Autocatalytic and DMSO-Promoted Regioselective Synthesis of Pyrimidine-Fused Quinolines from Anilines and Barbituric Acids

Pushpendra Yadav,[a,b] Deblina Chatterjee,[a] Suman Bhowmick,[a,b] Khushboo Tiwari,[a,b] Annapurna Awasthi,[a,b] and Dharmendra Kumar Tiwari*[†]

[a] Department of Biological and Synthetic Chemistry, Center of Biomedical Research (CBMR), SGPGIMS Campus, Raibareli Road, Lucknow, U.P. 226014, INDIA. Email: dkt80.org@gmail.com & dktiwari@cbmr.res.in

[b] Department of Chemistry, Institute of Science, Banaras Hindu Universiy, 221005, U.P. INDIA.

[c] Academy of Scientific & Innovative Research (AcSIR), CSIR- Human Resource Development Centre, (CSIR-HRDC) Campus Ghaziabad, Uttar Pradesh- 201 002.

Table of Contents

EXPERIMENTAL SECTION

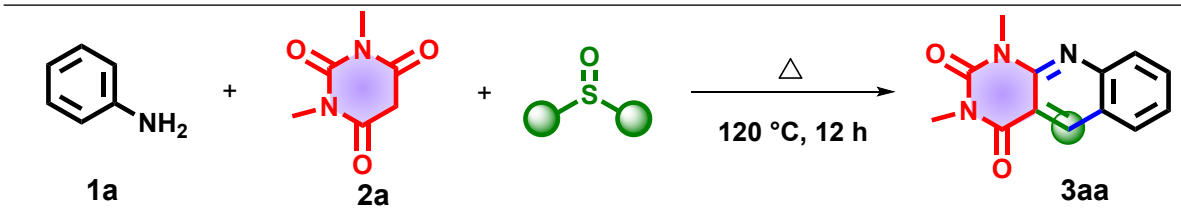
General Information

All reagents were purchased from Sigma Aldrich, Thermo-Fischer, TCI, and local vendors and were used without further purification. All experiments were carried out in ace pressure tubes. All the solvents used for the reaction were distilled before use. The product purification by column chromatography was accomplished using silica gel 100-200 mesh. Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. ^{1}H, ^{13}C NMR spectra were recorded on Avance III, and Bruker at 400 MHz, 101 MHz, and 376 MHz spectrometers respectively using $CDCl_3$. In the experimental section, the ^{1}H NMR chemical shifts are expressed in the form of ppm (δ) relative to δ = 7.26 for $CDCl_3$ whereas $^{13}C\{^{1}H\}$ NMR chemical shift are expressed relative to δ = 77.00. Multiplicities in the

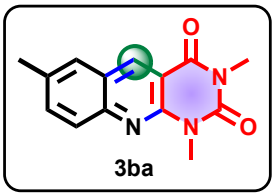
^{1}H NMR spectra are described as a s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet; coupling constants are reported in Hz. HRMS and Electron Spray Ionization (ESI) (m/z) spectra were recorded on Agilent Technologies 6530 Accurate- Mass Q-TOF LC/MS.

***General Procedure (GP1) for the Synthesis of 1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione* (3aa):**

A solution of aniline (**1a**, 1.0 mmol, 0.091 mL), 1,3-dimethyl barbituric acid (**2a**, 1.2 mmol; 0.19 g), and DMSO (3.0 mL) was placed in an Ace pressure tube and heated in a preheated oil bath at 120 °C. The mixture was stirred for 12 hours. After completion of the reaction, the mixture was allowed to cool to room temperature and was then diluted with ethyl acetate (10 mL). The organic layer was washed successively with water (10 mL), sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using a 20% ethyl acetate/hexane mixture on 100-200 mesh silica gel to afford the product **3aa** as a white solid (0.17 g, 70% yield); **Mp** 204 – 206 °C.; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.01 (s, 1H), 7.97 – 7.94 (m, 2H), 7.83 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.53 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.57, 151.78, 150.00, 148.55, 140.21, 133.31, 129.39, 128.25, 125.95, 124.83, 110.99, 29.79, 28.68; **HRMS** (ESI) m/z calcd for $C_{13}H_{12}N_3O_2$ [M+H] is 242.0885, found 242.0920.

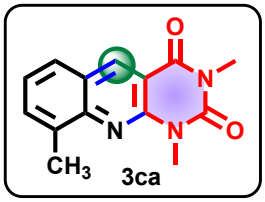


***1,3,7-trimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione* (3ba):**



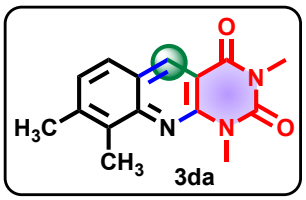
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2b**) to afford the compound **3ba** as a white solid (0.18 g, 71% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 80:20); **Mp:** 182 – 184 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.83 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.66 – 7.59 (m, 2H), 3.77 (s, 3H), 3.49 (s, 3H), 2.52 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.56, 151.66, 148.44, 147.90, 139.21, 135.82, 135.61, 127.90, 127.83, 124.75, 110.76, 29.65, 28.59, 21.52; HRMS (ESI) m/z calcd for $C_{14}H_{14}N_3O_2$ $[M+H]^+$ is 256.1081, found 256.1076.

1,3,9-trimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ca):**



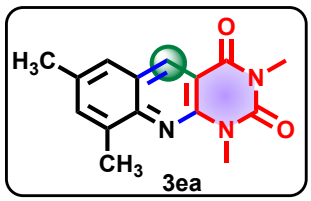
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2c**) to afford the compound **3ca** as a white solid (0.19 g, 73% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:10); **Mp:** 203 - 205 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.83 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.66 – 7.59 (m, 2H), 3.77 (s, 3H), 3.49 (s, 3H), 2.52 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.40, 151.51, 148.28, 147.74, 139.06, 135.67, 135.45, 127.74, 127.67, 124.59, 110.61, 29.49, 28.43, 21.37; **HRMS** (ESI) m/z calcd for $C_{14}H_{14}N_3O_2$ $[M+H]^+$ is 256.1081, found 256.1075.

1,3,8,9-tetramethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3da):**



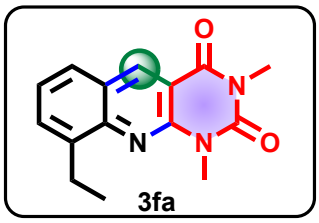
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2d**) to afford the compound **3da** as a white solid (0.2 g, 75% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 80:20); **Mp:** 220 – 222 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.83 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 2.65 (s, 3H), 2.51 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.54, 151.69, 148.50, 147.24, 141.66, 139.81, 133.40, 128.72, 126.00, 122.93, 109.35, 29.43, 28.41, 21.11, 13.28; **HRMS** (ESI) m/z calcd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$ is 270.1237, found 270.1252.

1,3,7,9-tetramethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ea):**



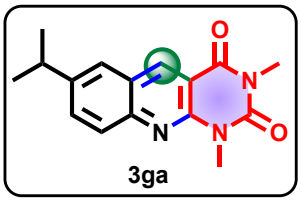
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2e**) to afford the compound **3ea** as a white solid (0.2 g, 74% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 80:20); **Mp:** 220 – 222 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.60 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 3.65 (s, 3H), 3.43 (s, 3H), 2.58 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.24, 151.35, 146.93, 146.40, 138.75, 135.55, 135.18, 125.34, 124.31, 109.90, 29.18, 28.29, 21.32, 17.55; **HRMS** (ESI) m/z calcd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$ is 270.1237, found 270.1251.

9-ethyl-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3fa):**



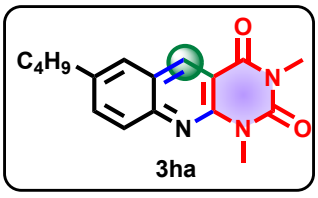
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2f**) to afford the compound **3fa** as a white solid (0.19 g, 73% yield); $\mathbf{R}_f$ = 0.3 (PE : EA = 90:10); **Mp:** 175 – 177 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.97 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 6.9 Hz, 1H), 7.49 – 7.41 (m, 1H), 3.83 (s, 3H), 3.53 (s, 3H), 3.23 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.55, 151.71, 148.19, 147.34, 141.91, 140.23, 131.57, 127.05, 125.69, 124.71, 110.39, 29.50, 28.49, 24.79, 14.52; **HRMS** (ESI) m/z calcd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$ is 270.1237, found 270.1216.

7-isopropyl-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ga):**



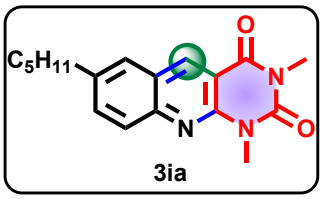
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2g**) to afford the compound **3ga** as a white solid (0.22 g, 76% yield); $\mathbf{R}_f$ = 0.3 (PE : EA = 90:10); **Mp:** 164 – 166 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.85 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.71 – 7.64 (m, 2H), 3.74 (s, 3H), 3.46 (s, 3H), 3.12 – 3.01 (m, 1H), 1.33 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 161.29, 151.43, 148.55, 147.75, 146.29, 139.29, 133.14, 127.79, 124.98, 124.55, 110.49, 33.77, 29.42, 28.35, 23.63; **HRMS** (ESI) m/z calcd for $C_{16}H_{18}N_3O_2$ $[M+H]^+$ is 284.1394, found 284.1409.

7-butyl-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ha):**



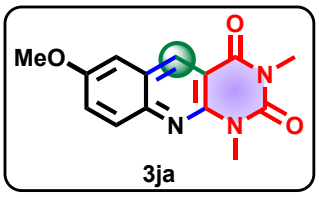
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2h**) to afford the compound **3ha** as a white solid (0.23 g, 76% yield); $\mathbf{R}_f$ = 0.3 (PE : EA = 90:10); **Mp:** 181 – 183 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.80 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.58 (m, 2H), 3.73 (s, 3H), 3.45 (s, 3H), 2.75 (t, *J* = 7.7 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.43 – 1.33 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, CDCl3)** δ 161.27, 151.40, 148.37, 147.66, 140.49, 139.08, 134.70, 127.65, 127.06, 124.51, 110.46, 35.26, 33.11, 29.41, 28.35, 22.27, 13.87; **HRMS** (ESI) m/z calcd for $C_{17}H_{20}N_3O_2$ $[M+H]^+$ is 298.1550, found 298.1546.

1,3-dimethyl-7-pentylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ia):**



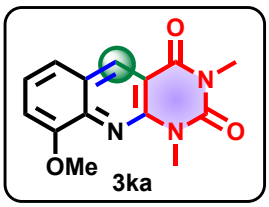
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2i**) to afford the compound **3ia** as a white solid (0.24 g, 78% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:10); **Mp:** 148 – 150 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.80 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 3H), 3.45 (s, 3H), 2.74 (t, *J* = 7.6 Hz, 2H), 1.73 – 1.62 (m, 2H), 1.35 - 132 (m, 4H), 0.89 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.27, 151.41, 148.38, 147.66, 140.53, 139.09, 134.70, 127.65, 127.06, 124.51, 110.46, 77.32, 77.00, 76.68, 35.53, 31.37, 30.67, 29.41, 28.35, 22.44, 13.96; **HRMS** (ESI) m/z calcd for $C_{18}H_{22}N_3O_2$ $[M+H]^+$ is 312.1707, found 312.1700.

7-methoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ja):**



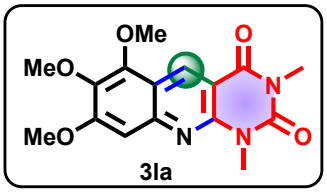
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2g**) to afford the compound **3ja** as a yellow solid (0.22 g, 80% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:10); **Mp:** 258 – 260 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.86 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.47 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H); **^{13}C NMR** (101 MHz, CDCl3) δ 161.52, 157.13, 151.55, 146.87, 145.98, 138.18, 129.43, 126.34, 125.50, 110.81, 105.76, 55.64, 29.51, 28.49; **HRMS** (ESI) m/z calcd for $C_{14}H_{14}N_3O_3$ $[M+H]^+$ is 272.1030, found 270.1025.

9-methoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ka):**



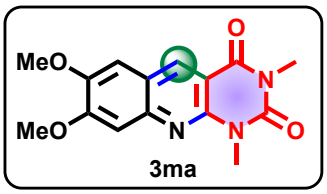
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2k**) to afford the compound **3ka** as a white solid (0.21 g, 79% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 80:20); **Mp:** 245 – 247 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.98 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.52 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.35, 154.37, 151.60, 147.69, 141.52, 140.05, 125.85, 125.74, 120.92, 111.38, 111.10, 56.32, 29.71, 28.53; **HRMS** (ESI) m/z calcd for $C_{14}H_{14}N_3O_3$ $[M+H]^+$ is 272.1030, found 272.1041.

6,7,8-trimethoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3la):**



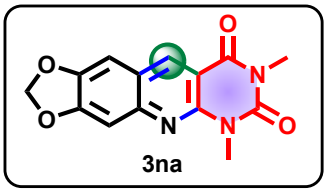
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2l**) to afford the compound **3la** as a white solid (0.28 g, 84% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 70:30); **Mp**: 210 – 212 °C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 9.07 (s, 1H), 7.03 (s, 1H), 4.12 (s, 3H), 4.04 (s, 3H), 3.97 (s, 3H), 3.75 (s, 3H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 161.36, 159.48, 151.57, 148.45, 148.05, 147.92, 139.48, 134.37, 115.97, 108.05, 102.37, 61.65, 61.26, 56.24, 29.38, 28.30; **HRMS** (ESI) m/z calcd for $C_{16}H_{18}N_3O_5$ $[M+H]^+$ is 332.1241, found 332.1237.

7,8-dimethoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ma):**



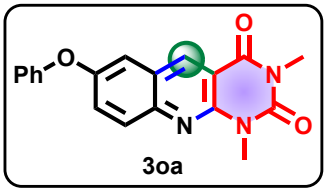
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2m**) to afford the compound **3ma** as a brown solid (0.25 g, 83% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 60:40); **Mp:** 270 – 275 °C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.69 (s, 1H), 7.24 (s, 1H), 7.06 (s, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 3.75 (s, 3H), 3.45 (s, 3H); **^{13}C NMR (101MHz, CDCl$_3$)** δ 161.50, 155.61, 151.54, 149.24, 147.57, 147.42, 137.02, 120.07, 108.49, 106.56, 105.80, 56.36, 56.11, 29.40, 28.32; **HRMS** (ESI) m/z calcd for $C_{15}H_{16}N_3O_4$ $[M+H]^+$ is 302.1135, found 302.1117.

6,8-dimethyl-[1,3]dioxolo[4,5-g]pyrimido[4,5-b]quinoline-7,9(6H,8H)-dione **(3na):**



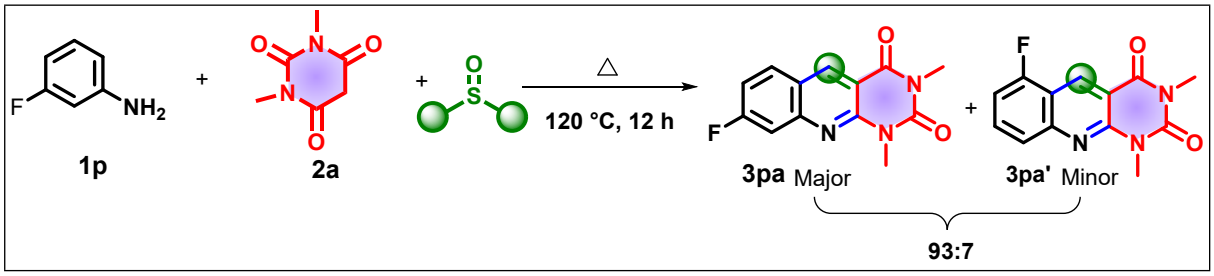
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2n**) to afford the compound **3na** as a sticky solid (0.23 g, 85% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 80:20); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.87 (s, 1H), 7.39 (d, J = 2.4 Hz, 2H), 6.28 (s, 2H), 3.91 (s, 3H), 3.64 (s, 3H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 161.61, 153.92, 149.15, 147.54, 147.50, 137.53, 121.45, 108.62, 104.73, 103.55, 102.25, 29.45, 28.44; **HRMS** (ESI) m/z calcd for $C_{14}H_{12}N_3O_4$ $[M+H]^+$ is 286.0822, found 286.0820.

1,3-dimethyl-7-phenoxypyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3oa):**



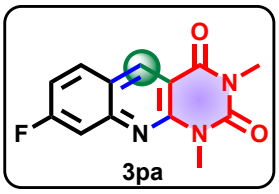
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2o**) to afford the compound **3oa** as a white solid (0.28 g, 84% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 60:40); **Mp:** 197 – 199 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.84 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.61 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 3.82 (s, 3H), 3.52 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.31, 156.11, 155.17, 151.54, 147.55, 146.59, 138.83, 130.09, 129.91, 126.91, 125.32, 124.36, 119.63, 113.55, 111.13, 29.59, 28.53; **HRMS** (ESI) m/z calcd for $C_{19}H_{16}N_3O_3$ $[M+H]^+$ is 334.1186, found 334.1174.

8-fluoro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3pa):**

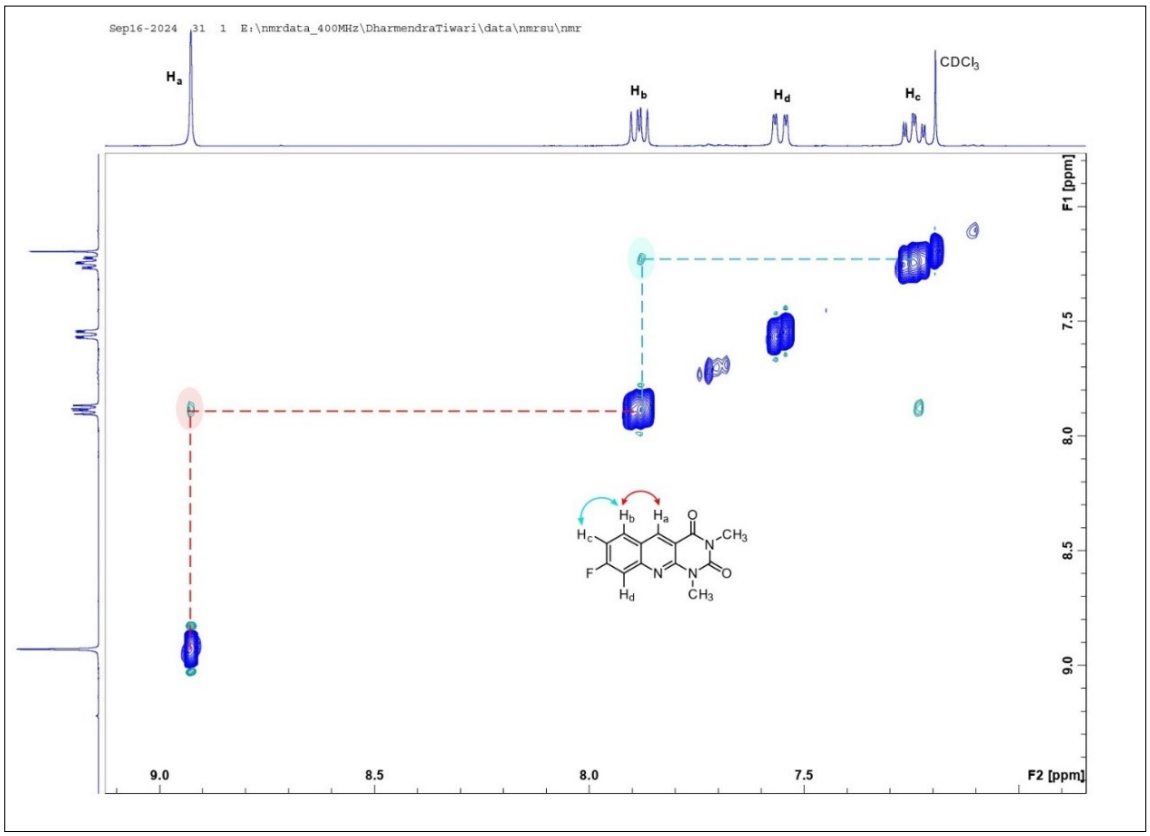


The general procedure (**GP1**) was followed on a 2.0 mmol scale (**2p**) to afford an inseparable mixture of **3pa** and **3pa'** in a 93:7 ratio confirmed by ^{1}H NMR.

The compound was purified by column chromatography using a 20% of ethylacetate: hexane solvent system furnished a mixture of **3pa** and **3pa'** as a white solid in a 93:7 ratio. The ^{1}H, ^{13}C, and melting point (Mp) of the mixture of **3pa** and **3pa'** were recorded. In the ^{1}H, and ^{13}C, NMR spectra, the peaks corresponding to the major product, **3pa**, were assigned.



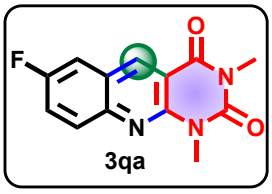
White solid (0.18 g, 68% yield); R_f = 0.3 (PE : EA = 80:20); Mp: 218 – 220 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.95 (s, 1H), 7.92 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.59 (dd, *J* = 10.1, 2.0 Hz, 1H), 7.29 (td, *J* = 8.8, 2.4 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.78 and 164.24 (d, $J_{(C-F)}$ = 255.4 Hz), 161.17, 151.47, 151.33 and 151.18 (d, $J_{(C-F)}$ = 14.1 Hz), 149.18, 139.78, 131.58, 131.48, 121.68, 116.70 and 116.44 (d, $J_{(C-F)}$ = 25.7 Hz), 112.14 and 111.93 (d, $J_{(C-F)}$ = 21.0 Hz), 29.64, 28.51; **^{19}F NMR (375 MHz, $CDCl_3$):** δ -102.96; **HRMS** (ESI) m/z calcd for $C_{13}H_{11}FN_3O_2$ $[M+H]^+$ is 260.0830, found 260.0844.



2D-NOESY spectra of **3pa**

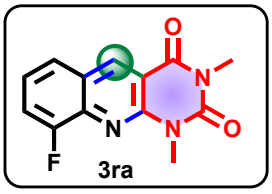
2D-NOESY spectra of **3pa:** Assigned interactions (red dotted lines) shown below easily indicate that H_a and H_b are close enough in major regioisomer, whereas in minor isomer fluorine atom easily substitutes H_b. Green-colored (dotted line) interaction proved that H_b and H_c are in ortho positions.

7-fluoro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3qa):**



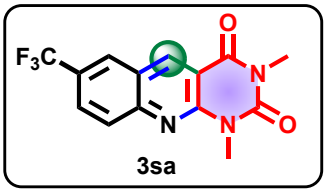
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2q**) to afford the compound **3qa** as a white solid (0.18 g, 69% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:10); **Mp:** 238 – 240 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.93 (s, 1H), 7.98 (dd, J = 8.9, 5.0 Hz, 1H), 7.63 – 7.51 (m, 2H), 3.80 (s, 3H), 3.52 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.10, 160.87 and 151.43 (d, $J_{(C-F)}$ = 248.6 Hz), , 147.95, 146.84, 139.24 and 139.19 (d, $J_{(C-F)}$ = 5.7 Hz), 130.51 and 130.43 (d, $J_{(C-F)}$ = 8.9 Hz), 124.98 and 124.88 (d, $J_{(C-F)}$ = 10.1 Hz), 123.55 and 123.29 (d, $J_{(C-F)}$ = 26 Hz), 112.00 and 111.78 (d, $J_{(C-F)}$ = 21.8 Hz), 111.45, 29.61, 28.57; **^{19}F NMR (375 MHz, $CDCl_3$):** δ -113.76; **HRMS** (ESI) m/z calcd for $C_{13}H_{11}FN_3O_2$ $[M+H]^+$ is 260.0830, found 260.0838.

9-fluoro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ra):**



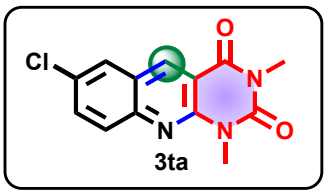
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2r**) to afford the compound **3ra** as a sticky solid (0.26 g, 70% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:21); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.03 (d, J = 1.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.48 – 7.43 (m, 1H), 3.85 (s, 3H), 3.53 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.07, 158.35 and 155.79 (d, $J_{(C\text{-}F)}$ = 257.2 Hz), 151.44, 148.54, 139.96 and 139.93 (d, $J_{(C\text{-}F)}$ = 2.9 Hz), 139.90 and 139.79 (d, $J_{(C\text{-}F)}$ = 11.6 Hz), 126.24 and 126.22 (d, $J_{(C\text{-}F)}$ = 2.2 Hz), 125.40 and 125.32 (d, $J_{(C\text{-}F)}$ = 7.5 Hz), 124.84 and 124.79 (d, $J_{(C\text{-}F)}$ = 4.8 Hz), 117.19 and 117.00 (d, $J_{(C\text{-}F)}$ = 18.7 Hz), 111.72, 29.78, 28.60; **^{19}F NMR (375 MHz, $CDCl_3$):** δ -124.84; **HRMS** (ESI) m/z calcd for $C_{13}H_{11}FN_3O_2$ $[M+H]^+$ is 260.0830, found 260.0848.

1,3-dimethyl-7-(trifluoromethyl)pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3sa):**



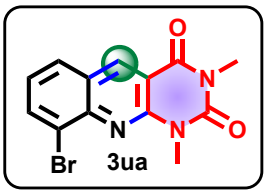
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2s**) to afford the compound **3sa** as a white solid (0.2 g, 67% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 70:30); **Mp:** 186 – 188 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.08 (s, 1H), 8.24 (s, 1H), 8.09 (d, J = 8.9 Hz, 1H), 7.96 (dd, J = 8.9, 1.7 Hz, 1H), 3.83 (s, 3H), 3.53 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.80, 151.37, 150.85, 149.90, 140.86, 129.28, 128.58 (q, $J_{(C\text{-}F)}$ = 2.9 Hz), 127.08 ($J_{(C\text{-}F)}$ = 4.3 Hz), 123.44 (t, $J_{(C\text{-}F)}$ = 272.2 Hz), , 111.95, 77.00, 29.79, 28.63. **^{19}F NMR (375 MHz, $CDCl_3$):** δ -62.43; HRMS (ESI) m/z calcd for $C_{14}H_{11}F_3N_3O_2$ $[M+H]^+$ is 310.0798, found 310.0810.

7-chloro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ta):**



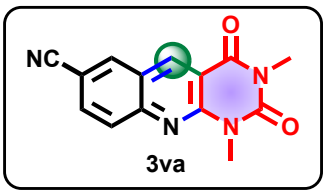
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2t**) to afford the compound **3ta** as a sticky solid (0.2 g, 71% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:10); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.91 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 3.53 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.07, 151.44, 148.59, 148.21, 139.05, 133.93, 131.41, 129.68, 127.55, 125.13, 111.57, 29.69, 28.61; **HRMS** (ESI) m/z calcd for $C_{13}H_{11}ClN_3O_2$ $[M+H]^+$ is 276.0534, found 276.0533.

9-bromo-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ua):**



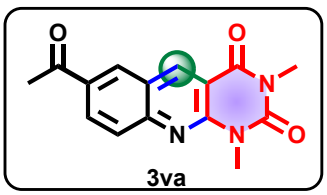
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2u**) to afford the compound **3ua** as a white solid (0.28 g, 70% yield); $\mathbf{R_f}$ = 0.3 (PE:EA = 90:10); **Mp:** 243 – 245 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.34 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.68 – 7.61 (m, 1H), 3.83 (s, 3H), 3.54 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 160.95, 151.49, 150.57, 149.00, 139.92, 133.13, 129.47, 127.91, 124.52, 123.38, 111.71, 29.77, 28.63; **HRMS** (ESI) m/z calcd for $C_{13}H_{11}BrN_3O_2$ $[M+H]^+$ is 320.0029, found 320.0030.

1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-b]quinoline-7-carbonitrile **(3va):**



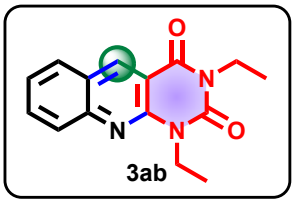
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2v**) to afford the compound **3va** as a white solid (0.18 g, 66% yield); $\mathbf{R_f}$ = 0.3 (PE : EA = 90:10); **Mp:** 239 – 241 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.06 (s, 1H), 8.34 (d, *J* = 1.3 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.94 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.84 (s, 3H), 3.54 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.60, 151.26, 150.89, 150.41, 140.48, 135.28, 133.40, 129.60, 123.85, 118.09, 112.38, 109.42, 29.91, 28.72; **HRMS** (ESI) m/z calcd for $C_{14}H_{11}N_4O_2$ $[M+H]^+$ is 267.0877, found 267.0876.

7-acetyl-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3wa):**



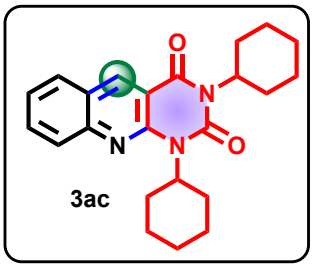
The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2w**) to afford the compound **3wa** as a white solid (0.2 g, 69% yield); $\mathbf{R_f}$ = 0.3 (PE:EA = 80:20); **Mp:** 258 – 260 °C; Hexane/Ethyl acetate (60/40, v/v); White solid; isolated yield: %. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.04 (s, 1H), 8.47 (d, *J* = 1.4 Hz, 1H), 8.30 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.47 (s, 3H), 2.67 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.78, 161.08, 152.08, 151.59, 150.23, 141.62, 134.33, 131.40, 131.33, 128.79, 123.89, 111.85, 29.96, 28.77, 26.74; **HRMS** (ESI) m/z calcd for $C_{15}H_{14}N_3O_3$ $[M+H]^+$ is 284.1030, found 284.1035.

