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Ethanol Initiated Titanocene Lewis Acid Catalyzed Diversity- oriented Synthesis of Quinazoline Derivatives

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1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker EQUINX55 (400 MHz for ^{1}H; 101 MHz for ^{13}C) spectrometer in $CDCl_3$. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ = 0) and ^{1}H NMR chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CDCl_3$ at 7.26 ppm) unless otherwise noted. The data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), and coupling constant in Hz. For ^{13}C NMR, $CDCl_3$ was used as internal standard (δ = 77.0) and spectra were obtained with complete proton decoupling. Infrared (IR) spectra were obtained using a Thermo Electron Nicolet 380 FT-IR spectrometer and reported as wavenumbers (cm^{-1}). Column chromatography was performed on silica gel (230-400 mesh) and analytical thin layer chromatography was carried out using 250 μm commercial silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance and stained with an iodine vapor.

2. Typical procedures for synthesis of quinazolinones

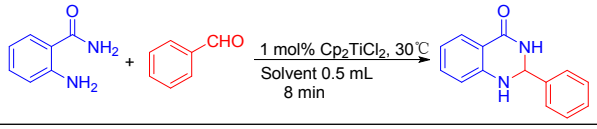
A 10 mL test tube, equipped with a magnetic stirrer and a septum, was charged with ethanol (0.5 mL), benzaldehyde (1.0 mmol), and anthralinamide (1.0 mmol), in one portion. Cp_2TiCl_2 (0.01mmol) was added at 30 °C and stirred until the reaction was completed as indicated by TLC. Upon completion of the reaction, the reaction mixture was quenched with distilled water (5.0 mL). The aqueous phase was extracted with ether (3×5 mL), dried over Na_2SO_4 and concentrated in vacuo to give desired products. The corresponding solid products were obtained through column chromatography by using 100−200 mesh silica gels.

3 Screening of solvent for synthesis of quinazolinones

To further investigate the effect of solvents, next we examined our reaction in different solvent systems as show in Table s1. The catalytic activity of Cp_2TiCl_2 in the reaction of anthranilamide and benzaldehyde was greatly influenced by solvents as show in Table s1. At first, non-polar solvent *n*-hexane was evaluated, we can found Cp_2TiCl_2 almost inert in *n*-hexane only obtained 20% yield (entry 1). CH_2Cl_2, THF and $PhCH_3$ can slightly accelerated Cp_2TiCl_2 in this reaction obtained 40%, 57 % and 45% yields respectively (entries 2-4). More polar solvent such as CH_3CN, DMF and DMSO were obviously accelerated Cp_2TiCl_2 in this reaction obtained 43%, 40% and 45% yields respectively (entries 5-7). To our surprise, when employing MeOH as solvent, the condensation reaction accelerated dramatically and furnished quinazoline in 87% yield a little lower than EtOH (entries 8 and 9). According to above result, we found that alcohols are a kind of effective solvent in promoting Cp_2TiCl_2 catalyzes the reaction of anthranilamide and *p*-anisaldehyde. In order to prove whether the protons and hydrogen-bonding promote the

reaction, water as the solvent was studied. However, only 6% yield was detected (entry10). The result indicates that neither protons nor hydrogen-bonding interaction is responsible for the catalytic activity of Cp_2TiCl_2.

Table s1, Screening of solvent for synthesis of quinazolinones

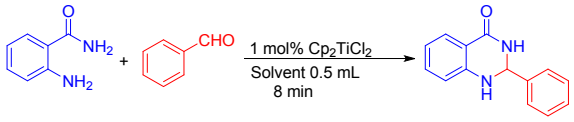


Entry	Solvent	Yield(%)[b]
1	*n*-hexnane	20
2	CH_2Cl_2	40
3	THF	52
4	$PhCH_3$	45
5	CH_3CN	43
6	DMF	40
7	DMSO	45
8	MeOH	87
9	EtOH	97
10	H_2O	6

[a]Reaction conditions: anthranilamide (1 mmol), benzaldehyde (1 mmol), catalyst 0.01mmol(1 mol %) and ethanol (0.5 mL) [b]Isolated yields.

4. Screening of temperature for synthesis of quinazolinones

Table s2. Screening of temperature



Entry	Temperature (℃)	Yield(%)[a]
1	30	97
2	40	90
3	50	87

[a]Yield of isolated product

In order to further optimize conditions, we checked the effect of temperature on the progress of the reaction, the results of these experiments are shown in Table s2.The model reaction was tested at different temperatures like 30℃, 40℃ and 50℃. According to the results in table 3 we can seen that 30℃ is the best reaction temperature, when raise the temperature, the yield did not increase.

5. NMR experiments

The interplay of Cp_2TiCl_2 and ethanol was investigated by ^1H NMR in mechanistic scenario. A general procedure was as follows: Cp_2TiCl_2 (10 μmol) was placed in CD_3OD (0.5mL) and the solution was detected immediately as observed by ^1H NMR spectroscopy. The mixture was allowed to stand for 1 h and was conducted by ^1H NMR spectroscopyas confirmed by ^1H NMR spectroscopy. After 1.0 equiv. of aniline was added in the above solution, one new Cp protons singlet appeared at δ 6.25 ppm. Titanocene chloride (**I**)was consumed gradually in CD_3OD in the presence of base and formed new titanocene species $Cp_2TiCl(OCH_3)$ (**III**), As the singlet at 6.25 ppm increased, one new Cp protons singlet $Cp_2Ti\ (OCH_2CH_3)_2$ (**II**)appeared at δ 6.34 ppm

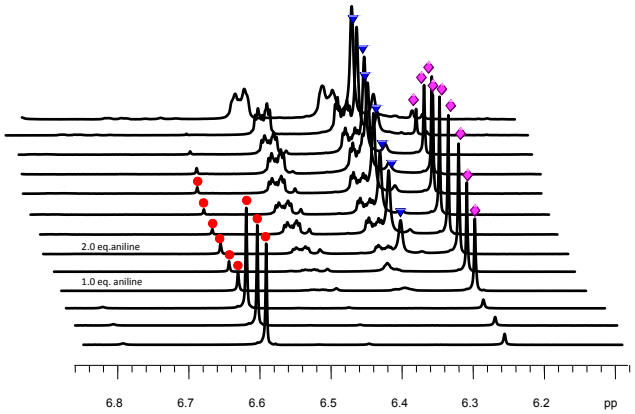


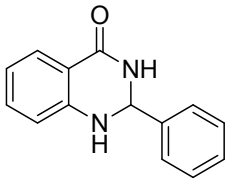
Fig. s1 Partial 400MHz ^1H NMR spectra (CD_3CD_2OD) of a solution containing Cp_2TiCl_2 with addition of aniline. ●6.59 ppm **I** [Cp_2TiCl_2]; ◆ 6.25 ppm **III** [$Cp_2TiCl\ (OCH_2CH_3)$]; ▼6.34 ppm **II** [$Cp_2Ti(OCH_2CH_3)_2$]

6. Spectrometric analysis

Mass spectrometric measurements were performed in aBruker EVOQ tandem mass spectrometer. As a general rule, scan mode was Q1MS, positiveion mode (otherwise indicated), tube lens potential was optimized in each case or for aseries of measurements that required equal conditions, a time span of 1 minute was used to collectspectra and average them. The tube lens potential was adjusted in a way that the most interest ions had almost no attenuation (around 70 V).

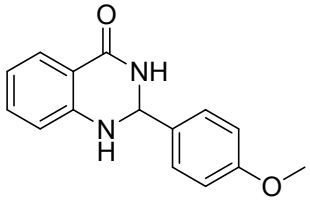
For CID experiments, the cations of interest were mass-selected using the first quadrupole (Q1) and interacted with argon in the T-wave collision cell at variable collision energies (Elaboratory= 3-15 eV). The ionic products of fragmentation were analyzed with the time-of-flight analyzer. The isolation width was 1Da and the most abundant isotopomer was mass-selected in the first quadrupole analyzer.

7. Characterization data of products



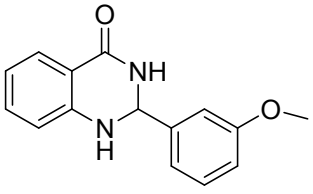
3a

2-Phenyl-2,3-dihydroquinazolin-4(1H)-one(3a), white solid. Yield: (96%).^{1}H NMR（400MHz，DMSO-d_6）δ：8.30（s，1H），7.64（d，J=7.6Hz，1H），7.51（d，J=7.2Hz，2H），7.40（s，3H），7.30-7.20（m，1H），7.12（s，1H），6.77（d，J=8.1Hz，1H），6.69（s，1H），5.77（s，1H）；^{13}C NMR（101MHz，DMSO-d_6）δ：165.50，149.76，143.52，135.20，130.34，130.21，129.25，128.75，119.01，116.85，116.30，68.47。



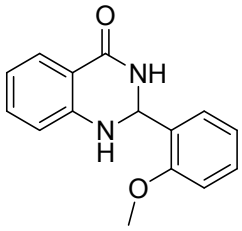
3b

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3b).white solid. Yield: (97%).^{1}H NMR（400MHz，DMSO-d_6）δ：8.19（s，1H），7.62（d，J=7.6Hz，1H），7.43（d，J=8.6Hz，2H），7.25（s，1H），7.02（s，1H），6.96（s，2H），6.75（d，J=8.1Hz，1H），6.68（s，1H），5.72（s，1H），3.75（s，3H）；^{13}C NMR（101MHz，DMSO-d_6）δ：165.59，161.32，149.90，135.36，135.12，130.10，129.23，118.97，116.89，116.30，115.52，68.20，57.06。



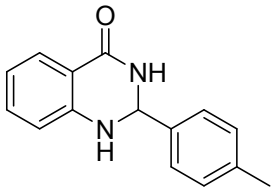
3c

2-(3-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3c).white solid. Yield: (96%).^{1}H NMR (400 MHz, DMSO) δ 8.30 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.29 (s, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 7.10 – 7.01 (m, 2H), 6.91 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.67 (s, 1H), 5.72 (s, 1H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.45, 161.10, 149.68, 145.21, 135.21, 131.32, 129.22, 120.80, 119.00, 116.85, 116.29, 115.56, 114.44, 68.14, 56.97.



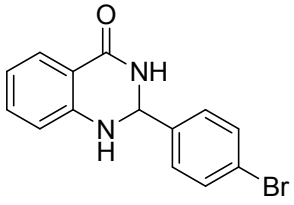
3d

2-(2-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3d).white solid. Yield: (94%).^{1}H NMR (400 MHz, DMSO) δ 8.02 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.22 (dd, *J* = 14.1, 6.6 Hz, 1H), 7.07 – 7.02 (m, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.81 – 6.75 (m, 2H), 6.67 (s, 1H), 6.08 – 5.98 (m, 1H), 3.81 (d, *J* = 18.9 Hz, 3H).^{13}C NMR (101 MHz, DMSO) δ 165.76, 158.24, 149.85, 135.13, 131.51, 130.84, 129.20, 128.75, 122.00, 118.91, 116.57, 116.38, 112.97, 62.86, 57.41.



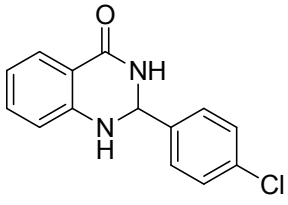
3e

2-(4-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one (3e).white solid. Yield: (95%).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.10 (s, 2H), 6.96 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.57 (s, 1H), 5.61 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.53, 149.79, 140.55, 139.60, 135.14, 130.69, 129.21, 128.67, 118.95, 116.87, 116.29, 68.24, 22.60.



3f

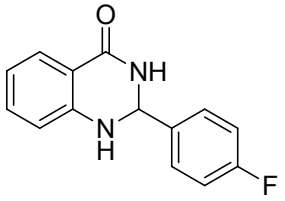
2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (3f).white solid. Yield: (96%).1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.60 (t, J = 7.4 Hz, 3H), 7.44 (d, J = 8.4 Hz, 2H), 7.25 (t, J = 7.7 Hz, ^{1}H), 7.15 (s, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.68 (t, J = 7.5 Hz, 1H), 5.76 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.38, 149.50, 142.98, 135.30, 133.12, 130.96, 129.26, 123.45, 119.19, 116.82, 116.35, 67.68.



3g

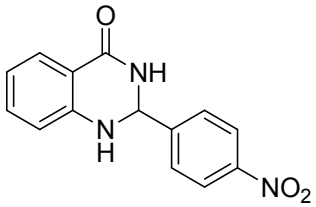
2-(4- chlorphenyl)-2,3-dihydroquinazolin-4(1H)-one (3g).white solid. Yield: (97%).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz,

2H), 7.25 (s, 1H), 7.14 (s, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.68 (s, 1H), 5.77 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.38, 149.53, 142.55, 135.30, 134.86, 130.63, 130.20, 129.25, 119.18, 116.82, 116.35, 67.63.



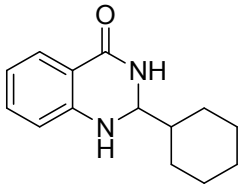
3h

2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3h).white solid. Yield: (98%).^{1}H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.53 (s, 2H), 7.22 (s, 3H), 7.09 (s, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.68 (s, 1H), 5.77 (s, 1H). ^{13}C NMR (101 MHz, DMSO) ^{13}C NMR (101 MHz, DMSO) δ 165.45, 149.67, 139.69, 135.25, 130.96, 130.87, 129.25, 119.15, 117.08, 116.87, 116.33, 67.80.



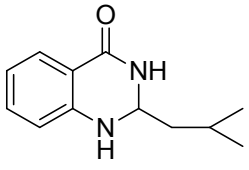
3i

2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (3i). yellow solid. Yield: (99%).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.33 (s, 1H), 7.26 (s, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.69 (s, 1H), 5.91 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.16, 151.21, 149.31, 149.11, 135.46, 129.91, 129.29, 125.47, 119.36, 116.78, 116.43, 67.16.



