Supporting Information

Diastereoselective synthesis of functionalised indolizino[8,7-*b*]indoles by a lactamisation/*N*-acyliminium-cyclisation cascade of β-enamino diketones

Jeniffer do Nascimento Ascencio Camargo,[a] Karlos Eduardo Pianoski,[a] Arthur Antunes Ferrarezi,[a] Sidnei Moura,[b] Camila Botin Francisco,[c] Fernanda Andreia Rosa*[a]

[a]Laboratory for Synthesis of Heterocycles (SINTHET), Chemistry Department, State University of Maringá - UEM, Maringá, Paraná 87020-900, Brazil

[b]Laboratory of Biotechnology of Natural and Synthesis Products (LBIOP), Technology Department, Biotechnology Institute, University of Caxias do Sul, Caxias do Sul, Rio Grande do Sul, Brazil.

[c]Chemical and Physical Sciences Department, University of Toronto, Mississauga, Ontario, L5L 1C6, Canada.

*correspondent author: farosa@uem.br

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1. General Information

Reagents and Solvents

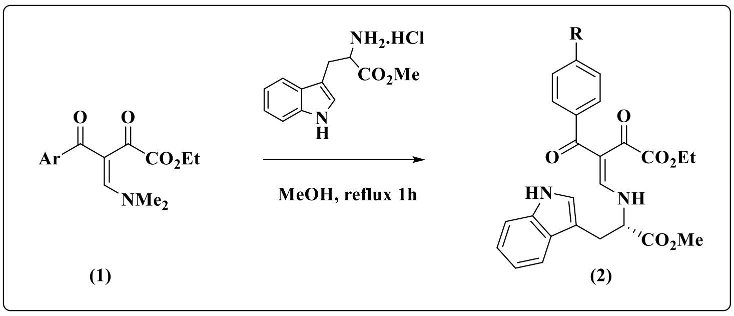
Reagents were used as obtained from commercial suppliers without further purification. Solvents were dried and purified according to recommended procedures.[1]

Analysis and Characterization

The reactions were monitored by thin-layer chromatography using Merck TLC silica gel plates and visualized with UV light. All melting points were measured with the BÜCHI Melting Point M-560 apparatus using platinum (Pt) as the internal standard. ^{1}H NMR and $^{13}C\{1H\}$ NMR experiments were run on Bruker Avance III HD apparatus operating at ^{1}H 300.06 MHz and ^{13}C 75.46 MHz or Bruker Avance III HD apparatus operating at ^{1}H 500.13 MHz and ^{13}C 125.77 MHz and all structural assignments were made with additional information from gHSQC and gHMBC experiments. Chemical shifts are reported in ppm using DMSO-d_6. The $J_{C\text{-}H}$ NMR values were obtained using a pip-HSQMBC-IPAP pulse sequence, with a spectral resolution of 0.90 Hz/point in F2 and 30.14 Hz/point in F1. ^{1}H chemical shifts were obtained in the 1D spectra, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The experiments were performed in a Bruker Avance III HD spectrometer, operating at 500 MHz for 1H and 125 MHz for 13C. ESI(+)-MS and tandem ESI(+)-MS/MS were acquired using a hybrid high-resolution and high accuracy microTof (Q-TOF) mass spectrometer (Bruker). For ESI(+)-MS, the energy for the collision-induced dissociations (CDI) was optimized for each component. For data acquisition and processing, the Q-TOF-control data analysis software (Bruker Scientific) was used.

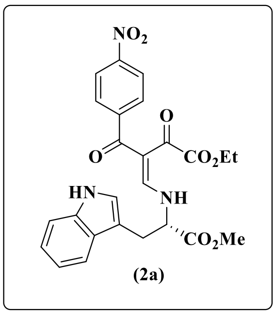
2. Experimental Procedures and Spectral Data

2.1 Synthesis of β-Enamino Diketones 2a-g

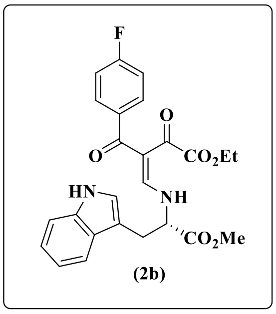


General method: The β-enamino diketone **1** (**1a** R = NO_2: 0.320 g, **1b** R = F: 0.293 g, **1c** Cl: 0.309 g, **1d** R = Br, 0.354 g, **1e** R = H: 0.275 g, **1f** R = OCH_3: 0.289 g, **1g** R = CH_3: 0.305 g, 1.00 mmols, 1.0 equiv) was solubilized in MeOH (10 mL) and added methyl *L*-tryptophan hydrochloride (1.2 equiv). The mixture was stirred under reflux for 1 h. Then, the mixture was cooled to 0 °C which induced crystallization, next the solid was filtered, washed with cold methanol (20 mL), and dried under vacuum. The β-enamino diketones **2a-g** were obtained in 69-91% yields.

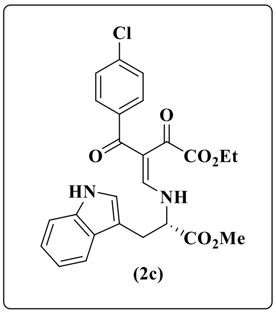
Note: The preparation of β-enamino diketones **1a-g** followed previously reported procedure,[2] and all these compounds are known.



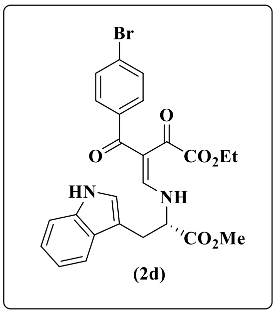
Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-nitrobenzoyl)-2-oxobut-3-enoate (2a): Yellow-orange solid (0.404 g, 82% yield); mp: 114.0 °C. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.91 (m, 1H), 8.39 (s, 1H), 7.93 (d, *J*= 8.7,1H), 7.45 (dd, *J*= 10.3, 8.1 Hz, 2H), 7.27 (ddd, *J*= 8.1, 7.0, 1.1 Hz, 1H), 7.13 (ddd, *J*= 8.1, 7.1, 1.0, 1H), 7.07 (s, 1H), 7.05 (m, 2H), 6.78 (d, *J*= 6.8 Hz,1H), 4.30 (dd, *J*= 7.1, 1.6 Hz, 2H), 4.20 (ddd, *J*= 10.4, 8.8, 3.6 Hz, 1H), 3.87 (s, 3H), 3.53 (dd, *J*= 14.8, 3.6, 0.9 Hz, 1H), 3.14 (dd, *J*= 14.7, 10.4 Hz, 1H), 1.34 (t, *J*= 7.2, 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 190.9, 187.5, 169.6, 165.2, 161.0, 148.9, 143.3, 136.5, 129.0, 126.3, 124.8, 123.5, 122.9, 120.5, 118.1, 112.0, 108.3, 106.9, 63.2, 62.0, 53.4, 30.6, 14.0. **HRMS (ESI)** m/z: [M+H]$^+$ calcd for $C_{25}H_{23}N_3O_8^+$, 494.1558; found, 494.1576.



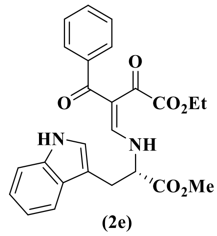
Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-fluorobenzoyl)-2-oxobut-3-enoate (2b): Pale Yellow (0.317 g, 68% yield); mp: 120.3 °C. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.84 (dd, *J*= 13.7, 8.9 Hz, 1H), 8.46 (s, 1H), 7.50 (dd, *J*= 8.9 Hz, 1H), 7.40 (dt, *J*= 8.2, 1.0, 1.0 Hz, 1H), 7.24 (ddd, *J*= 8.2, 7.1, 1.2 Hz, 1H), 7.14 (ddd, *J*= 8.0, 7.0,1.1 Hz, 1H), 7.04-7.07 (m, 3H), 6.98 (d, *J*= 13.7 Hz, 1H), 6.79 (t, *J*= 8.7, 8.7 Hz, 1H), 4.26 (q, *J*= 7.2, 7.2, 7.2 Hz, 2H), 4.19 (ddd, *J*= 9.6, 9.6, 3.6 Hz, 1H), 3.83 (s, 3H), 3.51 (dd, *J*= 14.7, 3.7, 0.8 Hz, 1H), 3.17 (dd, *J*= 14.7, 9.91 Hz, 1H), 1.31 (t, *J*= 7.2, 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 191.6, 187.7, 169.8, 166.3, 165.3, 163.3, 160.8, 136.5, 134.1 (d, $^4J_{C\text{-}F}$ = 3,15 Hz), 131.0 (d, $^3J_{C\text{-}F}$ = 8,97 Hz), 126.5, 124.5, 122.9, 120.4, 118.2, 115.4 (d, $^2J_{C\text{-}F}$ = 21,89 Hz), 111.9, 108.5, 107.4, 63.4, 61.9, 53.3, 30.4, 14.0. **HRMS (ESI)** m/z:[M+H]$^+$ calcd for $C_{25}H_{23}FN_2O_6^+$, 467.1613; found, 467.1629.



Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-chlorobenzoyl)-2-oxobut-3-enoate (2c): Beige (0.405 g, 84% yield); mp: 138.0 °C. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.87 (dd, *J*= 13.7, 8.9 Hz, 1H), 8.42 (s, 1H), 7.51 (d, *J*= 7.9 Hz, 1H), 7.43 (ddd, *J*= 8.3, 6.8, 1.4 Hz, 1H), 7.17 (ddd, *J*= 8.0, 7.0, 1.1 Hz, 1H), 7.11 (d, *J*= 8.5 Hz, 2H), 7.07 (d, *J*= 2.3 Hz, 1H), 6.98-6.95 (m, 3H), 6.79 (t, *J*= 8.7, 8.7 Hz, 1H), 4.28 (q, *J*= 7.1, 7.4, 7.1 Hz, 2H), 4.24-4.18 (m, 1H), 3.85 (s, 3H), 3.53 (dd, *J*= 14.7, 3.5 Hz, 1H), 3.19 (dd, *J*= 17.7, 10.0 Hz, 1H), 1.34 (t, *J*= 7.1, 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 191.8, 187.6, 169.8, 165.3, 160.9, 137.6, 136.5, 136.1, 129.9, 128.6, 126.4, 124.6, 122.8, 120.3, 118.1, 111.9, 108.3, 107.2, 63.3, 61.9, 53.3, 30.4, 14.0. **HRMS (ESI)** m/z: [M+H]$^+$ calcd for $C_{25}H_{23}ClN_2O_6^+$, 483.1317; found, 483.1316.

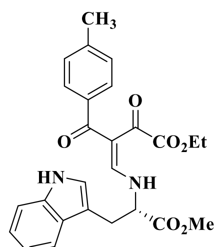


Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-bromobenzoyl)-2-oxobut-3-enoate (2d): Beige (0,353 g, 67% yield); mp: 135.2 °C. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): *δ* 10.85 (dd, *J*= 13.7, 9.1 Hz, 1H), 8.41 (s, 1H), 7.48 (d, *J*= 7.8 Hz, 1H), 7.40 (d, *J*= 8.2 Hz, 1H), 7.26-7.24 (m, 2H), 7.15 (ddd, *J*= 8.0, 7.0, 1.0 Hz, 1H), 7.04 (d, *J*= 2.5 Hz, 1H), 6.94 (d, *J*= 13.7 Hz, 1H), 6.88 (d, *J*= 8.5 Hz, 2H), 4.26 (q, *J*= 7.2, 6.9, 6.9 Hz, 2H), 4.19 (ddd, *J*= 9.5, 9.5, 3.7 Hz, 1H), 3.83 (s, 3H), 3.50 (dd, *J*= 14.7, 9.9 Hz, 1H), 3.16 (dd, *J*= 14.7, 9.9 Hz, 1H), 1.32 (t, *J*= 7.2, 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): *δ* 191.7, 187.5, 169.6, 165.1, 160.7, 136.6, 136.4, 131.5, 129.9, 126.3, 126.0, 124.3, 122.8, 120.3, 118.1, 111.8, 108.4, 107.2, 63.2, 61.8, 53.2, 30.3, 13.9. **HRMS (ESI)** m/z: [M+H]$^+$ calcd for $C_{25}H_{23}BrN_2O_6^+$, 527.0812; found, 527.0808.



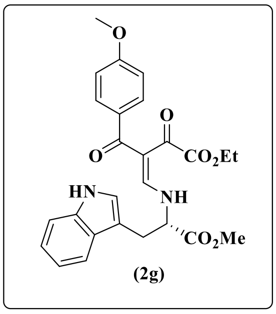
(2e)

Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-benzoyl-2-oxobut-3-enoate (2e): Yellow (0.273 g, 61% yield); mp: 111.7 ºC. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): *δ* 10.85 (dd, *J*= 13.7, 9.1 Hz, 1H), 8.40 (s, 1H), 7.49 (d, *J*= 8.1 Hz, 1H), 7.40 (dt, *J*= 8.1, 1.0, 1.0 Hz, 1H), 7.36-7.32 (m, 1H), 7.25-7.15 (m, 1H), 7.18-7.04 (m, 7H), 4.25 (q, *J*= 7.1, 7.1, 7.1 Hz, 2H), 4.17 (ddd, *J*= 9.2, 8.9, 3.6 Hz, 1H), 3.81 (s, 3H), 3.49 (ddd, *J*= 14.7, 3.9, 0.8 Hz, 1H), 3.18 (dd, *J*= 14.7, 9.6 Hz, 1H), 1.31 (t, *J*= 7.1, 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): *δ* 193.0, 187.7, 169.7, 165.2, 161.0, 137.8, 136.4, 131.4, 128.5, 128.3, 126.4, 122.6, 120.1, 118.0, 111.8, 108.2, 107.3, 63.3, 61.7, 53.2, 30.2, 13.9. **HRMS (ESI)** m/z: [M+H]$^+$ calcd for $C_{25}H_{24}N_2O_6^+$, 449.1707; found, 449.1654.



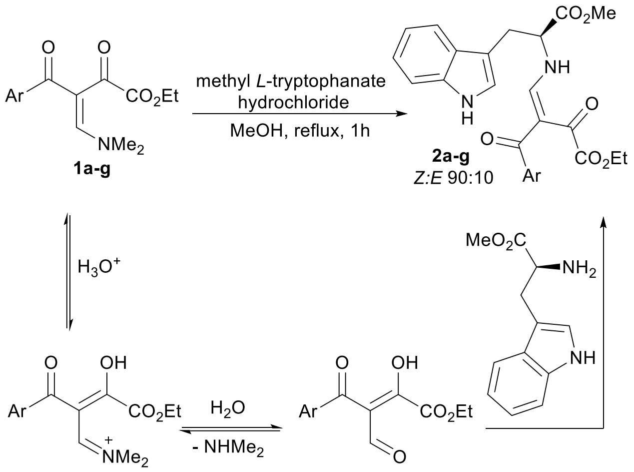
(2f)

Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-methylbenzoyl-2-oxobut-3-enoate (2f): Pale Yellow (0.277 g, 60% yield); mp: 81.3 ºC. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): *δ* 10.82 (dd, *J*= 13.7, 9.1 Hz, 1H), 8.41 (s, 1H), 7.49 (d, *J*= 7.3 Hz, 1H), 7.39 (dt, *J*= 8.1, 0.9, 0.9 Hz, 2H), 7.22 (ddd, *J*= 8.2, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J*= 8.0, 7.1, 1.2, 1H), 7.11 (s, 1H), 7.06 (d, *J*= 4.6 Hz, 1H), 6.94 (d, *J*= 8.5 Hz, 2H), 4.24 (q, *J*= 7.2, 7.1, 7.1 Hz, 2H), 4.17 (ddd, *J*= 9.2, 9.0, 3.9 Hz, 1H), 3.80 (s, 3H), 3.48 (ddd, *J*= 14.7, 3.8, 0.8 Hz, 1H), 3.18 (dd, *J*= 14.7, 9.5 Hz, 1H), 1.30 (t, *J*= 7.1, 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): *δ* 192.8, 187.6, 169.8, 165.3, 160.9, 141.9, 136.4, 135.0, 128.9, 128.6, 126.4, 124.4, 120.0, 118.0, 111.8, 108.4, 107.5, 63.1, 61.7, 53.1, 30.2, 21.4, 13.9. **HRMS (ESI)** m/z: [M+H]$^+$ calcd for $C_{26}H_{26}N_2O_6^+$, 463.1864; found, 463.1872.

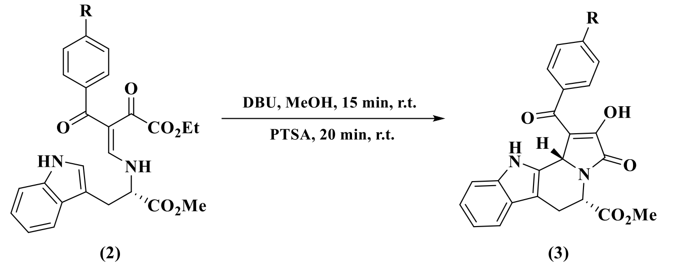


Ethyl-(S,Z)-4-((3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-methoxybenzoyl-2-oxobut-3-enoate (2g): Pale orange (0.268 g, 56% yield); mp: 127.6 ºC. Mixture of *Z* and *E* - 90:10. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.80 (dd, *J*= 13.7, 9.1 Hz, 1H), 8.52 (s, 1H), 7.52 (d, *J*= 7.9 Hz, 1H), 7.41 (d, *J*= 8.1 Hz, 1H), 7.23 (ddd, *J*= 8.2, 7.1, 1.2 Hz, 1H), 7.13 (ddd, *J*= 8.1, 7.1, 1.1, 1H), 7.08-7.03 (m, 4H), 6.58 (d, *J*= 8.9 Hz, 2H), 4.26 (q, *J*= 7.1, 7.1, 7.1 Hz, 2H), 4.17 (ddd, *J*= 9.5, 9.5, 3.7 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.50 (dd, *J*= 14.4, 3.7 Hz, 1H), 3.17 (dd, *J*= 14.7, 9.8 Hz, 1H), 1.31 (t, *J*= 7.1, 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 192.1, 187.8, 170.0, 165.5, 162.4, 160.8, 136.6, 131.0, 130.4, 126.6, 124.7, 122.8, 120.3, 118.3, 113.7, 112.0, 108.4, 107.6, 63.4, 61.9, 55.6, 53.4, 30.5, 14.1. **HRMS (ESI)** m/z: [M+H]$^+$ calcd for $C_{26}H_{26}N_2O_7^+$, 479.1813; found, 479.1819

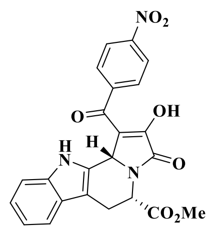
2.1.2. Proposed pathway for the conversion of 1 into 2



2.2 Synthesis of Methyl (5*S*)-1-benzoyl-2-hydroxy-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylates 3a-g

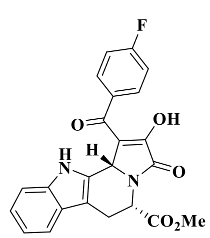


General method: The β-enamino diketone **2** (**2a** R = NO_2: 0.049 g, **2b** R = F: 0.047 g, **2c** R= Cl: 0.048 g, **2d** R = Br, 0.052 g, **2e** R = H_5: 0.045 g, **2f** R = OCH_3: 0.289 g, **2g** R = CH_3: 0.305 g, 0.10 mmols, 1.0 equiv) was solubilized in MeOH (3 mL) and added DBU (0.12 mmols, 1.2 equiv, 17.90 g). The mixture was stirred at room temperature for 15 minutes. After that, PTSA (0.12 mmols, 1.2 equiv, 22.37 g) was added to the mixture and stirred for 20 minutes more. Then, the reaction mixture was added to 60 mL of a 10% (w/w) HCl solution and stirred for 10 min. The resulting material was then filtered and washed with an additional 10 mL of water. The harmicine derivatives **3a-g** were obtained in 65-82% yields.



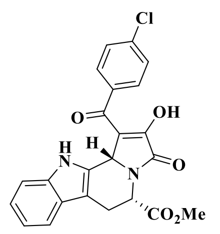
(3a)

Methyl(5*S*)-2-hydroxy-1-(4-nitrobenzoyl)-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (3a): Pale orange solid (0.036 g, 80% yield); mp: 224,5 °C. Diasterisomer ratio 99:1. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$ (300 MHz, DMSO) δ 10.15 (s, 1H), 8.30 (d, *J*= 8.8 Hz, 2H), 7.98 (d, *J*= 8.80 Hz, 2H), 7.46 (m, 2H), 7.07 (ddd, *J*= 8.60 Hz, 7.02 Hz, 1.28 Hz, 1H), 6.99 (ddd, *J*= 8.10 Hz, 7.01 Hz, 1.10 Hz, 1H), 5.99 (s, 1H), 5.58 (d, *J*= 6.89 Hz, 1H), 3.68 (s, 1H), 3.39 (d, *J*= 15.94 Hz, 1H), 3.09 (ddd, *J*= 15.88 Hz, 7.16 Hz, 2.26Hz, 1H). **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 189.3, 170.5, 165.0, 154.5, 149.3, 143.9, 136.5, 130.0, 130.0, 125.9, 123.3, 121.7, 119.0, 118.0, 117.4, 112.4, 104.8, 52.8, 52.5, 50.5, 23.6. **HRMS (ESI)** m/z: $[M-H]^-$ calcd for $C_{23}H_{16}N_3O_7^-$, 446.0994; found, 446.1008.



