Supporting Information

Two-Photon "Caging" Groups: Effect of Position-Isomery on the Photorelease Properties of Aminoquinoline-Derived Photolabile Protecting Groups

Christine Tran,[a] Thibault Gallavardin,[a] Morgane Petit,[a] Riadh Slimi,[a] Hamid Dhimane,[a] Mireille Blanchard-Desce,[b] Francine C. Acher,[a] David Ogden,[c] Peter I. Dalko[a]*

[a]Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, Université Paris Descartes, [b]Institut des Sciences Moléculaires, Université Bordeaux and [c]Laboratoire de Physiologie Cérébrale, Université Paris Descartes, France.

peter.dalko@parisdescartes.fr

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1. GENERALS

Chromatography: Thin layer chromatography was performed on aluminium-backed Merck Kieselgel 60 F 254 pre-coated plates.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 250 spectrometer (250 MHz and 63 MHz) and on a Bruker AV-500 spectrometer (500 MHz and 125 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane (TMS) and are referenced to residual proton in the NMR solvent ($CDCl_3$: δ 7.26, CD_3OD: δ 3.31). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.16, CD_3OD: δ 49.00). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet), coupling constants in Hertz (Hz). All solvents and inorganic reagents were from commercial sources and used without purification unless otherwise noted. Methods for HPLC analysis: the HPLC analyses were carried out on Waters device using X-Terra® MS C18 column (length: 75 mm, diameter: 4.6 mm, stationary phase: 2.5 µm) using a Waters 2487 Dual Absorbance Detector (260-360 nm) and an isocratic system of elution (MeOH-MeCN-H_2O 7-2-1 / H_2O $AcONH_4$ 10 mM pH 4.6). The volume of injection was 50 µL. The Mass analyser was an Agilent from ThermoFisher. The capillary tension was 3.5 kV. The cone tension was 24 V. The temperature of the source was 130 °C and the temperature of desolvatation was 350 °C. Data were treated on ThermoQuest.

The UV and NIR irradiation experiences were realized by irradiation for 0.5-1 hours of solution in roughly 0.1 mM concentration in an acetonitrile/TRIS buffer 1/1 solvent mixture (pH 7.4). The plot of ln *A versus* irradiation time showed a linear correlation for the disappearance of the starting material, which suggested a first order reaction, obtained by the linear least squares methodology for a straight line. The photochemical quantum yields (Q) were calculated based on time to 90% reaction ($t_{90\%}$), molar absorptivities (ε) and the incident photon flux (I_0), which was determined by using Dore's method.[1] The reference 7-dimethylaminoquinoline acetate was prepared according to ref. 1. For the UV irradiation, an aliquot (1 mL) of this solution was irradiated at approximately 366 nm by using 8W Carl Roth lamp. Single-photon quantum yields were determined by using Eq 1:[2]

$$Q_u = [1000\ \varepsilon(\lambda_{exc}) I_0(\lambda_{exc}) t_{90\%}]^{-1} \qquad \text{(Eq 1)}$$

where $\varepsilon(\lambda_{exc})$ is the molar extinction coefficient of the compound at the excitation wavelength in, L

(1) Davis, M. J.; Kragor, C. H.; Reddie, K. G.; Wilson, H. C.; Zhu, Y.; Dore, T. M. *J. Org. Chem.* **2009**, *74*, 1721.

(2) a) Furuta, T.; Wang, S. S. H.; Dantzker, J. L.; Dore, T. M.; Bybee, W. J.; Callaway, E. M.; Denk, W.; Tsien, R. Y. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 1193; b) Fedoryak, O. D.; Dore, T. M. *Org. Lett.* **2002**, *4*, 3419; c) Zhu, Y.; Pavlos, C. M.; Toscano, J. P.; Dore, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 4267; d) Lu, M.; Fedoryak, O. D.; Moister, B. R.; Dore, T. M. *Org. Lett.* **2003,** *5*, 2119.

$cm^{-1}millimole^{-1}$, $t_{90\%}$ is the time at which 90% of the cage was converted, as determined by HPLC, and $I_0(\lambda exc)$ is the light intensity at the excitation wavelength and is measured in einstein. cm^2. s^{-1}. Between each duration, a small aliquot (50 µL) of the solution was removed for analysis by reverse-phase HPLC using dual absorbance detection at 260 and 360 nm. Optical densities at 366 nm were kept around 0.1 so that inner-filtering of the irradiation and spatial gradients of concentrations could be neglected, and the progress curves were simple decaying exponentials. Dark hydrolysis rates were measured similarly except without illumination.

Uncaging two photon cross-sections (δ_u) were calculated from the fractional conversion of the cage with exposures of approx. 4 hours in a 45 microlitres cuvette of 3 mm pathlength. The expanded output of a MaiTai BB (Spectra-Physics) pulsed laser was focused with a 50 mm focal length lens into the cuvette. The two-photon excitation volume was entirely contained within the cuvette volume to obviate the need to measure the beam waist. Beam parameters were 720 or 730 nm with 100 fs pulse width at 80 MHz and 100 mW average power after the cuvette. Samples were centrifuged if necessary to remove particles if apparent in the transmitted beam. For reference the two-photon uncaging cross-section was compared to the widely used MNI-caged glutamate determined in this way was 0.05 GM (10^{-50} cm^4.s/photon). The conversion of the product was assayed by HPLC analysis of the remaining caged compound. The two-photon uncaging cross-section δ_u was calculated as follows:

$$\delta_u = (8.C.F.T.V.h^2c^2)/(C_0.\pi.n.t.\lambda.P^2) \quad \text{(Eq 2)}$$

where C/C_0 = fractional conversion; δ_u = TP uncaging cross-section (cm^4.s/photon); P = average power (W); λ = wavelength (cm); h = Planck constant (J. sec); c = velocity of light (cm/s); F = pulse frequency (Hz); T = pulse width (s); n = refractive index; V = sample volume (cm^3); t = exposure time (s).

The solubility of **36** was determined by sonicating a small amount of sample, around 0.25 mg, in 20 µL of 20 mM TRIS buffer (pH 7.4), for 30 min at 40 °C. The sample was centrifuged in a microfuge for 10 min and 4 µL of the supernatent diluted with 36 µL AcCN and used for measurements. The absorbance at 343 nm was determined in 2 µL samples in a 1 mm path Nanodrop spectrometer and compared with the known molar absorption coefficient at 343 nm of 2000 L/mol.cm in AcCN.

2. SYNTHESIS OF CARBOXY-SUBSTITUTED 8-DMAQ-ACETATES, **12**, **17**, **23**

N,*N*-Dimethyl-2-nitroaniline

A solution of dimethylamine in ethanol (5.6 M, 73.2 mL, 410 mmol, 10 eq) was slowly added to 2-fluoronitrobenzene **6** (5.8 g, 4.3 mL, 41 mmol, 1.0 eq) at 0 °C. The reaction was heated for 30 min at 65 °C. After cooling to room temperature an 10% aqueous solution of $NaHCO_3$ was added and the product was extracted with DCM. The organic layer was washed twice with water and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the compound as a dark orange oil (6.7 g, 98%). ^{1}H NMR (250 MHz): δ 7.71 (1H, d, J = 8.5 Hz,), 7.35 (1H, t, J = 8.5 Hz), 6.99 (1H, d, J = 8.5 Hz), 6.77 (1H, t, J = 8.5 Hz), 2.80 (6H, s). ^{13}C NMR (63 MHz): δ 146.2, 139.3, 133.3, 126.6, 118.1, 117.8, 42.3. MS (APCI): *m/z* = 167 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_8H_{10}N_2O_2+H]^+$ 167.0821, found 167.0814.

N^1,N^1-Dimethylbenzene-1,2-diamine

N,*N*-Dimethyl-2-nitroaniline (16.9 g, 101.5 mmol, 1.0 eq) was added to a suspension of Pd/C 10% (0.6 g, 0.5 mmol, 0.005 eq) in EtOH/AcOEt (200 mL/350 mL) under hydrogen atmosphere (1 atm) at room temperature. The reaction was supplied with hydrogen until the disappearance of the yellow starting product; the mixure was then filtered on cellite and concentrated under reduced pressure to afford the product as a brown oil (12.8 g, 93%). The product was used without further purification.^{1}H NMR (250 MHz): δ 7.05 (1H, d, J = 8.0 Hz), 6.94 (1H, t, J = 8.0 Hz), 6.77 (1H, t, J = 8.0 Hz), 6.75 (1H, d, J = 8.0 Hz), 3.99 (2H, s), 2.60 (6H, s). ^{13}C NMR (63 MHz): δ 141.5, 140.8, 124.3, 119.5, 118.6, 115.2, 43.7. MS (APCI): *m/z* = 137 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_8H_{12}N_2 + H]^+$ 137.1079, found 137.1073.

8-(Dimethylamino)quinaldine (7)

N^1,N^1-Dimethylbenzene-1,2-diamine (10.8 g, 79.4 mmol, 1.0 eq) was dissolved in a solution of aqueous HCl (6 M, 144 mL), after addition of crotonaldehyde (13 mL, 158.8 mmol, 2.0 eq) the mixture was stirred for 1 h at room temperature. Then toluene (75 mL) was added and the reaction was refluxed 4 h. After cooling down to room temperature, the organic layer was removed. The aqueous layer was neutralized by addition of NaOH, than the solution was extracted with DCM and the organic layer was washed twice with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM /Cyclohexane: 1/1). The quinoline was obtained as a yellow oil (6.53 g, 44 %). ^{1}H NMR (250 MHz): δ 7.97 (d, J = 8.0 Hz, 1H), 7.35, 7.31 (ABx, J = 10.0 Hz, J = 6.0 Hz, J = 3.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.06 (X, J = 6.0 Hz, J = 3.0 Hz, 1H), 3.09 (s, 6H), 2.76 (s, 3H). ^{13}C NMR (63 MHz): δ 156.3, 149.8, 142.1, 136.5, 127.8, 125.7, 121.5, 120.5, 115.4, 44.6, 25.7. MS (APCI): *m/z* = 187 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{14}N_2 + H]^+$ 187.1235, found 187.1227.

5-Bromo-8-(dimethylamino)-2-methylquinoline

8-(Dimethylamino)-2-methylquinoline **7** (250 mg, 1.3 mmol, 1.0 eq) was dissolved in chloroform (6.7 mL). Recrystallized *N*-bromosuccinimide (191 mg, 1.1 mmol, 0.8 eq) was then added and the reaction was stirred at room temperature for 1 h. The mixture was hydrolyzed by a solution of sodium thiosulfate and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product as a brown oil (354 mg, quant.). The product was used without further purification. ^{1}H NMR (250 MHz): δ 8.31 (1H, d, *J* = 8.0 Hz), 7.56 (1H, d, *J* = 8.0 Hz), 7.28 (1H, d, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 3.06 (6H, s), 2.76 (3H, s). ^{13}C NMR (63 MHz): δ 156.8, 149.7, 142.7, 135.8, 129.2, 126.5, 122.6, 115.7, 112.9, 44.4, 25.4. MS (ESI): *m/z* = 265, 267 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{13}BrN_2+H]^+$ 265.0340 and 267.0320, found 265.0340 and 267.0320.

8-(Dimethylamino)-2-methylquinoline-5-carbonitrile (8)

5-Bromo-8-(dimethylamino)-2-methylquinoline (196 mg, 0.7 mmol, 1.0 eq) and CuCN (113 mg, 1.3 mmol, 1.7 eq) were dissolved in DMF (576 µL). The mixture was heated at 170 °C for 12 h. After cooling down to room temperature, the crude product was poured on a solution of ice and water. The solid was solubilized in ethylene diamine and extracted with toluene. The organic phase was washed twice with KCN 10%, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the compound as a dark oil (144 mg, 92%). The product was used without further purification. ^{1}H NMR (250 MHz): δ 8.30 (1H, d, *J* = 8.7 Hz), 7.70 (1H, d, *J* = 8.7 Hz), 7.38 (1H, d, *J* = 8.7 Hz), 6.87 (1H, d, *J* = 8.7 Hz), 3.26 (6H, s), 2.74 (3H, s). ^{13}C NMR (63 MHz): δ 156.5, 153.4, 140.3, 133.7, 132.8, 123.4 (2 C), 118.4, 112.6, 98.5, 44.1, 25.4. MS (ESI): *m/z* = 212 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{13}N_3+H]^+$ 212.1188, found 212.1187.

Methyl 8-(dimethylamino)-2-methylquinoline-5-carboxylate (9)

8-(Dimethylamino)-2-methylquinoline-5-carbonitrile **8** (104 mg, 0.5 mmol, 1.0 eq) was dissolved in MeOH (4 mL). H_2SO_4 (cc, 1.5 mL) and H_2O (4 drops) were then added and the mixture was heated at 75 °C for 2 days. The crude product was neutralized with NaOH (2 M) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the compound as a dark oil (81 mg, 68%). ^{1}H NMR (250 MHz): δ 9.35 (1H, d, *J* = 8.5 Hz), 8.16 (1H, d, *J* = 8.5 Hz), 7.35 (1H, d, *J* = 8.5 Hz), 6.94 (1H, d, *J* = 8.5 Hz), 3.94 (3H, s), 3.23 (6H, s), 2.75 (3H, s). ^{13}C NMR (63 MHz): δ 167.2, 155.3, 153.9, 141.0, 134.7, 131.4, 127.1, 122.8, 116.4, 112.3, 51.62, 44.2, 25.3. MS (ESI): *m/z* = 245.3 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}N_2O_2+H]^+$ 245.1290 and 246.1324, found 245.1290 and 246.1324.

Methyl 8-(dimethylamino)-2-formylquinoline-5-carboxylate

To a solution of methyl 8-(dimethylamino)-2-methylquinoline-5-carboxylate **9** (81 mg, 0.3 mmol, 1.0 eq) in dioxane (1.7 mL), selenium dioxide (48 mg, 0.4 mmol, 1.3 eq) was then added and the mixture was heated at 80 °C for 3 h. After cooling to room temperature, the solution was filtered on celite and concentrated under reduced pressure to afford the compound as an orange solid (81 mg, 95%). The product was used without further purification. ^{1}H NMR (250 MHz): δ 10.17 (1H, s), 9.65 (1H, d, *J* = 8.9 Hz), 8.33 (1H, d, *J* = 8.9 Hz), 8.08 (1H, d, *J* = 8.9 Hz), 6.95 (1H, d, *J* = 8.9 Hz), 3.95 (3H, s), 3.39 (6H, s). ^{13}C NMR (125 MHz): δ 193.3, 167.0, 154.5, 148.7, 145.2, 140.7, 136.1, 135.2, 131.9, 118.5, 112.0, 52.0, 44.5. MS (ESI): *m/z* = 259 $[M+H]^+$, HRMS (ESI): *m/z* calcd for $[C_{14}H_{14}N_2O_3+H]^+$ 259.1083 and 260.1117, found 259.1082 and 260.1116.

Methyl 8-(dimethylamino)-2-(hydroxymethyl)quinoline-5-carboxylate (10)

Methyl 8-(dimethylamino)-2-formylquinoline-5-carboxylate (81 mg, 0.3 mmol, 1.0 eq) was dissolved in MeOH (1.6 mL). $NaBH_4$ (24 mg, 0.6 mmol, 2.0 eq) was then added and the mixture was stirred at 0 °C for 30 min. The crude product was then neutralized with HCl (1 M) and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained as a yellow solid (68 mg, 84%). ^{1}H NMR (250 MHz): δ 9.44 (1H, d, *J* = 8.8 Hz), 8.17 (1H, d, *J* = 8.8 Hz), 7.35 (1H, d, *J* = 8.8 Hz), 6.92 (1H, d, *J* = 8.8 Hz), 4.89 (2H, s), 3.92 (3H, s), 3.21 (6H, s). ^{13}C NMR (63 MHz): δ 167.2, 155.6, 153.6, 139.9, 135.8, 132.2, 128.6, 119.4, 116.4, 112.7, 64.4, 51.9, 44.2. MS (ESI): *m/z* = 261 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}N_2O_3+H]^+$ 261.1239, found 261.1239.

8-(Dimethylamino)-2-(hydroxymethyl)quinoline-5-carboxylic acid (11)

Methyl 8-(dimethylamino)-2-(hydroxymethyl)quinoline-5-carboxylate **10** (23 mg, 0.09 mmol, 1.0 eq) was dissolved in MeOH (270 µL) and H_2O (120 µL). LiOH (3.7 mg, 0.09 mmol, 1.0 eq) was added and the mixture was stirred at 5 °C for 12 h. The crude product was neutralized with HCl (1 M, pH 7-8), filtered on celite and concentrated under reduced pressure to afford the product as an orange solid (26 mg, quant.). ^{1}H NMR (250 MHz): δ 9.23 (1H, d, *J* = 8.8 Hz), 7.89 (1H, d, *J* = 8.8 Hz), 7.59 (1H, d, *J* = 8.8 Hz), 7.20 (1H, d, *J* = 8.8 Hz), 4.89 (2H, s), 3.03 (6H, s). ^{13}C NMR (125 MHz): δ 176.3, 160.4, 152.2, 142.5, 138.0, 132.4, 128.6, 128.0, 119.8, 116.5, 66.3, 45.2. MS (ESI): *m/z* = 247 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{14}N_2O_3+H]^+$ 247.1083 and 248.1116, found 247.1079 and 248.1113.

2-(Acetoxymethyl)-8-(dimethylamino)quinoline-5-carboxylic acid (12)

8-(Dimethylamino)-2-(hydroxymethyl)quinoline-5-carboxylic acid **11** (30.5 mg, 0.1 mmol, 1.0 eq) was solubilized in distilled pyridine (488 µL). Acetic anhydride (18 µL, 19 mg, 0.2 mmol, 1.5 eq) and DMAP (cat.) were added to the mixture. The yellow solution was stirred at room

temperature for 1 h, concentrated under reduced pressure and purified by chromatography on silica gel (DCM /MeOH: 98/2). The compound was obtained as a yellow oil (22 mg, 63%). ^{1}H NMR (250 MHz): δ 8.46 (1H, d, *J* = 8.8 Hz), 7.78 (1H, d, *J* = 8.1 Hz), 7.58 (1H, d, *J* = 9.0 Hz), 6.89 (1H, d, *J* = 9.0 Hz), 5.41 (2H, s), 3.32 (6H, s), 2.21 (3H, s). ^{13}C NMR (125 MHz): δ 171.5, 170.9, 154.8, 152.2, 140.6, 135.9, 134.3, 129.1, 120.6, 114.1, 112.0, 67.5, 44.4, 21.1. MS (ESI): *m/z* = 289 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{15}H_{16}N_2O_4\text{-}H]^-$ 287.1032, found 287.1020.

6-Bromo-8-fluoro-2-methylquinoline

4-Bromo-2-fluoroaniline **13** (950 mg, 5.0 mmol, 1.0 eq) was dissolved in a solution of aqueous HCl (6 M, 20 mL). After addition of crotonaldehyde (0.83 mL, 10.0 mmol, 2.0 eq) the mixture was stirred 1 h at room temperature. Then toluene (5 mL) was added and the reaction was heated at reflux temperature for 3 h. After cooling down to room temperature, the organic layer was removed. The aqueous layer was neutralized with NaOH and the solution was extracted with DCM. The organic layer was washed twice with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM /Cyclohexane: 2/1). The quinaldine was obtained as yellow crystals (636 mg, 53%). ^{1}H NMR (250 MHz): δ 7.90 (1H, dd, *J* = 8.7, 1.6 Hz), 7.65 (1H, m), 7.44 (1H, dd, *J* = 9.8, 2.1 Hz), 7.31 (1H, d, *J* = 8.7 Hz), 2.74 (3H, s). ^{13}C NMR (63 MHz): δ 159.9, 159.3, 155.1, 136.8 (d, *J* = 11.5 Hz), 134.7 (d, *J* = 3.1 Hz), 128.7 (d, *J* = 3.1 Hz), 125.4 (d, *J* = 4.8 Hz), 123.9, 117.8 (d, *J* = 8.6 Hz), 117.3, 25.5. MS (ESI): *m/z* = 239 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{10}H_7BrFN+H]^+$ 239.9824 and 241.9804, found 239.9817 and 241.9795.

8-Fluoro-2-methylquinoline-6-carbonitrile (14)

6-Bromo-8-fluoro-2-methylquinoline (500 mg, 1.0 mmol, 1.0 eq) and CuCN (317 mg, 3.5 mmol, 1.7 eq) were dissolved in DMF (1.4 mL). The mixture was heated at 170 °C for 12 h. After cooling down to room temperature, the crude product was poured on a solution of ice and water. The solid was solubilized in ethylene diamine and extracted with toluene. The organic phase was washed twice with KCN 10%, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product as a brown solid (335 mg, 87%). ^{1}H NMR (250 MHz): δ 8.11 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.97 (1H, m), 7.50 (2H, m), 2.82 (3H, s). ^{13}C NMR (63 MHz): δ 163.2, 159.6, 139.7 (d, *J* = 10.7 Hz), 136.2 (d, *J* = 2.5 Hz), 129.6 (d, *J* = 4.8 Hz), 127.7 (d, *J* = 3.0 Hz), 124.8, 117.6 (d, *J* = 9.3 Hz) , 114.6 (d, *J* = 23.0 Hz), 108.9 (d, *J* = 9.8 Hz), 25.8. MS (ESI): *m/z* = 187 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{11}H_7FN_2+H]^+$ 187.0672 and 188.0706, found 187.0671 and 188.0704.

8-Fluoro-2-formylquinoline-6-carbonitrile

8-Fluoro-2-methylquinoline-6-carbonitrile **14** (100 mg, 0.5 mmol, 1.0 eq) was dissolved in dioxane (2.7 mL). Selenium dioxide (77 mg, 0.8 mmol, 1.3 eq) was then added and the mixture

was heated at 80 °C for 3h. After cooling to room temperature, the solution was filtered on celite and concentrated under reduced pressure to obtain the compound as an orange solid (129 mg, quant.). ^{1}H NMR (250 MHz): δ 10.29 (s, 1H), 8.45 (d, *J* = 8.8 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.14 (s, 1H), 7.68 (dd, *J* = 9.4, 1.6 Hz, 1H). ^{13}C NMR (63 MHz): δ 192.5, 160.8, 156.6, 154.6, 138.1, 131.0, 129.9 (d, *J* = 5.5 Hz), 120.0, 117.2, 115.7 (d, *J* = 22.5 Hz), 112.9 (d, *J* = 10.0 Hz). MS (ESI): *m/z* = 201 $[M+H]^+$, HRMS (ESI): *m/z* calcd for $[C_{11}H_5FN_2O+H]^+$ 201.0464 and 202.0498, found 200.0463 and 202.0496.

8-(Dimethylamino)-2-formylquinoline-6-carbonitrile

8-Fluoro-2-methylquinoline-6-carbonitrile (277 mg, 1.1 mmol, 1.0 eq) was dissolved in a solution of dimethylamine in ethanol (5.6 M, 3.7 mL, 20 mmol, 19 eq). The reaction was heated at 65 °C for 12 h. After cooling down to room temperature, the mixture was then concentrated under reduced pressure. A solution of $NaHCO_3$ 10% was added to the crude product and the solution was extracted with DCM. The organic layer was washed twice with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography on silica gel (DCM) and the quinoline was obtained as an orange solid (217 mg, 85%). ^{1}H NMR (500 MHz): δ 10.21 (1H, s), 8.28 (1H, d, *J* = 8.5 Hz), 8.08 (1H, d, *J* = 8.7 Hz), 7.69 (1H, s), 7.14 (1H, s), 3.31 (6H, s). ^{13}C NMR (125 MHz): δ 192.9, 151.5, 151.4, 142.8, 138.5, 131.3, 123.9, 118.9, 118.5, 115.4, 113.4, 44.4. MS (ESI): *m/z* = 226 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{11}N_3O+H]^+$ 226.0980 and 227.1014, found 226.0982 and 227.1016.

8-(Dimethylamino)-2-(hydroxymethyl)quinoline-6-carbonitrile (15)

To a solution of 8-(dimethylamino)-2-formylquinoline-6-carbonitrile (52 mg, 0.23 mmol, 1.0 eq) in MeOH (1.2 mL), $NaBH_4$ (17 mg, 0.5 mmol, 2 eq) was then added and the mixture was stirred at 0 °C for 30 min. The crude product was then quenched with HCl (1 M) and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the compound as a yellow solid (60 mg, quant.). ^{1}H NMR (250 MHz): δ 8.08 (1H, d, *J* = 8.5 Hz), 7.66 (1H, d, *J* = 1.9 Hz), 7.41 (1H, d, *J* = 8.5 Hz), 7.10 (1H, d, *J* = 1.9 Hz), 4.94 (2H, s), 3.13 (6H, s). ^{13}C NMR (63 MHz): δ 159.7, 150.4, 142.1, 137.8, 128.3, 125.3, 119.6, 119.2, 115.8, 110.2, 64.8, 44.1. MS (ESI): *m/z* = 228.1 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{13}N_3O+H]^+$ 228.1137 and 229.1176, found 228.1135 and 229.1170.

Methyl 8-(dimethylamino)-2-(hydroxymethyl)quinoline-6-carboxylate

To a solution of 8-(dimethylamino)-2-(hydroxymethyl)quinoline-6-carbonitrile **15** (56 mg, 0.25 mmol, 1.0 eq) in MeOH (2.3 mL). H_2SO_4 (cc, 813 µL) and H_2O (3 drops) were then added and the mixture was heated at 65 °C for 12 h. The crude product was neutralized with NaOH (2 M) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4,

filtered and concentrated under reduced pressure. The product was obtained as a red solid (47 mg, 72%). ^{1}H NMR (500 MHz): δ 8.19 (1H, d, *J* = 8.3 Hz), 8.13 (1H, s), 7.70 (1H, s), 7.34 (1H, d, *J* = 8.3 Hz), 4.95 (2H, s), 3.90 (3H, s), 3.16 (6H, s). ^{13}C NMR (125 MHz): δ 167.2, 159.0, 149.9, 142.9, 138.9, 128.3, 128.1, 123.3, 118.9, 115.4, 64.8, 52.5, 44.5. MS (ESI): *m/z* = 261 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}N_2O_3+H]^+$ 261.1239, found 261.1239.

Methyl 2-(acetoxymethyl)-8-(dimethylamino)quinoline-6-carboxylate (16)

Methyl 8-(dimethylamino)-2-(hydroxymethyl)quinoline-6-carboxylate (47 mg, 0.18 mmol, 1.0 eq) was dissolved in MeOH (563 µL) and H_2O (188 µL). LiOH (7.5 mg, 0.18 mmol, 1.0 eq) was added and the mixture was stirred at 5 °C for 12 h. The crude product was neutralized with HCl (1 M), filtered on celite and concentrated under reduced pressure to afford the compound as an orange solid (70 mg, quant.). ^{1}H NMR (500 MHz): δ 8.34 (1H, d, *J* = 8.4 Hz), 8.15 (1H, d, *J* = 1.5 Hz), 7.88 (1H, 1H, d, *J* = 1.5 Hz), 7.63 (1H, d, *J* = 8.4 Hz), 4.90 (2H, s), 3.04 (6H, s). ^{13}C NMR (125 MHz): δ 174.1, 161.6, 150.2, 143.8, 139.7, 136.0, 129.3, 124.6, 119.9, 118.5, 66.3, 45.2. MS (ESI): *m/z* = 247 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{14}N_2O_3+H]^+$ 247.1083 and 248.1117, found 247.1077 and 248.1048.

2-(Acetoxymethyl)-8-(dimethylamino)quinoline-6-carboxylic acid (17)

To a solution of methyl 2-(acetoxymethyl)-8-(dimethylamino)quinoline-5-carboxylate **16** (35 mg, 0.14 mmol, 1.0 eq) in pyridine (683 µL), acetic anhydride (20 µL, 22 mg, 0.21 mmol, 1.5 eq), and DMAP (cat.) were added to the mixture. The yellow solution was stirred at room temperature for 1 h, concentrated under reduced pressure and purified by chromatography on silica gel (MeOH). The product was obtained as a yellow oil (28 mg, 69%). ^{1}H NMR (500 MHz): δ 8.35 (1H, d, *J* = 8.4 Hz), 8.18 (1H, s), 7.81 (1H, s), 7.56 (1H, d, *J* = 8.4 Hz), 5.41 (2H, s), 3.08 (6H, s), 2.20 (3H, s). ^{13}C NMR (125 MHz): δ 180.6, 174.8, 172.5, 156.4, 150.3, 143.9, 139.9, 129.5, 124.0, 120.3, 118.4, 68.2, 45.0, 24.2. MS (ESI): *m/z* = 289 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{15}H_{16}N_2O_4-H]^-$ 287.1100, found 287.1082.

7-Bromo-2-methyl-8-nitroquinoline

7-Bromo-2-methylquinoline **18**[3] (2.5 g, 11 mmol, 1.0 eq) was dissolved in H_2SO_4 (cc, 5 mL). A solution of H_2SO_4 (cc, 5 mL) and HNO_3 (cc, 2.5 mL) was added to the mixture at 0 °C. The crude was stirred at room temperature for 30 min and was then heated at 50 °C for 30 min and extracted with DCM. The organic layer was neutralized with NaOH, dried over Na_2SO_4, concentrated under reduced pressure and the quinoline was obtained as a brown solid (2.4 g, 83%). ^{1}H NMR (250 MHz): δ 8.07 (1H, d, *J* = 8.5 Hz), 7.75 (1H, d, *J* = 8.5 Hz), 7.64 (1H, d, *J* =

(3) Petit, M.; Bort, G.; Doan, B.-T.; Sicard, C.; Ogden, D.; Scherman, D.; Ferroud, C.; Dalko, P. I. *Angew. Chem. Int. Ed.* **2011**, *50*, 9708.

8.5 Hz), 7.41 (1H, d, *J* = 8.5 Hz), 2.73 (3H, s). ^{13}C NMR (63 MHz): δ 162.9, 140.1, 135.7, 130.0, 129.0 (2 C), 126.1, 124.2, 113.5, 25.7. MS (ESI): *m/z* = 267 and 269 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{10}H_7BrN_2O_2]^+$ 265.9691 and 267.9670 found 265.9721 and 267.9681.

7-Bromo-2-methylquinolin-8-amine

To a solution of 7-bromo-2-methyl-8-nitroquinoline (1.8 g, 6.6 mmol, 1.0 eq) in EtOAc (34 mL), $SnCl_2$ (3.76 g, 20 mmol, 3.0 eq) was added and the mixture was stirred at 50 °C for 12 h. The crude was then dissolved in a saturated aqueous solution of $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure to afford the product as a red solid (2 g, quant.). The quinoline was used without further purification. ^{1}H NMR (250 MHz): δ 7.44 (1H, d, *J* = 8.9 Hz), 7.12 (1H, d, *J* = 8.9 Hz), 6.79 (1H, d, *J* = 8.9 Hz), 6.56 (1H, d, *J* = 8.9 Hz), 5.14 (2H, br), 2.37 (3H, s). ^{13}C NMR (63 MHz): δ 156.5, 141.2, 137.3, 135.7, 129.1, 125.3, 121.9, 115.5, 104.0, 24.9. MS (ESI): *m/z* = 237 and 239 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{10}H_9BrN_2+H]^+$ 236.9900 and 238.9900, found 237.0027 and 239.0005.

7-Bromo-8-(dimethylamino)quinaldine (19)

7-Bromo-2-methylquinolin-8-amine (2 g, 8.4 mmol, 1.0 eq) was dissolved in DMF (14 mL). K_2CO_3 (3.5 g, 25 mmol, 3.0 eq) and CH_3I (1.6 mL, 3.6 g, 25 mmol, 3.0 eq) were added to the mixture. The reaction was stirred at room temperature for 3 days. The crude was filtered and the solid was solubilized in DCM, dried over Na_2SO_4 and concentrated under reduced pressure to provide the compound as a brown solid (1.4 g, 63%).^{1}H NMR (250 MHz): δ 7.93 (1H, d, *J* = 7.8 Hz), 7.60 (1H, d, *J* = 8.5 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.20 (1H, d, *J* = 7.8 Hz), 3.16 (6H, s), 2.72 (3H, s). ^{13}C NMR (63 MHz): δ 157.4, 148.1, 147.3, 136.4, 130.3, 127.3, 124.7, 124.2, 121.5, 44.4, 25.7. MS (ESI): *m/z* = 265 and 267 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{13}BrN_2+H]^+$ 265.0300 and 267.0300, found 265.0200 found 267.0300.

8-(Dimethylamino)-2-methylquinoline-7-carbonitrile (20)

7-Bromo-8-*N*,*N*-(dimethylamino)-quinaldine **19** (265 mg, 1.0 mmol) and CuCN (152 mg, 1.7 mmol) were dissolved in DMF (1.0 mL). The mixture was heated at 170 °C for 12 h. After cooling down to room temperature, the crude product was poured on a solution of ice and water. The solid was solubilized in ethylene diamine and extracted with toluene. The organic phase was washed twice with KCN 10%, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The quinoline was obtained as a brown solid (172 mg, 81%). ^{1}H NMR (500 MHz): δ 7.89 (1H, d, *J* = 8.3 Hz), 7.35 (1H, d, *J* = 8.3 Hz), 7.29 (1H, d, *J* = 8.3 Hz), 7.20 (1H, d, *J* = 8.3 Hz), 3.39 (6H, s), 2.70 (3H, s).^{13}C NMR (125 MHz): δ 157.2, 154.5, 146.3, 136.3, 129.9, 128.6, 123.6, 120.2, 120.1, 101.3, 45.3, 25.5. MS (ESI): *m/z* = 212 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{13}N_3+H]^+$ 212.1100 and 213.1100, found 212.1186 and 213.1220.

Methyl 8-(dimethylamino)-2-methylquinoline-7-carboxylate

8-(Dimethylamino)-2-methylquinoline-7-carbonitrile **20** (154 mg, 0.07 mmol, 1.0 eq) was dissolved in MeOH (8 mL). H_2SO_4 (cc, 5 mL) and H_2O (12 drops) were then added and the mixture was heated at 75 °C for 7 days. The crude product was neutralized with NaOH (2 M) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the quinaldine as a dark oil (80 mg, 45%). ^{1}H NMR (250 MHz): δ 7.93 (1H, d, *J* = 8.5 Hz), 7.51 (1H, d, *J* = 8.5 Hz), 7.30 (1H, d, *J* = 8.5 Hz), 7.25 (1H, d, *J* = 8.5 Hz), 3.95 (3H, s), 3.19 (6H, s), 2.74 (3H, s). ^{13}C NMR (63 MHz): δ 169.7, 157.2, 149.8, 144.8, 136.4, 129.0, 126.2, 124.3, 122.7, 120.6, 52.3, 44.8, 25.9. MS (ESI): *m/z* = 245 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}N_2O_2+H]^+$ 245.1200 and 246.1200, found 245.1284 and 246.1318.

Methyl 8-(dimethylamino)-2-formylquinoline-7-carboxylate

To a solution of methyl 8-(dimethylamino)-2-methylquinoline-7-carboxylate (80 mg, 0.3 mmol, 1.0 eq) in dioxane (1.7 mL), selenium dioxide (48 mg, 0.4 mmol, 1.3 eq) was added and the mixture was heated at 80 °C for 3 h. After cooling to room temperature, the solution was filtered on celite and concentrated under reduced pressure. The compound was obtained as an orange solid (89 mg, quant.). ^{1}H NMR (500 MHz): δ 10.17 (1H, s), 8.17 (1H, d, *J* = 8.9 Hz), 7.99 (1H, d, *J* = 8.9 Hz), 7.72 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 3.96 (3H, s), 3.27 (6H, s). ^{13}C NMR (125 MHz): δ 193.4, 168.8, 151.1, 150.5, 144.7, 137.6, 133.2, 130.7, 123.1, 119.2, 118.3, 52.5, 45.2. MS (ESI): *m/z* = 259 $[M+H]^+$, HRMS (ESI): *m/z* calcd for $[C_{14}H_{14}N_2O_3+H]^+$ 259.1000 and 260.1000, found 259.1082 and 260.1116.

Methyl 8-(dimethylamino)-2-(hydroxymethyl)quinoline-7-carboxylate (21)

Methyl 8-(dimethylamino)-2-formylquinoline-7-carboxylate (89 mg, 0.3 mmol, 1.0 eq) was dissolved in MeOH (1.7 mL). $NaBH_4$ (26 mg, 0.7 mmol, 2.0 eq) was then added and the mixture was stirred at 0 °C for 30 min. The crude product was then neutralized with HCl (1 M) and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained as a yellow solid (73 mg, 82%). ^{1}H NMR (250 MHz): δ 8.05 (1H, d, *J* = 8.5 Hz), 7.58 (1H, d, *J* = 8.5 Hz), 7.36 (1H, d, *J* = 8.5 Hz), 7.27 (1H, d, *J* = 8.5 Hz), 4.90 (2H, s), 3.96 (3H, s), 3.17 (6H, s). ^{13}C NMR (63 MHz): δ 169.3, 157.4, 149.3, 143.7, 137.4, 130.3, 127.1, 125.3, 120.9, 119.2, 64.2, 52.5, 44.8. MS (ESI): *m/z* = 261 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}N_2O_3+H]^+$ 261.1200, found 261.1228.

8-(Dimethylamino)-2-(hydroxymethyl)quinoline-7-carboxylic acid (22)

Methyl 8-(dimethylamino)-2-(hydroxymethyl)quinoline-7-carboxylate **21** (15 mg, 0.06 mmol, 1.0 eq) was dissolved in MeOH (394 μL). NaOH (2 M, 200 μL) was added and the mixture

was then stirred at room temperature for 2 days. The crude product was neutralized with HCl (1 M), filtered and concentrated under reduced pressure. The product was obtained as a yellow solid (7 mg, 49%). ^{1}H NMR (500 MHz): δ 8.43 (1H, d, *J* = 8.7 Hz), 8.26 (1H, d, *J* = 8.7 Hz), 7.87 (1H, d, *J* = 8.7 Hz), 7.54 (1H, d, *J* = 8.7 Hz), 5.02 (2H, s), 3.34 (6H, s). ^{13}C NMR (125 MHz): δ 167.6, 160.2, 145.3, 143.1, 138.1, 131.4, 128.1, 127.8, 127.7, 120.4, 64.0, 44.3. MS (ESI): *m/z* = 247 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{14}N_2O_3+H]^+$ 247.1000 and 248.1000, found 247.1081 and 248.1115.

2-(Acetoxymethyl)-8-(dimethylamino)quinoline-7-carboxylic acid (23)

8-(Dimethylamino)-2-(hydroxymethyl)quinoline-7-carboxylic acid **22** (11 mg, 0.05 mmol, 1.0 eq) was solubilized in DCM (225 µL). Acetic anhydride (6.3 µL, 6.8 mg, 0.07 mmol, 1.5 eq), triethylamine (9.5 µL, 4.5 mg, 0.05 mmol, 1.5 eq) and DMAP (cat.) were added to the mixture. The yellow solution was stirred at room temperature for 1 h, concentrated under reduced pressure and purified by chromatography on silica gel (DCM /MeOH: 98/2). The carboxylic acid was obtained as a yellow solid (12 mg, 92%). ^{1}H NMR (250 MHz): δ 8.43 (1H, d, *J* = 8.2 Hz), 8.26 (1H, d, *J* = 8.2 Hz), 7.85 (1H, d, *J* = 8.2 Hz), 7.57 (1H, d, *J* = 8.2 Hz), 5.44 (2H, s), 3.32 (6H, s), 2.23 (3H, s). ^{13}C NMR (63 MHz): δ 170.6, 167.7, 156.2, 145.5, 143.5, 138.0 (2 C), 131.2, 127.9 (2 C), 120.9, 67.0, 44.1, 21.0. MS (ESI): *m/z* = 289 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{15}H_{16}N_2O_4-H]^-$ 287.1100, found 287.1016.

3. SYNTHESIS OF C5 BRANCHED ANALOGS

3.1 Synthesis of the 5-Acryl-8-DMAQ Acetate (**27**)

(*E*)-*tert*-Butyl 3-(8-(dimethylamino)-2-methylquinolin-5-yl)acrylate (24)

In a suspension of 5-bromo-8-(dimethylamino)-2-methylquinolin (250 mg) and K_2CO_3 in dimethyl acetamide (DMA, 10 ml) were added $Pd(OAc)_2$ (28 mg), $P(tBu)_3$ (4 ml) and *tert*-butyl acrylate (0.4 ml). The tube was sealed, and the reaction was stirred at 80 °C overnight, then cooled to rt, filtered through a pad of Celite and concentrated. The product was obtained after purification on silica gel using cyclohexane/AcOEt gradient eluent mixture. Amorphous brown solid (62%). ^{1}H NMR (250 MHz): δ 1.57 (s, 9H), 2.76 (s, 3H), 3.16 (s, 6H), 6.37 (d, *J*= 16.1 Hz, 1H), 7.00 (d, *J*= 8.1 Hz, 1H), 7.30 (d, *J*= 9.7 Hz, 1H), 7.67 (d, *J*= 8.1 Hz, 1H), 8.26 (d, *J*= 16.1 Hz, 1H), 8.38 (d, *J*= 9.7 Hz, 1H).^{13}C NMR (63 MHz): δ 25.4, 28.3, 44.2, 80.2, 114.4, 119.4, 121.9, 123.2, 124.9, 126.0, 131.9, 139.2, 141.4, 151.4, 155.8, 166.6. MS (ESI): *m/z* = 313 ($[M+H]^+$), HRMS (ESI): *m/z* calcd for $[C_{19}H_{25}O_2N_2]^+$ 313.1911, found 313.1911.

