Supplementary Material

Synthetic route design and development for an anthranilic diamide compound containing 2-methyl-2-amino-propanamide group as a potential insecticide

Junwu Ying, Shuang Liang, Xuesong Li, Gang Wang, Zhongbao Ren, Xiaochen Bai, Jie Lang, Bin Li, Huibin Yang,* and Haibo Yu*

State Key Laboratory of the Discovery and Development of Novel Pesticide, National Engineering Research Center of Pesticide, Shenyang Sinochem Agrochemicals Research and Development Co., Ltd, Shenyang 110021, China
Email: yanghuibin@yangnongchem.com , yuhaibo@sinochem.com

Table of Contents

1. General procedures for compound 1

1.1. General method for optimizing reaction conditions for synthesis of compound 6.

To a round-bottom flask was added 2-amino-3,5-dichlorobenzoic acid **2** (1 g, 5 mmol) and toluene (10 mL). Thionyl chloride (2.95 g, 25 mmol) was slowly added, and the mixture was heated at reflux for 4 hours. Evaporation under reduced pressure afforded intermediate **4** as a brown oil.

To a round-bottom flask was added compound **3** (0.72 g, 6 mmol), acetonitrile (10 mL), sodium hydroxide (0.24 g, 6 mmol), sodium bicarbonate (0.5 g, 6 mmol) and water (10 mL). The mixture was stirred until well blended. After cooling the mixture in an ice bath for 0.5 hours, the above intermediate **4** in acetonitrile (5 mL) was slowly added to the mixture. After 2 hours at room temperature, ethyl acetate (50 mL) and water (10 mL) were added for extraction. The organic layer was washed with saturated sodium chloride solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified using silica gel column chromatography. Elution with ethyl acetate/petroleum ether (1:3 v/v) afforded the title compound **6**.

The solvent was selected from ethyl acetate, dichloromethane, toluene, 1,4-dioxane, THF, 2-methoxy-2-methylpropane, acetonitrile.

Reaction detection and product analysis were performed by HPLC.

1.2. General method for optimizing reaction conditions for synthesis of compound 16.

To a round-bottom flask was added compound **8** (1.3 g, 5 mmol) and chlorobenzene (20 mL). The solution was slowly added thionyl chloride (1.19 g, 10 mmol) and heated to 80 °C for 2 hours. After cooling the solution to room temperature, sulfuryl chloride (0.34 g, 2.5 mmol) and AIBN (4 mg, 0.025 mmol) were added to the mixture and heated to 80 °C for another 4 hours. Intermediate **9** was obtained by evaporating under reduced pressure as a brown oil.

To a round-bottom flask was added intermediate **6** (1.36 g, 5 mmol) and acetonitrile (20 mL). The solution was heated to reflux and the above intermediate **9** in acetonitrile (10 mL) was slowly added. The mixture was heated at reflux for 2 hours. After cooling the solution to room temperature, ethyl acetate (50 mL) and water (20 mL) was added to the mixture for extraction. The organic layer was washed with saturated sodium chloride solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified using silica gel column chromatography. Elution with ethyl acetate/petroleum ether (1:1 v/v) afforded the title compound **16**.

The solvent was selected from chlorobenzene, DMF, toluene, xylene, acetonitrile.

Reaction detection and product analysis were performed by HPLC.