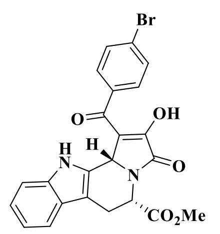
(3b)

Methyl (5*S*)-1-(4-fluorobenzoyl)-2-hydroxy-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (3b): Pale orange solid (0.027 g, 65% yield); mp: 195.5 °C. Diasterisomer ratio 98:2. ^{1}**H NMR** (500.13 MHz, DMSO-d$_6$): δ 10.12 (s, 1H), 7.88 (dd, *J*= 8.60 Hz, 5.60 Hz, 2H), 7.44 (dd, *J*= 8.73 Hz, 2H), 7.32 (t, *J*= 8.84 Hz, 2H), 7.05 (ddd, *J*= 8.30 Hz, 6.96 Hz, 1.20 Hz, 1H), 6.98 (t, *J*= 7.60 Hz, 1H), 5.98 (s, 1 H), 5.56 (d, *J*= 7.04 Hz, 1 H), 3.67 (s, 1H), 3.38 (d, *J*= 15,85 Hz, 1H), 3.08 (ddd, *J*= 185.87 Hz, 7.22 Hz, 2.30 Hz, 1 H). ^{13}**C{^{1}H} NMR** (125.77 MHz, DMSO-d$_6$): δ 189.7, 171.0, 166.2, 165.6, 164.2, 152.5, 136.9, 135.1 (d, $^4J_{C\text{-}F}$ = 2.59 Hz), 132.4 (d,$^3J_{C\text{-}F}$ = 9.43 Hz), 130.2, 126.3, 122.1, 119.5, 118.8, 118.4, 115.6 (dd,$^2J_{C\text{-}F}$ = 22.07 Hz, 1.73 Hz), 112.8, 105.2, 53.2, 53.2, 51.0, 24.1. **HRMS (ESI)** m/z: $[M\text{-}H]^-$ calcd for $C_{23}H_{16}FN_2O_5^-$, 419.1049; found, 419.1053.



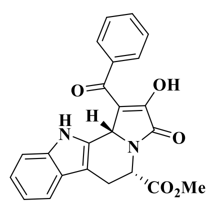
(3c)

Methyl (5S)-1-(4-chlorobenzoyl)-2-hydroxy-3-oxo-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole-5-carboxylate (3c): Pale orange solid (0.034 g, 78% yield); mp: 190.5 °C. Diasterisomer ratio 99:1. ^{1}**H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.13 (s, 1H), 7.80 (d, *J*= 8.60 Hz, 2H), 7.56(d, *J*= 8.61 Hz, 2H), 7.44 (d, *J*= 8.77 Hz, 2H), 7.05 (ddd, *J*= 8.41 Hz, 7.04 Hz, 1.32 Hz, 1H), 6.98 (ddd, *J*= 7.70 Hz, 7.21 Hz, 1.07 Hz, 1H), 5.96 (s, 1H), 5.55 (d, *J*= 6.76 Hz, 1H), 3.37 (d, *J*= 15. 89 Hz, 1H), 3.07 (ddd, *J*= 15.82 Hz, 7.12 Hz, 2.29 Hz, 1H). ^{13}**C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 189.6, 170.5, 165.1, 152.4, 137.4, 136.8, 136.5, 130.9, 129.8, 128.2, 125.9, 119.0, 118.2, 118.0, 112.4, 104.7, 52.8, 50.5, 23.6. **HRMS (ESI)** m/z: $[M\text{-}H]^-$ calcd for $C_{23}H_{16}ClN_2O_5^-$, 437.0886; found, 437.0899.



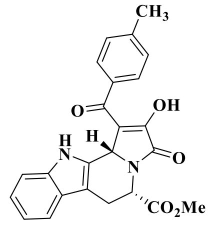
(3d)

Methyl (5*S*)-1-(4-bromobenzoyl)-2-hydroxy-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (3d): Pale orange solid (0,036 g, 76% yield); mp: 188.2 °C. Diasterisomer ratio 99:1. ^{1}**H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.13 (s, 1H), 7.71 (s, 4H), 7.44 (d, *J*= 8.84 Hz, 2H), 7.04 (dd, *J*= 7.34 Hz, 1.23 Hz, 1H), 6.98 (dt, *J*= 7.15 Hz, 1.09 Hz, 1H), 5.97 (s, 1H), 5.55 (d, *J*= 6.84 Hz, 1H), 3.67 (s, 1H), 3.37 (d, *J*= 15.91 Hz, 1H), 3.08 (ddd, *J*= 15.84 Hz, 7.16 Hz, 2.27 Hz, 1H). ^{13}**C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 189.8, 170.5, 165.1, 152.5, 137.2, 136.5, 131.2, 131.0, 129.8, 126.5, 125.9, 121.7, 119.0, 118.2, 118.0, 112.4, 104.7, 52.8, 52.7, 50.5, 23.67. **HRMS (ESI)** m/z: $[M\text{-}H]^-$ calcd for $C_{23}H_{16}BrN_2O_5^-$, 479.0248; found, 479.0238.



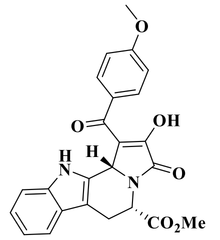
(3e)

Methyl (5*S*)-1-benzoyl-2-hydroxy-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (3e): Pale orange solid (0.031 g, 78% yield); mp: 218.3 °C. Diasterisomer ratio 99:1. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.12, 7.60, 7.78, 7.61, 7.47, 7.05, 6.98, 5.99, 5.56, 3.38, 3.09. **^{13}C{^{1}H} NMR** (75.45 MHz, DMSO-d$_6$): δ 190.9, 170.6, 165.2, 151.9, 138.1, 136.5, 132.7, 129.8, 129.0, 125.9, 121.7, 119.0, 118.6, 118.0, 112.4, 104.7, 52.8, 52.8, 50.5, 23.7. **HRMS (ESI)** m/z: [M-H]$^-$ calcd for $C_{23}H_{17}N_2O_5^-$, 401.1143; found, 401.1147.



(3f)

Methyl (5*S*)-2-hydroxy-1-(4-methylbenzoyl)-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (3f): Pale orange solid (0.034 g, 82% yield); mp: 188.15 °C. Diasterisomer ratio 96:4. **^{1}H NMR** (500.13 MHz, DMSO-d$_6$): δ 10.12 (s, 1H), 7.82 (d, *J*= 8.93 Hz, 2H), 7.42-7.44 (m, 2H), 7.00-7.06 (m, 3H), 6.98 (ddd, *J*= 7.88 Hz, 6.99 Hz, 1.06 Hz, 1H), 6.00 (s, 1H), 5.56 (d, *J*= 7.08 Hz, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.38 (dd, *J*= 15.81 Hz, 1.17 Hz, 1H), 3.18 (ddd, *J*= 15.82, 7.20 Hz, 2.32 Hz, 1H). **^{13}C{^{1}H} NMR** (125.77 MHz, DMSO-d$_6$): δ 190.5, 170.6, 165.3, 151.3, 143.2, 136.5, 135.4, 129.9, 129.3, 128.7, 125.9, 121.7, 119.0, 118.9, 118.0, 112.4, 104.7, 52.9, 52.8, 50.6, 23.7, 21.3. **HRMS (ESI)** m/z: [M-H]$^-$ calcd for $C_{24}H_{19}N_2O_5^-$, 415.1299; found, 415.1307.



(3g)

Methyl (5*S*)-2-hydroxy-1-(4-methoxybenzoyl)-3-oxo-5,6,11,11*b*-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (3g): Pale orange solid (0.035 g, 82% yield); mp: 183.9 °C. Diasterisomer ratio 99:1. **^{1}H NMR** (300.06 MHz, DMSO-d$_6$): δ 10.13 (s, 1H), 7,83 (d, *J*= .85 Hz,2H), 7.43 (m, 2H), 7.04 (ddd, *J*= 8.2, 6.9, 1.1 Hz, 1H), 7.01 (d, *J*= 8.7, 2H), 6.98 (ddd, *J*= 7.9, 7.0, 1.1 Hz, 1H), 5.99 (s, 1H), 5.56 (d, *J*= 7.1 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.38 (d, *J*= 15.8 Hz, 1H), 3.08 (ddd, *J*= 15.7, 7.1, 2.3 Hz, 1H). **^{13}C{^{1}H} NMR** (125.77 MHz, DMSO-d$_6$): δ 189.1, 170.7, 165.5, 163.1, 150.8, 136.5, 131.7, 130.6, 130.0, 125.9, 121.7, 119.0, 119.0, 118.0, 113.4, 112.4, 104.6, 55.6, 52.9, 52.8, 50.5, 23.7. **HRMS (ESI)** m/z: $[M-H]^-$ calcd for $C_{24}H_{19}N_2O_6^-$, 431.1249; found, 431.1261.

3. Computational Details

For the theoretical data, a conformational search was performed for both *cis* and *trans* **3a** structures, using the software CREST[3] interfaced with ORCA 5.0,[4] at the xtb2 theory level. The lowest-energy conformer was optimized in M06-2X/cc-pVTZ (integration grid DEFGRID3) with implicit solvation in DMSO (CPCM). From the optimized geometry of the minimum energy conformer, $J_{C\text{-}H}$ coupling constants (PBE0/aug-pcJ-1) and ^{1}H chemical shifts (PBE0/aug-pcSseg-2) were calculated in DMSO, using the ^{1}H isotropic shifts of tetramethyl silane as internal reference ($\delta_H = \sigma_{iso(TMS)} - \sigma_{iso(H)}$).

Cartesian Coordinates

Cis – **3a**

C	-2.556609962122930	-2.854225427306460	0.309805250547890
C	-3.462187507934840	-2.009059424432450	-0.372937189674920
C	-4.559622738783370	-2.576972348984120	-1.032182818591660
C	-4.722150694999090	-3.948068022114610	-0.996140115372460
C	-3.809095101346570	-4.770177810748730	-0.312809498991760
C	-2.718299233773440	-4.238850881002320	0.347844957614780
C	-1.849781707971070	-0.756701680273920	0.551449320753370
C	-2.988785953654400	-0.666296489698040	-0.198642413537270
H	-5.265606681585610	-1.950031409468630	-1.562264486092540
H	-5.564073890833680	-4.402799291337880	-1.500527719948350
H	-3.964697821465760	-5.840764503569870	-0.303573809847090
H	-2.015359586691430	-4.868635972506610	0.876704688862670
C	-3.583722760185380	0.635052733373690	-0.643774616658170
H	-3.333224249106190	0.867456881234670	-1.681487820005030
H	-4.671487046890500	0.614638494691260	-0.568662132821450
C	-3.036941774045410	1.732528516751600	0.266830994183580
H	-3.439716465410990	1.601018655950790	1.274662744803640
C	-1.025859120688000	0.412638025153090	0.999276702612500
H	-1.057594148152730	0.509353140509090	2.088916285690410
N	-1.589351965065520	1.606556117051690	0.372892507960230
C	0.414322733913420	0.419441787372230	0.526346039563610
C	0.590209344661870	1.481696044191560	-0.281295972397130
C	-0.707668773552850	2.206955101628080	-0.448295606601470
O	-0.868858983424780	3.151778366120100	-1.199985828817080
O	1.650281925535690	1.942286481549790	-0.913446405848910
H	1.386946333591660	2.737092067076420	-1.411000520478460
C	1.357171664081640	-0.537897233033710	1.096156160991260
O	0.989674069323020	-1.294626002537420	1.980672607091690
C	-3.429854539778100	3.136396846280220	-0.168065095748610
O	-4.128344666825810	3.378054021423420	-1.116816537955330
O	-2.961012612699900	4.047934588970130	0.673121045306360
C	-3.229160157851810	5.411932272034040	0.320782175976450
H	-2.805108340017820	5.625171808542800	-0.658451285786700
H	-4.301944631752260	5.589641340344040	0.304193472757050
H	-2.751507943776420	6.013996349287970	1.085252987076540
C	2.777579501893790	-0.584763468794140	0.634934204758590
C	3.106954758624350	-0.557926480595150	-0.715907970793490
C	3.768511251751710	-0.731864206834200	1.603178121972020
C	4.430710930194830	-0.680099994511940	-1.106340421477930
H	2.335229682543710	-0.455401465798480	-1.465665227067030

C	5.096073721796960	-0.830917348999850	1.229150194181430
H	3.493527319774240	-0.762336539285470	2.648202356256030
C	5.394973122002370	-0.805633160690800	-0.122346369202120
H	4.711233717599460	-0.676879190603950	-2.148259209251110
H	5.881864821517110	-0.933332401470820	1.961449727616010
N	6.806816144053330	-0.923842346320380	-0.530142736355980
O	7.637696769620190	-1.069859402348020	0.339970722198460
O	7.062892179264750	-0.869369063415620	-1.713531506848560
N	-1.584780878787970	-2.063245584846920	0.867965261031480
H	-0.800747432569410	-2.370284718006170	1.422938496364550

Final Single Point Energy: -1577.45164810821 Eh

Trans-**3a**

C	-2.437331769090860	2.377206096669980	-0.426279399542260
C	-3.218364766052470	1.713879686084460	0.548439733582080
C	-4.235644063205770	2.417488174727510	1.204685746381280
C	-4.445928493883960	3.742788454763210	0.878129773158380
C	-3.658595747356880	4.384331635071600	-0.093919222907570
C	-2.647537615474770	3.715707019091760	-0.757018585161610
C	-1.700405798313030	0.281433107354800	-0.267945889386690
C	-2.729171002020300	0.368566771818780	0.626667330457300
H	-4.843111553562760	1.928325628964150	1.955915985289650
H	-5.227866568166070	4.299922730474580	1.376505382888890
H	-3.849432046008220	5.423237103733210	-0.327756383014530
H	-2.041630012736690	4.208260251070780	-1.505976478607090
C	-3.204892998352180	-0.791657197602650	1.443976914807320
H	-2.749863208208960	-0.798879538976560	2.436477885783640
H	-4.284765340575730	-0.766299500796170	1.580031035198200
C	-2.801851540708480	-2.093277306590130	0.727049647939520
C	-0.924170489085860	-0.963113842636210	-0.559156637011670
H	-1.074733692923000	-1.256819946943130	-1.601600694514120
N	-1.410730479706820	-2.016265461643530	0.329859395306520
C	0.562833094227210	-0.924068488812120	-0.267757355227130
C	0.848474817249380	-1.895791703669350	0.616934187429670
C	-0.416691967121210	-2.563866072989080	1.056236936641790
O	-0.474797468250990	-3.419666148697160	1.920000159025080
O	1.994340294096770	-2.322520338559980	1.114022509857160
H	1.804670866903500	-3.048613173484210	1.734032322985910
C	1.418948549082350	-0.047267002089060	-1.065367026438370
O	0.966168544871220	0.486398672427770	-2.065118749223640
C	2.828869436599330	0.232177017412630	-0.660266333328640
C	3.183968363462730	0.358602364989670	0.679055225138530
C	3.762286208479430	0.473090159492040	-1.666568865333240
C	4.471288690176420	0.739399659803920	1.020143747797690
H	2.452242169356170	0.189011756022860	1.456351568040600
C	5.057381680031120	0.829048112739780	-1.341095128560890
H	3.464806694109430	0.384499961915330	-2.701853627128570
C	5.378083808191170	0.960638048191030	-0.000354110458860
H	4.766150909983640	0.868078865216780	2.050105934553260
H	5.801239371670210	1.011653889563190	-2.101229466300330
N	6.748240871721690	1.372568738174600	0.354063748258270
O	7.537430031719530	1.548378957509020	-0.548586662111650
O	7.012294166920600	1.515080189297530	1.528245991850510
N	-1.523037002337240	1.476465698036130	-0.914122755205120
H	-0.827634120688220	1.646523147043790	-1.624397818981560

H	-2.900868109442210	-2.943665005257010	1.402111208890570
C	-3.674915739918250	-2.374679350624670	-0.487298132480820
C	-5.883977149478240	-2.664883488184140	-1.213412173500670
H	-5.777574758267070	-1.909973318093460	-1.988925898316850
H	-5.700742210352430	-3.651962388525400	-1.631668081354740
H	-6.868291311086630	-2.616069878333080	-0.762060046452980
O	-3.265378012833130	-2.559460416720700	-1.604577017873110
O	-4.956252833643440	-2.402923718433120	-0.149512262839110

Final Single Point Energy: -1577.4539000407 Eh

4. ^{1}H, and $^{13}C\{1H\}$ NMR Spectra

4.1 ^{1}H NMR Spectra from optimization reactions

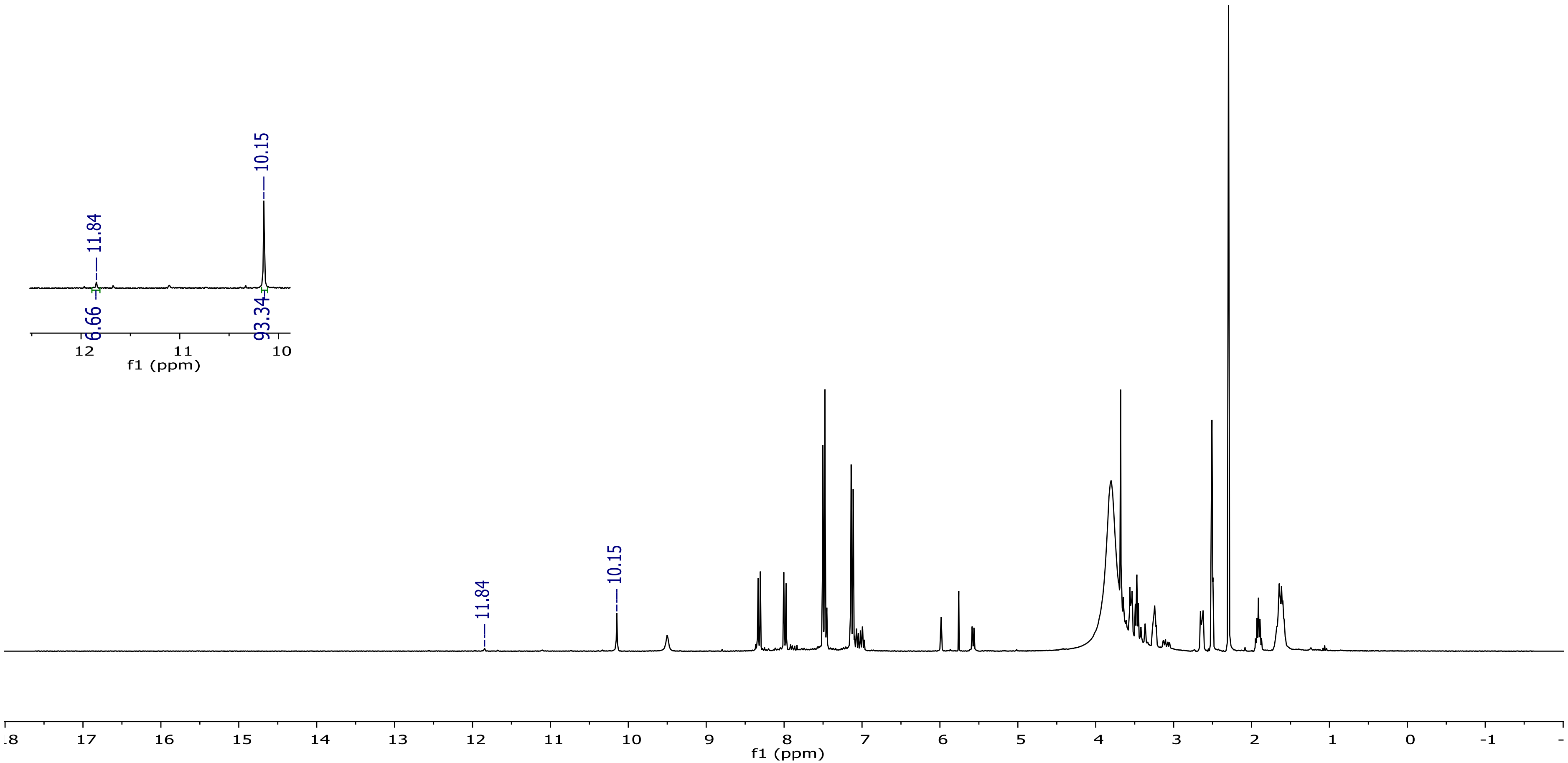


Figure S1. ^{1}H NMR spectrum of crude **3a** obtained under the conditions in Table 1, entry 1 (DMSO-$_{d6}$ 300.06 MHz).

