Supporting Information

The Application of "Plug-in Molecules" Method in Novel Strobilurin Fungicides Screening

Xuelian Liu,[a†] Dongyan Yang,[a†] Fahong Yin,[a] Jia-Qi Li,[a] Yumei Xiao,[a] Bin Fu[a] and Zhaohai Qin[a*]

College of Science, China Agricultural University, Beijing 100193，China

** Corresponding author: qinzhaohai@263.net*

† These authors contributed equally to this work.

Synthesis of compound

Preparation of 6-chloro-3-acetylpyridine (1). (a) Magnesium chloride (51 g, 0.53 mol) was added to a solution of diethyl malonate (119g, 0.9mol) and triethylamine (183.2g, 1.8moll) in toluene (700 ml) and the reaction mixture was maintained for 1 h at 25 °C. A solution of 6-chloronicotinoyl chloride (0.75 mol) in toluene (100 mL) was added dropwise and maintained temperature at 25°C . The reaction mixture continues stirring for 40 minutes and acidify with concentrated HCl solution (261 g, 2,32 mol). The organic layer was washed with brine (3 × 300 mL), dried (sodium sulfate), and was concentrated to provide crude diethyl 2-(6-chloronicotinoyl) maionate as a yellowy solid.

(b) This crude product is dissolved in DMSO (650 ml) and water (29 ml), and is heated at 155°C for three hours. The mixture is poured onto crushed ice and the product is extracted using ethyl acetate. Drying of the organic phase over sodium sulfate, filtering and evaporation of the solvents. The residue was purified by chromatography on silica gel with petroleum ether as the eluent to give 6-chloro-3-acetylpyridine in 65% yield.

Preparation of the key precursor 3. 12 mmol of 6-chloro-3-acetylpyridine (**1**) and 13.2 mmol of substituted phenols (**2**) were dissolved in 30 mL of DMF, 12mmol of $Cs2CO_3$ were added, and the mixture was stirred and heated to reflux for 1 hour. The cooled mixture was filtered, and solvent was removed

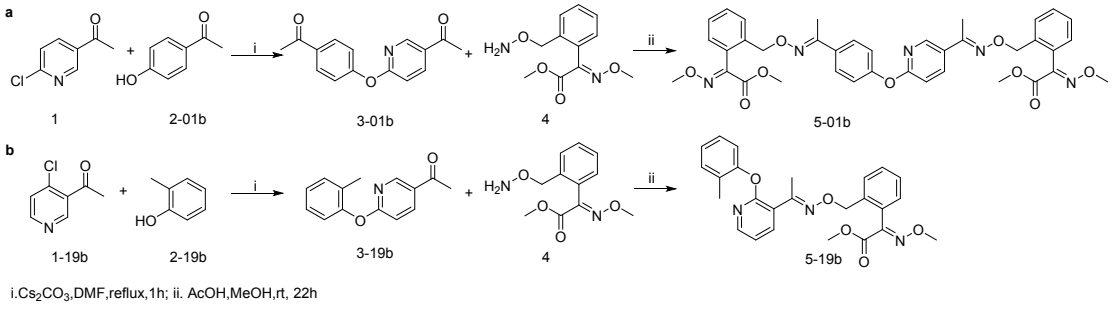
from the filtrate by vacuum rotary evaporation. The residue was dissolved in CH_2Cl_2 and purified by flash column chromatography on silica gel to give the key precursor **3**.

Preparation of methyl (E)-2-(2-((aminooxy)methyl)phenyl)-2-(methoxyimino)acetate (4). (a) To a dry 250 ml round bottom flask equipped with magnetic stirrer added 0.1 mol of N-hydroxyphthalimide and 100 ml of DMF. The reaction mixture was heated until the solid dissolves, and followed by the addition of the methyl (*E*)-2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate (0.121 mol). The mixture was stirred and heated to 60℃ for 5 min, then 0.121 mol of triethylamine was added. The mixture was stirred at 60℃ for 1 h, then poured into ice and stirred for 0.5 h to afford a solid which was collected by vacuum filtration and washed with water, and dried under vacuum at 40°C to obtain methyl (*E*)-2-(2-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)phenyl)-2-(methoxyimino)acetate in 98% yield.

(b) To a 250 ml round-bottom flask equipped with magnetic stirrer was charged 0.1 mol of methyl (*E*)-2-(2-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)phenyl)-2-(methoxyimino) acetate and 100 ml of anhydrous methanol. The reaction was stirred and 0.1 mol of hydrazine monohydrate was dropped. The mixture was stirred at ambient temperature for 2 hours. The resulting solid was removed by filtration and the filtrate was concentrated on the rotary evaporator to obtain the crude methyl (*E*)-2-(2-((aminooxy)methyl)phenyl)-2-(methoxyimino) acetate.

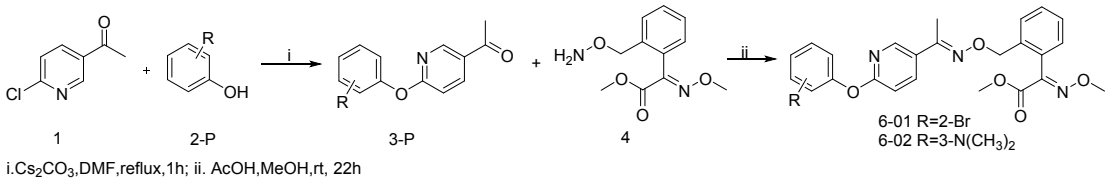
Preparation of target compound 5. To a 250 ml round-bottom flask equipped with magnetic stirrer was charged 0.1 mol of compound **4** and 100 ml of anhydrous methanol. The reaction was stirred and then 0.1mol of compounds **3** and two drops of acetic acid were added. The mixture was stirred at ambient temperature for 24 hours. The mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate (v/v = 10: 1) as the eluent to give the target compound **5**.

Preparation of target compound 5-01b and 5-19b. The compound synthesis method is similar to compound 5.



Scheme S1 Preparation of compounds 5-01b and 5-19b.

Preparation of target compound 6. The synthesis methods were the same as compound **5**.



Scheme S2 Preparation of compounds 6

Biological assays

Inhibition experiment of mycelium growth

Sclerotinia sclerotiorum(Lib.) de Bary, *Botrytis cinerea*, *Phytophthora infestans (Mont.)De Bary*, *Pythium aphanidermatum*, *Rhizoctonia solani,Setosphaeria turcica*, *Pyricularia grisea* and *Colletotrichum orbiculare (Berk. & Ment.)* were provided by the Laboratory of Institute of Plant Protection, Chinese Academy of Agricultural Sciences. The strains were incubated in PDA at 25 °C for several days to get new mycelia for the antifungal assay. Azoxystrobin and trifloxystrobin, obtained from Jiangsu Frey Chemicals Co., were used as commercial control drugs. The fungicidal activity of the title compounds was tested in vitro against plant pathogens using the mycelia growth inhibition method as described previously.The synthesized compounds and controls were dissolved in DMSO and tested at a concentration of 50 mg/L for primary screening. Their relative inhibition ratio (%) was calculated using the following equation:

$$The\ relative\ inhibition\ ratio\ (\%) = \frac{(colony\ diameter\ of\ control - colony\ diameter\ of\ treatment)}{(colony\ diameter\ of\ control - mycelial\ disk\ diameter)} \times 100\%$$

This experiment was conducted with three replicates, and the inhibition rate of the compounds were listed in Table 1. The inhibition rate of the title compounds for plant pathogens. was further tested at the concentration of 100, 50, 12.5, 6.25 and 3.12 μg/mL, repeating the experiments above, and the corresponding EC_{50} values were calculated by SPSS Statistics v17.0.

Cytotoxicity assay

In vitro cytotoxicity was measured by the CCK-8 assay according to the manufacturer's protocol. Hela Cells were seeded into a 96-well plate with 100 μL Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum and 1% double antibody (penicillin mixture) (v/v) and treated with compounds **5-1** and **6-02** at 0, 6.25, 12.5, 25, 50 and 100 μg/ml for 24h at 37°C with 5% CO_2. Then, Hela cells were incubated with 10 μL CCK-8 reagents (Signalway Antibody) for 1 hours at 37°C. Measure the absorbance at 450 nm with a microplate reader. Three parallel experiments were performed for each concentration.

Transmission electron microscopy

Fresh *Sclerotinia scleotiorum* cake was inoculated in 50ug/ml PDA medium containing compound **5-01**, cultured in the dark at 26°C for 2 days, and marginal mycelium was taken and fixed with 2.5% (v/v) glutaraldehyde, 1% (v /v) Osmium tetroxide is fixed. The slice preparation and visualization used a jem1400 flash transmission electron microscope.[1]

Building 3D-QSAR model

The Build module of Sybyl 7.3 was used to build three-dimensional structures of the compounds. Using the minimize module to optimize the molecular conformation. The Powell method was selected, the energy convergence standard was 0.005 kcal/(mol*A), the number of iterations was 1000, the Gasteuger-Hückel charge was loaded and the Tripos force field was used to obtain the low-energy conformation of each molecule. Compound **5-06** was used as the template for alignment, and the alignment skeleton and molecular aligning diagram were shown in Fig. S2. These compounds were divided into a training set and

a test set (compounds **5-02**, **5-14**, **5-15**, **5-19**, **5-24**, **5-25**, **5-28** and **5-31**). The training set used comparative molecular force field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) to construct the model, and the text set was used to verity the model.

Experimental Data

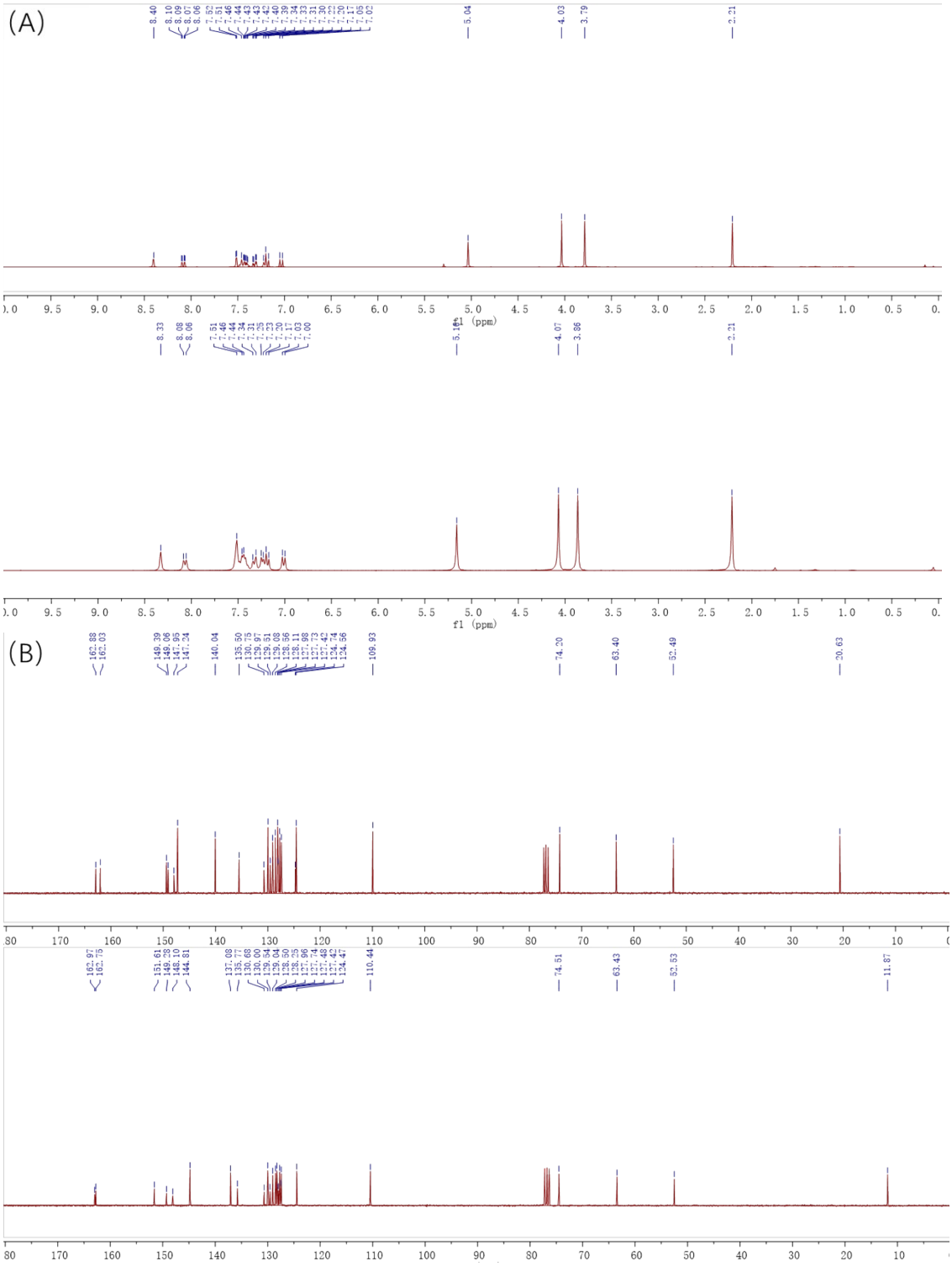


Figure S1 ^{1}H NMR (A) and ^{13}C NMR (B) -Spectra overlay of compounds 5-26 (above) and 5-26b (below).

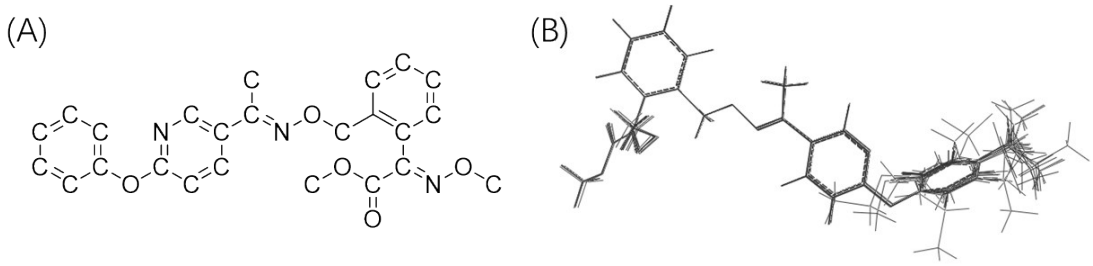


Figure S2 The superimposed skeleton (A) and molecular superimposed diagram (B) of the model

Table S1 The parameters of CoMFA and CoMSIA

Model	q^2	components	SE	r^2	F	S	E
CoMFA	0.552	4	0.168	0.888	35.724	0.698	0.302
CoMSIA	0.548	4	0.236	0.791	12.846	0.359	0.641

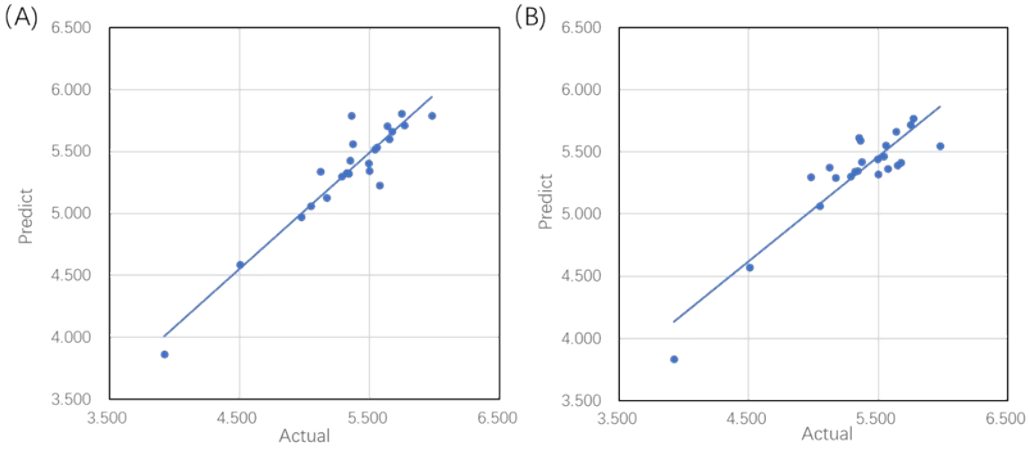


Figure S3 Linear relationship between actual value and predicted value of pEC_{50}. (A) CoMFA; (B) CoMSIA

Table S2 The effect of compound **5-01** and **6-02** on the proliferation ability of Hela cells

compounds	The inhibition rate of cell proliferation in different concentrations				
	6.25	12.5	25	50	100
5-01	-13.28±1.18	1.39±1.18	4.68±1.40	24.27±1.30	47.35±1.06
6-02	-10.76±1.64	-0.56±1.96	2.25±1.86	3.93±1.96	8.19±1.91

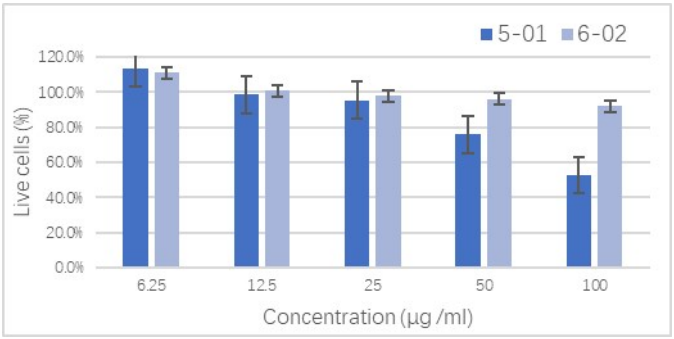


Figure S4 The results of the cytotoxicity of compounds 5-01 and 6-02 in Hela cells as assessed using CCK-8 assay.

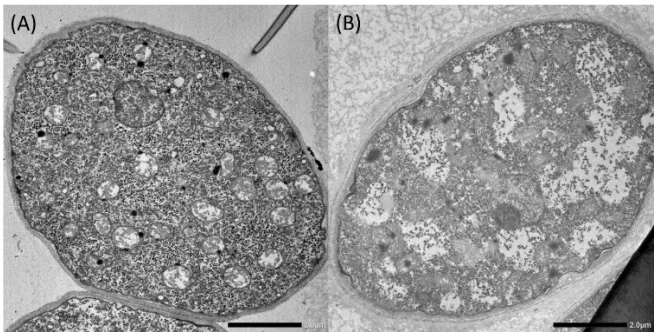
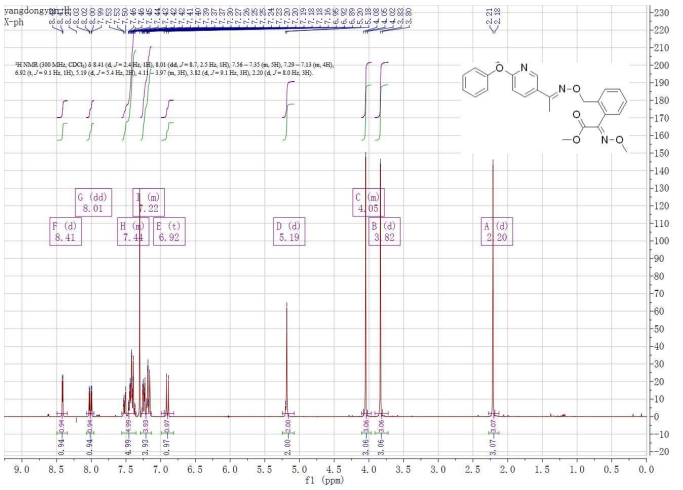
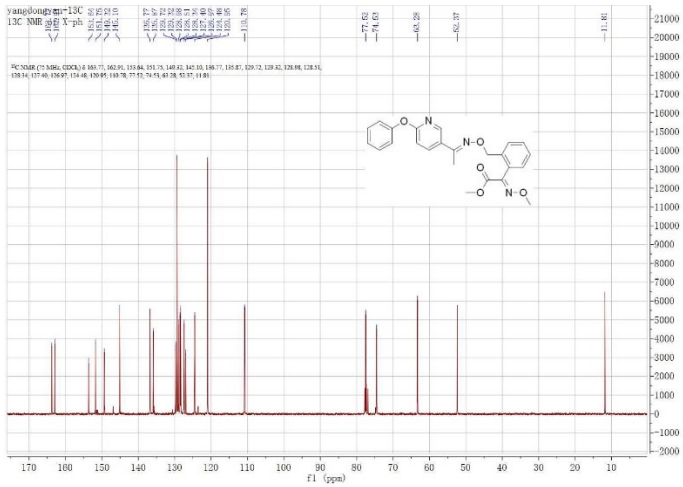


Figure S5. TEM micrographs of Sclerotinia scleotiorum observed at scale bar of 2 μm. (A) the control without treated, (B) compound **5-01** at 50 μg/ml

Compound Characterization

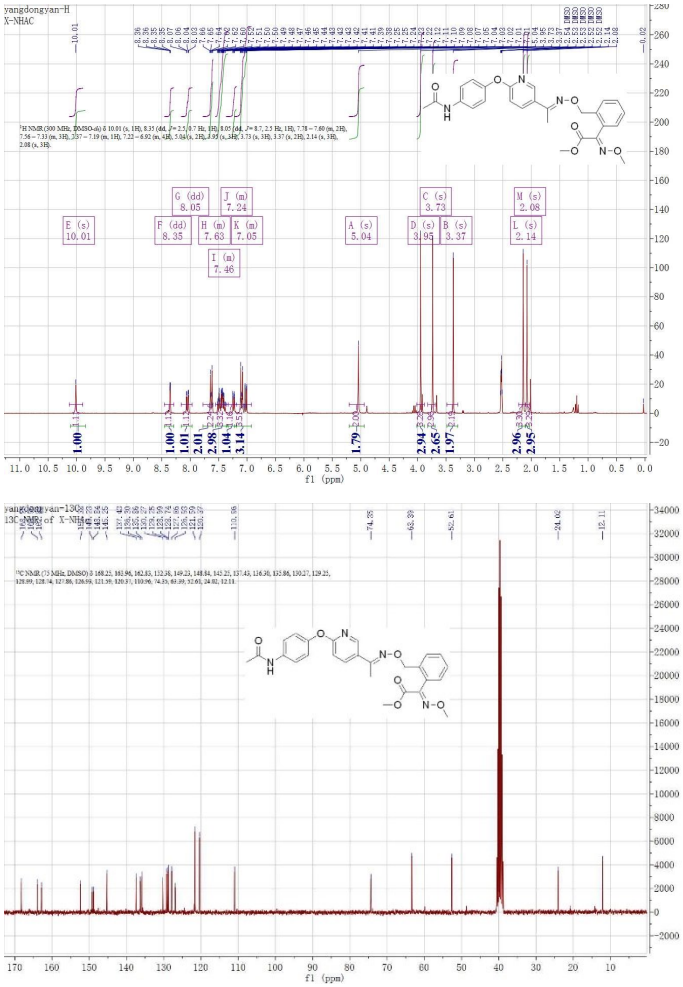
Data for **(5-01)**. white solid; mp 57-58 °C; yield 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.4 Hz, 1H), 8.01 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.56 – 7.35 (m, 5H), 7.29 – 7.13 (m, 4H), 6.92 (t, *J* = 9.1 Hz, 1H), 5.19 (d, *J* = 5.4 Hz, 2H), 4.11 – 3.97 (m, 3H), 3.82 (d, *J* = 9.1 Hz, 3H), 2.20 (d, *J* = 8.0 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.77, 162.91, 153.64, 151.75, 149.32, 145.10, 136.77, 135.87, 129.72, 129.32, 128.98, 128.51, 128.34, 127.40, 126.97, 124.48, 120.95, 110.78, 77.52, 74.53, 63.28, 52.37, 11.81. HRMS (ESI) m/z calcd for $C_{24}H_{24}N_3O_5$ $(M+H)^+$ 434.1710, found 434.1712.