(*E*)-*tert*-Butyl 3-(8-(dimethylamino)-2-formylquinolin-5-yl)acrylate

To a solution of **24** (78 mg) in dioxane (3 ml) SeO_2 (57 mg) is introduced. The reaction is stirred at 80 °C for 3 h then filtered through Celite and concentrated under reduced pressure. The

product is obtained after purification on silica gel using cyclohexane/AcOEt gradient eluent mixture. Orange amorphous solid (55%). ^{1}H NMR (250 MHz): δ 1.59 (s, 9H), 3.34 (s, 6H), 6.40 (d, *J*= 16.1 Hz, 1H), 7.09 (d, *J*= 8.1 Hz, 1H), 7.88 (d, *J*= 8.1 Hz, 1H), 8.07 (d, *J*= 9 Hz, 1H), 8.27 (d, *J*= 16.1 Hz, 1H), 8.66 (d, *J*= 9 Hz, 1H), 10.22 (s, 1H). ^{13}C NMR (63 MHz): δ 28.3, 44.4, 80.6, 114.4, 117.5, 120.3, 122.4, 128.8, 130.2, 133.2, 138.4, 141.1, 149.3, 152.3, 166.4, 193.2. MS (ESI): *m/z* = 327 ($[M+H]^+$), HRMS (ESI): *m/z* calcd for $[C_{19}H_{22}O_3N_2 + H]^+$, 327.1700, found 327.1703.

(*E*)-*tert*-Butyl 3-(8-(dimethylamino)-2-(hydroxymethyl)quinolin-5-yl) acrylate (25)

To a solution of aldehyde (237 mg) in methanol (4 ml) $NaBH_4$ (57.6 mg) was added at 0 °C. The reaction was stirred at room temperature for 1h, then quenched with a drop of HCl (1 M), reduced to dryness and extracted with water/DCM. The product was obtained after purification on silica gel using cyclohexane/AcOEt gradient eluent mixture. Orange amorphous solid (76%).^{1}H NMR (250 MHz): δ 1.51 (s, 9H), 3.35 (s, 6H), 4.94 (s, 2H), 6.38 (d, *J*= 15.7 Hz, 1H), 7.44 (d, *J*= 9 Hz, 1H), 7.74 (m, *m,* 2H), 8.13 (d, *J*= 15.7 Hz, 1H), 8.42 (d, *J*= 8.7 Hz, 1H). ^{13}C NMR (63 MHz): δ 28.2, 45.7, 64.7, 81.0, 118.6, 119.9, 123.3, 125.0, 126.5, 129.4, 132.9, 137.8, 139.3, 144.5, 160.1, 165.8. MS (ESI): *m/z* = 329 ($[M+H]^+$), HRMS (ESI): *m/z* calcd for $[C_{19}H_{25}O_3N_2]^+$ 329.1860, found 329.1867.

(*E*)-tert-Butyl 3-(2-(acetoxymethyl)-8-(dimethylamino)quinolin-5-yl)acrylate (26)

25 (12 mg) was acylated in DCM (250 µl) with Ac_2O (5.7 µl) in the presence of Et_3N (9 µl) and a catalytic amount of DMAP. The mixture was stirred at room temperature for 1 hour then concentrated and the crude purified on silica gel using cyclohexane/AcOEt gradient eluent mixture. Yellow amorphous solid (88%). ^{1}H NMR (250 MHz): δ 1.58 (s, 9H), 2.22 (s, 3H), 3.21 (s, 6H), 5.44 (s, 2H), 6.39 (d, *J*= 15.6 Hz, 1H), 7.05 (d, *J*= 8.3 Hz, 1H), 7.52 (d, *J*= 8.7 Hz, 1H), 7.76 (d, *J*= 8.7 Hz, 1H), 8.28 (d, *J*= 15.6 Hz, 1H), 8.55 (d, *J*= 8.3 Hz, 1H). ^{13}C NMR (63 MHz): δ 21.0, 28.3, 44.3, 67.4, 80.4, 114.6, 119.3, 119.8, 123.0, 126.0, 127.3, 132.9, 139.0, 141.1, 151.6, 153.0, 166.6, 170.7. MS (ESI): *m/z* = 371 ($[M+H]^+$), HRMS (ESI): *m/z* calcd for $[C_{21}H_{27}O_4N_2]^+$ 371,1965 found 371.1963.

(*E*)-3-(2-(Acetoxymethyl)-8-(dimethylamino)quinolin-5-yl) acrylic acid (27)

26 (10 mg) was treated with HCl (4M in dioxane, 500 µl). The reaction was stirred under argon for 4 h, concentrated and purified under reverse phase HPLC. Yellow solid (94%). ^{1}H NMR (250 MHz): δ 2.25 (s, 3H), 3.51 (s, 6H), 5.53 (s, 2H), 6.73 (d, *J*= 15.7 Hz, 1H), 7.91 (d, *J*= 9.3 Hz, 1H), 8.15 (d, *J*= 6.6 Hz, 1H), 8.25 (d, *J*= 6.6 Hz, 1H), 8.46 (d, *J*= 15.7 Hz, 1H), 8.88 (d, *J*= 9.3 Hz, 1H). ^{13}C NMR (63 MHz): δ 20.7, 47.1, 67.7, 122.3, 122.9, 125.8, 126.3, 127.8, 135.5, 139.5, 140.1, 140.5, 140.6, 160.1, 169.2, 172.3. MS (ESI): *m/z* = 315 ($[M+H]^+$), HRMS (ESI): *m/z* calcd for $[C_{17}H_{19}O_4N_2]^+$ 315.1339 found 315.1344.

3.2 Synthesis of the 5-Benzoyl-8-DMAQ Acetate (**36**)

8-(Dimethylamino)quinoline-2-carbaldehyde

Selenium dioxide (190 mg, 1.7 mmol, 1.3 eq) in suspension in dioxane (10 mL) and water (0.1 mL) was heated at 80 °C for 30 min. 8-(dimethylamino)quinaldine **7** (250 mg, 1.34 mmol, 1.0 eq) was then introduced and the mixture was vigorously stirred at 80 °C for 3 h. After cooling to room temperature, the mixture was filtered on Celite, eluted with DCM and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (DCM /Cyclohexane: 1/1) and the compound was obtained as a red dark oil (245 mg, 90%). ^{1}H NMR (250 MHz): δ 10.24 (1H, s), 8.24 (1H, d, *J* = 8.5 Hz), 8.00 (1H, d, *J* = 8.5 Hz), 7.56 (1H, t, *J* = 8.5 Hz), 7.40 (1H, d, *J* = 8.5 Hz), 7.14 (1H, d, *J* = 8.5 Hz), 3.22 (6H, s). ^{13}C NMR (63 MHz): δ 193.8, 151.1, 149.9, 142.0, 137.7, 131.9, 129.8, 119.8, 117.0, 115.8, 44.6. MS (APCI): *m/z* = 201 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{12}N_2O + H]^+$ 201.1028, found 201.1027.

5-Bromo-8-(dimethylamino)quinoline-2-carbaldehyde

To a solution of 8-(dimethylamino)quinoline-2-carbaldehyde (800 mg, 4.0 mmol, 1.0 eq) in chloroform (20 mL), was added recrystallized *N*-bromosuccinimide (570 mg, 3.2 mmol, 0.8 eq), the mixture was stirred at room temperature for 3 h. The mixture was then washed with a solution of $Na_2S_2O_3$ and extracted with DCM. The organic layer was washed twice with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The compound was obtained as a yellow solid and used without further purification (1.0 g, 90%). ^{1}H NMR (250 MHz): δ 10.23 (1H, s), 8.60 (1H, d, *J* = 8.2 Hz), 8.05 (1H, d, *J* = 8.2 Hz), 7.77 (1H, d, *J* = 8.2 Hz), 6.96 (1H, d, *J* = 8.2 Hz), 3.20 (6H, s). ^{13}C NMR (63 MHz): δ 192.9, 150.8, 149.8, 142.3, 137.2, 133.1, 130.0, 117.9, 115.8, 111.5, 44.4. MS (ESI): *m/z* = 279.1, 281 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{11}BrN_2O+H]^+$ 279.0100 and 281.0100, found 279.0135 and 281.0114.

(5-Bromo-8-(dimethylamino)quinolin-2-yl)methanol (28)

5-Bromo-8-(dimethylamino)quinoline-2-carbaldehyde (1.0 g, 3.6 mmol, 1.0 eq) was dissolved in MeOH (18 mL). $NaBH_4$ (271 mg, 7.2 mmol, 2.0 eq) was then added and the mixture was stirred at 0 °C for 30 min. The crude product was then neutralized with HCl (1 M) and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained as a yellow solid (830 mg, 82%). ^{1}H NMR (250 MHz): δ 8.46 (1H, d, *J* = 8.8 Hz), 7.65 (1H, d, *J* = 8.8 Hz), 7.38 (1H, d, *J* = 8.8 Hz), 6.96 (1H, d, *J* = 8.5 Hz), 4.95 (2H, s), 3.09 (6H, s). ^{13}C NMR (63 MHz): δ 157.8, 149.3, 141.5, 136.4, 129.7, 127.4, 119.1, 116.1, 112.9, 64.7, 44.3. MS (ESI): *m/z* = 281, 283 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{13}BrN_2O+H]^+$ 281.0200 and 283.0200, found 281.0289 and 283.0268.

5-Bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-dimethylquinolin-8-amine (29)

A solution of the (5-bromo-8-(dimethylamino)quinolin-2-yl)methanol **28** (777 mg, 2.8 mmol, 1.0 eq), TBSCl (833 mg, 5.5 mmol, 2.0 eq) and imidazole (374 mg, 5.5 mmol, 2.0 eq) in DMF (5 mL) was stirred at room temperature overnight, then the solvent was removed under reduced pressure. CH_2Cl_2 was added and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The compound was obtained as a brown oil (1.1 g, quant.) and was used without further purification. ^{1}H NMR (250 MHz) δ 8.50 (1H, d, *J* = 8.8 Hz), 7.76 (1H, d, *J* = 8.8 Hz), 7.61 (1H, d, *J* = 7.8 Hz), 6.91 (1H, d, *J* = 7.8 Hz), 5.06 (2H, s), 3.06 (6H, s), 0.98 (9H, s), 0.14 (6H, s). ^{13}C NMR (63 MHz): δ 159.7, 149.6, 142.1, 136.3, 129.4, 127.3, 119.1, 115.6, 112.9, 66.6, 44.3, 25.8, 18.2, -5.4. MS (ESI): *m/z* = 395, 397 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{18}H_{27}BrN_2OSi+H]^+$ 395.1149 and 397.1149, found 395.1142 and 397.1120.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*,*N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-8-amine (31)

To a solution of 5-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N,N*-dimethylquinolin-8-amine **29** (200 mg, 0.5 mmol, 1.0 eq) in dry Et_3N (510 µL) and dry THF (2.55 mL), $Pd(PPh_3)_4$ (18 mg, 0.02 mmol, 0.03 eq) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane **30** (82 µL, 0.6 mmol, 1.1 eq) were added. The mixture was heated at 100°C overnight in a sealed tube under argon, and then was filtered through silica gel and concentrated under reduced pressure. The product was obtained as a yellow oil (250 mg, quant.). ^{1}H NMR (250 MHz) δ 9.12 (1H, d, *J* = 9.1 Hz), 7.99 (1H, d, *J* = 7.6 Hz), 7.69 (1H, d, *J* = 9.1 Hz), 7.02 (1H, d, *J* = 7.6 Hz), 5.03 (2H, s), 3.13 (6H, s), 1.39 (12H, s), 0.98 (9H, s), 0.14 (6H, s). ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.2, 152.8, 141.1, 137.7, 136.5, 132.7, 128.5, 118.4, 114.7, 83.4, 67.1, 44.4, 26.0, 25.0, 18.4, -5.2. MS (ESI): *m/z* = 443 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{24}H_{39}BN_2O_3Si+H]^+$ 443.2896, found 443.2885.

***tert*-Butyl-4-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-(dimethylamino)quinolin-5-yl)benzoate (33)**

A mixture of *tert*-butyl 4-bromobenzoate **32**[4] (65 mg, 0.03 mmol, 1.1 eq), the boronate **31** (102 mg, 0.02 mmol, 1.0 eq), $Pd(PPh_3)_4$ (13 mg, 0.01 mmol, 0.05 eq), 2M Na_2CO_3 (230 µL) and DME (1.2 mL) were heated to 80°C overnight under argon. The mixture was extracted in EtOAc and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (Cyclohexane/EtOAc: 9/1). The benzoate was obtained as a yellow oil (62 mg, 55%). ^{1}H NMR (250 MHz) δ 8.22 (1H, d, *J* = 8.0 Hz), 8.10 (2H, d, *J* = 8.0 Hz), 7.63 (1H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 7.35 (1H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 5.07 (2H, s), 3.13 (6H, s), 1.63

(4) (a) Egawa, T.; Hirabayashi, K.; Koide, Y.; Kobayashi, C.; Takahashi, N.; Mineno, T.; Terai, T.; Ueno, T.; Komatsu, T.; Ikegaya, Y.; Matsuki, N.; Nagano, T.; Hanaoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 3874; (b) Mineno, T.; Ueno, T.; Urano, Y.; Kojima, H.; Nagano T. *Org. Lett.* **2006**, *8*, 5963.

(9H, s), 0.97 (9H, s), 0.14 (6H, s). ^{13}C (125 MHz, $CDCl_3$) δ 165.8, 159.3, 150.0, 144.4, 141.6, 135.0, 132.0, 130.8, 130.1, 129.6, 126.9, 126.7, 118.4, 114.9, 81.1, 67.1, 44.7, 28.4, 26.1, 18.5, -5.2. MS (ESI): *m/z* = 493 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{29}H_{40}N_2O_3Si+H]^+$ 493.2881, found 493.2893.

tert-Butyl 4-(8-(dimethylamino)-2-(hydroxymethyl)quinolin-5-yl)benzoate (34)

To a solution of *tert*-butyl 4-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-(dimethylamino)quinolin-5-yl)benzoate **33** (61 mg, 0.1 mmol, 1.0 eq) in acetonitrile (620 µL), a solution of HF/pyridine (8 drops) was added. The mixture was stirred at room temperature for 1h and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The alcohol was obtained as a yellow solid (94 mg, quant.). ^{1}H NMR (250 MHz): δ 8.17 (1H, d, *J* = 8.1 Hz), 8.10 (2H, d, *J* = 8.4 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.25 (1H, d, *J* = 7.9 Hz), 7.18 (1H, d, *J* = 7.9 Hz), 4.94 (2H, s), 3.16 (6H, s), 1.64 (9H, s). ^{13}C NMR (63 MHz): δ 165.7, 156.6, 149.5, 144.2, 140.9, 135.4, 132.0, 130.9, 130.1, 129.7, 127.4, 127.0, 118.3, 115.5, 81.3, 64.6, 44.5, 28.4. MS (ESI): *m/z* = 379 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{23}H_{26}N_2O_3+H]^+$ 379.2016, found 379.2021.

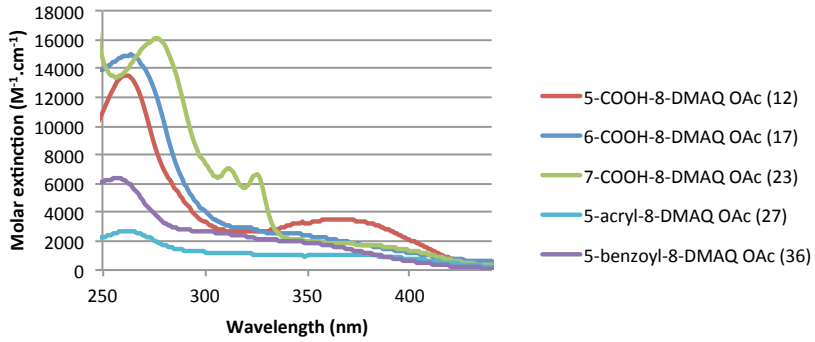
tert-Butyl-4-(2-(acetoxymethyl)-8-(dimethylamino)quinolin-5-yl)benzoate (35)

tert-Butyl 4-(8-(dimethylamino)-2-(hydroxymethyl)quinolin-5-yl)benzoate **34** (29 mg, 0.08 mmol, 1.0 eq) was solubilized in DCM (383 µL). Acetic anhydride (11 µL, 12 mg, 0.1 mmol, 1.5 eq), triethylamine (14 µL, 11 mg, 0.1 mmol, 1.5 eq) and DMAP (cat.) were added to the mixture. The yellow solution was stirred at room temperature for 1 h, concentrated under reduced pressure and purified by chromatography on silica gel (DCM /MeOH: 98/2). The compound was obtained as a yellow oil (13 mg, 40%). ^{1}H NMR (250 MHz): δ 8.20 (1H, d, *J* = 7.9 Hz), 8.09 (2H, d, *J* = 7.9 Hz), 7.48 (2H, d, *J* = 7.9 Hz), 7.39 (2H, d, *J* = 7.9 Hz), 7.14 (1H, d, *J* = 7.9 Hz), 5.45 (2H, s), 3.15 (6H, s), 2.19 (3H, s), 1.63 (9H, s). ^{13}C NMR (63 MHz): δ 170.8, 165.8, 153.4, 150.1, 144.2, 141.8, 135.4, 131.7, 130.9, 130.1, 129.7, 127.7, 127.0, 119.1, 115.2, 81.3, 67.8, 44.6, 28.4, 21.1. MS (ESI): *m/z* = 421 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_2O_4+H]^+$ 421.2122, found 421.2123.

4-(2-(Acetoxymethyl)-8-(dimethylamino)quinolin-5-yl)benzoic acid (36)

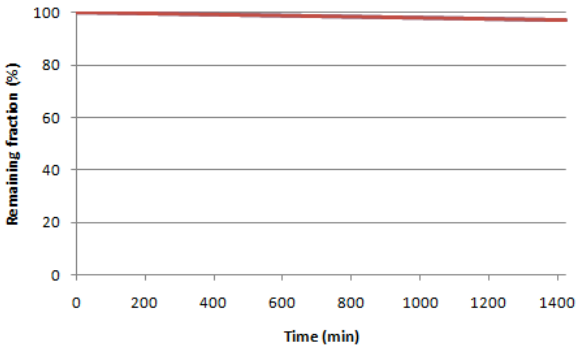
tert-Butyl 4-(2-(acetoxymethyl)-8-(dimethylamino)quinolin-5-yl)benzoate **35** (13 mg, 0.03 mmol, 1.0 eq) was dissolved in a solution of HCl in dioxane (4 M, 1 mL). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The benzoic acid **36** was obtained as an orange solid (11 mg, quant.). ^{1}H NMR (250 MHz): δ 8.29 (1H, d, *J* = 8.1Hz), 8.07 (2H, d, *J* = 8.1 Hz), 7.52-7.41 (4H, m), 7.31 (1H, d, *J* = 8.1Hz) 5.42 (2H, s), 3.08 (6H, s), 2.19 (3H, s). ^{13}C NMR (63 MHz): δ 172.5, 160.1, 155.3, 150.6, 142.9, 136.8, 135.3, 134.8, 130.5 (2C), 128.6, 128.2, 120.2, 117.2, 68.1, 45.0, 20.8. MS (ESI): *m/z* = 365 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{21}H_{20}N_2O_4+H]^+$ 365.1500, found 365.1496.

4. ABSORPTION SPECTRA OF **12, 17, 23, 27** AND **36,** IN ACETONITRILE/TRIS BUFFER (20 MM) 1/1 AT 293 K

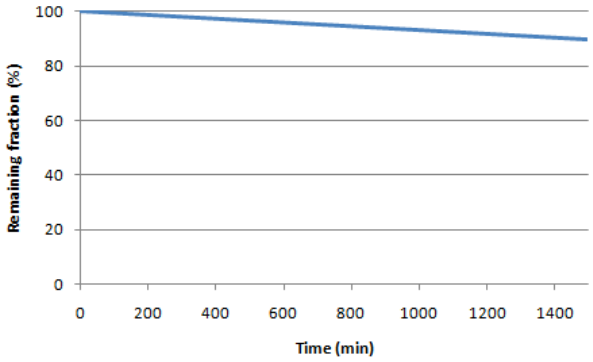


5. DARK HYDROLYSIS

5.1 The dark Hydrolysis of **36** in Acetonitrile/TRIS Buffer (20 mM) 1/1 at 293 K

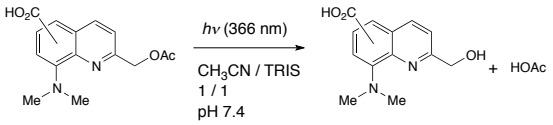


5.2 The dark hydrolysis of **36** in TRIS buffer (20 mM) at 293 K



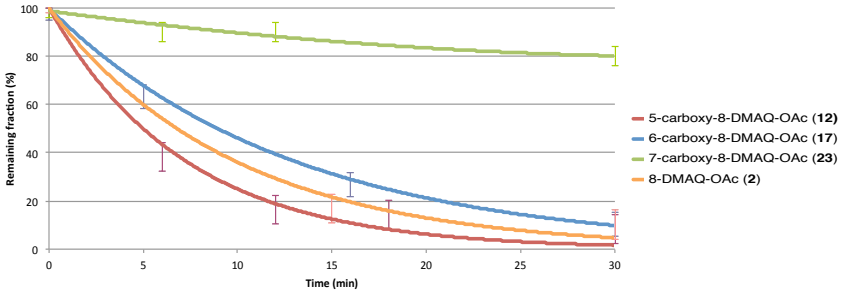
6. UV PHOTOLYSIS

6.1 The Photolysis of **12, 17** and **23** in Acetonitrile/TRIS Buffer (20 mM) 1/1 at 293 K Compared to 8-DMAQ-OAc at 366 nm with the Calculated Time Course Determined by HPLC[5]

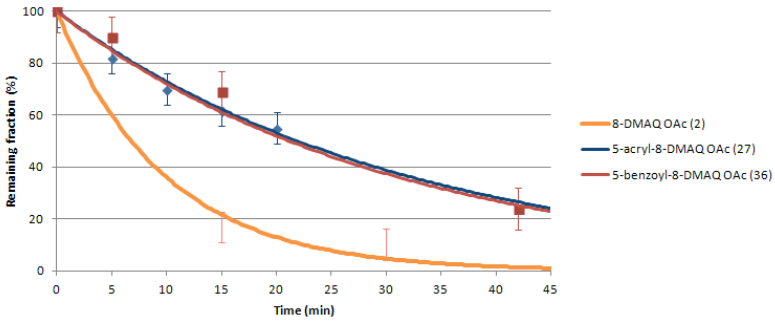


5-carboxy-8-DMAQ-OAc (**12**)
6-carboxy-8-DMAQ-OAc (**17**)
7-carboxy-8-DMAQ-OAc (**23**)

5-carboxy-8-DMAQ-OH (**11**)
6-carboxy-8-DMAQ-OH (**16**)
7-carboxy-8-DMAQ-OH (**22**)



6.2 The Photolysis of **27** and **36**, in Acetonitrile/TRIS Buffer (20 mM) 1/1 at 293 K Compared to 8-DMAQ-OAc at 366 nm with the Calculated Time Course Determined by HPLC

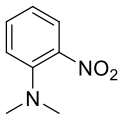


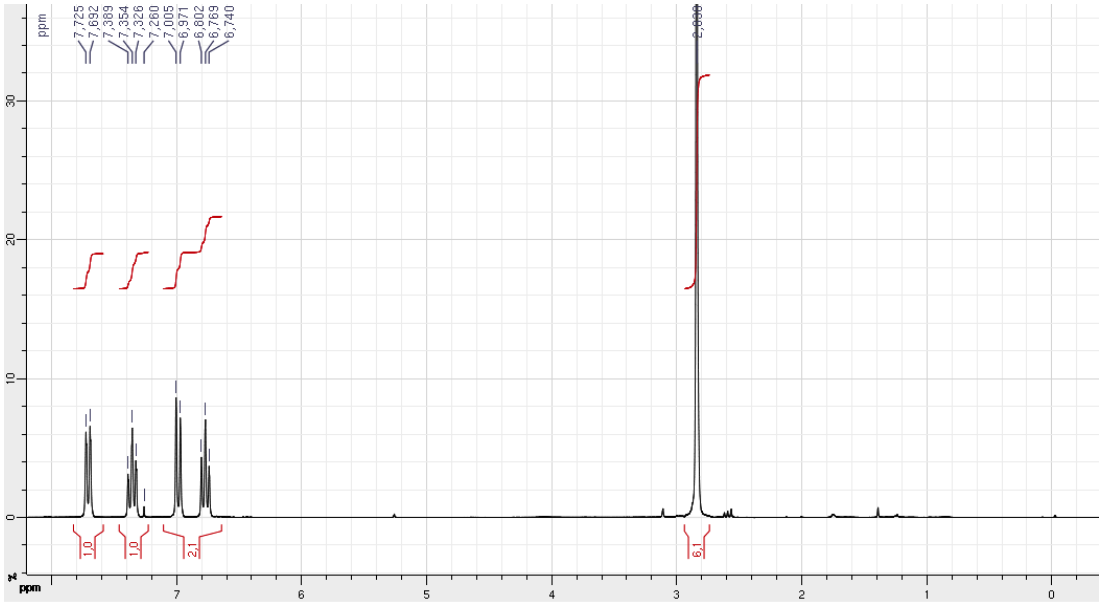
5 The calculated curves take into account the the background hydrolysis.

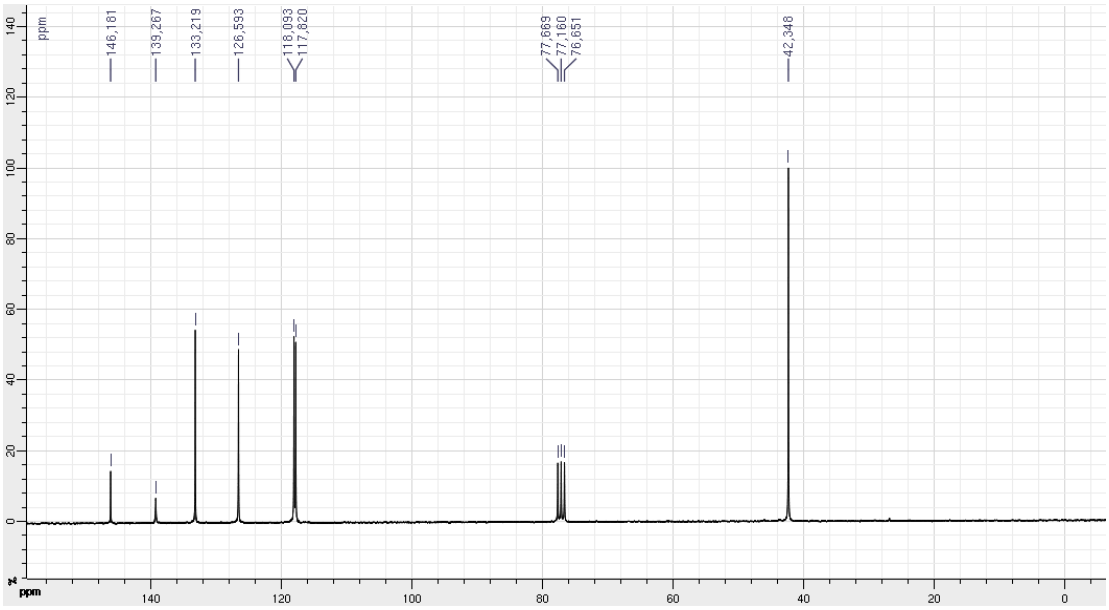
7. TP PHOTOLYSIS OF CARBOXY-8-DMAQ ACETATES **12**, **27** AND **36**

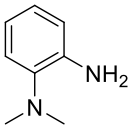
Two-photon uncaging cross-sections (δ_u) values of 5-carboxy-8-DMAQ acetate, **12**, 5-acrylate-8-DMAQ acetate, **27** and 5-benzoyl-8-DMAQ acetate, **36** were measured directly from the fractional conversion of the acetate to the free carbinol. No quantitative analysis of the liberated acetate was made. A 45 µl volume was irradiated in a 3 mm pathlength quartz cuvettes by the beam of a TiS mode-locked laser (MaiTai BB; SpectraPhysics) at 730 nm wavelength with 100 fs pulses at 86 MHz. The expanded beam was focused with a 50 mm fl lens so that the whole of the excitation volume was contained in the cuvette. Samples were irradiated for 2-4 hours at 100 mW average power. The loss of the cage was measured by HPLC and the photolysis cross-sections calculated from the rate of reduction of the fractional cage concentration at the laser beam parameters given above. It was seen, that the 5-carboxy-8-DMAQ acetate **12** had δ_u = 0.11 GM (10^{-50} cm^4s/photon) photolysis cross-section, **27** had δ_u = 0.25 GM photolysis cross-section and **36** had δ_u = 2.0 GM photolysis cross-section, respectively.

8. ^{1}H AND ^{13}C NMR SPECTRA





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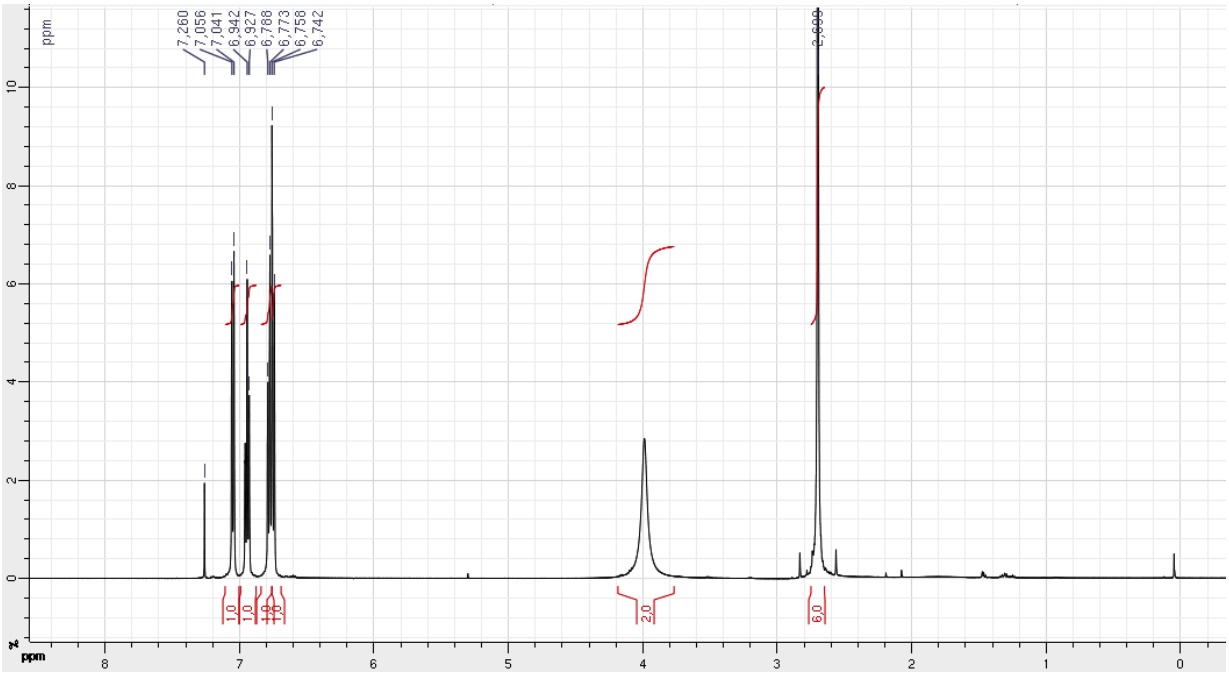
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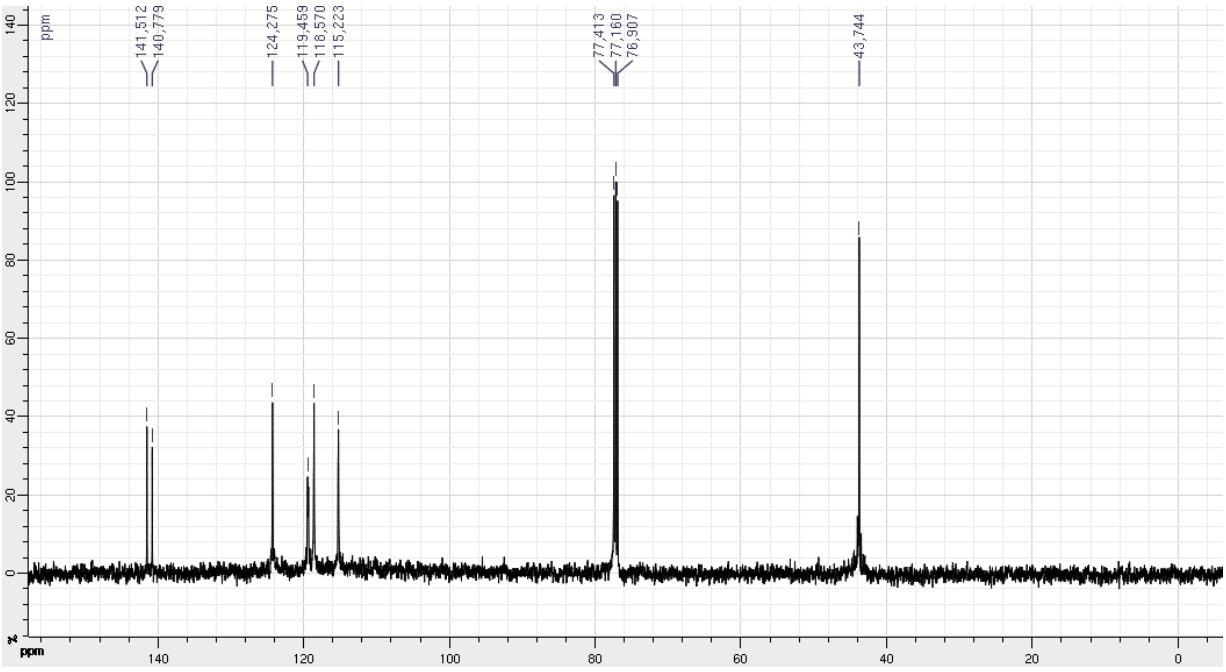
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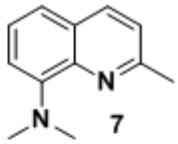
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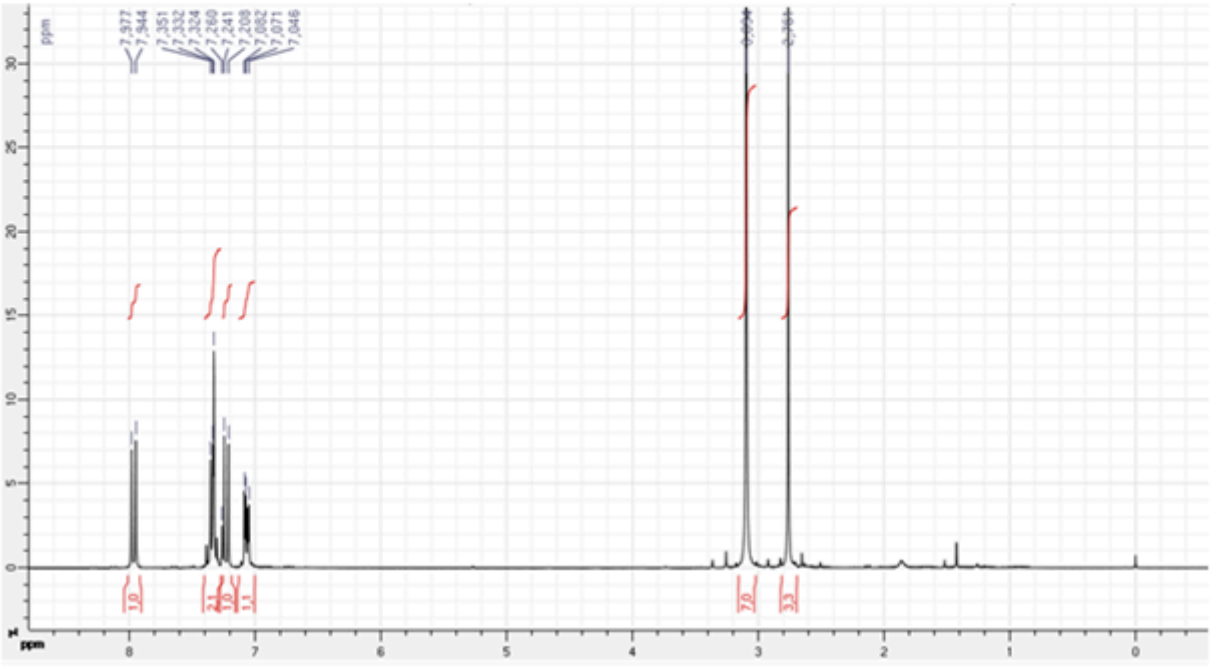
N