1.3. General method for optimizing reaction conditions for synthesis of compound 1.

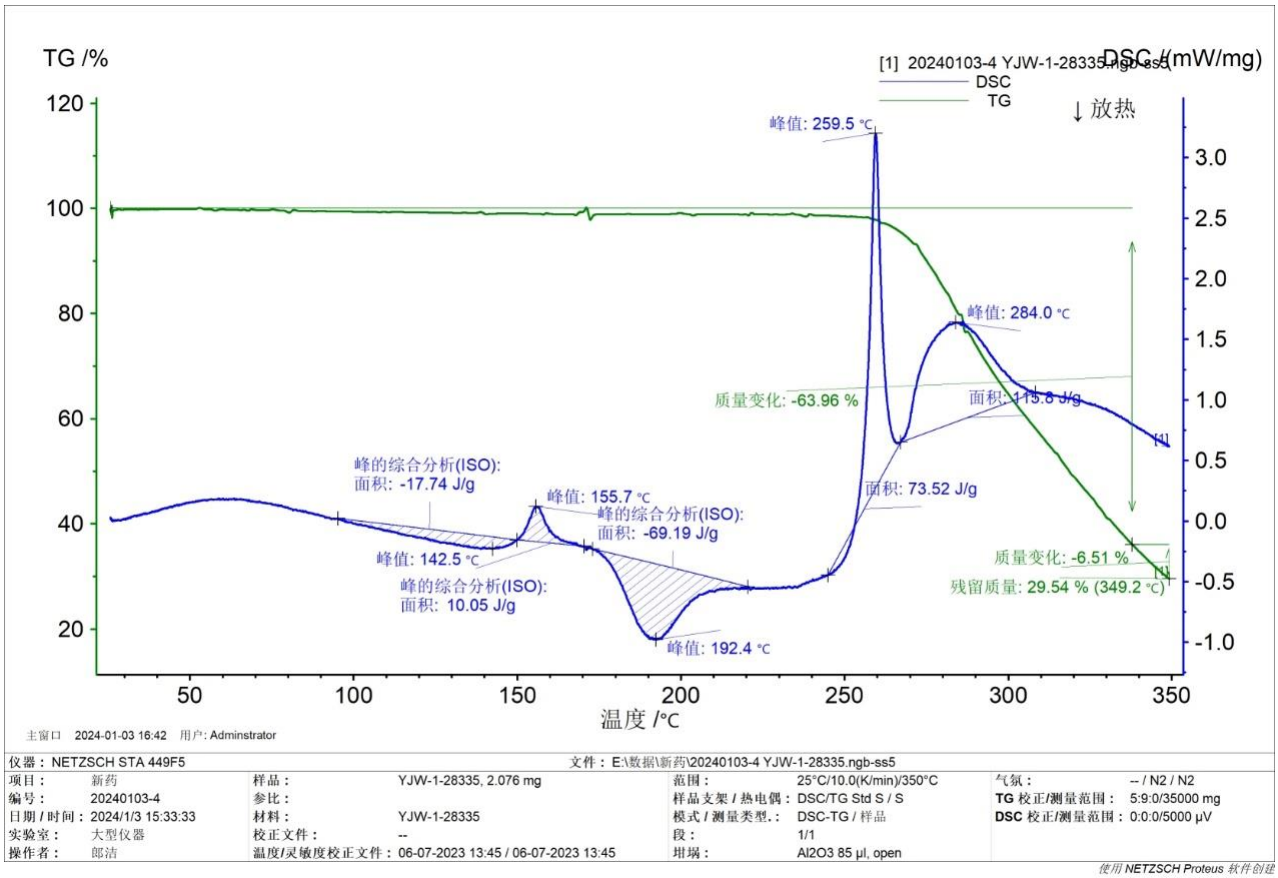
To a three-neck round-bottom flask was added concentrated hydrochloric acid (100 mL) and heated to 36-38 °C. The solution was stirred intensely and intermediate **16** (53 g, 104.5 mmol) was added slowly while keeping the temperature below 40 °C. After 30 minutes at 36-38 °C, the mixture was poured into ice water-and stirred for half an hour while keeping the temperature below 10 °C. The resulting solid was collected by filtration, and dried to give the title compound **1**.

The solvent was selected from concentrated hydrochloric acid, dilute sulfuric acid aqueous solution.

