Supplementary Information (SI) for RSC Mechanochemistry.
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Supplementary Information

Eco-friendly anaerobic oxidation of aryl diazo esters with heterocyclic N-oxide under ball milling: Synthesis of 1,2-dicarbonyl systems

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Content and page numbers

1. General Information:

All milling reactions were conducted using a (RETSCH 400™) under open-air atmosphere unless otherwise stated. Liquids and solutions were transferred with syringes. Solvents used were dried and purified by following standard procedures. Technical grade solvents for extraction or chromatography (ethyl acetate, and Hexane) were distilled prior to use. Used chemicals were purchased from Sigma-Aldrich, TCI, Alfa-Aesar used without further purification. All the liquid chemicals distilled freshly prior to use. Analytical thin-layer chromatography (TLC) was performed on using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by UV radiation, basic aqueous potassium permangante ($KMnO_4$), p-anisaldehyde stains and heat as developing agents. Column chromatography was performed on silica gel 60-120 mesh, using the indicated solvents. Organic solutions were concentrated under reduced pressure on Heidolph rotary evaporator. NMR spectra were acquired on a Bruker AVANCE 400 MHz FT-NMR instrument running at 400 MHz for ^{1}H, 100 MHz ^{13}C, 376 MHz ^{19}F respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). Data are reported as follows: chemical shift, multiplicity (br = broad singlet, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet), coupling constants (Hz), and integration. MS analyses were carried out using an Agilent 6540 accurate-mass Q-TOF LC/MS (Agilent Technologies, U.S.A.). MS analyses were performed under the following operation parameters: dry gas temperature 350 °C, dry gas (N_2) flow rate 10 L/min, nebulizer pressure 30 psi, Vcap 4000, and fragmentor voltage 110 V. Mass spectra were acquired in the positive ion mode by scanning from 100 to 1500 in the mass-to-charge ratio (m/z). The mobile-phase composition used for UHPLC-QTOF MS comprises H_2O (A) and ACN (B), with optimized linear gradient elution. The injection volume was 0.5-1 µL. The flow rate was set at 0.3 mL/min. Accurate mass analysis calibration was carried out by ESI-low concentration tuning mix solution provided by Agilent Technologies, U.S.A. The accuracy error threshold was set at 5 ppm. HPLC experiments were carried out on the Agilent 1290 infinity series of the LC system (Agilent Technologies, U.S.A.) with a photodiode array/ELSD detector. HPLC experiments were carried out on a Waters Alliance System (Milford, MA) consisting of an e2695 separation module and a 2998 photodiode-array detector. The HPLC system was controlled with EMPOWER software (Waters Corporation, Milford, MA). IR spectra were recorded on Thermo Fisher Scientific Nicolet iS20 FTIR Infrared Spectrophotometer as neat for both semi-solid and solid compounds and represented as IR (neat).

1.1 Milling details

All milling reactions were conducted using a (RETSCH 400™) High Energy Mixer Mill in Stainless Steel vessels (5 mL inner volume, diameter 27 mm) from VERDER Scientific and using Stainless Steel balls (5 mm diameter) weighing 0.32 gm (Figure S1).

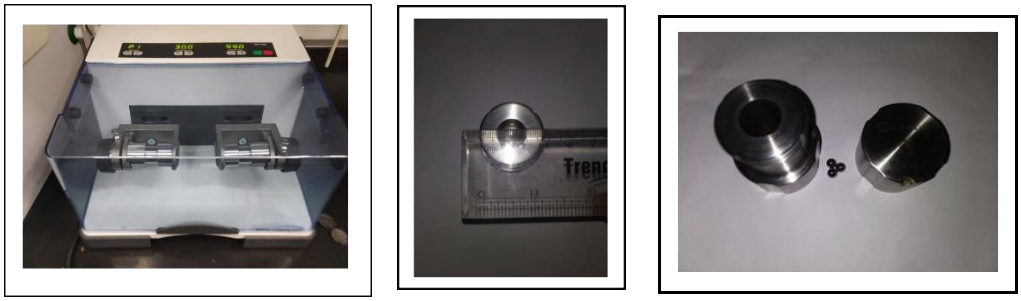
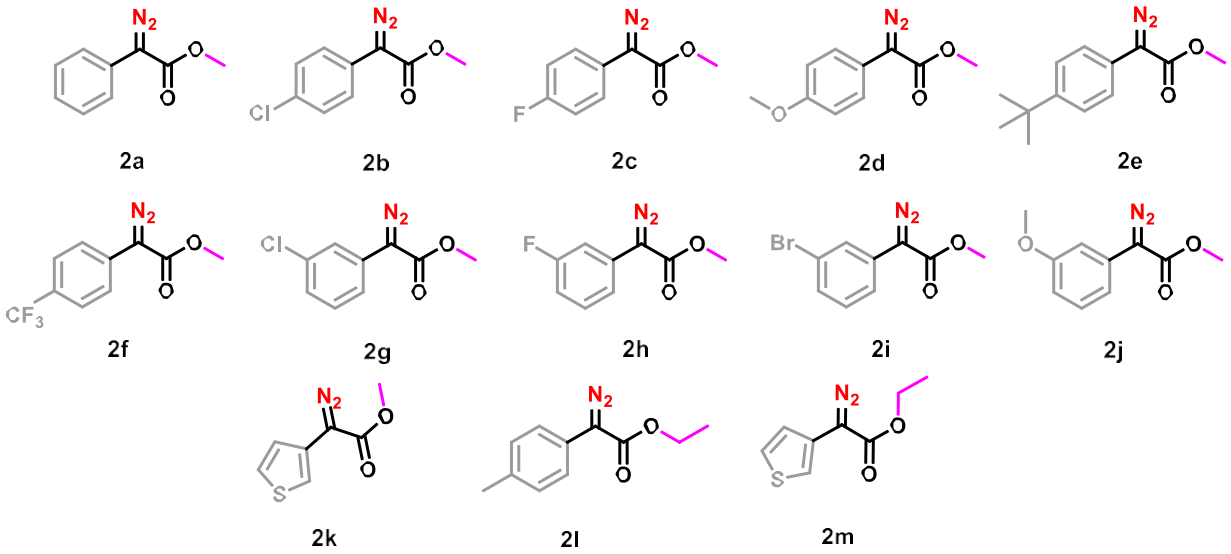
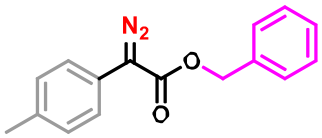


Figure S1: From left (RETSCH 400™) High Energy Mixer Mill, 27 mm stainless steel jar and 5 mm stainless steel balls.

2. List of substrates prepared:

2.1 List of diazo compounds prepared: [1]





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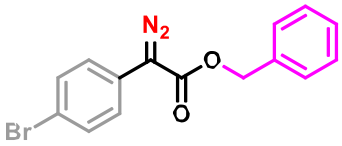

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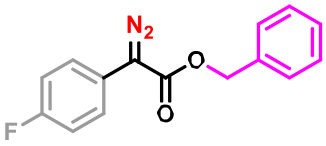

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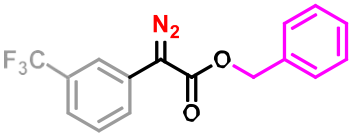

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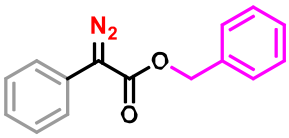

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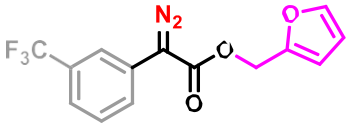

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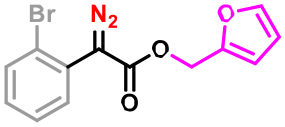

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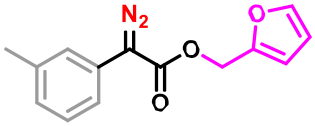

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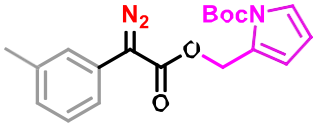

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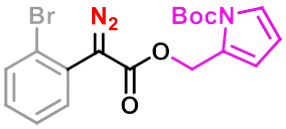

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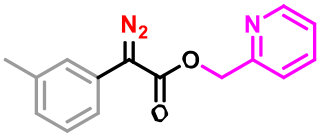

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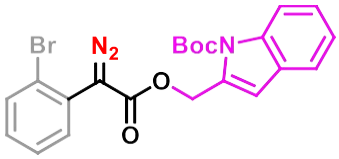

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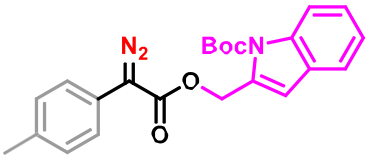

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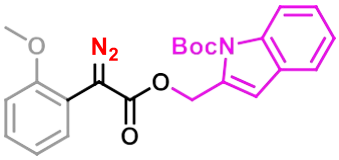

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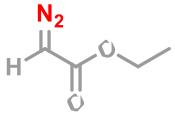

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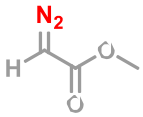

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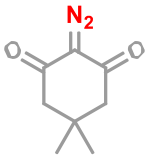

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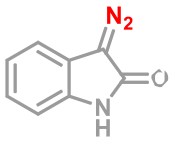

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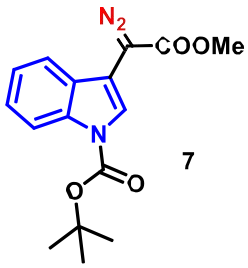
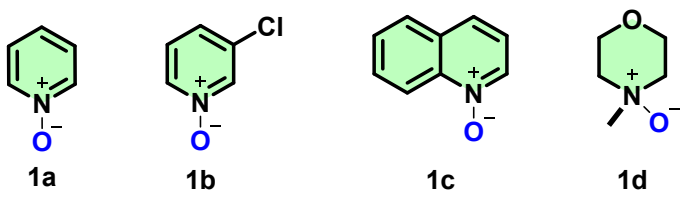


7

2.2 List of heterocyclic *N*-oxides



3. Experimental procedure for preparation of 1,2-dicarbony systems

3.1 Synthesis of aryl diazoesters (2a-2m, 2aa-2ae, 2ba-2bi, 2ca-2cd):

All aryl diazoacetates were synthesized following a reported procedure[ref-7-1(i)]. Aryl acetates (1 equiv., 5 mmol) were dissolved in acetonitrile (5 ml) in a clean, oven-dried round bottom flask. DBU (1.8-Diazabicyclo[5.4.0]undec-7-ene) (1.2 equiv., 6 mmol) or triethyl amine (1.2 equiv.) was added, and the mixture was stirred for 10 minutes. *p*-ABSA (4-Acetamidobenzenesulfonyl azide) (1.2 equiv., 6 mmol) was then added, and the reaction was stirred in the dark at room temperature for 10-12 hours. Upon completion, acetonitrile was removed under vacuum, and the residue was diluted with ethyl acetate (10 ml), washed with water, and the organic layer was dried over brine and sodium sulfate. The product was purified by column chromatography on silica gel [SiO_2, Hexane/EtOAc (98:2 to 95:5) R_f = 0.3] to give a 95% yield. All diazo compounds were stable when stored in a refrigerator and kept in the dark.

3.2 General procedure A:

Under air atmosphere, 0.52 mmol of heterocyclic *N*-oxide **1a**, diverse diazoesters **2** (1.05 mmol), additional catalyst CuI (10 mol%) and 3 stainless-steel ball (Ø = 5 mm, m_{tot} = 0.987 gm) were placed in a ball milling jar (stainless-steel, 5 mL), {N.B.: Additional η = 0.5 µL mg^{-1} of LAG as 1,2-DCE was added as a grinding auxiliary with respect to heterocyclic *N*-oxide}. Then, the mixture was milled at 30 Hz for 5-7 hrs. Subsequently, the content of the jar was washed out with minimal amount of EtOAc and filtered through a pad of celite. The solvent was concentrated in vacuo, and the product was purified by column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2].

3.3 Scale-up reaction for the synthesis of 3a:

Under air atmosphere, 0.0073 mol of heterocyclic *N*-oxide **1a**, methyl 2-diazo-2-phenylacetate **2a** (0.0147 mol), and 2 stainless-steel ball (Ø = 10 mm, m_{tot} = 2.71 gm) were placed in a ball milling jar (stainless-steel, 10 mL), {N.B.: Additional η = 0.5 µL mg^{-1} of LAG as 1,2-DCE was added as a grinding auxiliary with respect to heterocyclic *N*-oxide}. Then, the mixture was milled at 30 Hz for 10 h. Subsequently, the content of the jar was washed out with minimal amount of EtOAc and filtered through a pad of celite. The solvent was concentrated in vacuo, and the product was purified by column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2] to afford **3a** in 74% yield.

3.4 Amidation reaction of 3a for the synthesis of 5:

For successful amidation of **3a**, firstly 1,2-dicarbonyl system synthesized according to the **General procedure A**. TLC monitoring indicates the formation of **3a** which then treated with cyclic amine without additional LAG. Then, the mixture was milled at 30 Hz for another 3 h until the TLC confirms the formation of **5**. Subsequently, the content of the jar was washed out with minimal amount of EtOAc and filtered through a pad of celite. The solvent was concentrated in vacuo, and the product was purified by column chromatography on silica gel [SiO_2, Hexane/EtOAc (80:20) R_f = 0.2] to afford **5**.

3.5 Stepwise synthesis of Compound 7:

A: esterification of 2-(1*H*-indol-3-yl)acetic acid: Commercially available IAA (2gm) was diluted in 5 mL of methanol. Then 8-10 drops of Conc. H_2SO_4 were added. The reaction mixture was stirred at r.t. to refluxing condition for about 10 h, then concentrated in vacuo, diluted in EtOAc washed with water, sat. $NaHCO_3$, dried over (Na_2SO_4) and concentrated in vacuo. Without purification the next step was preceded.

B: Boc protection of Methyl 2-(1*H*-indol-3-yl)acetate: Methyl 2-(1*H*-indol-3-yl)acetate was diluted in 10 mL CH_2Cl_2, then DMAP (15 mol%) and Boc_2O (3 equiv.) were added. The reaction mixture was stirred at r.t. for 4 h then diluted with additional CH_2Cl_2 and washed with water, brine, dried over (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography on silica gel [SiO_2, Hexane/EtOAc (90:10) R_f = 0.3] gave *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate.

C: Diazotization of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate: In the next step, *p*-ABSA (2 equiv.) was added to a solution of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate and DBU (3 equiv.) in CH_3CN (10 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. over 10 h, then concentrated in vacuo and diluted in CH_2Cl_2. The organic phase was washed with brine, dried over (Na_2SO_4) and concentrated in vacuo and the product was purified by column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2] to afford **7**. (N.B. Due to unstable nature of 7, compound loss occurred during purification.)

3.6 A note about milling reaction temperature measurements:

The temperature of the interior wall of the milling vessels as well as that of the stainless-steel balls were measured using a laser thermometer immediately after the cessation of several reactions. It has been found that, both for 5 mL and 10 mL SS jar temperature did not rise more than 47 °C.

5 mL SS vessel (5 mm SS ball) → At 30 Hz after 6 h: 45.6 °C (inside wall and ball).
10 mL SS vessel (10 mm SS ball) → At 30 Hz after 6 h: 42.0 °C (inside wall and ball).

3.7 Additional note regarding milling:

In our current reaction methodology, N_2 is released from aryl diazoesters during the metal-carbenoid formation. The Retsch-MM 400 instrument comes with screw-top grinding jars, which is not equipped with inlet pressure valve. Based on our reaction scale (200-300 mg and up to 1-2 gm), the diazo transfer reaction has not caused any issues. However, we advise using the instrument with caution for this type of reaction.

4. Reaction Analysis:

4.1 Internal reaction monitoring of the 1,2-dicarbonyl system formation:

To gain the insight into the reaction mechanism, the progress of the reaction was monitored through the ^{1}H-NMR analysis using **1a** heterocyclic *N*-oxide (50 mg, 0.52 mmol), and **2a** methyl 2-diazo-2-phenylacetate (180 mg, 1.05 mmol) under standard condition (General Procedure A) [$CDCl_3$ as LAG]. Data were collected at 0 min/ 40 min/ 80 min/120 min respectively.

NB: Crude reaction mixture passes through 0.7 mL of $CDCl_3$ using Nylon-66 (0.45 Micron pore size) syringe filters.

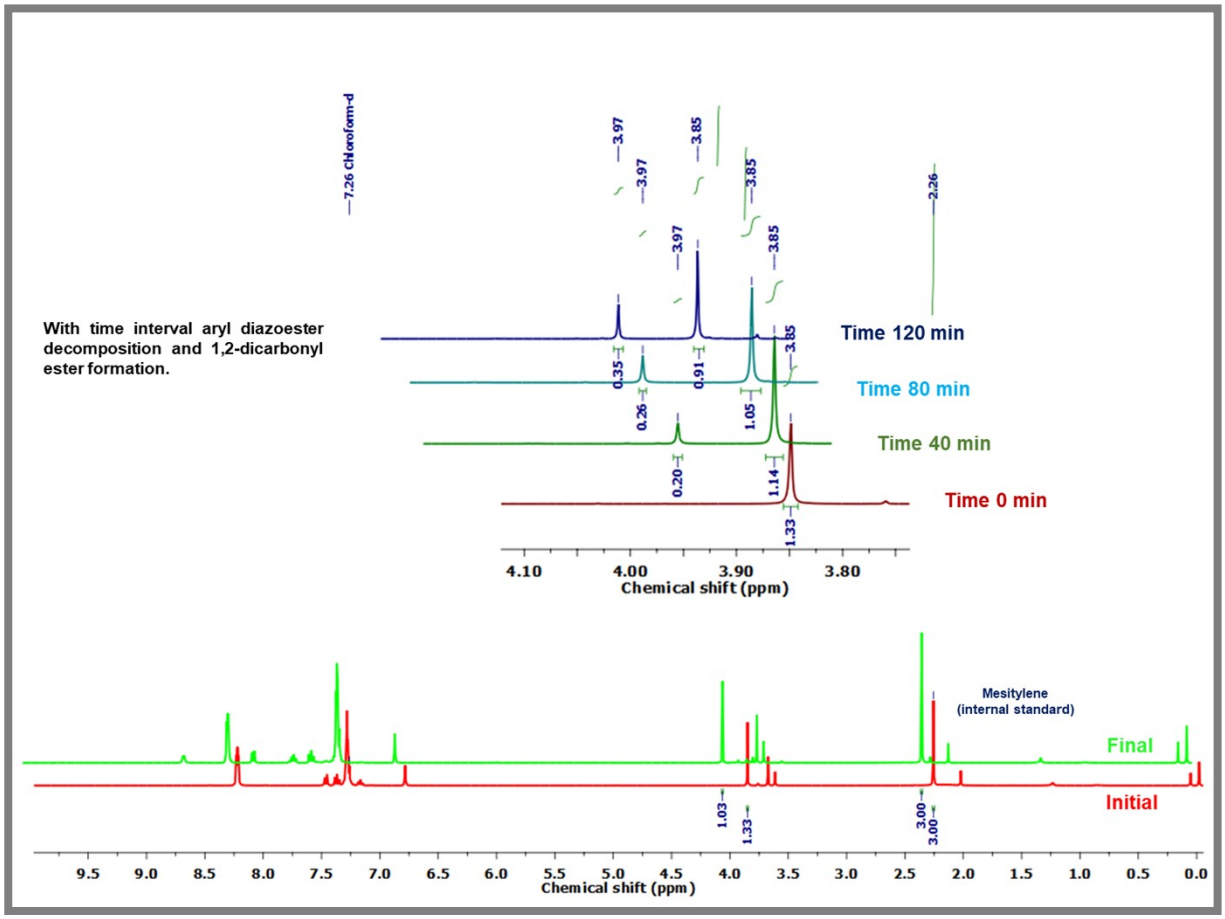
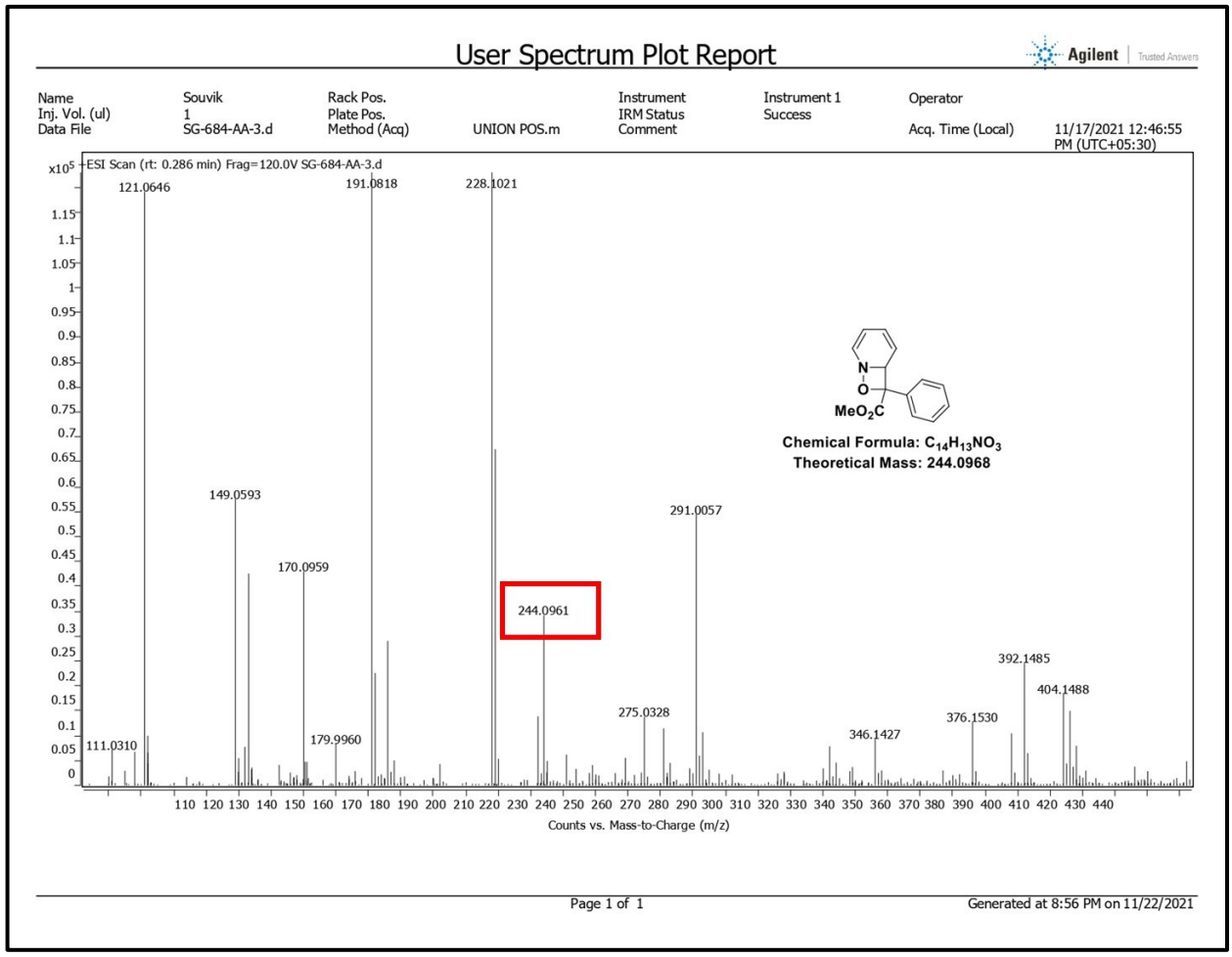


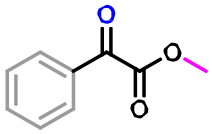
Figure S2: Progress of the reaction monitor through ^{1}H-NMR analysis.

4.2 Mass data related with mechanistic pathway:



5. Analytical Data of the Synthesized Compounds:

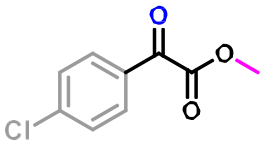
5.1 Methyl 2-oxo-2-phenylacetate (3a)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-phenylacetate **2a** (180 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3a** was obtained as a yellow oil. (136.7 mg isolated amount, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 – 7.91 (m, 2H), 7.79 – 7.57 (m, 1H), 7.59 – 7.44 (m, 2H), 3.98 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

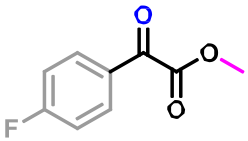
5.2 Methyl 2-(4-chlorophenyl)-2-oxoacetate (3ba)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-(4-chlorophenyl)-2-diazoacetate **2b** (200 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ba** was obtained as a yellow oil. (132.4 mg isolated amount, 73% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dt, J = 8, 16 Hz, 2H), 7.47 (dt, J = 8, 16 Hz, 2H), 3.96 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

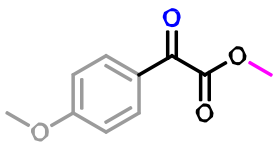
5.3 Methyl 2-(4-fluorophenyl)-2-oxoacetate (3ca)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo- 2-(4-fluorophenyl)acetate **2c** (188 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ca** was obtained as a colorless oil. (128.1 mg isolated amount, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 – 7.99 (m, 2H), 7.22 – 7.07 (m, 2H), 3.96 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

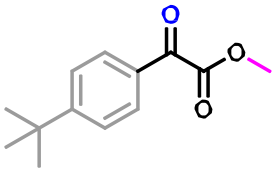
5.4 Methyl 2-(4-methoxyphenyl)-2-oxoacetate (3da)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-(4-methoxyphenyl)acetate **2d** (200 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3da** was obtained as a colorless oil. (140.8 mg isolated amount, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01(d, J = 8 Hz, 2H), 6.97 (dt, J = 8, 16 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

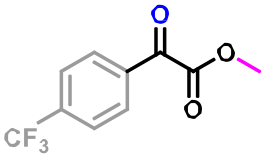
5.5 Methyl 2-(4-(*tert*-butyl)phenyl)-2-oxoacetate (3ea)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate **2e** (200 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ea** was obtained as a colorless oil. (187.8 mg isolated amount, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.55 – 7.50 (m, 2H), 3.97 (s, 3H), 1.35 (s, 9H). ppm.

