Supporting Information

Synthesis and evaluation of tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-ones as new tubulin polymerization inhibitors

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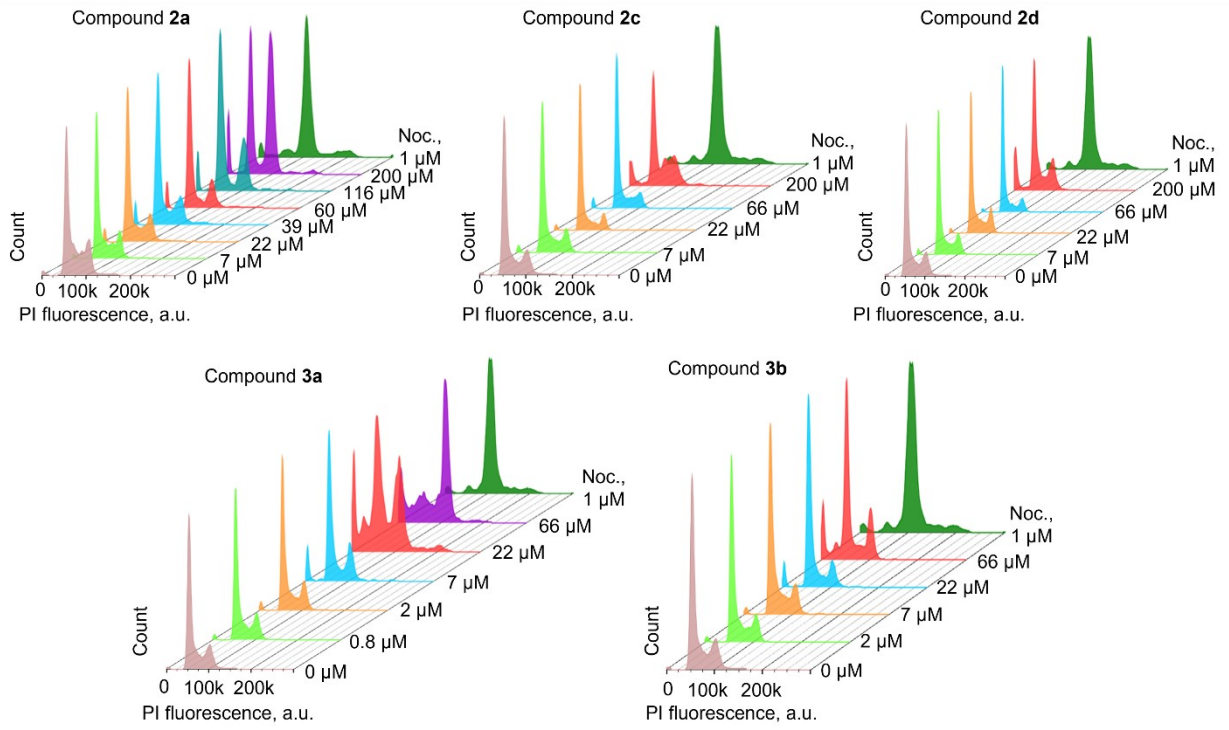


Figure S1. Representative DNA content histograms for A549 cells untreated (control) and treated with compounds 2 and 3 in a wide range of concentrations for 24 h. Nocodazole (Noc.) added at 1 μM concentration was used as a positive control. Each displayed histogram is based on one representative experiment. Experiments were repeated 2-4 times for each condition.

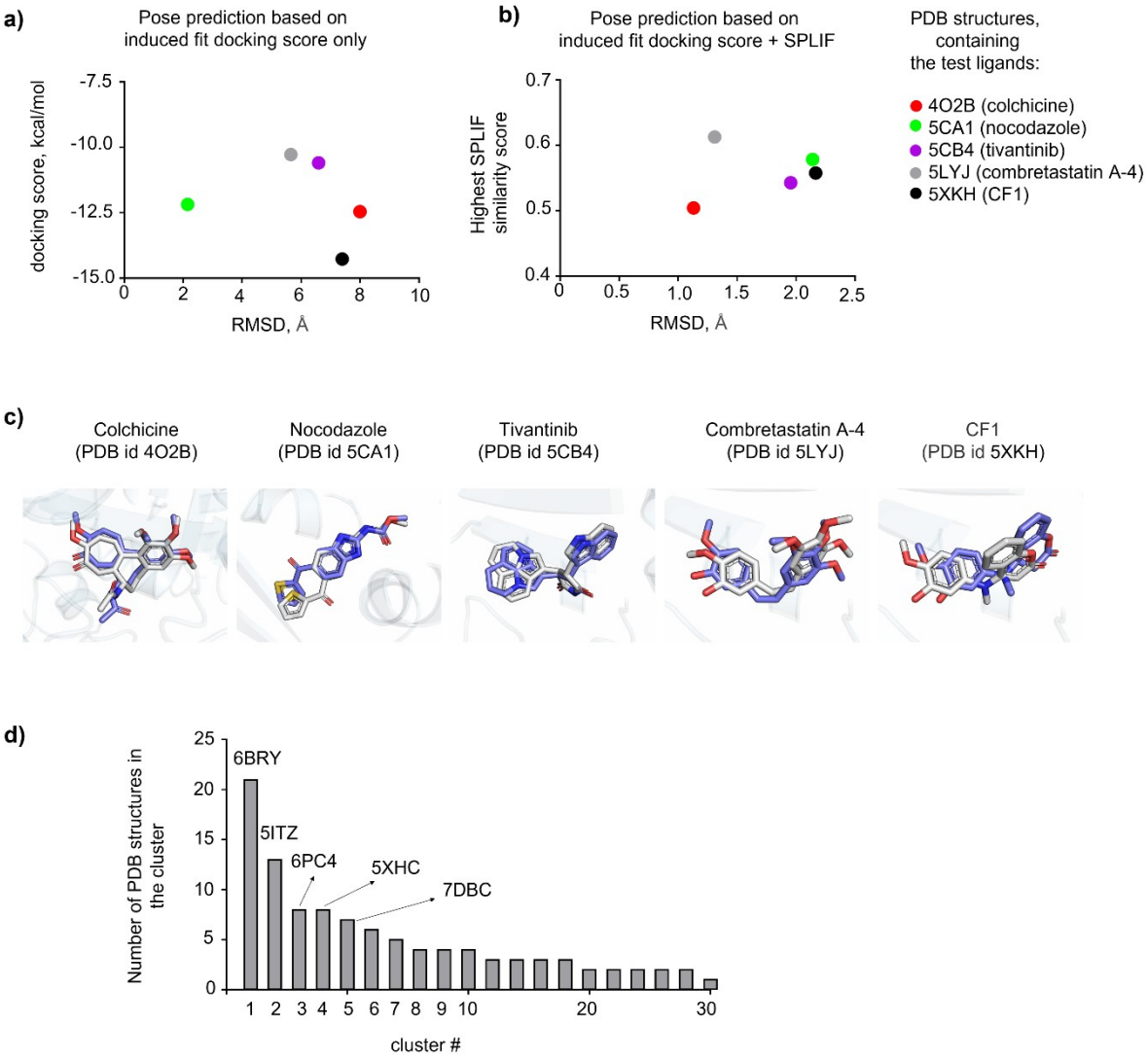


Figure S2. Prediction of tubulin-ligand interactions based on a combination of induced fit docking and SPLIF analysis. a) Testing the accuracy of the ligand pose prediction based on the induced fit docking score only. Each dot represents one best pose based on docking score for the five randomly selected test ligands docked into five receptors and its accuracy (root mean square deviation (RMSD) relative to the experimentally determined structure from the PDB). The accuracy in this case is rather poor, and it exhibits no correlation with the docking score. b) Testing the accuracy of the ligand pose prediction using the induced fit docking approach enhanced with SPLIF analysis. With this approach, the accuracy of the ligand pose prediction is significantly improved (RMSD for the 5 test ligands is within 1.0 and 2.5 Å). c) Overlay of experimentally determined (white) and predicted (blue) ligand poses in the colchicine site of tubulin, corresponding to panel b. d) Distribution of the PDB structure cluster sizes (for the clusterization algorithm threshold = 0.6). PDB IDs of centroid tubulin structures for 5 most populated clusters are shown above the bars.

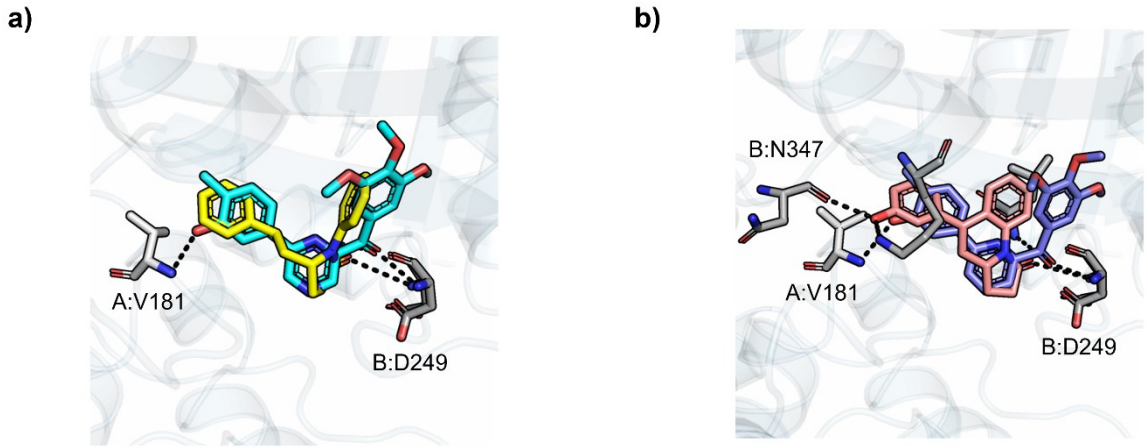


Figure S3. Comparison of the predicted poses of compounds 2a and 3c with experimental structures with similar hydrogen bond positions. a) [6-(3-hydroxy-4-methylphenyl)pyrazin-2-yl](3,4,5-trimethoxyphenyl)methanone from the PDB structure 6XES[S1] is shown in cyan together with compound **2a** (yellow) in the colchicine site of tubulin. Note the positions of the hydrogen bonds. b) [6-(3-hydroxy-4-methylphenyl)pyridin-2-yl](3,4,5-trimethoxyphenyl)methanone from the PDB structure 6AGK[S2] is shown in purple together with compound **3c** (orange). Note the similarity of the hydrogen bond positions.

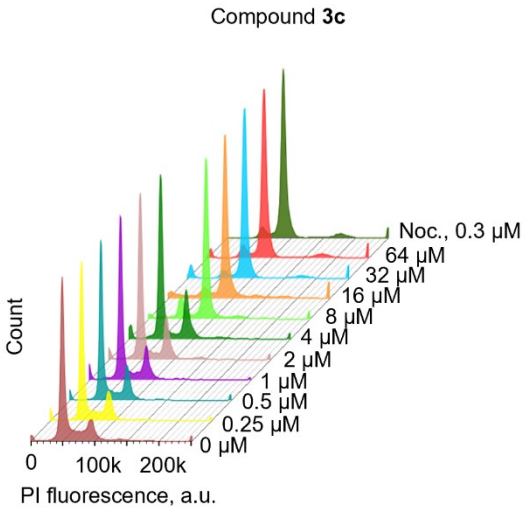


Figure S4. Representative DNA content histograms for A549 cells treated with compound 3c at various concentrations for 24 hours. Nocodazole (Noc.) at 0.3 μM was used as a positive control. An example from one biological experiment is shown.

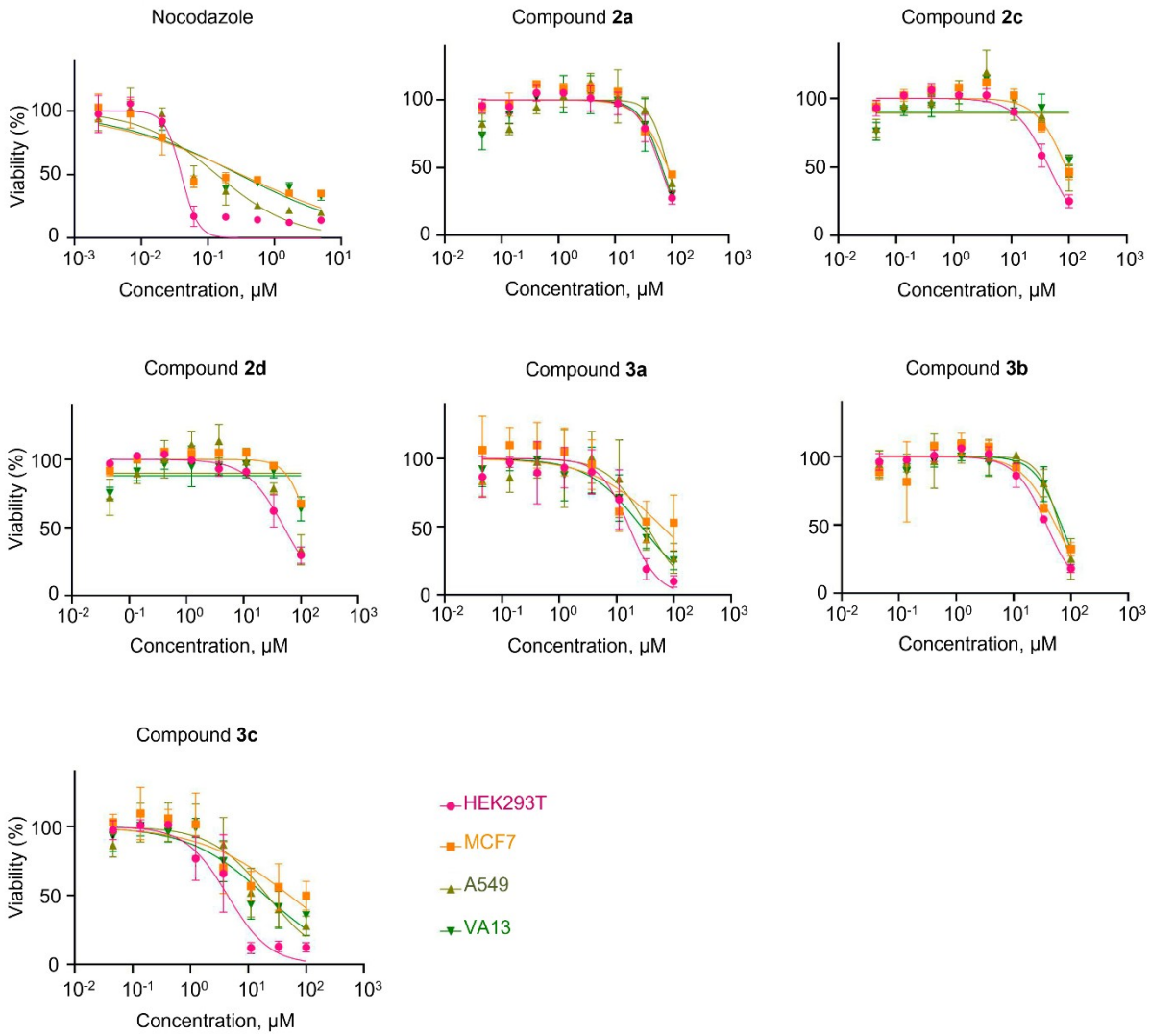


Figure S5. Evaluation of the cytotoxicity of compounds 2 and 3 using the MTT assay for cell proliferation. Mean values and s.d. are shown based on two independent repeats with 3 technical replicates. Solid lines represent fits using cooperative dose-response equations: $Y = 100/(1 + \left(\frac{X}{IC50}\right)^{HillSlope})$. Compounds **2c** and **2d** did not display a noticeable activity with A549 and VA13 cell lines, so the fits appear as straight lines. IC_{50} values are reported in Table S1.

Table S1. IC_{50} values (μM) for compounds 2 and 3 based on the MTT assay for cell proliferation

Compound	Cell line			
	HEK293T	MCF7	A549	VA13
2d	51 ± 4	>100	61 ± 5	>100
2e	56 ± 6	>100	>100	>100
2a	63 ± 5	85 ± 9	85 ± 3	67 ± 3
2c	45 ± 3	89 ± 3	>100	>100
3a	18 ± 2	37 ± 4	35 ± 6	27 ± 3
3b	28 ± 4	54 ± 6	71 ± 6	68 ± 4
3c	4.1 ± 0.5	51 ± 1	21 ± 3	20 ± 3
Nocodazole	0.040 ± 0.005	0.32 ± 0.01	0.136±0.003	0.29 ± 0.01

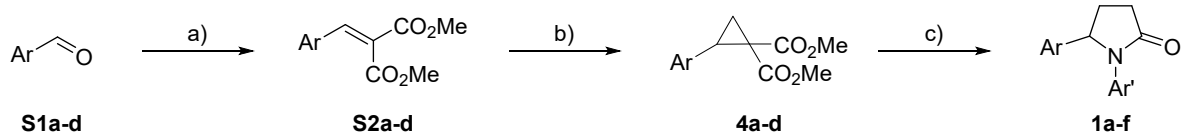
Chemistry

General Methods

All solvents and chemicals were of reagent grade. Unless otherwise stated, they were purchased from commercial vendors and used as received. Flash column chromatography was performed on silica gel 60 Macherey-Nagel (230-400 mesh) or aluminum oxide 90 Macherey-Nagel (standardized). Analytical thin-layer chromatography (TLC) was carried out using pre-coated aluminum sheets of silica gel 60 (F254). The visualization of the TLC plates was done by a UV lamp (254 nm). Solvents used include petroleum ether (PE), ethyl acetate (EA), dichloromethane, and methanol. NMR spectra were recorded on Bruker AM-400 (400 MHz for ^{1}H and 101 MHz for ^{13}C), and Bruker Avance 600 (600 MHz for ^{1}H and 151 MHz for ^{13}C) spectrometers at room temperature if not specified other; the chemical shifts δ were measured in ppm with respect to solvent ($CDCl_3$: ^{1}H: δ = 7.27 ppm, ^{13}C: δ = 77.16 ppm; DMSO-d_6: ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.5 ppm; CD_3OD: ^{1} H: δ = 3.31 ppm, ^{13}C: δ = 49.0 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets and br. (broad). Coupling constants (*J*) are given in Hz. The structures of synthesized compounds were elucidated with the aid of 1D (^{1}H, ^{13}C) and 2D NMR (HSQC and HMBC ^{1}H-^{13}C, NOESY ^{1}H-^{1}H) spectroscopies. IR spectra were recorded on Thermo Nicolet IR 200 FT-IR spectrometer. Registration of spectra was carried out at a resolution of 4 cm^{-1}, the number of scans 20. Samples were placed on the working surface of the internal reflection (ATR) element from ZnSe with the angle of incidence of 45°. High resolution and accurate mass measurements were carried out using a BrukermicrOTOF-QTM ESI-TOF (Electro Spray Ionization/Time of Flight). Elemental analyses were performed with Fisons EA-1108 CHNS elemental analyzer instrument. Melting points (mp) were determined using an Electrothermal 9100 capillary melting point apparatus. Cyclopropanes **4** were prepared by Knoevenagel/Corey-Chaykovsky reactions sequence from the corresponding aldehydes.[S3] (*E*)-3-(3-hydroxyphenyl)acrylaldehyde and compounds **1c**, **2a**, **3a** were synthesized according to a described procedures.[S4-S6] The purity of all compounds for biological testing is >95% assessed by elemental analysis or by relative quantitative (q) HNMR spectroscopy.[S7]

Schemes depicting synthetic routes

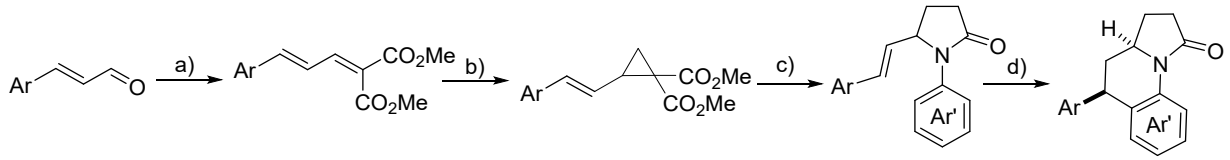
Scheme S1. Synthesis of compounds **1**.



S1a-d **S2a-d** **4a-d** **1a-f**

Reagents and conditions: a) dimethyl malonate, AcOH, piperidine, benzene, reflux (for **S2a-c**) or $TiCl_4$, CCl_4, dimethyl malonate, pyridine, THF, 0 °C to r.t. (for **S2d**); b) trimethylsulfoxonium iodide, NaH (60% suspension in mineral oil), dry DMF, r.t.; c) 1) Ar'NH_2, $Ni(ClO_4)_2 \cdot 6H_2O$, DCE, r.t.; 2) AcOH, toluene, reflux; 3) NaOH, EtOH/H_2O, r.t.; 4) toluene, reflux.

Scheme S2. Synthesis of compounds **2** and **3**.

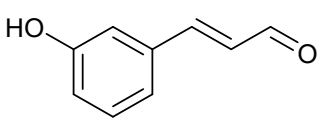


S1e-g **S2e-g** **4e-g** **2a-e** **3a-c**

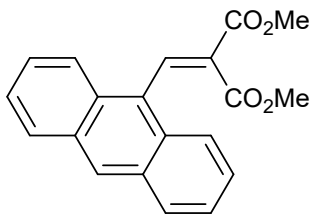
Reagents and conditions: a) dimethyl malonate, AcOH, piperidine, benzene, reflux; b) trimethylsulfoxonium iodide, NaH (60% suspension in mineral oil), dry DMF, r.t.; c) 1) Ar'NH_2, $Ni(ClO_4)_2 \cdot 6H_2O$, DCE, r.t.; 2) AcOH, toluene, reflux; 3) NaOH, EtOH/H_2O, r.t.; 4) toluene, reflux (for **2a-d**) or 1) Ar'NH_2, $Y(OTf)_3$, DCE, r.t.; 2) AcOH, 1,4-dioxane, reflux; 3) NaOH, EtOH/H_2O, r.t.; 4) PhCl/dioxane (1:1), reflux (for **2e**); d) PPA, 100 °C (for **3a,b**) or MsOH/DCM (1:3), 40 °C (for **3c**).

Synthesis of key intermediates

(*E*)-3-(3-Hydroxyphenyl)acrylaldehyde (S1g). To a solution of 3-hydroxybenzaldehyde (5.93 g, 48.60 mmol), 20% (w/v) aqueous NaOH (81 mL, 1.66 mL/mmol) and ethanol (112 mL, 2.33 mL/mmol) acetaldehyde (12.1 mL, 0.25 mL/mmol) was added dropwise at –2 °C. The solution was allowed to stir at 0–4 °C for 75 minutes, during which time the progress of the reaction was monitored by TLC. The reaction mixture was poured into ice-cooled 10% HCl (200 mL) and extracted with ethyl acetate (4×100 mL). Combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography using EA/PE (1:3) to afford compound **S1** (2.20 g, 31%; 84% purity) as an orange solid; mp 108–109 °C (lit.,[S4] 115–117 °C); R_f = 0.51 (EA/PE 1:2). The spectral data were in accordance with the literature ones.[S4]



Dimethyl 2-(anthracen-9-ylmethylene)malonate (S2d). Anhydrous THF (23 mL) was added dropwise to a solution of $TiCl_4$ (1.1 mL, 10.0 mmol) in CCl_4 (2.4 mL) at 0 °C under Ar atmosphere. Anthracene-9-carbaldehyde (1.00 g, 4.85 mmol) and dimethyl malonate (555 μL, 4.85 mmol) were added to the resulting mixture. Then, a solution of pyridine (1.6 mL, 19.9 mmol) in anhydrous THF (1.3 mL) was added dropwise using a syringe, and the resulting mixture was stirred at 0 °C for 1 h. The obtained mixture was stirred at room temperature overnight and quenched with brine (40 mL). THF was evaporated under reduced pressure. The resulting mixture was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallization from PE afforded the product **S2d** (1.40 g, 90%) as an orange solid; mp 129–130 °C; R_f = 0.58 (EA/PE 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.45 (s, 1H), 8.04–7.98 (m, 4H), 7.54–7.45 (m, 4H), 3.99 (s, 3H), 3.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 164.1, 144.0 (2C), 132.1, 130.9, 128.7 (2C), 128.6 (2C), 128.3, 127.5, 126.2 (2C), 125.4 (2C), 125.1 (2C), 52.8, 52.0. HRMS (ESI-TOF): m/z calcd for $[M + Na]^+$ $C_{20}H_{16}NaO_4$ 343.0941; found 343.0945.



Dimethyl (*E*)-2-[3-(3-hydroxyphenyl)allylidene]malonate (S2g). To a suspension of aldehyde **S1g** (1.73 g, 11.7 mmol) and dimethyl malonate (1.34 mL, 11.7 mmol) in benzene (5.9 mL, 2 M) glacial acetic acid (134 μL, 2.34 mmol) and piperidine (58 μL, 0.59 mmol) were added. The mixture was refluxed with the Dean-Stark trap for 2.5 h. Upon cooling, benzene was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel using EA/PE (from 1:5 to 2:3) to afford alkene **S2g** (1.28 g, 42%) as a yellow solid; mp 109–111 °C; R_f = 0.47 (EA/PE 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (dd, ^3J = 11.6 Hz, ^4J = 0.7 Hz, 1H), 7.17 (dd, ^3J = 15.4 Hz, ^3J = 11.6 Hz, 1H), 7.14 (d, ^3J = 8.1 Hz, 1H), 6.98–6.93 (m, 3H), 6.80 (ddd, ^3J = 8.1 Hz, ^4J = 2.4 Hz, ^4J = 1.0 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H). Signal of OH-moiety is not observed. ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.1, 165.5, 157.1, 146.9, 145.8, 136.8, 130.0, 123.3, 123.1, 120.1, 117.5, 114.0, 52.5, 52.4. IR (KBr): 3362, 1715, 1681, 1614, 1592, 1446, 1425, 1348, 1295, 1214, 1177, 1154, 1066, 982, 953, 934, 880, 847 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + Na]^+$ $C_{14}H_{14}NaO_5$ 285.0733; found 285.0733.

