Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Brønsted-Acid Catalyzed Selective Friedel-Crafts Monoalkylation of Isatins with Indolizines in Water.

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1. General Information

Commercially available chemicals and solvents were used without further purification unless otherwise noted. All reactions were performed under ambient atmosphere in oven-dried open-flask glassware with magnetic stirring. Reaction progress was monitored by thin-layer chromatography (TLC) performed on silica gel (aluminum foils). The TLC plates were visualized with UV light (254 nm and/or 365 nm) and sulfuric vanillin followed by heating. Products purification were carried out by flash column chromatography using silica gel (230–400 mesh). ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were measured at 250, 400, 500 MHz ^{1}H NMR and 63, 101, 126 MHz for ^{13}C NMR, in $CDCl_3$ and DMSO-d6 at room temperature. Chemical shifts (δ) were reported in ppm and the coupling constants (J) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double of double doublet (ddd), triplet (t), triple doublet (td), multiplet (m), and broad singlet (bs). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) mass spectrometer.

All starting materials were known compounds and synthesized according previous reports: indolizines[1,2] and *N*-methyl-isatins[3]. Oxindole **6** was synthesized according a procedure reported by Bisai.[4]

*Note: A special care with possible traces of acid in NMR solvent used to record the spectrum is recommended due the observed instability of the Friedel-Crafts products **3** in these conditions.*

2. Procedure for reaction optimization: organic solvents investigation

In a 5 mL round bottle flask were added isatin **2** (8.0 mg, 0.05 mmol, 1. equiv), indolizine **1** (0.115 mmol, 20.1 mg, 2.30 equiv), DPP (1.25 mg, 0.005 mmol, 0.1 equiv) and 830 µL of an organic solvent (0.06 M or 17 mL/mmol). The flask was closed, and the reaction was stirred at room temperature until the total consumption of **2** or until no detectable progress was observed. The reaction medium was diluted with 30 mL of AcOEt and washed with water (3 × 10 mL), then dried over Na_2SO_4 and concentrated in vacuum. The crude residue was purified by column chromatography (silica flash, AcOEt/Hexane 30-50%) to furnish **3aa** as pure compound.

3. General procedure for the synthesis of mono-addition Friedel-Crafts adducts 3

In a 5 mL round bottle flask were added isatin **2** (0.25 mmol, 1.0 equiv), indolizine **1** (0.3 mmol, 1.20 equiv), SDS (7.2 mg, 0.025 mmol, 0.1 equiv), DPP (6.3 mg, 0.025 mmol, 0.1 equiv) and 4.2 mL of water (0.06 M or 17 mL/mmol). The flask was closed, and the suspension was stirred (magnetic bar - 5 mm x 15 mm) at 600 rotations per minute (rpm), at room temperature, until the total consumption of **2** or until no detectable progress was observed. The reaction medium was diluted with 30 mL of AcOEt and washed with brine (3 × 10 mL), then the organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography (silica flash, AcOEt/Hexane 30-50%) to furnish **3** as pure compound.

Some notes concerning to this reaction:

1) It is especially important to use a flask as fulfilled as possible to avoid that some of the solid come out of the suspension.
2) Magnetic bar dimensions and stirring velocity are important to ensure a proper contact between the reagents in the suspension. In case of scale up, consider rising up these 2 factors too.
3) The color of the suspension gradually changes during the reaction: the predominantly orange color (from isatin) turns pale yellow through time but it does not necessarily mean that it is over (see, Figure S1). The only exception was the reaction with 5-Nitro-*N*-methyl-isatin that changed colors twice: at the

beginning the reaction is yellow (from isatin), after 30 min, turns to reddish and then slowly pales out towards a pale red color at the end (see, Figure S2). This color change at 30 min only occurs in the presence of the indolizine. So, we believe that this change may not be caused by an isatin–DPP interaction.

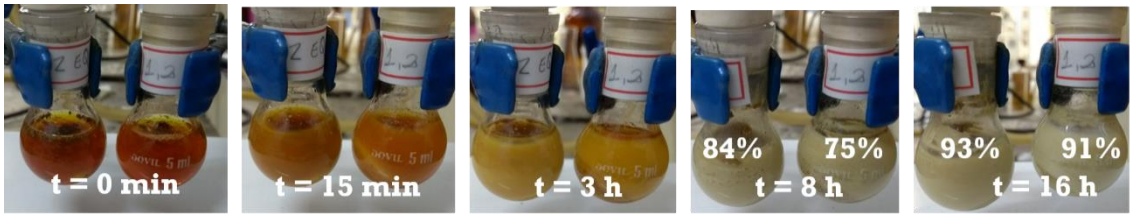


Figure S1. Relationship between reaction color and conversion. Left reaction flask: FC using 2.0 equiv of indolizine (Table 1, entry 8); right reaction flask: FC using 1.2 equiv of indolizine (Table 1, entry 9 – the optimized condition)

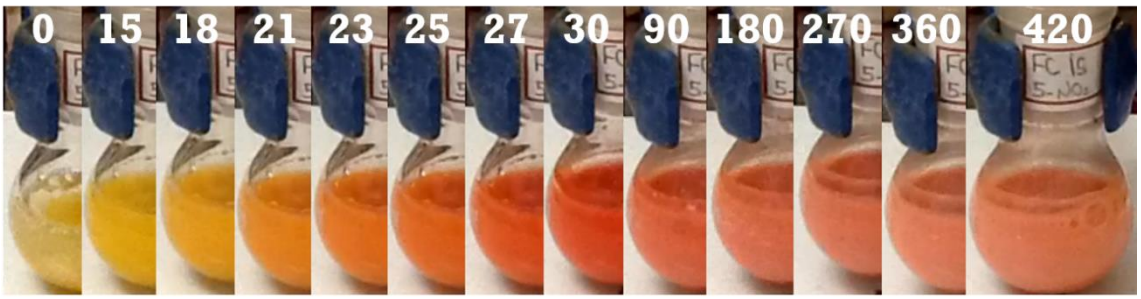


Figure S2. Color change through time (in minutes) for the synthesis of **3ma** using **2m** (5-NO_2-isantin).

4) The reaction monitoring was done by micro-extraction of reaction medium with AcOEt (it is advisable to use a capillary of greater thickness) with increased stirring (900 rpm). After taking the aliquot, the stirring came back to 600 rpm.
5) To purify the reaction, the mobile phase AcOEt/Hexane 30% was kept isocratic until the orange band (isatin) comes out, then it was risen to 50% and kept isocratic until the product **3** was recovered.
6) There is a less green alternative for the purification but with a better resolution. Then, a mixture of three solvent was used as eluent (Hexane/AcOEt/DCM). It began the column with a mixture in a ratio 70:15:15, until the orange band comes out and then it was changed to a ratio 50: 25: 25 until the product **3** was recovered.

7) Some of the compounds were recrystallized. So, the viscous oils obtained after solvent removal was dissolved in a tiny amount of dichloromethane. The resulting solution was then diluted with the same amount of hexane. The mixture was evaporated under reduced pressure and this operation was repeated 2 ou 3 times to obtain the corresponding pure solids.

4. Synthesis of bisindole adduct 7 starting from 3aa

In a 4 mL vial, a mixture of mono-addition adduct **3aa** (33.6 mg, 0.10 mmol), indole (**5**) (11.9 mg, 0.10 mmol|) and DPP (2.50 mg, 0.01 mmol) in 1,2-DCE (1 mL) was stirred at room temperature for 8 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (40% to 50% EtOAc/Hex) to provide the corresponding bis-indole product **7** in almost quantitative yield.

5. Synthesis of indolizine-indole 3,3'- disubstituted oxindole 8

In 4 ml vial charged with 3-hydroxy-3-indole-oxindole **6** (27.9 mg, 0.10 mmol), indolizine **1a** (17.6 mg, 0.10 mmol) and DPP (2.50 mg, 0.01 mmol) was added DCE (1 mL) and the resulting solution was stirred at room temperature for 3 h. Then, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (40% to 50% EtOAc/Hex) yielding **8** in 84%.

Note: After about 3 hours the reaction product precipitated. Prolonging the time was not productive.

6. Stability of Friedel-Crafts adduct 3aa in the presence of DPP in organic solvent

In a 4mL vial charged with Friedel-Crafts adduct 3**aa** (33.6 mg, 0.1 mmol) and DPP (2.5 mg, 0.01 mmol) was added 1 mL of 1,2-DCE and the resulting solution was stirred at room temperature for 8 hours. The reaction was monitored by TLC and was possible to observe the presence of free isatin **2a** and indolizine since the beginning (Figure S3, first lane). During the 8 hours of monitoring we could observe a progressive disappearance of starting material and the appearance of double-addition Friedel-Crafts adduct **4aa**

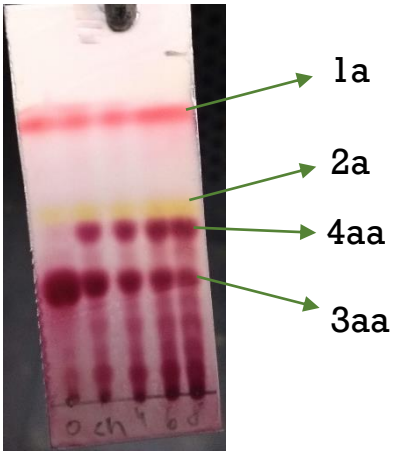
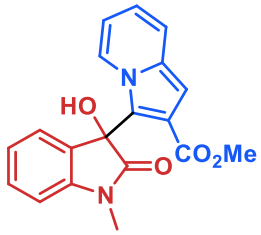


Figure S3. TLC plate of stability test of Friedel-Crafts adduct **3aa** in the presence of DPP in organic solvent. From left to the right, reaction spots in intervals of two hours.

7. Characterization Data of New Compounds

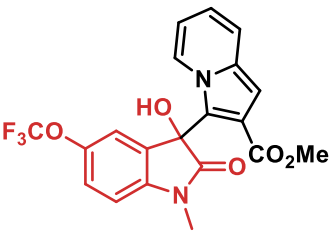
*Single addition adduct **3aa** were synthesized with indolizine **1a** and isatin **2a** following the general procedure described in topic 3.*



3aa

Methyl 3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)indolizine-2-carboxylate (3aa). Starting from a mixture of isatin **2a** (42.7 mg, 0.27 mmol), indolizine **1a** (53.0 mg, 0.32 mmol), DPP (6.6, 0.028 mmol) and SDS (7.5 mg, 0.028 mmol), to provide **3aa** as a pale yellowish solid (80.0 mg, 90% yield) after 16 h. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (bs, 1H), 7.90 (s, 1H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.46 – 7.33 (m, 2H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.46 – 6.37 (m, 2H), 6.17 (s), 3.96 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.0, 168.1, 144.0, 131.6, 130.2, 130.1, 125.7, 125.6, 123.3, 119.7, 119.4, 119.1, 117.9, 112.6, 112.5, 108.7, 75.3, 52.6, 26.4. **HRMS** (ESI) m/z calcd for $C_{19}H_{17}N_2O_4^+$ $[M+H]^+$ 337.1183, found 337.1175.

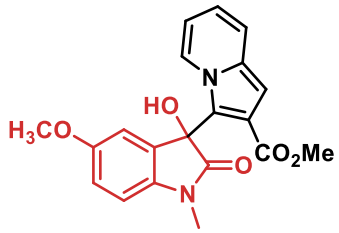
*Single addition adducts **3ba to 3ma** were synthesized with indolizine **1a** following the general procedure described in topic 3.*



3ba

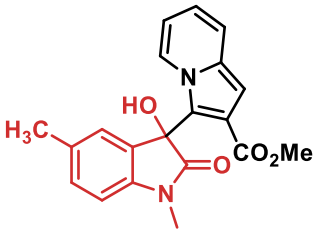
Methyl 3-[3-hydroxy-1-methyl-2-oxo-5-(trifluoromethoxy)-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ba). Starting from from a mixture of isatin **2b** (46.2 mg, 0.19 mmol), indolizine **1a** (37.6 mg, 0.23 mmol), DPP (4.7, 0.019 mmol) and SDS (5.3 mg, 0.019 mmol) to provide product **3ba** as a pale yellowish (58.4 mg, 74% yield) after 48 h. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.32 (bs, 1H), 7.92 (s, 1H), 7.77 (d, *J* = 5.9 Hz, 1H), 7.29 (d, *J* = 15.3 Hz, 1H), 7.26 (s,

1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.66 – 6.35 (m, 2H), 6.20 (s, 1H), 3.96 (s, 3H), 3.22 (s, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.8, 168.1, 145.3, 142.6, 133.0, 130.2, 125.7, 123.2, 120.7 (q, J_{F-C} = 256.9 Hz), 119.9, 119.7, 119.5, 119.1, 117.9, 112.8, 111.5, 109.1, 75.2, 52.7, 26.5. **HRMS** (ESI) m/z calcd for $C_{20}H_{15}F_3N_2NaO_5^+$ $[M+Na]^+$ 443.0825, found 443.0831.



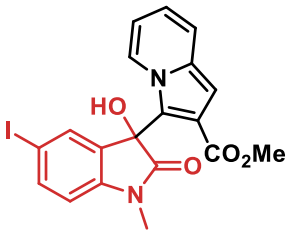
3ca

Methyl 3-[3-hydroxy-1-methyl-2-oxo-5-methoxy-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ca). Starting from isatin **2c** (31.6 mg, 0.17 mmol), indolizine **1a** (33.0 mg, 0.20 mmol), DPP (4.1, 0.017 mmol) and SDS (4.7 mg, 0.017 mmol), product **3ca** was obtained as a pale yellowish solid (13.1 mg. 22% yield) in 48 h. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.91 (s, 1H), 7.75 (d, *J* = 6.8, 1.3 Hz, 1H), 7.06 (d, *J* = 2.7 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.50 – 6.39 (m, 2H), 6.20 (d, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 3.75 (s, 3H), 3.18 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.8, 168.2, 156.6, 137.4, 132.7, 130.2, 125.6, 124.8, 119.7, 119.5, 119.2, 117.9, 115.2, 112.7, 112.3, 109.2, 75.6, 56.0, 52.7, 26.5. **HRMS** (ESI) m/z calcd for $C_{20}H_{19}N_2HO_5^+$ $[M+H]^+$ 367.1288, found 367.1260.



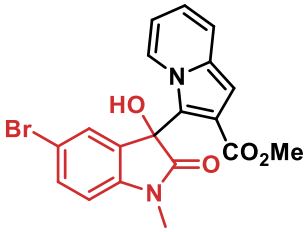
3da

Methyl 3-[3-hydroxy-1-methyl-2-oxo-5-methyl-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3da). Starting from isatin **2d** (47.2 mg, 0.27 mmol), indolizine **1a** (53.8 mg, 0.34 mmol), DPP (6.7, 0.028 mmol) and SDS (7.6 mg, 0.028 mmol) product **3da** was obtained as a pale yellowish solid (11.6 mg, 12% yield) in 48 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ δ 8.12 (bs, 1H), 7.90 (s, 1H), 7.79 – 7.70 (m, 1H), 7.23 (s, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.49 – 6.36 (m, 2H), 6.23 (s, 1H), 3.96 (s, 3H), 3.19 (s, 3H), 2.30 (s, 3H).**^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.9, 168.1, 141.4, 132.8, 131.5, 130.2, 130.1, 126.2, 125.5, 119.6, 119.4, 119.0, 117.7, 112.5, 108.4, 75.3, 52.5, 26.3, 21.2. **HRMS** (ESI) m/z calcd for $C_{20}H_{18}N_2NaO_4^+$ $[M+Na]^+$ 373.1159, found 373.1163.



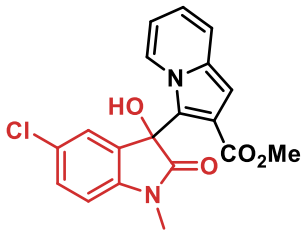
3ea

Methyl 3-[3-hydroxy-5-iodo-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ea). Starting from isatin **2e** (64.8 mg, 0.23 mmol), indolizine **1a** (45.1 mg, 0.27 mmol), DPP (5.6, 0.023 mmol) and SDS (6.4 mg, 0.023 mmol), product **3ea** was obtained as a pale yellowish solid (55.0 mg, 53% yield) in 17 h. Amorphous pale yellowish solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.90 (s, 1H), 7.81 – 7.75 (m, 1H), 7.70 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.54 – 6.47 (m, 2H), 6.39 (s, 1H), 3.95 (s, 3H), 3.21 (s, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.3, 167.9, 143.6, 138.8, 134.3, 134.0, 125.7, 119.7, 119.6, 119.3, 117.7, 112.8, 111.7, 110.7, 85.7, 75.2, 52.7, 26.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}IN_2NaO_4^+$ $[M+Na]^+$ 484.9969, found 484.9976.



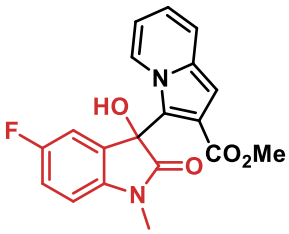
3fa

Methyl 3-[5-bromo-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3fa). Starting from isatin **2f** (37.2 mg, 0.16 mmol), indolizine **1a** (31.0 mg, 0.19 mmol), DPP (3.8, 0.016 mmol) and SDS (4.4 mg, 0.016 mmol) product **3fa** was obtained as a pale yellowish solid (52.0 mg, 81% yield) in 12 h. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.09 (s, 1H), 7.90 (s, 1H), 7.81 – 7.71 (m, 1H), 7.53 – 7.46 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.56 – 6.45 (m, 2H), 6.39 (bs, 1H), 3.94 (s, 3H), 3.21 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.4, 167.9, 142.9, 133.7, 132.8, 130.2, 128.7, 125.7, 119.7, 119.6, 119.2, 117.7, 115.9, 112.8, 111.6, 110.1, 75.3, 52.7, 26.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}BrN_2NaO_4^+$ $[M+Na]^+$ 437.0107, found 437.0112.



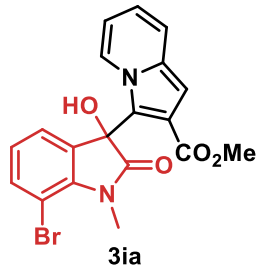
3ga

Methyl 3-[5-chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ga). Starting from isatin **2g** (43.4 mg, 0.22 mmol), indolizine **1a** (44.3 mg, 0.27 mmol), DPP (5.5, 0.022 mmol) and SDS (6.3 mg, 0.022 mmol) product **3ga** was obtained as a pale yellowish solid (66.4 mg, 81% yield) in 7 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.02 (s, 1H), 7.90 (s, 1H), 7.84 – 7.65 (m, 1H), 7.36 (s, 1H), 7.33 (d, *J* = 2.2 Hz, 1H), 6.84 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.60 – 6.43 (m, 2H), 6.38 (bs, 1H), 3.94 (s, 3H), 3.21 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.5, 168.0, 142.4, 133.4, 130.2, 129.9, 128.7, 126.0, 125.7, 119.7, 119.6, 119.2, 117.7, 112.8, 111.7, 109.6, 75.3, 52.7, 26.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}ClN_2NaO_4^+$ $[M+Na]^+$ 393.0613, found 393.0616.



3ha

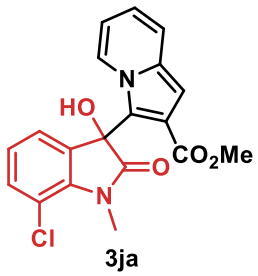
Methyl 3-[5-fluoro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ha). Starting from isatin **2h** (47.5 mg, 0.27 mmol), indolizine **1a** (53.0 mg, 0.32 mmol), DPP (6.6, 0.027 mmol) and SDS (7.5 mg, 0.027 mmol), product **3ha** was obtained as a pale yellowish solid (66.4 mg, 90% yield) in 7 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (bs, 1H), 7.89 (s, 1H), 7.80 – 7.70 (m, 1H), 7.14 (dd, *J* = 7.7, 2.7 Hz, 1H), 7.06 (td, *J* = 8.8, 2.7 Hz, 1H), 6.83 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.50 – 6.42 (m, 2H), 6.29 (bs, 1H), 3.93 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.6, 168.0, 159.6 (d, J_{F-C} = 241.8 Hz), 139.7, 133.3 (d, J_{F-C} = 7.7 Hz), 130.0, 125.7, 119.8, 119.5, 119.0, 117.6, 116.1 (d, J_{F-C} = 23.8 Hz), 113.5 (d, J_{F-C} = 24.6 Hz), 112.7, 111.7, 109.2 (d, J_{F-C} = 7.7 Hz), 75.3, 52.6, 26.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}FN_2NaO_4^+$ $[M+Na]^+$ 377.0908, found 377.0909.



3ia

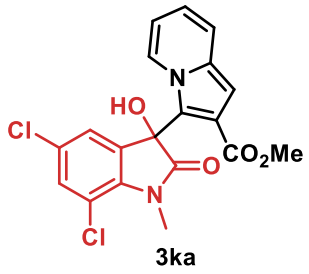
Methyl 3-[5-bromo-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ia). Starting from isatin **2i** (38.1 mg, 0.16 mmol), indolizine **1a** (31.7 mg, 0.19 mmol), DPP (3.9, 0.016 mmol) and SDS (4.5 mg, 0.016 mmol), product **3ia** was obtained as a pale yellowish solid (66.0 mg. 91% yield) in 7 h. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.26 (s, 1H), 7.89 (s, 1H), 7.79 – 7.65 (m, 1H), 7.48 (dd, J = 8.2, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.92 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.52 – 6.40 (m, 2H), 6.23 (bs, 1H), 3.94 (s, 4H), 3.58 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.3, 168.0, 141.3, 135.6, 134.7, 130.2,

125.7, 124.8, 124.5, 119.8, 119.5, 119.2, 117.8, 112.7, 111.8, 102.7, 74.6, 52.6, 30.0. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}BrN_2NaO_4^+$ [M+Na]$^+$ 437.0107, found 437.0109.



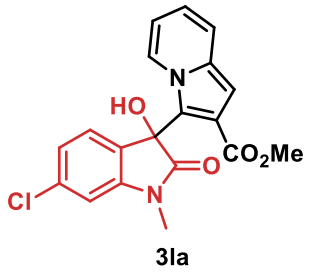
3ja

Methyl 3-[7-chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ja). Starting from isatin **2j** (43.6 mg, 0.22 mmol), indolizine **1a** (44.5 mg, 0.27 mmol), DPP (5.5, 0.022 mmol) and SDS (6.3 mg, 0.022 mmol), product **3ja** was obtained as a dark yellow viscous oil (59.6 mg, 72% yield) in 7 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.14 (bs, 1H), 7.90 (s, 1H), 7.81 – 7.69 (m, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.74 – 6.30 (m, 2H), 6.25 (bs, 1H), 3.95 (s, 3H), 3.57 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 177.2, 168.0, 139.8, 134.4, 132.2, 130.2, 125.7, 124.2, 124.0, 119.8, 119.4, 119.2, 117.7, 115.8, 112.6, 111.8, 74.7, 52.6, 29.7. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}ClN_2NaO_4^+$ [M+Na]$^+$ 393.0613, found 393.0618.



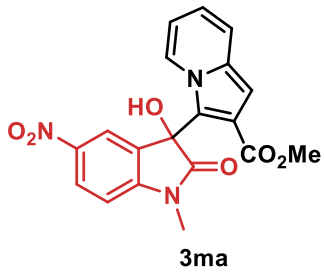
3ka

Methyl 3-[5,7-chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ka). Starting from isatin **2k** (51.3 mg, 0.22 mmol), indolizine **1a** (44.5 mg, 0.27 mmol), DPP (5.5, 0.022 mmol) and SDS (6.3 mg, 0.022 mmol), product **3ka** was obtained as an off-white solid (86.8 mg, 96% yield) in 19 h. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.88 (s, 1H), 7.78 (dt, *J* = 6.9, 1.3 Hz, 1H), 7.29 (s, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.63 – 6.34 (m, 3H), 3.92 (s, 3H), 3.57 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.7, 167.8, 138.5, 135.7, 131.5, 130.3, 128.7, 125.8, 124.6, 119.8, 119.7, 119.0, 117.5, 116.2, 112.8, 111.0, 74.9, 52.6, 29.7.**HRMS** (ESI) m/z calcd for $C_{19}H_{14}Cl_2N_2NaO_4^+$ [M+Na]$^+$ 427.0223, found 427.0226.



3la

Methyl 3-[6-chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3la). Starting from isatin **2l** (46.6 mg, 0.24 mmol), indolizine **1a** (47.5 mg, 0.29 mmol), DPP (5.9, 0.024 mmol) and SDS (6.7 mg, 0.024 mmol), product **3la** was obtained as an off-white solid (44.9 mg, 51% yield) in 24 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.07 (s, 1H), 7.91 (s, 1H), 7.86 – 7.65 (m, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.57 – 6.36 (m, 2H), 6.34 (s, 1H), 3.95 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.9, 168.0, 145.2, 135.8, 130.2, 130.0, 126.6, 125.7, 123.1, 119.8, 119.5, 119.3, 117.8, 112.8, 111.8, 109.5, 74.9, 52.7, 26.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}ClN_2NaO_4^+$ [M+Na]$^+$ 393.0613, found 393.0616.

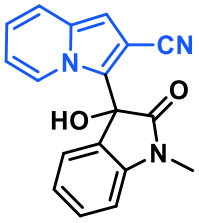


3ma

Methyl 3-[3-hydroxy-1-methyl-5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl]indolizine-2-carboxylate (3ma). Starting from isatin **2m** (47.7 mg, 0.23 mmol), indolizine **1a** (46.2 mg, 0.28 mmol), DPP (5.7, 0.023 mmol) and SDS (6.5 mg, 0.023 mmol), product **3ma** was obtained as a yellow foam (44.9 mg, 77% yield) in 7 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.33 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 7.90 (s, 1H), 7.83 – 7.77 (m,

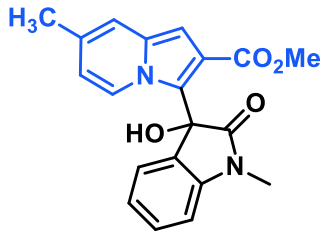
1H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.85 – 6.46 (m, 3H), 3.91 (s, 3H), 3.31 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.1, 167.5, 149.5, 143.8, 132.7, 130.6, 127.1, 125.9, 121.1, 120.0, 119.6, 119.1, 117.4, 112.9, 110.4, 108.3, 75.0, 52.6, 26.8. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}ClKN_3O_6^+$ $[M+K]^+$ 420.0592, found 420.0572.

