Efficient synthesis of fused oxazepino-isoquinoline scaffolds *via* an Ugi, followed by an intramolecular cyclization

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General Information

^{1}H and ^{13}C NMR were recorded on a Bruker 400 spectrometer. ^{1}H NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t= triplet, m = multiplet), coupling constant (Hz), relative intensity. ^{13}C NMR data are reported as follows: chemical shift in ppm (δ). HPLC-MS analyses were performed on a Shimadzu-2020 LC-MS instrument using the following conditions: Shim-pack VPODS C18 column (reverse phase, 150 x 2.0mm); 80% acetonitrile and 20% water over 6.0 min; flow rate of 0.4 mL/min; UV photodiode array detection from 200 to 300nm. The products were purified by Biotage Isolera™ Spektra Systems and Hexane/EtOAc solvent systems. All reagents and solvents were obtained from commercial sources and used without further purification.

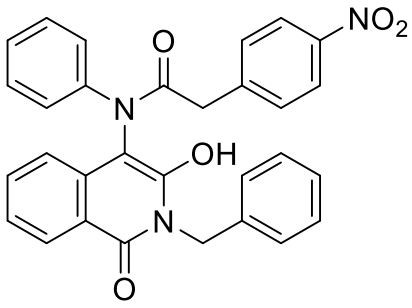
Microwave Irradiation Experiments

All microwave irradiation experiments were carried out in a Biotage® Initiator Classic microwave apparatus with continuous irradiation power from 0 to 400W with utilization of the standard absorbance level of 250W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to 50 ^{o}C with gas jet cooling.

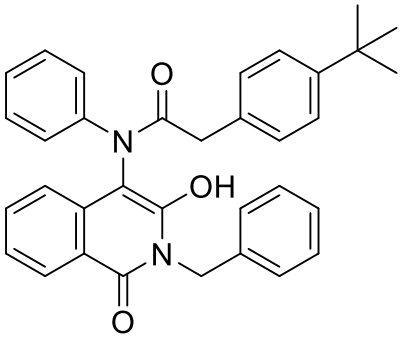
General procedures for compounds **6** {*1-7,1-7,1-5*}.

A solution of aldehyde (0.50 mmol) and amine (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 10 min in a 5 mL microwave vial. Acid (0.50 mmol) and isonitrile (0.50 mmol) were added to the vial sequentially, and the resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, as determined by the disappearance of the isonitrile by TLC, the solvent was removed under a gentle stream of nitrogen. The resulting residue was dissolved in DMF (3 mL) with the same microwave vial. TEA (1.0 mmol) was then added to the vial, which was sealed and heated under microwave irradiation at 100 °C for 10 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed sequentially with saturated Na_2CO_3 solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to a, which residue was purified by column chromatography over silica gel eluting with a gradient of ethyl acetate/hexane (0 to 60%) to afford the relative oxazepino-isoquinoline compound **6**{*1-7, 1-7，1-5*}.

***N*-(2-benzyl-3-hydroxy-1-oxo-1, 2-dihydroisoquinolin-4-yl)-2-(4-nitrophenyl)-*N*-phenylacetamide** (Compound **6**{*1,1,1*}), white solid, yield 65%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.3 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.63 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.31 (m, 5H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 3.8 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 5.91 (s, 1H), 5.25 – 5.10 (m, 2H), 3.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.84, 168.98, 163.55, 147.02, 141.89, 136.61, 136.27, 134.00, 130.09, 129.51, 129.13, 128.74, 128.59, 128.41, 127.42, 125.44, 125.33, 123.54, 43.96, 40.63. HRMS (ESI) m/z calcd for $C_{30}H_{23}N_3O_5^+$ $(M+H)^+$ 506.17105, found 506.17072.

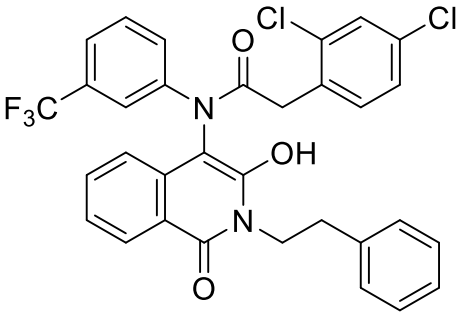


***N*-(2-benzyl-3-hydroxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(4-(tert-butyl)phenyl)-*N*-phenylacetamide** (Compound **6** {*1,2,1*}), white solid, yield 62%, ^{1}H NMR (400



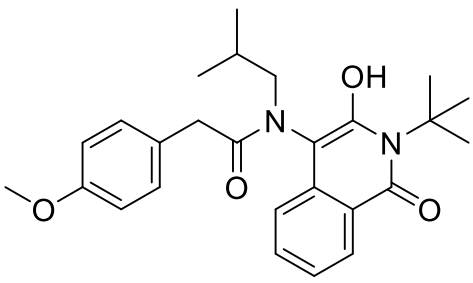
MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 6H), 7.27 – 7.20 (m, 6H), 6.94 (d, *J* = 8.2 Hz, 2H), 5.96 (s, 1H), 5.16 (q, *J* = 14.1 Hz, 2H), 3.59 – 3.45 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 169.14, 163.69, 149.62, 136.74, 133.88, 131.41, 129.72, 129.31, 128.77, 128.66, 128.48, 127.30, 125.67, 125.30, 43.86, 40.18, 34.41, 31.36. HRMS (ESI) m/z calcd for $C_{34}H_{33}N_2O_3^+$ $(M+H)^+$ 517.24857, found 517.24841.

2-(2,4-dichlorophenyl)-*N*-(3-hydroxy-1-oxo-2-phenethyl-1,2-dihydroisoquinolin-4-yl)-*N*-(3-(trifluoromethyl)phenyl)acetamide (Compound **6**{*6,3,2*}), white solid,



yield 70%, ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.77 – 7.64 (m, 4H), 7.59 (dd, *J* = 17.3, 7.9 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.24 (m, 5H), 7.23 – 7.12 (m, 3H), 5.70 (s, 1H), 4.30 – 4.08 (m, 2H), 3.59 (dd, *J* = 47.4, 16.3 Hz, 2H), 2.85 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.56, 168.77, 163.31, 142.19, 138.52, 135.89, 134.60, 134.01, 133.88, 132.85, 132.53, 132.24, 131.10, 130.78, 129.43, 129.18, 128.97, 128.82, 128.47, 127.26, 126.48, 125.92, 125.74, 125.25, 124.58, 121.87, 42.20, 38.58, 34.01. HRMS (ESI) m/z calcd for $C_{32}H_{24}Cl_2F_3N_2O_3^+$ $(M+H)^+$ 611.11106, found 611.11066.

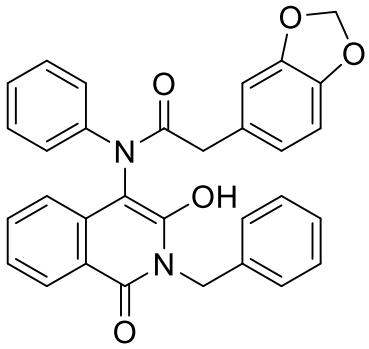
***N*-(2-(tert-butyl)-3-hydroxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-*N*-isobutyl-2-(4-methoxyphenyl)acetamide** (Compound **6**{*7,4,3*}), white solid, yield 58%, ^1H NMR



(400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.04 (m, 3H), 6.83 (d, *J* = 8.5 Hz,

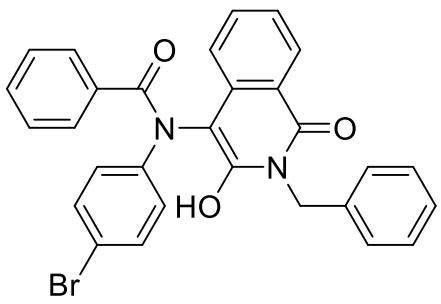
2H), 5.03 (s, 1H), 3.78 (s, 3H), 3.71 (d, *J* = 2.9 Hz, 2H), 3.43 (dd, *J* = 15.0, 7.1 Hz, 1H), 3.33 (dd, *J* = 15.0, 7.0 Hz, 1H), 1.95 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.67 (s, 9H), 1.06 (t, *J* = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.40, 170.13, 165.84, 158.55, 136.05, 132.79, 129.92, 128.61, 128.23, 127.80, 126.41, 123.89, 114.08, 61.05, 55.26, 39.82, 31.58, 29.42, 14.19, 14.10. HRMS (ESI) m/z calcd for $C_{26}H_{33}N_2O_4^+$ $(M+H)^+$ 437.24348, found 437.24312.

2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2-benzyl-3-hydroxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-*N*-phenylacetamide (Compound **6**{*1,5,1*}), white solid, yield 63%, ^{1}H NMR



(400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 23.3, 4.1 Hz, 7H), 7.23 (dd, *J* = 6.4, 2.7 Hz, 3H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 1.1 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 5.91 (s, 3H), 5.16 (q, *J* = 14.1 Hz, 2H), 3.50 – 3.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.28, 169.10, 163.67, 147.62, 146.49, 136.73, 133.92, 129.77, 129.34, 128.77, 128.53, 128.40, 127.99, 127.33, 125.62, 125.33, 122.24, 109.65, 108.11, 100.92, 43.87, 40.36. HRMS (ESI) m/z calcd for $C_{31}H_{25}N_2O_5^+$ $(M+H)^+$ 505.17580, found 505.17568.

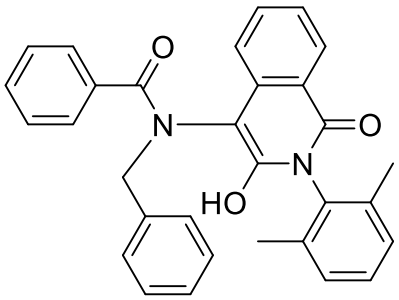
***N*-(2-benzyl-3-hydroxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-*N*-(4-bromophenyl)benzamide** (Compound **6**{*3,6,1*}), white solid, yield 72 %, ^{1}H NMR (400 MHz, $CDCl_3$)



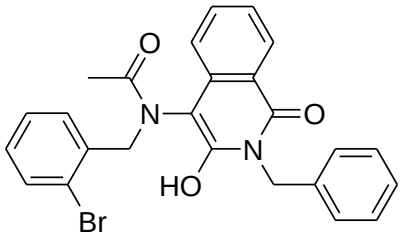
δ8.27 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 4.0 Hz, 2H), 7.52 (dt, *J* = 8.3, 4.1 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 4H), 7.32 – 7.26 (m, 4H), 7.22 (dd, *J* = 14.0, 6.6 Hz, 4H), 6.98 (s, 2H), 6.09 (s, 1H), 5.21 (dd, *J* = 35.3, 14.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.15, 168.91, 163.62, 136.65,

165.48, 134.24, 133.93, 132.54, 130.67, 129.67, 129.29, 128.92, 128.75, 128.47, 128.10, 127.45, 125.37, 121.14, 43.90. HRMS (ESI) m/z calcd for $C_{29}H_{22}BrN_2O_3^+$ $(M+H)^+$ 525.08083, found 525.08051.

***N*-benzyl-*N*-(2-(2,6-dimethylphenyl)-3-hydroxy-1-oxo-1,2-dihydroisoquinolin-4-yl)benzamide** (Compound **6**{*4,6,5*}), white solid, yield 57%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 3H), 7.46 (dt, *J* = 13.8, 7.5 Hz, 7H), 7.37 – 7.31 (m, 2H), 7.24 (dd, *J* = 8.7, 6.1 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 2H), 5.19 (s, 1H), 4.94 (dd, *J* = 57.1, 15.1 Hz, 2H), 2.21 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.13, 169.22, 163.40, 137.40, 136.69, 135.75, 134.95, 134.06, 133.69, 130.31, 129.64, 129.19, 128.97, 128.82, 128.66, 128.42, 128.22, 128.12, 127.00, 125.21, 124.04, 58.06, 17.96, 17.93. HRMS (ESI) m/z calcd for $C_{31}H_{27}N_2O_3^+$ $(M+H)^+$ 475.20162, found 475.20193.



***N*-(2-benzyl-3-hydroxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-*N*-(2-bromobenzyl)acetamide** (Compound **6**{*5,7,1*}), white solid, yield 76%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 14.7, 7.6 Hz, 4H), 7.37 – 7.32 (m, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.19 (m, 3H), 7.10 (s, 1H), 5.63 (s, 1H), 5.16 (q, *J* = 14.0 Hz, 2H), 4.84 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.90, 169.53, 163.77, 136.78, 136.47, 134.31, 133.75, 133.28, 131.21, 130.08, 129.10, 128.73, 128.45, 128.06, 127.92, 127.46, 125.16, 124.85, 124.34, 43.85, 21.85. HRMS (ESI) m/z calcd for $C_{25}H_{22}BrN_2O_3^+$ $(M+H)^+$ 477.08083, found 477.08078.

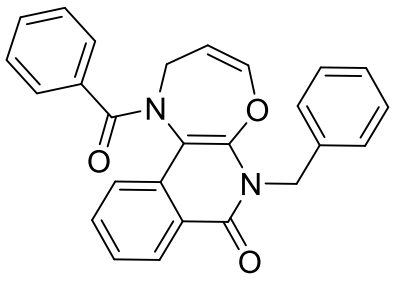


General procedures for compounds **9**{*6-12, 1-5*}.

A solution of aldehyde (0.50 mmol) and amine (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 10 min in a 5 mL microwave vial. Acid (0.50 mmol) and isonitrile (0.50 mmol) were added to the vial sequentially, and the resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, as determined by the disappearance of the isonitrile by TLC, the solvent was removed under a gentle stream of nitrogen. The resulting residue was dissolved in DMF (3 mL) with the same microwave vial. TEA (1.0 mmol) was then added to the vial, which was sealed and heated under microwave irradiation at 100 °C for 10 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed sequentially with saturated Na_2CO_3 solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to a, which residue was purified by column chromatography over silica gel eluting with a gradient of ethyl acetate/hexane (0 to 60%) to afford the relative oxazepino-isoquinoline compound **9**{*6-12,1-5*}.

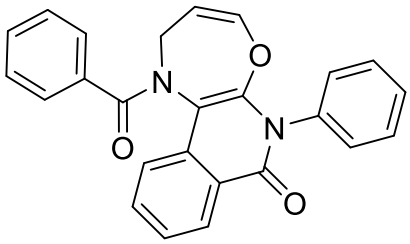
1-benzoyl-6-benzyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinolin-7(2*H*)-one

(Compound **9**{*6,1*}), white solid, yield 73 %, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.44 (dt, *J* = 15.5, 7.7 Hz, 8H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.20 (m, 1H), 6.11 – 6.02 (m, 1H), 5.61 (dd, *J* = 5.8, 2.4 Hz, 1H), 5.27 (dd, *J* = 37.6, 14.2 Hz, 2H), 4.73 – 4.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.96, 168.87, 163.68, 140.16, 137.08, 135.28, 134.17, 131.10, 130.50, 129.09, 128.52, 128.21, 127.27, 126.88, 124.94, 124.68, 74.75, 57.18, 44.17. HRMS (ESI) m/z calcd for $C_{26}H_{21}N_2O_3^+$ $(M+H)^+$ 409.15467, found 409.15469.



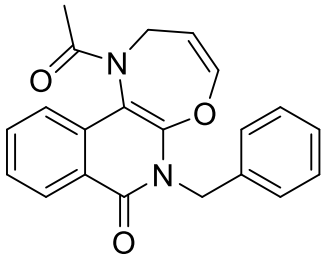
1-benzoyl-6-phenyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinolin-7(2*H*)-one

(Compound **9**{*6,4*}), white solid, yield 68%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.56 – 7.47 (m, 6H), 7.42 (dd, *J* = 10.0, 7.3 Hz,



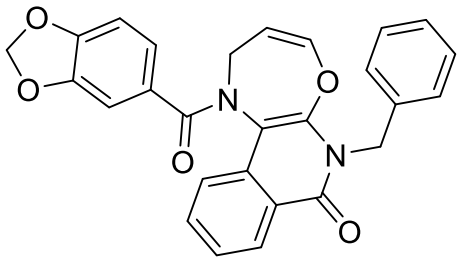
4H), 7.32 (d, *J* = 7.5 Hz, 2H), 6.13 (d, *J* = 6.0 Hz, 1H), 5.81 (d, *J* = 6.1 Hz, 1H), 4.69 (dd, *J* = 15.0, 1.7 Hz, 1H), 4.54 (dd, *J* = 14.9, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.93, 169.17, 163.95, 140.19, 135.49, 135.23, 134.34, 131.00, 130.52, 129.21, 128.61, 128.50, 126.93, 125.37, 124.93, 74.84, 57.18. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_3^+$ $(M+H)^+$ 395.13902, found 395.13904.

1-acetyl-6-benzyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinolin-7(2*H*)-one



(Compound **9**{*7,1*}), white solid, yield 72%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.4 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.46 – 7.36 (m, 3H), 7.28 (dd, *J* = 12.8, 5.1 Hz, 2H), 7.21 (dd, *J* = 7.5, 4.7 Hz, 2H), 6.16 – 6.06 (m, 1H), 5.57 (dt, *J* = 5.9, 2.1 Hz, 1H), 5.21 (dd, *J* = 38.4, 14.2 Hz, 2H), 4.79 – 4.56 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.04, 168.35, 163.63, 140.12, 137.00, 134.10, 131.74, 129.01, 128.47, 128.35, 128.15, 127.68, 127.27, 124.91, 124.44, 74.18, 55.67, 44.13, 22.04. HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3^+$ $(M+H)^+$ 347.13902, found 347.13904.

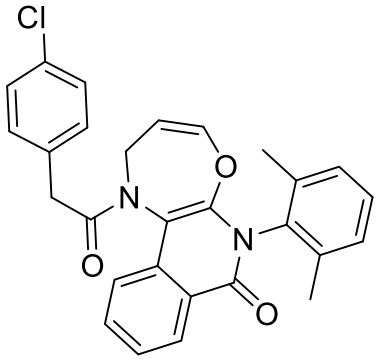
1-(benzo[*d*][1,3]dioxole-5-carbonyl)-6-benzyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]is



oquinolin-7(2*H*)-one (Compound **9**{*8,1*}), white solid, yield 67%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.17 (m, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.11 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.04 (d, *J* = 1.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.10 (d, *J* = 6.2 Hz, 1H), 6.01 (s, 2H), 5.61 (d, *J* = 6.2 Hz, 1H), 5.38 – 5.15 (m, 2H), 4.70 (ddt, *J* = 46.5, 14.9, 2.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.02, 168.16, 163.69, 149.52, 147.68, 140.21, 137.11, 134.17, 131.00, 129.02, 128.83, 128.46, 128.27, 127.26, 125.01, 121.82, 108.17, 107.90, 101.58, 74.90, 57.29, 44.14.

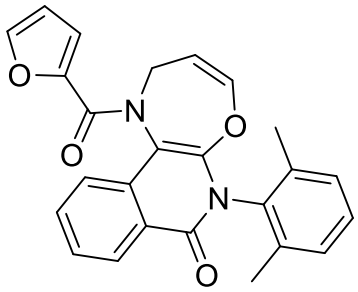
HRMS (ESI) m/z calcd for $C_{27}H_{21}N_2O_5^+$ $(M+H)^+$ 453.14450, found 453.14450.

1-(2-(4-chlorophenyl)acetyl)-6-(2,6-dimethylphenyl)-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinolin-7(2*H*)-one (Compound **9**{*9,5*}),



white solid, yield 65%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1H), 7.54 – 7.44 (m, 1H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.09 (m, 5H), 6.11 (d, *J* = 6.1 Hz, 1H), 5.75 (d, *J* = 6.2 Hz, 1H), 4.62 (ddd, *J* = 16.4, 14.4, 12.3 Hz, 2H), 3.84 – 3.58 (m, 2H), 2.18 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.97, 168.27, 163.06, 140.35, 136.79, 134.58, 134.23, 133.67, 133.09, 131.99, 131.38, 130.25, 129.31, 128.89, 128.75，128.10, 127.81, 124.87, 124.49, 74.98, 55.09, 41.02, 17.83, 17.73. HRMS (ESI) m/z calcd for $C_{28}H_{24}ClN_2O_3^+$ $(M+H)^+$ 471.14700, found 471.14700.

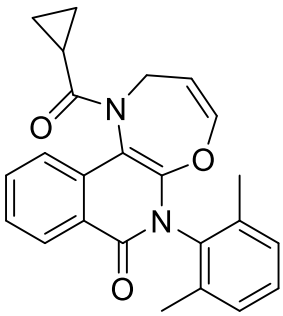
6-(2,6-dimethylphenyl)-1-(furan-2-carbonyl)-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinolin-7(2*H*)-one (Compound **9**{*10,5*}),



white solid, yield 58%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.23 (m, 1H), 7.62 (td, *J* = 7.7, 1.2 Hz, 1H), 7.56 (s, 1H), 7.48 (dd, *J* = 11.0, 4.1 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.17 – 7.09 (m, 3H), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.25 (d, *J* = 6.2 Hz, 1H), 5.81 (d, *J* = 6.2 Hz, 1H), 5.13 (ddd, *J* = 17.7, 15.6, 13.6 Hz, 2H), 2.23 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.02, 163.18, 156.74, 147.75, 144.86, 140.66, 136.90, 134.62, 134.40, 133.75, 130.16, 129.22, 128.75，128.64, 128.42, 128.05, 125.07, 124.49, 118.07, 111.94, 76.19, 55.97 , 17.92，19.79. HRMS (ESI) m/z calcd for $C_{25}H_{21}N_2O_4^+$ $(M+H)^+$ 413.14958, found 413.15002.