1,3-diethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione **(3ab):**



The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2a**) to afford the compound **3ab** as a white solid (0.19 g, 72% yield); $\mathbf{R_f}$ = 0.3 (PE:EA = 90:10); **Mp:** 143 – 145 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.02 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.12, 150.70, 150.02, 147.94, 140.02, 132.96, 129.19, 128.22, 125.65, 124.71, 111.21, 37.81, 37.08, 13.21, 13.11; **HRMS** (ESI) m/z calcd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$ is 270.1237, found 270.1247.

***1,3-dicyclohexylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione* (3ac):**

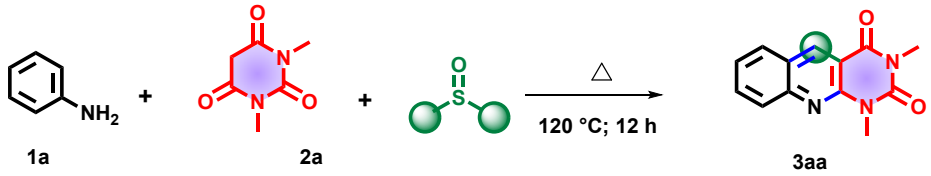


3ac

The general procedure (**GP1**) was followed on a 1.0 mmol scale (**2a**) to afford the compound **3ac** as a white solid (0.25 g, 66% yield); $\mathbf{R_f}$ = 0.3 (PE:EA = 90:10); **Mp:** 248 – 250 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.00 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 5.57 (s, 1H), 5.00 – 4.83 (m, 1H), 2.75 – 2.71 (m, 2H), 2.56 – 2.47 (m, 2H), 1.96 – 1.88 (m, 4H), 1.80 – 1.70 (m, 6H), 1.59 – 1.27 (m, 6H); **^{13}C NMR (101 MHz, CDCl3)**: δ 161.75, 150.88, 149.44, 148.57, 140.03, 132.72, 129.03, 128.15, 125.54, 124.62, 111.90, 55.41, 55.12, 29.03, 28.99, 26.66, 26.49, 25.56, 25.36; **HRMS** (ESI) m/z calcd for $C_{23}H_{28}N_3O_2$ $[M+H]^+$ is 378.2176, found 378.2197.

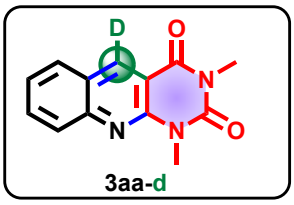
Gram Scale Experiments:

A solution of aniline (**1a**, 12.0 mmol, 1.12 g), 1,3-dimethyl barbituric acid (**2a**, 14.4 mmol; 2.25 g), and DMSO (36 mL) was placed in an ace pressure tube and heated in a preheated oil bath at 120 °C. The mixture was stirred for 12 hours. After completion of the reaction, the mixture was allowed to cool to room temperature and was then diluted with ethyl acetate (150 mL). The organic layer was washed successively with water (100 mL), sodium bicarbonate solution (60 mL), and brine (60 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using a 20% ethyl acetate/hexane mixture on 100-200 mesh silica gel to afford the product **3aa** as a white solid (2.0 g, 69% yield).



Synthesis of **3aa** in gram scale level

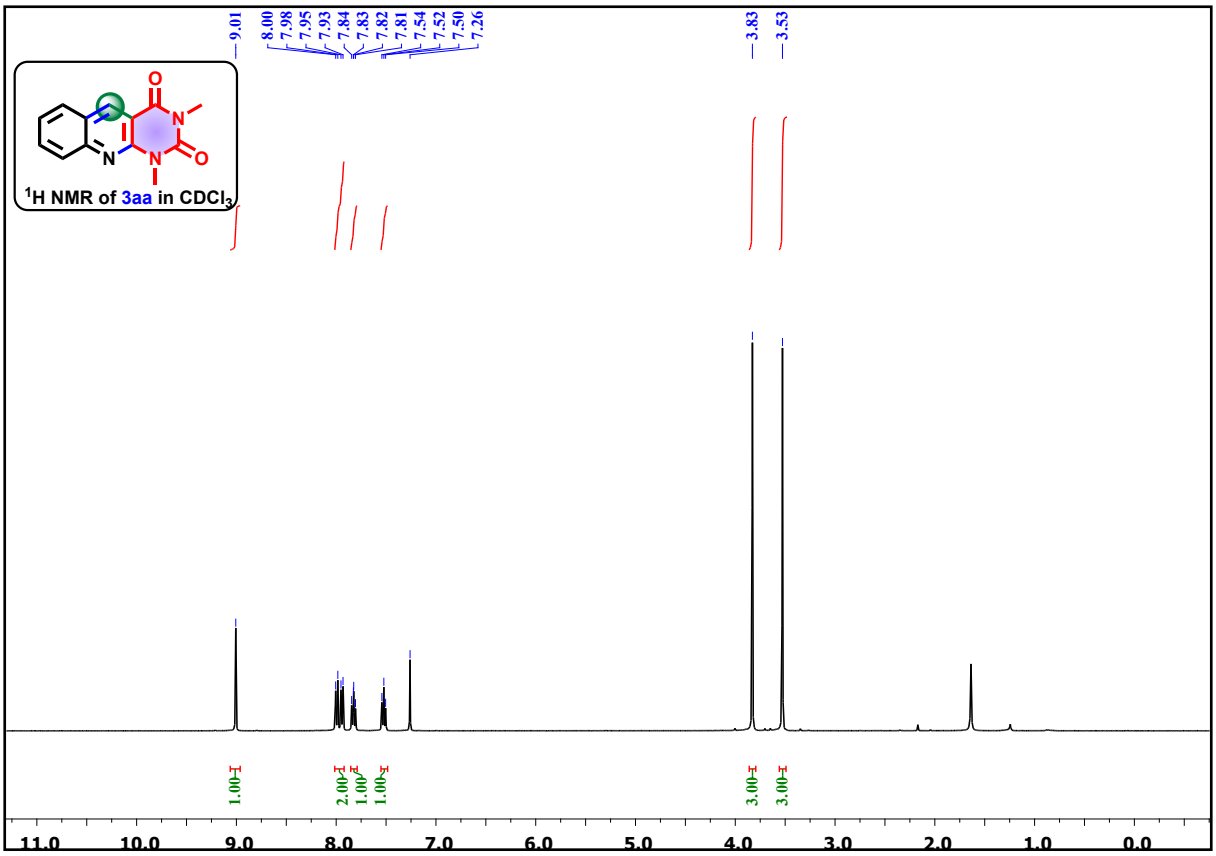
1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione-5-d **(3aa-d):**

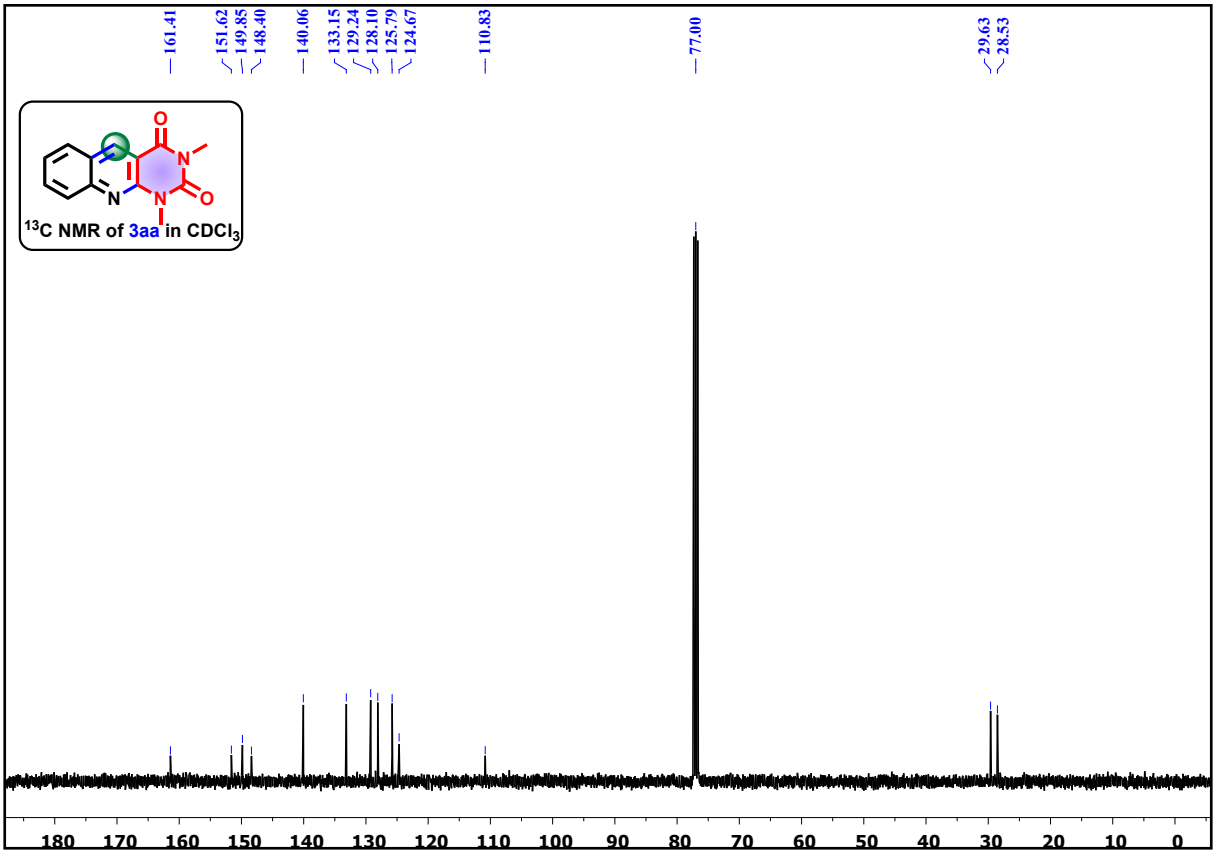


A solution of aniline (**1a**, 1.0 mmol, 0.091 mL), barbituric acid (**2a**, 1.2 mmol; 0.15g), and DMSO d_6 (3.0 mL) was placed in an Ace pressure tube and heated in a preheated oil bath at 120 °C. The mixture was stirred for 12 hours. After completion of the reaction, the mixture was allowed to cool to room temperature and was then diluted with ethyl acetate (10 mL). The organic layer was washed successively with water (10 mL), sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using a 20% ethyl acetate/hexane mixture on 100-200 mesh silica gel to afford the product **3aa-d** as a white solid (0.17 g, 69% yield); **Mp:** 200-202 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 7.57 – 7.49 (m, 1H), 3.84 (s, 3H), 3.53 (s, 3H); HRMS (ESI) m/z calcd for $C_{13}H_{11}DN_3O_2$ $[M+H]^+$ is 243.0987, found 243.0981.

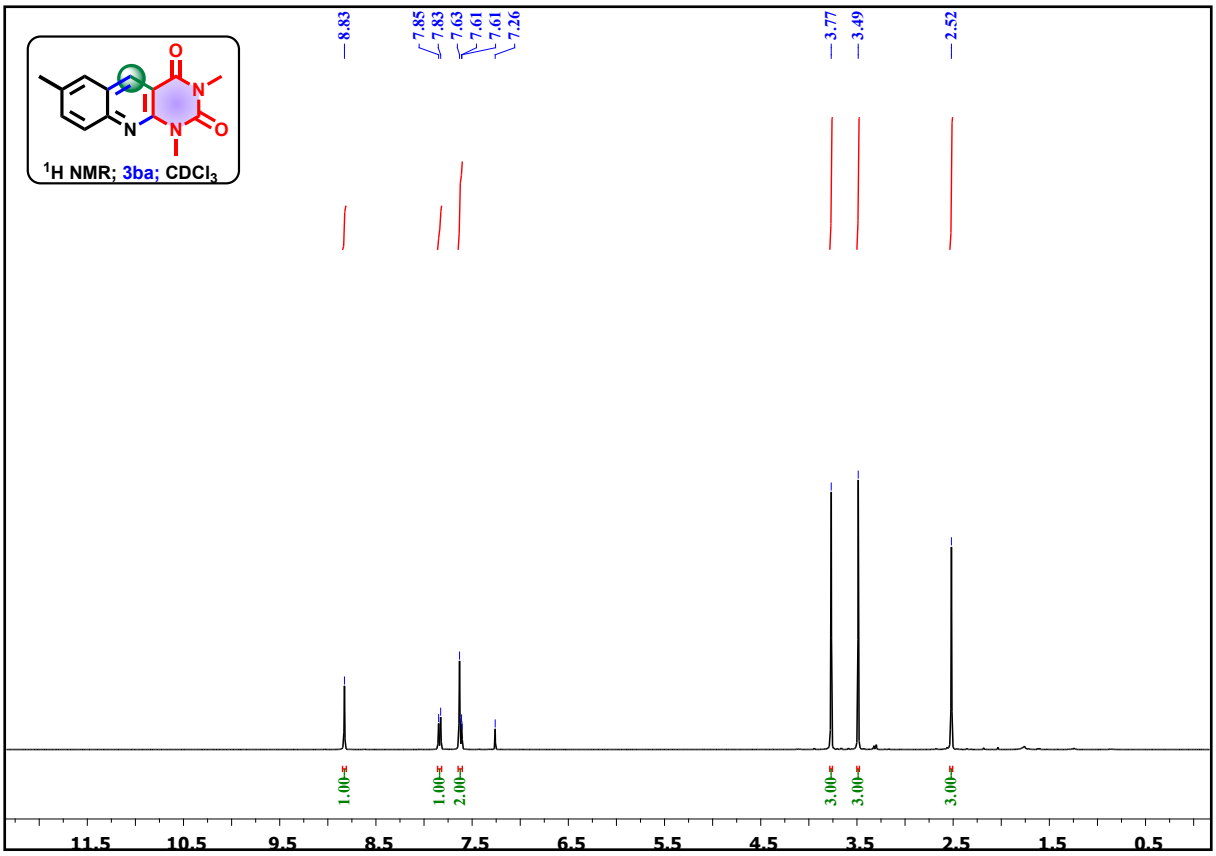
---

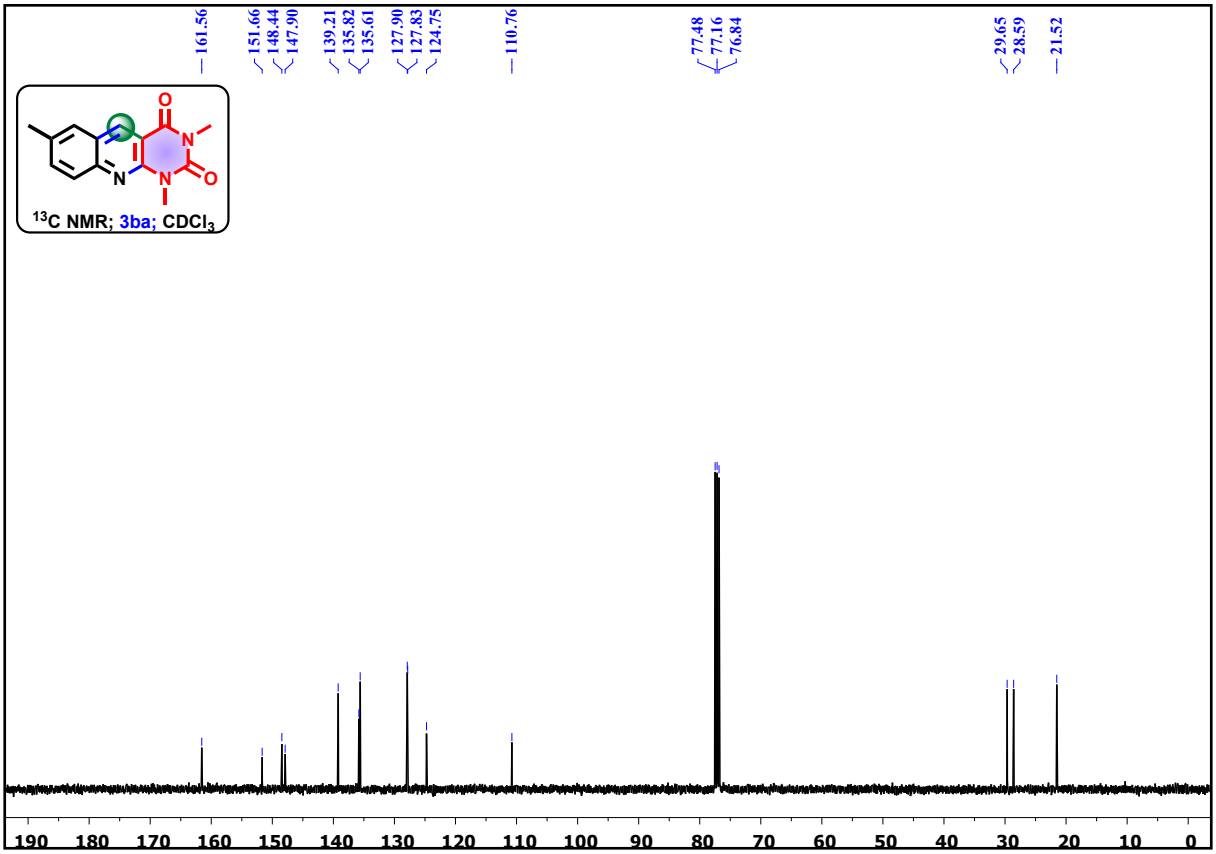
^{1}H and ^{13}C NMR of **3aa** in $CDCl_3$



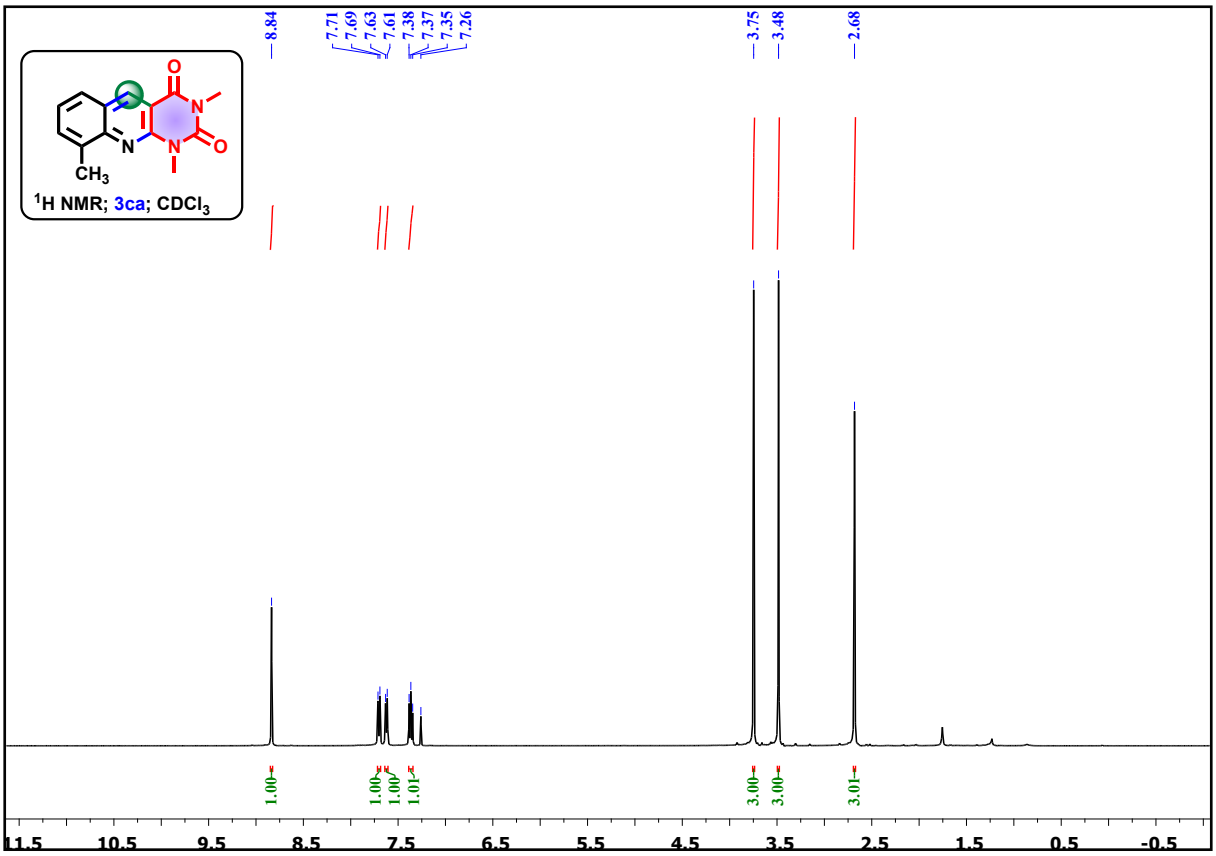


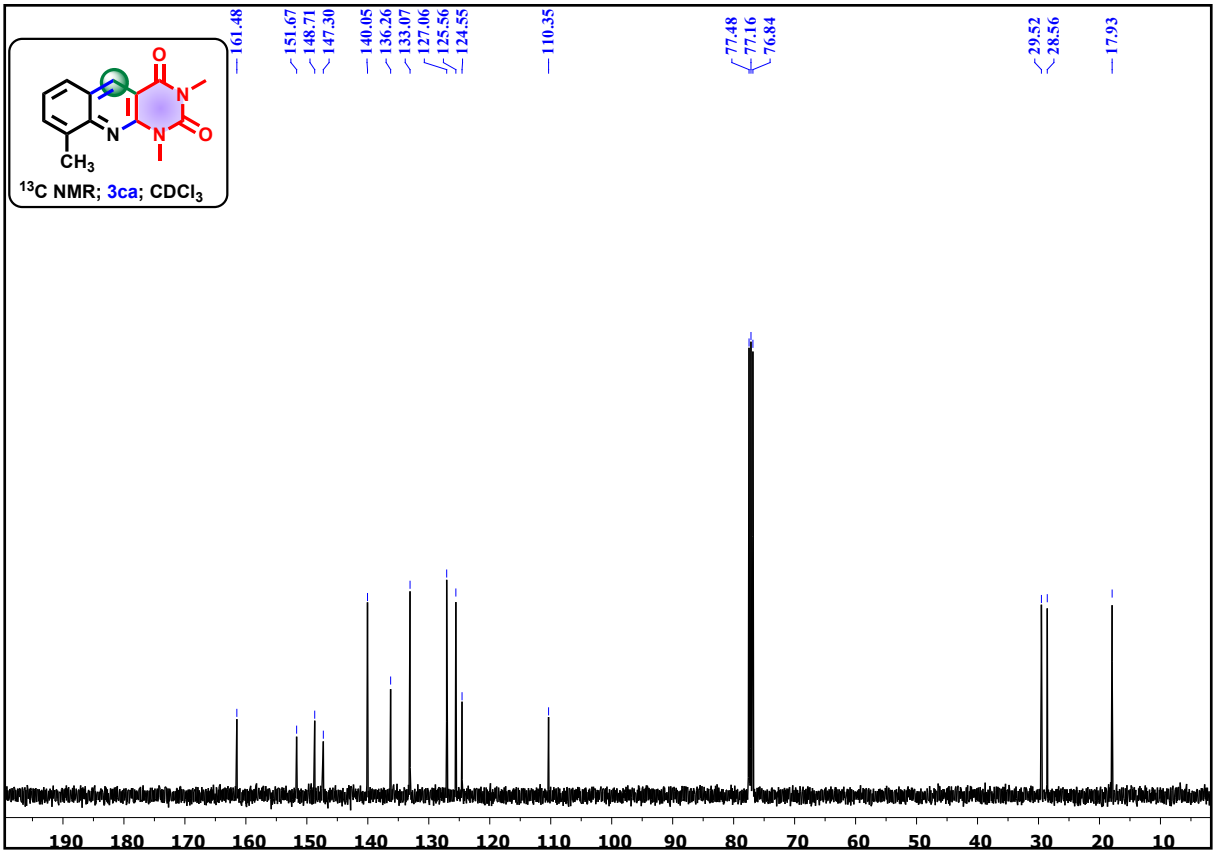
^{1}H and ^{13}C NMR of **3ba** in CDCl$_3$



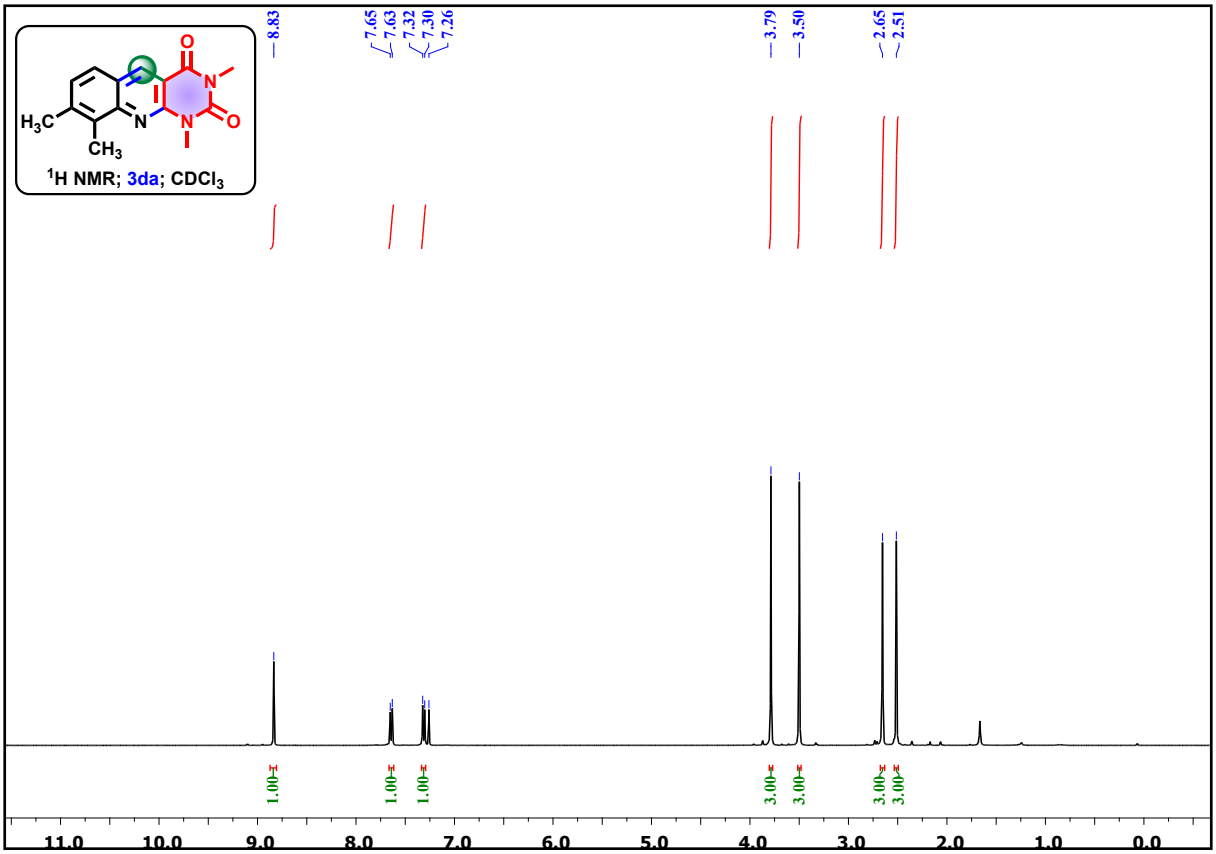


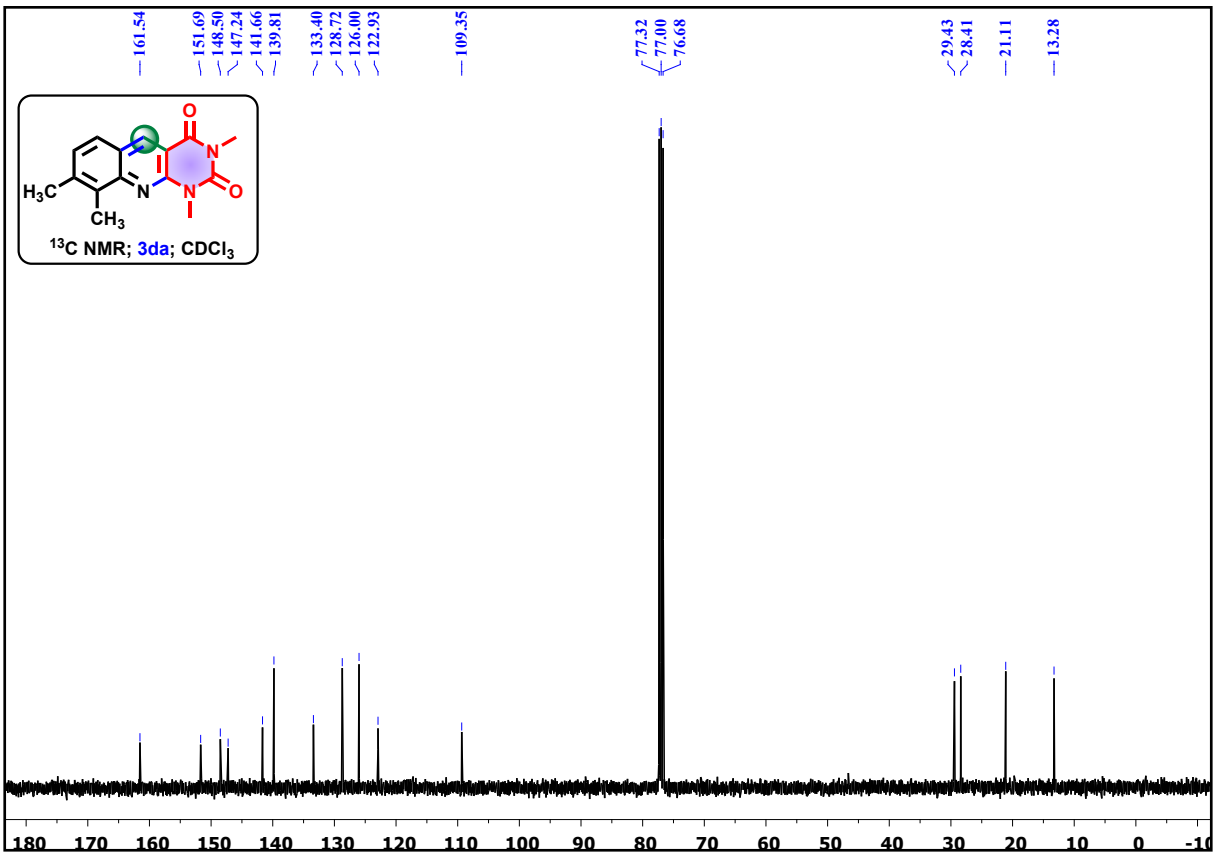
^{1}H and ^{13}C NMR of **3ca** in CDCl$_3$


