Electronic Supplementary Information

Metal- and Radical-Free Aerobic Oxidation of Heteroaromatic Methanes: An Efficient Synthesis of Heteroaromatic Aldehydes

Rongzi Ye,[a] Yuanjie Cao,[a] Xiaoxiang Xi,[a] Long Liu,[b] and Tieqiao Chen*[a,b]

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha, 410082, China

[b] Key Laboratory of Ministry of Education for Advanced Materials in Tropical Island Resources, College of Materials and Chemical Engineering, Hainan University, Haikou, 570228, China.

E-mail: chentieqiao@hnu.edu.cn

Contents

1. General information

All reactions were carried out under air atmosphere (1 atm) using standard Schlenk technique in the parallel synthesizer. All reagent/reactant were commercially available unless other noted. I_2 was purchased from Energy Chemical. TsOH (*p*-toluenesulfonic acid) was purchased from Aladdin Chemical. DMSO was purchased from Aladdin Chemical and handled by calcium hydride. Column chromatography was performed using Silica Gel 60 (particle size 37-54 μm). The pure products were obtained by column chromatography using ethyl acetate/petroleum ether (triethylamine were added sometimes) as the eluent and characterized by NMR spectroscopy using d_6-DMSO or $CDCl_3$ as the deuterium solvent. GC analysis was performed on GC 7820A (Shimadzu). GC-MS results were recorded on GC-MS QP2010 (Shimadzu). The ^1H NMR and ^{13}C NMR data were acquired on a Brucker ADVANCE III spectrometer (400 MHz for ^1H NMR spectroscopy and 100 MHz for ^{13}C NMR spectroscopy).

2. Experimental procedures.

A: A typical experimental procedure

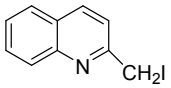
An oven-dried Schlenk tube containing a stir bar was charged with I_2 (0.04 mmol) and p-toluenesulfonic acid (0.1 mmol). After addition of 1 mL DMSO and 2-methylquinoline **1a** (0.1 mmol) under air atmosphere, the mixture was stirred at 130 ^oC for 16 h. The reaction solution was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), evaporated and subsequently passed through a short

silica chromatography column [particle size 37–54 μm, petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure **2a** in 92% isolated yield.

B: A typical 1 mmol-scale experimental procedure

An oven-dried 100 mL Schlenk tube containing a stir bar was charged wit h I_2 (0.4 mmol, 102 mg), p-toluenesulfonic acid (1 mmol, 172 mg). After addi tion of 10 mL DMSO, **1a** 2-methylquinoline (1 mmol, 0.135 mL) under air at mosphere, the mixture was stirred at 130 °C for 16 h. After reaction, the mixt ure was washed with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3× 15 mL). Then the organic layer was dried by Na_2SO_4, evaporated and the resi dues were passed through a short silica chromatography column [particle size 3 7–54 μm, petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytical ly pure product **2a** (141 mg, 90% yield).

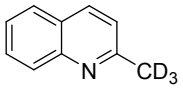
*C: Synthetic procedures for **3**[1] and **1a**-CD_3[1]*



3

A 25 mL Schlenk tube was charged with PPh_3 (0.03 mmol), $NaHCO_3$ (0.45 mmol), I_2 (0.45 mmol) and a stir bar, then degassed and refilled with N_2 for 3 times. After addition of 2 mL anhydrous THF and **1a** (0.3 mmol) under N_2 atmosphere with stirring, the mixture was further stirred overnight at 120 °C and then cooled to room temperature. The mixture was quenched with 5-10 mL saturated $Na_2S_2O_3$ solution. Afterwards, the solution was extracted with CH_2Cl_2 (3×3 mL) and washed with brine (3×5 mL). The organic layer was dried over Na_2SO_4 (10-30 min) and concentrated, the residues were passed through a short silica chromatography column [particle size

37–54 μm, petroleum ether/ethyl acetate (20:1) as eluent] to afford analytically pure product **3** as a yellow solid.

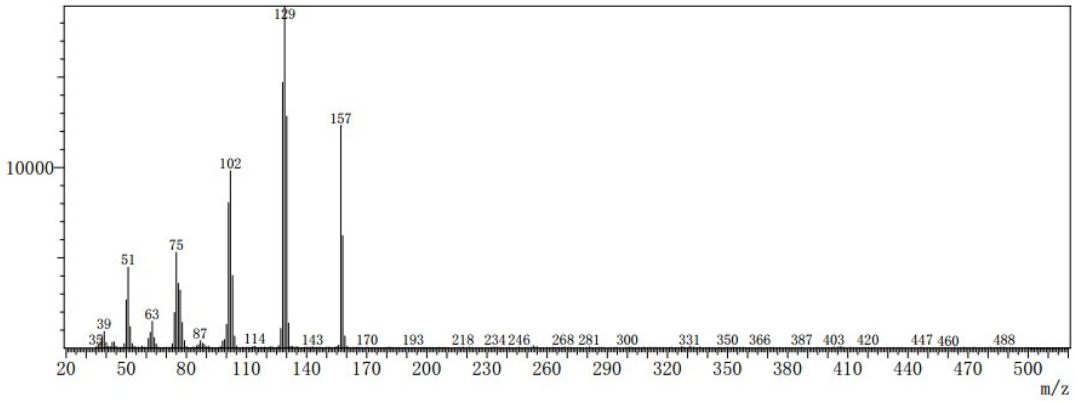


1a-CD$_3$

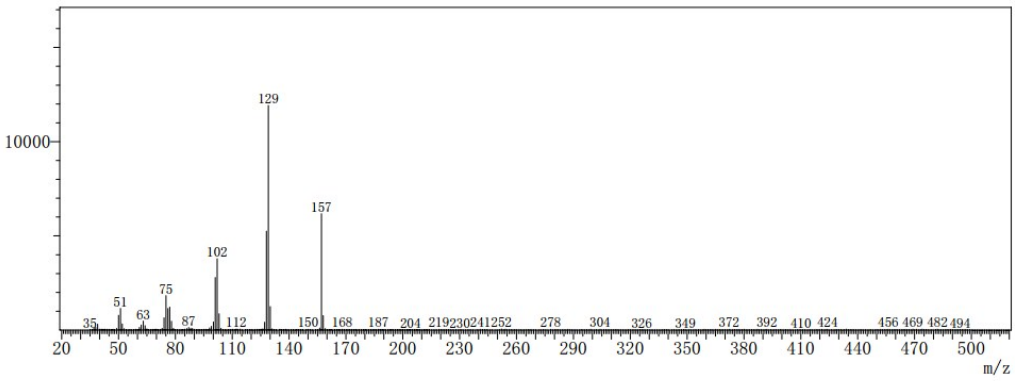
A 10 mL Schlenk tube was charged with **1a** (0.135 mL, 1 mmol), D_2O (1 mL), PhC(O)OH (9.2 mg, 0.075 mmol) and a stir bar. The mixture was heated at 80 °C for 6 h and cooled to room temperature. The mixture was neutralized with 5 mL saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (3×5 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford analytically pure product **1a-CD$_3$** as a yellow liquid (D-96%) .^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, 2H *J* = 8.4 Hz), 7.69 (d, 1H, *J* = 8.0 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.40 (t, 1H, *J* = 8.4 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 2.64 (s, 0.12H)

D: KIE experiment procedure

1a-CD$_3$: An oven-dried Schlenk tube containing a stir bar was charged with I_2 (0.04 mmol, 10.2 mg). p-toluenesulfonic acid (0.1 mmol, 17.2 mg). Then 1 mL DMSO, **1a-CD$_3$** (0.05 mmol, 7.3 mg) and **1a** (0.05 mmol, 7.2 mg) were charged into the tube. Then the mixture was stirred at 130 °C for 3 h. After reaction, the mixture was diluted with 3-5 mL CH_2Cl_2. The mixture was analyzed by GC using tridecane as the internal standard and the total yield of **2a** and **2a**-D was ca.30%. The ratio of **2a**/**2a**-D was determined by GC-MS and the value is 2.0.



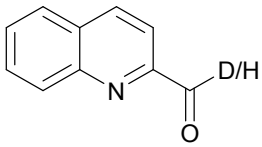
The GC-MS data of the reaction mixture involving **2a** and **2a**-D.



The GC-MS data of pure **2a**.

3. Characterized Data of Products

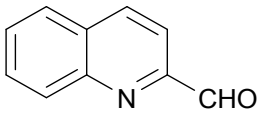
Quinoline-2-carbaldehyde-d (**2a**-D)



Following the typical procedure (120 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2a**-D as a yellow solid (89% yield, 14.0 mg, mp 69.3-72 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22(s, 0.13H), 8.29 (d, 1H, J = 8.0 Hz), 8.23

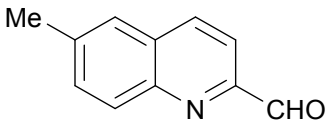
(d, 1H, J = 8.4 Hz), 8.01 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.0 Hz), 7.81 (t, 1H, J = 7.2 Hz), 7.68 (t, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 152.5, 147.9, 137.4, 130.5, 130.4, 130.0, 129.2, 127.8, 117.3.

Quinoline-2-carbaldehyde (**2a**)[2].



Following the typical procedure (130 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2a** as a yellow solid (92% yield, 14.4 mg, mp 69-71.6 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ10.23 (s, 1H), 8.31 (d, 1H, J = 8.4 Hz), 8.25 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.90 (d, 1H, J = 8.0 Hz), 7.83 (t, 1H, J = 8.0 Hz), 7.69 (t, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 152.6, 147.9, 137.4, 130.5, 130.4, 130.1, 129.2, 127.8, 117.3.

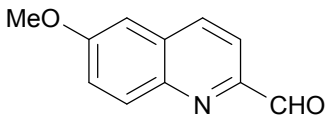
6-Methylquinoline-2-carbaldehyde (**2b**)[2].



Following the typical procedure (120 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2b** as a yellow solid (90% yield, 15.4 mg, mp 104-

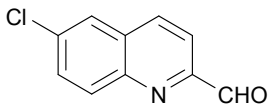
105.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.19 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 9.2 Hz), 7.98 (d, 1H, *J* = 8.4 Hz), 7.65-7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 151.9, 146.5, 139.7, 136.5, 132.8, 130.1, 130.0, 126.7, 117.4, 21.8.

6-Methoxyquinoline-2-carbaldehyde (**2c**)[2].



Following the typical procedure (120 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2c** as a yellow solid (91% yield, 17.0 mg, mp 101.6-103 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.10-8.05(m, 2H), 7.92 (d, 2H, *J* = 8.4 Hz), 7.40 (d, 2H, *C*= 9.2 Hz), 7.05-7.02 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 159.9, 150.5, 143.9, 135.6, 131.8, 131.6, 123.6, 117.8, 105.0, 55.7.

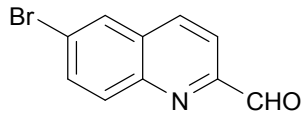
6-Chloroquinoline-2-carbaldehyde (**2d**)[2].



Following the typical procedure (120 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to

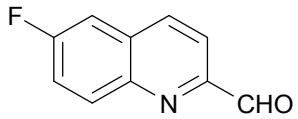
afford analytically pure product **2d** as a yellow solid (85% yield, 16.2 mg, mp 136-138 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.25-8.19 (m, 2H), 8.05(d, 1H, *J* = 8.4 Hz), 7.90 (s, 1H), 7.77 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 152.7, 146.3, 136.4, 135.2, 131.9, 131.6, 130.6, 126.5, 118.2.

6-Bromoquinoline-2-carbaldehyde (**2e**)[2].



Following the typical procedure (120 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2e** as a yellow solid (87% yield, 20.3 mg, mp 162-163.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.20 (d, 1H, *J* = 8.4 Hz), 8.10-8.01 (m, 3H), 7.86 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 152.7, 146.4, 136.3, 134.1, 132.0, 130.9, 129.9, 123.6, 118.2.

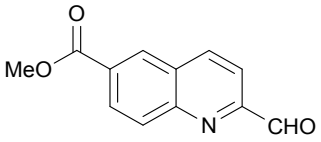
6-Fluoroquinoline-2-carbaldehyde (**2f**)[2].



Following the typical procedure (120 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to

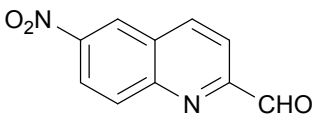
afford analytically pure product **2f** as a yellow solid (93% yield, 16.2 mg, mp 118.5-118.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.25 (d, 2H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.59 (t, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 162.0 (d, J_{F-C} = 251.4 Hz), 152.1 (d, J_{F-C} = 2.9Hz), 145.0, 136.7 (d, J_{F-C} =5.6Hz), 133.1 (d, J_{F-C} =9.5Hz), 131.0 (d, J_{F-C} = 12.9 Hz), 121.0(d, J_{F-C} = 25.9 Hz), 118.1, 111.0(d, J_{F-C} = 21.9 Hz).

Methyl 2-formylquinoline-6-carboxylate (**2g**)[3].



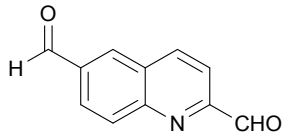
Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2g** as a yellow solid (65% yield, 13.9 mg, mp 164.5-166 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.64 (s, 1H), 8.42-8.37 (m, 2H), 8.28 (d, 1H, J = 8.8 Hz), 8.07 (d, 1H, J = 8.4 Hz), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 166.1, 154.0, 149.6, 138.8, 130.7, 130.7, 130.3, 129.9, 129.2, 118.0, 52.6.

6-Nitroquinoline-2-carbaldehyde (**2h**)[4].



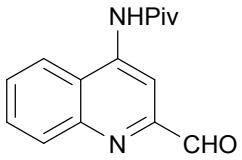
Following the typical procedure (120 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2h** as a yellow solid (80% yield, 16.1 mg, mp 191-193 °C). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.12 (s, 1H), 9.12 (s, 1H), 8.88 (d, 1H, J = 8.8 Hz), 8.52 (d, 1H, J = 9.2 Hz), 8.37 (d, 1H, J = 9.2 Hz), 8.10 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, d_6-DMSO): δ 193.7, 155.2, 149.4, 146.9, 140.9, 132.1, 129.1, 125.6, 124.3, 119.1.

Quinoline-2,6-dicarbaldehyde (**2i**).[5]



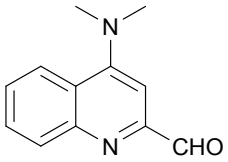
Following the typical procedure (120 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2i** as a yellow solid (81% yield, 14.9 mg, mp 172-174.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.48 (d, 1H, J = 8.4 Hz), 8.41 (s, 1H), 8.35 (d, 1H, J = 8.8 Hz), 8.27 (d, 1H, J = 8.4 Hz), 8.11 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 191.1, 154.4, 150.4, 138.9, 136.0, 133.1, 131.7, 129.4, 127.6, 118.3.

N-(2-formylquinolin-4-yl)pivalamide (**2j**).



Following the typical procedure (130 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (5:1) as the eluent] to afford analytically pure product **2j** as a yellow solid (70% yield, 17.9 mg; mp 179-181 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.73 (s, 1H), 8.26 (s, 1H), 8.20 (d, 1H, *J* = 8.4 Hz), 7.81-7.74 (m, 2H), 7.69-7.65 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 177.0, 153.3, 148.5, 141.7, 131.6, 130.2, 128.9, 121.9, 119.2, 107.7, 40.5, 27.6. IR (ATR, cm^{-1}) *v* 2975, 2959, 1713, 1698, 1568, 1532, 1501, 1171, 767. HRMS (EI) m/z: $[M+H]^+$ calcd for: $C_{15}H_{16}N_2O_2H^+$ 257.1285; found 257.1280.

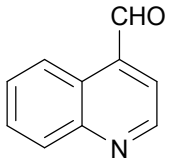
4-(Dimethylamino)quinoline-2-carbaldehyde (**2k**).



Following the typical procedure (130 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (5:1) as the eluent] to afford analytically pure product **2k** as a yellow liquid (60% yield, 12.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.16 (d, 1H, *J* = 8.0 Hz), 8.10 (d, 1H, *J* = 8.0 Hz),

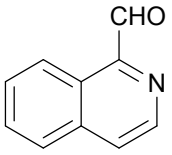
7.74-7.70 (m, 1H), 7.59-7.55 (m, 1H), 7.38 (s, 1H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 153.4, 147.6, 144.4, 125.6, 124.5, 121.7, 119.6, 119.2, 97.7, 38.6. HRMS (EI) m/z: $[M+H]^+$ calcd for: $C_{12}H_{12}N_2OH^+$ 201.1022; found 201.1025.

Quinoline-4-carbaldehyde (**2l**)[2].



Following the typical procedure (130 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2l** as a yellow solid (82% yield, 12.8 mg, mp 52-53.3 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 9.11 (d, 1H, J = 4.0 Hz), 8.92 (d, 1H, J = 8.4 Hz), 8.14 (d, 1H, J = 8.4 Hz), 7.74 (t, 1H, J = 7.2 Hz), 7.69 (d, 1H, J = 3.6 Hz), 7.64 (t, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 150.4, 149.1, 136.6, 130.1, 129.9, 129.3, 125.7, 124.3, 123.7.

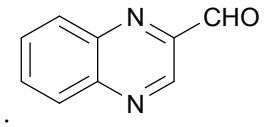
Isoquinoline-1-carbaldehyde (**2m**)[6].



Following the typical procedure (130 ^{o}C, N-Methyl-2-naphthamide instead of acid, dioxygen atmosphere), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica

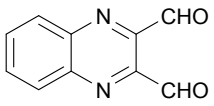
chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2m** as a yellow solid (70% yield, 11.0 mg, mp 80-82.5 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 9.30 (d, 1H, J = 5.6 Hz), 8.74 (d, 1H, J = 5.6 Hz), 7.88 (m, 2H), 7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 149.8, 142.4, 136.8, 130.7, 130.0, 126.9, 126.3, 125.7, 125.5, 77.3, 77.0, 76.7.

Quinoxaline-2-carbaldehyde (**2n**)[2]



Following the typical procedure (130 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2n** as a pink solid (87% yield, 13.7 mg， mp 109-110.6 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 9.38 (s, 1H), 8.22-8.16 (m, 2H), 7.93-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 145.9, 144.4, 142.4, 141.8, 132.8, 131.1, 130.4, 129.6

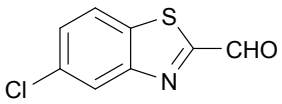
Quinoxaline-2,3-dicarbaldehyde (**2o**)[7].



Following the typical procedure (130 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to

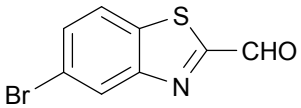
afford analytically pure product **2o** as a yellow solid (60% yield, 11.1 mg, mp 181-183 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 9.42 (s, 1H), 8.26-8.20 (m, 2H),7.95-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 145.9, 144.4, 142.5, 141.9, 133.0, 132.1, 131.2, 130.5, 129.6.

5-Chlorobenzo[d]thiazole-2-carbaldehyde (**2p**)[8].



Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2p** as a yellow solid (92% yield, 18.0 mg, mp 138-140 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.19 (s, 1H), 7.90 (d, 1H, J = 8.4 Hz), 7.52 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.1, 166.9, 154.2, 134.5, 133.5, 129.0, 125.2, 123.4.

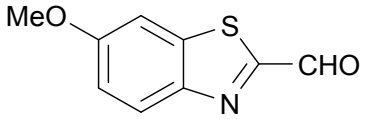
5-Bromobenzo[d]thiazole-2-carbaldehyde (**2q**)[8]



Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2q** as a yellow solid (83% yield, 20.0 mg, mp 145-

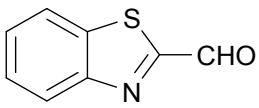
147 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ10.13(s, 1H), 8.37(s, 1H), 7.86(d, 1H, *J* = 7.6 Hz), 7.66 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 185.2, 166.6, 154.5, 135.1, 131.6, 128.4, 123.7, 121.1.

6-Methoxybenzo[d]thiazole-2-carbaldehyde (**2r**)[9]



Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (10:1) as the eluent] to afford analytically pure product **2r** as a yellow solid (76% yield, 14.6 mg, mp 120-122.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.038 (s, 1H), 8.04 (d, 1H, *J* = 9.2 Hz), 7.32 (s, 1H), 7.15 (d, 1H, *J* = 8.8 Hz), 3.87(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 162.8, 160.2, 148.2, 138.5, 126.4, 118.2, 103.6, 55.8.

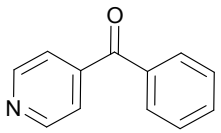
Benzo[d]thiazole-2-carbaldehyde (**2s**)[8].



Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2s** as a yellow solid (83% yield, 13.5 mg, mp 67-68.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ10.169 (s, 1H), 8.25 (d, 1H, *J* = 8.0 Hz), 8.01 (d,

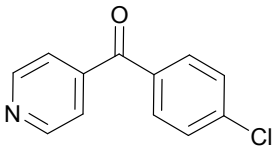
1H, J = 8.0 Hz), 7.64-7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 160.6, 148.8, 131.6, 123.6, 122.6, 121.0, 117.9.

Phenyl(pyridin-4-yl)methanone (**2t**)[10]



Following the typical procedure (100 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2t** as a yellow solid (91% yield, 16.6 mg, mp 69-72 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, 2H, J = 4.4 Hz), 7.81 (d, 2H, J = 8.0 Hz), 7.64 (t, 1H, J = 6.8 Hz), 7.57 (d, 2H, J = 4.4 Hz), 7.51 (t, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 150.3, 144.4, 135.9, 133.5, 130.1, 128.6, 122.9.

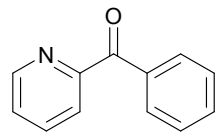
(4-Chlorophenyl)(pyridin-4-yl)methanone (**2u**)[10]



Following the typical procedure (100 ^{o}C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2u** as a yellow solid (80% yield, 17.3 mg, mp 111-111.8 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, 2H, J = 3.6 Hz), 7.71 (d, 2H, J =

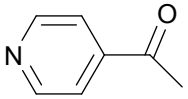
7.2 Hz), 7.51-7.49 (m, 2H), 7.43 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 150.4, 143.9, 140.1, 134.1, 131.4, 129.0, 122.7.

Phenyl(pyridin-2-yl)methanone (**2v**)[10].



Following the typical procedure (100 ^{o}C), the reaction was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (20:1) as the eluent] to afford analytically pure product **2v** as a yellow solid (93% yield, 17.3 mg, mp 42-43.3 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, 1H, J = 3.6 Hz), 8.05 (t, 3H, J = 8.0 Hz), 7.89 (t, 1H, J = 7.6Hz), 7.59 (t, 1H, J = 7.6Hz), 7.48 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 155.1, 148.5, 137.0, 136.2, 132.9, 131.0, 128.1, 126.1, 124.6.

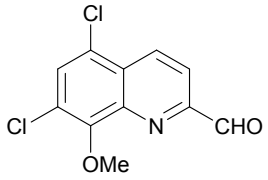
1-(Pyridin-4-yl)ethan-1-one (**2w**)[10].



A mixture of 4-ethylpyridine (0.1 mmol), I_2 (0.04 mmol), N-Methyl-2-naphthamide (0.1 mmol) in DMSO (1 mL) was heated at 100 ^{o}C for 16 h under dioxygen atmosphere. the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (10:1) as the eluent] to afford analytically pure product **2w** as a yellow liquid (56% yield, 6.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ

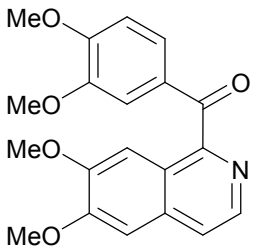
8.76 (s, 2H), 7.69 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 150.9, 142.7, 121.2, 26.6.

5,7-dichloro-8-methoxyquinoline-2-carbaldehyde (**2x**)[11].



Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (10:1) as the eluent] to afford analytically pure product **2x** as a yellow solid (61% yield, 155.5 mg, mp 162.9-163.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.62 (d, 1H, J = 8.8 Hz), 8.07 (d, 1H, J = 8.8 Hz),7.72 (s, 1H), 4.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 152.5, 152.1, 143.2, 135.1, 130.3, 127.9, 127.5, 126.1, 118.0, 62.8.

(6,7-Dimethoxyisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (**2y**)[12].



Following the typical procedure (130 °C), the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic layer was dried by Na_2SO_4, evaporated and the residues were passed through a short silica chromatography column [petroleum ether/ethyl acetate (1:1) as the eluent] to

afford analytically pure product **2y** as a yellow solid (52% yield, 183.5 mg, mp 202-204.5 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41(d, 1H, J = 4.0 Hz), 7.67 (s, 1H), 7.60 (d, 1H, J = 3.6 Hz), 7.50 (s, 1H), 7.38 (d, 1H, J = 8.4 Hz), 7.10 (s, 1H), 6.82 (d, 1H, J = 8.4 Hz),4.03 (s, 3H), 3.91 (s, 6H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 153.8, 153.7, 153.1, 151.0, 149.0, 140.0, 133.9, 129.9 126.9, 122.8, 121.2, 111.9, 109.9, 104.8, 104.0, 56.1, 56.1, 56.0, 56.0.

4. References

(1) M. Liu., X. Chen, T. Chen, Q. Xu and S.-F. Yin, *Org. Biomol. Chem.*, 2017*,* **15***,* 9845.

(2) G. Zheng, H. Liu and M. Wang, *Chin. J. Chem.*, 2016, **34**, 519.

(3) K. Jones, C. Rye, N. Chessum, M. Cheeseman, A. E. Pasqua and K. G.Pike, Faulder, P. F. PCT Int. Appl. 2015049535, 2015.

(4) L. Jiang, Y. Huang, Y. Yan and Y. Xie, *Tetrahedron Lett.*, 2016, **57**, 4149.

(5) L. Achremowicz, *Synth. Commun.*, 1996, **26**, 1681.

(6) J. M. Ganley, M. Christensen, Y.-h. Lam, Z. Peng, A. R. Angeles and C. S. Yeung, *Org. Lett.*, 2018, **20**, 5752.

(7) E. Vismara, F. Fontana and F. Minisci, *Gazzetta Chimica Italiana*, 1987, **117**, 135.

(8) Y. Nagasawa, Y. Tachikawa, E. Yamaguchi, N. Tada, T. Miura and A. Itoh, *Adv. Synth. Catal*., 2016, **358**, 178.

(9) T. B. Shaik, S. A. Hussaini, V. L. Nayak, M. L. Sucharitha, M. S. Malik and A. Kamal, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 2549.

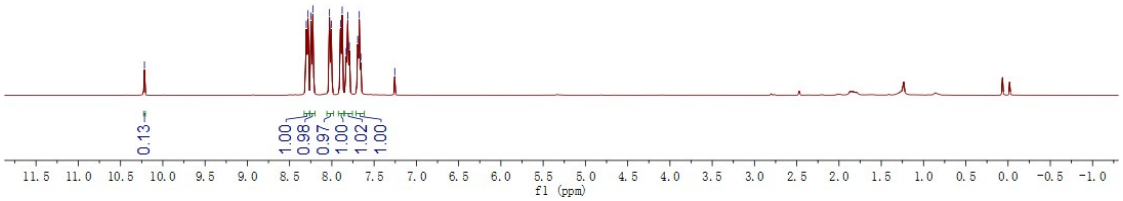
(10) J. Liu, X. Zhang, H. Yi, C. Liu, R. Liu, H. Zhang, K. Zhuo and A. Lei, *Angew. Chem. Int. Ed.*, 2015, **54**, 1261.

(11) J. W. Chen, C. W. Huang, P. T. Chang, R. S. Talekar, PCT Int. Appl. 2014163622, 2014.

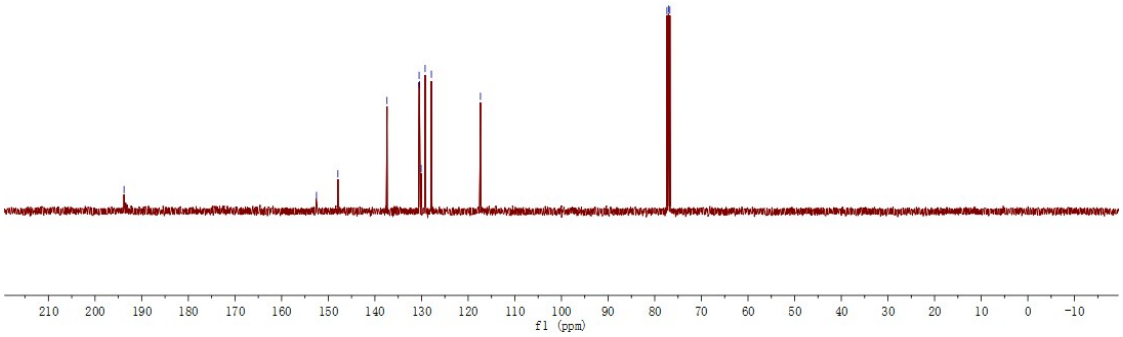
(12) H. Gan, Y. Lu, Y. Huang, L. Ni, J. Xu, H. Yao and X. Wu, *Tetrahedron Lett.*, 2011, **52**, 1320.

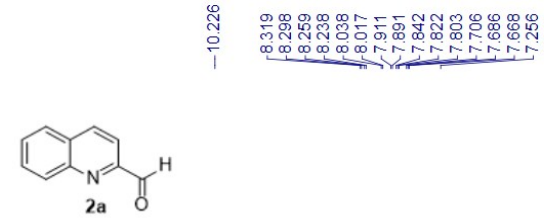
5.Copies of ^{1}H NMR and ^{13}C NMR spectroscopies

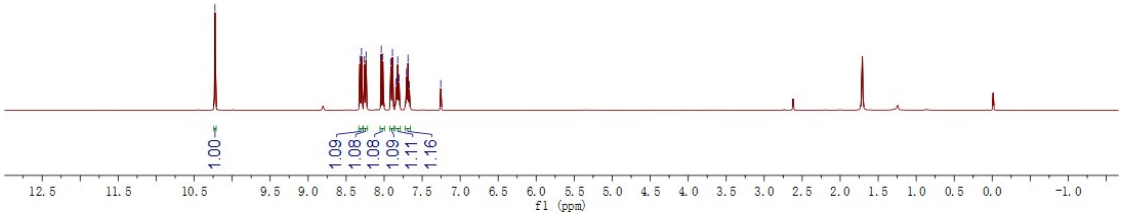
2a-D, 87%D



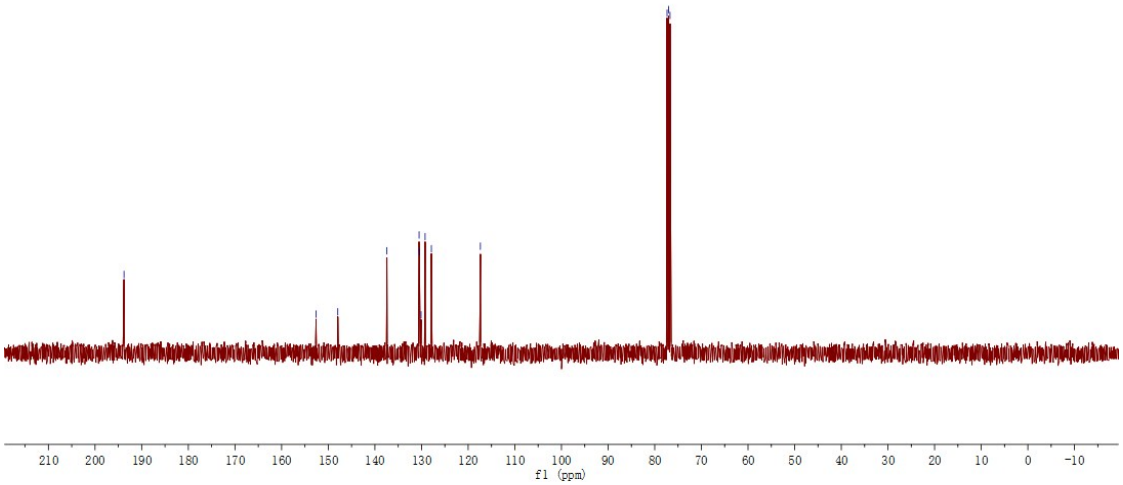
2a-D, 87%D

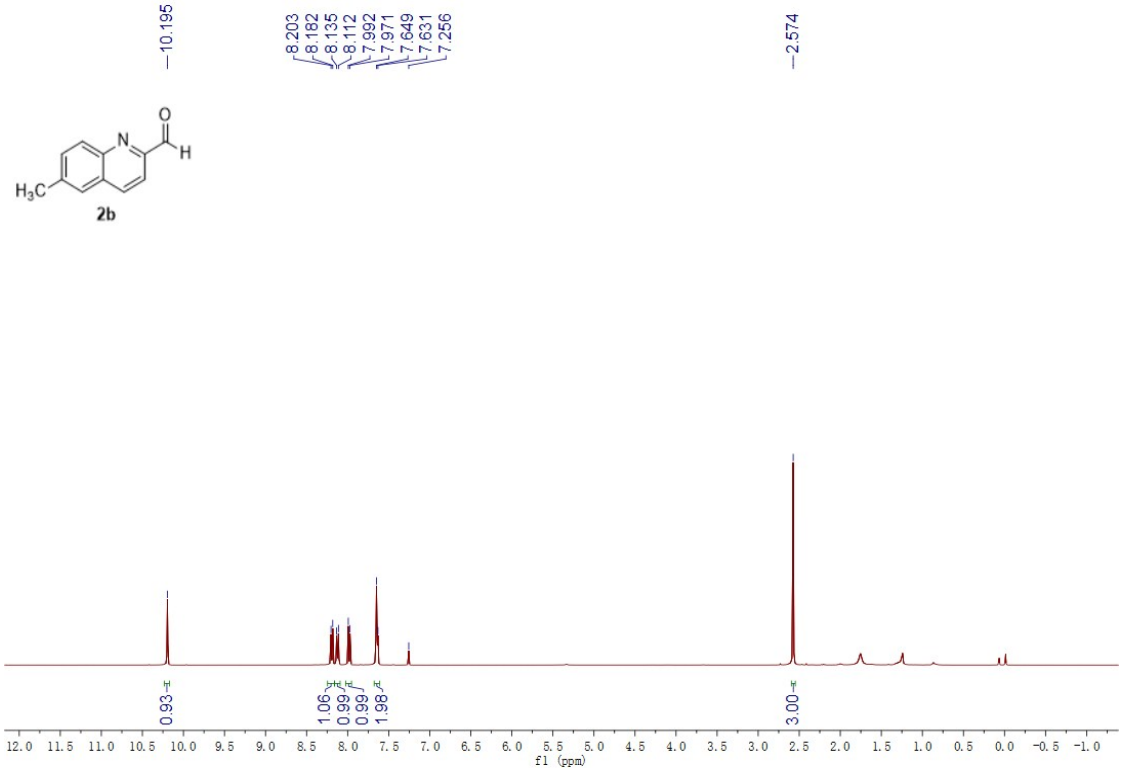


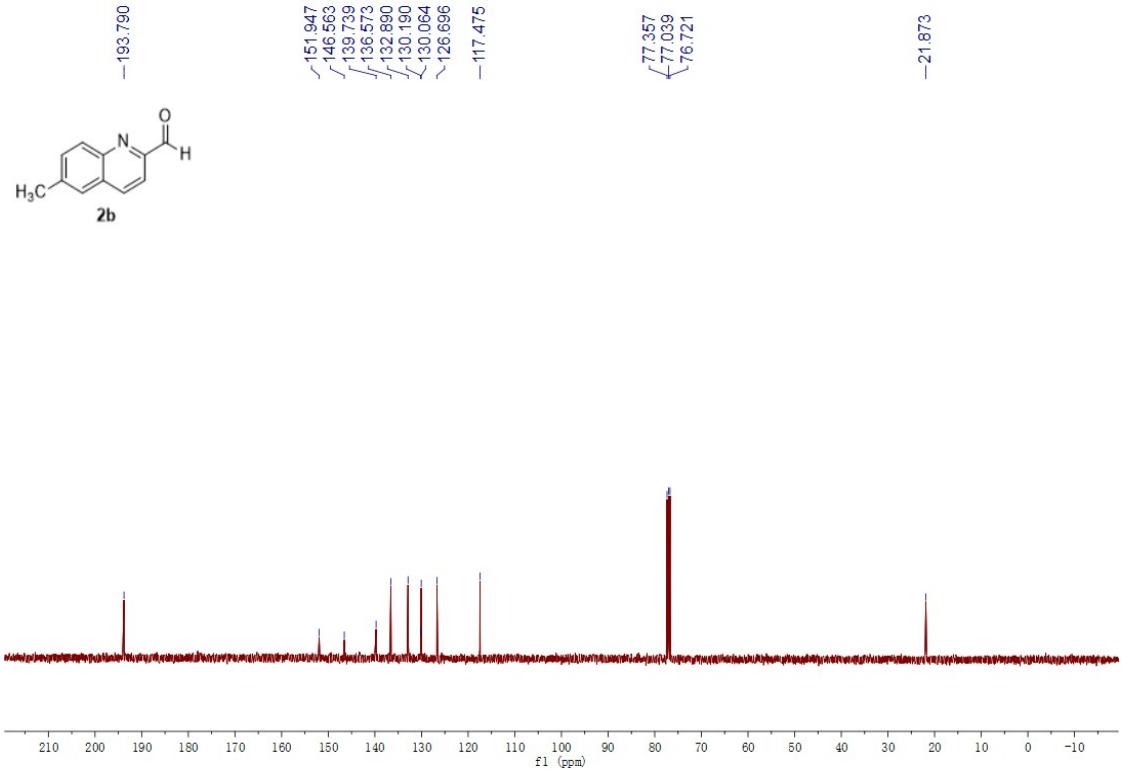

10.226
8.319
8.298
8.259
8.238
8.038
8.017
7.911
7.891
7.842
7.822
7.803
7.706
7.686
7.668
7.256
N
H
O
2a