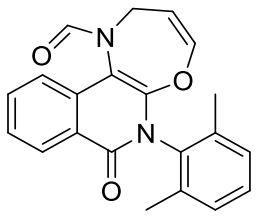
1-(cyclopropanecarbonyl)-6-(2,6-dimethylphenyl)-1,6-dihydro-[1,4]oxazepino[2,3

-*c*]isoquinolin-7(2*H*)-one (Compound **9** {*11,5*}), white solid, yield 63%, ^{1}H NMR



(400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.63 (td, *J* = 7.7, 1.3 Hz, 1H), 7.45 (dd, *J* = 11.0, 4.2 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.21 – 7.07 (m, 3H), 6.21 (d, *J* = 6.1 Hz, 1H), 5.77 (d, *J* = 6.1 Hz, 1H), 4.87 (ddd, *J* = 16.3, 14.3, 12.2 Hz, 2H), 2.13 (s, 3H), 2.09 (s, 3H), 1.84 – 1.67 (m, 1H), 0.89 – 0.73 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.48, 170.20, 163.15, 140.95, 136.80, 134.63, 134.26, 131.50, 129.26, 128.61, 128.24, 128.09, 125.04, 124.35, 74.83, 54.96, 31.57, 22.63, 17.78, 14.08, 12.50, 8.01, 7.49. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_3^+$ $(M+H)^+$ 387.17032, found 387.17038.

6-(2,6-dimethylphenyl)-7-oxo-6,7-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-1(2*H*)-carbaldehyde (Compound **9**{*12,5*}), white solid, yield 54%, ^{1}H NMR (400 MHz,



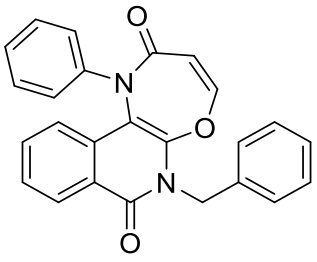
$CDCl_3$) δ 8.37 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.51 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.15 (dd, *J* = 12.3, 7.1 Hz, 2H), 6.21 (d, *J* = 6.1 Hz, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 4.87 – 4.69 (m, 2H), 2.17 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45, 162.95, 159.76, 139.62, 136.69, 134.48, 131.15, 129.31, 128.78, 128.64, 128.14, 127.61, 125.46, 124.44, 73.30, 53.63, 17.90, 17.76. HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3^+$ $(M+H)^+$ 347.13902, found 347.13904.

General procedures for compounds **11**{*1-10, 1-5, 13-14*}.

A solution of aldehyde (0.50 mmol) and amine (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 10 min in a 5 mL microwave vial. Acid (0.50 mmol) and isonitrile (0.50 mmol) were added to the vial sequentially, and the resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, as determined by the disappearance of the isonitrile by TLC, the solvent was removed under a gentle stream of nitrogen. The resulting residue was dissolved in DMF (3 mL) with the same microwave vial. TEA (1.0 mmol) was then added to the vial, which was sealed and heated under microwave irradiation at 100 °C for 10 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed sequentially with saturated Na_2CO_3 solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to a, which residue was purified by column chromatography over silica gel eluting with a gradient of ethyl acetate/hexane (0 to 60%) to afford the relative oxazepino-isoquinoline compound **11**{*1-10, 1-5, 13-14*}.

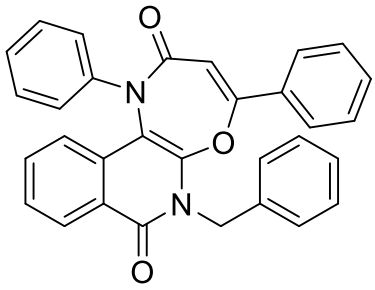
6-benzyl-1-phenyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione

(Compound **11**{*1,1,13*}), white solid, yield 66%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.8 Hz, 1H), 7.64 (td, *J* = 7.7, 1.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 5H), 7.14 – 7.07 (m, 3H), 7.05 – 7.00 (m, 2H), 6.92 (d, *J* = 5.8 Hz, 1H), 6.50 (d, *J* = 5.8 Hz, 1H), 5.23 – 5.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.18, 167.01, 162.60, 147.43, 136.11, 135.96, 134.89, 134.24, 130.12, 129.79, 129.17, 128.73, 128.57， 128.10, 127.78, 126.26, 125.88, 125.12, 123.45, 73.53, 44.55. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_3^+$ $(M+H)^+$ 395.13902, found 395.13898.



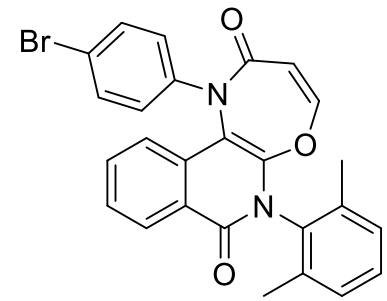
6-benzyl-1,4-diphenyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione

(Compound **11**{*1,1,14*}), white solid, yield 58%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21

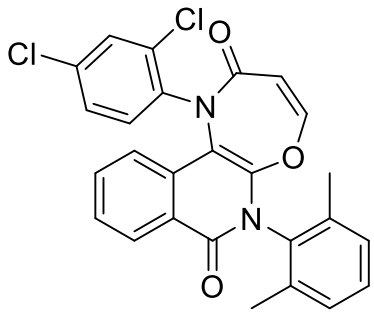


(d, *J* = 7.5 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.50 (dt, *J* = 26.6, 7.8 Hz, 2H), 7.23 (d, *J* = 5.2 Hz, 1H), 7.18 (td, *J* = 9.4, 1.8 Hz, 5H), 7.09 (ddd, *J* = 15.0, 7.6, 2.3 Hz, 5H), 6.88 (d, *J* = 7.6 Hz, 2H), 6.78 (s, 1H), 6.74 (d, *J* = 7.7 Hz, 2H), 5.16 – 5.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.98, 167.44, 162.55, 159.30, 135.71, 135.03, 134.88, 130.36, 129.99, 129.64, 129.28, 129.01, 128.49, 127.69, 126.95, 126.52, 126.42, 126.00, 124.10, 73.72, 44.29. HRMS (ESI) m/z calcd for $C_{31}H_{23}N_2O_3^+$ (M+H) $^+$471.17032, found 471.17032.

1-(4-bromophenyl)-6-(2,6-dimethylphenyl)-4-phenyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione (Compound **11**{*3,5,14*}), white solid, yield 54%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.35 (t, *J* = 8.1 Hz, 3H), 7.24 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 18.5, 7.5 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.73 (s, 1H), 1.26 (d, *J* = 5.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.42, 165.82, 161.82, 160.21, 135.51, 135.25, 134.97, 132.57, 130.75, 130.58，130.18, 129.14, 129.01，128.61, 128.44，127.50, 127.28, 126.50, 124.66, 121.68, 75.04, 16.75, 16.37. HRMS (ESI) m/z calcd for $C_{32}H_{24}BrN_2O_3^+$ $(M+H)^+$ 563.09648, found 563.09607.

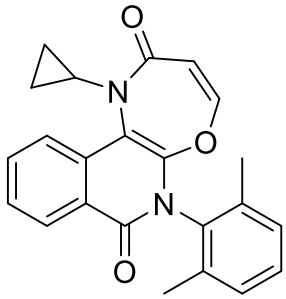


1-(2,4-dichlorophenyl)-6-(2,6-dimethylphenyl)-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione (Compound **11**{*9,5,13*}), white solid, yield 71%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.27 (m, 1H), 7.74 (dt, *J* = 16.7, 6.8 Hz, 2H), 7.67 – 7.59 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 9.1, 5.5 Hz, 1H), 7.15 (dd, *J* = 8.5, 5.0 Hz, 3H), 7.09 – 7.02 (m, 1H), 6.90 – 6.82 (m,

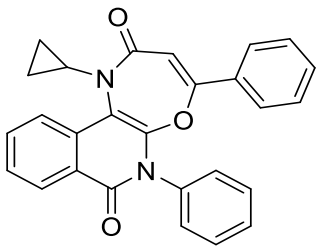


1H), 6.60 (dd, *J* = 5.5, 3.1 Hz, 1H), 2.08 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.92, 166.05, 161.80, 148.71, 135.09, 134.92, 134.81, 134.68, 133.38, 132.95, 132.03, 131.29, 130.30, 129.26, 128.75, 127.72，127.59，127.42, 125.23, 74.35, 17.83, 17.12. HRMS (ESI) m/z calcd for $C_{26}H_{19}Cl_2N_2O_3^+$ $(M+H)^+$ 477.07672, found 477.07672.

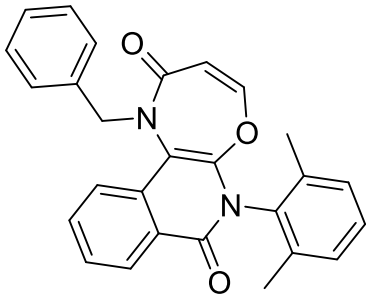
1-cyclopropyl-6-(2,6-dimethylphenyl)-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione (Compound **11**{*10,5,13*}), white solid, yield 63%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.19 (d, *J* = 4.3 Hz, 2H), 6.91 (d, *J* = 5.7 Hz, 1H), 6.36 (d, *J* = 5.7 Hz, 1H), 2.62 (dd, *J* = 9.9, 5.8 Hz, 1H), 2.11 (s, 6H), 0.78 (dd, *J* = 15.0, 7.2 Hz, 2H), 0.54 – 0.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.98, 166.58, 162.37, 147.67, 135.42, 135.30, 134.91, 134.71, 133.24, 130.22, 129.71, 129.20, 128.70, 128.23, 125.47, 125.00, 74.38, 24.62, 17.86, 17.70, 5.87, 3.33. HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2O_3^+$ $(M+H)^+$ 373.15467, found 373.15436.



1-cyclopropyl-4,6-diphenyl-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione (Compound **11**{*10,4,14*}), white solid, yield 62%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.32 (m, 1H), 7.72 (td, *J* = 7.7, 1.2 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 6.8 Hz, 3H), 7.36 (dd, *J* = 10.5, 7.8 Hz, 2H), 7.26 (t, *J* = 3.5 Hz, 2H), 7.00 (d, *J* = 7.4 Hz, 2H), 6.95 (s, 2H), 6.58 (s, 1H), 2.37 – 2.27 (m, 1H), 0.79 – 0.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.93, 168.21, 163.11, 159.27, 135.29, 135.22, 134.49, 130.46, 130.41, 129.94, 129.83, 129.45, 129.06, 127.95, 126.97, 126.34, 126.17, 124.43, 73.96, 23.74, 4.89, 4.47. HRMS (ESI) m/z calcd for $C_{27}H_{21}N_2O_3^+$ $(M+H)^+$ 421.15467, found 421.15460.

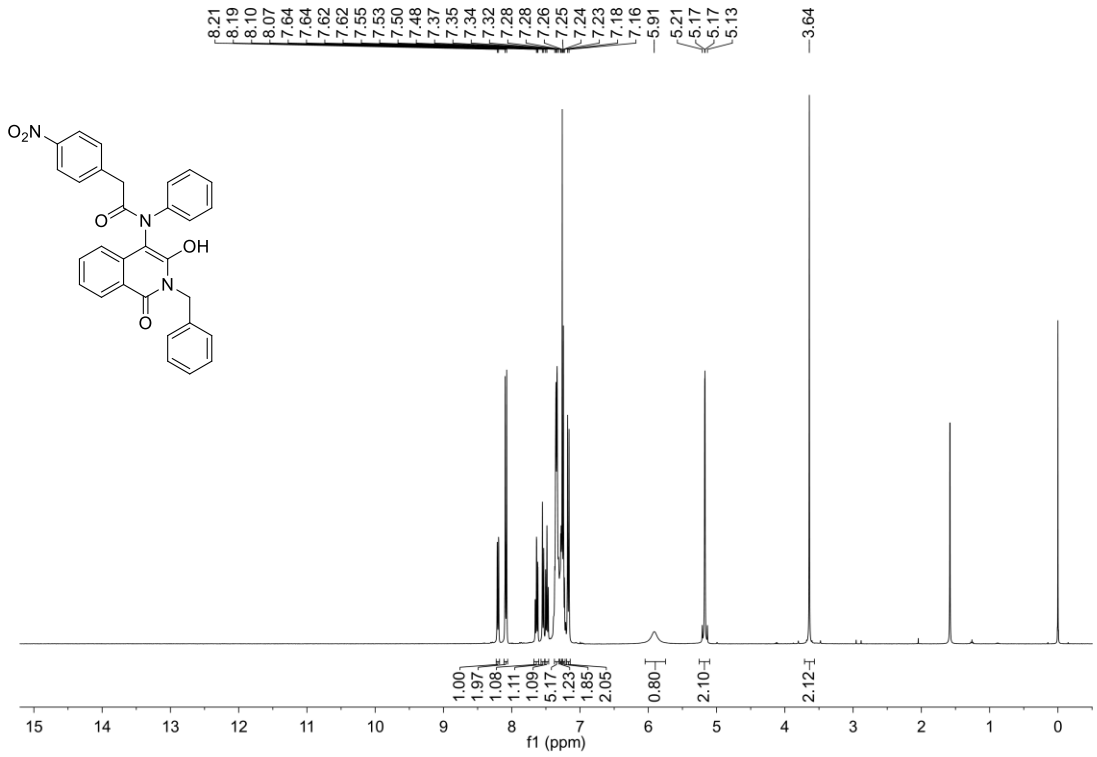


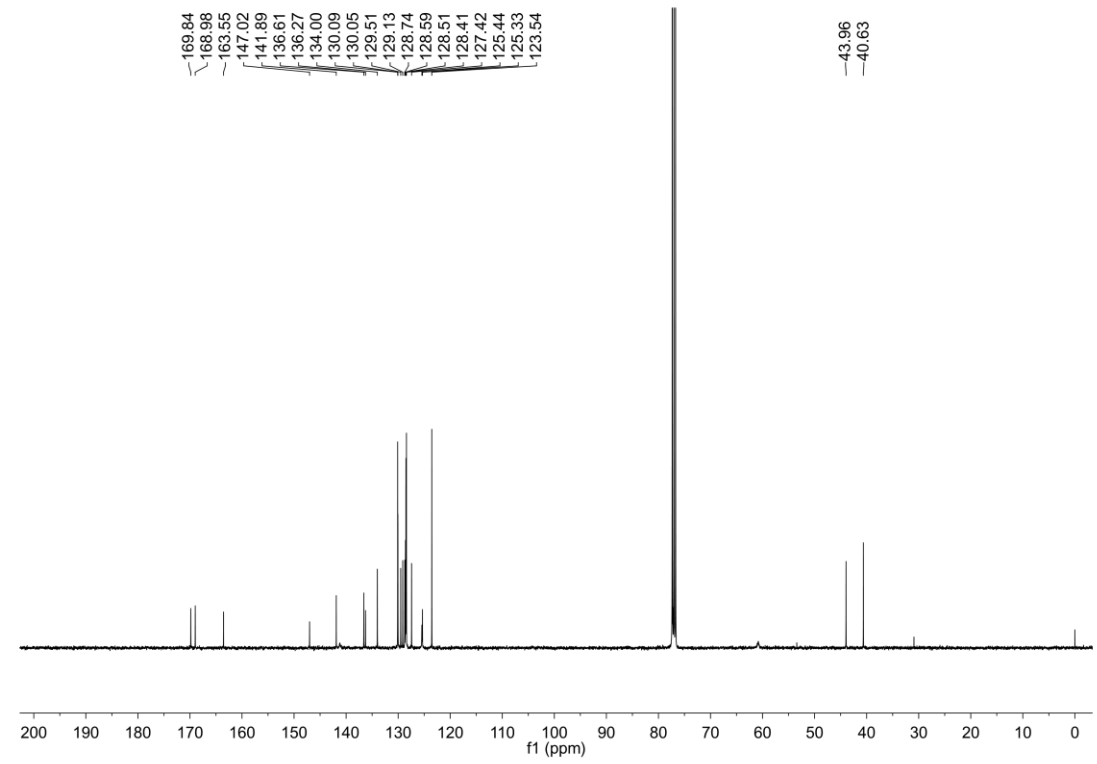
1-benzyl-6-(2,6-dimethylphenyl)-1,6-dihydro-[1,4]oxazepino[2,3-*c*]isoquinoline-2,7-dione (Compound **11**{*4,5,13*}), white solid, yield 52 %, ^{1}H NMR (400 MHz, $CDCl_3$)

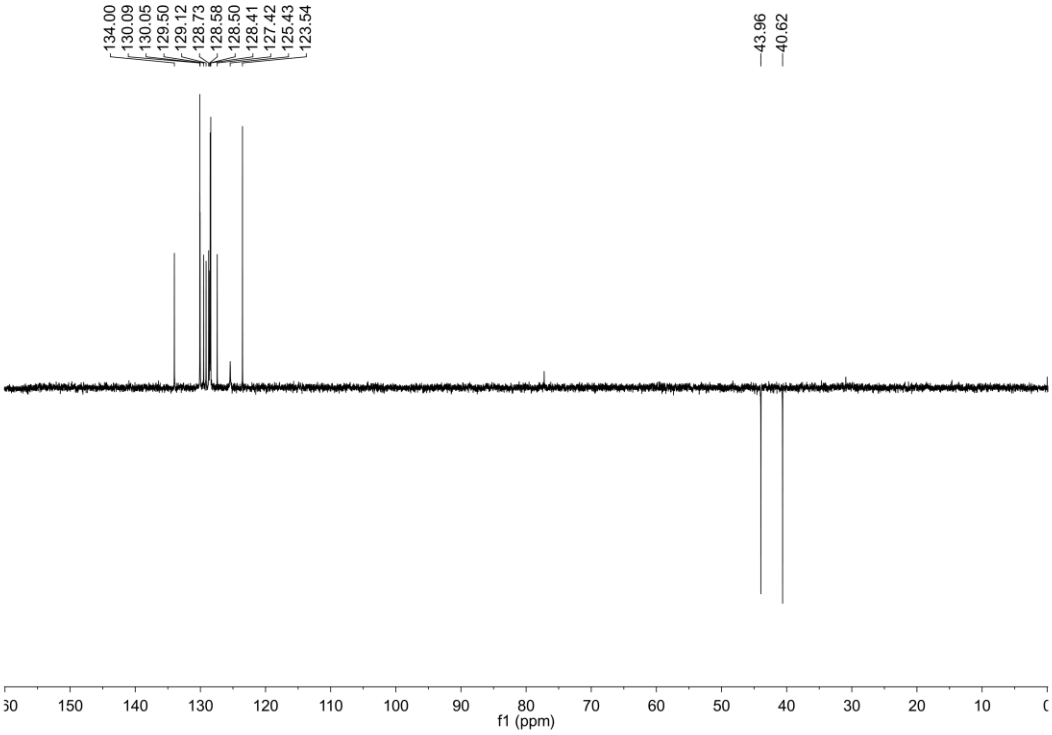


δ 8.23 (d, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.16 (dd, *J* = 7.1, 2.9 Hz, 2H), 7.08 (dd, *J* = 7.4, 4.1 Hz, 5H), 6.97 (d, *J* = 5.7 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.44 (d, *J* = 5.7 Hz, 1H), 4.88 (d, *J* = 15.2 Hz, 1H), 4.19 (d, *J* = 15.2 Hz, 1H), 2.08 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.54, 166.34, 162.28, 147.64, 135.50, 135.34，134.53, 134.22, 133.47, 133.26, 129.74, 129.38，129.19, 128.75, 128.50，128.30，127.59, 127.45, 126.66, 124.91, 73.78, 45.68, 17.93，17.90. HRMS (ESI) m/z calcd for $C_{27}H_{23}N_2O_3^+$ $(M+H)^+$ 423.17032, found 423.17032.