Dimethyl 2-(anthracen-9-yl)cyclopropane-1,1-dicarboxylate (4d). To a suspension of NaH (60% suspension in mineral oil, 142 mg, 3.55 mmol) in dry DMF (3.1 mL) trimethylsulfoxonium iodide (649 mg, 2.95 mmol) was added in one portion under argon atmosphere. The resulting mixture was stirred at room temperature for 55 min and immersed in an ice-water bath. A solution of alkene **S2d** (823 mg, 2.57 mmol) in dry DMF (3.1 mL) was added dropwise *via* a syringe. The resulting mixture was stirred at room temperature for 2 h, quenched with ice and satd. aq. NH_4Cl solution (25 mL) and extracted with EA (3×10 mL). The combined organic phases were washed with brine (7×15 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using EA/PE (from 1:10 to 1:4) mixture to give the desired product **4d** (618 mg, 72%) as a viscous orange oil; R_f = 0.44 (EA/PE 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53–8.44 (m, 2H), 8.38 (s, 1H), 8.02–7.95 (m, 2H), 7.53–7.50 (m, 2H), 7.48–7.44 (m, 2H), 3.97 (s, 3H), 3.89 (dd, ^3J = 9.4 Hz, ^3J = 8.6 Hz, 1H), 2.89 (s, 3H), 2.44 (dd, ^2J = 4.6 Hz, ^3J = 8.6 Hz, 1H), 2.36 (dd, ^2J = 4.6 Hz, ^3J = 9.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 167.6, 131.6, 131.1 (2C), 130.9, 129.3, 128.5, 127.4, 127.3, 125.5 (2C), 125.1, 125.0, 124.8, 124.7, 53.0, 51.7, 36.5, 28.4, 24.1. IR (KBr): 3496, 3026, 3005, 2953, 2921, 2851, 2755, 2389, 2294, 2192, 2103, 2209, 1959, 1914, 1732, 1665, 1603, 1550, 1522, 1496, 1437, 1384, 1346, 1268, 1181, 1147, 1077, 1020 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + Na]^+$ $C_{21}H_{18}NaO_4$ 357.1097; found 357.1094.

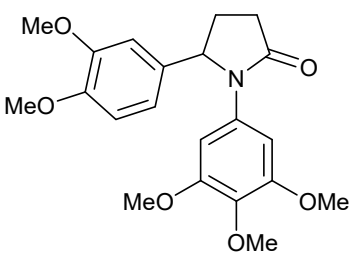
Dimethyl (*E*)-2-(3-hydroxystyryl)cyclopropane-1,1-dicarboxylate (4g). To a stirred suspension of NaH (386 mg, 9.65 mmol, 60% suspension in oil) in dry DMSO (15.7 mL) trimethylsulfoxonium iodide (2.12 g, 9.65 mmol) was added in a one portion under an argon atmosphere at room temperature. The vigorous evolution of hydrogen lasted ca. 10 min, after which the reaction mixture was stirred for an additional 30 min. Then alkene **S2g** (1.23 g, 4.71 mmol) was added in a single portion. The resulting mixture was stirred

for 10 min, poured into ice-cooled 10% AcOH (30 mL) and extracted with ethyl acetate (4×15 mL). The combined organic fractions were washed with brine (3×20 mL), dried with Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using EA/PE (from 1:5 to 1:2) mixture to provide styrylcyclopropane **4g** (986 mg, 76%) as a yellowish oil; R_f = 0.53 (EA/PE 1;2). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.14 (dd, ^3J = 8.1 Hz, ^3J = 7.6 Hz, 1H), 6.84 (br. d, ^3J = 7.6 Hz, 1H), 6.78 (dd, ^4J = 2.5 Hz, ^4J = 1.6 Hz, 1H), 6.71 (br. dd, ^3J = 8.1 Hz, ^4J = 2.5 Hz, 1H), 6.56 (d, ^3J = 15.7 Hz, 1H), 5.77 (dd, ^3J = 15.7 Hz, ^3J = 8.7 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.74 (ddd, ^3J = 8.9 Hz, ^3J = 8.7 Hz, ^3J = 7.6 Hz, 1H), 1.85 (dd, ^2J = 5.0 Hz, ^3J = 7.6 Hz, 1H), 1.70 (dd, ^2J = 5.0 Hz, ^3J = 8.9 Hz, 1H). Signal of OH-moiety is not observed. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 170.2, 168.3, 156.1, 138.4, 133.8, 129.9, 124.9, 118.9, 114.9, 112.9, 53.0, 52.9, 36.2, 31.9, 21.5. IR (KBr): 3434, 2953, 1707, 1608, 1581, 1489, 1436, 1286, 1209, 1156, 1127, 1013, 997, 962, 938, 901, 873, 781 cm^{-1}. HRMS (ESI/TOF): m/z calcd for [M + H]$^+$ $C_{15}H_{17}O_5$ 277.1076; found 277.1077.

Synthesis of target compounds

General procedure 1 for the synthesis of γ–pyrrolidones 1, 2. To 0.2 M solution of (substituted) aniline (1.0–1.2 equiv) in 1,2-dichloroethane (DCE) molecular sieves 4 Å, Lewis acid ($Ni(ClO_4)_2·6H_2O$ or $Y(OTf)_3$, 0.2 equiv) and cyclopropane (1.0 equiv) were sequentially added under Ar atmosphere. The reaction mixture was stirred at room temperature for 1–3 h, diluted with dichloromethane and filtered through a short pad of silica gel using EA as an eluent. The filtrate was concentrated *in vacuo*; the residue was dissolved in toluene, obtaining *ca*. 0.13 M solution. Acetic acid (2.0 equiv) was added to this solution, the reaction mixture was stirred under reflux for 7 h. Then, the solvent was removed *in vacuo* and residue was dissolved in ethanol, providing *ca*. 0.17 M solution. 1 M aq. solution of sodium hydroxide (2.0 equiv) was added in one portion. The reaction mixture was stirred at room temperature for 2 h. Ethanol was evaporated under reduced pressure. The residue was diluted with water, and 1 M HCl was added until pH 1. The resulting mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in toluene (0.07 M) and was refluxed for 7 h. The solvent was removed under reduced pressure; the crude residue was purified by column chromatography to give the desired compound **1**, **2**.

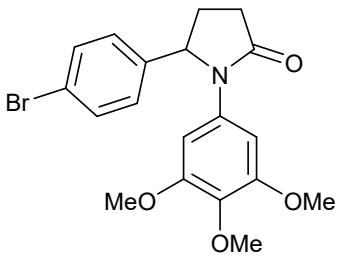
5-(3,4-Dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)pyrrolidin-2-one (1a) was



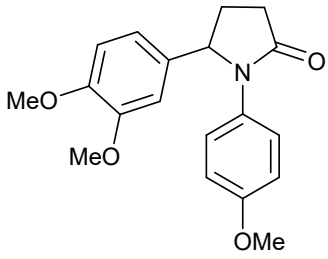
obtained from 3,4,5-trimethoxyaniline (623 mg, 3.4 mmol), dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (1.00 g, 3.4 mmol), $Ni(ClO_4)_2·6H_2O$ (249 mg, 0.68 mmol), DCE (17.0 mL), AcOH (390 μL), toluene (26.7 mL), NaOH (272 mg, 6.8 mmol), ethanol (19.6 mL), water (6.8 mL) according to the **general procedure 1**. Yield 1.03 g (78%); thick yellow oil; R_f = 0.35 (EA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.79 (d, ^3J = 8.0 Hz, 1H, Ar), 6.77 (dd, ^3J = 8.0 Hz, ^4J = 1.8 Hz, 1H, Ar), 6.70 (d, ^4J = 1.8 Hz, 1H, Ar), 6.64 (s, 2H, Ar), 5.10 (dd, ^3J = 7.4 Hz, ^3J = 4.4 Hz, 1H, CH), 3.83

(s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 6H, 2×OCH_3), 2.79–2.72 (m, 1H, CH_2), 2.63–2.56 (m, 2H, CH_2), 2.03–1.98 (m, 1H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8 (CO), 152.9 (2×C, Ar), 149.5 (C, Ar), 148.6 (C, Ar), 135.4 (C, Ar), 134.1 (C, Ar), 133.7 (C, Ar), 118.4 (CH, Ar), 111.3 (CH, Ar), 108.8 (CH, Ar), 100.6 (2×CH, Ar), 64.5 (CH), 60.8 (OCH_3), 56.0 (2×OCH_3), 55.9 (OCH_3), 55.8 (OCH_3), 31.3 (CH_2), 29.0 (CH_2). IR (film): 3315, 3134, 3062, 2933, 2835, 2589, 2466, 2428, 2366, 2251, 2131, 2006, 1959, 1833, 1703, 1687, 1592, 1511, 1463, 1392, 1232, 1184, 1102, 1036, 920 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{21}H_{26}NO_6$ 388.1755; found 388.1755. Purity was 95.2%, as determined by qNMR.

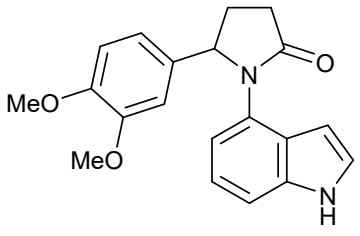
5-(4-Bromophenyl)-1-(3,4,5-trimethoxyphenyl)pyrrolidin-2-one (1b) was obtained from 3,4,5-trimethoxyaniline (585 mg, 3.2 mmol), dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (1.00 g, 3.2 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (234 mg, 0.64 mmol), DCE (16.0 mL), AcOH (370 μL), toluene (26.7 mL), NaOH (256 mg, 6.4 mmol), ethanol (18.5 mL), water (3.2 mL) according to the **general procedure 1**. Yield 804 mg (62%); yellow oil; R_f = 0.38 (EA/PE 4:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, ^3J = 8.4 Hz, 2H), 7.11 (d, ^3J = 8.4 Hz, 2H), 6.61 (s, 2H), 5.14 (dd, ^3J = 7.6 Hz, ^3J = 4.7 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 6H), 2.77–2.69 (m, 1H), 2.65–2.58 (m, 2H), 1.99–1.93 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.7, 153.0 (2×C), 140.5, 135.5, 133.8, 132.2 (2×C), 127.7 (2×C), 121.7, 100.5 (2×C), 63.9, 60.8, 56.1 (2×C), 31.2, 28.8. IR (film): 3368, 3135, 3087, 3062, 2940, 2834, 2594, 2468, 2429, 2249, 2133, 2003, 1961, 1902, 1696, 1596, 1511, 1463, 1421, 1386, 1333, 1271, 1236, 1189, 1131, 1072, 1042, 1010, 912 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{19}H_{21}{}^{79}BrNO_4$ 406.0648; found 406.0648. Anal. calcd (%) for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45; found: C, 56.14; H, 4.89; N, 3.42.



5-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (1c) was obtained from 4-methoxyaniline (293 mg, 2.38 mmol), dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (700 mg, 2.38 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (174 mg, 476 μmol), DCE (11.9 mL), AcOH (275 μL), toluene (18.7 mL), NaOH (192 mg, 4.8 mmol), ethanol (13.7 mL), water (4.8 mL) according to the **general procedure 1**. Yield 553 mg (71%); yellowish oil; R_f = 0,38 (EA/PE 4:1). The spectral data were in accordance with the literature ones.[S5] Anal. calcd (%) for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; found: C, 69.70; H, 6.45; N, 4.28.

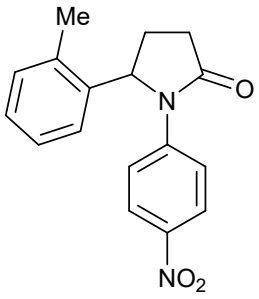


5-(3,4-Dimethoxyphenyl)-1-(1*H*-indol-4-yl)pyrrolidin-2-one (1d) was obtained from 4-aminoindole (135 mg, 1.02 mmol), dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (300 mg, 1.02 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (75 mg, 0.205 mmol), DCE (5.1 mL), AcOH (120 μL), toluene (8.0 mL), NaOH (84 mg, 2.1 mmol), ethanol (5.9 mL), water (2.0 mL) according to the

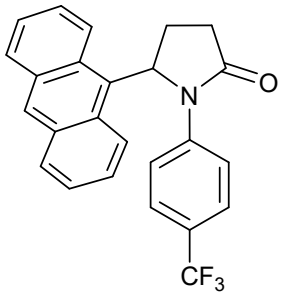


general procedure 1. Yield 130 mg (38%); white solid; mp 111–113 °C; R_f = 0.37 (EA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.77 (s, 1H, NH), 7.01 (d, ^3J = 8.2 Hz, 1H, Ar), 6.95–6.90 (m, 2H, Ar), 6.77–6.72 (m, 3H, Ar), 6.64 (d, ^3J = 8.2 Hz, 1H, Ar), 6.43–6.42 (m, 1H, Ar), 5.33–5.26 (m, 1H, CH), 3.73 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 2.90–2.79 (m, 1H, CH_2), 2.78–2.64 (m, 2H, CH_2), 2.18–2.07 (m, 1H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.7 (CO), 149.0 (C, Ar), 148.3 (C, Ar), 137.1 (C, Ar), 134.0 (C, Ar), 130.0 (C, Ar), 124.7 (CH, Ar), 124.5 (C, Ar), 121.4 (CH, Ar), 119.0 (CH, Ar), 116.4 (CH, Ar), 110.8 (CH, Ar), 110.5 (CH, Ar), 109.2 (CH, Ar), 100.5 (CH, Ar), 65.1 (CH_2), 55.7 (2×OCH_3), 31.3 (CH_2), 29.9 (CH_2). IR (KBr): 3351, 3125, 3044, 2996, 2957, 2936, 2853, 1731, 1683, 1615, 1581, 1516, 1463, 1452, 1441, 1422, 1394, 1374, 1344, 1307, 1261, 1233, 1138, 1109, 1025 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + Na]^+$ $C_{20}H_{20}N_2NaO_3$ 359.1366; found 359.1368. Purity was 95.1%, as determined by qNMR.

5-(2-Methylphenyl)-1-(4-nitrophenyl)pyrrolidin-2-one (1e) was obtained from 4-nitroaniline (167 mg, 1.2 mmol), dimethyl 2-(2-methylphenyl)cyclopropane-1,1-dicarboxylate (300 mg, 1.2 mmol), $Ni(ClO_4)_2{\cdot}6H_2O$ (88 mg, 0.24 mmol), DCE (6 mL), AcOH (138 μL), toluene (8 mL), NaOH (96 mg, 2.4 mmol), ethanol (7 mL), water (2.4 mL) according to the **general procedure 1** but the first step was carried out under reflux for 2 h. Yield 261 mg (73%); dark yellow oil, R_f = 0.27 (EA/PE 1:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (d, ^3J = 9.0 Hz, 2H, Ar), 7.65 (d, ^3J = 9.0 Hz, 2H, Ar), 7.26 (d, ^3J = 7.4 Hz, 1H, Ar), 7.20–7.18 (m, 1H, Ar), 7.11–7.08 (m, 1H, Ar), 6.95 (d, ^3J = 7.9 Hz, 1H, Ar), 5.50–5.48 (m, 1H, CH), 2.81–2.74 (m, 1H, CH_2), 2.72–2.62 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.01–1.95 (m, 1H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.7 (CO), 144.2 (C, Ar), 143.3 (C, Ar), 137.6 (C, Ar), 134.3 (C, Ar), 131.6 (CH, Ar), 128.1 (CH, Ar), 126.9 (CH, Ar), 124.5 (2×CH, Ar), 124.1 (CH, Ar), 120.2 (2×CH, Ar), 60.5 (CH), 31.1 (CH_2), 27.0 (CH_2), 19.2 (CH_3). IR (film): 3120, 3078, 3020, 2973, 2949, 1713, 1593, 1514, 1497, 1462, 1425, 1375, 1338, 1327, 1314, 1299, 1231, 1207, 1175, 1147, 1115, 1093, 1051, 1023 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{17}H_{17}N_2O_3$ 297.1234; found 297.1240. Anal. calcd (%) for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45; found: C, 69.20; H, 5.45; N, 9.45.

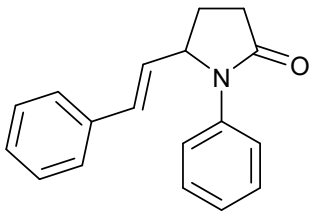


5-(Anthracen-9-yl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-one (1f) was obtained from 4-trifluoromethylaniline (74 μL, 0.59 mmol), dimethyl 2-(2-anthracen-9-yl)cyclopropane-1,1-dicarboxylate (193 mg, 0.58 mmol), $Ni(ClO_4)_2{\cdot}6H_2O$ (42.2 mg, 115 μmol), DCE (2.9 mL), AcOH (66 μL), toluene (5 mL), NaOH (46 mg, 1.15 mmol), ethanol (3.3 mL), water (1.2 mL) according to the **general procedure 1** but the first step was carried out under reflux for 3 h. Yield 35 mg (15%); yellow solid; mp 192–193 °C (dec.); R_f = 0.27 (EA/PE 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, ^3J = 8.9 Hz, 1H), 8.40–8.38 (m, 2H), 8.05 (d, ^3J = 8.4 Hz, 1H), 7.94 (d, ^3J = 8.4 Hz, 1H), 7.70–7.66 (m, 1H), 7.56–7.52 (m, 1H), 7.47–7.43 (m, 1H), 7.41–7.37 (m, 3H), 7.22 (d, ^3J = 8.6 Hz, 2H), 6.91–6.87 (m, 1H), 3.13–2.96 (m, 2H), 2.87–2.66 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.7, 140.5, 132.0, 131.2, 130.5, 130.3, 130.2, 129.6, 129.0, 128.3, 127.7, 126.6, 126.5 (q, $^2J_{CF}$ = 29 Hz), 125.5

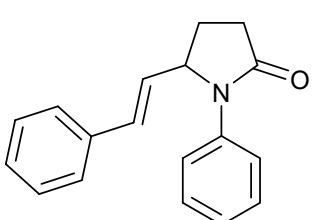


(q, $^3J_{CF}$ = 4 Hz, 2×C), 125.0 (2×C), 123.4, 122.1 (2×C), 121.4, 58.8, 32.3, 26.4. The signal of the carbon atom of CF_3 group was not observed. IR (KBr): 3092, 3054, 2968, 2938, 1708, 1611, 1585, 1516, 1488, 1478, 1462, 1446, 1422, 1404, 1353, 1325, 1285, 1272, 1238, 1214, 1192, 1165, 1141, 1119, 1068, 1046, 1011 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{25}H_{19}F_3NO$ 406.1413; found 406.1398. Purity was 98.4%, as determined by qNMR.

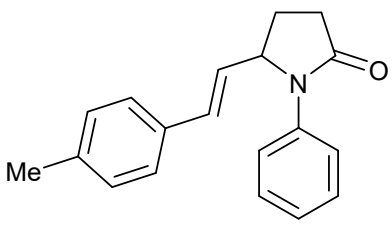
(*E*)-1-Phenyl-5-styrylpyrrolidin-2-one (2a) was obtained from aniline (107 mg, 1.15 mmol), dimethyl (*E*)-2-styrylcyclopropane-1,1-dicarboxylate (300 mg, 1.15 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (84 mg, 0.23 mmol), DCE (5.7 mL), AcOH (140 μL), toluene (8 mL), NaOH (92 mg, 2.3 mmol), ethanol (6.9 mL), water (2.4 mL) according to the **general procedure 1**. Yield 155 mg (51%); yellow solid; mp 71–73 °C; R_f = 0.38 (EA/PE 1:1). The spectral data were in accordance with the literature ones.[S6] Purity was 99.0%, as determined by qNMR.



(*E*)-1-(4-*tert*-Butylphenyl)-5-styrylpyrrolidin-2-one (2b) was obtained from 4-*tert*-butylaniline (143 mg, 0.96 mmol), dimethyl (*E*)-2-styrylcyclopropane-1,1-dicarboxylate (250 mg, 0.96 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (71 mg, 194 μmol), DCE (4.8 mL), AcOH (110 μL), toluene (6.7 mL), NaOH (80 mg, 2.0 mmol), ethanol (5.6 mL), water (1.9 mL) according to the **general procedure 1**. Yield 172 mg (56%); yellowish thick oil; R_f = 0.48 (EA/PE 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, ^3J = 8.8 Hz, 2H), 7.36–7.24 (m, 7H), 6.53 (d, ^3J = 15.9 Hz, 1H), 6.15 (dd, ^3J = 15.9 Hz, ^3J = 7.4 Hz, 1H), 4.83–4.80 (m, 1H), 2.74–2.69 (m, 1H), 2.60–2.55 (m, 1H), 2.49–2.44 (m, 1H), 2.03–1.98 (m, 1H), 1.29 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 148.1, 136.1, 135.5, 131.9, 129.2, 128.6 (2×C), 128.0, 126.5 (2×C), 125.7 (2×C), 122.4 (2×C), 62.4, 31.4, 31.3 (3×C), 31.1, 26.6. IR (film) cm^{-1}: 3369, 3056, 3025, 2963, 2903, 2868, 1694, 1605, 1577, 1516, 1498, 1475, 1458, 1450, 1418, 1371, 1296, 1281, 1267, 1222, 1148, 1127, 1093, 1073, 1048, 1026, 1016, 965 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{22}H_{26}NO$ 320.2009; found 320.2006. Anal. calcd (%) for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38; found: C, 83.01; H, 7.75; N, 4.46.

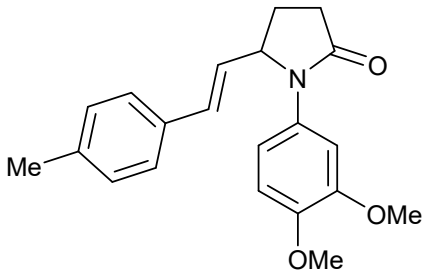


(*E*)-5-(4-Methylstyryl)-1-phenylpyrrolidin-2-one (2c) was obtained from aniline (80 mg, 0.86 mmol), dimethyl (*E*)-2-(4-methylstyryl)cyclopropane-1,1-dicarboxylate (235 mg, 0.86 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (63 mg, 172 μmol), DCE (4.3 mL), AcOH (98 μL), toluene (6.3 mL), NaOH (69 mg, 1.72 mmol), ethanol (5.0 mL), water (1.8 mL) according to the **general procedure 1**. Yield 76 mg (32%); light yellow solid; mp 117–118 °C; R_f = 0.30 (EA/PE 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (m, 2H, Ar), 7.35–7.33 (m, 2H, Ar), 7.22–7.20 (d, ^3J = 7.9 Hz, 2H, Ar), 7.15–7.10 (m, 3H, Ar), 6.49 (d, ^3J = 15.9 Hz, 1H, CH=), 6.08 (dd, ^3J = 15.9 Hz, ^3J = 7.5 Hz, 1H, CH=), 4.84–4.80 (m, 1H, CH), 2.75–2.69 (m, 1H,

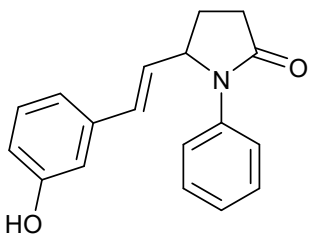


CH_2), 2.61–2.55 (m, 1H, CH_2), 2.49–2.43 (m, 1H, CH_2), 2.33 (s, 3H, CH_3), 2.03–1.98 (m, 1H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5 (CO), 138.2 (C, Ar), 138.0 (C, Ar), 133.3 (C, Ar), 132.1 (CH=), 129.4 (2×CH, Ar), 128.8 (2×CH, Ar), 127.9 (CH=), 126.5 (2×CH, Ar), 125.3 (CH, Ar), 123.0 (2×CH, Ar), 62.5 (CH), 31.3 (CH_2), 26.7 (CH_2), 21.3 (CH_3). IR (KBr): 2858, 1678, 1597, 1499, 1294, 966 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{19}H_{20}NO$ 278.1539; Found 278.1538. Anal. calcd (%) for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05; found: C, 82.33; H, 6.84; N, 5.09.

(*E*)-1-(3,4-Dimethoxyphenyl)-5-(4-methylstyryl)pyrrolidin-2-one (2d) was obtained from 3,4-dimethoxyaniline (129 mg, 0.84 mmol), dimethyl (*E*)-2-(4-methylstyryl)cyclopropane-1,1-dicarboxylate (230 mg, 0.84 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (62 mg, 0.17 mmol), DCE (4.2 mL), AcOH (96 μL), toluene (6.2 mL), NaOH (68 mg, 1.7 mmol), ethanol (4.8 mL), water (1.7 mL) according to the **general procedure 1**. Yield 147 mg (52%); dark yellow viscous oil; R_f = 0.30 (Al_2O_3, EA/PE 3:2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, ^3J = 7.9 Hz, 2H, Ar), 7.16 (d, ^4J = 2.5 Hz, 1H, Ar) 7.11 (d, ^3J = 7.9 Hz, 2H, Ar), 6.86 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, Ar), 6.80 (d, ^3J = 8.9 Hz, 1H, Ar), 6.47 (d, ^3J = 15.8 Hz, 1H, CH=), 6.08 (dd, ^3J = 15.8 Hz, ^3J = 7.9 Hz, 1H, CH=), 4.75–4.70 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.75–2.67 (m, 1H, CH_2), 2.62–2.54 (m, 1H, CH_2), 2.51–2.46 (m, 1H, CH_2), 2.33 (s, 3H, CH_3), 2.04–1.96 (m, 1H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (CO), 148.9 (C, Ar), 146.8 (C, Ar), 138.1 (C, Ar), 133.3 (C, Ar), 132.3 (CH=), 131.5 (C, Ar), 129.4 (2×CH, Ar), 128.1 (CH=), 126.4 (2×CH, Ar), 115.7 (CH, Ar), 111.1 (CH, Ar), 108.1 (CH, Ar), 63.2 (CH), 56.0 (OCH_3), 56.0 (OCH_3), 31.2 (CH_2), 26.6 (CH_2), 21.3 (CH_3). IR (film): 2833, 1686, 1511, 1385, 1234, 1024, 969 cm^{-1}. HRMS ESI/TOF): m/z calcd for $[M + H]^+$ $C_{21}H_{24}NO_3$ 338.1751; found 338.1758. Purity was 95.3%, as determined by qNMR.



