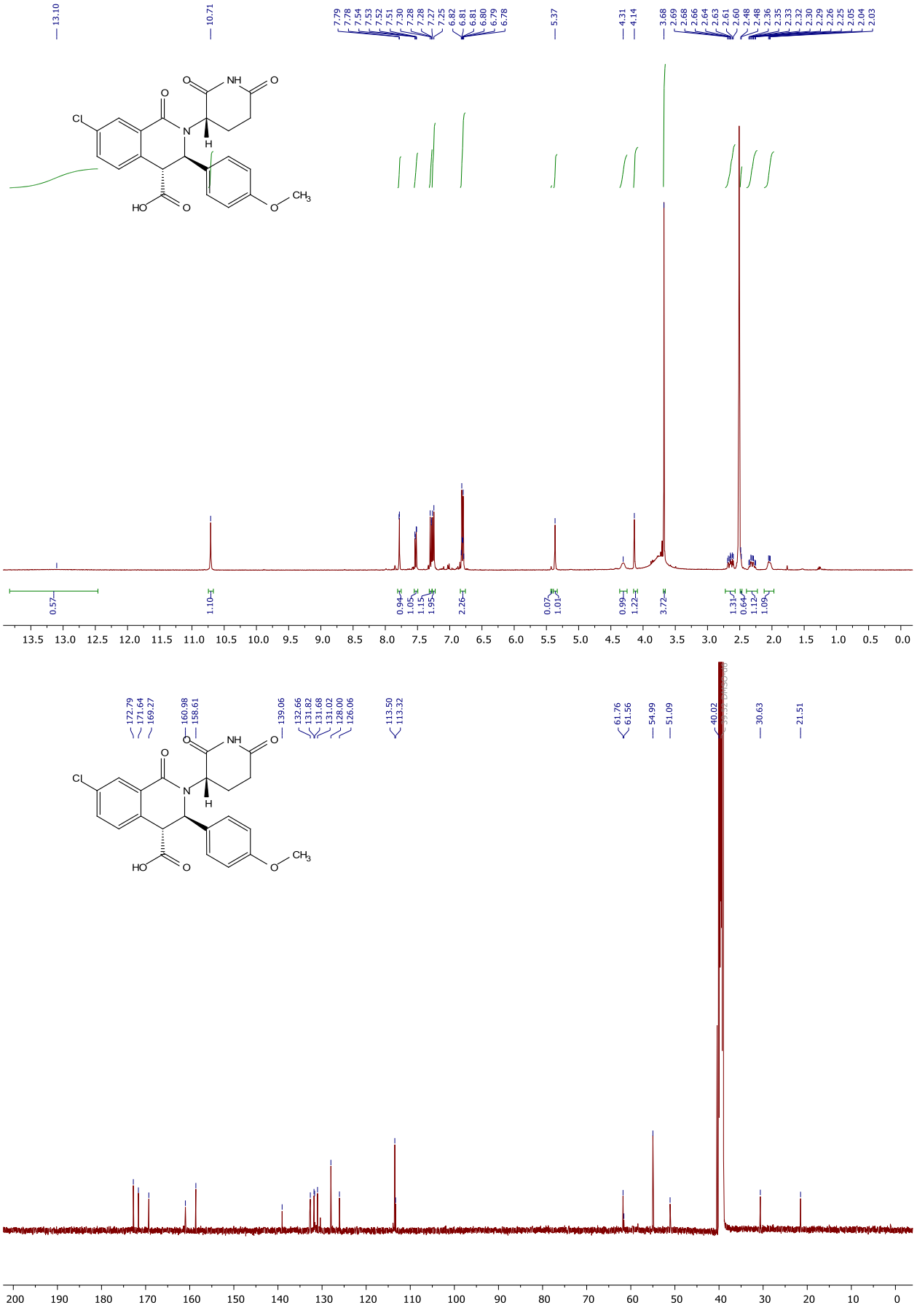
^{1}H and ^{13}C NMR spectra of compound *trans*-***4j***



