Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Palladium-Catalyzed Arylation of β-Methylene C(sp^3)–H Bonds at Room Temperature: Desymmetrization of Simple Cycloalkyl Carboxylic Acids

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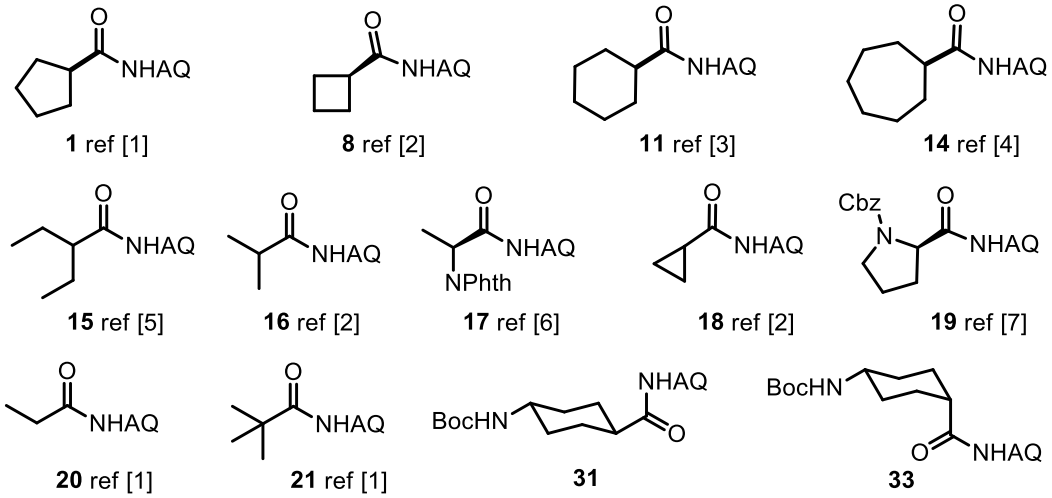
1. Reagents: All commercial materials were used as received unless otherwise noted. Anhydrous solvents were obtained from a JC Meyer solvent dispensing system and used without further purification. Flash chromatography was performed using 230-400 mesh SiliaFlash 60® silica gel (Silicycle Inc.). $Pd(OAc)_2$ (98%, Aldrich), silver carbonate (99%, Aldrich), silver acetate (99%, Alfa Aesar), dichloromethane (99.5%, Merck) were used in Pd-catalyzed reactions. 8-aminoquinoline (AQ) was purchased from Matrix Scientific and used without further purification. *cis*-4-aminocyclohexanecarboxylic acid and *trans*-4-aminocyclohexanecarboxylic acid were purchased from Chem-Impex International.

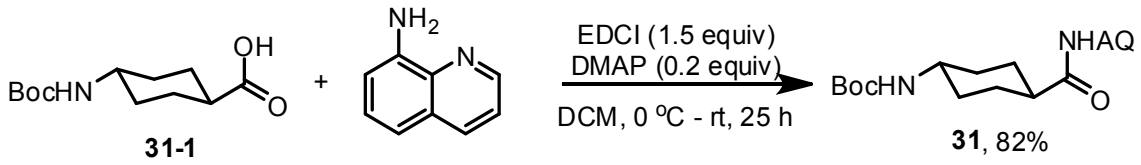
2. Instruments: NMR spectra were recorded on Bruker CDPX-300, DPX-300, DRX-400 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, br s = broad singlet, m = multiplet. High resolution ESI mass experiments were operated on a Waters LCT Premier instrument.

3. Preparation of Substrates:



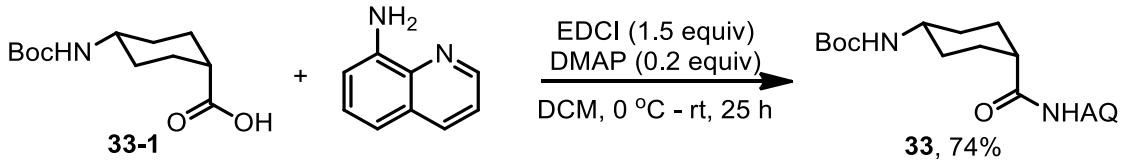
Scheme S1 List of all substrates used in this study

All known compounds were prepared following the reported procedure and spectra data are consistent with those reported in the literature.



Scheme S2

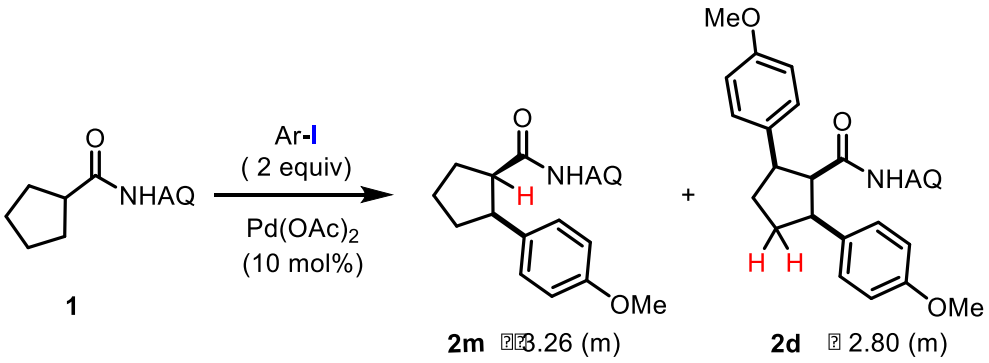
Trans Boc-4-aminocyclohexanecarboxylic acid **28-1** (2 mmol, 487 mg, 1.0 equiv), DMAP (0.4 mmol, 50 mg, 0.2 equiv), and 8-aminoquinoline (1.6 mmol, 231 mg, 0.8 equiv) were dissolved in CH_2Cl_2 (2 mL). The reaction was cooled to 0 ^oC in an ice bath and EDCI (3.0 mmol, 466 mg, 1.5 equiv) was added. The reaction was then allowed to warm to RT. After 24hours, the reaction mixture was washed with water, sat. $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$. Purification by silica gel flash column chromatography (EtOAc/Hex) gave the desired products as white solids in 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.80 – 8.66 (m, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.37 (dd, J = 8.2, 4.2 Hz, 1H), 4.56 (s, 1H), 3.47 (s, 1H), 2.36 (t, J = 12.1 Hz, 1H), 2.10 (d, J = 9.1 Hz, 2H), 1.73 (q, J = 12.2 Hz, 2H), 1.41 (s, 9H), 1.19 (q, J = 12.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.90, 155.23, 148.13, 138.38, 136.35, 134.42, 127.89, 127.34, 121.58, 121.42, 116.43, 79.13, 49.09, 45.88, 32.66, 28.60, 28.44. HRMS: calculated for $C_{21}H_{28}N_3O_3$ [M+H^+]: 370.2125; found: 370.2118.



Scheme S3

Compound **30** was prepared follow the same procedure as compound **28** in 74% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.84-8.72 (m, 2H), 8.16 (d, J = 8.3 Hz, 1H), 7.59-7.37 (m, 3H), 4.82-4.73 (m, 1H), 3.80 (m, 1H), 2.59 (m, 1H), 2.03-1.72 (m, 8H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.33, 148.26, 138.49, 136.53, 134.54, 128.03, 127.53, 121.72, 121.54, 116.50, 79.22, 44.33, 29.68, 28.53, 25.03. HRMS: calculated for $C_{21}H_{28}N_3O_3$ [M+H^+]: 370.2125; found: 370.2117.

4. Reaction optimization in Table 1



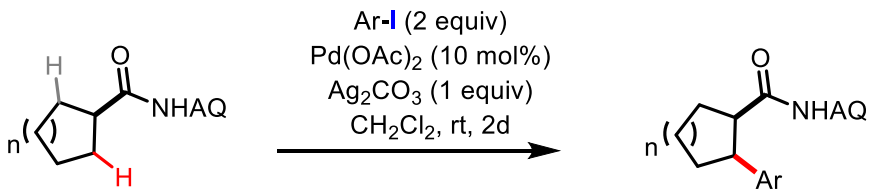
Scheme S4

Reactions were performed in 4 mL capped vials according to the conditions listed in Table 1 at a 0.2 mmol scale. After completion, the reactions were diluted with dichloromethane (5 mL) and filtered through a pad of Celite. Following evaporation, the crude residue was dissolved in 600 μL of deuterated chloroform for ^{1}H-NMR analysis. Dibromomethane (34.8 mg, 0.2 mmol, 1 equiv, set the integration of this singlet peak around 4.95 ppm as 1.00) was added as internal standard for determining the yield. Yields of mono- and di-arylated product were determined as follows:

Yield (**2m**) = integration of (δ 3.26) × 200%

Yield (**2d**) = integration of (δ 2.80) × 100%

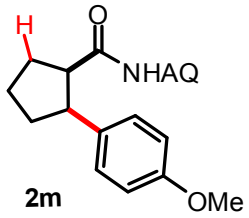
5. General Procedure for AQ-directed Pd-catalyzed C–H arylation



Scheme S5

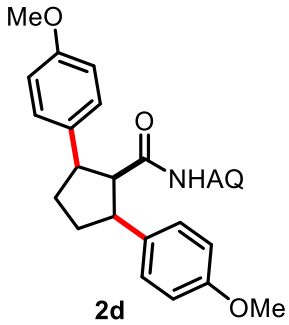
A mixture of carboxylic amide (0.2 mmol, 1 equiv), corresponding aryl iodide (0.4 mmol, 2 equiv), Ag_2CO_3 (55mg, 0.2 mmol, 1 equiv), and $Pd(OAc)_2$ (4.5 mg, 0.1 equiv, 0.02 mmol) in CH_2Cl_2 (1 mL) was stirred vigorously at room temperature for 2 days. Then the mixture was filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated *in vacuo*

and the residue was purified by silica gel flash column chromatography to gave the arylated products.



2m

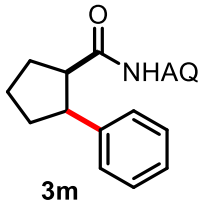
Compound **2m** was isolated in 80% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.67 (d, J = 3.0 Hz, 1H), 8.53 (d, J = 6.9 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.54 – 7.31 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.48 (s, 4H), 3.25 (dd, J = 13.1, 7.7 Hz, 1H), 2.36 (td, J = 13.0, 7.7 Hz, 1H), 2.30 – 2.13 (m, 2H), 2.13 – 2.00 (m, 2H), 1.81 (dd, J = 19.5, 9.0 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.96, 157.89, 147.67, 138.14, 135.95, 134.39, 133.14, 128.79, 127.62, 127.14, 121.23, 120.90, 115.95, 113.42, 54.85, 52.95, 49.42, 31.10, 28.42, 24.39. HRMS: calculated for $C_{22}H_{23}N_2O_2$ [M+H$^+$] : 347.1754; found: 347.1750.



2d

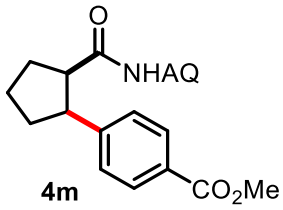
Compound **2d** was isolated in 4% yield as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.15 (s, 1H), 8.59 (dd, J = 4.0, 1.4 Hz, 1H), 8.50 (d, J = 6.7 Hz, 1H), 7.99 (dd, J = 8.2, 1.1 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.33 (d, J = 8.6 Hz, 5H), 7.30 (dd, J = 8.2, 4.2 Hz, 1H), 6.68 (d, J = 8.7 Hz, 4H), 3.68 (d, J = 7.1 Hz, 2H), 3.57 (s, 6H), 3.46 (t, J = 5.9 Hz, 1H), 2.77 (td, J = 7.4, 2.8 Hz, 2H), 2.31 (t, J = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.77, 157.99, 147.68, 138.17, 135.99,

134.35, 133.27, 128.89, 127.67, 127.17, 121.25, 121.00, 116.17, 113.60, 60.24, 55.08, 49.53, 29.02; HRMS: calculated for $C_{29}H_{29}N_2O_3$ [M+H$^+$] : 453.2173; found: 453.2169.



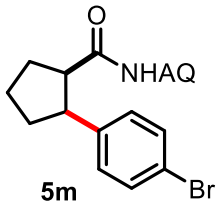
3m

Compound **3m** was isolated in 68% yield as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.35 (s, 1H), 8.68 (dd, J = 4.0, 1.3 Hz, 1H), 8.53 (d, J = 6.4 Hz, 1H), 8.04 (dd, J = 8.2, 1.2 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.30 (d, J = 7.5 Hz, 2H), 7.06 (t, J = 7.7 Hz, 2H), 6.89 (t, J = 7.3 Hz, 1H), 3.53 (dd, J = 17.6, 8.0 Hz, 1H), 3.32 (dd, J = 13.3, 7.9 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.35 – 2.26 (m, 1H), 2.24 – 2.15 (m, 1H), 2.15 – 2.05 (m, 2H), 1.90 – 1.76 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.73, 147.63, 141.10, 138.06, 135.90, 134.25, 127.92, 127.82, 127.53, 127.06, 126.11, 121.18, 120.86, 115.86, 52.81, 50.03, 30.90, 28.56, 24.43. HRMS: calculated for $C_{21}H_{21}N_2O$ [M+H$^+$] : 317.1648; found: 317.1644.



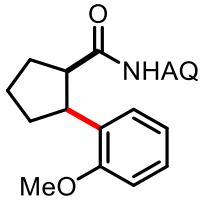
4m

Compound **4m** was isolated in 53% yield as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 9.32 (s, 1H), 8.61 (d, J = 2.7 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.45 – 7.27 (m, 5H), 3.69 (s, 3H), 3.51 (dd, J = 16.7, 8.1 Hz, 1H), 3.30 (dd, J = 12.6, 7.5 Hz, 1H), 2.44 – 2.23 (m, 2H), 2.20 – 1.94 (m, 3H), 1.90 – 1.65 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.40, 166.74, 147.77, 146.88, 138.03, 135.99, 134.03, 129.30, 127.89, 127.9, 127.06, 121.23, 121.14, 116.04, 52.793, 51.65, 49.99, 30.74, 28.68, 24.44; HRMS: calculated for $C_{23}H_{23}N_2O_3$ [M+H$^+$] : 375.1703; found: 375.1704.



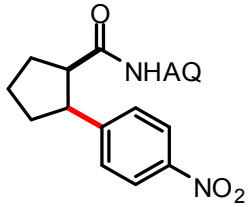
5m

Compound **5m** was isolated in 57% yield as a pale yellow solid. 1H NMR (300 MHz, CDCl3) δ 9.31 (s, 1H), 8.68 (dd, J = 4.0, 1.3 Hz, 1H), 8.50 (dd, J = 5.6, 3.3 Hz, 1H), 8.09 (dd, J = 8.2, 1.4 Hz, 1H), 7.50 – 7.31 (m, 3H), 7.14 (s, 4H), 3.46 (dd, J = 16.7, 8.1 Hz, 1H), 3.28 (dd, J = 12.8, 7.7 Hz, 1H), 2.44 – 2.28 (m, 1H), 2.28 – 2.12 (m, 2H), 2.13 – 2.00 (m, 2H), 1.92 – 1.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.69, 147.99, 140.39, 136.29, 134.28, 131.19, 129.79, 127.86, 127.33, 121.56, 121.35, 120.20, 116.26, 52.95, 49.75, 31.01, 28.70, 24.51; HRMS: calculated for $C_{21}H_{20}BrN_2O$ [M+H$^+$] : 395.0754; found: 395.0744.



6m

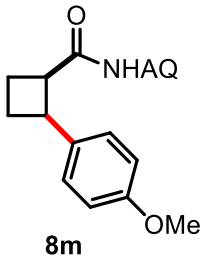
Compound **6m** was isolated in 24% yield as a white solid and spectra data are consistent with those reported in the literature.[1]



7m

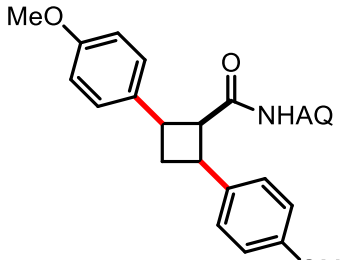
Compound **7m** was isolated in 50% yield as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 4.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.51 – 7.30 (m, 5H), 3.59 (dd, J = 16.2, 8.2 Hz, 1H), 3.46 – 3.25 (m, 1H), 2.49 – 2.29 (m, 2H), 2.28 – 2.21 (m, 1H), 2.21 – 2.01 (m, 3H), 1.86 (dd, J = 16.8, 6.7 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 172.19, 149.56, 147.99, 146.46, 138.16, 136.44, 133.96, 128.90, 127.85, 127.31, 123.35, 121.63, 116.33, 53.05, 50.06, 31.03, 28.95, 24.74. HRMS: calculated for

$C_{21}H_{20}N_3O_3$ [M+H$^+$] : 362.1499; found: 362.1495.



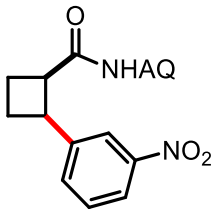
8m

Compound **8m** was isolated in 32% yield as a pale yellow solid and spectra data are consistent with those reported in the literature.[8]



8d

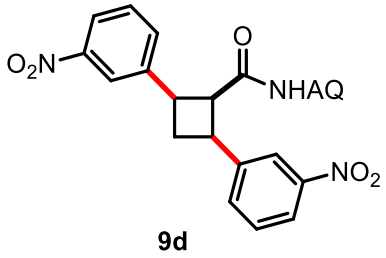
Compound **8d** was isolated in 64% yield as a colorless oil and spectra data are consistent with those reported in the literature.[8]



9m

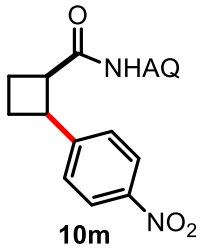
Compound **9m** was isolated in 25% yield as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 9.39 (s, 1H), 8.65 (d, J = 2.7 Hz, 1H), 8.52 – 8.33 (m, 1H), 8.14 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.47 – 7.29 (m, 3H), 7.18 (t, J = 7.9 Hz, 1H), 4.15 (dd, J = 17.1, 8.2 Hz, 1H), 3.79 (d, J = 6.5 Hz, 1H), 2.86 – 2.67 (m, 1H), 2.67 – 2.53 (m, 1H), 2.52 – 2.25 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.60, 148.03, 147.92, 142.93, 138.04,

136.23, 133.89, 133.37, 128.96, 127.71, 127.15, 122.56, 121.56, 121.42, 121.35, 116.11, 47.59, 42.59, 24.74, 20.56. HRMS: calculated for $C_{20}H_{18}N_3O_3$ [M+H$^+$]: 348.1343; found: 348.1328.



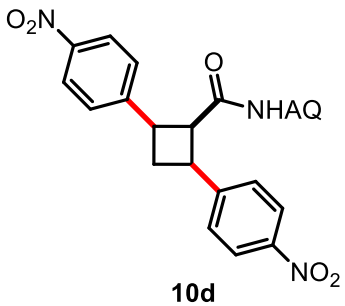
9d

Compound **9d** was isolated in 64% yield as a white solid and spectra data are consistent with those reported in the literature.[8]



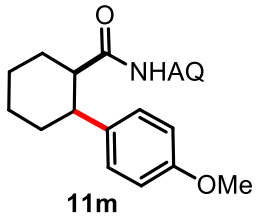
10m

Compound **10m** was isolated in 27% yield as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 9.46 (s, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.58 – 8.37 (m, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.53 – 7.30 (m, 5H), 4.17 (dd, J = 16.6, 8.1 Hz, 1H), 3.84 (s, 1H), 2.89 – 2.69 (m, 1H), 2.69 – 2.54 (m, 1H), 2.54 – 2.28 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 170.71, 148.91, 148.03, 136.59, 133.97, 128.25, 127.94, 127.43, 123.47, 121.67, 116.50, 47.79, 42.92, 25.06, 20.96. HRMS: calculated for $C_{20}H_{18}N_3O_3$ [M+H$^+$]: 348.1343; found: 348.1348.



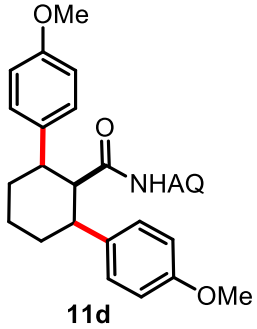
10d

Compound **10d** was isolated in 47% yield as a yellow solid and spectra data are consistent with those reported in the literature.[8]



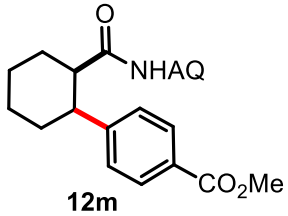
11m

Compound **11m** was isolated in 54% yield as a colorless oil and spectra data are consistent with those reported in the literature.[3]



11d

Compound **11d** was isolated in 17% yield as a white solid and spectra data are consistent with those reported in the literature.[3]

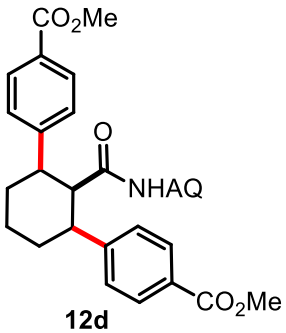


12m

Compound **12m** was isolated in 33% yield as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 9.24 (s, 1H), 8.62 (d, J = 7.2 Hz, 1H), 8.58 (d, J = 4.0 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 3H), 7.34 (dd, J = 8.3, 4.3 Hz, 2H), 3.78 (s, 3H), 3.09 (d, J = 5.5 Hz, 2H), 2.56 (dd, J = 22.4, 10.4 Hz, 1H), 2.26 (d, J = 12.4 Hz, 1H),

2.12 (d, J = 12.8 Hz, 1H), 2.02 (d, J = 14.8 Hz, 1H), 1.92 (d, J = 4.2 Hz, 1H), 1.92 (d, J = 4.2 Hz, 1H), 1.91 – 1.74 (m, 2H), 1.65 (d, J = 12.9 Hz, 2H), 1.48 (dd, J = 24.5, 12.4 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.69, 167.13, 150.09, 147.87, 138.24, 136.23, 134.38, 129.74, 128.12, 127.82, 127.34, 121.41, 121.28, 116.25, 51.94, 48.60, 45.90, 29.95, 26.64, 26.07, 21.75;

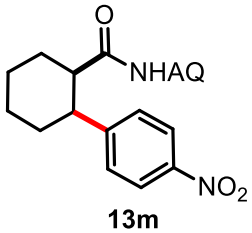
HRMS: calculated for $C_{24}H_{26}N_2O_3$ [M+H$^+$] : 389.1860; found: 389.1860.



12d

Compound **12d** was isolated in 15% yield as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 8.57 (s, 1H), 8.40 (d, J = 6.7 Hz, 1H), 8.36 (d, J = 3.3 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.1 Hz, 4H), 7.39 (d, J = 7.9 Hz, 4H), 7.36 – 7.29 (m, 2H), 7.22 (dd, J = 8.1, 4.2 Hz, 1H), 3.75 (s, 5H), 3.31 – 3.11 (m, 3H), 2.80 (qd, J = 12.9, 3.1 Hz, 2H), 2.26 (d, J = 12.8 Hz, 1H), 1.83 (d, J = 11.2 Hz, 2H), 1.66 (dd, J = 27.0, 13.7 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.25, 166.99, 149.32, 129.81, 128.37, 127.69, 127.05, 121.44, 121.13, 56.334, 51.93, 47.80, 26.38, 25.35;

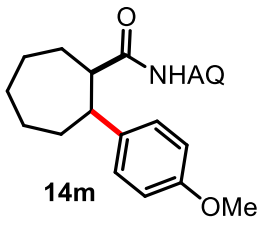
HRMS: calculated for $C_{32}H_{31}N_2O_5$ [M+H$^+$]: 523.2227; found: 523.2218.



13m

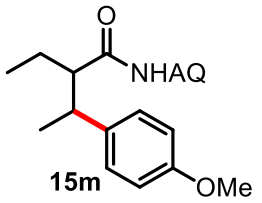
Compound **13m** was isolated in 25% yield as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 9.27 (s, 1H), 8.58 (s, 2H), 8.08 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.53 – 7.39 (m, 4H), 7.36 (dd, J = 8.0, 4.2 Hz, 1H), 3.10 (s, 2H), 2.59 (dd, J = 23.3, 11.9 Hz, 1H), 2.28 (d, J = 12.9 Hz,

1H), 2.15 (d, J = 16.3 Hz, 1H), 2.05 (d, J = 6.5 Hz, 2H), 1.93 (d, J = 13.0 Hz, 1H), 1.83 (d, J = 13.8 Hz, 1H), 1.68 (d, J = 12.2 Hz, 1H), 1.50 (dd, J = 24.7, 12.2 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 172.24, 152.54, 147.92, 146.56, 138.17, 136.45, 134.17, 128.70, 127.92, 127.38, 123.65, 121.61, 116.37, 48.50, 45.83, 30.04, 26.55, 25.98, 21.62. HRMS: calculated for $C_{22}H_{22}N_3O_3$ [M+H$^+$]: 376.1656; found: 376.1650.



14m

Compound **14m** was isolated in 43% yield as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.17 (s, 1H), 8.66 (dd, J = 4.1, 1.5 Hz, 1H), 8.55 (dd, J = 7.5, 1.2 Hz, 1H), 8.08 (dd, J = 8.2, 1.1 Hz, 1H), 7.47 – 7.34 (m, 3H), 7.14 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 8.7 Hz, 2H), 3.45 (s, 3H), 3.30 – 3.23 (m, 1H), 3.05 (dd, J = 14.3, 6.5 Hz, 1H), 2.36 (dt, J = 14.9, 8.0 Hz, 1H), 2.15 (dd, J = 10.2, 5.1 Hz, 2H), 1.97 (t, J = 8.7 Hz, 4H), 1.55 (t, J = 8.7 Hz, 2H), 1.53 – 1.41 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.97, 157.78, 147.77, 138.29, 137.41, 136.17, 134.60, 128.81, 127.81, 127.39, 121.38, 121.00, 116.18, 113.61, 55.03, 53.51, 47.38, 31.43, 30.81, 29.38, 28.93, 26.73; HRMS: calculated for $C_{24}H_{27}N_2O_2$ [M+H$^+$] : 375.2067; found: 375.2062.



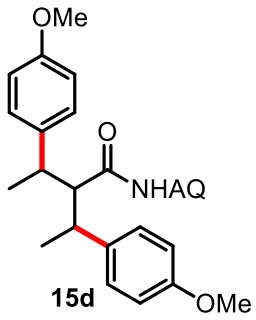
15m

Diastereomer A: 27%
Diastereomer B: 16%
Absolute stereochemistry unassigned

Diastereomer **A** was isolated in 27% yield as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 9.90 (s, 1H), 8.89 (d, J = 7.0 Hz, 1H), 8.83 (d, J = 4.0 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.48 (dd, J = 8.2, 4.3 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 3.04 (dq, J = 14.6, 7.2 Hz, 1H), 2.47 (td, J = 10.4, 2.8 Hz, 1H), 1.76 – 1.51 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 174.27, 158.26, 148.27, 137.38, 134.37, 128.60, 128.17, 127.61, 121.74, 121.65, 116.75, 113.98, 58.66, 55.36, 42.47, 25.05, 21.12, 12.34; HRMS: calculated for $C_{22}H_{25}N_2O_2$ [M+H$^+$]: 349.1911; found: 349.1898.

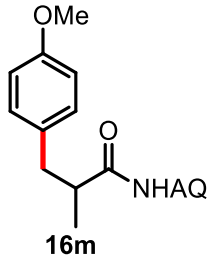
Diastereomer **B** was isolated in 16% yield as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 9.48

(s, 1H), 8.80 – 8.70 (m, 1H), 8.65 (dd, J = 6.8, 1.9 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.51 – 7.32 (m, 3H), 7.19 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 3.59 (s, 3H), 3.12 (dt, J = 14.3, 7.1 Hz, 1H), 2.53 (dd, J = 14.7, 8.3 Hz, 1H), 1.95 – 1.74 (m, 2H), 1.37 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H).[13]C NMR (75 MHz, $CDCl_3$) δ 173.71, 158.04, 148.06, 137.56, 136.27, 128.26, 127.83, 127.49, 121.55, 121.12, 116.29, 113.71, 58.71, 55.09, 41.84, 23.33, 19.20, 12.42; HRMS: calculated for $C_{22}H_{25}N_2O_2$ [M+H$^+$]: 349.1911; found: 349.1902.



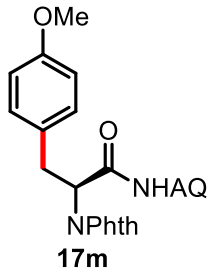
15d

Compound **15d** was isolated in 12% yield and spectra data are consistent with those reported in the literature.[5]



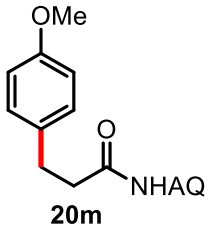
16m

Compound **16m** was isolated in 19% yield as a colorless oil and spectra data are consistent with those reported in the literature.[9]



17m

Compound **17m** was isolated in 30% yield as a white solid and spectra data are consistent with those reported in the literature.[10]

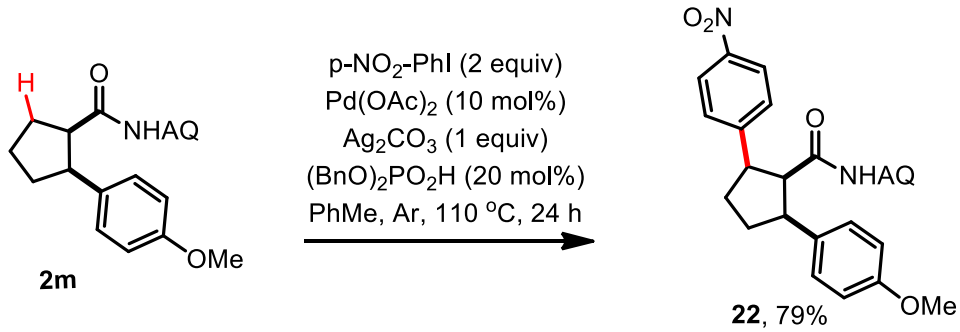


20m

Compound **20m** was isolated in 23% yield as a white solid and spectra data are consistent with those reported in the literature.[11]

6. Pd-catalyzed sequential C-H functionalization of cycloalkyl carboxamides

A: C-H Arylation



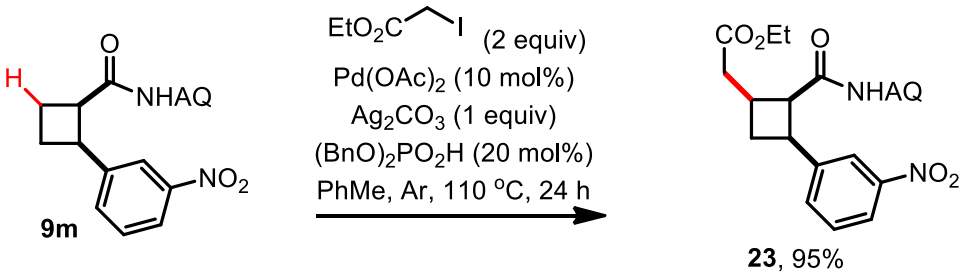
2m **22**, 79%

Scheme S6

Compound **2m** (34.6 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.1 equiv), Ag_2CO_3 (27.5 mg, 0.1 mmol, 1.0 equiv), 1-iodo-4-nitrobenzene (49.8 mg, 0.2 mmol, 2 equiv), $(BnO)_2PO_2H$ (5.5 mg, 0.02 mol, 0.2 equiv) and PhMe (0.5 mL) were added to a 10 mL vial. The vial was flushed with argon, sealed with a PTFE cap, and heated to 110 °C with stirring. After 24 hours, the reaction was cooled to RT, filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by silica gel flash column chromatography (30% EtOAc/Hex) to give 37mg (79% yield) of **22** as a yellow solid. ^{1}H NMR (300 MHz, CDCl3) δ 9.12 (s, 1H), 8.57 (d, J = 2.7 Hz, 1H), 8.49 – 8.29 (m, 1H), 8.13 – 7.92 (m, 3H), 7.55 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 5.0 Hz, 3H), 7.33 (d, J = 4.1 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 3.87 – 3.65 (m, 2H), 3.54 (s, J = 10.0 Hz, 4H), 2.92 – 2.66 (m, 2H), 2.50 – 2.24 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.95, 158.26, 149.66, 147.84, 146.44,

138.10, 136.21, 133.88, 132.35, 128.88, 128.77, 127.73, 127.16, 123.47, 121.53, 121.46, 116.31, 113.74, 59.99, 55.12, 49.79, 49.64, 28.92, 28.69; HRMS: calculated for $C_{28}H_{26}N_3O_4$ [M+H$^+$]: 468.1918; found: 468.1906.

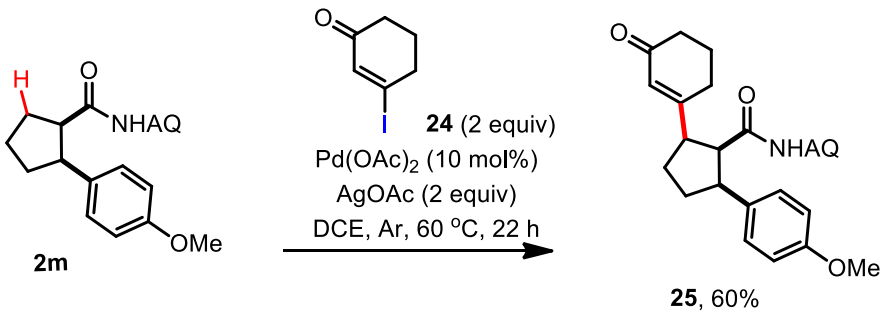
B: C-H Alkylation



Scheme S7

Compound **9m** (69.5 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mol, 0.1 equiv), Ag_2CO_3 (55 mg, 0.2 mol, 1 equiv), ethyl iodoacetate (47 µL, 0.4 mol, 2.0 equiv), $(BnO)_2PO_2H$ (11.1 mg, 0.04 mol, 0.2 equiv) and PhMe (1 mL) were added to a 10 mL vial. The vial was flushed with argon, sealed with a PTFE cap, and heated to 110 ^oC with stirring. After 24 hours, the reaction was cooled to RT, filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by silica gel flash column chromatography (25% EtOAc/Hex) to give 82 mg (95% yield) of **23** as a white solid. ^1H NMR (300 MHz, CDCl3) δ 9.69 (s, 1H), 8.74 (dd, J = 4.2, 1.6 Hz, 1H), 8.47 (dd, J = 7.1, 1.8 Hz, 1H), 8.08 (dd, J = 8.0, 1.6 Hz, 2H), 7.89 (dd, J = 8.1, 1.4 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.47 – 7.27 (m, 5H), 4.08 – 3.80 (m, 4H), 3.32 – 3.07 (m, 1H), 3.01 – 2.75 (m, 2H), 2.71 (d, J = 6.8 Hz, 1H), 2.65 (d, J = 6.9 Hz, 1H), 2.63 – 2.44 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.59, 169.52, 148.15, 148.08, 143.25, 138.17, 136.32, 133.96, 132.98, 128.88, 128.62, 128.04, 127.81, 127.18, 121.90, 121.64, 121.14, 116.36, 60.37, 51.48, 39.00, 35.49, 31.23, 30.910, 13.98; HRMS: calculated for $C_{24}H_{24}N_3O_5$ [M+H$^+$]: 434.1710; found: 434.1705.