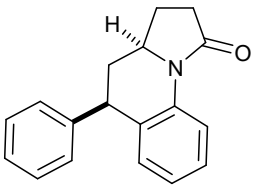
(*E*)-5-(3-Hydroxystyryl)-1-phenylpyrrolidin-2-one (2e). To a solution of aniline (328 μL, 3.60 mmol) in DCE (17 mL, 0.2 M) and cyclopropane **4g** (946 mg, 3.42 mmol) $Y(OTf)_3$ (367 mg, 0.685 mmol) was added under Ar atmosphere. The resulting mixture was stirred at room temperature for 1.5 h and filtered through a short pad of silica gel using EA as eluent. The filtrate was concentrated under vacuum; the residue was dissolved in 1,4-dioxane (27 mL, 0.13 M). Next, acetic acid (391 μL, 6.85 mmol) was added, and the reaction mixture was stirred under reflux for 7 h. Then, solvent was removed under vacuum, and residue was dissolved in ethanol (20 mL, 0.17 M); 1M aq. solution of sodium hydroxide (411 mg, 10.3 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 2 h, poured into 10% aq. AcOH solution (30 mL) and diluted with satd. NaCl solution (30 mL). The resulting mixture was extracted with EA (4×15 mL). Combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in PhCl/1,4-dioxane (1:1 mixture, 49 mL, 0.07 M) and refluxed for 10 h (bp ≈ 122 °C). The solvent was removed under vacuum and the resulting residue was purified by column chromatography



on silica gel using EA/CH_2Cl_2 (1:20 to 1:4) mixture to provide pyrrolidin-2-one **2e** (518 mg, 54%) as a white foam; mp 59–60 °C; R_f = 0.35 (EA/PE 3:2). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.44 (br. dd, ^3J = 8.6 Hz, ^4J = 1.1 Hz, 2H), 7.31 (br. dd, ^3J = 8.6 Hz, ^3J = 7.4 Hz, 2H), 7.15–7.10 (m, 2H), 6.82 (ddd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, ^4J = 0.9 Hz, 1H), 6.76 (dd, ^4J = 2.5 Hz, ^4J = 1.6 Hz, 1H), 6.71 (ddd, ^3J = 8.1 Hz, ^4J = 2.5 Hz, ^4J = 0.9 Hz, 1H), 6.56 (br. s, 1H), 6.42 (br. d, ^3J = 15.8 Hz, 1H), 6.04 (dd, ^3J = 15.8 Hz, ^3J = 7.6 Hz, 1H), 4.79 (dddd, ^3J = 7.6 Hz, ^3J = 7.2 Hz, ^3J = 4.9 Hz, ^4J = 1.0 Hz, 1H), 2.70 (ddd, ^2J = 17.2 Hz, ^3J = 9.2 Hz, ^3J = 7.2 Hz, 1H), 2.58 (ddd, ^2J = 17.2 Hz, ^3J = 9.2 Hz, ^3J = 6.2 Hz, 1H), 2.44 (dddd, ^2J = 12.8 Hz, ^3J = 9.2 Hz, ^3J = 7.2 Hz, ^3J = 7.2 Hz, 1H), 1.97 (dddd, ^2J = 12.8 Hz, ^3J = 9.2 Hz, ^3J = 6.2 Hz, ^3J = 4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 175.2, 156.6, 137.8, 137.5, 132.4, 129.9, 129.0 (2×C), 128.8, 125.8, 123.4 (2×C), 119.0, 115.5, 113.2, 62.9, 31.3, 26.6. IR (KBr): 3238, 1663, 1592, 1580, 1496, 1451, 1387, 1285, 1212, 1155, 1114, 967, 872, 778 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + Na]^+$ $C_{18}H_{17}NNaO_2$ 302.1151; Found 302.1153.

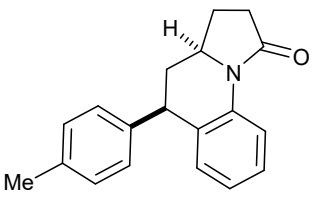
General procedure 2 for the synthesis of tetrahydrobenz[*g*]indolizines 3. Pyrrolidone **2** was dissolved in polyphosphoric acid (PPA, 2 g/mmol) in triple evacuated/N_2-filled vial. The obtained mixture was stirred at 100 °C for 45 min, cooled and quenched with satd. $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate (3×5 mL). Combined organic phases were dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo*; pure product was isolated as a single *cis*-diastereomer by silica gel column chromatography.

(3a*RS*,5*RS*)-5-Phenyl-3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2*H*)-one (3a) was



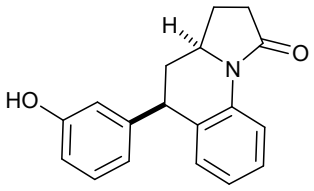
obtained from **2a** (50 mg, 0.19 mmol) and PPA (400 mg) according to the general procedure **2**. Yield: 27 mg (54%); dark ivory solid; mp 174–176 °C; R_f = 0.69 (EA/PE 1:1). The spectral data were in accordance with the literature ones.[S6] Anal. calcd (%) for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32; found: C, 82.43; H, 6.29; N, 5.12.

(3a*RS*,5*RS*)-5-(4-Methylphenyl)-3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2*H*)-



one (3b) was obtained from **2c** (50 mg, 0.18 mmol) and PPA (400 mg) according to the general procedure **2**. Yield 32 mg (64%); pale yellow solid; mp 127–128 °C; R_f = 0.43 (EA/PE 1:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.72 (d, ^3J = 8.4 Hz, 1H, Ar), 7.22–7.20 (m, 1H, Ar), 7.15 (d, ^3J = 8.0 Hz, 2H, Ar), 7.07 (d, ^3J = 8.0 Hz, 2H, Ar), 6.94–6.91 (m, 1H, Ar), 6.80–6.79 (m, 1H, Ar), 4.19–4.16 (m, 1H, CH), 4.13–4.08 (m, 1H, CH), 2.69–2.63 (m, 1H, CH_2), 2.57–2.52 (m, 1H, CH_2), 2.38–2.29 (m, 5H, CH_2 + CH_3), 1.96–1.89 (m, 1H, CH_2), 1.79–1.72 (m, 1H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 173.5 (CO), 142.1 (C, Ar), 137.0 (C, Ar), 136.5 (C, Ar), 130.0 (CH, Ar), 129.7 (C, Ar), 129.5 (2×CH, Ar), 128.6 (2×CH, Ar), 127.2 (CH, Ar), 123.8 (CH, Ar), 119.1 (CH, Ar), 57.8 (CH), 44.7 (CH), 40.4 (CH_2), 32.2 (CH_2), 25.2 (CH_2), 21.2 (CH_3). IR (KBr): 2867, 1687, 1486, 1296, 1111 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{19}H_{20}NO$

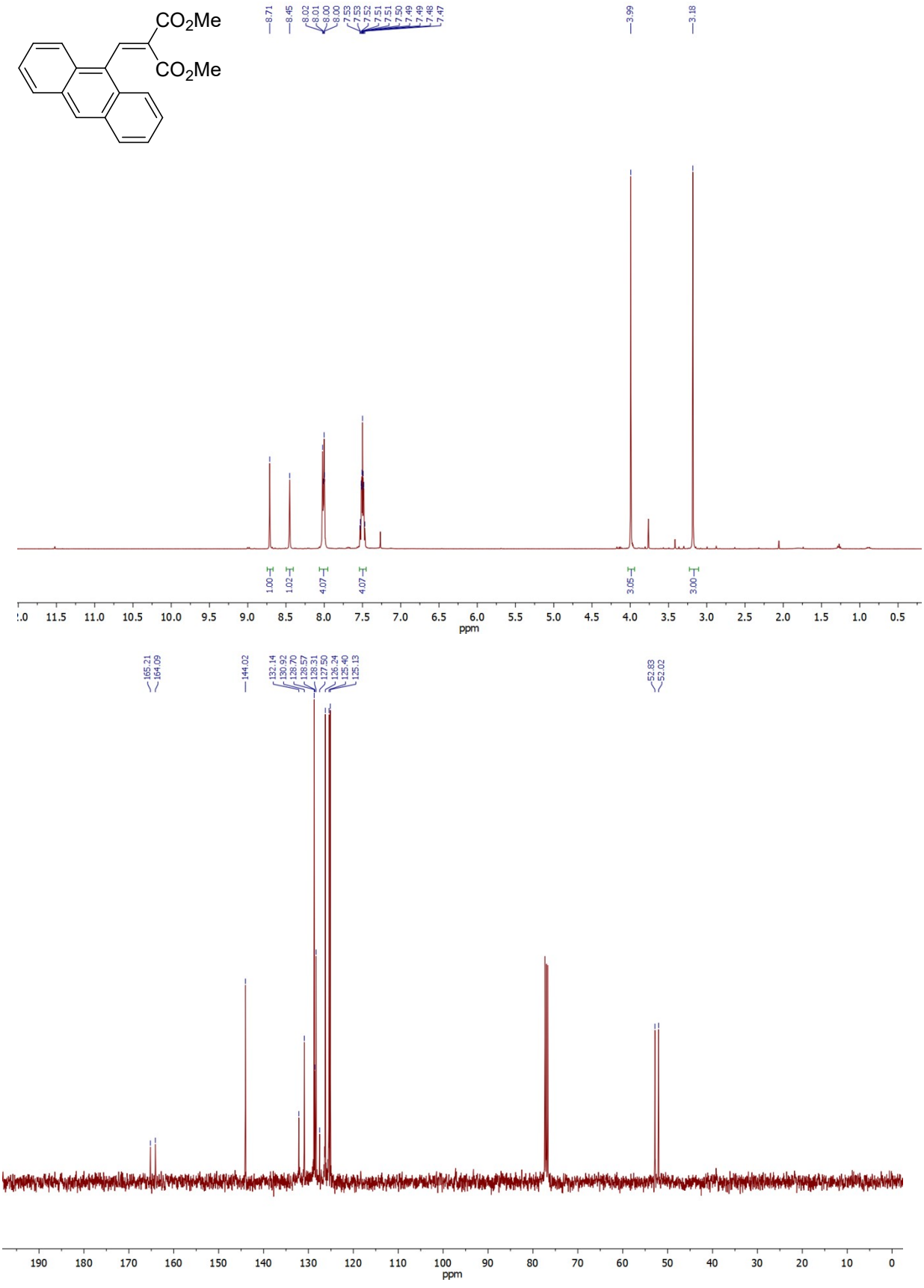
278.1539; Found 278.1545. Anal. calcd (%) for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05; found: C, 82.19; H, 6.68; N, 5.04.

(3a*RS*,5*RS*)-5-(3-Hydroxyphenyl)-3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2*H*)-one (3c). 

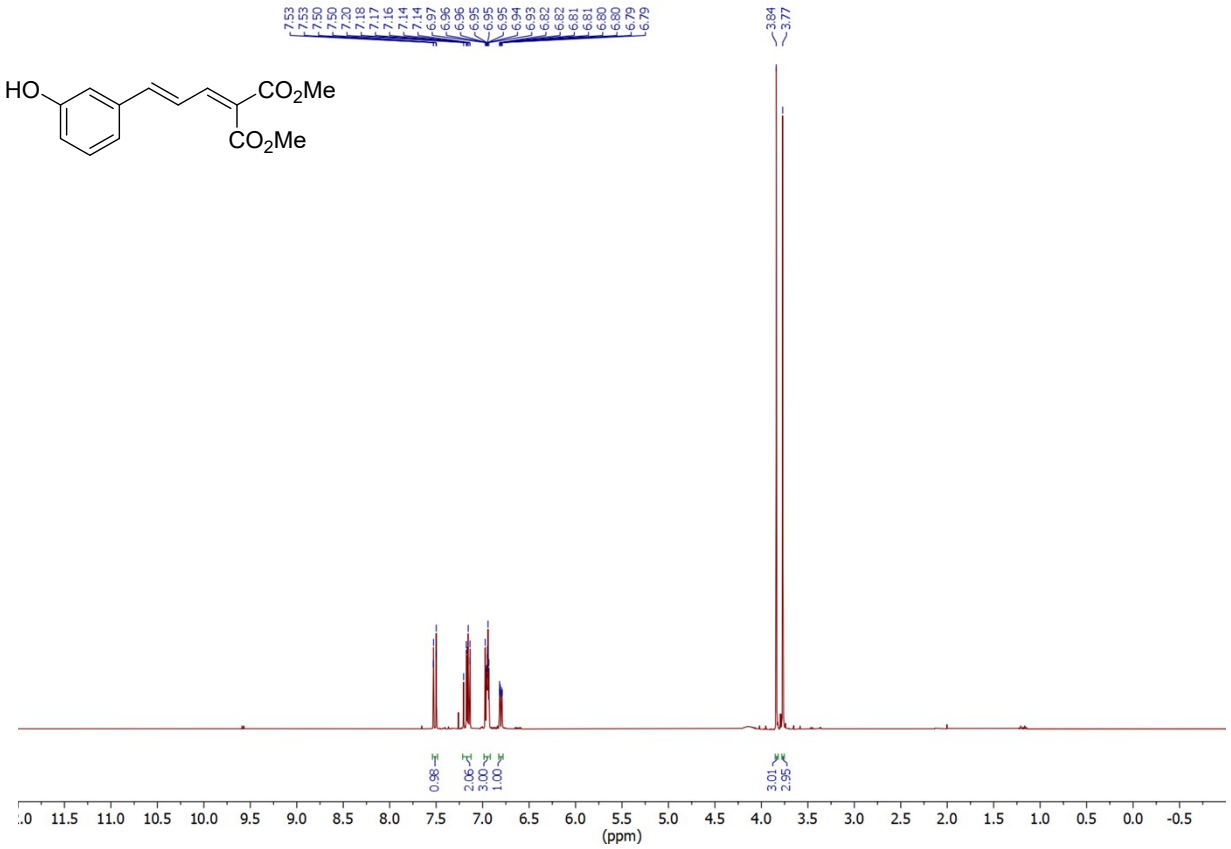
To a solution of pyrrolidin-2-one **2e** (76 mg, 0.273 mmol) in CH_2Cl_2 (1.6 mL, 0.17 M) MsOH (0.53 mL, 8.17 mmol) was added and the resulting mixture was stirred in a closed vial at 40 °C for 4 h. Then the reaction mixture was poured into 10% AcONa solution (10 mL) and extracted with CH_2Cl_2 (4×7 mL). Combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel using EA/CH_2Cl_2 (from 1:20 to 1:4) to provide compound **3c** (33 mg, 43%) as white solid; mp 230–232 °C; R_f = 0.47 (EA/PE 3:2). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 9.25 (br.s, 1H, OH), 8.61 (dd, ^3J = 8.4 Hz, ^4J = 1.3 Hz, 1H, Ar), 7.16 (ddd, ^3J = 8.4 Hz, ^4J = 7.1 Hz, ^4J = 2.4 Hz, 1H, Ar), 7.12 (dd, ^3J = 8.1 Hz, ^3J = 7.8 Hz, 1H, Ar), 6.91 (ddd, ^3J = 8.1 Hz, ^4J = 7.1 Hz, ^4J = 1.3 Hz, 1H, Ar), 6.70 (br. d, ^3J = 8.1 Hz, 1H, Ar), 6.65 (dd, ^3J = 8.1 Hz, ^4J = 2.4 Hz, 1H, Ar), 6.63 (br. d, ^3J = 7.8 Hz, 1H, Ar), 6.56 (br. s, 1H, Ar), 4.16 (dd, ^3J = 12.3 Hz, ^3J = 5.7 Hz, 1H, CH), 4.08 (dddd, ^3J = 11.6 Hz, ^3J = 9.0 Hz, ^3J = 6.7 Hz, ^3J = 2.5 Hz, 1H, CH), 2.59 (ddd, ^2J = 16.8 Hz, ^3J = 11.0 Hz, ^3J = 9.5 Hz, 1H, CH_2), 2.38 (ddd, ^2J = 16.8 Hz, ^3J = 9.5 Hz, ^3J = 2.2 Hz, 1H, CH_2), 2.28 (ddd, ^2J = 13.0 Hz, ^3J = 5.7 Hz, ^3J = 2.5 Hz, 1H, CH_2), 2.23 (dddd, ^2J = 12.1 Hz, ^3J = 9.6 Hz, ^3J = 6.7 Hz, ^3J = 2.2 Hz, 1H, CH_2), 1.82 (ddd, ^2J = 13.0 Hz, ^3J = 12.3 Hz, ^3J = 11.6 Hz, 1H, CH_2), 1.71 (dddd, ^2J = 12.1 Hz, ^3J = 11.0 Hz, ^3J = 9.5 Hz, ^3J = 9.0 Hz, 1H, CH_2). ^{13}C NMR (DMSO-d_6, 151 MHz): δ 173.0 (C=O), 157.4 (C, Ar), 146.4 (C, Ar), 136.7 (C, Ar), 129.6 (C, Ar), 129.0 (2×CH, Ar), 126.4 (CH, Ar), 122.9 (CH, Ar), 119.1 (CH, Ar), 118.0 (CH, Ar), 115.1 (CH, Ar), 113.5 (CH, Ar), 56.8 (CH), 43.8 (CH), 38.8 (CH_2), 31.5 (CH_2), 24.4 (CH_2). IR (KBr): 3239, 1651, 1597, 1487, 1453, 1401, 1375, 1299, 1268, 1231, 1157, 1117, 971, 876, 846, 800, 770 cm^{-1}. HRMS (ESI/TOF): m/z calcd for $[M + H]^+$ $C_{18}H_{18}NO_2$ 280.1332; found 280.1332. Anal. calcd (%) for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01; found: C, 77.41; H, 6.26; N, 5.00.

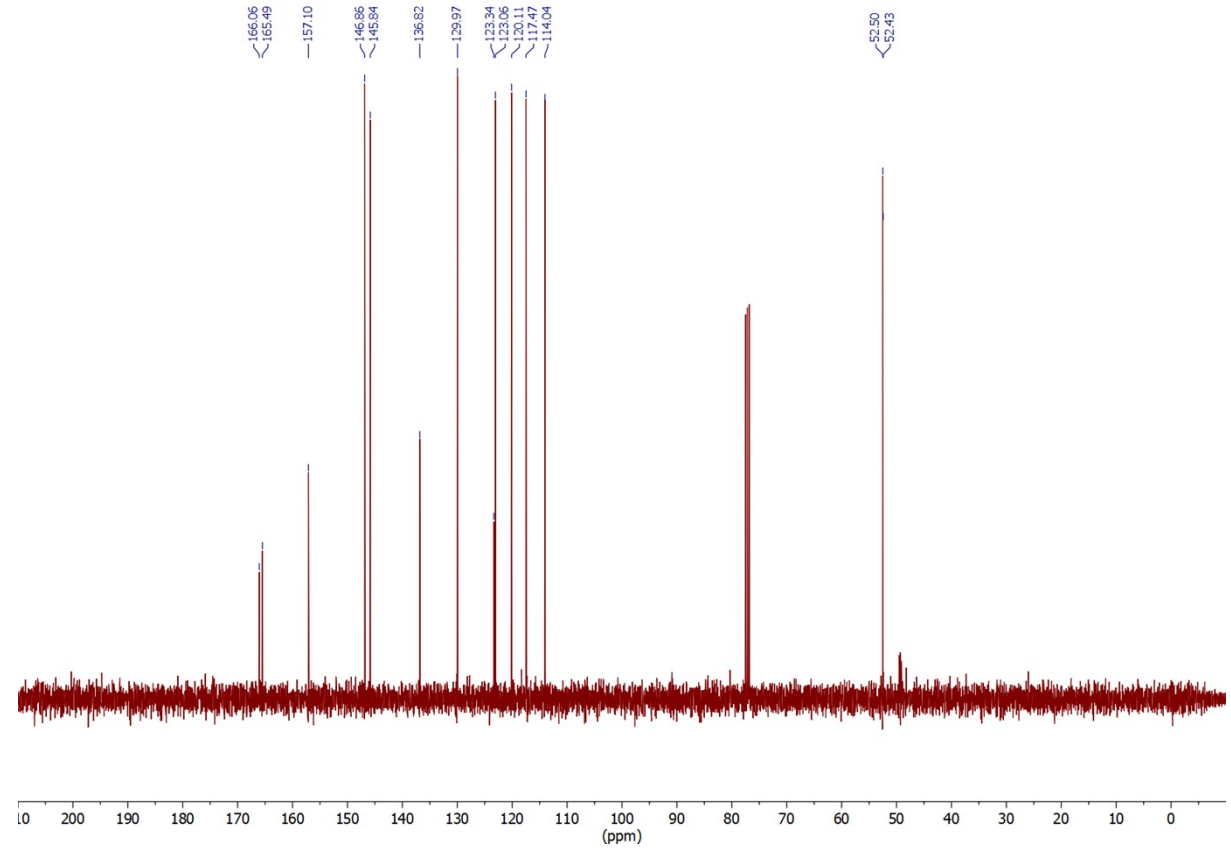
Copies of NMR spectra

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) spectra of **S2d**

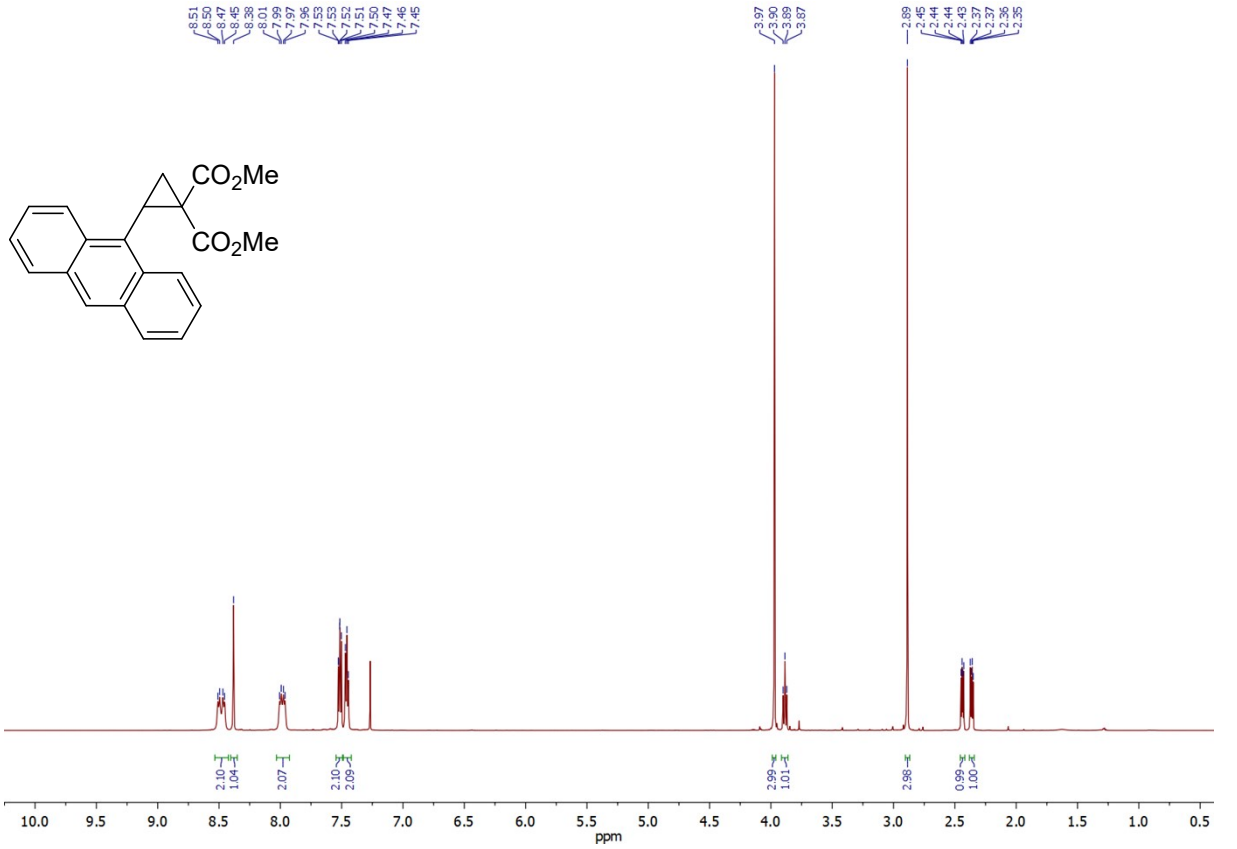


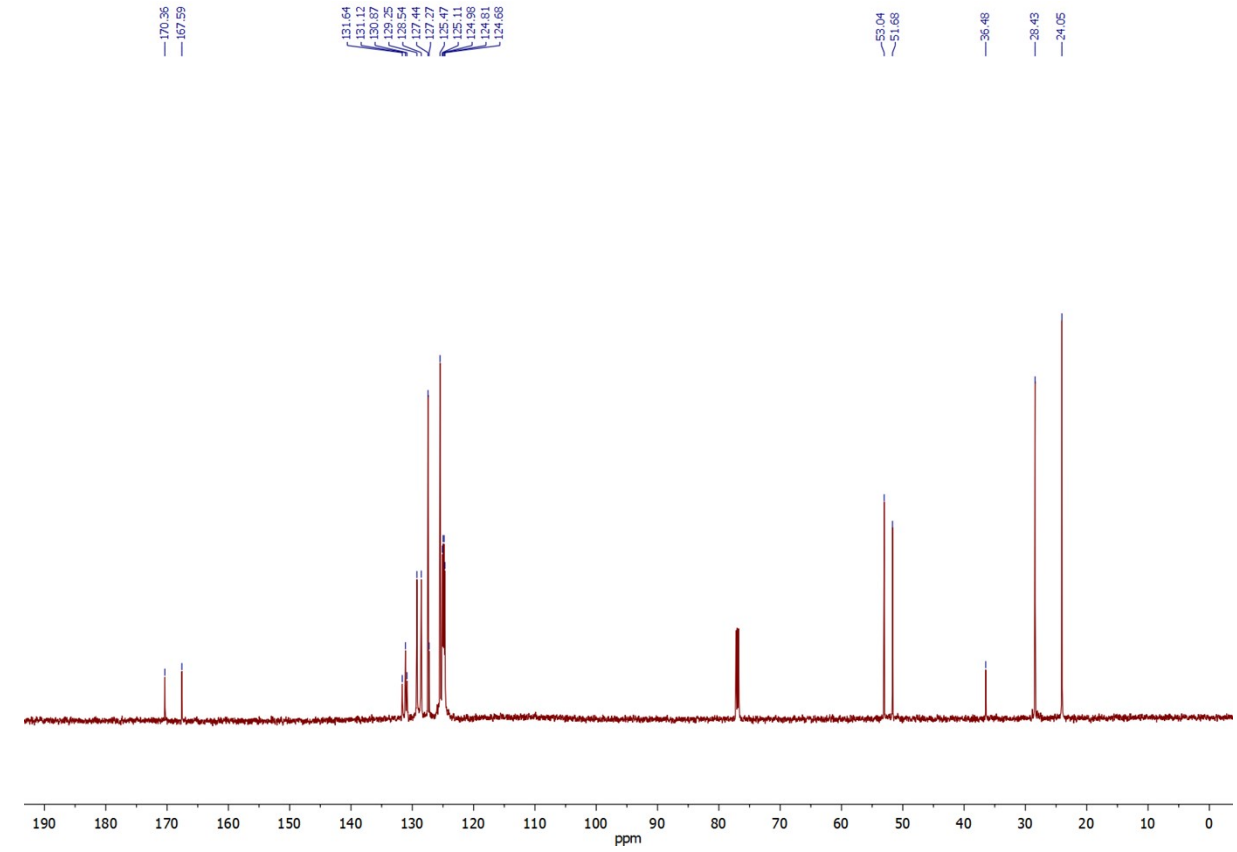
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) spectra of **S2g**



