

Novel 8-arylidene tetrahydroquinazoline N-oxides: synthesis, photophysical properties and biological evaluation

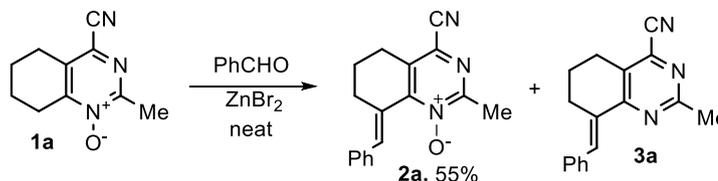
Kseniya N. Sedenkova, Dmitry A. Vasilenko, Denis V. Zverev,
Kirill S. Sadovnikov, Yulia A. Gracheva, Yuri K. Grishin,
Tamara S. Kuznetsova, Elena R. Milaeva and Elena B. Averina

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Optimization of the condensation conditions

Table S1. Optimization of the condensation conditions.



PhCHO, equiv.	ZnBr ₂ , equiv.	<i>t</i> /h	<i>T</i> /°C	Ratio 1a/2a/3a ^a	Yield 2a , % ^c
2	0.12	5	115	2.5:1:0.3	n/d
5	0.12	5	115	2:1:0.5	n/d
10	0.12	3	115	1:1:0.2 (1.4:1:0.2^b)	31 (55^d)
10	0.50	3	115	0.8:1:0.3	n/d
10	0.12	5	115	0.4:1:0.2	n/d
10	0.12	7	115	0.2:1:0.2 (0.3:1:0.2 ^b)	20 (22 ^d)
10	0.12	3	100	2.7:1:0.1	n/d
10	0.12	5	100	2:1:0.2	n/d
10	0.12	7	100	1.5:1:0.3	n/d

^a ¹H NMR data.

^b Ratio of isolated compounds.

^c Isolated yield.

^d Isolated yield counted for the reacted **1a**.

Experimental Section

^1H , ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer Agilent 400-MR (400.0, 100.6 and 376.3 MHz for ^1H , ^{13}C and ^{19}F , respectively) at room temperature; chemical shifts δ were measured with reference to the solvent for ^1H (CDCl_3 , $\delta = 7.26$ ppm) and ^{13}C (CDCl_3 , $\delta = 77.16$ ppm) and to CFCl_3 as external standard for ^{19}F . When necessary, assignments of signals in NMR spectra were made using 2D techniques. Accurate mass measurements (HRMS) were obtained on JEOL GCMate II mass spectrometer with electrospray ionization (ESI) and a time-of-flight (TOF) detector. Mass spectra MALDI-TOF were registered on "Bruker Daltonics Autoflex II" spectrometer. Ultraviolet/Visible spectra were obtained on Agilent Cary 60 spectrophotometer. Fluorescence spectra in solutions were recorded on Hitachi F2700 fluorescence spectrophotometer. Fluorescence quantum yield ($\pm 10\%$) determined relative to quinine sulfate in 0.05 M H_2SO_4 ($\psi = 53\%$) as standard. Analytical thin layer chromatography was carried out with silica gel plates (supported on aluminum); the detection was done by UV lamp (254 and 365 nm). Column chromatography was performed on silica gel (Merck, 230–400 mesh). Starting compounds **1a,b** were obtained as described [S1]. All other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified according to literature procedures prior to use.

Condensation of 4-cyanotetrahydroquinazoline N-oxides 1a,b with aldehydes (general procedure). A mixture of a 4-cyanotetrahydroquinazoline N-oxide **1** (0.5 mmol), the corresponding aldehyde (5 mmol) and ZnBr_2 (0.06 mmol, 14 mg) was stirred at 115°C for 2–7 h under argon. The resulting hot mixture was poured into saturated solution of NaHCO_3 (5 ml) and extracted with EtOAc (3×5 ml). The combined organic extracts were washed with saturated solution of NaHCO_3 (3×5 ml) and water (5 ml) and dried over MgSO_4 . The solvent was evaporated *in vacuo*. If possible, the residual aldehyde was pumped-off *in vacuo*, and the product was isolated by column chromatography (SiO_2). Unreacted starting compound **1** was also isolated and reused.

(E)-8-Benzylidene-2-methyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (2a). Reaction proceeded for 3 h. Yield 43 mg (55%). * Yellow solid, R_f 0.1 (petroleum ether:EtOAc 10:1), m.p. $143\text{--}145^\circ\text{C}$ (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): $\delta = 1.88$ (2H, m, CH_2^6), 2.72 (3H, s, CH_3), 2.86 (2H, m, CH_2^7), 3.04 (2H, ps.t, J 6.3 Hz, CH_2^5), 7.30–7.44 (5H, m, 5CH, Ph), 9.52 (1H, br.s, =CH); ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 20.6$ (CH_3), 21.3 (CH_2^6), 27.0 (CH_3^5), 28.2 (CH_2^7), 115.2 (CN), 123.0 (C^4), 126.5 (C^8), 128.4 (CH, Ph), 128.5 (2CH, Ph), 130.0 (2CH, Ph), 134.3 (C^{4a}), 136.6 (C, Ph), 139.3 (=CH), 149.5 (C^{8a}), 161.0 (C^2). HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 278.1288, found: 278.1291.

(E)-8-Benzylidene-2-ethyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (2b). Reaction proceeded for 3 h. Yield 51 mg (42%). Yellow solid, R_f 0.4 (petroleum ether:EtOAc 6:1), m.p. $136\text{--}138^\circ\text{C}$ (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): 1.36 (1H, t, J 7.2 Hz, CH_3), 1.88 (2H, m, CH_2^6), 2.85 (2H, m, CH_2^7), 3.03 (2H, ps.t, J 6.2 Hz, CH_2^5), 3.08 (2H, q, J 7.2 Hz, CH_2 , Et),

* All the yields are given counted for the reacted tetrahydroquinazoline N-oxide **1**

7.28–7.44 (5H, m, 5CH, Ph), 9.50 (1H, br.s, =CH); ¹³C NMR (100.6 MHz, CDCl₃): 9.5 (CH₃), 21.3 (CH₂⁶), 25.9 (CH₂⁵), 27.0 (CH₂⁷), 28.2 (CH₂, Et), 115.4 (CN), 123.0 (C⁴), 126.6 (C⁸), 128.3 (CH, Ph), 128.4 (2CH, Ph), 129.9 (2CH, Ph), 134.0 (C^{4a}), 136.7 (C, Ph), 139.0 (=CH), 149.3 (C^{8a}), 164.2 (C²). HRMS (ESI) calcd for C₁₈H₁₇N₃O [M+H]⁺: 292.1444, found: 292.1446.

(E)-2-Methyl-8-(2,6-dimethylbenzylidene)-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2c**). Reaction proceeded for 7 h. Yield 43 mg (36%). Yellow solid, R_f 0.4 (petroleum ether:EtOAc 6:1), m.p. 187–189 °C (from CDCl₃). ¹H NMR (400.0 MHz, CDCl₃): 1.83 (2H, m, CH₂⁶), 2.19 (6H, s, 2CH₃), 2.31 (2H, m, CH₂⁷), 2.74 (3H, s, CH₃), 3.05 (2H, ps.t, *J* 6.4 Hz, CH₂⁵), 7.06–7.17 (3H, m, 3CH, Ar), 9.39 (1H, br.s, =CH); ¹³C NMR (100.6 MHz, CDCl₃): 20.48 (CH₃), 20.54 (2CH₃), 21.1 (CH₂⁶), 27.3 (CH₂⁵), 27.8 (CH₂⁷), 115.2 (CN), 123.1 (C⁴), 127.4 (CH, Ar), 127.5 (C⁸ + 2CH, Ar), 134.1 (C^{4a}), 135.0 (2C, Ar), 136.3 (C, Ar), 140.0 (=CH), 148.7 (C^{8a}), 161.0 (C²). HRMS (ESI) calcd for C₁₉H₁₉N₃O [M+H]⁺: 306.1601, found: 306.1600.

(E)-8-(4-Methoxybenzylidene)-2-methyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2d**). Reaction proceeded for 2 h. Yield 65 mg (64%). Yellow solid, R_f 0.1 (petroleum ether:EtOAc 10:1), m.p. 166–167 °C (from CDCl₃). ¹H NMR (400.0 MHz, CDCl₃): 1.89 (2H, m, CH₂⁶), 2.72 (3H, s, CH₃), 2.90 (2H, m, CH₂⁷), 3.02 (2H, ps.t, *J* 6.2 Hz, CH₂⁵), 3.85 (3H, s, OCH₃), 6.92–6.97 (2H, m, 2CH, Ar), 7.36–7.43 (2H, m, 2CH, Ar), 9.51 (1H, br.s, =CH); ¹³C NMR (100.6 MHz, CDCl₃): 20.6 (CH₃), 21.3 (CH₂⁶), 27.1 (CH₂⁵), 28.5 (CH₂⁷), 55.5 (OCH₃), 114.0 (2CH, Ar), 115.3 (CN), 122.9 (C⁴), 124.7 (C, Ar), 129.0 (C⁸), 132.2 (2CH, Ar), 134.2 (C^{4a}), 139.0 (=CH), 149.8 (C^{8a}), 160.0 (C, Ar), 161.0 (C²). HRMS (ESI) calcd for C₁₈H₁₇N₃O₂ [M+H]⁺: 308.1394, found: 308.1396.

(E)-8-(4-Ethoxybenzylidene)-2-methyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2e**). Reaction proceeded for 2.5 h. Yield 48 mg (56%). Yellow solid, R_f 0.1 (petroleum ether:EtOAc 6:1), m.p. 164–166 °C (from CDCl₃). ¹H NMR (400.0 MHz, CDCl₃): 1.44 (3H, t, *J* 7.0 Hz, CH₃), 1.89 (2H, m, CH₂⁶), 2.71 (3H, s, CH₃), 2.90 (2H, m, CH₂⁷), 3.02 (2H, ps.t, *J* 6.3 Hz, CH₂⁵), 4.08 (2H, q, *J* 7.0 Hz, OCH₂), 6.92–6.97 (2H, m, 2CH, Ar), 7.32–7.42 (2H, m, 2CH, Ar), 9.51 (1H, br.s, =CH); ¹³C NMR (100.6 MHz, CDCl₃): 14.9 (CH₃), 20.6 (CH₃), 21.3 (CH₂⁶), 27.1 (CH₂⁵), 28.5 (CH₂⁷), 63.7 (OCH₂), 114.5 (2CH, Ar), 115.3 (CN), 122.9 (C⁴), 124.6 (C, Ar), 128.8 (C⁸), 132.2 (2CH, Ar), 134.2 (C^{4a}), 139.1 (=CH), 149.8 (C^{8a}), 159.4 (C, Ar), 161.0 (C²). HRMS (ESI) calcd for C₁₉H₁₉N₃O₂ [M+H]⁺: 322.1550, found: 322.1549.

(E)-8-(3,4,5-Trimethoxybenzylidene)-2-methyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2f**). Reaction proceeded for 7 h. Yield 62 mg (56%). Yellow solid, R_f 0.1 (petroleum ether:EtOAc 3.5:1), m.p. 214–215 °C with decomposition (from CDCl₃). ¹H NMR (400.0 MHz, CDCl₃): 1.91 (2H, m, CH₂⁶), 2.72 (3H, s, CH₃), 2.90 (2H, m, CH₂⁷), 3.04 (2H, ps.t, *J* 6.3 Hz, CH₂⁵), 3.87 (6H, s, 2OCH₃), 3.89 (3H, s, OCH₃), 6.62 (2H, s, 2CH, Ar), 9.49 (1H, br.s, =CH); ¹³C NMR (100.6 MHz, CDCl₃): 20.6 (CH₃), 21.3 (CH₂⁶), 27.0 (CH₂⁵), 28.5 (CH₂⁷), 56.4 (2OCH₃), 61.1 (OCH₃), 107.6 (2CH, Ar), 115.2 (CN), 123.1 (C⁴), 126.1 (C⁸), 132.0 (C, Ar), 134.3 (C^{4a}), 138.5 (C, Ar), 139.3 (=CH), 149.5 (C^{8a}), 153.2 (2C, Ar), 161.1 (C²). HRMS (ESI) calcd for C₂₀H₂₁N₃O₄ [M+H]⁺: 368.1605, found: 368.1599.

(8*E*)-8-(4-dimethylaminophenylmethylidene)-2-methyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2g**). Reaction proceeded for 6 h. Yield 20 mg (18%). Yellow solid, R_f 0.3 (petroleum ether: EtOAc 4:1), m.p. 186–188 °C with decomposition (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): 1.89 (2H, m, CH_2^6), 2.71 (3H, s, CH_3), 2.93–3.01 (4H, m, CH_2^7 , CH_2^5), 3.03 (2H, s, $\text{N}(\text{CH}_3)_2$), 6.69–6.74 (2H, m, 2CH, Ar), 7.39–7.44 (2H, m, 2CH, Ar), 9.56 (1H, br.s, =CH); ^{13}C NMR (100.6 MHz, CDCl_3): 20.7 (CH_3), 21.3 (CH_2^6), 27.2 (CH_2^5), 29.1 (CH_2^7), 40.3 ($\text{N}(\text{CH}_3)_2$), 111.7 (2CH, Ar), 115.5 (CN), 122.0 (C^4), 122.7 (C^8), 124.0 (C, Ar), 133.0 (2CH, Ar), 134.0 (C^{4a}), 139.8 (=CH), 150.1 (C^{8a}), 150.6 (C, Ar), 160.9 (C^2). HRMS (MALDI, dithranol, PEG-300) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}$ [$\text{M}+\text{H}$] $^+$: 321.1710, found: 321.1766.

(*E*)-8-(4-Fluorobenzylidene)-2-methyl-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2h**). Reaction proceeded for 5.5 h. Yield 56 mg (65%). Yellow solid, R_f 0.2 (petroleum ether:EtOAc 6:1), m.p. 147–150 °C (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): 1.89 (2H, m, CH_2^6), 2.72 (3H, s, CH_3), 2.83 (2H, m, CH_2^7), 3.04 (2H, ps.t, J 6.4 Hz, CH_2^5), 7.06–7.14 (2H, m, 2CH, Ar), 7.32–7.40 (2H, m, 2CH, Ar), 9.49 (1H, br.s, CH=); ^{13}C NMR (100.6 MHz, CDCl_3): 20.6 (CH_3), 21.3 (CH_2^6), 27.0 (CH_2^5), 28.2 (CH_2^7), 115.2 (CN), 115.7 (d, J_{CF} 22 Hz, 2CH, Ar), 123.1 (C^4), 126.4 (C^8), 131.9 (d, J_{CF} 9 Hz, 2CH, Ar), 132.6 (d, J_{CF} 3 Hz, C, Ar), 134.3 (C^{4a}), 138.1 (CH=), 149.4 (C^{8a}), 161.1 (C^2), 162.6 (d, J_{CF} 249 Hz, CF); ^{19}F NMR (376.3 MHz, CDCl_3): -112.33 (tt, J 8.4 Hz, J 5.5 Hz). HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{FN}_3\text{O}$ [$\text{M}+\text{H}$] $^+$: 296.1194, found: 296.1199.

(*E*)-2-Methyl-8-(4-nitrobenzylidene)-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2i**). Reaction proceeded for 6 h. Yield 60 mg (48%). Yellow solid, R_f 0.3 (petroleum ether:EtOAc 8:1), m.p. 168–170 °C (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): 1.92 (2H, m, CH_2^6), 2.73 (3H, s, CH_3), 2.80 (2H, m, CH_2^7), 3.08 (2H, ps.t, J 6.4 Hz, CH_2^5), 7.47–7.52 (2H, m, 2CH, Ar), 8.24–8.29 (2H, m, 2CH, Ar), 9.54 (1H, br.s, =CH); ^{13}C NMR (100.6 MHz, CDCl_3): 20.5 (CH_3), 21.2 (CH_2^6), 26.9 (CH_2^5), 28.3 (CH_2^7), 115.0 (CN), 123.3 (C^4), 123.8 (2CH, Ar), 129.3 (C^8), 130.4 (2CH, Ar), 134.6 (C^{4a}), 136.4 (=CH), 143.4 (C, Ar), 147.3 (CNO_2 , Ar), 148.6 (C^{8a}), 161.2 (C^2). HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 323.1139, found: 323.1143.

(8*E*)-2-Methyl-8-(4-(*E*)-styrylbenzylidene)-5,6,7,8-tetrahydroquinazoline-4-carbonitrile (**2j**). Reaction proceeded for 5 h. Yield 78 mg (40%). Yellow solid, R_f 0.3 (petroleum ether:EtOAc 10:1), m.p. 181–183 °C (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): 1.91 (2H, m, CH_2^6), 2.73 (3H, s, CH_3), 2.92 (2H, m, CH_2^7), 3.04 (2H, ps.t, J 6.3 Hz, CH_2^5), 7.11 (1H, d, J 16.3 Hz, =CH), 7.18 (1H, d, J 16.3 Hz, =CH), 7.27–7.60 (9H, m, 9CH, Ar), 9.53 (1H, br.s, =CH); ^{13}C NMR (100.6 MHz, CDCl_3): 20.6 (CH_3), 21.3 (CH_2^6), 27.0 (CH_2^5), 28.5 (CH_2^7), 115.2 (CN), 123.0 (C^4), 126.3 (C^8), 126.6 (2CH, Ar), 126.8 (2CH, Ar), 128.0 (=CH), 128.1 (CH, Ar), 128.9 (2CH, Ar), 129.9 (=CH), 130.8 (2CH, Ar), 134.4 (C^{4a}), 135.8 (C, Ar), 137.2 (C, Ar), 137.7 (C, Ar), 138.8 (=CH), 149.5 (C^{8a}), 161.0 (C^2). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}$ [$\text{M}+\text{H}$] $^+$: 380.1757, found: 380.1752.

(*E*)-2-Methyl-8-(2-naphthylmethylidene)-5,6,7,8-tetrahydroquinazoline-4-carbonitrile (**2k**). Reaction proceeded for 5 h. Yield 93 mg (54%). Orange solid, R_f 0.3 (petroleum ether:EtOAc 7:1), m.p. 207–210 °C with decomposition (from CDCl_3). ^1H NMR (400.0 MHz, CDCl_3): 1.86

(2H, m, CH₂⁶), 2.69 (2H, m, CH₂⁷), 2.77 (3H, s, CH₃), 3.08 (2H, ps.t, *J* 6.3 Hz, CH₂⁵), 7.37–7.42 (1H, m, CH, Ar), 7.47–7.57 (3H, m, 3CH, Ar), 7.83–8.01 (3H, m, 3CH, Ar), 9.99 (1H, br.s, =CH); ¹³C NMR (100.6 MHz, CDCl₃): 20.6 (CH₃), 21.4 (CH₂⁶), 27.2 (CH₂⁵), 28.5 (CH₂⁷), 115.2 (CN), 123.2 (C⁴), 125.2 (CH, Ar), 125.3 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.6 (CH, Ar), 128.2 (C⁸), 128.65 (CH, Ar), 128.67 (CH, Ar), 131.5 (C, Ar), 133.6 (C, Ar), 134.2 (C^{4a}), 134.3 (C, Ar), 138.1 (CH=), 149.2 (C^{8a}), 161.0 (C²). HRMS (ESI) calcd for C₂₁H₁₇N₃O [M+H]⁺: 328.1444, found: 328.1438.

(E)-2-Methyl-8-[(5-methylfuran-2-yl)methylidene]-5,6,7,8-tetrahydroquinazoline-4-carbonitrile 1-oxide (**2l**). Reaction proceeded for 3.5 h. Yield 47 mg (34%). Yellow solid, R_f 0.1 (petroleum ether:EtOAc 10:1), m.p. 180–183 °C with decomposition (from CDCl₃). ¹H NMR (400.0 MHz, CDCl₃): 1.93 (2H, m, CH₂⁶), 2.39 (3H, s, CH₃), 2.69 (3H, s, CH₃), 2.97 (2H, m, CH₂⁵), 3.02 (2H, m, CH₂⁷), 6.15–6.19 (1H, m, CH, Fur), 6.66 (1H, d, *J* 3.3 Hz, CH, Fur), 9.46–9.51 (1H, m, CH=); ¹³C NMR (100.6 MHz, CDCl₃): 14.3 (CH₃), 20.62 (CH₃), 20.64 (CH₂⁶), 27.1 (CH₂⁵), 29.0 (CH₂⁷), 109.6 (CH, Fur), 115.4 (CN), 119.7 (CH, Fur), 120.8 (C⁸), 122.4 (C⁴), 124.6 (CH=), 134.5 (C^{4a}), 149.5 (C^{8a}), 151.2 (C, Fur), 156.3 (C, Fur), 160.9 (C²). HRMS (ESI) calcd for C₁₆H₁₅N₃O₂ [M+H]⁺: 282.1237, found 282.1235.

(8E)-2-Methyl-8-(2-thienylmethylidene)-5,6,7,8-tetrahydroquinazoline-4-carbonitrile (**2m**). Reaction proceeded for 5 h. Yield 3 mg (5%). Dark-brown solid, R_f 0.2 (petroleum ether:EtOAc 7:1), m.p. 181–182 °C with decomposition (from CDCl₃). ¹H NMR (400.0 MHz, CDCl₃): 1.99 (2H, m, CH₂⁶), 2.72 (3H, s, CH₃), 2.92–3.00 (4H, m, CH₂⁵, CH₂⁷), 7.18 (1H, dd, *J* 5.1 Hz, *J* 3.7 Hz, CH, Thienyl), 7.40–7.43 (1H, m, CH, Thienyl), 7.59–7.62 (1H, m, CH, Thienyl), 9.92–9.95 (1H, m, CH=); ¹³C NMR (100.6 MHz, CDCl₃): 20.6 (CH₂⁶), 20.7 (CH₃), 27.0 (CH₂⁵), 29.3 (CH₂⁷), 115.3 (CN), 122.2 (C⁸), 122.4 (C⁴), 127.9 (CH, Thienyl), 131.11 (CH, Thienyl), 131.15 (CH=), 133.9 (CH, Thienyl), 134.7 (C^{4a}), 139.6 (C, Thienyl), 149.3 (C^{8a}), 161.1 (C²). HRMS (ESI) calcd for C₁₅H₁₃N₃OS [M+H]⁺: 284.0852, found: 284.0854.

Photophysical properties of compounds 2,3

Table S2. Photophysical properties of compounds **2** and their deoxygenated analogues **3**.