7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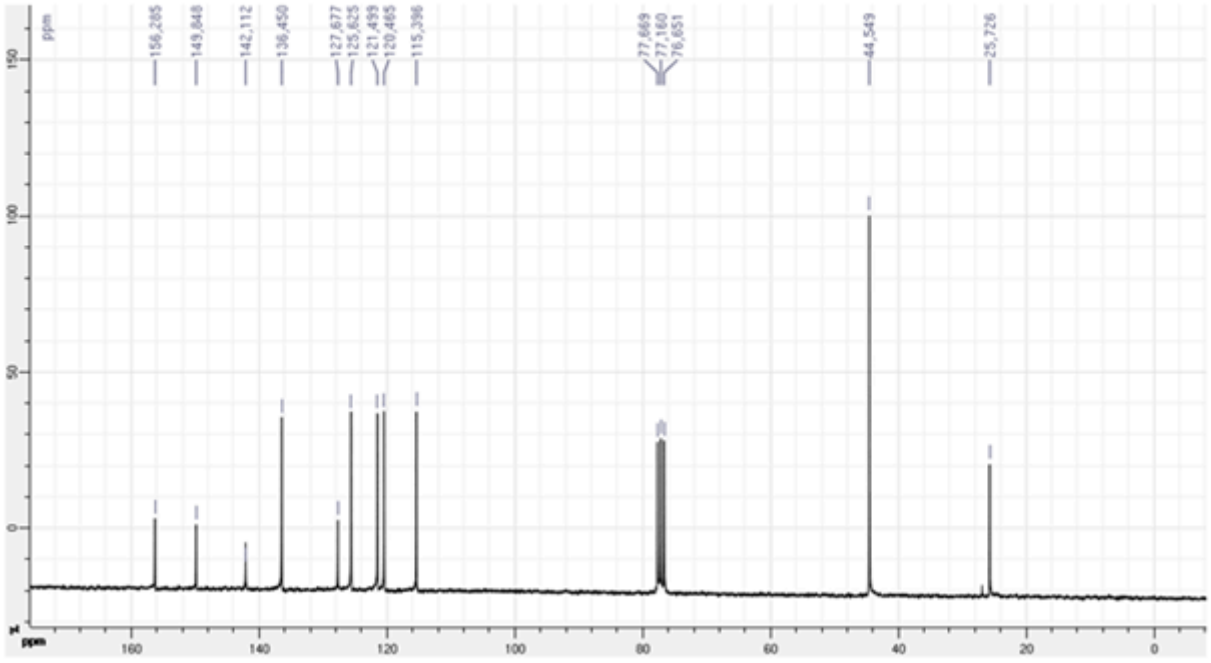
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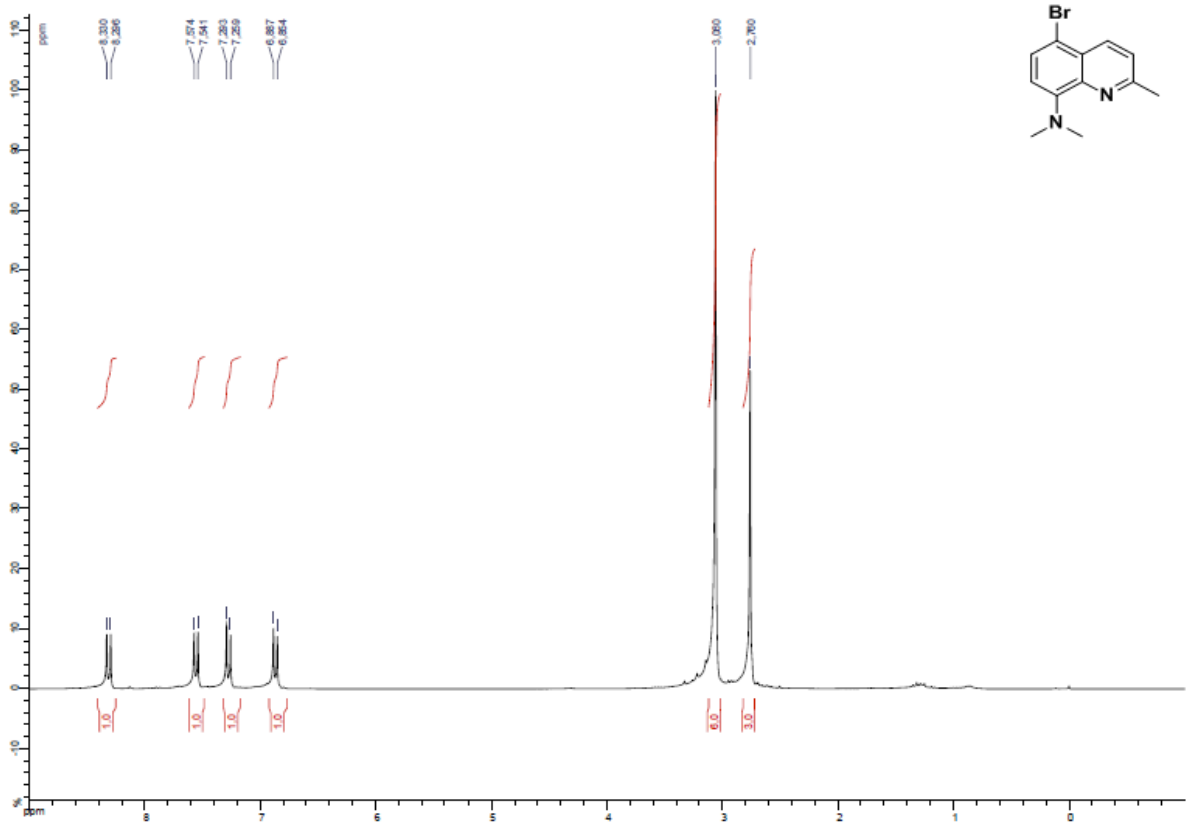
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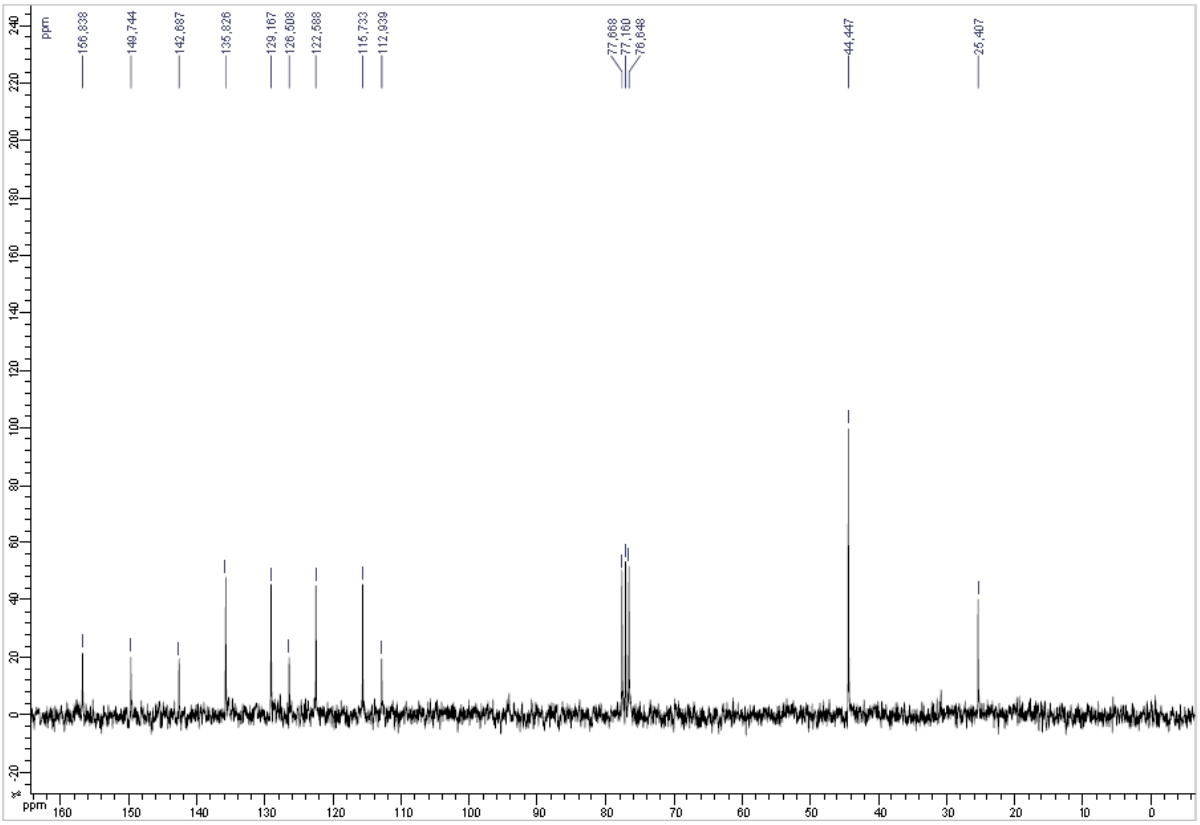
3.0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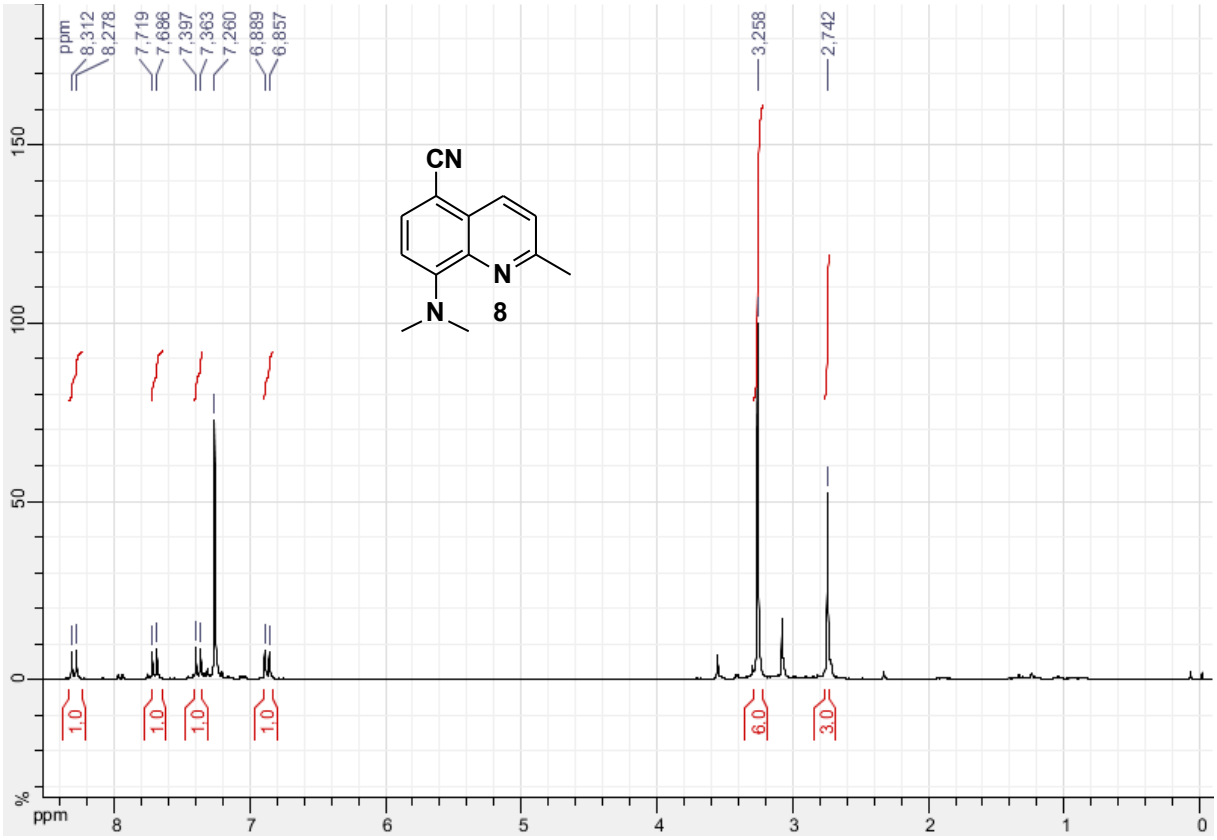
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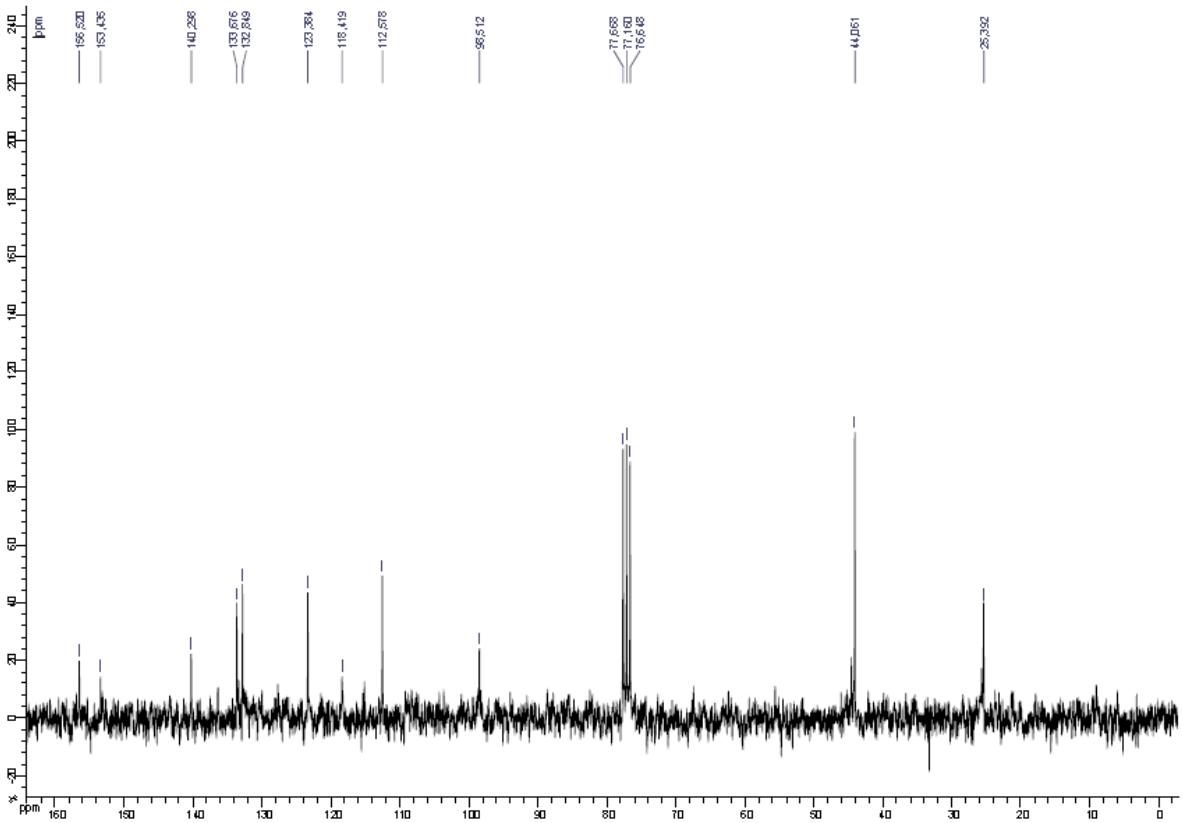
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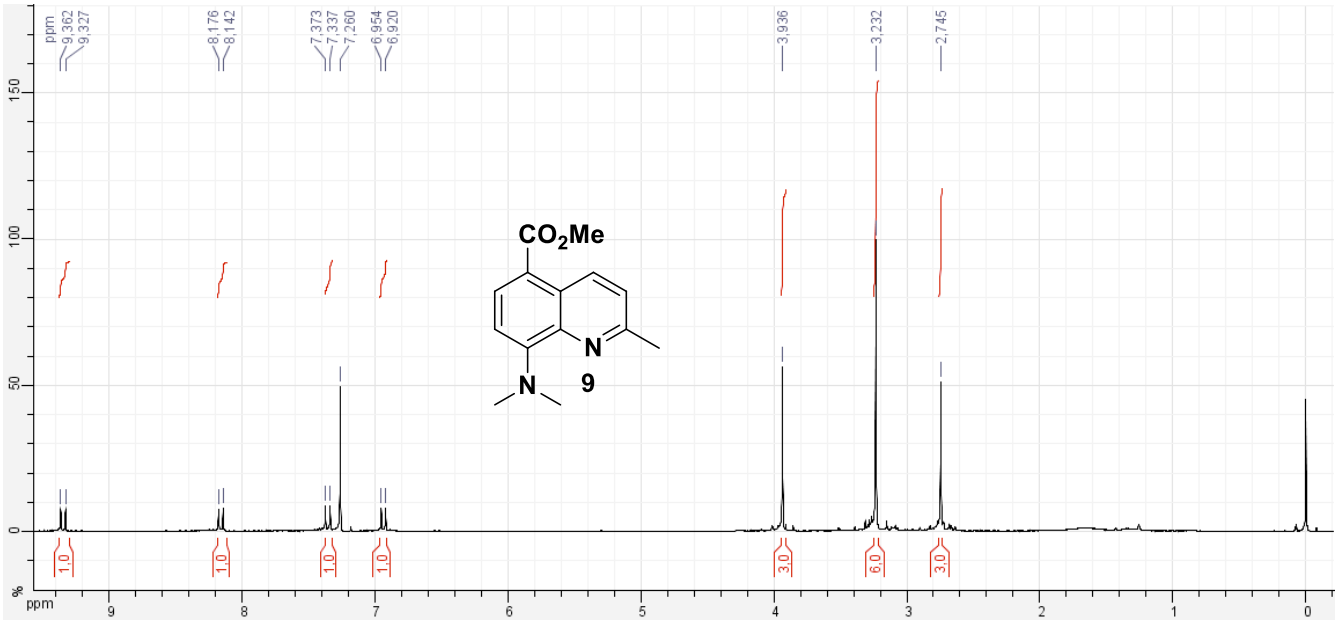
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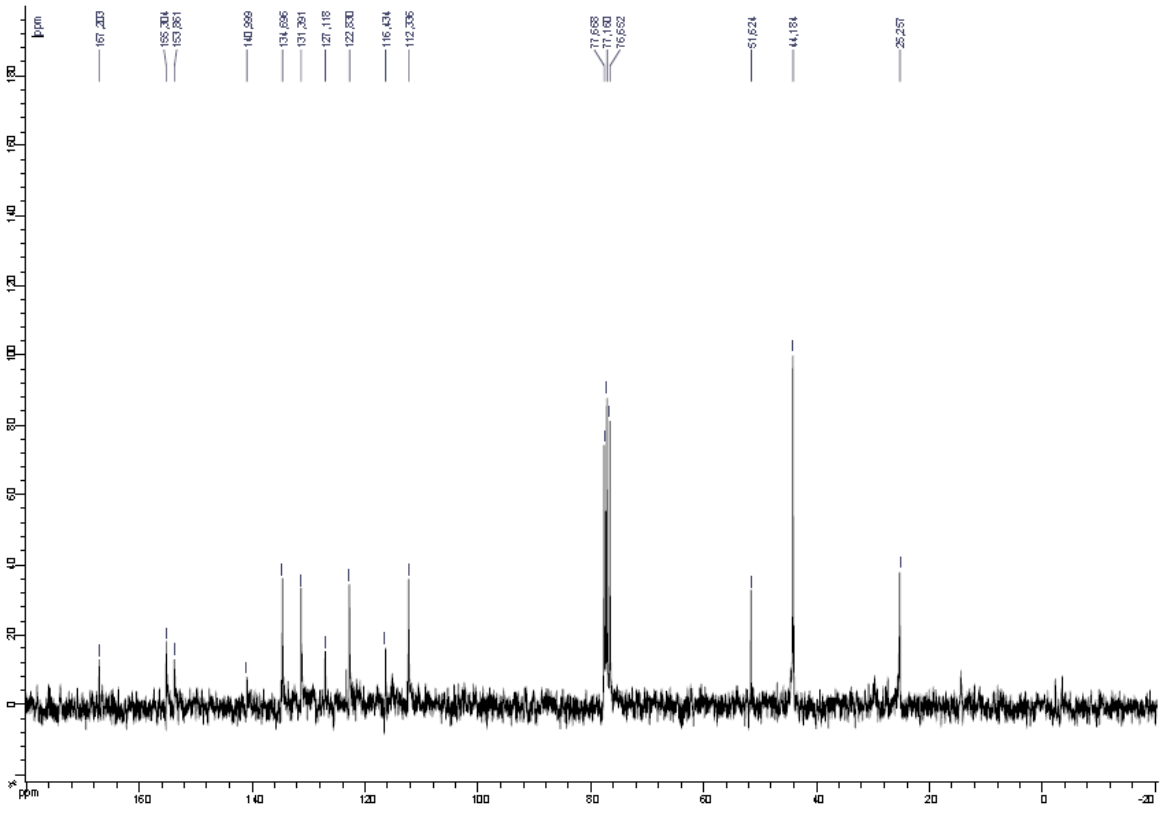
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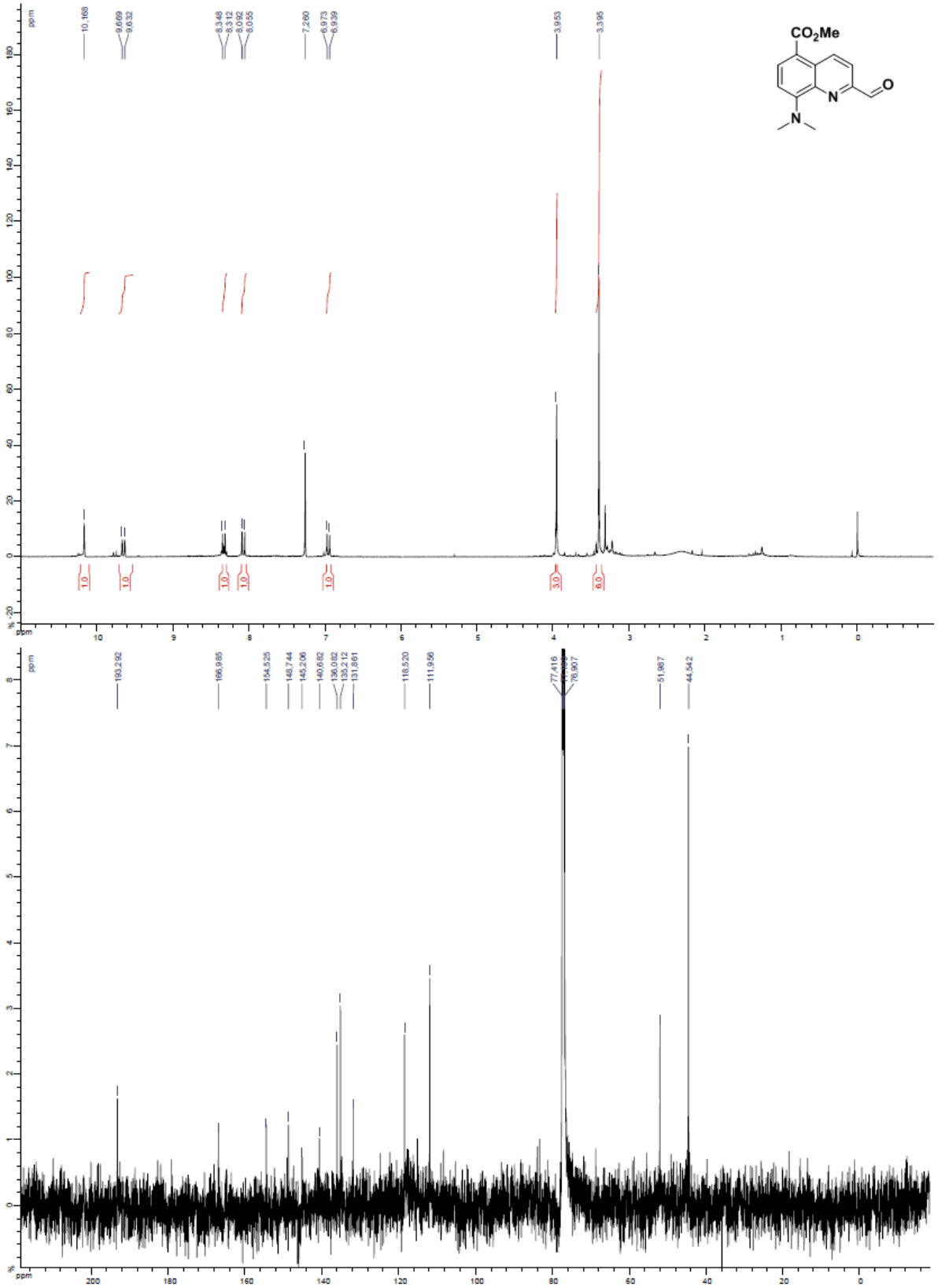
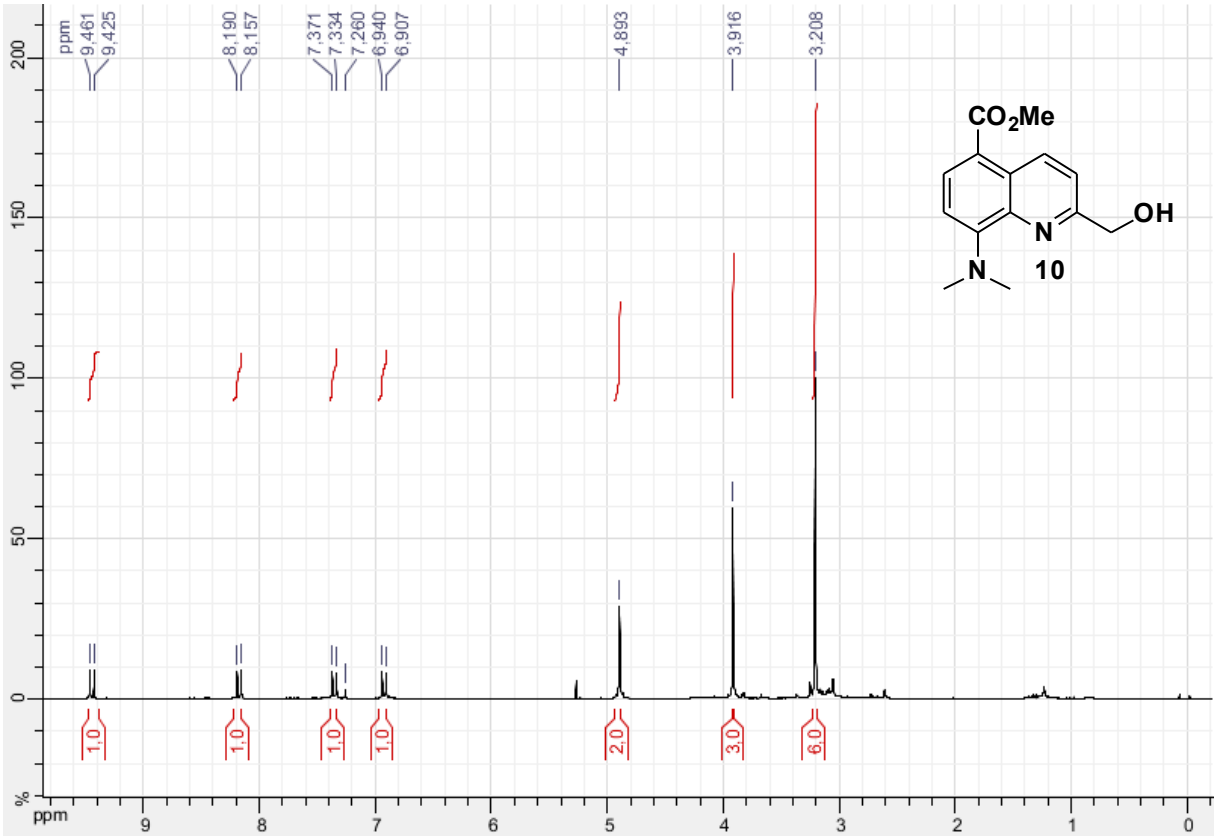
25.257


10.168
9.669
9.632
8.348
8.311
8.092
8.055
7.260
6.973
6.939
3.953
3.395
CO2Me
O
N
N
193.292
166.985
154.525
148.744
145.206
140.682
136.082
135.212
131.861
118.520
111.996
77.416
77.000
76.907
51.987
44.542
ppm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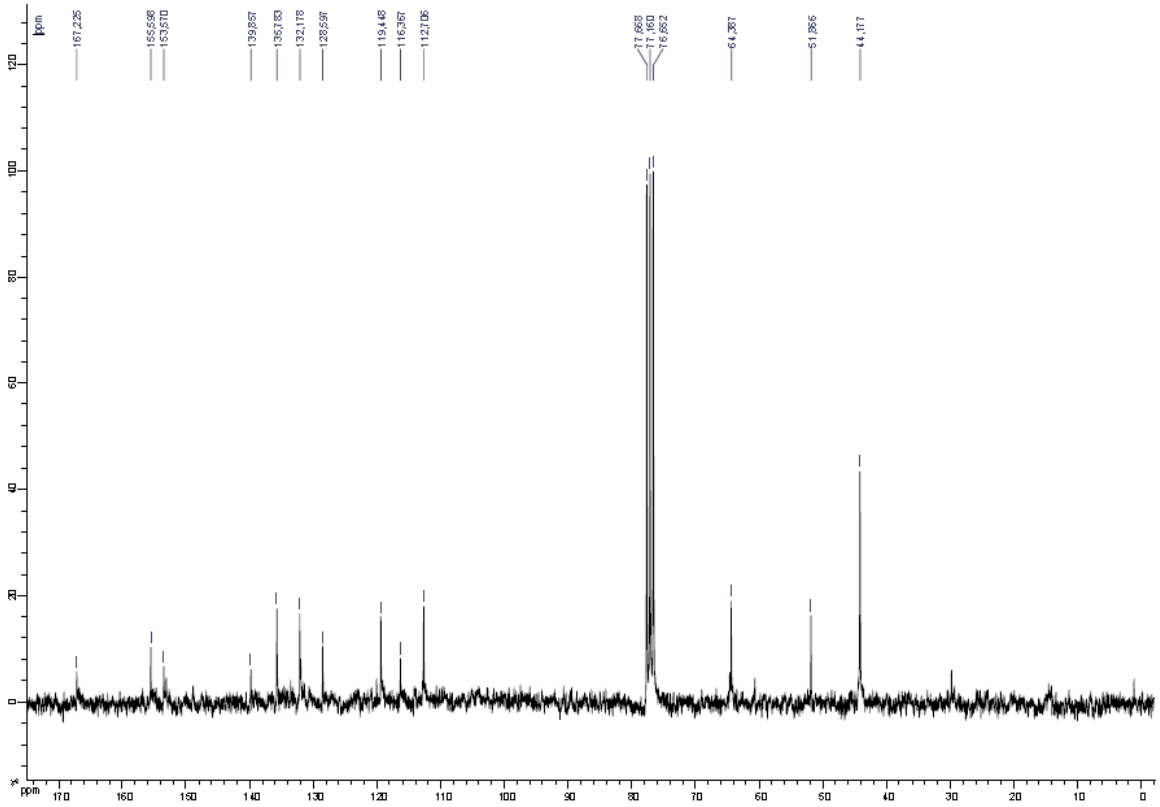
9,461
9,425
8,190
8,157
7,371
7,334
7,260
6,940
6,907
4,893
3,916
3,208
CO2Me
OH
N
N
10
1,0
1,0
1,0
1,0
2,0
3,0
6,0


ppm
167,225
155,598
153,570
139,857
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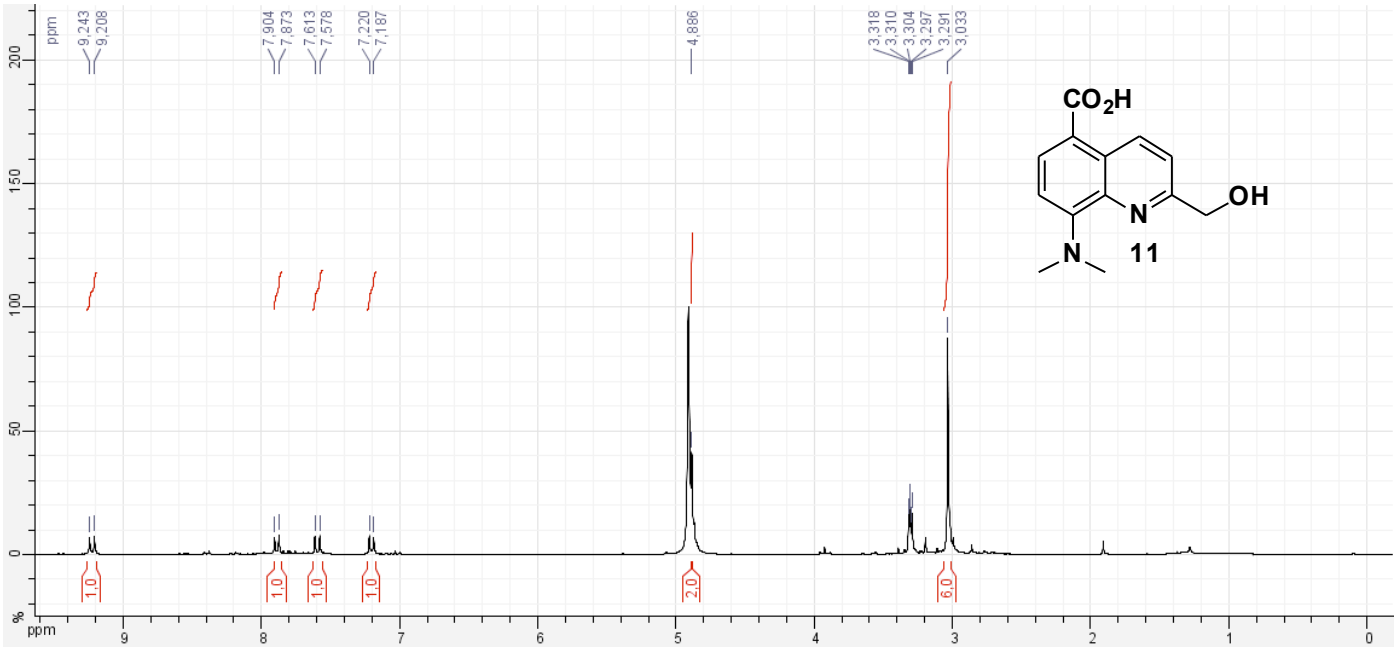
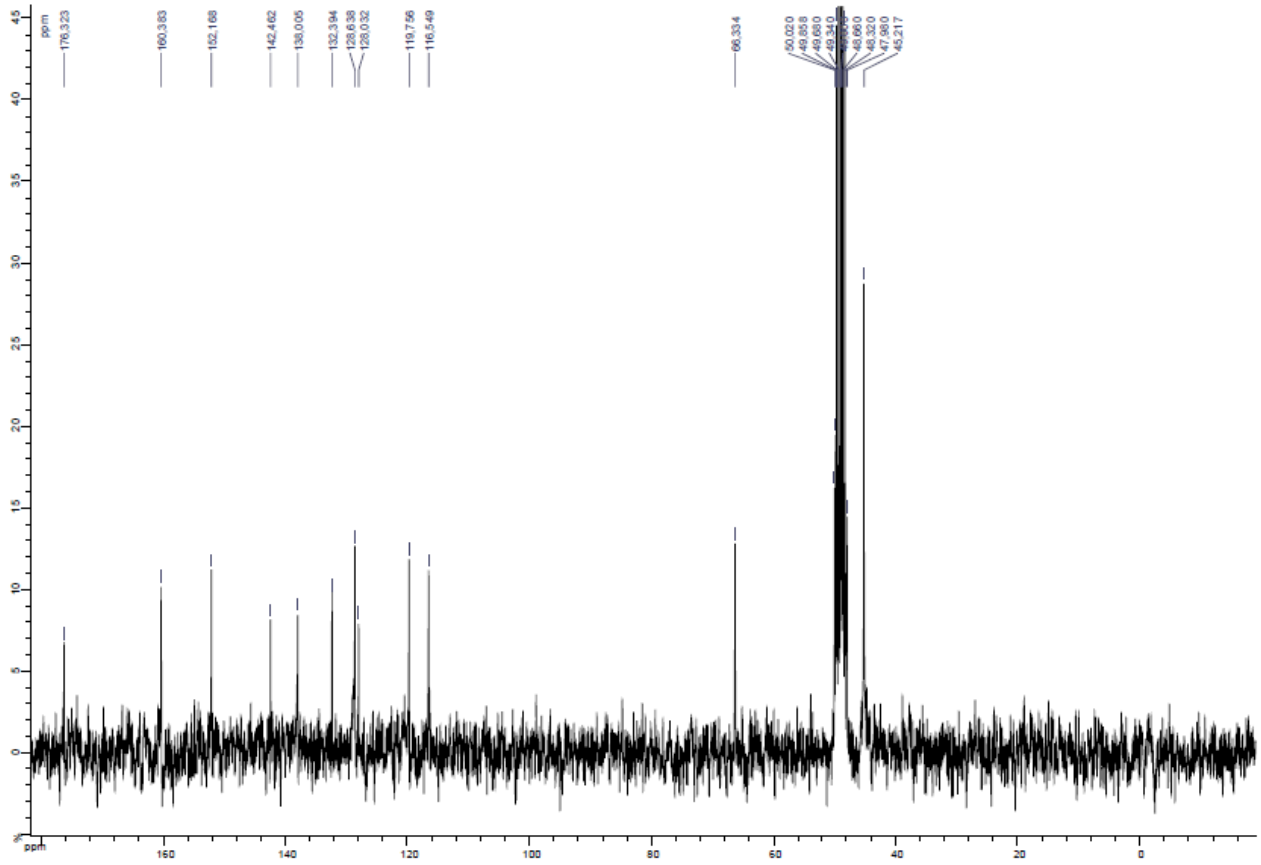
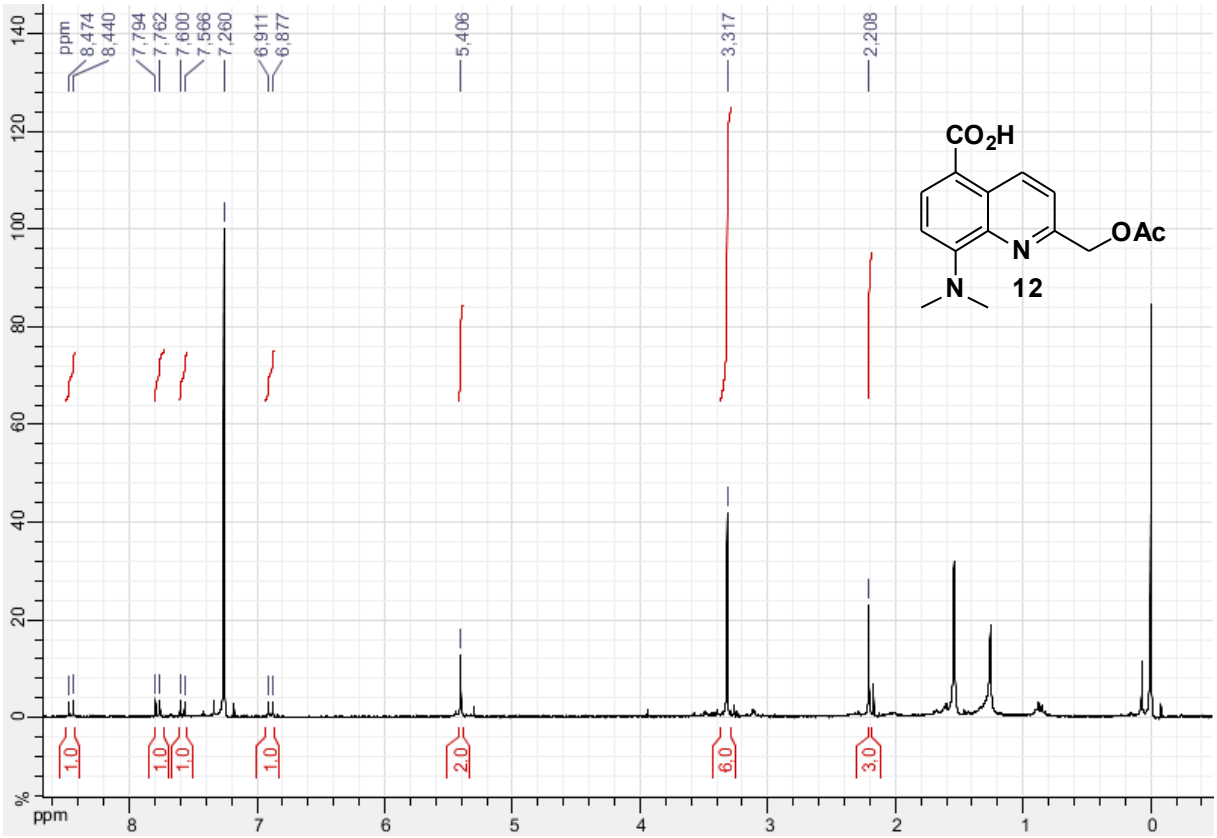
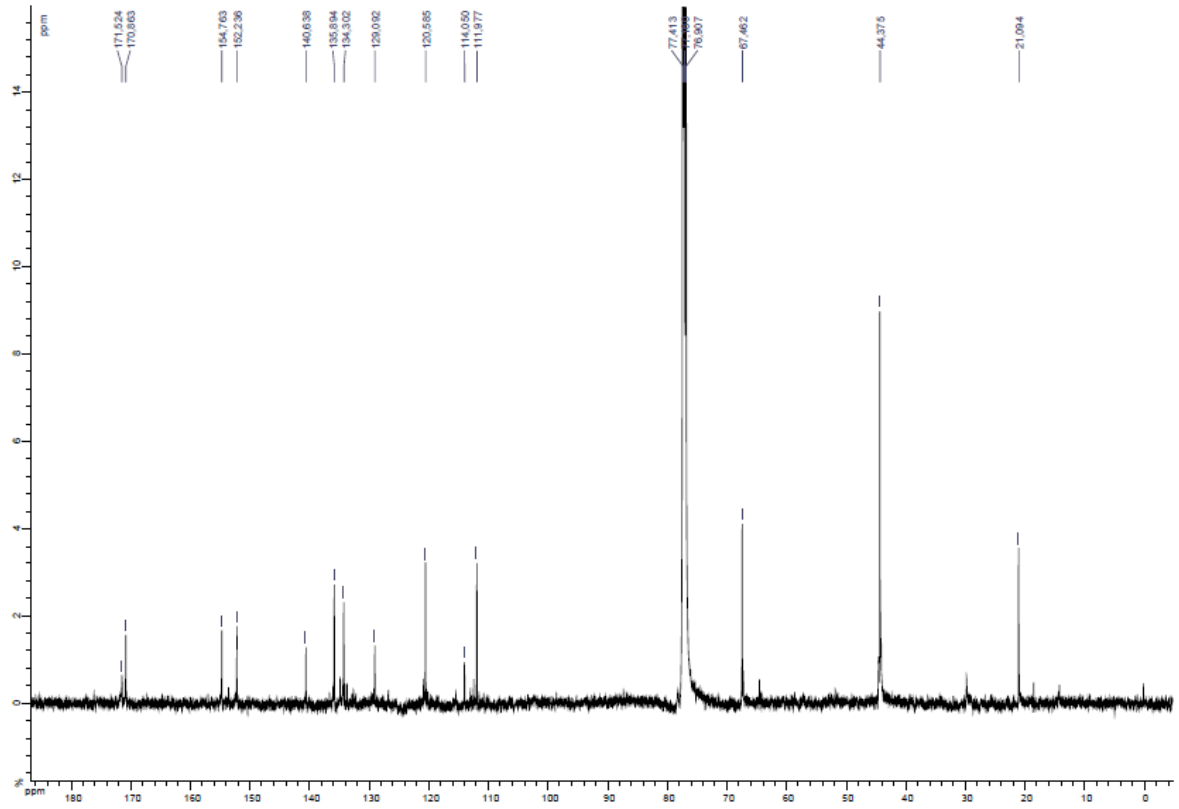
132,178
128,597
119,448
116,367
112,705
77,668
77,160
76,652
64,387
51,866
44,177


ppm
9.243
9.208
7.904
7.873
7.613
7.578
7.220
7.187
4.886
3.318
3.310
3.304
3.297
3.291
3.033
1.0
1.0
1.0
1.0
2.0
6.0
CO2H
OH
N
N
11


ppm
176.323
160.383
152.168
142.462
138.005
132.394
128.638
128.032
119.756
116.549
66.334
50.020
49.858
49.680
49.340
48.660
48.320
47.980
45.217


ppm
8.474
8.440
7.794
7.762
7.600
7.566
7.260
6.911
6.877
5.406
3.317
2.208
CO2H
OAc
N
N
12
1.0
1.0
1.0
1.0
2.0
6.0
3.0


