

4-Azidotetrahydroquinazoline derivatives in CuAAC reaction

**Anna A. Nazarova, Kseniya N. Sedenkova, Dmitry A. Vasilenko, Yuri K. Grishin,
Tamara S. Kuznetsova and Elena B. Averina**

<u>Experimental details</u>	<u>S1</u>
<u>Optimization of CuAAC reaction conditions</u>	<u>S7</u>
<u>NMR titration of compound 3 with TFA in CDCl₃</u>	<u>S8</u>
<u>Calculation details</u>	<u>S9</u>
<u>NMR spectra</u>	<u>S13</u>

Experimental details

¹H, ¹³C and ¹⁹F NMR spectra were recorded on a 400 MHz spectrometer Agilent 400-MR (400.0, 100.6 and 376.3 MHz for ¹H, ¹³C and ¹⁹F, respectively) at room temperature; chemical shifts δ were measured with reference to the solvent for ¹H (CDCl₃, δ = 7.26 ppm) and ¹³C (CDCl₃, δ = 77.16 ppm) and to CFCl₃ as external standard for ¹⁹F. 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. IR spectra were recorded on Nicolet™ iS™ 5 FTIR Spectrometer. 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). 4-Fluoro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide **1** was obtained as described [K. N. Sedenkova *et al*, *Tetrahedron Lett.*, 2015, **56**, 4927]. All other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified according to literature procedures prior to use.

Caution: *Although we did not experience any problems in handling azidotetrahydroquinazoline derivatives, anyway, full safety precautions should be taken due to their potentially explosive nature.*

4-Azido-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (2). Method A. To a solution of 4-fluoro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide **1** (0.36 g, 2 mmol) in benzene (1 ml) trimethylsilyl azide (0.69 g, 6 mmol) was added under argon. The resulting mixture was stirred for

12 h at room temperature, and then the solvent was evaporated under reduced pressure. Product **2** was used without additional purification. Yield 0.40 g (98%). Yellow oil, R_f 0.1 (light petroleum–EtOAc–MeOH 3:1:0.3). *Method B.* To a solution of fluoro hetarene (0.52 g, 2.9 mmol) in DMSO (10 ml) sodium azide (0.37 g, 5.7 mmol) was added. The resulting mixture was stirred for 12 h at room temperature, then quenched with icy water (10 ml) and extracted with CH_2Cl_2 (3×5 ml). The combined organic layers were washed with water (6×5 ml), and dried over MgSO_4 . The solvent was evaporated under reduced pressure. Compound **2** was obtained as yellow oil and used without additional purification. Yield 0.36 g (60%). IR (film, cm^{-1}): 1104, 1215, 1263, 1301, 1336, 1358, 1384, 1425, 1548, 1593, 1671, 2134, 2220, 2343, 2362, 2867. ^1H NMR (CDCl_3 , δ , ppm): 1.69–1.78 (m, 2H, CH_2), 1.80–1.90 (m, 2H, CH_2), 2.52 (br.t, $^3J = 6.2$ Hz, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.91 (br.t, $^3J = 6.3$ Hz, 2H, CH_2). ^{13}C NMR (CDCl_3 , δ , ppm): 19.8 (CH_3), 20.7 (CH_2), 21.0 (CH_2), 22.8 (CH_2), 25.1 (CH_2), 119.6 (C(4a)), 147.3 (C(4)), 156.0 (C(8a)), 156.8 (C(2)). HRMS (ESI+, m/z): calcd. for $\text{C}_9\text{H}_{11}\text{N}_5\text{O}^+$ [M+H] 206.1036, found 206.1044.

4-Azido-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (3). To a solution of *N*-oxide **2** (0.90 g, 4.4 mmol) in CH_2Cl_2 (20 ml), PCl_3 (0.75 ml, 1.18 g, 8.8 mmol) was added under argon. The resulting mixture was refluxed for 2 h, cooled to room temperature and quenched with saturated aqueous NaHCO_3 (30 ml). The organic layer was separated, the aqueous one was extracted with CH_2Cl_2 (3×5 ml). The combined organic layers were washed with water (3×50 ml) and dried over MgSO_4 . The solvent was evaporated under reduced pressure. Compound **3** was isolated by preparative column chromatography (SiO_2). Yield 0.54 g (65%). White solid, $R_f = 0.25$ (petroleum ether:ethyl acetate 3:1), m. p. 105–107 °C. IR (film, cm^{-1}): 967, 988, 1077, 1137, 1181, 1258, 1282, 1385, 1419, 1450, 1507, 1553, 1624, 1701, 1716, 1735, 2109, 2343, 2361, 2868. ^1H NMR (CDCl_3 , δ , ppm): 1.88–2.01 (m, 4H, 2 CH_2), 2.88–2.94 (m, 2H, CH_2), 3.06 (s, 3H, CH_3), 3.07–3.12 (m, 2H, CH_2). ^{13}C NMR (CDCl_3 , δ , ppm): 19.5 (CH_3), 21.0 (CH_2), 22.1 (CH_2), 23.1 (CH_2), 30.9 (CH_2), 116.6 (C(4a)), 144.9 (C(2)), 149.8 (C(8a)), 153.7 (C(4)). HRMS (ESI, m/z): calcd. for $\text{C}_9\text{H}_{11}\text{N}_5$ [M+H] $^+$ 190.1087, found 190.1090.

4-Triazolyl-2-methyl-5,6,7,8-tetrahydroquinazoline N-oxides 4a-n (general method). 4-Azidotetrahydroquinazoline 1-oxide **2** (0.25 g, 1.2 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (24 mg, 0.12 mmol), Et_3N (13 mg, 0.24 mmol) and CH_2Cl_2 (4 ml) were mixed under argon. The corresponding alkyne (1.44 mmol) and sodium ascorbate (98 mg, 0.48 mmol) were added under stirring. The resulting mixture was refluxed for 24 h, cooled to room temperature and quenched with saturated aqueous Trilon B (5 ml). The organic layer was separated; the aqueous one was extracted with CH_2Cl_2 (3×5 ml). The combined organic layers were washed with saturated aqueous Trilon B (3×5 ml) and

water (3×10 ml), and dried over MgSO₄. The solvent was evaporated under reduced pressure. Product was isolated *via* preparative column chromatography (SiO₂).

2-Methyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-5,6,7,8-tetrahydroquinazoline N-oxide (4a). Yield 0.33 g (89%). Yellow solid, $R_f = 0.33$ (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 113–115 °C. ¹H NMR (CDCl₃, δ, ppm): 1.75–1.86 (m, 2H, CH₂), 1.92–2.02 (m, 2H, CH₂), 2.77 (s, 3H, CH₃), 3.02 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.20 (br.t, ³J = 6.1 Hz, 2H, CH₂), 7.35–7.41 (m, 1H, CH), 7.43–7.50 (m, 2H, 2CH), 7.90–7.95 (m, 2H, 2CH), 8.59 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.12 (CH₂), 26.17 (CH₂), 119.4 (CH, triazolyl), 123.0 (C(4a)), 126.1 (2CH), 128.8 (CH), 129.1 (2CH), 129.8 (C, Ph), 139.7 (C(4)), 147.3 (C, triazolyl), 155.7 (C(2)), 158.7 (C(8a)). HRMS (ESI, m/z): calcd. for C₁₇H₁₇N₅O [M+H]⁺ 308.1515, found 308.1506.

2-Methyl-4-[4-(p-tolyl)-1H-1,2,3-triazol-1-yl]-5,6,7,8-tetrahydroquinazoline 1-oxide (4b). Yield 0.32 g (83%). Yellow solid, $R_f = 0.38$ (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. = 113–115 °C. ¹H NMR (CDCl₃, δ, ppm): 1.70–1.83 (m, 2H, CH₂), 1.91–2.00 (m, 2H, CH₂), 2.40 (s, 3H, CH₃, Ar), 2.77 (s, 3H, CH₃), 3.01 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.19 (br.t, ³J = 6.2 Hz, 2H, CH₂), 7.24–7.29 (m, 2H, 2CH), 7.78–7.83 (m, 2H, 2CH), 8.54 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 21.5 (CH₃, Ar), 26.12 (CH₂), 26.15 (CH₂), 119.0 (CH, triazolyl), 122.9 (C(4a)), 125.9 (2CH), 127.0 (C, Ar), 129.8 (2CH), 138.8 (C, Ar), 139.8 (C(4)), 147.3 (C, triazolyl), 155.7 (C(2)), 158.7 (C(8a)). HRMS (ESI, m/z): calcd. for C₁₈H₁₉N₅O [M+H]⁺ 322.1662, found 322.1661.

2-Methyl-4-[4-(4-tert-butylphenyl)-1H-1,2,3-triazol-1-yl]-5,6,7,8-tetrahydroquinazoline 1-oxide (4c). Yield 0.29 g (66%). Brown oil, $R_f = 0.25$ (light petroleum–EtOAc–MeOH 3:1:0.5). ¹H NMR (CDCl₃, δ, ppm): 1.35 (s, 9H, 3CH₃, *t*-Bu), 1.74–1.82 (m, 2H, CH₂), 1.91–2.00 (m, 2H, CH₂), 2.77 (s, 3H, CH₃), 3.00 (br.t, ³J = 6.4 Hz, 2H, CH₂), 3.19 (br.t, ³J = 6.2 Hz, 2H, CH₂), 7.45–7.51 (m, 2H, 2CH), 7.82–7.87 (m, 2H, 2CH), 8.55 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.18 (CH₂), 26.20 (CH₂), 31.4 (3CH₃, *t*-Bu), 34.9 (C, *t*-Bu), 119.1 (CH, triazolyl), 123.0 (C(4a)), 125.9 (2CH), 126.1 (2CH), 127.0 (C, Ar), 139.8 (C(4)), 147.3 (C, triazolyl), 152.0 (C, Ar), 155.7 (C(2)), 158.7 (C(8a)). HRMS (ESI, m/z): calcd. for C₂₁H₂₅N₅O [M+H]⁺ 364.2132, found 364.2125.

4-(4-Mesityl-1H-1,2,3-triazol-1-yl)-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (4d). Yield 0.27 g (65%). Yellow oil, $R_f = 0.33$ (light petroleum–EtOAc–MeOH 3:1:0.5). ¹H NMR (CDCl₃, δ, ppm): 1.78–1.86 (m, 2H, CH₂), 1.94–2.02 (m, 2H, CH₂), 2.18 (s, 6H, 2CH₃, Ar), 2.34 (s, 3H, CH₃, Ar), 2.77 (s, 3H, CH₃), 3.04 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.25 (br.t, ³J = 6.2 Hz, 2H, CH₂), 6.98 (s, 2H, CH), 8.29 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂),

20.9 (2CH₃), 21.25 (CH₃), 21.32 (CH₂), 26.18 (CH₂), 26.23 (CH₂), 122.6 (CH, triazolyl), 122.8 (C(4a)), 126.4 (C, Ar), 128.6 (2CH, Ar), 137.8 (2C, Ar), 138.6 (C, Ar), 139.8 (C(4)), 145.2 (C, triazolyl), 155.7 (C(2)), 158.6 (C(8a)). HRMS (ESI, m/z): calcd. for C₂₀H₂₃N₅O [M+H]⁺ 350.1966, found 350.1975.

2-Methyl-4-[4-(4-dimethylaminophenyl)-1H-1,2,3-triazol-1-yl]-5,6,7,8-tetrahydroquinazoline 1-oxide (4e). Yield 0.32 g (77%). Brown solid, R_f = 0.27 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 154-156 °C. ¹H NMR (CDCl₃, δ, ppm): 1.75-1.84 (m, 2H, CH₂), 1.92-2.01 (m, 2H, CH₂), 2.77 (s, 3H, CH₃), 3.02 (br.t, ³J = 6.4 Hz, 2H, CH₂), 3.02 (s, 6H, N(CH₃)₂), 3.20 (br.t, ³J = 6.2 Hz, 2H, CH₂), 6.76-6.82 (m, 2H, 2CH), 7.76-7.83 (m, 2H, 2CH), 8.44 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.4 (CH₂), 26.19 (CH₂), 26.20 (CH₂), 40.6 (N(CH₃)₂), 112.5 (2CH), 117.6 (CH, triazolyl), 117.8 (C, Ar), 122.9 (C(4a)), 127.1 (2CH), 140.0 (C(4)), 147.8 (C, triazolyl), 150.8 (C, Ar), 155.6 (C(2)), 158.6 (C(8a)). HRMS (ESI, m/z): calcd. for C₁₉H₂₂N₆O [M+H]⁺ 351.1928, found 351.1922.

3-[1-(2-Methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)-1H-1,2,3-triazol-4-yl]aniline (4f). Yield 77 mg (20%). Yellow solid, R_f = 0.33 (light petroleum–EtOAc–MeOH 3:1:1), m.p. 222-224 °C. ¹H NMR (CDCl₃, δ, ppm): 1.76-1.85 (m, 2H, CH₂), 1.93-2.02 (m, 2H, CH₂), 2.78 (s, 3H, CH₃), 3.02 (br.t, ³J = 6.4 Hz, 2H, CH₂), 3.20 (br.t, ³J = 6.2 Hz, 2H, CH₂), 3.80 (br.s, 2H, NH₂), 6.72 (dt, ³J = 6.5 Hz, ³J = 2.4 Hz, 2H, CH), 7.22-7.29 (m, 2H, 2CH), 7.34 (br.t, 1H, CH), 8.54 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.14 (CH₂), 26.19 (CH₂), 112.5 (CH), 115.5 (CH), 116.4 (CH), 119.5 (CH, triazolyl), 123.0 (C(4a)), 130.1 (C, Ar), 130.8 (CH), 139.7 (C(4)), 147.1 (C, Ar), 147.4 (C, triazolyl), 155.7 (C(2)), 158.7 (C(8a)). HRMS (ESI, m/z): calcd. for C₁₇H₁₈N₆O [M+H]⁺ 323.1615, found 323.1609.

4-[4-(4-Methoxyphenyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (4g). Yield 0.16 g (40%). Yellow solid, R_f = 0.28 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 158-160 °C. ¹H NMR (CDCl₃, δ, ppm): 1.75-1.85 (m, 2H, CH₂), 1.93-2.02 (m, 2H, CH₂), 2.78 (s, 3H, CH₃), 3.03 (br.t, ³J = 6.4 Hz, 2H, CH₂), 3.21 (br.t, ³J = 6.2 Hz, 2H, CH₂), 3.87 (s, 3H, OCH₃), 6.97-7.04 (m, 2H, 2CH), 7.83-7.89 (m, 2H, 2CH), 8.50 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.17 (CH₂), 26.20 (CH₂), 55.5 (OCH₃), 114.5 (2CH, Ar), 118.5 (CH, triazolyl), 122.5 (C, Ar), 123.0 (C(4a)), 127.4 (2CH, Ar), 139.8 (C(4)), 147.2 (C, triazolyl), 155.7 (C(2)), 158.7 (C(8a)), 160.2 (C, Ar). HRMS (ESI, m/z): calcd. for C₁₈H₁₉N₅O₂ [M+H]⁺ 338.1612, found 338.1603.

4-[4-(1,2,3-Trimethoxyphenyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (4h). Yield 0.21 g (45%). Yellow solid, R_f = 0.17 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 196-198 °C. ¹H NMR (CDCl₃, δ, ppm): 1.76-1.85 (m, 2H, CH₂), 1.93-2.02 (m, 2H,

CH₂), 2.79 (s, 3H, CH₃), 3.03 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.20 (br.t, ³J = 6.3 Hz, 2H, CH₂), 3.90 (s, 3H, OCH₃), 3.96 (s, 6H, 2OCH₃), 7.17 (s, 2H, 2CH), 8.54 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.15 (CH₂), 26.20 (CH₂), 56.4 (2CH₃O), 61.1 (CH₃O), 103.3 (2CH), 119.1 (CH, triazolyl), 123.0 (C(4a)), 125.4 (C, Ar), 138.7 (C, Ar), 139.6 (C(4)), 147.3 (C, triazolyl), 153.9 (2C, Ar), 155.8 (C(2)), 158.8 (C(8a)). HRMS (ESI, m/z): calcd. for C₂₀H₂₃N₅O₄ [M+H]⁺ 398.1828, found 398.1813.

4-[4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (4i). Yield 0.19 g (49%). Yellow solid, R_f = 0.21 (light petroleum–EtOAc–MeOH 3:1:0.2), m.p. 124–126 °C. ¹H NMR (CDCl₃, δ, ppm): 1.76–1.85 (m, 2H, CH₂), 1.94–2.02 (m, 2H, CH₂), 2.77 (s, 3H, CH₃), 3.02 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.20 (br.t, ³J = 6.2 Hz, 2H, CH₂), 7.17 (t, ³J_{HH} = ³J_{HF} = 8.7 Hz, 2H, 2CH), 7.91 (dd, ³J_{HH} = 8.7 Hz, ³J_{HF} = 5.2 Hz, 2H, 2CH), 8.55 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.13 (CH₂), 26.19 (CH₂), 116.1 (d, ²J_{CF} = 22 Hz, 2CH), 119.2 (CH, triazolyl), 123.0 (C(4a)), 126.1 (d, ⁴J_{CF} = 3 Hz, C, Ar), 127.9 (d, ³J_{CF} = 8 Hz, 2CH), 139.6 (C(4)), 146.5 (C, triazolyl), 155.8 (C(2)), 158.8 (C(8a)), 163.1 (d, ¹J_{CF} = 249 Hz, CF). ¹⁹F NMR (CDCl₃, δ, ppm): -112.63 (tt, ³J_{HF} = 8.7 Hz, ⁴J_{HF} = 5.2 Hz). HRMS (ESI, m/z): calcd. for C₁₇H₁₆FN₅O [M+H]⁺ 326.1412, found 326.1422.

4-[4-(4-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (4j). Yield 0.34 g (75%). Yellow solid, R_f = 0.42 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 102–104 °C. ¹H NMR (CDCl₃, δ, ppm): 1.77–1.85 (m, 2H, CH₂), 1.94–2.03 (m, 2H, CH₂), 2.78 (s, 3H, CH₃), 3.02 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.20 (br.t, ³J = 6.2 Hz, 2H, CH₂), 7.73 (br.d, ³J = 8.1 Hz, 2H, 2CH), 8.05 (br.d, ³J = 8.1 Hz, 2H, 2CH), 8.68 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.7 (CH₃), 20.6 (CH₂), 21.2 (CH₂), 26.0 (CH₂), 26.1 (CH₂), 120.3 (CH, triazolyl), 123.0 (C(4a)), 124.1 (q, ¹J_{CF} = 272 Hz, CF₃), 126.0 (q, ³J_{CF} = 4 Hz, 2CH), 126.0 (2CH), 130.6 (q, ²J_{CF} = 32 Hz, C, Ar), 133.3 (C, Ar), 139.3 (C(4)), 145.8 (C, triazolyl), 155.8 (C(2)), 158.7 (C(8a)). ¹⁹F NMR (CDCl₃, δ, ppm): -62.70 (s, CF₃). HRMS (ESI, m/z): calcd. for C₁₈H₁₆F₃N₅O [M+H]⁺ 376.1380, found 376.1387.

4-[4-(4-Cyanophenyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (4k). Yield 0.33 g (83%). White solid, R_f = 0.33 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 117–119 °C. ¹H NMR (CDCl₃, δ, ppm): 1.75–1.85 (m, 2H, CH₂), 1.93–2.04 (m, 2H, CH₂), 2.76 (s, 3H, CH₃), 3.01 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.19 (br.t, ³J = 6.2 Hz, 2H, CH₂), 7.73–7.79 (m, 2H, 2CH), 8.02–8.08 (m, 2H, 2CH), 8.70 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.7 (CH₃), 20.6 (CH₂), 21.2 (CH₂), 26.0 (CH₂), 26.1 (CH₂), 112.1 (CN), 118.7 (C, Ar), 120.7 (CH, triazolyl), 123.0 (C(4a)), 126.4 (2CH, Ar), 132.9 (2CH, Ar), 134.2 (C, Ar), 139.1 (C(4)), 145.4 (C, triazolyl),

155.8 (C(2)), 158.8 (C(8a)). HRMS (ESI, m/z): calcd. for C₁₈H₁₆N₆O [M+H]⁺ 333.1468, found 333.1458.

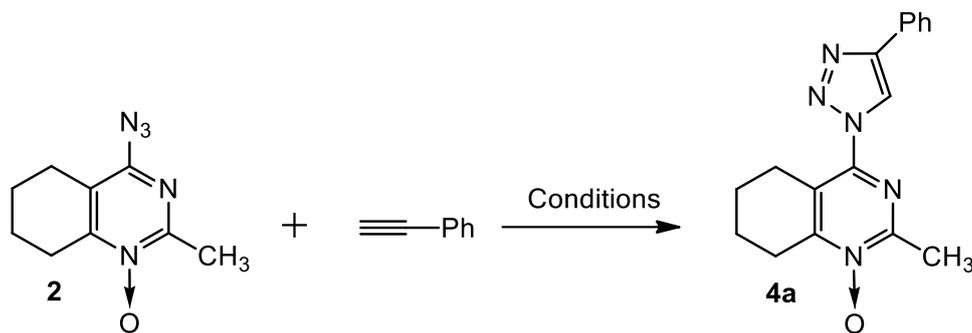
4-[4-(4-Methoxycarbonyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (**4l**). Yield 0.32 g (72%). Yellow solid, R_f = 0.30 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 122-124 °C. ¹H NMR (CDCl₃, δ, ppm): 1.75-1.85 (m, 2H, CH₂), 1.93-2.01 (m, 2H, CH₂), 2.77 (s, 3H, CH₃), 3.01 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.19 (br.t, ³J = 6.2 Hz, 2H, CH₂), 3.94 (s, 3H, CH₃, COOMe), 8.00 (br.d, ³J = 8.4 Hz, 2H, 2CH), 8.13 (br.d, ³J = 8.3 Hz, 2H, 2CH), 8.67 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.1 (CH₂), 26.2 (CH₂), 52.4 (OCH₃), 120.4 (CH, triazolyl), 123.0 (C(4a)), 125.9 (2CH), 130.2 (C, Ar), 130.4 (2CH), 134.1 (C, Ar), 139.4 (C(4)), 146.3 (C, triazolyl), 155.8 (C(2)), 158.8 (C(8a)), 166.8 (COO). HRMS (ESI, m/z): calcd. for C₁₉H₁₉N₅O₃ [M+H]⁺ 366.1554, found 366.1561.

2-Methyl-4-[4-(tert-butyl)-1H-1,2,3-triazol-1-yl]-5,6,7,8-tetrahydroquinazoline 1-oxide (**4m**). Yield 0.22 g (65%). Brown oil, R_f = 0.13 (light petroleum–EtOAc–MeOH 3:1:0.5). ¹H NMR (CDCl₃, δ, ppm): 1.42 (s, 9H, 3CH₃, *t*-Bu), 1.72-1.80 (m, 2H, CH₂), 1.90-2.00 (m, 2H, CH₂), 2.75 (s, 3H, CH₃), 3.01 (br.t, ³J = 6.4 Hz, 2H, CH₂), 3.15 (br.t, ³J = 6.2 Hz, 2H, CH₂), 8.07 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.8 (CH₃), 20.7 (CH₂), 21.3 (CH₂), 26.13 (CH₂), 26.17 (CH₂), 30.28 (C, *t*-Bu), 30.32 (3CH₃, *t*-Bu), 118.7 (CH, triazolyl), 122.9 (C(4a)), 140.2 (C(4)), 155.6 (C(2)), 157.3 (C, triazolyl), 158.6 (C(8a)). HRMS (ESI, m/z): calcd. for C₁₅H₂₁N₅O [M+H]⁺ 288.1819, found 288.1820.

4-[4-(1H-Indol-1-ylmethyl)-1H-1,2,3-triazol-1-yl]-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (**4n**). Yield 0.17 g (40%). Brown, R_f = 0.43 (light petroleum–EtOAc–MeOH 3:1:0.5), m.p. 144-146 °C. ¹H NMR (CDCl₃, δ, ppm): 1.70-1.78 (m, 2H, CH₂), 1.88-1.97 (m, 2H, CH₂), 2.67 (s, 3H, CH₃), 2.97 (br.t, ³J = 6.5 Hz, 2H, CH₂), 3.08 (br.t, ³J = 6.3 Hz, 2H, CH₂), 5.53 (s, 2H, CH₂), 6.54-6.60 (m, 1H, CH), 7.10-7.17 (m, 1H, CH), 7.20-7.26 (m, 2H, 2CH), 7.43 (d, ³J = 8.3 Hz, 1H, CH), 7.65 (d, ³J = 7.9 Hz, 1H, CH), 8.01 (s, 1H, CH, triazolyl). ¹³C NMR (CDCl₃, δ, ppm): 19.6 (CH₃), 20.6 (CH₂), 21.1 (CH₂), 25.9 (CH₂), 26.1 (CH₂), 41.9 (CH₂), 102.4 (CH), 109.5 (CH), 119.9 (CH, triazolyl), 121.2 (CH), 121.9 (CH), 122.1 (CH), 122.9 (C(4a)), 127.9 (CH), 128.9 (C, indolyl), 135.9 (C, indolyl), 139.3 (C(4)), 144.4 (C, triazolyl), 155.7 (C(2)), 158.6 (C(8a)). HRMS (ESI, m/z): calcd. for C₂₀H₂₀N₆O [M+H]⁺ 361.1771, found 361.1766.