8.84
7.71
7.69
7.63
7.61
7.38
7.37
7.35
7.26
3.75
3.48
2.68
1.00
1.00
1.00
1.01
3.00
3.00
3.01
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
^{1}H NMR; 3ca; $CDCl_3$

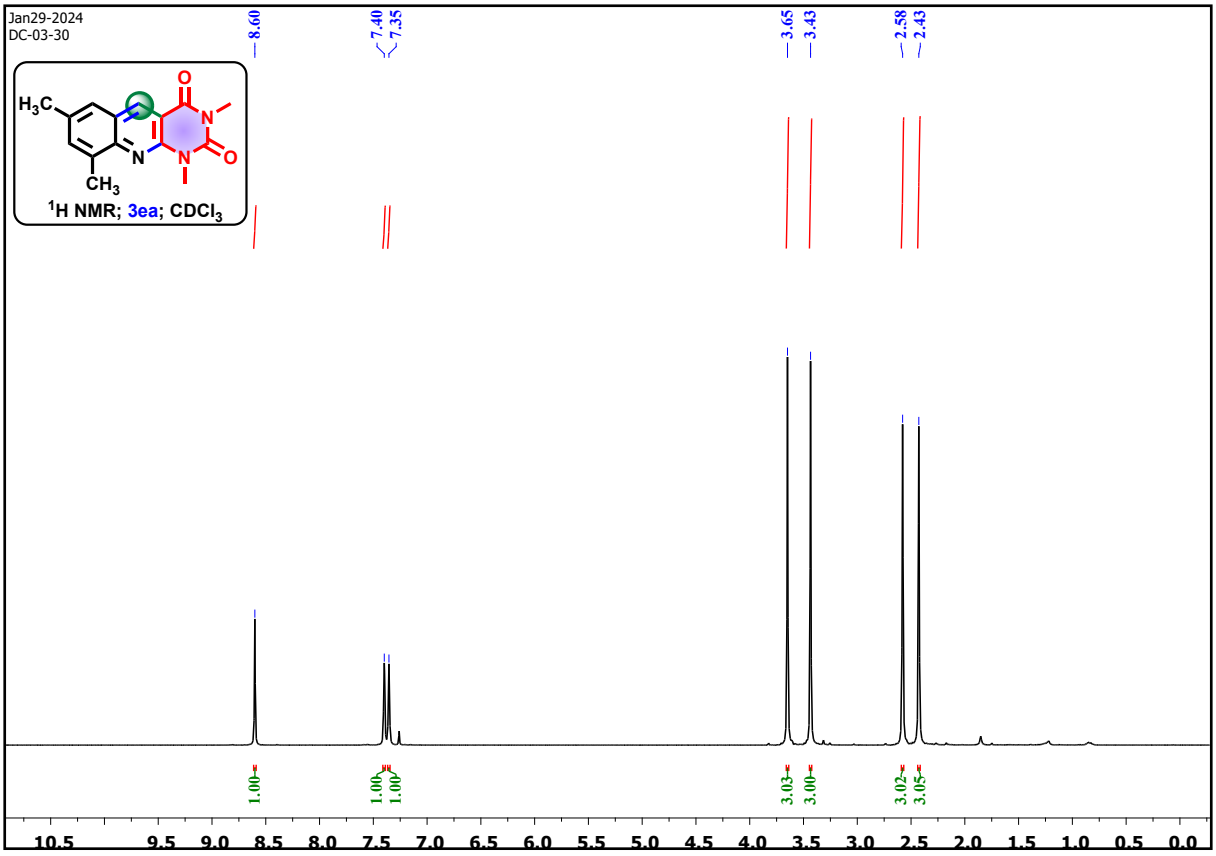

161.48
151.67
148.71
147.30
140.05
136.26
133.07
127.06
125.56
124.55
110.35
77.48
77.16
76.84
29.52
28.56
17.93
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
^{13}C NMR; 3ca; $CDCl_3$

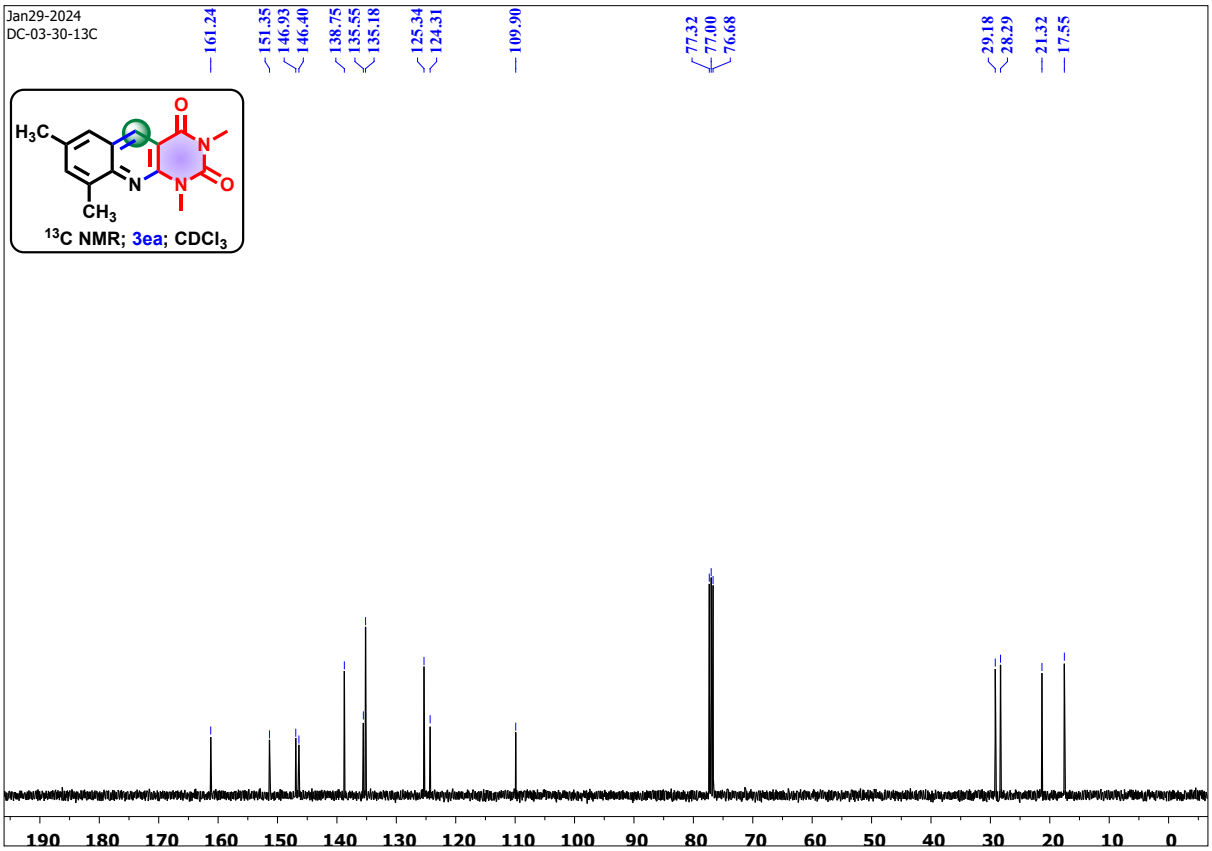
^{1}H and ^{13}C NMR of **3da** in $CDCl_3$



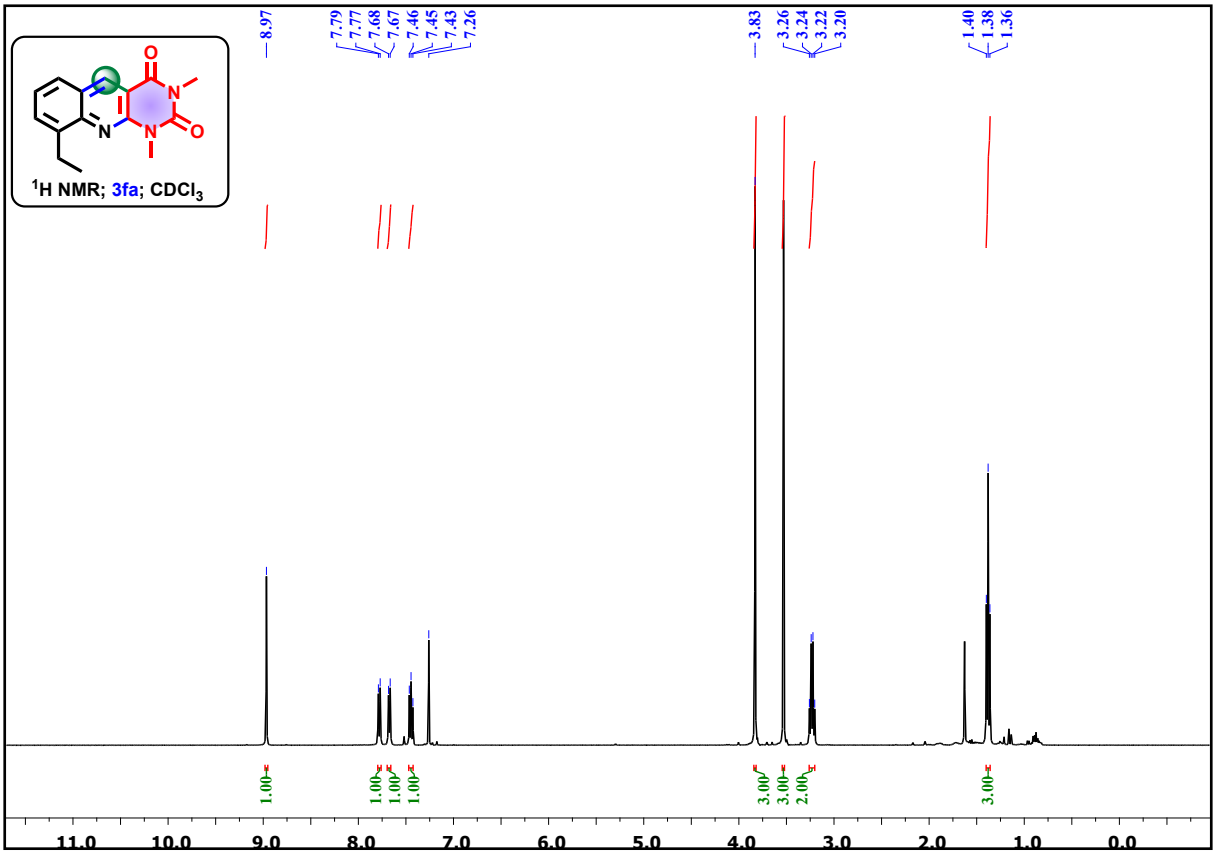


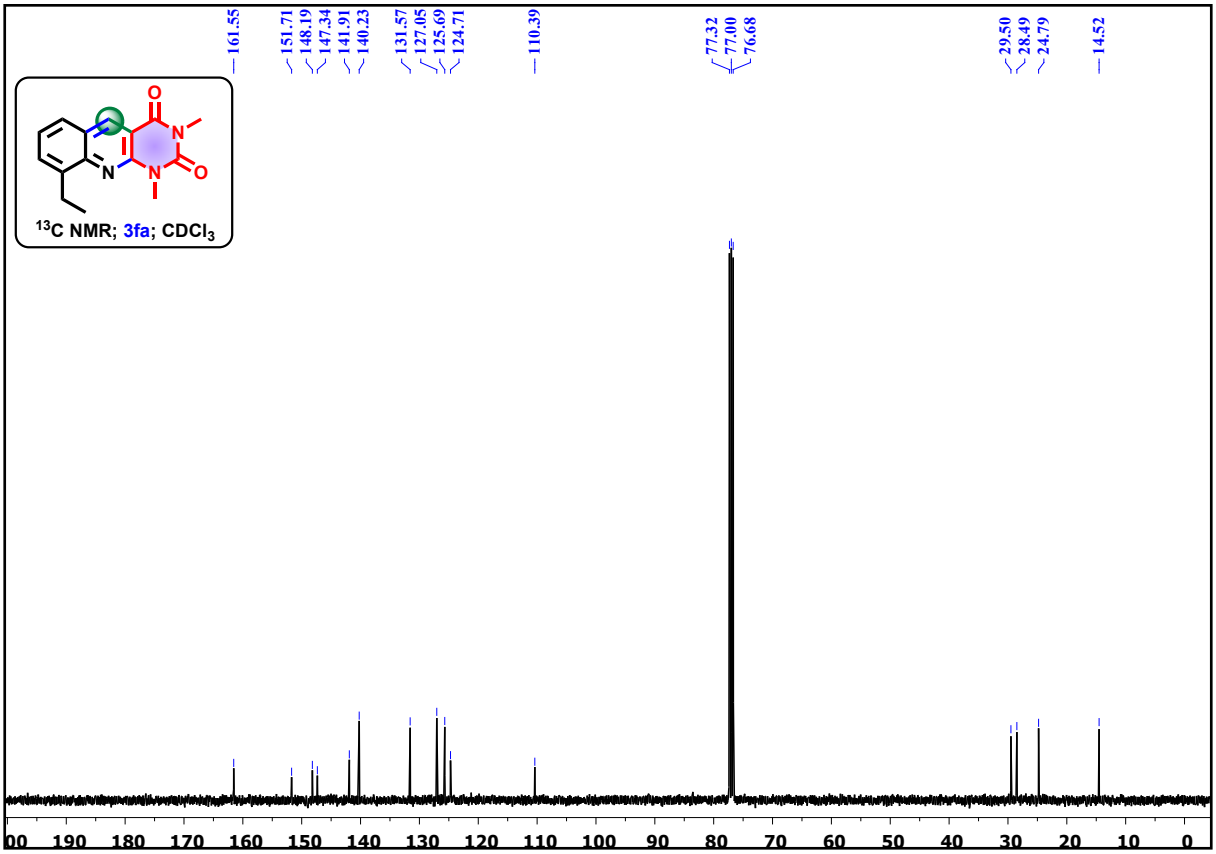
^{1}H and ^{13}C NMR of **3ea** in $CDCl_3$



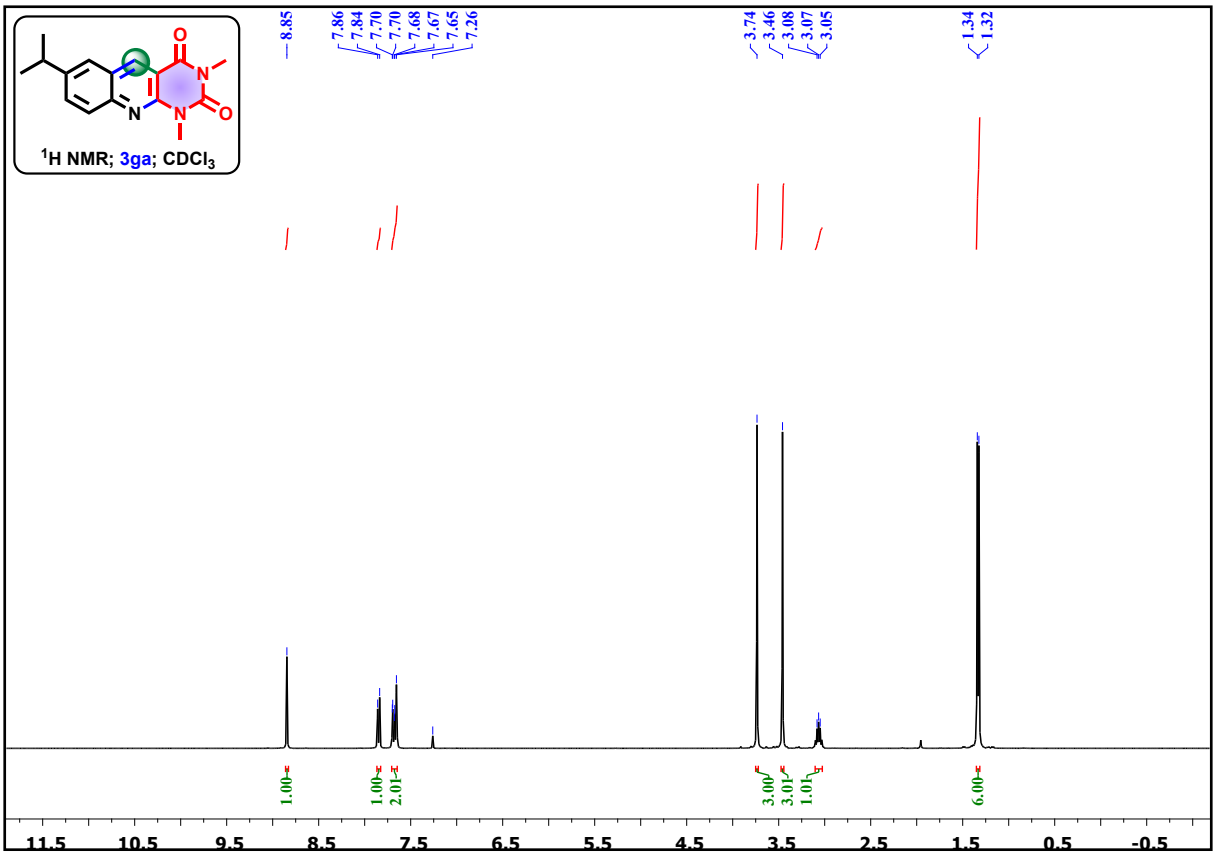


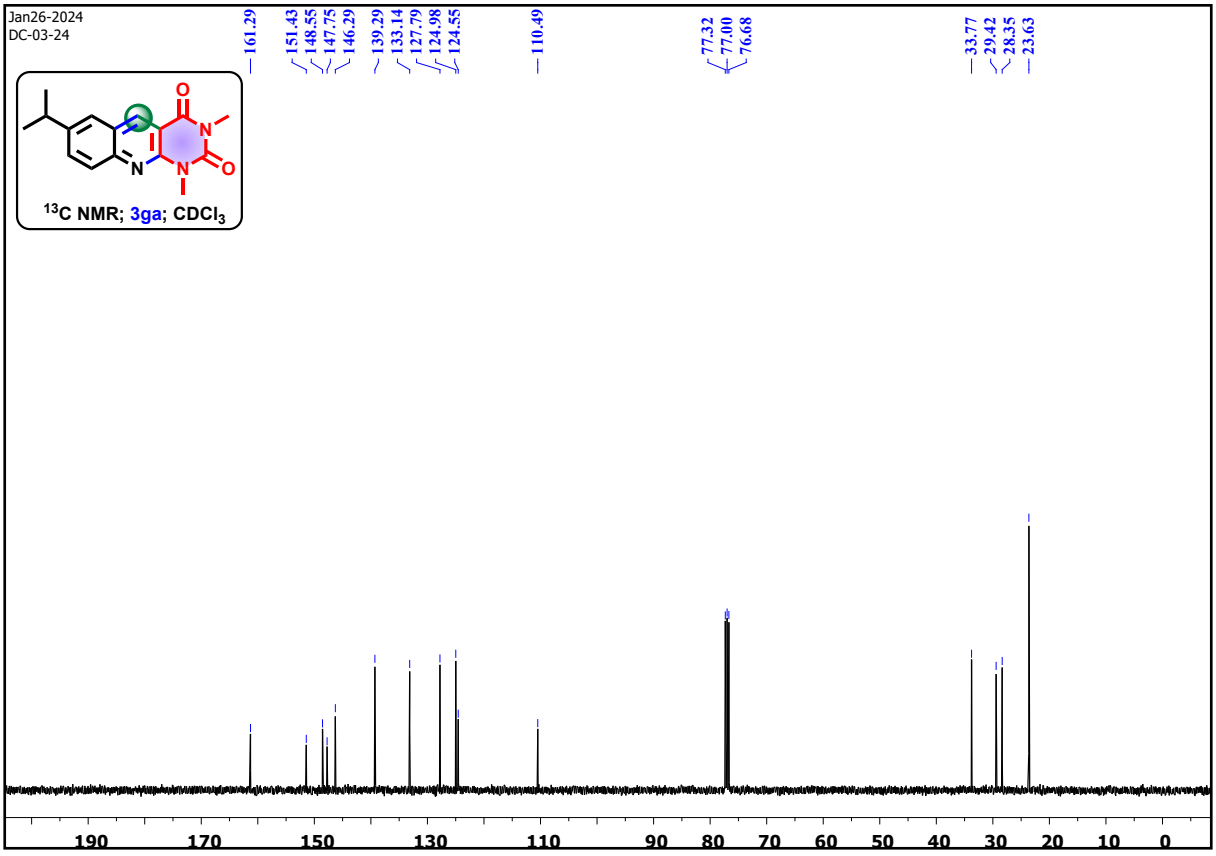
^{1}H and ^{13}C NMR of **3fa** in $CDCl_3$



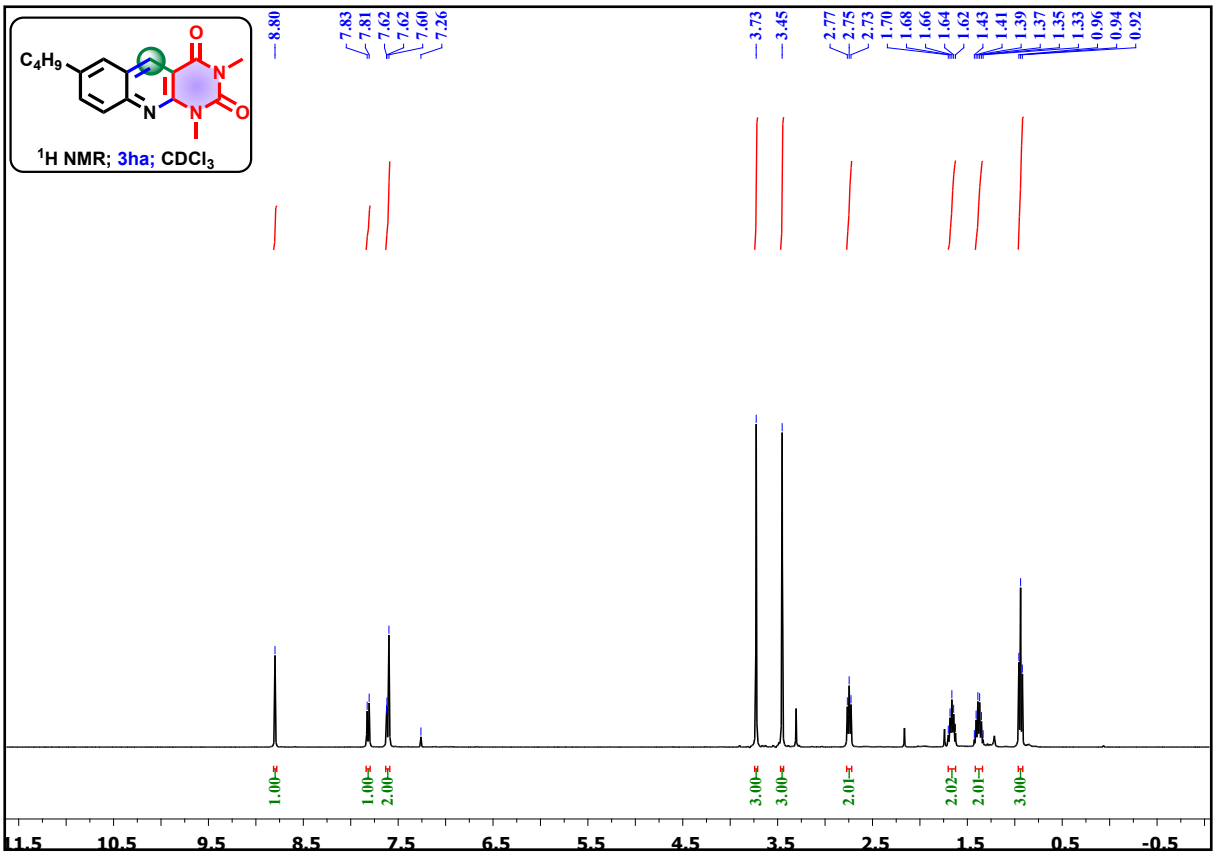


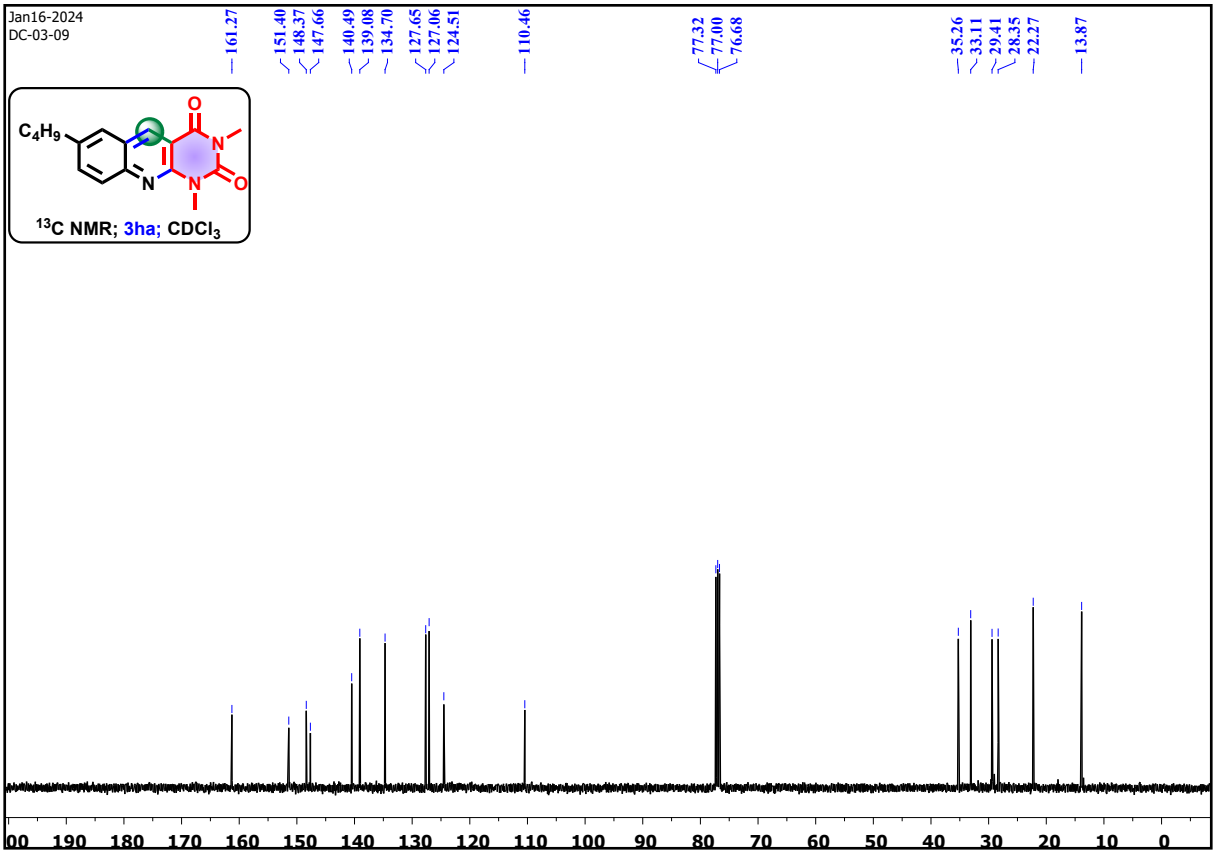
^{1}H and ^{13}C NMR of **3ga** in $CDCl_3$



