Rapid Access to α-Carbolines *via* a One-pot Tamdem Reaction of α, β-Unsaturated Ketones with 2-Nitrophenylacetonitrile and the Anti-proliferative activities of the Products

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Experimental section

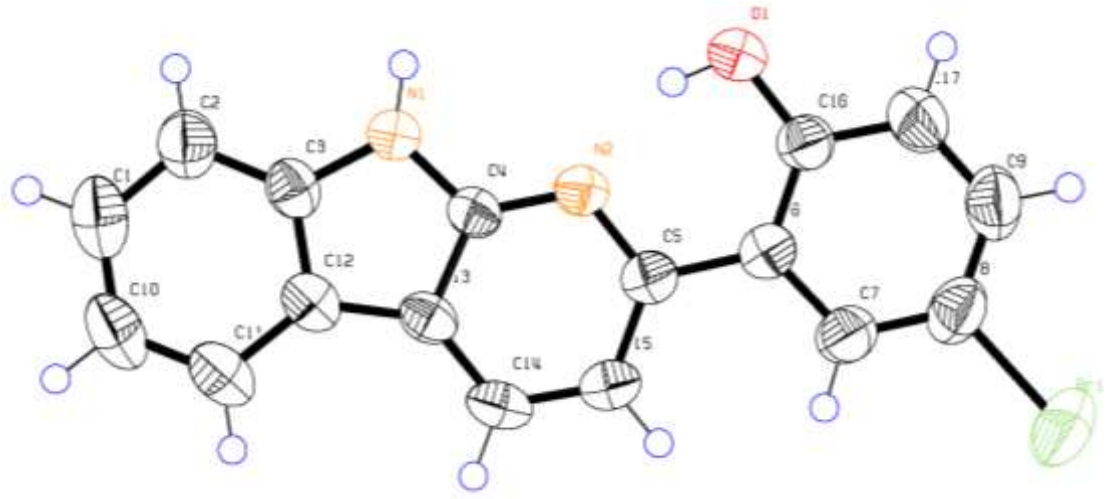
General experimental: The resgents were purchased from commercial sources and used without futher purification. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness, Yantai Huiyou Company, China). Column chromatography was carried out on silica gel (200-300 mesh). Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Varian Mercury-300/400 and Varian Mercury-400/500 spectrometers. Tetramethylsilane (TMS) was used as internal standard (^{1}H NMR: TMS at 0.00 ppm; $CHCl_3$ at 7.26 ppm; DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm; DMSO-d_6 at 39.6 ppm). HRMS spectra were recorded on a Micromass Ultra Q-TOF spectrometer. Melting points were measured by Büchi 510 melting point apparatus and were uncorrected.

General procedure of biology: The sulforhodamine B (SRB) assay: cells were seeded into 96-well plates on day 0 and exposed to 2-fold serial drug dilutions on day 1. On day 4, the cells were fixed by adding 10% pre-cooled trichloroacetic acid. After 1 h at 4 ℃, the plates were washed with distilled water, dried, and then stained with SRB (Sigma, MO) in 1% acetic acid. SRB in the cells was dissolved in 10 mM Tris-HCl and was measured at 515 nm using spectra-MAX190 (Molecular Devices, CA). The cell proliferation inhibition rate was calculated as: proliferation inhibition (%) = $[1-(A515_{treated}/A515_{control})] \times 100\%$.

General procedure for the synthesis of compounds 3a-3l: chromone **1a** (73 mg, 0.5 mmol), 2-nitrophenylactonitrile **2** (162 mg, 1 mmol), Zn dust (262 mg, 4 mmol), TEA (154 mg, 1.5 mmol) and AcOH (904mg, 15mmol) were added to a reaction flask. The reaction mixture was stirred and heated to refulx for 4 h. After completion of the reaction, the mixture was added with water and extracted by EtOAc. After dryed by anhydrou Na_2SO_4, EtOAc was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (8:1) as the eluent to provide the product **3a**.

General procedure for the synthesis of compounds 5a-5n: Benzylidene acetone **4a** (73 mg, 0.5 mmol), 2-nitrophenylactonitrile 2 (162 mg, 1 mmol), Zn dust (262 mg, 4 mmol), TEA (154 mg, 1.5 mmol) and AcOH (904mg, 15mmol) were added to a reaction flask. The reaction mixture was stirred and heated to 80 ℃ for 2 h. After completion of the reaction, the mixture was added with water and extracted by EtOAc. After dryed by anhydrou Na_2SO_4, EtOAc was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4:1) as the eluent to provide the product **5a**.

X-ray crystallography of compound 3f and 5l



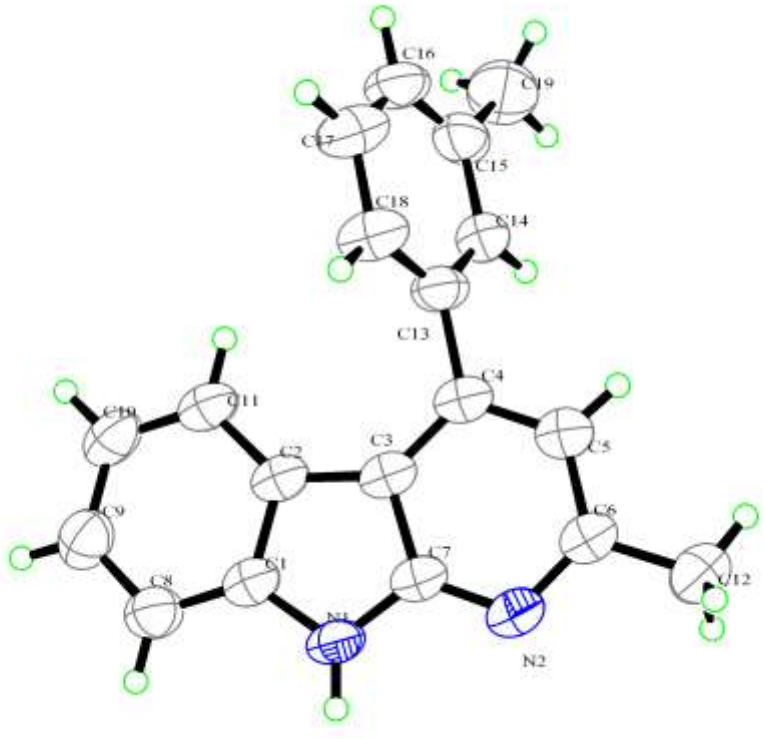
3f

A specimen of $C_{17}H_{11}BrN_2O$, approximate dimensions 0.480 mm x 0.500 mm x 0.550 mm, was used for the X-ray crystallographic analysis.The X-ray intensity data were measured.

The total exposure time was 2.68 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 9004 reflections to a maximum θ angle of 25.00° (0.84 Å resolution), of which 2408 were independent (average redundancy 3.739, completeness = 100.0%, R_{int} = 3.94%, R_{sig} = 4.30%) and 1782 (74.00%) were greater than $2\sigma(F^2)$.The final cell constants of a = 14.5336(5) Å, b = 6.3146(2) Å, c = 15.7054(6) Å, β = 108.490(2)°, volume = 1366.94(8) $Å^3$, are based upon the refinement of the XYZ-centroids of 2941 reflections above 20 σ(I) with 5.329° < 2θ <46.44°.Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.707. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.0199 and 0.3793.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{17}H_{11}BrN_2O$.The final anisotropic full-matrix least-squares refinement on F^2 with 194 variables converged at R1 = 3.28%, for the observed data and wR2 = 8.09% for all data. The goodness-of-fit was 1.021. The largest peak in the final difference electron density synthesis was 0.216 $e^-/Å^3$ and the largest hole was -0.330 $e^-/Å^3$ with an RMS deviation of 0.046 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.648 g/cm^3 and F(000), 680 e^-.

CCDC-955664 (**3f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.



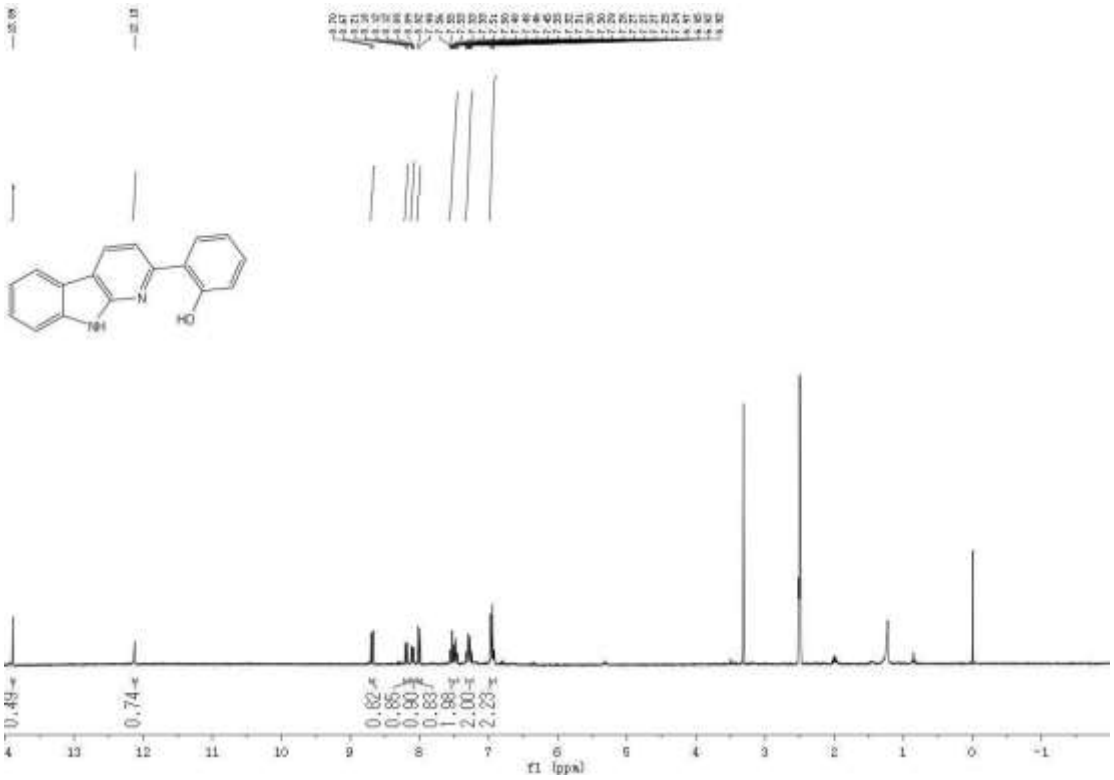
5l

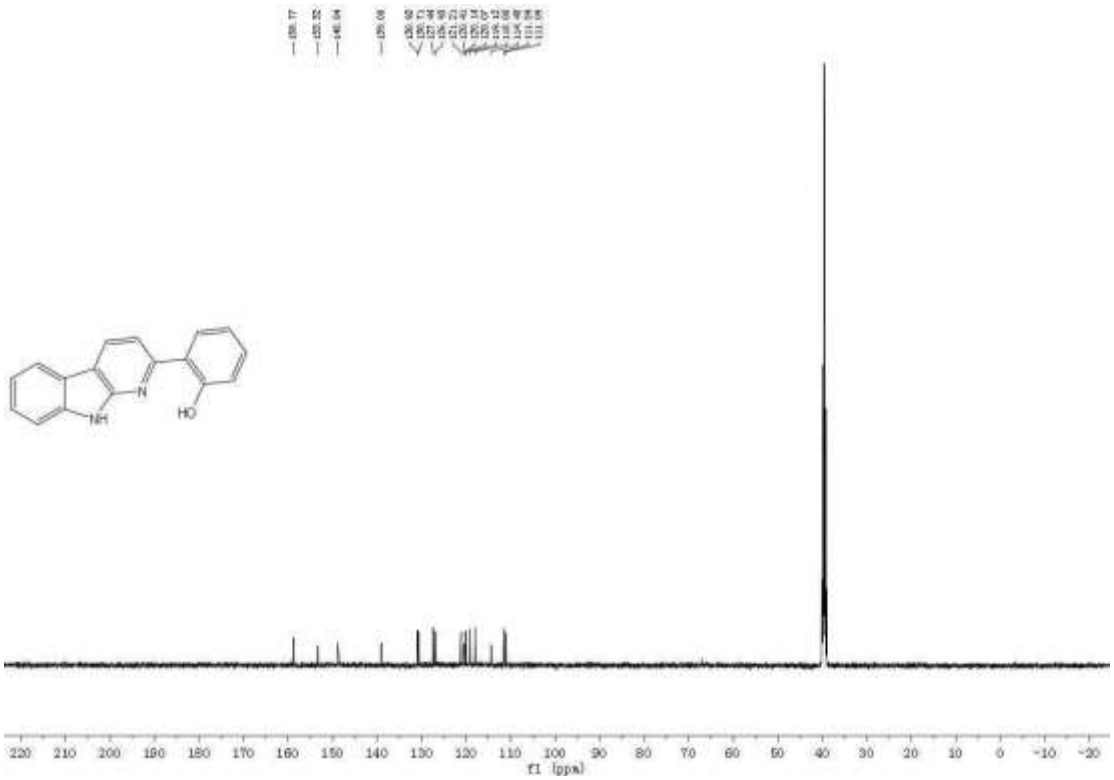
A specimen of $C_{19}H_{16}N_2$, approximate dimensions 0.050 mm x 0.120 mm x 0.400 mm, was used for the X-ray crystallographic analysis.The X-ray intensity data were measured.The total exposure time was 7.56 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 10627 reflections to a maximum θ angle of 25.00° (0.84 Å resolution), of which 2556 were independent (average redundancy 4.158, completeness = 99.3%, R_{int} = 2.45%, R_{sig} = 2.56%) and 1826 (71.44%) were greater than $2\sigma(F^2)$.The final cell constants of a = 4.8242(17) Å, b = 12.372(4) Å, c = 12.693(5) Å, α = 104.81(2)°, β = 95.57(2)°, γ = 90.93(2)°, volume = 728.3(4) $Å^3$, are based upon the refinement of the XYZ-centroids of 3298 reflections above 20 σ(I) with 5.352° < 2θ <50.45°.Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.917. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9712 and 0.9963.

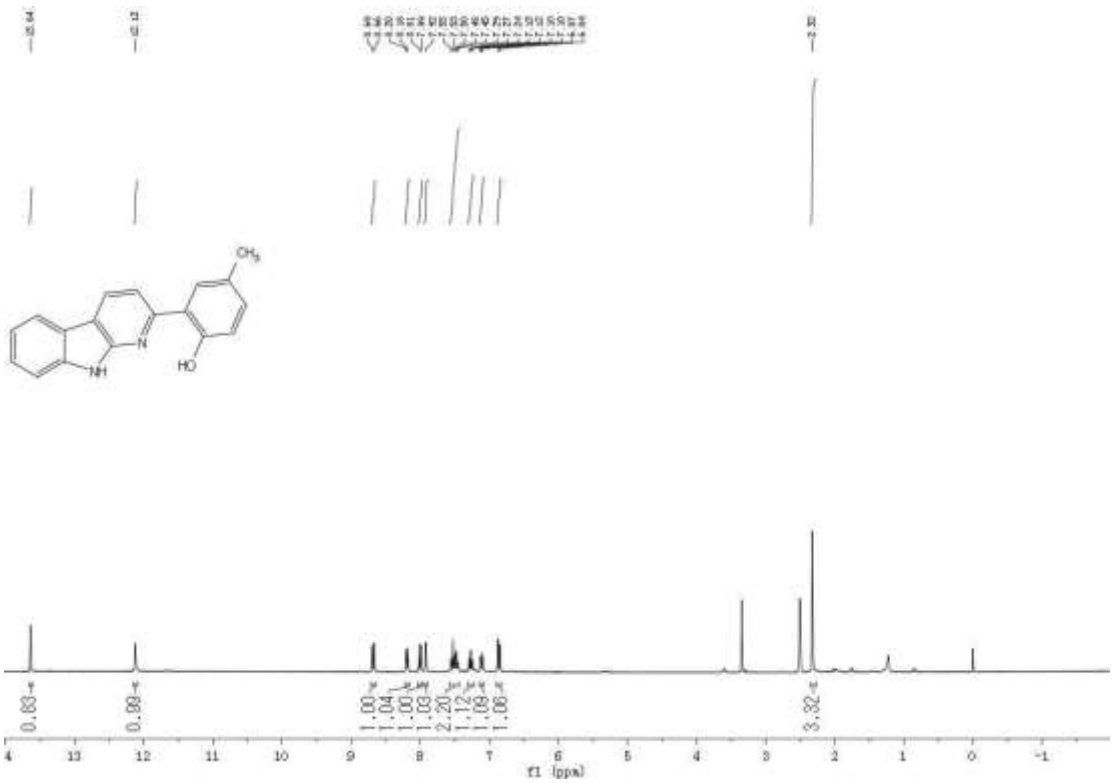
The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 2 for the formula unit, $C_{19}H_{16}N_2$.The final anisotropic full-matrix least-squares refinement on F^2 with 192 variables converged at R1 = 4.42%, for the observed data and wR2 = 12.47% for all data. The goodness-of-fit was 1.033. The largest peak in the final difference electron density synthesis was 0.134 $e^-/Å^3$ and the largest hole was -0.184 $e^-/Å^3$ with an RMS deviation of 0.033 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.242 g/cm^3 and F(000), 288 e^-.