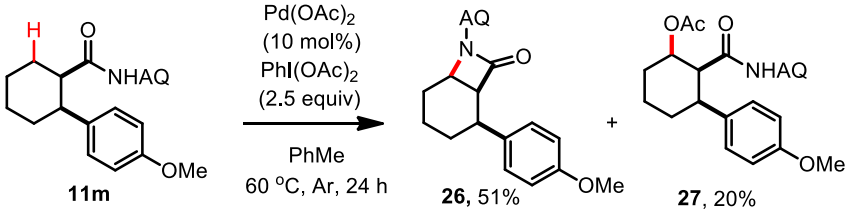
C: C-H Alkenylation



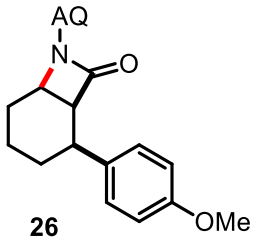
Scheme S8

Compound **2m** (34.6 mg, 0.1 mol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mol, 0.1 equiv), AgOAc (33.4 mg, 0.2 mol, 2 equiv), 3-iodocyclohex-2-enone (44.4 mg, 0.2 mol, 2.0 equiv) and DCE (0.5 mL) were added to a 10 mL vial. The vial was flushed with argon, sealed with a PTFE cap, and heated to 60 ^{o}C with stirring. After 24 hours, the reaction was cooled to RT, filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated invacuo and the residue purified by silica gel flash column chromatography (40% EtOAc/Hex) to give 26mg (60% yield) of **25** as a yellow solid. ^{1}H NMR (300 MHz, CDCl3) δ 9.28 (s, 1H), 8.64 (d, J = 3.0 Hz, 1H), 8.56 – 8.42 (m, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.57 – 7.32 (m, 3H), 7.23 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 6.08 (s, 1H), 3.60 (dd, J = 15.9, 9.4 Hz, 1H), 3.51 (s, 2H), 3.48 – 3.39 (m, 1H), 3.22 (dd, J = 14.2, 7.4 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.44 (td, J = 11.3, 5.5 Hz, 2H), 2.31 – 2.13 (m, 3H), 2.10 (dd, J = 18.3, 11.0 Hz, 1H), 1.84 (dt, J = 12.2, 6.1 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 199.98, 170.04, 165.45, 158.27, 147.98, 136.23, 132.22, 128.85, 127.83, 127.34, 126.17, 121.52, 116.40, 113.72, 57.63, 55.10, 51.37, 49.39, 37.52, 29.63, 28.36, 26.27, 22.90; HRMS: calculated for $C_{28}H_{29}N_2O_3$ [M+H$^+$]: 441.2173; found: 441.2175.

D: Intramolecular C-H amination

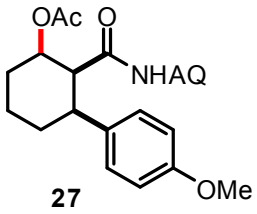


Scheme S9



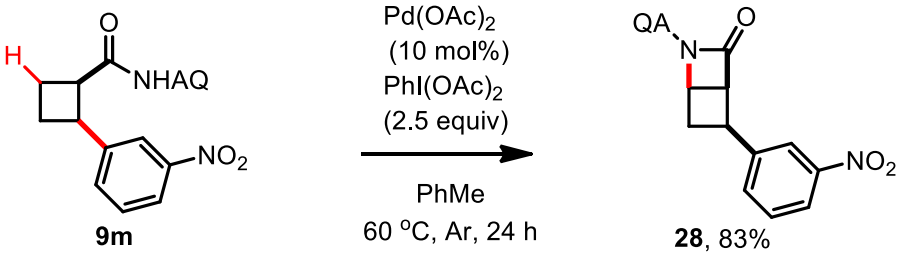
26

Compound **11m** (36 mg, 0.1 mol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mol, 0.1 equiv), $PhI(OAc)_2$ (80.5 mg, 0.25 mol, 2.5 equiv) and PhMe (1 mL) were added to a 10 mL vial. The vial was flushed with argon, sealed with a PTFE cap, and heated to 60 ^oC with stirring. After 24 hours, the reaction was cooled to RT, filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by silica gel flash column chromatography (10% EtOAc/Hex) to give 18.1mg (51% yield) of **26** as a colorless oil. ^1H NMR (300 MHz, CDCl3) δ 8.86 (d, J = 2.6 Hz, 1H), 8.50 (d, J = 7.1 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.56 (q, J = 8.4 Hz, 5H), 7.41 (dd, J = 8.3, 4.1 Hz, 2H), 6.92 (d, J = 8.5 Hz, 3H), 5.58 – 5.40 (m, 1H), 3.81 (s, 3H), 3.80 – 3.68 (m, 2H), 3.17 (ddd, J = 10.7, 6.3, 3.5 Hz, 1H), 2.19 – 1.73 (m, 5H), 1.79 – 1.40 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.05, 158.25, 148.96, 136.21, 134.54, 129.33, 129.15, 127.04, 123.87, 121.35, 113.93, 57.11, 55.38, 54.21, 38.37, 27.09, 22.70, 15.9; HRMS: calculated for $C_{23}H_{23}N_2O_2$ $[M+H^+]$: 359.1754; found: 359.1748.



27

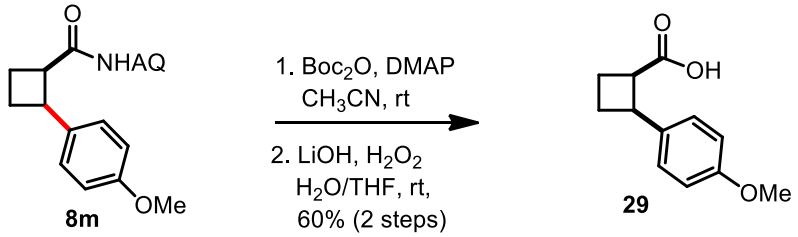
Compound **27** was isolated in 20% yield as a colorless oil. ^1H NMR (300 MHz, CDCl3) δ 9.18 (s, 1H), 8.66 – 8.53 (m, 2H), 8.06 (d, J = 7.1 Hz, 1H), 7.44 (q, J = 8.1 Hz, 2H), 7.35 (dd, J = 8.2, 4.2 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 5.40 (d, J = 2.3 Hz, 1H), 3.52 (s, 3H), 3.41 – 3.22 (m, 1H), 3.13 (s, 1H), 2.55 – 2.26 (m, 2H), 2.18 (s, 3H), 1.81 (dd, J = 23.7, 8.7 Hz, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 169.82, 158.21, 147.81, 136.11, 135.41, 134.28, 127.77, 127.26, 121.45, 113.92, 71.16, 55.07, 53.34, 40.58, 26.69, 26.21, 21.67, 21.086; HRMS: calculated for $C_{25}H_{27}N_2O_4$ $[M+H^+]$: 419.1960; found: 419.1952.



Scheme S10

Compound **9m** (35 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mol, 0.1 equiv), $PhI(OAc)_2$ (80.5 mg, 0.25 mol, 2.5 equiv) and PhMe (1 mL) were added to a 10 mL vial. The vial was flushed with argon, sealed with a PTFE cap, and heated to 60 °C with stirring. After 24 hours, the reaction was cooled to RT, filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by silica gel flash column chromatography (15% EtOAc/Hex) to give 29 mg (83% yield) of **28** as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 8.82 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 7.1 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.59 – 7.34 (m, 4H), 5.43 (s, 1H), 4.26 (d, J = 9.0 Hz, 1H), 4.15 (dd, J = 16.7, 9.5 Hz, 1H), 3.29 – 3.00 (m, 1H), 2.62 (dd, J = 13.9, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.82, 148.90, 148.21, 143.12, 139.78, 136.09, 133.77, 129.26, 129.02, 127.01, 123.32, 122.34, 121.73, 121.42, 119.35, 56.07, 53.81, 35.16, 33.77; HRMS: calculated for $C_{20}H_{16}N_3O_3$ [M+H$^+$]: 346.1181; found: 346.1181.

E: Removal of AQ

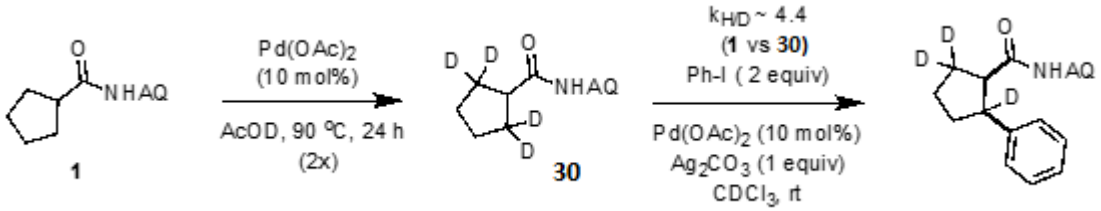


Scheme S11

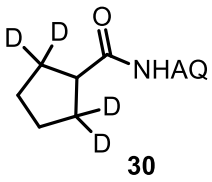
Compound **8m** (104 mg, 0.315 mmol, 1.0 equiv) was dissolved in CH_3CN (3 mL) and DMAP (43 mg, 0.35 mmol, 0.1 equiv), Boc_2O (110 mg, 0.5 mmol, 1.6 equiv) was added. The reaction was allowed to stir overnight at RT. The reaction was filtered through a pad of silica and eluted with EtOAc. The solvent was then evaporated *in vacuo* and the residue applied directly to the

next step. Boc-protected product obtained above was dissolved in THF (2.0 mL) and H_2O (0.75 mL) and the reaction was dooled to 0 ^oC, LiOH (15 mg) then H_2O_2 (0.3 mL) were added. The reaction was held at 0 ^oC for 3 hours, then another portion of LiOH (15 mg) and H_2O_2 (0.3 mL) were added. After 3 additional hours, the reaction mixture was diluted with CH_2Cl_2, quenched with aq. $Na_2S_2O_3$, and acidified to pH 2 with 0.5 M HCl (aq). The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were then washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue purified by column chromatography (10% CH_2Cl_2 in MeOH) to give 40 mg of **29** as a white solid (60% yield). ^1H NMR (500 MHz, CDCl3) δ 7.13 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.92 (t, J = 8.7 Hz, 1H), 3.78 (s, 2H), 3.47 (d, J = 3.1 Hz, 1H), 2.55 (t, J = 9.0 Hz, 1H), 2.29 (dd, J = 12.3, 9.0 Hz, 1H), 2.17 (dd, J = 10.6, 8.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.99, 158.38, 132.75, 128.41, 113.70, 55.31, 45.01, 42.21, 25.10, 20.32; HRMS: calculated for $C_{12}H_{15}O_3$ [$M+H^+$]: 207.1016; found: 207.1026.

7. Kinetic isotope effect study



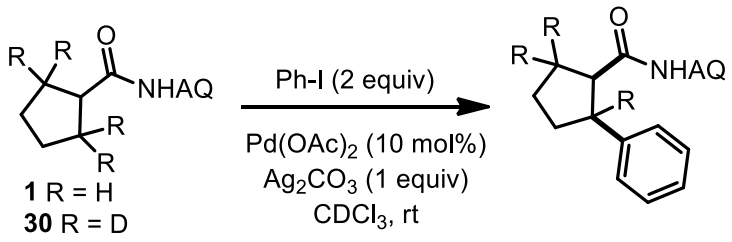
Scheme S12



A mixture of **1** (481 mg, 2 mmol, 1.0 equiv), $Pd(OAc)_2$ (45 mg, 0.2 mol, 0.1 equiv) in CH_3CO_2D (5 mL) in a 12 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 90 ^oC. After 24 hours, the reaction was cooled to RT, filtered through a pad of celite and eluted with EtOAc. The filtrate was concentrated *in vacuo* and the residue was subjected to the deuteration reaction a second time following the same procedure. The product was purified by silica gel flash column

chromatography (10% EtOAc/Hex) to give 300 mg (62% yield) of **30** as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 9.83 (s, 1H), 8.77 (d, J = 7.5 Hz, 1H), 8.73 (d, J = 2.8 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.51 – 7.39 (m, 1H), 7.35 (dd, J = 8.3, 4.2 Hz, 1H), 2.87 (s, 1H), 1.69 (dq, J = 13.9, 6.7 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.99, 147.99, 138.24, 136.22, 134.64, 127.81, 127.30, 127.20, 121.45, 121.14, 116.19, 46.96, 25.87, 25.76; HRMS: calculated for $C_{15}H_{13}D_4N_2O$ [M+H$^+$]: 245.1586; found: 245.1576.

Measurement of Kinetic Isotope effect:



Deuterated substrate **30** (98 mg, 0.4 mmol, 1.0 equiv) or non-deuterated substrate **1** (96 mg, 0.4 mmol, 1.0 equiv) were added to separate 10 mL vials. Iodobenzene (90 μL, 0.8 mmol, 2.0 equiv), $Pd(OAc)_2$ (9 mg, 0.04 mol, 0.1 equiv), Ag_2CO_3 (110 mg, 0.4 mol, 1 equiv), and $CDCl_3$ (2 mL, 0.2M) were then added to each substrate. The resulting reaction mixture was stirred vigorously for 6 hours. Every hour, stirring was stopped and the solids suspended in the reaction mixture were allowed to settle. 0.1 mL of supernatant was removed by syringe and dissolved in 400 μL $CDCl_3$ for ^{1}H NMR measurement. $K_{H/D}$ (~4.4) was estimated based on the ratio of arylation yield.

Time (h)	1	2	3	4	5	6
Yield of R = H (%)	1.1	4.2	5.3	7.5	10.5	14.1
Yield of R = D (%)	0.4	1.9	1.6	2.5	2.4	3.3

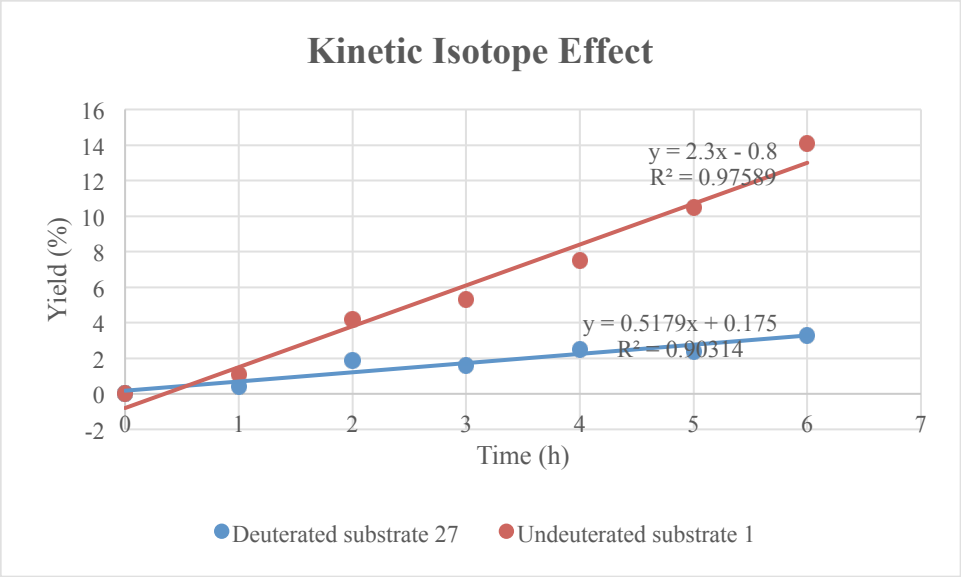
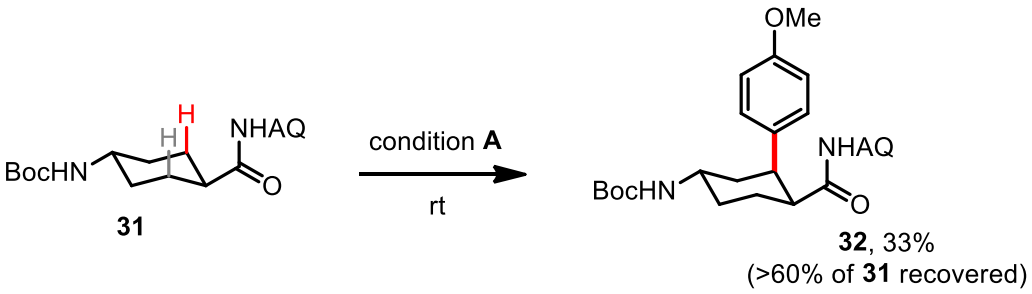


Table S1

$K_H/K_D = 2.3/0.5179 = 4.4$

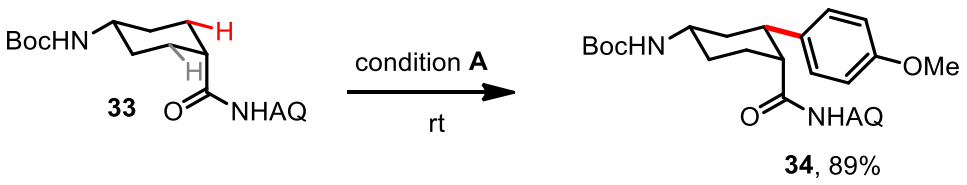
C-H Arylation of 31 VS 33:



Scheme S13

Compound **32** was prepared following the general room temperature arylation procedure in 33% yield as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 9.50 (s, 1H), 8.73 (d, J = 2.7 Hz, 1H), 8.59 (dd, J = 5.5, 3.4 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.56 – 7.33 (m, 3H), 7.19 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 4.47 (s, J = 73.8 Hz, 1H), 3.70 (s, 1H), 3.60 (s, 3H), 3.08 (t, J = 11.9 Hz, 1H), 2.59 (t, J = 10.4 Hz, 1H), 2.40 – 2.14 (m, 3H), 1.96 (dd, J = 23.5, 12.5 Hz, 1H), 1.44 (s, J = 9.8 Hz, 11H), 1.37 – 1.28 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 173.20, 148.06, 136.35, 135.49, 134.63, 128.26, 127.40, 121.71, 116.55, 113.97, 55.09, 53.03, 45.11, 29.44,

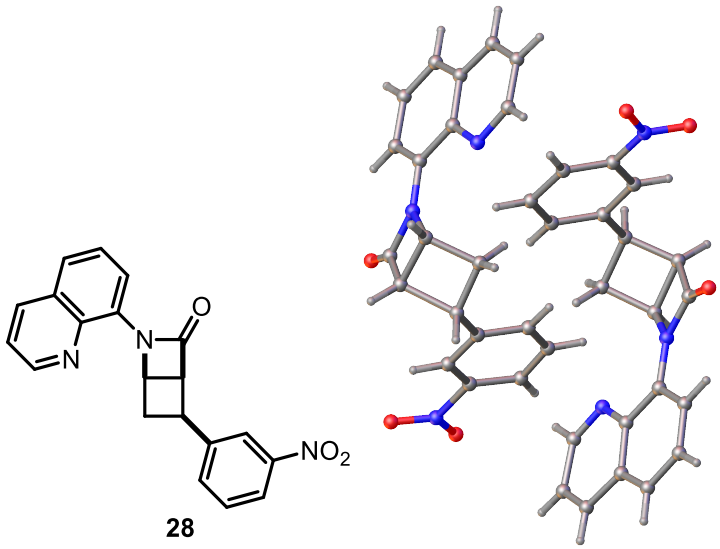
28.41; HRMS: calculated for $C_{28}H_{34}N_3O_4$ [M+H$^+$]: 476.2544; found: 476.2527.



Scheme S14

Compound **34** was prepared following the general room temperature arylation procedure in 89% yield as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 9.18 (s, 1H), 8.62 (d, J = 7.1 Hz, 1H), 8.57 (d, J = 3.1 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.53 – 7.35 (m, 2H), 7.32 (dd, J = 8.2, 4.2 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 8.3 Hz, 2H), 4.69 (d, J = 7.9 Hz, 1H), 3.69 (s, 1H), 3.53 (s, 3H), 3.03 (d, J = 13.0 Hz, 1H), 2.94 (s, 1H), 2.38 (dd, J = 24.4, 12.2 Hz, 1H), 2.25 (d, J = 12.5 Hz, 1H), 2.05 (d, J = 13.1 Hz, 2H), 2.01 – 1.77 (m, 3H), 1.44 (s, 11H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.71, 158.10, 155.38, 147.76, 138.15, 136.06, 135.21, 134.38, 128.37, 127.73, 127.19, 121.39, 121.22, 116.09, 113.78, 79.08, 54.98, 50.04, 47.52, 44.33, 33.61, 28.84, 28.48; HRMS: calculated for $C_{28}H_{34}N_3O_4$ [M+H$^+$]: 476.2544; found: 476.2526.

8. X-ray structure of compound 28



Single crystals of $C_{20}H_{15}N_3O_3$ [wun1m] were grown from diffusion of hexanes in an EtOAc solution of **28**. A suitable crystal was selected and mounted on a Bruker SMART APEX CCD

area detector diffractometer. The crystal was kept at 298(2) K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the XL [3] refinement package using Least Squares minimization.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal structure determination of [wun1m]

Crystal Data for $C_{20}H_{15}N_3O_3$ (M =345.35 g/mol): monoclinic, space group I2/a (no. 15), a = 13.6461(19) Å, b = 10.7230(15) Å, c = 22.268(4) Å, β = 90.915(2)°, V = 3258.0(9) Å^3, Z = 8, T = 298(2) K, μ(MoKα) = 0.097 mm^{-1}, *Dcalc* = 1.408 g/cm^3, 12321 reflections measured (3.66° ≤ 2Θ ≤ 56.62°), 4046 unique (R_{int} = 0.0311, R_{sigma} = 0.0367) which were used in all calculations. The final R_1 was 0.1530 (>2sigma(I)) and wR_2 was 0.3402 (all data).

Refinement:

The structure was refined without any restraints. The hydrogen atoms were placed geometrically and their positions refined using the riding model.

Table 1 Crystal data and structure refinement for wun1m.

Identification code	wun1m
Empirical formula	$C_{20}H_{15}N_3O_3$
Formula weight	345.35
Temperature/K	298(2)
Crystal system	monoclinic
Space group	I2/a
a/Å	13.6461(19)
b/Å	10.7230(15)
c/Å	22.268(4)
α/°	90.00
β/°	90.915(2)
γ/°	90.00

Volume/Å^3	3258.0(9)
Z	8
ρ_{calc}g/cm^3	1.408
μ/mm^{-1}	0.097
F(000)	1440.0
Crystal size/mm^3	0.2 × 0.16 × 0.14
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.66 to 56.62
Index ranges	-13 ≤ h ≤ 18, -14 ≤ k ≤ 13, -29 ≤ l ≤ 29
Reflections collected	12321
Independent reflections	4046 [R_{int} = 0.0311, R_{sigma} = 0.0367]
Data/restraints/parameters	4046/0/235
Goodness-of-fit on F^2	2.199
Final R indexes [I>=2σ (I)]	R_1 = 0.1530, wR_2 = 0.3373
Final R indexes [all data]	R_1 = 0.1590, wR_2 = 0.3402
Largest diff. peak/hole / e Å^{-3}	0.49/-0.42

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for wun1m. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	5989(2)	6066(3)	4843.5(11)	36.8(7)
N2	5898(2)	6911(3)	3864.3(12)	25.6(7)
C6	6881(3)	8256(3)	3216.7(14)	23.6(8)
O2	3951(4)	5991(4)	6397.1(16)	77.1(14)
C15	3822(3)	7843(4)	4786.9(18)	34.5(9)
N1	6078(2)	8446(3)	2867.3(13)	33.4(8)
C14	3829(3)	7184(4)	4193.9(16)	33.0(9)
N3	3861(3)	7106(4)	6422.8(16)	47.5(10)
C20	3860(3)	7184(4)	5323.8(17)	32.3(9)
C12	4958(3)	6770(3)	3537.1(16)	29.0(8)
C2	7606(3)	7237(4)	4091.8(15)	32.7(9)
C11	4567(3)	6080(3)	4102.4(15)	29.8(9)
C19	3817(3)	7824(4)	5858.0(18)	36.3(9)
C4	8611(3)	8532(4)	3472.9(18)	37.1(9)
C1	6800(3)	7457(3)	3731.5(14)	23.3(7)
C5	7812(3)	8784(3)	3093.7(16)	30.9(9)
C9	7852(4)	9564(4)	2582.1(19)	42.8(11)
C10	5574(3)	6299(3)	4373.2(15)	24.4(8)
C8	7045(4)	9758(4)	2239.7(19)	47.4(12)
C13	4238(3)	7845(4)	3632.9(18)	41.3(10)

C7	6175(4)	9174(4)	2397.3(17)	42.0(11)
C18	3763(4)	9103(4)	5896(2)	49.1(12)
C3	8503(3)	7781(4)	3959.7(18)	39.3(10)
C17	3732(4)	9751(4)	5361(3)	63.5(16)
C16	3762(4)	9140(4)	4816(2)	48.8(12)
O3	3811(4)	7663(4)	6891.1(16)	101.4(17)

The single crystal data of compound **28** has been deposited at CCDC (#1451082).

9. References

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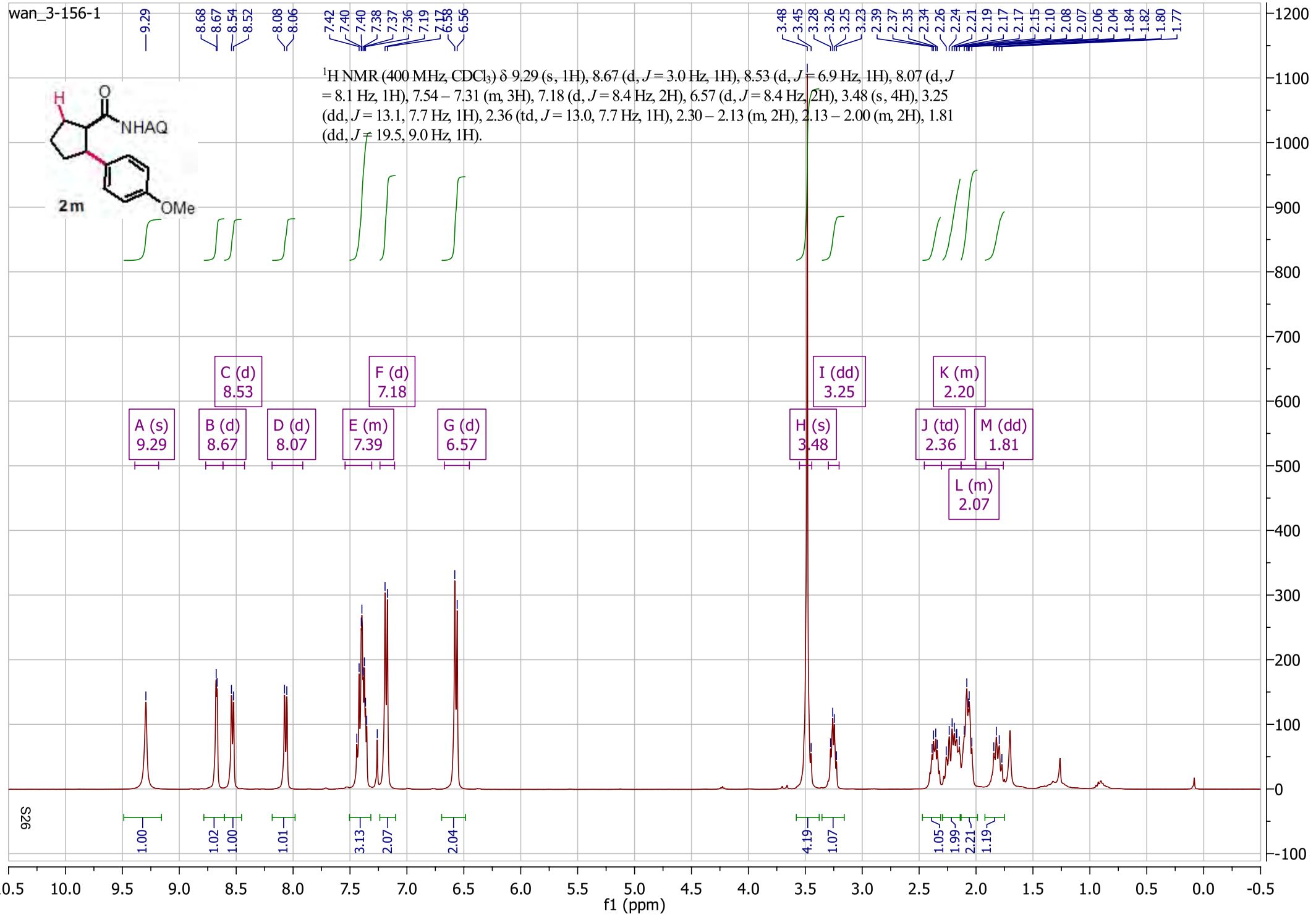
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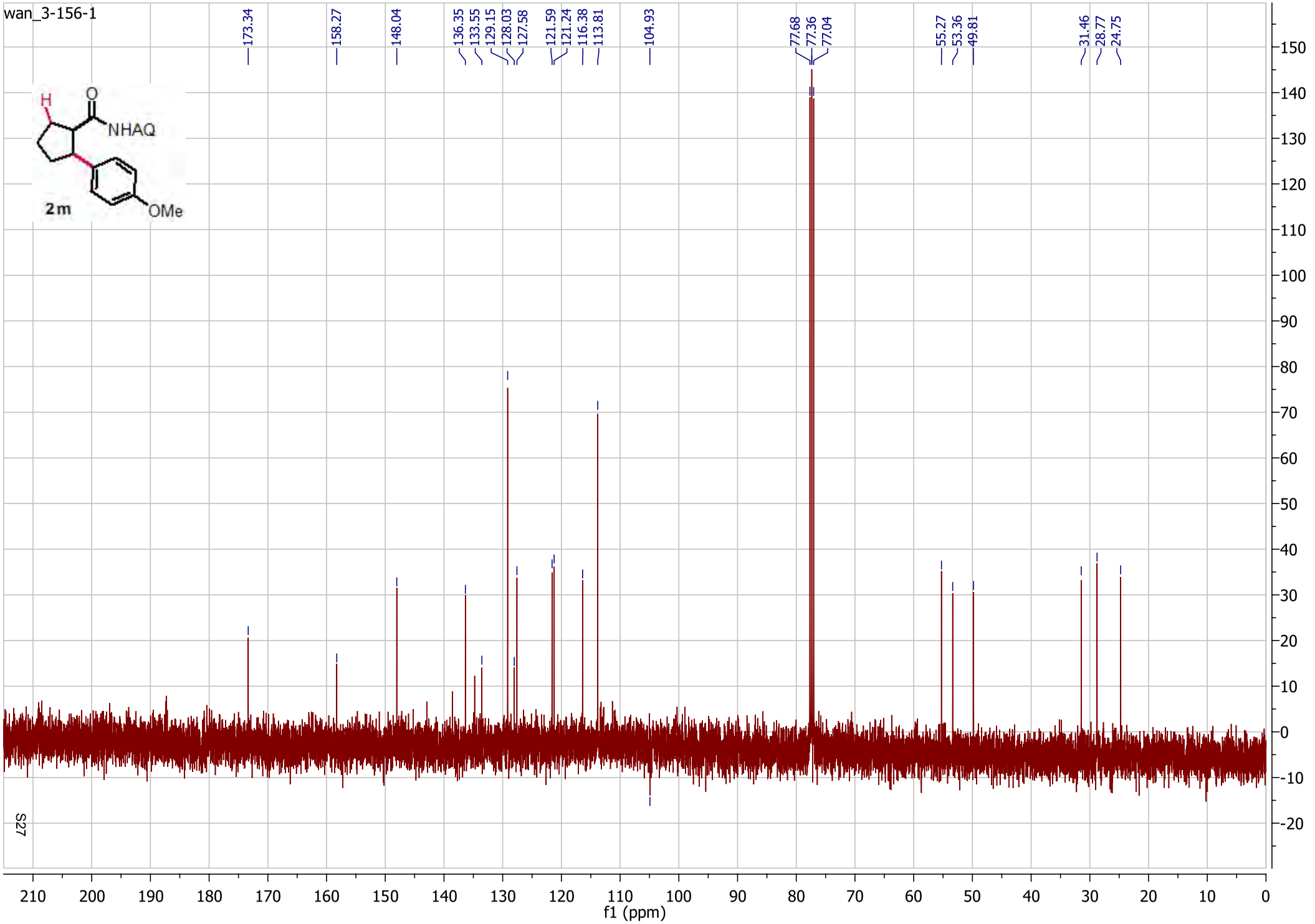
2.17
2.17
2.15
2.10
2.08
2.07
2.06
2.04
1.84
1.82
1.80
1.77
[1]H NMR (400 MHz, CDCl3) δ 9.29 (s, 1H), 8.67 (d, J = 3.0 Hz, 1H), 8.53 (d, J = 6.9 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.54 – 7.31 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.48 (s, 4H), 3.25 (dd, J = 13.1, 7.7 Hz, 1H), 2.36 (td, J = 13.0, 7.7 Hz, 1H), 2.30 – 2.13 (m, 2H), 2.13 – 2.00 (m, 2H), 1.81 (dd, J = 19.5, 9.0 Hz, 1H).
H
O
NHAQ
2m
OMe
A (s) 9.29
B (d) 8.67
C (d) 8.53
D (d) 8.07
E (m) 7.39
F (d) 7.18
G (d) 6.57
H (s) 3.48
I (dd) 3.25
J (td) 2.36
K (m) 2.20
L (m) 2.07
M (dd) 1.81
1.00
1.02
1.00
1.01
3.13
2.07
2.04
4.19
1.07
1.05
1.99
2.21
1.19
S26
f1 (ppm)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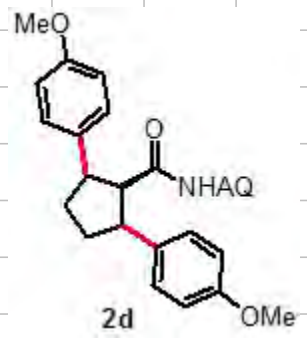
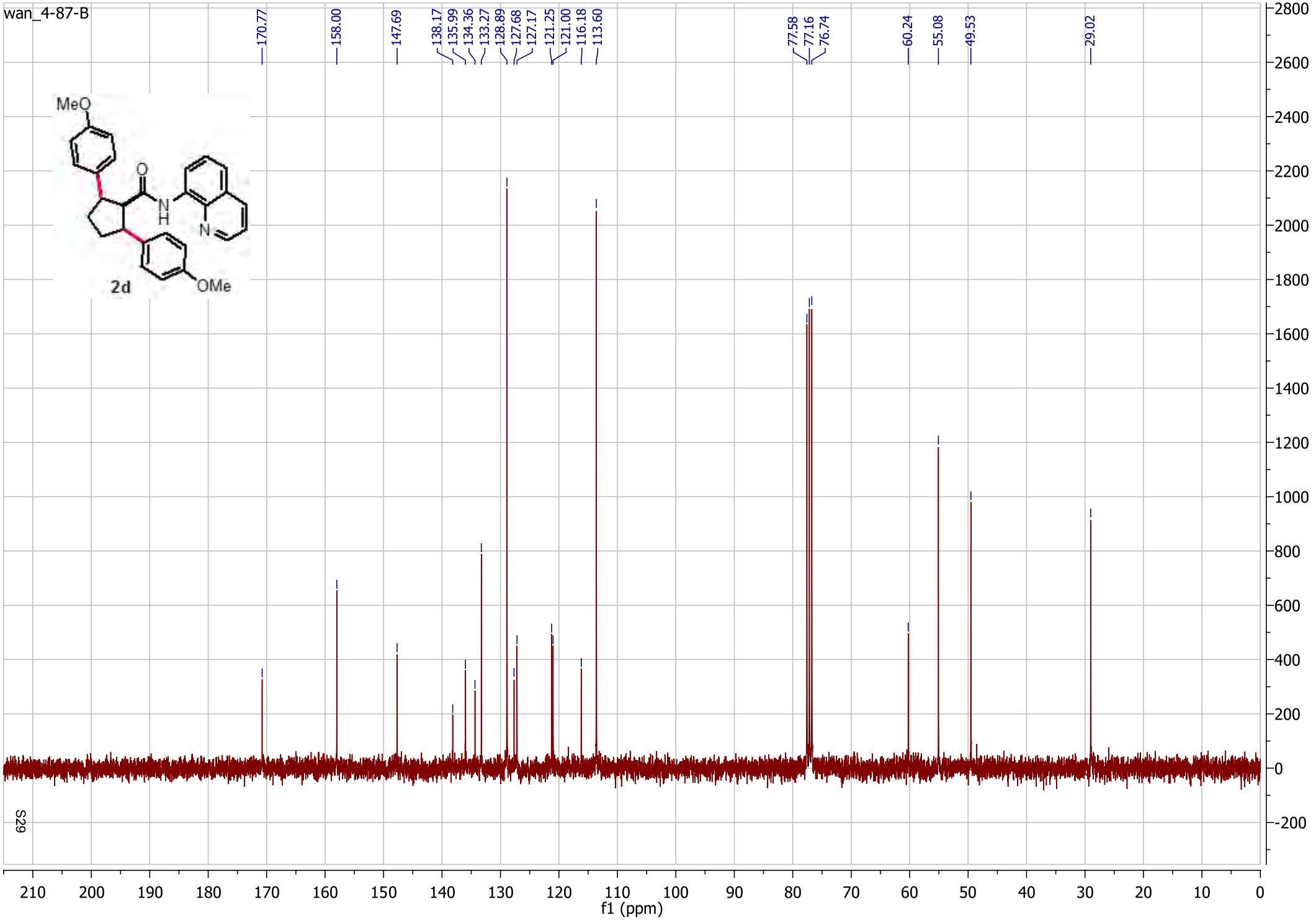
OMe
S27
f1 (ppm)

