Electronic supplementary information

Efficient and Scalable ultrasound-assisted synthesis of Hydroxy Imidazole N-oxides; Mechanistic insights into the deoximation reactions of Dioximes

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1. General information

All reagents were purchased from Aldrich Chemicals, TCI, and Thomas Baker and used without further purification. All solvents were purchased from commercial suppliers and used after distillation. For column chromatography, 60–120 mesh silica gel (SRL, India) was used and for TLC, Merck plates coated with silica gel 60, F_{254}were used.^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data were recorded on a BRUKER AVANCE 400 spectrometer. Parts per million (ppm) is used to represent chemical shift values (δ), while Hz is used to indicate coupling constants (J). Tetramethyl silane (TMS), an internal standard, was used to record proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) in $CDCl_3$, d^{6}-DMSO, and MeOD. Bruker Alpha III spectrophotometer was used to record FT-IR spectra of the prepared compound in the wave number region from 4000 to 400 cm^{-1} in dry KBr. HRMS data were obtained on Agilent LC_QTOF_HRMS Premier mass spectrometer. Melting points were determined on the BHA melting point apparatus and are uncorrected. The EnSpectr R532 Raman microscope system was used to perform Raman measurements. The Olympus CX41 microscope, equipped with a 532 nm wavelength and a maximum laser power of 50mW, was used as the excitation source. The microscope was outfitted with a 20x objective lens for sample focusing, and the Levenhuk C310 NG was employed for visualization. All the reactions were performed in a 40 KHz sonication bath with ultrasonic power of 50W (Labman scientific instrument, Model No: LMUC-2).

2. Equipment setup

2.1 Reaction setup

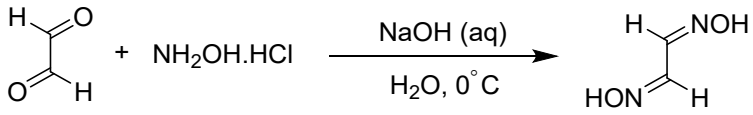
Initially, the most powerful hotspot zone of the ultrasonication bath was identified using a previously described technique[1]. This involved immersion of a small piece of aluminium foil into the bath, identifying the area with the most erosion, and placing a 25 ml round bottom flask containing the reaction mixture in the same X-Y-Z position to ensure reproducibility. The temperature of the bath was maintained at 30º C by the addition or removal of water from ultrasonic bath as an aggregate rise in temperature occurs during any ultrasonic process. The position of the round bottom flask and the level of the water filled in the bath were maintained constant for all the experimental studies. The ultrasonication bath was then operated for the duration specified in the protocol provided.

2.2 Reaction monitoring setup using Raman microscope

The aliquot of the reaction mixture was periodically transferred to a 1 mm thick glass slide and quenched for Raman measurements. The cover slide was used to achieve a uniform surface of the sample. The Raman spectra were accumulated for an interval of 15 minutes for pathway C until the reaction reached completion (90 minutes). The integration time for Raman measurement was 30 seconds for each.

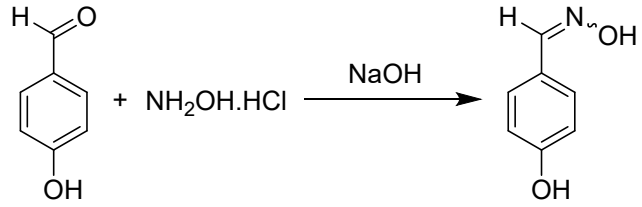
3. Preparation of substrates

3.1 Preparation of glyoxime



The preparation method for glyoxime was adapted from the work of Spencer J. Williams et. al.[2] with some modifications. A solution of NaOH in water (17.2 mL, 172 mmol, 2.00 equiv, 10.0 M) was cooled in an ice bath (0 ºC), and then hydroxylamine hydrochloride (12.0 g, 172 mmol, 2.00 equiv) was added dropwise to the solution. Another solution of glyoxal (12.5 mL, 86.2 mmol, 1 equiv, 40% w/w in water) in water (30 mL) were prepared in a beaker and cooled to 0 °C which was then added dropwise to the solution of NaOH and hydroxylamine hydrochloride. The reaction mixture was stirred for 4 h at 0 °C. The product mixture was then filtered. The obtained solid was recrystallized as white crystals from water (5.41 g, 71.27%).

3.2 Preparation of 4-hydroxybenzaldoxime

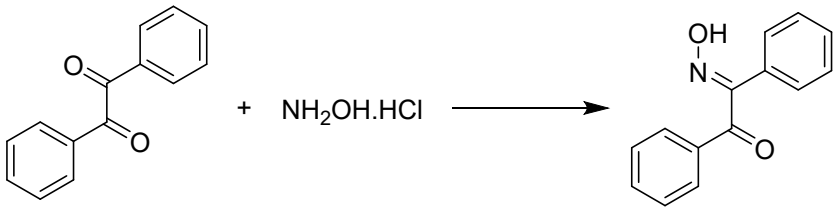


4-hydroxybenzaldoxime was prepared according to the method reported by Rastko D. Vukicevicet.al[3]. 4-Hydroxybenzaldehyde (2.44 g, 20 mmol, 1 equiv), hydroxylamine hydrochloride (1.68 g, 24 mmol, 1.2 equiv) and sodium hydroxide (0.96 g, 24 mmol 1.2 equiv) were ground in a mortar pestle for about 20 minutes or till the spot of aldehyde disappear in TLC. The product mixture was then washed with water to remove inorganic

salts, and the residue was dried in a desiccator to obtain the pure product (2.24 g, 82.11%, m.p. 112ºC).

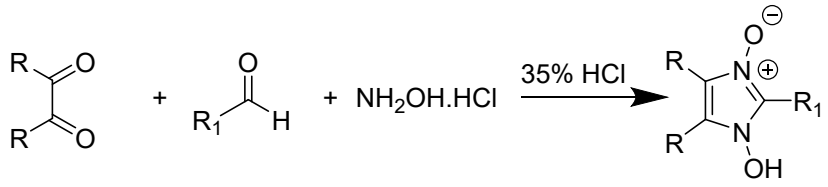
3.3 Preparation α- benzil monoxime

α- Benzil monoxime was prepared according to the reported method[4]. Benzil (21g. 0.1 mol, 1 equiv) was ground to a thin paste with little ethanol, and a concentrated aqueous solution of hydroxylamine hydrochloride (8.75 g, 0.125 mol, 1.25 equiv) was added to it. The entire mixture was then cooled to -5ºC in an ice bath, and 20% aqueous solution of sodium hydroxide (12g, 0.3 mole, 3 equiv) was added drop wise to the stirring solution. Care was taken to keep the temperature below 0ºC during the process. After 90 minutes, the reaction mixture was diluted with water, and the small amount of unreacted benzil was filtered off. The filtrate was just acidified with acetic acid, allowed to stand for 30 minutes to obtain the crude pinkish α- benzil monoxime, and recrystallized from 60% aqueous ethanol (16.3 g, 72.44%, m.p. 142º C).



4. General procedure for the preparation of 2-substituted-1-hydroxy-1H-imidazole 3-oxide

4.1 Pathway A

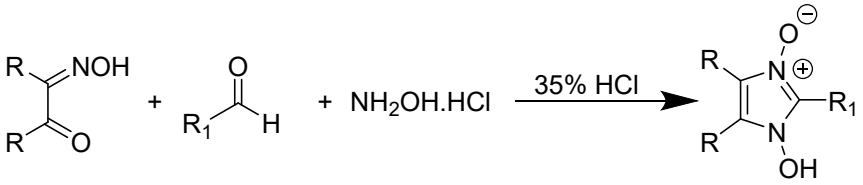


R= H, CH_3, Ph; R_1= any group from aldehyde

α-Dicarbonyl (1 mmol, 2 equiv), hydroxylamine hydrochloride (2.2 mmol, 4.4 equiv), appropriate aldehyde (0.5 mmol, 1 equiv), and 35% HCl (0.315 g, 3 mmol of net HCl) were weighed in a 25 ml round bottom flask and sonicated for 2 h at room temperature (at 50 ºC for **3a**, **3b**, and **3c**). 10-15 ml of 20% methanol-dichloromethane (or an adequate amount to fully dissolve the reaction mixture) was added, and then sodium carbonate was added in a portion-wise manner while the solution was continuously stirred at room temperature in a

magnetic stirrer until the pH of the solution reached 7 (as monitored by pH paper). The reaction mixture was then filtered, and the filtrate was transferred to a separating funnel containing 20 ml of water. The organic layer was isolated. The aqueous layer was further extracted with 20 ml of a 20% methanol-dichloromethane mixture (8 x 20 ml). The organic parts were combined and subsequently dried over sodium sulfate. The dried solution was concentrated to dryness and triturated with diethyl ether or ethyl acetate (8 x 5 ml) to obtain a crude product. To further purify, the crude solid product was recrystallized in methanol (with yields up to 70%).

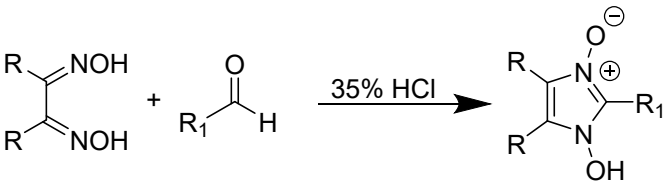
4.2 Pathway B



R= CH_3, Ph; R_1= any group from aldehyde

Monoxime of α-dicarbonyl (1mmol, 2 equiv), hydroxylamine hydrochloride (1.2mmol, 2.4 equiv), appropriate aldehyde (0.5 mmol, 1 equiv), and 35% HCl(0.120g, 1.1mmolof net HCl) were weighed in a 25 ml round bottom flask and sonicated for 30 minutes at room temperature (at 50 ºC for **3a**, **3b** and **3c**). 10-15 ml of 20% methanol-dichloromethane (or an adequate amount to fully dissolve the reaction mixture) was added, and then sodium carbonate was added in a portion-wise manner while the solution was continuously stirred at room temperature in a magnetic stirrer until the pH of the solution reached 7 (as monitored by pH paper). The reaction mixture was then filtered, and the filtrate was transferred to a separating funnel containing 20 ml of water. The organic layer was isolated. The aqueous layer was further extracted with 20 ml of a 20% methanol-dichloromethane mixture (8 x 20 ml). The organic parts were combined and subsequently dried over sodium sulfate. The dried solution was concentrated to dryness and triturated with diethyl ether or ethyl acetate (8 x 5 ml) to obtain a crude product. To further purify, the crude solid product was recrystallized in methanol (with yields up to 96%).

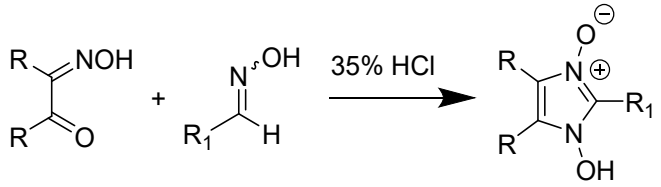
4.3 PathwayC



R= H, CH_3, Ph; R_1= any group from aldehyde

Dioxime of α-dicarbonyl (1 mmol, 2 equiv), appropriate aldehyde (0.5 mmol, 1 equiv), and 35% HCl (0.315g, 3 mmol of net HCl) were weighed in a 25 ml round bottom flask and sonicated for 1 hour 30 minutes at room temperature (at 50 ºC for **3a**, **3b** and **3c**). 10-15 ml of 20% methanol-dichloromethane (or an adequate amount to fully dissolve the reaction mixture) was added, and then sodium carbonate was added in a portion-wise manner while the solution was continuously stirred at room temperature in a magnetic stirrer until the pH of the solution reached 7 (as monitored by pH paper). The reaction mixture was then filtered, and the filtrate was transferred to a separating funnel containing 20 ml of water. The organic layer was isolated. The aqueous layer was further extracted with 20 ml of a 20% methanol-dichloromethane mixture (8 x 20 ml). The organic parts were combined and subsequently dried over sodium sulfate. The dried solution was concentrated to dryness and triturated with diethyl ether or ethyl acetate (8 x 5 ml) to obtain a crude product. To further purify, the crude solid product was recrystallized in methanol (with yields up to 96%).

4.4 Pathway D



R= H, CH_3, Ph; R_1= any group from aldehyde

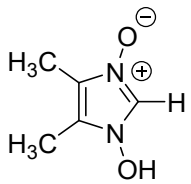
Monoximes of α-dicarbonyl compounds (1mmol, 2 equiv), appropriate aldehyde oxime (0.5 mmol, 1 equiv), and 35% HCl (0.120g, 1.1 mmol of net HCl) were weighed in a 25 ml round bottom flask and sonicated for 15 minutes at room temperature (at 50 ºC for **3a**, **3b** and **3c**). 10-15 ml of 20% methanol-dichloromethane (or an adequate amount to fully dissolve the reaction mixture) was added, and then sodium carbonate was added in a portion-wise manner while the solution was continuously stirred at room temperature in a magnetic stirrer until the pH of the solution reached 7 (as monitored by pH paper). The reaction mixture was then filtered, and the filtrate was transferred to a separating funnel containing 20 ml of water. The

organic layer was isolated. The aqueous layer was further extracted with 20 ml of a 20% methanol-dichloromethane mixture (8 x 20 ml). The organic parts were combined and subsequently dried over sodium sulfate. The dried solution was concentrated to dryness and triturated with diethyl ether or ethyl acetate (8 x 5 ml) to obtain a crude product. To further purify, the crude solid product was recrystallized in methanol (with yields up to 96%).

4.5 Method for gram scale synthesis

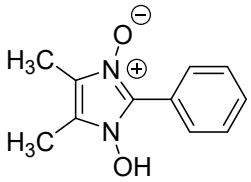
3.438g of diacetyl monoxime (34 mmol, 2 equiv), 2.835 g of hydroxylamine hydrochloride (40.8 mmol, 2.4 equiv), 2.076 g of p- hydroxy benzaldehyde (17 mmol, 1 equiv), and 35% HCl (3.9 g, 37.4 mmol of net HCl) were weighed in a 100 ml round bottom flask, mixed thoroughly with the help of glass rod and sonicated for 40 minutes at room temperature. 60-70 ml of 20% methanol-dichloromethane (or an adequate amount to fully dissolve the reaction mixture) was added, and then sodium carbonate was added in a portion-wise manner while the solution was continuously stirred at room temperature in a magnetic stirrer until the pH of the solution reached 7 (as monitored by pH paper). The reaction mixture was then filtered, and the filtrate was transferred to a separating funnel containing 60 ml of water. The organic layer was isolated. The aqueous layer was further extracted with 50 ml of a 20% methanol-dichloromethane mixture (8 x 50 ml). The organic parts were combined and subsequently dried over sodium sulfate. The dried solution was concentrated to dryness and triturated with diethyl ether or ethyl acetate (8 x 15 ml) to obtain the crude product. To further purify, the crude solid product was recrystallized in methanol (Isolated yield = 3.440 g (91.9%).

5. Characterization of products



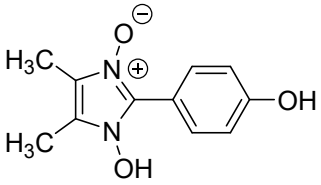
(1a)

1-hydroxy-4,5-dimethyl-1H-imidazole 3-oxide(1a). According to the pathway B,**1a** was synthesized (light brown crystal,123 mg, 96% yield, m.p. found- 203-204 ºC, lit. m.p.[5]-204-205ºC).^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H), 9.06 (s, 1H), 2.00 (s, 6H). ^{13}C NMR (101 MHz, D2O) δ 122.38, 121.69, 6.19.Compound **1a** was reported earlier in the literature.[5]



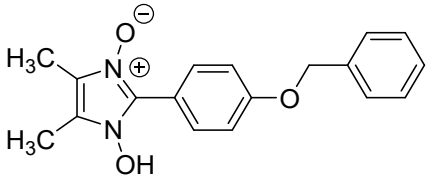
1b

1-hydroxy-4,5-dimethyl-2-phenyl-1H-imidazole 3-oxide (1b). According to the pathway B, **1b** was synthesized (off-white crystal, 196mg, 96 % yield, m.p.-175-176ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.62 (s, 1H), 8.02 – 7.92 (m, 2H), 7.65 (dd, J = 5.2, 1.9 Hz, 3H), 2.28 (s, 6H).^{13}C NMR (101 MHz, DMSO) δ 137.05, 133.65, 131.95, 129.60, 123.22, 119.58, 7.80.**1b** was also reported earlier by G. LaParola[6].



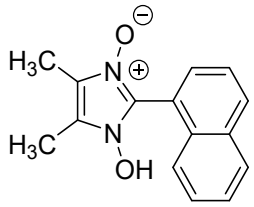
1c

1-hydroxy-2-(4-hydroxyphenyl)-4,5-dimethyl-1H-imidazole 3-oxide (1c). According to the pathway B, **1c**was synthesized (white crystal,212 mg, 94 % yield, m.p. found- 166-169 ºC lit. m.p.[7]-165-168 ºC).^{1}H NMR (400 MHz,DMSO-d_6) δ 13.41 (s, 1H), 10.29 (s, 1H), 7.83 – 7.81 (m, 2H), 7.01 – 6.97 (m, 2H), 2.26 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 161.00, 135.37, 132.02, 122.22, 116.25, 110.83, 7.73.**1c** was reported earlier in the literature.[7].



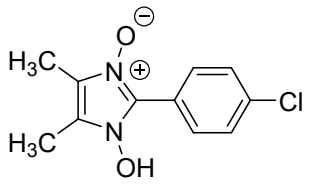
1d

2-(4-(benzyloxy) phenyl)-1-hydroxy-4,5-dimethyl-1H-imidazole 3-oxide (1d). According to the pathway B, **1d** was synthesized (white crystal, 288mg, 93%, yield, m.p.-172-173ºC).^{1}H NMR (400 MHz,DMSO-d_6) δ 7.90 – 7.86 (m, 2H), 7.50 – 7.46 (m, 2H), 7.42 – 7.36 (m, 3H), 7.29 – 7.21 (m, 2H), 5.22 (s, 2H), 2.21 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 161.08, 137.04, 134.42, 131.70, 129.12, 128.91, 128.42, 122.29, 115.72, 112.91, 70.09, 7.61. HRMS (m/z): $[M+H]^+$ calcd for$C_{18}H_{18}N_2O_3$,311.1396; found,311.1395.



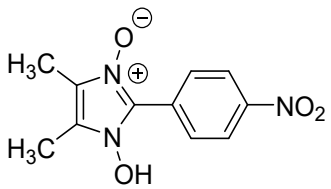
1e

1-hydroxy-4,5-dimethyl-2-(naphthalen-1-yl)-1H-imidazole 3-oxide (1e). According to the pathway B, **1e** was synthesized (brown, 233.6 mg, 91.86% yield, m.p.-217- 218ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 7.1 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.64 (t, 2H), 2.36 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 134.43, 133.54, 133.01, 131.97, 131.19, 129.13, 128.37, 127.52, 125.78, 125.73, 123.27, 118.02, 7.96. LCMS (m/z): $[M+H]^+$ calcd for $C_{15}H_{15}N_2O_2$ 255.1134; found,255.2500.



1f

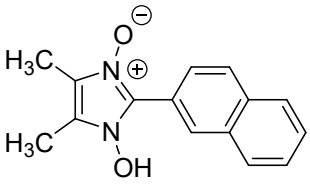
2-(4-chlorophenyl)-1-hydroxy-4,5-dimethyl-1H-imidazole 3-oxide (1f). According to pathway B, **1f** was synthesized (off-white, 0.216 mg, yield 90.75%,m.p. found- 240-244 ºC, lit. m.p.[8] 244).^{1}H NMR (400 MHz,DMSO-d_6) δ 10.36 (s, 1H), 8.04 (d, J = 8.9 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 2.29 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 137.05, 133.65, 131.95, 129.60, 123.22, 119.58, 7.80.**1f** was reported earlier in the literature[8].



1g

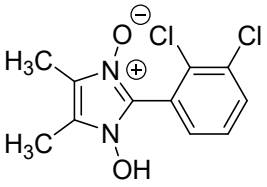
1-hydroxy-4,5-dimethyl-2-(4-nitrophenyl)-1H-imidazole 3-oxide (1g). According to the pathway B, **1g**was synthesized (yellow crystal, 239 mg, 95.9 % yield,m.p. found- 256- 258 ºC, lit. m.p.[8]- 257 ºC). ^{1}H NMR (400 MHz,DMSO-d_6) δ 8.49 – 8.46 (m, 2H), 8.26 – 8.22 (m,

2H), 2.29 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 145.82, 135.66, 132.09, 131.19, 124.54, 123.95, 7.73.**1g** was reported earlier in the literature.[8]



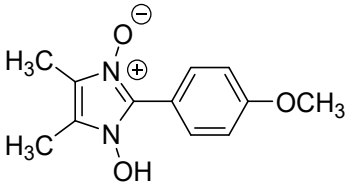
1h

1-hydroxy-4,5-dimethyl-2-(naphthalen-2-yl)-1H-imidazole 3-oxide (1h). According to the pathway B, **1h** was synthesized (white,228.6 mg, 90% yield, m.p.-224- 225ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.66 (d, 1H), 7.84 – 7.75 (m, 3H), 7.46 – 7.44 (m, 2H), 1.85 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 134.02, 133.56, 132.52, 130.34, 129.32, 128.98, 128.86, 128.38, 127.84, 125.39, 122.56, 118.19, 7.42. HRMS (m/z): $[M+H]^+$ calcd for$C_{15}H_{14}N_2O_2$,255.1134; found,255.1135.