Optimization of CuAAC reaction conditions

Table S1 Optimization of CuAAC reaction conditions.



Entry	Catalytic system	Solvent	Conditions	Conversion, % ^a
1	CuSO ₄ (0.1 eq)/AscNa	Bu ^t OH/H ₂ O (2:1)	25°C, 12 h	-
2	CuSO ₄ (0.1 eq)/AscNa	THF/H ₂ O (4:1)	50°C, 5 h	25
3	CuSO ₄ (0.1 eq)/AscNa	THF/H ₂ O (4:1)	50°C, 11 h	33
4	CuSO ₄ (0.1 eq)/AscNa	THF/H ₂ O (4:1)	50°C, 25 h	50
5	CuSO ₄ (0.1 eq)/AscNa	THF/H ₂ O (4:1)	50°C, 96 h	10
6	CuSO ₄ (0.1 eq)/AscNa	THF/H ₂ O (4:1)	70°C, 36 h	14
7	CuI (0.1 eq)/TTTA ^b /DIPEA	DMF	50°C, 4 h	20
8	CuI (0.1 eq)/Et ₃ N	H ₂ O	55°C, 12 h	traces
9	CuSO ₄ (0.1 eq)/AscNa	Bu ^t OH/H ₂ O/MeOH (1:2:1)	25°C, 12 h	10
10	CuSO ₄ (0.1 eq)/AscNa	Bu ^t OH/H ₂ O/MeOH (1:2:1)	50°C, 12 h	-
11	CuSO ₄ (1 eq)/AscNa	THF/H ₂ O (4:1)	50°C, 24 h	50
12	CuSO ₄ (0.1 eq)/AscNa/TBTA ^c	THF/H ₂ O (4:1)	50°C, 12 h	60
13	CuSO ₄ (0.1 eq)/AscNa/Et ₃ N	CH ₂ Cl ₂	50°C, 24 h	80
14	Cu(OAc) ₂ (0.1 eq)/AscNa/Et ₃ N	CH ₂ Cl ₂	40°C, 24 h	100
15	Cu(OAc) ₂ (0.1 eq)/AscNa/Et ₃ N/TBTA	CH ₂ Cl ₂	40°C, 24 h	100

^aEstimated *via* ¹H NMR spectra; ^bTTTA – tris(*tert*-butyltriazolylmethyl)amine; ^cTBTA – tris(benzyltriazolylmethyl)amine.

NMR titration of compound **3** with TFA in CDCl₃

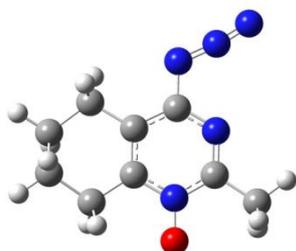
To compound **3** (0.05 mmol, 9.4 mg) in CDCl₃ in an NMR tube at room temperature TFA was added. TFA/**3** ratios were 5:1, 5:2, 5:3, 5:4, 1:1, 1:2, 1:5 and 1:10. NMR spectra were then registered. After treatment with the excess of aqueous NaHCO₃ the original spectrum recovered.



Figure S1 The high-field fragments of ¹H NMR spectra of compound **3** without TFA (a); with compound **3**: TFA ratios 1:1 (b) and 1:5 (c).

Calculation details

Table S2 Cartesian coordinates of optimized structure of **2-A**.



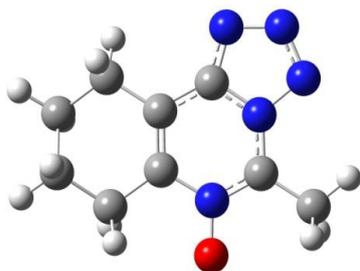
Number of imaginary frequency: 0

Sum of electronic and zero-point Energies= -697.90115228 (Hartree)

Final Gibbs free enthalpy = -697.95123956 (Hartree)

Center Number	Atom	Coordinates (Angstroms)		
		X	Y	Z
1	C	-2.79015	-1.50371	0.39585
2	C	-1.33392	-1.73244	-0.02723
3	C	-0.53056	-0.45245	-0.01793
4	C	-1.15622	0.78820	-0.00746
5	C	-2.63987	0.98177	-0.02844
6	C	-3.38808	-0.31451	-0.36238
7	H	-3.37021	-2.41392	0.20983
8	H	-0.84723	-2.46408	0.62656
9	C	0.87219	-0.44452	-0.01883
10	H	-2.94579	1.36966	0.95405
11	H	-3.32388	-0.50535	-1.44207
12	C	0.97608	1.84412	0.03181
13	H	-1.30295	-2.15981	-1.03962
14	H	-2.83214	-1.30730	1.47591
15	H	-4.44913	-0.19101	-0.12104
16	H	-2.86987	1.78256	-0.73980
17	N	1.59764	0.67669	0.00344
18	C	1.72738	3.13042	0.06681
19	H	1.47144	3.69722	0.96931
20	H	2.79864	2.92456	0.04652
21	H	1.44805	3.75739	-0.78753
22	N	1.53179	-1.68925	-0.04428
23	N	2.77401	-1.65552	-0.04838
24	N	3.90464	-1.76292	-0.05683
25	N	-0.39668	1.93669	0.03542
26	O	-0.96659	3.09946	0.07838
27	C	-2.79015	-1.50371	0.39585

Table S3 Cartesian coordinates of optimized structure of **2-T**.

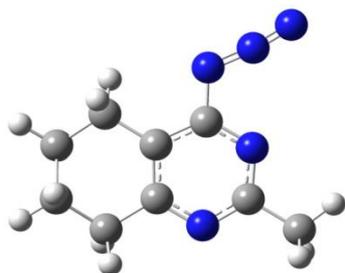


Number of imaginary frequency: 0

Sum of electronic and zero-point Energies= -697.90013069 (Hartree)

Final Gibbs free enthalpy = -697.94814699 (Hartree)

Center Number	Atom	Coordinates (Angstroms)		
		X	Y	Z
1	C	-3.14818	-1.07536	0.39939
2	C	-1.82734	-1.73000	-0.02131
3	C	-0.68886	-0.74006	-0.02294
4	C	-0.89722	0.61538	-0.01360
5	C	-2.25051	1.25417	-0.02471
6	C	-3.35595	0.24191	-0.35508
7	H	-3.97477	-1.76694	0.20583
8	H	-1.56858	-2.56437	0.63989
9	C	0.65381	-1.18537	-0.02901
10	H	-2.42013	1.71546	0.95837
11	H	-3.35529	0.04380	-1.43512
12	C	1.46958	1.09295	0.01180
13	H	-1.91858	-2.15462	-1.03088
14	H	-3.13217	-0.88087	1.48003
15	H	-4.32799	0.68170	-0.10918
16	H	-2.23634	2.08310	-0.73973
17	N	1.65960	-0.25647	-0.01664
18	N	0.19458	1.51618	0.02242
19	O	-0.04417	2.78370	0.06805
20	C	2.58422	2.06723	0.04388
21	H	2.51918	2.67146	0.95603
22	H	3.54268	1.54984	0.00822
23	H	2.49534	2.75415	-0.80514
24	N	1.22262	-2.39766	-0.04321
25	N	2.54866	-2.18063	-0.03967
26	N	2.85756	-0.91438	-0.02334
27	C	-3.14818	-1.07536	0.39939

Table S4 Cartesian coordinates of optimized structure of **3-A**.

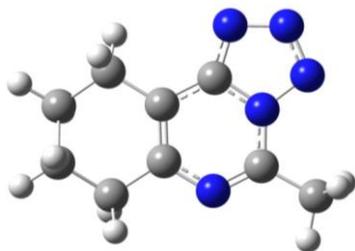
Number of imaginary frequency: 0

Sum of electronic and zero-point Energies= -622.77359878 (Hartree)

Final Gibbs free enthalpy = -622.82117353 (Hartree)

Center Number	Atom	Coordinates (Angstroms)		
		X	Y	Z
1	C	-2.80093	-1.52486	0.36738
2	C	-1.32992	-1.74671	-0.00798
3	C	-0.53521	-0.46168	0.00647
4	C	-1.13248	0.80583	0.01321
5	C	-2.63451	0.96134	0.02592
6	C	-3.37263	-0.31810	-0.38420
7	H	-3.37492	-2.43134	0.14526
8	H	-0.86297	-2.47345	0.66652
9	C	0.86590	-0.44547	-0.00488
10	H	-2.93064	1.24984	1.04544
11	H	-3.26212	-0.47719	-1.46583
12	C	0.92492	1.82878	0.02357
13	H	-1.26925	-2.18687	-1.01407
14	H	-2.88185	-1.34847	1.44887
15	H	-4.44389	-0.20541	-0.18366
16	H	-2.89948	1.80721	-0.61828
17	N	1.60154	0.67056	0.00668
18	N	-0.40878	1.94191	0.02312
19	C	1.72682	3.10175	0.04098
20	H	1.49217	3.68464	0.93914
21	H	2.79629	2.88214	0.02410
22	H	1.47085	3.72295	-0.82483
23	N	1.52656	-1.69219	-0.03046
24	N	2.77006	-1.65017	-0.04275
25	N	3.89959	-1.75465	-0.05808
26	C	-2.80093	-1.52486	0.36738

Table S5 Cartesian coordinates of optimized structure of **3-A**.



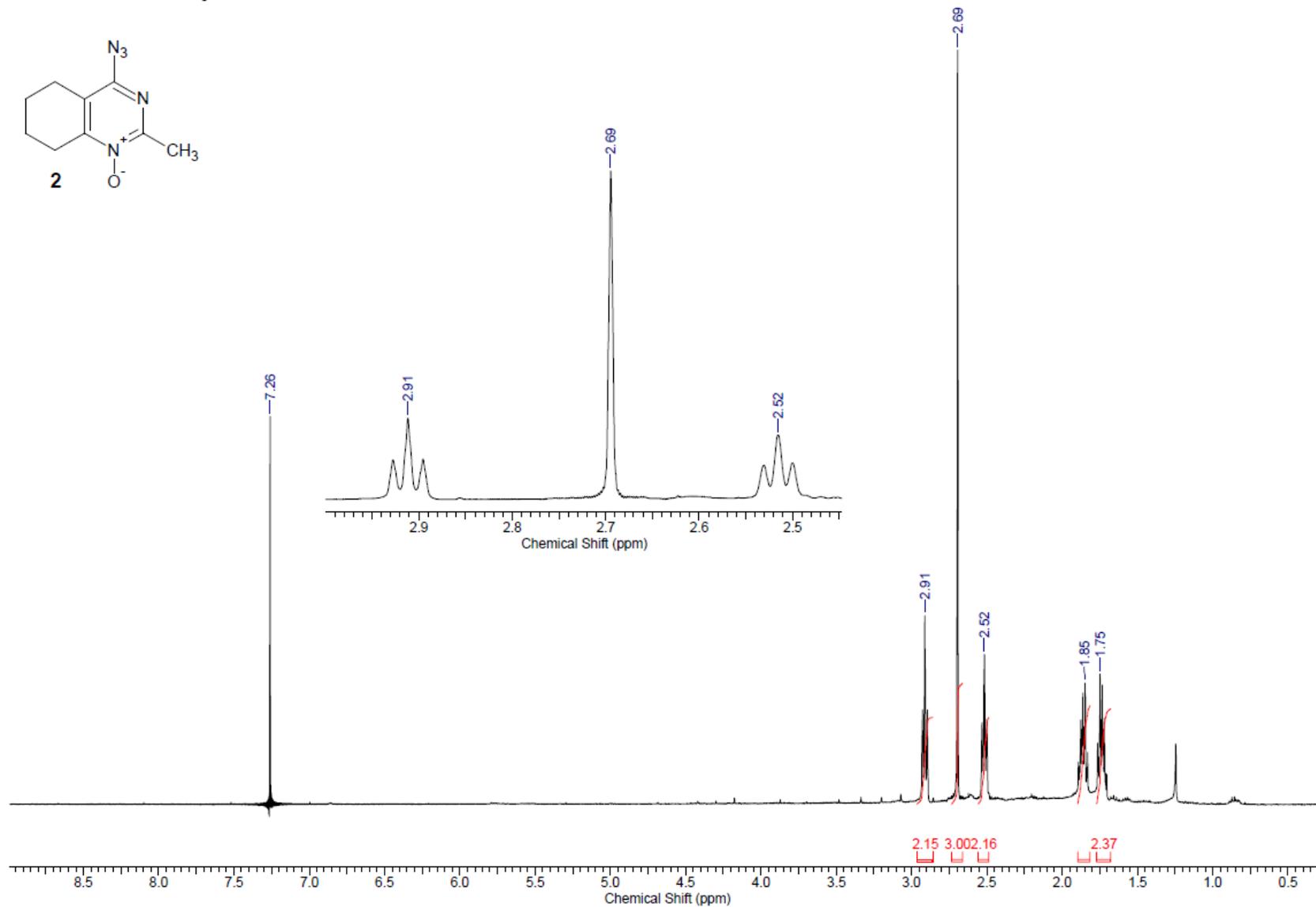
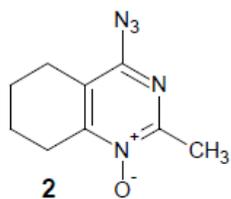
Number of imaginary frequency: 0

Sum of electronic and zero-point Energies= -622.77825364 (Hartree)

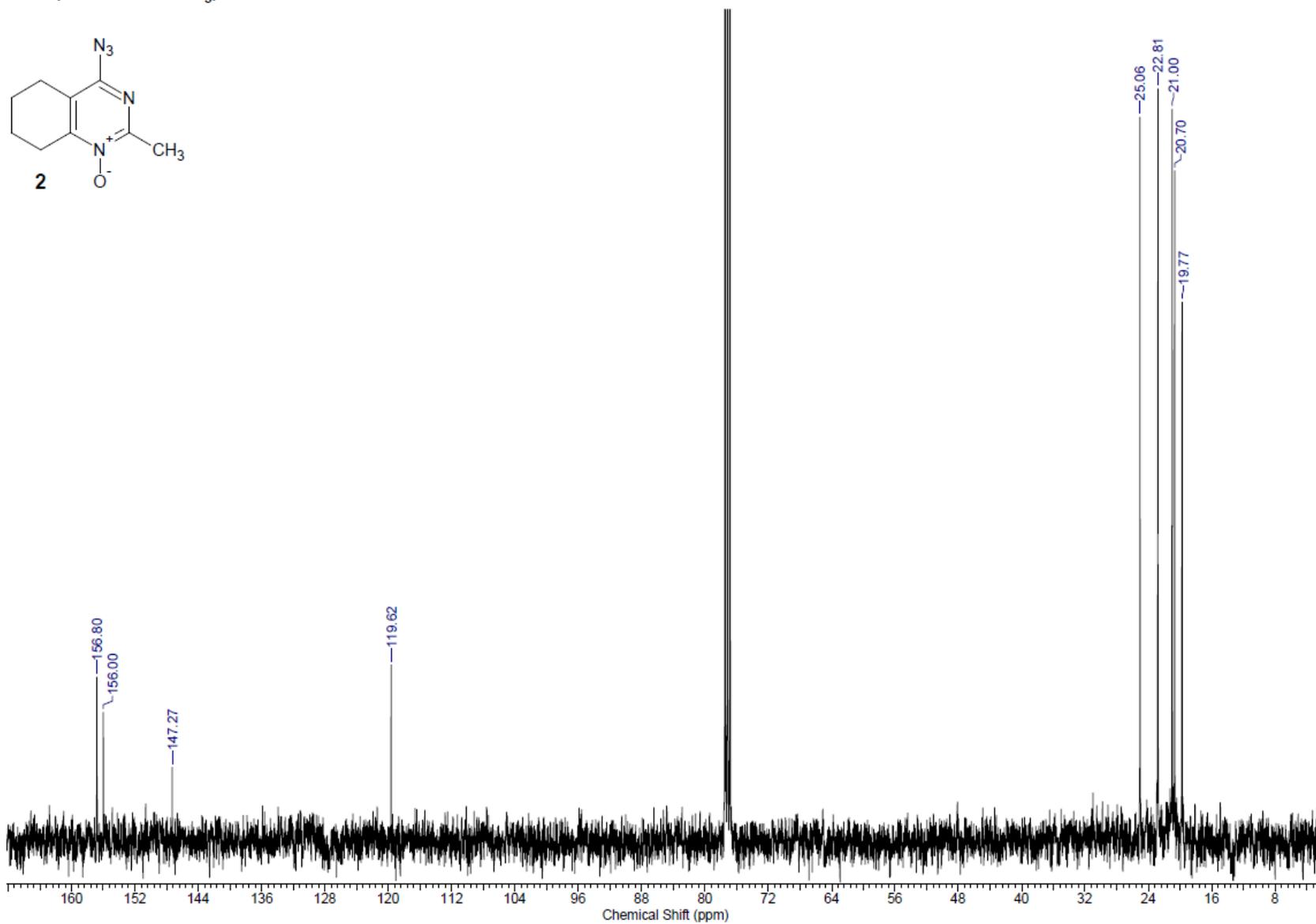
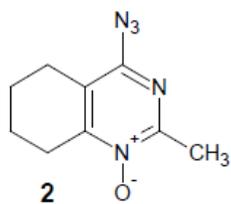
Final Gibbs free enthalpy = -622.82446751 (Hartree)

Center Number	Atom	Coordinates (Angstroms)		
		X	Y	Z
1	C	-3.16386	-0.84945	0.37331
2	C	-1.83623	-1.50619	-0.02461
3	C	-0.69750	-0.51803	-0.01172
4	C	-0.86938	0.85354	0.01059
5	C	-2.24342	1.47404	0.02532
6	C	-3.34722	0.48229	-0.36295
7	H	-3.99022	-1.53333	0.15124
8	H	-1.59517	-2.34334	0.64090
9	C	0.64578	-0.96023	-0.02579
10	H	-2.42613	1.86627	1.03675
11	H	-3.31478	0.30462	-1.44659
12	C	1.41451	1.32973	0.02711
13	H	-1.91630	-1.93403	-1.03437
14	H	-3.17353	-0.67061	1.45703
15	H	-4.32662	0.91836	-0.13794
16	H	-2.23675	2.34456	-0.64069
17	N	1.65018	-0.02801	-0.00717
18	N	0.18071	1.74705	0.03510
19	C	2.59298	2.24333	0.05290
20	H	3.21508	2.04060	0.93209
21	H	3.21801	2.08788	-0.83380
22	H	2.24182	3.27550	0.07995
23	N	1.22022	-2.16896	-0.05314
24	N	2.55177	-1.94224	-0.04899
25	N	2.85127	-0.67848	-0.02334
26	C	-3.16386	-0.84945	0.37331

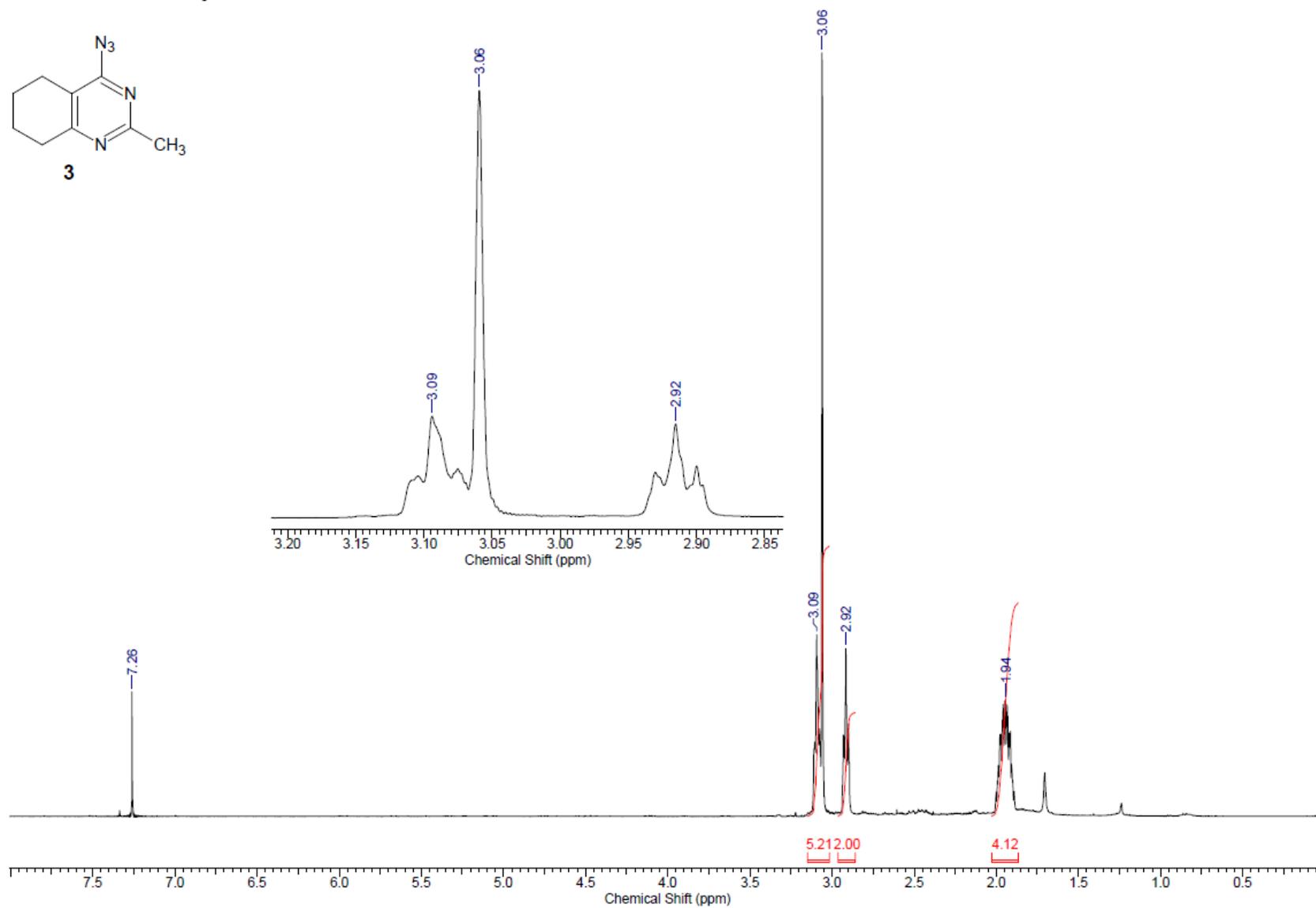
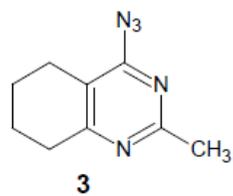
¹H NMR (400 MHz, CDCl₃)