*Single addition adducts **3ac** to **3aj** were synthesized with indolizine **1a** following the general procedure described in topic 3.*



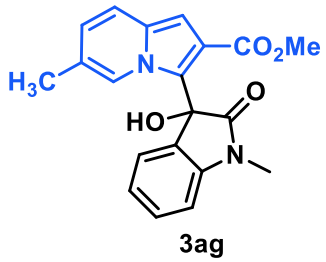
3ac

3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)indolizine-2-carbonitrile (3ac). Starting from isatin **2a** (38.0 mg, 0.24 mmol), indolizine **1c** (38.21 mg, 0.28 mmol), DPP (5.8, 0.024 mmol) and SDS (6.7 mg, 0.024 mmol), product **3ac** was obtained as an off-white solid (10.9 mg, 15% yield) in 19 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 9.04 (d, *J* = 7.2 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.47 (td, *J* = 7.8, 1.2 Hz, 1H), 7.34 (dt, *J* = 9.1, 1.3 Hz, 1H), 7.14 (td, *J* = 7.6, 1.0 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.85 (ddd, *J* = 9.1, 6.6, 1.1 Hz, 1H), 6.68 (ddd, *J* = 7.9, 6.5, 1.4 Hz, 1H), 6.61 (s, 1H), 3.24 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 174.5, 143.5, 134.5, 131.7, 128.5, 127.0, 125.3, 124.1, 123.9, 120.3, 119.7, 115.0, 113.0, 109.4, 104.5, 97.0, 75.8, 26.7. **HRMS** (ESI) m/z calcd for $C_{18}H_{13}N_3NaO_2^+$ $[M+Na]^+$ 326.0900, found 326.0905.



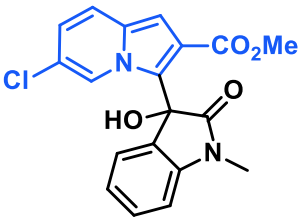
3af

Methyl 7-Methyl-3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)indolizine-2-carboxylate (3af). Starting from isatin **2a** (33.3 mg, 0.21 mmol), indolizine **1f** (44.5 mg, 0.25 mmol), DPP (5.1, 0.021 mmol) and SDS (5.8 mg, 0.021 mmol), product **3af** was obtained as a pale yellowish solid (73.0 mg, 99% yield) in 4 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.19 (bs, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.47 – 7.32 (m, 2H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.24 (dd, *J* = 7.2, 1.7 Hz, 1H), 5.84 (bs, 1H), 3.92 (s, 3H), 3.19 (s, 3H), 1.95 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 177.0, 168.2, 143.8, 131.6, 130.4, 129.9, 129.1, 125.5, 125.0, 123.1, 119.2, 117.7, 117.1, 115.3, 110.6, 108.5, 75.2, 52.5, 26.3, 21.6. **HRMS** (ESI) m/z calcd for $C_{20}H_{18}N_2NaO_4^+$ $[M+Na]^+$ 373.1159, found 373.1166.



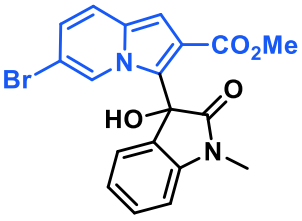
3ag

Methyl 6-Methyl-3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)indolizine-2-carboxylate (3ag). Starting from isatin **2a** (33.3 mg, 0.21 mmol), indolizine **1g** (44.5 mg, 0.25 mmol), DPP (5.1, 0.021 mmol) and SDS (5.8 mg, 0.021 mmol), product **3ag** was obtained as a pale yellowish solid (30.8 mg, 43% yield) in 5.5 h. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.25 (bs, 1H), 7.81 (s, 1H), 7.53 (s, 1H), 7.45 – 7.33 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.27 (dd, *J* = 9.6, 1.5 Hz, 1H), 6.04 (d, *J* = 9.7 Hz, 1H), 3.95 (s, 3H), 3.20 (s, 3H), 2.10 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 177.0, 168.2, 143.9, 131.7, 130.1, 129.2, 125.6, 123.2, 122.7, 122.7, 122.1, 119.3, 118.7, 117.3, 112.4, 108.6, 75.3, 52.6, 26.3, 18.1. **HRMS** (ESI) m/z calcd for $C_{20}H_{18}N_2NaO_4^+$ $[M+Na]^+$ 373.1159, found 373.1161.



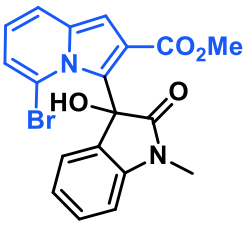
3ah

Methyl 6-Chloro-3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)indolizine-2-carboxylate (3ah). Starting from isatin **2a** (30.1 mg, 0.19 mmol), indolizine **1h** (44.7 mg, 0.27 mmol), DPP (4.6, 0.019 mmol) and SDS (5.3 mg, 0.019 mmol), product **3ah** was obtained as a pale yellowish solid (34.0 mg, 49% yield (34.0 mg) in 4 days. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 7.97 (bs, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.43 – 7.33 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.38 (dd, *J* = 10.0, 1.8 Hz, 1H), 6.18 (bs, 1H), 3.95 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.8, 167.6, 144.0, 131.2, 130.4, 128.6, 125.7, 123.4, 122.9, 121.3, 120.9, 120.2, 119.8, 118.7, 114.2, 108.8, 75.2, 52.8, 26.4. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}ClN_2NaO_4^+$ $[M+Na]^+$ 393.0613, found 393.0616.



3ai

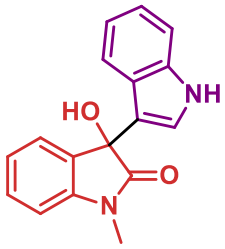
Methyl 6-Bromo-3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)indolizine-2-carboxylate (3ai). Starting from isatin **2a** (35.15 mg, 0.22 mmol), indolizine **1i** (63.2 mg, 0.26 mmol), DPP (5.4, 0.022 mmol) and SDS (6.2 mg, 0.022 mmol), product **3ai** was obtained as a pale yellowish solid, (45.4 mg, 50% yield) in 3 days. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 7.97 (s, 1H), 7.91 (s, 1H), 7.85 (s, 1H), 7.46 – 7.31 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.47 (dd, *J* = 10.0, 1.4 Hz, 1H), 6.12 (s, 1H), 3.95 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$) δ** 176.8, 167.6, 144.0, 131.2, 130.4, 128.6, 125.6, 125.2, 123.4, 122.7, 120.3, 119.6, 118.5, 114.1, 108.8, 108.0, 75.2, 52.8, 26.4. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}BrN_2NaO_4^+$ $[M+Na]^+$ 437.0107, found 437.0110.



3aj

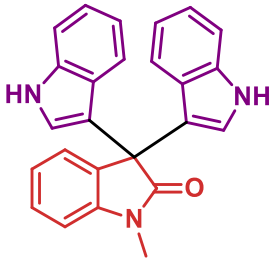
Methyl 5-Bromo-3-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)indolizine-2-carboxylate (3aj). Starting from isatin **2a** (35.0 mg, 0.22 mmol), indolizine **1i** (62.8 mg, 0.26 mmol), DPP (5.4, 0.022 mmol) and SDS (6.1 mg, 0.022 mmol), product **3ai** was obtained as a pale yellowish solid (76.9 mg, 90% yield) in 3 days. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.24 (s, 1H), 8.00 (bs, 1H), 7.47 – 7.33 (m, 2H), 7.16 – 7.05 (m, 1H), 6.96 – 6.89 (m, 1H), 6.84 – 6.77 (m, 1H), 6.46 – 6.25 (m, 2H), 3.99 (s, 3H), 3.22 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.8, 167.6, 144.0, 131.2, 130.4, 128.6, 125.6, 125.2, 123.4, 122.7, 120.3, 119.6, 118.5, 114.1, 108.8, 108.0, 75.2, 52.8, 26.4. **HRMS** (ESI) m/z calcd for $C_{19}H_{15}BrN_2NaO_4^+$ $[M+Na]^+$ 437.0107, found 437.0113.

*The Friedel-Crafs reaction between indole (**4**) (35.1 mg, 0.3 mmol) and isatin (**2a**) (40.3 mg, 0.25 mmol) was carried out as described in general topic 3, affording the products **5** and **6**.*



6

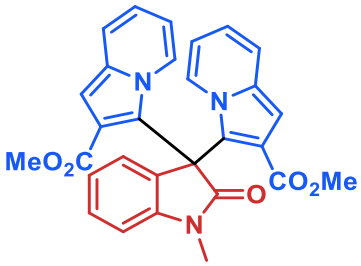
3-hydroxy-3-(1*H*-indol-3-yl)-1-methylindolin-2-one (6)[5]. Obtained as a white solid (7.1 mg, 16%). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 11.00 (bs, 1H), 7.40 – 7.25 (m, 4H), 7.11 – 6.98 (m, 4H), 6.93 – 6.80 (m, 1H), 6.42 (s, 1H), 3.16 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.6, 143.1, 136.8, 132.7, 129.2, 124.9, 124.3, 123.6, 122.4, 121.1, 120.3, 118.5, 115.1, 111.5, 108.5, 74.6, 26.0.



7

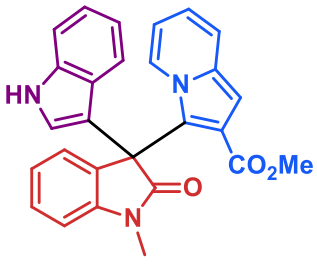
1'-methyl-1*H*,1''*H*-[3,3':3',3''-terindol]-2'(1'*H*)-one (7). Obtained in a form of a white solid (40.2 mg, 71%). **^{1}H NMR (250 MHz, DMSO-d6)** δ 10.95 (s, 2H), 7.39 – 7.22 (m, 4H), 7.16 (m, 3H), 7.08 – 6.94 (m, 3H), 6.84 (d, *J* = 2.5 Hz, 2H), 6.78 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 2H), 3.26 (s, 3H). **^{13}C NMR (63 MHz, DMSO-d6)** δ 176.9, 142.7, 136.9, 133.7, 127.9, 125.6, 124.6, 124.3, 122.1, 120.9, 120.7, 118.3, 114.0, 111.6, 108.6, 52.1, 26.2. **HRMS** (ESI) m/z calcd for $C_{25}H_{19}N_3ONa^+$ $[M+Na]^+$ 400.1420, found 400.1390.

*Characterization of 3,3 diakylated adducts **4aa**, and **8**.*



4aa

Methyl 3-{3-[2-(methoxycarbonyl)indolizin-3-yl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}indolizine-2-carboxylate (4aa). Product **4aa** was obtained following the procedure described in the topic 2, starting with isatin **2a** (20 mg, 0.12 mmol), indolizine **1a** (50 mg, 0.29 mmol) and DPP (3.0 mg, 0.012 mmol) a white solid (61%) after 4 days in DCE (2 mL). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.78 (s, 1H), 7.73 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H), 7.28 (dt, *J* = 9.0, 1.1 Hz, 1H), 7.01 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.90 (td, *J* = 7.5, 0.9 Hz, 1H), 6.59 (ddd, *J* = 9.0, 6.5, 0.9 Hz, 1H), 6.55 (s, 1H), 6.38 (td, *J* = 6.9, 1.1 Hz, 1H), 6.27 (ddd, *J* = 9.5, 6.5, 1.0 Hz, 1H), 6.12 (ddd, *J* = 7.6, 6.6, 1.4 Hz, 1H), 5.50 (d, *J* = 9.5 Hz, 1H), 3.72 (s, 3H), 3.32 (s, 3H), 3.30 (s, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 176.6, 167.4, 164.7, 145.5, 133.3, 131.7, 131.0, 129.2, 126.7, 125.4, 124.8, 122.0, 121.6, 119.4, 119.1, 118.8, 118.3, 118.0, 117.7, 117.5, 112.4, 110.4, 109.3, 107.9, 100.3, 53.1, 52.3, 52.3, 51.7, 26.9. **HRMS** (ESI) m/z calcd for $C2_9H_{23}N_3NaO_5^+$ $[M+Na]^+$ 516.1530, found 516.1536.



8

Methyl 3-(3-(1*H*-indol-2-yl)-1-methyl-2-oxoindolin-3-yl)indolizine-2-carboxylate (8). Product **8** was obtained following the procedure described in *topic 5* as a white solid (36.6 mg, 84%). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 8.17 (d, *J* = 7.1 Hz, 1H), 8.08 (s, 1H), 7.32-7-30 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.04 – 6.91 (m, 3H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.44-6-40 (m, 2H), 6.23-6-22 (m, 2H), 3.58 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 177.55, 164.47, 143.65, 137.08, 133.10, 131.93, 127.85, 126.20, 126.13, 123.36, 122.78, 122.25, 121.60, 121.30, 118.69, 118.13, 117.83, 117.17, 117.09, 115.77, 111.52, 110.41, 108.20, 52.08, 51.10, 26.3. HRMS (ESI) m/z calcd for $C_{27}H_{21}N_3O_3Na^+$ $[M+Na]+$ 458.1475, found 458.1477.

8. References

(1) Protocols to synthetize indolizines **1a** and **1c**-**1k**: a) Silva, T. S.; Zeoly, L. A.; Coelho, F. Catalyst-Free Conjugate Addition of Indolizines to In Situ -Generated Oxidized Morita–Baylis–Hillman Adducts. *J. Org. Chem.* **2020**, *85*, 5438–5448. b) Correia, J. T. M.; List, B.; Coelho, F. Catalytic Asymmetric Conjugate Addition of Indolizines to *α,β*-Unsaturated Ketones. Angew. Chemie - Int. Ed. **2017**, *56*, 7967–7970; c) Teodoro, B. V. M.; Correia, J. T. M.; Coelho, F. Selective Hydrogenation of Indolizines: An Expeditious Approach To Derive Tetrahydroindolizines and Indolizidines from Morita–Baylis–Hillman Adducts. *J. Org. Chem.* **2015**, *80*, 2529–2538.

(2) Protocol to synthetize indolizine **1b** from hydrolysis of **1a**: Xue, Y.; Tang, J.; Ma, X.; Li, Q.; Xie, B.; Hao, Y.; Jin, H.; Wang, K.; Zhang, G.; Zhang, L.; et al. Synthesis and Biological Activities of Indolizine Derivatives as Alpha-7 NAChR Agonists. *Eur. J. Med. Chem.* **2016**, *115*,94−108.

(3) Protocol to synthesize isatins **2a-2m**: Amrita A. Nagle; A. A.; Reddy, S. A.; Bertrand. H.; Tajima, H.; Dang, T.-M.; Wong, S.-C.; Hayes, J. D.; Wells, G.; Chew, E.-H. 3-(2-Oxoethylidene)indolin-2-one Derivatives Activate Nrf2 and Inhibit Nrf2: Potential Candidates for Chemoprevention. *ChemMedChem*, **2014**, *9*, 1763–1767.

(4) Naresh Babu, K.; Kariyandi, N. R.; Saheeda M. K., S.; Kinthada, L. K.; Bisai, A. Lewis Acid-Catalyzed Malonate Addition onto 3-Hydroxy-2-Oxindoles: Mechanistic Consideration and Synthetic Approaches to the Pyrroloindoline Alkaloids. *J. Org. Chem.* **2018**, *83*, 12664–12682.

(5) Li, C.; Guo, F.; Xu, K.; Zhang, S.; Hu, Y.; Zha, Z.; Wang, Z. Copper-Catalyzed Enantioselective Friedel–Crafts Alkylation of Pyrrole with Isatins. *Org. Lett.* **2014**, *16*, 3192–3195.

9. NMR Spectra

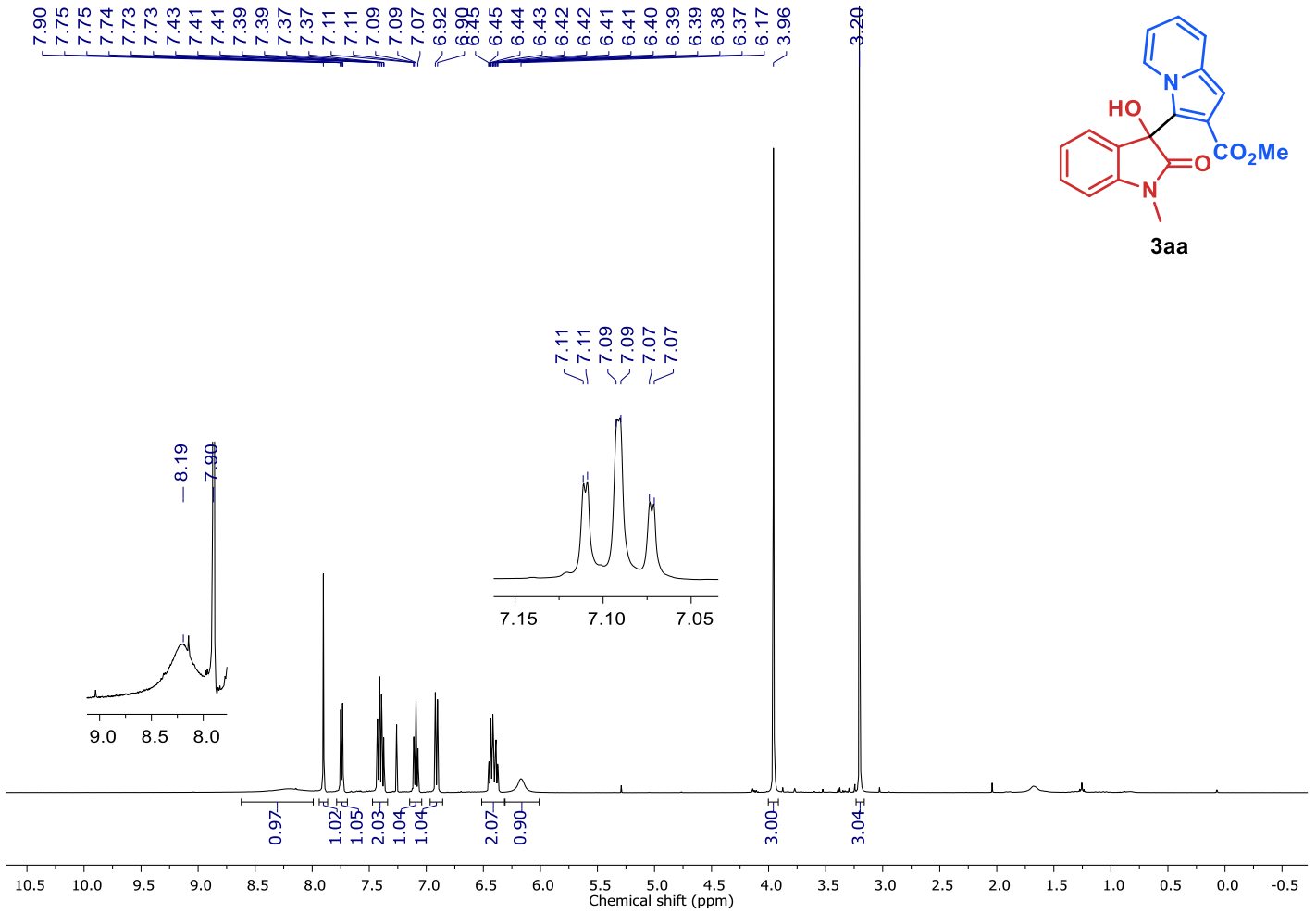


Figure S4. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**.

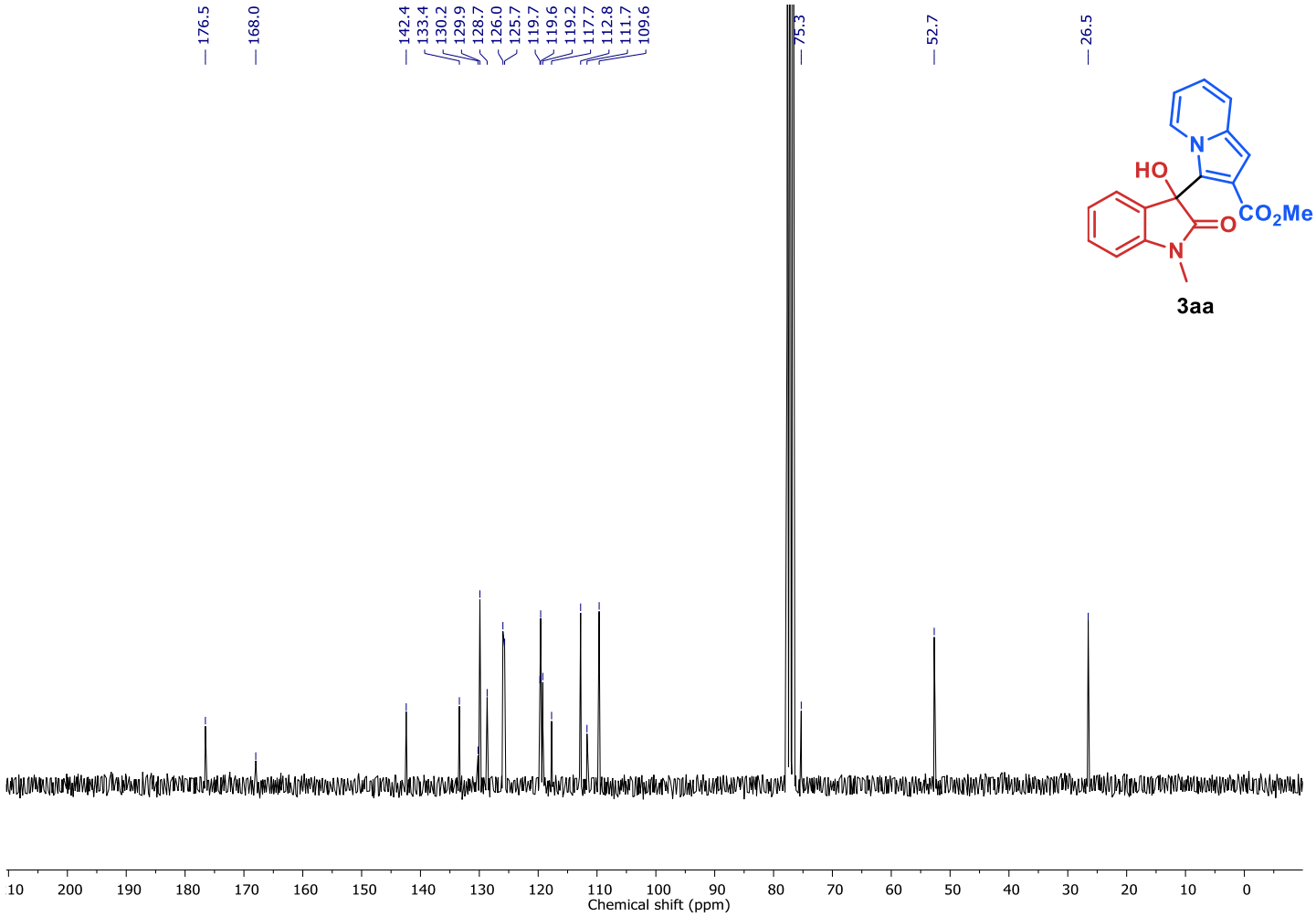


Figure S5. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3aa**.

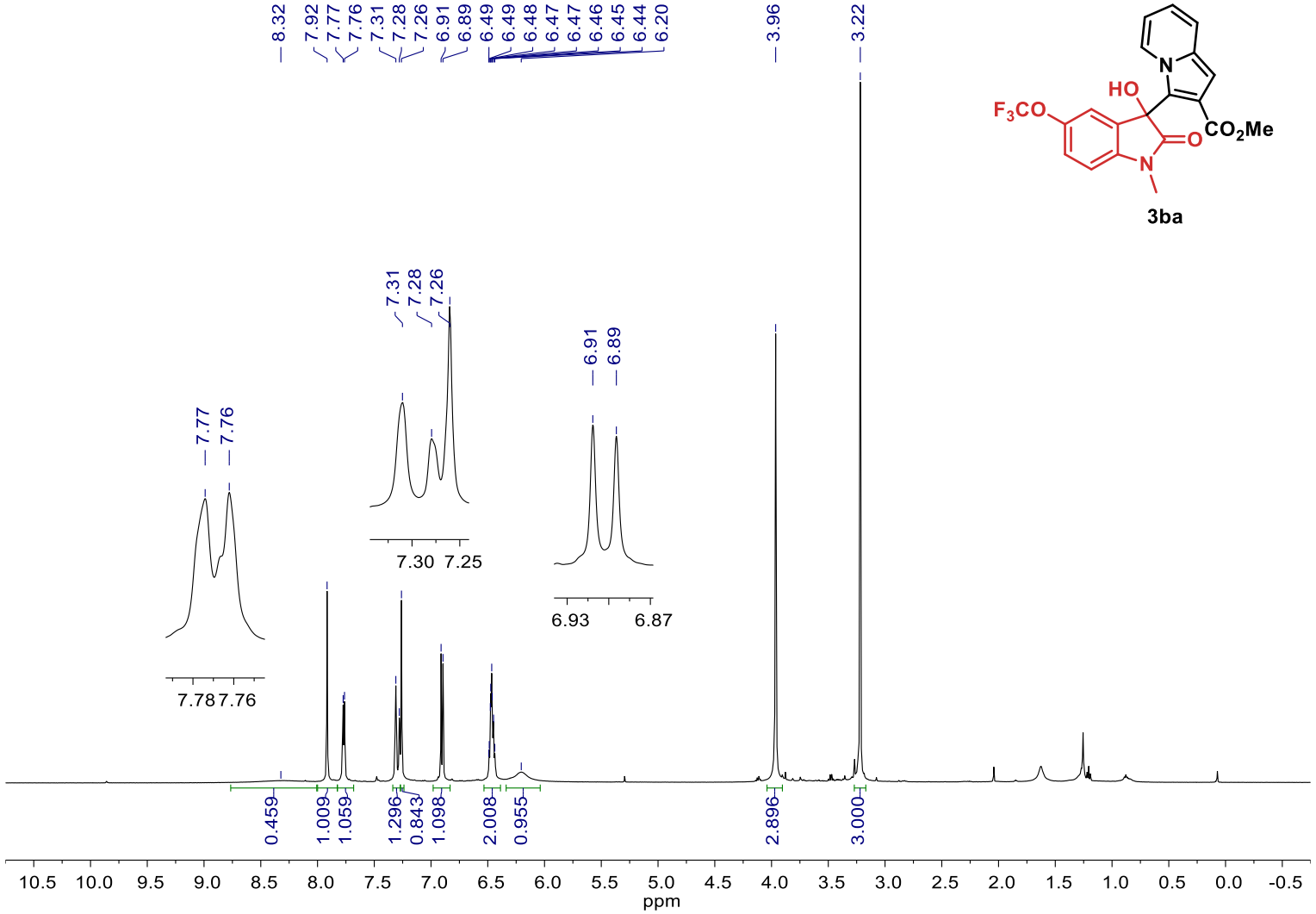


Figure S6. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3ba**.