1i

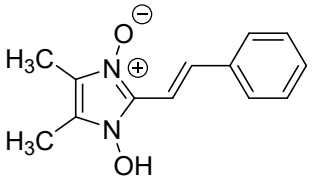
2-(2,3-dichlorophenyl)-1-hydroxy-4,5-dimethyl-1H-imidazole 3-oxide (1i). According to the pathway B, **1i** was synthesized (off-white crystal, 251.16 mg, 91.9 %, yield m.p.-213-214 ºC).^{1}H NMR (400 MHz, DMSO-d_6) δ 13.74 (s, 1H), 8.00 (dd, J = 8.1, 1.5 Hz, 1H), 7.78 (dd, J = 7.8, 1.5 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 2.31 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 134.84, 133.19, 133.12, 132.00, 129.40, 128.91, 123.52, 122.59, 7.80. HRMS (m/z): $[M+H]^+$ calcd for $C_{11}H_{11}Cl_2N_2O_2$,273.0198; found,273.0192.



1j

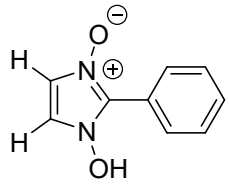
1-hydroxy-2-(4-methoxyphenyl)-4,5-dimethyl-1H-imidazole 3-oxide (1j). According to pathway B,**1j**was synthesized (off-white crystal, 224.45 mg, 95.81% yield, m.p. found- 220-

223 ºC, lit. m.p[8].- 224 ºC)^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 2.26 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 162.13, 134.89, 131.91, 122.42, 114.99, 112.59, 56.14, 7.70.**1j** was reported earlier in the literature.[8]



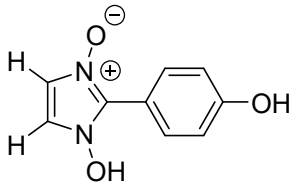
1k

1-hydroxy-4,5-dimethyl-2-styryl-1H-imidazole 3-oxide (1k). According to pathway B, **1k** was synthesized (yellow, 209.3mg, 90.89% yield, m.p.-211-212 ºC).^{1}H NMR (400 MHz, MeOD) δ 7.98 (d, J = 16.7 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.49 – 7.42 (m, 3H), 7.04 (dd, J = 16.7, 1.7 Hz, 1H), 2.17 (s, 6H).^{13}C NMR (101 MHz, MeOD) δ 140.16, 137.55, 135.34, 129.92, 128.95, 127.16, 122.61, 119.89, 112.64, 105.04, 5.61.HRMS (m/z): $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_2$,231.1134; found,231.1138.



2a

1-hydroxy-2-phenyl-1H-imidazole 3-oxide (2a). According to pathway C, **2a** was synthesized (light brown, 168.96 mg, 95.9% yield, m.p.- above 250 ºC)^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 5.9 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.11 (s, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 148.54, 143.62, 130.90, 128.43, 128.29, 116.08.**2a** was also reported earlier by M. S. Pevzner[9].

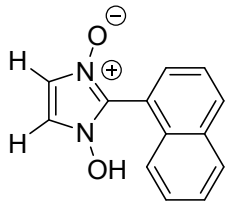


2b

1-hydroxy-2-(4-hydroxyphenyl)-1H-imidazole 3-oxide (2b)

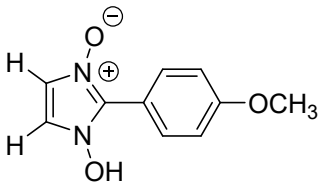
According to pathway C, **2b** was synthesized (white crystal, 184.48 mg, 96% yield, m.p.-decomposed at 248 ºC) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, J = 4.5 Hz, 2H), 7.23-

7.14(m, 2H), 6.76– 6.72 (m, 4H).^{13}C NMR (101 MHz, DMSO-d_6) δ 159.56, 132.57, 130.73, 115.87, 115.58, 113.19. HRMS (m/z): $[M+H]^+$ calcd for $C_9H_9N_2O_3$,193.0613; found,193.0610.



2c

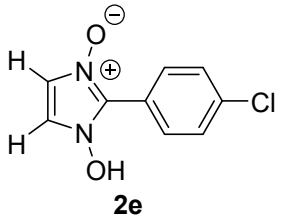
1-hydroxy-2-(naphthalene-1-yl)-1H-imidazole 3-oxide (2c). According to pathway C, **2c** was synthesized (light brown, 201.14 mg, 88.9% yield, m.p.-212-215 ºC)**.**^{1}H NMR (400 MHz, DMSO) δ 8.02 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.40 – 7.34 (m, 2H), 7.27 – 7.21 (m, 4H).^{13}C NMR (101 MHz, DMSO) δ 133.50, 132.51, 131.58, 131.39, 130.80, 128.81, 127.43, 126.96, 126.00, 125.45, 120.16, 116.44.



2d

1-hydroxy-2-(4-methoxyphenyl)-1H-imidazole 3-oxide (2d)

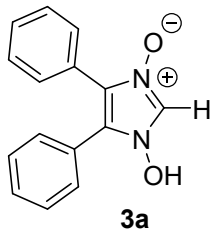
According to pathway C, **2f** was synthesized (off-white crystal, 195.7 mg, 94.9% yield, m.p.-207-208 ºC)^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.15 (m, 2H), 7.03 – 6.83 (m, 4H), 3.79 (s, 3H).^{13}C NMR (101 MHz, DMSO-d6) δ 160.461, 145.939, 131.508, 130.283,116.199,114.091,55.773. HRMS (m/z): $[M+H]^+$ calcd for$C_{10}H_{10}N_2O_3$, 207.0770; found,207.0792.



2e

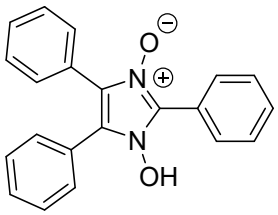
2-(4-chlorophenyl)-1-hydroxy-1H-imidazole 3-oxide (2e). According to pathway C, **2d**was synthesized (off white, 193.20 mg, 91.73% yield,m.p.- above 250 ºC)^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.91 (d, J = 7.8 Hz, 2H), 7.48- 7.30 (m, 4H).^{13}C NMR (101 MHz, DMSO-d_6) δ 134.93, 130.52, 129.89, 128.79, 121.67, 116.89.HRMS (m/z): $[M+H]^+$ calcd for$C_9H_7ClN_2O_2$,211.0724; found,211.0720.



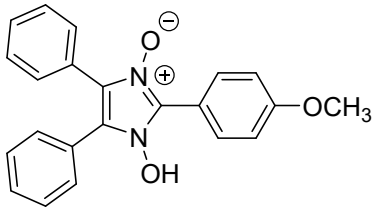
3a

1-hydroxy-4,5-diphenyl-1H-imidazole 3-oxide (3a). According to pathway B, **3a**was synthesized (white crystal, 241.92 mg, 95.89 % yield, m.p. found -226-229 ºC, lit m.p.[5] 227–229 ◦C) ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 7.46 – 7.34 (m, 10H).^{13}C NMR (101 MHz, DMSO-d_6) δ 130.72, 130.29, 129.24, 128.10, 126.44, 124.81.**3a** was also reported earlier by S. Bartz[5].



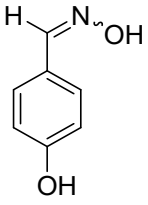
3b

1-hydroxy-2,4,5-triphenyl-1H-imidazole 3-oxide (3b). According to pathway B, **3b**was synthesized (pale purple crystal, 308.3 mg, 93.88% yield, m.p.-215- 218ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 – 8.18 (m, 2H), 7.72 – 7.66 (m, 3H), 7.59 – 7.54 (m, 4H), 7.49 – 7.44 (m, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 136.76, 132.74, 131.09, 130.87, 130.57, 129.48, 129.36, 126.85, 124.61, 120.39. LCMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{16}N_2O_2$ 329.1290; found, 329.2223.



3c

1-hydroxy-2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole 3-oxide (3c). According to pathway B, **3c** was synthesized (off white, 336.5 mg, 93.89% yield, m.p.-233-235 ºC)^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 7.94 (m, 2H), 7.54 – 7.40 (m, 8H), 7.29 – 7.18 (m, 2H), 7.14 – 7.07 (m, 2H), 3.84 (s, 3H).**3c** was also reported earlier in the literature[7].

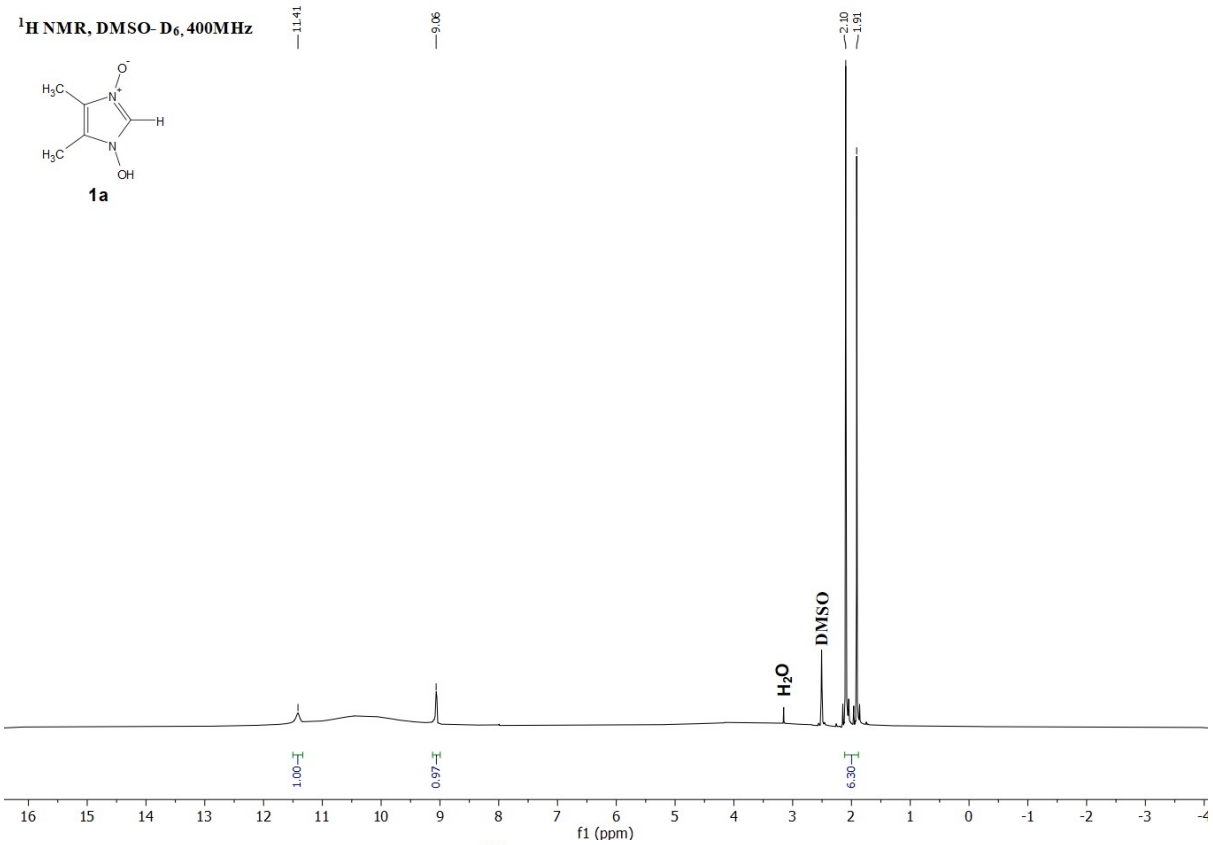


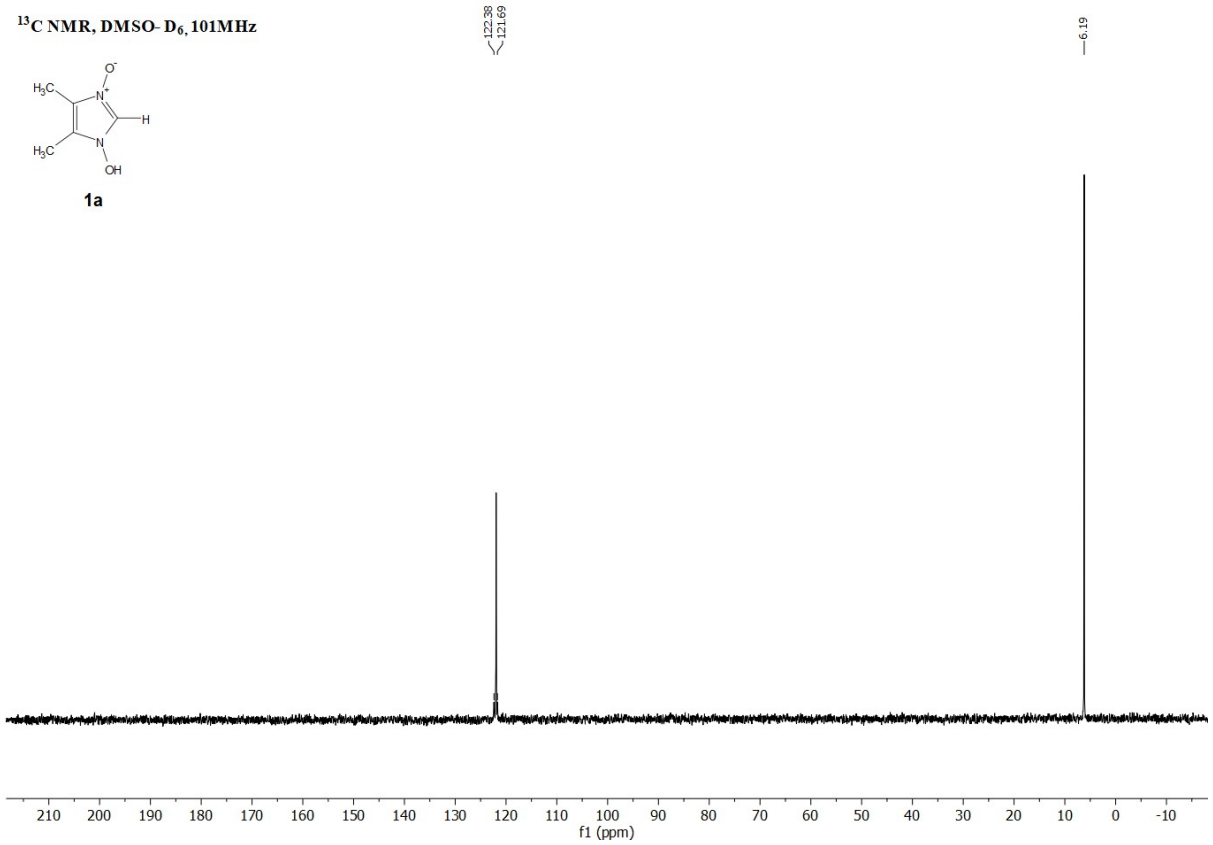
4

4-Hydroxybenzaldehyde oxime(4). Off white, m.p. found- 110- 112ºC lit m.p.[10]- 112º C^{1}H NMR (400 MHz, DMSO- d_6) δ 10.85 (s, 1H), 9.80 (s, 1H), 8.00 (s, 1H), 7.40 (d, J = 8.3 Hz, 2H), 6.80 – 6.74 (m, 2H).. ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.05, 159.09, 133.05, 128.53, 124.57, 116.11, 115.61.

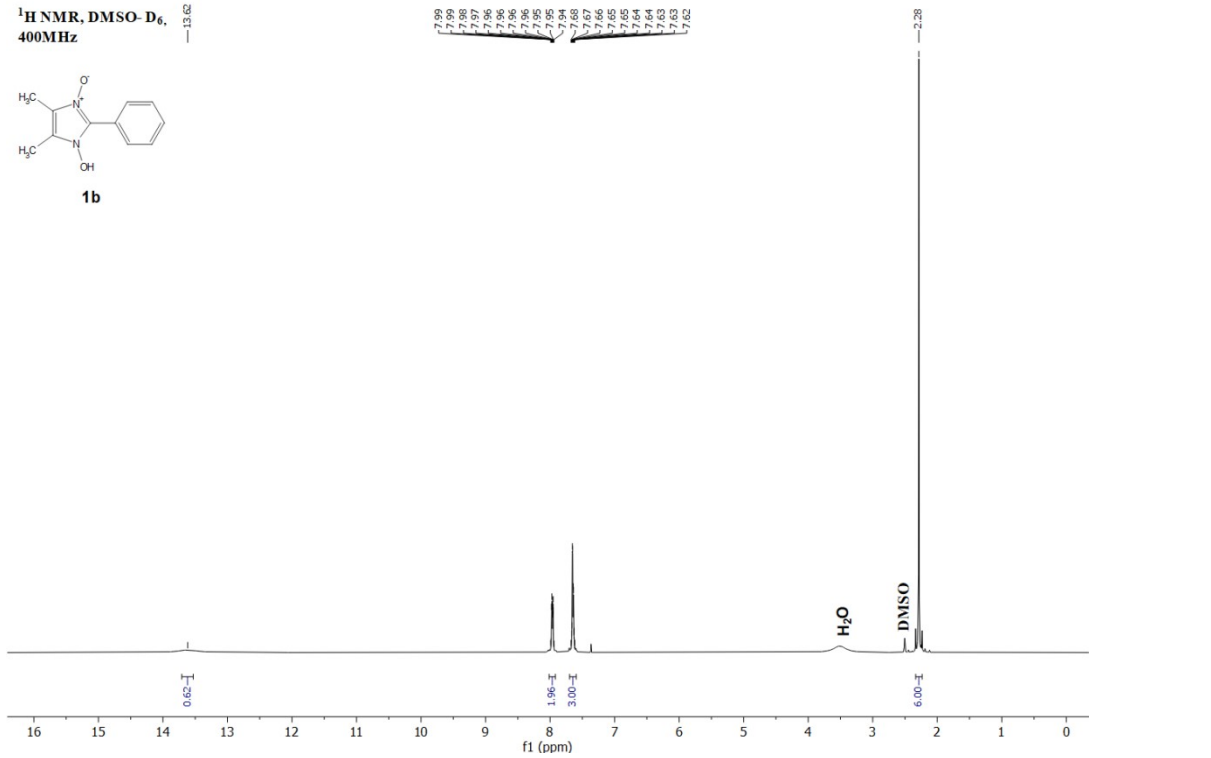
6.^{1}H and C^{13} NMR spectra

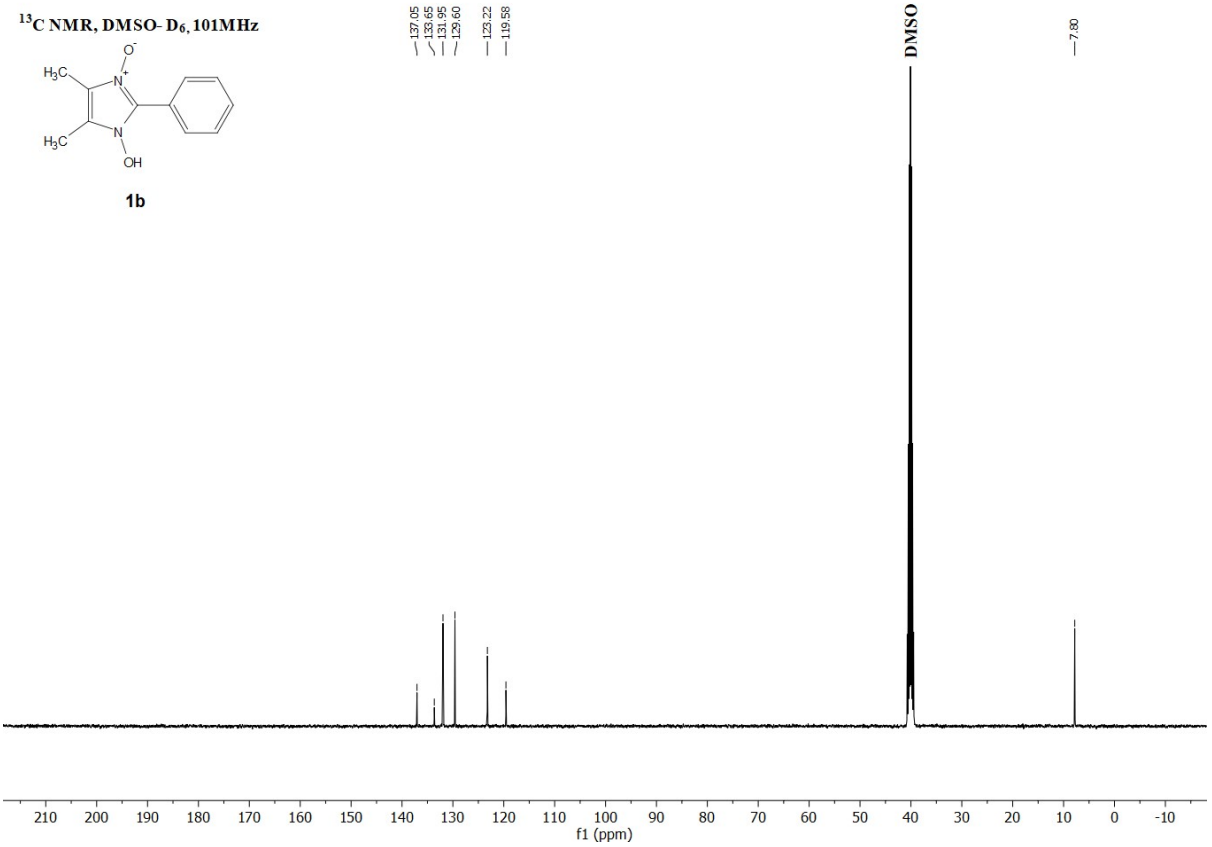
6.1.^{1}H and C^{13} NMR spectra of compound 1a