3j

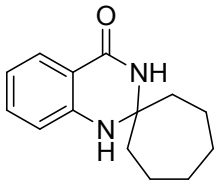
2-cyclohexane-2,3-dihydroquinazolin-4(1H)-one(3j). white solid. Yield: (95%).^{1}H NMR（400MHz，DMSO-d_6）δ：7.87（s，1H），7.55（d，J=7.6Hz，1H），7.19（s，1H），6.74（d，J=8.1Hz，1H），6.60（s，1H），6.54（s，1H），4.44（s，1H），1.70（d，J=10.6Hz，6H），1.11（s，5H）；^{13}C NMR（101MHz，DMSO-d_6）δ：165.58，150.24，134.90，129.11，118.30，116.68，115.96，70.45，44.74，41.63，41.42，41.21，28.88，28.56，27.82，27.50，27.44。



3k

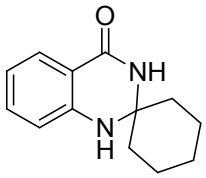
2-methylpropyl-2,3-dihydroquinazolin-4(1H)-one(3k), white solid. Yield: (95%).^{1}H

NMR（400MHz，DMSO-d_6）δ：7.89（s，1H），7.58（d，J=7.4Hz，1H），7.23（s，1H），6.75（d，J=8.1Hz，1H），6.66（s，1H），6.55（s，1H），4.71（s，1H），1.87（s，1H），1.52（s，2H），0.89（d，J=6.5Hz，6H）；^{13}CNMR（101MHz，DMSO-d_6）δ：165.71，150.20，134.90，129.25，118.82，117.10，116.40，64.59，46.16，24.75，24.62，24.35。



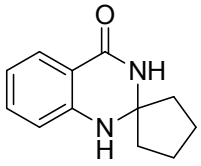
3l

1'H-Spiro [cycloheptane -1,2'-quinazolin]-4'(3'H)-one(3l), white solid. Yield: (96%).^{1}H NMR（400MHz，DMSO-d_6）δ：8.02（s，1H），7.54（d，J=7.7Hz，1H），7.20（t，J=7.6Hz，1H），6.71（s，2H），6.59（s，1H），1.87（s，4H），1.50（s，8H）；^{13}C NMR（101MHz，DMSO-d_6）δ：164.48，148.62，134.98，128.94，118.18，116.22，116.13，73.80，42.88，31.08，22.74。



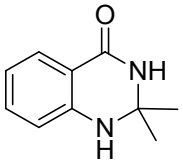
3m

1'H-Spiro [cyclohexane-1,2'-quinazolin]-4'(3'H)-one(3m), white solid. Yield: (98%).^{1}H NMR（400MHz，DMSO-d_6）δ：7.93（s，1H），7.58（d，J=7.6Hz，1H），7.21（t，J=7.6Hz，1H），6.81（d，J=8.1Hz，1H），6.69-6.58（m，2H），1.83-1.68（m，2H），1.66-1.50（m，6H），1.46-1.38（m，1H），1.25（d　　d，J=13.0、6.5Hz，1H）；^{13}C NMR（101MHz，DMSO-d_6）δ：165.10，148.65，134.99，128.98，118.36，116.46，116.33，69.69，39.05，26.53，22.77。



3n

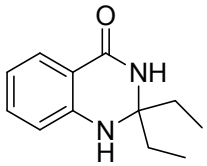
1'H-Spiro [cyclopentane-1,2'-quinazolin]-4'(3'H)-one(3n), white solid. Yield: (90%). white solid. Yield: (96%).^{1}H NMR（400MHz，DMSO-d_6）δ：8.10（s，1H），7.58（d，J=7.6Hz，1H），7.21（s，1H），6.74（s，2H），6.63（s，1H），1.79（s，4H），1.66（s，4H）；^{13}C NMR（101MHz，DMSO-d_6）δ：165.31，149.41，134.88，129.13，118.43，116.48，116.22，78.96，42.05，23.87。



3o

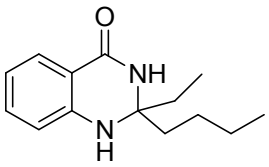
2,2-dimethyl-2,3-Dihydro-quinazolin-4(1H)-one(3o), white solid. Yield:

(96%).^{1}HNM（400MHz， DMSO-d_6）δ：7.94（s，1H），7.58（d，J=7.6Hz，1H），7.22（s，1H），6.65（d，J=1.0Hz，3H），1.38（s，6H）；^{13}C NMR（101MHz，DMSO-d_6）δ：164.95，148.96，135.08，129.06，118.32，116.12，115.73，68.72，30.88。



3p

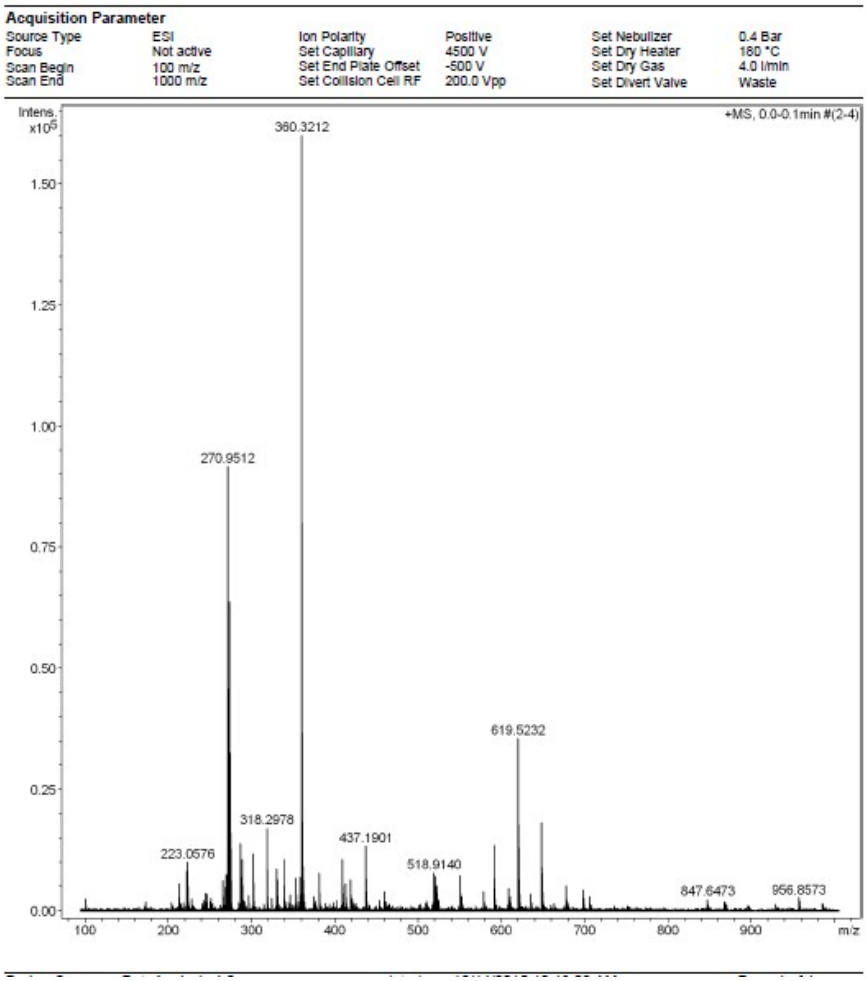
2,2-diethyl-2,3-Dihydro-quinazolin-4(1H)-one(3p), white solid. Yield: (95%).^{1}HNMR（400MHz，DMSO-d_6）δ：7.75（s，1H），7.53（d，J=7.6Hz，1H），7.17（s，1H），6.65（d，J=8.1Hz，1H），6.54（s，1H），6.49（s，1H），1.59（d，J=3.1Hz，4H），0.86（s，6H）；^{13}C NMR（101MHz，DMSO-d_6）δ：165.24，149.56，135.02，128.87，117.40，115.44，114.89，73.84，34.62，9.78。



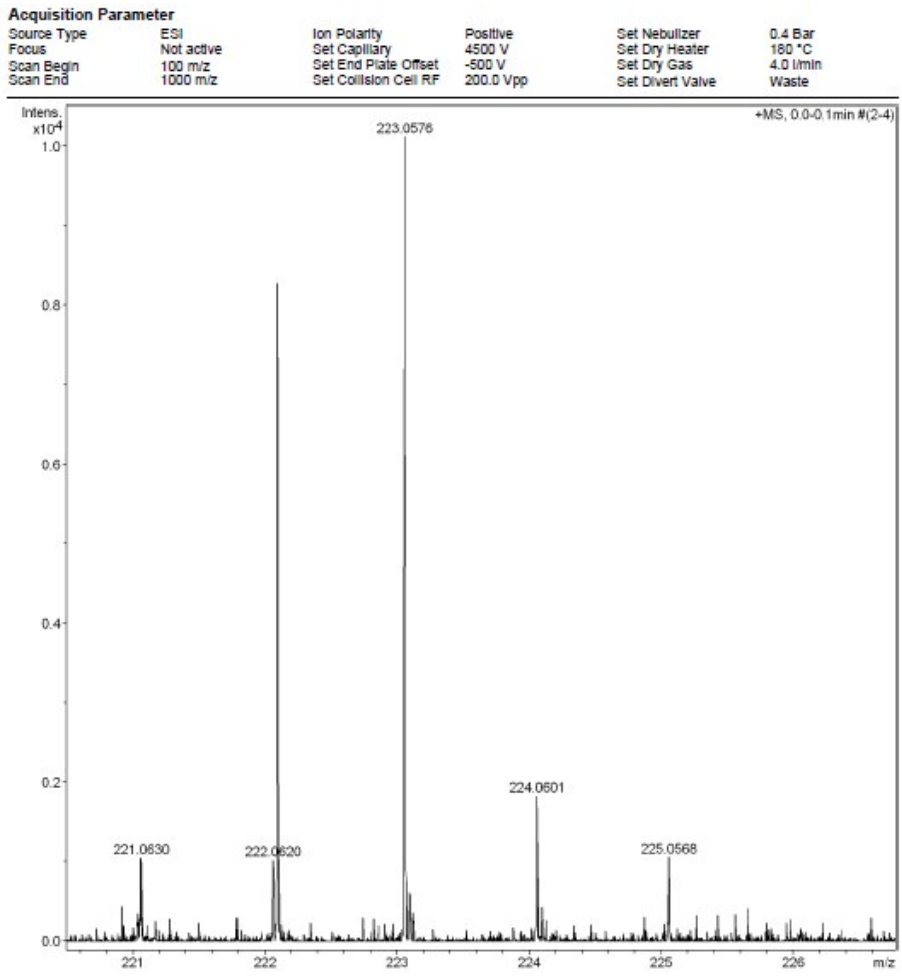
3q

2-ethyl-2-(n-butyl) -2,3-dihydro-quinazolin-4(1H)-one (3q), white solid. Yield: (97%).^{1}H NMR（400MHz，DMSO-d_6）δ：7.74（s，1H），7.52（d，J=7.6Hz，1H），7.21-7.13（m，1H），6.62（d，J=8.1Hz，1H），6.53（s，1H），6.48（s，1H），1.56（s，4H），1.23（d，J=6.9Hz，4H），0.85（d，J=5.3Hz，6H）；^{13}CNMR（101MHz，DMSO-d_6）δ：165.11，149.49，135.01，128.86，117.37，115.40，114.82，73.47，41.89，35.04，27.18，24.28，15.93，9.79。