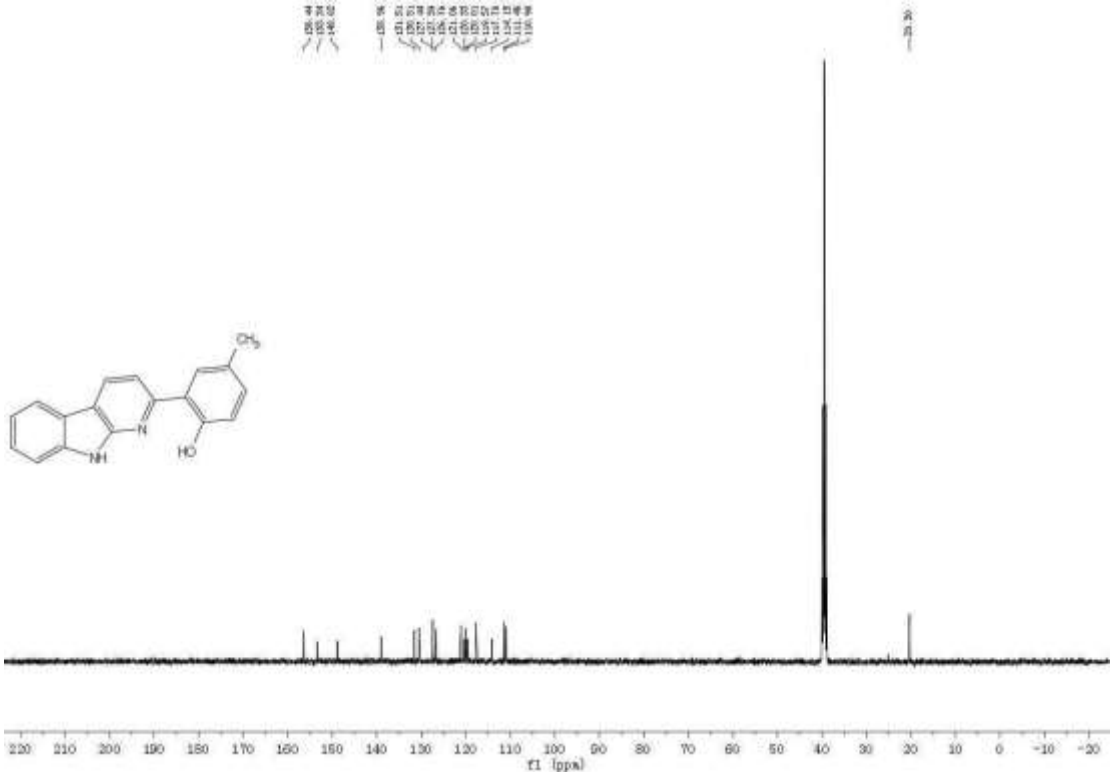
CCDC-955665 (**5l**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

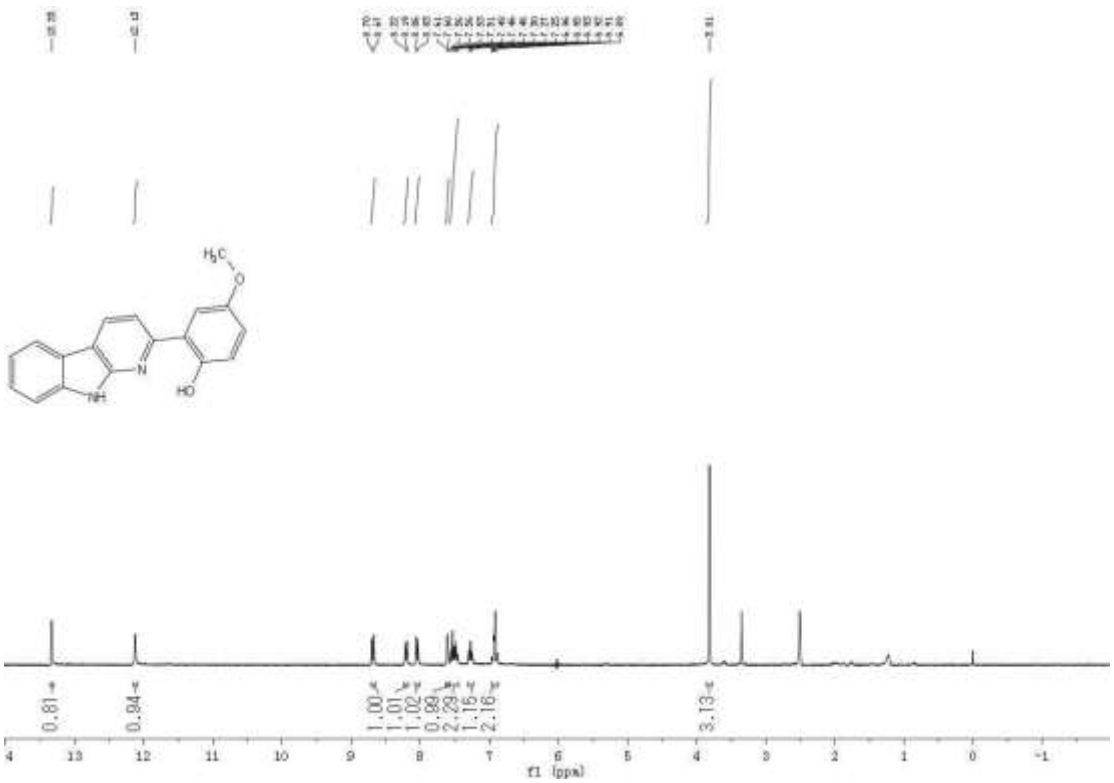
^{1}H NMR and ^{13}C NMR spectra of 3a-3l, 5a-5n

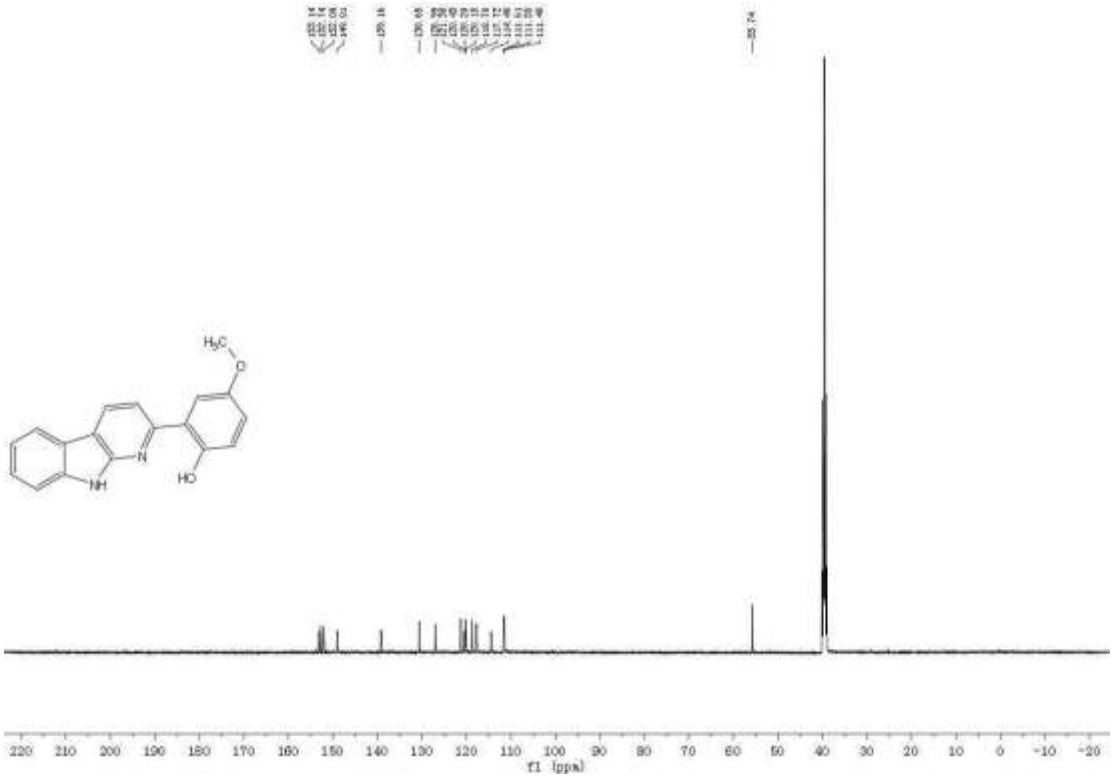


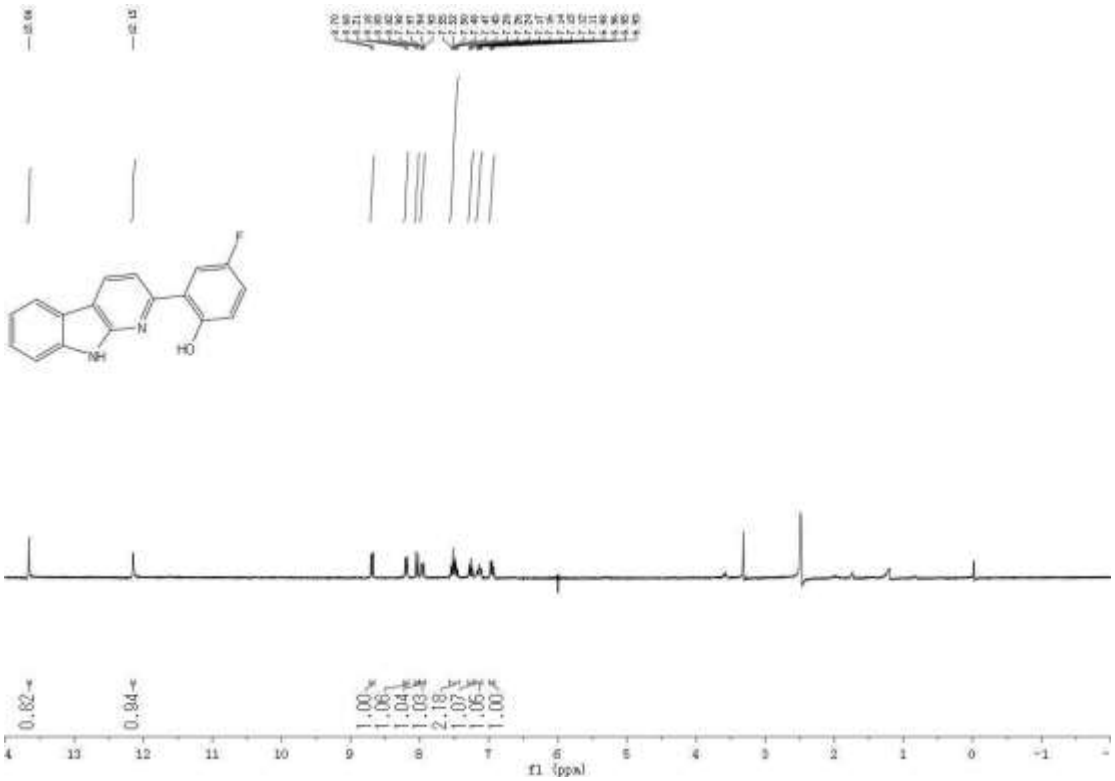








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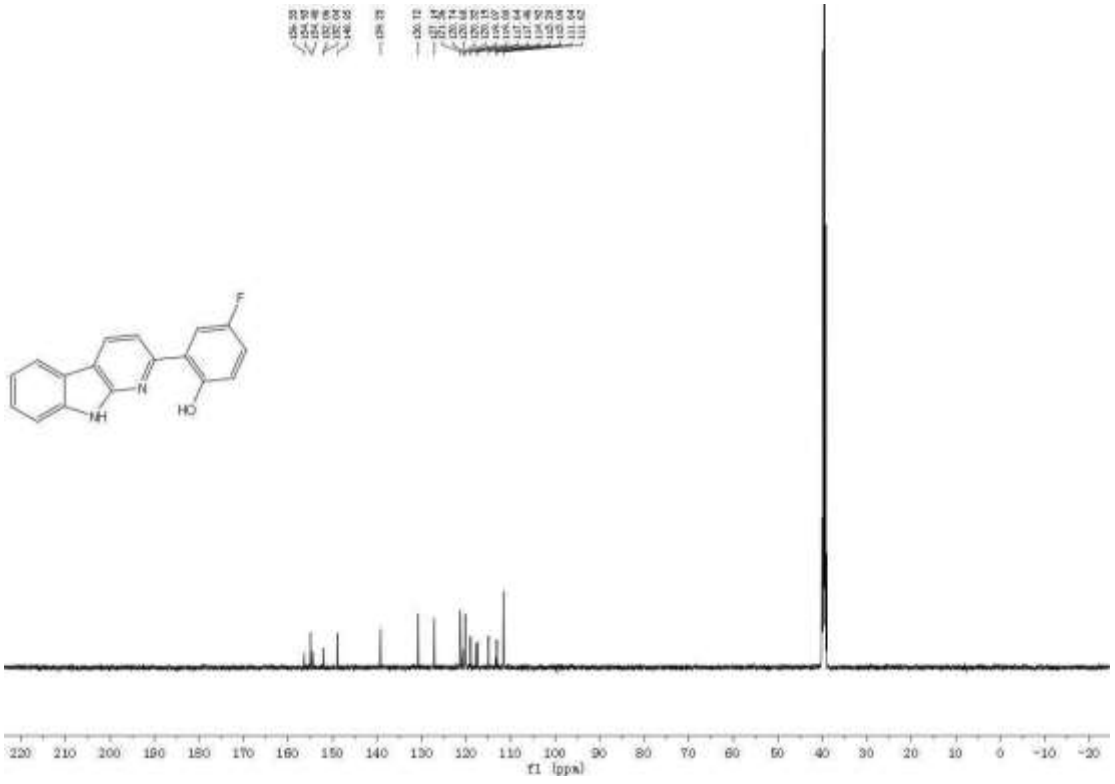
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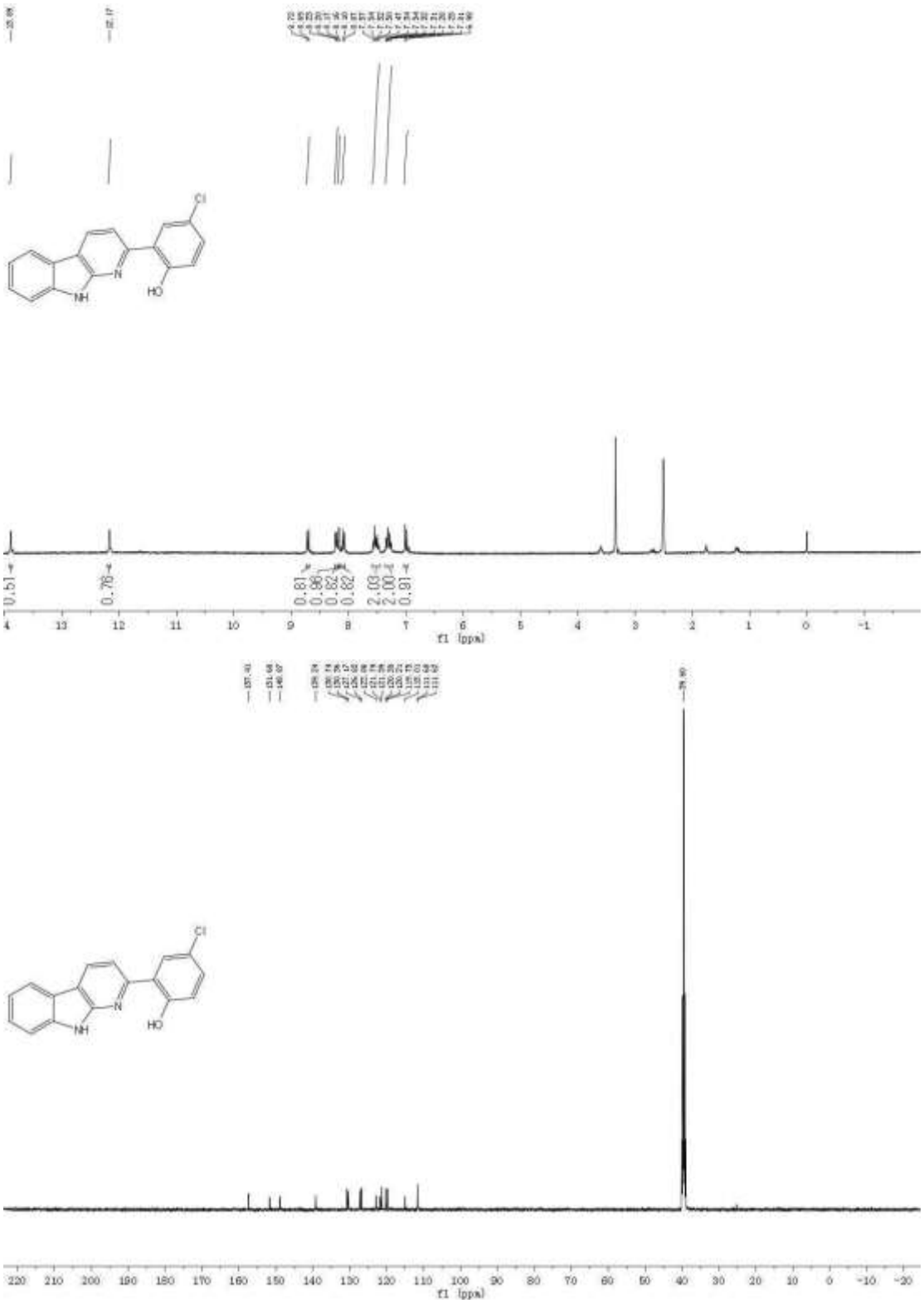