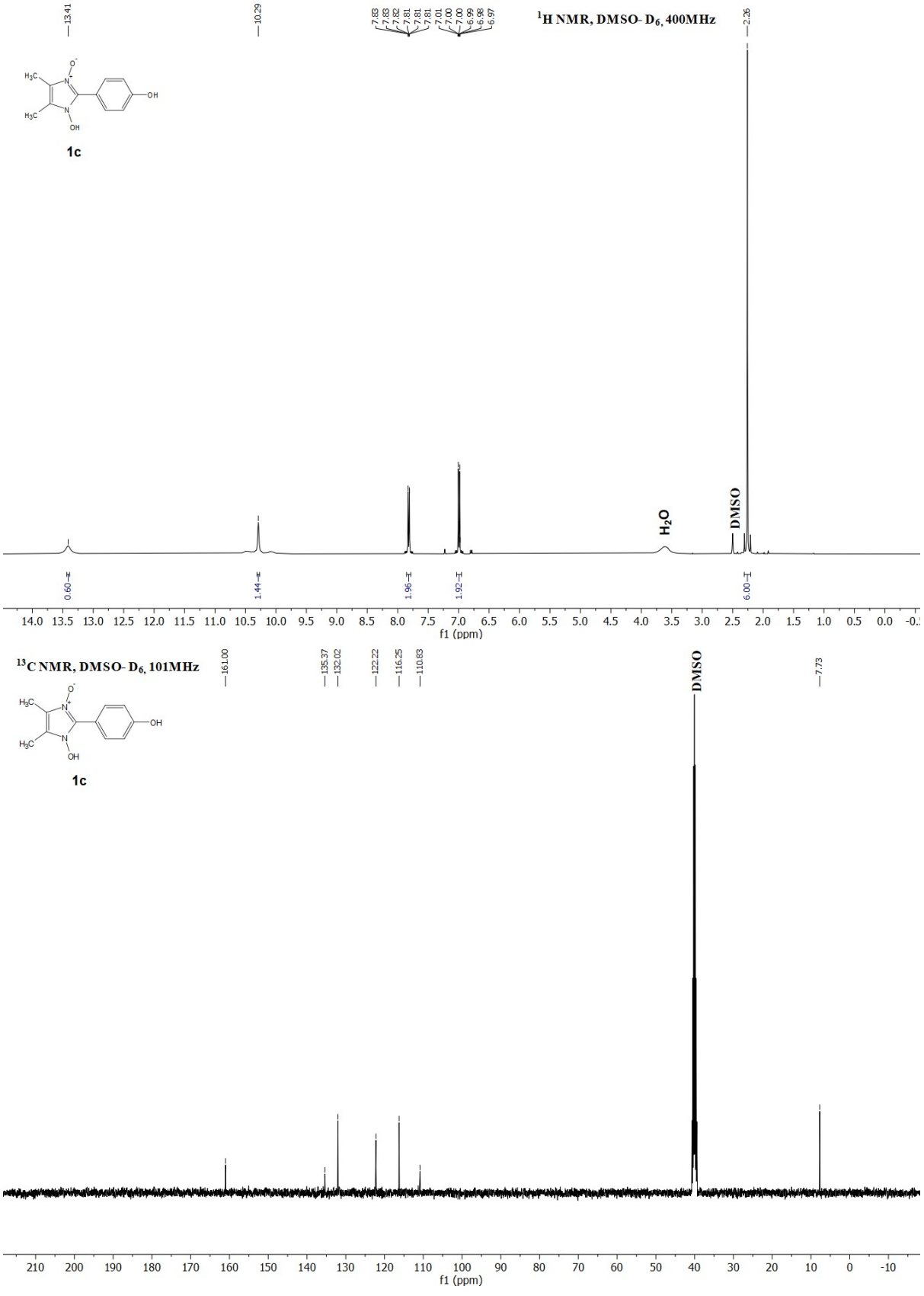


6.2.^{1}H and C^{13} NMR spectra of compound 1b

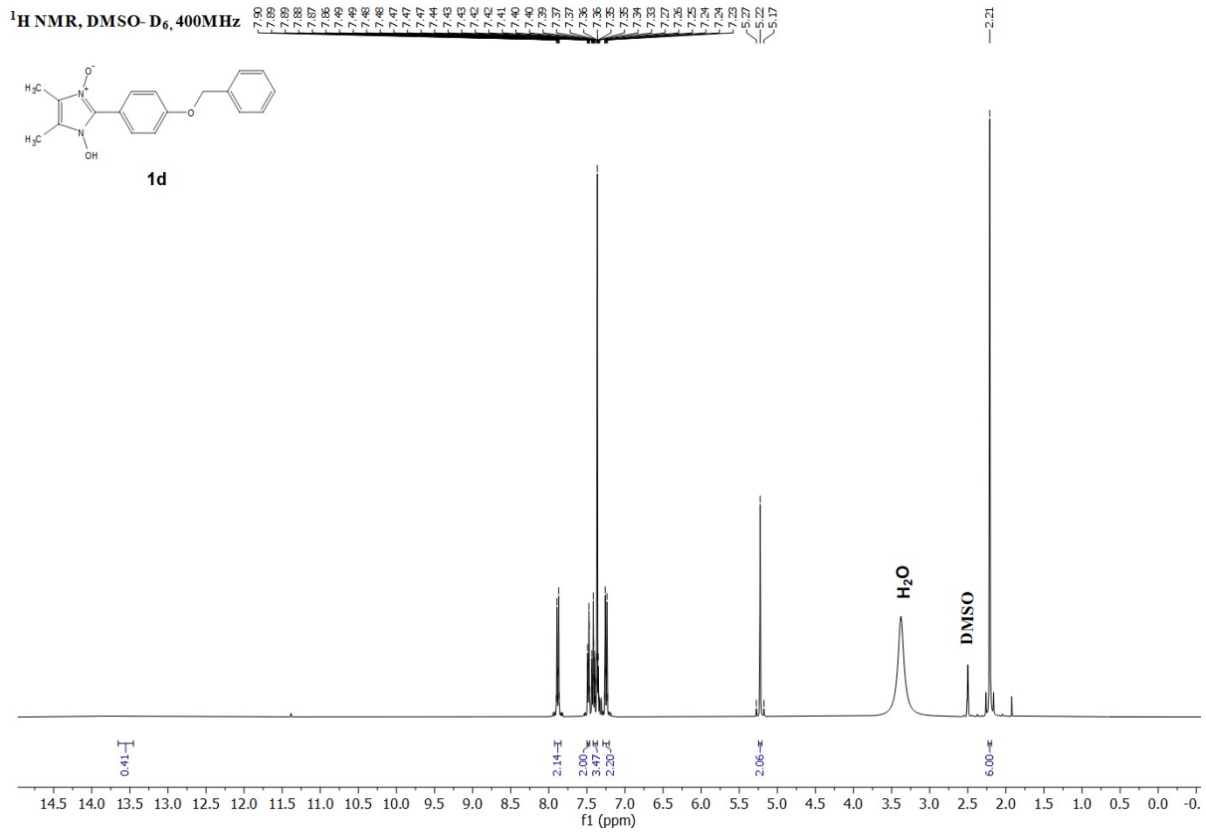


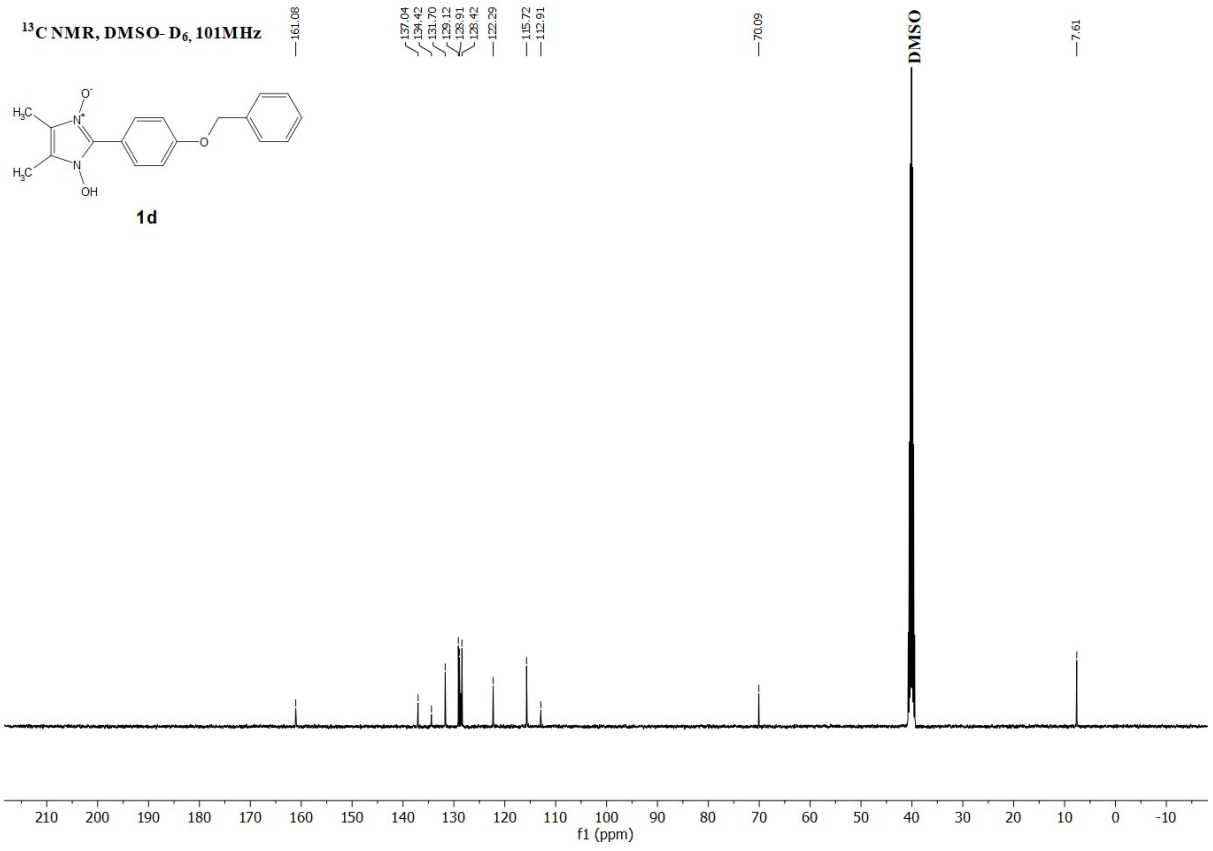


6.3.^{1}H and C^{13} NMR spectra of compound 1c

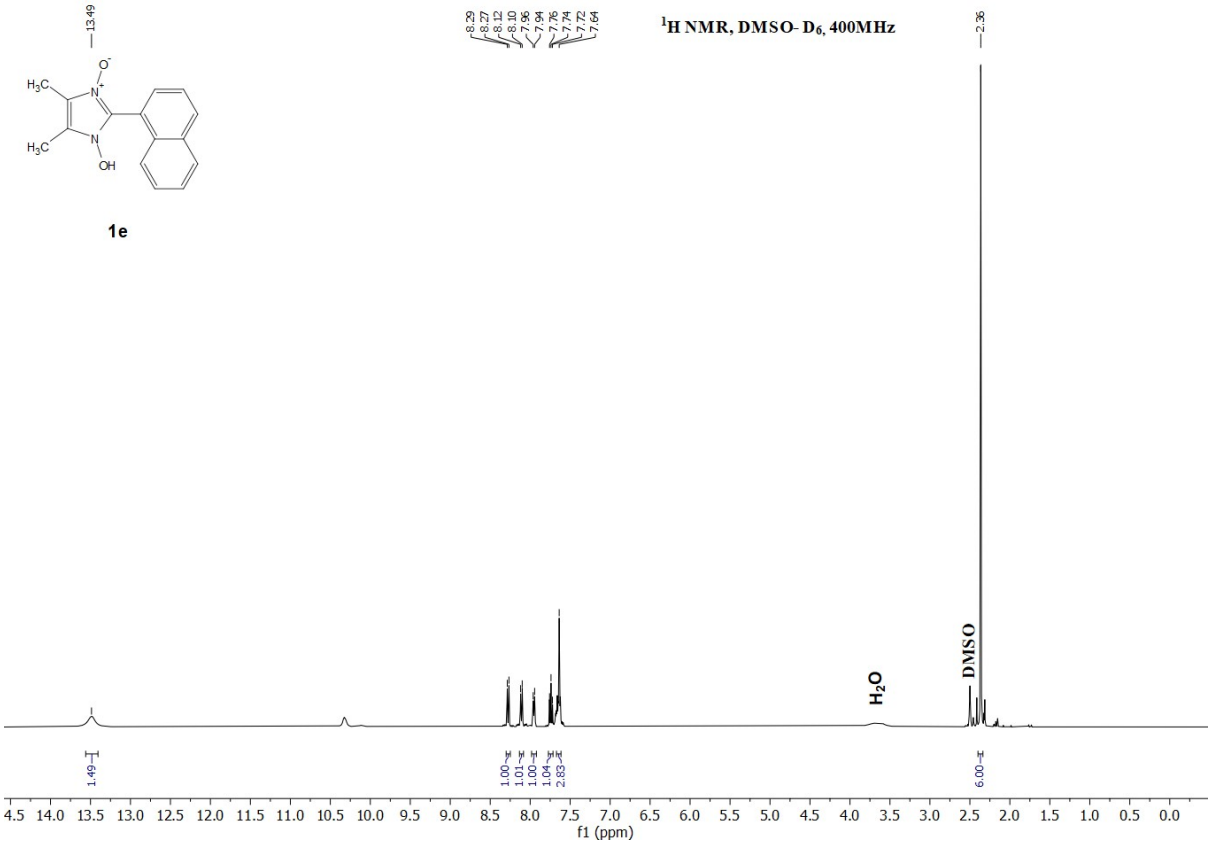


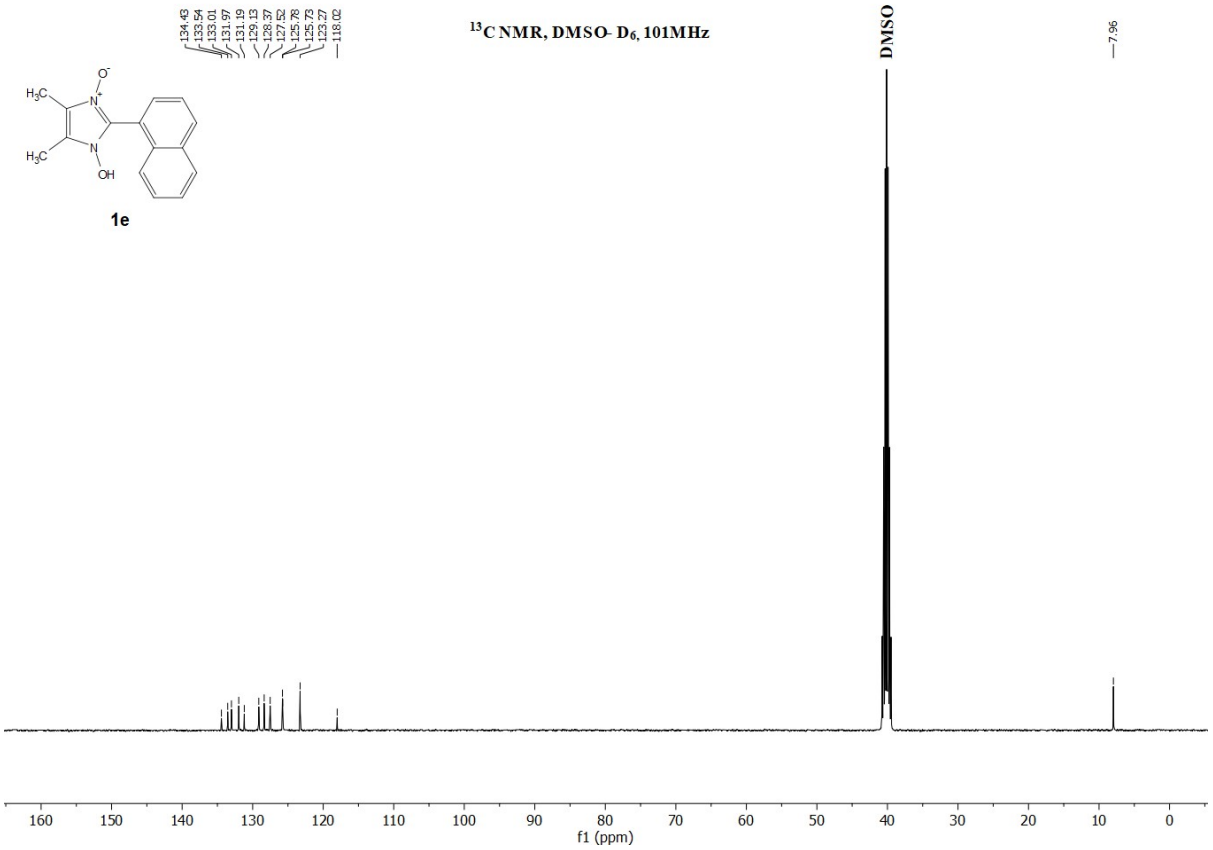
6.4.^{1}H and C^{13} NMR spectra of compound 1d