8. HRMS spectra

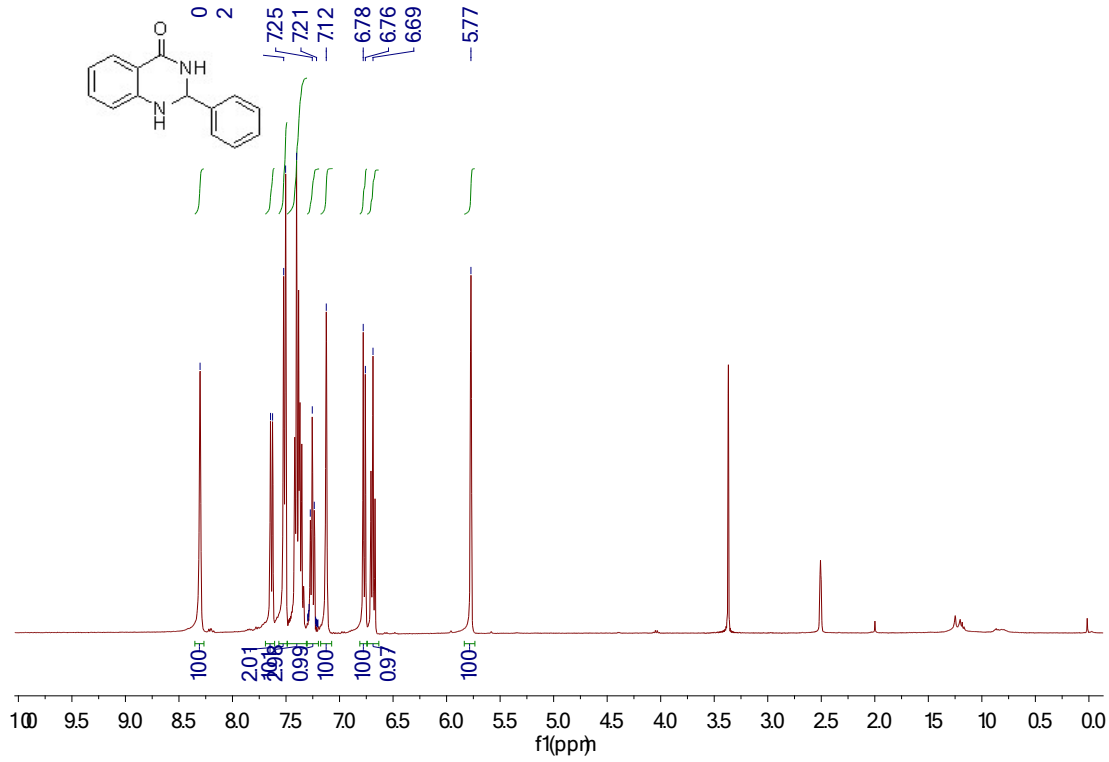


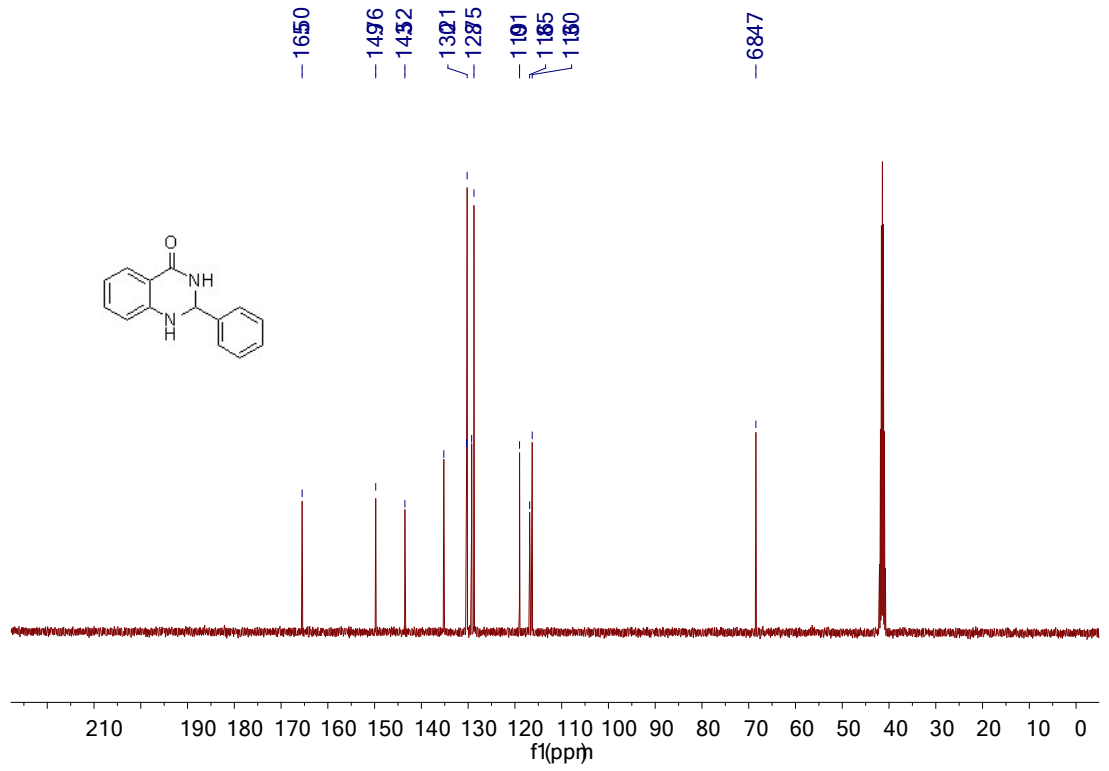
FigureS2: ESI(+)-MS for CID of Cp_2TiCl_2 inCH_3OH solution (m/z 100-1000).

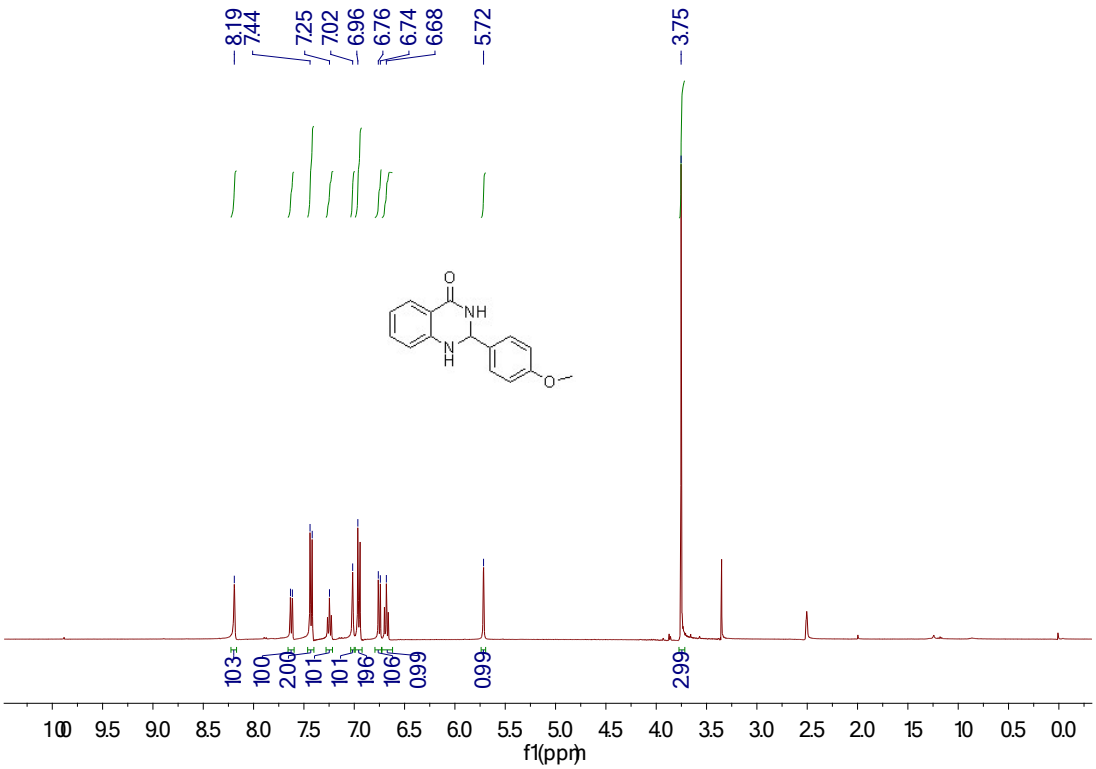


FigureS3: HR-MS for CID of Cp_2TiCl_2 inCH_3OH solution (m/z 200-227).