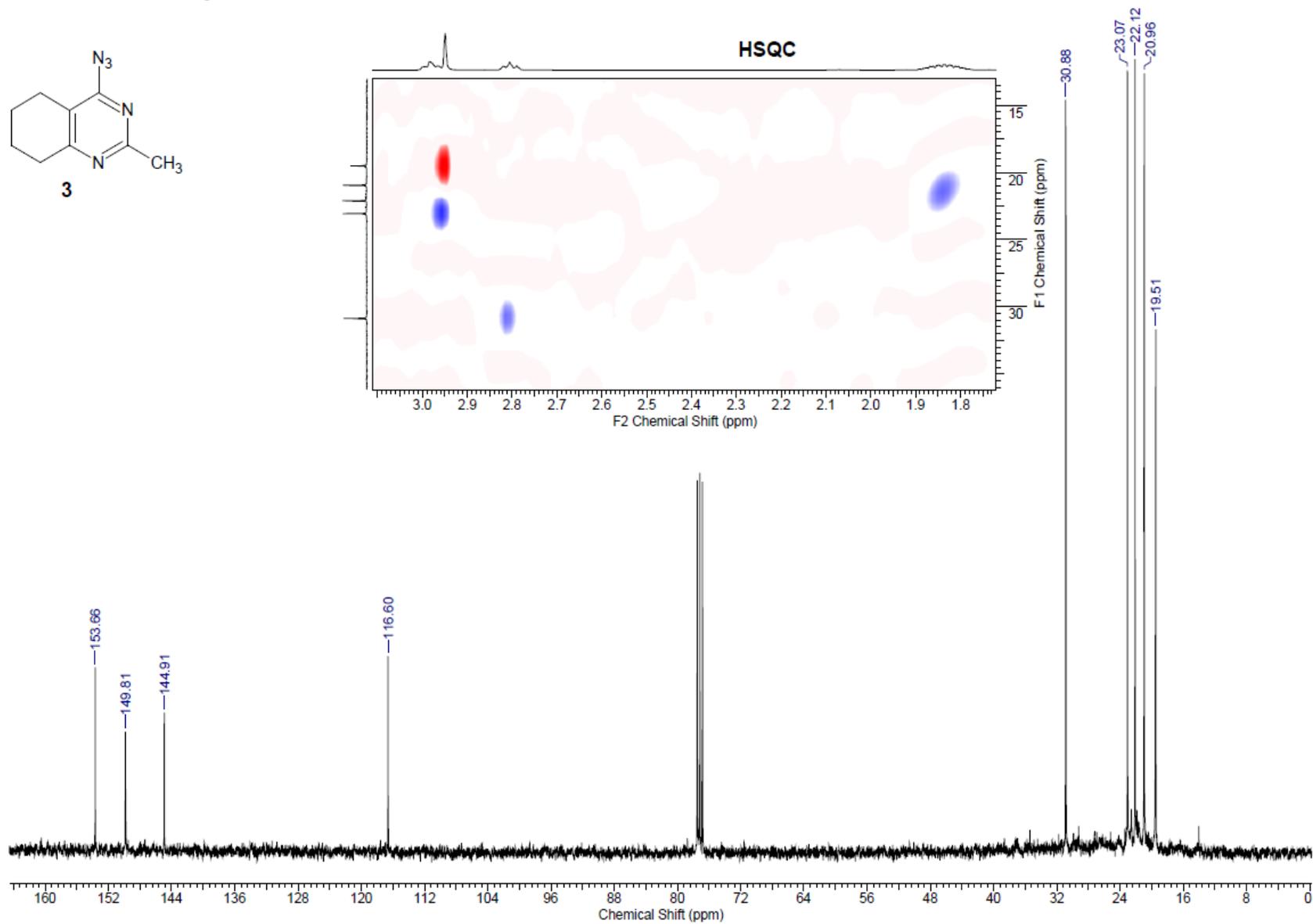
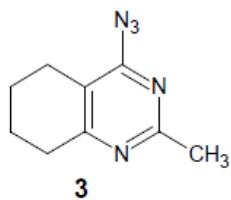
^{13}C NMR (101 MHz, CDCl_3)



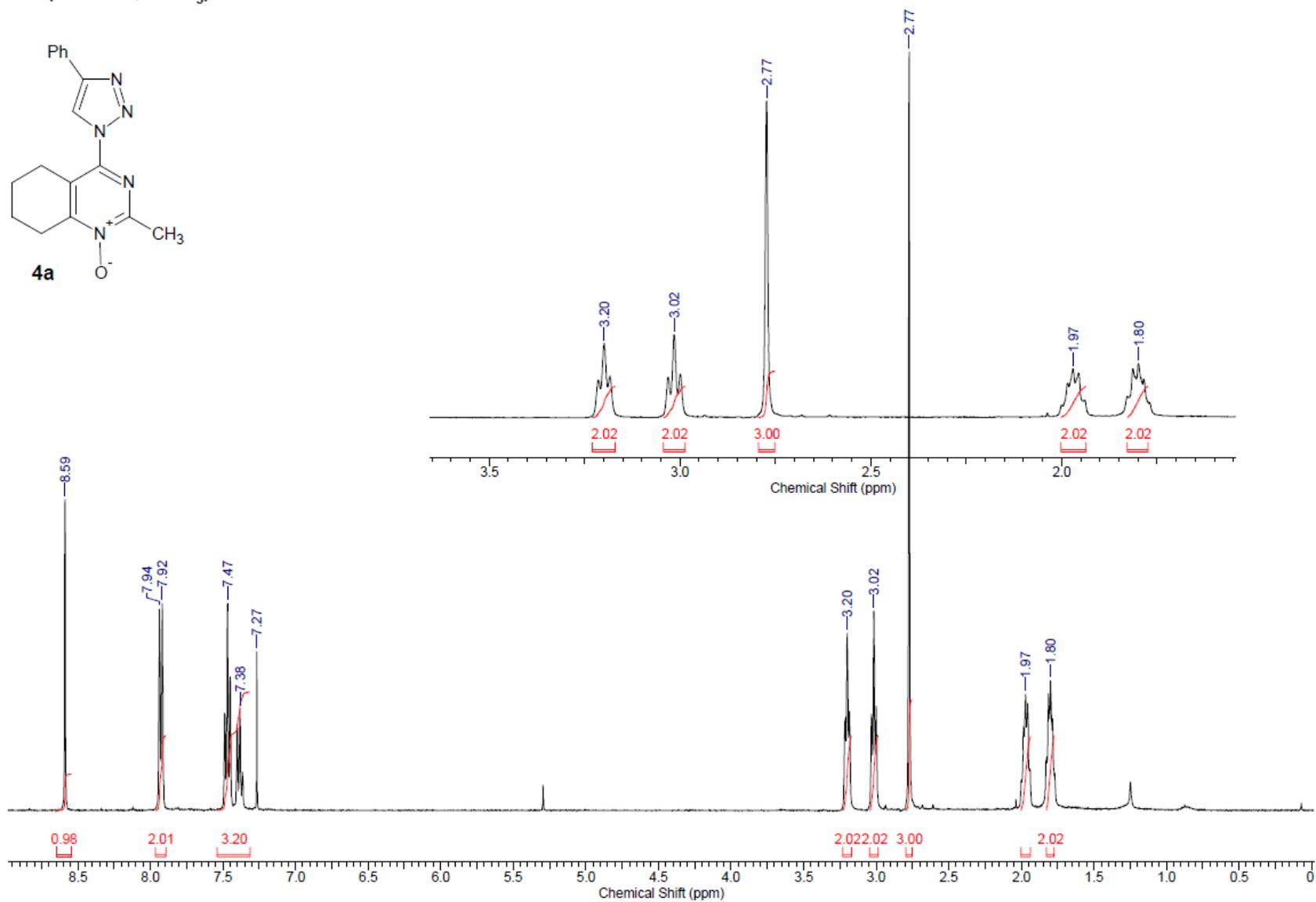
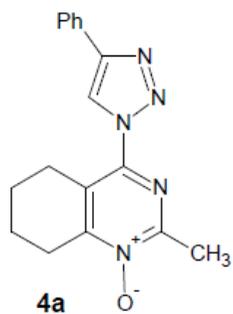
¹H NMR (400 MHz, CDCl₃)



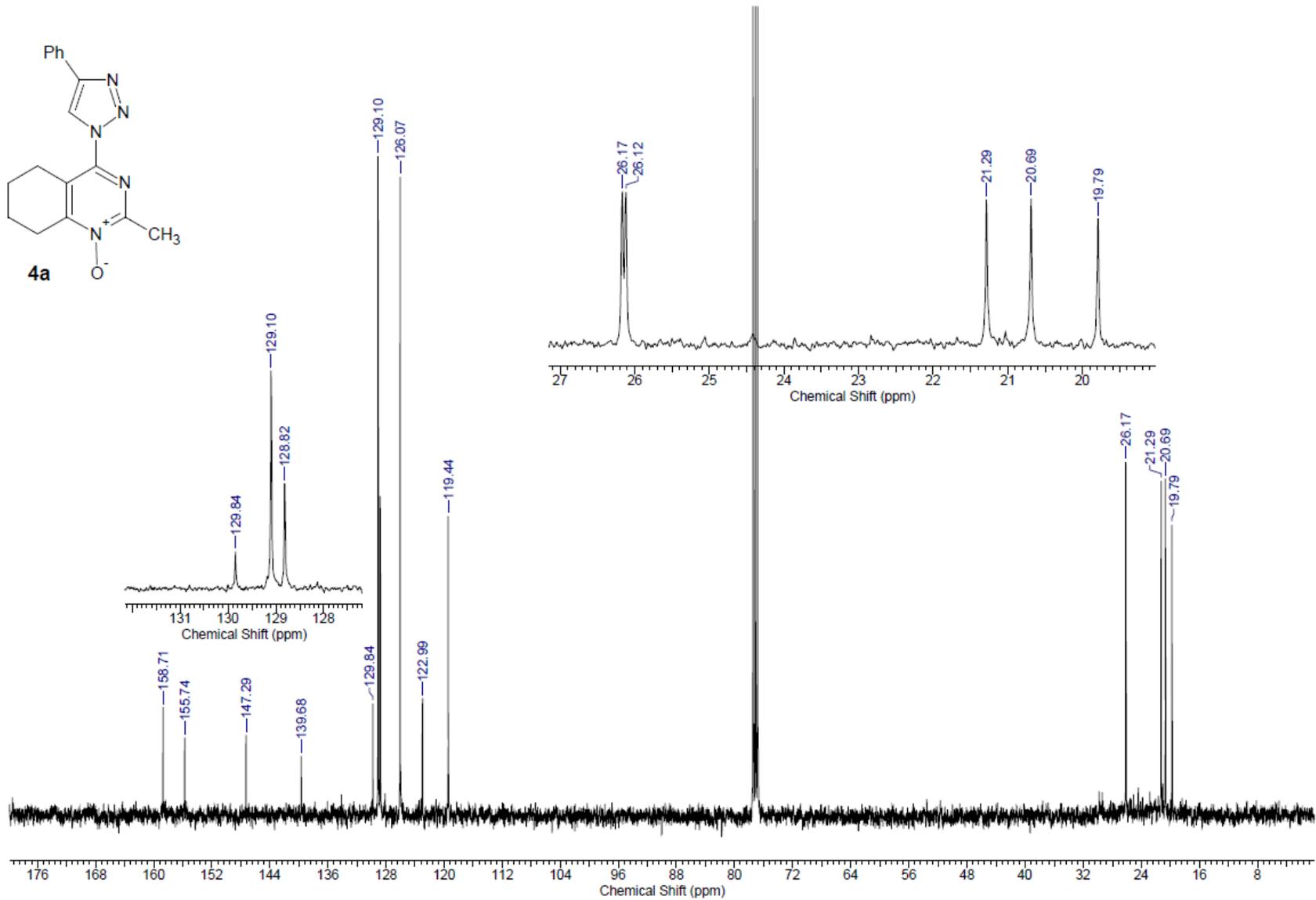
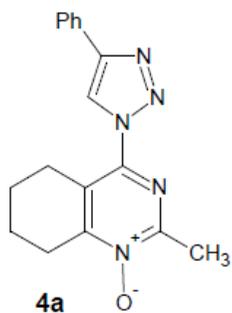
¹³C NMR (101 MHz, CDCl₃)

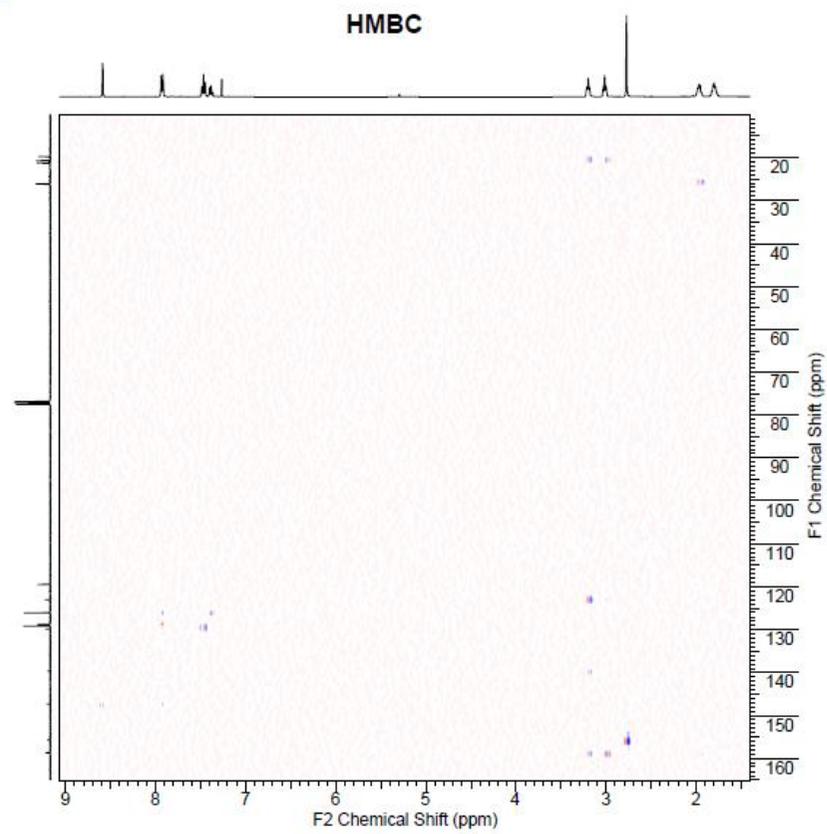
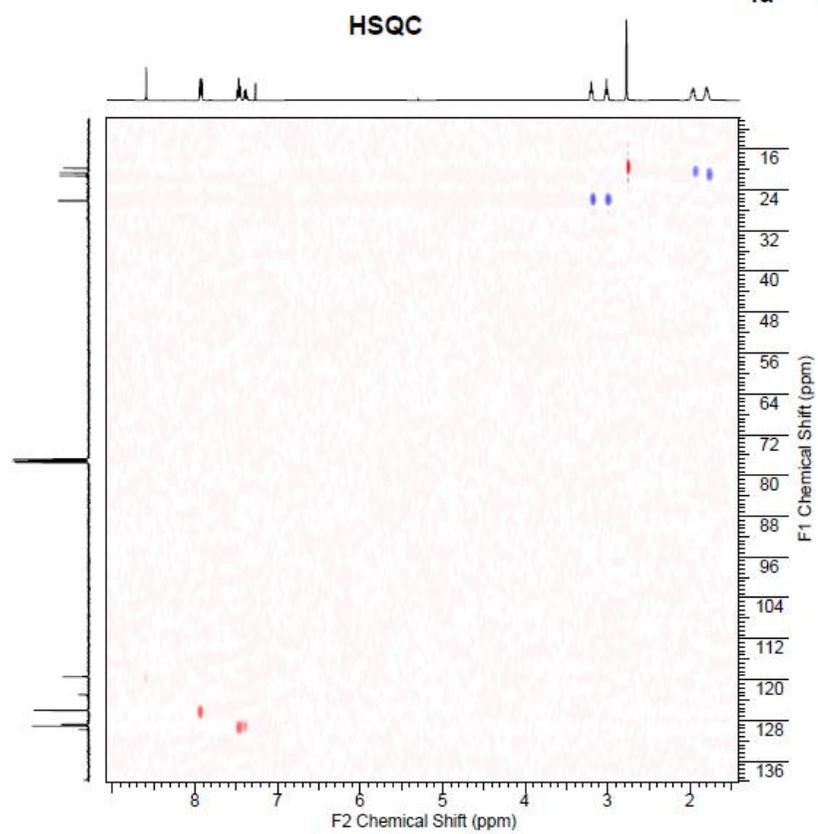
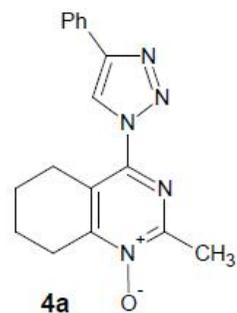


¹H NMR (400 MHz, CDCl₃)

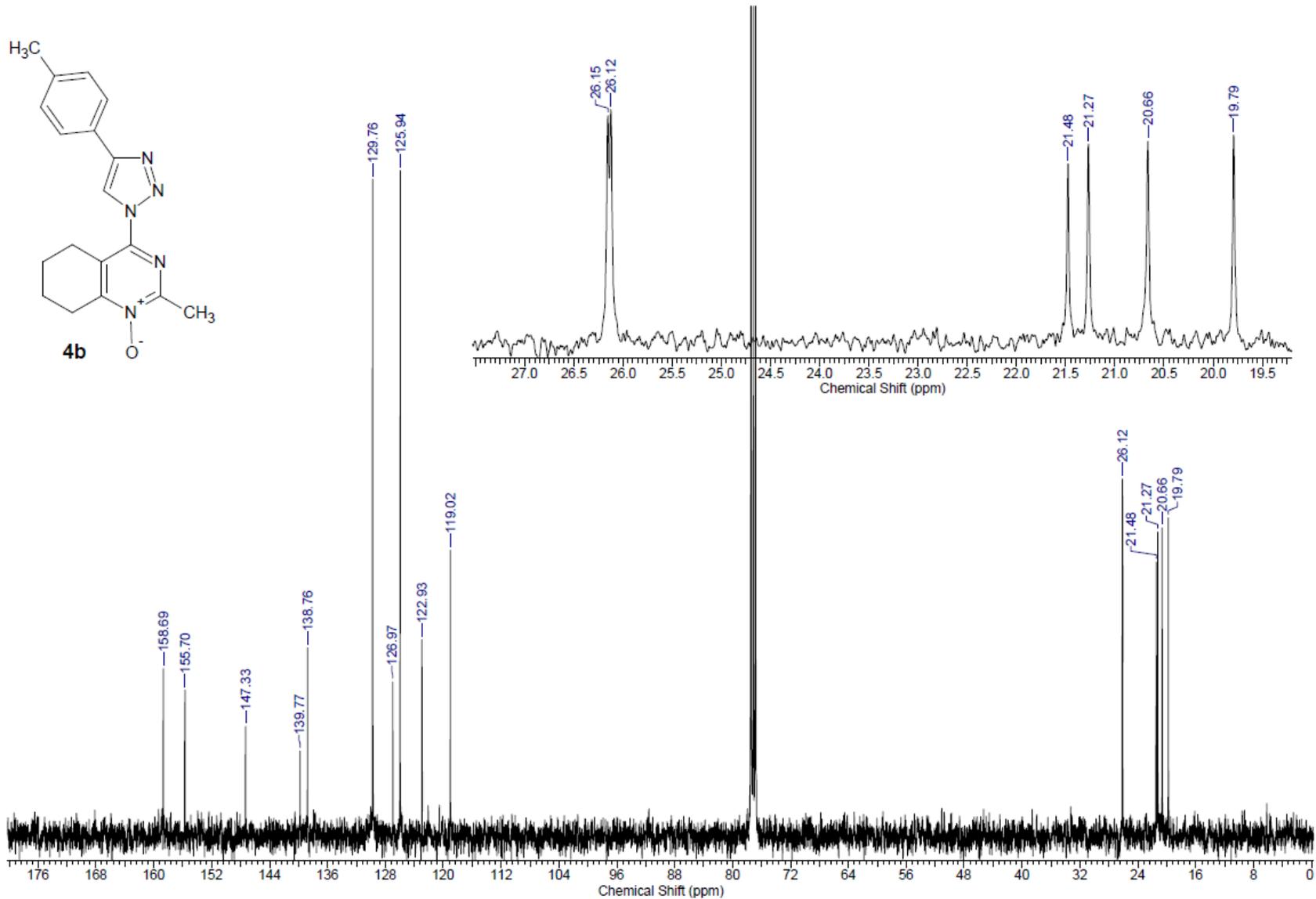


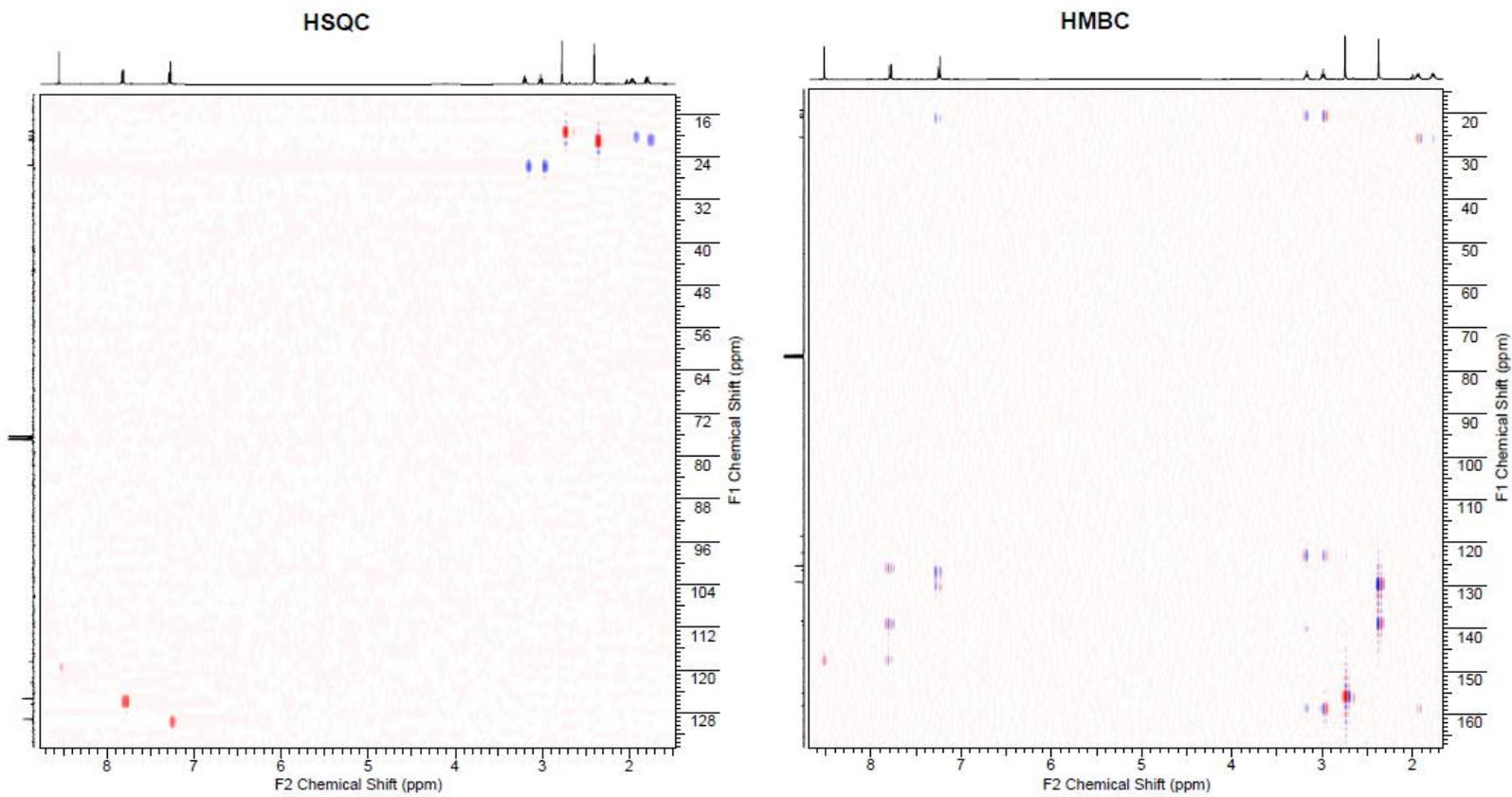
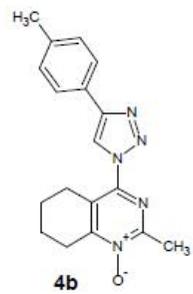
¹³C NMR (101 MHz, CDCl₃)