These data are in accordance with the previous report. SI[I]

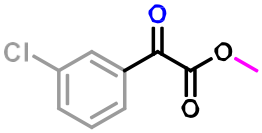
5.6 Methyl 2-oxo-2-(4-(trifluoromethyl)phenyl)acetate (3fa)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate **2f** (250 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3fa** was obtained as a colorless oil. (157.2 mg isolated amount, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 2H), 7.68 – 7.62 (m, 2H), 3.97 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

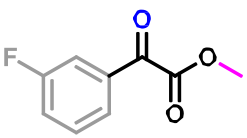
5.7 Methyl 2-(3-chlorophenyl)-2-oxoacetate (3ga)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-(3-chlorophenyl)-2-diazoacetate **2g** (220 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ga** was obtained as a colorless oil. (144.2 mg isolated amount, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (t, J = 1.8 Hz, 1H), 7.93 – 7.89 (m, 1H), 7.62 (ddd, J = 8.0, 2.1, 1.0 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 3.98 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

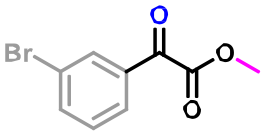
5.8 Methyl 2-(3-fluorophenyl)-2-oxoacetate (3ha)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-(3-fluorophenyl)acetate **2h** (200 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ha** was obtained as a colorless oil. (137.0 mg isolated amount, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 1H), 7.74 (ddd, J = 9.1, 2.4, 1.7 Hz, 1H), 7.50 (td, J = 8.0, 5.4 Hz, 1H), 7.36 (tdd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.99 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

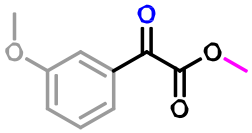
5.9 Methyl 2-(3-bromophenyl)-2-oxoacetate (3ia)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-(3-bromophenyl)-2-diazoacetate **2i** (250 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ia** was obtained as a colorless oil. (98.7 mg isolated amount, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (t, J = 1.7 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.77 (ddd, J = 8.0, 1.8, 1.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 3.98 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

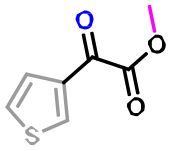
5.10 Methyl 2-(3-methoxyphenyl)-2-oxoacetate (3ja)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-(3-methoxyphenyl)acetate **2j** (210 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ja** was obtained as a colorless oil. (140.1 mg isolated amount, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.23 – 7.18 (m, 1H), 3.98 (s, 3H), 3.86 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

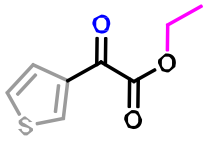
5.11 Methyl 2-oxo-2-(thiophen-3-yl)acetate (3ka)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-(thiophen-3-yl)acetate **2k** (185 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ka** was obtained as a colorless oil. (134.6 mg isolated amount, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 2.9, 1.2 Hz, 1H), 7.68 (dd, J = 5.1, 1.1 Hz, 1H), 7.35 (dd, J = 5.1, 2.9 Hz, 1H), 3.95 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

5.12 Ethyl 2-oxo-2-(thiophen-3-yl)acetate (3kb)

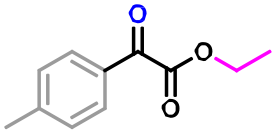


Prepared according to the general procedure A for 1,2-dicarbonyl system formation using ethyl 2-diazo-2-(thiophen-3-yl)acetate **2m** (200 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3kb** was obtained as a colorless oil. (266.8 mg isolated amount,

80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 2.9, 1.1 Hz, 1H), 7.66 (dd, J = 5.1, 1.1 Hz, 1H), 7.34 (dd, J = 5.1, 2.9 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H) ppm.

These data are in accordance with the previous report. SI[I]

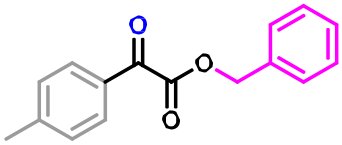
5.13 Ethyl 2-oxo-2-(*p*-tolyl)acetate (3lc)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using ethyl 2-diazo-2-(*p*-tolyl)acetate **2l** (206 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3lc** was obtained as a colorless oil. (153.5 mg isolated amount, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H) ppm.

These data are in accordance with the previous report. SI[I]

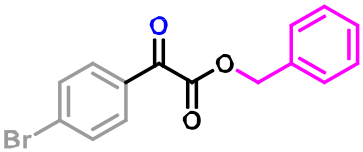
5.14 Benzyl 2-oxo-2-(*p*-tolyl)acetate (3ld)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using benzyl 2-diazo-2-(*p*-tolyl)acetate **2aa** (250 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ld** was obtained as a colorless oil. (190.0 mg isolated amount, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.48 (dd, J = 7.7, 1.5 Hz, 2H), 7.45 – 7.39 (m, 3H), 7.31 (d, J = 8.1 Hz, 2H), 5.44 (s, 2H), 2.45 (s, 3H) ppm.

These data are in accordance with the previous report. SI[I]

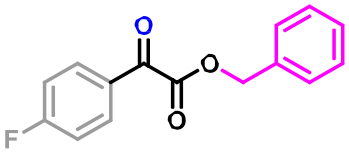
5.15 Benzyl 2-(4-bromophenyl)-2-oxoacetate (3md)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using benzyl 2-(4-bromophenyl)-2-diazoacetate **2ab** (350 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3md** was obtained as a colorless oil. (228.2 mg isolated amount, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.66 – 7.61 (m, 2H), 7.47 – 7.36 (m, 5H), 5.41 (s, 2H) ppm.

These data are in accordance with the previous report. SI[I]

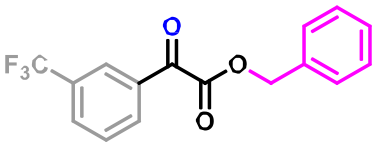
5.16 Benzyl 2-(4-fluorophenyl)-2-oxoacetate (3cd)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using benzyl 2-diazo- 2-(4-fluorophenyl)acetate **2ac** (250 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3cd** was obtained as a colorless oil. (180.5 mg isolated amount, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 2H), 7.46 (dd, J = 5.0, 3.0 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.34 (dd, J = 6.9, 4.1 Hz, 1H), 7.16 (t, J = 8.6 Hz, 2H), 5.42 (s, 2H) ppm.

These data are in accordance with the previous report. SI[I]

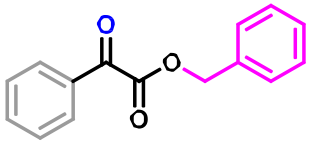
5.17 Benzyl 2-oxo-2-(3-(trifluoromethyl)phenyl)acetate (3nd)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using benzyl 2-diazo- 2-(3-(trifluoromethyl)phenyl)acetate **2ad** (330 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3nd** was obtained as a colorless oil. (224.6 mg isolated amount, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.47 (dd, J = 7.6, 1.7 Hz, 5H), 5.44 (s, 2H) ppm.

These data are in accordance with the previous report. SI[I]

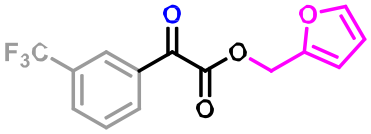
5.18 Benzyl 2-oxo-2-phenylacetate (3ad)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using benzyl 2-diazo-2-phenylacetate **2ae** (265 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ad** was obtained as a colorless oil. (186 mg isolated amount, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.3, 1.1 Hz, 2H), 7.64 (d, J = 7.5 Hz, 1H), 7.52 – 7.43 (m, 4H), 7.43 – 7.36 (m, 3H), 5.43 (s, 2H) ppm.

These data are in accordance with the previous report. SI[I]

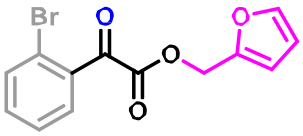
5.19 Furan-2-ylmethyl 2-oxo-2-(3-(trifluoromethyl)phenyl)acetate (3ne)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using furan-2-ylmethyl 2-diazo-2-(3-(trifluoromethyl)phenyl)acetate **2ba** (310 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f= 0.2], the expected product **3ne** was obtained as a colorless oil.

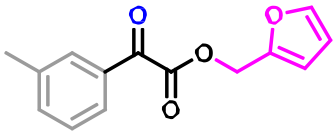
(203.0 mg isolated amount, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 1.1 Hz, 1H), 6.56 (d, J = 3.2 Hz, 1H), 6.41 (dd, J = 3.2, 1.9 Hz, 1H), 5.40 (s, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 184.2, 162.4, 147.9, 144.1, 143.8, 133.2, 131.8, 129.7, 127.1 (q, $J_{C\text{-}CF3}$ = 11 Hz), 126.1-123.9 (q, $J_{C\text{-}CF3}$ = 224 Hz) 112.25, 110.9, 59.7 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ (-) 63.00 ppm. **HRMS (ESI) m/z**: $[M + H]^+$ Calcd for $C_{14}H_{10}F_3O_4$ 299.0526; Found 299.0541. **IR (Neat)** ν_{max} = 2200.3, 1725.3, 1645.4, 1520,2, 1442.2, 1356.8, 1151.1, 739.7, 474.7 cm^{-1}.

5.20 Furan-2-ylmethyl 2-(2-bromophenyl)-2-oxoacetate (3oe)



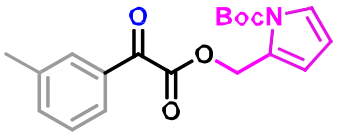
Prepared according to the general procedure A for 1,2-dicarbonyl system formation using furan-2-ylmethyl 2-(2-bromophenyl)-2-diazoacetate **2bb** (320 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3oe** was obtained as a colorless oil. (218.7 mg isolated amount, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 1H), 7.61 (dd, J = 7.0, 2.0 Hz, 1H), 7.46 – 7.39 (m, 3H), 6.53 (d, J = 3.2 Hz, 1H), 6.38 (dd, J = 3.0, 1.9 Hz, 1H), 5.33 (s, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.8, 162.1, 147.9, 143.8, 135.4, 134.3, 133.8, 132.0, 127.8, 121.8, 112.3, 110.8, 59.9 ppm. **HRMS (ESI) m/z**: $[M + Na]^+$ Calcd for $C_{13}H_9Br^{[79]}O_4Na$ 330.9576; Found 330.9565. **IR (Neat)** ν_{max} = 2355.8, 1626.7, 1516.9, 1346.8, 1192.0, 1083.7, 873.1, 729.8, 439.3 cm^{-1}.

5.21 Furan-2-ylmethyl 2-oxo-2-(*m*-tolyl)acetate (3pe)



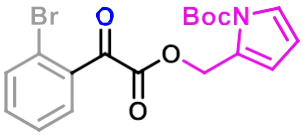
Prepared according to the general procedure A for 1,2-dicarbonyl system formation using furan-2-ylmethyl 2-diazo-2-(*m*-tolyl)acetate **2bc** (250 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3pe** was obtained as a colorless oil. (180.2 mg isolated amount, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, J = 9.2 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 6.54 (d, J = 3.2 Hz, 1H), 6.40 (dd, J = 3.1, 1.9 Hz, 1H), 5.37 (s, 2H), 2.39 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.1, 163.7, 148.2, 143.8, 138.9, 135.9, 132.4, 130.5, 128.9, 127.4, 112.0, 110.9, 59.3, 21.38 ppm. **HRMS (ESI) m/z**: $[M + Na]^+$ Calcd for $C_{14}H_{12}O_4Na$ 267.0628; Found 267.0620. **IR (Neat)** ν_{max} = 2854.5, 1626.7, 1424.8, 1278.8, 1095.6, 951.7, 789.5, 726.8, 603.8 cm^{-1}.

5.22 *Tert*-butyl 2-((2-oxo-2-(*m*-tolyl)acetoxy)methyl)-1*H*-pyrrole-1-carboxylate (3pg)



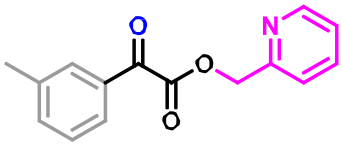
Prepared according to the general procedure A for 1,2-dicarbonyl system formation using *tert*-butyl 2-((2- diazo-2-(*m*-tolyl)acetoxy)methyl)-1*H*-pyrrole-1-carboxylate **2bd** (360 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3pg** was obtained as a colorless oil. (263.0 mg isolated amount, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.32 (dd, J = 3.3, 1.8 Hz, 1H), 6.41 (dd, J = 3.2, 1.8 Hz, 1H), 6.16 (t, J = 3.3 Hz, 1H), 5.58 (s, 2H), 2.40 (s, 3H), 1.57 (s, 9H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.8, 164.0, 148.8, 138.8, 135.8, 132.5, 130.4, 128.8, 127.4, 123.4, 117.1, 110.3, 84.5, 60.8, 28.0, 21.3 ppm. **HRMS (ESI) m/z**: $[M + Na]^+$Calcd for $C_{19}H_{21}NO_5Na$ 366.1312; Found 366.1327. **IR (Neat)** ν_{max} = 2134.9, 1722.9, 1645.2, 1520.1, 1344.3, 1267.6, 1075.9, 783.3, 578.5, 476.5 cm^{-1}.

5.23 *Tert*-butyl-2-((2-(2-bromophenyl)-2-oxoacetoxy)methyl)-1*H*-pyrrole-1-carboxylate (3og)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using *tert*-butyl 2-((2- (2-bromophenyl)-2-diazoacetoxy)methyl)-1*H*-pyrrole-1-carboxylate **2be** (400 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3og** was obtained as a colorless oil. (290.7 mg isolated amount, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 1H), 7.63 – 7.59 (m, 1H), 7.43 – 7.38 (m, 2H), 7.31 (dt, J = 4.9, 2.4 Hz, 1H), 6.40 (dd, J = 3.1, 1.8 Hz, 1H), 6.15 (t, J = 3.3 Hz, 1H), 5.56 (s, 2H), 1.56 (s, 9H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.0, 162.3, 148.8, 135.4, 134.0, 132.1, 127.7, 127.0, 123.4, 121.8, 117.2, 110.3, 84.5, 84.2, 61.4, 28.0 ppm. **HRMS (ESI) m/z**: $[M + H]^+$Calcd for $C_{18}H_{19}Br^{[81]}NO_5$ 410.0423; Found 410.0411. **IR (Neat)** ν_{max} = 2356.4, 1739.0, 1629.6, 1512.0, 1348.9, 1208.6, 1150.5, 1025.8, 628.5, 536.3 cm^{-1}.

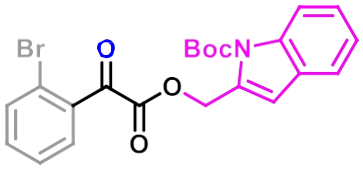
5.24 Pyridin-2-ylmethyl 2-oxo-2-(*m*-tolyl)acetate (3pf)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using pyridin-2- ylmethyl 2-diazo-2-(*m*-tolyl)acetate **2bf** (250 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3pf** was obtained as a colorless oil. (170.0 mg isolated amount, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 5.6 Hz, 2H), 7.71 (td, J = 7.7, 1.6 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.25 (dd, J = 6.9, 4.8 Hz, 1H), 5.51 (s, 2H), 2.39 (s, 3H). ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.2, 163.6, 154.5, 149.6, 138.9, 137.0, 135.9, 132.4, 130.5, 128.8, 127.4, 123.3, 121.9, 67.8, 21.3 ppm. **HRMS (ESI) m/z**: $[M + H]^+$ Calcd for $C_{15}H_{14}NO_3$ 256.0968; Found

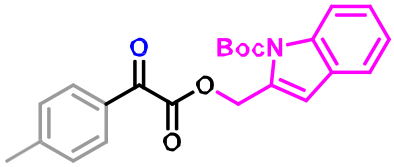
256.0970. **IR (Neat)** ν_{max} = 2255.3, 1722.0, 1523.9, 1372.8, 1258.1, 1150.5, 1074.2, 782.7, 730.9, 583.5 cm^{-1}.

5.25 *Tert*-butyl-2-((2-(2-bromophenyl)-2-oxoacetoxy)methyl)-1*H*-indole-1-carboxylate (3oh)



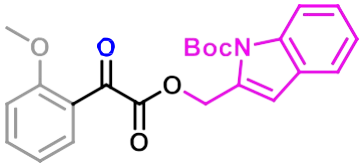
Prepared according to the general procedure A for 1,2-dicarbonyl system formation using *tert*-butyl 2-((2- (2-bromophenyl)-2-diazoacetoxy)methyl)-1*H*-indole-1-carboxylate **2bg** (400 mg) (25 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3oh** was obtained as a colorless oil. (308.7 mg isolated amount, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.1 Hz, 1H), 7.75 (s, 1H), 7.68 – 7.61 (m, 2H), 7.59 (dd, J = 5.8, 3.3 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.36 – 7.32 (m, 1H), 7.29 – 7.24 (m, 1H), 5.55 (s, 2H), 1.68 (s, 9H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.0, 162.4, 149.4, 135.5, 134.1, 133.7, 131.9, 129.1, 127.7, 126.8, 125.0, 123.1, 121.7, 119.3, 115.4, 114.0, 84.2, 60.3, 28.2 ppm. **HRMS (ESI) m/z**: $[M + H]^+$ Calcd for $C_{22}H_{21}Br^{[79]}NO_5$ 458.0598; Found 458.0586. **IR (Neat)** ν_{max} = 1724.8, 1642.4, 1523.9, 1355.5, 1254.9, 1148.0, 1081.8, 1021.1, 787.0 cm^{-1}.

5.26 *Tert*-butyl 2-((2-oxo-2-(*p*-tolyl)acetoxy)methyl)-1*H*-indole-1-carboxylate (3ph)



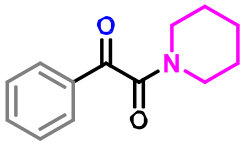
Prepared according to the general procedure A for 1,2-dicarbonyl system formation using *tert*-butyl 2-((2- diazo-2-(*p*-tolyl)acetoxy)methyl)-1*H*-indole-1-carboxylate **2bh** (400 mg) (50 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3ph** was obtained as a colorless oil. (261.2 mg isolated amount, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.76 (s, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.32 – 7.28 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 5.57 (s, 2H), 2.41 (s, 3H), 1.68 (s, 9H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 185.8, 164.1, 149.5, 146.4, 135.7, 130.2, 130.0, 129.7, 129.1, 126.7, 125.0, 123.1, 119.3, 115.5, 114.4, 84.3, 59.6, 28.3, 22.0 ppm. **HRMS (ESI) m/z**: $[M + H]^+$ Calcd for $C_{23}H_{24}NO_5$ 394.1649; Found 394.1664. **IR (Neat)** ν_{max} = 2015.0, 1954.9, 1726.8, 1694.0, 1443.6, 1362.8, 1148.2, 1052.9, 726.1, 471.9 cm^{-1}.

5.27 *Tert*-butyl-2-((2-(2-methoxyphenyl)-2-oxoacetoxy)methyl)-1*H*-indole-1-carboxylate (3qh)



Prepared according to the general procedure A for 1,2-dicarbonyl system formation using *tert*-butyl 2-((2- diazo-2-(2-methoxyphenyl)acetoxy)methyl)-1*H*-indole-1-carboxylate **2bi** (400 mg) (50 µL of 1,2-DCE as grinding auxiliary, η = 0.5 µL mg^{-1}). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) R_f = 0.2], the expected product **3qh** was obtained as a colorless oil. (268.5 mg isolated amount, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 1H), 7.87 (dd, J = 7.8, 1.7 Hz, 1H), 7.77 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.27 (dd, J = 10.7, 4.3 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.53 (s, 2H), 3.42 (s, 3H), 1.69 (s, 9H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.3, 165.2, 160.3, 149.5, 136.4, 135.6, 130.8, 129.3, 126.5, 124.9, 123.1, 122.7, 121.2, 119.5, 115.4, 114.8, 111.8, 84.2, 59.2, 55.6, 28.2 ppm. **HRMS (ESI) m/z**: $[M+ H]^+$ Calcd for $C_{23}H_{24}NO_6$ 410.1598; Found 410.1612. **IR (Neat)** ν_{max} = 2854.3, 1722.3, 1642.2, 1523.5, 1445.8, 1280.0, 1150.8, 796.4, 742.4, 586.6, 453.7 cm^{-1}.

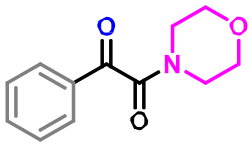
5.28 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (5a)



Prepared according to the two-step ball milling process. The first step follows the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-phenylacetate **2a** (185 mg). TLC monitoring indicates the formation of **3a** then second step follows the general procedure for amidation reaction [Piperidine as cyclic base (1.56 mmol, 156 µL)]. After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (80:20) R_f = 0.2], the expected product **5a** was obtained as a colorless oil. (140.1 mg isolated amount, 83% over all yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.3, 1.2 Hz, 2H), 7.67 – 7.61 (m, 1H), 7.51 (dd, J = 10.7, 4.7 Hz, 2H), 3.71 (s, 2H), 3.31 – 3.26 (m, 2H), 1.69 (dd, J = 5.9, 2.8 Hz, 4H), 1.58 – 1.50 (m, 2H) ppm.

These data are in accordance with the previous report. SI[I]

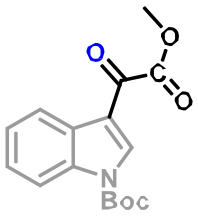
5.29 1-morpholino-2-phenylethane-1,2-dione (5b)



Prepared according to the two-step ball milling process. The first step follows the general procedure A for 1,2-dicarbonyl system formation using methyl 2-diazo-2-phenylacetate **2a** (185 mg). TLC monitoring indicates the formation of **3a** then second step follows the general procedure for amidation reaction [Morpholine as cyclic base (1.56 mmol, 134 µL)]. After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (80:20) R_f = 0.2], the expected product **5b** was obtained as a colorless oil. (132.0 mg isolated amount, 79% over all yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 2H), 7.69 – 7.64 (m, 1H), 7.52 (dd, J = 10.7, 4.7 Hz, 2H), 3.79 (d, J = 6.6 Hz, 4H), 3.68 – 3.63 (m, 2H), 3.41 – 3.36 (m, 2H) ppm.

These data are in accordance with the previous report. SI[I]

5.30 *Tert*-butyl 3-(2-methoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate (8)

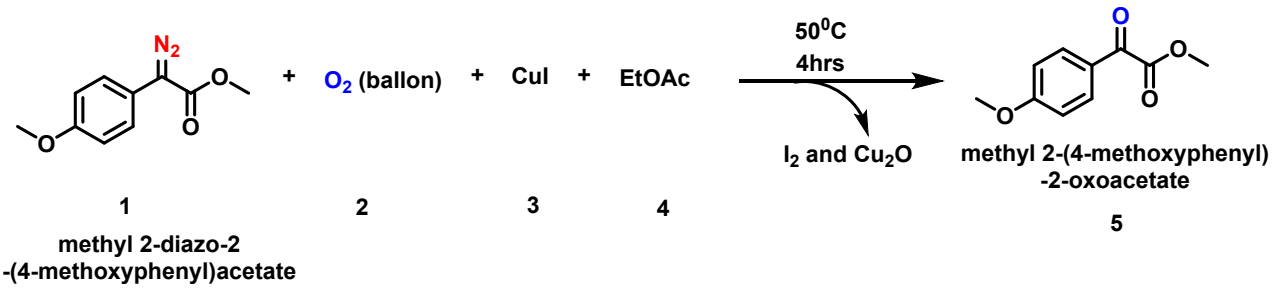


Prepared according to the general procedure A for 1,2-dicarbonyl system formation using *tert*-butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate **7** (406 mg) and heterocyclic *N*-oxide **1a** (60 mg) (30 µL of 1,2-DCE as grinding auxiliary, $\eta = 0.5\ \mu L\ mg^{-1}$). After gravity column chromatography on silica gel [SiO_2, Hexane/EtOAc (95:5 to 90:10) $R_f = 0.2$], the expected product **8** was obtained as a colorless oil. (237.0 mg isolated amount, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.42 – 8.38 (m, 1H), 8.17 (dd, $J = 6.7$, 2.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 3.98 (s, 3H), 1.71 (s, 9H) ppm.

These data are in accordance with the previous report. SI[I]

6. Green Matrices Assessment:

6.1 Solution based process: [7. ref-1-(f)]



Downstream Operations:

After cooling to room temperature, ethyl acetate (20 mL) and water (20 mL) were added to the reaction mixture. The aqueous layer was extracted by ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and purified by silica gel column chromatography with petroether/ethyl acetate (50:1) as the eluent to give the desired products.

NB:

- Since there isn't enough specific information available for all the downstream operations, we are not including this in green metrics calculations.
- Eco-Scale calculated considering downstream operations.