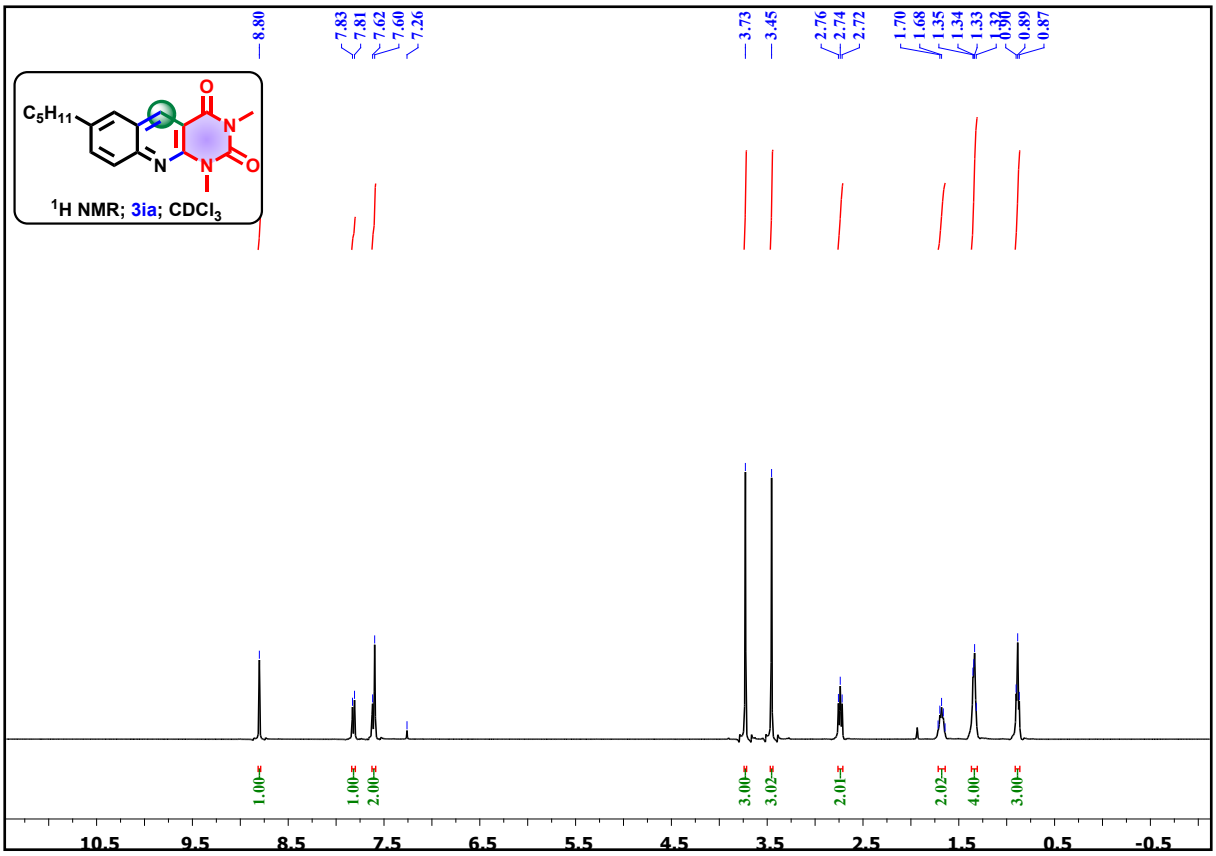


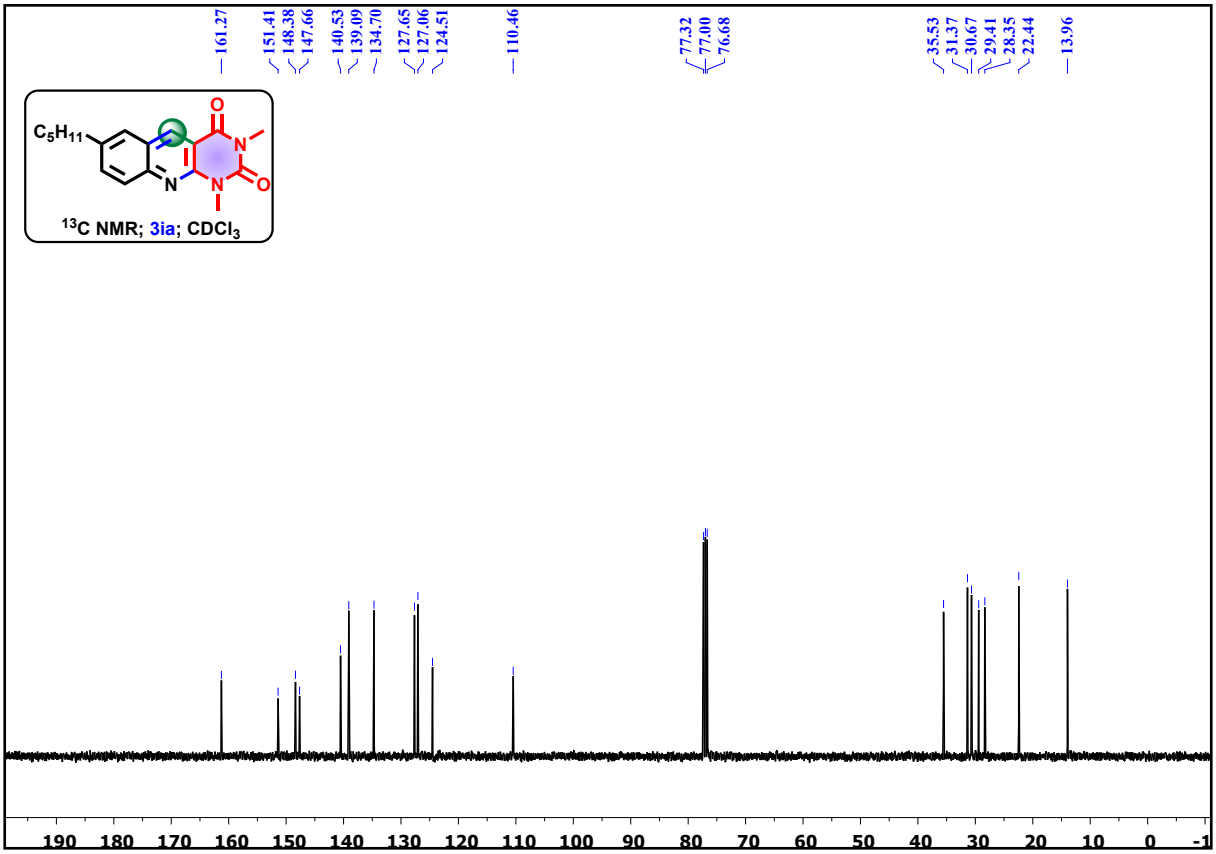
^{1}H and ^{13}C NMR of **3ha** in CDCl$_3$



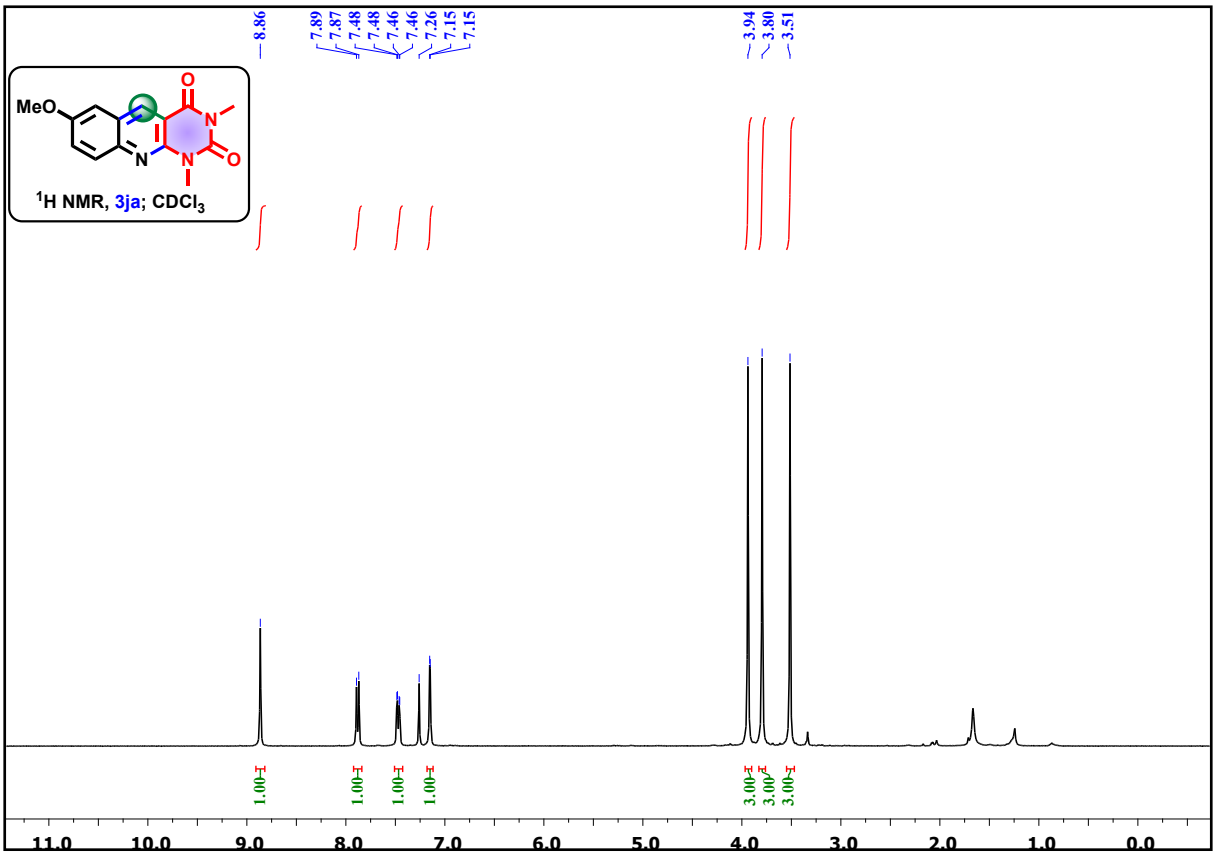


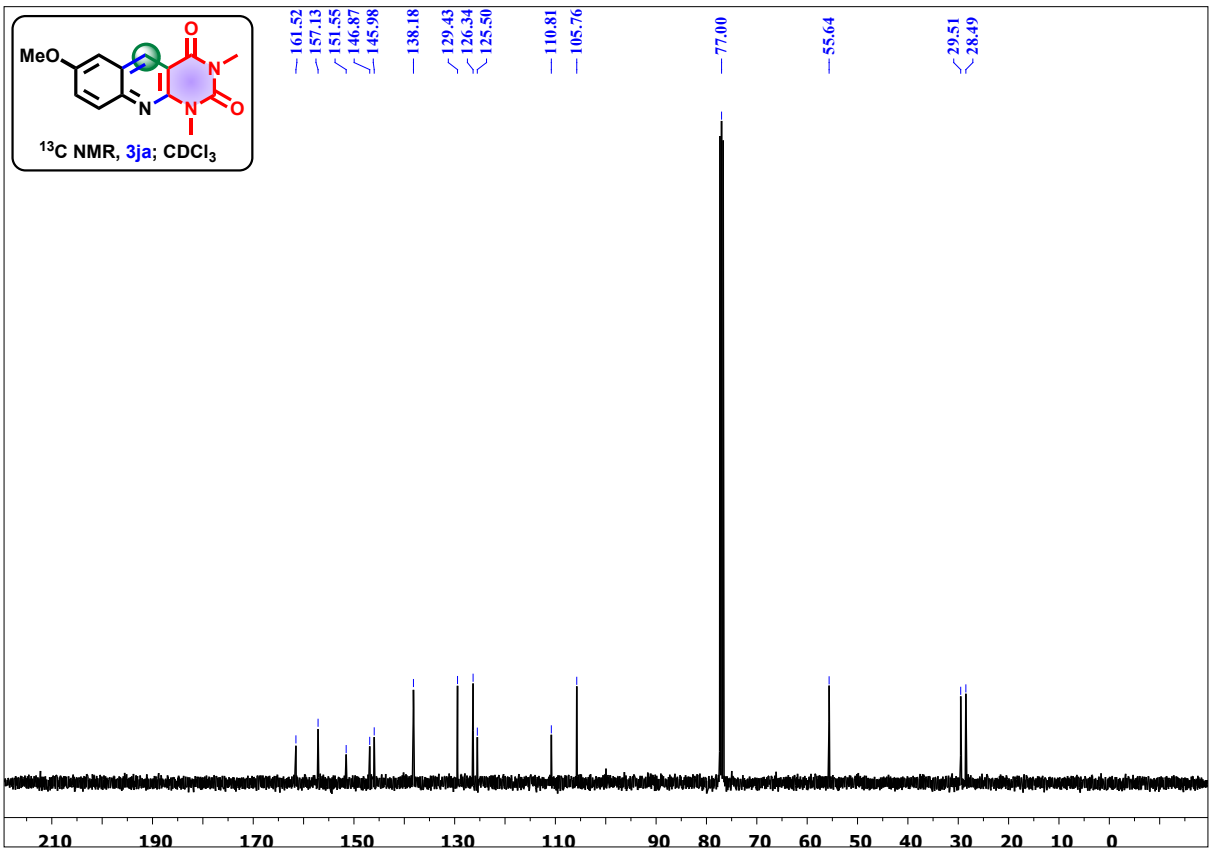
^{1}H and ^{13}C NMR of **3ia** in $CDCl_3$



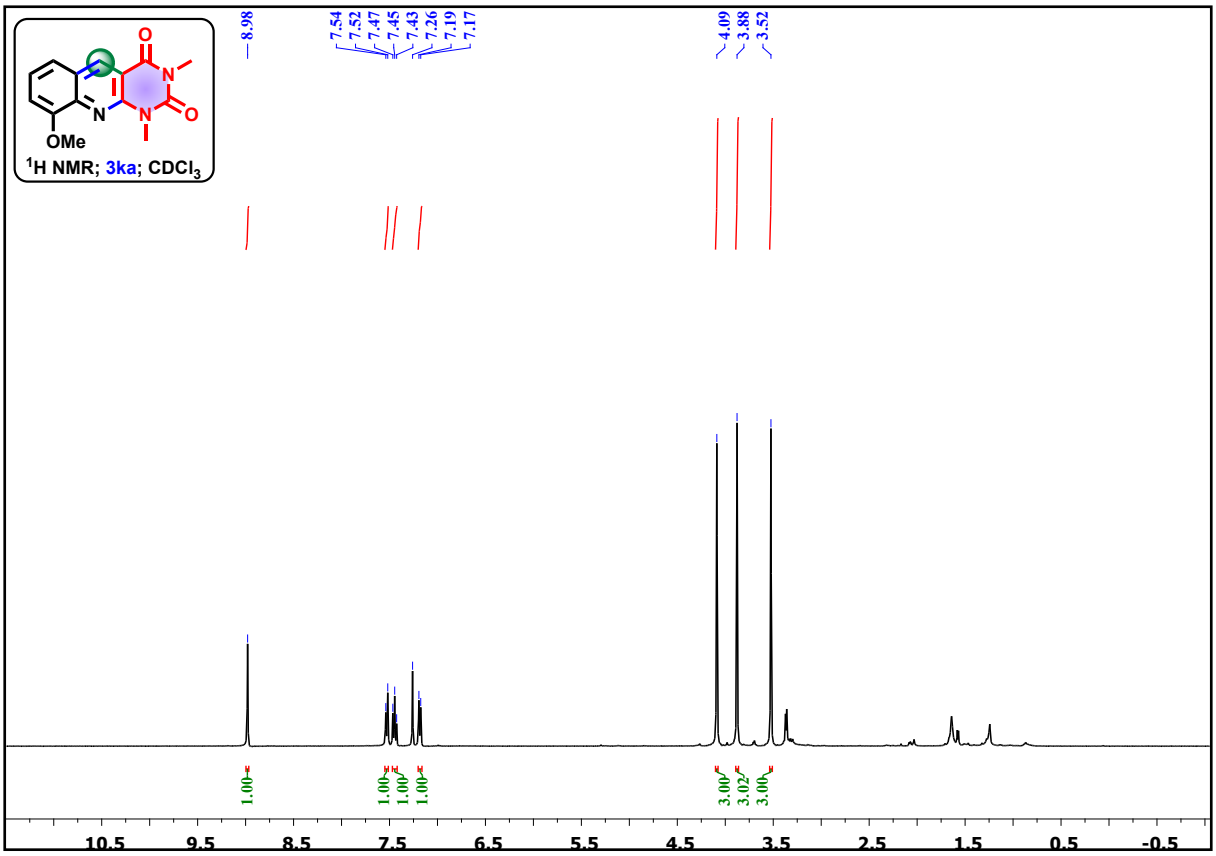


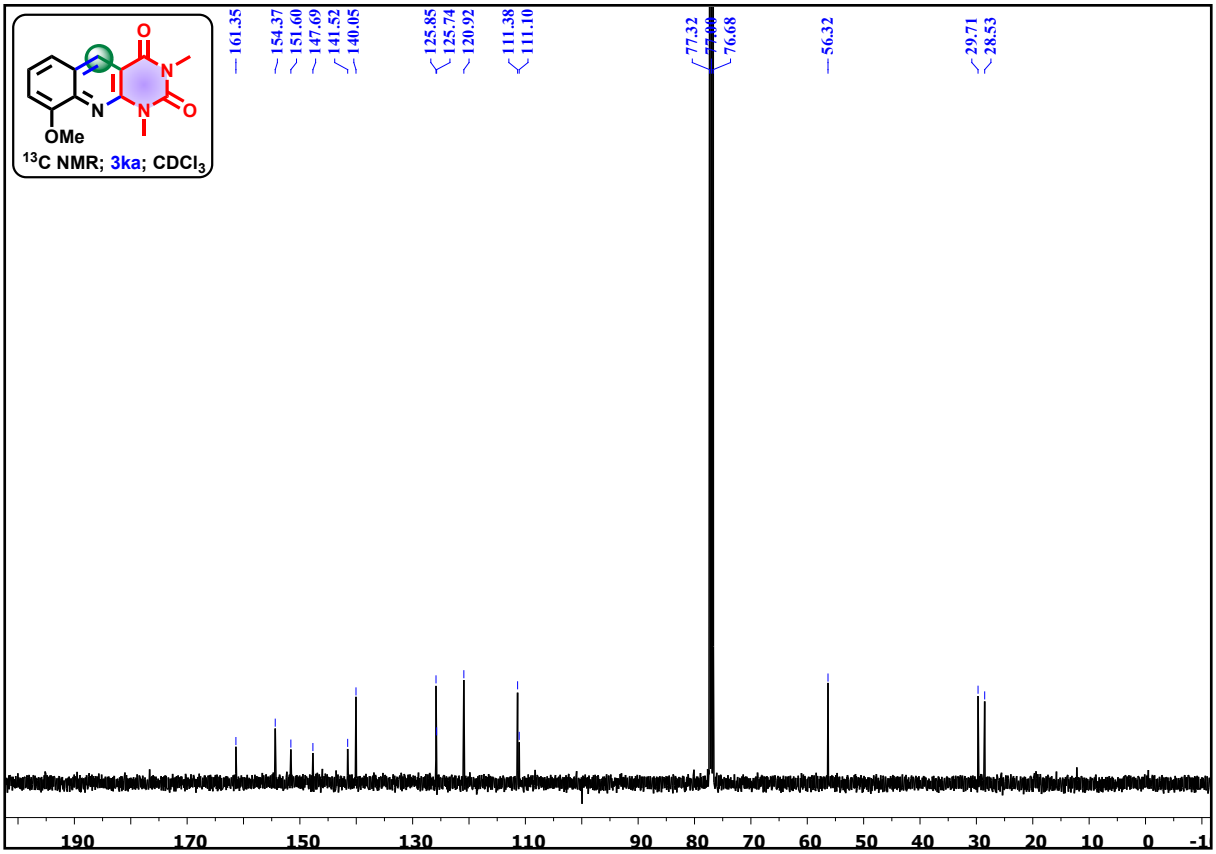
^{1}H and ^{13}C NMR of **3ja** in $CDCl_3$



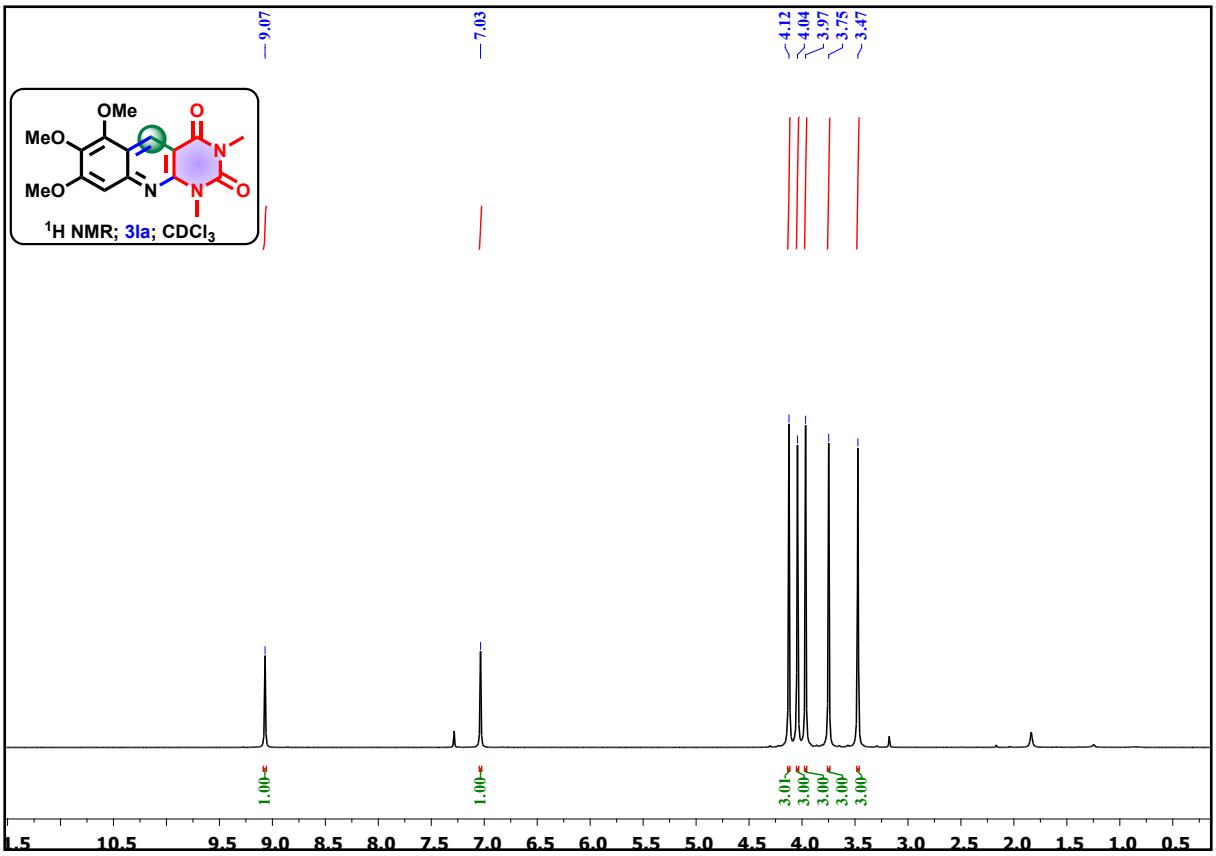


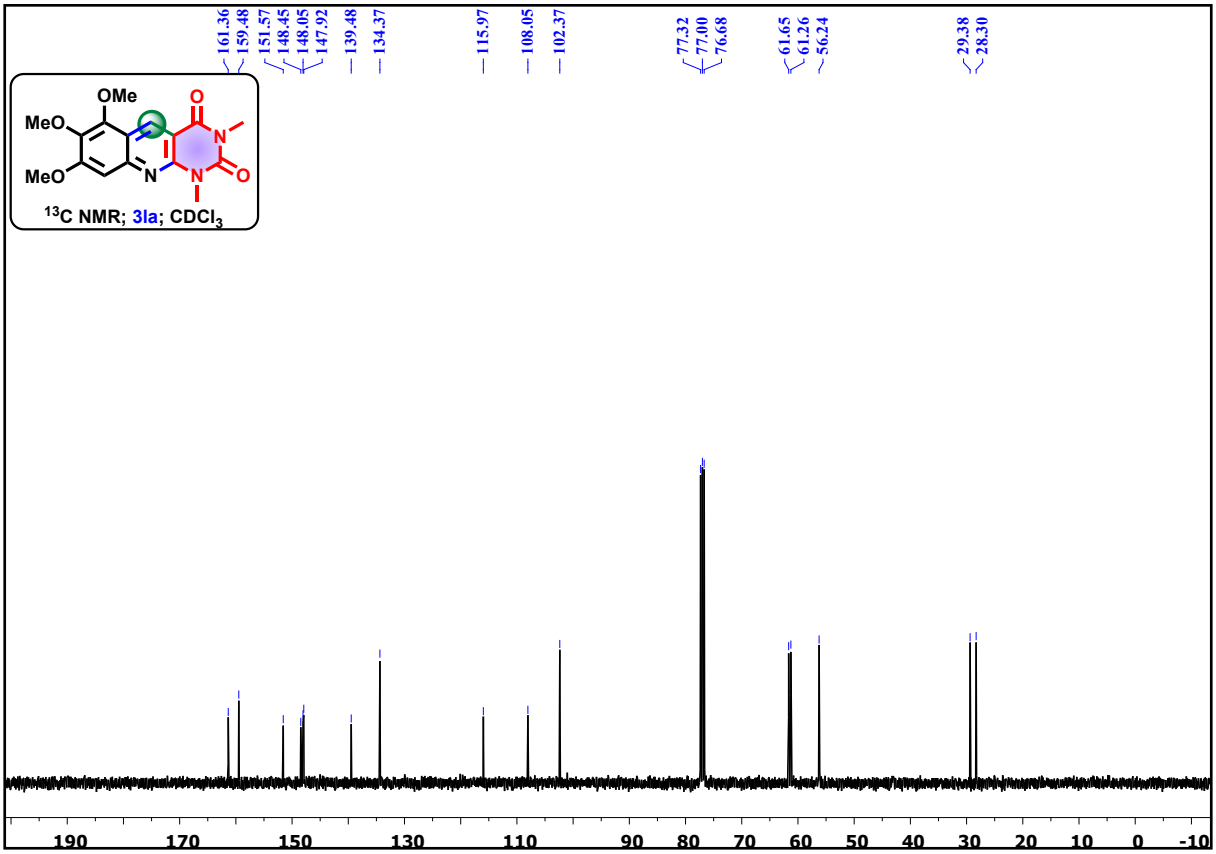
^{1}H and ^{13}C NMR of **3ka** in CDCl$_3$



