Supporting Information

Metal- and Acid-Free C–H Formylation of Nitrogen Heterocycles: Using Trioxane as an Aldehyde Equivalent Enabled by an Organic-Soluble Oxidant

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1. General Considerations

Methods:

All reactions were performed in scintillation or microwave vials under a nitrogen atmosphere unless otherwise specified. Reactions were monitored by liquid chromatography/mass spectrometry (LCMS) or by thin layer chromatography (TLC) on Silica Gel 60 F_{254} plates (EMD) and visualized with UV light (254 nm). Flash chromatography was performed using pre-packed 12 gram RediSep R_f silica gel columns on a Teledyne Isco CombiFlash R_f automated chromatography system. Organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator.

Materials and Reagents:

All reagents and solvents were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Strem, Acros) and used without further purification unless otherwise specified. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used without further purification unless otherwise specified. $CDCl_3$ was treated with and stored over K_2CO_3. $(N^nBu_4)_2S_2O_8$ was prepared according to the method of Kim:[1] $N(^nBu_4)HSO_4$ (40 mmol, 13.2 g) and $K_2S_2O_8$ (20 mmol, 5.4 g) were dissolved in 100 mL water and stirred for 30 min. The aqueous solution was then extracted with CH_2Cl_2 (100 mL x 3), and the combined organic layer was washed with a sat'd NaCl solution (100 mL), and dried over Mg_2SO_4. After filtration, the solvent was removed *in vacuo* to give $(N^nBu_4)_2S_2O_8$ as a white solid, which was used without any further purification.

Instrumentation:

Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were recorded on a Varian 500 (500 MHz) NMR spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm). Proton resonances are referenced to residual protium in the NMR solvent. Carbon resonances are referenced to the carbon resonances of the NMR solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) in Hertz (Hz), integration.

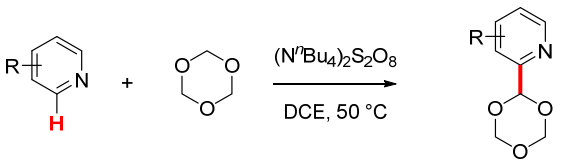
LCMS samples were run on an Agilent 1100 or 1200 system. High-resolution mass spectrometry (HRMS) data were recorded on a Waters Xevo G2 QTof instrument in either ESI^+ or ESI^- (electrospray) ionization mode.

Abbreviations Used:

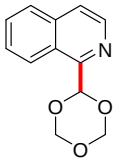
calc'd = calculated, h = hours, min = minutes, rt = room temperature

[1] Choi, H. C.; Cho, K. I.; Kim, Y. H. *Het. Chem.* **1995**, *6*, 333-338.

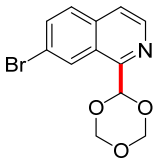
2. Coupling with Heterocycles with Trioxane



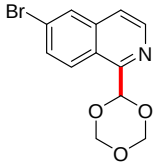
General Procedure: To a 0.5-dram vial was added heterocycle (0.4 mmol), trioxane (6 mmol, 15 equiv.), N(^{n}Bu$_4$)$_2$S$_2$O$_8$ (1 mmol, 2.5 equiv.), and $(CH_2Cl)_2$ (0.2 M). The resulting solution was heated to 50 ºC and stirred for 1–4 h until LCMS analysis indicated that conversion had ceased. After cooling to rt, the reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash chromatography on silica gel to afford analytically pure product.



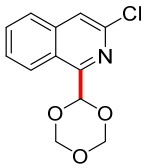
1-(1,3,5-Trioxan-2-yl)isoquinoline (3a): 73.8 mg, 84%, 10% EtOAc/CH_2Cl_2. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, *J* = 8.4 Hz, 1H), 8.52 (d, *J* = 5.6 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.75–7.67 (m, 3H), 6.45 (s, 1H), 5.49 (dd, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.2, 141.2, 137.2, 130.3, 127.5, 127.0, 126.6, 126.1, 122.7, 105.1, 94.1. HRMS (ESI) *m/z* calc'd for $C_{12}H_{12}NO_3$ [M+H]: 218.0817, found: 218.0812.



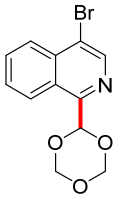
7-Bromo-1-(1,3,5-trioxan-2-yl)isoquinoline (3b): 87.5 mg, 74%, CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (d, *J* = 1.9 Hz, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 5.6 Hz, 1H), 6.40 (s, 1H), 5.49 (dd, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.4, 141.6, 135.6, 134.0, 129.0, 128.6, 127.0, 122.4, 121.6, 104.9, 94.0. HRMS (ESI) m/z calc'd for $C_{12}H_{11}BrNO_3$ [M+H]: 295.9922, found: 295.9916.



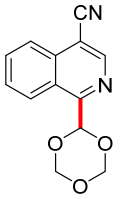
6-Bromo-1-(1,3,5-trioxan-2-yl)isoquinoline (3c): 87.0 mg, 74%, 0–5% EtOAc/CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, *J* = 9.1 Hz, 1H), 8.52 (d, *J* = 5.6 Hz, 1H), 8.04 (s, 1H), 7.74 (d, 1H), 7.62 (d, *J* = 5.6 Hz, 1H), 6.39 (s, 1H), 5.47 (dd, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.6, 142.2, 138.3, 131.0, 129.0, 128.7, 125.3, 124.5, 121.6, 105.2, 94.1. HRMS (ESI) m/z calc'd for $C_{12}H_{11}BrNO_3$ [M+H]: 295.9922, found: 295.9933.



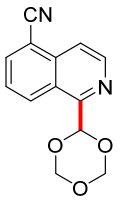
3-Chloro-1-(1,3,5-trioxan-2-yl)isoquinoline (3d): 61.8 mg, 61%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 8.6 Hz, 1H), 7.82–7.78 (m, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 6.37 (s, 1H), 5.46 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.0, 143.5, 139.4, 131.3, 127.7, 127.3, 126.2, 125.0, 121.9, 105.1, 94.1. HRMS (ESI) m/z calc'd for $C_{12}H_{11}ClNO_3$ [M+H]: 252.0427, found: 252.0427.



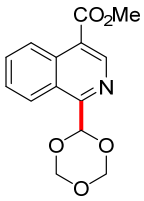
4-Bromo-1-(1,3,5-trioxan-2-yl)isoquinoline (3e): 97.0 mg, 82%, 0–5% EtOAc/CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, *J* = 8.5 Hz, 1H), 8.70 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 6.39 (s, 1H), 5.46 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.7, 142.9, 135.8, 131.6, 128.4, 127.3, 127.2, 126.3, 121.7, 104.8, 94.0. HRMS (ESI) m/z calc'd for $C_{12}H_{11}BrNO_3$ [M+H]: 295.9922, found: 295.9910.



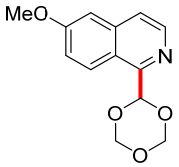
1-(1,3,5-Trioxan-2-yl)isoquinoline-4-carbonitrile (3f): 58.1 mg, 60%, 20% CH_2Cl_2/hexanes with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.6 Hz, 1H), 8.88 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.97 (t, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 6.46 (s, 1H), 5.49 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.1, 146.5, 135.9, 132.9, 129.2, 127.9, 125.3, 124.4, 115.7, 107.8, 104.6, 94.0. HRMS (ESI) m/z calc'd for $C_{13}H_{11}N_2O_3$ [M+H]: 243.0769, found: 243.0766.



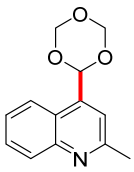
1-(1,3,5-Trioxan-2-yl)isoquinoline-5-carbonitrile (3g): 70.9 mg, 73%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 8.7 Hz, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 8.14 (dd, *J* = 21.3, 6.5 Hz, 2H), 7.76 (t, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 5.48 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.3, 143.6, 136.5 (d, *J* = 4.0 Hz), 132.6, 126.6, 125.7, 119.7, 116.6, 109.9, 105.4, 94.1. HRMS (ESI) m/z calc'd for $C_{13}H_{11}N_2O_3$ [M+H]: 243.0769, found: 243.0760.



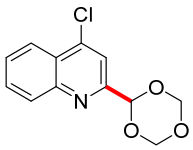
Methyl 1-(1,3,5-trioxan-2-yl)isoquinoline-4-carboxylate (3h): 65.7 mg, 60%, 20% CH_2Cl_2/hexanes with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.97 (dd, *J* = 14.3, 8.7 Hz, 2H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 6.48 (s, 1H), 5.49 (dd, 4H), 4.06 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.6, 156.9, 144.7, 135.2, 132.0, 127.7, 127.0, 125.9, 125.2, 122.3, 104.8, 94.1, 52.5. HRMS (ESI) m/z calc'd for $C_{14}H_{14}NO_5$ [M+H]: 276.0872, found: 276.0861.



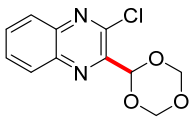
6-Methoxy-1-(1,3,5-trioxan-2-yl)isoquinoline (3i): 76.1 mg, 77%, 0–5% EtOAc/CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, *J* = 9.3 Hz, 1H), 8.42 (d, *J* = 5.7 Hz, 1H), 7.60 (d, *J* = 5.7 Hz, 1H), 7.29 (dd, 1H), 7.09 (d, *J* = 2.6 Hz, 1H), 6.37 (s, 1H), 5.46 (dd, 4H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.7, 152.7, 141.7, 139.4, 128.5, 121.9, 121.8, 120.5, 105.2, 104.4, 94.1, 55.5. HRMS (ESI) m/z calc'd for $C_{13}H_{14}NO_4$ [M+H]: 248.0923, found: 248.0919.



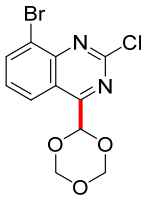
2-Methyl-4-(1,3,5-trioxan-2-yl)quinolone (3j): 58.6 mg, 63.4%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.68 (s, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 6.11 (s, 1H), 5.45 (dd, *J* = 6.3 Hz, 4H), 2.78 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.8, 147.1, 146.0, 130.2, 129.5, 128.4, 127.0, 123.8, 118.9, 102.2, 93.7, 19.0. HRMS (ESI) m/z calc'd for $C_{13}H_{14}NO_3$ [M+H]: 232.0973, found: 232.0966.



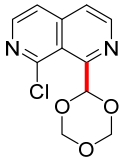
4-Chloro-2-(1,3,5-trioxan-2-yl)quinolone (3k): 158.5 mg (0.8 mmol scale), 79%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.94 (s, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 6.11 (s, 1H), 5.43 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.2, 148.1, 143.9, 130.8, 130.0, 128.3, 126.6, 124.1, 118.8, 101.2, 93.7. HRMS (ESI) m/z calc'd for $C_{12}H_{11}ClNO_3$ [M+H]: 252.0427, found: 252.0427.



2-Chloro-3-(1,3,5-trioxan-2-yl)quinoxaline (3l): 26.4 mg, 26%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.92–7.80 (m, 2H), 6.52 (s, 1H), 5.50 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.2, 145.3, 142.2, 140.3, 132.1, 130.8, 129.9, 128.2, 98.3, 94.0. HRMS (ESI) m/z calc'd for $C_{11}H_{10}ClN_2O_3$ [M+H]: 253.0380, found: 253.0365.



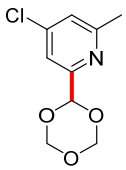
8-Bromo-2-chloro-4-(1,3,5-trioxan-2-yl)quinazoline (3m): 80.7 mg, 61%, 70% CH_2Cl_2/hexanes. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 6.32 (s, 1H), 5.45 (dd, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.1, 157.1, 151.0, 138.8, 128.5, 127.0, 122.7, 122.1, 103.5, 93.9. HRMS (ESI) m/z calc'd for $C_{11}H_9BrClN_2O_3$ [M+H]: 330.9485, found: 330.9470.



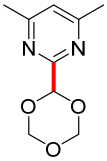
1-Chloro-8-(1,3,5-trioxan-2-yl)-2,7-naphthyridine (3n): 72.3 mg, 71.5%, 5% EtOAc/CH_2Cl_2. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* = 5.5 Hz, 1H), 8.47 (d, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 5.5 Hz, 1H), 7.65 (d, *J* = 5.5 Hz, 1H), 7.36 (s, 1H), 5.52 (dd, *J* = 4.4 Hz, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.9, 148.8, 145.7, 144.8, 143.2, 121.2, 120.6, 120.2, 98.4, 94.0. HRMS (ESI) m/z calc'd for $C_{11}H_{10}ClN_2O_3$ [M+H]: 253.0380, found: 253.0370.

4-Chloro-7-(1,3,5-trioxan-2-yl)-1*H*-pyrazolo[3,4-*c*]pyridine (3o): 32.5 mg, 34%, CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.28 (d, *J* = 11.9 Hz, 2H), 6.29 (s, 1H), 5.48 (dd, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.1, 136.8, 134.7, 132.8, 128.1, 124.6, 102.1, 93.770. HRMS (ESI) m/z calc'd for $C_9H_9ClN_3O_3$ [M+H]: 242.03332, found: 242.0325.

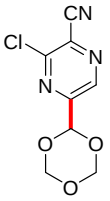
7-(1,3,5-Trioxan-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-4-carbonitrile (3p): 41.4 mg, 45%, 5% EtOAc/CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.57 (s, 1H), 7.64 (t, *J* = 2.8 Hz, 1H), 6.84 (t, *J* = 2.5 Hz, 1H), 6.32 (s, 1H), 5.46 (dd, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 142.4, 141.8, 135.3, 131.2, 129.5, 116.7, 102.9, 101.4, 101.3, 93.8. HRMS (ESI) m/z calc'd for $C_{11}H_{10}N_3O_3$ [M+H]: 232.0722, found: 232.0719.



4-Chloro-2-methyl-6-(1,3,5-trioxan-2-yl)pyridine (3q): 62.2 mg, 72%, 10% EtOAc/CH_2Cl_2. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.22 (s, 1H), 5.90 (s, 1H), 5.38 (dd, 4H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.7, 155.9, 145.2, 124.2, 118.8, 100.6, 93.6, 24.3. HRMS (ESI) m/z calc'd for $C_9H_{11}ClNO_3$ [M+H]: 216.0427, found: 216.0420.

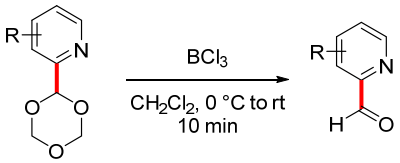


4,6-Dimethyl-2-(1,3,5-trioxan-2-yl)pyrimidine (3r): 55.6 mg, 71%, 10% EtOAc/CH_2Cl_2. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.00 (s, 1H), 5.43 (dd, *J* = 43.9, 6.2 Hz, 4H), 2.57 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.7, 162.0, 120.6, 100.8, 93.8, 24.1. HRMS (ESI) m/z calc'd for $C_9H_{13}N_2O_3$[M+H]: 197.0926, found: 197.0916.

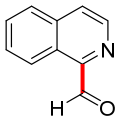


3-Chloro-5-(1,3,5-trioxan-2-yl)pyrazine-2-carbonitrile (3s): 40.0 mg, 44%, 10% EtOAc/CH_2Cl_2. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 6.03 (s, 1H), 5.39 (dd, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.4, 150.5, 141.6, 130.7, 113.4, 98.5, 93.5. HRMS (ESI) m/z calc'd for $C_8H_7ClN_3O_3$ [M+H]: 228.0176, found: 228.0182.

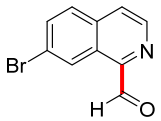
3. Deprotection of Trioxanes



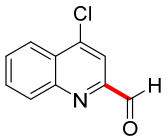
General Procedure: To a 0.5 dram vial was added acetal (0.2 mmol) and CH_2Cl_2 (0.5 M). The resulting solution was cooled to 0°C in an ice bath, then BCl_3 (1.0 M in CH_2Cl_2, 0.4 mL, 2 equiv.) was added dropwise. The reaction was then warmed to rt, stirred for 10 min, and then quenched with H_2O (0.3 mL) and stirred for 30 min at this temperature. The solution was basified with 1 M LiOH, and the aqueous layer was extracted with CH_2Cl_2 (1 mL x 3). The combined organic fractions were collected and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel to afford analytically pure product.



Isoquinoline-1-carbaldehyde (4a): 71.3 mg (0.6 mmol scale), 76%, CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 9.34 (d, 1H), 8.78 (d, *J* = 5.5 Hz, 1H), 7.99–7.87 (m, 2H), 7.84–7.73 (m, 2H). Spectral data are in agreement with reported literature values.[2]



7-Bromoisoquinoline-1-carbaldehyde (4b): 30.7 mg, 65%, CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 9.57 (s, 1H), 8.80 (d, *J* = 5.5 Hz, 1H), 7.91–7.84 (m, 2H), 7.81 (d, *J* = 8.8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.2, 148.7, 142.9, 135.3, 134.5, 128.4, 128.1, 126.9, 125.3, 124.7. HRMS (ESI) m/z calc'd for $C_{10}H_7BrNO$ [M+H]: 235.9711, found: 235.9707.



4-Chloroquinoline-2-carbaldehyde (4k): 24.8 mg, 65%, CH_2Cl_2 with 1% Et_3N. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 7.91 (t, *J* = 7.5 Hz, 2H), 7.82 (t, *J* = 7.7 Hz, 1H). Spectral data are in agreement with reported literature values.[3]

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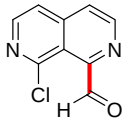
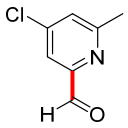
[2] (a) Yamazaki, T.; Kikumoto, S.; Ono, M.; Saitou, A.; Takahashi, H.; Kumakura, S.; Hirose, K.; Yanaka, M.; Takemura, Y.; Suzuki, S.; Matsui, R. Amine compounds and use thereof. Eur. Pat. Appl. 1550657, 2005. (b) Pascu, M.; Clarkson, G. J.; Kariuki, B. M.; Hannon, M. J. *Dalton Trans.* **2006**, 2635-2642. (c) Setoguchi, M.; Iimura, S.; Sugimoto, Y.; Yoneda, Y.; Chiba, J.; Watanabe, T.; Muro, F.; Iigo, Y.; Takayama, G.; Yokoyama, M.; Taira, T.; Aonuma, M.; Takashi, T.; Nakayama, A.; Machinaga, N. *Bioorg. Med. Chem.* **2012**, *20*, 1201-1212. (d) Nyiranshuti, L.; Kennedy, D. P.; DiPasquale, A. G.; Rheingold, A. L.; Planalp, R. P. *Polyhedron* **2016**, *109*, 147-153. (e) Haym, I.; Huynh, T. H. V.; Hansen, S. W.; Pedersen, M. H. F.; Ruiz, J. A.; Erichsen, M. N.; Gynther, M.; Bjørn-Yoshimoto, W. E.; Abrahamsen, B.; Bastlund, J. F.; Bundgaard, C.; Eriksen, A. L.; Jensen, A. A.; Bunch, L. *ChemMedChem* **2016**, *11*, 403-419. (f); Khusnutdinov, R. I.; Baiguzina, A. R.; Mukminov, R. R. *Russ. J. Org. Chem.* **2010**, *46*, 706-708.

[3] Chierrito, T. P. C.; Pedersoli-Mantoani, S.; Roca, C.; Requena, C.; Sebastian-Perez, V.; Castillo, W. O.; Moreira, N. C. S.; Pérez, C.; Sakamoto-Hojo, E. T.; Takahashi, C. S.; Jiménez-Barbero, J.; Cañada, F. J.; Campillo, N. E.; Martinez, A.; Carvalho, I. *Eur. J. Med. Chem.* **2017**, *139*, 773-791.



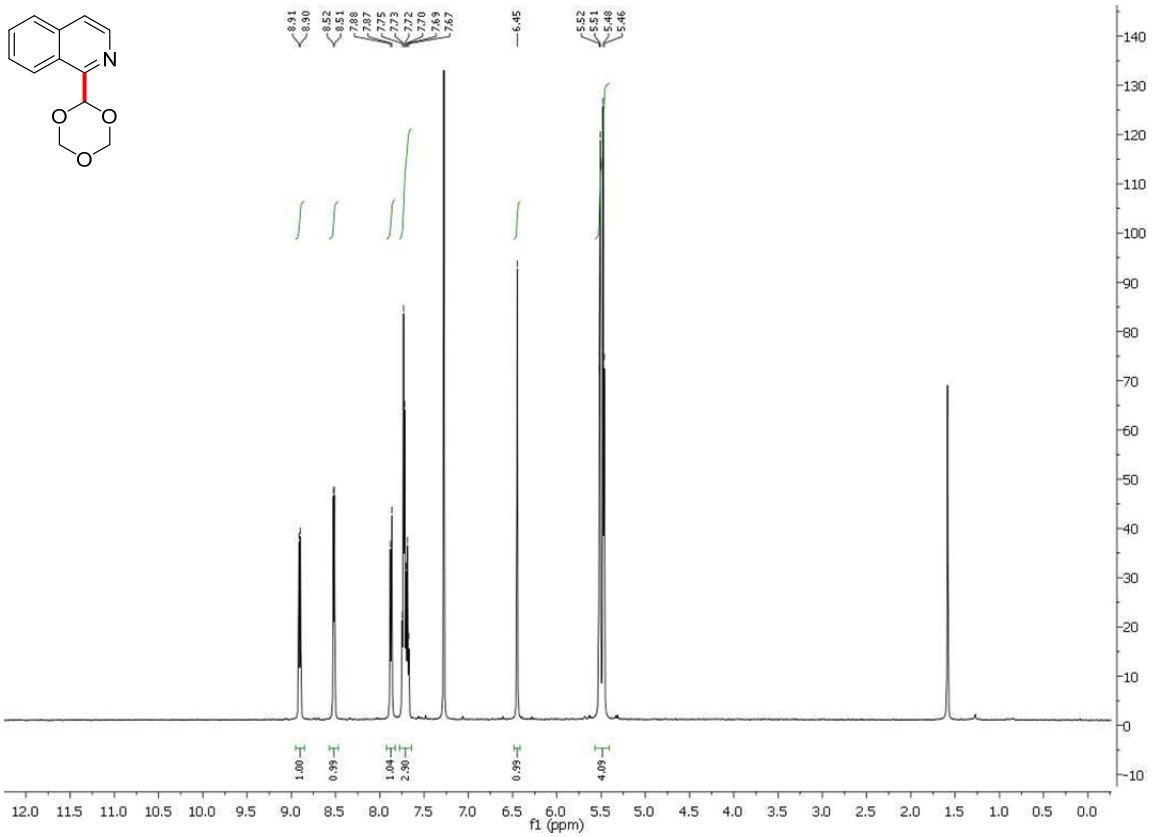
8-Chloro-2,7-naphthyridine-1-carbaldehyde (4n): 24.8 mg, 64%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.88 (d, *J* = 5.5 Hz, 1H), 8.56 (d, *J* = 5.6 Hz, 1H), 7.83 (d, *J* = 5.5 Hz, 1H), 7.71 (d, *J* = 5.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.7, 155.9, 149.5, 146.6, 146.0, 142.4, 121.8, 120.5, 119.5. HRMS (ESI) m/z calc'd for $C_9H_6ClN_2O$ [M+H]: 193.0168, found: 193.0158.