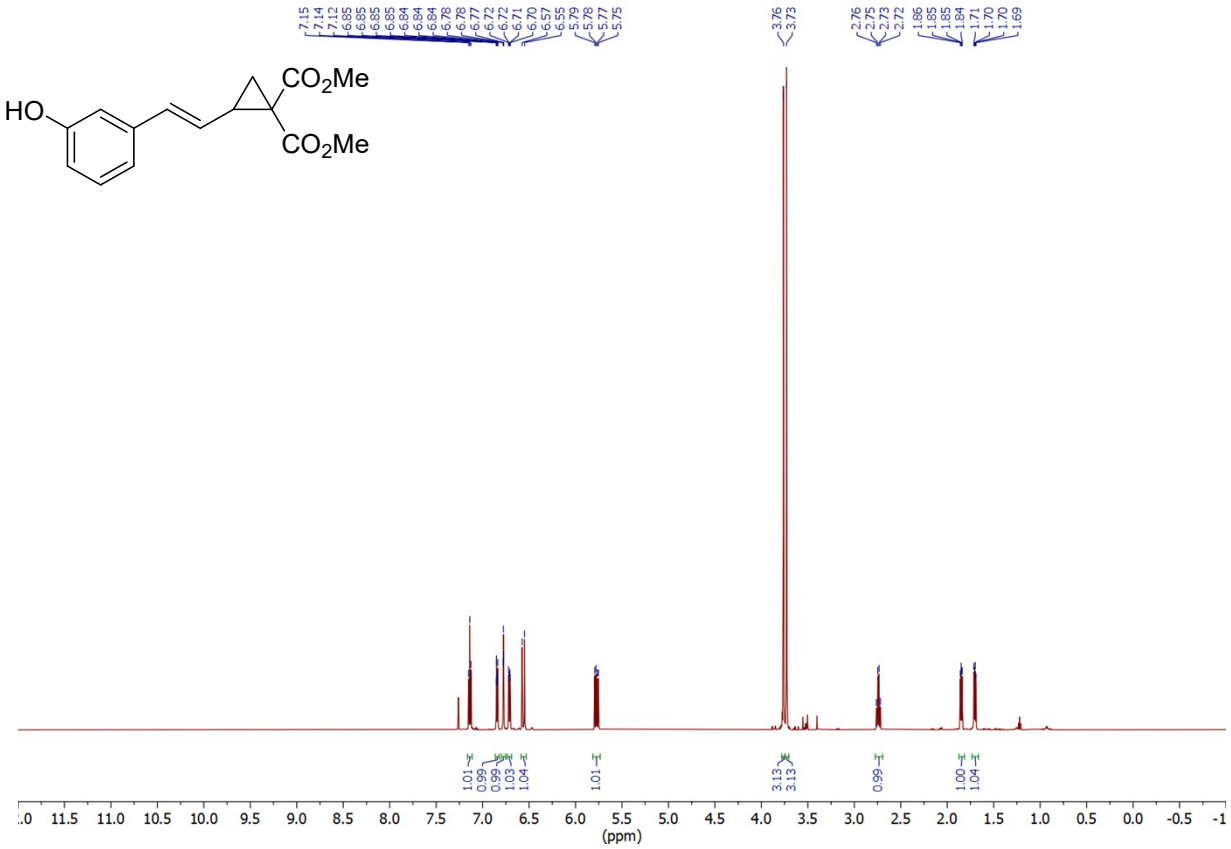


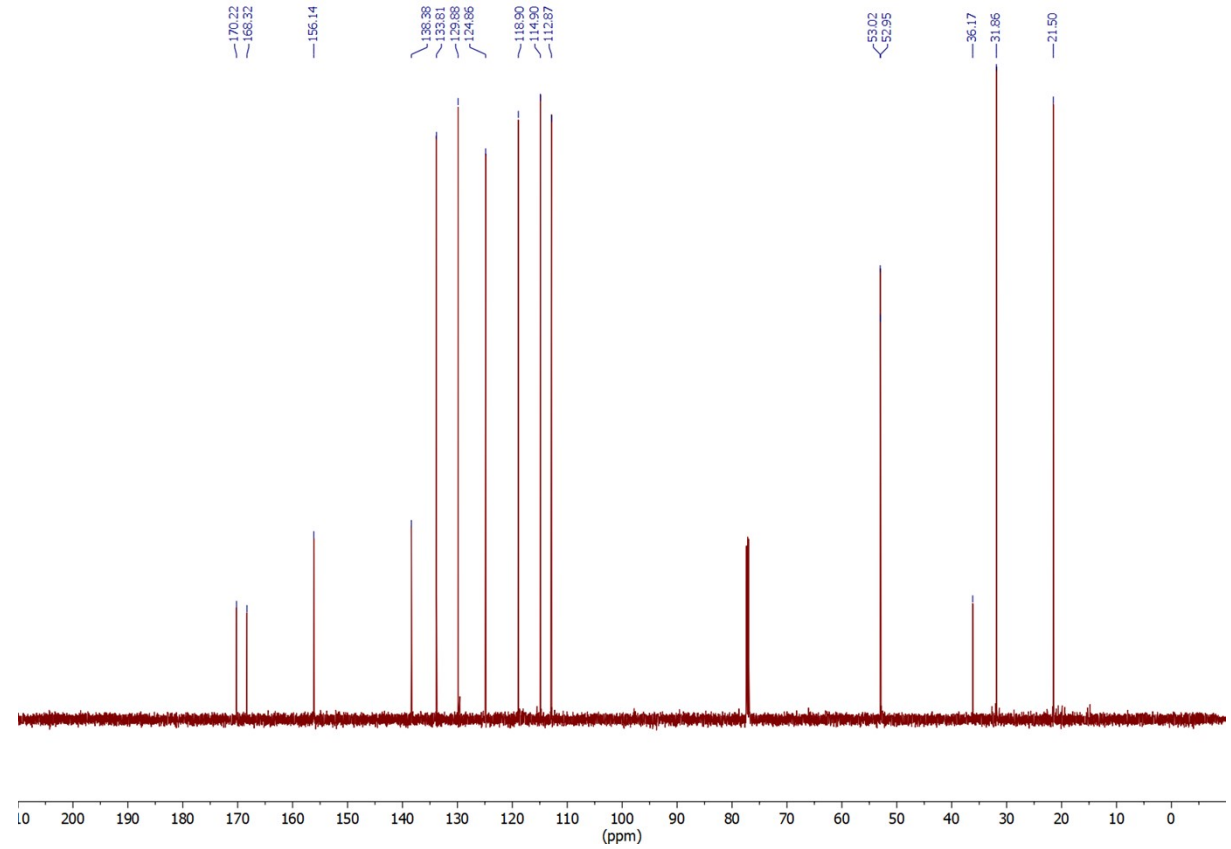
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) spectra of **4d**



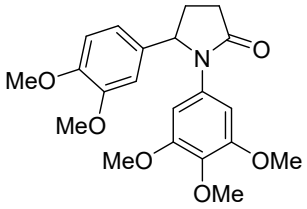


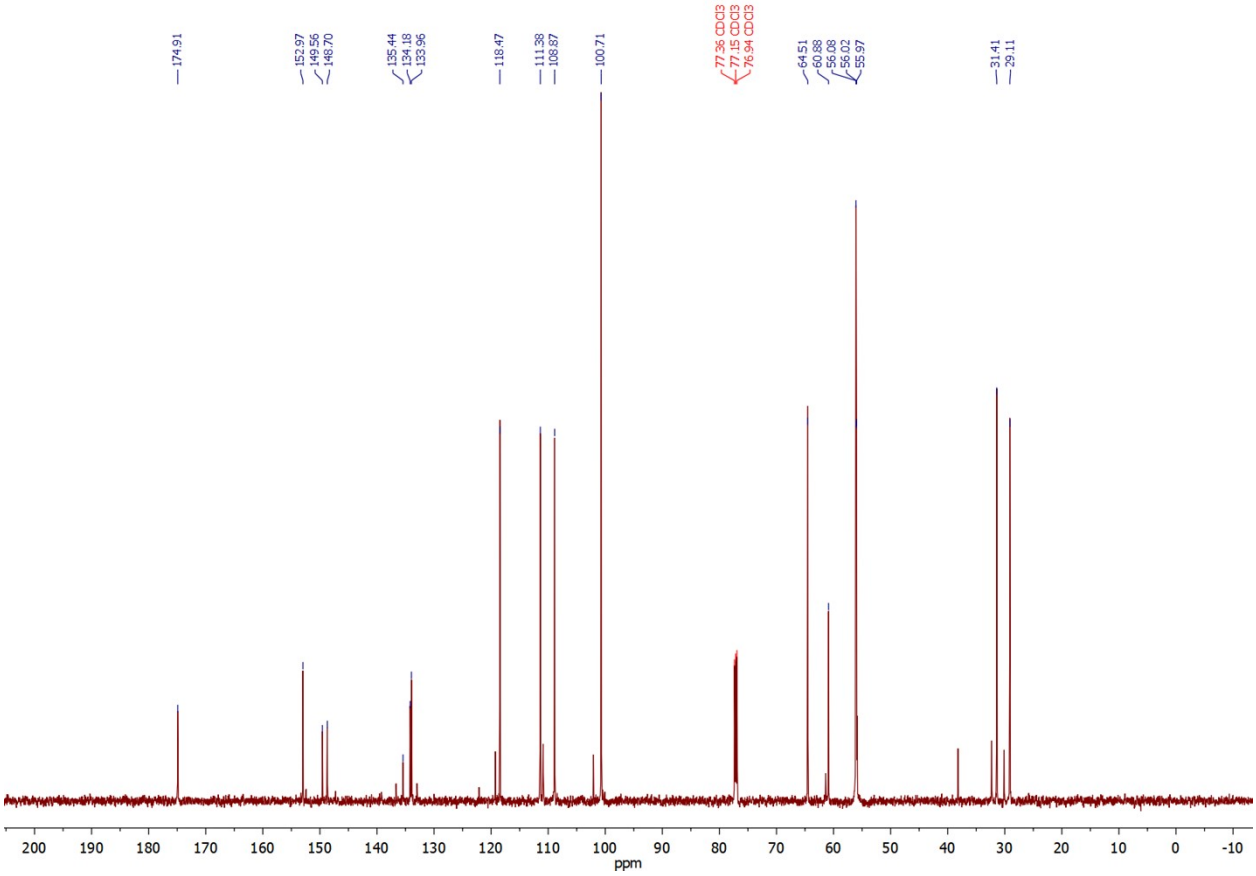
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **4g**



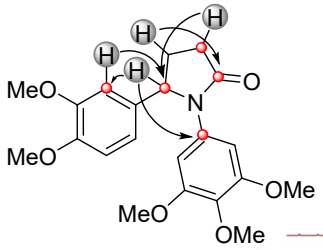


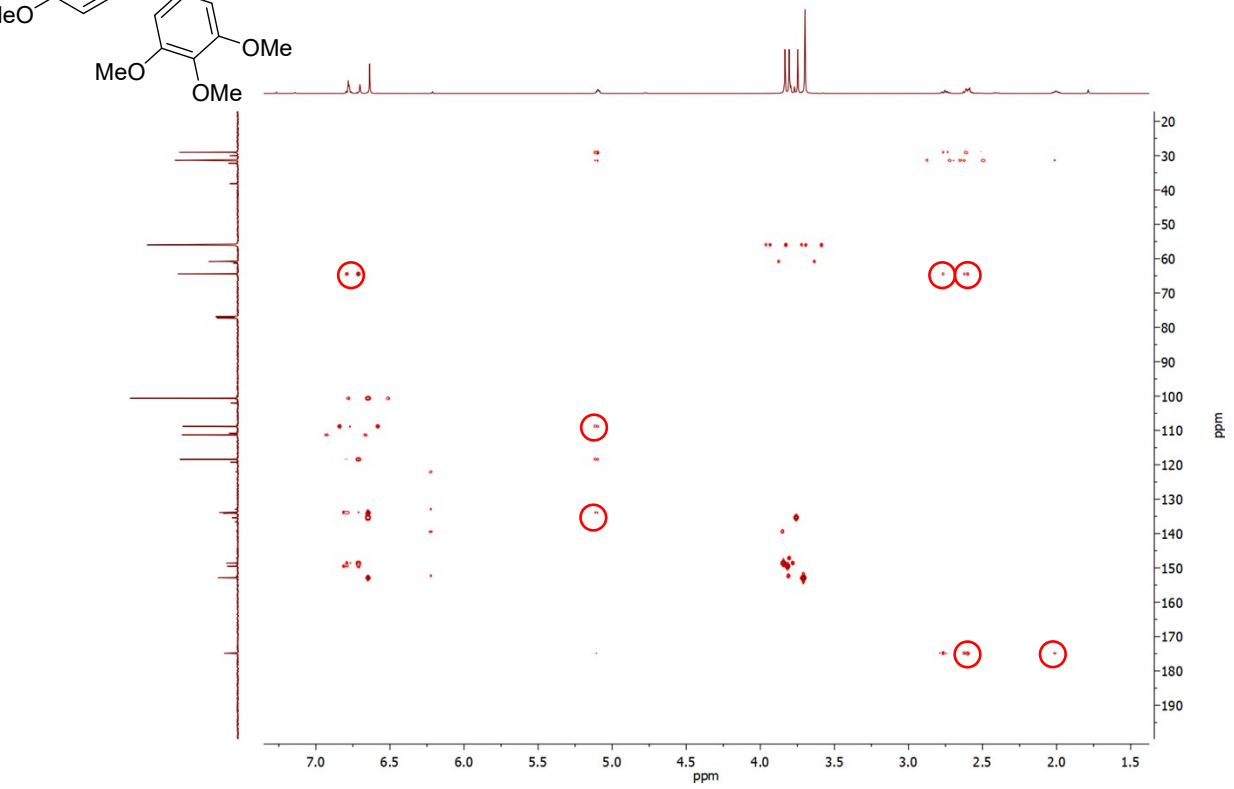
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **1a**

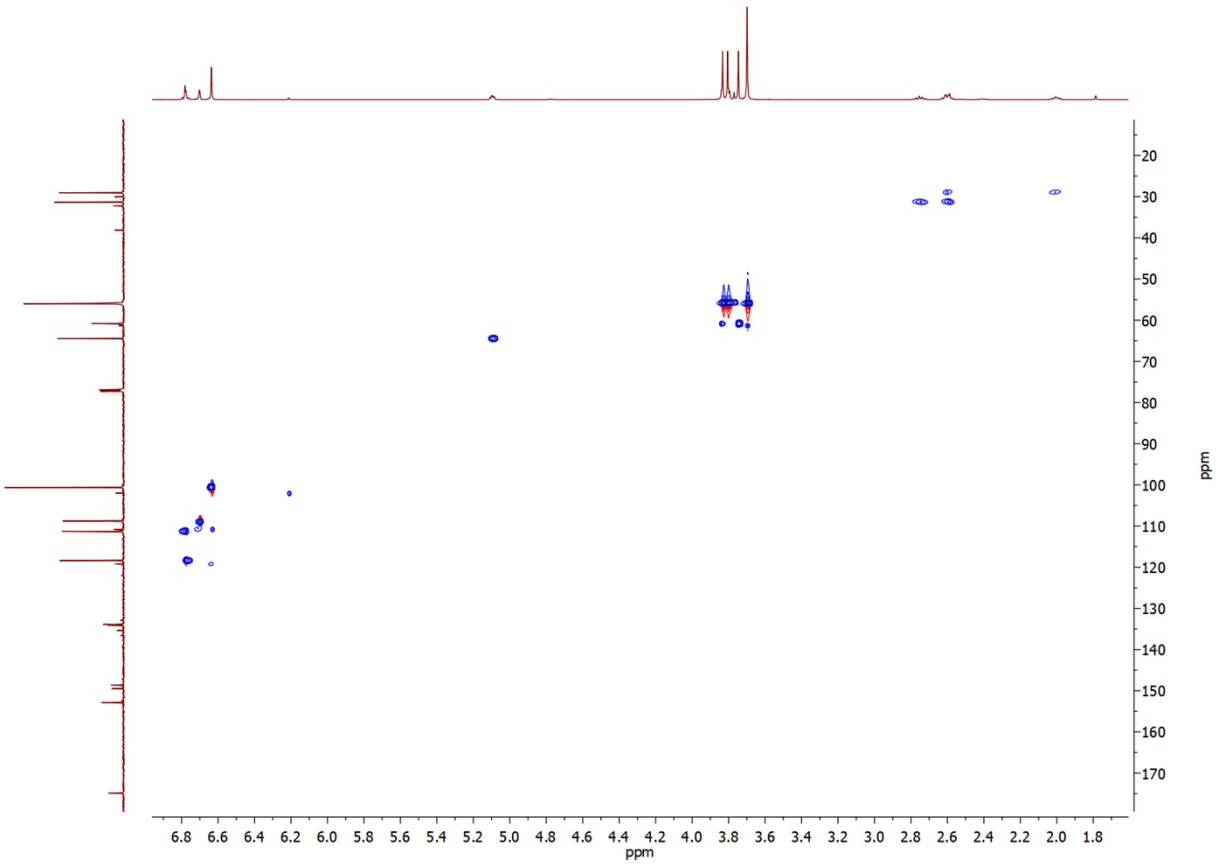




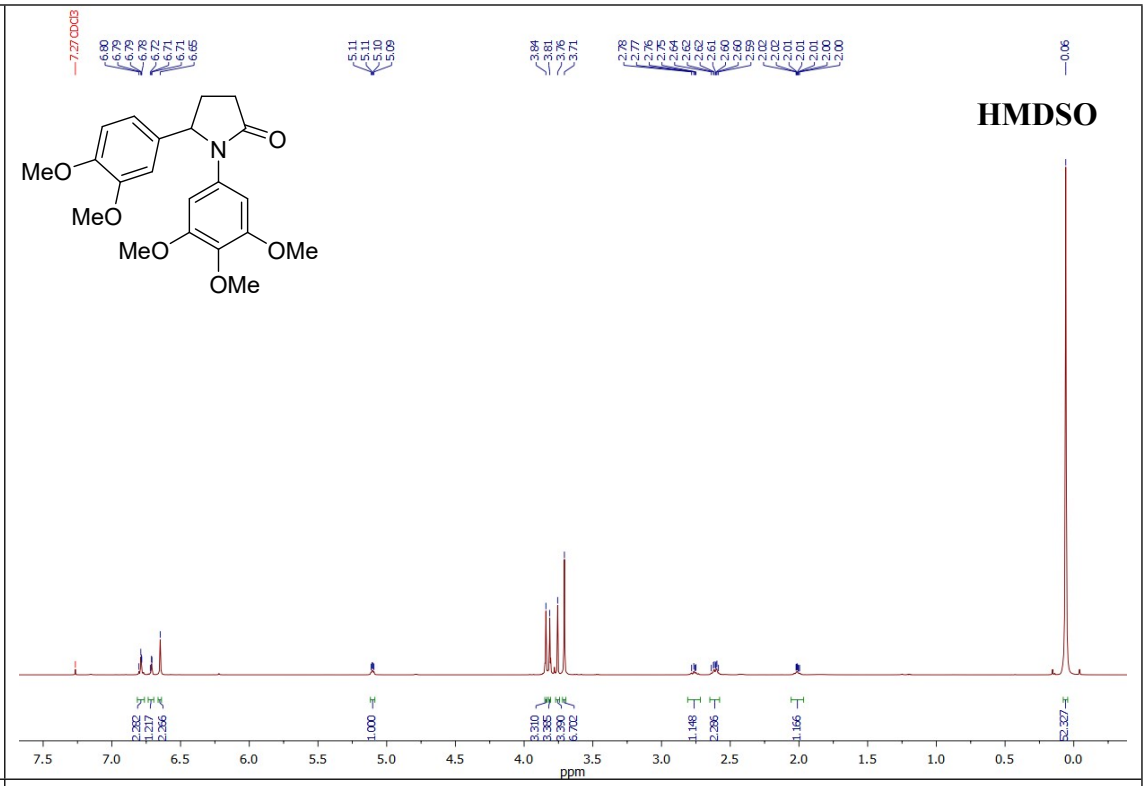
^{1}H-^{13}C HMBC ($CDCl_3$) and ^{1}H-^{13}C HSQC ($CDCl_3$) spectra of **1a**