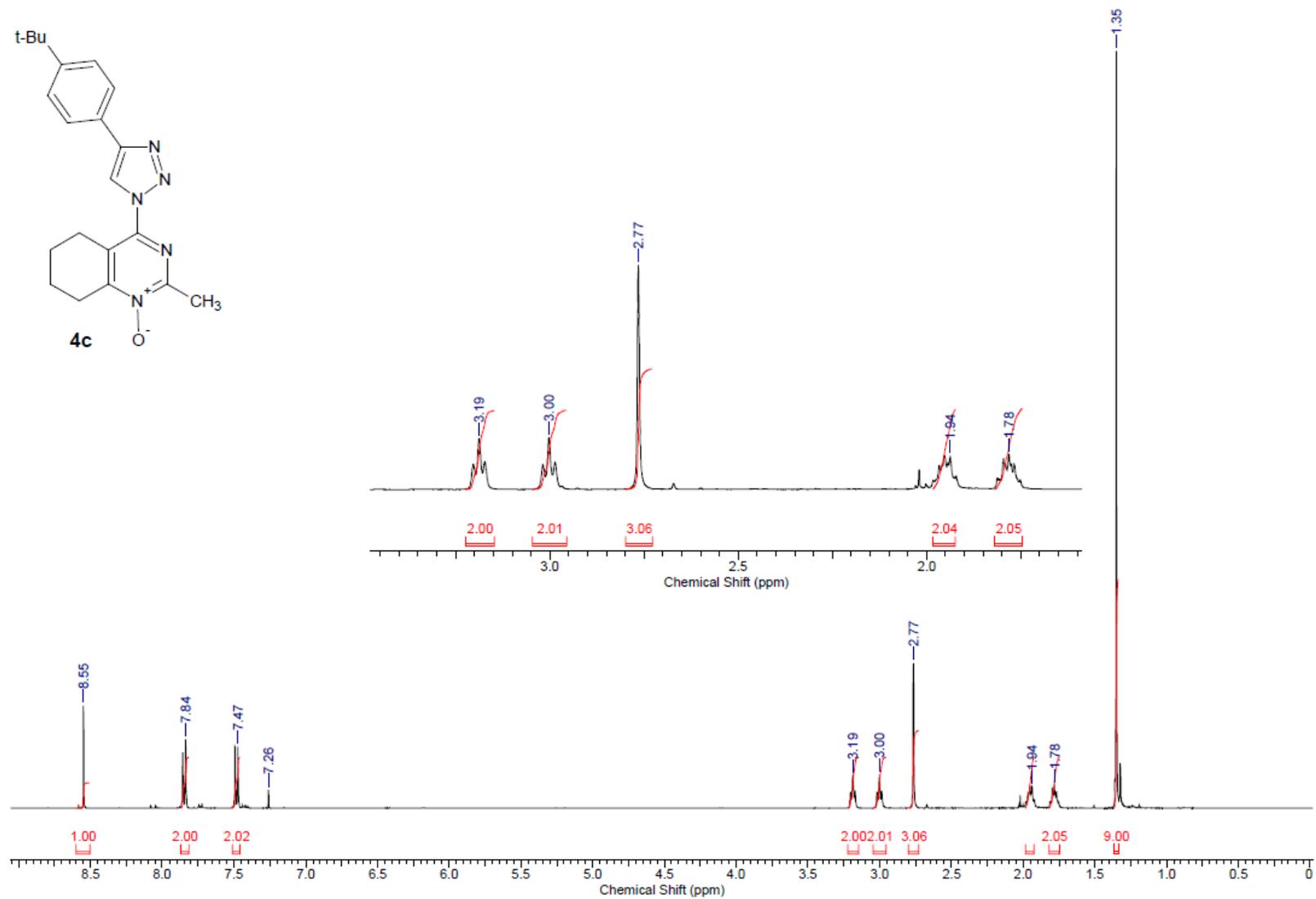
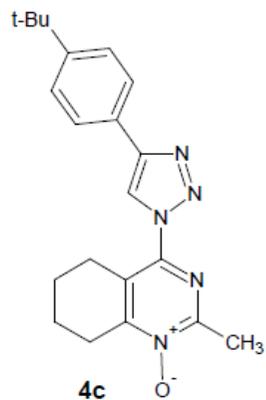


¹³C NMR (101 MHz, CDCl₃)

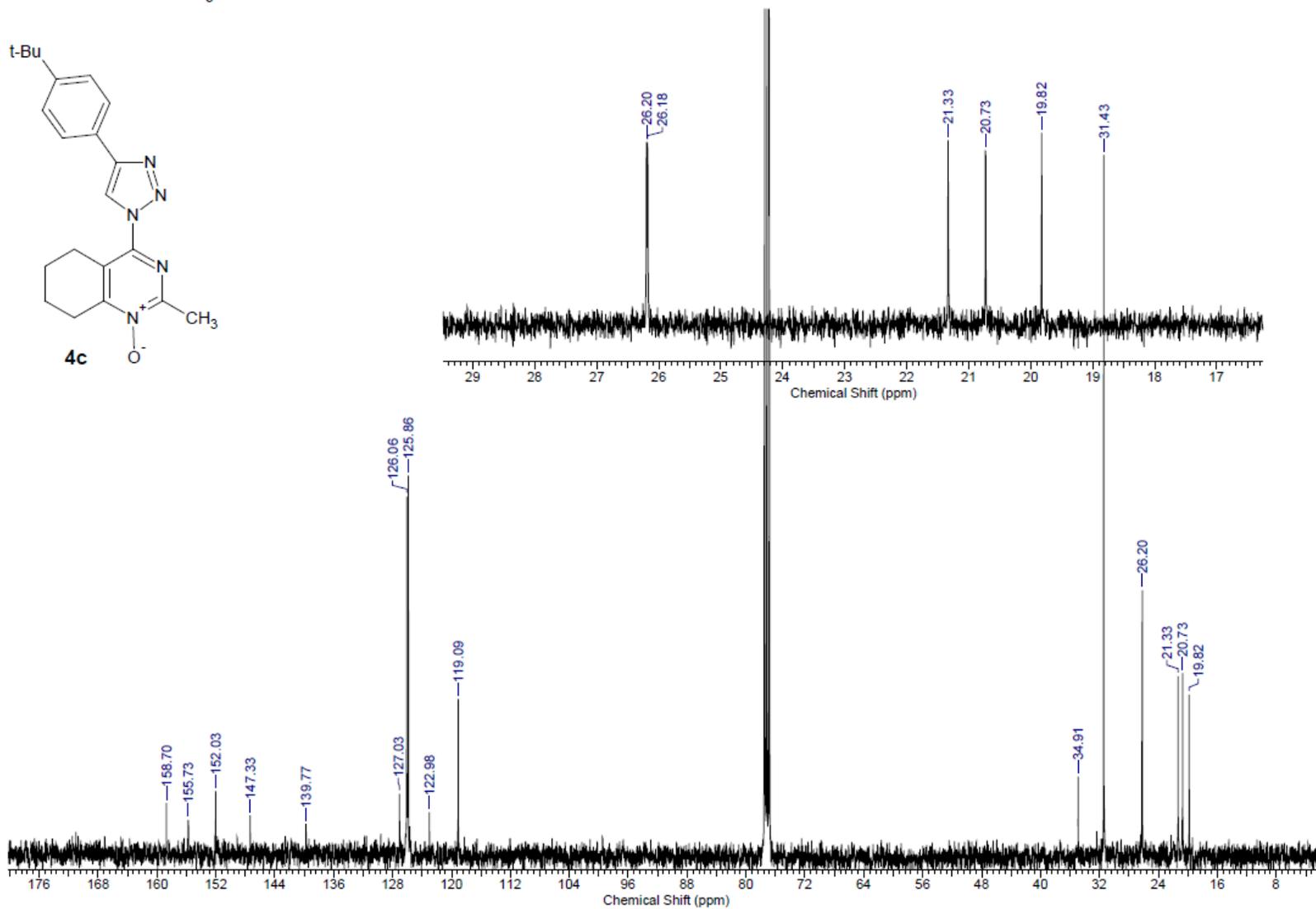
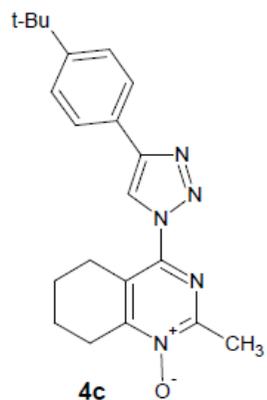




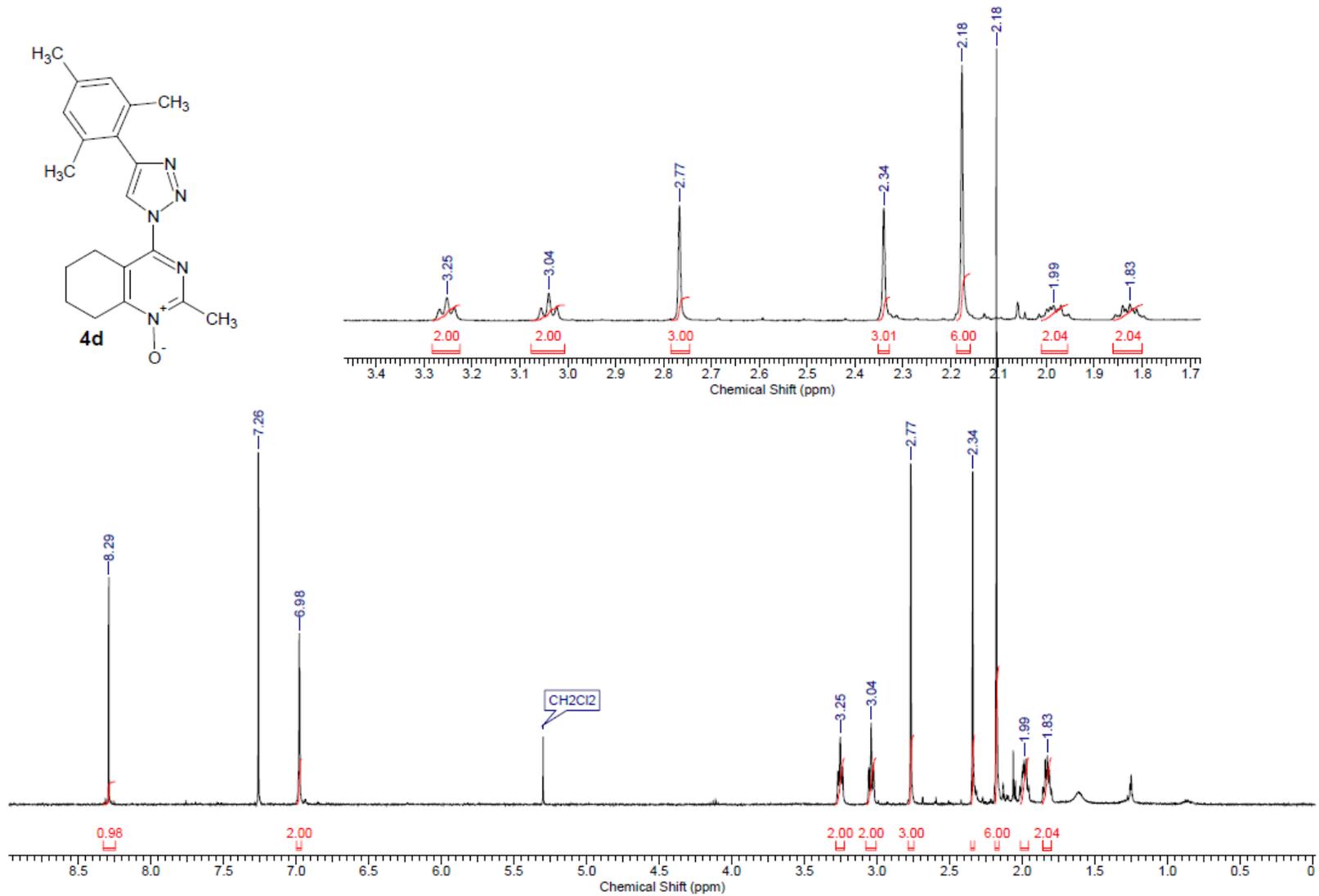
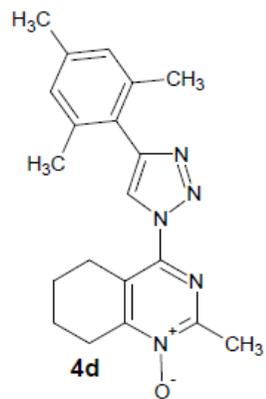
¹H NMR (400 MHz, CDCl₃)



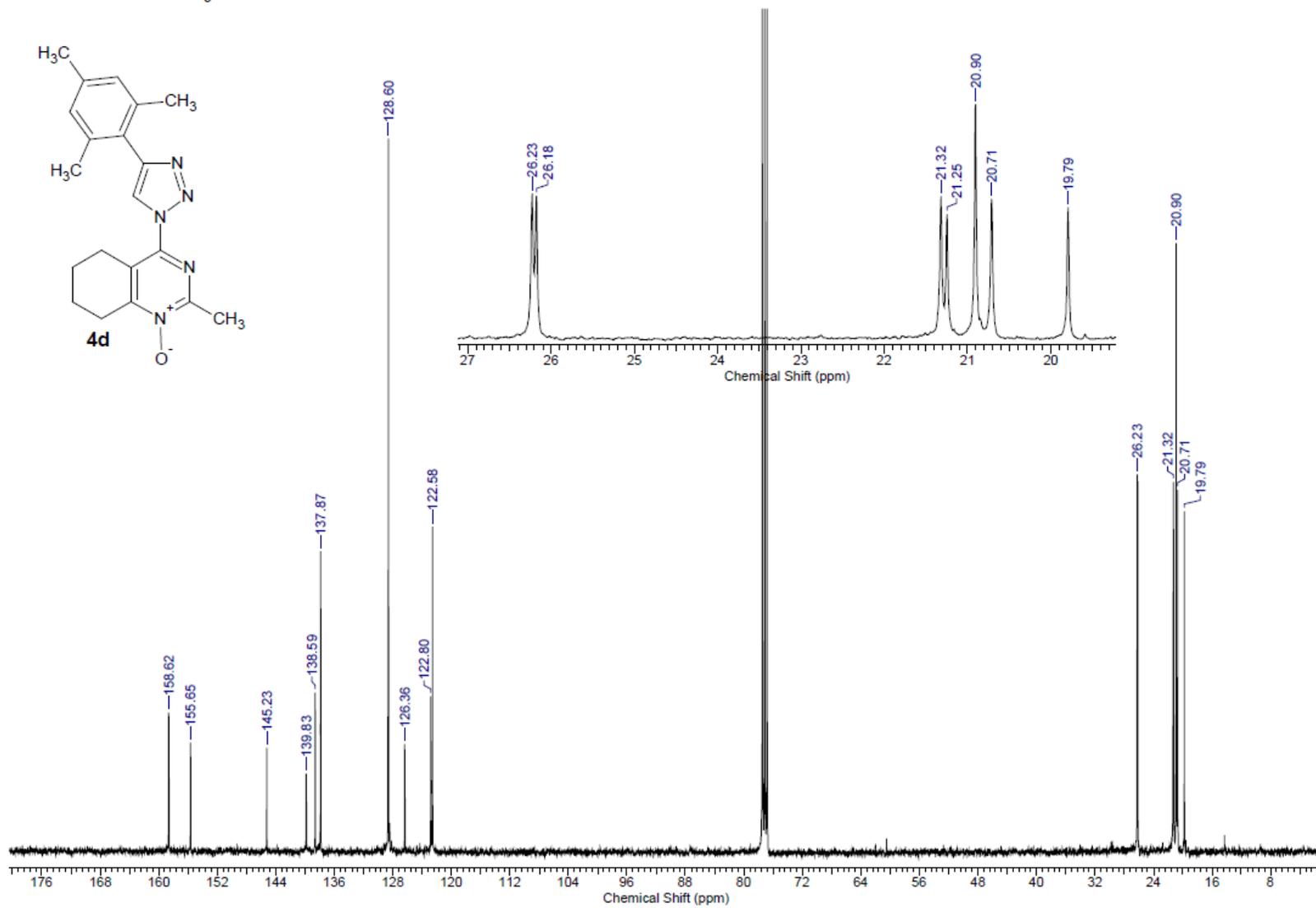
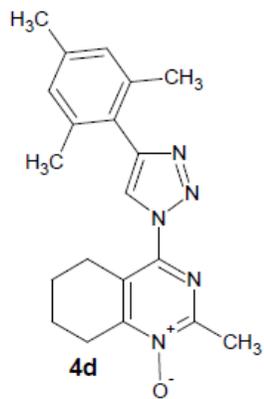
¹³C NMR (101 MHz, CDCl₃)



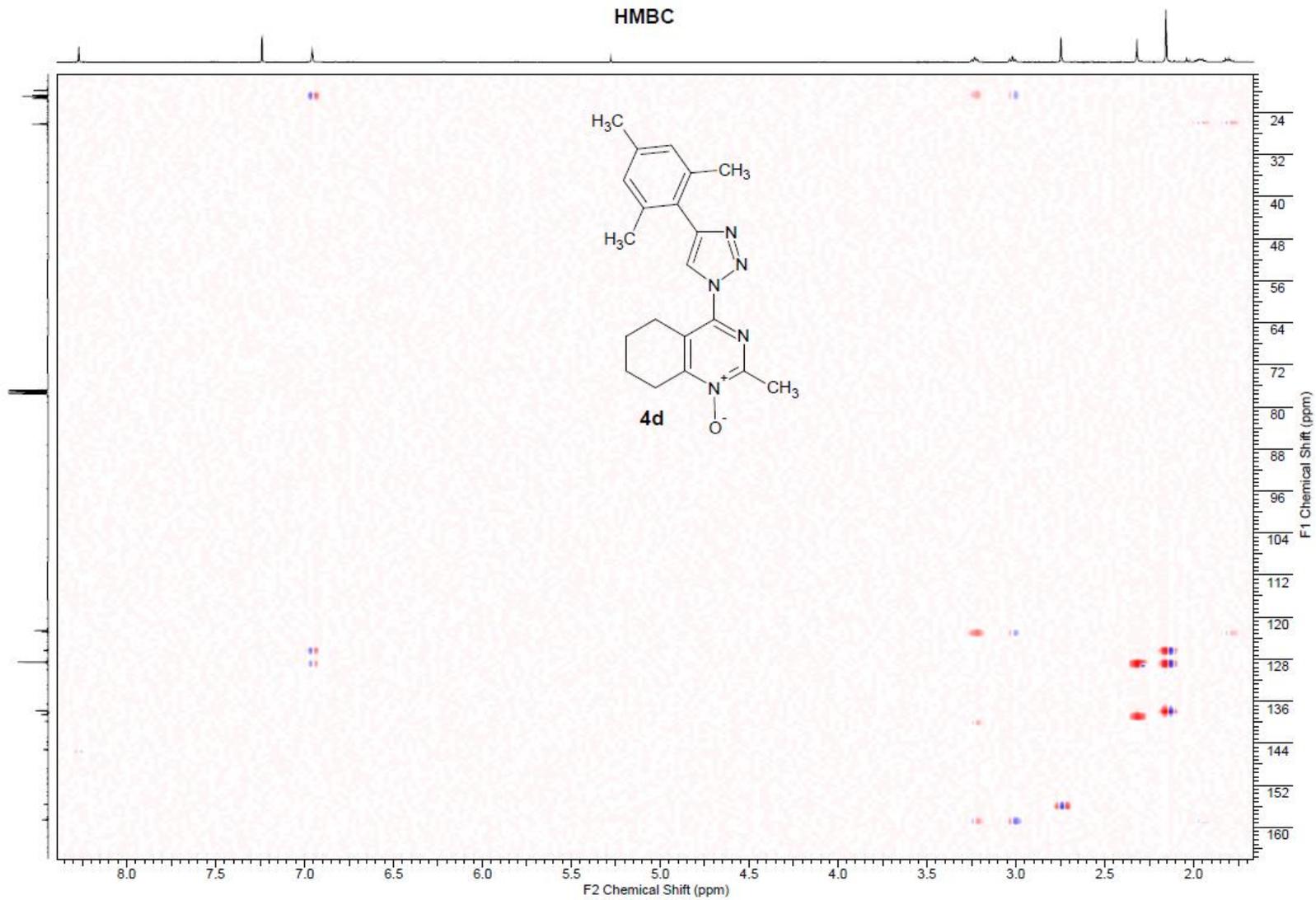
^1H NMR (400 MHz, CDCl_3)



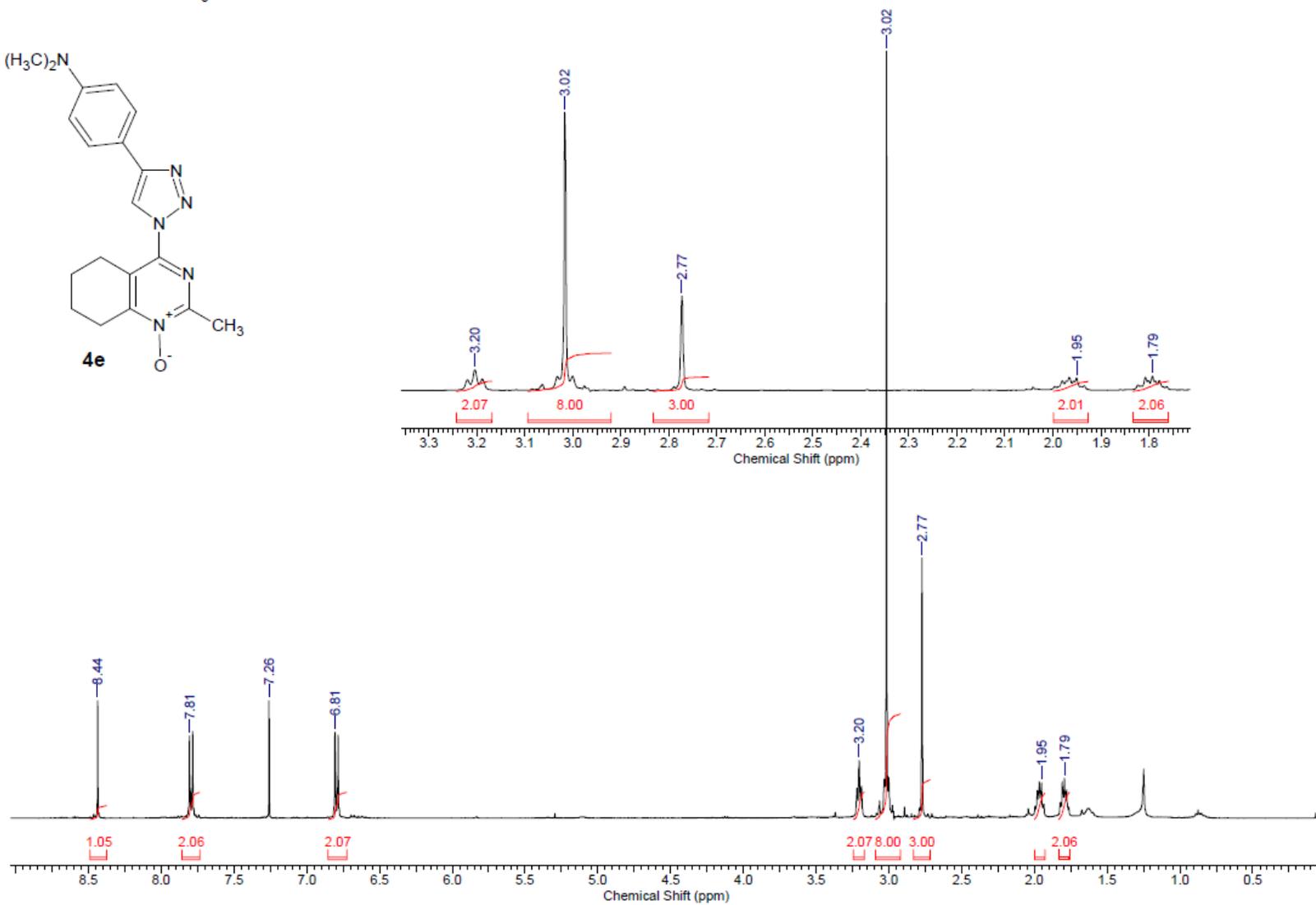
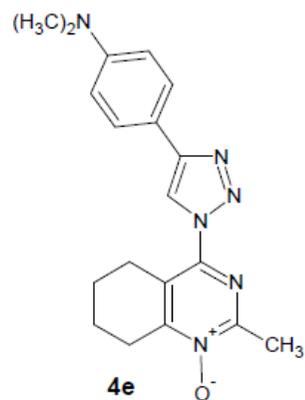
¹³C NMR (101 MHz, CDCl₃)