9 Copies of ^{1}H NMR and ^{13}C NMR spectra



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7.02
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6.76
6.74
6.68
5.72
3.75
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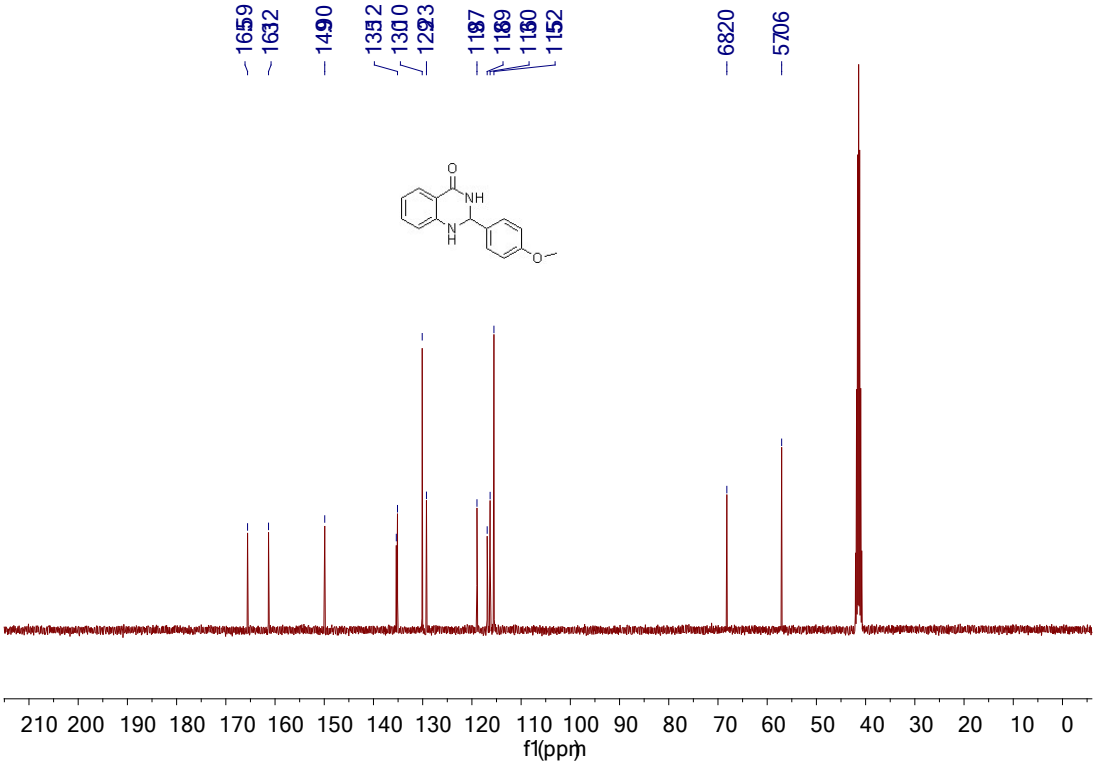
N
H
O
1.03
1.00
2.00
1.01
1.01
1.96
1.06
0.99
0.99
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1(ppm)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129.23
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NH
N
H
O
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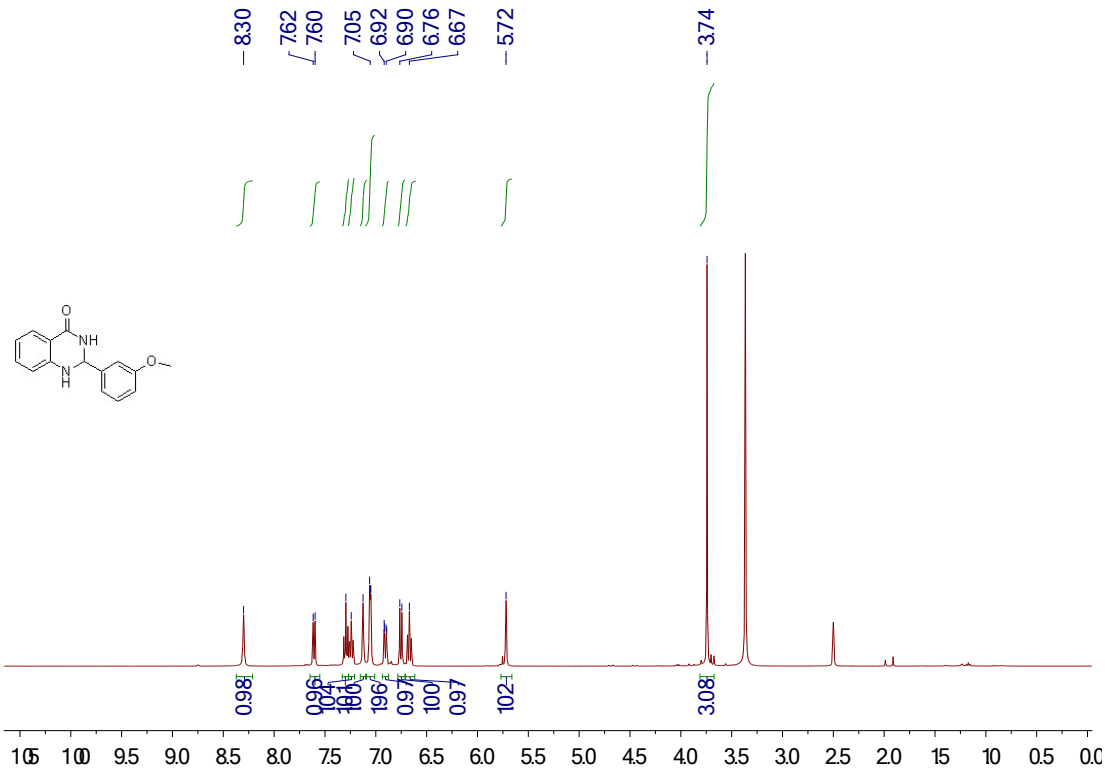
f1(ppm)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6.90
6.76
6.67
5.72
3.74
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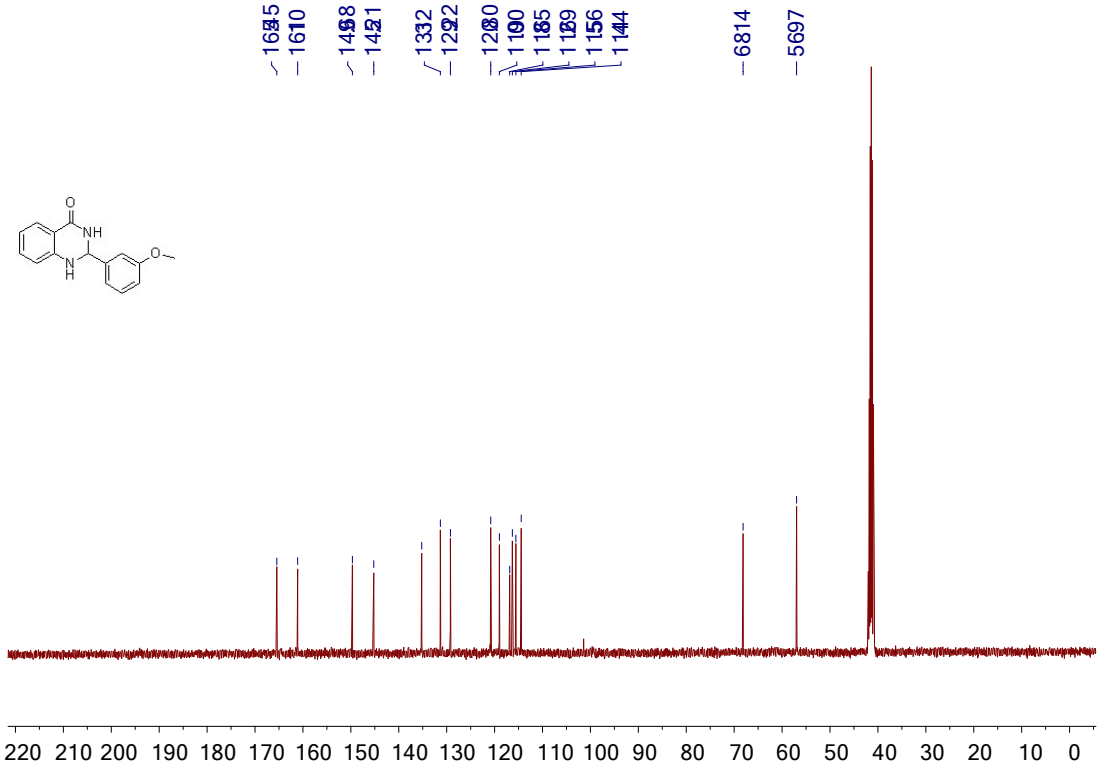
N
H
O
0.98
0.96
0.97
1.96
1.00
0.97
1.02
3.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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161.10