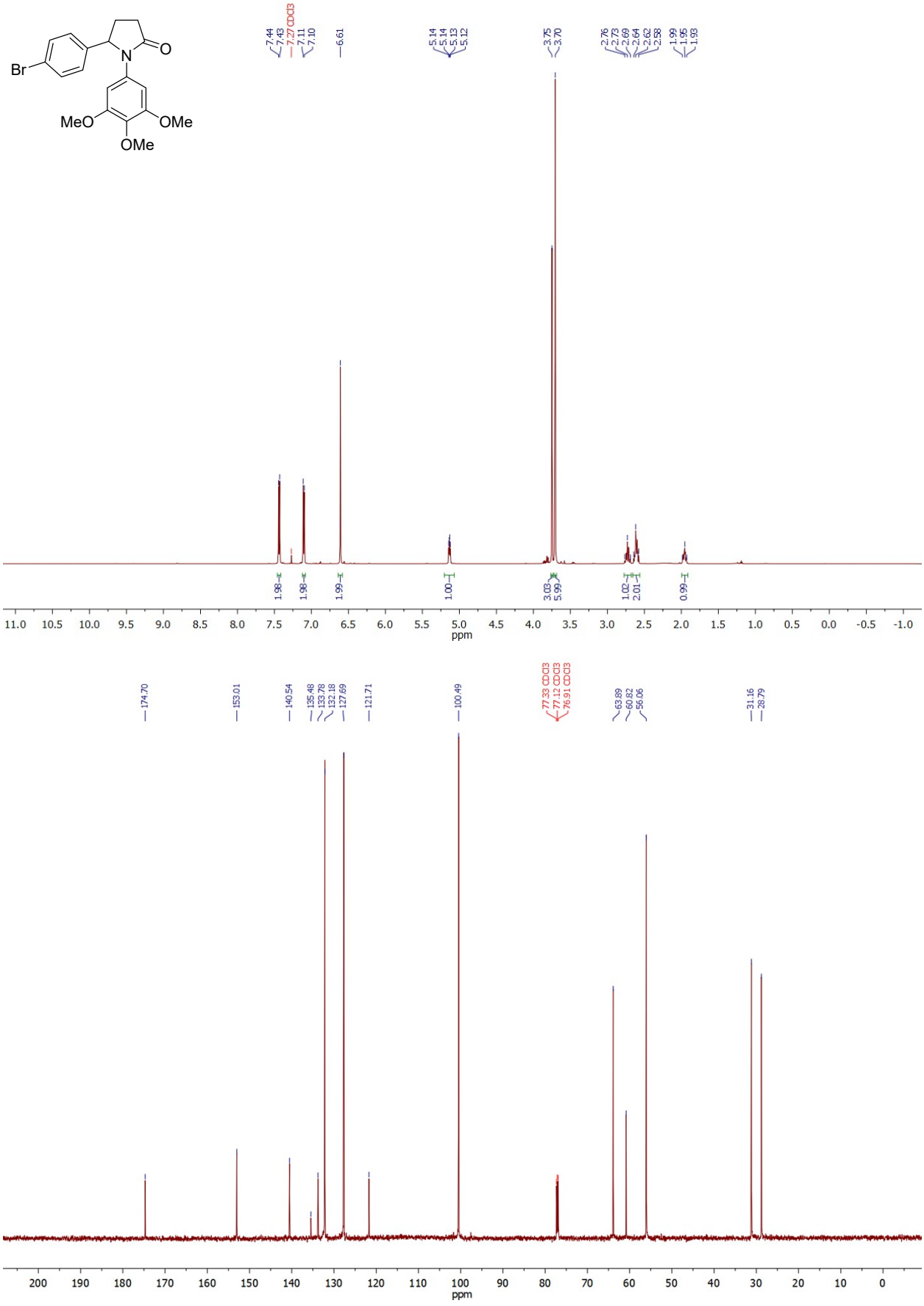




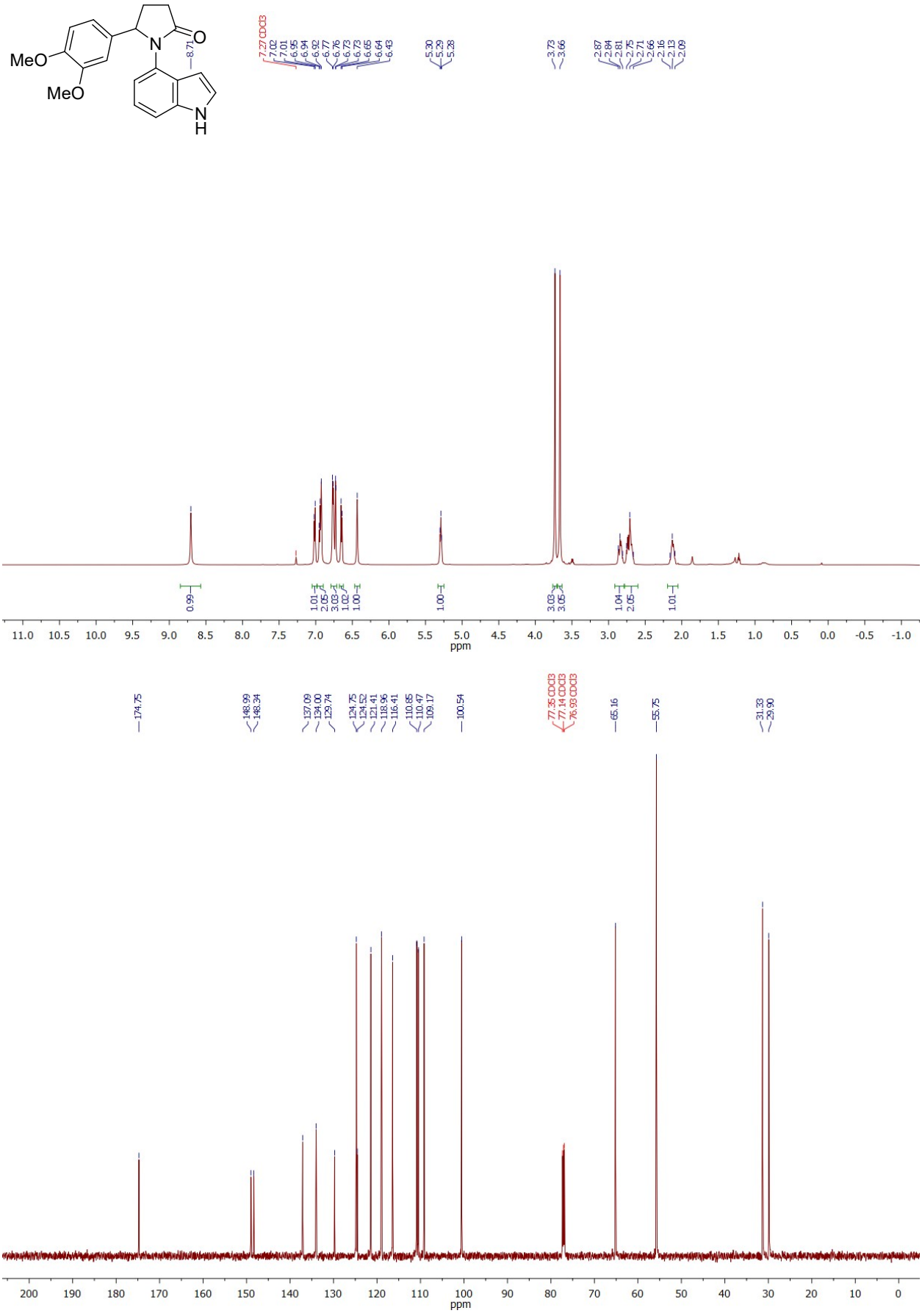
Quantitative analysis of compound **1a** purity

Step 1	
Step 1	$\boldsymbol{m_s}$ = 22.7 mg, $\boldsymbol{m_{IC}}$ = 23.4 mg, $\boldsymbol{P_{IC}}$ = 99.9%
Step 2	$\boldsymbol{Int_t}$ = 1.126, $\boldsymbol{n_t}$ = 1
Step 3	$\boldsymbol{Int_{IC}}$ = 52.327, $\boldsymbol{n_{IC}}$ = 18
Step 4	$\boldsymbol{MW_t}$ = 387.43 g/mol, $\boldsymbol{MW_{IC}}$ = 162.42 g/mol
Step 5	$P\,[\%] = \frac{n^{IC} \cdot Int^{t} \cdot MW^{t} \cdot [m^{IC} \cdot P^{IC}]}{n^{t} \cdot Int^{IC} \cdot MW^{IC} \cdot m^{s}} \cdot 100 = 95.2\%$

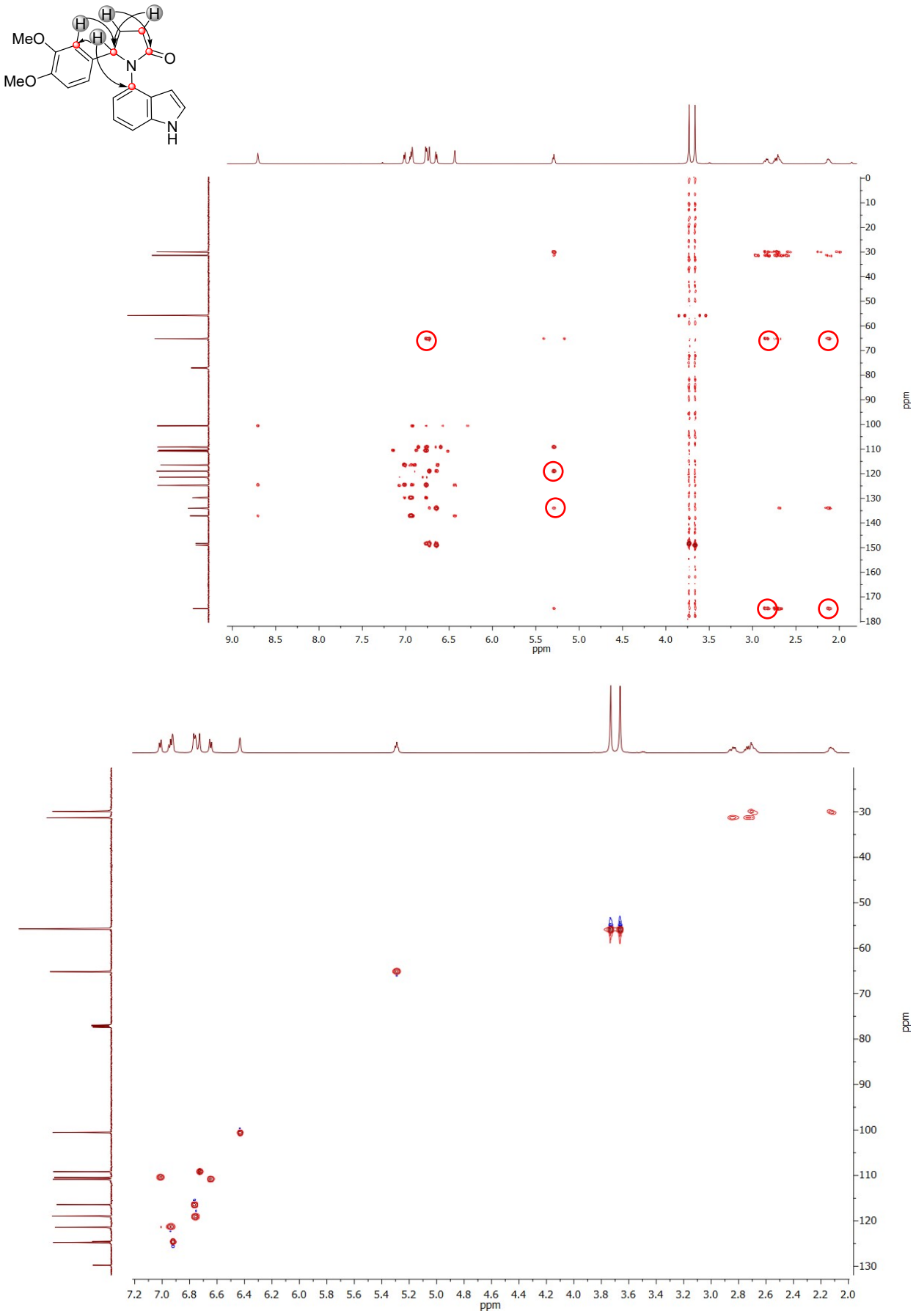
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **1b**



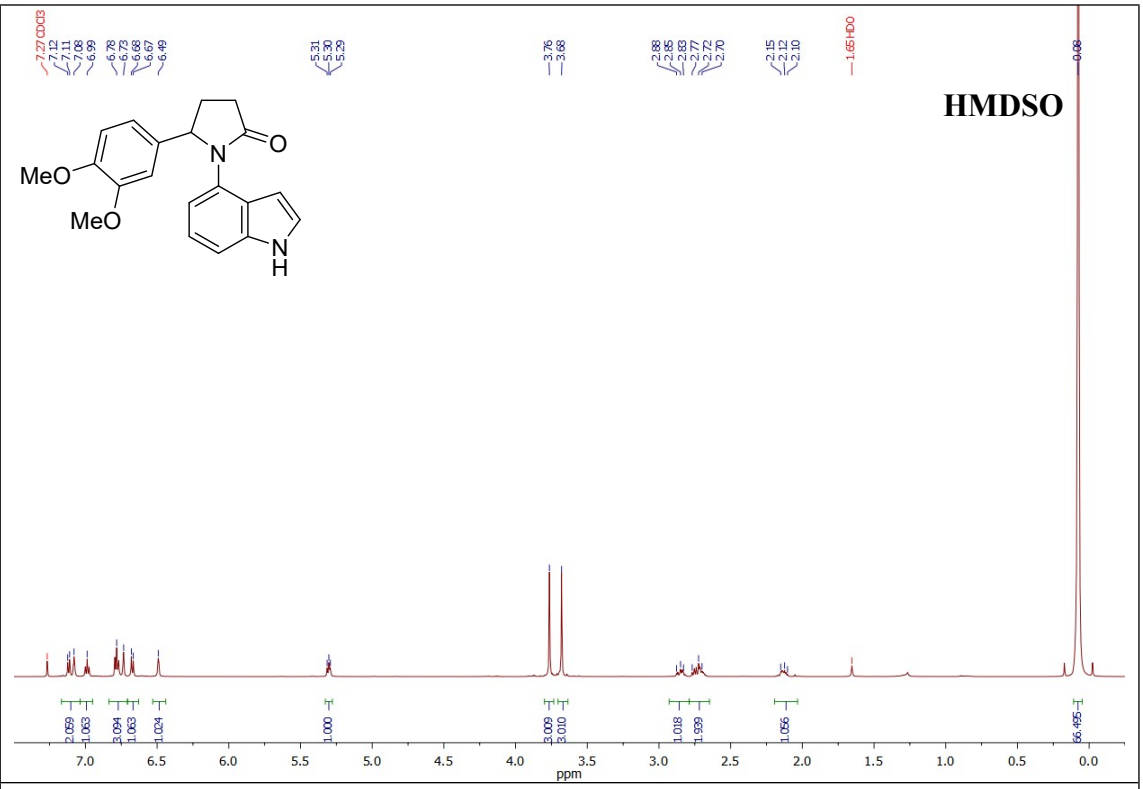
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **1d**



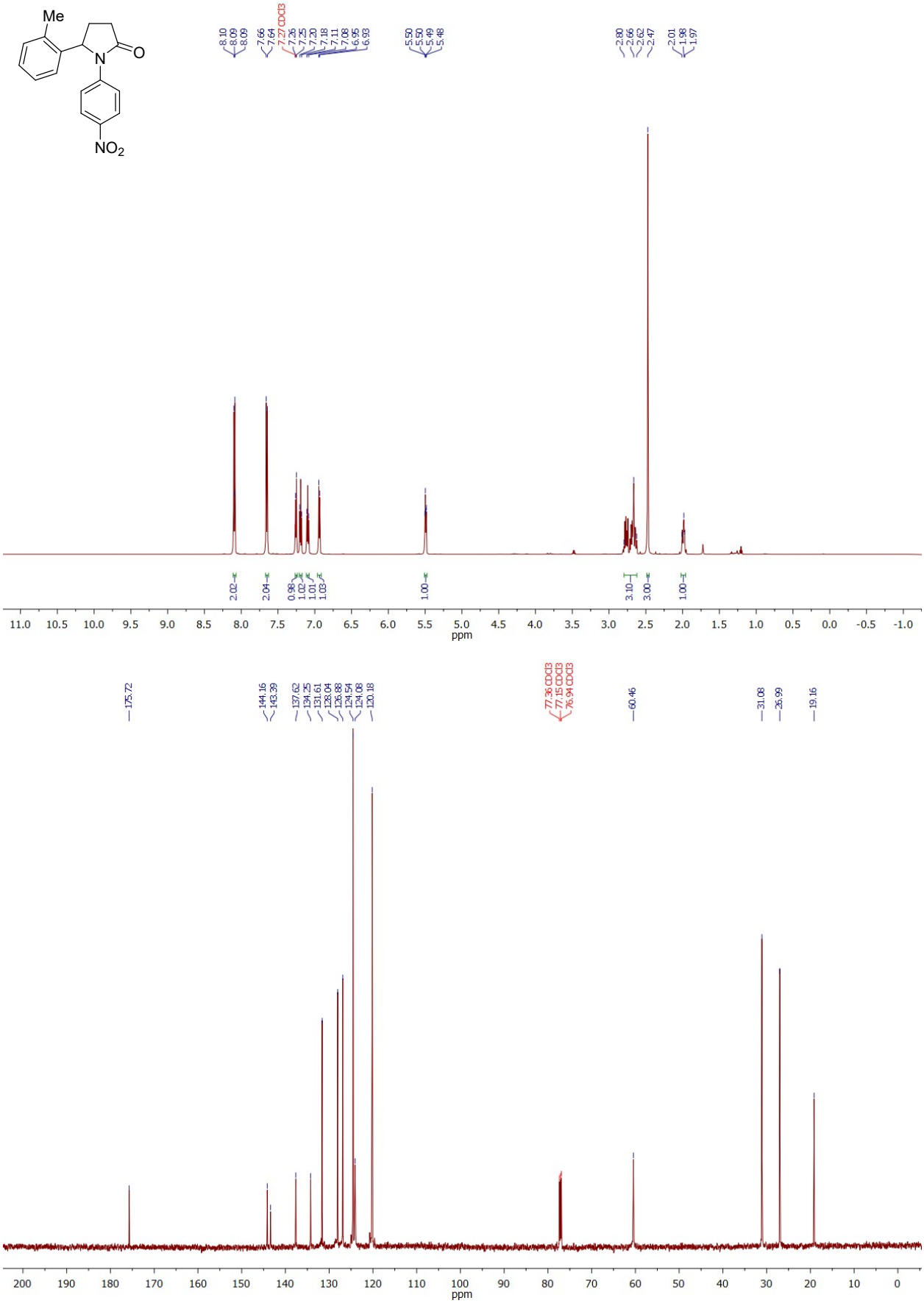
^{1}H-^{13}C HMBC ($CDCl_3$) and ^{1}H-^{13}C HSQC ($CDCl_3$) spectra of **1d**



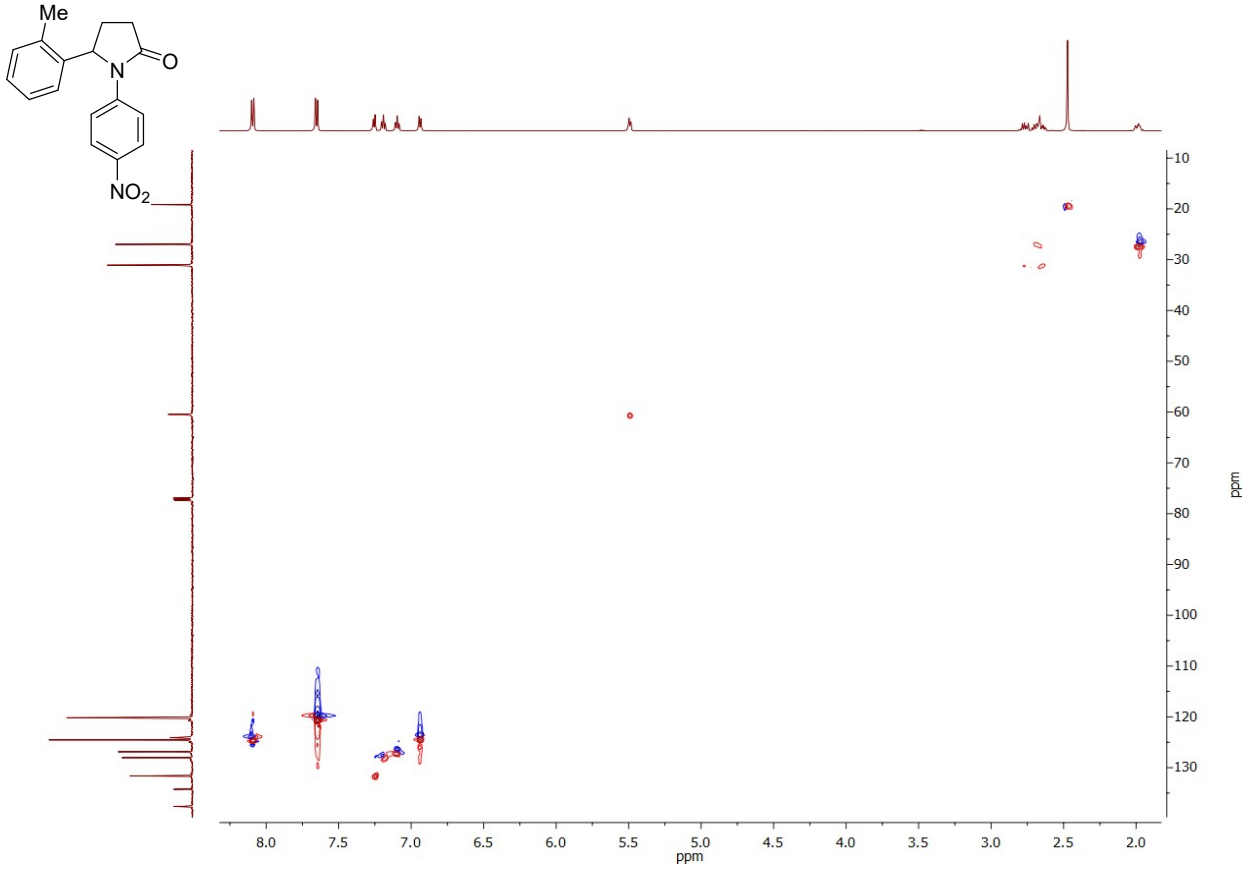
Quantitative analysis of compound **1d** purity

Step 1	
Step 1	$\boldsymbol{m_s}$ = 11.6 mg, $\boldsymbol{m_{IC}}$ = 19.3 mg, $\boldsymbol{P_{IC}}$ = 99.9%
Step 2	$\boldsymbol{Int_t}$ = 1.02, $\boldsymbol{n_t}$ = 1
Step 3	$\boldsymbol{Int_{IC}}$ = 66.495, $\boldsymbol{n_{IC}}$ = 18
Step 4	$\boldsymbol{MW_t}$ = 336.39 g/mol, $\boldsymbol{MW_{IC}}$ = 162.42 g/mol
Step 5	$P\,[\%] = \frac{n_{IC} \cdot Int_t \cdot MW_t \cdot [m_{IC} \cdot P_{IC}]}{n_t \cdot Int_{IC} \cdot MW_{IC} \cdot m_s} \cdot 100 = 95.1\%$

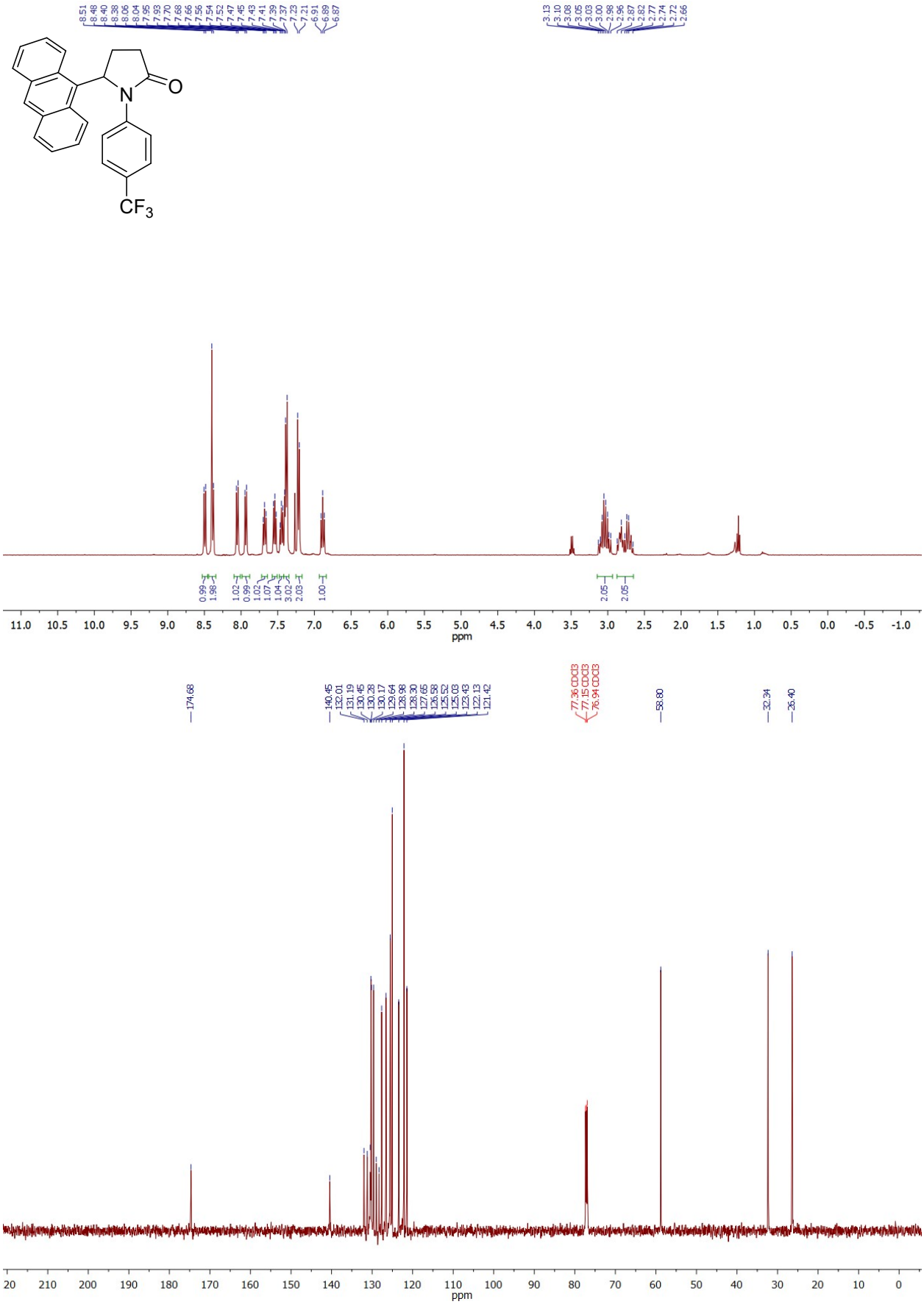
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **1e**