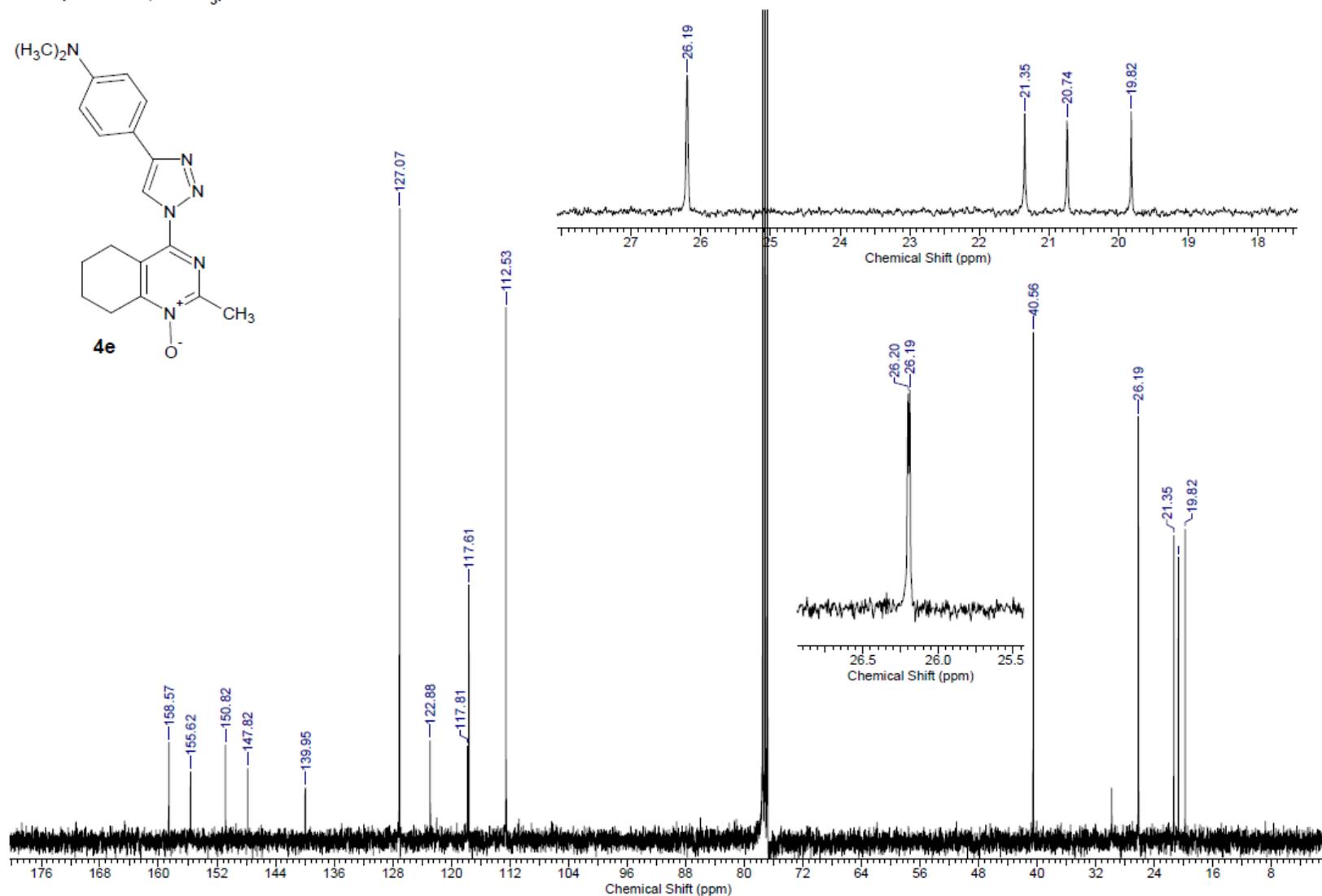
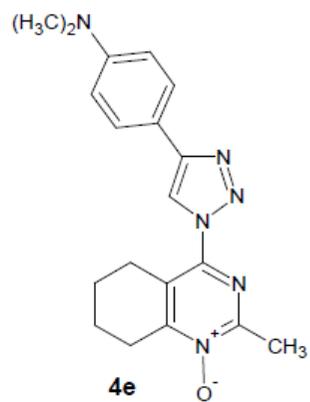
HMBC

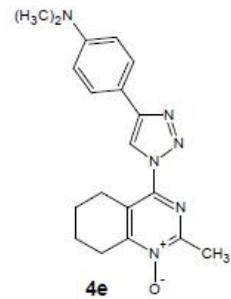


¹H NMR (400 MHz, CDCl₃)

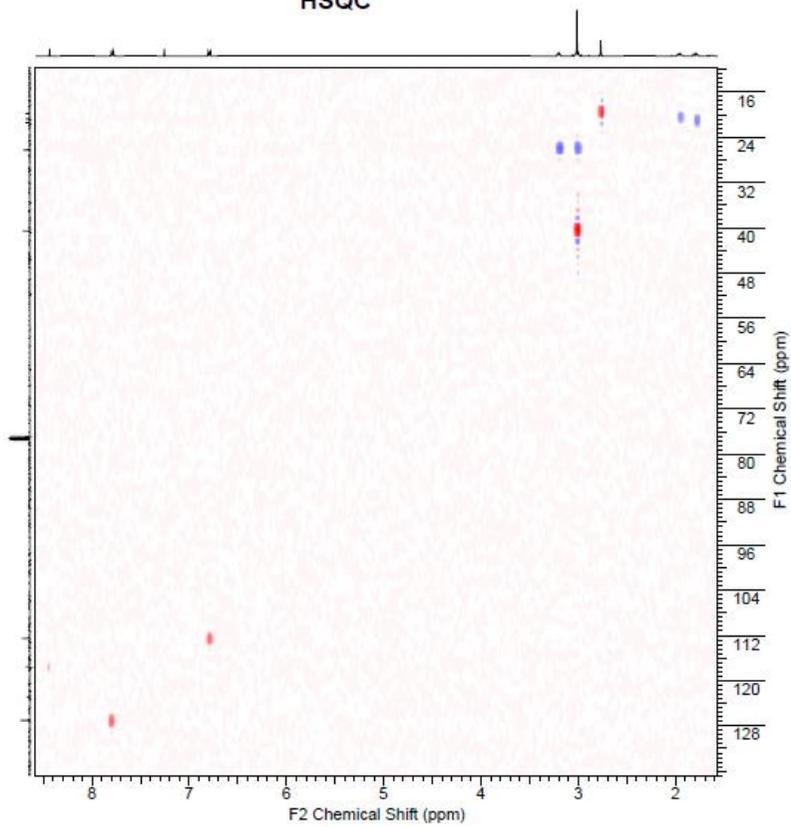


¹³C NMR (101 MHz, CDCl₃)

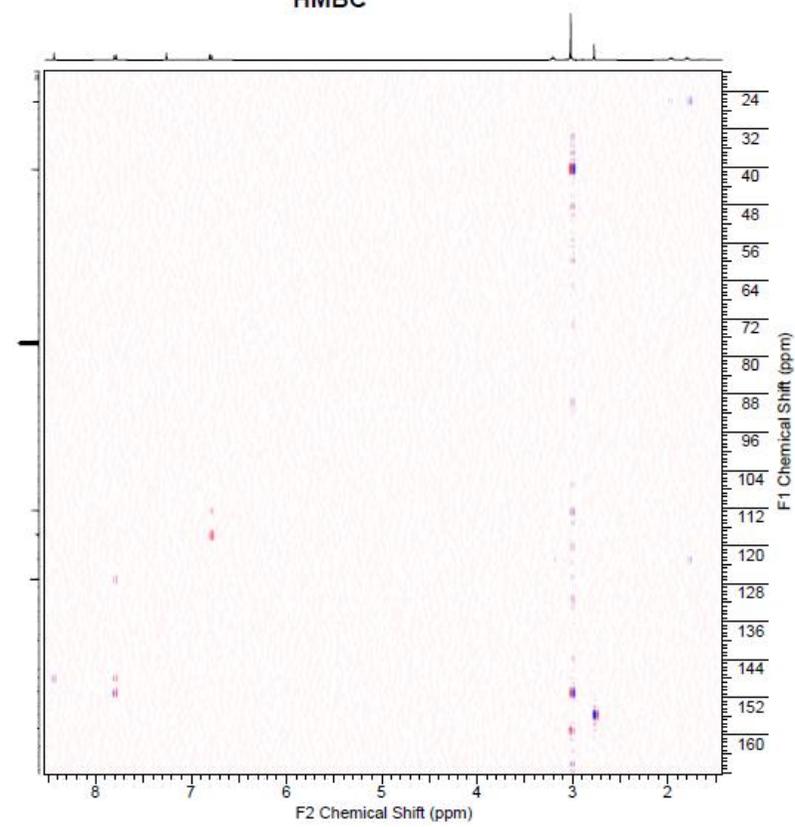




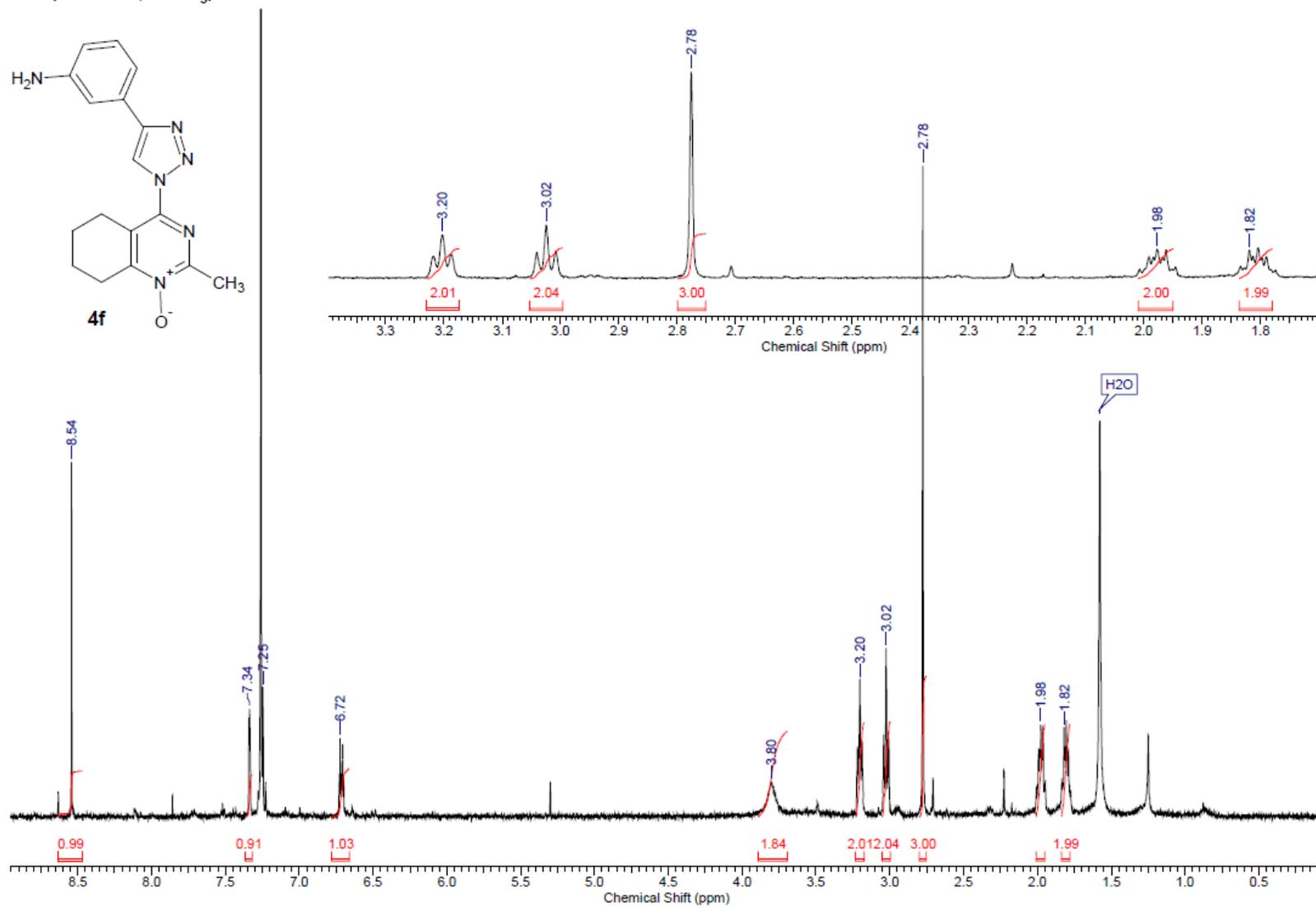
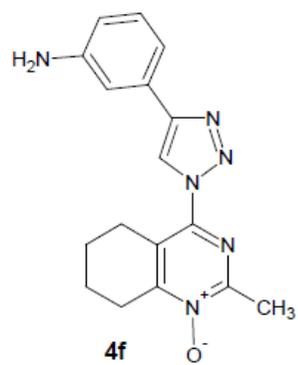
HSQC



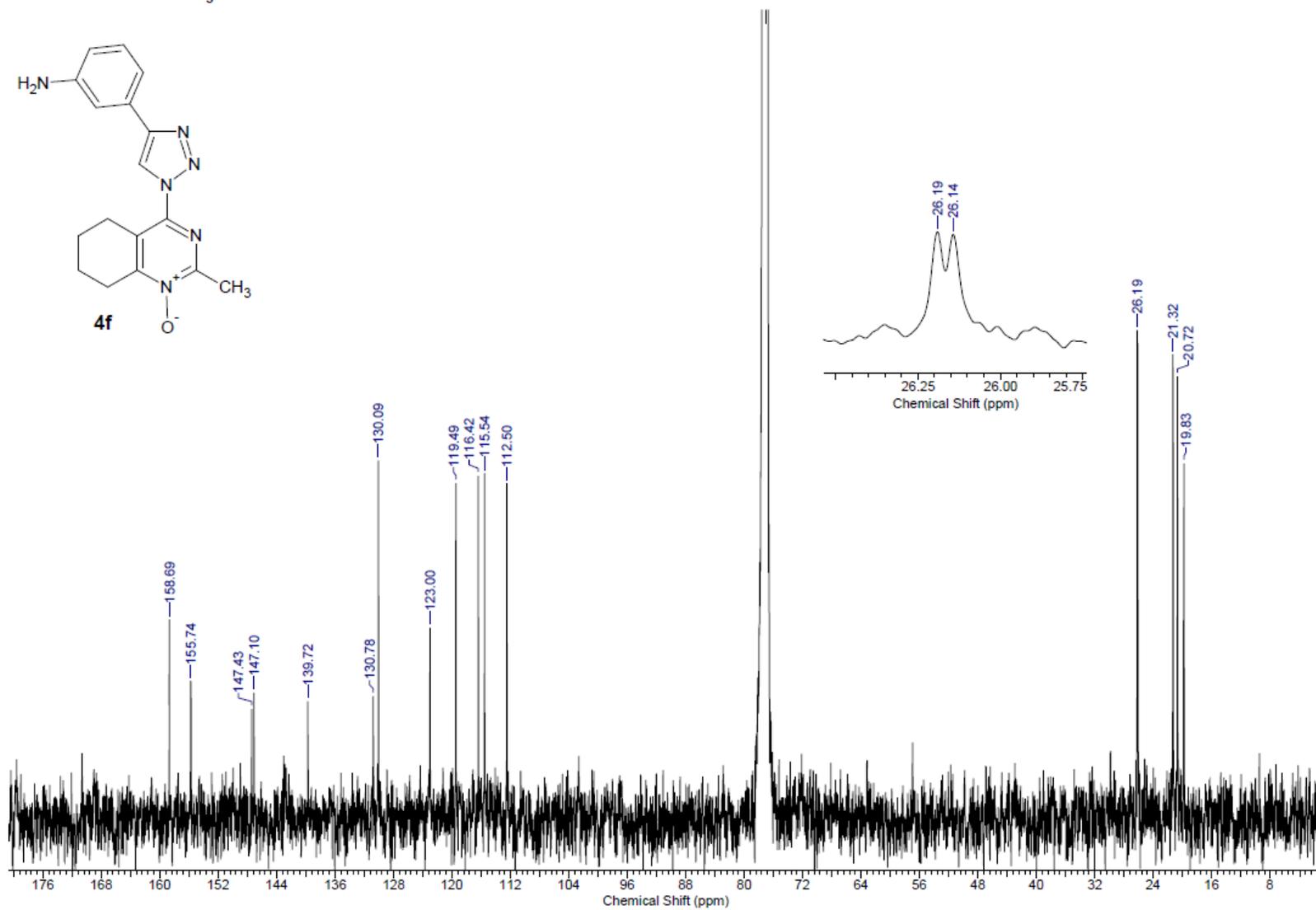
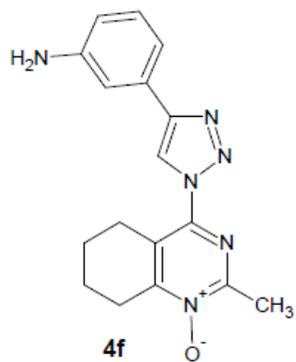
HMBC



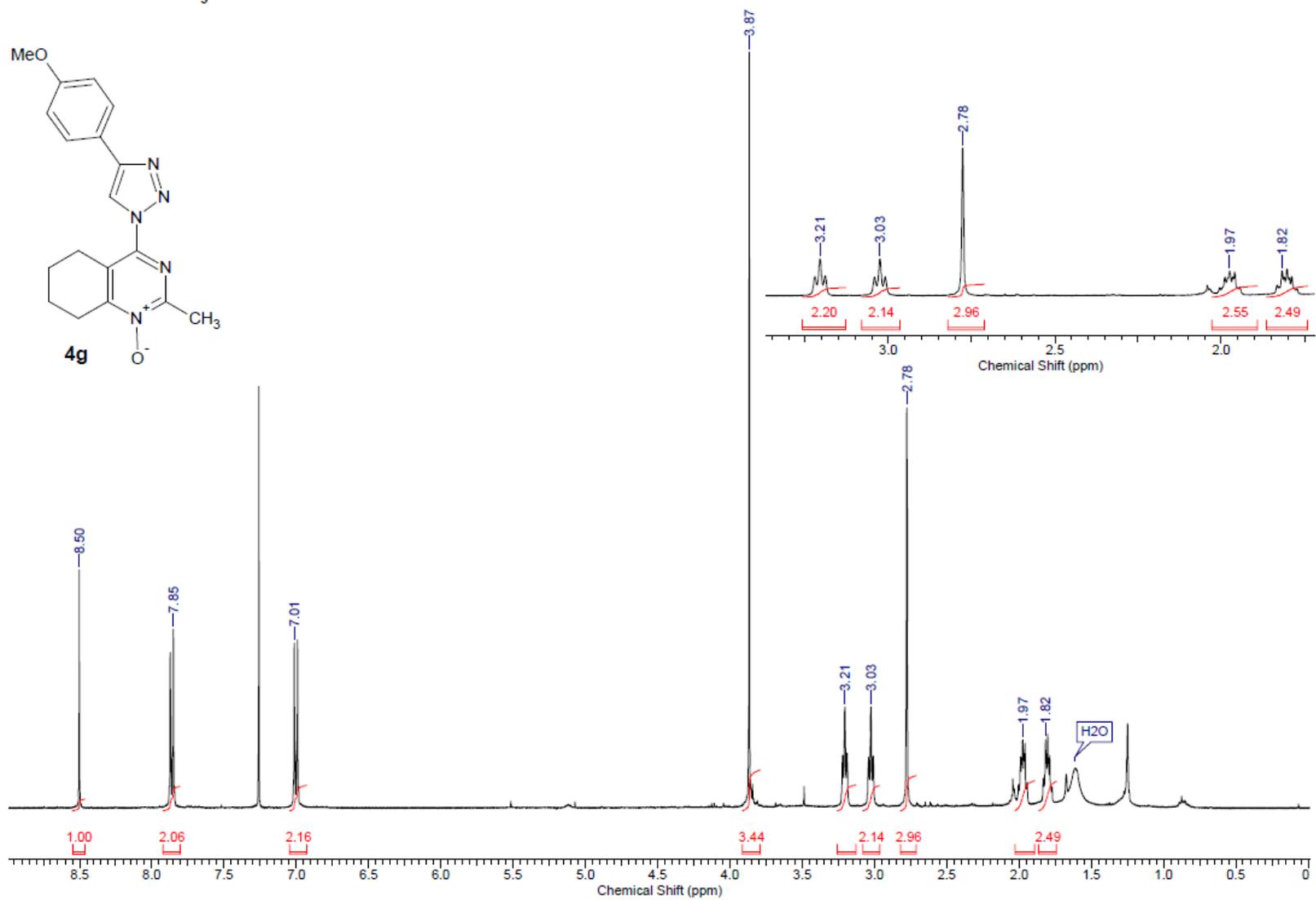
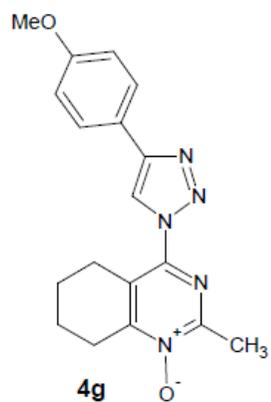
¹H NMR (400 MHz, CDCl₃)



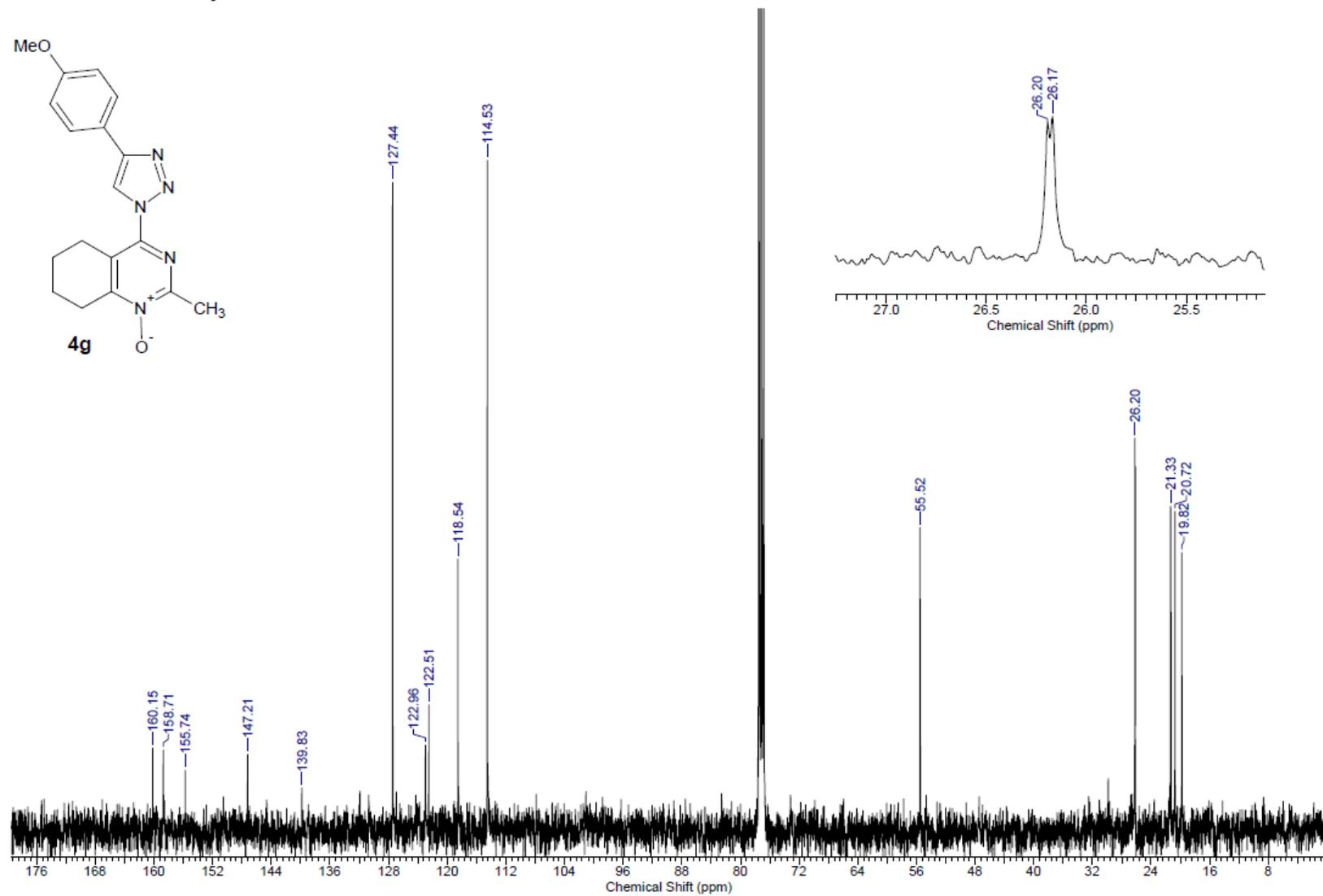
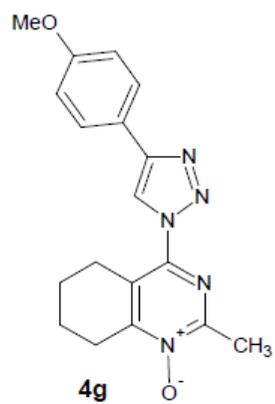
¹³C NMR (101 MHz, CDCl₃)