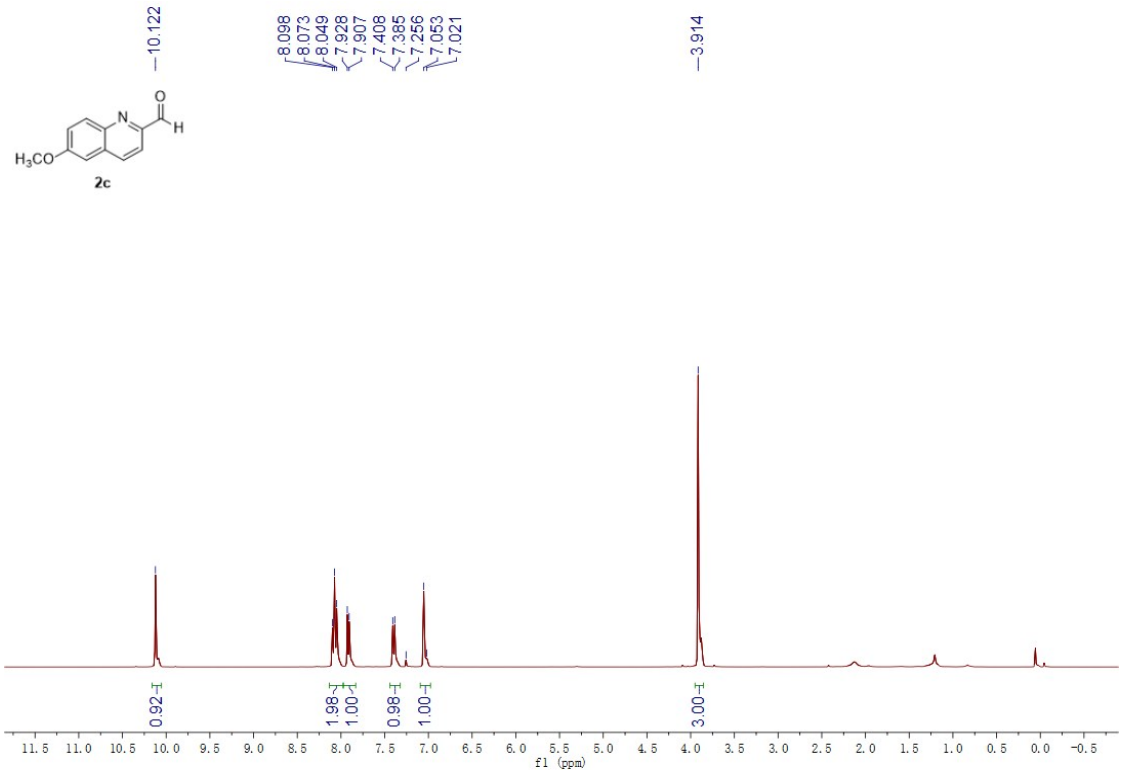

1.00
1.09
1.08
1.08
1.09
1.11
1.16
f1 (ppm)

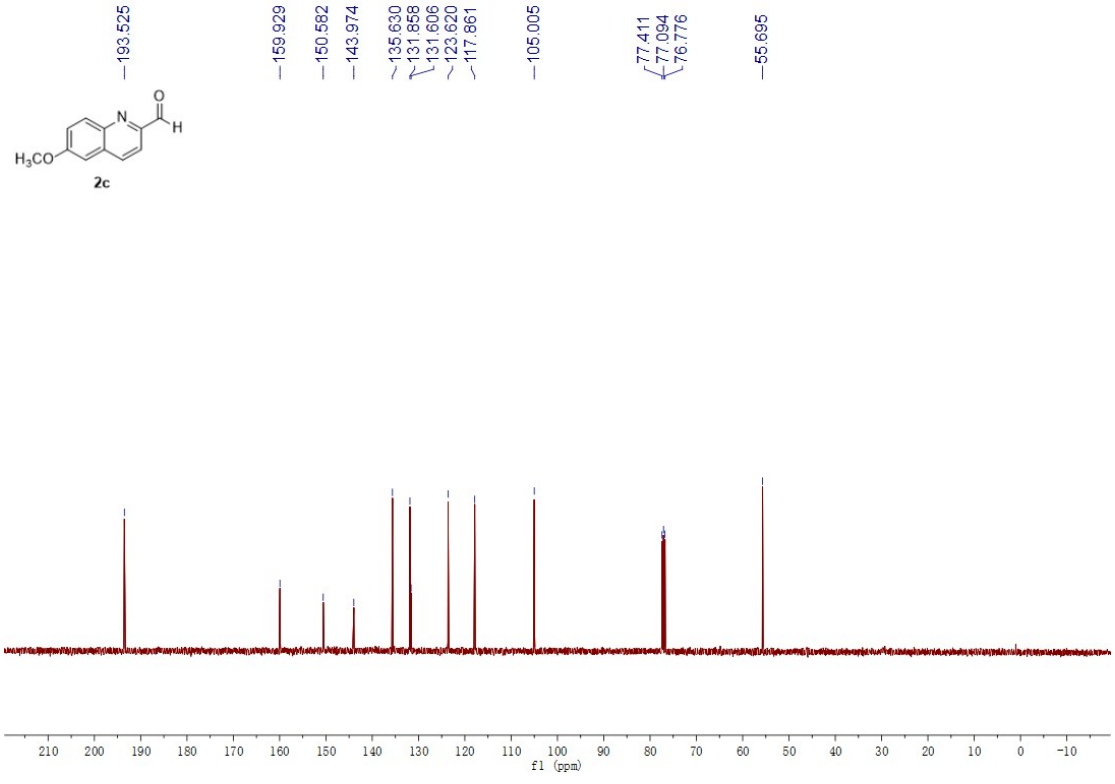

193.781
152.616
147.953
137.422
130.521
130.445
130.097
129.232
127.887
117.378
77.358
77.040
76.723
N
H
O
2a


f1 (ppm)

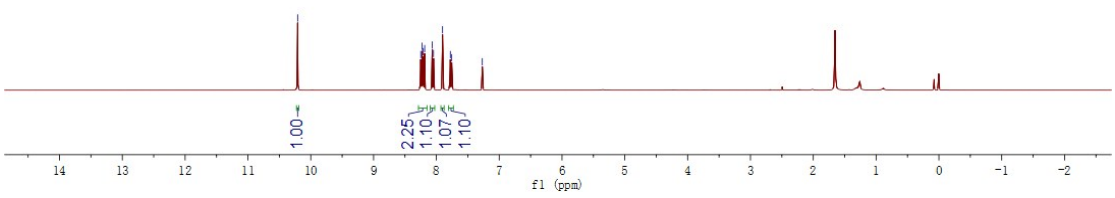

10.195
8.203
8.182
8.135
8.112
7.992
7.971
7.649
7.631
7.256
2.574
O
N
H
H3C
2b
0.93
1.06
0.99
0.99
1.98
3.00
f1 (ppm)


193.790
151.947
146.563
139.739
136.573
132.890
130.190
130.064
126.696
117.475
77.357
77.039
76.721
21.873
O
N
H
H3C
2b
f1 (ppm)

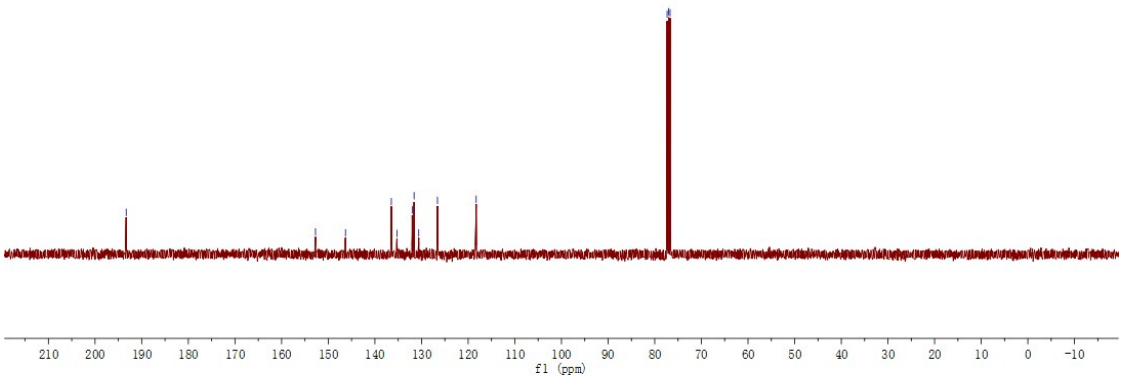

10.122
8.098
8.073
8.049
7.928
7.907
7.408
7.385
7.256
7.053
7.021
3.914
O
N
H
H3CO
2c
0.92
1.98
1.00
0.98
1.00
3.00
f1 (ppm)

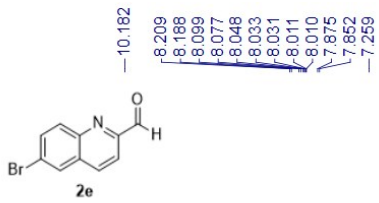

193.525
159.929
150.582
143.974
135.630
131.858
131.606
123.620
117.861
105.005
77.411
77.094
76.776
55.695
O
N
H
H3CO
2c
f1 (ppm)


10.209
8.249
8.228
8.209
8.187
8.067
8.046
7.901
7.778
7.756
7.269
O
H
N
Cl
2d

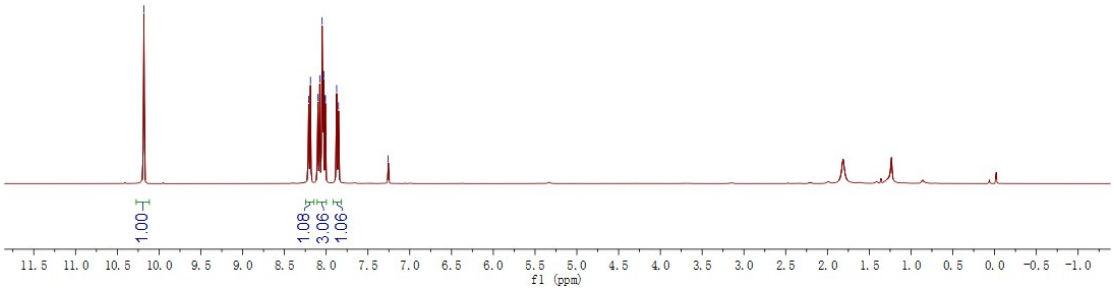

1.00
2.25
1.10
1.07
1.10
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

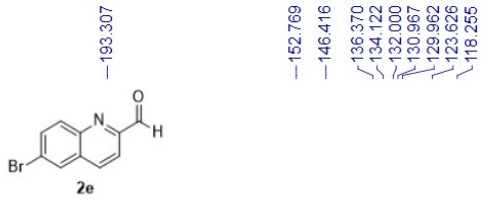

193.320
152.731
146.305
136.473
135.280
131.994
131.597
130.595
126.581
118.285
77.345
77.028
76.710
O
H
N
Cl
2d


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


10.182
8.209
8.188
8.099
8.077
8.048
8.033
8.031
8.011
8.010
7.875
7.852
7.259
O
H
N
Br

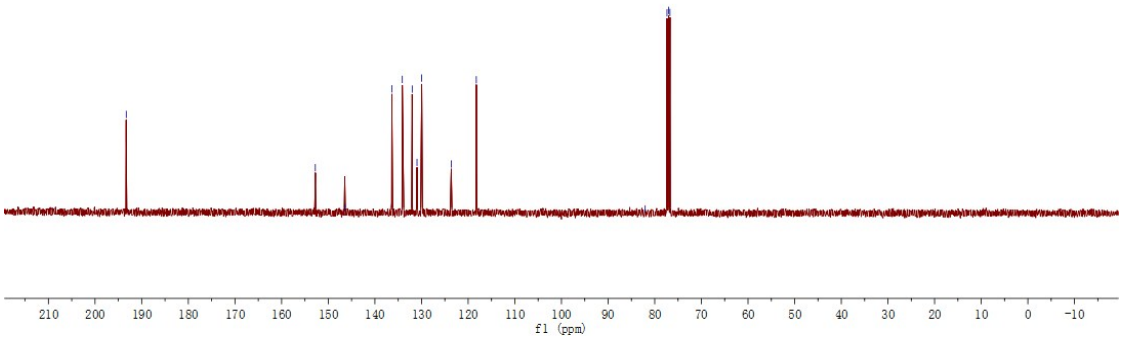
2e

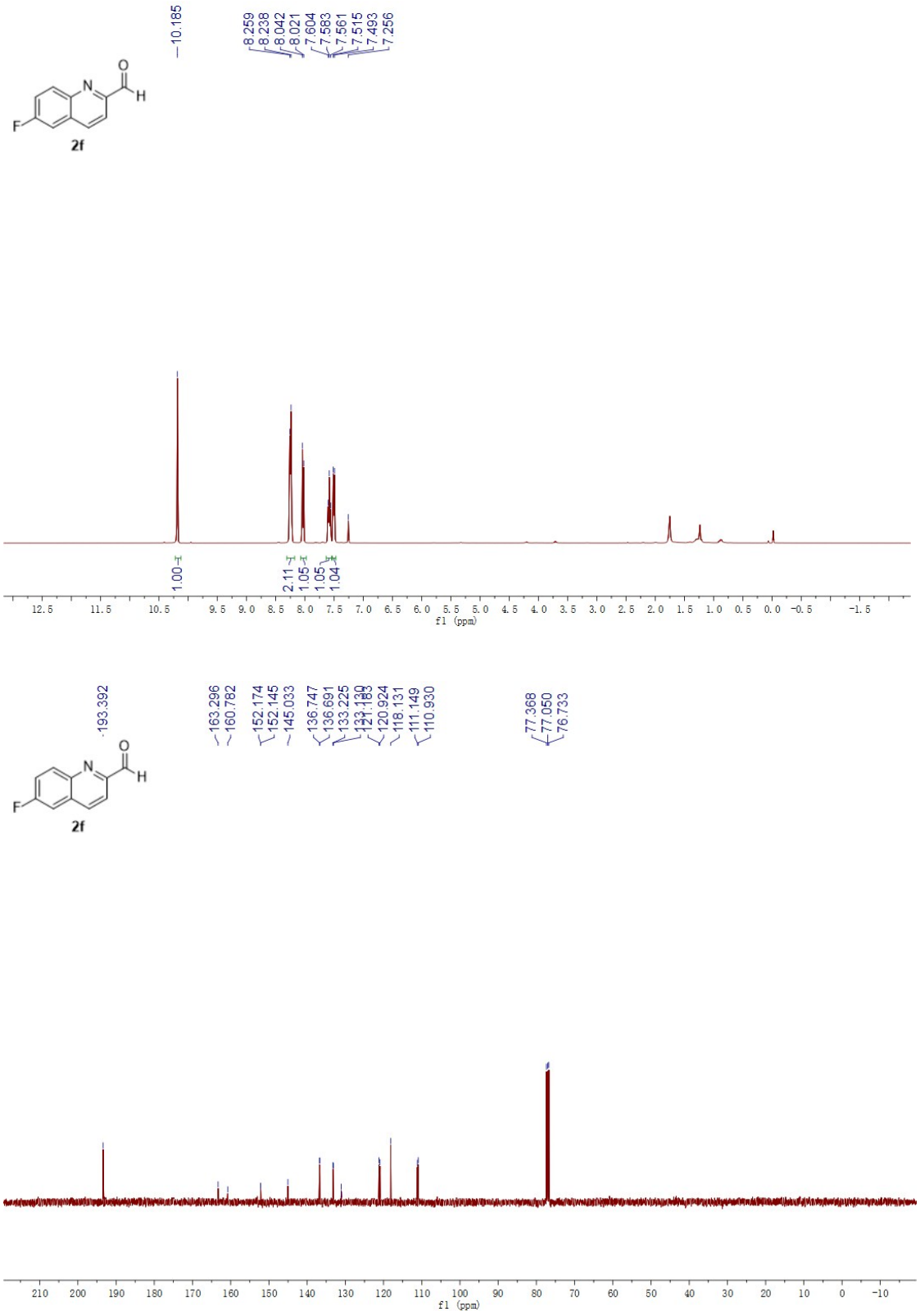

1.00
1.08
3.06
1.06
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

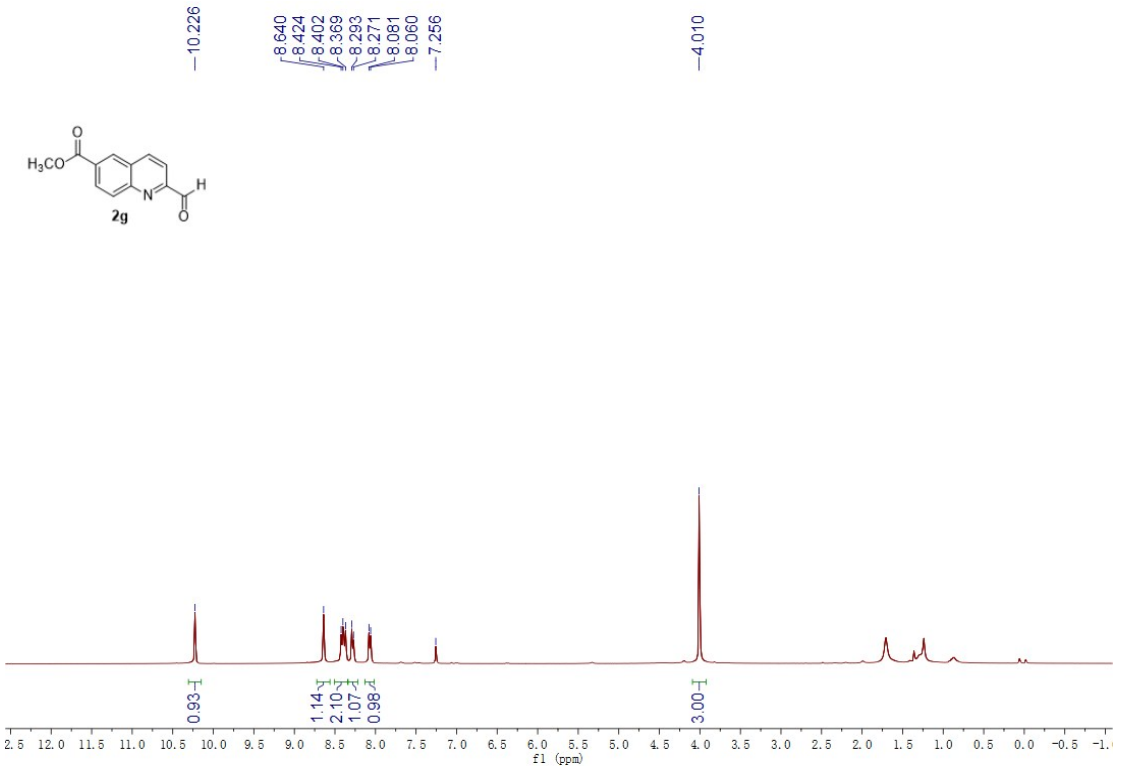

193.307
O
H
N
Br

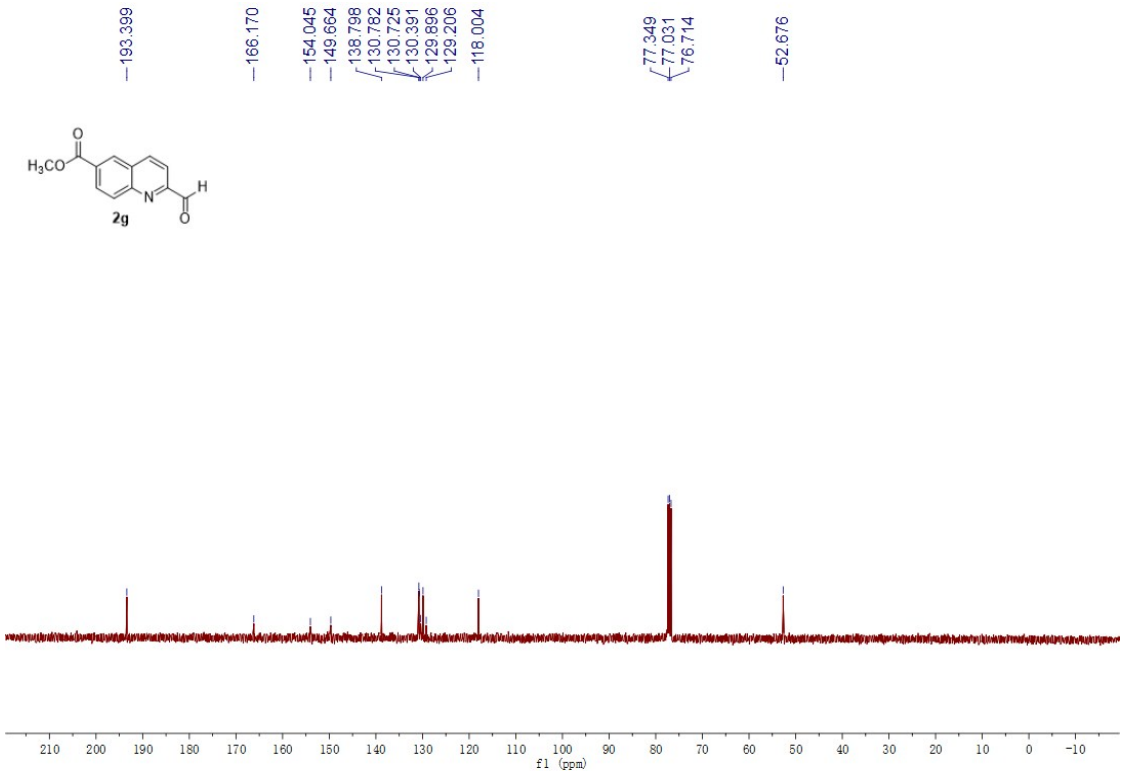
152.769
146.416
136.370
134.122
132.000
130.967
129.962
123.626
118.255