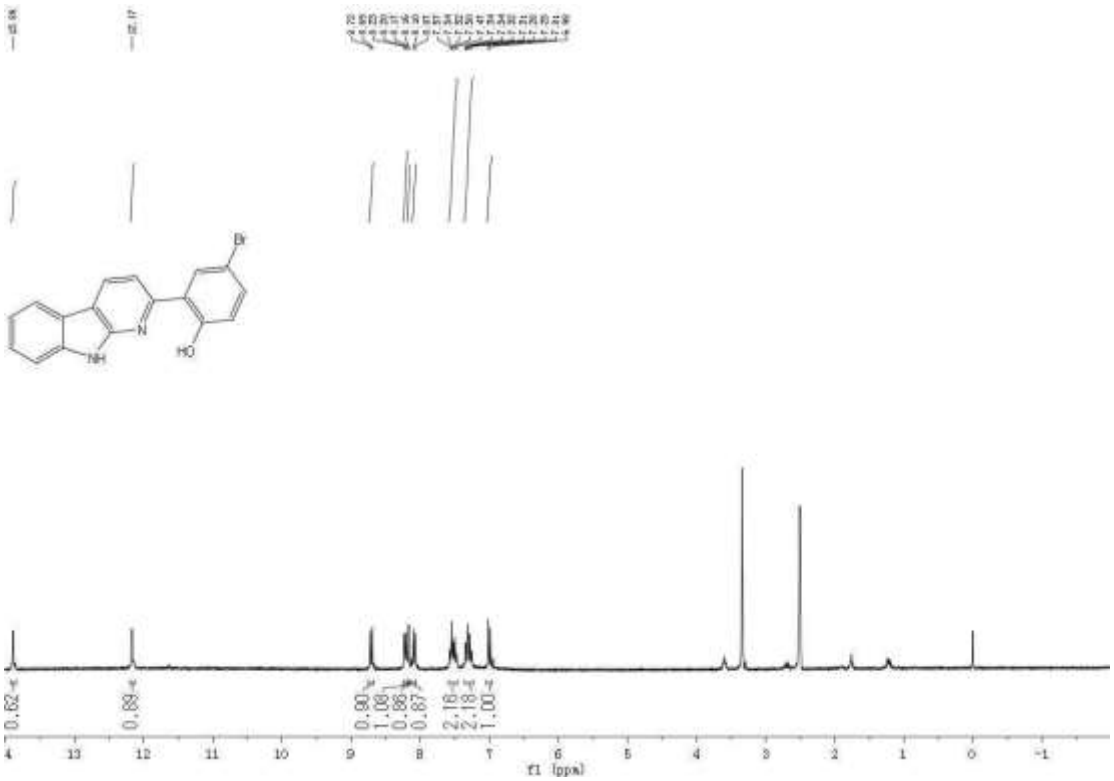
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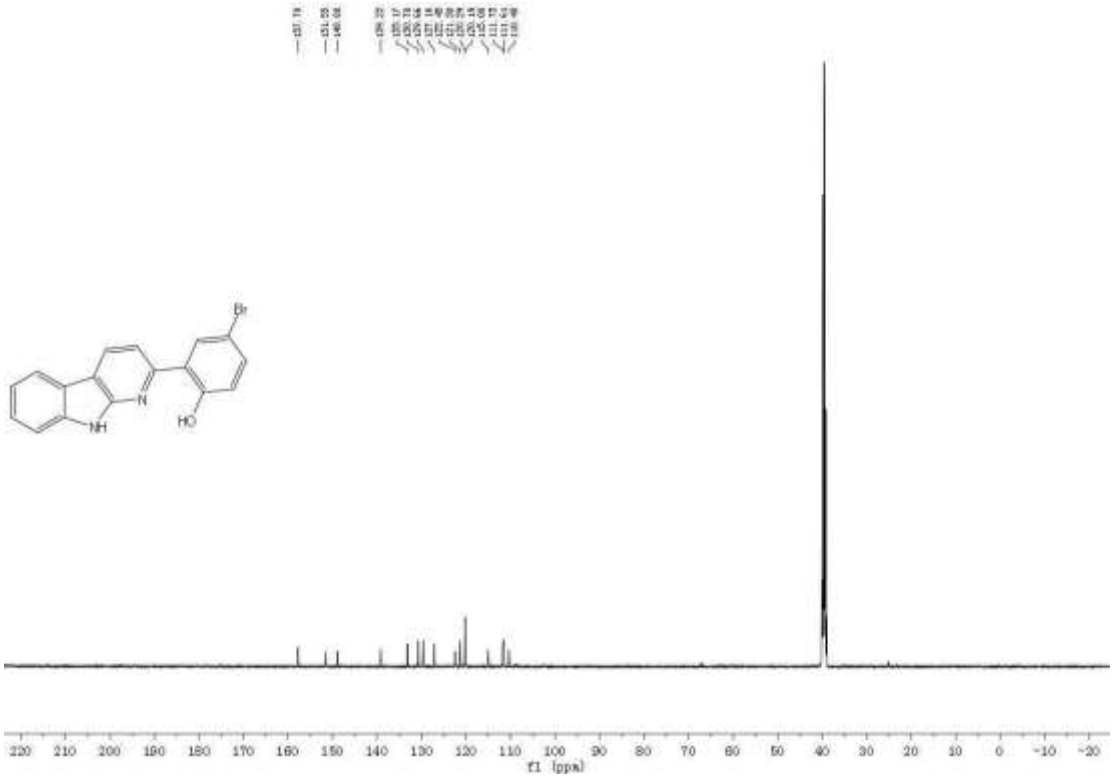
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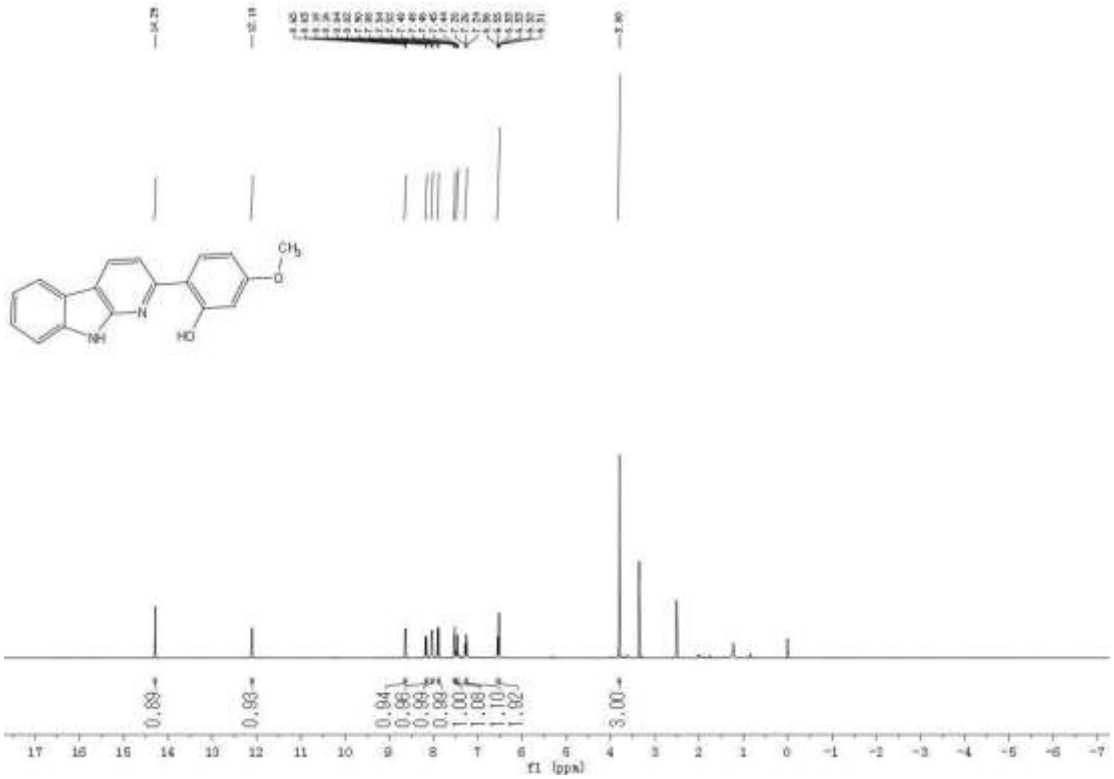

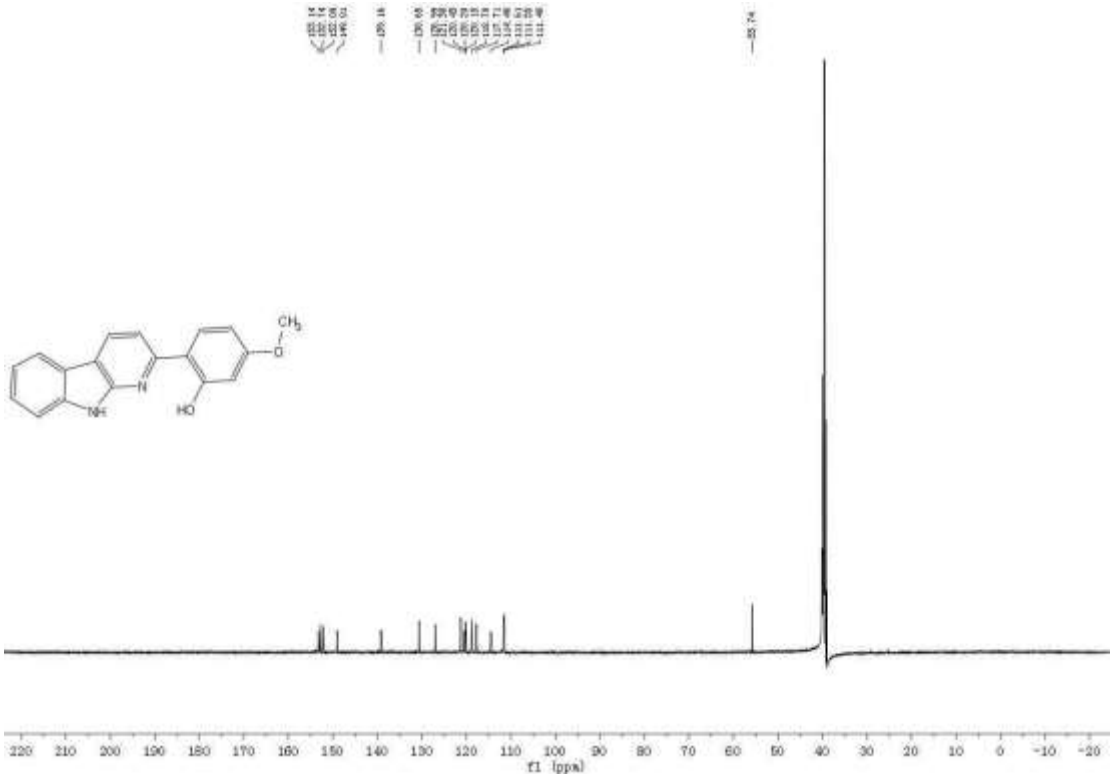

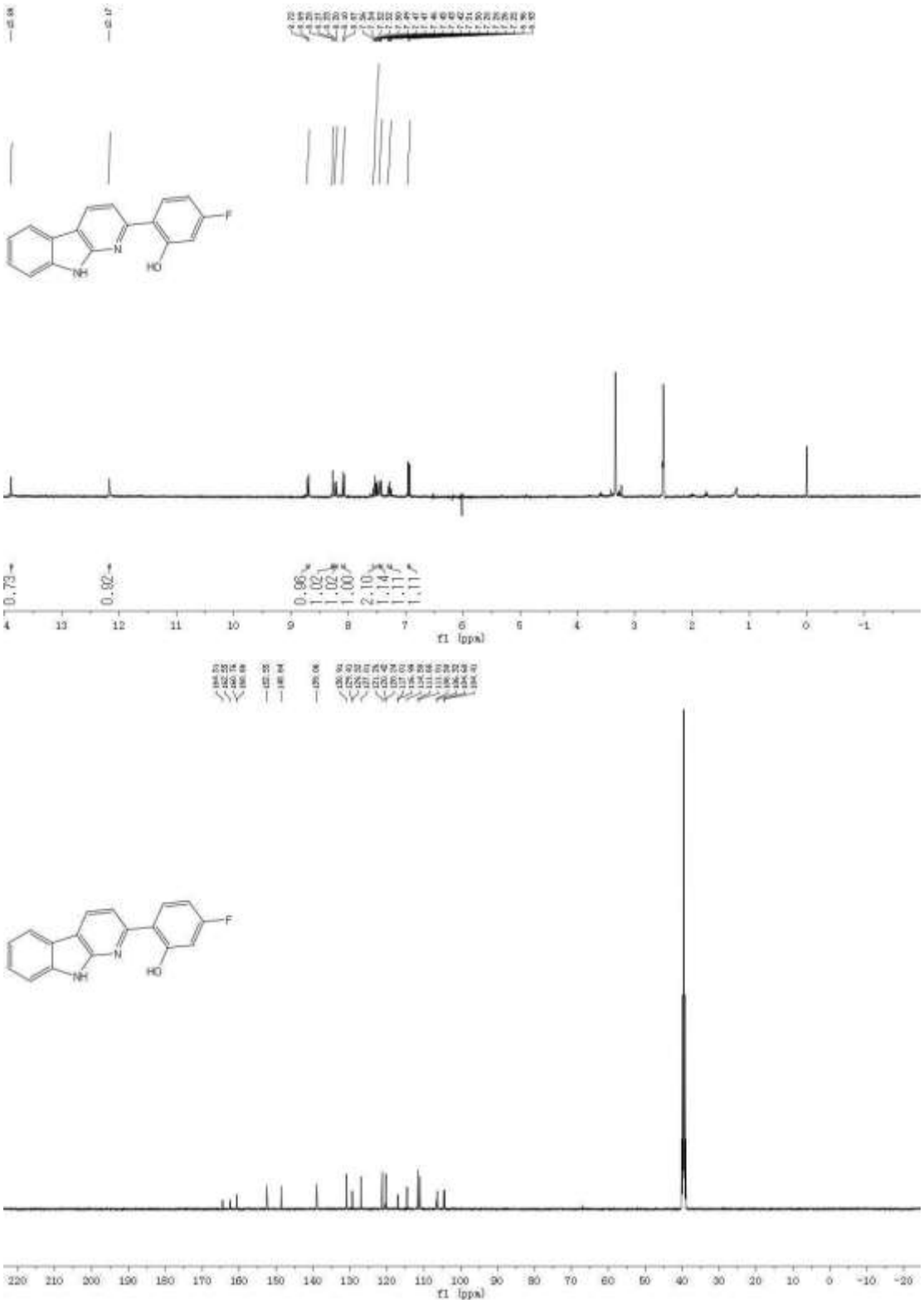
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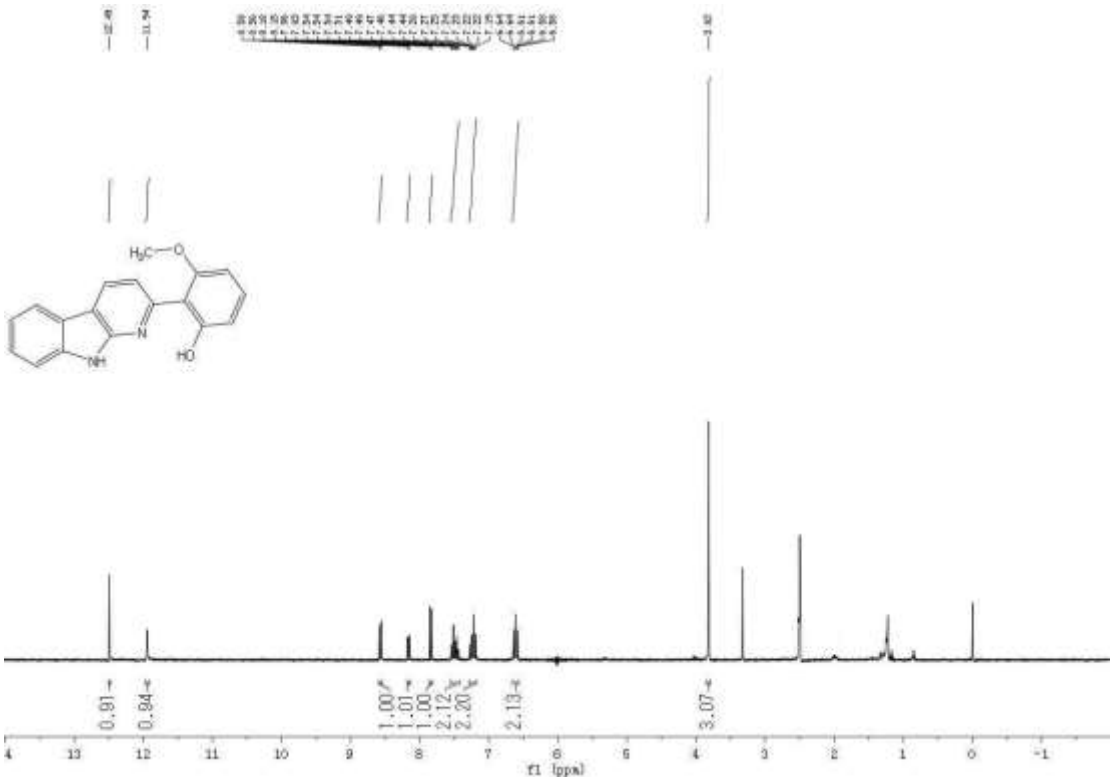
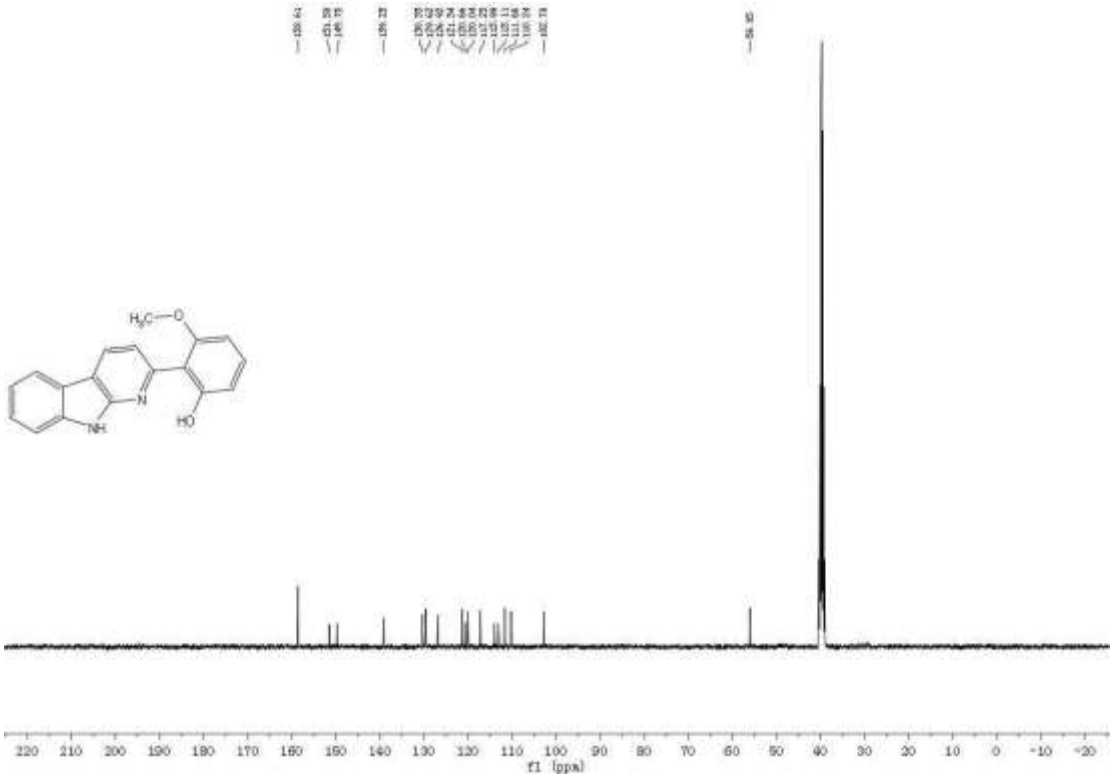
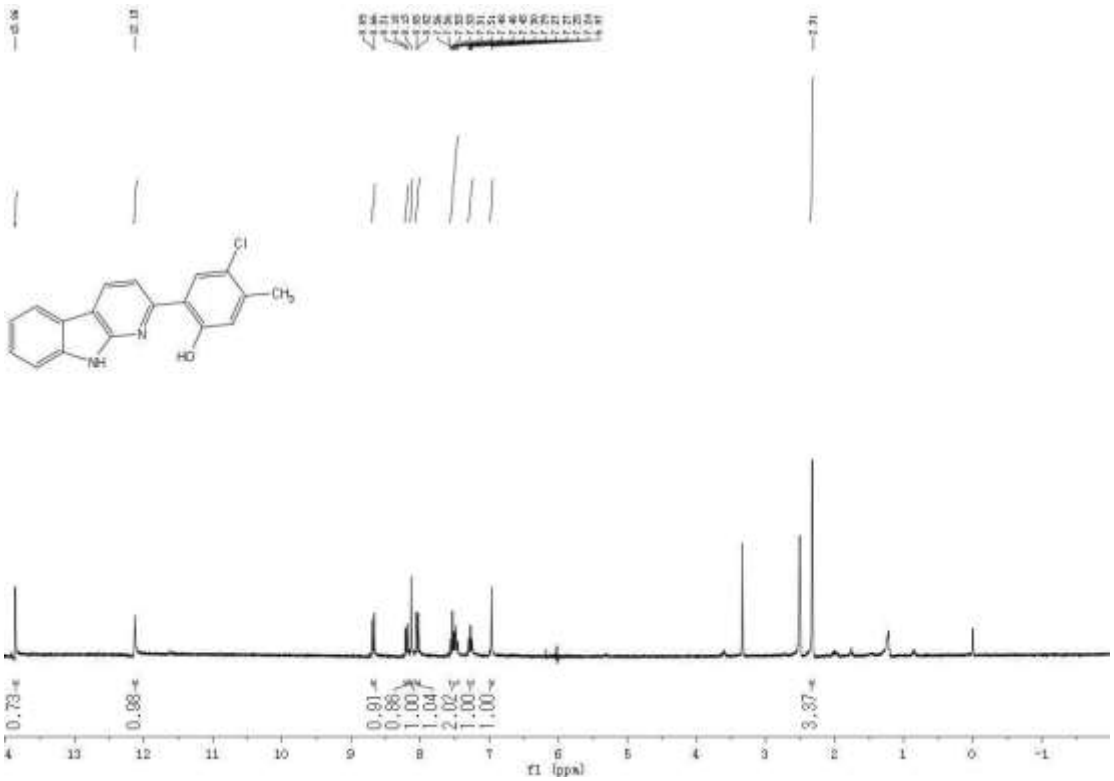
f1 (ppm)
F
N
NH
HO
f1 (ppm)