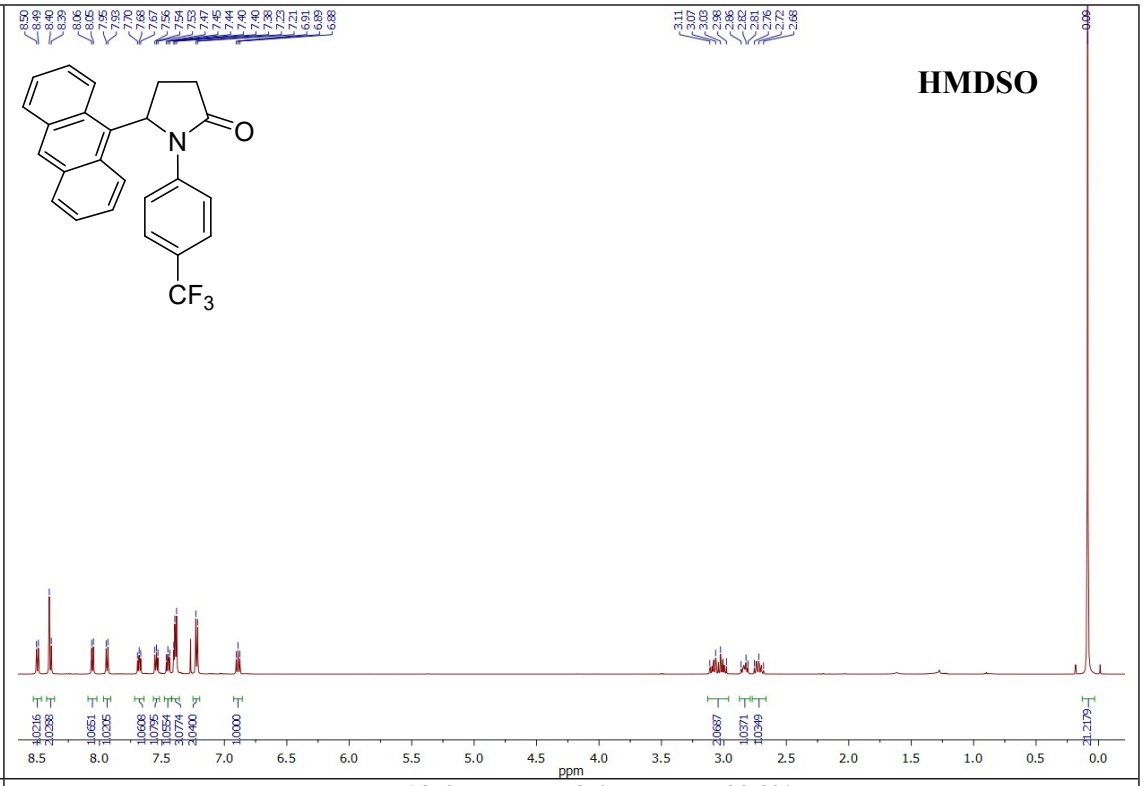
^{1}H-^{13}C HSQC ($CDCl_3$) spectrum of **1e**



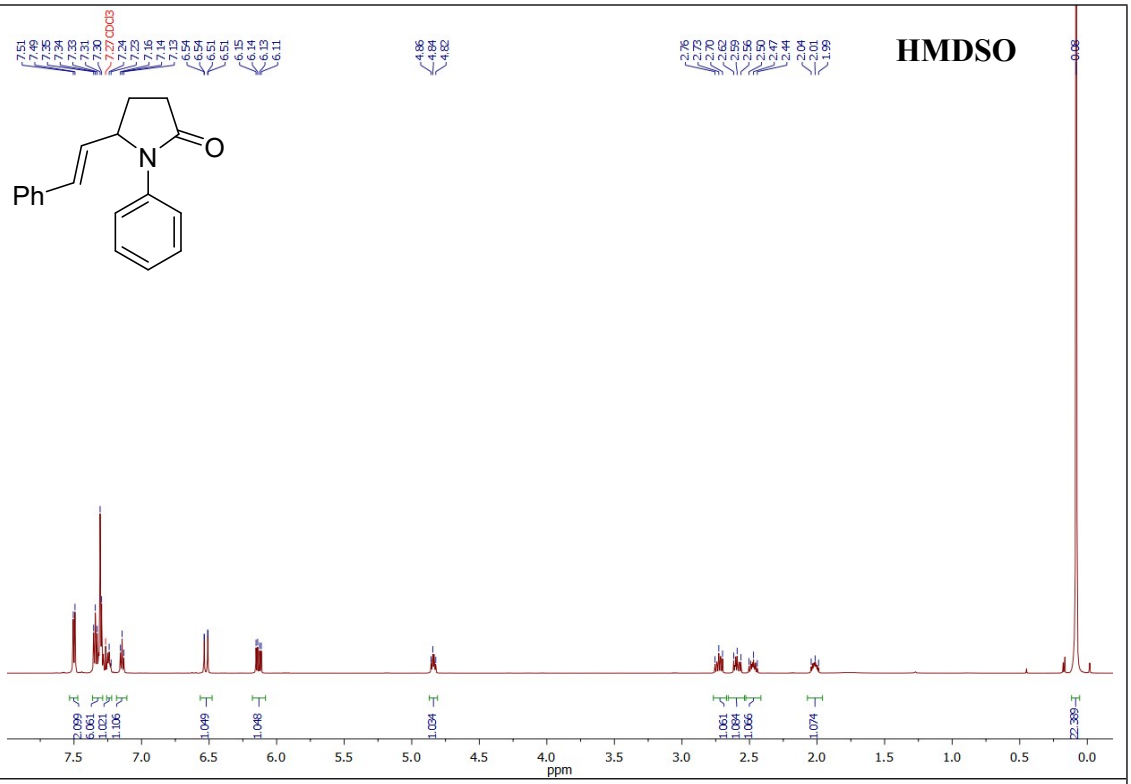
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **1f**



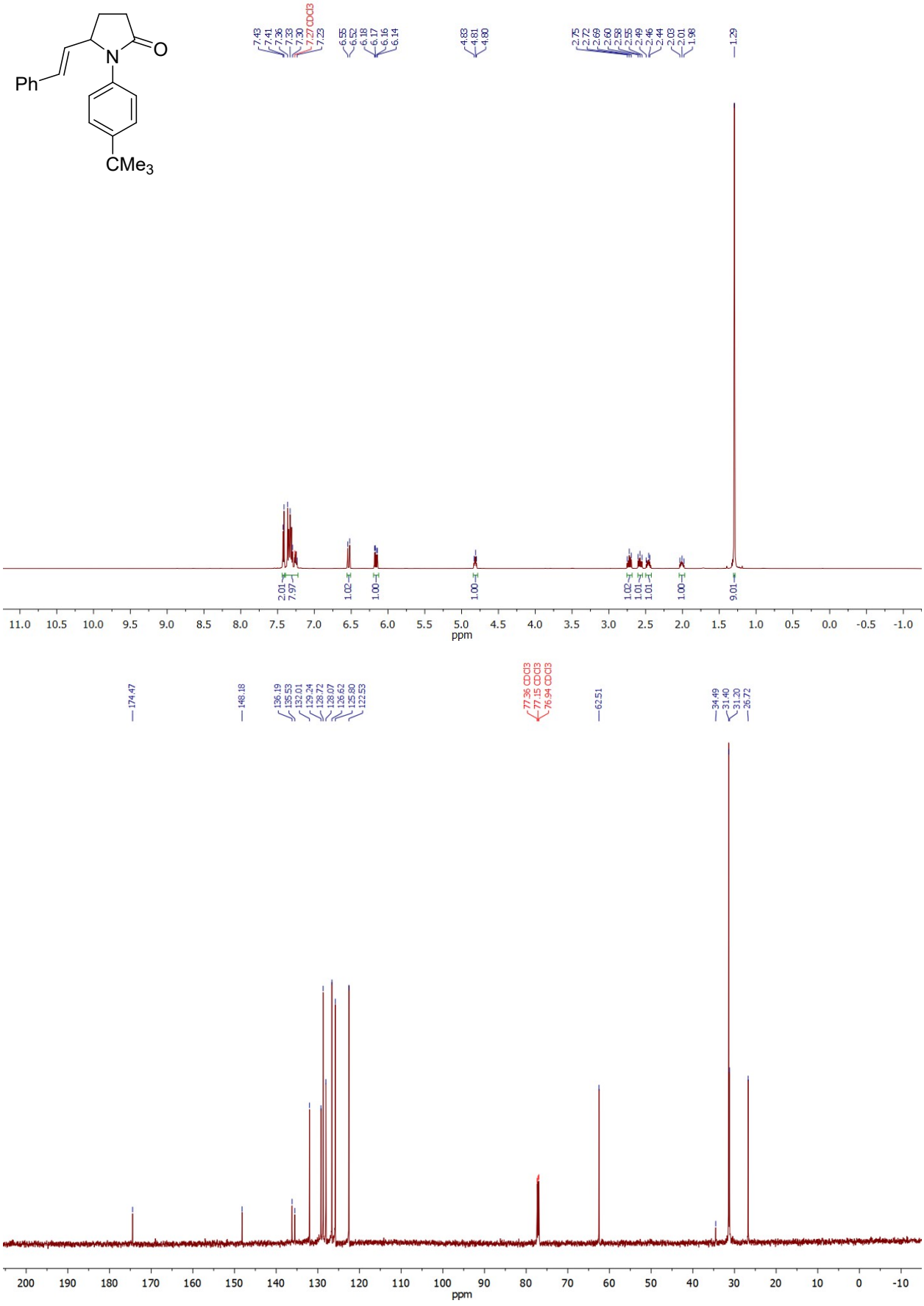
Quantitative analysis of compound **1f** purity

Step 1	
Step 1	$\boldsymbol{m_s}$ = 18.6 mg, $\boldsymbol{m_{IC}}$ = 8.4 mg, $\boldsymbol{P_{IC}}$ = 99.9%
Step 2	$\boldsymbol{Int_t}$ = 1.03, $\boldsymbol{n_t}$ = 1
Step 3	$\boldsymbol{Int_{IC}}$ = 21.2179, $\boldsymbol{n_{IC}}$ = 18
Step 4	$\boldsymbol{MW_t}$ = 405.42 g/mol, $\boldsymbol{MW_{IC}}$ = 162.42 g/mol
Step 5	$P\,[\%] = \frac{n^{IC} \cdot Int^{t} \cdot MW^{t} \cdot [m^{IC} \cdot P^{IC}]}{n^{t} \cdot Int^{IC} \cdot MW^{IC} \cdot m^{s}} \cdot 100 = 98.4\%$

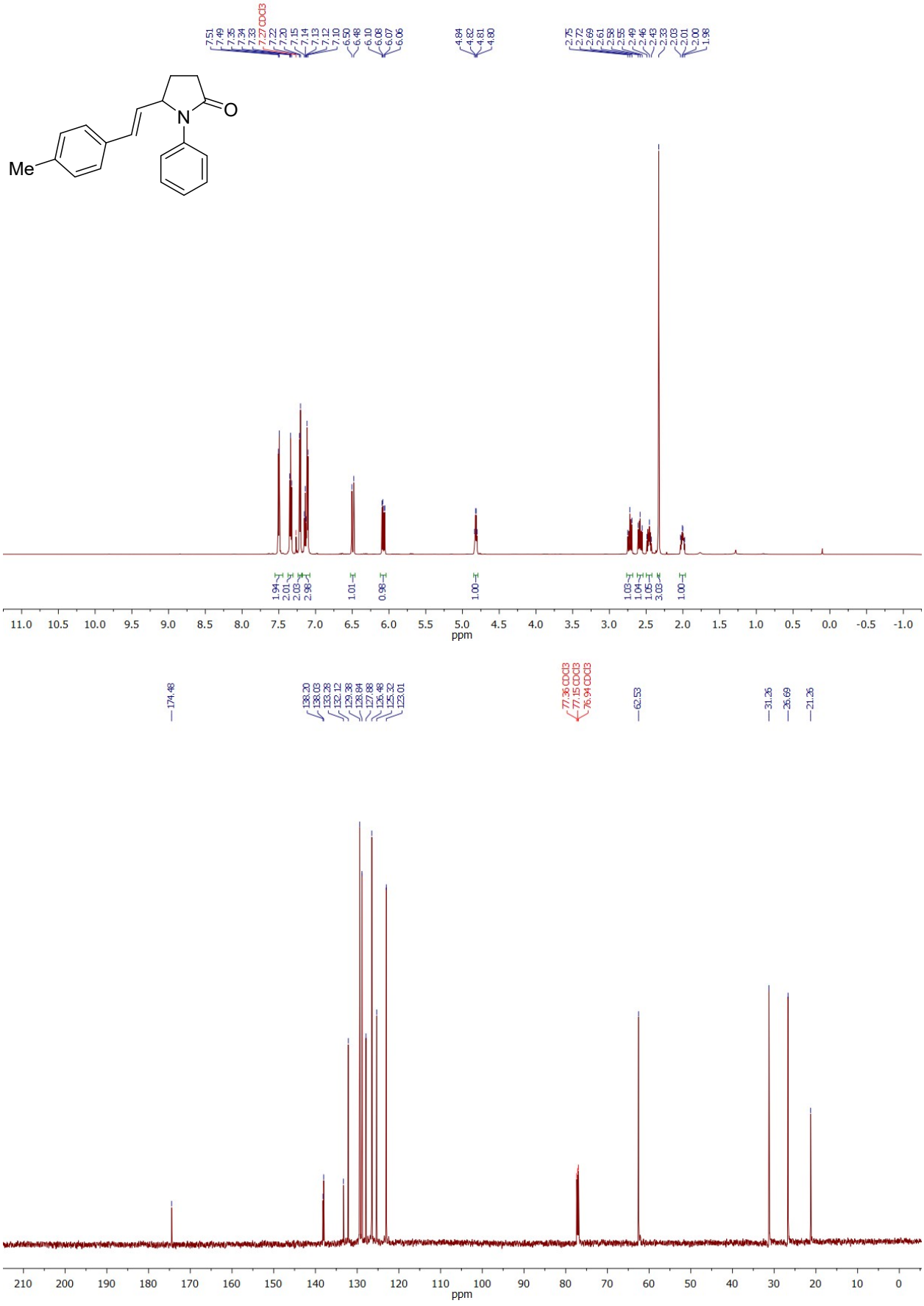
Quantitative analysis of compound **2a** purity

Step 1	
Step 1	$\boldsymbol{m_s}$ = 15.6 mg, $\boldsymbol{m_{IC}}$ = 11.4 mg, $\boldsymbol{P_{IC}}$ = 99.9%
Step 2	$\boldsymbol{Int_t}$ = 1.04, $\boldsymbol{n_t}$ = 1
Step 3	$\boldsymbol{Int_{IC}}$ = 22.389, $\boldsymbol{n_{IC}}$ = 18
Step 4	$\boldsymbol{MW_t}$ = 263.34 g/mol, $\boldsymbol{MW_{IC}}$ = 162.42 g/mol
Step 5	$P\,[\%] = \frac{n^{IC} \cdot Int^{t} \cdot MW^{t} \cdot [m^{IC} \cdot P^{IC}]}{n^{t} \cdot Int^{IC} \cdot MW^{IC} \cdot m^{s}} \cdot 100 = 99.0\%$

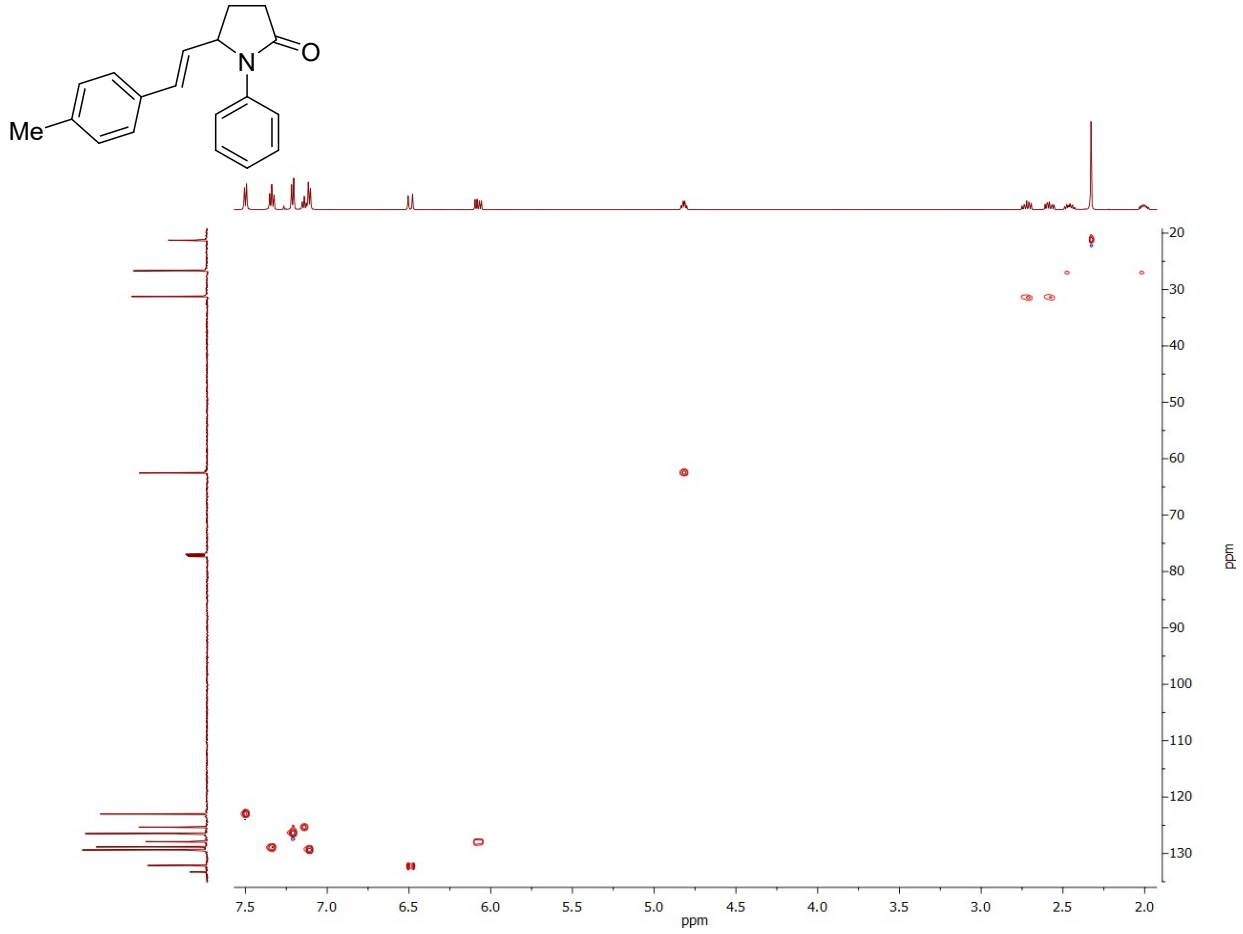
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **2b**



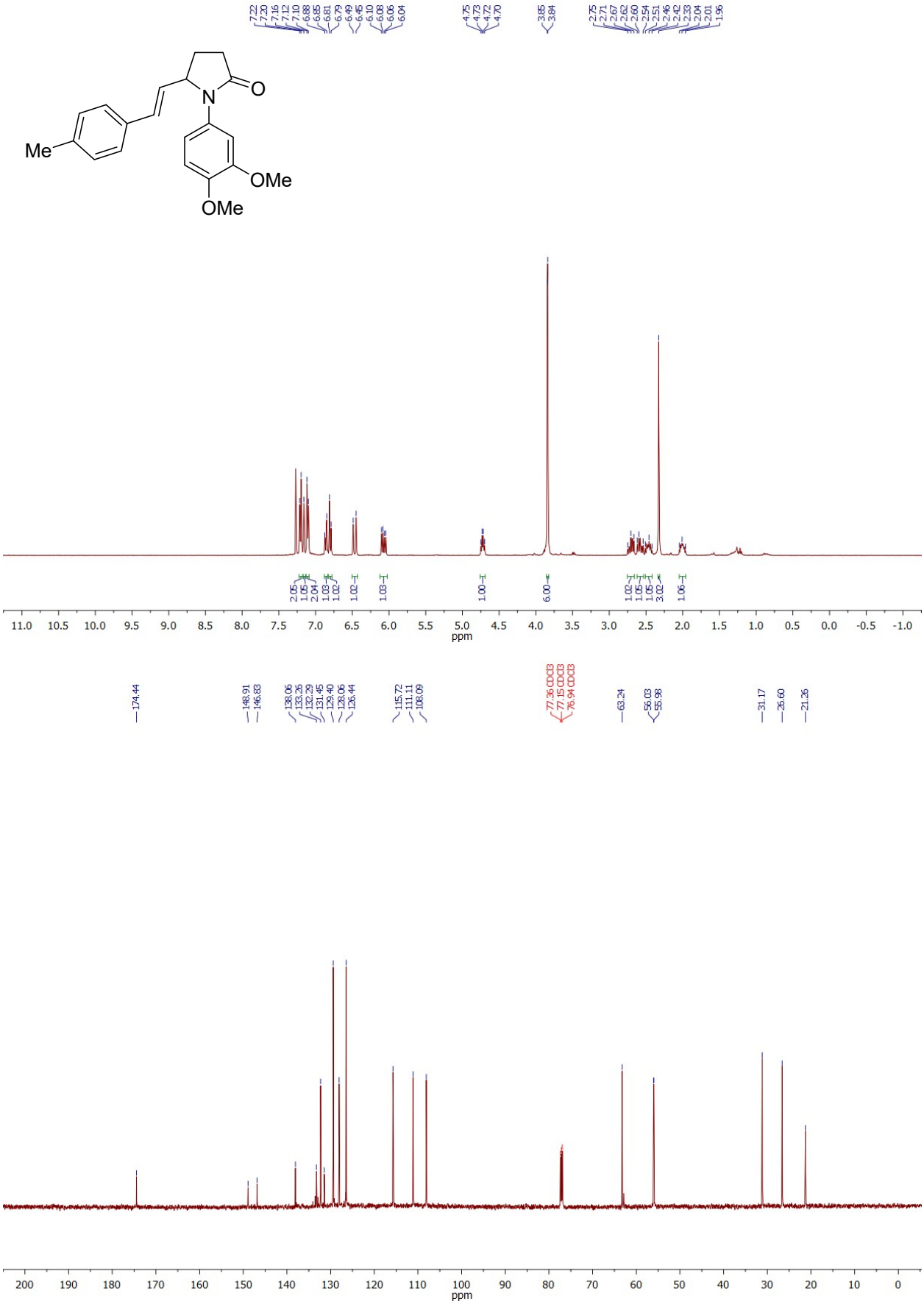
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **2c**



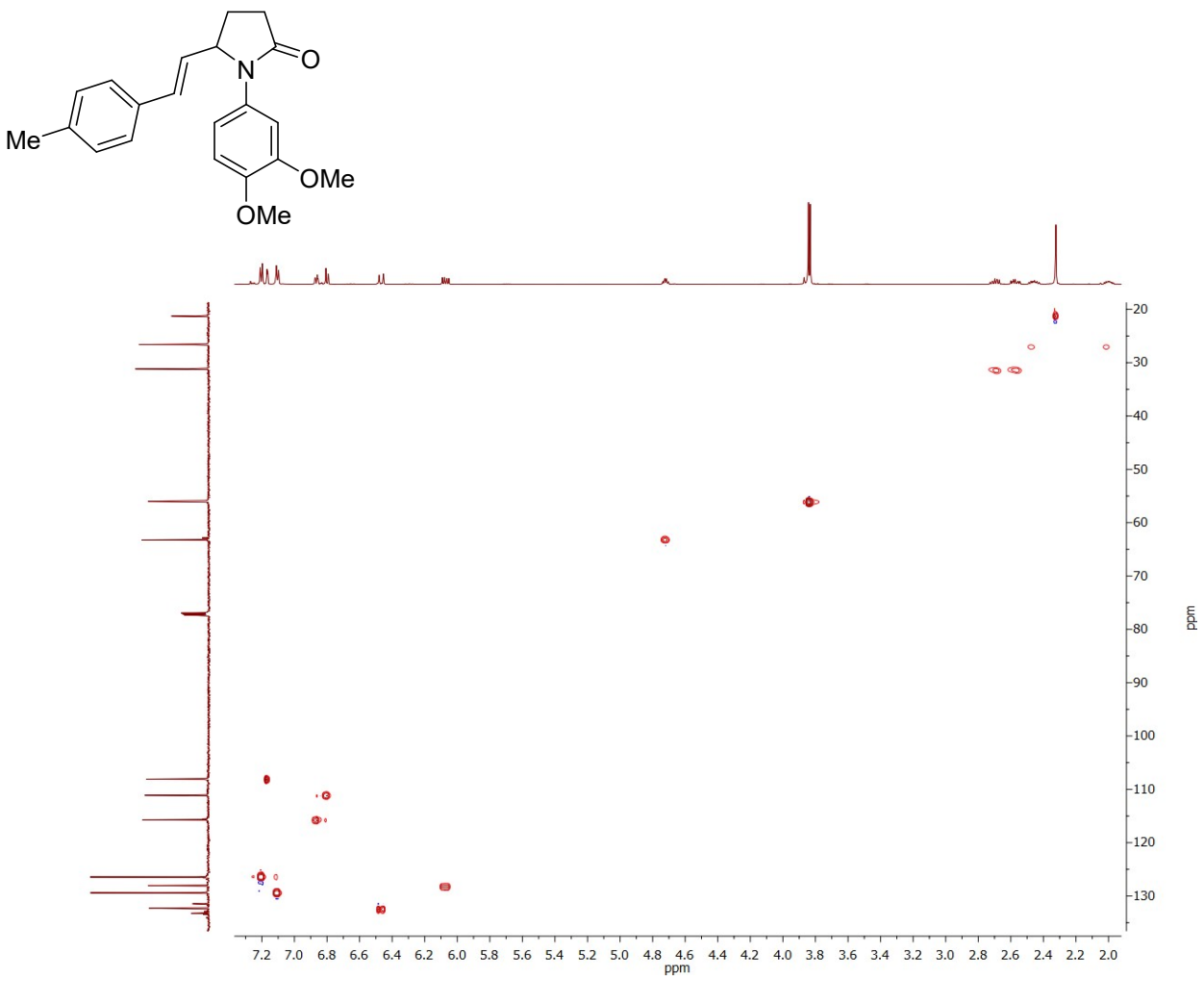
^{1}H-^{13}C HSQC ($CDCl_3$) spectrum of **2c**