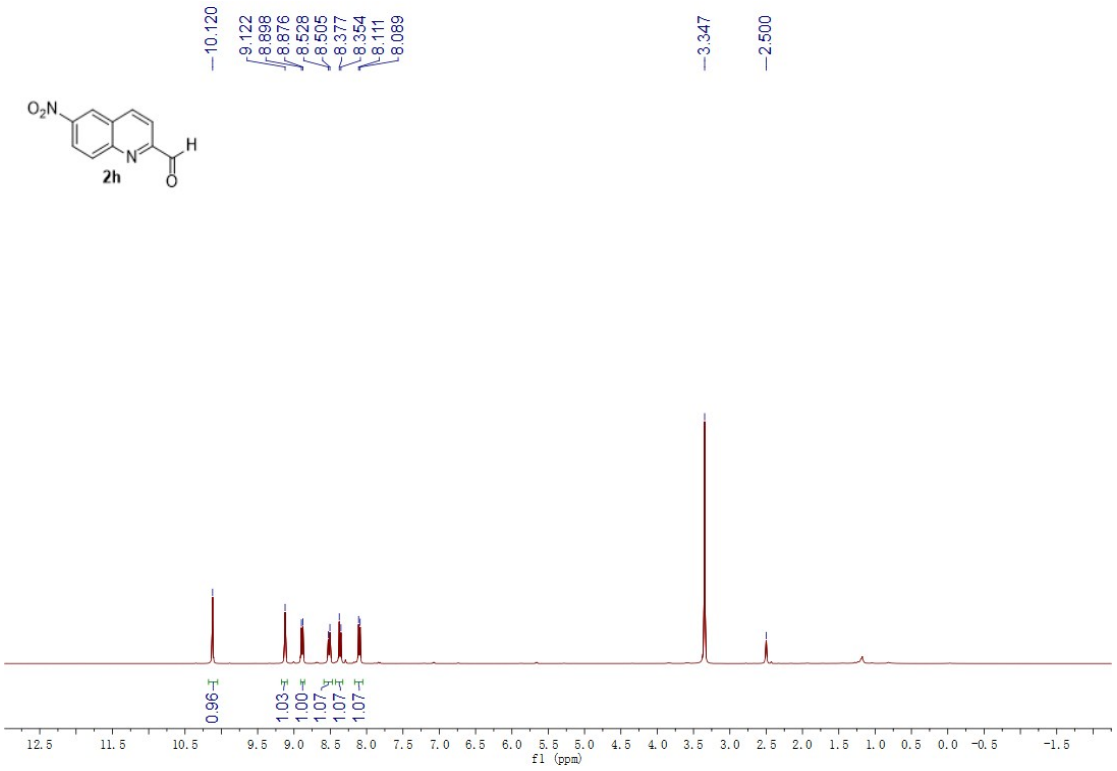
82.046
77.370
77.053
76.735

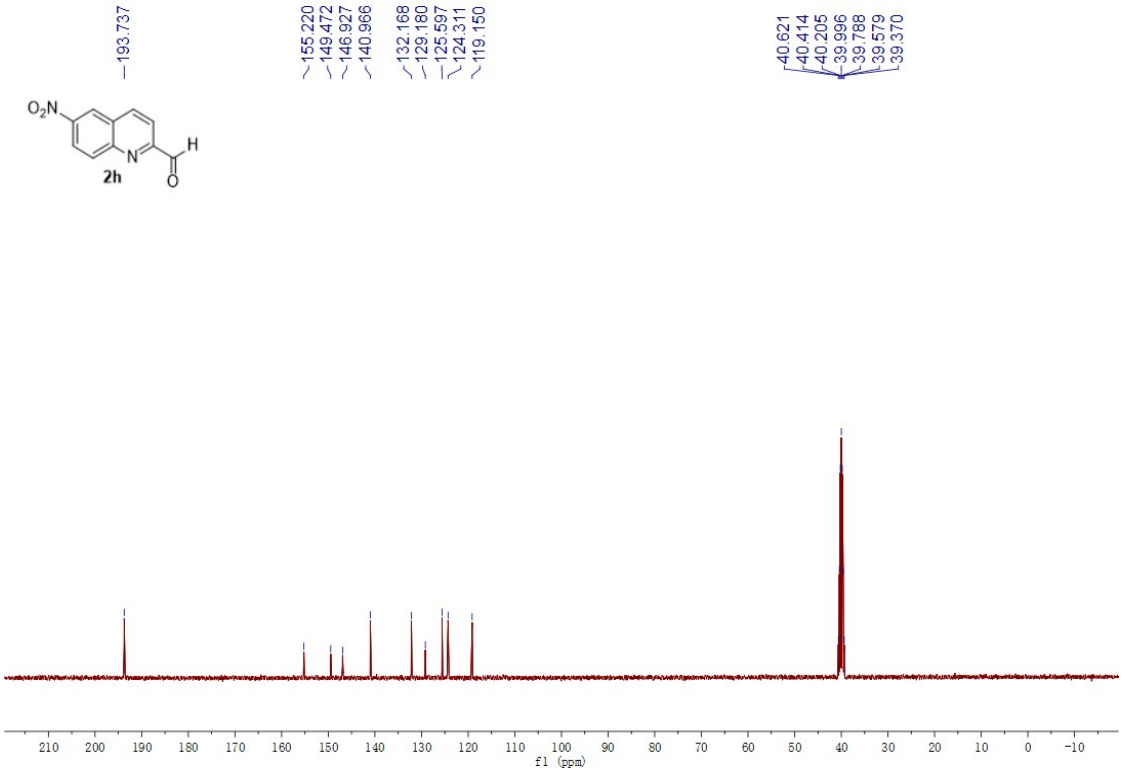

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

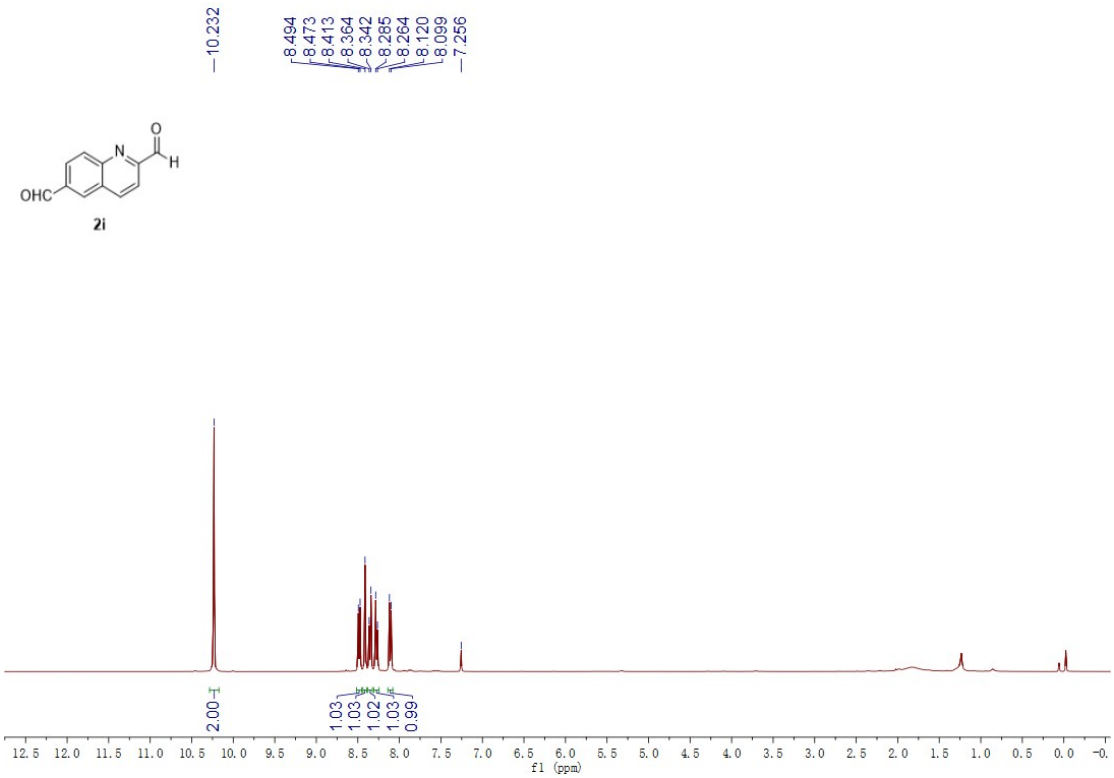

10.185
8.259
8.238
8.042
8.021
7.604
7.583
7.561
7.515
7.493
7.256
2f
1.00
2.11
1.05
1.05
1.04
f1 (ppm)
193.392
163.296
160.782
152.174
152.145
145.033
136.747
136.691
133.225
120.924
118.131
111.149
110.930
77.368
77.050
76.733
2f
f1 (ppm)

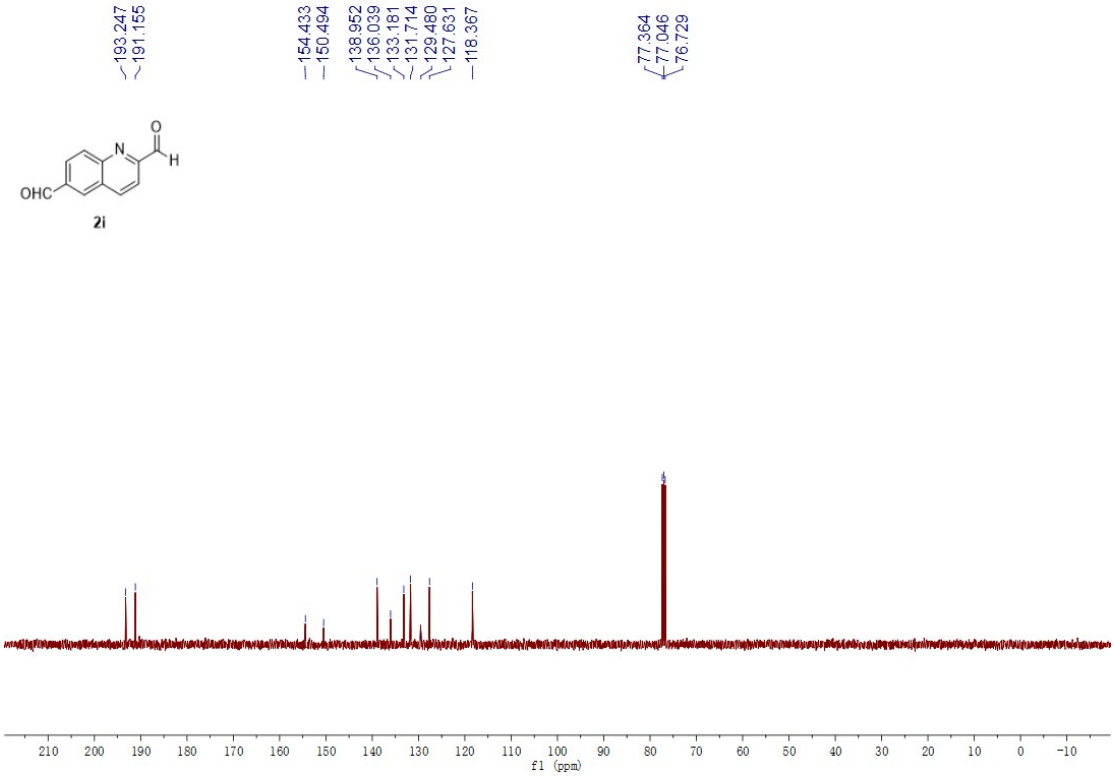

10.226
8.640
8.424
8.402
8.369
8.293
8.271
8.081
8.060
7.256
4.010
2g
0.93
1.14
2.10
1.07
0.98
3.00
f1 (ppm)

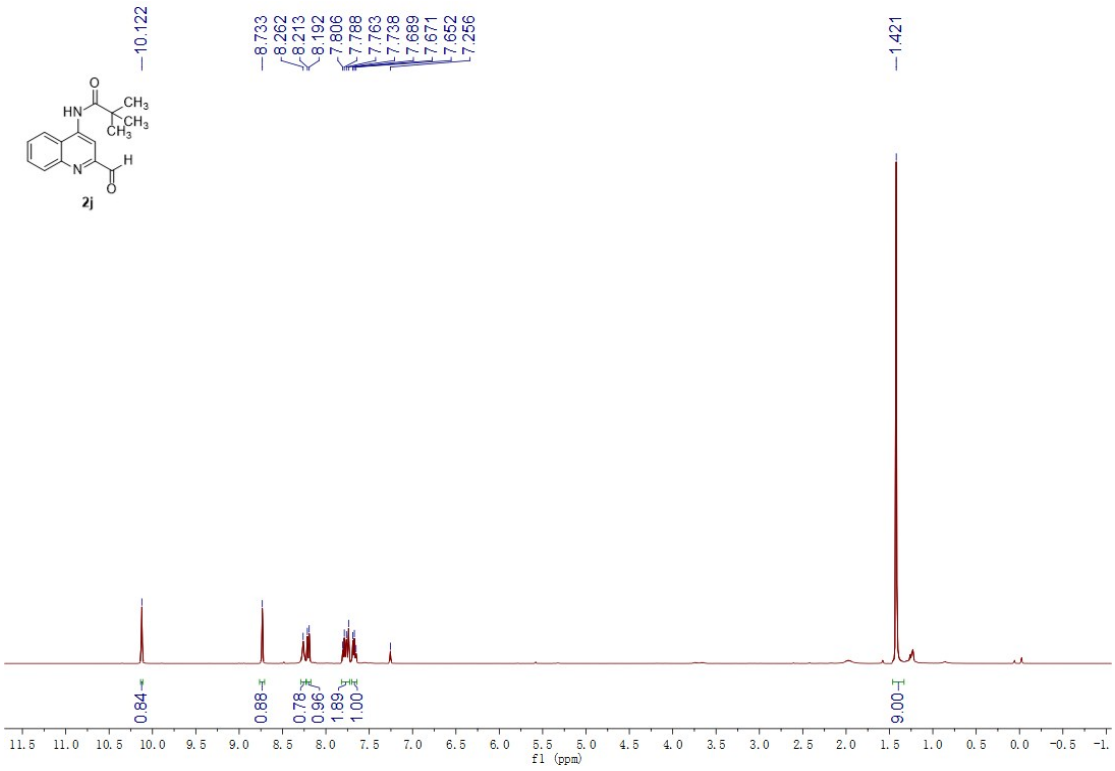

193.399
166.170
154.045
149.664
138.798
130.782
130.725
130.391
129.896
129.206
118.004
77.349
77.031
76.714
52.676
2g
f1 (ppm)

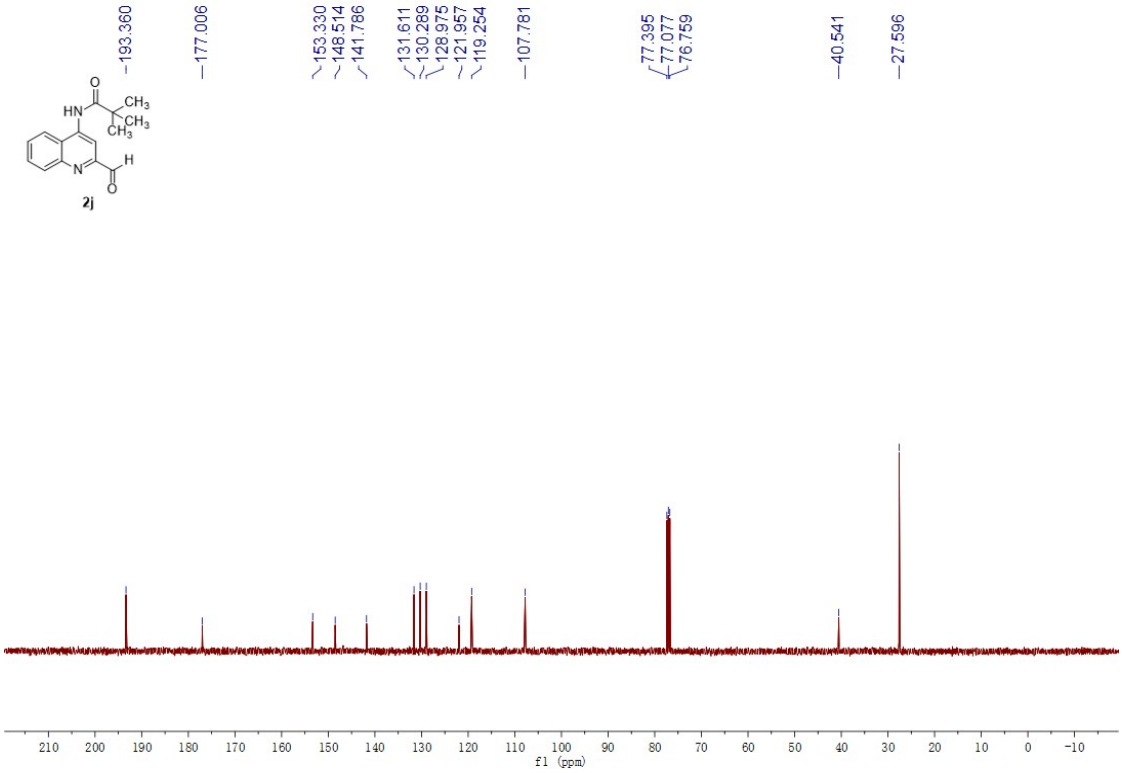

10.120
9.122
8.898
8.876
8.528
8.505
8.377
8.354
8.111
8.089
3.347
2.500
O_2N
N
H
O
2h
0.96
1.03
1.00
1.07
1.07
1.07
f1 (ppm)