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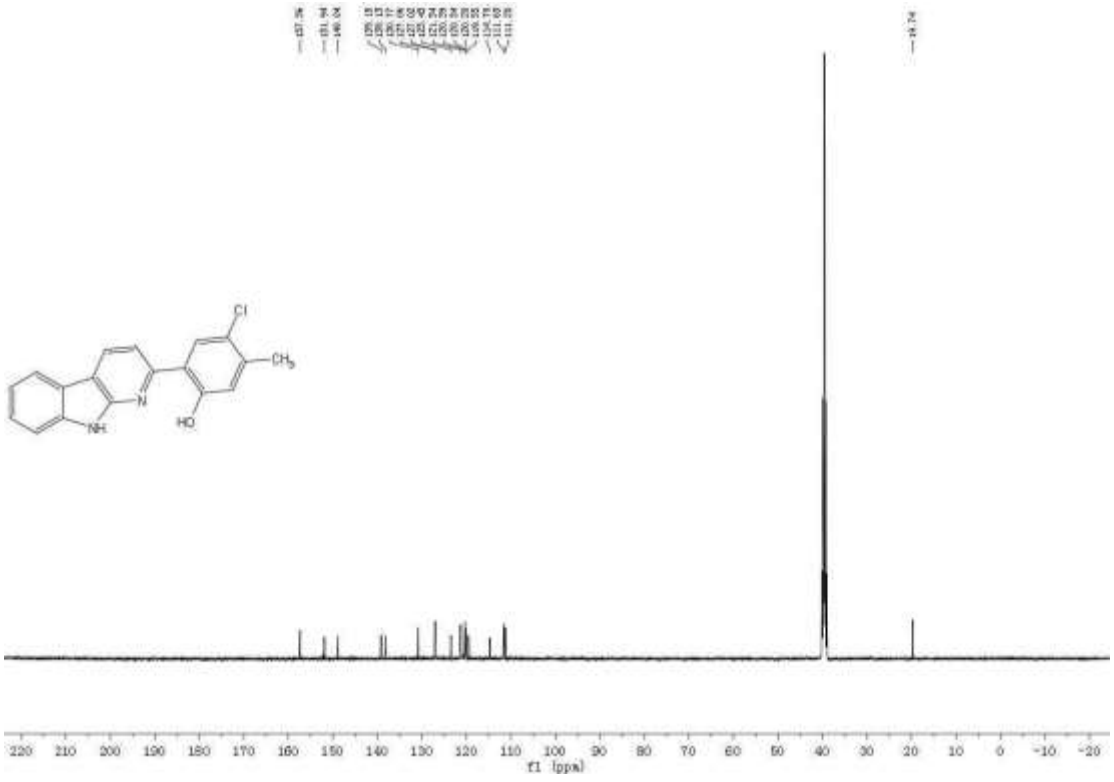
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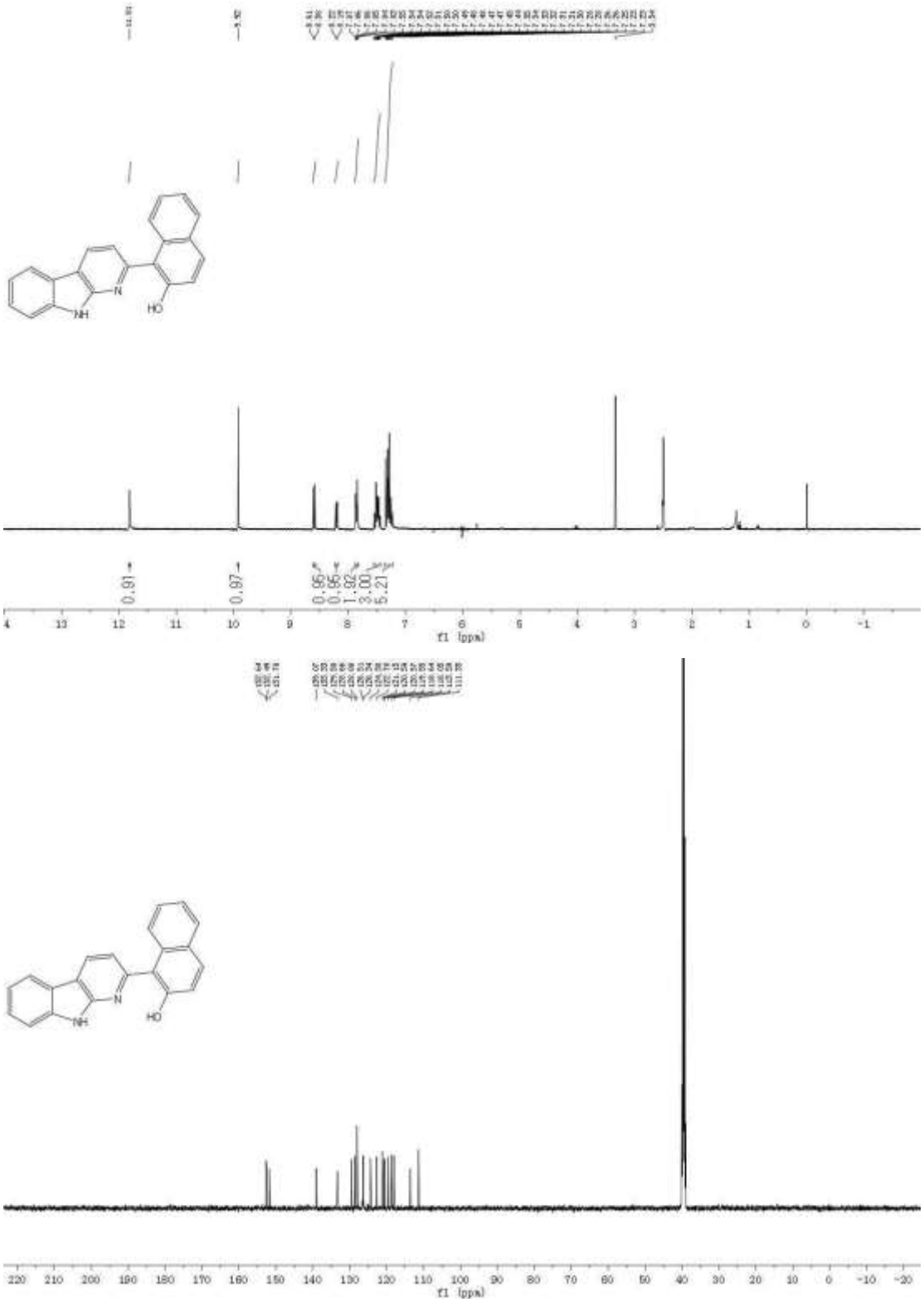
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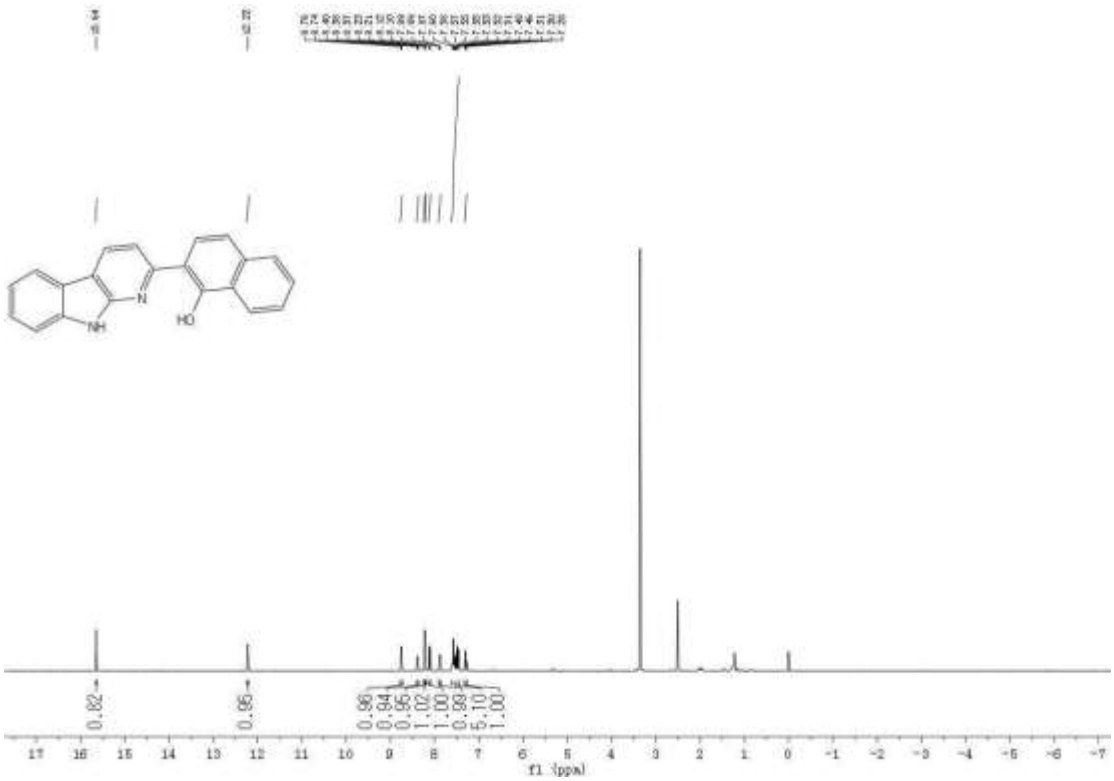
HO
f1 (ppm)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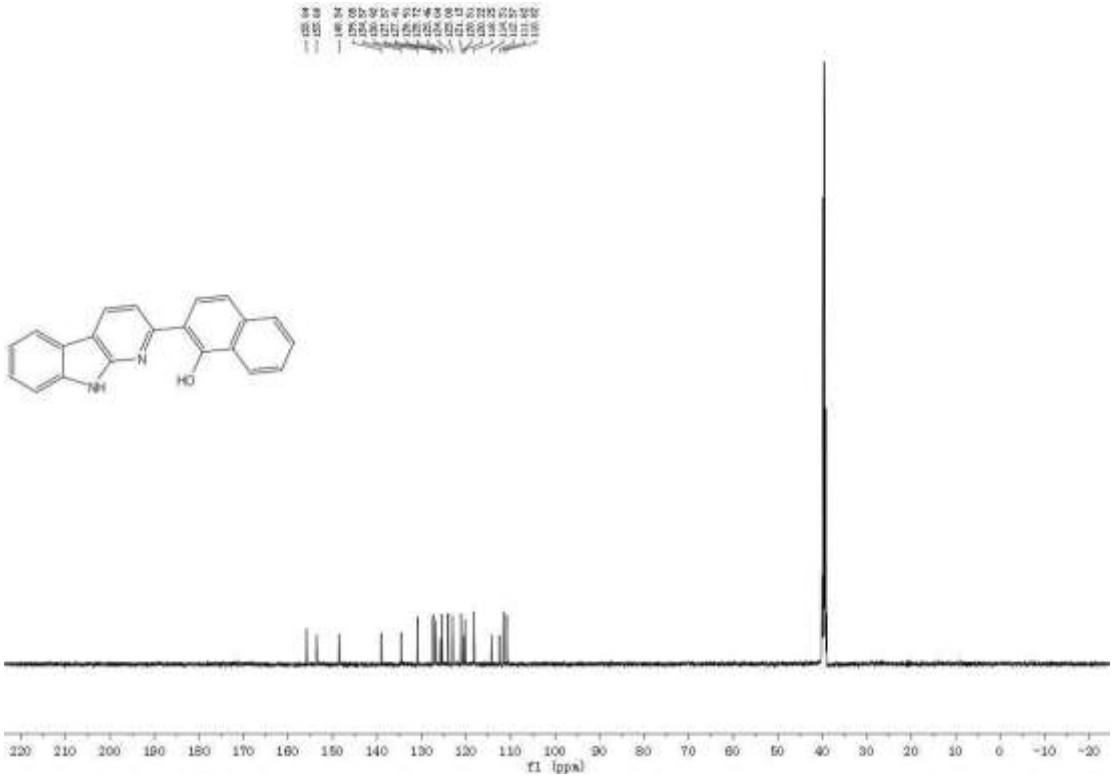
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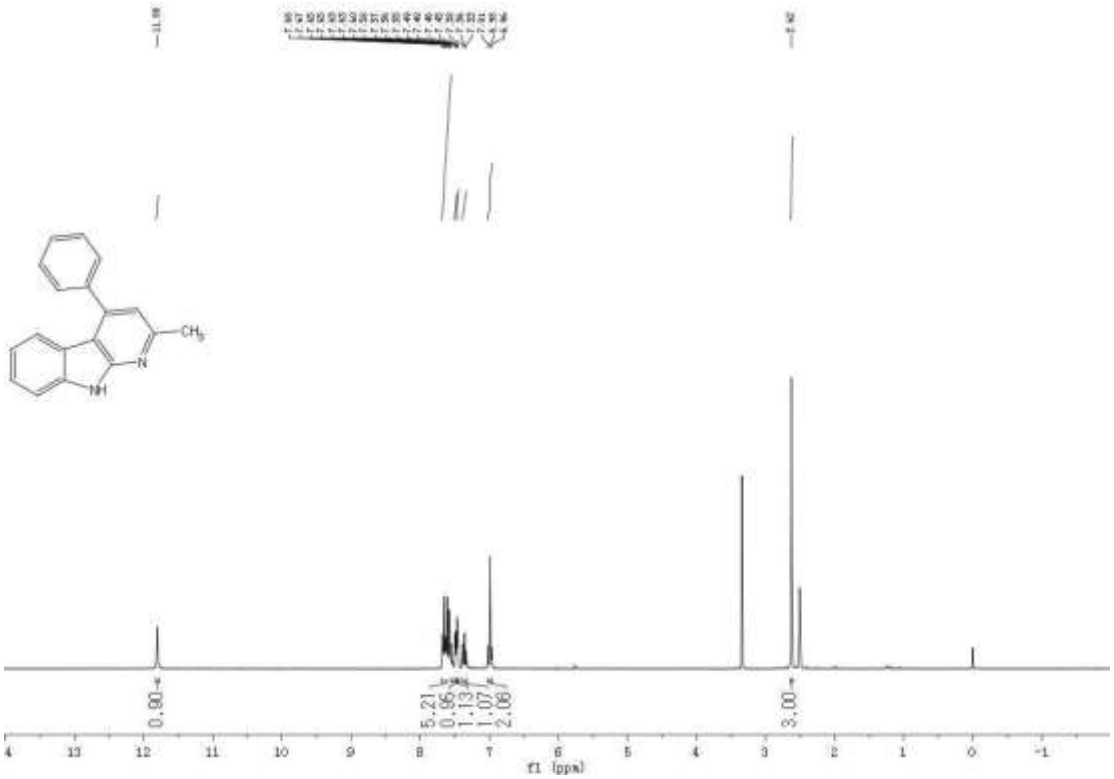
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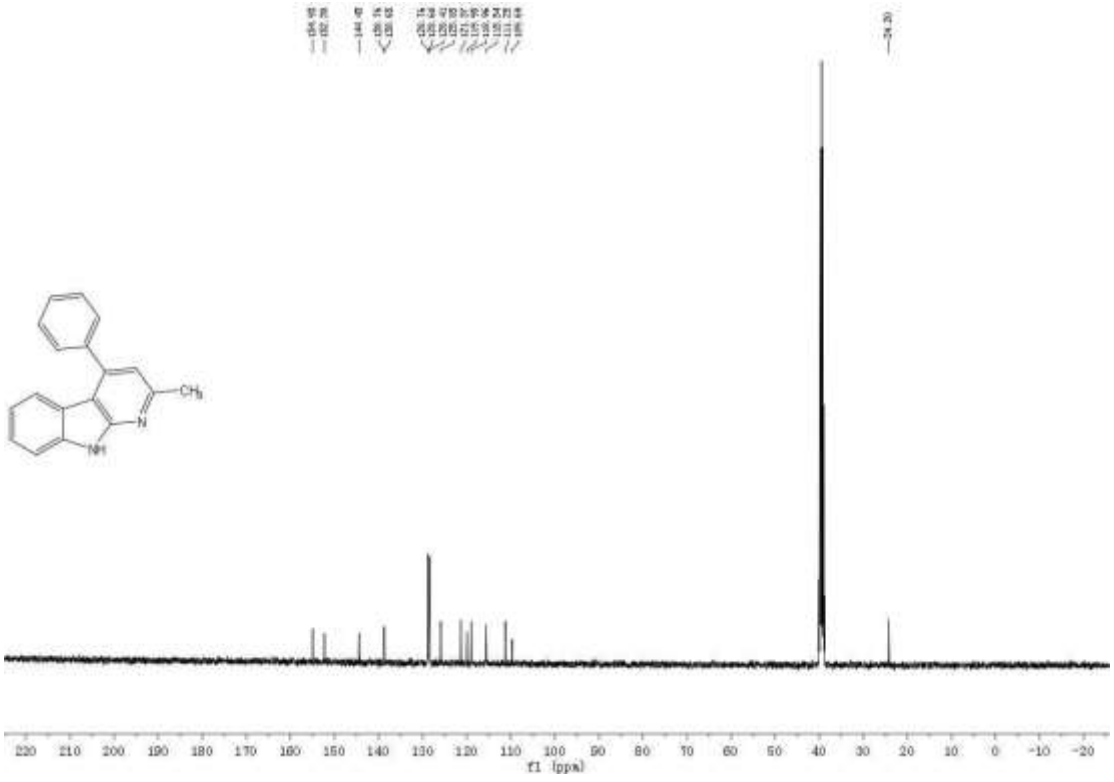