WAN87B



^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.59 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.50 (d, *J* = 6.7 Hz, 1H), 7.99 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.33 (d, *J* = 8.6 Hz, 5H), 7.30 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 4H), 3.68 (d, *J* = 7.1 Hz, 2H), 3.57 (s, 6H), 3.46 (t, *J* = 5.9 Hz, 1H), 2.77 (td, *J* = 7.4, 2.8 Hz, 2H), 2.31 (t, *J* = 6.0 Hz, 2H).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116.18
113.60
77.58
77.16
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H
N
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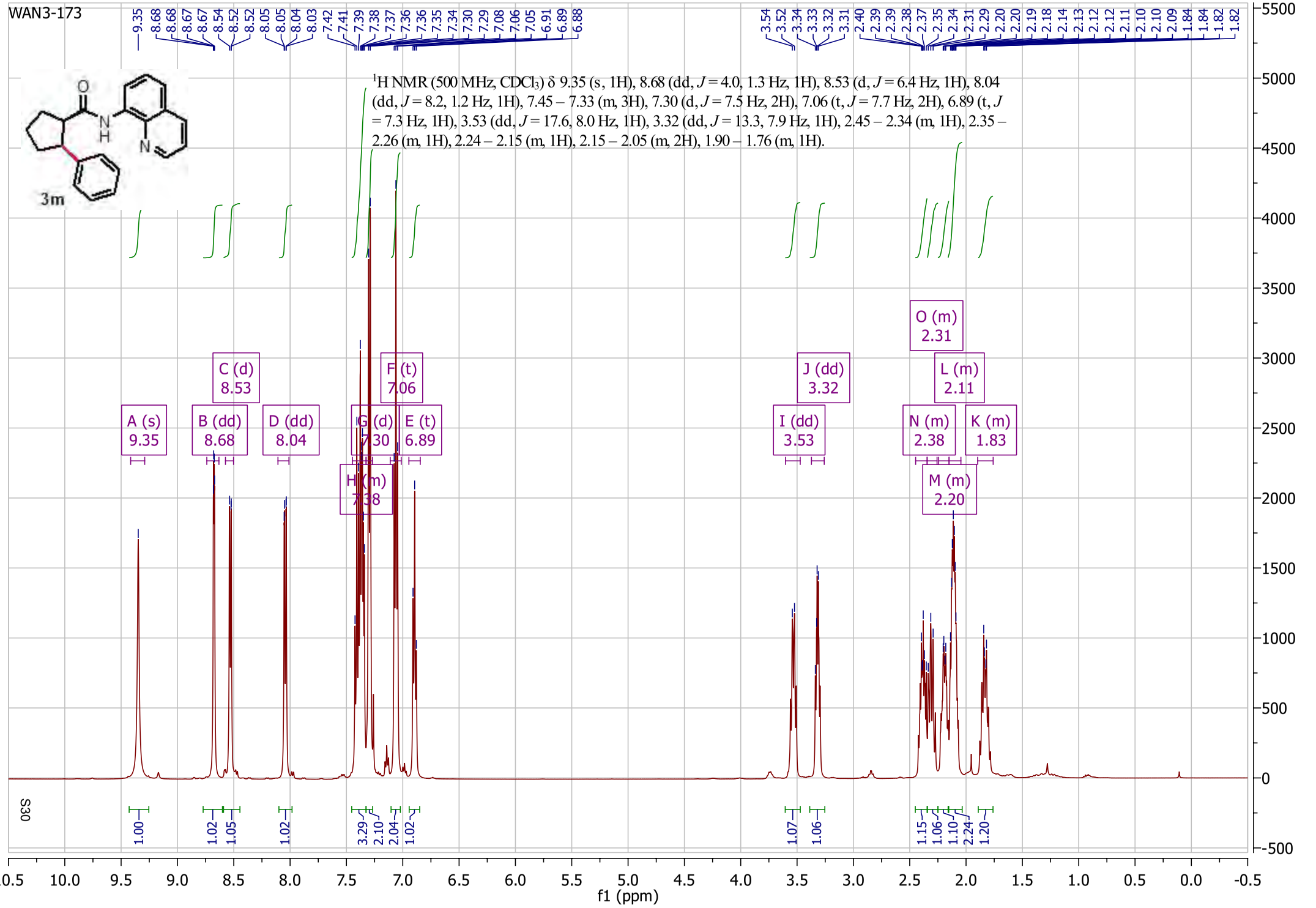
2d
S29
f1 (ppm)


WAN3-173
3m
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.68 (dd, *J* = 4.0, 1.3 Hz, 1H), 8.53 (d, *J* = 6.4 Hz, 1H), 8.04 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.06 (t, *J* = 7.7 Hz, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 3.53 (dd, *J* = 17.6, 8.0 Hz, 1H), 3.32 (dd, *J* = 13.3, 7.9 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.35 – 2.26 (m, 1H), 2.24 – 2.15 (m, 1H), 2.15 – 2.05 (m, 2H), 1.90 – 1.76 (m, 1H).
A (s) 9.35
B (dd) 8.68
C (d) 8.53
D (dd) 8.04
F (t) 7.06
E (t) 6.89
I (dd) 3.53
J (dd) 3.32
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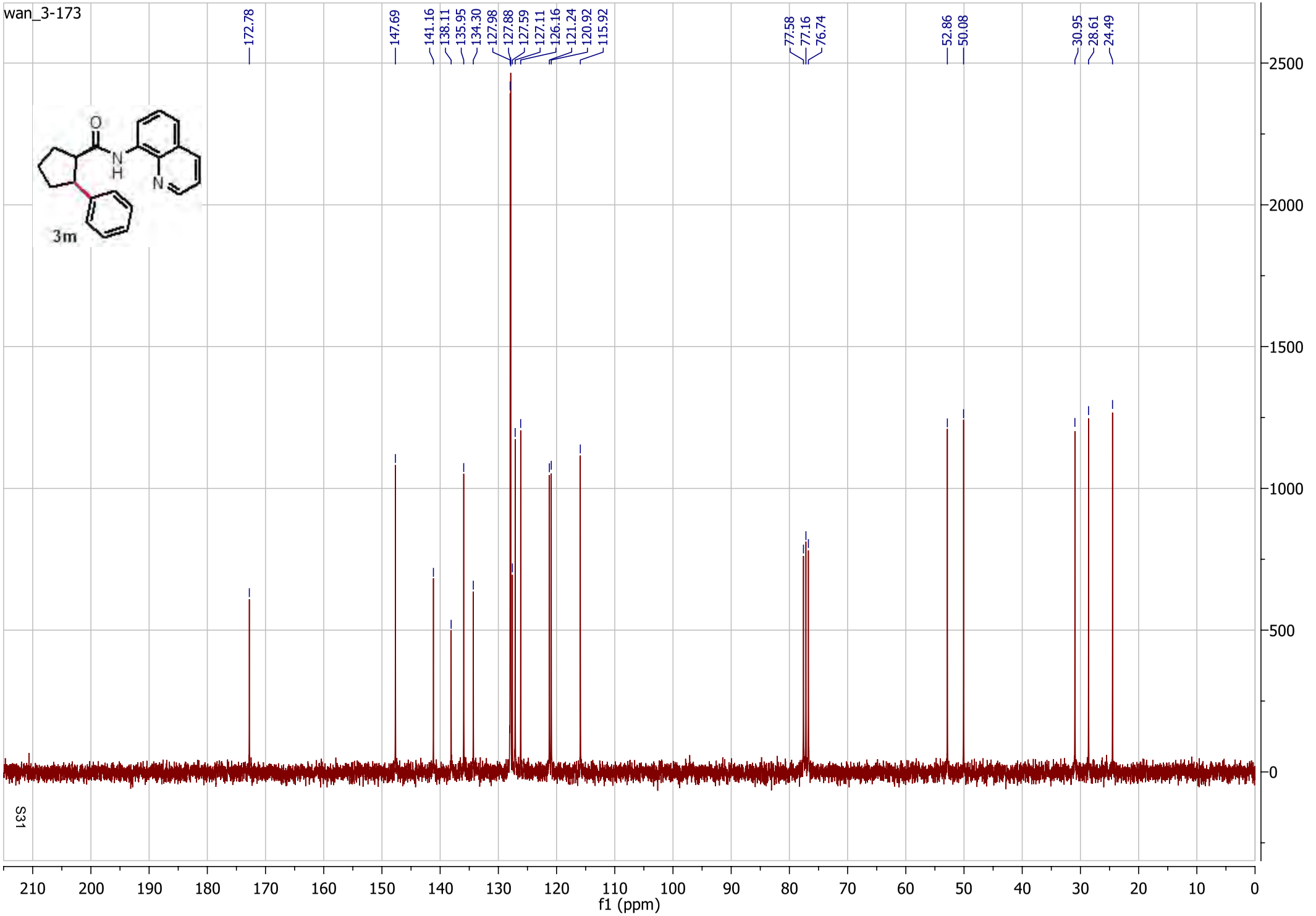
S30
f1 (ppm)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H
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2500
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1000
500
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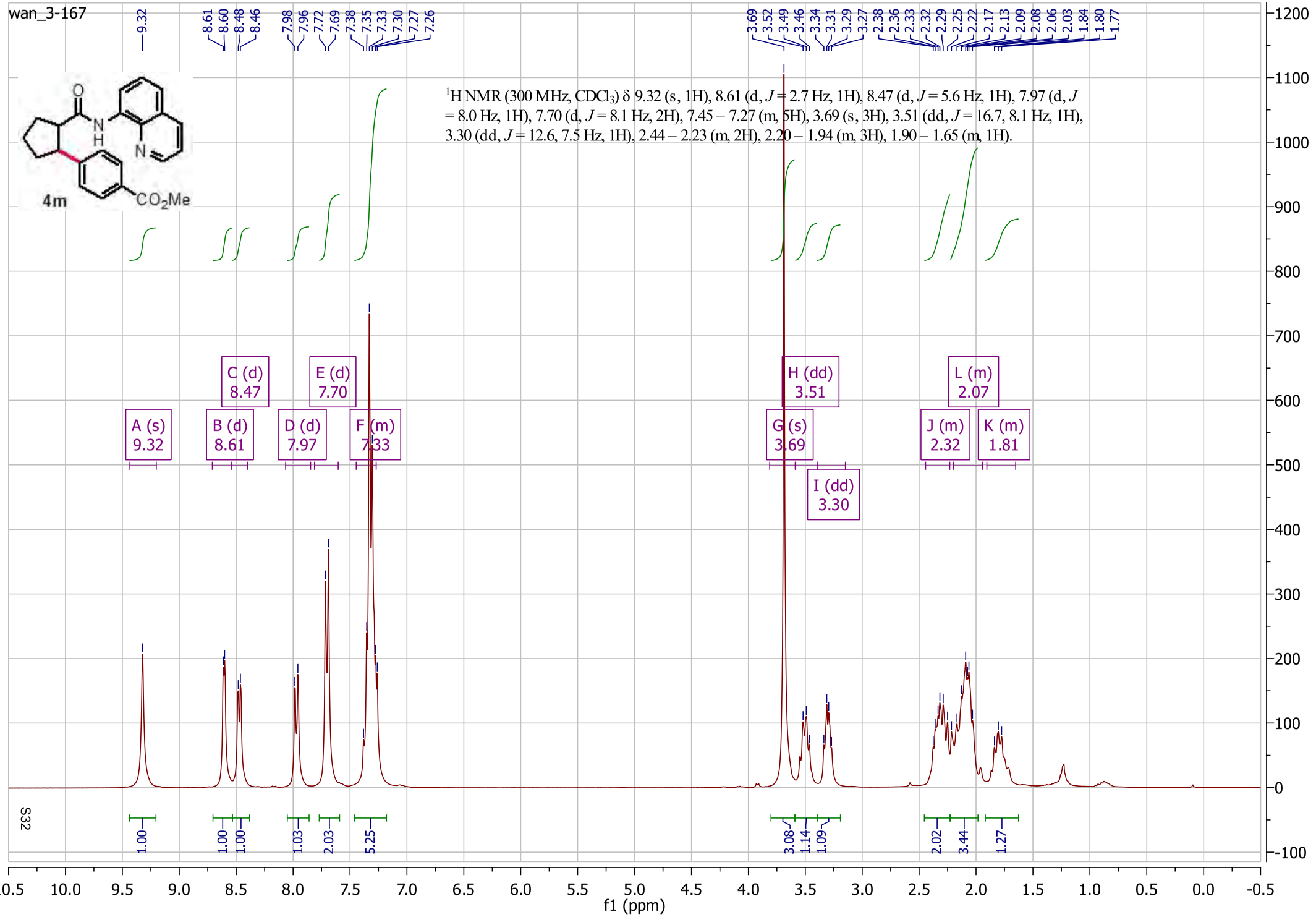
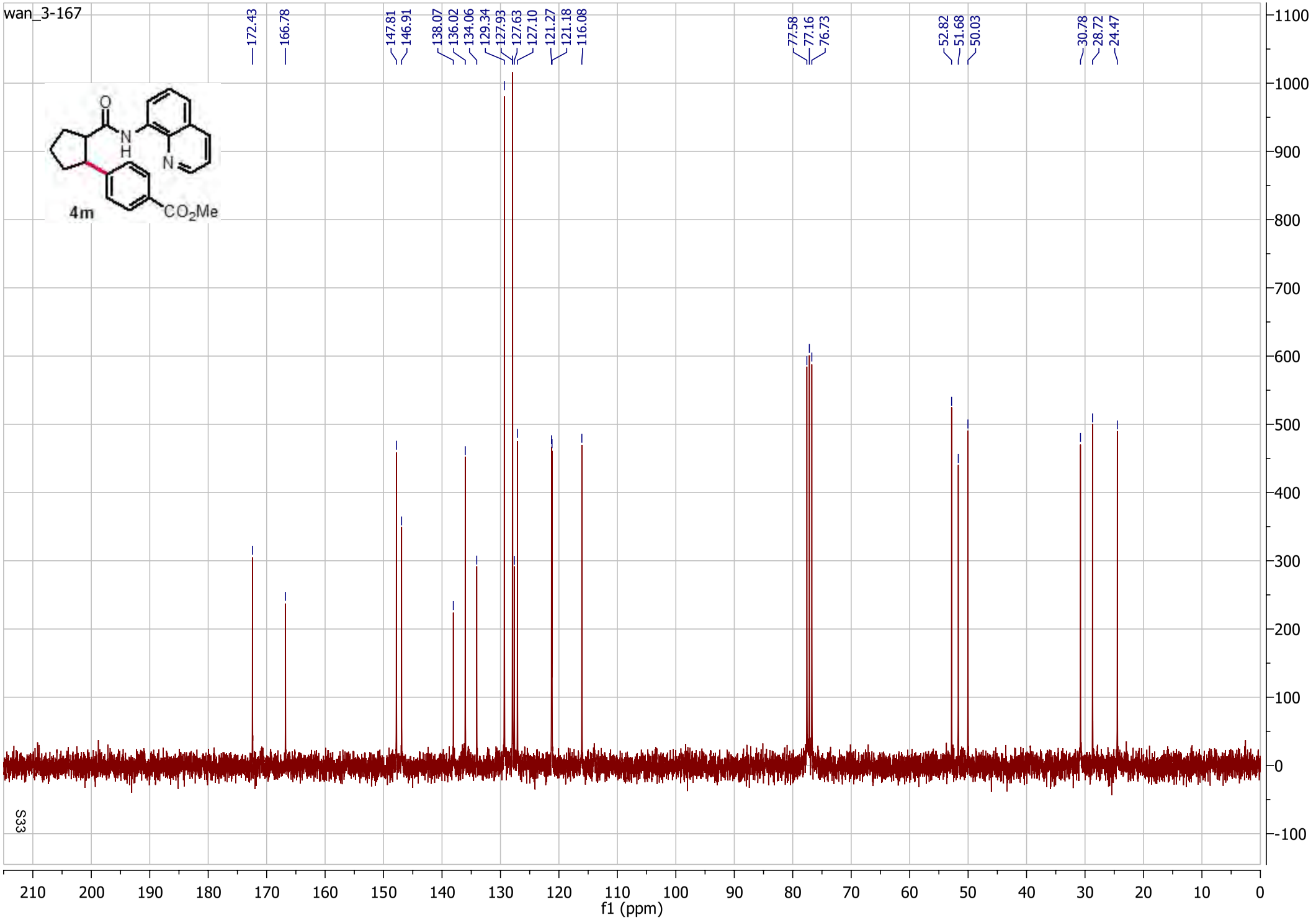
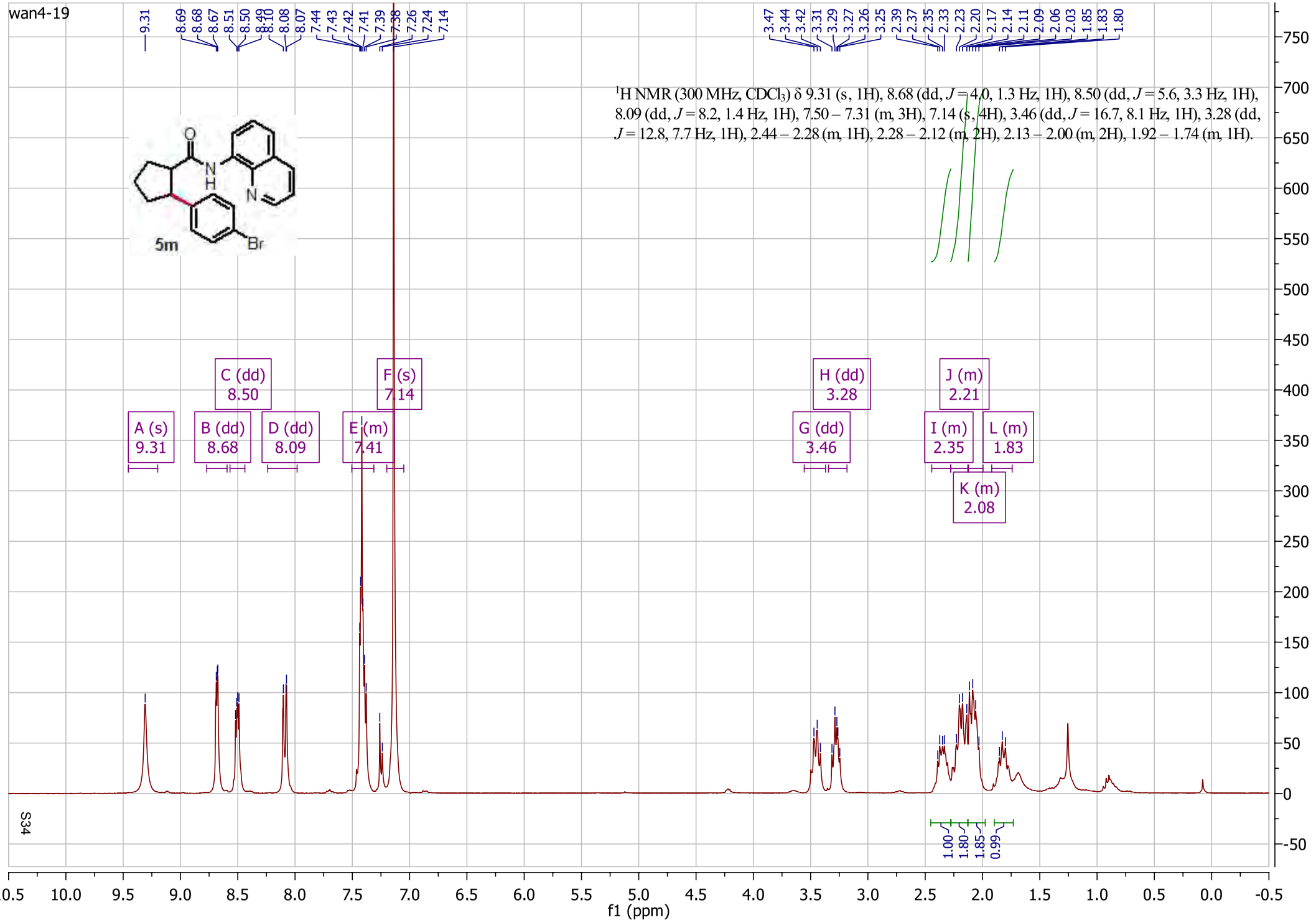
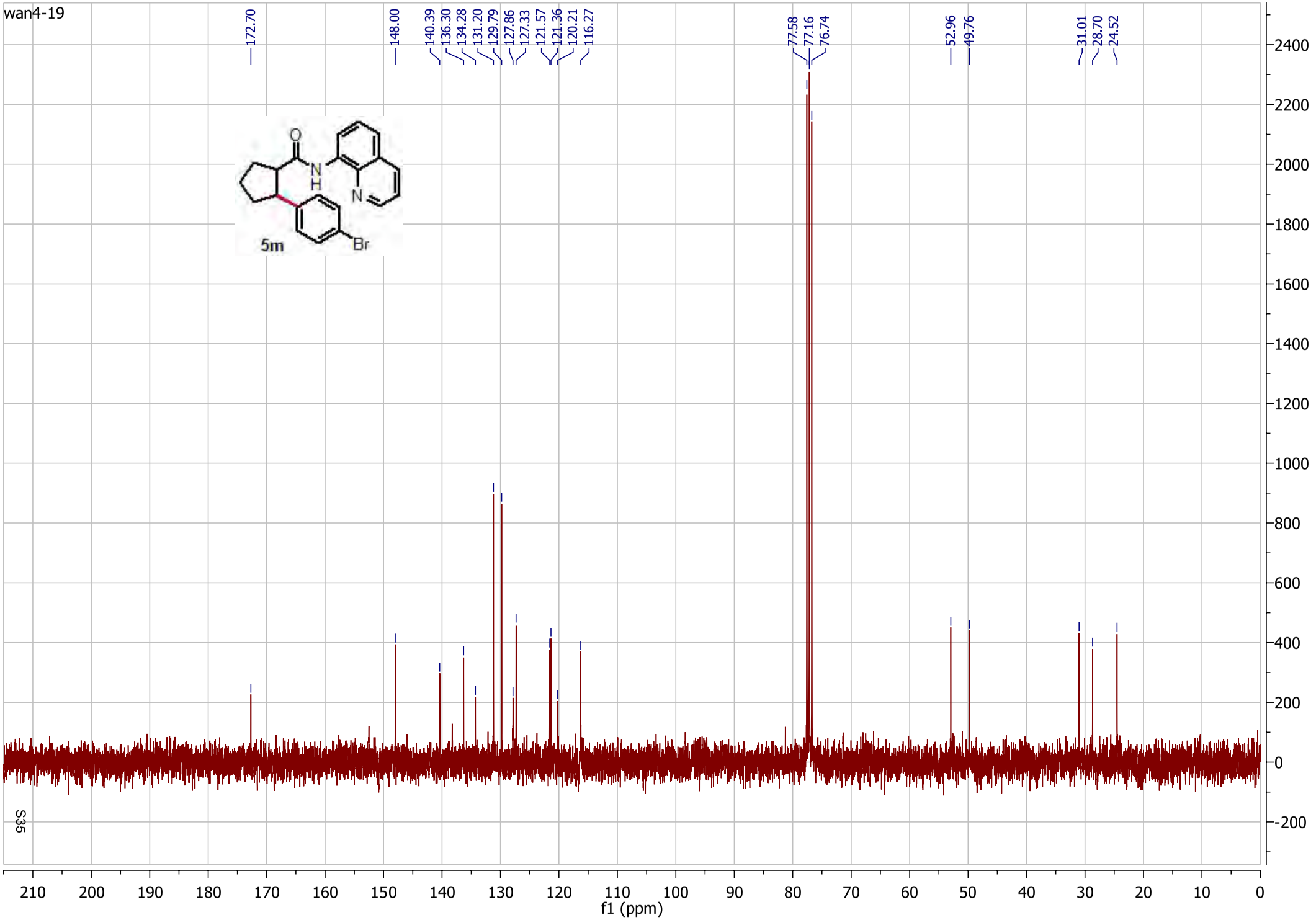
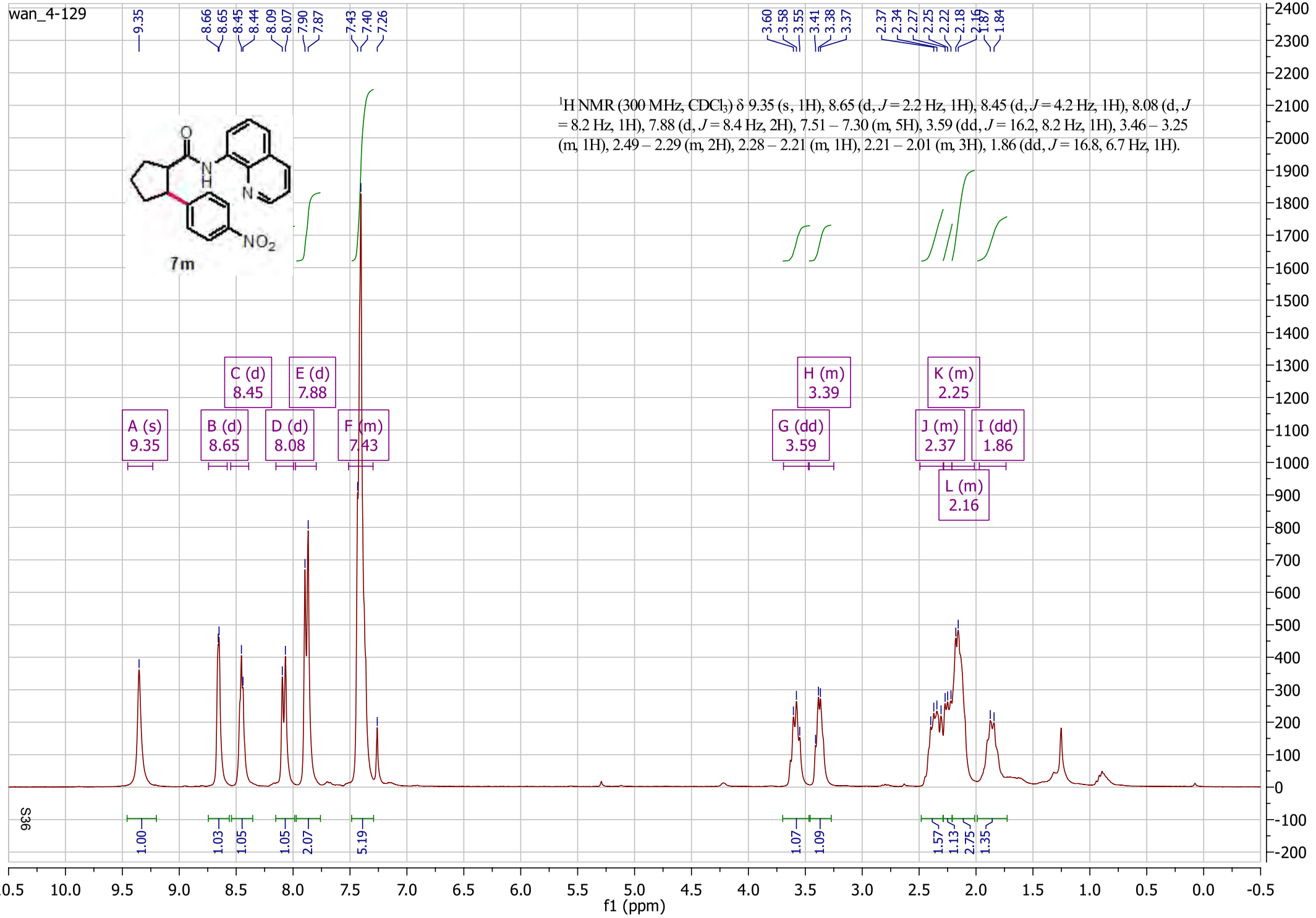
f1 (ppm)

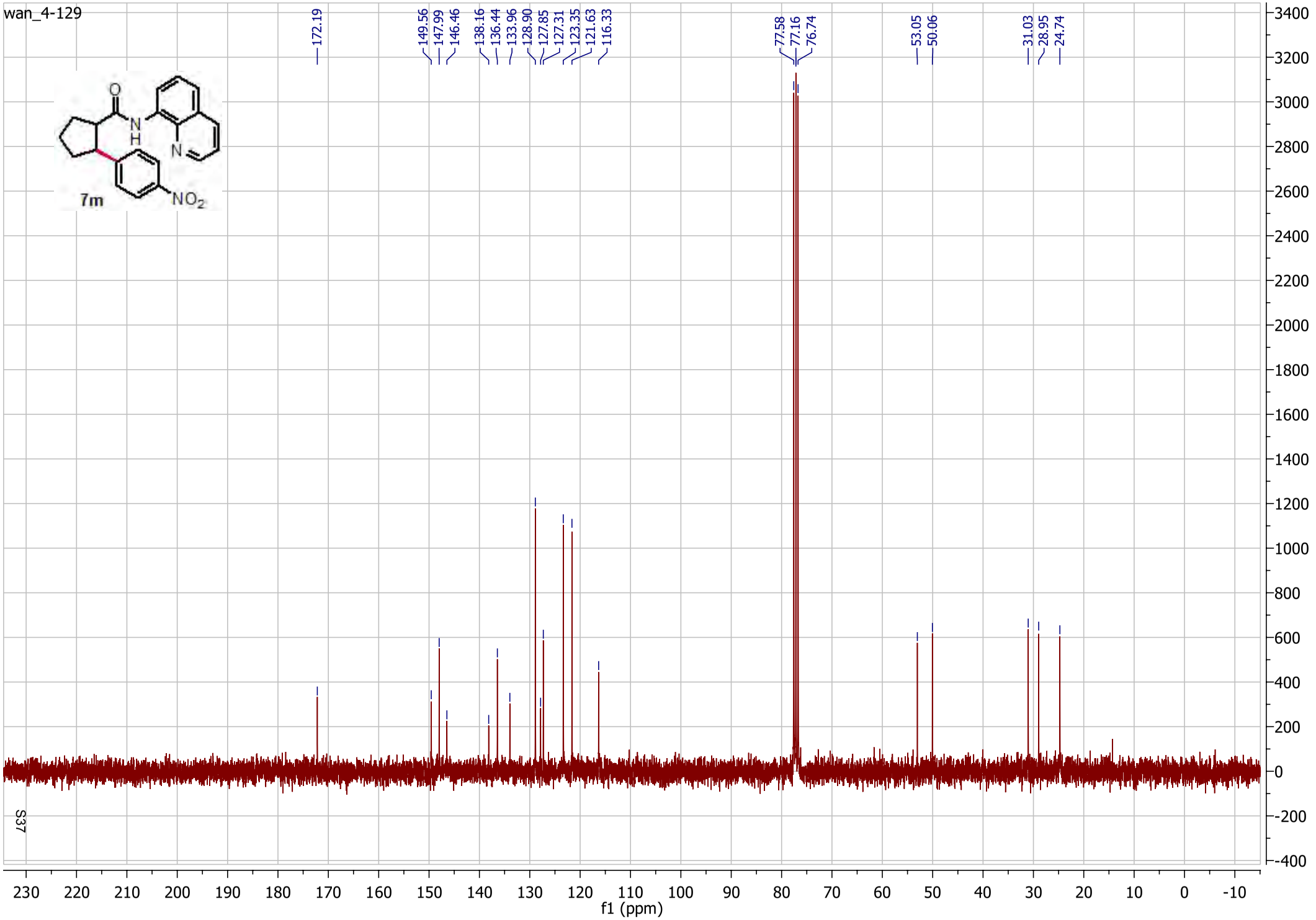

wan_3-167
4m
CO2Me
1H NMR (300 MHz, CDCl3) δ 9.32 (s, 1H), 8.61 (d, J = 2.7 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.45 – 7.27 (m, 5H), 3.69 (s, 3H), 3.51 (dd, J = 16.7, 8.1 Hz, 1H), 3.30 (dd, J = 12.6, 7.5 Hz, 1H), 2.44 – 2.23 (m, 2H), 2.20 – 1.94 (m, 3H), 1.90 – 1.65 (m, 1H).
A (s) 9.32
B (d) 8.61
C (d) 8.47
D (d) 7.97
E (d) 7.70
F (m) 7.33
G (s) 3.69
H (dd) 3.51
I (dd) 3.30
J (m) 2.32
K (m) 1.81
L (m) 2.07
S32
f1 (ppm)