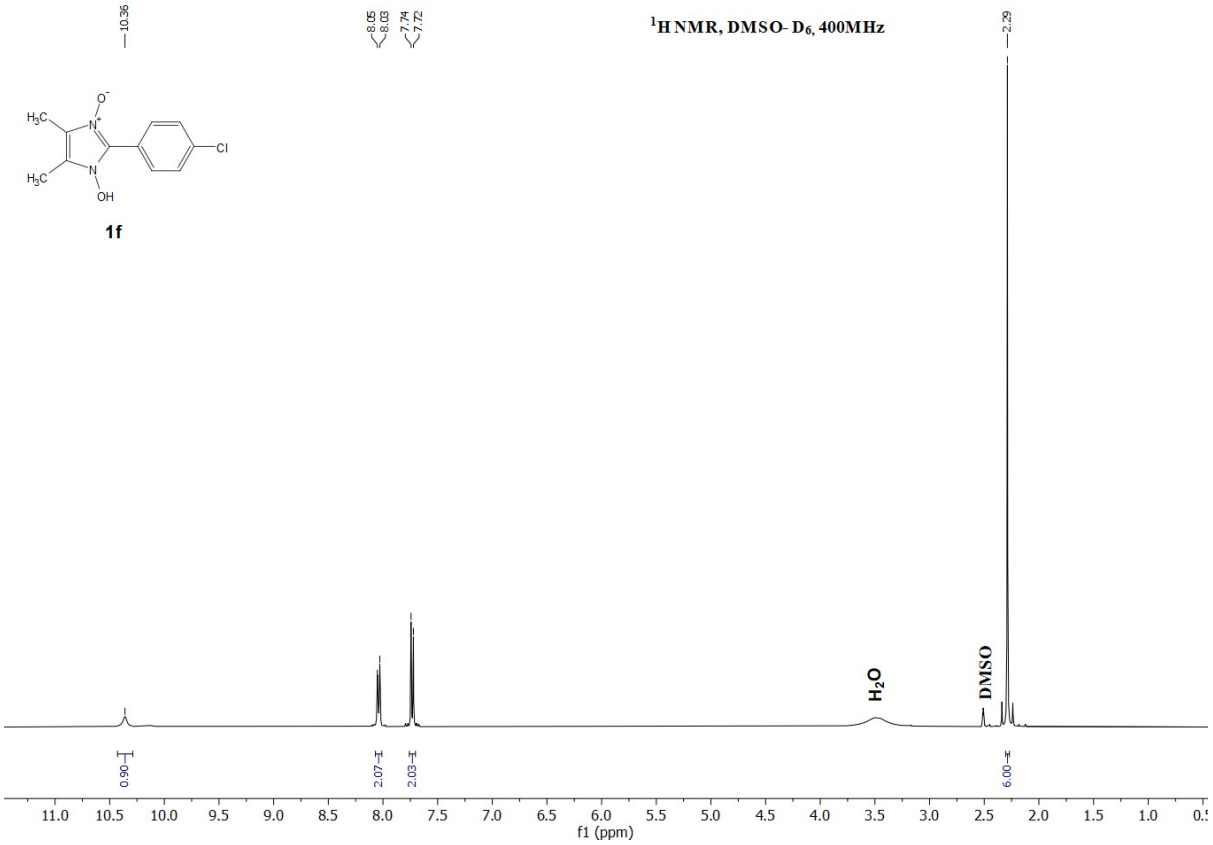


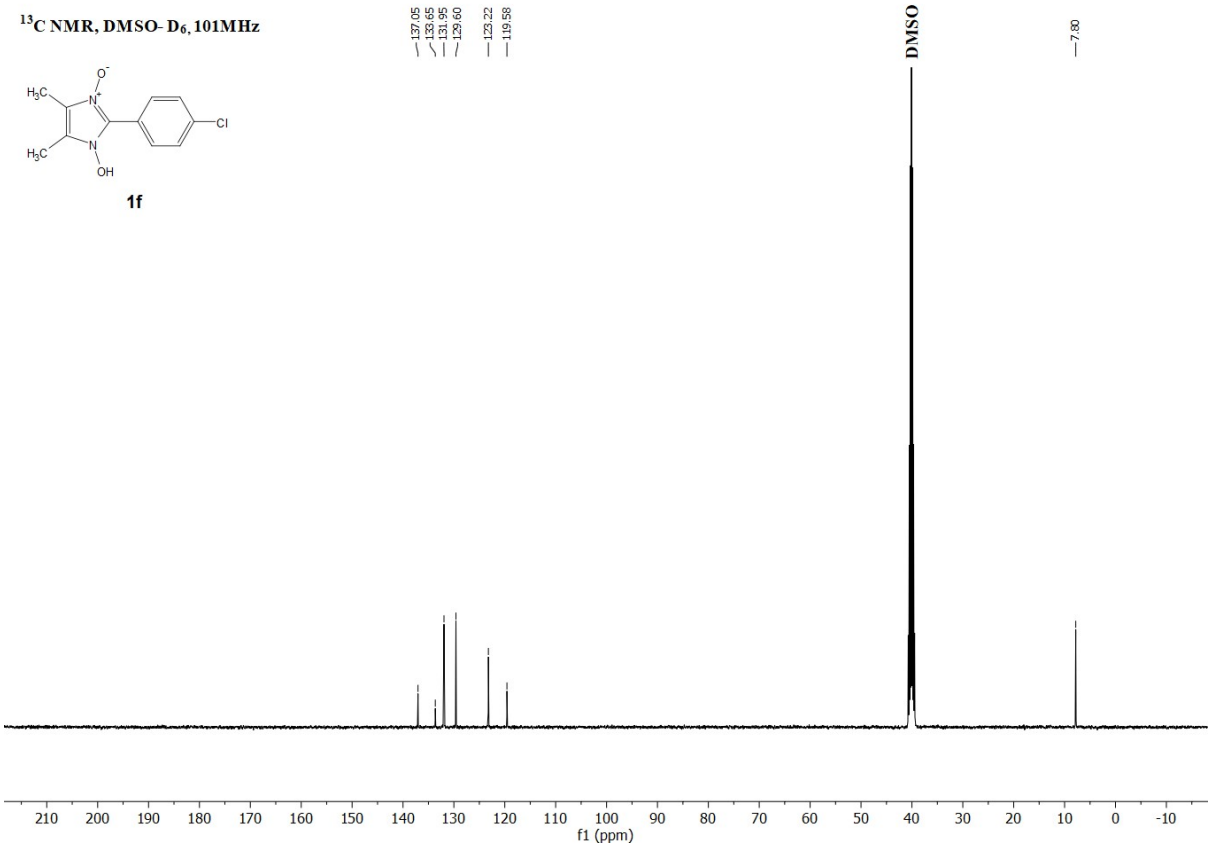
6.5.^{1}H and C^{13} NMR spectra of compound 1e



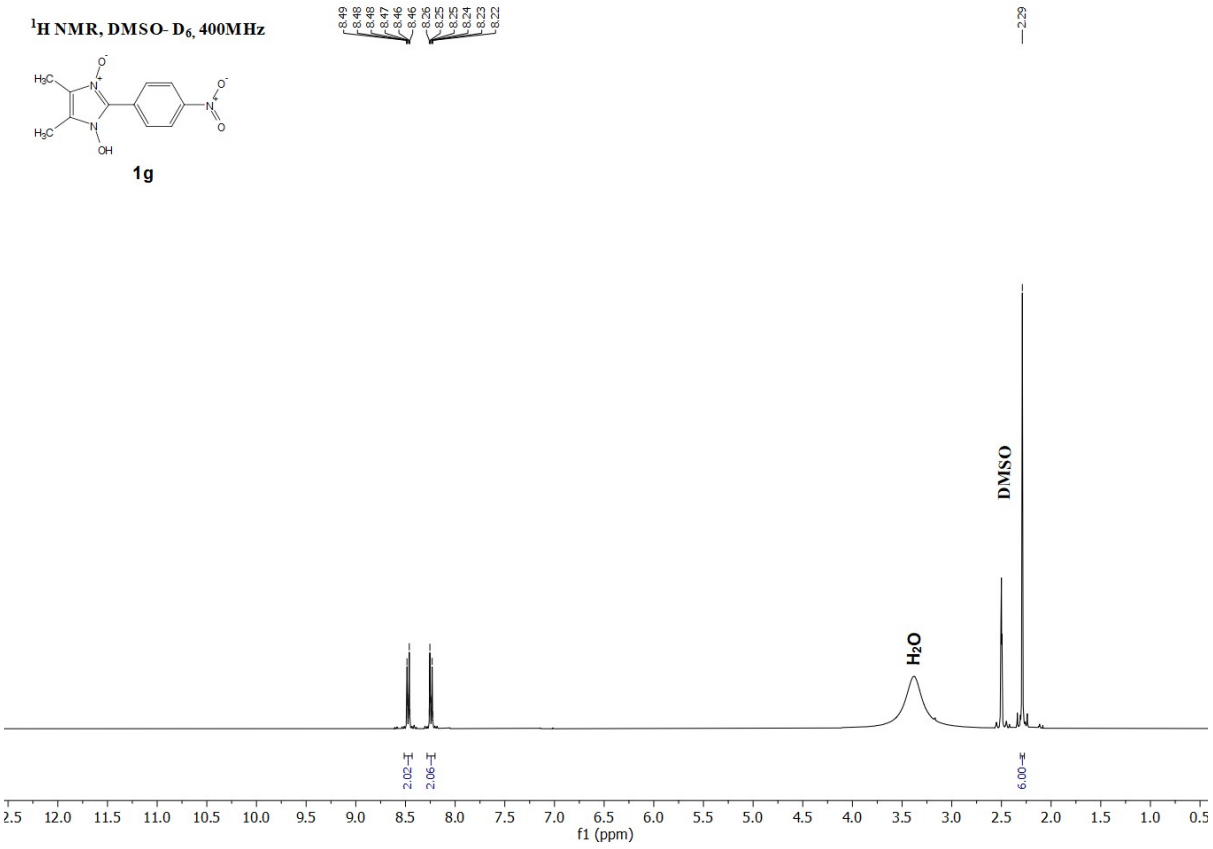


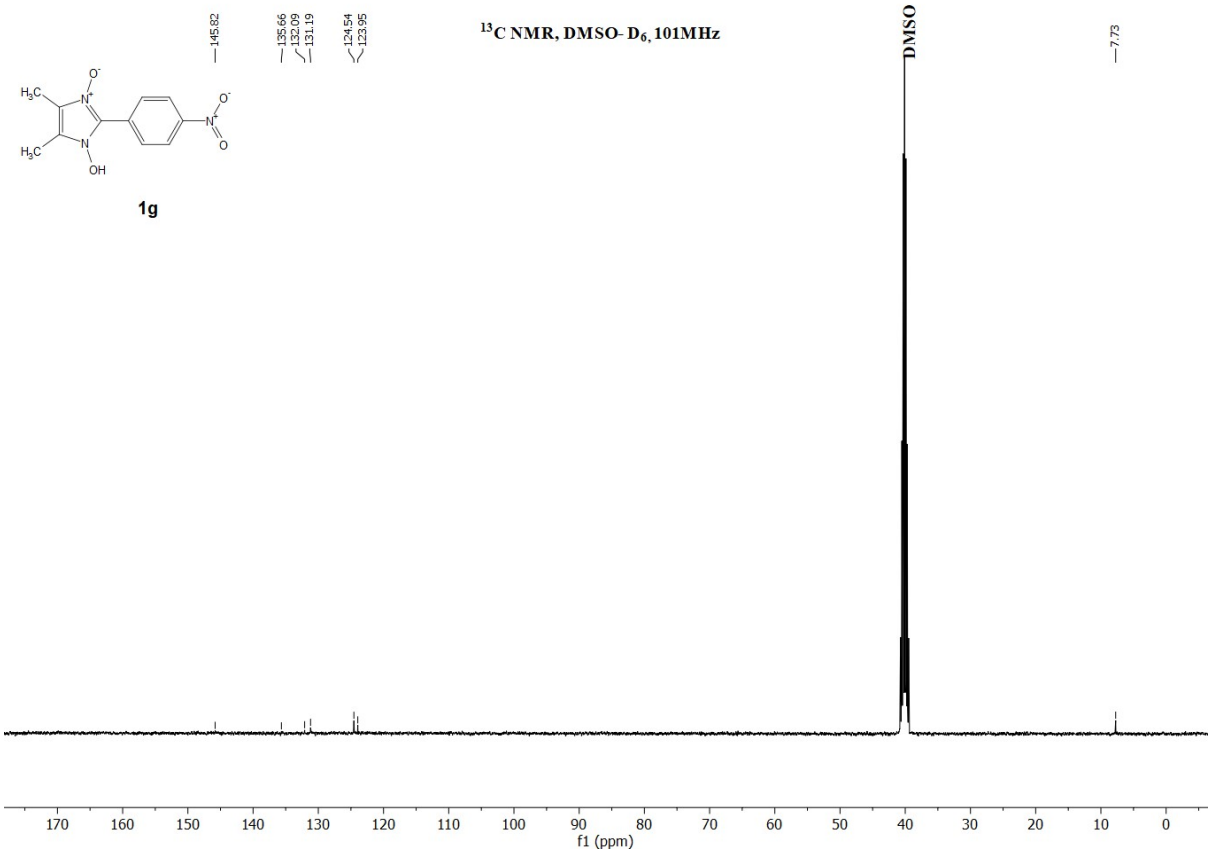
6.6.^{1}H and C^{13} NMR spectra of compound 1f



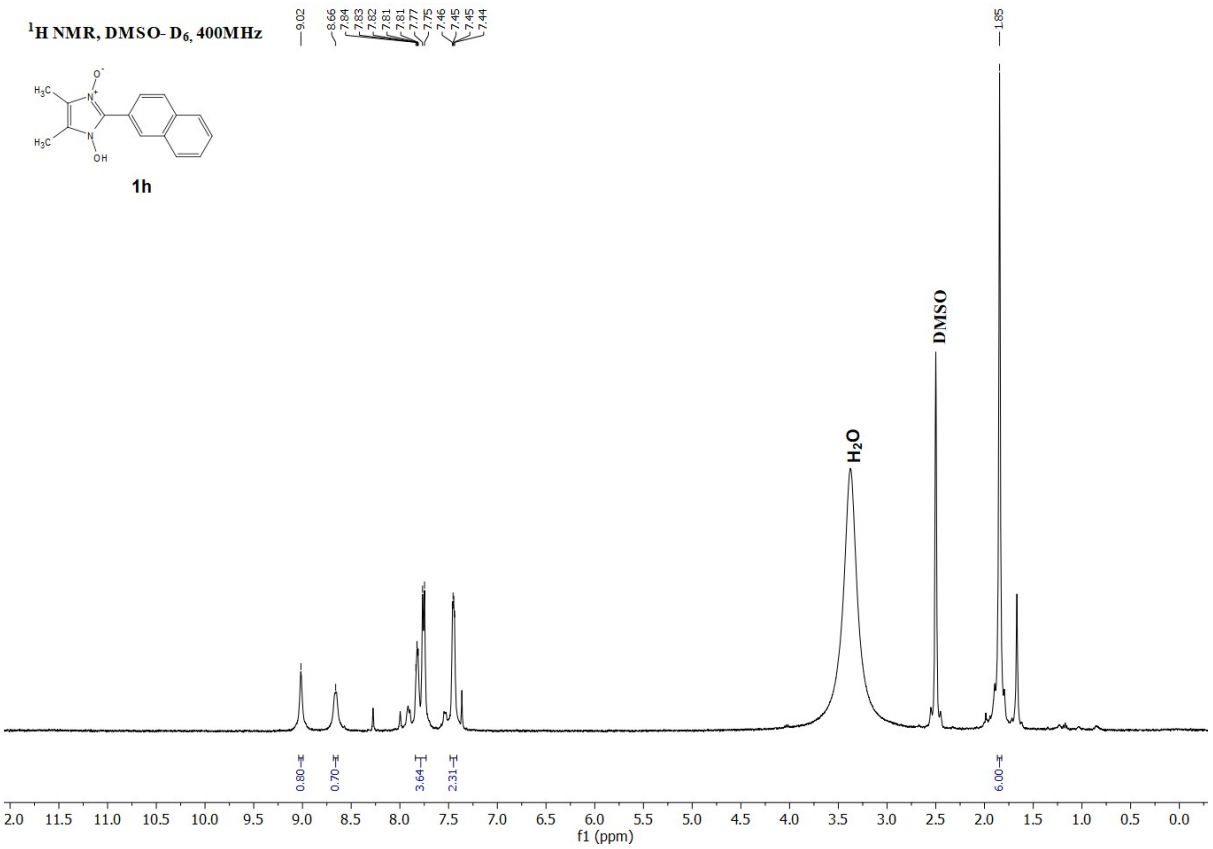


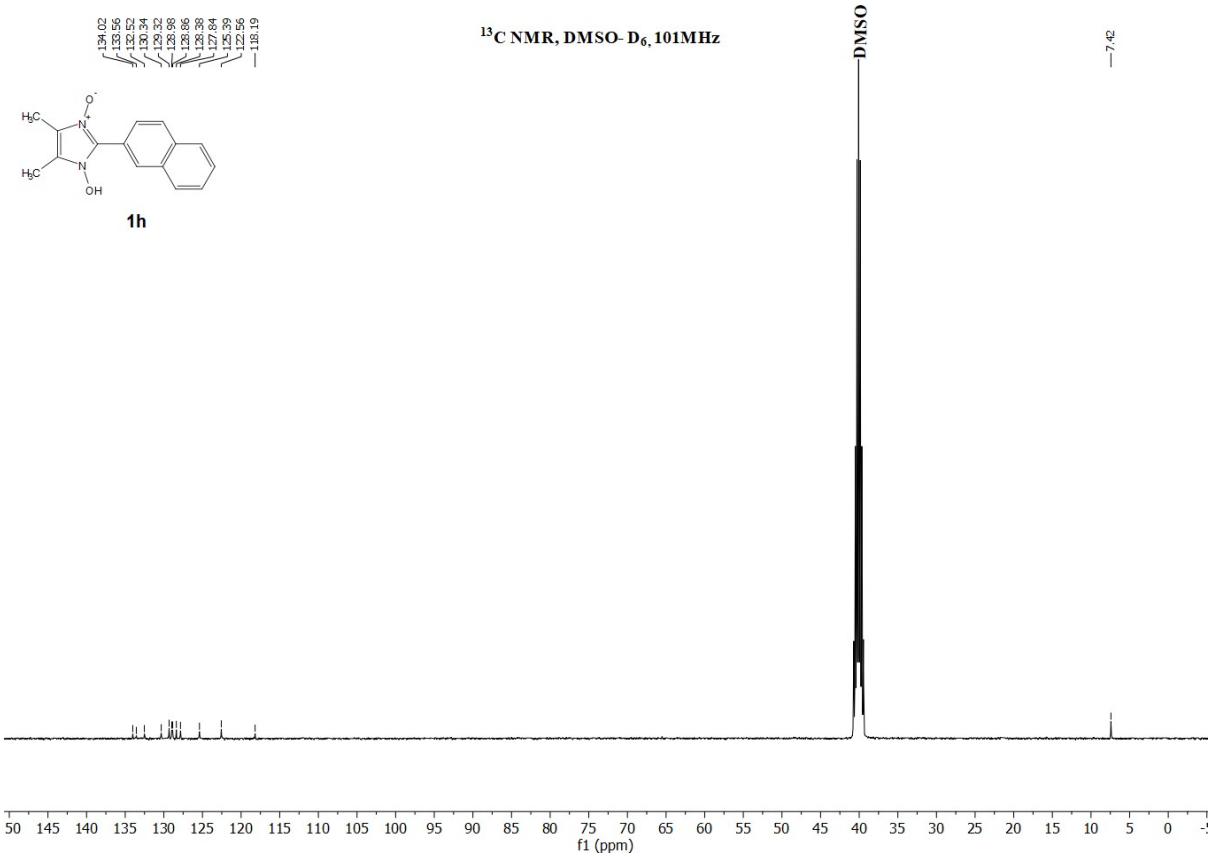
6.7.^{1}H and C^{13} NMR spectra of compound 1g