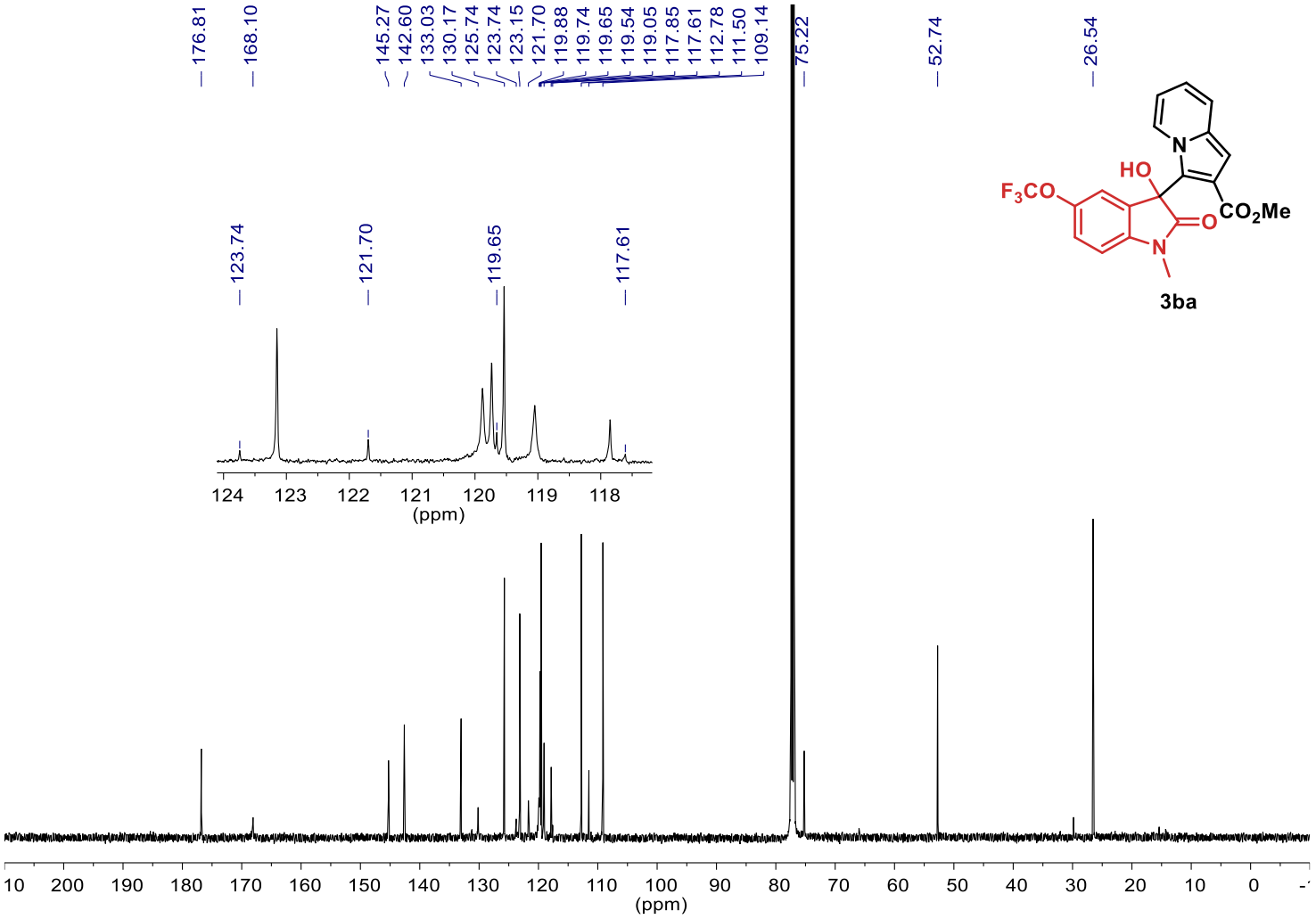


Figure S7.^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3ba**.

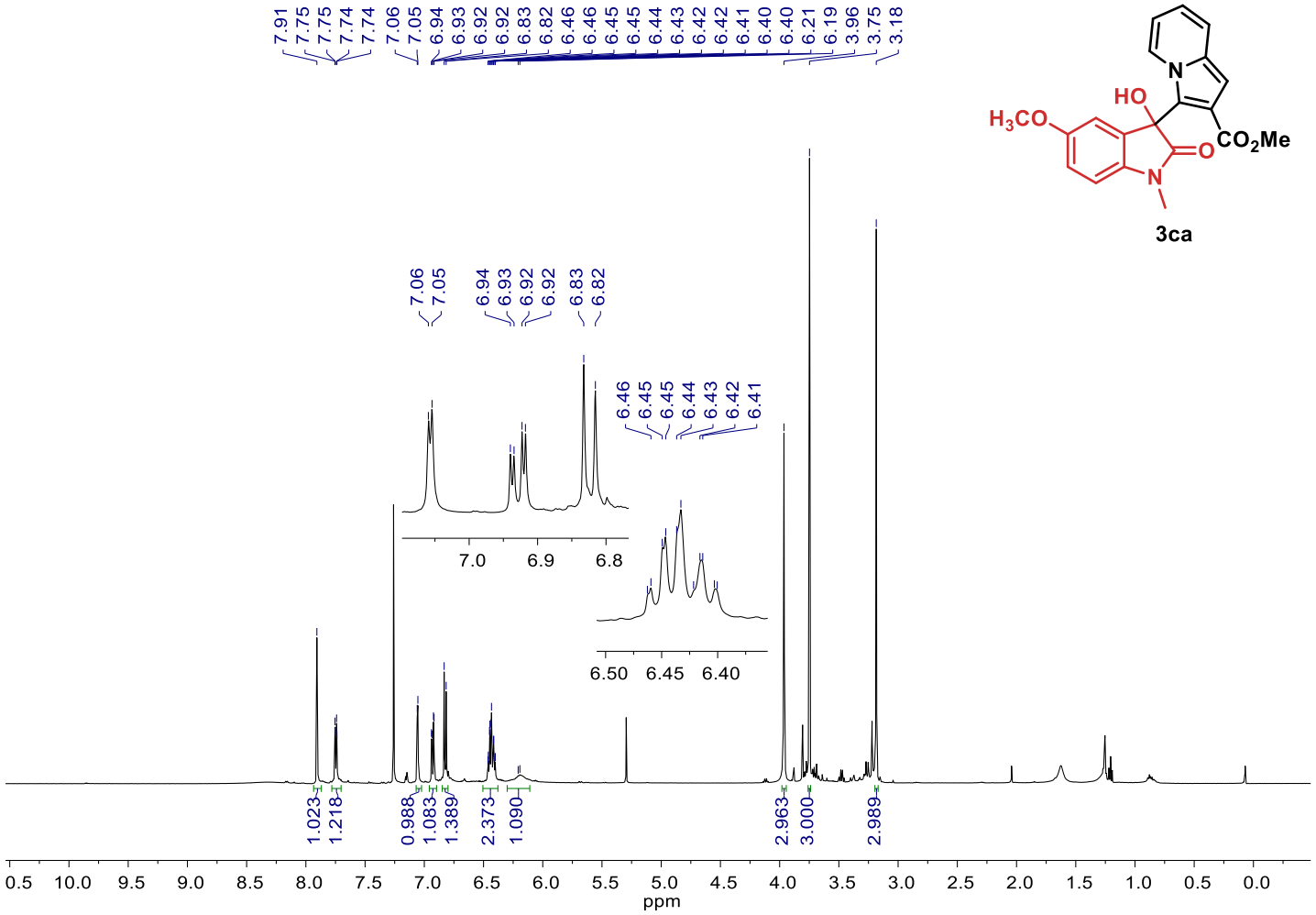


Figure S8. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3ca**.

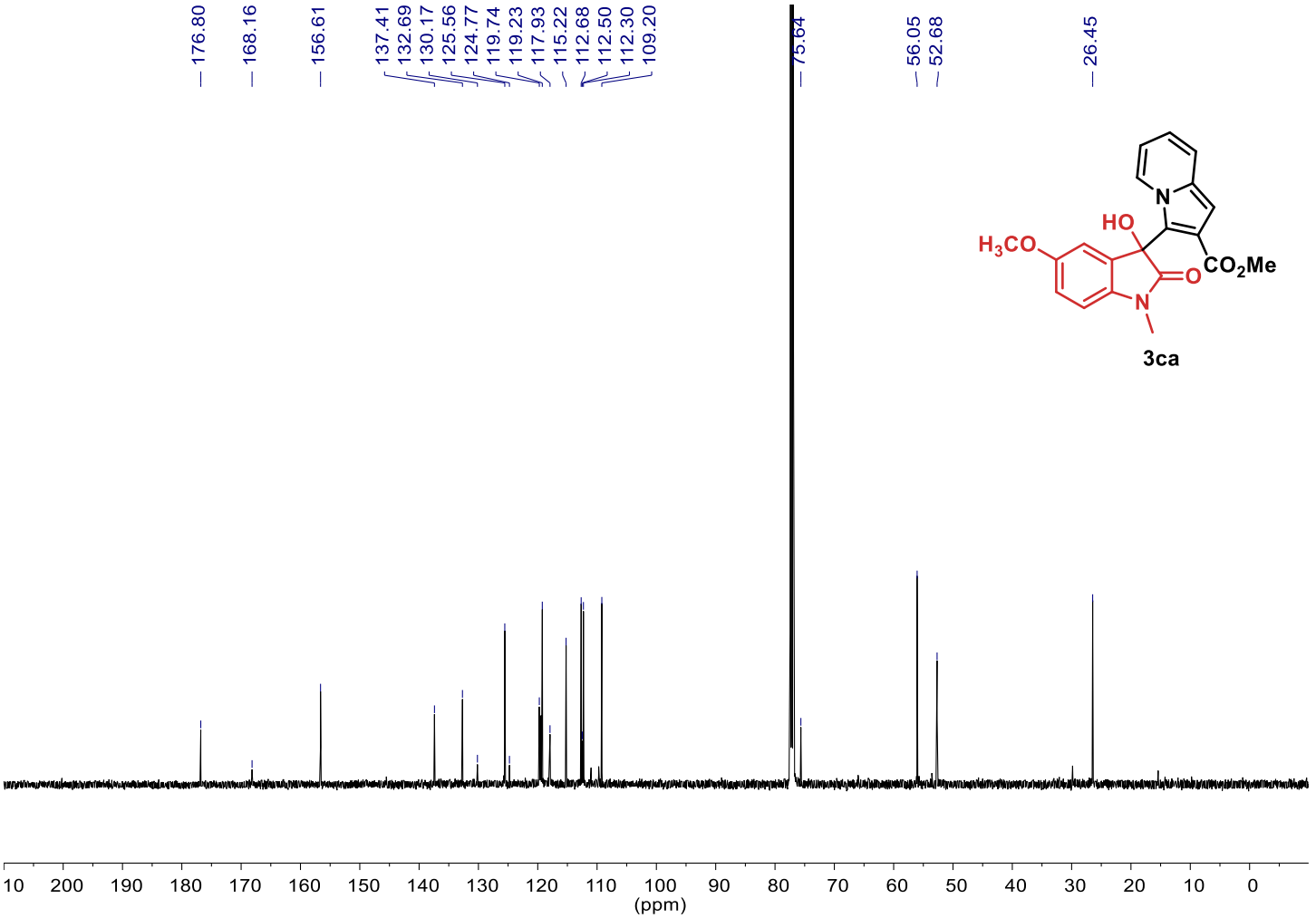


Figure S9. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3ca**.

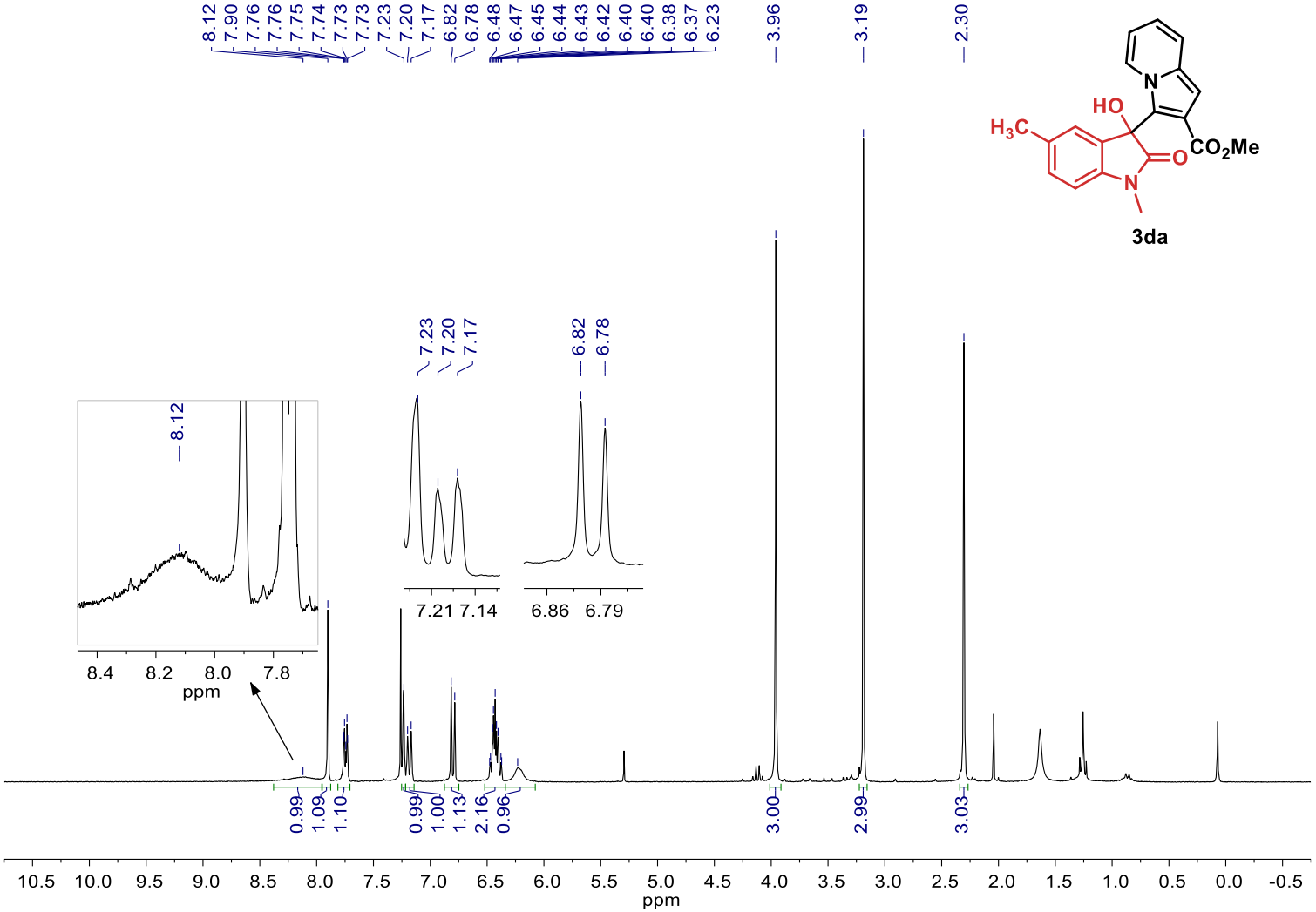


Figure S10. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3da**.

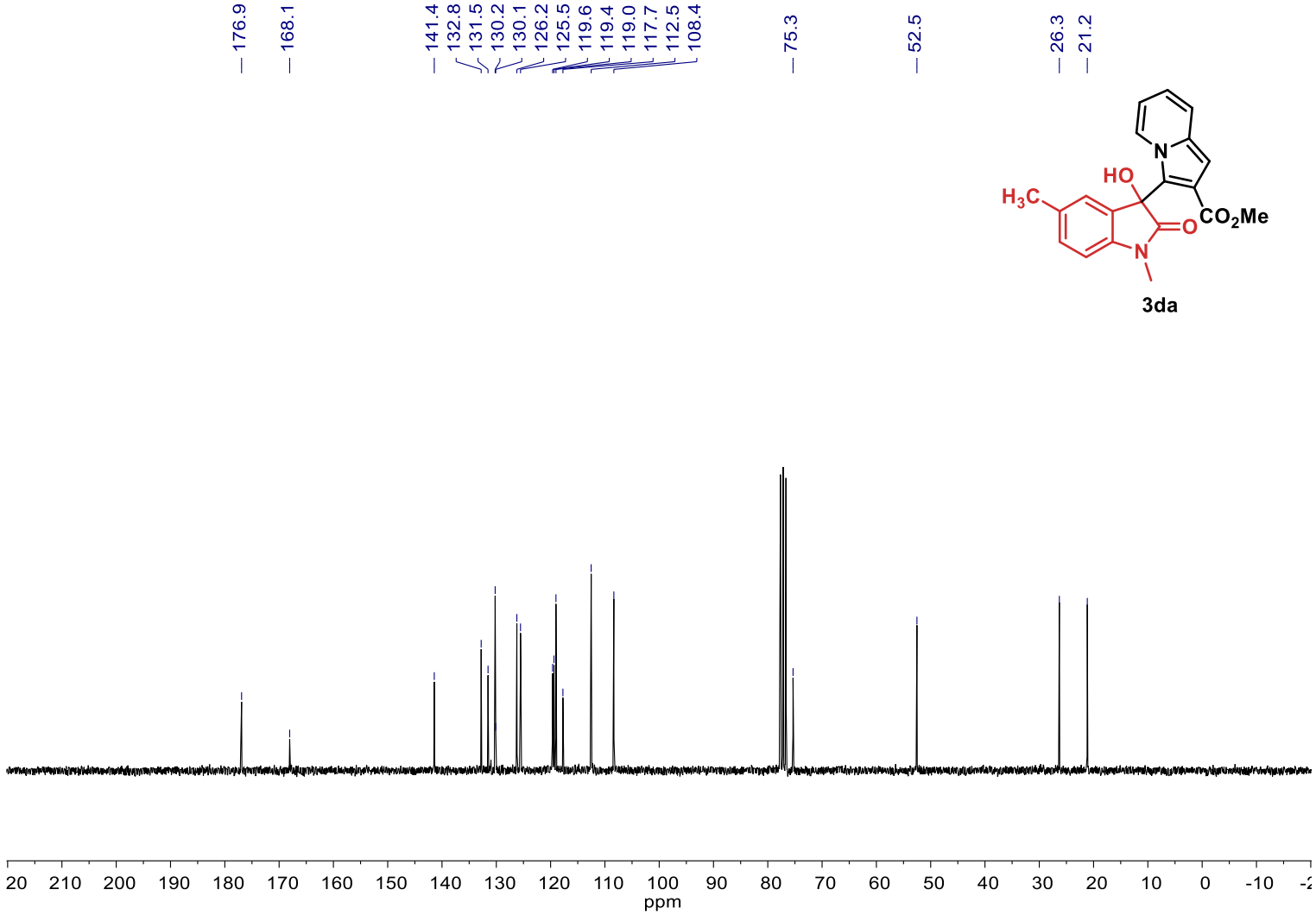


Figure S11. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3da**.

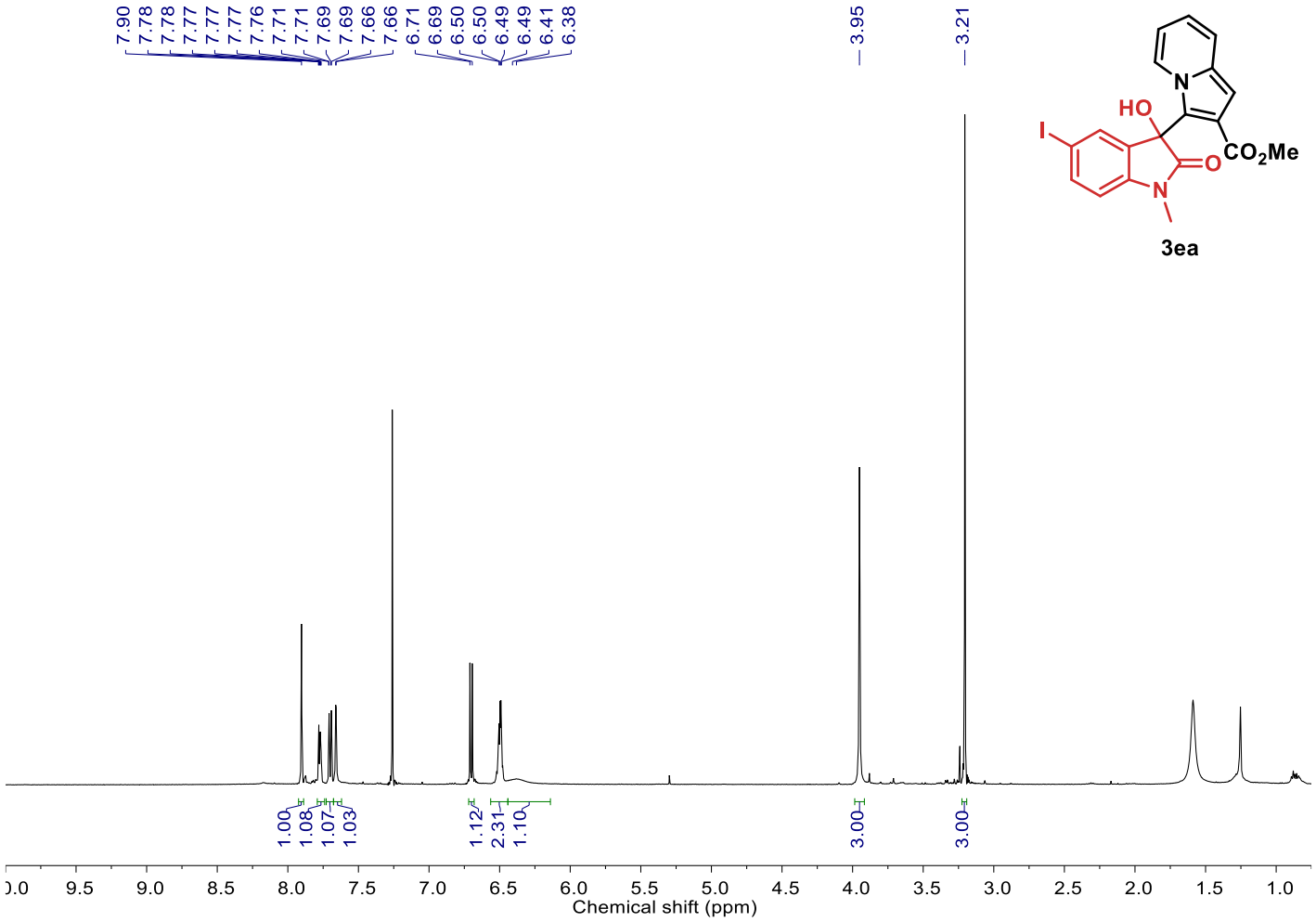


Figure S12. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3ea**.

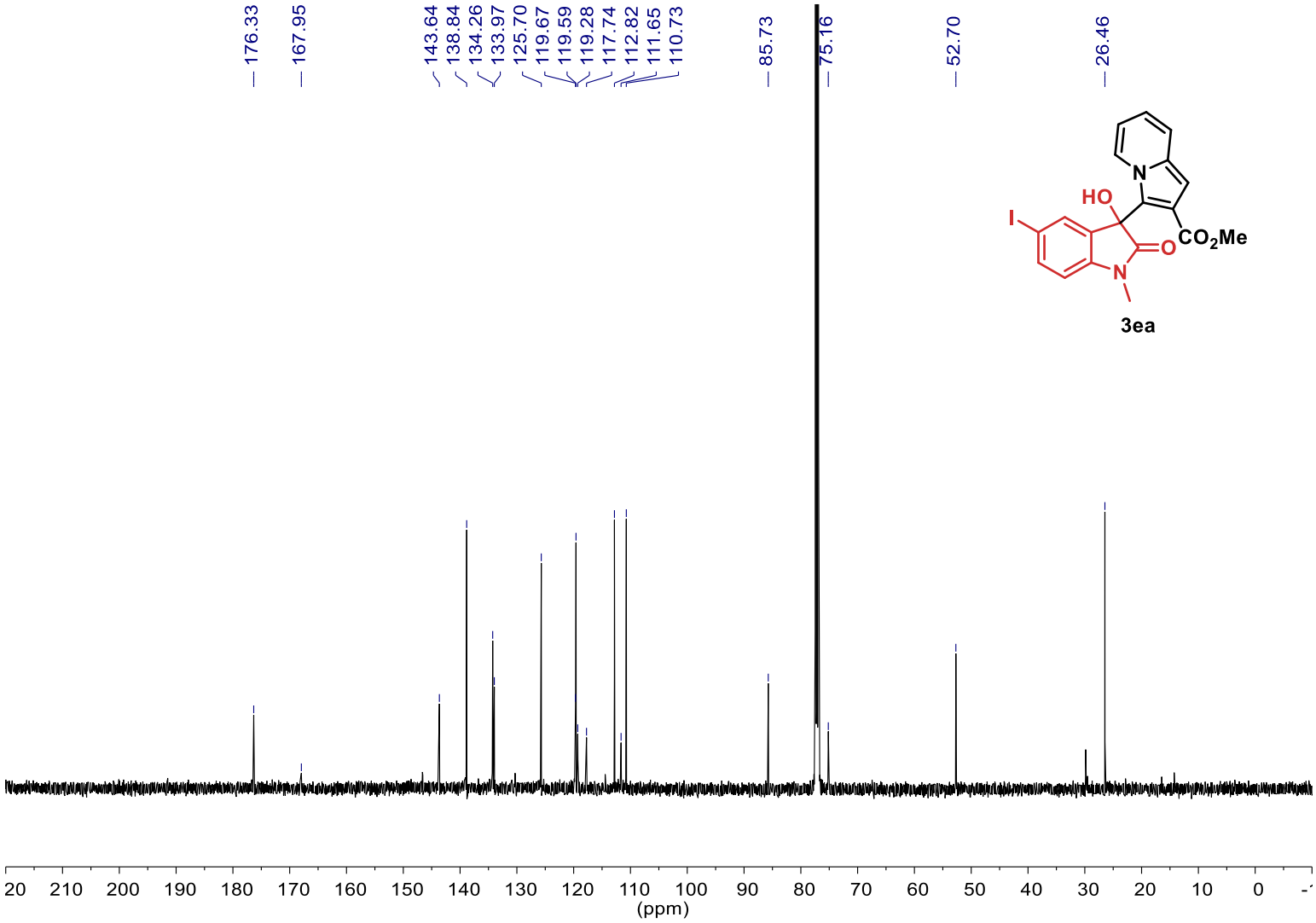


Figure S13. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3ea**.