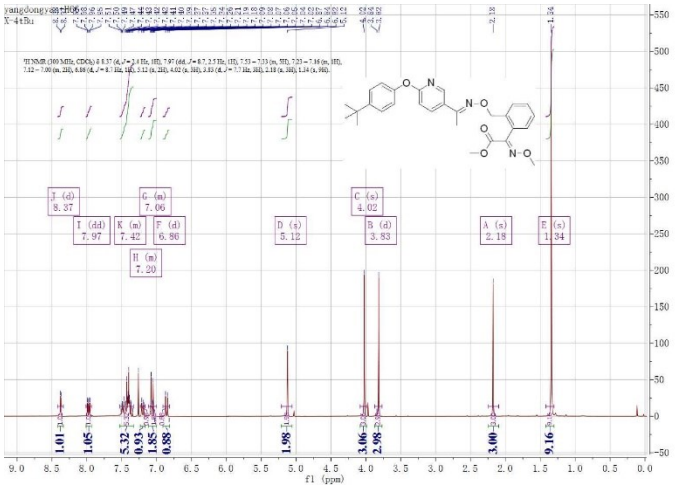


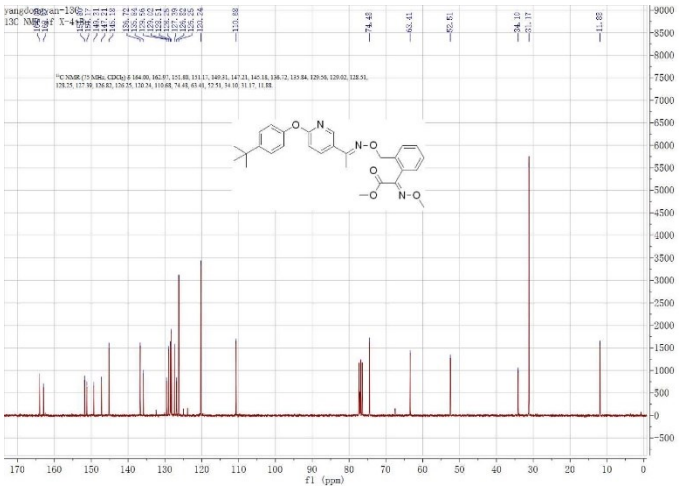
Data for **(5-02)**. white powder; mp 124-125 °C; yield 61%; ^{1}H NMR (300 MHz, DMSO) δ 10.01 (s, 1H), 8.35 (d, *J* = 2.5 Hz, 1H), 8.05 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.56 – 7.33 (m, 3H), 7.24 (d, *J* = 6.8

Hz, 1H), 7.06 (dd, *J* = 22.4, 8.8 Hz, 3H), 5.04 (s, 2H), 3.95 (s, 3H), 3.73 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 168.25, 163.96, 162.83, 152.38, 149.23, 148.84, 145.25, 137.43, 136.30, 135.86, 130.27, 129.25, 128.99, 128.74, 127.86, 126.93, 121.59, 120.37, 110.96, 74.35, 63.39, 52.61, 24.02, 12.11. HRMS (ESI) m/z calcd for $C_{26}H_{27}N_4O_6$ $(M+H)^+$ 491.1925, found 491.1927.

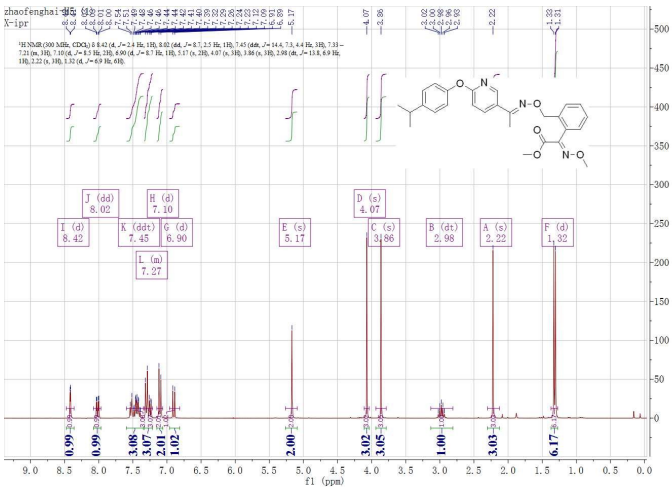


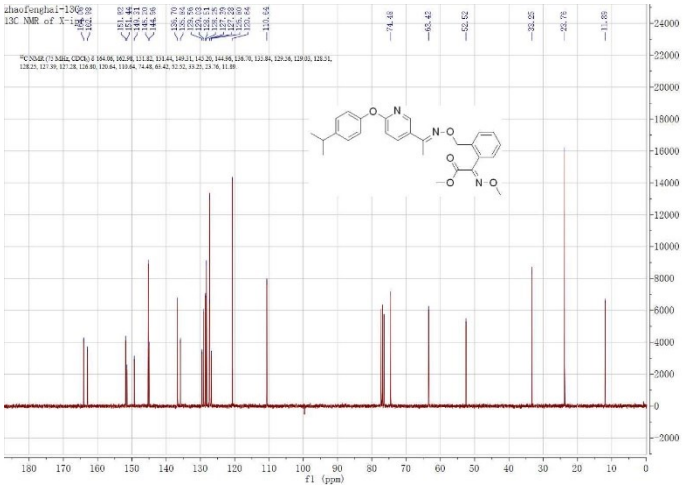
Data for **(5-03)**. colorless oil; yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.4 Hz, 1H), 7.97 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.53 – 7.33 (m, 5H), 7.23 – 7.16 (m, 1H), 7.12 – 7.00 (m, 2H), 6.86 (d, *J* = 8.7 Hz, 1H), 5.12 (s, 2H), 4.02 (s, 3H), 3.83 (d, *J* = 7.7 Hz, 3H), 2.18 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.00, 162.97, 151.80, 151.17, 149.31, 147.21, 145.18, 136.72, 135.84, 129.56, 129.02, 128.51, 128.25, 127.39, 126.82, 126.25, 120.24, 110.68, 74.48, 63.41, 52.51, 34.10, 31.17, 11.88. HRMS (ESI) m/z calcd for $C_{28}H_{32}N_3O_5$ $(M+H)^+$ 490.2336, found 490.2340.



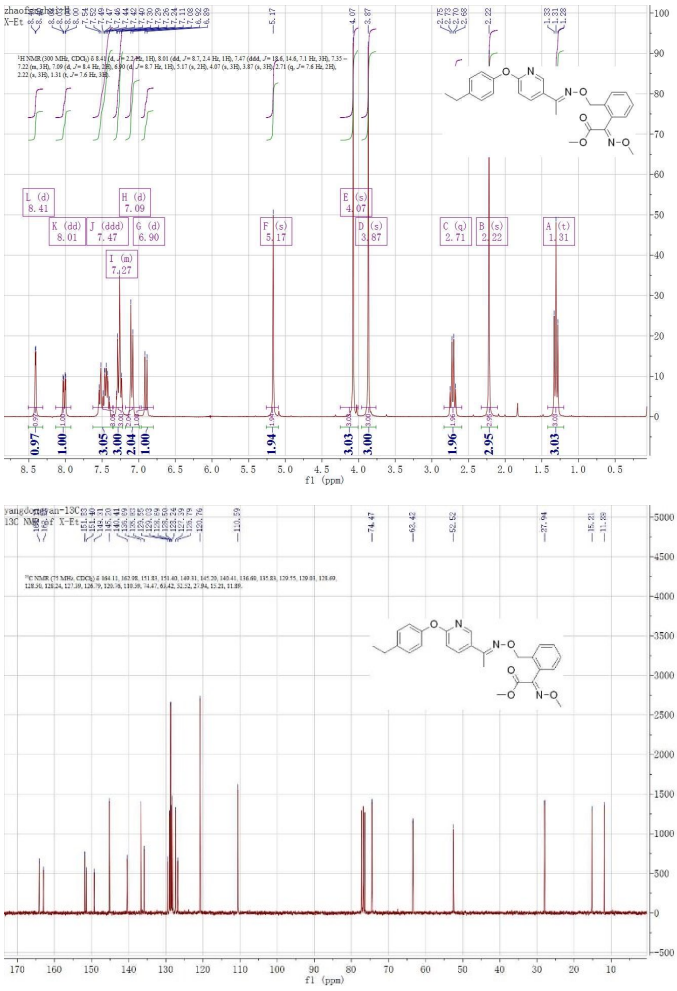


Data for **(5-04)**. white crystal; mp 81-82 °C; yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.45 (ddt, *J* = 14.4, 7.3, 4.4 Hz, 3H), 7.33 – 7.21 (m, 3H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 2.98 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.22 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.06, 162.98, 151.82, 151.44, 149.31, 145.20, 144.96, 136.70, 135.84, 129.56, 129.03, 128.51, 128.25, 127.39, 127.28, 126.80, 120.64, 110.64, 74.48, 63.42, 52.52, 33.25, 23.76, 11.89. HRMS (ESI) m/z calcd for $C_{27}H_{30}N_3O_5$ $(M+H)^+$ 476.2180, found 476.2185.



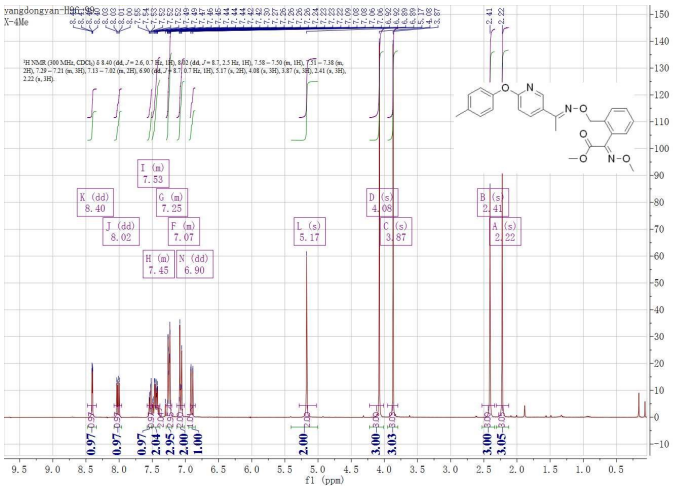


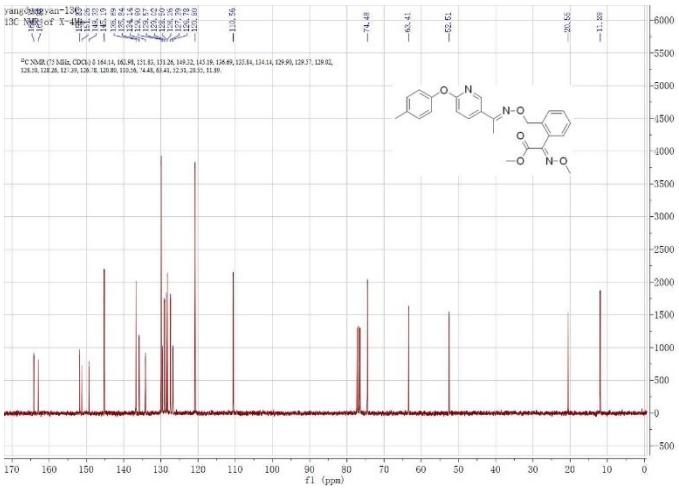
Data for **(5-05)**. white crystal; mp 80-81 °C; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.2 Hz, 1H), 8.01 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.47 (ddd, *J* = 18.6, 14.6, 7.1 Hz, 3H), 7.35 – 7.22 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.07 (s, 3H), 3.87 (s, 3H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.22 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.11, 162.98, 151.83, 151.40, 149.31, 145.20, 140.41, 136.69, 135.83, 129.55, 129.03, 128.69, 128.50, 128.24, 127.39, 126.79, 120.76, 110.59, 74.47, 63.42, 52.52, 27.94, 15.21, 11.89. HRMS (ESI) m/z calcd for $C_{26}H_{28}N_3O_5$ $(M+H)^+$ 462.2023, found 462.2027.



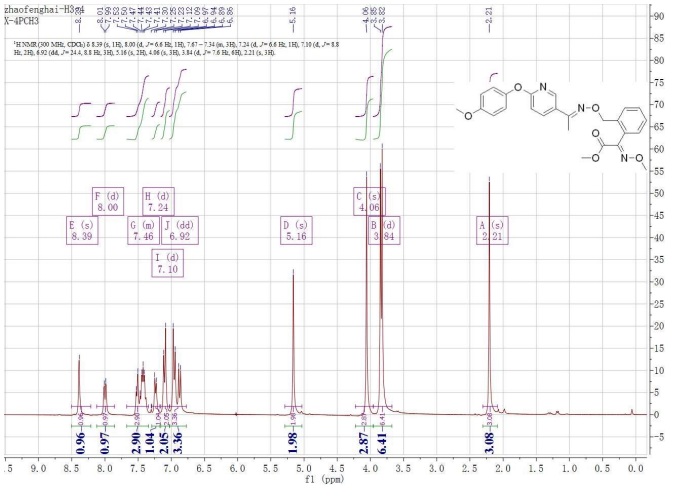
Data for **(5-06)**. white crystal; mp 61-62 °C; yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.9 Hz, 1H), 8.02 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.44 (dtd, *J* = 12.7, 7.3, 1.7 Hz, 2H), 7.29 – 7.21 (m, 3H),

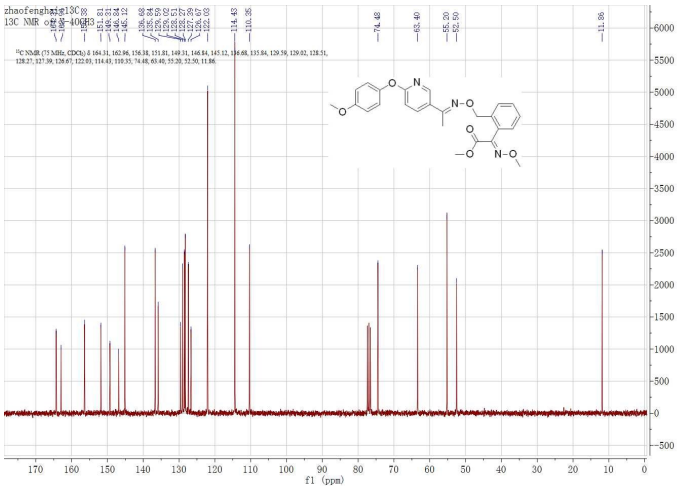
7.13 – 7.02 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.08 (s, 3H), 3.87 (s, 3H), 2.41 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.14, 162.98, 151.83, 151.26, 149.32, 145.19, 136.69, 135.84, 134.14, 129.90, 129.57, 129.02, 128.50, 128.26, 127.39, 126.78, 120.80, 110.56, 74.48, 63.41, 52.51, 20.55, 11.89. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O_5$ $(M+H)^+$ 448.1867, found 448.1871.



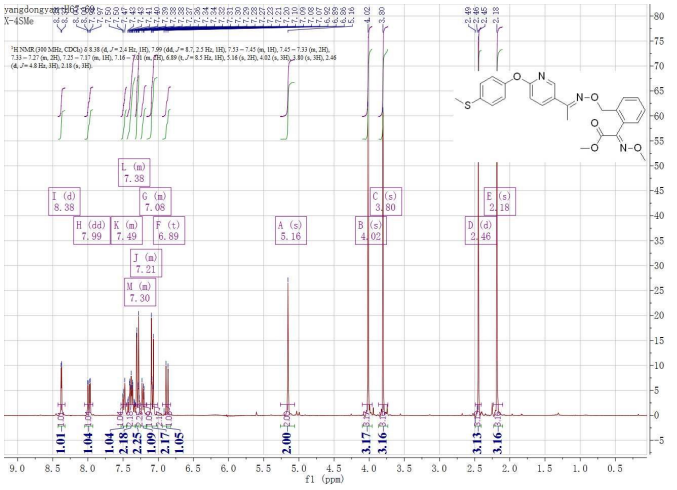


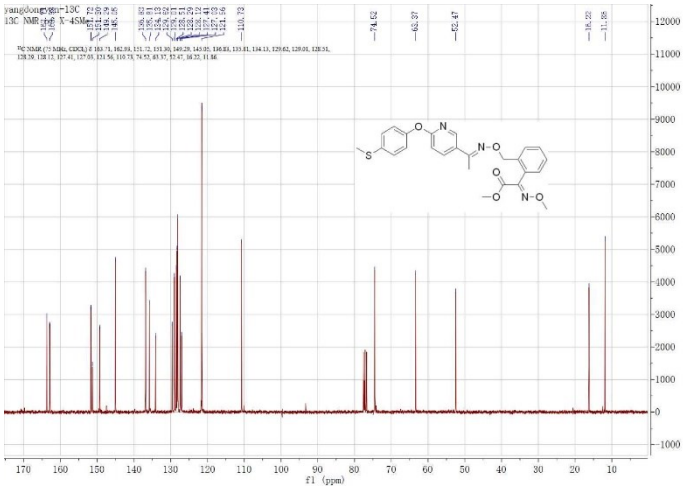
Data for **(5-07)**. white crystal; mp 67-68 °C; yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.00 (d, *J* = 6.6 Hz, 1H), 7.67 – 7.34 (m, 3H), 7.24 (d, *J* = 6.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.92 (dd, *J* = 24.4, 8.8 Hz, 3H), 5.16 (s, 2H), 4.06 (s, 3H), 3.84 (d, *J* = 7.6 Hz, 6H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.31, 162.96, 156.38, 151.81, 149.31, 146.84, 145.12, 136.68, 135.84, 129.59, 129.02, 128.51, 128.27, 127.39, 126.67, 122.03, 114.43, 110.35, 74.48, 63.40, 55.20, 52.50, 11.86. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O_6$ $(M+H)^+$ 464.1816, found 464.1819.



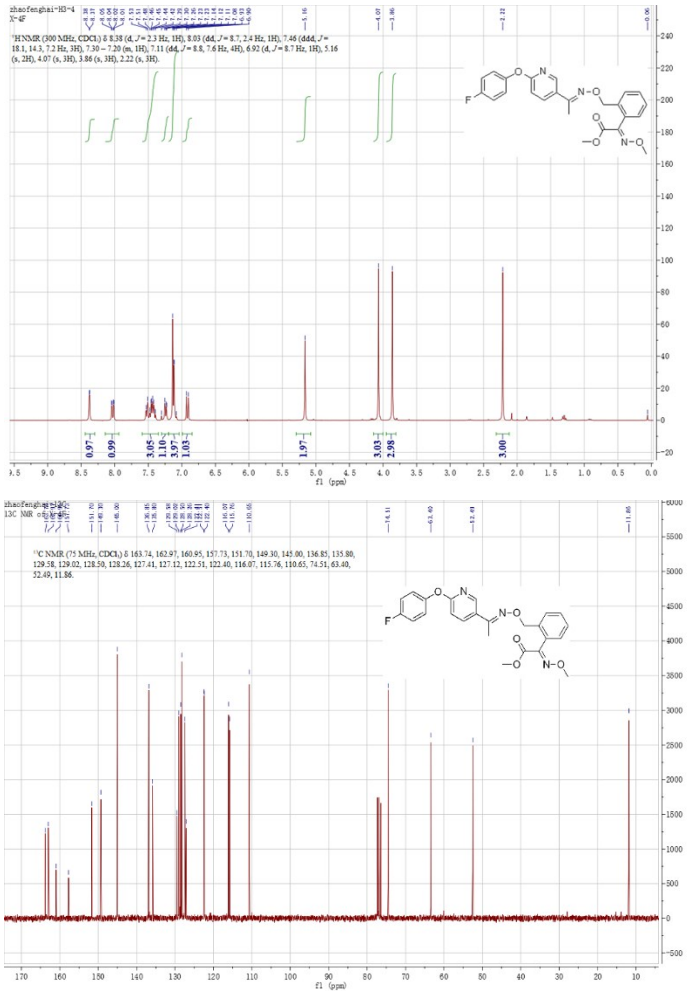


Data for **(5-08)**. yellow solid; mp 47-48 °C; yield 69%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.4 Hz, 1H), 7.99 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.45 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.17 (m, 1H), 7.16 – 7.01 (m, 2H), 6.89 (t, *J* = 8.5 Hz, 1H), 5.16 (s, 2H), 4.02 (s, 3H), 3.80 (s, 3H), 2.46 (d, *J* = 4.8 Hz, 3H), 2.18 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.71, 162.93, 151.72, 151.30, 149.29, 145.05, 136.83, 135.81, 134.13, 129.62, 129.01, 128.51, 128.29, 128.12, 127.41, 127.03, 121.56, 110.73, 74.52, 63.37, 52.47, 16.22, 11.86. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O_5S$ (M+H)$^+$ 480.1588, found 480.1588.