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142.11
133.32
129.22
128.80
119.90
118.85
118.39
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68.14
56.97
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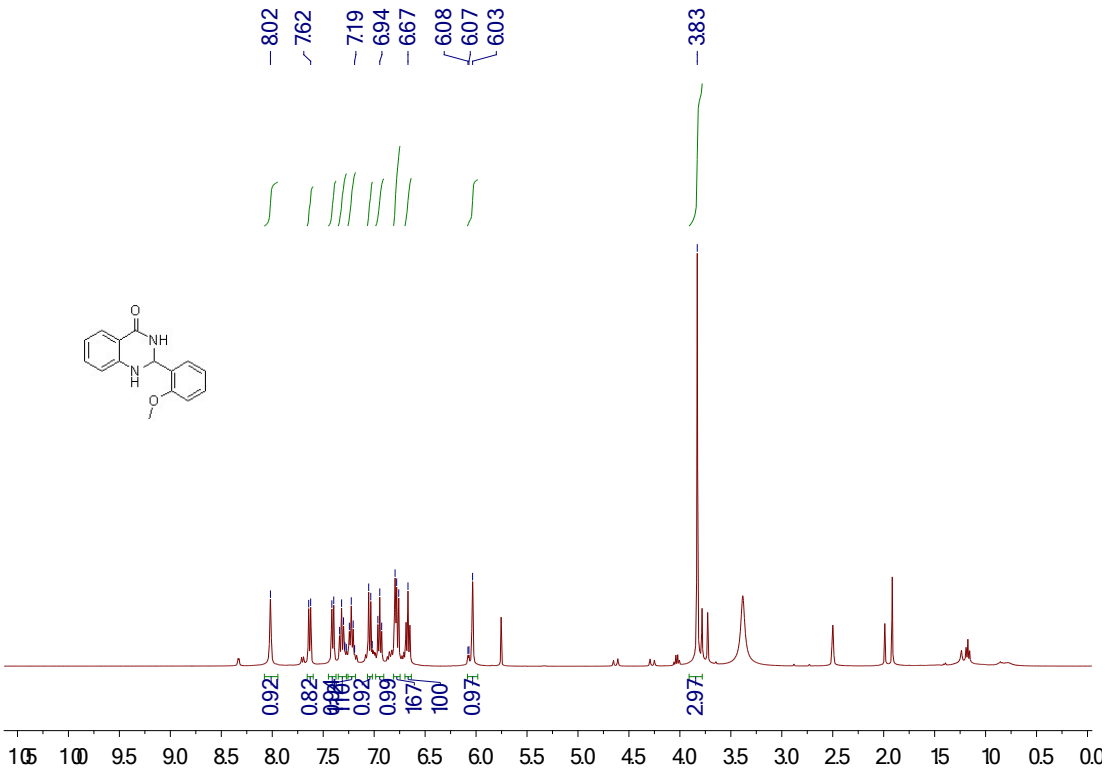
NH
N
H
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.19
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6.67
6.08
6.07
6.03
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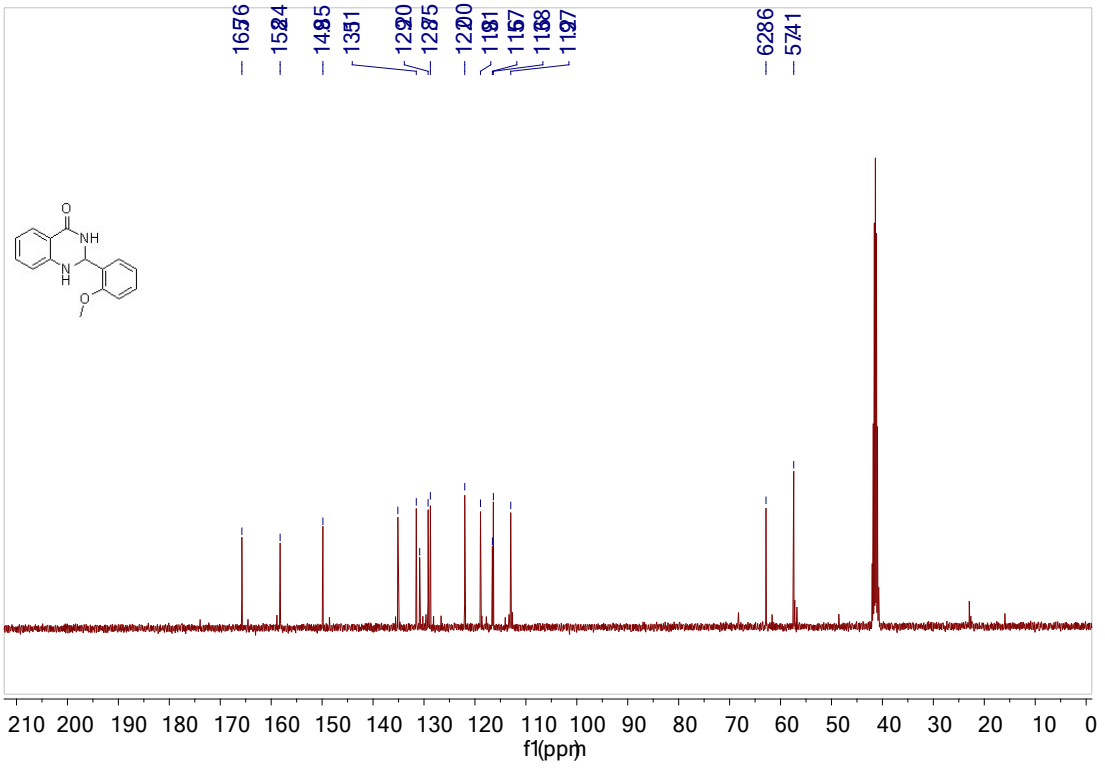
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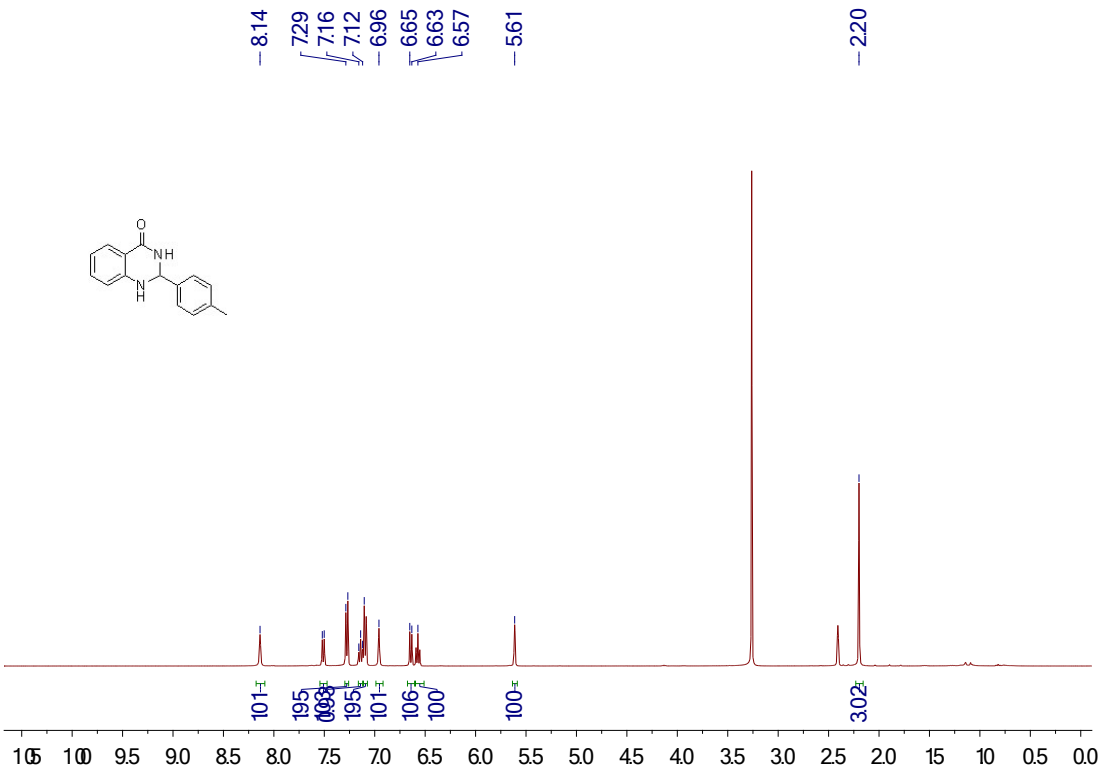
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1.95
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1.00
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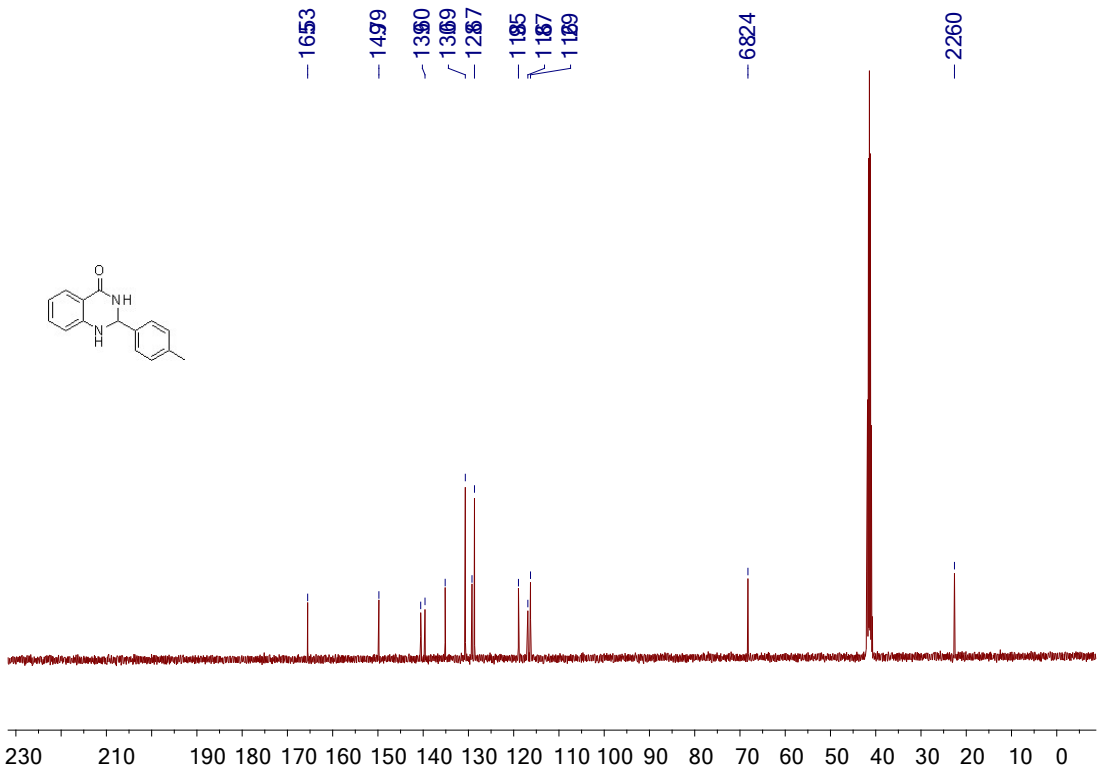
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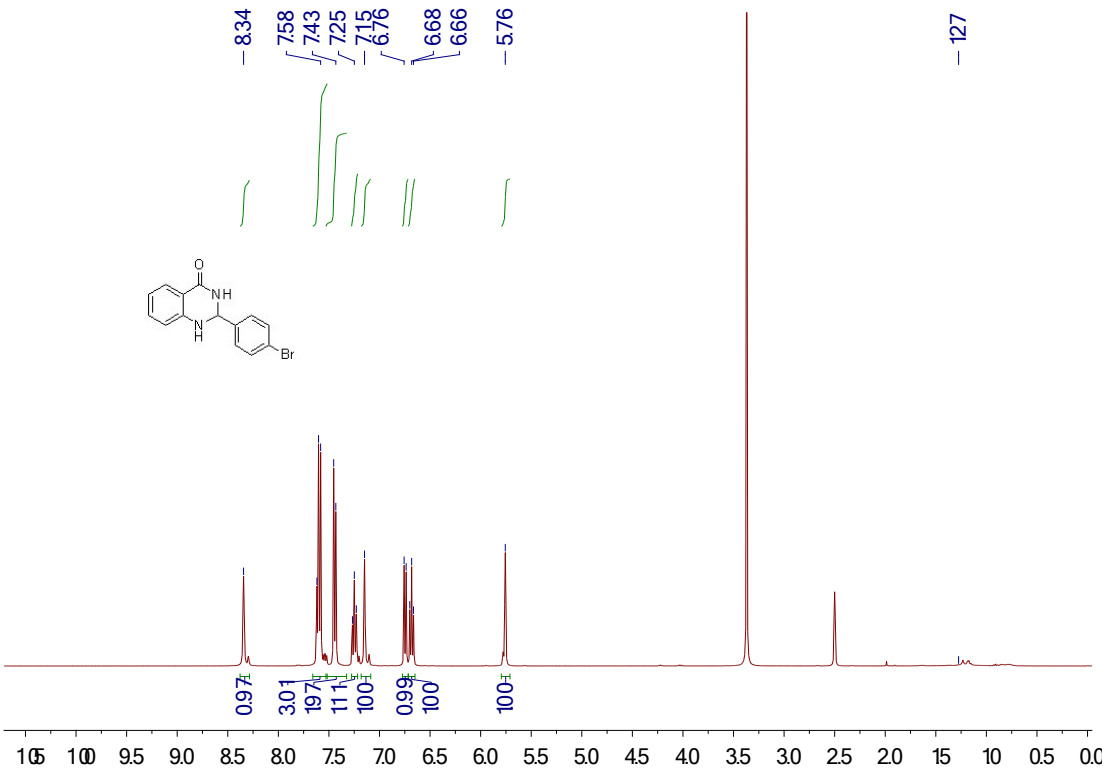
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1.11
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0.99