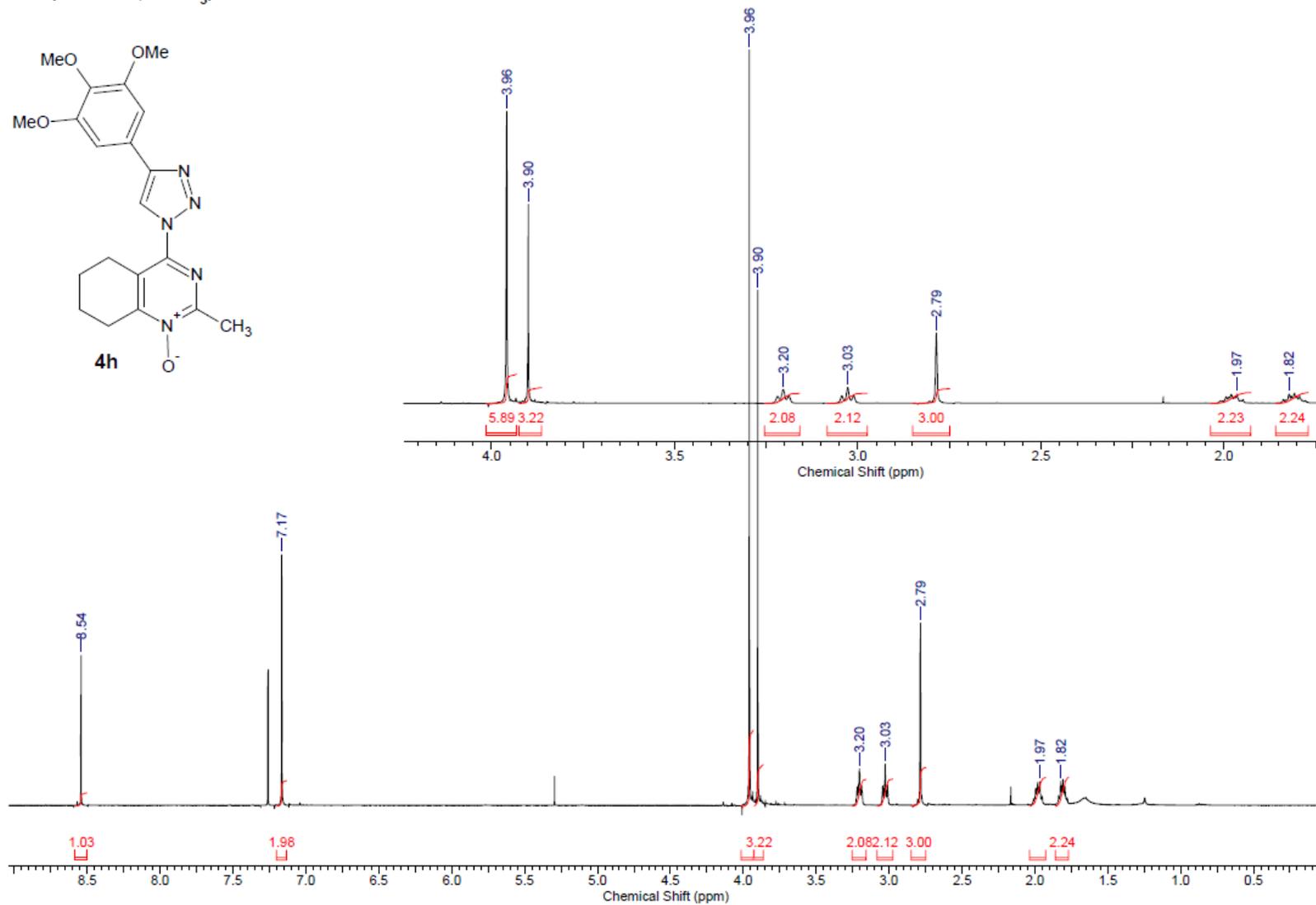
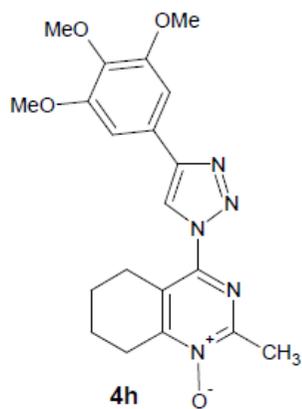
¹H NMR (400 MHz, CDCl₃)



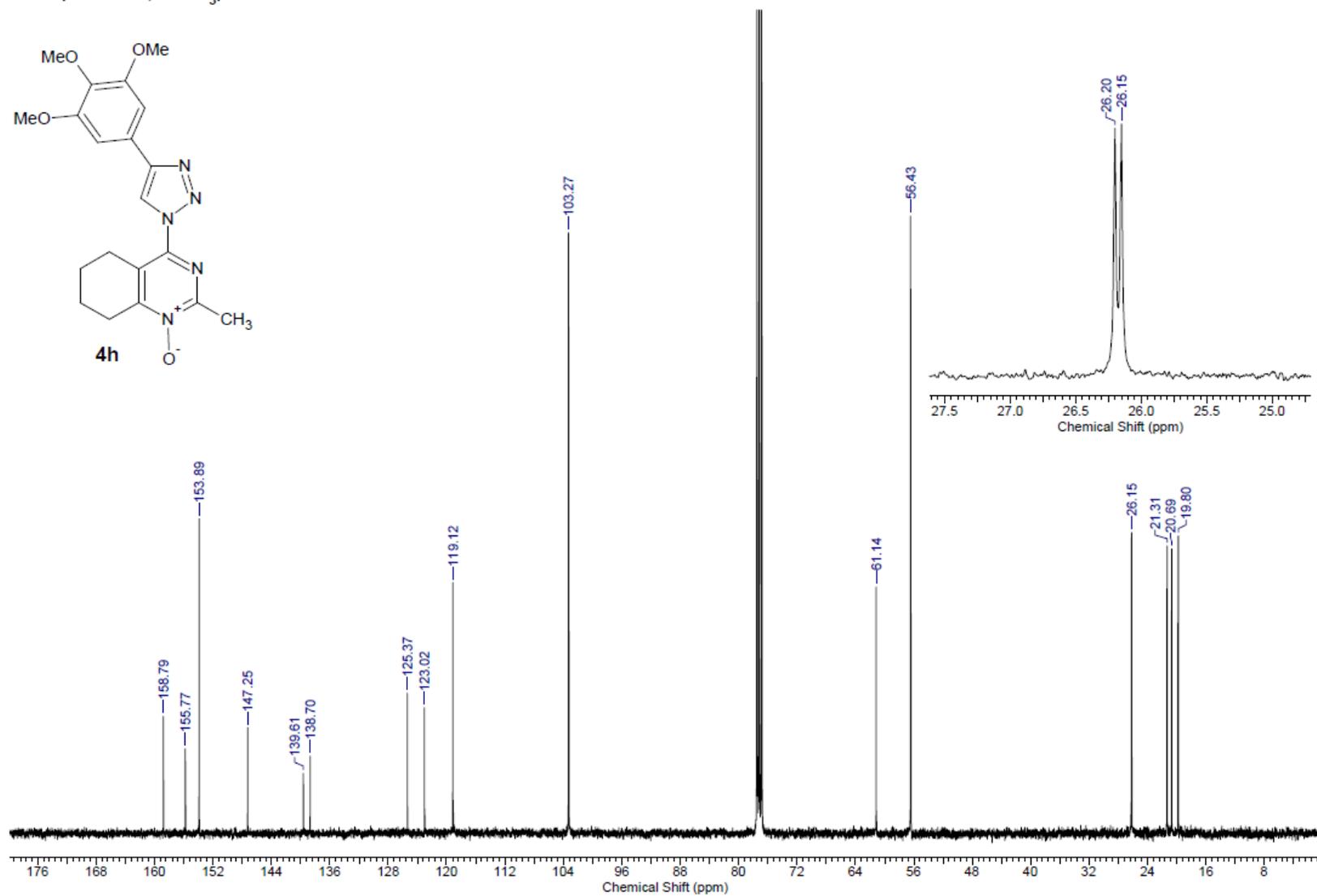
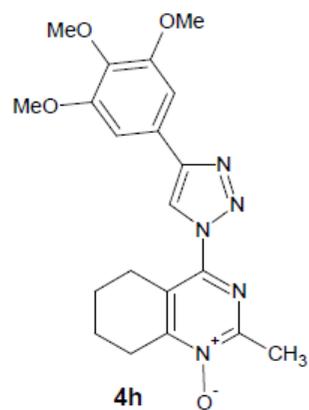
^{13}C NMR (101 MHz, CDCl_3)

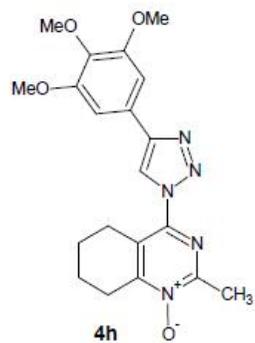


¹H NMR (400 MHz, CDCl₃)

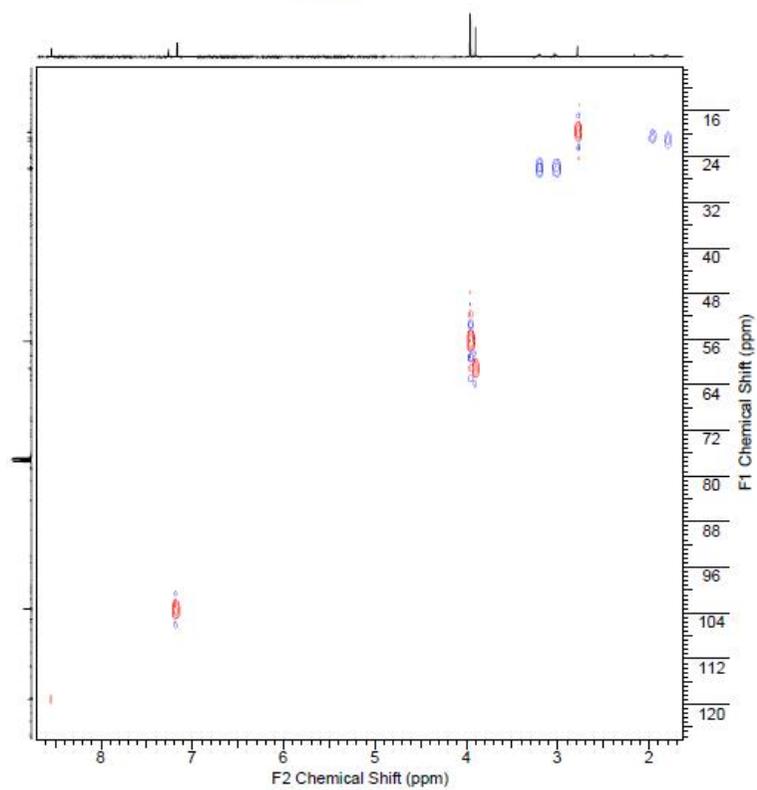


¹³C NMR (101 MHz, CDCl₃)

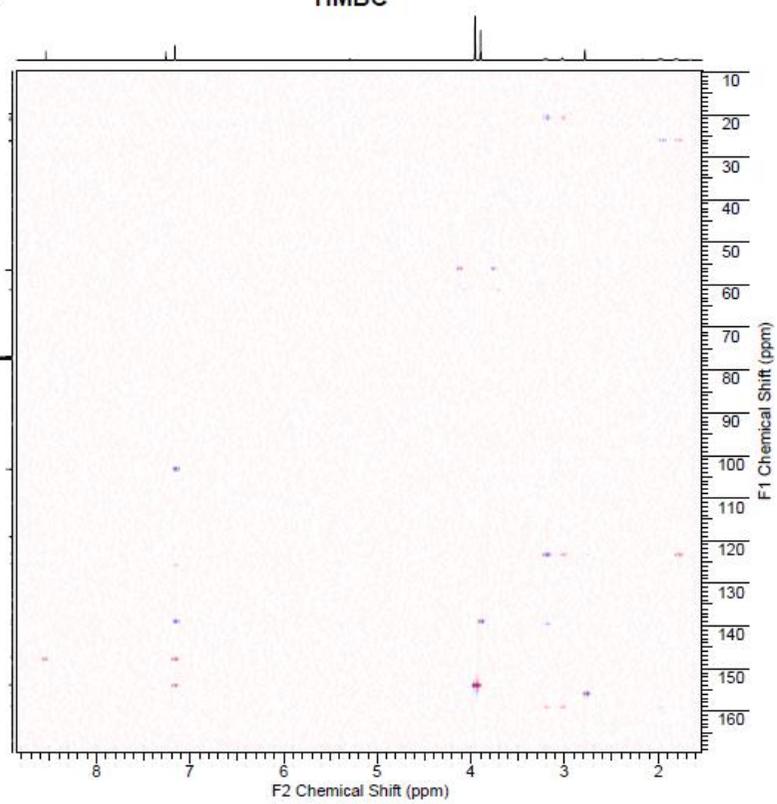




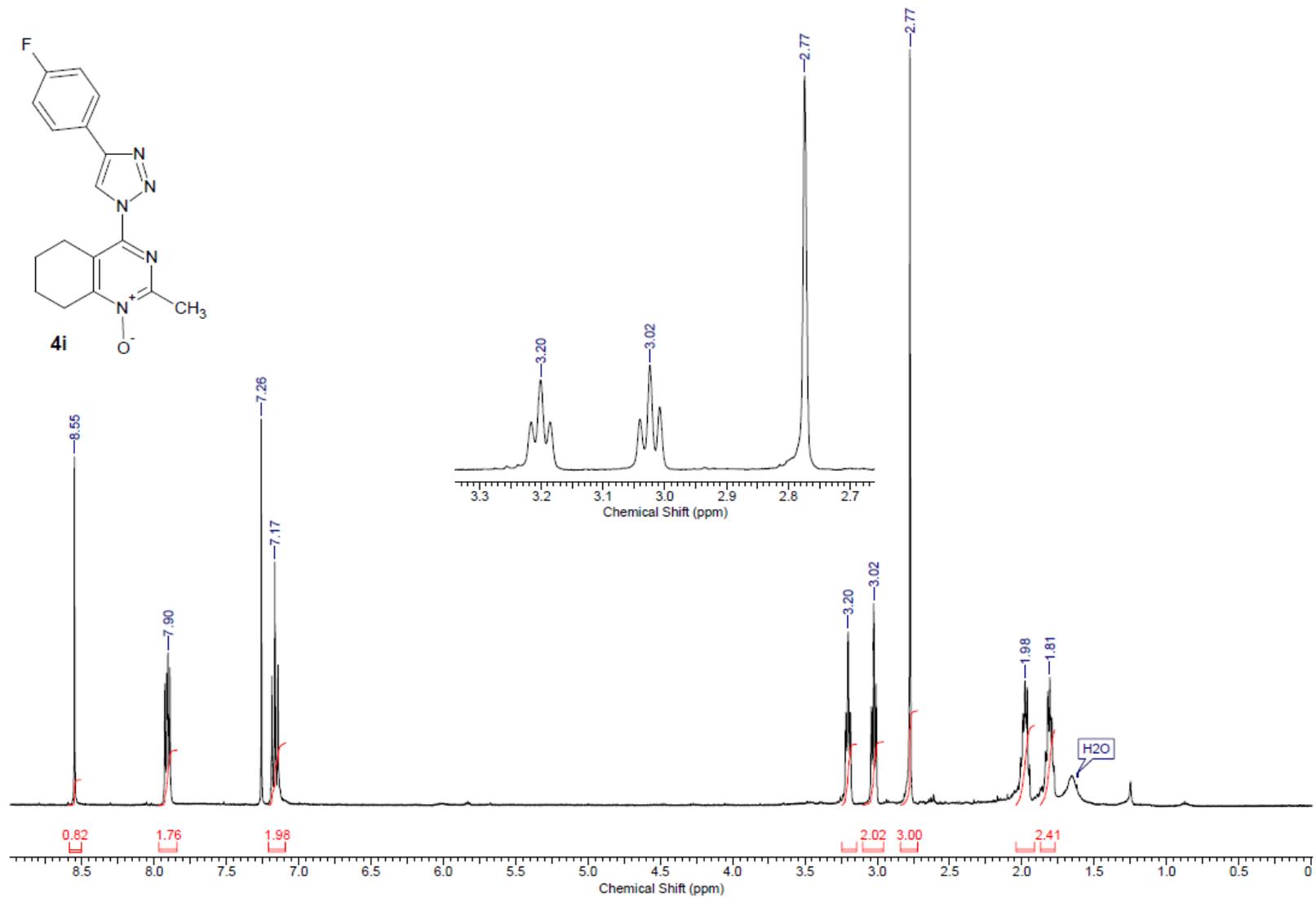
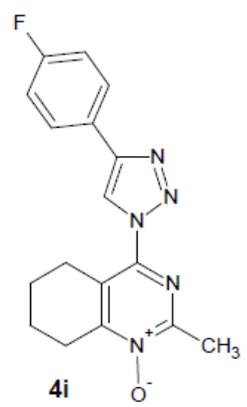
HSQC



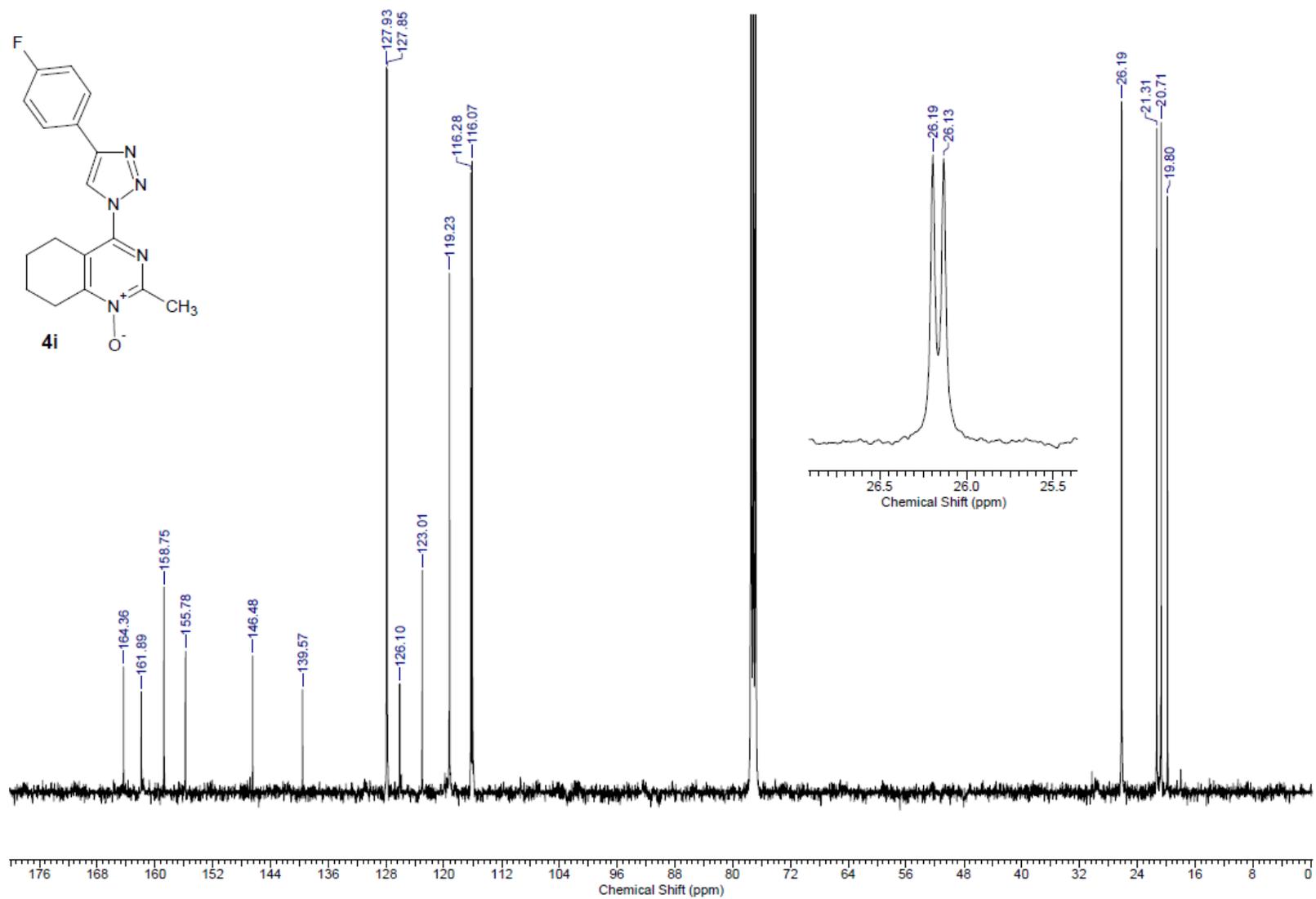
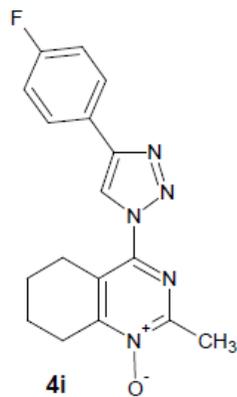
HMBC



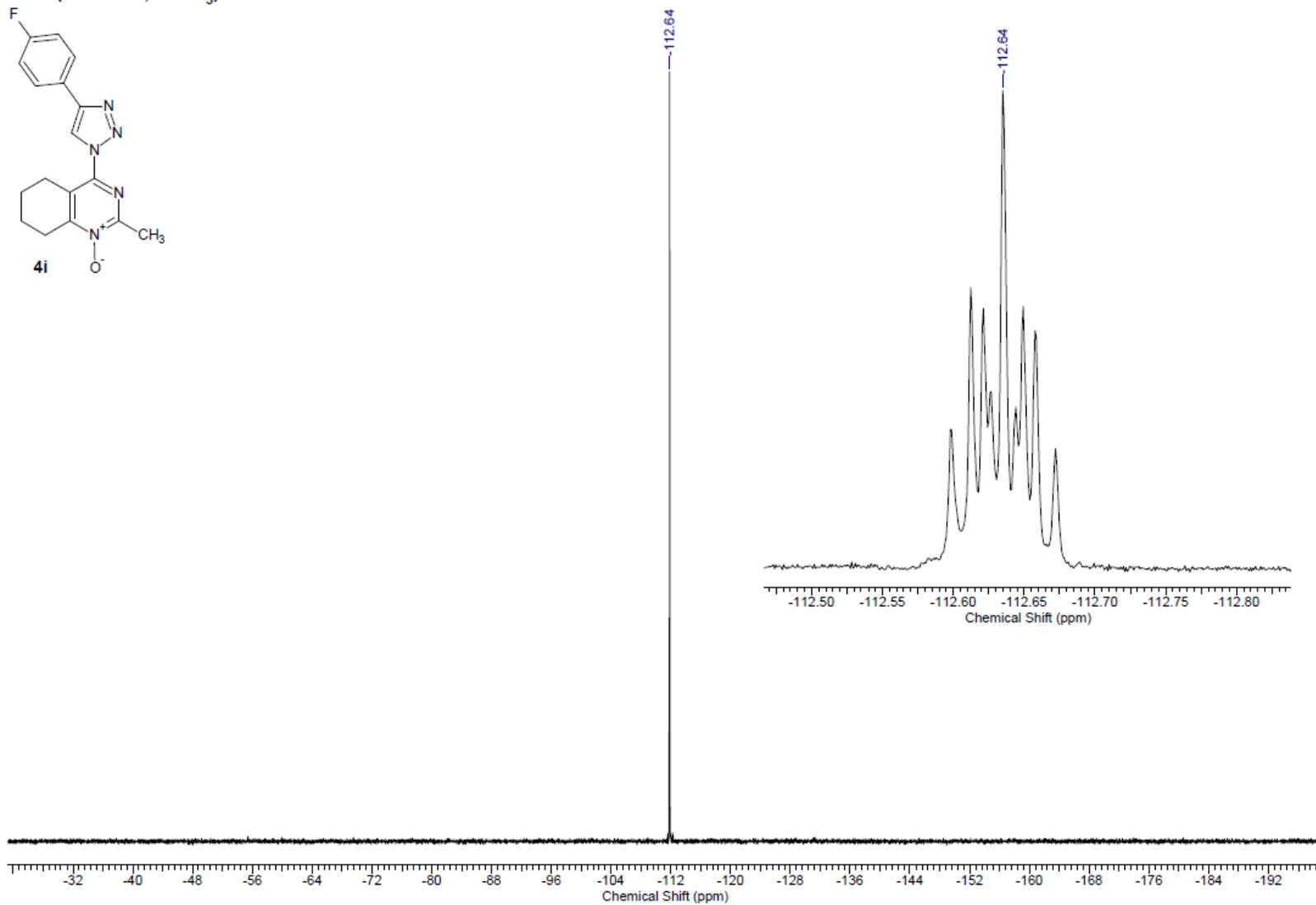
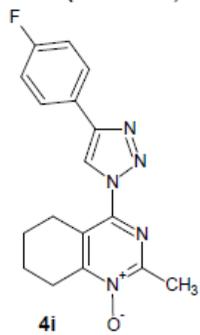
¹H NMR (400 MHz, CDCl₃)