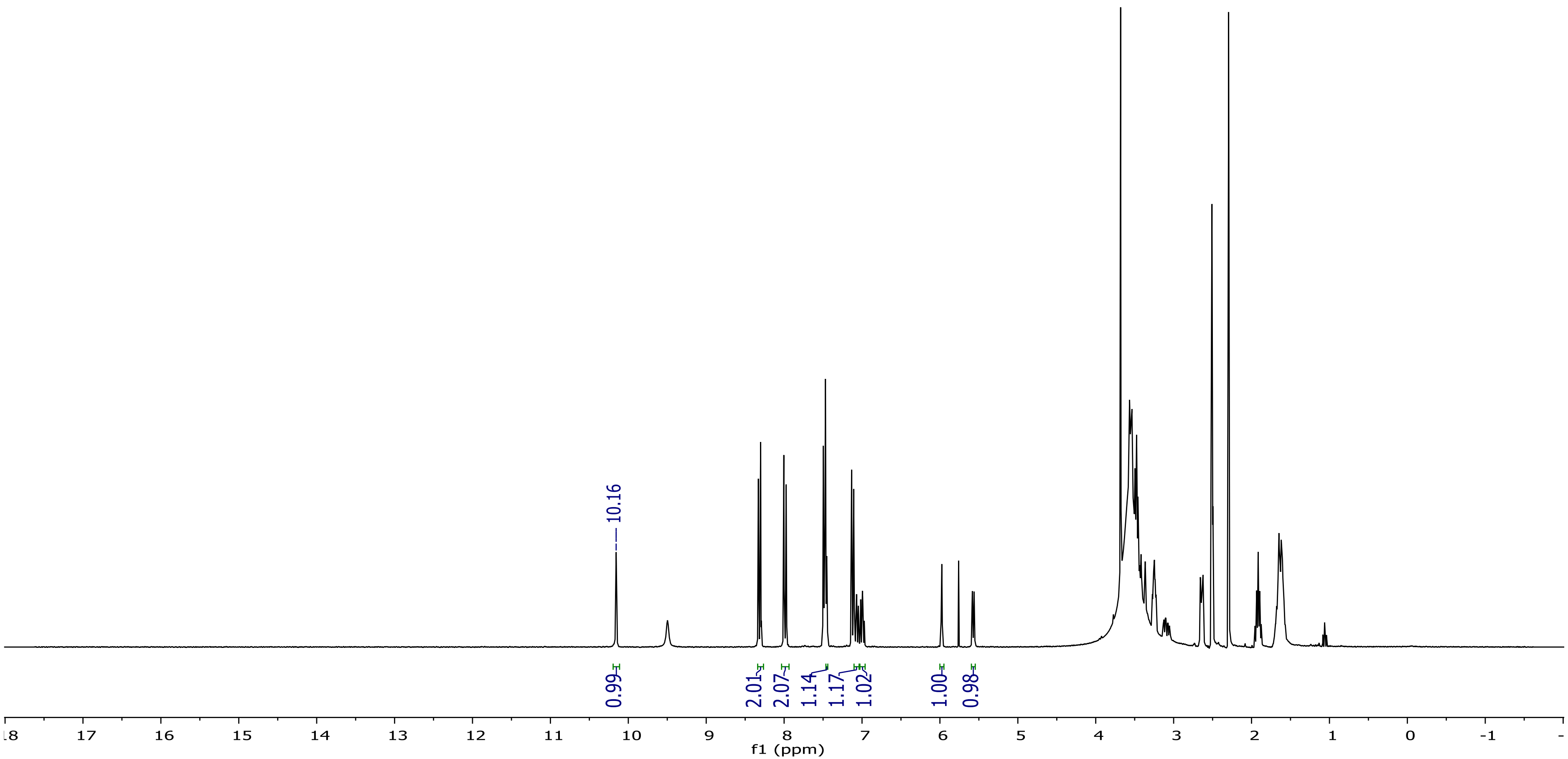


Figure S2. ^{1}H NMR spectrum of crude **3a** obtained under the conditions in Table 1, entry 2 (DMSO-$_{d6}$ 300.06 MHz).

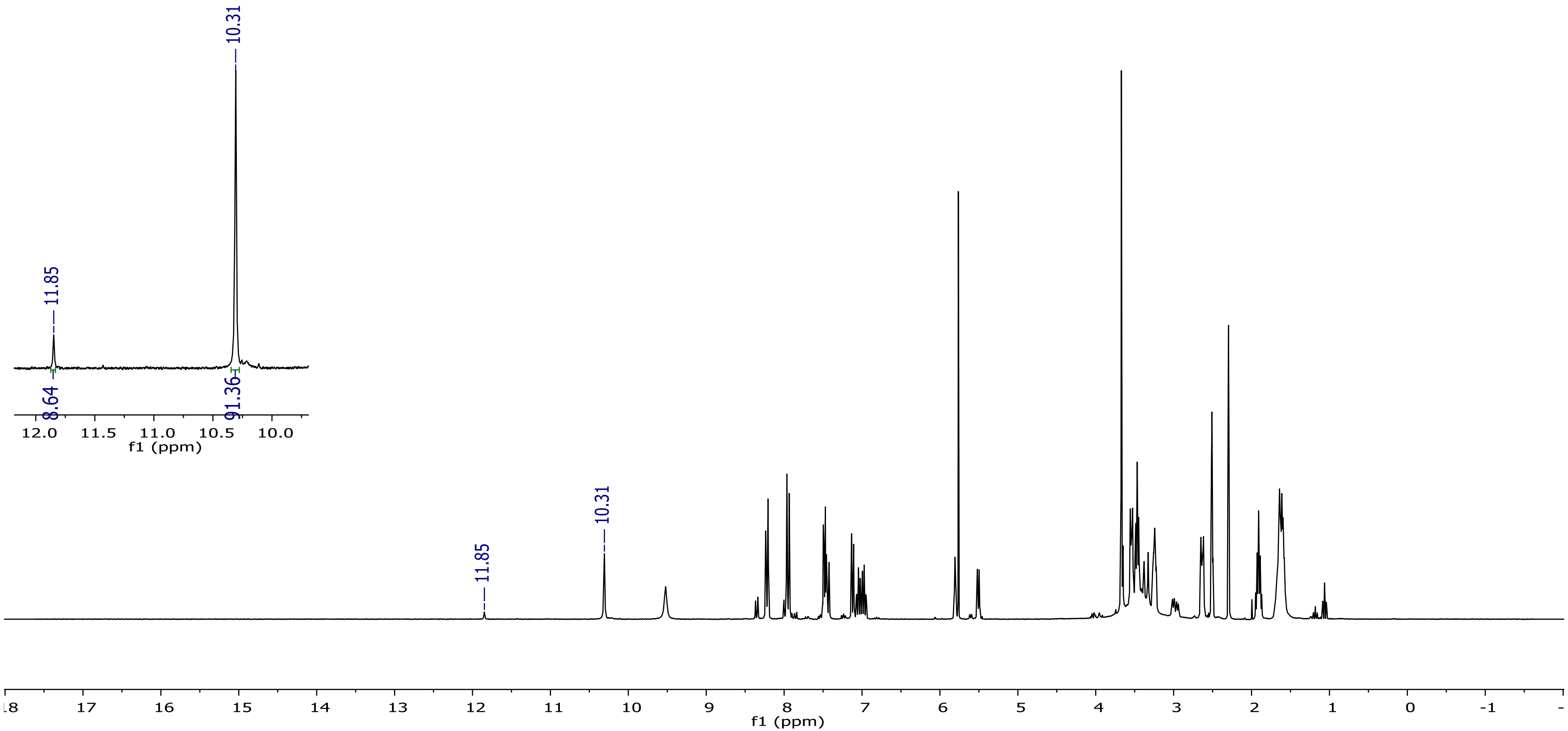


Figure S3. [1]H NMR spectrum of crude **3a** obtained under the conditions in Table 1, entry 3 (DMSO-$_{d6}$ 300.06 MHz)

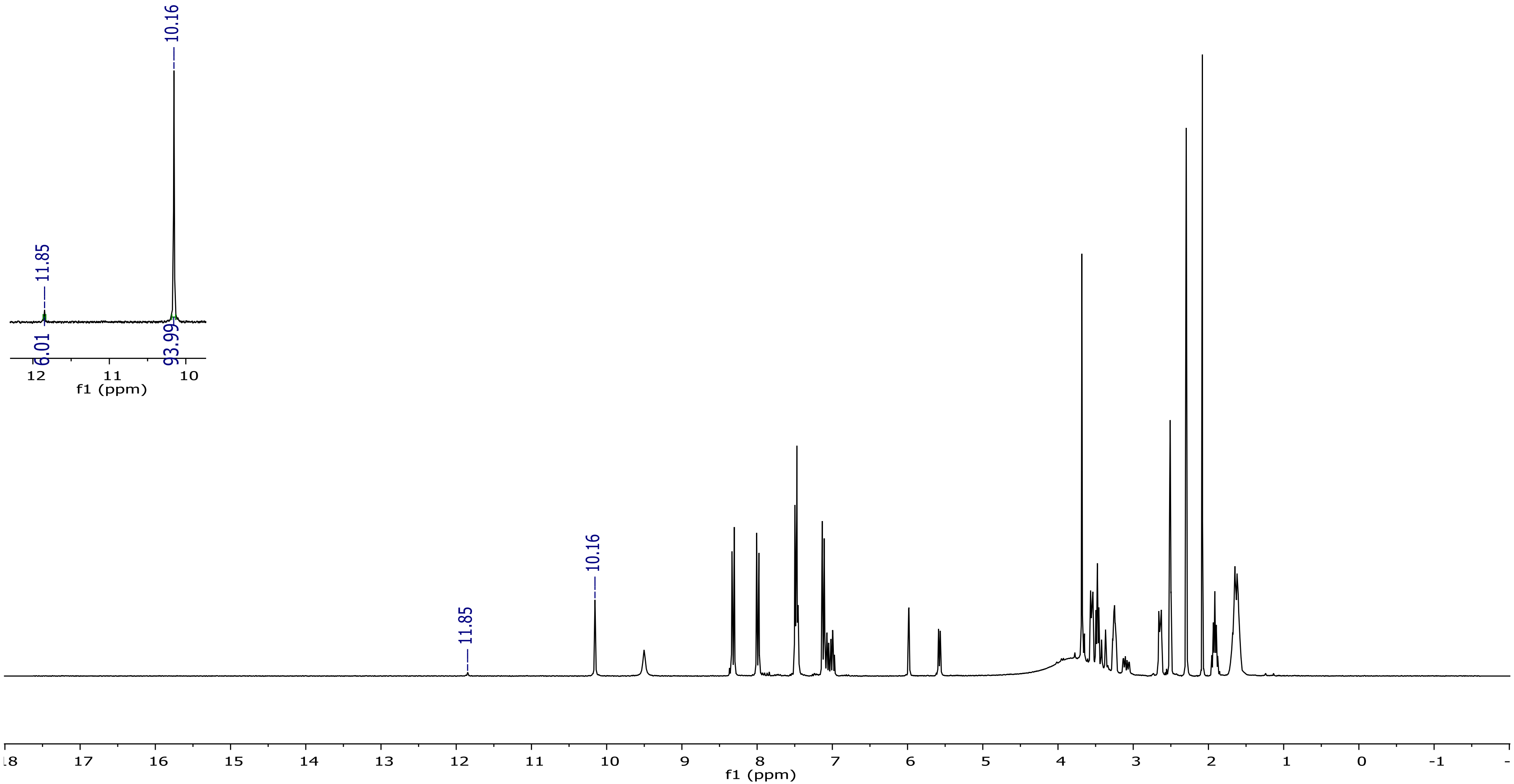


Figure S4 . ^{1}H NMR spectrum of crude **3a** obtained under the conditions in Table 1, entry 5 (DMSO-$_{d6}$ 300.06 MHz).

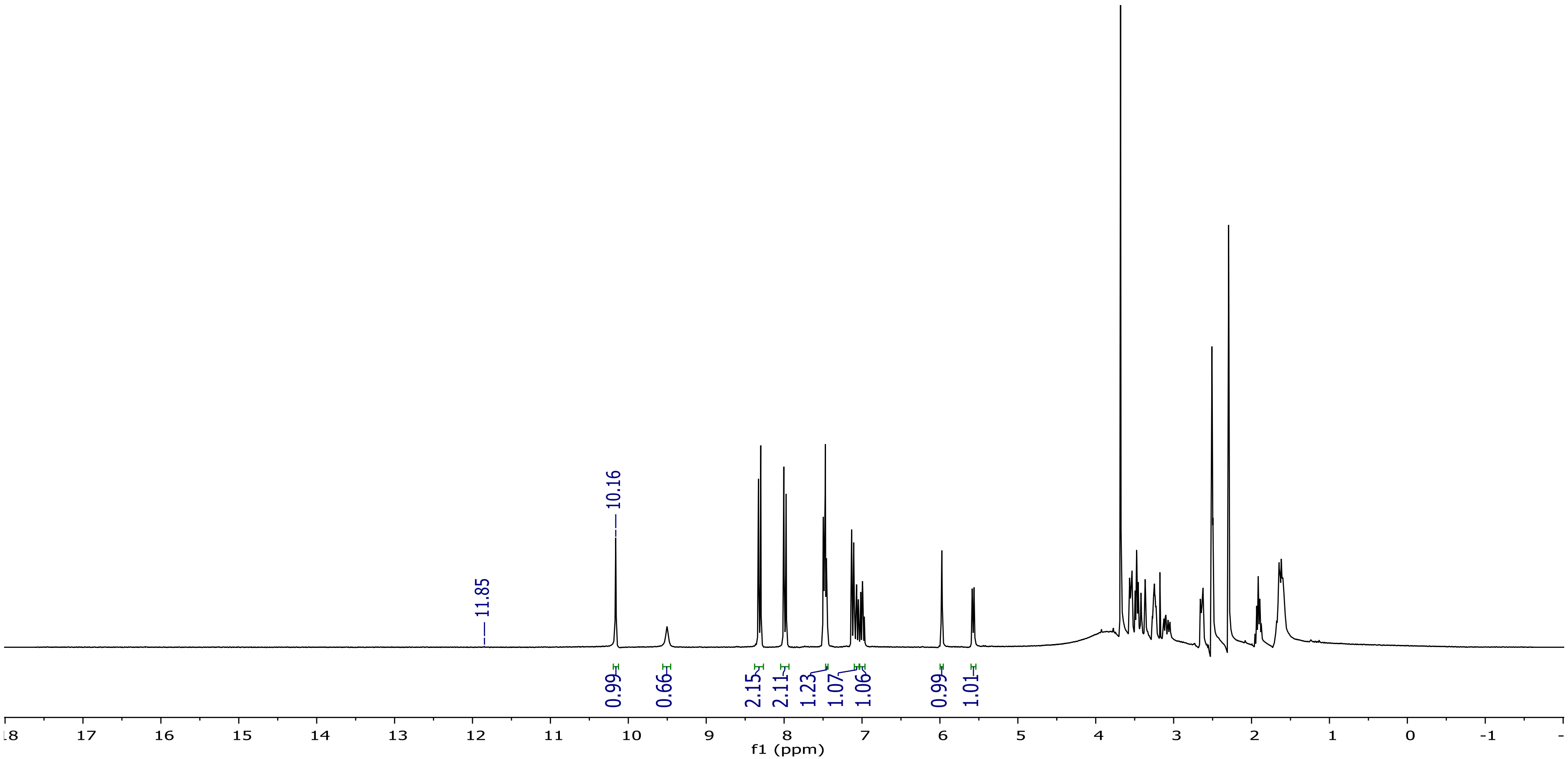


Figure S6 . ^{1}H NMR spectrum of crude **3a** obtained under the conditions in Table 1, entry 6 (DMSO-$_{d6}$ 300.06 MHz)

4.2 ^{1}H and ^{13}C{1H} NMR spectra of 2a-g

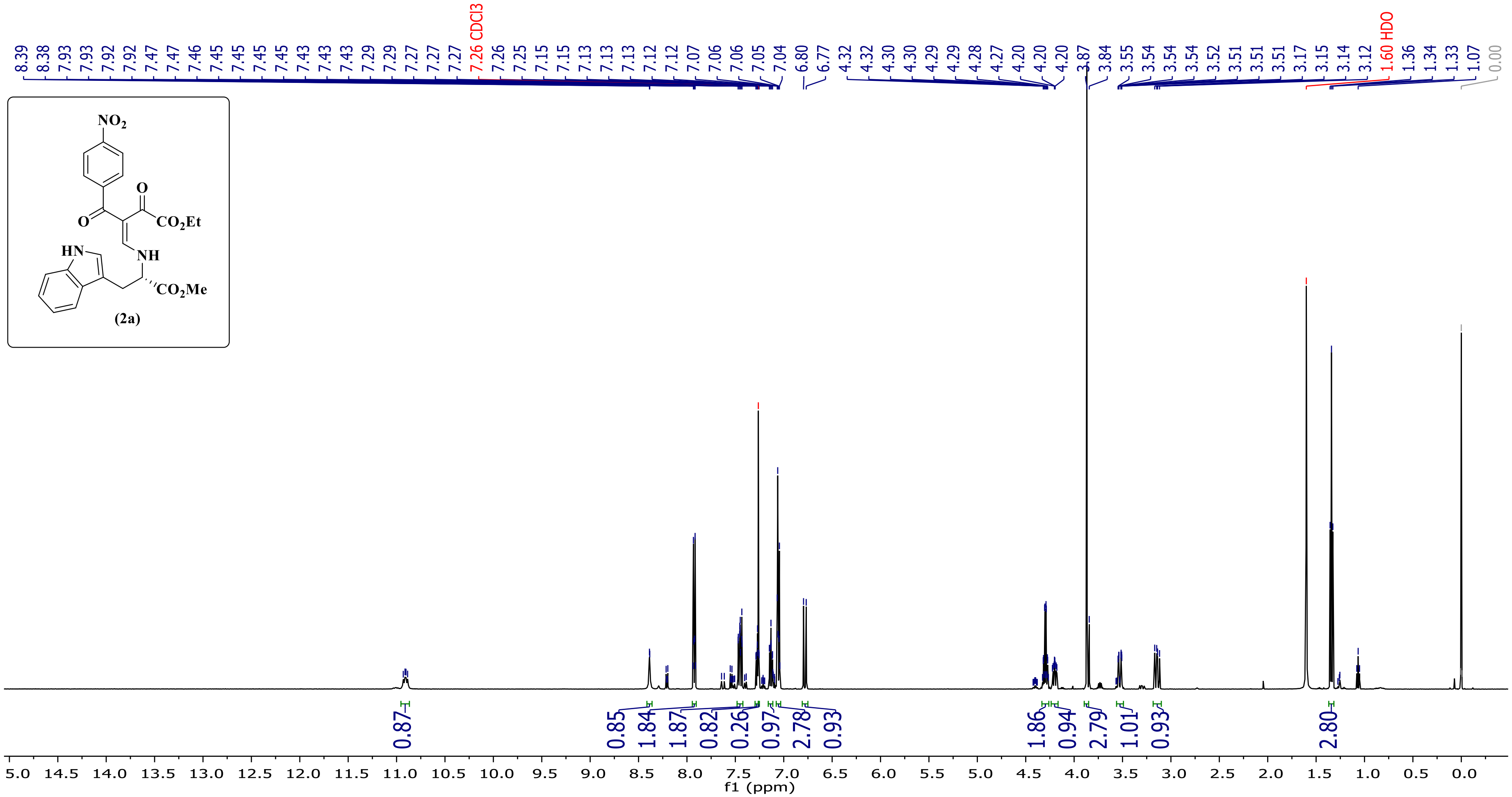


Figure S7. ^{1}H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2a** ($CDCl_3$, 300.06 MHz)