	1	**2**	**3**	**4**	**5**	**I_2**	**Cu_2O**
Molecular weight [gm/mol]	206.2	32.0	190.4	88.1	194.2	253.8	143.1
Mass engaged [mg]	61.8	9.6	12.0	2706.0	42.0	-	
n	0.30	0.30	0.06	30.71	0.21	0.06	0.06

[mmol]							
eq.	1.00	-	0.02	102.00	-	-	
Waste Mass [mg]	-	-	-	2706.00	-	15.22	8.58
% yield	-	-	-	-	71	-	-
Theoretical mass of product [mg]				58			

E_{factor} = waste mass / mass of product = [(2706+15.22+8.58)/42] = 65

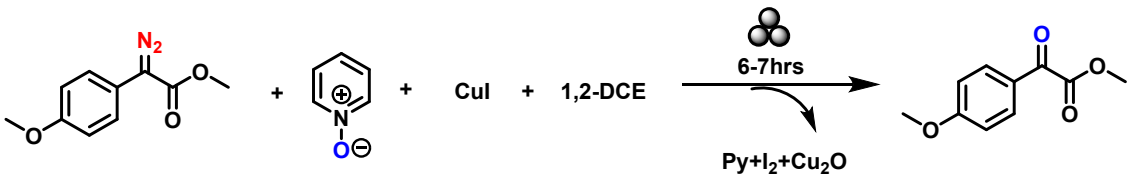
AE = [194.1860/(206.2010+32+190.45)] * 100 = 45.30

PMI = PMI_{RRC} + PMI_{sol} = [(61.80+9.6+12)/42 + 2706/42] = 66.41

Eco scale = 100 – sum of individual penalties

Entry	Parameters	Penalty points
1	Yield (71%)	-14.0
2	Price/availability	-13.0
3	Safety	-5
4	Technical set-up (gas atmosphere)	-1
5	Temperature/time (heating, > 1h)	-3.0
6	Work-up & Purification (cooling to room temperature, adding solvent, simple filtration, washing, distillation, classical column chromatography)	-16.0
	Eco-scale score	49

6.2 Ball-Milling Process:



1 2 3 4 5

methyl 2-diazo-2 -(4-methoxyphenyl)acetate

pyridine *N*-oxide

methyl 2-(4-methoxyphenyl) -2-oxoacetate

	1	2	3	4	5	I_2	Cu_2O
Molecular weight [gm/mol]	206.2	95.1	190.4	98.9	194.2	79.1	253.8
Mass engaged [mg]	60.0	14.3	5.7	31.2	43.0	-	-
n [mmol]	0.30	0.15	0.03	0.31	0.22	0.15	0.03
eq.	1.00	0.5	0.01	1.05	-	-	-
Waste Mass [mg]	-	-	-	31.25	-	11.86	7.61
% yield	-	-	-	-	74.2	-	-
Theoretical mass of product [mg]				58			

E_{factor} = waste mass / mass of product = [(31.25+11.86+7.61+4.29)/43] = 1.27

AE= [194.1860/(95.1010+206.2010+190.45)] * 100 = 39.48

PMI = PMI_{RRC} + PMI_{sol} = [(60+14.26+5.71)/43 + 31.25/43] = 2.58

Eco scale = 100 – sum of individual penalties

Entry	Parameters	Penalty points
1	Yield (71%)	-13.0
2	Price/availability	-5.0
3	Safety	-10
4	Technical set-up (gas atmosphere)	-2
5	Temperature/time (heating, > 1h)	-1.0
6	Work-up & Purification (cooling to room temperature, adding solvent, simple filtration, washing, distillation, classical column chromatography)	-16.0
	Eco-scale score	53

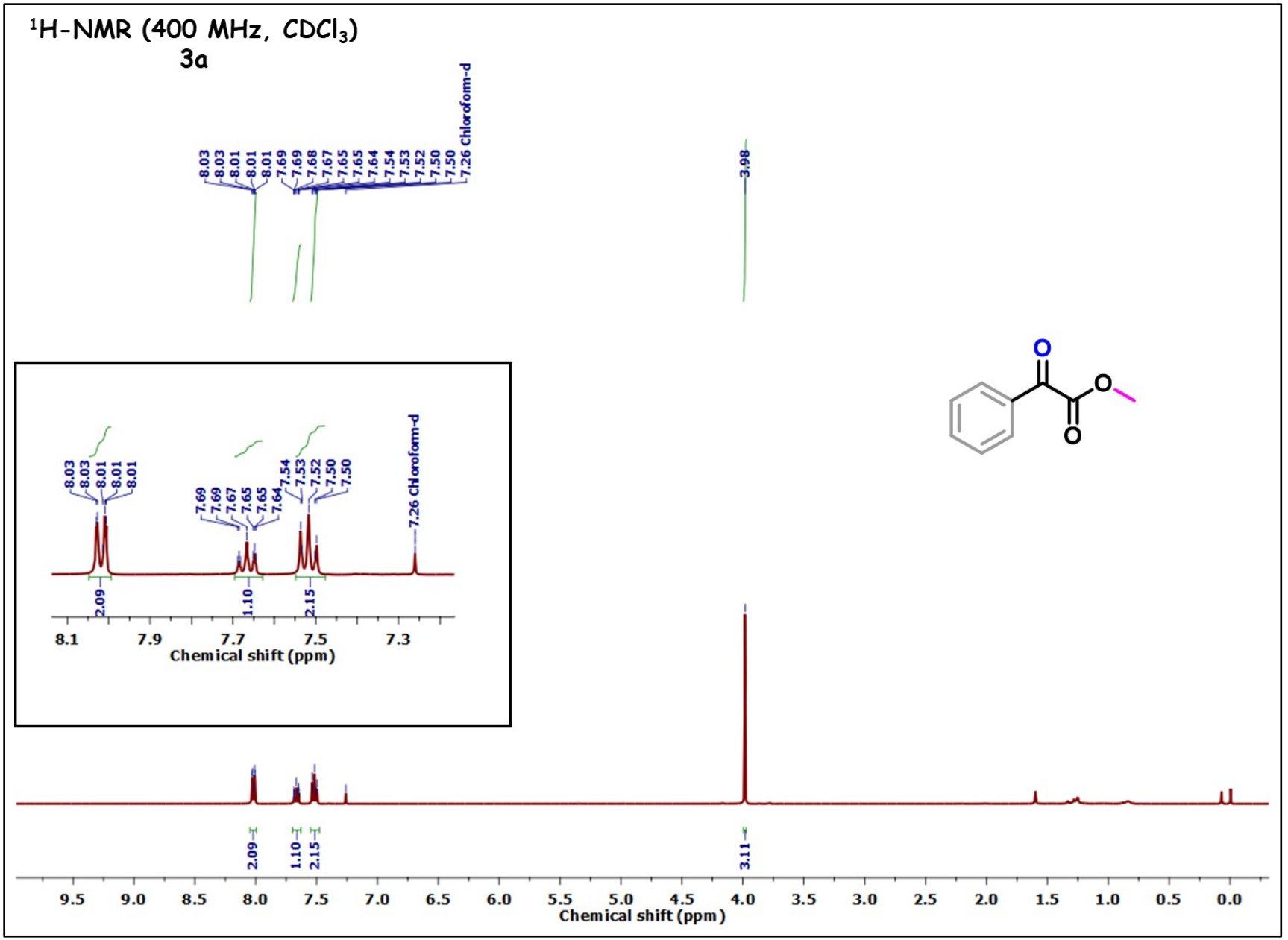
6.3 Green metrics values for the synthesis of dicarbonyl system based on data:

Method	AE [100%]	E-Factor [0]	PMI [1]	EcoScale [100]	Yield [%]
Solution	45.30	64.99	66.41	49	71
BM	39.48	1.27	2.58	53	74

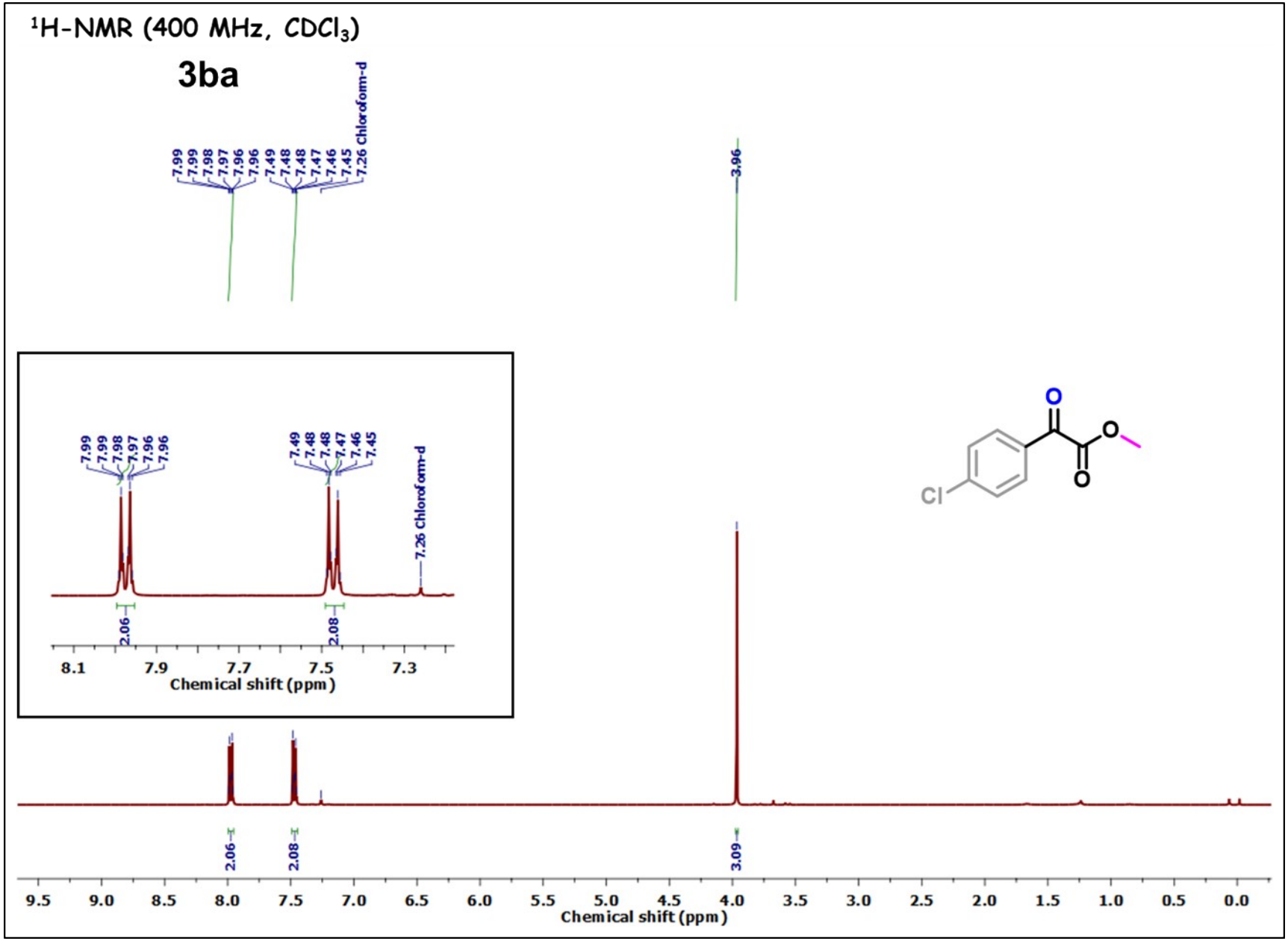
7 References:

[1] a) O'Connor, N.R., Bolgar, P. and Stoltz, B.M., Development of a simple system for the oxidation of electron-rich diazo compounds to ketones. *Tetrahedron Letters*, **2016**, *57(8)*, 849-851; b) Chen, J., Li, F., Wang, F., Hu, Y., Zhang, Z., Zhao, M. and Zhang, W., Pd $(OAc)_2$-catalyzed asymmetric hydrogenation of α-iminoesters. *Organic letters*, **2019**, *21(22)*, 9060-9065; c) Duan, H.F., Xie, J.H., Qiao, X.C., Wang, L.X. and Zhou, Q.L., Enantioselective rhodium-catalyzed addition of arylboronic acids to α-ketoesters. *Angew. Chem. Int. Ed*, **2008**, *47(23)*, 4351-4353; d) Vadagaonkar, K.S., Kalmode, H.P., Shinde, S.L. and Chaskar, A.C., An Efficient and Metal–free Synthesis of α-Ketoesters via Oxidative Cross Coupling of Arylglyoxals with Alcohols. *ChemistrySelect*, **2017**, *2(3)*, 900-903; e) Sagar, A., Vidyacharan, S. and Sharada, D.S. I_2-promoted cross-dehydrogenative coupling of α- carbonyl aldehydes with alcohols for the synthesis of α-ketoesters. *RSC Advances*, **2014**, *4(70)*, 37047-37050; f) Xu, C., Wang, Y. and Bai, L. Copper (I)-Catalyzed Aerobic Oxidation of α-Diazoesters. *The Journal of Organic Chemistry*, **2020**, *85(19)*, pp.12579-12584; g) Luo, X., He, R., Liu, Q., Gao, Y., Li, J., Chen, X., Zhu, Z., Huang, Y. and Li, Y. Metal-Free Oxidative Esterification of Ketones and Potassium Xanthates: Selective Synthesis of α-Ketoesters and Esters. *The Journal of Organic Chemistry*, **2020**, *85(8)*, 5220-5230; h) Du, F.T. and Ji, J.X. Copper-catalyzed direct oxidative synthesis of α-ketoamides from aryl methyl ketones, amines, and molecular oxygen. *Chemical Science*, **2012**, *3(2)*, 460-465; i) Roy, S., Kumar, G. and Chatterjee, I. Photoinduced diverse reactivity of diazo compounds with nitrosoarenes. *Organic Letters*, **2021**, *23(17)*, 6709-6713; j) Liu, R., Liu, Q., Meng, H., Ding, H., Hao, J., Ji, Z., Yue, H. and Wei, W. Metal-free visible- light-induced aerobic oxidation of α-diazoesters leading to α-ketoesters in air. *Organic Chemistry Frontiers*, **2021**, *8(9)*, 1970-1975.

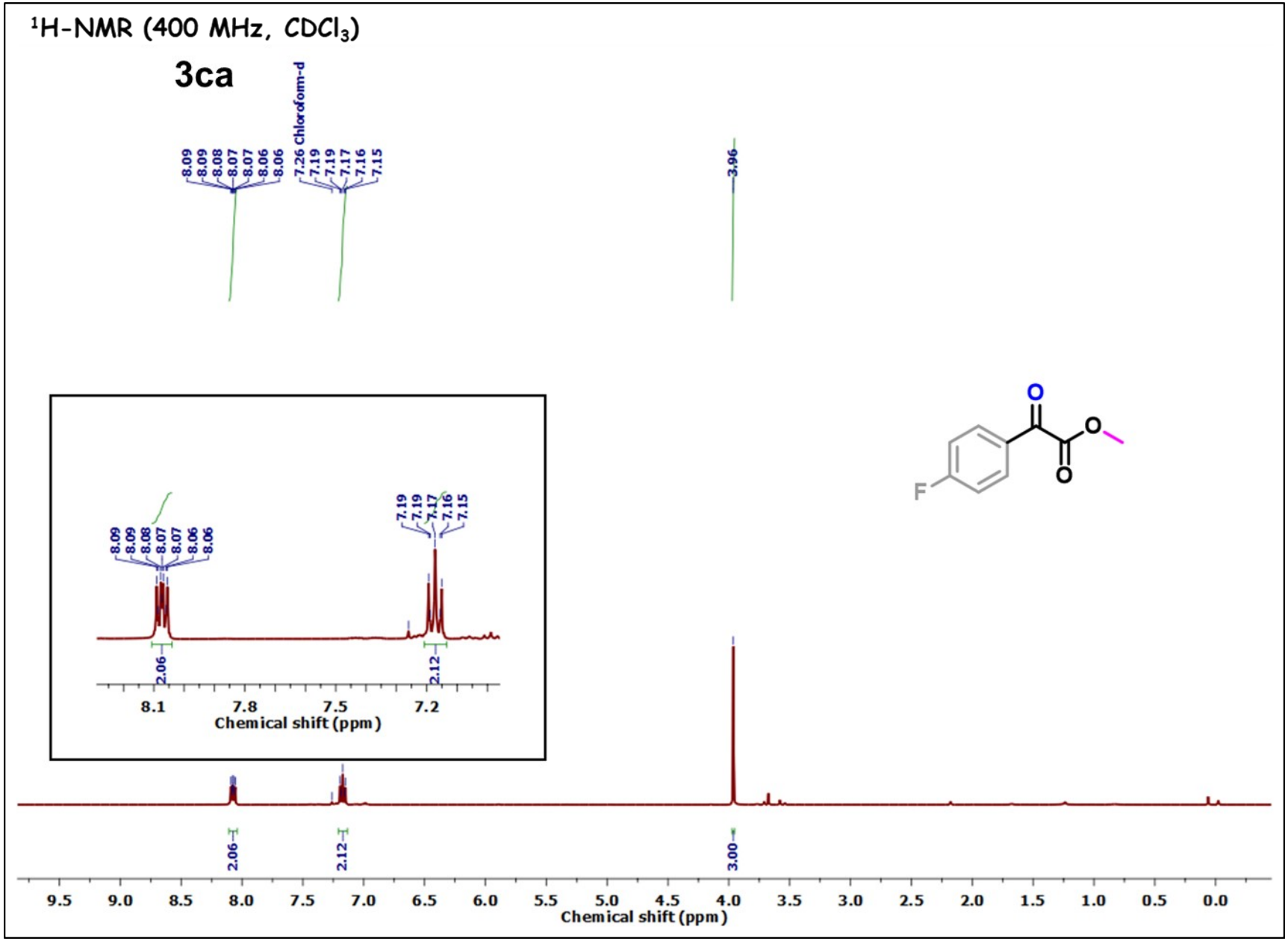
8. Spectral Data of Synthesized Compounds:



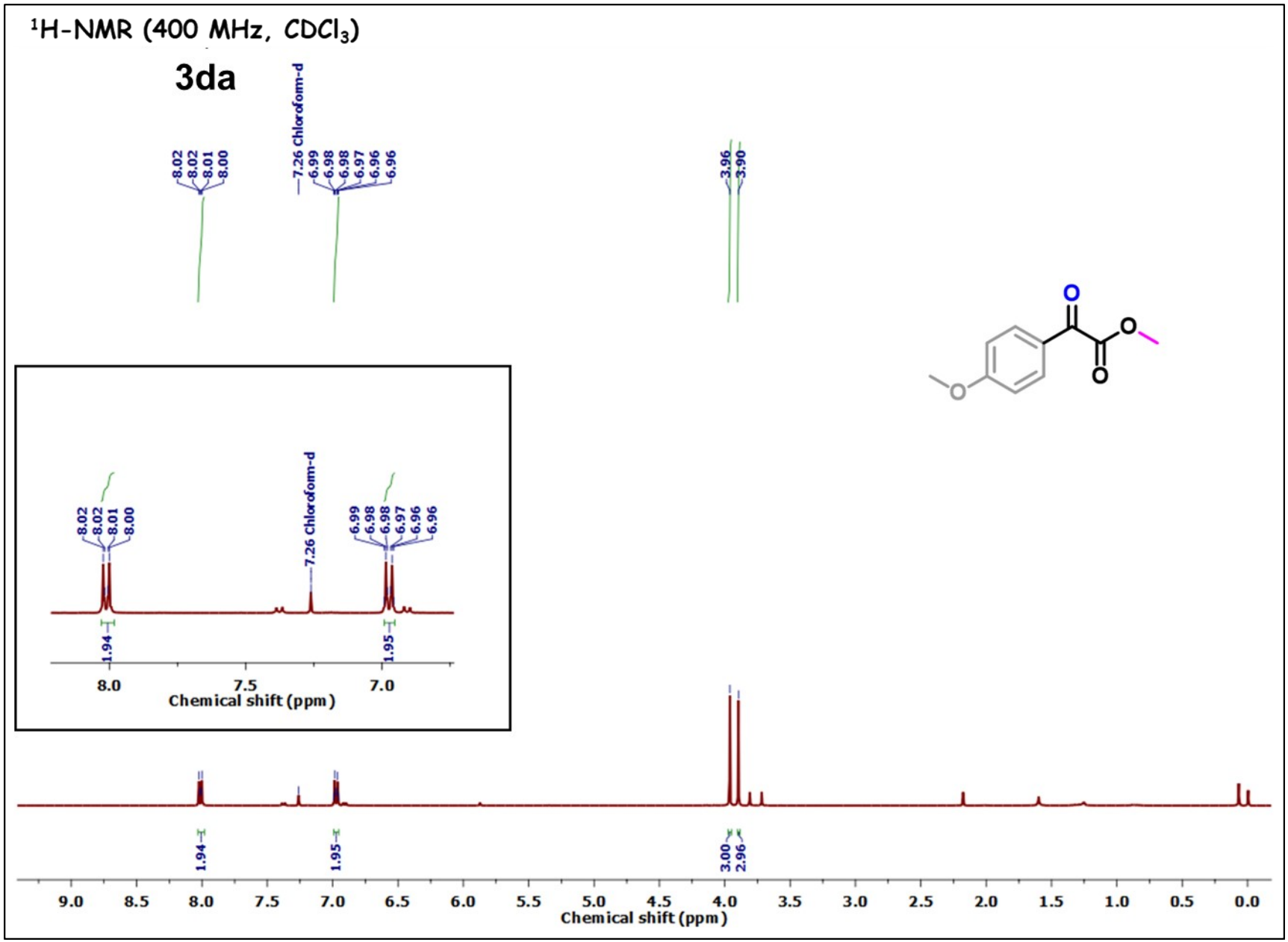
^{1}H-NMR (400 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, $CDCl_3$)

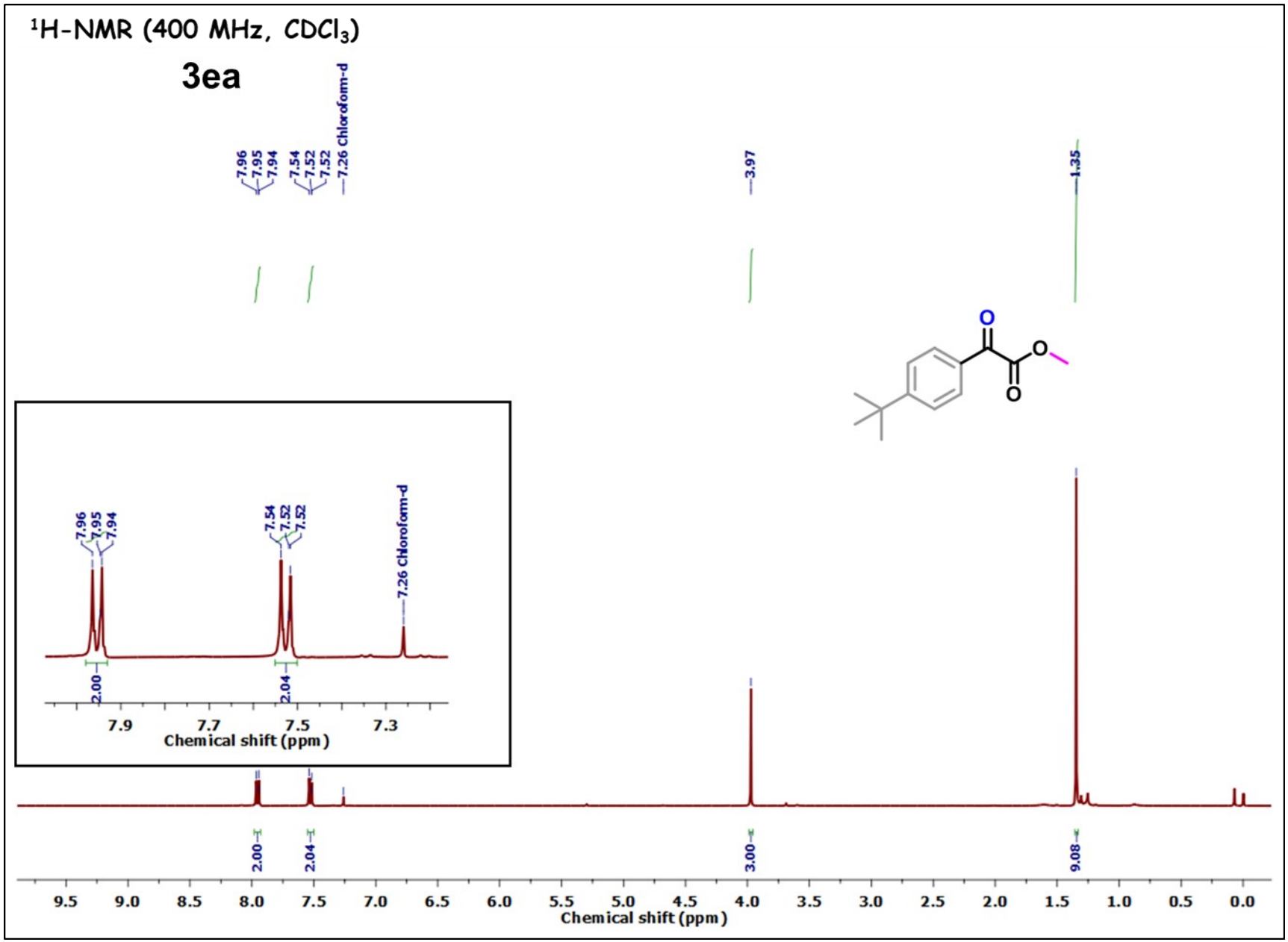


^{1}H-NMR (400 MHz, $CDCl_3$)