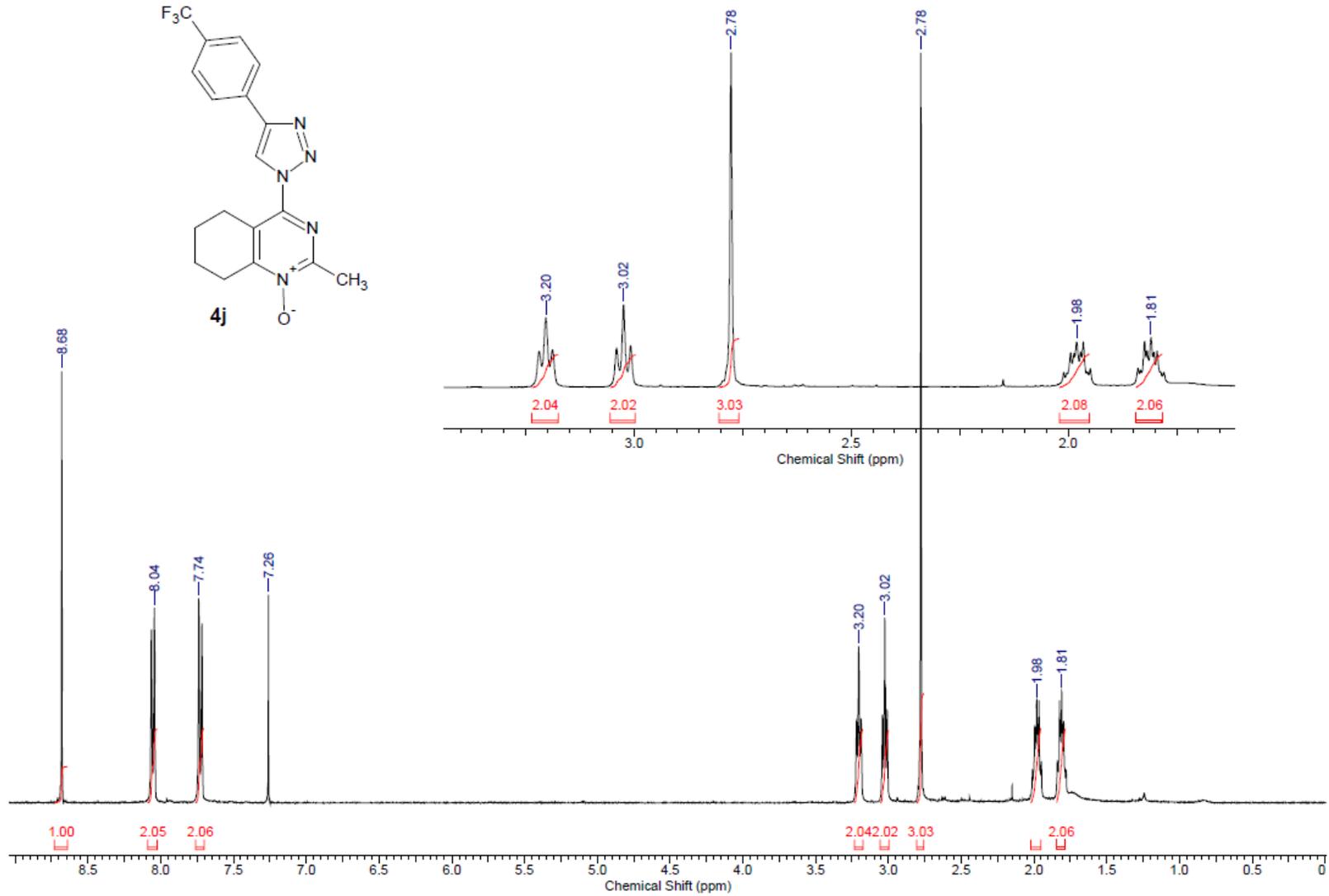
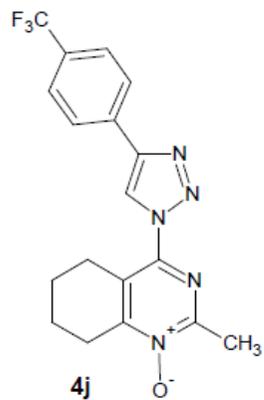
¹³C NMR (101 MHz, CDCl₃)



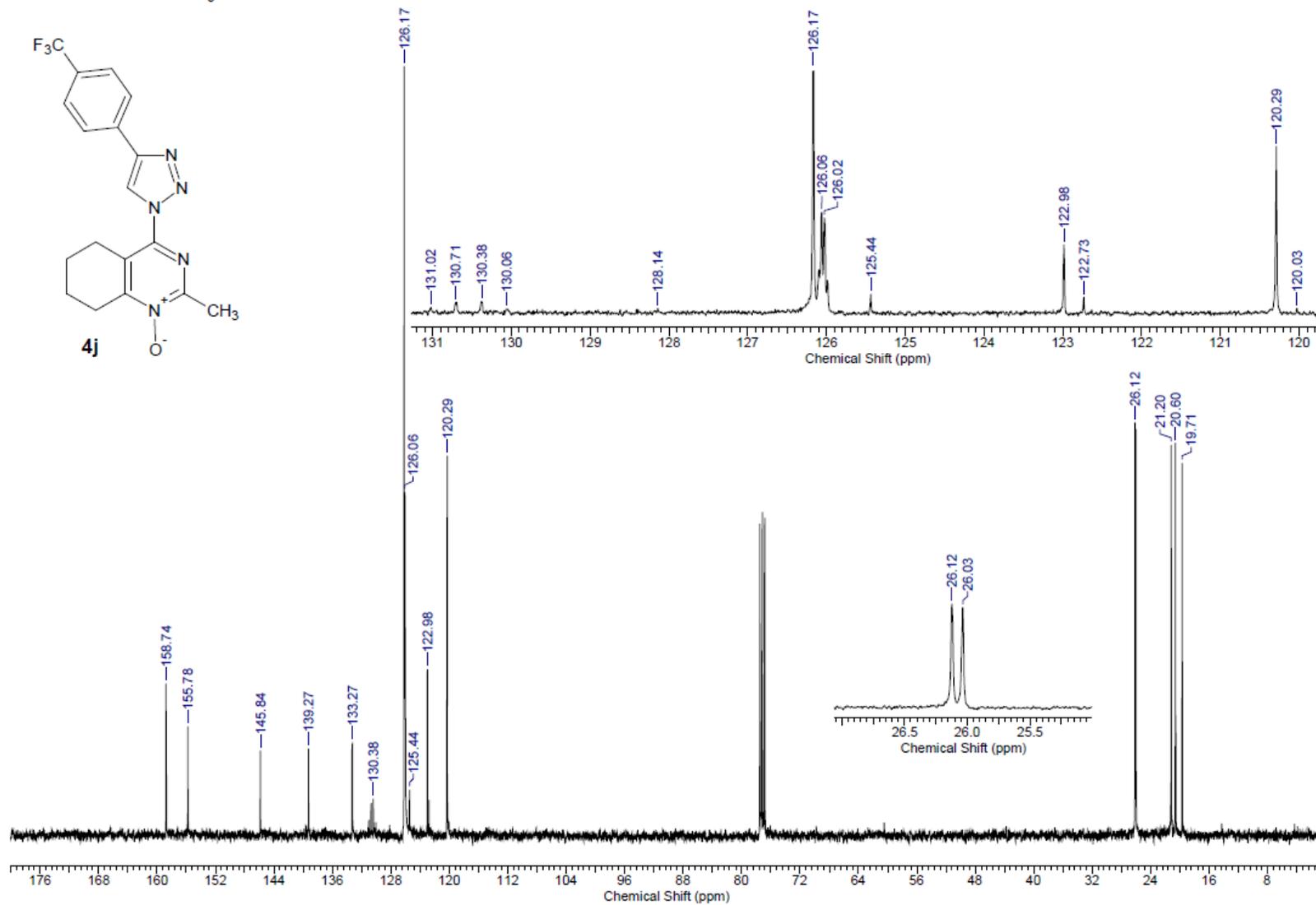
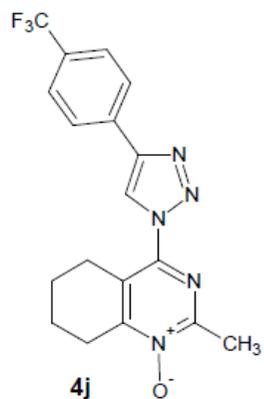
¹⁹F NMR (376 MHz, CDCl₃)



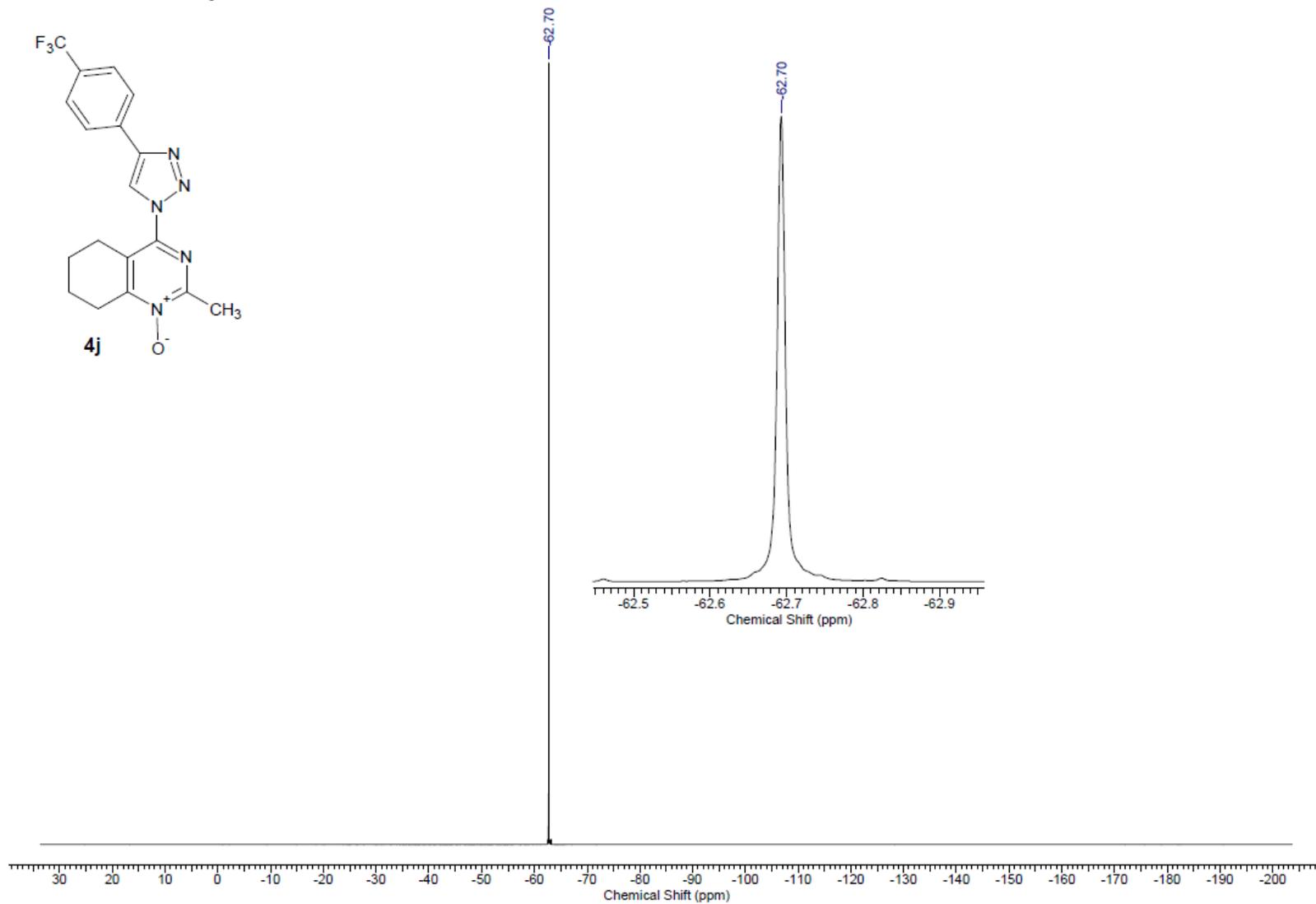
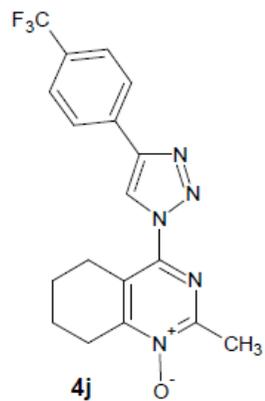
¹H NMR (400 MHz, CDCl₃)



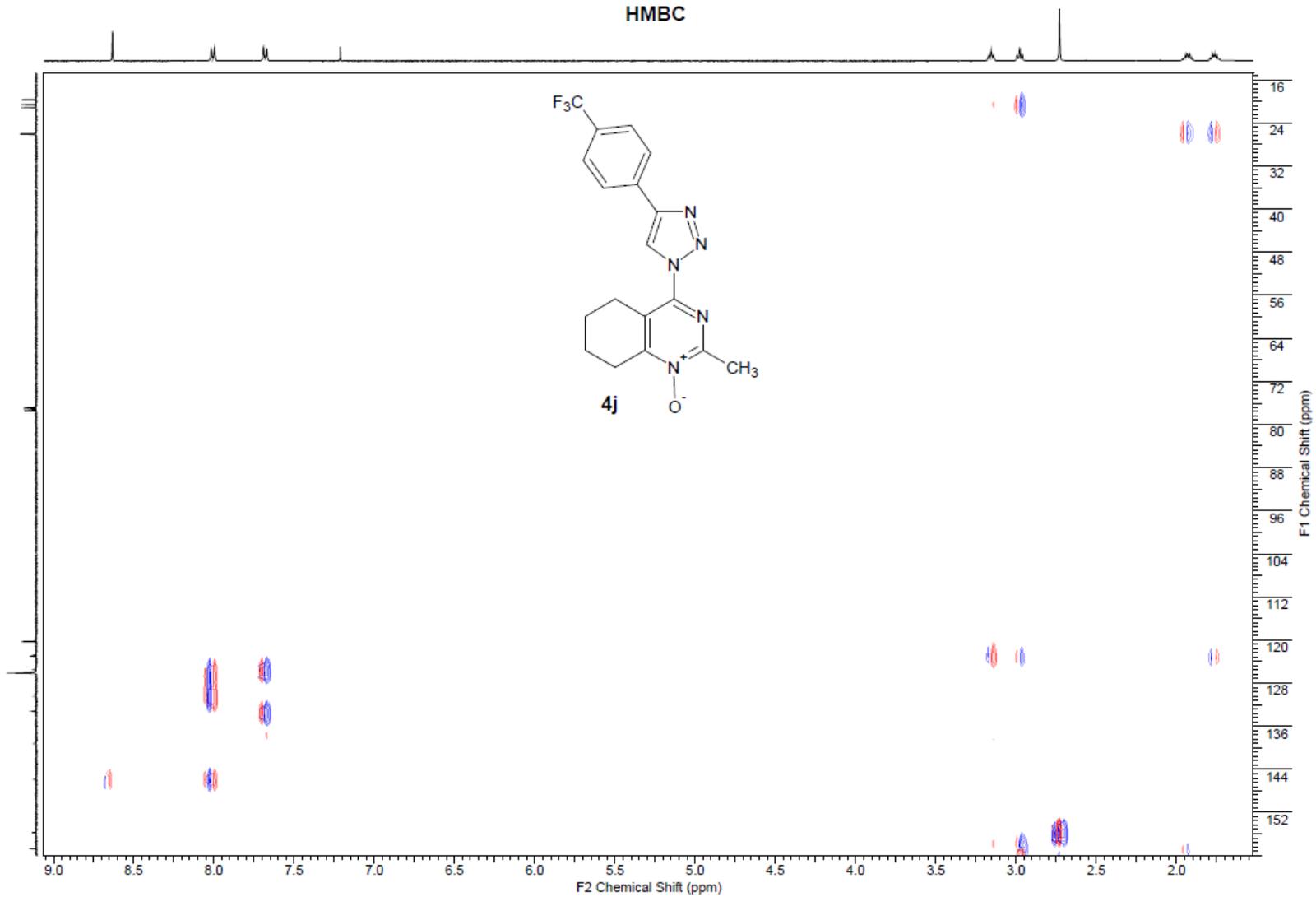
¹³C NMR (101 MHz, CDCl₃)



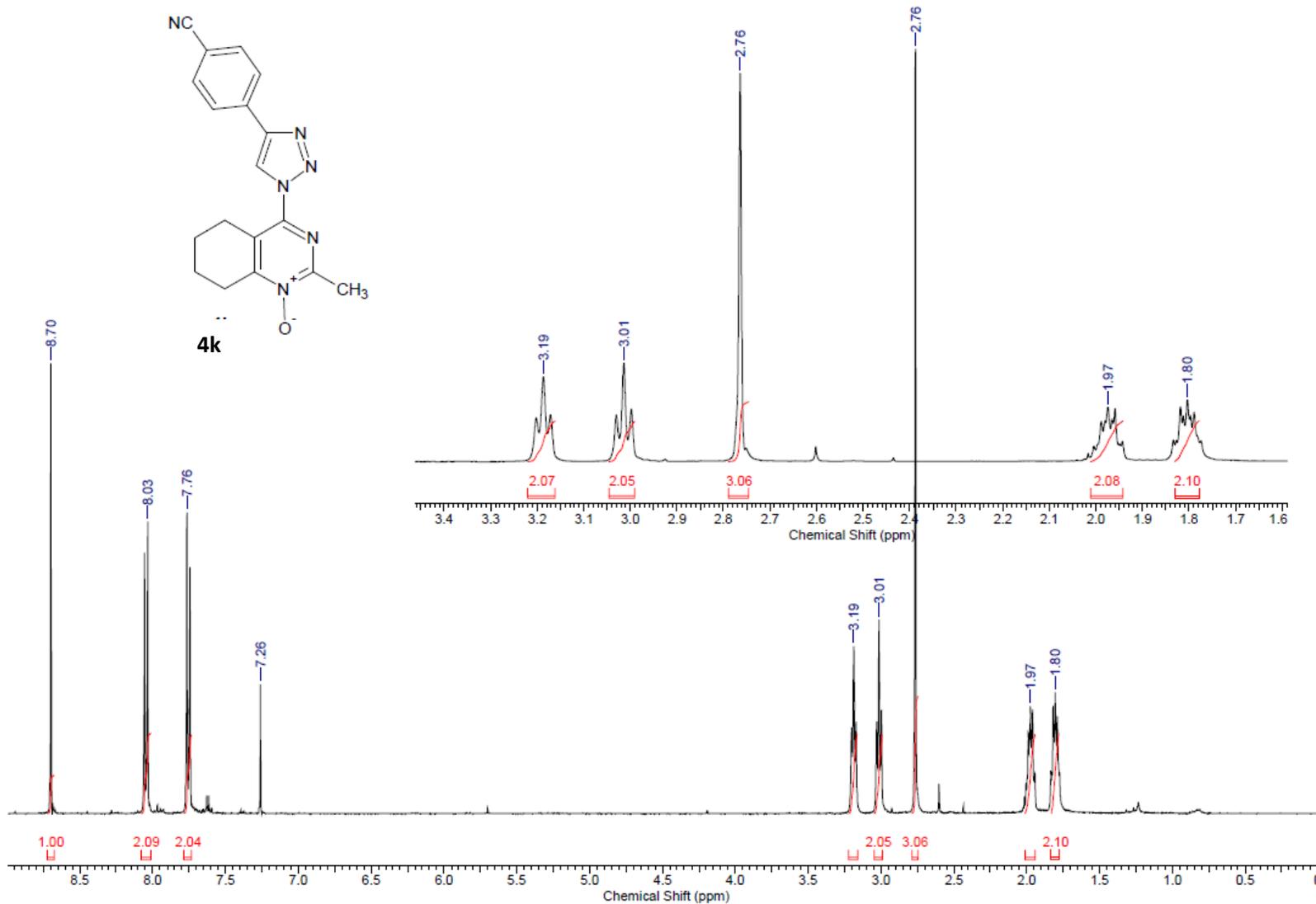
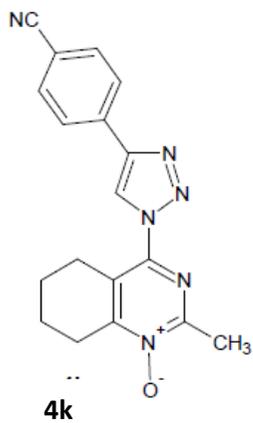
¹⁹F NMR (376 MHz, CDCl₃)



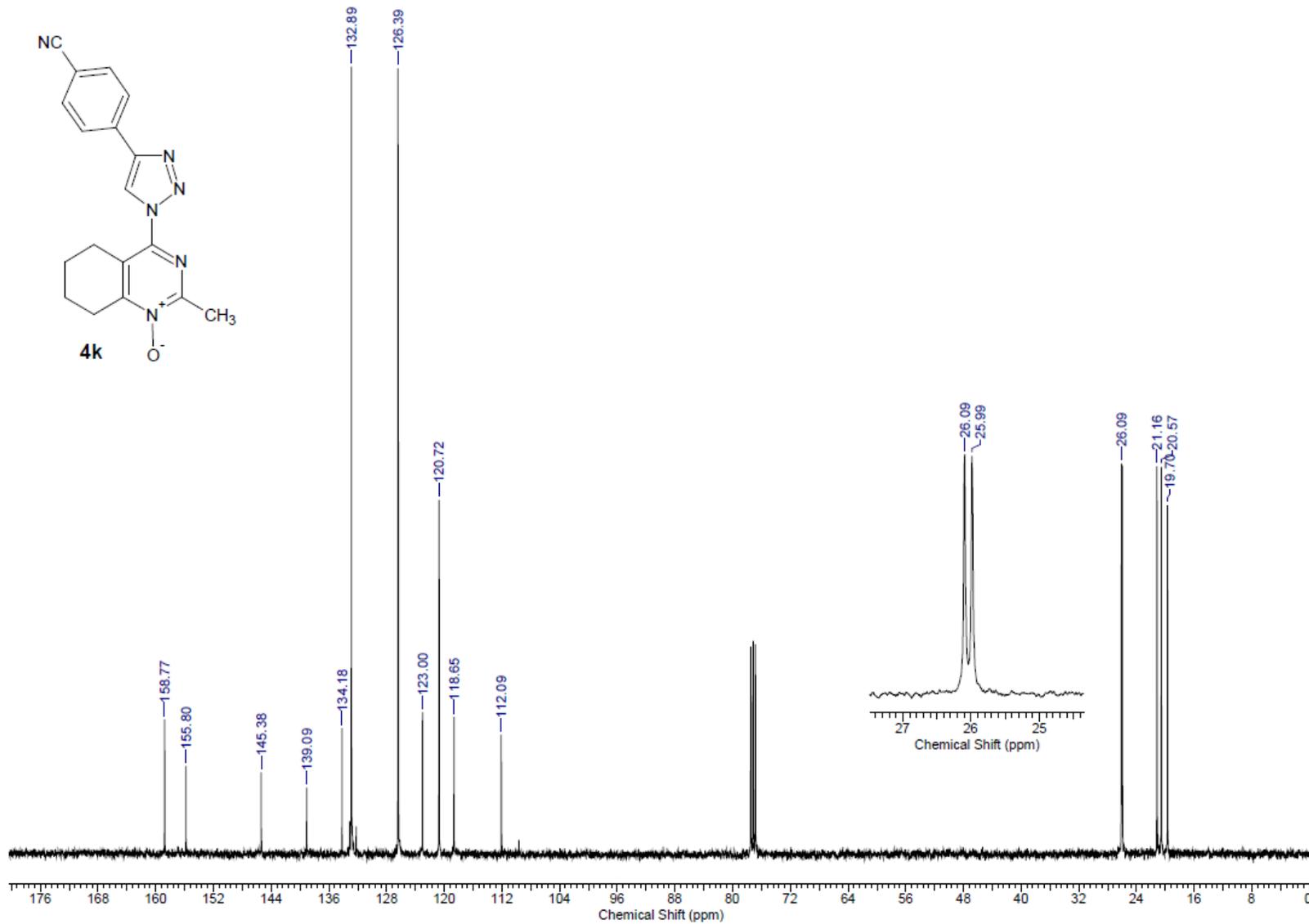
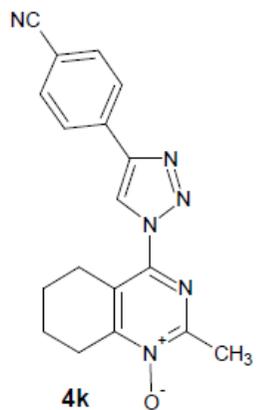
HMBC