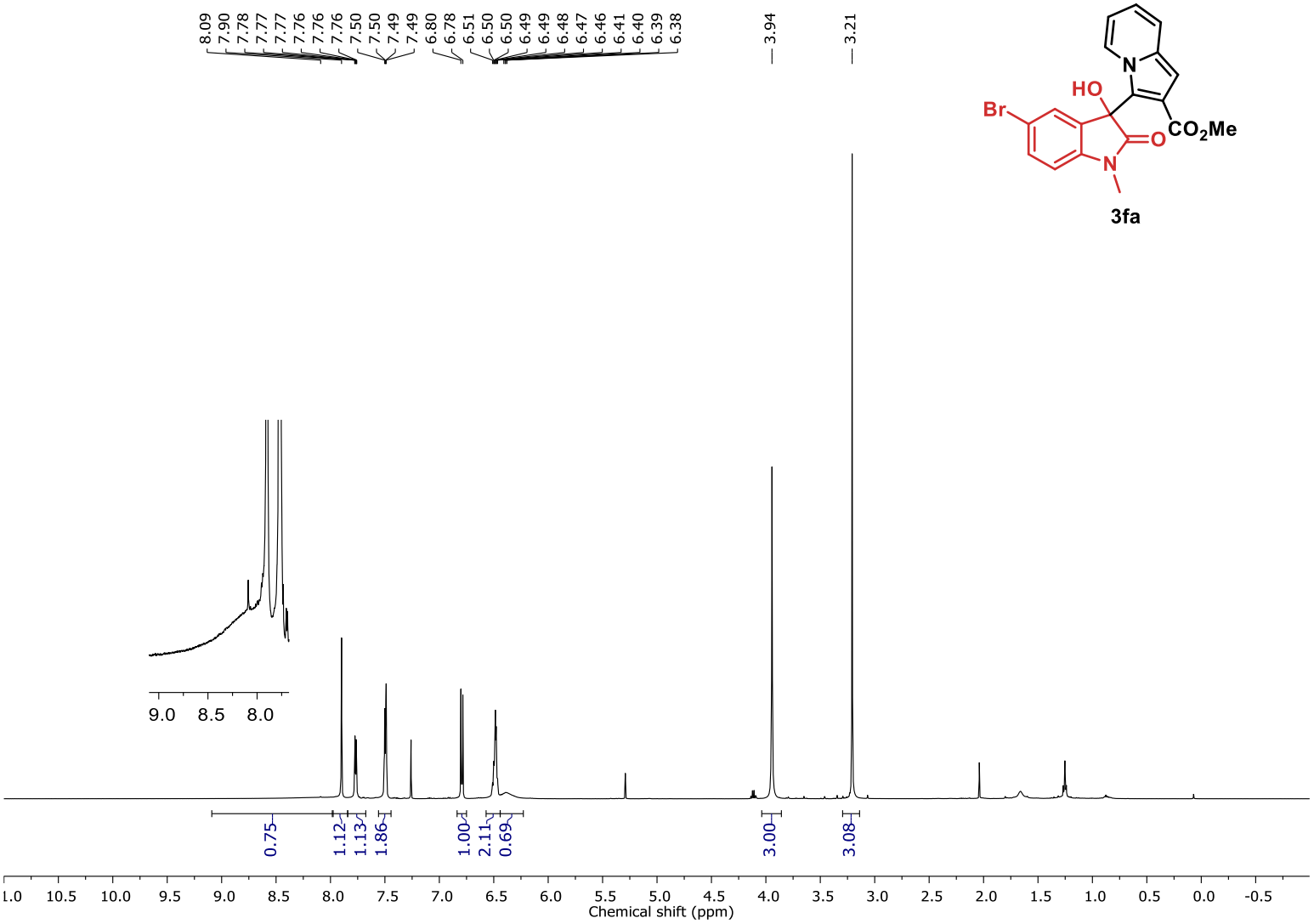


Figure S14. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3fa**.

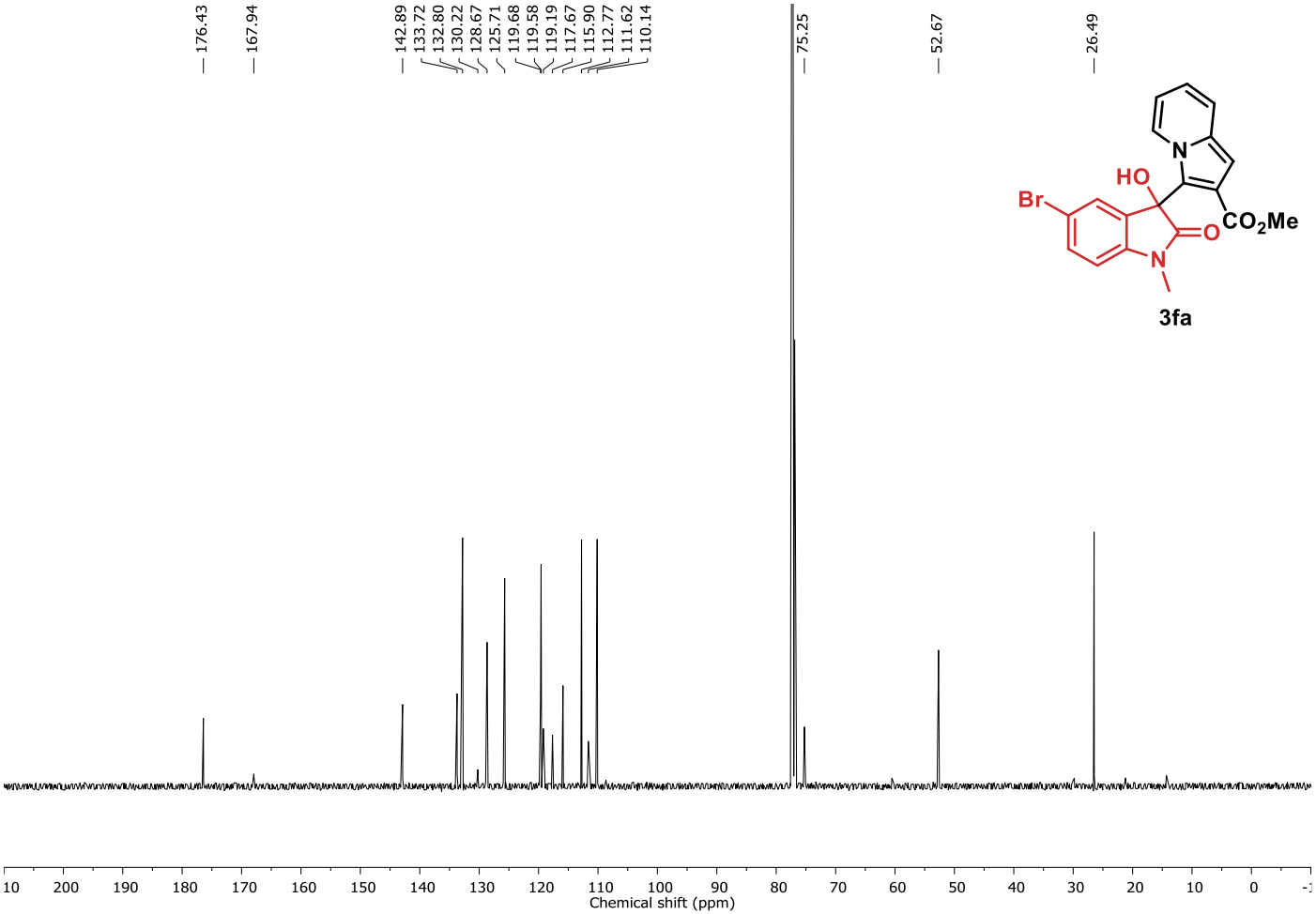


Figure S15. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3fa**.

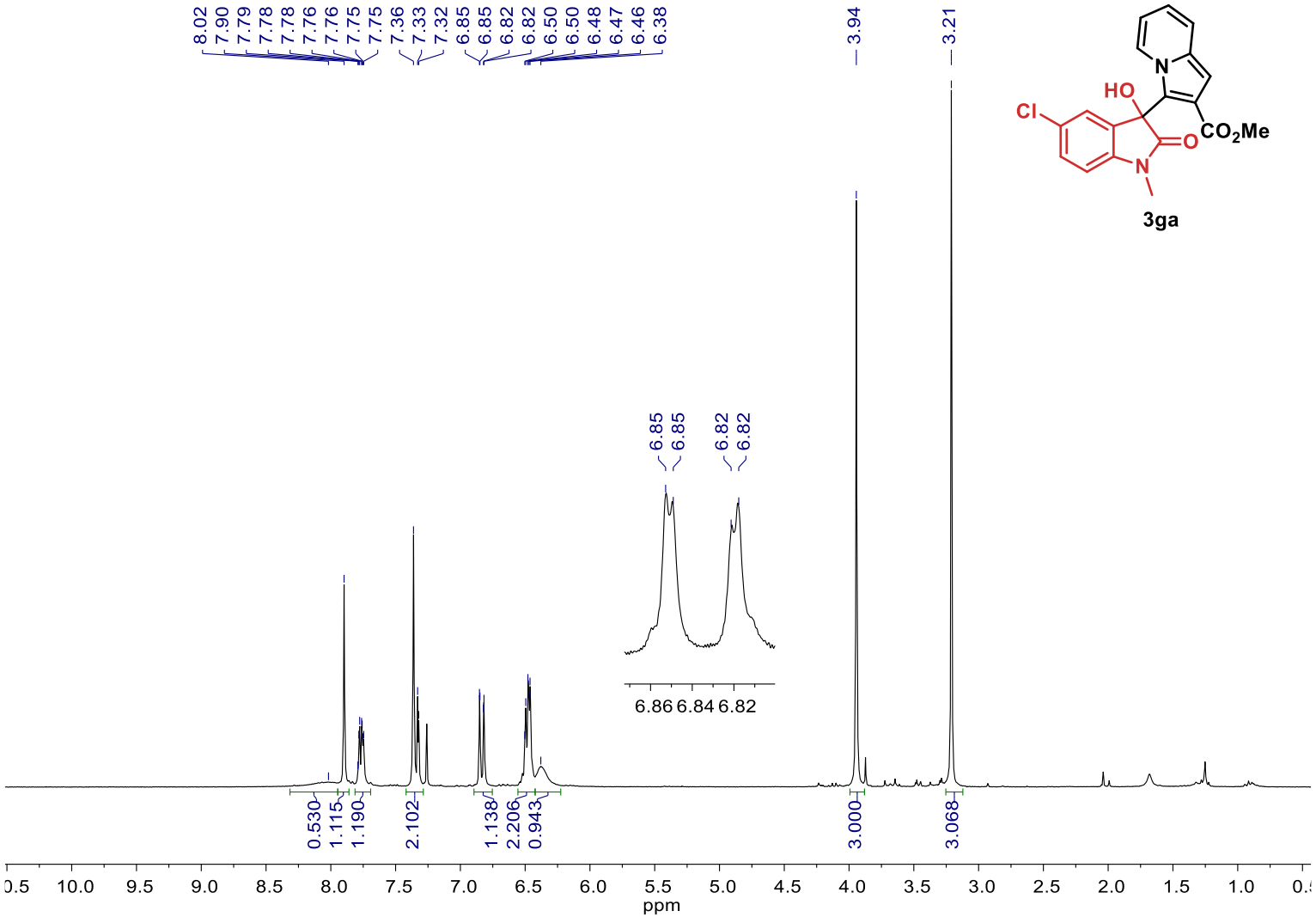


Figure S16. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3ga**.

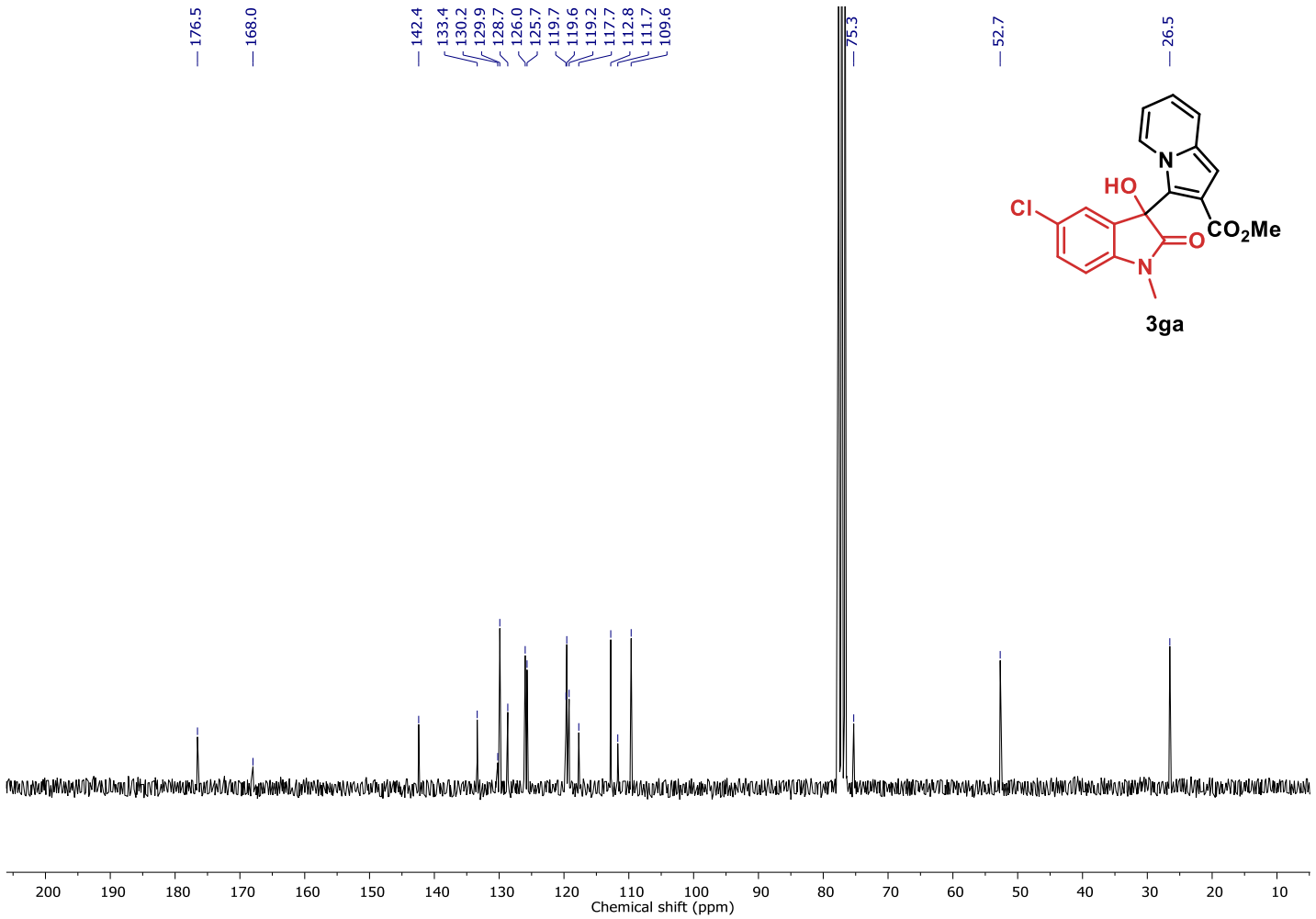


Figure S17. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3ga**.

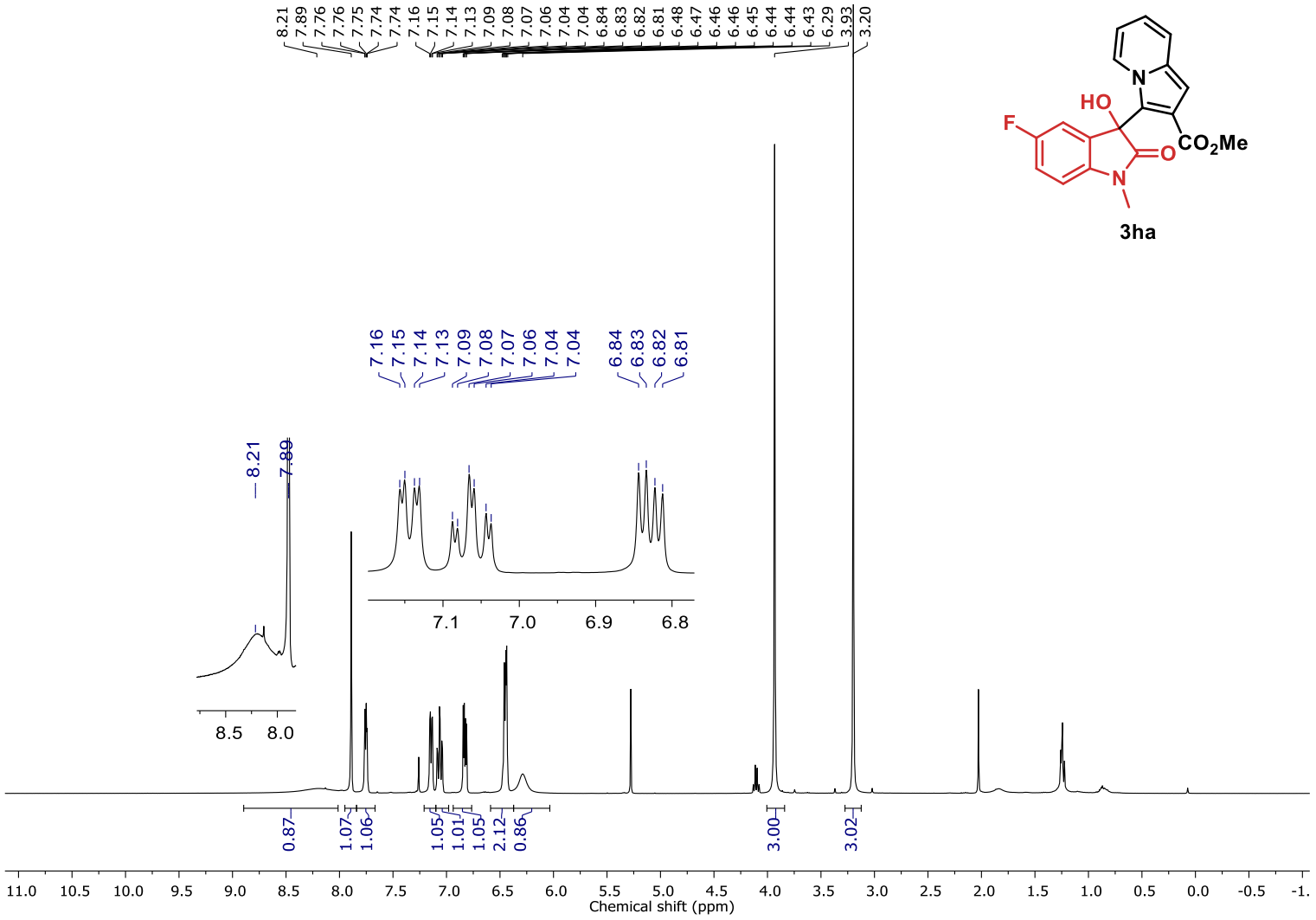


Figure S18. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ha**.

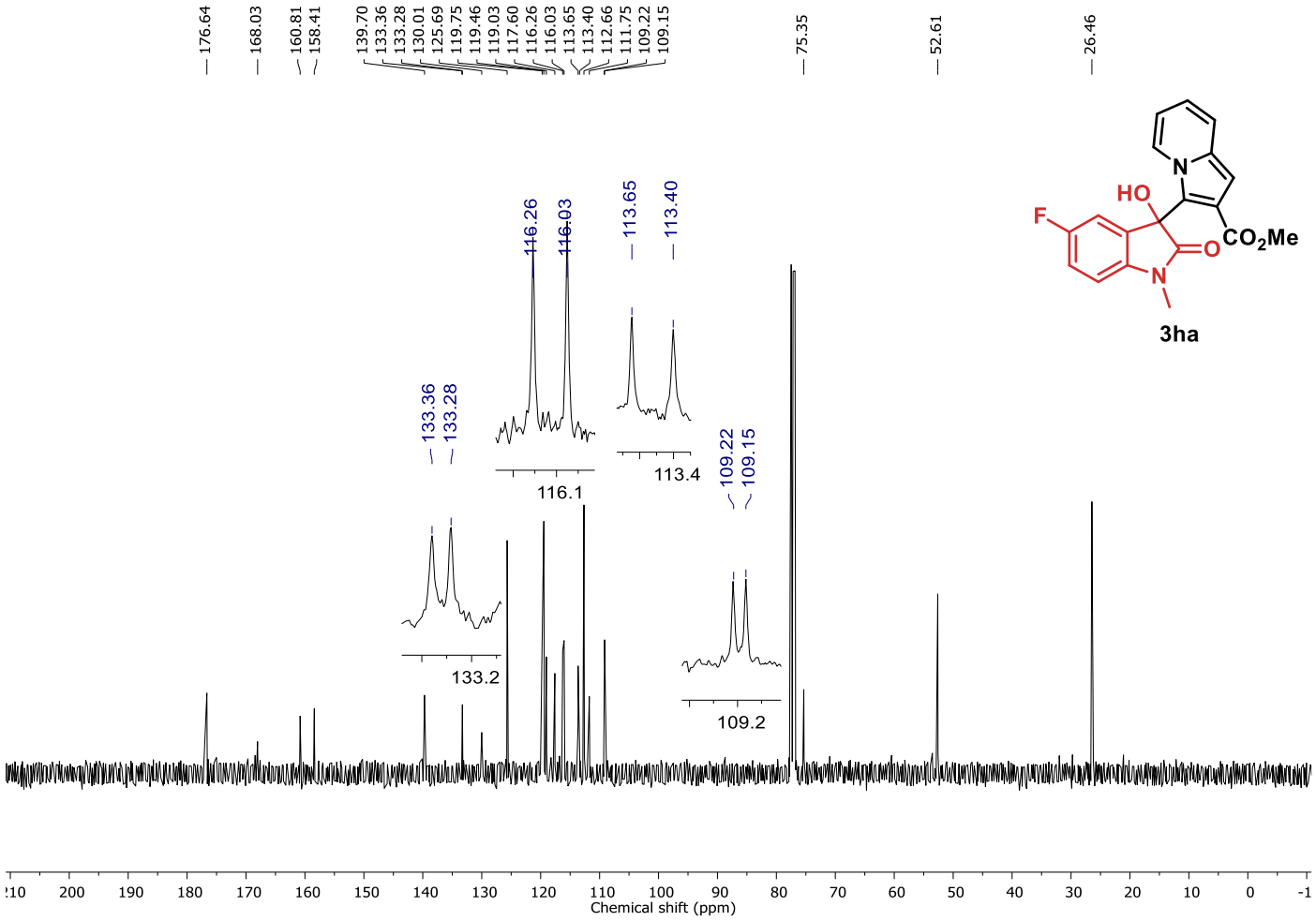


Figure S19. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3ha**.

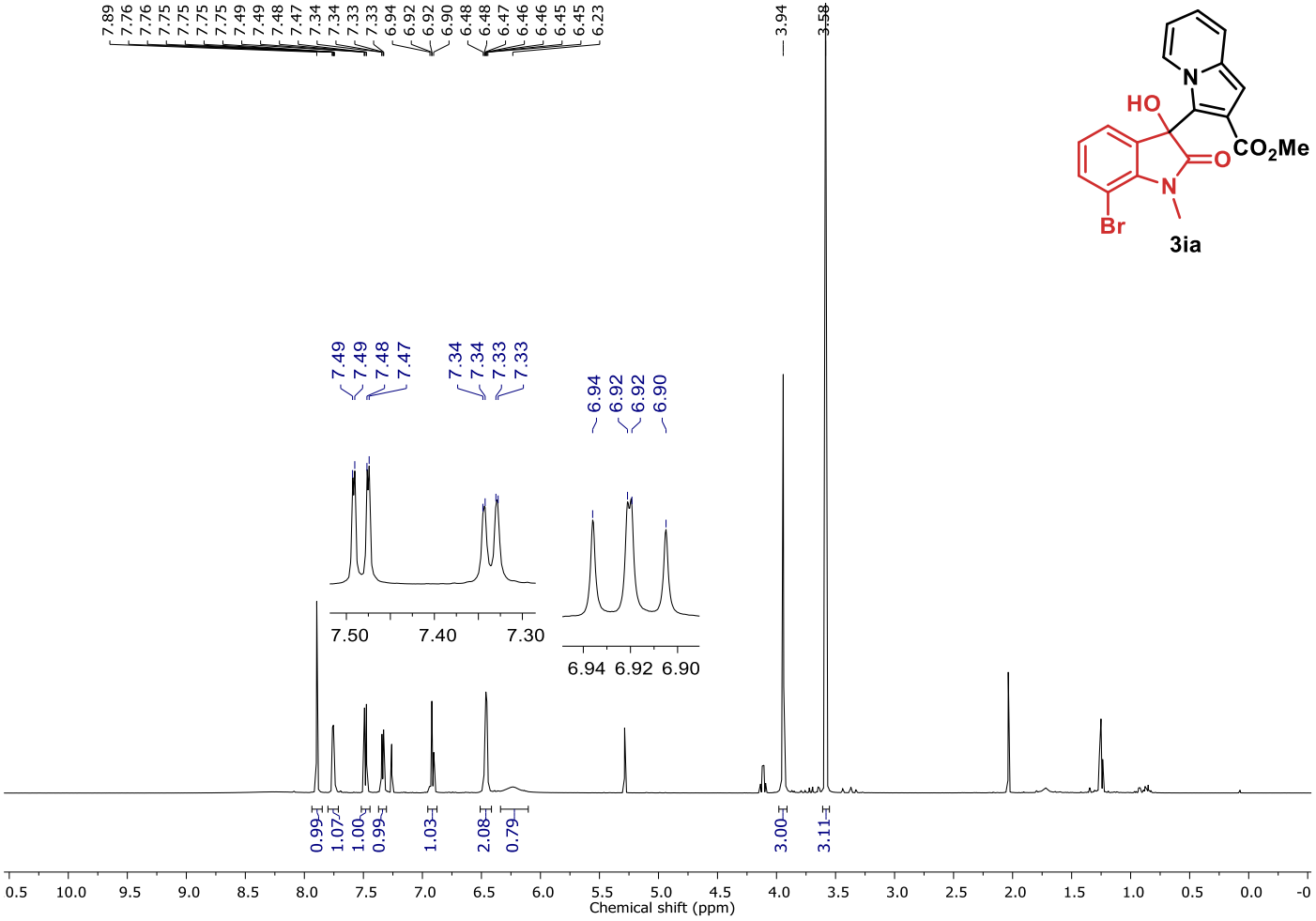


Figure S20. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3ia**.

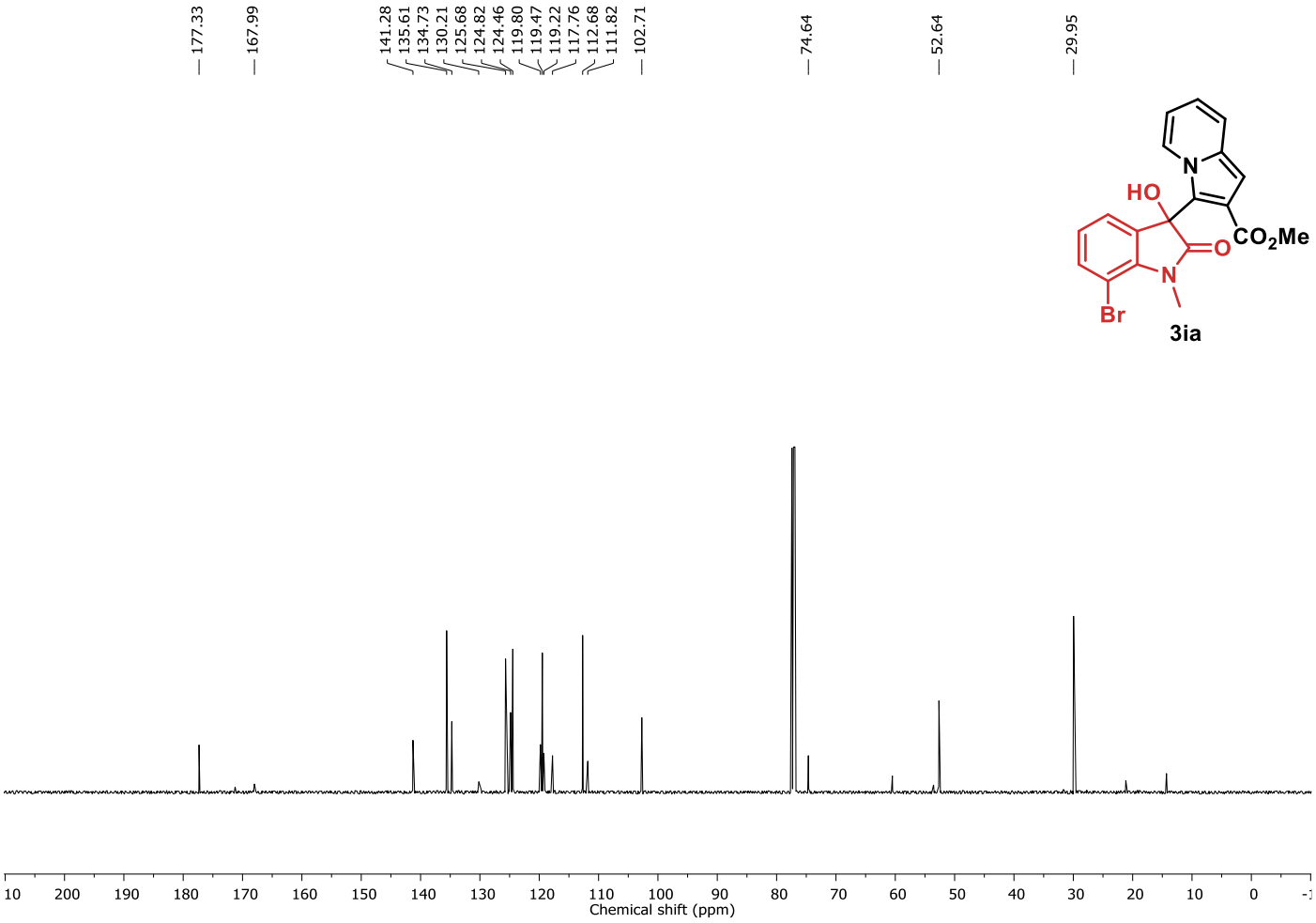


Figure S21. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3ia**.