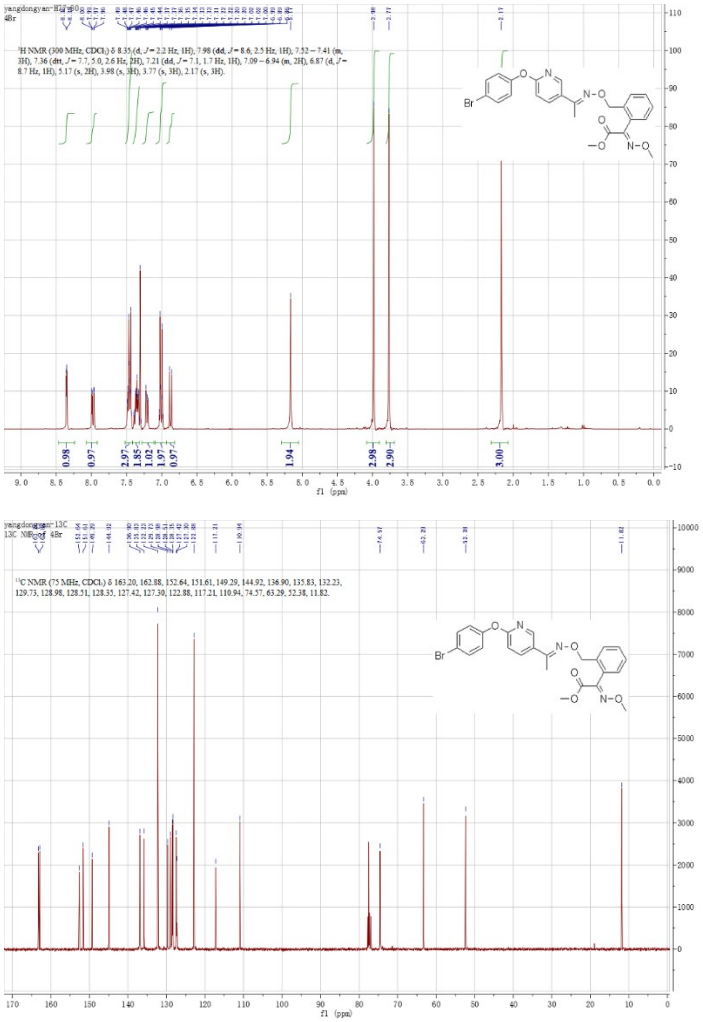


Data for **(5-09)**. white solid; mp 62-63 °C; yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.46 (ddd, *J* = 18.1, 14.3, 7.2 Hz, 3H), 7.30 – 7.20 (m, 1H), 7.11 (dd, *J* = 8.8, 7.6 Hz, 4H), 6.92 (d, *J* = 8.7 Hz, 1H), 5.16 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.74, 162.97, 160.95, 157.73, 151.70, 149.30, 145.00, 136.85, 135.80, 129.58, 129.02, 128.50, 128.26, 127.41, 127.12, 122.51, 122.40, 116.07, 115.76, 110.65, 74.51, 63.40, 52.49, 11.86. HRMS (ESI) m/z calcd for $C_{24}H_{23}FN_3O_5$ (M+H)+ 452.1616, found 452.1621.

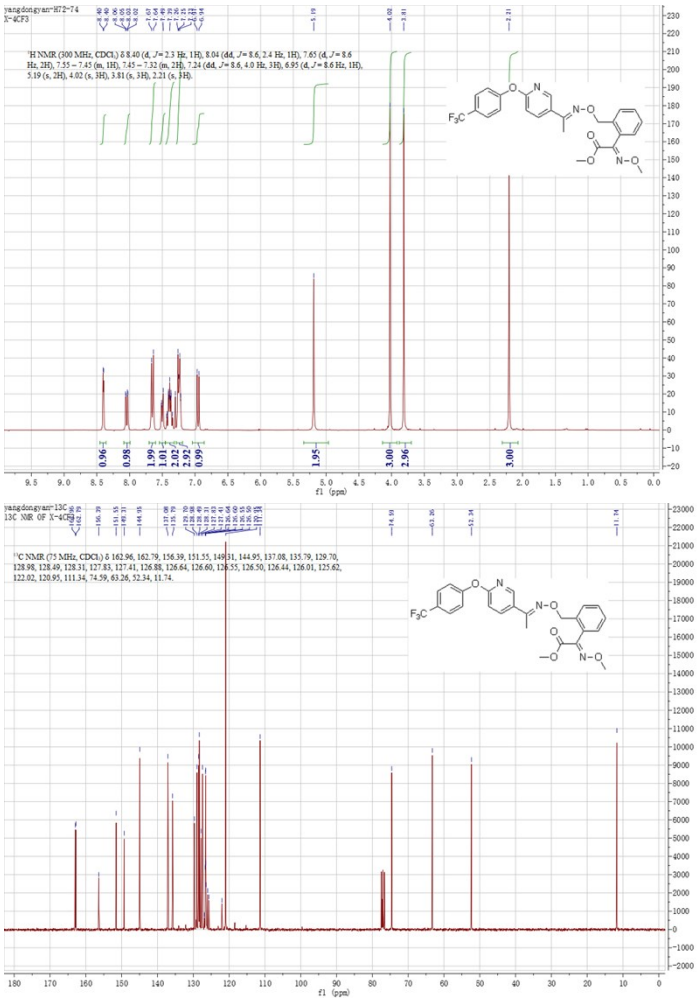


Data for **(5-10)**. white solid; mp 63-64 °C; yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.2 Hz, 1H), 7.98 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.36 (dtt, *J* = 7.7, 5.0, 2.6 Hz, 2H), 7.21 (dd, *J* = 7.1, 1.7 Hz,

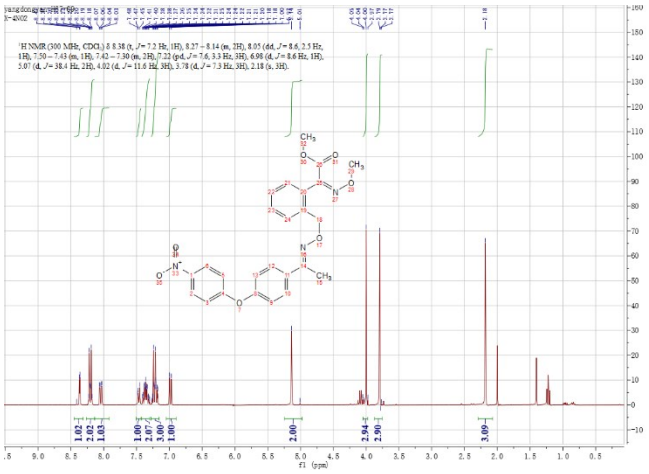
1H), 7.09 – 6.94 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 2.17 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.20, 162.88, 152.64, 151.61, 149.29, 144.92, 136.90, 135.83, 132.23, 129.73, 128.98, 128.51, 128.35, 127.42, 127.30, 122.88, 117.21, 110.94, 74.57, 63.29, 52.38, 11.82. HRMS (ESI) m/z calcd for $C_{24}H_{23}BrN_3O_5$ $(M+H)^+$ 512.0816, found 512.0818.

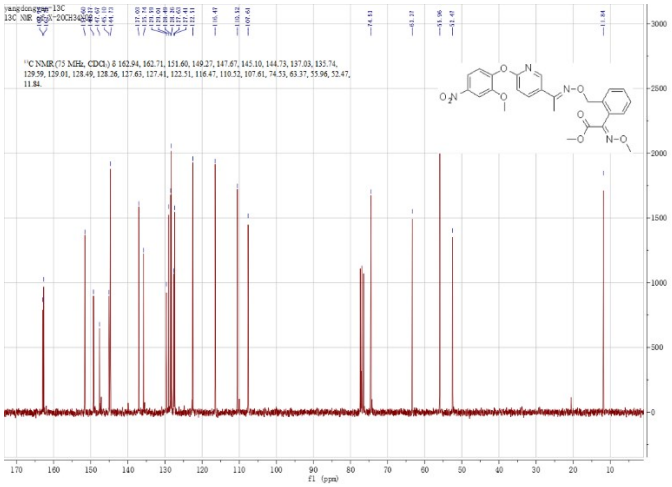


Data for **(5-11)**. light yellow solid; mp 39-40 °C; yield 85%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.3 Hz, 1H), 8.04 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.55 – 7.45 (m, 1H), 7.45 – 7.32 (m, 2H), 7.24 (dd, *J* = 8.6, 4.0 Hz, 3H), 6.95 (d, *J* = 8.6 Hz, 1H), 5.19 (s, 2H), 4.02 (s, 3H), 3.81 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.96, 162.79, 156.39, 151.55, 149.31, 144.95, 137.08, 135.79, 129.70, 128.98, 128.49, 128.31, 127.83, 127.41, 126.88, 126.64, 126.60, 126.55, 126.50, 126.44, 126.01, 125.62, 122.02, 120.95, 111.34, 74.59, 63.26, 52.34, 11.74. HRMS (ESI) m/z calcd for $C_{25}H_{23}F_3N_3O_5$ $(M+H)^+$ 502.1584, found 502.1588.

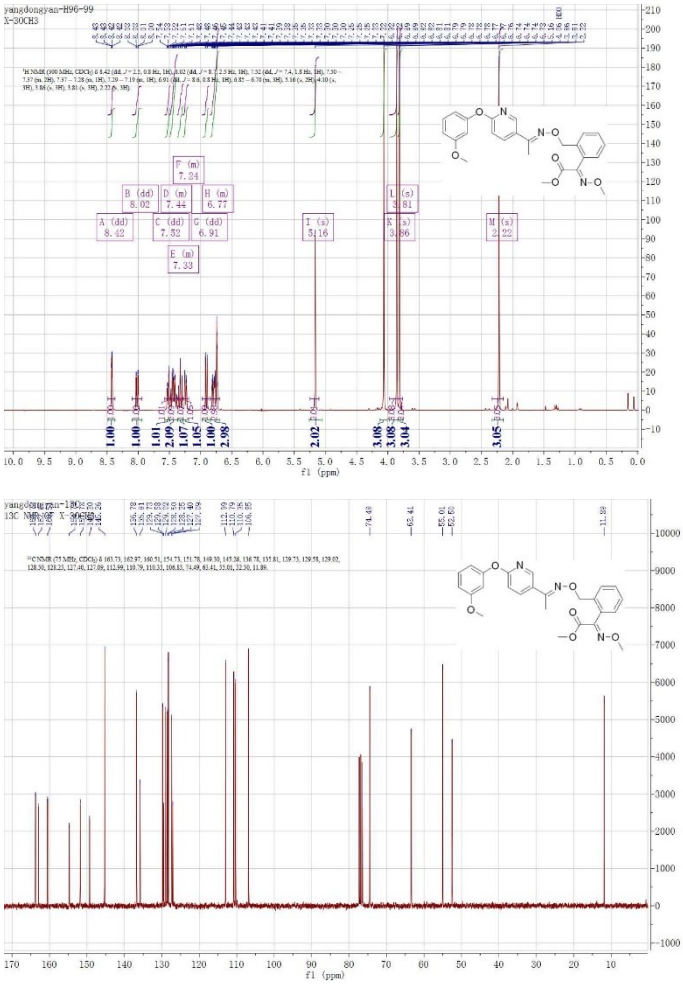


Data for **(5-12)**. white crystal; mp 71-72 °C; yield 74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.4 Hz, 1H), 8.31 – 8.17 (m, 2H), 8.07 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.56 – 7.32 (m, 3H), 7.31 – 7.14 (m, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 5.16 (s, 2H), 4.03 (s, 3H), 3.83 (s, 3H), 2.21 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.93, 162.09, 158.91, 151.44, 149.25, 144.94, 143.72, 137.34, 135.69, 129.63, 129.00, 128.50, 128.46, 128.29, 127.44, 125.09, 120.68, 111.79, 74.61, 63.36, 52.46, 11.84. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_4O_7$ $(M+H)^+$ 479.1561, found 479.1564.



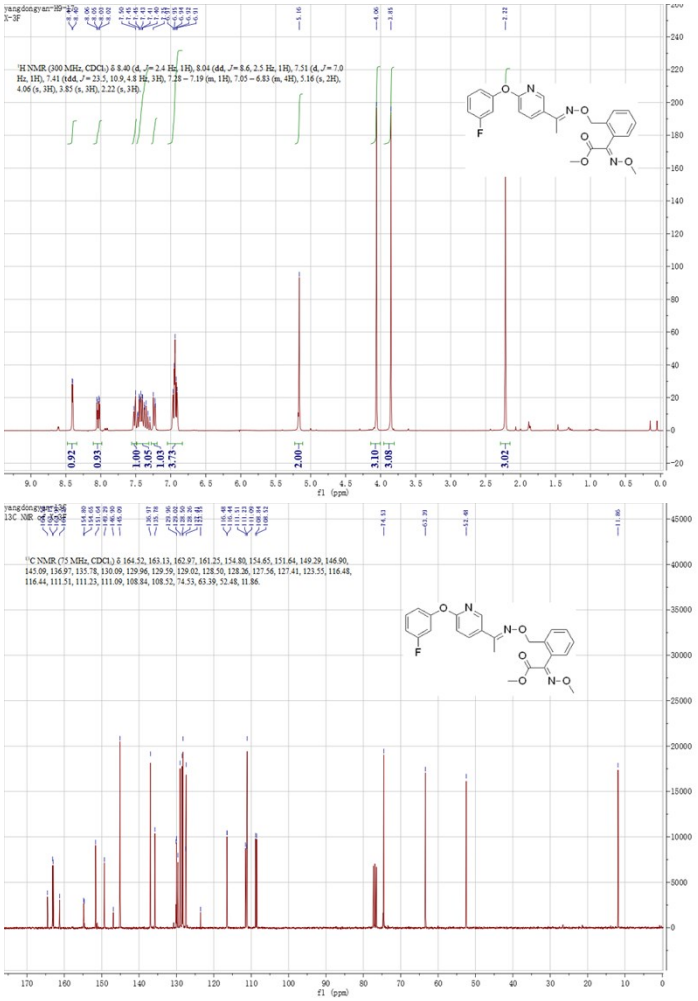


Data for **(5-13)**. white solid; mp 72-73 °C; yield 58%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.52 (d, *J* = 7.1 Hz, 1H), 7.50 – 7.37 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.19 (m, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.85 – 6.70 (m, 3H), 5.16 (s, 2H), 4.06 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.73, 162.97, 160.51, 154.73, 151.78, 149.30, 145.26, 136.78, 135.81, 129.73, 129.58, 129.02, 128.50, 128.25, 127.40, 127.09, 112.99, 110.79, 110.35, 106.85, 74.49, 63.41, 55.01, 52.50, 11.89. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O_6$ $(M+H)^+$ 464.1816, found 464.1819.

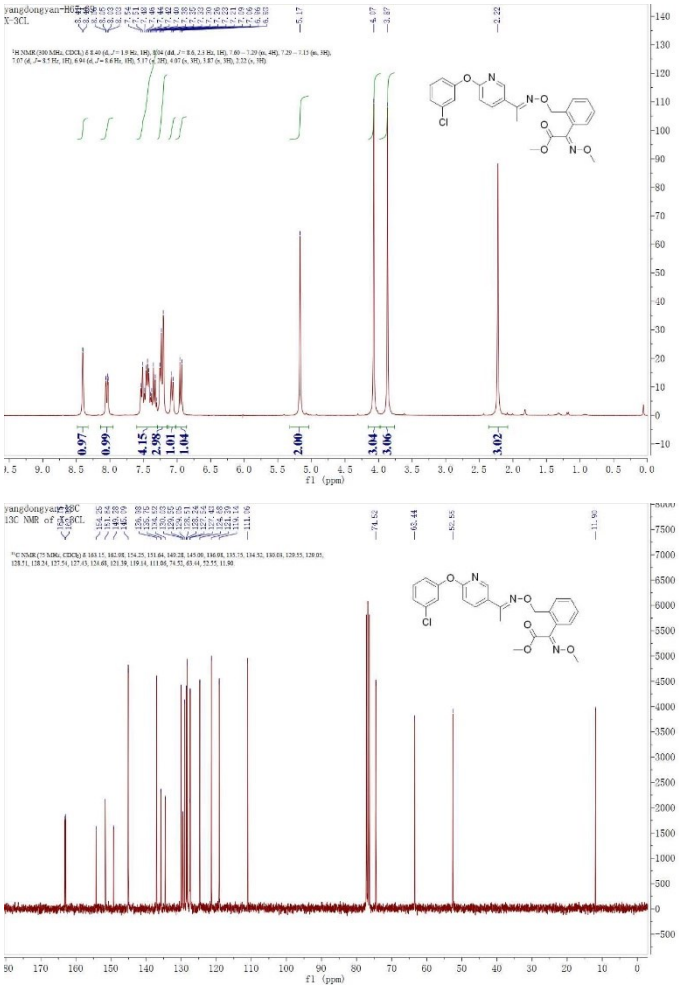


Data for **(5-14)**. white crystal; mp 66-67 °C; yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.4 Hz, 1H), 8.04 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.51 (d, *J* = 7.0 Hz, 1H), 7.41 (tdd, *J* = 23.5, 10.9, 4.8 Hz, 3H), 7.28 – 7.19 (m,

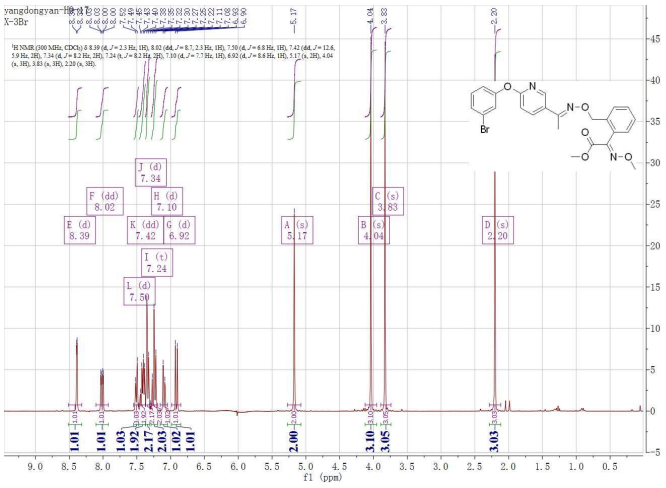
1H), 7.05 – 6.83 (m, 4H), 5.16 (s, 2H), 4.06 (s, 3H), 3.85 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.52, 163.13, 162.97, 161.25, 154.80, 154.65, 151.64, 149.29, 146.90, 145.09, 136.97, 135.78, 130.09, 129.96, 129.59, 129.02, 128.50, 128.26, 127.56, 127.41, 123.55, 116.48, 116.44, 111.51, 111.23, 111.09, 108.84, 108.52, 74.53, 63.39, 52.48, 11.86. HRMS (ESI) m/z calcd for $C_{24}H_{23}FN_3O_5$ $(M+H)^+$ 452.1616, found 452.1618.

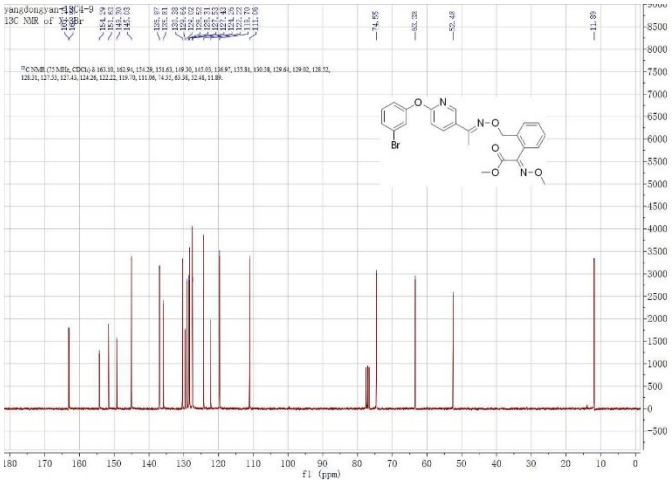


Data for **(5-15)**. white crystal; mp 59-60 °C; yield 67%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.9 Hz, 1H), 8.04 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.60 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 5.17 (s, 2H), 4.07 (s, 3H), 3.87 (s, 3H), 2.22 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.15, 162.98, 154.25, 151.64, 149.28, 145.09, 136.98, 135.75, 134.52, 130.03, 129.55, 129.05, 128.51, 128.24, 127.54, 127.43, 124.68, 121.39, 119.14, 111.06, 74.52, 63.44, 52.55, 11.90, -16.54. HRMS (ESI) m/z calcd for $C_{24}H_{23}ClN_3O_5$ $(M+H)^+$ 468.1321, found 468.1319.

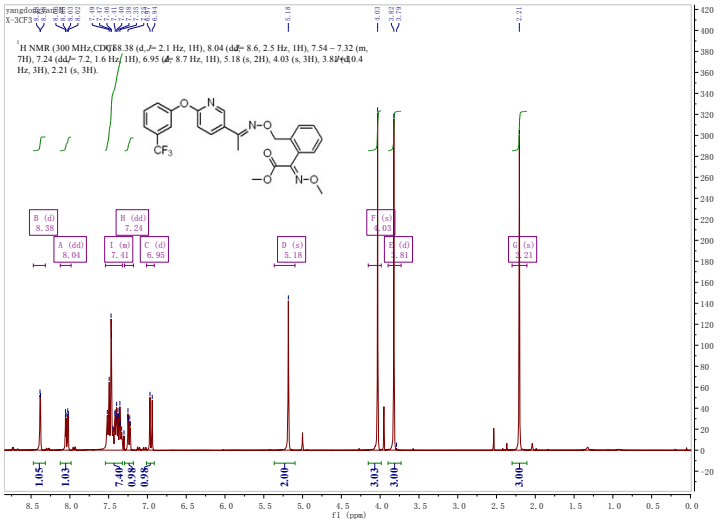


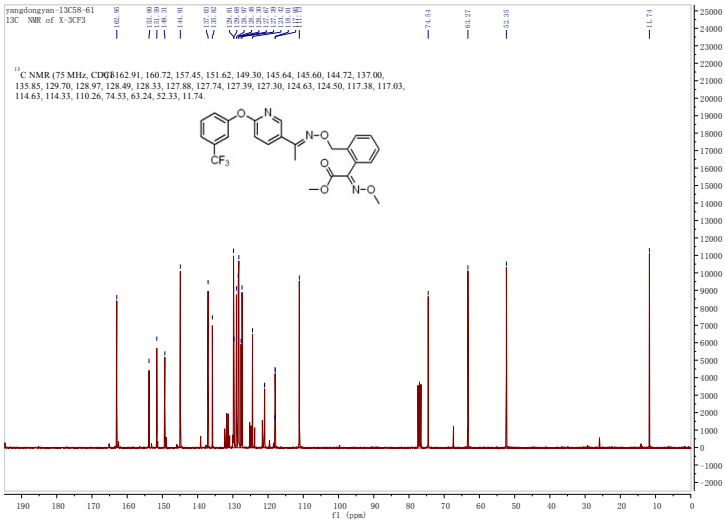
Data for **(5-16)**. white crystal; mp 65-66 °C; yield 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.3 Hz, 1H), 8.02 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 1H), 7.42 (dd, *J* = 12.6, 5.9 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.24 (t, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 5.17 (s, 2H), 4.04 (s, 3H), 3.83 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.10, 162.94, 154.29, 151.63, 149.30, 145.03, 136.97, 135.81, 130.38, 129.64, 129.02, 128.52, 128.31, 127.53, 127.43, 124.26, 122.22, 119.70, 111.06, 74.55, 63.38, 52.48, 11.89. HRMS (ESI) m/z calcd for $C_{24}H_{23}BrN_3O_5$ $(M+H)^+$ 512.0816, found 512.0816.