1.00
1.00
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10.0
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9.0
8.5
8.0
7.5
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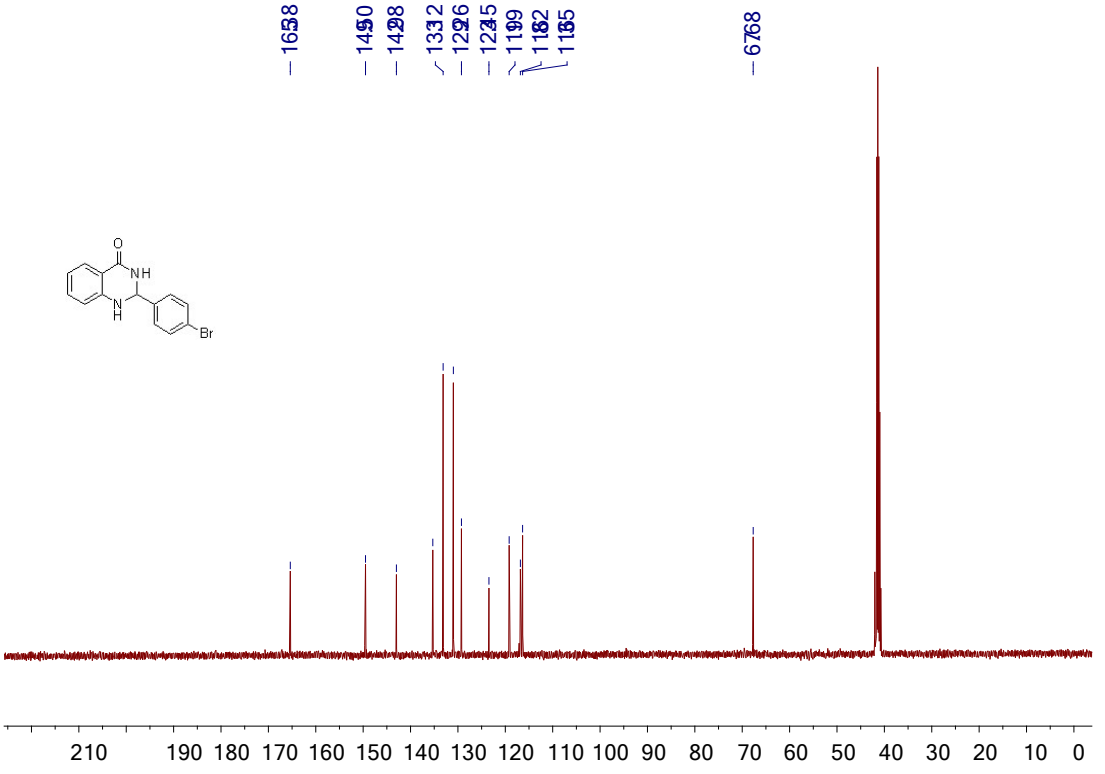
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H
Br
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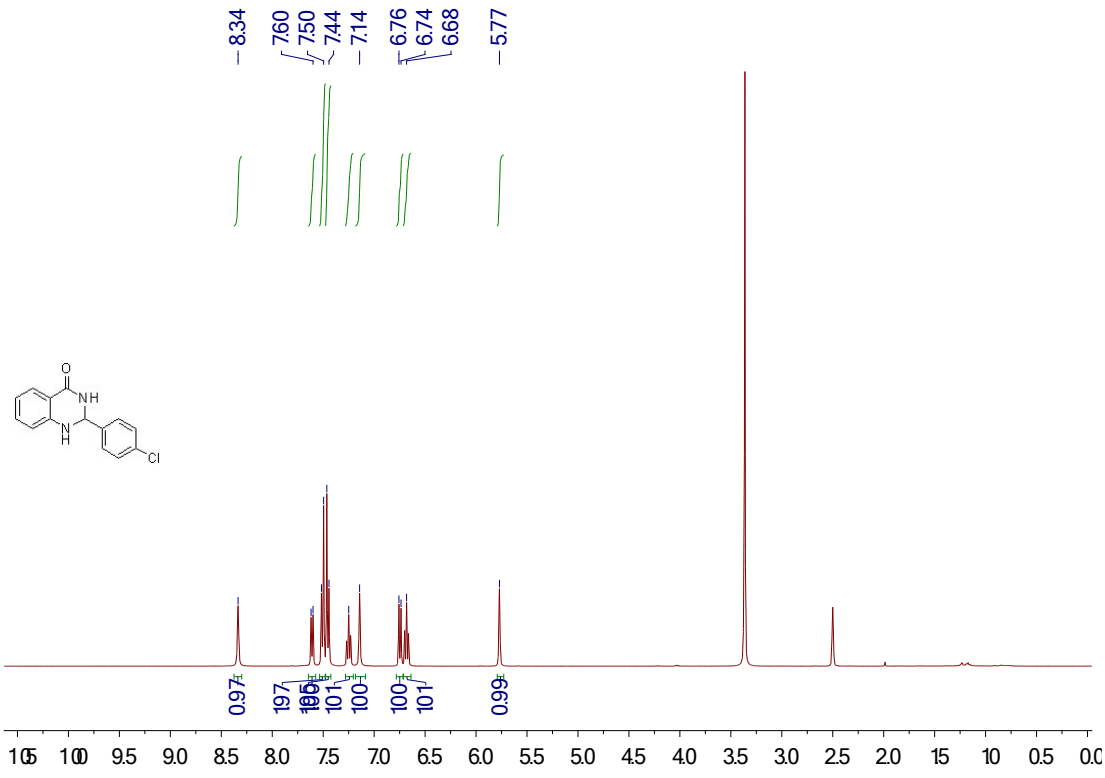
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0.99
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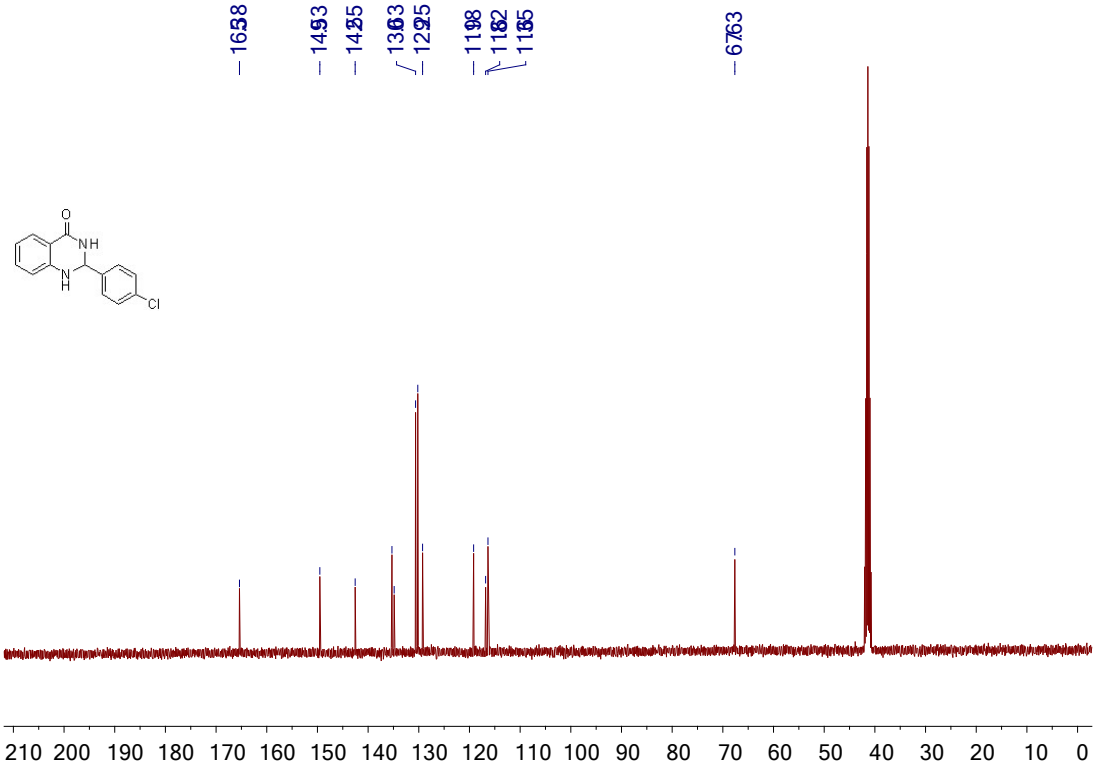
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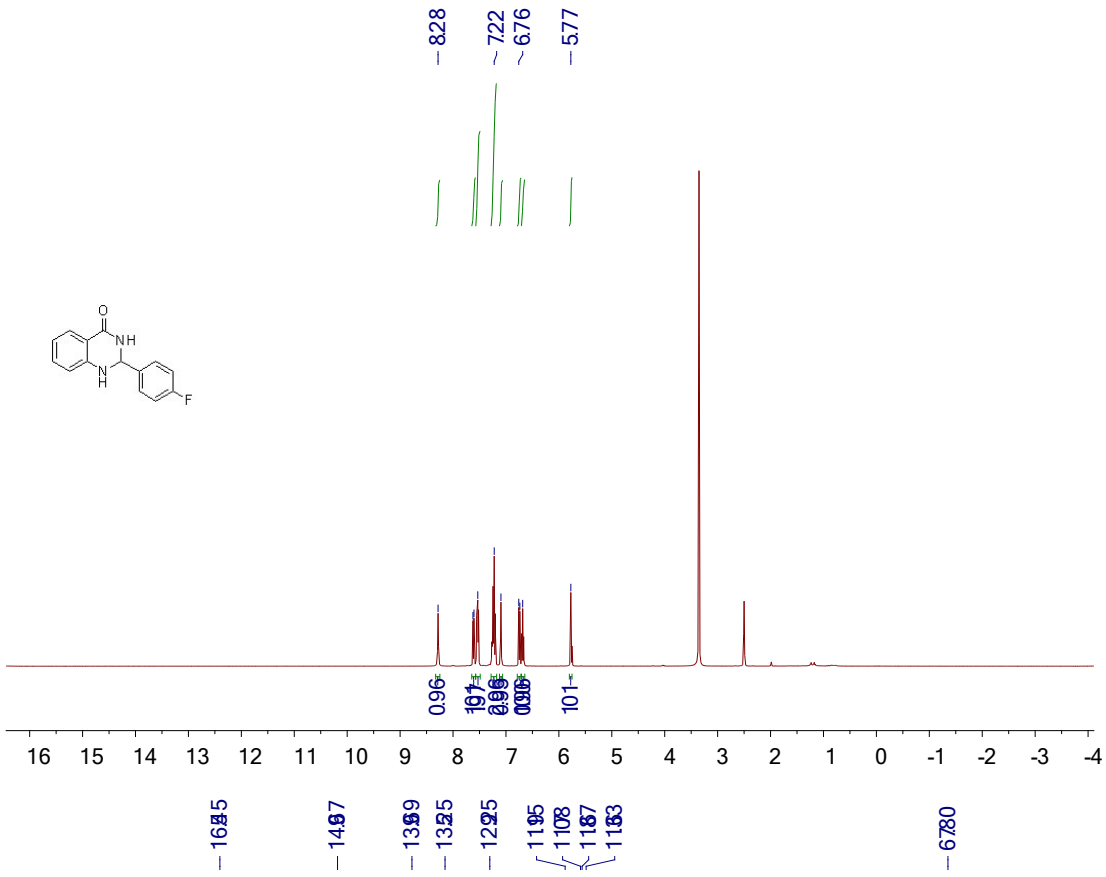
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0.96
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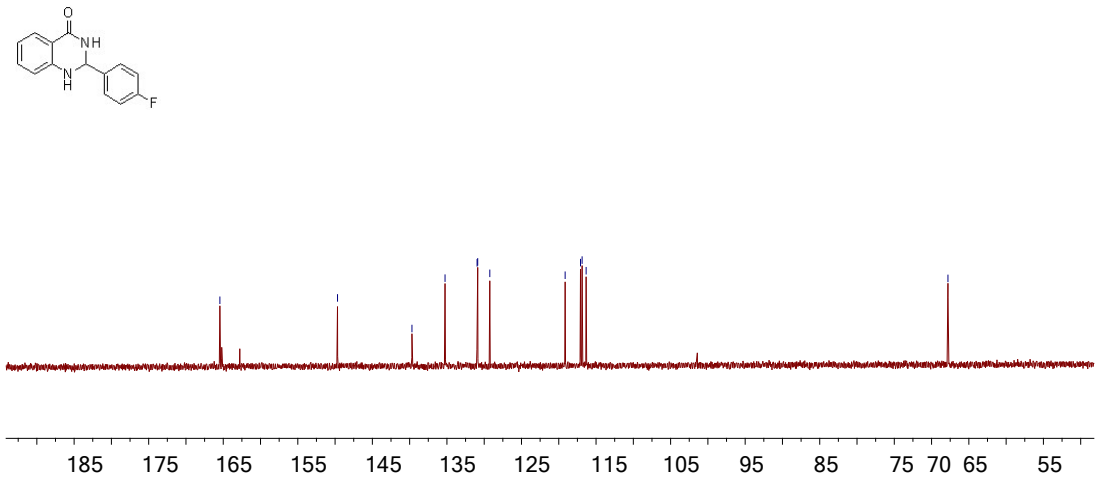
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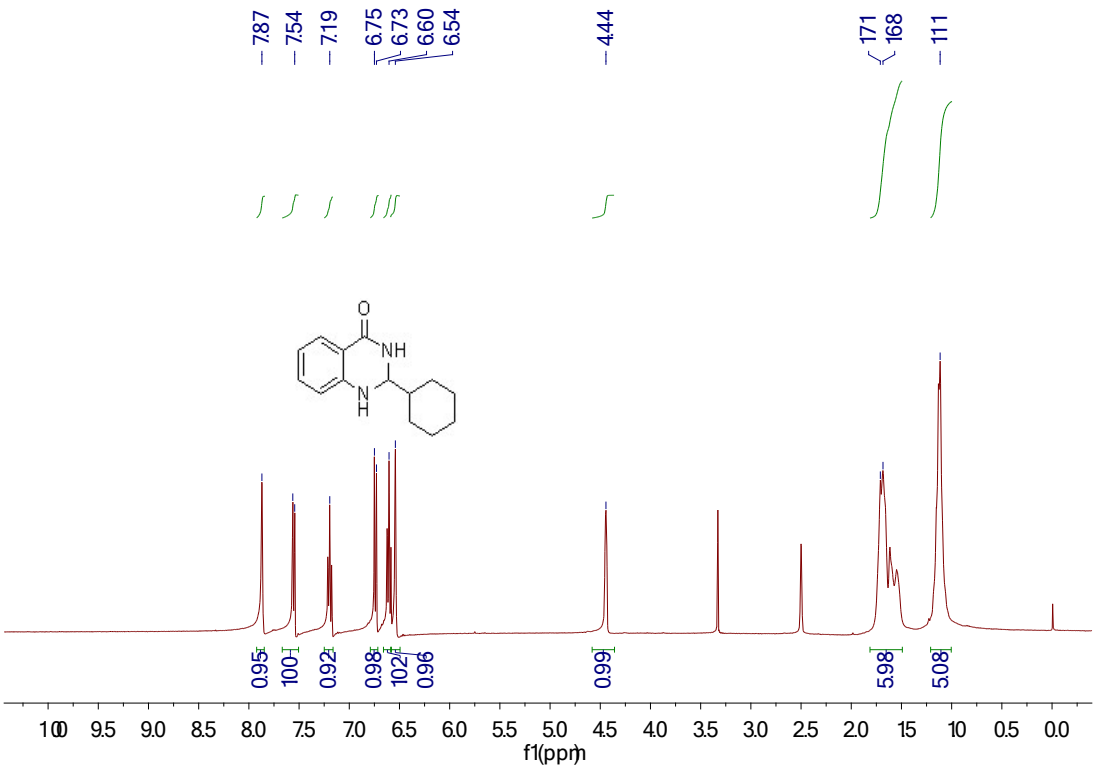
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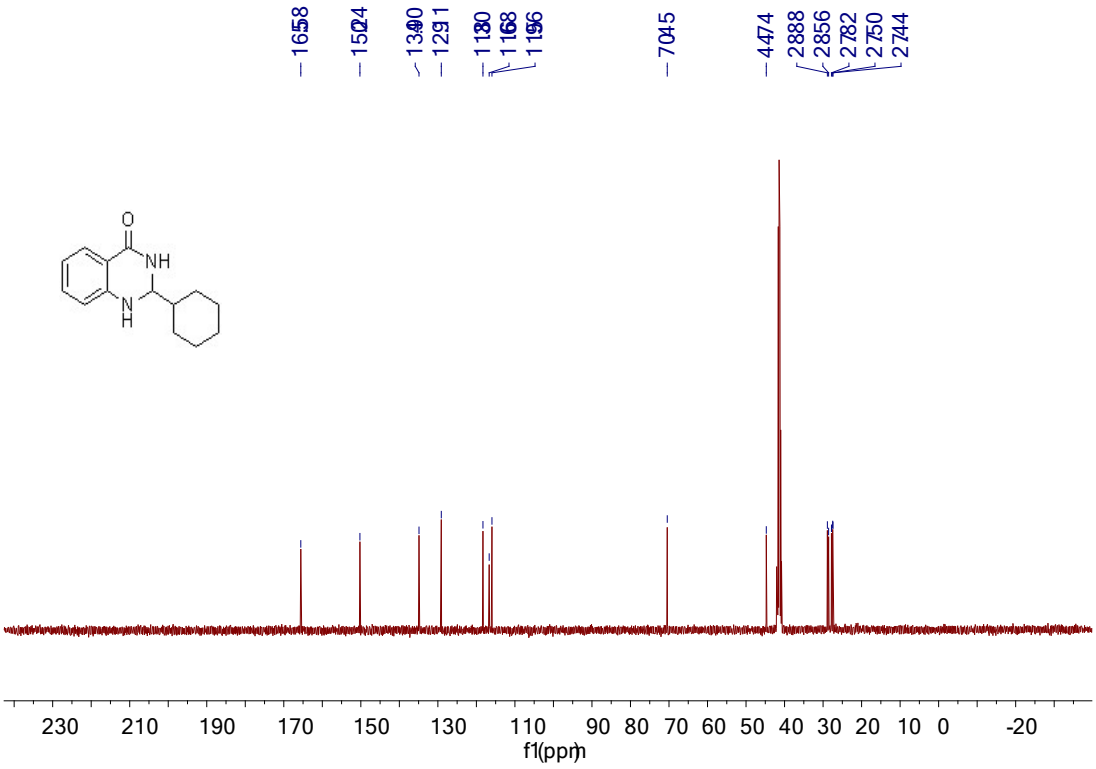