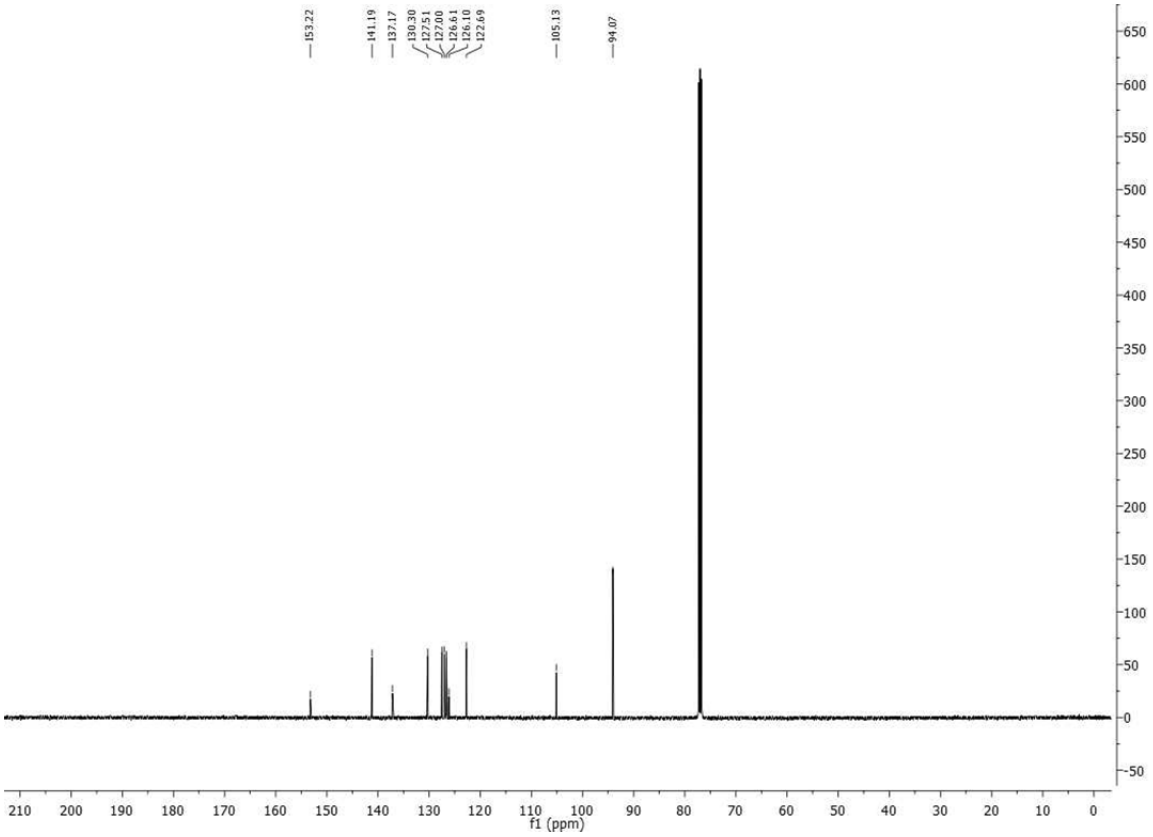


4-Chloro-6-methylpicolinaldehyde (4q): 23.0 mg, 74%, CH_2Cl_2 with 1% Et_3N. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.78 (s, 1H), 7.41 (s, 1H), 2.66 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.4, 160.8, 153.4, 145.5, 127.4, 119.4, 24.1. HRMS (ESI) m/z calc'd for C_7H_7ClNO [M+H]: 156.0216, found: 156.0208.

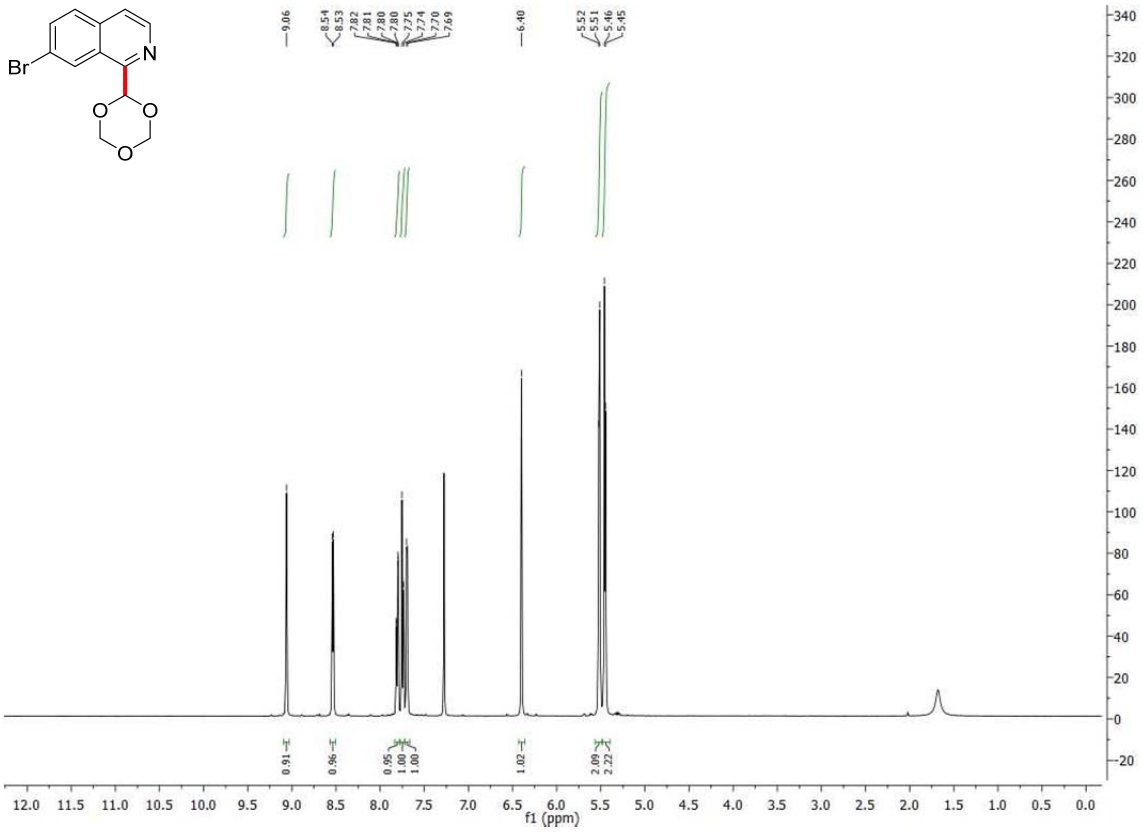
4. ^{1}H and $^{13}C\{^{1}H\}$ Spectra of Trioxane and Aldehyde Products

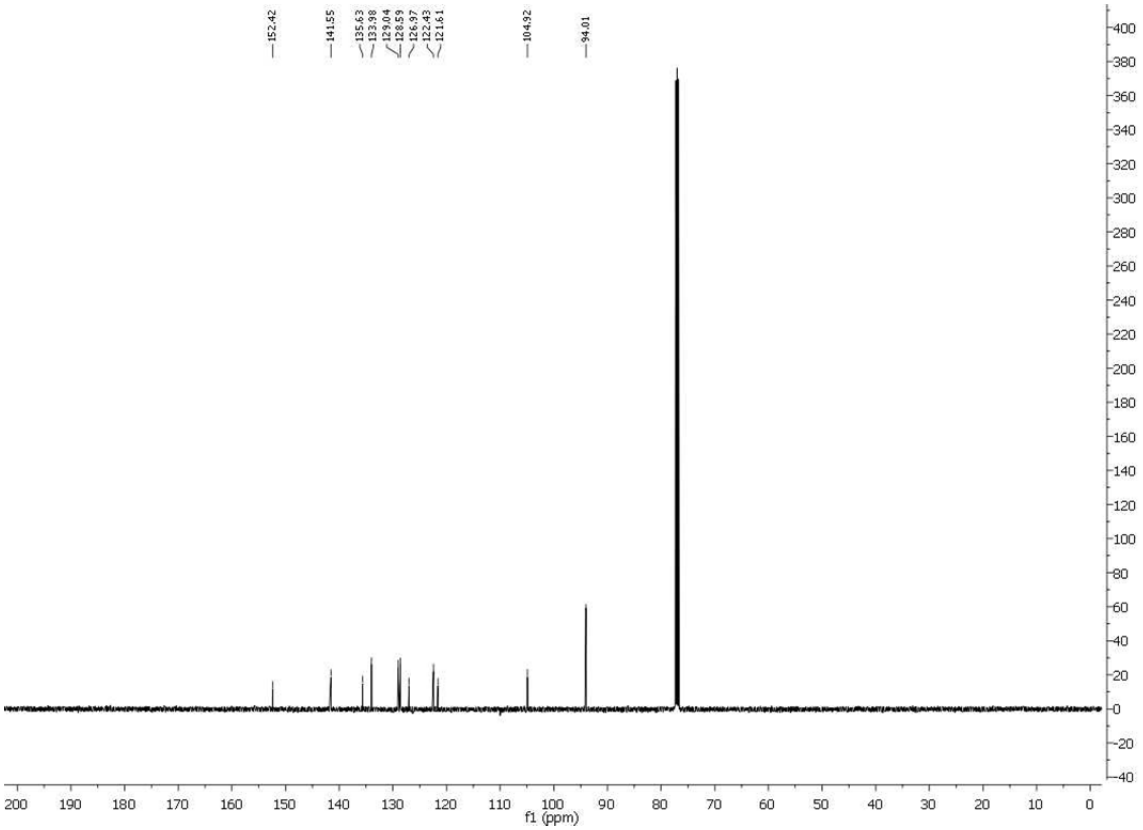
1-(1,3,5-Trioxan-2-yl)isoquinoline (3a)



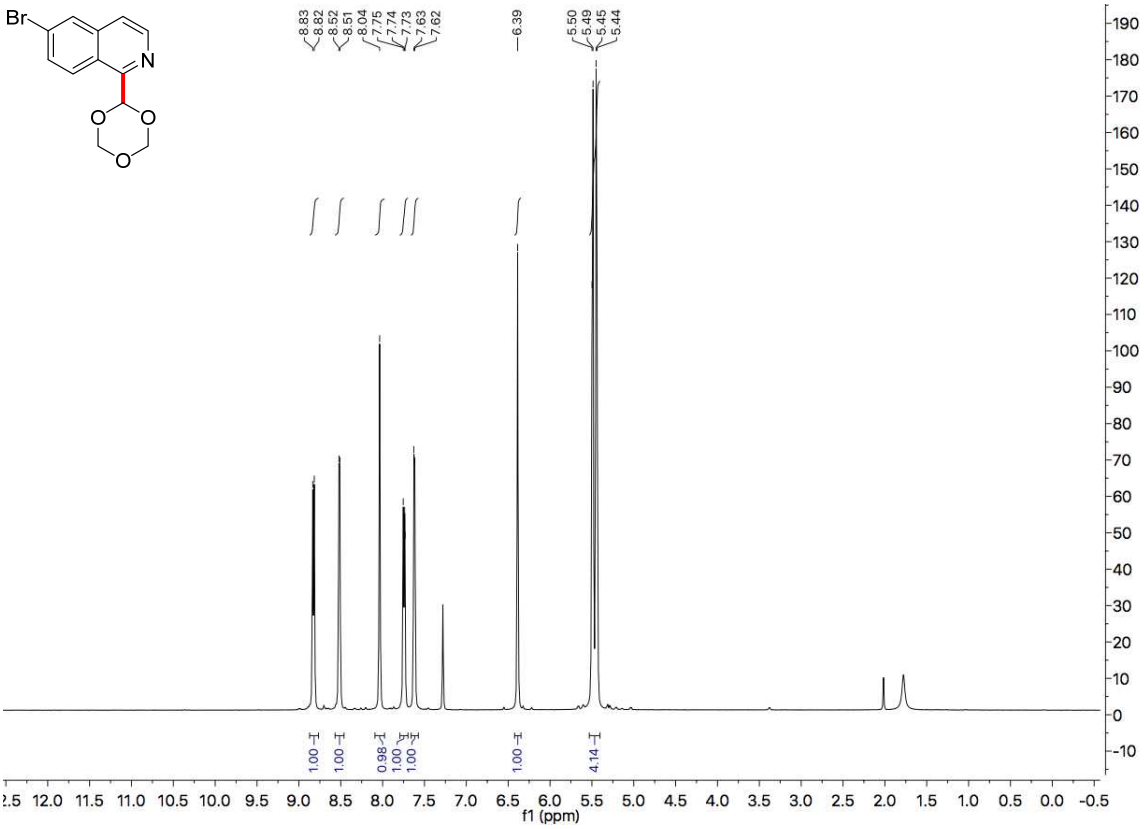


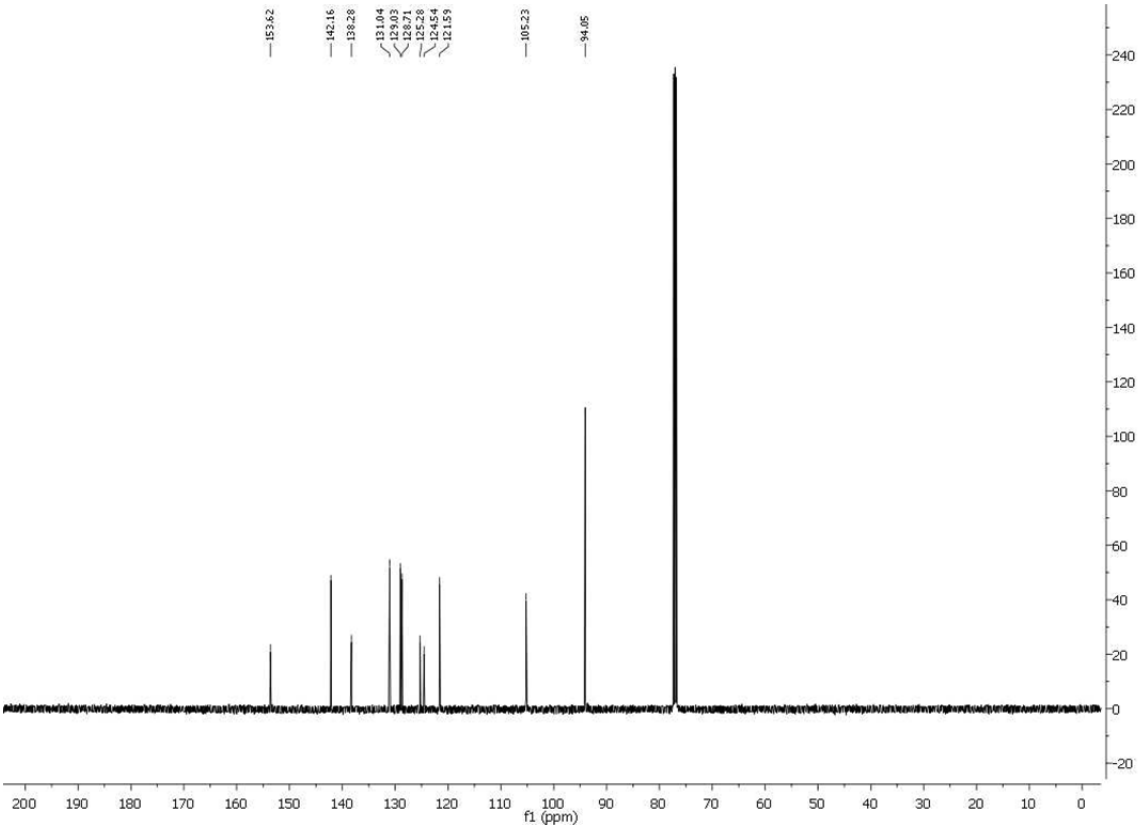
7-Bromo-1-(1,3,5-trioxan-2-yl)isoquinoline (3b)



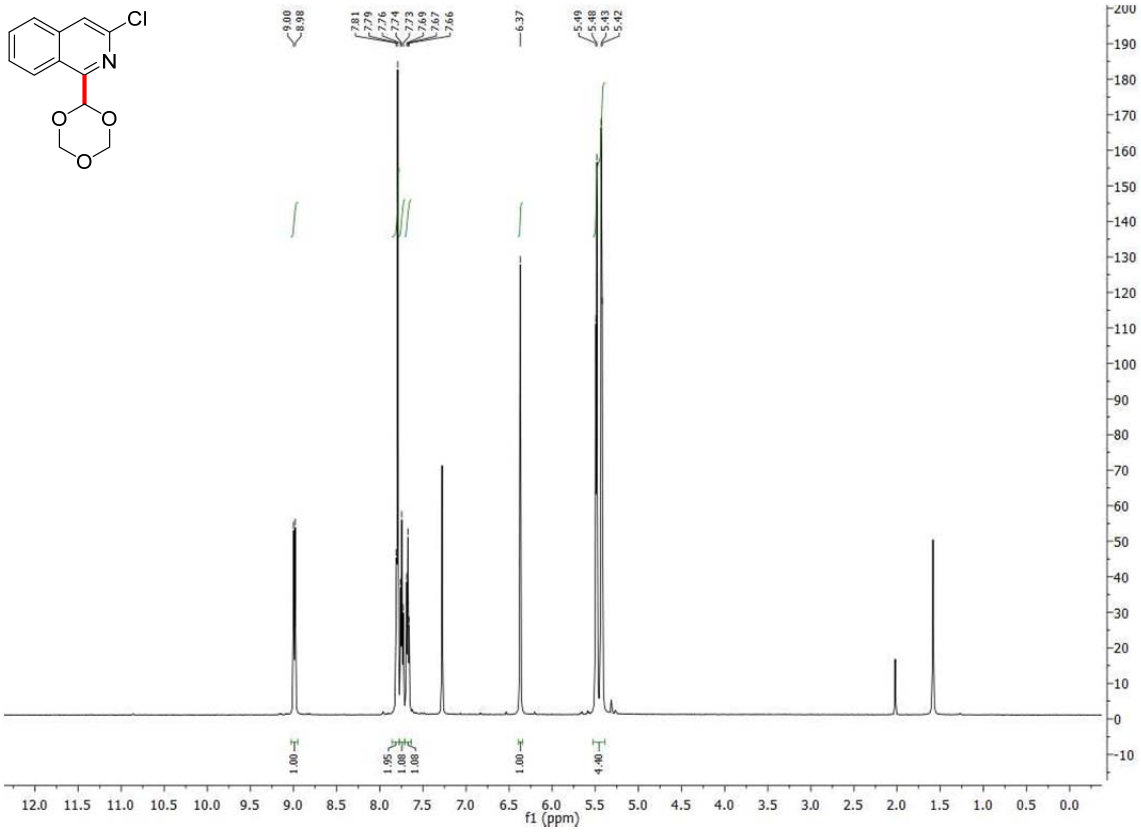


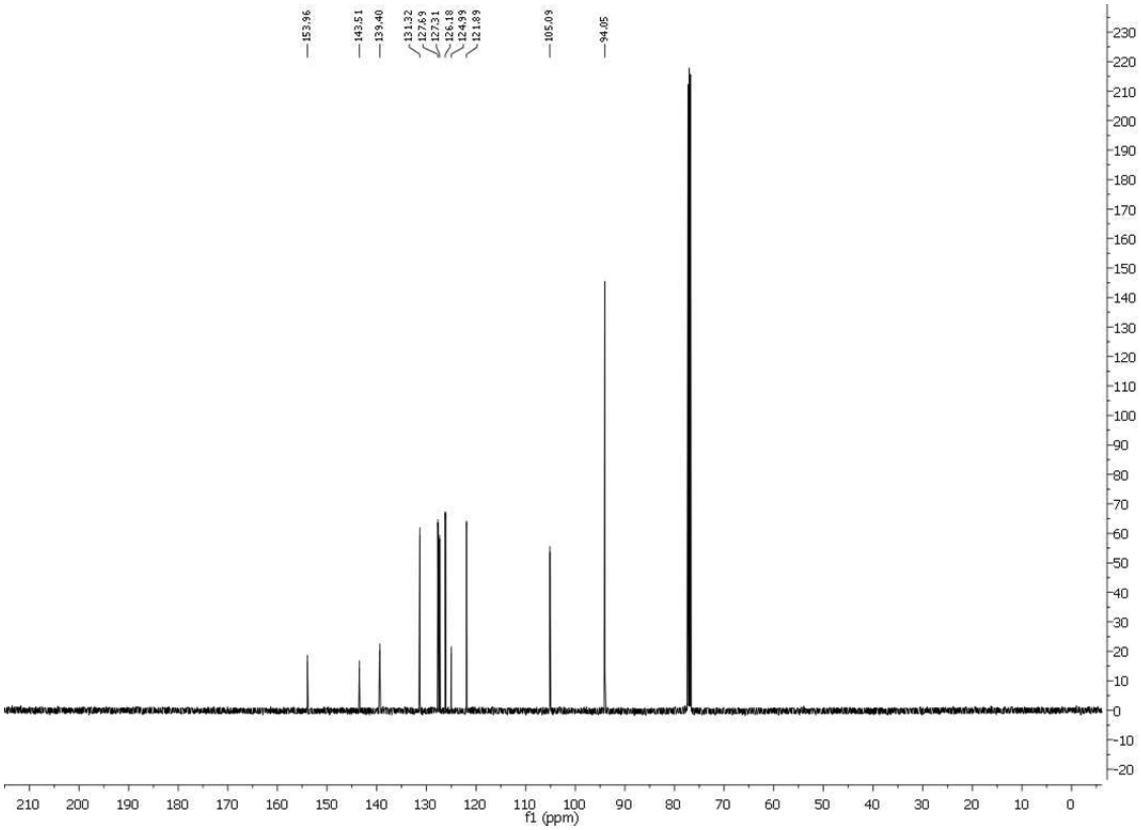
6-Bromo-1-(1,3,5-trioxan-2-yl)isoquinoline (3c)



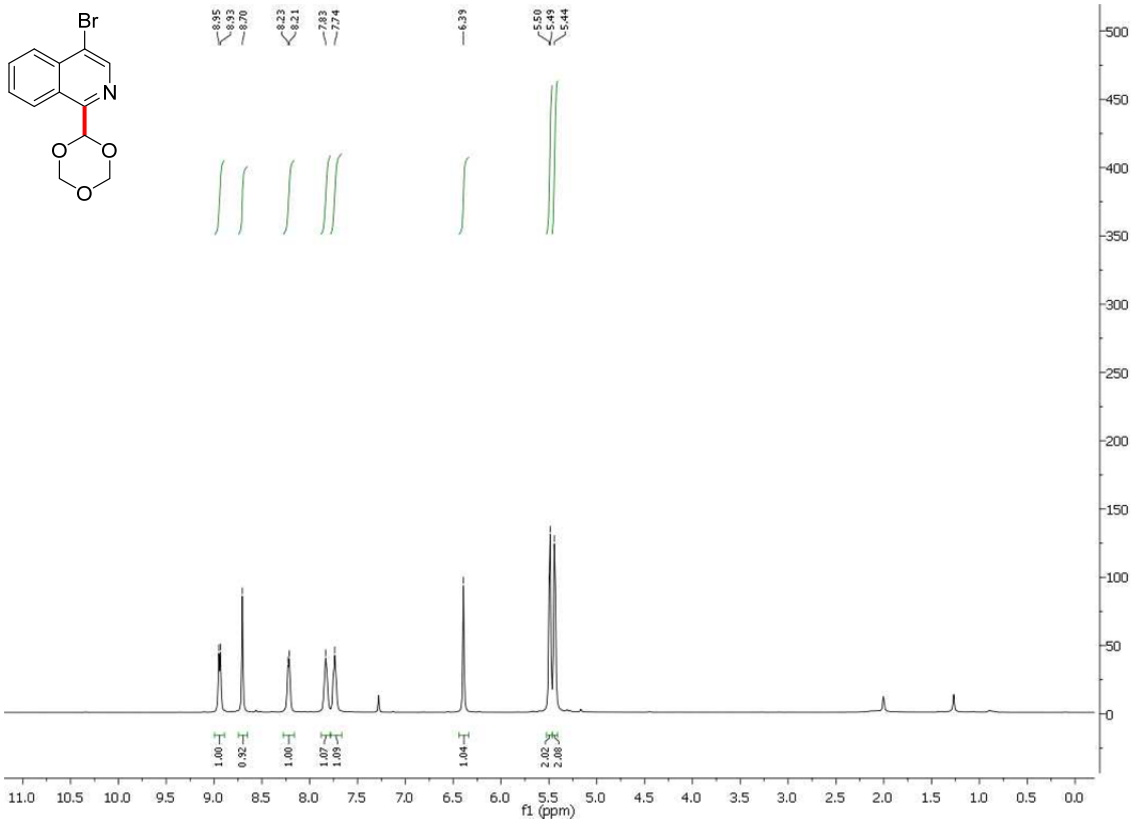


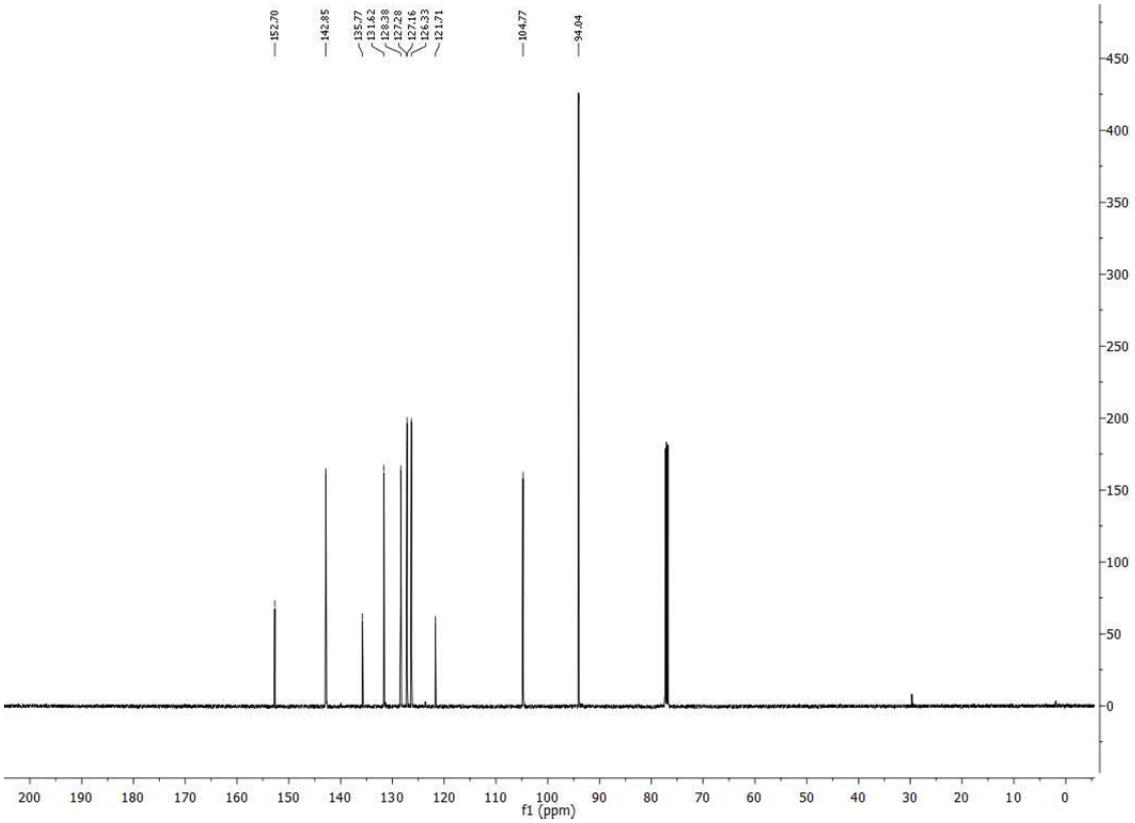
3-Chloro-1-(1,3,5-trioxan-2-yl)isoquinoline (3d)