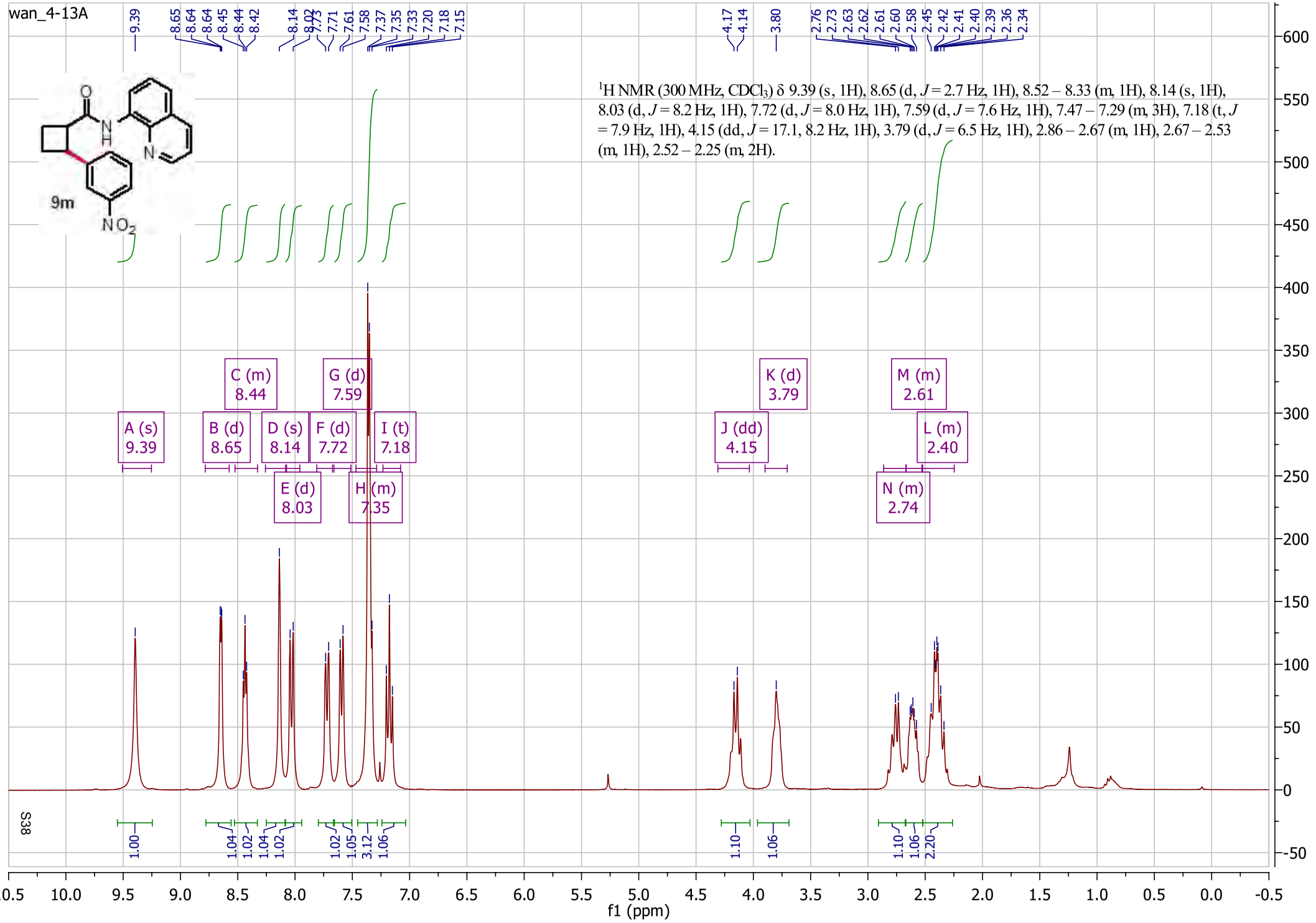

wan_3-167
172.43
166.78
147.81
146.91
138.07
136.02
134.06
129.34
127.93
127.63
127.10
121.27
121.18
116.08
77.58
77.16
76.73
52.82
51.68
50.03
30.78
28.72
24.47
O
N
H
N
4m
CO2Me
S33
f1 (ppm)

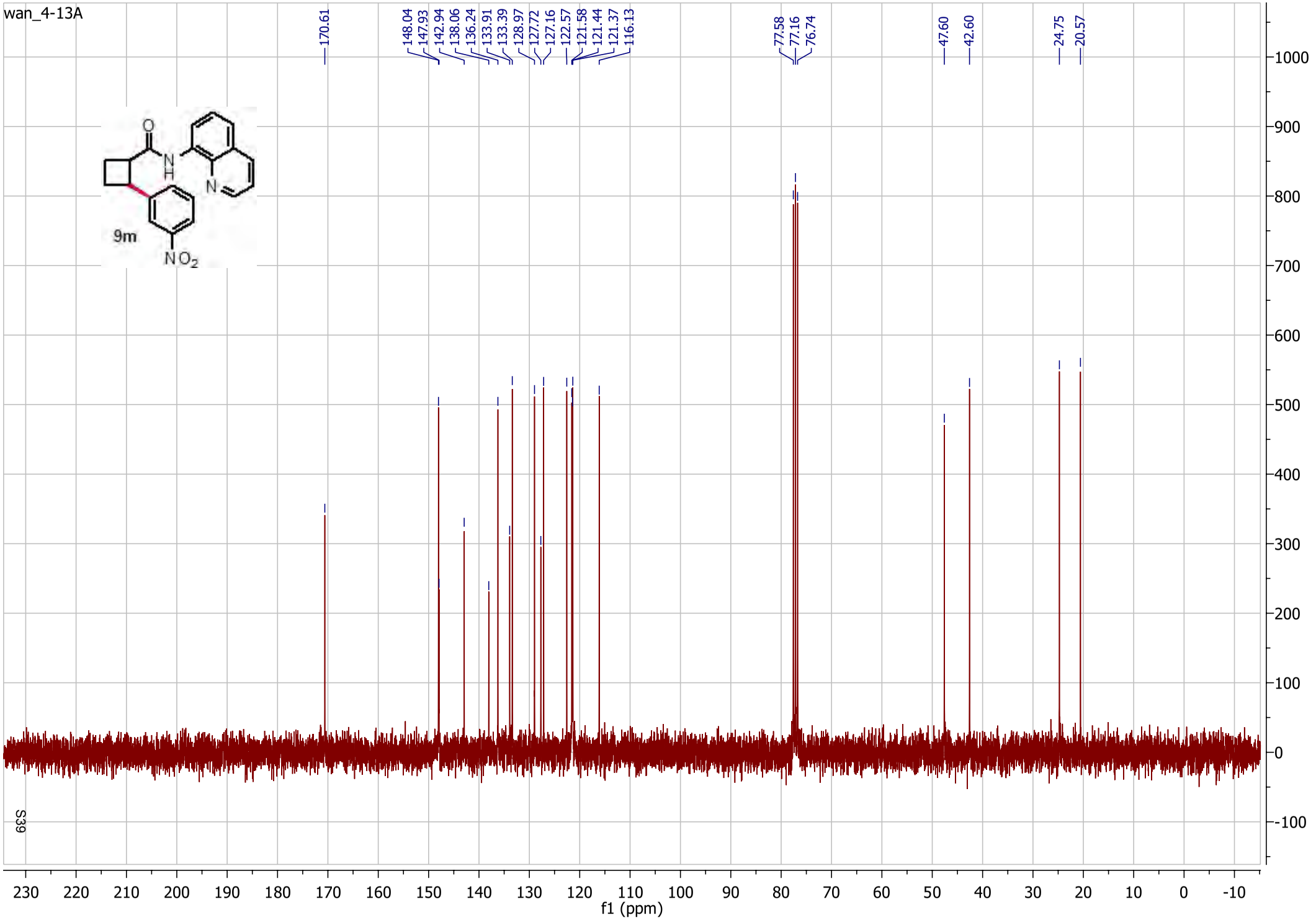

wan4-19
9.31
8.69
8.68
8.67
8.51
8.50
8.49
8.10
8.08
8.07
7.44
7.43
7.42
7.41
7.39
7.38
7.26
7.24
7.14
3.47
3.44
3.42
3.31
3.29
3.27
3.26
3.25
2.39
2.37
2.35
2.33
2.23
2.20
2.17
2.14
2.11
2.09
2.06
2.03
1.85
1.83
1.80
O
N
H
N
Br
5m
^{1}H NMR (300 MHz, CDCl$_3$) δ 9.31 (s, 1H), 8.68 (dd, J = 4.0, 1.3 Hz, 1H), 8.50 (dd, J = 5.6, 3.3 Hz, 1H), 8.09 (dd, J = 8.2, 1.4 Hz, 1H), 7.50 – 7.31 (m, 3H), 7.14 (s, 4H), 3.46 (dd, J = 16.7, 8.1 Hz, 1H), 3.28 (dd, J = 12.8, 7.7 Hz, 1H), 2.44 – 2.28 (m, 1H), 2.28 – 2.12 (m, 2H), 2.13 – 2.00 (m, 2H), 1.92 – 1.74 (m, 1H).
A (s) 9.31
B (dd) 8.68
C (dd) 8.50
D (dd) 8.09
E (m) 7.41
F (s) 7.14
G (dd) 3.46
H (dd) 3.28
I (m) 2.35
J (m) 2.21
K (m) 2.08
L (m) 1.83
1.00
1.80
1.85
0.99
S34
f1 (ppm)

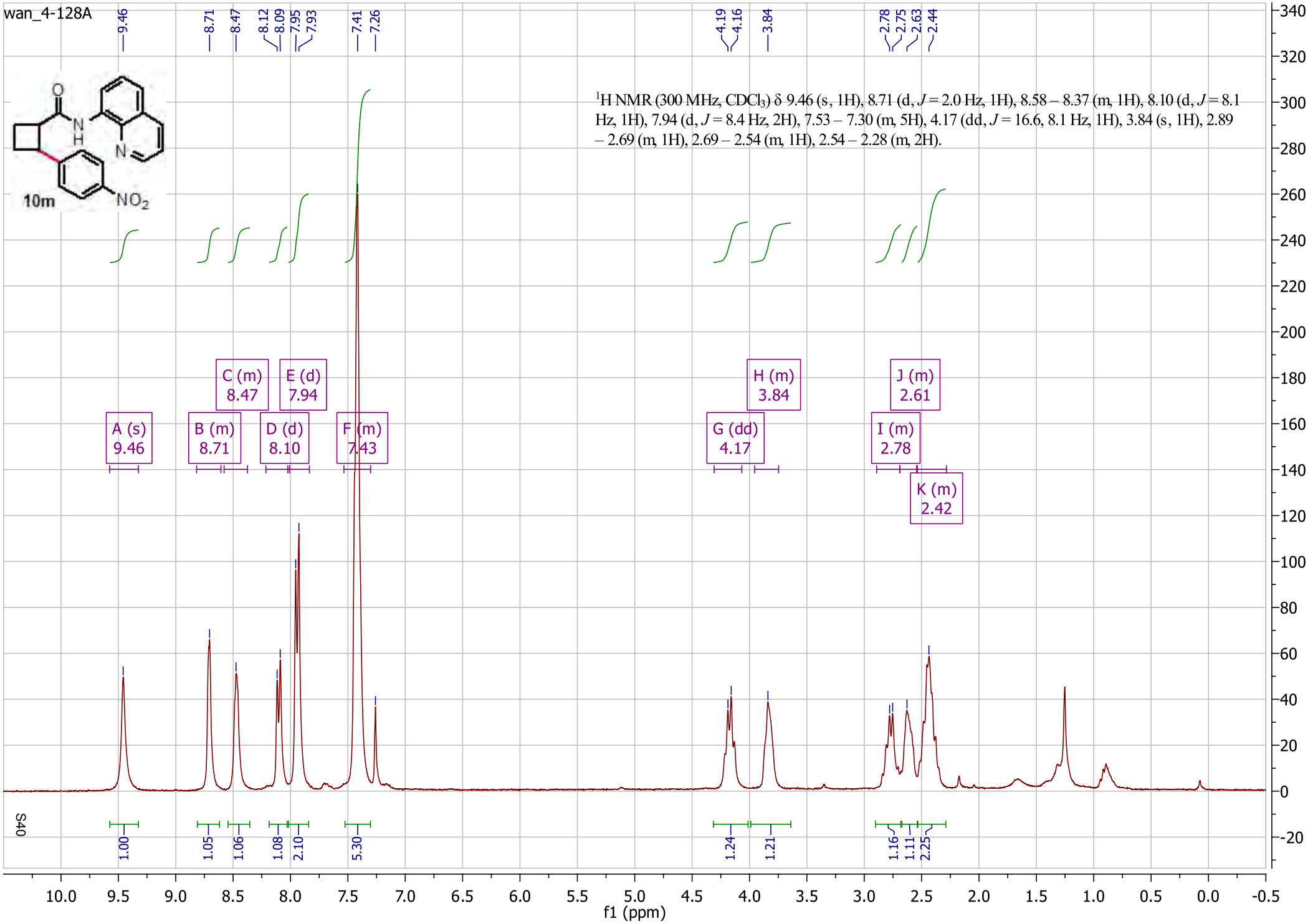

wan4-19
172.70
148.00
140.39
136.30
134.28
131.20
129.79
127.86
127.33
121.57
121.36
120.21
116.27
77.58
77.16
76.74
52.96
49.76
31.01
28.70
24.52
O
N
H
N
Br
5m
S35
f1 (ppm)

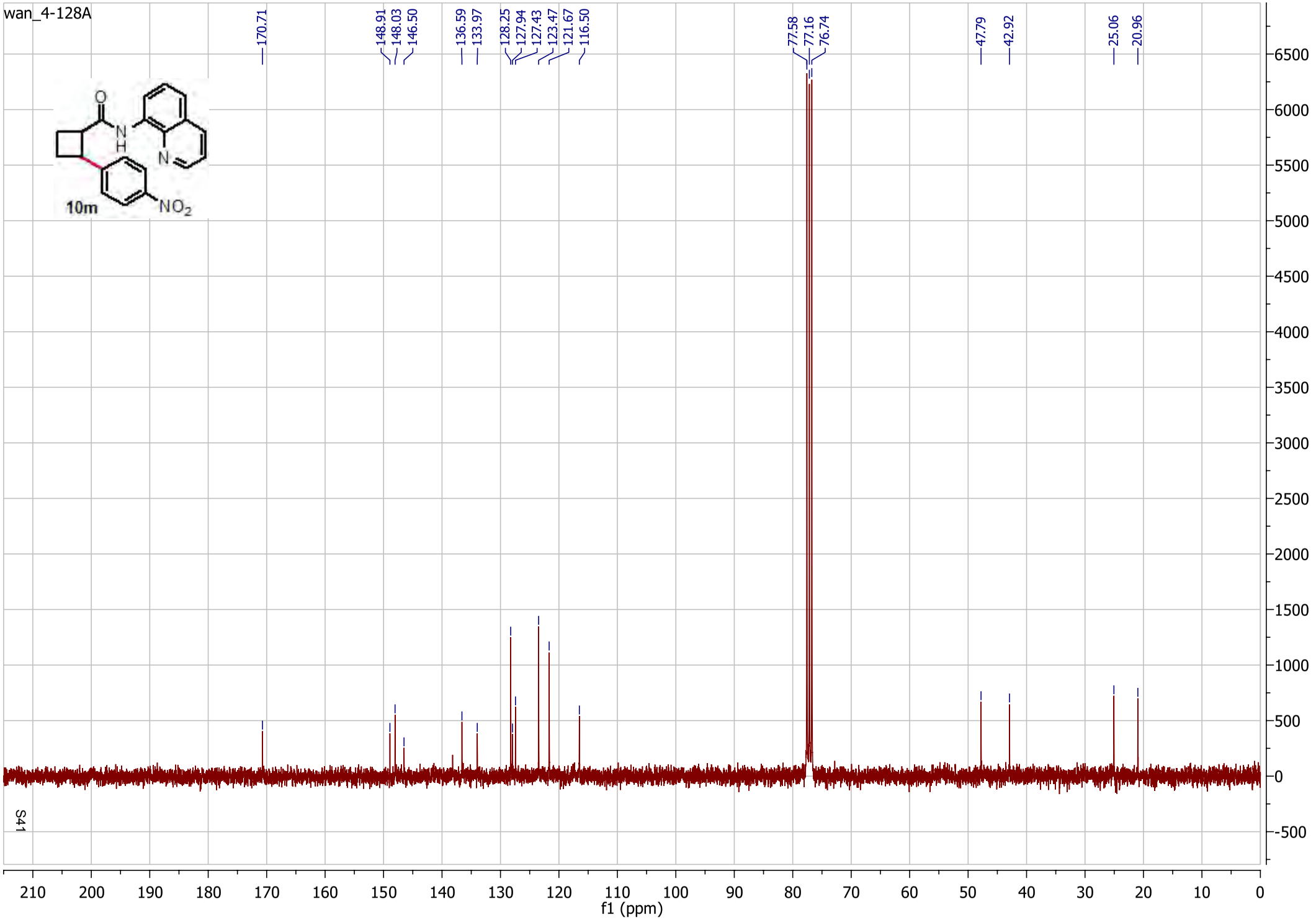

wan_4-129
9.35
8.66
8.65
8.45
8.44
8.09
8.07
7.90
7.87
7.43
7.40
7.26
3.60
3.58
3.55
3.41
3.38
3.37
2.37
2.34
2.27
2.25
2.22
2.18
2.16
1.87
1.84
O
N
H
N
NO2
7m
1H NMR (300 MHz, CDCl3) δ 9.35 (s, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 4.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.51 – 7.30 (m, 5H), 3.59 (dd, J = 16.2, 8.2 Hz, 1H), 3.46 – 3.25 (m, 1H), 2.49 – 2.29 (m, 2H), 2.28 – 2.21 (m, 1H), 2.21 – 2.01 (m, 3H), 1.86 (dd, J = 16.8, 6.7 Hz, 1H).
A (s) 9.35
B (d) 8.65
C (d) 8.45
D (d) 8.08
E (d) 7.88
F (m) 7.43
G (dd) 3.59
H (m) 3.39
I (dd) 1.86
J (m) 2.37
K (m) 2.25
L (m) 2.16
S36
1.00
1.03
1.05
1.05
2.07
5.19
1.07
1.09
1.57
1.13
2.75
1.35
f1 (ppm)


wan_4-129
172.19
149.56
147.99
146.46
138.16
136.44
133.96
128.90
127.85
127.31
123.35
121.63
116.33
77.58
77.16
76.74
53.05
50.06
31.03
28.95
24.74
O
N
H
N
7m
NO2
S37
f1 (ppm)


wan_4-13A
9.39
8.65
8.64
8.64
8.45
8.44
8.42
8.14
8.02
7.73
7.71
7.61
7.58
7.37
7.35
7.33
7.20
7.18
7.15
4.17
4.14
3.80
2.76
2.73
2.63
2.62
2.61
2.60
2.58
2.45
2.42
2.41
2.40
2.39
2.36
2.34
O
N
H
N
9m
NO2
1H NMR (300 MHz, CDCl3) δ 9.39 (s, 1H), 8.65 (d, J = 2.7 Hz, 1H), 8.52 – 8.33 (m, 1H), 8.14 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.47 – 7.29 (m, 3H), 7.18 (t, J = 7.9 Hz, 1H), 4.15 (dd, J = 17.1, 8.2 Hz, 1H), 3.79 (d, J = 6.5 Hz, 1H), 2.86 – 2.67 (m, 1H), 2.67 – 2.53 (m, 1H), 2.52 – 2.25 (m, 2H).
A (s) 9.39
B (d) 8.65
C (m) 8.44
D (s) 8.14
E (d) 8.03
F (d) 7.72
G (d) 7.59
H (m) 7.35
I (t) 7.18
J (dd) 4.15
K (d) 3.79
L (m) 2.40
M (m) 2.61
N (m) 2.74
1.00
1.04
1.02
1.04
1.02
1.02
1.05
3.12
1.06
1.10
1.06
1.10
1.06
2.20
S38
f1 (ppm)

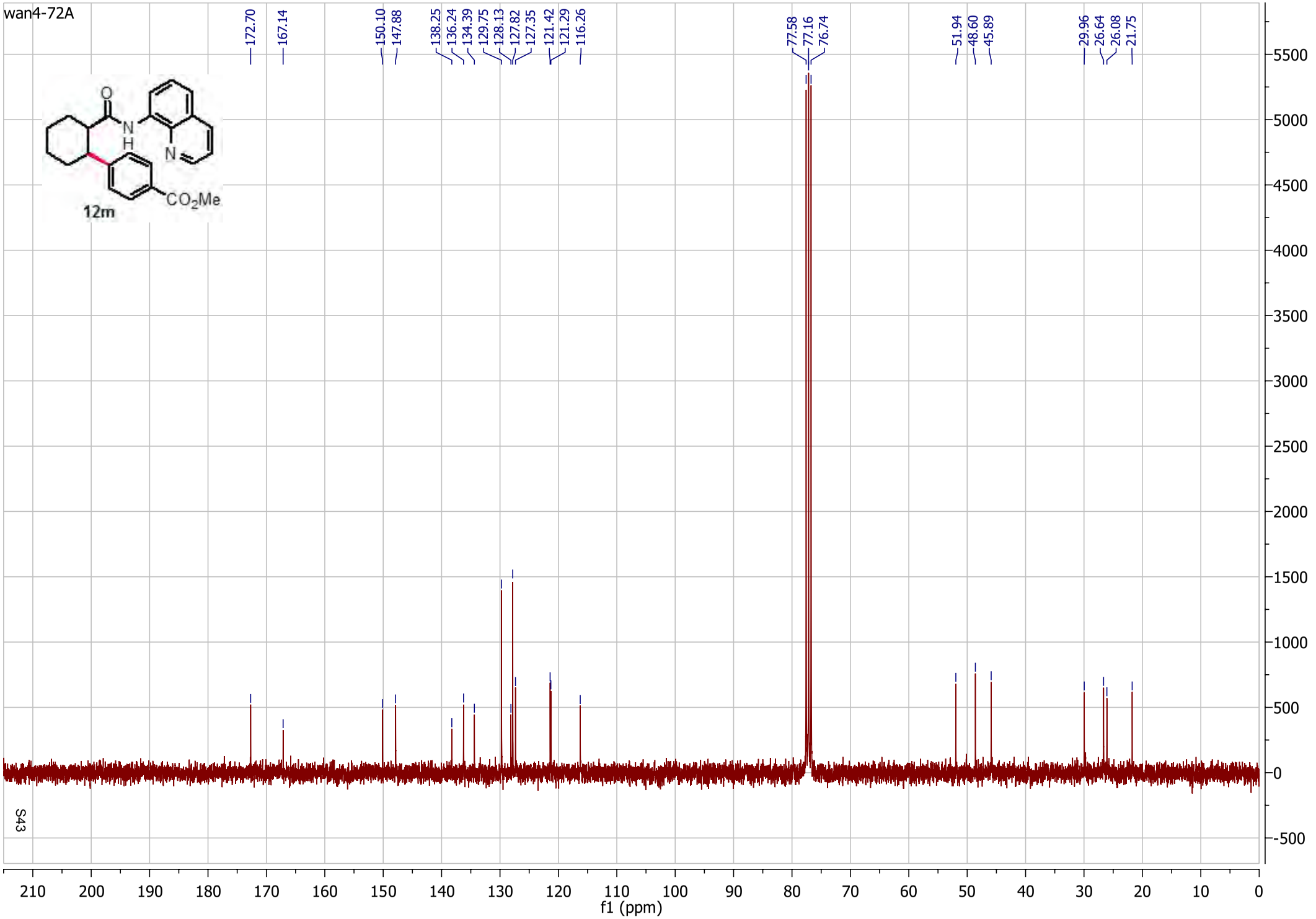

wan_4-13A
170.61
148.04
147.93
142.94
138.06
136.24
133.91
133.39
128.97
127.72
127.16
122.57
121.58
121.44
121.37
116.13
77.58
77.16
76.74
47.60
42.60
24.75
20.57
O
N
H
N
9m
NO2
S39
f1 (ppm)


wan_4-128A
9.46
8.71
8.47
8.12
8.09
7.95
7.93
7.41
7.26
4.19
4.16
3.84
2.78
2.75
2.63
2.44
10m
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.58 – 8.37 (m, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.53 – 7.30 (m, 5H), 4.17 (dd, J = 16.6, 8.1 Hz, 1H), 3.84 (s, 1H), 2.89 – 2.69 (m, 1H), 2.69 – 2.54 (m, 1H), 2.54 – 2.28 (m, 2H).
A (s) 9.46
B (m) 8.71
C (m) 8.47
D (d) 8.10
E (d) 7.94
F (m) 7.43
G (dd) 4.17
H (m) 3.84
I (m) 2.78
J (m) 2.61
K (m) 2.42
1.00
1.05
1.06
1.08
2.10
5.30
1.24
1.21
1.16
1.11
2.25
S40
f1 (ppm)


wan_4-128A
170.71
148.91
148.03
146.50
136.59
133.97
128.25
127.94
127.43
123.47
121.67
116.50
77.58
77.16
76.74
47.79
42.92
25.06
20.96
O
N
H
N
10m
NO2
S41
f1 (ppm)

wan4-72A

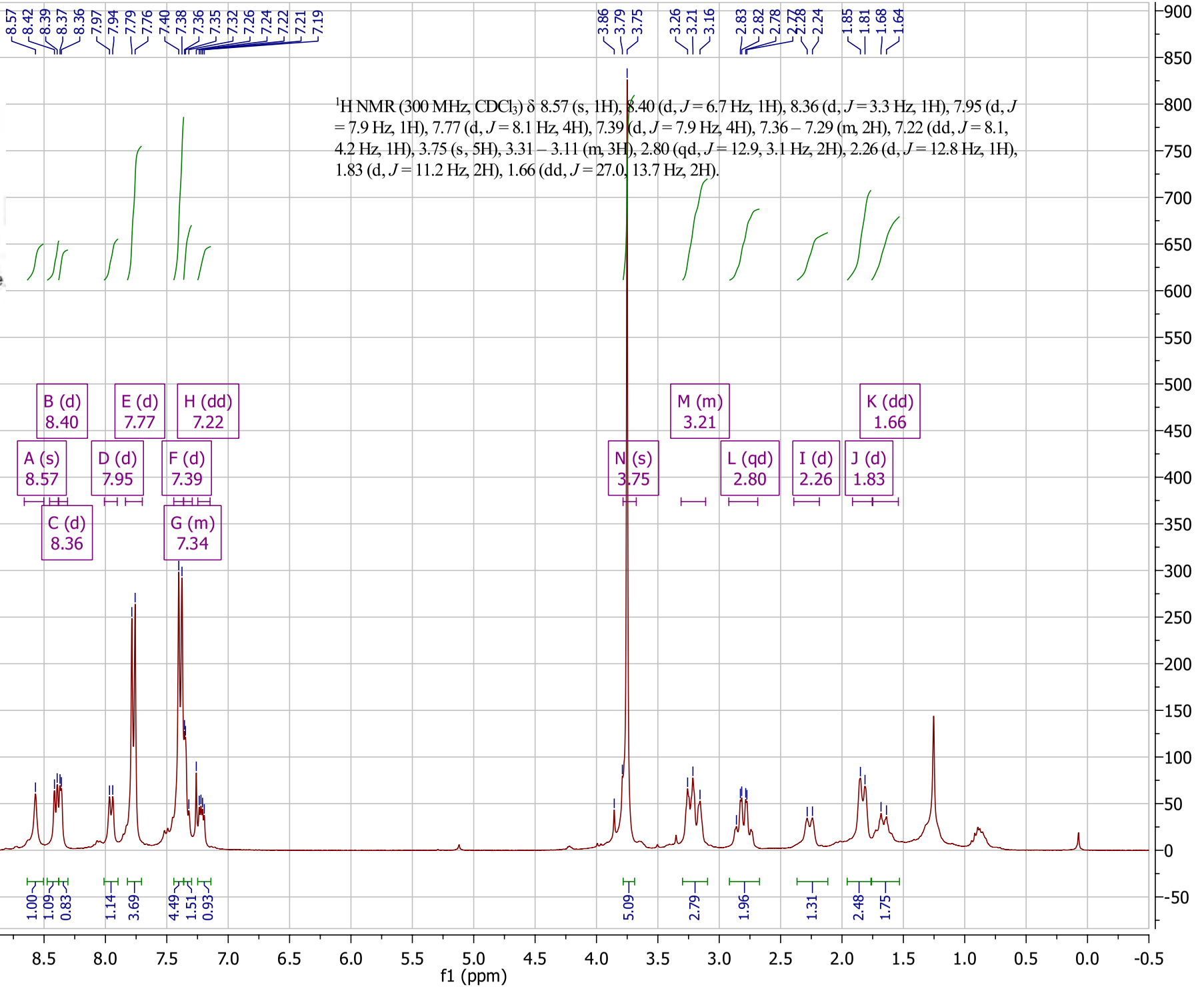
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.62 (d, *J* = 7.2 Hz, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 3H), 7.34 (dd, *J* = 8.3, 4.3 Hz, 1H), 3.78 (s, 3H), 3.10 (s, 2H), 2.56 (dd, *J* = 23.2, 11.3 Hz, 1H), 2.26 (d, *J* = 12.4 Hz, 1H), 2.12 (d, *J* = 12.8 Hz, 1H), 2.02 (d, *J* = 14.8 Hz, 1H), 1.95 – 1.75 (m, 2H), 1.65 (d, *J* = 12.9 Hz, 2H), 1.48 (dd, *J* = 24.5, 12.4 Hz, 1H).