Compounds	R ¹	X	$\lambda^{\max}_{\text{abs}}$, nm	$\lambda^{\max}_{\text{em}}$, nm	$\Delta\lambda$, cm ⁻¹	ϵ , M ⁻¹ ·cm ⁻¹	ψ , %
2a	Ph	N→O	340	-	-	10300	-
3a [S1]	Ph	N	344	432	5922	10600	0.05
2c	2,6-Me ₂ C ₆ H ₃	N→O	328	-	-	7060	-
3c [S1]	2,6-Me ₂ C ₆ H ₃	N	324	-	-	9900	-
2d	4-MeOC ₆ H ₄	N→O	396	-	-	5490	-
3d [S1]	4-MeOC ₆ H ₄	N	370	464	5475	15000	0.15
2e	4-EtOC ₆ H ₄	N→O	394	-	-	11310	-
3e [S1]	4-EtOC ₆ H ₄	N	374	474	5641	13700	0.16
2f	3,4,5-(MeO) ₃ C ₆ H ₂	N→O	358	496	7772	9110	0.05
3f [S1]	3,4,5-(MeO) ₃ C ₆ H ₂	N	370	518	7722	6600	1.36
2g	4-Me ₂ NC ₆ H ₄	N→O	332	449	7850	3650	0.07
2h	4-FC ₆ H ₄	N→O	346	-	-	10330	-
3h [S1]	4-FC ₆ H ₄	N	343	430	5899	9200	0.07
2i	4-O ₂ NC ₆ H ₄	N→O	338	-	-	14840	-
3i ¹	4-O ₂ NC ₆ H ₄	N	348	-	-	23500	-
2j	4-PhC=CHC ₆ H ₄	N→O	404	455	2774	14100	0.22
3j [S1]	4-PhC=CHC ₆ H ₄	N	387	488	5348	15200	0.93
2k	2-naphthyl	N→O	353	456	6400	8040	0.07
2l	5-methylfuran-2-yl	N→O	421	474	2656	15060	0.09
3l [S1]	5-methylfuran-2-yl	N	399	490	4654	22400	0.82
2m	2-thienyl	N→O	397	506	5426	10880	0.13

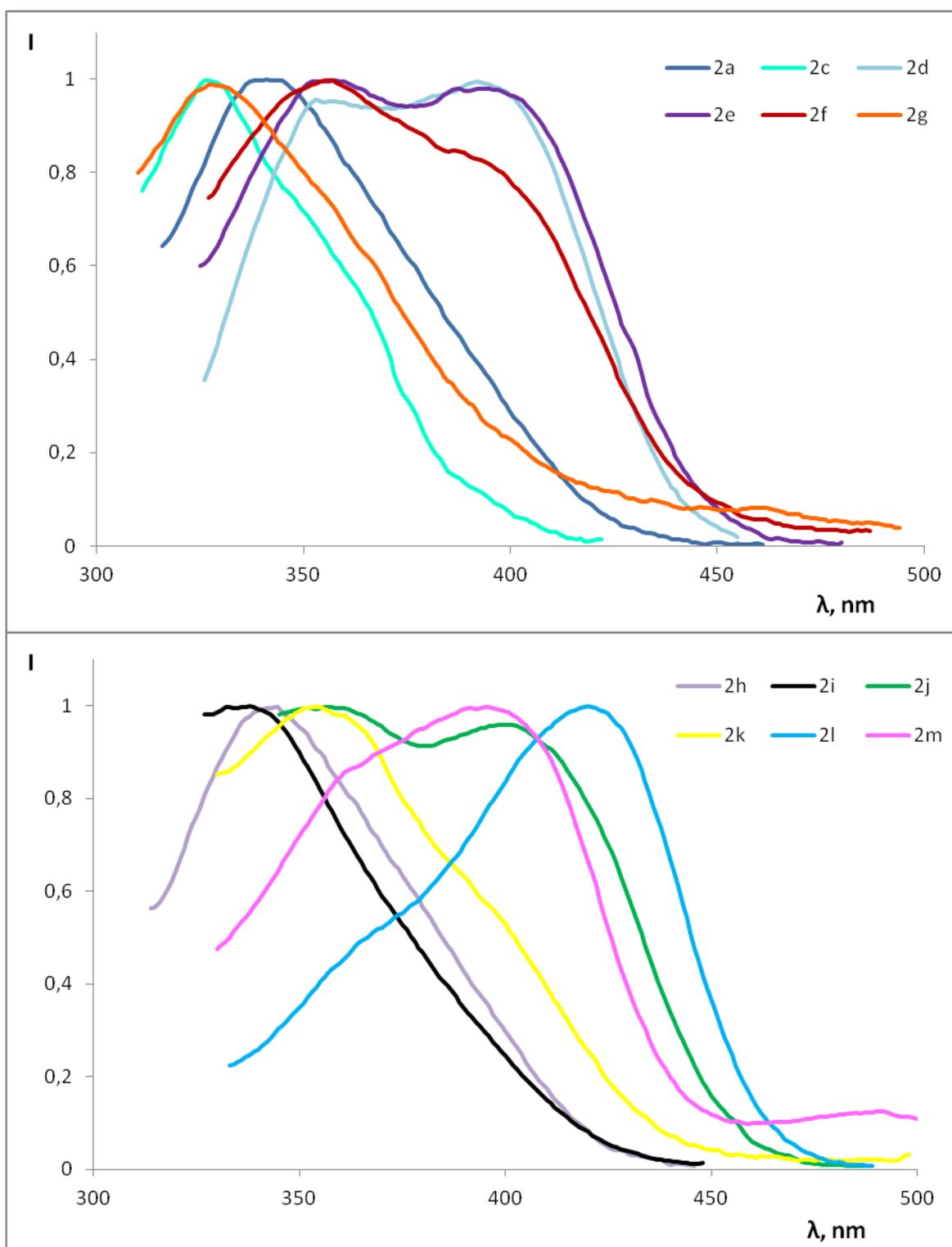


Figure S1. Normalized absorption spectra of compounds **2a,c-g** (a) and **2h-m** (b) in CH_2Cl_2 solutions at r.t. at $C = (5.0\text{--}8.0) \times 10^{-6}$ M.

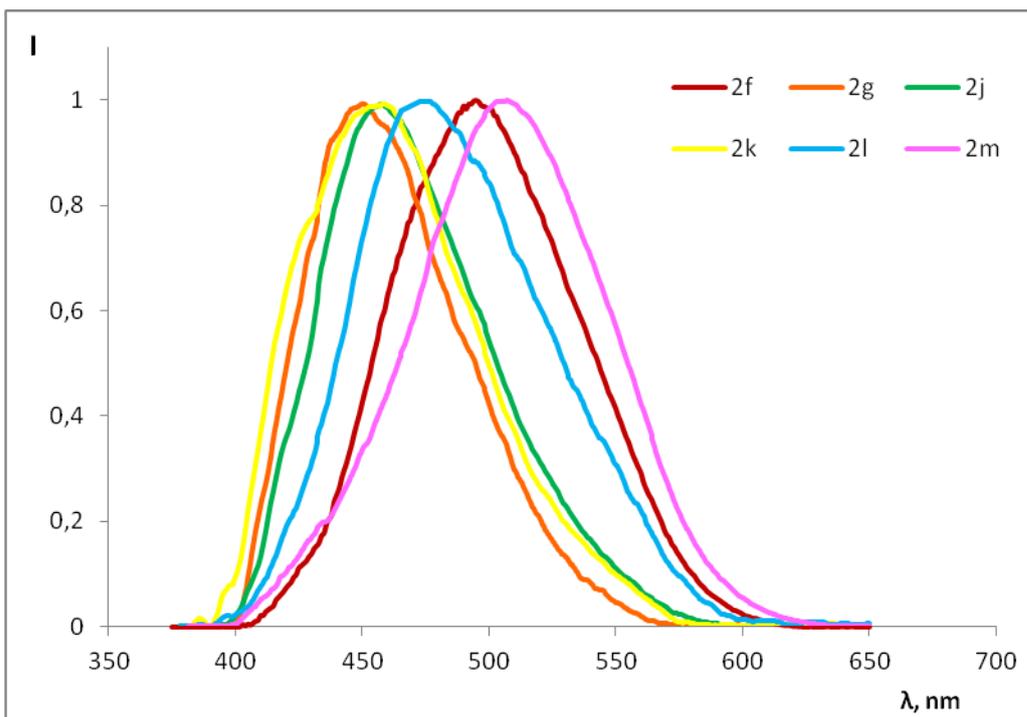


Figure S2. Normalized emission spectra of compounds **2f,g,j,k-m** in CH_2Cl_2 solutions at r.t. at $C = (5.0\text{--}8.0) \times 10^{-6}$ M.

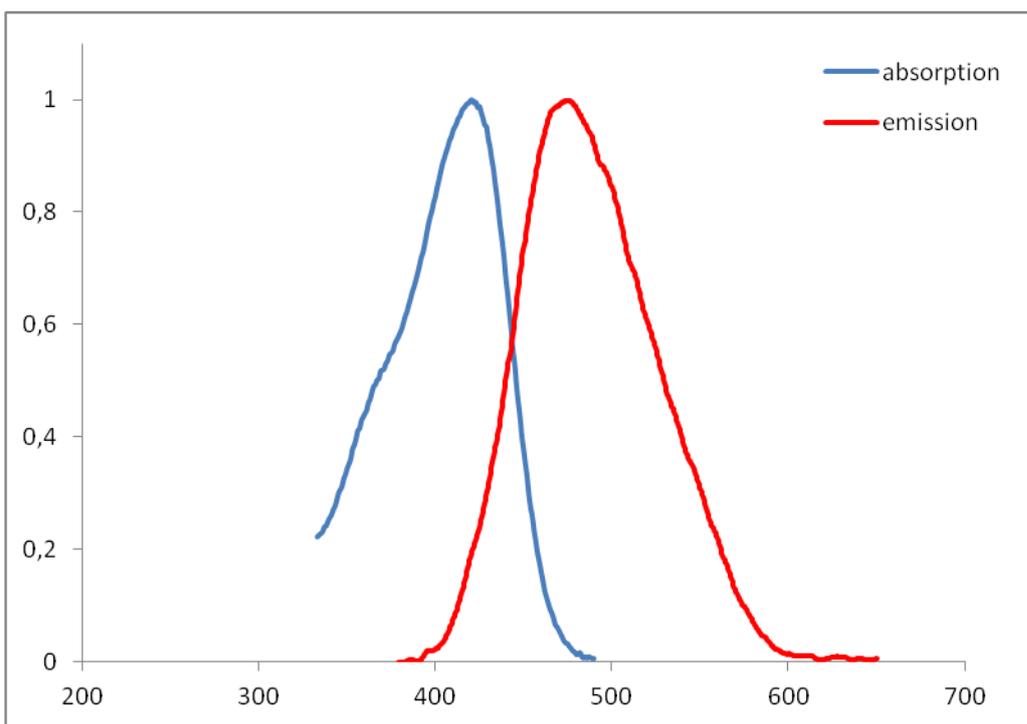


Figure S3. Normalized absorption and emission spectra of **2l** CH_2Cl_2 solution at r.t. at $C = 7.0 \times 10^{-6}$ M.

Evaluation of Biological Activity

The MTT test of compounds **2a,c,e,f,j,k** was performed as described [S1].

Table S3. The results of MTT test on MCF-7 (human breast cancer), HCT116 (human colon cancer), A549 (human lung carcinoma) and WI 38 (normal human lung fibroblasts) cell lines

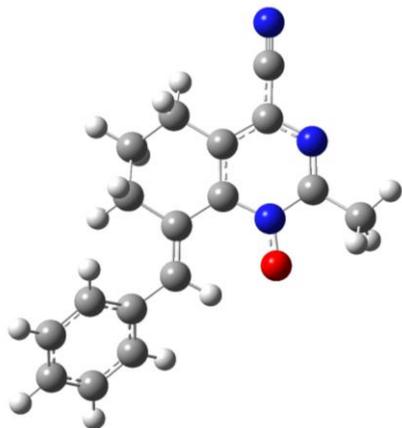
Compounds	IC50, μM			
	MCF-7	HCT-116	A549	WI38
2a	49.3 \pm 7	26.6 \pm 7	60.1 \pm 25	26.5 \pm 4.5
3a [S1]	n/a	68.5 \pm 21	117.2 \pm 30	n/a
2c	160.1	75.8 \pm 55	118	63.9 \pm 22
2e	113.5	161	109	84.6 \pm 19
3e [S1]	n/a	102.5 \pm 23	150.8	n/a
2f	36.4 \pm 7.5	29 \pm 13	43.4 \pm 8.6	53.9 \pm 9.8
3f [S1]	n/a	16.6 \pm 3	35 \pm 3.1	n/a
2j	127.4	109.1	72.3 \pm 16.2	46.22 \pm 8
2k	109.4	80.6 \pm 45	54.9 \pm 18	49.1 \pm 6

Computation details

Computations were carried out using ORCA 4.0.1. [S2]. Structure optimizations were performed using the pure DFT functional B3LYP [S3] in conjunction with Grimme's dispersion correction D3(BJ) [S4,S5] and the def2-TZVP basis set [S6] (notation B3LYP-D3/def2-TZVP). RIJCOSX [S7] approximation was used to speed up the calculations. Convergence criteria were set tight for both optimizations (TIGHTOPT) and SCF calculations (TIGHTSCF). Thermodynamic properties were calculated for ideal gas at 298.15 K using QRRHO approach [S8] for vibrational entropy correction. The nature of optimized intermediates and transition states was verified by frequency analysis.

References

- [S1] K. N. Sedenkova, A. V. Terekhin, I. V. Abdrashitova, D. A. Vasilenko, K. S. Sadovnikov, Yu. A. Gracheva, Yu. K. Grishin, T. Holt, A. G. Kutateladze, T. S. Kuznetsova, E. R. Milaeva and E. B. Averina. *Tetrahedron Lett.*, 2020, **61**, 151605.
- [S2] F. Neese, *WIREs Comput. Mol. Sci.*, 2018, **8**, e1327.
- [S3] A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
- [S4] S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, **132**, 154104.
- [S5] Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456.
- [S6] F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297.
- [S7] F. Neese, F. Wennmohs, A. Hansen and U. Becker, *Chem. Phys.*, 2009, **356**, 98.
- [S8] S. Grimme, *Chem. Eur. J.*, 2012, **18**, 9955.

Table S4. Cartesian coordinates of optimized structure of **2a**.

Number of imaginary frequency: 0

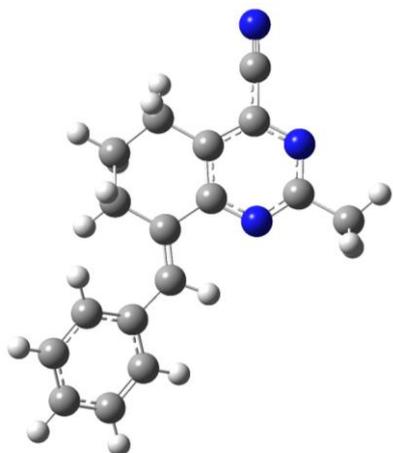
Electronic energy = -896.12271096 (Hartree)

Total thermal correction = 0.01737785 (Hartree)

Non-thermal (ZPE) correction = 0.28606323 (Hartree)

Final Gibbs free enthalpy = -895.87917116 (Hartree)

Center Number	Atom	Coordinates (Angstroms)		
		X	Y	Z
1	C	0.46014	-2.44073	0.70581
2	C	1.83280	-2.09162	0.16104
3	C	2.04055	-0.60493	0.06002
4	C	0.95270	0.29223	0.01985
5	C	-0.61000	-1.68331	-0.06459
6	H	0.28813	-3.51517	0.62079
7	H	2.62555	-2.52436	0.77173
8	C	3.32946	-0.09193	-0.00943
9	H	-0.58288	-2.00905	-1.11124
10	C	2.59427	2.04802	-0.19644
11	H	1.95314	-2.52561	-0.83796
12	H	0.40105	-2.18244	1.76724
13	H	-1.59448	-1.94441	0.31788
14	N	3.59535	1.21517	-0.15490
15	C	-0.43548	-0.17957	0.01830
16	C	-1.51165	0.64195	0.10815
17	H	-1.32286	1.68750	0.27725
18	C	-2.92863	0.28146	0.03502
19	C	-3.83013	1.01480	0.82261
20	C	-3.45018	-0.69280	-0.82825
21	C	-5.19112	0.75125	0.78554
22	H	-3.44660	1.79184	1.47233
23	C	-4.81469	-0.94174	-0.88078
24	H	-2.78933	-1.23238	-1.49054
25	C	-5.68868	-0.23084	-0.06601
26	H	-5.86701	1.31912	1.41199
27	H	-5.19782	-1.68751	-1.56535
28	H	-6.75144	-0.43354	-0.10466
29	C	4.46565	-0.96531	0.05610
30	N	5.36320	-1.68556	0.11317
31	C	2.80748	3.50630	-0.38361
32	H	2.20644	3.87319	-1.21658
33	H	2.47373	4.05994	0.49631
34	H	3.86461	3.68316	-0.56315
35	N	1.27058	1.64055	-0.06720
36	O	0.38849	2.55979	-0.05820

Table S5. Cartesian coordinates of optimized structure of **3a**.

Number of imaginary frequency: 0

Electronic energy = -820.95613094 (Hartree)

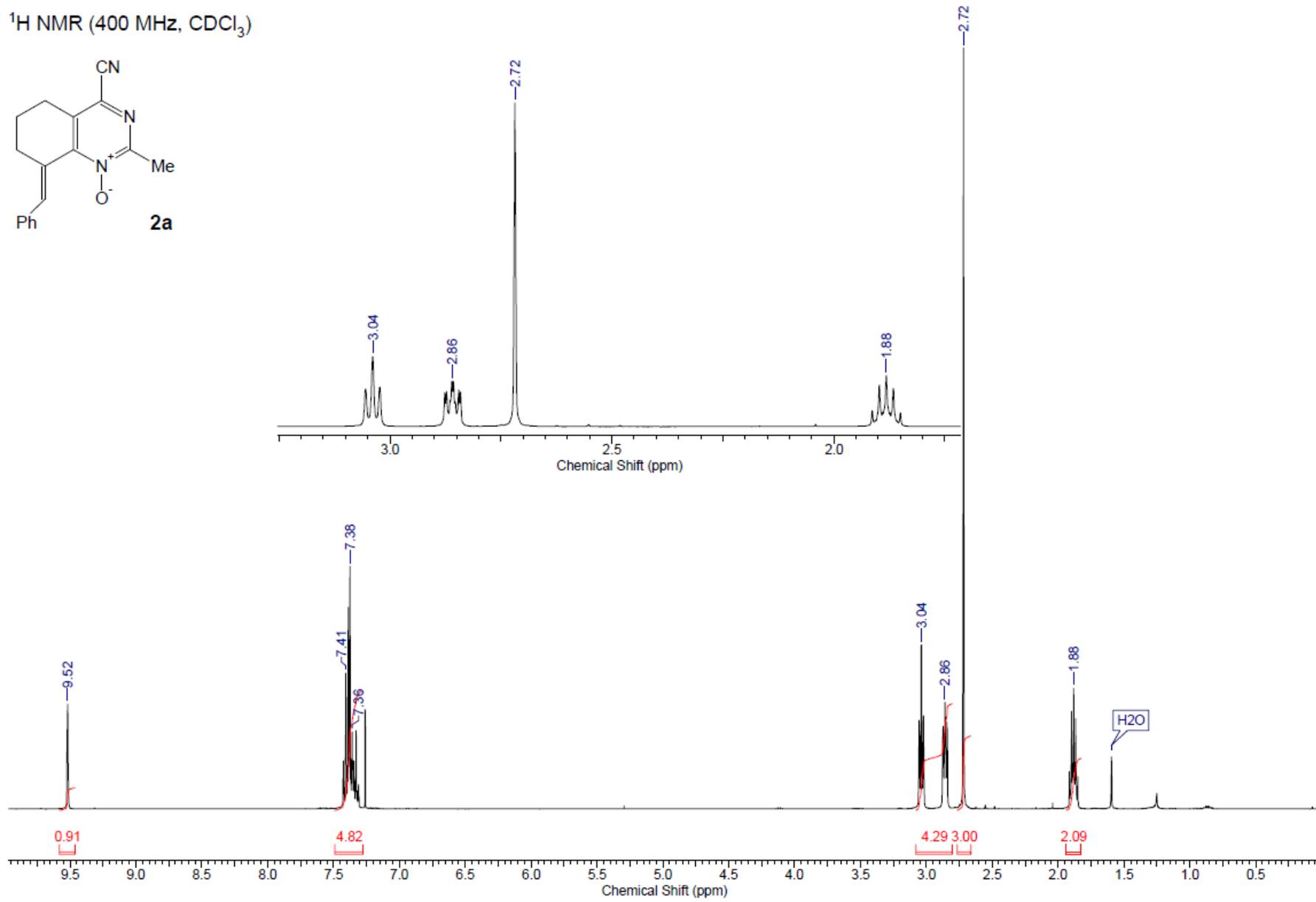
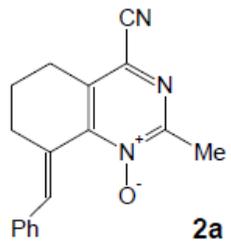
Total thermal correction = 0.01599686 (Hartree)

Non-thermal (ZPE) correction = 0.28136689 (Hartree)

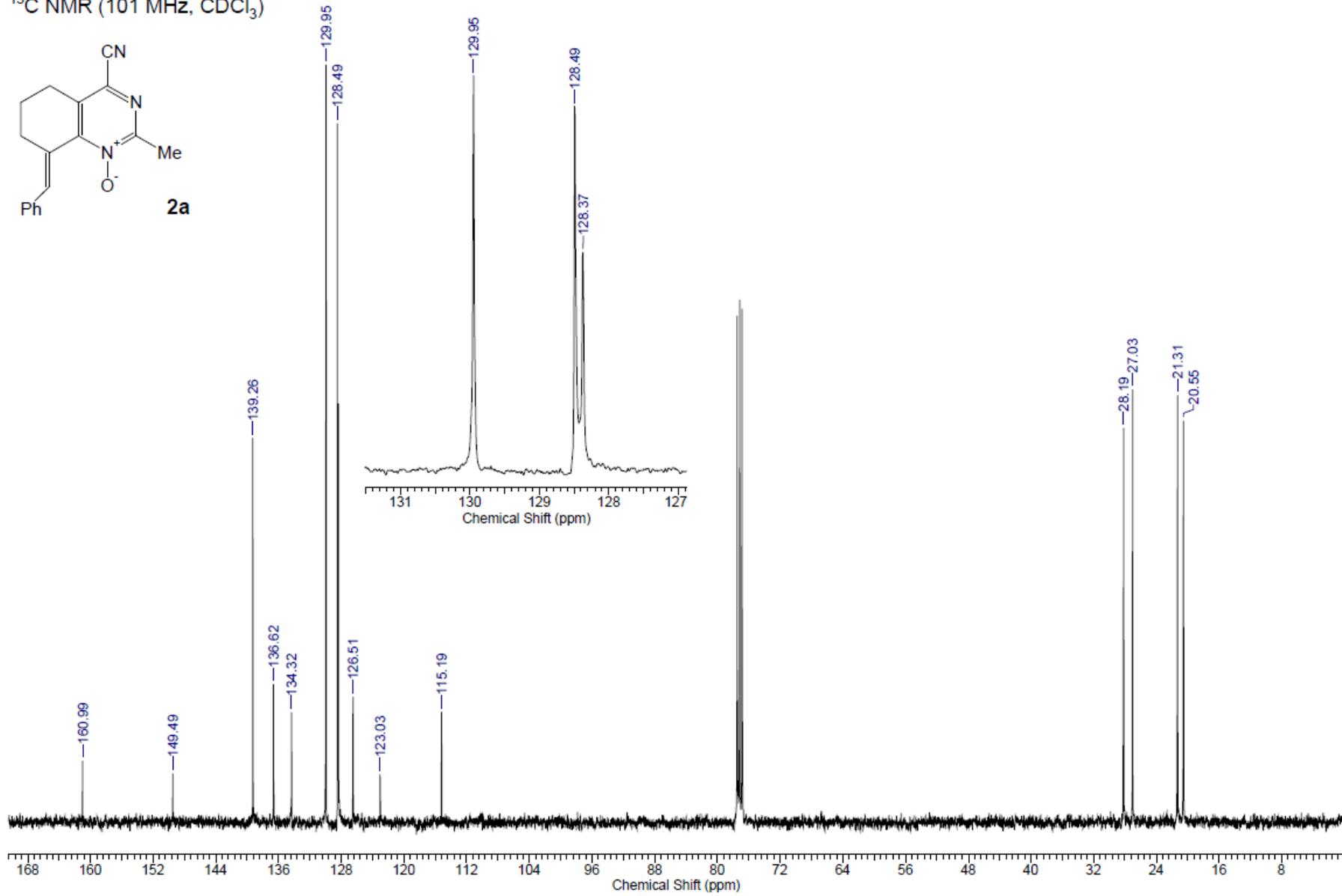
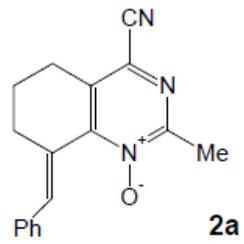
Final Gibbs free enthalpy = -820.71606628 (Hartree)

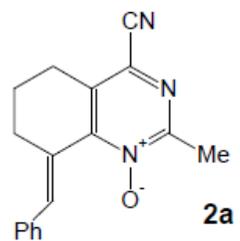
Center Number	Atom	Coordinates (Angstroms)		
		X	Y	Z
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2	C	1.95325	-2.16290	0.00726
3	C	2.09725	-0.66913	0.00524
4	C	0.97960	0.18911	-0.04310
5	C	-0.54631	-1.84881	-0.10221
6	H	0.47217	-3.66080	0.45848
7	H	2.77457	-2.61819	0.56219
8	C	3.33581	-0.03264	0.04878
9	H	-0.60252	-2.17861	-1.14723
10	C	2.38210	2.01511	-0.09388
11	H	2.04619	-2.52844	-1.02239
12	H	0.58648	-2.37292	1.65421
13	H	-1.48956	-2.13650	0.36142
14	N	3.50071	1.29215	-0.00145
15	N	1.14968	1.51577	-0.09527
16	C	-0.39742	-0.34830	-0.05242
17	C	-1.42504	0.52319	0.00924
18	H	-1.14130	1.56475	0.10959
19	C	-2.86543	0.28943	-0.00869
20	C	-3.68646	1.25679	0.59459
21	C	-3.49168	-0.80112	-0.63275
22	C	-5.06568	1.12443	0.61185
23	H	-3.22228	2.11784	1.05967
24	C	-4.87412	-0.92461	-0.62982
25	H	-2.90083	-1.53405	-1.15988
26	C	-5.66696	0.02782	0.00049
27	H	-5.67383	1.87960	1.09328
28	H	-5.33669	-1.76518	-1.13116
29	H	-6.74420	-0.07866	0.00388
30	C	4.54193	-0.81649	0.15524
31	N	5.49061	-1.46323	0.23933
32	C	2.52160	3.50136	-0.20978
33	H	1.93726	3.86338	-1.05620
34	H	2.12349	3.98608	0.68431
35	H	3.56558	3.77813	-0.33525