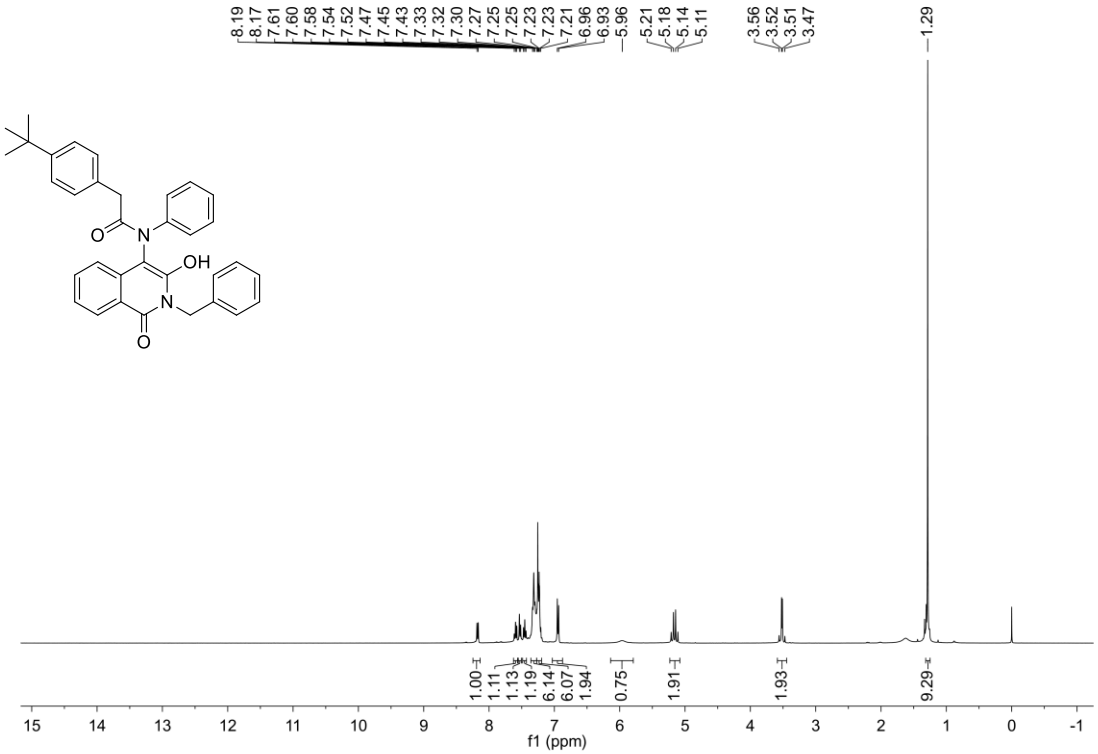
Compound **6**{*1,1,1*}

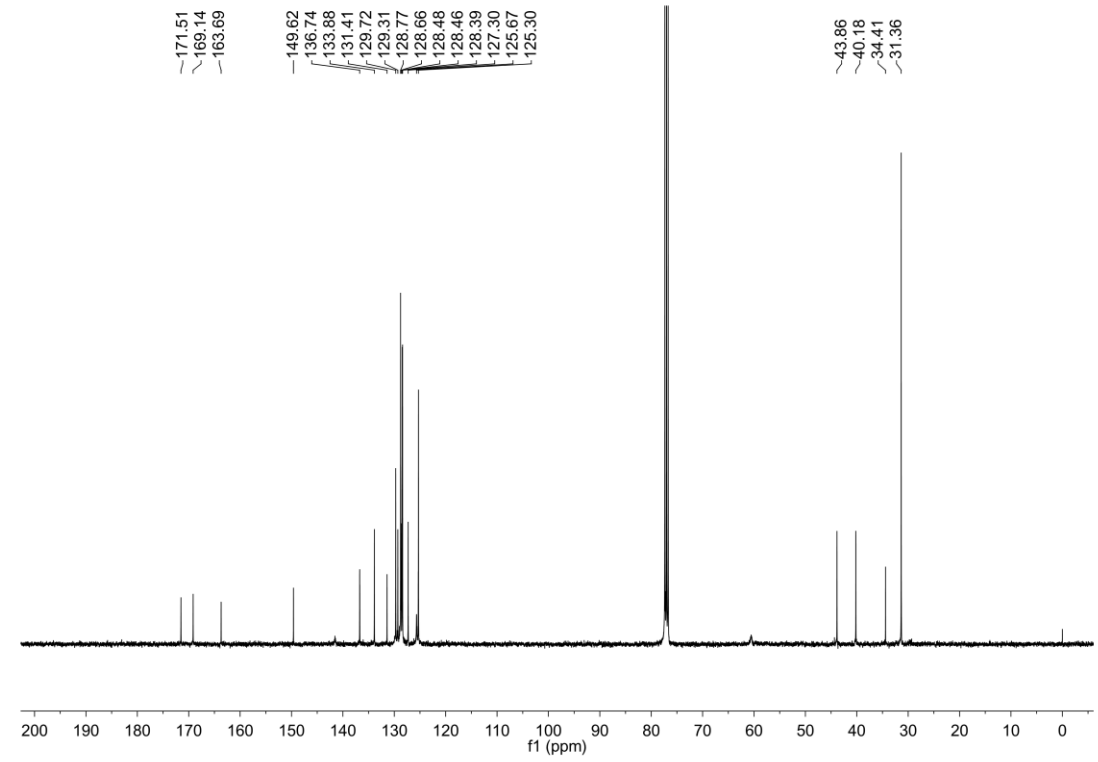




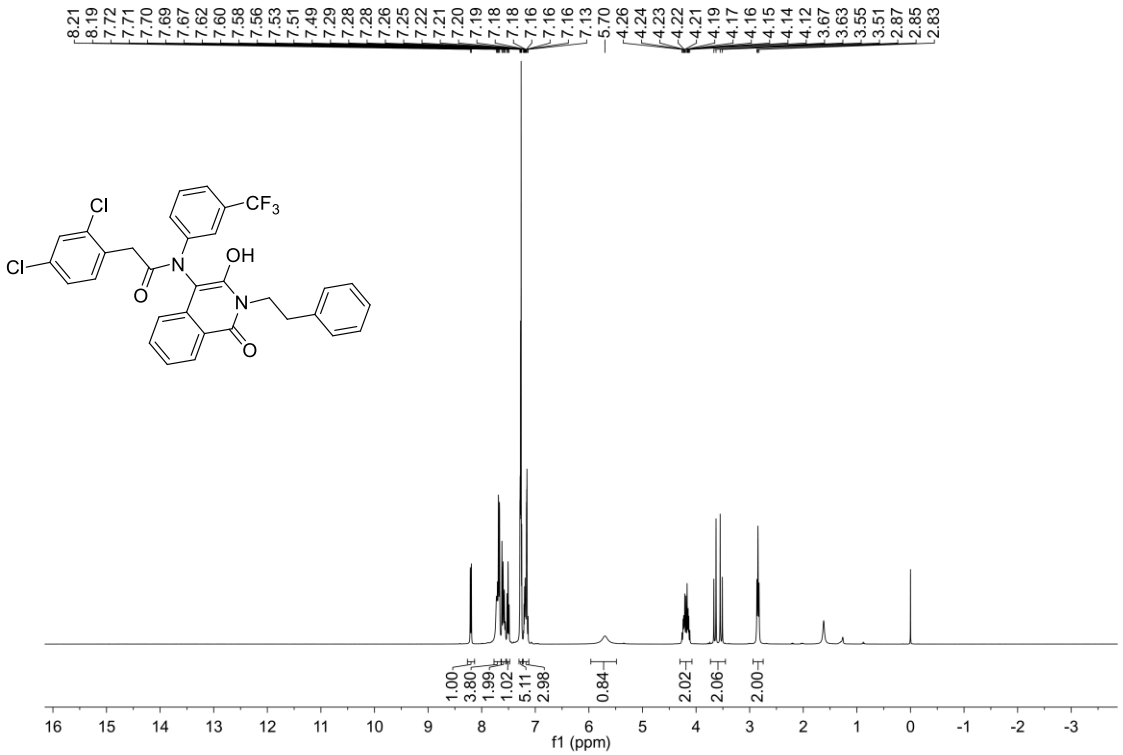

134.00
130.09
130.05
129.50
129.12
128.73
128.58
128.50
128.41
127.42
125.43
123.54
43.96
40.62
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