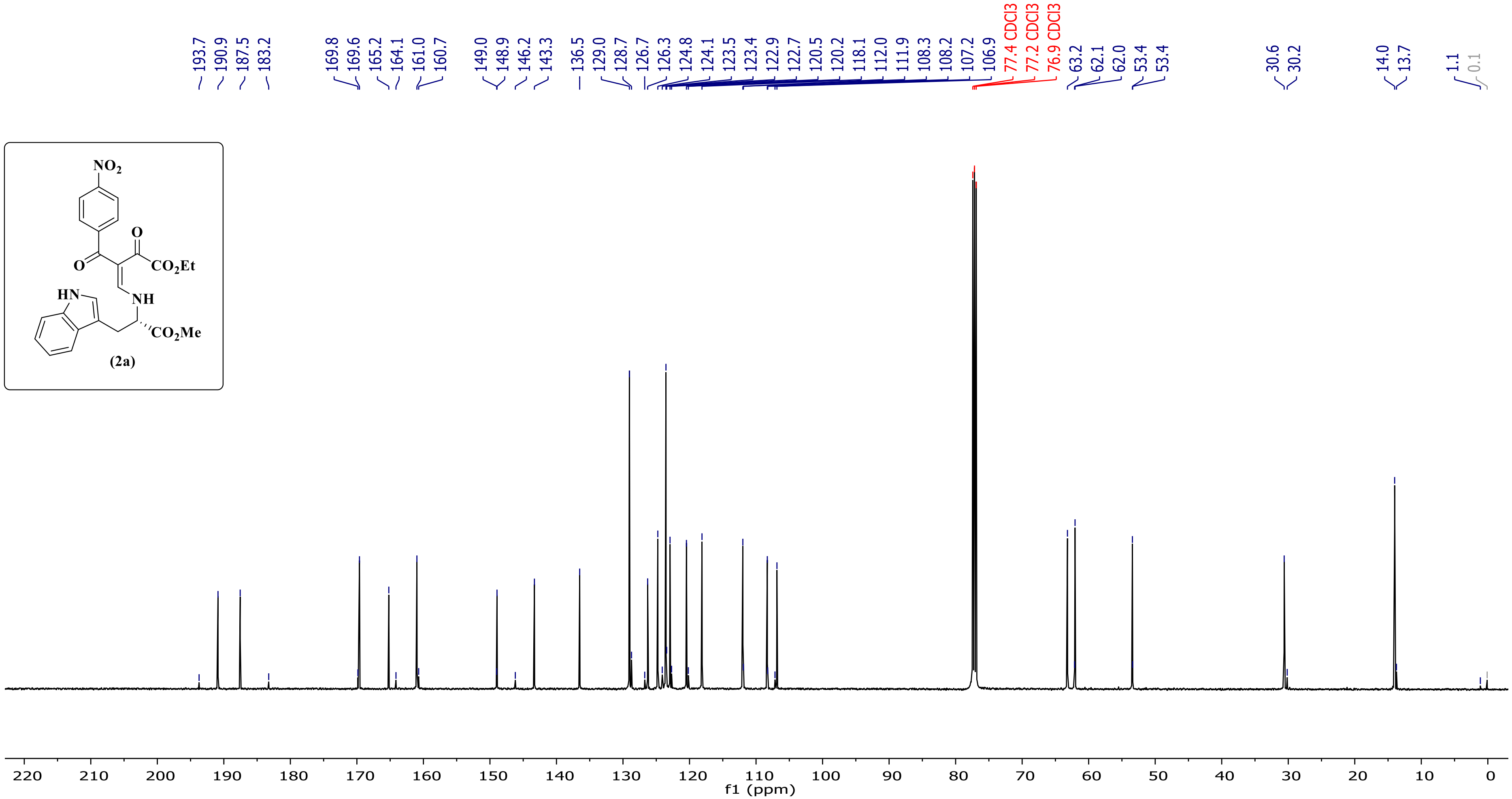


Figure S8. ^{13}C NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2a** ($CDCl_3$, 75.46 MHz)

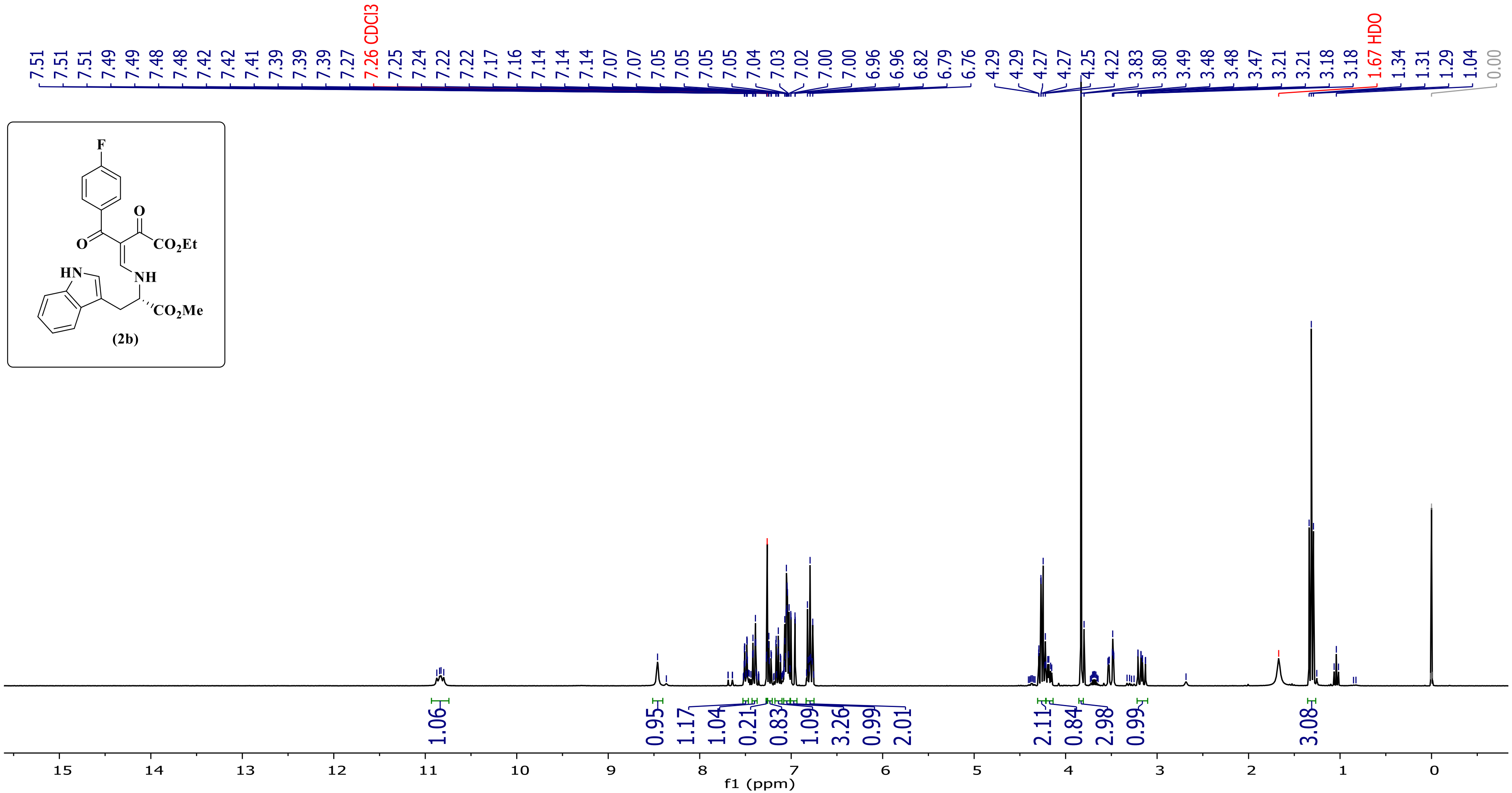


Figure S9. ^{1}H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2b** (DMSO-d_6, 300.06 MHz)

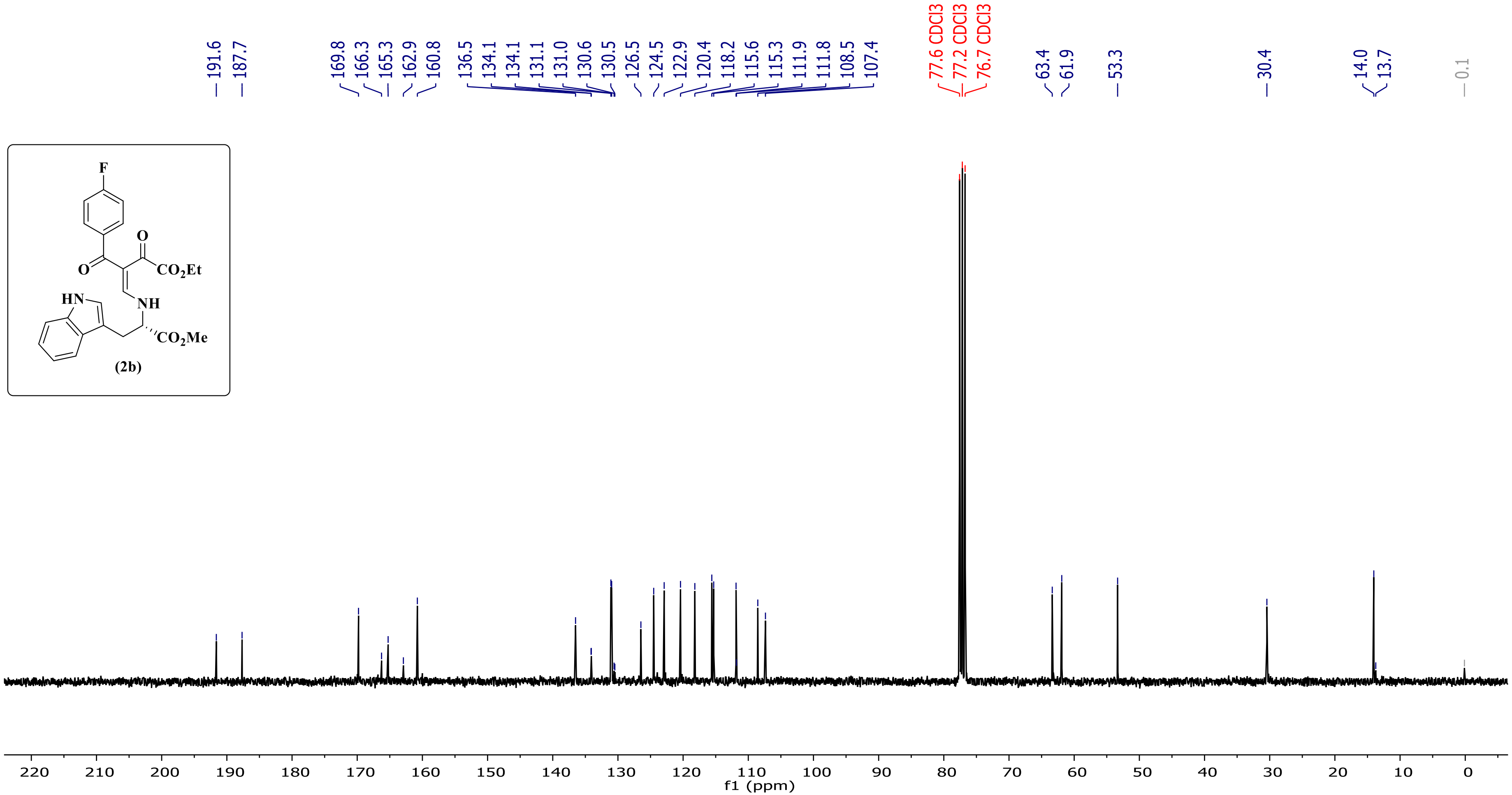


Figure S10. ^{13}C NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2b** (DMSO-d_6, 75.46 MHz)

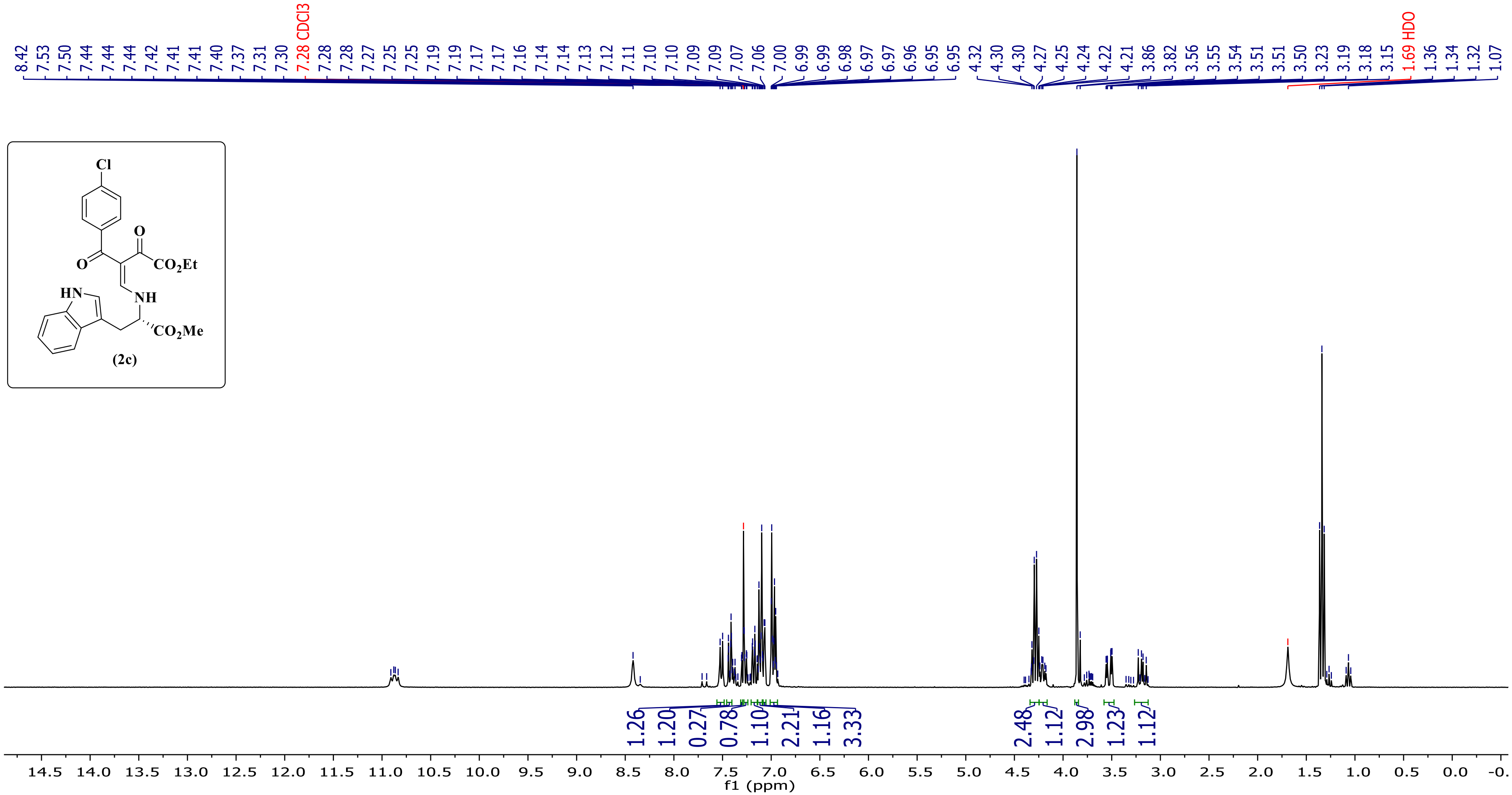


Figure S11. ^{1}H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2c** ($CDCl_3$, 300.06 MHz)

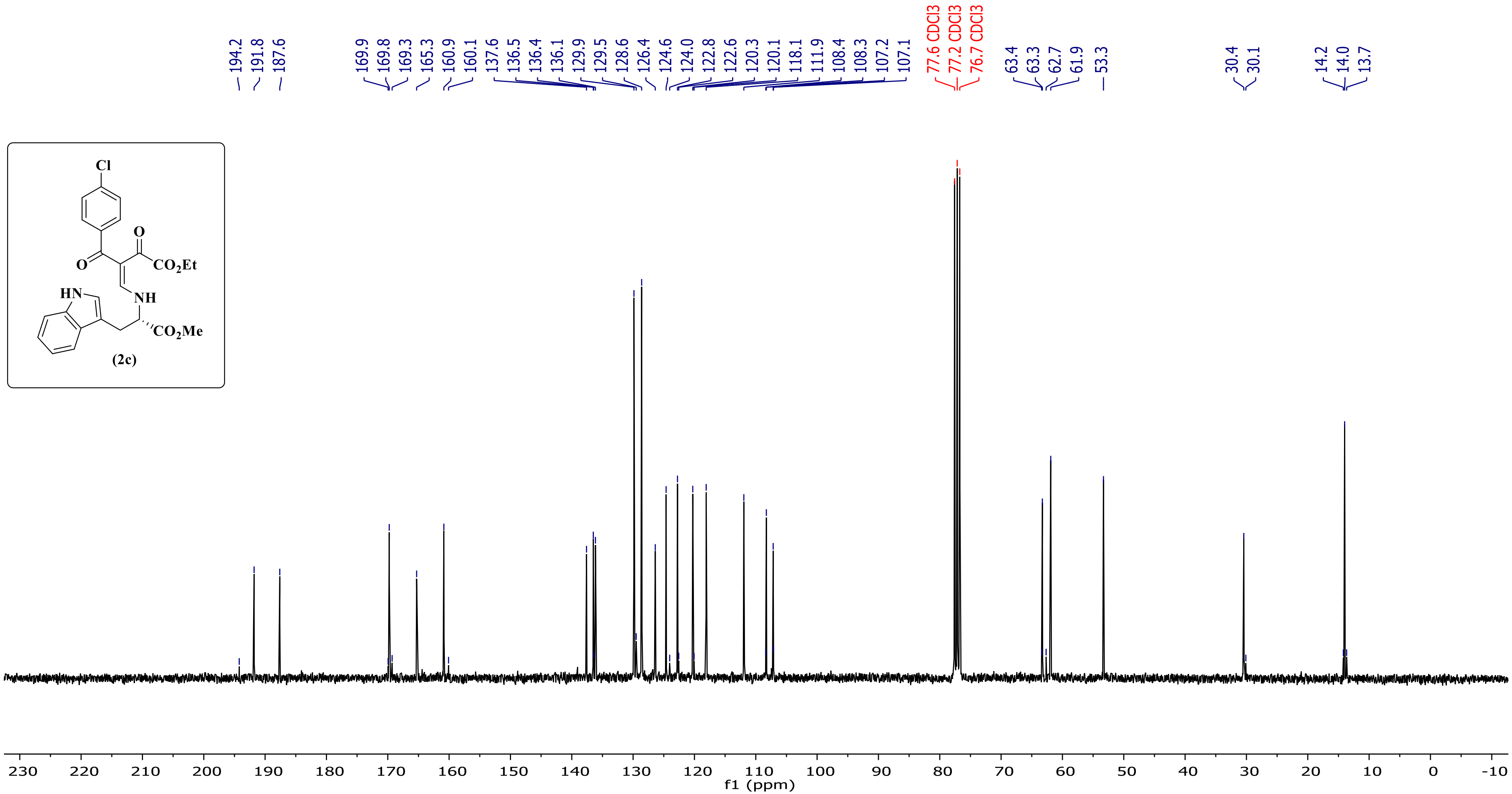


Figure S12. ^{13}C NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2c** ($CDCl_3$, 75.46 MHz)

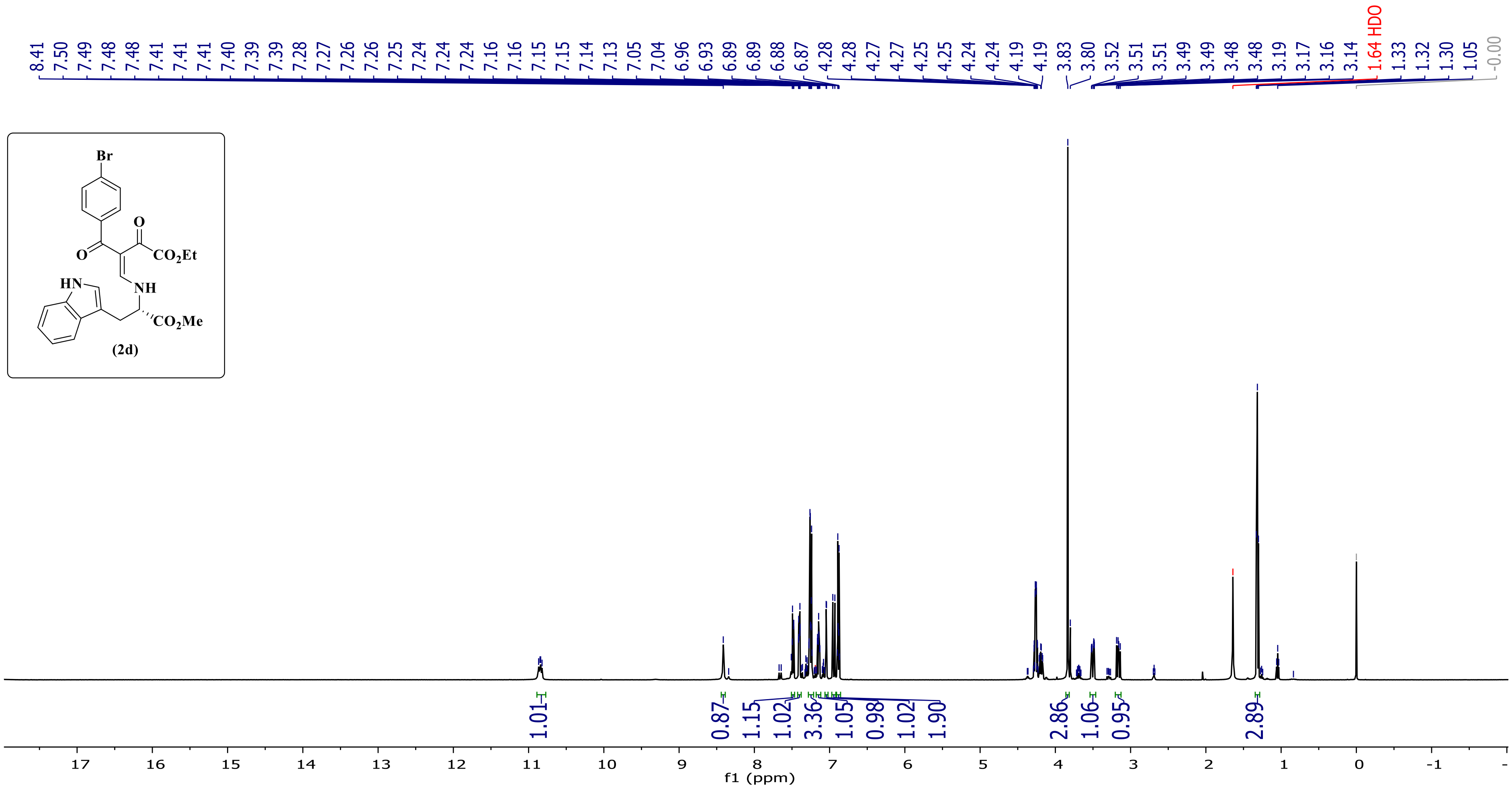


Figure S13. ^{1}H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2d** ($CDCl_3$, 500.13 MHz)