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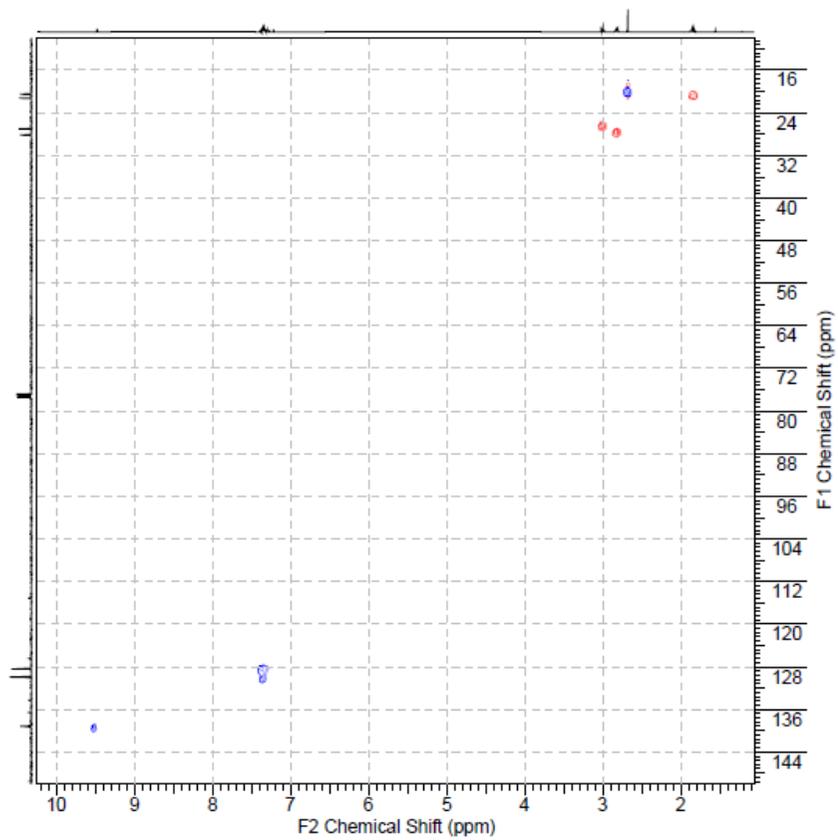


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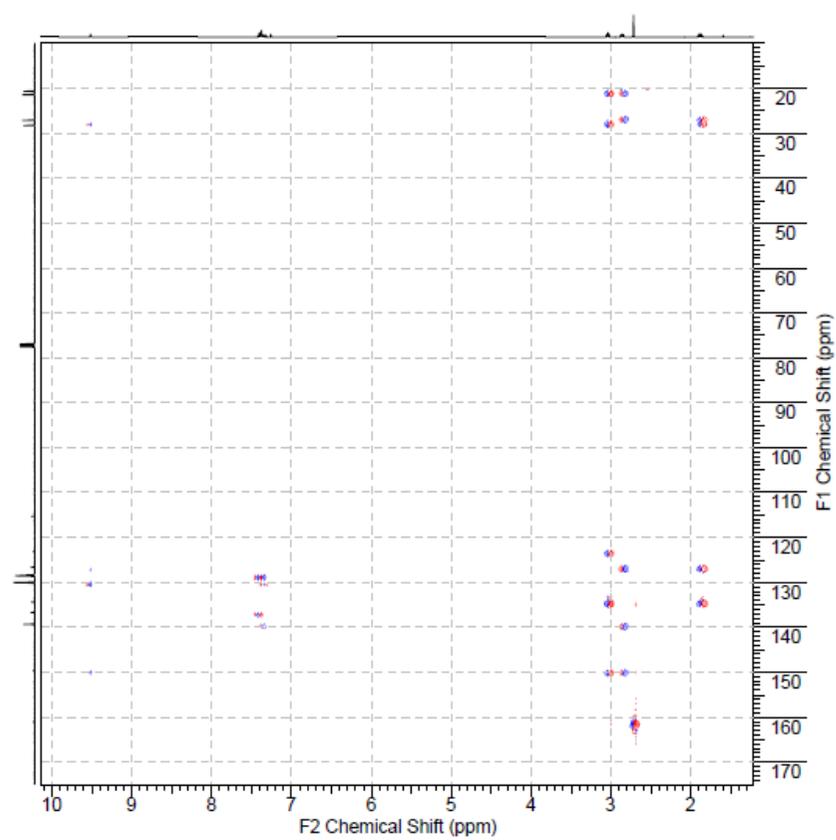




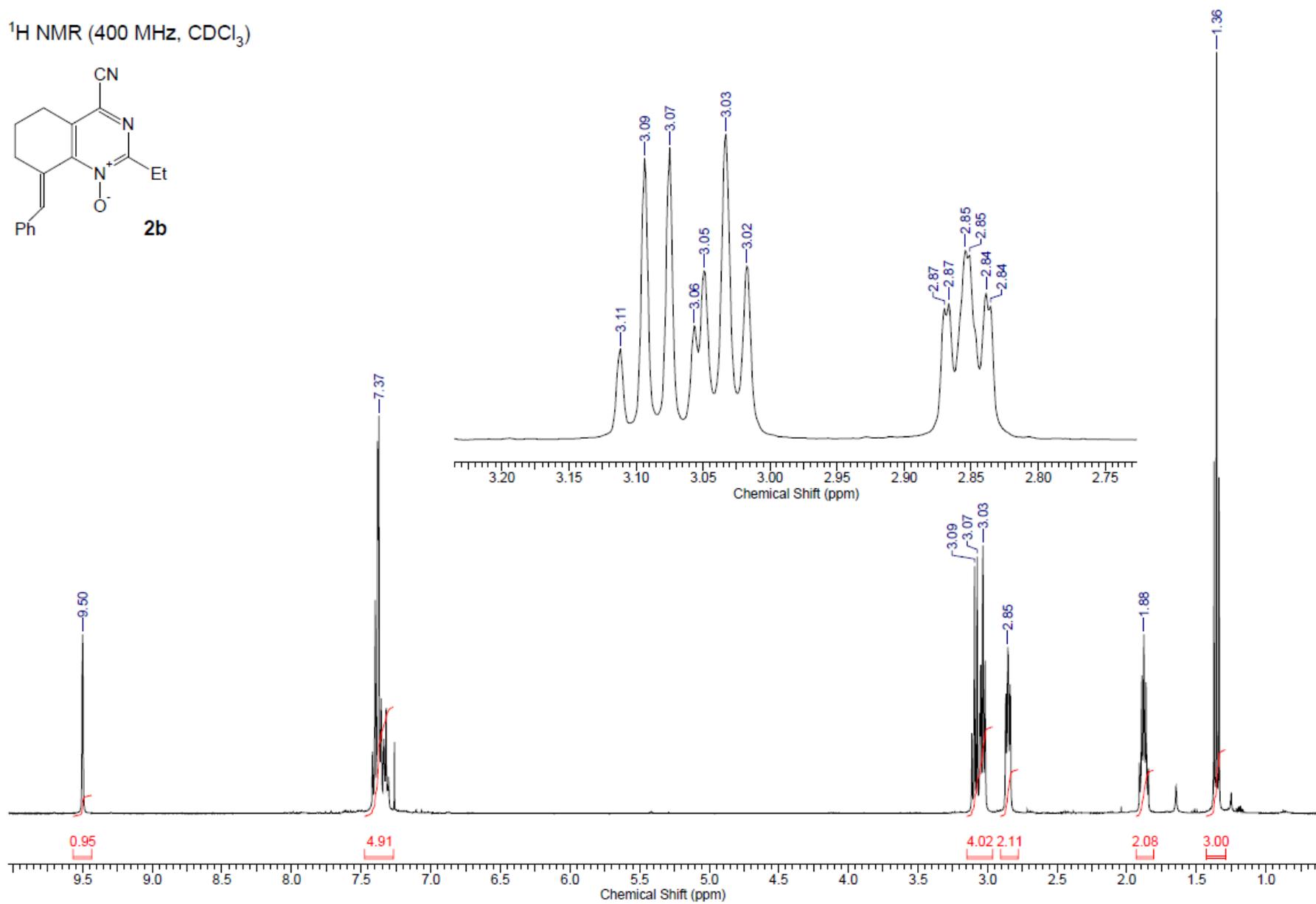
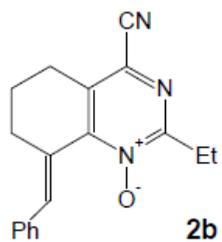
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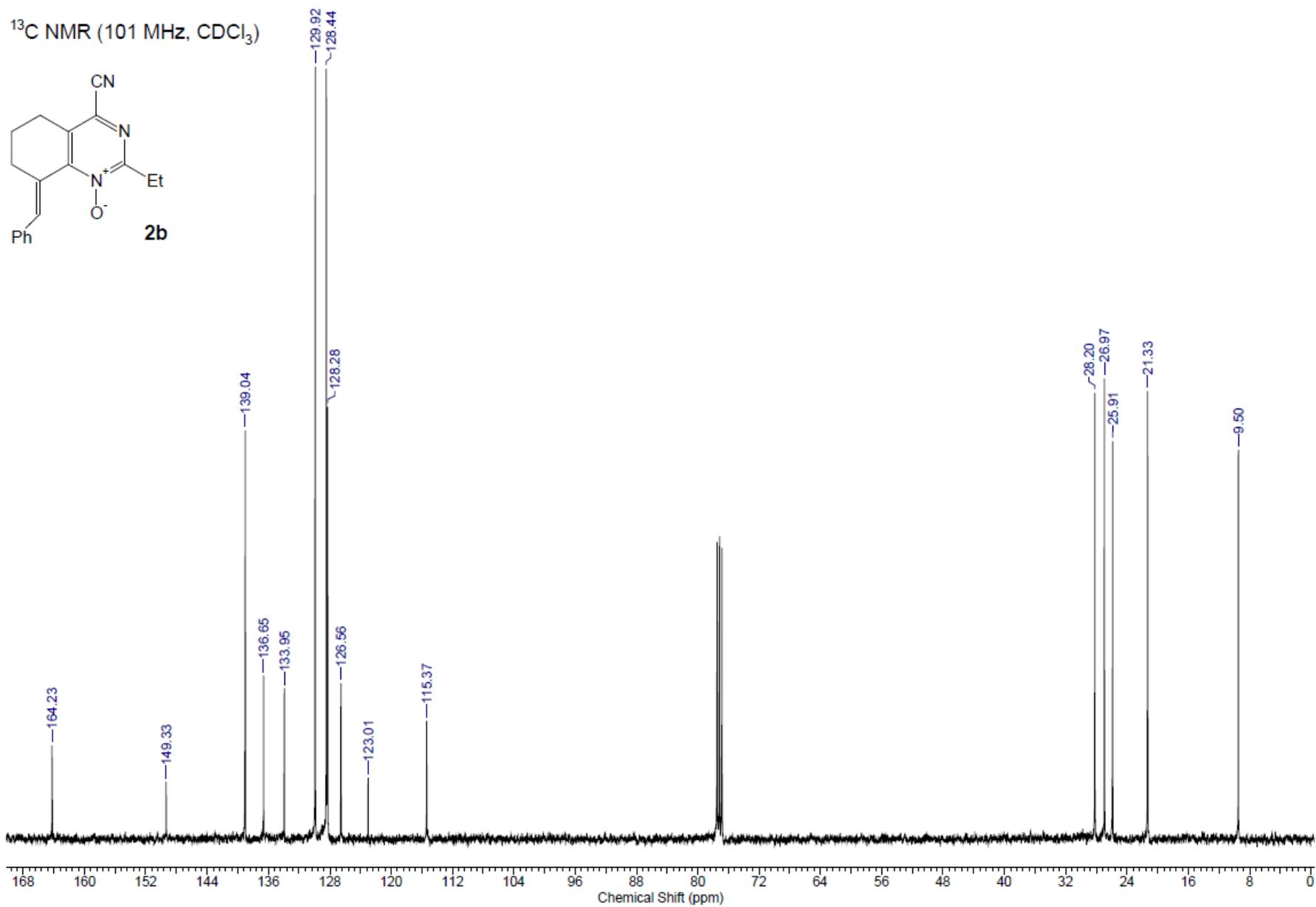
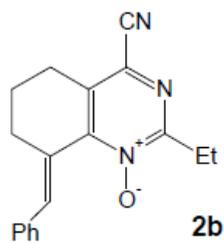
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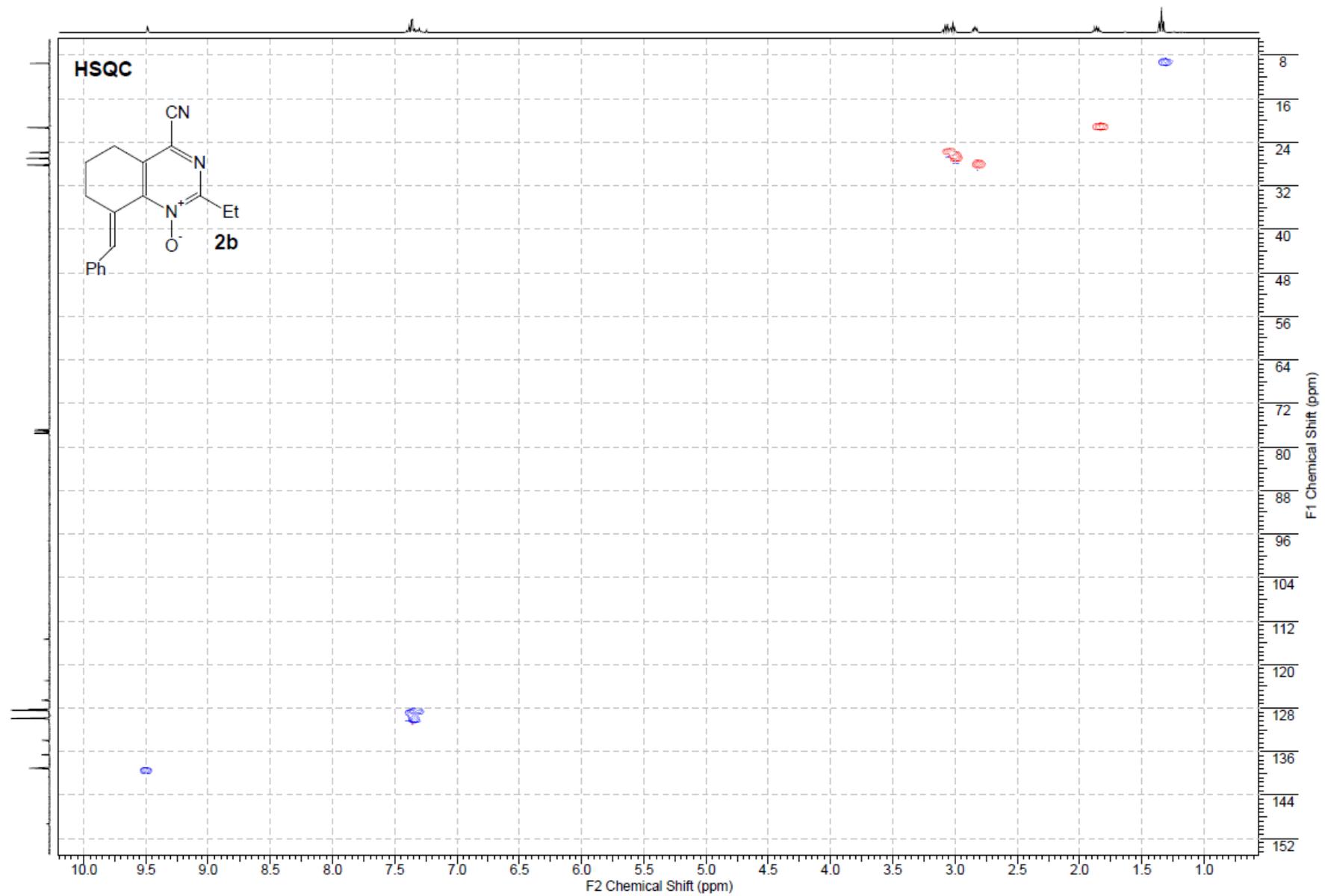


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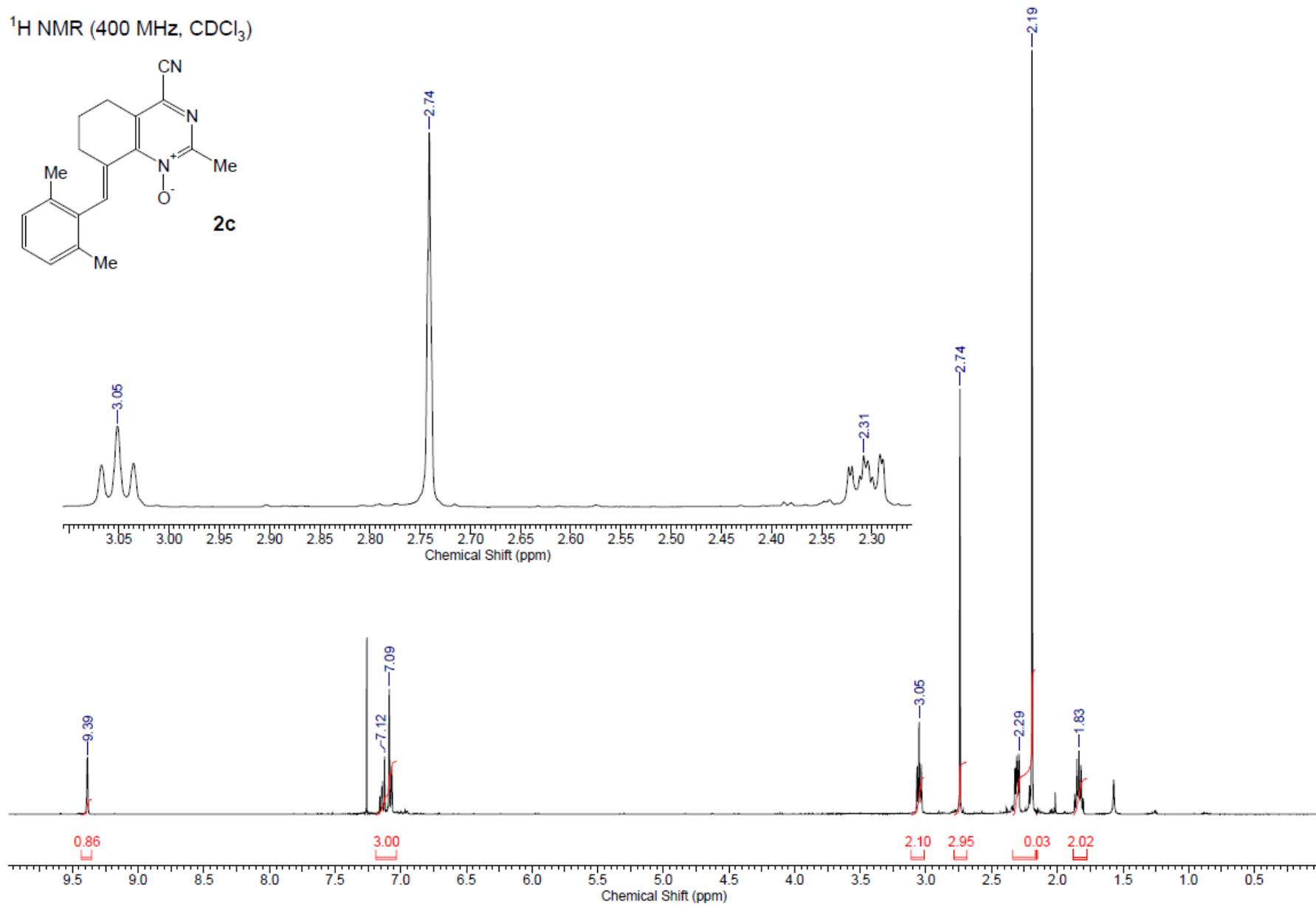
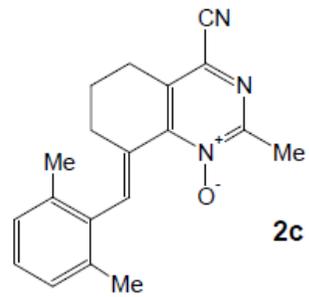


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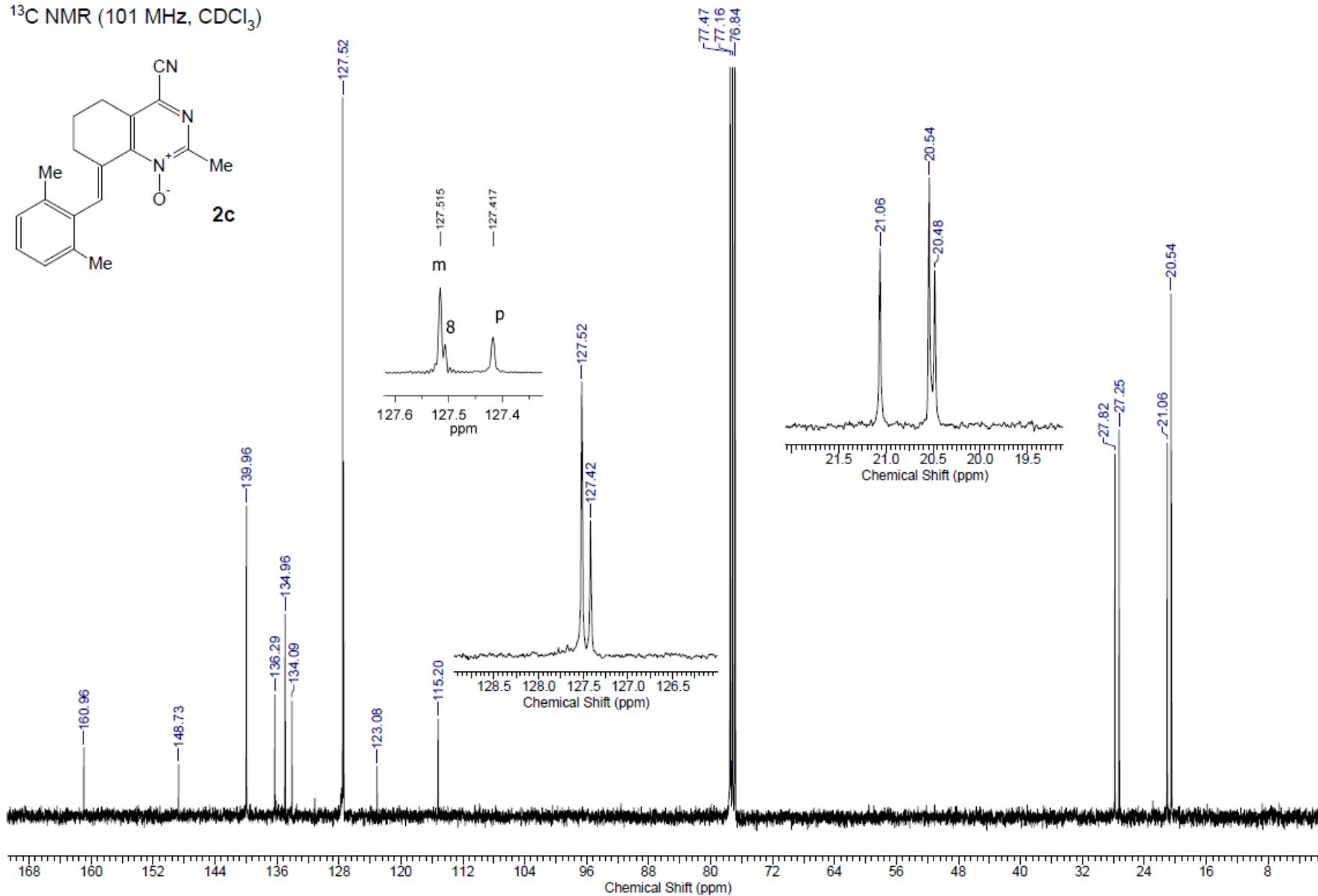
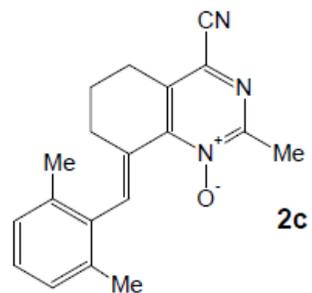