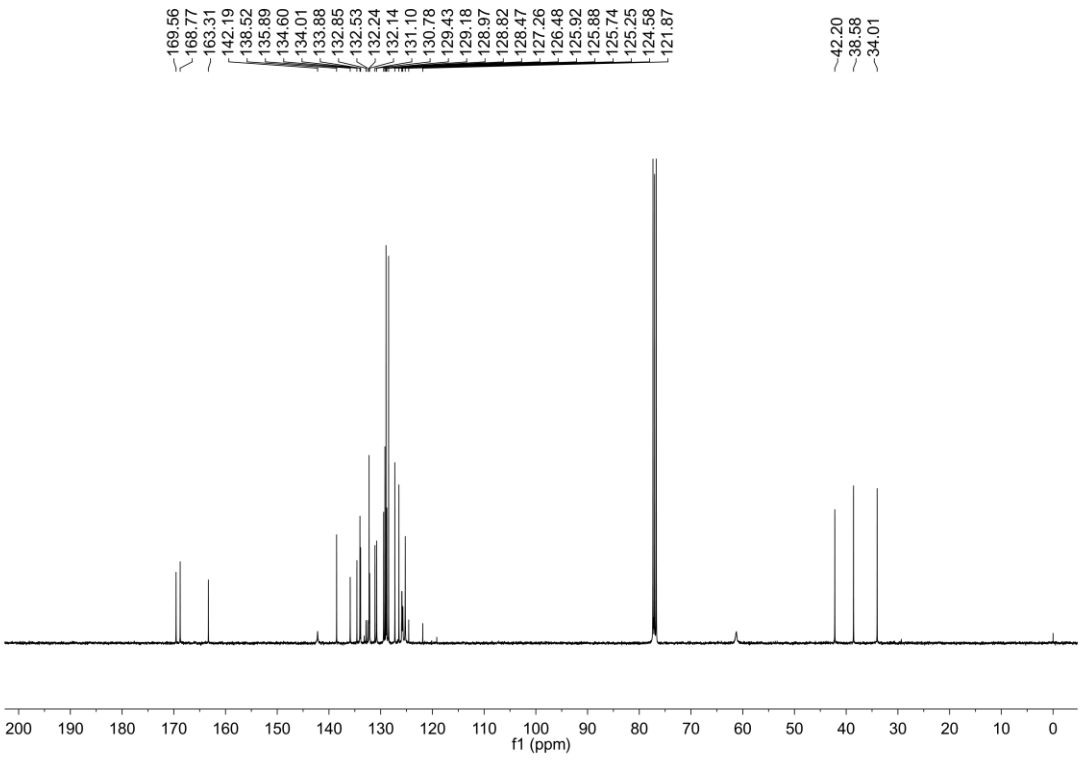
Compound **6**{*1,2,1*}



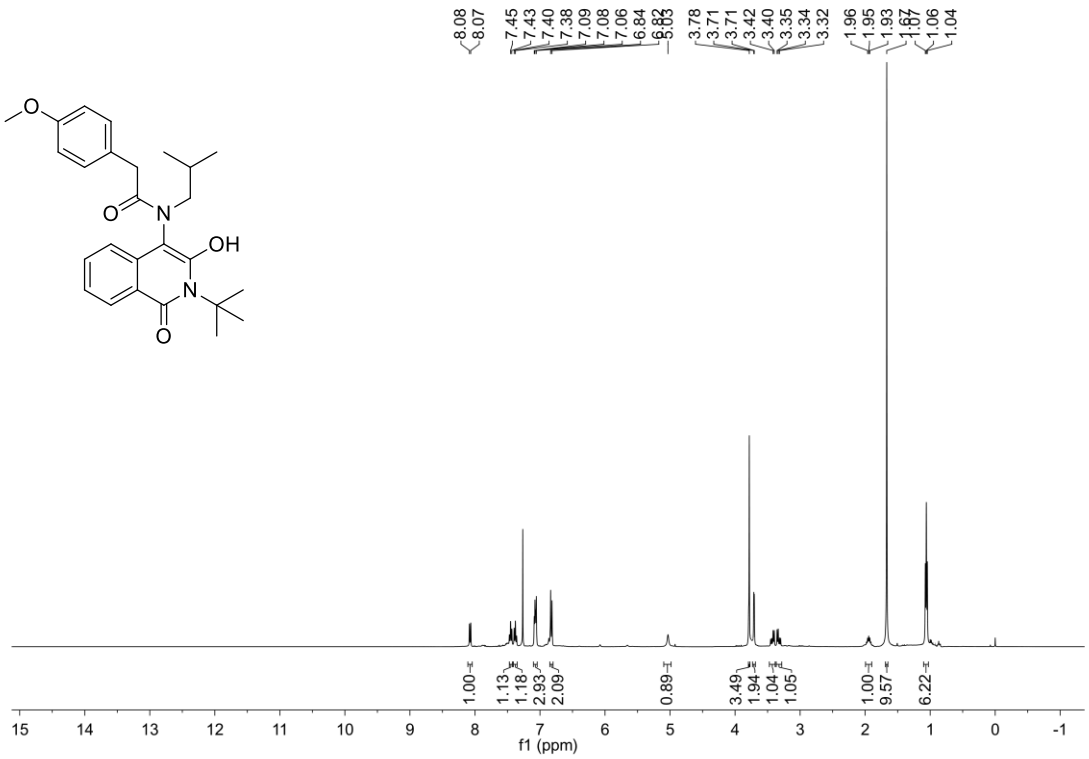


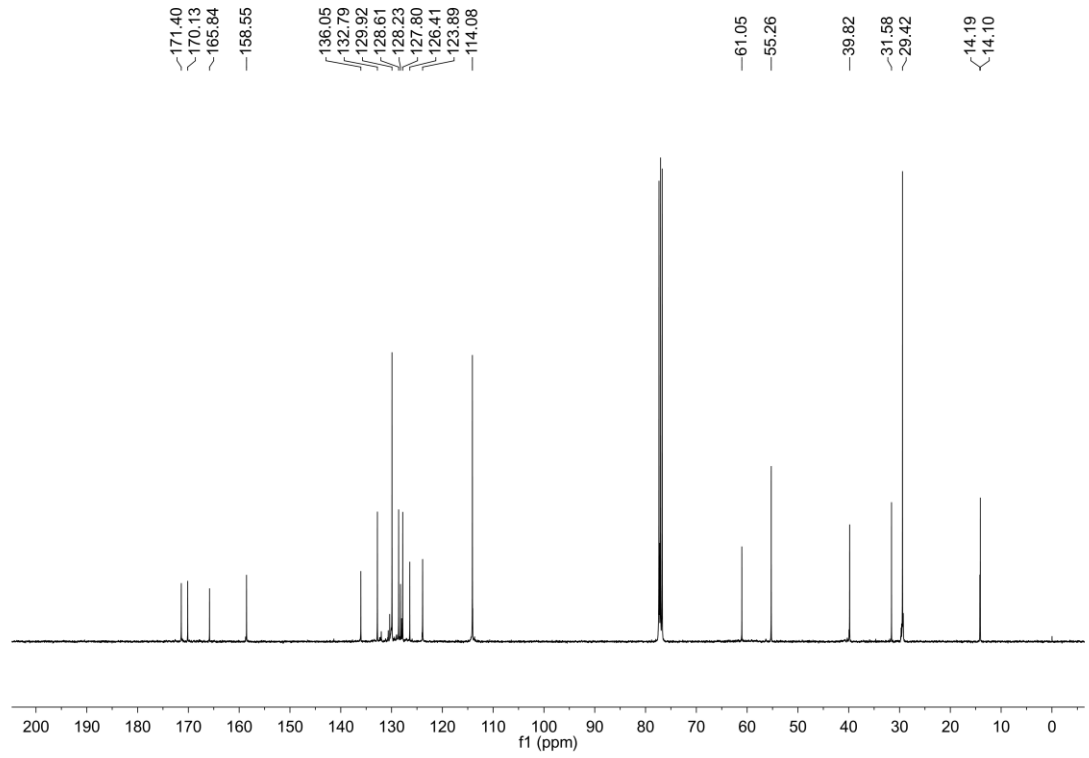
Compound **6**{*6,3,2*}



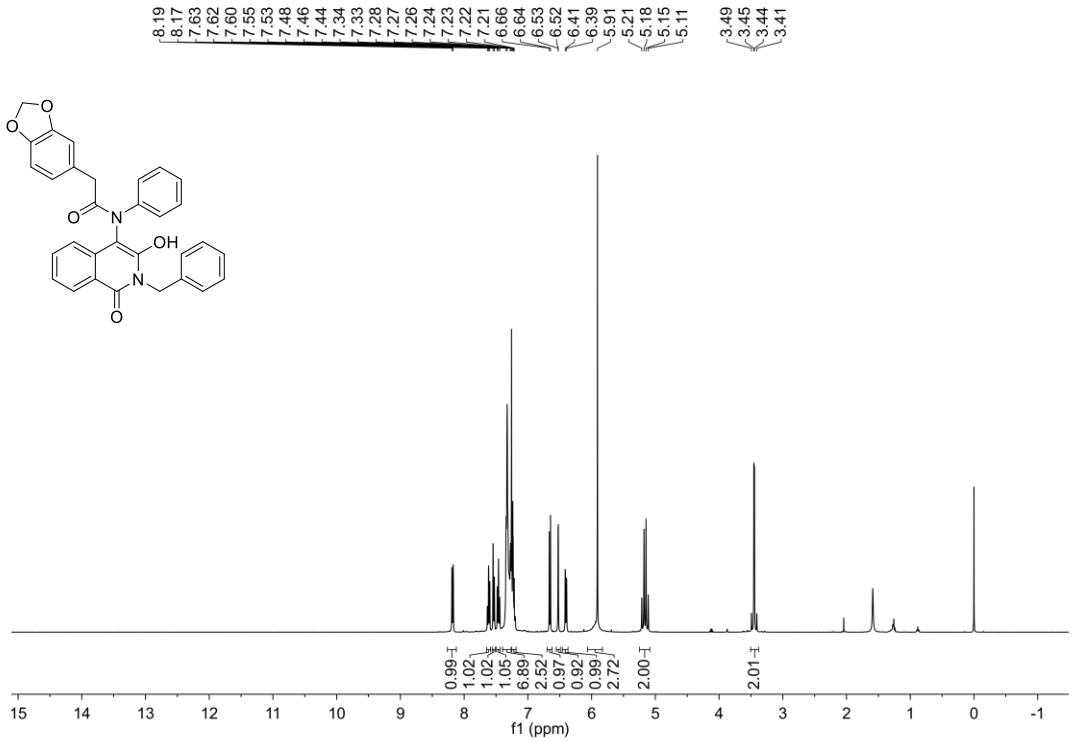


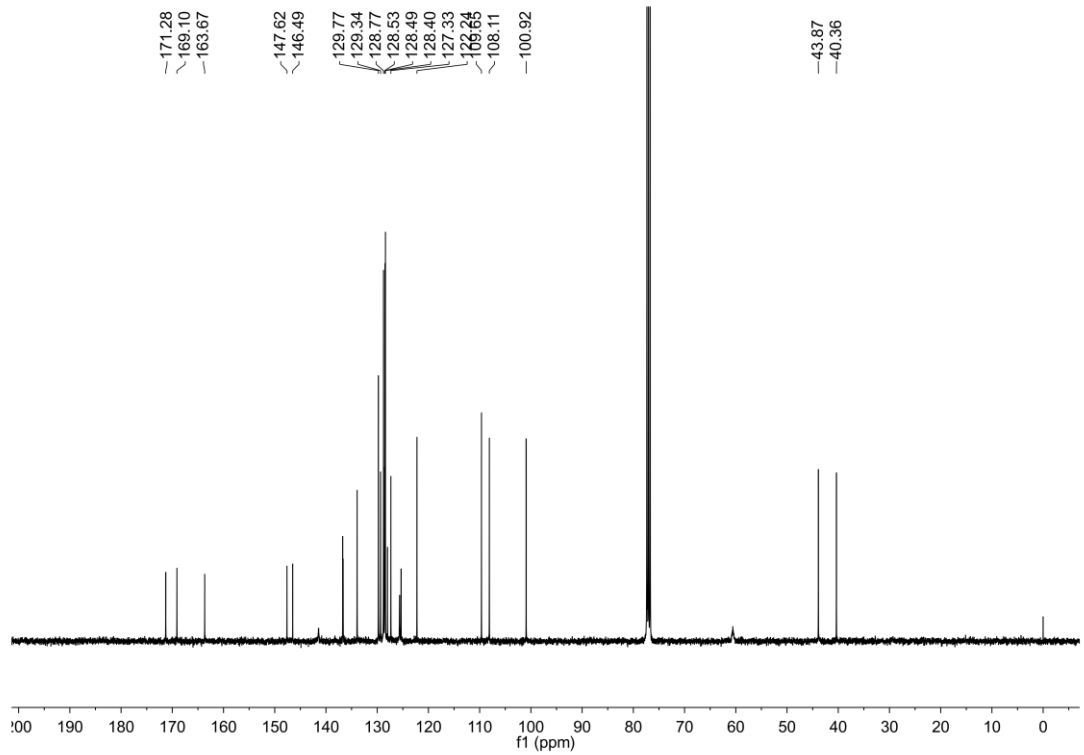
Compound **6**{*7,4,3*}

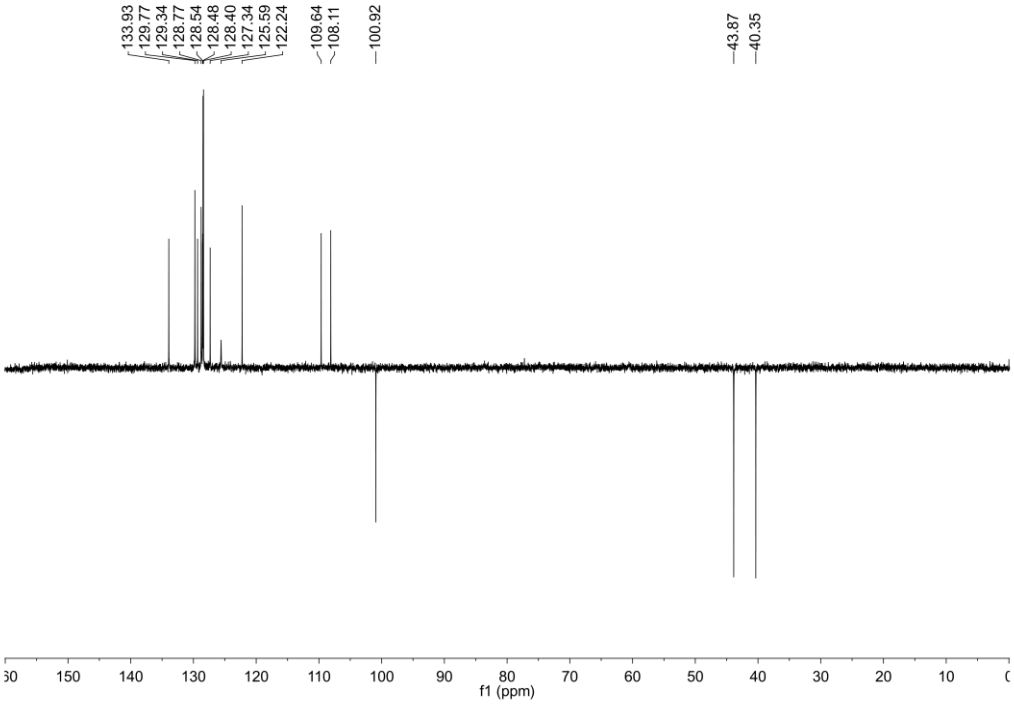




Compound **6**{*1,5,1*}



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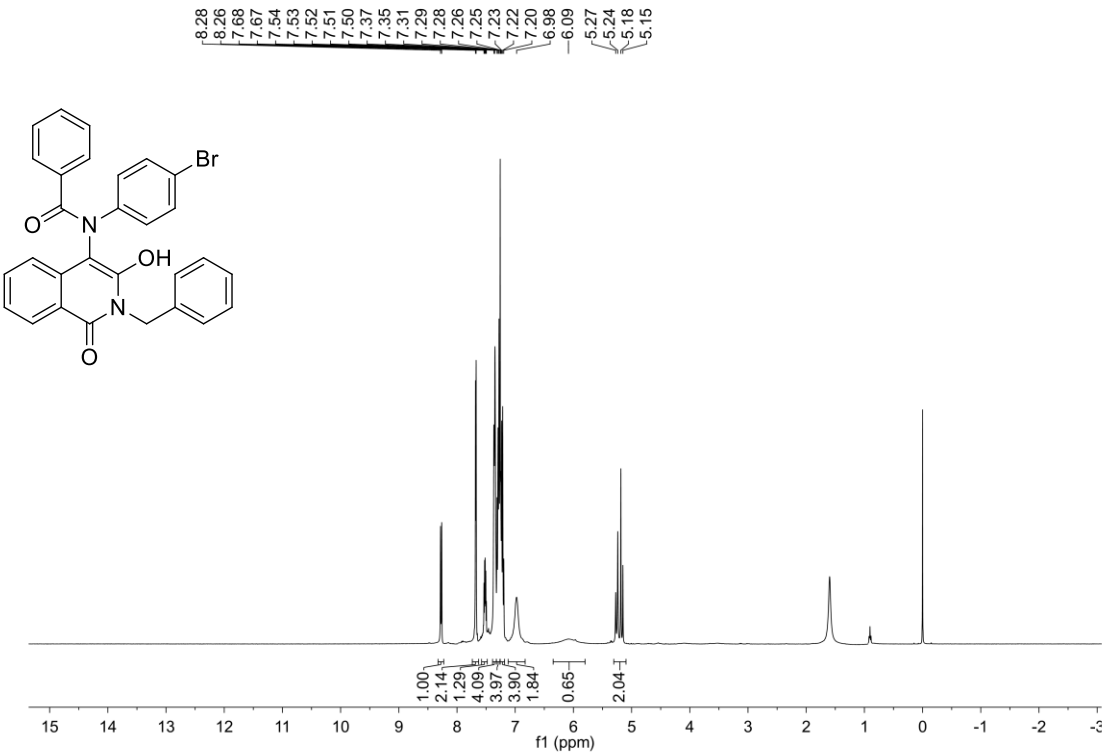
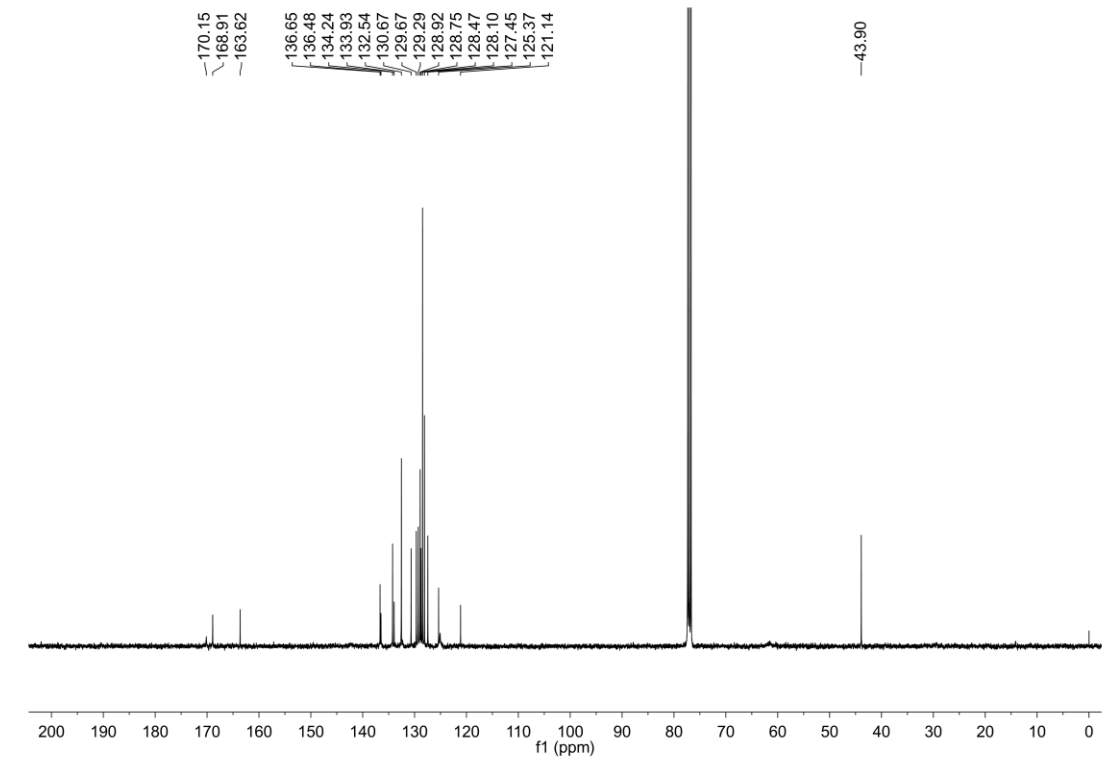
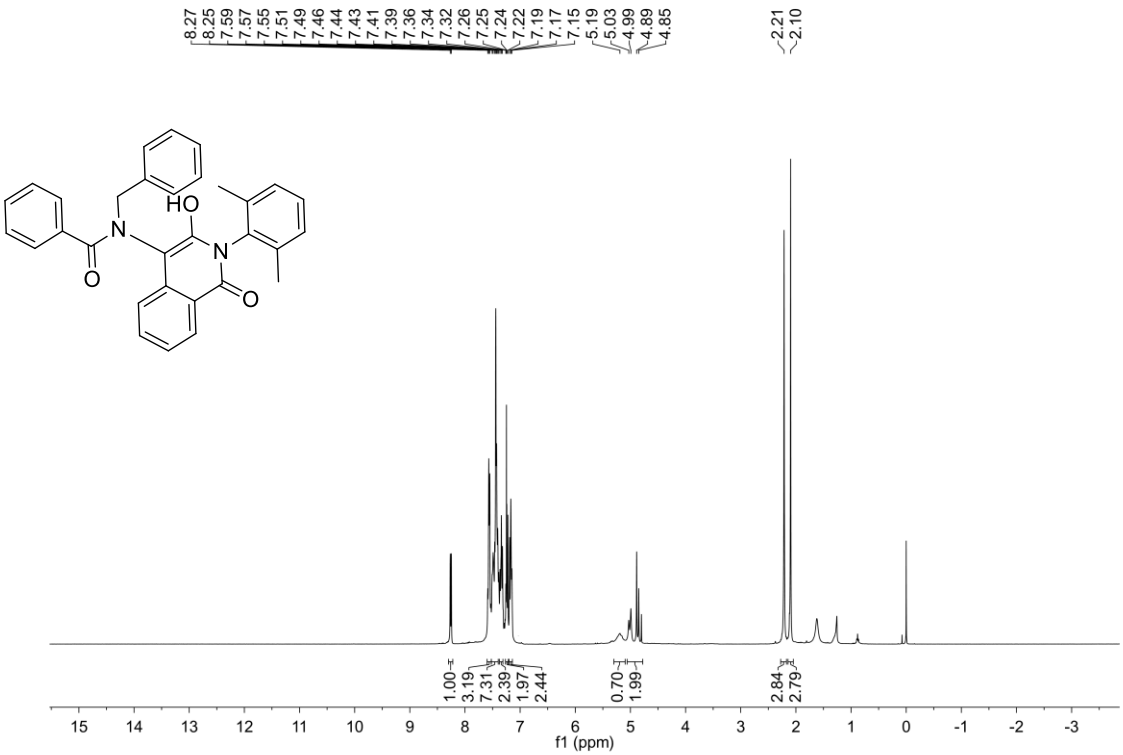
129.77
129.34
128.77
128.54
128.48
128.40
127.34
125.59
122.24
109.64
108.11
100.92
43.87
40.35
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