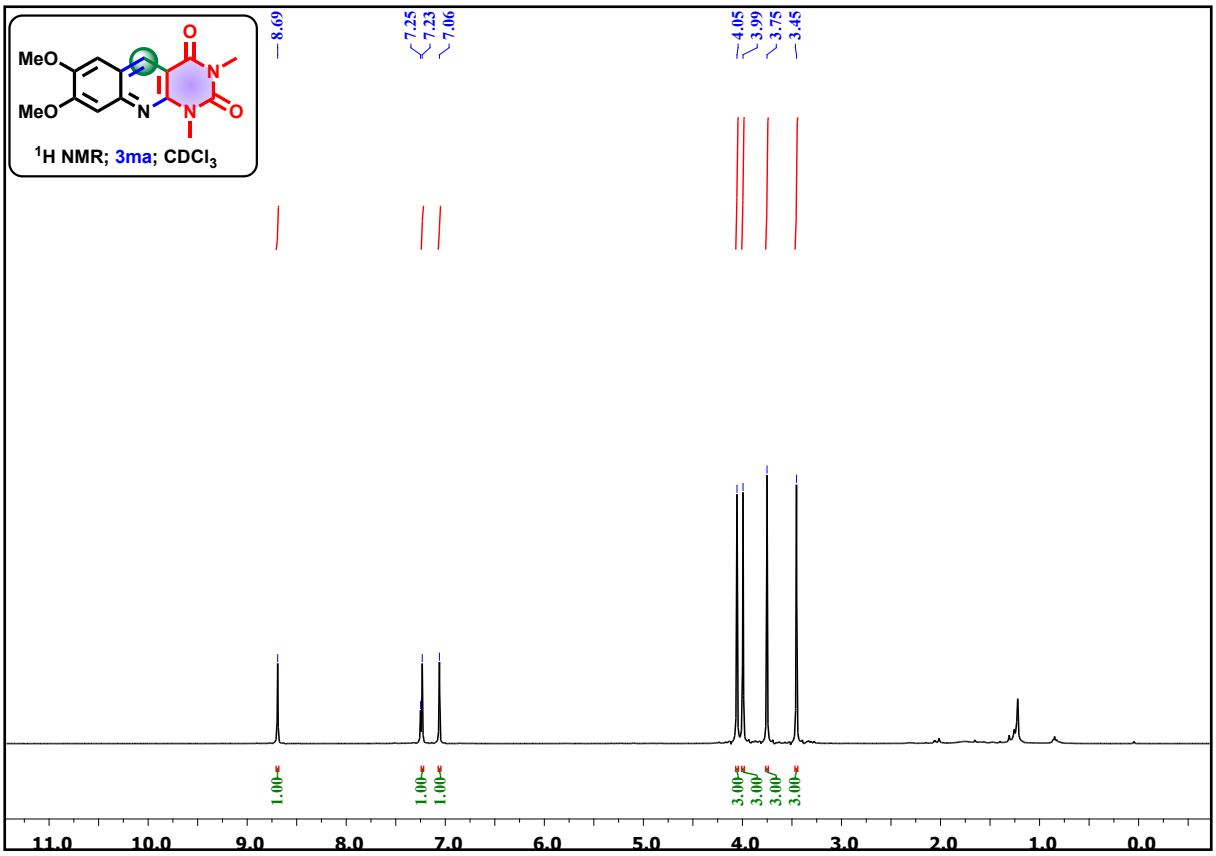


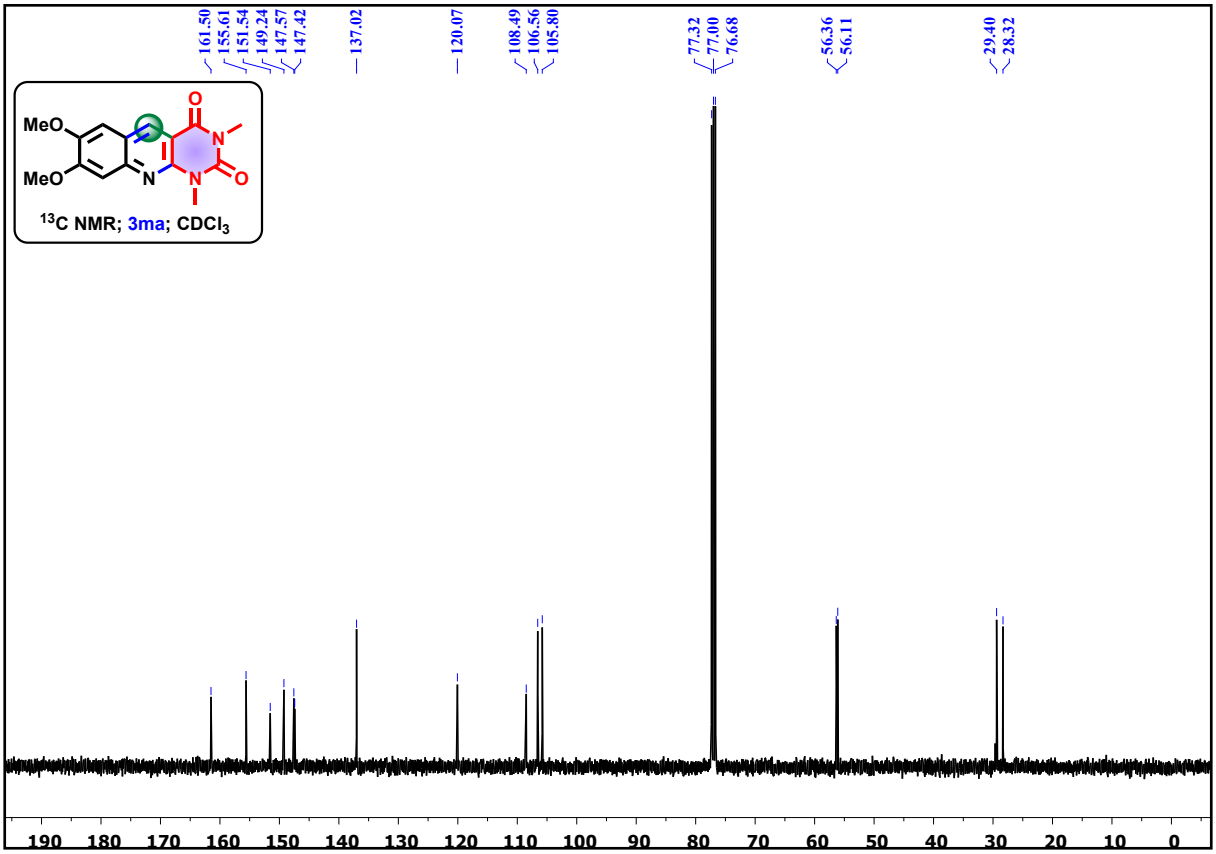
^{1}H and ^{13}C NMR of **3la** in CDCl$_3$



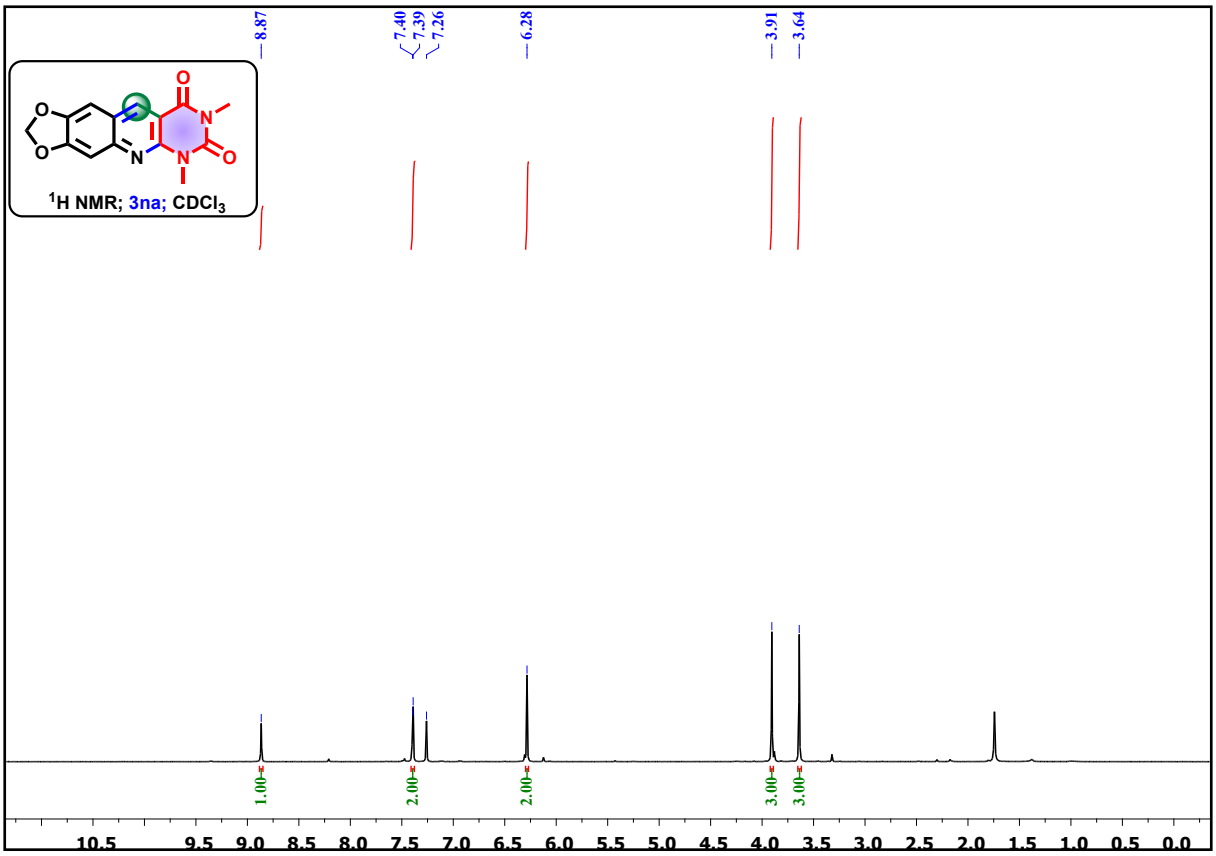


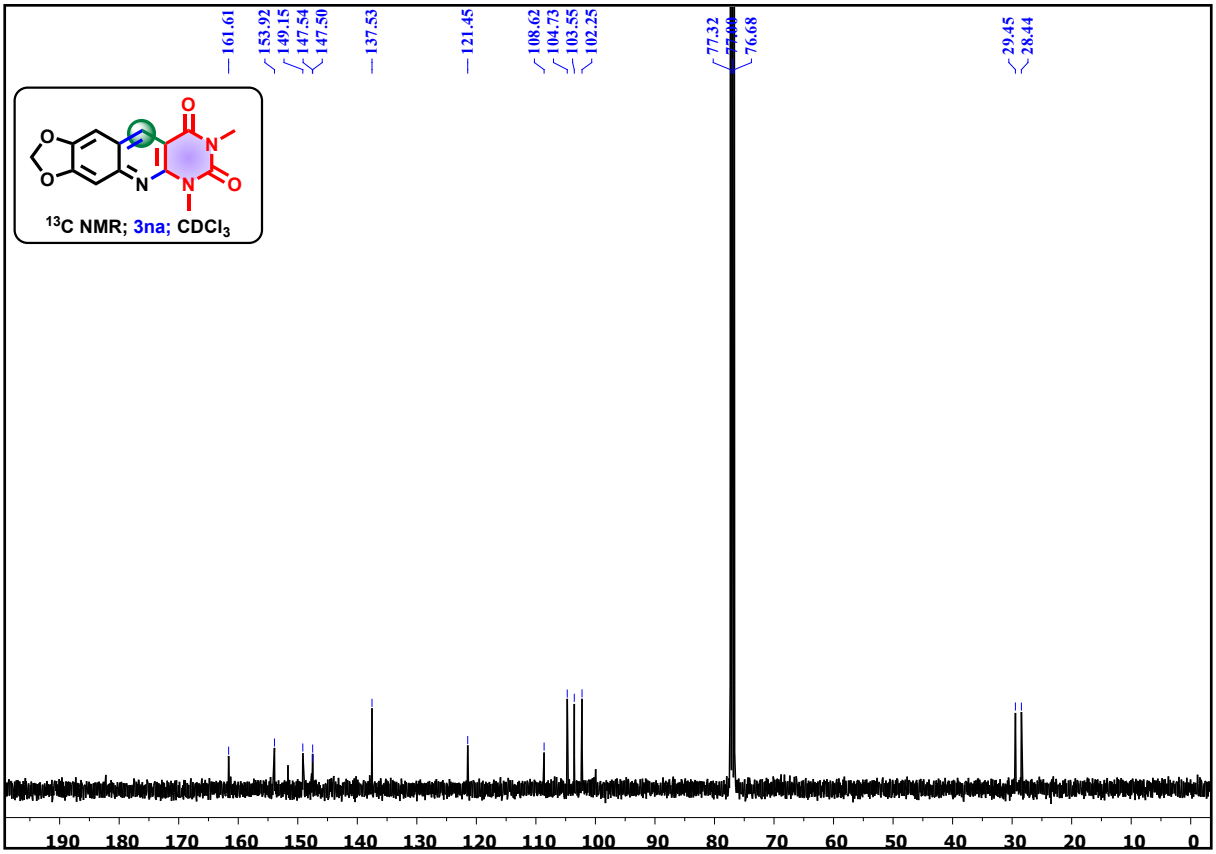
^{1}H and ^{13}C NMR of **3ma** in CDCl$_3$



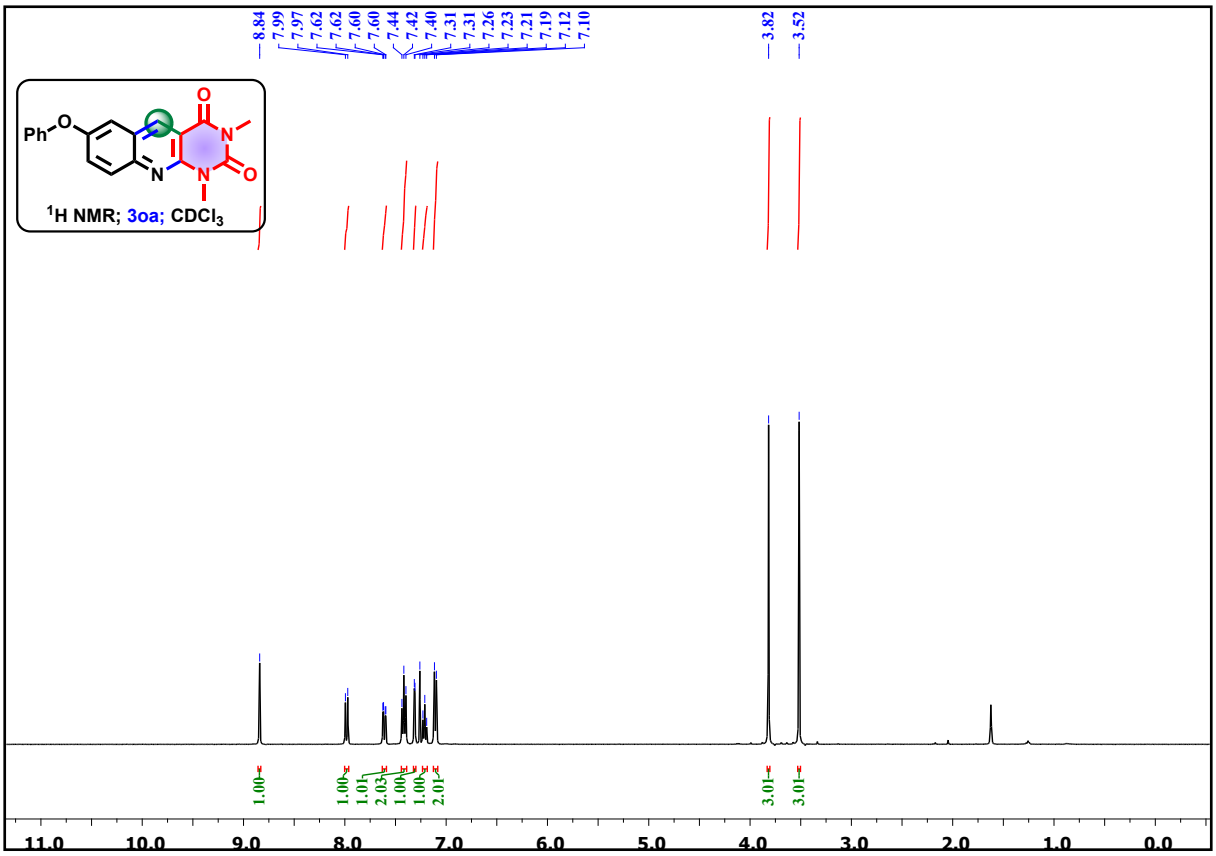


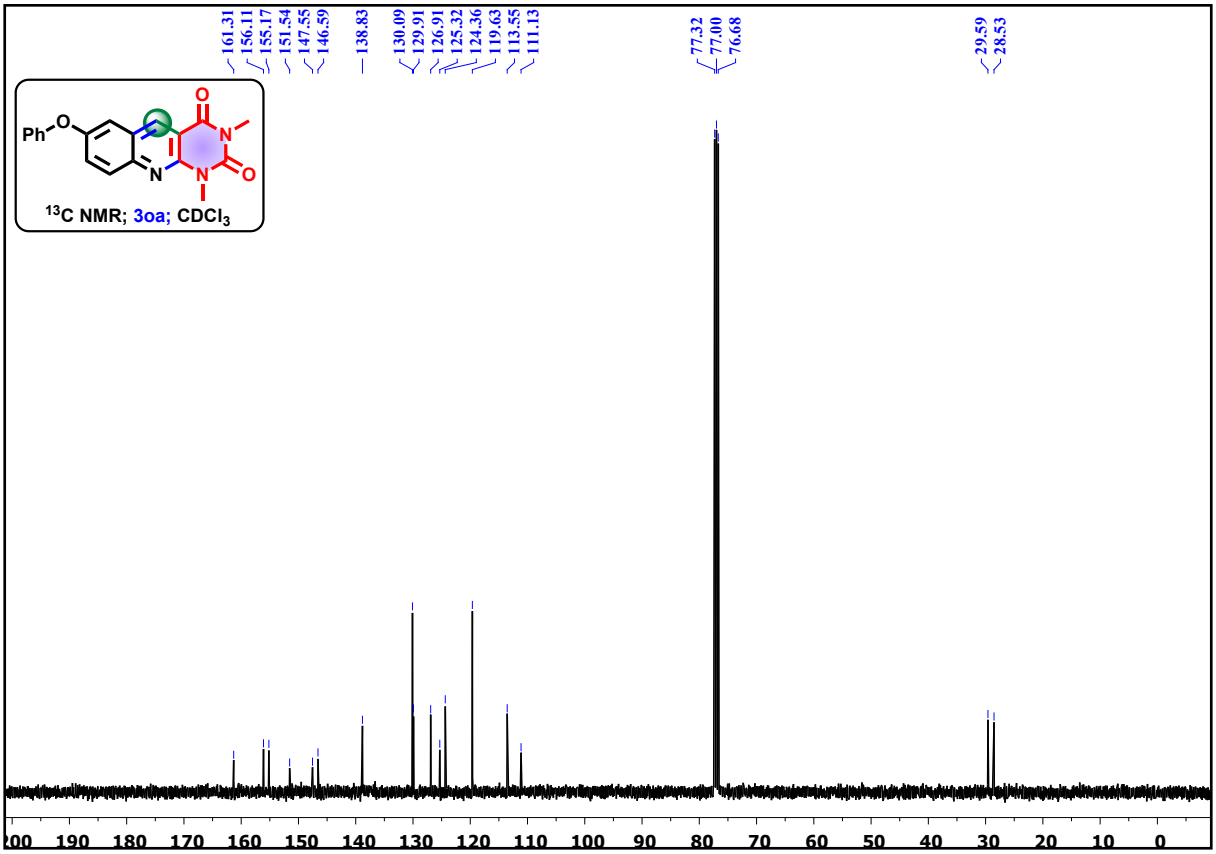
^{1}H and ^{13}C NMR of **3na** in CDCl$_3$



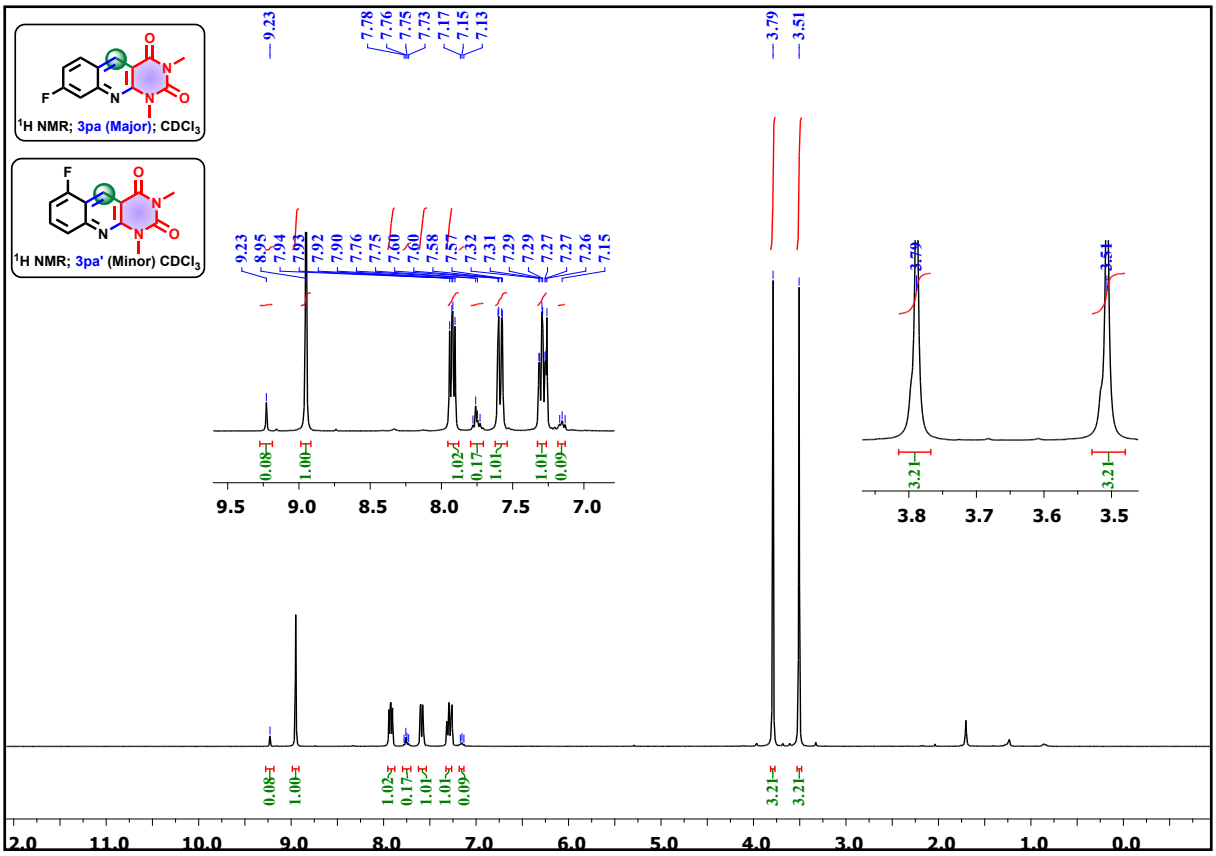


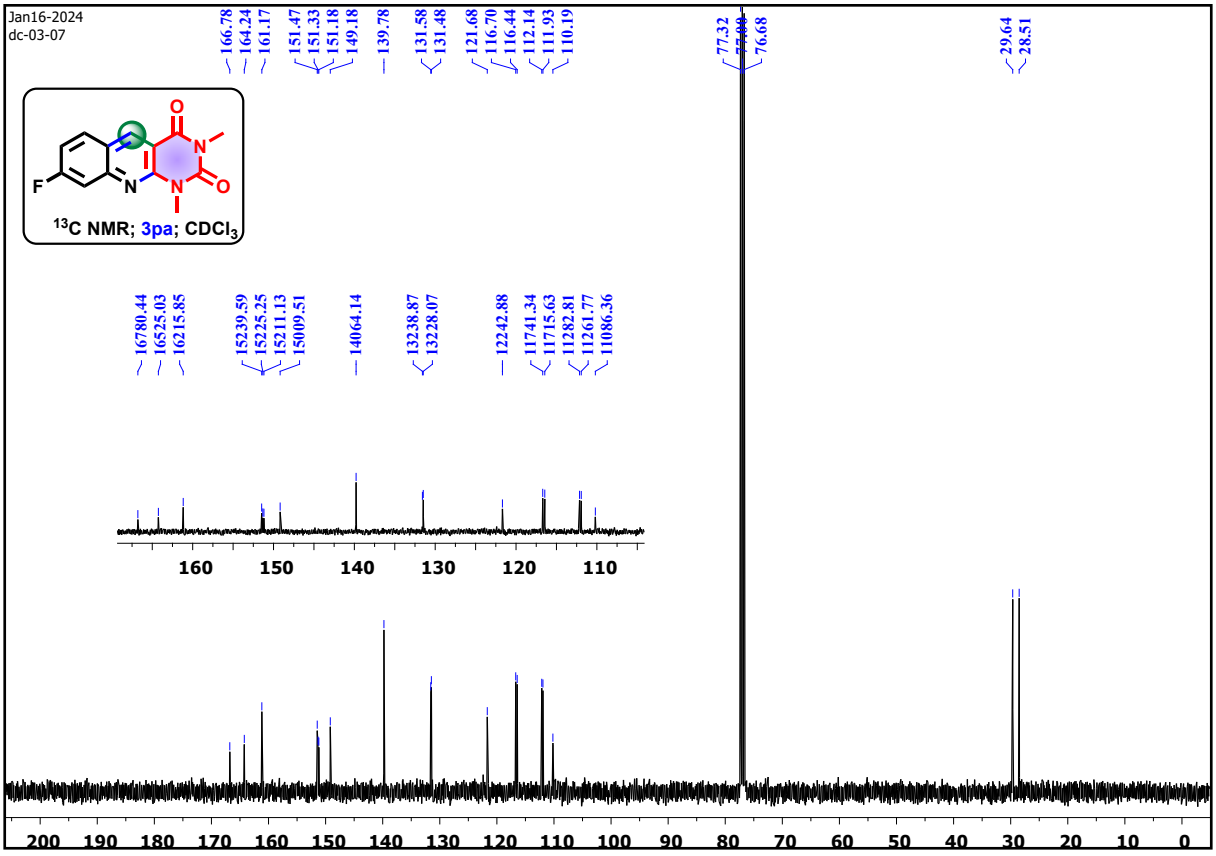
^{1}H and ^{13}C NMR of **3oa** in CDCl$_3$

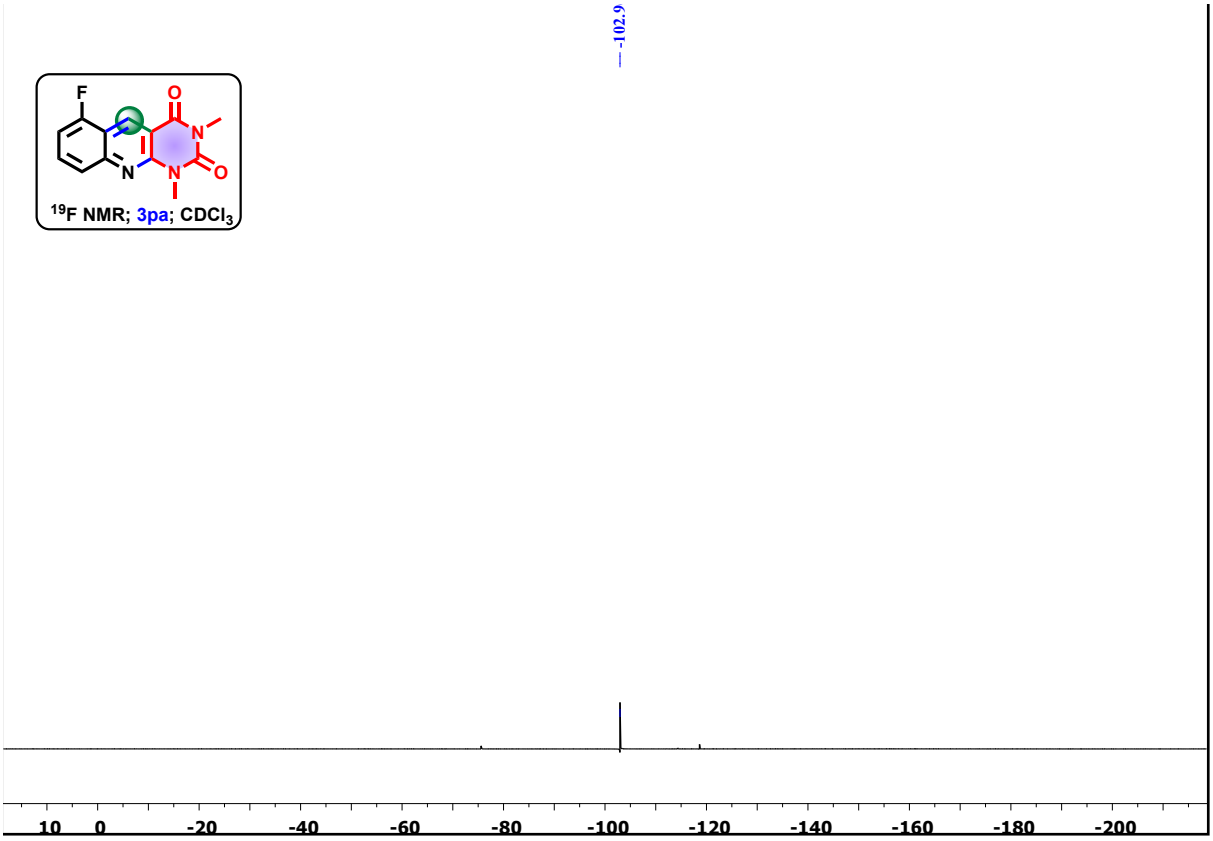




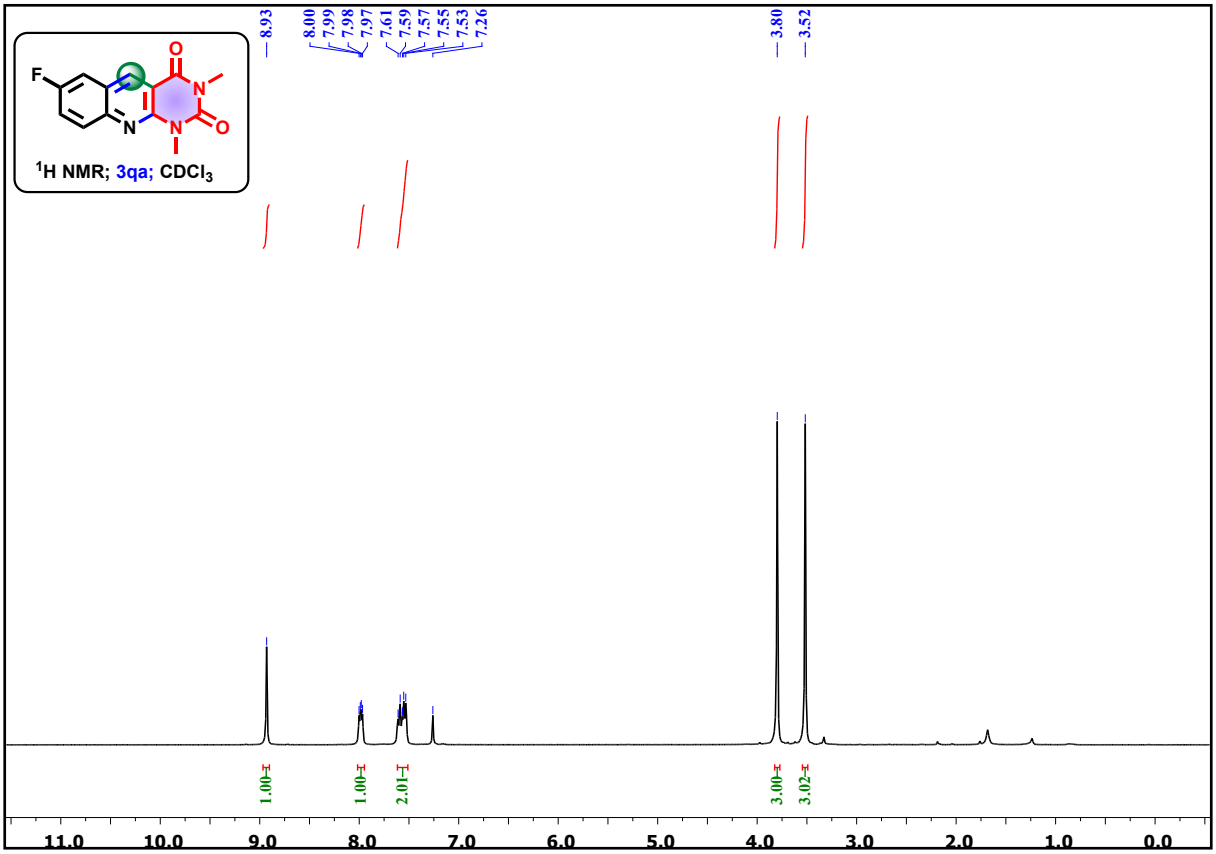
^{1}H and ^{13}C NMR of mixture of **3pa** and **3pa'** in $CDCl_3$