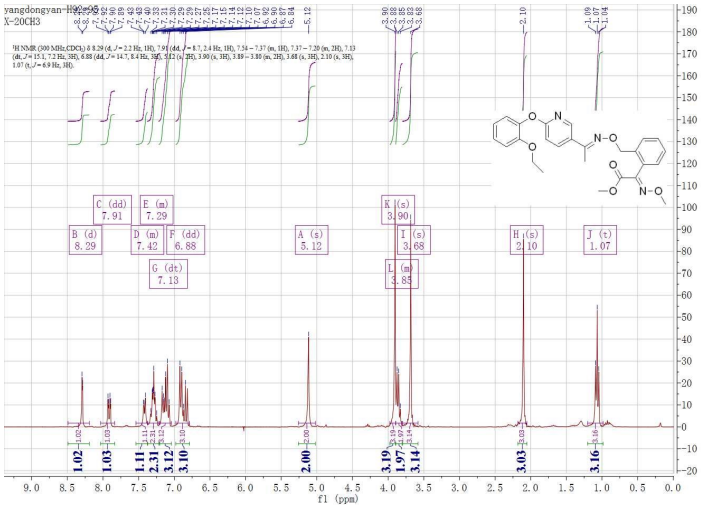


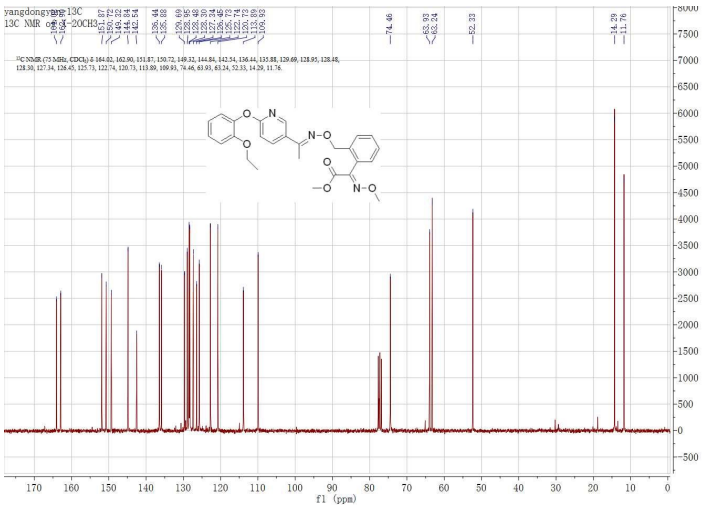
Data for **(5-17)**. white solid; mp 46-47 °C; yield 64%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.4 Hz, 1H), 8.04 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.55 – 7.32 (m, 7H), 7.28 – 7.21 (m, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 5.19 (s, 2H), 4.03 (s, 3H), 3.82 (s, 3H), 2.21 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.94, 153.81, 151.58, 149.31, 144.88, 137.01, 135.84, 132.14, 131.71, 131.27, 130.84, 129.82, 129.74, 128.95, 128.48, 128.32, 127.65, 127.38, 125.27, 124.47, 121.66, 121.00, 120.95, 118.06, 118.01, 117.96, 117.91, 111.11, 74.55, 63.20, 52.27, 11.68. HRMS (ESI) m/z calcd for $C_{25}H_{23}F_3N_3O_5$ (M+H) $^+$ 502.1584, found 502.1585.



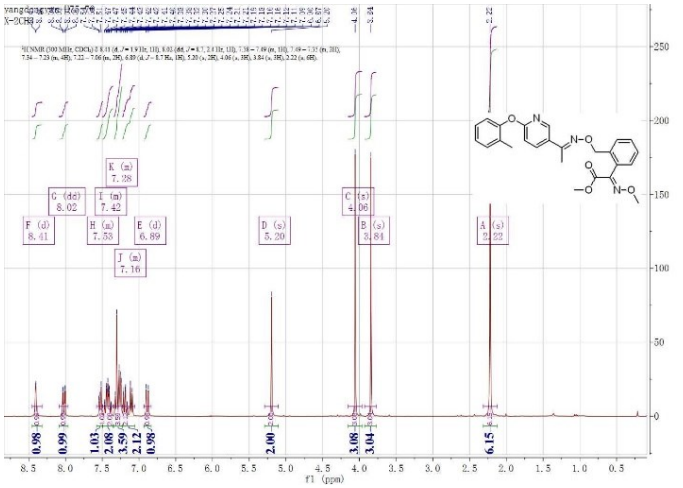


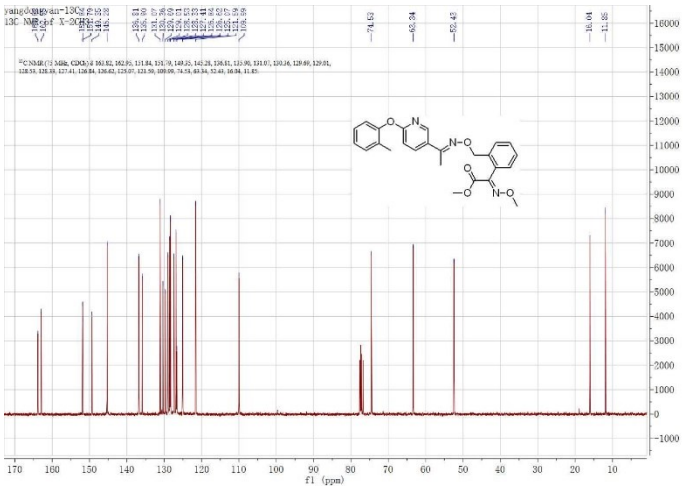
Data for **(5-18)**. white solid; mp 57-58 °C; yield 67%; ^{1}H NMR (300 MHz,$CDCl_3$) δ 8.29 (d, *J* = 2.2 Hz, 1H), 7.91 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.54 – 7.37 (m, 1H), 7.37 – 7.20 (m, 2H), 7.13 (dt, *J* = 15.1, 7.2 Hz, 3H), 6.88 (dd, *J* = 14.7, 8.4 Hz, 3H), 5.12 (s, 2H), 3.90 (s, 3H), 3.89 – 3.80 (m, 2H), 3.68 (s, 3H), 2.10 (s, 3H), 1.07 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.02, 162.90, 151.87, 150.72, 149.32, 144.84, 142.54, 136.44, 135.88, 129.69, 128.95, 128.48, 128.30, 127.34, 126.45, 125.73, 122.74, 120.73, 113.89, 109.93, 74.46, 63.93, 63.24, 52.33, 14.29, 11.76. HRMS (ESI) m/z calcd for $C_{26}H_{28}N_3O_6$ $(M+H)^+$ 478.1973, found 478.1977.



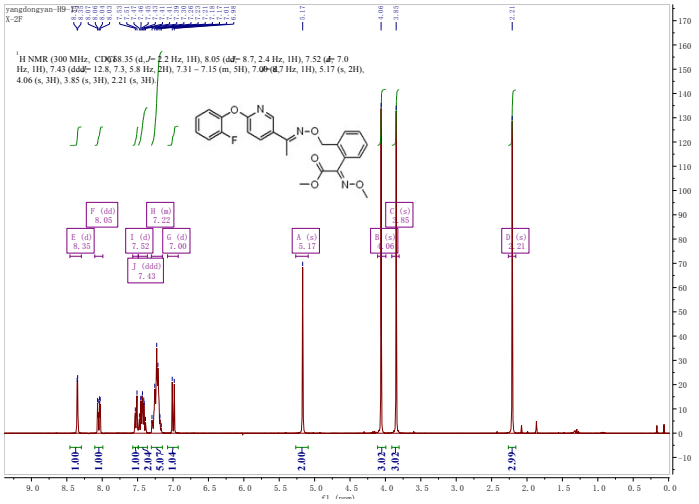


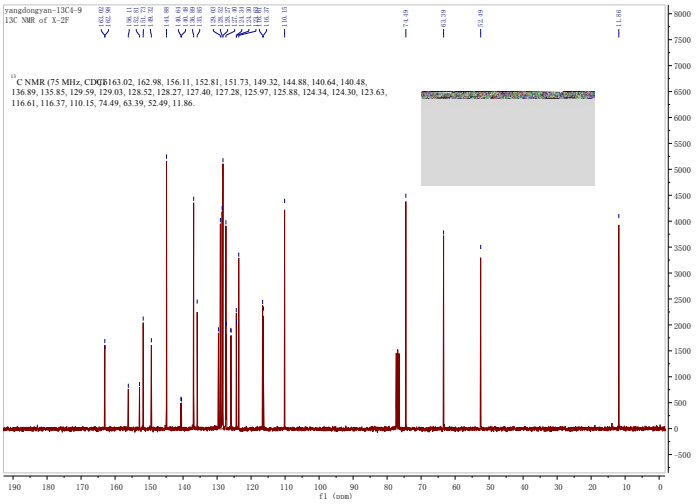
Data for **(5-19)**. colorless oil; yield 64%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 1.9 Hz, 1H), 8.02 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.49 – 7.35 (m, 2H), 7.34 – 7.23 (m, 4H), 7.22 – 7.06 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.20 (s, 2H), 4.06 (s, 3H), 3.84 (s, 3H), 2.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.82, 162.95, 151.84, 151.79, 149.35, 145.28, 136.81, 135.90, 131.07, 130.36, 129.69, 129.01, 128.53, 128.33, 127.41, 126.84, 126.62, 125.07, 121.59, 109.99, 74.53, 63.34, 52.43, 16.04, 11.85. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O_5$ $(M+H)^+$ 448.1867, found 448.1868.



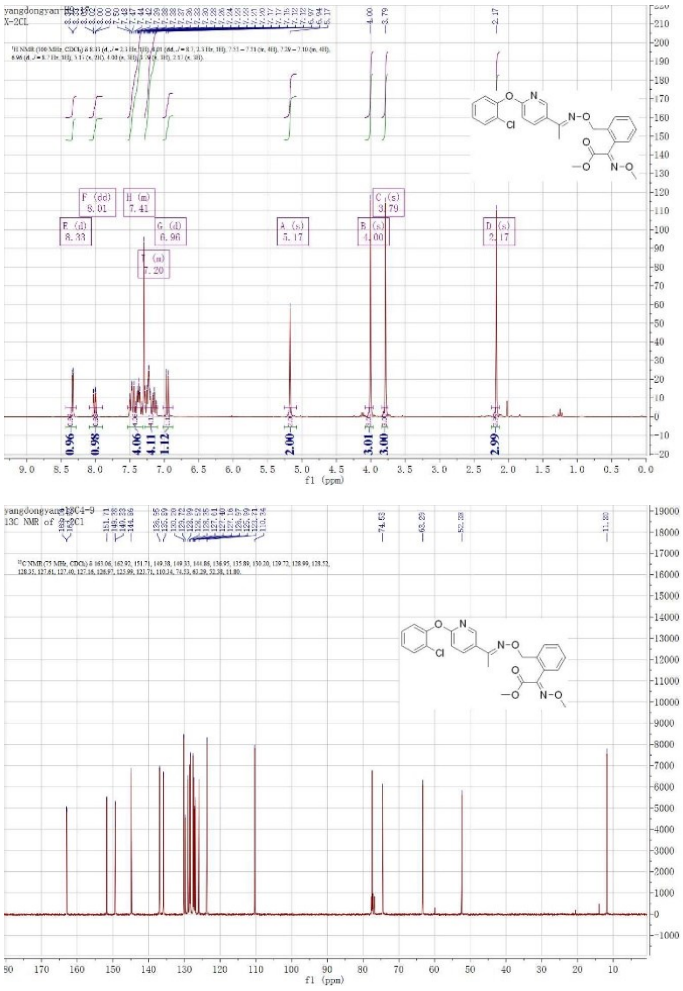


Data for **(5-20)**. white crystal; mp 55-56 °C; yield 74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.2 Hz, 1H), 8.05 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.43 (ddd, *J* = 12.8, 7.3, 5.8 Hz, 2H), 7.31 – 7.15 (m, 5H), 7.00 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.06 (s, 3H), 3.85 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.02, 162.98, 156.11, 152.81, 151.73, 149.32, 144.88, 140.64, 140.48, 136.89, 135.85, 129.59, 129.03, 128.52, 128.27, 127.40, 127.28, 125.97, 125.88, 124.34, 124.30, 123.63, 116.61, 116.37, 110.15, 74.49, 63.39, 52.49, 11.86. HRMS (ESI) m/z calcd for $C_{24}H_{23}FN_3O_5$ $(M+H)^+$ 452.1616, found 452.1616.



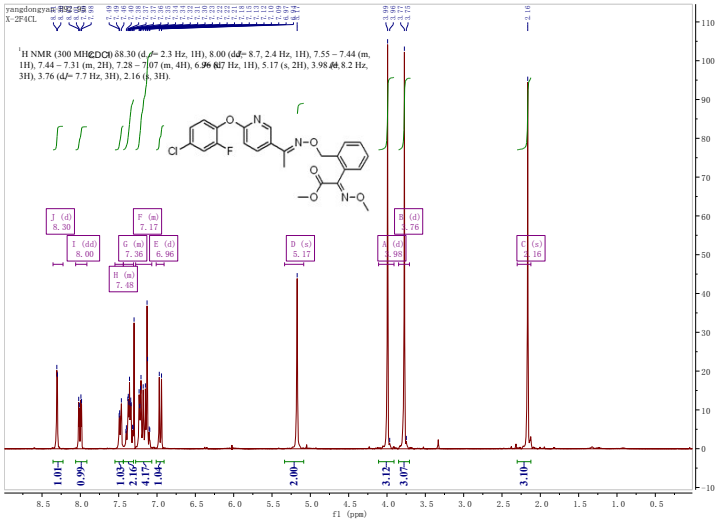


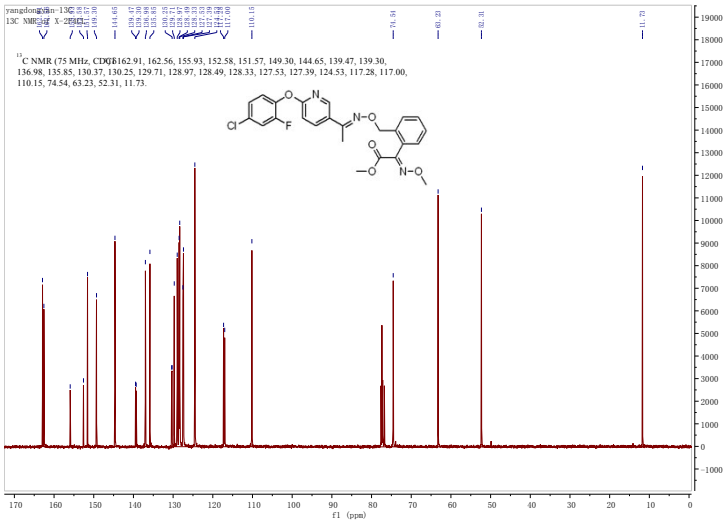
Data for **(5-21)**. colorless oil; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.3 Hz, 1H), 8.01 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.53 – 7.31 (m, 4H), 7.29 – 7.10 (m, 4H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.00 (s, 3H), 3.79 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.06, 162.92, 151.71, 149.38, 149.33, 144.86, 136.95, 135.89, 130.20, 129.72, 128.99, 128.52, 128.35, 127.61, 127.40, 127.16, 126.97, 125.99, 123.71, 110.34, 74.53, 63.29, 52.38, 11.80. HRMS (ESI) m/z calcd for $C_{24}H_{23}ClN_3O_5$ $(M+H)^+$ 468.1321, found 468.1322



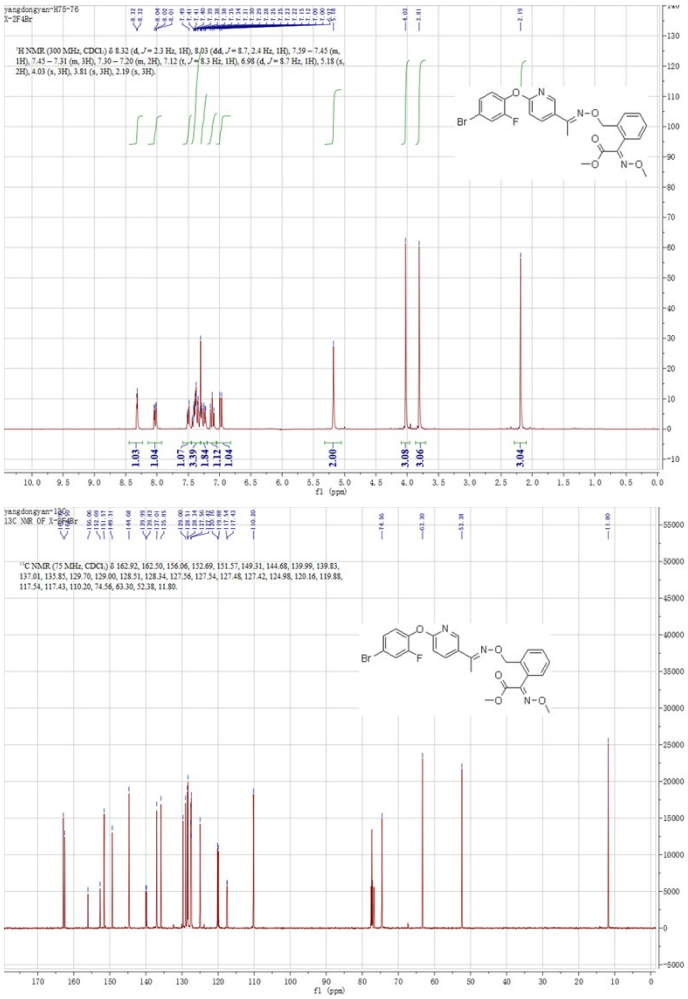
Data for **(5-22)**. light yellow oil; yield 68%; ^{1}H NMR (300 MHz,$CDCl_3$) δ 8.30 (d, *J* = 2.3 Hz, 1H), 8.00 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.55 – 7.44 (m, 1H), 7.44 – 7.31 (m, 2H), 7.28 – 7.07 (m, 4H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.17

(s, 2H), 3.98 (d, *J* = 8.2 Hz, 3H), 3.76 (d, *J* = 7.7 Hz, 3H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.91, 162.56, 155.93, 152.58, 151.57, 149.30, 144.65, 139.47, 139.30, 136.98, 135.85, 130.37, 130.25, 129.71, 128.97, 128.49, 128.33, 127.53, 127.39, 124.53, 117.28, 117.00, 110.15, 74.54, 63.23, 52.31, 11.73. HRMS (ESI) m/z calcd for $C_{24}H_{22}ClFN_3O_5$ $(M+H)^+$ 486.1227, found 486.1226.

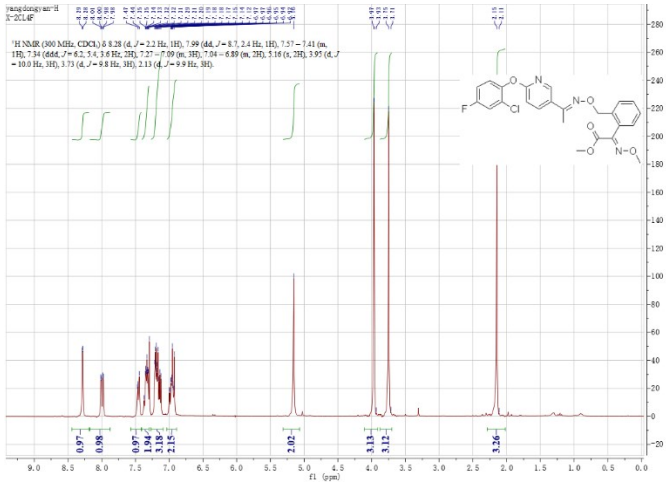


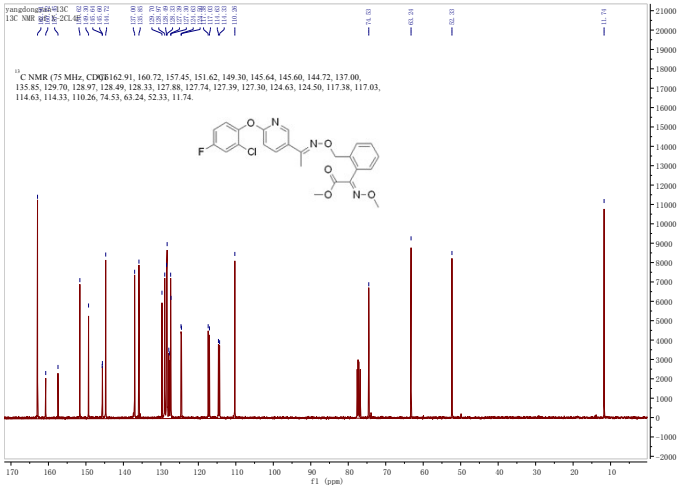


Data for **(5-23)**. light yellow oil; yield 62%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.59 – 7.45 (m, 1H), 7.45 – 7.31 (m, 3H), 7.30 – 7.20 (m, 2H), 7.12 (t, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 5.18 (s, 2H), 4.03 (s, 3H), 3.81 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.92, 162.50, 156.06, 152.69, 151.57, 149.31, 144.68, 139.99, 139.83, 137.01, 135.85, 129.70, 129.00, 128.51, 128.34, 127.56, 127.54, 127.48, 127.42, 124.98, 120.16, 119.88, 117.54, 117.43, 110.20, 74.56, 63.30, 52.38, 11.80. HRMS (ESI) m/z calcd for $C_{24}H_{22}BrFN_3O_5$ $(M+H)^+$ 530.0721, found 530.0720.