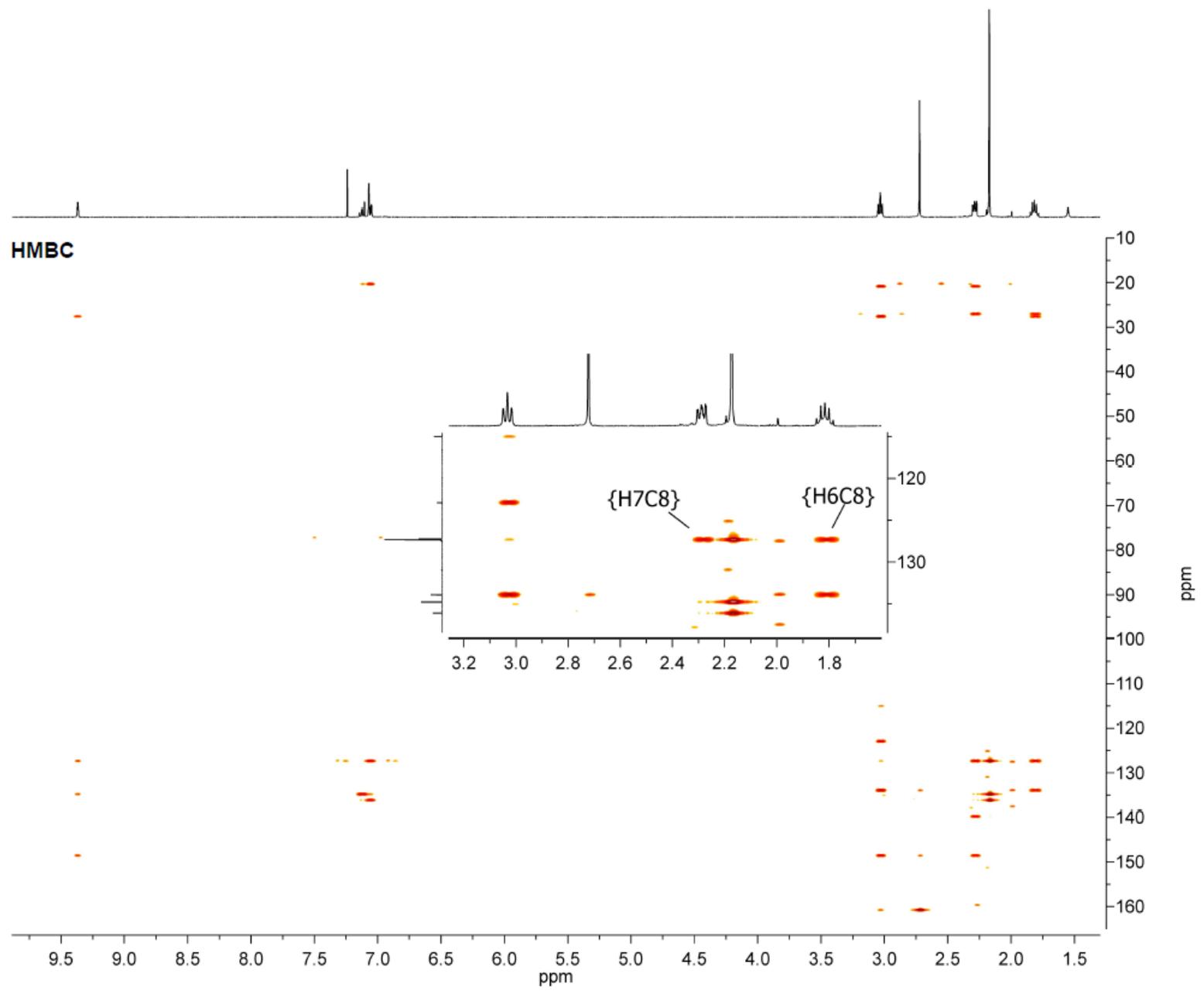
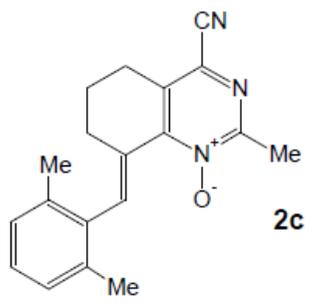


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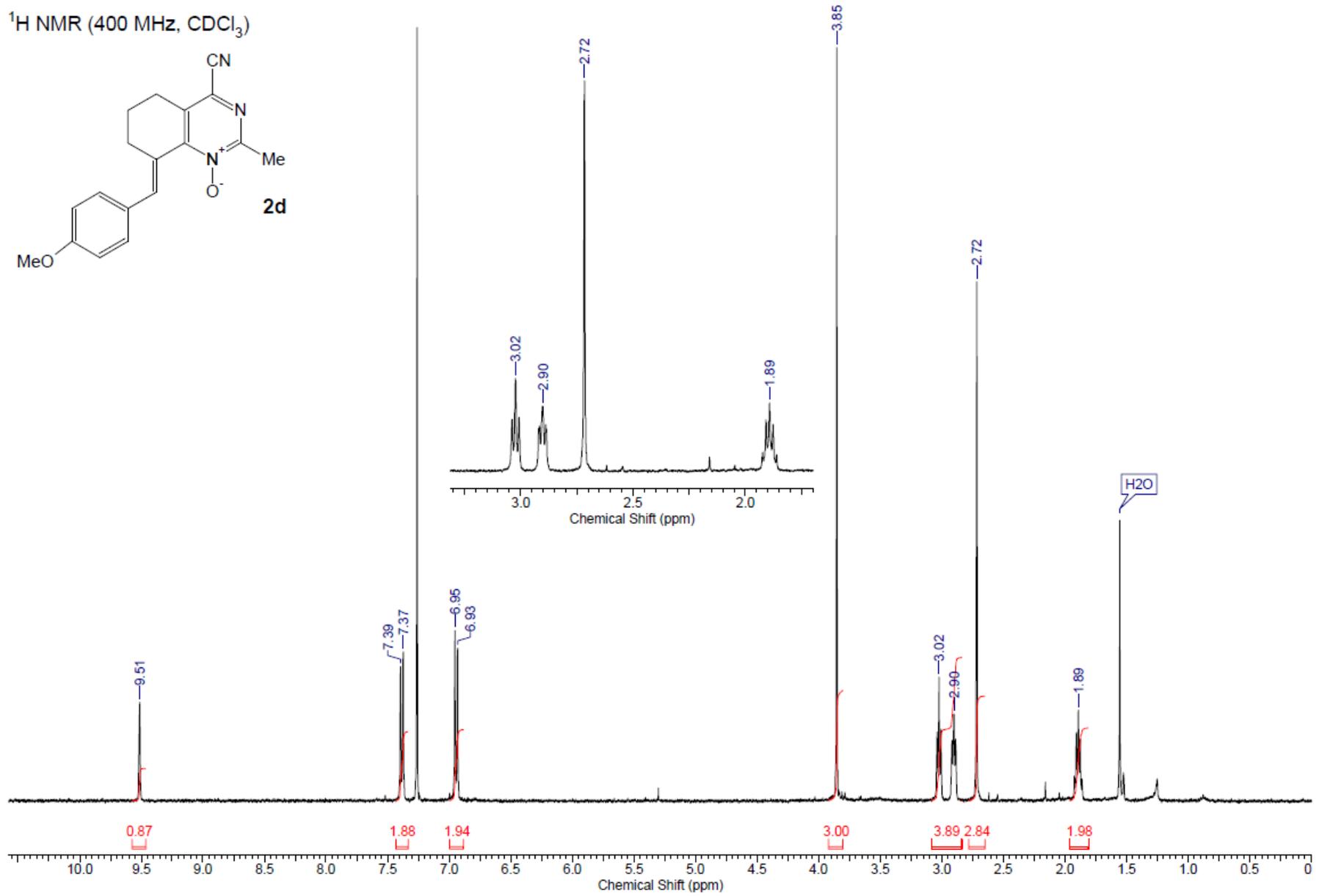
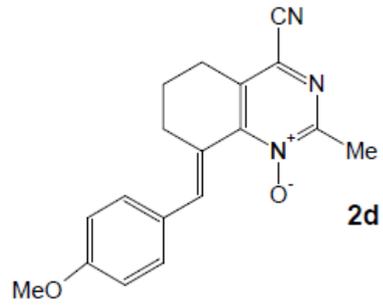


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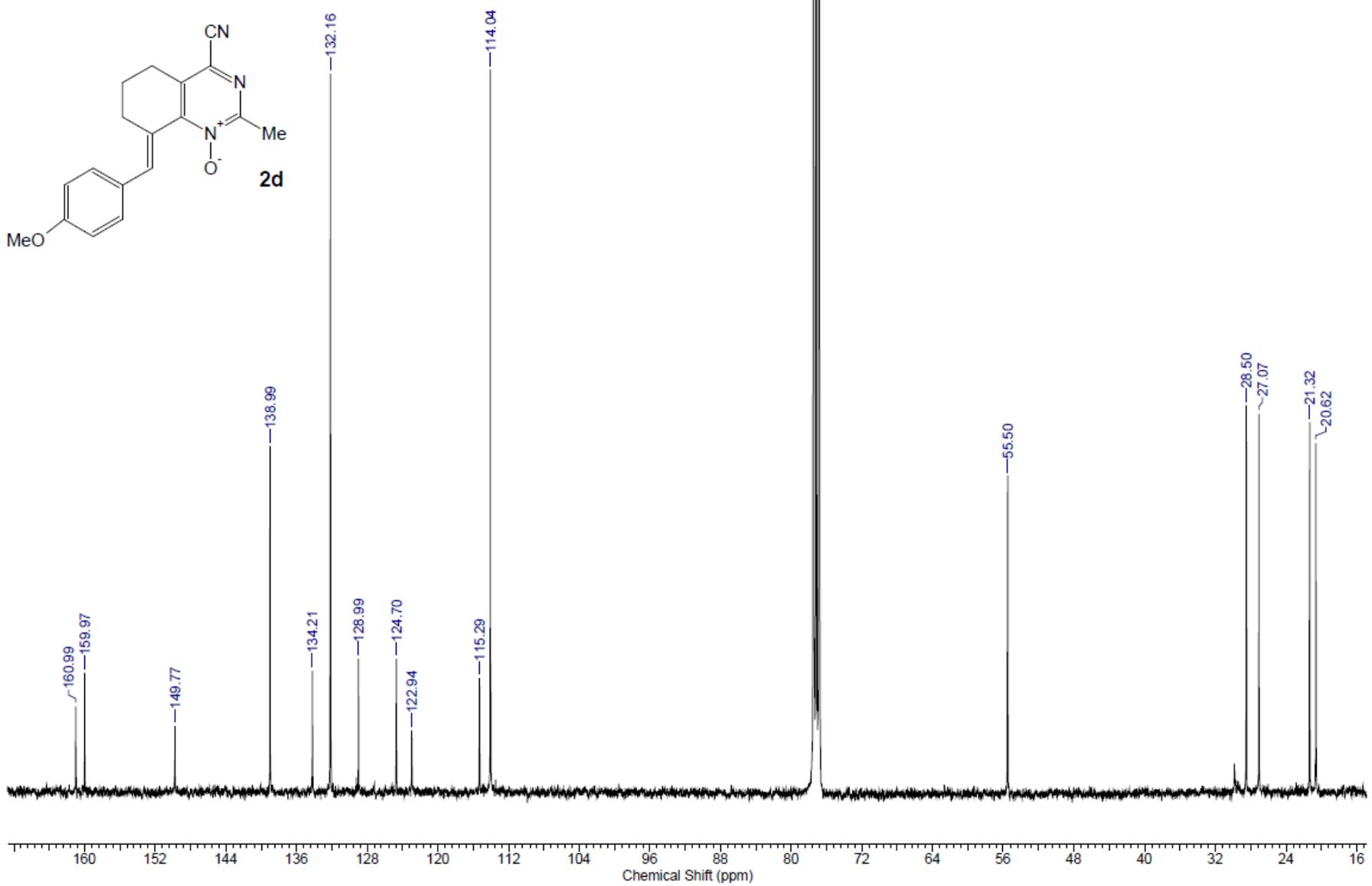
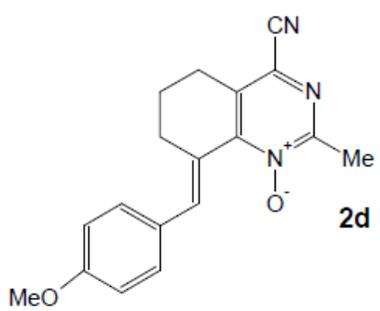


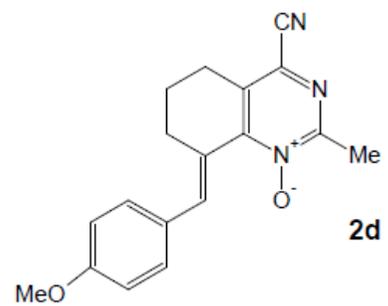


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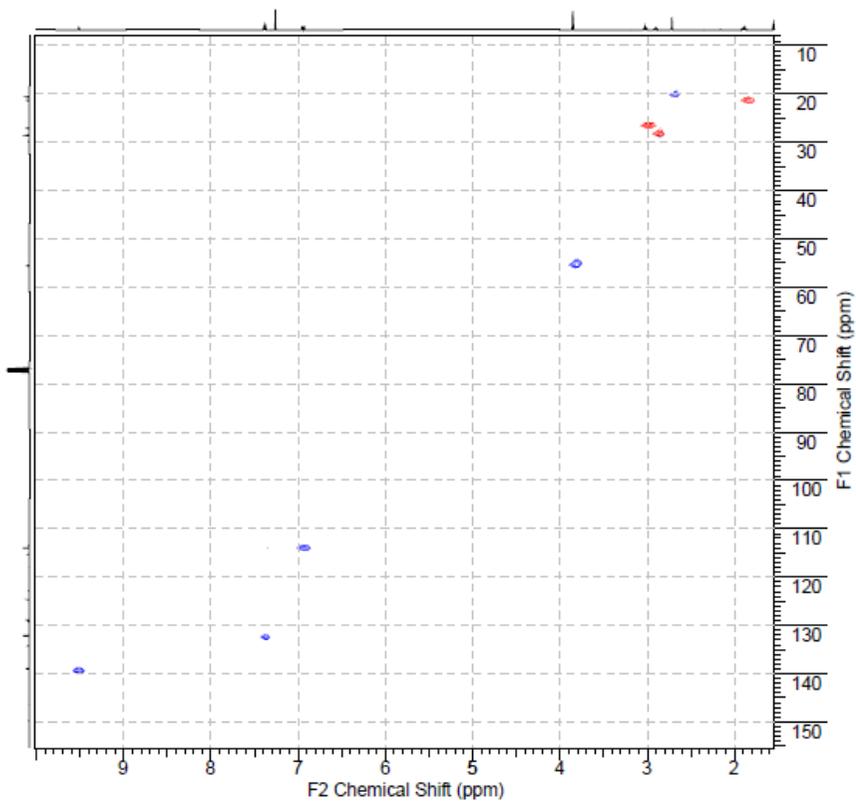


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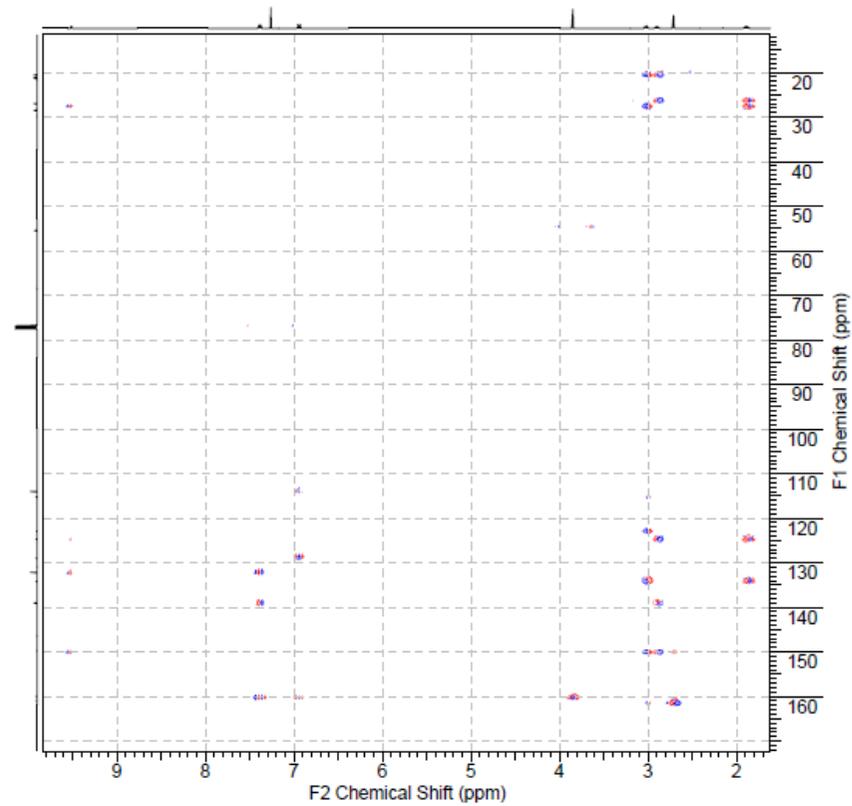