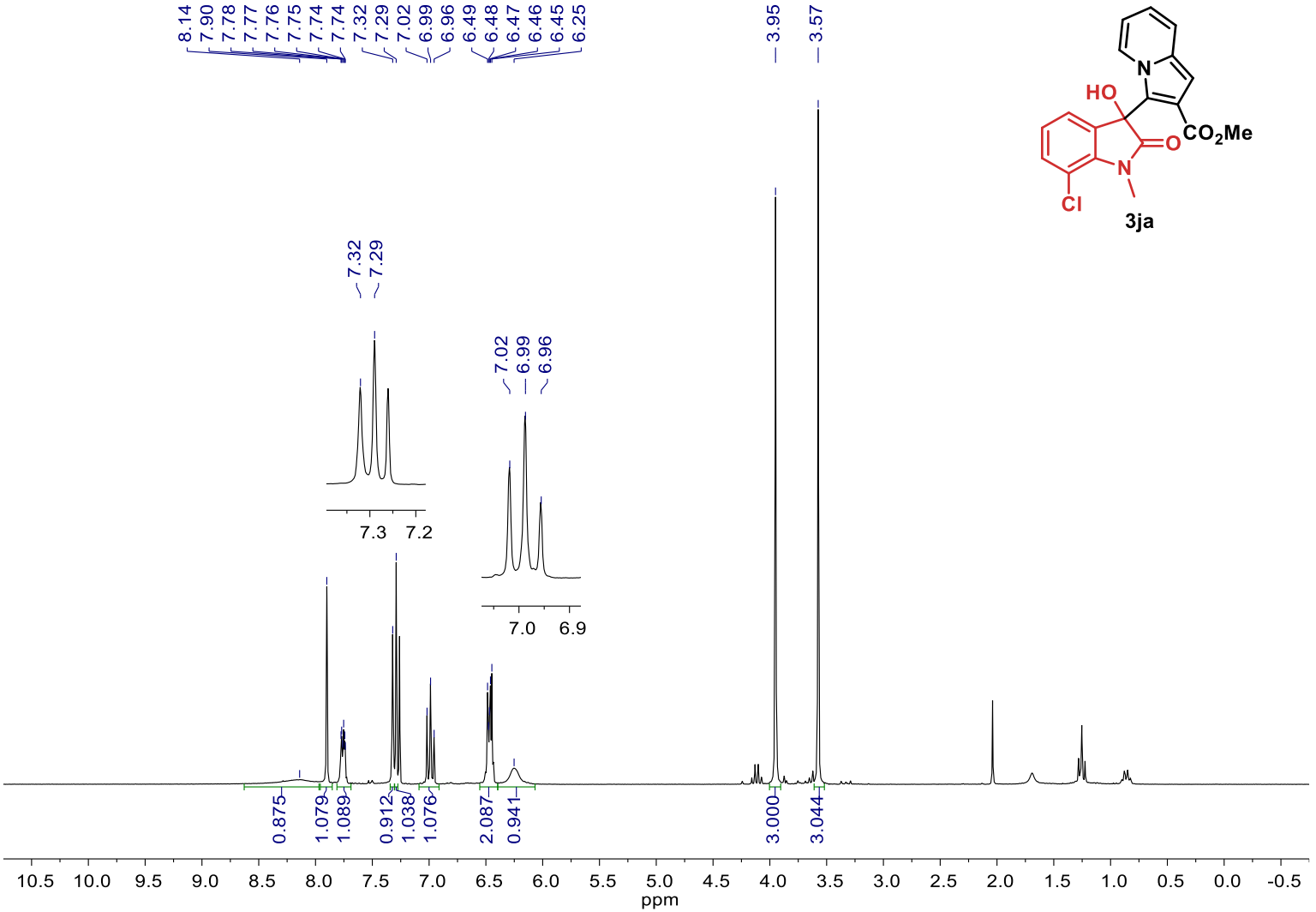


Figure S22. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3ja**.

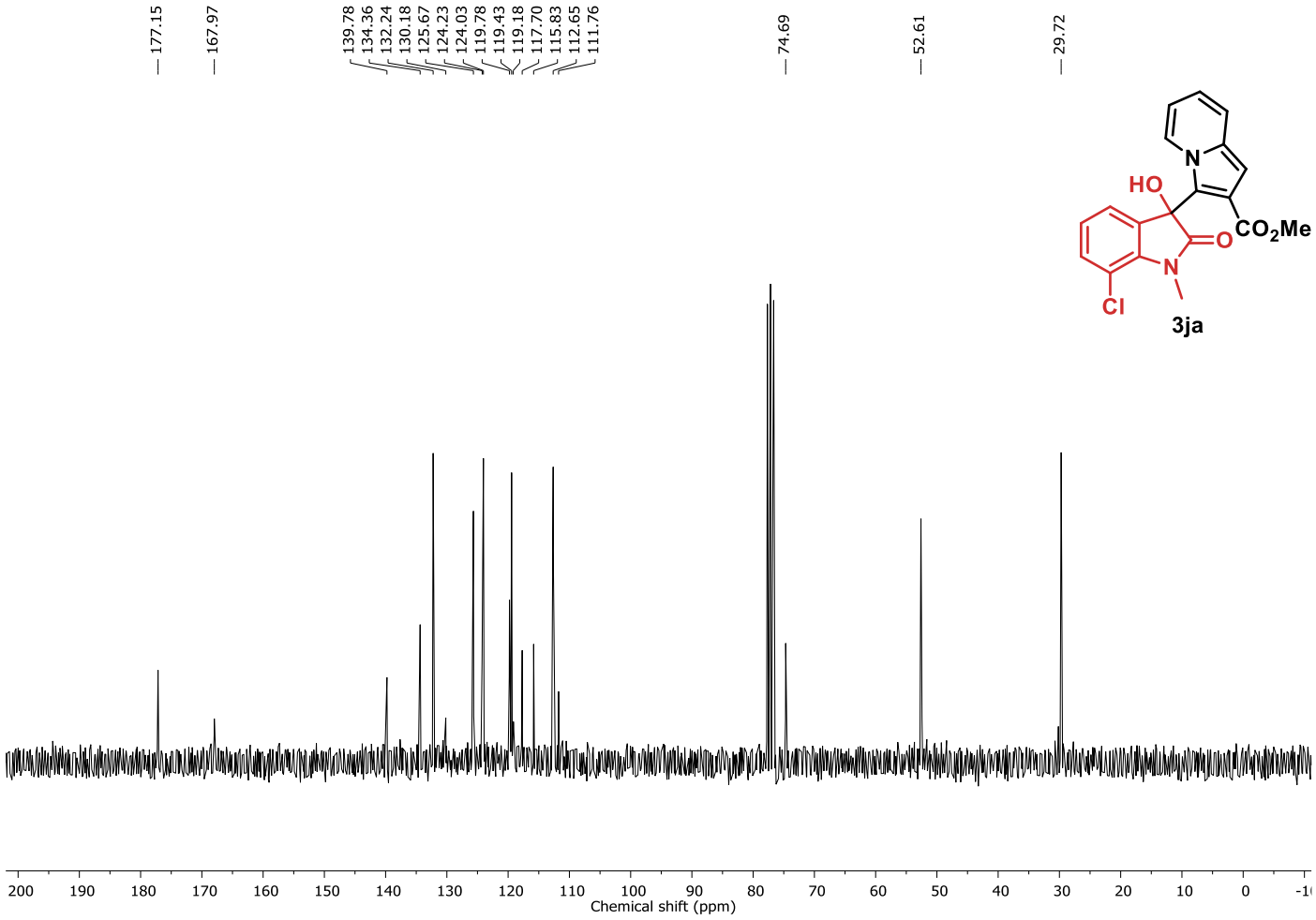


Figure S23. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3ja**.

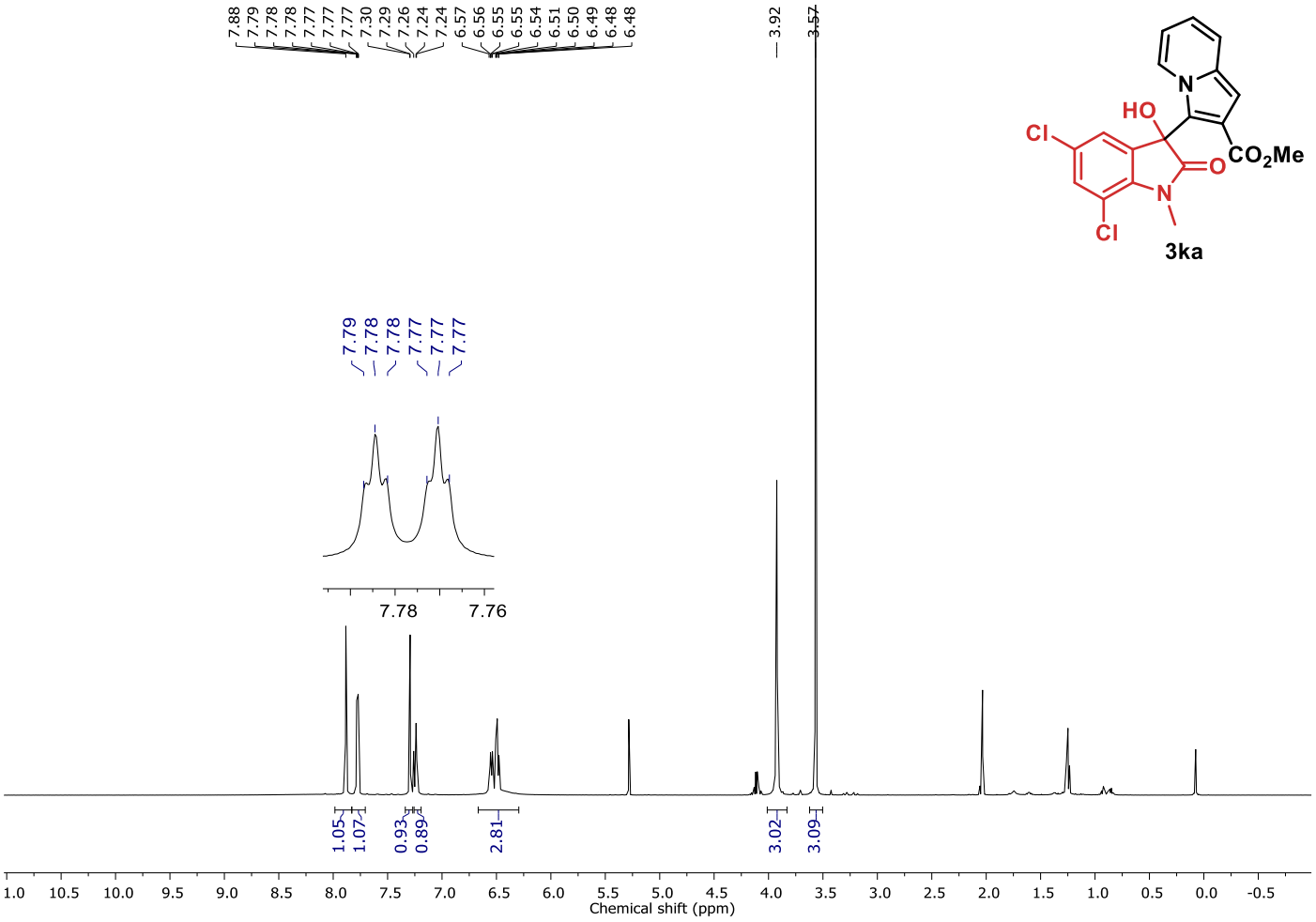


Figure S24. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3ka**.

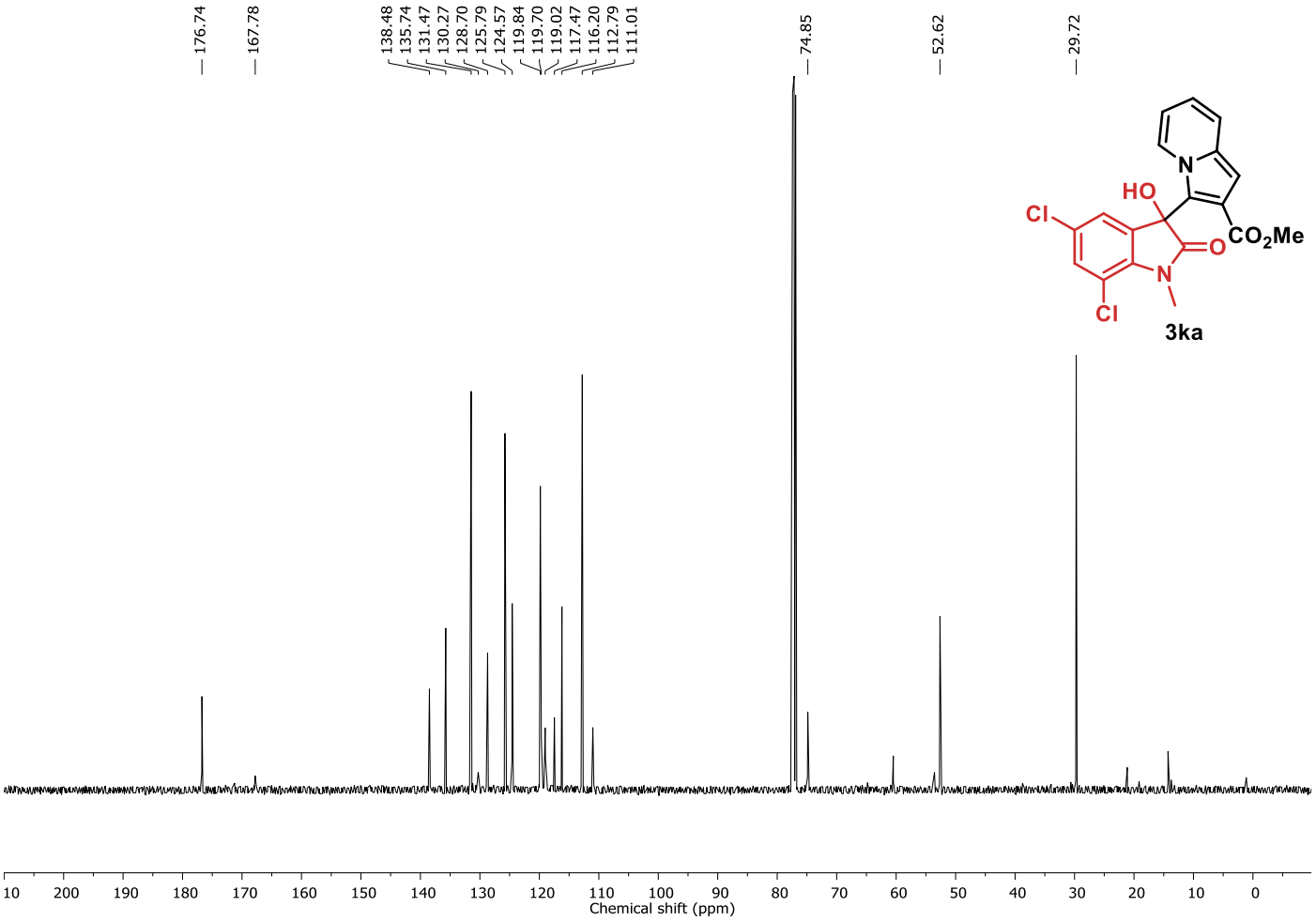


Figure S25. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3ka**.

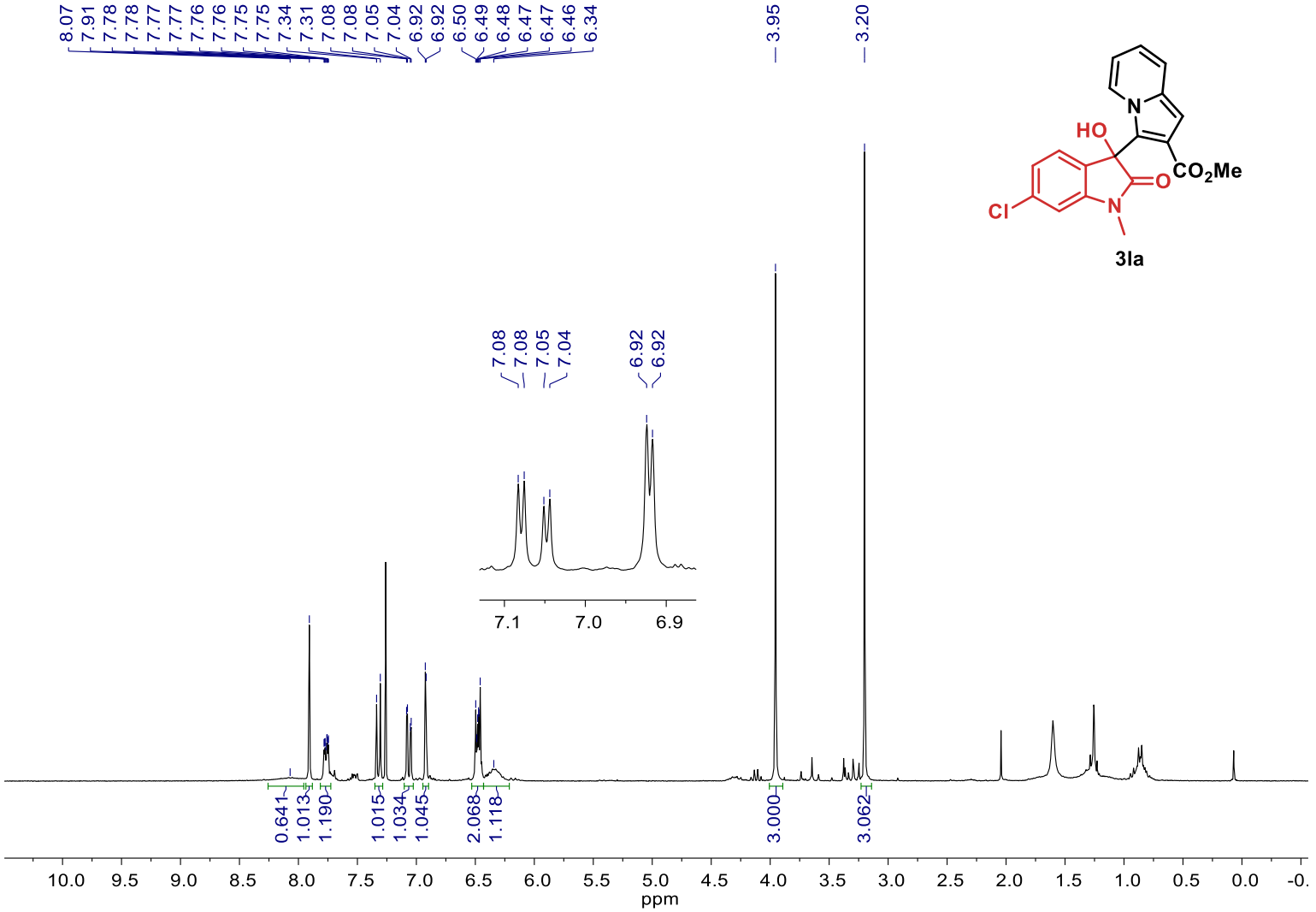


Figure S26. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3la.**

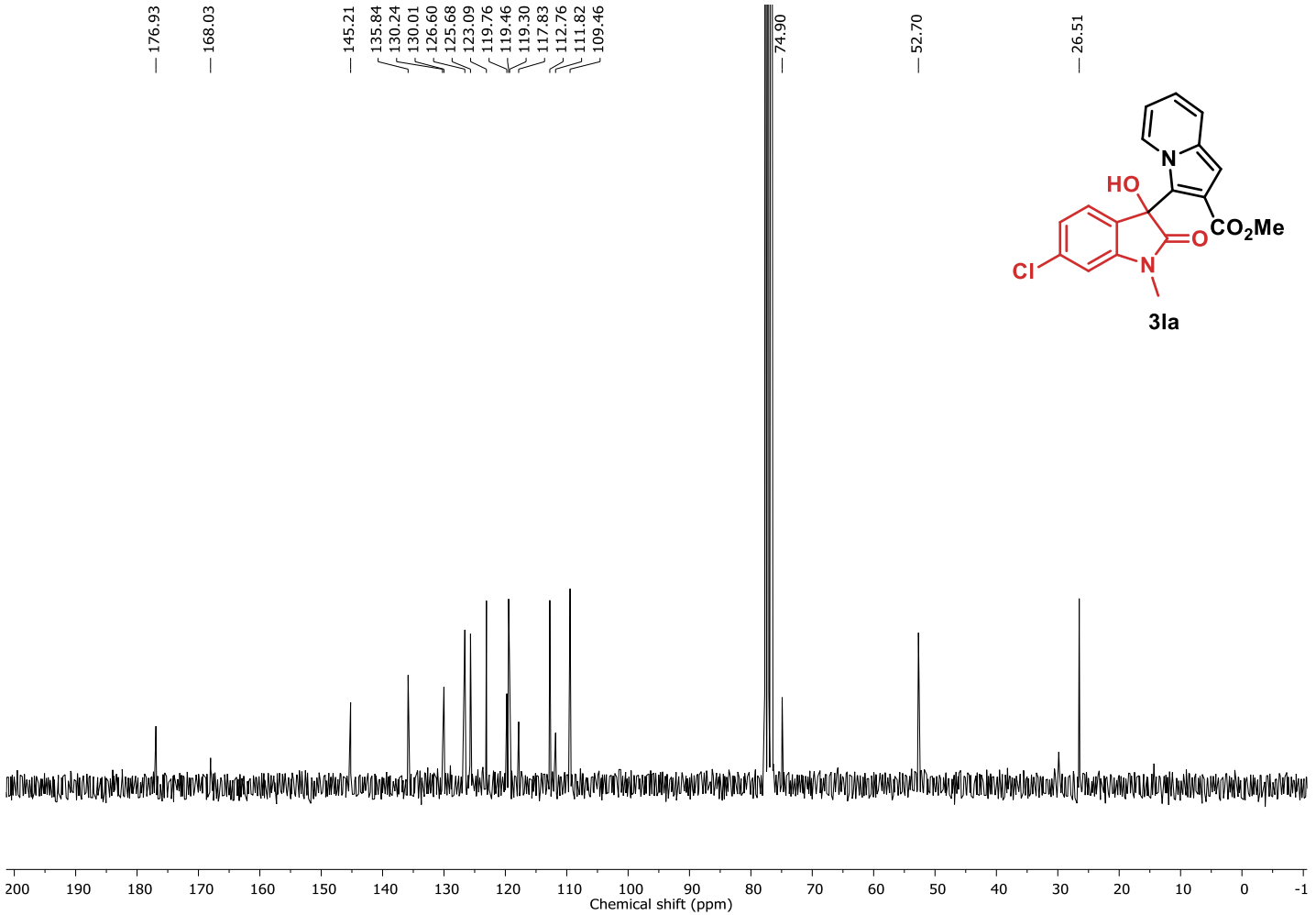


Figure 27. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3la.**

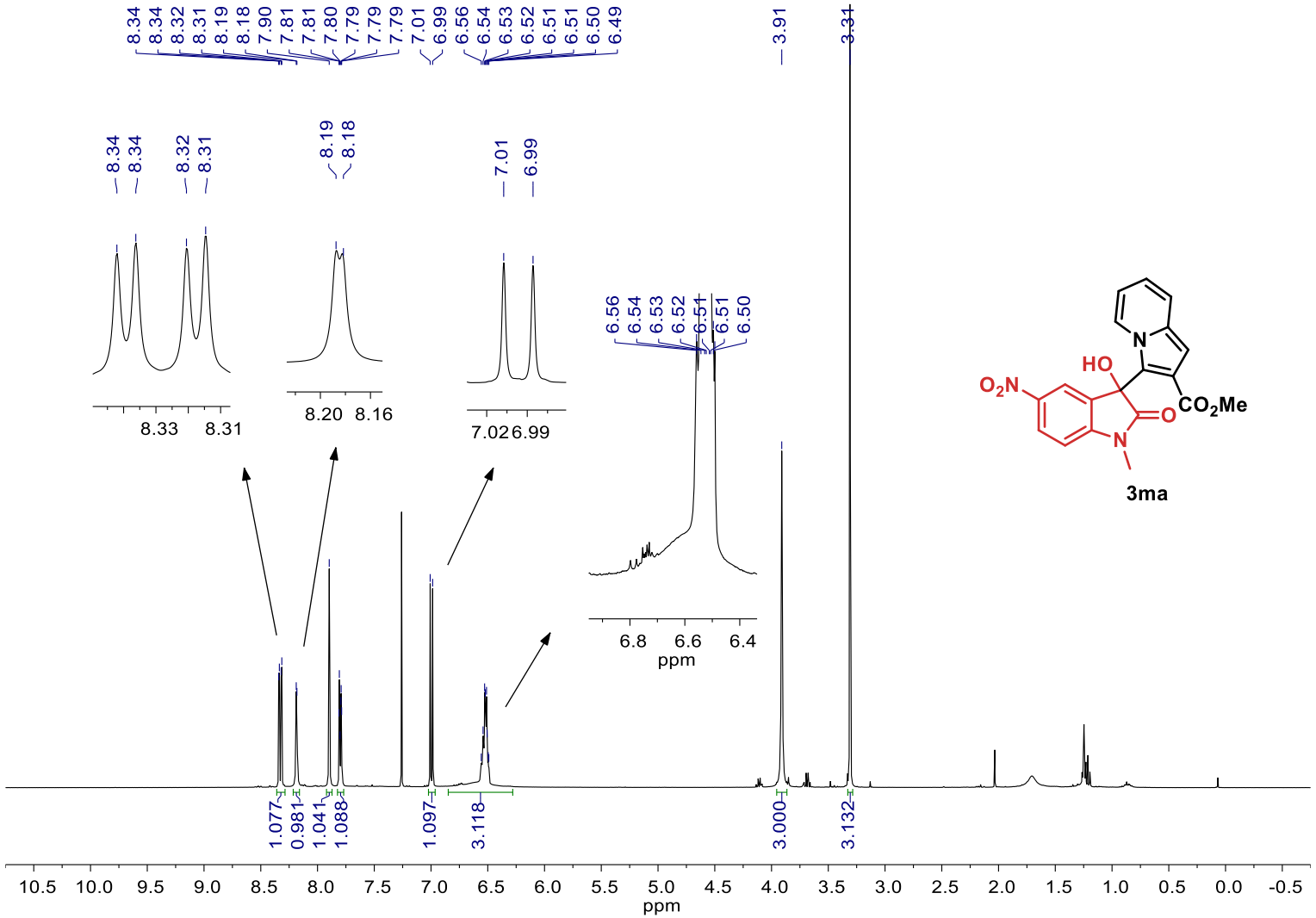


Figure S28. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ma**.

