

Copper-catalyzed C-H/N-H cross-coupling reactions for the synthesis of
3-heteroaryl quinoxalin-2(1H)-ones

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Supplementary Information

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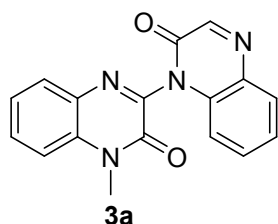
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1 General Experimental

Reactions were monitored by thin layer chromatography (TLC), on glass plates coated with silica gel with Fluorescent indicator (Huanghai, HSGF254). Flash chromatography was performed on silica gel (Huanghai, 300-400) using hexane-EtOAc as eluent. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM500 (500, 400MHz) with chemical shift values in ppm relative to TMS (δH 0.00 and δC 0.0) or residual chloroform (δH 7.28 and δC 77.1) as standard. Mass spectra were recorded on Thermo-Q Exactive Plus instrument or HP-5989A instrument.

2 General procedure for the synthesis of 3-heteroaryl quinoxalin-2(1H)-ones

0.5 mL DMAc was added into the flask charged with quinoxalin-2(1H)-ones (**1**, 0.375 mmol), unprotected 2-quinoxalinones or 2-quinolinones (**2**, 0.25 mmol), $\text{Cu}(\text{OAc})_2$ (10 mol%), K_2CO_3 (0.1 mmol). The mixture was stirred at 120 °C under air for 8h. Then the reaction was cooled down to room temperature, diluted with 20 mL ethyl acetate and washed with 10 mL H_2O . The aqueous layer was extracted twice with ethyl acetate (5 mL) and the combined organic phase was dried over Na_2SO_4 . After evaporation of the solvents the residue was purified by flash column chromatography (silica gel, PE-EtOAc, 3:1 to 1:1) to afford the desired products.



4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

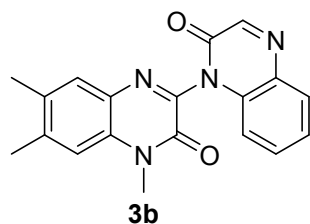
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 258-260 °C

^1H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.97 – 7.93 (m, 2H), 7.88 – 7.84 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 3.75 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 153.5, 151.2, 150.7, 145.4, 134.6, 132.7, 132.2, 131.7, 131.4, 131.0, 130.0, 129.8, 124.6, 124.4, 115.5, 115.3, 30.0

IR (KBr) 2922, 2853, 1655, 1600, 1460, 1219, 729 cm^{-1}

HRMS for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 305.10330, found 305.10321



4',6',7'-trimethyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

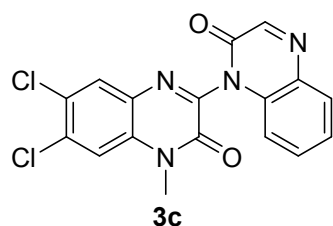
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 236-238 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 7.94 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.69 (s, 1H), 7.58 (s, 1H), 7.53 – 7.49 (m, 1H), 7.45 – 7.41 (m, 1H), 7.14 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.72 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.4, 151.1, 150.7, 144.0, 142.9, 133.3, 132.6, 132.2, 131.8, 131.3, 129.7, 129.6, 129.3, 124.4, 115.6, 115.1, 29.9, 20.2, 18.6

IR (KBr) 2921, 2852, 1656, 1458, 1312, 1298, 1040, 755 cm⁻¹

HRMS for C₁₉H₁₇N₄O₂⁺(M⁺+H): calcd. 333.13460, found 333.13409



6',7'-dichloro-4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

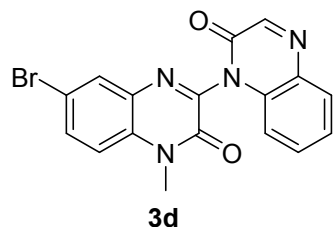
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 247-249 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 8.27 (s, 1H), 8.11 (s, 1H), 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.48 – 7.44 (m, 1H), 7.31 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.74 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.3, 150.8, 150.5, 146.8, 135.1, 134.5, 132.1, 131.5, 131.3, 130.6, 130.3, 129.7, 126.4, 124.6, 117.3, 115.3, 30.5

IR (KBr) 2921, 2852, 1660, 1598, 1461, 1299, 1189, 1101, 756 cm⁻¹

HRMS for C₁₇H₁₁Cl₂N₄O₂⁺(M⁺+H): calcd. 373.02536, found 373.02505



7'-bromo-4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

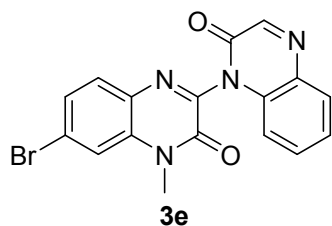
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 266-268 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.99 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.51 – 7.47 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.4, 151.0, 150.6, 145.7, 135.8, 132.1, 131.6, 131.5, 131.3, 130.0, 129.7, 127.3, 126.1, 124.6, 118.3, 115.3, 30.2

IR (KBr) 2921, 2851, 1664, 1594, 1458, 1294, 1078, 831, 781 cm⁻¹

HRMS for C₁₇H₁₂BrN₄O₂⁺(M⁺+H): calcd. 383.01381, found 383.01373



6'-bromo-4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

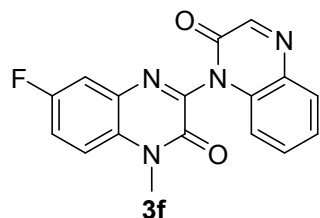
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 279-281 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (s, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.00 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.48 – 7.43 (m, 1H), 7.29 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.73 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.4, 151.0, 150.6, 146.6, 135.0, 134.0, 132.1, 131.9, 131.7, 131.6, 131.3, 129.7, 124.6, 117.6, 115.9, 115.3, 30.2

IR (KBr) 2921, 2852, 1662, 1456, 1299, 1188, 814, 755 cm⁻¹

HRMS for C₁₇H₁₂BrN₄O₂⁺(M⁺+H): calcd. 383.01381, found 383.01389



7'-fluoro-4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

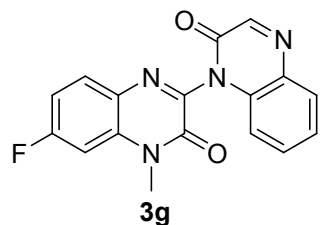
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 265-267 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (s, 1H), 8.01 – 7.94 (m, 2H), 7.70 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.47 – 7.38 (m, 2H), 7.28 – 7.26 (m, 1H), 3.71 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 164.1 (d, *J*_{C-F} = 248.8 Hz), 153.4, 151.1, 150.6, 144.4 (d, *J*_{C-F} = 4.3 Hz), 136.5 (d, *J*_{C-F} = 12.5 Hz), 132.4 (d, *J*_{C-F} = 11.8 Hz), 132.1, 131.7, 131.3, 129.7, 128.0, 124.5, 115.3, 112.3 (d, *J*_{C-F} = 24.3 Hz), 102.5 (d, *J*_{C-F} = 28.0 Hz), 30.4

IR (KBr) 2920, 2851, 1659, 1598, 1460, 1223, 1093, 763 cm⁻¹

HRMS for C₁₇H₁₂FN₄O₂⁺(M⁺+H): calcd. 323.09388, found 323.09348



6'-fluoro-4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 270-271 °C

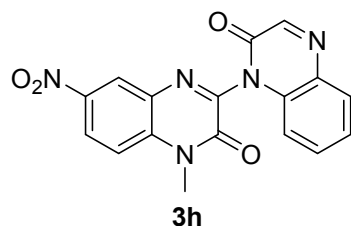
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.80 (m, 3H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ 158.3 (d, *J*_{C-F} = 240.4 Hz), 153.4, 150.9, 150.6, 146.8, 132.1, 131.7 (d, *J*_{C-F} = 1.8 Hz), 131.6, 131.5 (d, *J*_{C-F} = 12.4 Hz), 131.4, 129.8, 124.6, 120.4 (d, *J*_{C-F} = 22.9 Hz), 117.3

(d, $J_{C-F} = 8.6$ Hz), 115.3, 115.0 (d, $J_{C-F} = 22.1$ Hz), 30.4

IR (KBr) 2922, 2853, 1651, 1601, 1456, 1265, 1123, 814, 755 cm^{-1}

HRMS for $\text{C}_{17}\text{H}_{12}\text{FN}_4\text{O}_2^+(\text{M}^++\text{H})$: calcd. 323.09388, found 323.09357



4'-methyl-7'-nitro-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

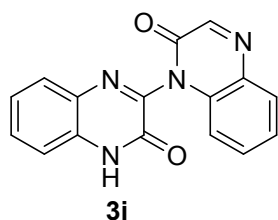
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 307-309 °C

^1H NMR (500 MHz, DMSO- d_6) δ 8.72 (s, 1H), 8.62 (dd, $J = 9.5, 2.0$ Hz, 1H), 8.44 (s, 1H), 7.97 (d, $J = 9.0$ Hz, 2H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 8.5$ Hz, 1H), 3.79 (s, 3H)

^{13}C NMR (125 MHz, DMSO- d_6) δ 153.4, 151.2, 150.6, 147.8, 143.1, 139.4, 132.2, 131.5, 131.4, 130.1, 129.8, 126.6, 125.2, 124.8, 117.0, 115.4, 30.7

IR (KBr) 2921, 2852, 1683, 1600, 1457, 1343, 1040, 748 cm^{-1}

HRMS for $\text{C}_{17}\text{H}_{12}\text{N}_5\text{O}_4^+(\text{M}^++\text{H})$: calcd. 350.08838, found 350.08826



2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

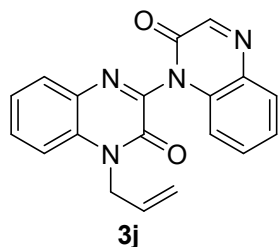
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 298-300 °C

^1H NMR (400 MHz, DMSO- d_6) δ 13.2 (s, 1H), 8.45 (s, 1H), 8.00 – 7.98 (m, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.78 (t, $J = 7.2$ Hz, 1H), 7.57 – 7.46 (m, 4H), 7.30 (d, $J = 8.4$ Hz, 1H)

^{13}C NMR (100 MHz, DMSO- d_6) δ 153.4, 151.4, 150.6, 146.6, 133.5, 132.3, 132.1, 131.7, 131.4, 130.9, 129.7, 129.1, 124.5, 124.0, 116.0, 115.2

IR (KBr) 2920, 2852, 1687, 1588, 1346, 1172, 1042, 748 cm^{-1}

HRMS for $\text{C}_{16}\text{H}_{11}\text{N}_4\text{O}_2^+(\text{M}^++\text{H})$: calcd. 291.08765, found 291.08752



4'-allyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 211-213 °C

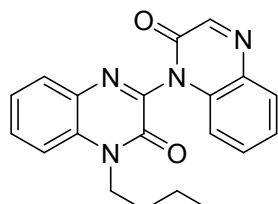
^1H NMR (500 MHz, DMSO- d_6) δ 8.42 (s, 1H), 7.96 (d, $J = 8.0$ Hz, 2H), 7.83 (t, $J = 7.5$ Hz, 1H), 7.71

(d, $J = 8.5$ Hz, 1H), 7.56 – 7.52 (m, 2H), 7.46 (t, $J = 7.5$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 6.03 – 5.96 (m, 1H), 5.26 – 5.18 (m, 2H), 5.04 – 4.95 (m, 2H)

^{13}C NMR (125 MHz, DMSO- d_6) δ 153.4, 150.8, 150.6, 145.3, 133.6, 132.6, 132.1, 131.7, 131.4, 131.2, 131.0, 130.1, 129.7, 124.5, 124.4, 117.5, 115.7, 115.2, 44.8

IR (KBr) 2921, 2852, 1658, 1600, 1460, 1298, 1078, 760 cm^{-1}

HRMS for $\text{C}_{19}\text{H}_{15}\text{N}_4\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 331.11895, found 331.11887



3k

4'-butyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

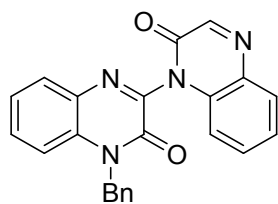
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 175-177 $^{\circ}\text{C}$

^1H NMR (400 MHz, DMSO- d_6) δ 8.42 (s, 1H), 7.97 – 7.94 (m, 2H), 7.85 – 7.81 (m, 2H), 7.55 – 7.50 (m, 2H), 7.47 – 7.43 (m, 1H), 7.27 (dd, $J = 8.4, 0.8$ Hz, 1H), 4.41 – 4.26 (m, 2H), 1.73 – 1.66 (m, 2H), 1.46 – 1.37 (m, 2H), 0.92 (t, $J = 7.6$ Hz, 3H)

^{13}C NMR (100 MHz, DMSO- d_6) δ 153.4, 150.9, 150.6, 145.3, 133.6, 132.7, 132.1, 131.7, 131.4, 131.2, 130.2, 129.7, 124.5, 124.2, 115.3, 115.2, 42.4, 29.0, 19.5, 13.6

IR (KBr) 2924, 2858, 1660, 1603, 1463, 1314, 1191, 1109, 748 cm^{-1}

HRMS for $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 347.15025, found 347.15027



3l

4'-benzyl-2H-[1,2'-biquinoxaline]-2,3'(4'H)-dione

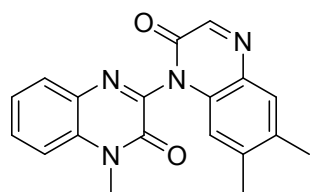
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 223-225 $^{\circ}\text{C}$

^1H NMR (400 MHz, DMSO- d_6) δ 8.48 (s, 1H), 8.02 – 7.99 (m, 2H), 7.81 – 7.77 (m, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.63 – 7.59 (m, 1H), 7.55 – 7.47 (m, 2H), 7.44 (dd, $J = 8.4, 0.8$ Hz, 1H), 7.40 – 7.39 (m, 4H), 7.35 – 7.30 (m, 1H), 5.75 (d, $J = 16.0$ Hz, 1H), 5.55 (d, $J = 16.0$ Hz, 1H)

^{13}C NMR (100 MHz, DMSO- d_6) δ 153.5, 151.5, 150.6, 145.5, 135.3, 133.6, 132.7, 132.2, 131.7, 131.5, 131.3, 130.2, 129.8, 128.8, 127.6, 126.9, 124.6, 124.5, 115.7, 115.3, 45.8

IR (KBr) 2921, 2852, 1668, 1601, 1455, 1261, 1109, 1020, 733 cm^{-1}

HRMS for $\text{C}_{23}\text{H}_{17}\text{N}_4\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 381.13460, found 381.13474



3m

4',6,7-trimethyl-2H-[1,2'-biquinoxaline]-2,3'(4H)-dione

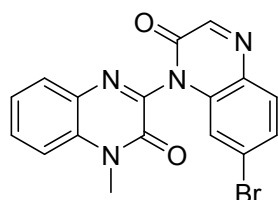
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 4 : 1). Yellow solid. mp 273-274 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 3.75 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.6, 151.2, 149.2, 145.5, 141.4, 134.6, 133.2, 132.5, 131.0, 130.6, 129.9, 129.7, 129.5, 124.2, 115.4, 115.2, 30.0, 19.5, 18.7

IR (KBr) 2920, 2850, 1687, 1603, 1458, 1242, 1098, 765 cm⁻¹

HRMS for C₁₉H₁₇N₄O₂⁺(M⁺+H): calcd. 333.13460, found 333.13480



3n

7-bromo-4'-methyl-2H-[1,2'-biquinoxaline]-2,3'(4H)-dione

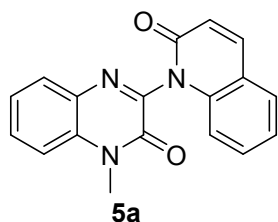
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 4 : 1). Yellow solid. mp 228-231 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 7.93 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 3.73 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.3, 151.4, 151.1, 145.0, 134.9, 132.9, 132.6, 131.4, 131.2, 131.2, 129.9, 127.7, 124.8, 124.2, 118.0, 115.5, 30.0

IR (KBr) 2922, 2852, 1650, 1586, 1344, 1078, 742 cm⁻¹

HRMS for C₁₇H₁₂BrN₄O₂⁺(M⁺+H): calcd. 383.01381, found 383.01389



5a

1-methyl-3-(2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

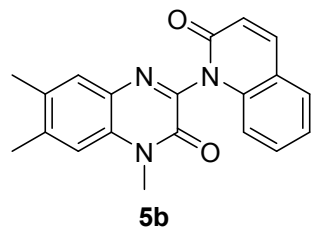
Purified by flash chromatograph column (PE : EtOAc = 2 : 1). Yellow solid. mp 284-286 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.12 (d, *J* = 9.6 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.84 – 7.80 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.47 – 7.43 (m, 1H), 7.32 – 7.28 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H)

^{13}C NMR (100 MHz, DMSO- d_6) δ 161.1, 151.6, 147.6, 141.5, 138.9, 134.4, 132.1, 131.0, 130.9, 129.8, 128.9, 124.1, 122.9, 121.1, 119.6, 115.3, 114.7, 29.9

IR (KBr) 2922, 2853, 1652, 1585, 1448, 1212, 827, 787 cm^{-1}

HRMS for $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 304.10805, found 304.10818



1,6,7-trimethyl-3-(2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

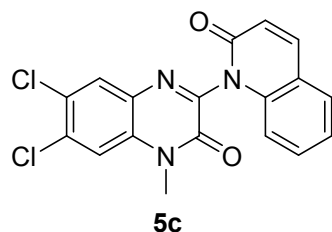
Purified by flash chromatograph column (CH_2Cl_2 : EtOAc = 4 : 1). Yellow solid. mp 221-223°C

^1H NMR (400 MHz, DMSO- d_6) δ 8.10 (d, J = 10.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.54 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 9.6 Hz, 1H), 3.70 (s, 3H), 2.46 (s, 3H), 2.35 (s, 3H)

^{13}C NMR (100 MHz, DMSO- d_6) δ 161.1, 151.6, 146.3, 142.1, 141.3, 139.0, 132.9, 132.4, 130.8, 129.4, 129.4, 128.8, 122.7, 121.1, 119.6, 115.4, 114.5, 29.7, 20.1, 18.6

IR (KBr) 2921, 2853, 1651, 1620, 1376, 1219, 1005, 755 cm^{-1}

HRMS for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 332.13935, found 332.13904



6,7-dichloro-1-methyl-3-(2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

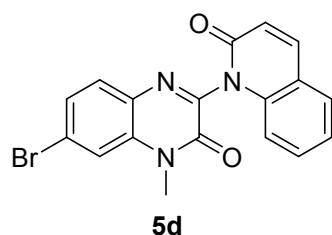
Purified by flash chromatograph column (CH_2Cl_2 : EtOAc = 4 : 1). Yellow solid. mp 221-223 °C

^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (s, 1H), 8.12 (d, J = 9.6 Hz, 1H), 8.06 (s, 1H), 7.83 – 7.81 (m, 1H), 7.48 – 7.43 (m, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 9.6 Hz, 1H), 3.70 (s, 3H)

^{13}C NMR (100 MHz, DMSO- d_6) δ 161.0, 151.3, 149.1, 141.7, 138.7, 134.5, 134.4, 130.9, 130.5, 130.4, 128.9, 126.1, 123.0, 120.9, 119.6, 117.2, 114.8, 30.3

IR (KBr) 2919, 2849, 1652, 1590, 1452, 1251, 798, 722 cm^{-1}

HRMS for $\text{C}_{18}\text{H}_{12}\text{Cl}_2\text{N}_3\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 372.03011, found 372.03012



7-bromo-1-methyl-3-(2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

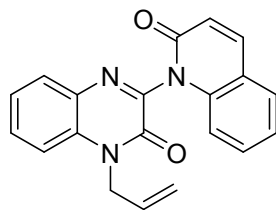
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 4 : 1). Yellow solid. mp 209-211 °C

¹H NMR (400 MHz, DMSO-d₆) δ 8.15 – 8.13 (m, 2H), 7.97 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H)

¹³C NMR (100 MHz, DMSO-d₆) δ 161.1, 151.4, 148.9, 141.6, 138.8, 134.5, 133.9, 132.0, 131.6, 130.9, 128.9, 123.0, 121.0, 119.6, 117.4, 115.7, 114.8, 30.1

IR (KBr) 2921, 2852, 1655, 1592, 1450, 1215, 819, 747 cm⁻¹

HRMS for C₁₈H₁₃BrN₃O₂⁺(M⁺+H): calcd. 382.01857, found 382.01849



5e

1-allyl-3-(2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

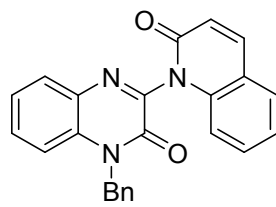
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 5 : 1). Yellow solid. mp 205-207 °C

¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (d, *J* = 10.0 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 9.6 Hz, 1H), 6.06 – 5.97 (m, 1H), 5.27 – 5.17 (m, 2H), 5.06 – 4.95 (m, 2H)

¹³C NMR (100 MHz, DMSO-d₆) δ 161.1, 151.3, 147.6, 141.5, 138.9, 133.4, 132.1, 131.3, 131.1, 131.0, 130.0, 128.9, 124.2, 122.9, 121.0, 119.6, 117.4, 115.6, 114.7, 44.6

IR (KBr) 2933, 1654, 1601, 1443, 1220, 1108, 761 cm⁻¹

HRMS for C₂₀H₁₆N₃O₂⁺(M⁺+H): calcd. 330.12370, found 330.12344



5f

1-benzyl-3-(2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

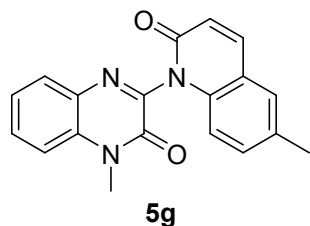
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 3 : 1). Yellow solid. mp 257-259 °C

¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (d, *J* = 9.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.53 – 7.46 (m, 2H), 7.35 – 7.29 (m, 6H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 9.6 Hz, 1H), 5.76 – 5.70 (m, 1H), 5.56 – 5.49 (m, 1H)

¹³C NMR (100 MHz, DMSO-d₆) δ 161.2, 151.9, 147.8, 141.6, 138.9, 135.4, 133.4, 132.2, 131.4, 131.0, 130.1, 129.0, 128.8, 127.5, 126.9, 124.3, 123.0, 121.0, 120.0, 115.5, 114.7, 45.6

IR (KBr) 2921, 1654, 1586, 1447, 1252, 1078, 748 cm⁻¹

HRMS for C₂₄H₁₈N₃O₂⁺(M⁺+H): calcd. 380.13935, found 380.13943



1-methyl-3-(6-methyl-2-oxoquinolin-1(2H)-yl)quinoxalin-2(1H)-one

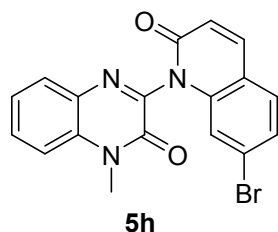
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 4 : 1). Yellow solid. mp 243-245 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (d, *J* = 9.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 8.8, 1.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 2.36 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.0, 151.6, 147.7, 141.2, 137.0, 134.4, 132.1, 132.0, 131.9, 131.0, 129.7, 128.4, 124.1, 121.0, 119.6, 115.3, 114.6, 29.8, 20.1

IR (KBr) 2922, 1648, 1554, 1316, 1215, 1094, 753 cm⁻¹

HRMS for C₁₉H₁₆N₃O₂⁺(M⁺+H): calcd. 318.12370, found 318.12396



3-(7-bromo-2-oxoquinolin-1(2H)-yl)-1-methylquinoxalin-2(1H)-one

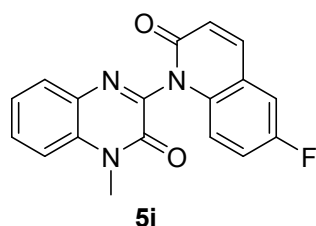
Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 4 : 1). Yellow solid. mp 254-256 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15 (d, *J* = 9.6 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.78 (m, 3H), 7.56 – 7.52 (m, 3H), 6.77 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.9, 151.8, 147.2, 141.0, 139.9, 134.7, 132.1, 131.2, 130.6, 129.8, 126.0, 124.6, 124.0, 121.4, 118.7, 117.3, 115.3, 29.8

IR (KBr) 2923, 1668, 1581, 1394, 1212, 1083, 795, 757 cm⁻¹

HRMS for C₁₈H₁₃BrN₃O₂⁺(M⁺+H): calcd. 382.01857, found 382.01859



3-(6-fluoro-2-oxoquinolin-1(2H)-yl)-1-methylquinoxalin-2(1H)-one

Purified by flash chromatograph column (CH₂Cl₂ : EtOAc = 4 : 1). Yellow solid. mp 261-263 °C

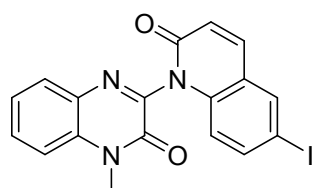
¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (d, *J* = 9.6 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.34 (td, *J* = 9.2, 2.8 Hz, 1H), 7.20 – 7.17 (m, 1H), 6.78 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.8, 157.5 (d, *J*_{C-F} = 238.4 Hz), 151.6, 147.4, 140.5 (d, *J*_{C-F} = 2.7 Hz), 135.6, 134.5, 132.2, 131.1, 129.8, 124.1, 122.4, 120.6 (d, *J*_{C-F} = 9.6 Hz), 118.5 (d, *J*_{C-F} = 23.3 Hz),

116.9 (d, $J_{C-F} = 8.2$ Hz), 115.3, 113.8 (d, $J_{C-F} = 22.9$ Hz), 29.9

IR (KBr) 2922, 2853, 1652, 1602, 1439, 1250, 750 cm^{-1}

HRMS for $\text{C}_{18}\text{H}_{13}\text{FN}_3\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 322.09863, found 322.09872



5j

3-(6-iodo-2-oxoquinolin-1(2H)-yl)-1-methylquinoxalin-2(1H)-one

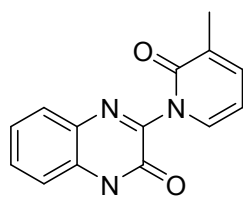
Purified by flash chromatograph column (CH_2Cl_2 : EtOAc = 4 : 1). Yellow solid. mp 282-284 °C

^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, $J = 1.6$ Hz, 1H), 8.08 (d, $J = 9.2$ Hz, 1H), 7.90 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.75 – 7.71 (m, 2H), 7.51 (t, $J = 7.2$ Hz, 1H), 6.95 (d, $J = 9.2$ Hz, 1H), 6.74 (d, $J = 9.6$ Hz, 1H), 3.73 (s, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 151.5, 147.1, 140.3, 138.8, 138.4, 136.8, 134.4, 132.3, 131.0, 129.8, 124.1, 122.1, 121.7, 117.1, 115.3, 86.5, 29.9

IR (KBr) 2922, 1661, 1602, 1471, 1205, 1136, 824, 762 cm^{-1}

HRMS for $\text{C}_{18}\text{H}_{13}\text{IN}_3\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 430.00470, found 430.00510



5k

1-methyl-3-(3-methyl-2-oxopyridin-1(2H)-yl)quinoxalin-2(1H)-one

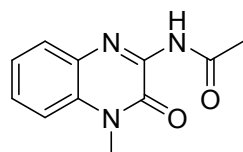
Purified by flash chromatograph column (CH_2Cl_2 : EtOAc = 4 : 1). Yellow solid. mp 210-211 °C

^1H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, $J = 8.0$ Hz, 1H), 7.77 – 7.74 (m, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 6.0$ Hz, 1H), 7.48 – 7.44 (m, 2H), 6.30 (t, $J = 6.8$ Hz, 1H), 3.70 (s, 3H), 2.04 (s, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 151.2, 149.7, 138.2, 134.5, 134.1, 131.7, 130.5, 129.5, 128.9, 124.0, 115.1, 105.2, 29.6, 16.3

IR (KBr) 2924, 1653, 1606, 1541, 1458, 1298, 1155, 754 cm^{-1}

HRMS for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_2^+(\text{M}^+\text{+H})$: calcd. 268.10805, found 268.10760



6

N-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)acetamide

Purified by flash chromatograph column (CH_2Cl_2 : EtOAc = 10 : 1). Yellow solid. mp 208-210 °C ^[1]

^1H NMR (400 MHz, CDCl_3) δ 9.02 (s, 1H), 7.75 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.38 –

7.34 (m, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 3.76 (s, 3H), 2.61 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 151.1, 144.2, 131.8, 131.1, 128.8, 128.2, 124.7, 113.8, 30.0, 25.8

Reference

[1] J. Yuan, S. Liu, Y. Xiao, P. Mao, L. Yang and L. Qu, *Org. Biomol. Chem.*, 2019, **17**, 876

3 General procedure for antiproliferative activity assays

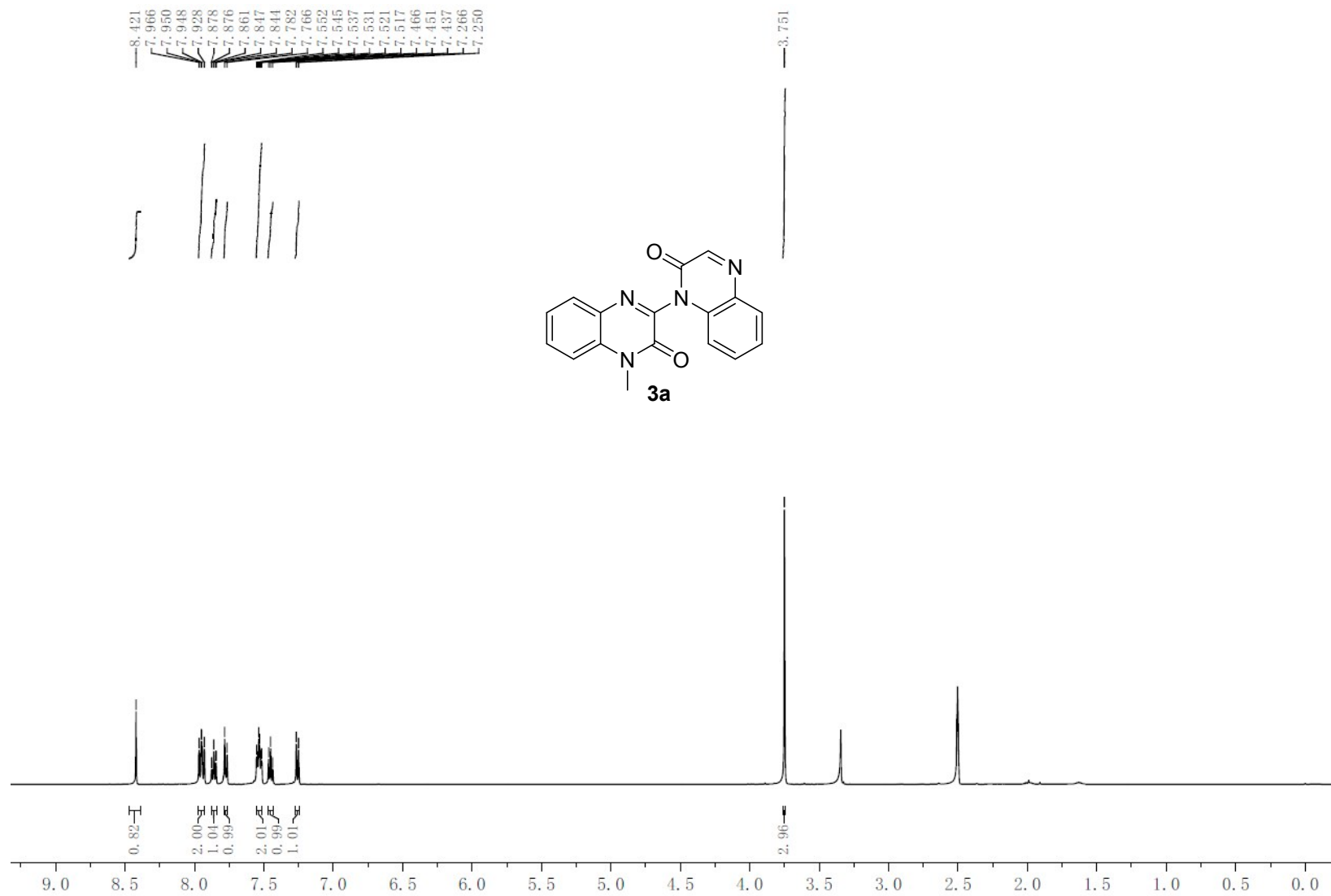
Exponentially growing cells were seeded into 96-well plates at a concentration of 5×10^3 cells per well. After 24 h incubation at 37 °C, the culture medium was removed and replaced with fresh medium containing the candidate compounds in different concentrations. The cells were incubated for another 72 h. Afterward, 20 μL of MTT solution (5 mg/mL) was added to all wells and incubated for 4 h at 37 °C. Discarded the suspension and added 150 μL of dimethyl sulfoxide (DMSO) to each well and shook the plates to dissolve the dark blue crystals (formazan); the absorbance was measured using a microplate reader at a wavelength of 562 nm. Each concentration was analyzed in triplicate and the experiment was repeated three times. The average 50% inhibitory concentration (IC_{50}) was determined from the dose-response curves according to the inhibition ratio for each concentration.

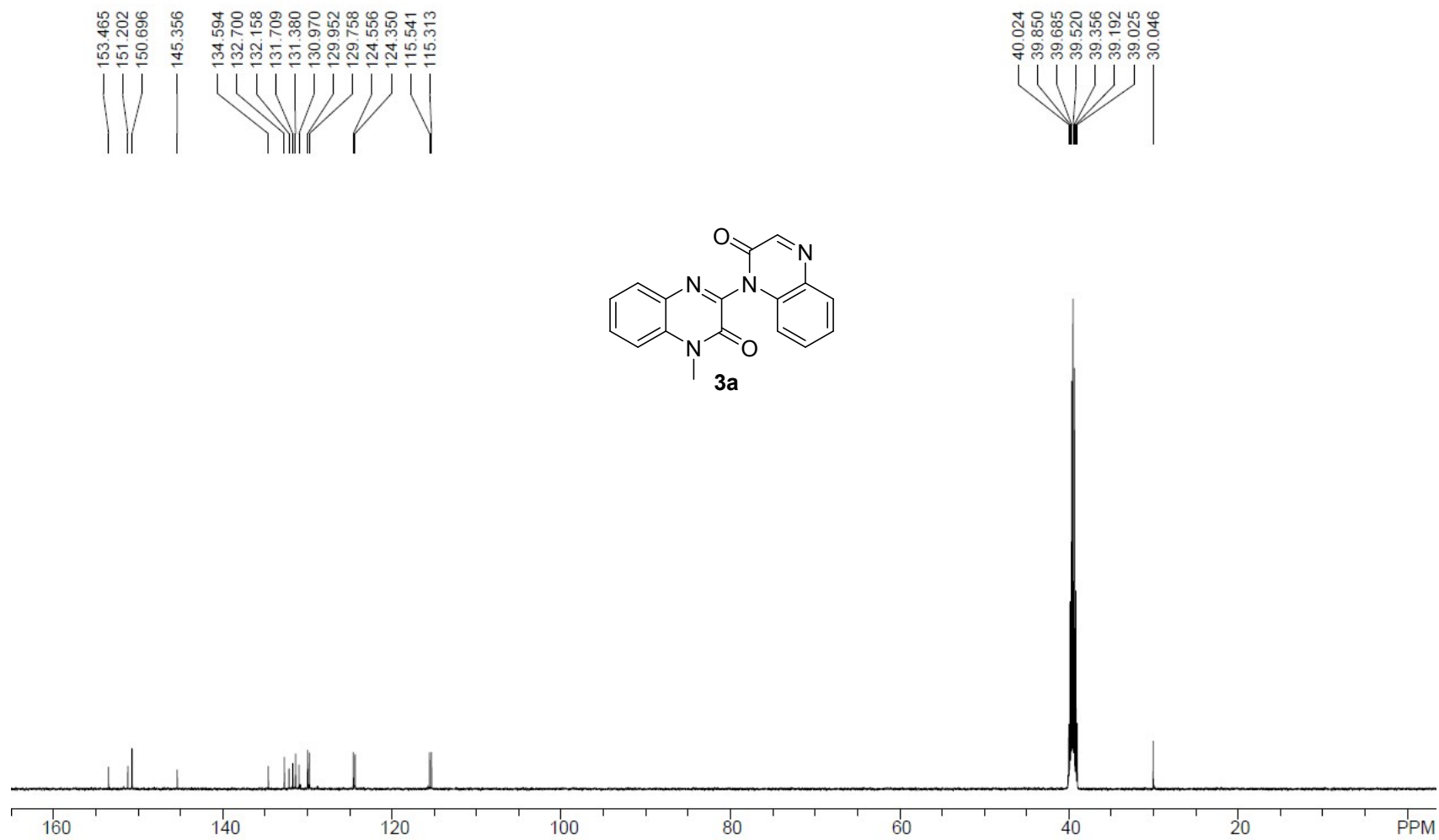
In vitro antiproliferative activity of products on EC109 (human esophageal carcinoma), Te-1 (human esophageal carcinoma), BGC-823 (human gastric carcinoma), and MGC-803 (human gastric carcinoma)

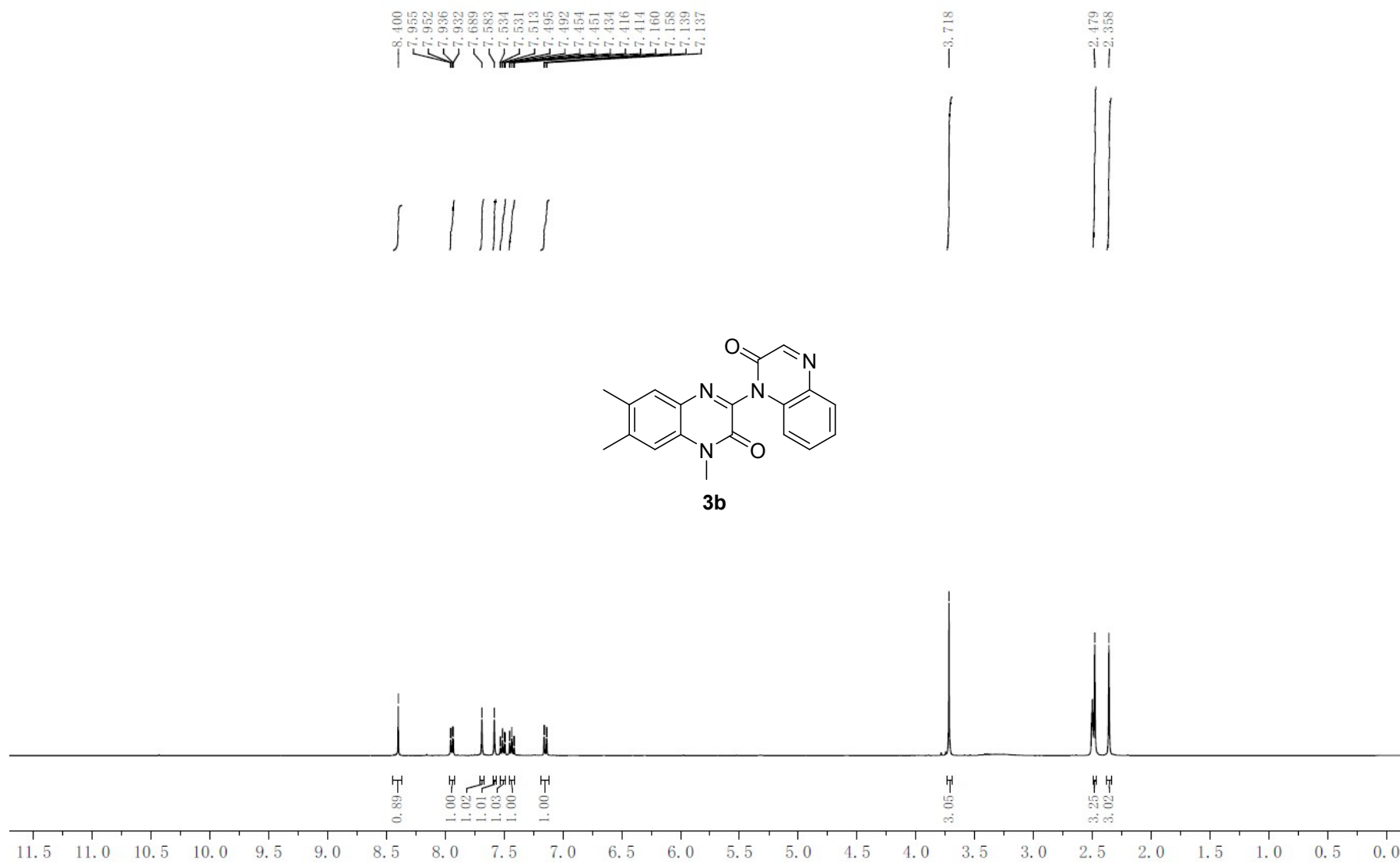
Compound	IC_{50} (μM)			
	EC109	Te-1	BGC-823	MGC-803
3a	>128	>128	97.4 \pm 13.1	110.9 \pm 14.3
3c	>128	>128	113.7 \pm 20.1	117 \pm 18.8
3e	>128	>128	102.2 \pm 14.2	103.3 \pm 16.3
3f	>128	>128	115.8 \pm 21.0	108.8 \pm 17.5
3g	>128	>128	95.2 \pm 7.3	80.3 \pm 12.1
3h	>128	>128	26.4 \pm 4.3	28.2 \pm 6.6
3j	>128	>128	>128	107.2 \pm 14.7
3k	>128	>128	118.0 \pm 18.5	117.5 \pm 20.3
3l	>128	>128	111.8 \pm 22.7	112.5 \pm 16.2
5c	>128	>128	>128	121.1 \pm 17.3
5e	>128	>128	107.7 \pm 19.6	104.8 \pm 10.3