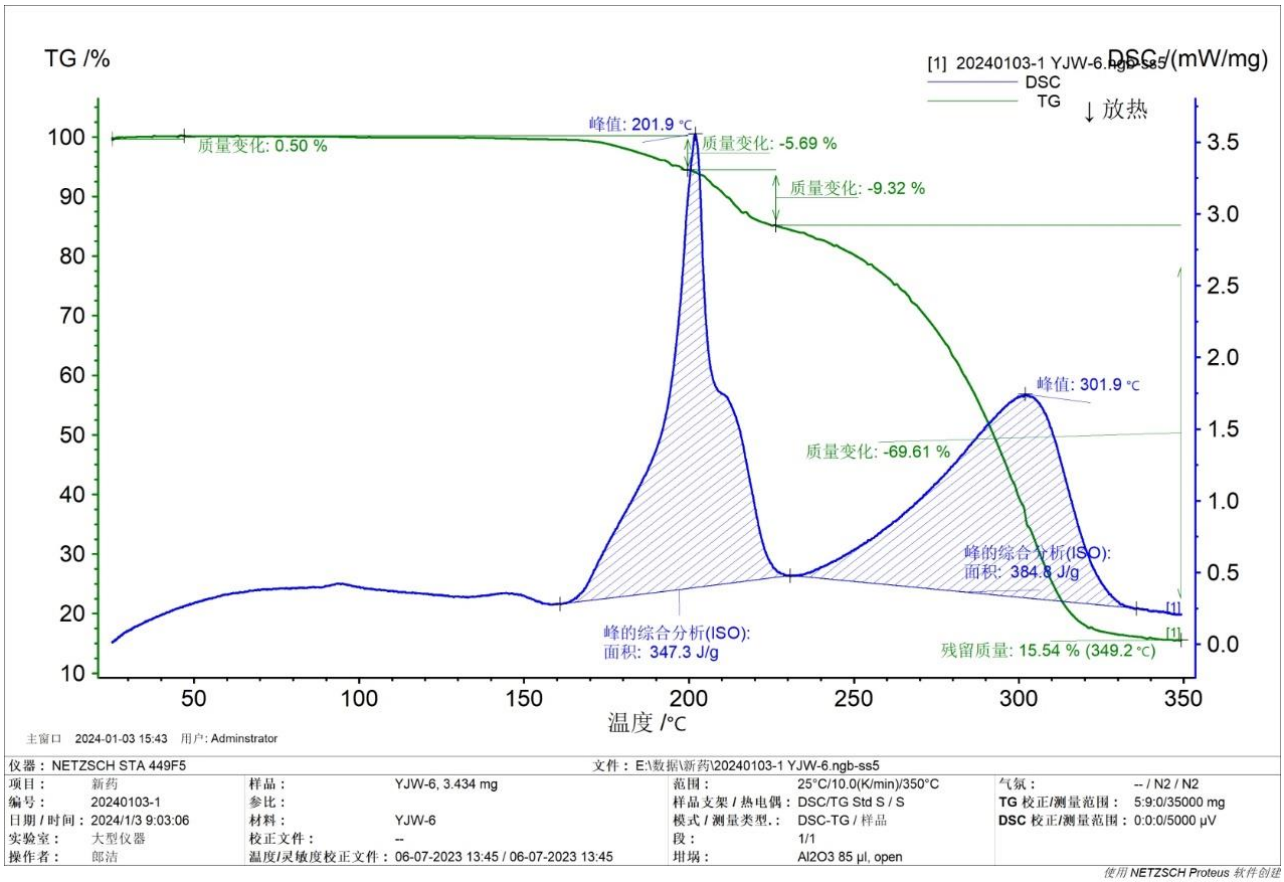
Reaction and product analysis were performed by HPLC.