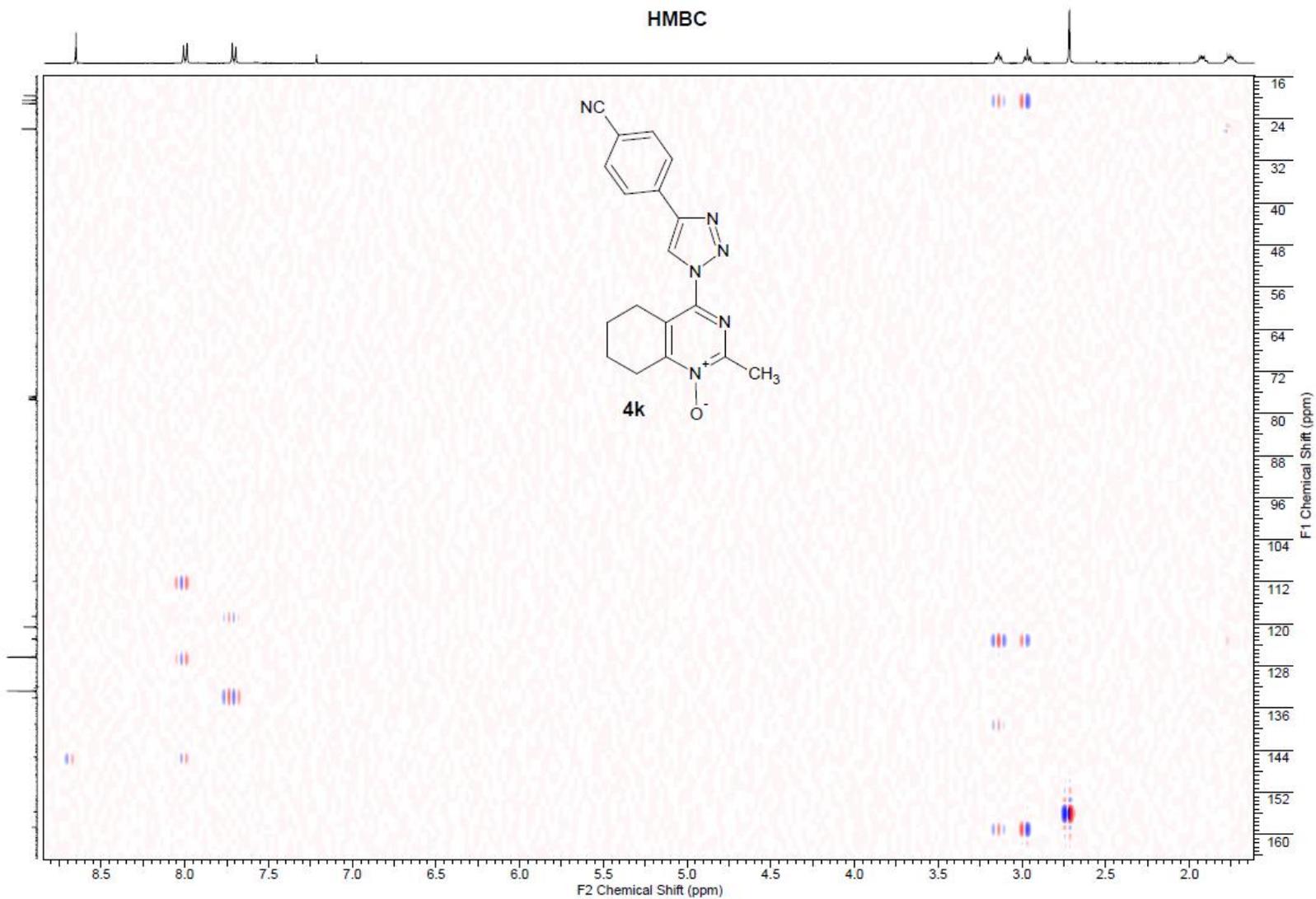


¹H NMR (400 MHz, CDCl₃)

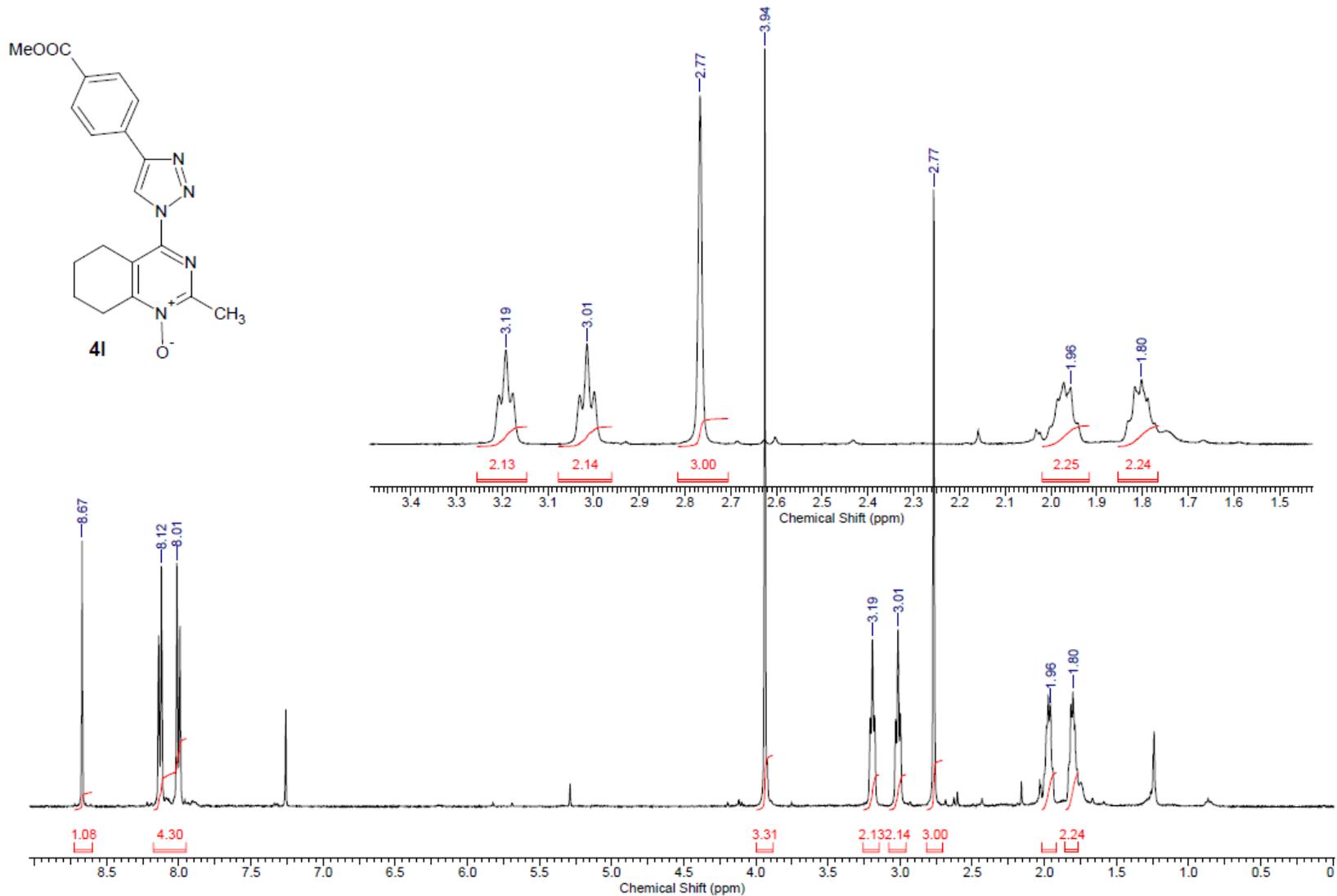


¹³C NMR (101 MHz, CDCl₃)

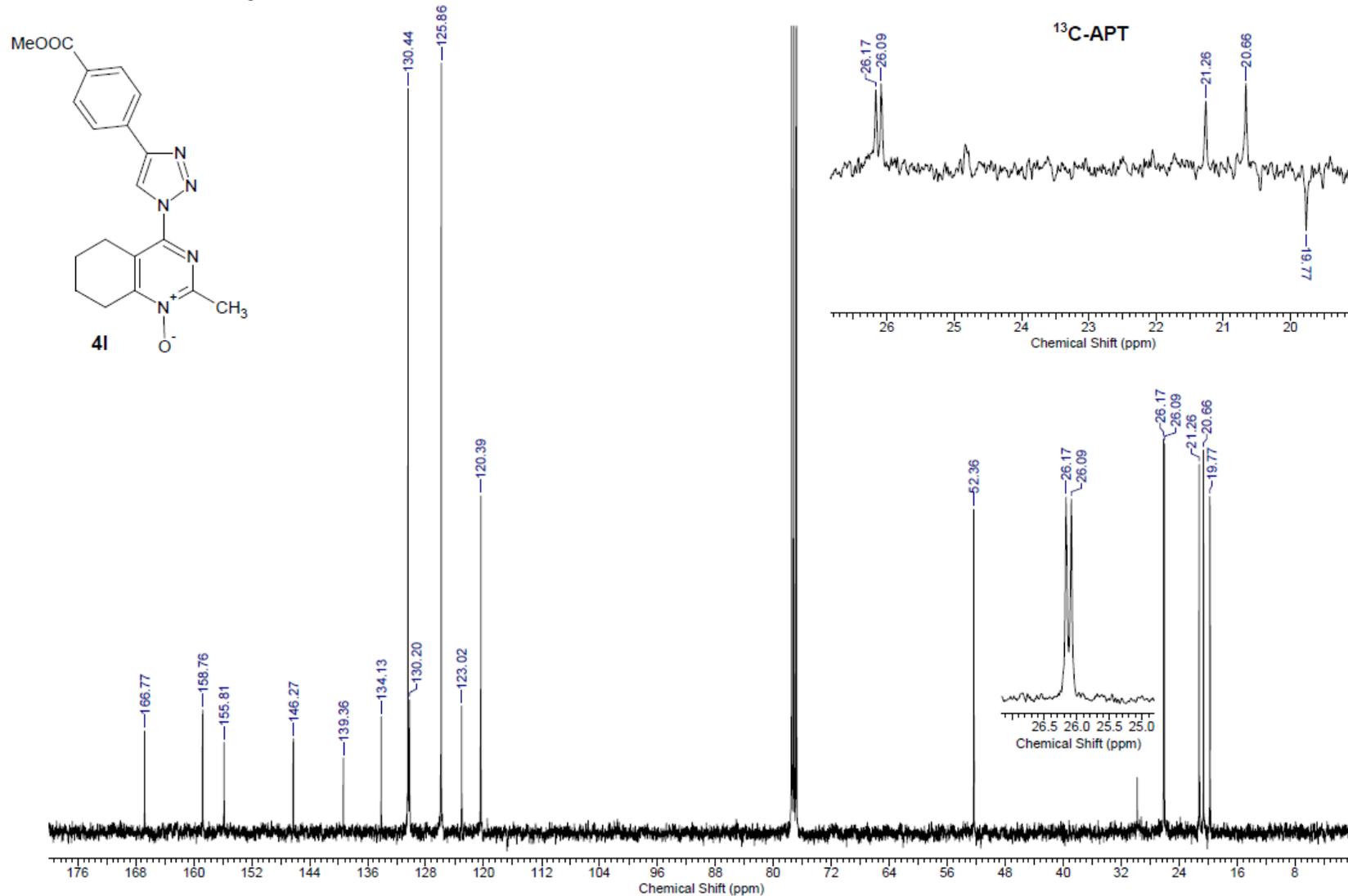




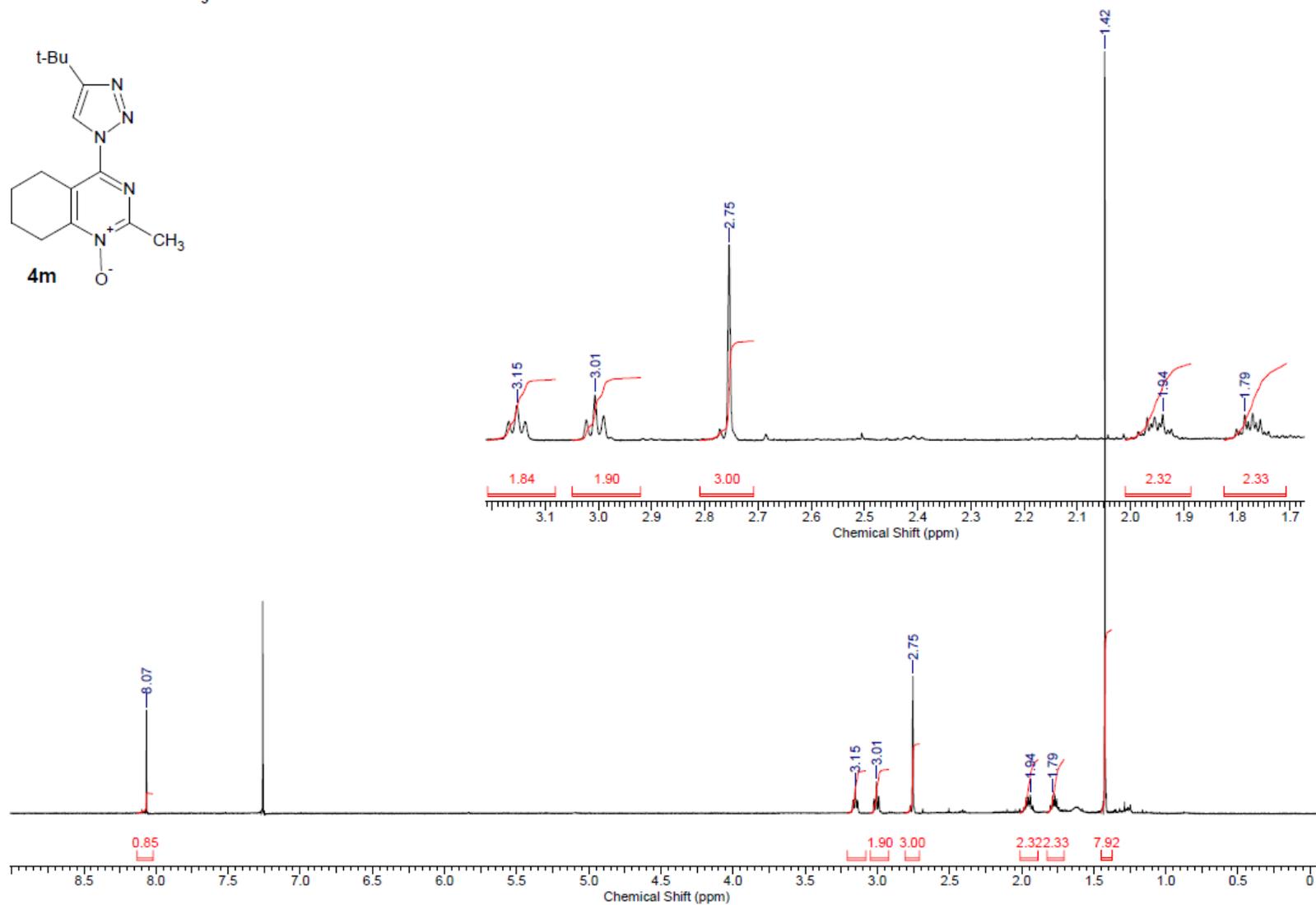
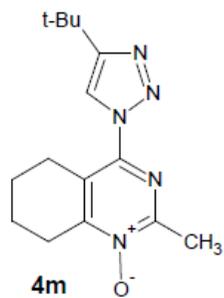
¹H NMR (400 MHz, CDCl₃)



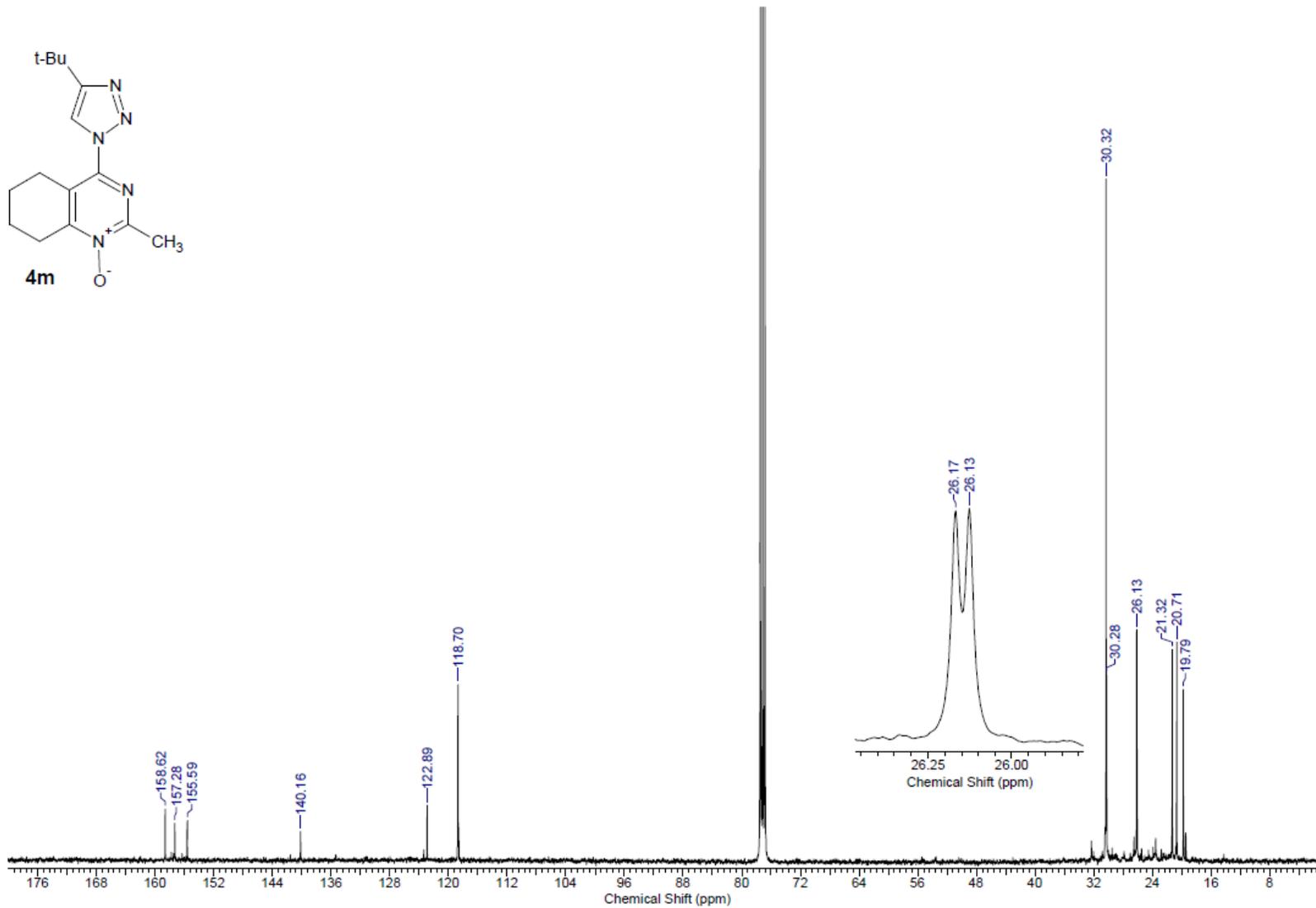
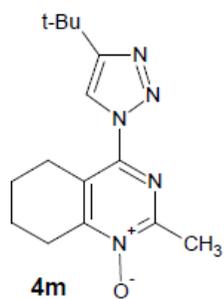
¹³C NMR (101 MHz, CDCl₃)



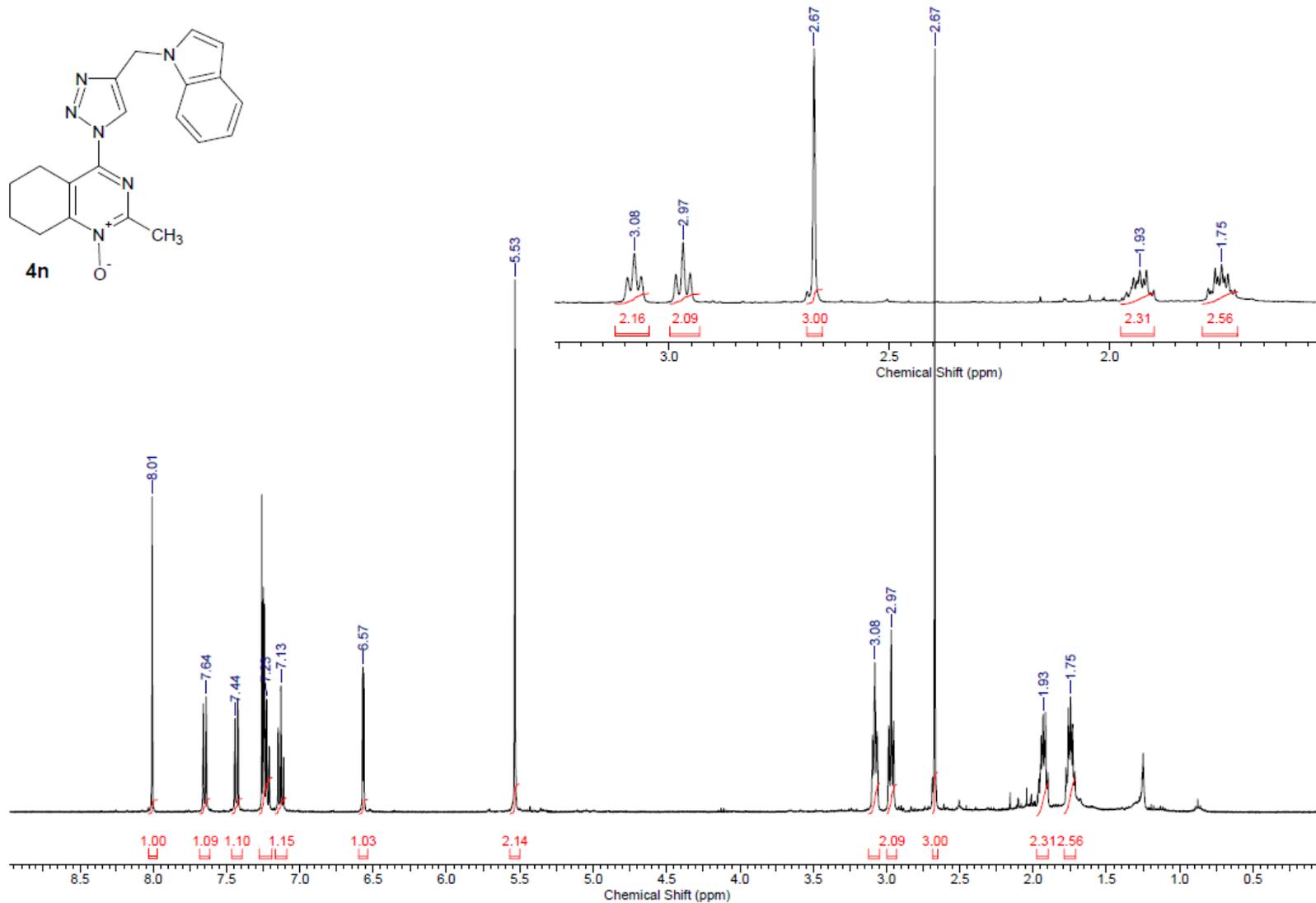
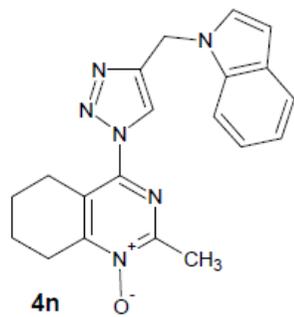
¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)



¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