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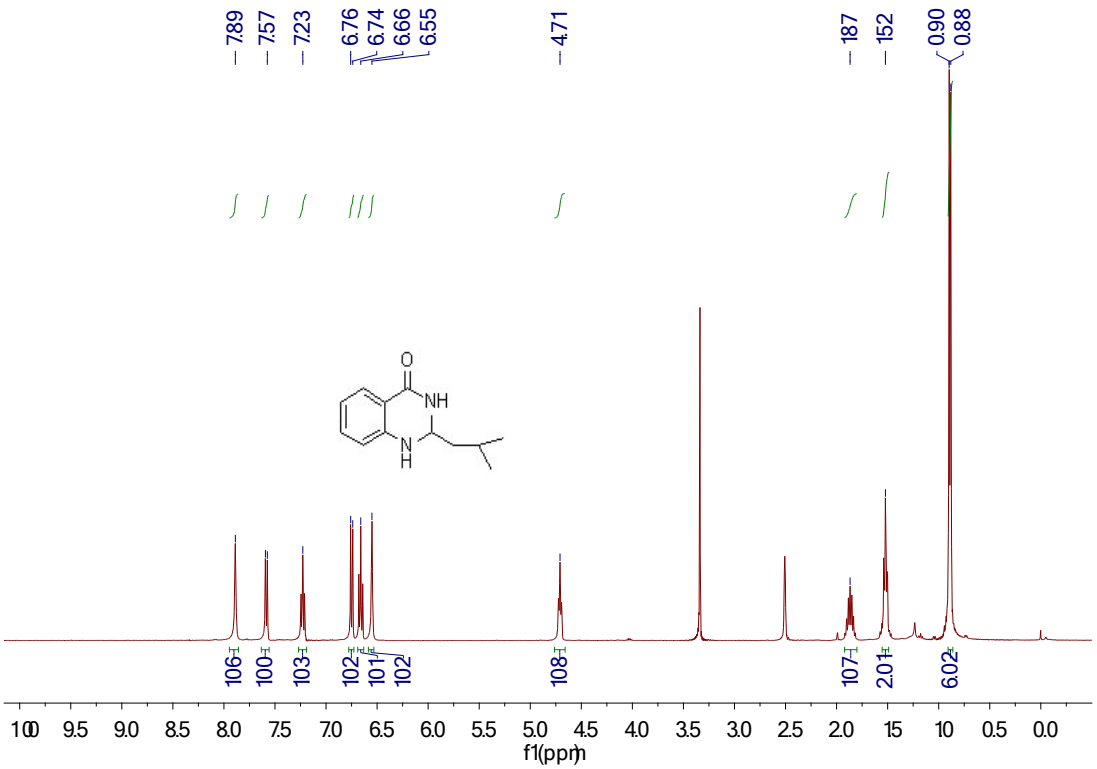
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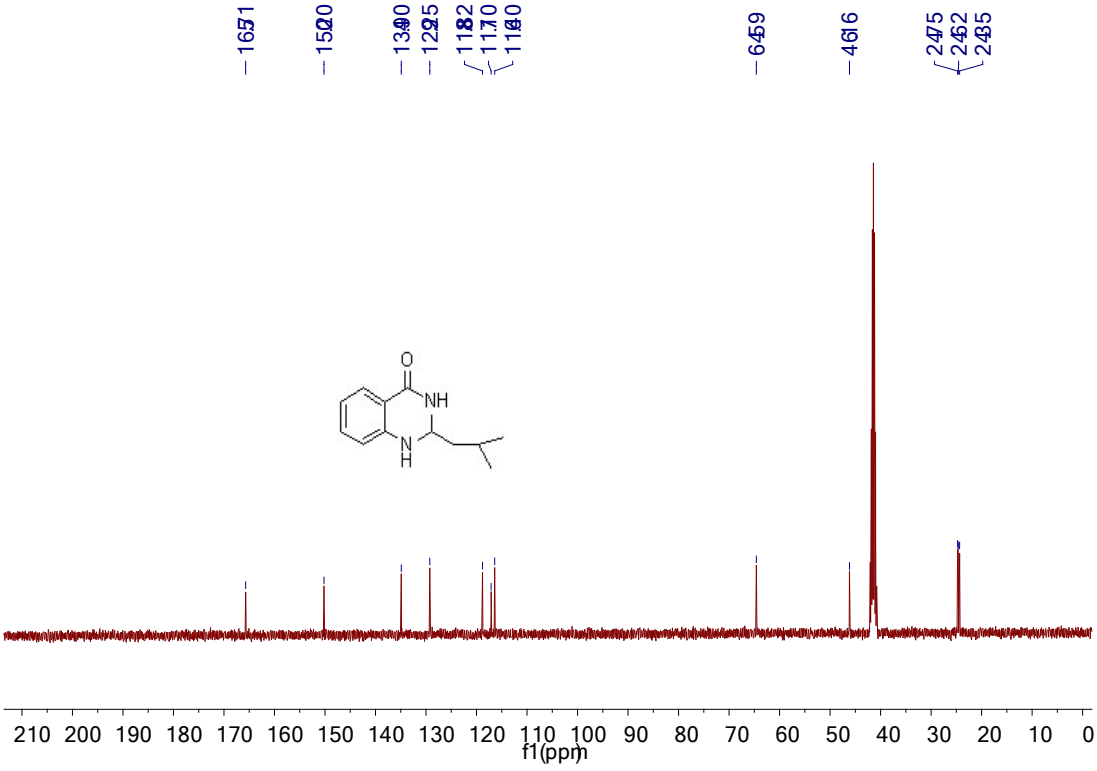
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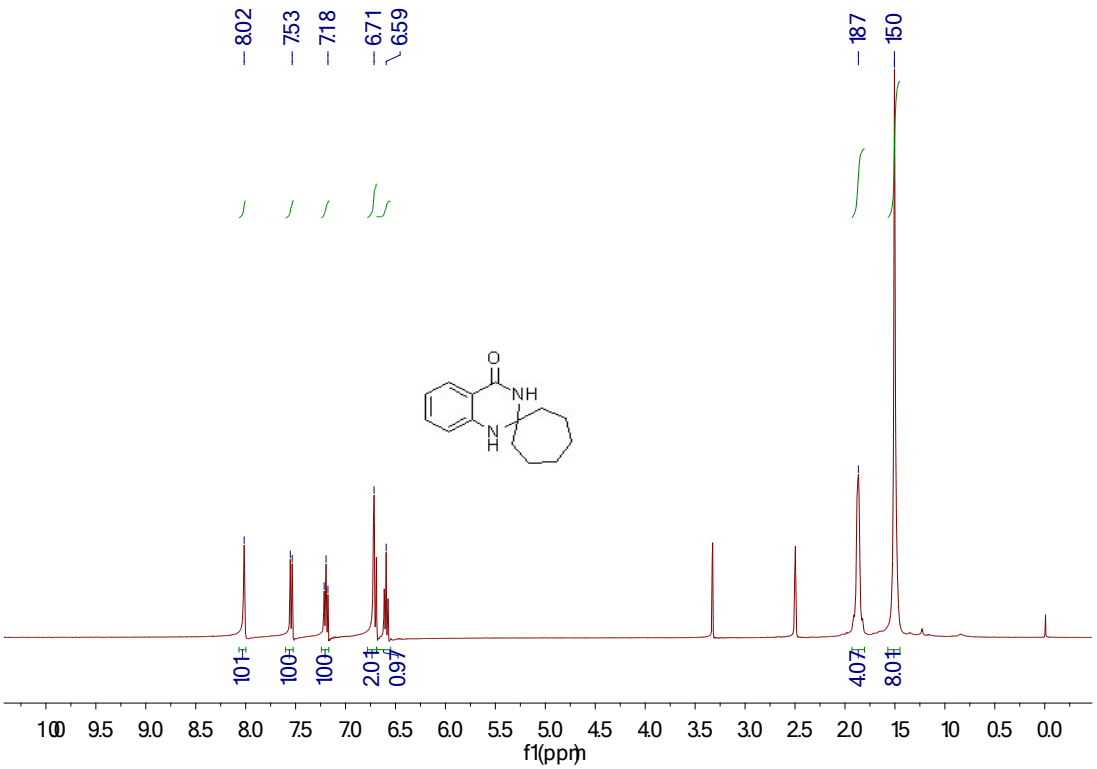
f1(ppm)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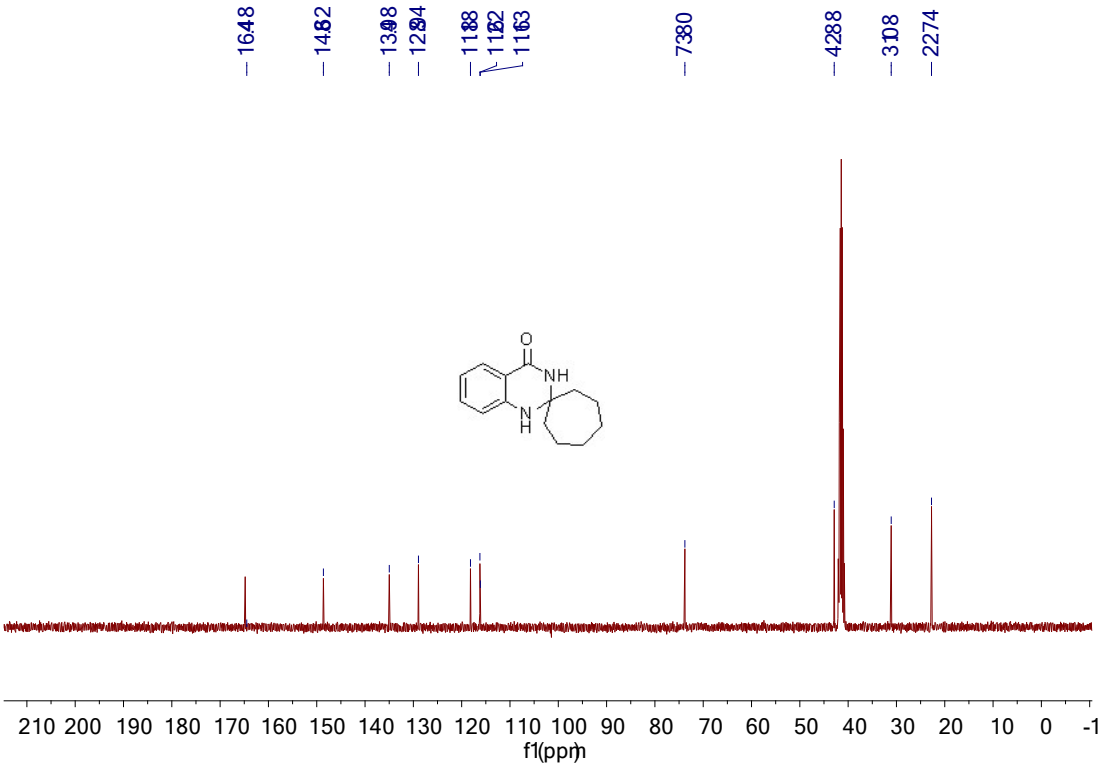
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H
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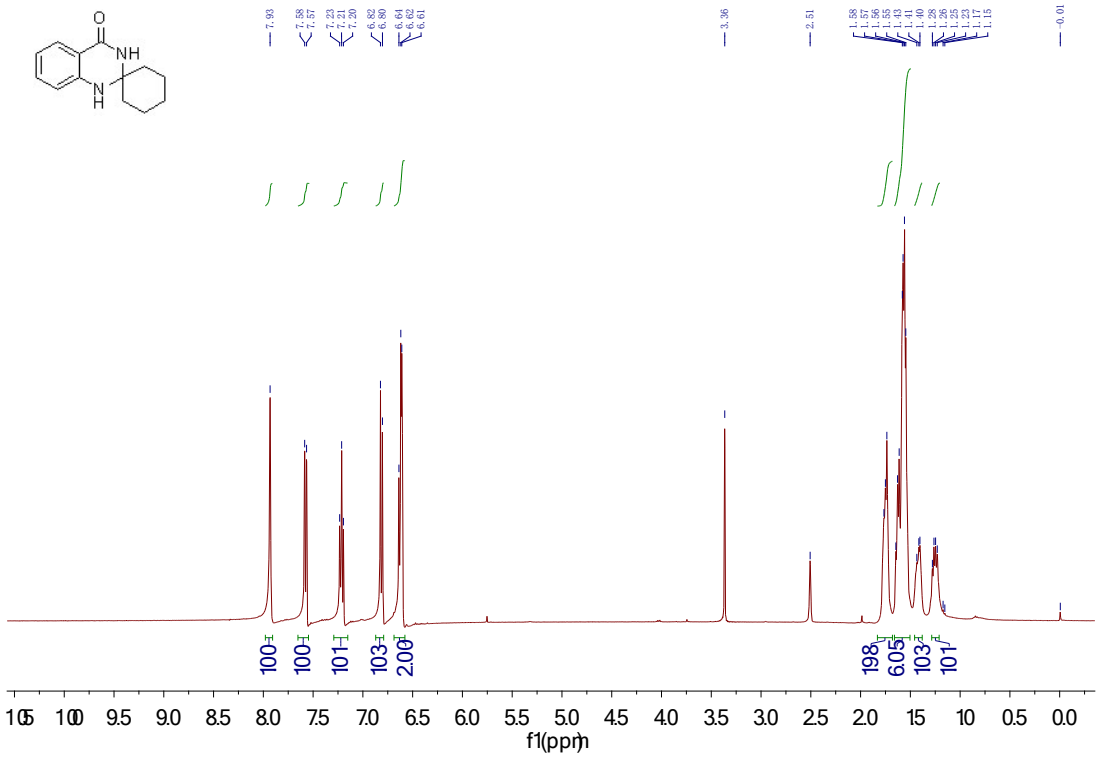
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1.57
1.56
1.55
1.43
1.41
1.40
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1.26
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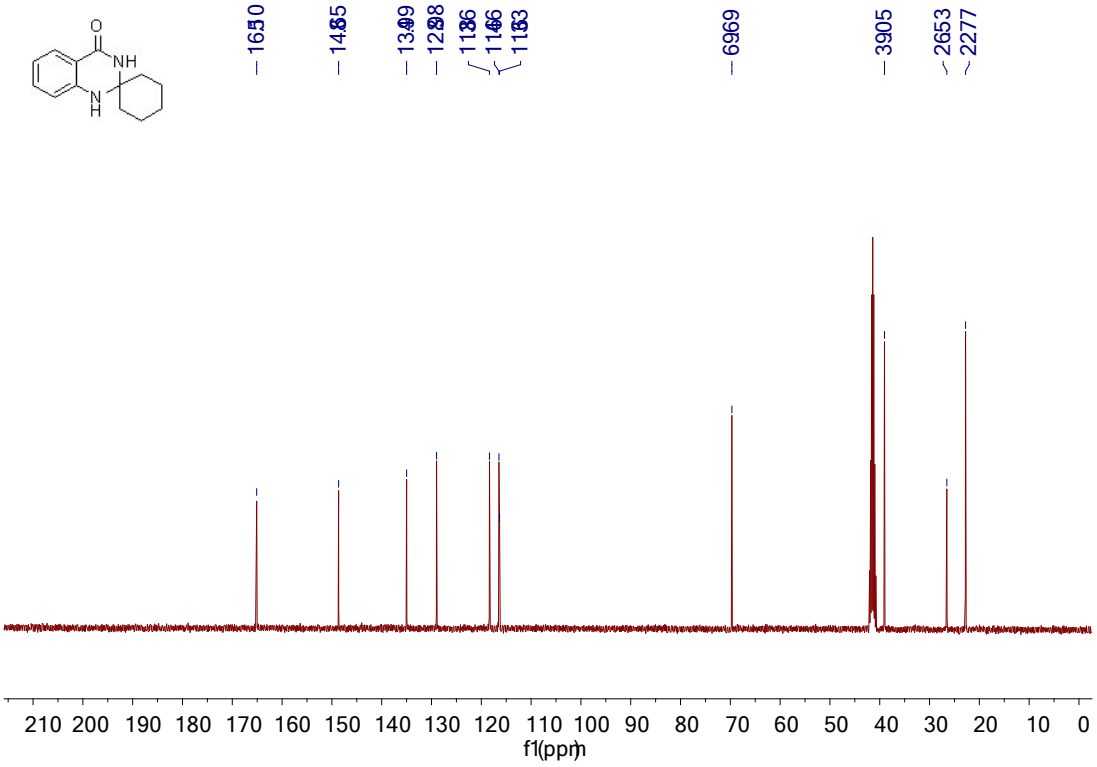
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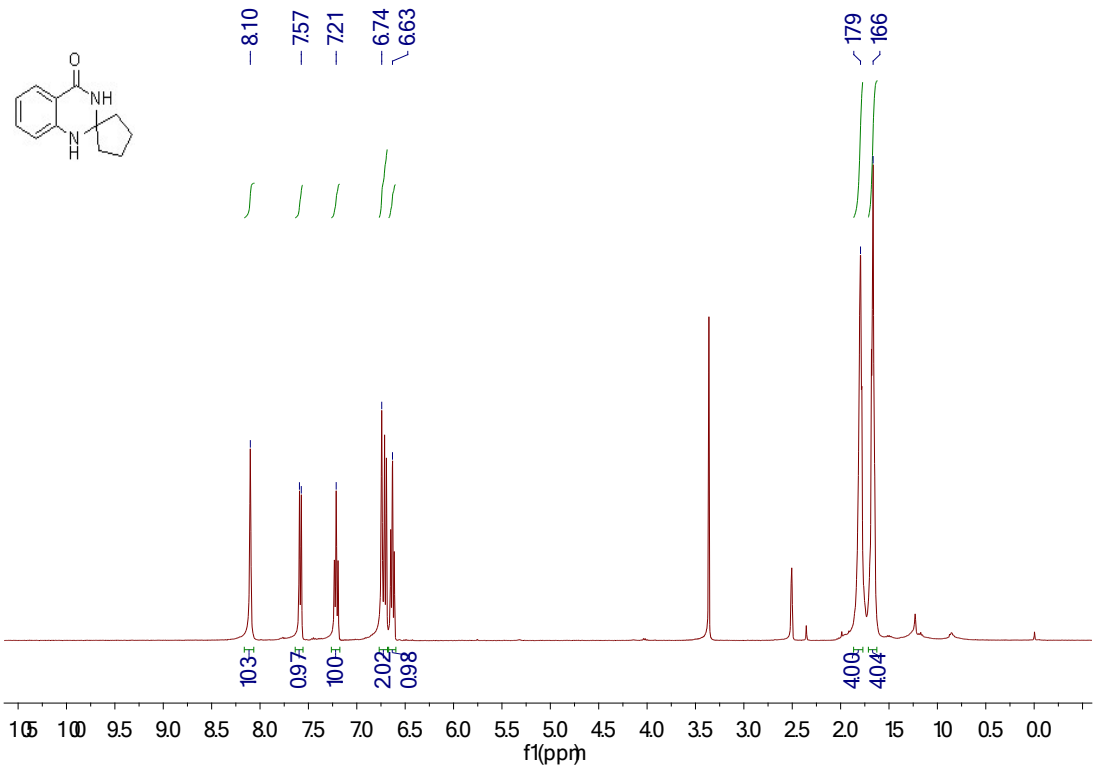
22.77
f1(ppm)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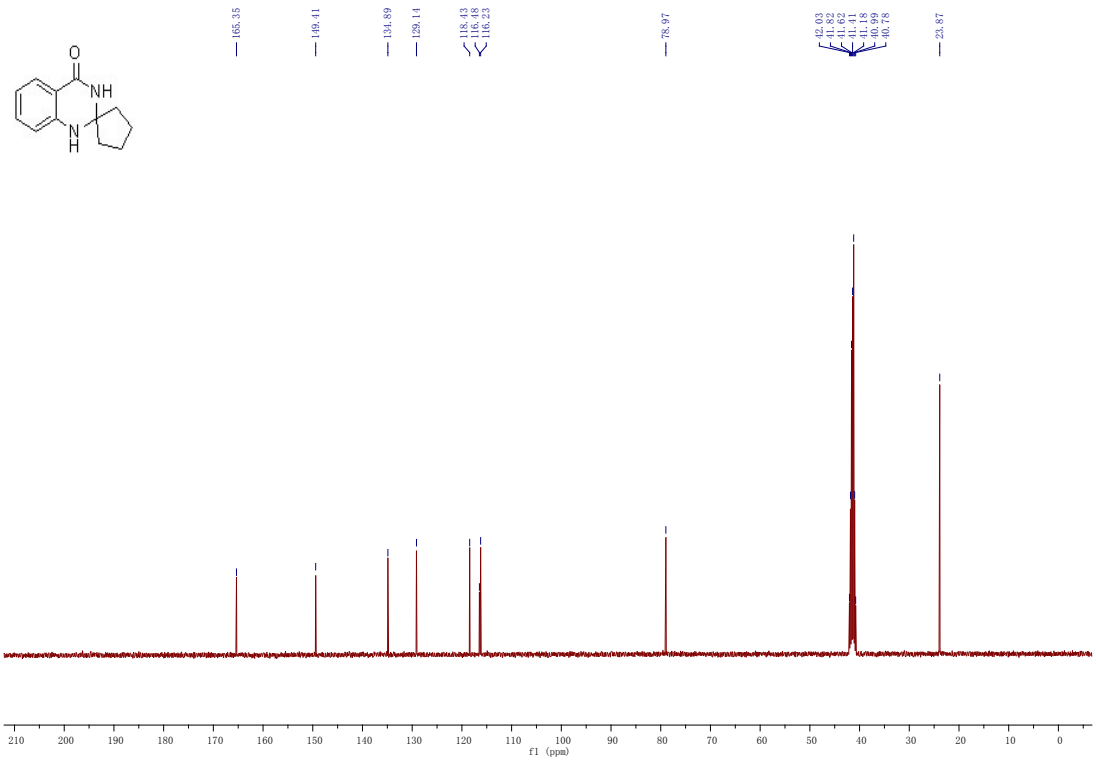