ppm
171.524
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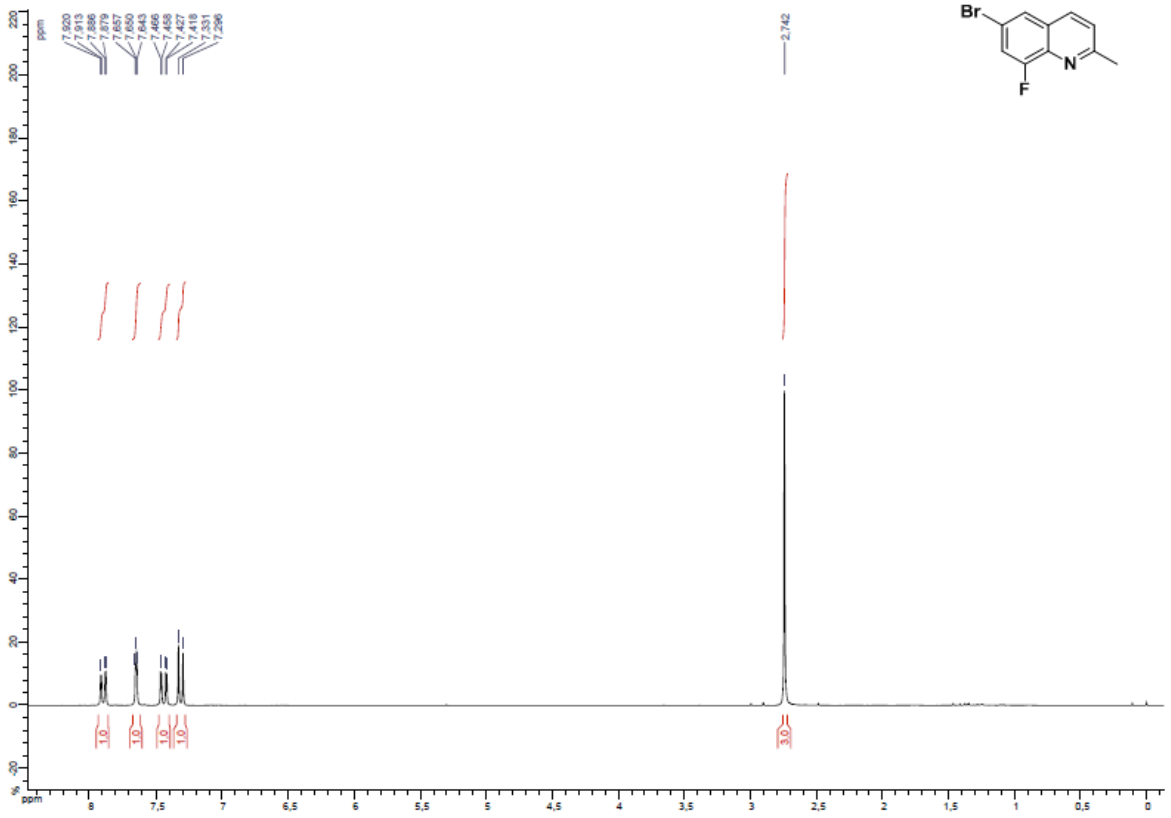
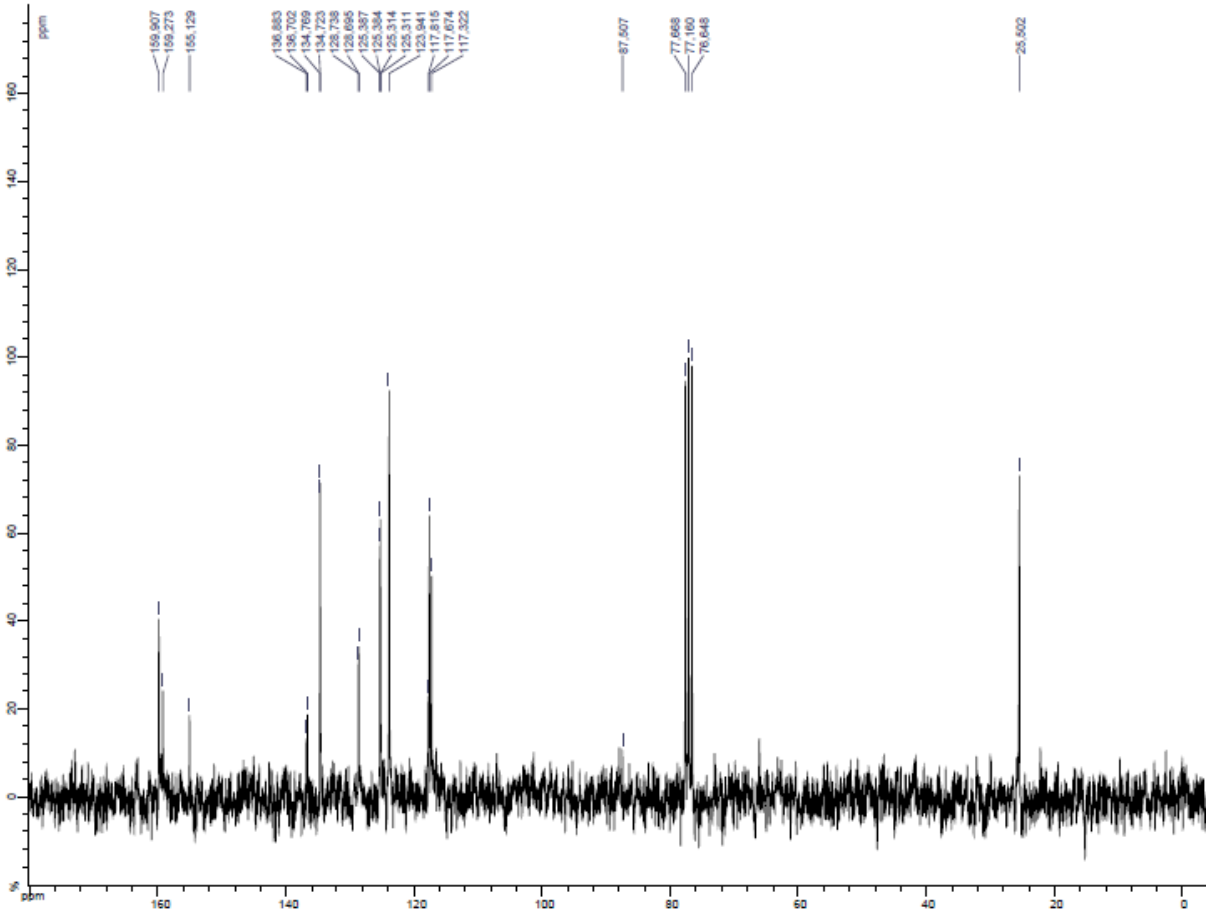
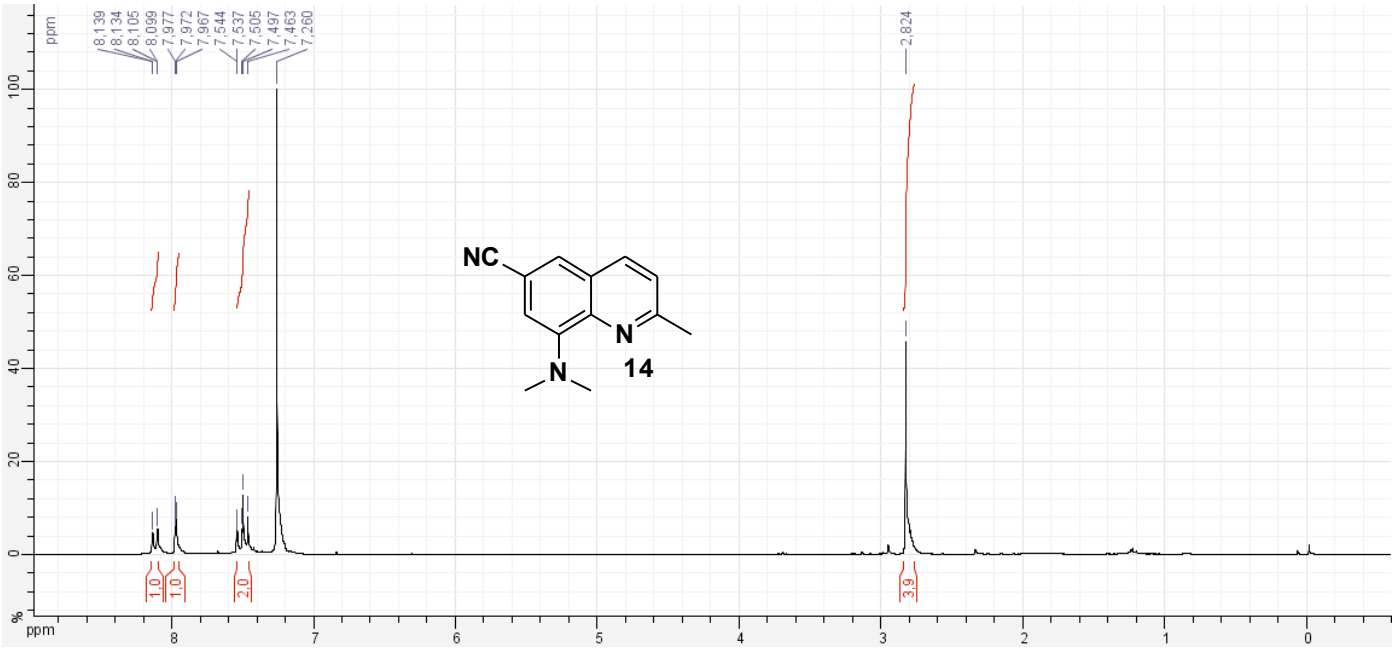
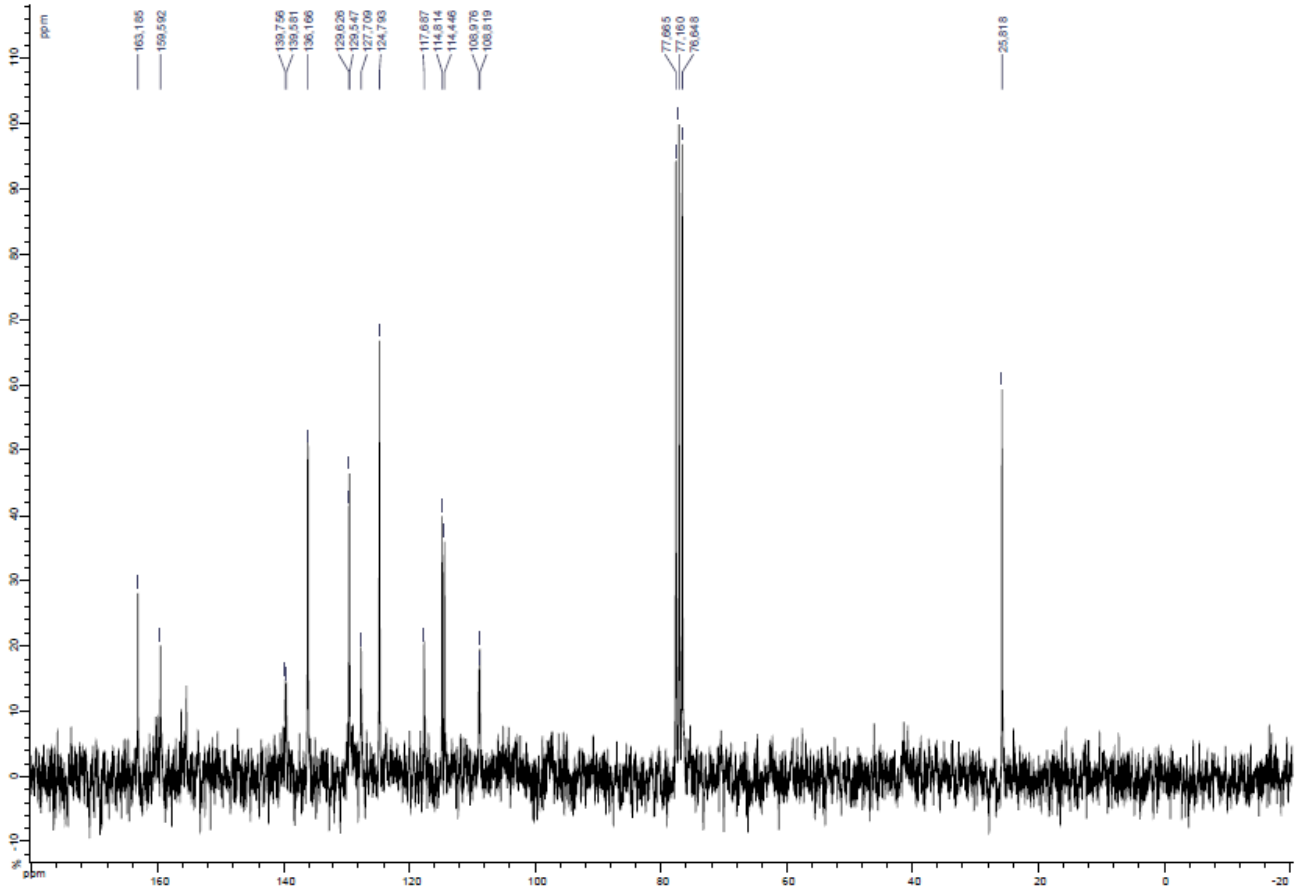
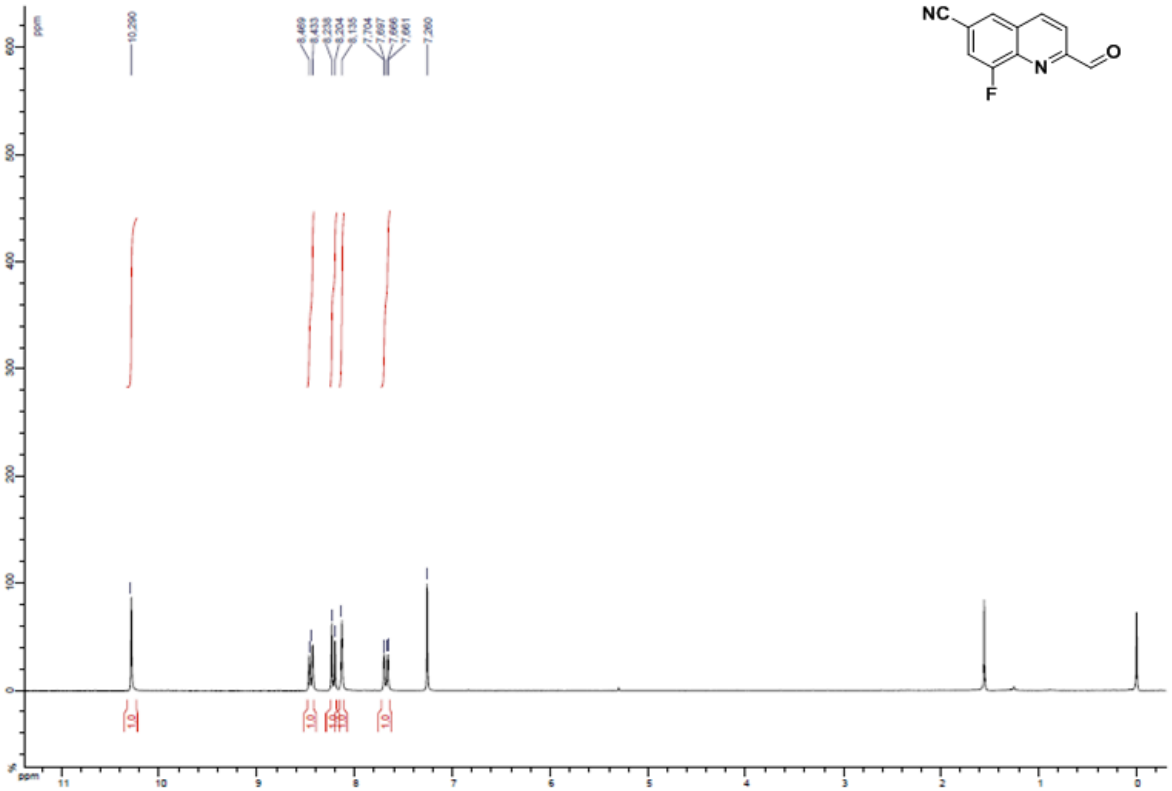
154.763
152.236
140.638
135.894
134.302
129.092
120.585
114.050
111.977
77.413
76.907
67.462
44.375
21.094

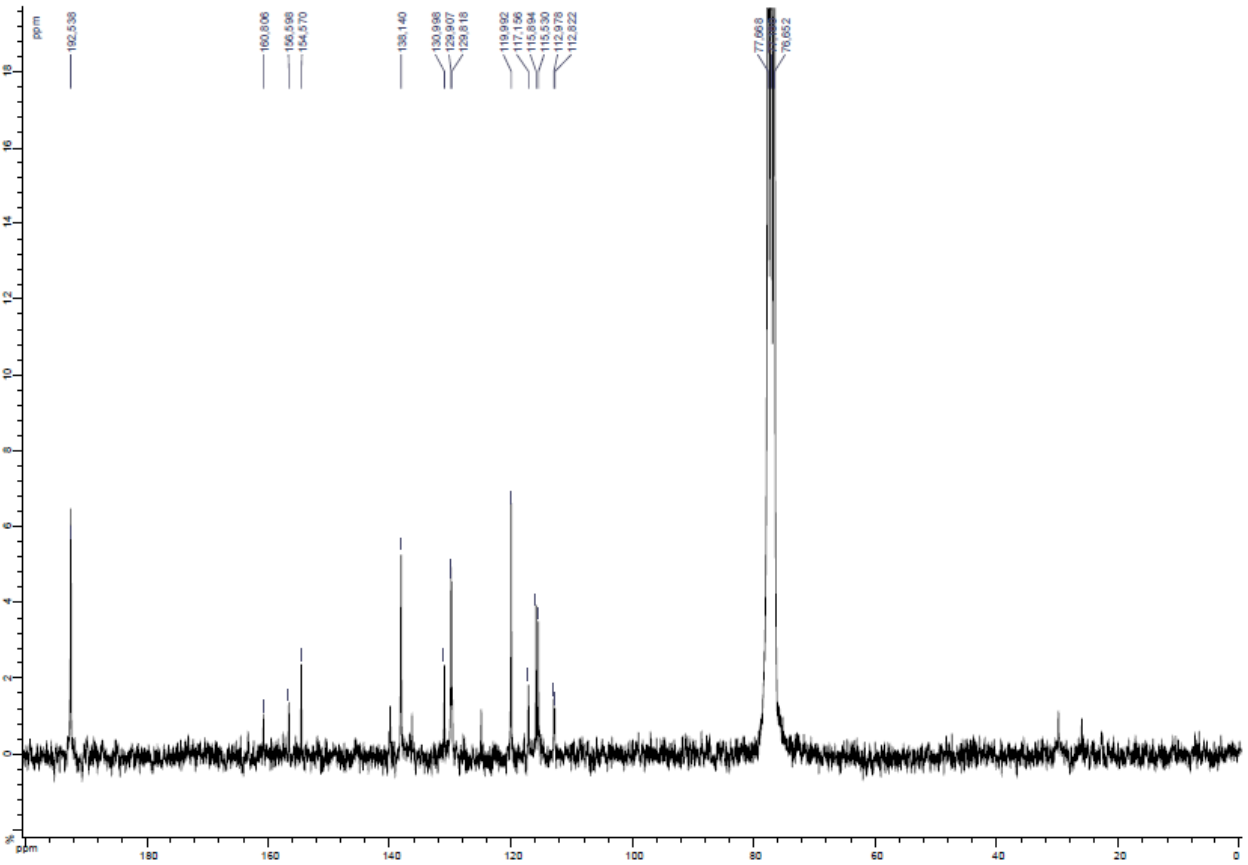

ppm
7.920
7.913
7.886
7.879
7.657
7.650
7.643
7.466
7.458
7.427
7.418
7.331
7.296
2.742
Br
N
F
1.0
1.0
1.0
1.0
3.0

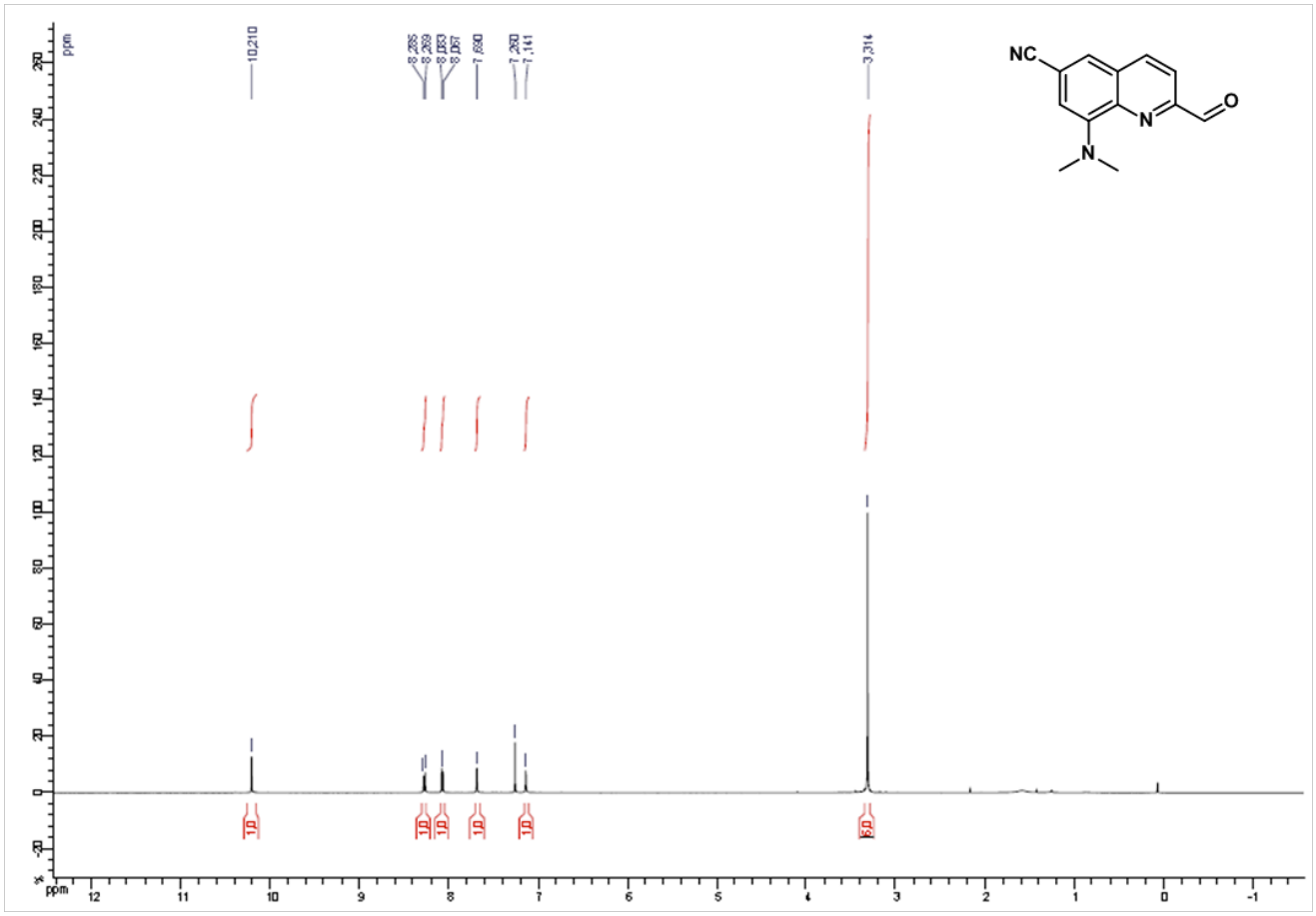

ppm
159.907
159.273
155.129
136.883
136.702
134.769
134.723
128.738
128.696
125.387
125.384
125.314
125.311
123.941
117.815
117.674
117.322
87.507
77.668
77.160
76.648
25.502

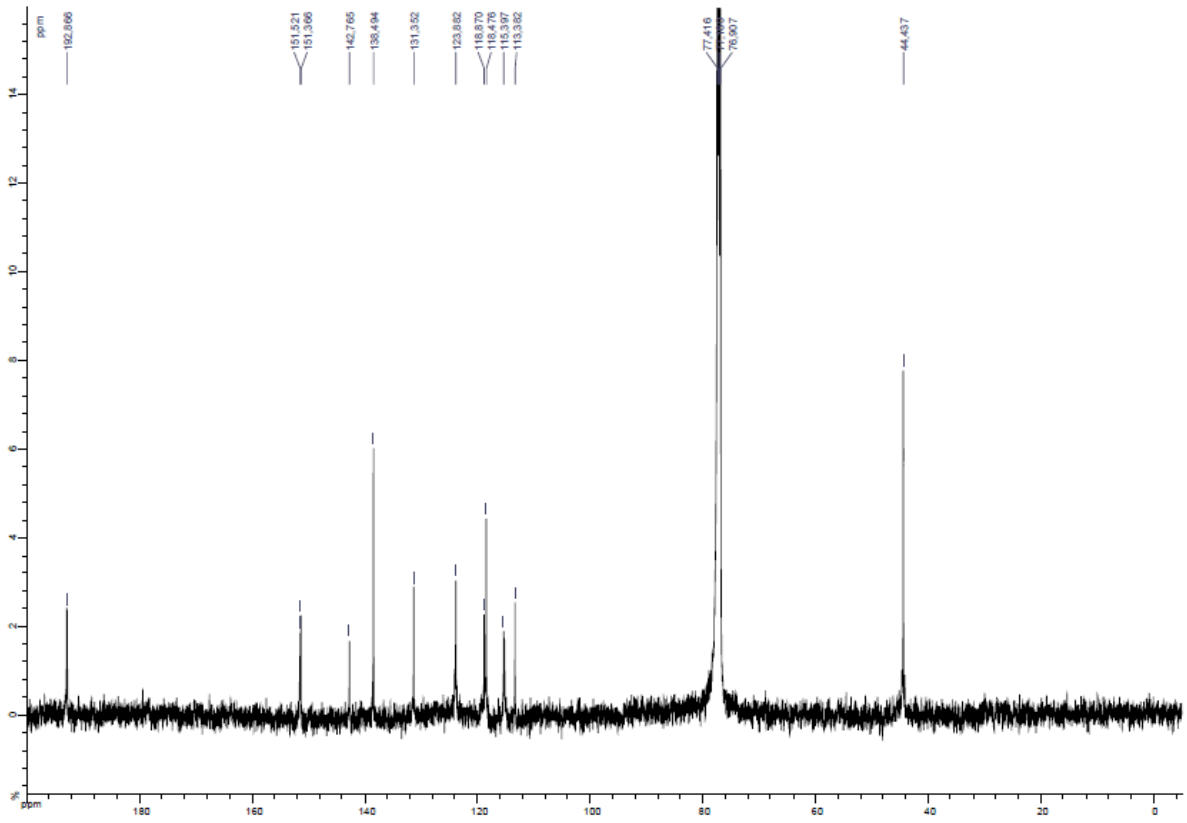

8.139
8.134
8.105
8.099
7.977
7.972
7.967
7.544
7.537
7.505
7.497
7.463
7.260
2.824
NC
N
N
14
1.0
1.0
2.0
3.9
ppm


163.185
159.592
139.756
139.581
136.166
129.626
129.547
127.709
124.793
117.687
114.814
114.446
108.976
108.819
77.085
77.160
76.848
25.818
ppm


NC
O
N
F
10.290
8.469
8.433
8.238
8.204
8.135
7.704
7.697
7.686
7.661
7.260
ppm


192.538
160.806
156.598
154.570
138.140
130.998
129.907
129.616
119.992
117.156
115.894
115.530
112.978
112.822
77.668
76.652
ppm


ppm
10.210
8.255
8.239
8.233
8.217
7.690
7.360
7.141
3.314
NC
O
N
N
1.0
1.0
1.0
1.0
1.0
6.0
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
-1


ppm
192.866
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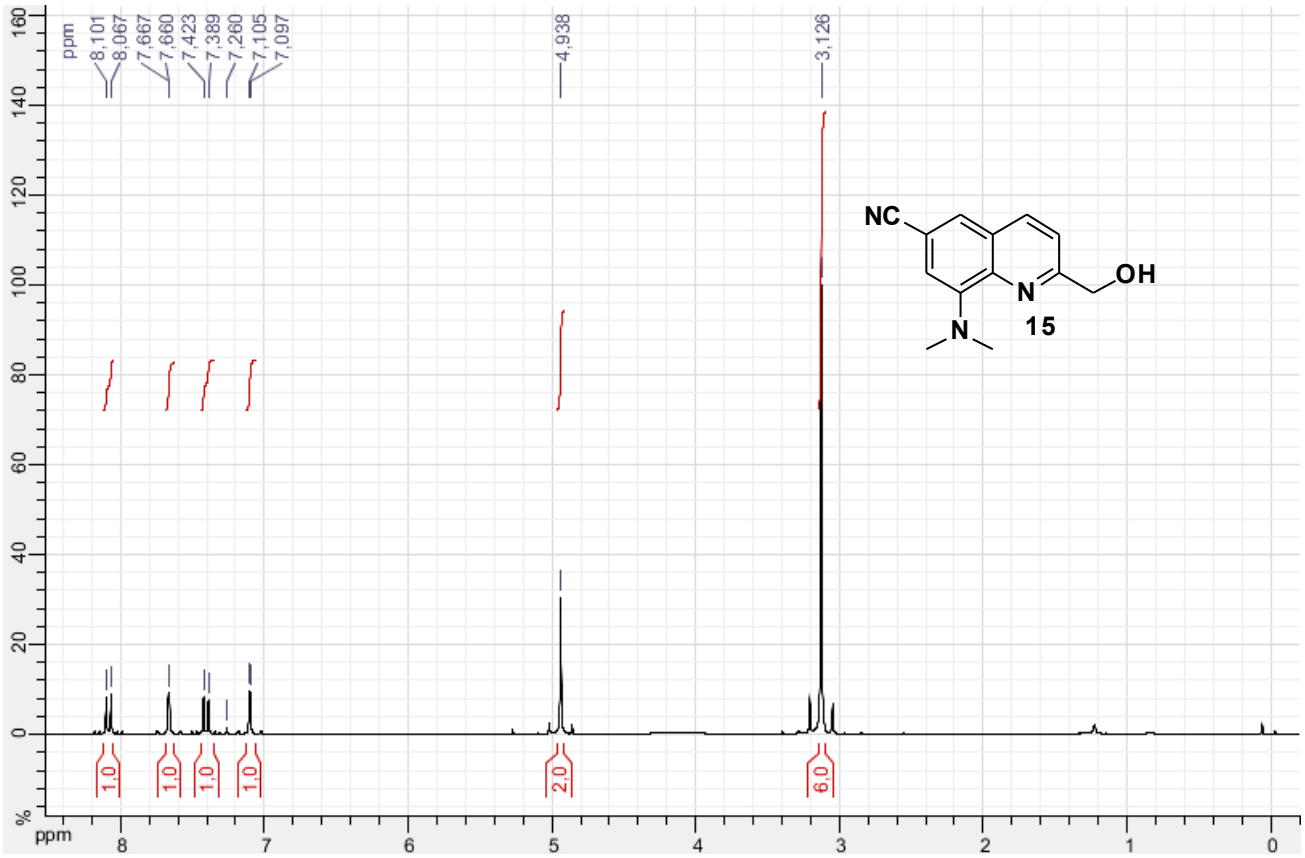
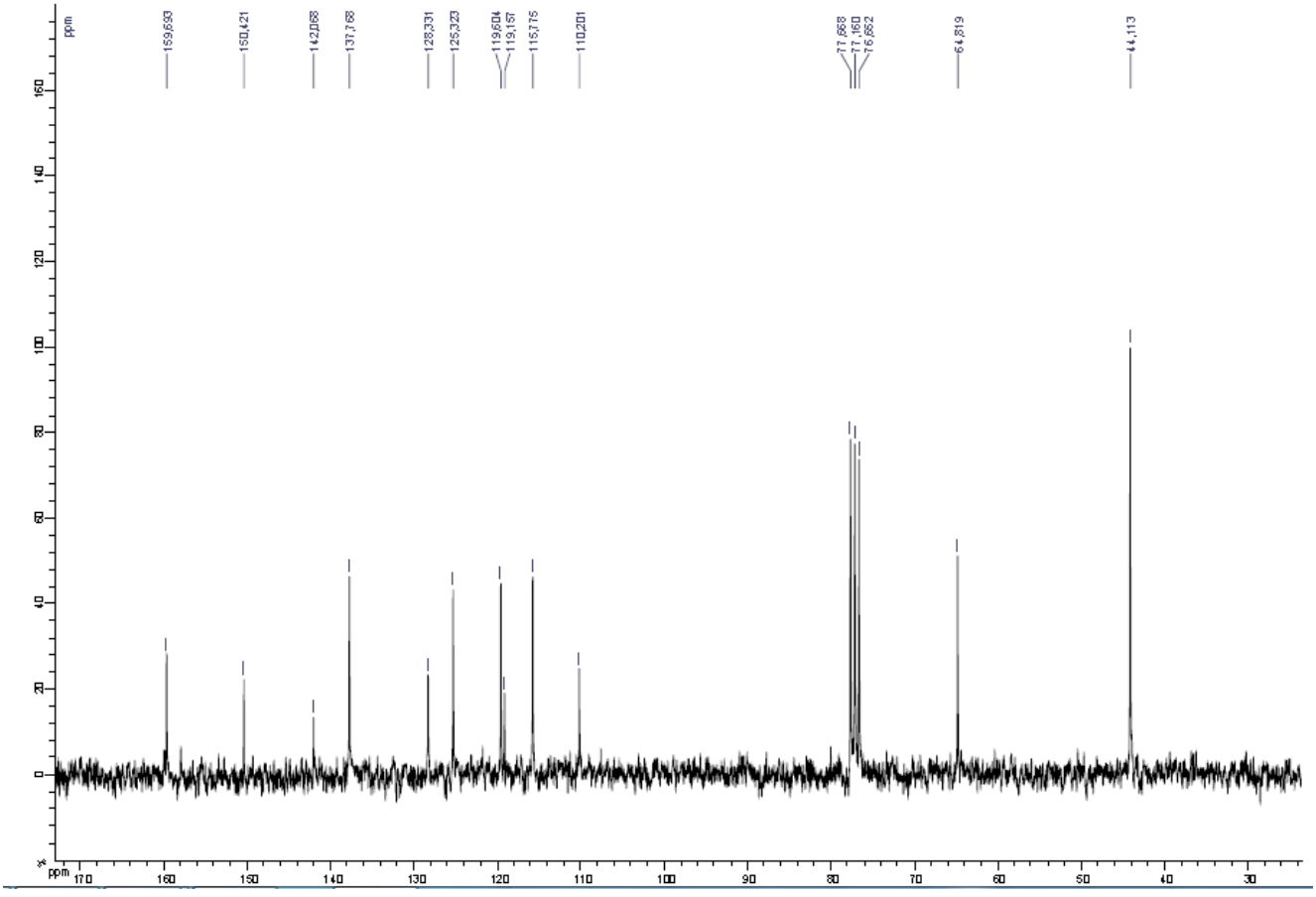
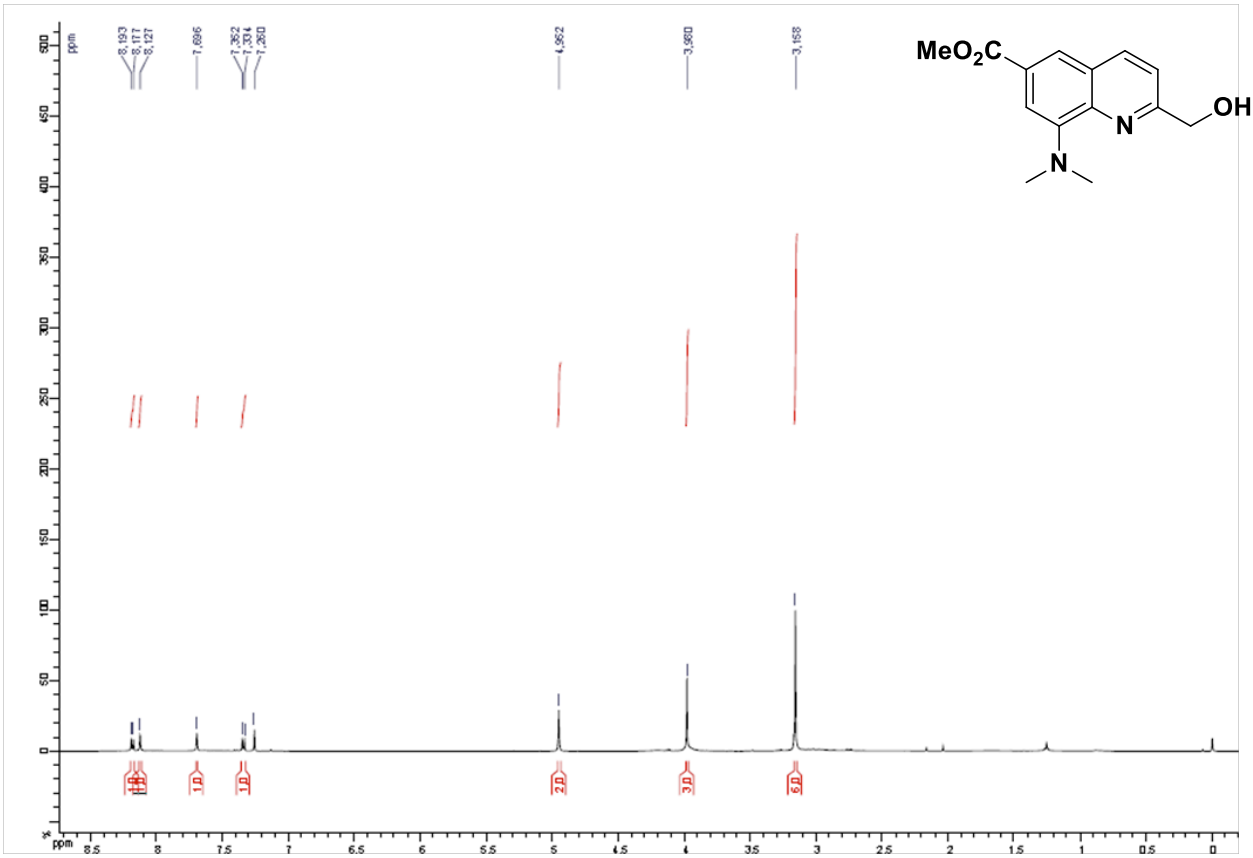
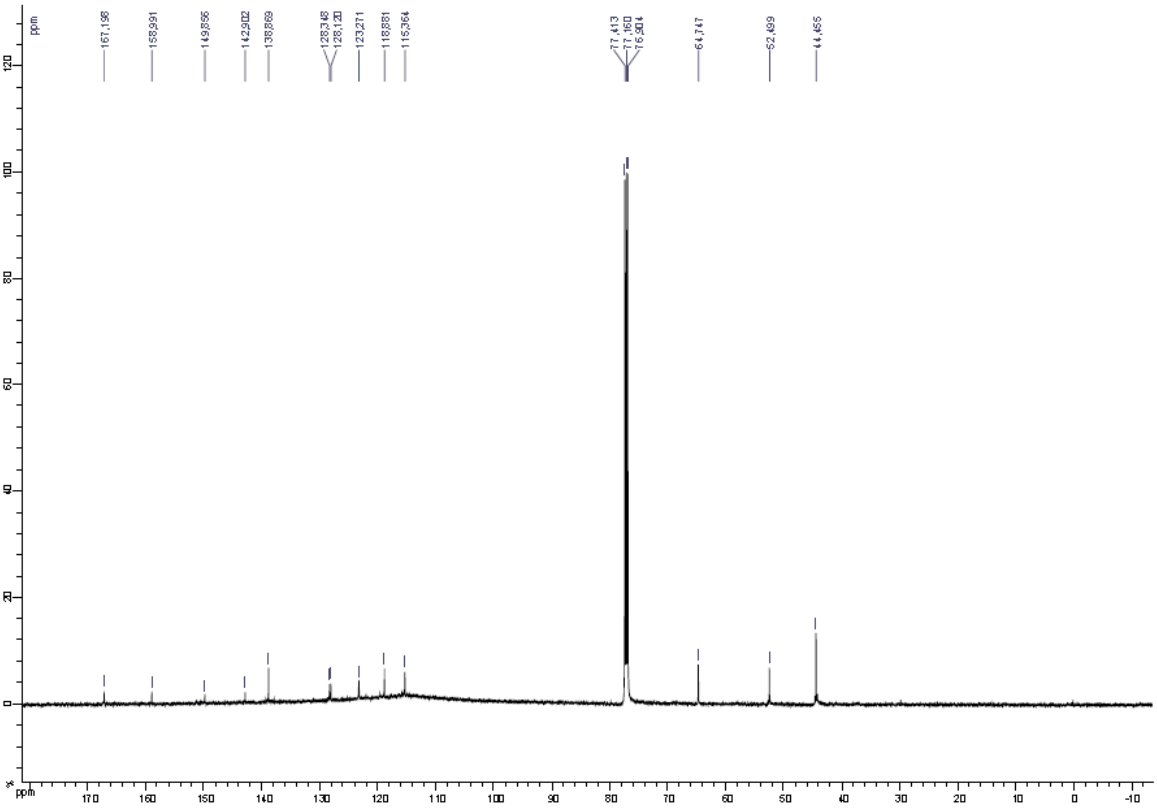
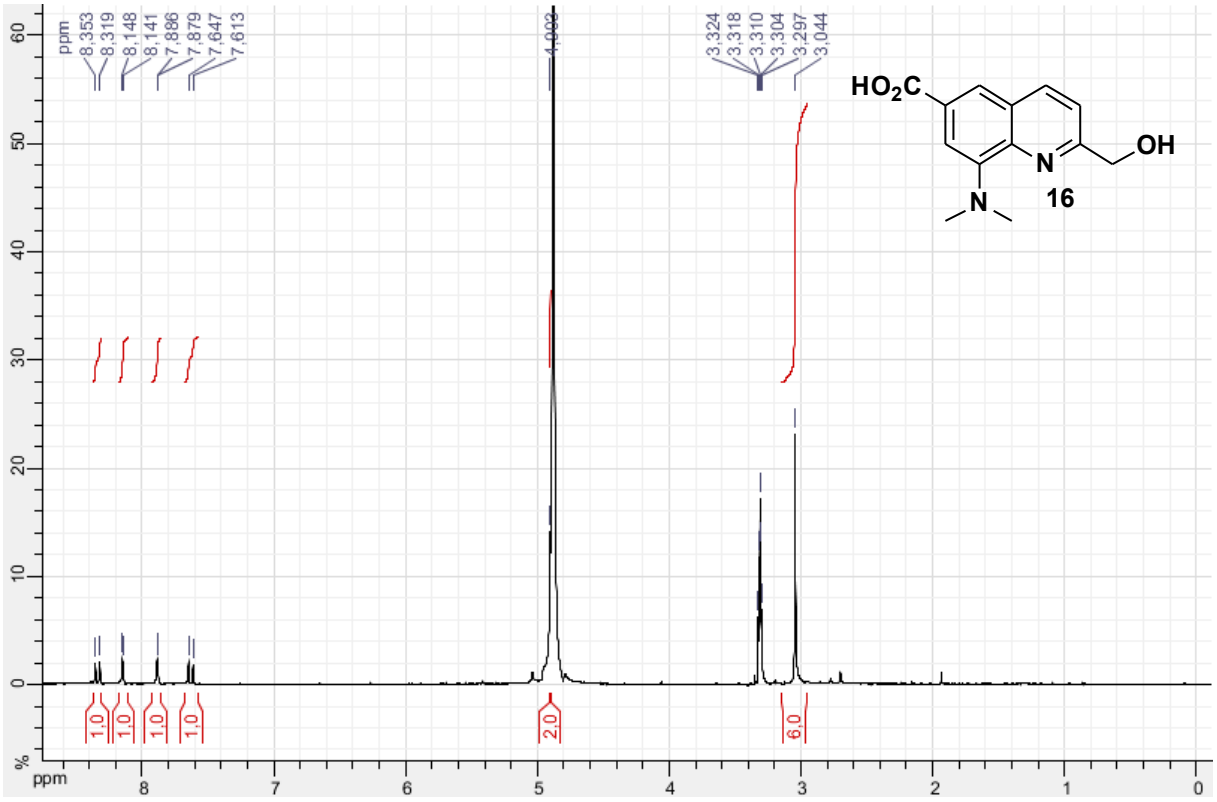
151.366
142.765
138.494
131.352
123.882
118.870
118.476
115.397
113.382
77.416
77.000
76.907
44.437
180
160
140
120
100
80
60
40
20
0


ppm
8,101
8,067
7,667
7,660
7,423
7,389
7,260
7,105
7,097
4,938
3,126
NC
OH
N
N
15
1,0
1,0
1,0
1,0
2,0
6,0