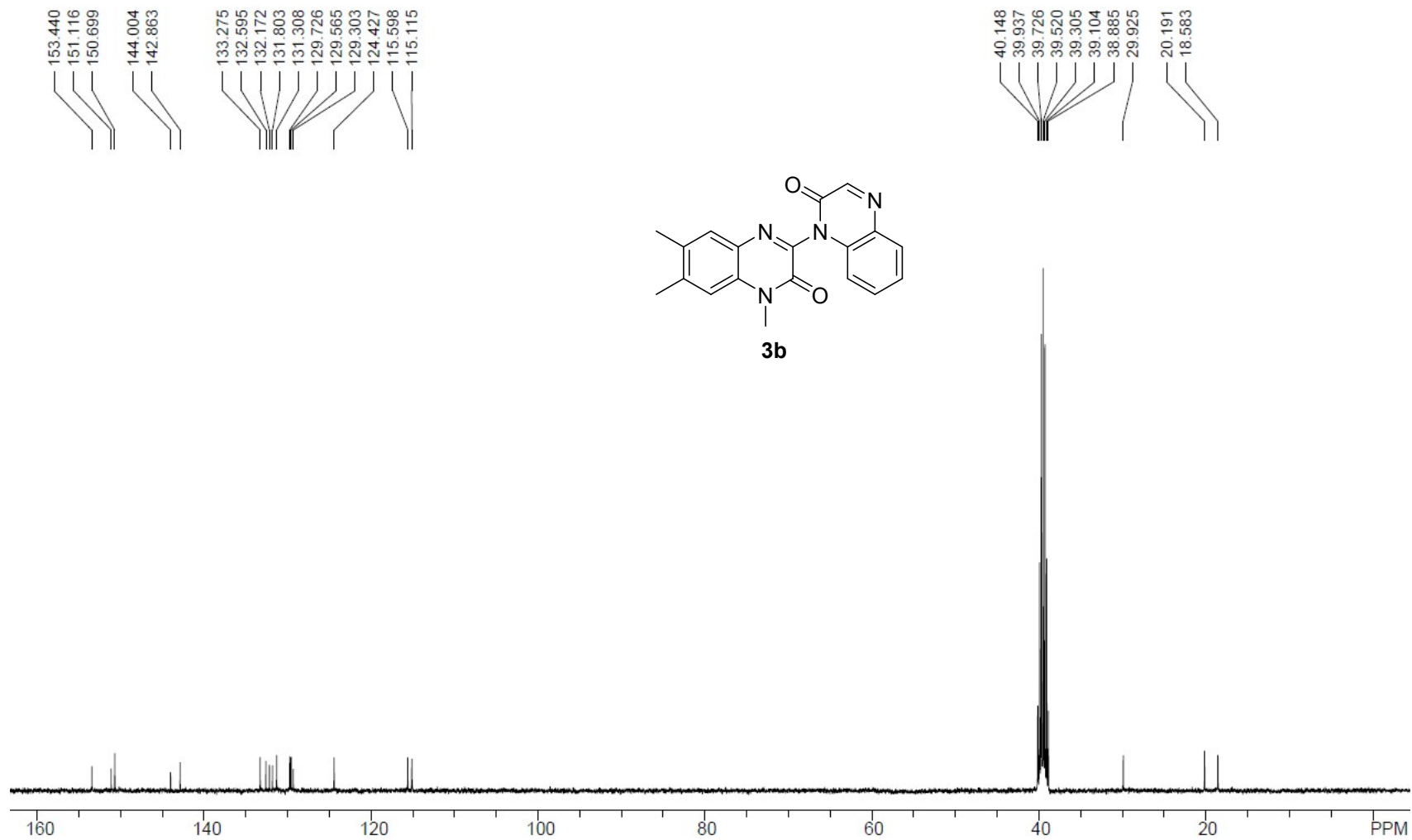
5f	>128	>128	108.1±17.8	112.0±9.4
5g	>128	>128	114.3±20.8	121.2±19.3
5h	>128	>128	117.5±24.4	90.1±11.1
5j	100.9±13.8	>128	101.3±16.8	82.3±13.8

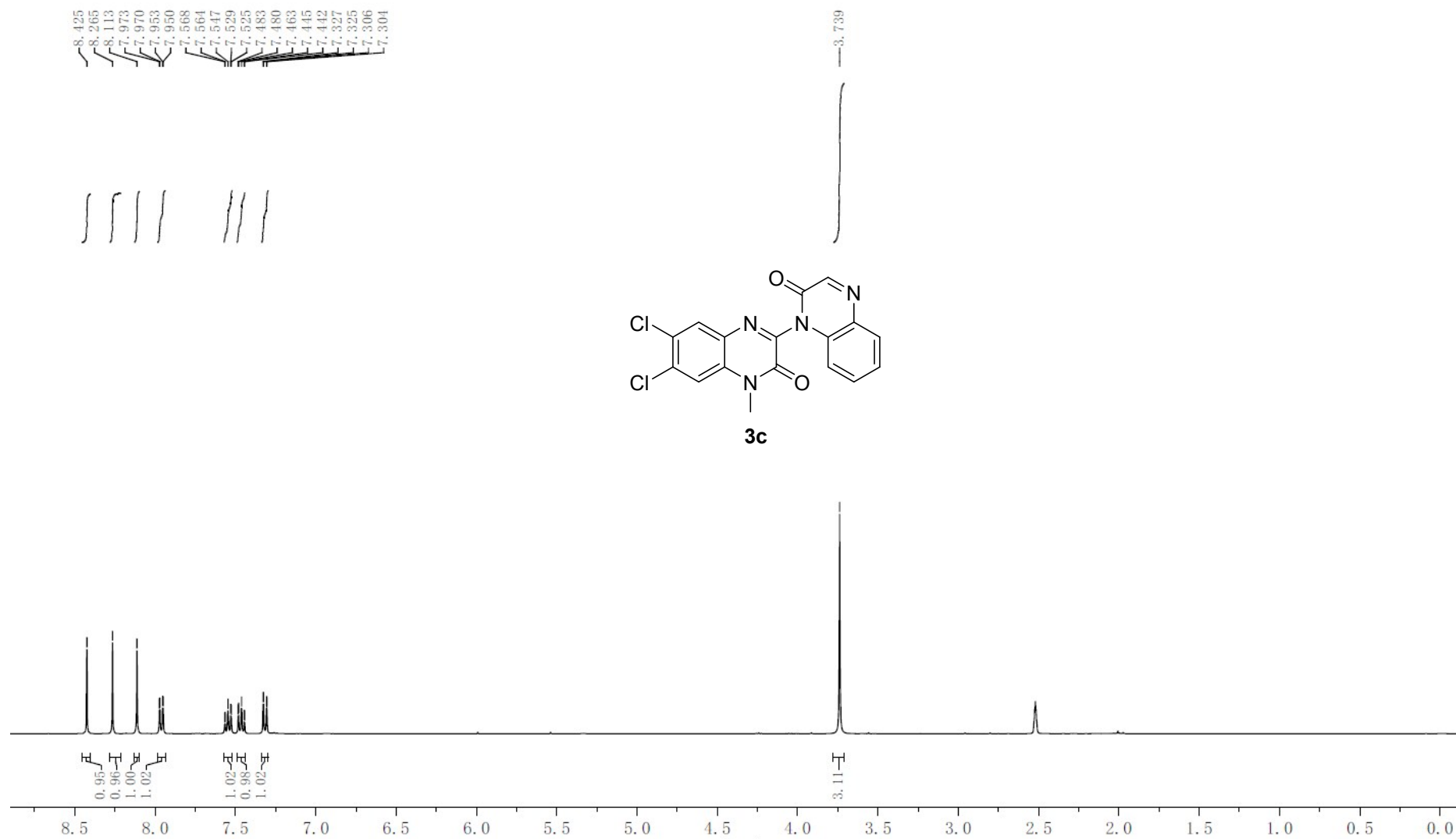
4 Copies of ¹H and ¹³C NMR Spectra

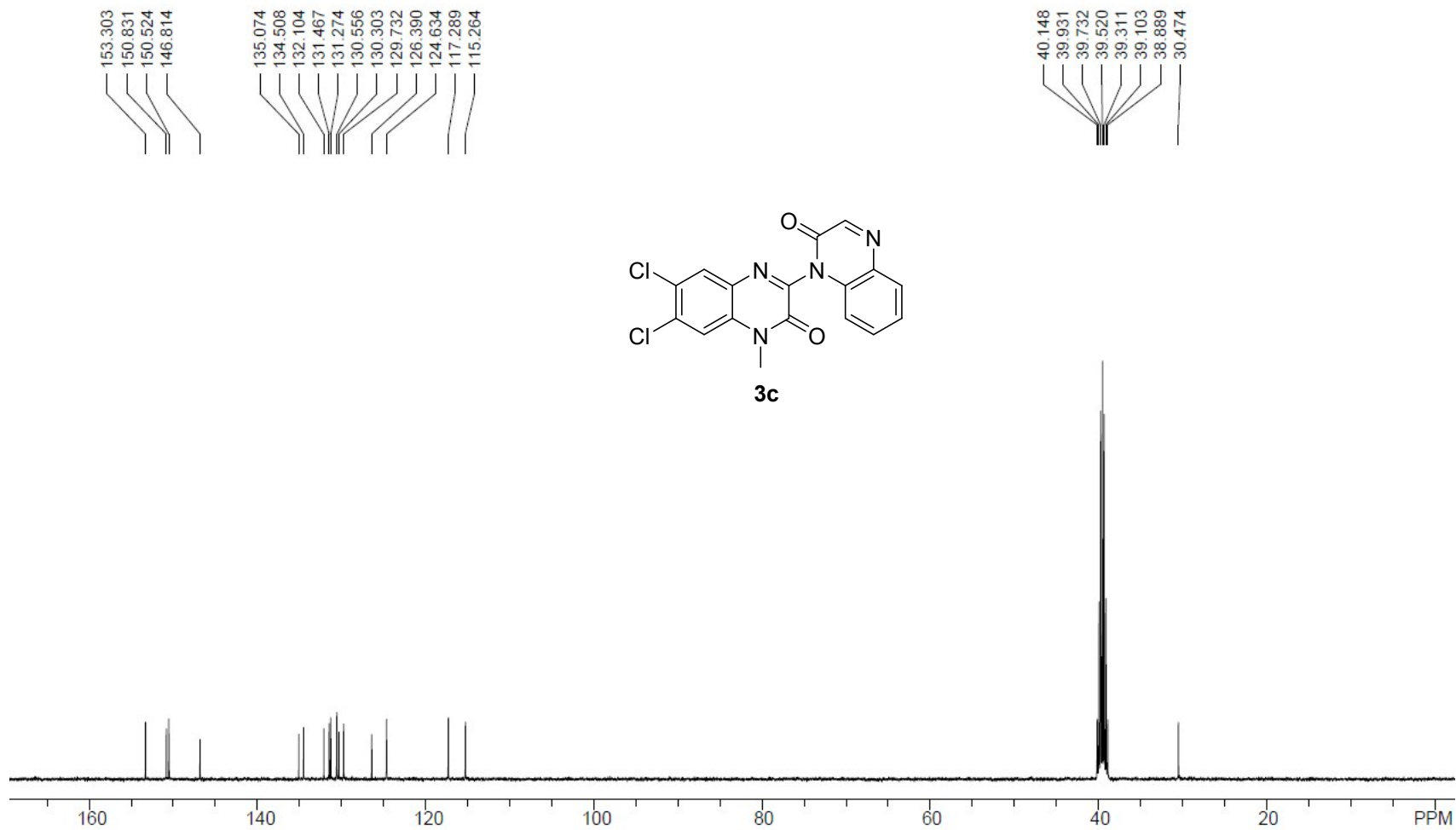




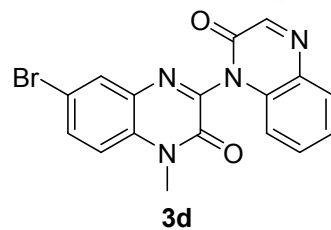




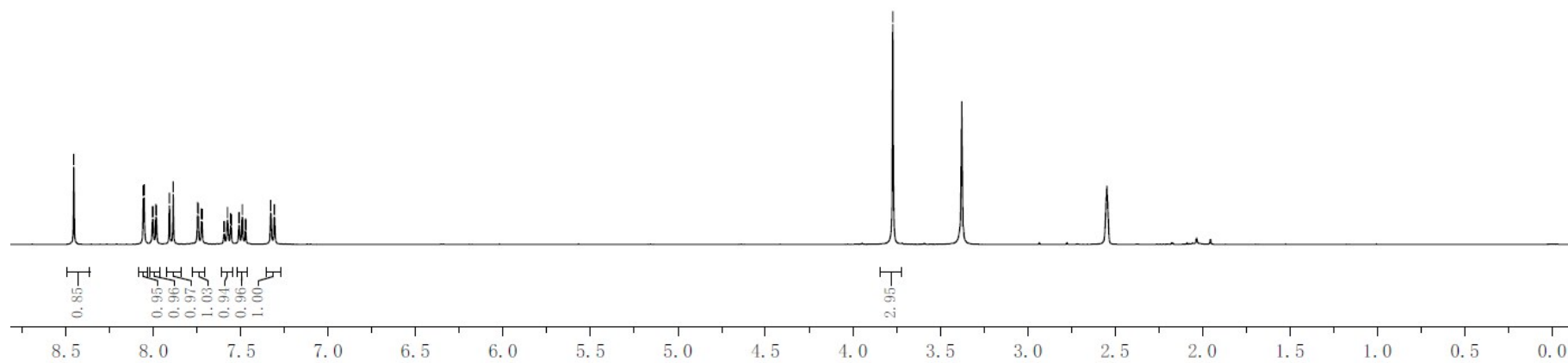


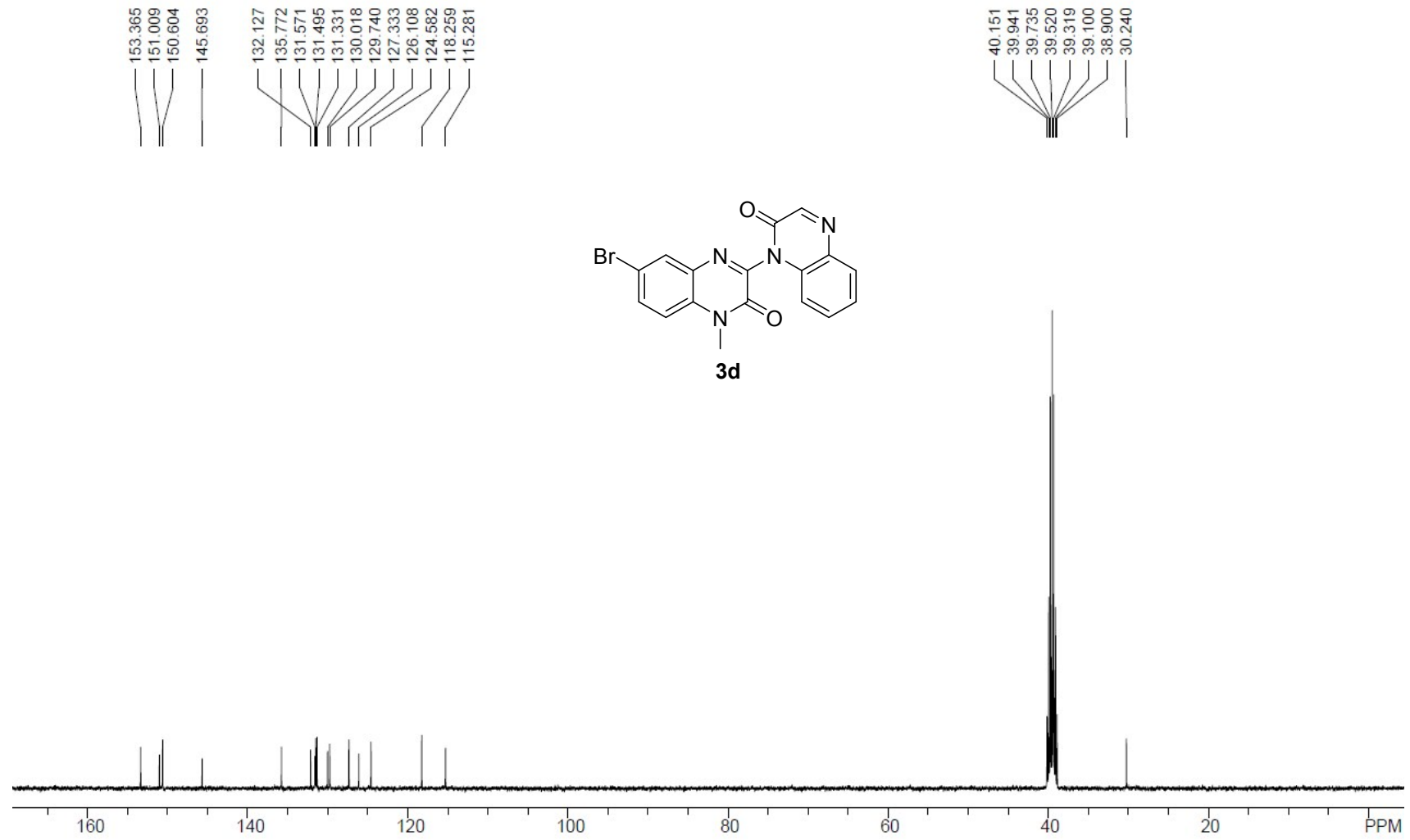


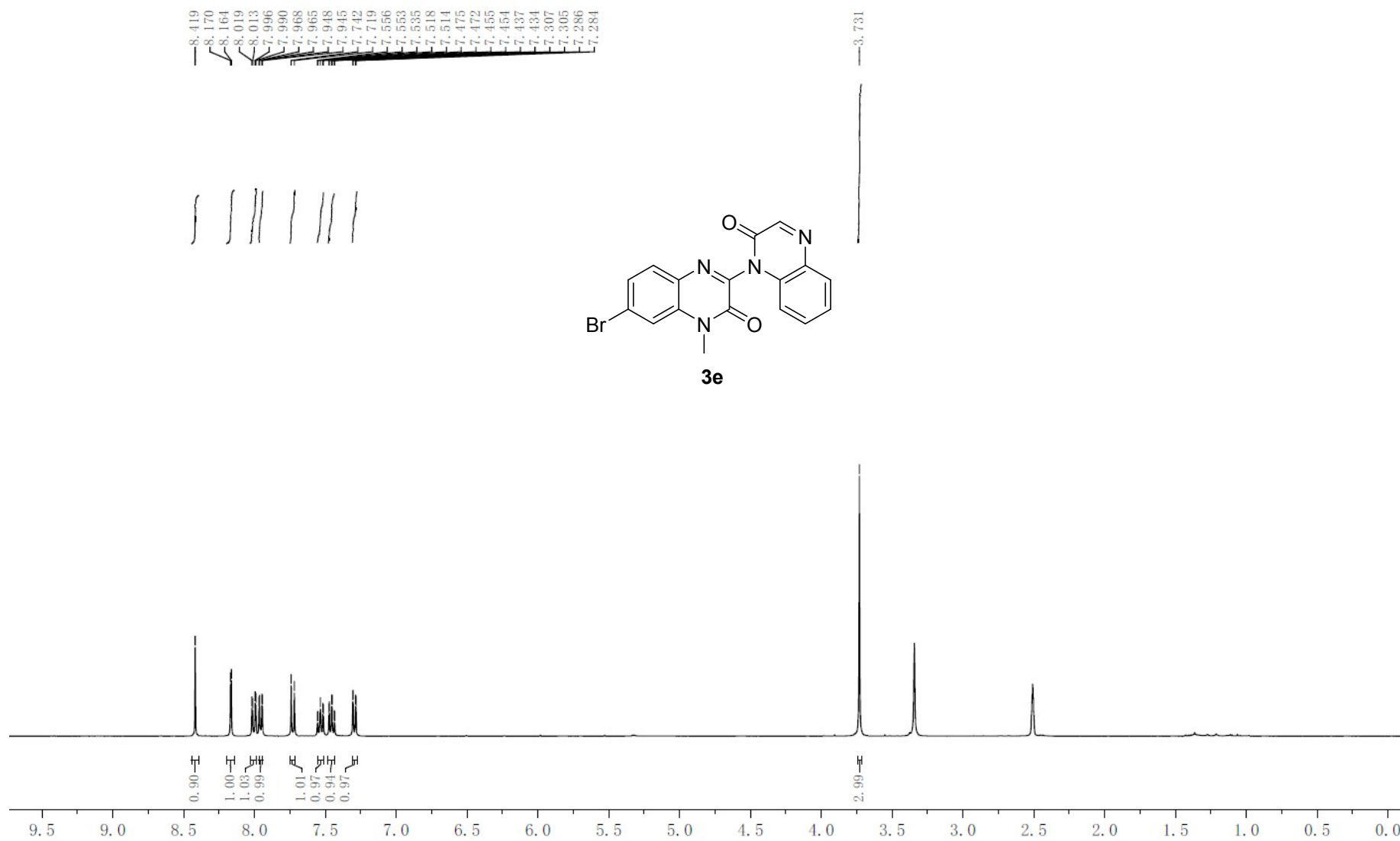
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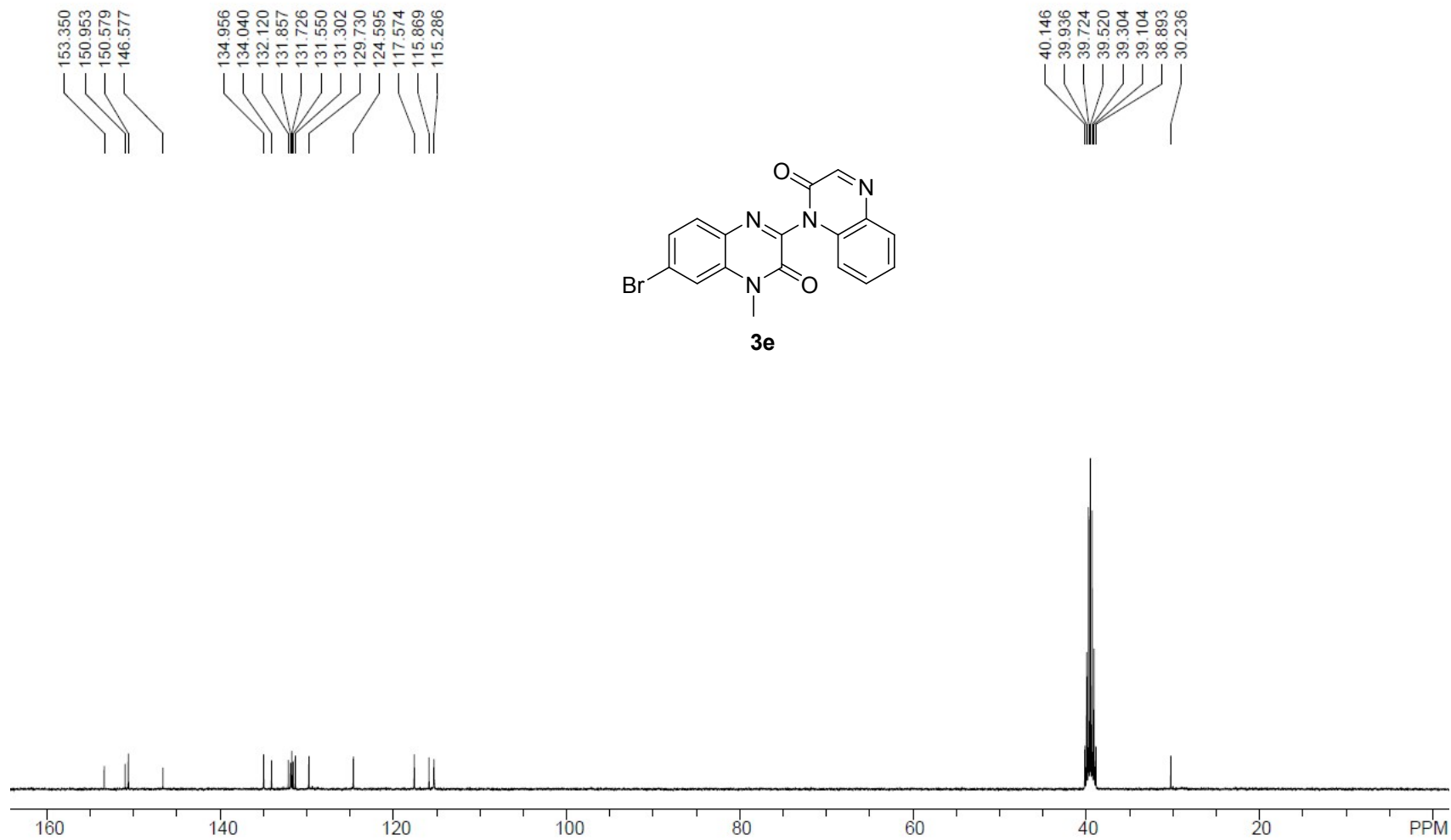