2. DSC traces

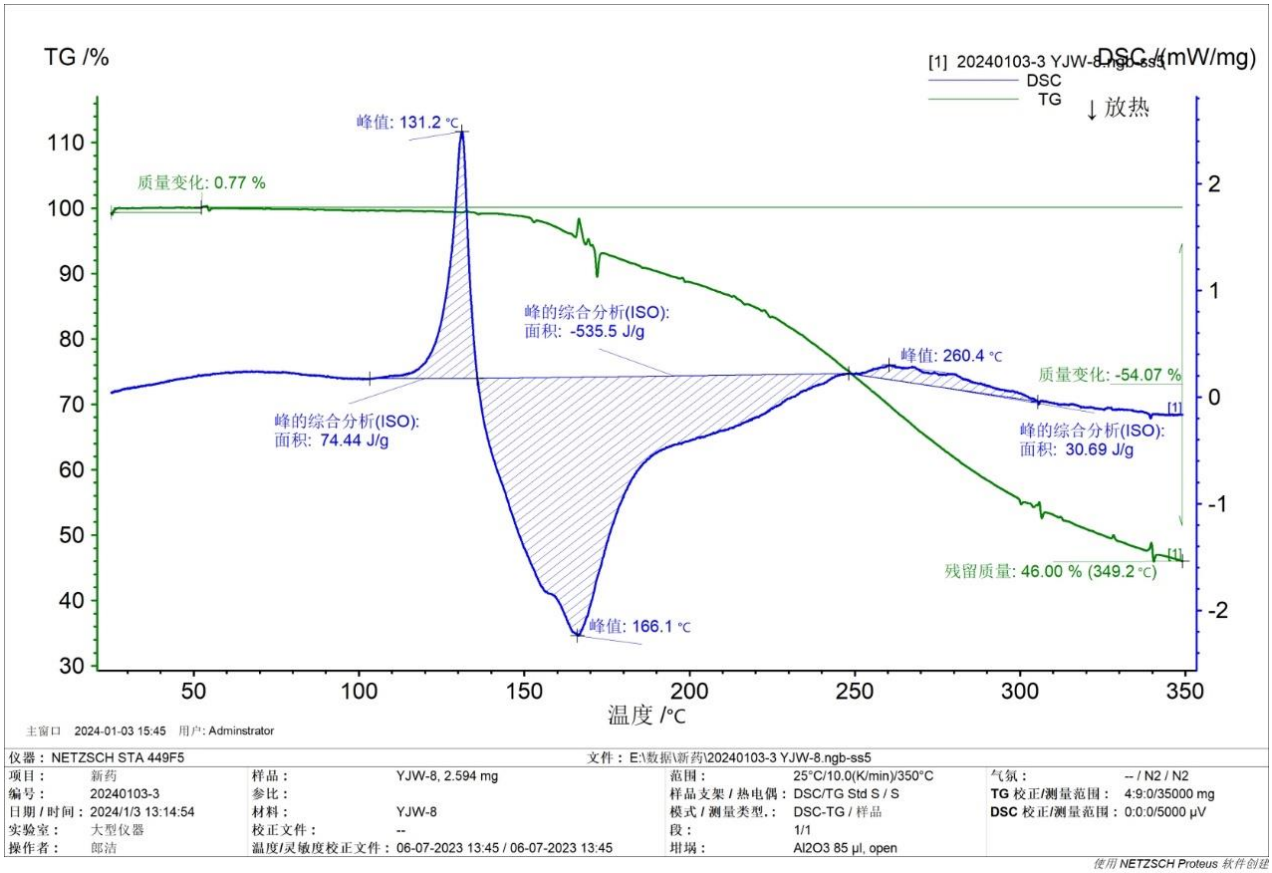
DSC trace for compound **1**



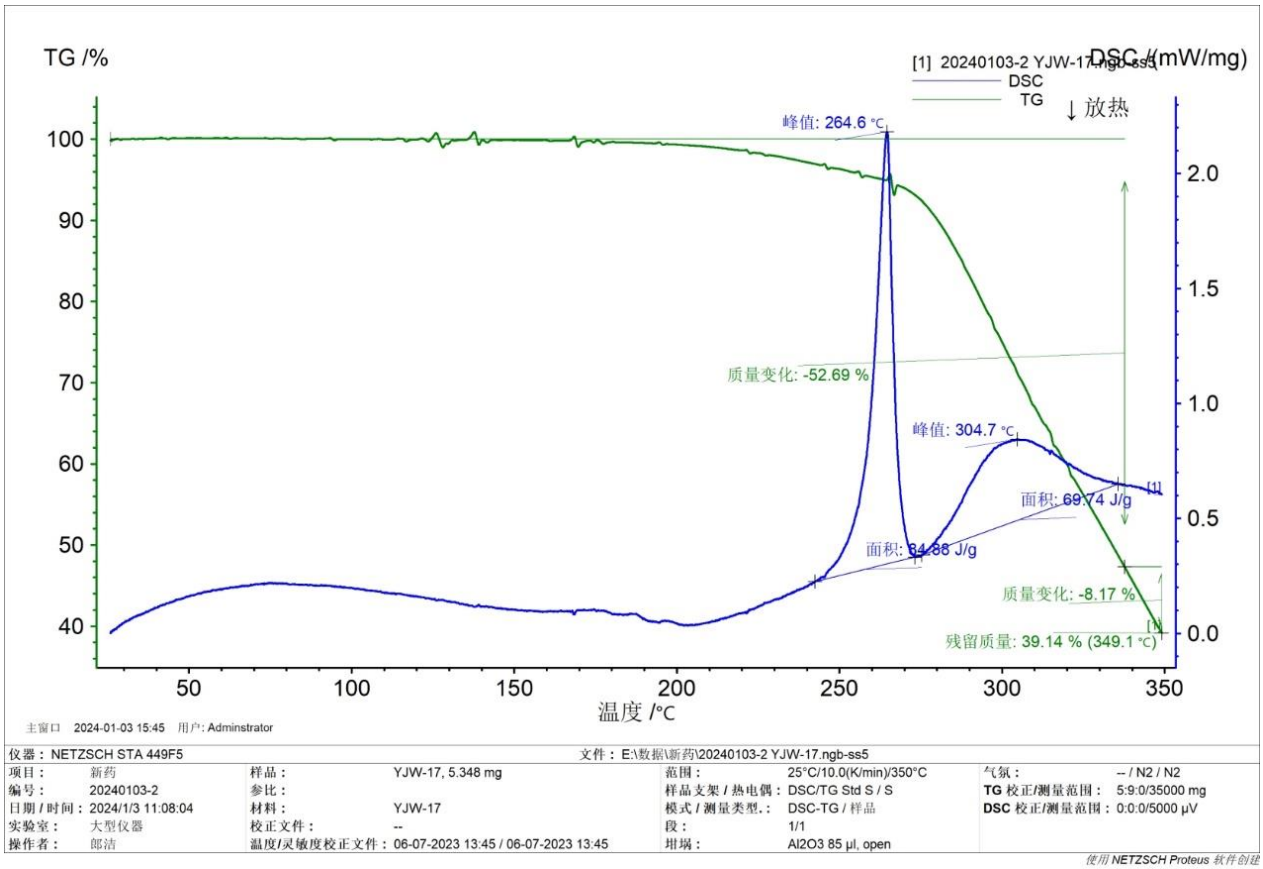