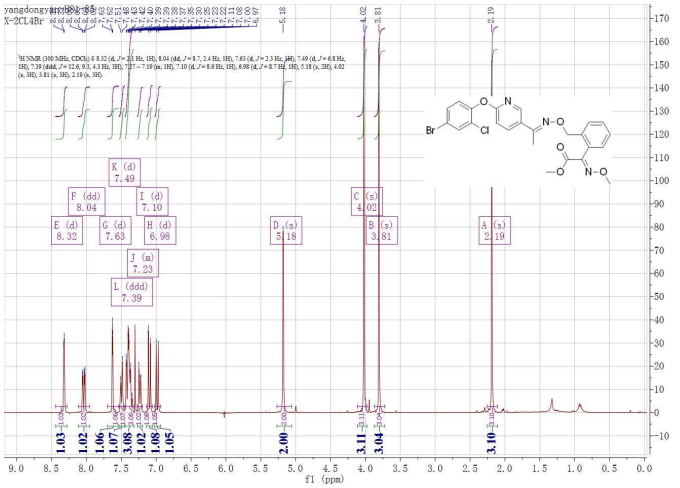


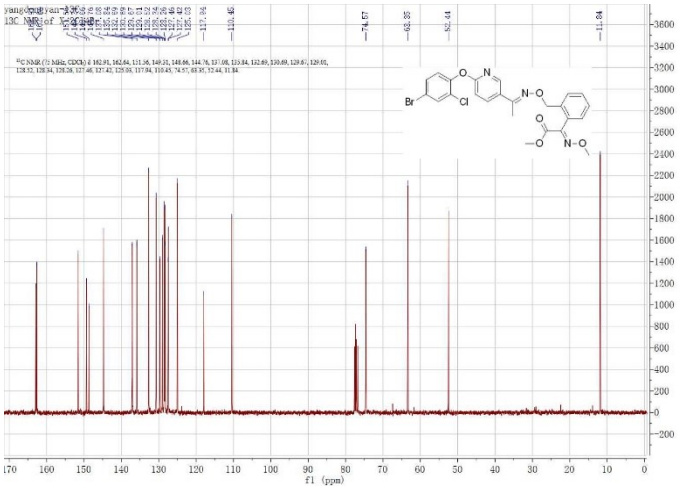
Data for **(5-24)**. light yellow solid; mp 51-52 °C; yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.2 Hz, 1H), 7.99 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.57 – 7.41 (m, 1H), 7.34 (ddd, *J* = 6.2, 5.4, 3.6 Hz, 2H), 7.27 – 7.09 (m, 3H), 7.04 – 6.89 (m, 2H), 5.16 (s, 2H), 3.95 (d, *J* = 10.0 Hz, 3H), 3.73 (d, *J* = 9.8 Hz, 3H), 2.13 (d, *J* = 9.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.91, 160.72, 157.45, 151.62, 149.30, 145.64, 145.60, 144.72, 137.00, 135.85, 129.70, 128.97, 128.49, 128.33, 127.88, 127.74, 127.39, 127.30, 124.63, 124.50, 117.38, 117.03, 114.63, 114.33, 110.26, 74.53, 63.24, 52.33, 11.74. HRMS (ESI) m/z calcd for $C_{24}H_{22}ClFN_3O_5$ $(M+H)^+$ 486.1227, found 486.1228.



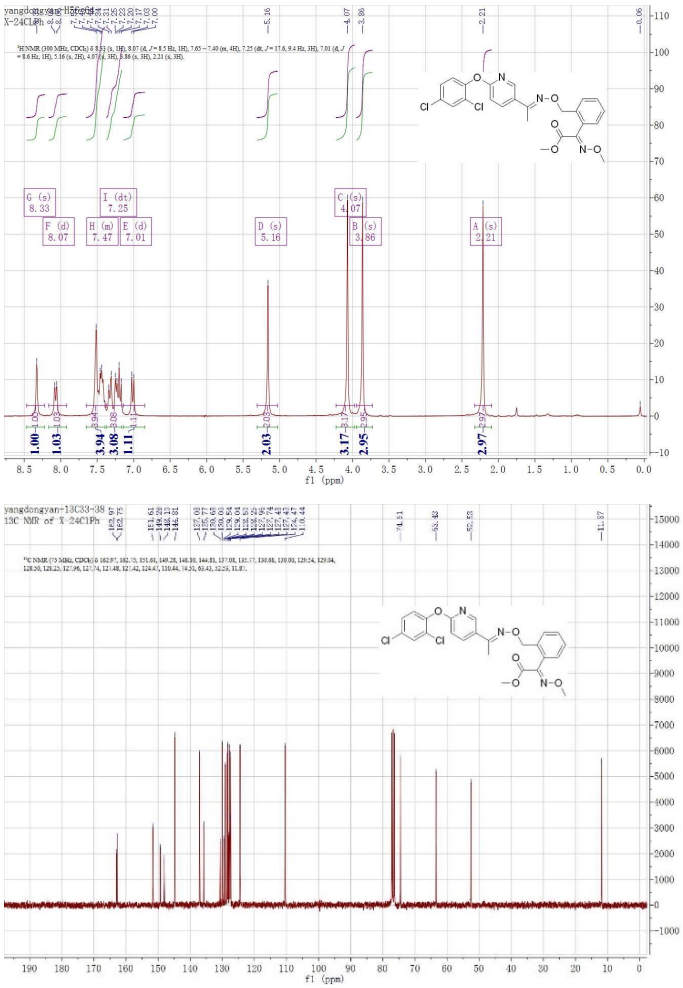


Data for **(5-25)**. white crystal; mp 74-75 °C; yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 2.1 Hz, 1H), 8.04 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.63 (d, *J* = 2.3 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.39 (ddd, *J* = 12.6, 9.3, 4.3 Hz, 3H), 7.27 – 7.19 (m, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 5.18 (s, 2H), 4.02 (s, 3H), 3.81 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.91, 162.64, 151.56, 149.31, 148.66, 144.76, 137.08, 135.84, 132.69, 130.69, 129.67, 129.01, 128.52, 128.34, 128.26, 127.46, 127.42, 125.03, 117.94, 110.45, 74.57, 63.35, 52.44, 11.84. HRMS (ESI) m/z calcd for $C_{24}H_{21}BrClN_3NaO_5$ $(M+Na)^+$ 568.0245, found 568.0245.

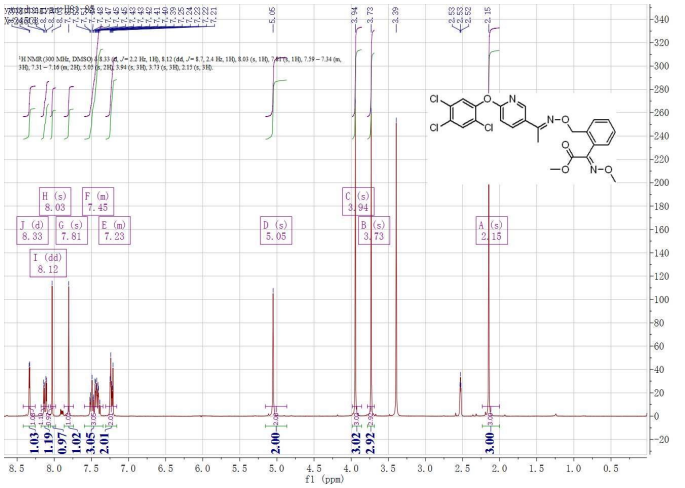


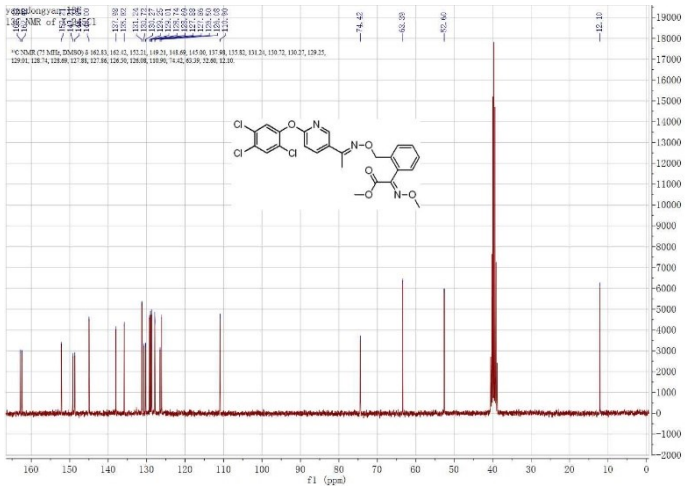


Data for **(5-26)**. white solid; mp 68-69 °C; yield 66%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.65 – 7.40 (m, 4H), 7.25 (dt, *J* = 17.6, 9.4 Hz, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 5.16 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.97, 162.75, 151.61, 149.28, 148.10, 144.81, 137.08, 135.77, 130.68, 130.00, 129.54, 129.04, 128.50, 128.25, 127.96, 127.74, 127.48, 127.42, 124.47, 110.44, 74.51, 63.43, 52.53, 11.87. HRMS (ESI) m/z calcd for $C_{24}H_{22}Cl_2N_3O_5$ $(M+H)^+$ 502.0931, found 502.0933.

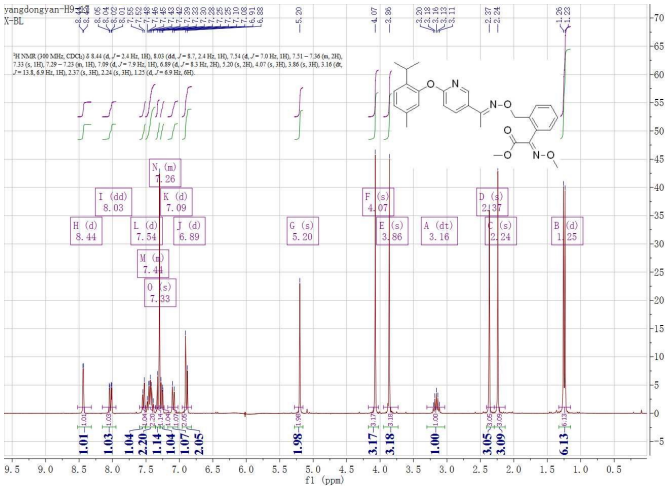


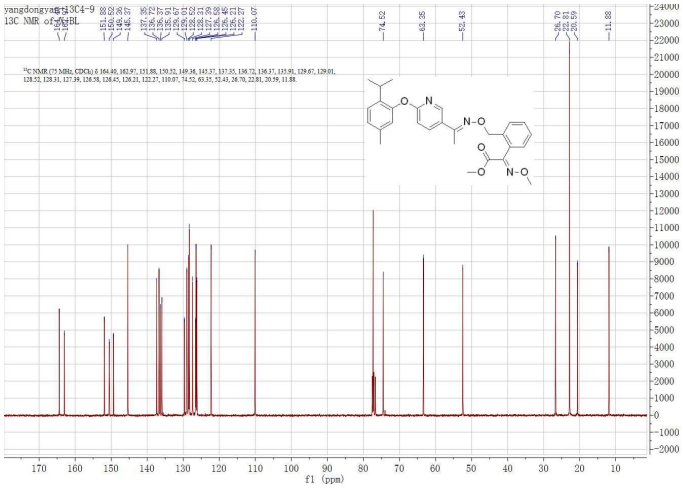
Data for **(5-27)**. white solid; mp 102-103 °C; yield 71%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (d, *J* = 2.2 Hz, 1H), 8.12 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.59 – 7.34 (m, 3H), 7.31 – 7.16 (m, 2H), 5.05 (s, 2H), 3.94 (s, 3H), 3.73 (s, 3H), 2.15 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 162.83, 162.42, 152.21, 149.21, 148.69, 145.00, 137.98, 135.82, 131.24, 130.72, 130.27, 129.25, 129.01, 128.74, 128.69, 127.88, 127.86, 126.50, 126.08, 110.90, 74.42, 63.39, 52.60, 12.10. HRMS (ESI) m/z calcd for $C_{24}H_{20}Cl_3N_3NaO_5$ $(M+Na)^+$ 558.0361, found 558.0368.



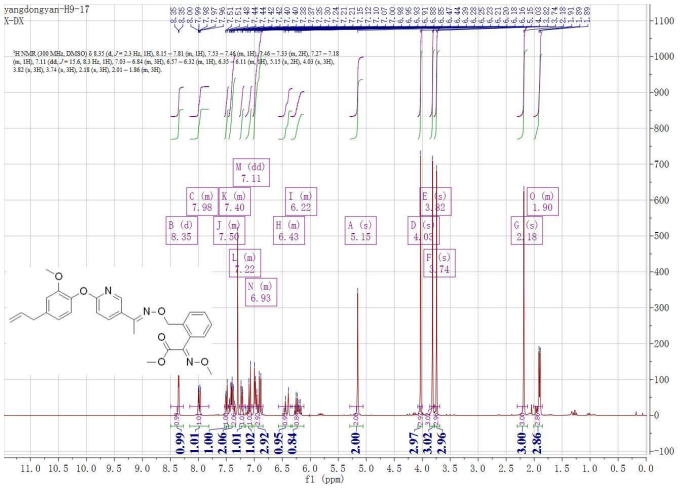


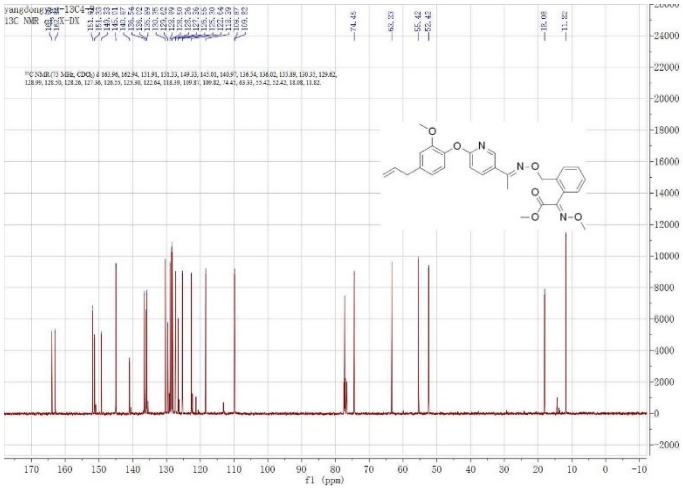
Data for **(5-28)**.light yellow solid; mp 50-51 °C; yield 61%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.51 – 7.36 (m, 2H), 7.33 (s, 1H), 7.29 – 7.23 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.20 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 3.16 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.40, 162.97, 151.88, 150.52, 149.36, 145.37, 137.35, 136.72, 136.37, 135.91, 129.67, 129.01, 128.52, 128.31, 127.39, 126.58, 126.45, 126.21, 122.27, 110.07, 74.52, 63.35, 52.43, 26.70, 22.81, 20.59, 11.88. HRMS (ESI) m/z calcd for $C_{28}H_{32}N_3O_5$ $(M+H)^+$ 490.2336, found 490.2341.



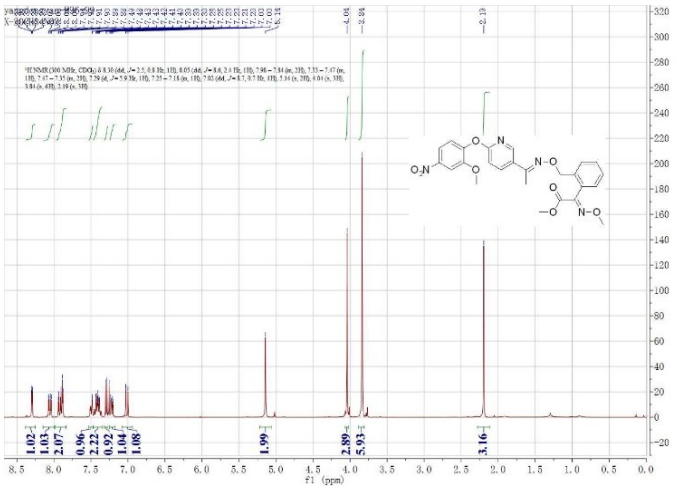


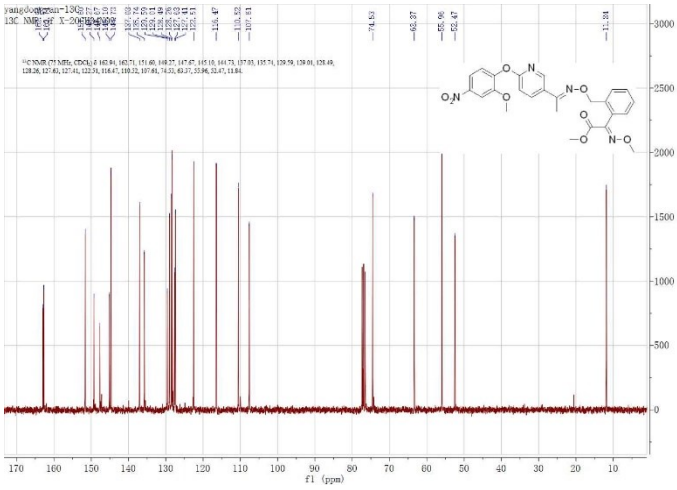
Data for **(5-29)**. colorless oil; yield 44%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.3 Hz, 1H), 8.15 – 7.81 (m, 1H), 7.53 – 7.46 (m, 1H), 7.46 – 7.33 (m, 2H), 7.27 – 7.18 (m, 1H), 7.11 (dd, *J* = 15.6, 8.3 Hz, 1H), 7.03 – 6.84 (m, 3H), 6.57 – 6.32 (m, 1H), 6.35 – 6.11 (m, 1H), 5.15 (s, 2H), 4.03 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 2.18 (s, 3H), 2.01 – 1.86 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.96, 162.94, 151.91, 151.33, 149.33, 145.01, 140.97, 136.54, 136.02, 135.89, 130.35, 129.62, 128.99, 128.50, 128.26, 127.36, 126.55, 125.30, 122.64, 118.39, 109.87, 109.82, 74.45, 63.33, 55.42, 52.42, 18.08, 11.82. HRMS (ESI) m/z calcd for $C_{28}H_{30}N_3O_6$ $(M+H)^+$ 504.2129, found 504.2133.



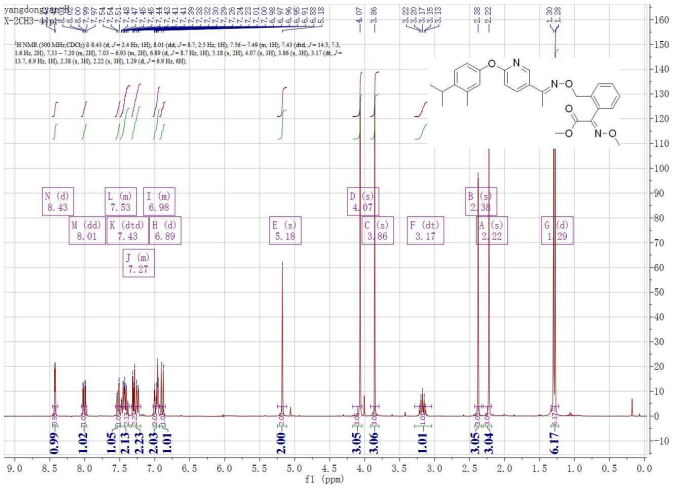


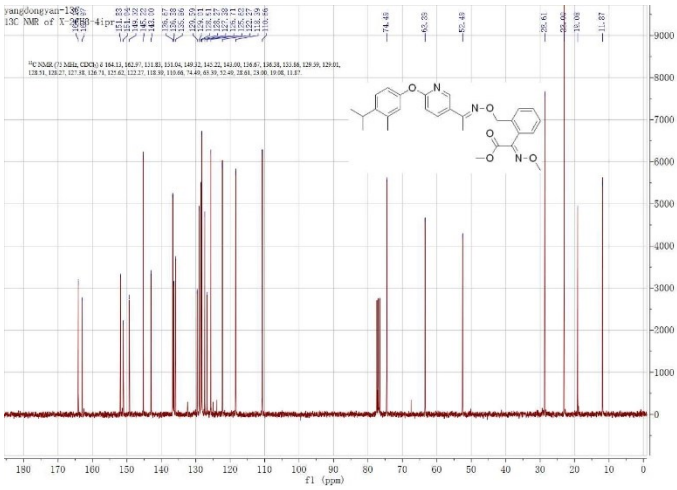
Data for **(5-30)**. light yellow oil; yield 68%;^{1}H NMR (300 MHz,$CDCl_3$) δ 8.29 (d, *J* = 2.4 Hz, 1H), 8.05 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.98 – 7.84 (m, 2H), 7.53 – 7.47 (m, 1H), 7.47 – 7.35 (m, 2H), 7.29 (d, *J* = 5.9 Hz, 1H), 7.21 (dd, *J* = 8.4, 6.4 Hz, 1H), 7.03 (t, *J* = 8.5 Hz, 1H), 5.14 (s, 2H), 4.04 (s, 3H), 3.84 (s, 6H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.94, 162.71, 151.60, 149.27, 147.67, 145.10, 144.73, 137.03, 135.74, 129.59, 129.01, 128.49, 128.26, 127.63, 127.41, 122.51, 116.47, 110.52, 107.61, 74.53, 63.37, 55.96, 52.47, 11.84. HRMS (ESI) m/z calcd for $C_{25}H_{25}N_4O_8$ $(M+H)^+$ 509.1667, found 509.1672



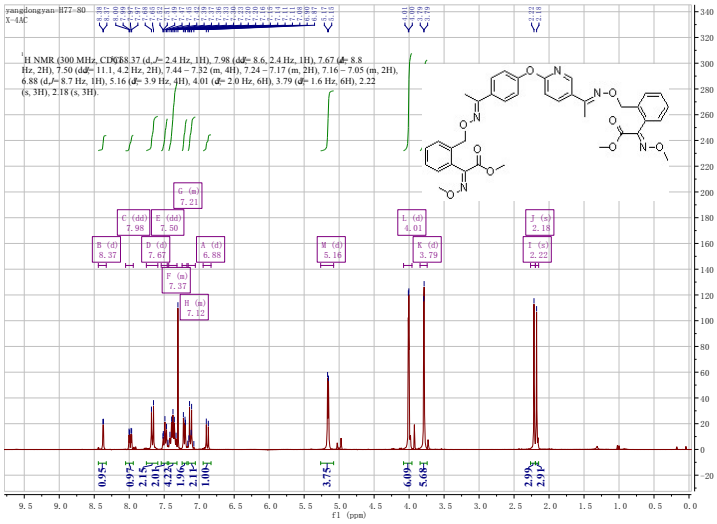


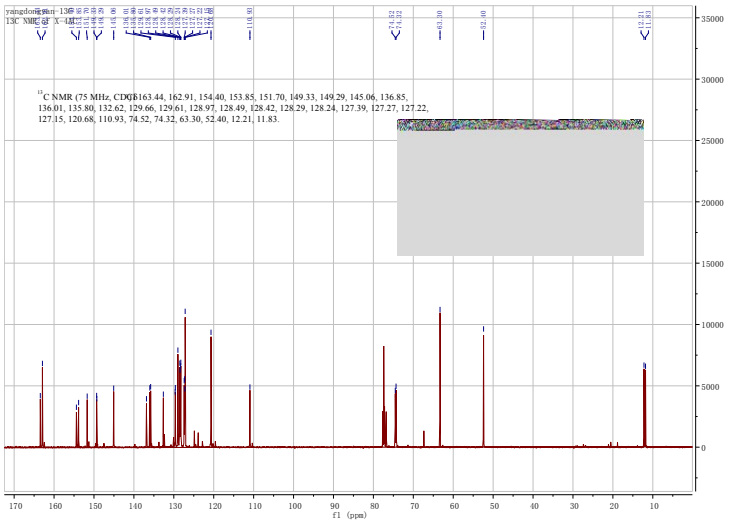
Data for **(5-31)**. colorless oil； yield 56%;^{1}H NMR (300 MHz,$CDCl_3$) δ 8.43 (d, *J* = 2.4 Hz, 1H), 8.01 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.43 (dtd, *J* = 14.5, 7.3, 1.6 Hz, 2H), 7.33 – 7.20 (m, 2H), 7.03 – 6.93 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.18 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 3.17 (dt, *J* = 13.7, 6.9 Hz, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.13, 162.97, 151.83, 151.04, 149.32, 145.22, 143.00, 136.67, 136.38, 135.86, 129.59, 129.01, 128.51, 128.27, 127.38, 126.71, 125.62, 122.27, 118.39, 110.66, 74.49, 63.39, 52.49, 28.61, 23.00, 19.08, 11.87. HRMS (ESI) m/z calcd for $C_{28}H_{32}N_3O_5$ $(M+H)^+$ 490.2336, found 490.2337.