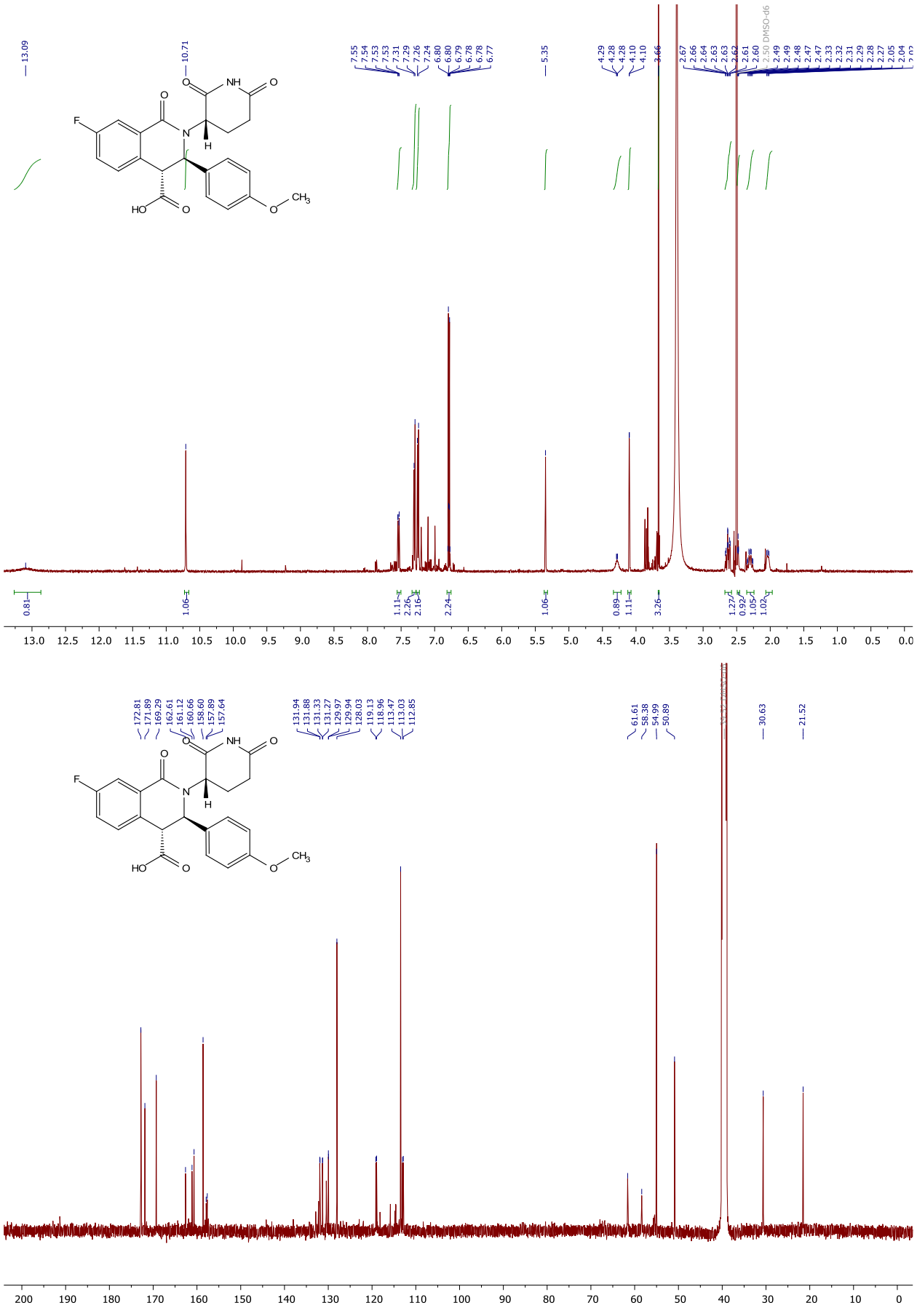
^{1}H and ^{13}C NMR spectra of compound *trans-**4k***



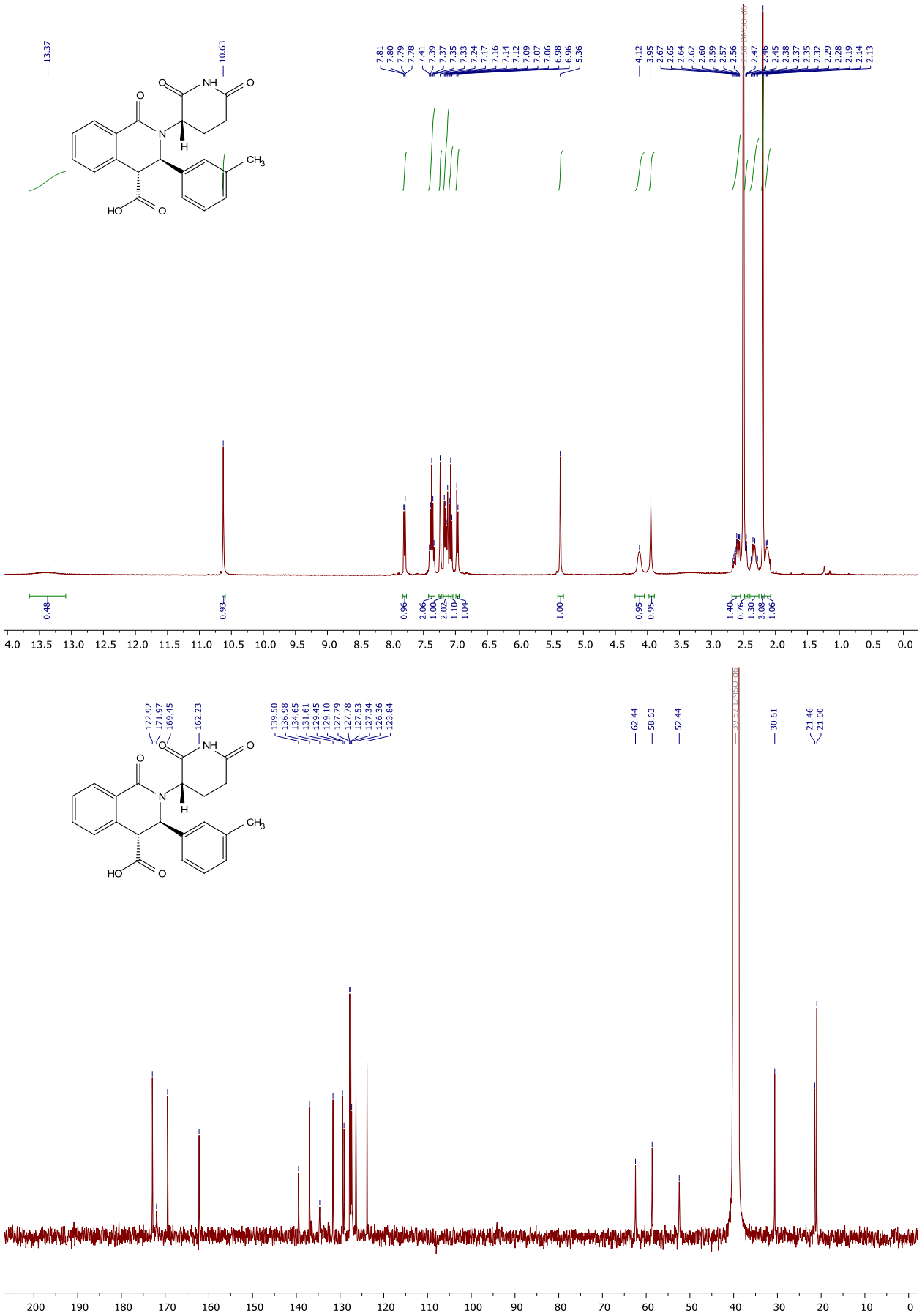