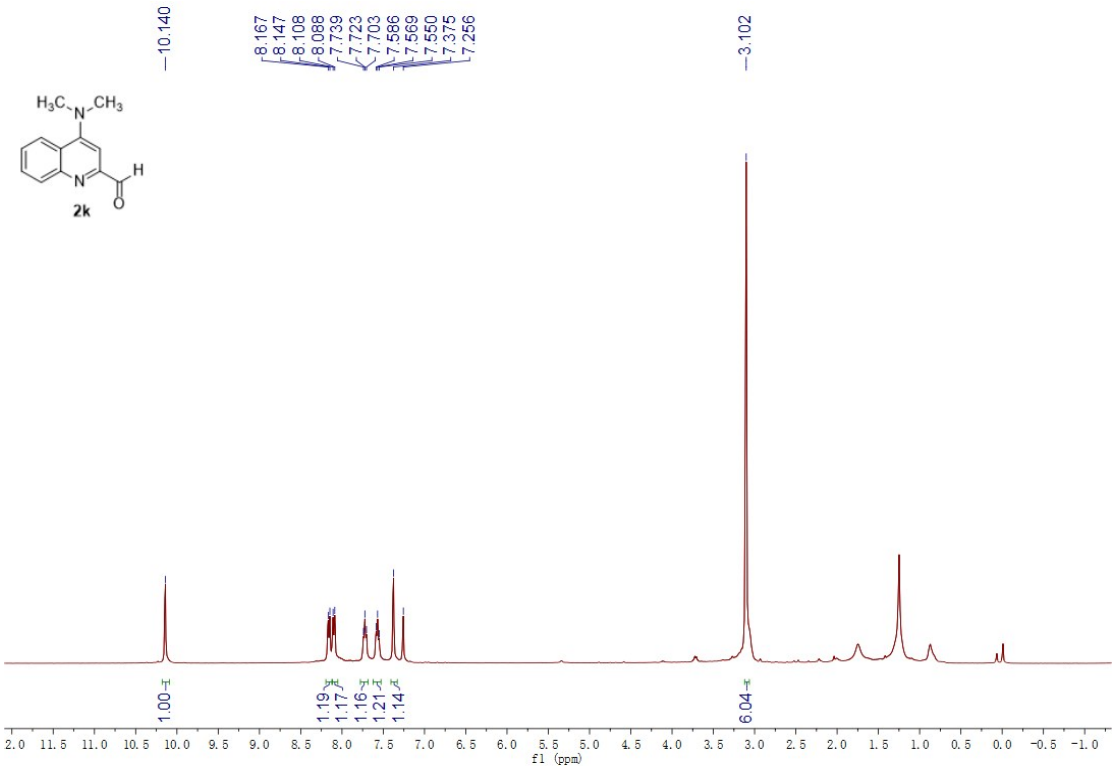

193.737
155.220
149.472
146.927
140.966
132.168
129.180
125.597
124.311
119.150
40.621
40.414
40.205
39.996
39.788
39.579
39.370
O_2N
N
H
O
2h
f1 (ppm)

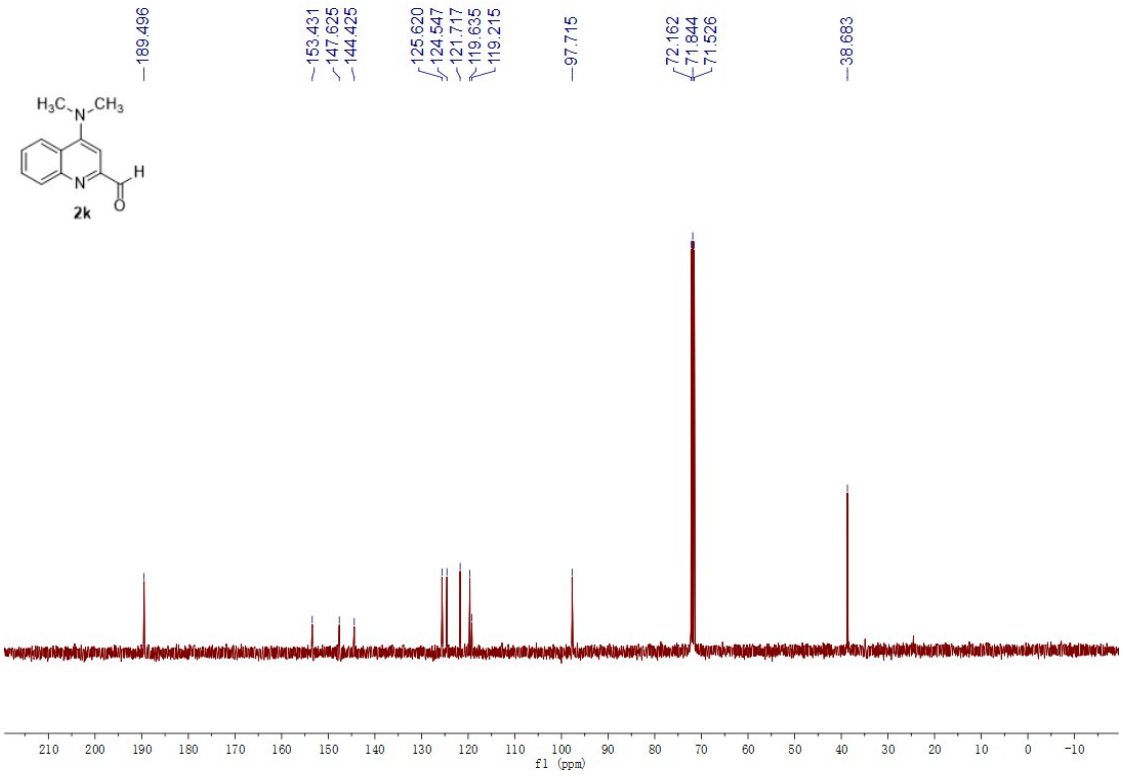

10.232
8.494
8.473
8.413
8.364
8.342
8.285
8.264
8.120
8.099
7.256
O
H
N
OHC
2i
2.00
1.03
1.03
1.02
1.03
0.99
f1 (ppm)

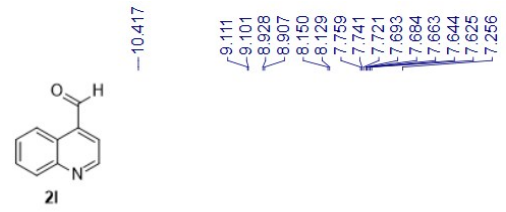

193.247
191.155
154.433
150.494
138.952
136.039
133.181
131.714
129.480
127.631
118.367
77.364
77.046
76.729
O
H
N
OHC
2i
f1 (ppm)

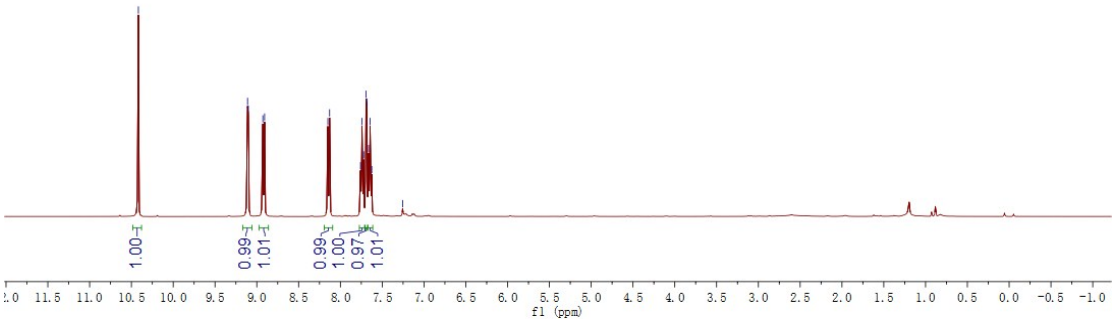

10.122
8.733
8.262
8.213
8.192
7.806
7.788
7.763
7.738
7.689
7.671
7.652
7.256
1.421
2j
0.84
0.88
0.78
0.96
1.89
1.00
9.00
f1 (ppm)

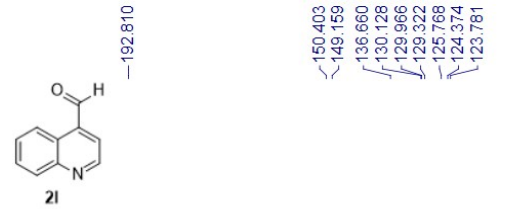

193.360
177.006
153.330
148.514
141.786
131.611
130.289
128.975
121.957
119.254
107.781
77.395
77.077
76.759
40.541
27.596
2j
f1 (ppm)

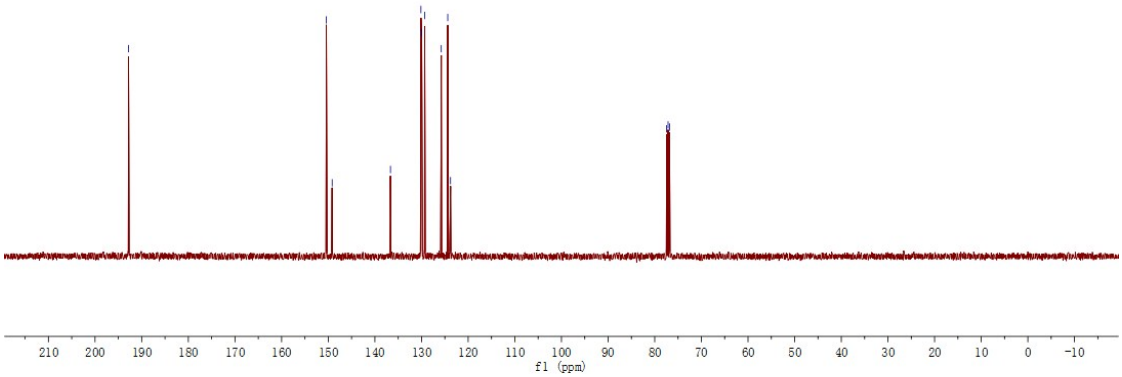

10.140
8.167
8.147
8.108
8.088
7.739
7.723
7.703
7.586
7.569
7.550
7.375
7.256
3.102
1.00
1.19
1.17
1.16
1.21
1.14
6.04
f1 (ppm)

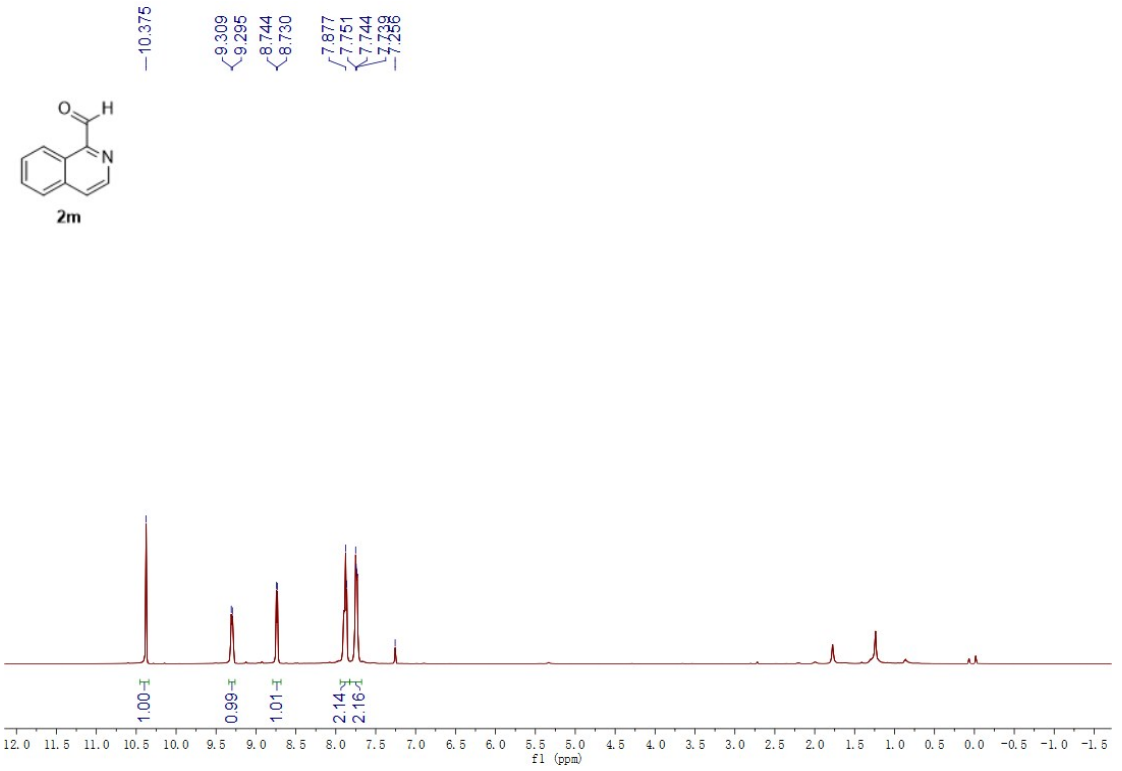

189.496
153.431
147.625
144.425
125.620
124.547
121.717
119.635
119.215
97.715
72.162
71.844
71.526
38.683
f1 (ppm)

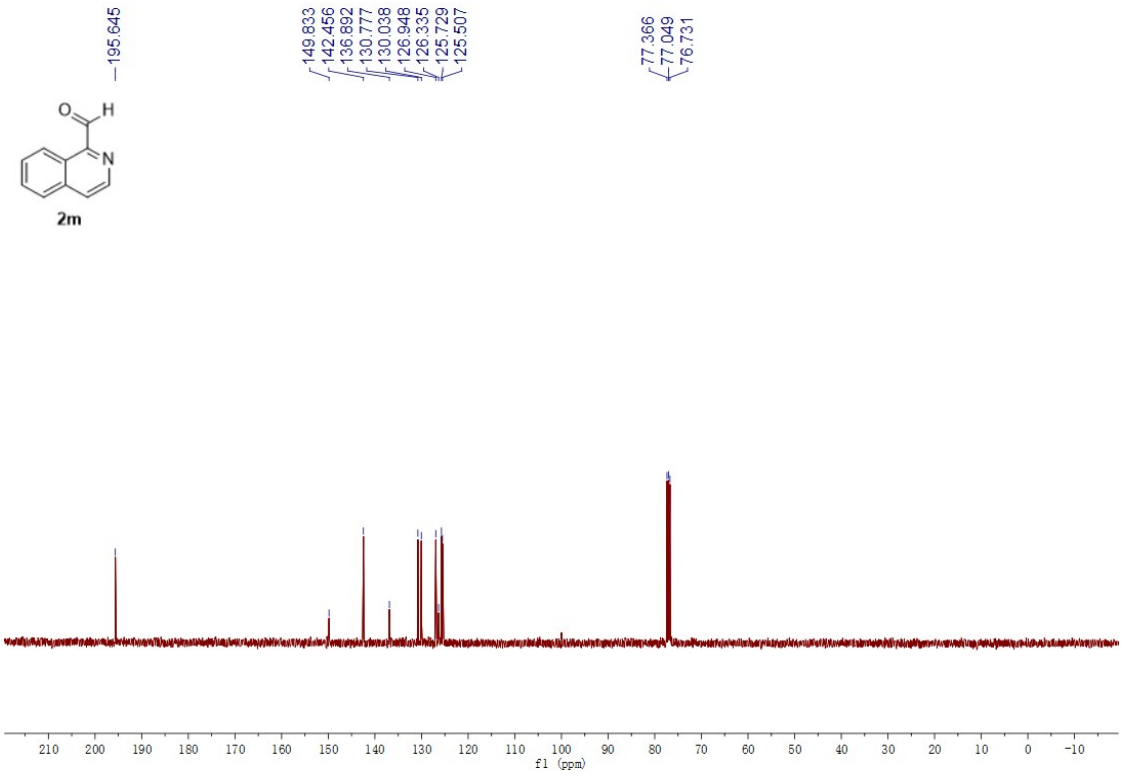

10.417
9.111
9.101
8.928
8.907
8.150
8.129
7.759
7.741
7.721
7.693
7.684
7.663
7.644
7.625
7.256
O
H
N
2l

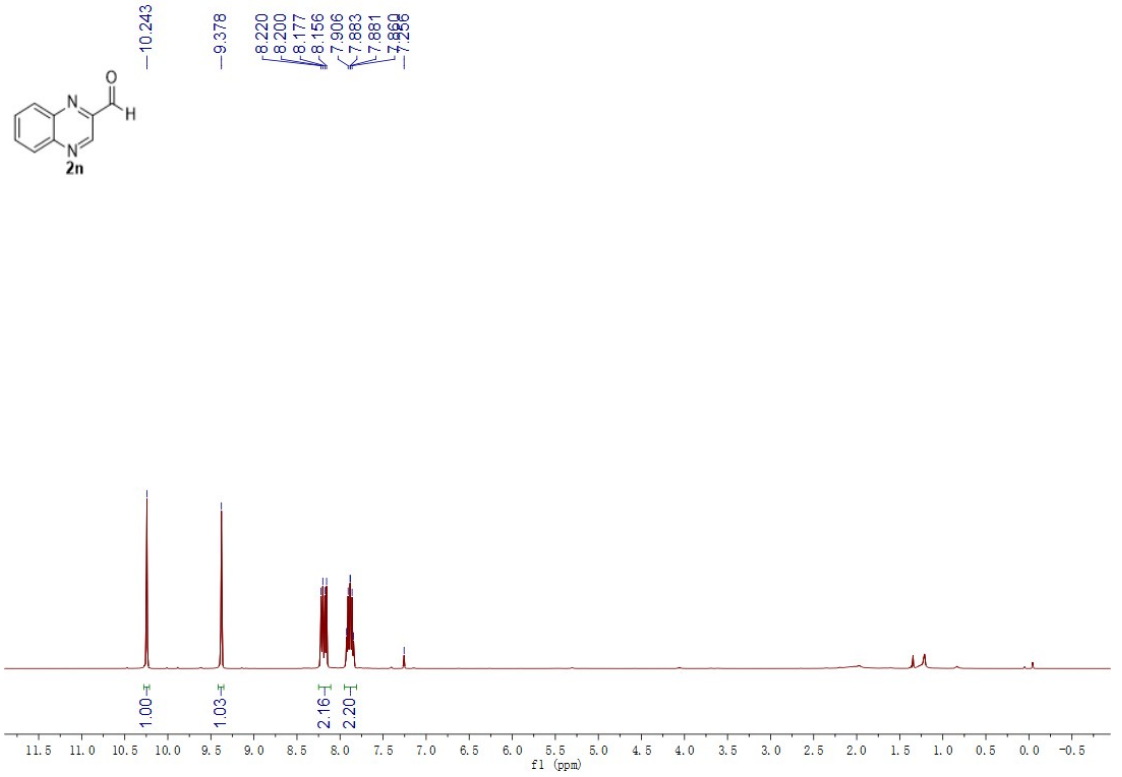

1.00
0.99
1.01
0.99
1.00
0.97
1.01
f1 (ppm)