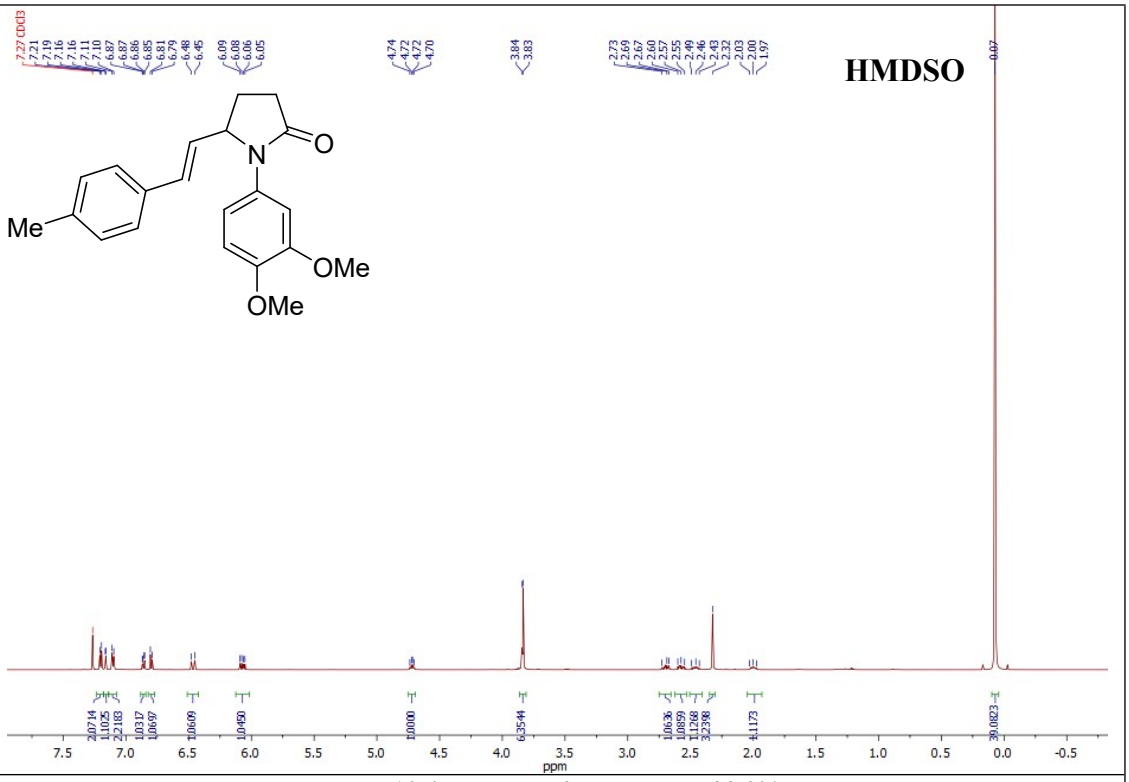
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **2d**



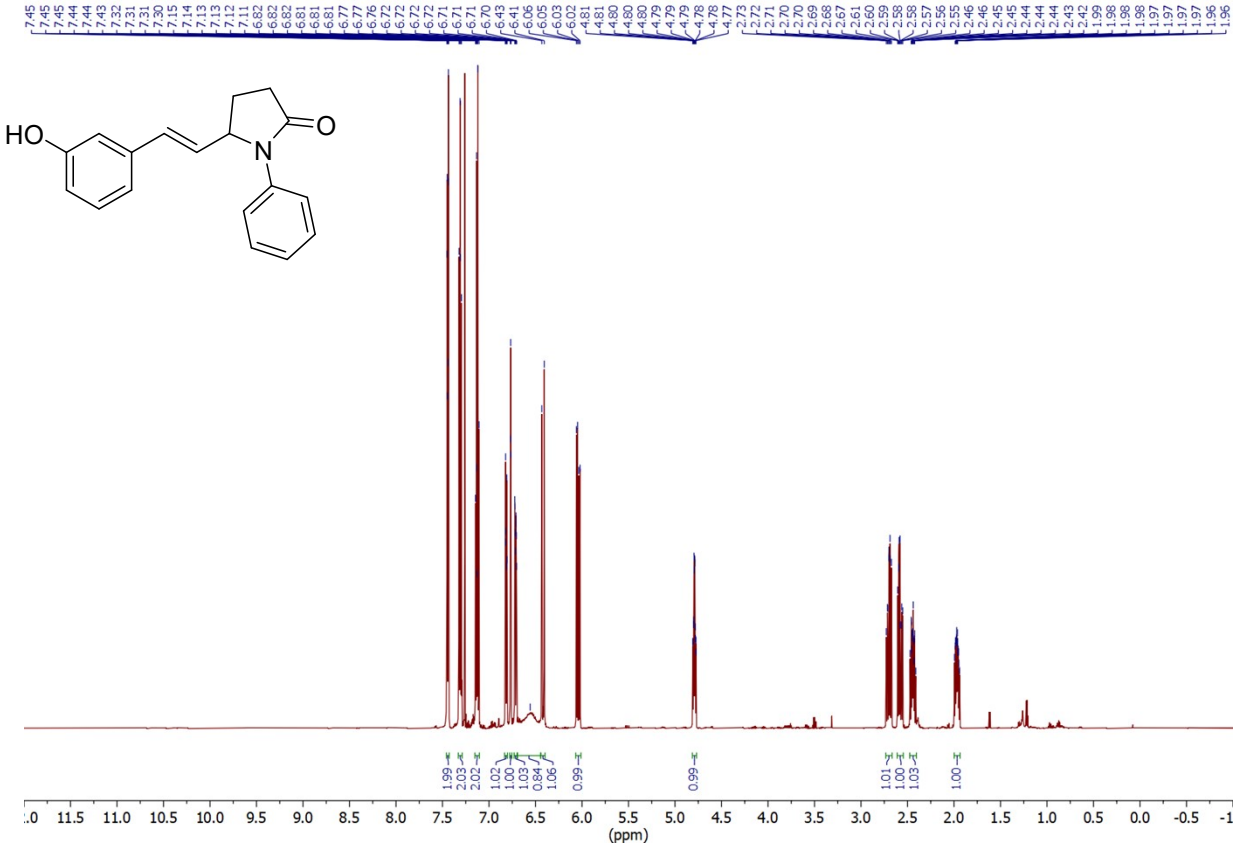
^{1}H-^{13}C HSQC ($CDCl_3$) spectrum of **2d**

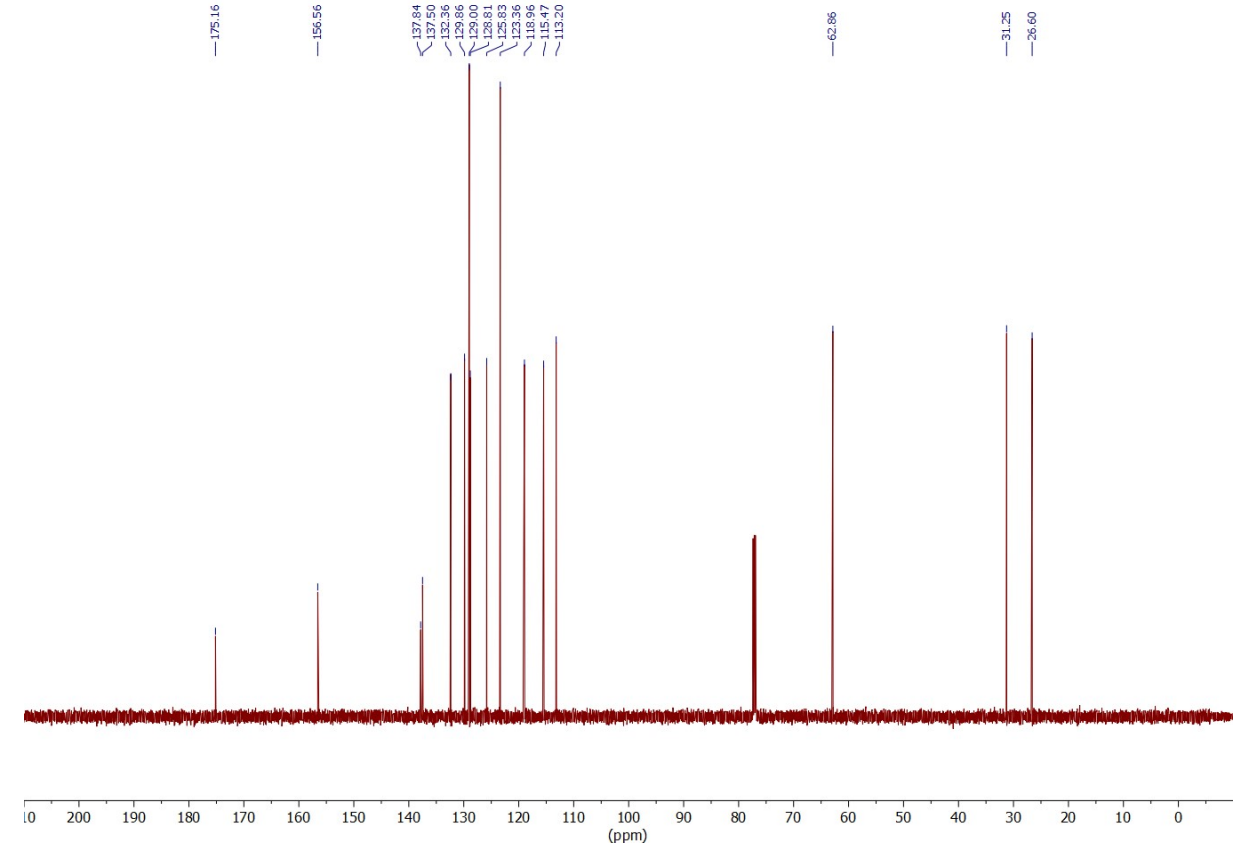


Quantitative analysis of compound **2d** purity

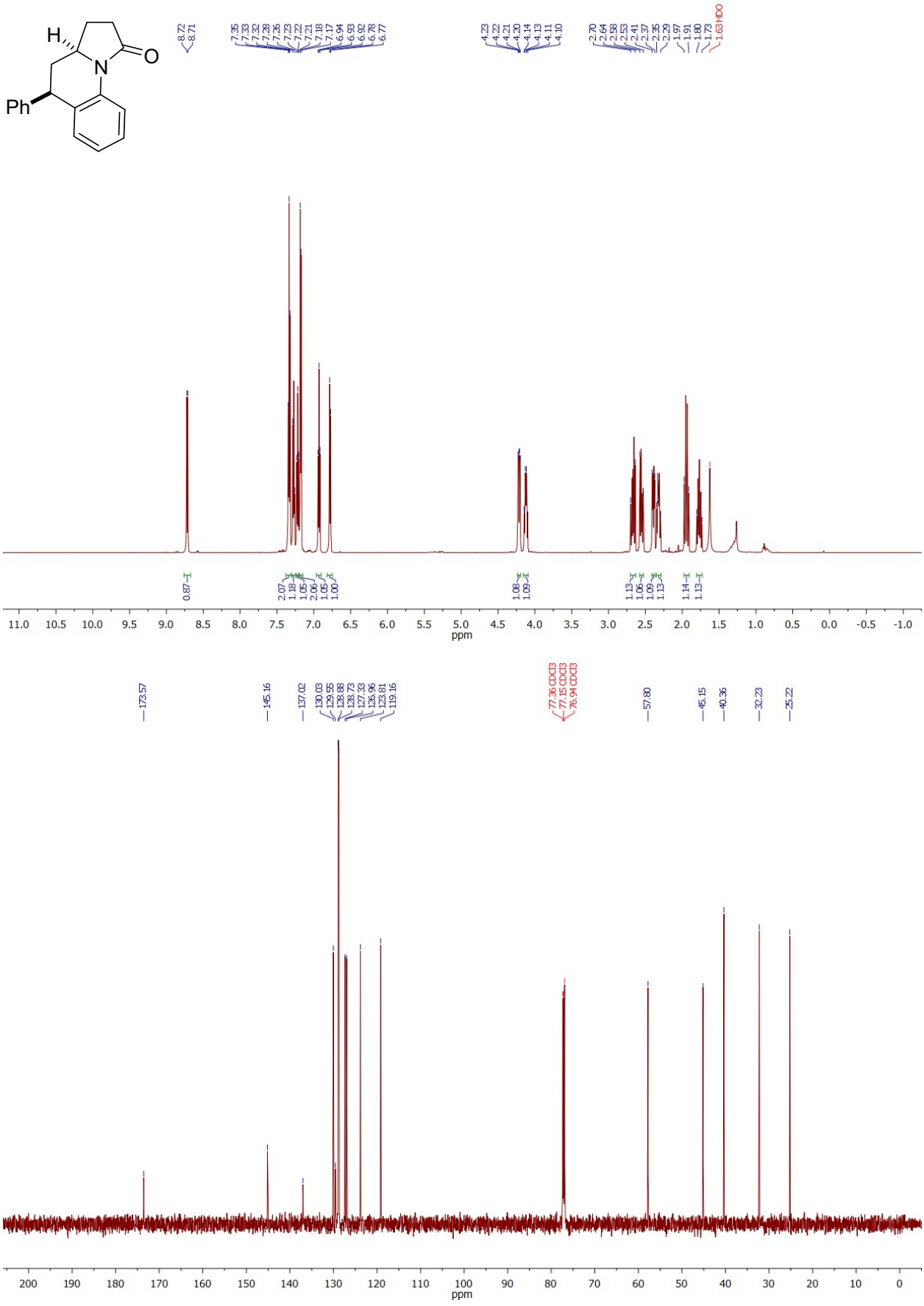
Step 1	
Step 1	$\boldsymbol{m_s}$ = 10.4 mg, $\boldsymbol{m_{IC}}$ = 9.7 mg, $\boldsymbol{P_{IC}}$ = 99.9%
Step 2	$\boldsymbol{Int_t}$ = 1.07, $\boldsymbol{n_t}$ = 1
Step 3	$\boldsymbol{Int_{IC}}$ = 39.0823, $\boldsymbol{n_{IC}}$ = 18
Step 4	$\boldsymbol{MW_t}$ = 337.42 g/mol, $\boldsymbol{MW_{IC}}$ = 162.42 g/mol
Step 5	$P\,[\%] = \frac{n_{IC} \cdot Int_t \cdot MW_t \cdot [m_{IC} \cdot P_{IC}]}{n_t \cdot Int_{IC} \cdot MW_{IC} \cdot m_s} \cdot 100 = 95.3\%$

^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **2e**

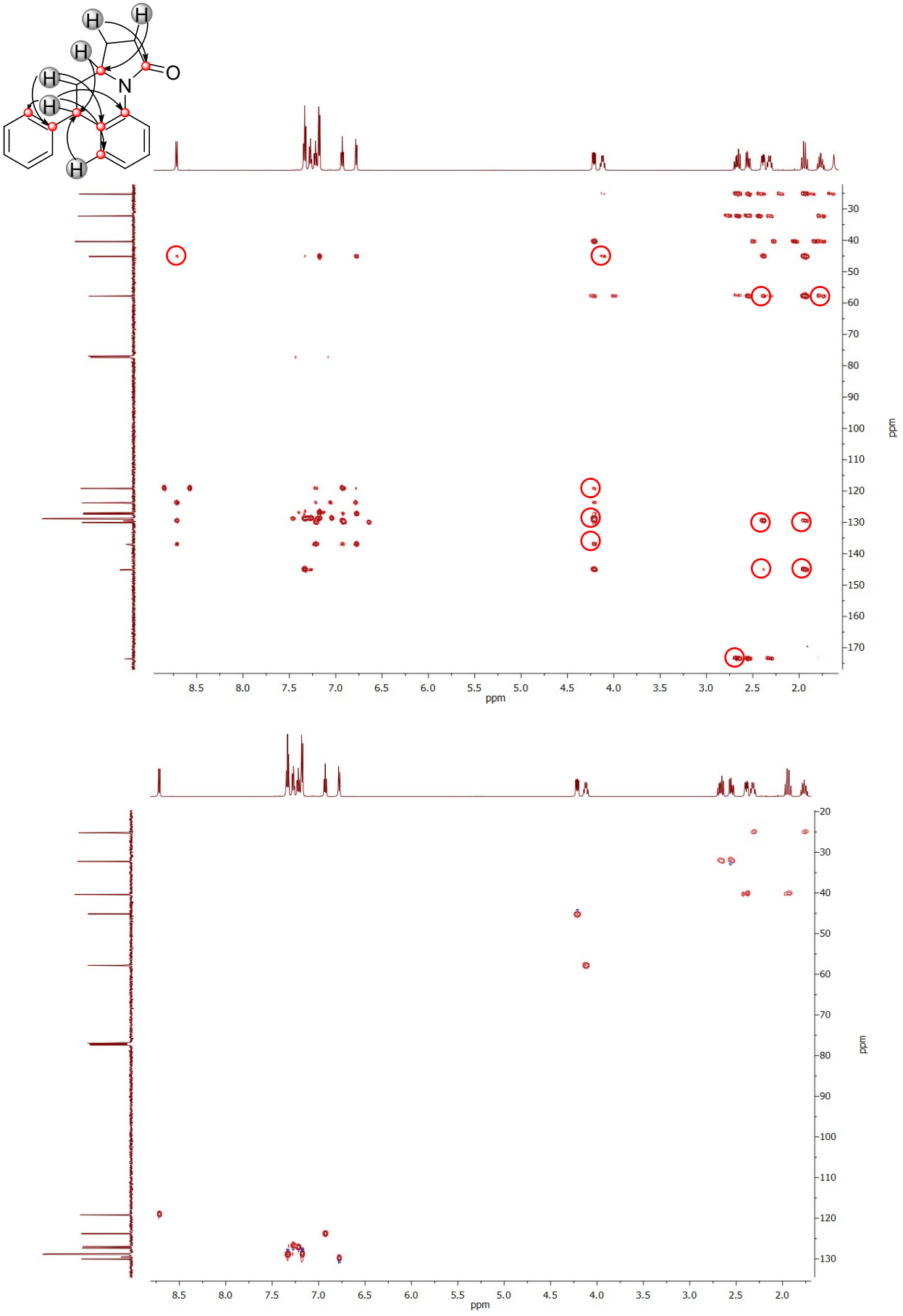




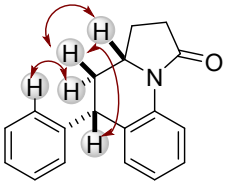
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **3a**