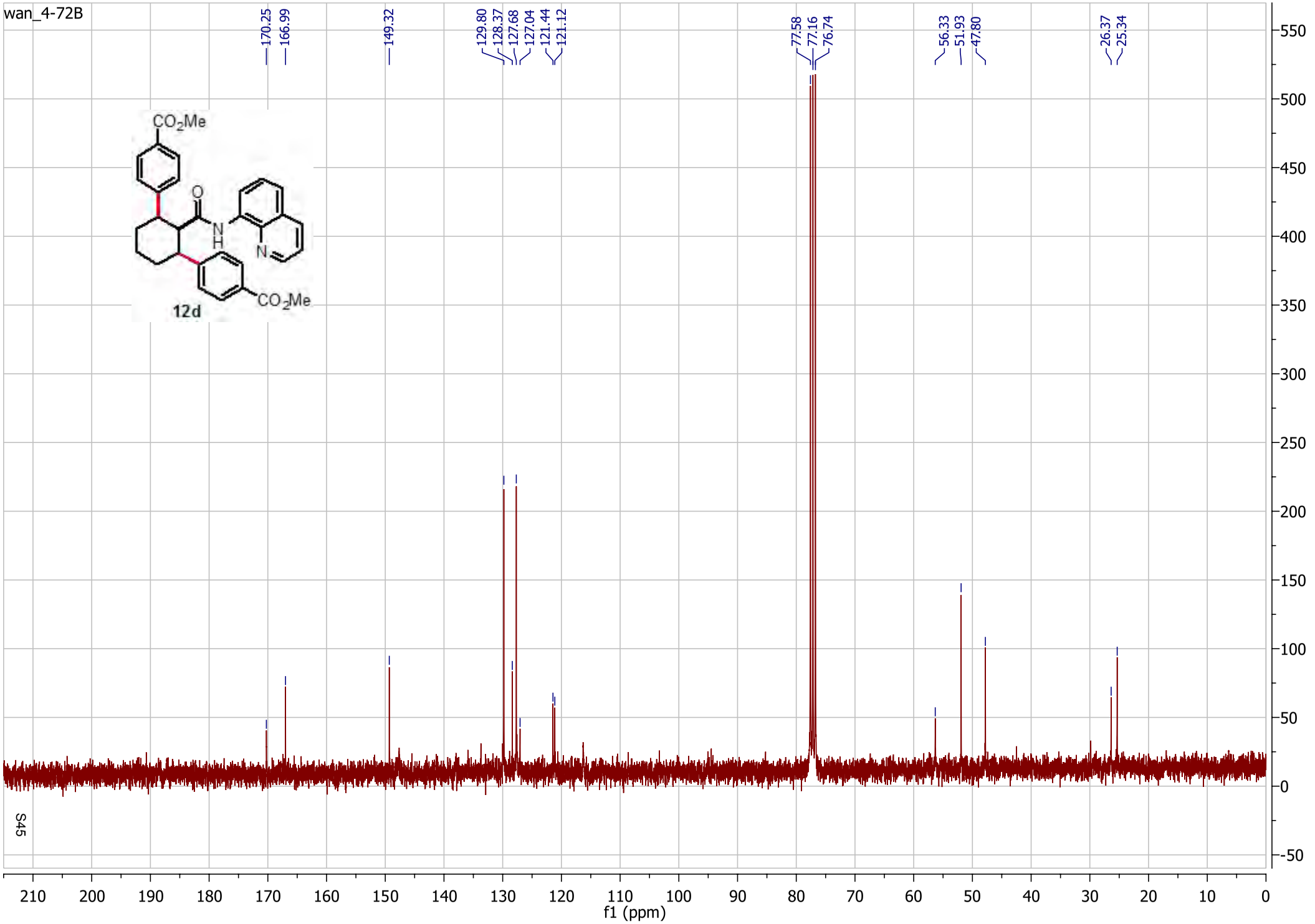

wan4-72A
172.70
167.14
150.10
147.88
138.25
136.24
134.39
129.75
128.13
127.82
127.35
121.42
121.29
116.26
77.58
77.16
76.74
51.94
48.60
45.89
29.96
26.64
26.08
21.75
O
N
H
N
CO2Me
12m
S43
f1 (ppm)

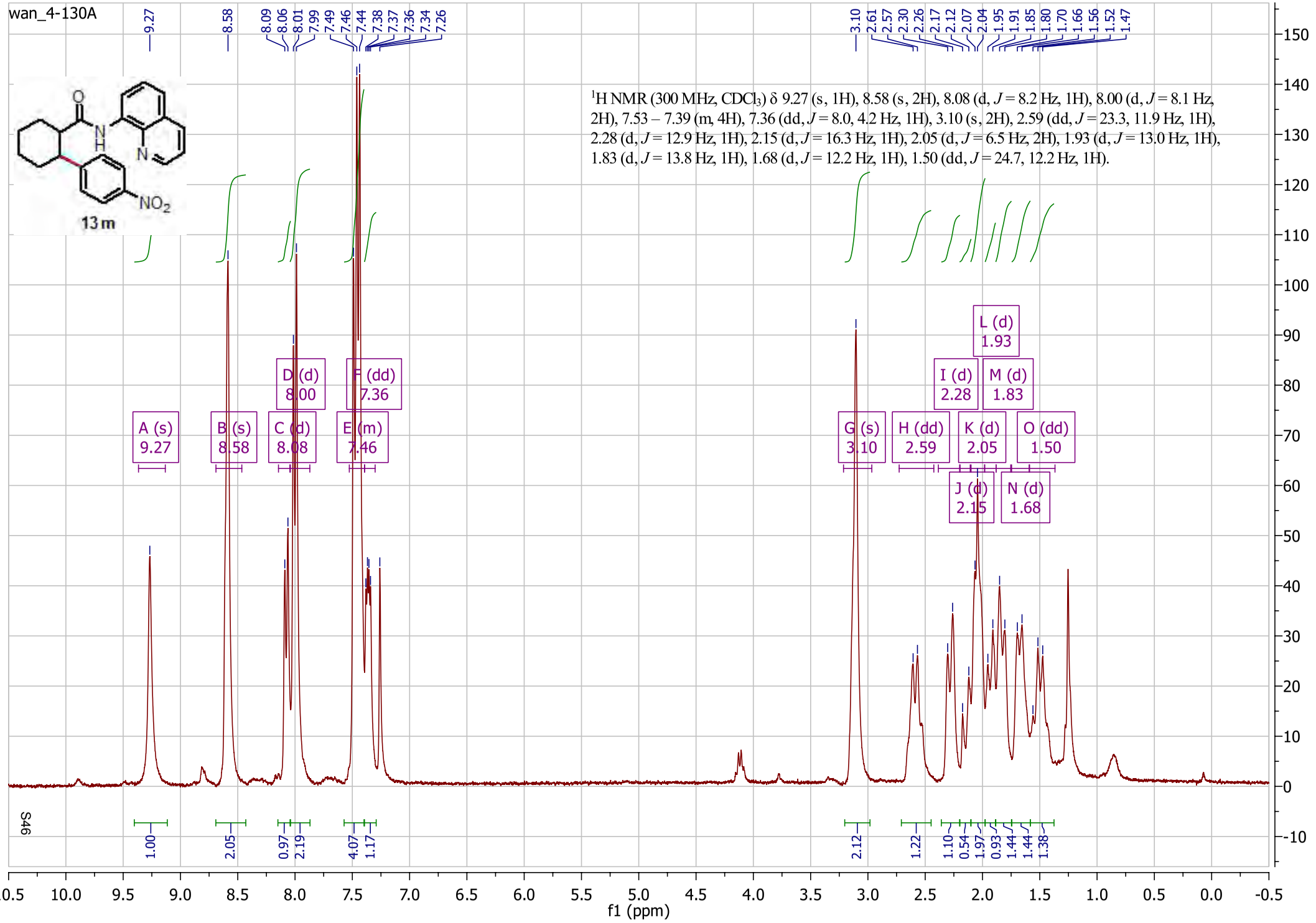
wan_4-72B

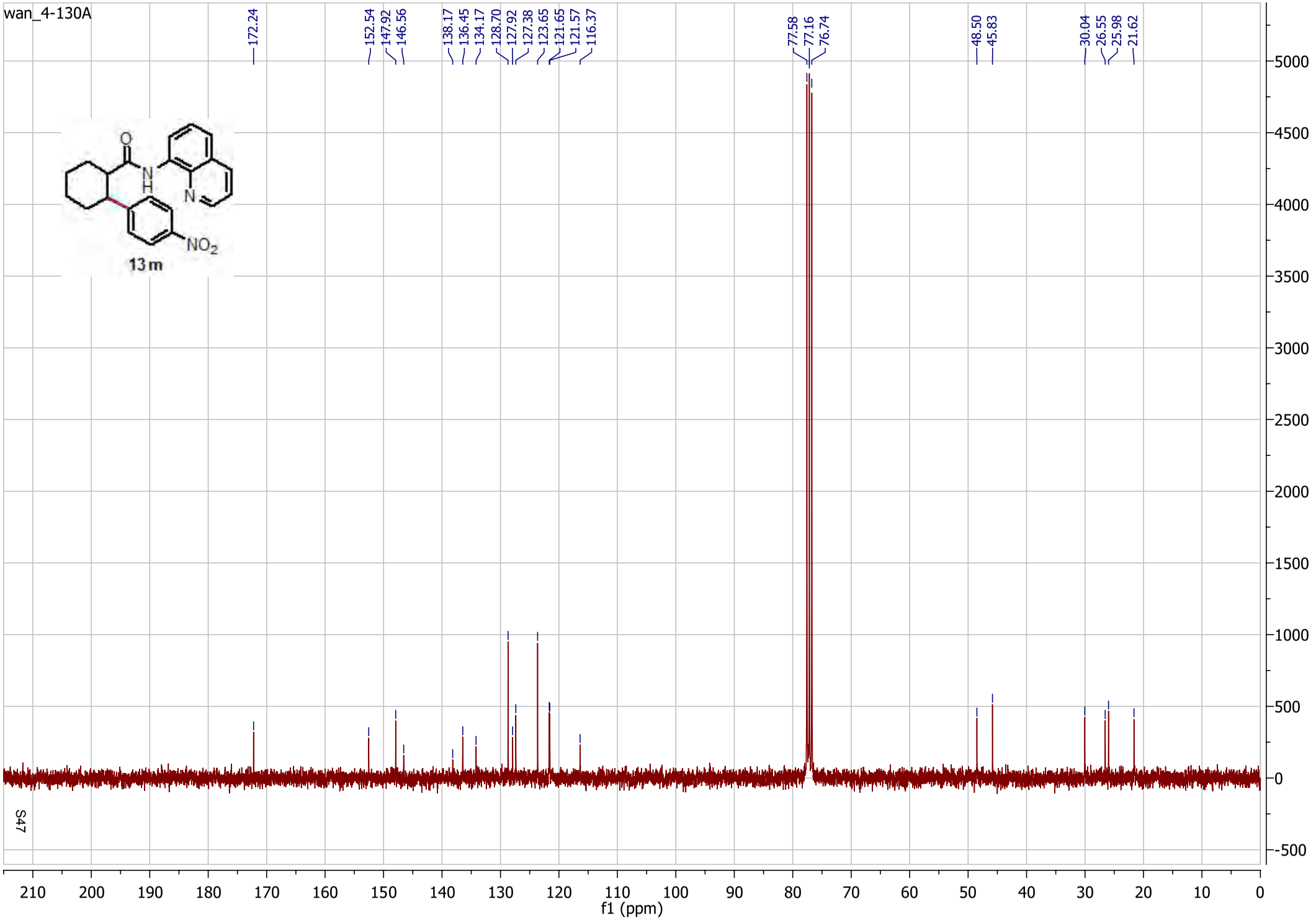
12d

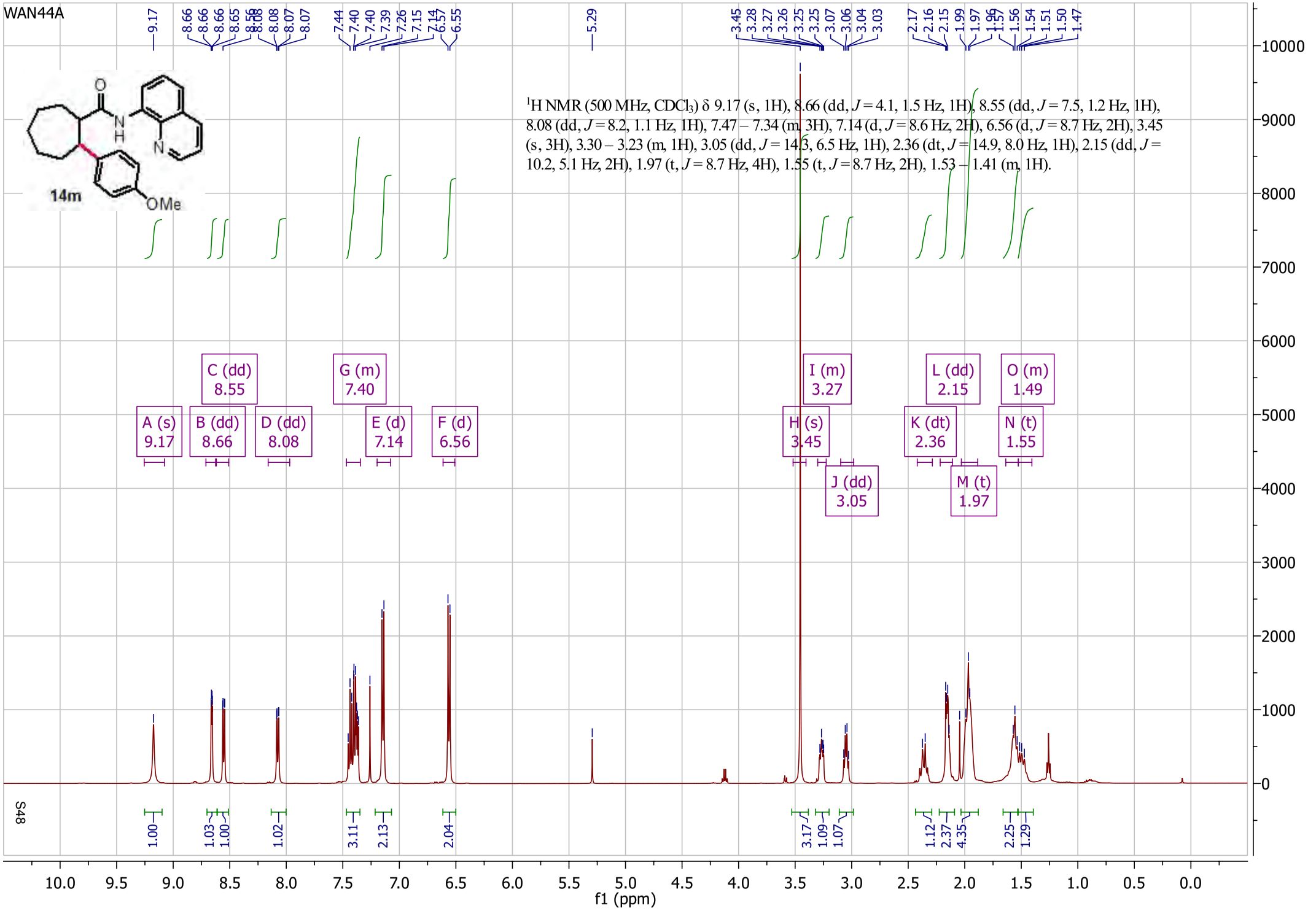
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.40 (d, J = 6.7 Hz, 1H), 8.36 (d, J = 3.3 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.1 Hz, 4H), 7.39 (d, J = 7.9 Hz, 4H), 7.36 – 7.29 (m, 2H), 7.22 (dd, J = 8.1, 4.2 Hz, 1H), 3.75 (s, 5H), 3.31 – 3.11 (m, 3H), 2.80 (qd, J = 12.9, 3.1 Hz, 2H), 2.26 (d, J = 12.8 Hz, 1H), 1.83 (d, J = 11.2 Hz, 2H), 1.66 (dd, J = 27.0, 13.7 Hz, 2H).

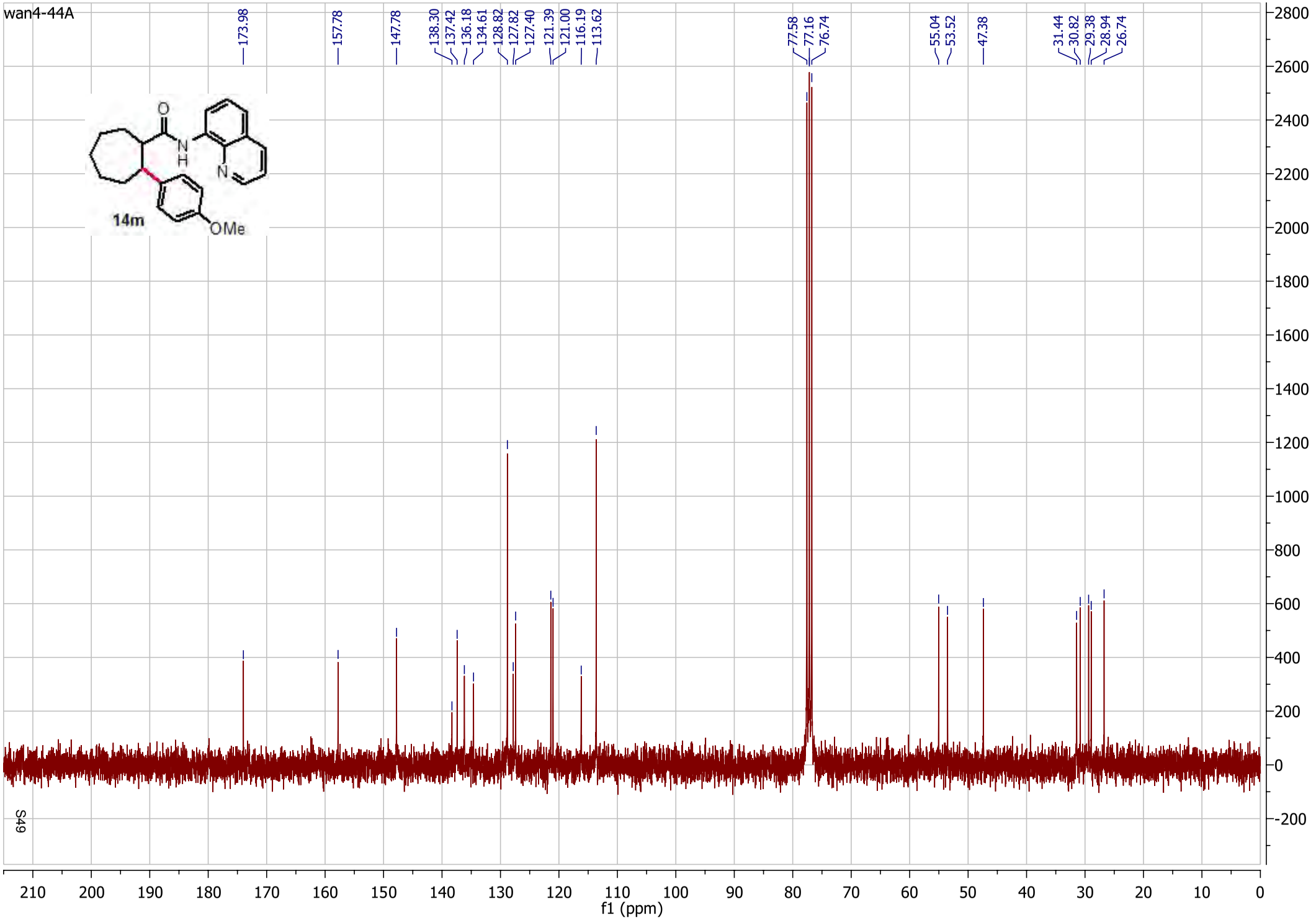


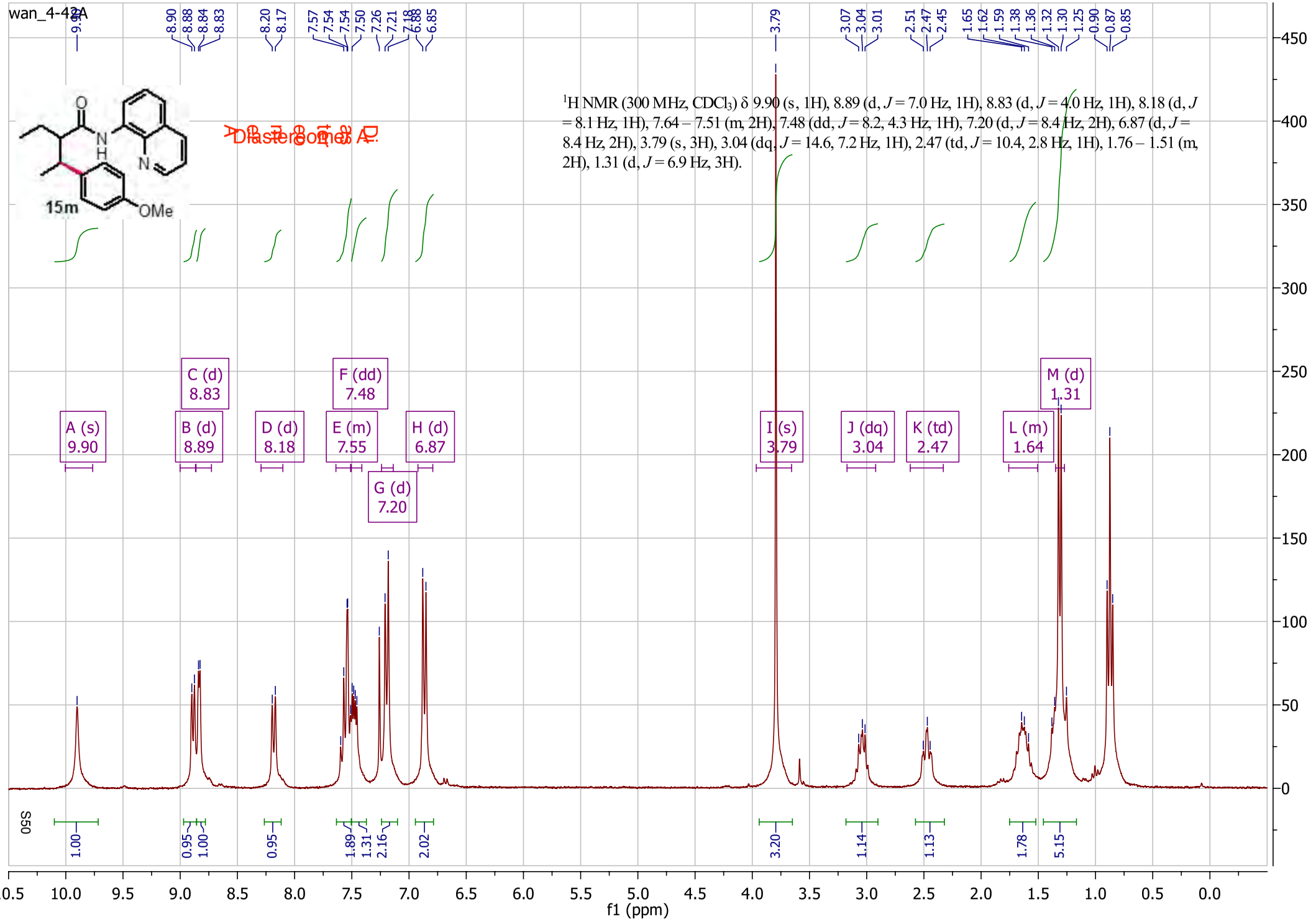

wan_4-72B
170.25
166.99
149.32
129.80
128.37
127.68
127.04
121.44
121.12
77.58
77.16
76.74
56.33
51.93
47.80
26.37
25.34
CO2Me
O
N
H
N
CO2Me
12d
S45
f1 (ppm)

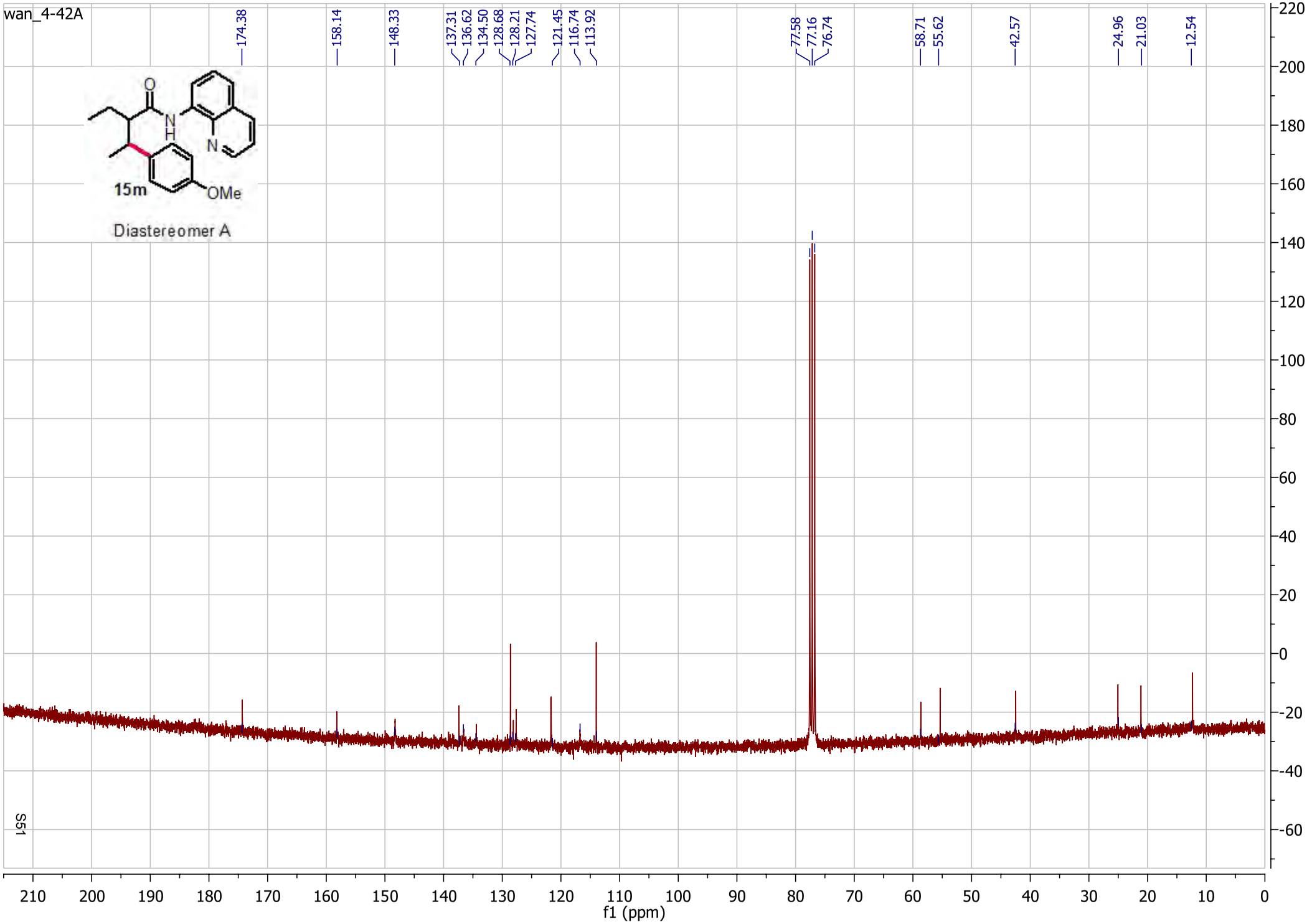

wan_4-130A
9.27
8.58
8.09
8.06
8.01
7.99
7.49
7.46
7.44
7.38
7.37
7.36
7.34
7.26
3.10
2.61
2.57
2.30
2.26
2.17
2.12
2.07
2.04
1.95
1.91
1.85
1.80
1.70
1.66
1.56
1.52
1.47
O
N
H
N
NO2
13m
1H NMR (300 MHz, CDCl3) δ 9.27 (s, 1H), 8.58 (s, 2H), 8.08 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.53 – 7.39 (m, 4H), 7.36 (dd, J = 8.0, 4.2 Hz, 1H), 3.10 (s, 2H), 2.59 (dd, J = 23.3, 11.9 Hz, 1H), 2.28 (d, J = 12.9 Hz, 1H), 2.15 (d, J = 16.3 Hz, 1H), 2.05 (d, J = 6.5 Hz, 2H), 1.93 (d, J = 13.0 Hz, 1H), 1.83 (d, J = 13.8 Hz, 1H), 1.68 (d, J = 12.2 Hz, 1H), 1.50 (dd, J = 24.7, 12.2 Hz, 1H).
A (s) 9.27
B (s) 8.58
C (d) 8.08
D (d) 8.00
E (m) 7.46
F (dd) 7.36
G (s) 3.10
H (dd) 2.59
I (d) 2.28
J (d) 2.15
K (d) 2.05
L (d) 1.93
M (d) 1.83
N (d) 1.68
O (dd) 1.50
S46
1.00
2.05
0.97
2.19
4.07
1.17
2.12
1.22
1.10
0.54
1.97
0.93
1.44
1.44
1.38
f1 (ppm)

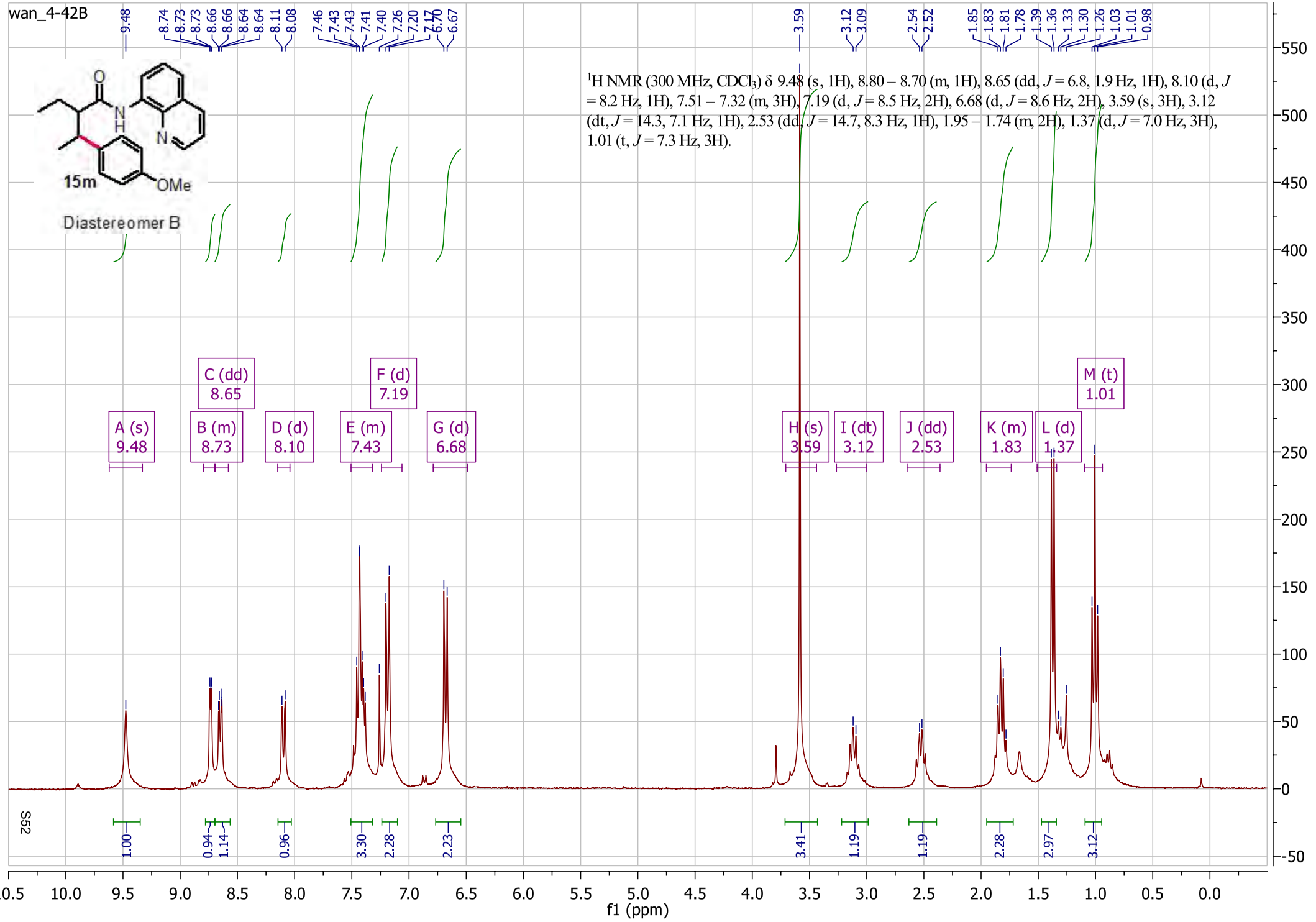

wan_4-130A
172.24
152.54
147.92
146.56
138.17
136.45
134.17
128.70
127.92
127.38
123.65
121.65
121.57
116.37
77.58
77.16
76.74
48.50
45.83
30.04
26.55
25.98
21.62
O
N
H
N
NO2
13m
S47
f1 (ppm)

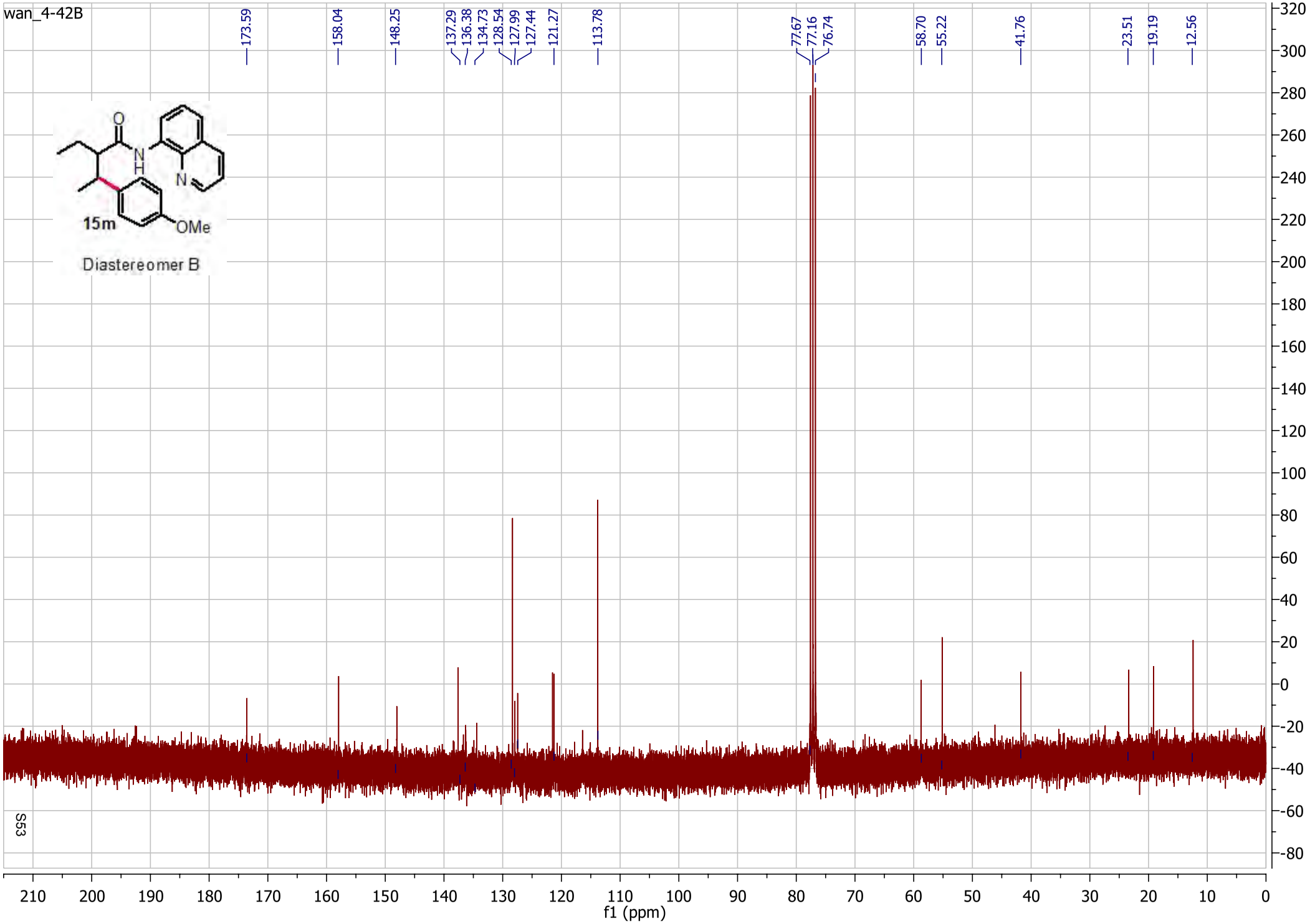

WAN44A
14m
OMe
[1]H NMR (500 MHz, CDCl3) δ 9.17 (s, 1H), 8.66 (dd, J = 4.1, 1.5 Hz, 1H), 8.55 (dd, J = 7.5, 1.2 Hz, 1H), 8.08 (dd, J = 8.2, 1.1 Hz, 1H), 7.47 – 7.34 (m, 3H), 7.14 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 8.7 Hz, 2H), 3.45 (s, 3H), 3.30 – 3.23 (m, 1H), 3.05 (dd, J = 14.3, 6.5 Hz, 1H), 2.36 (dt, J = 14.9, 8.0 Hz, 1H), 2.15 (dd, J = 10.2, 5.1 Hz, 2H), 1.97 (t, J = 8.7 Hz, 4H), 1.55 (t, J = 8.7 Hz, 2H), 1.53 – 1.41 (m, 1H).
A (s) 9.17
B (dd) 8.66
C (dd) 8.55
D (dd) 8.08
E (d) 7.14
F (d) 6.56
G (m) 7.40
H (s) 3.45
I (m) 3.27
J (dd) 3.05
K (dt) 2.36
L (dd) 2.15
M (t) 1.97
N (t) 1.55
O (m) 1.49
S48
f1 (ppm)