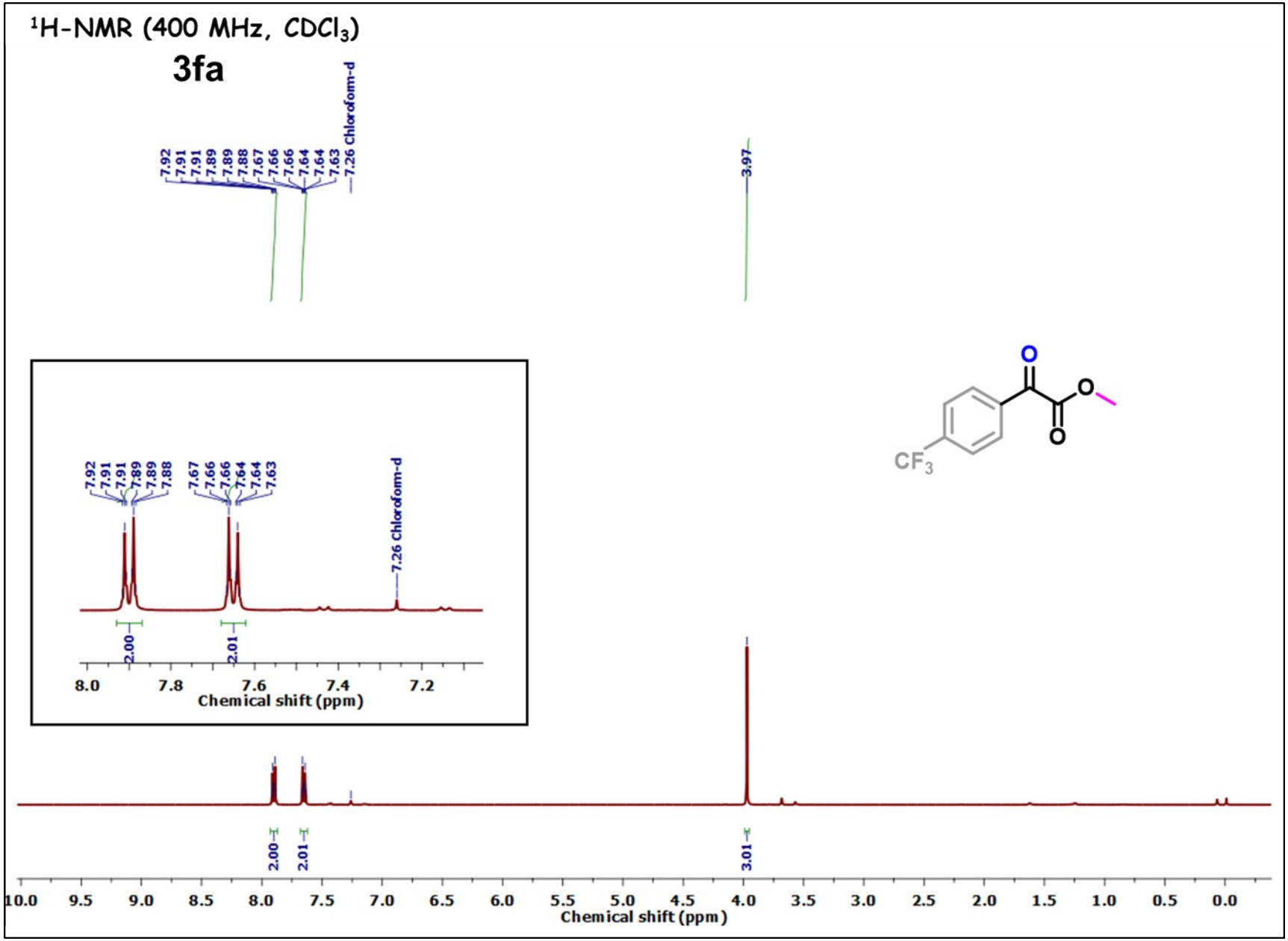
^{1}H-NMR (400 MHz, $CDCl_3$)

3ea



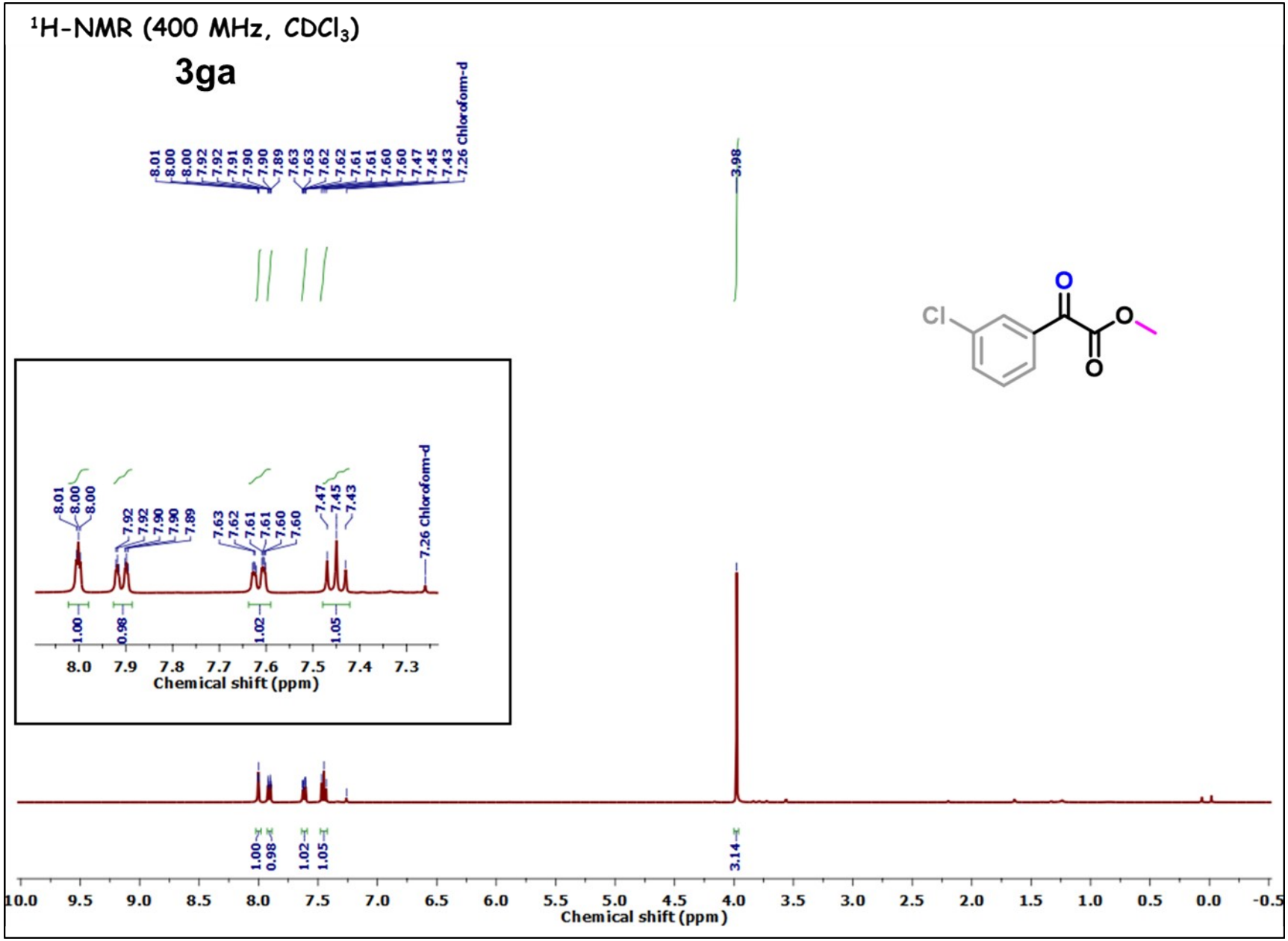
^{1}H-NMR (400 MHz, $CDCl_3$)

3fa

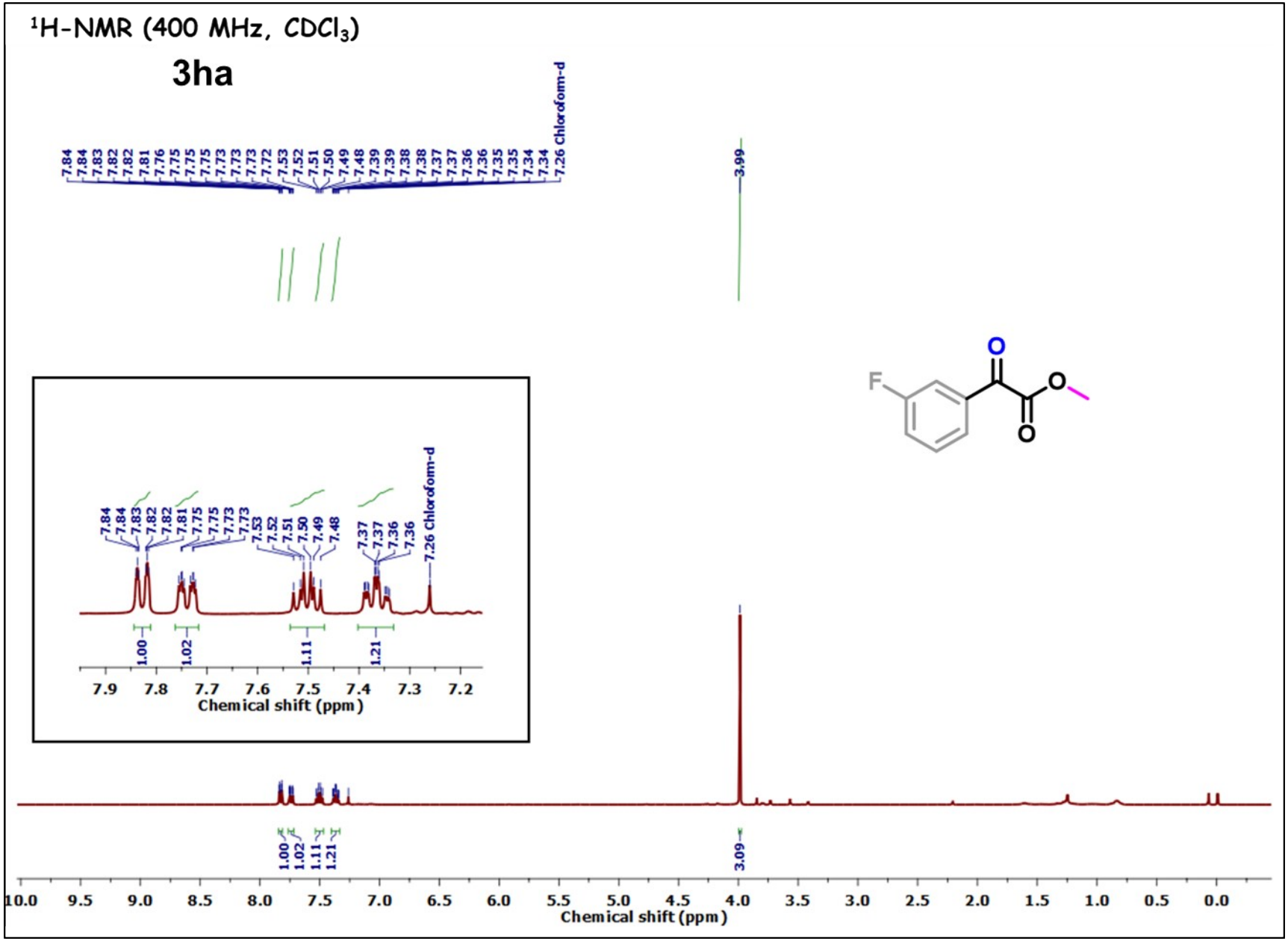


^{1}H-NMR (400 MHz, $CDCl_3$)

3ga

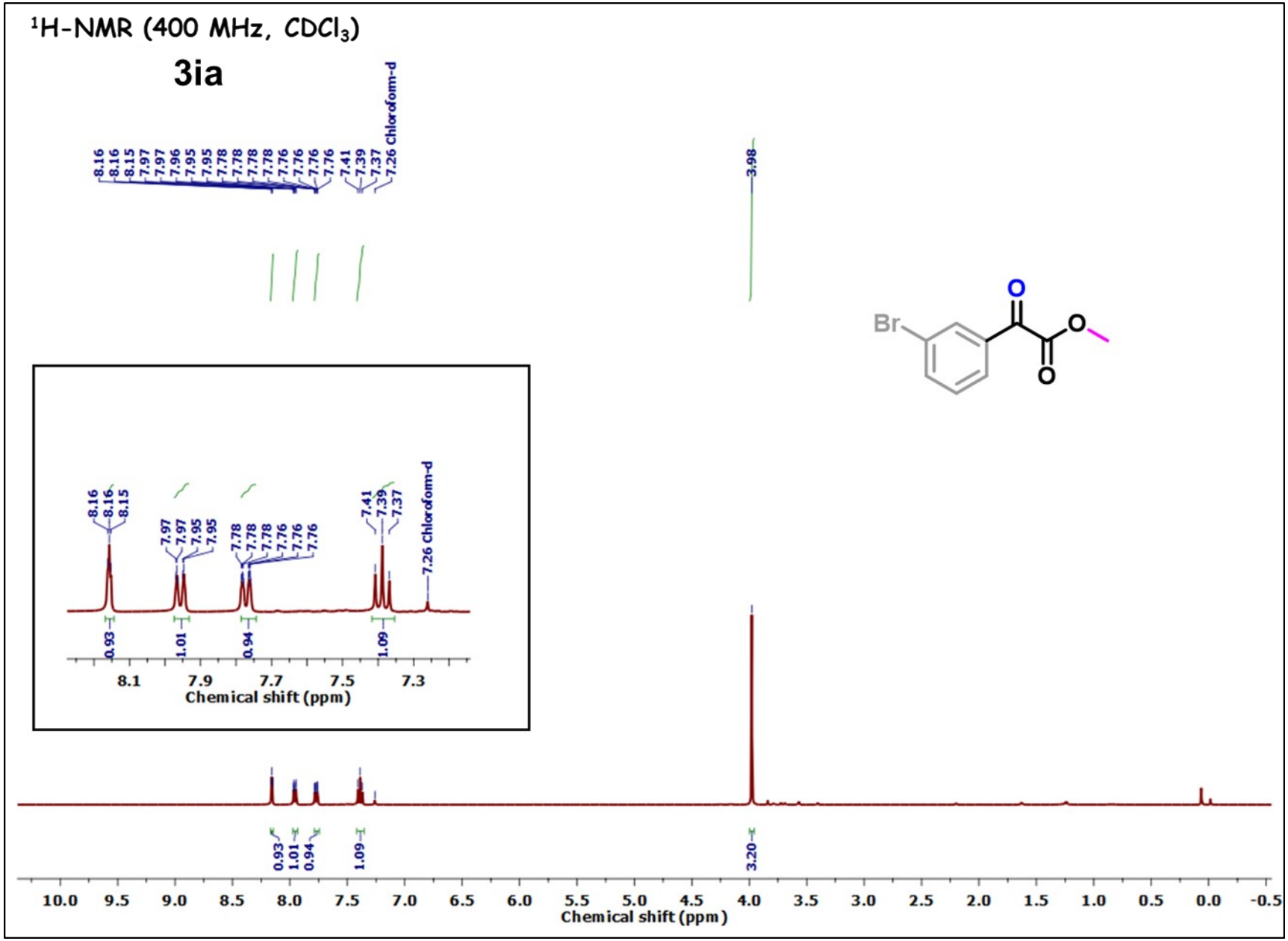


^{1}H-NMR (400 MHz, $CDCl_3$)



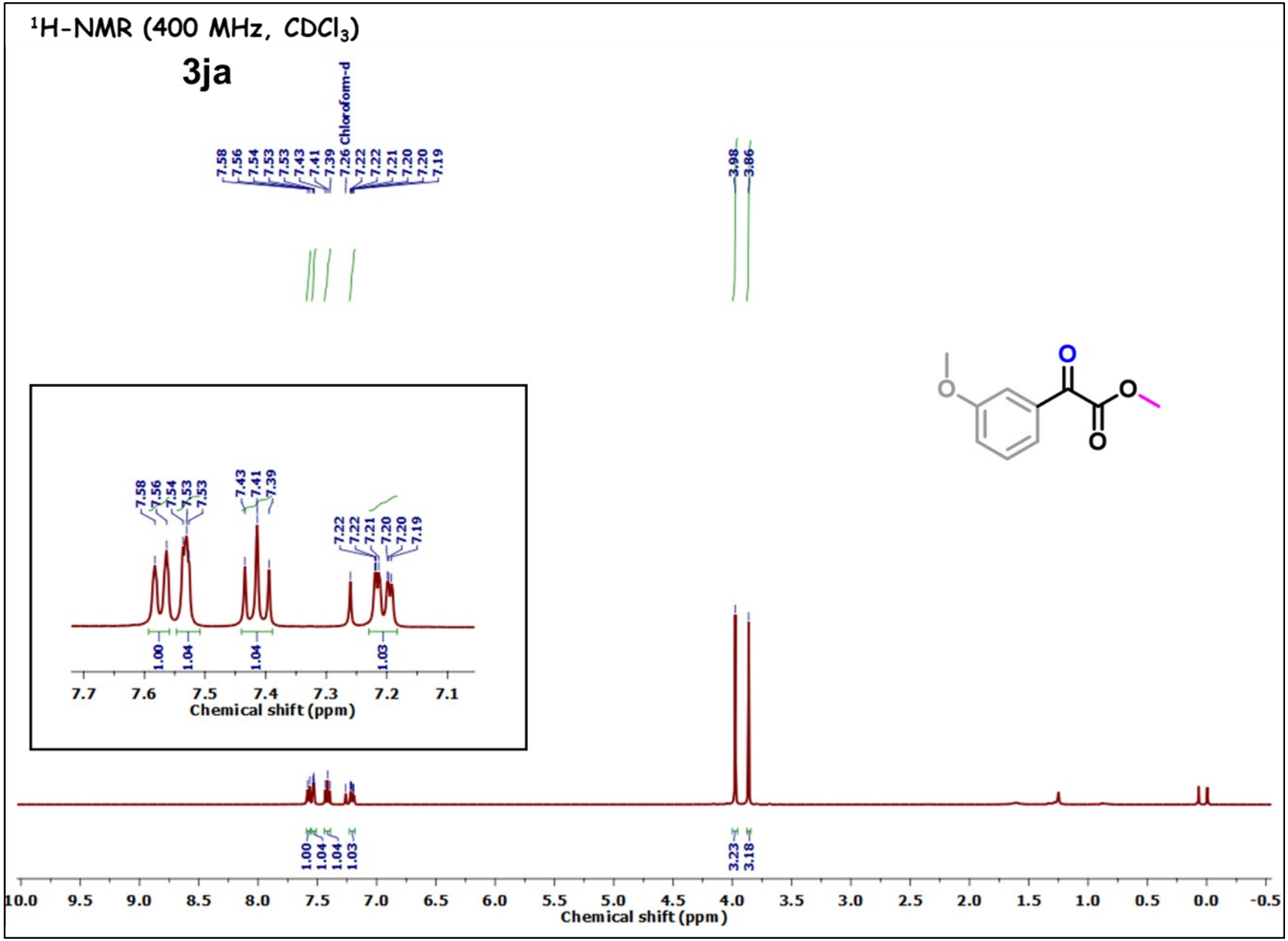
^{1}H-NMR (400 MHz, $CDCl_3$)

3ia

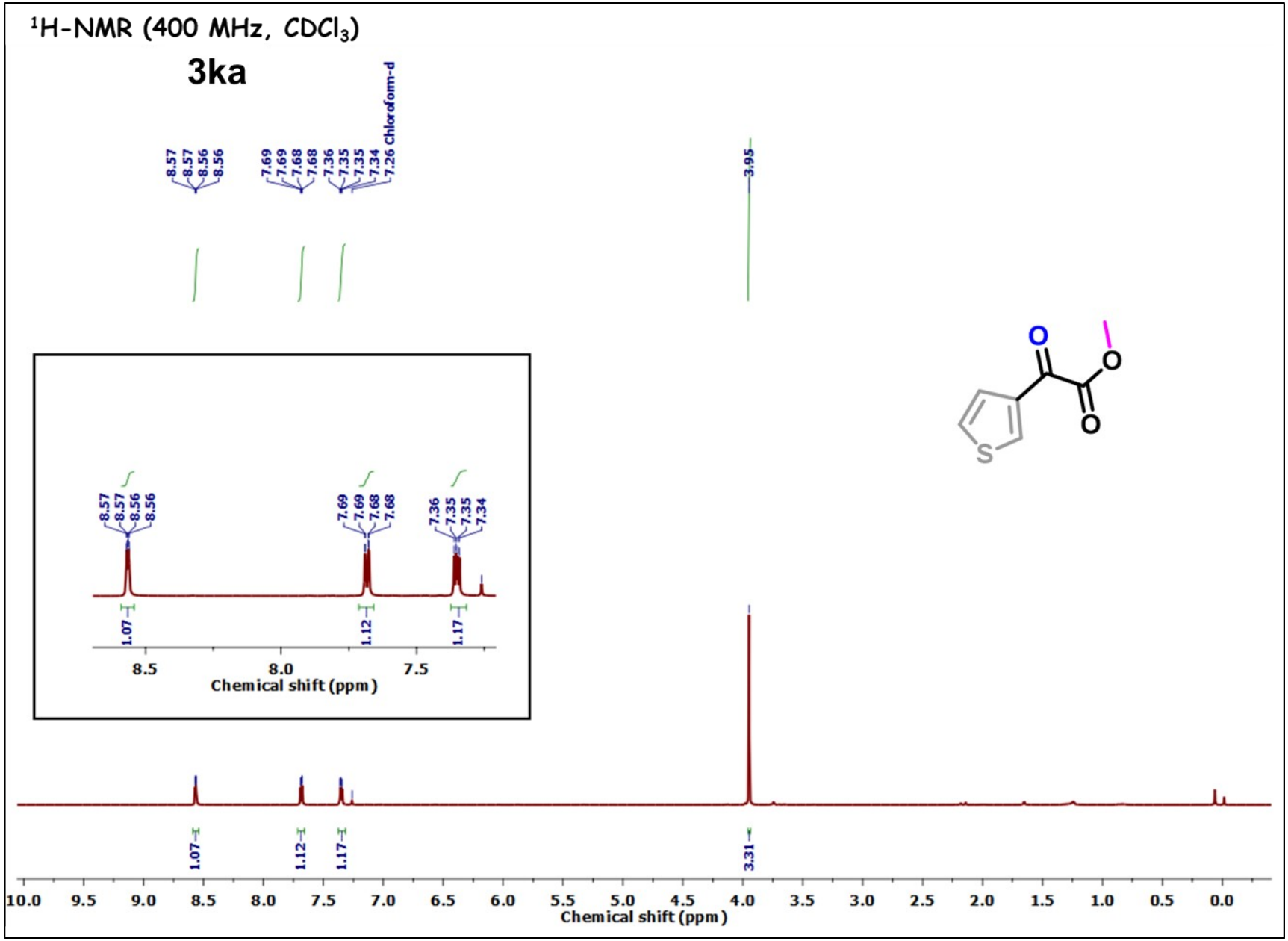


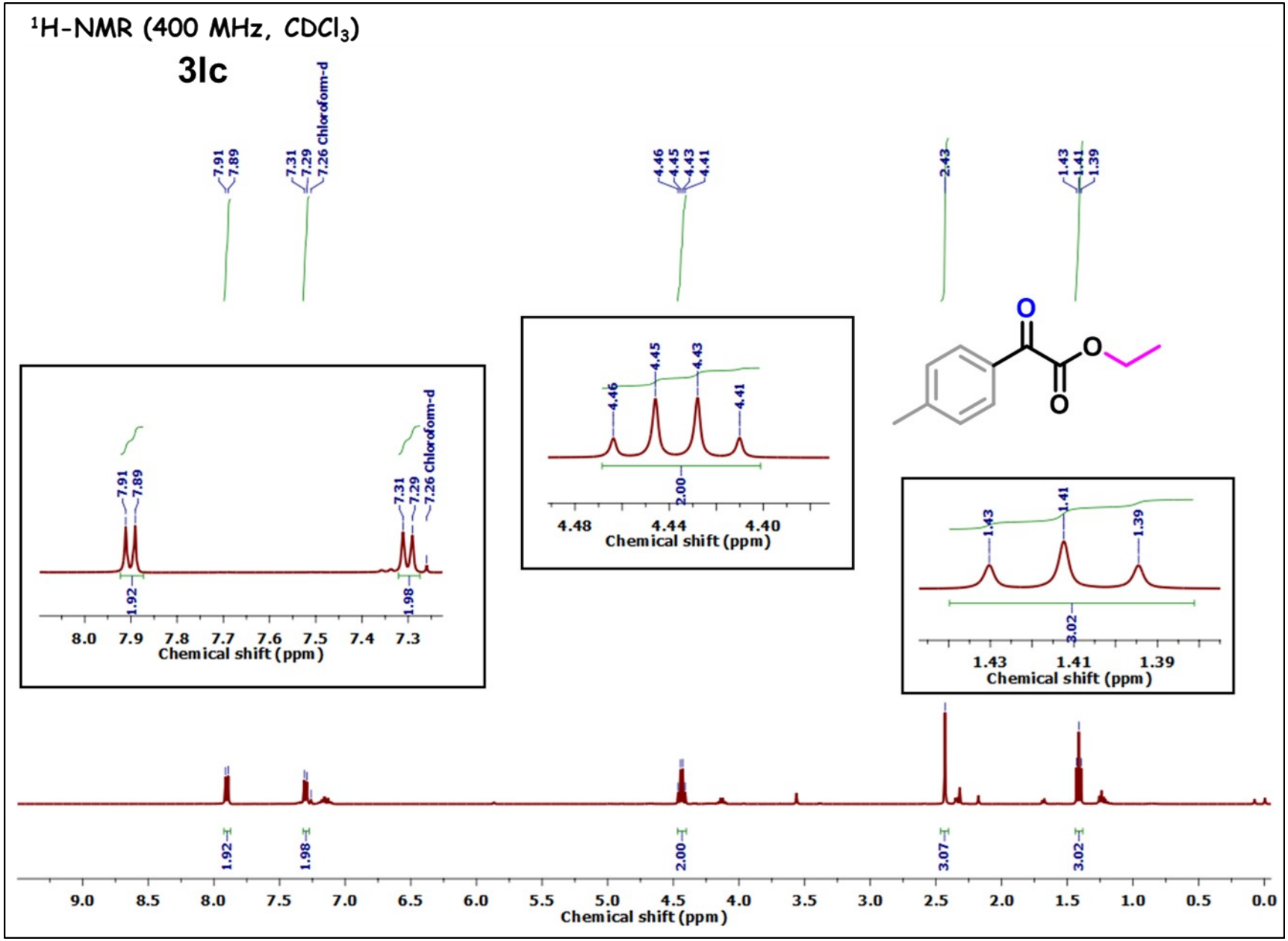
^{1}H-NMR (400 MHz, $CDCl_3$)