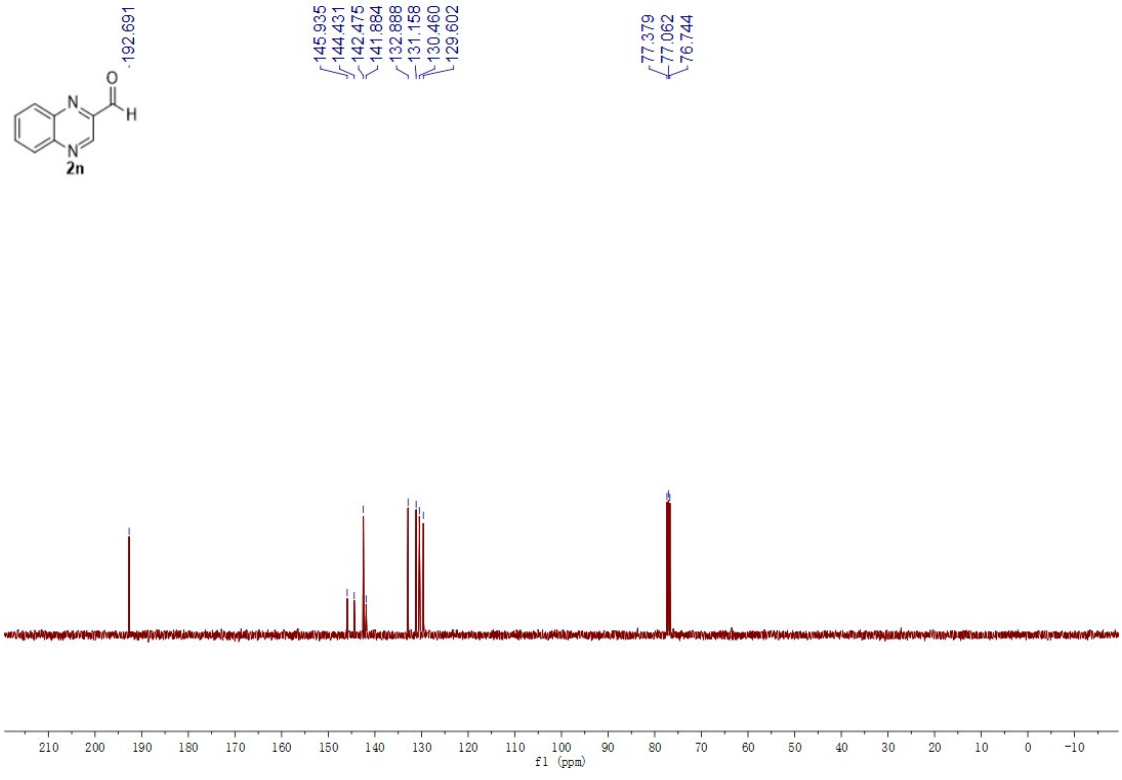

192.810
150.403
149.159
136.660
130.128
129.966
129.322
125.768
124.374
123.781
77.458
77.139
76.822
O
H
N
2l

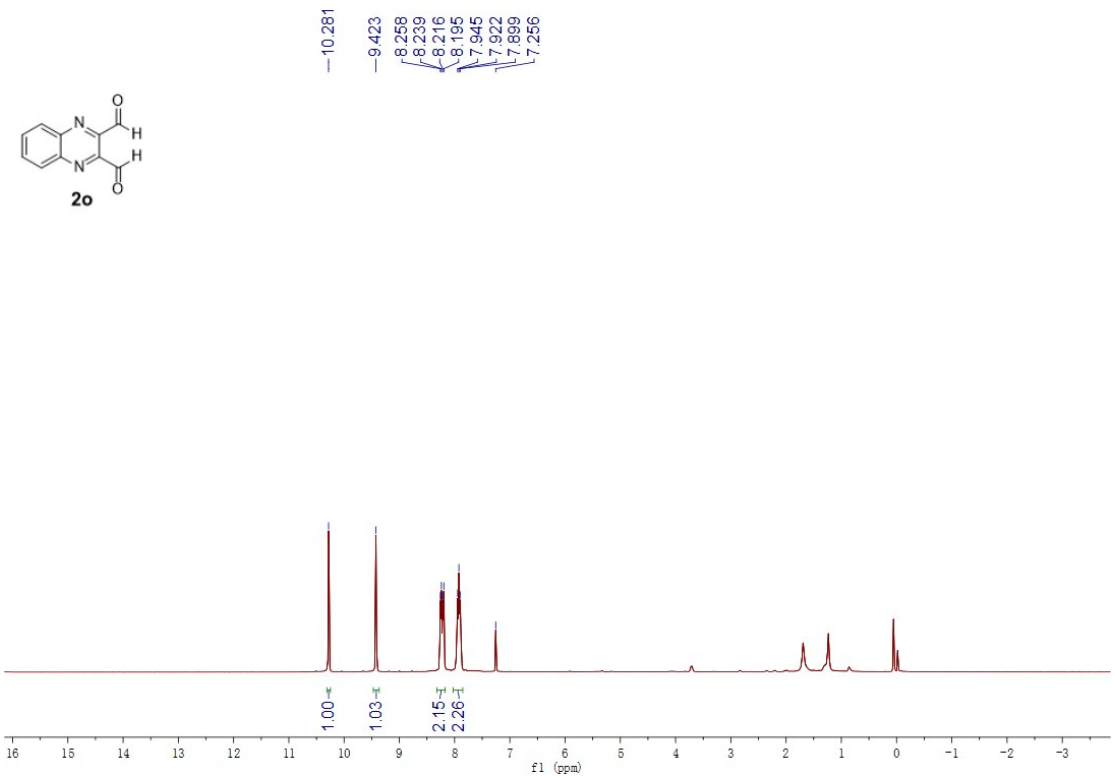

f1 (ppm)

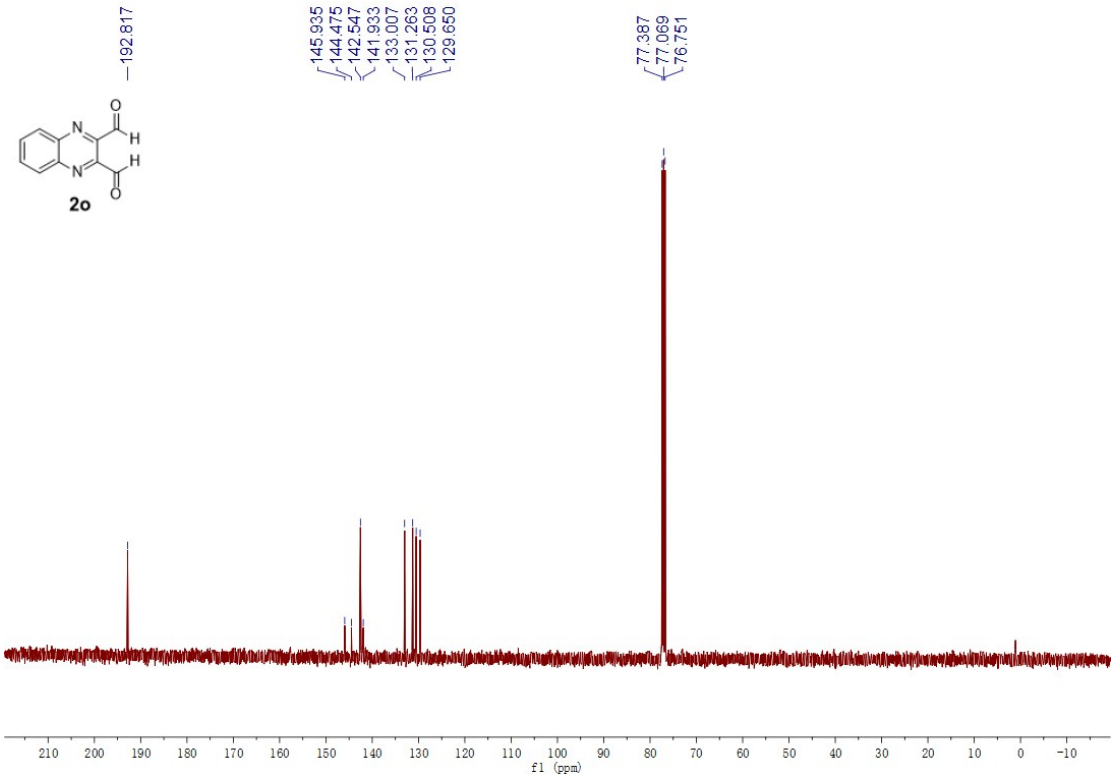

10.375
9.309
9.295
8.744
8.730
7.877
7.751
7.744
7.739
7.256
2m
1.00
0.99
1.01
2.14
2.16
f1 (ppm)

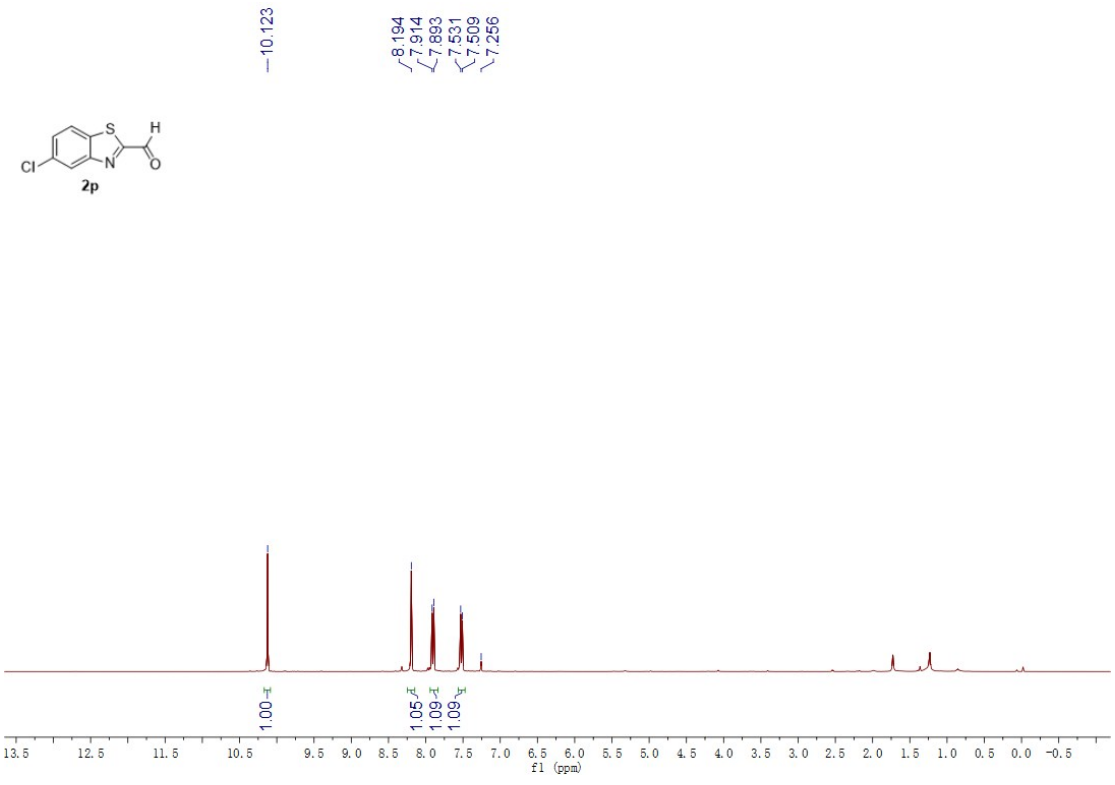

195.645
149.833
142.456
136.892
130.777
130.038
126.948
126.335
125.729
125.507
77.366
77.049
76.731
2m
f1 (ppm)

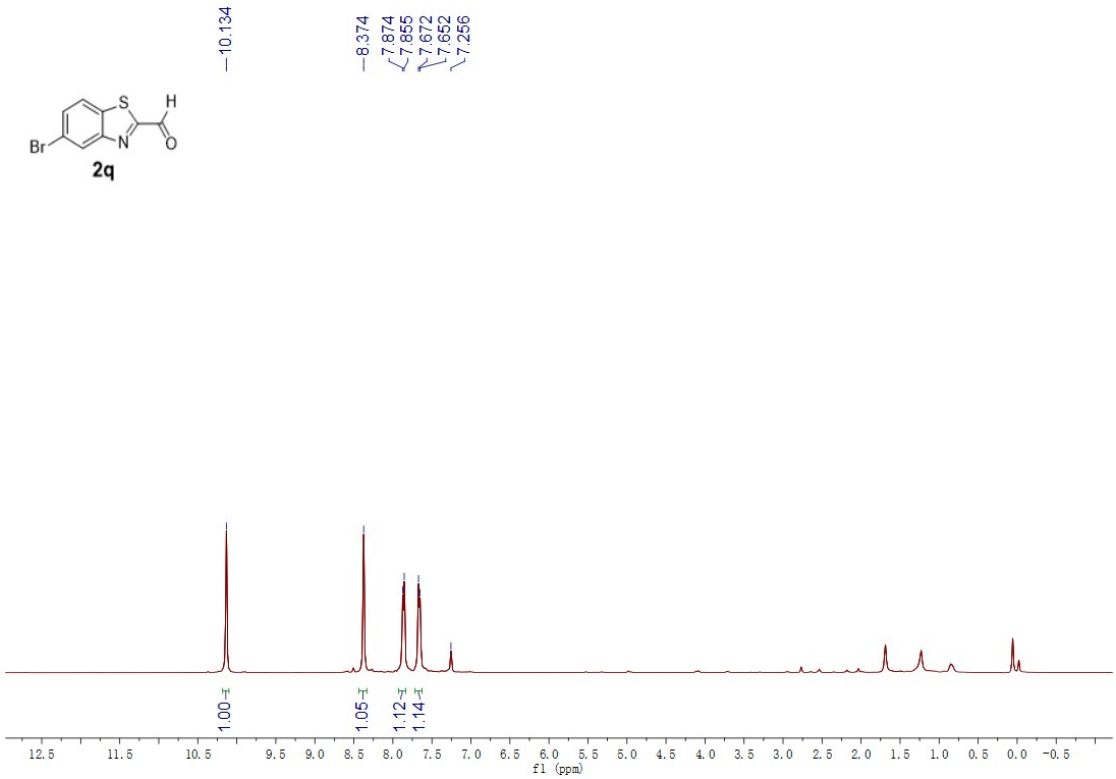

10.243
9.378
8.220
8.200
8.177
8.156
7.906
7.883
7.881
7.860
7.258
O
H
N
N
2n
1.00
1.03
2.16
2.20
f1 (ppm)

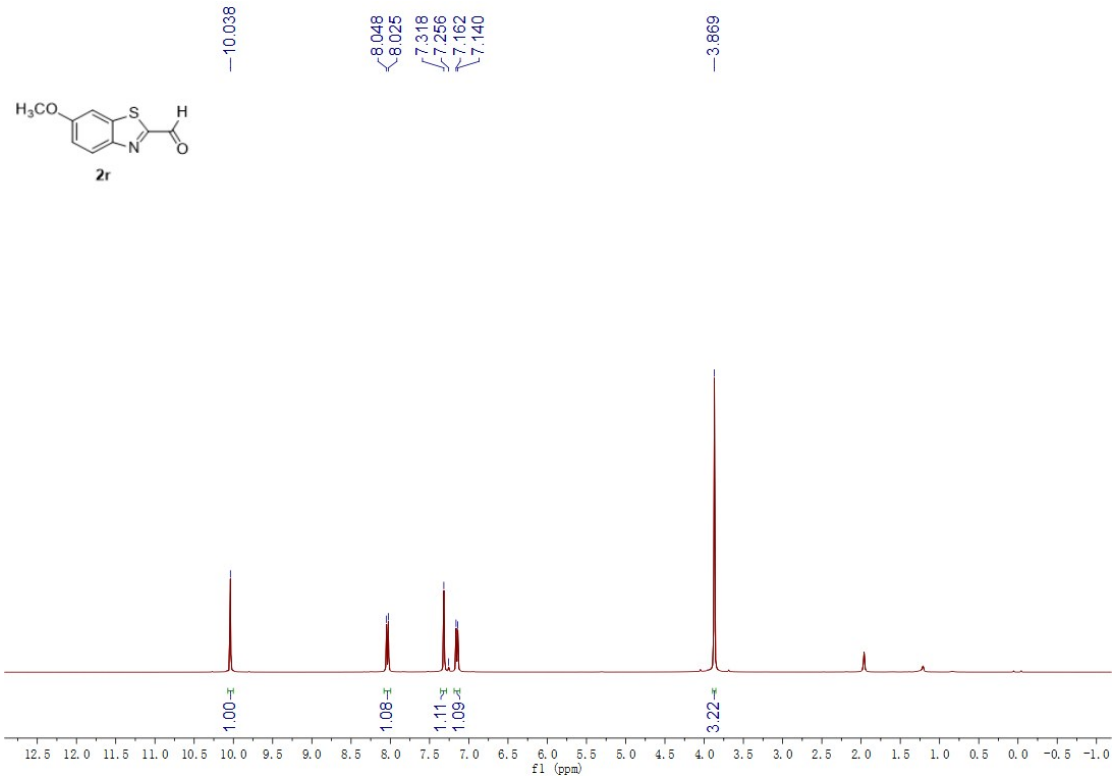

192.691
145.935
144.431
142.475
141.884
132.888
131.158
130.460
129.602
77.379
77.062
76.744
O
H
N
N
2n
f1 (ppm)