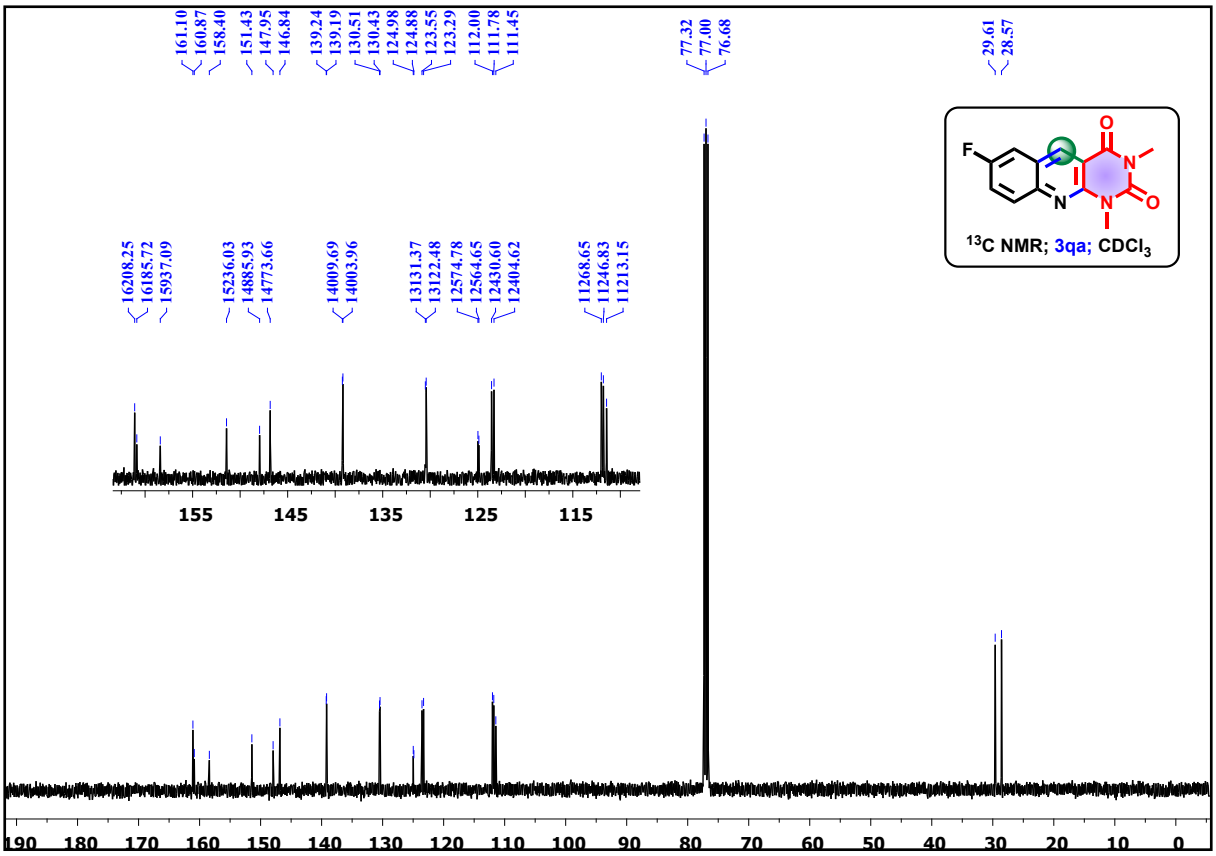

^{1}H NMR; 3pa (Major); CDCl$_3$
^{1}H NMR; 3pa' (Minor) CDCl$_3$
9.23
7.78
7.76
7.75
7.73
7.17
7.15
7.13
3.79
3.51


Jan16-2024
dc-03-07
^{13}C NMR; 3pa; CDCl$_3$
166.78
164.24
161.17
151.47
151.33
151.18
149.18
139.78
131.58
131.48
121.68
116.70
116.44
112.14
111.93
110.19
77.32
76.68
29.64
28.51
16780.44
16525.03
16215.85
15239.59
15225.25
15211.13
15009.51
14064.14
13238.87
13228.07
12242.88
11741.34
11715.63
11282.81
11261.77
11086.36