^{1}H and ^{13}C NMR spectra of compound *trans-**4l***



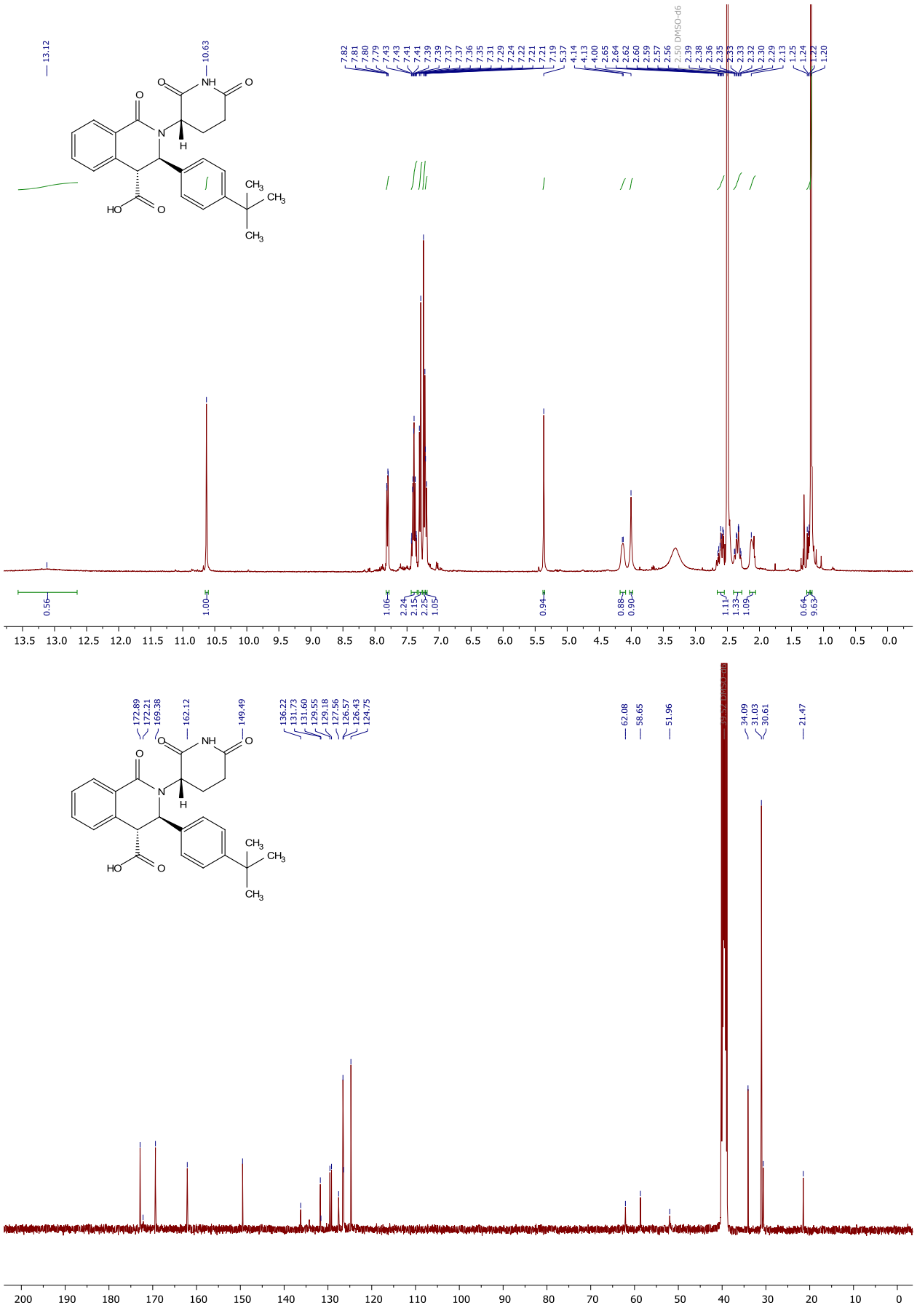