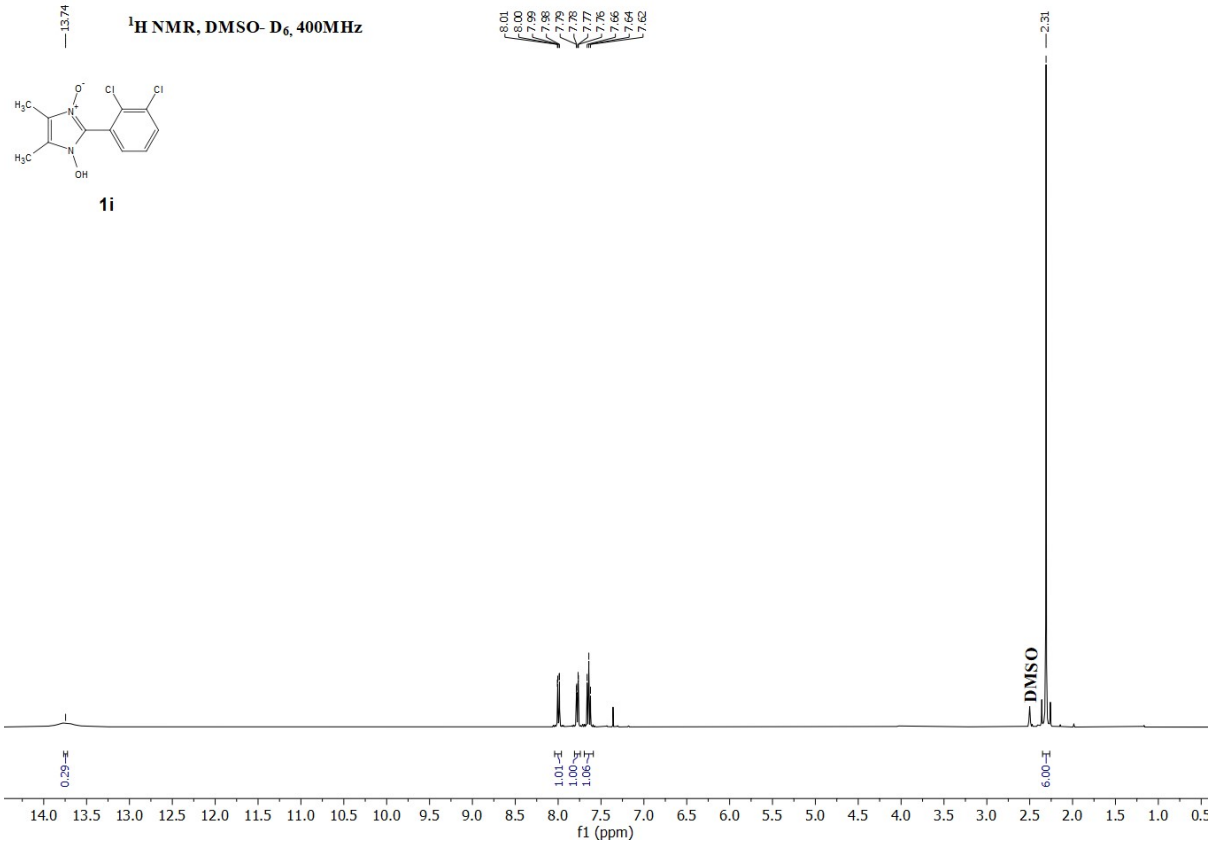


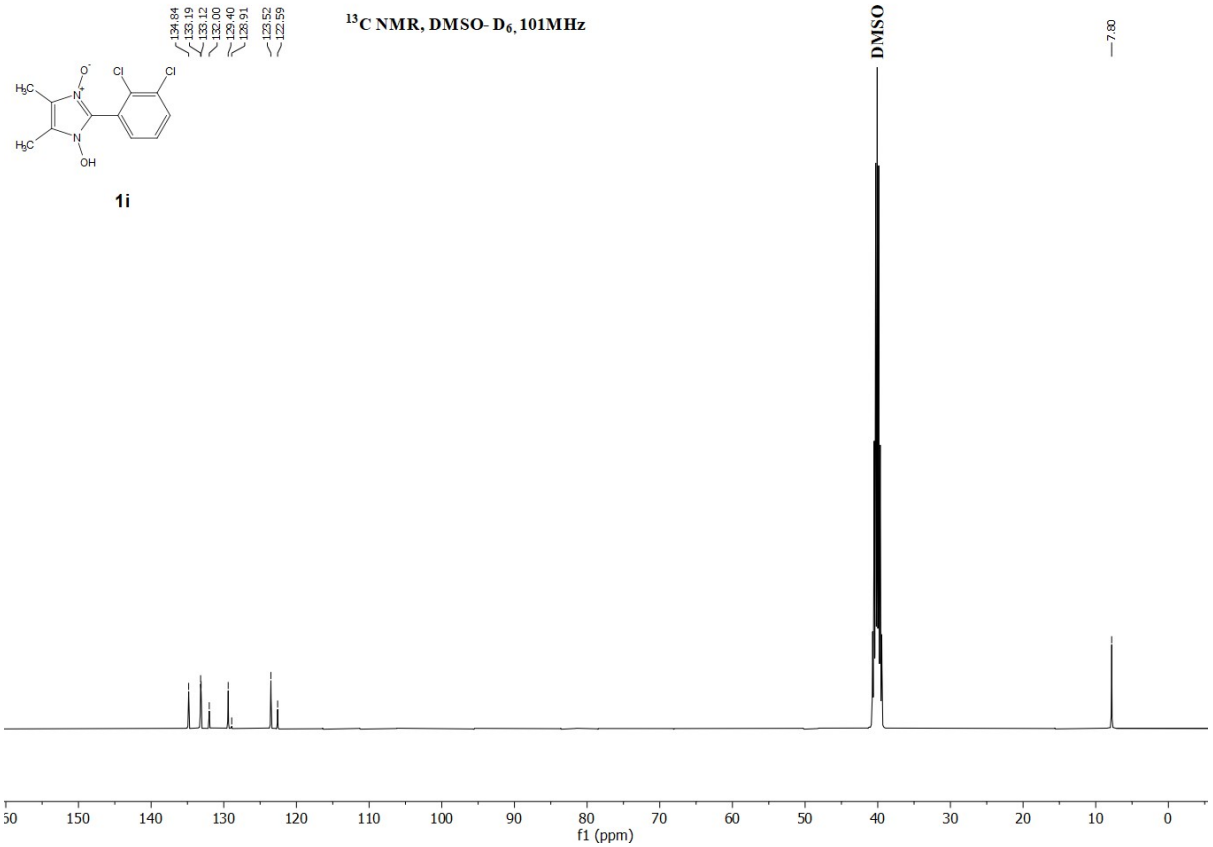
6.7.^{1}H and C^{13} NMR spectra of compound 1h



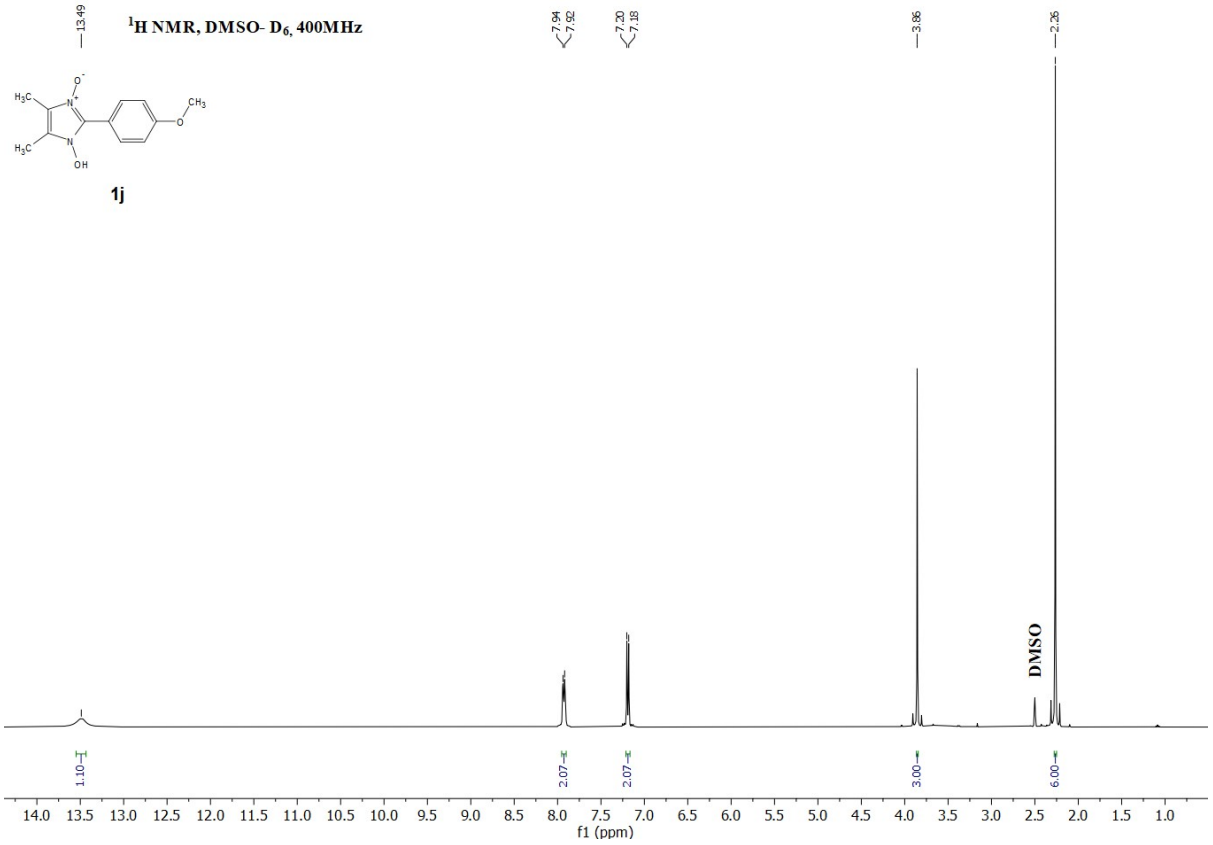


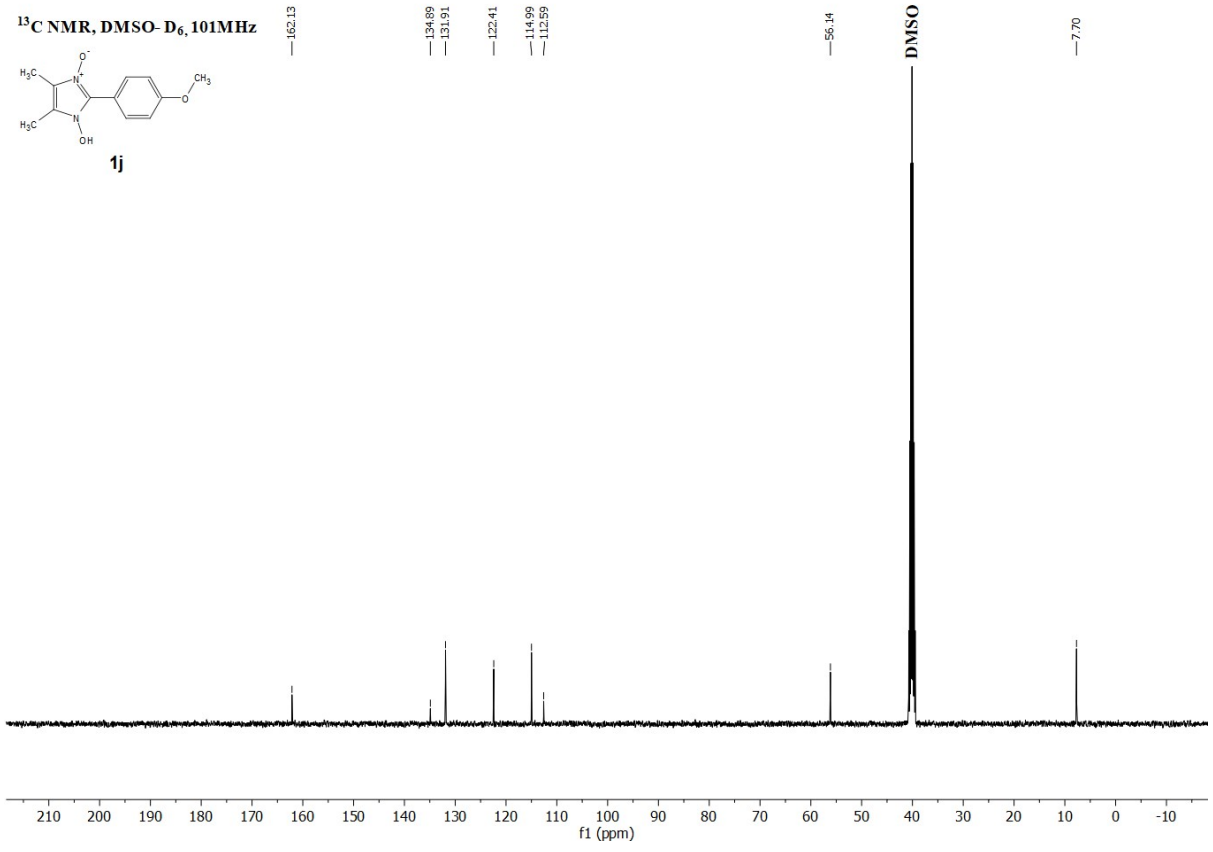
6.8.^{1}H and C^{13} NMR spectra of compound 1i



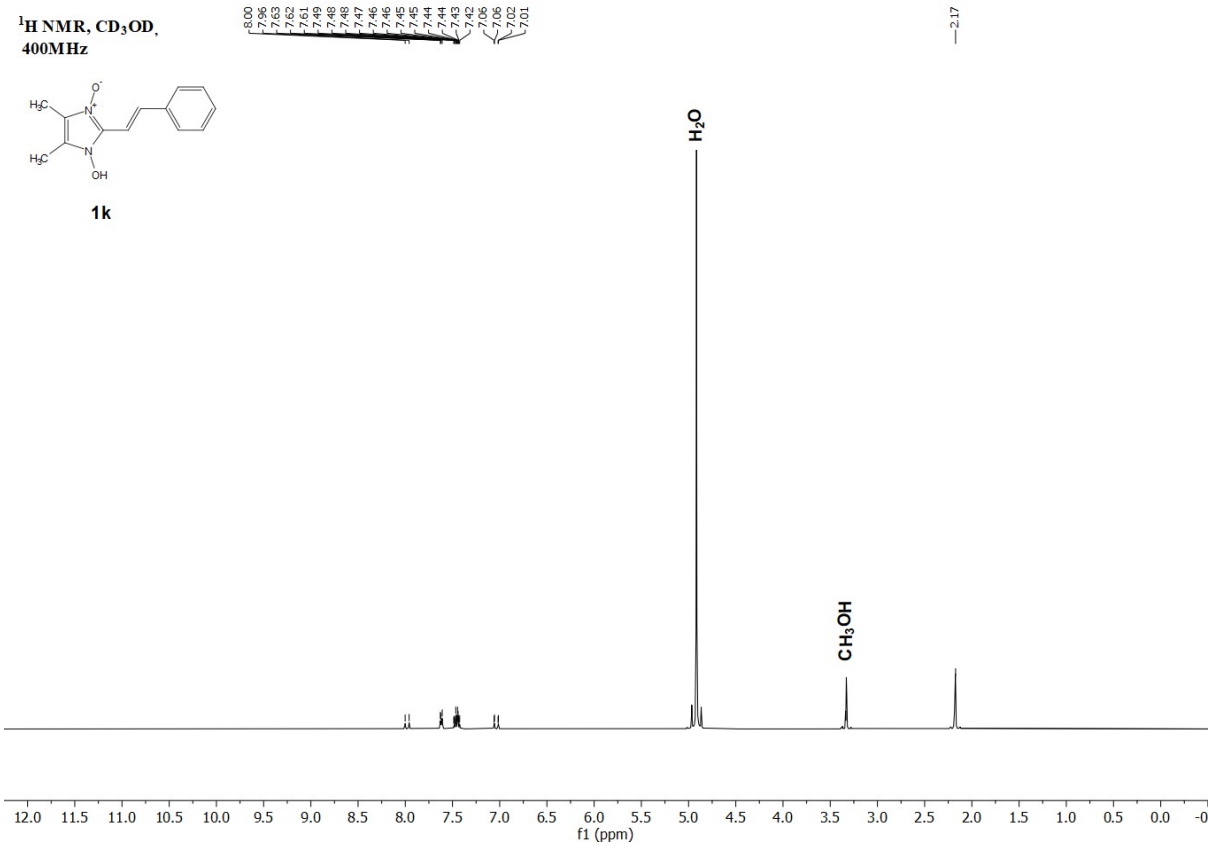


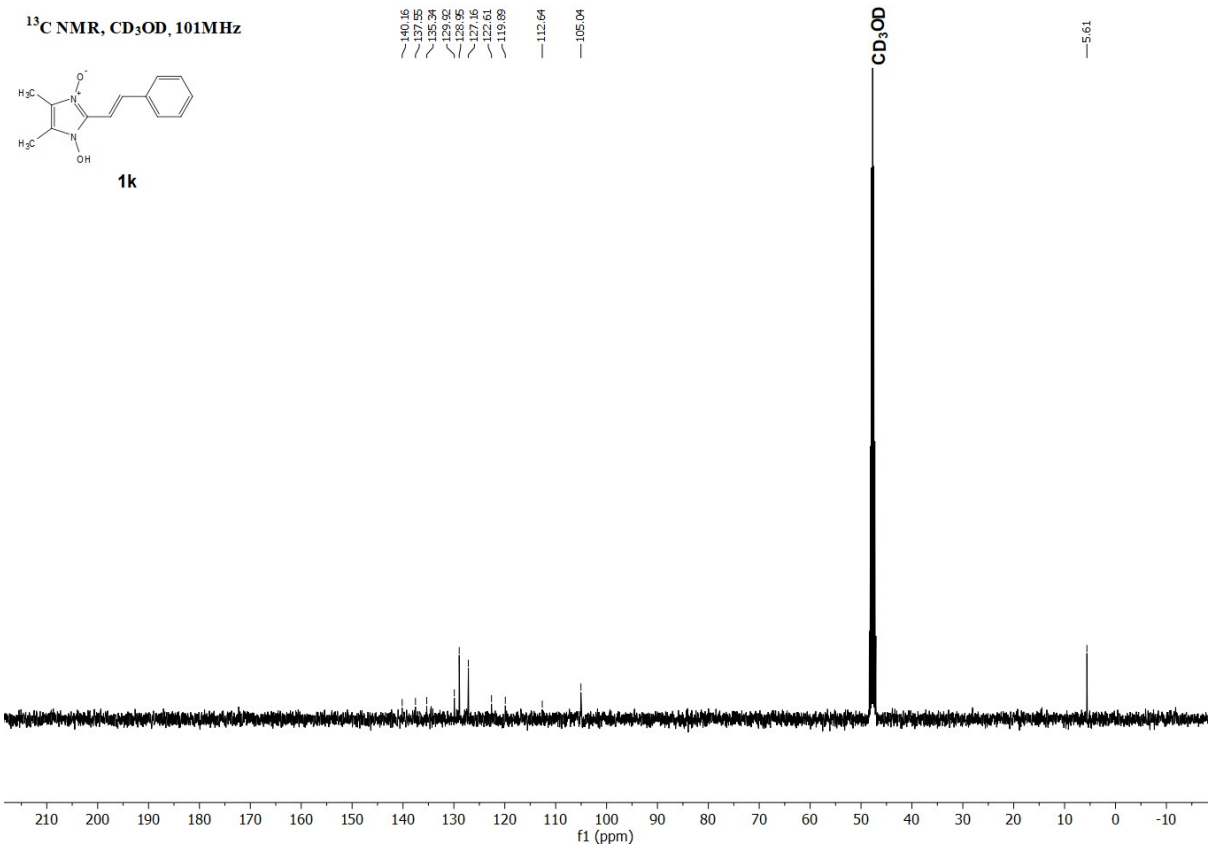
6.9.^{1}H and C^{13} NMR spectra of compound 1j