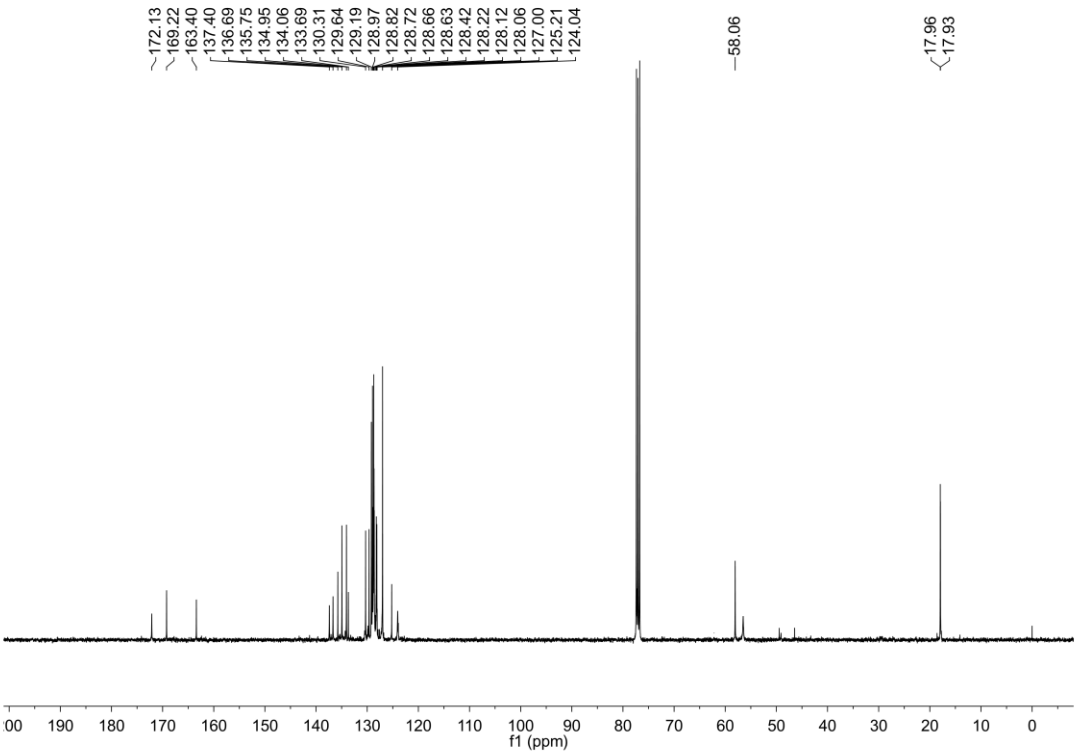
Compound **6**{*3,6,1*}



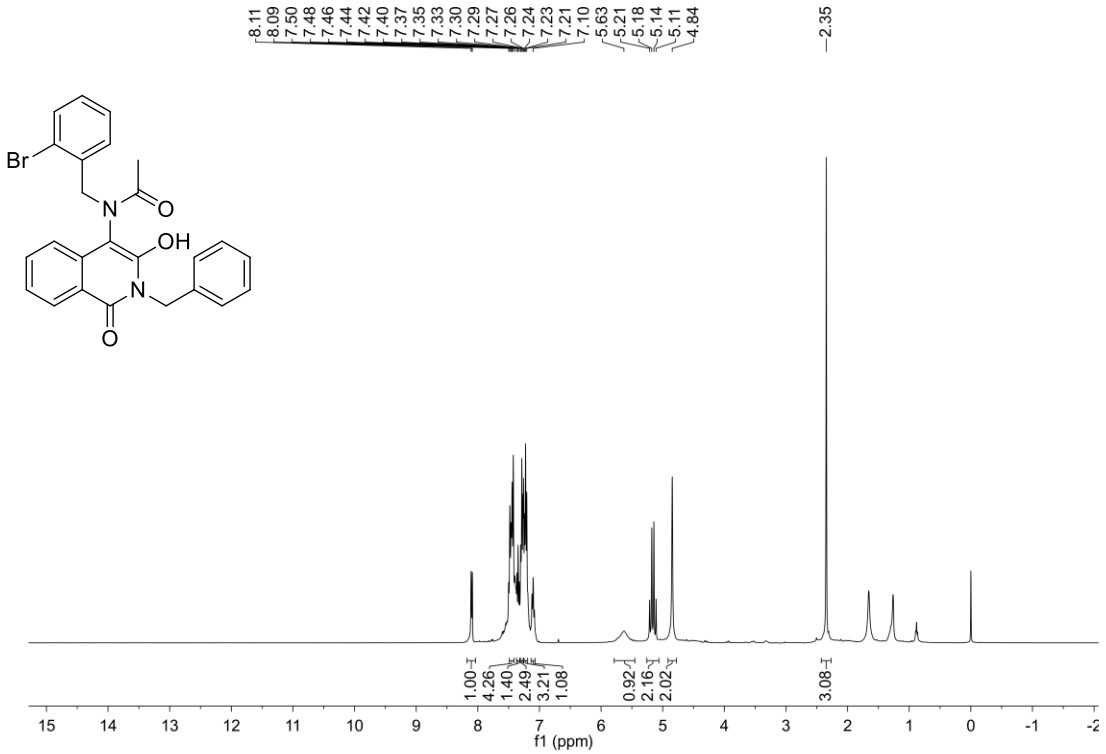


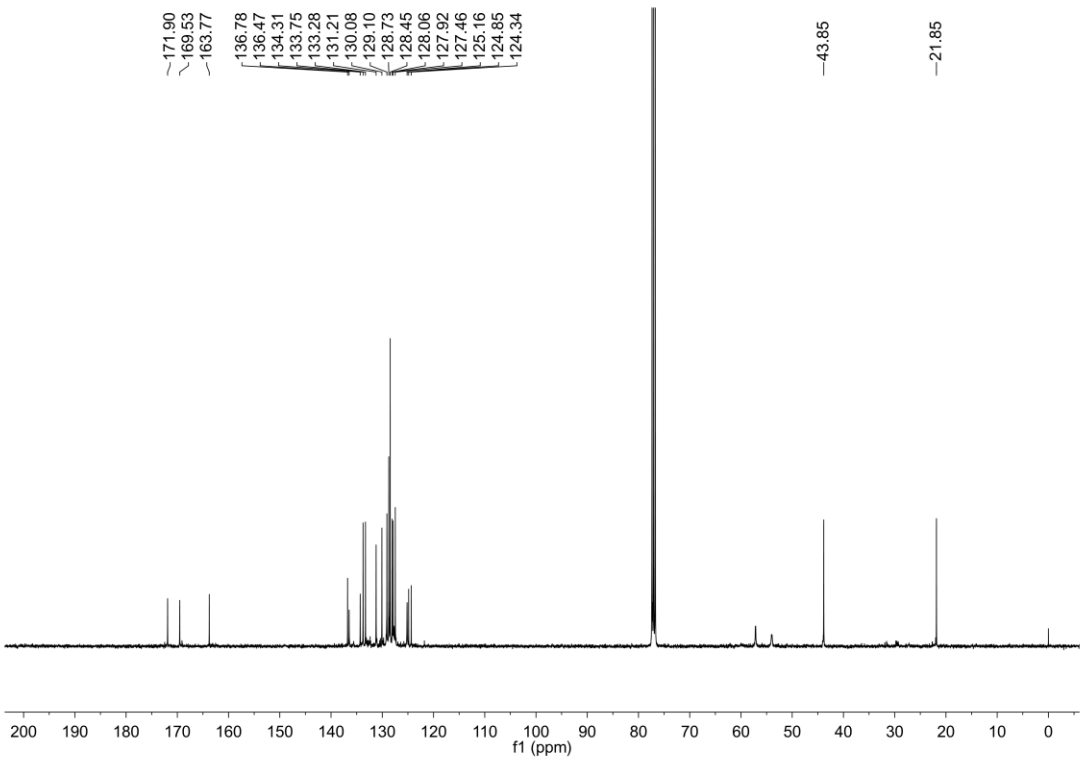
Compound **6**{*4,6,5*}



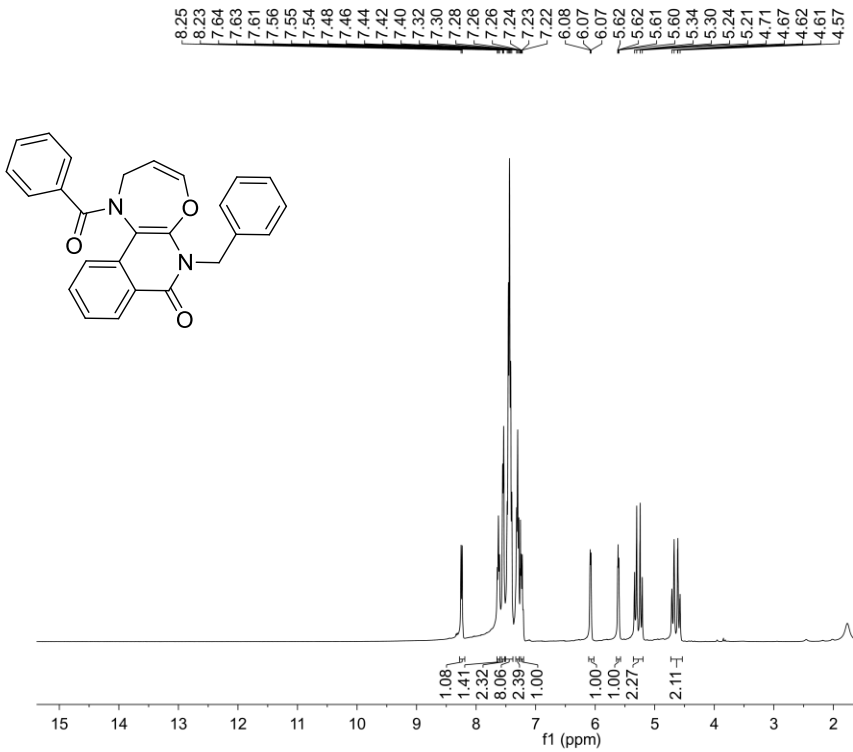


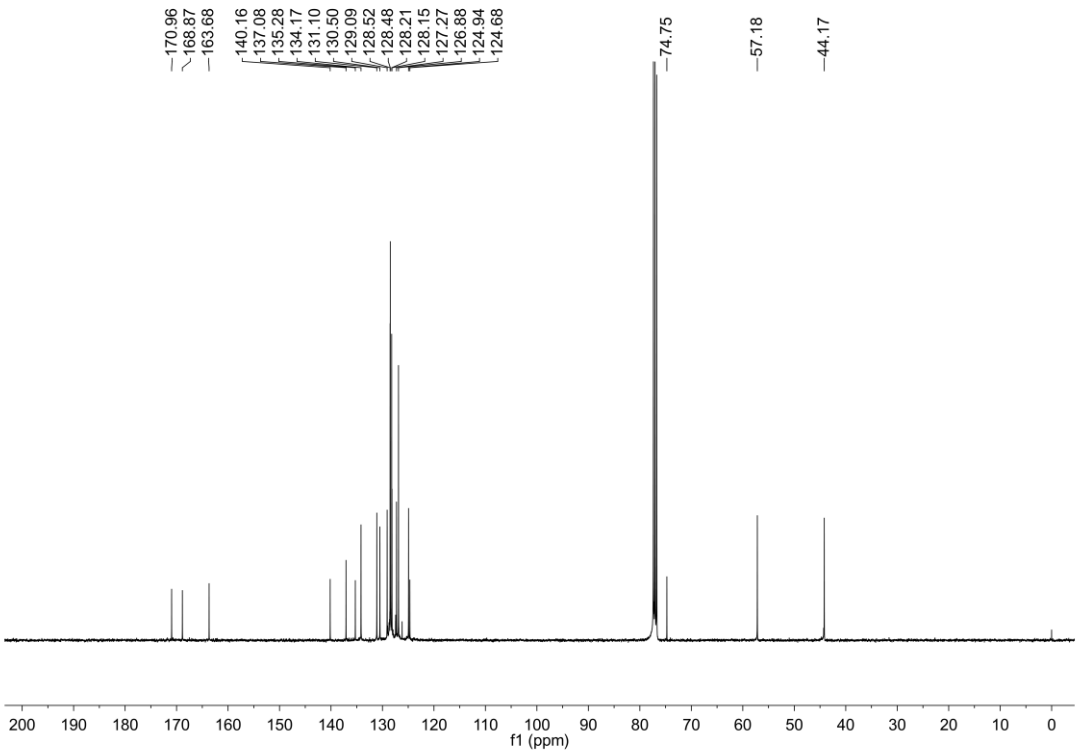
Compound **6**{*5,7,1*}



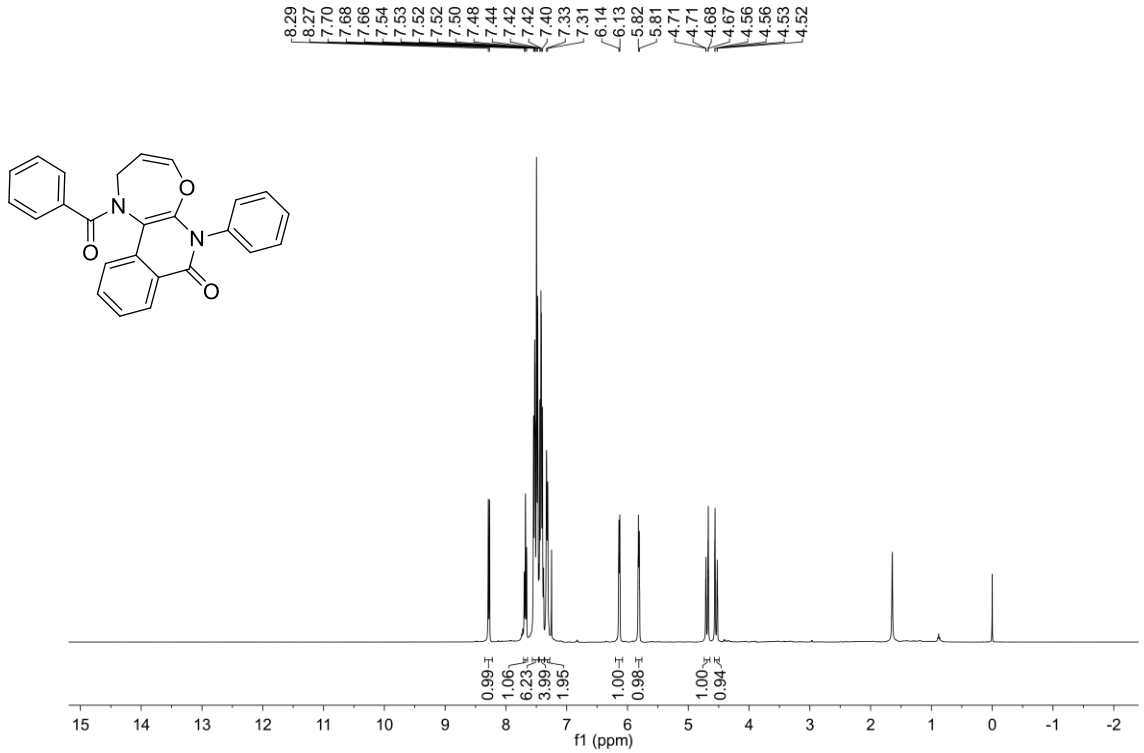


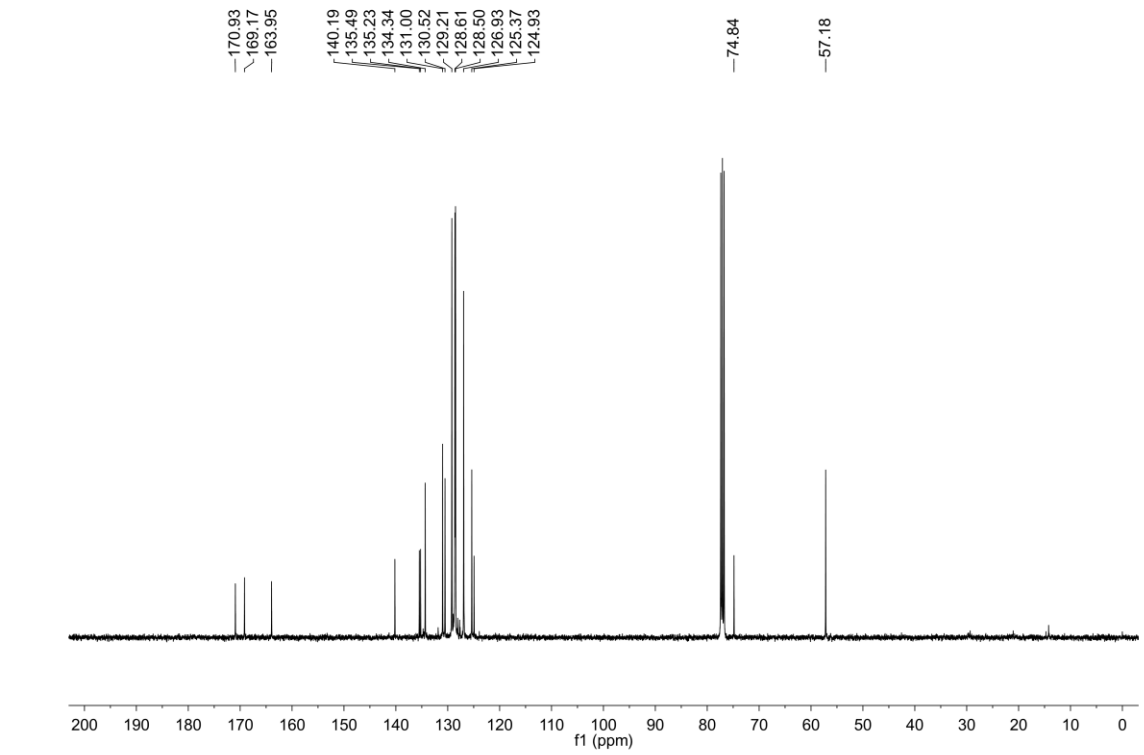
Compound **9**{*6,1*}

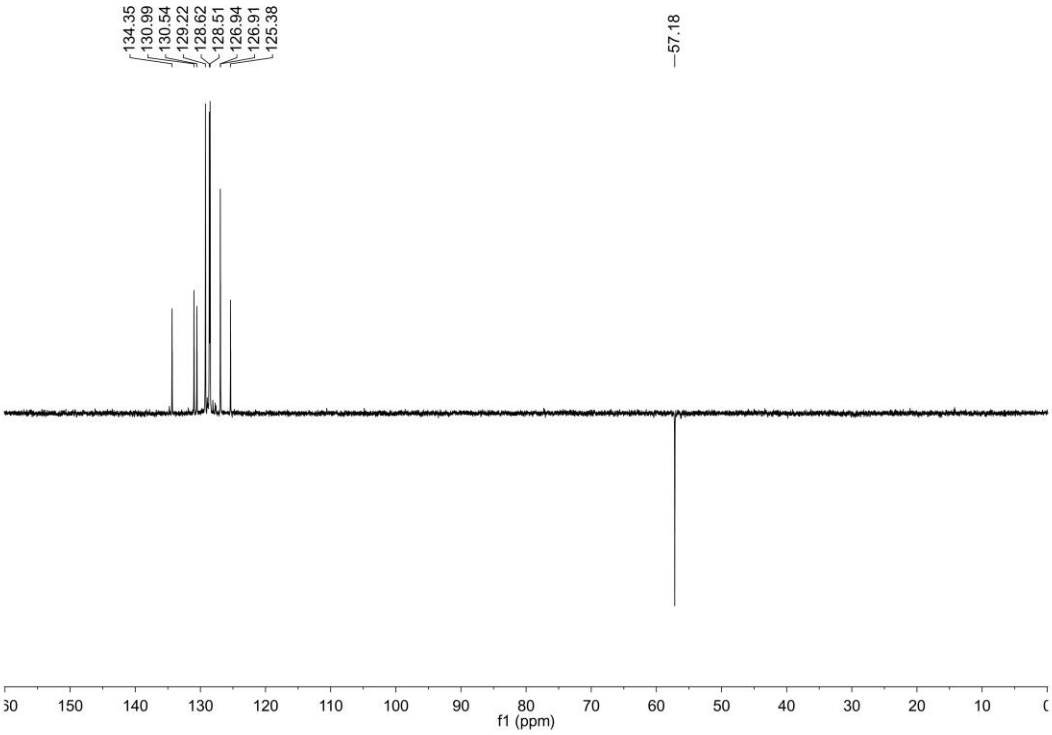




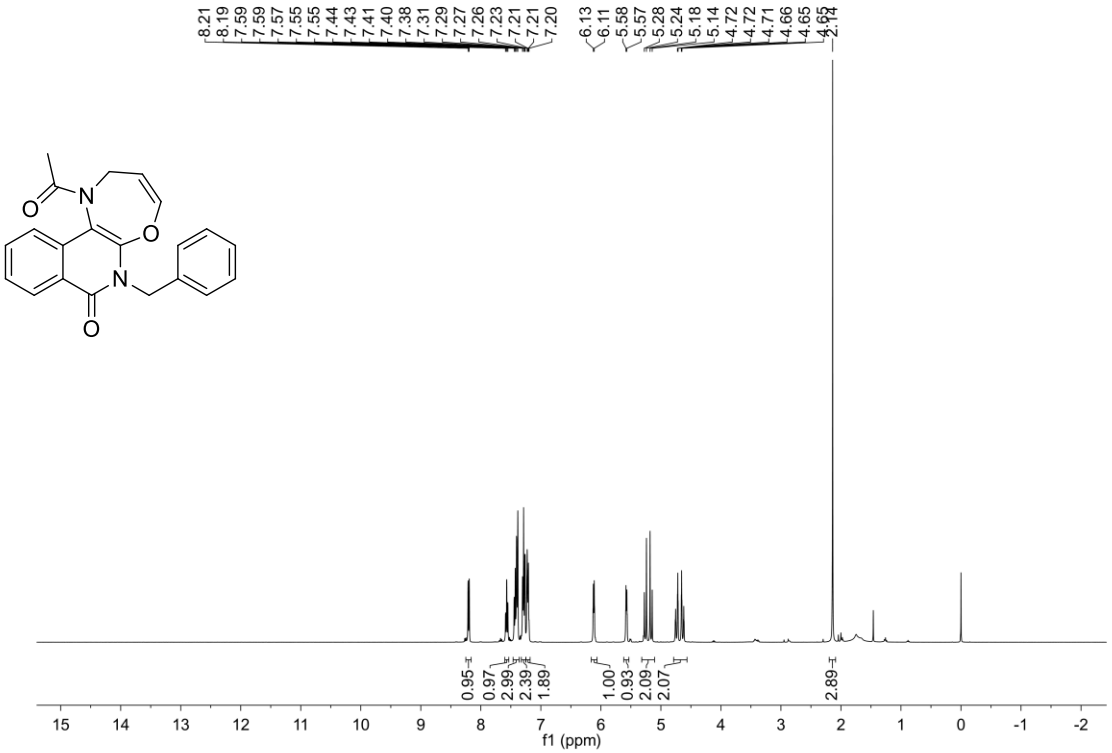
Compound **9**{*6,4*}

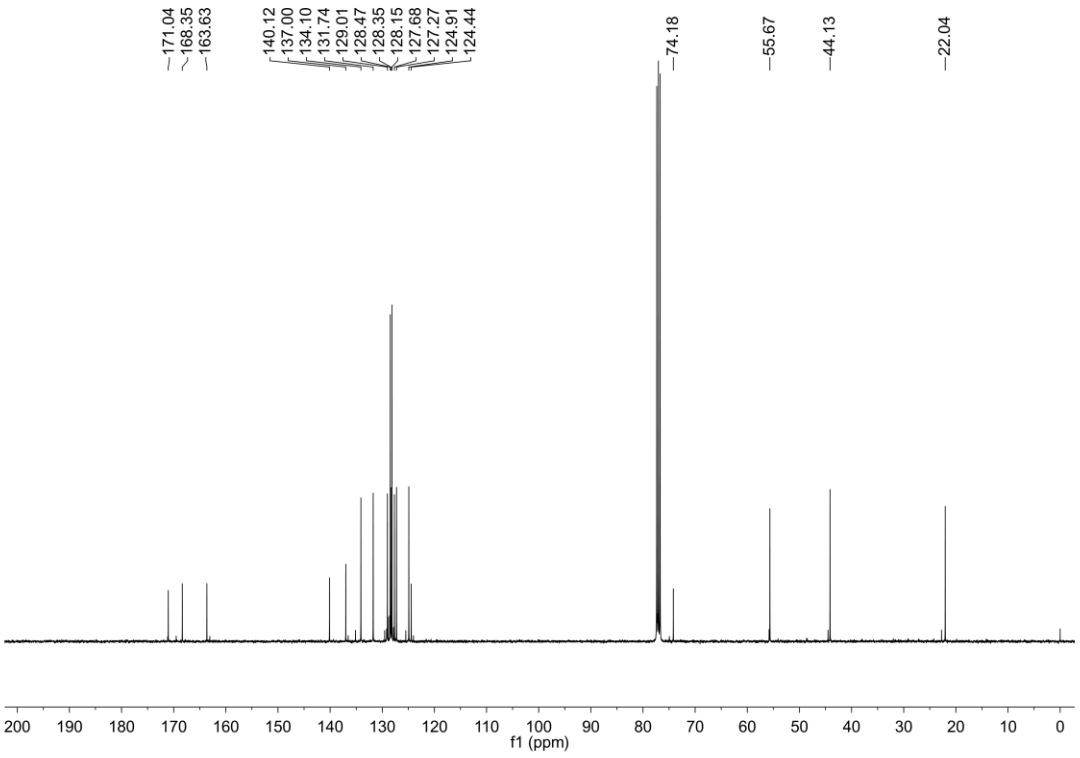




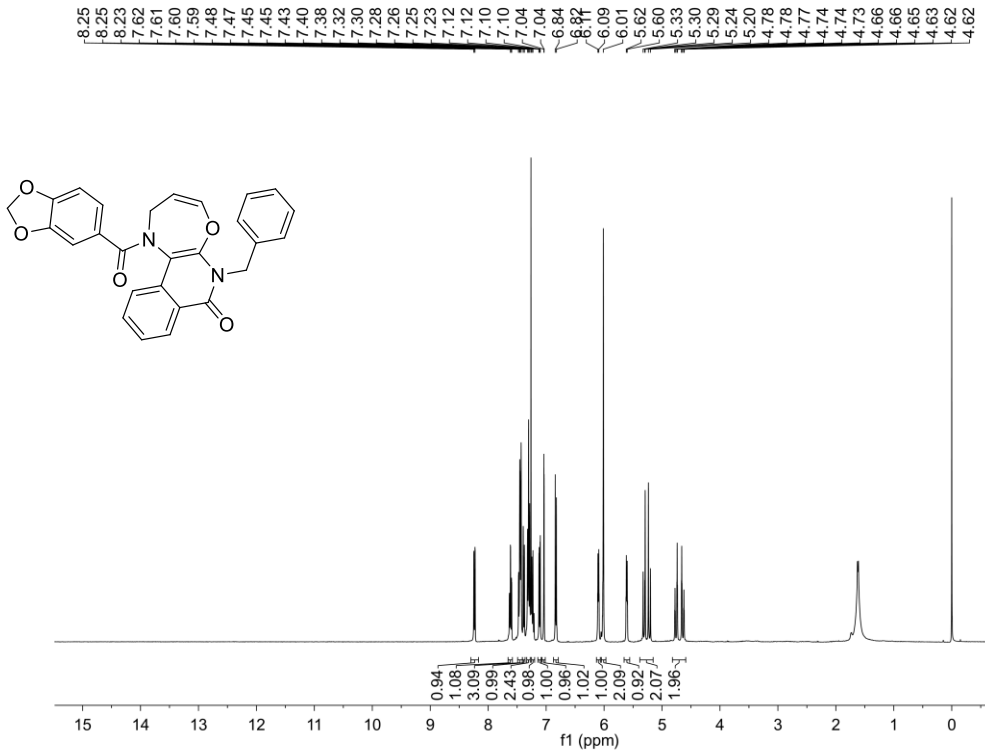

134.35
130.99
130.54
129.22
128.62
128.51
126.94
126.91
125.38
57.18
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