DSC trace for compound **6**



DSC trace for compound **8**

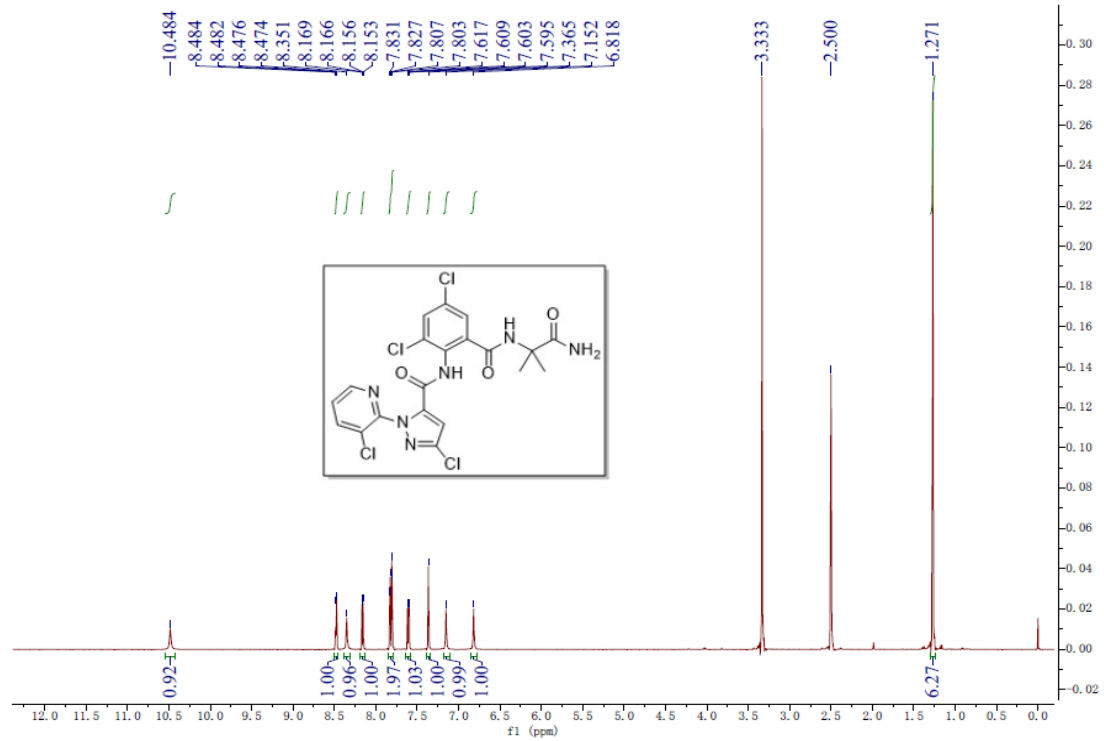


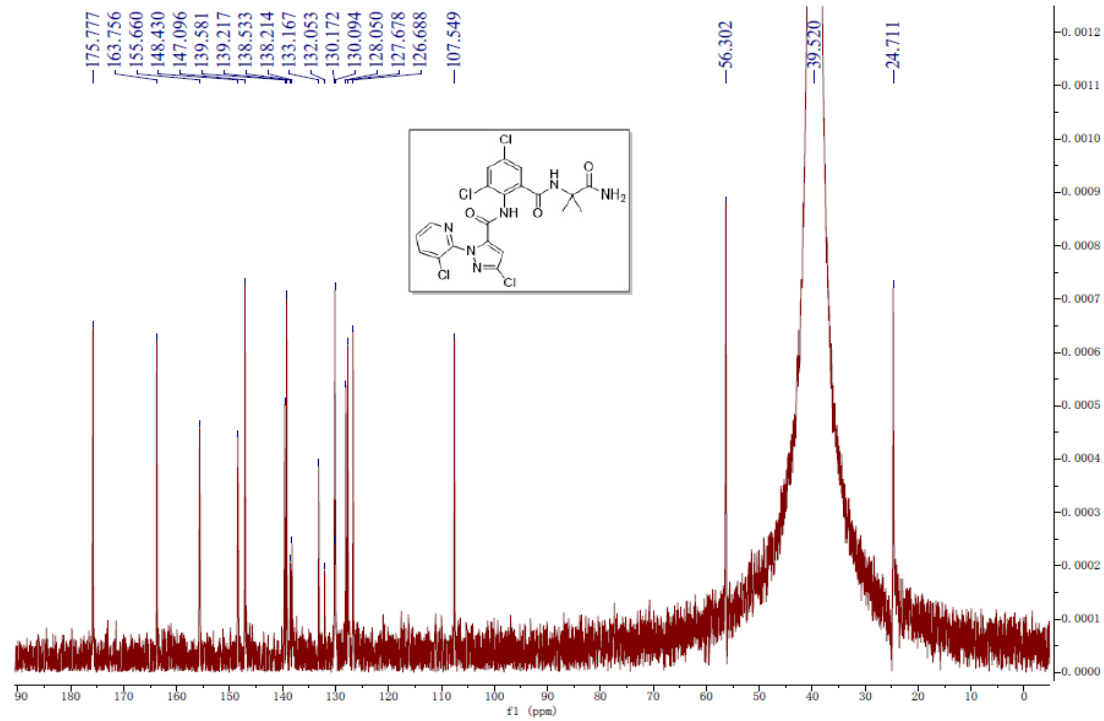