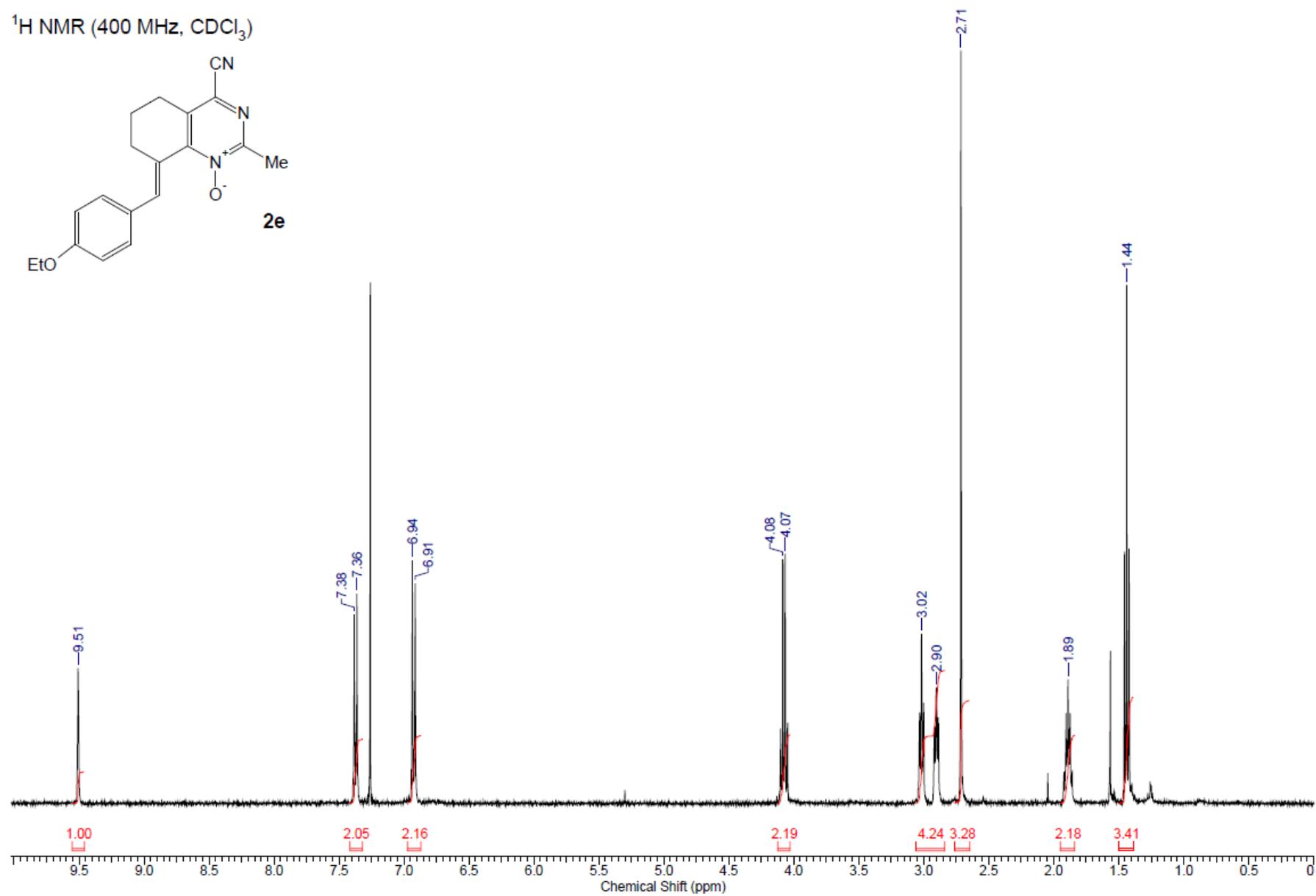
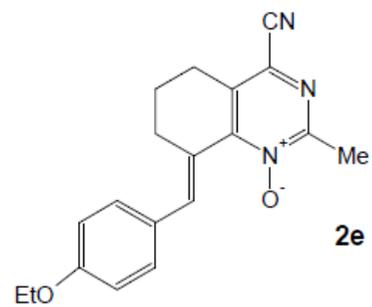
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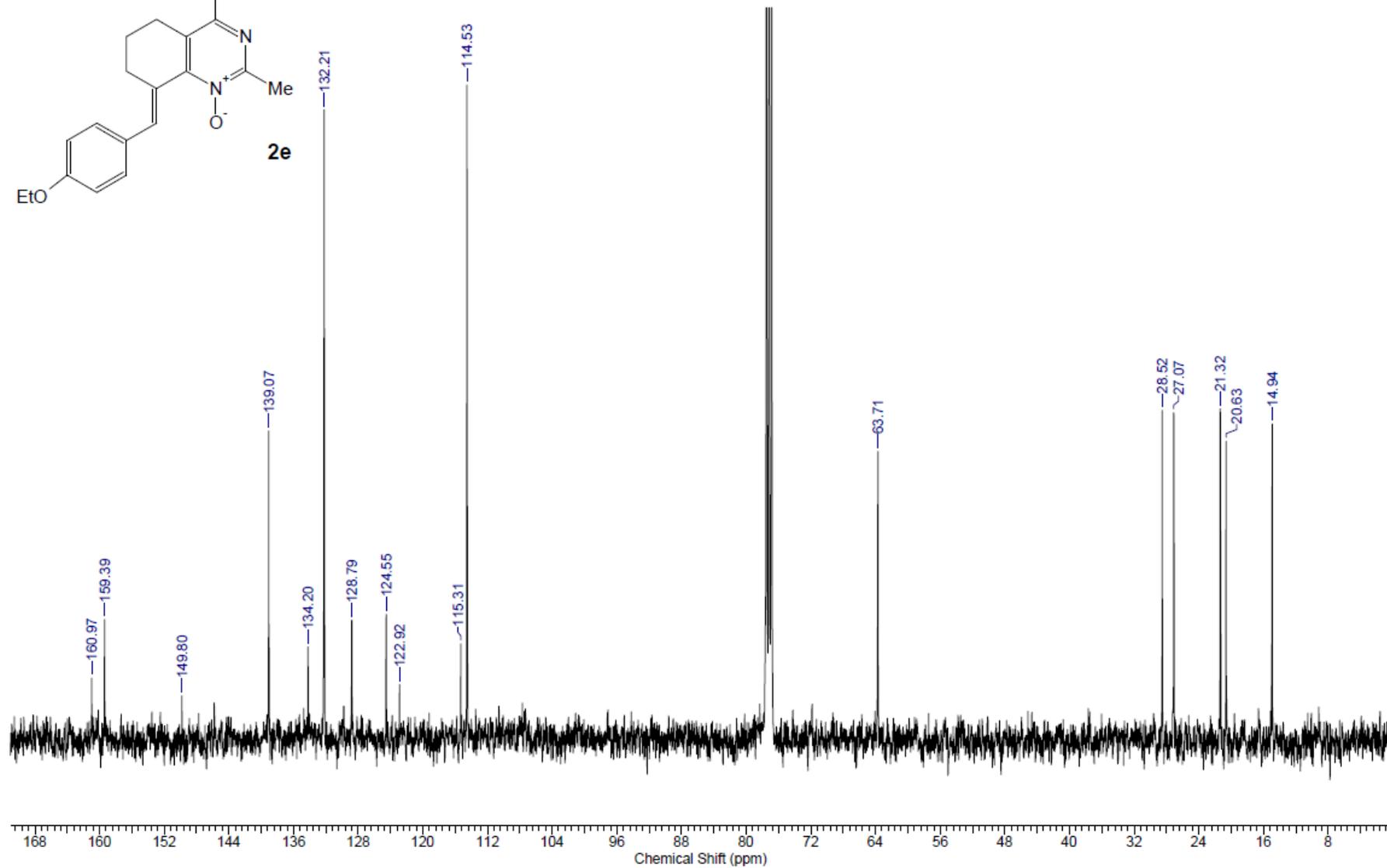
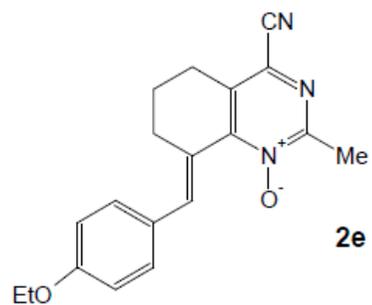
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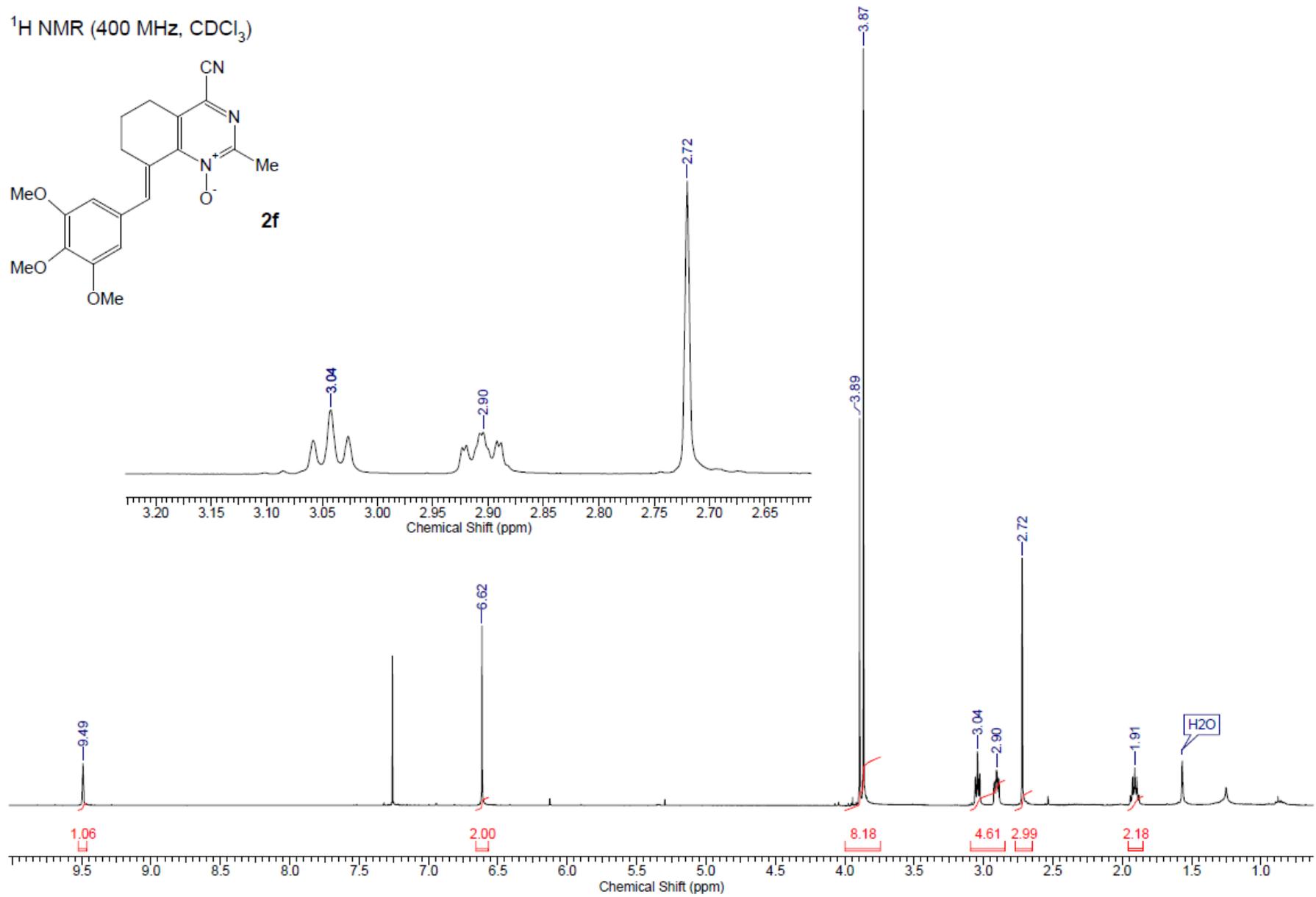
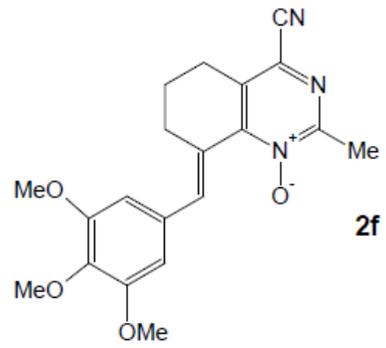
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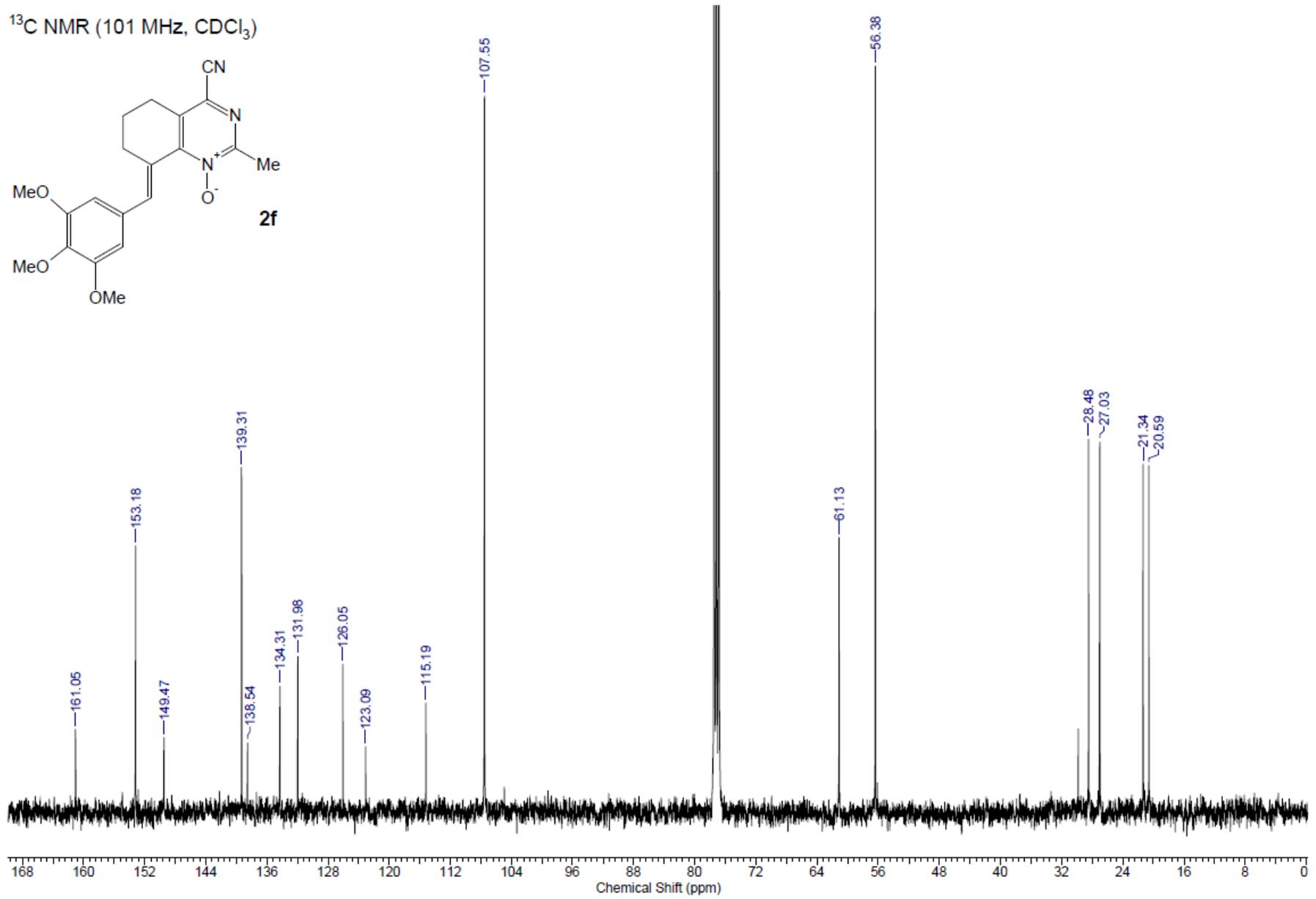
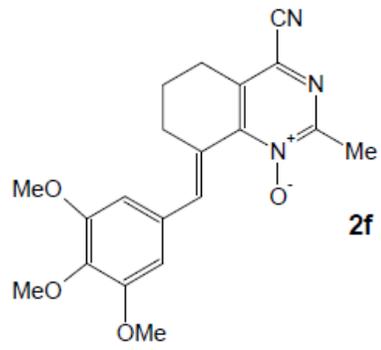
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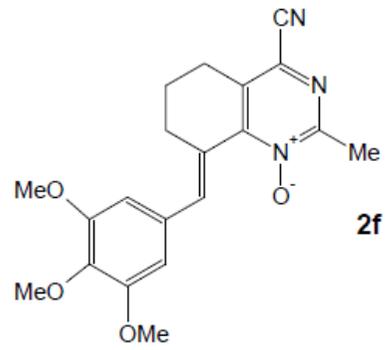


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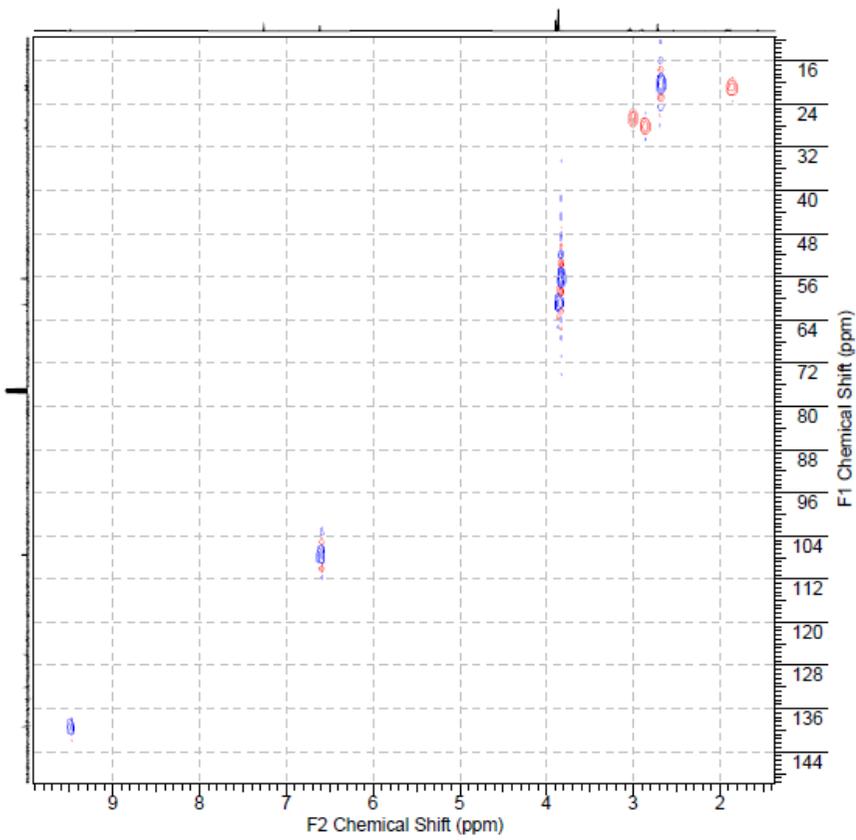


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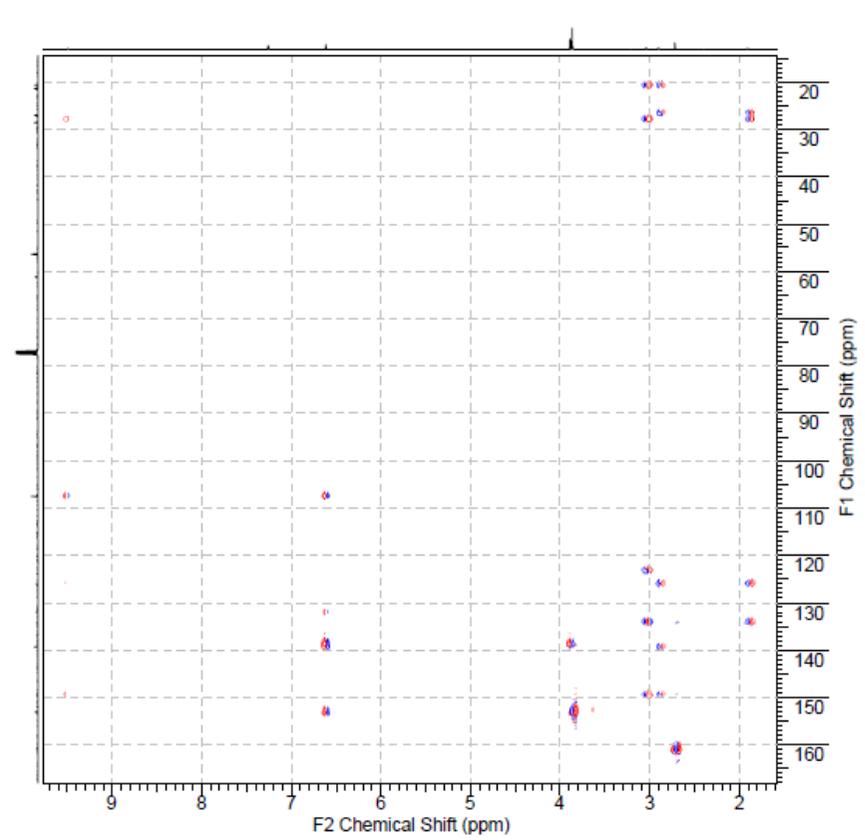




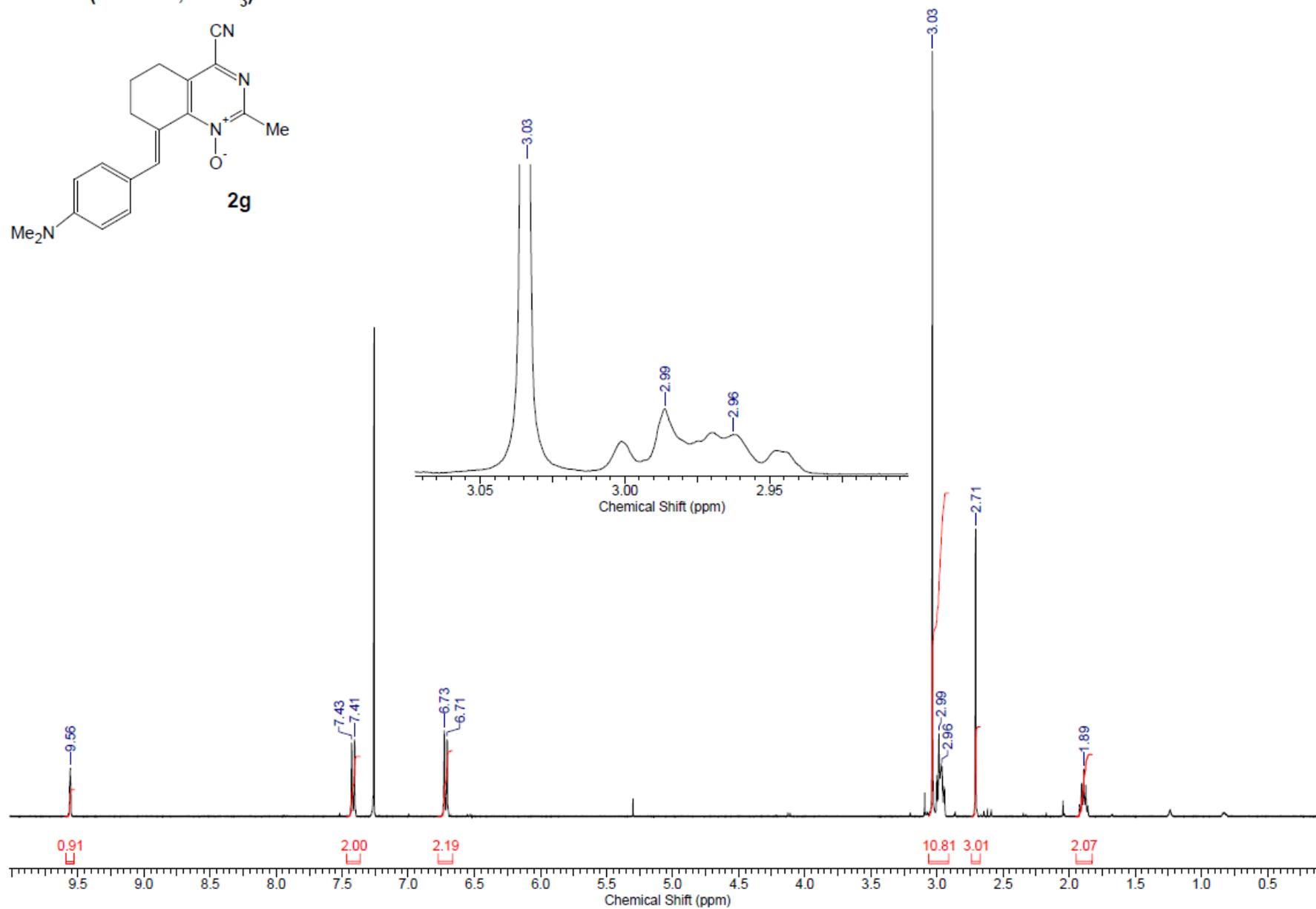
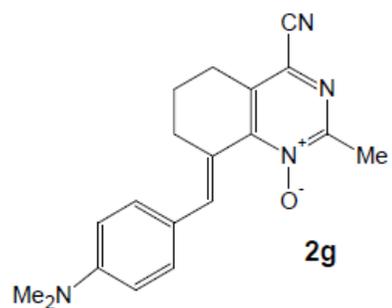
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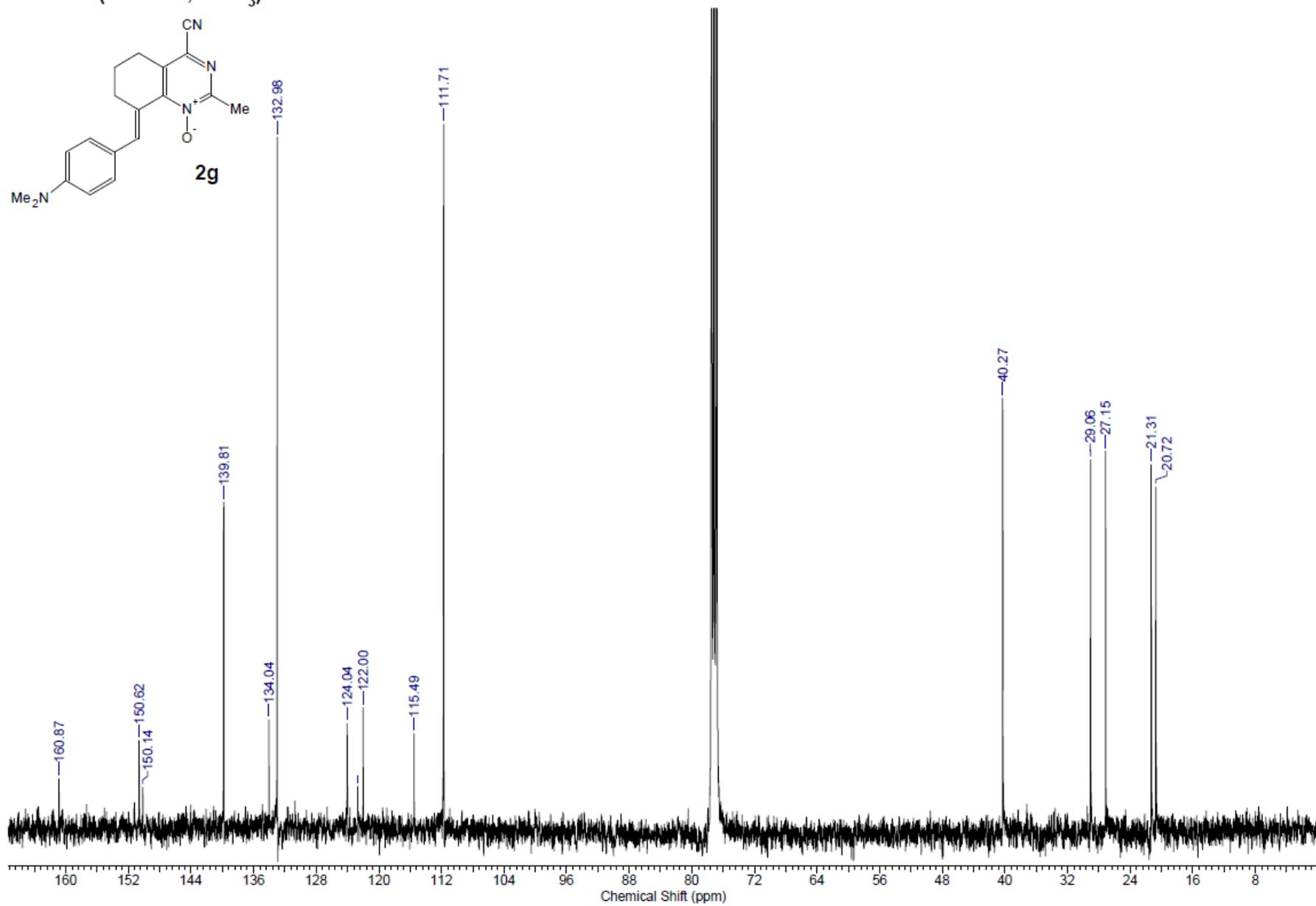
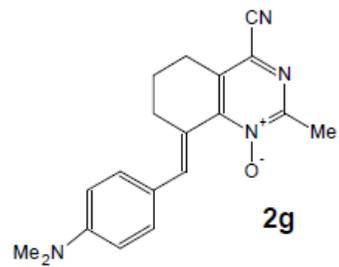
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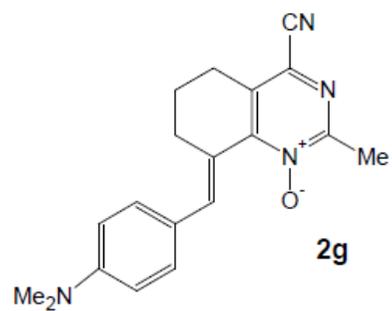


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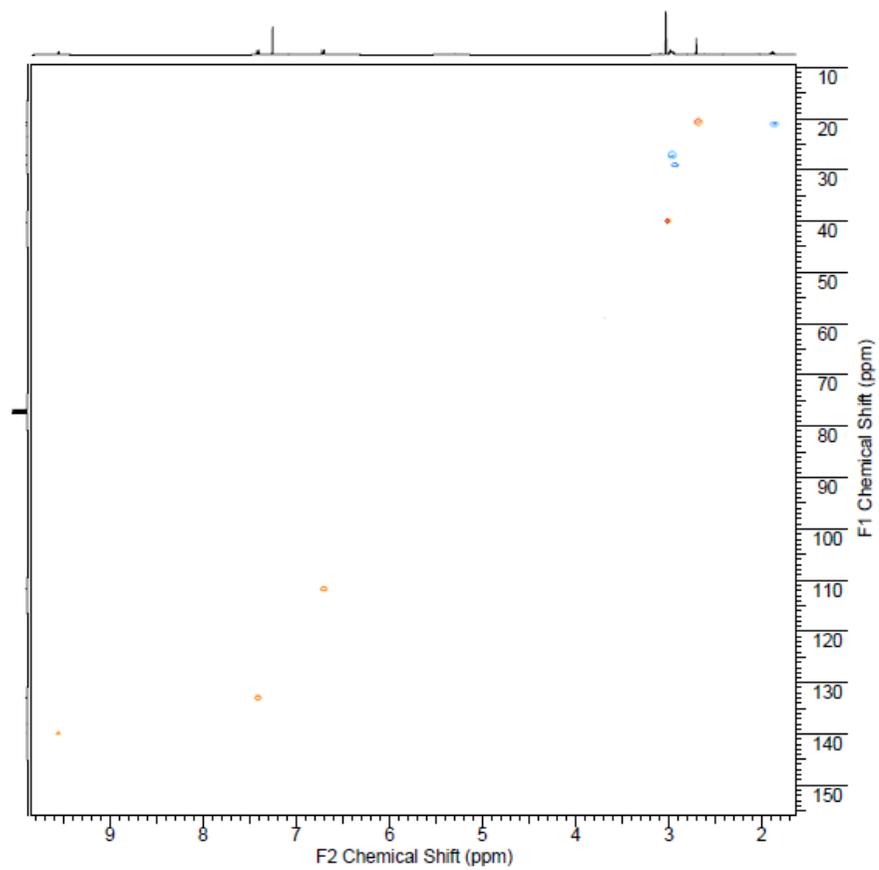