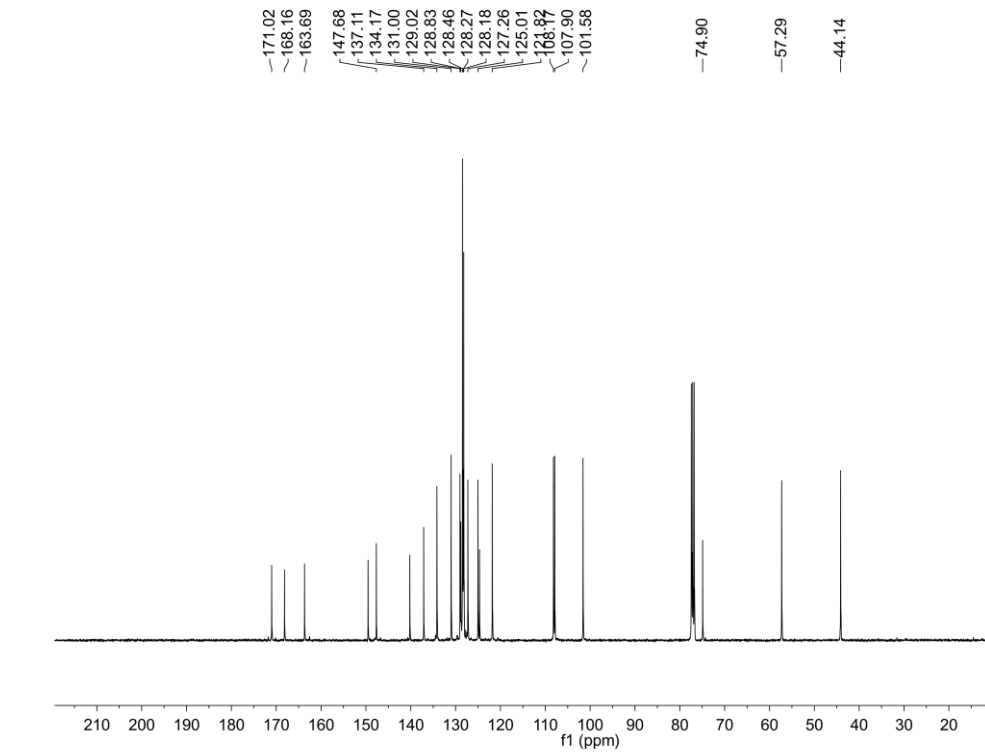
Compound **9**{*7,1*}



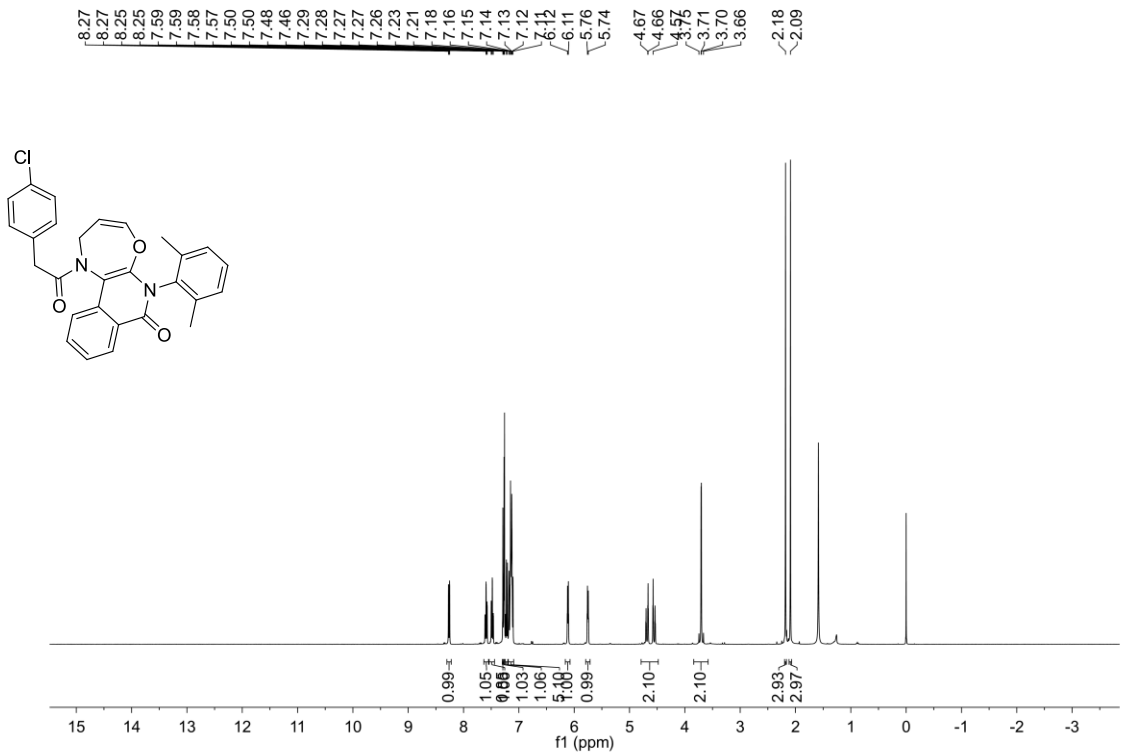


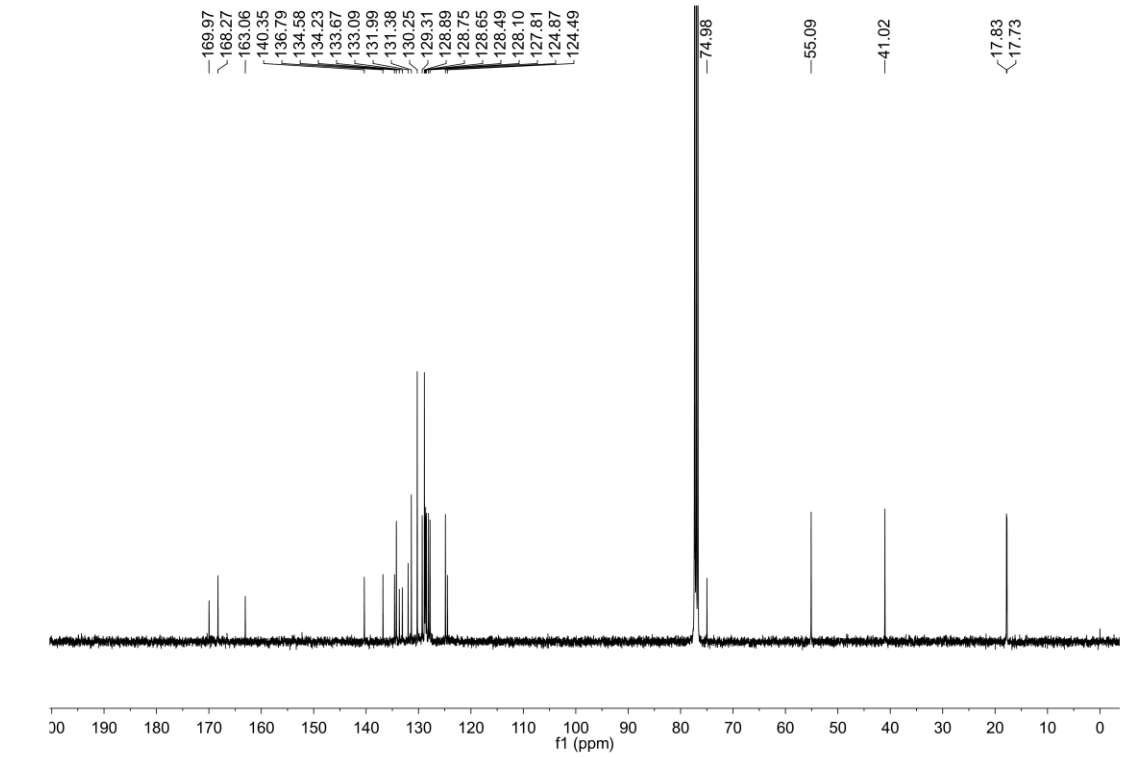
Compound **9**{*8,1*}



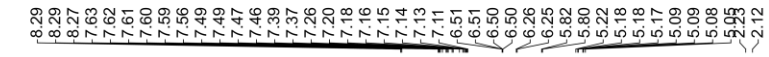


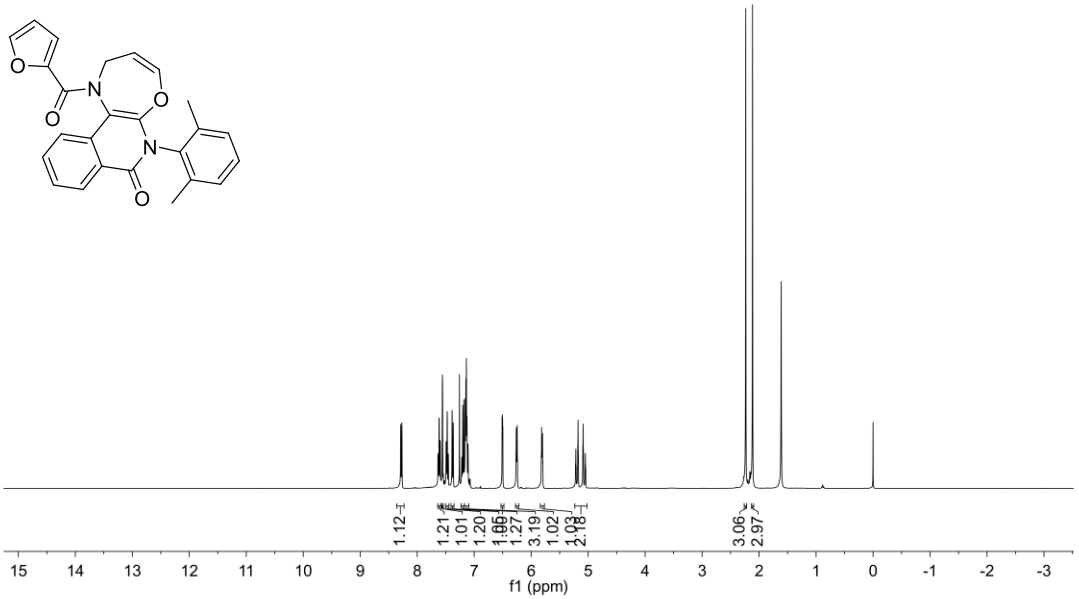
Compound **9**{*9,5*}

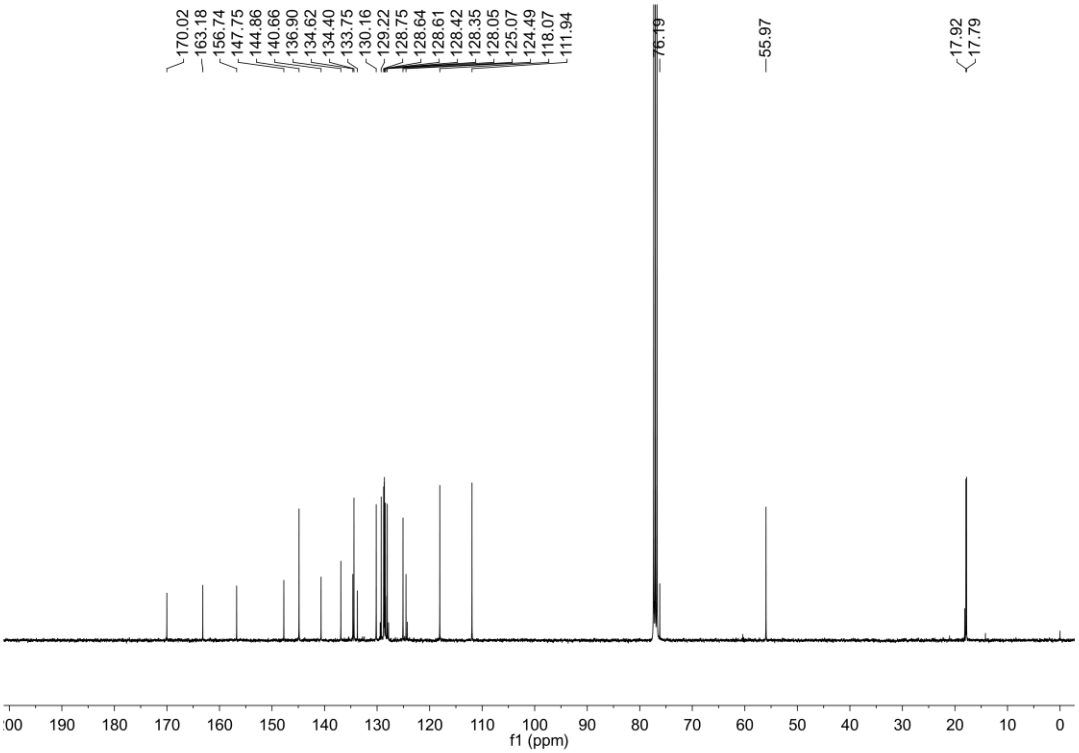




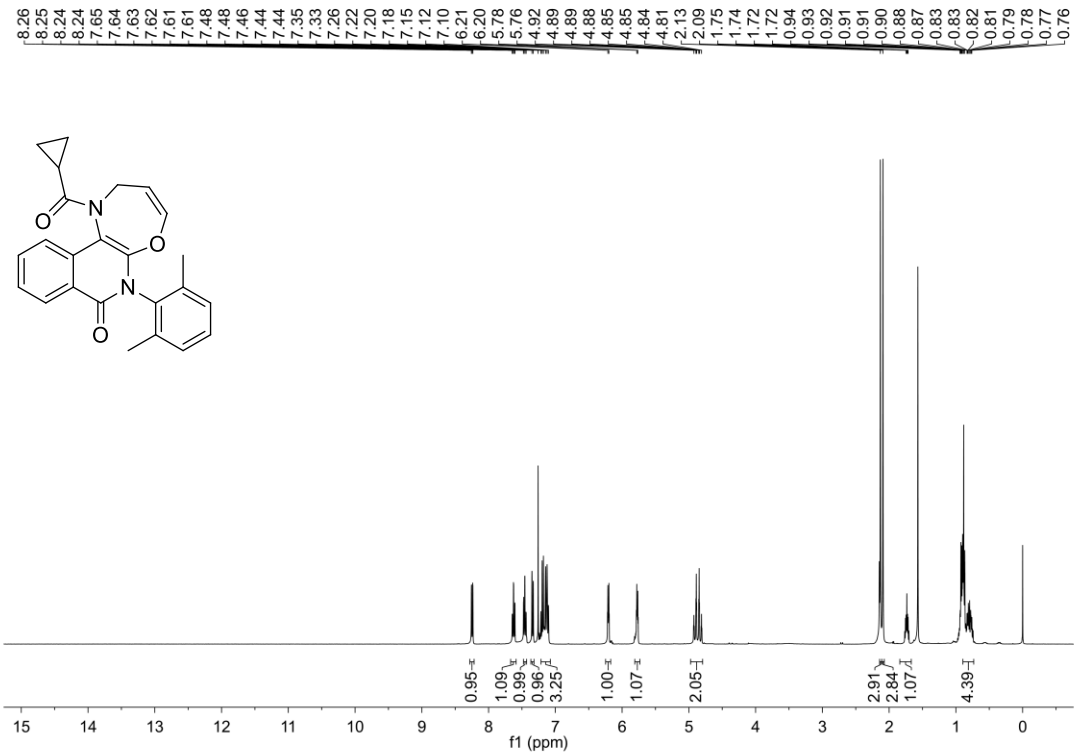
Compound **9**{*10,5*}

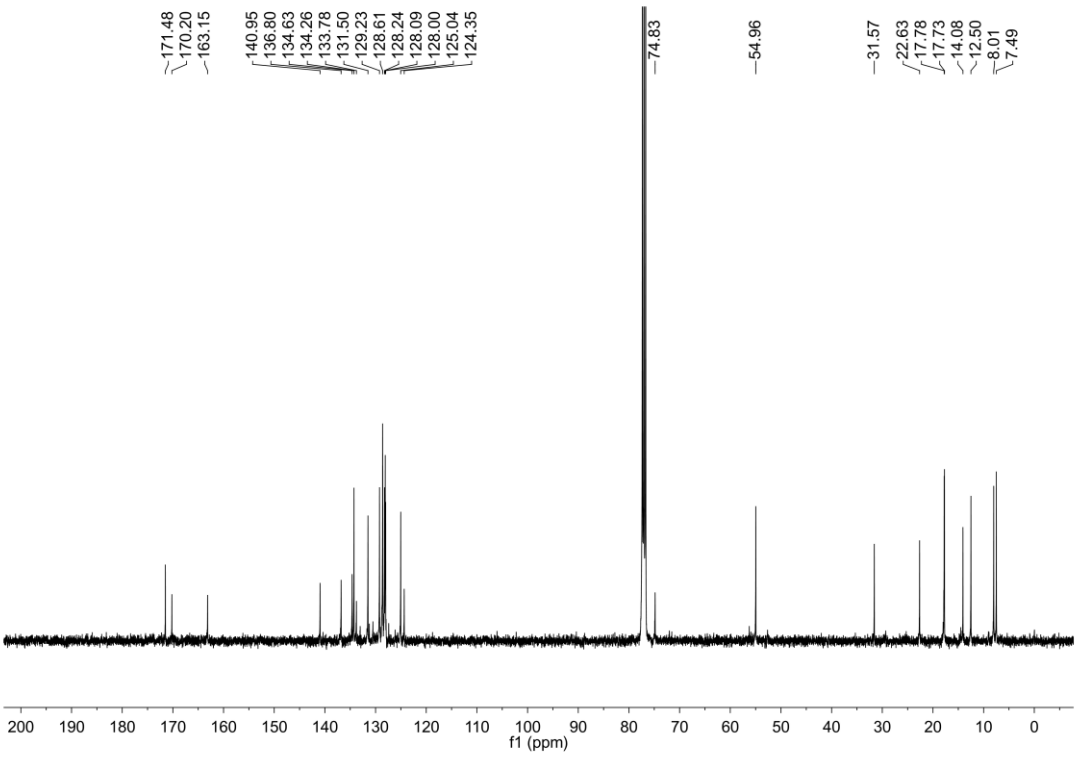




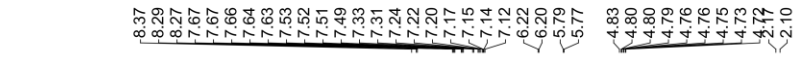


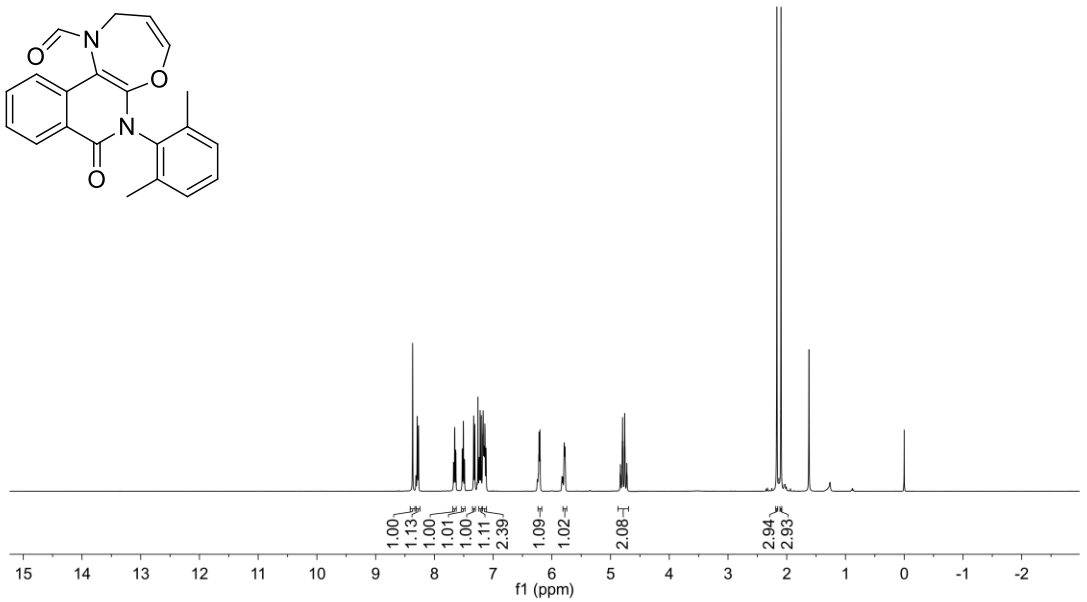
Compound **9**{*11,5*}

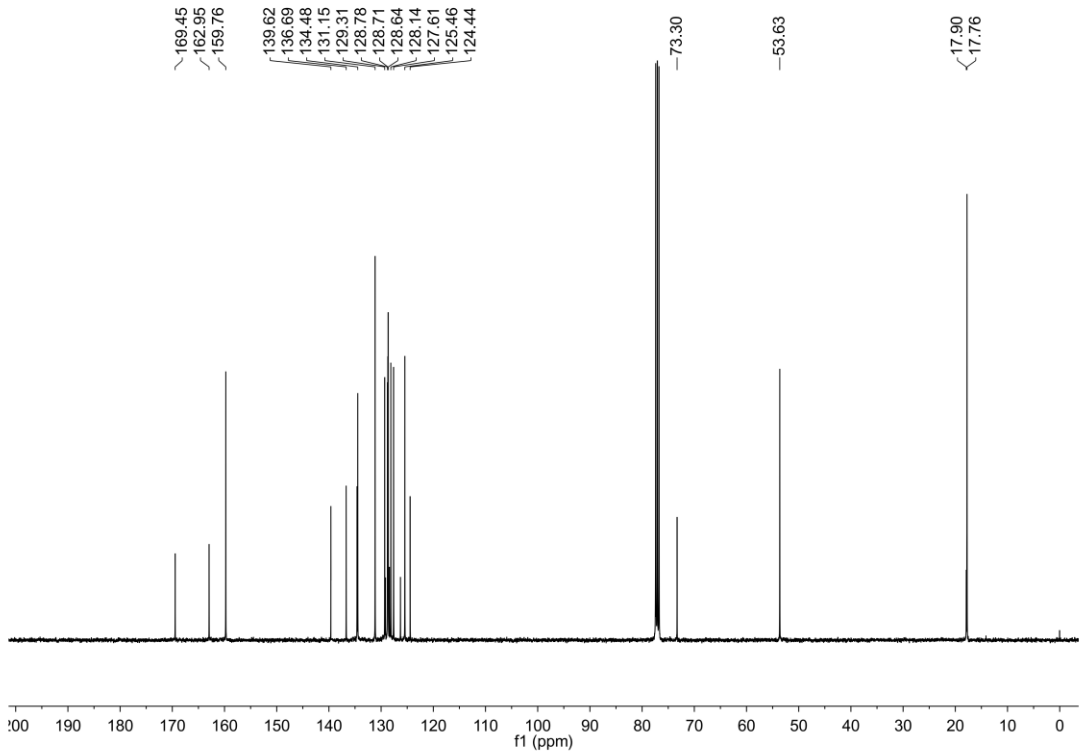




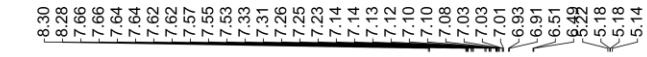
Compound **9**{*12,5*}

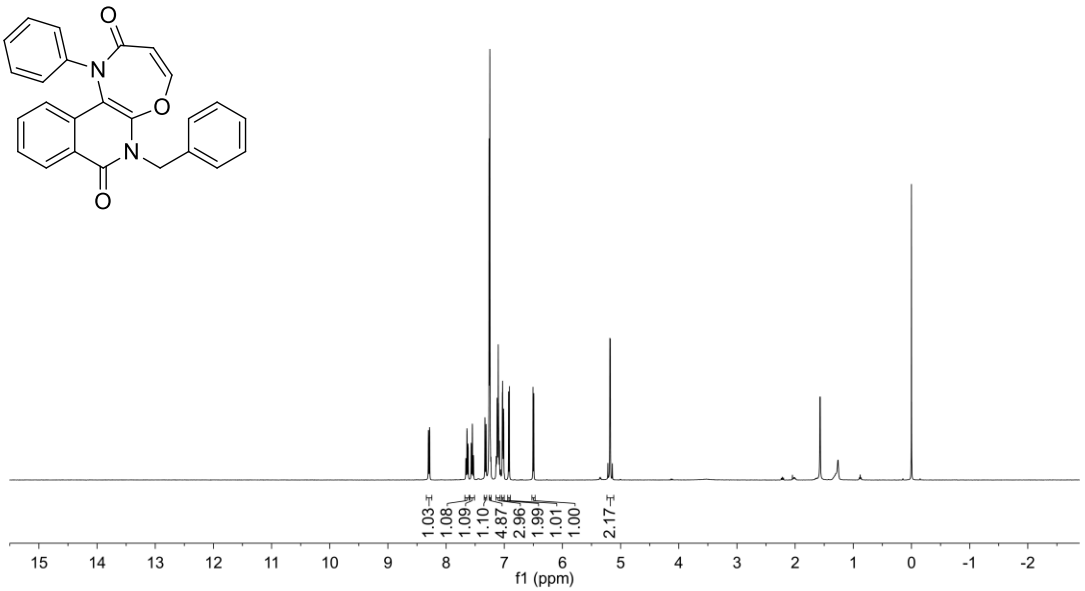