3ja



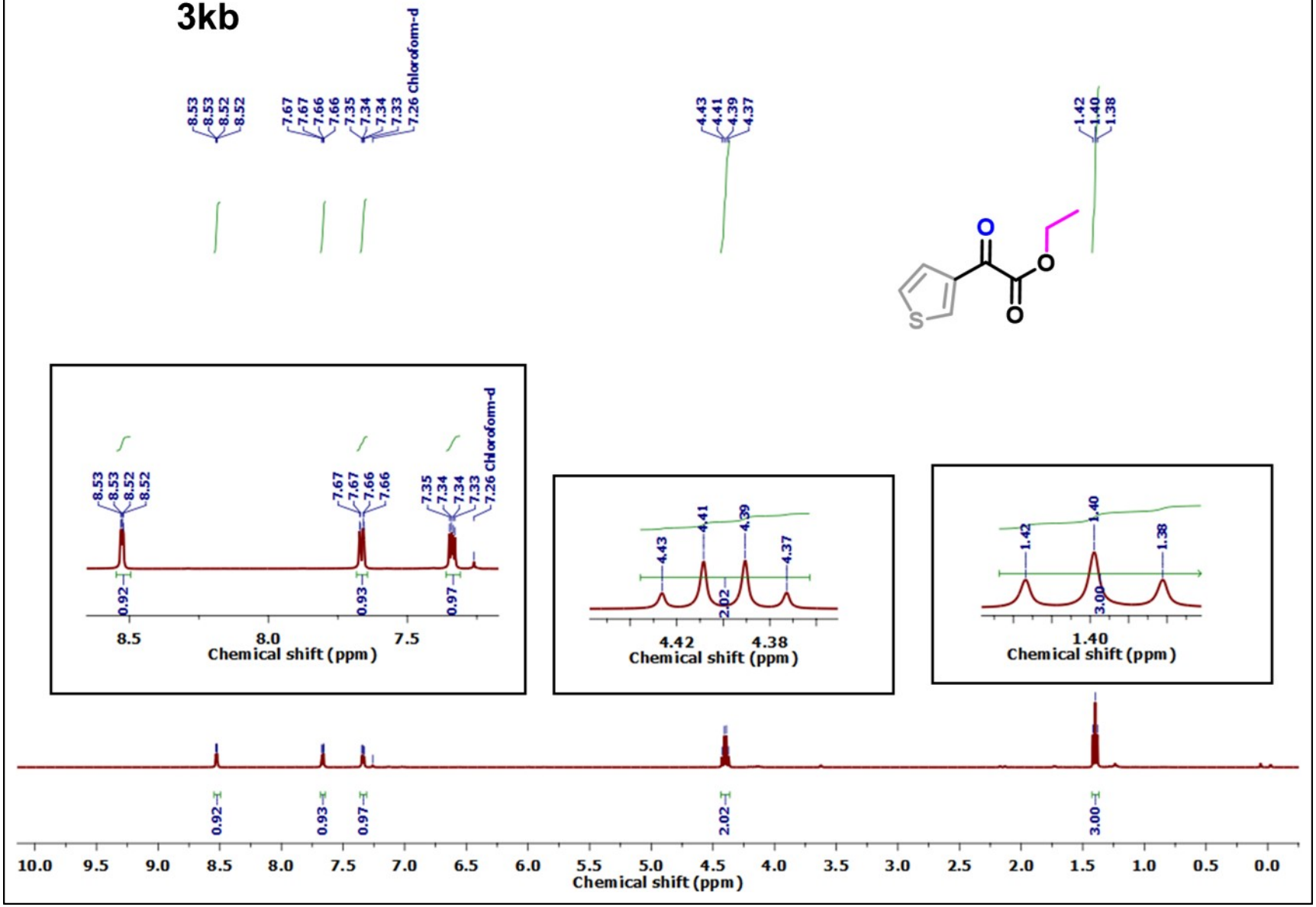
^{1}H-NMR (400 MHz, $CDCl_3$)




^{1}H-NMR (400 MHz, $CDCl_3$)
3Ic
7.91
7.89
7.31
7.29
7.26 Chloroform-d
4.46
4.45
4.43
4.41
2.43
1.43
1.41
1.39
O
O
O
1.92
1.98
2.00
3.07
3.02
Chemical shift (ppm)

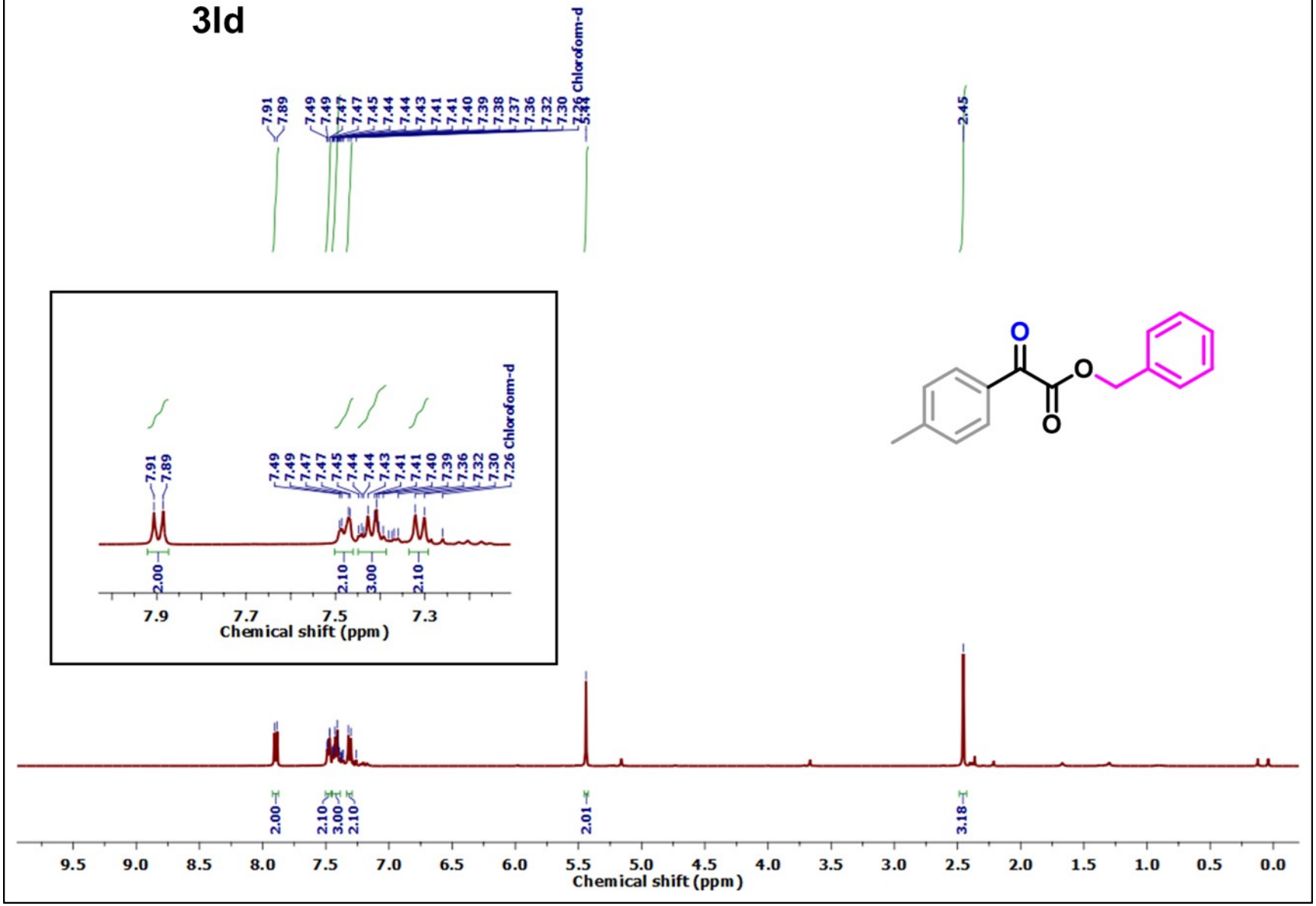
^{1}H-NMR (400 MHz, $CDCl_3$)

3kb

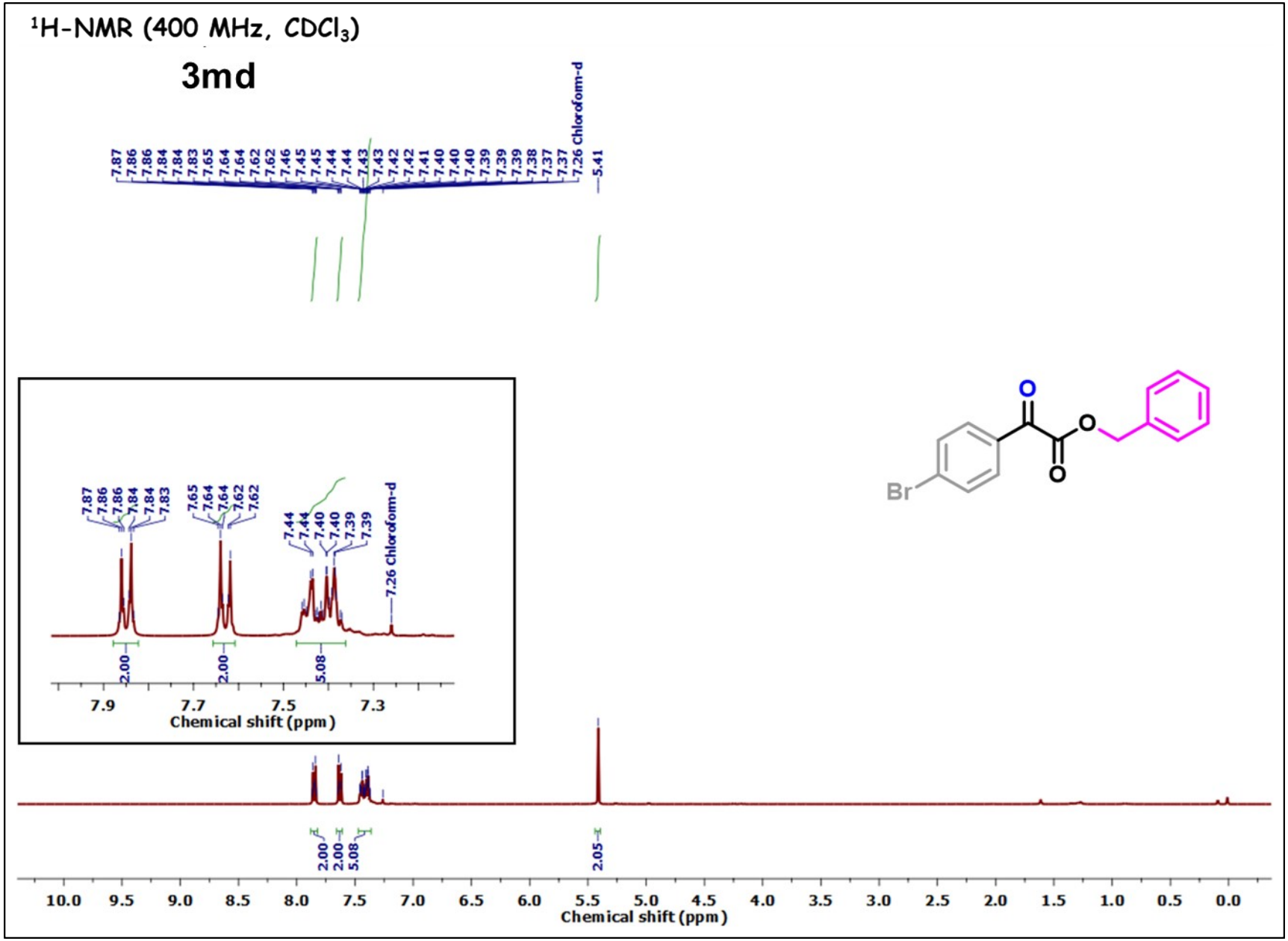


^{1}H-NMR (400 MHz, $CDCl_3$)

3ld

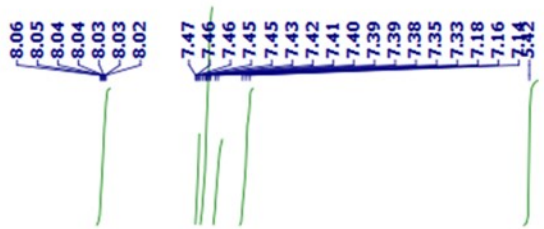


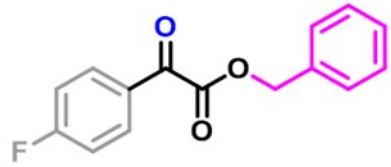
^{1}H-NMR (400 MHz, $CDCl_3$)

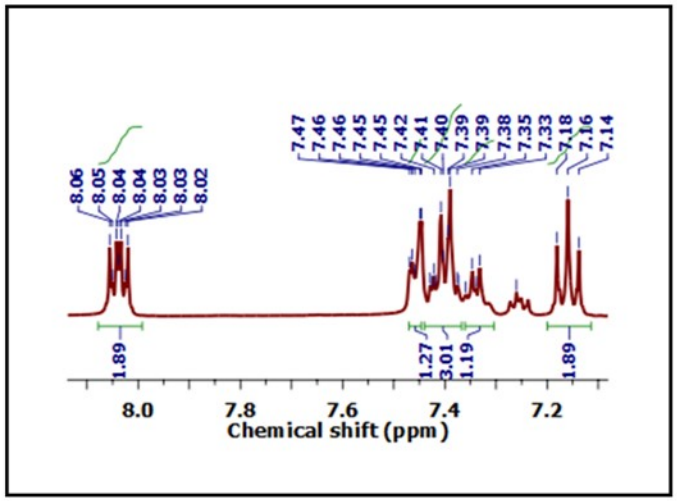


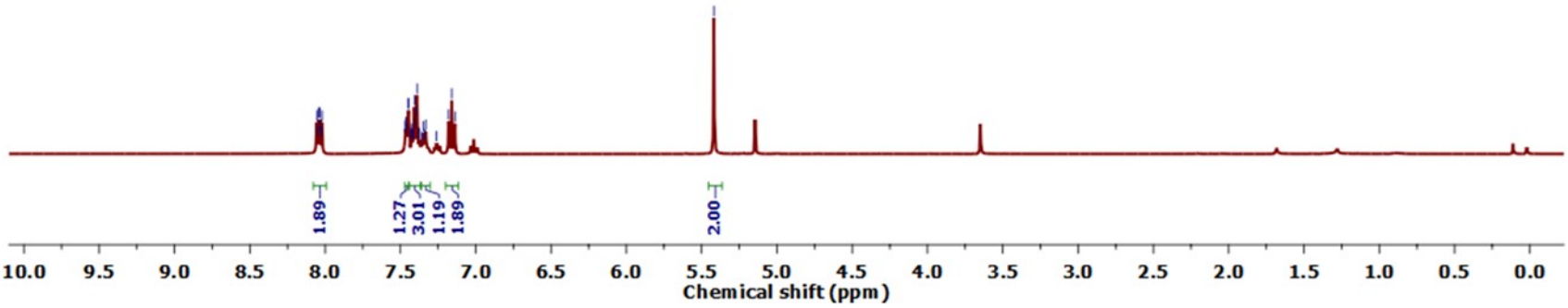
^{1}H-NMR (400 MHz, $CDCl_3$)

3cd

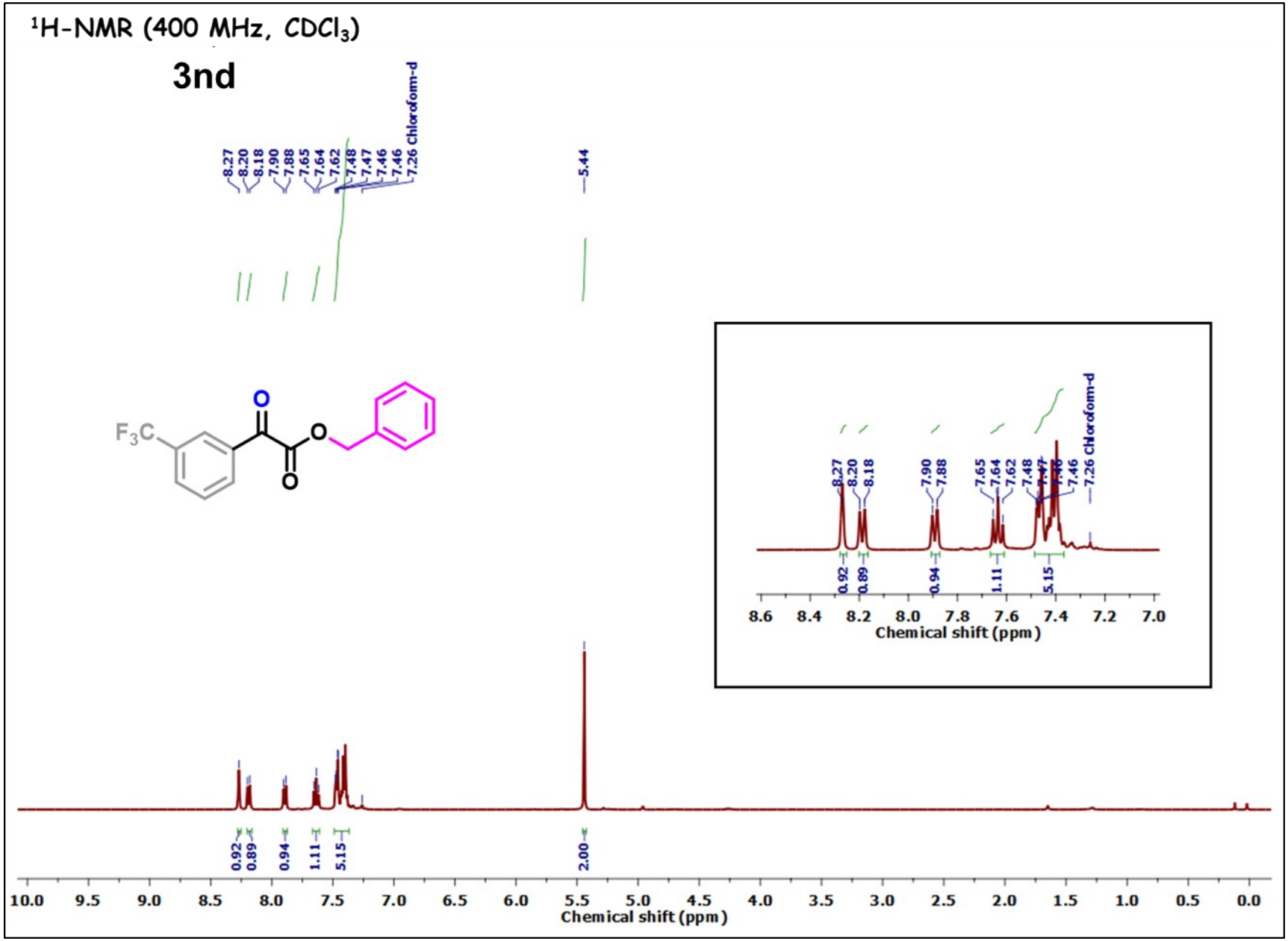






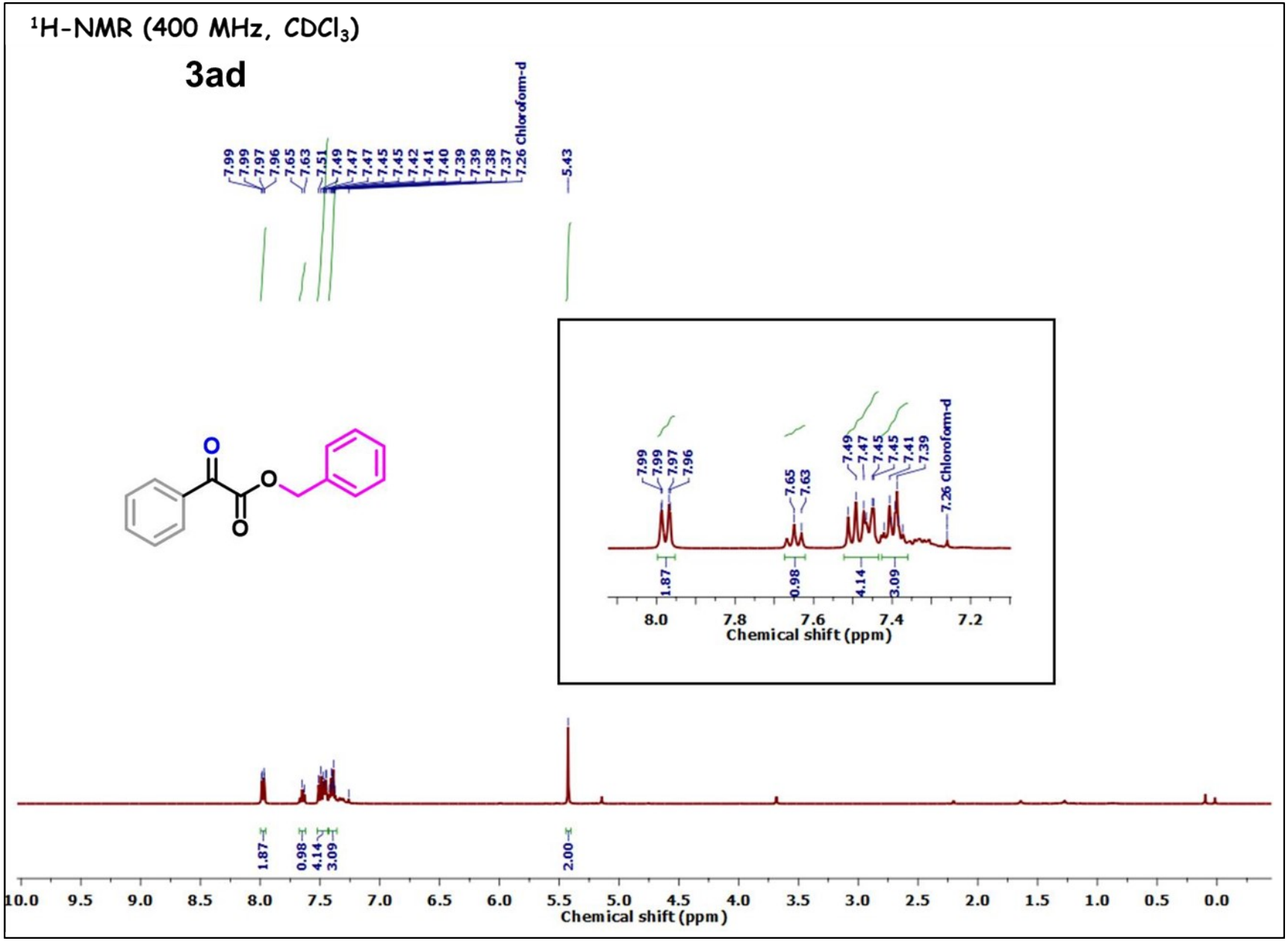


^{1}H-NMR (400 MHz, $CDCl_3$)