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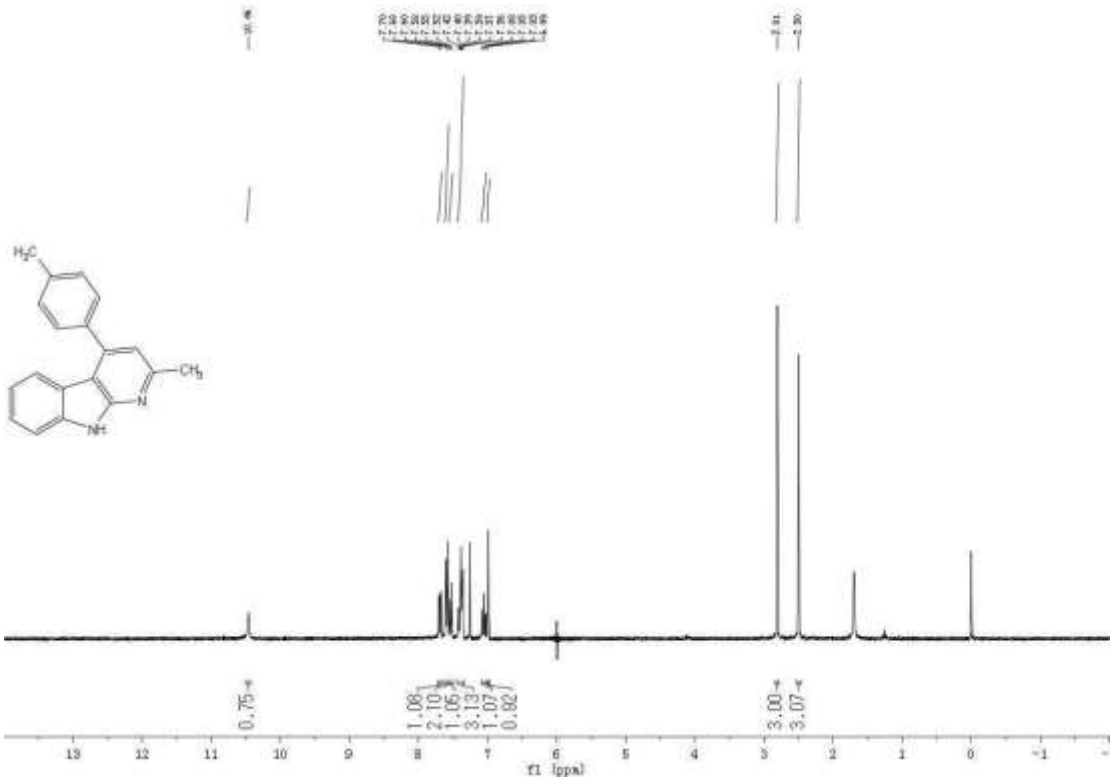
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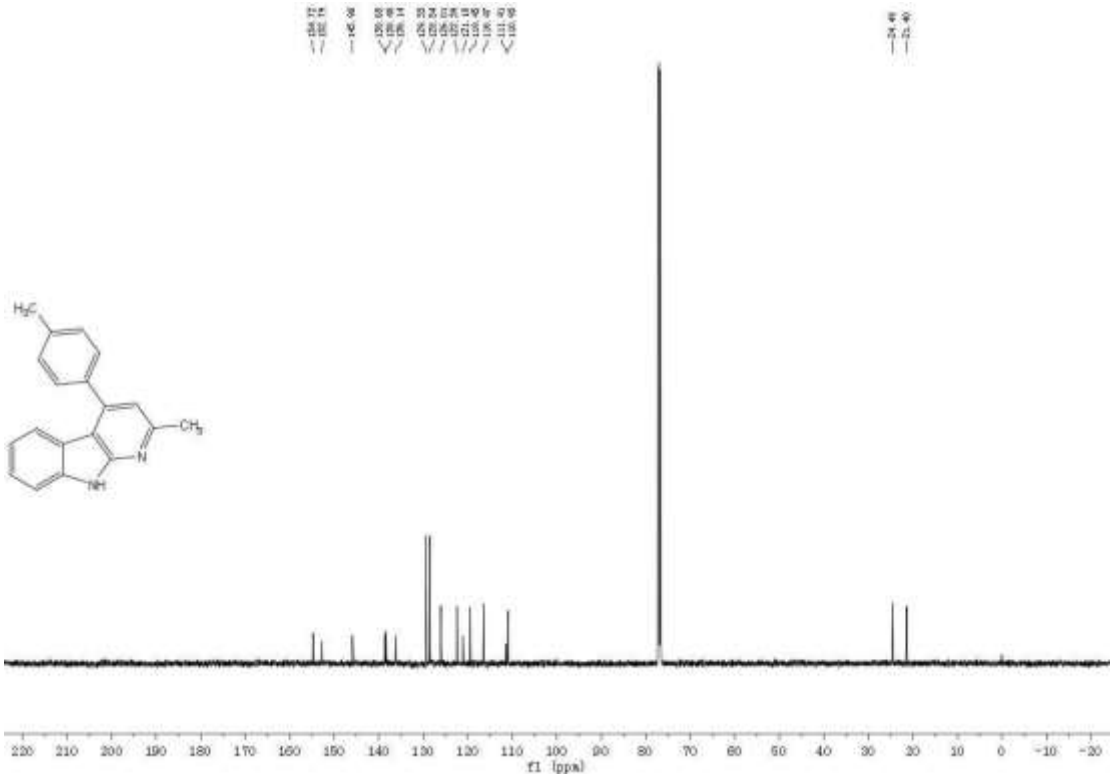
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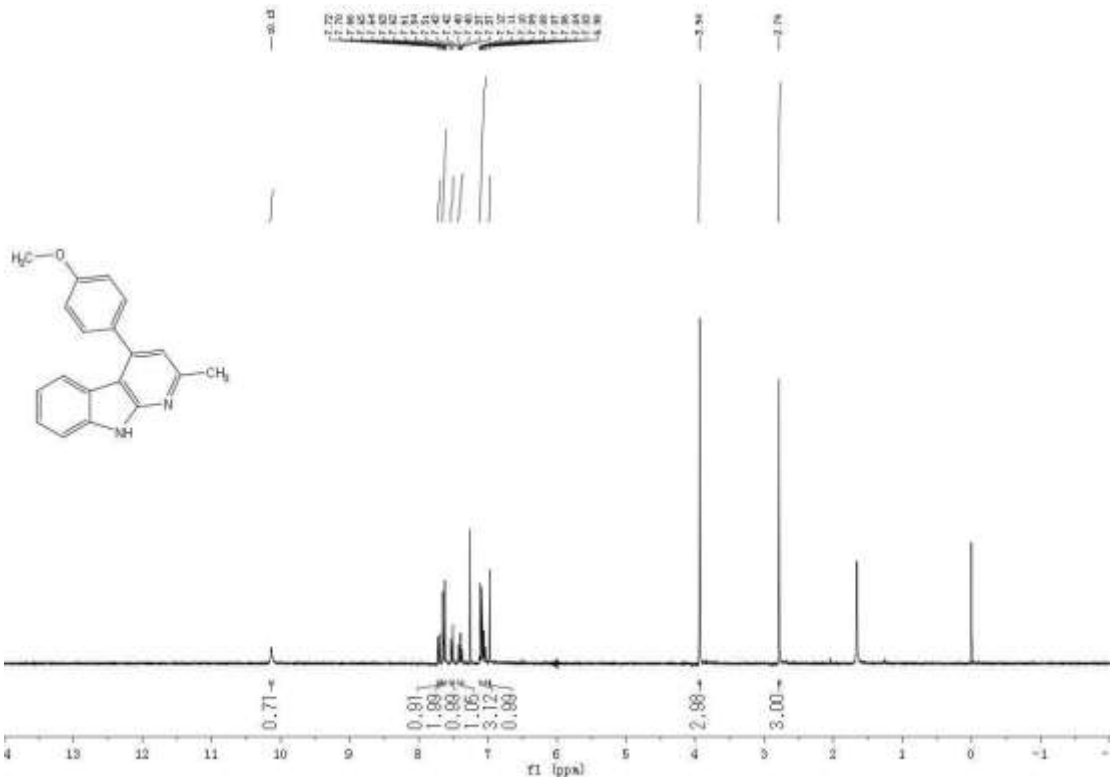
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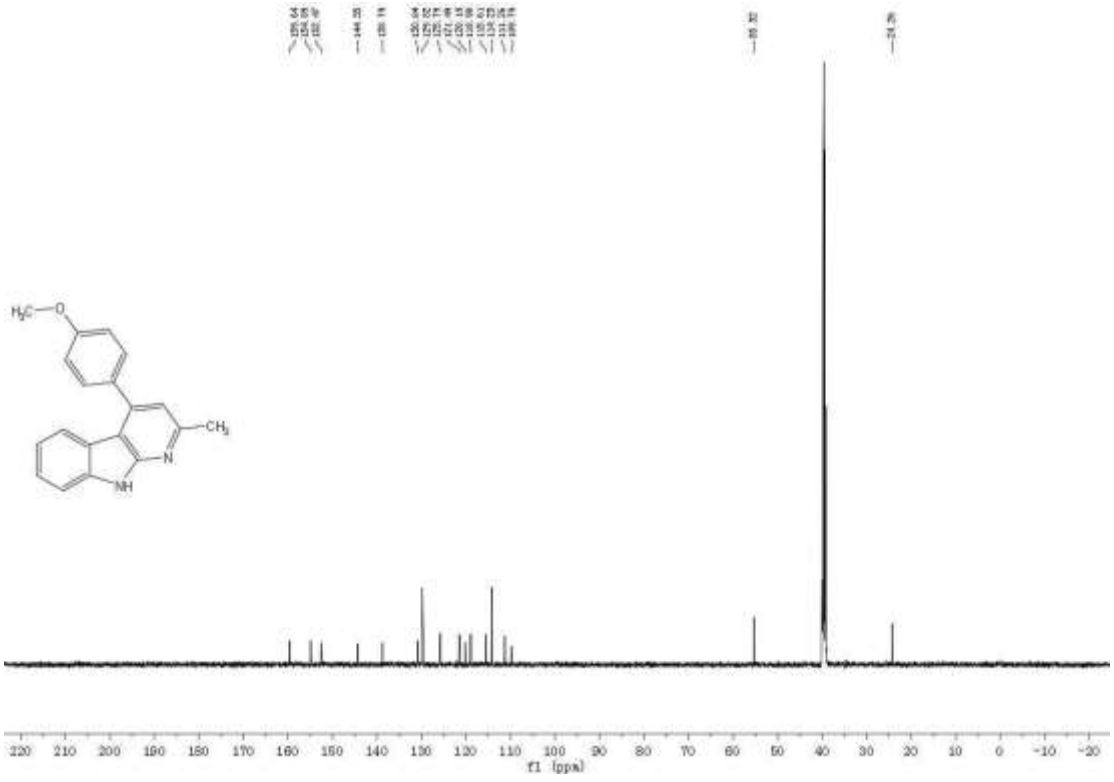
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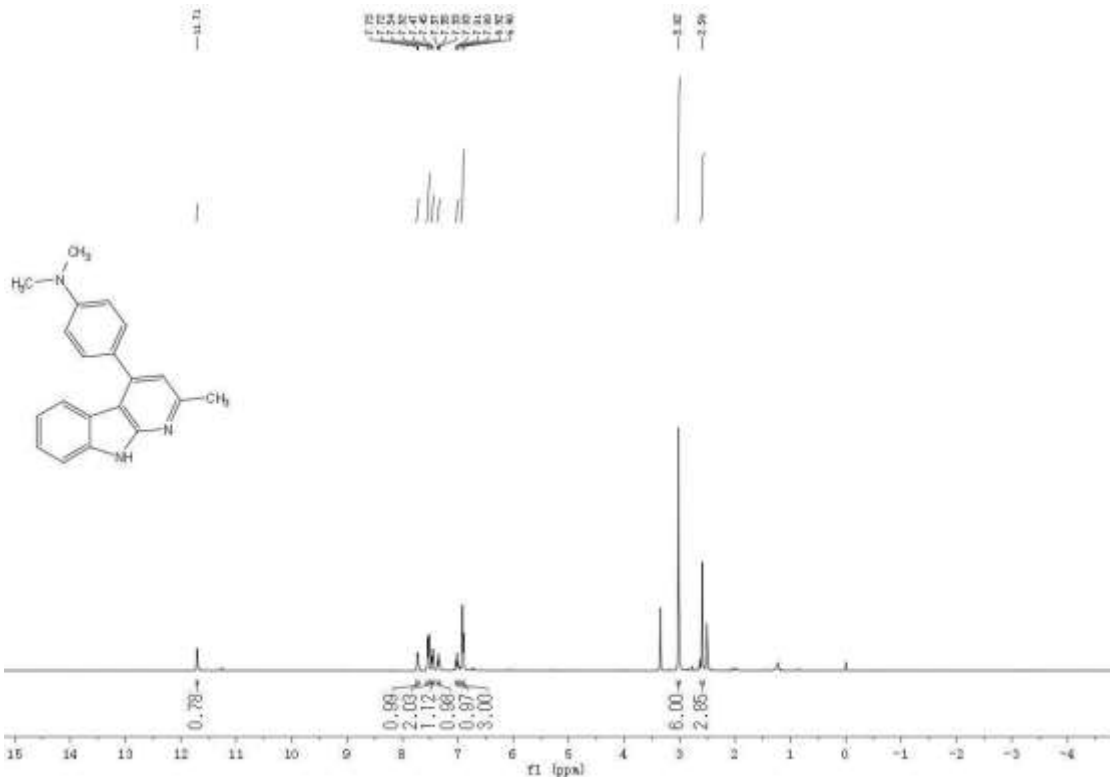
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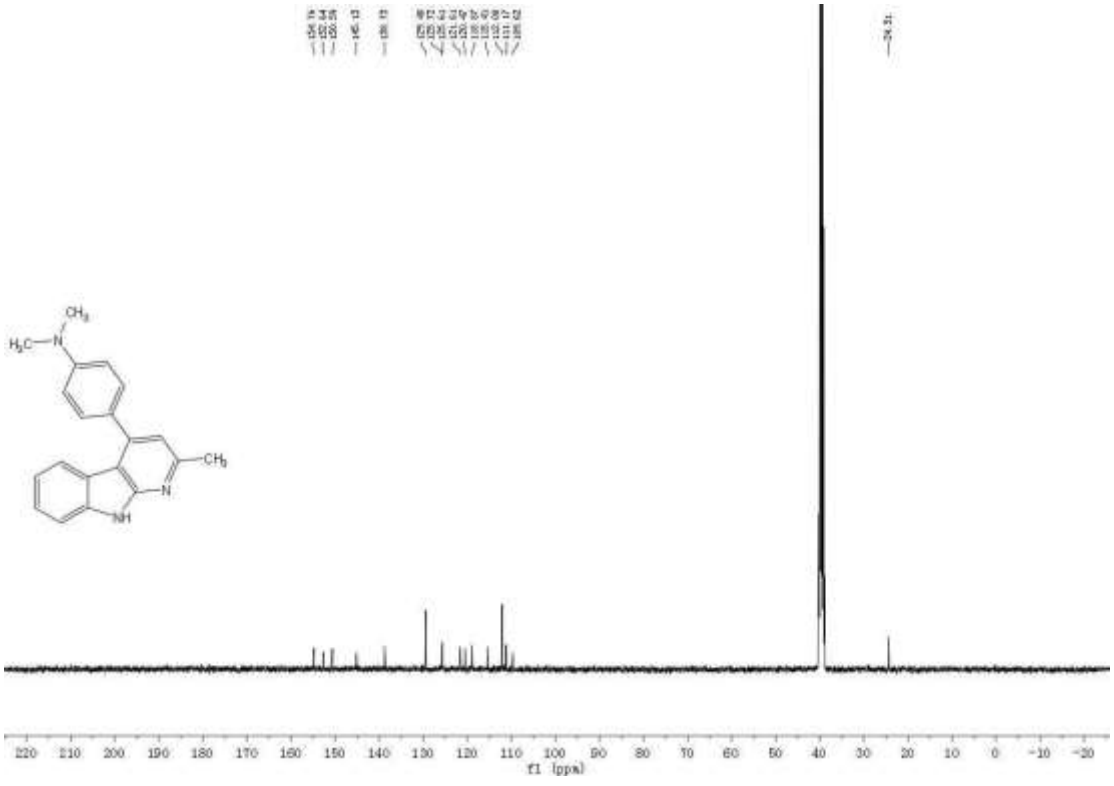