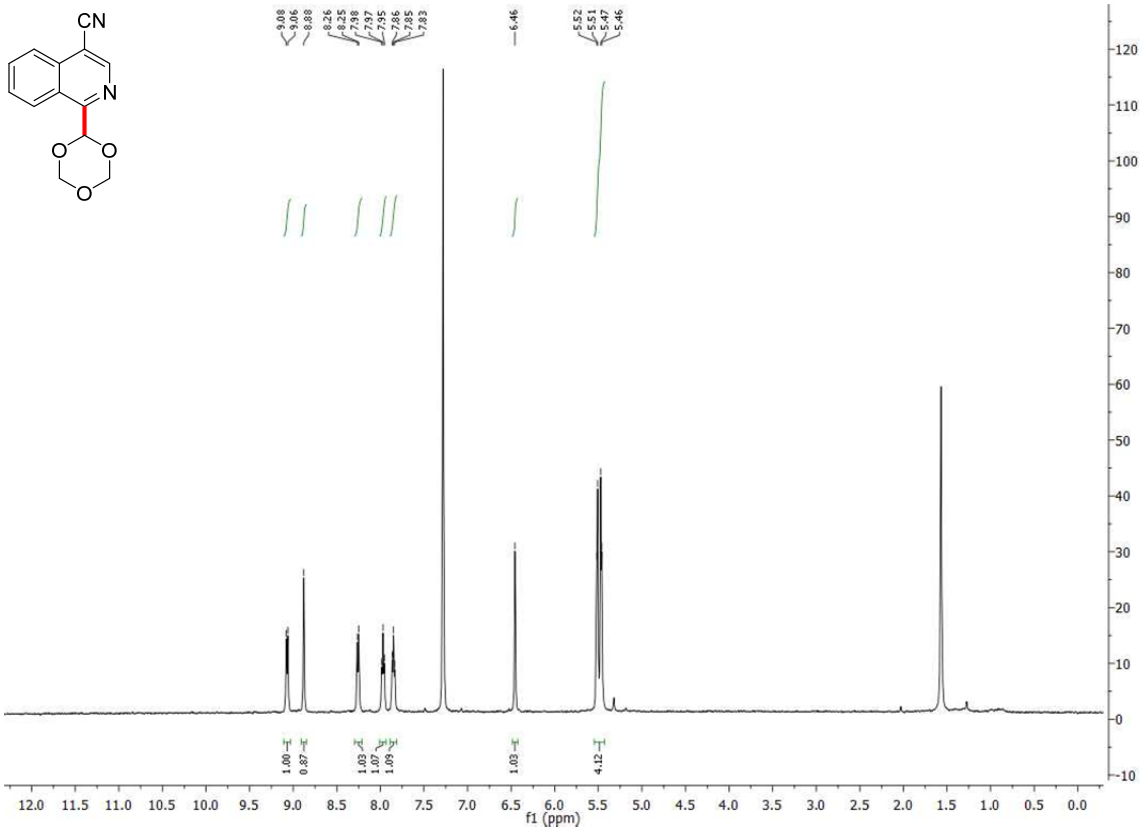


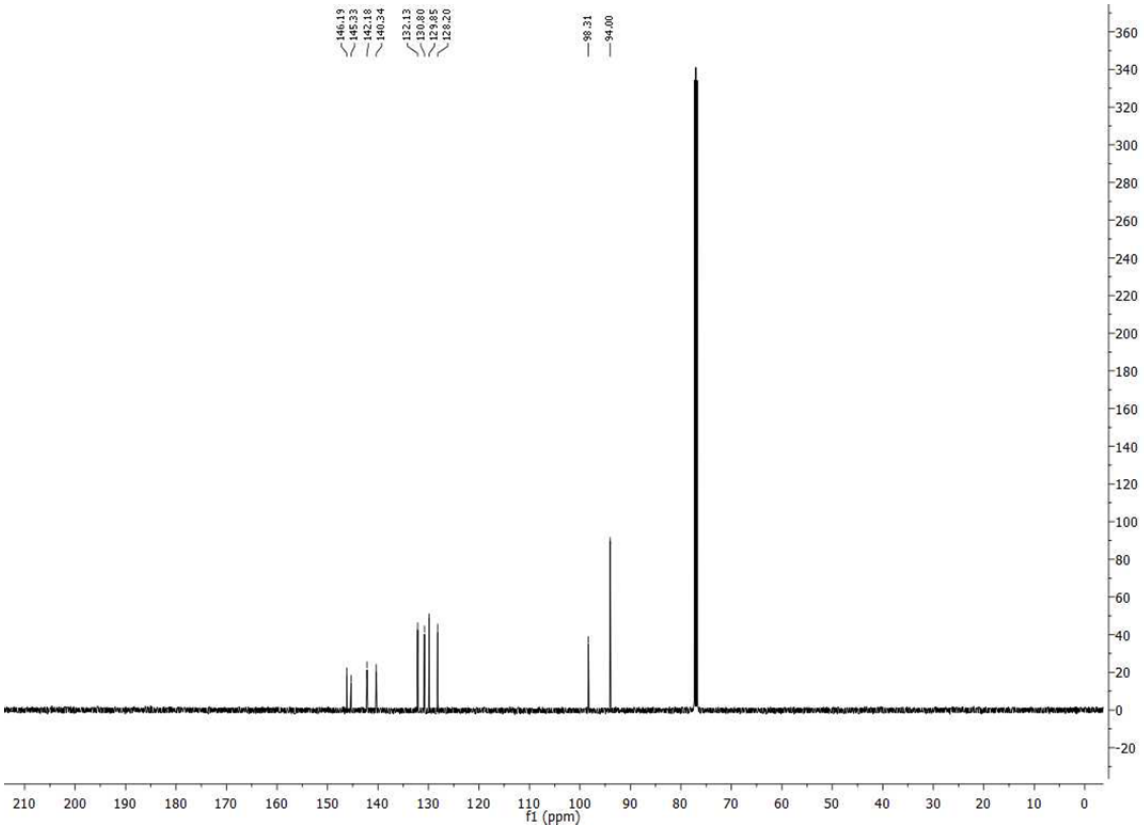
4-Bromo-1-(1,3,5-trioxan-2-yl)isoquinoline (3e)



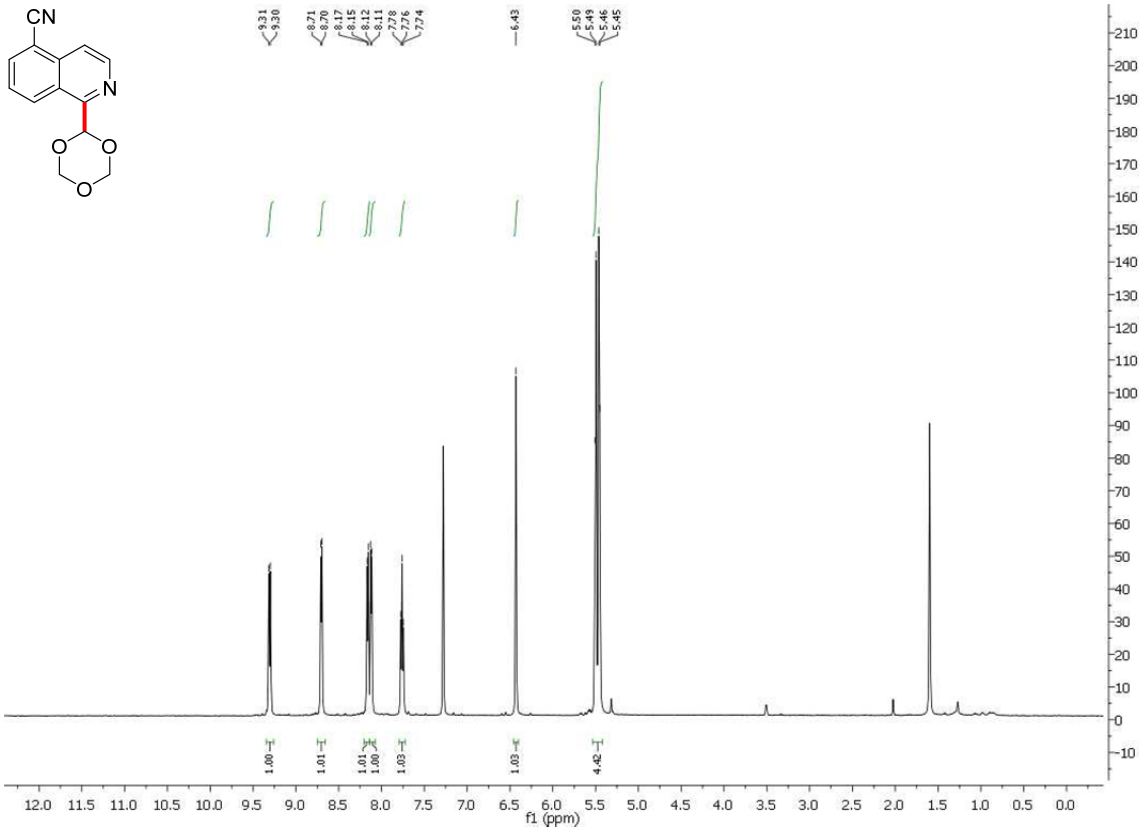


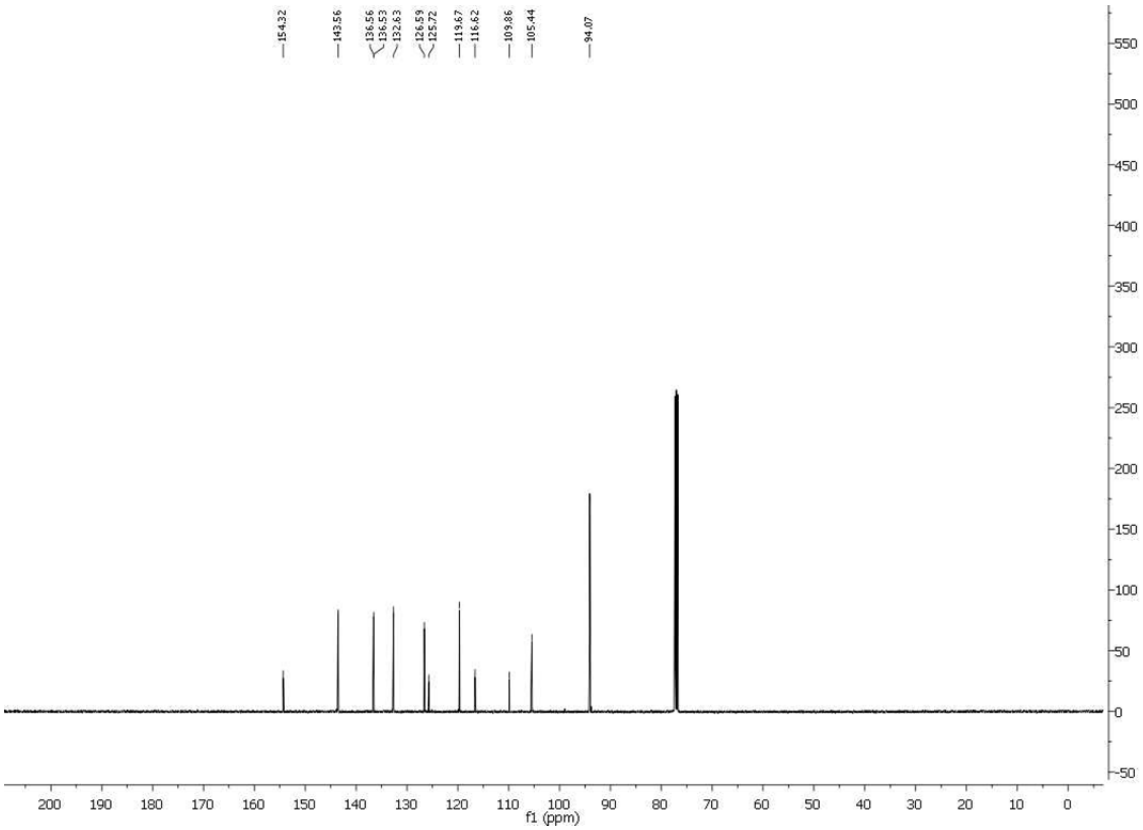
1-(1,3,5-Trioxan-2-yl)isoquinoline-4-carbonitrile (3f)



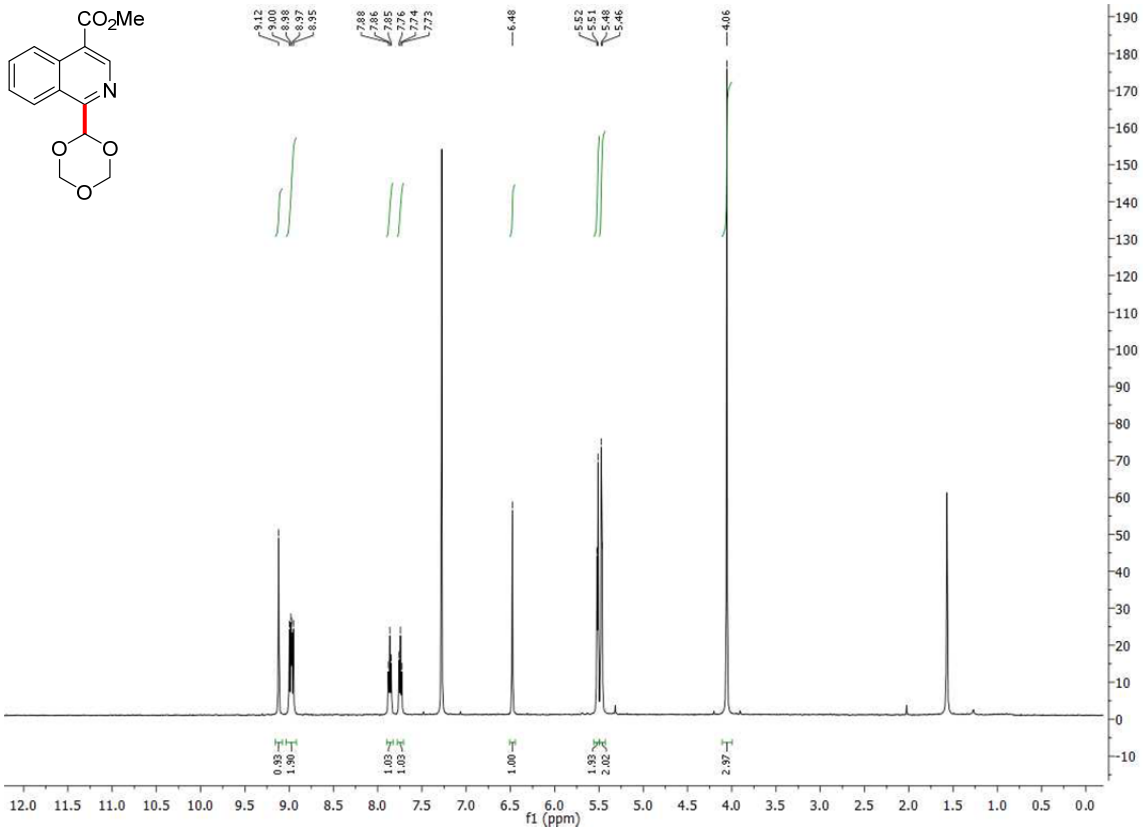


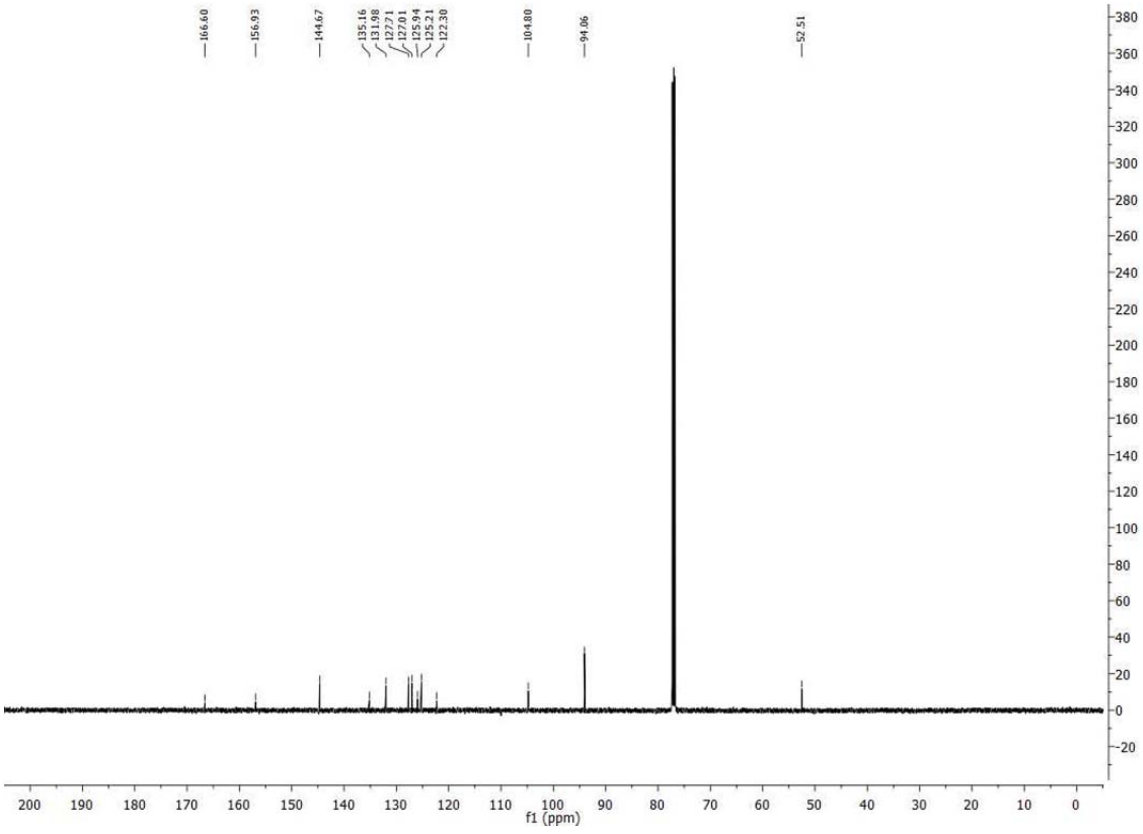
1-(1,3,5-Trioxan-2-yl)isoquinoline-5-carbonitrile (3g)



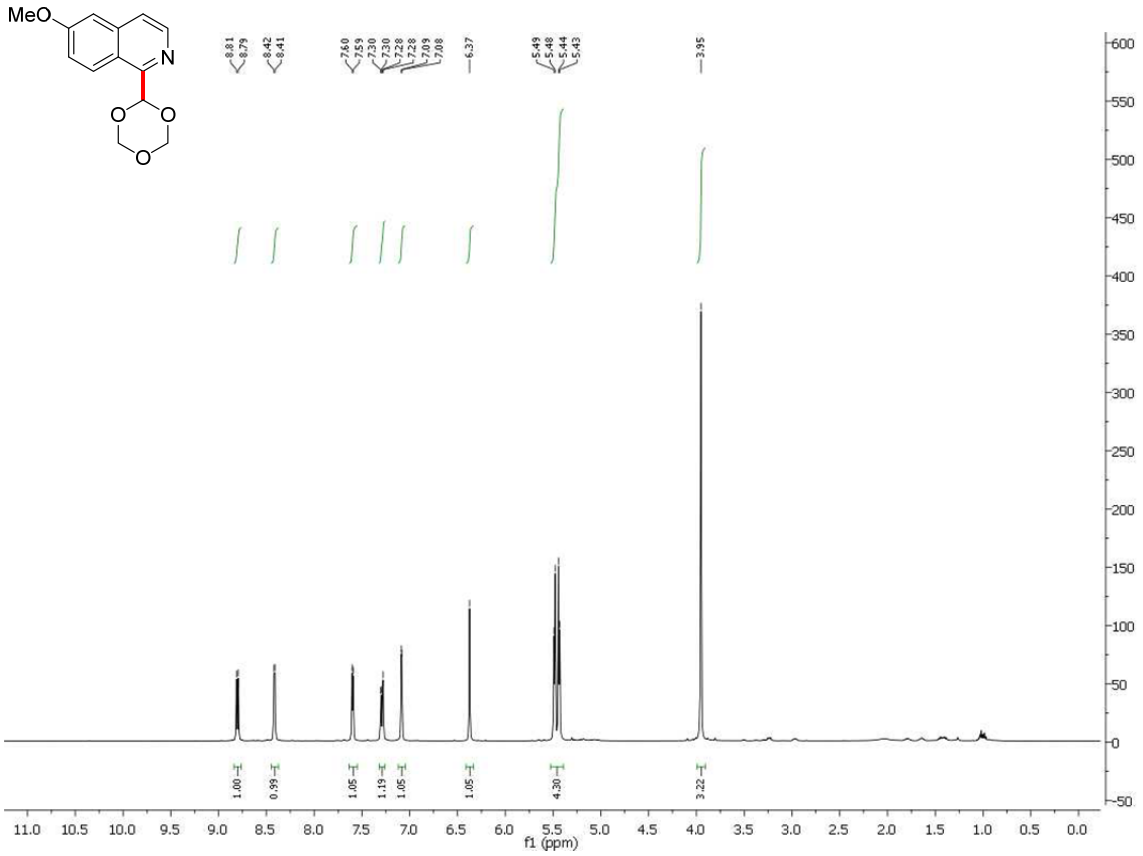


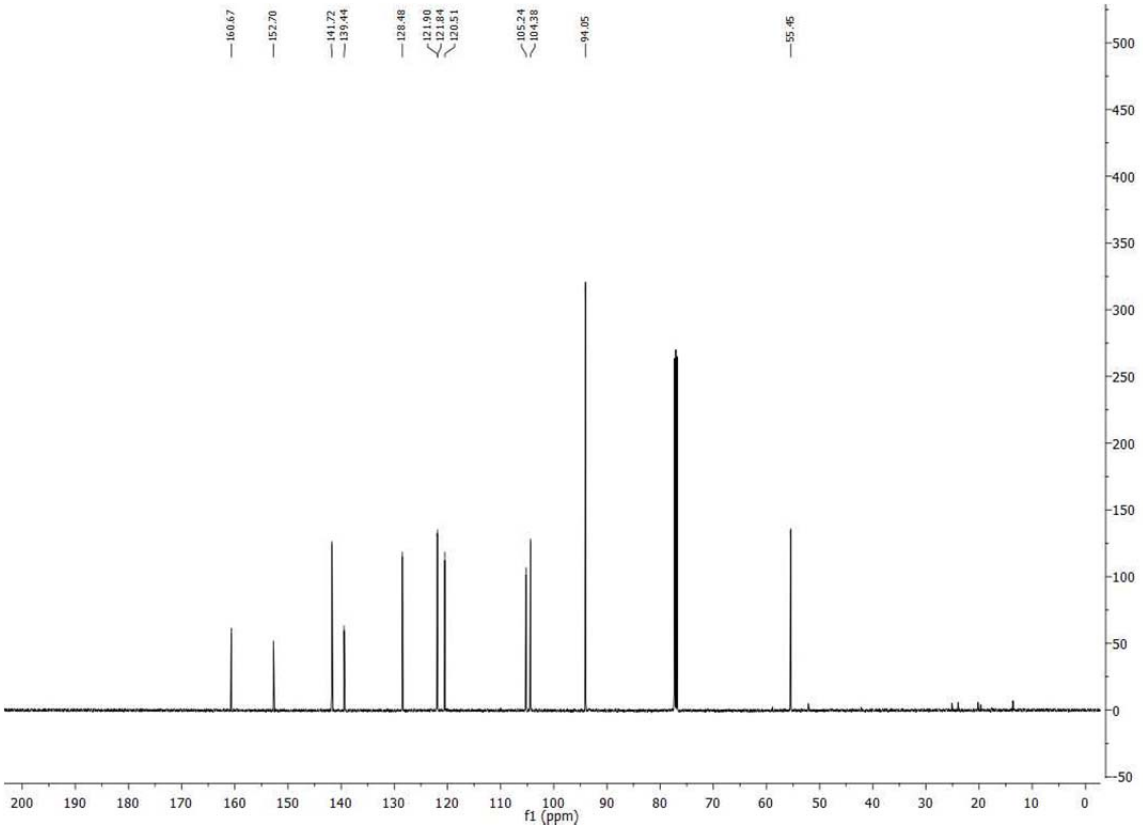
Methyl 1-(1,3,5-trioxan-2-yl)isoquinoline-4-carboxylate (3h)