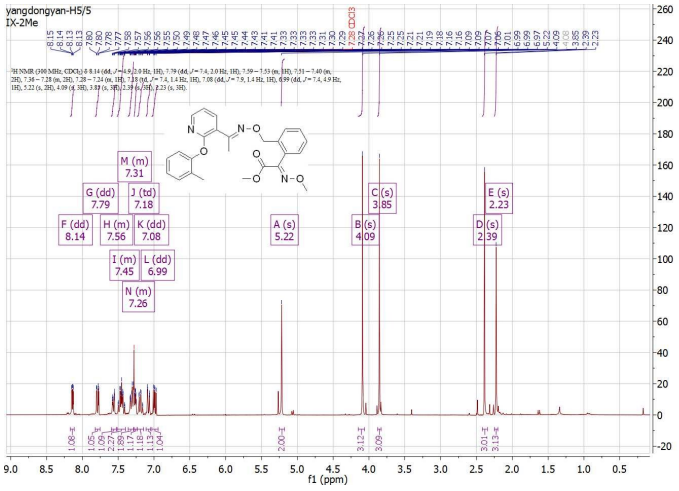


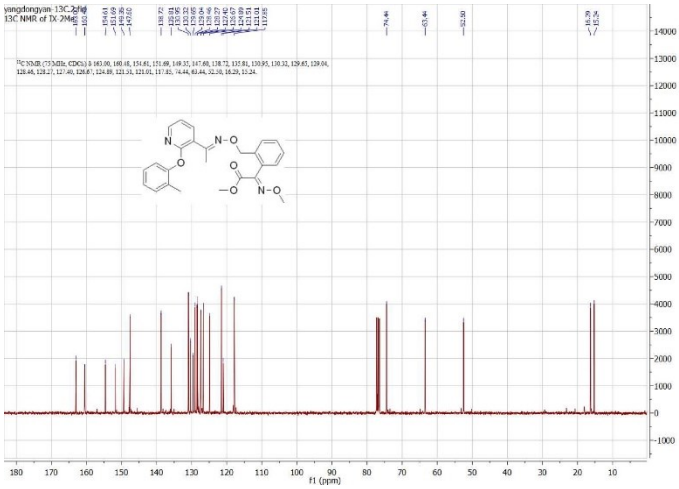
Data for **(5-01b)**. colorless oil; yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.4 Hz, 1H), 7.98 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* = 11.1, 4.2 Hz, 2H), 7.44 – 7.32 (m, 4H), 7.24 – 7.17 (m, 2H), 7.16 – 7.05 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 5.16 (d, *J* = 3.9 Hz, 4H), 4.01 (d, *J* = 2.0 Hz, 6H), 3.79 (d, *J* = 1.6 Hz, 6H), 2.22 (s, 3H), 2.18 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.44, 162.91, 154.40, 153.85, 151.70, 149.33, 149.29, 145.06, 136.85, 136.01, 135.80, 132.62, 129.66, 129.61, 128.97, 128.49, 128.42, 128.29, 128.24, 127.39, 127.27, 127.22, 127.15, 120.68, 110.93, 74.52, 74.32, 63.30, 52.40, 12.21, 11.83. HRMS (ESI) m/z calcd for $C_{37}H_{37}N_5NaO_9$ $(M+Na)^+$ 718.2483, found 718.2486.



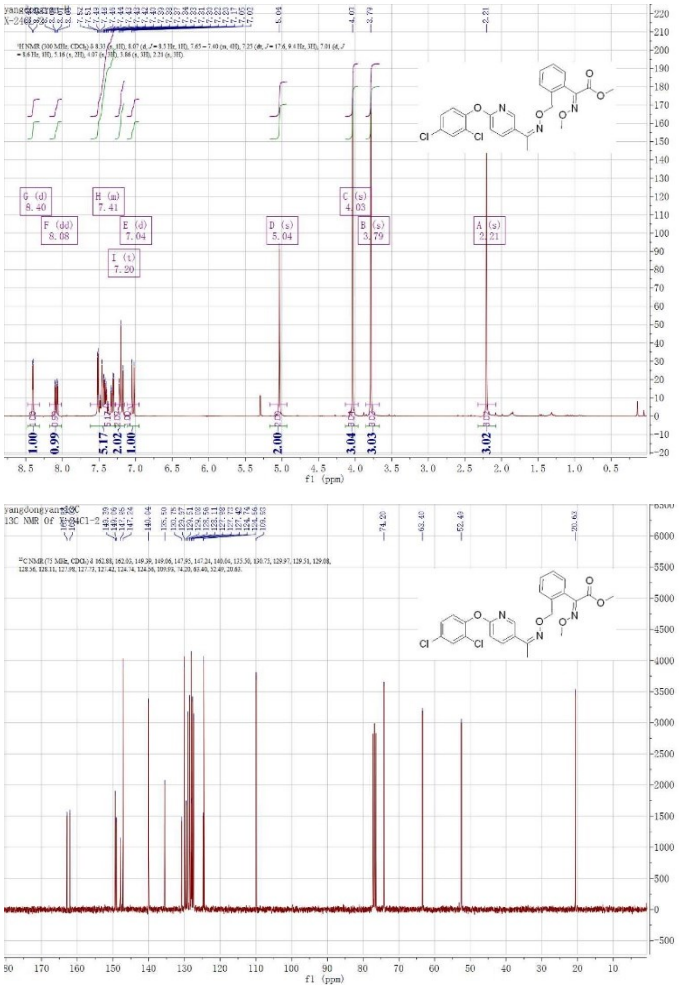


Data for **(5-19b)**. colorless oil; yield 73%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 4.9, 2.0 Hz, 1H), 7.79 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.51 – 7.40 (m, 2H), 7.36 – 7.28 (m, 2H), 7.28 – 7.24 (m, 1H), 7.18 (td, *J* = 7.4, 1.4 Hz, 1H), 7.08 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.99 (dd, *J* = 7.4, 4.9 Hz, 1H), 5.22 (s, 2H), 4.09 (s, 3H), 3.85 (s, 3H), 2.39 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.00, 160.48, 154.61, 151.69, 149.35, 147.60, 138.72, 135.81, 130.95, 130.32, 129.65, 129.04, 128.46, 128.27, 127.40, 126.67, 124.89, 121.51, 121.01, 117.85, 74.44, 63.44, 52.50, 16.29, 15.24. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O_5$ $(M+H)^+$ 448.1867, found 448.1867.

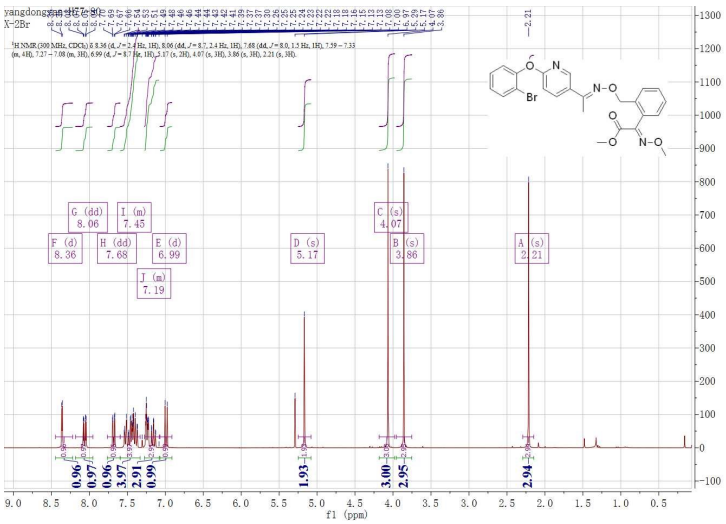


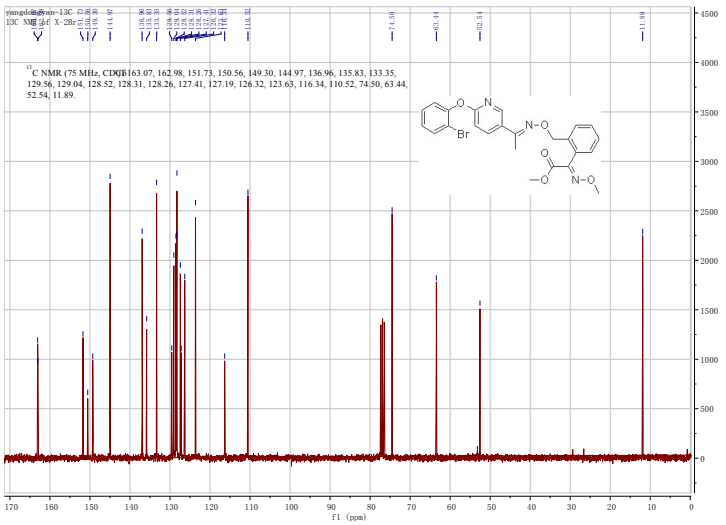


Data for **(5-26b)**. colorless oil; yield 12%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.65 – 7.40 (m, 4H), 7.25 (dt, *J* = 17.6, 9.4 Hz, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 5.16 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 2.21 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.88, 162.03, 149.39, 149.06, 147.95, 147.24, 140.04, 135.50, 130.75, 129.97, 129.51, 129.08, 128.56, 128.11, 127.98, 127.73, 127.42, 124.74, 124.56, 109.93, 74.20, 63.40, 52.49, 20.63. HRMS (ESI) m/z calcd for $C_{24}H_{22}Cl_2N_3O_5$ $(M+H)^+$ 502.0931, found 502.0934.

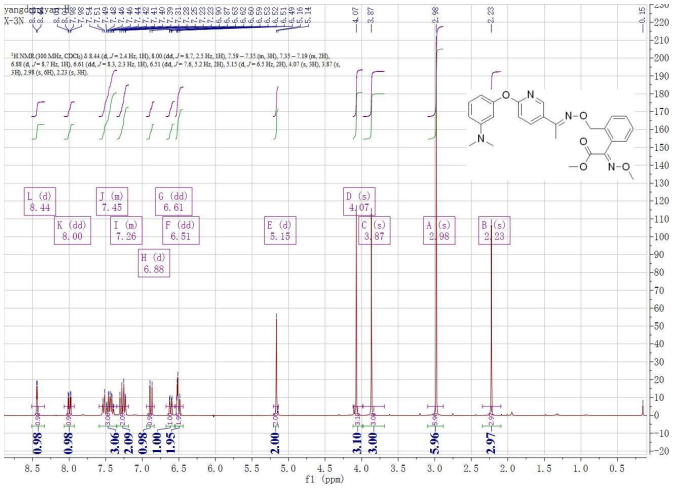


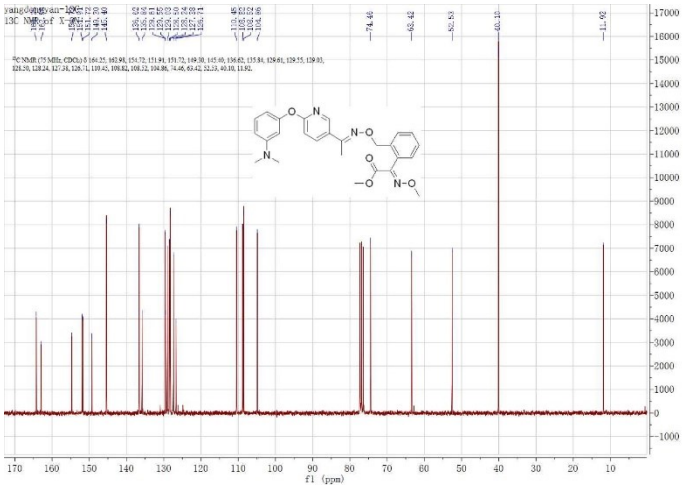
Data for **(6-01)**. colorless oil; yield 53%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.59 – 7.33 (m, 4H), 7.27 – 7.08 (m, 3H), 6.99 (d, *J* = 8.7 Hz, 1H), 5.17 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 2.21 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.07, 162.98, 151.73, 150.56, 149.30, 144.97, 136.96, 135.83, 133.35, 129.56, 129.04, 128.52, 128.31, 128.26, 127.41, 127.19, 126.32, 123.63, 116.34, 110.52, 74.50, 63.44, 52.54, 11.89. HRMS (ESI) m/z calcd for $C_{24}H_{23}BrN_3O_5$ $(M+H)^+$ 512.0816, found 512.0815.



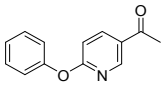


Data for **(6-02)**. white powder; mp 77-78 °C; yield 78%;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.4 Hz, 1H), 8.00 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.59 – 7.35 (m, 3H), 7.35 – 7.19 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.51 (dd, *J* = 7.6, 5.2 Hz, 2H), 5.15 (d, *J* = 6.5 Hz, 2H), 4.07 (s, 3H), 3.87 (s, 3H), 2.98 (s, 6H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.25, 162.98, 154.72, 151.91, 151.72, 149.30, 145.40, 136.62, 135.84, 129.61, 129.55, 129.03, 128.50, 128.24, 127.38, 126.71, 110.45, 108.82, 108.52, 104.86, 74.46, 63.42, 52.53, 40.10, 11.92. HRMS (ESI) m/z calcd for $C_{26}H_{29}N_4O_5$ $(M+H)^+$ 477.2132, found 477.2134.

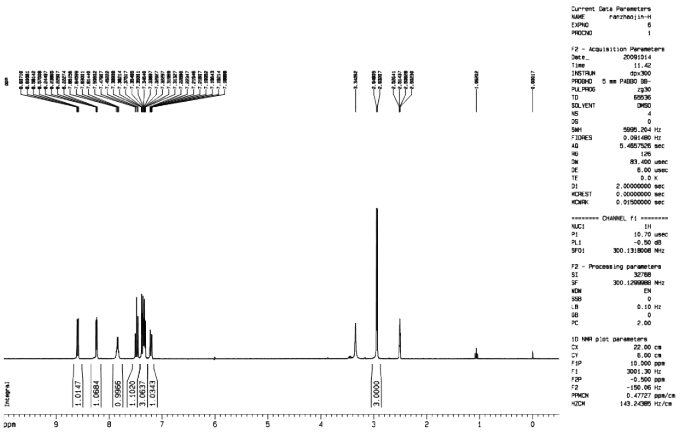


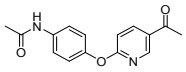


The date and 1H NMR spectrum of the intermediates 3

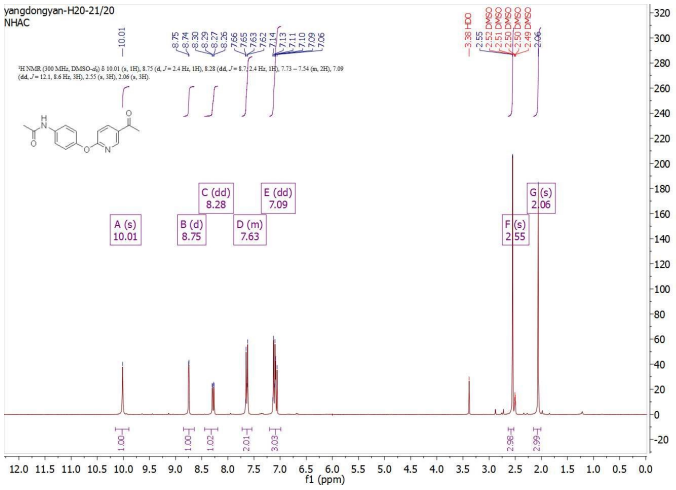


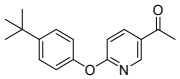
Data for **(3-01)**. White powder; mp 142-144 °C; yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59(dd, *J*=7.7Hz, *J*=1.9Hz, 1H), 8.23(dd, *J* =1.9, 4.8Hz, 1H), 7.83(t, *J*=5.1Hz, 1H), 7.47(m, 1H),7.35(m, 3H),7.19(m, 3H),2.94(s, 3H).



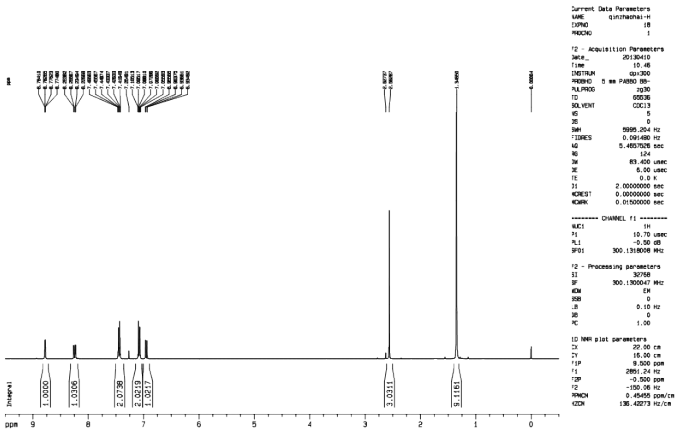


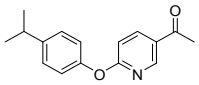
Data for **(3-02)**. slight yellow crystal; mp 134-136 °C; yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.73 – 7.54 (m, 2H), 7.09 (dd, *J* = 12.1, 8.6 Hz, 3H), 2.55 (s, 3H), 2.06 (s, 3H)



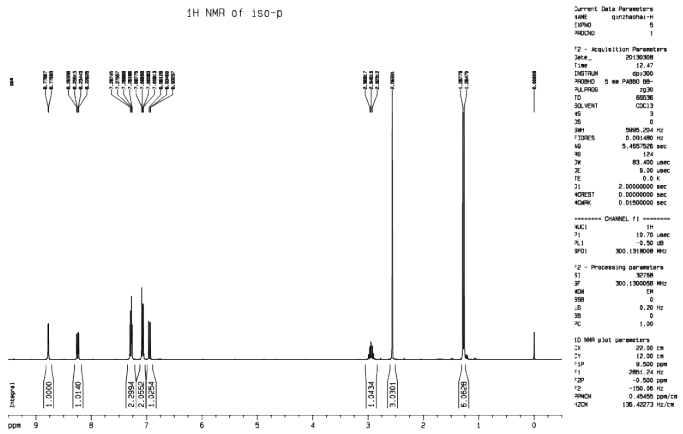


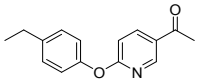
Data for **(3-03)**. White solid; mp 74-76 °C; yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J=0.4, 2.4Hz, 1H), 8.24 (dd, J=2.4, 8.7 Hz, 1H), 7.43 (dt, J=3.0, 8.8Hz, 2H), 7.07 (dt, J=3.0, 8.8Hz, 2H), 6.94 (dd, J=0.4, 8.7Hz, 1H), 2.56 (s, 3H), 1.34 (s, 9H)



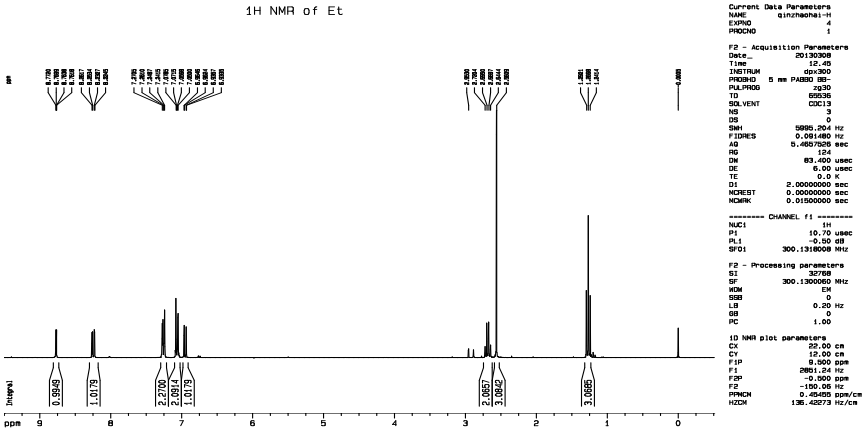


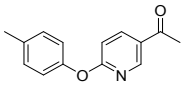
Data for **(3-04)**. White solid; mp 76-78 °C; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J=2.4Hz, 1H), 8.24 (dd, J=2.4, 8.7 Hz, 1H), 7.26 (dd, J=6.6, 8.5Hz, 2H), 7.06 (dd, J=6.6, 8.5Hz, 2H), 6.90 (d, J=8.7Hz, 1H), 2.94 (qt, J=6.9Hz, 1H), 2.56 (s, 3H), 1.27 (d, J=6.9Hz, 6H).