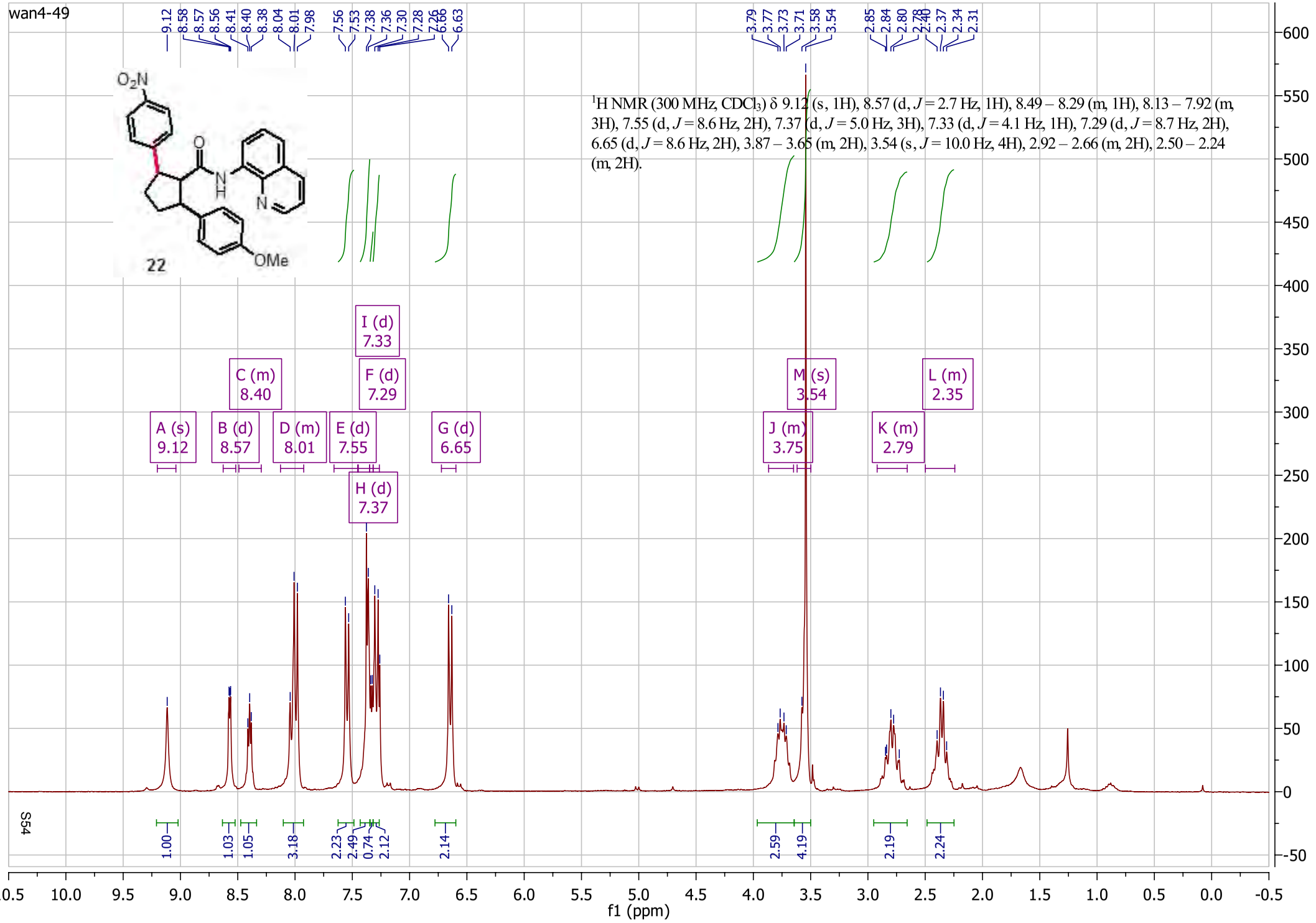

wan4-44A
173.98
157.78
147.78
138.30
137.42
136.18
134.61
128.82
127.82
127.40
121.39
121.00
116.19
113.62
77.58
77.16
76.74
55.04
53.52
47.38
31.44
30.82
29.38
28.94
26.74
O
N
H
N
14m
OMe
S49
f1 (ppm)

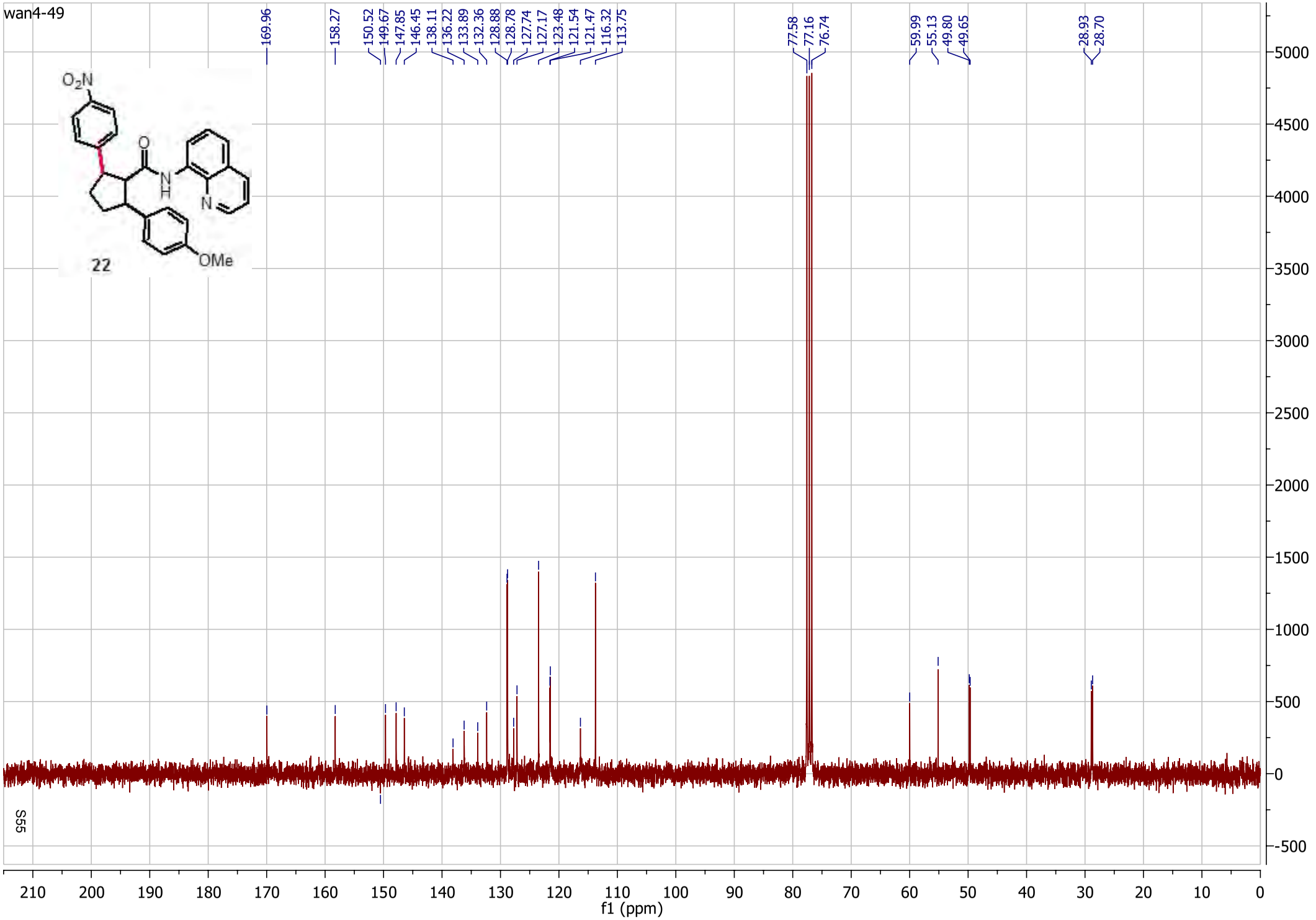

wan_4-42A
9.90
8.90
8.88
8.84
8.83
8.20
8.17
7.57
7.54
7.54
7.50
7.26
7.21
7.18
6.88
6.85
3.79
3.07
3.04
3.01
2.51
2.47
2.45
1.65
1.62
1.59
1.38
1.36
1.32
1.30
1.25
0.90
0.87
0.85
15m
OMe
N
H
O
N
Diastereomer A
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.89 (d, J = 7.0 Hz, 1H), 8.83 (d, J = 4.0 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.48 (dd, J = 8.2, 4.3 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 3.04 (dq, J = 14.6, 7.2 Hz, 1H), 2.47 (td, J = 10.4, 2.8 Hz, 1H), 1.76 – 1.51 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H).
A (s) 9.90
B (d) 8.89
C (d) 8.83
D (d) 8.18
E (m) 7.55
F (dd) 7.48
G (d) 7.20
H (d) 6.87
I (s) 3.79
J (dq) 3.04
K (td) 2.47
L (m) 1.64
M (d) 1.31
1.00
0.95
1.00
0.95
1.89
1.31
2.16
2.02
3.20
1.14
1.13
1.78
5.15
f1 (ppm)

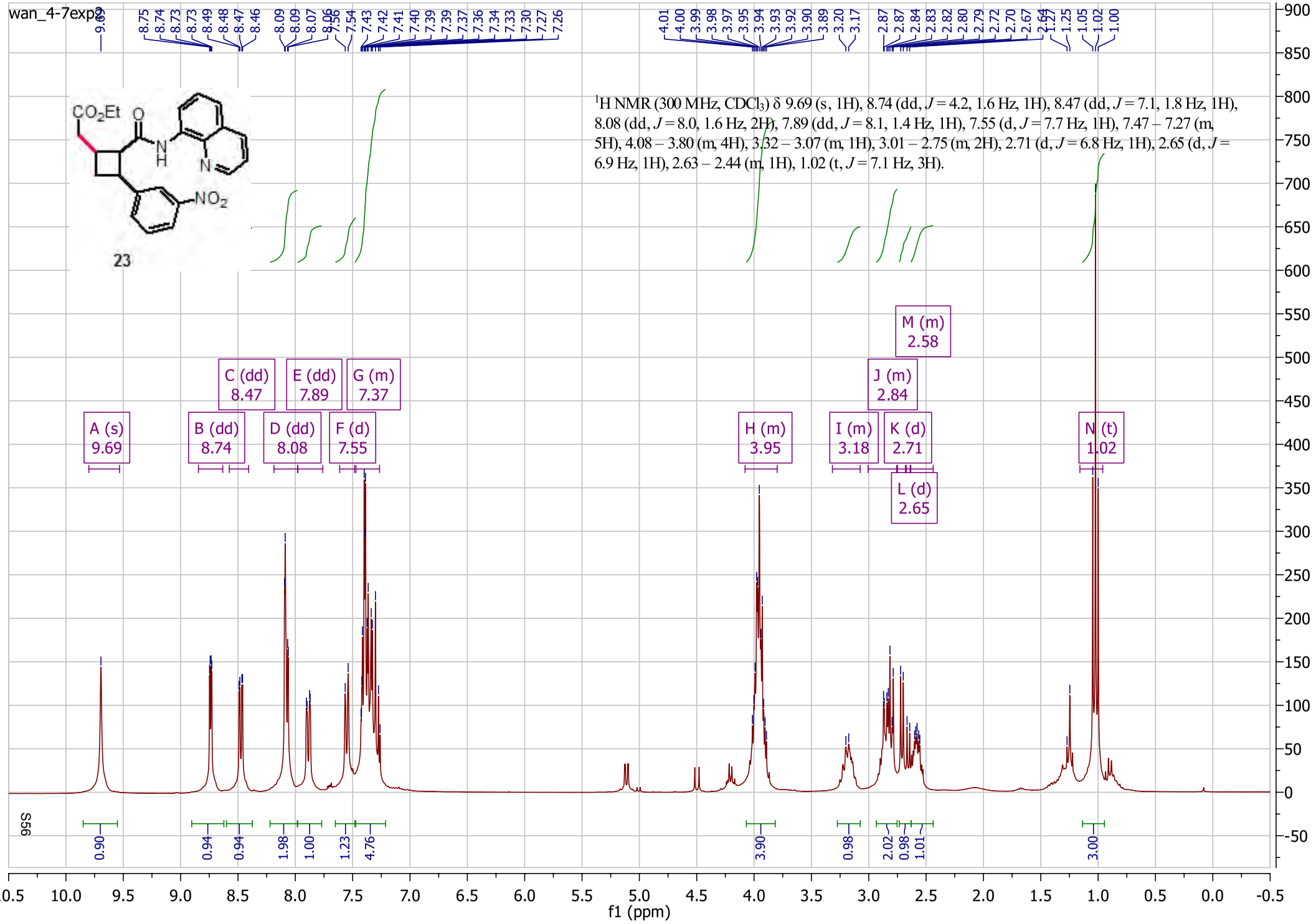

wan_4-42A
174.38
158.14
148.33
137.31
136.62
134.50
128.68
128.21
127.74
121.45
116.74
113.92
77.58
77.16
76.74
58.71
55.62
42.57
24.96
21.03
12.54
O
N
H
N
15m
OMe
Diastereomer A
S51
f1 (ppm)

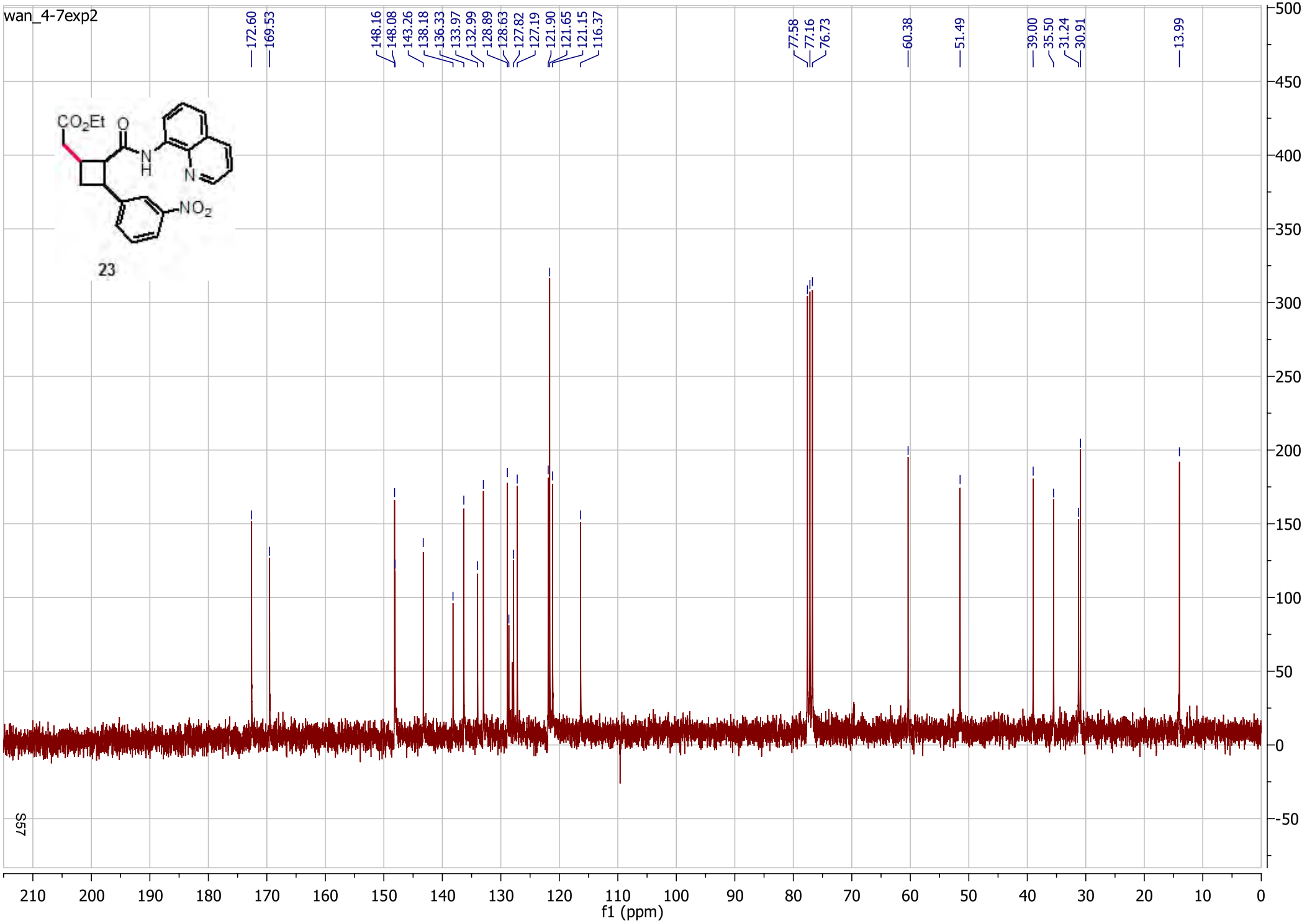

wan_4-42B
15m
OMe
Diastereomer B
[1]H NMR (300 MHz, CDCl3) δ 9.48 (s, 1H), 8.80 – 8.70 (m, 1H), 8.65 (dd, J = 6.8, 1.9 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.51 – 7.32 (m, 3H), 7.19 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 3.59 (s, 3H), 3.12 (dt, J = 14.3, 7.1 Hz, 1H), 2.53 (dd, J = 14.7, 8.3 Hz, 1H), 1.95 – 1.74 (m, 2H), 1.37 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H).
A (s) 9.48
B (m) 8.73
C (dd) 8.65
D (d) 8.10
E (m) 7.43
F (d) 7.19
G (d) 6.68
H (s) 3.59
I (dt) 3.12
J (dd) 2.53
K (m) 1.83
L (d) 1.37
M (t) 1.01
S52
f1 (ppm)

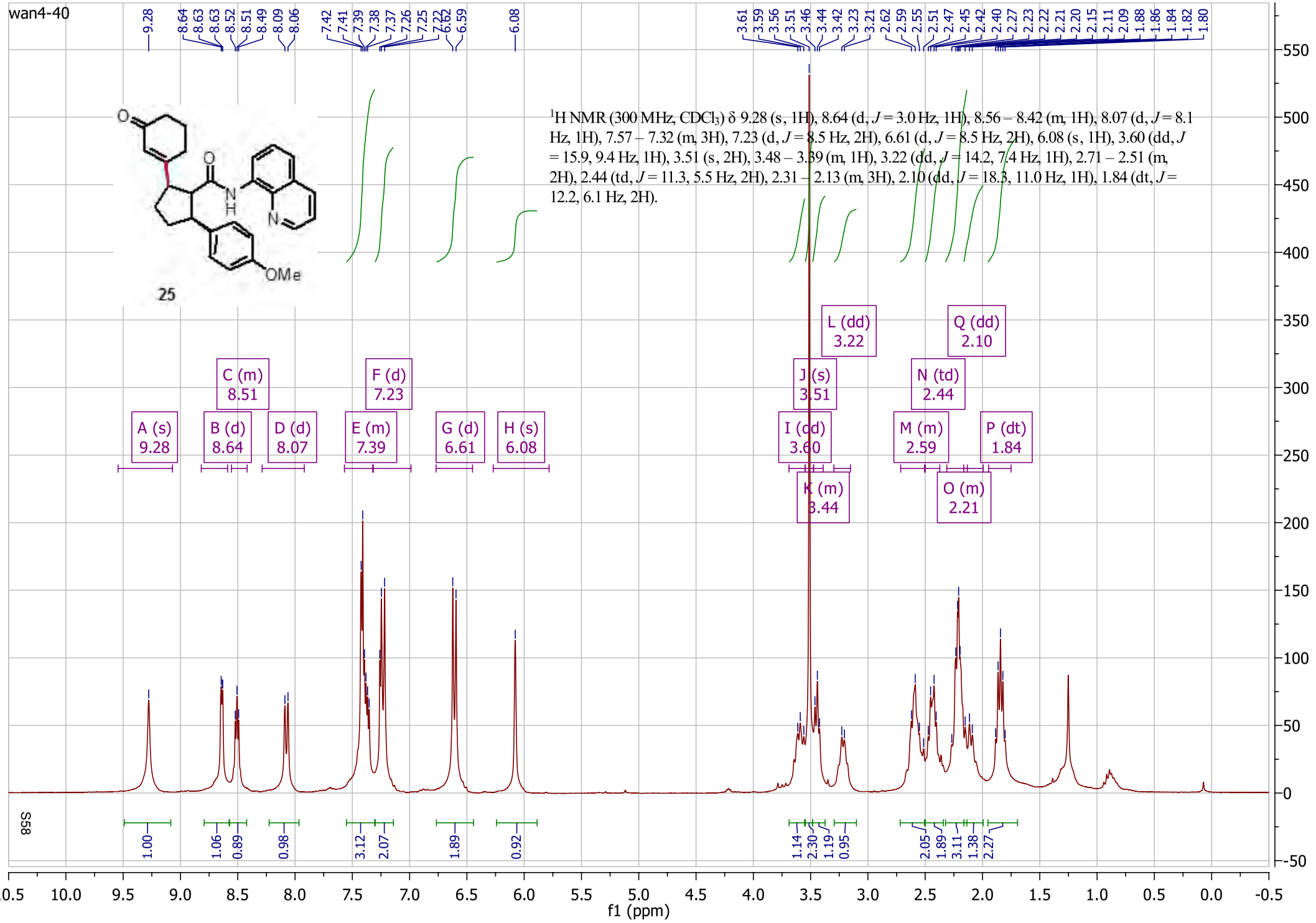

wan_4-42B
173.59
158.04
148.25
137.29
136.38
134.73
128.54
127.99
127.44
121.27
113.78
77.67
77.16
76.74
58.70
55.22
41.76
23.51
19.19
12.56
O
N
H
N
15m
OMe
Diastereomer B
S53
f1 (ppm)

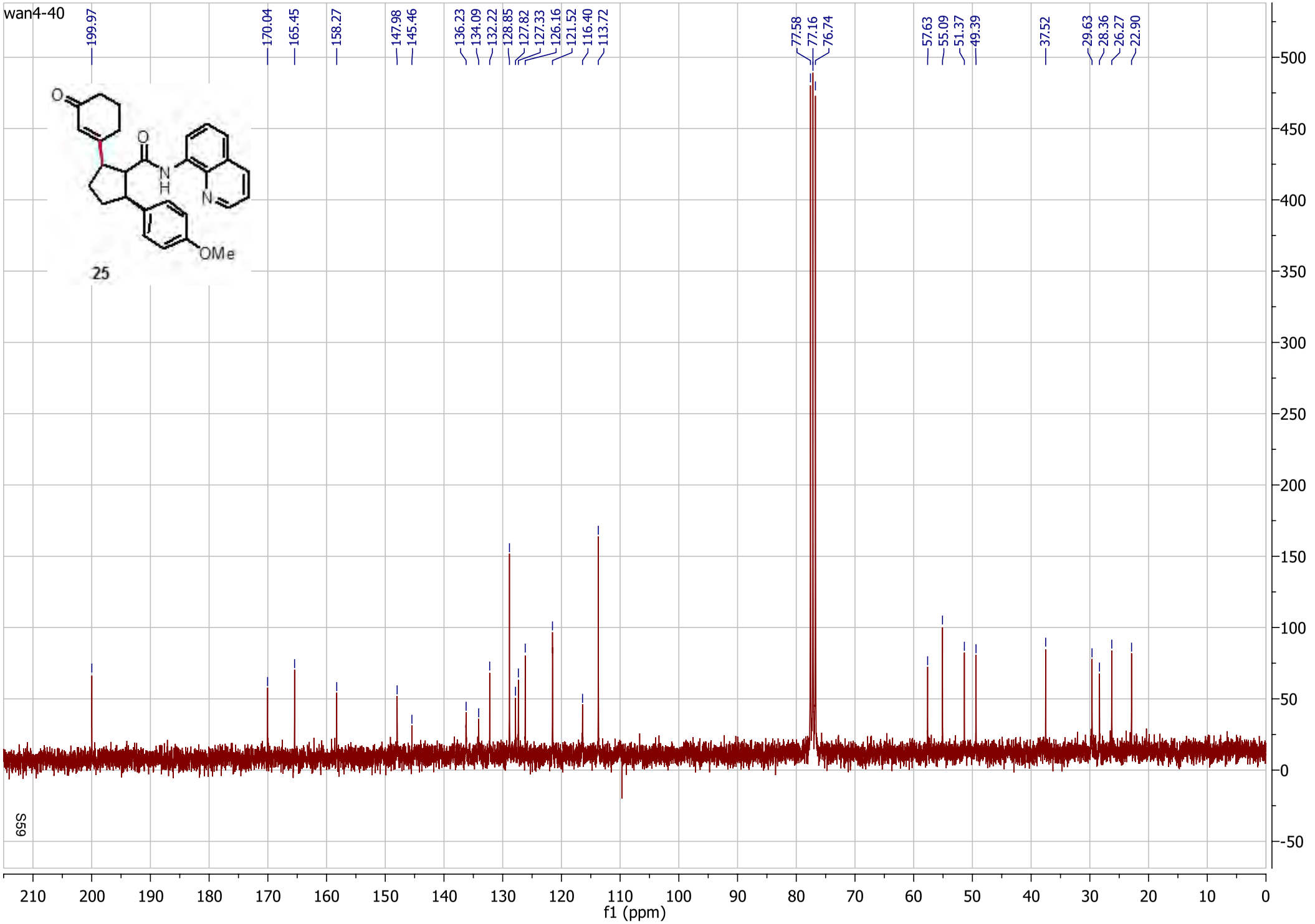

wan4-49
9.12
8.58
8.57
8.56
8.41
8.40
8.38
8.04
8.01
7.98
7.56
7.53
7.38
7.36
7.30
7.28
7.26
6.66
6.63
3.79
3.77
3.73
3.71
3.58
3.54
2.85
2.84
2.80
2.78
2.40
2.37
2.34
2.31
O2N
O
N
H
N
22
OMe
1H NMR (300 MHz, CDCl3) δ 9.12 (s, 1H), 8.57 (d, J = 2.7 Hz, 1H), 8.49 – 8.29 (m, 1H), 8.13 – 7.92 (m, 3H), 7.55 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 5.0 Hz, 3H), 7.33 (d, J = 4.1 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 3.87 – 3.65 (m, 2H), 3.54 (s, J = 10.0 Hz, 4H), 2.92 – 2.66 (m, 2H), 2.50 – 2.24 (m, 2H).
I (d) 7.33
C (m) 8.40
F (d) 7.29
M (s) 3.54
L (m) 2.35
A (s) 9.12
B (d) 8.57
D (m) 8.01
E (d) 7.55
G (d) 6.65
J (m) 3.75
K (m) 2.79
H (d) 7.37
S54
1.00
1.03
1.05
3.18
2.23
2.49
0.74
2.12
2.14
2.59
4.19
2.19
2.24
f1 (ppm)

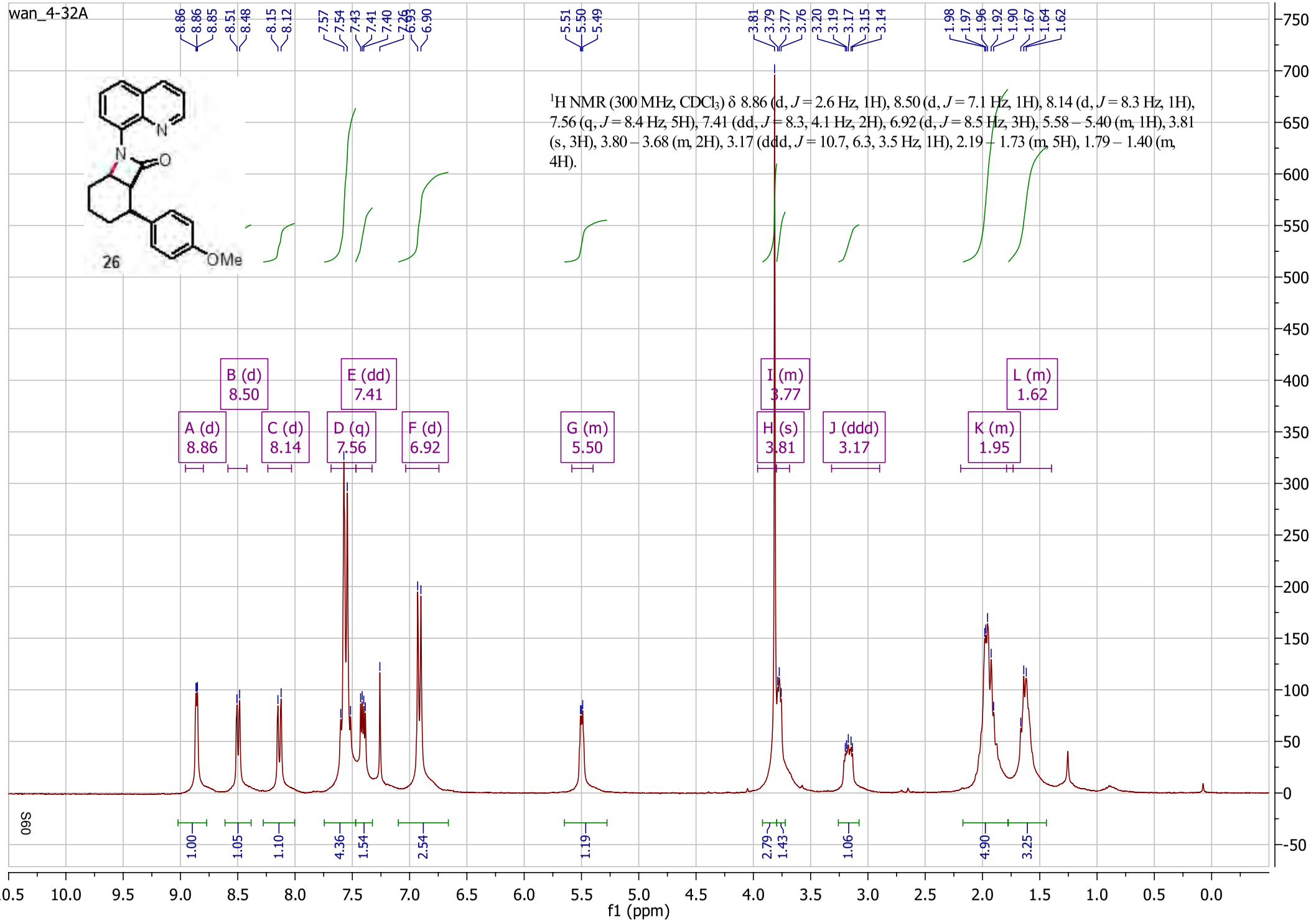

wan4-49
169.96
158.27
150.52
149.67
147.85
146.45
138.11
136.22
133.89
132.36
128.88
128.78
127.74
127.17
123.48
121.54
121.47
116.32
113.75
77.58
77.16
76.74
59.99
55.13
49.80
49.65
28.93
28.70
O2N
O
NH
N
OMe
22
S59
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

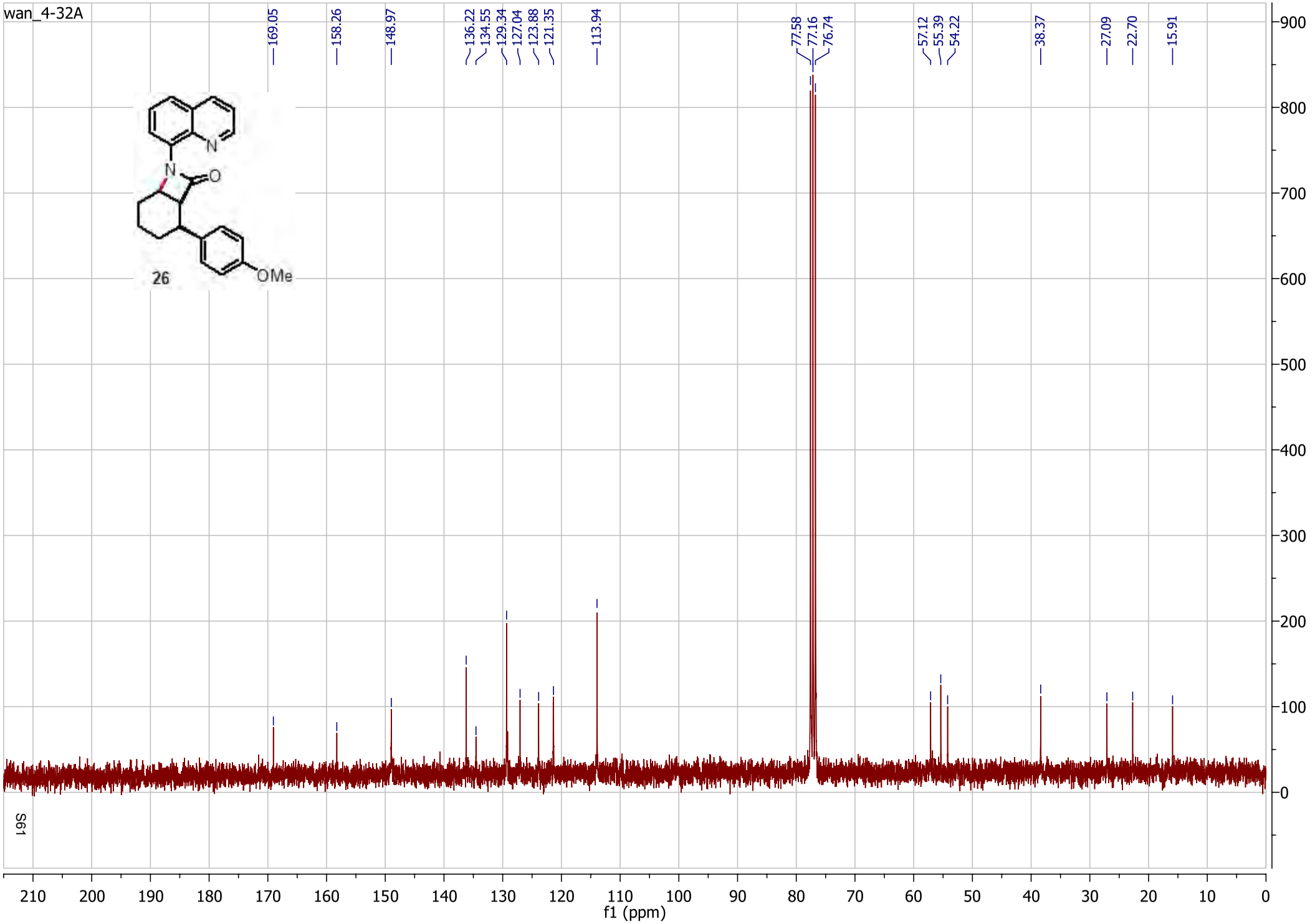

wan_4-7exp2
CO2Et
O
N
H
N
NO2
23
1H NMR (300 MHz, CDCl3) δ 9.69 (s, 1H), 8.74 (dd, J = 4.2, 1.6 Hz, 1H), 8.47 (dd, J = 7.1, 1.8 Hz, 1H), 8.08 (dd, J = 8.0, 1.6 Hz, 2H), 7.89 (dd, J = 8.1, 1.4 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.47 – 7.27 (m, 5H), 4.08 – 3.80 (m, 4H), 3.32 – 3.07 (m, 1H), 3.01 – 2.75 (m, 2H), 2.71 (d, J = 6.8 Hz, 1H), 2.65 (d, J = 6.9 Hz, 1H), 2.63 – 2.44 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H).
A (s) 9.69
B (dd) 8.74
C (dd) 8.47
D (dd) 8.08
E (dd) 7.89
F (d) 7.55
G (m) 7.37
H (m) 3.95
I (m) 3.18
J (m) 2.84
K (d) 2.71
L (d) 2.65
M (m) 2.58
N (t) 1.02
0.90
0.94
0.94
1.98
1.00
1.23
4.76
3.90
0.98
2.02
0.98
1.01
3.00
f1 (ppm)


wan_4-7exp2
172.60
169.53
148.16
148.08
143.26
138.18
136.33
133.97
132.99
128.89
128.63
127.82
127.19
121.90
121.65
121.15
116.37
77.58
77.16
76.73
60.38
51.49
39.00
35.50
31.24
30.91
13.99
CO2Et
O
N
H
N
NO2
23
S57
f1 (ppm)