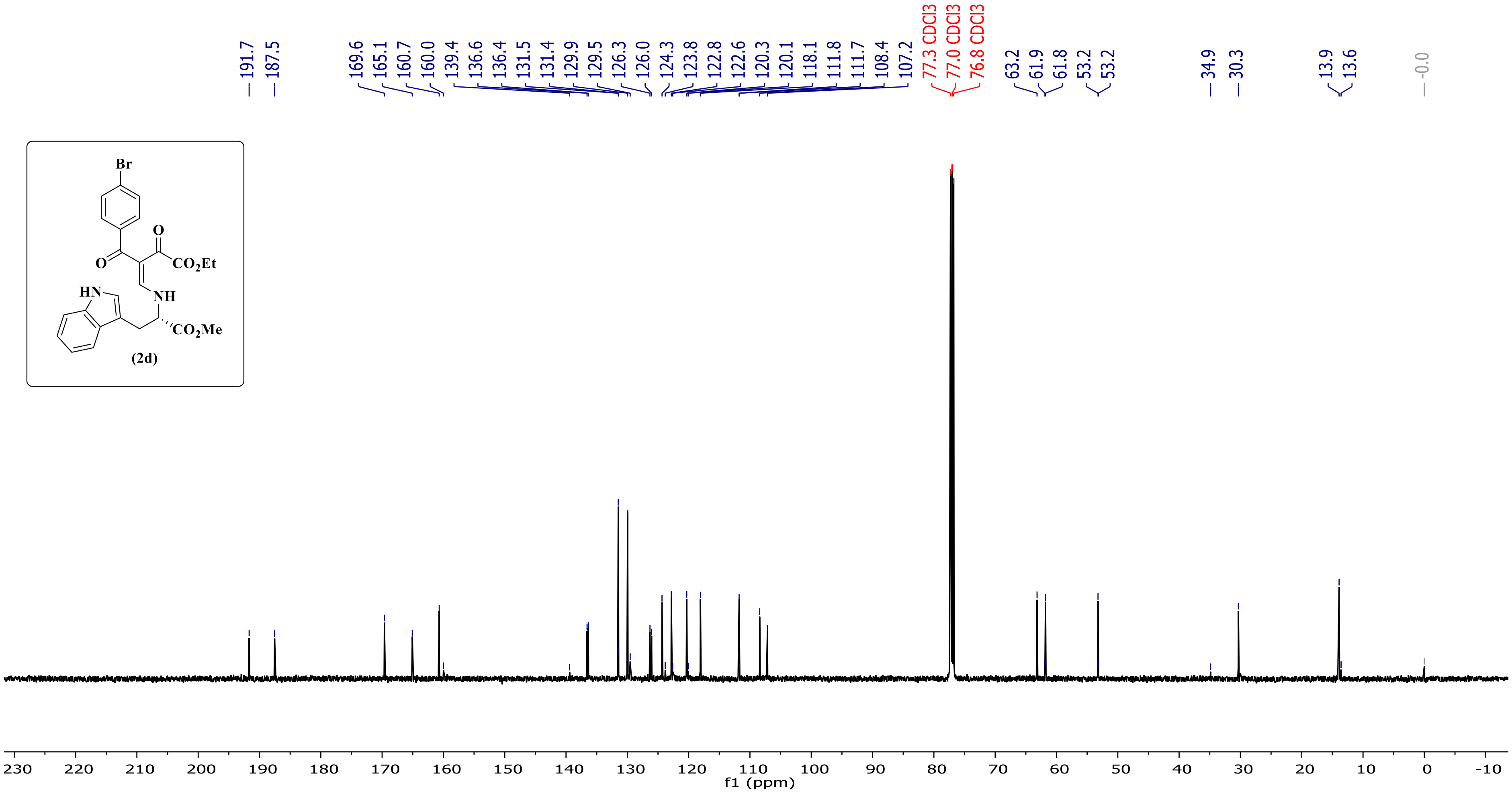


Figure S14. ^{13}C NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2d** ($CDCl_3$, 125.77 MHz)

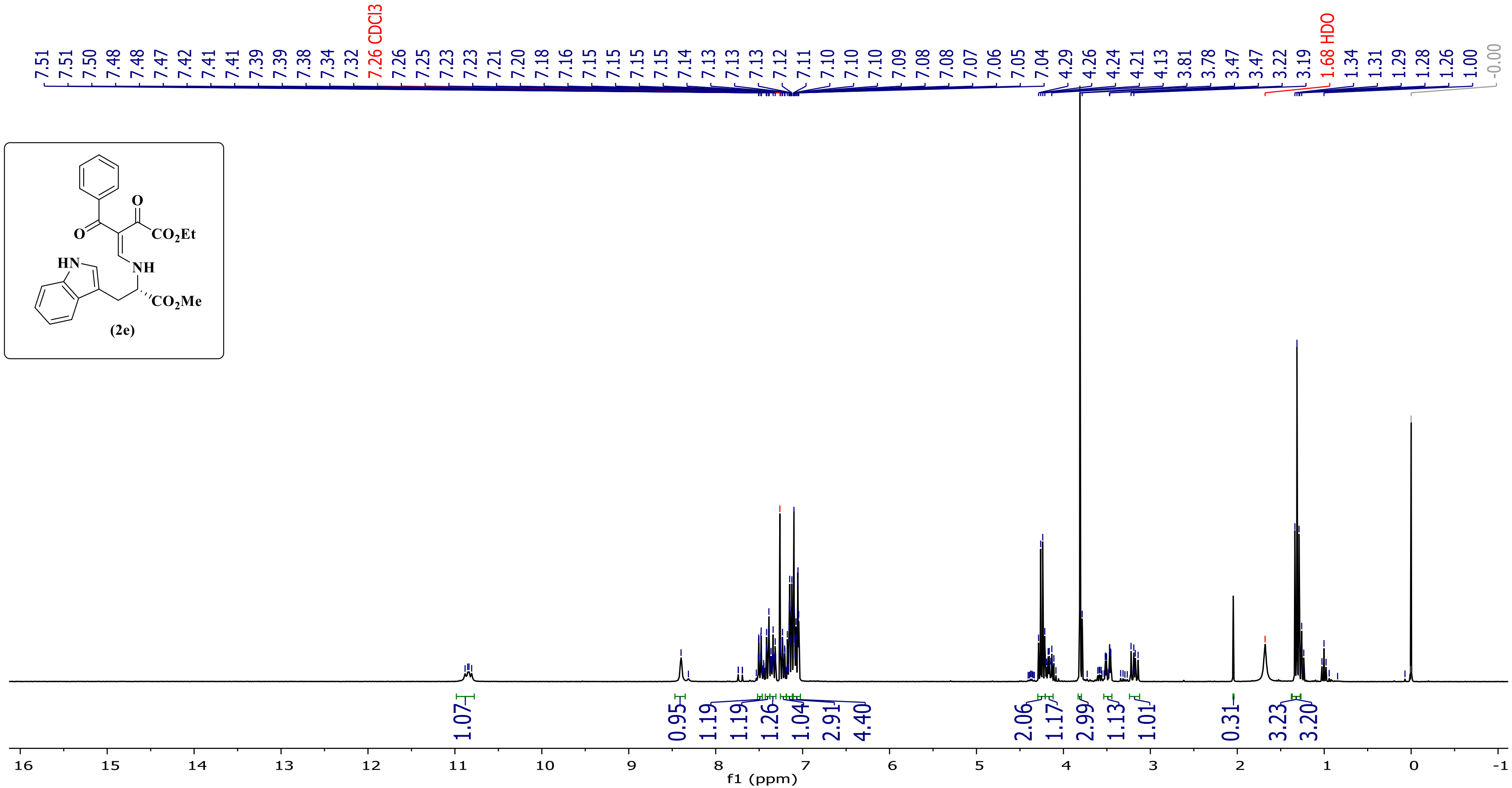


Figure S15. [1]H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2e** ($CDCl_3$, 300.06 MHz)

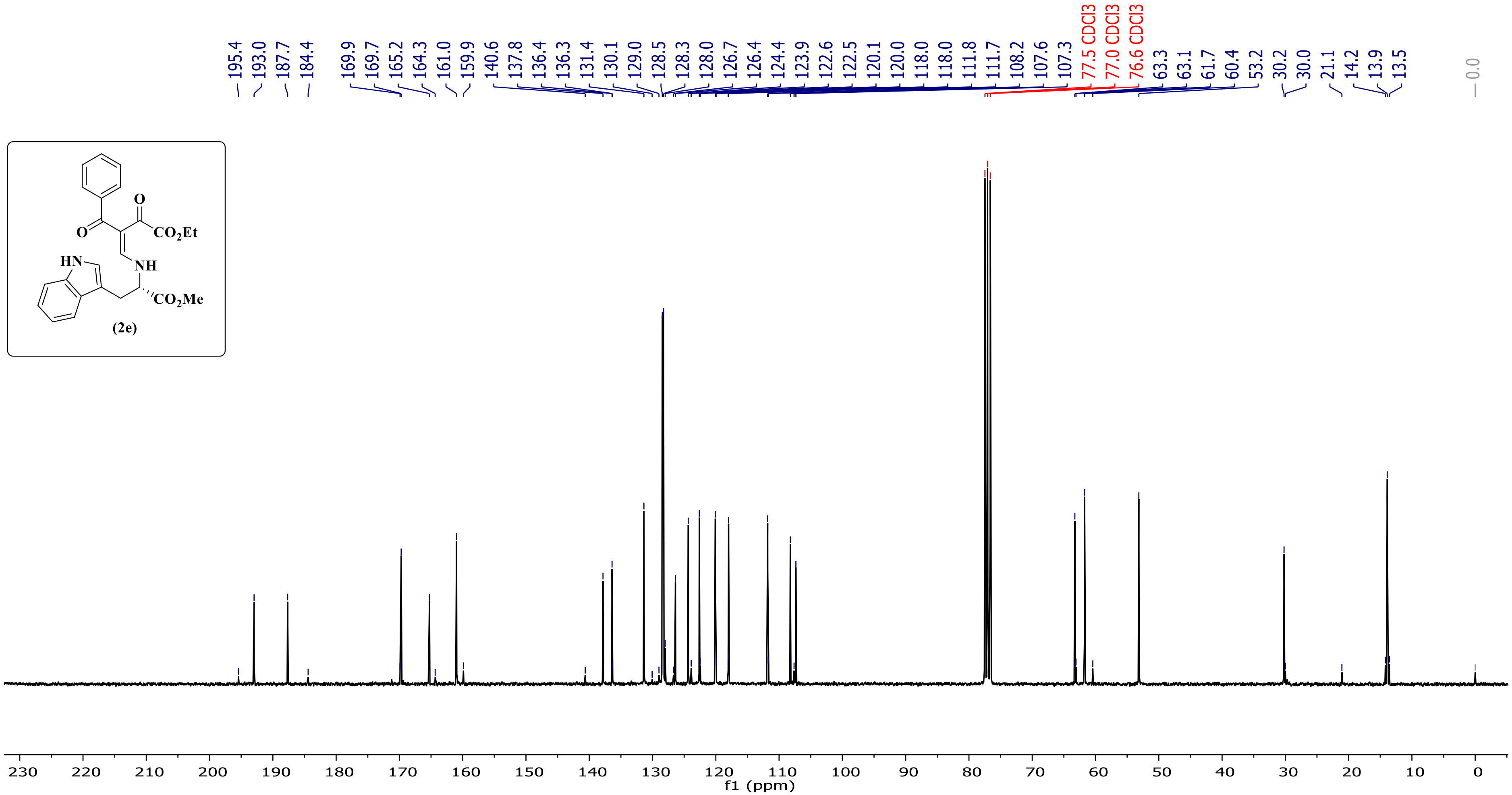


Figure S16. [1]H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2e** ($CDCl_3$, 75.46 MHz)

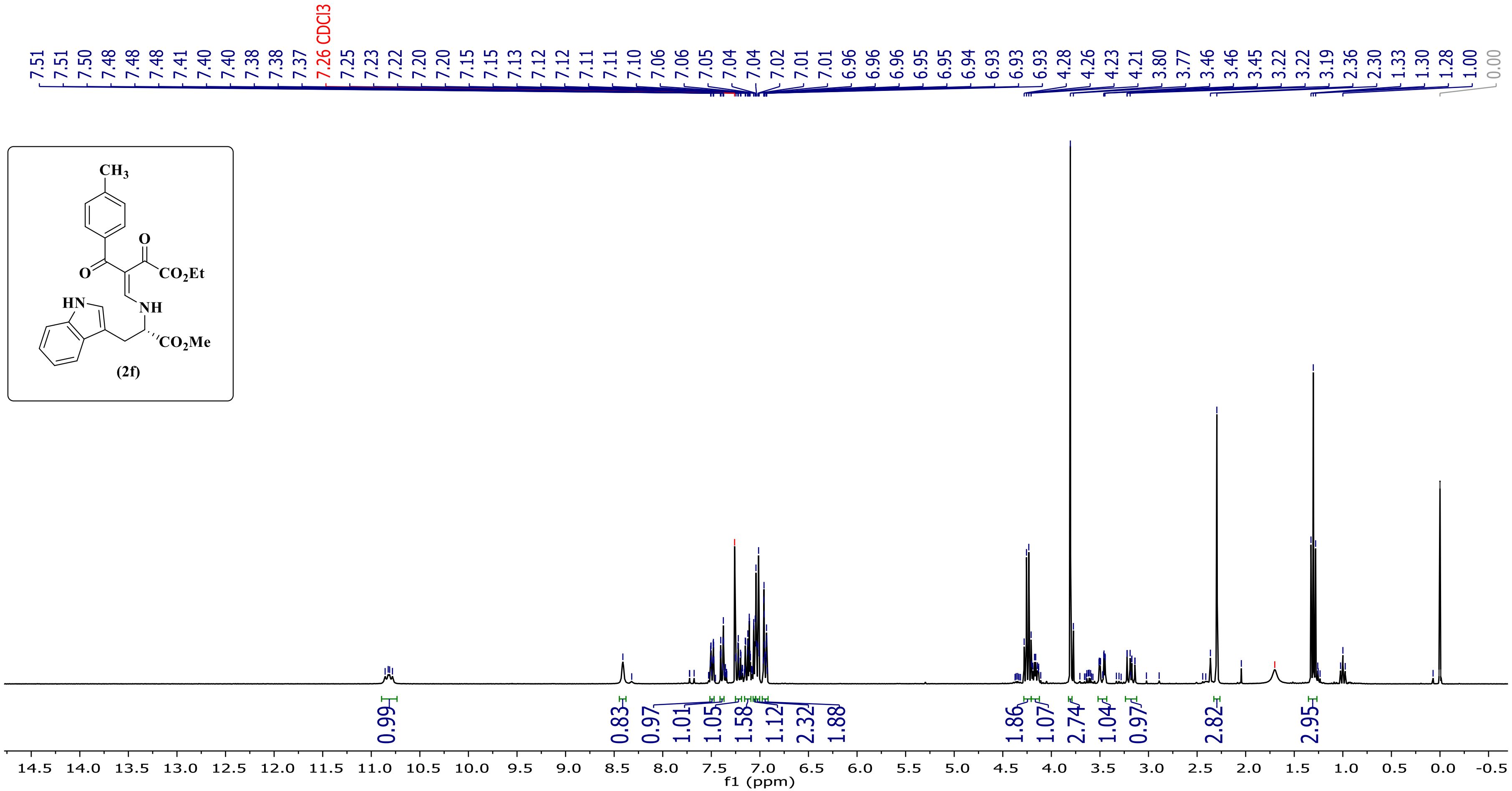


Figure S17. ¹H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2f** ($CDCl_3$, 300.06 MHz)

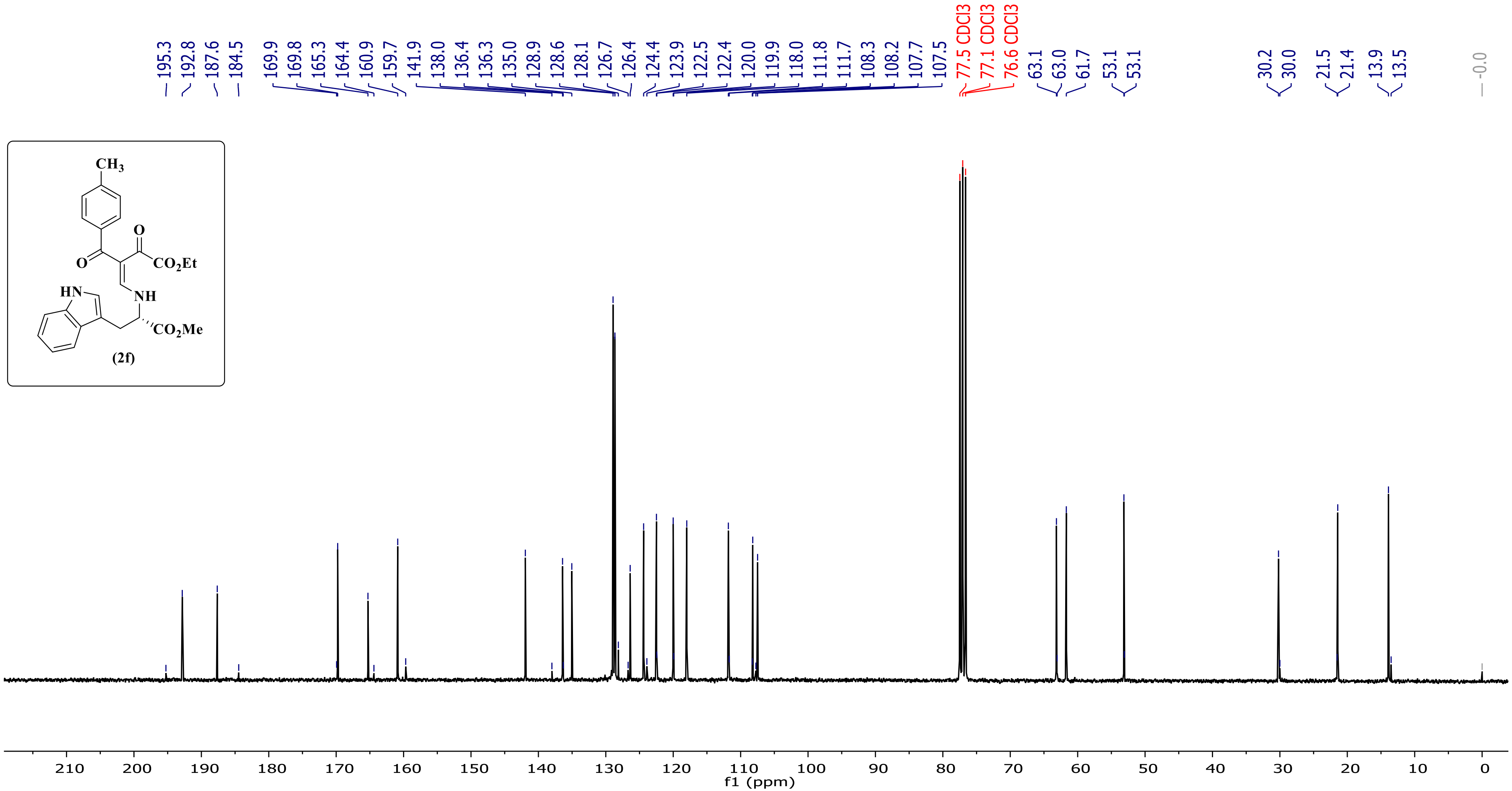


Figure S18. ^{13}C NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2f** ($CDCl_3$, 75.46 MHz)