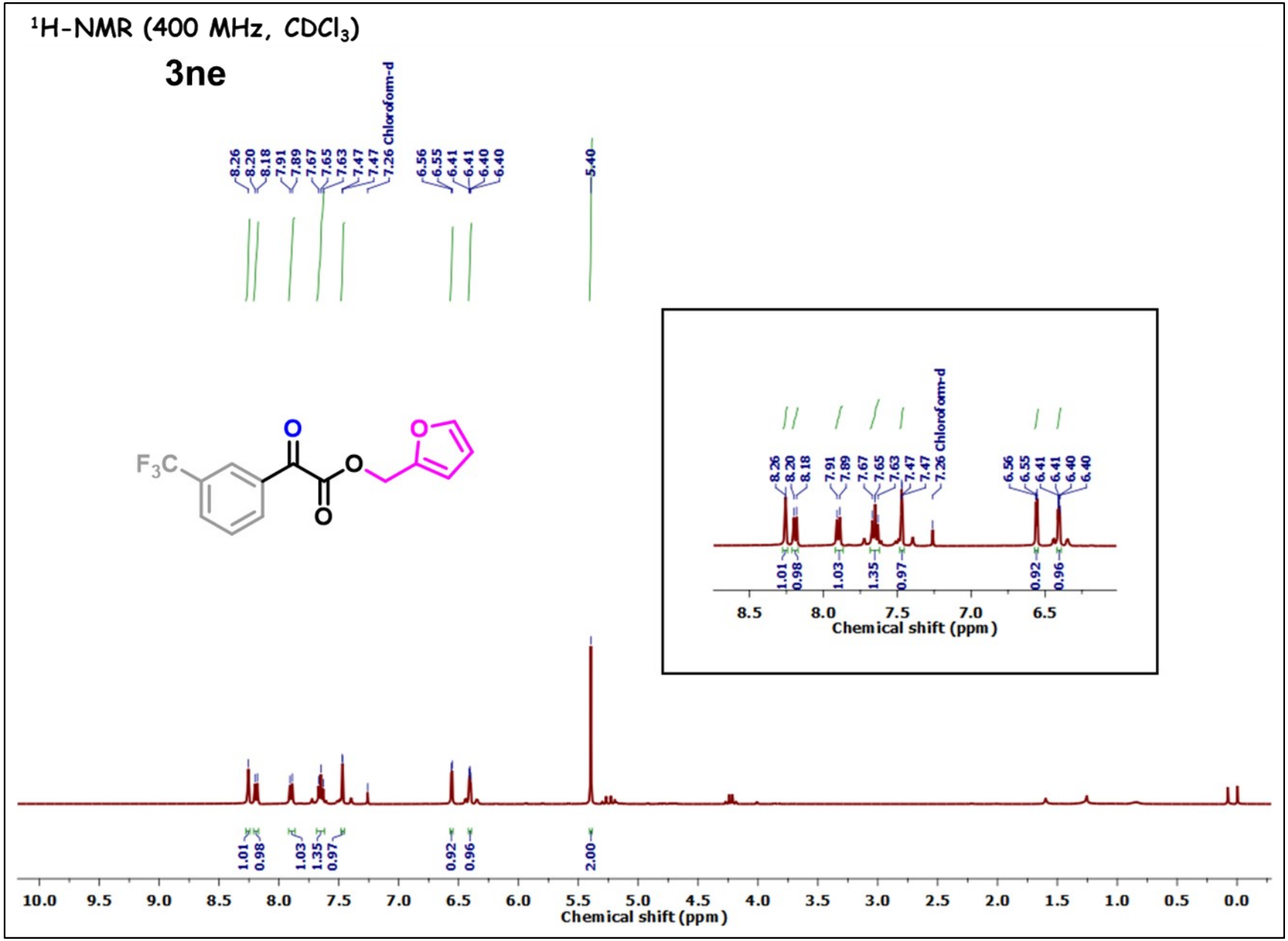
^{1}H-NMR (400 MHz, $CDCl_3$)

3ad



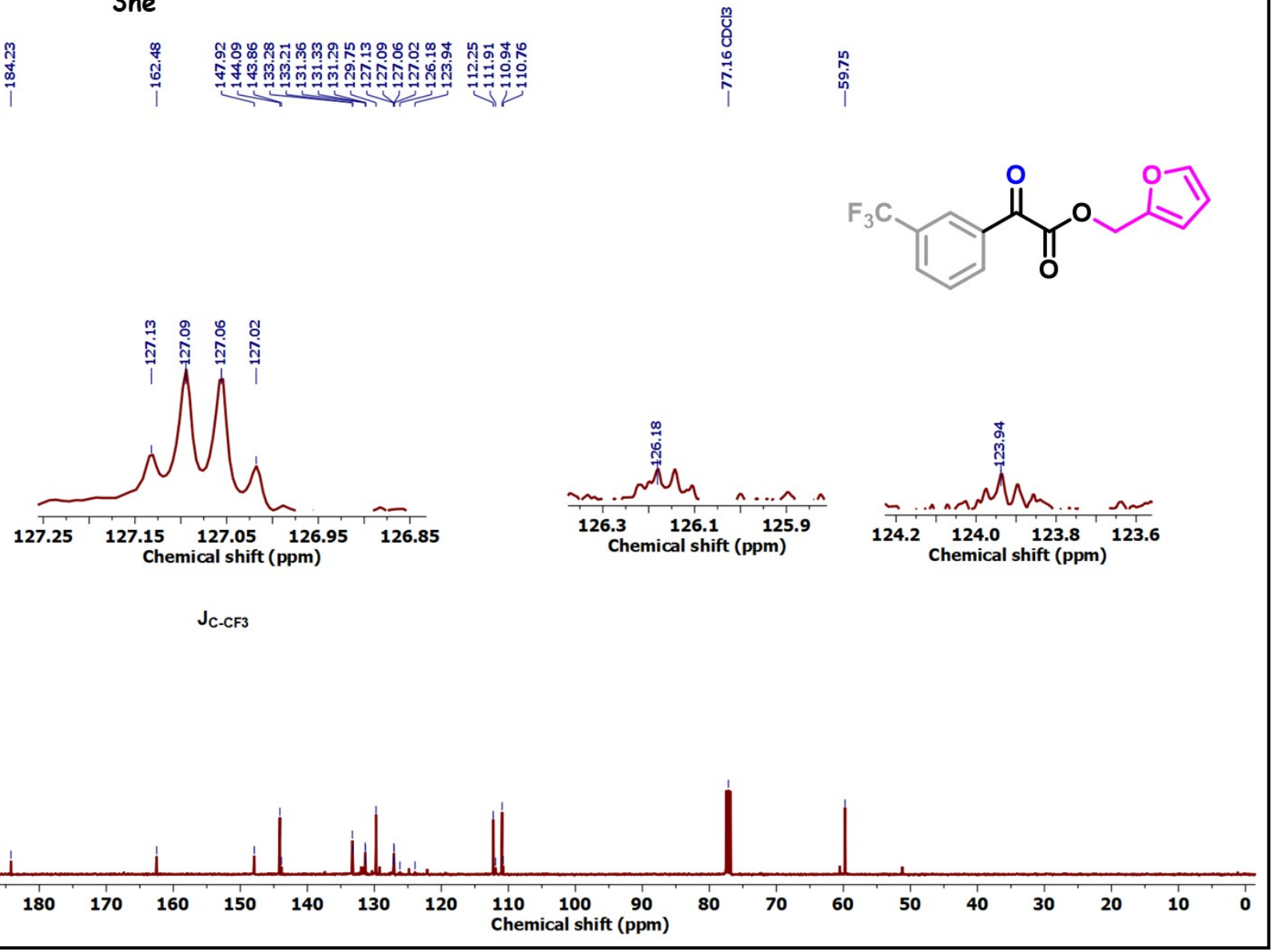
^{1}H-NMR (400 MHz, $CDCl_3$)

3ne



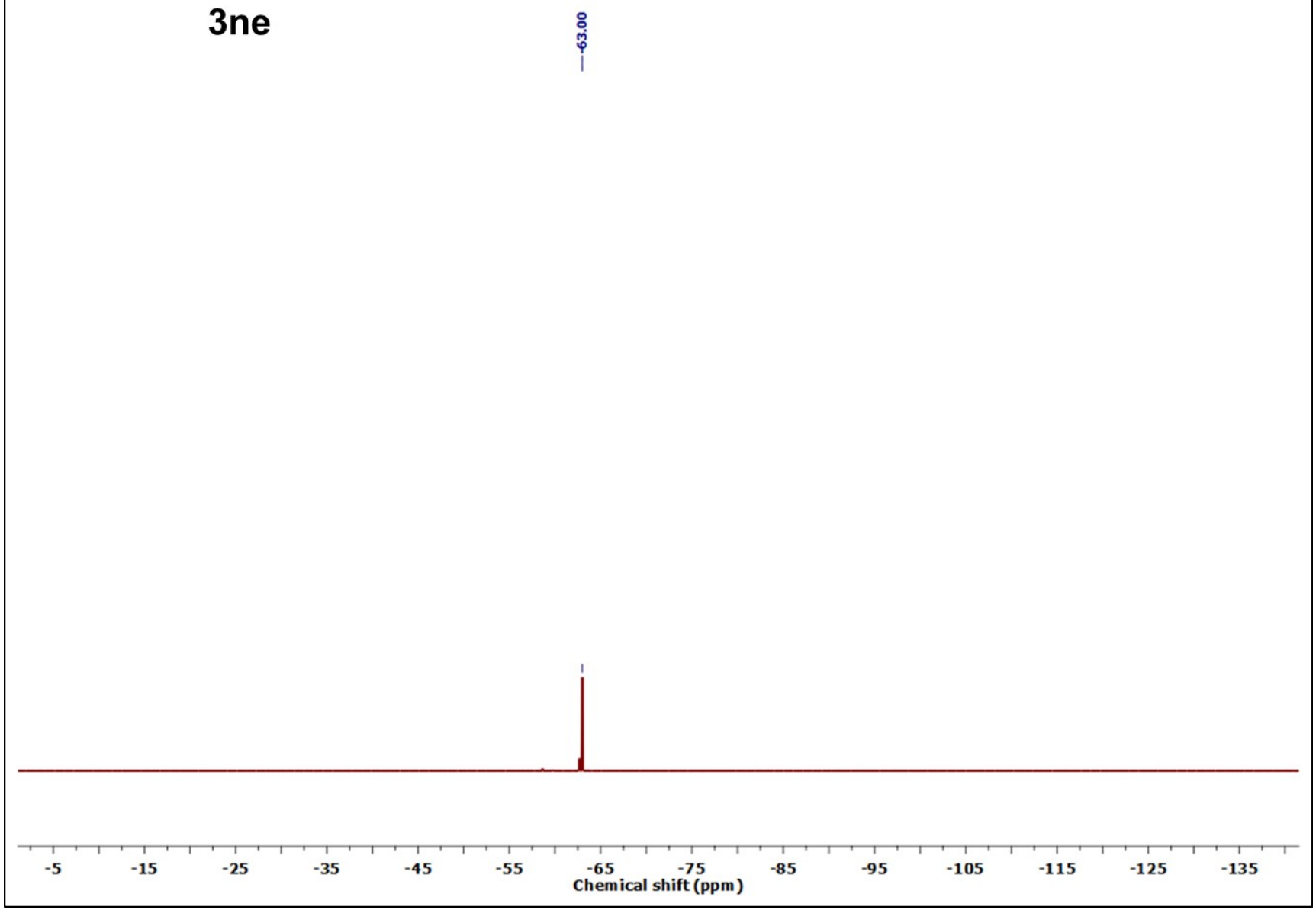
$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)

3ne



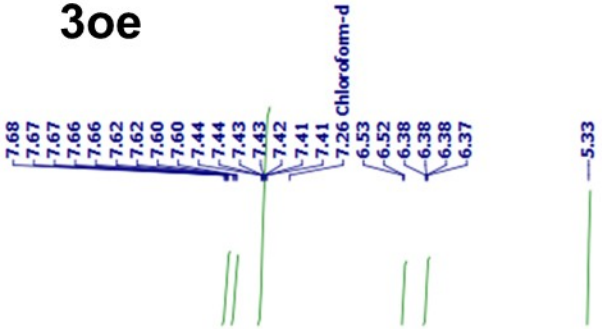
^{19}F-NMR (376 MHz, $CDCl_3$)

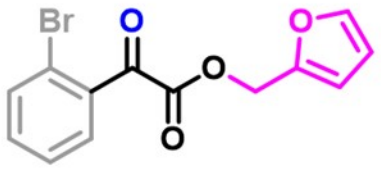
3ne

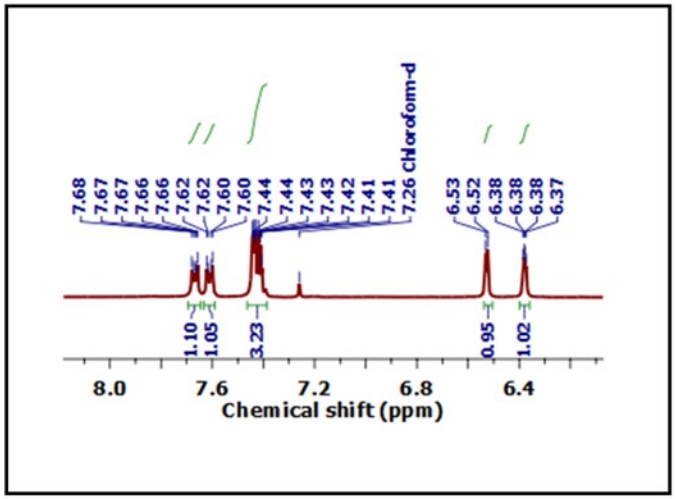


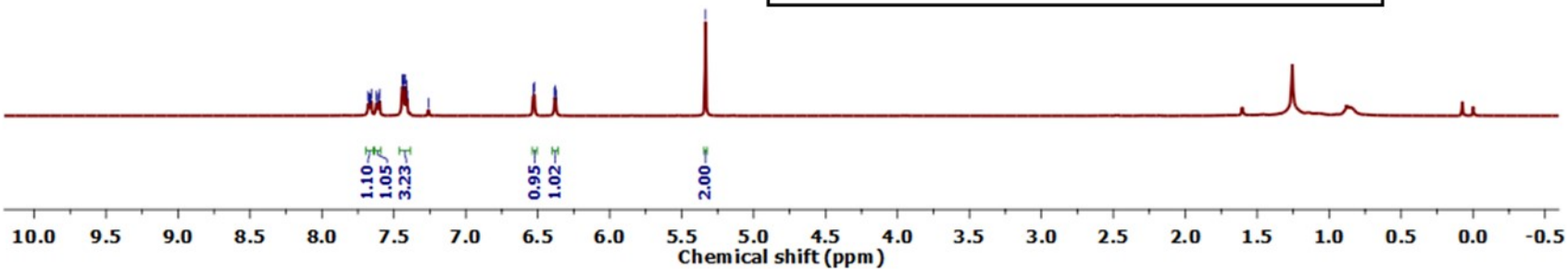
^{1}H-NMR (400 MHz, $CDCl_3$)

3oe



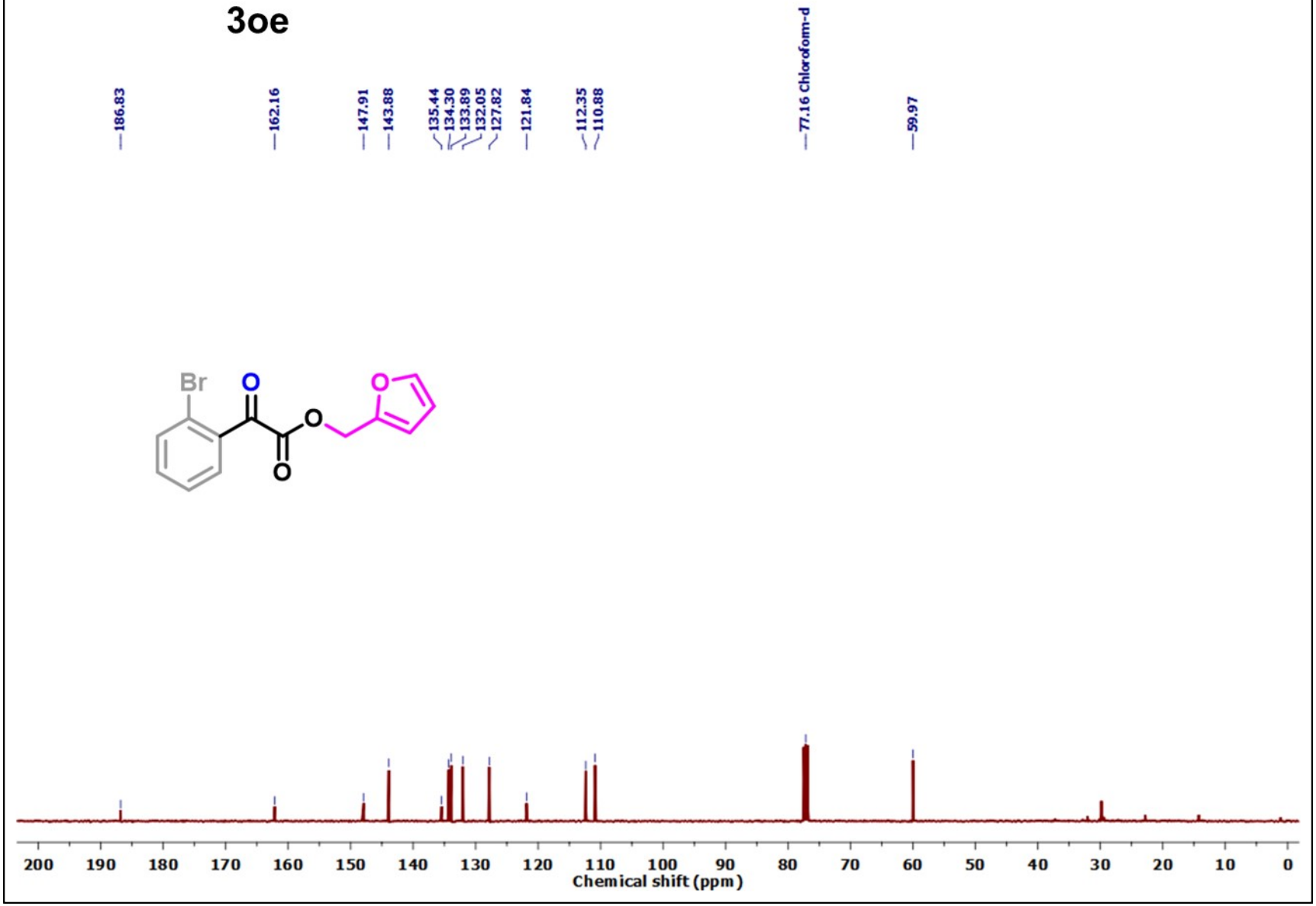






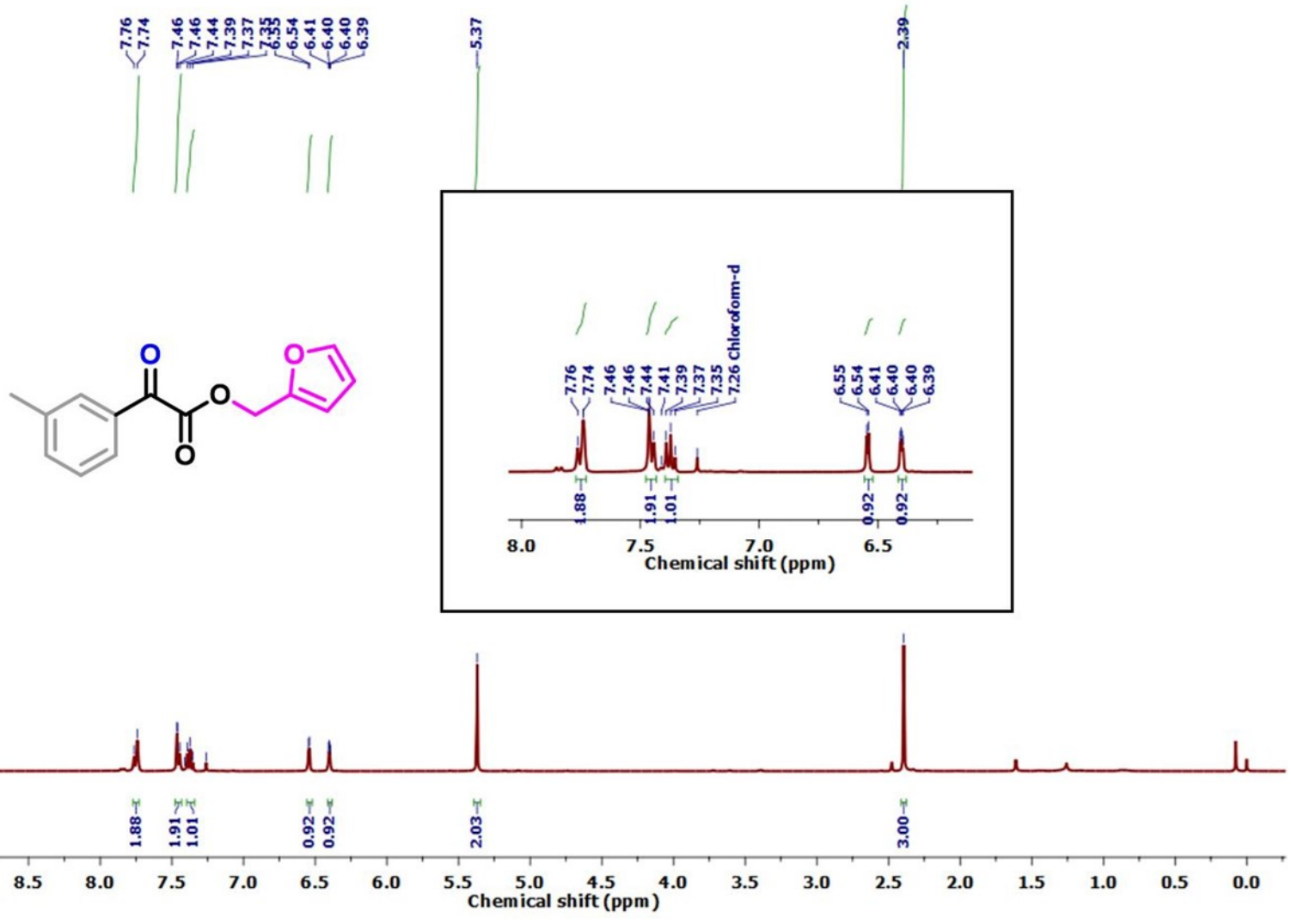
$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)

3oe



^{1}H-NMR (400 MHz, $CDCl_3$)

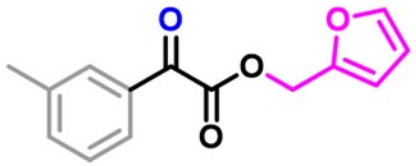
3pe

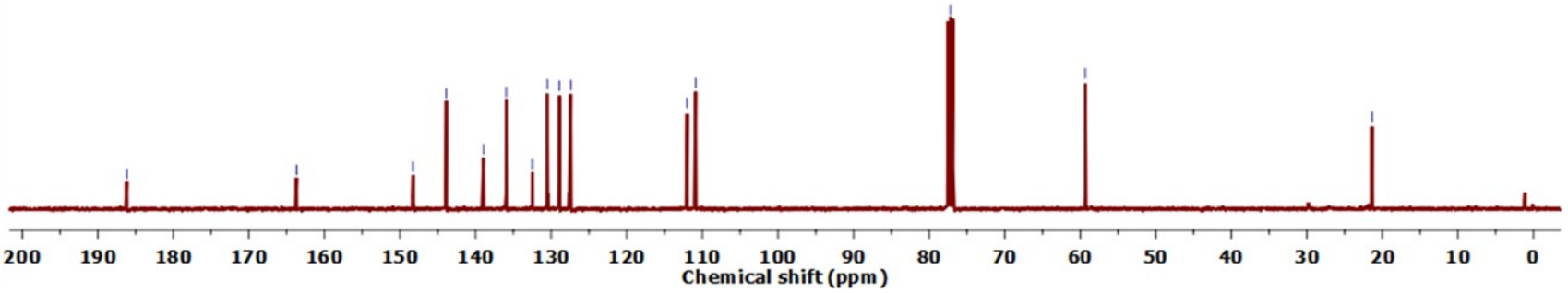


$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)