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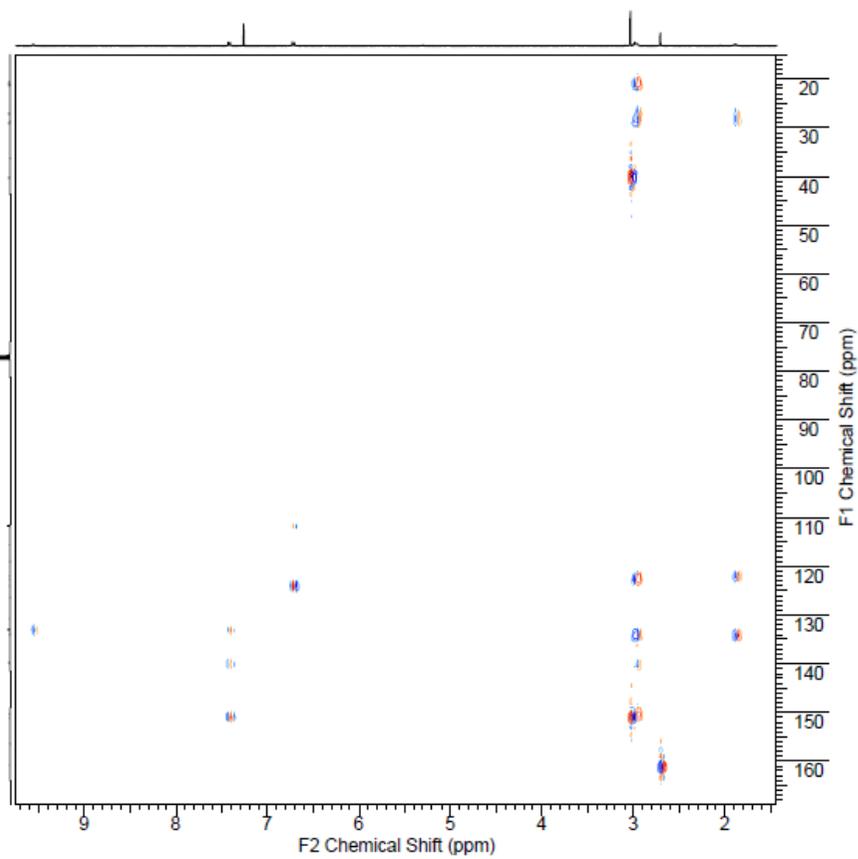




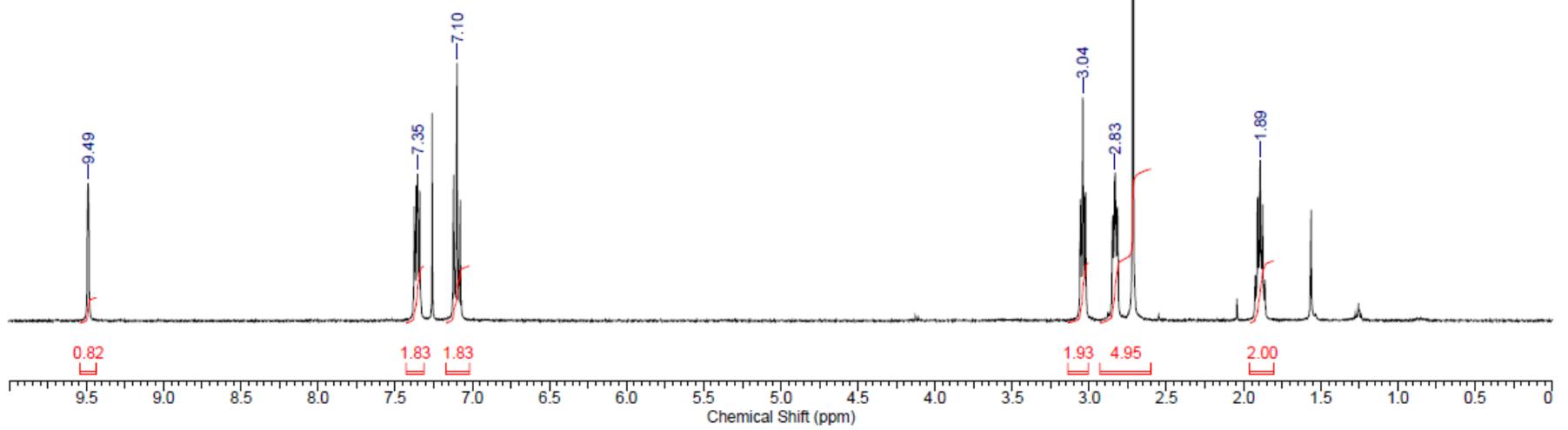
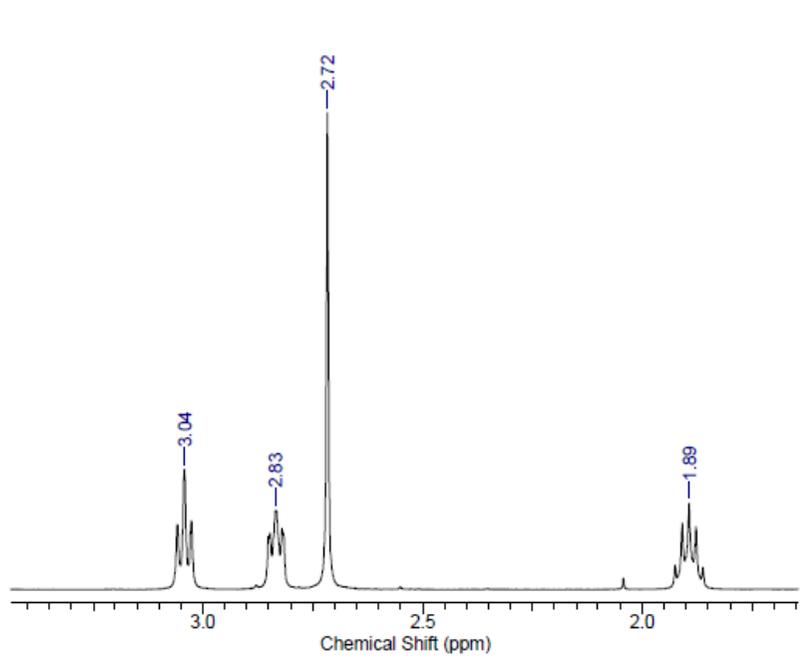
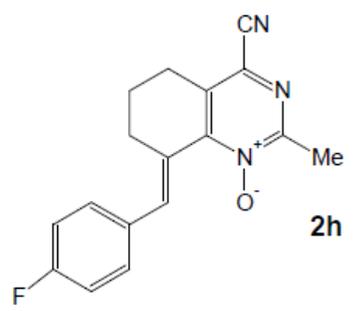
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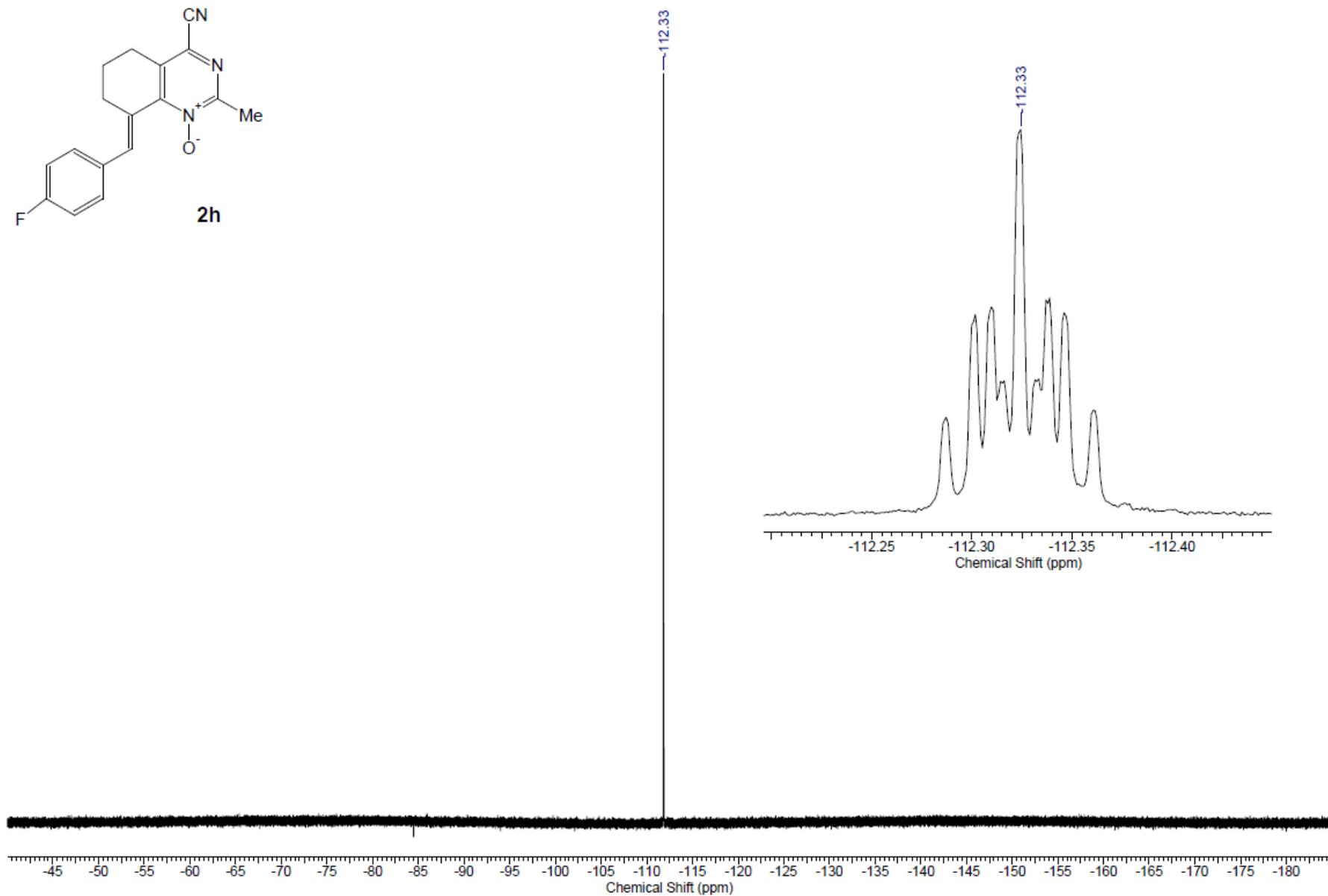
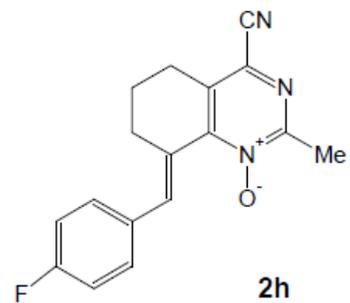
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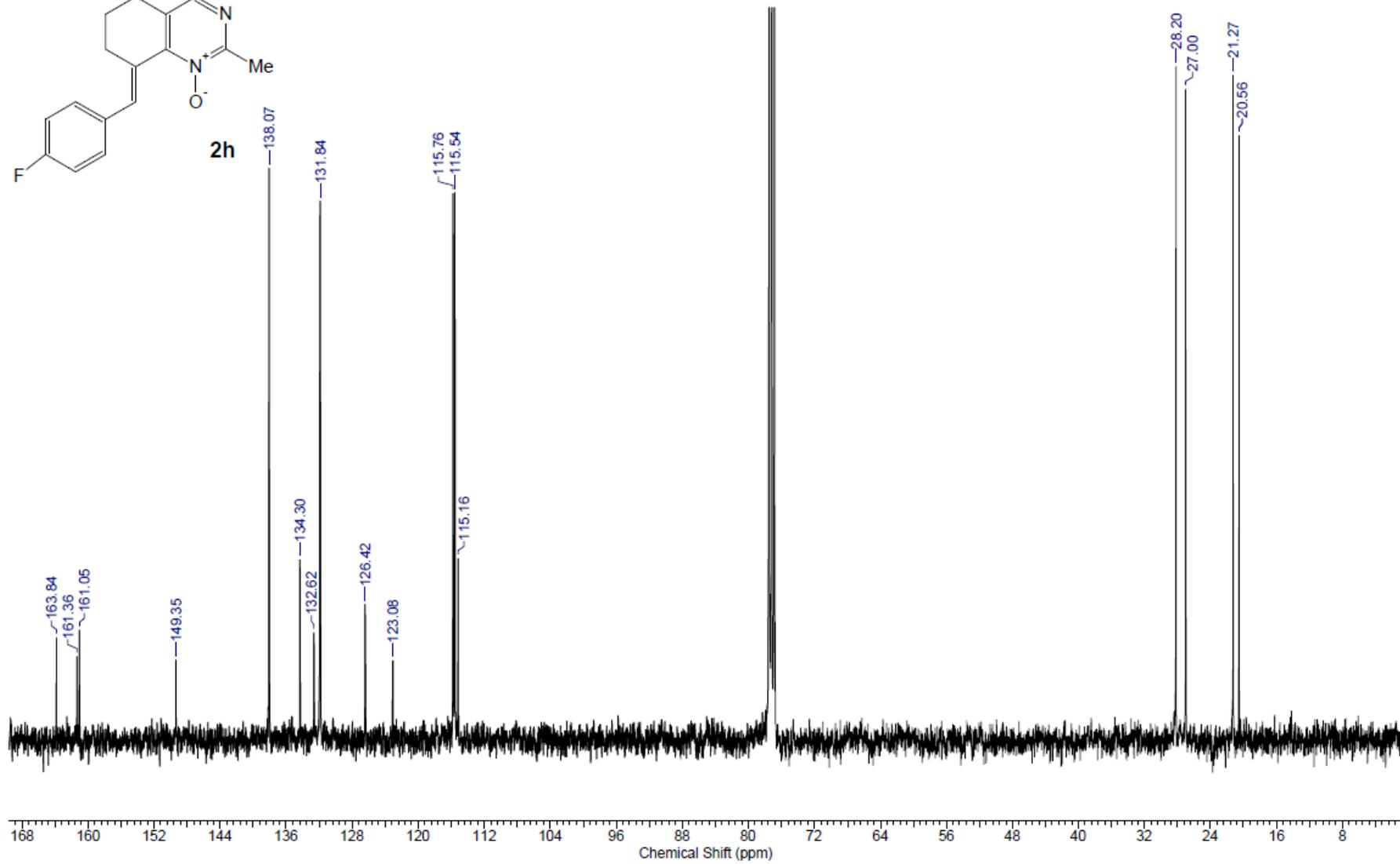
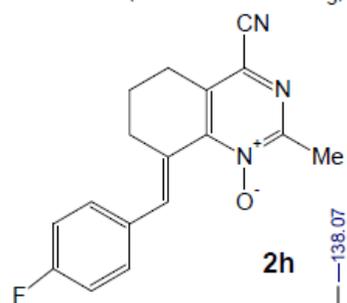
¹H NMR (400 MHz, CDCl₃)



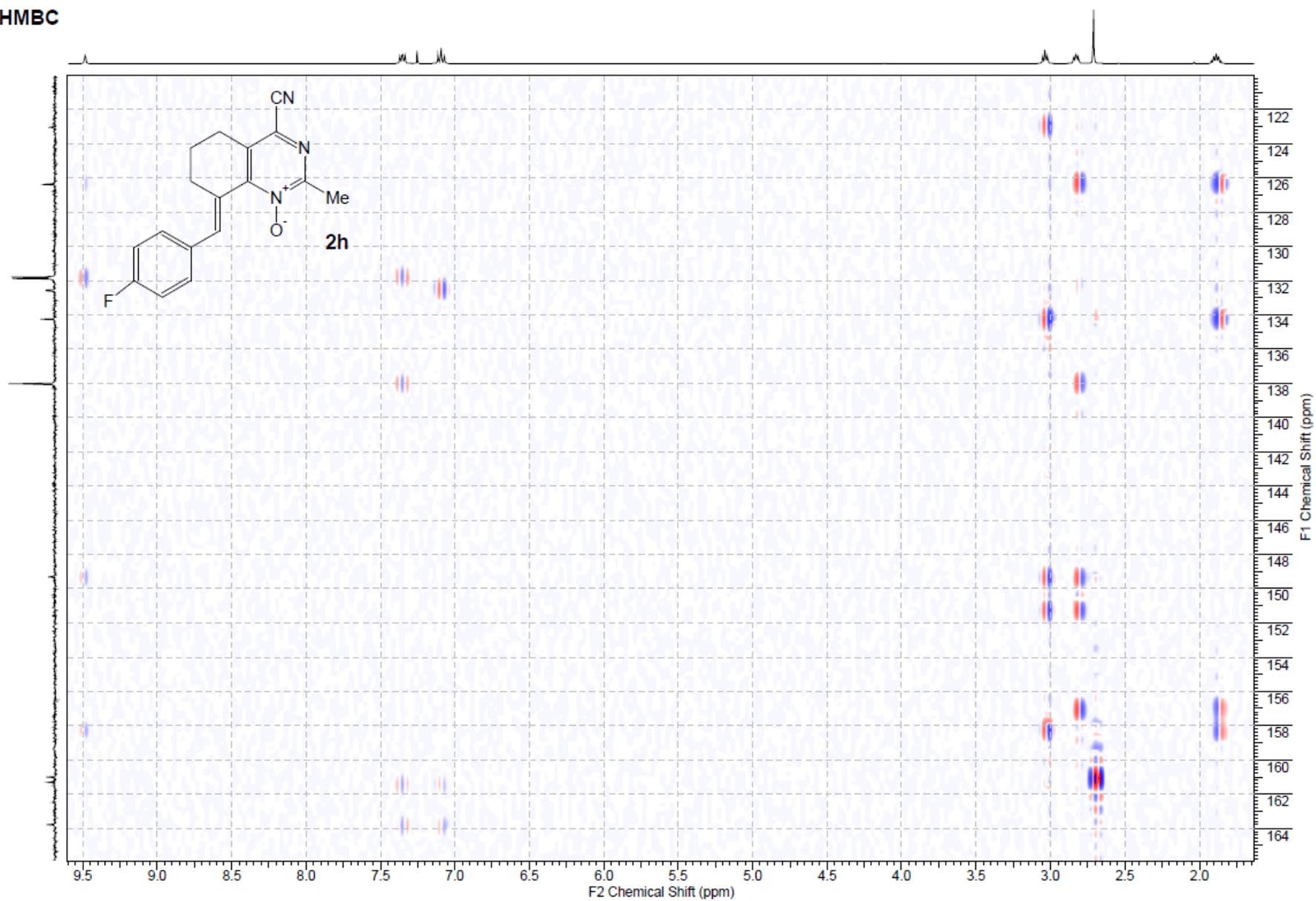
¹⁹F NMR (376 MHz, CDCl₃)



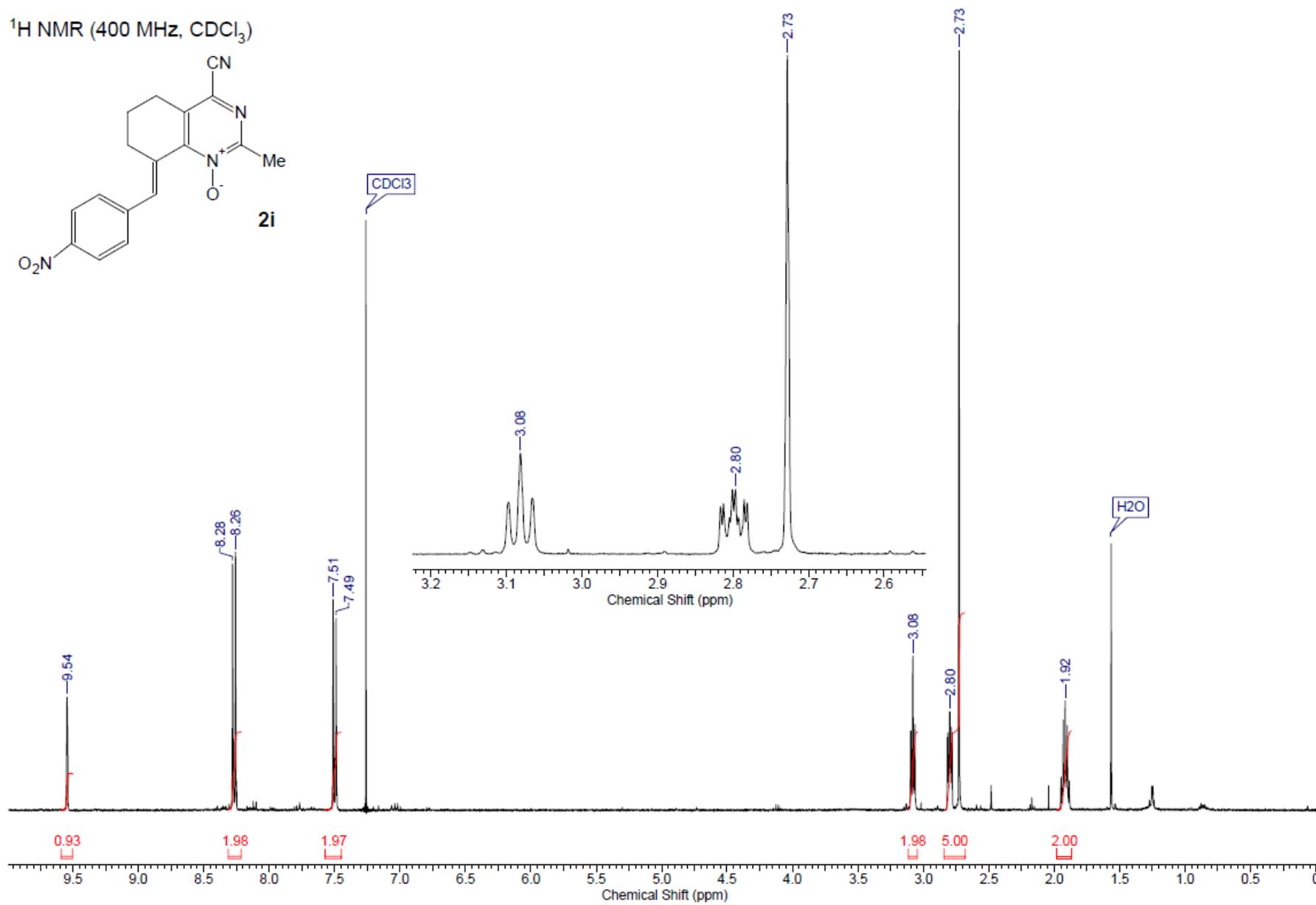
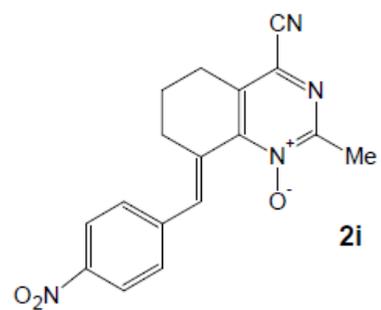
¹³C NMR (101 MHz, CDCl₃)



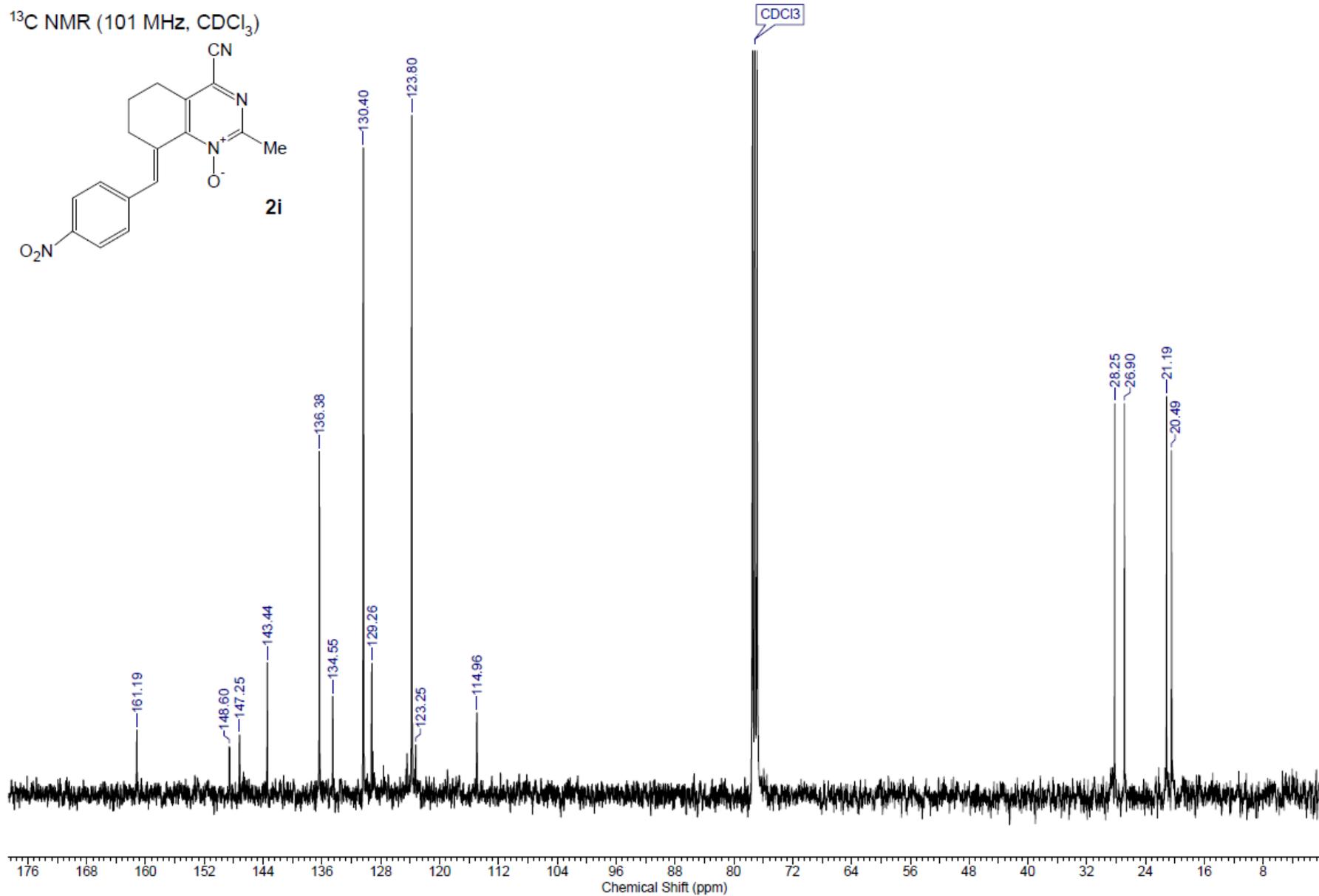
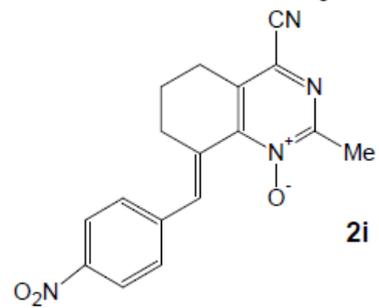
HMBC