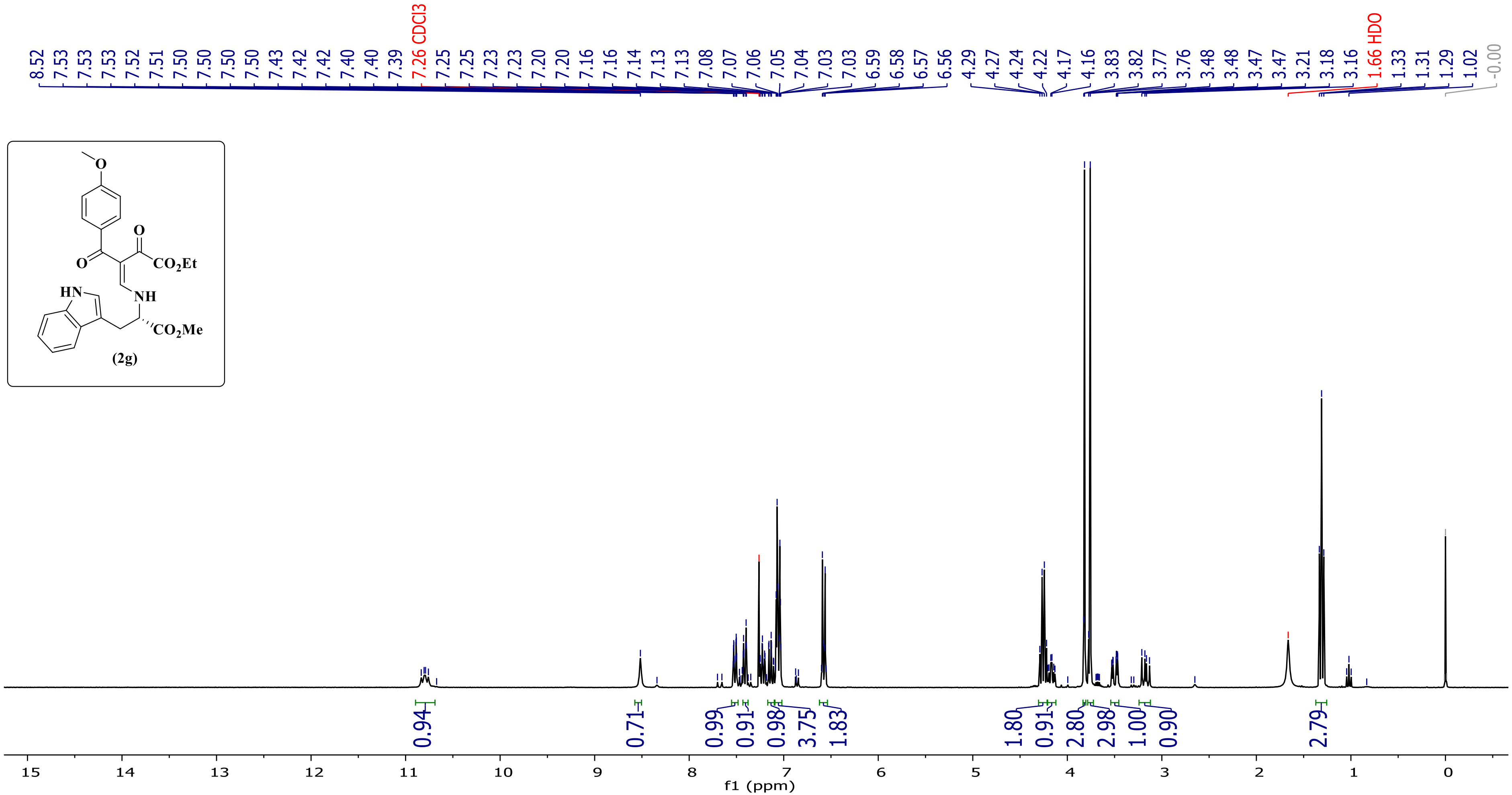


Figure S19. [1]H NMR spectrum of *Z* and *E* isomers mixture (92:8) of **2g** ($CDCl_3$, 300.06 MHz)

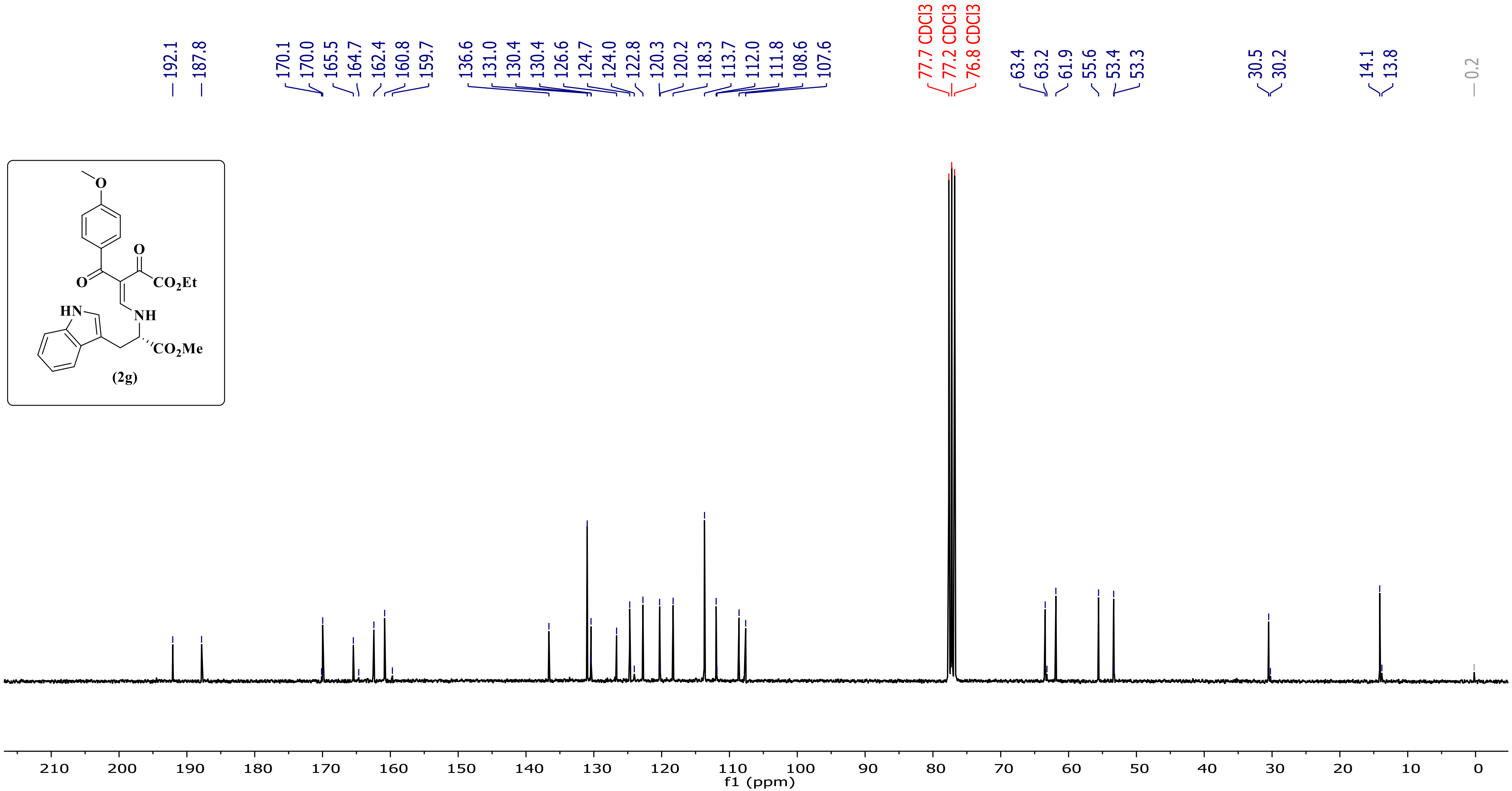


Figure S20. [1]H NMR spectrum of *Z* and *E* isomers mixture (90:10) of **2g** ($CDCl_3$, 75.46 MHz)

4.3 ^{1}H and ^{13}C{1H} NMR spectra of 3a-g

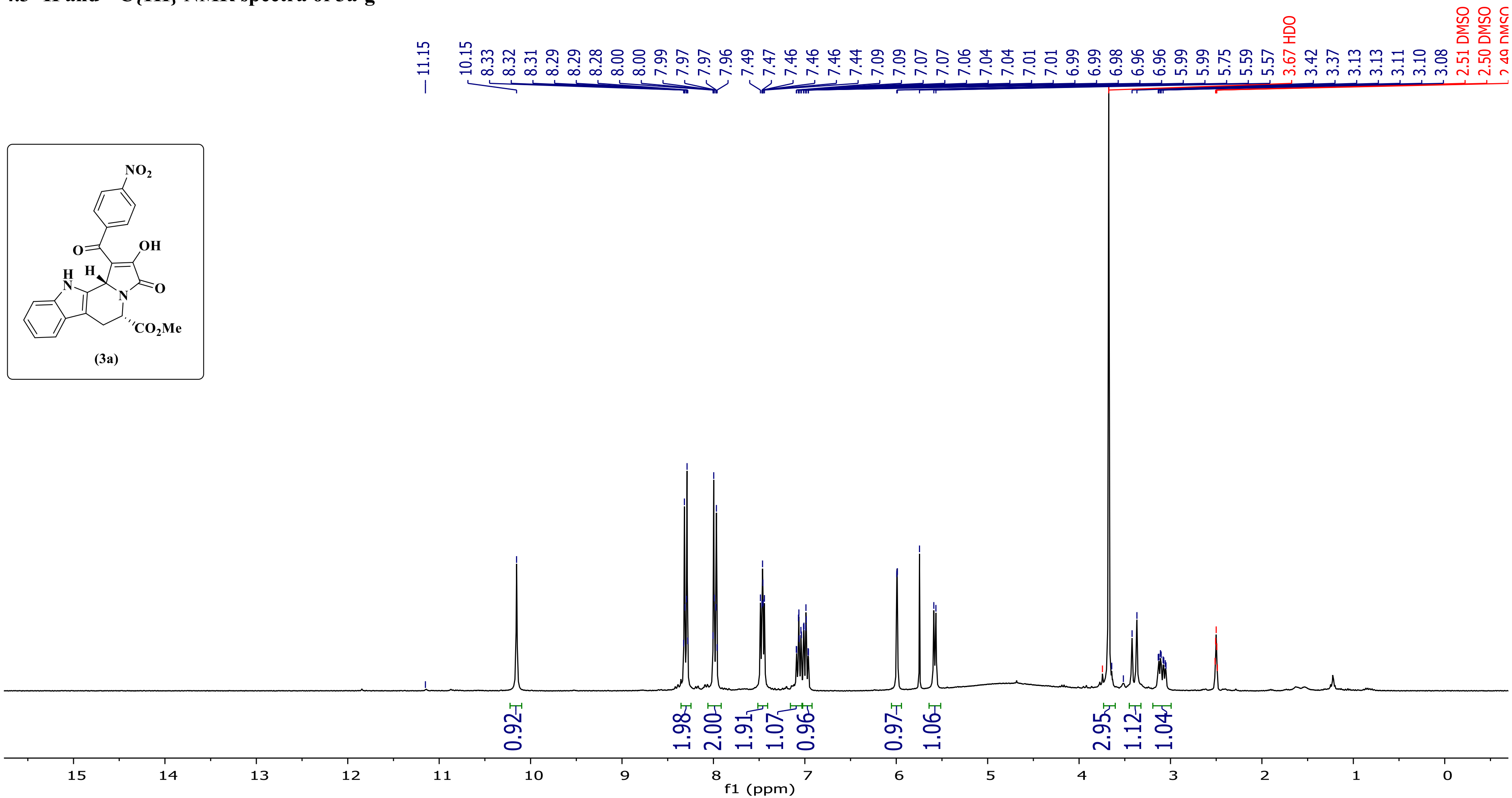


Figure S21. ^{1}H NMR spectrum of **3a** (DMSO-$_{d6}$ 300.06 MHz)

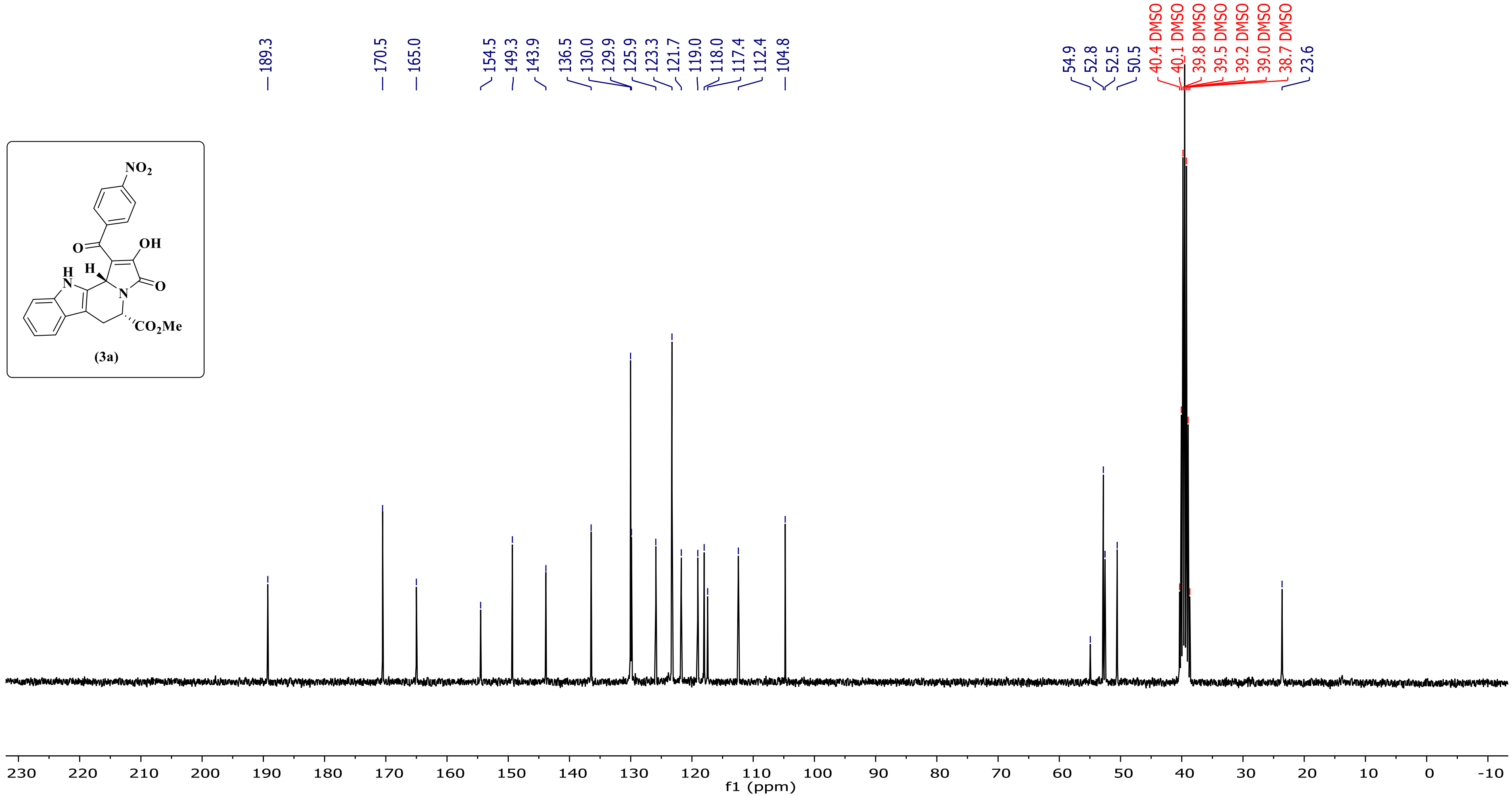


Figure S22. ^{13}C NMR spectrum of **3a** (DMSO-$_{d6}$ 75.46 MHz)

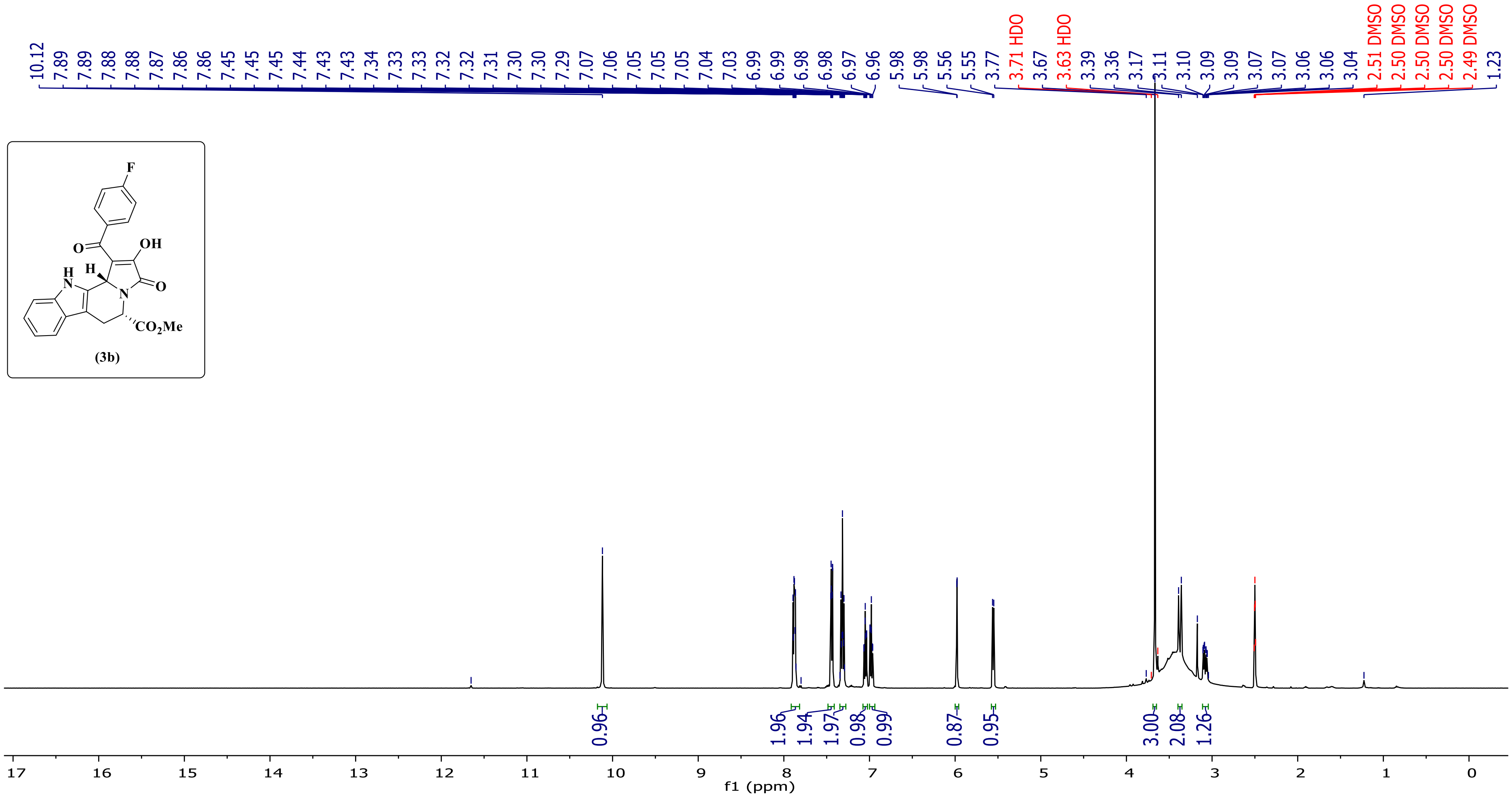


Figure S23. [1]H NMR spectrum of **3b** (DMSO-$_{d6}$ 500.13 MHz)