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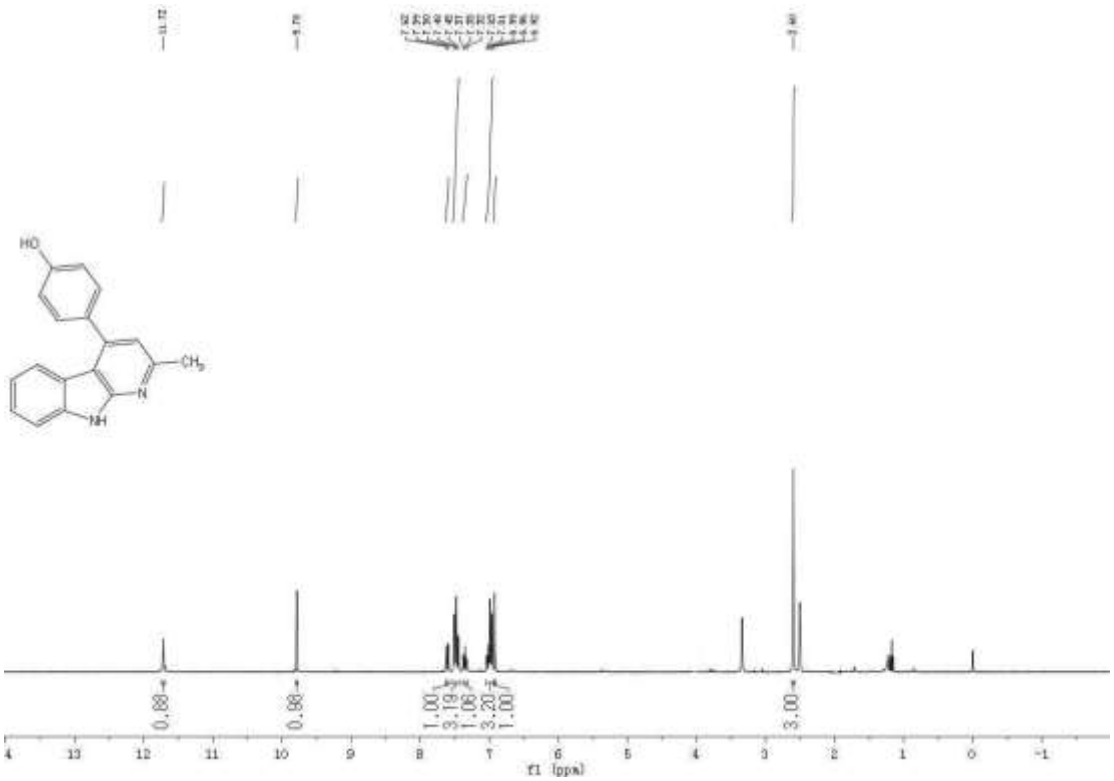
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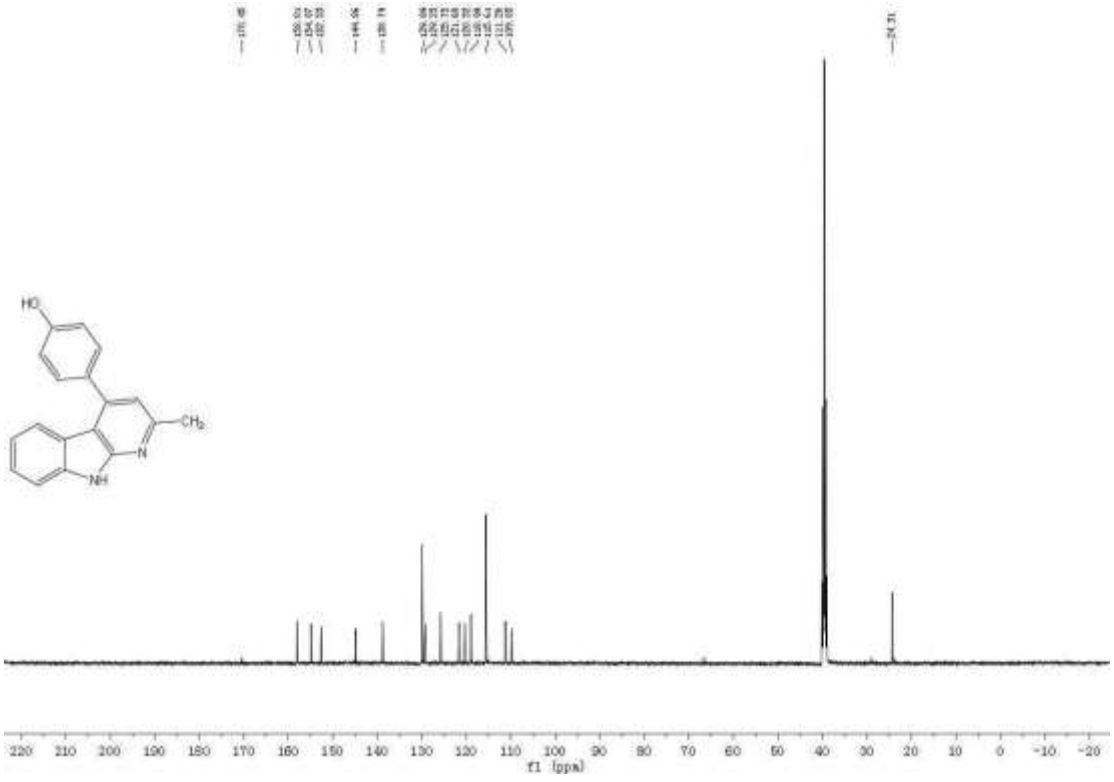
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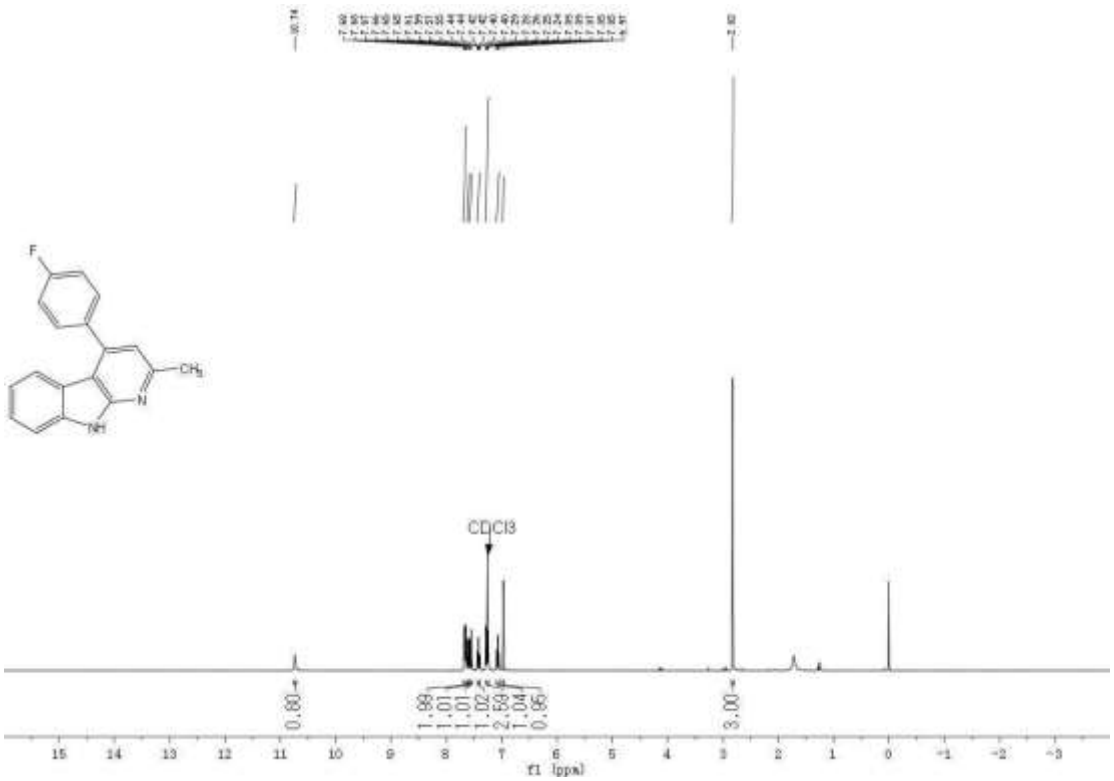
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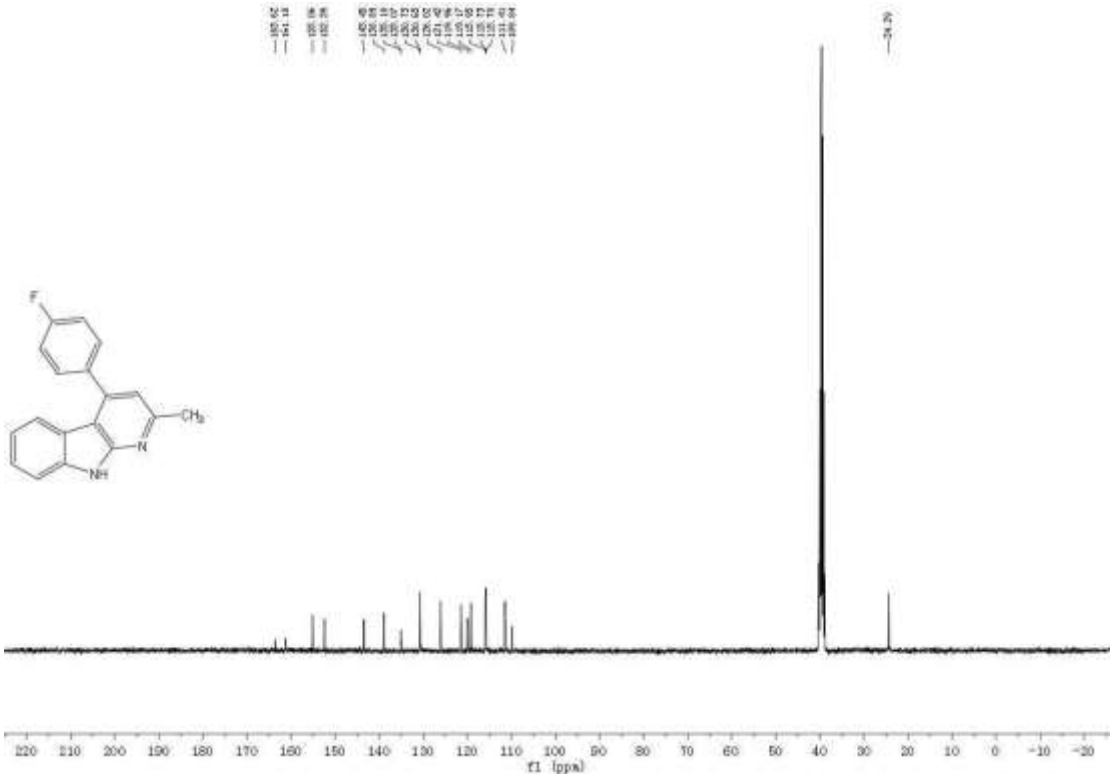
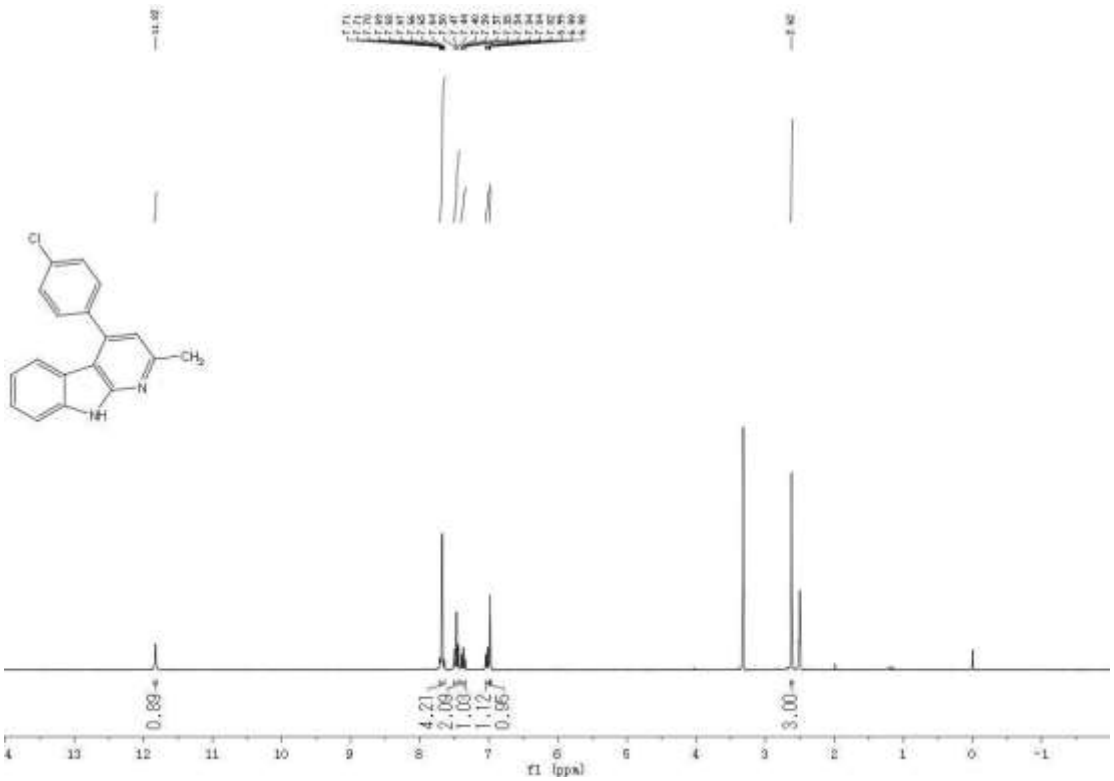
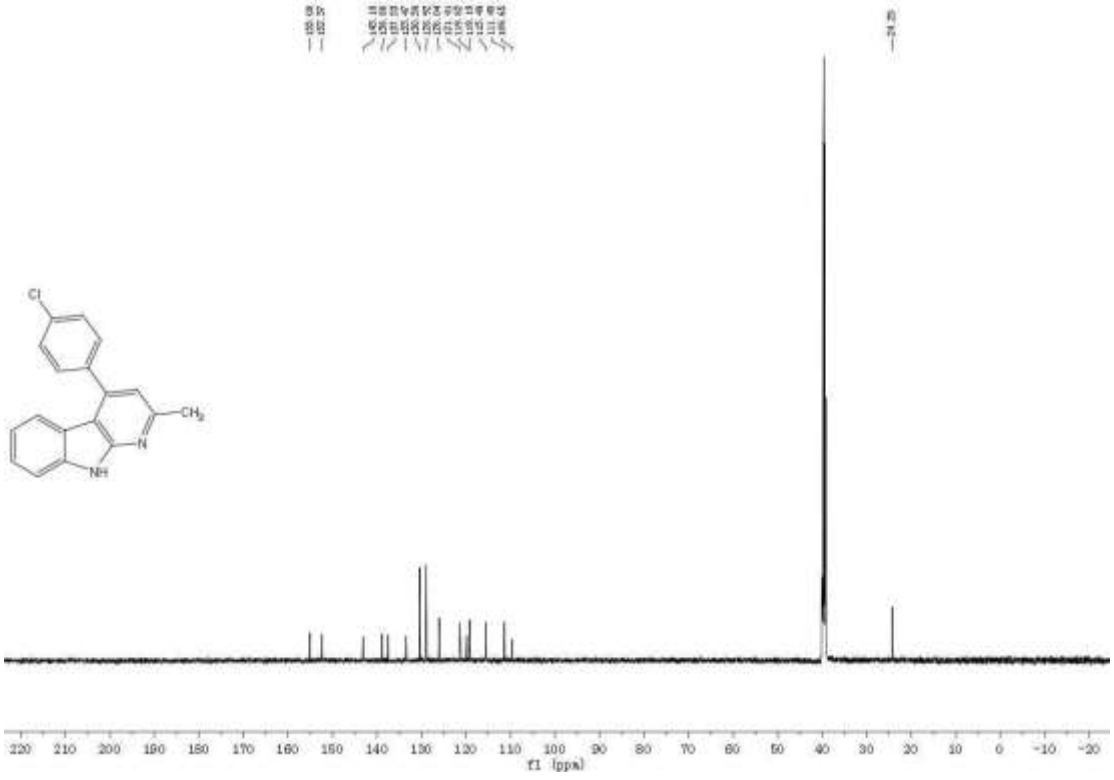
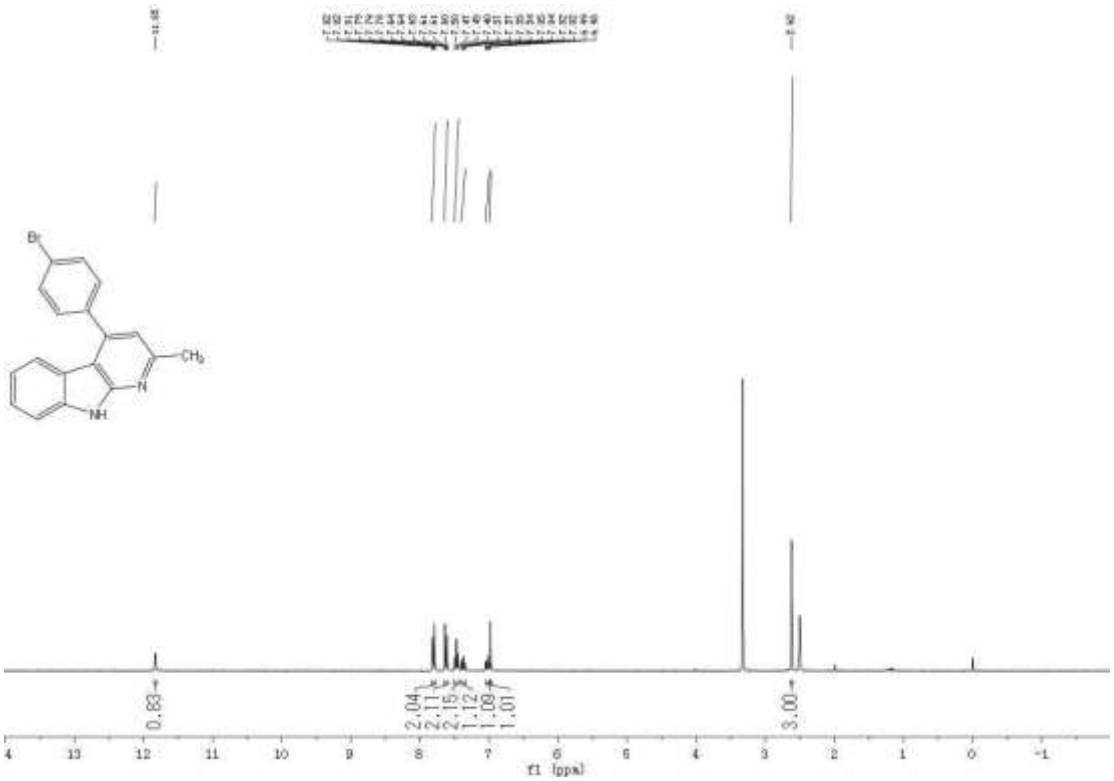
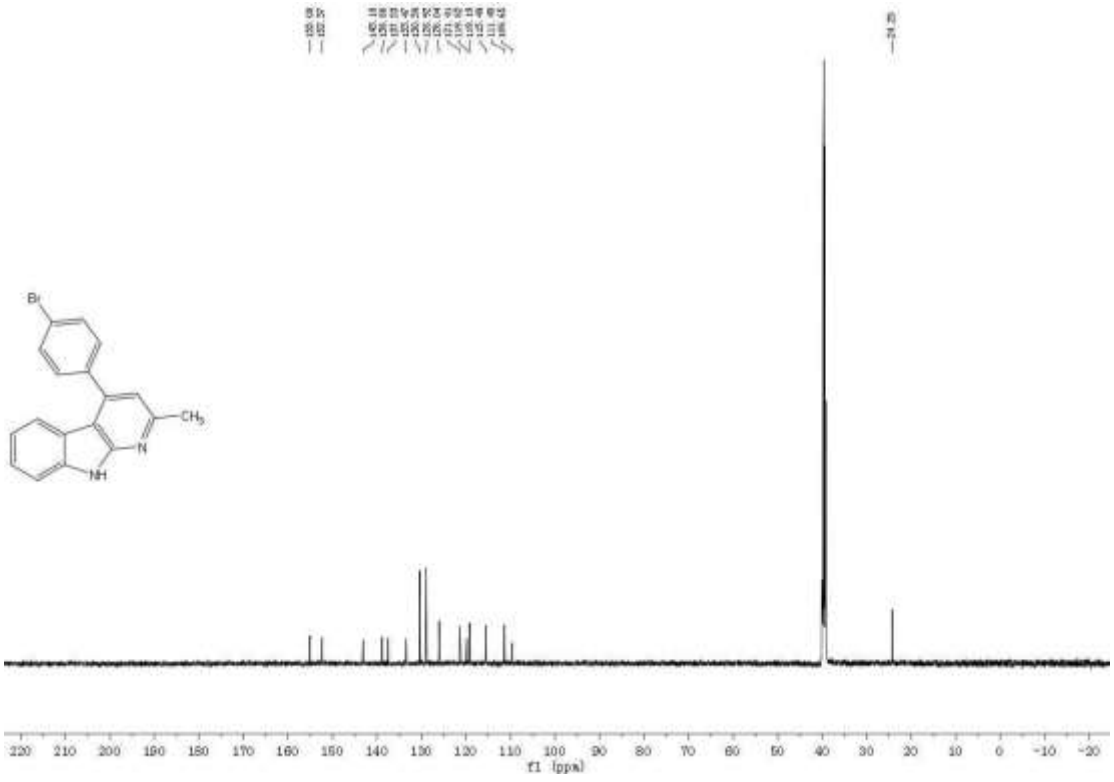
3.00
f1 (ppm)