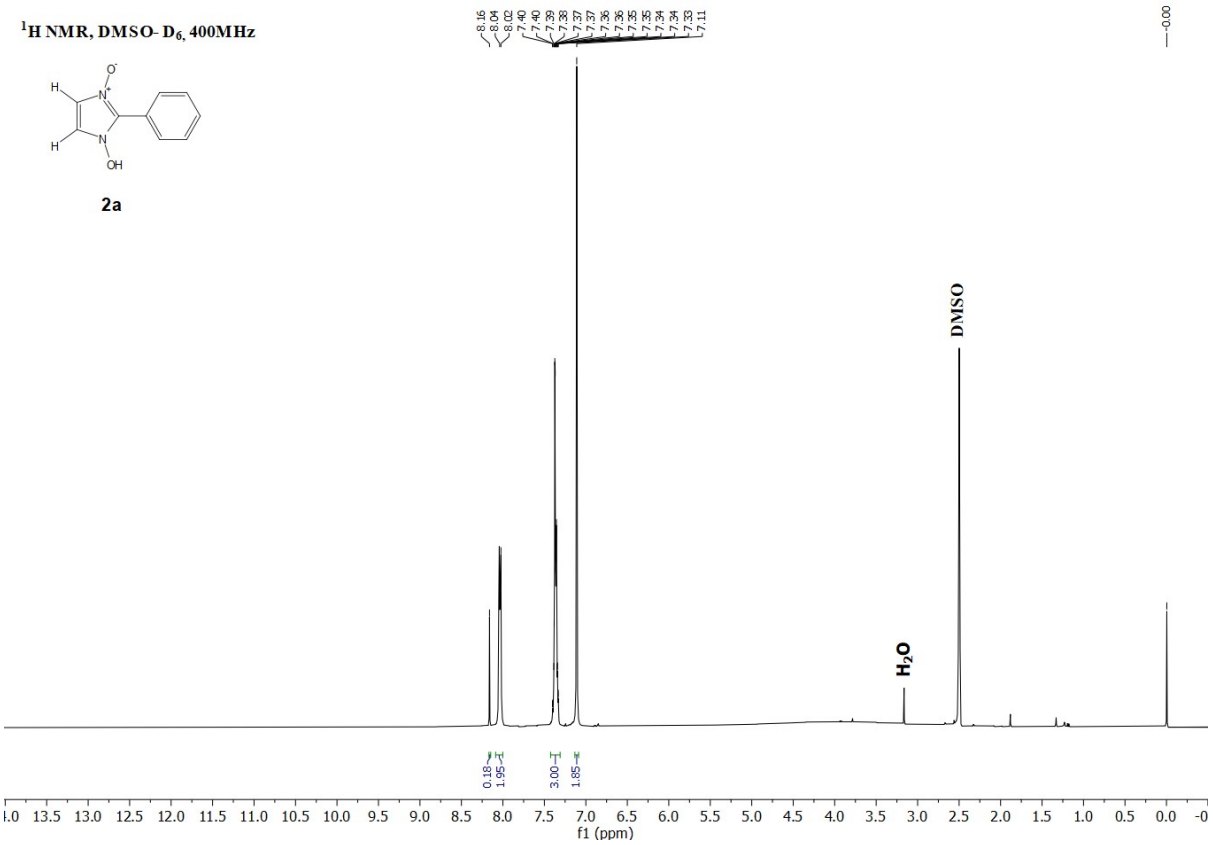


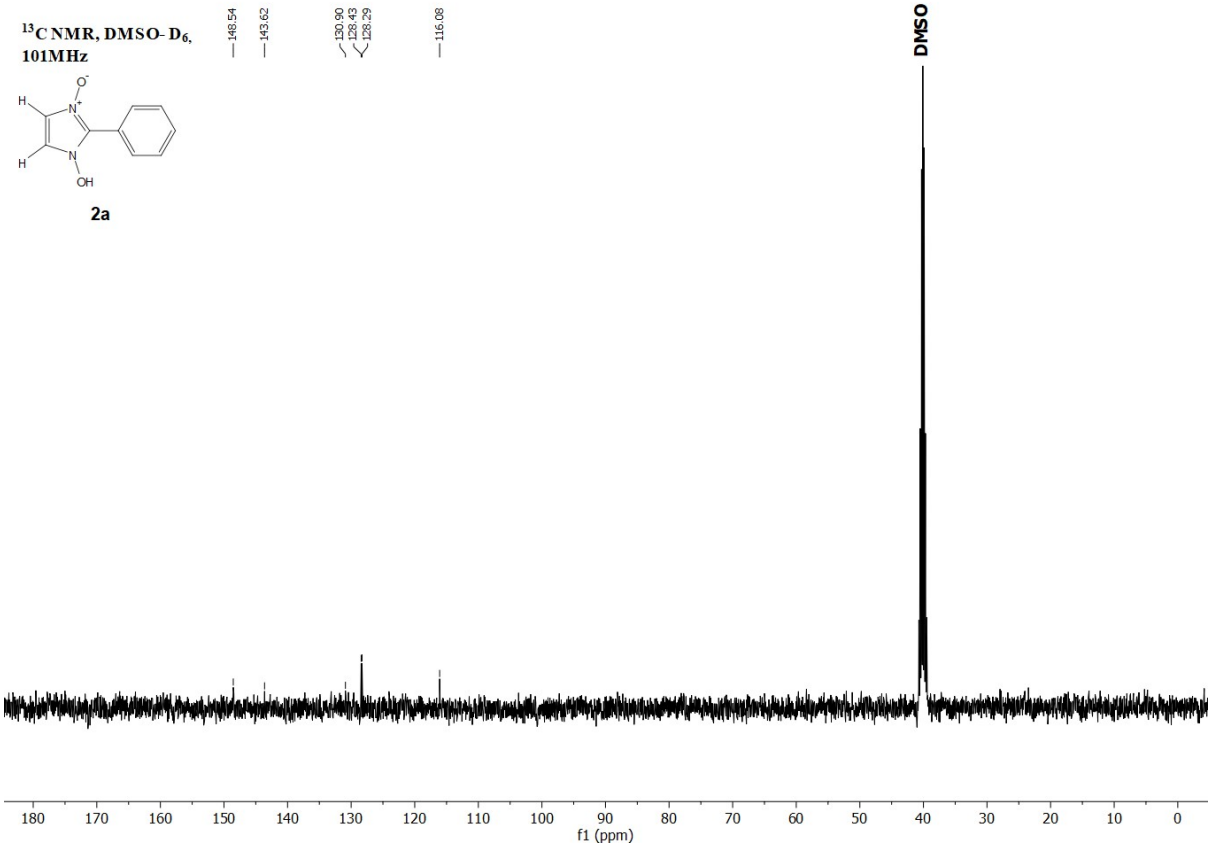
6.10.^{1}H and C^{13} NMR spectra of compound 1k



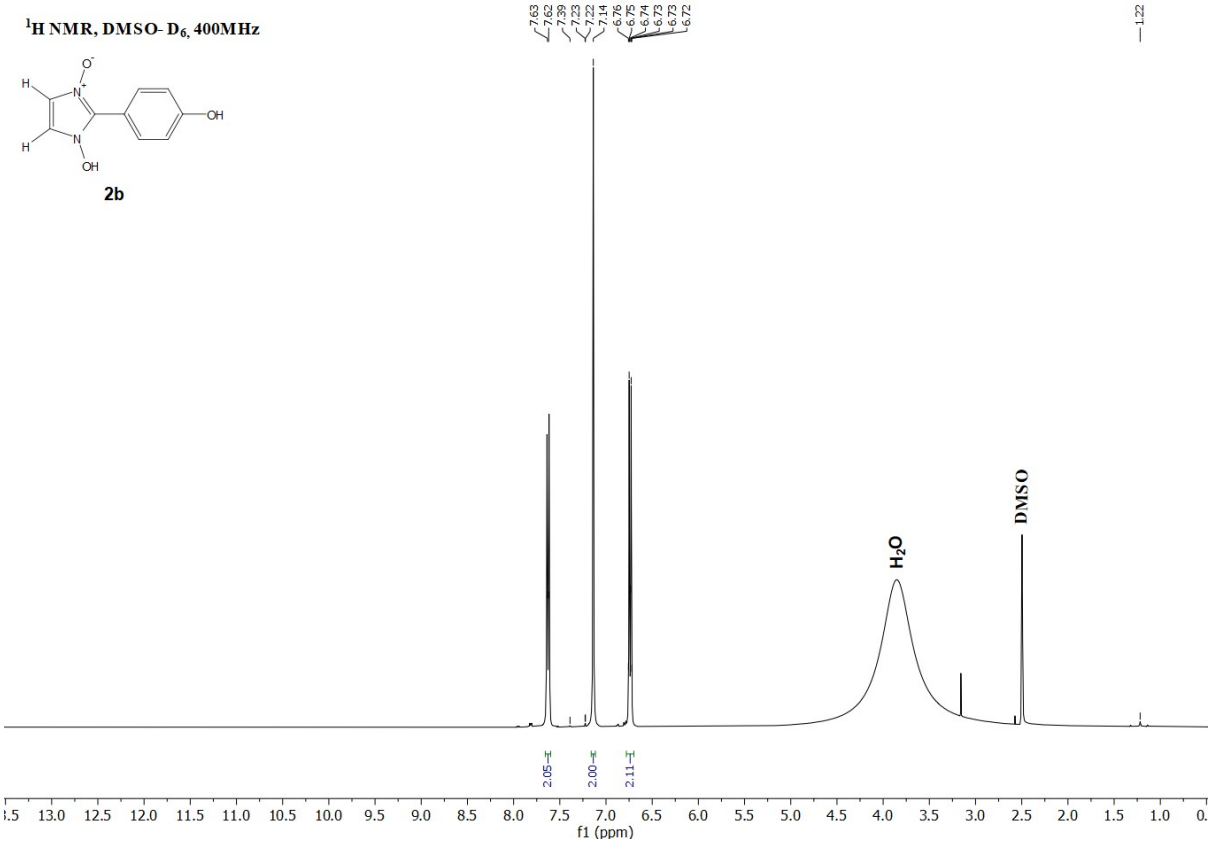


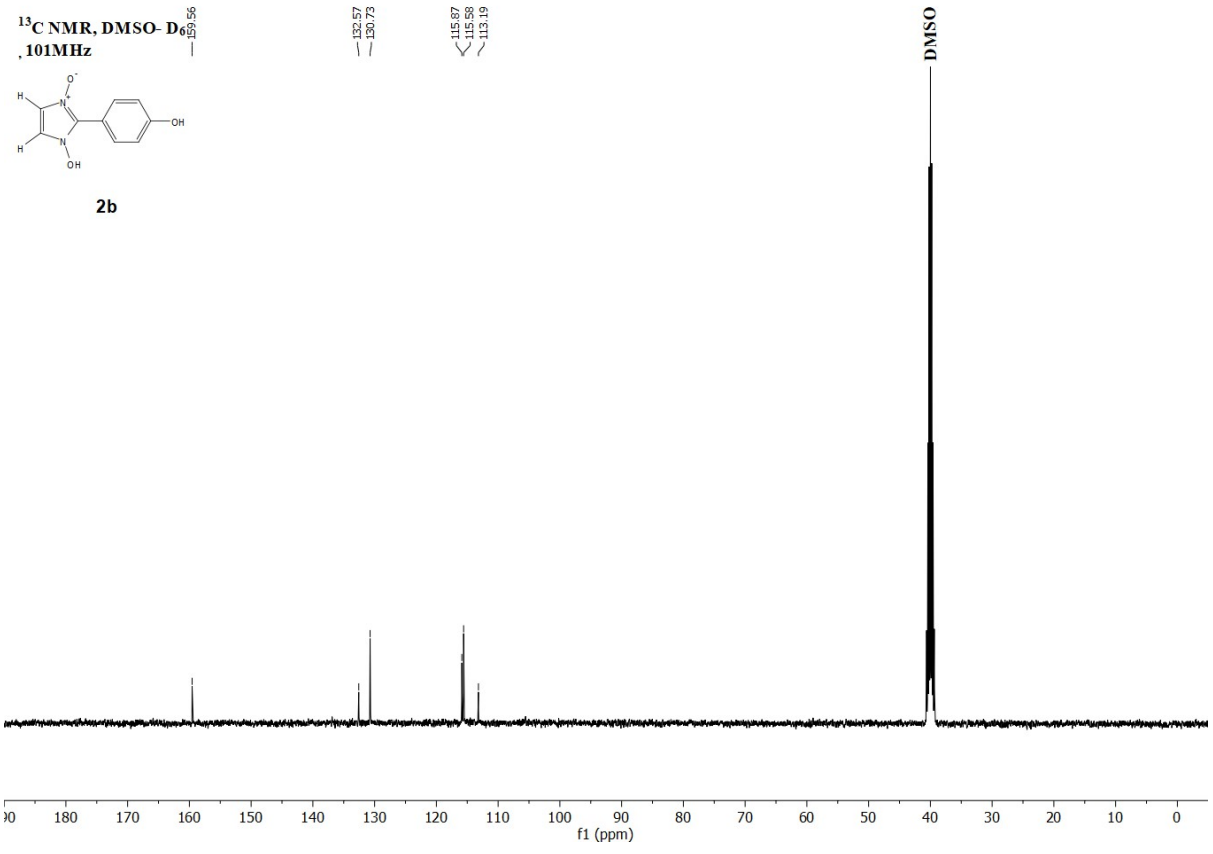
6.11.^{1}H and C^{13} NMR spectra of compound 2a



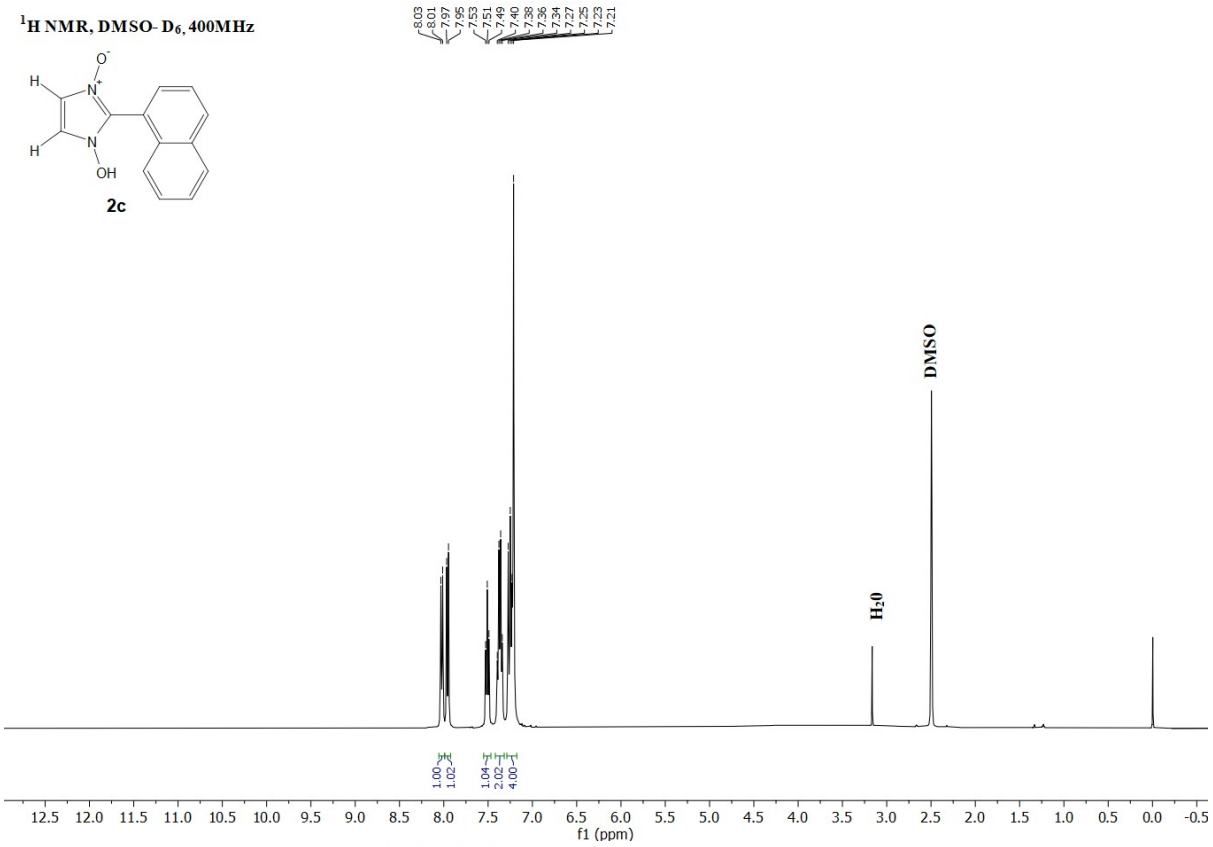


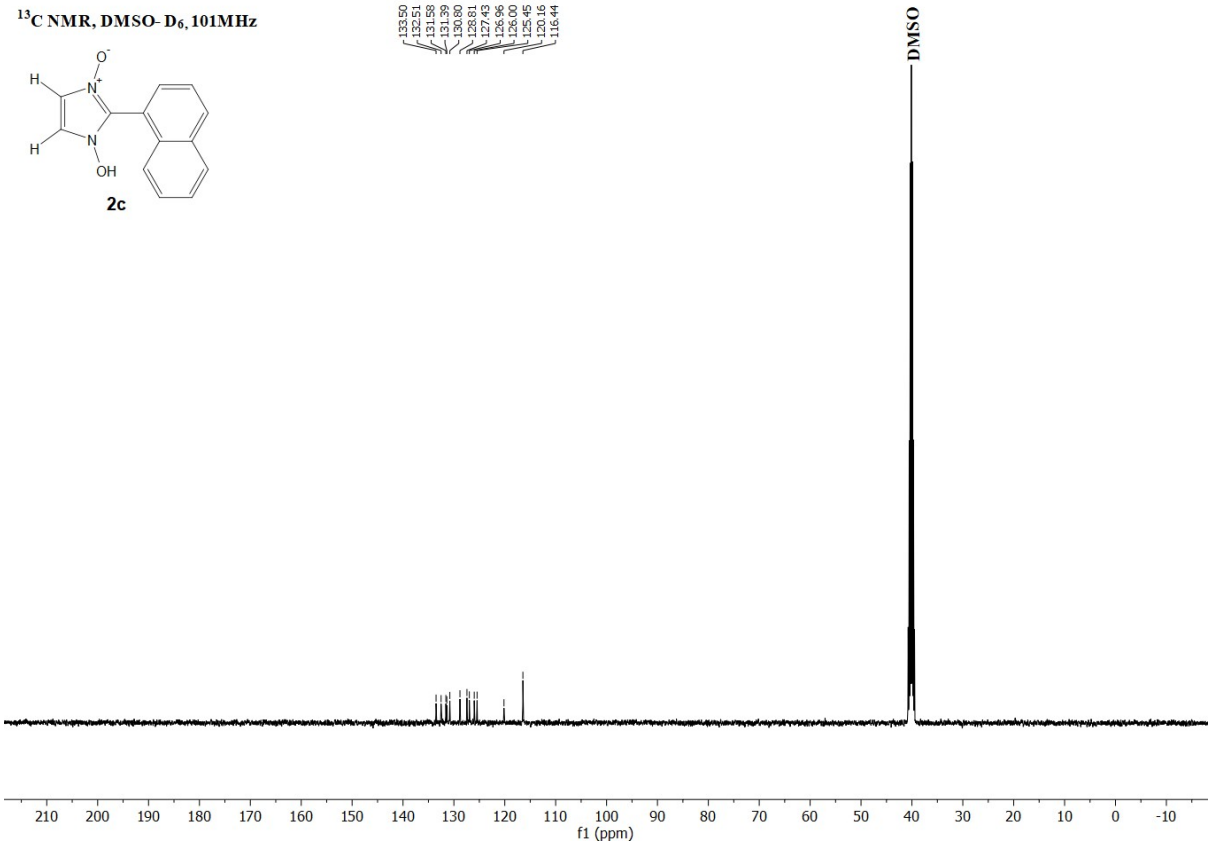
6.12.^{1}H and C^{13} NMR spectra of compound 2b