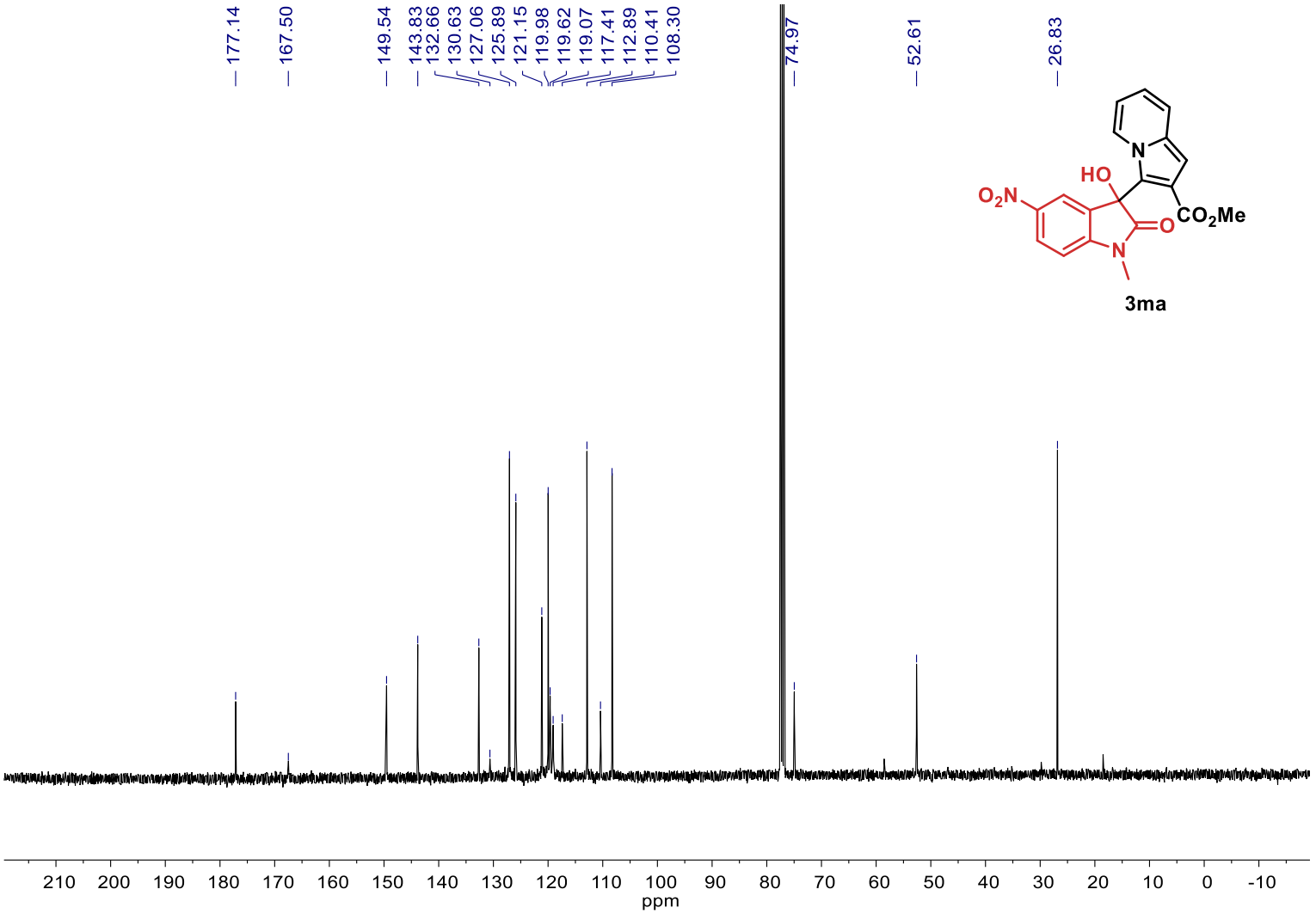


Figure S29. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3ma**.

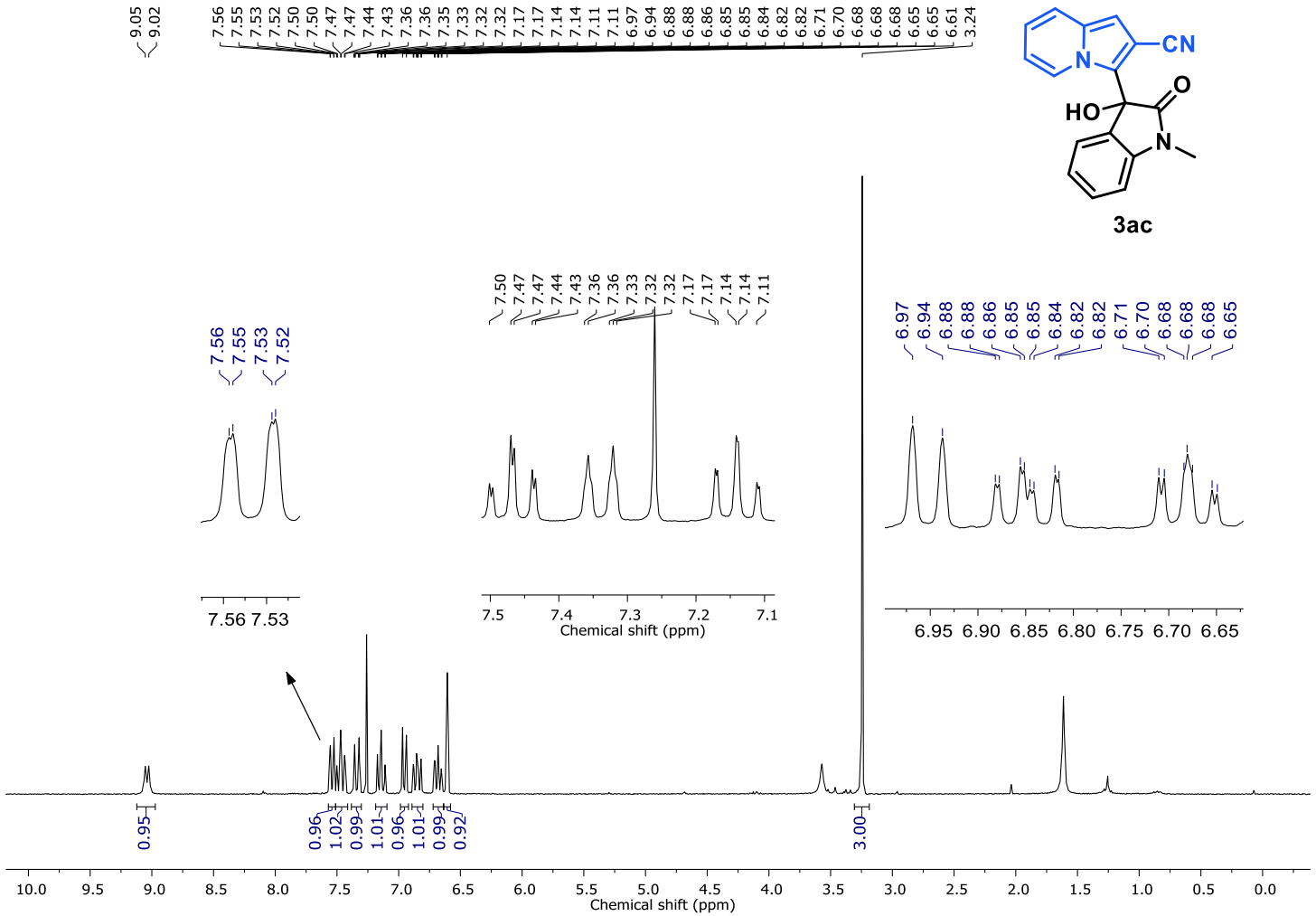


Figure S30. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound 3ac.

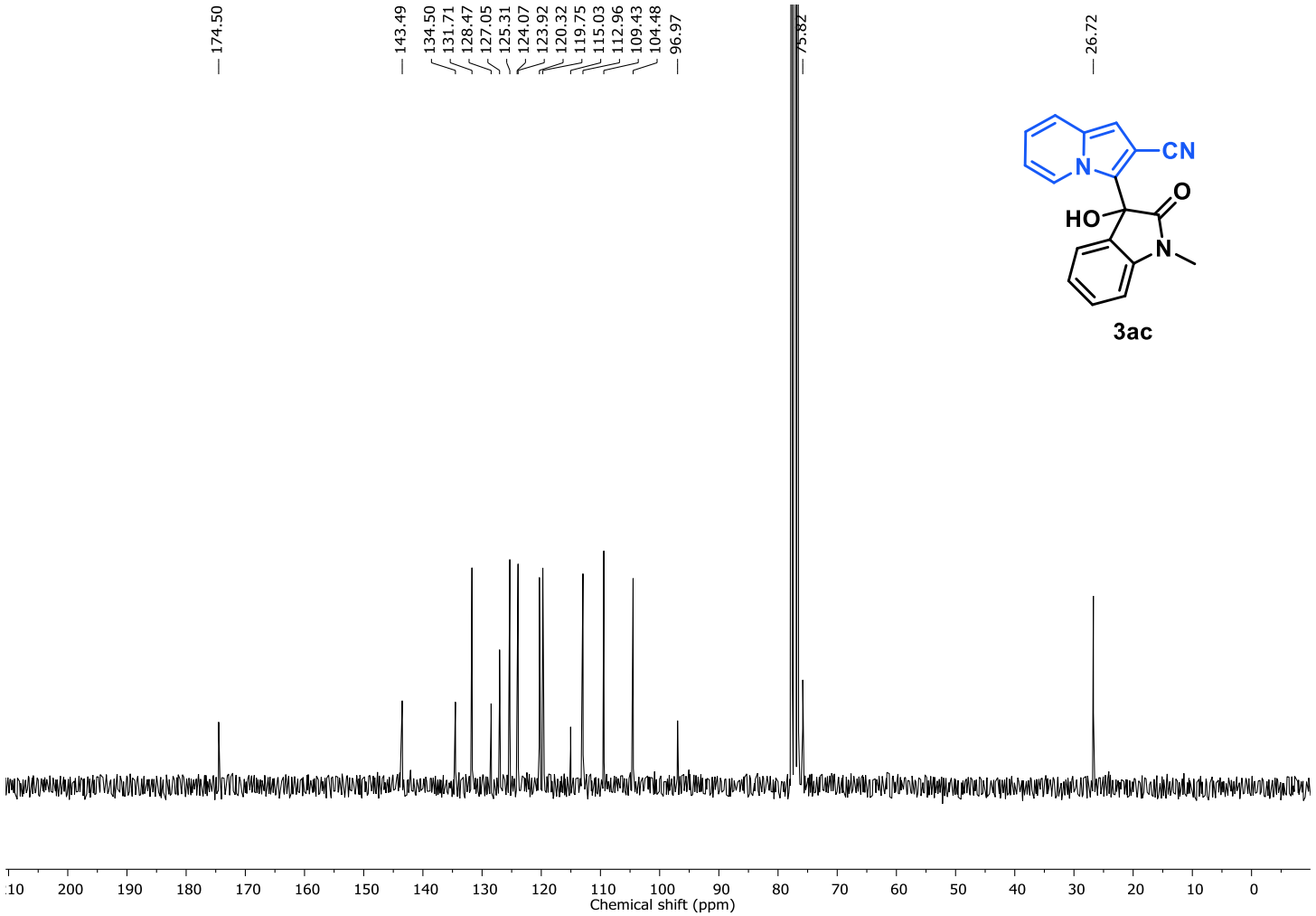


Figure S31. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3ac.**

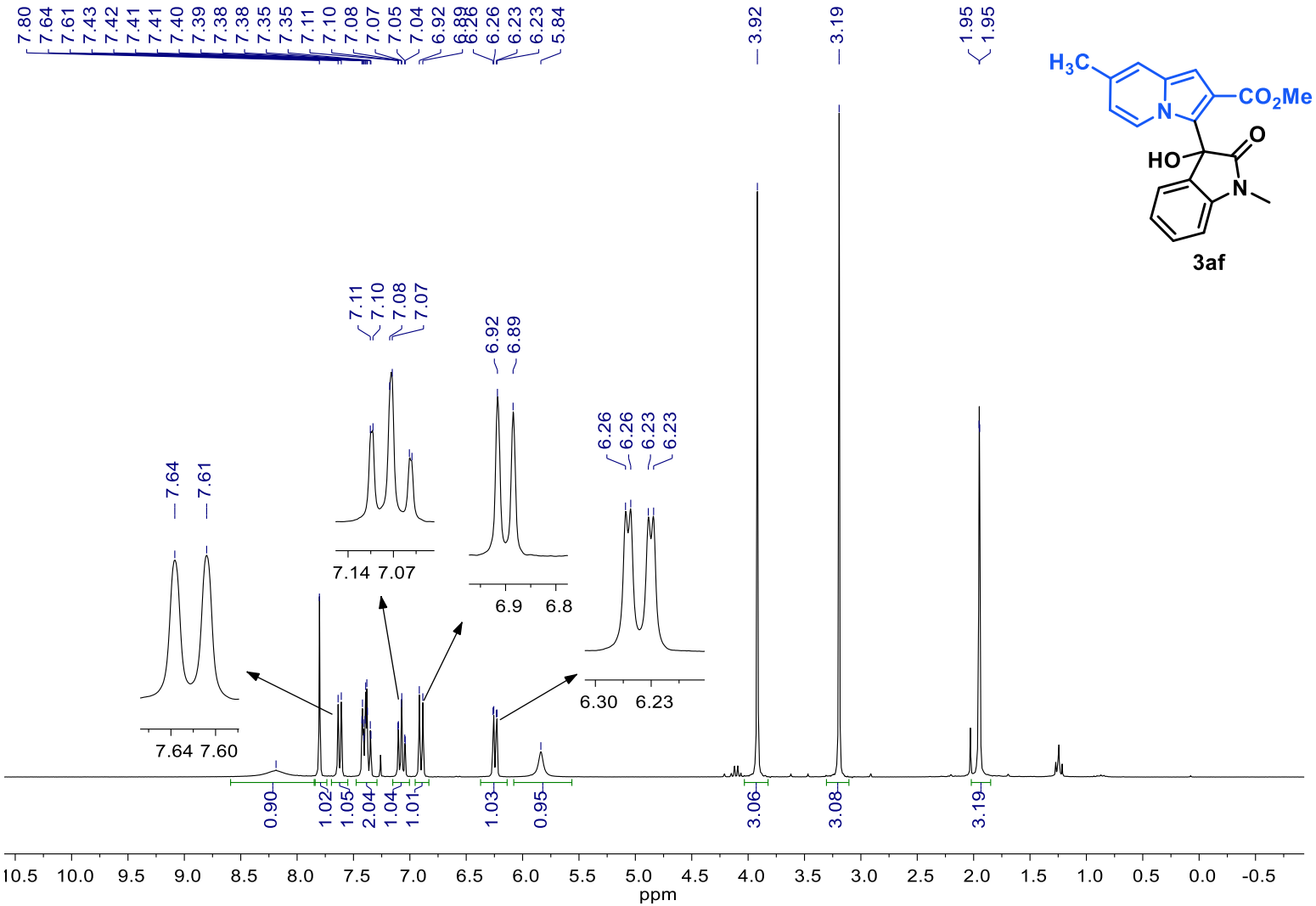


Figure S32. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3af.**

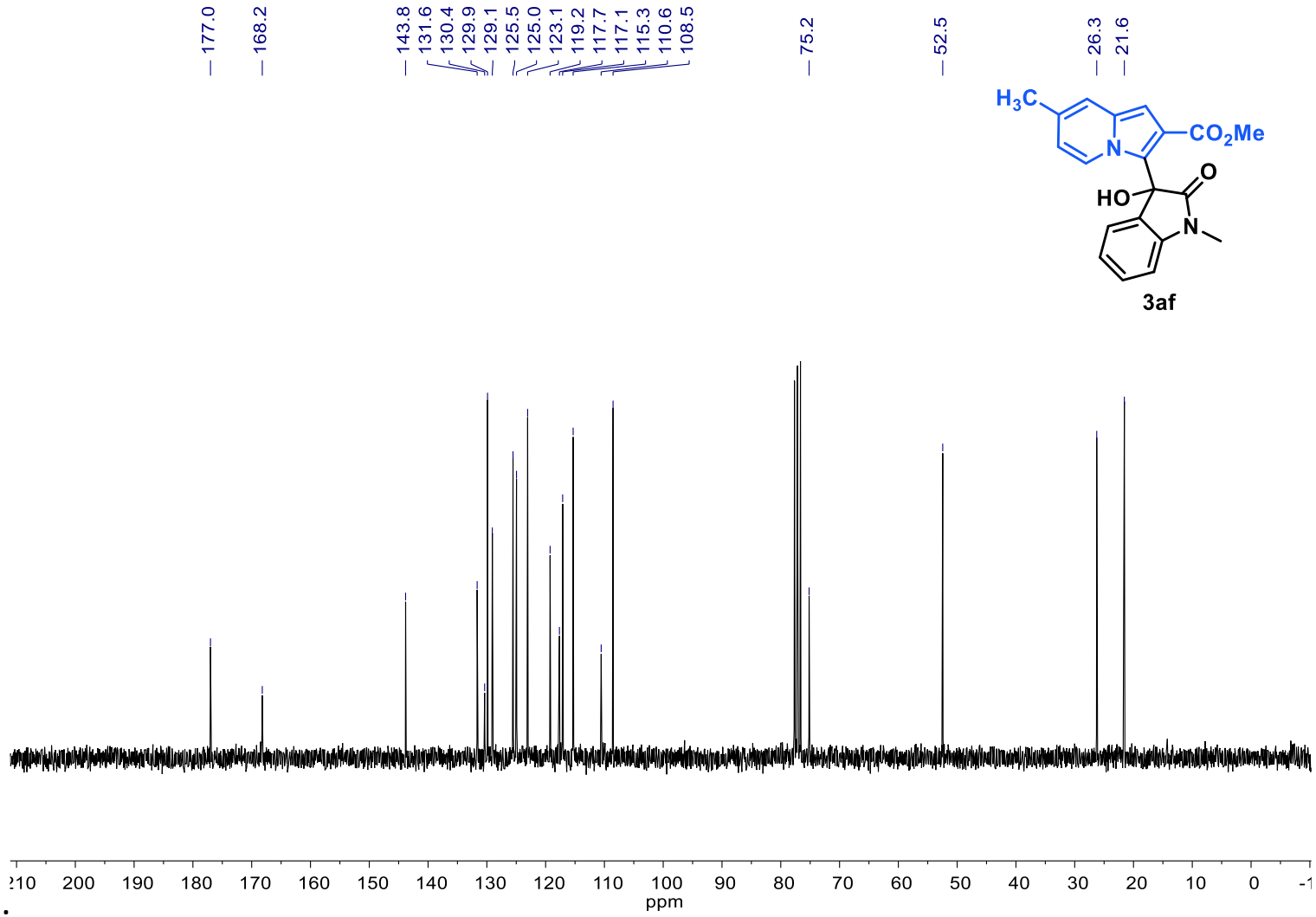


Figure S33. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3af**.

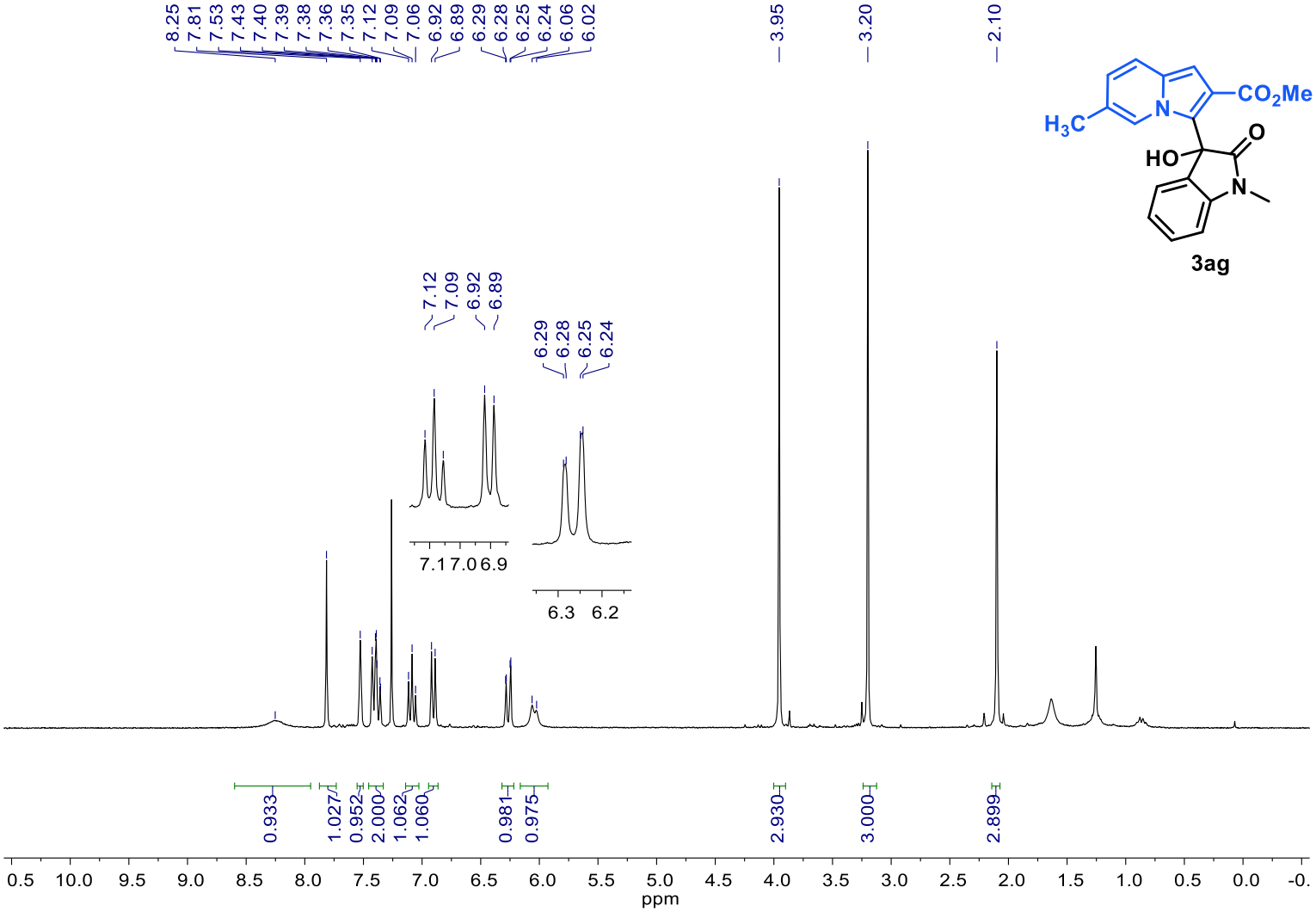


Figure S34. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3ag**.

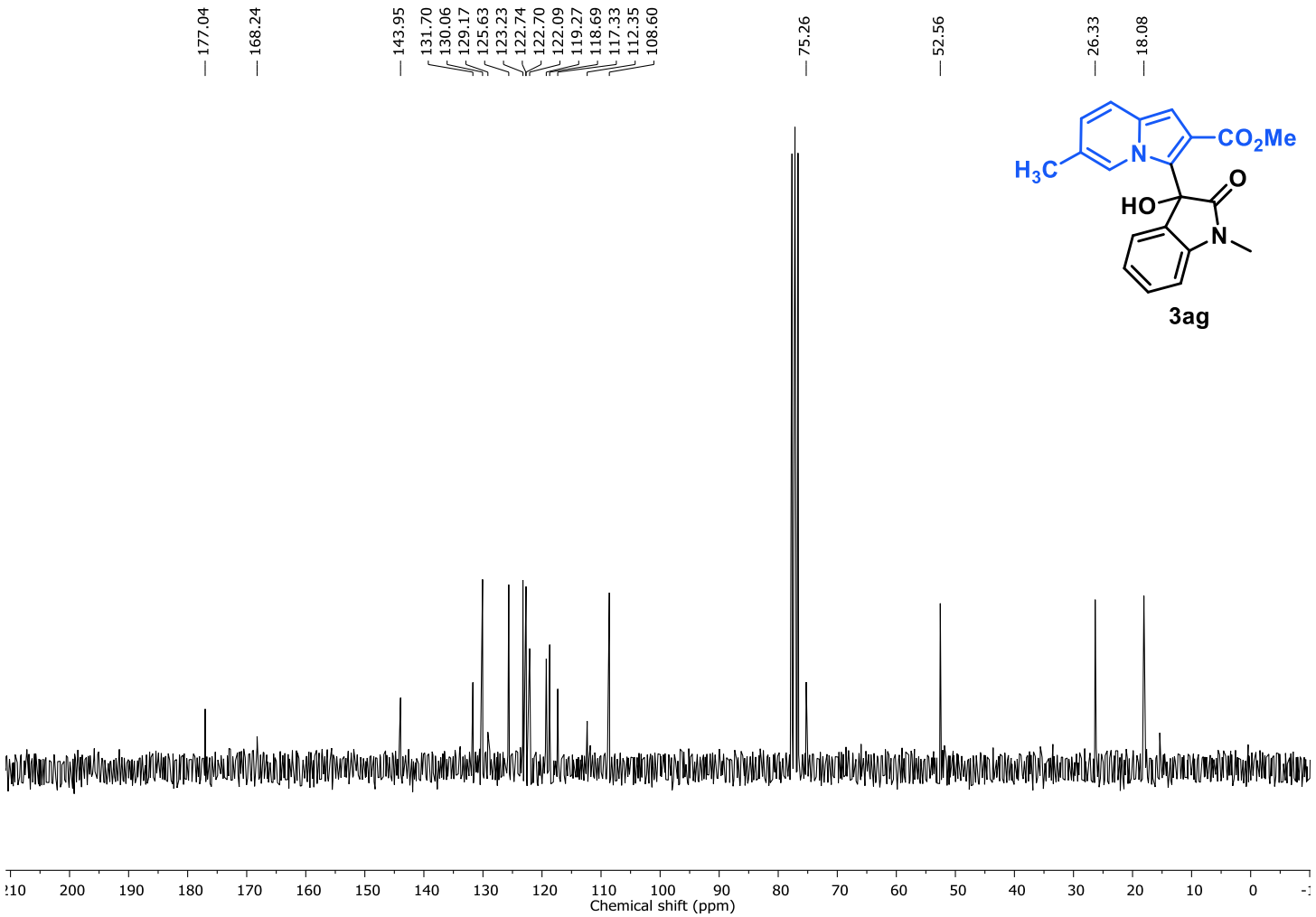


Figure S35. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3ag**.