^{1}H and ^{13}C NMR spectra of compound *trans-**4m***



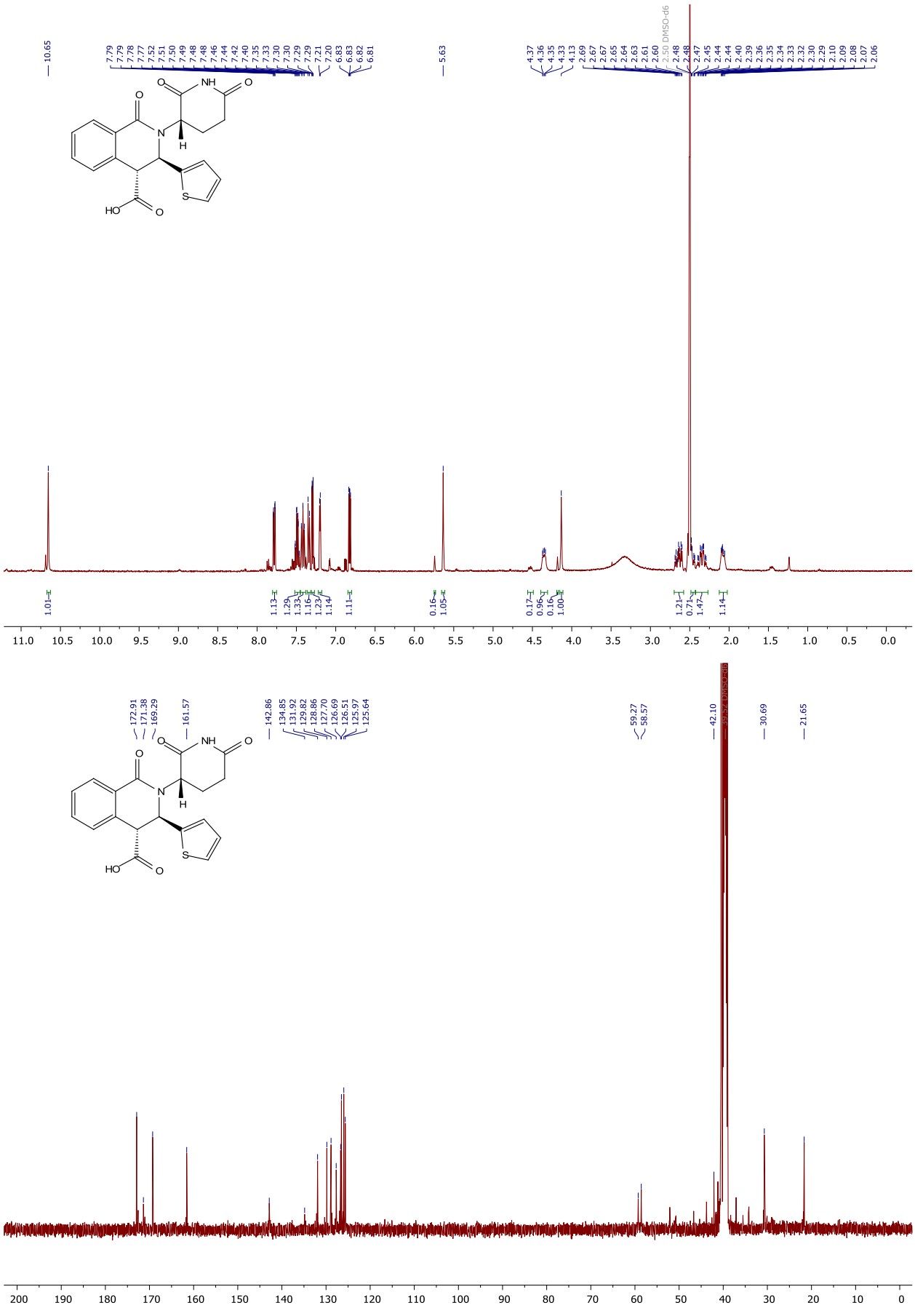