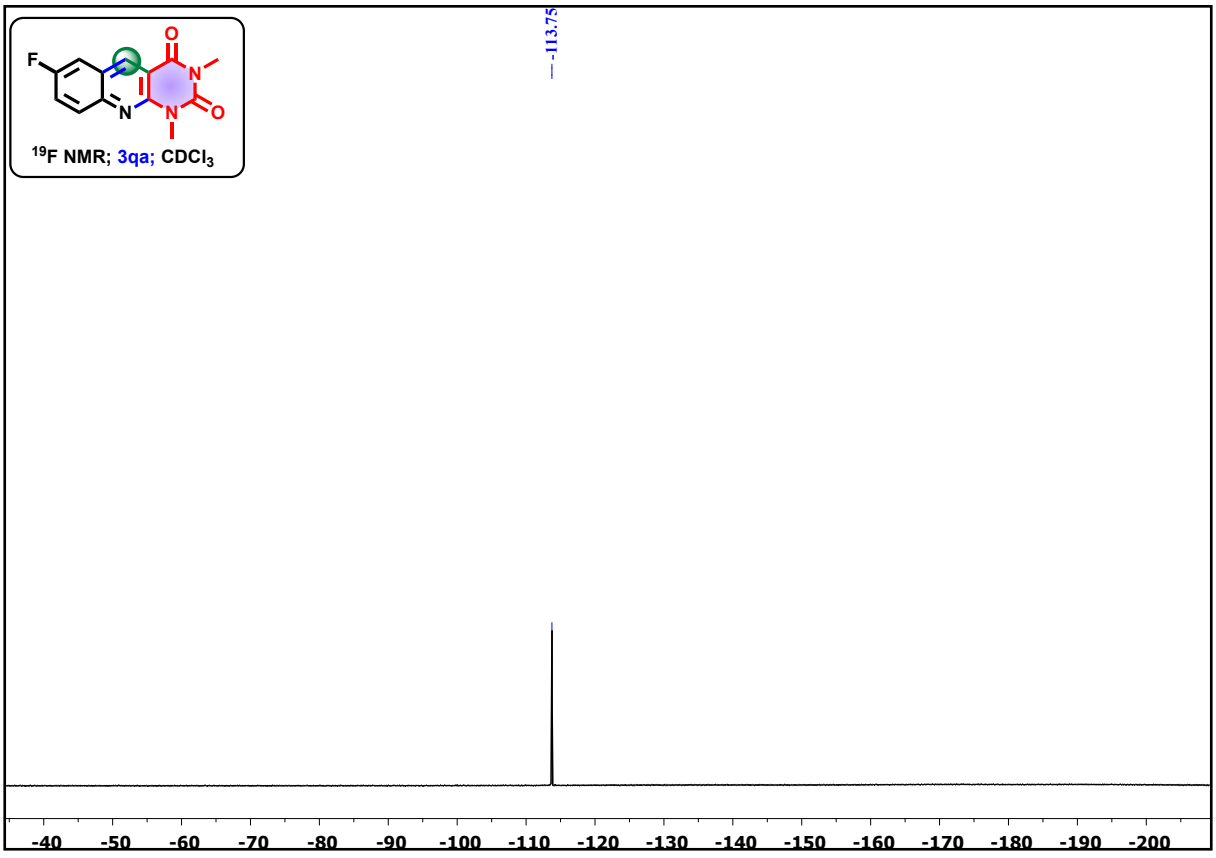


^{1}H and ^{13}C NMR of **3qa** in CDCl$_3$

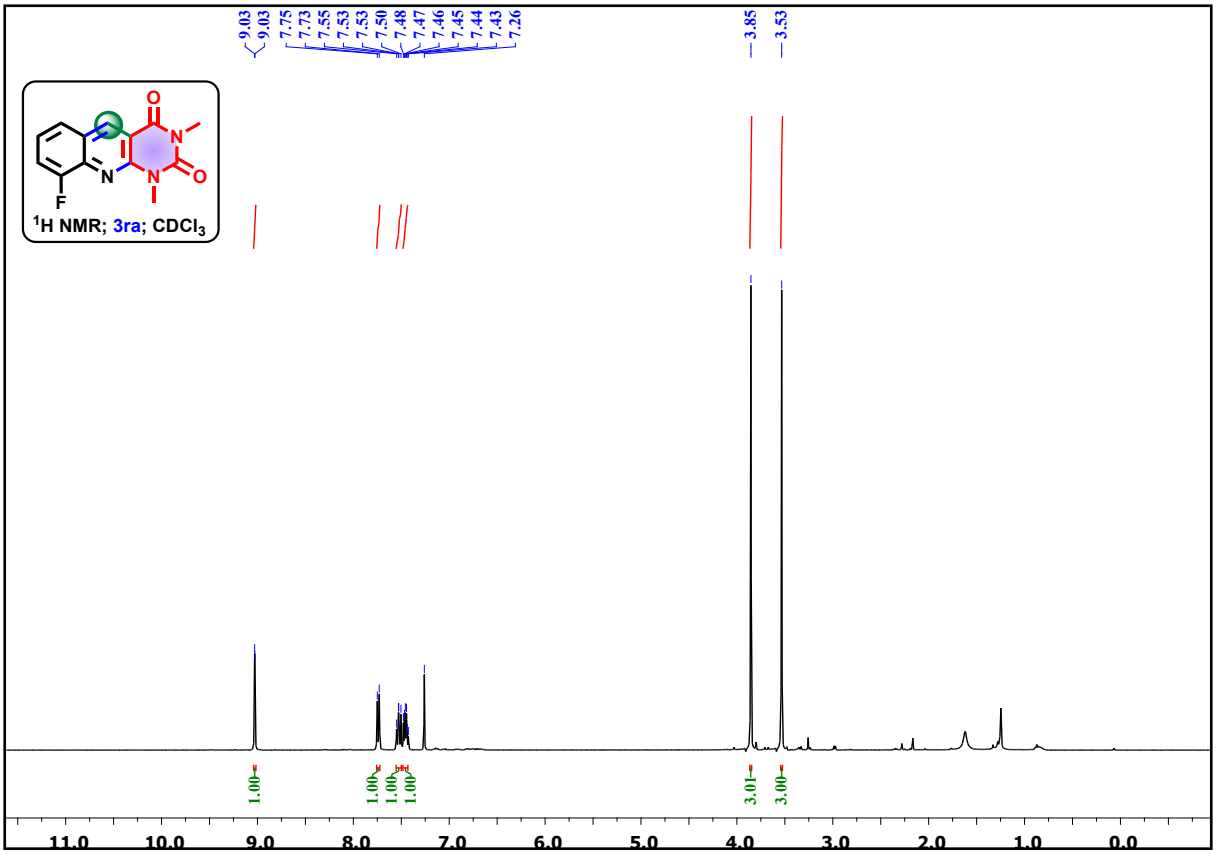


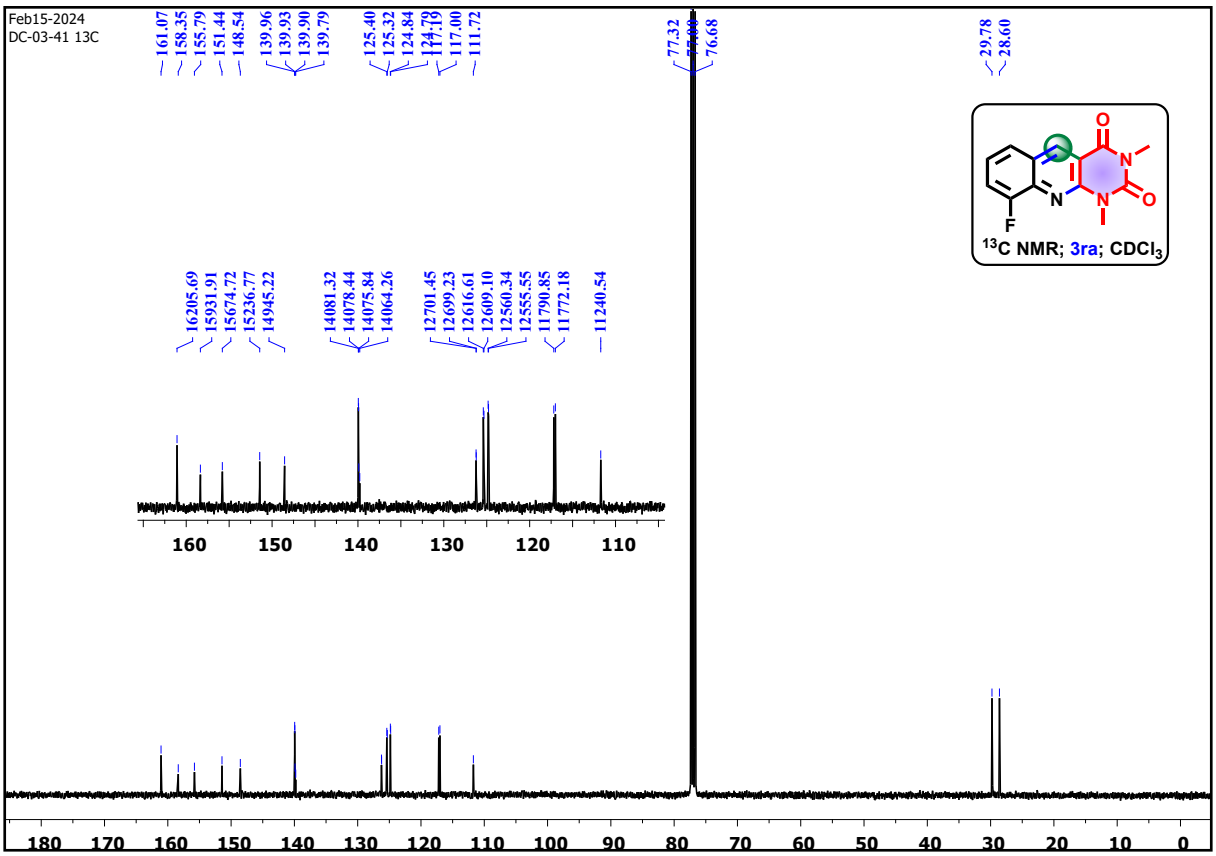


^{19}F NMR of **3qa** in $CDCl_3$

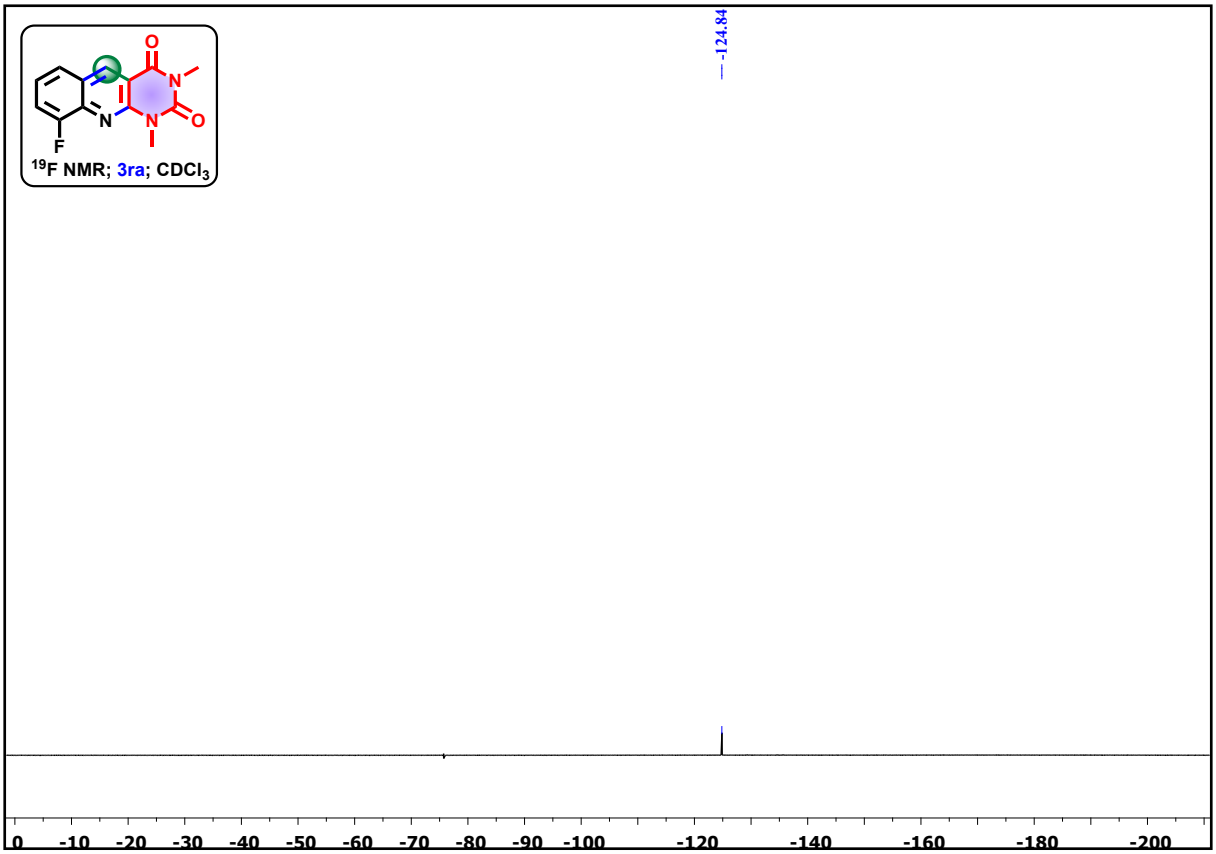


^{1}H and ^{13}C NMR of **3ra** in $CDCl_3$

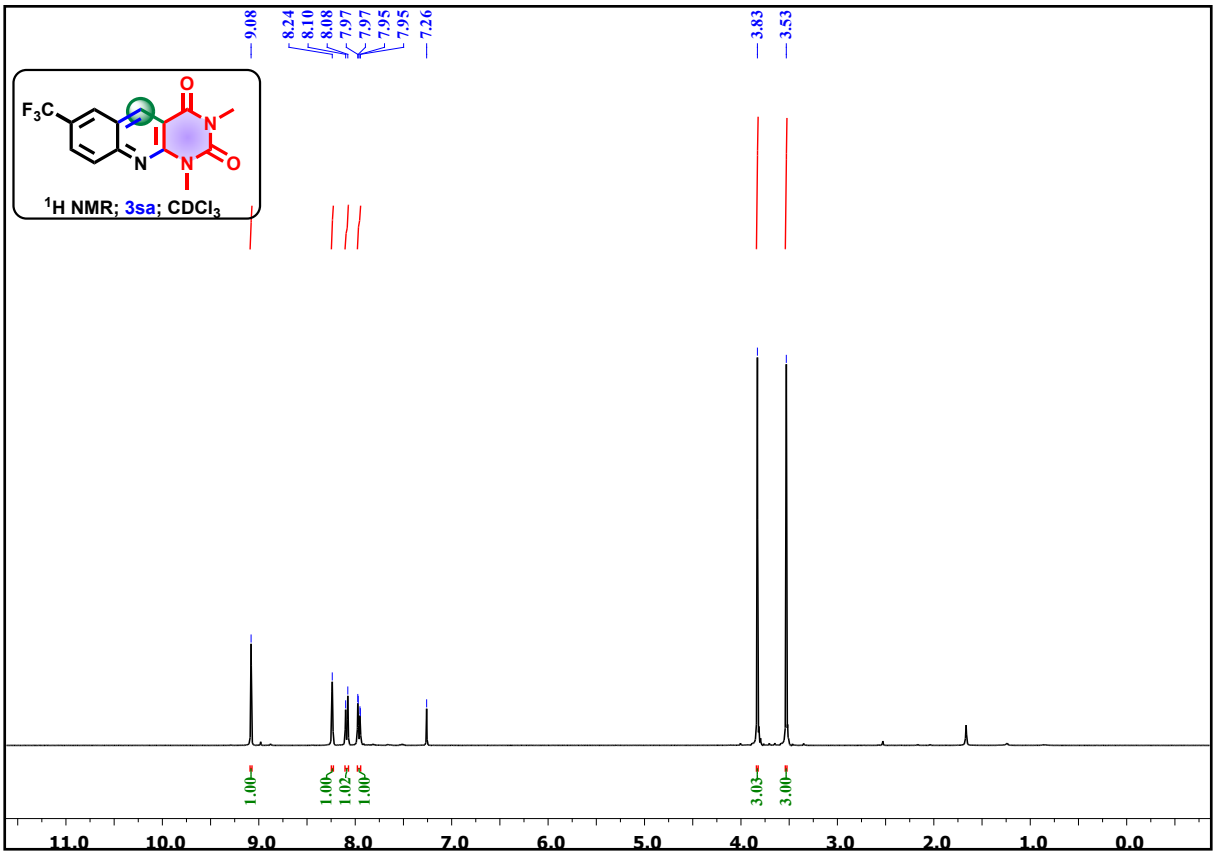




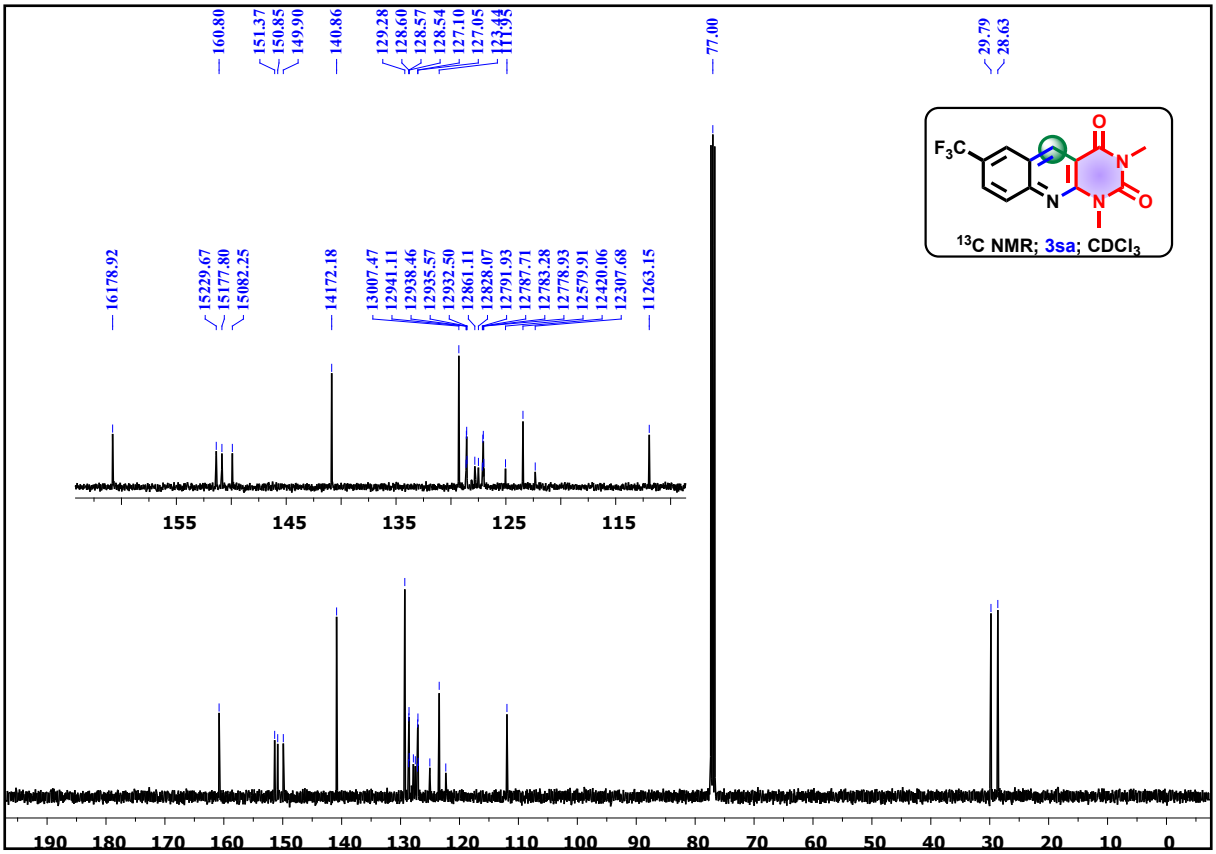
^{19}F NMR of **3ra** in $CDCl_3$

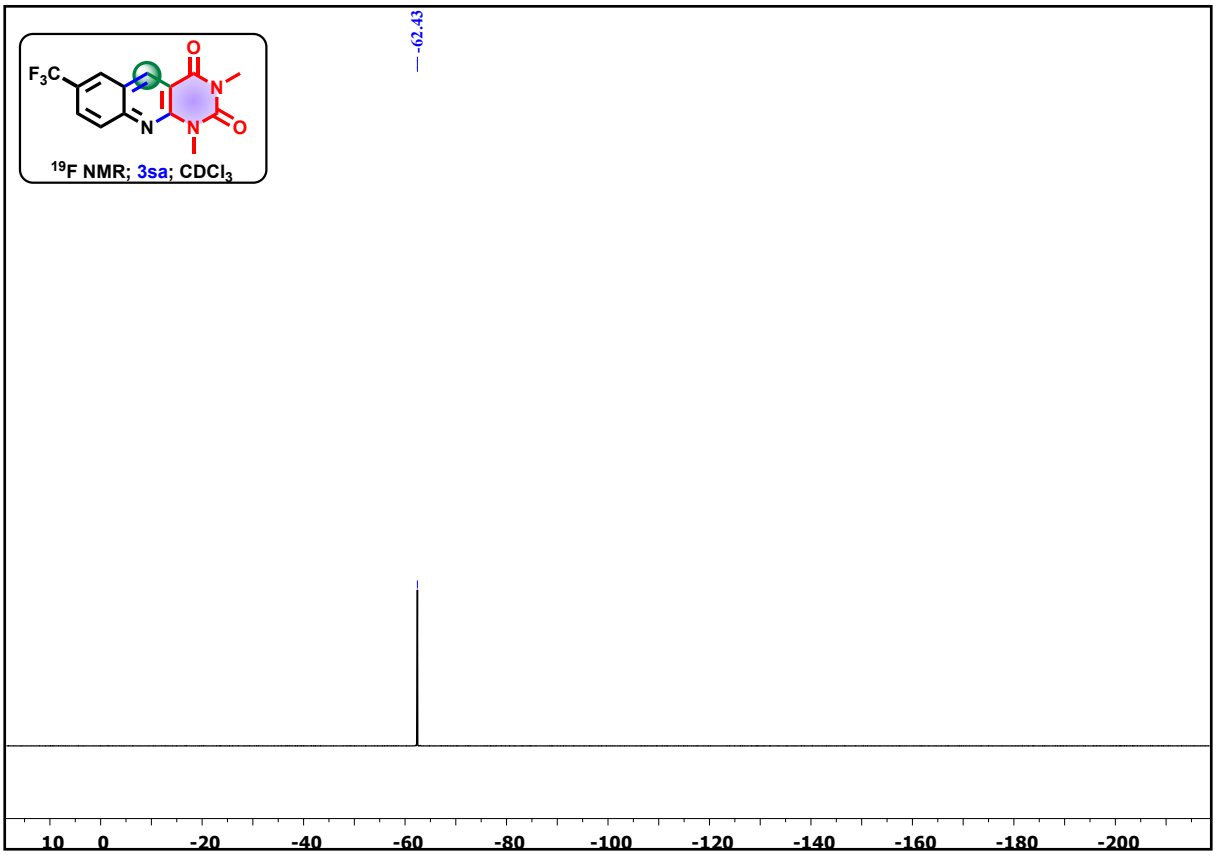


^{1}H, ^{13}C , and ^{19}F NMR of **3sa** in $CDCl_3$

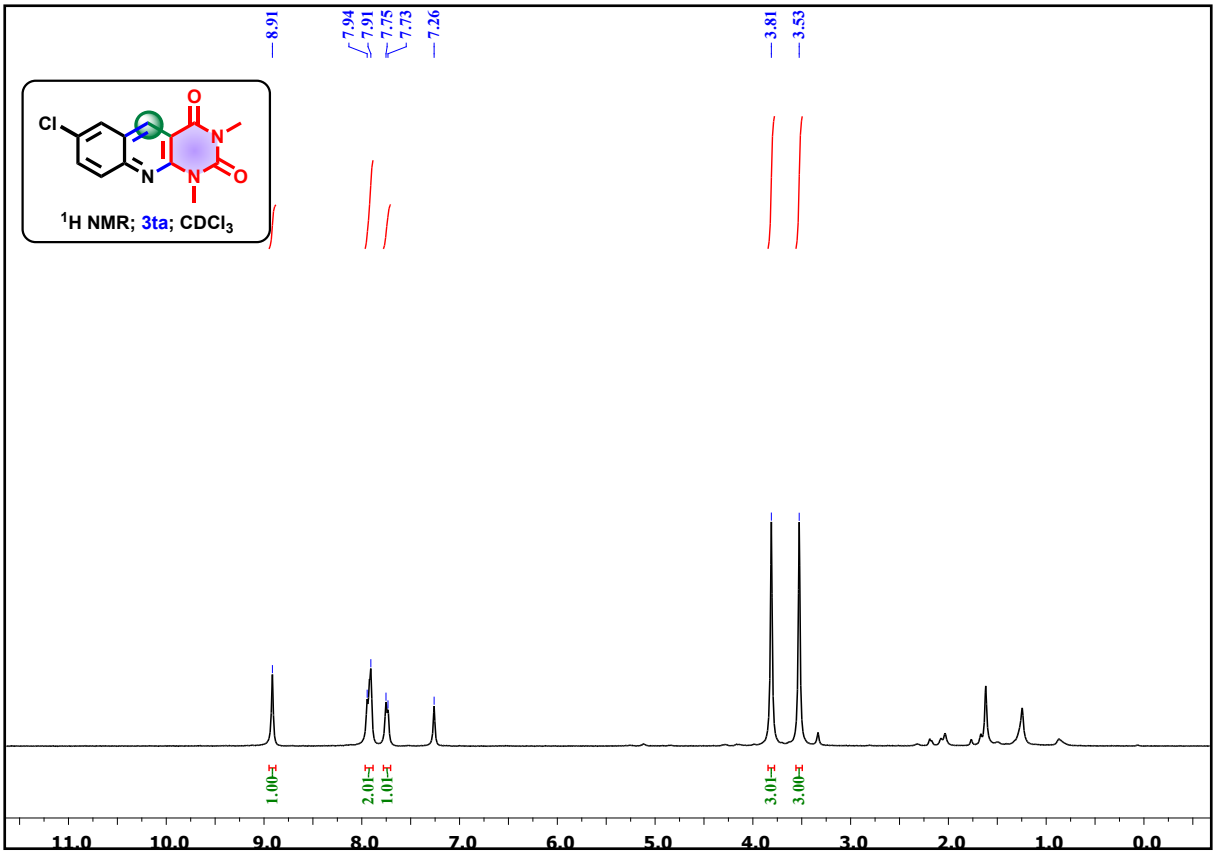


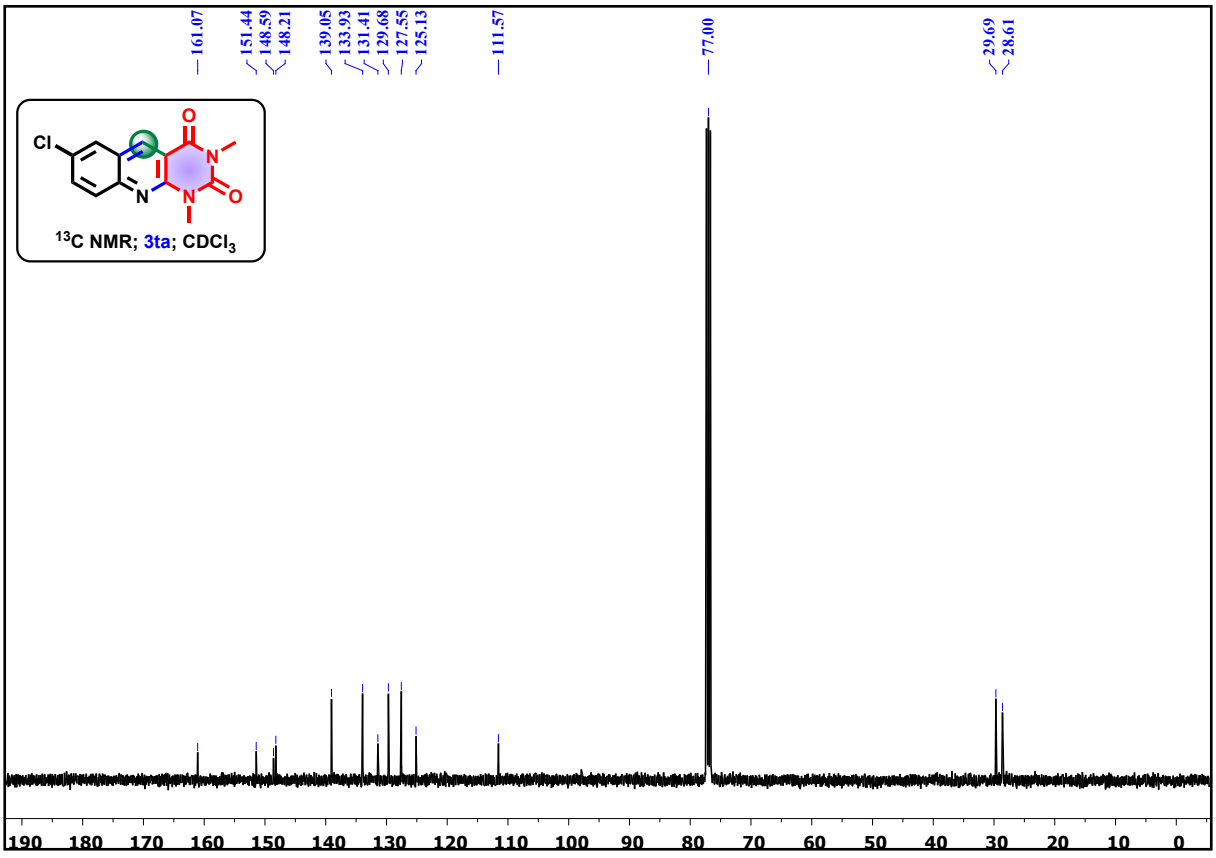
^{1}H and ^{13}C NMR of **3sa** in $CDCl_3$



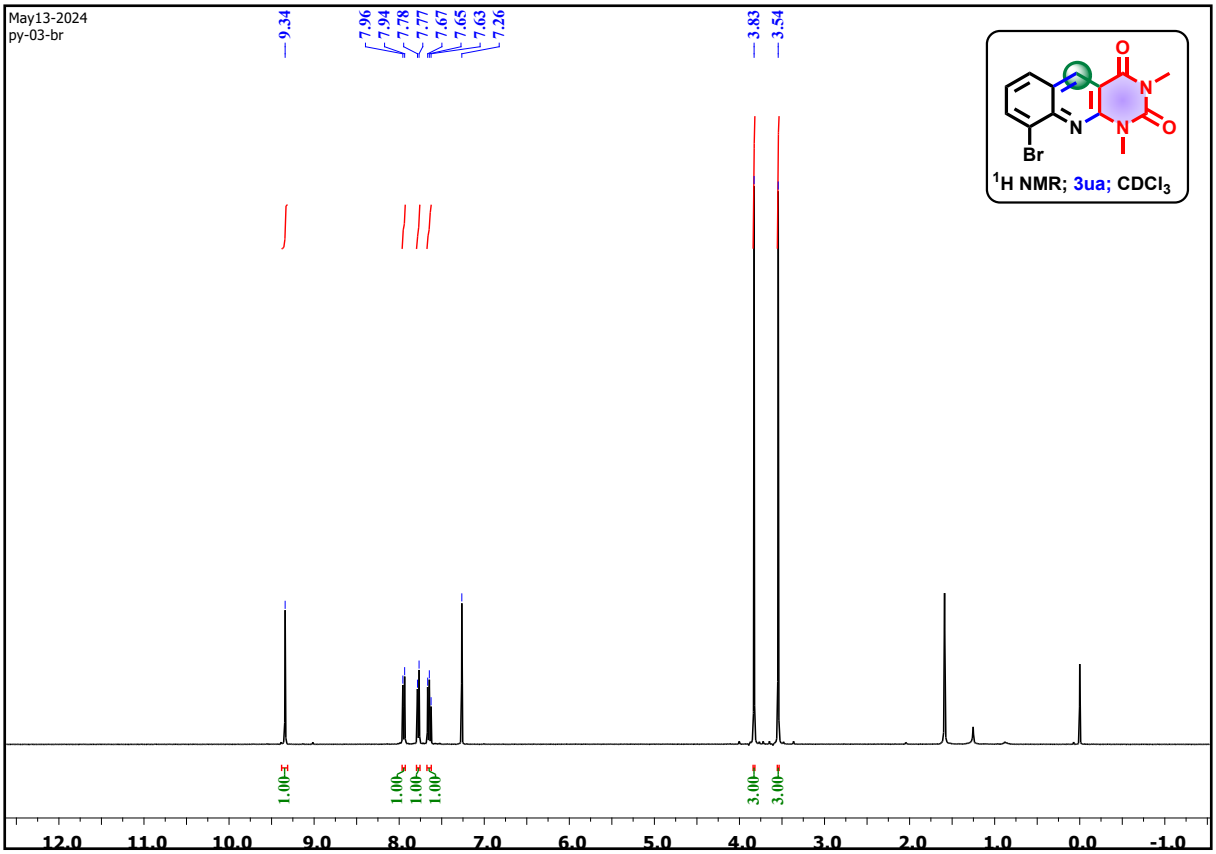


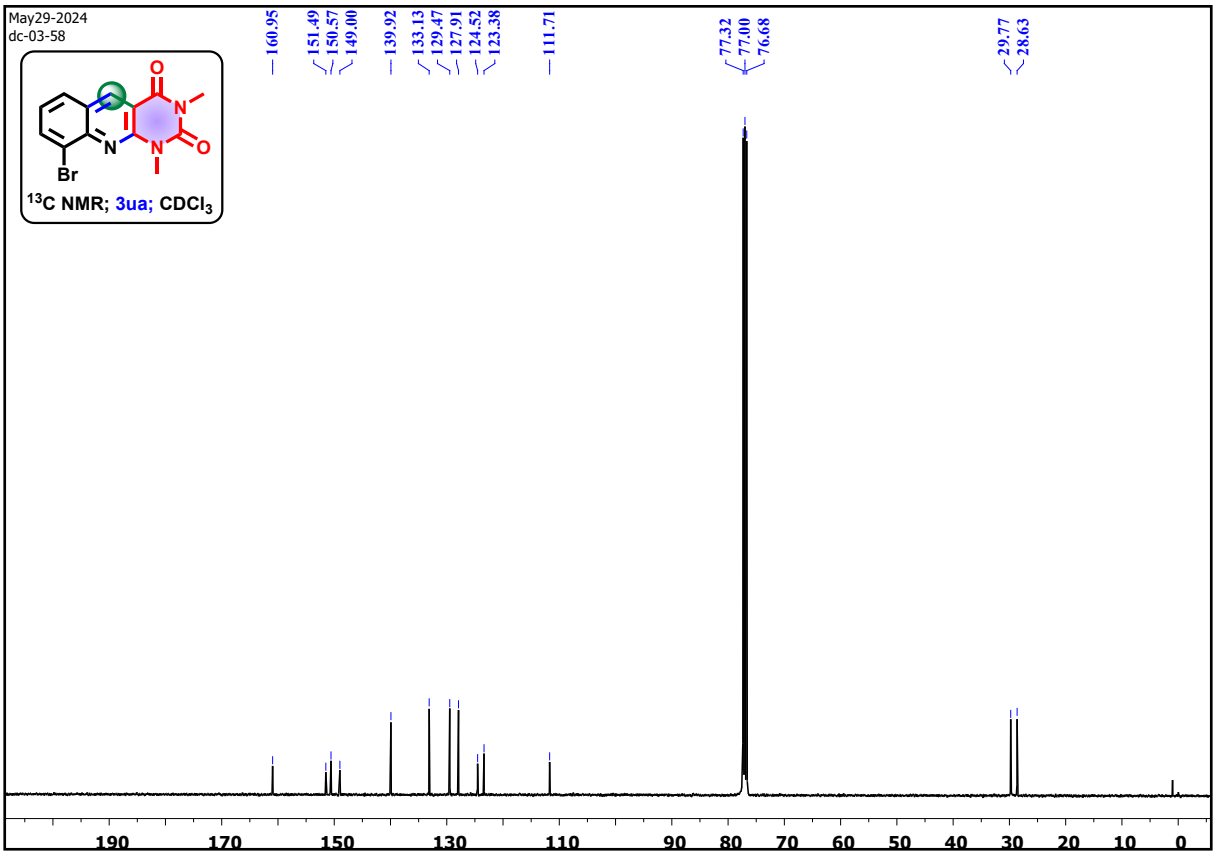
^{1}H and ^{13}C NMR of **3ta** in $CDCl_3$



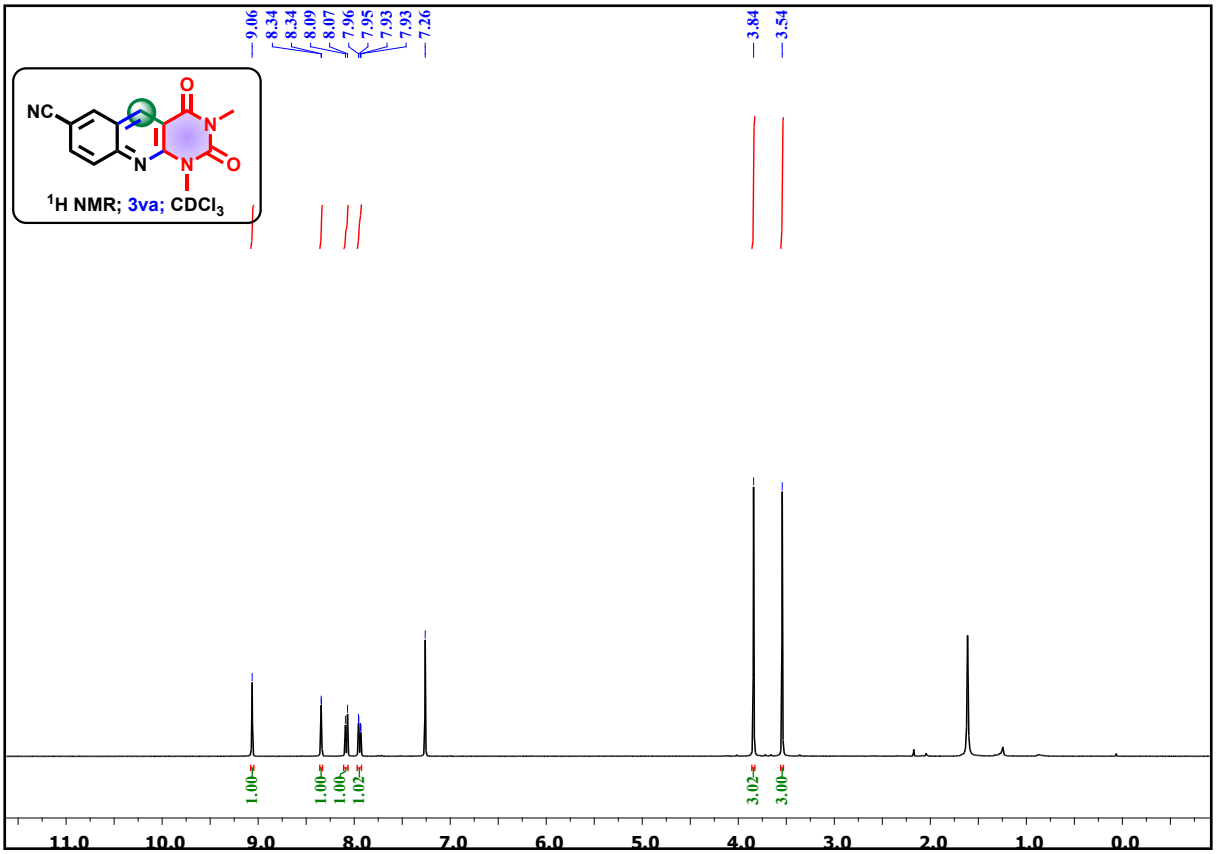


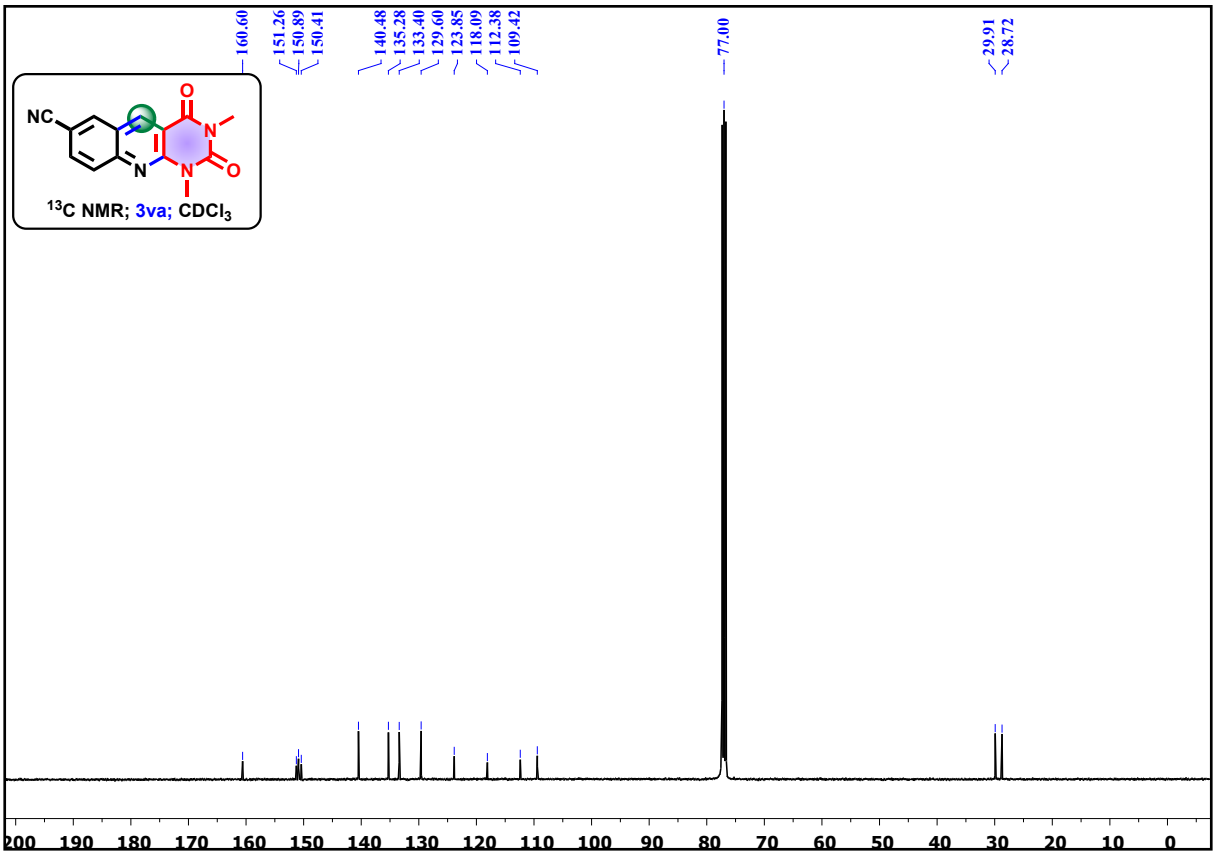
^{1}H and ^{13}C NMR of **3ua** in $CDCl_3$



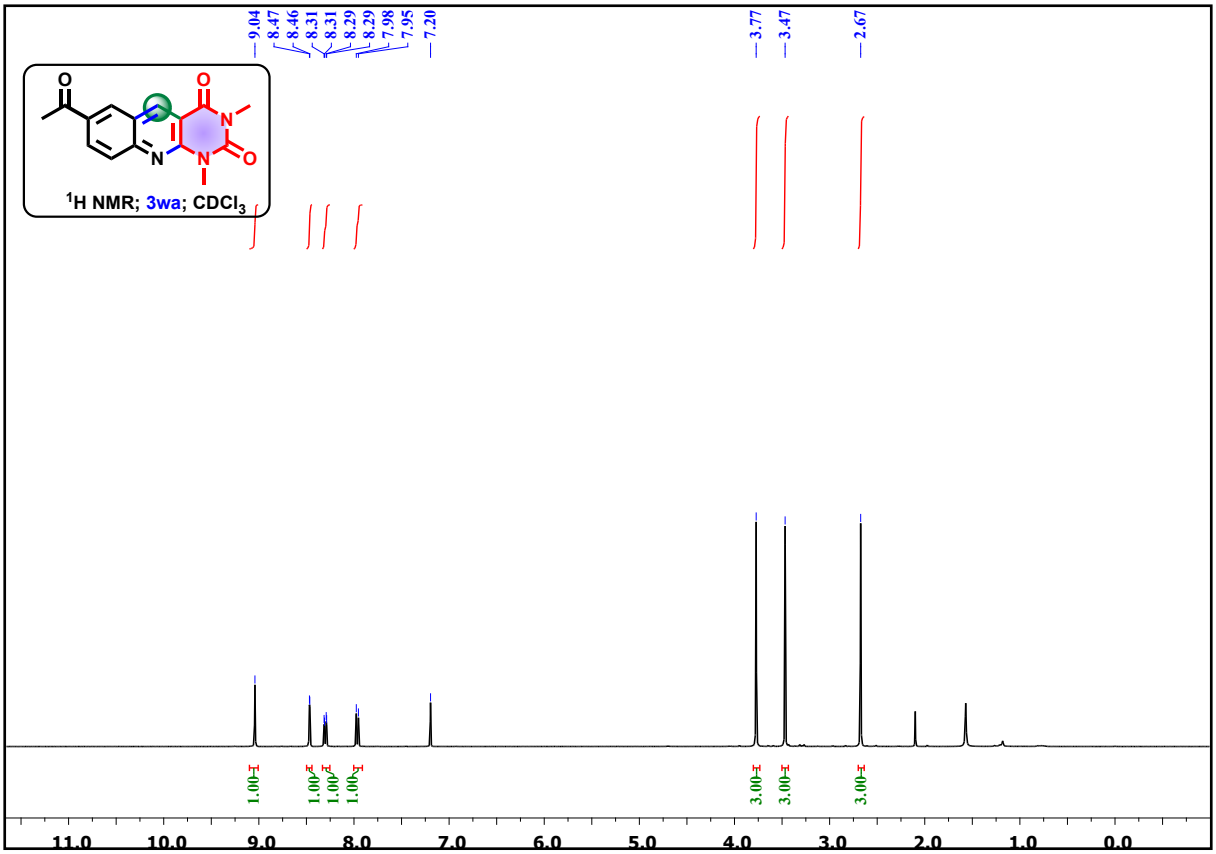


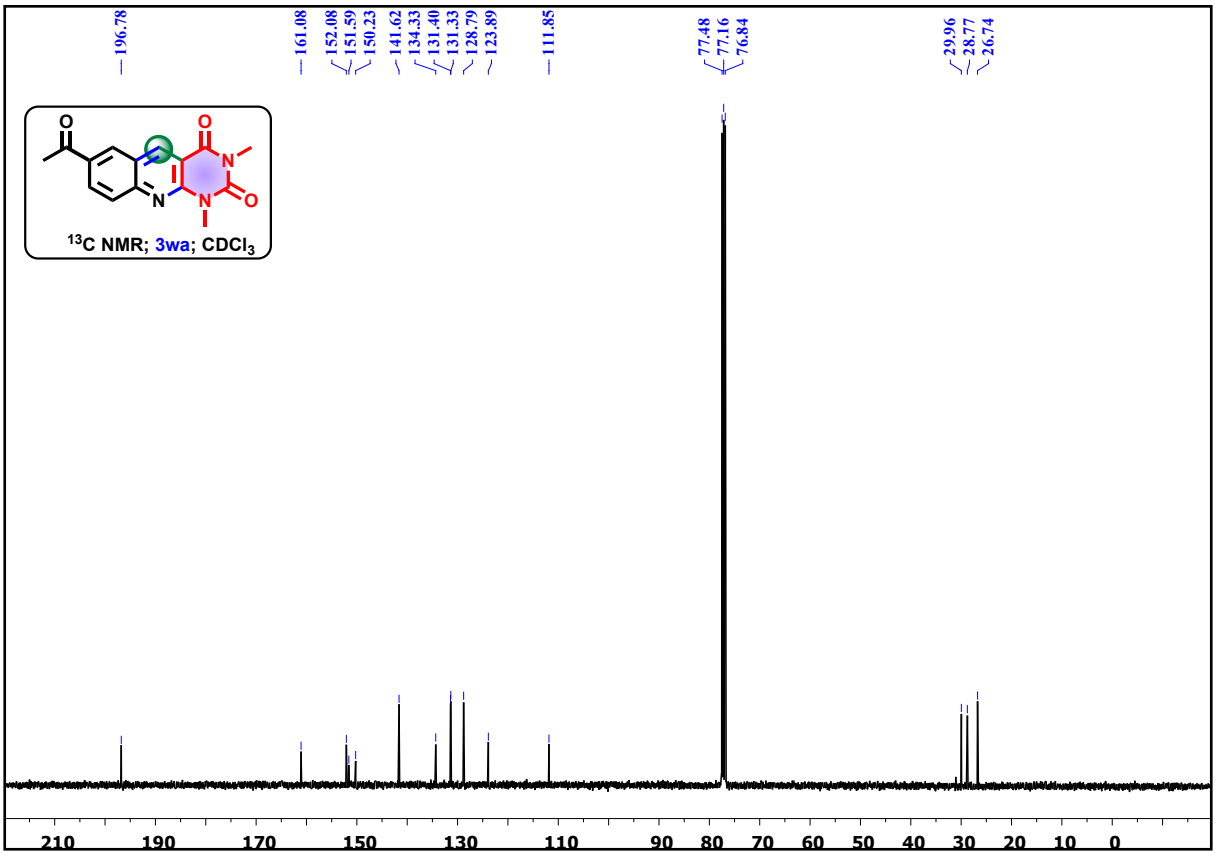
^{1}H and ^{13}C NMR of **3va** in $CDCl_3$