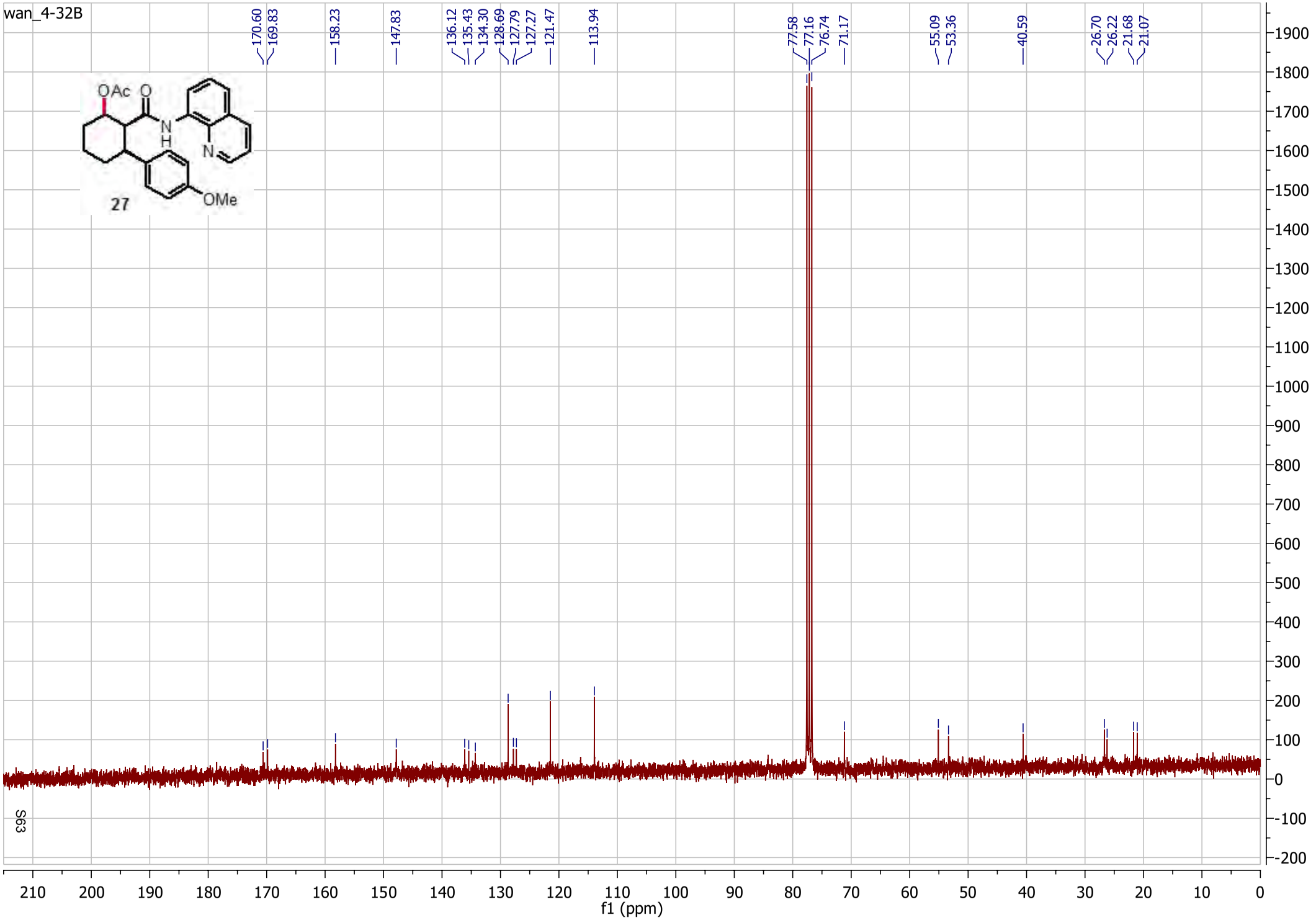

wan4-40
9.28
8.64
8.63
8.63
8.52
8.51
8.49
8.09
8.06
7.42
7.41
7.39
7.38
7.37
7.26
7.25
7.22
6.62
6.59
6.08
3.61
3.59
3.56
3.51
3.46
3.44
3.42
3.23
3.21
2.62
2.59
2.55
2.51
2.47
2.45
2.42
2.40
2.27
2.23
2.22
2.21
2.20
2.15
2.11
2.09
1.88
1.86
1.84
1.82
1.80
O
O
N
H
N
OMe
25
1H NMR (300 MHz, CDCl3) δ 9.28 (s, 1H), 8.64 (d, J = 3.0 Hz, 1H), 8.56 – 8.42 (m, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.57 – 7.32 (m, 3H), 7.23 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 6.08 (s, 1H), 3.60 (dd, J = 15.9, 9.4 Hz, 1H), 3.51 (s, 2H), 3.48 – 3.39 (m, 1H), 3.22 (dd, J = 14.2, 7.4 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.44 (td, J = 11.3, 5.5 Hz, 2H), 2.31 – 2.13 (m, 3H), 2.10 (dd, J = 18.3, 11.0 Hz, 1H), 1.84 (dt, J = 12.2, 6.1 Hz, 2H).
A (s) 9.28
B (d) 8.64
C (m) 8.51
D (d) 8.07
E (m) 7.39
F (d) 7.23
G (d) 6.61
H (s) 6.08
I (dd) 3.60
J (s) 3.51
K (m) 3.44
L (dd) 3.22
M (m) 2.59
N (td) 2.44
O (m) 2.21
P (dt) 1.84
Q (dd) 2.10
S58
1.00
1.06
0.89
0.98
3.12
2.07
1.89
0.92
1.14
2.30
1.19
0.95
2.05
1.89
3.11
1.38
2.27
f1 (ppm)

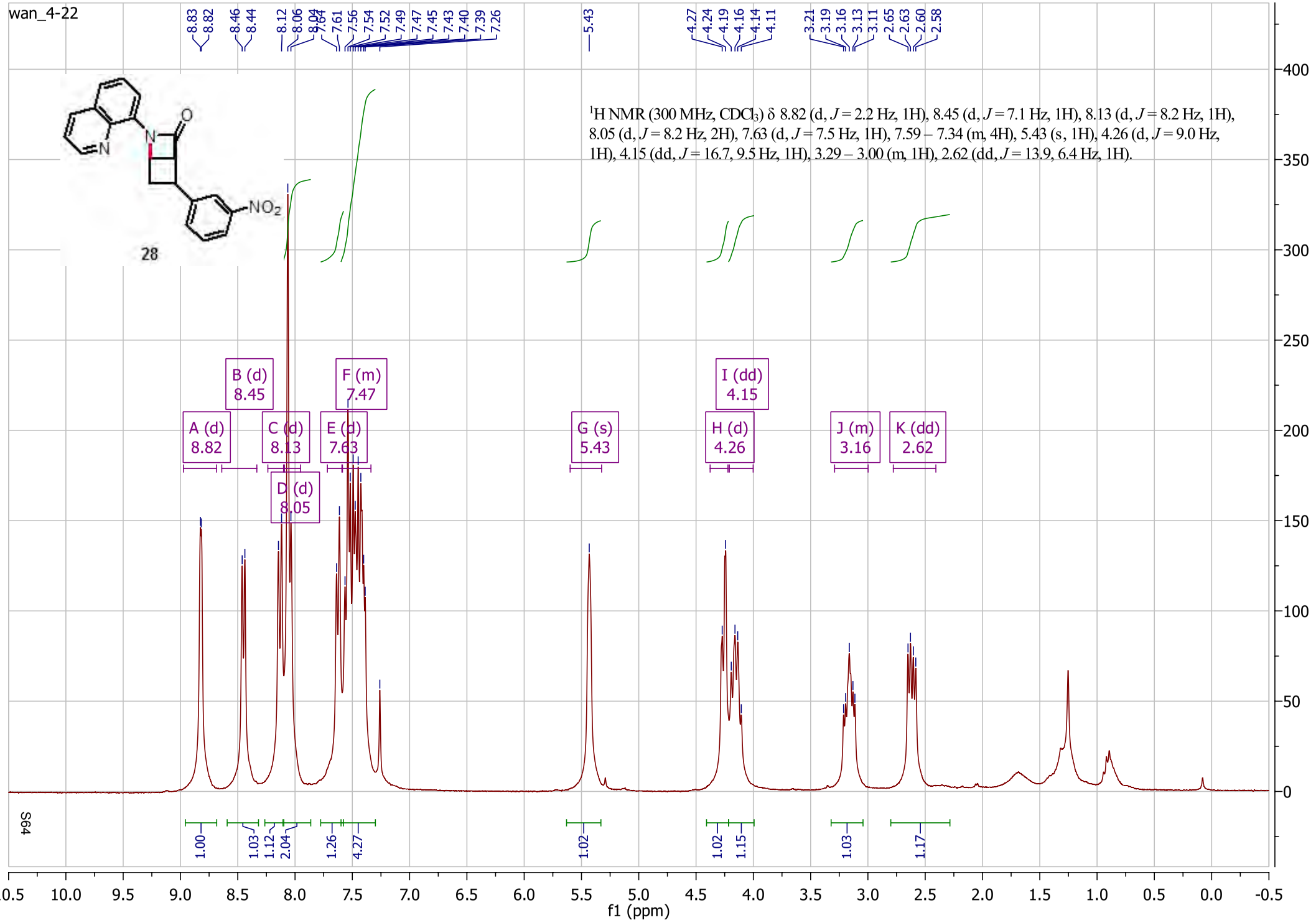

wan4-40
199.97
170.04
165.45
158.27
147.98
145.46
136.23
134.09
132.22
128.85
127.82
127.33
126.16
121.52
116.40
113.72
77.58
77.16
76.74
57.63
55.09
51.37
49.39
37.52
29.63
28.36
26.27
22.90
O
O
N
H
N
OMe
25
S59
f1 (ppm)

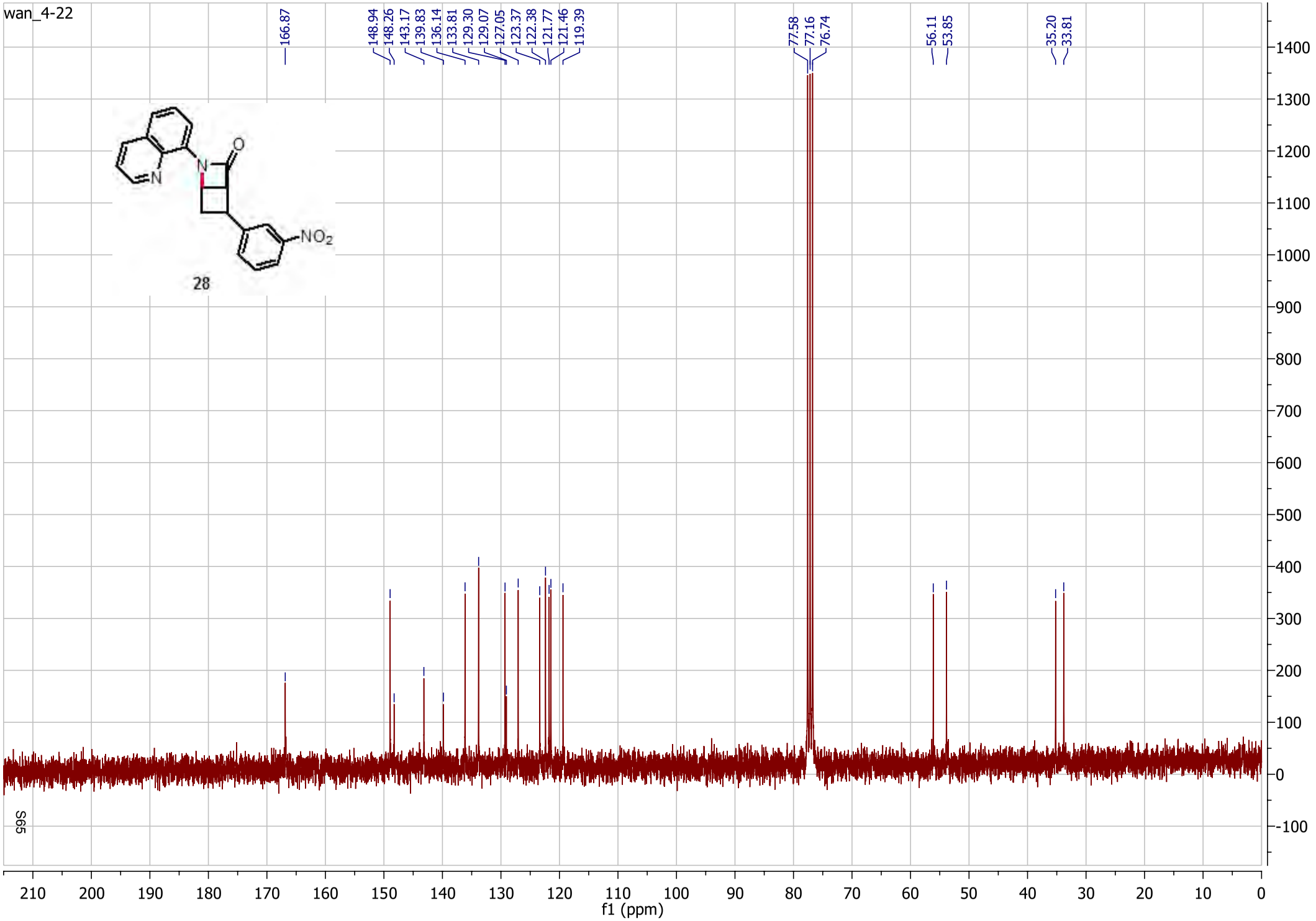

wan_4-32A
8.86 8.86 8.85 8.51 8.48 8.15 8.12 7.57 7.54 7.43 7.41 7.40 7.26 6.93 6.90
5.51 5.50 5.49
3.81 3.79 3.77 3.76 3.20 3.19 3.17 3.15 3.14
1.98 1.97 1.96 1.92 1.90 1.67 1.64 1.62
N
N
O
26
OMe
1H NMR (300 MHz, CDCl3) δ 8.86 (d, J = 2.6 Hz, 1H), 8.50 (d, J = 7.1 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.56 (q, J = 8.4 Hz, 5H), 7.41 (dd, J = 8.3, 4.1 Hz, 2H), 6.92 (d, J = 8.5 Hz, 3H), 5.58 – 5.40 (m, 1H), 3.81 (s, 3H), 3.80 – 3.68 (m, 2H), 3.17 (ddd, J = 10.7, 6.3, 3.5 Hz, 1H), 2.19 – 1.73 (m, 5H), 1.79 – 1.40 (m, 4H).
A (d) 8.86
B (d) 8.50
C (d) 8.14
D (q) 7.56
E (dd) 7.41
F (d) 6.92
G (m) 5.50
H (s) 3.81
I (m) 3.77
J (ddd) 3.17
K (m) 1.95
L (m) 1.62
1.00 1.05 1.10 4.36 1.54 2.54 1.19 2.79 1.43 1.06 4.90 3.25
S60
f1 (ppm)

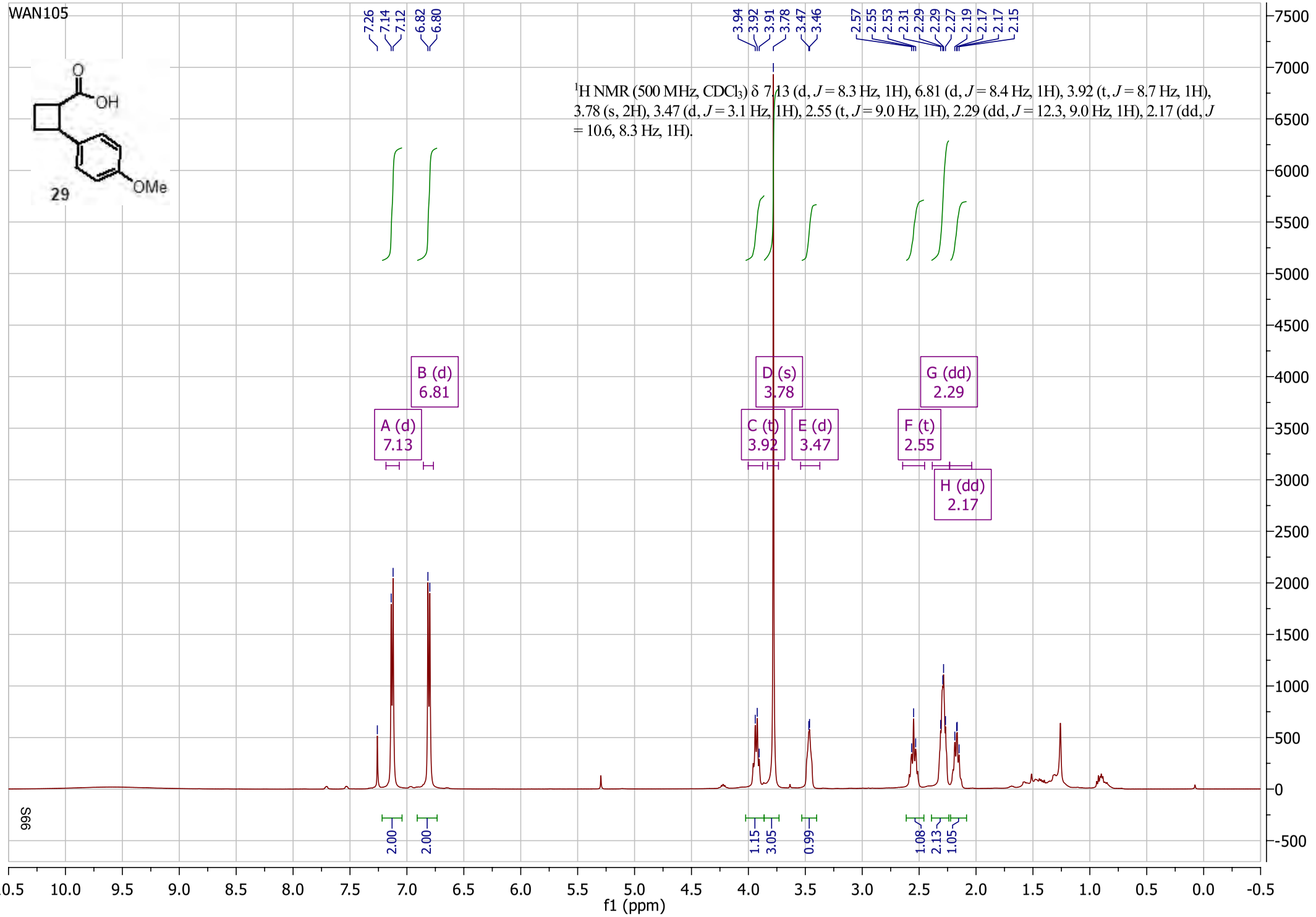

wan_4-32A
169.05
158.26
148.97
136.22
134.55
129.34
127.04
123.88
121.35
113.94
77.58
77.16
76.74
57.12
55.39
54.22
38.37
27.09
22.70
15.91
N
N
O
OMe
26
S61
f1 (ppm)

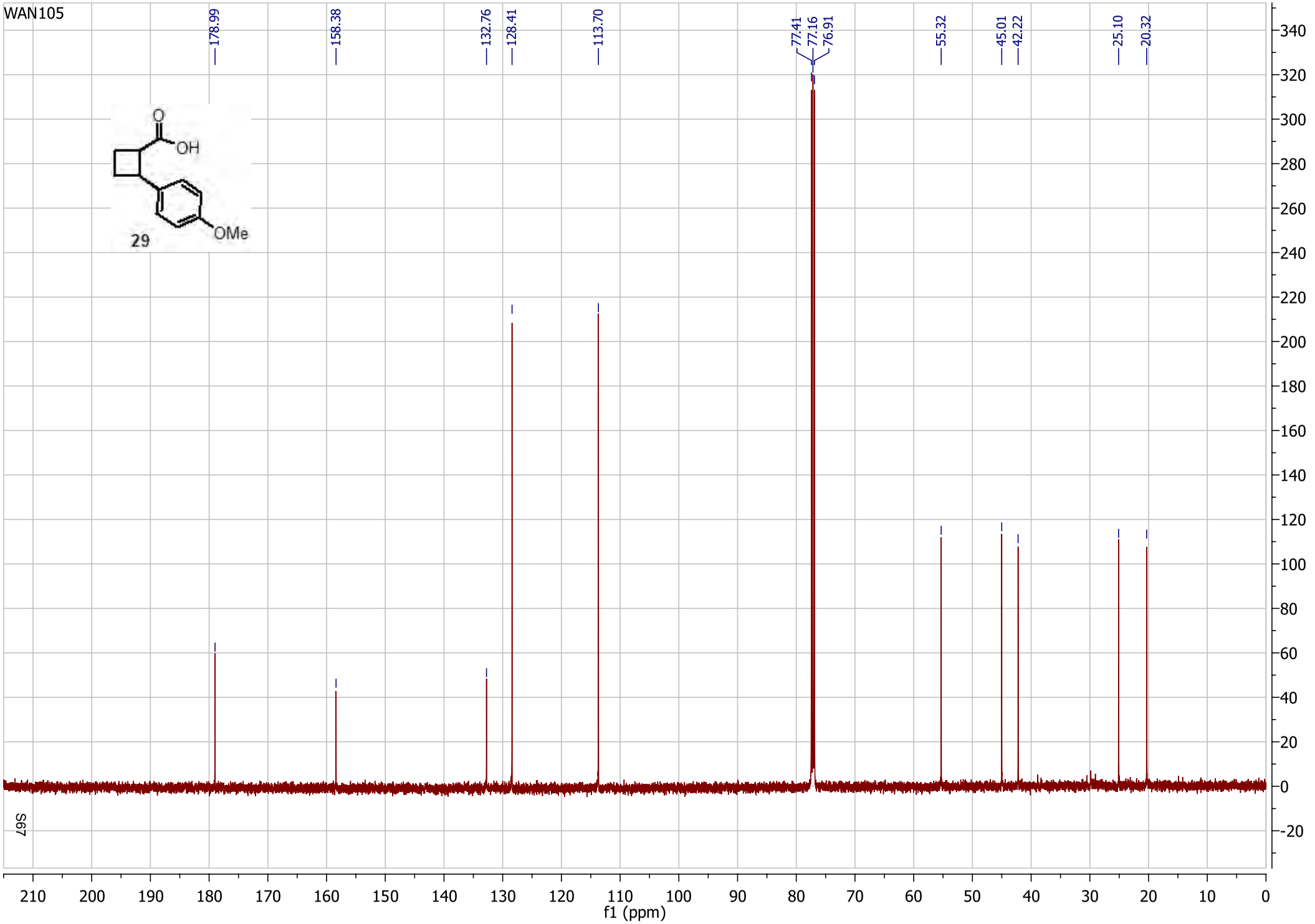

wan_4-32B
9.18
8.61
8.61
8.59
8.08
8.05
7.45
7.43
7.38
7.36
7.35
7.26
7.19
7.16
6.66
6.63
5.41
5.40
3.73
3.52
3.32
3.28
3.13
2.44
2.42
2.40
2.36
2.22
2.18
1.87
1.82
1.77
1.76
OAc
O
N
H
N
OMe
27
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.66 – 8.53 (m, 2H), 8.06 (d, J = 7.1 Hz, 1H), 7.44 (q, J = 8.1 Hz, 2H), 7.35 (dd, J = 8.2, 4.2 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 5.40 (d, J = 2.3 Hz, 1H), 3.52 (s, 3H), 3.41 – 3.22 (m, 1H), 3.13 (s, 1H), 2.55 – 2.26 (m, 2H), 2.18 (s, 3H), 1.81 (dd, J = 23.7, 8.7 Hz, 4H).
A (s) 9.18
B (m) 8.60
D (d) 8.06
F (dd) 7.35
G (d) 7.18
H (q) 7.44
E (d) 6.65
I (d) 5.40
J (s) 3.52
K (m) 3.30
L (s) 3.13
M (m) 2.40
N (s) 2.18
O (dd) 1.81
S62
1.00
1.93
1.00
2.28
1.01
1.95
1.91
0.94
2.65
1.03
0.96
2.30
2.70
4.44
f1 (ppm)

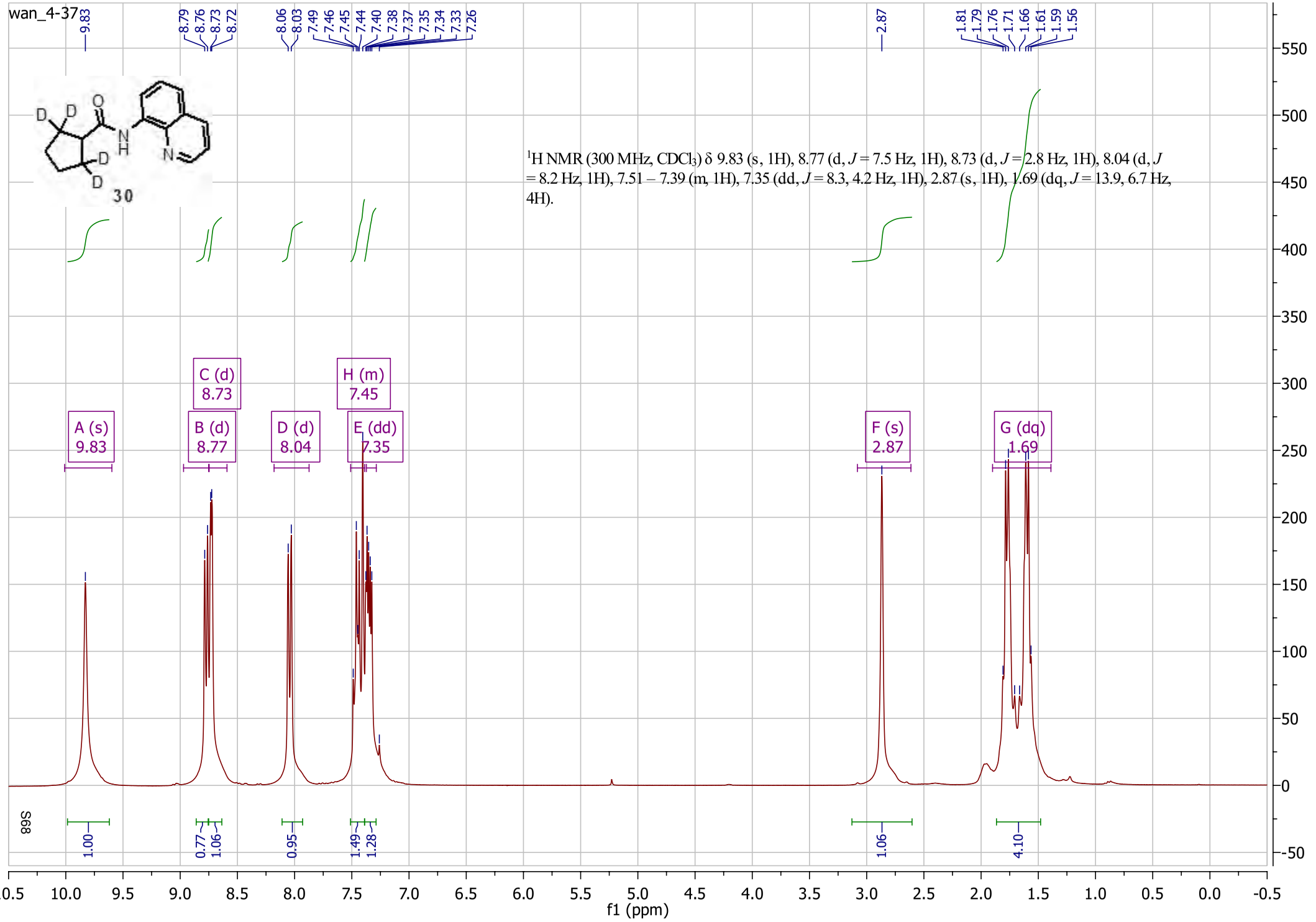

wan_4-32B
170.60
169.83
158.23
147.83
136.12
135.43
134.30
128.69
127.79
127.27
121.47
113.94
77.58
77.16
76.74
71.17
55.09
53.36
40.59
26.70
26.22
21.68
21.07
OAc
O
N
H
N
OMe
27
S63
f1 (ppm)

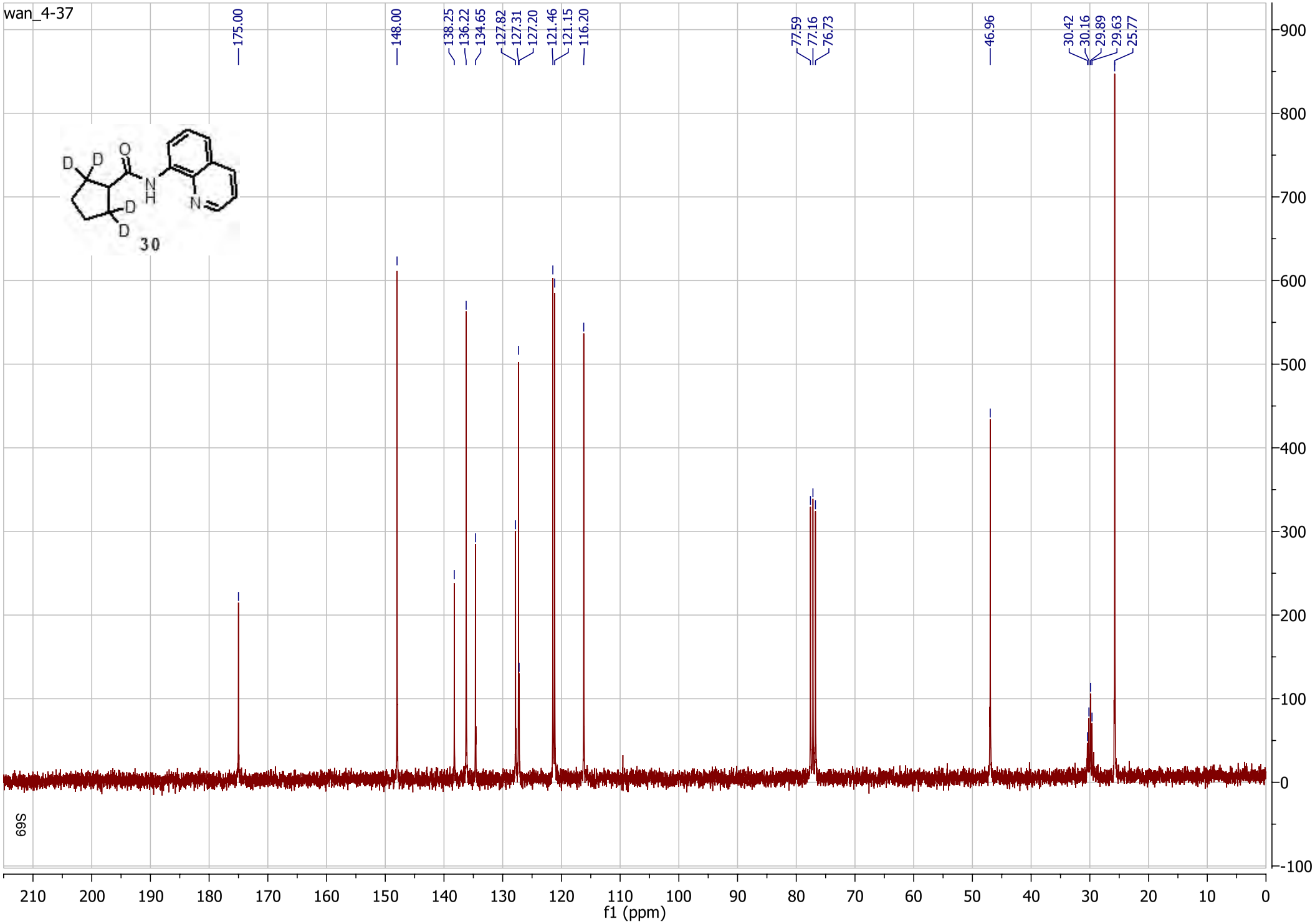

wan_4-22
8.83
8.82
8.46
8.44
8.12
8.06
8.04
7.64
7.61
7.56
7.54
7.52
7.49
7.47
7.45
7.43
7.40
7.39
7.26
5.43
4.27
4.24
4.19
4.16
4.14
4.11
3.21
3.19
3.16
3.13
3.11
2.65
2.63
2.60
2.58
O
N
N
NO2
28
1H NMR (300 MHz, CDCl3) δ 8.82 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 7.1 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.59 – 7.34 (m, 4H), 5.43 (s, 1H), 4.26 (d, J = 9.0 Hz, 1H), 4.15 (dd, J = 16.7, 9.5 Hz, 1H), 3.29 – 3.00 (m, 1H), 2.62 (dd, J = 13.9, 6.4 Hz, 1H).
A (d) 8.82
B (d) 8.45
C (d) 8.13
D (d) 8.05
E (d) 7.63
F (m) 7.47
G (s) 5.43
H (d) 4.26
I (dd) 4.15
J (m) 3.16
K (dd) 2.62
1.00
1.03
1.12
2.04
1.26
4.27
1.02
1.02
1.15
1.03
1.17
S94
400
350
300
250
200
150
100
50
0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


wan_4-22
166.87
148.94
148.26
143.17
139.83
136.14
133.81
129.30
129.07
127.05
123.37
122.38
121.77
121.46
119.39
77.58
77.16
76.74
56.11
53.85
35.20
33.81
O
N
N
NO2
28
S69
f1 (ppm)