159,693
150,421
142,068
137,768
128,331
125,323
119,604
119,157
115,776
110,201
77,668
77,160
76,652
64,819
44,113


MeO2C
N
OH
N




ppm
8,353
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8,141
7,886
7,879
7,647
7,613
4,992
3,324
3,318
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3,304
3,297
3,044
HO2C
OH
N
N
16
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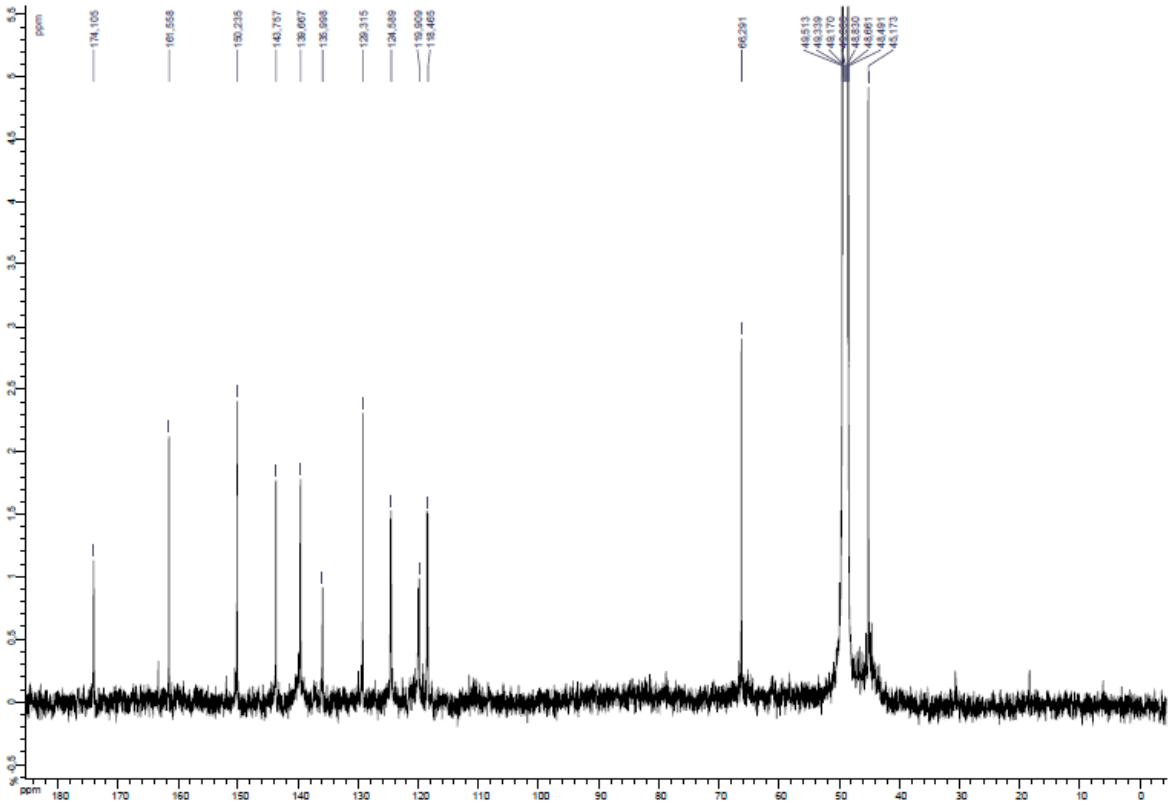
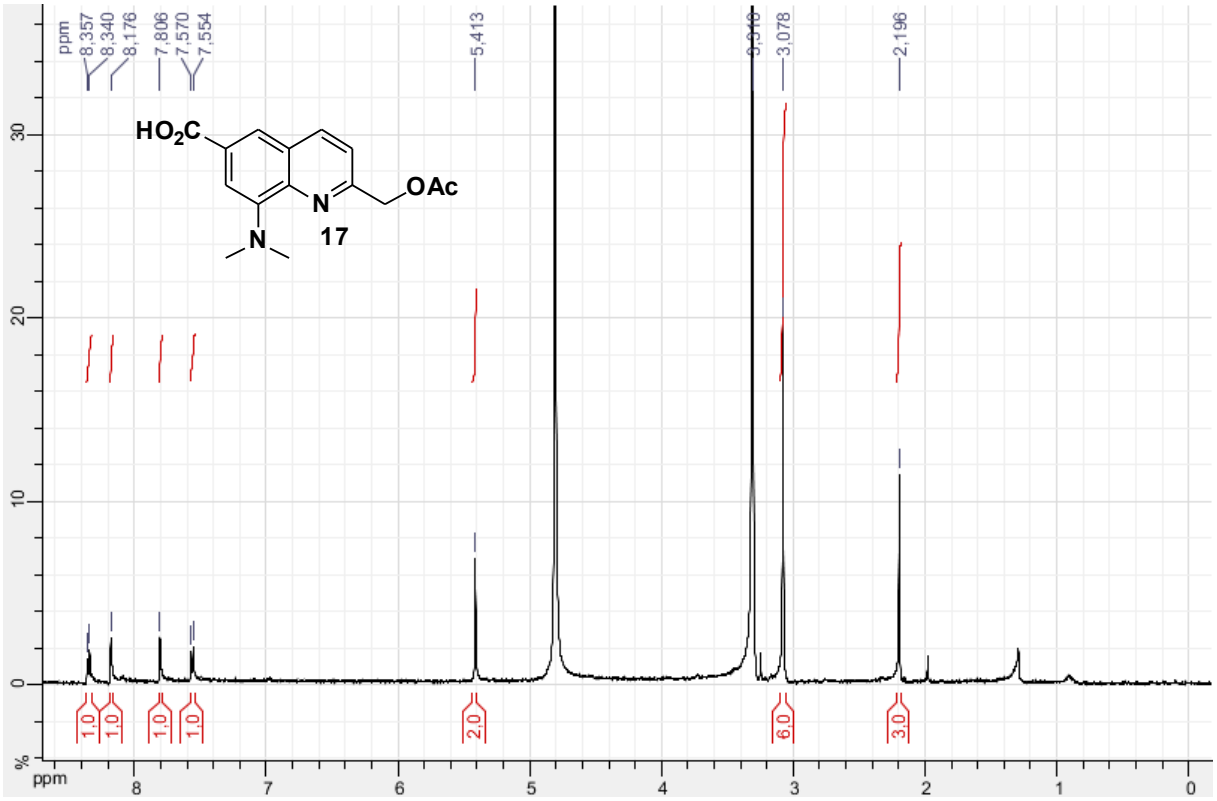
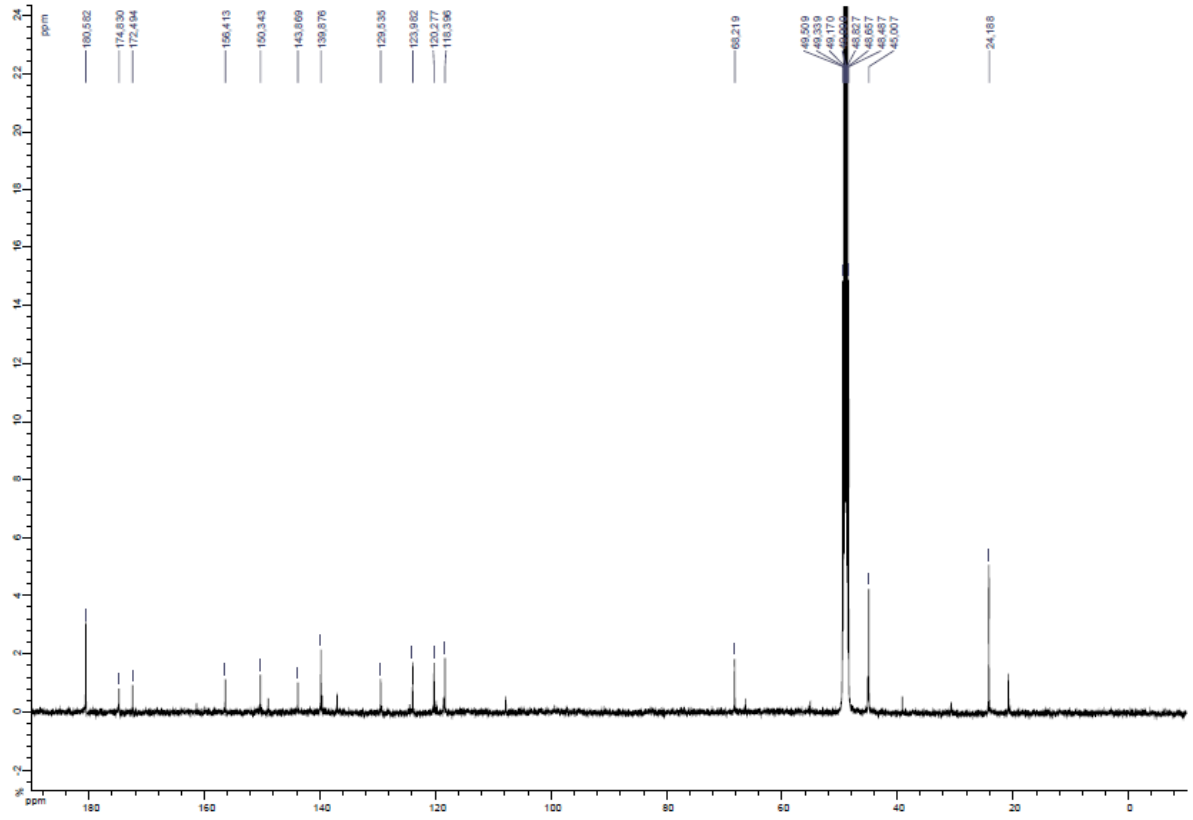
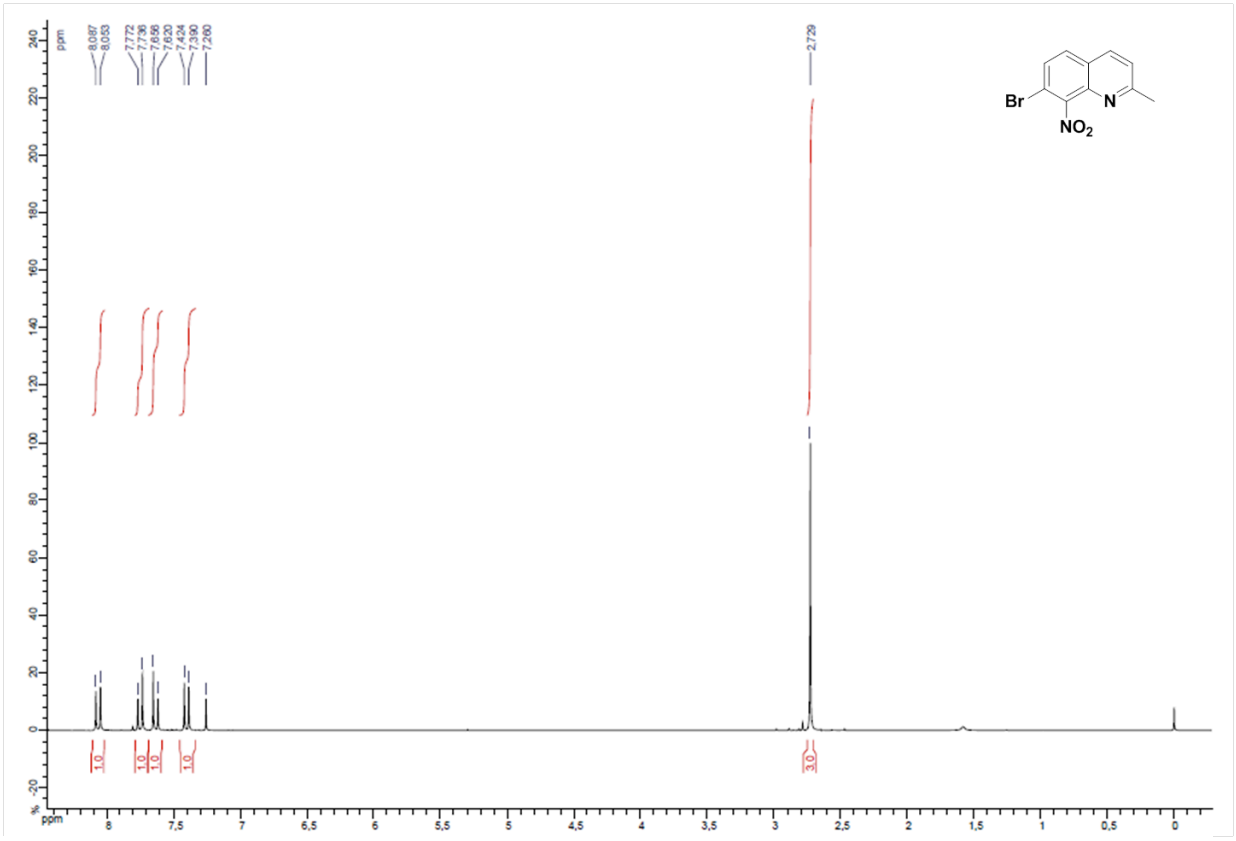
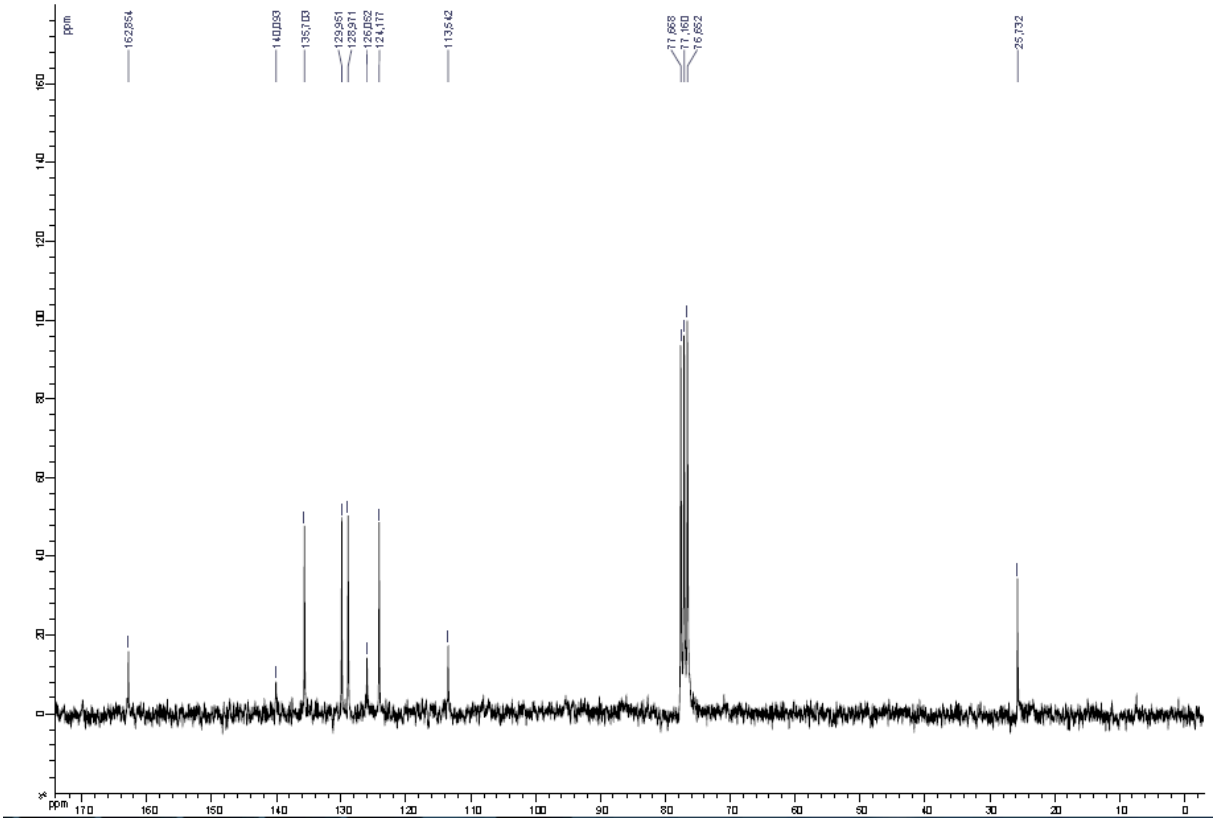
1,0
1,0
1,0
2,0
6,0
ppm

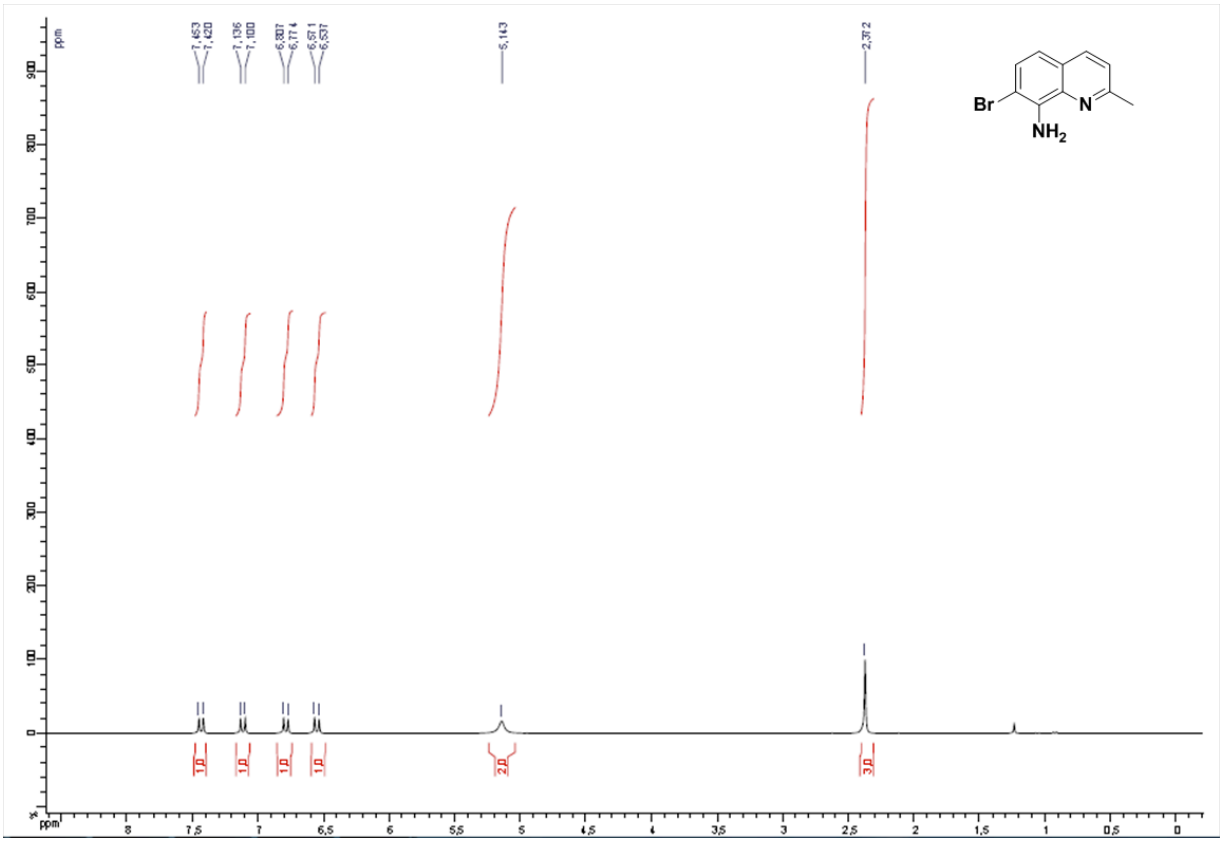

ppm
174,105
161,558
150,235
143,757
139,667
135,998
129,315
124,589
119,909
118,465
66,291
48,513
48,339
48,170
48,000
47,830
47,661
47,491
47,173
ppm


ppm
8,357
8,340
8,176
7,806
7,570
7,554
5,413
3,078
2,196
HO2C
OAc
N
N
17
1,0
1,0
1,0
1,0
2,0
6,0
3,0


ppm
180,582
174,830
172,494
156,413
150,343
143,869
139,876
129,535
123,982
120,277
118,396
68,219
49,509
49,339
49,170
48,827
48,657
48,487
45,007
24,188


Br
N
NO2




7.453
7.420
7.136
7.100
6.887
6.774
6.671
6.637
5.143
2.372
Br
N
NH2
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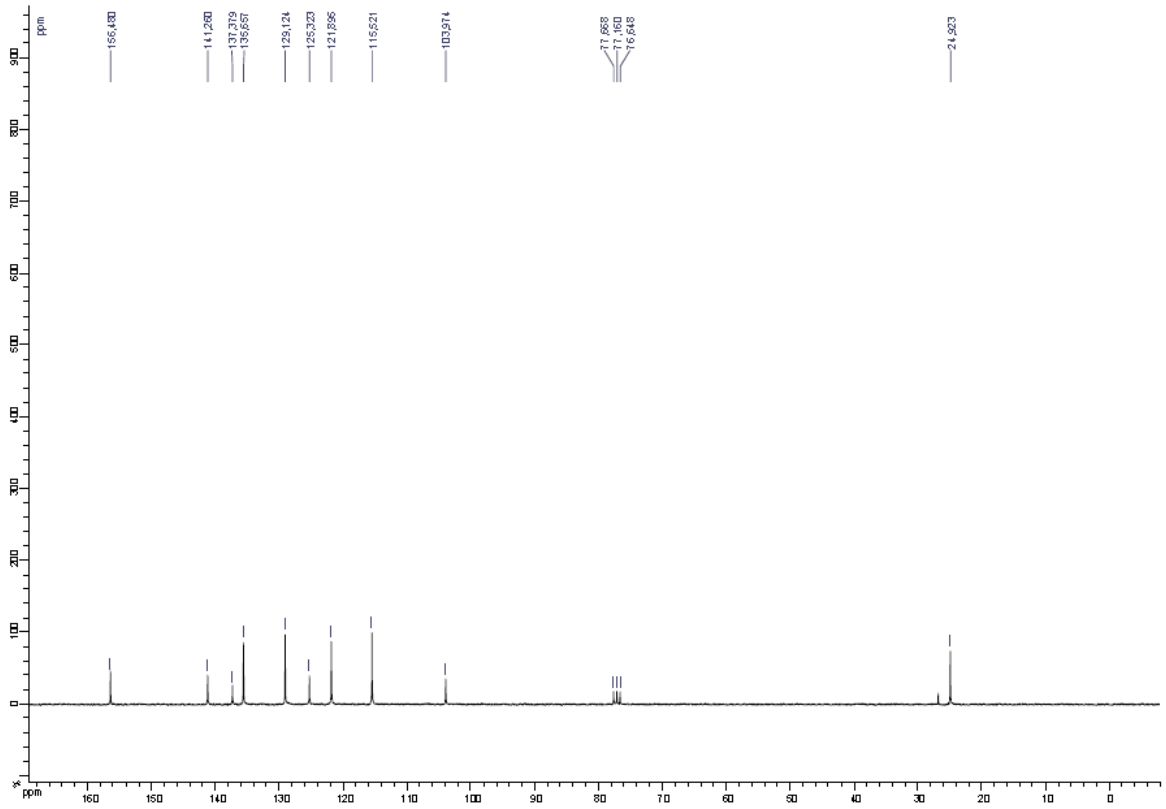
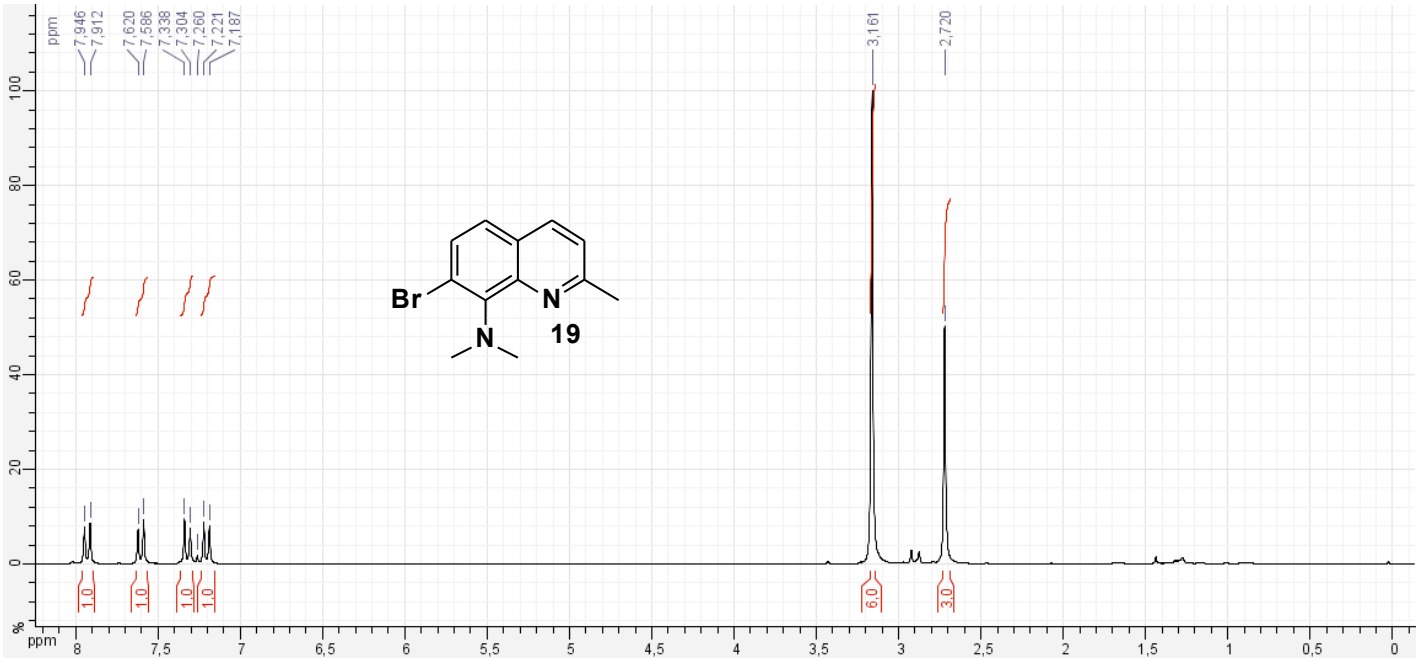
1.0
1.0
1.0
2.0
3.0
ppm


156.480
141.260
137.379
135.657
129.124
125.323
121.896
115.521
103.974
77.668
77.160
76.648
24.923
ppm


ppm
7,946
7,912
7,620
7,586
7,338
7,304
7,260
7,221
7,187
3,161
2,720
Br
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19
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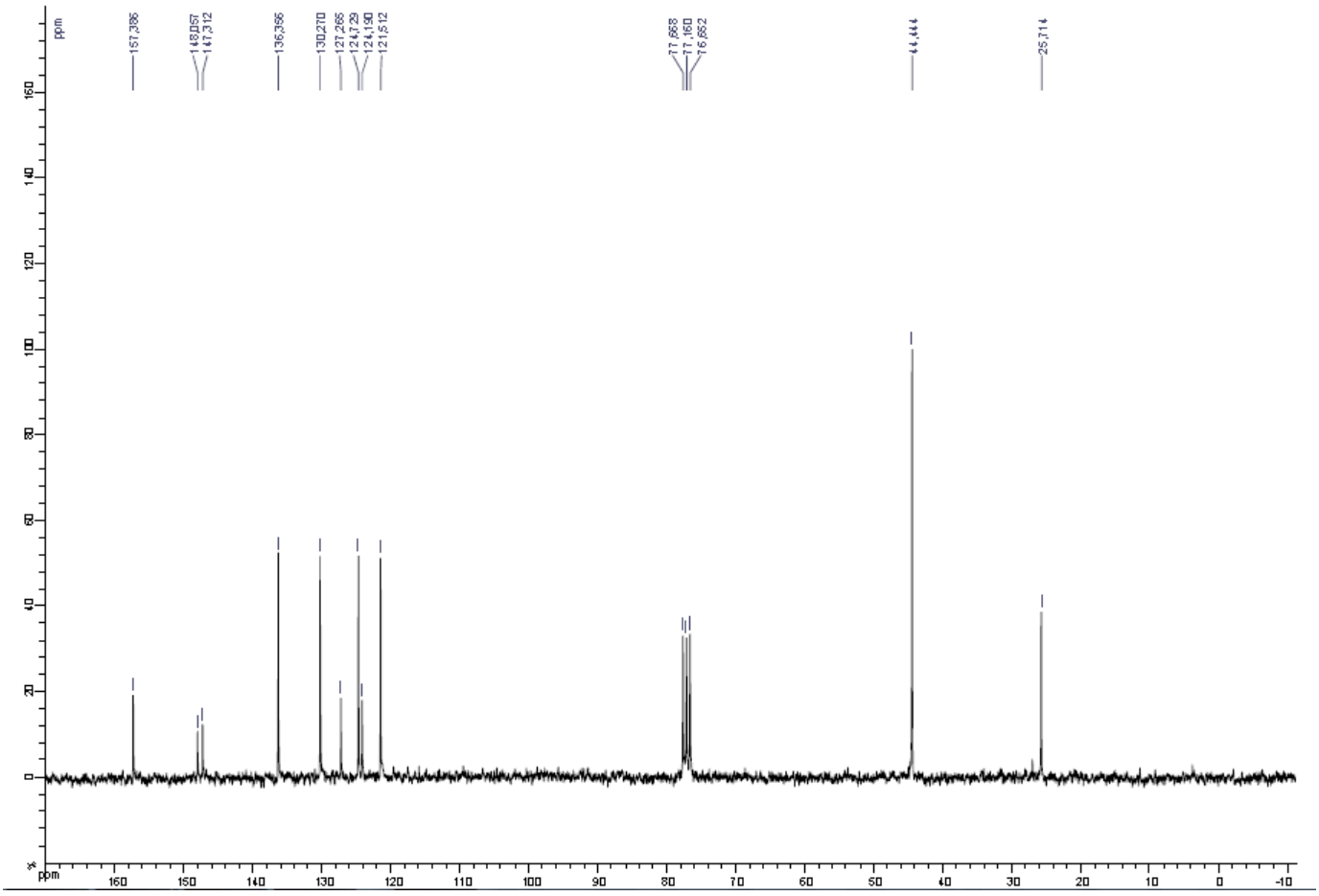
1,0
1,0
1,0
6,0
3,0


ppm
157,386
148,057
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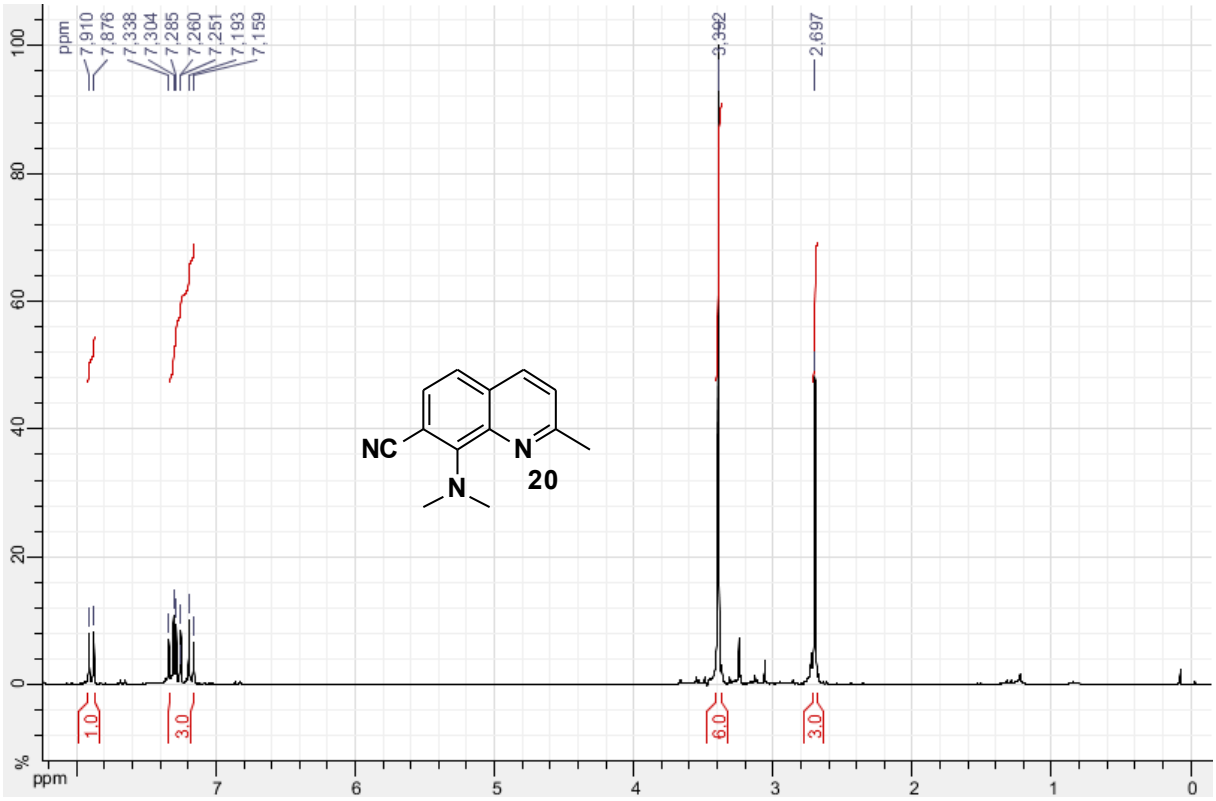
136,396
130,270
127,265
124,729
124,190
121,512
77,668
77,160
76,652
44,444
25,714


ppm
7,910
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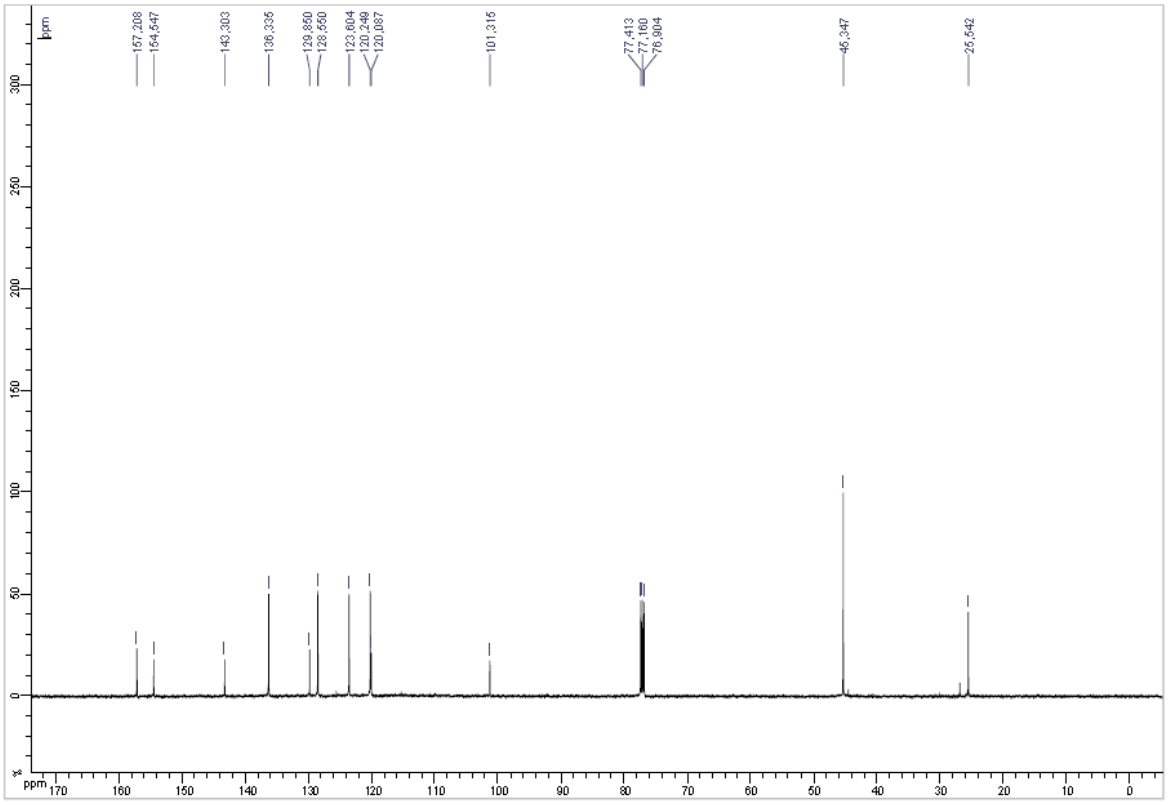
7,338
7,304
7,285
7,260
7,251
7,193
7,159
3,392
2,697
NC
N
N
20
1.0
3.0
6.0
3.0
%
ppm