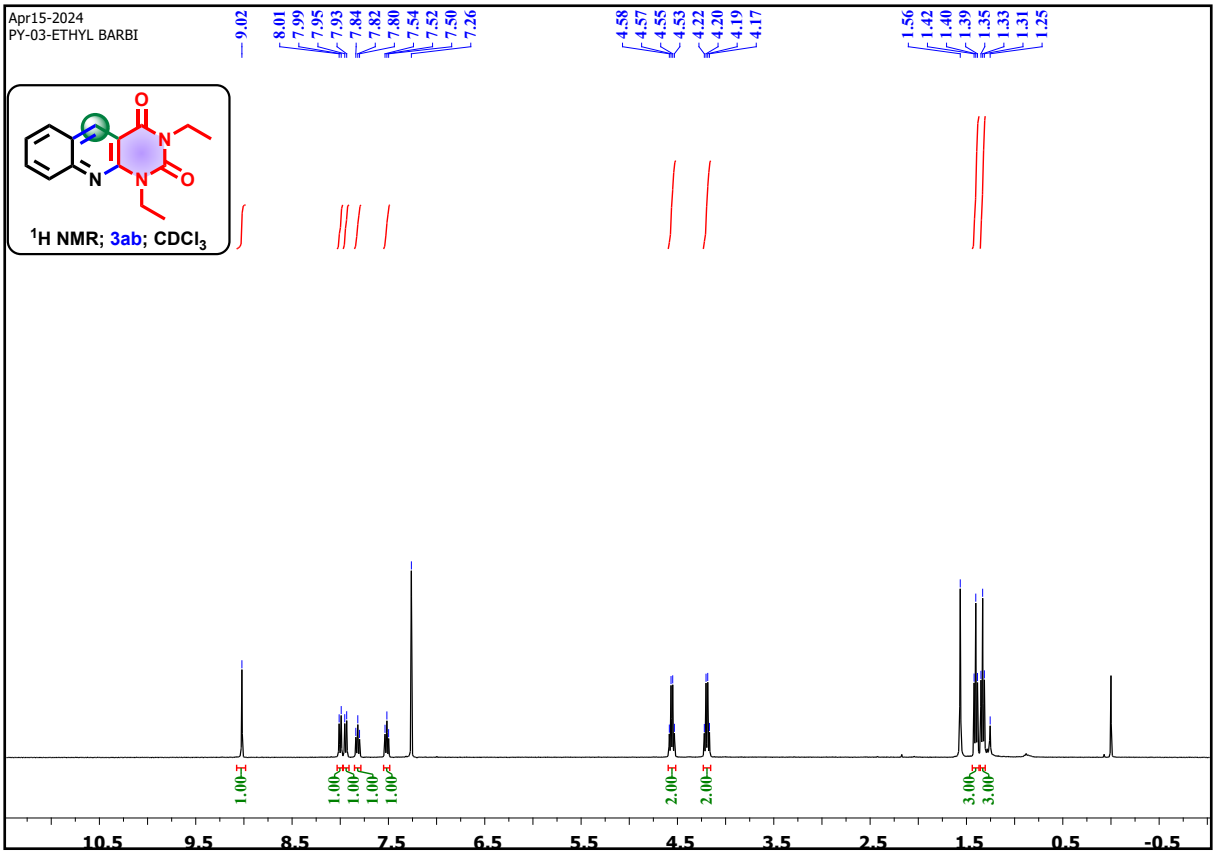


^{1}H and ^{13}C NMR of **3wa** in $CDCl_3$

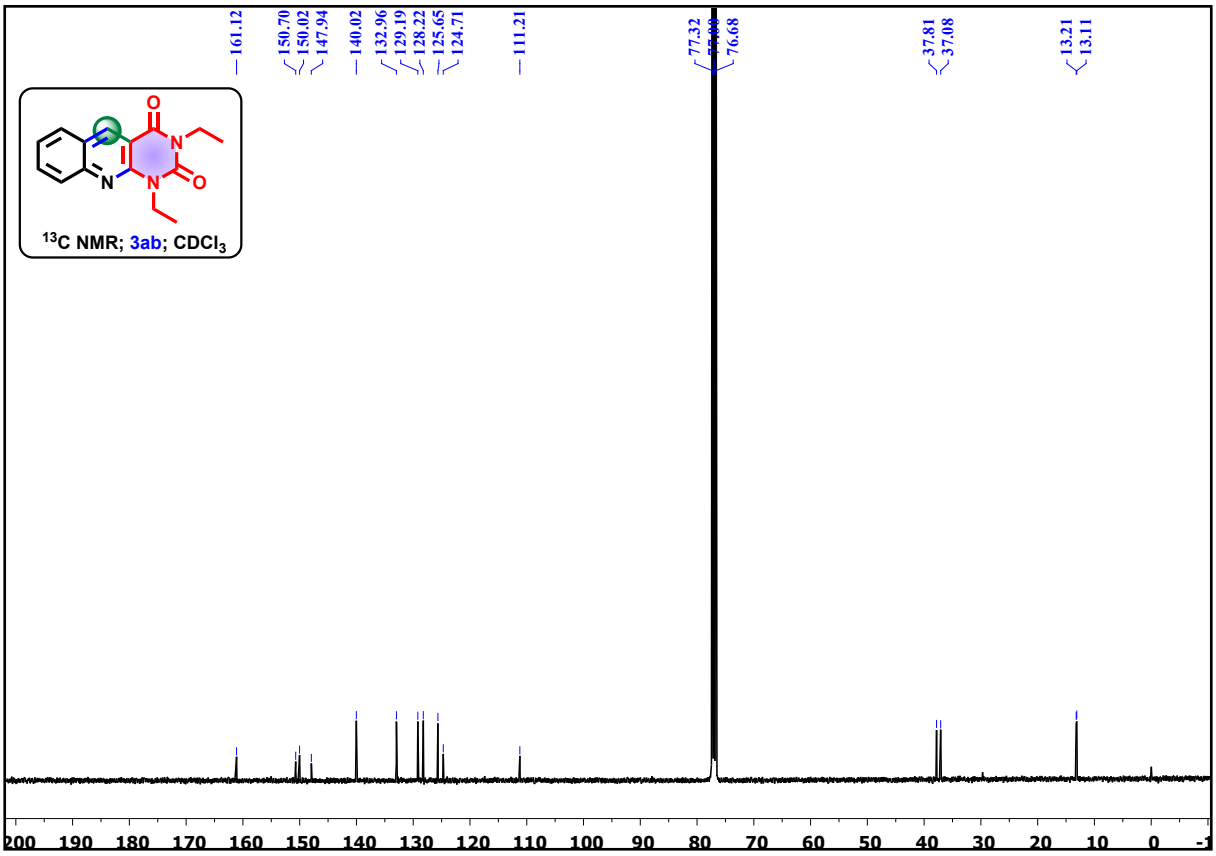




^{1}H and ^{13}C NMR of **3ab** in $CDCl_3$

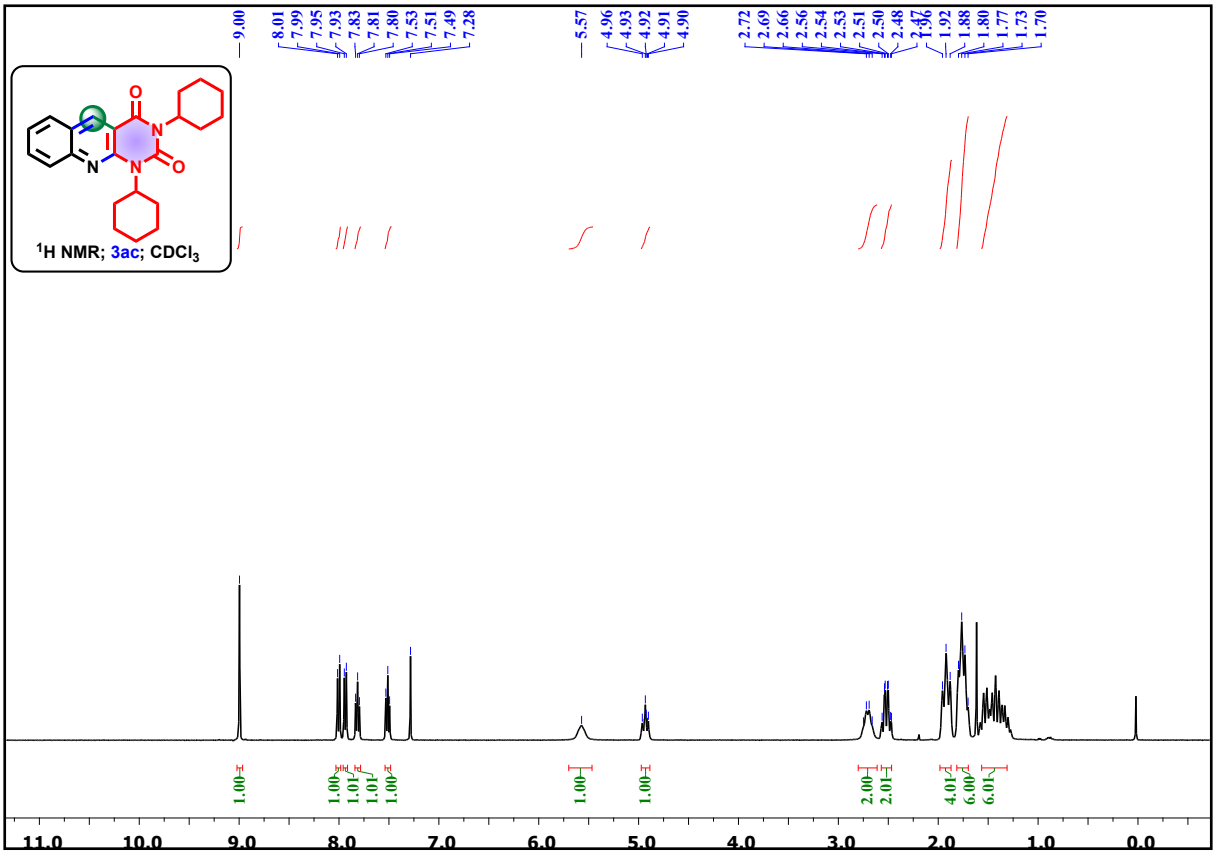


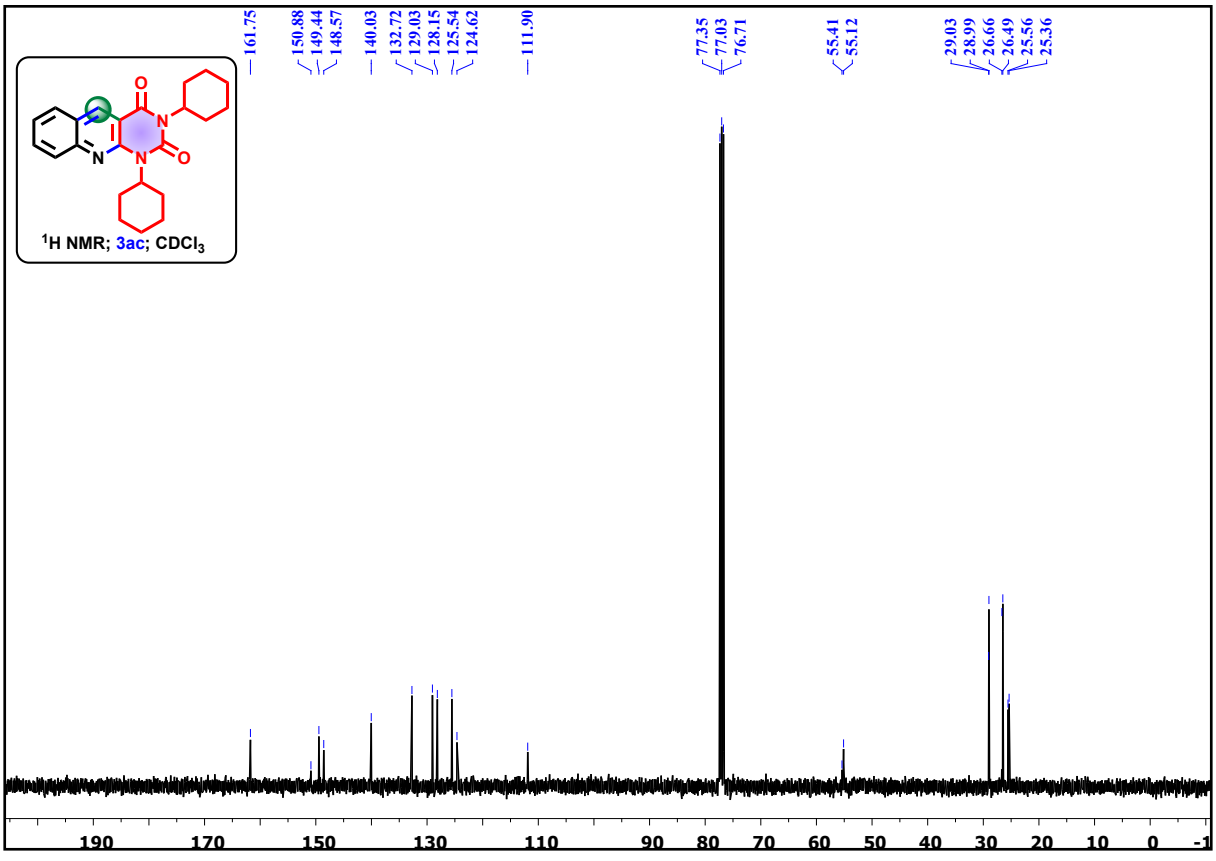
^{1}H NMR; 3ab; $CDCl_3$



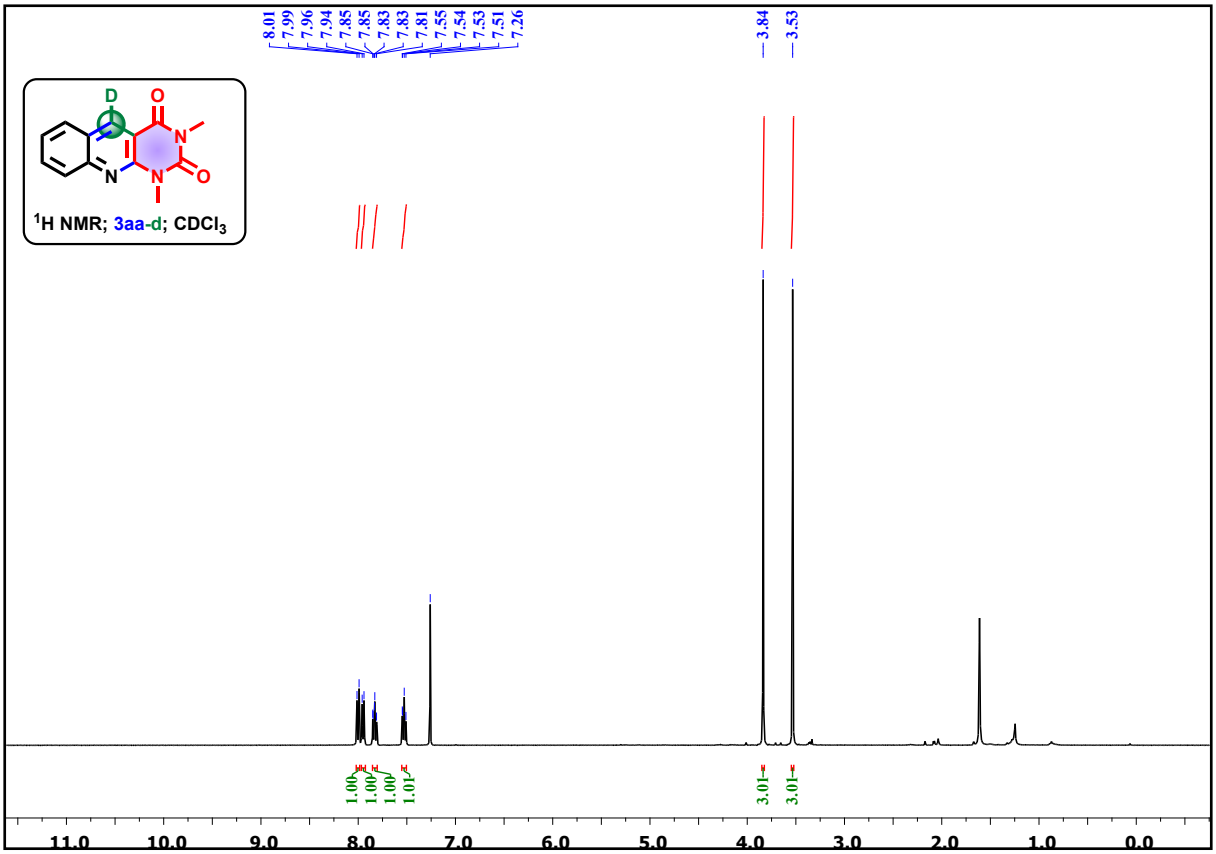
^{13}C NMR; 3ab; $CDCl_3$

^{1}H and ^{13}C NMR of **3ac** in $CDCl_3$





^{1}H and ^{13}C NMR of **3aa-d** in $CDCl_3$



Single crystal X-ray crystallography data of 3aa (ccdc 2358964)

Compound **3aa** was dissolved in a solution of 10% $CHCl_3$/Hexane and 10 mL pear-shaped round bottom flask at room temperature. An appropriate single crystal was selected under a microscope and mounted with paratone oil on a Cryoloop. X-ray data was collected at 100K on Bruker APEX-II CCD Photon 100 difractometer using monochromated Mo Kα radiation (λ = 0.71073 Å). Integrations and scaling were performed using SAINT program[1a] and adsorption correction was done by applying the SADABS program.[1b] The crystal structure was solved by SHELXT 2018/2 (Sheldrick, 2018) and refined by full-matrix least square method using SHELXL-2018/3 (Sheldrick, 2018)[1c] and WinGX v2021.3[1d]. All the non-hydrogen atoms in the structure were refined anisotropically. The hydrogen atoms were fixed by HFIX in their ideal positions and refined using a riding model with isotropic thermal parameters. CCDC 2358964 contains supplementary Crystallographic data for the structure. This dataset can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge

Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0) 1223 336 033; Email: deposit@ccdc.cam.ac.uk]

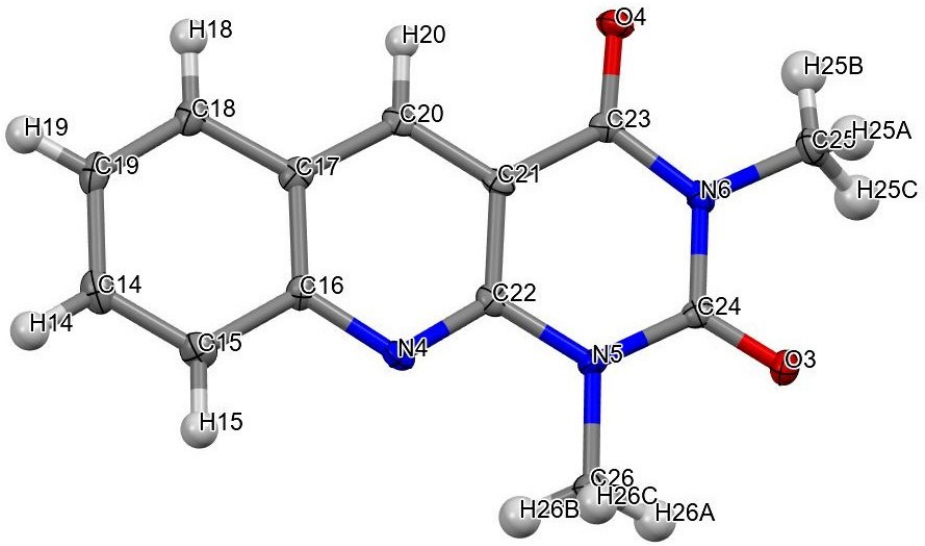


Figure 1. Image of single crystal X-Ray of molecule **3aa** with the 30% ellipsoid probability.

Crystal data of 3aa

Mol. Formula = $C_{13}H_{11}N_3O_2$	Z = 4	Reflections with $I > 2\sigma(I)$ = 2392
M_r = 241.25 g/mol	$F(000)$ = 504	$(\Delta/\sigma)_{max} < 0.001$
Triclinic, P	D_c = 1.472 Mg m^{-3}	$\Delta\rho_{max}$ = 0.32 e Å^{-3}
a = 8.252 (2) Å	Mo $K\alpha$ radiation, λ = 0.71073 Å	$\Delta\rho_{min}$ = −0.32 e Å^{-3}
b = 10.694 (3) Å	θ_{max} = 26.0°, θ_{min} = 2.4°	S = 1.06
c = 12.745 (3) Å	μ = 0.10 mm^{-1}	Least-squares matrix: full
α = 81.615 (13)°	T = 100 K	$R[F^2 > 2\sigma(F^2)]$ = 0.108
β = 82.031 (12)°	θ = 2.4–25.2°	$wR(F^2)$ = 0.269
γ = 80.082 (14)°	Measured reflections = 4193	R_{int} = 0.1079
V = 1088.5 (5) Å^3	Independent reflections = 4193	

$w = 1/[\sigma^2(F_o^2) + (0.075P)^2 + 0.7036P]$ where $P = (F_o^2 + 2F_c^2)/3$
$Fc^* = kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Bond length (Å)

O3—C24	1.211 (5)	C9—C8	1.426 (6)
O4—C23	1.231 (5)	C22—C21	1.418 (6)
O2—C11	1.230 (5)	C5—H5	0.9500
O1—C10	1.205 (5)	C5—C4	1.420 (6)
N5—C24	1.371 (6)	C5—C6	1.354 (6)

N5—C22	1.397 (6)	C20—H20	0.9500
N5—C26	1.474 (5)	C20—C21	1.362 (6)
N3—C11	1.384 (6)	C20—C17	1.410 (6)
N3—C10	1.406 (6)	C4—C7	1.408 (6)
N3—C12	1.464 (6)	C23—C21	1.465 (6)
N2—C9	1.390 (5)	C26—H26A	0.9800
N2—C10	1.368 (6)	C26—H26B	0.9800
N2—C13	1.471 (5)	C26—H26C	0.9800
N6—C24	1.401 (6)	C7—H7	0.9500
N6—C23	1.381 (6)	C7—C8	1.361 (6)
N6—C25	1.466 (5)	C18—H18	0.9500
N4—C16	1.370 (6)	C18—C17	1.415 (6)
N4—C22	1.318 (5)	C2—H2	0.9500
N1—C3	1.366 (5)	C6—H6	0.9500
N1—C9	1.316 (6)	C13—H13A	0.9800
C11—C8	1.464 (6)	C13—H13B	0.9800
C16—C17	1.418 (6)	C13—H13C	0.9800
C16—C15	1.419 (6)	C15—H15	0.9500
C19—H19	0.9500	C15—C14	1.374 (7)
C19—C18	1.359 (6)	C14—H14	0.9500
C19—C14	1.414 (7)	C25—H25A	0.9800
C3—C4	1.419 (6)	C25—H25B	0.9800
C3—C2	1.414 (6)	C25—H25C	0.9800
C1—H1	0.9500	C12—H12A	0.9800
C1—C2	1.363 (7)	C12—H12B	0.9800
C1—C6	1.407 (7)	C12—H12C	0.9800

Bond angle (°)

C24—N5—C22	123.3 (4)	N2—C10—N3	116.9 (4)
C24—N5—C26	116.5 (4)	N5—C26—H26A	109.5
C22—N5—C26	120.1 (4)	N5—C26—H26B	109.5
C11—N3—C10	125.3 (4)	N5—C26—H26C	109.5
C11—N3—C12	118.8 (4)	H26A—C26—H26B	109.5
C10—N3—C12	115.8 (4)	H26A—C26—H26C	109.5
C9—N2—C13	119.5 (4)	H26B—C26—H26C	109.5
C10—N2—C9	123.6 (4)	C4—C7—H7	120.3
C10—N2—C13	116.7 (4)	C8—C7—C4	119.5 (4)
C24—N6—C25	116.7 (4)	C8—C7—H7	120.3
C23—N6—C24	124.7 (4)	C22—C21—C23	120.6 (4)
C23—N6—C25	118.6 (4)	C20—C21—C22	118.3 (4)
C22—N4—C16	116.5 (4)	C20—C21—C23	121.0 (4)
C9—N1—C3	117.6 (4)	C19—C18—H18	120.0
O3—C24—N5	122.7 (4)	C19—C18—C17	120.1 (5)
O3—C24—N6	119.9 (4)	C17—C18—H18	120.0
N5—C24—N6	117.4 (4)	C3—C2—H2	119.7
O2—C11—N3	121.4 (4)	C1—C2—C3	120.6 (5)
O2—C11—C8	123.2 (4)	C1—C2—H2	119.7

N3—C11—C8	115.5 (4)	C1—C6—H6	120.1
N4—C16—C17	124.0 (4)	C5—C6—C1	119.9 (4)
N4—C16—C15	117.6 (4)	C5—C6—H6	120.1
C17—C16—C15	118.4 (4)	N2—C13—H13A	109.5
C18—C19—H19	119.9	N2—C13—H13B	109.5
C18—C19—C14	120.3 (5)	N2—C13—H13C	109.5
C14—C19—H19	119.9	H13A—C13—H13B	109.5
N1—C3—C4	122.9 (4)	H13A—C13—H13C	109.5
N1—C3—C2	118.8 (4)	H13B—C13—H13C	109.5
C2—C3—C4	118.4 (4)	C20—C17—C16	116.2 (4)
C2—C1—H1	119.5	C20—C17—C18	123.5 (5)
C2—C1—C6	121.1 (5)	C18—C17—C16	120.2 (4)
C6—C1—H1	119.5	C9—C8—C11	120.1 (4)
N2—C9—C8	118.5 (4)	C7—C8—C11	120.8 (4)
N1—C9—N2	118.0 (4)	C7—C8—C9	119.0 (4)
N1—C9—C8	123.5 (4)	C16—C15—H15	120.0
N5—C22—C21	118.0 (4)	C14—C15—C16	120.0 (5)
N4—C22—N5	117.6 (4)	C14—C15—H15	120.0
N4—C22—C21	124.4 (4)	C19—C14—H14	119.5
C4—C5—H5	119.6	C15—C14—C19	121.0 (5)
C6—C5—H5	119.6	C15—C14—H14	119.5
C6—C5—C4	120.8 (4)	N6—C25—H25A	109.5
C21—C20—H20	119.7	N6—C25—H25B	109.5
C21—C20—C17	120.5 (4)	N6—C25—H25C	109.5
C17—C20—H20	119.7	H25A—C25—H25B	109.5
C3—C4—C5	119.3 (4)	H25A—C25—H25C	109.5
C7—C4—C3	117.6 (4)	H25B—C25—H25C	109.5
C7—C4—C5	123.1 (4)	N3—C12—H12A	109.5
O4—C23—N6	122.0 (4)	N3—C12—H12B	109.5
O4—C23—C21	122.3 (4)	N3—C12—H12C	109.5
N6—C23—C21	115.8 (4)	H12A—C12—H12B	109.5
O1—C10—N3	119.9 (4)	H12A—C12—H12C	109.5
O1—C10—N2	123.2 (4)	H12B—C12—H12C	109.5
O4—C23—C21—C22	−179.7 (4)	C22—N4—C16—C15	−179.6 (4)
O4—C23—C21—C20	−1.0 (6)	C5—C4—C7—C8	−179.6 (4)
O2—C11—C8—C9	−179.2 (4)	C4—C3—C2—C1	0.3 (6)
O2—C11—C8—C7	−1.9 (7)	C4—C5—C6—C1	0.0 (7)
N5—C22—C21—C20	179.0 (4)	C4—C7—C8—C11	−178.5 (4)
N5—C22—C21—C23	−2.3 (6)	C4—C7—C8—C9	−1.2 (6)
N3—C11—C8—C9	0.0 (6)	C23—N6—C24—O3	−176.6 (4)
N3—C11—C8—C7	177.2 (4)	C23—N6—C24—N5	3.5 (6)
N2—C9—C8—C11	−2.2 (6)	C10—N3—C11—O2	−179.3 (4)
N2—C9—C8—C7	−179.5 (4)	C10—N3—C11—C8	1.6 (6)
N6—C23—C21—C22	0.2 (6)	C10—N2—C9—N1	−178.3 (4)
N6—C23—C21—C20	178.9 (4)	C10—N2—C9—C8	3.2 (6)
N4—C16—C17—C20	0.1 (6)	C26—N5—C24—O3	−2.8 (6)
N4—C16—C17—C18	180.0 (4)	C26—N5—C24—N6	177.0 (4)
N4—C16—C15—C14	179.9 (4)	C26—N5—C22—N4	2.4 (6)

N4—C22—C21—C20	−1.1 (6)	C26—N5—C22—C21	−177.7 (4)
N4—C22—C21—C23	177.7 (4)	C21—C20—C17—C16	−0.1 (6)
N1—C3—C4—C5	−179.6 (4)	C21—C20—C17—C18	−180.0 (4)
N1—C3—C4—C7	1.1 (6)	C18—C19—C14—C15	0.1 (7)
N1—C3—C2—C1	179.8 (4)	C2—C3—C4—C5	0.0 (6)
N1—C9—C8—C11	179.4 (4)	C2—C3—C4—C7	−179.4 (4)
N1—C9—C8—C7	2.1 (6)	C2—C1—C6—C5	0.2 (7)
C24—N5—C22—N4	−174.7 (4)	C6—C1—C2—C3	−0.3 (7)
C24—N5—C22—C21	5.3 (6)	C6—C5—C4—C3	−0.1 (6)
C24—N6—C23—O4	179.1 (4)	C6—C5—C4—C7	179.2 (4)
C24—N6—C23—C21	−0.8 (6)	C13—N2—C9—N1	−3.8 (6)
C11—N3—C10—O1	179.1 (4)	C13—N2—C9—C8	177.7 (4)
C11—N3—C10—N2	−0.7 (6)	C13—N2—C10—O1	3.7 (6)
C16—N4—C22—N5	−179.0 (3)	C13—N2—C10—N3	−176.4 (3)
C16—N4—C22—C21	1.1 (6)	C17—C16—C15—C14	0.8 (6)
C16—C15—C14—C19	−0.4 (7)	C17—C20—C21—C22	0.5 (6)
C19—C18—C17—C16	0.8 (6)	C17—C20—C21—C23	−178.3 (4)
C19—C18—C17—C20	−179.4 (4)	C15—C16—C17—C20	179.2 (4)
C3—N1—C9—N2	−179.8 (3)	C15—C16—C17—C18	−1.0 (6)
C3—N1—C9—C8	−1.3 (6)	C14—C19—C18—C17	−0.3 (7)
C3—C4—C7—C8	−0.3 (6)	C25—N6—C24—O3	1.9 (6)
C9—N2—C10—O1	178.4 (4)	C25—N6—C24—N5	−178.0 (4)
C9—N2—C10—N3	−1.8 (6)	C25—N6—C23—O4	0.6 (6)
C9—N1—C3—C4	−0.3 (6)	C25—N6—C23—C21	−179.3 (4)
C9—N1—C3—C2	−179.8 (4)	C12—N3—C11—O2	2.9 (6)
C22—N5—C24—O3	174.4 (4)	C12—N3—C11—C8	−176.3 (4)
C22—N5—C24—N6	−5.8 (6)	C12—N3—C10—O1	−3.0 (6)
C22—N4—C16—C17	−0.6 (6)	C12—N3—C10—N2	177.2 (4)

Reference:

1. (a) SMART & SAINT. Software Reference manuals. Versions 6.28a & 5.625, Bruker Analytical X-ray System Inc., Madison, Wisconsin, USA, 2001. (b) Sheldrick, G. M. Siemens Area Detector Absorption Correction Program, University of Götingen, Götingen, Germany, 1994. (c) Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3-8. (d) Farrugia, L. J. WinGX-A Windows Program for Crystal Structure Analysis, *J. Appl. Cryst.* **1999**, *32*, 83.