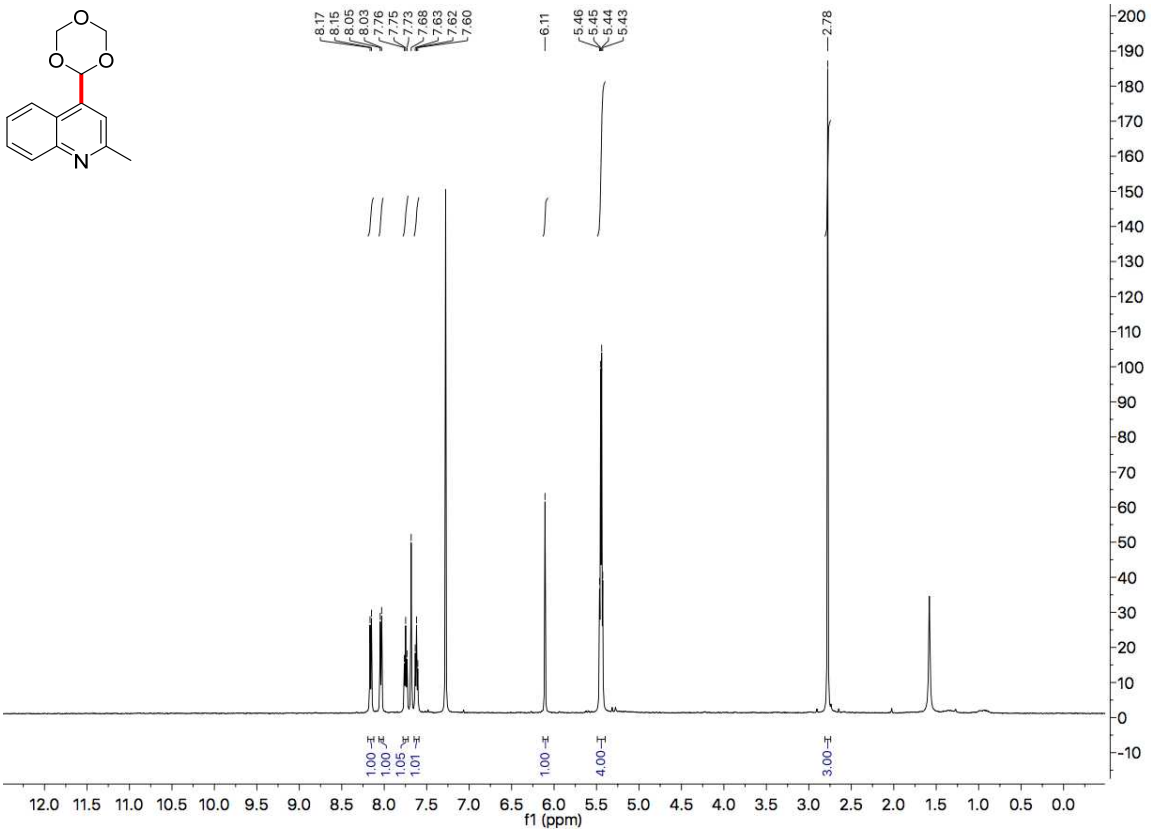


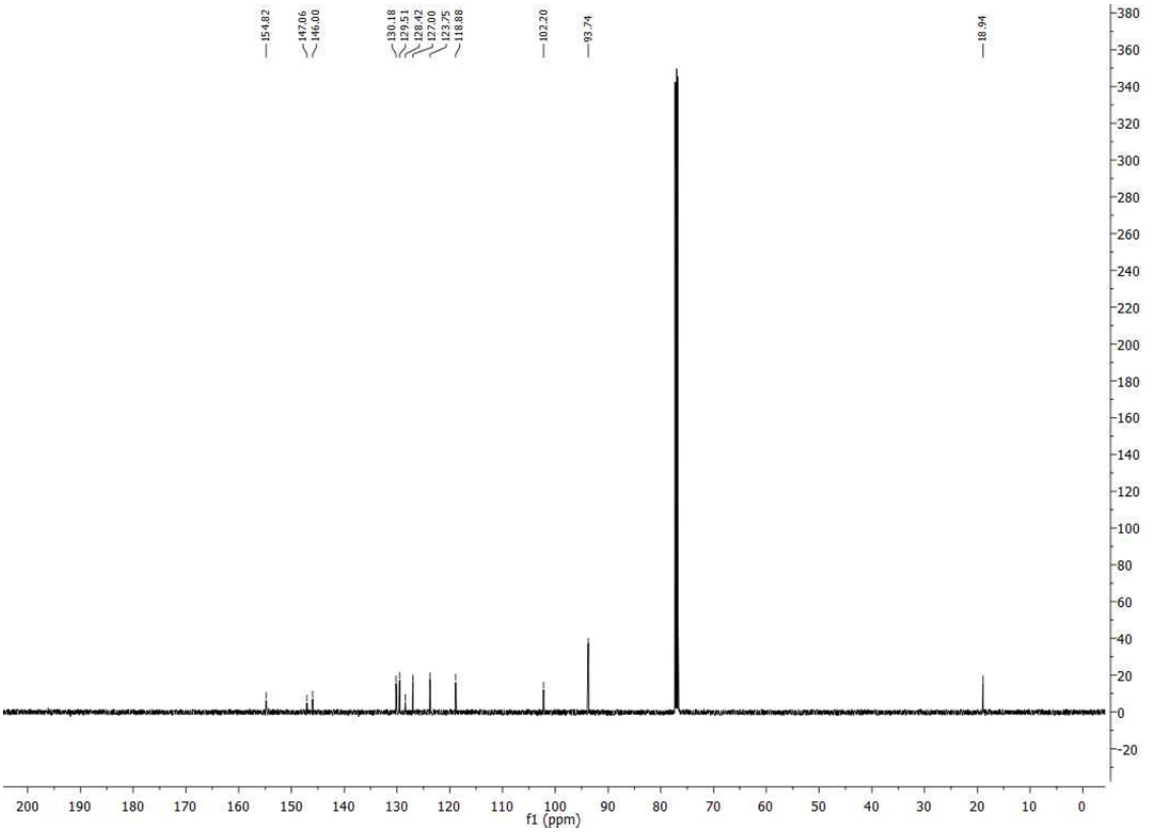
6-Methoxy-1-(1,3,5-trioxan-2-yl)isoquinoline (3i)



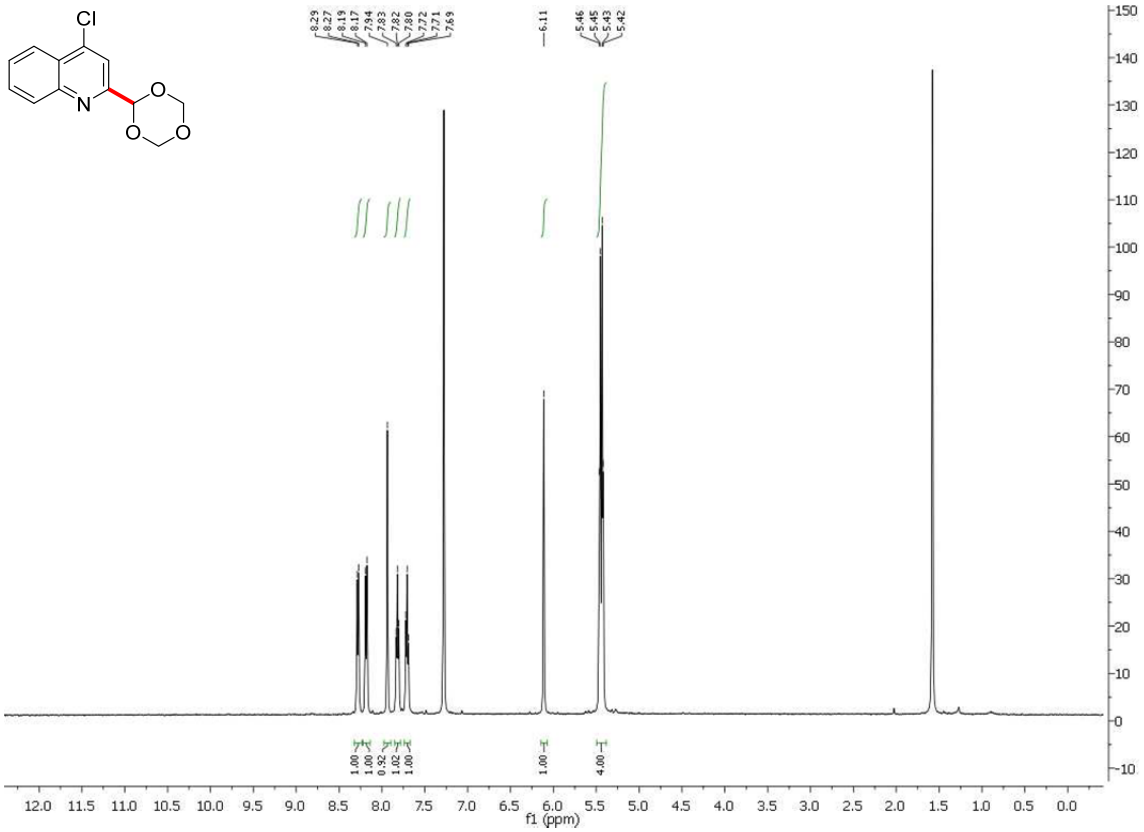


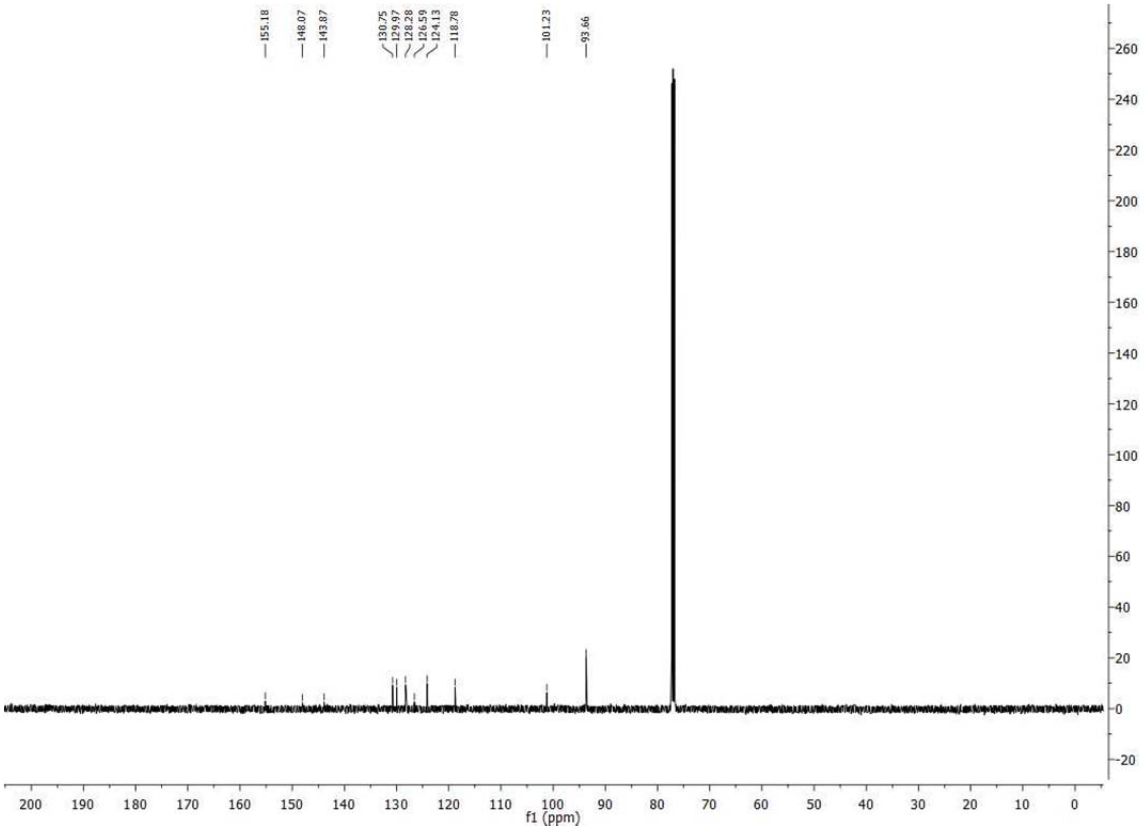
2-Methyl-4-(1,3,5-trioxan-2-yl)quinolone (3j)



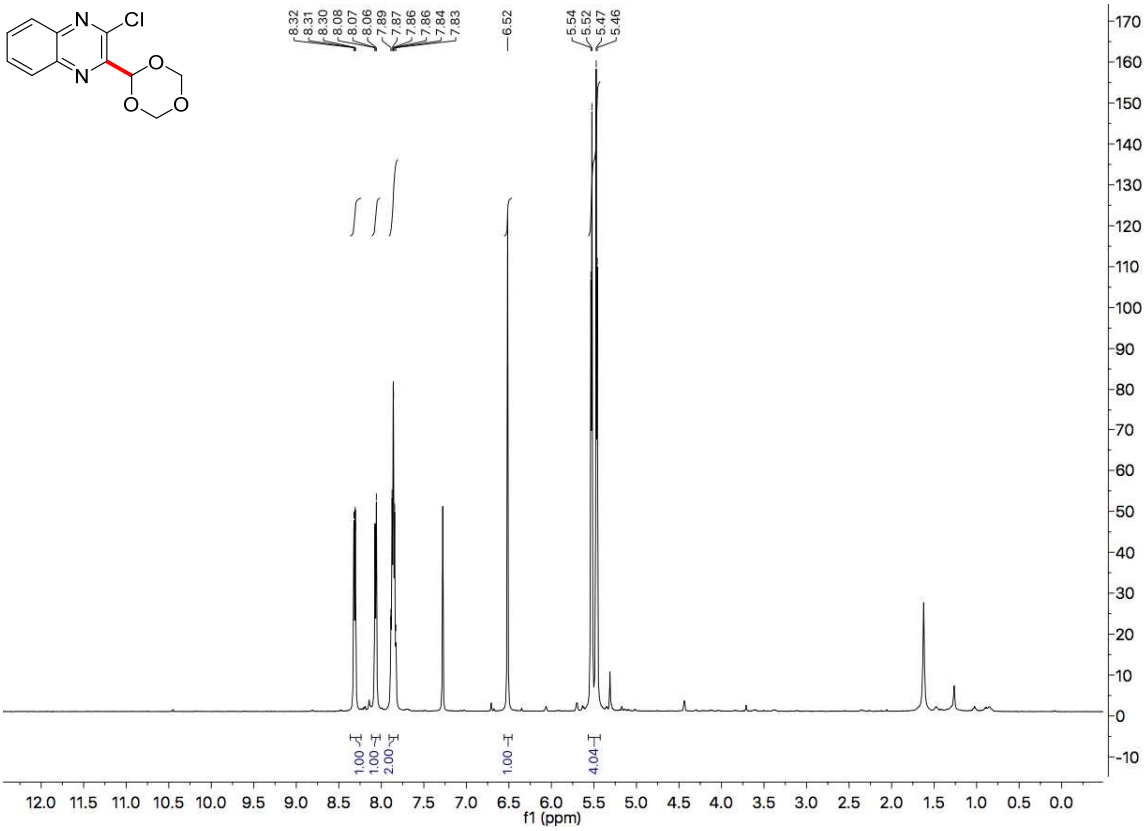


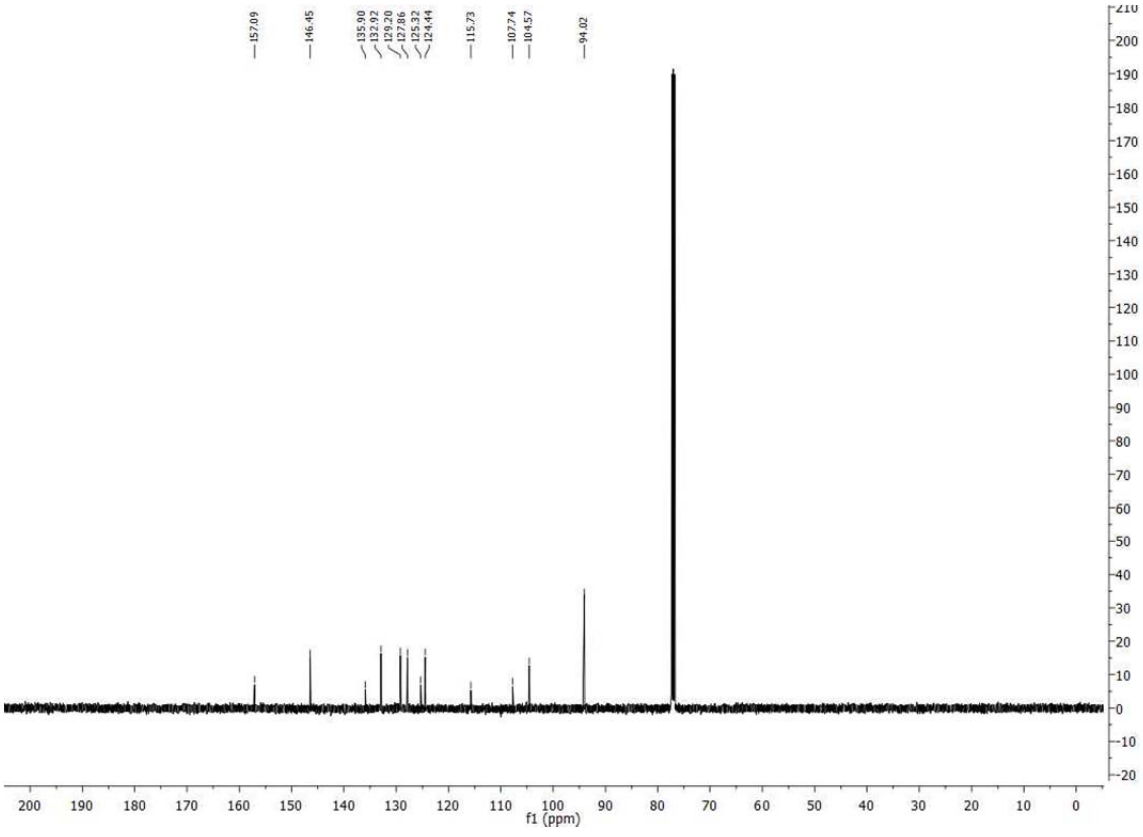
4-Chloro-2-(1,3,5-trioxan-2-yl)quinolone (3k)



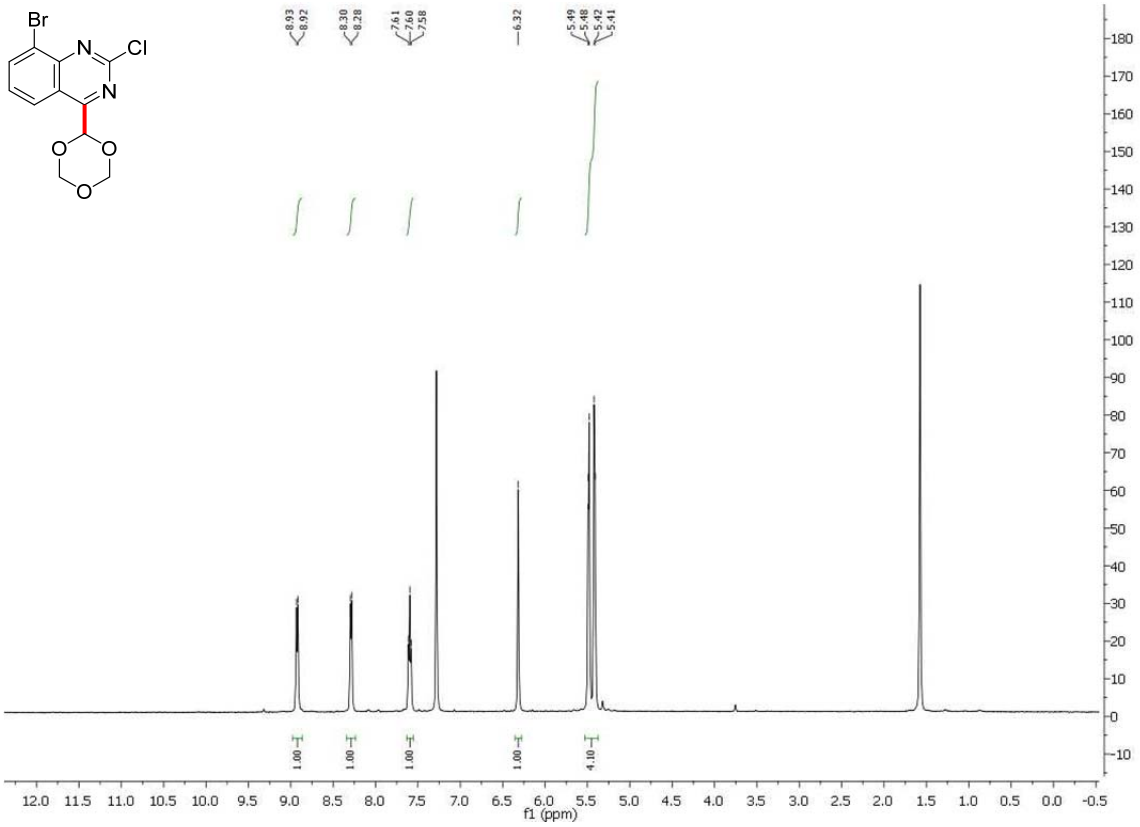


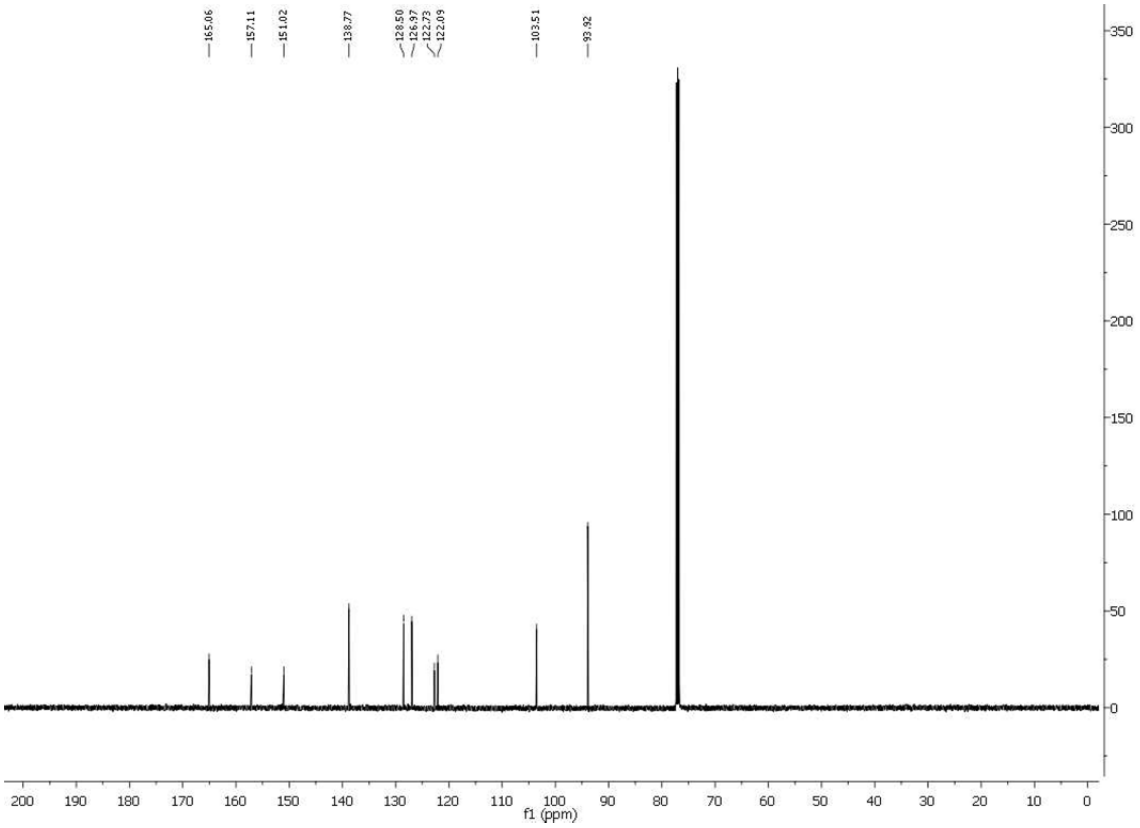
2-Chloro-3-(1,3,5-trioxan-2-yl)quinoxaline (3l)