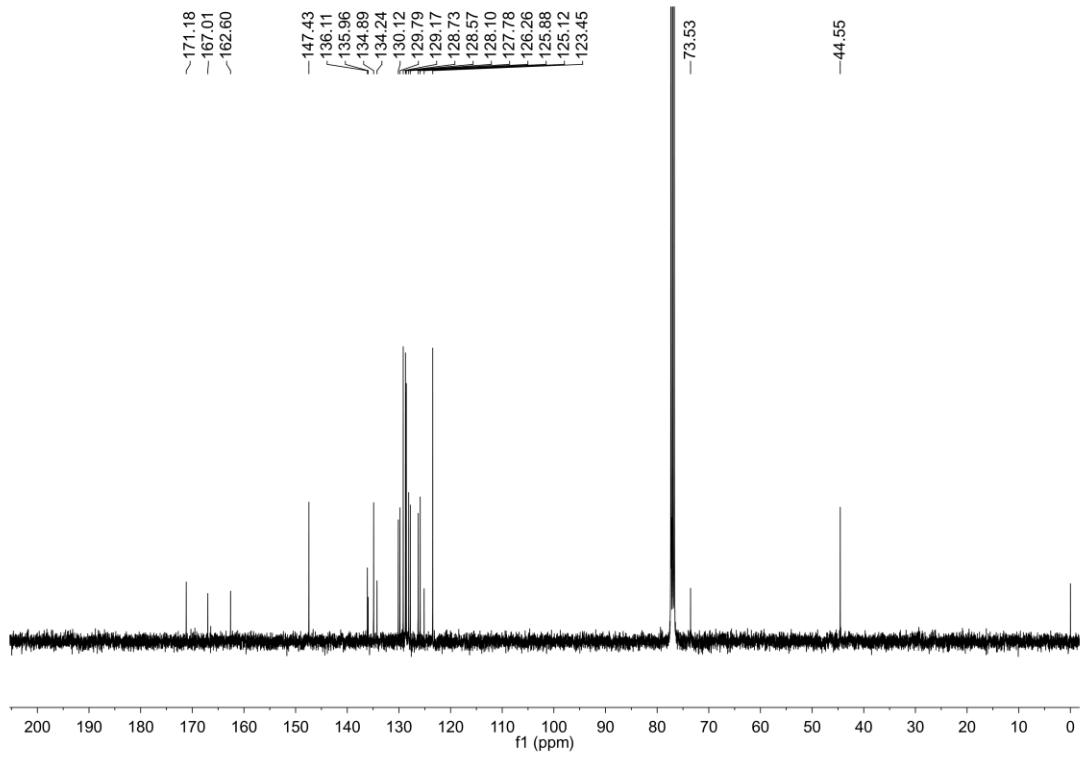


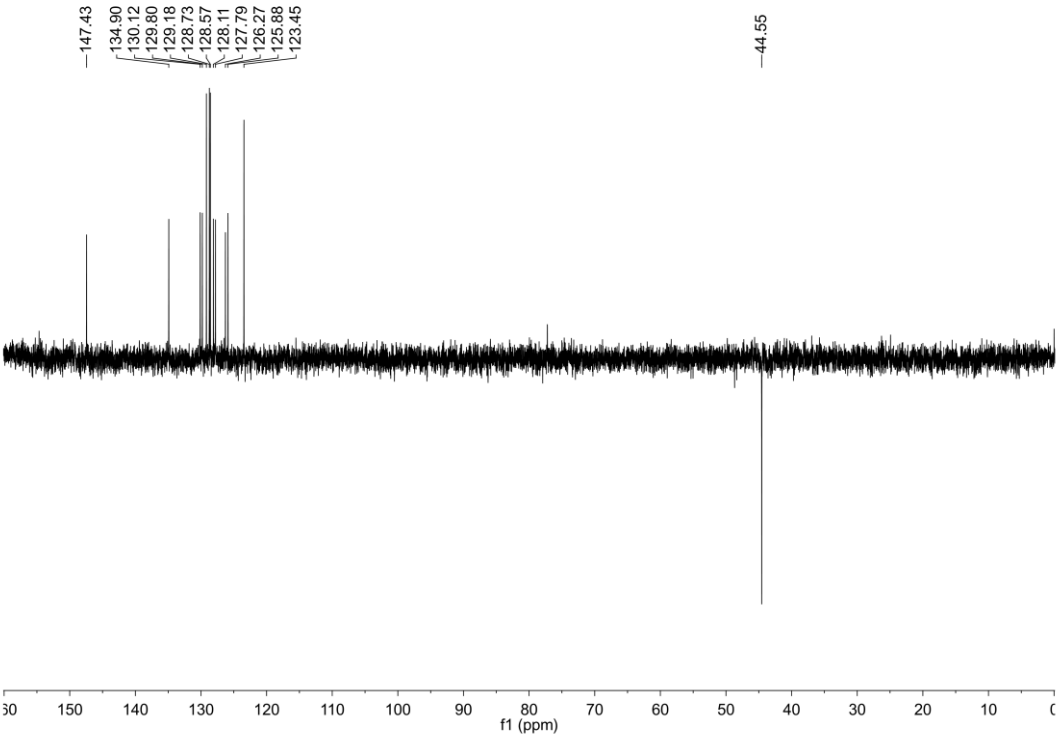


Compound **11**{*1,1,13*}





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127.79
126.27
125.88
123.45
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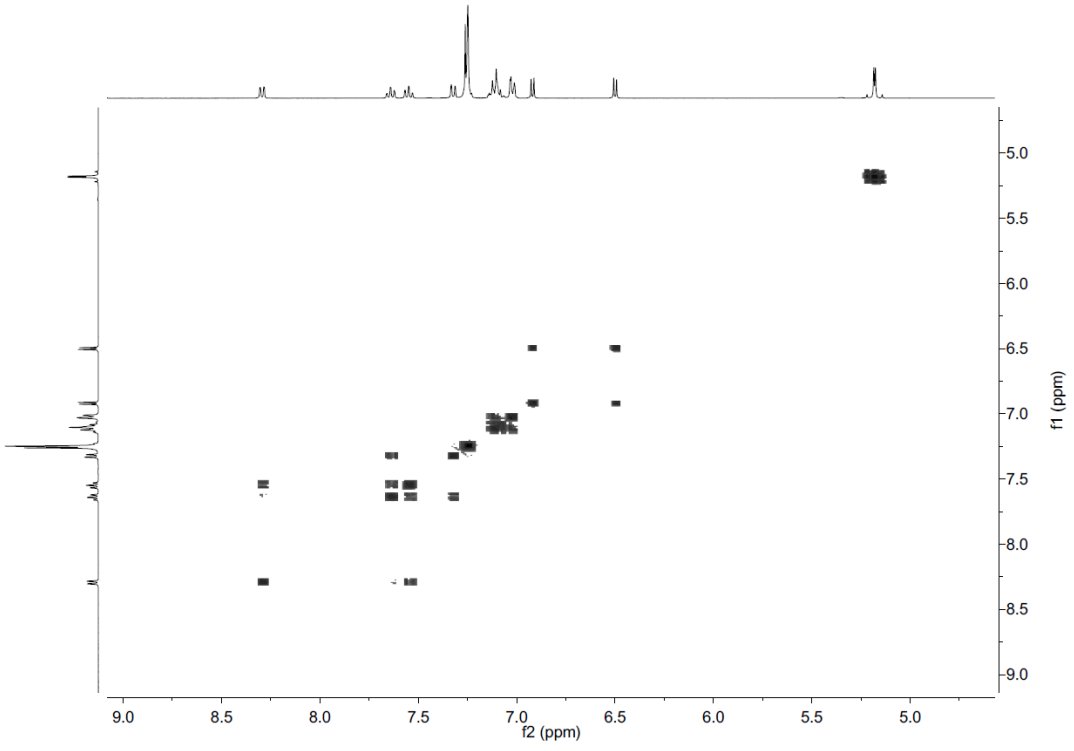
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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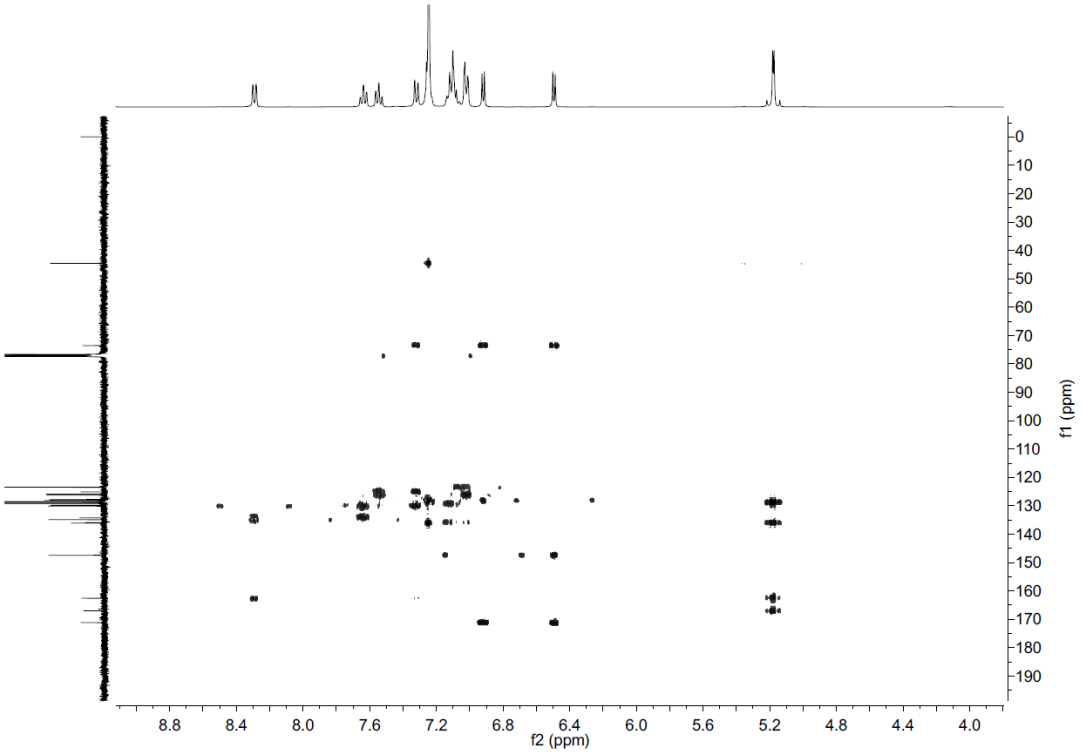
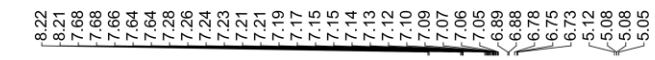
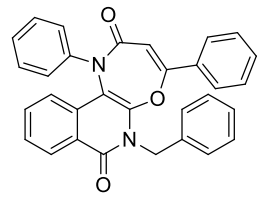
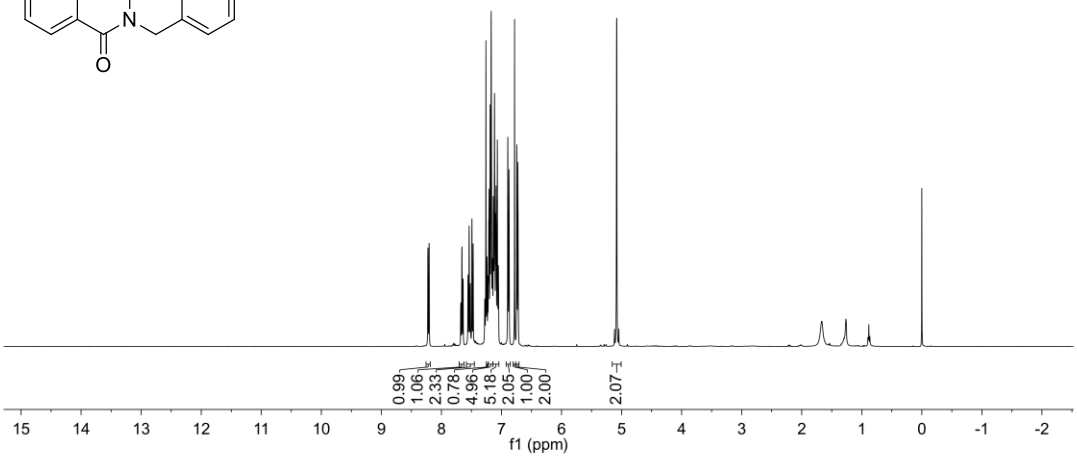
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f2 (ppm)

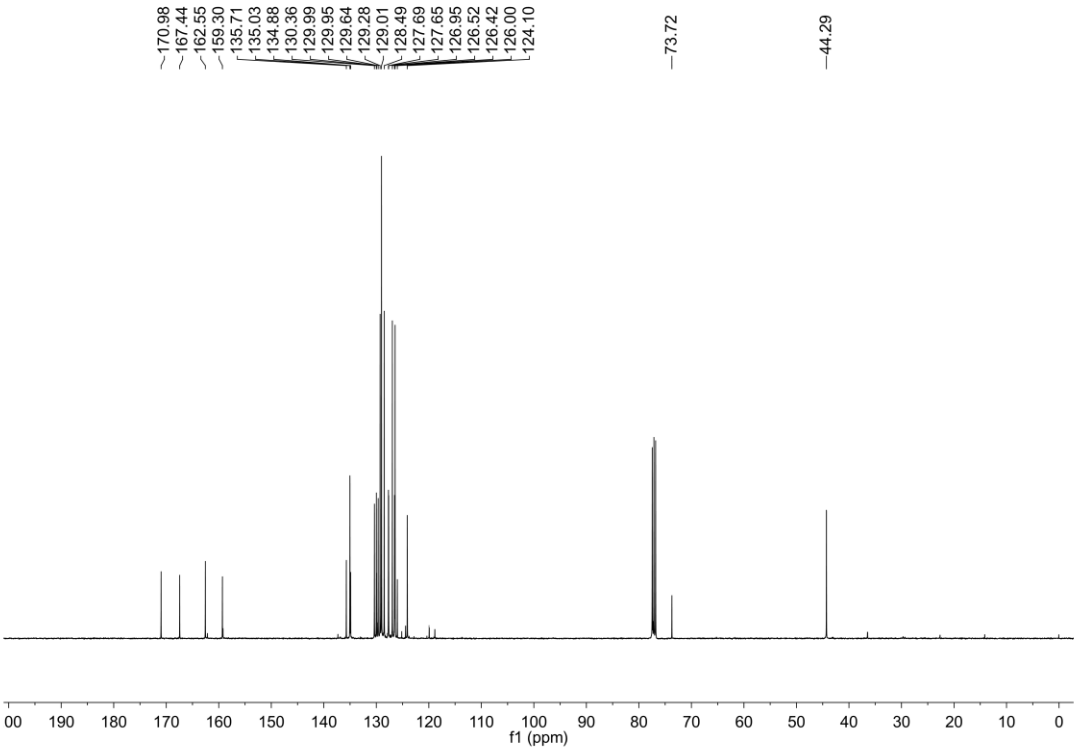

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
f2 (ppm)