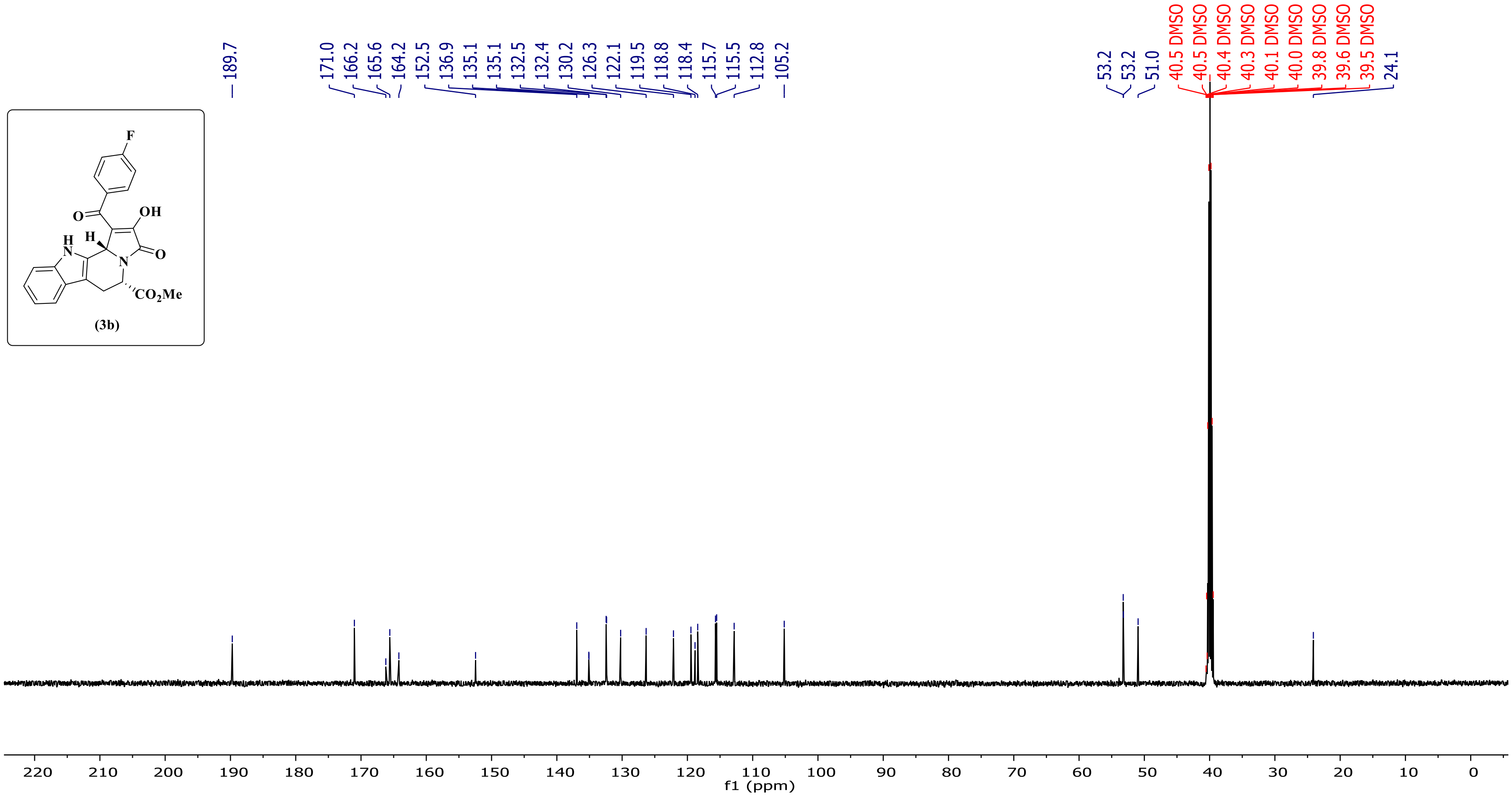


Figure S24. ^{13}C NMR spectrum of **3b** (DMSO-$_{d6}$ 125.77 MHz)

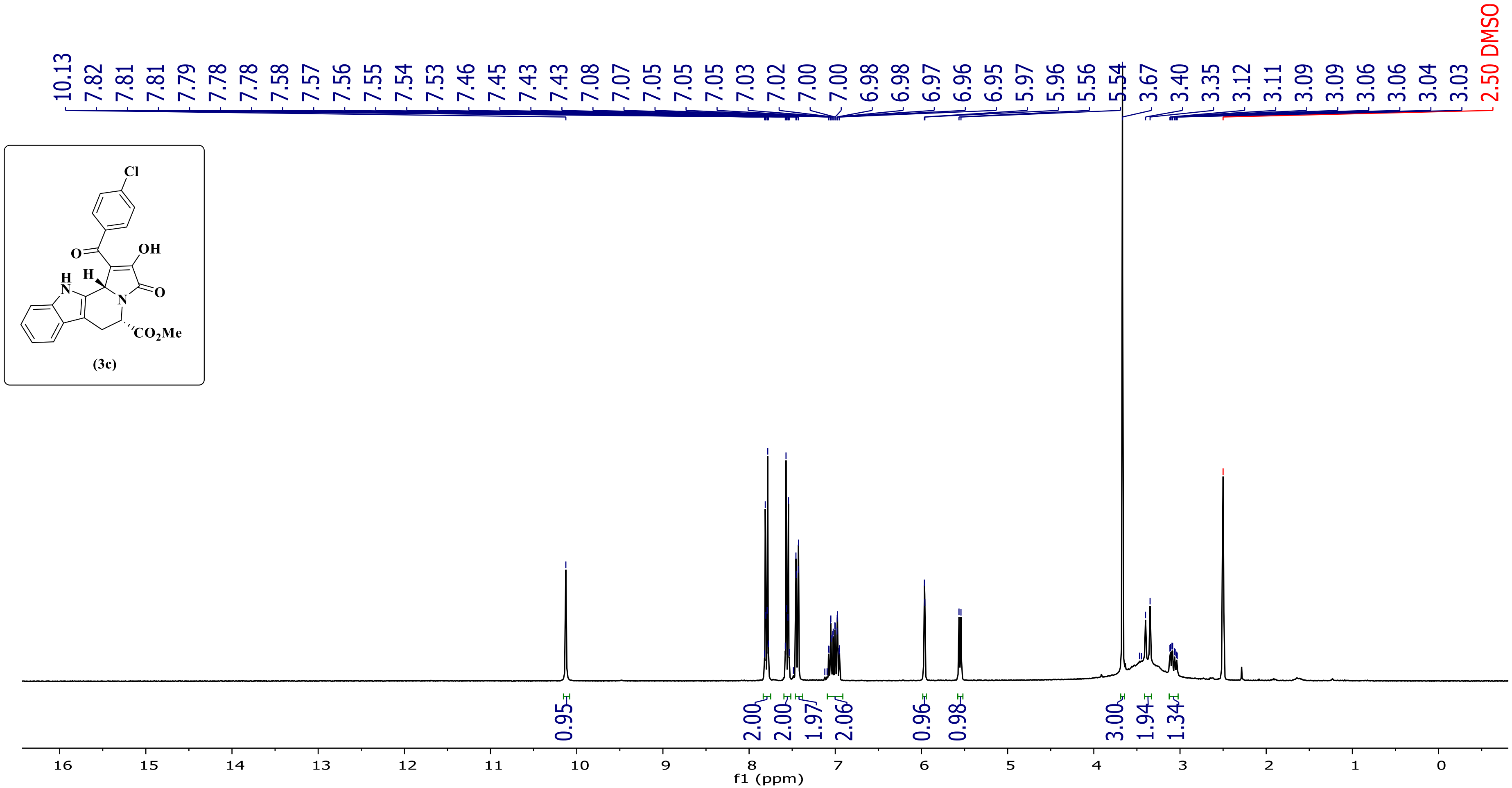


Figure S25. ¹H NMR spectrum of **3c** (DMSO-$_{d6}$ 300.06 MHz)

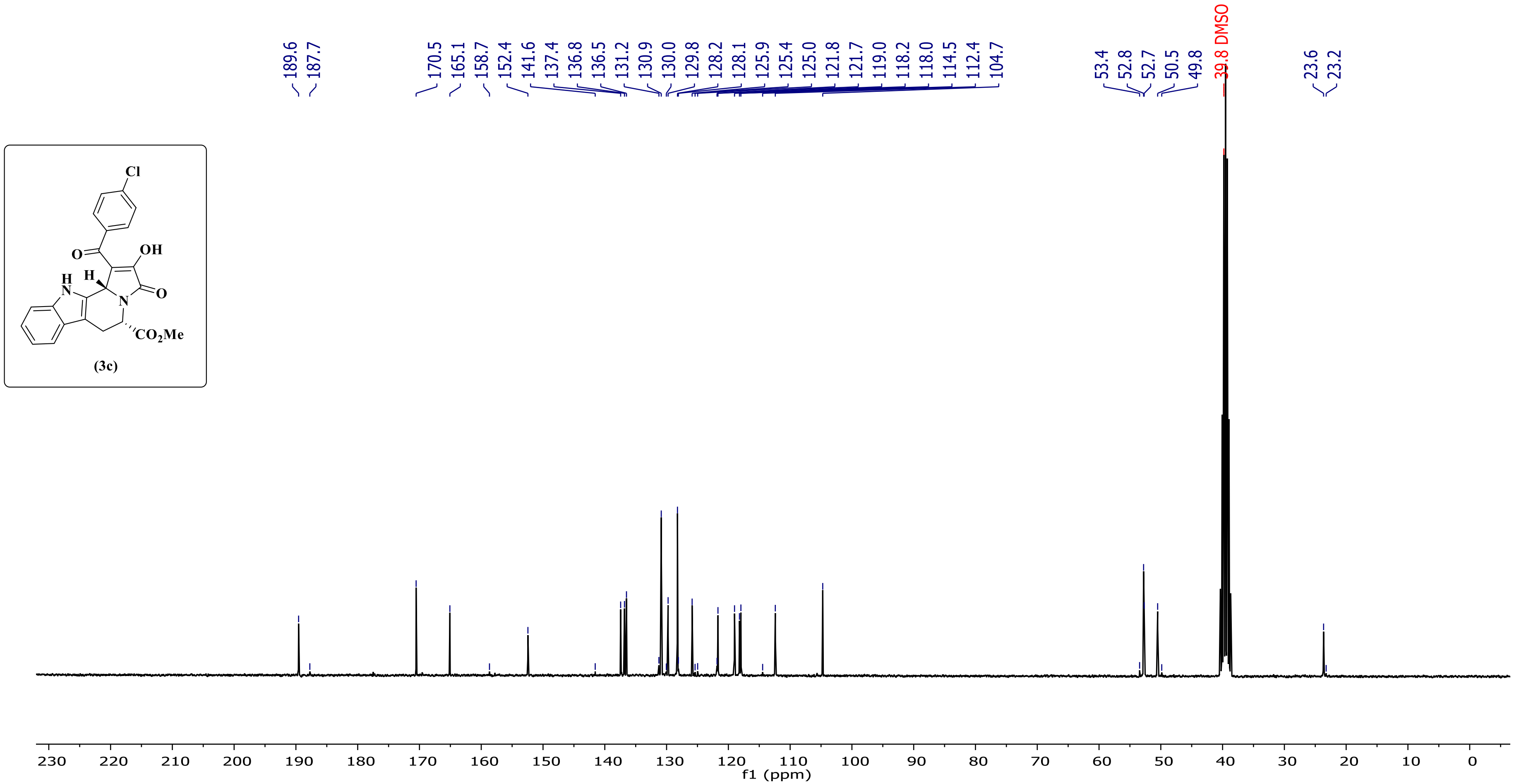


Figure S26. ^{13}C NMR spectrum of **3c** (DMSO-$_{d6}$ 75.46 MHz)

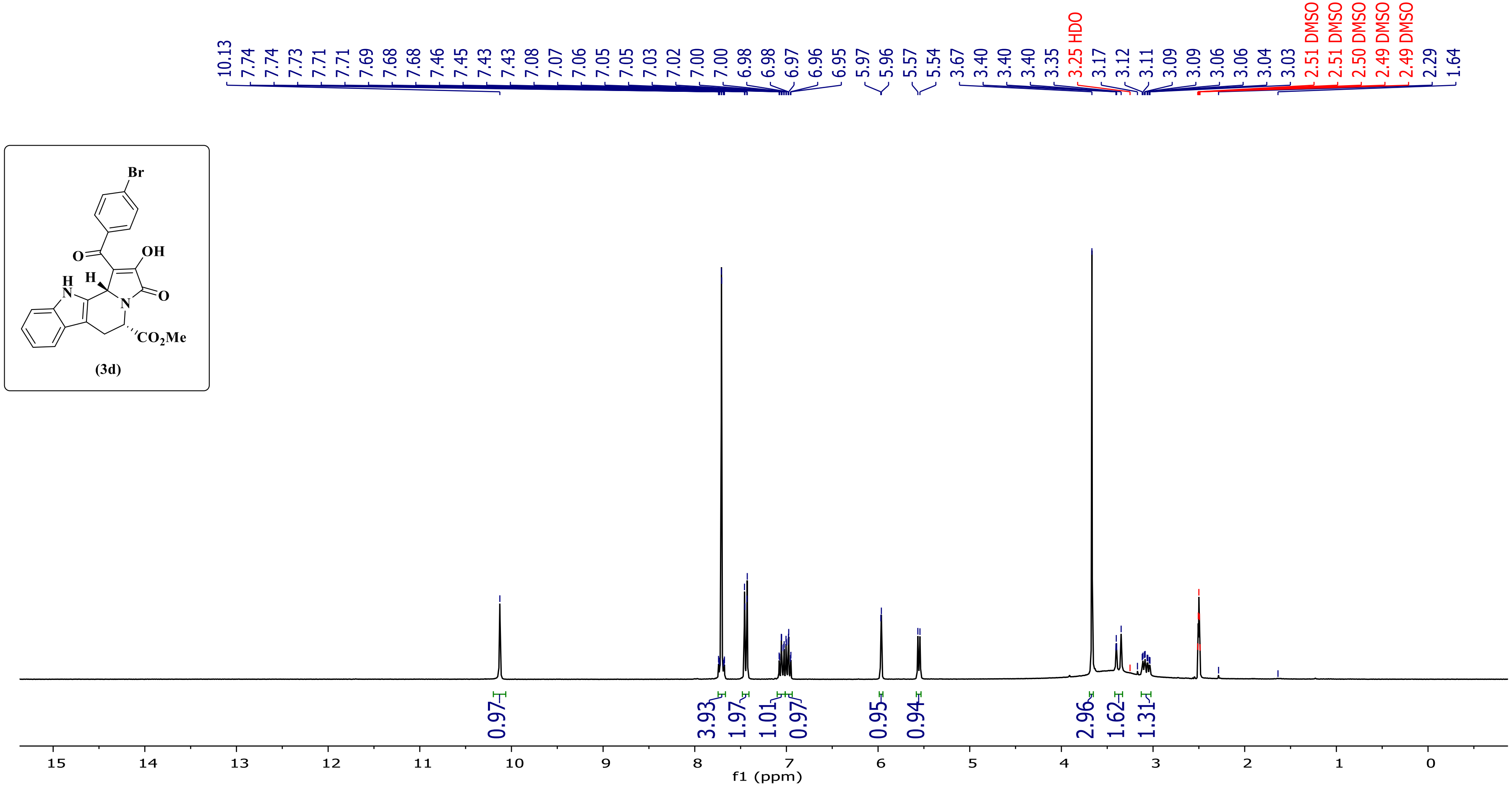


Figure S27. [1]H NMR spectrum of **3d** (DMSO-$_{d6}$ 300.06 MHz)

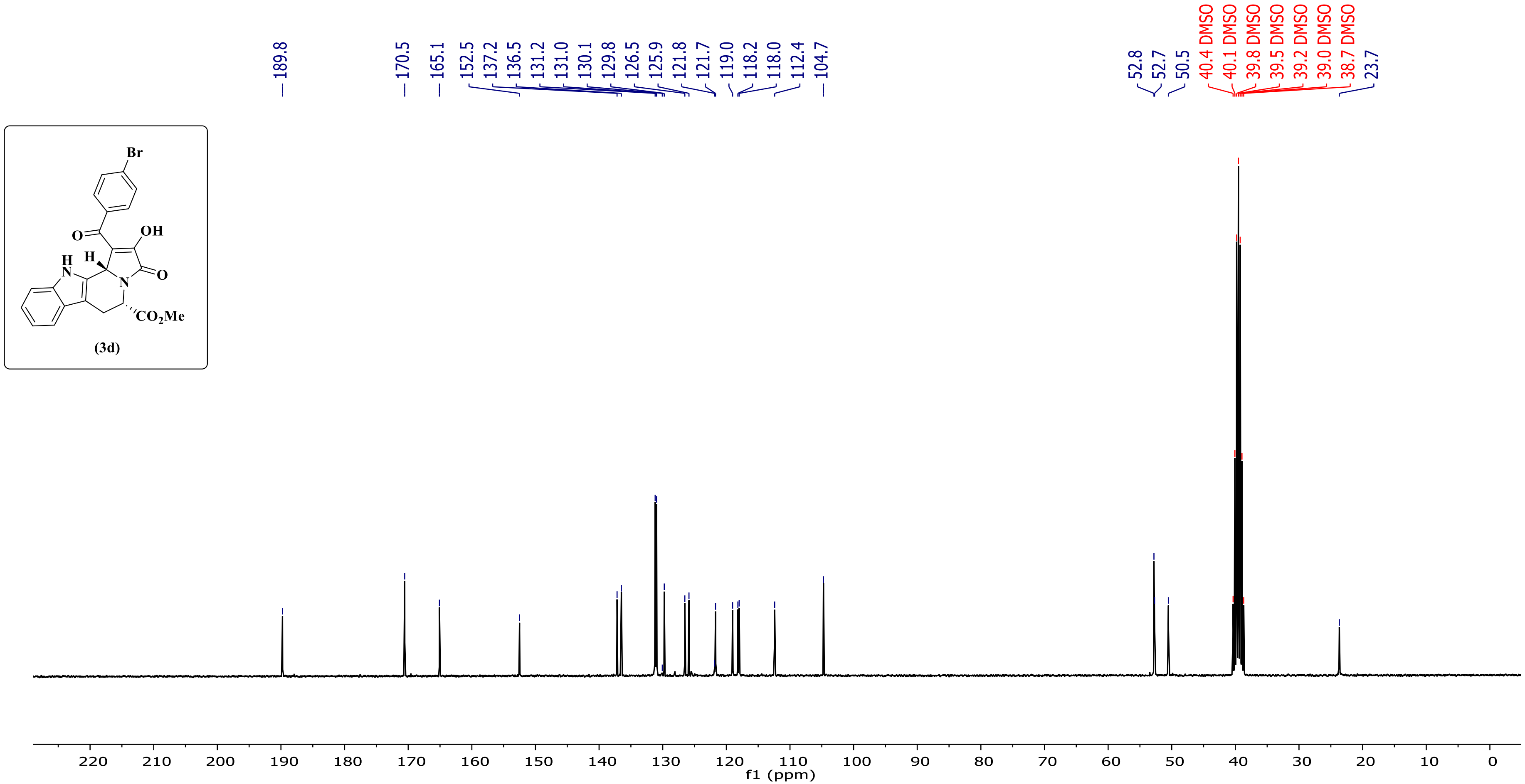


Figure S28. ^{13}C NMR spectrum of **3d** (DMSO-$_{d6}$ 75.46 MHz)

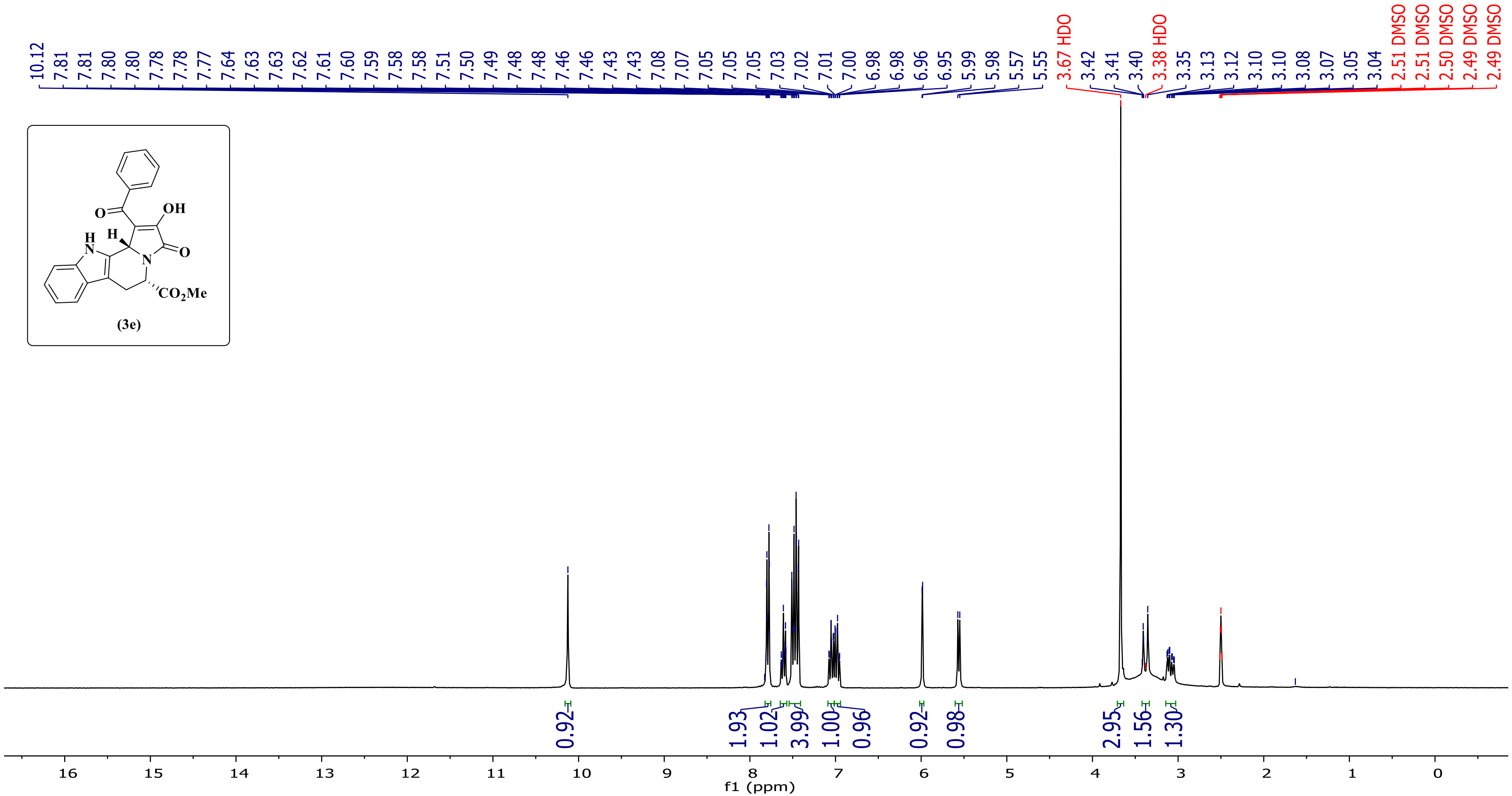
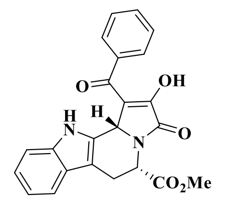