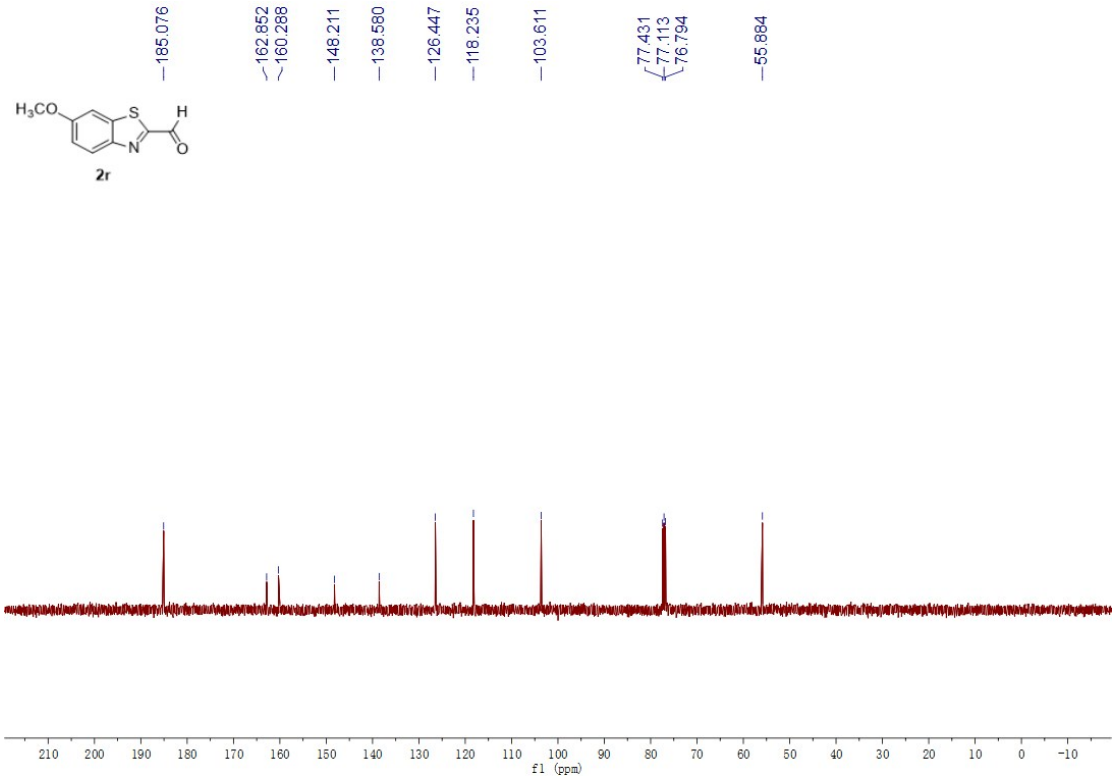

10.281
9.423
8.258
8.239
8.216
8.195
7.945
7.922
7.899
7.256
2o
1.00
1.03
2.15
2.26
f1 (ppm)

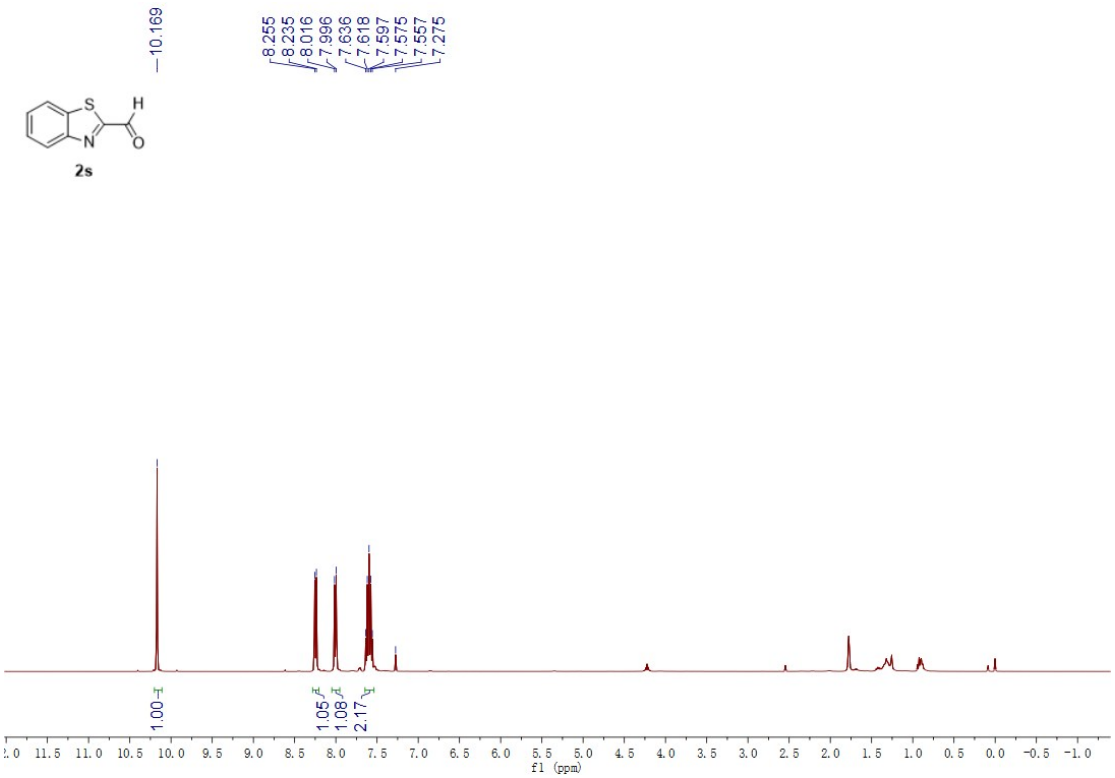

192.817
145.935
144.475
142.547
141.933
133.007
131.263
130.508
129.650
77.387
77.069
76.751
2o
f1 (ppm)

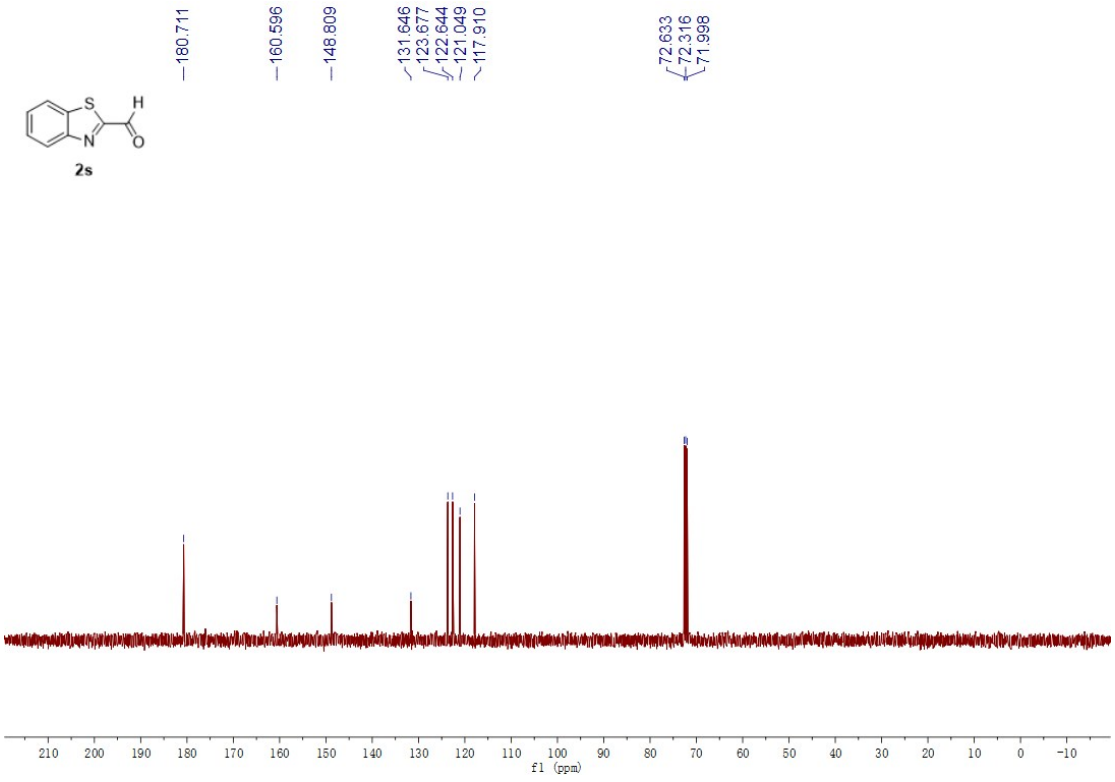

10.123
8.194
7.914
7.893
7.531
7.509
7.256
2p
1.00
1.05
1.09
1.09
f1 (ppm)
185.132
166.903
154.285
134.574
133.573
129.017
125.292
123.415
2p
f1 (ppm)

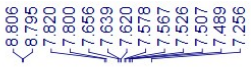

10.134
8.374
7.874
7.855
7.672
7.652
7.256
Br
S
N
H
O
2q
1.00
1.05
1.12
1.14
f1 (ppm)
185.219
166.654
154.594
135.096
131.633
128.440
123.762
121.129
77.409
77.091
76.774
Br
S
N
H
O
2q
f1 (ppm)

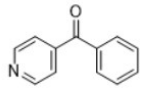

10.038
8.048
8.025
7.318
7.256
7.162
7.140
3.869
H3CO
S
N
H
O
2r
1.00
1.08
1.11
1.09
3.22
f1 (ppm)


185.076
162.852
160.288
148.211
138.580
126.447
118.235
103.611
77.431
77.113
76.794
55.884
H3CO
S
N
H
O
2r
f1 (ppm)

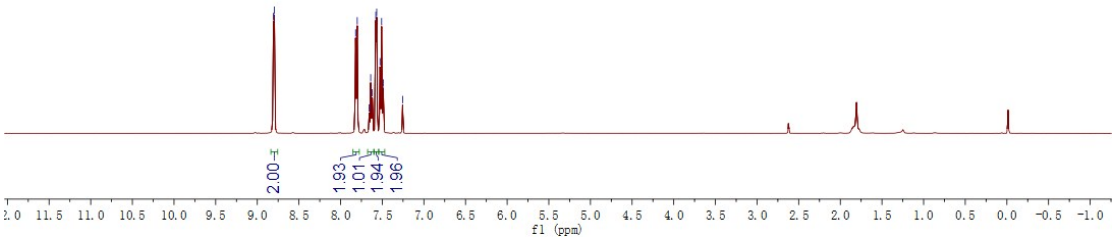

10.169
8.255
8.235
8.016
7.996
7.636
7.618
7.597
7.575
7.557
7.275
2s
1.00
1.05
1.08
2.17
f1 (ppm)


180.711
160.596
148.809
131.646
123.677
122.644
121.049
117.910
72.633
72.316
71.998
2s
f1 (ppm)

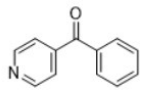

8.806
8.795
7.820
7.800
7.656
7.639
7.620
7.578
7.567
7.526
7.507
7.489
7.256



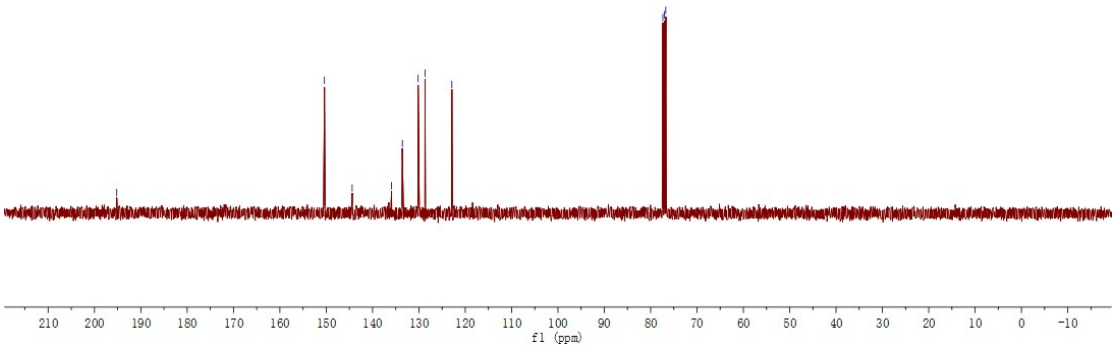
2t

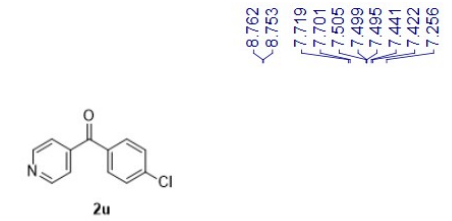

2.00
1.93
1.01
1.94
1.96
f1 (ppm)

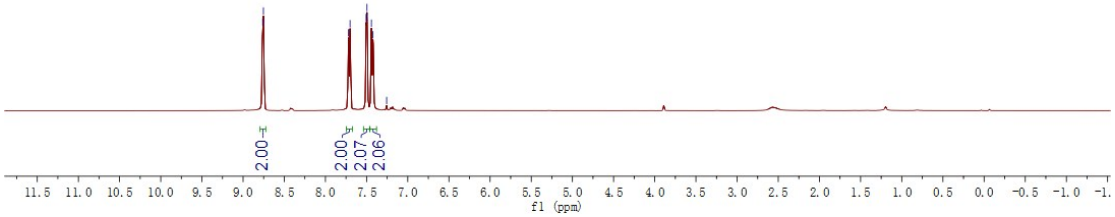

195.198
150.378
144.400
135.909
133.567
130.163
128.679
122.897
77.365
77.047
76.730

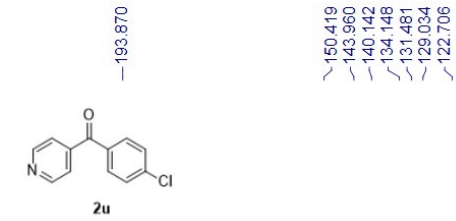


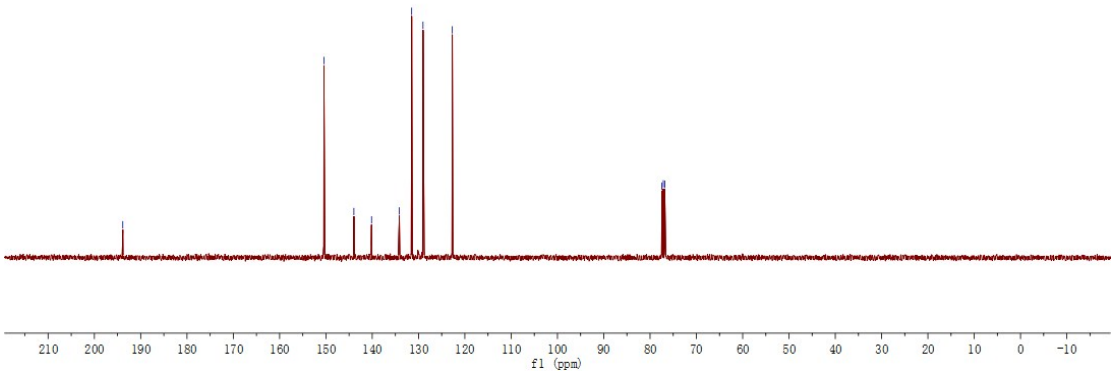
2t

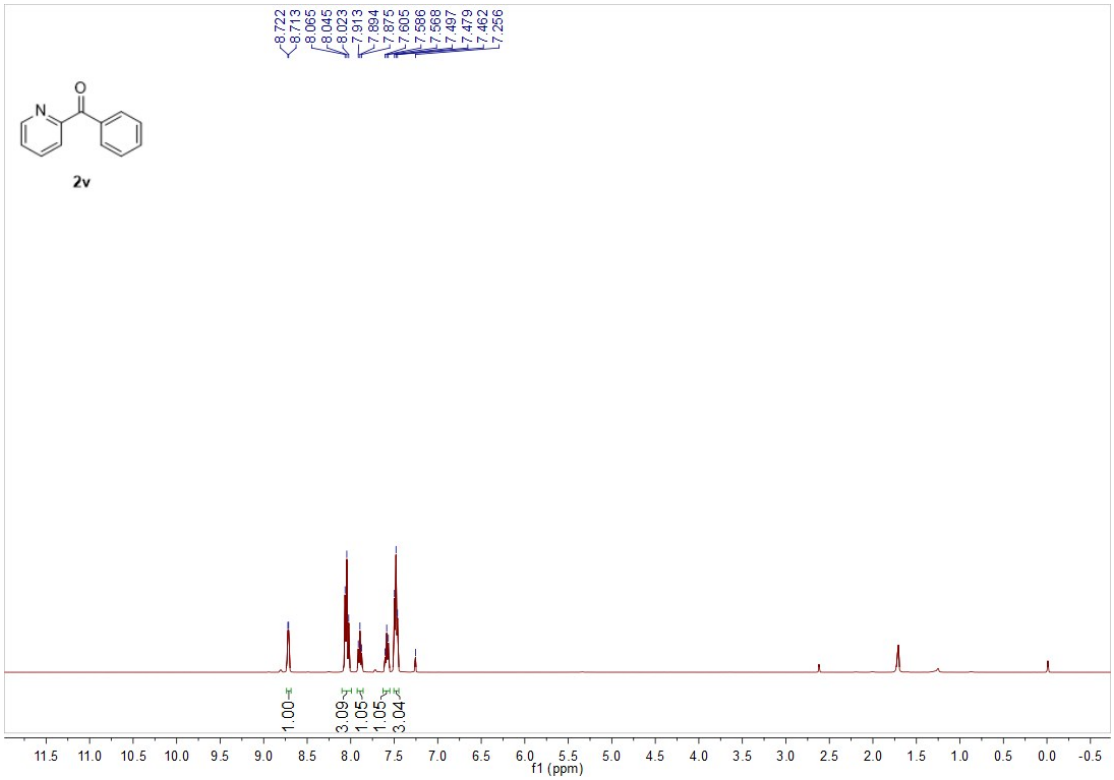

f1 (ppm)