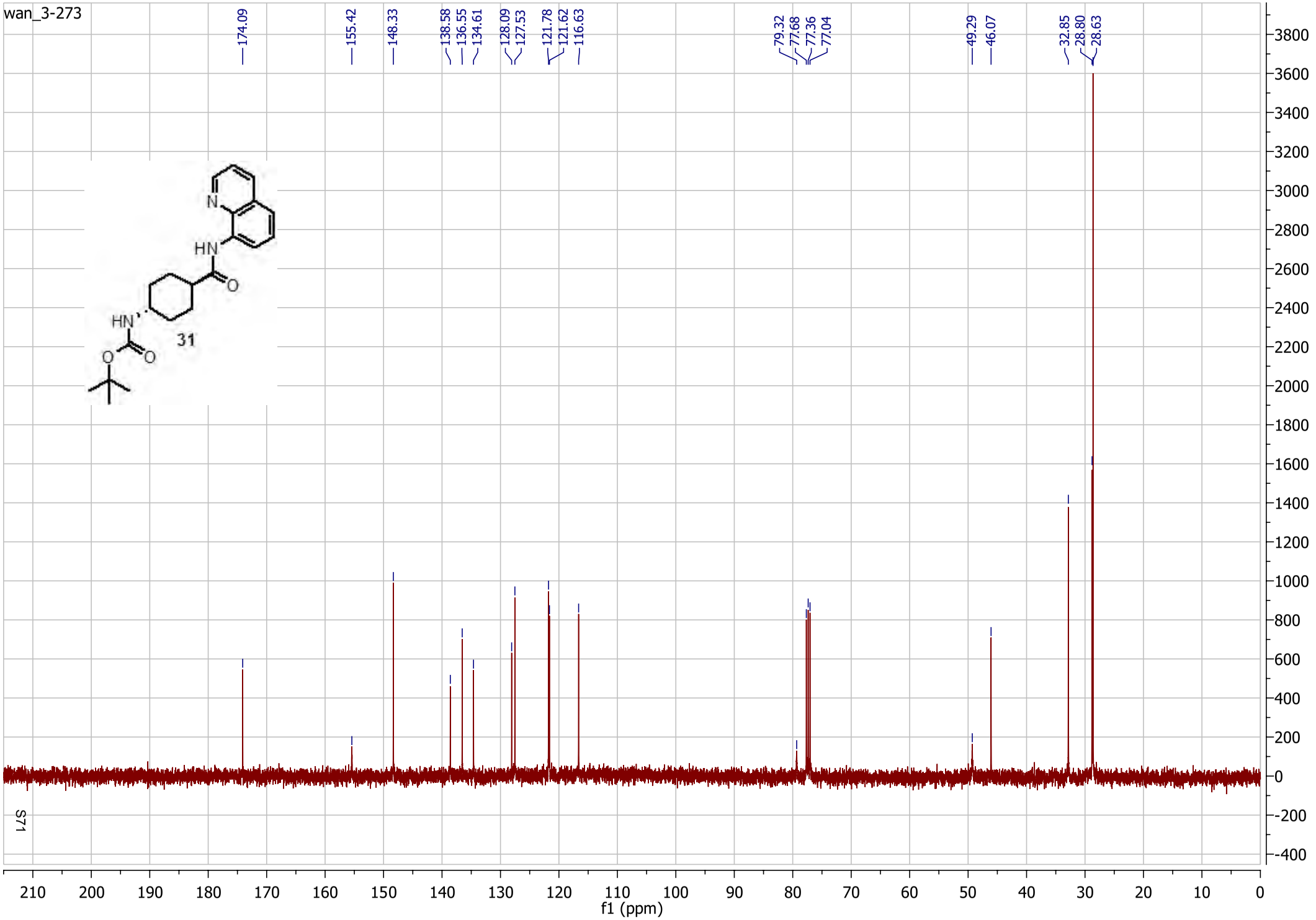

WAN105
O
OH
OMe
29
7.26
7.14
7.12
6.82
6.80
3.94
3.92
3.91
3.78
3.47
3.46
2.57
2.55
2.53
2.31
2.29
2.29
2.27
2.19
2.17
2.17
2.15
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.92 (t, J = 8.7 Hz, 1H), 3.78 (s, 2H), 3.47 (d, J = 3.1 Hz, 1H), 2.55 (t, J = 9.0 Hz, 1H), 2.29 (dd, J = 12.3, 9.0 Hz, 1H), 2.17 (dd, J = 10.6, 8.3 Hz, 1H).
B (d)
6.81
A (d)
7.13
D (s)
3.78
C (t)
3.92
E (d)
3.47
G (dd)
2.29
F (t)
2.55
H (dd)
2.17
S66
2.00
2.00
1.15
3.05
0.99
1.08
2.13
1.05
f1 (ppm)

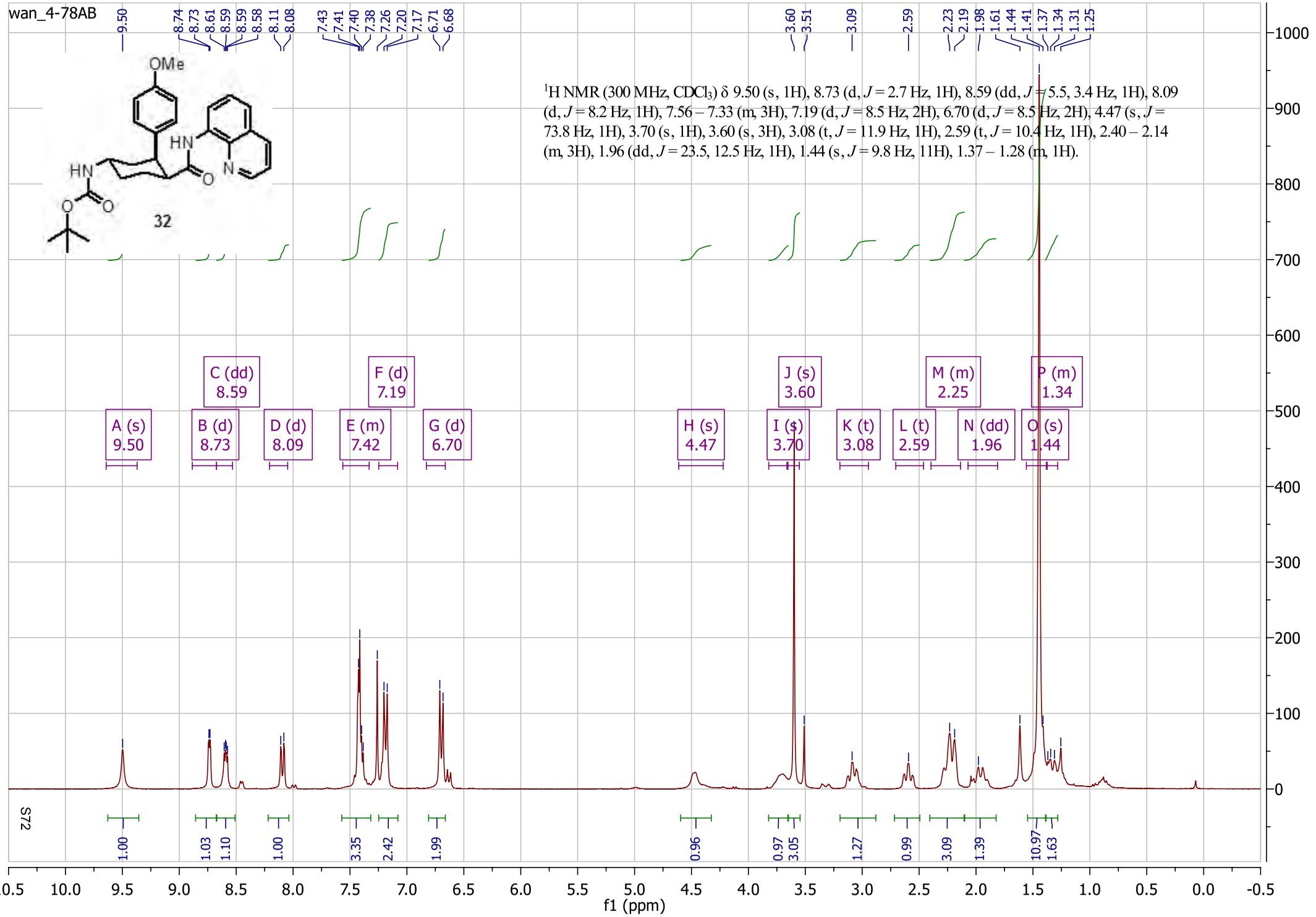

WAN105
178.99
158.38
132.76
128.41
113.70
77.41
77.16
76.91
55.32
45.01
42.22
25.10
20.32
O
OH
OMe
29
S67
f1 (ppm)

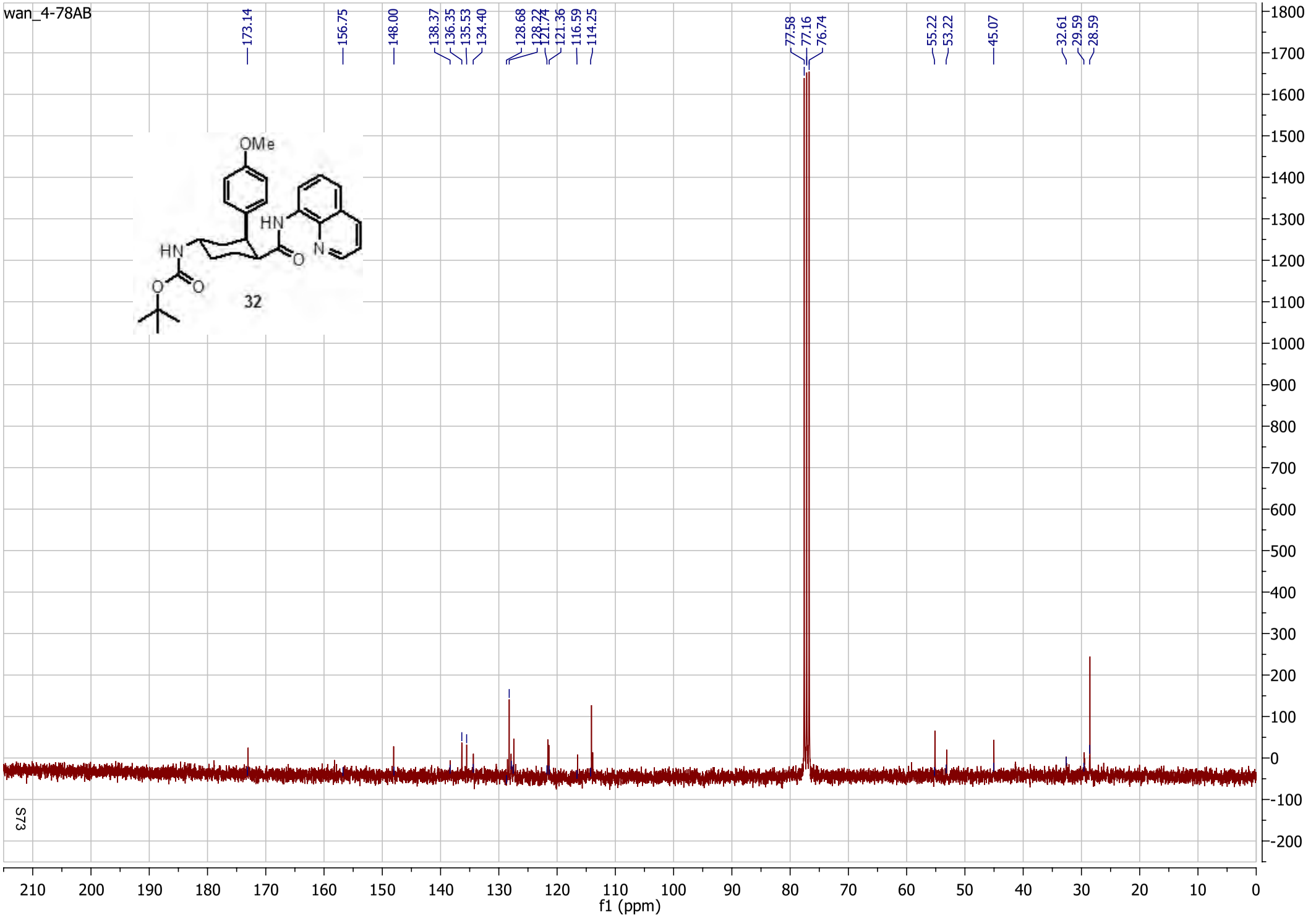

wan_4-37
9.83
8.79
8.76
8.73
8.72
8.06
8.03
7.49
7.46
7.45
7.44
7.40
7.38
7.37
7.35
7.34
7.33
7.26
2.87
1.81
1.79
1.76
1.71
1.66
1.61
1.59
1.56
O
D
D
N
H
N
D
D
30
1H NMR (300 MHz, CDCl3) δ 9.83 (s, 1H), 8.77 (d, J = 7.5 Hz, 1H), 8.73 (d, J = 2.8 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.51 – 7.39 (m, 1H), 7.35 (dd, J = 8.3, 4.2 Hz, 1H), 2.87 (s, 1H), 1.69 (dq, J = 13.9, 6.7 Hz, 4H).
A (s) 9.83
C (d) 8.73
B (d) 8.77
D (d) 8.04
H (m) 7.45
E (dd) 7.35
F (s) 2.87
G (dq) 1.69
1.00
0.77
1.06
0.95
1.49
1.28
1.06
4.10
f1 (ppm)

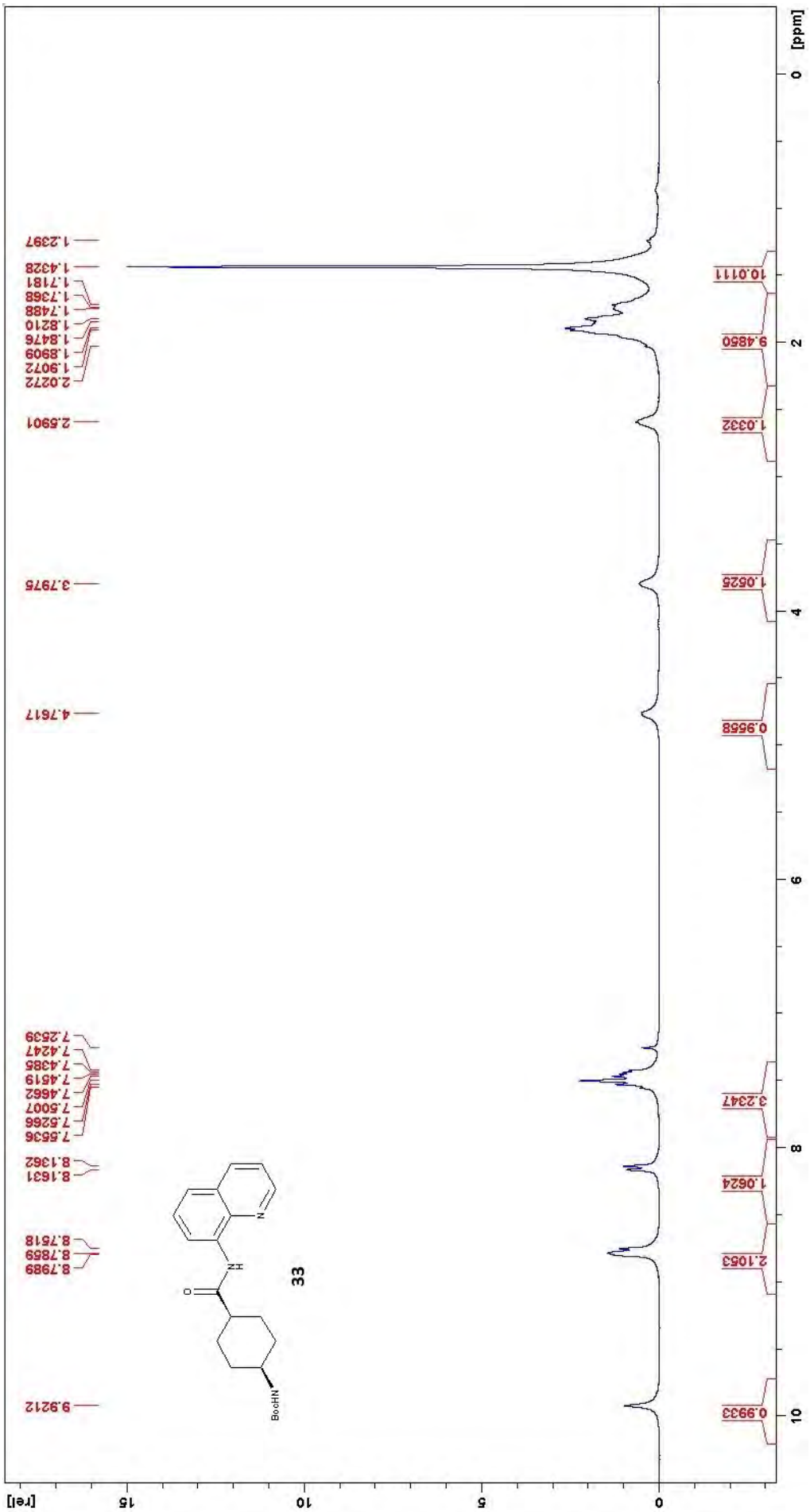

wan_4-37
175.00
148.00
138.25
136.22
134.65
127.82
127.31
127.20
121.46
121.15
116.20
77.59
77.16
76.73
46.96
30.42
30.16
29.89
29.63
25.77
O
D
D
N
H
N
D
D
30
S69
f1 (ppm)

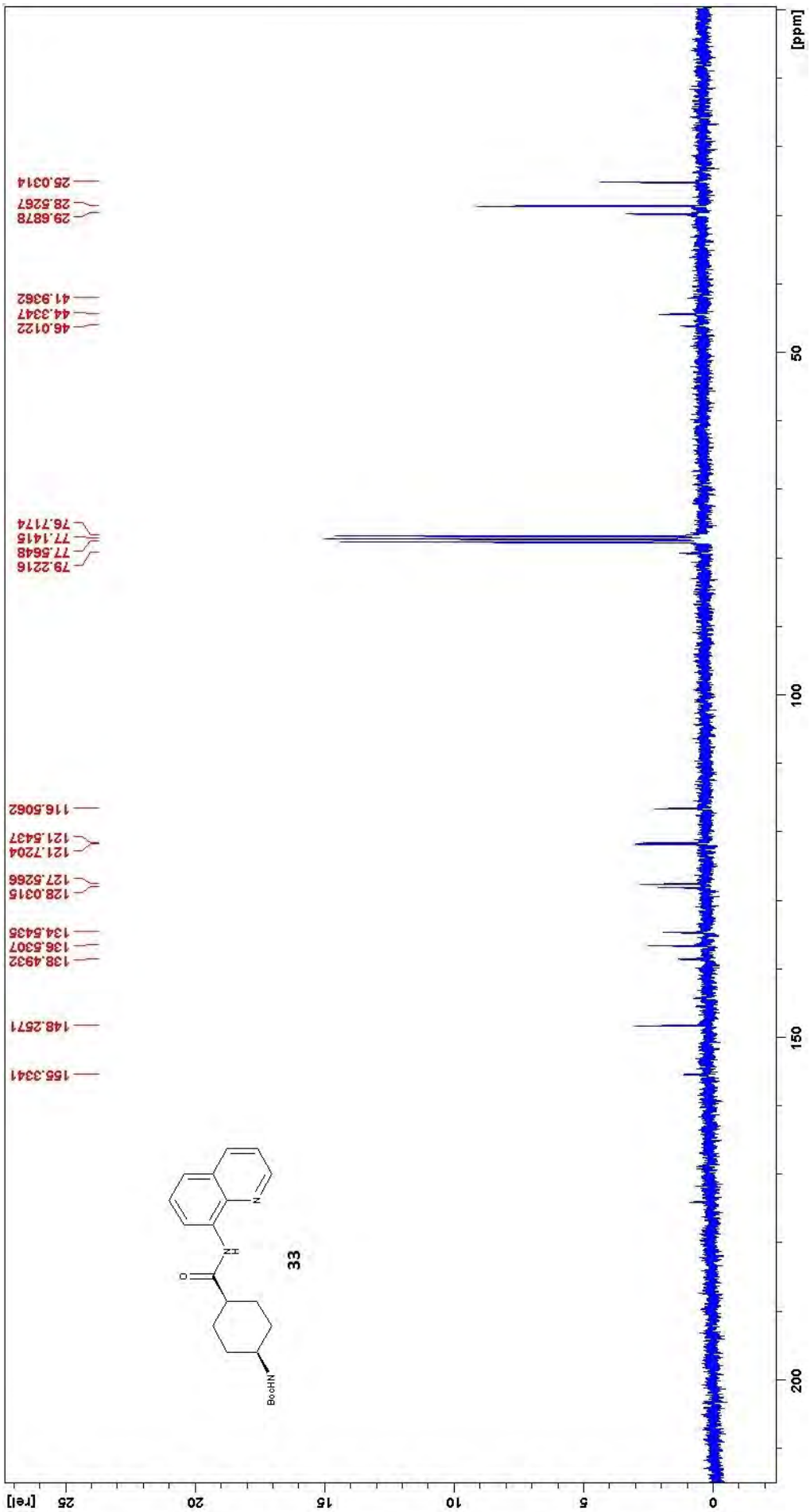

wan_3-273
9.84
8.74
8.73
8.73
8.71
8.71
8.08
8.06
7.47
7.45
7.43
7.43
7.41
7.39
7.38
7.37
7.36
7.26
4.56
3.47
2.39
2.39
2.36
2.33
2.12
2.09
1.99
1.77
1.74
1.71
1.68
1.41
1.23
1.20
1.17
1.14
N
HN
O
HN
O
O
31
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.80 – 8.66 (m, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.37 (dd, J = 8.2, 4.2 Hz, 1H), 4.56 (s, 1H), 3.47 (s, 1H), 2.36 (t, J = 12.1 Hz, 1H), 2.10 (d, J = 9.1 Hz, 2H), 1.73 (q, J = 12.2 Hz, 2H), 1.41 (s, 9H), 1.19 (q, J = 12.0 Hz, 1H).
M (s) 9.84
L (m) 8.72
K (d) 8.07
N (dd) 7.37
J (m) 7.44
I (s) 4.56
H (s) 3.47
G (t) 2.36
F (d) 2.10
E (q) 1.73
B (s) 1.41
A (q) 1.19
1.00
2.09
1.03
2.11
1.11
1.06
1.04
1.08
4.36
2.22
10.10
2.47
f1 (ppm)

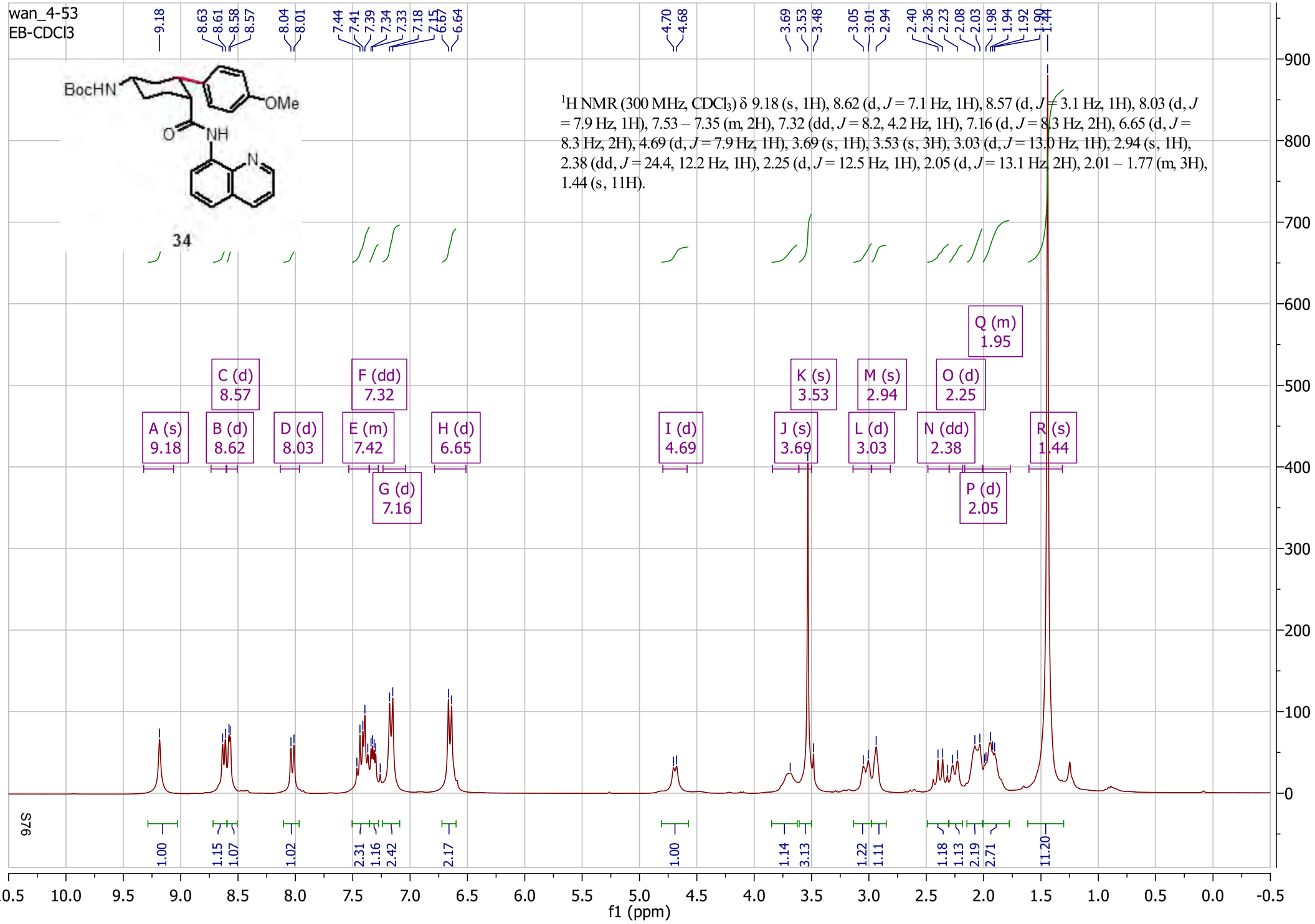

wan_3-273
174.09
155.42
148.33
138.58
136.55
134.61
128.09
127.53
121.78
121.62
116.63
79.32
77.68
77.36
77.04
49.29
46.07
32.85
28.80
28.63
N
HN
O
HN
O
O
31
S71
f1 (ppm)

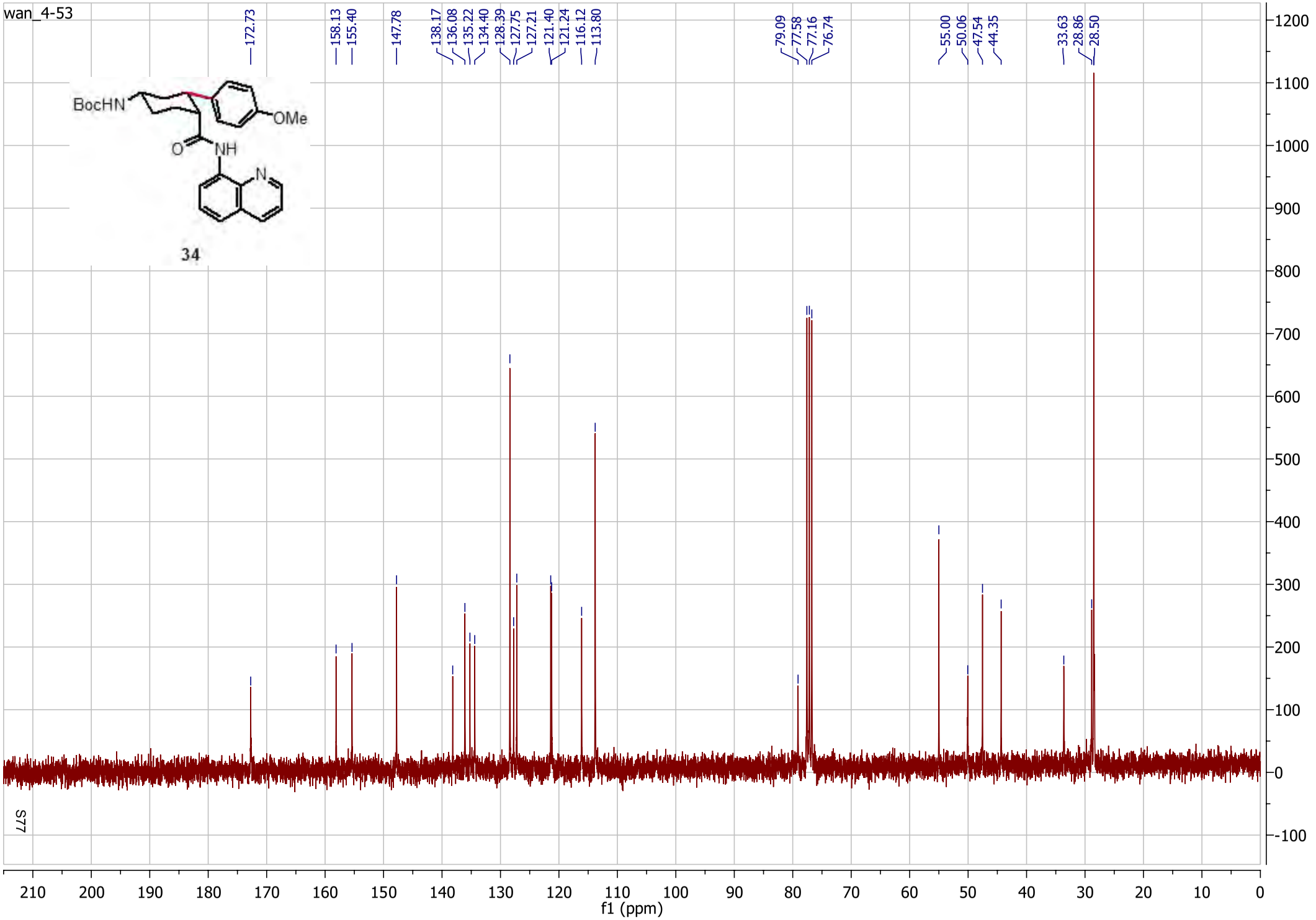

wan_4-78AB
9.50
8.74
8.73
8.61
8.59
8.59
8.58
8.11
8.08
7.43
7.41
7.40
7.38
7.26
7.20
7.17
6.71
6.68
3.60
3.51
3.09
2.59
2.23
2.19
1.98
1.61
1.44
1.41
1.37
1.34
1.31
1.25
OMe
HN
HN
O
O
O
N
32
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.73 (d, J = 2.7 Hz, 1H), 8.59 (dd, J = 5.5, 3.4 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.56 – 7.33 (m, 3H), 7.19 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 4.47 (s, J = 73.8 Hz, 1H), 3.70 (s, 1H), 3.60 (s, 3H), 3.08 (t, J = 11.9 Hz, 1H), 2.59 (t, J = 10.4 Hz, 1H), 2.40 – 2.14 (m, 3H), 1.96 (dd, J = 23.5, 12.5 Hz, 1H), 1.44 (s, J = 9.8 Hz, 11H), 1.37 – 1.28 (m, 1H).
A (s) 9.50
B (d) 8.73
C (dd) 8.59
D (d) 8.09
E (m) 7.42
F (d) 7.19
G (d) 6.70
H (s) 4.47
I (s) 3.70
J (s) 3.60
K (t) 3.08
L (t) 2.59
M (m) 2.25
N (dd) 1.96
O (s) 1.44
P (m) 1.34
S72
1.00
1.03
1.10
1.00
3.35
2.42
1.99
0.96
0.97
3.05
1.27
0.99
3.09
1.39
10.97
1.63
f1 (ppm)


wan_4-78AB
173.14
156.75
148.00
138.37
136.35
135.53
134.40
128.68
128.22
121.74
121.36
116.59
114.25
77.58
77.16
76.74
55.22
53.22
45.07
32.61
29.59
28.59
OMe
HN
HN
O
N
O
O
32
S73
f1 (ppm)


[rel]
15
10
5
0
[ppm]
0
2
4
6
8
10
9.9212
8.7989
8.7859
8.7518
8.1631
8.1362
7.5536
7.5266
7.5007
7.4662
7.4519
7.4385
7.4247
7.2539
4.7617
3.7975
2.5901
2.0272
1.9072
1.8909
1.8476
1.8210
1.7488
1.7368
1.7181
1.4328
1.2397
0.9933
2.1053
1.0624
3.2347
0.9558
1.0526
1.0332
9.4850
10.0111
33
BocHN
NH
O
N


155.3341
148.2571
138.4932
136.5307
134.5435
128.0315
127.5266
121.7204
121.5437
116.5062
79.2216
77.5648
77.1415
76.7174
46.0122
44.3347
41.9362
29.6878
28.5267
25.0314
33
BocHN
[rel]
[ppm]


wan_4-53
EB-CDCl3
BocHN
OMe
O
NH
N
34
[1]H NMR (300 MHz, CDCl3) δ 9.18 (s, 1H), 8.62 (d, J = 7.1 Hz, 1H), 8.57 (d, J = 3.1 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.53 – 7.35 (m, 2H), 7.32 (dd, J = 8.2, 4.2 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 8.3 Hz, 2H), 4.69 (d, J = 7.9 Hz, 1H), 3.69 (s, 1H), 3.53 (s, 3H), 3.03 (d, J = 13.0 Hz, 1H), 2.94 (s, 1H), 2.38 (dd, J = 24.4, 12.2 Hz, 1H), 2.25 (d, J = 12.5 Hz, 1H), 2.05 (d, J = 13.1 Hz, 2H), 2.01 – 1.77 (m, 3H), 1.44 (s, 11H).
A (s) 9.18
B (d) 8.62
C (d) 8.57
D (d) 8.03
E (m) 7.42
F (dd) 7.32
G (d) 7.16
H (d) 6.65
I (d) 4.69
J (s) 3.69
K (s) 3.53
L (d) 3.03
M (s) 2.94
N (dd) 2.38
O (d) 2.25
P (d) 2.05
Q (m) 1.95
R (s) 1.44
S76
f1 (ppm)


wan_4-53
172.73
158.13
155.40
147.78
138.17
136.08
135.22
134.40
128.39
127.75
127.21
121.40
121.24
116.12
113.80
79.09
77.58
77.16
76.74
55.00
50.06
47.54
44.35
33.63
28.86
28.50
BocHN
OMe
O
NH
N
34
S77
f1 (ppm)