Compound **11**{*1,1,14*}

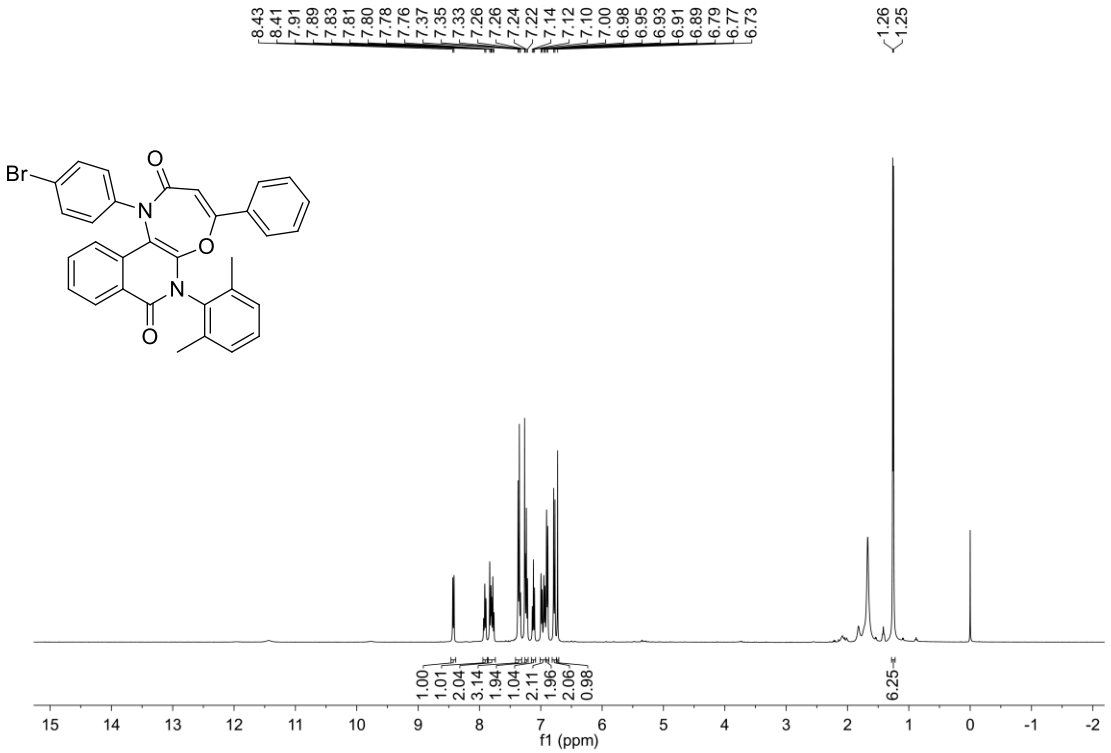


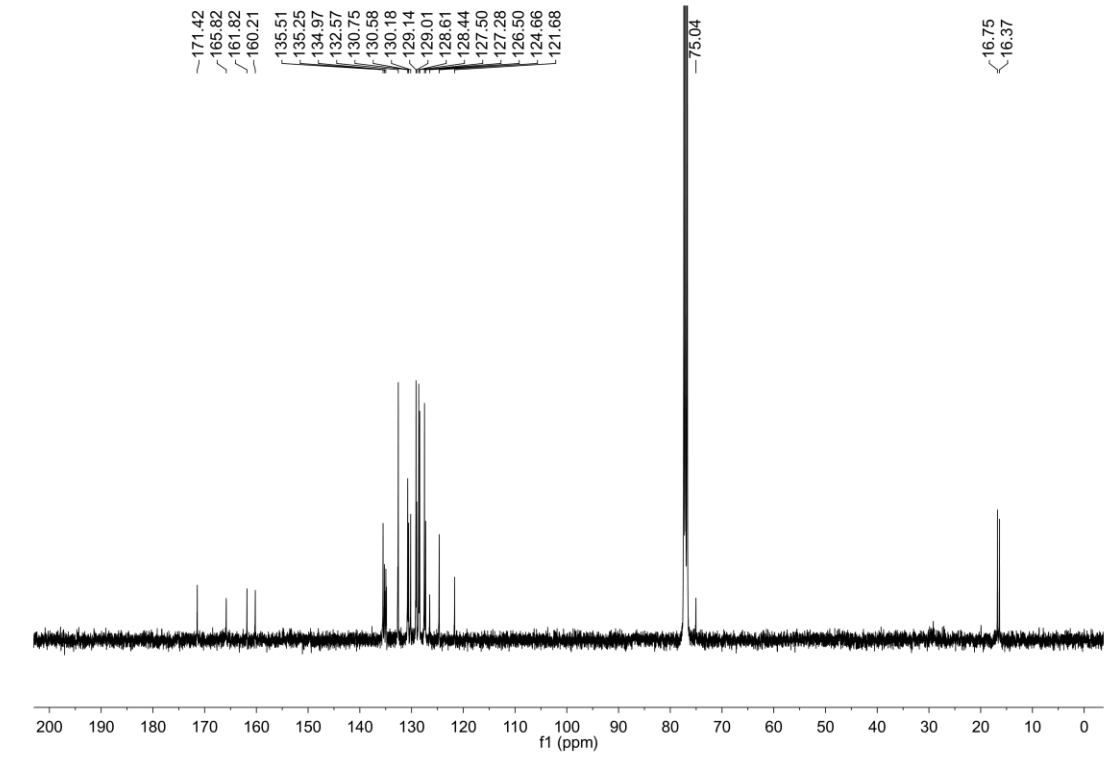




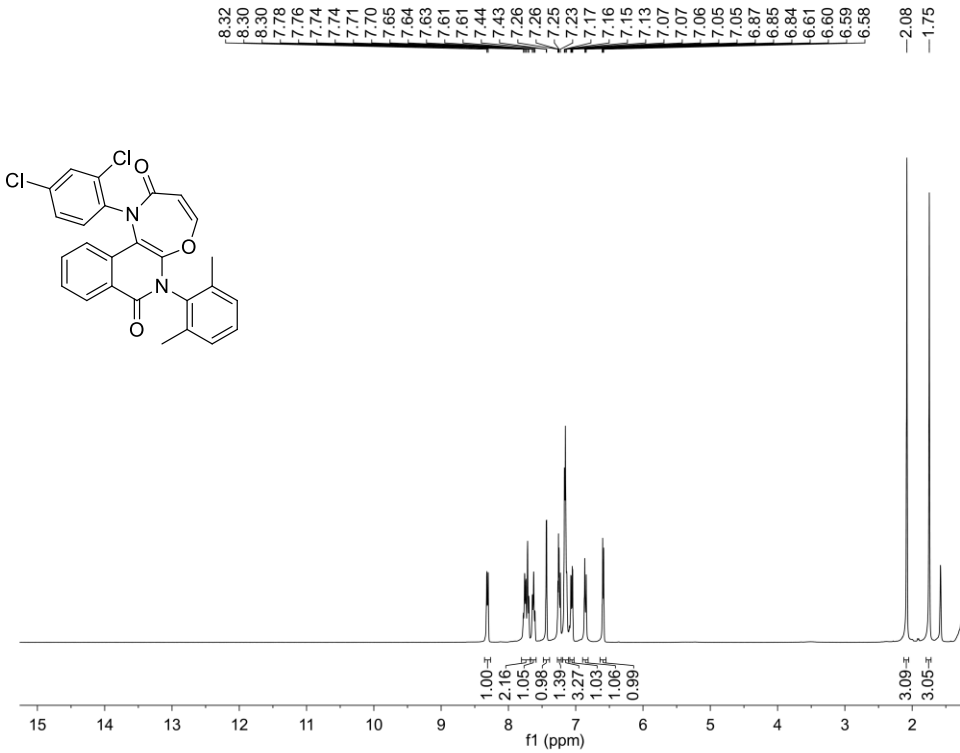


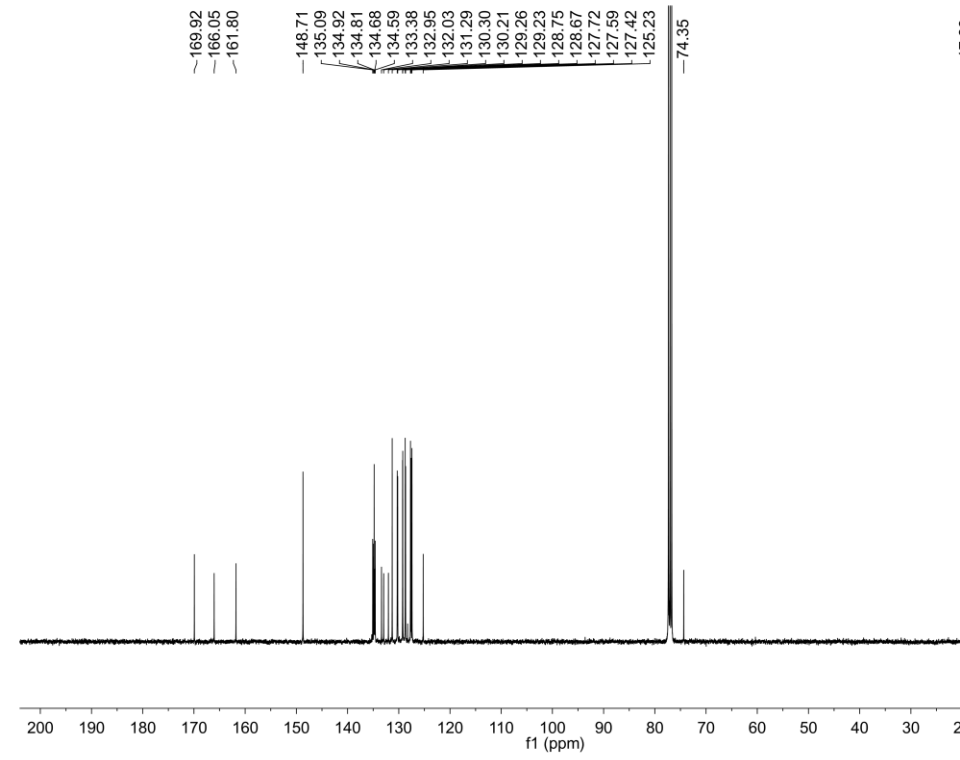
Compound **11**{*3,5,14*}



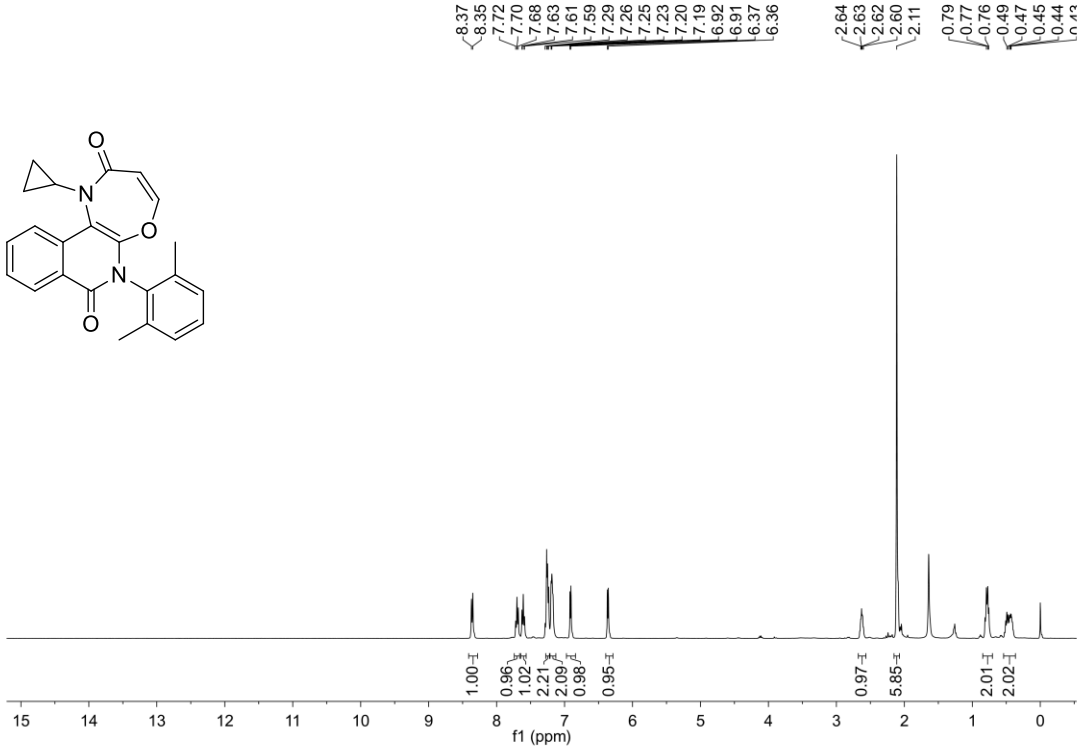


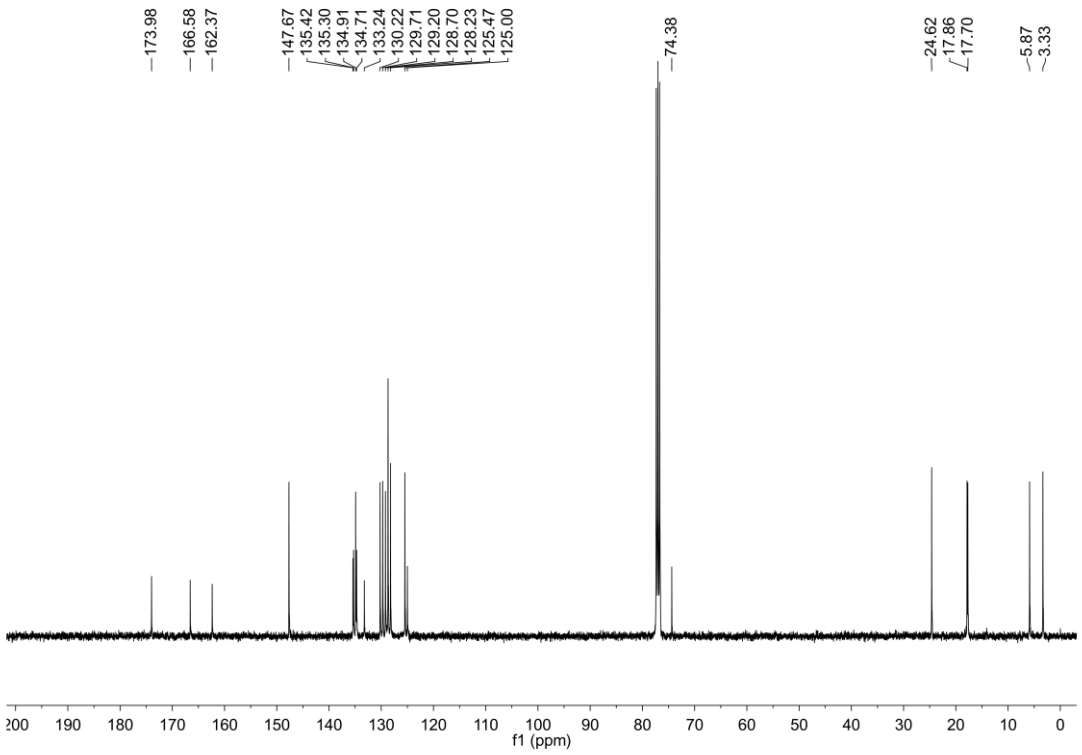
Compound **11**{*9,5,13*}

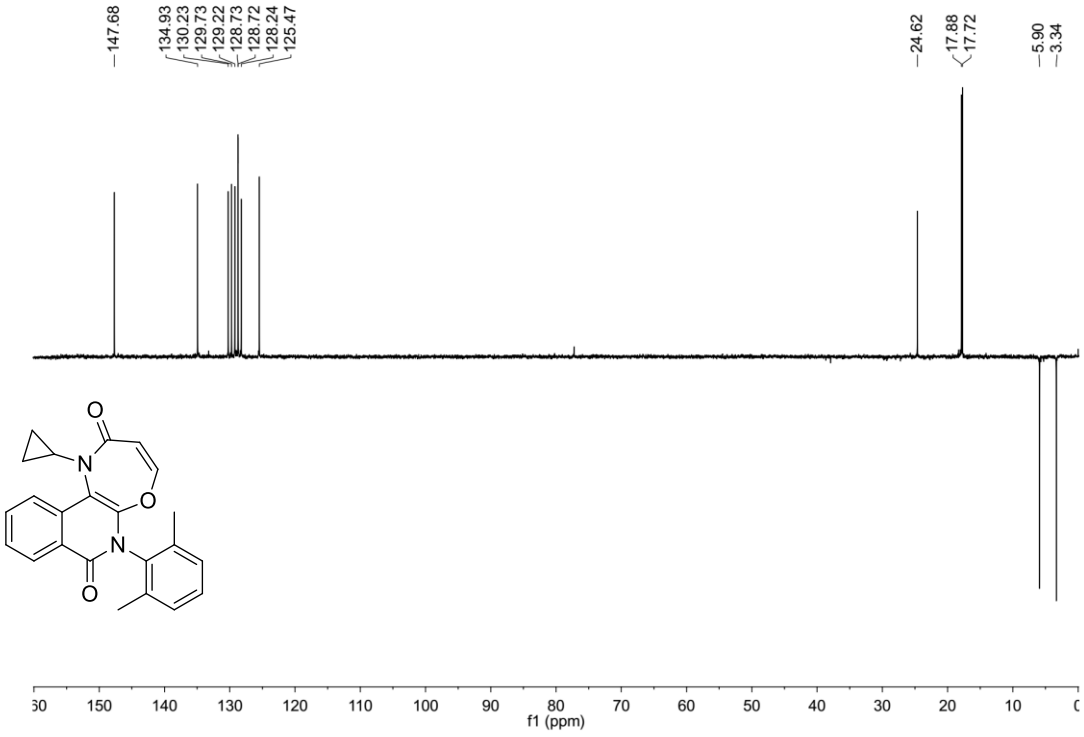


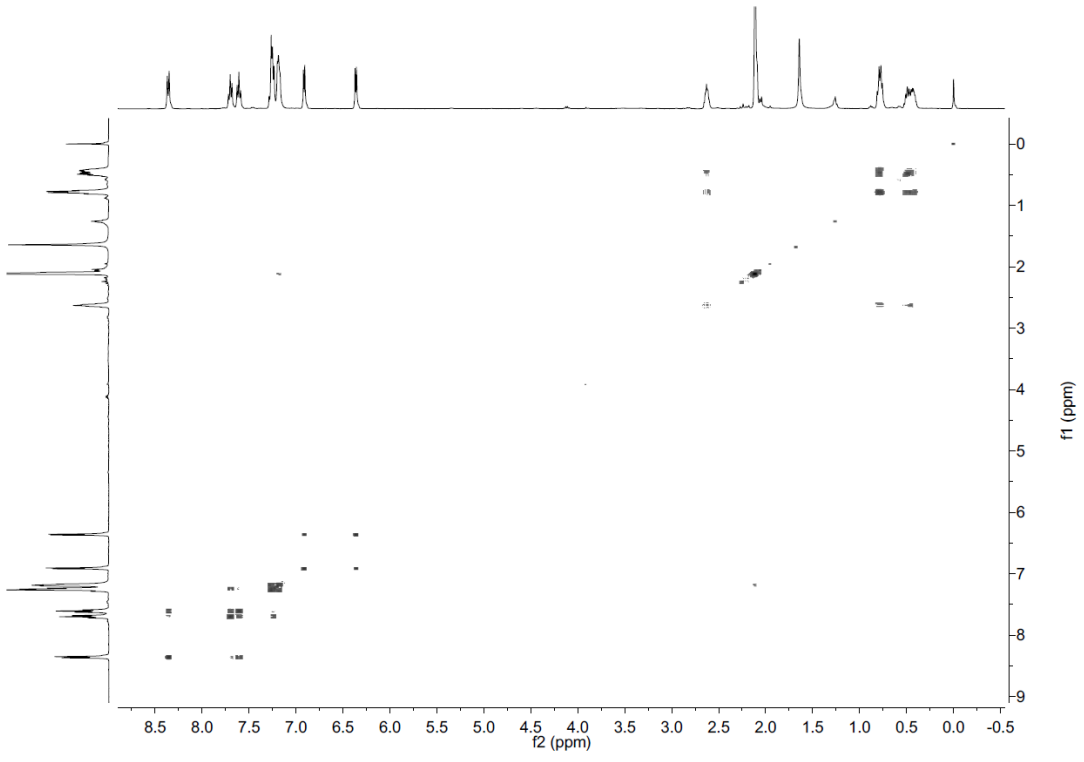


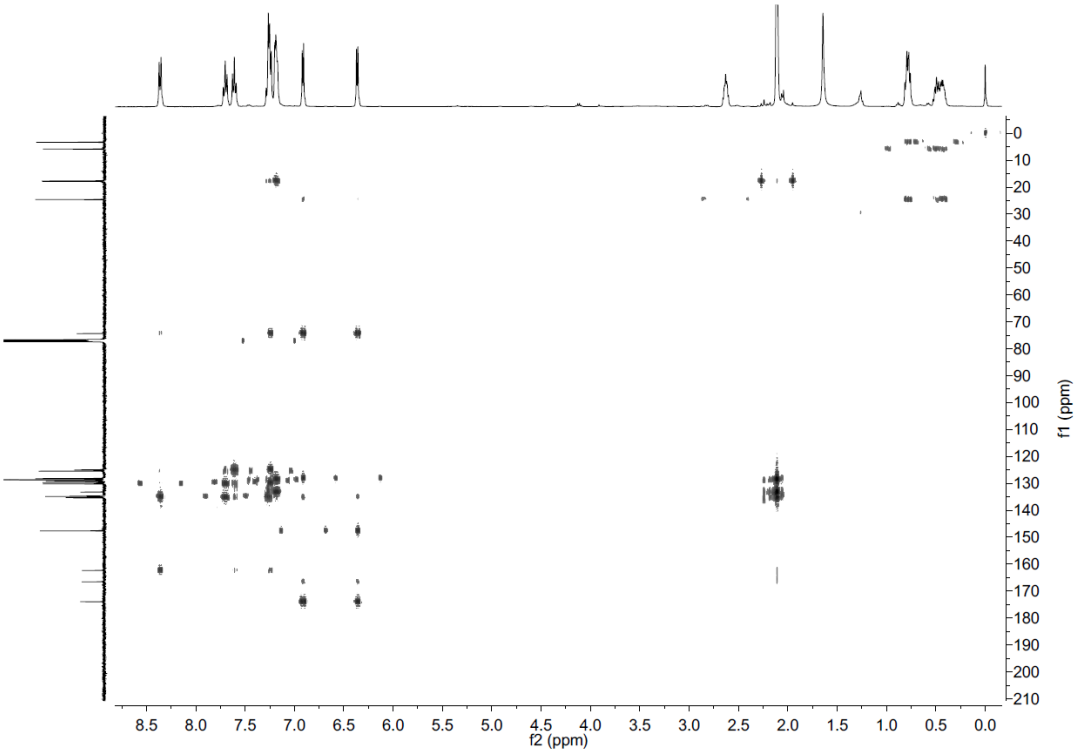
Compound **11**{*10,5,13*}



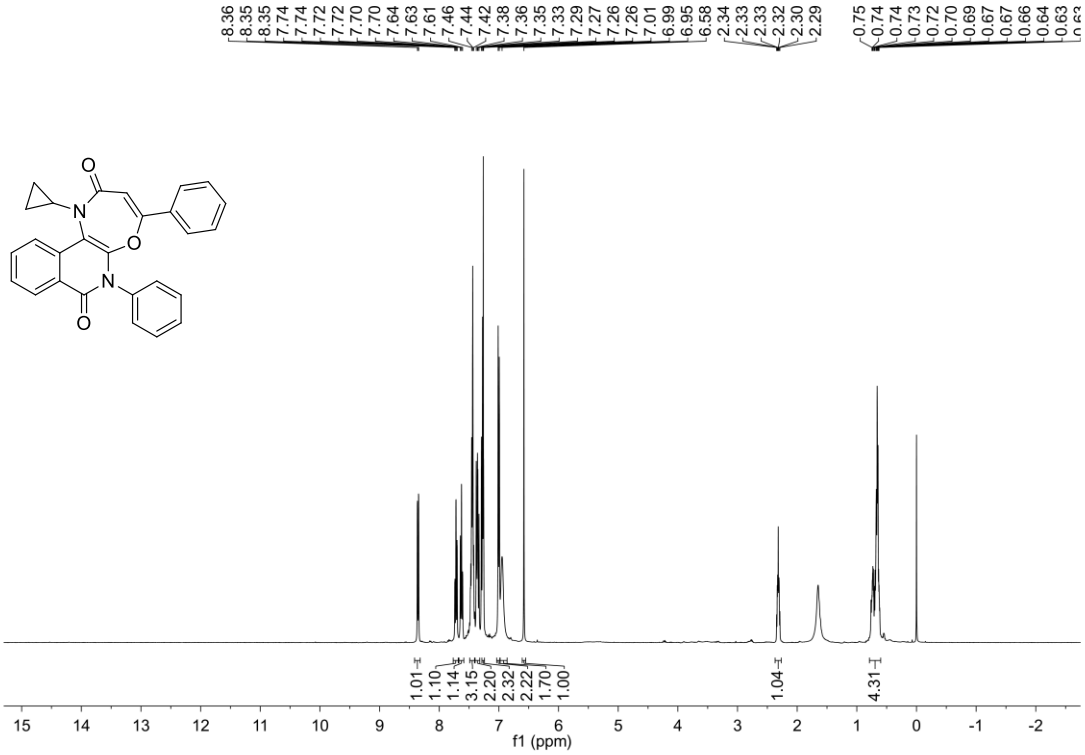


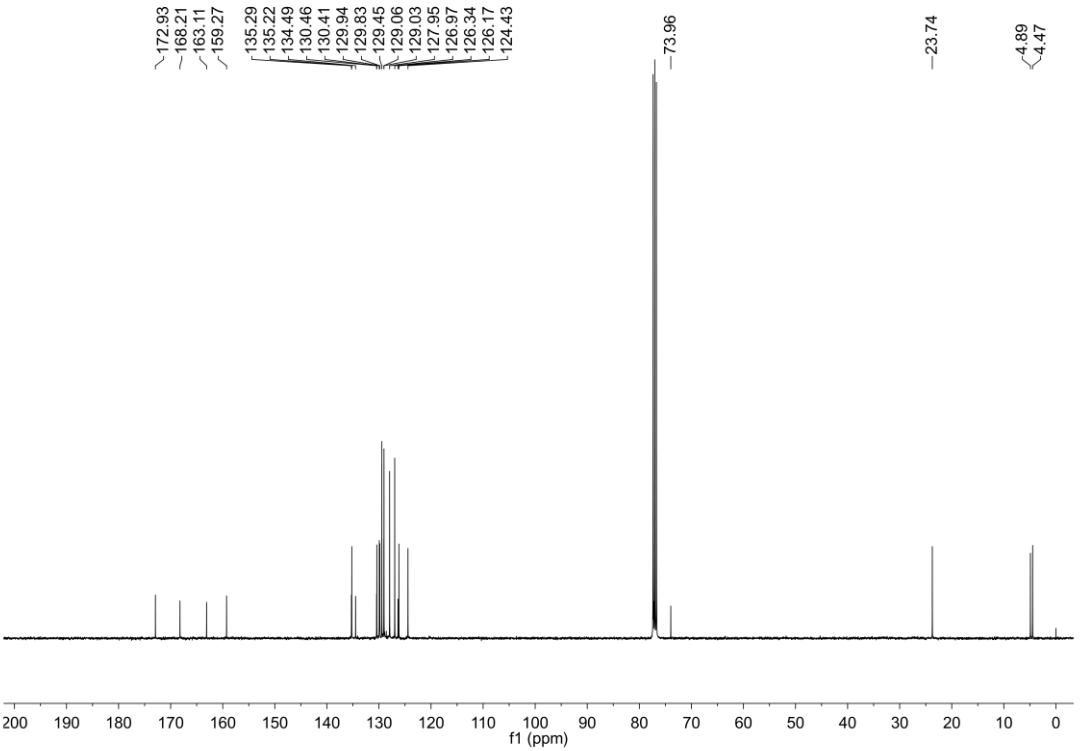

147.68
134.93
130.23
129.73
129.22
128.73
128.72
128.24
125.47
24.62
17.88
17.72
5.90
3.34
O
N
O
N
O
f1 (ppm)


f2 (ppm)
f1 (ppm)


f1 (ppm)
f2 (ppm)

Compound **11**{*10,4,14*}





Compound **11**{*4,5,13*}