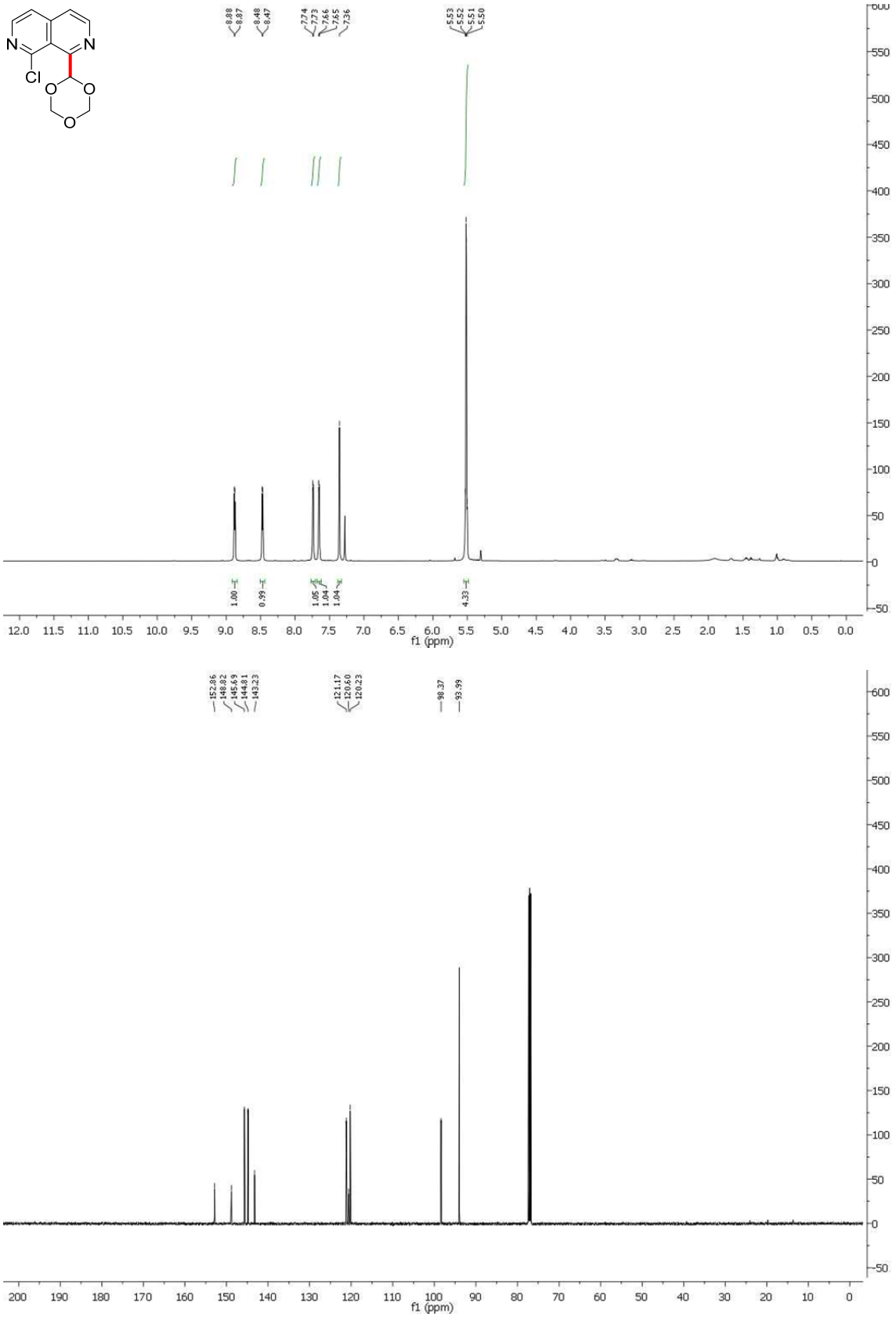


8-Bromo-2-chloro-4-(1,3,5-trioxan-2-yl)quinazoline (3m)

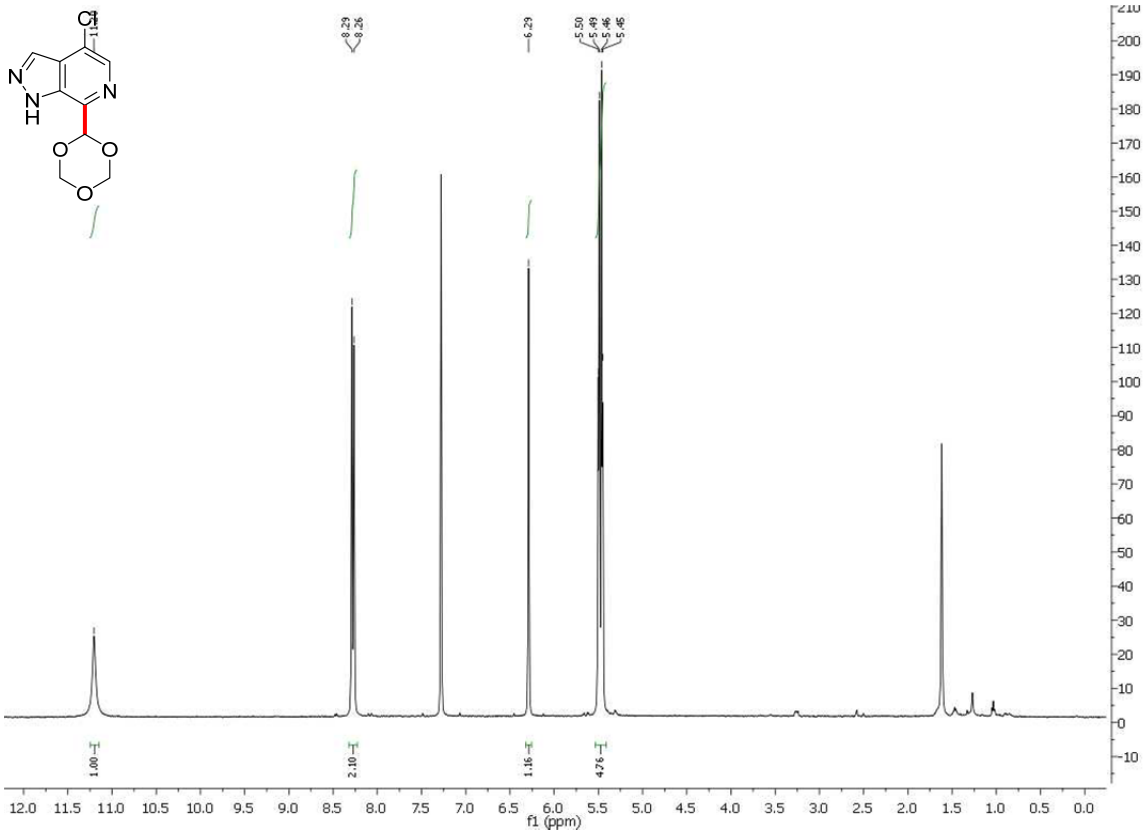


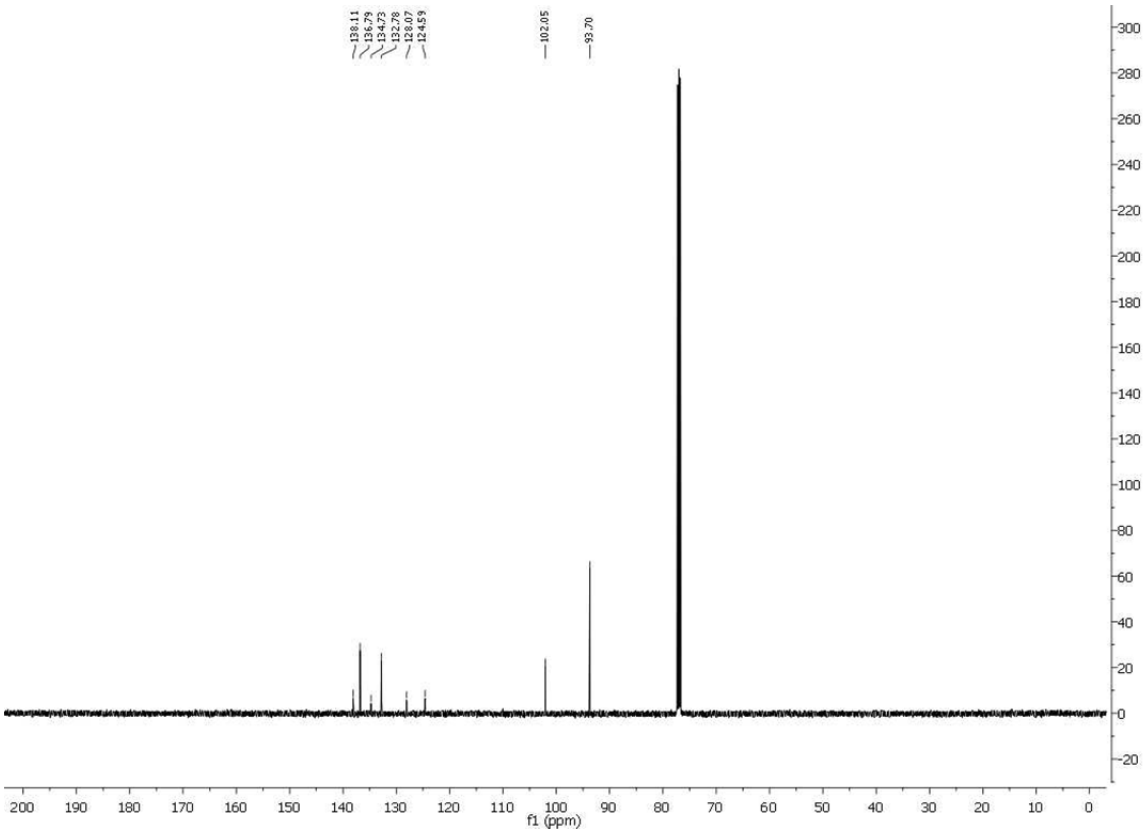


1-Chloro-8-(1,3,5-trioxan-2-yl)-2,7-naphthyridine (3n)



4-Chloro-7-(1,3,5-trioxan-2-yl)-1*H*-pyrazolo[3,4-*c*]pyridine (3o)






O
14
15
13
O
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8
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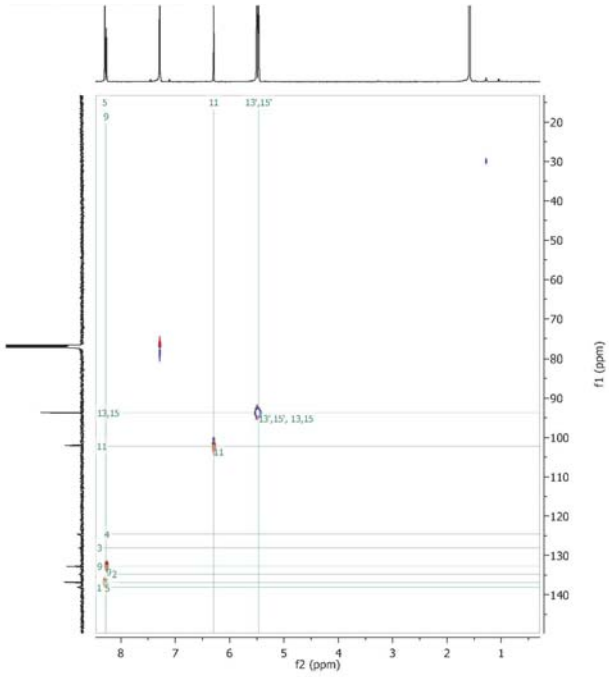
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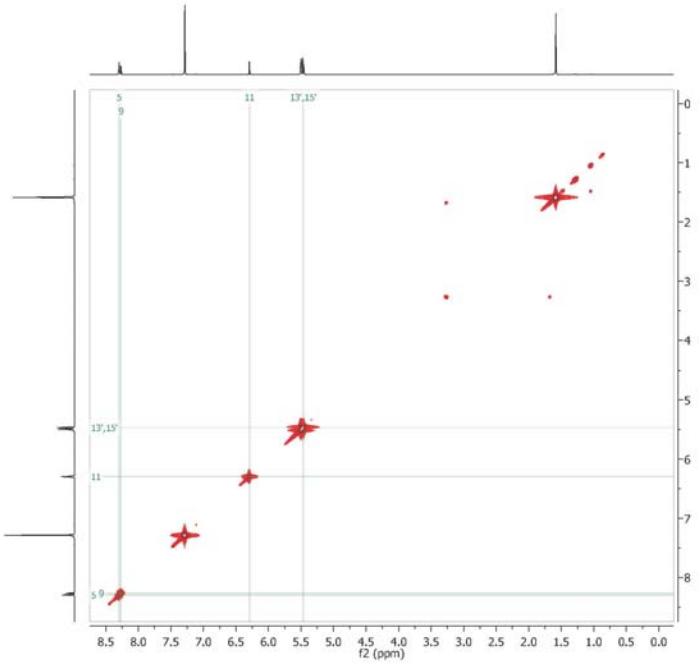
3
9
2
1
5
f2 (ppm)
f1 (ppm)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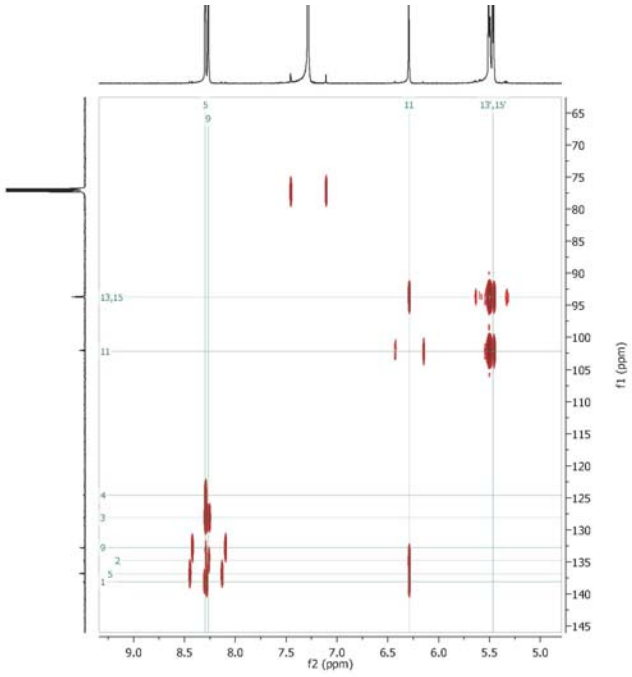
5 9
f2 (ppm)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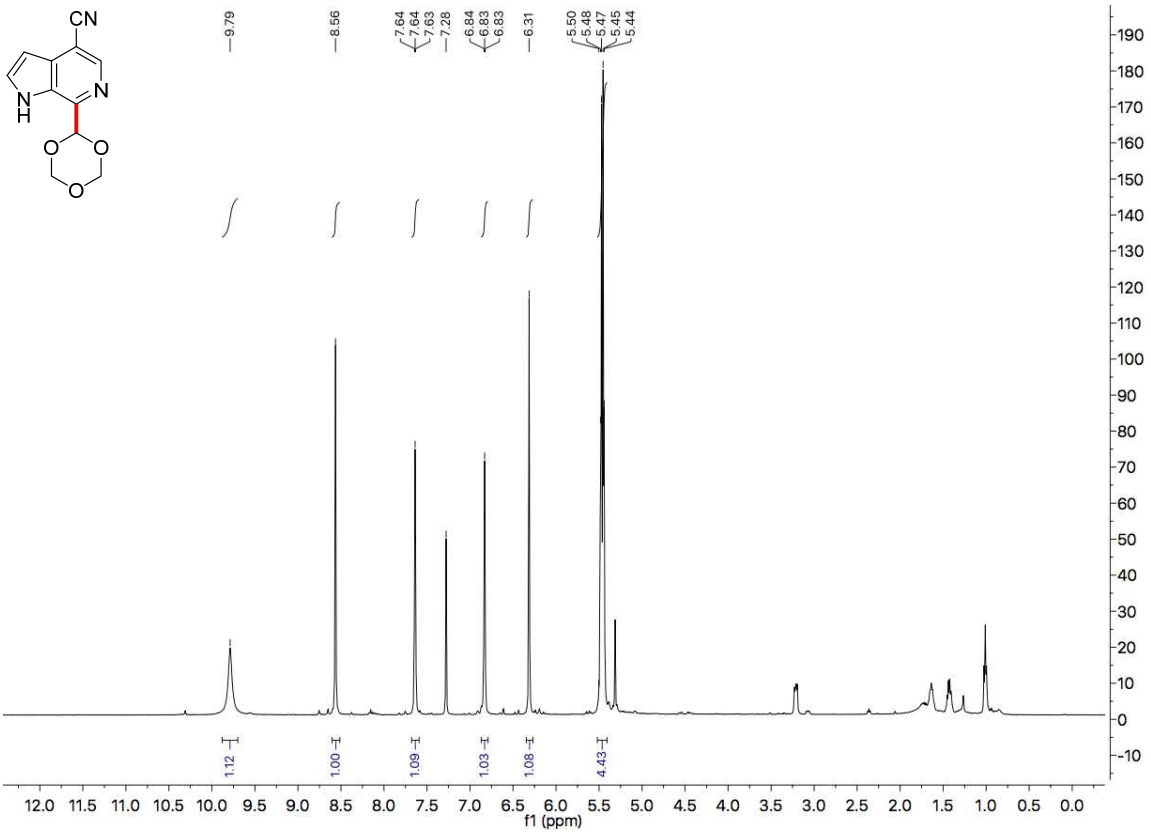
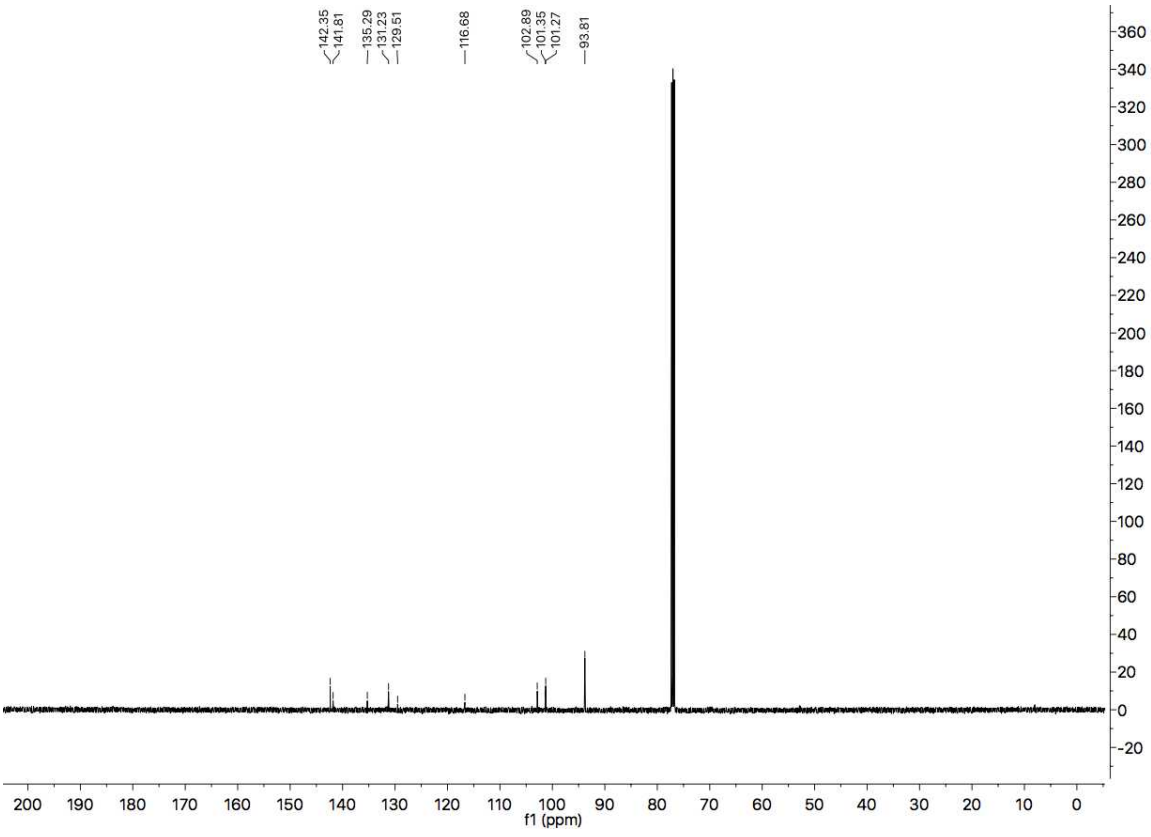
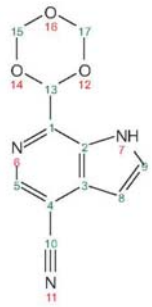
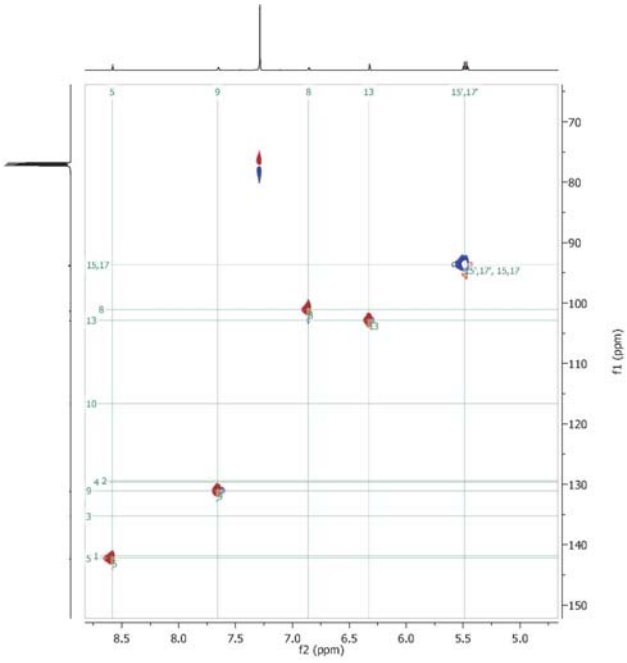
11
4
3
9
2
5
1
f2 (ppm)
f1 (ppm)

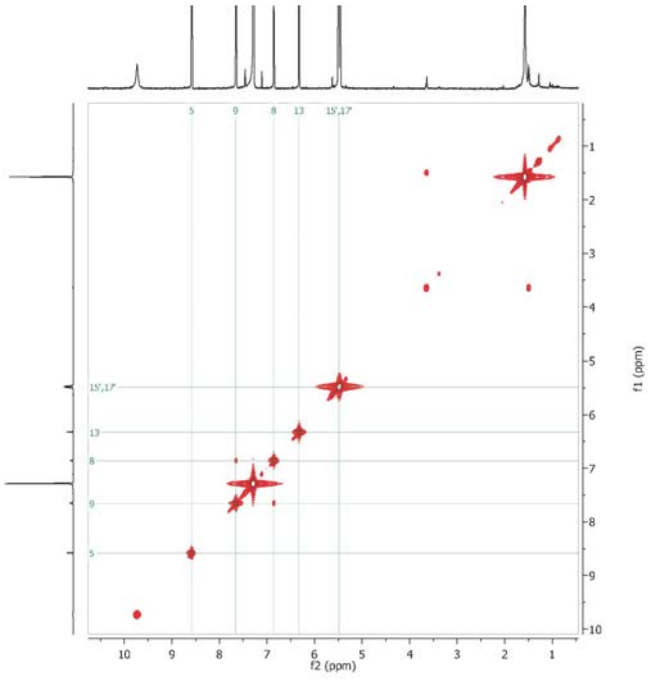
7-(1,3,5-Trioxan-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-4-carbonitrile (3p)