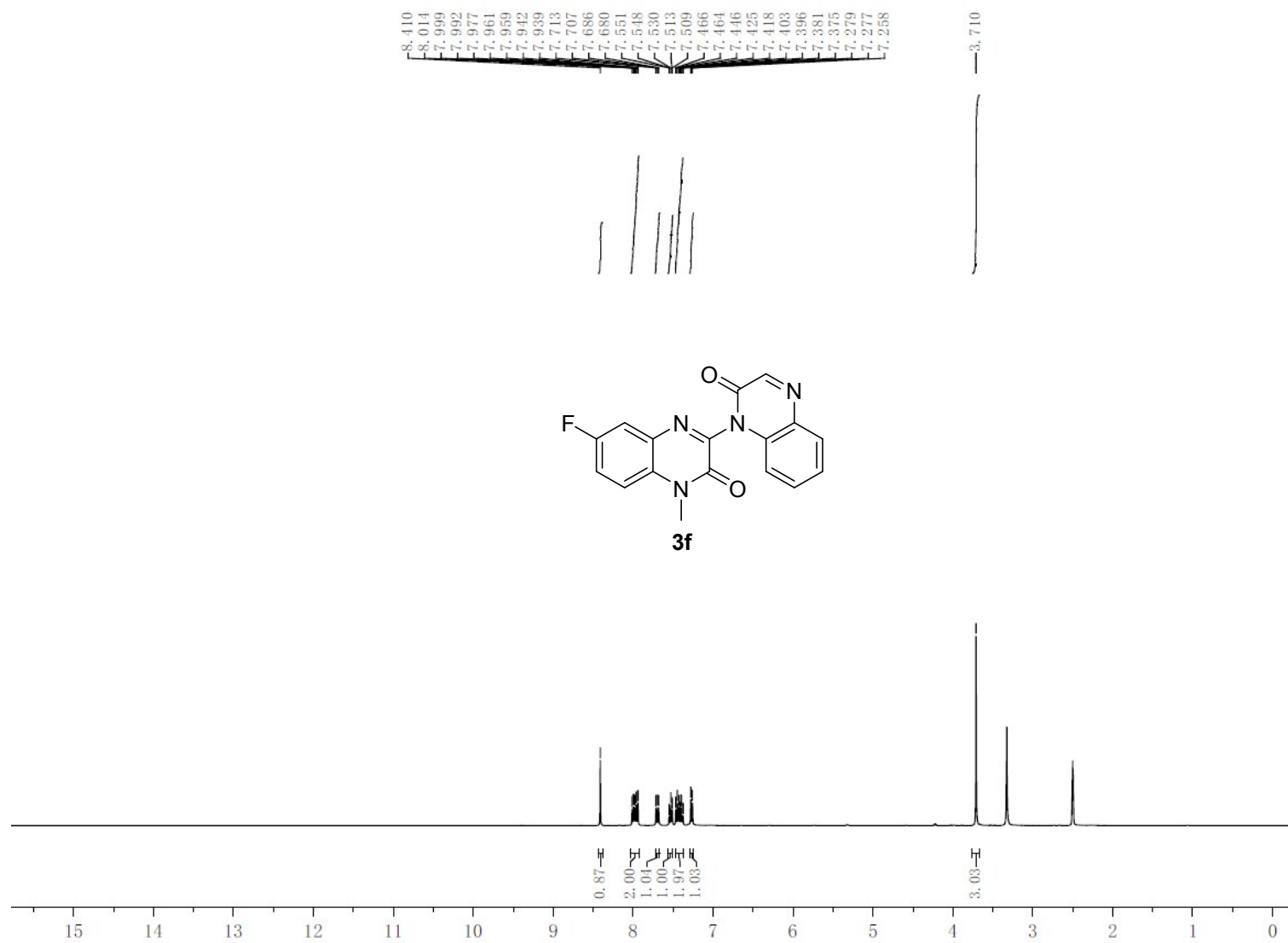
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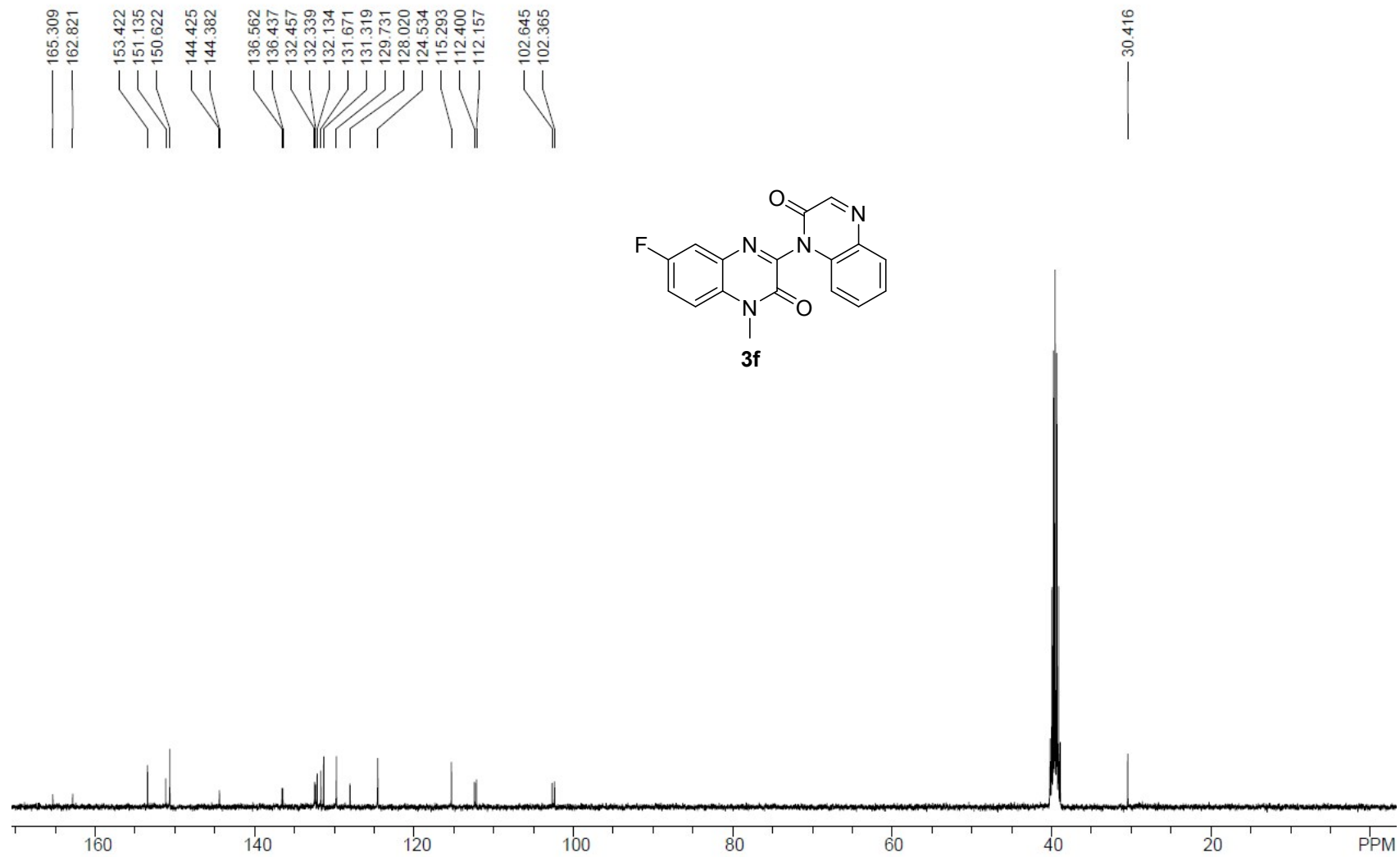


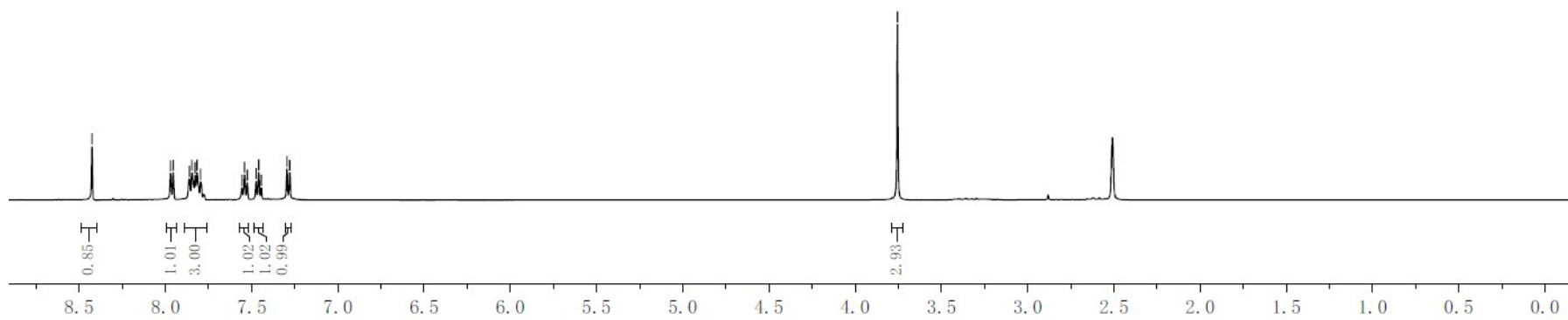
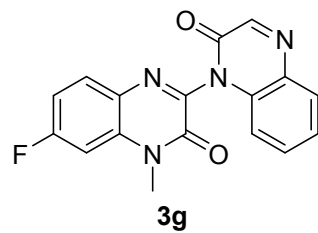
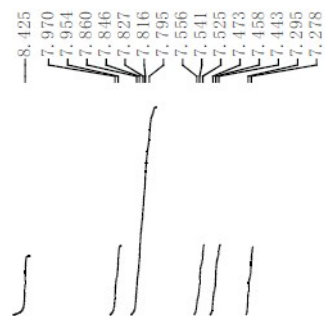


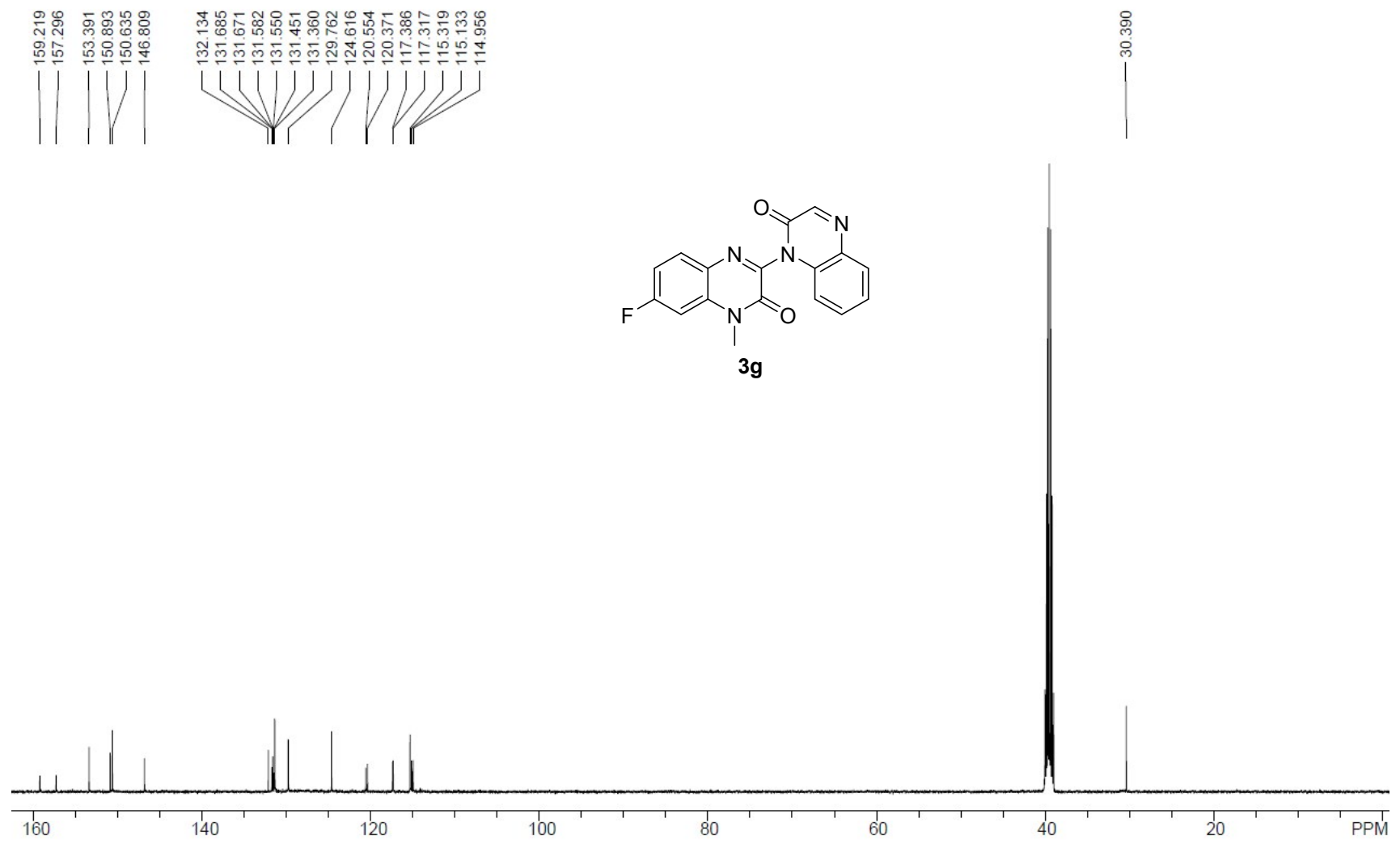








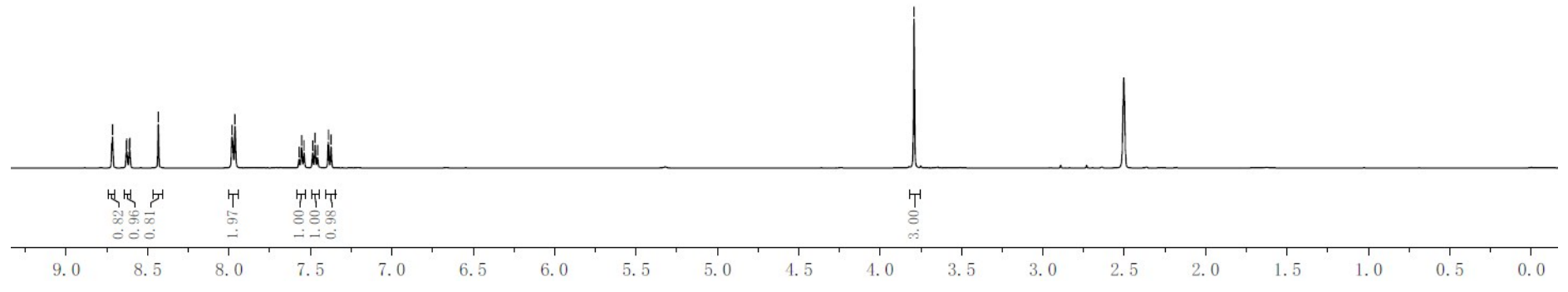
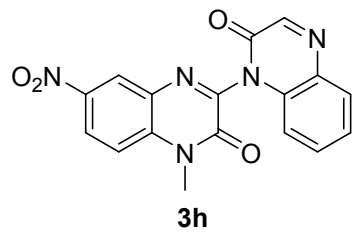