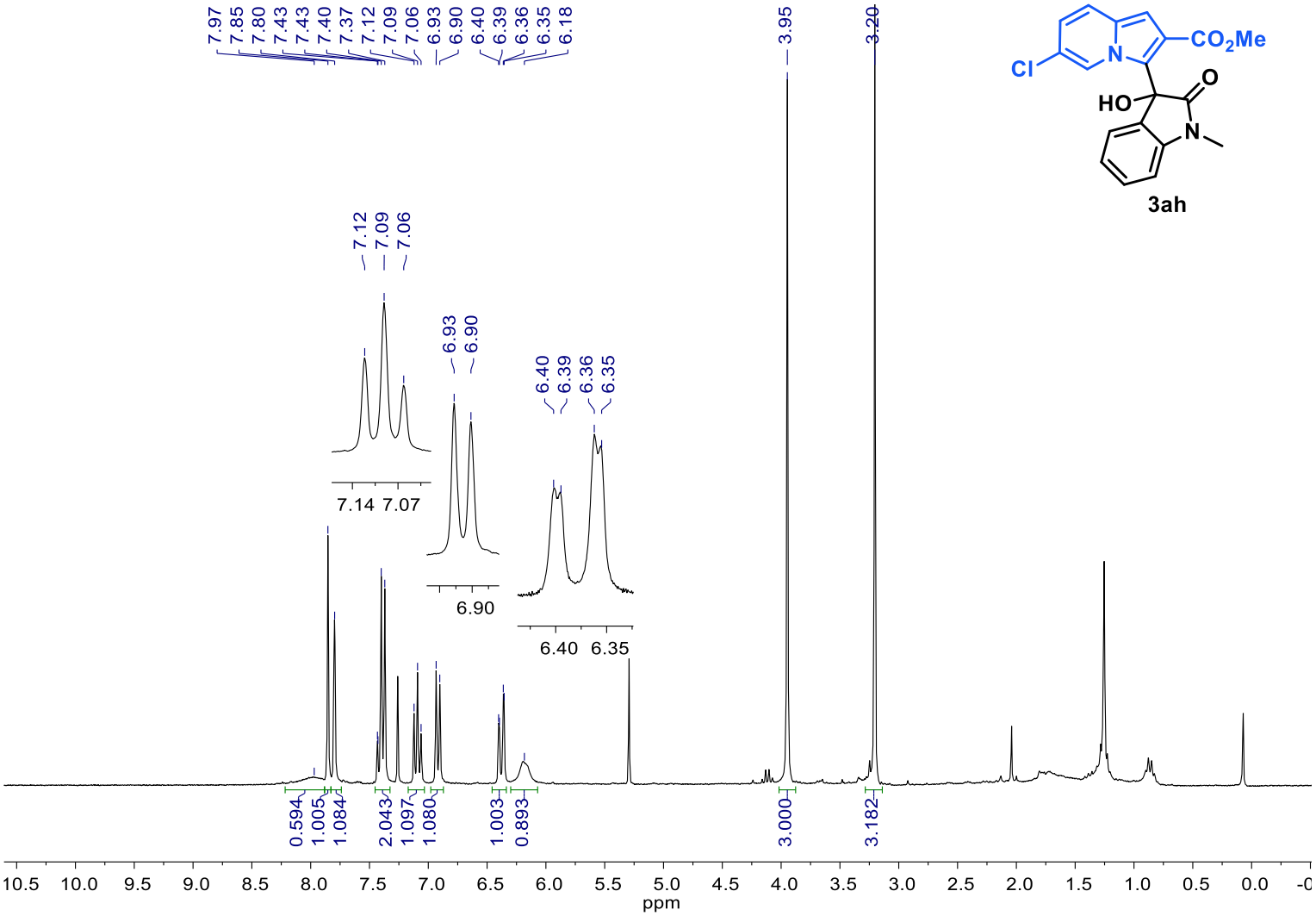


Figure S36. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3ah**.

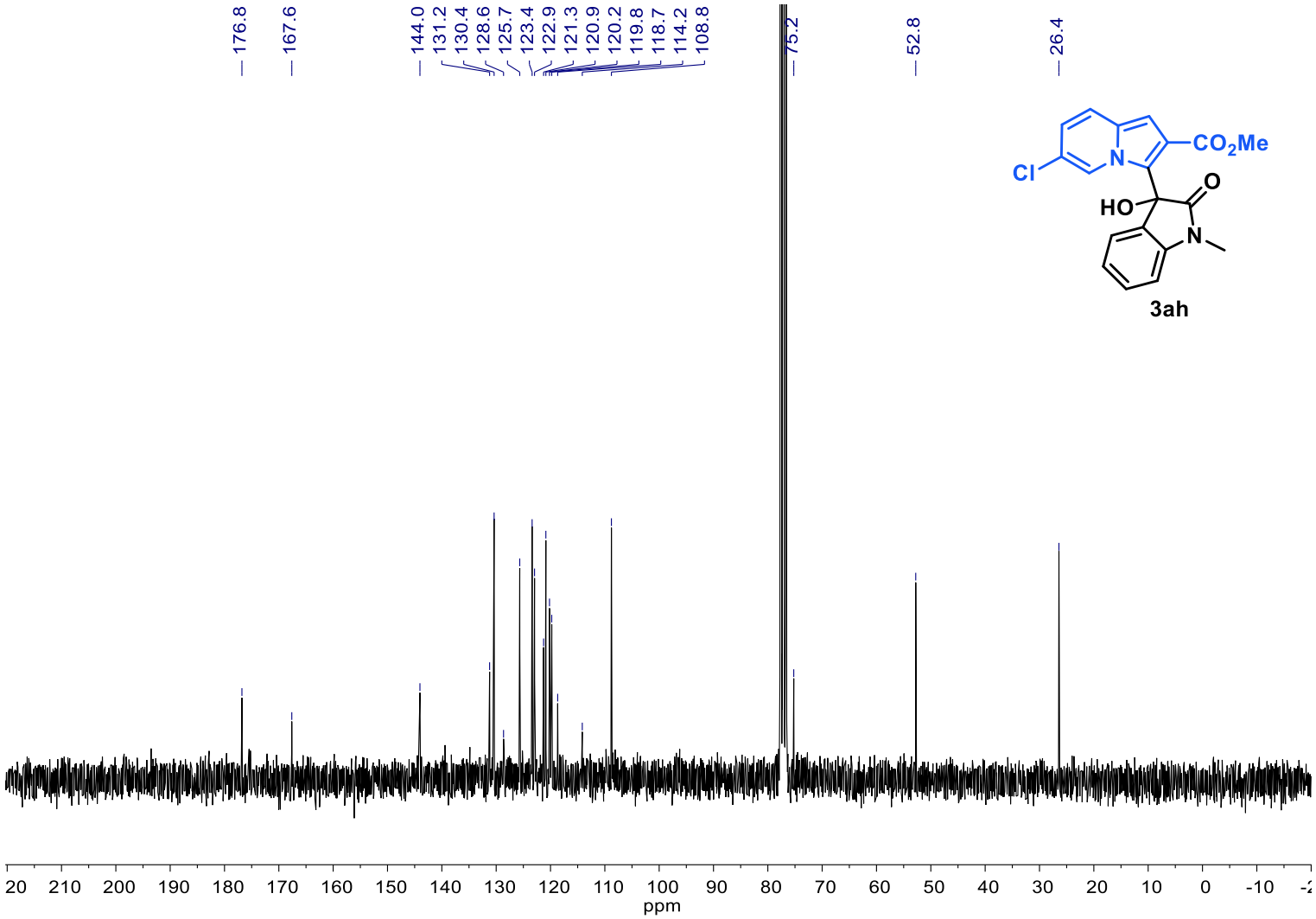


Figure S37. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3ah**.

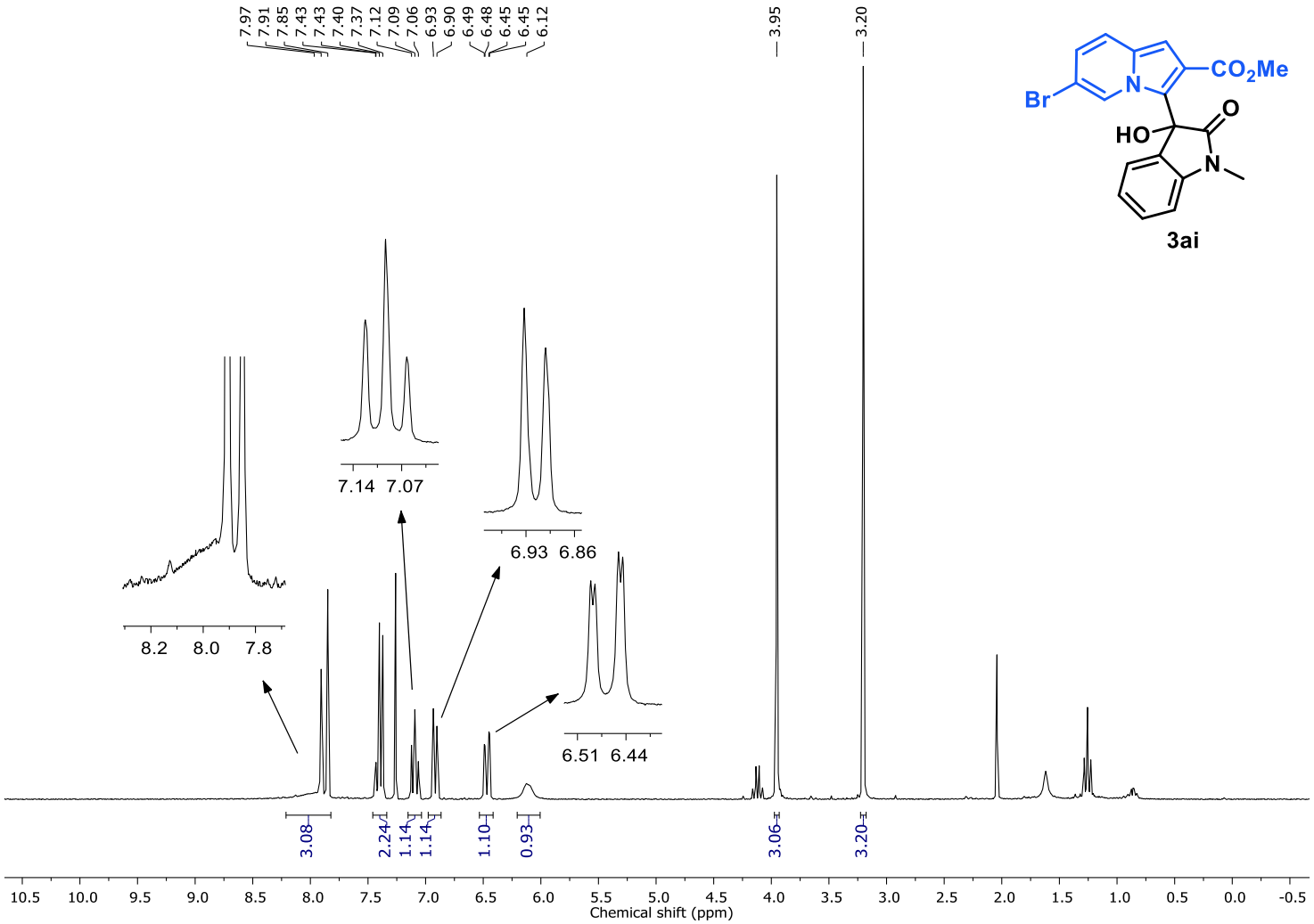


Figure S38. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3ai**.

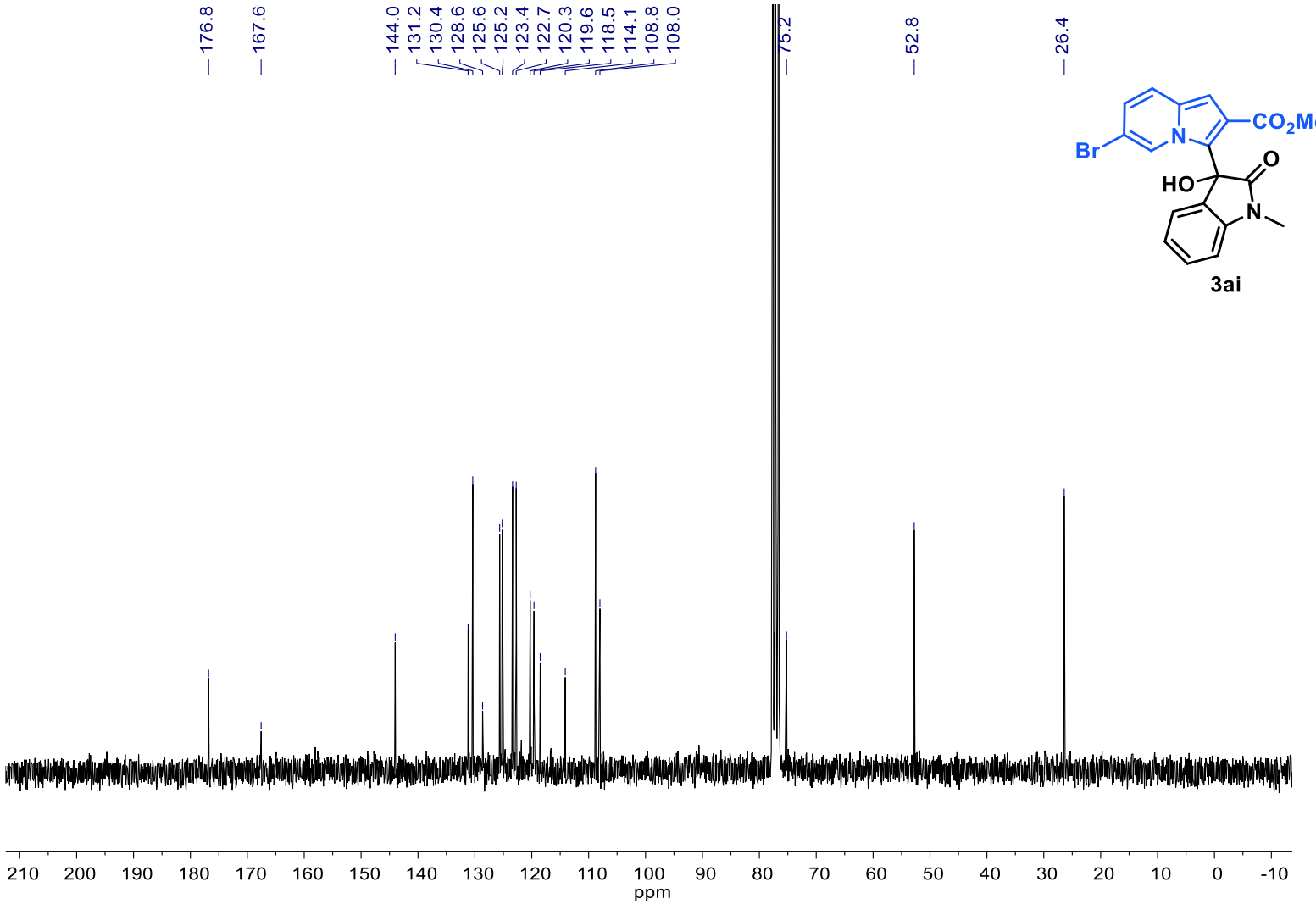


Figure S39. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3ai**.

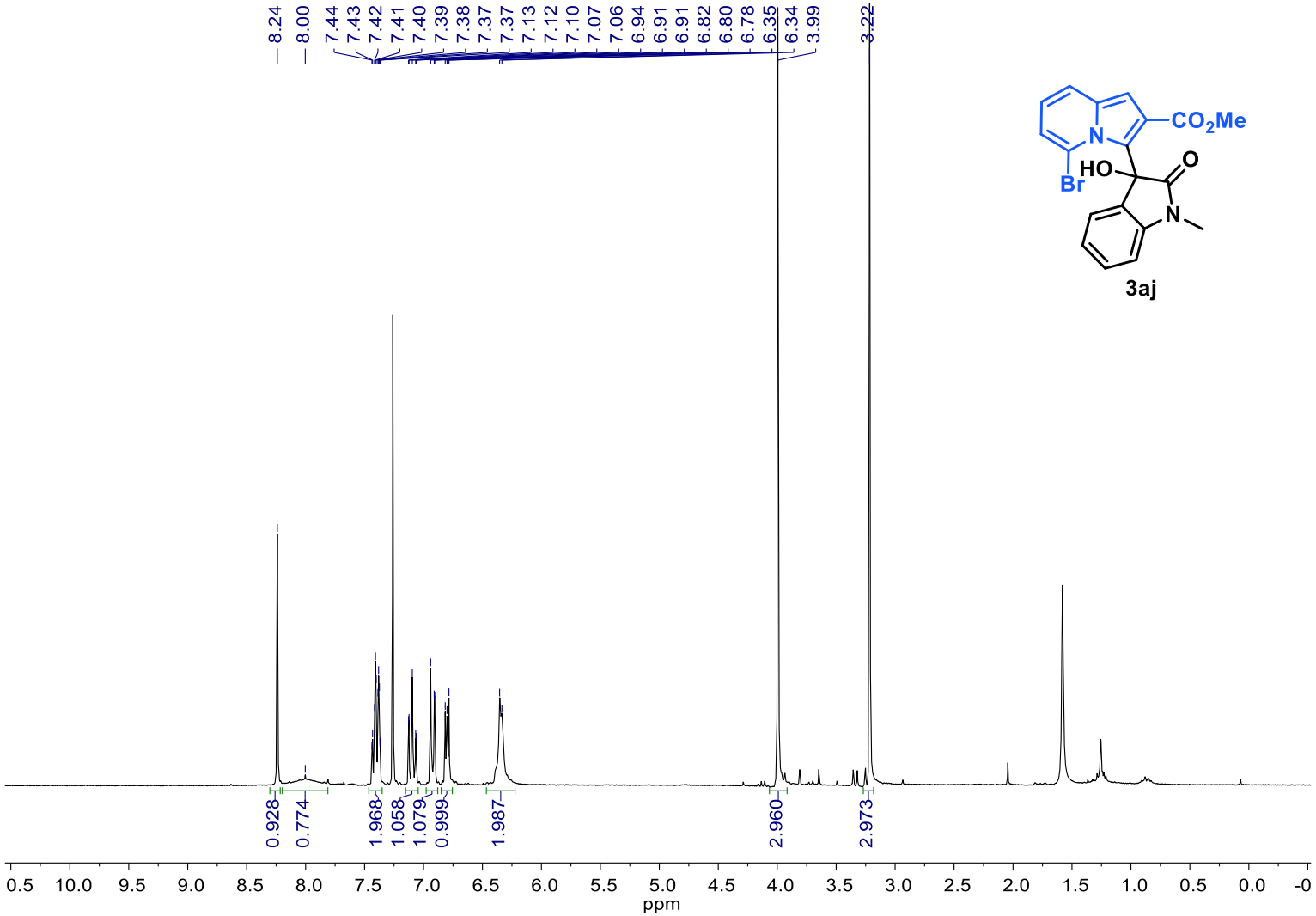


Figure S40. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **3aj**.

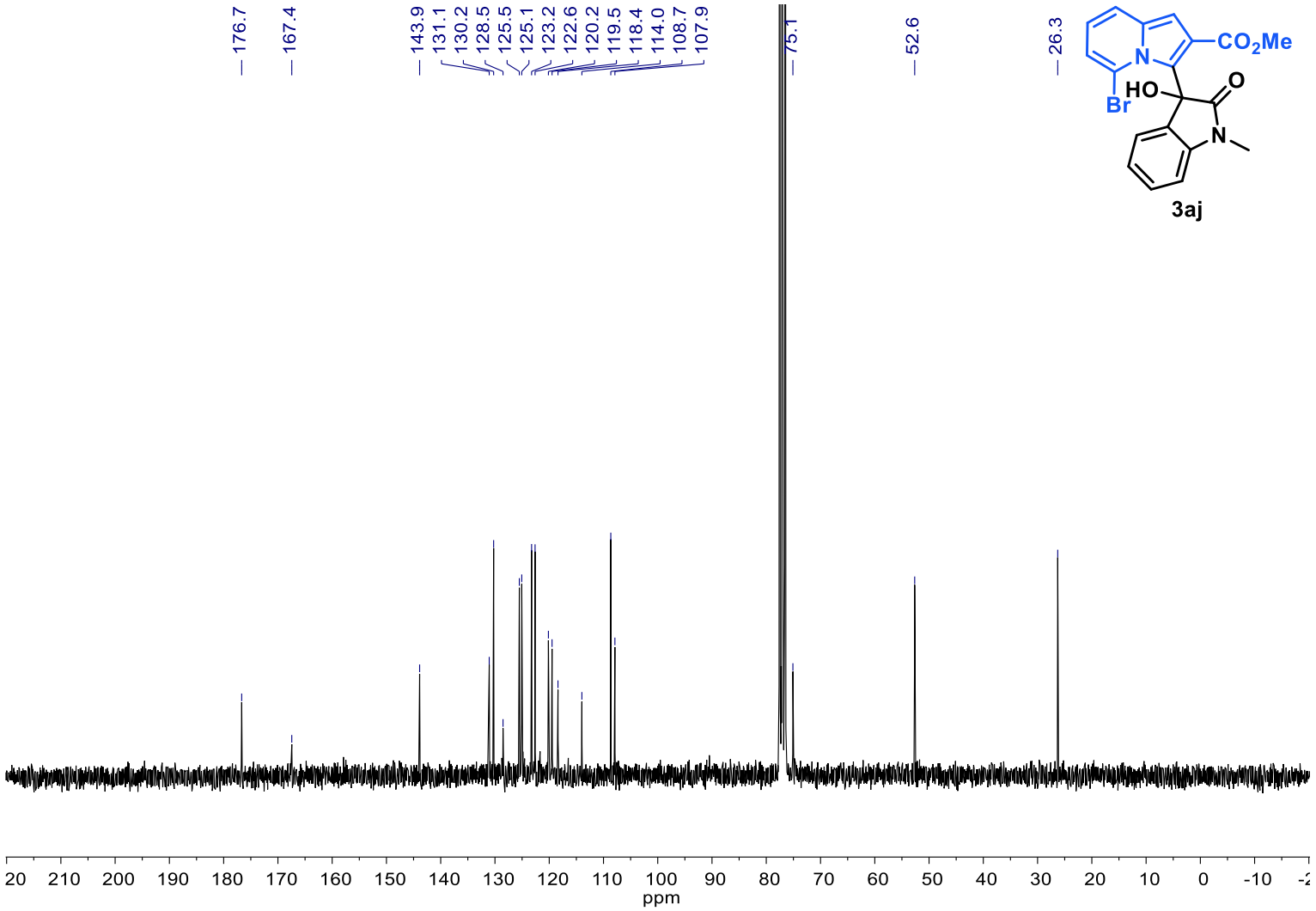


Figure S41. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **3aj**.

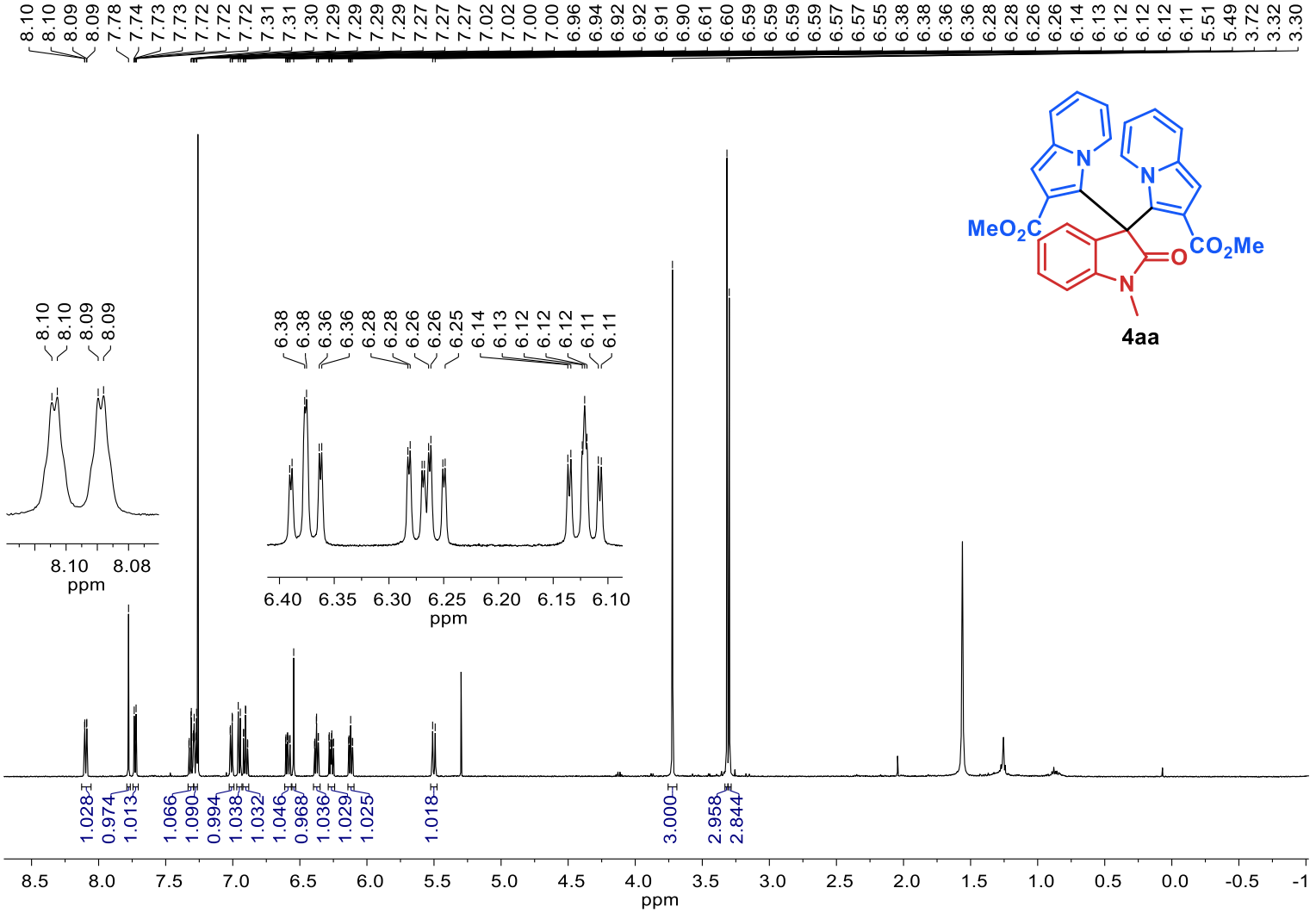


Figure S42. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4aa**.