ppm
157,208
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143,303
136,335
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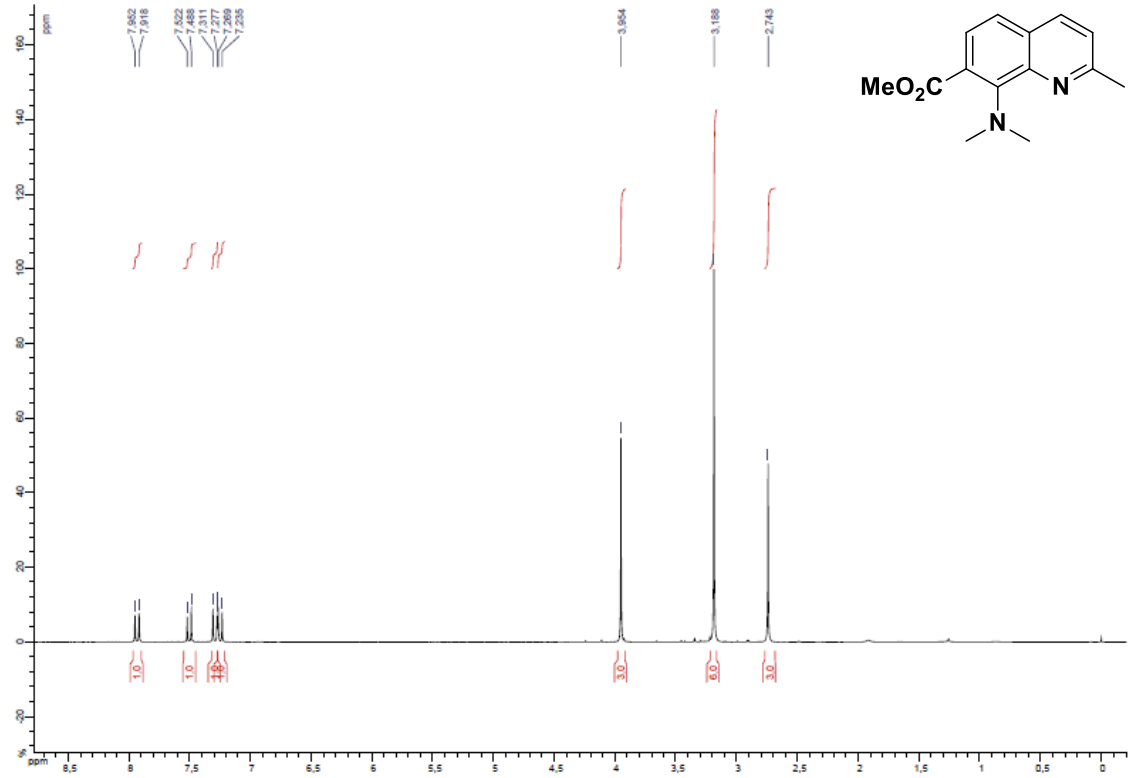
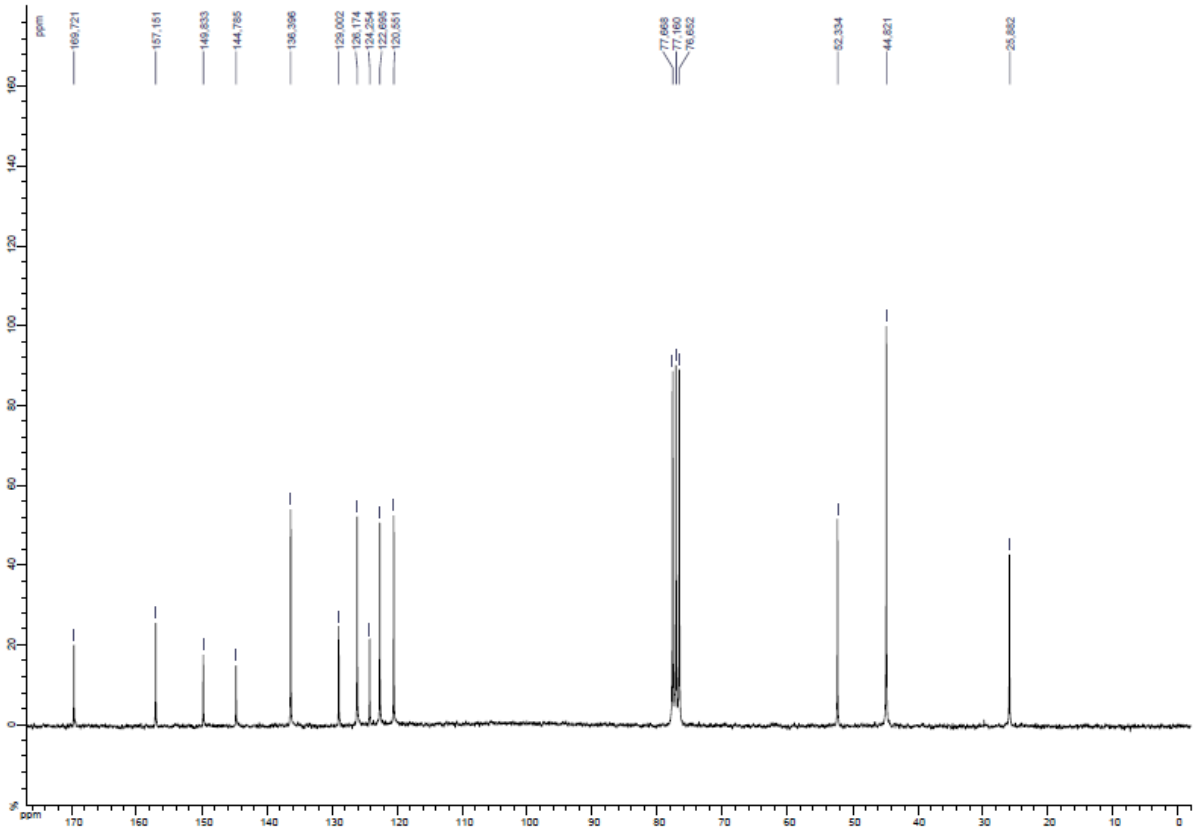
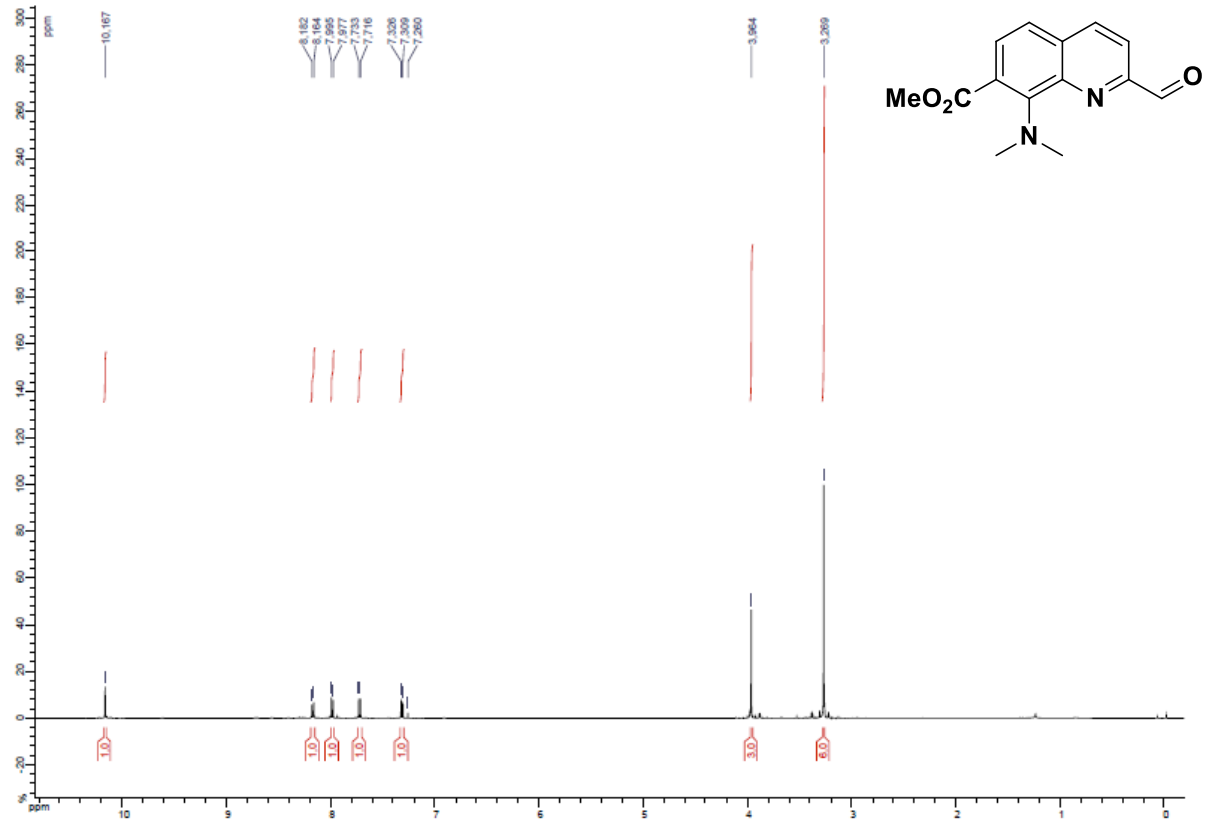
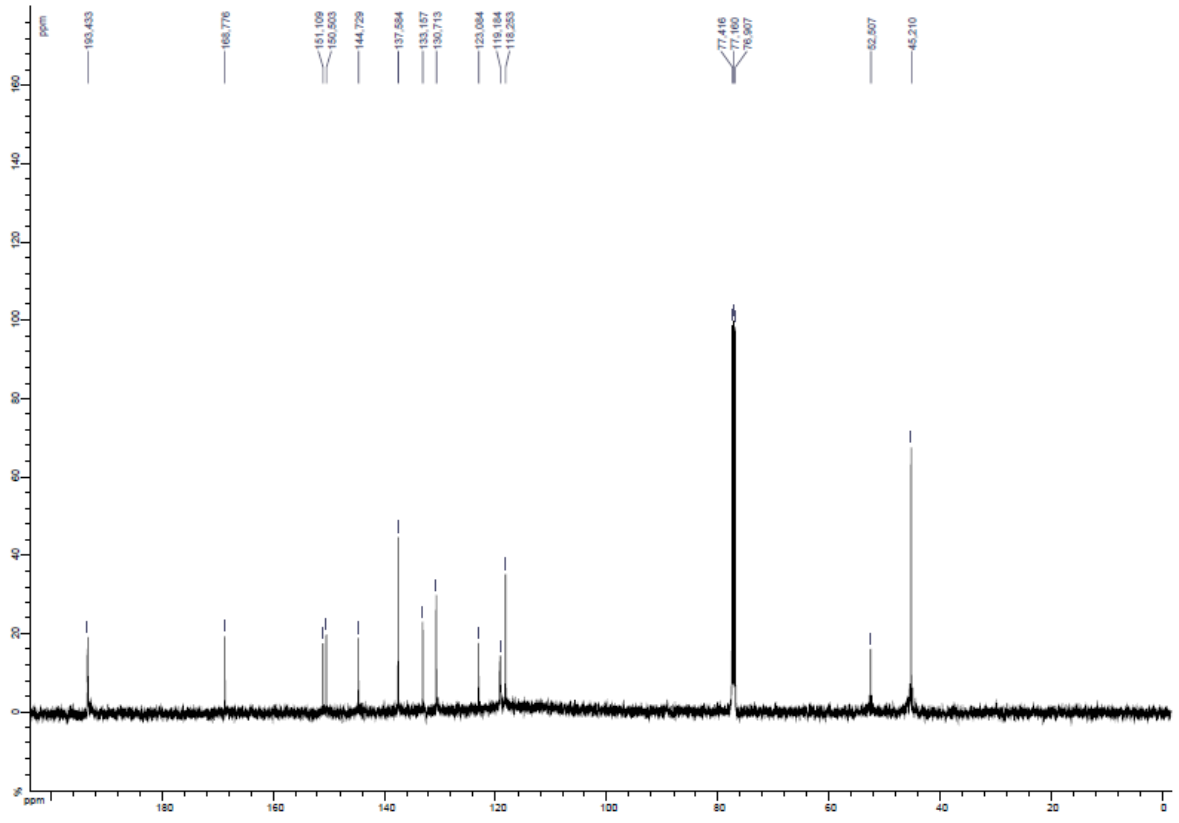
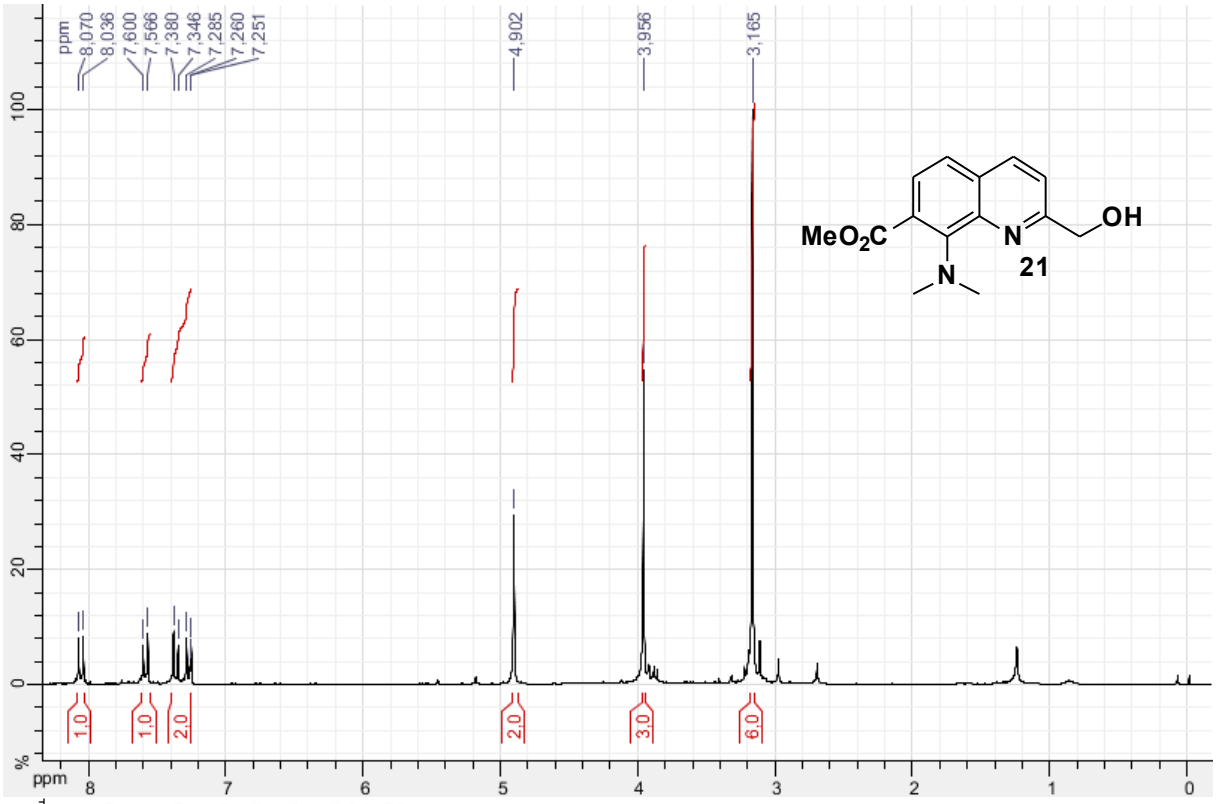
128,660
123,604
120,249
120,087
101,316
77,413
77,160
76,904
46,347
25,542
%
ppm


7.952
7.918
7.522
7.485
7.311
7.277
7.269
7.235
3.954
3.188
2.743
MeO2C
N
N
1.0
1.0
3.0
6.0
3.0


169.721
157.151
149.833
144.785
136.396
129.002
126.174
124.254
122.695
120.551
77.668
77.160
76.652
52.334
44.821
25.882


10.167
8.182
8.164
7.995
7.977
7.733
7.716
7.326
7.309
7.260
3.964
3.269
MeO2C
N
O
N


193.433
168.776
151.109
150.503
144.729
137.584
133.157
130.713
123.084
119.184
118.283
77.416
77.160
76.907
52.507
45.210


ppm
8,070
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7,566
7,380
7,346
7,285
7,260
7,251
4,902
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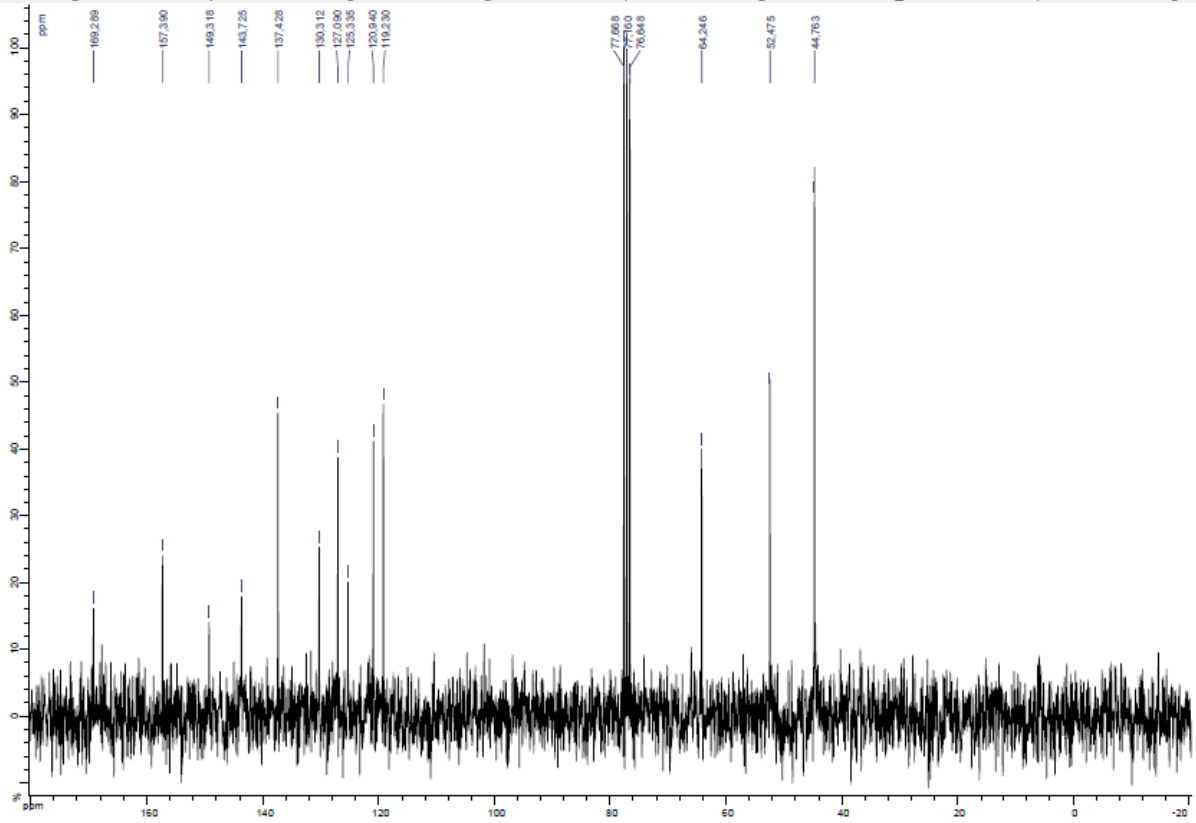
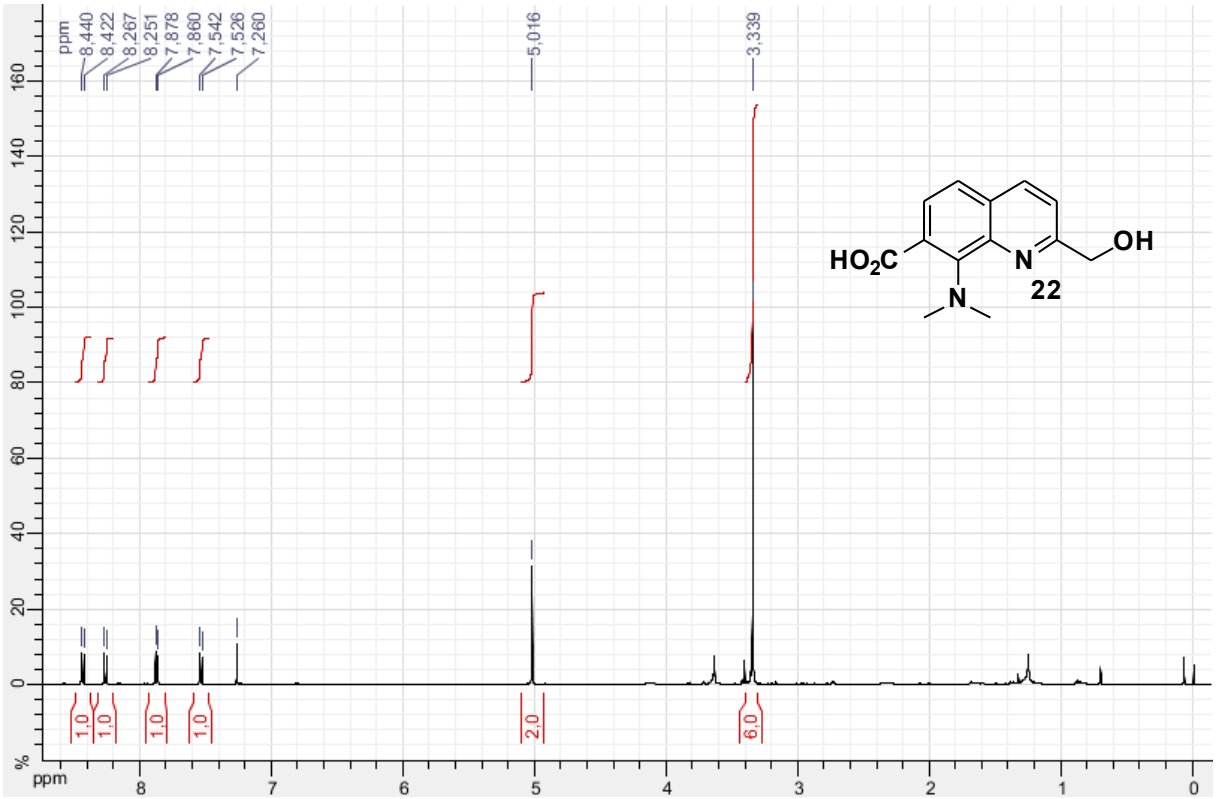
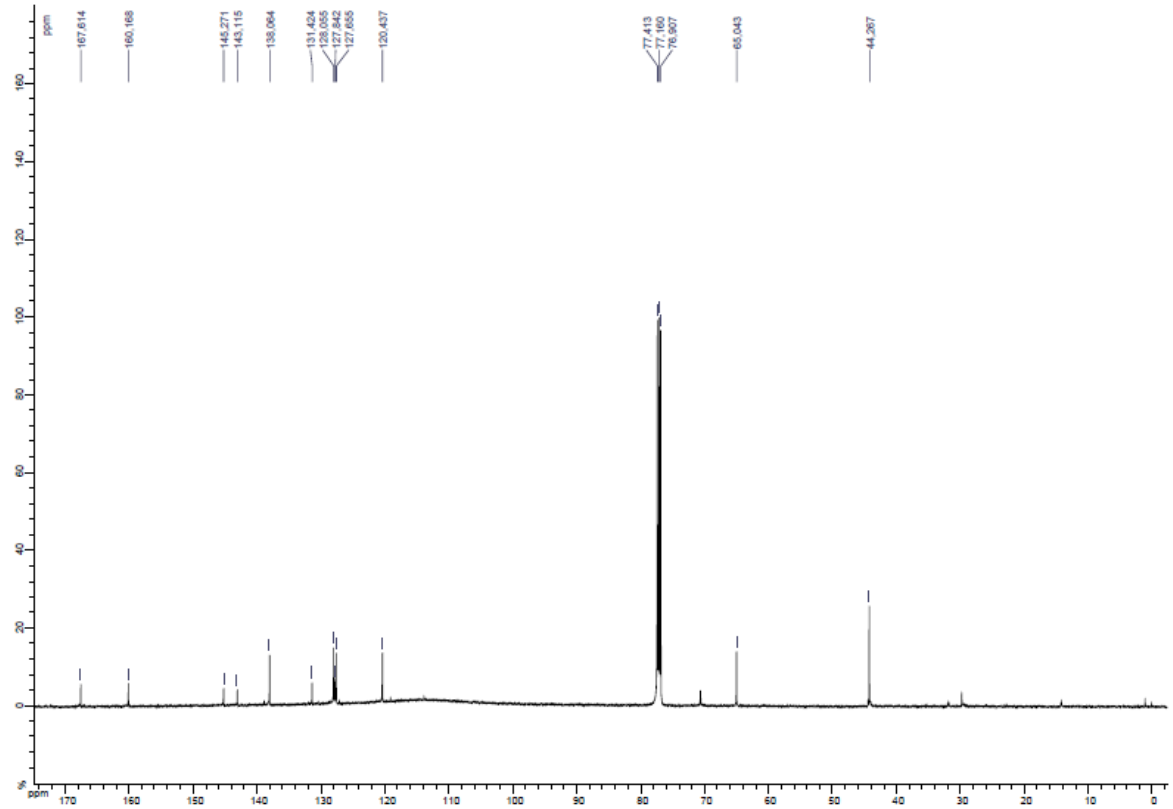
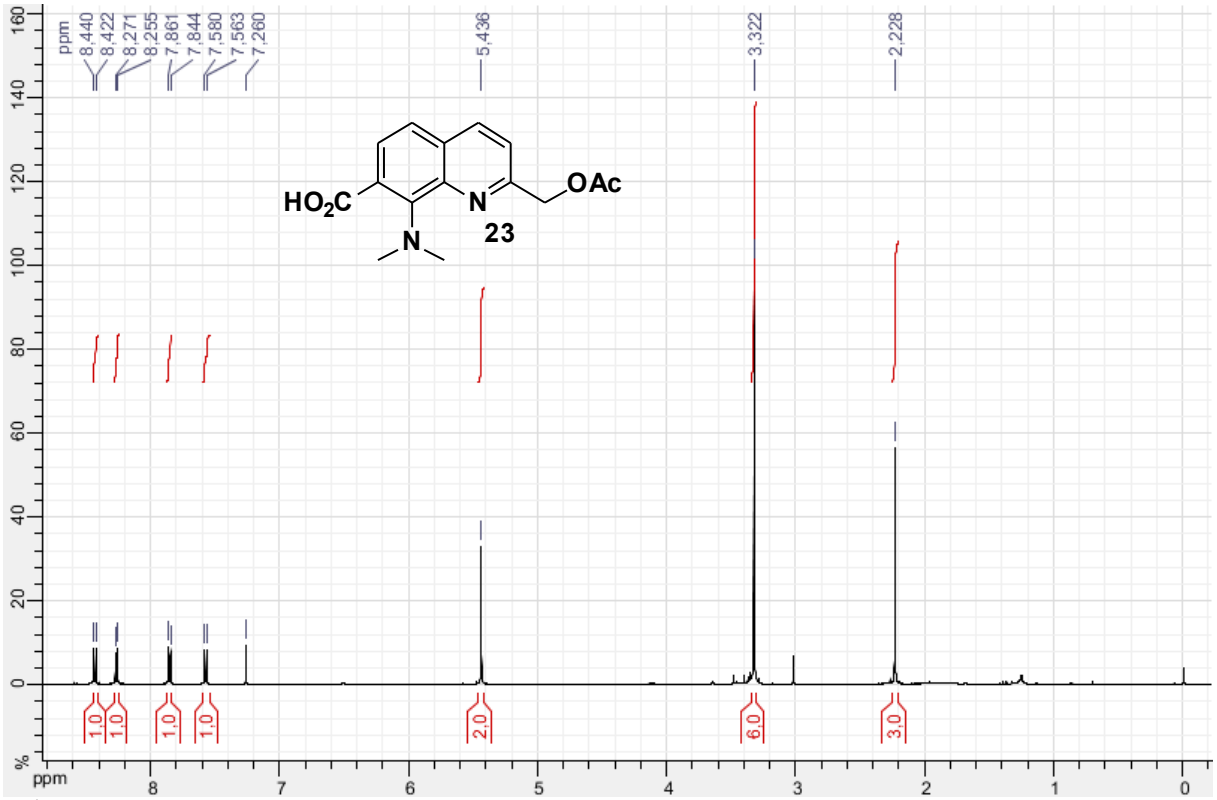
1,0
2,0
2,0
3,0
6,0
MeO2C
N
OH
N
21


169,289
157,390
149,316
143,725
137,428
130,312
127,090
125,335
120,940
119,230
77,668
77,160
76,648
64,246
52,475
44,763


ppm
8,440
8,422
8,267
8,251
7,878
7,860
7,542
7,526
7,260
5,016
3,339
1,0
1,0
1,0
1,0
2,0
6,0
HO2C
N
OH
N
22


167,614
160,168
145,271
143,115
138,064
131,424
129,655
127,842
127,666
120,437
77,413
77,160
76,907
65,043
44,267


ppm
8,440
8,422
8,271
8,255
7,861
7,844
7,580
7,563
7,260
5,436
3,322
2,228
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N
OAc
N
23
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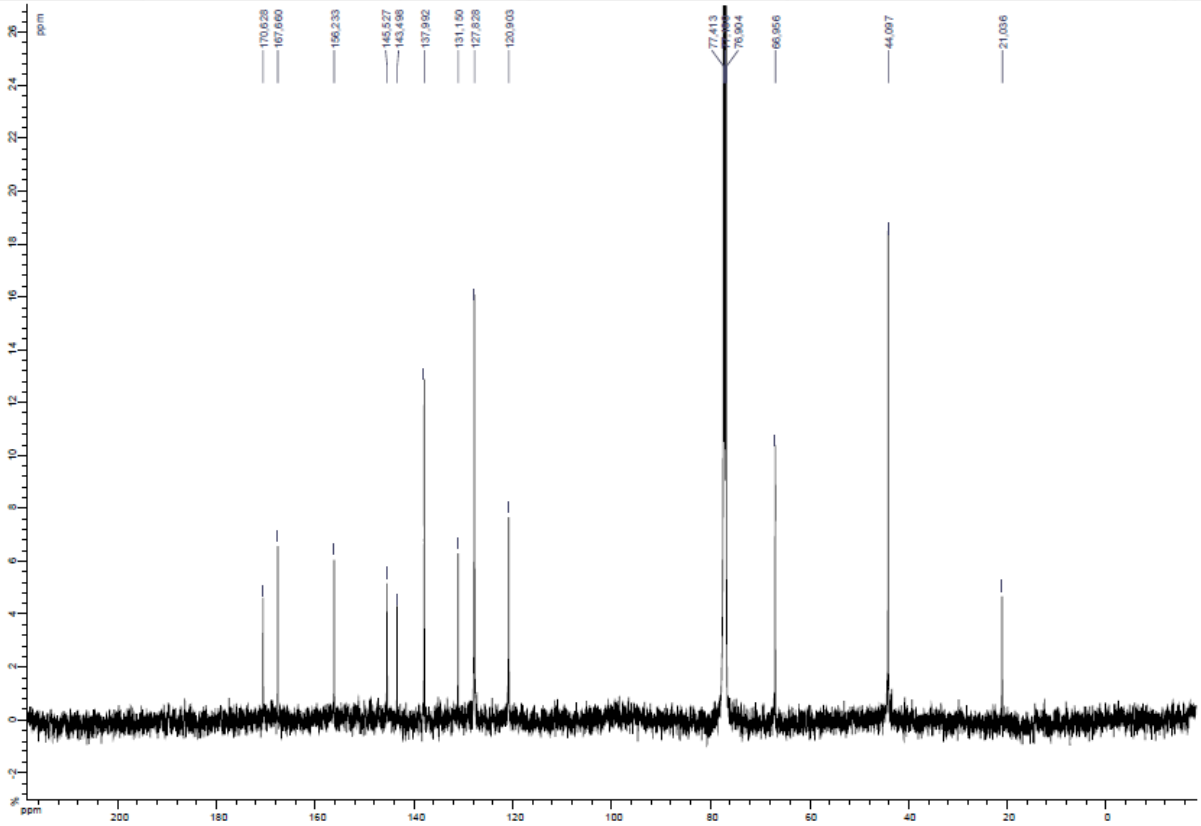
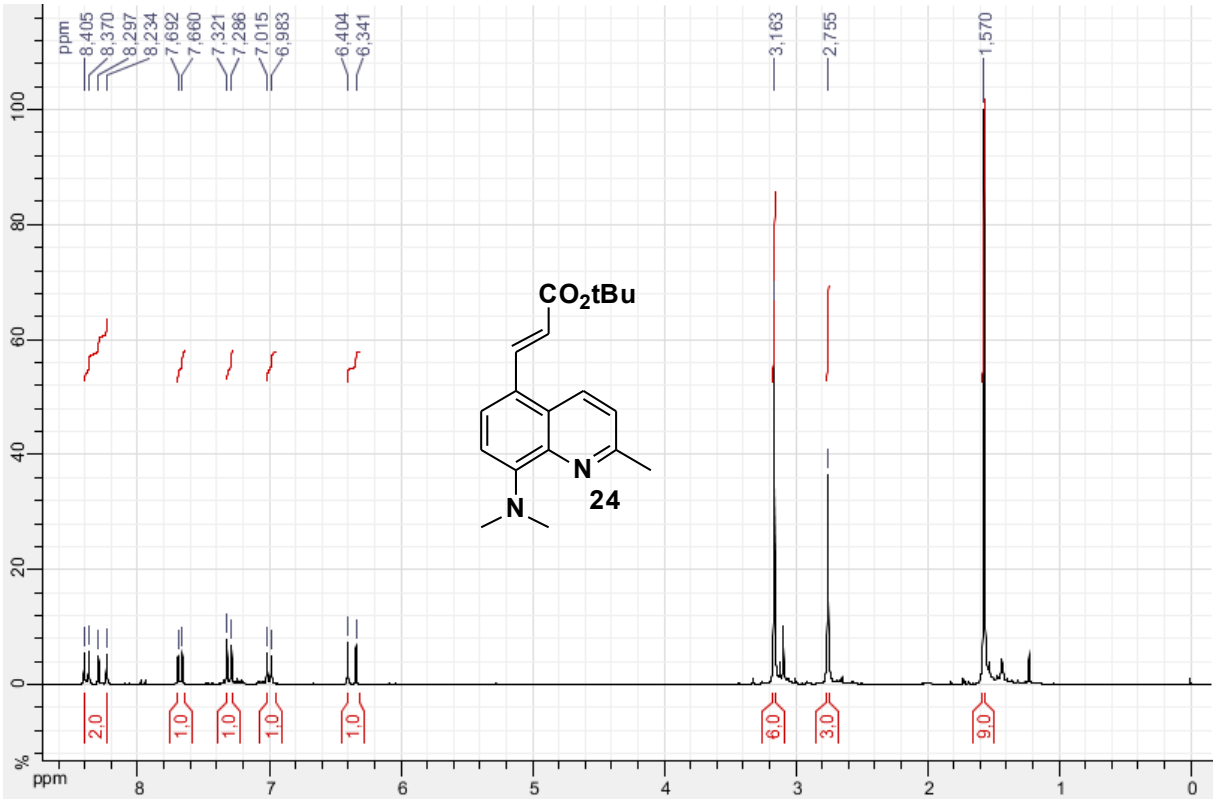
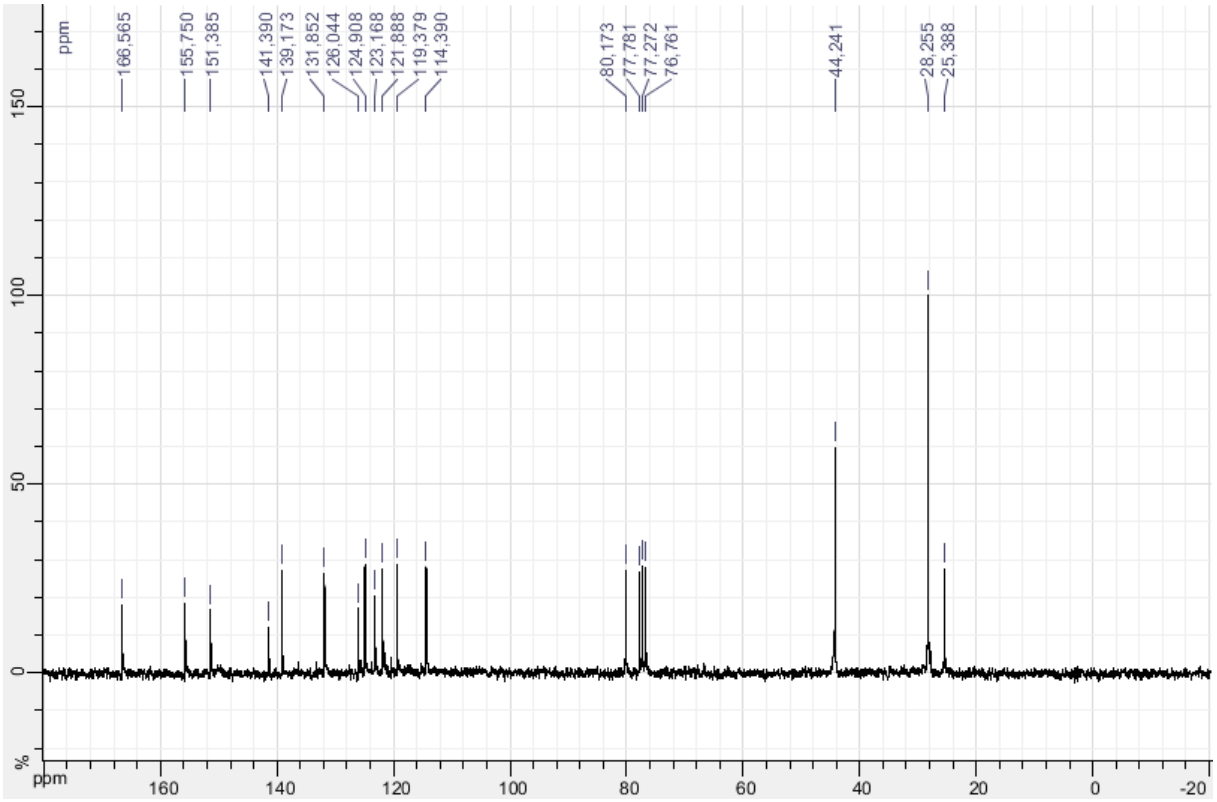
1,0
1,0
1,0
2,0
6,0
3,0


ppm
170,628
167,660
156,233
145,527
143,498
137,992
131,150
127,828
120,903
77,413
76,904
66,956
44,097
21,036


ppm
8,405
8,370
8,297
8,234
7,692
7,660
7,321
7,286
7,015
6,983
6,404
6,341
3,163
2,755
1,570
CO2tBu
N
N
24
2,0
1,0
1,0
1,0
1,0
6,0
3,0
9,0
%
ppm


ppm
166,565
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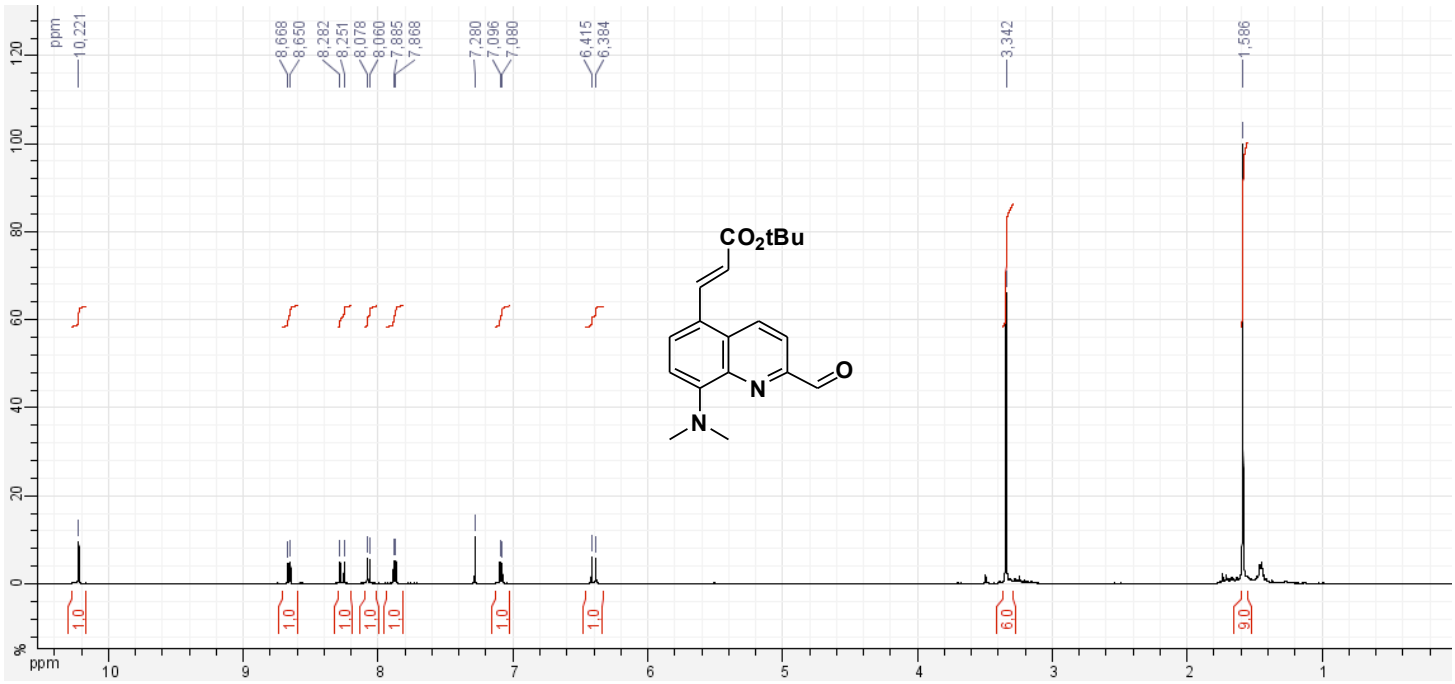
151,385
141,390
139,173
131,852
126,044
124,908
123,168
121,888
119,379
114,390
80,173
77,781
77,272
76,761
44,241
28,255
25,388
%
ppm