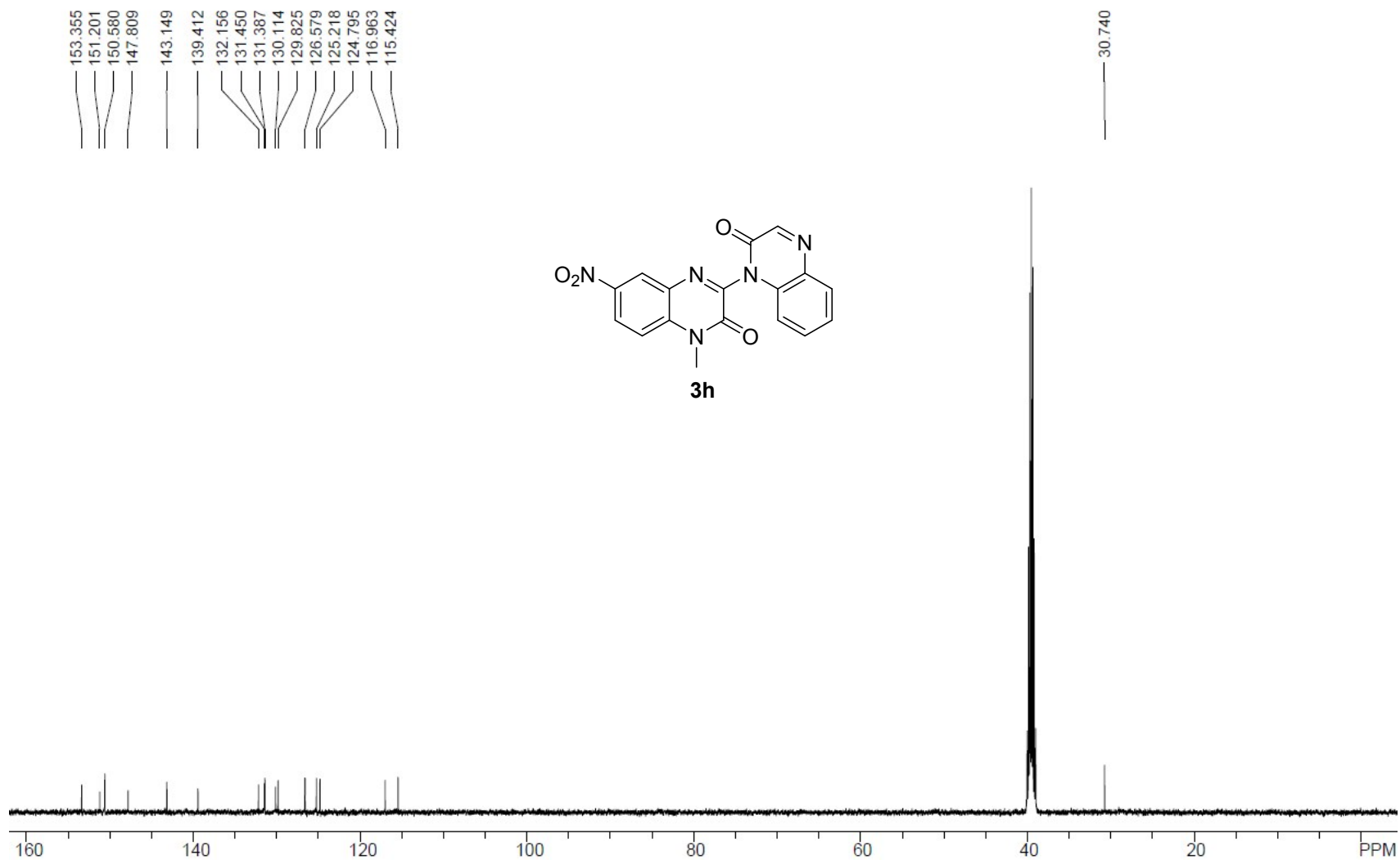


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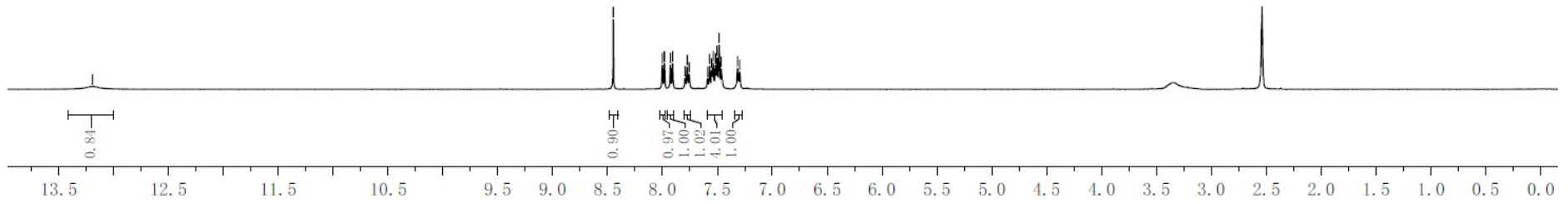
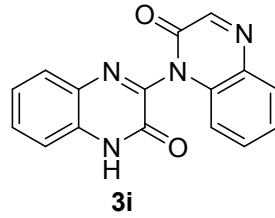
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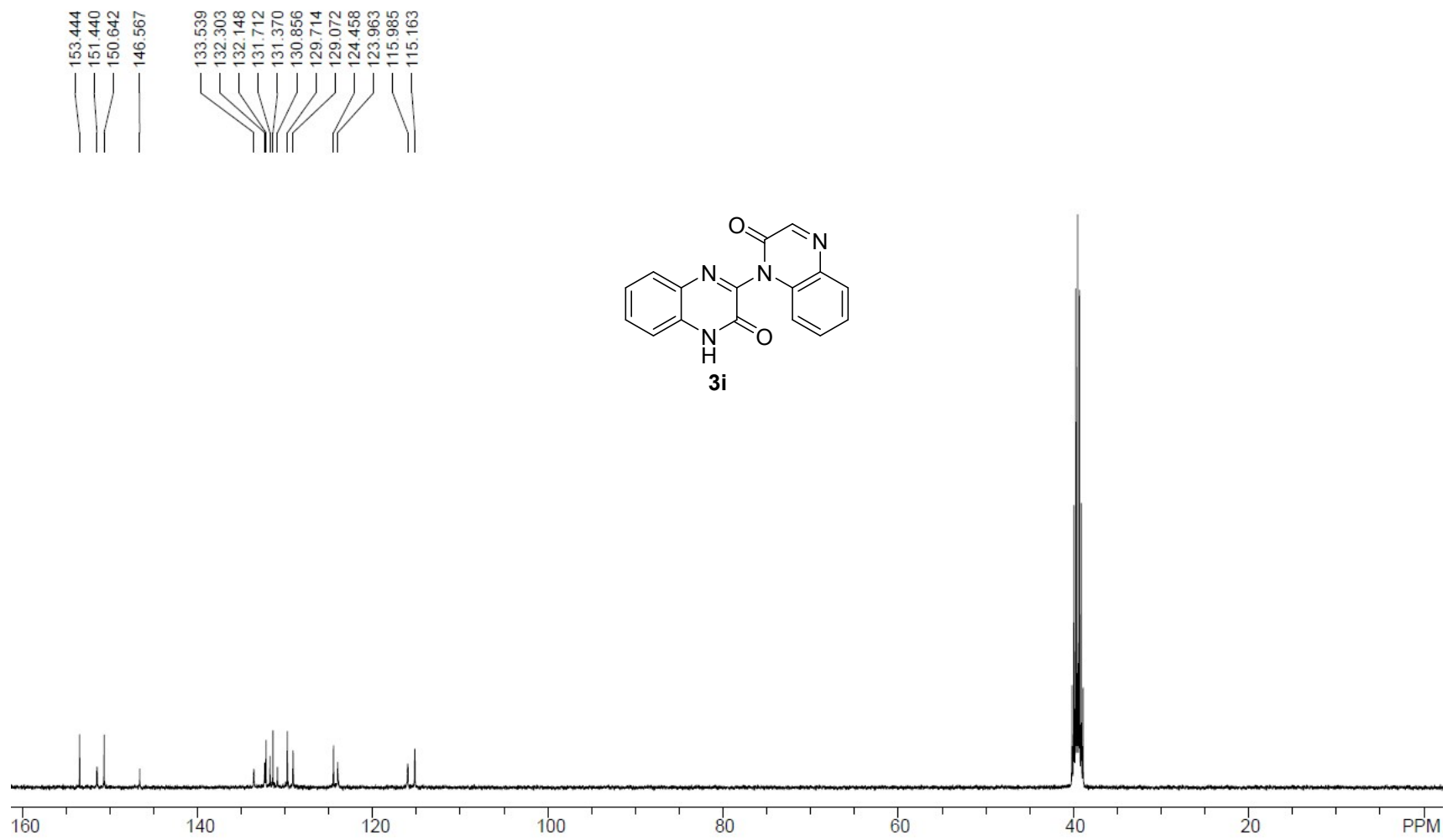


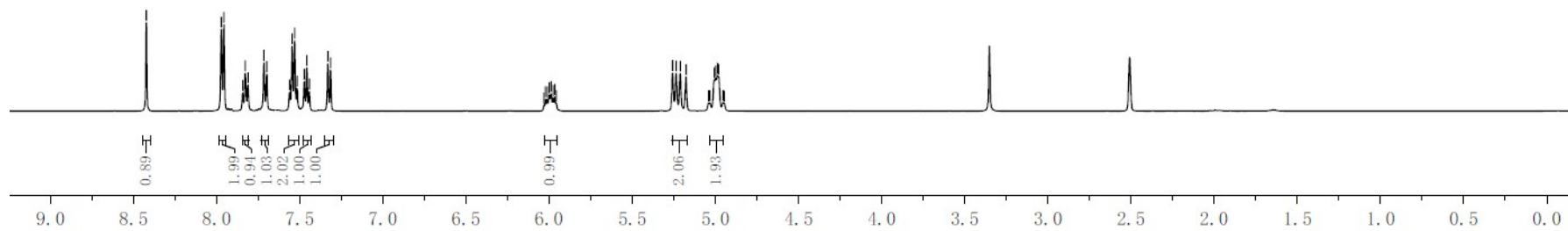
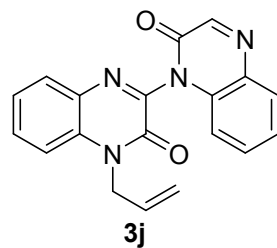
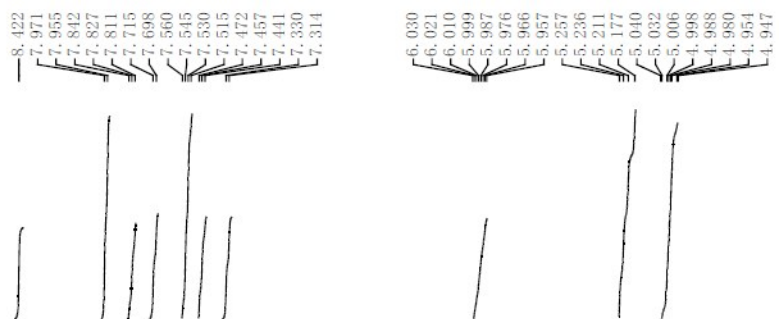


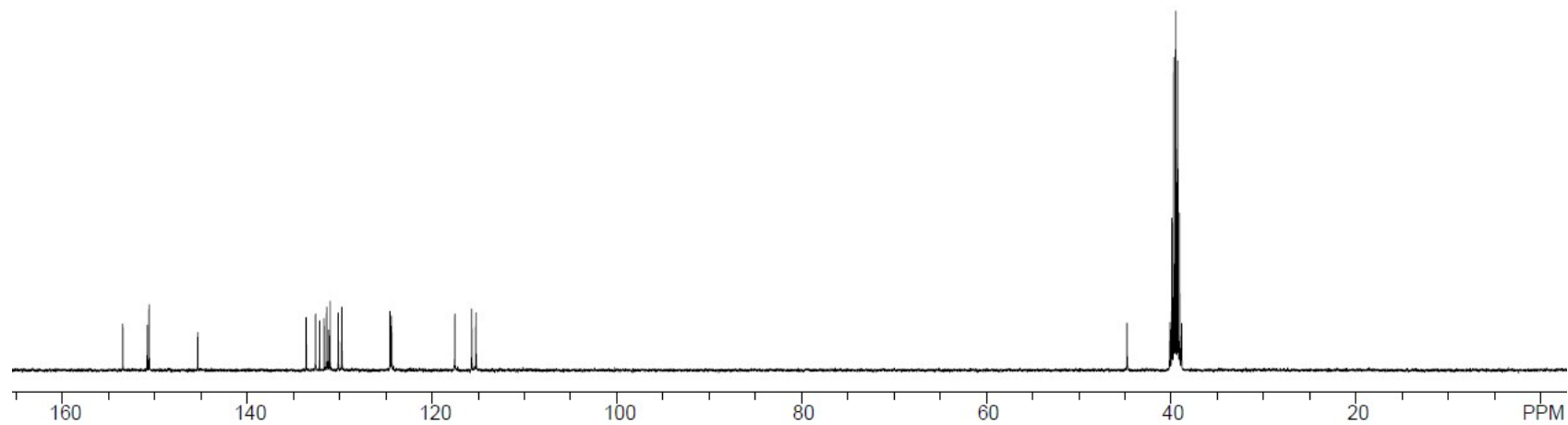
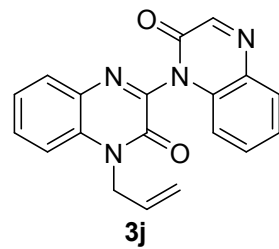
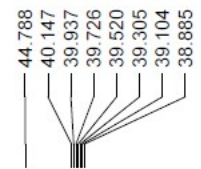
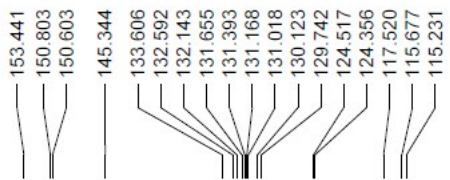
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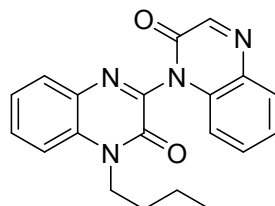
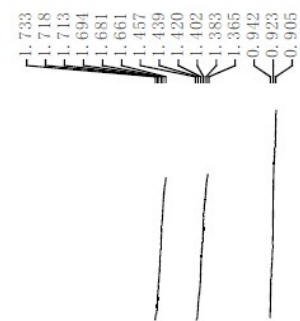
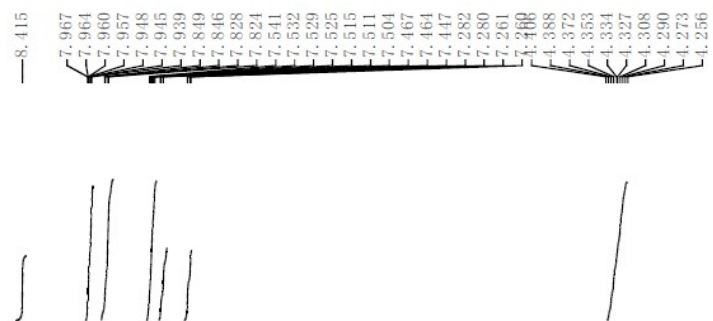
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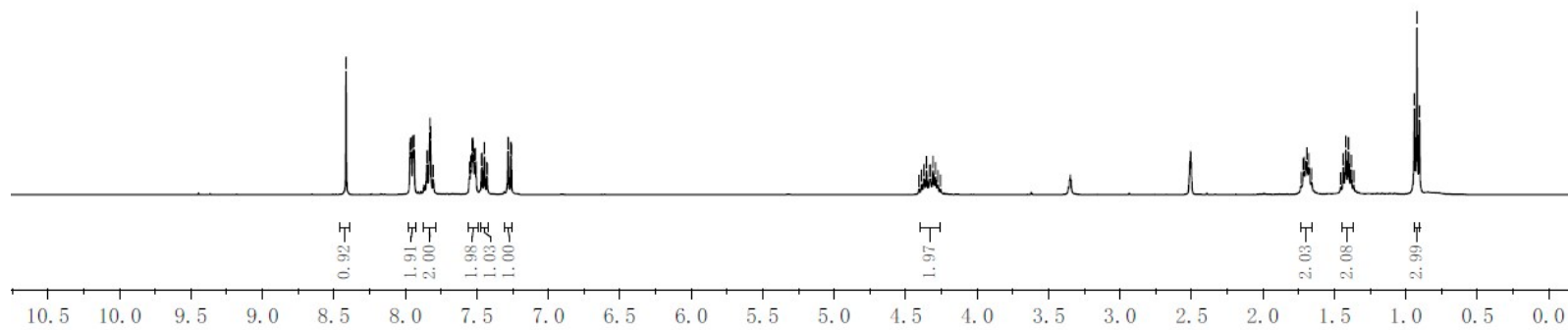


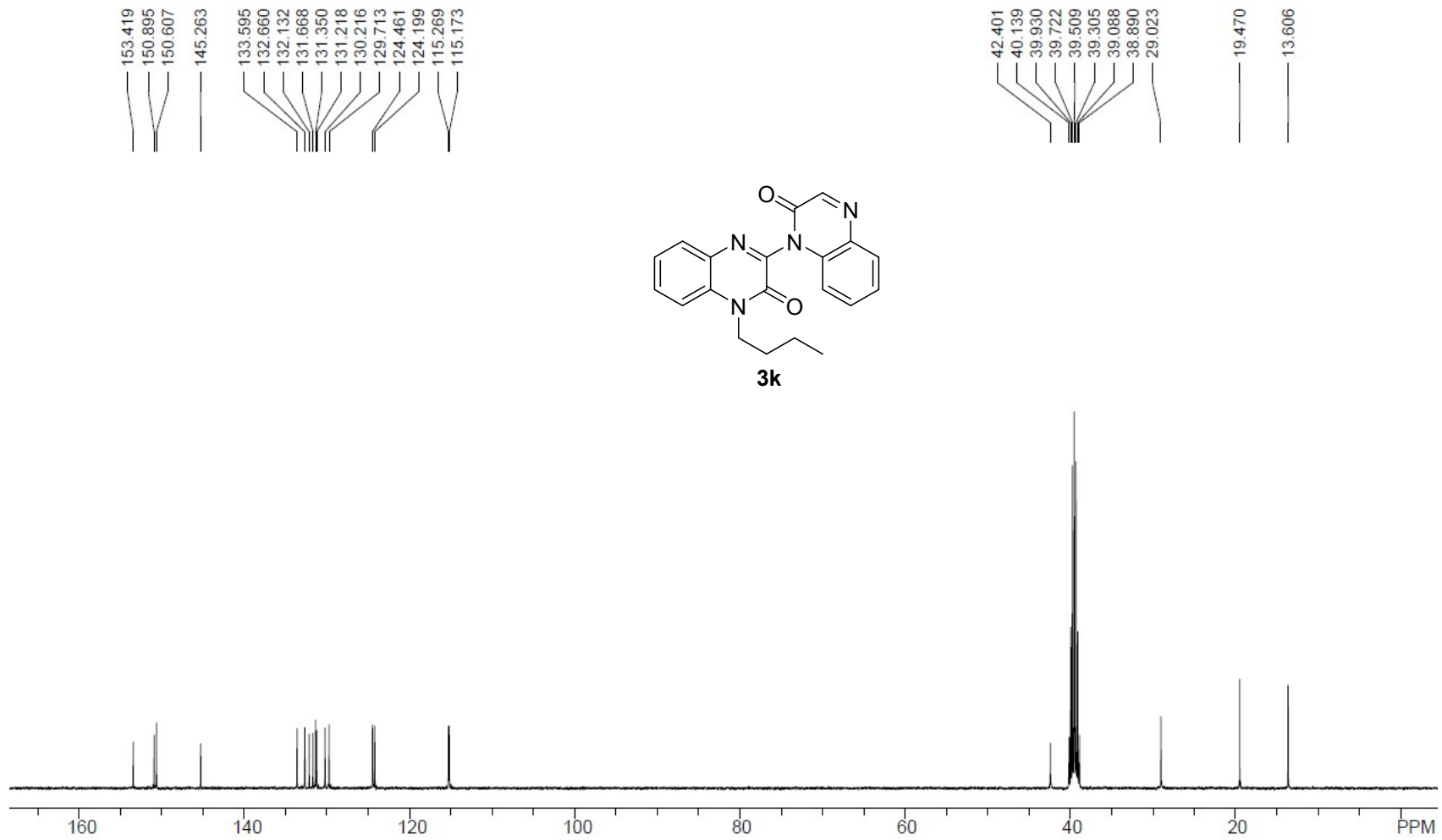




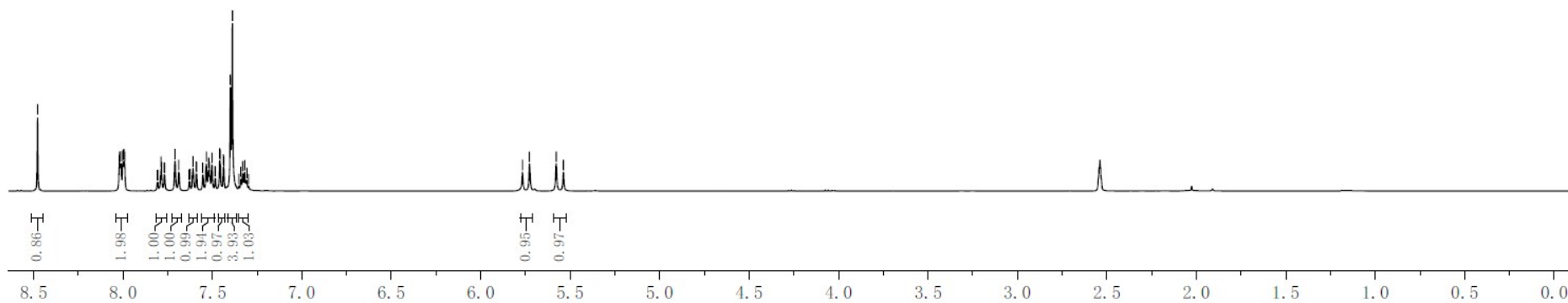
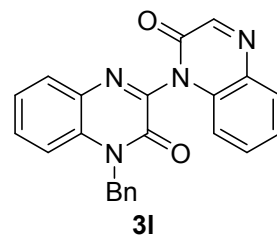


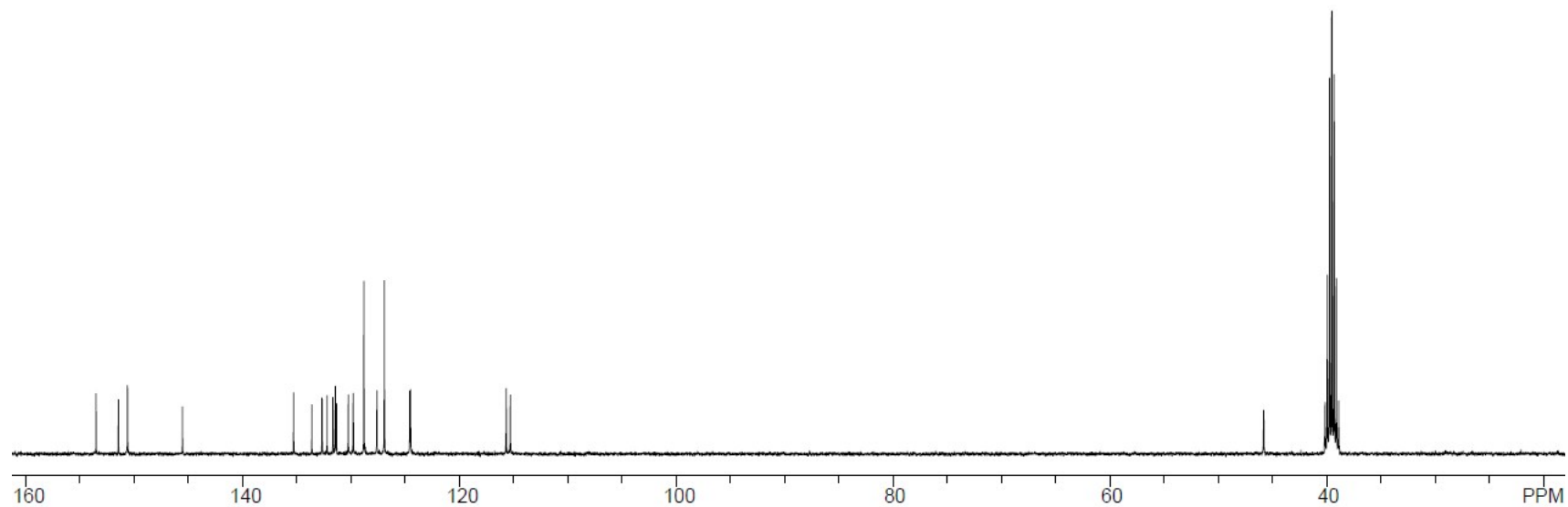
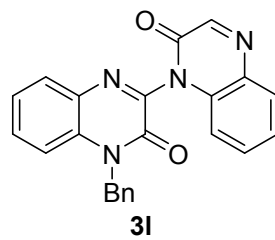
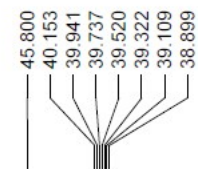
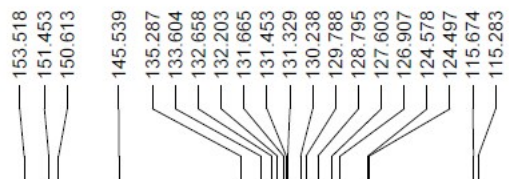
3k





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7.587
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5.538