Figure S29. ^{1}H NMR spectrum of **3e** (DMSO-$_{d6}$ 300.06 MHz)



(3e)

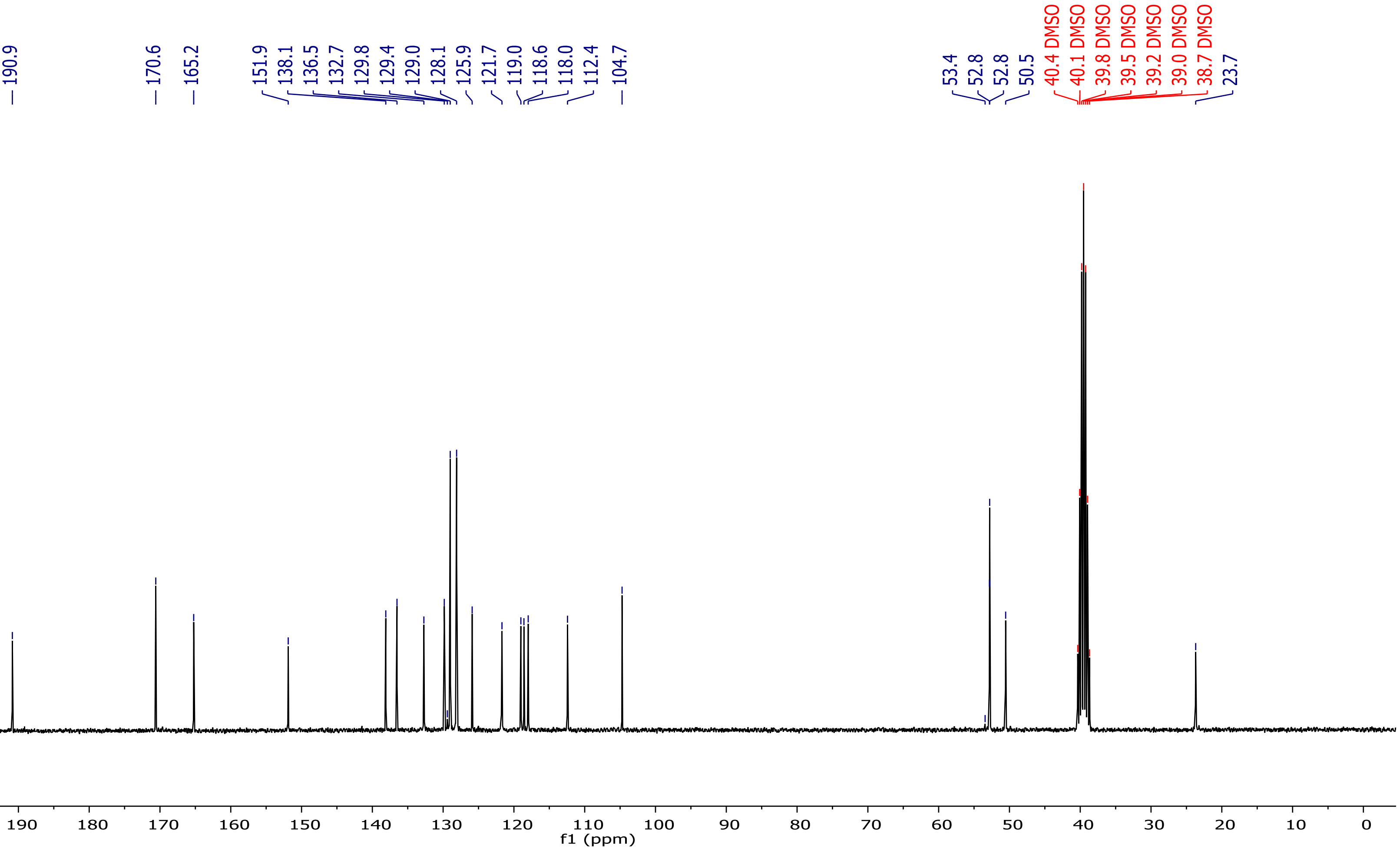


Figure S30. ^{13}C NMR spectrum of **3e** (DMSO-$_{d6}$ 75.46 MHz)

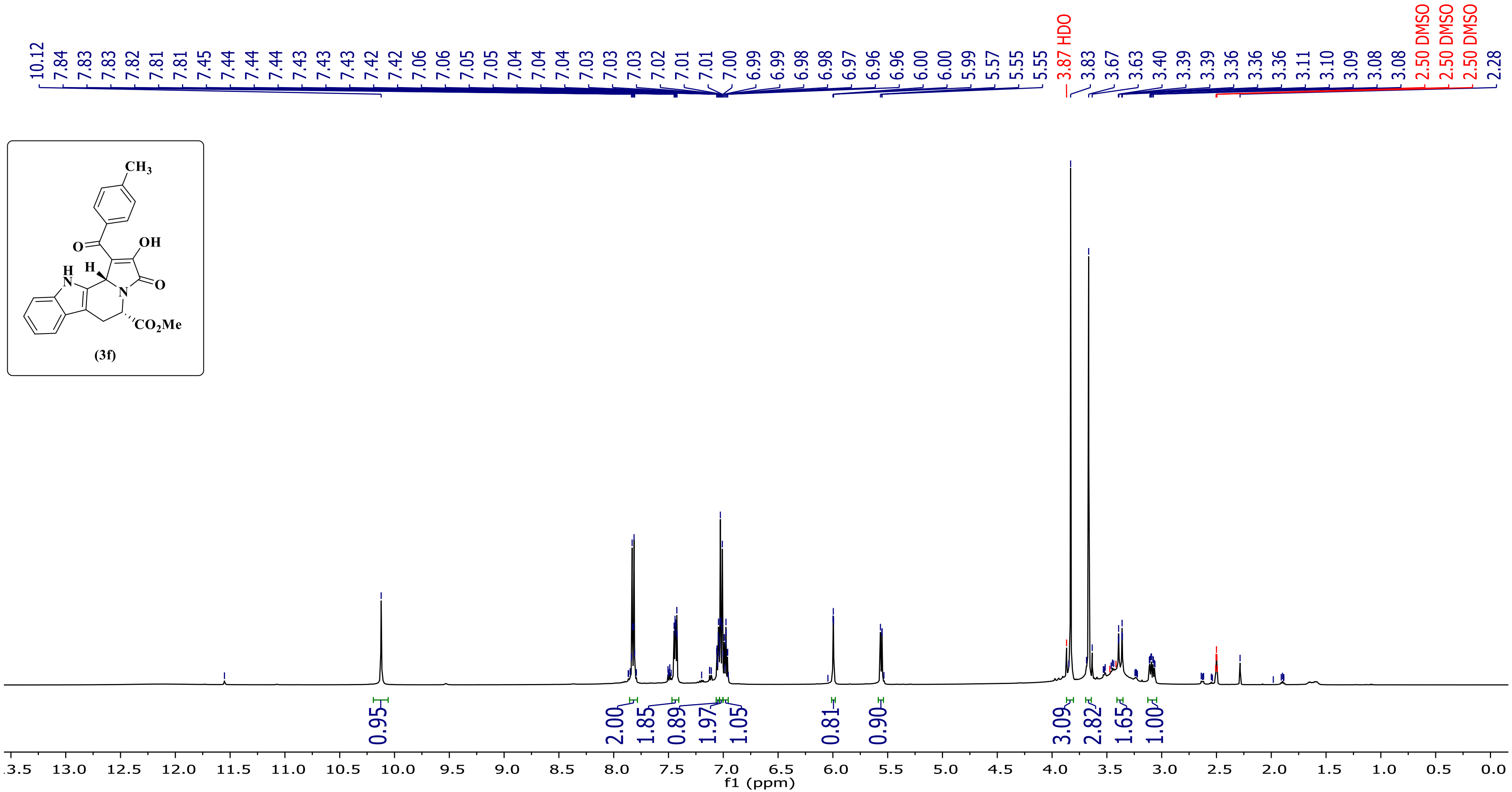


Figure S31. [1]H NMR spectrum of **3f** (DMSO-d6 500.13 MHz)

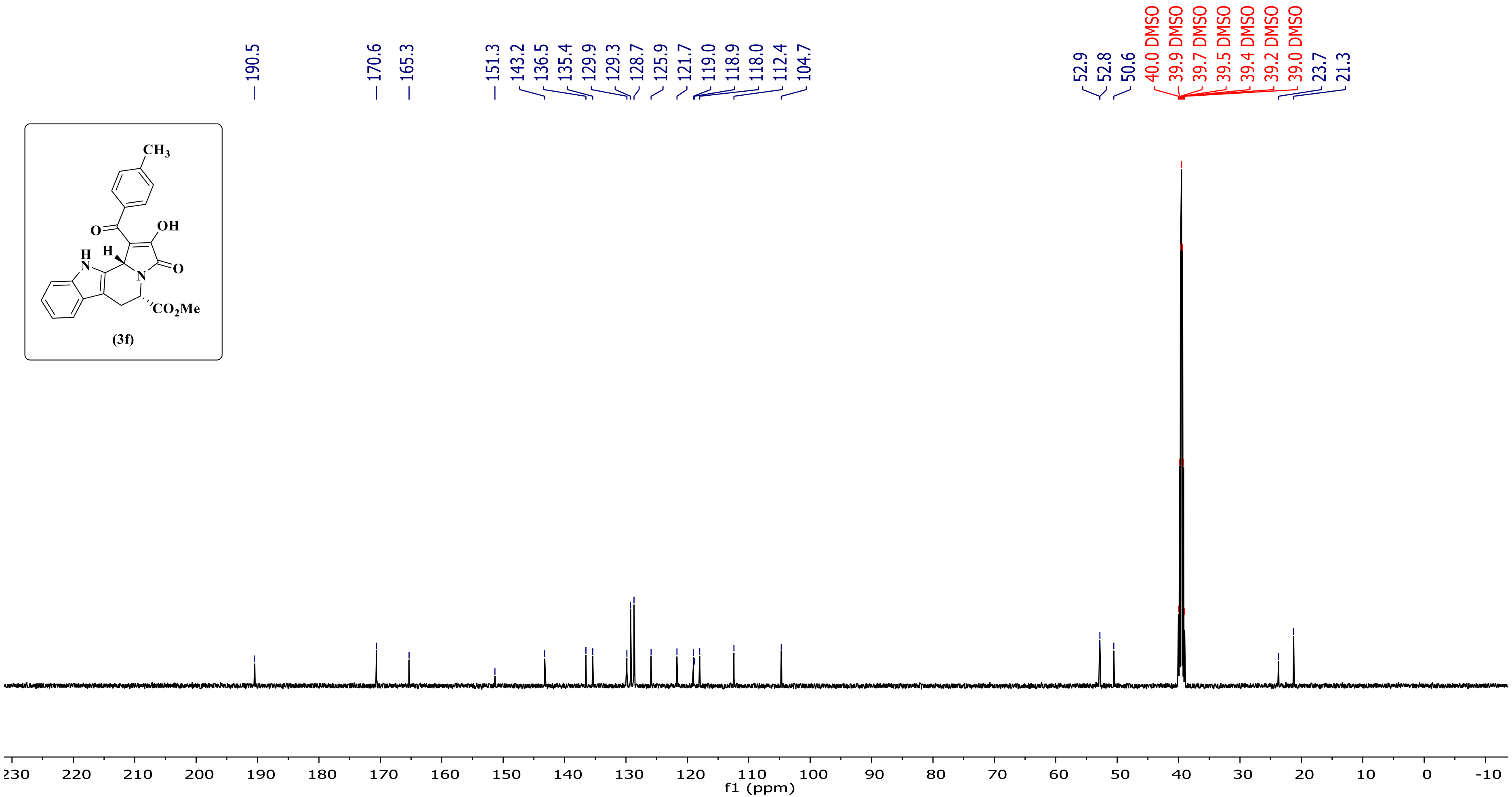


Figure S32. ^{13}C NMR spectrum of **3f** (DMSO-$_{d6}$ 122.77 MHz)

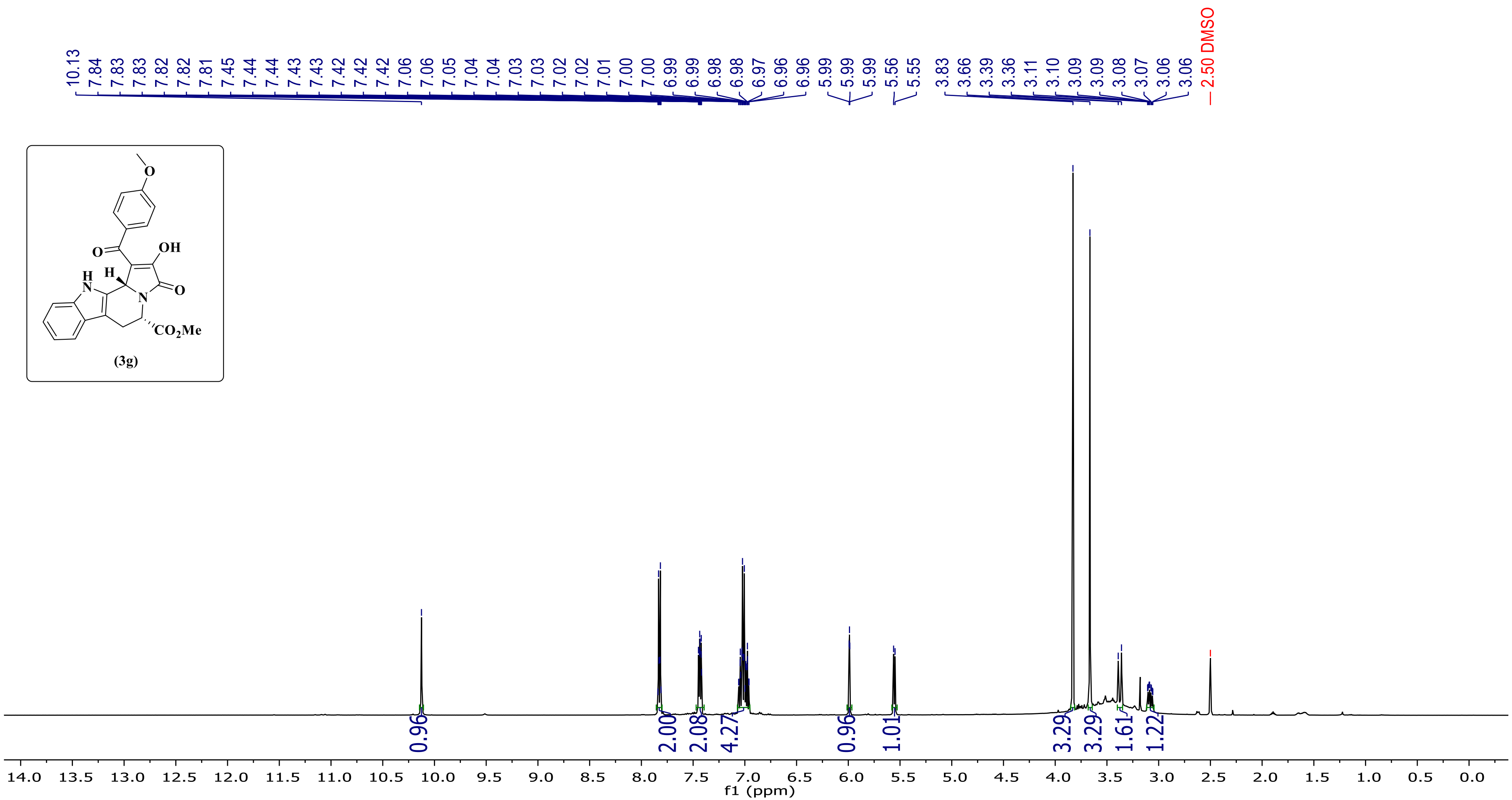
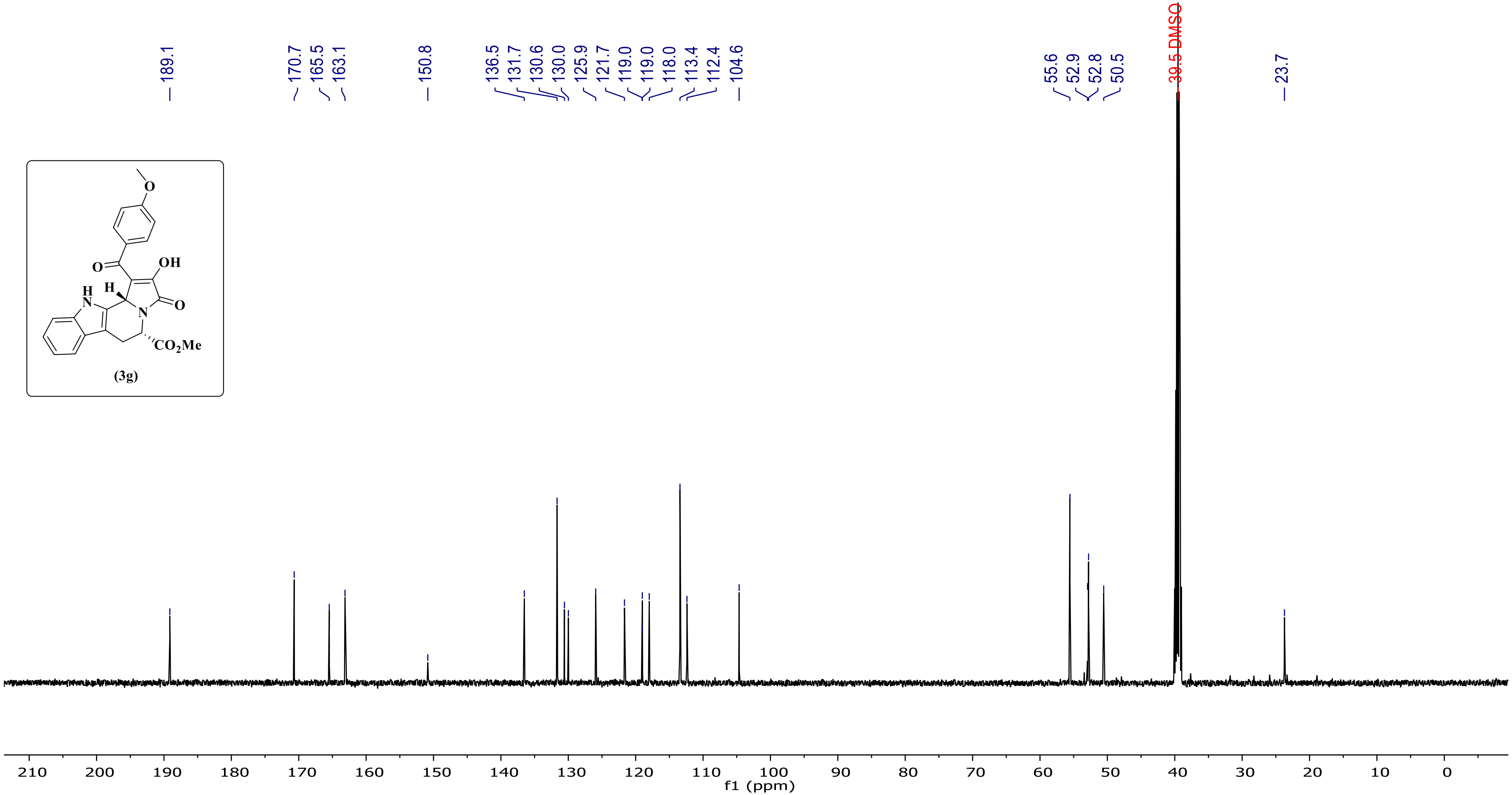


Figure S33. [1]H NMR spectrum of **3g** (DMSO-$_{d6}$ 300.06 MHz)



(3g)

Figure S34. ^{13}C NMR spectrum of **3g** (DMSO-$_{d6}$ 75.46 MHz)

5. References

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