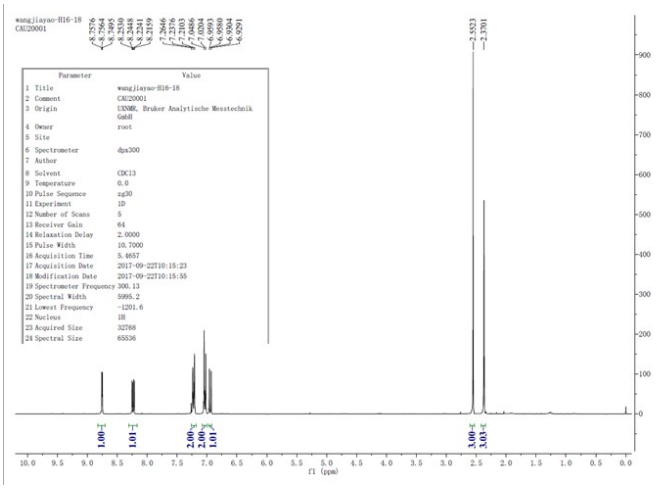


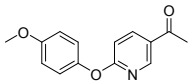
Data for **(3-05)**. White solid; mp 70-72 °C; yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76(dd, J=7.68 Hz, J=1.62Hz ,1H), 8.24(dd, J =4.77Hz, J=1.89Hz, 1H), 7.25(m, 2H), 7.06(m,2H), 6.94(q, 1H, J=0.68Hz), 2.68(q, J=7.6, 2H), 2.56(s, 3H), 1.26(t, J=7.6,3H).



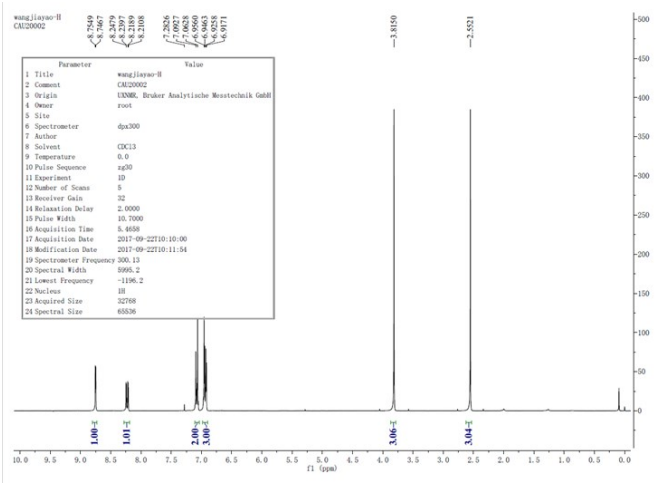


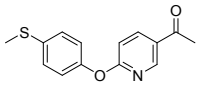
Data for **(3-06)**. White powder; mp 125-127 °C; yield 59%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58(dd, *J*=0.7, 1.7Hz, 1H), 8.20(dd, *J* =4.8,1.7Hz, 1H), 7.30(m, 2H) 7.06(t, *J*=3.20 Hz, 2H), 7.00(q, *J*=0.7, 4.8Hz, 1H), 2.93(s, 3H), 2.33(s, 3H).



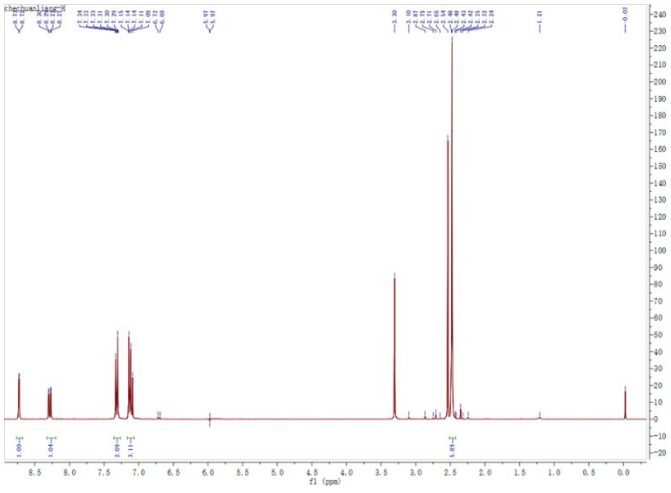


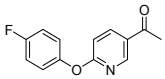
Data for **(3-07)**. White powder; mp 123-125 °C; yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57(dd,*J*=7.72Hz, *J*=1.92Hz,1H), 8.21(dd, *J*=4.79Hz, *J*=1.93Hz,1H), 7.90(t, *J*=5.28 Hz, 2H), 7.49(m, 2H), 7.32(m, 1H), 7.26(m, 1H), 3.36(s, 3H), 1.19(s, 3H).



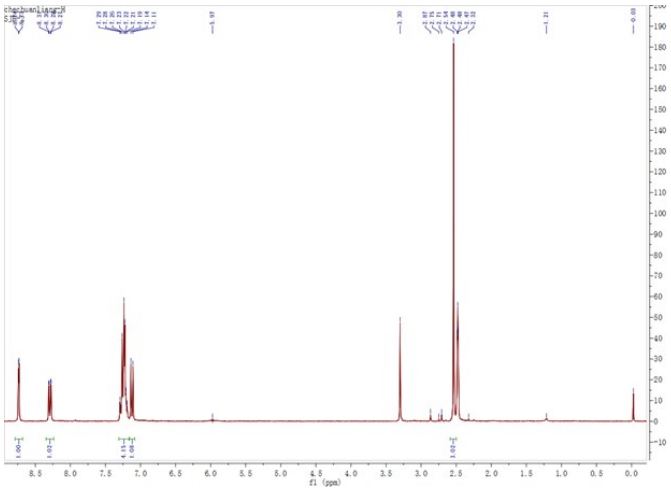


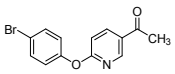
Data for **(3-08)**. Yellow solid; mp 97-98 °C; yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.5 Hz, 1H), 8.28 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.40 – 7.22 (m, 2H), 7.18 – 7.02 (m, 3H), 2.54 (s, 3H), 2.48 (s, 3H)



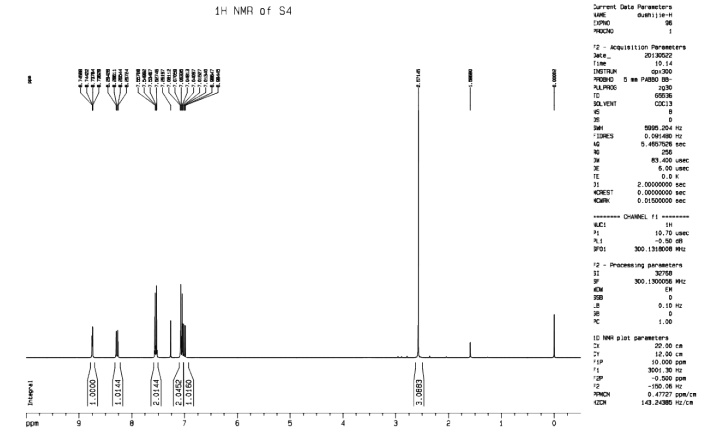


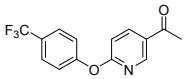
Data for **(3-09)**. slight yellow solid; mp 114-115 °C; yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 2.4 Hz, 1H), 8.29 (dd, J = 8.6, 2.5 Hz, 1H), 7.33 – 7.17 (m, 4H), 7.12 (d, J = 8.7 Hz, 1H), 2.54 (s, 3H)



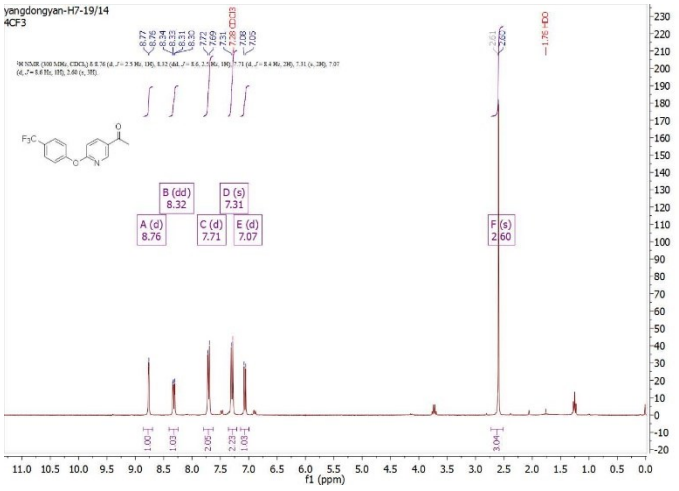


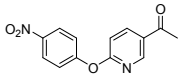
Data for **(3-10)**. yellow solid; mp 70-72 °C; yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.73 – 7.54 (m, 2H), 7.09 (dd, *J* = 12.1, 8.6 Hz, 3H), 2.55 (s, 3H), 2.06 (s, 3H)



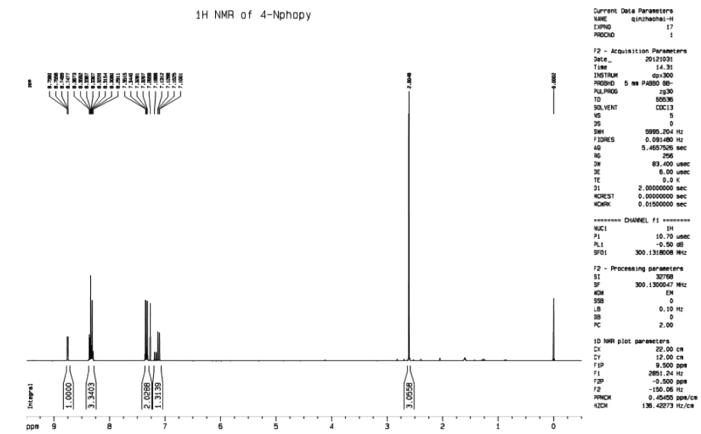


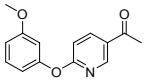
Data for **(3-11)**. yellow crystal; mp 50-51 °C; yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.5 Hz, 1H), 8.32 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 2H), 7.07 (d, *J* = 8.6 Hz, 1H), 2.60 (s, 3H)



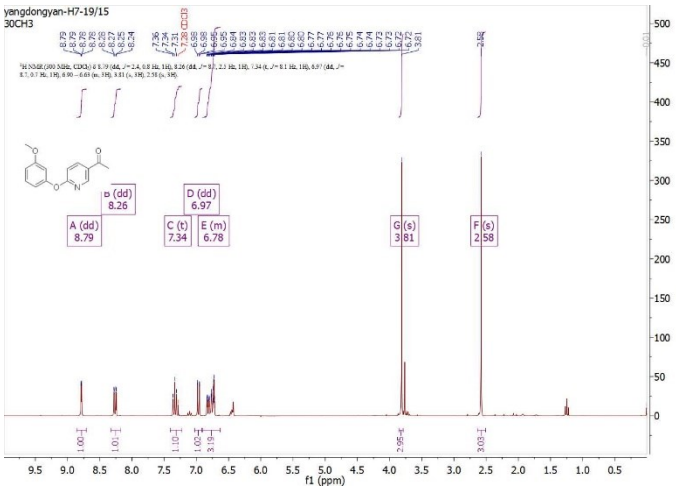


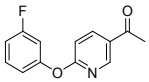
Data for **(3-12)**. slight yellow crystal; mp 90-91 °C; yield 66%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J*=0.7, 2.4Hz, 1H), 8.33(m, 3H), 7.33(m, 2H),7.11 (m, 1H), 2.60(s, 3H)



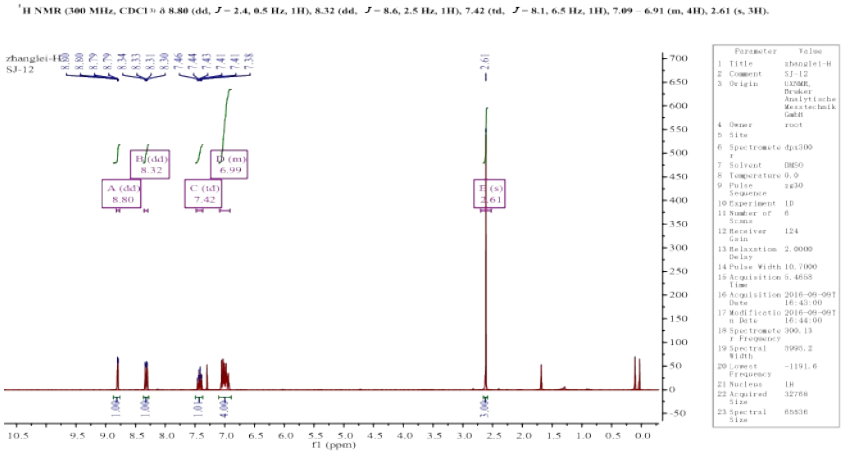


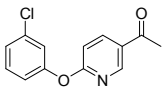
Data for **(3-13)**. white solid; mp 44-45 °C; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.26 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.90 – 6.63 (m, 3H), 3.81 (s, 3H), 2.58 (s, 3H).



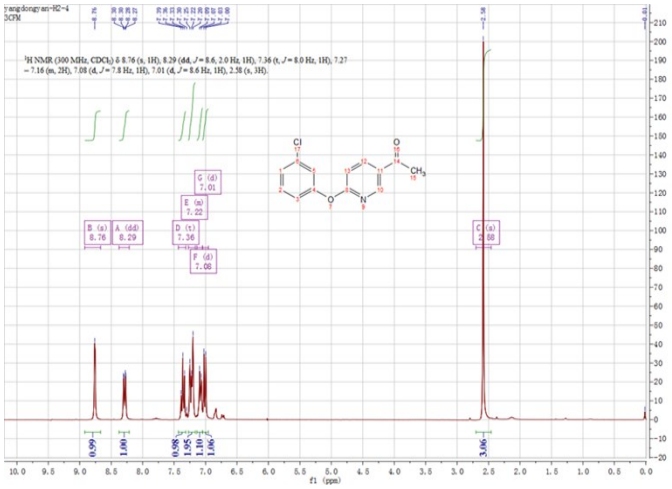


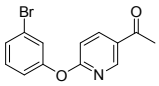
Data for **(3-14)**. White crystal; mp 51-52 °C; yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 2.4, 0.5 Hz, 1H), 8.32 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.42 (td, *J* = 8.1, 6.5 Hz, 1H), 7.09 – 6.91 (m, 4H), 2.61 (s, 3H)



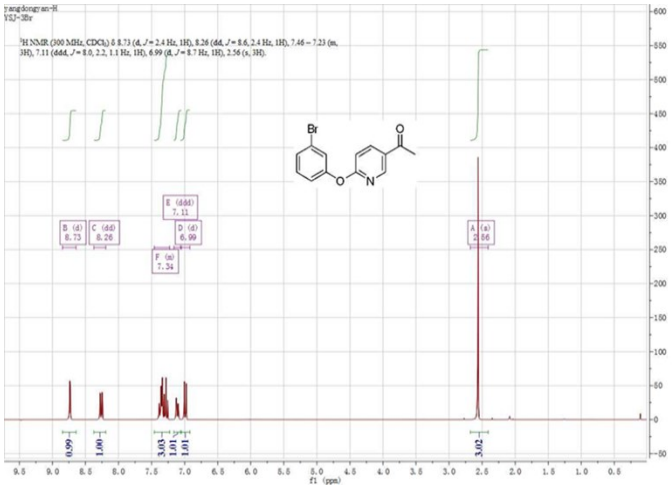


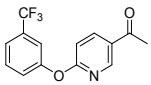
Data for **(3-15)**. White solid; mp 43-44 °C; yield 95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.29 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27 – 7.16 (m, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 2.58 (s, 3H)



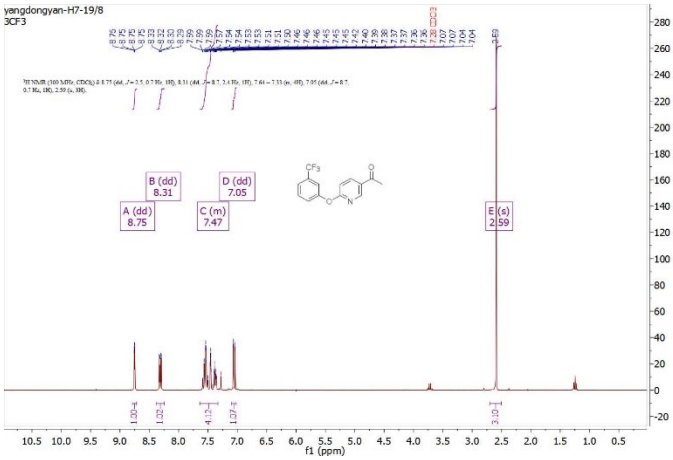


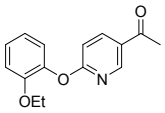
Data for **(3-16)**. white crystal; mp 58-59 °C; yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.26 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.46 – 7.23 (m, 3H), 7.11 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 2.56 (s, 3H)



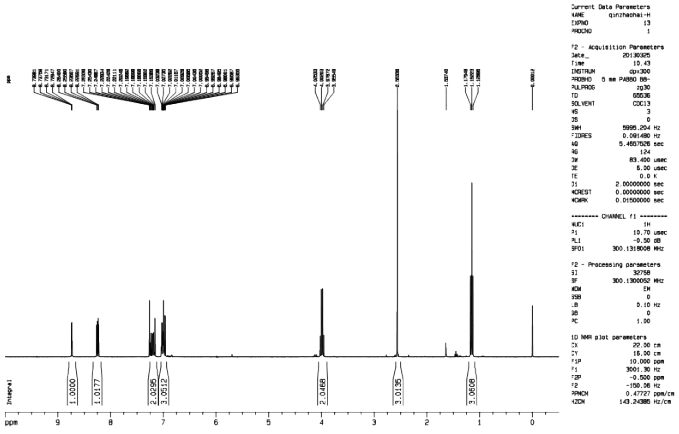


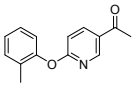
Data for **(3-17)**. Yellow transparent liquid; yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.31 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.64 – 7.33 (m, 4H), 7.05 (dd, *J* = 8.7, 0.7 Hz, 1H), 2.59 (s, 3H)



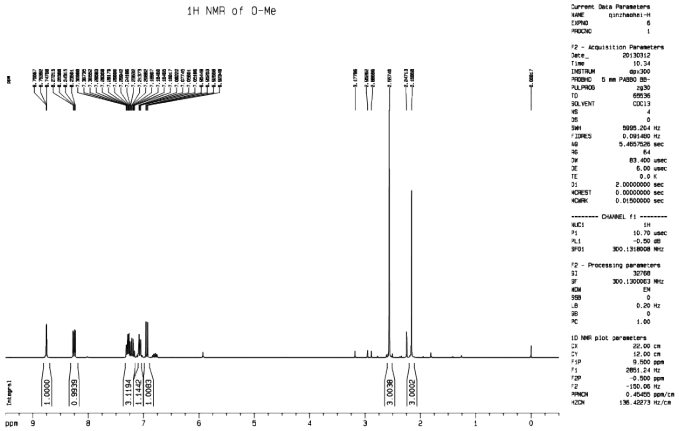


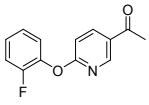
Data for **(3-18)**. White solid; mp 50-52 °C; yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (dd, *J* =0.6, 2.4 Hz, 1H), 8.26 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.03 – 6.96 (m, 3H), 4.01 (q, *J* = 7.0, 2H), 2.56 (s, 3H), 1.16 (t, *J* = 7.0, 3H)



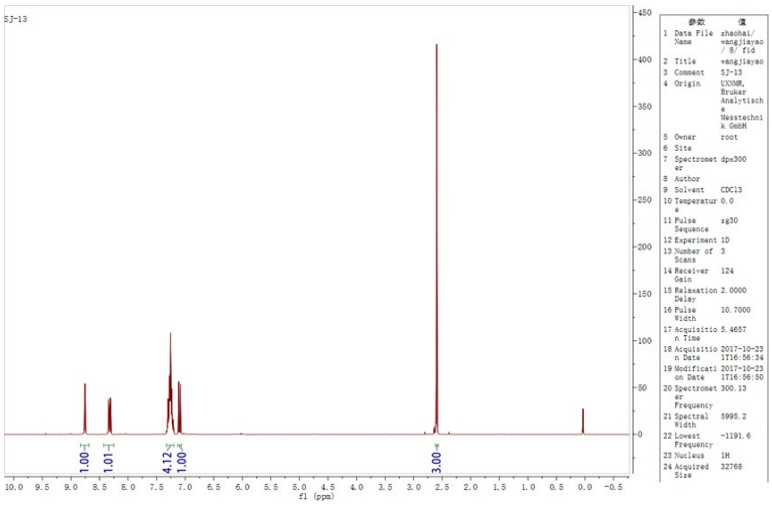


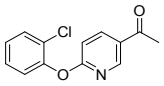
Data for **(3-19)**. white solid; mp 84-86 °C; yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (dd, *J* =0.6, 2.4 Hz, 1H), 8.25 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.30 – 7.16 (m, 3H), 7.08 – 7.05 (m, 1H), 6.94 (dd, *J* = 0.6,8.7, 1H), 2.56 (s, 3H), 2.15(s, 3H)