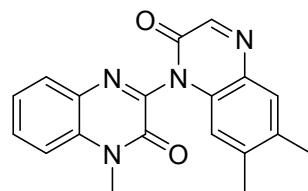
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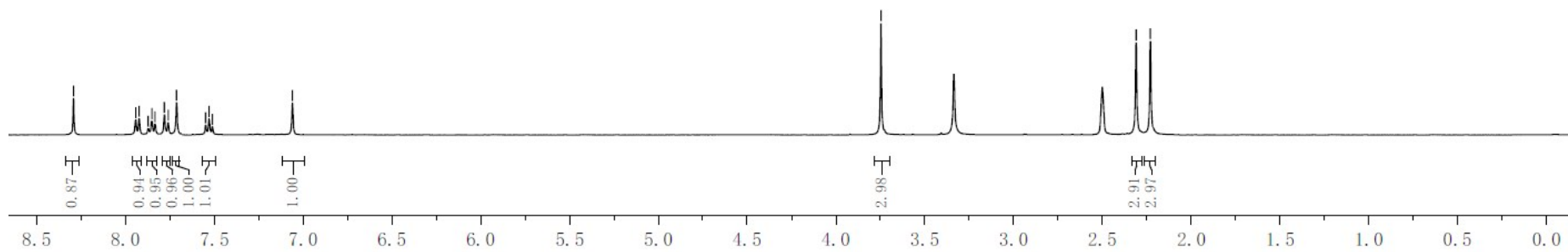
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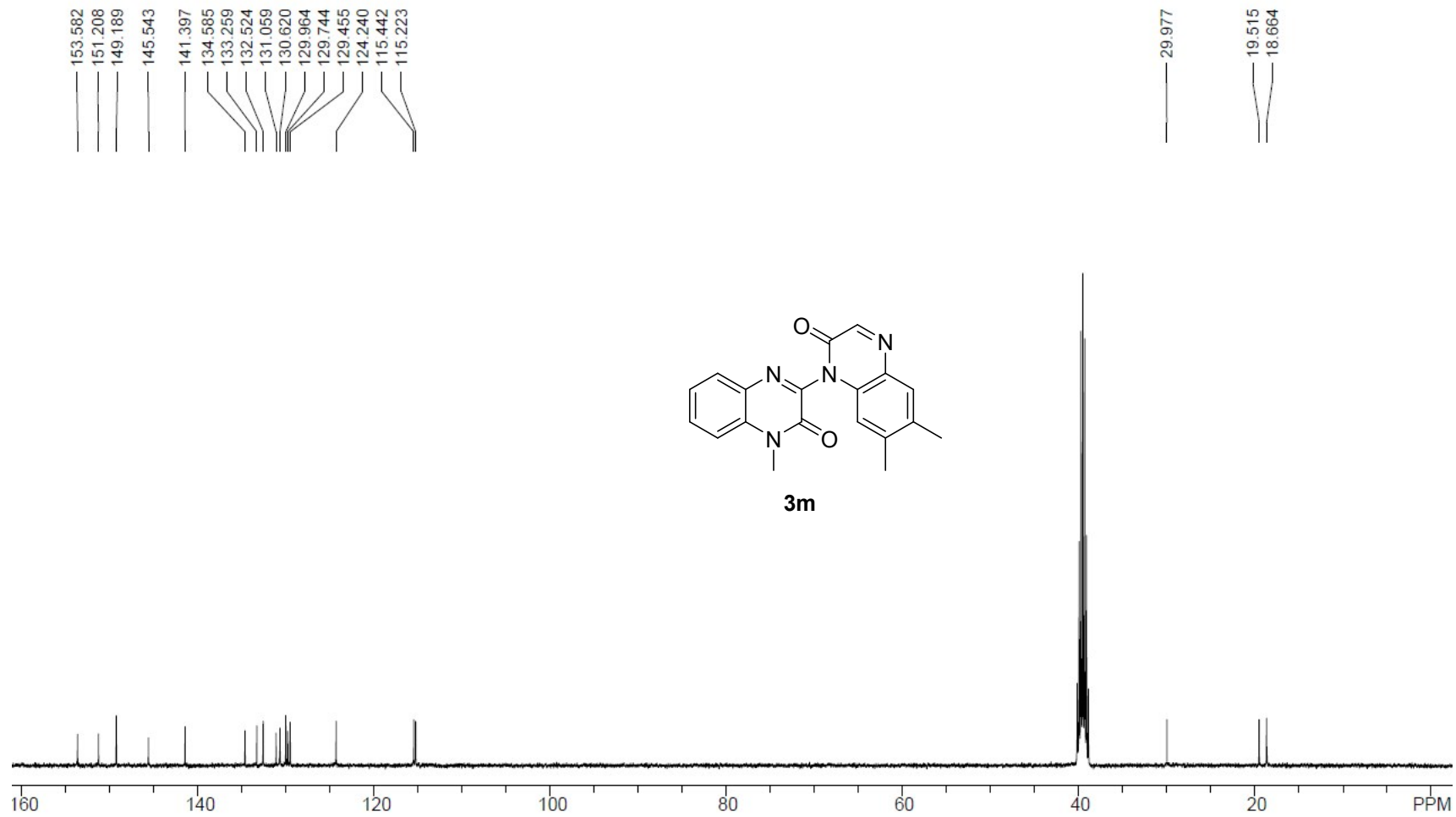


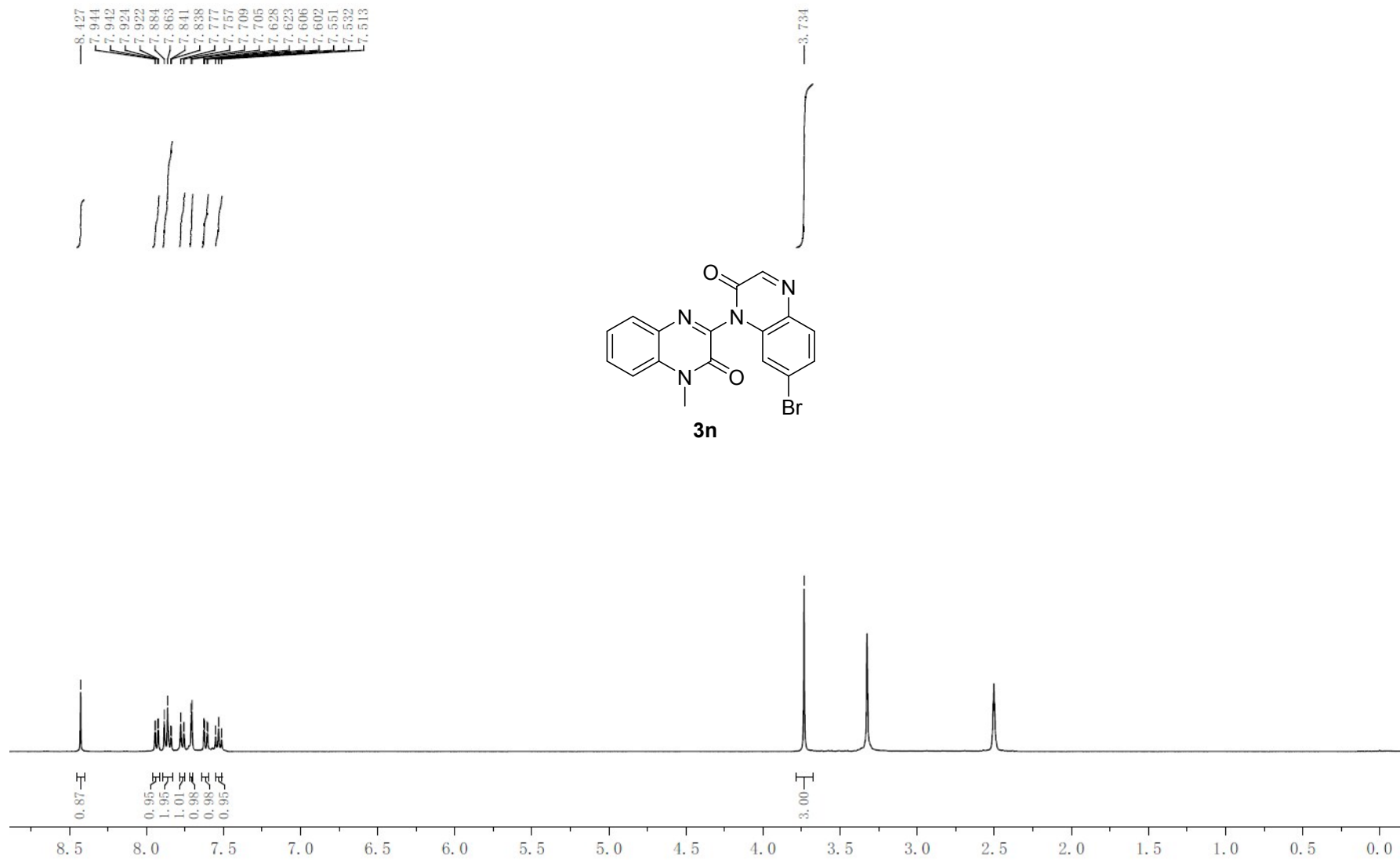
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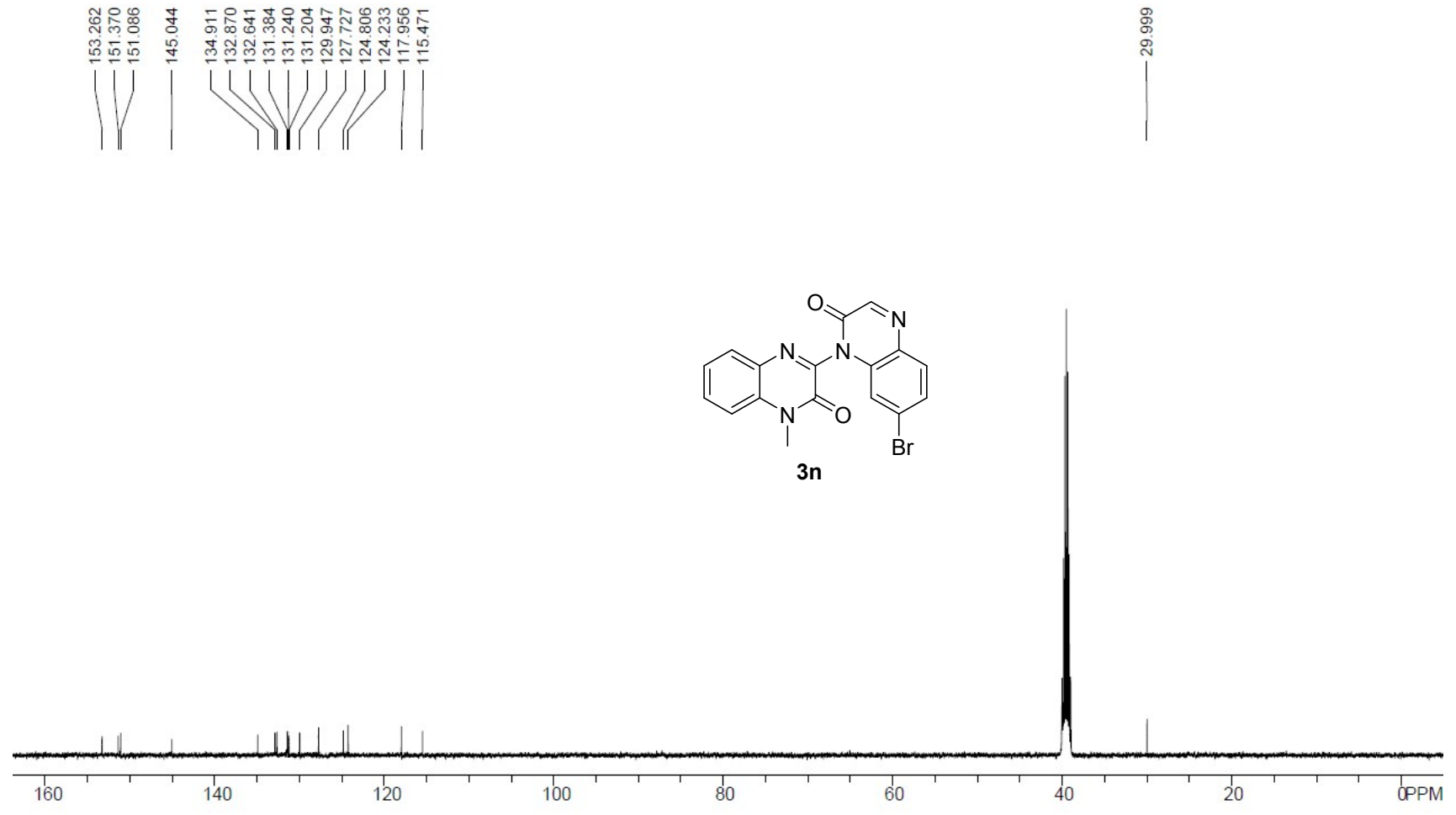


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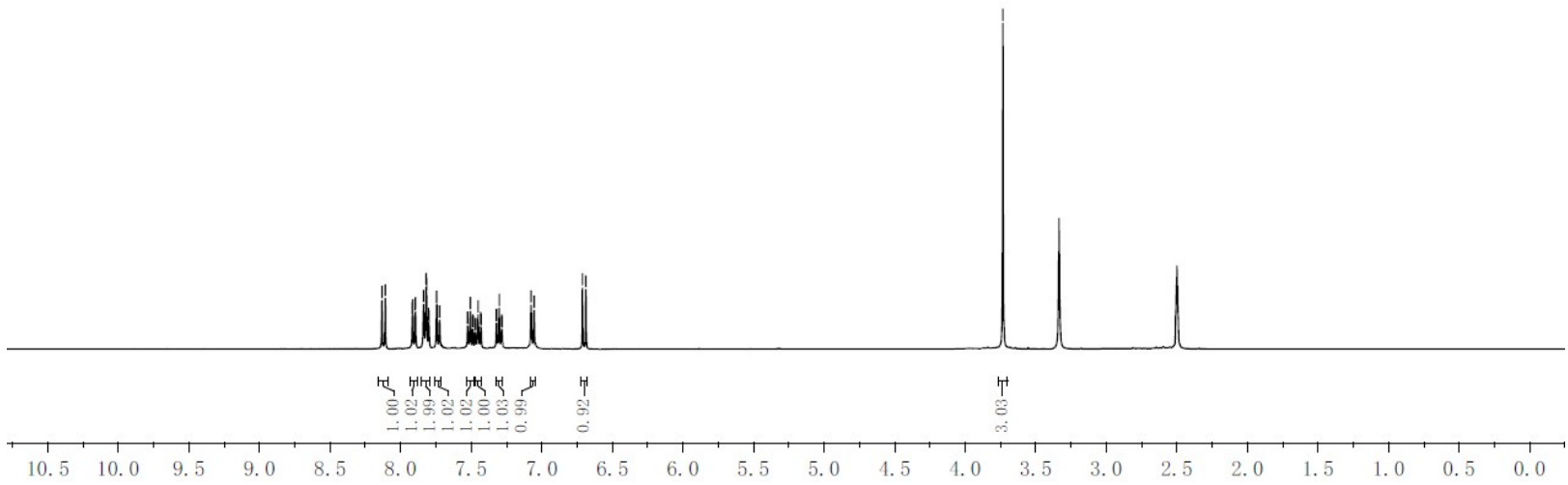


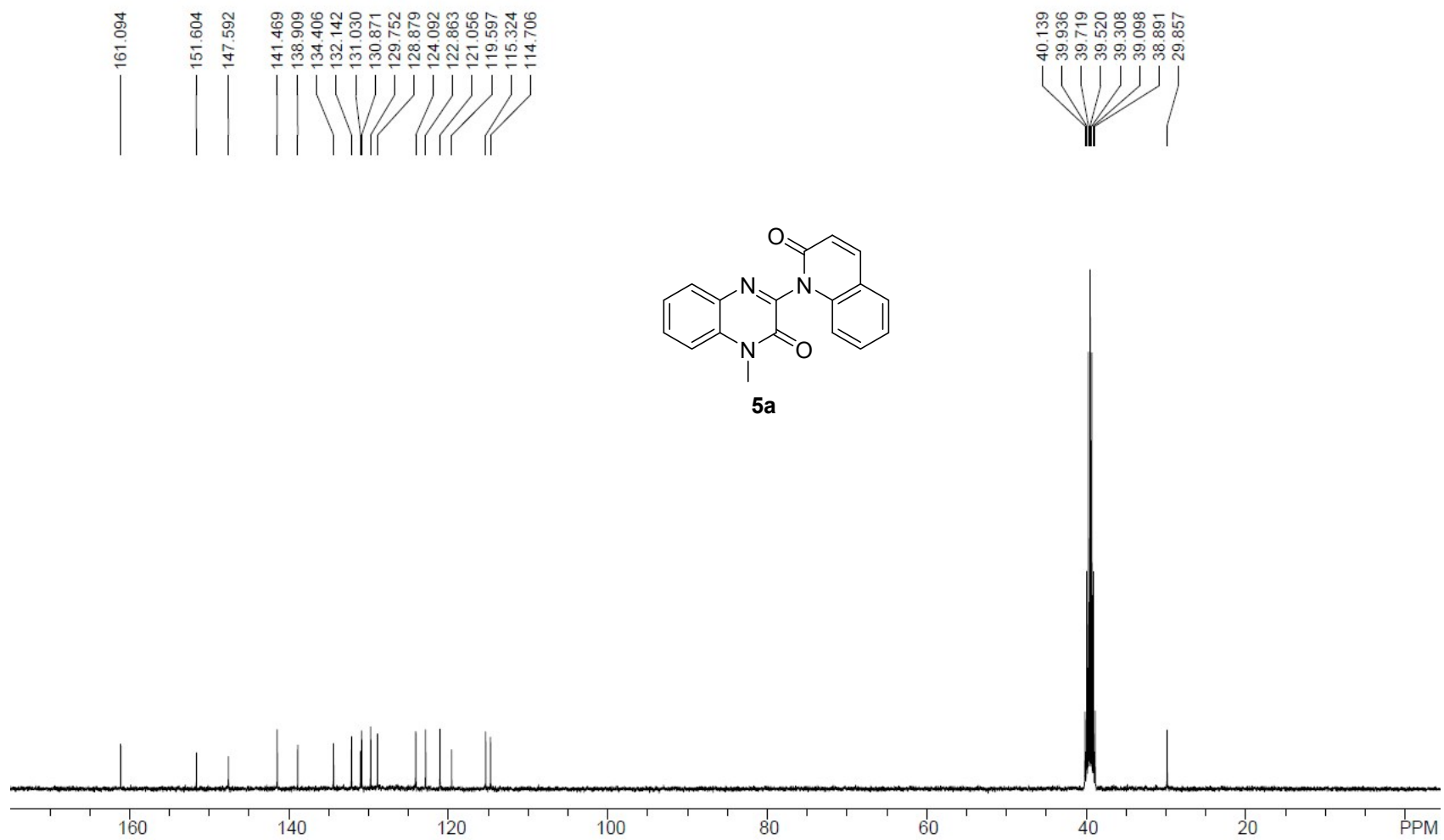


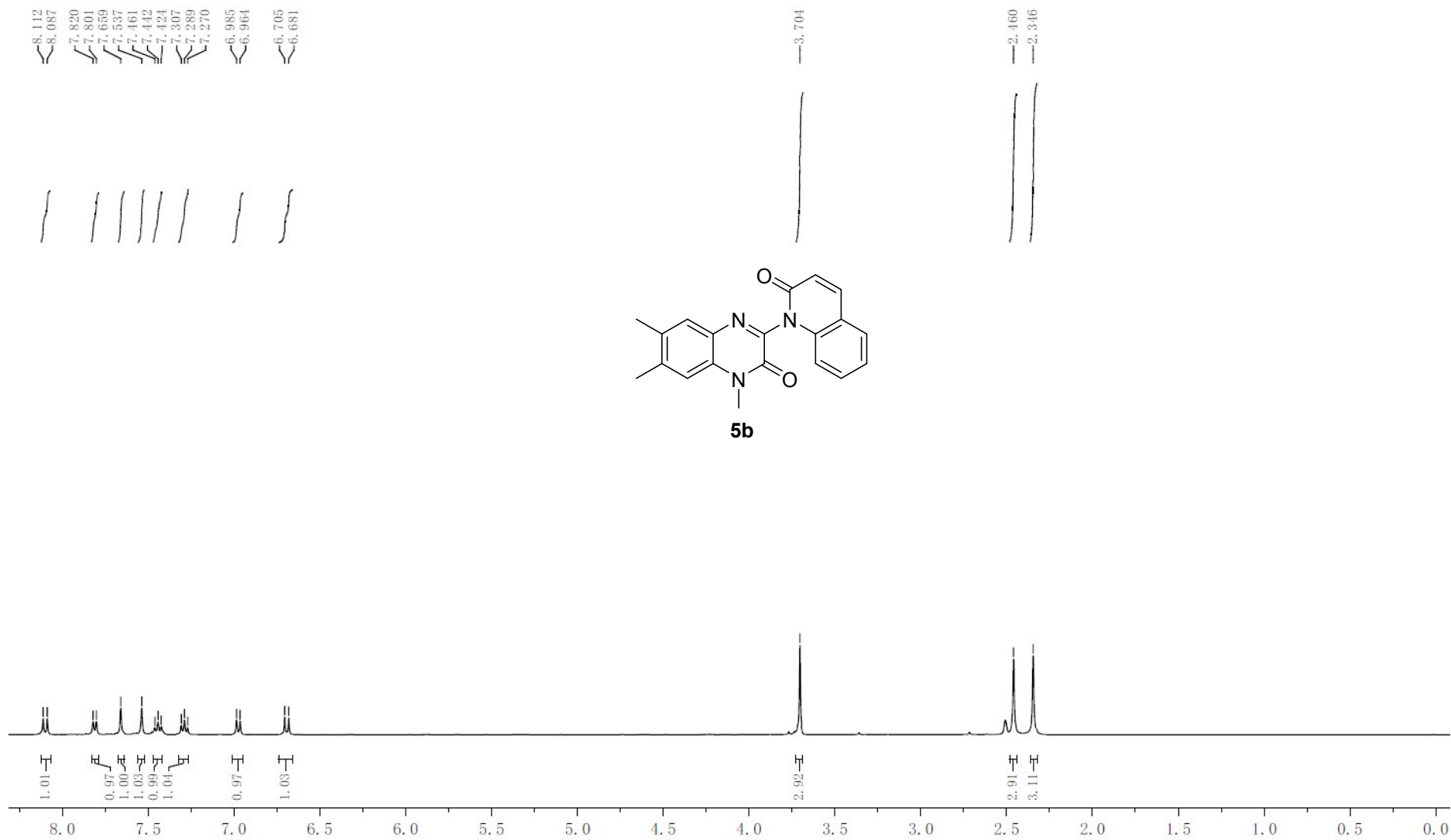
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7.507
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7.486
7.473
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6.688