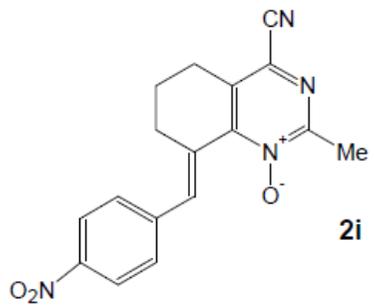


¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

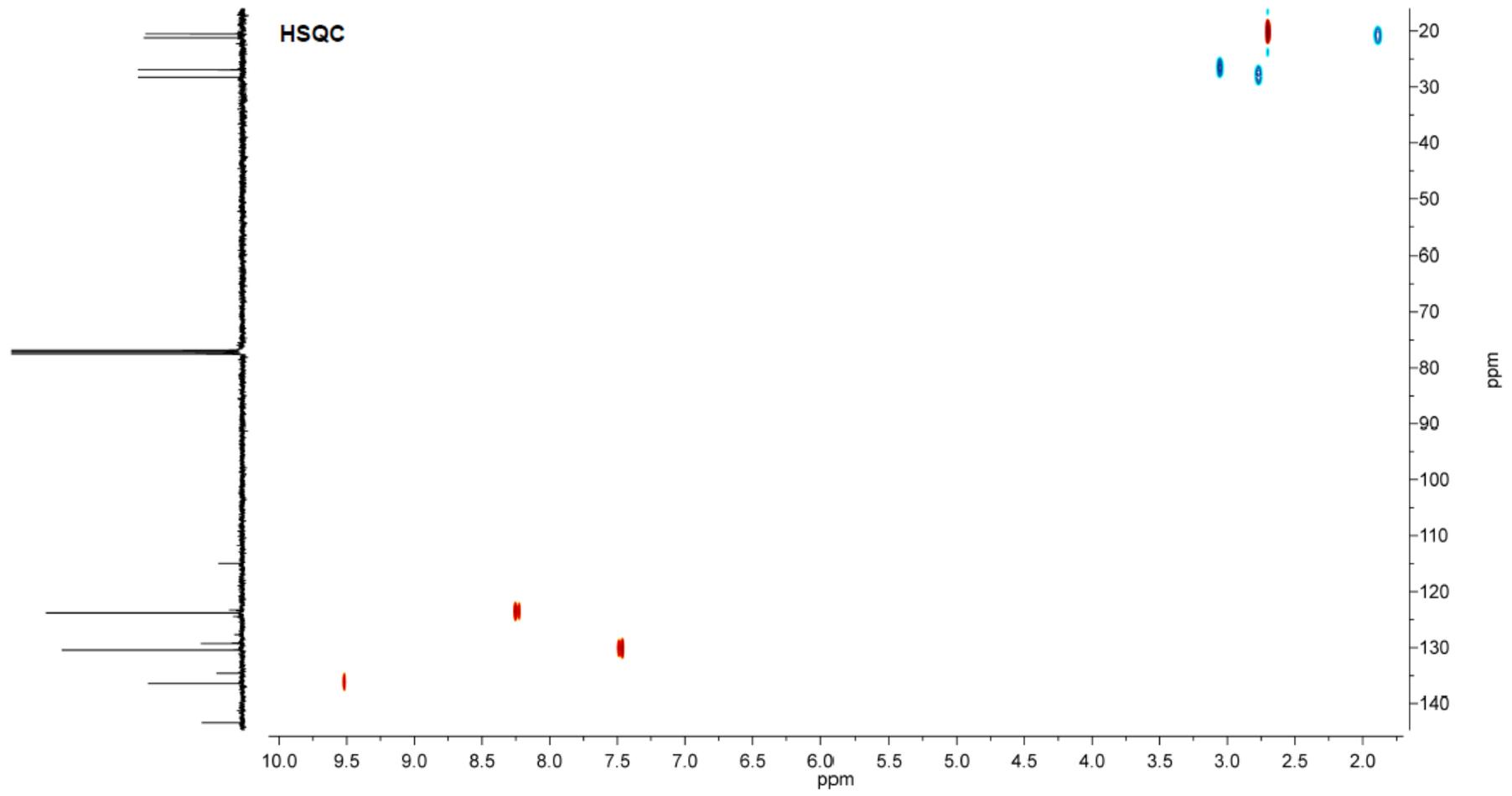


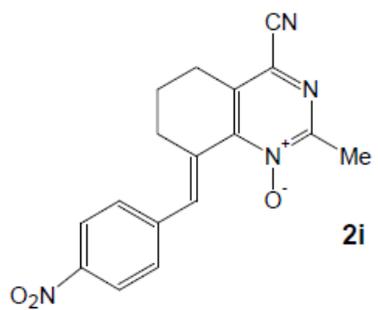


2i

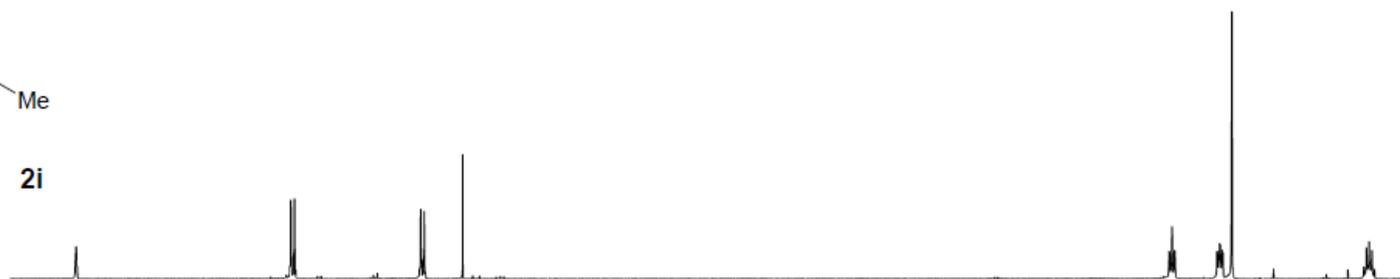


HSQC

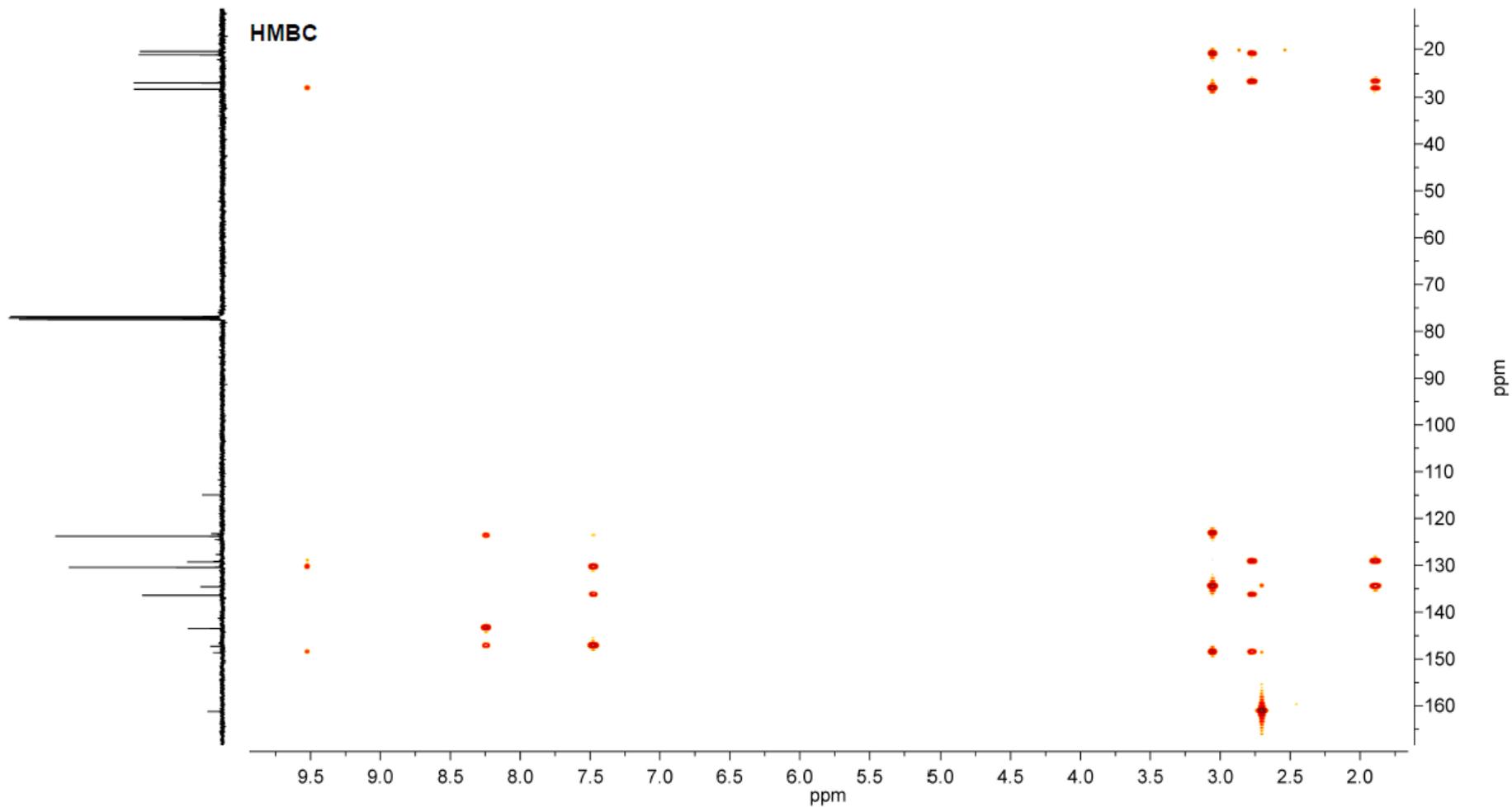




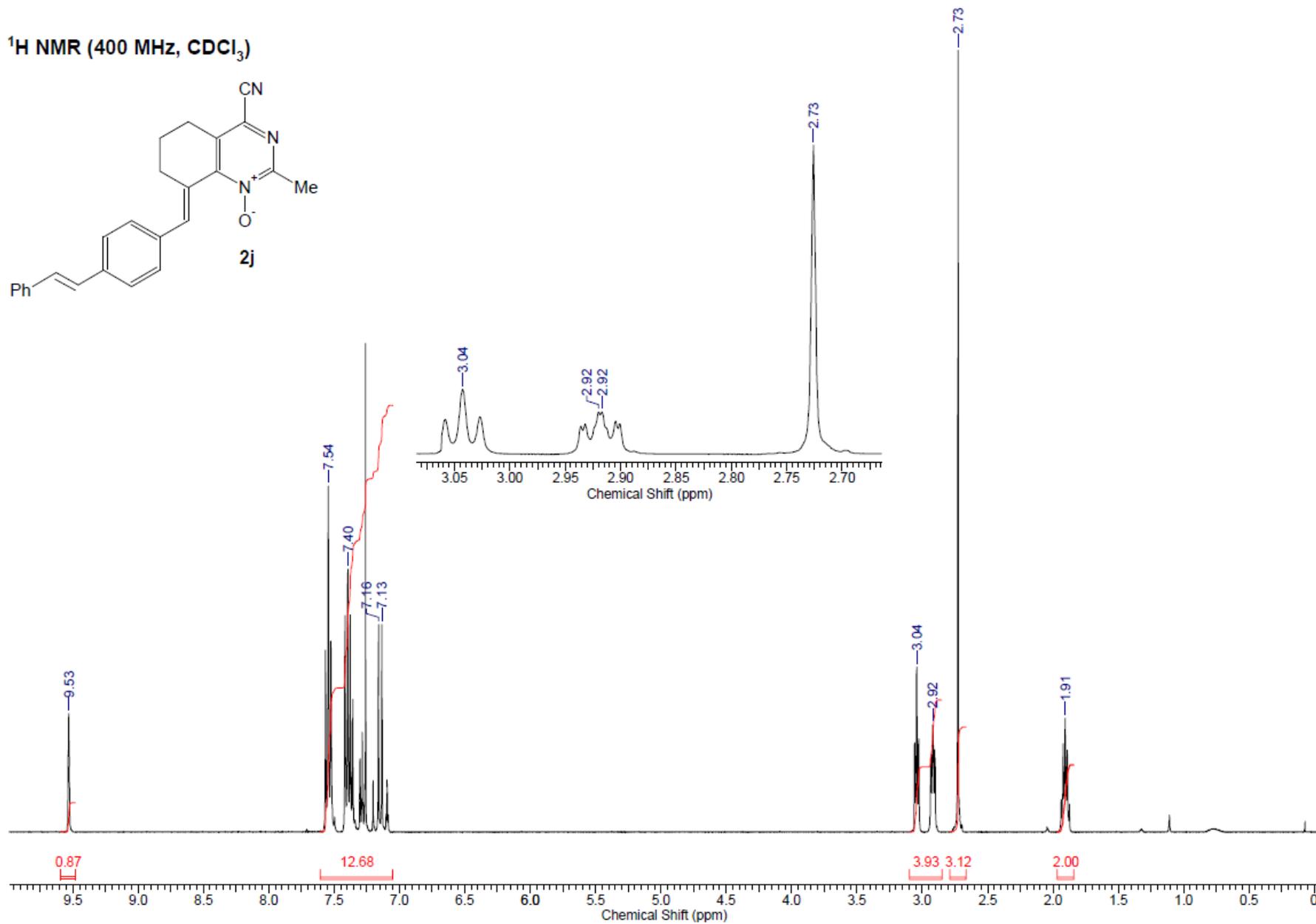
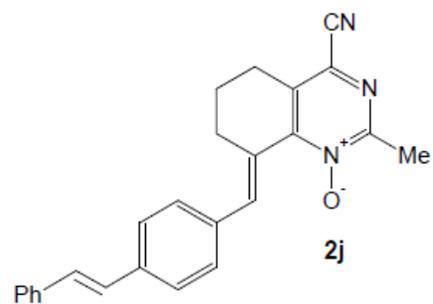
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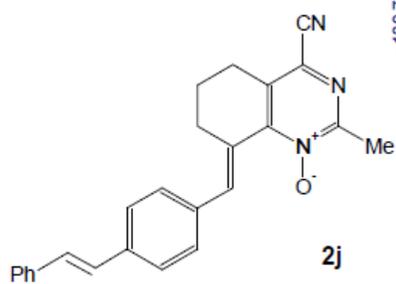
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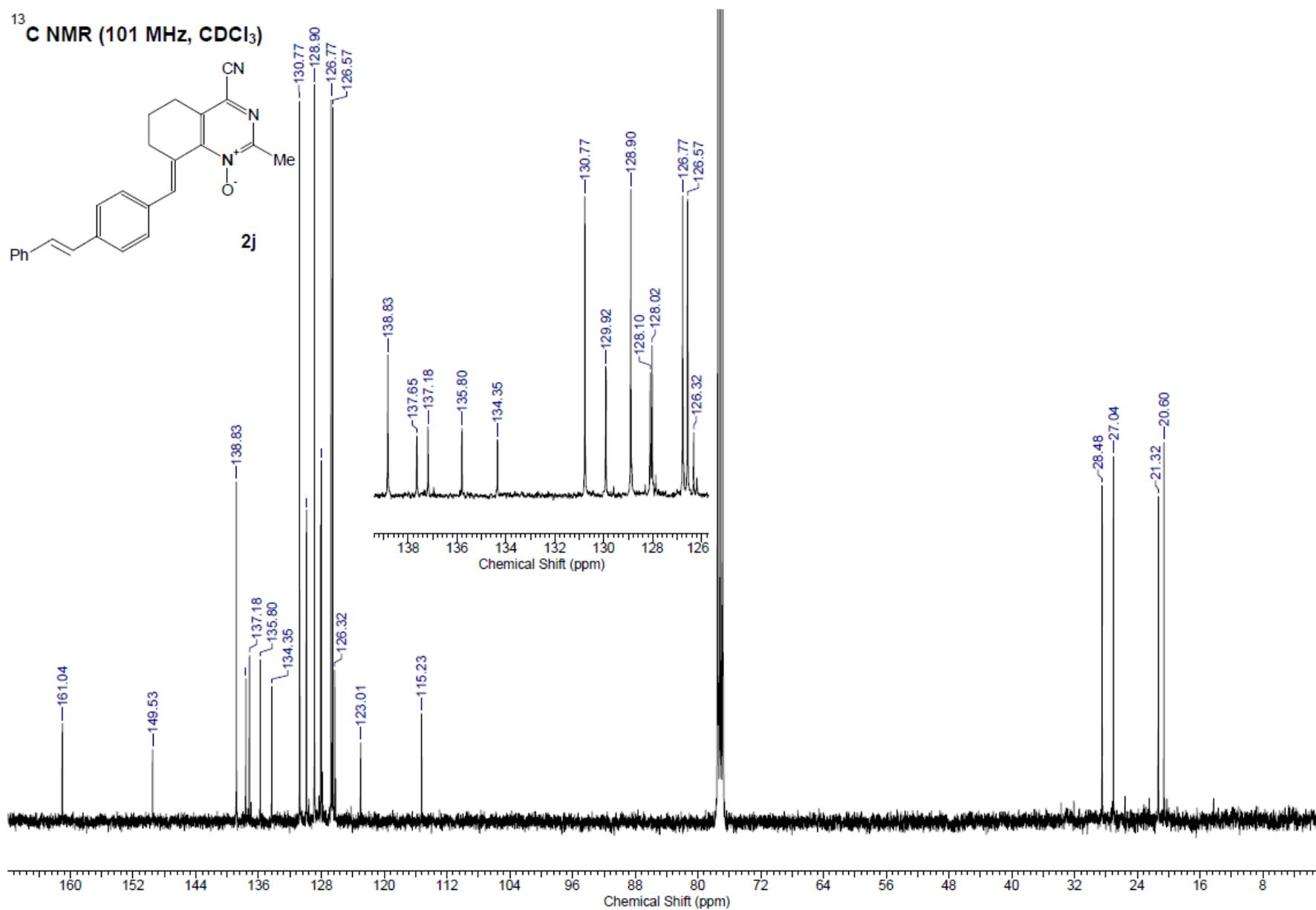
^1H NMR (400 MHz, CDCl_3)



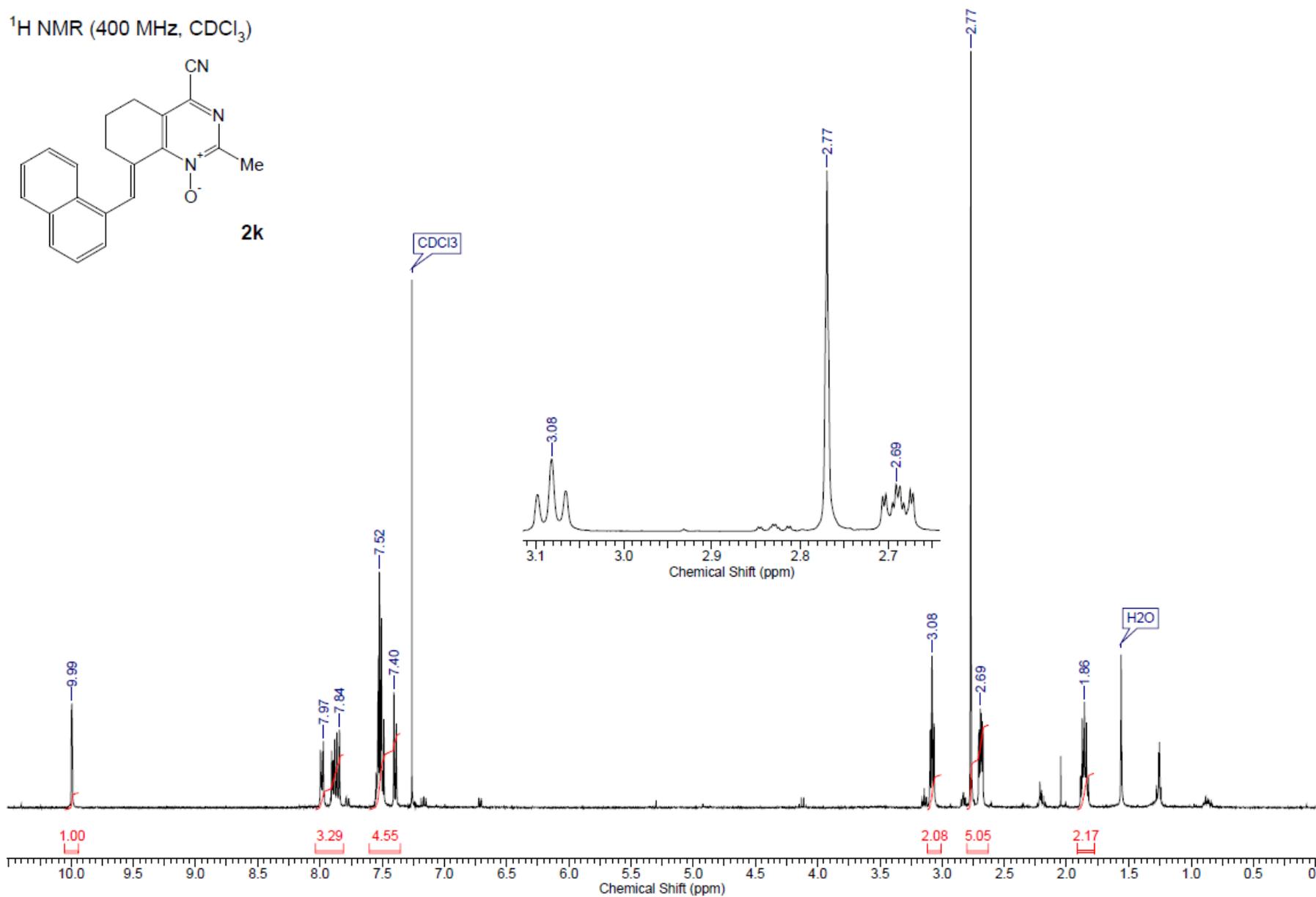
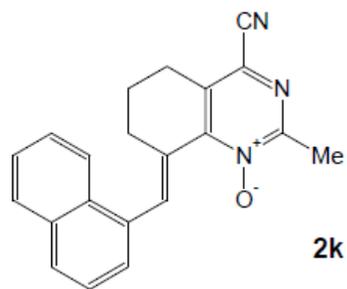
¹³C NMR (101 MHz, CDCl₃)