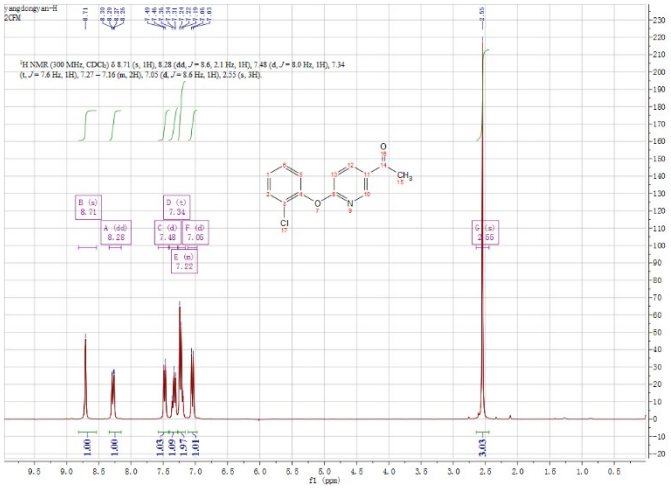


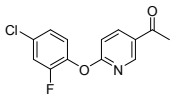
Data for **(3-20)**. slight yellow crystal; mp 51-52 °C; yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.32 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.33 – 7.18 (m, 4H), 7.10 (dd, *J* = 8.7, 0.8 Hz, 1H), 2.59 (s, 3H)



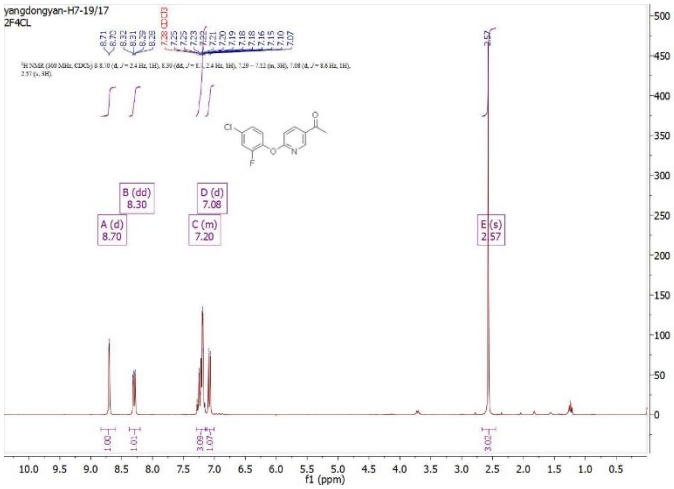


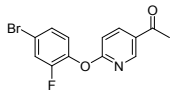
Data for **(3-21)**. White solid; mp 59-60 °C; yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.28 (dd, J = 8.6, 2.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.27 – 7.16 (m, 2H), 7.05 (d, J = 8.6 Hz, 1H), 2.55 (s, 3H)



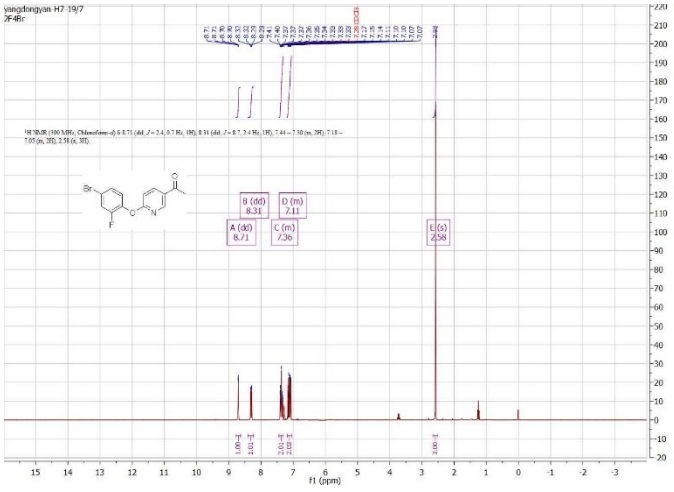


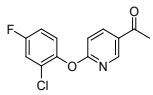
Data for **(3-22)**. White solid; mp 54-56 °C; yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 2.4 Hz, 1H), 8.30 (dd, J = 8.7, 2.4 Hz, 1H), 7.29 – 7.12 (m, 3H), 7.08 (d, J = 8.6 Hz, 1H), 2.57 (s, 3H)



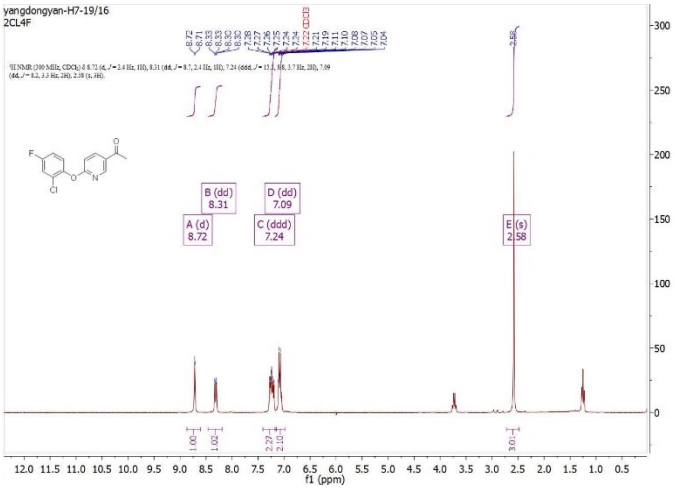


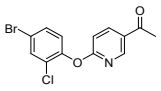
Data for **(3-23)**. white crystal; mp 59-60 °C; yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.31 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.44 – 7.30 (m, 2H), 7.18 – 7.05 (m, 2H), 2.58 (s, 3H)



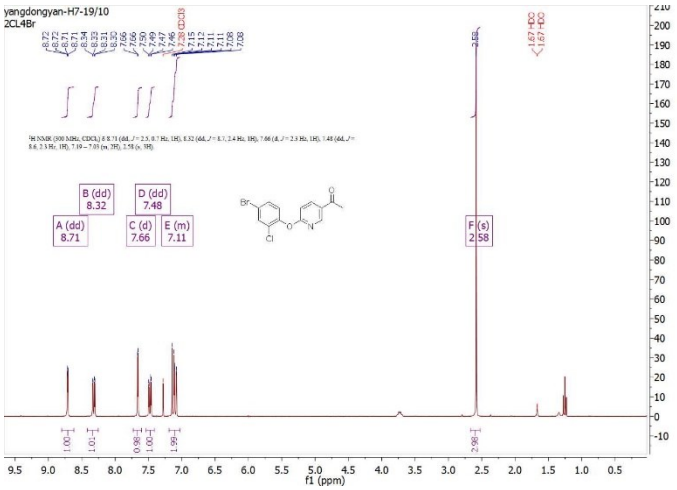


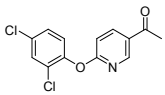
Data for **(3-24)**. slight yellow powder; mp 79-80 °C; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.4 Hz, 1H), 8.31 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.24 (ddd, *J* = 15.5, 8.8, 3.7 Hz, 2H), 7.09 (dd, *J* = 8.2, 3.3 Hz, 2H), 2.58 (s, 3H)



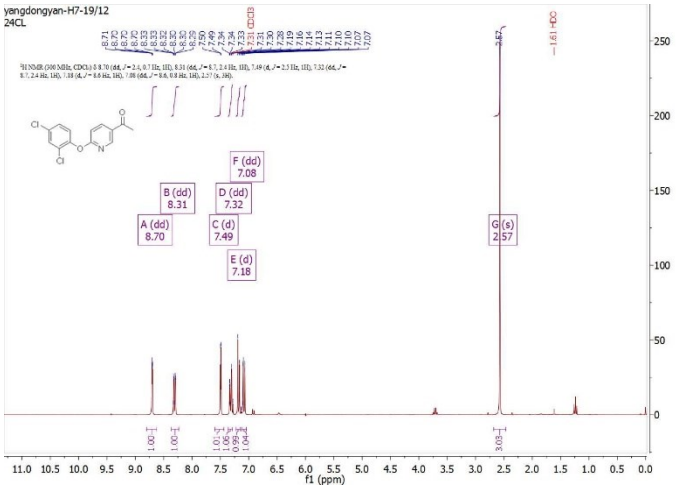


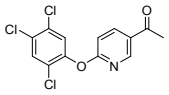
Data for **(3-25)**. White solid; mp 48-49 °C; yield 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.32 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.66 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.19 – 7.03 (m, 2H), 2.58 (s, 3H)



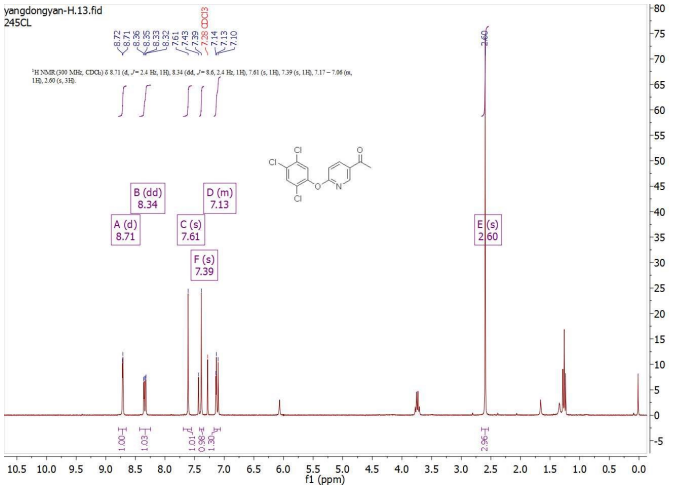


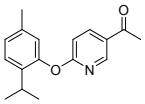
Data for **(3-26)**. slight yellow solid; mp 49-50 °C; yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.31 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.32 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.08 (dd, *J* = 8.6, 0.8 Hz, 1H), 2.57 (s, 3H)



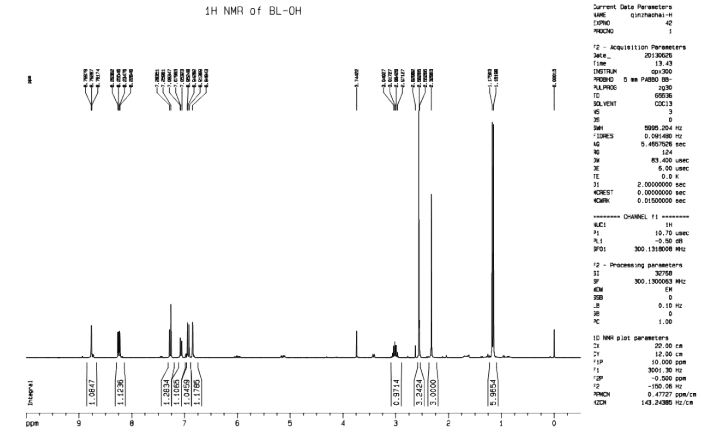


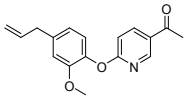
Data for **(3-27)**. White solid; mp 73-74 °C; yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 2.4 Hz, 1H), 8.34 (dd, J = 8.6, 2.4 Hz, 1H), 7.61 (s, 1H), 7.39 (s, 1H), 7.17 – 7.06 (m, 1H), 2.60 (s, 3H)



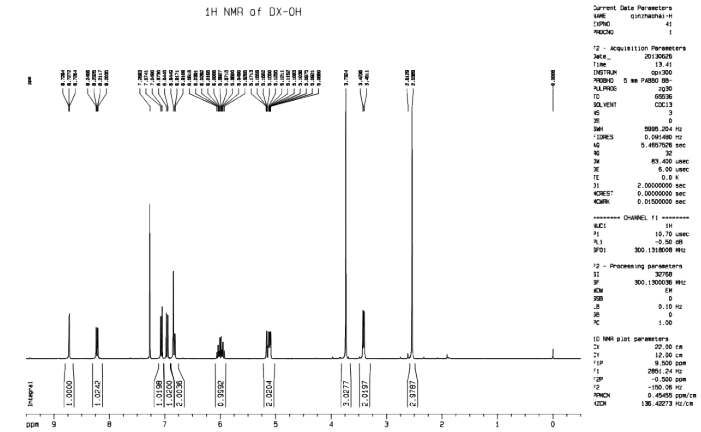


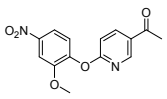
Data for **(3-28)**. white solid; mp 46-47 °C; yield 73%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.24 (dd, J = 8.6, 2.4 Hz, 1H), 7.28 (s, 1H), 7.08-7.05 (m, 1H), 6.95-6.91 (m, 1H), 6.84 (s, 1H), 3.01 (q, J = 6.9 Hz, 1H), 2.56 (s, 3H), 2.32 (s, 3H), 1.16 (d, J = 6.9 Hz, 6H)



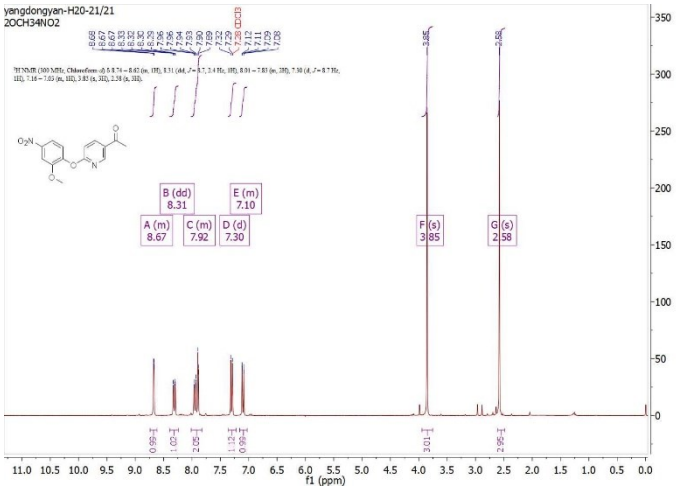


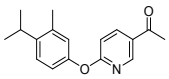
Data for **(3-29)**. slight yellow solid; mp 58-59 °C; yield 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.4, 1H), 8.22 (dd, *J* = 6.2, 2.4 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.84 – 6.81 (m, 2H), 6.06-5.92 (m, 1H), 5.17 – 5.08 (m, 2H), 3.73 (s, 3H), 3.41(d, J=6.8, 2H), 2.53 (s, 3H)



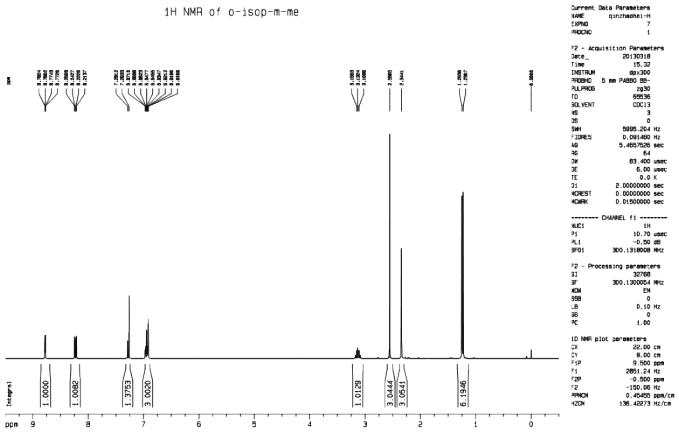


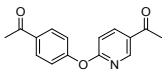
Data for **(3-30)**. slight yellow crystal; mp 110-111 °C; yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 – 8.62 (m, 1H), 8.31 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.01 – 7.83 (m, 2H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.16 – 7.03 (m, 1H), 3.85 (s, 3H), 2.58 (s, 3H)



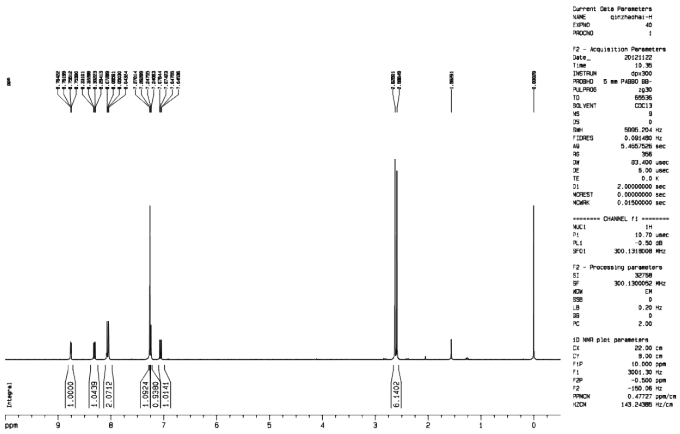


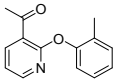
Data for **(3-31)**. White solid; mp 47-48 °C; yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, *J* =0.6, 2.4 Hz, 1H), 8.23 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.97-6.91 (m, 3H), 3.11 (q, *J* = 6.9 Hz, 1H), 2.55 (s, 3H), 2.34 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 6H)



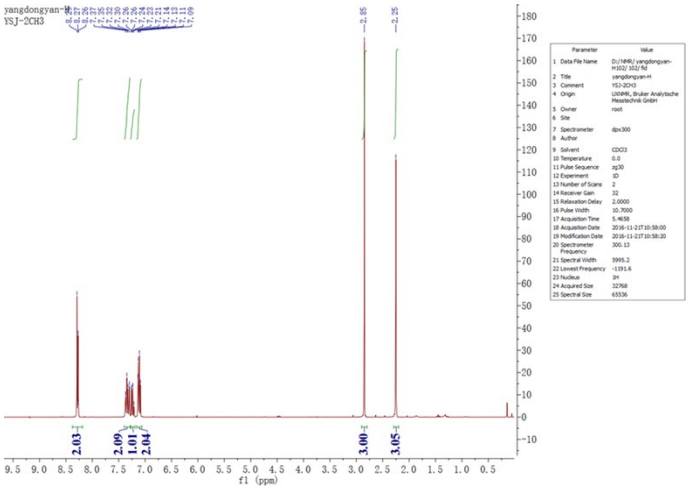


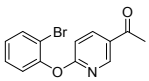
Data for **(3-01b)**. White solid; mp 93-95 °C; yield 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76(dd, *J*=0.7, 2.4Hz,1H), 8.31(dd, *J*=2.4, 8.6Hz,1H), 8.05(dd, 2H), 7.25(dd, 2H), 7.06(dd, *J*=0.7, 8.6Hz 1H), 2.63(s, 3H), 2.59(s, 3H).



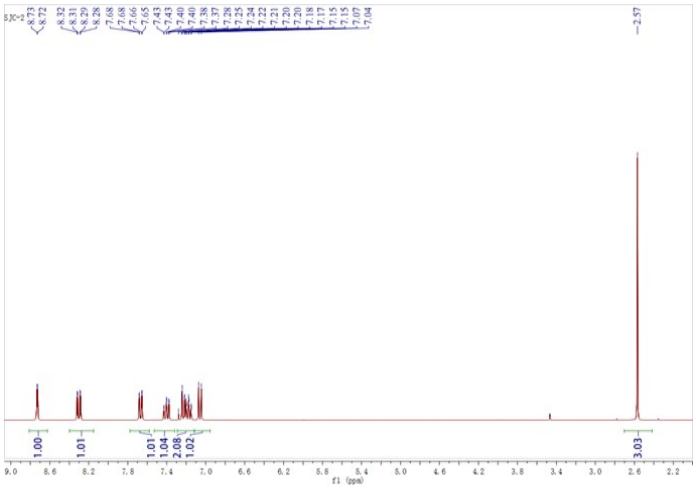


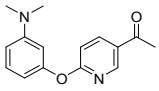
Data for **(3-19b)**. white crystal; mp 36-37 °C; yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 – 8.18 (m, 2H), 7.33 (dd, J = 13.7, 7.6 Hz, 2H), 7.24 (dt, J = 7.4, 3.7 Hz, 1H), 7.11 (dd, J = 10.4, 3.9 Hz, 2H), 2.85 (s, 3H), 2.25 (s, 3H)



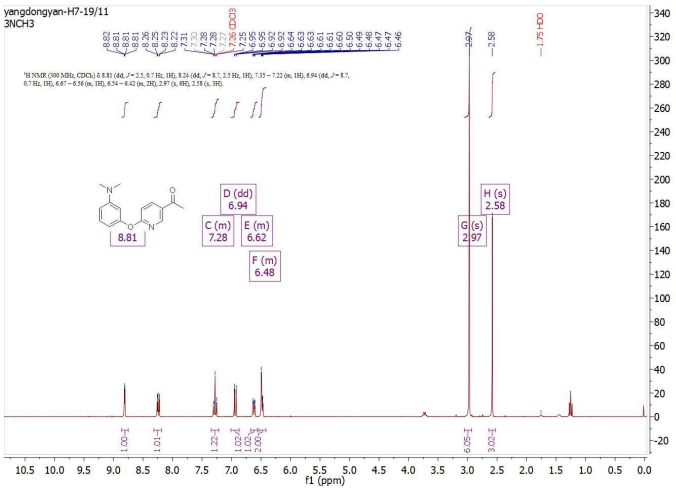


Data for **(3-p1)**. White solid; mp 63-64 °C; yield 94%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53-7.32(m, 1H), 7.29-7.12(m, 2H) , 7.06 (d, *J* = 8.7 Hz, 1H), 2.57 (s, 3H)





Data for **(3-p2)**. white solid; mp 63-64 °C; yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (dd, J = 2.5, 0.7 Hz, 1H), 8.24 (dd, J = 8.7, 2.5 Hz, 1H), 7.35 – 7.22 (m, 1H), 6.94 (dd, J = 8.7, 0.7 Hz, 1H), 6.67 – 6.56 (m, 1H), 6.54 – 6.42 (m, 2H), 2.97 (s, 6H), 2.58 (s, 3H)



1. Y.-B. Xu, H.-P. Li, J.-B. Zhang, B. Song, F.-F. Chen, X.-J. Duan, H.-Q. Xu and Y.-C. Liao, *Fungal Genet. Biol.*, 2010, **47**, 205-215.