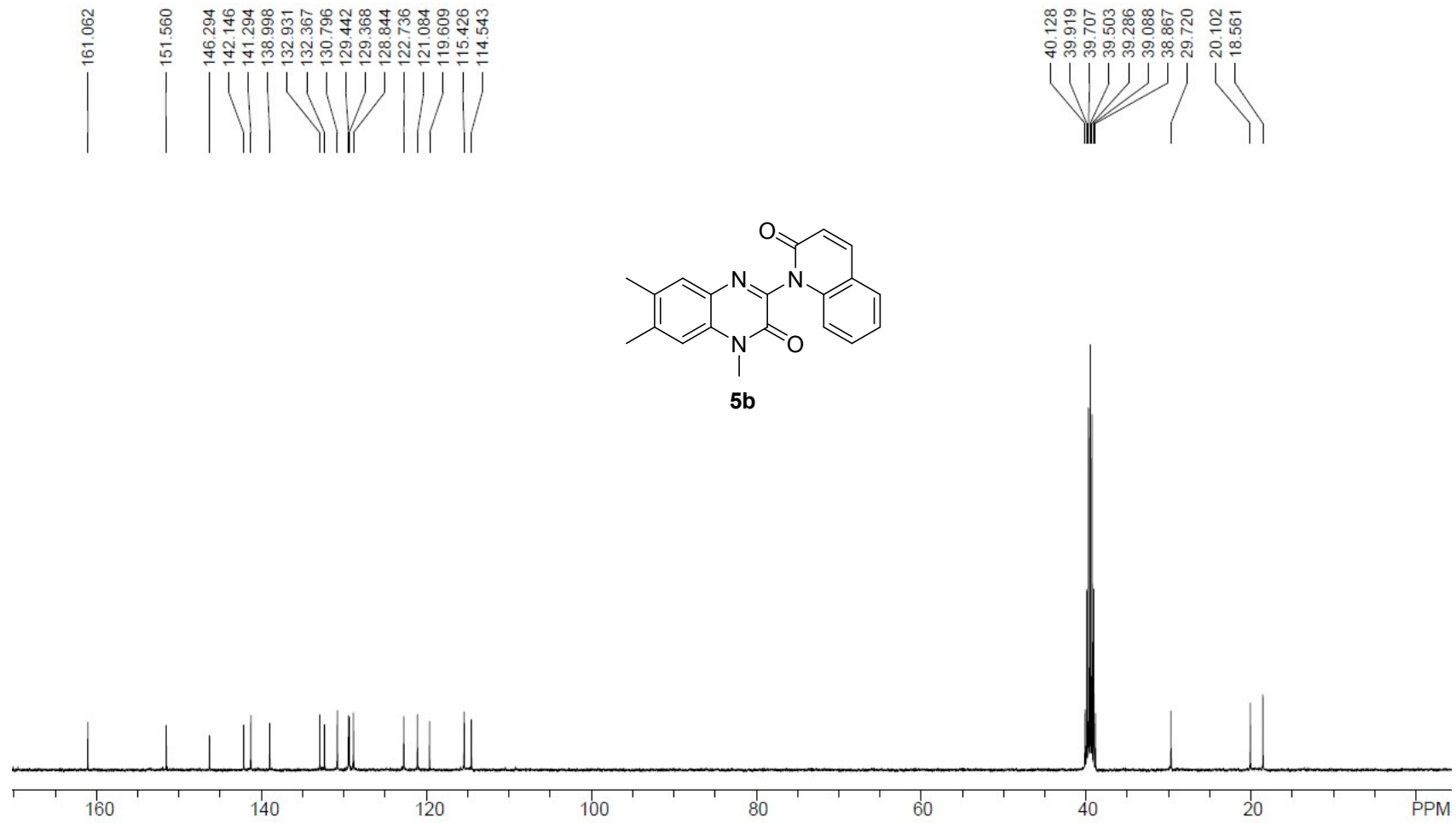


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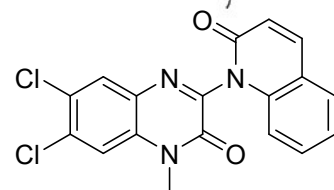






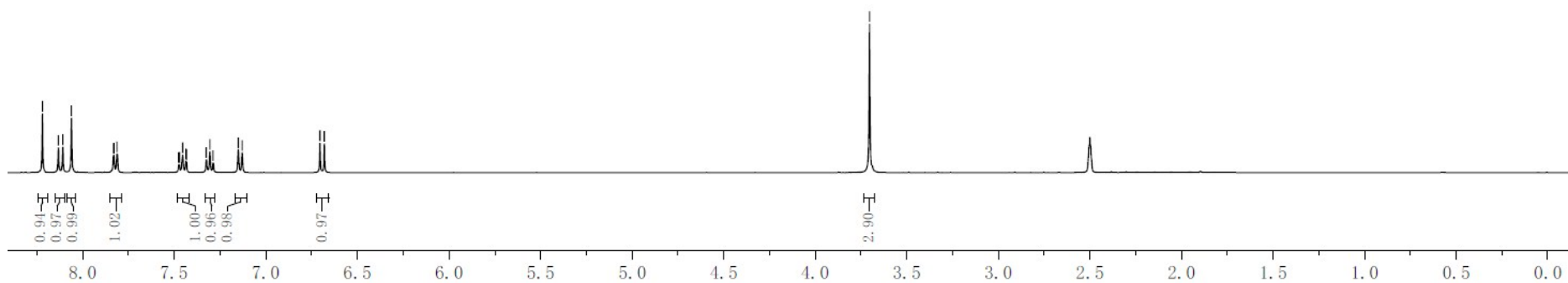


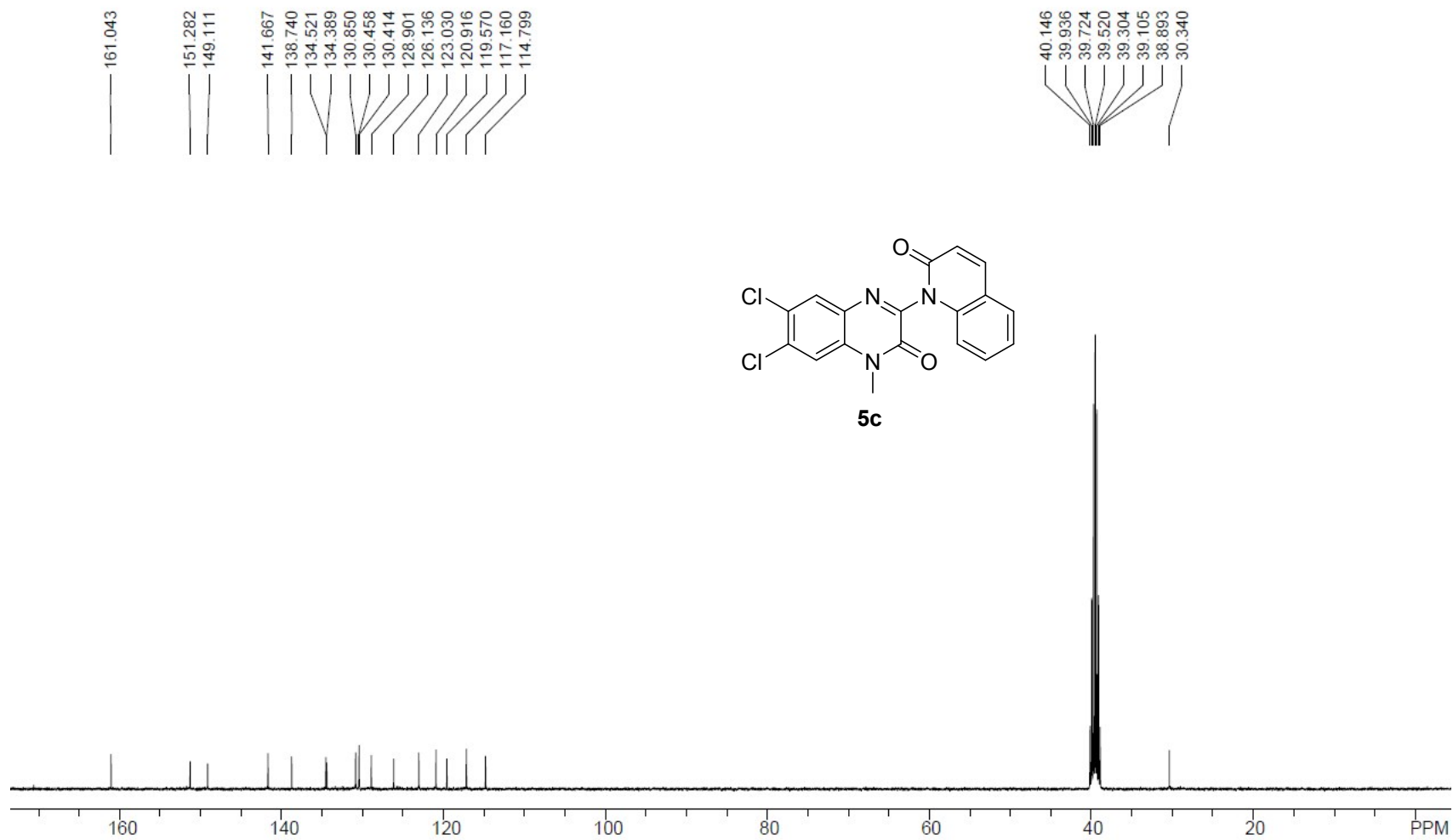
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6.704
6.680

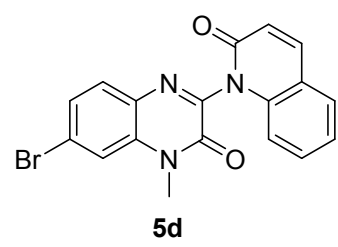
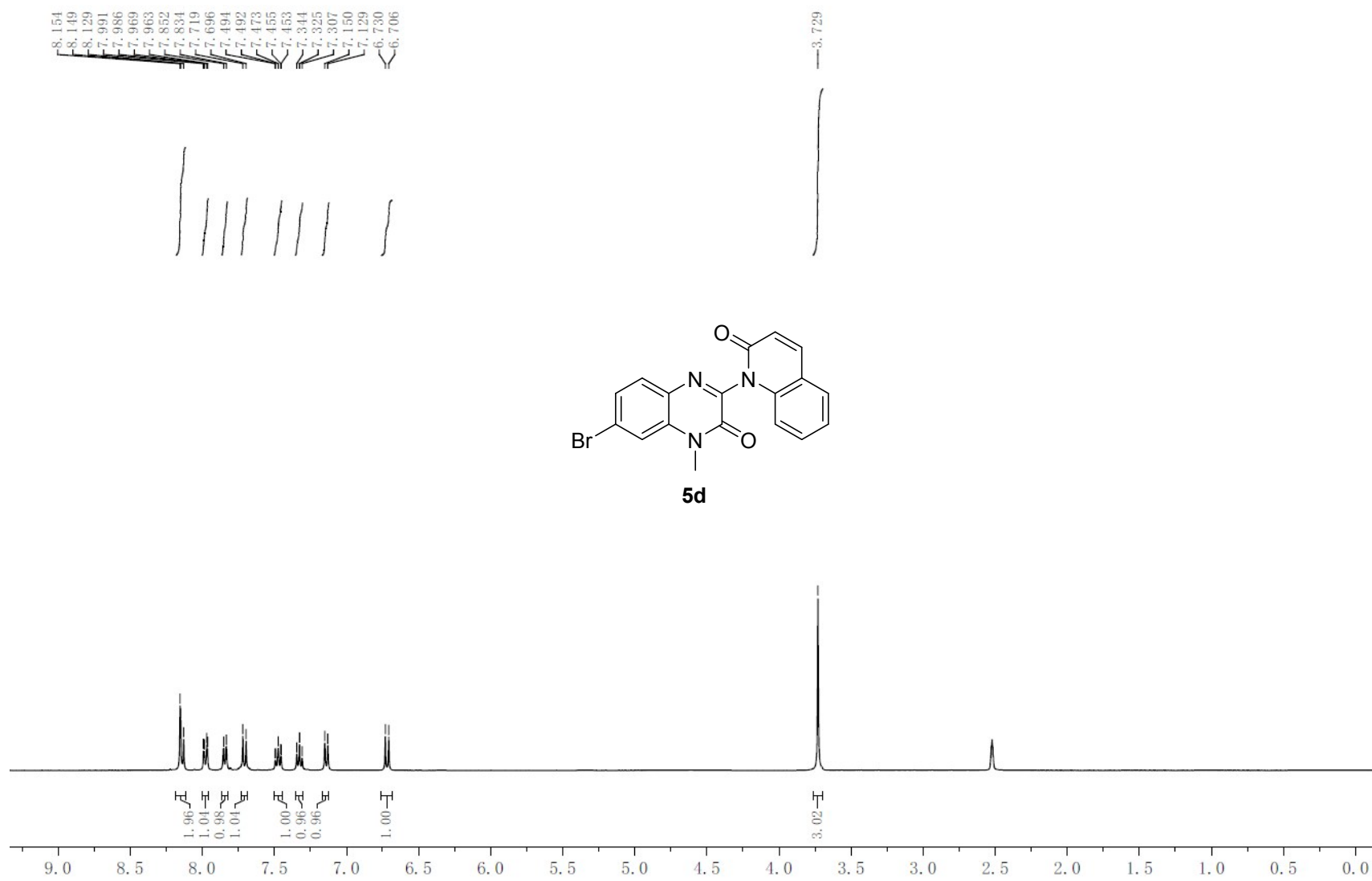


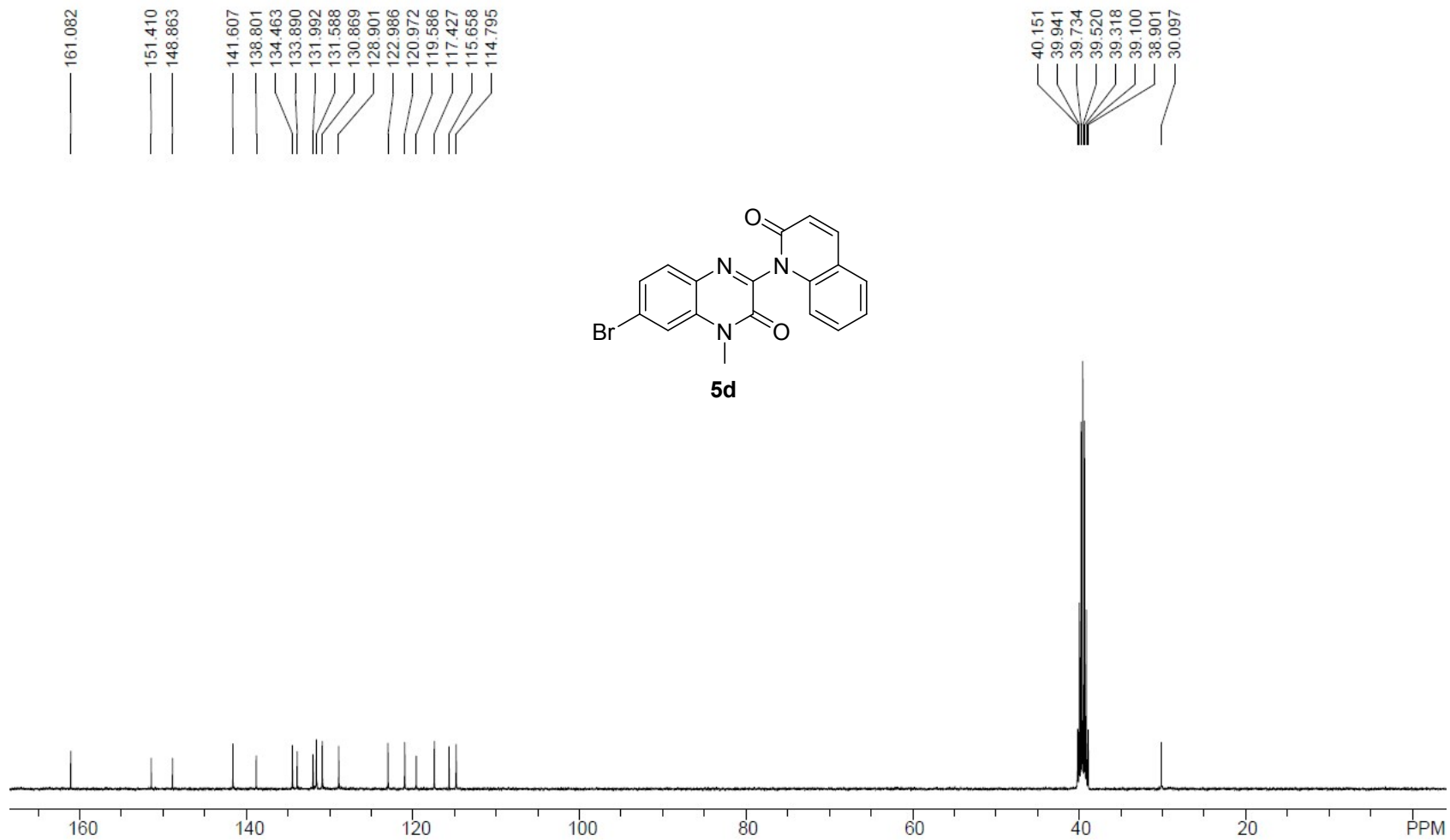
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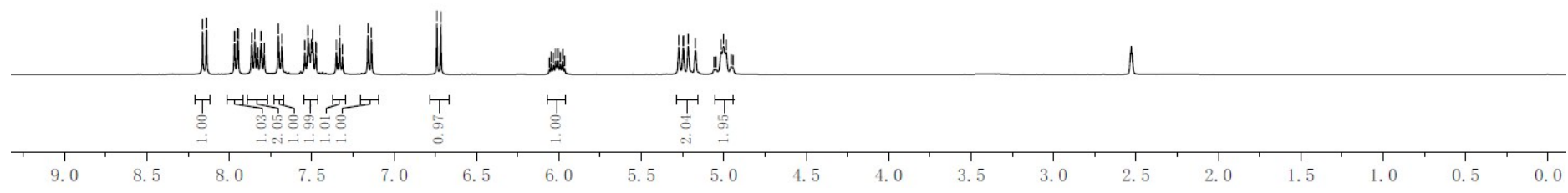
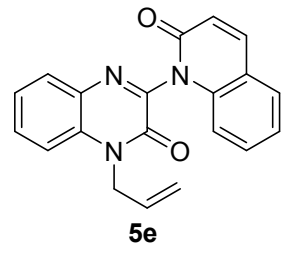
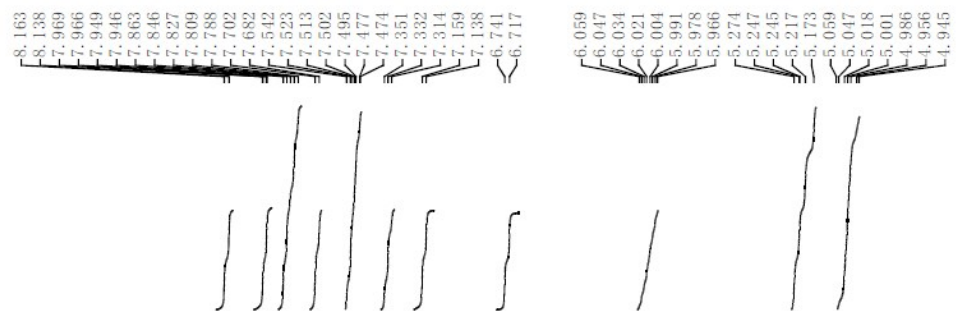
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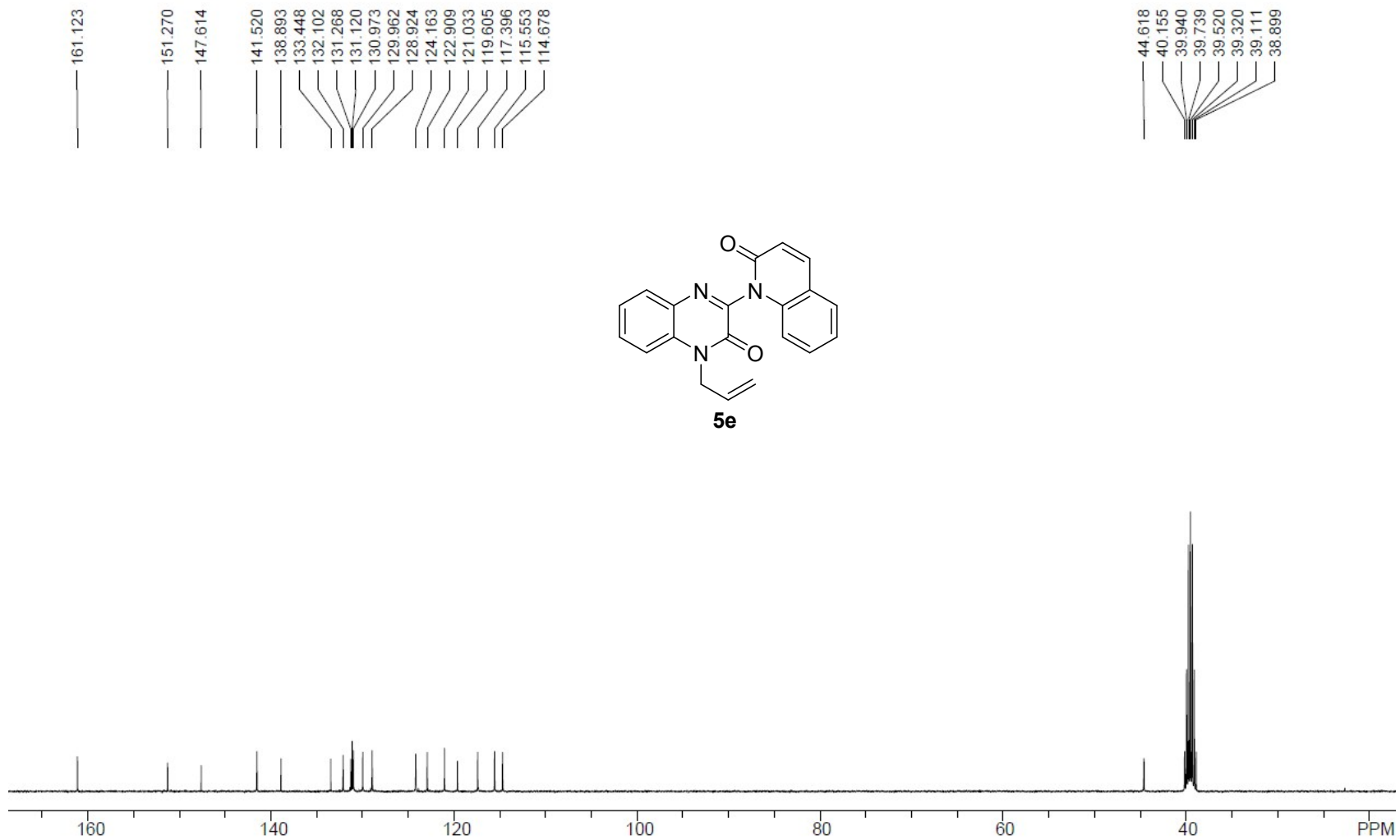