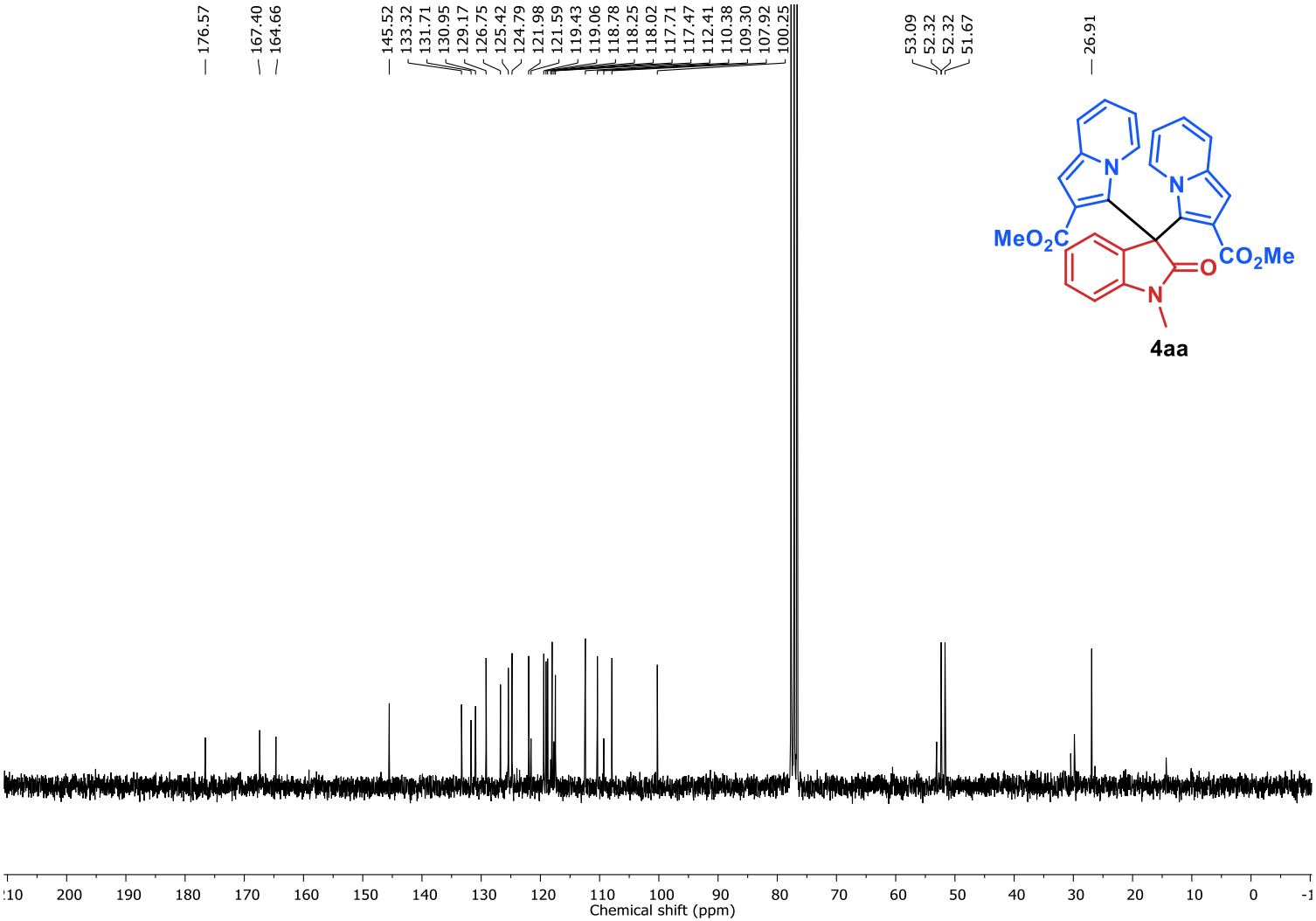


Figure S43. ^{13}C NMR (63 MHz, $CDCl_3$) spectrum of compound **4aa**.

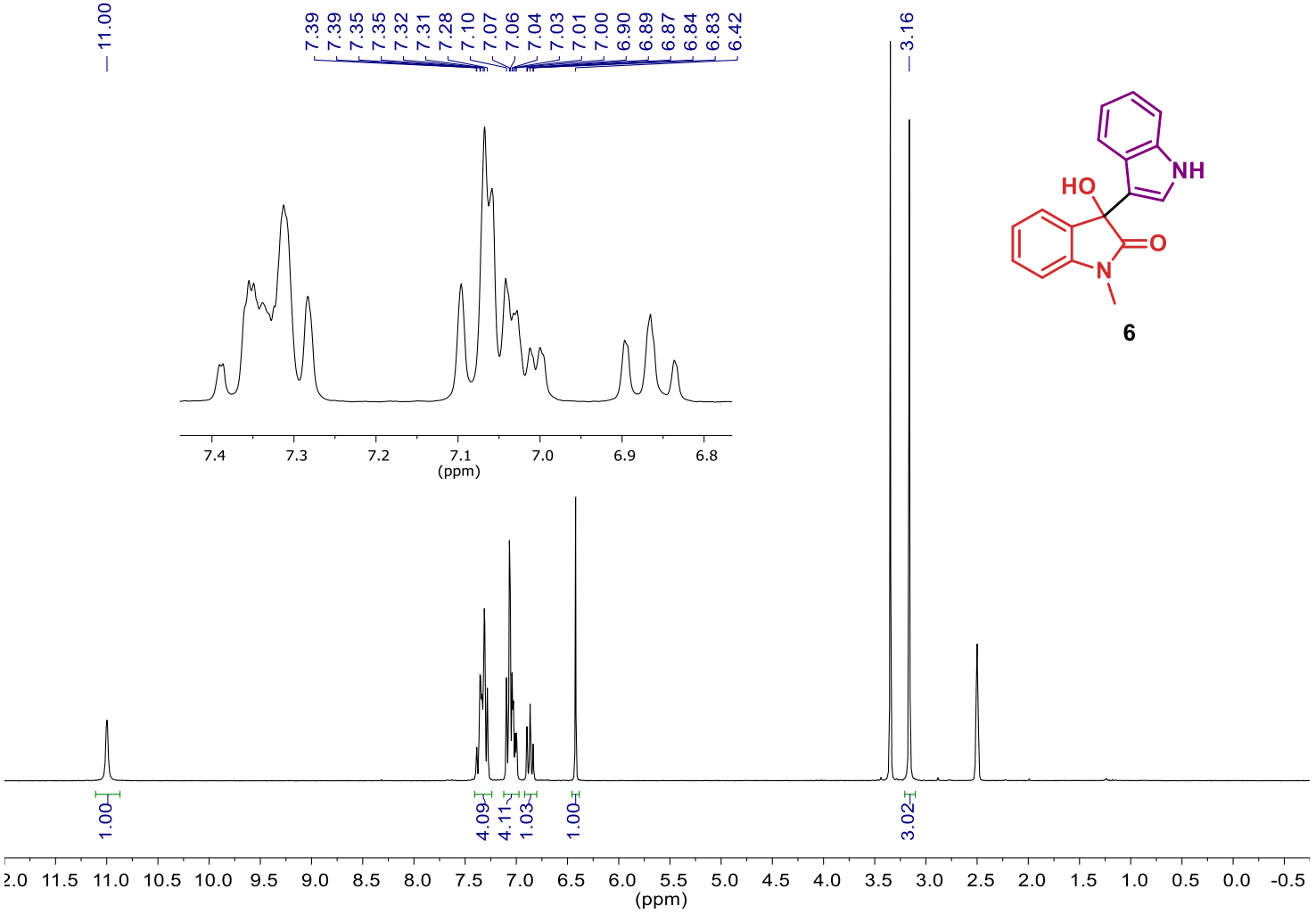


Figure S44. ^{1}H NMR (250 MHz, DMSO) spectrum of compound **6**.

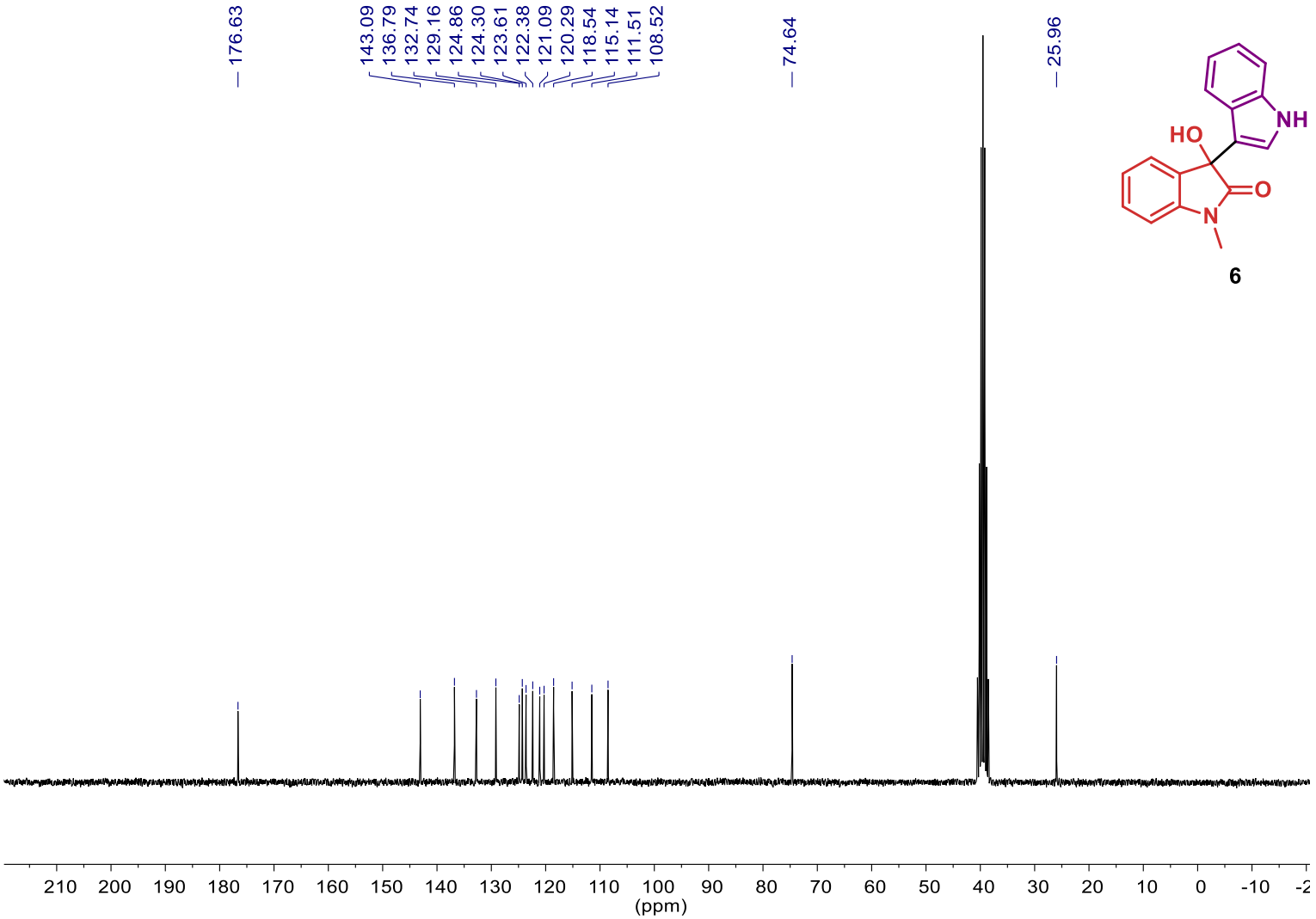


Figure S45. ^{13}C NMR (63 MHz, DMSO) spectrum of compound **6**.

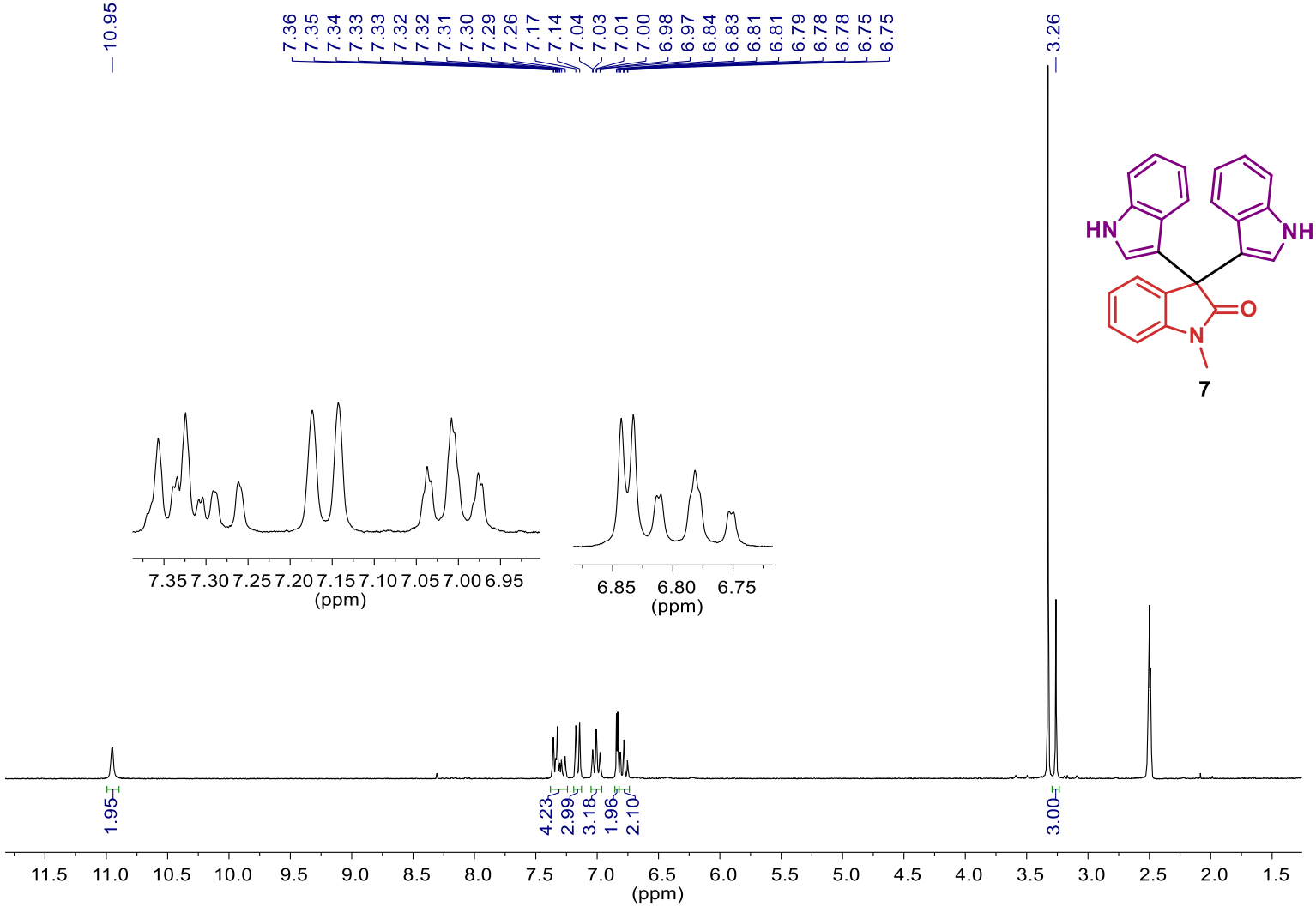


Figure 46. ^{1}H NMR (250 MHz, DMSO) spectrum of compound **7**.

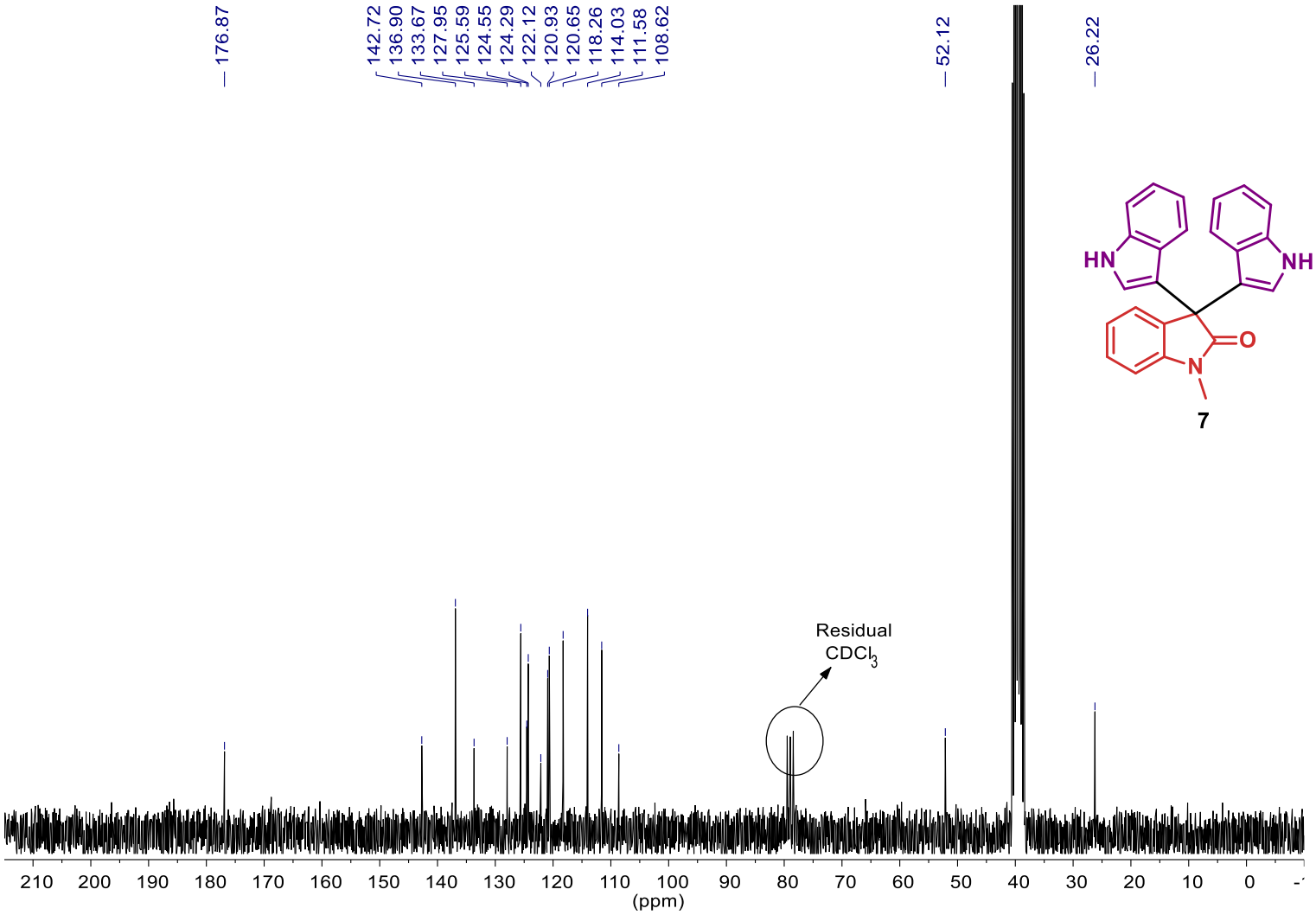


Figure S47. ^{13}C NMR (63 MHz, DMSO) spectrum of compound **7**.

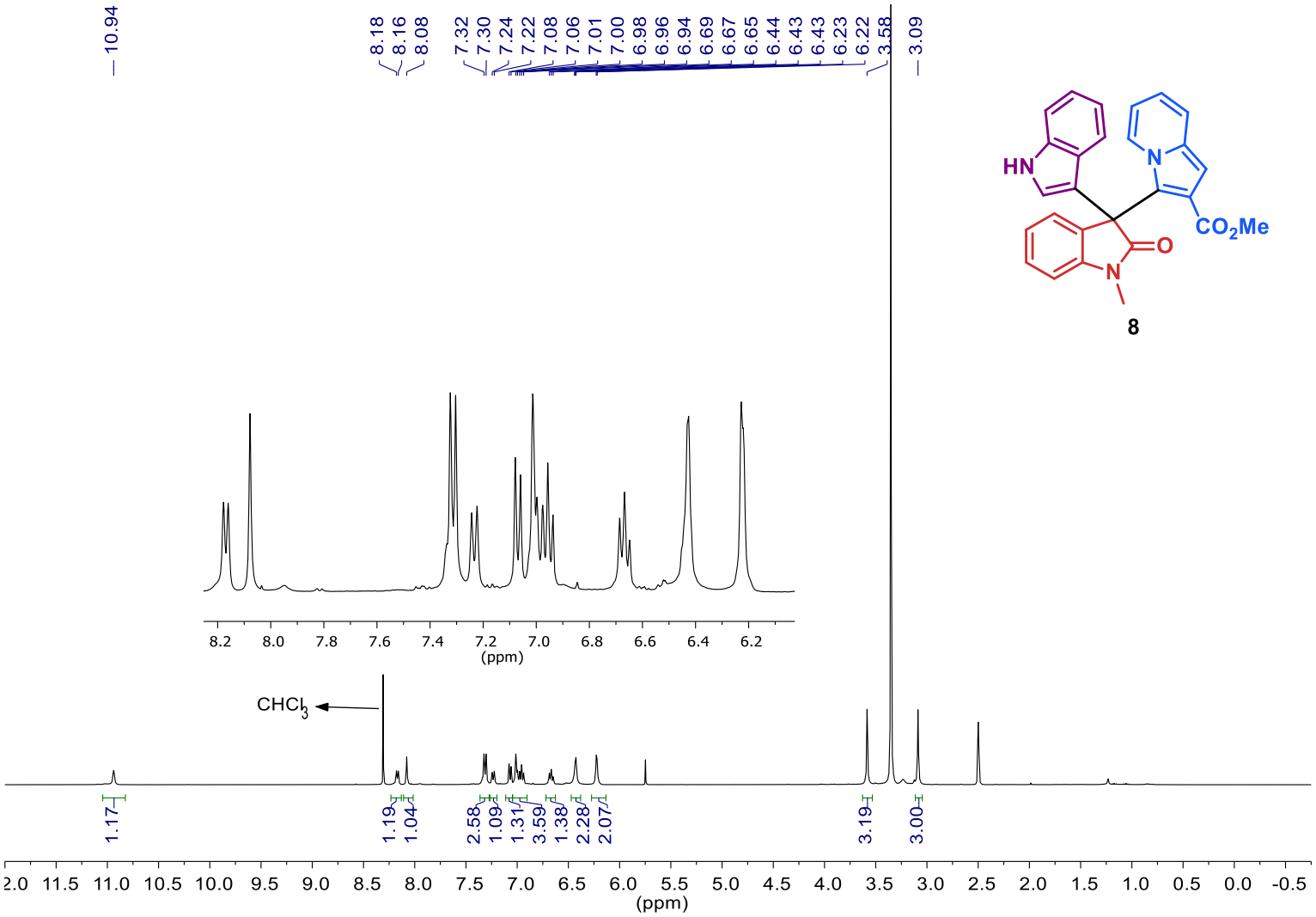


Figure S48. ^{1}H NMR (400 MHz, DMSO) spectrum of compound **8**.

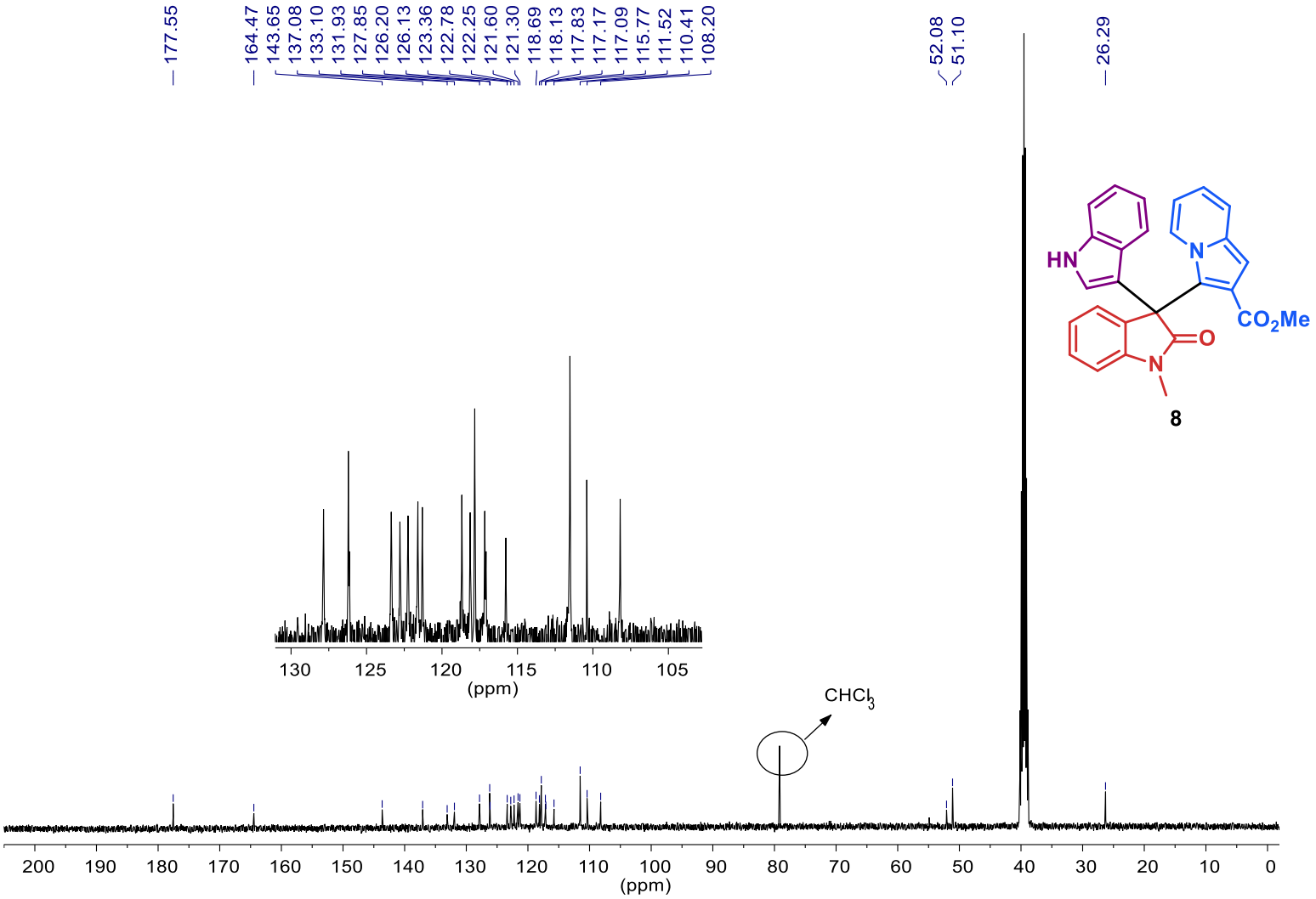


Figure S49. ^{13}C NMR (101 MHz, DMSO) spectrum of compound **8**.