ppm
10,221
8,668
8,650
8,282
8,251
8,078
8,060
7,885
7,868
7,280
7,096
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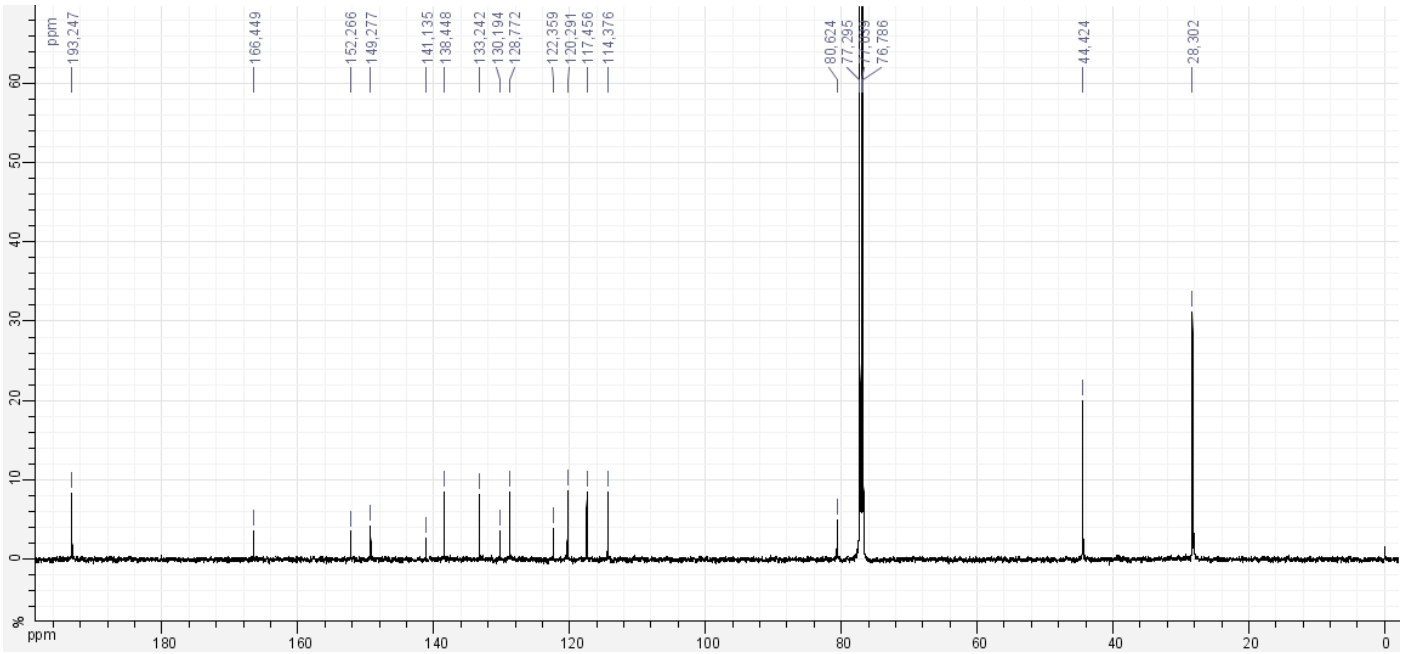
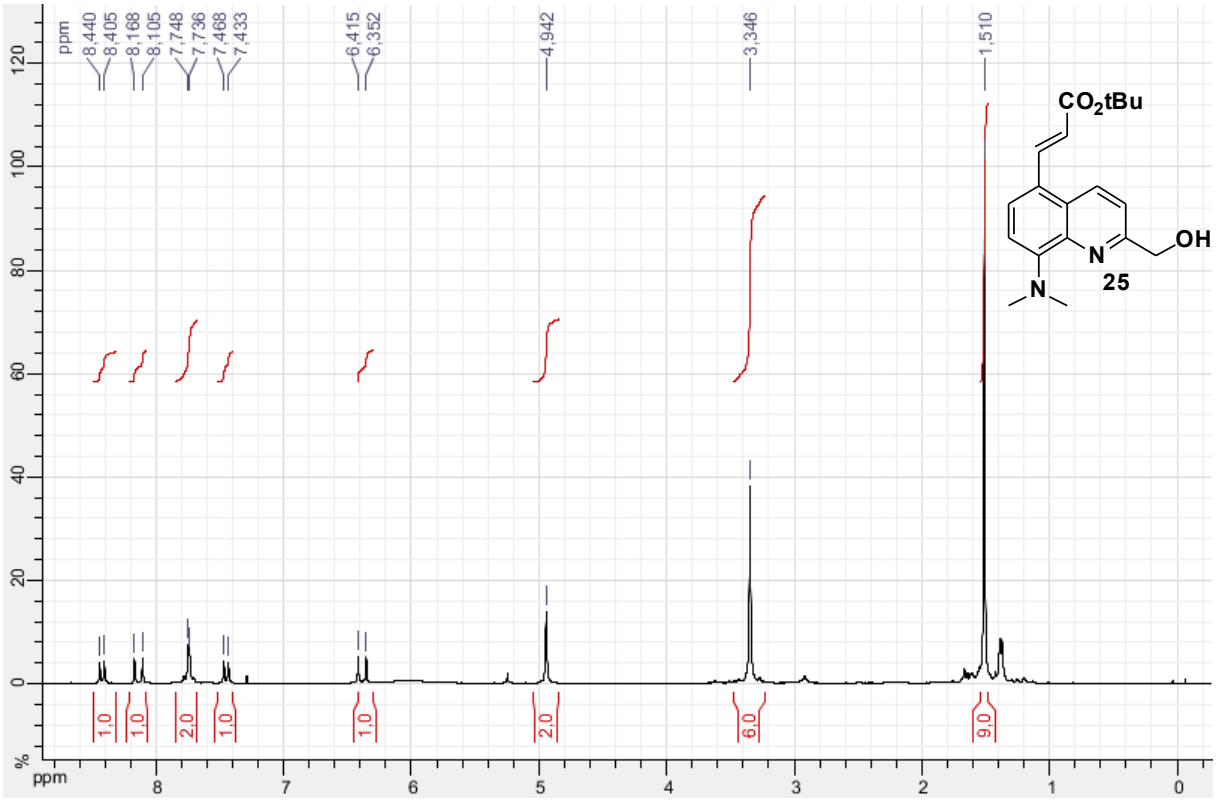
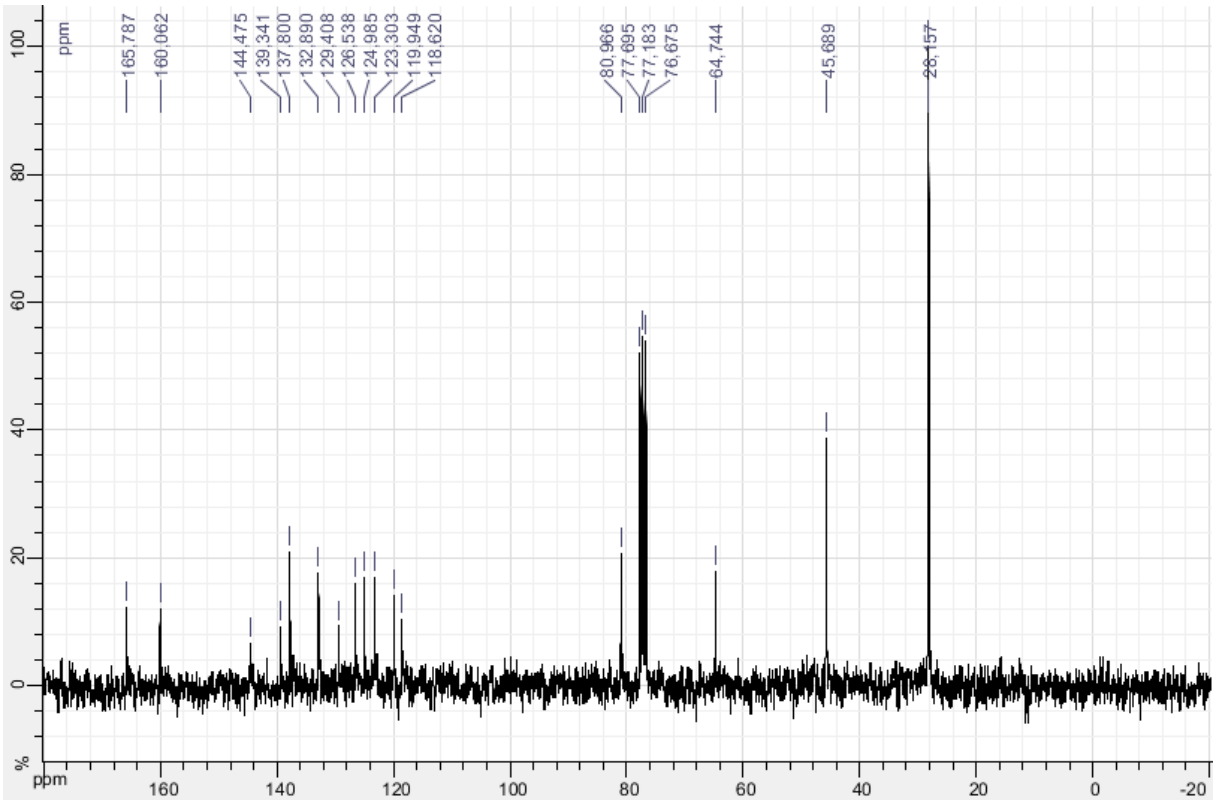
6,384
3,342
1,586
CO2tBu
O
N
N
1,0
1,0
1,0
1,0
1,0
1,0
1,0
6,0
9,0


ppm
193,247
166,449
152,266
149,277
141,135
138,448
133,242
130,194
128,772
122,359
120,291
117,456
114,376
80,624
77,295
76,786
44,424
28,302


ppm
8,440
8,405
8,168
8,105
7,748
7,736
7,468
7,433
6,415
6,352
4,942
3,346
1,510
1,0
1,0
2,0
1,0
1,0
2,0
6,0
9,0
CO2tBu
OH
N
N
25


ppm
165,787
160,062
144,475
139,341
137,800
132,890
129,408
126,538
124,985
123,303
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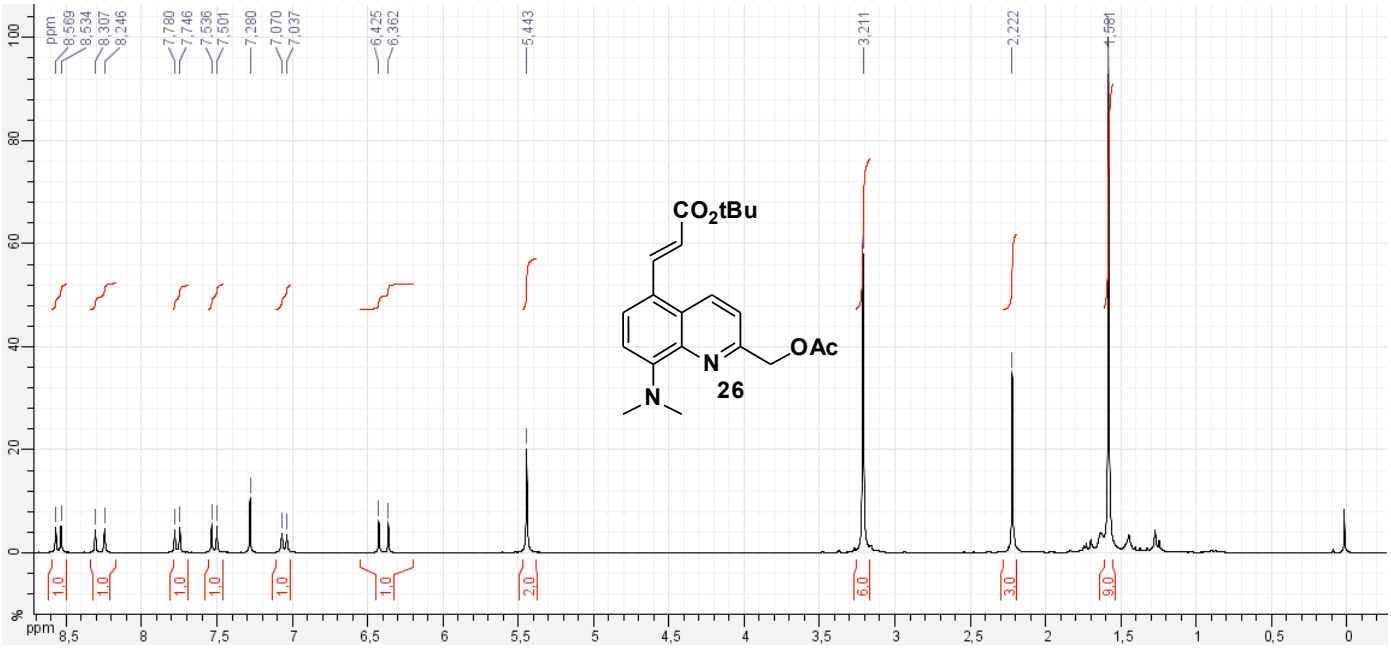
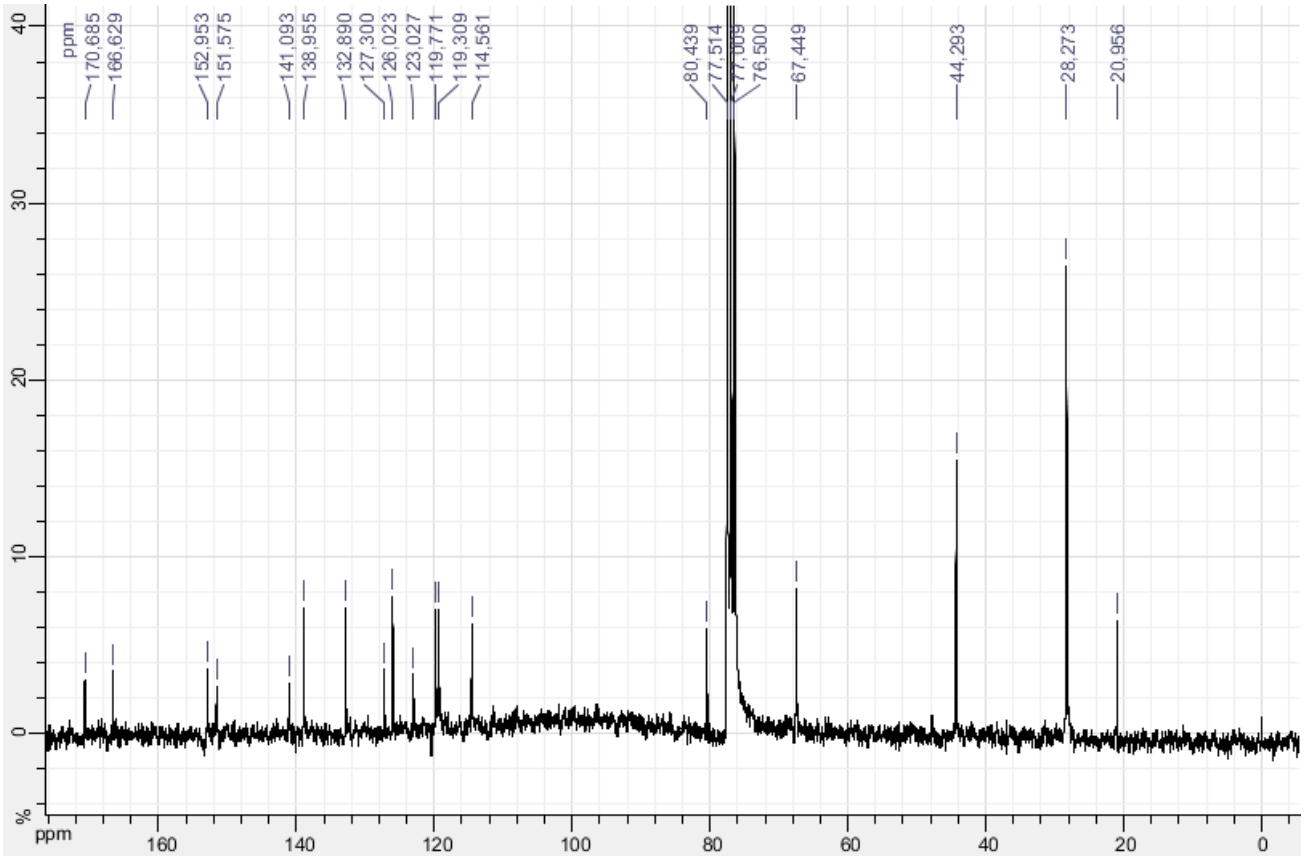
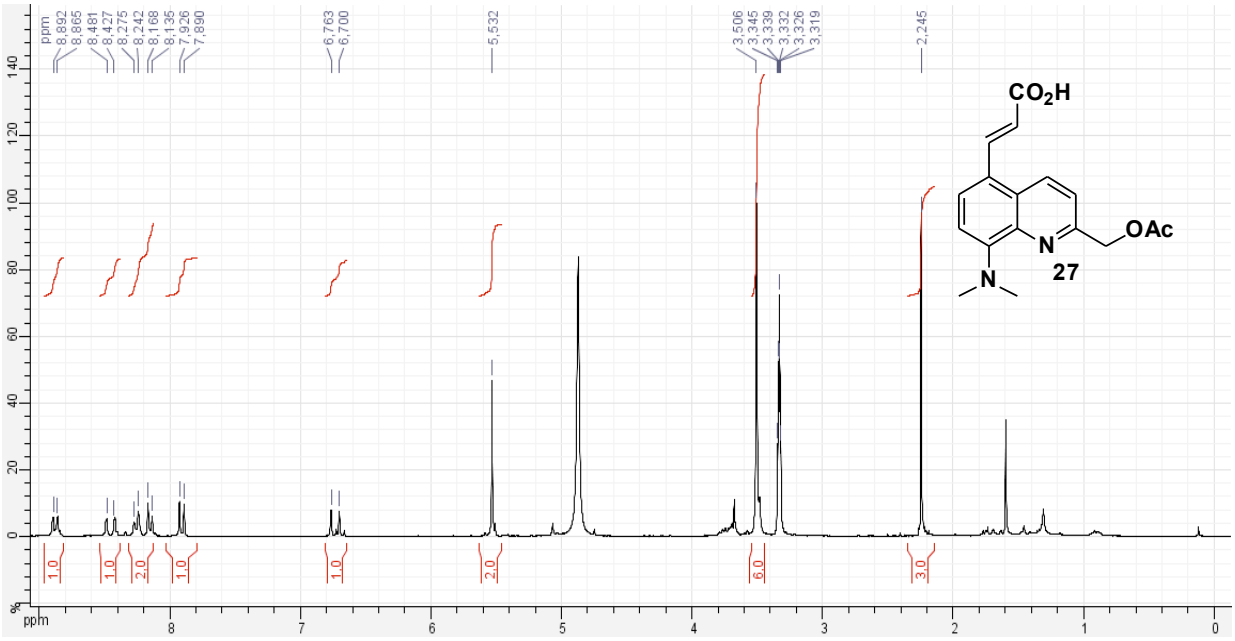
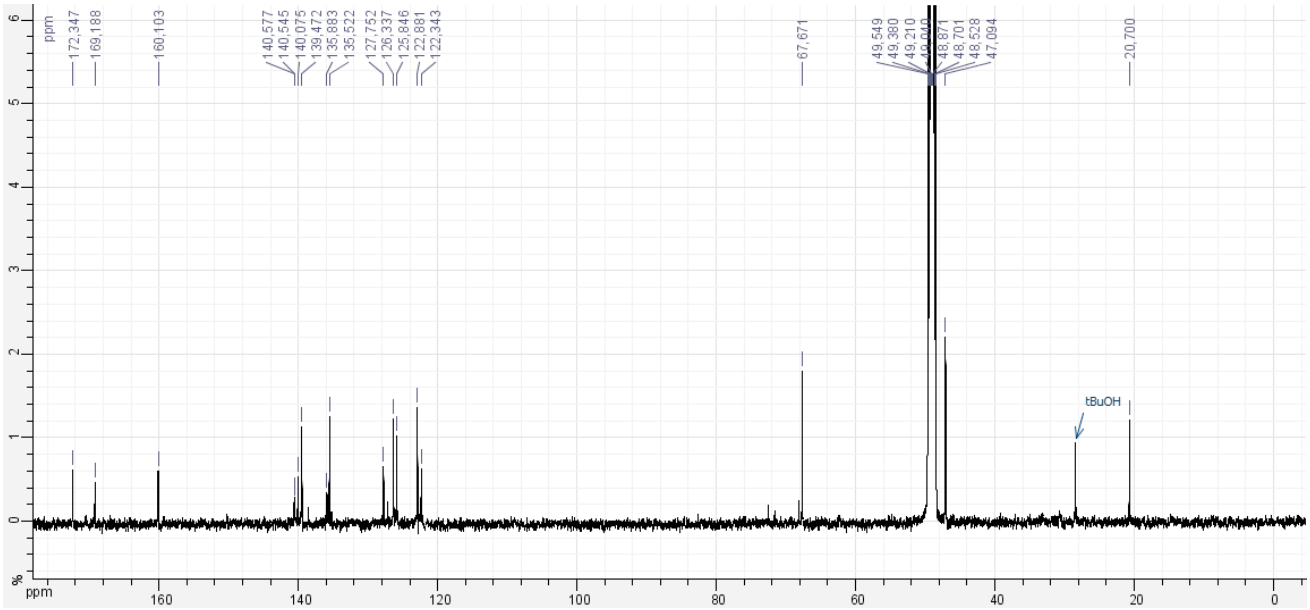
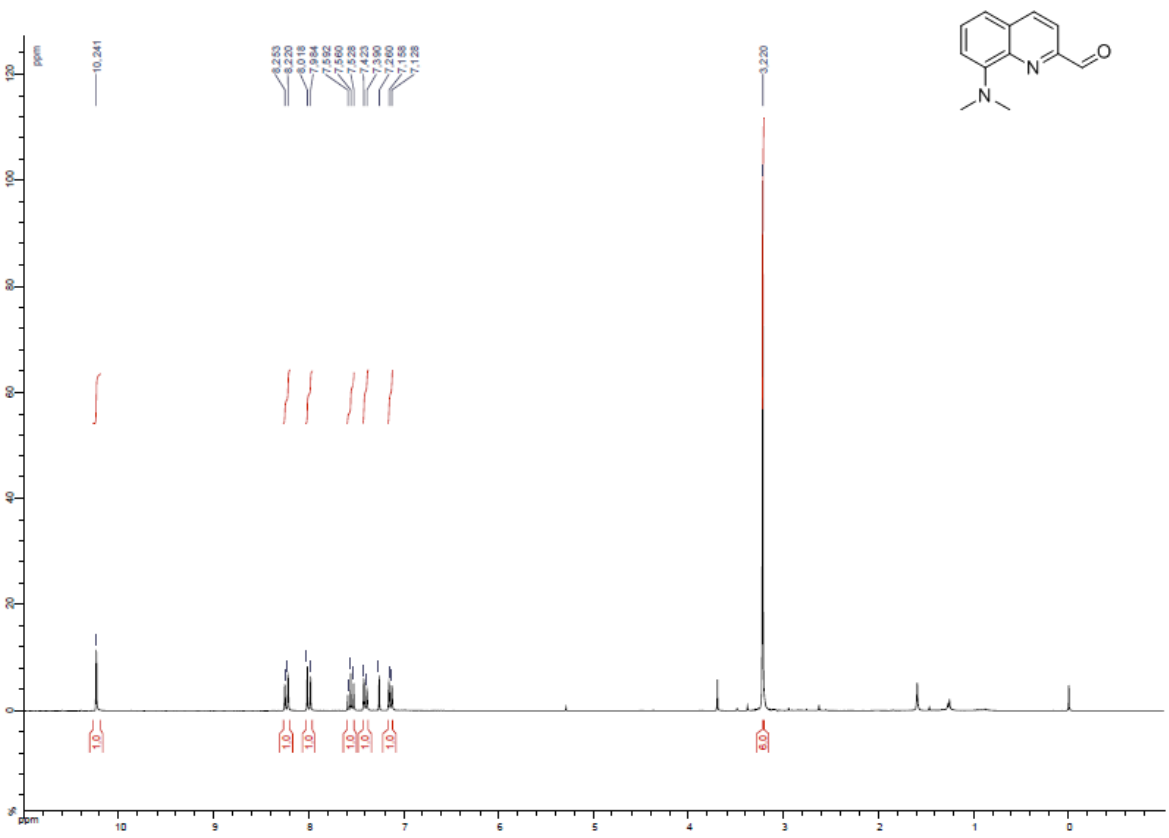
77,695
77,183
76,675
64,744
45,689
28,157

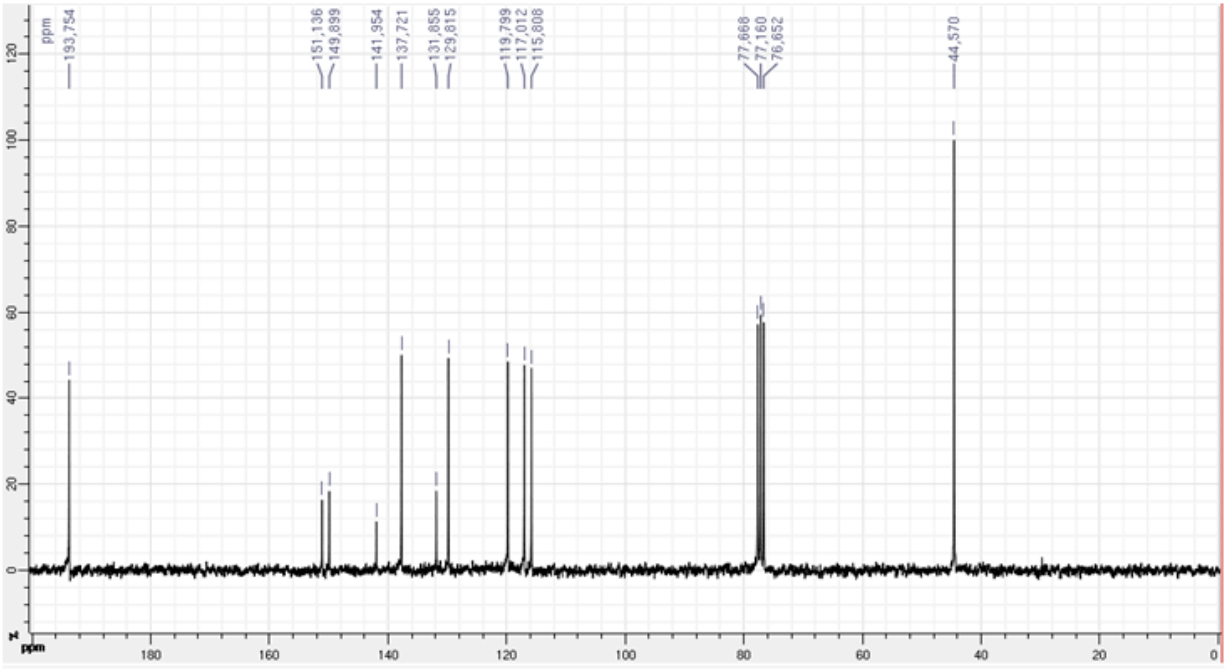

ppm
8,569
8,534
8,307
8,246
7,780
7,746
7,536
7,501
7,280
7,070
7,037
6,425
6,362
5,443
3,211
2,222
1,581
CO2tBu
OAc
N
N
26
1,0
1,0
1,0
1,0
1,0
1,0
2,0
6,0
3,0
9,0

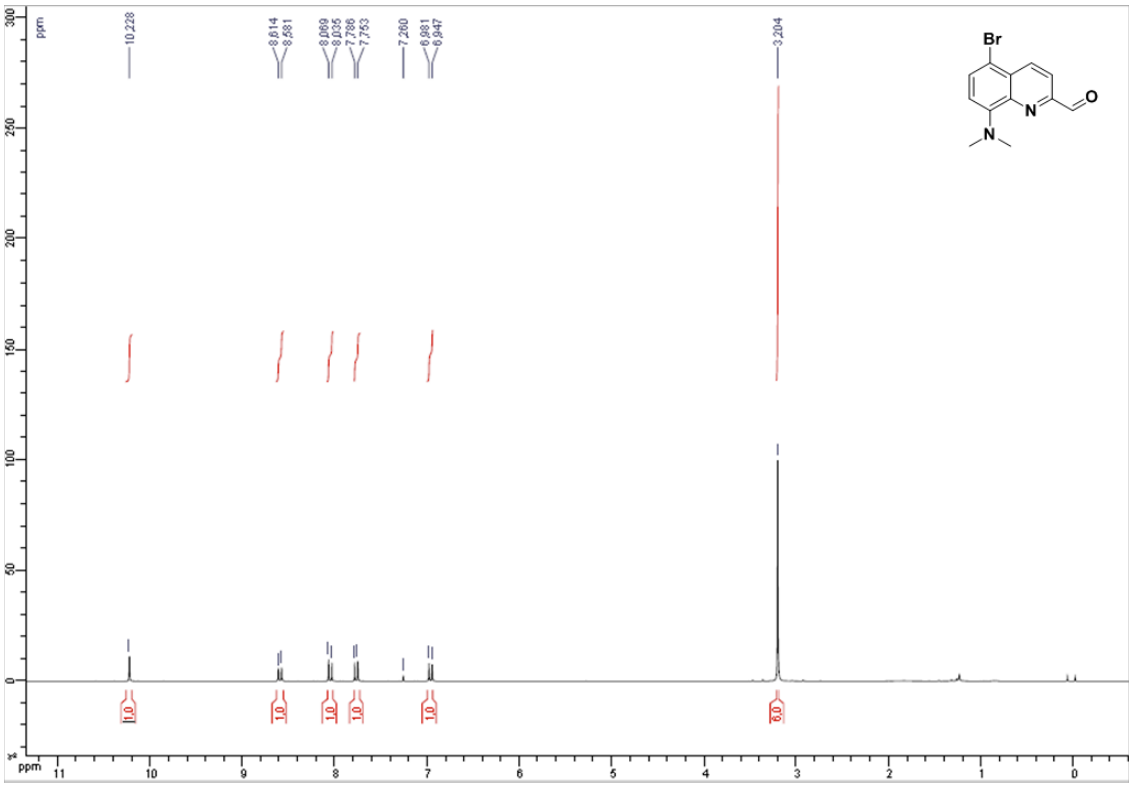

ppm
170,685
166,629
152,953
151,575
141,093
138,955
132,890
127,300
126,023
123,027
119,771
119,309
114,561
80,439
77,514
77,069
76,500
67,449
44,293
28,273
20,956


ppm
8.892
8.865
8.481
8.427
8.275
8.242
8.168
8.135
7.926
7.890
6.763
6.700
5.532
3.506
3.345
3.339
3.332
3.326
3.319
2.245
1.0
1.0
2.0
1.0
1.0
2.0
6.0
3.0
CO2H
OAc
N
N
27


ppm
172.347
169.188
160.103
140.577
140.545
140.075
139.472
135.883
135.522
127.752
126.337
125.846
122.881
122.343
67.671
49.549
49.380
49.210
48.871
48.701
48.528
47.064
20.700
tBuOH


10.241
8.253
8.220
8.018
7.984
7.592
7.560
7.528
7.423
7.390
7.260
7.158
7.128
3.220
1.0
1.0
1.0
1.0
1.0
1.0
6.0
ppm


ppm
193,754
151,136
149,899
141,954
137,721
131,855
129,815
119,799
117,012
115,866
77,666
77,160
76,652
44,570


ppm
10.228
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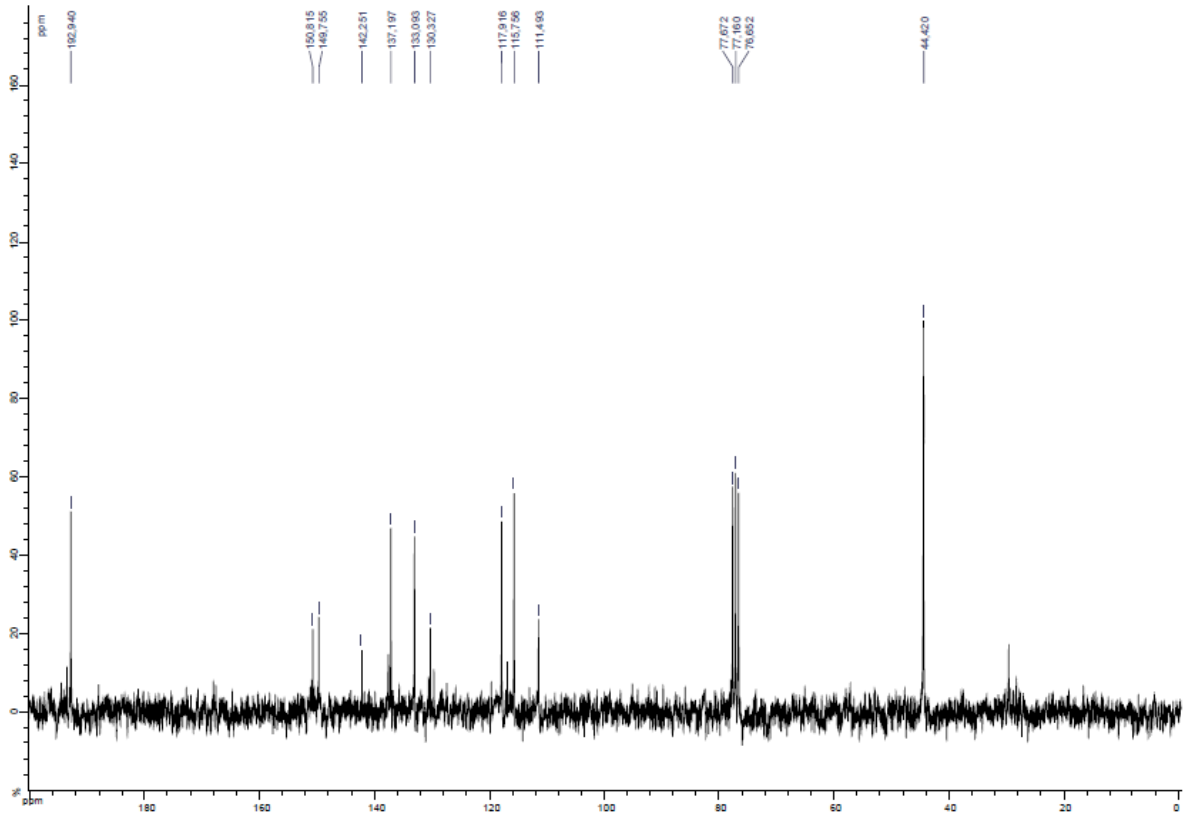
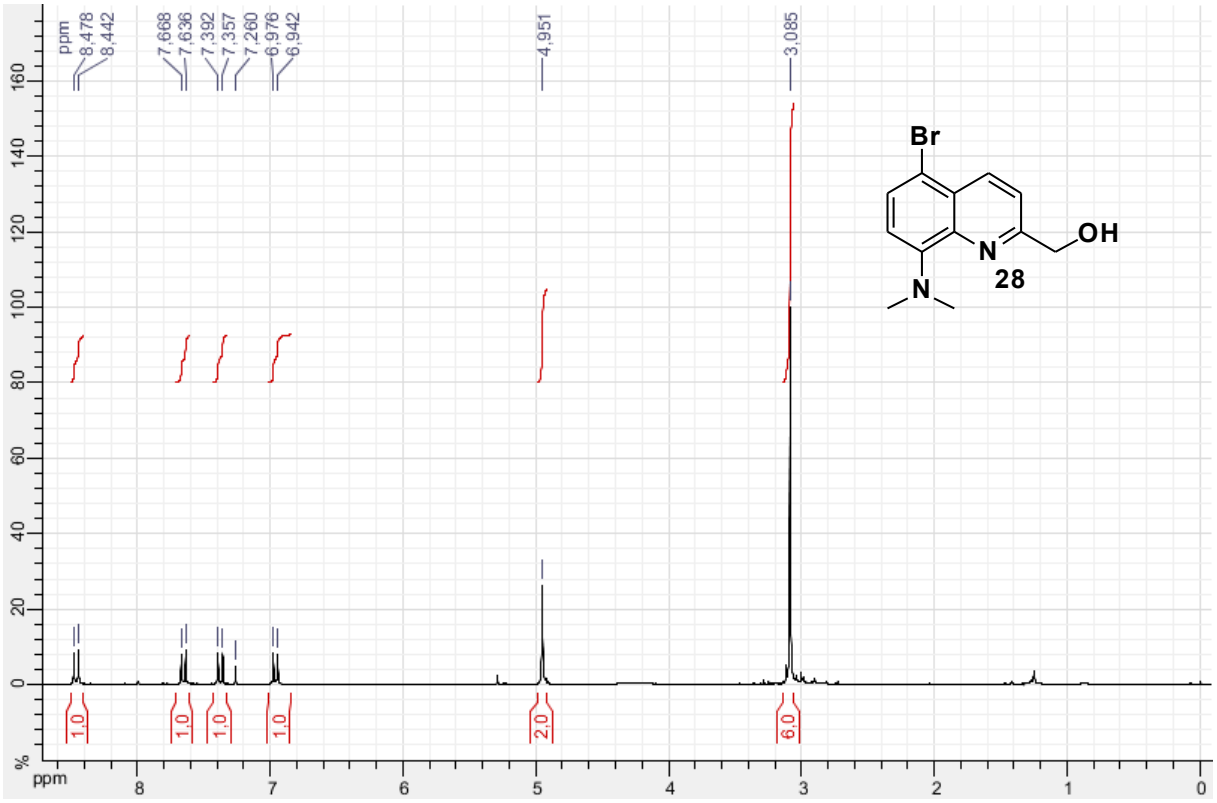
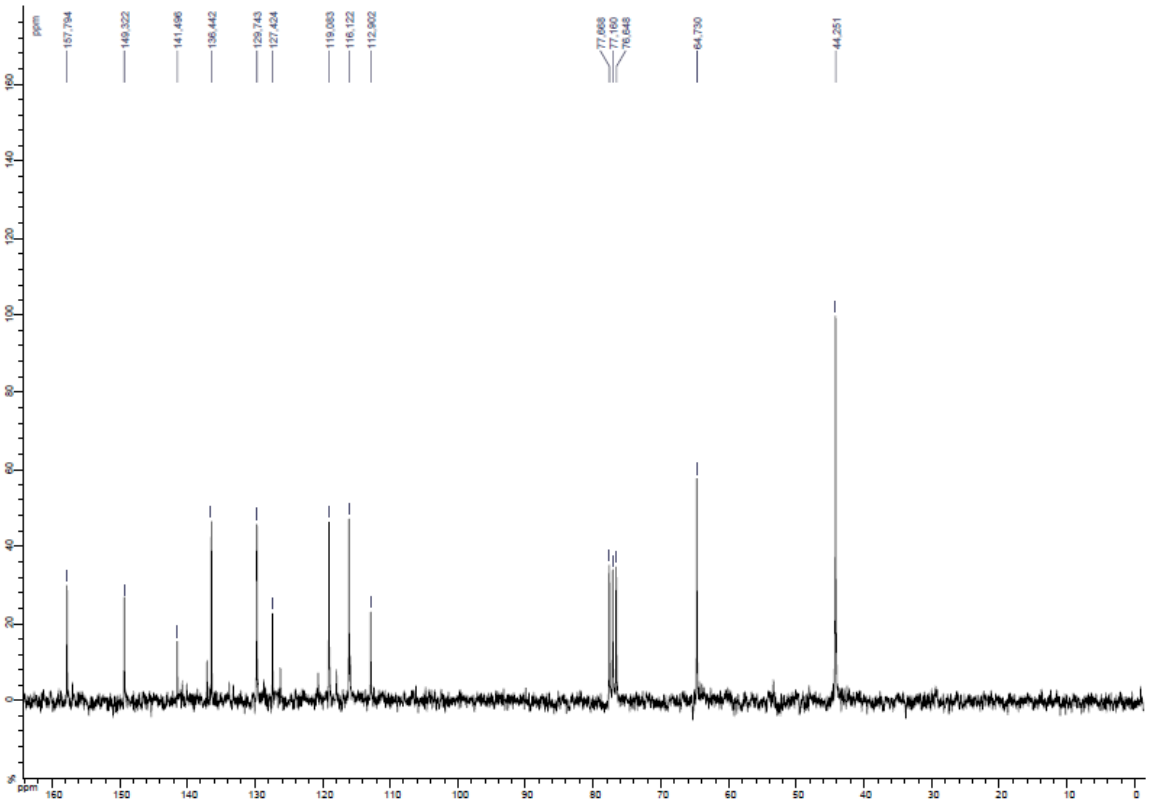
8.581
8.069
8.035
7.786
7.753
7.260
6.881
6.847
3.204
Br
O
N
N
1.0
1.0
1.0
1.0
1.0
6.0
ppm