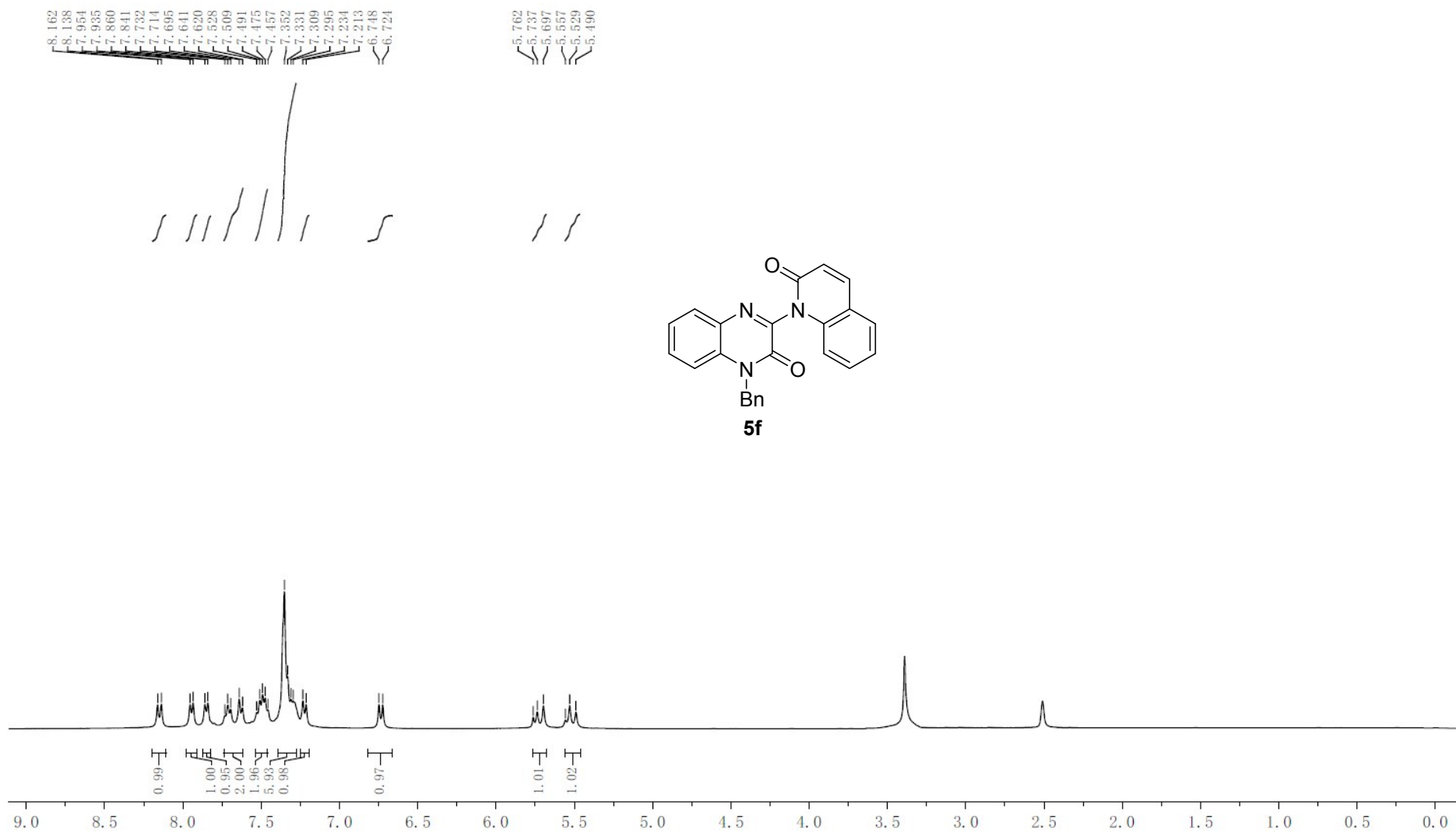


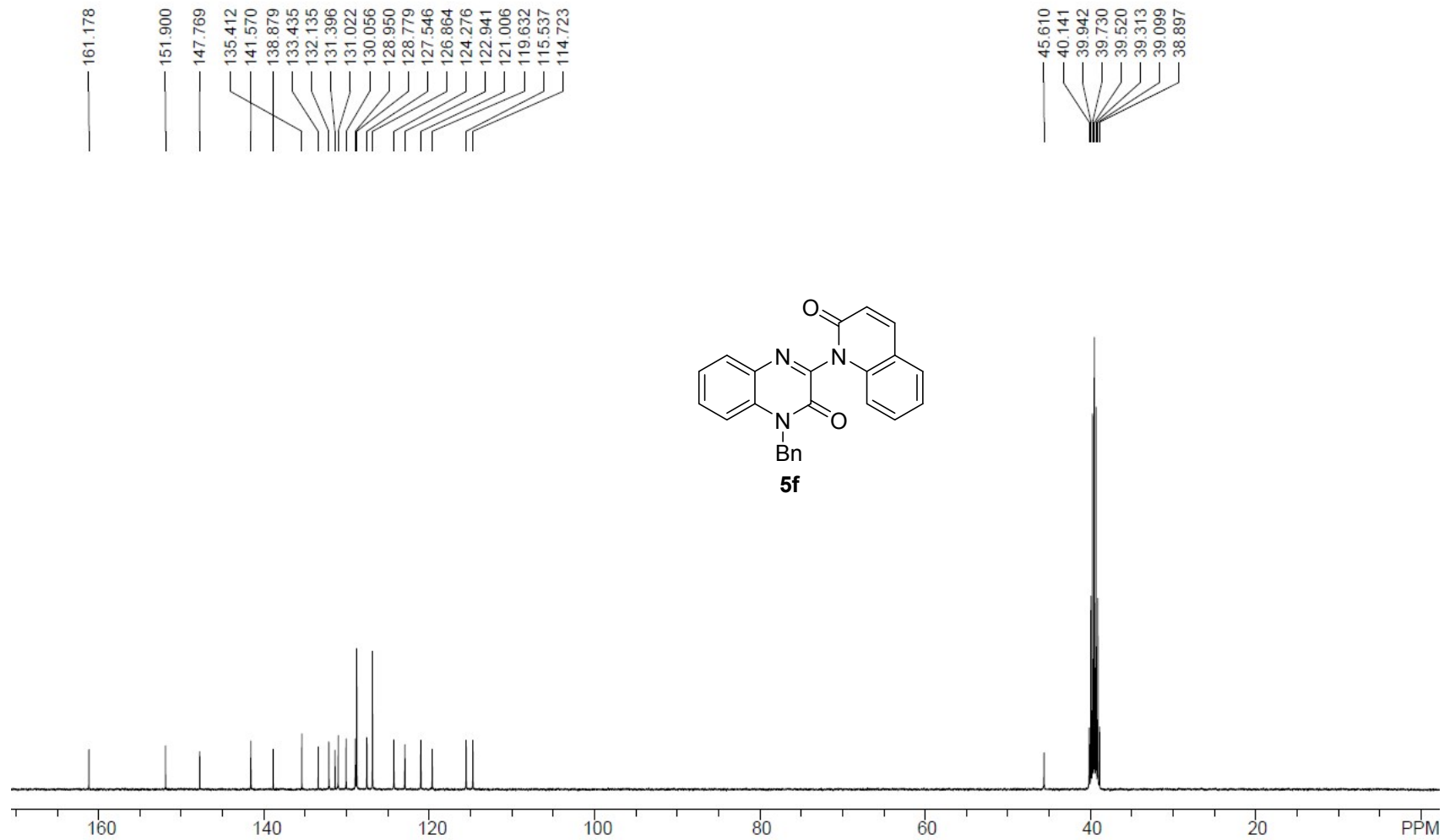


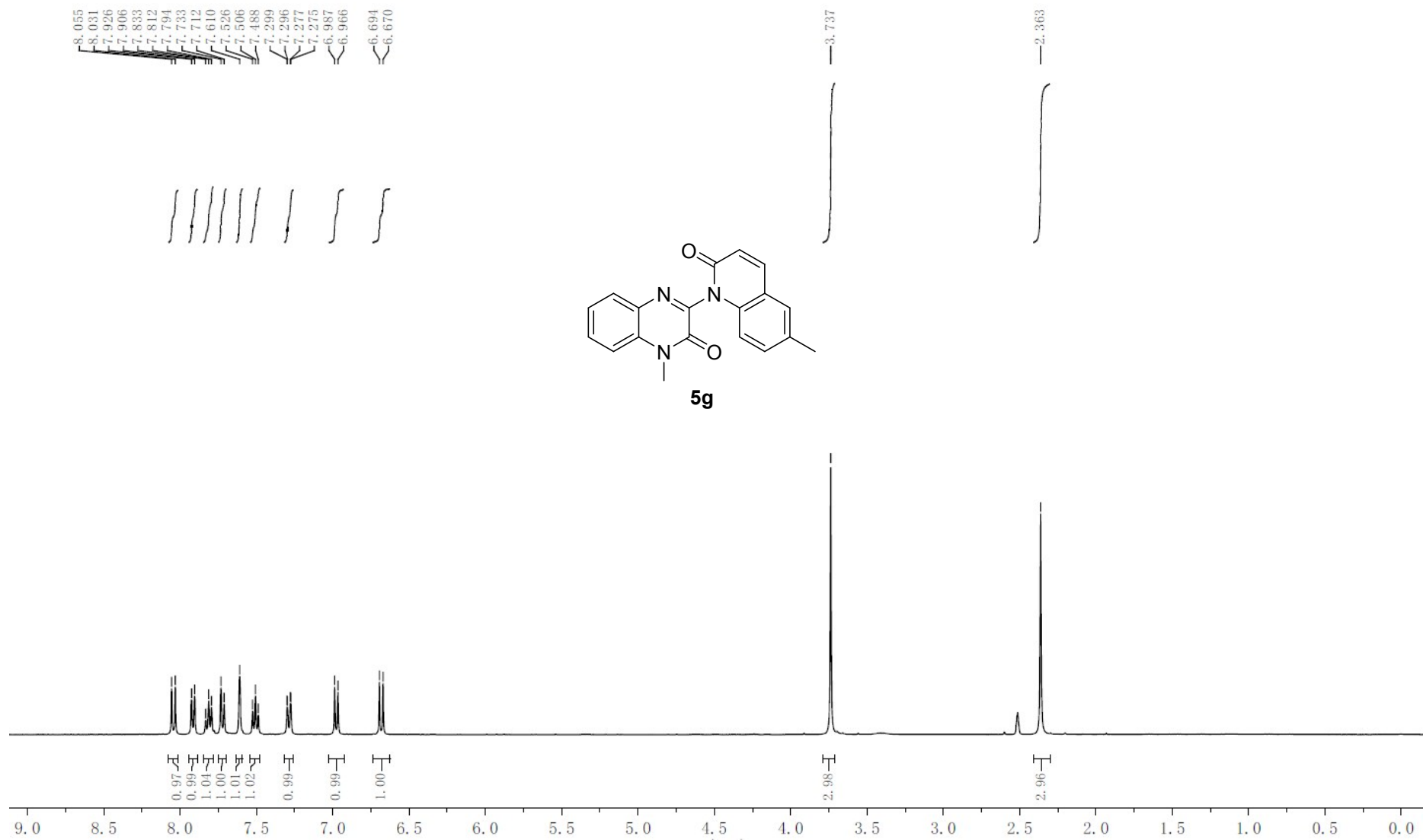


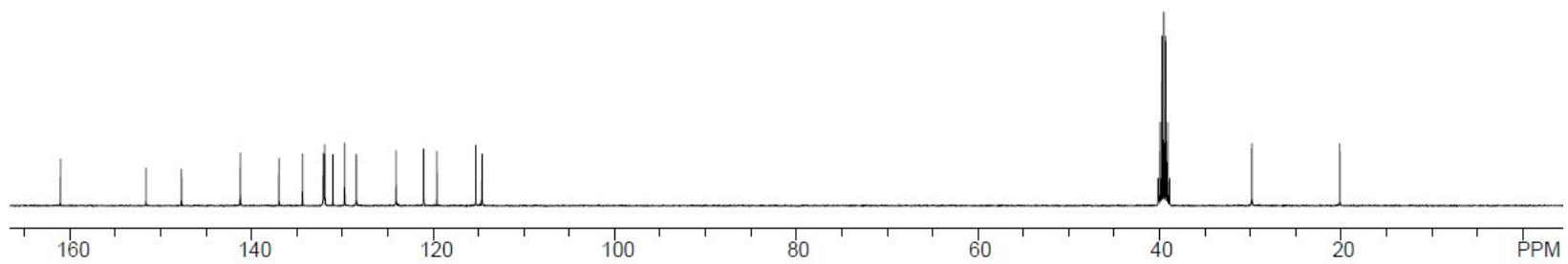
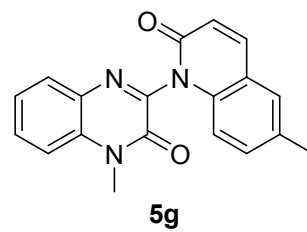
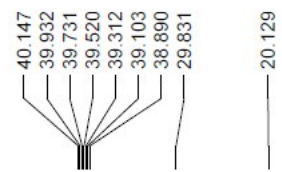
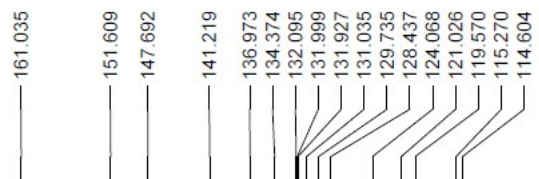


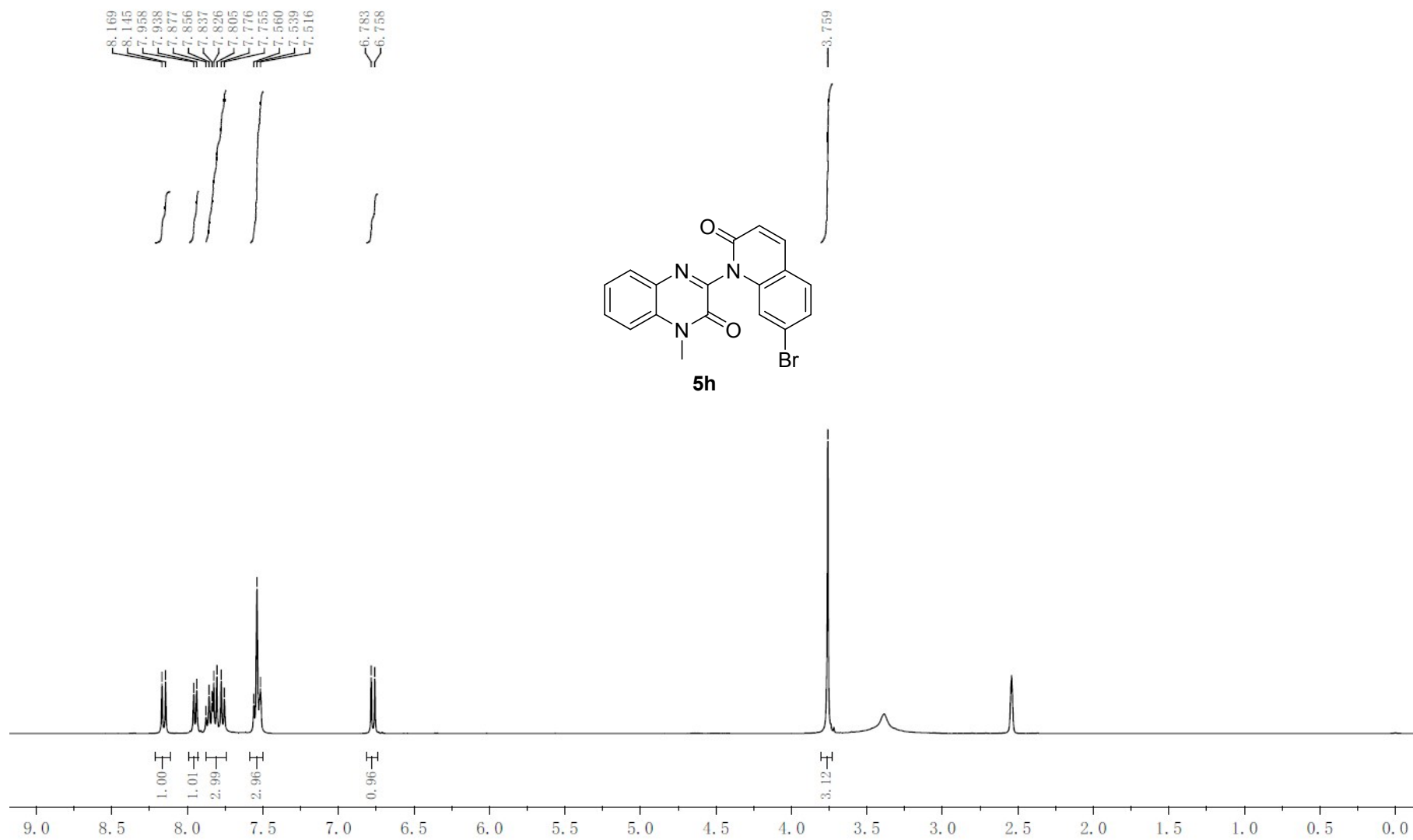


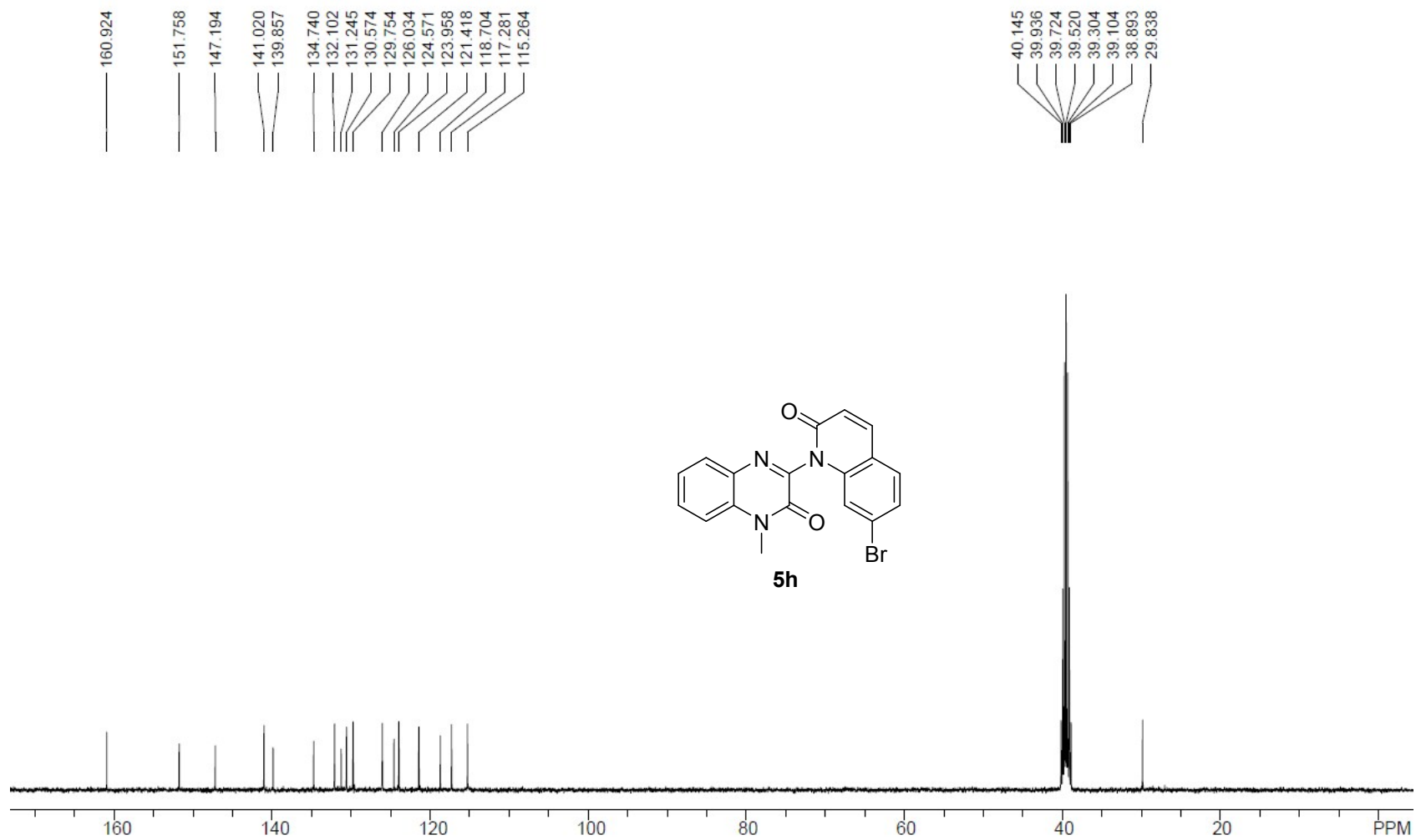




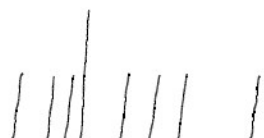








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7.167
6.795
6.771



3.734