^{1}H and ^{13}C NMR spectra of compound *trans-**4b***



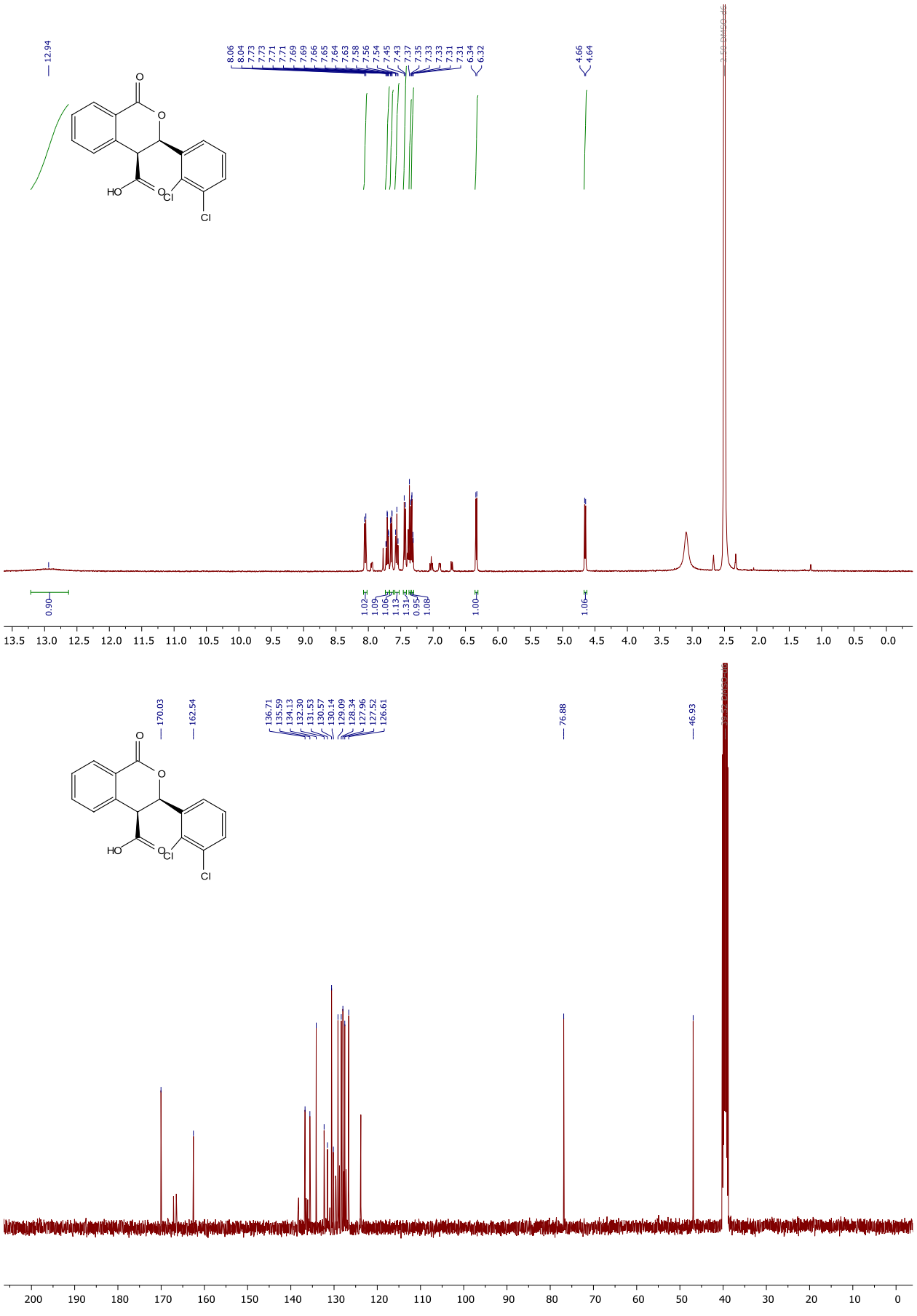
^{1}H and ^{13}C NMR spectra