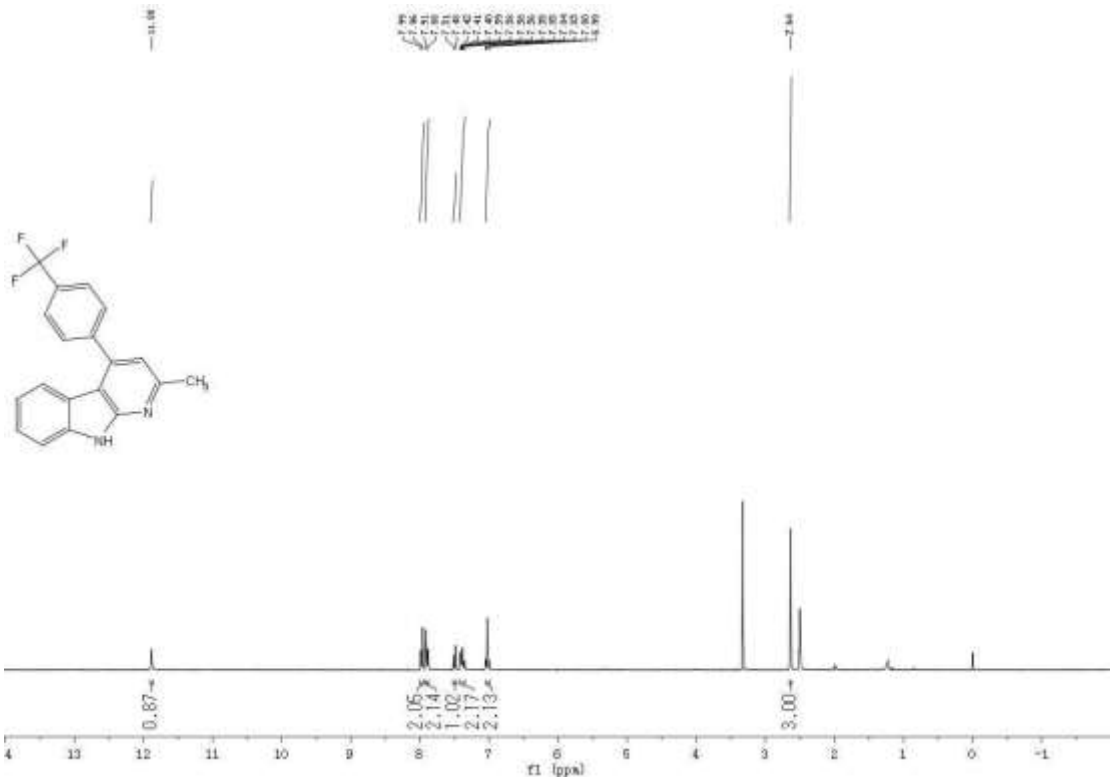

F
CH3
N
NH
f1 (ppm)