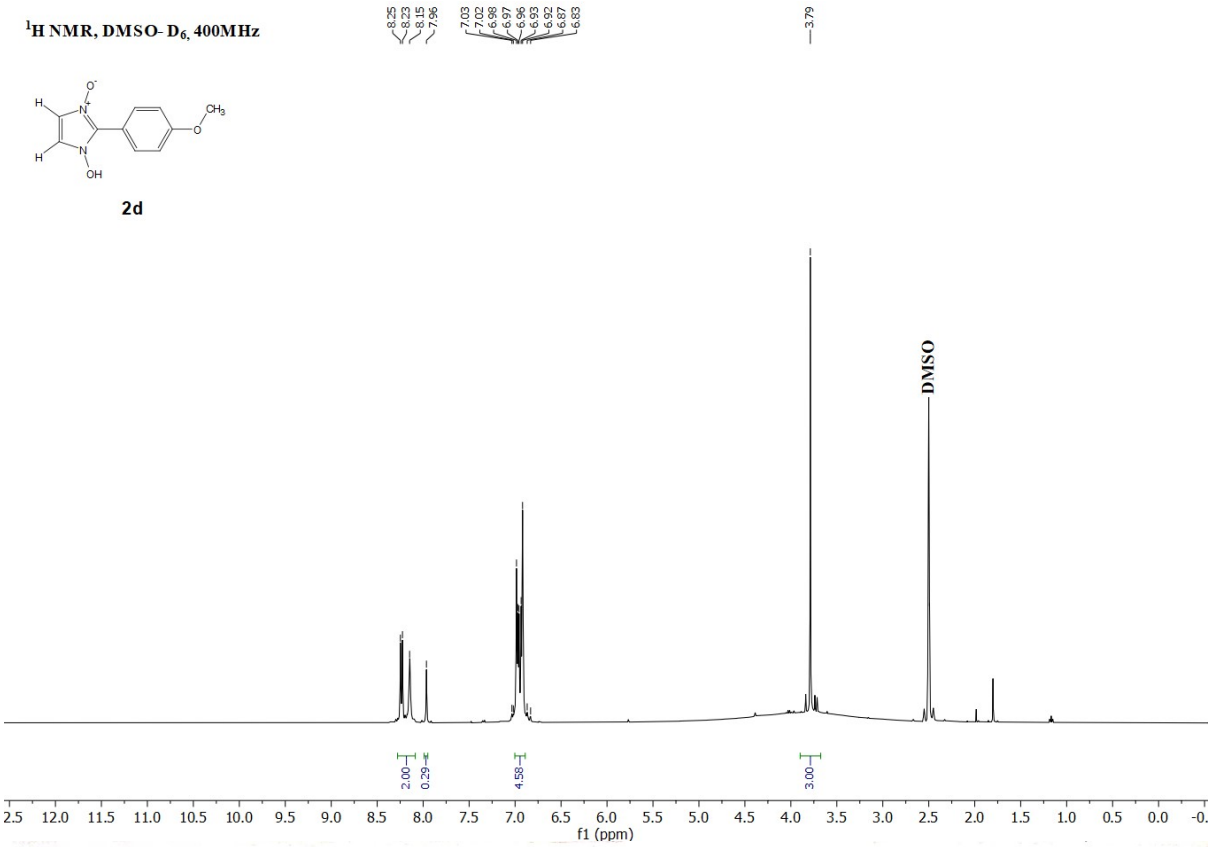


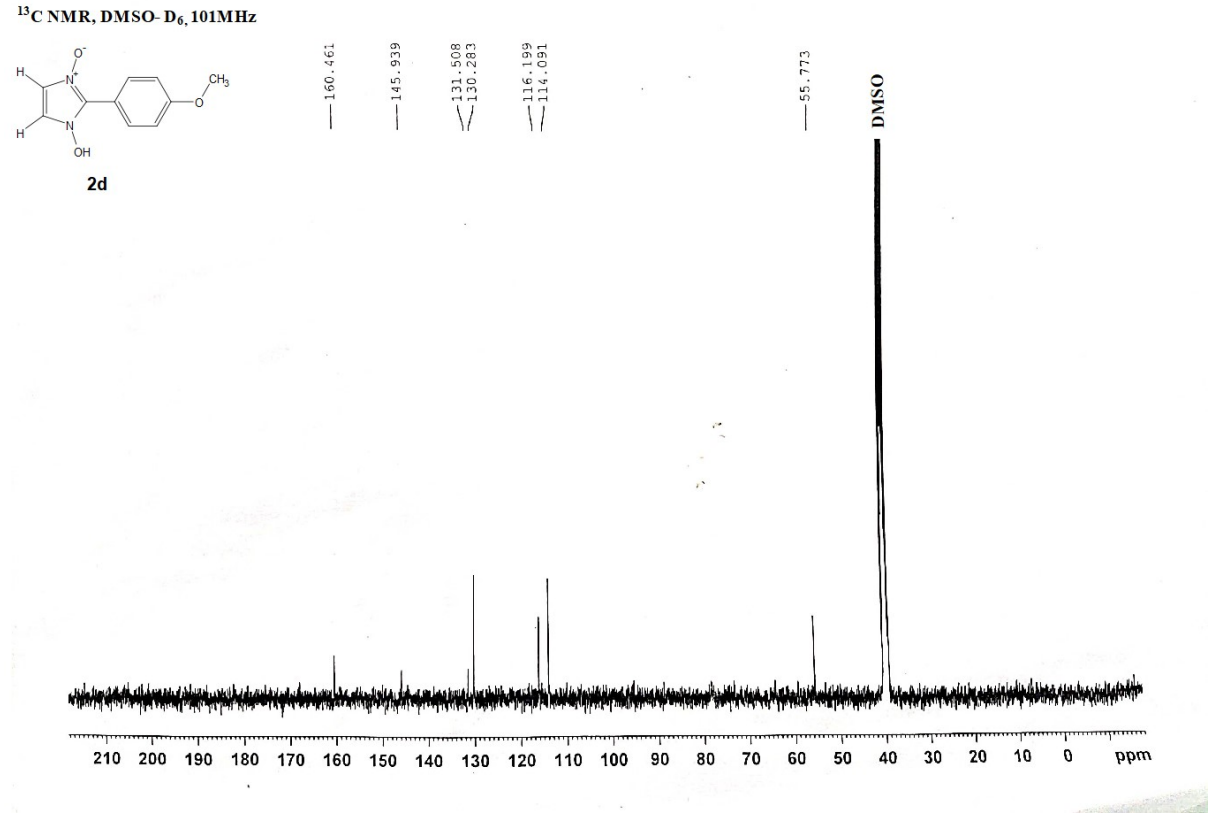
6.13. ^{1}H and C^{13} NMR spectra of compound 2c



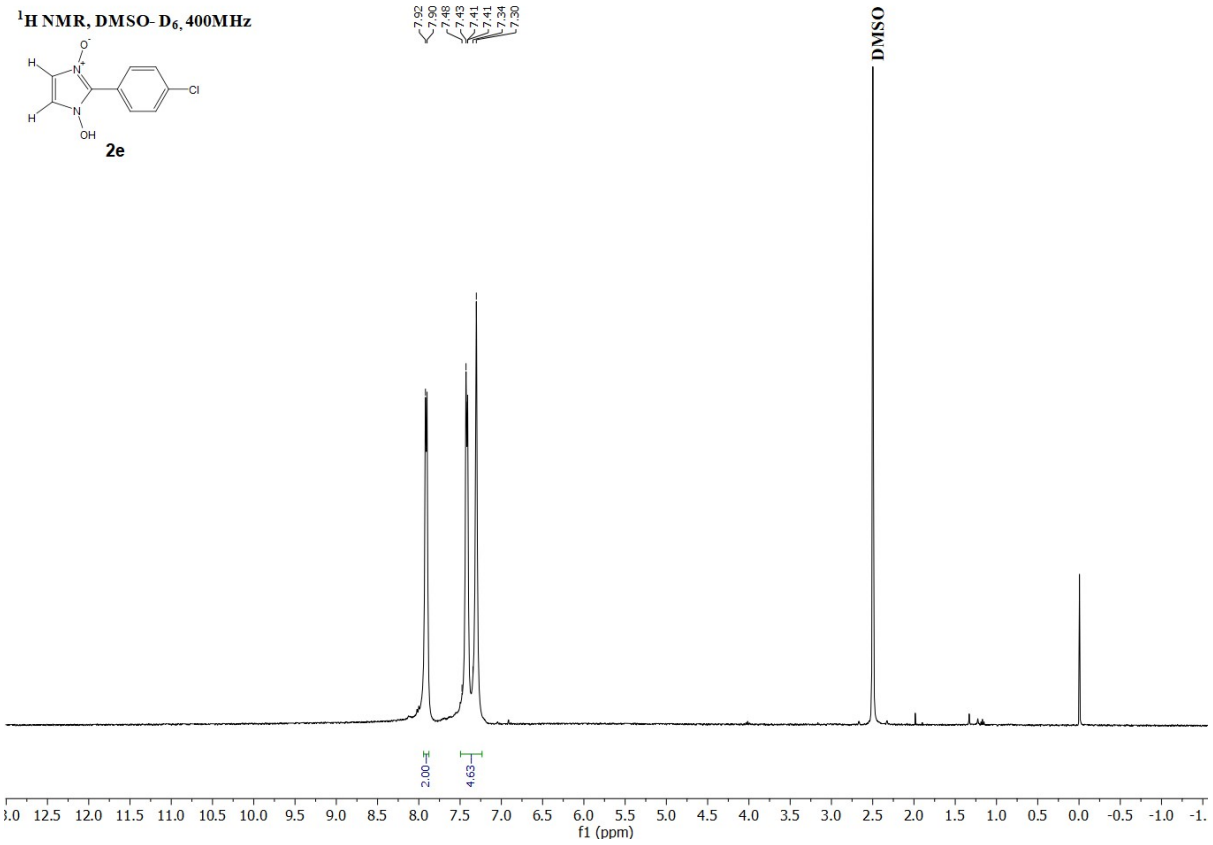


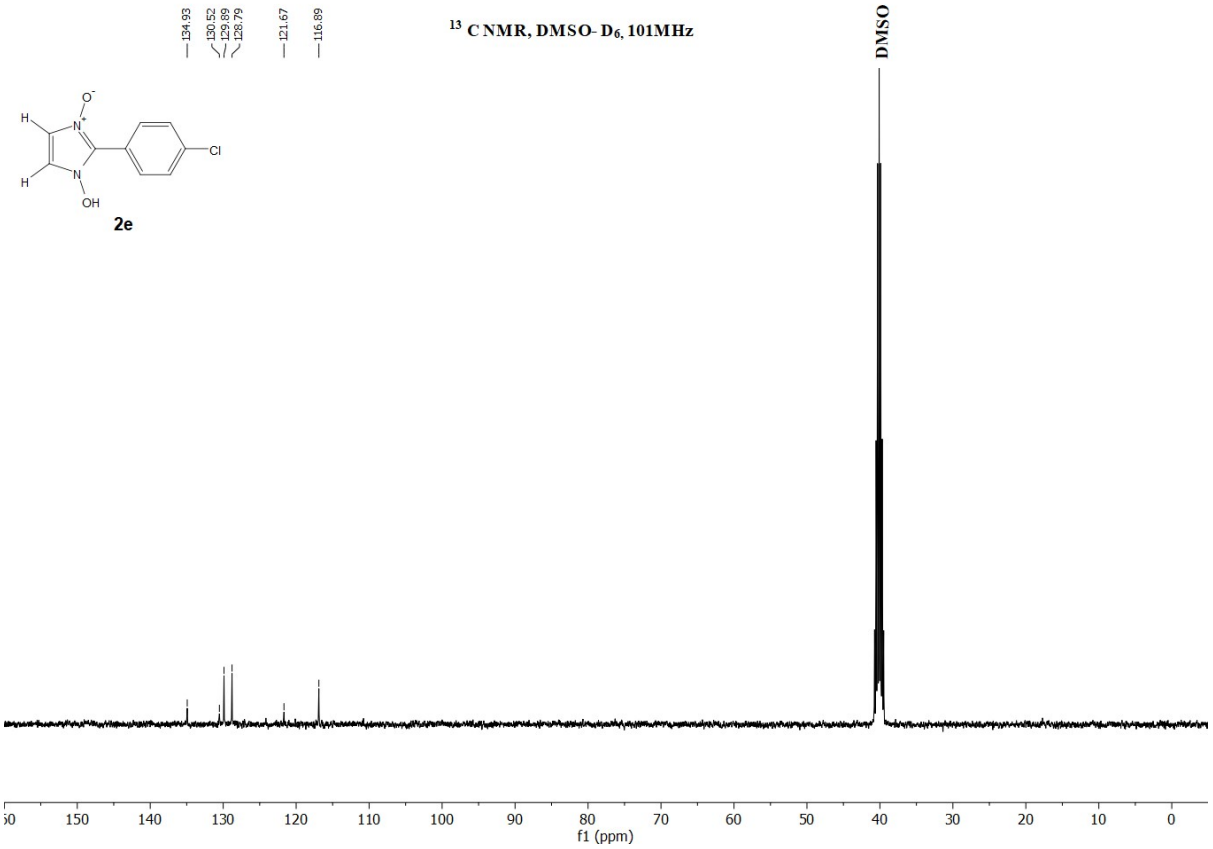
6.14. ^{1}H and C^{13} NMR spectra of compound 2d



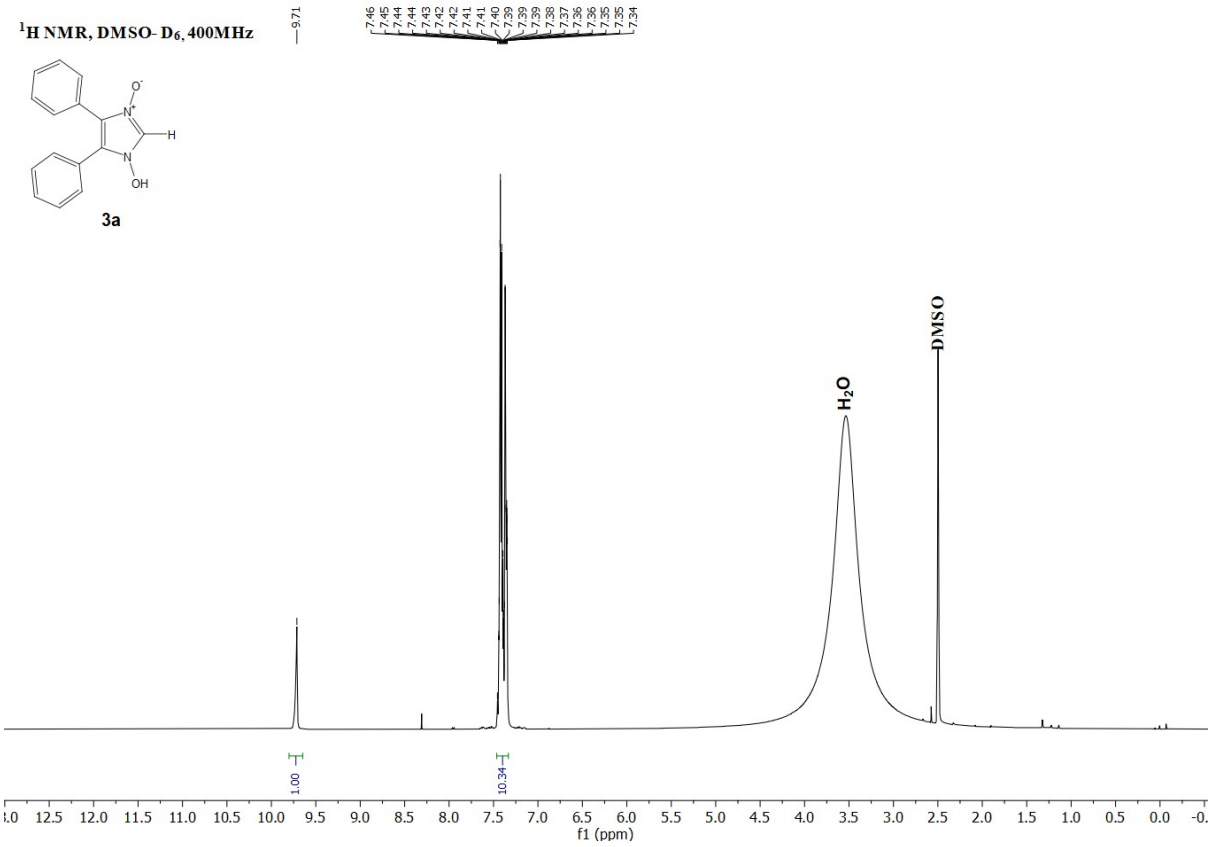


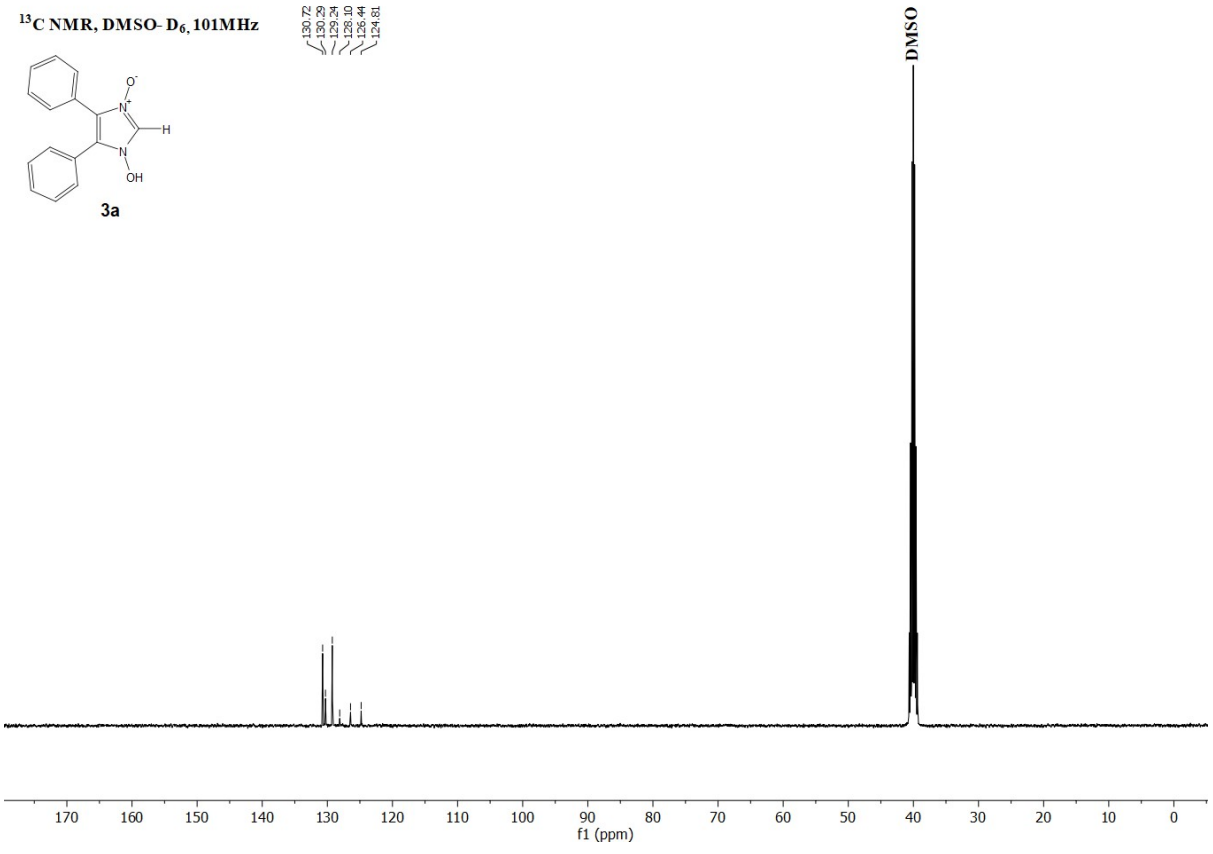
6.15. ^{1}H and C^{13} NMR spectra of compound 2e



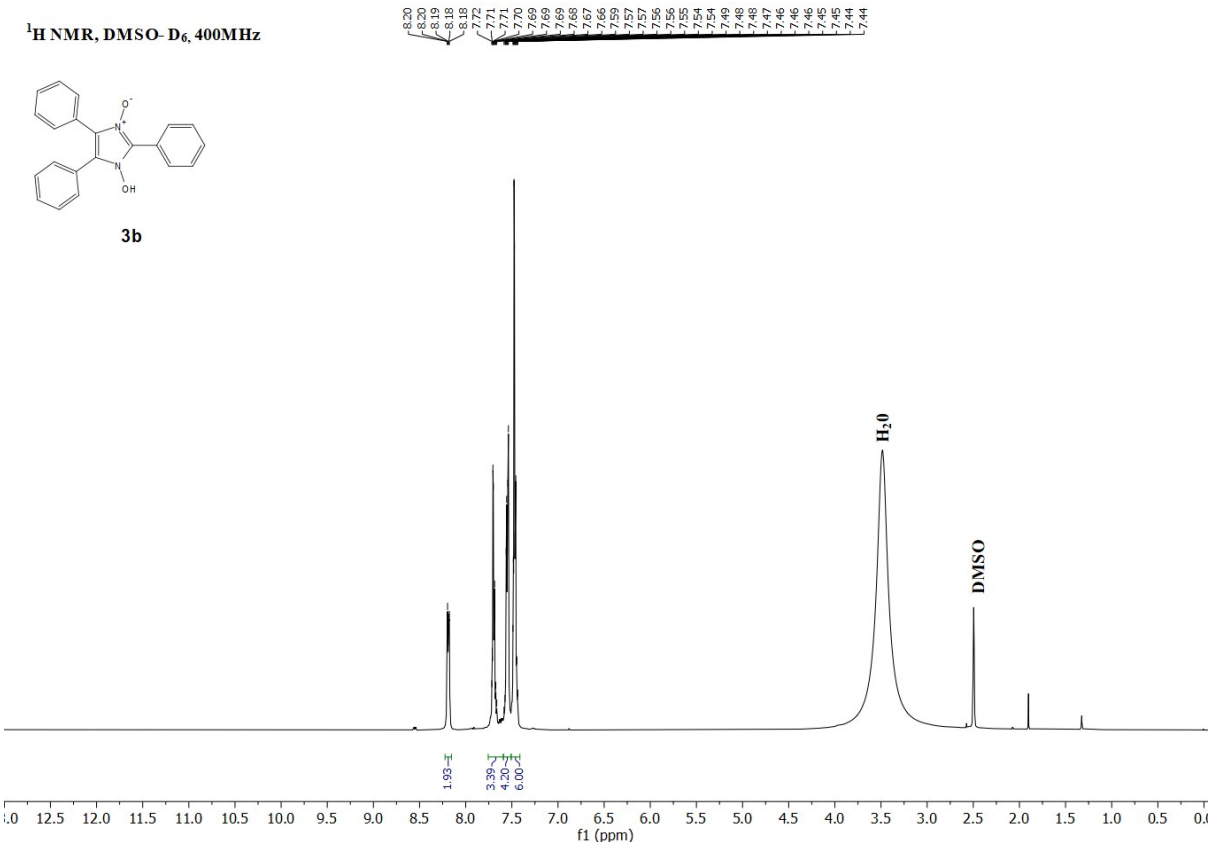


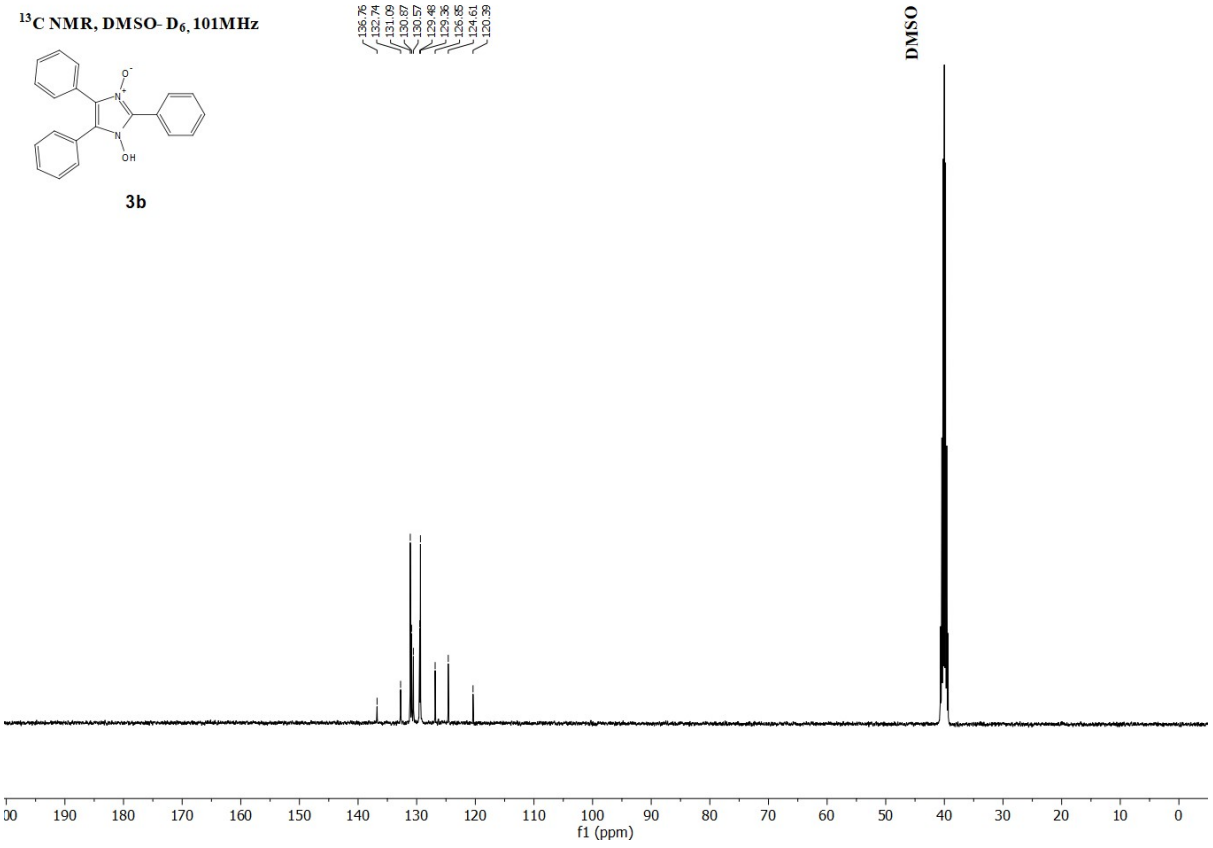
6.16. ^{1}H and C^{13} NMR spectra of compound 3a