3pe

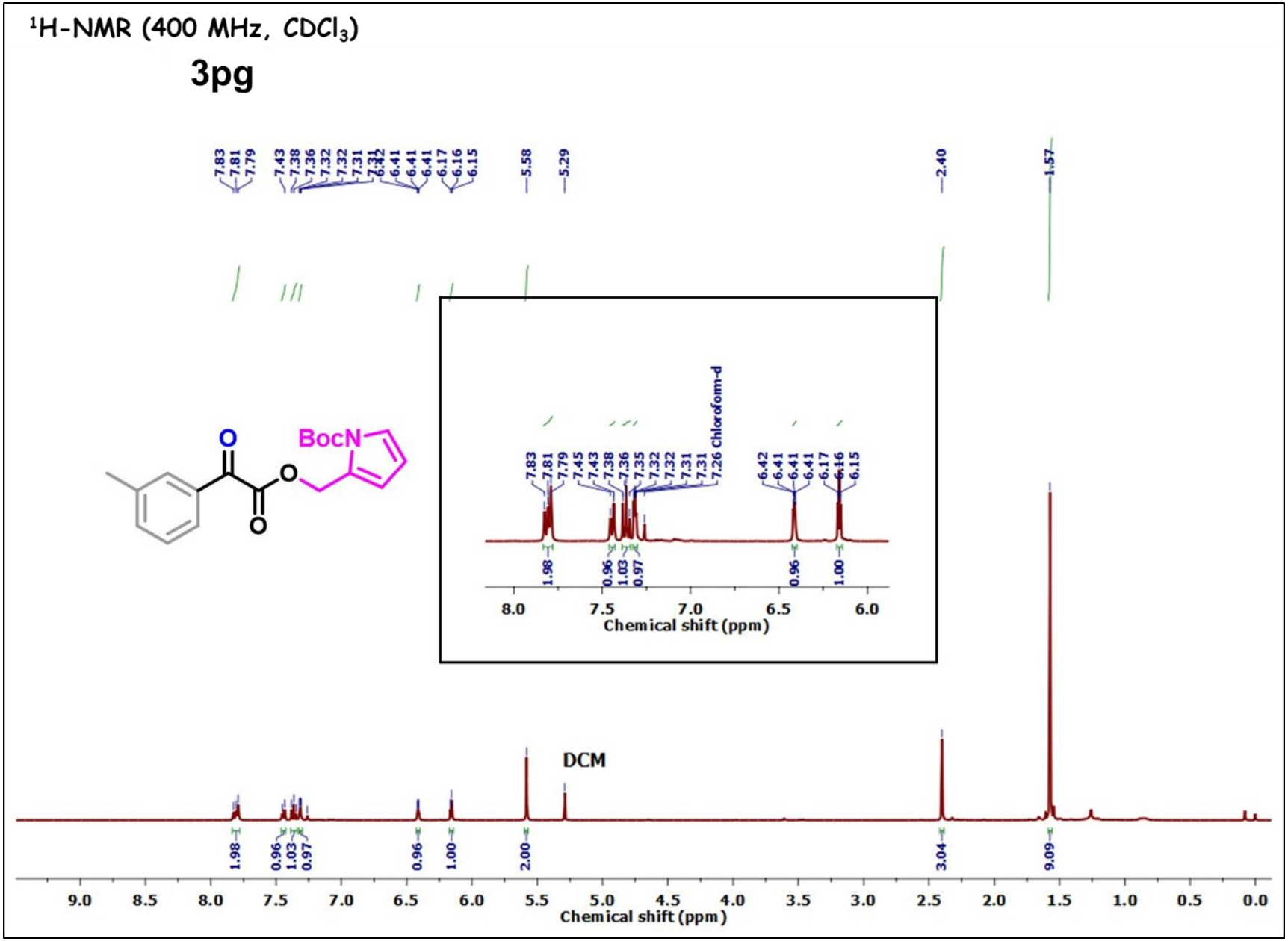
186.17
163.71
148.28
143.88
138.96
135.95
132.49
130.52
128.91
127.43
112.02
110.90
77.16 Chloroform-d
59.32
21.38





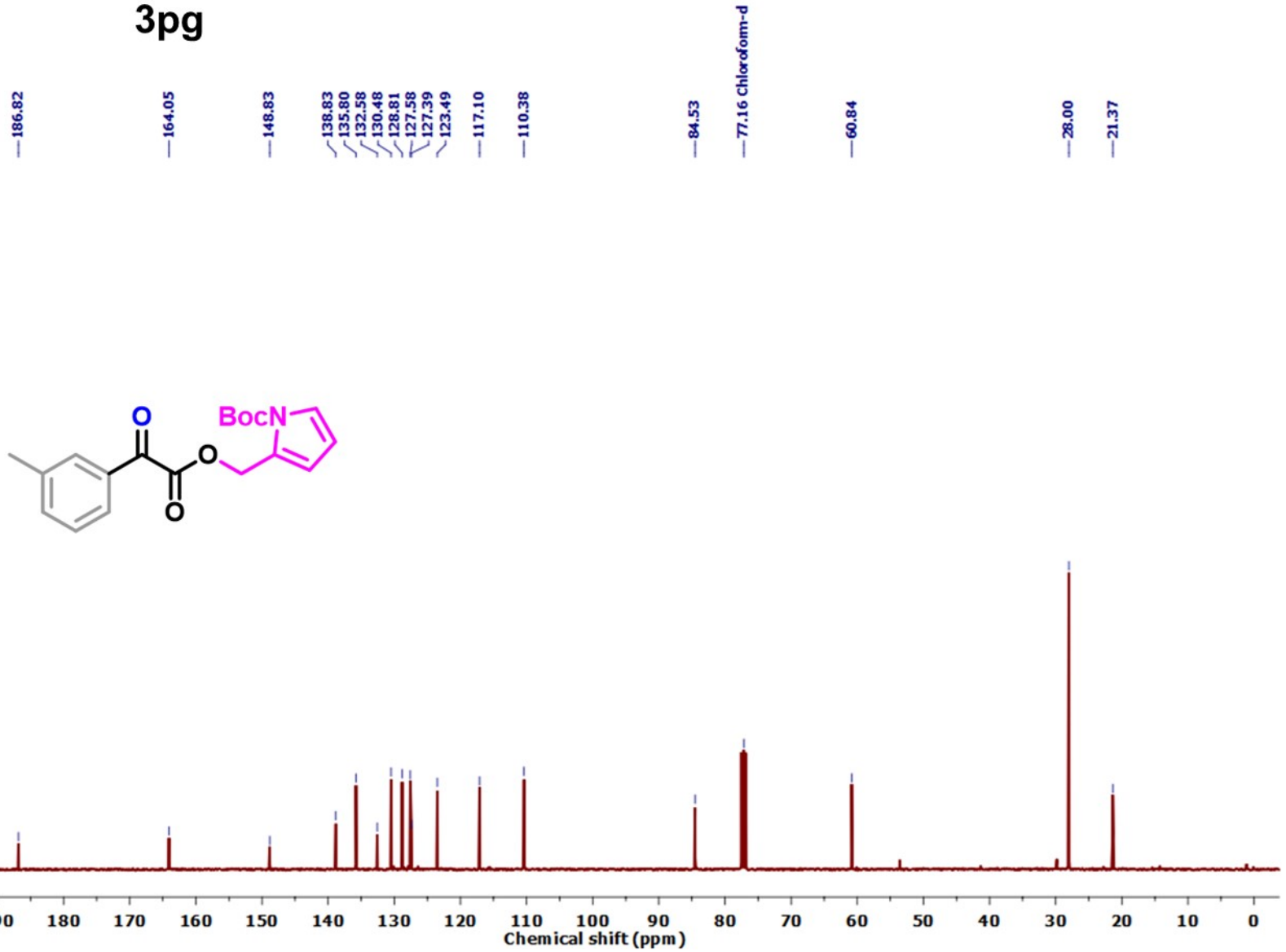
^{1}H-NMR (400 MHz, $CDCl_3$)

3pg



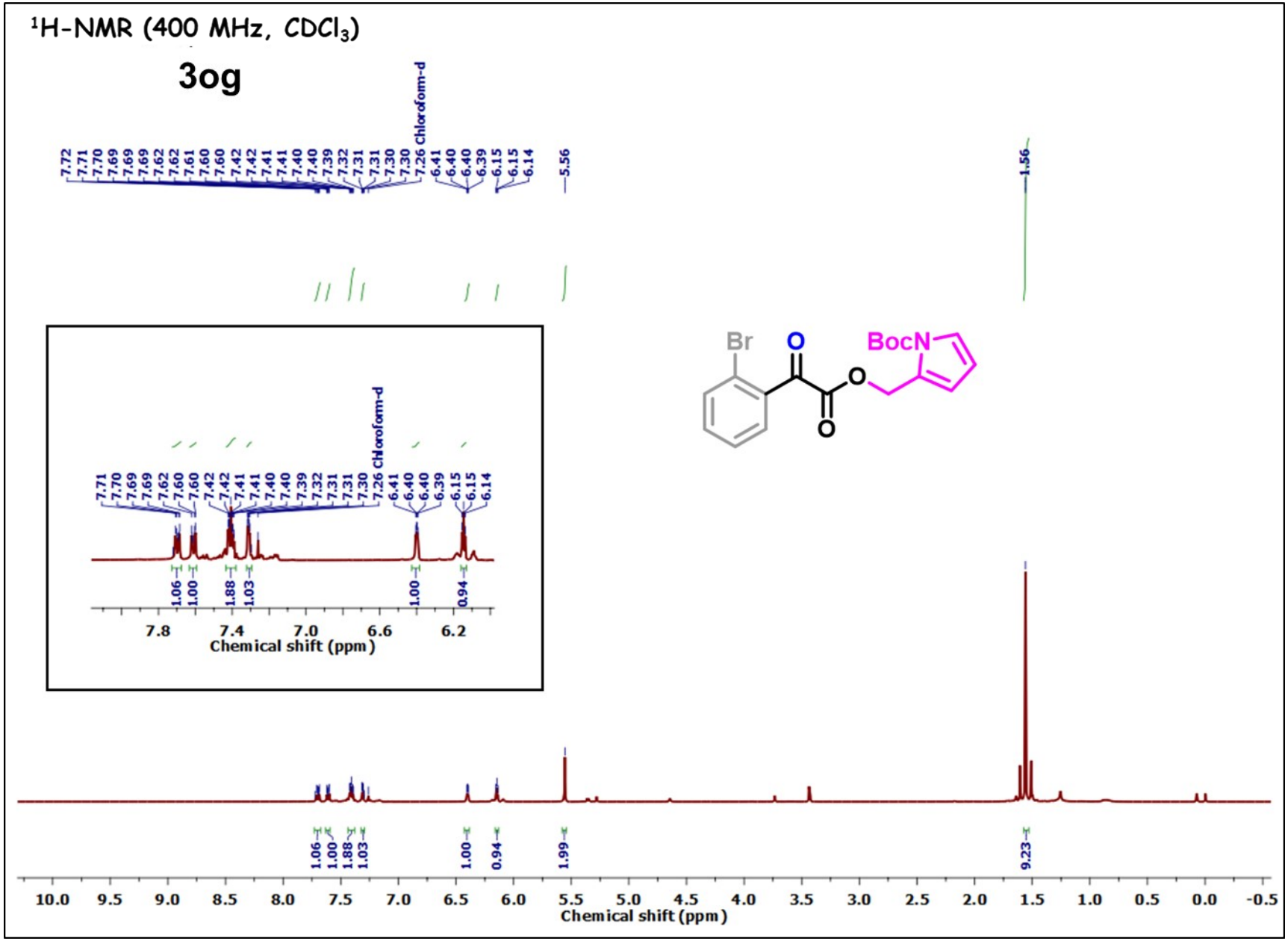
$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)

3pg



^{1}H-NMR (400 MHz, $CDCl_3$)

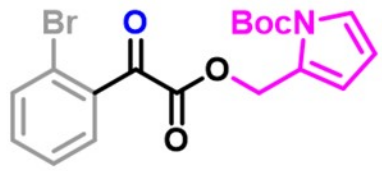
3og

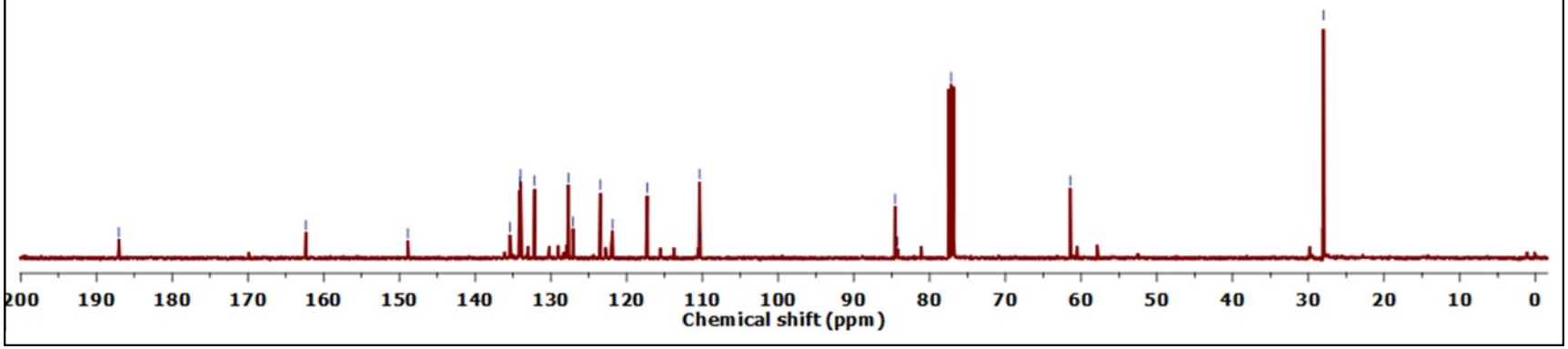


$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)

3og

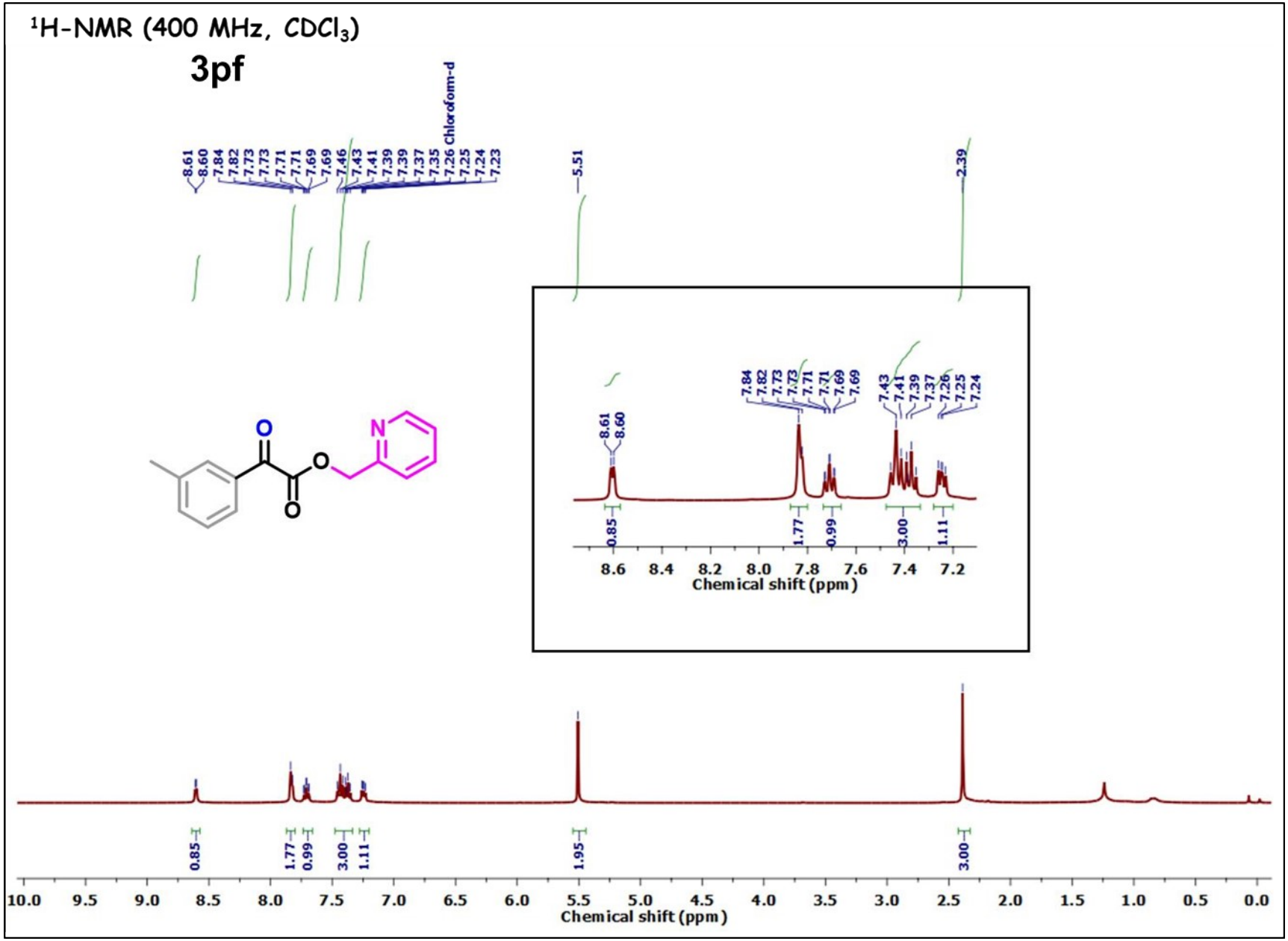
187.04
162.33
148.89
135.40
134.11
134.00
132.15
127.70
127.07
123.45
121.88
117.29
110.37
110.27
84.55
84.23
77.16 Chloroform-d
61.44
28.01



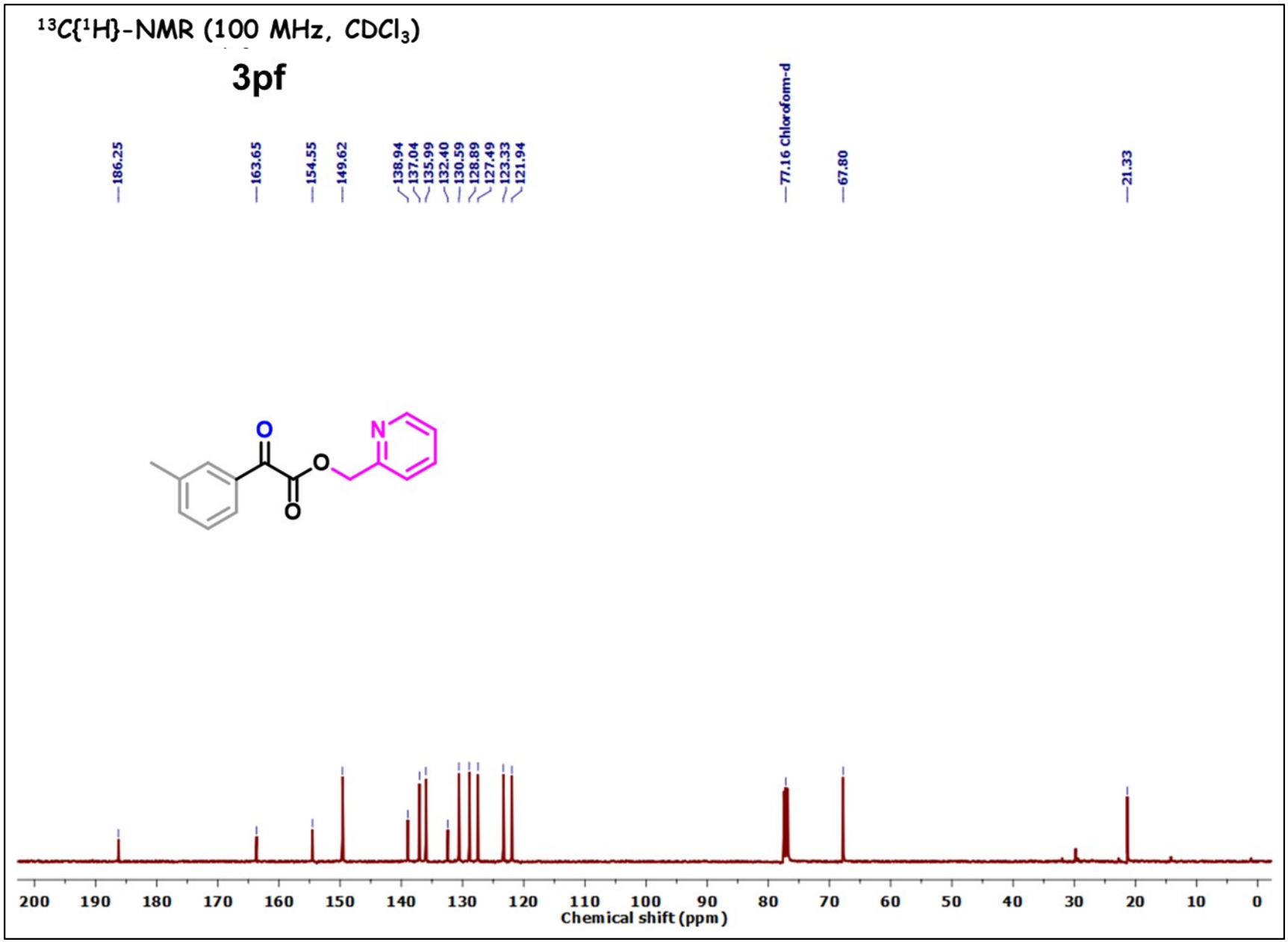


^{1}H-NMR (400 MHz, $CDCl_3$)

3pf

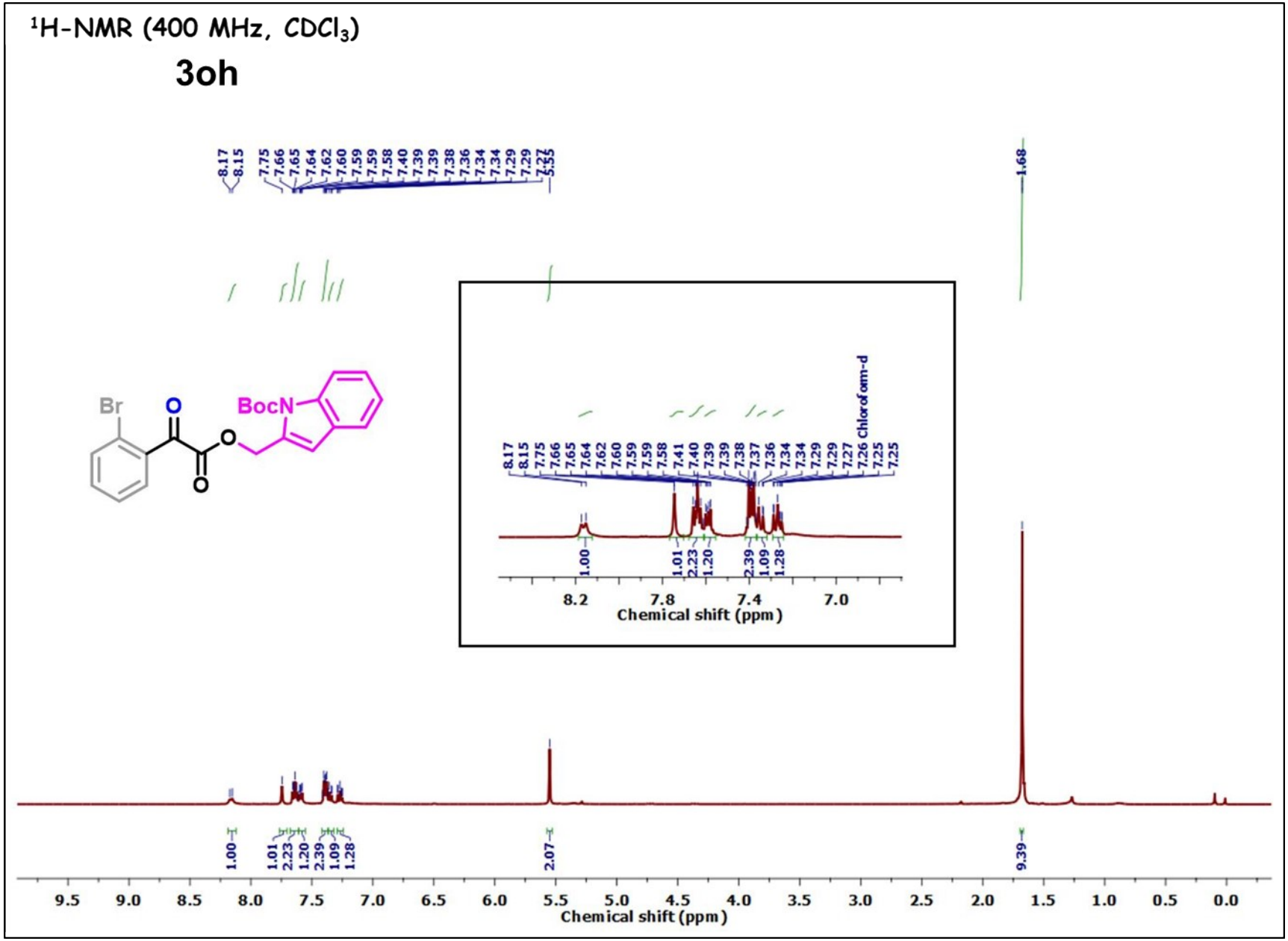


$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)