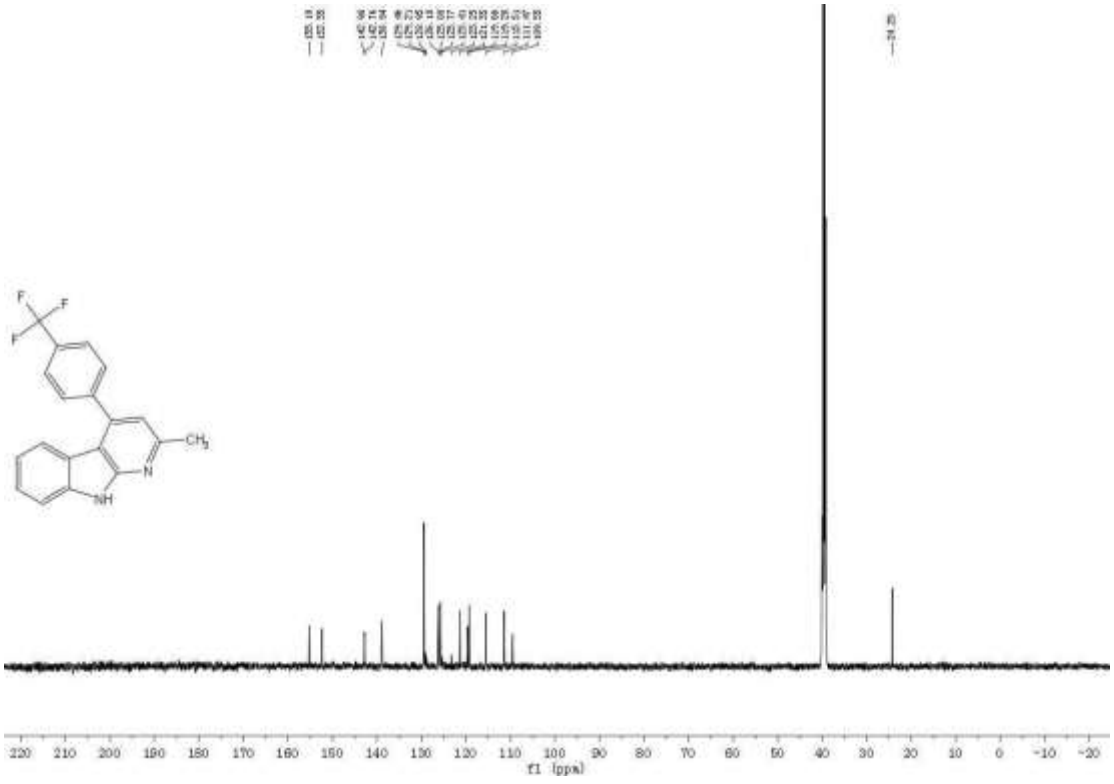


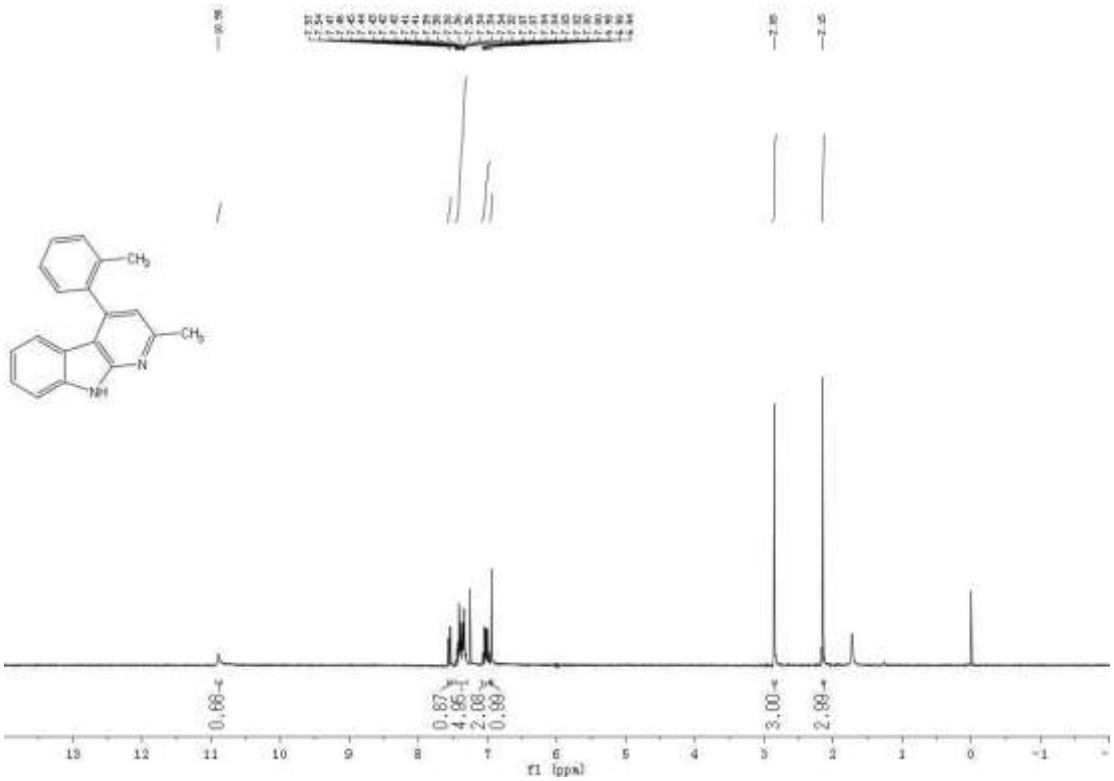


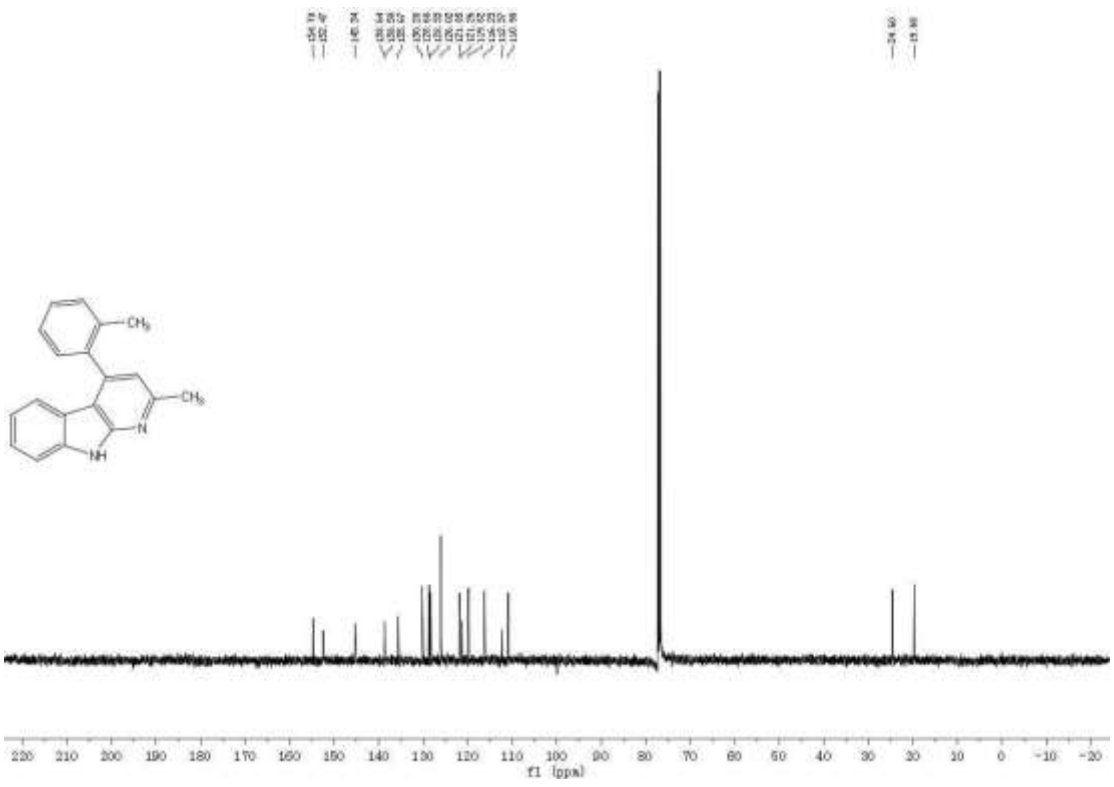


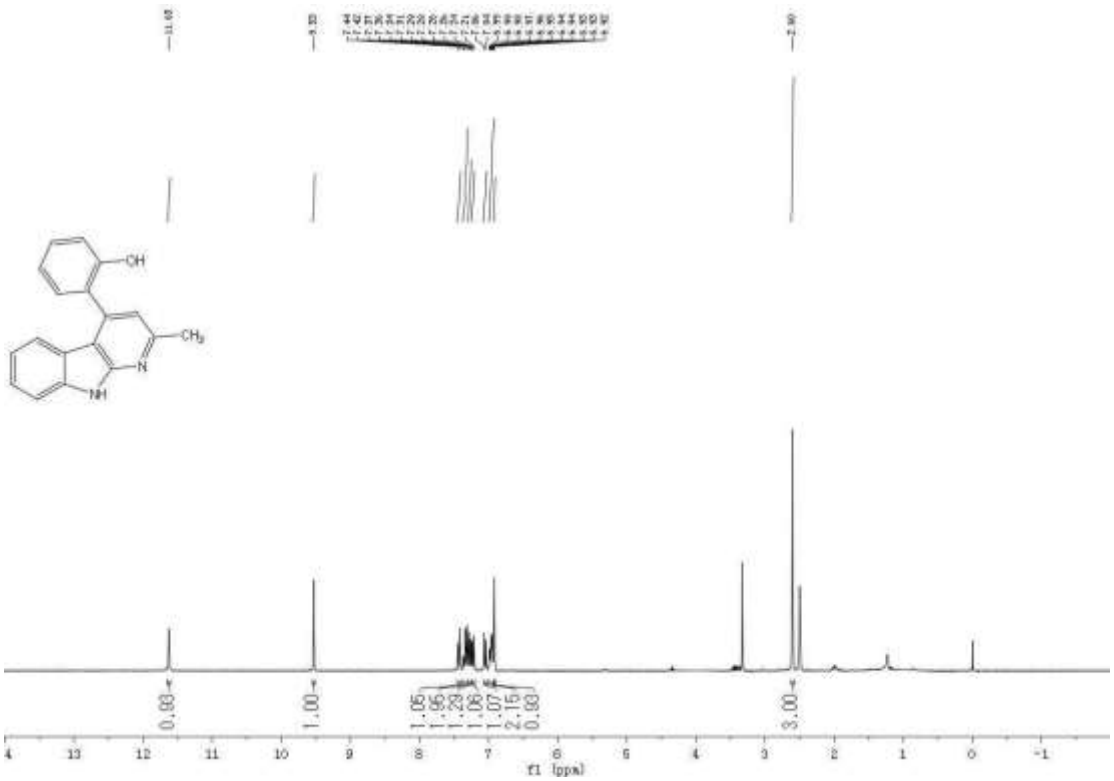


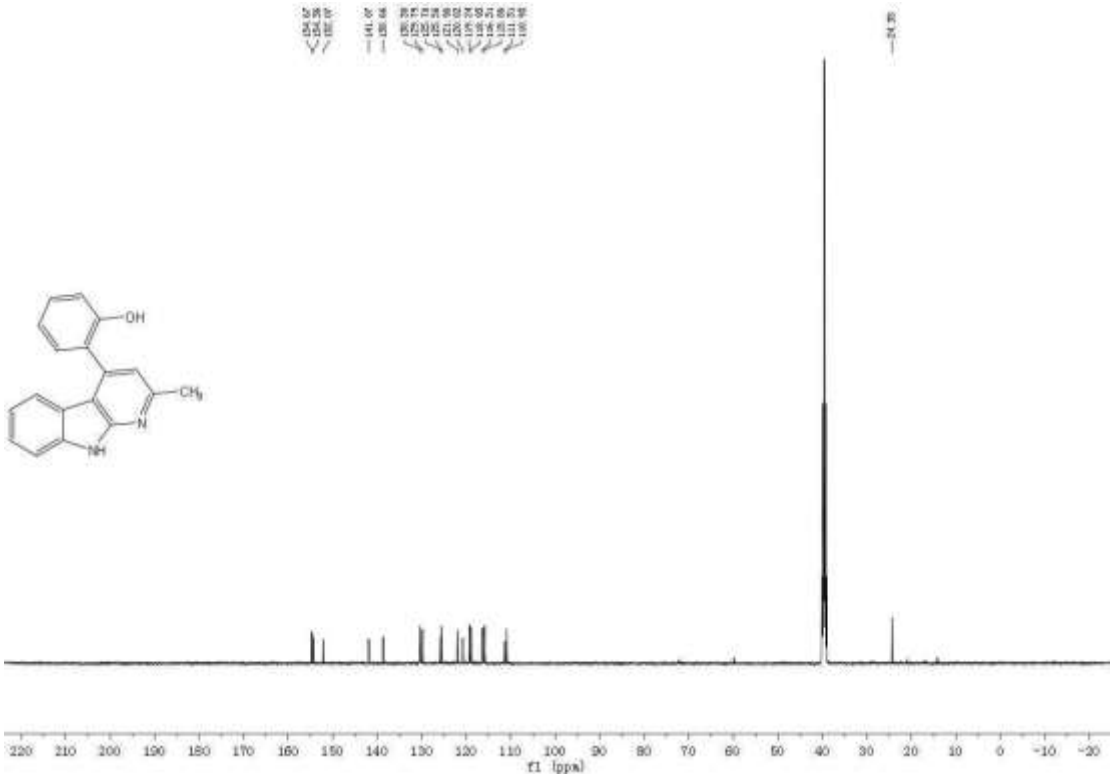

F
F
F
CH3
N
NH
0.87
2.05
2.14
1.02
2.17
2.13
3.00
f1 (ppm)

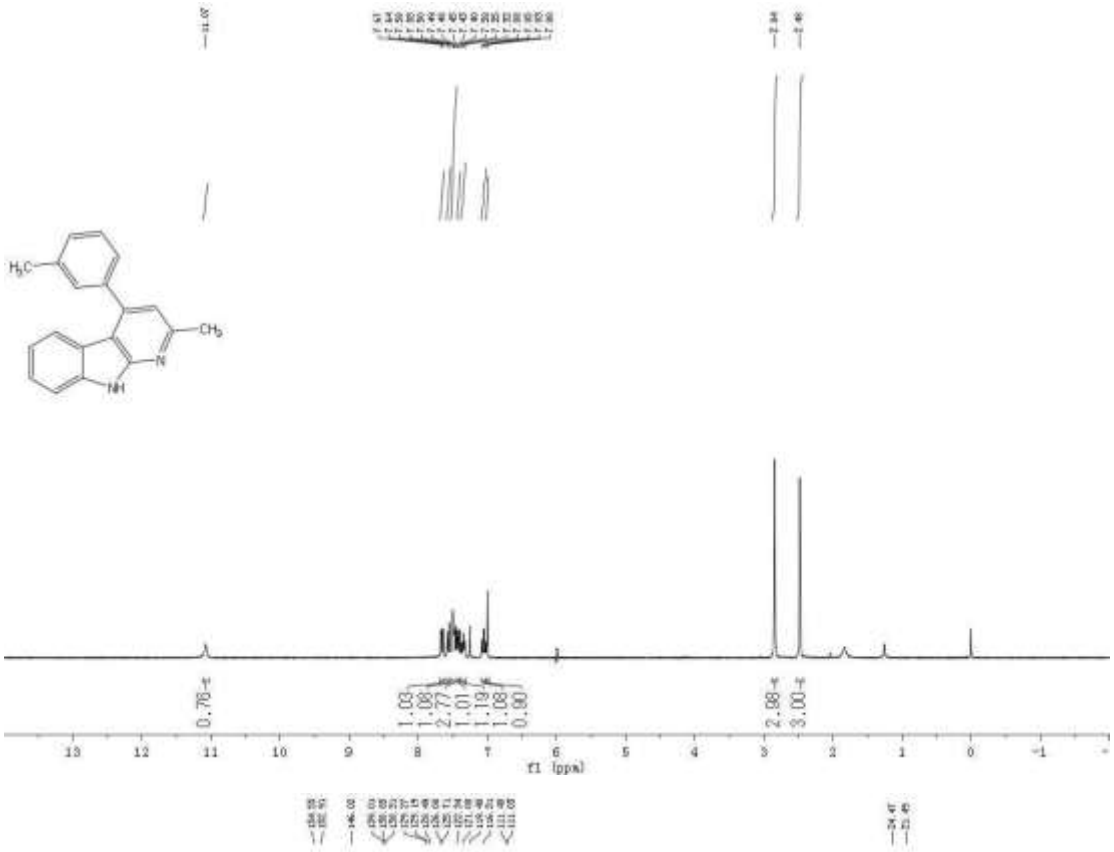

F
F
F
CH3
N
NH
f1 (ppm)

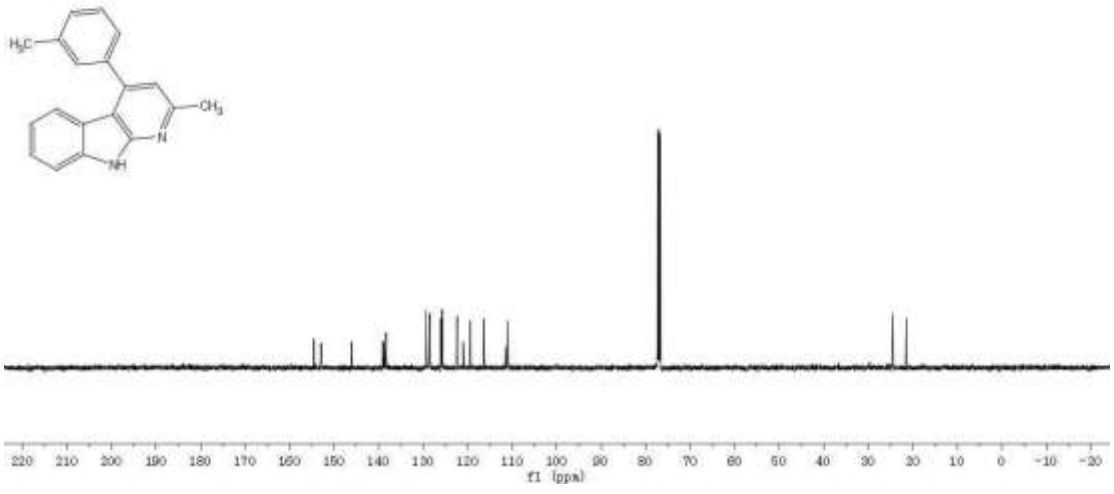

CH3
CH3
N
NH
0.66
0.87
4.95
2.08
0.99
3.00
2.98
f1 (ppm)

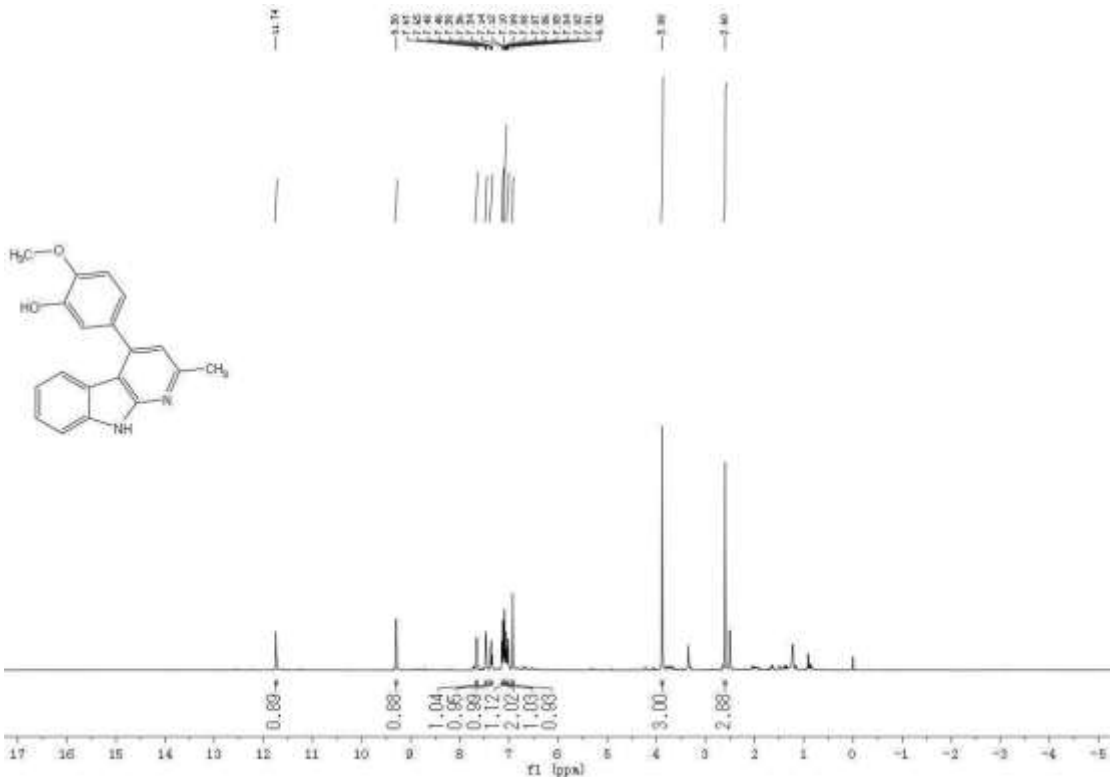

CH3
CH3
N
NH
f1 (ppm)

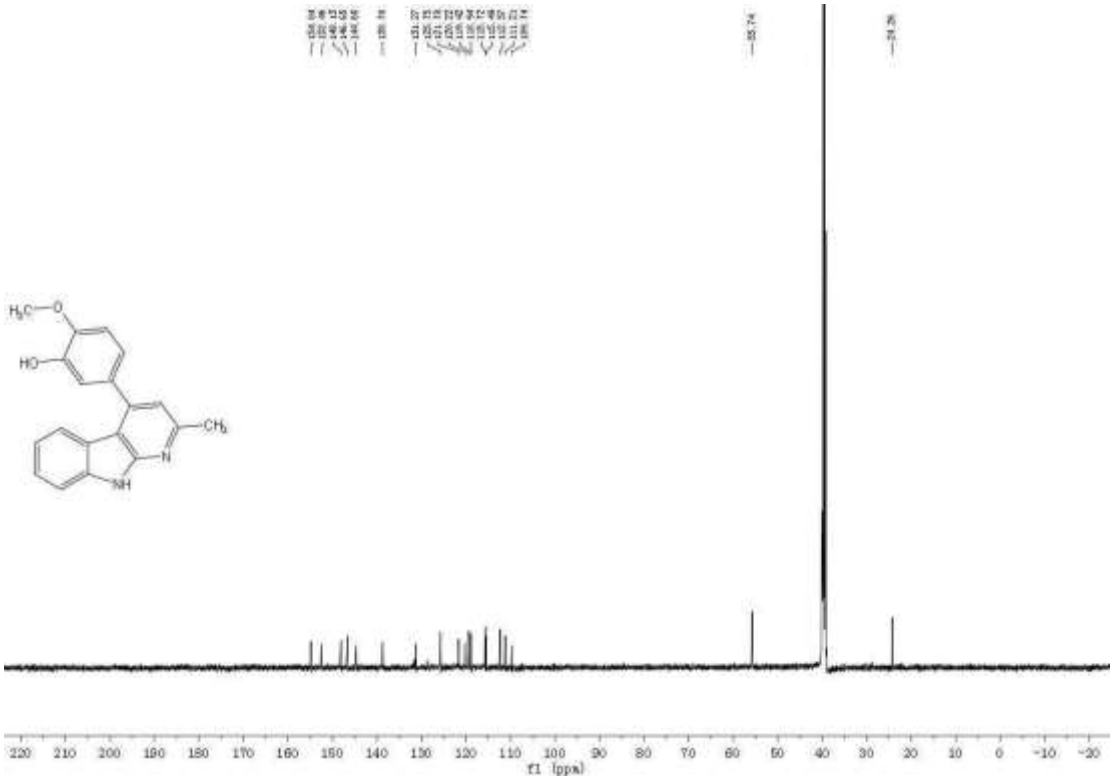

OH
CH3
N
NH
0.93
1.00
1.05
1.06
1.23
1.08
1.07
2.15
0.93
3.00
f1 (ppm)

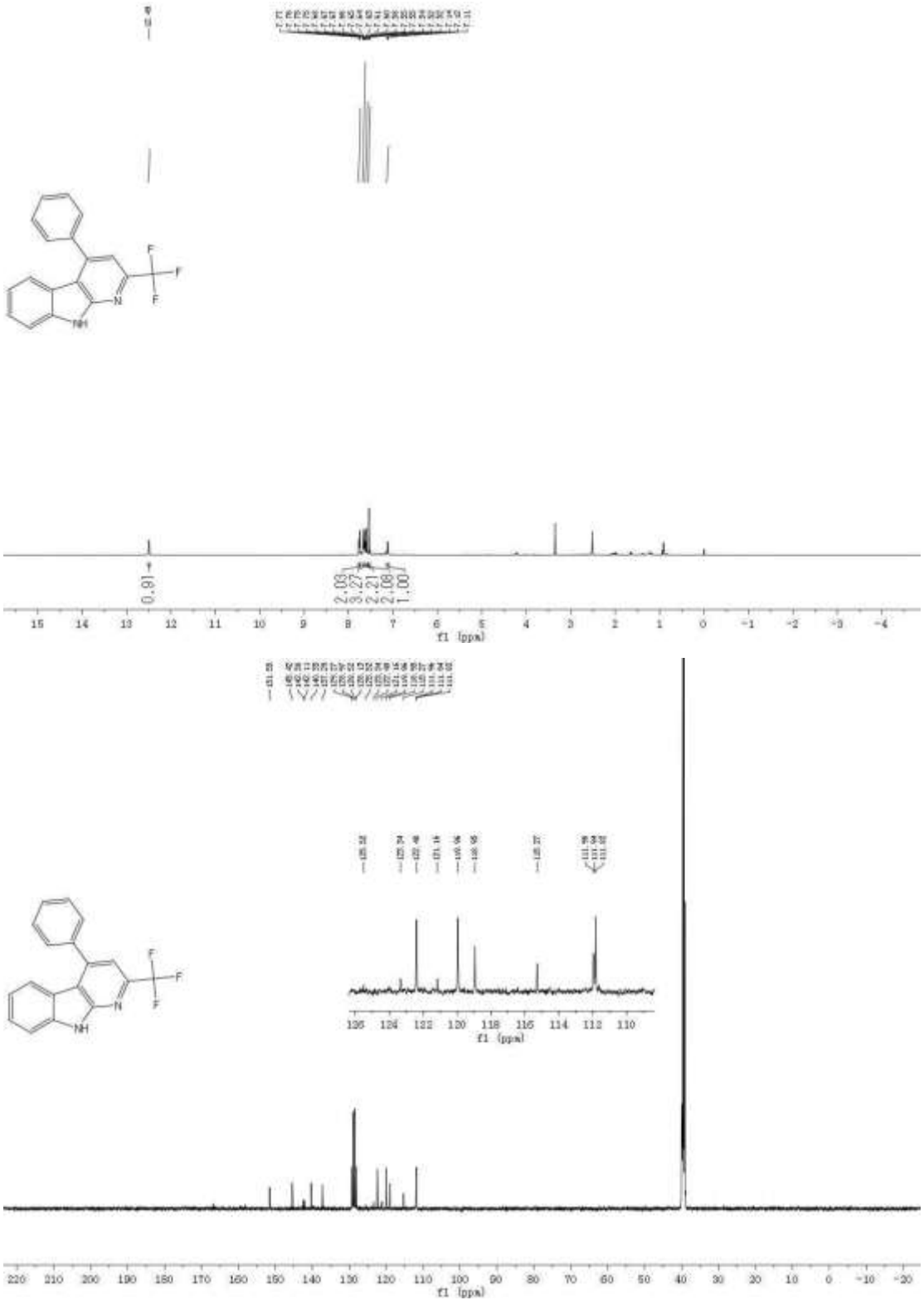

OH
CH3
N
NH
f1 (ppm)


H3C
CH3
N
NH
0.76
1.03
1.08
2.77
2.01
1.19
1.08
0.90
2.88
3.00
f1 (ppm)


H3C
CH3
N
NH
f1 (ppm)


H3C
O
HO
CH3
N
NH
0.89
0.88
1.04
0.96
0.88
1.12
2.02
1.03
0.93
3.00
2.88
f1 (ppm)


H3C
O
HO
CH3
N
NH
f1 (ppm)


F
F
F
N
NH
0.91
2.03
2.27
3.21
2.08
1.00
f1 (ppm)
f1 (ppm)
f1 (ppm)