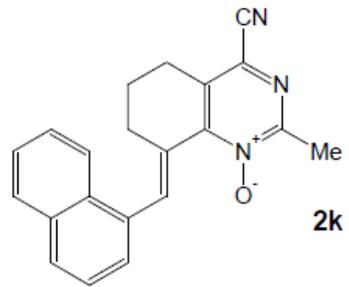


2j

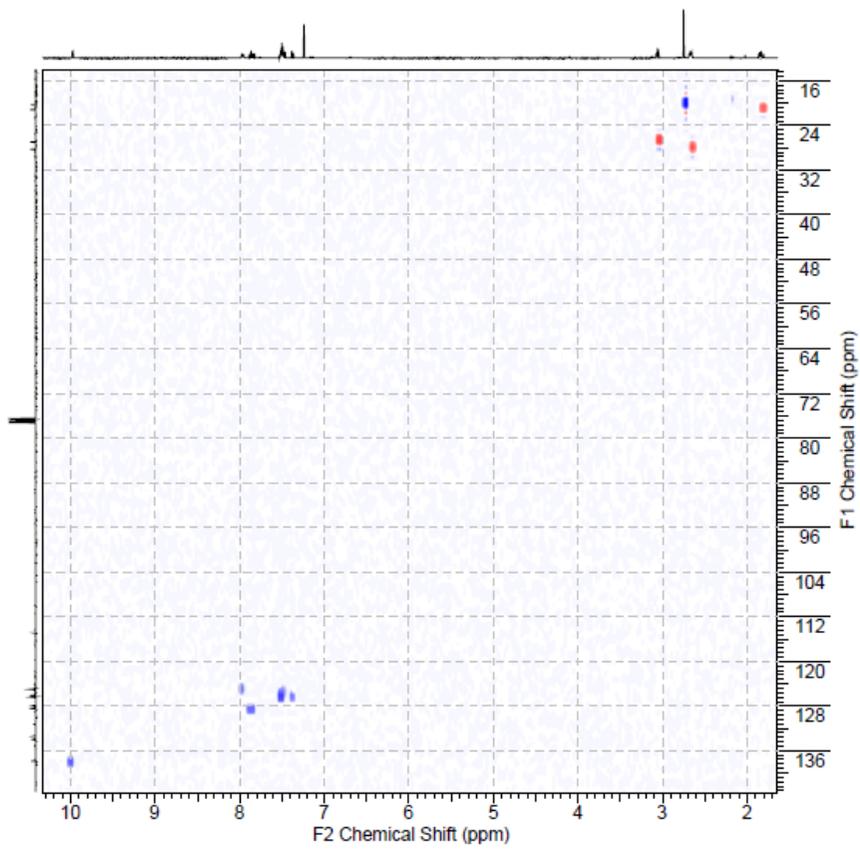


^1H NMR (400 MHz, CDCl_3)

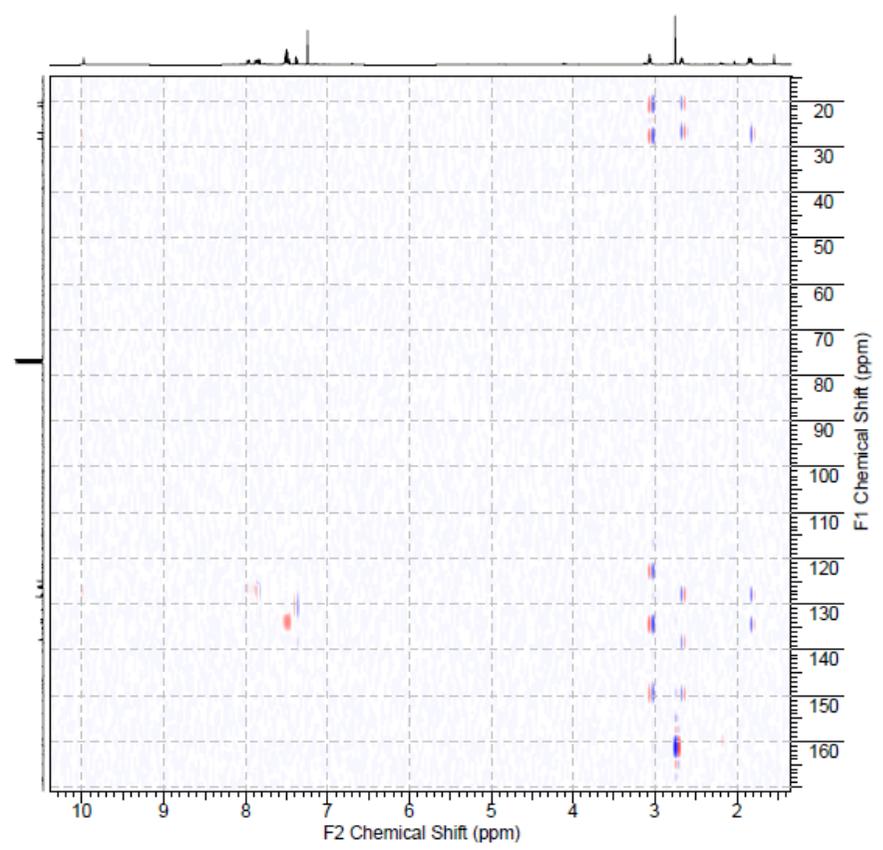




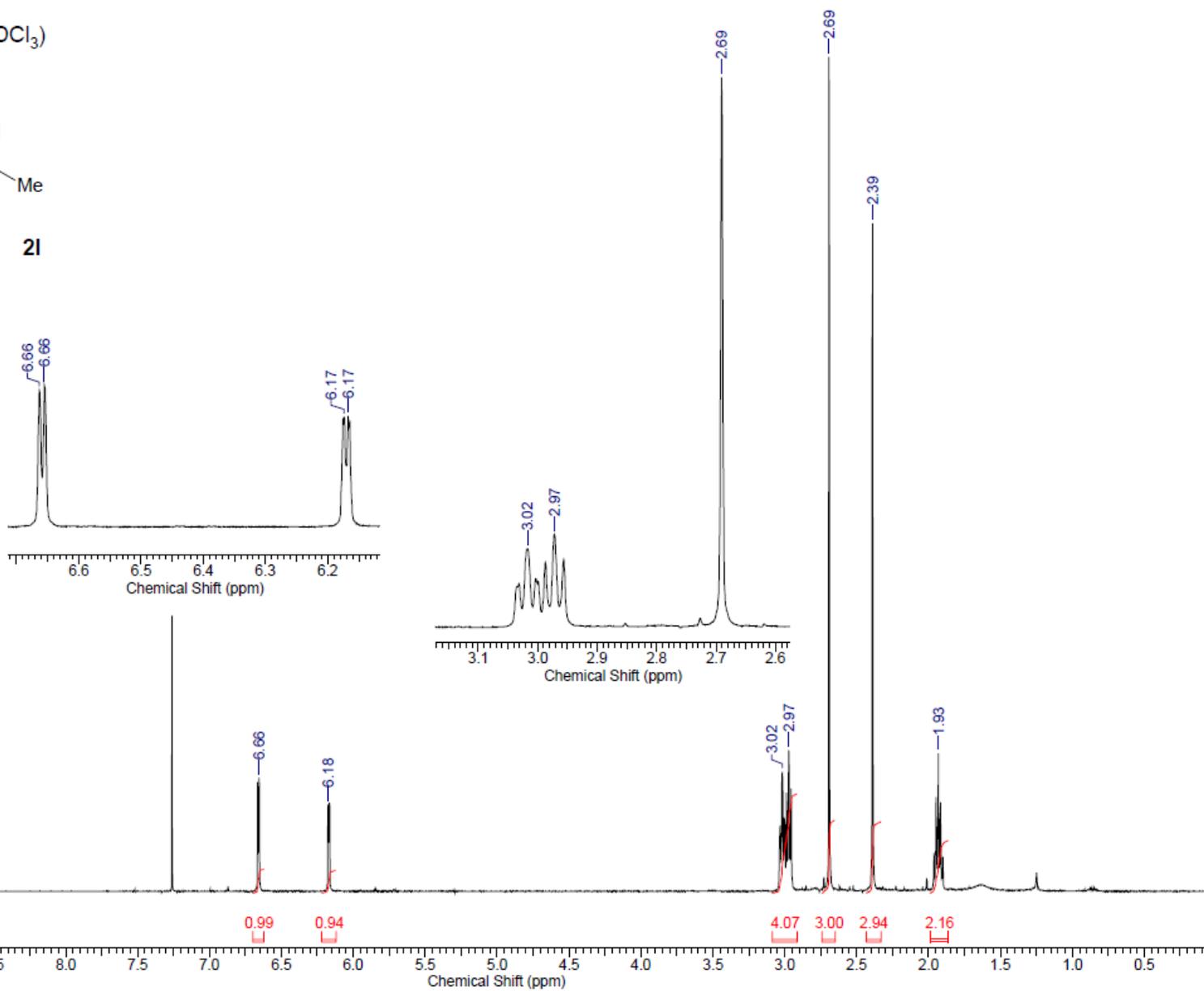
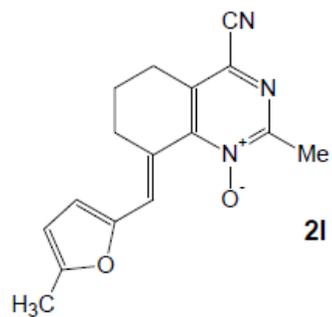
HSQC



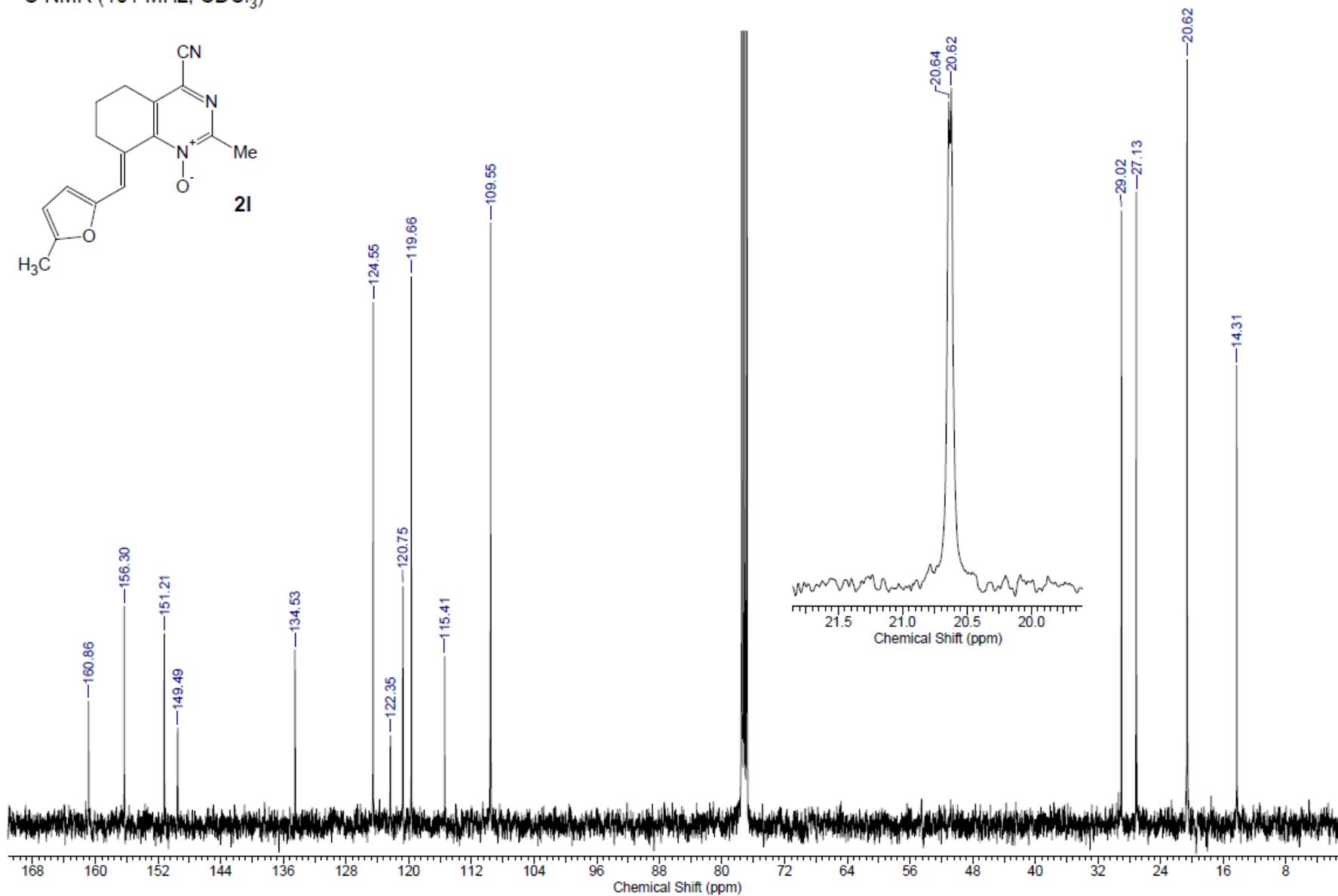
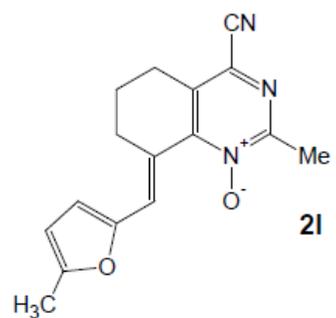
HMBC

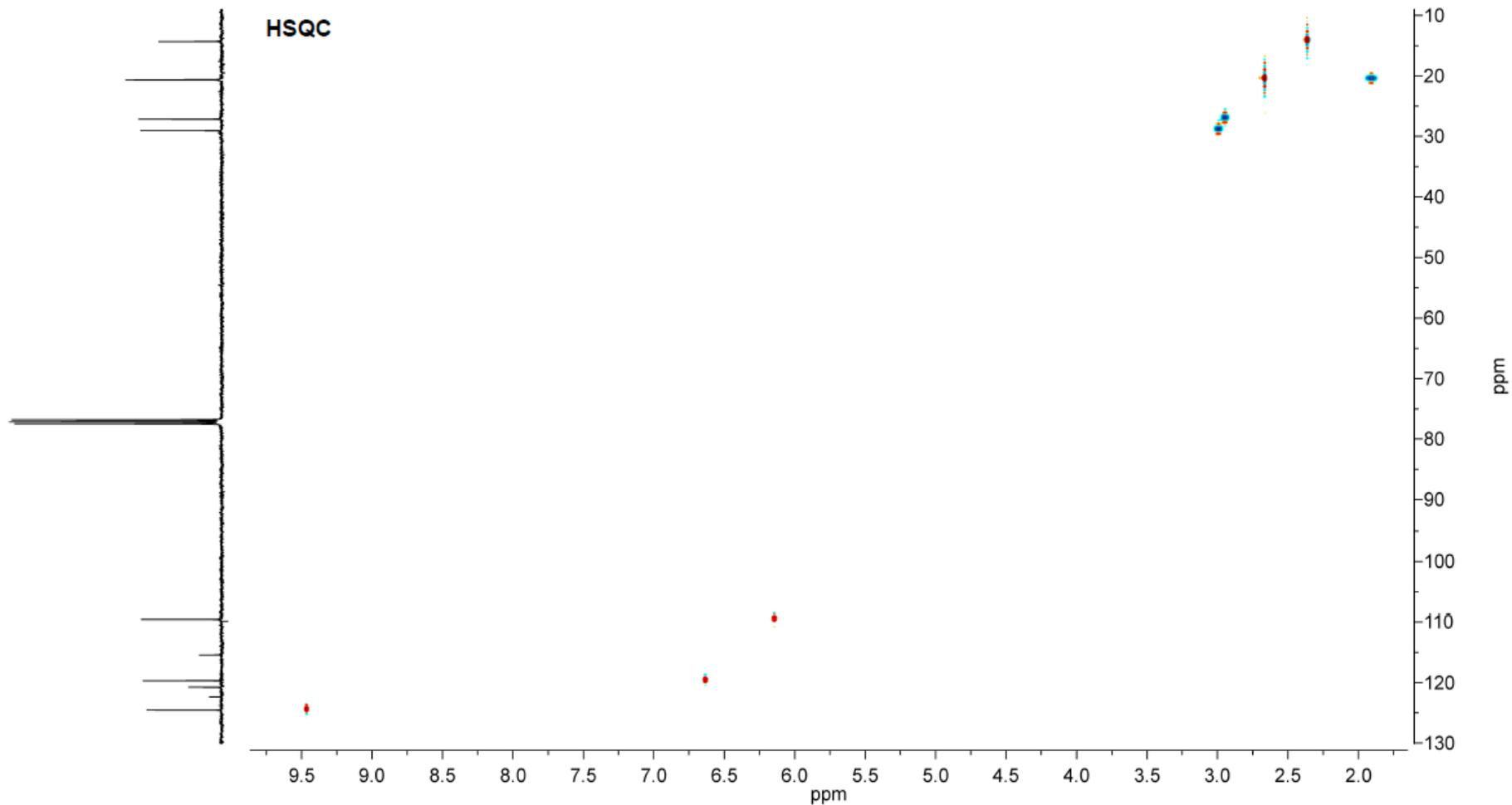
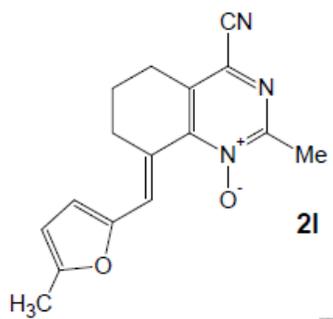


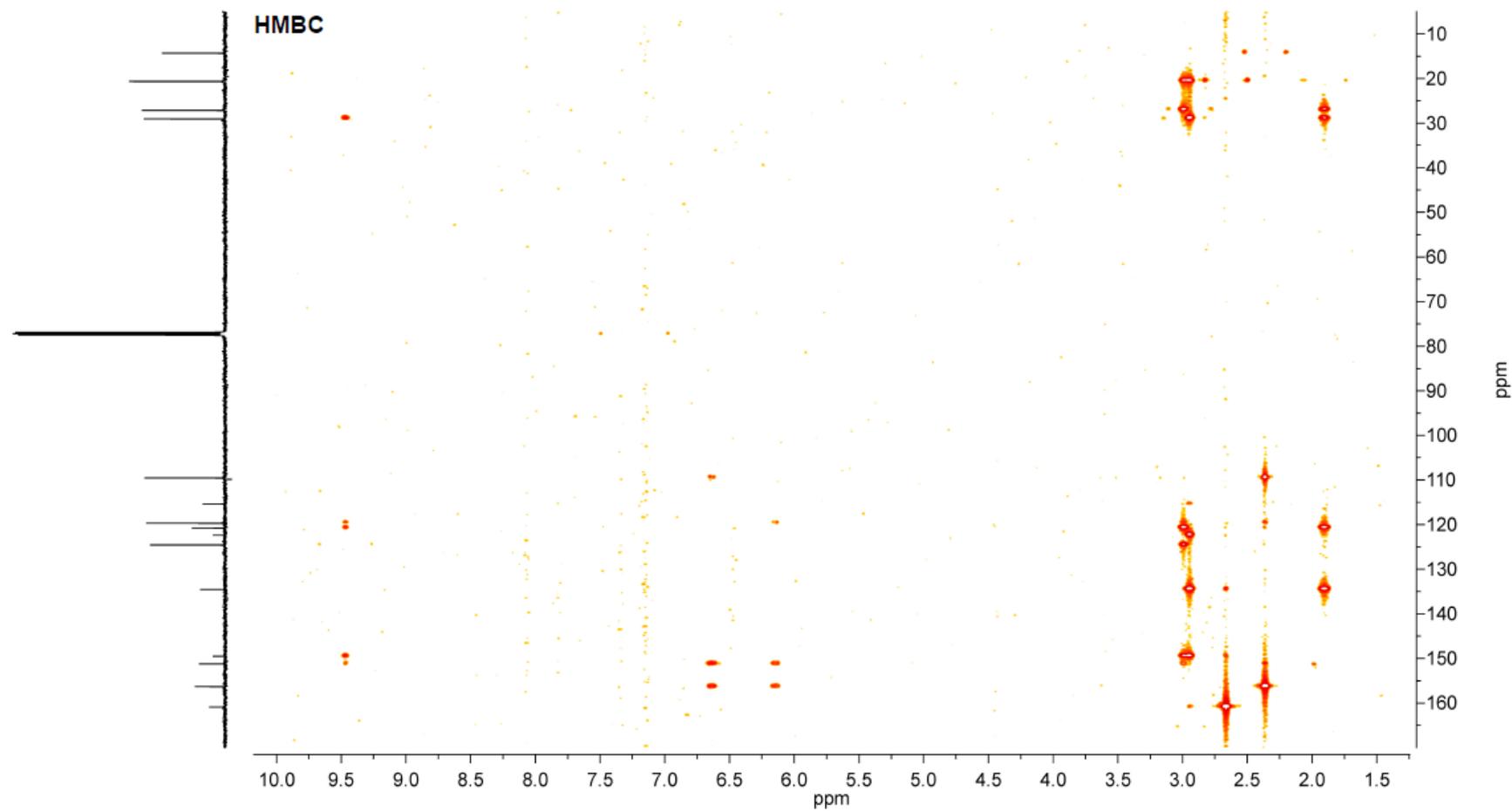
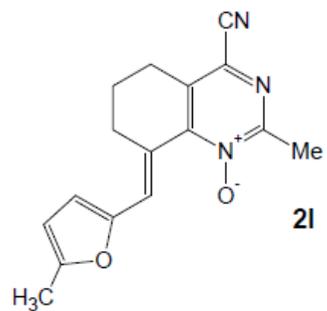
^1H NMR (400 MHz, CDCl_3)



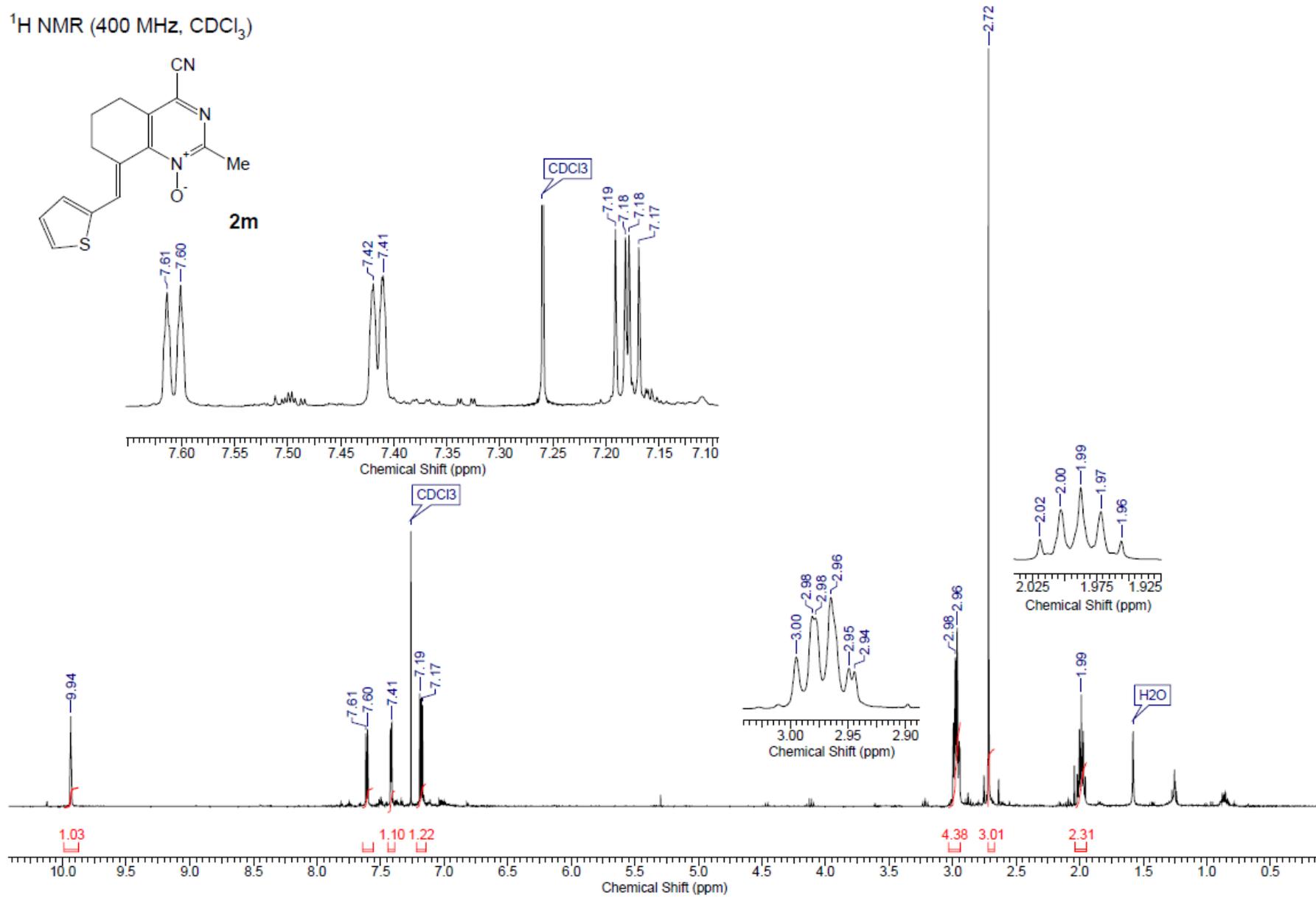
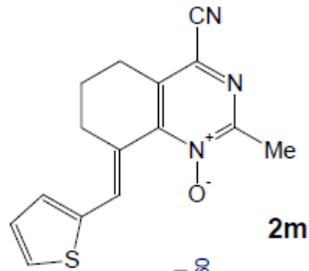
¹³C NMR (101 MHz, CDCl₃)







^1H NMR (400 MHz, CDCl_3)



^{13}C NMR (101 MHz, CDCl_3)