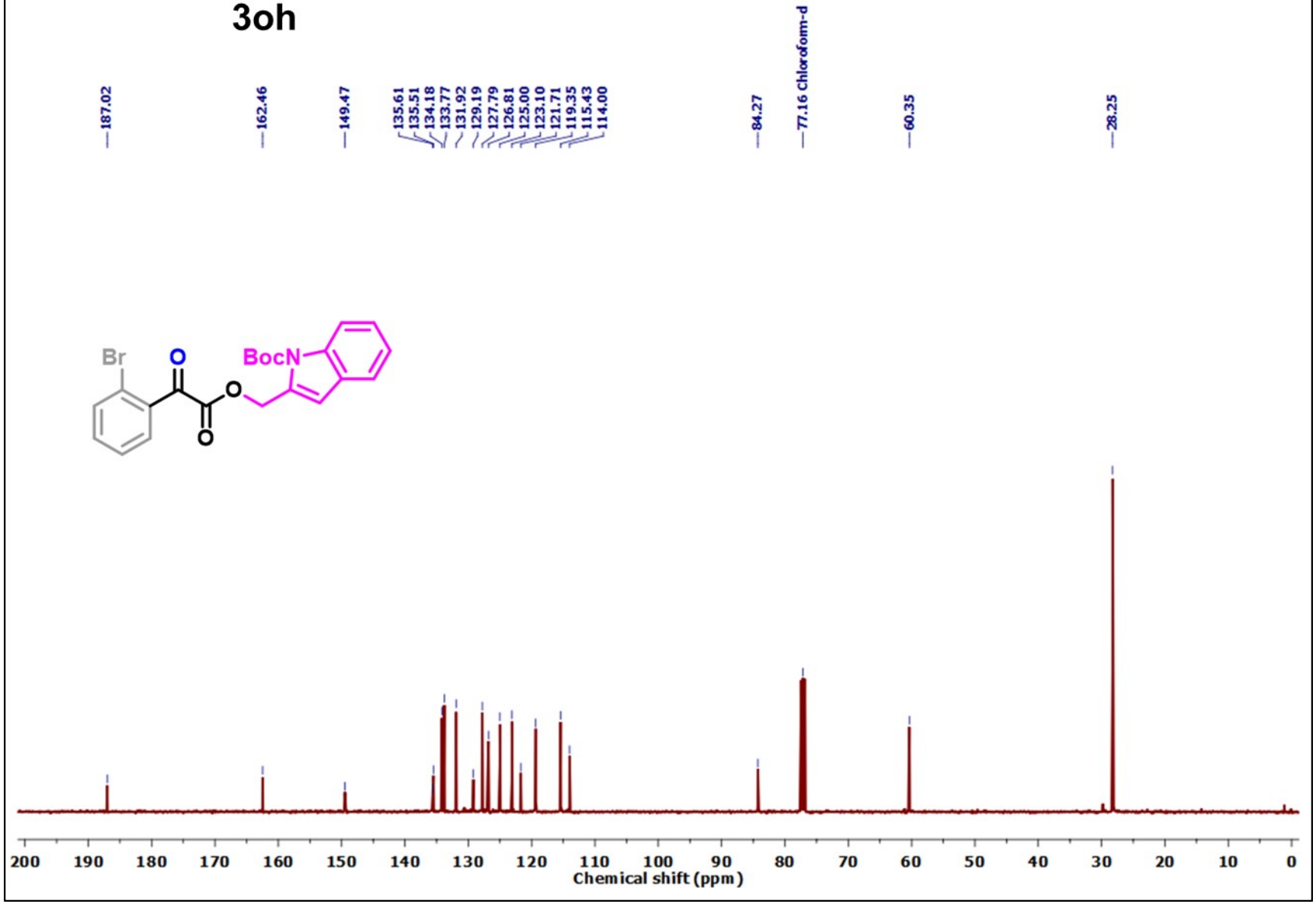
^{1}H-NMR (400 MHz, $CDCl_3$)

3oh



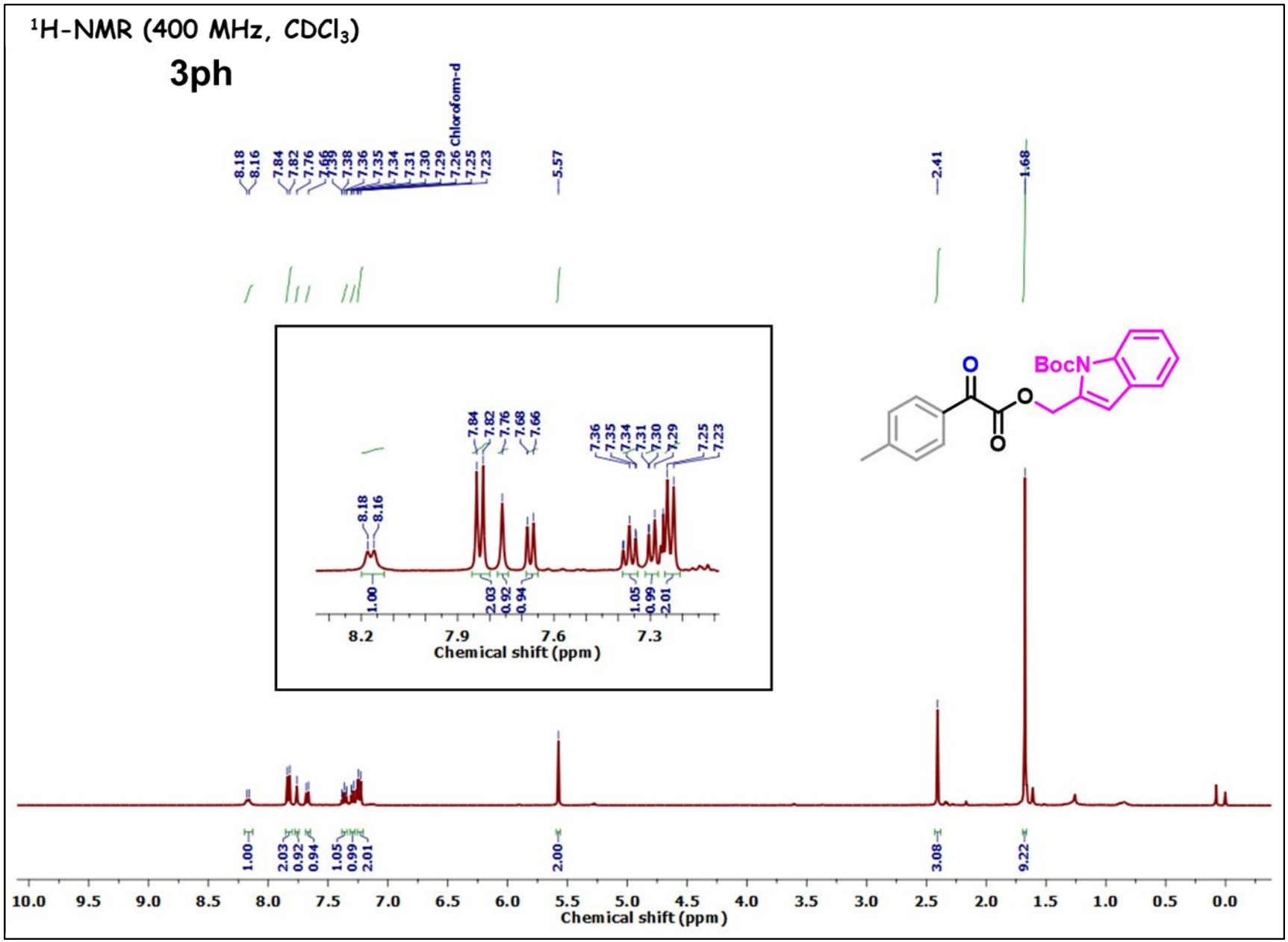
$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)

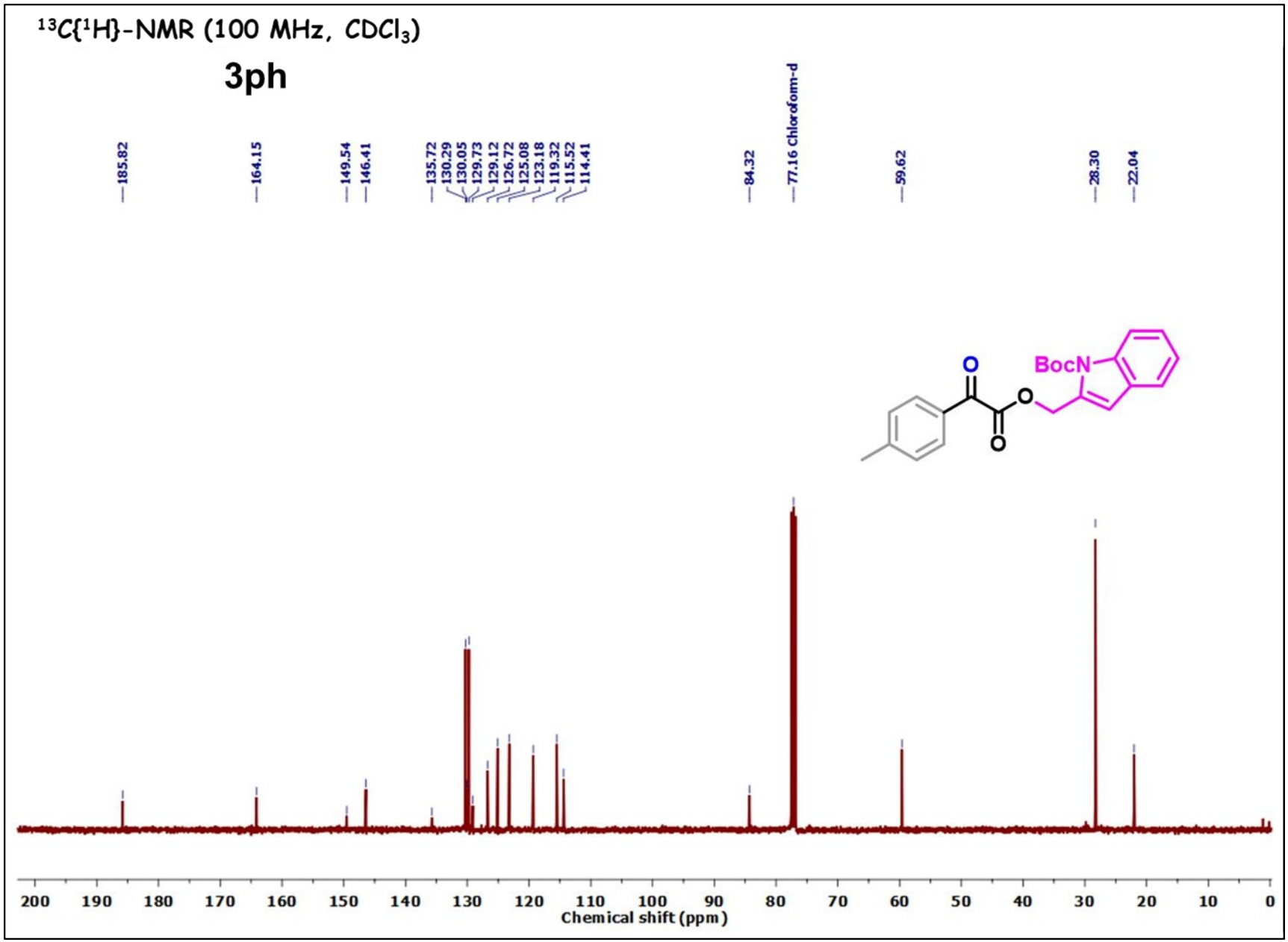
3oh



^{1}H-NMR (400 MHz, $CDCl_3$)

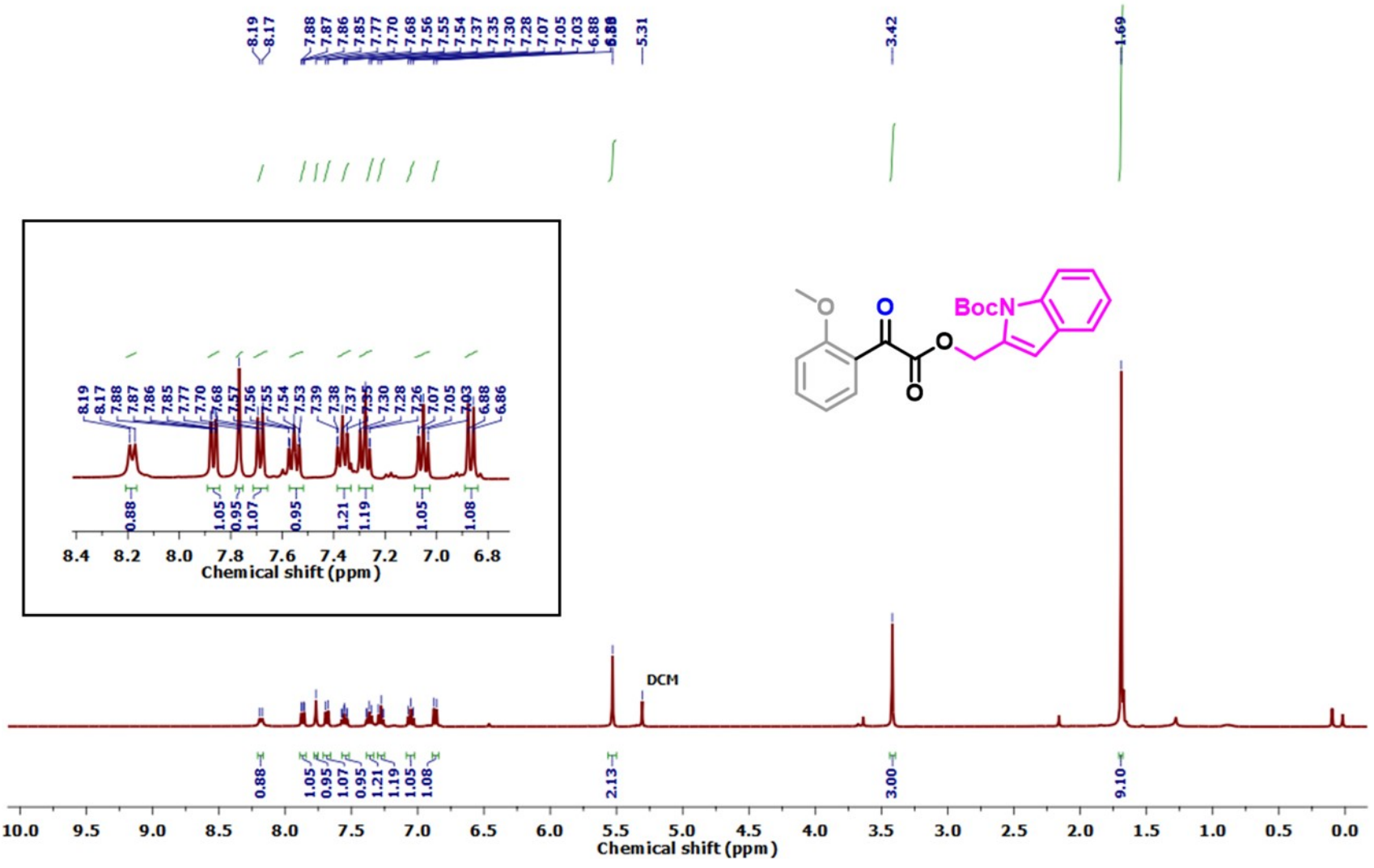
3ph



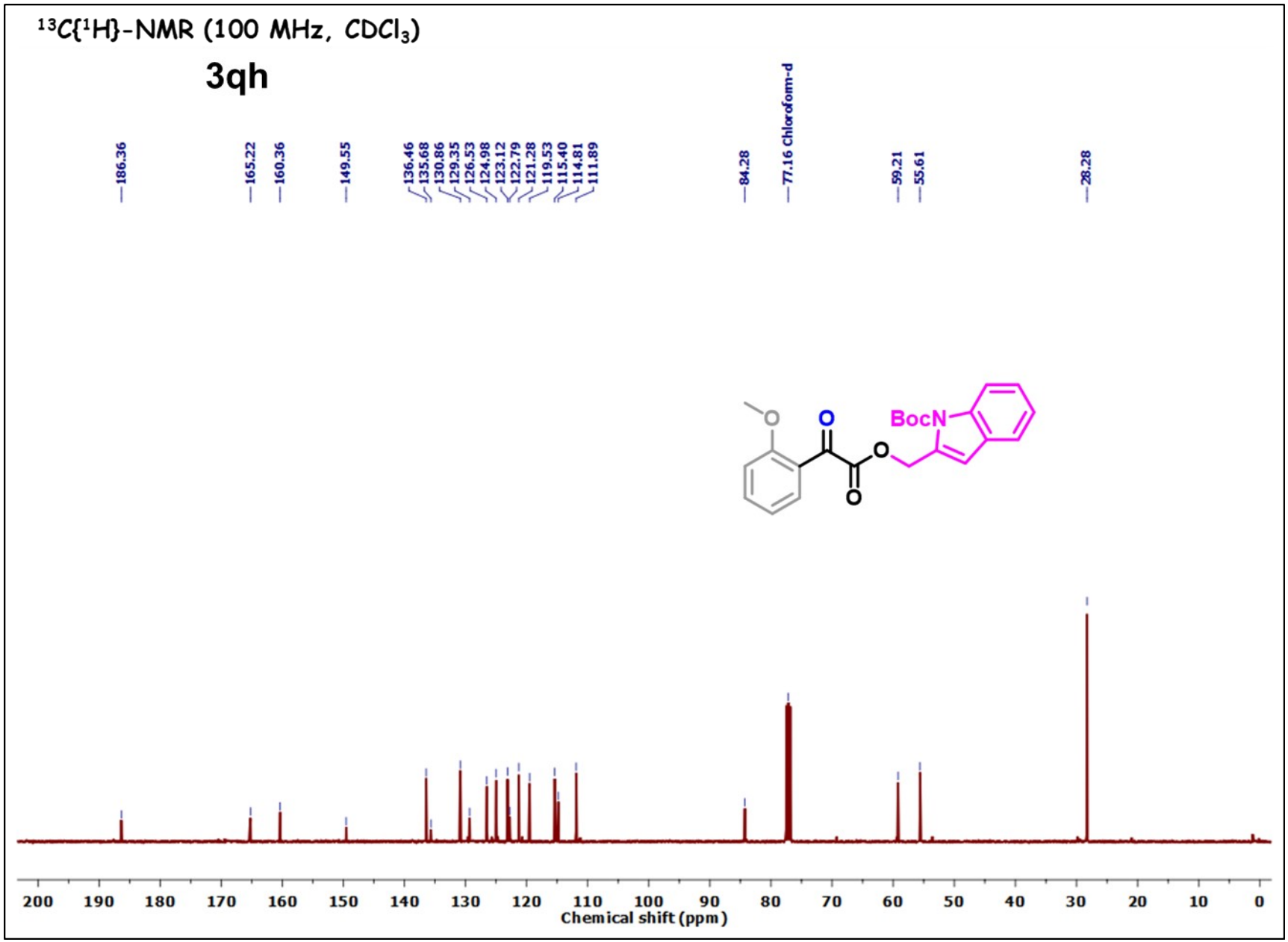

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)
3ph
185.82
164.15
149.54
146.41
135.72
130.29
130.05
129.73
129.12
126.72
125.08
123.18
119.32
115.52
114.41
84.32
77.16 Chloroform-d
59.62
28.30
22.04
O
BocN
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical shift (ppm)

^{1}H-NMR (400 MHz, $CDCl_3$)

3qh

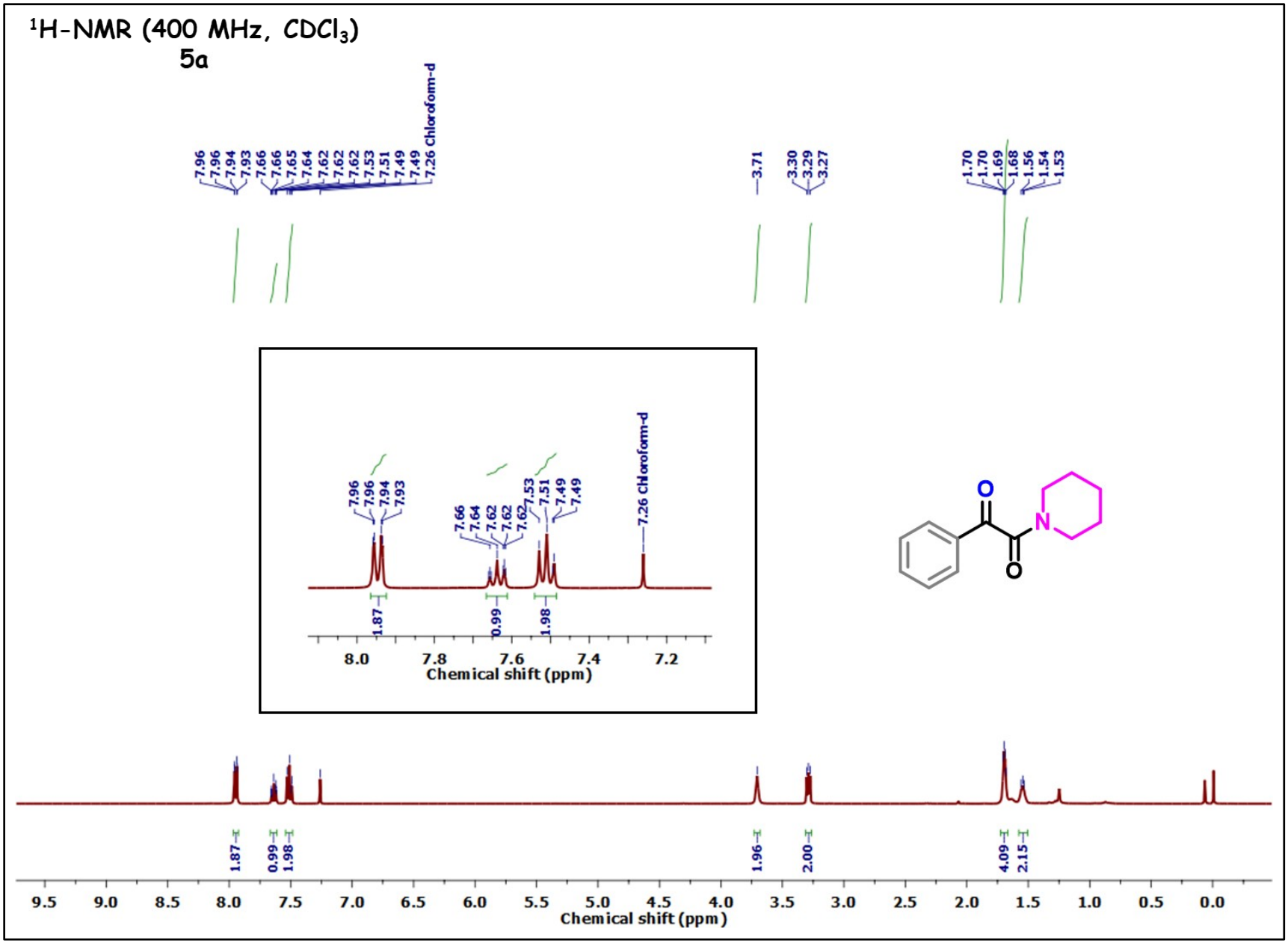


$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)



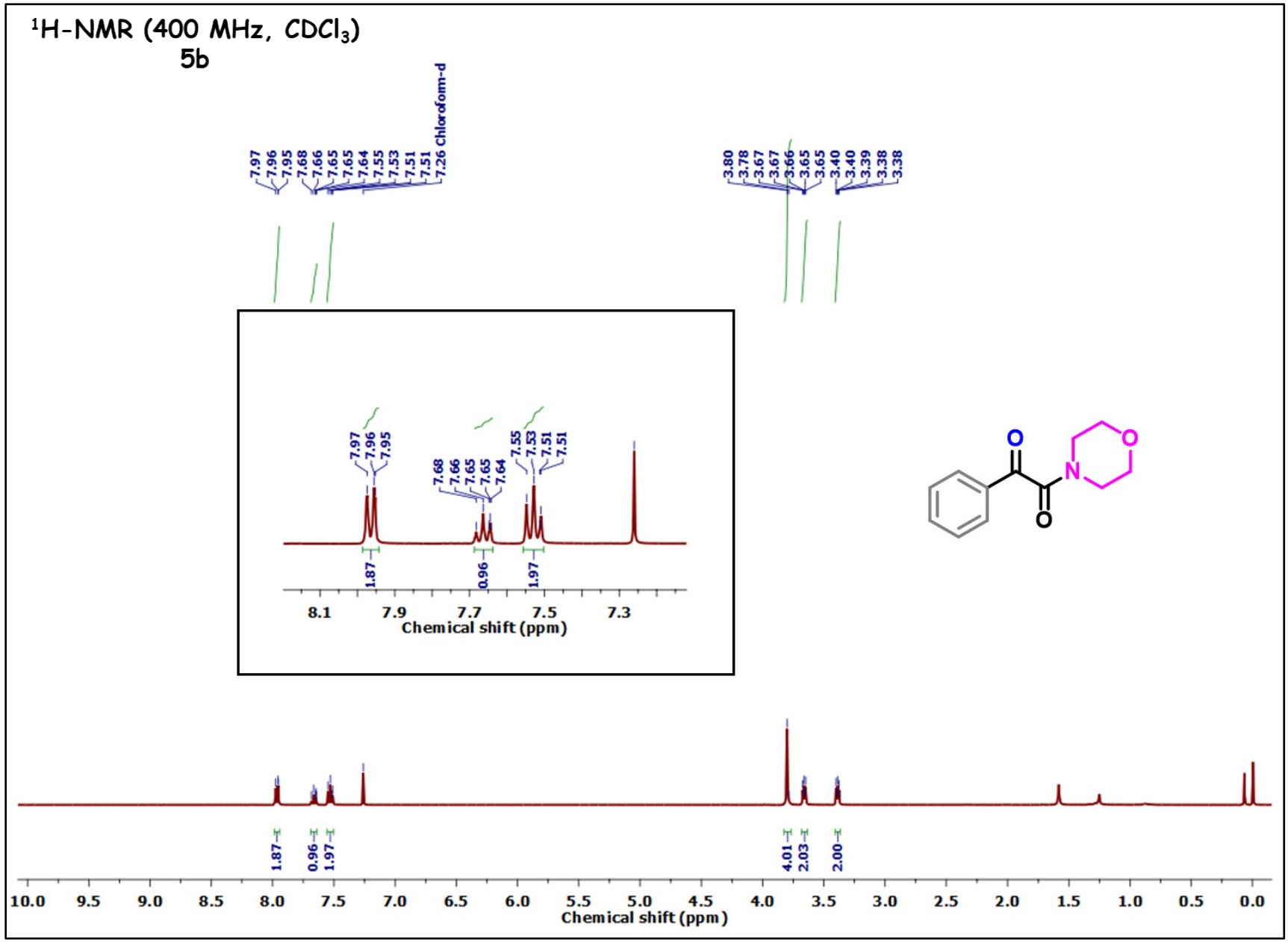
^{1}H-NMR (400 MHz, $CDCl_3$)

5a



^{1}H-NMR (400 MHz, $CDCl_3$)

5b



^{1}H-NMR (400 MHz, $CDCl_3$)

8