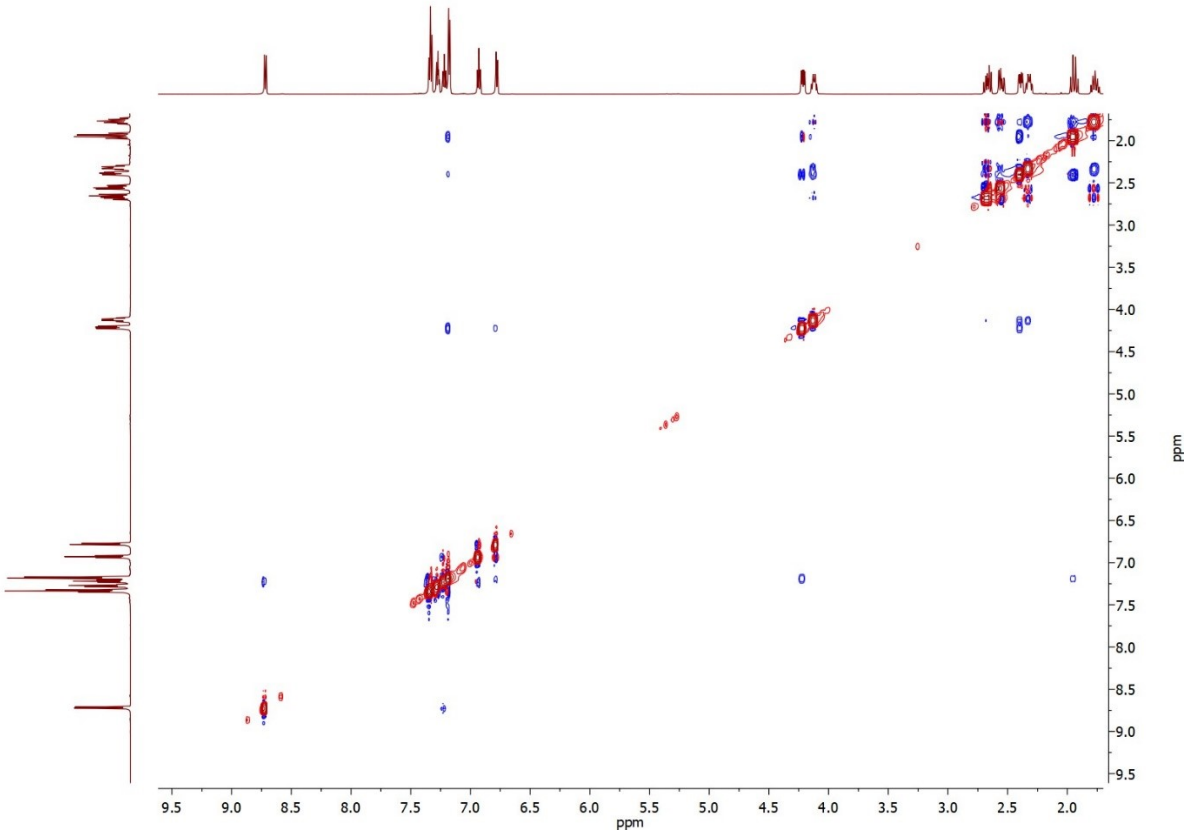


^{1}H-^{13}C HMBC ($CDCl_3$) and ^{1}H-^{13}C HSQC ($CDCl_3$) spectra of **3a**

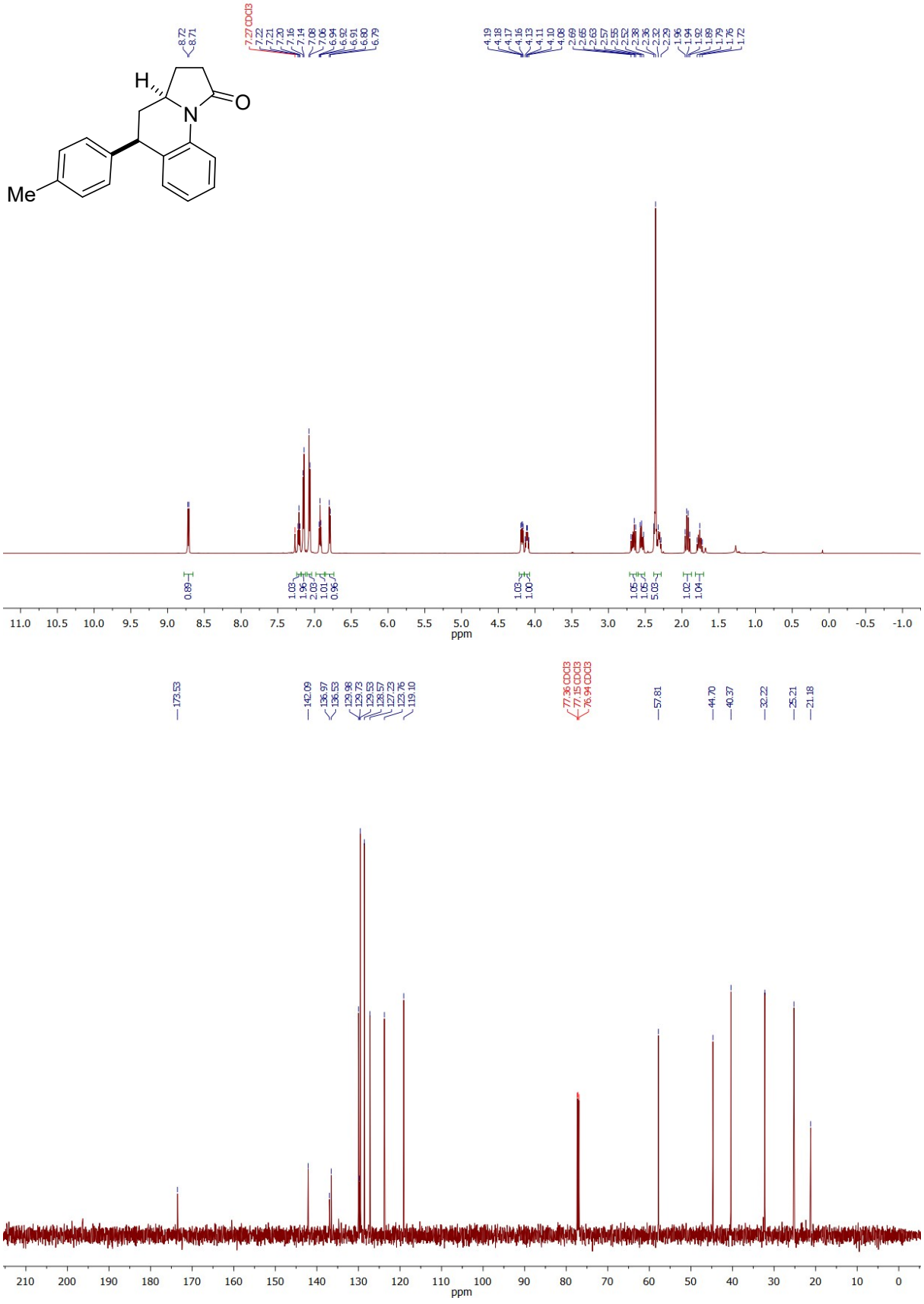


^{1}H-^{1}H NOESY ($CDCl_3$) spectrum of **3a**

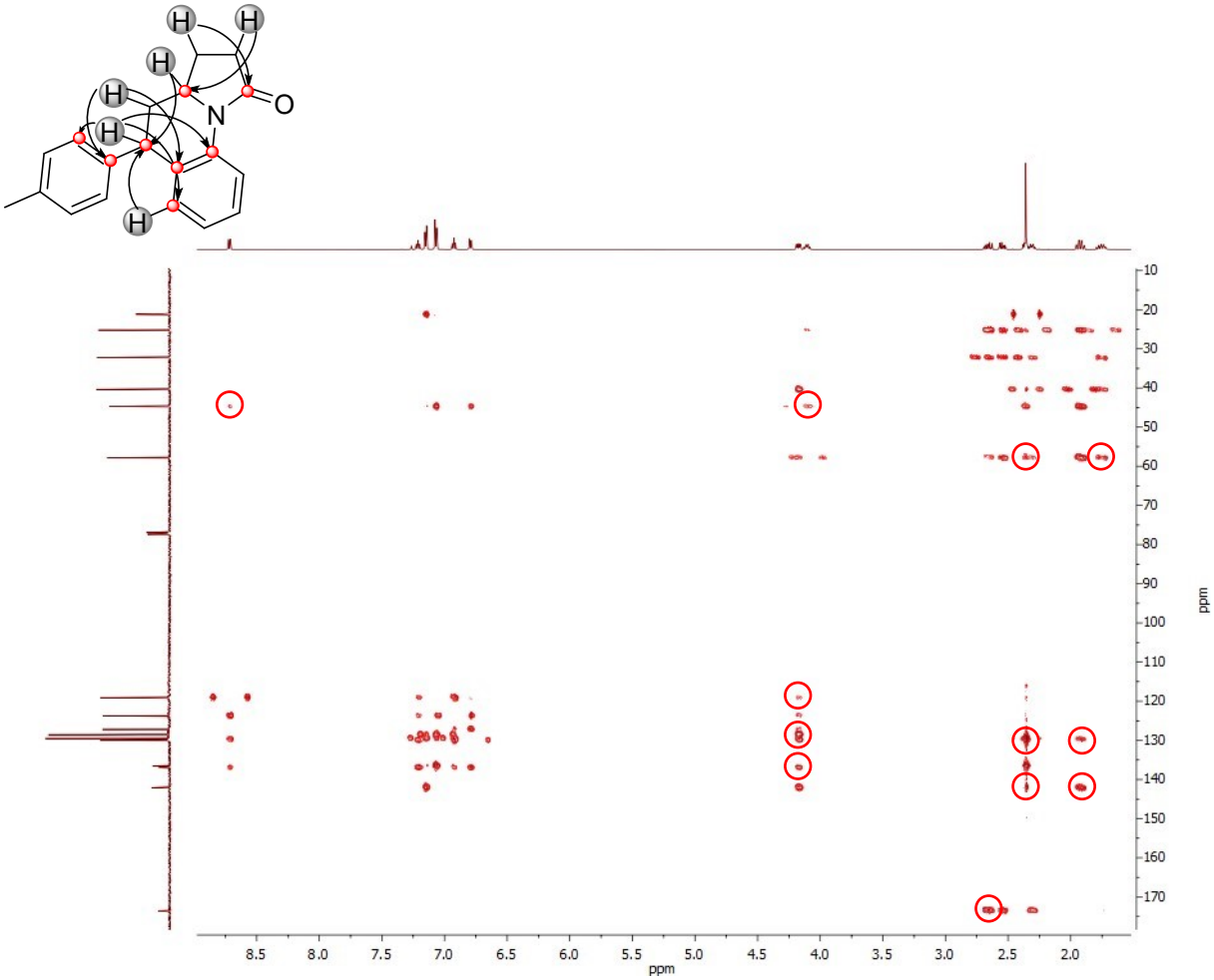


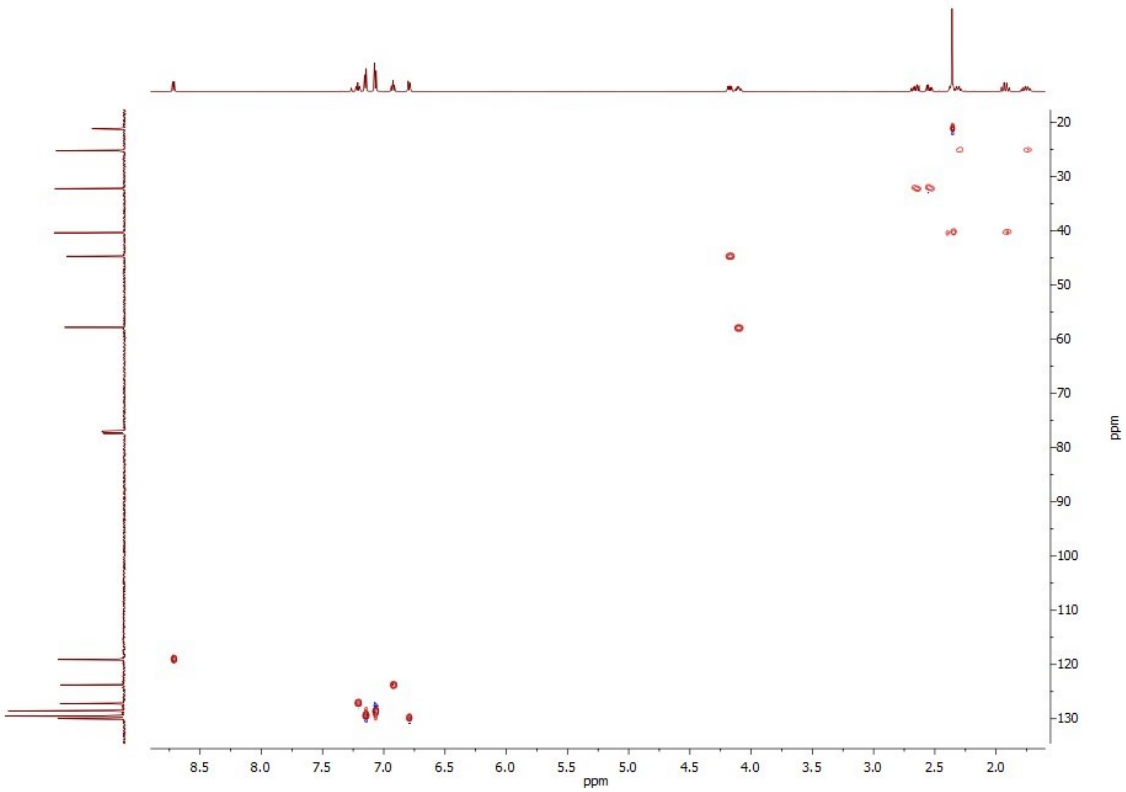


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra of **3b**

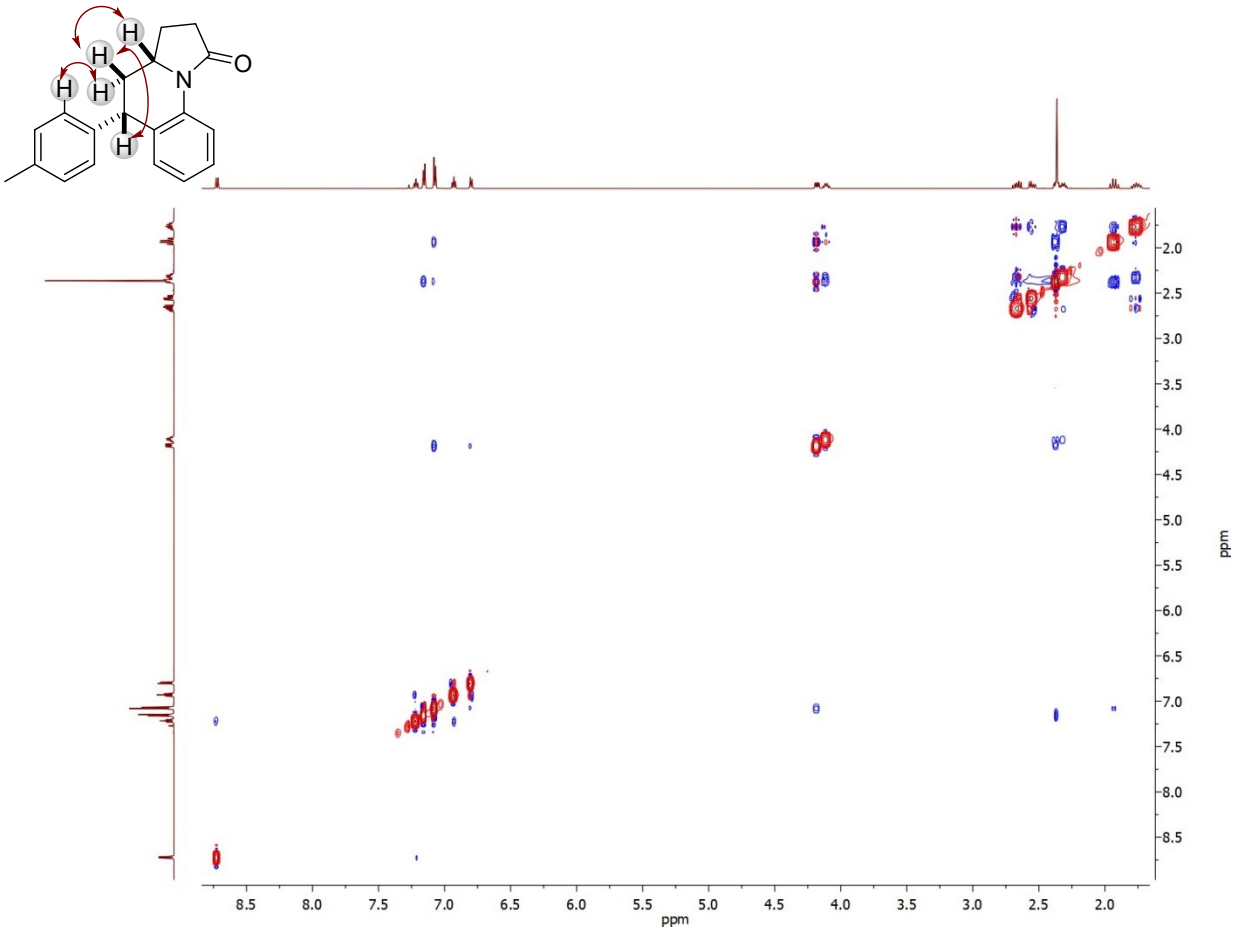


^{1}H-^{13}C HMBC ($CDCl_3$) and ^{1}H-^{13}C HSQC ($CDCl_3$) spectra of **3b**

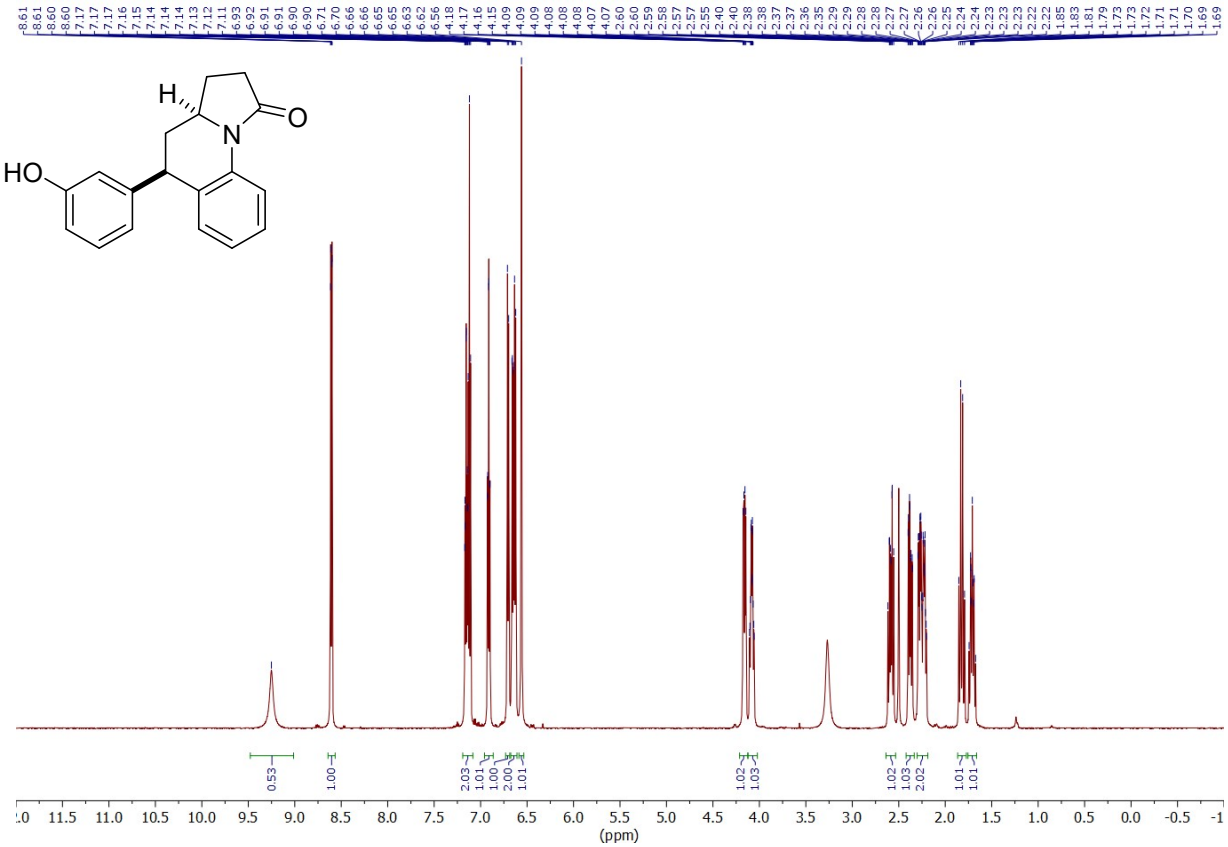


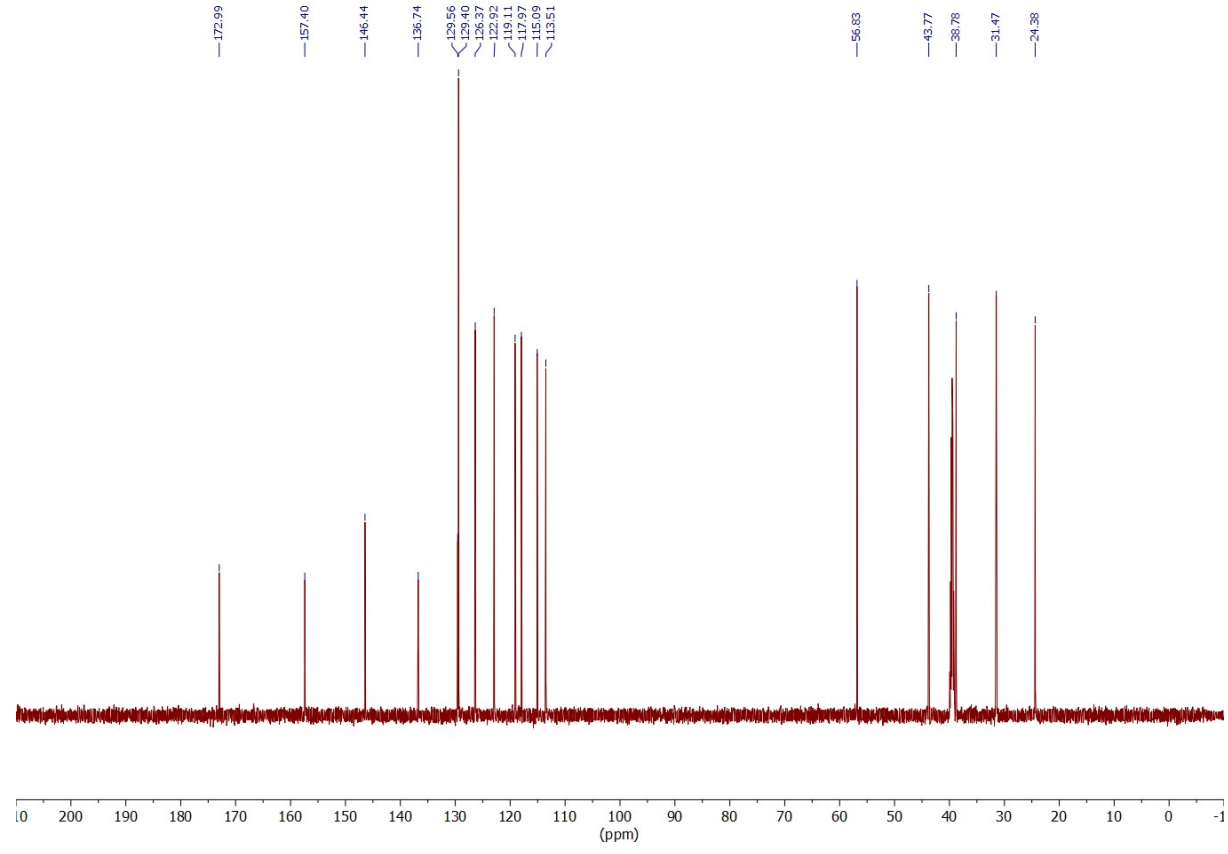


^{1}H-^{1}H NOESY ($CDCl_3$) spectrum of **3b**

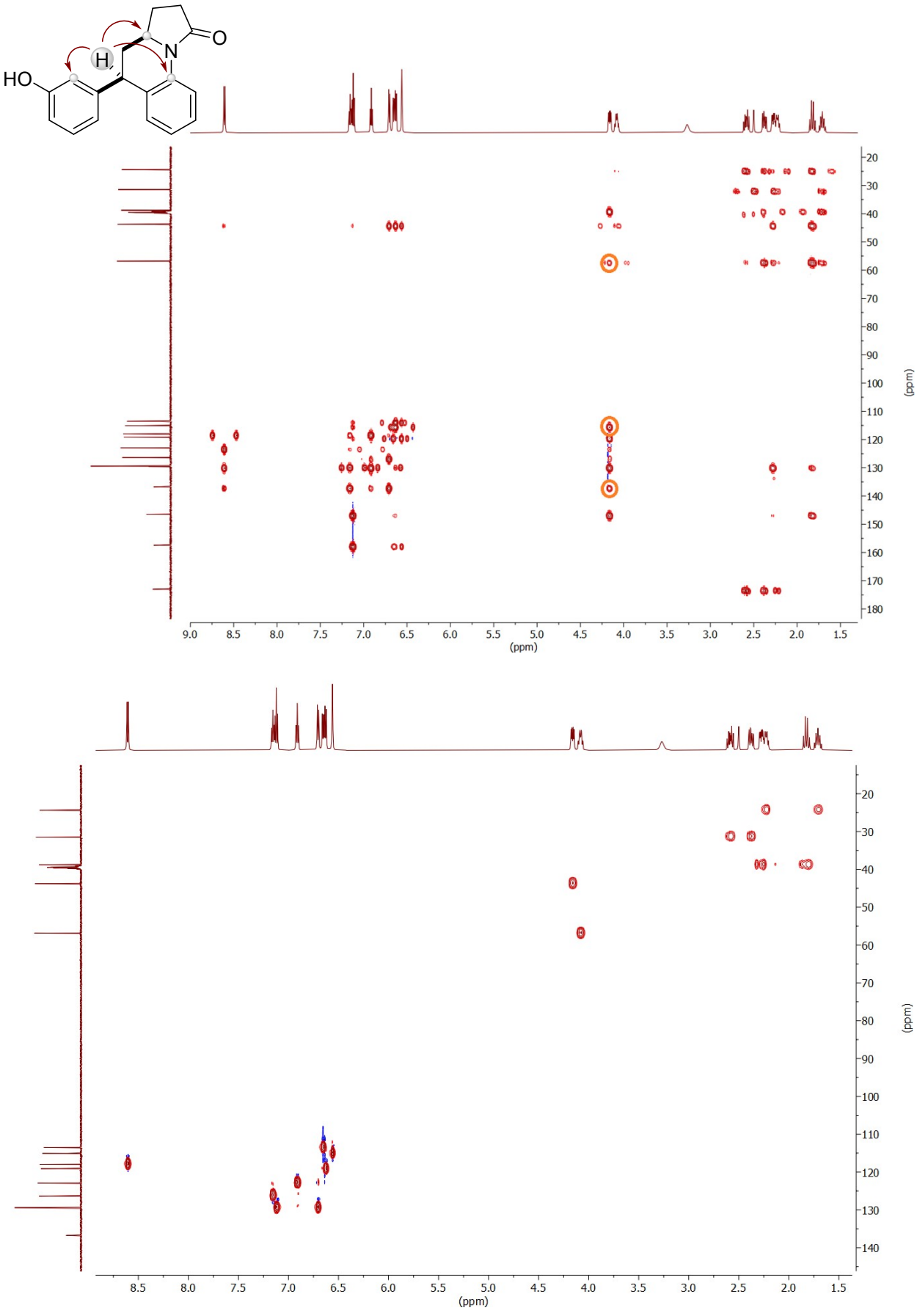


^{1}H NMR (600 MHz, DMSO-d_6) and ^{13}C NMR (151 MHz, DMSO-d_6) spectra of **3c**

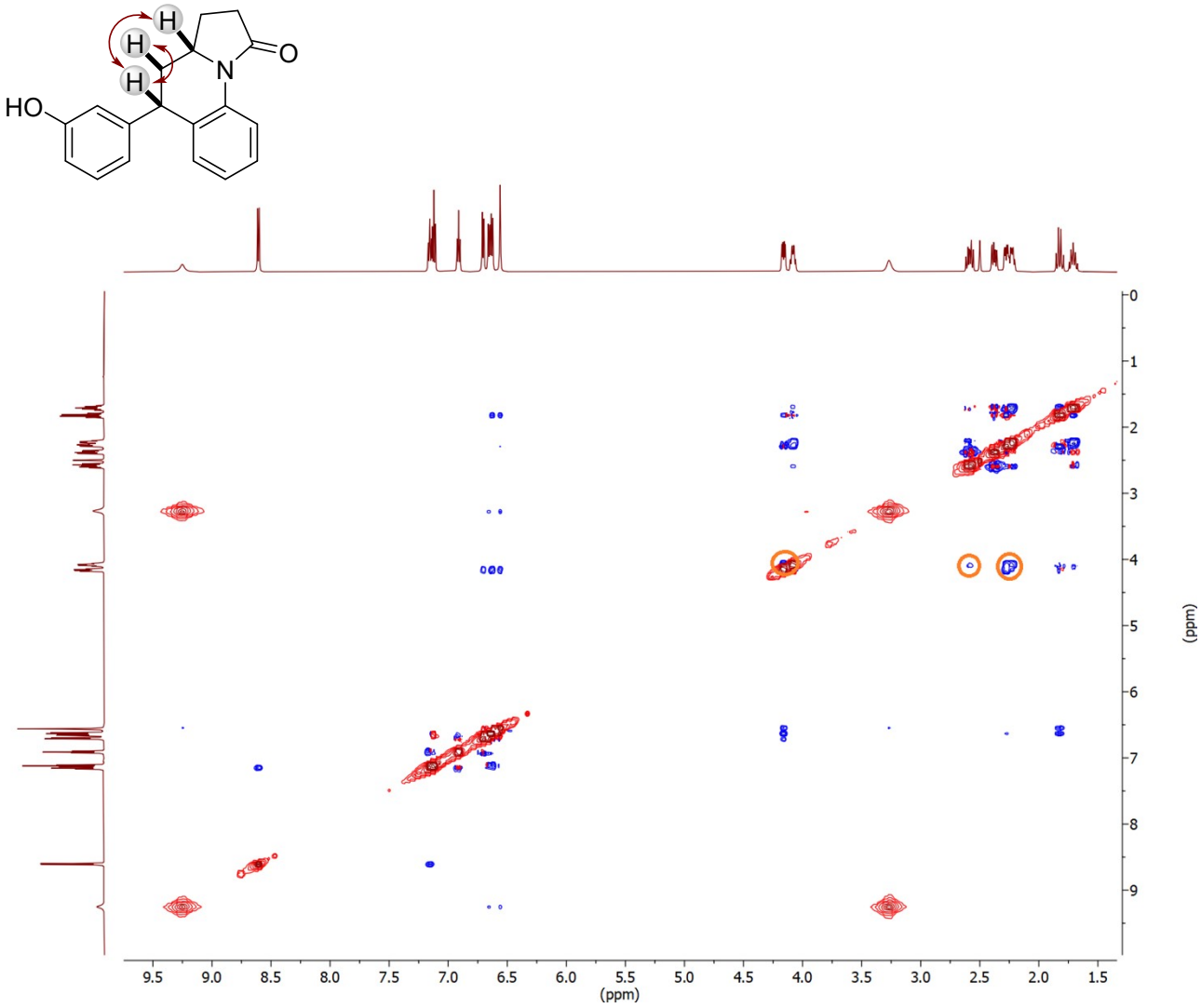




^{1}H-^{13}C HMBC (DMSO-d_6) and ^{1}H-^{13}C HSQC (DMSO-d_6) spectra of **3c**



^{1}H-^{1}H NOESY (DMSO-d_6) spectrum of **3c**



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