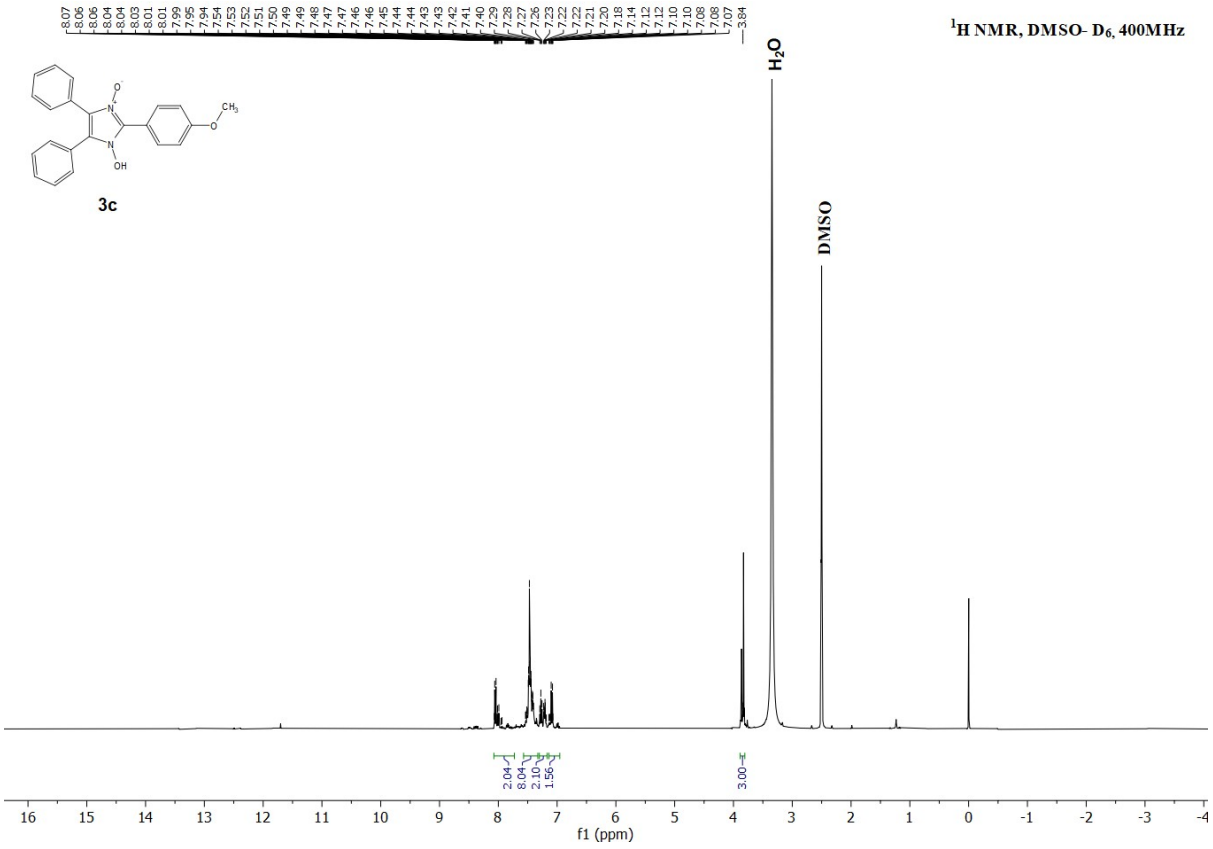


6.17. ^{1}H and C^{13} NMR spectra of compound 3b

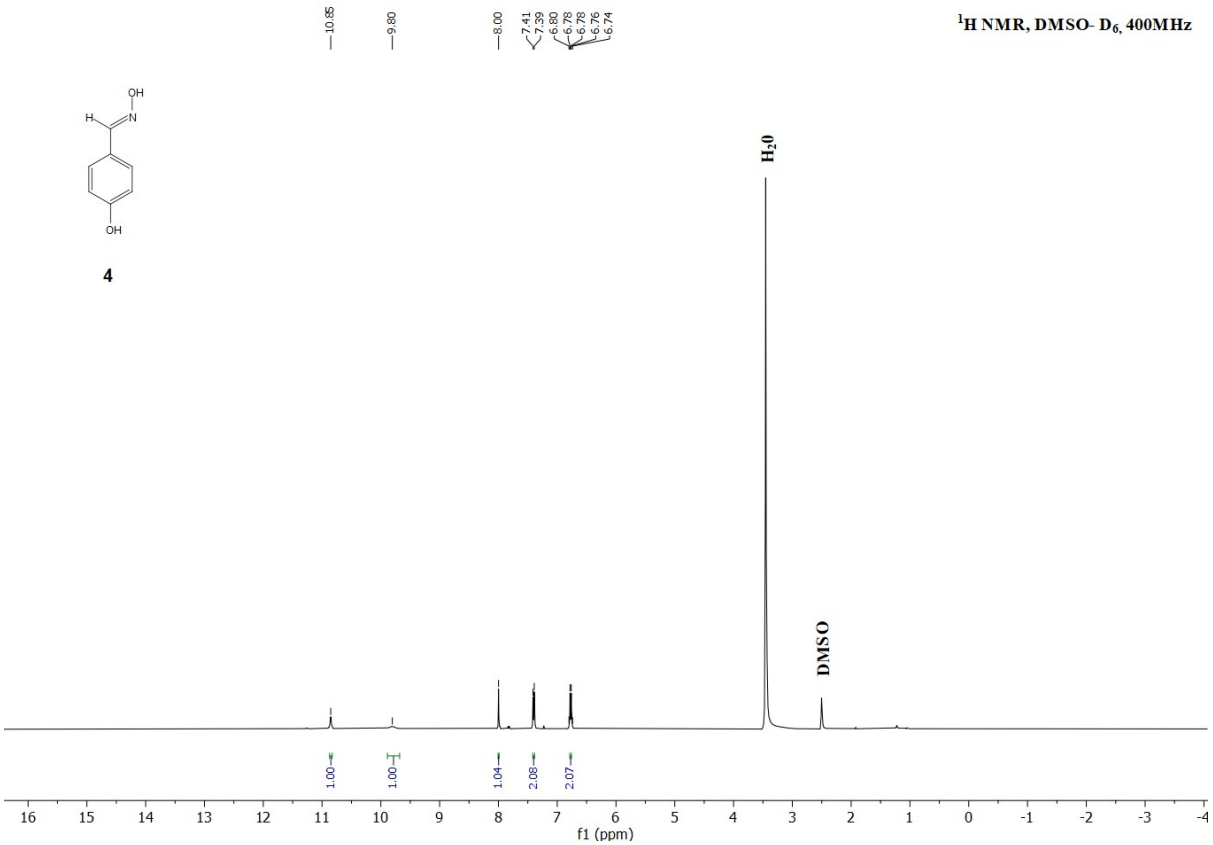


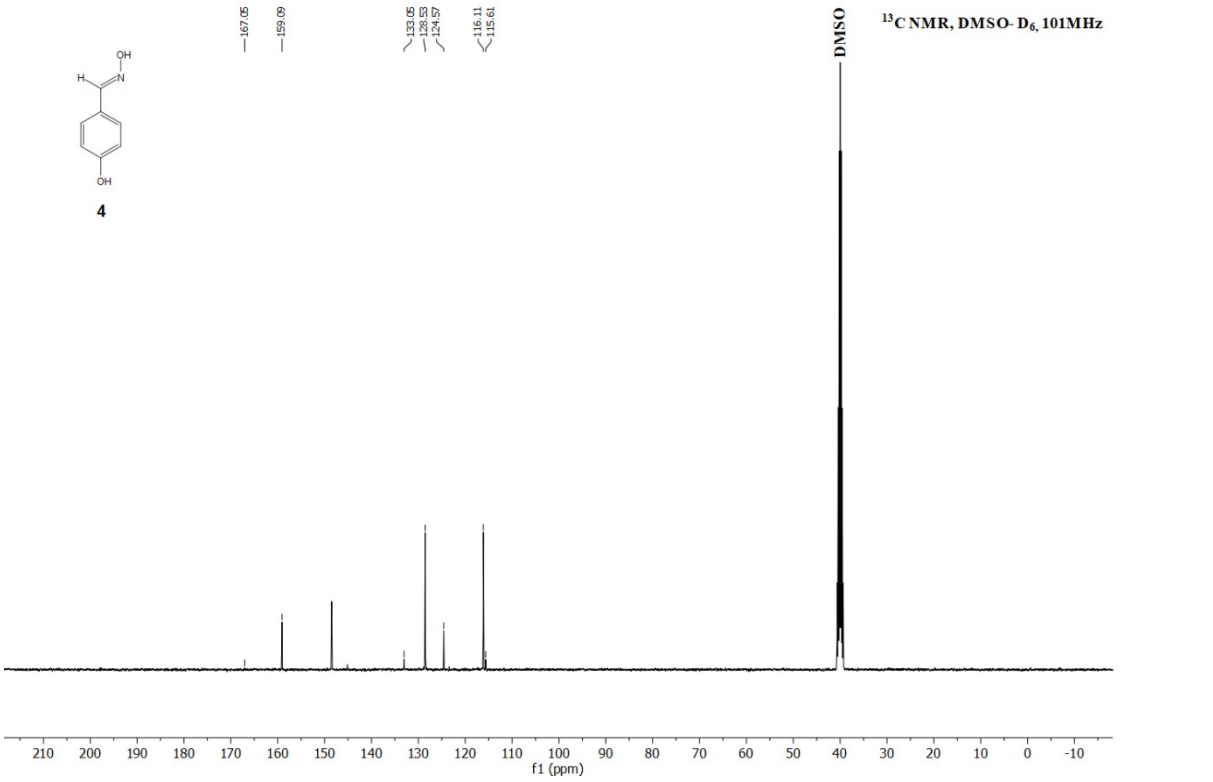


6.18. ^{1}H and C^{13} NMR spectra of compound 3c



6.19. ^{1}H and C^{13} NMR spectra of compound 4





7. X-ray single crystal structural determination, refinement and bonding interactions

Table 1: Crystal data collection and structure refinement for compound **2c**.

Crystal data	
CCDC reference number	2388769
Empirical formula	$C_{13}H_{10}N_2O_2$
Moiety formula	$C_{13}H_{10}N_2O_2$
Formula weight	226.23
Crystal system	Monoclinic
Space group	P 2_1/c
Colour, habit	Colourless
Size, mm	0.536×0.126×0.096
Unit cell dimensions	
	a = 8.9333(5) Å
	b = 10.9751(6) Å
	c = 11.0707(6) Å
	β = 90.371(2)°
Volume Å^3	1085.39(10)
Z	4
Density (calculated), Mg/m^3	1.384
Absorption coefficient, mm^{-1}	0.096
F(000)	472
Data collection	
Temperature, K	304(2)
Theta range for data collection	2.613° to 25.035°
Index ranges	-10 ≤ h ≤ 10
	-13 ≤ k ≤ 13
	-13 ≤ l ≤ 13
Reflections collected	27414
Unique reflections	1923
Observed reflections (>2σ*(I)*)	1693
R_{int}	0.0563
Completeness to θ, %	25.035°, 99.9
Absorption correction	Multi-scan (CrysAlisPro, 1.171.39.29d, Rigaku Oxford Diffraction, 2017)
	T_{min} = 0.986, T_{max} = 0.991
Refinement	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1923 / 1 / 194
Goodness-of-fit on F^2	1.088
Final R indices [I > 2σ(I)]	R_1 = 0.0358, wR_2 = 0.0923
R indices (all data)	R_1 = 0.0412, wR_2 = 0.0970
Largest diff. peak and hole	0.149 and -0.289 e.Å^{-3}

Table 2 Selected bond lengths (Å) and torsion angles (°)for compound **2c.**

Bond lengths (Å)			
O(1)-N(1)	1.3542(15)	O(2)-N(2)	1.3657(15)
Torsion angles (°)			
N(1)-C(11)-C(1)-C(10)	-59.4(2)	N(2)-C(11)-C(1)-C(2)	-54.1(2)

Table 3 Hydrogen bonded geometries in compound **2c.**

Bond	D - H	H···A	D···A	D - H···A
O(2)–H(2A)···O(1)^{i}	0.997(19)	1.448(19)	2.4413(15)	173(2)
O(2)–H(2A)···N(1)^{i}	0.997(19)	2.25(2)	3.1525(15)	150.5(15)
C(2)–H(2)···O(1)^{i}	0.99(2)	2.502(19)	3.4009(19)	150.8(14)
C(12)–H(12)···O(2)^{ii}	0.940(18)	2.307(19)	3.2236(18)	164.9(16)

Symmetry codes: (i) x,1/2-y,-1/2+z; (ii) 1-x,-1/2+y,1/2-z.

Table 4C–H···*Cg*interactions incompound **2c.**

Bond	H···*Cg*	H-Perp	Gamma	X - H··· *Cg*
C(13)–H(13)···*Cg*3^{ii}	2.689(18)	2.67	6.28	155.8(14)
C(13)–H(13)···*Cg*3^{ii}	2.821(18)	2.66	19.21	137.4(14)

Symmetry codes: (ii) 1-x,-1/2+y,1/2-z.Cg3 is the centroid of C5 – C10 ring.

Table 5*Cg*···*Cg*interactions in compound **2c.**

Cg(I)···*Cg*(J)	*Cg*–*Cg*	CgI_Perp	CgJ_Perp	Slippage
*Cg*2···*Cg*3^{iii}	3.8473(10)	3.4218(6)	3.3719(7)	1.853
*Cg*3···*Cg*2^{iii}	3.8473(10)	3.3720(7)	3.4218(6)	1.759
*Cg*3···*Cg*3^{iii}	3.8278(9)	3.3824(7)	3.3823(7)	1.792
*Cg*3···*Cg*4^{iii}	3.6402(9)	3.3994(7)	3.4054(5)	1.286
*Cg*4···*Cg*3^{iii}	3.6401(9)	3.4054(5)	3.3993(7)	1.302
*Cg*4···*Cg*4^{iii}	3.8519(8)	3.4030(5)	3.4030(5)	1.805

Symmetry codes: (iii) -x, 1-y, 1-z.Cg2, Cg3 and Cg4 are the centroids of C1 – C10, C5 – C10 and C1 – C8 rings respectively.

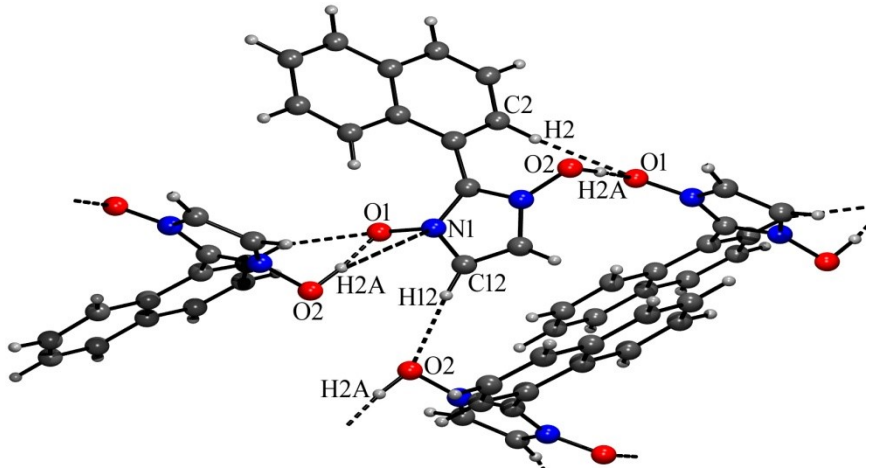


Fig. 1. Different hydrogen bonding interactions present in compound (**2c**).

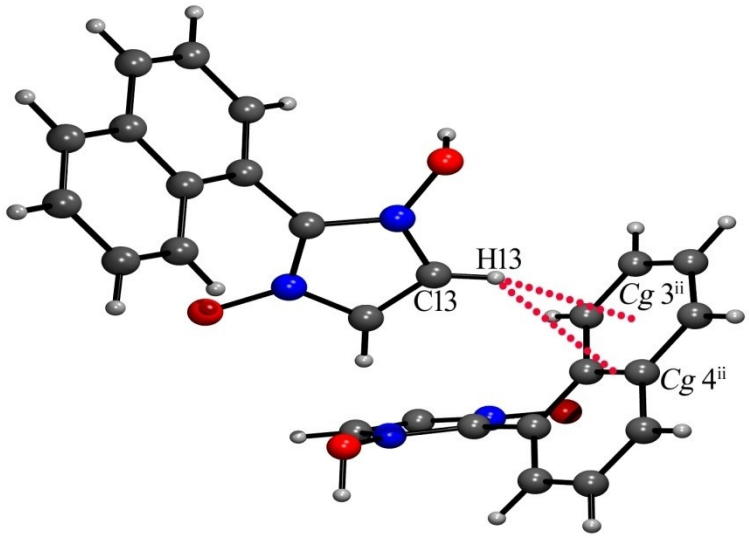


Fig. 2. Different C–H···*Cg* interactions present in compound (**2c**); *Symmetry code: (ii) 1-x,-1/2+y,1/2-z.*

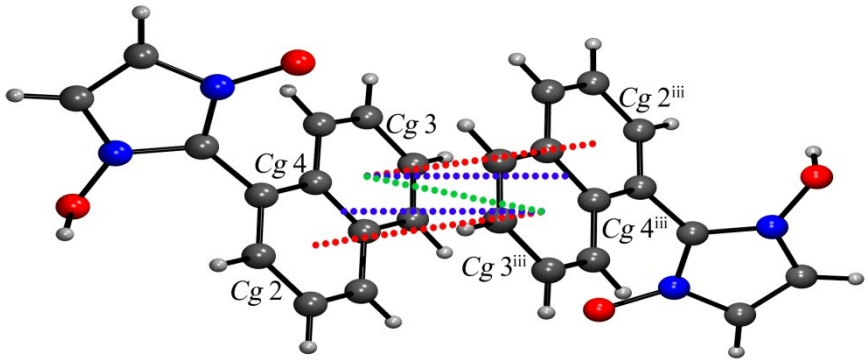


Fig. 3. Different *Cg*···*Cg* interactions present in compound (**2c**); *Symmetry code: (iii) -x,1-y,1-z.*

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