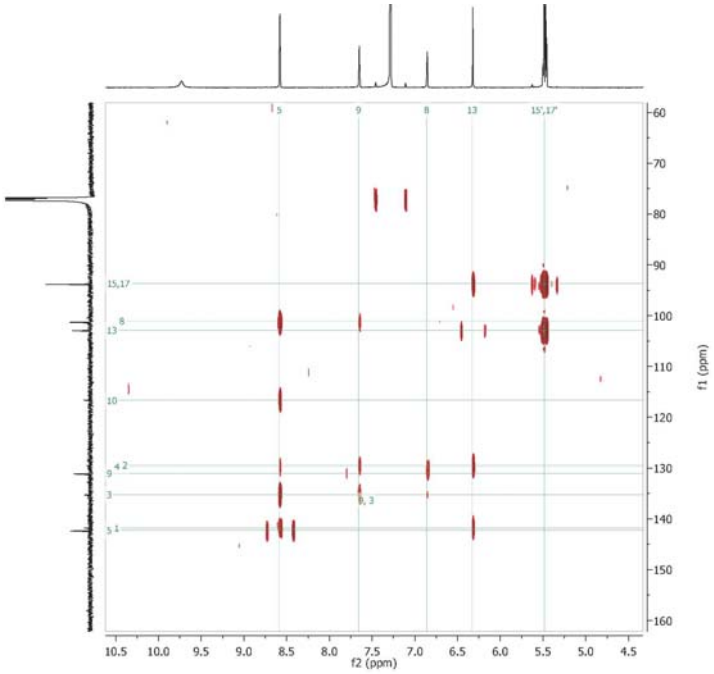




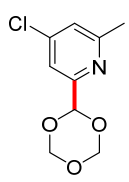

O
15
16
17
O
14
13
12
O
1
2
NH
7
N
6
9
5
3
8
4
10
N
11

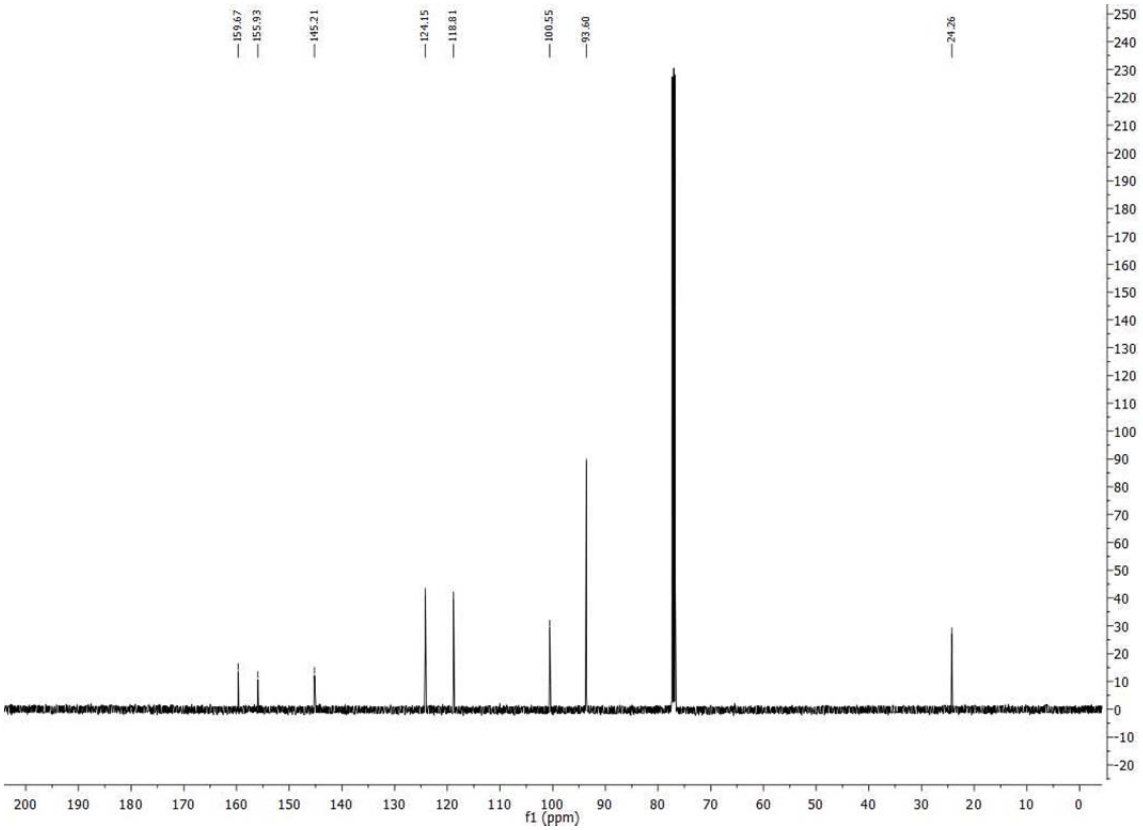

5
9
8
13
15',17'
15,17
8
13
10
4 2
9
3
5 1
15',17', 15,17
f1 (ppm)
f2 (ppm)


5
9
8
13
15',17'
15',17'
13
8
9
5
f1 (ppm)
f2 (ppm)

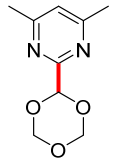

5
9
8
13
15',17'
15,17
8
13
10
4 2
9
3
5 1
f1 (ppm)
f2 (ppm)

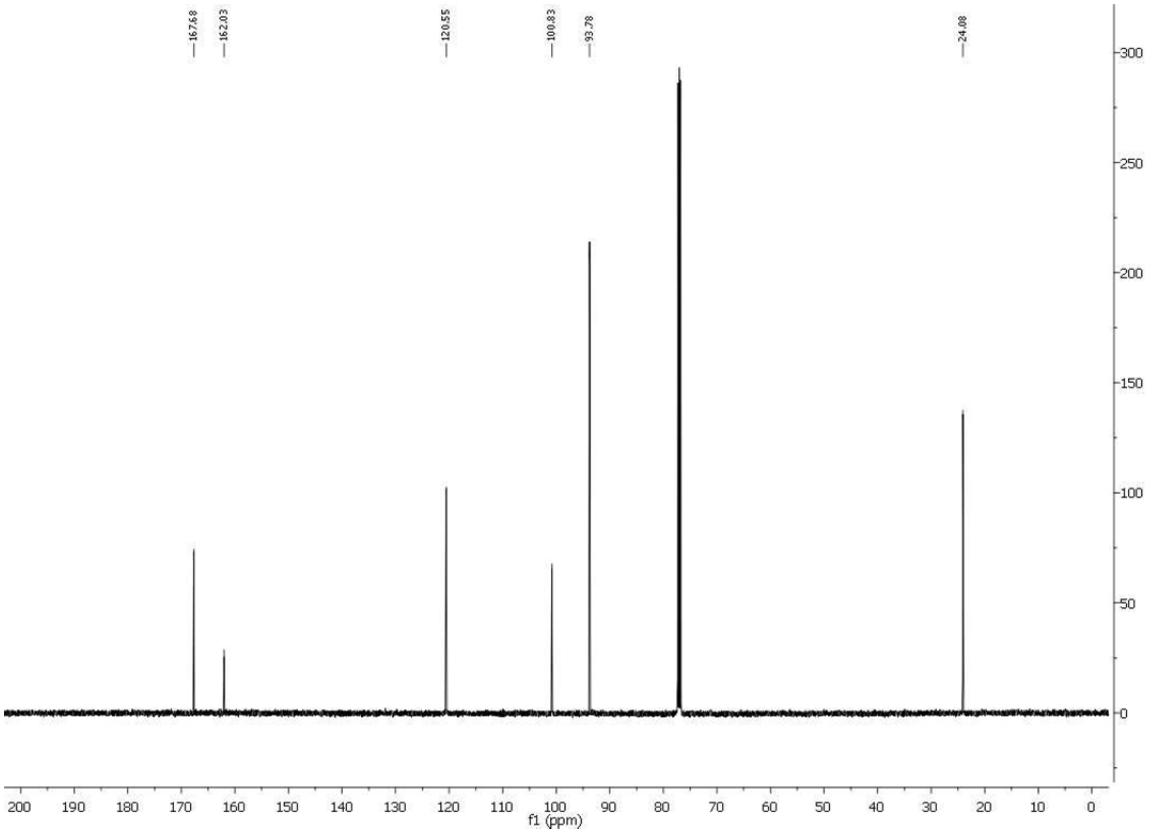
4-Chloro-2-methyl-6-(1,3,5-trioxan-2-yl)pyridine (3q)



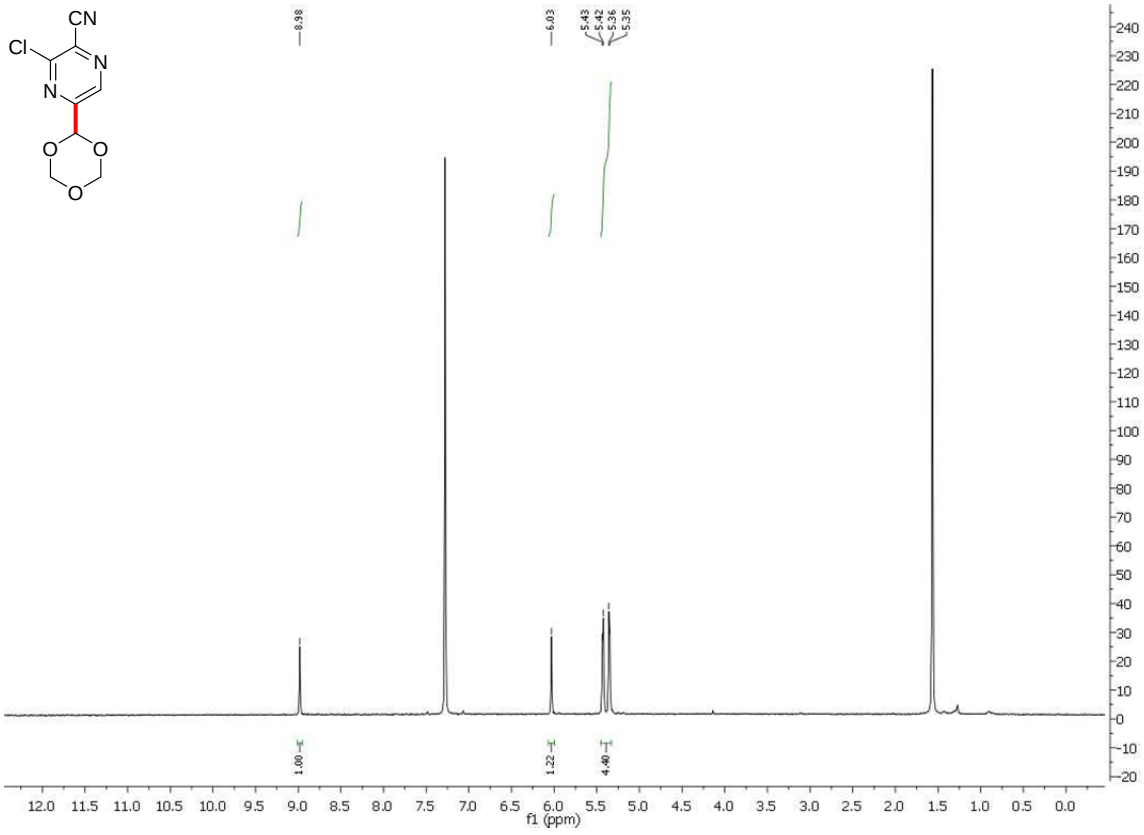


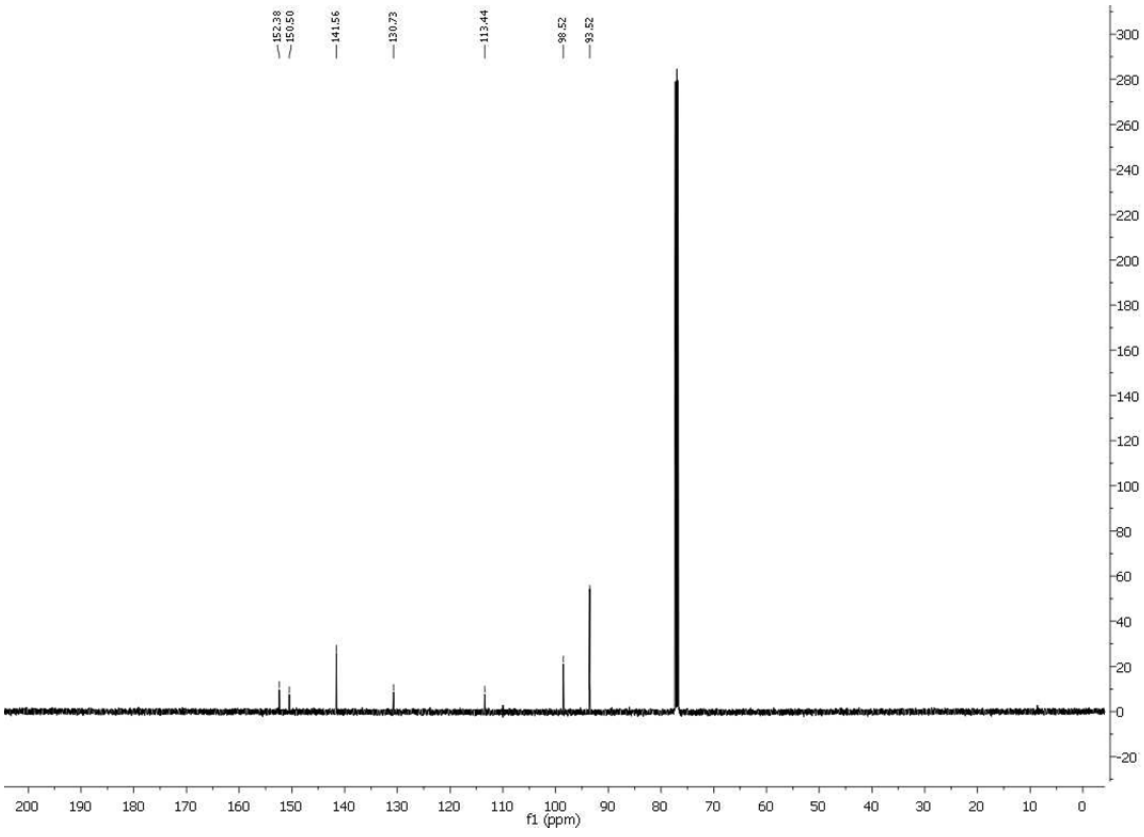
4,6-Dimethyl-2-(1,3,5-trioxan-2-yl)pyrimidine (3r)

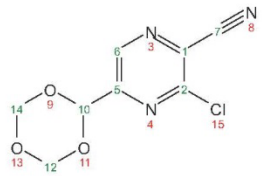


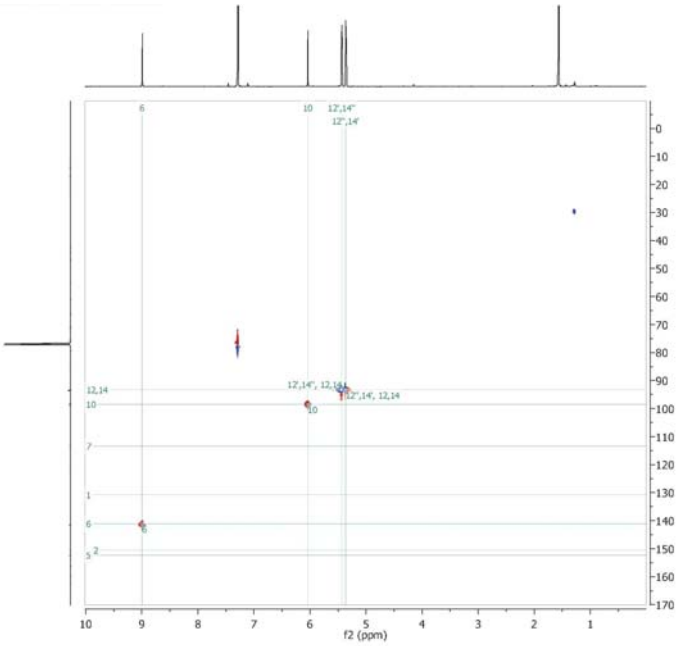


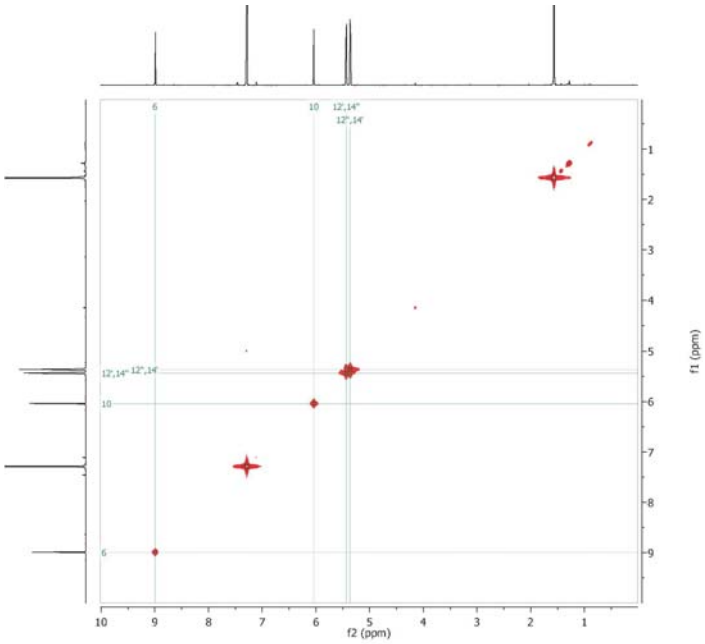
3-Chloro-5-(1,3,5-trioxan-2-yl)pyrazine-2-carbonitrile (3s)

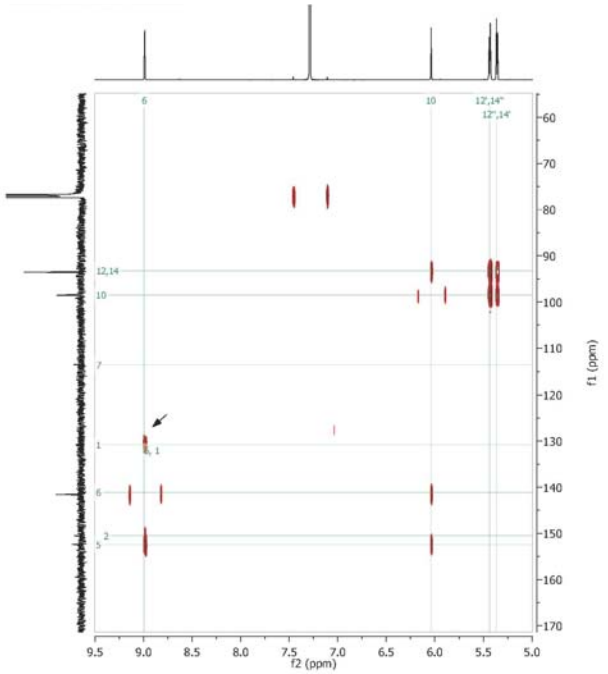


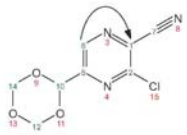




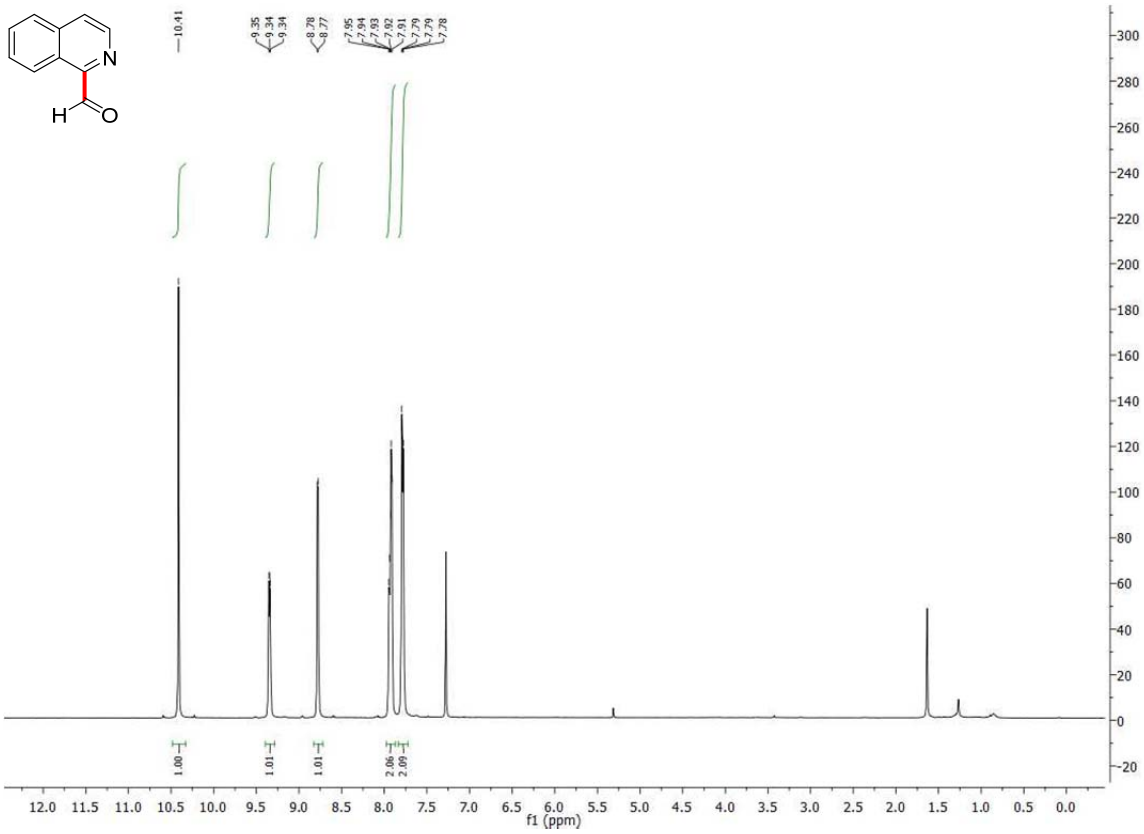

f2 (ppm)

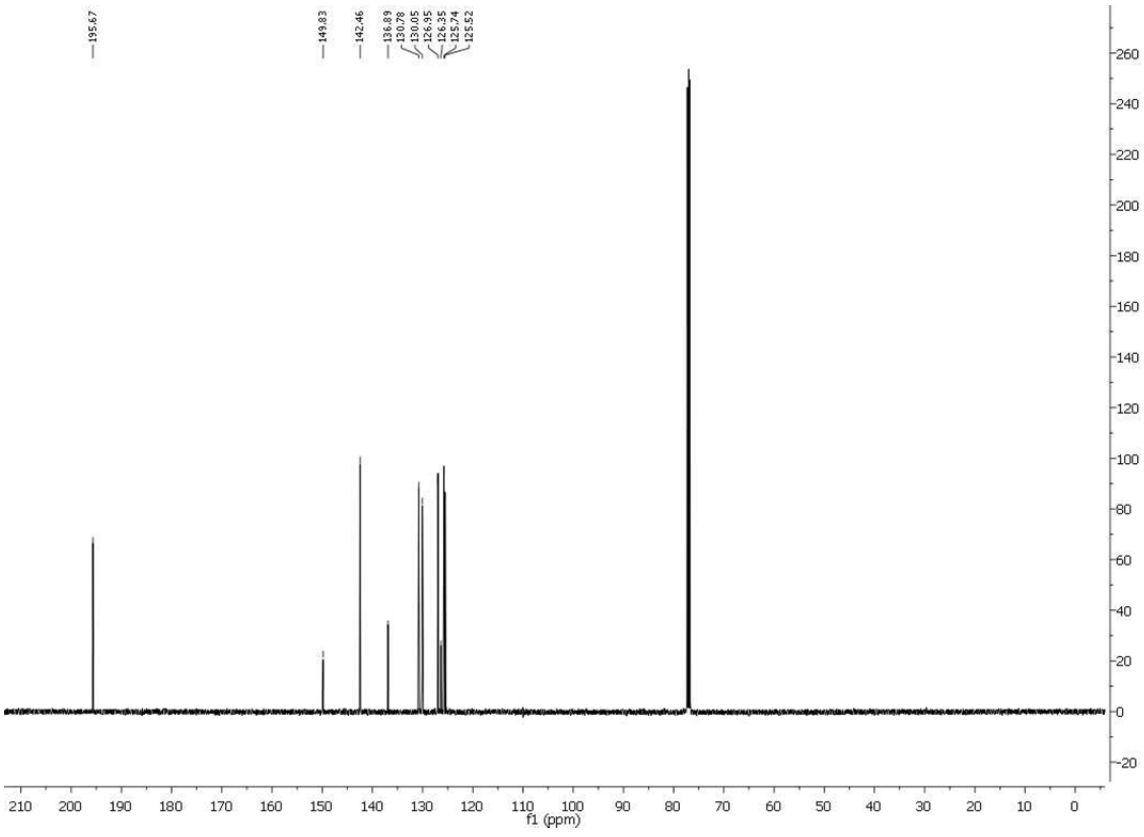

f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)