ppm
192.940
150.815
149.755
142.251
137.197
133.093
130.327
117.916
115.756
111.493
77.672
77.160
76.652
44.420
ppm


ppm
8,478
8,442
7,668
7,636
7,392
7,357
7,260
6,976
6,942
4,951
3,085
Br
OH
N
N
28
1,0
1,0
1,0
1,0
2,0
6,0
%
ppm


ppm
157,794
149,322
141,496
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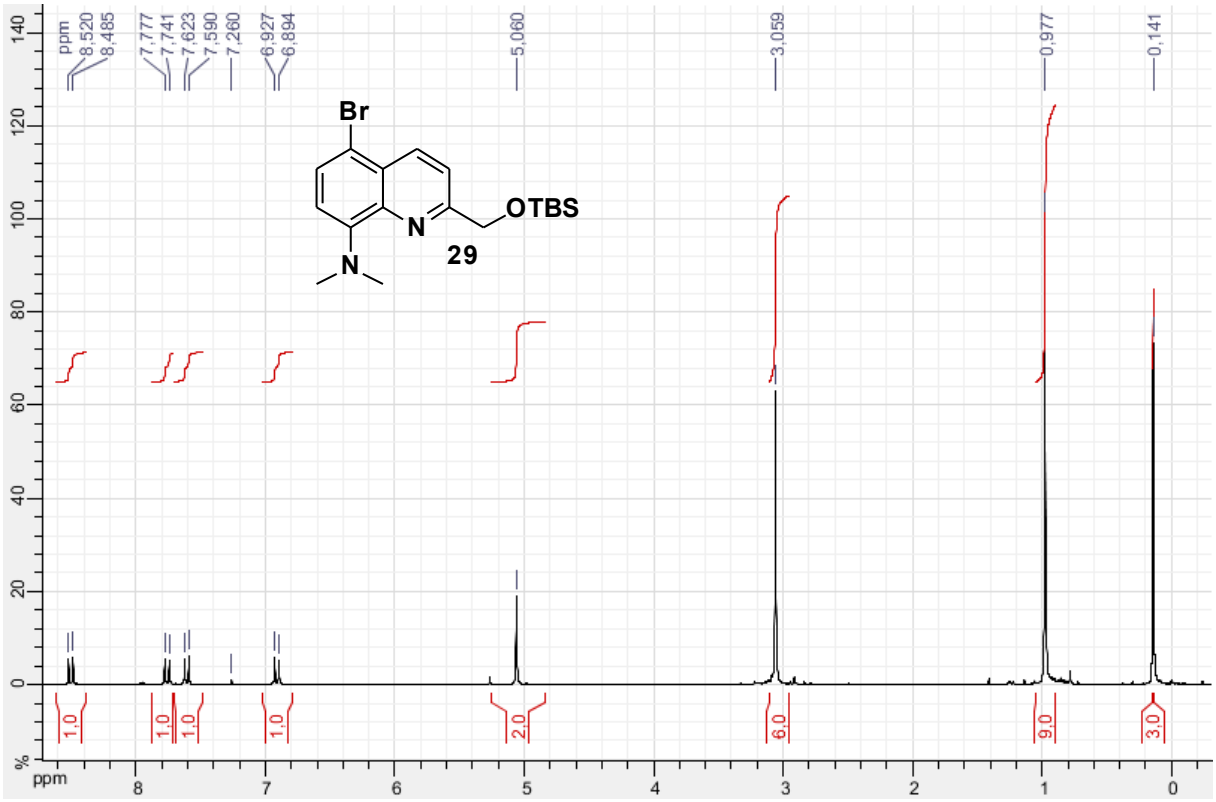
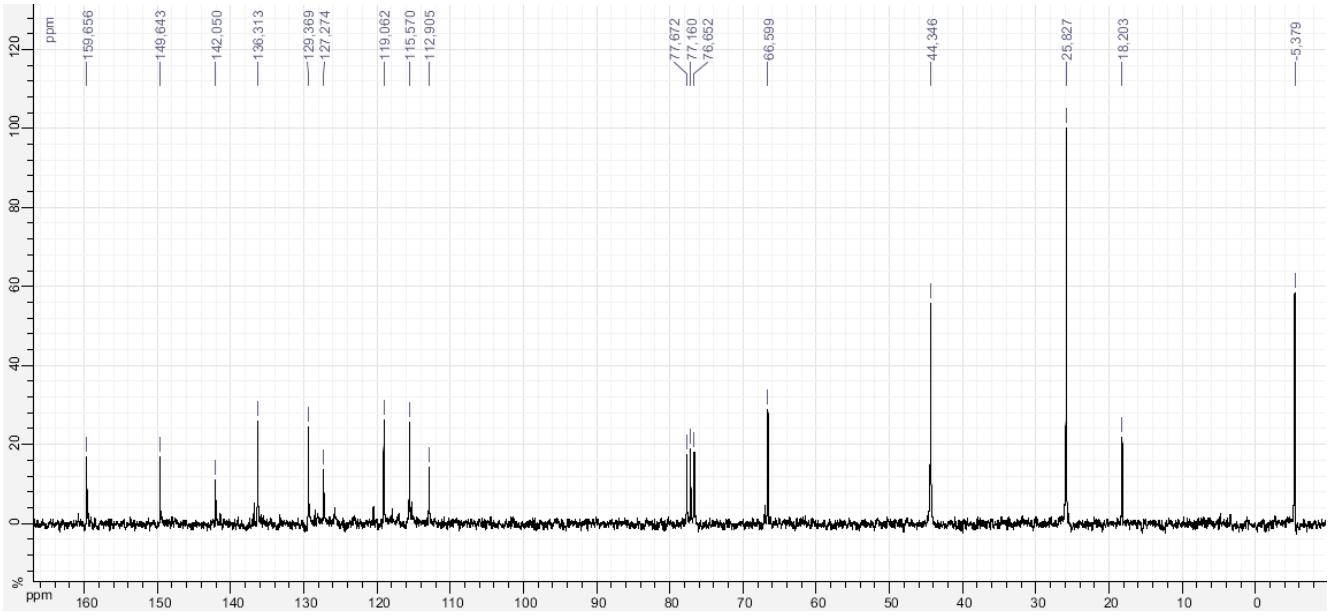
129,743
127,424
119,083
116,122
112,902
77,668
77,160
76,648
64,730
44,251
%
ppm


ppm
8,520
8,485
7,777
7,741
7,623
7,590
7,260
6,927
6,894
5,060
3,059
0,977
0,141
Br
N
OTBS
N
29
1,0
1,0
1,0
1,0
2,0
6,0
9,0
3,0
%
ppm


ppm
159,656
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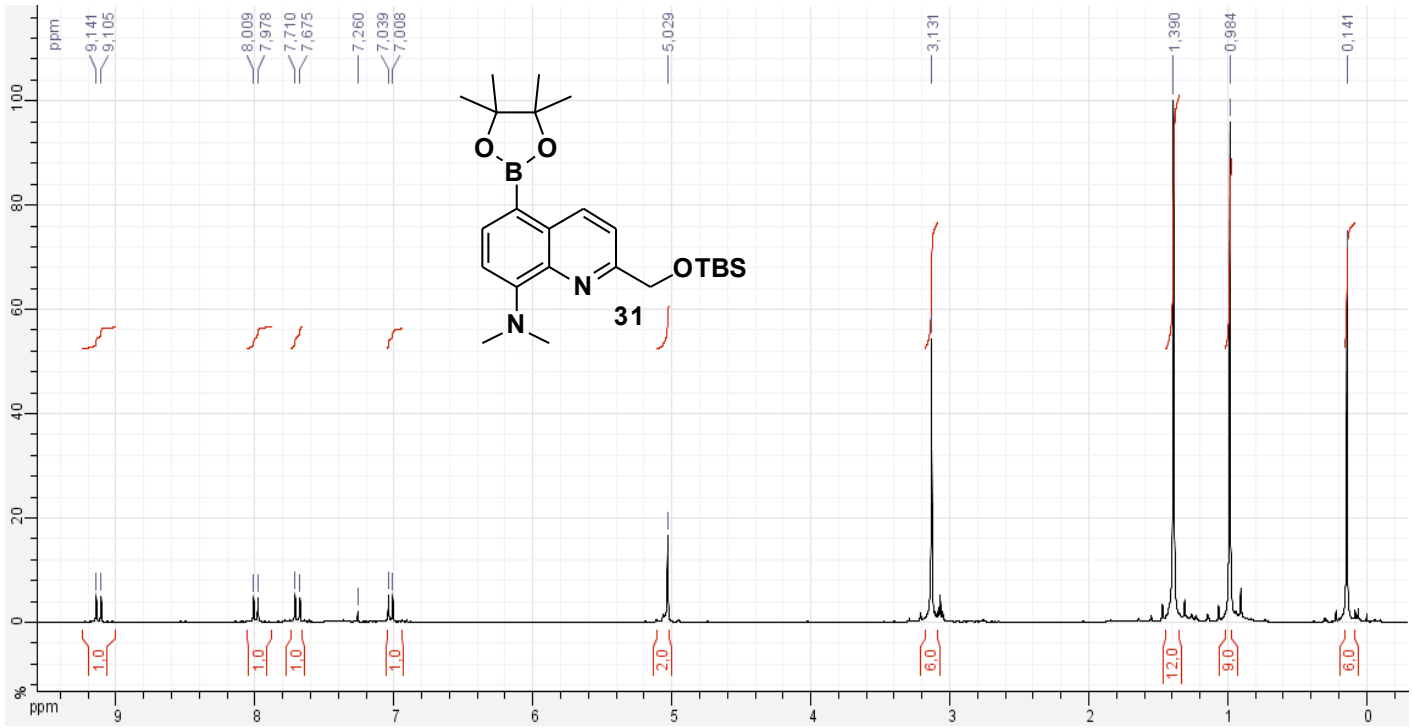
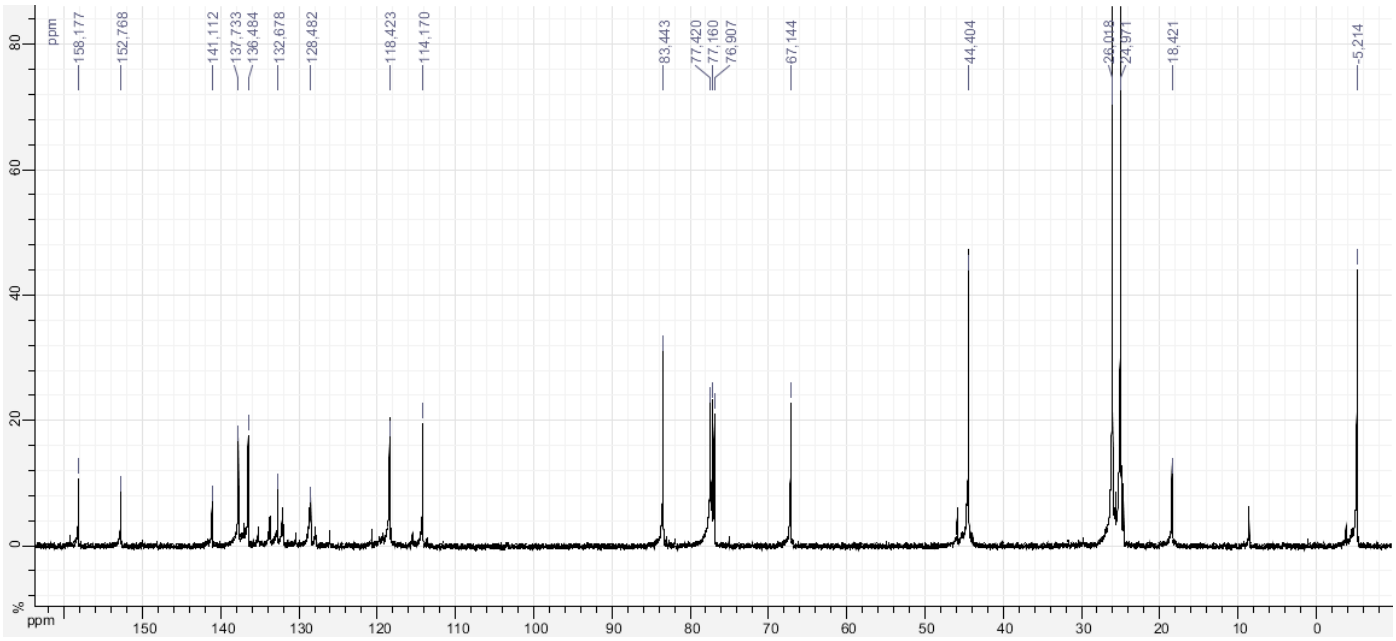
142,050
136,313
129,369
127,274
119,062
115,570
112,905
77,672
77,160
76,652
66,599
44,346
25,827
18,203
-5,379
%
ppm


ppm
9.141
9.105
8.009
7.978
7.710
7.675
7.260
7.039
7.008
5.029
3.131
1.390
0.984
0.141
OTBS
N
B
O
O
N
31
1.0
1.0
1.0
1.0
2.0
6.0
12.0
9.0
6.0


ppm
158.177
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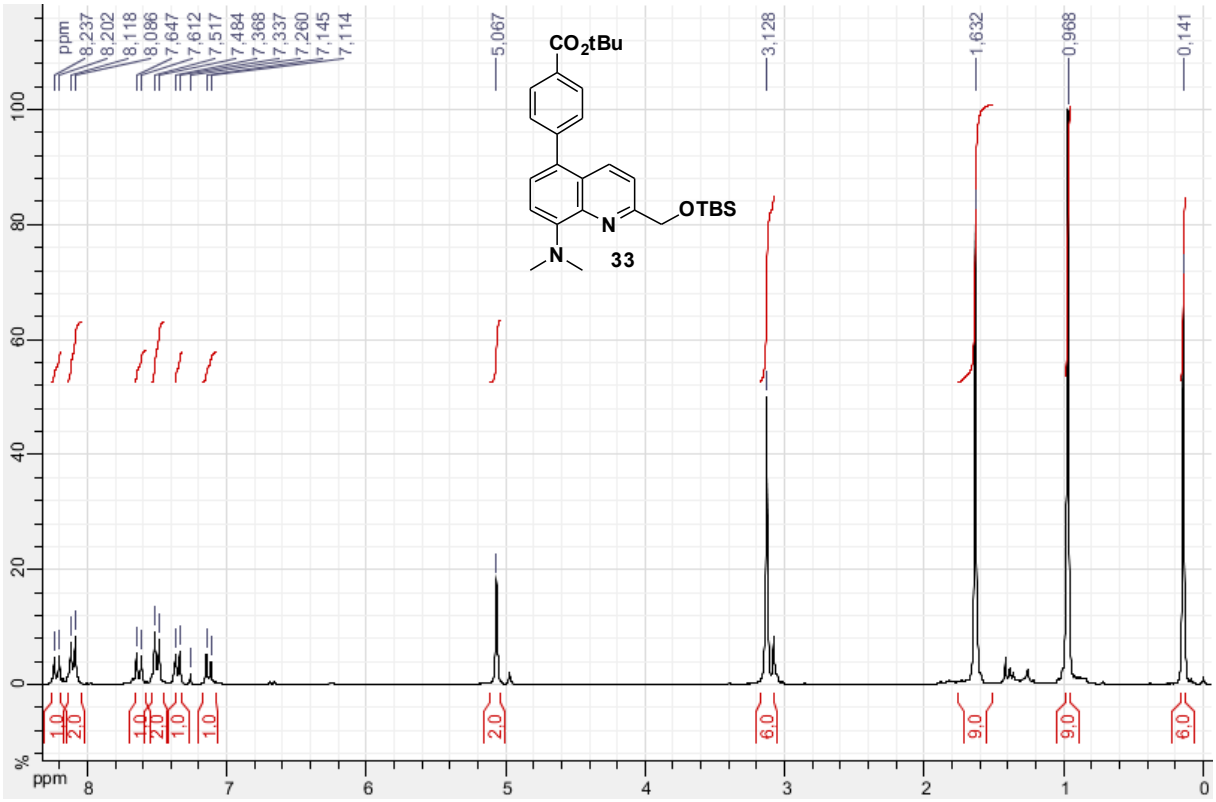
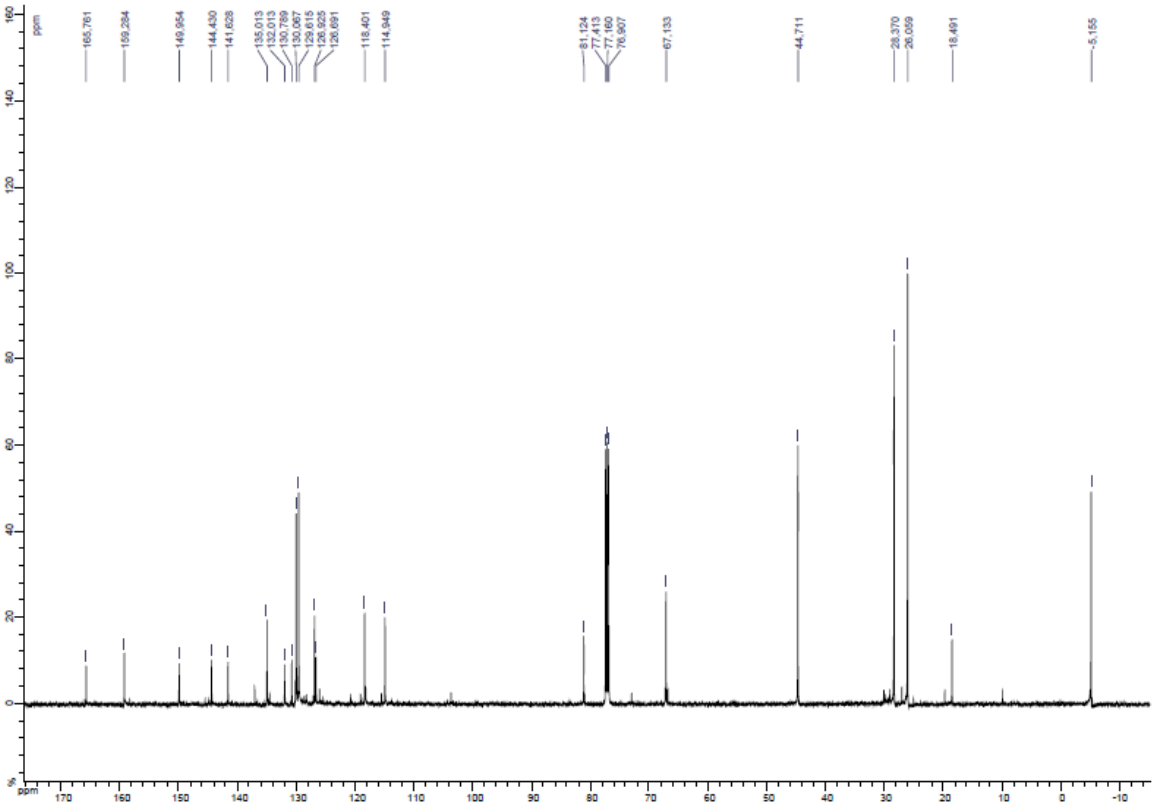
141.112
137.733
136.484
132.678
128.482
118.423
114.170
83.443
77.420
77.160
76.907
67.144
44.404
26.018
24.971
18.421
-5.214


ppm
8,237
8,202
8,118
8,086
7,647
7,612
7,517
7,484
7,368
7,337
7,260
7,145
7,114
5,067
3,128
1,632
0,968
0,141
CO2tBu
OTBS
N
N
33
1,0
2,0
1,0
2,0
1,0
1,0
2,0
6,0
9,0
9,0
6,0


ppm
165,761
159,284
149,954
144,430
141,628
135,013
132,013
130,789
130,067
129,615
126,925
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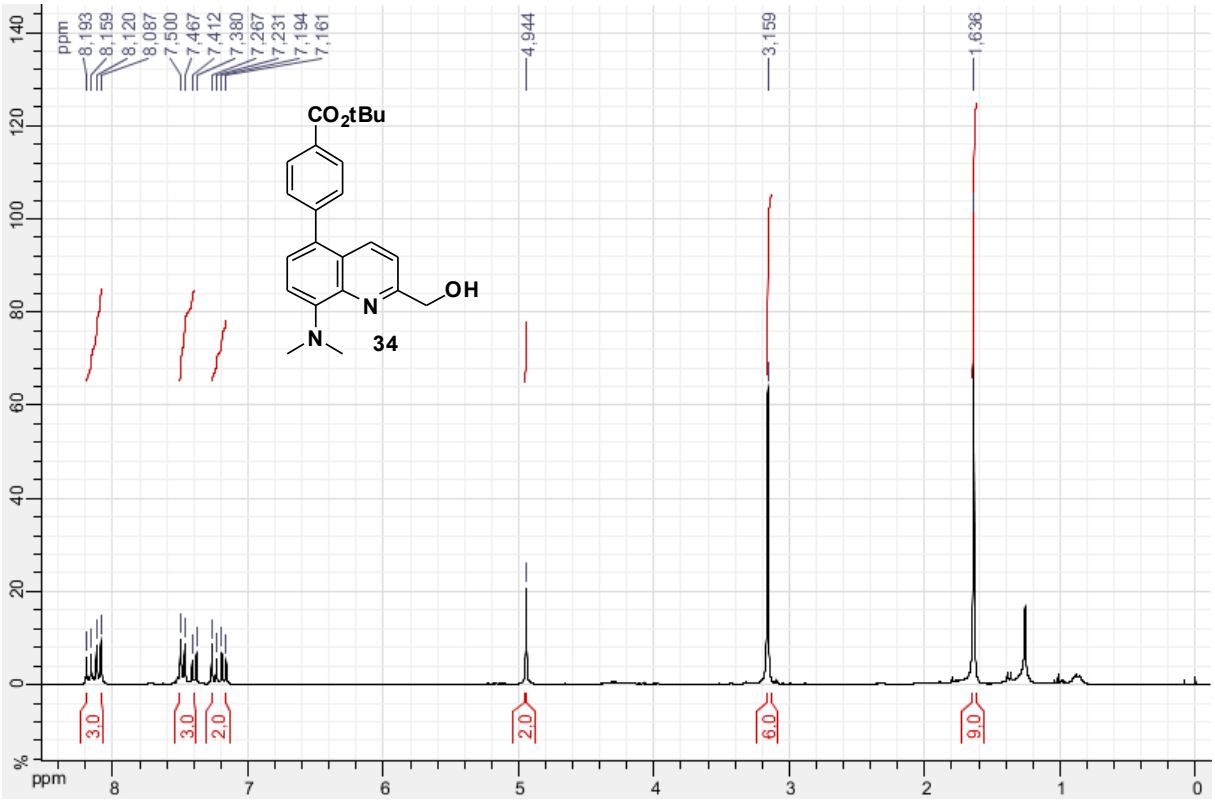
44,711
28,370
26,059
18,491
-5,155


ppm
8,193
8,159
8,120
8,087
7,500
7,467
7,412
7,380
7,267
7,231
7,194
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4,944
3,159
1,636
CO2tBu
OH
N
N
34
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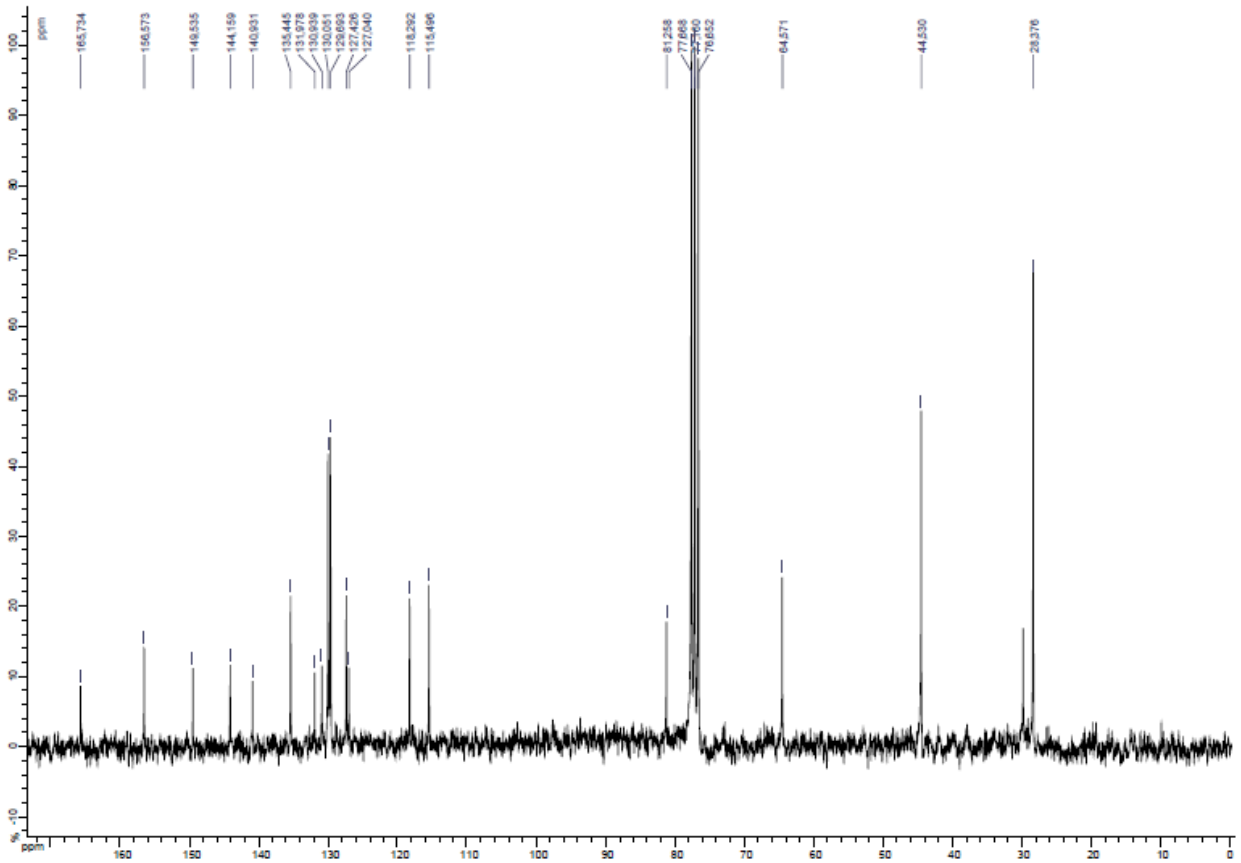
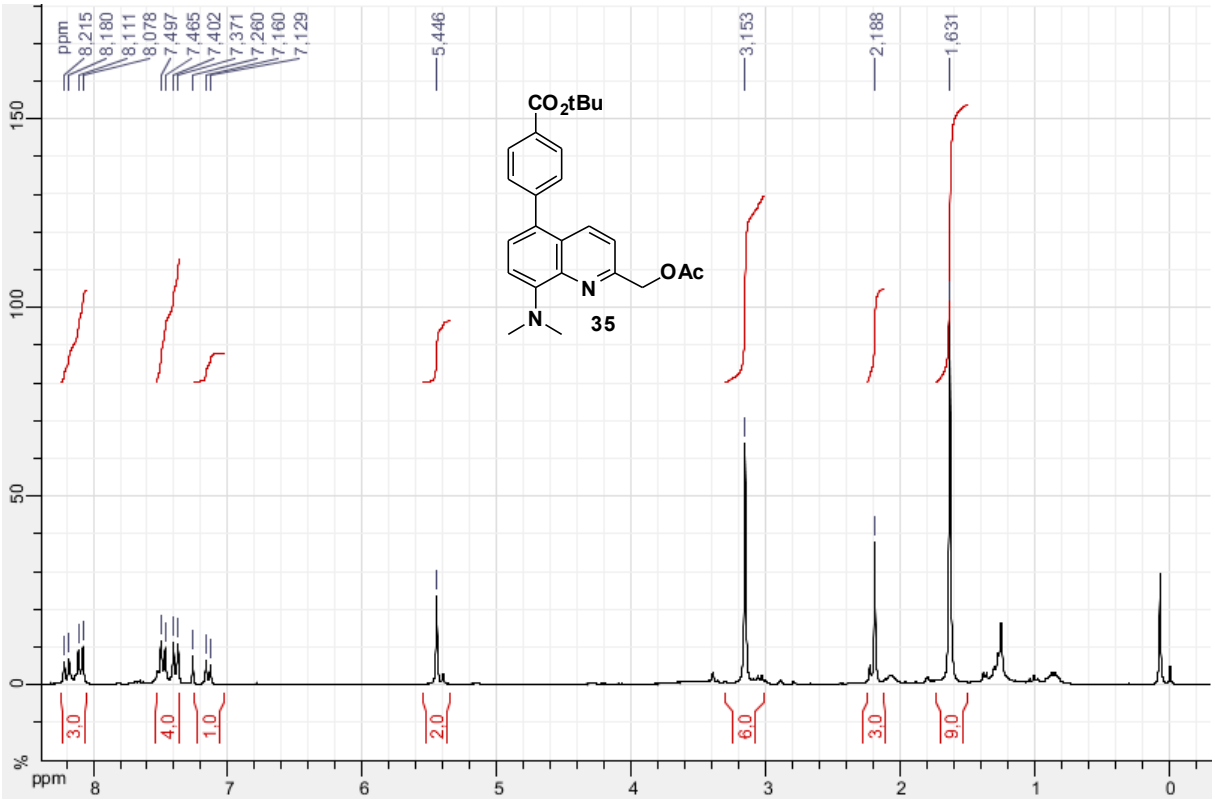
3,0
2,0
2,0
6,0
9,0
%
ppm


ppm
165,734
156,573
149,535
144,159
140,931
135,445
131,978
130,839
130,651
129,693
127,426
127,040
118,292
115,496
81,258
77,668
77,360
76,852
64,571
44,530
28,376
%
ppm


ppm
8,215
8,180
8,111
8,078
7,497
7,465
7,402
7,371
7,260
7,160
7,129
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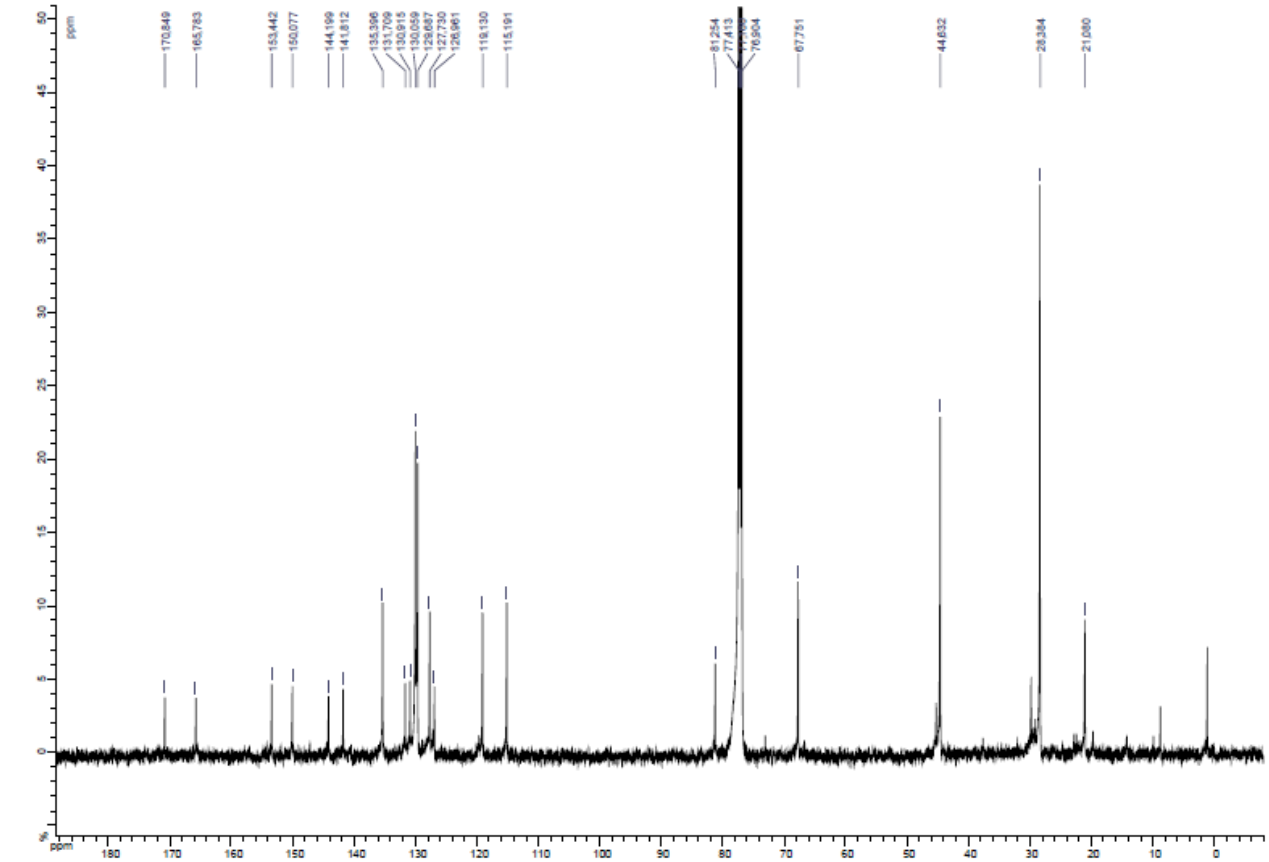
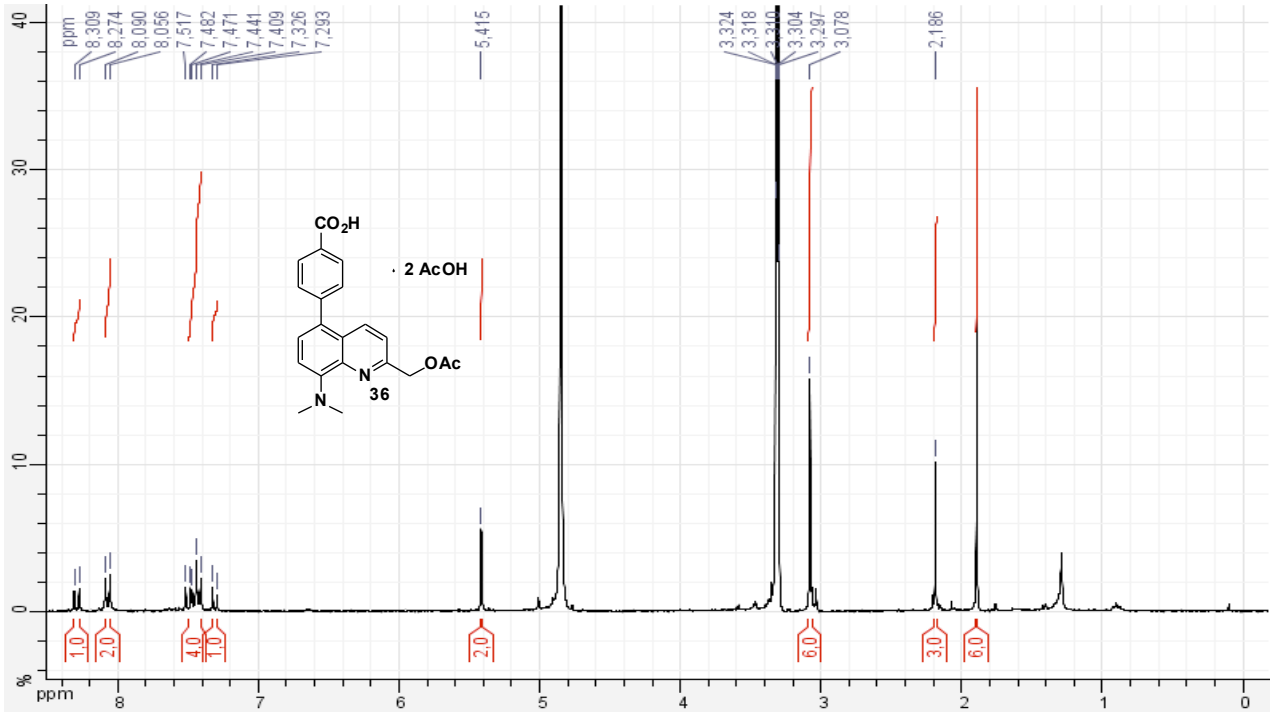
3,153
2,188
1,631
CO2tBu
OAc
N
N
35
3,0
4,0
1,0
2,0
6,0
3,0
9,0


ppm
170,849
165,783
153,442
150,077
144,199
141,812
135,386
131,709
130,915
130,059
129,687
127,730
126,861
119,130
115,191
81,254
77,413
76,904
67,751
44,632
28,384
21,080


ppm
8,309
8,274
8,090
8,056
7,517
7,482
7,471
7,441
7,409
7,326
7,293
5,415
3,324
3,318
3,310
3,304
3,297
3,078
2,186
CO2H
· 2 AcOH
OAc
N
N
36
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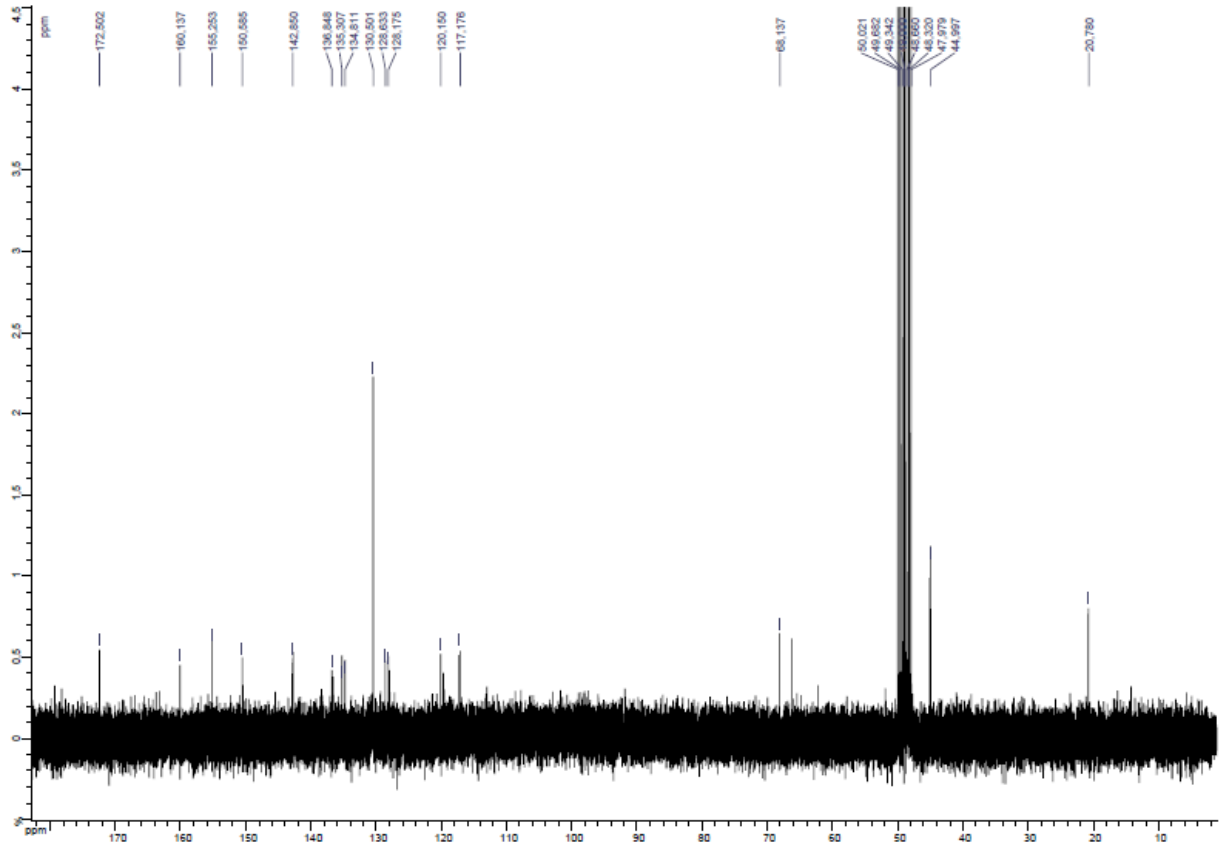
2,0
4,0
1,0
2,0
6,0
3,0
6,0


ppm
172,502
160,137
155,253
150,585
142,850
136,848
135,307
134,811
130,501
128,633
128,175
120,150
117,176
68,137
50,021
49,682
49,342
48,660
48,320
47,979
44,997
20,780