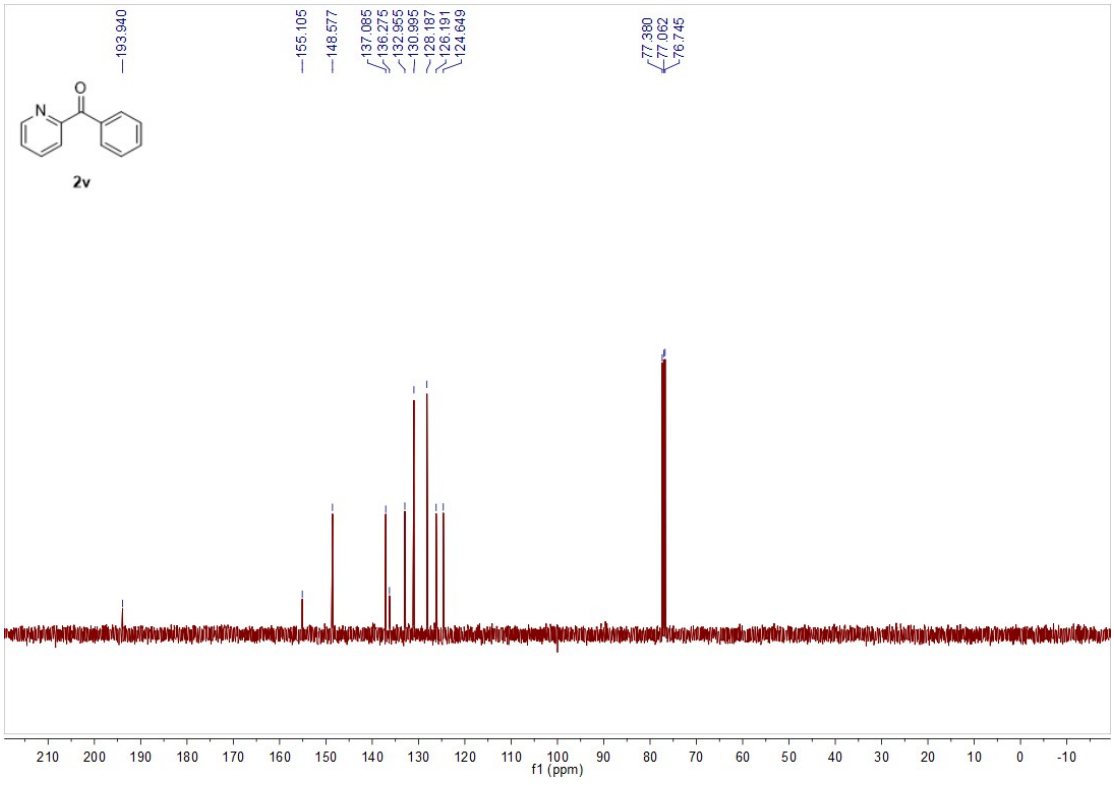

8.762
8.753
7.719
7.701
7.505
7.499
7.495
7.441
7.422
7.256
O
N
Cl
2u

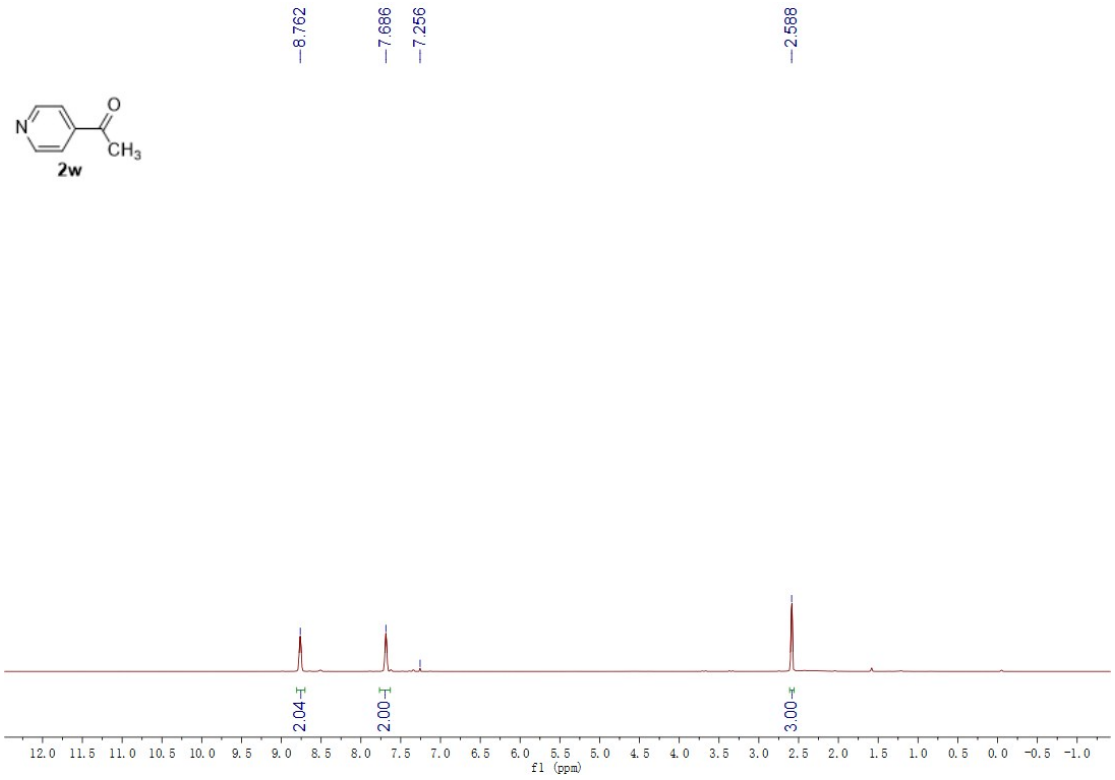

2.00
2.00
2.07
2.06
f1 (ppm)

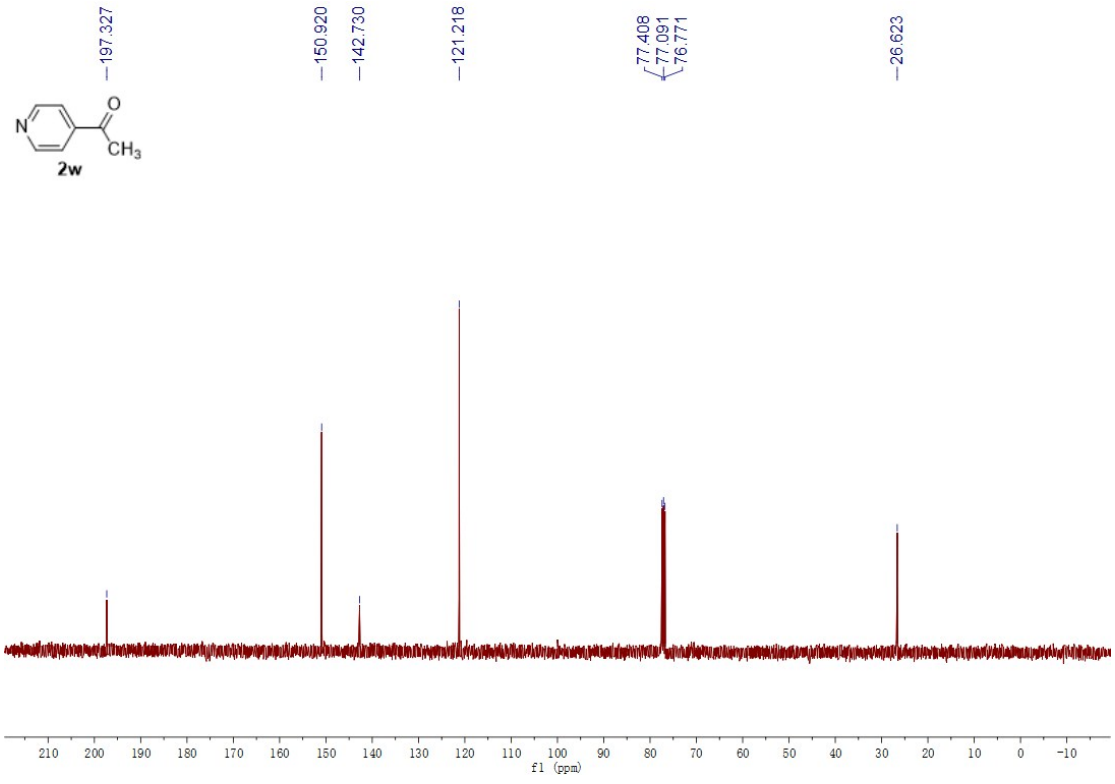

193.870
150.419
143.960
140.142
134.148
131.481
129.034
122.706
77.460
77.142
76.824
O
N
Cl
2u

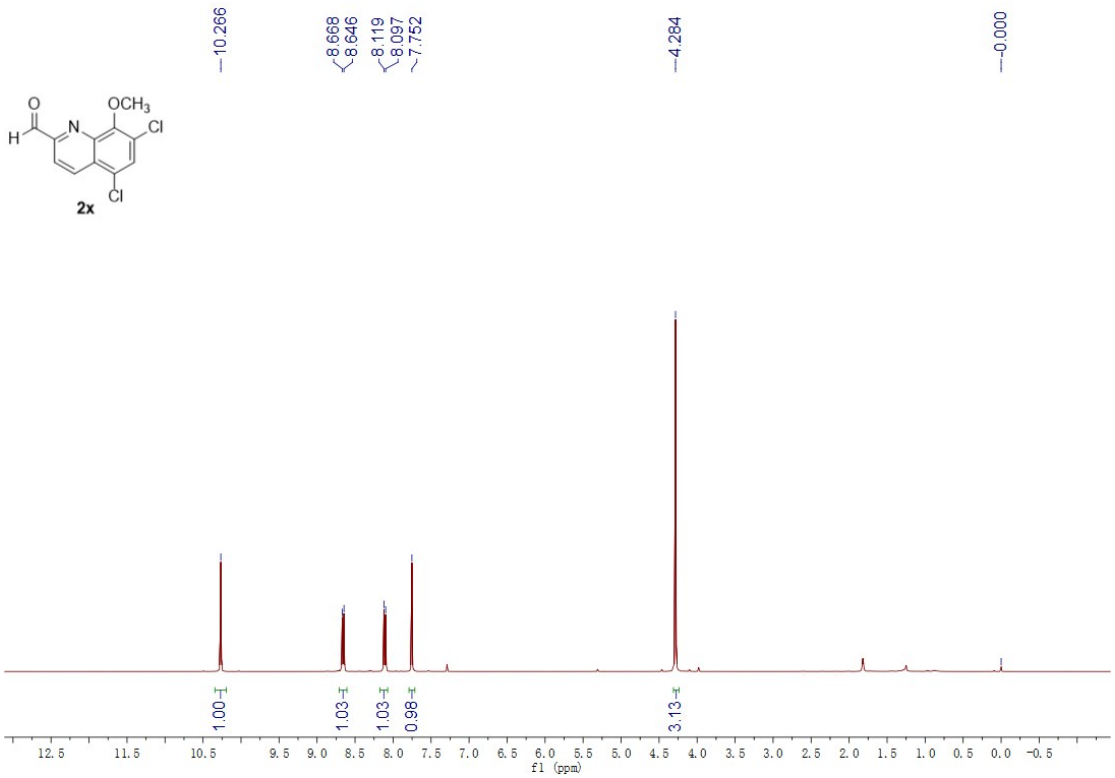

f1 (ppm)

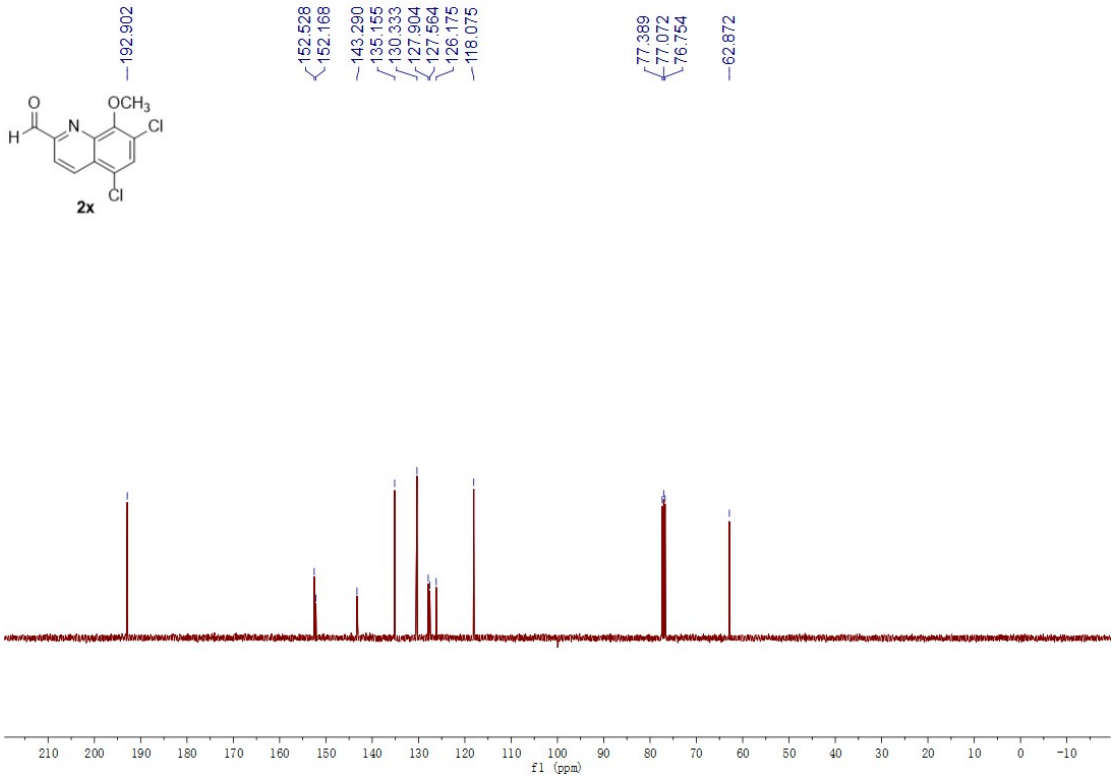

8.722
8.713
8.065
8.045
8.023
7.913
7.894
7.875
7.605
7.586
7.568
7.497
7.479
7.462
7.256
2v
1.00
3.09
1.05
1.05
3.04
f1 (ppm)

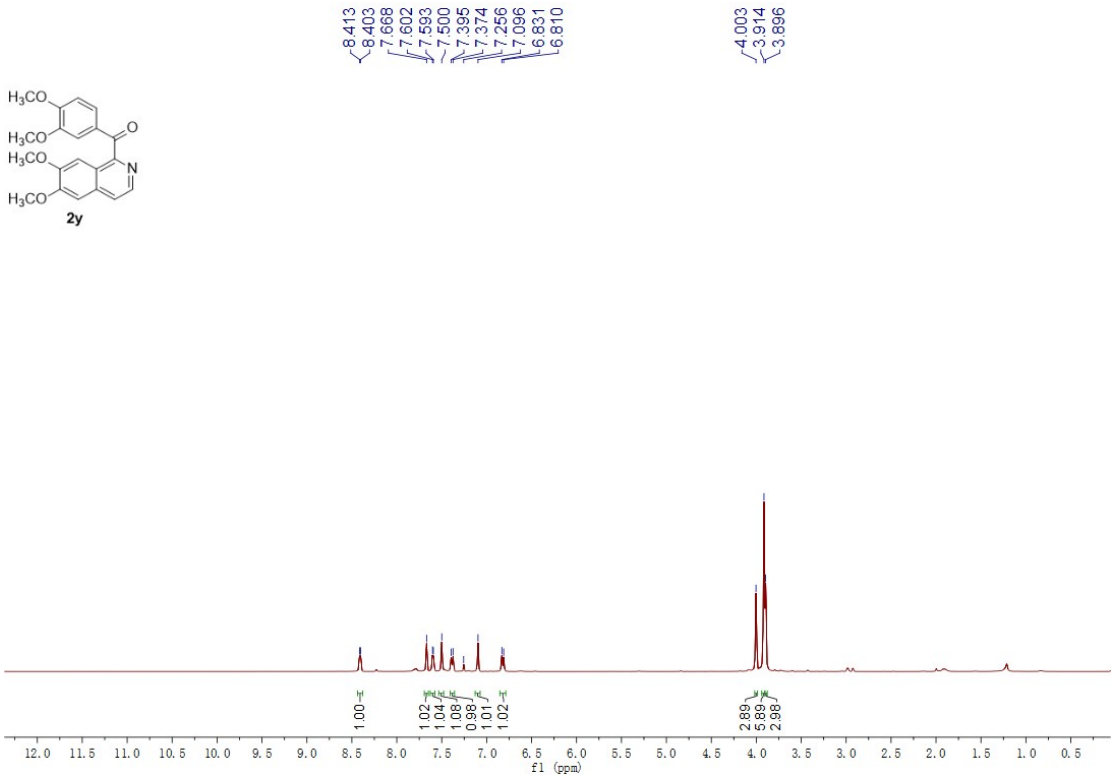

193.940
155.105
148.577
137.085
136.275
132.955
130.995
128.187
126.191
124.649
77.380
77.062
76.745
2v
f1 (ppm)

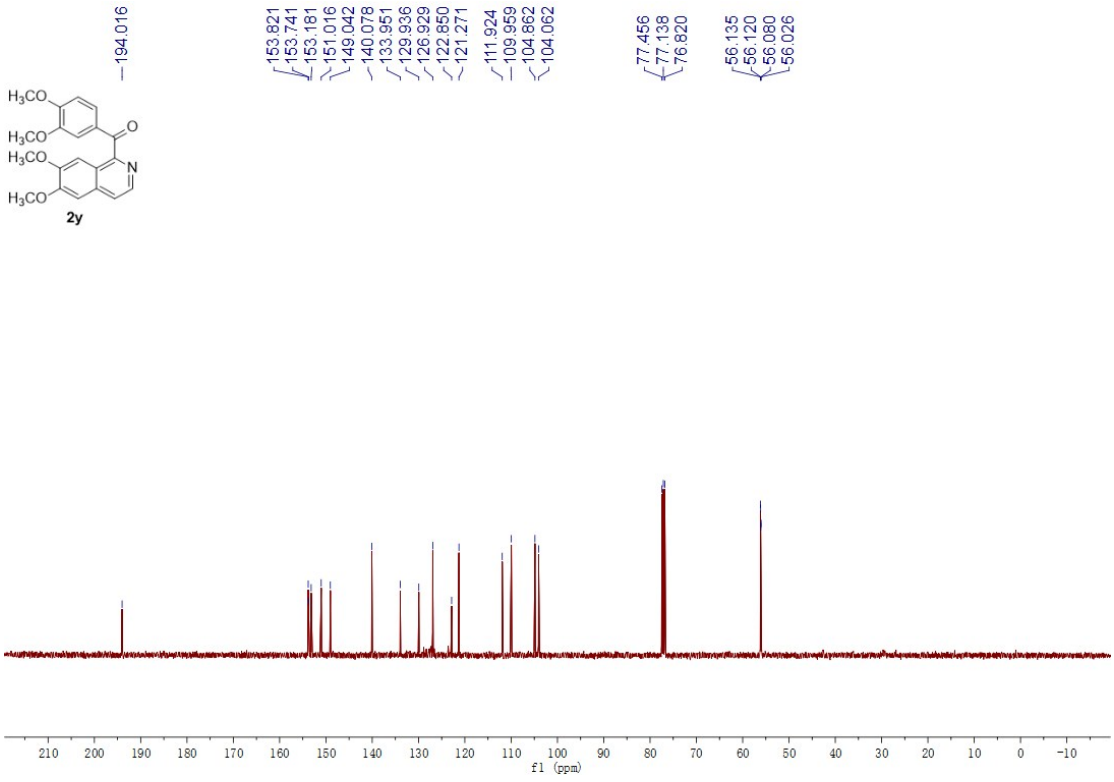

8.762
7.686
7.256
2.588
2w
2.04
2.00
3.00
f1 (ppm)


197.327
150.920
142.730
121.218
77.408
77.091
76.771
26.623
2w
f1 (ppm)


10.266
8.668
8.646
8.119
8.097
7.752
4.284
0.000
OCH3
Cl
Cl
O
H
N
2x
1.00
1.03
1.03
0.98
3.13
f1 (ppm)


192.902
152.528
152.168
143.290
135.155
130.333
127.904
127.564
126.175
118.075
77.389
77.072
76.754
62.872
OCH3
Cl
Cl
O
H
N
2x
f1 (ppm)


8.413
8.403
7.668
7.602
7.593
7.500
7.395
7.374
7.256
7.096
6.831
6.810
4.003
3.914
3.896
2y
1.00
1.02
1.04
1.08
0.98
1.01
1.02
2.89
5.89
2.98
f1 (ppm)


194.016
153.821
153.741
153.181
151.016
149.042
140.078
133.951
129.936
126.929
122.850
121.271
111.924
109.959
104.862
104.062
77.456
77.138
76.820
56.135
56.120
56.080
56.026
2y
f1 (ppm)