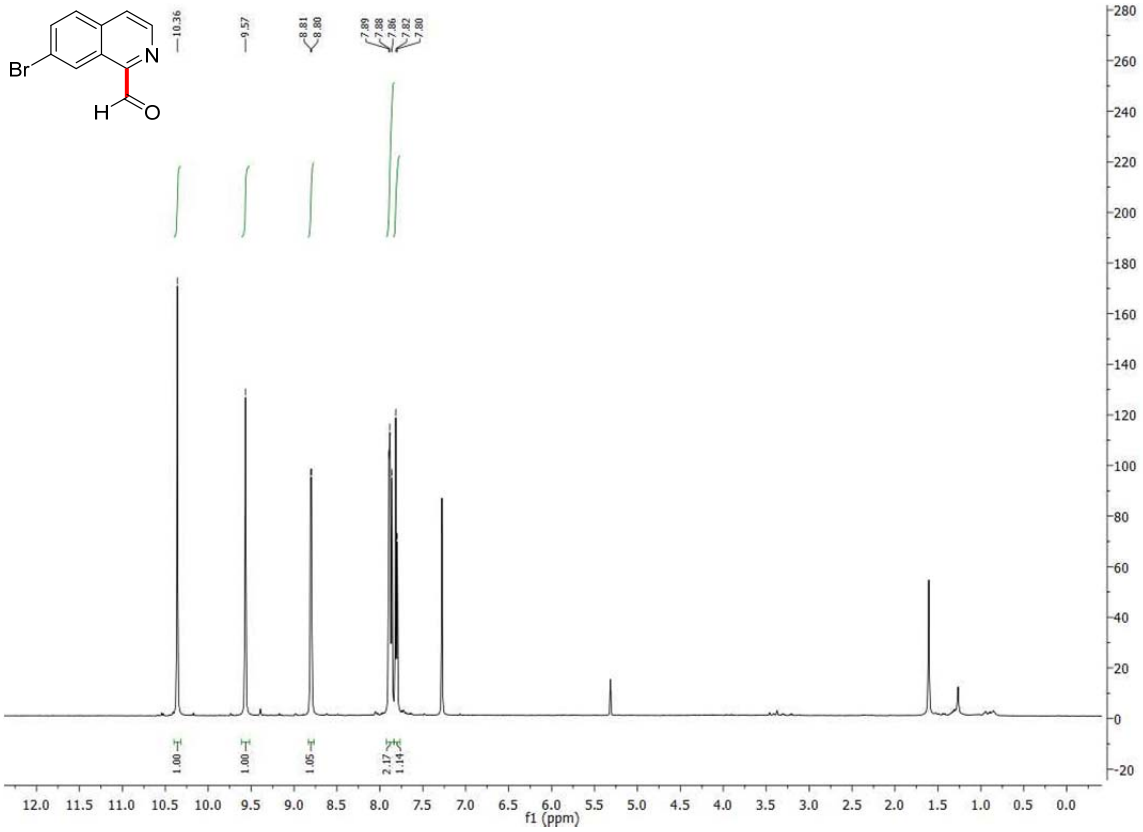


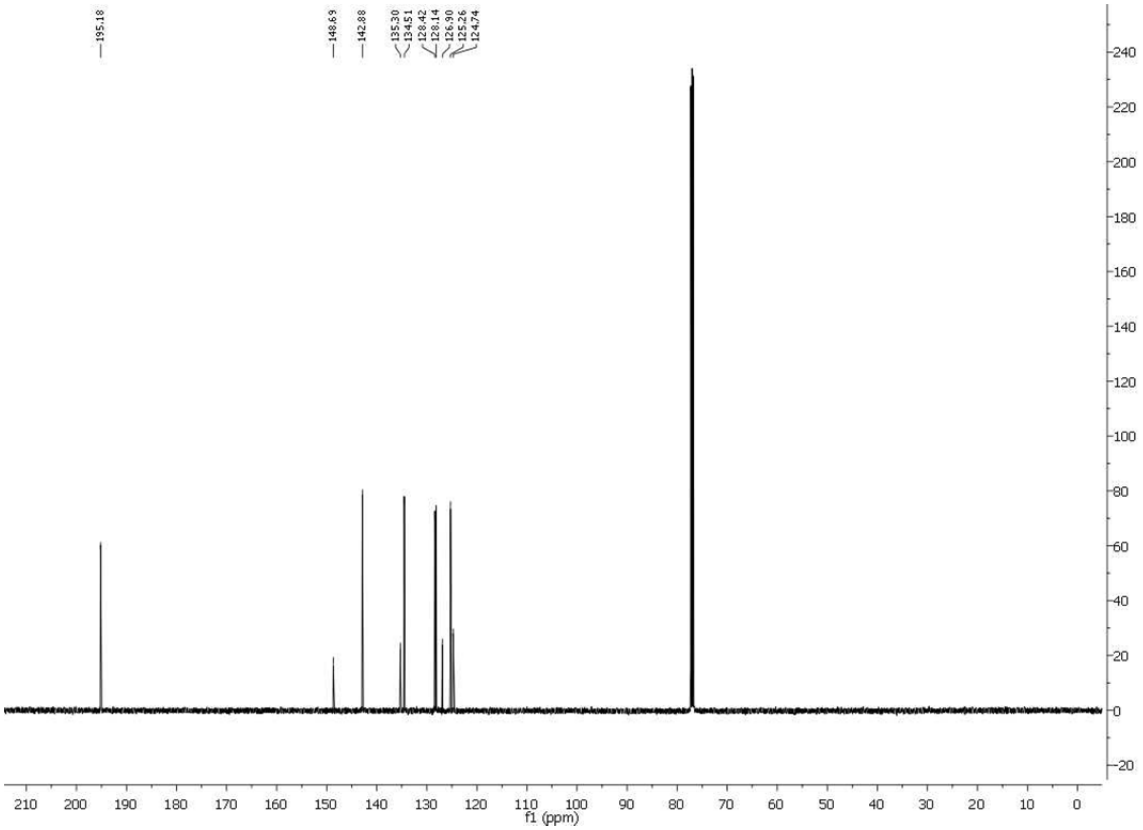
Isoquinoline-1-carbaldehyde (4a)



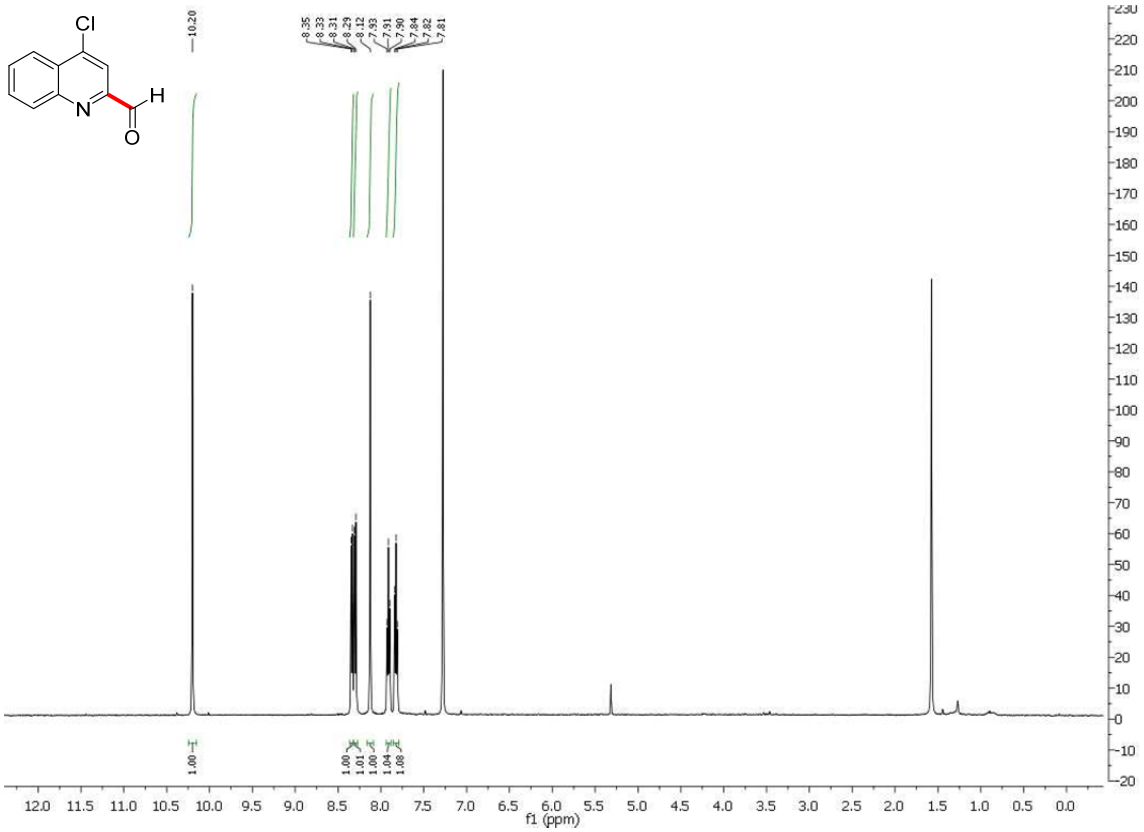


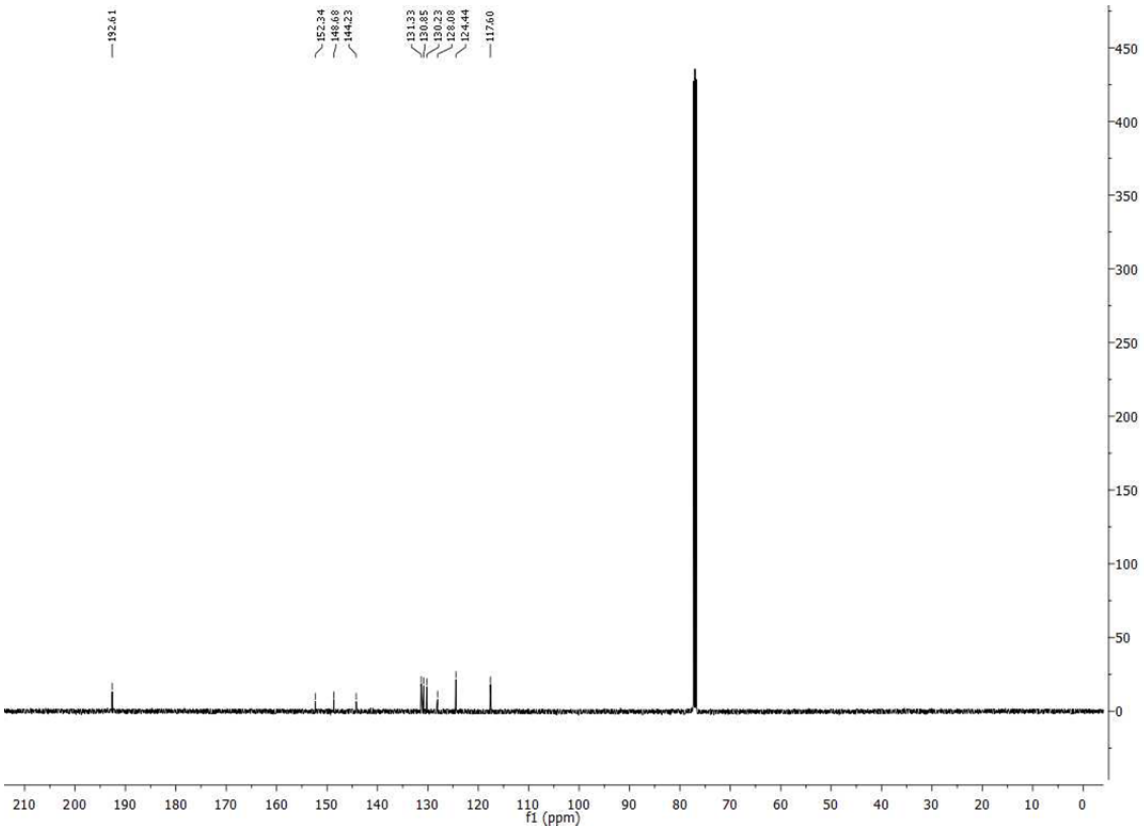
7-Bromoisoquinoline-1-carbaldehyde (4b)



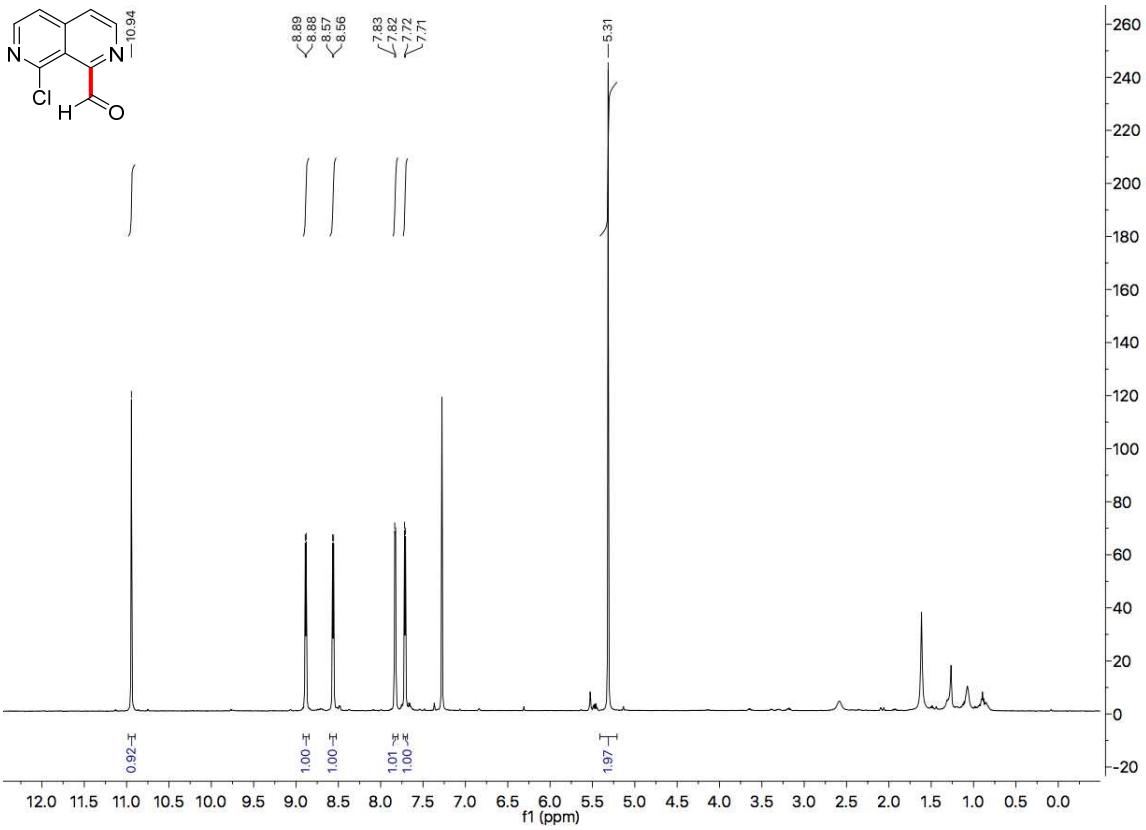


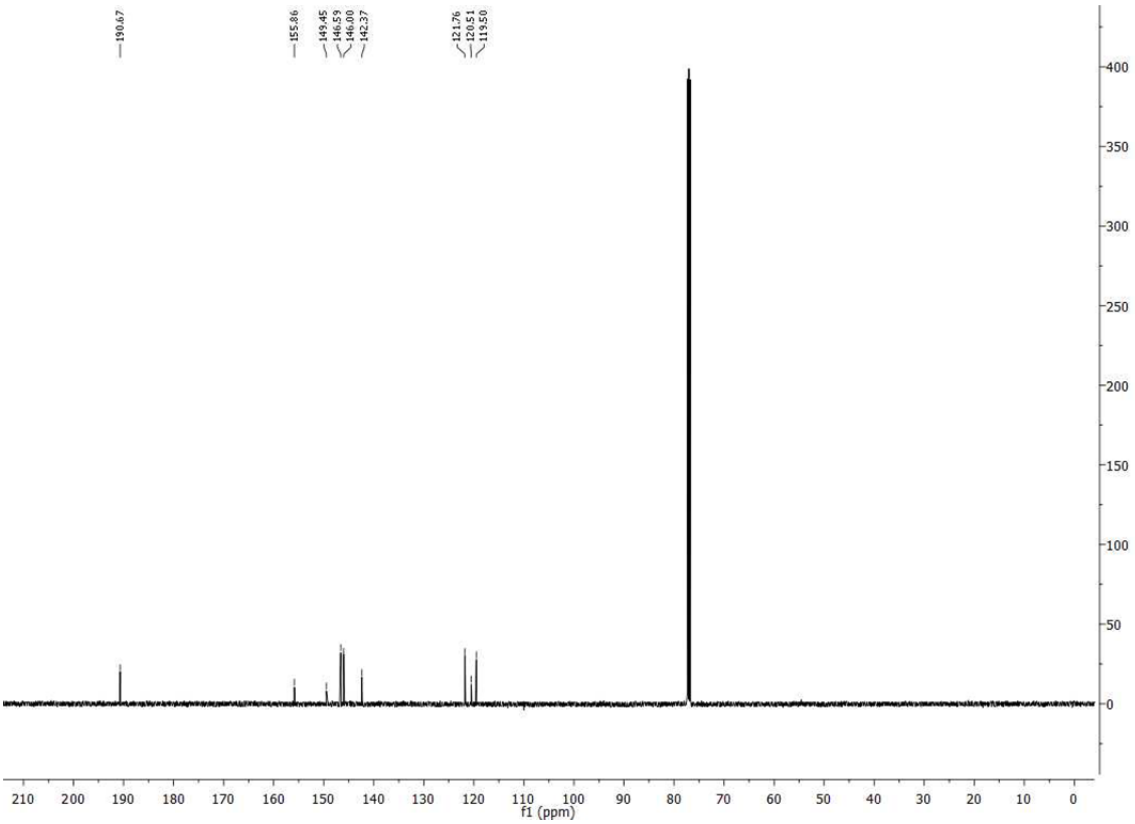
4-Chloroquinoline-2-carbaldehyde (4k)



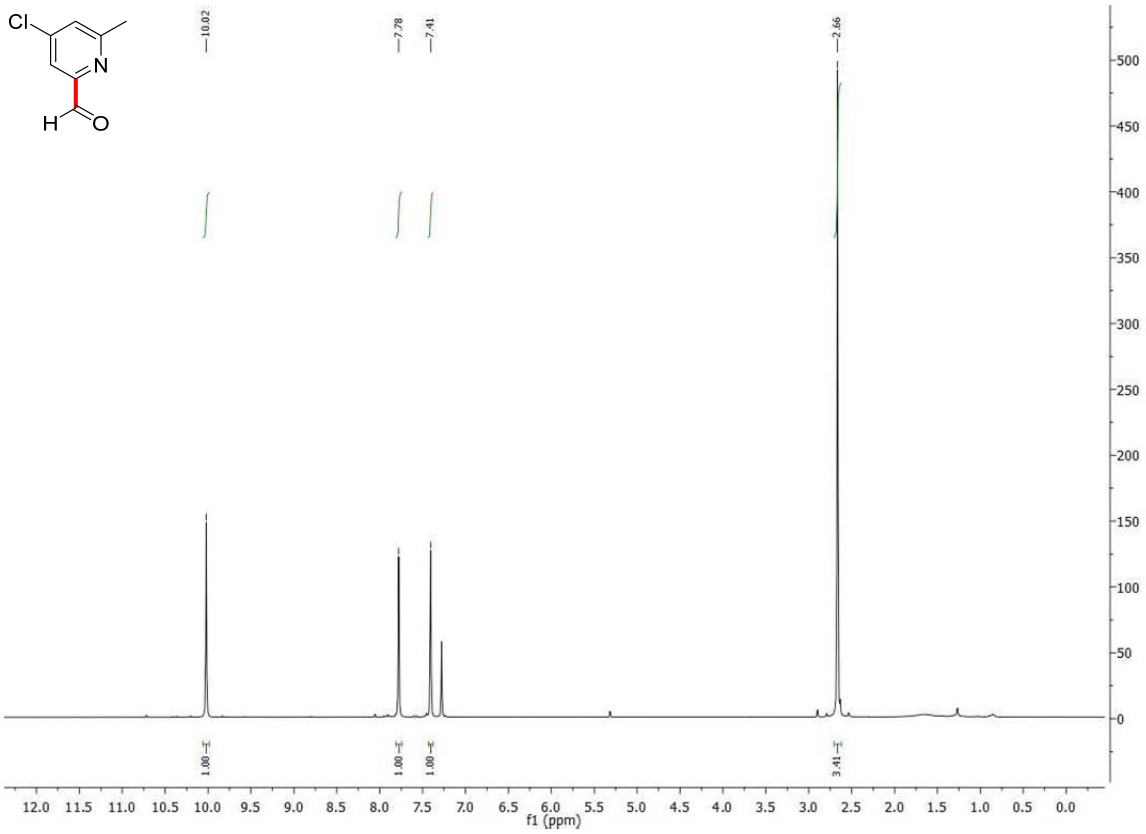


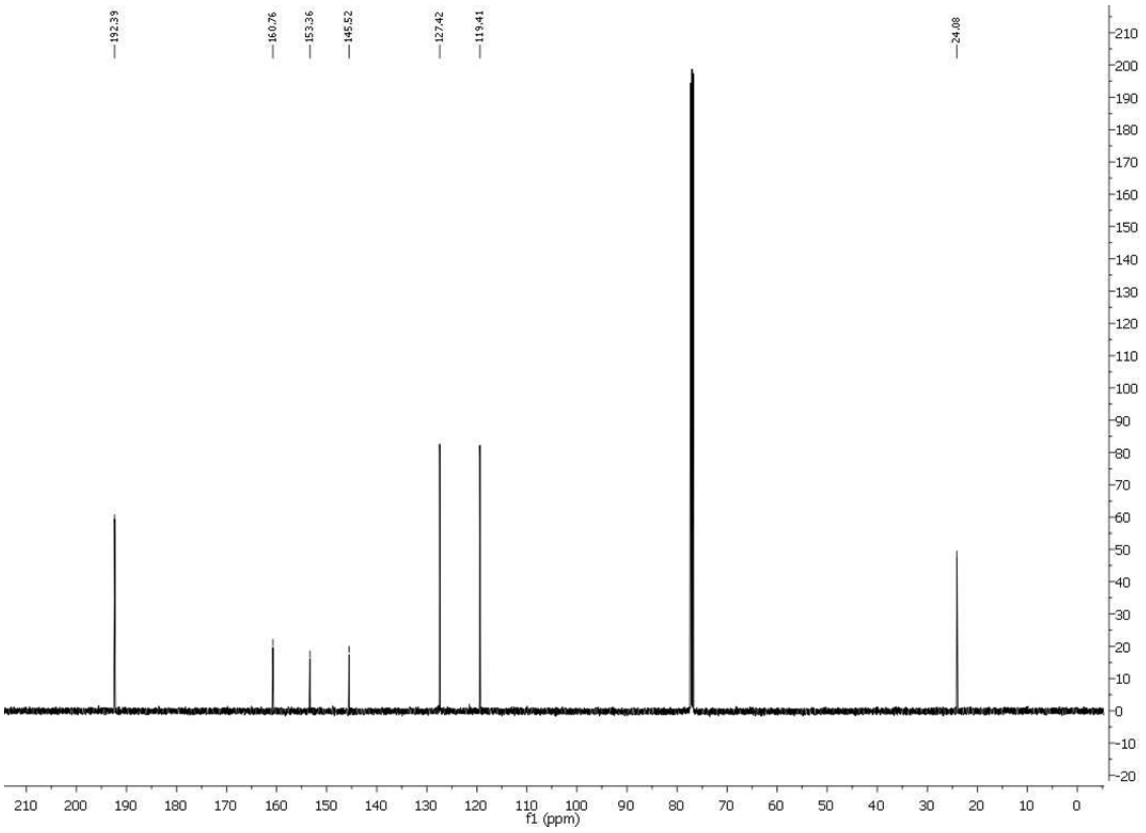
8-Chloro-2,7-naphthyridine-1-carbaldehyde (4n)





4-Chloro-6-methylpicolinaldehyde (4q)





5. Computational Methods and Supporting Data

Fukui indices were calculated using *AMPAC 9.2.1*[4] by a finite difference method proposed by Yang and Mortier,[5] with the geometries of the reactants optimized by AM1.[6]

Geometry optimizations and frequency calculations were performed at the B3LYP/6-31G** level of theory.[7] Single-point energies were evaluated for the optimized structures with the B3LYP functional and the 6-311++G** basis set. All of the density functional computations were performed using *Gaussian 16*.[8]

[4] A**MPAC**™ 9, Semichem, Inc.

[5] Yang, W.; Mortimer, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.