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40.99
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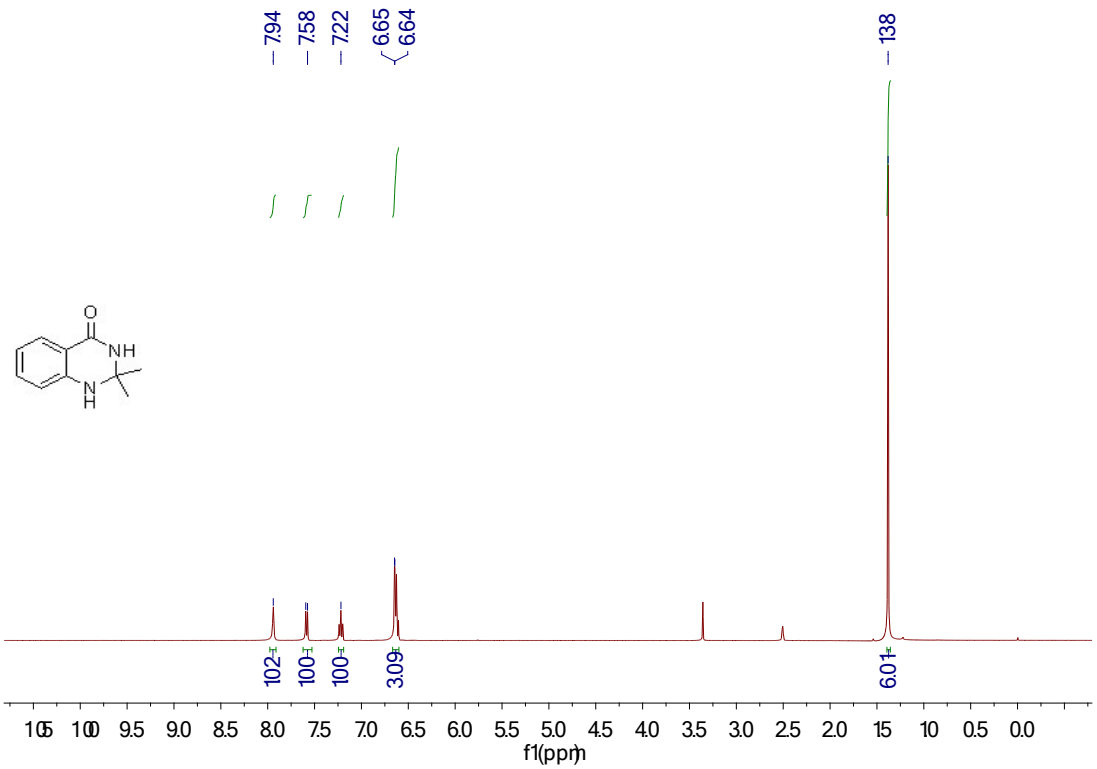
23.87
f1 (ppm)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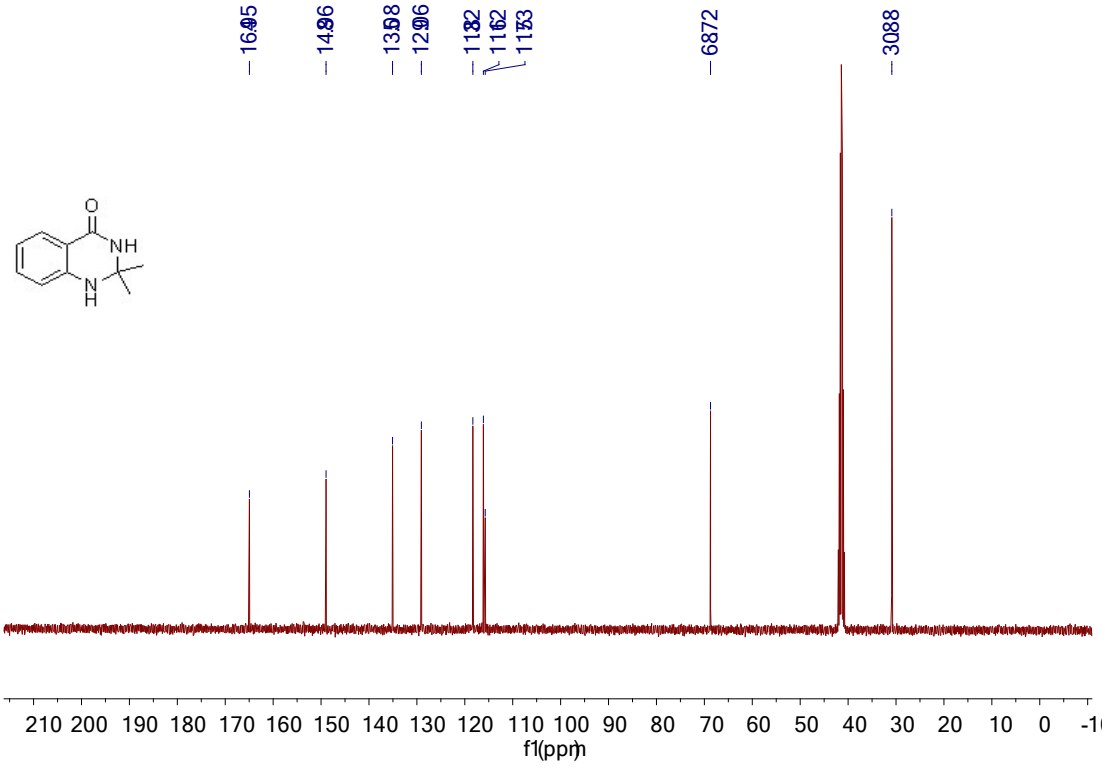
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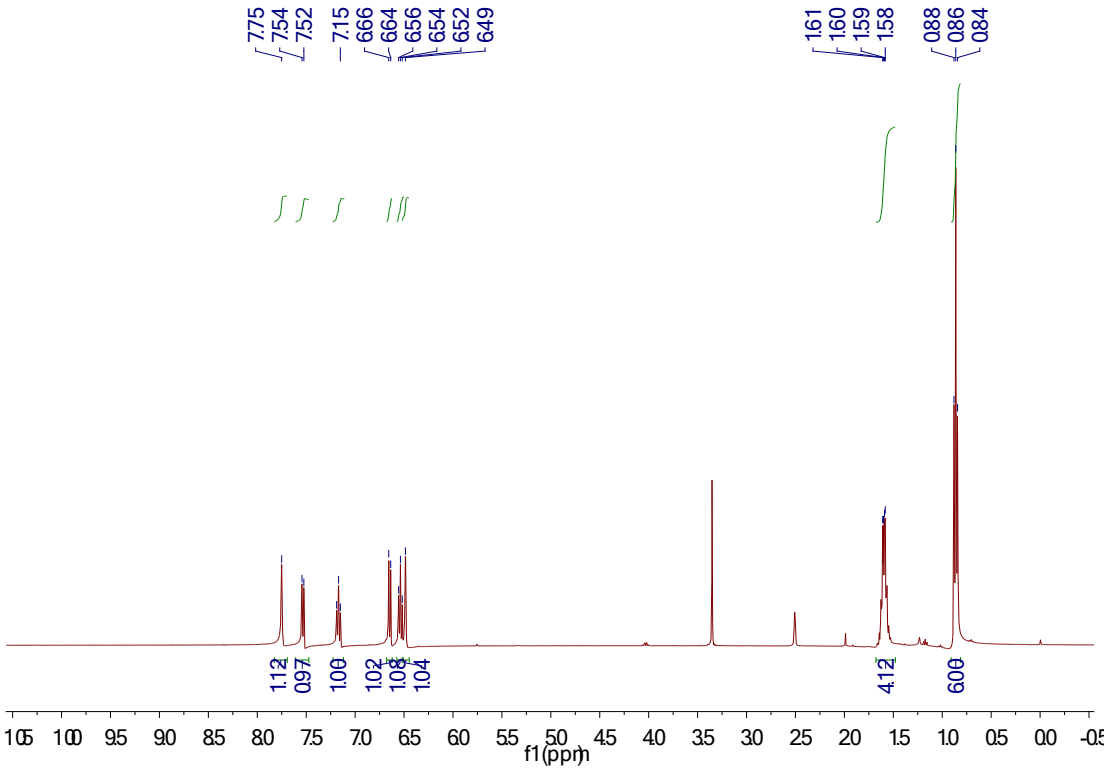
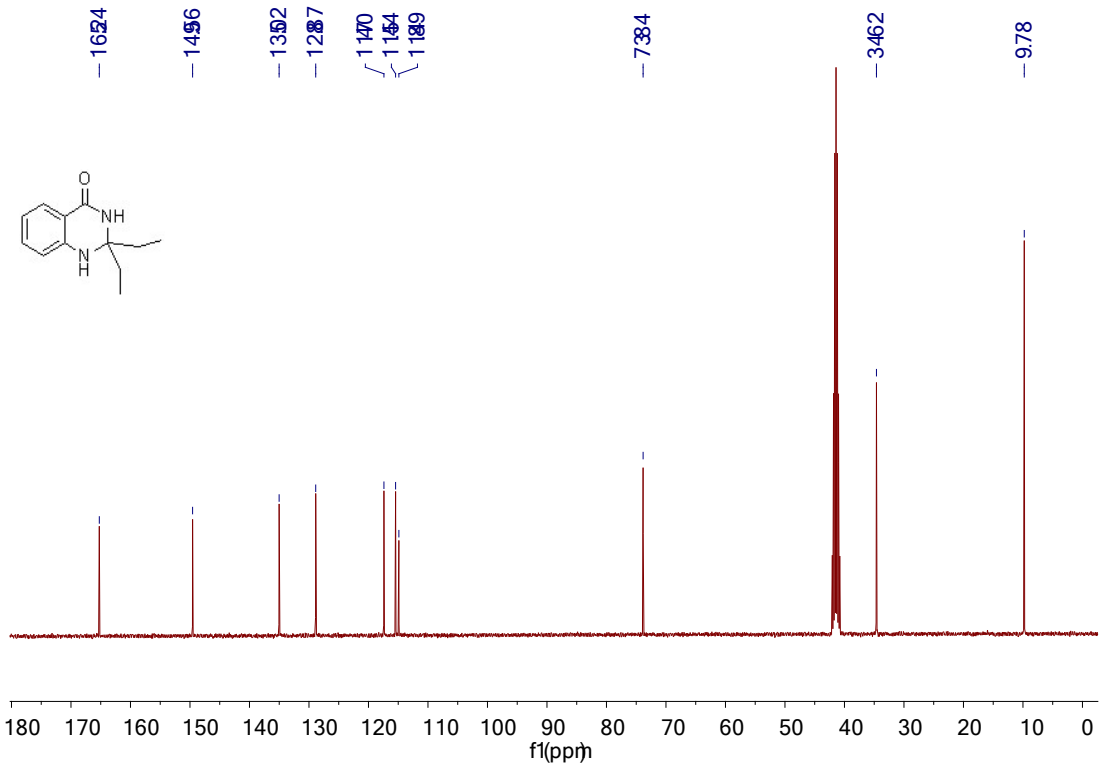
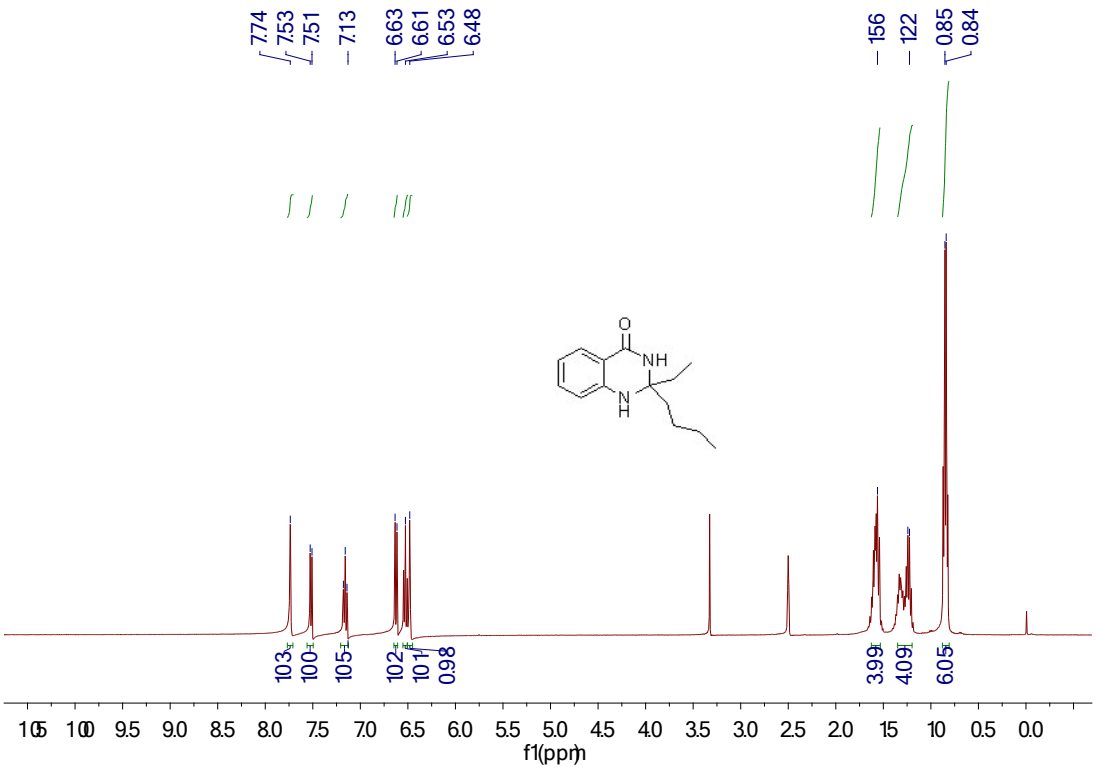
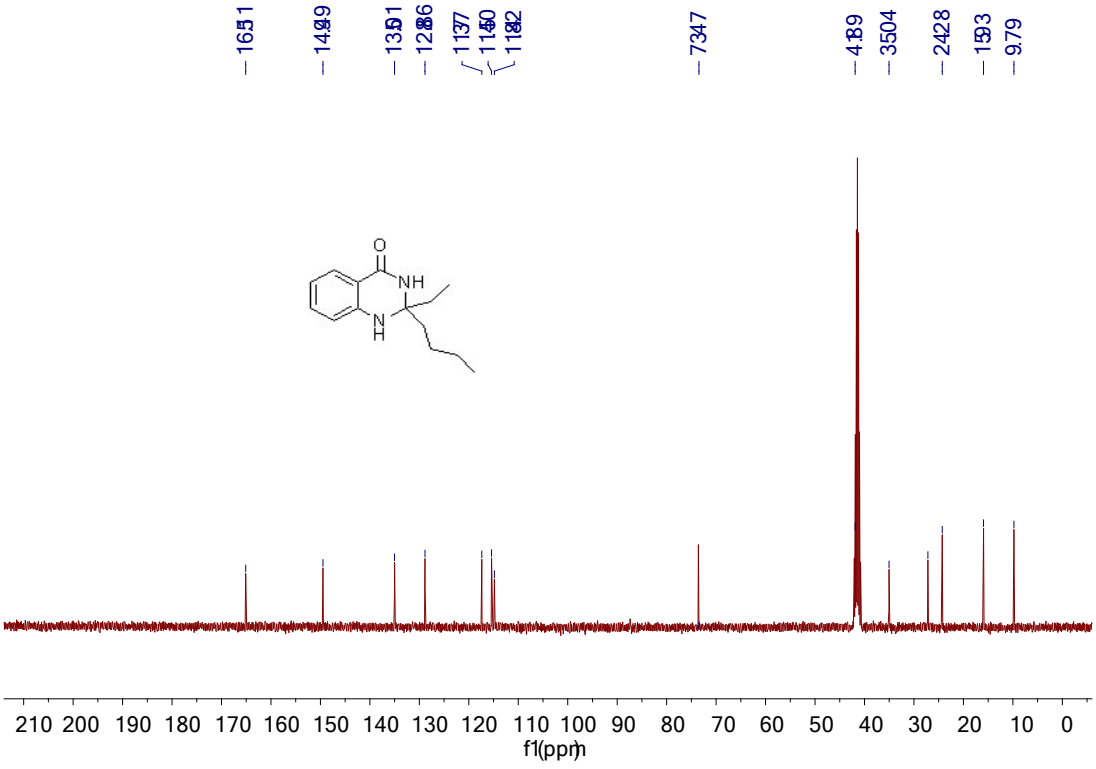
H
f1(ppm)


7.75
7.54
7.52
7.15
6.66
6.64
6.56
6.54
6.52
6.49
1.61
1.60
1.59
1.58
0.88
0.86
0.84
1.12
0.97
1.00
1.02
1.08
1.04
4.12
6.00
f1 (ppm)


162.24
145.56
135.52
128.87
114.70
114.54
113.89
73.84
34.62
9.78
O
NH
N
H
f1 (ppm)


7.74
7.53
7.51
7.13
6.63
6.61
6.53
6.48
1.56
1.22
0.85
0.84
O
NH
N
H
1.03
1.00
1.05
1.02
1.01
0.98
3.99
4.09
6.05
f1(ppm)


165.11
149.29
135.01
128.86
113.77
114.60
118.82
73.47
41.89
35.04
24.28
15.93
9.79
O
NH
N
H
f1(ppm)