of compound *trans-**4c***



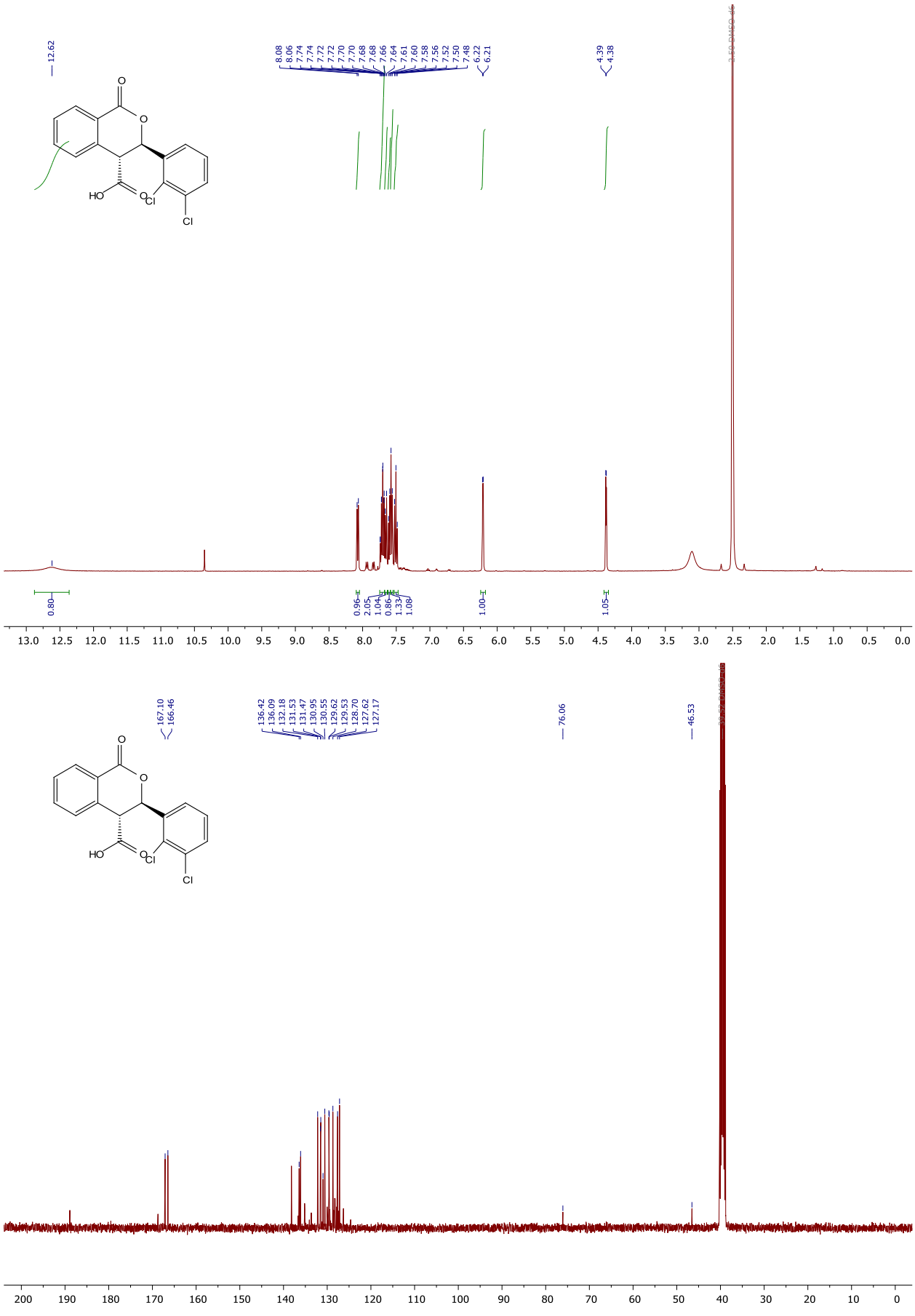
^{1}H and ^{13}C NMR spectra of compound *trans-**4i***



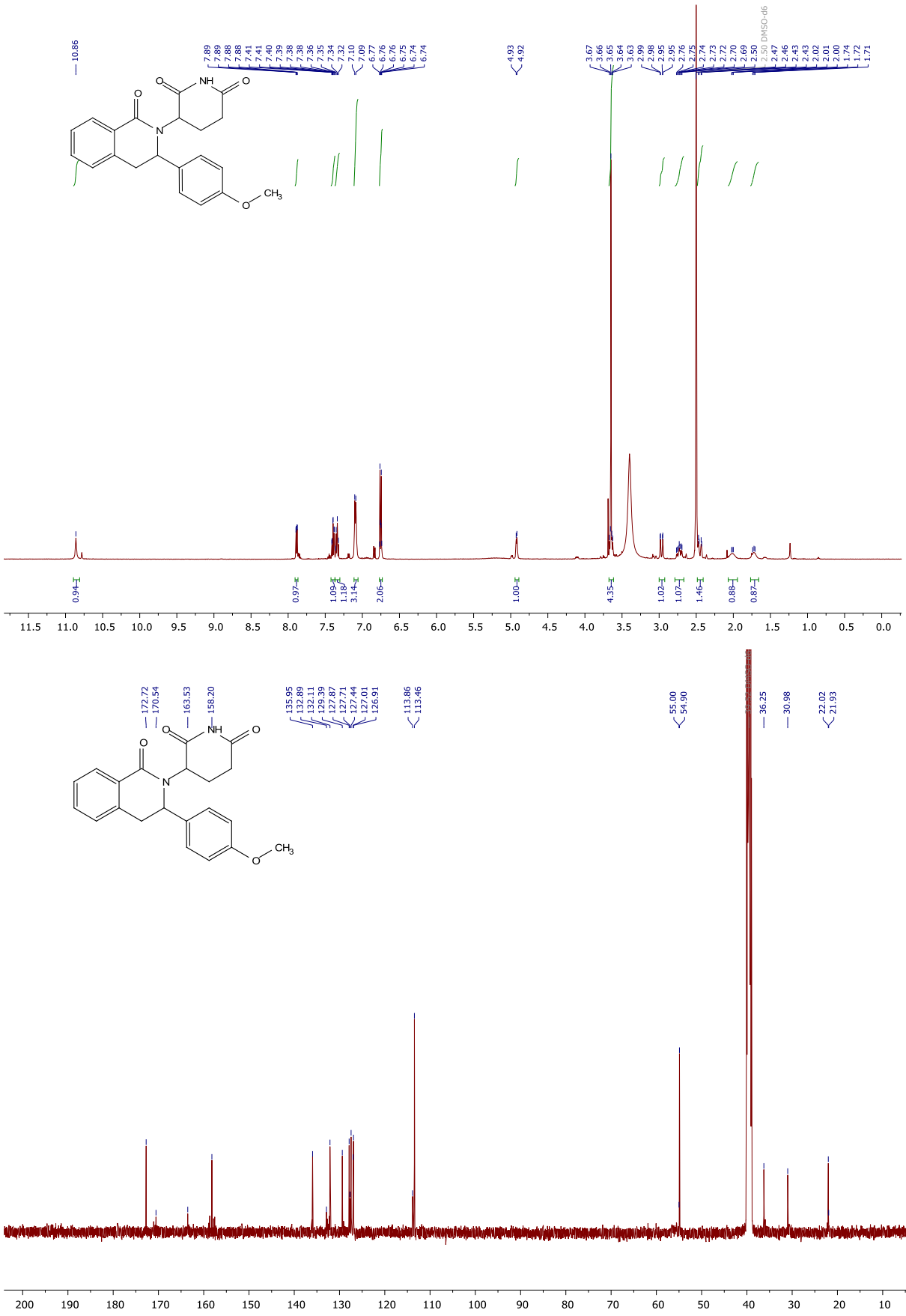
^{1}H and ^{13}C NMR spectra of compound *cis*-***5***



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



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