[6] Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

[7] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988,** *37*, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200. (d) Stephens, P. J.; Devlin, F. G.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

[8] Gaussian 16, Revision A.03, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

A. Computed Fukui indices

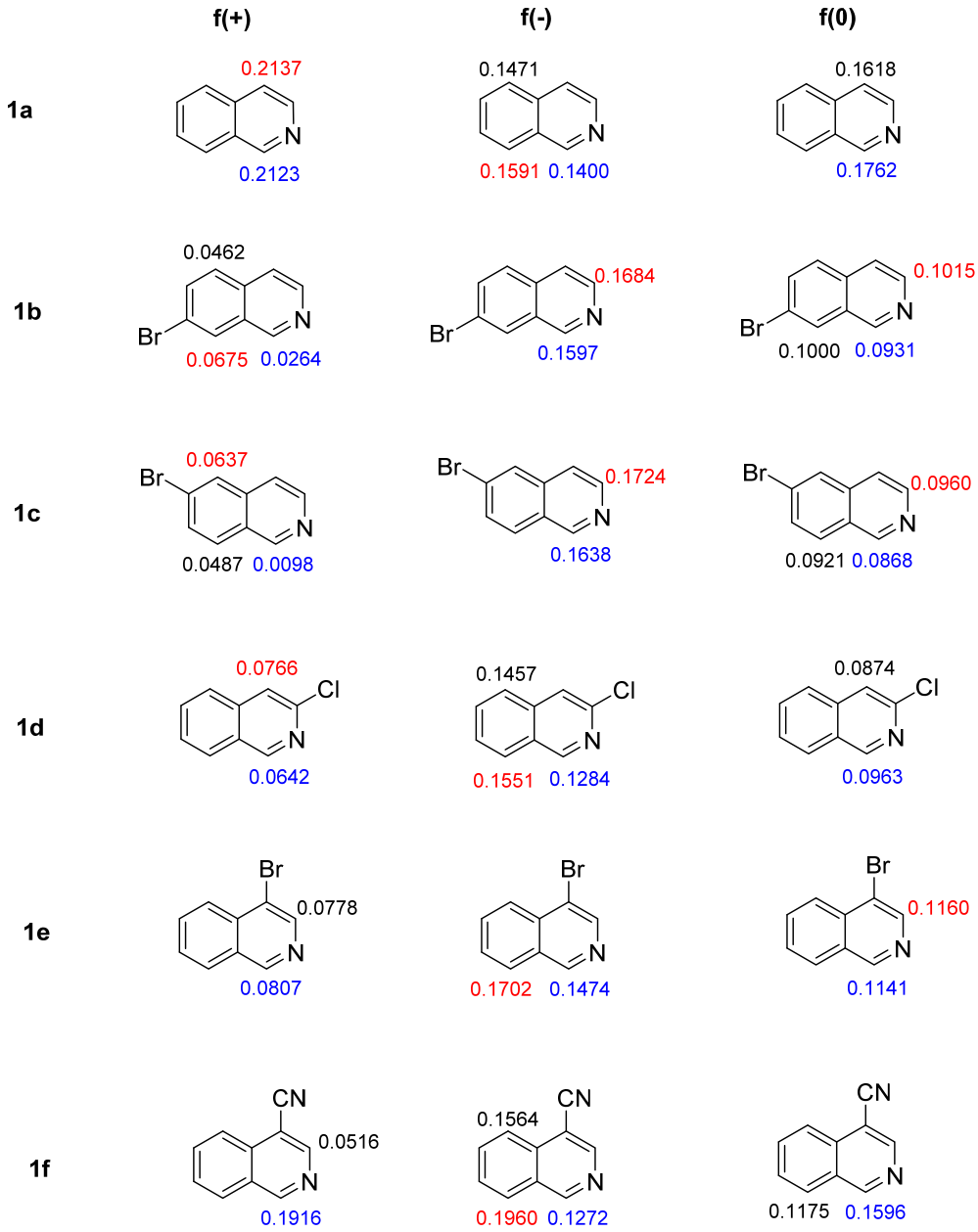


Figure S1.1. The C atoms of potential sites of C–H formylation with the top two Fukui indices values are labeled. The highest Fukui index is labeled in red if it is not at the experimentally observed site. The site of formylation observed in experiment is indicated in blue.

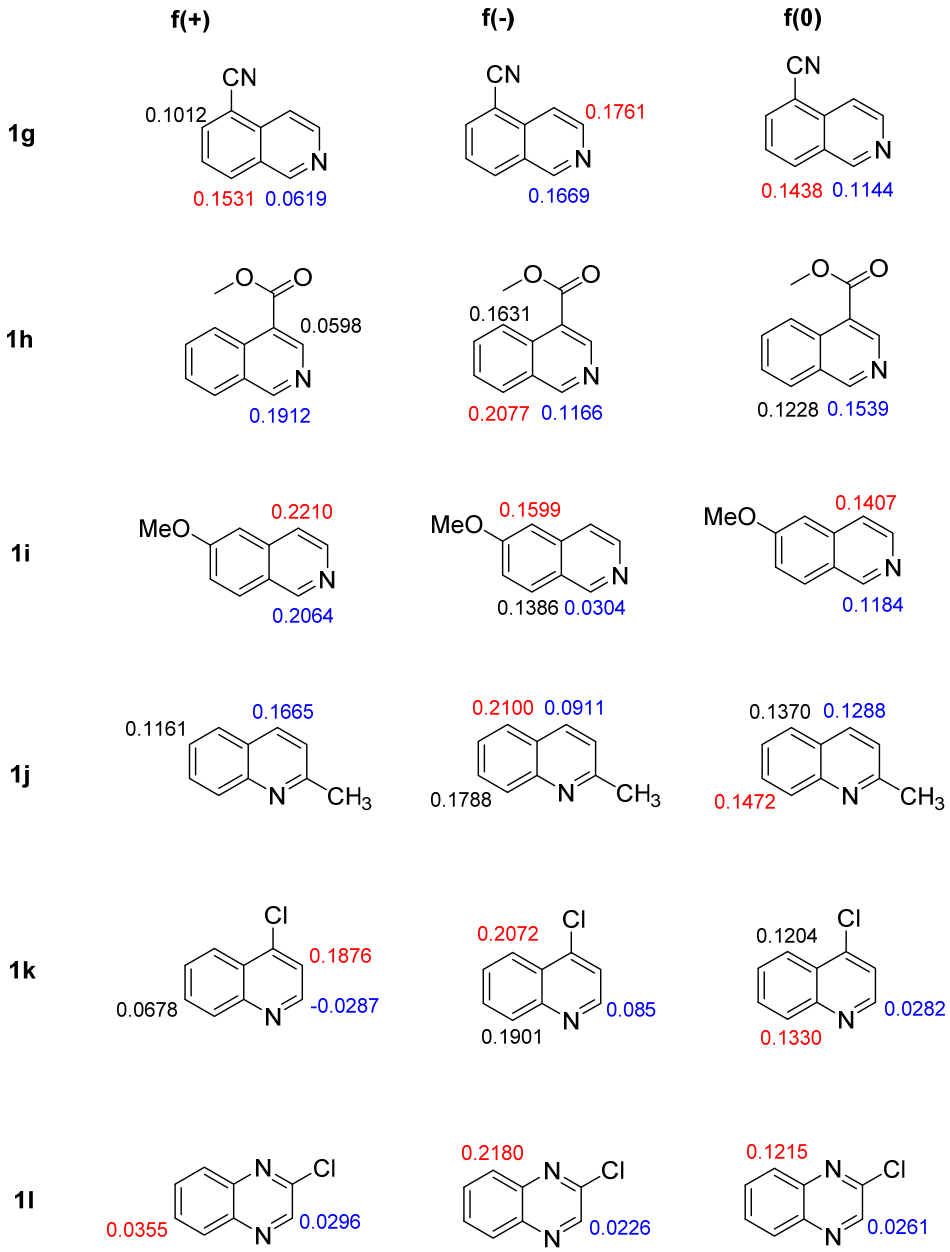


Figure S1.2. The C atoms of potential sites of C–H formylation with the top two Fukui indices values are labeled. The highest Fukui index is labeled in red if it is not at the experimentally observed site. The site of formylation observed in experiment is indicated in blue.

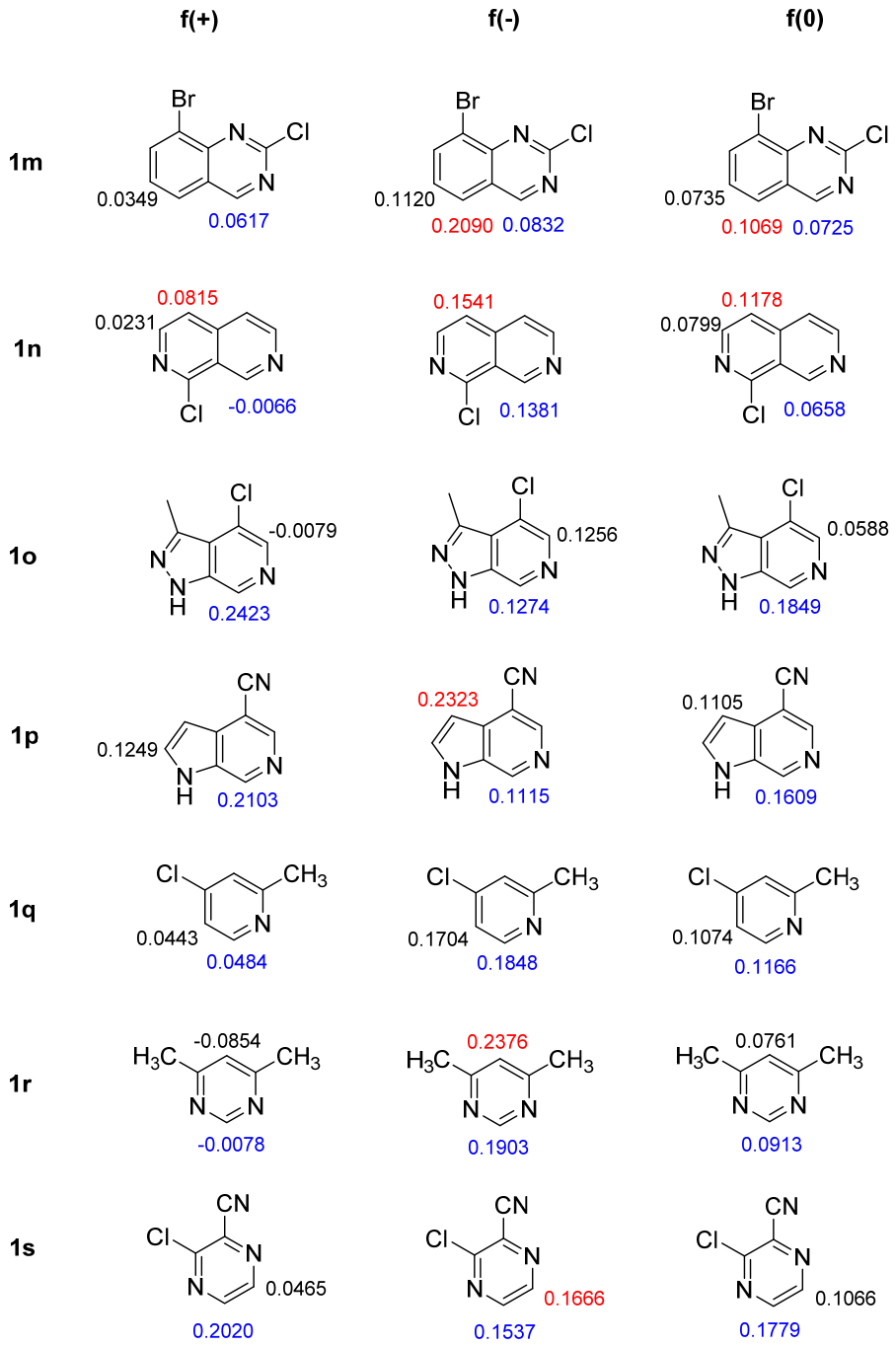


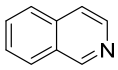
Figure S1.3. The C atoms of potential sites of C–H formylation with the top two Fukui indices values are labeled. The highest Fukui index is labeled in red if it is not at the experimentally observed site. The site of formylation observed in experiment is indicated in blue.

B. Cartesian coordinates and energies of optimized structures

Trioxane radical

C	-1.14844	-0.66063	0.18290
C	-0.00168	1.35705	0.18223
C	1.14999	-0.65797	0.18284
H	-0.00306	2.40386	-0.10716
H	-1.18449	-0.76076	1.28026
H	-2.01777	-1.12378	-0.28269
H	2.02056	-1.11886	-0.28273
H	1.18650	-0.75796	1.28023
O	-1.17269	0.71635	-0.16061
O	1.17086	0.71939	-0.16054
O	0.00172	-1.29490	-0.32582

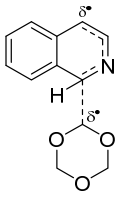
Electronic energy (UB3LYP/6-31G**) = -342.911467360
Sum of electronic and zero-point Energies = -342.825440
Sum of electronic and thermal Energies = -342.820570
Sum of electronic and thermal Enthalpies = -342.819626
Sum of electronic and thermal Free Energies = -342.854231
Electronic energy (UB3LYP/6-311++G**) = -343.012311192



Heterocycle **1a**

C	-2.41651	0.70987	-0.00000
C	-2.41510	-0.70815	-0.00000
C	-1.22533	-1.39999	-0.00000
C	0.00856	-0.69967	-0.00000
C	0.00944	0.72895	-0.00000
C	-1.23412	1.41526	-0.00000
C	1.26900	-1.35902	-0.00000
N	2.43348	-0.74388	-0.00000
C	2.41988	0.61814	-0.00000
C	1.27200	1.37600	-0.00000
H	-3.36387	1.24124	0.00001
H	-3.35940	-1.24424	-0.00001
H	-1.21510	-2.48689	-0.00000
H	-1.23815	2.50189	-0.00000
H	1.29087	-2.44979	0.00001
H	3.39694	1.09568	-0.00000
H	1.32740	2.46098	-0.00000

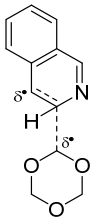
Electronic energy (RB3LYP/6-31G**) = -401.939831601
Sum of electronic and zero-point Energies = -401.803959
Sum of electronic and thermal Energies = -401.797274
Sum of electronic and thermal Enthalpies = -401.796330
Sum of electronic and thermal Free Energies = -401.835127
Electronic energy (RB3LYP/6-311++G**) = -402.029147927



TS for addition of trioxane radical to **1a** at C1

C	-0.05331	0.08768	1.00270
C	-1.37150	-0.25125	0.50265
C	-2.14725	0.78908	-0.08672
C	-1.59911	2.10353	-0.07302
C	-0.38223	2.32382	0.54787
H	-1.29034	-2.34967	1.00444
H	0.42848	-0.63788	1.65718
C	-1.88637	-1.56268	0.54844
C	-3.42012	0.47244	-0.62310
H	-2.15404	2.93011	-0.50619
H	0.01455	3.33574	0.61412
C	-3.90221	-0.82116	-0.56993
C	-3.13505	-1.84656	0.02202
H	-4.01331	1.26354	-1.07403
H	-4.87986	-1.05239	-0.98287
H	-3.52731	-2.85822	0.06435
N	0.36830	1.36691	1.12880
C	3.21229	-1.07159	0.59597
C	1.24533	-0.70916	-0.62820
C	2.97306	0.86736	-0.59583
H	0.48034	-1.18473	-1.23526
H	2.88772	-0.57711	1.52451
H	3.89469	-1.89444	0.80633
H	3.47806	1.52517	-1.30175
H	2.61807	1.40244	0.29404
O	2.07653	-1.64108	-0.05261
O	1.83811	0.33193	-1.28131
O	3.87080	-0.16084	-0.24402

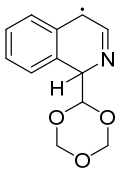
Electronic energy (UB3LYP/6-31G**) = -744.845188361
Sum of electronic and zero-point Energies = -744.622369
Sum of electronic and thermal Energies = -744.610010
Sum of electronic and thermal Enthalpies = -744.609066
Sum of electronic and thermal Free Energies = -744.662919
Electronic energy (UB3LYP/6-311++G**) = -745.031344421



TS for addition of trioxane radical to **1a** at C3

C	-0.78161	-1.26457	0.96338
C	-1.94382	-0.67323	0.36772
C	-1.94199	0.74969	0.19691
C	-0.78538	1.45142	0.58742
C	0.36185	0.74287	1.01837
H	-3.06267	-2.50452	0.14012
H	-0.80004	-2.33647	1.17184
C	-3.07813	-1.42603	0.00250
C	-3.11138	1.36630	-0.33113
H	-0.75091	2.53434	0.50381
H	1.12395	1.28794	1.57118
C	-4.20540	0.60461	-0.68263
C	-4.19546	-0.80122	-0.52075
H	-3.12595	2.44529	-0.45939
H	-5.08905	1.08747	-1.09044
H	-5.06714	-1.38299	-0.80366
N	0.29576	-0.61755	1.31576
C	2.71043	-1.35618	-0.56318
C	1.71377	0.76564	-0.66769
C	3.76349	0.42288	0.41515
H	1.17074	1.44630	-1.31789
H	2.26147	-1.65172	0.39320
H	2.86654	-2.20630	-1.22629
H	4.72457	0.92500	0.52199
H	3.33999	0.16193	1.39764
O	1.80860	-0.47771	-1.23798
O	2.89587	1.33883	-0.24489
O	3.95802	-0.73318	-0.35823

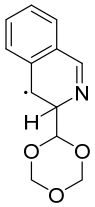
Electronic energy (UB3LYP/6-31G**) = -744.840139690
Sum of electronic and zero-point Energies = -744.617403
Sum of electronic and thermal Energies = -744.605086
Sum of electronic and thermal Enthalpies = -744.604142
Sum of electronic and thermal Free Energies = -744.658147
Electronic energy (UB3LYP/6-311++G**) = -745.026119413



Radical formed from addition of trioxane radical to **1a** at C1

C	-0.13587	-0.13194	-0.95791
C	1.28475	-0.28968	-0.44474
C	1.97300	0.84234	0.06474
C	1.32567	2.11031	-0.01761
C	0.06170	2.21351	-0.63680
H	1.43088	-2.39274	-0.88235
H	-0.21218	-0.61255	-1.94551
C	1.93339	-1.52483	-0.46232
C	3.28016	0.68700	0.58027
H	1.82264	3.00205	0.35130
H	-0.38029	3.20544	-0.74768
C	3.89666	-0.55470	0.57706
C	3.22652	-1.66467	0.04578
H	3.79819	1.55840	0.97164
H	4.90076	-0.66516	0.97525
H	3.71242	-2.63542	0.02607
N	-0.64823	1.21728	-1.10905
C	-3.35895	-0.27150	-0.54201
C	-1.13403	-1.00214	-0.09323
C	-2.36930	0.39789	1.40746
H	-0.66670	-1.98451	0.01754
H	-3.08338	0.67368	-1.02852
H	-4.27927	-0.68307	-0.95836
H	-2.52067	0.47338	2.48538
H	-2.11013	1.37569	0.97980
O	-2.35153	-1.24507	-0.76359
O	-1.30318	-0.52202	1.22440
O	-3.56740	-0.07111	0.83851

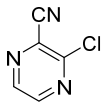
Electronic energy (UB3LYP/6-31G**) = -744.867466984
Sum of electronic and zero-point Energies = -744.642563
Sum of electronic and thermal Energies = -744.630350
Sum of electronic and thermal Enthalpies = -744.629406
Sum of electronic and thermal Free Energies = -744.682439
Electronic energy (UB3LYP/6-311++G**) = -745.052358987



Radical formed from addition of trioxane radical to **1a** at C3

C	-0.67382	-1.41129	0.72060
C	-1.89365	-0.73942	0.29893
C	-1.84927	0.68793	0.16447
C	-0.65395	1.34124	0.47306
C	0.55168	0.60076	0.96562
H	-3.07866	-2.52162	0.11832
H	-0.70906	-2.50313	0.78441
C	-3.06606	-1.43947	0.01206
C	-3.02936	1.35553	-0.27361
H	-0.58788	2.42184	0.37345
H	0.77926	0.92466	1.99904
C	-4.17985	0.63940	-0.55016
C	-4.21037	-0.76189	-0.40894
H	-3.01218	2.43608	-0.38484
H	-5.07198	1.16315	-0.88131
H	-5.12015	-1.31061	-0.63001
N	0.44509	-0.85497	1.02035
C	2.36253	-0.52478	-1.50067
C	1.83786	1.06731	0.19769
C	3.52632	-0.59539	0.46875
H	1.83301	2.16191	0.23685
H	1.68762	-1.32456	-1.16510
H	2.47609	-0.54256	-2.58562
H	4.53181	-0.66834	0.88540
H	2.87018	-1.38360	0.85996
O	1.82277	0.74768	-1.18043
O	3.03298	0.68158	0.84415
O	3.63848	-0.70277	-0.93370

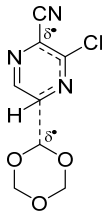
Electronic energy (UB3LYP/6-31G**) = -744.861870820
Sum of electronic and zero-point Energies = -744.637449
Sum of electronic and thermal Energies = -744.625166
Sum of electronic and thermal Enthalpies = -744.624222
Sum of electronic and thermal Free Energies = -744.677631
Electronic energy (UB3LYP/6-311++G**) = -745.046956514



Heterocycle **1s**

C	-2.22171	0.84955	0.00019
C	-2.27681	-0.54591	0.00019
C	-0.01412	-0.65004	-0.00039
C	0.05712	0.76105	0.00005
H	-3.12663	1.45069	-0.00093
N	-1.05910	1.50238	-0.00002
N	-1.16747	-1.29238	0.00004
H	-3.22565	-1.07619	-0.00030
C	1.31385	1.46060	0.00007
N	2.32483	2.03296	-0.00001
Cl	1.44203	-1.60746	0.00003

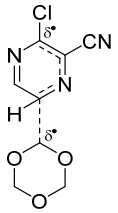
Electronic energy (RB3LYP/6-31G**) = -816.149251249
Sum of electronic and zero-point Energies = -816.083813
Sum of electronic and thermal Energies = -816.076775
Sum of electronic and thermal Enthalpies = -816.075830
Sum of electronic and thermal Free Energies = -816.116222
Electronic energy (RB3LYP/6-311++G**) = -816.266785945



TS for addition of trioxane radical to **1s** at C5

C	0.27041	1.16130	-1.02402
C	-0.58553	2.18846	-0.52271
C	-2.14840	0.63205	0.07184
C	-1.35510	-0.36492	-0.54684
H	1.09402	1.42193	-1.68306
N	-0.20820	-0.11607	-1.12800
C	3.50513	-0.17004	-0.52715
C	1.80618	0.98698	0.61324
C	2.03779	-1.35380	0.76634
H	1.56499	1.89065	1.16535
H	2.94116	-0.41529	-1.43940
H	4.56141	-0.01781	-0.74237
H	1.97527	-2.09235	1.56326
H	1.43729	-1.63619	-0.10669
O	3.01891	1.07152	-0.00168
O	1.50386	-0.13495	1.30986
O	3.39018	-1.19004	0.42410
Cl	-1.93330	-2.02226	-0.60178
C	-3.39594	0.34181	0.70347
N	-4.40970	0.11272	1.22823
N	-1.74609	1.93111	0.03836
H	-0.27086	3.22991	-0.56014

Electronic energy (UB3LYP/6-31G**) = -1159.05956354
Sum of electronic and zero-point Energies = -1158.907190
Sum of electronic and thermal Energies = -1158.894375
Sum of electronic and thermal Enthalpies = -1158.893431
Sum of electronic and thermal Free Energies = -1158.949776
Electronic energy (UB3LYP/6-311++G**) = -1159.27428148



TS for addition of trioxane radical to **1s** at C6

C	-0.32928	-1.06624	-1.02500
C	0.56436	-2.10136	-0.58733
C	2.10147	-0.55504	0.02602
C	1.33066	0.46385	-0.57437
H	-1.14044	-1.33418	-1.69804
N	0.15418	0.20882	-1.15075
C	-3.56761	0.07988	-0.51578
C	-1.76023	-0.93915	0.58888
C	-2.13631	1.38345	0.70094
H	-1.46572	-1.80904	1.17094
H	-3.04625	0.33175	-1.45200
H	-4.61908	-0.13787	-0.69642
H	-2.09513	2.15202	1.47059
H	-1.57617	1.67056	-0.19762
O	-2.99697	-1.11353	0.02998
O	-1.52320	0.21600	1.26762
O	-3.48658	1.13577	0.40004
N	1.73243	-1.83990	-0.03713
H	0.27580	-3.14820	-0.66631
C	1.79717	1.82631	-0.63467
N	2.14255	2.93492	-0.67951
Cl	3.61856	-0.19459	0.80514

Electronic energy (UB3LYP/6-31G**) = -1159.05447676
Sum of electronic and zero-point Energies = -1158.902218
Sum of electronic and thermal Energies = -1158.889433
Sum of electronic and thermal Enthalpies = -1158.888488
Sum of electronic and thermal Free Energies = -1158.944637
Electronic energy (UB3LYP/6-311++G**) = -1159.26891352