DSC trace for compound **16**

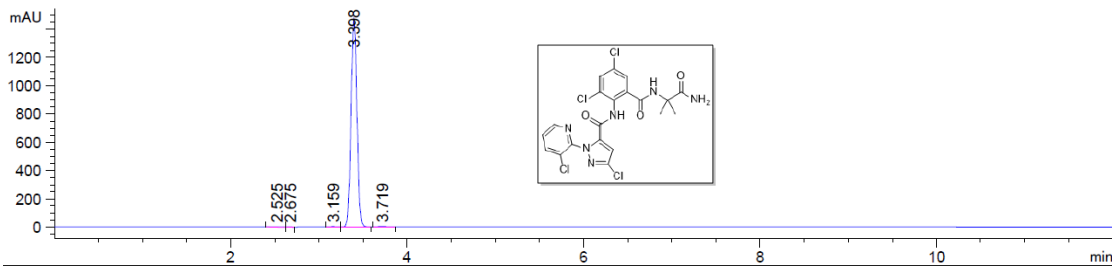


3. ^{1}H NMR, ^{13}C NMR spectra and HPLC chromatograms of compounds

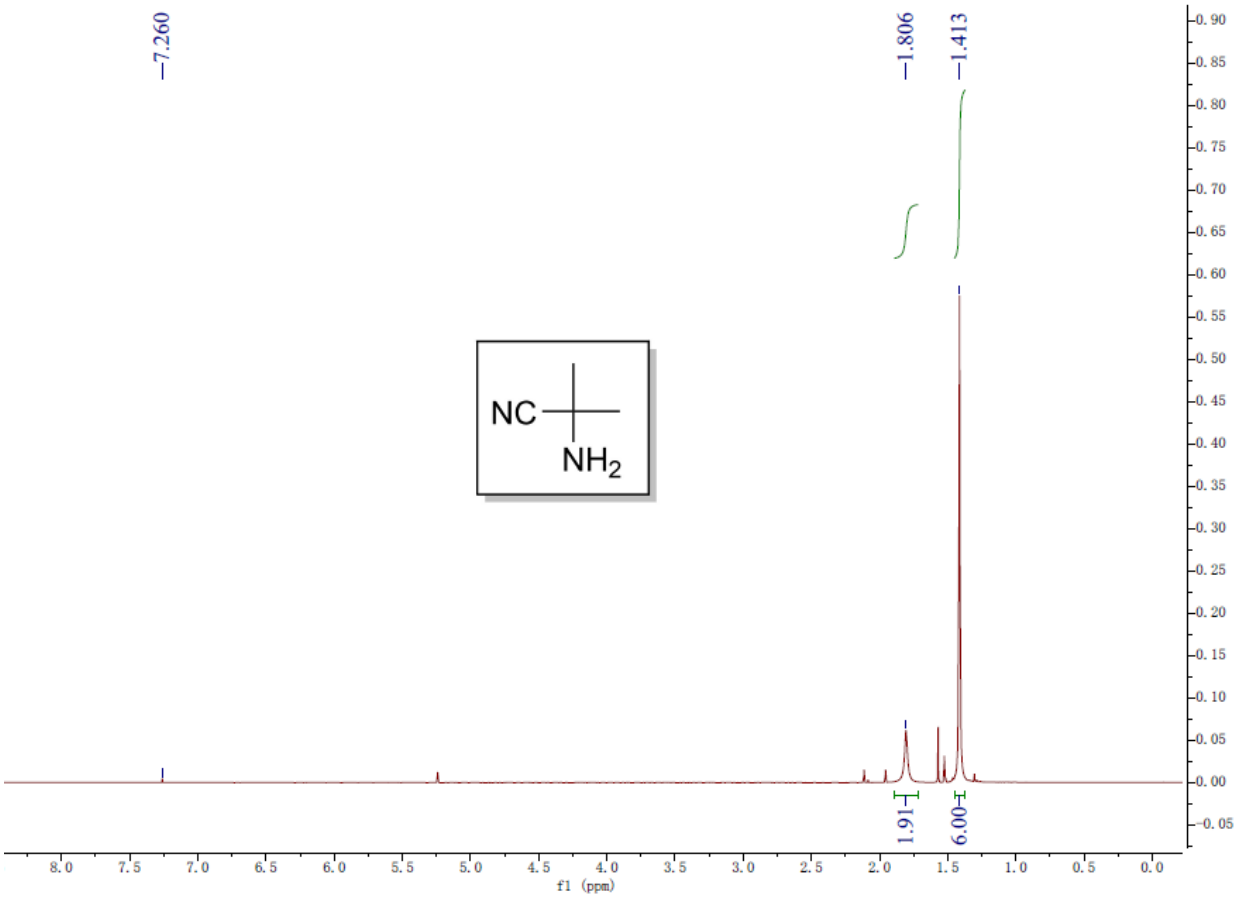
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR 150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **1**

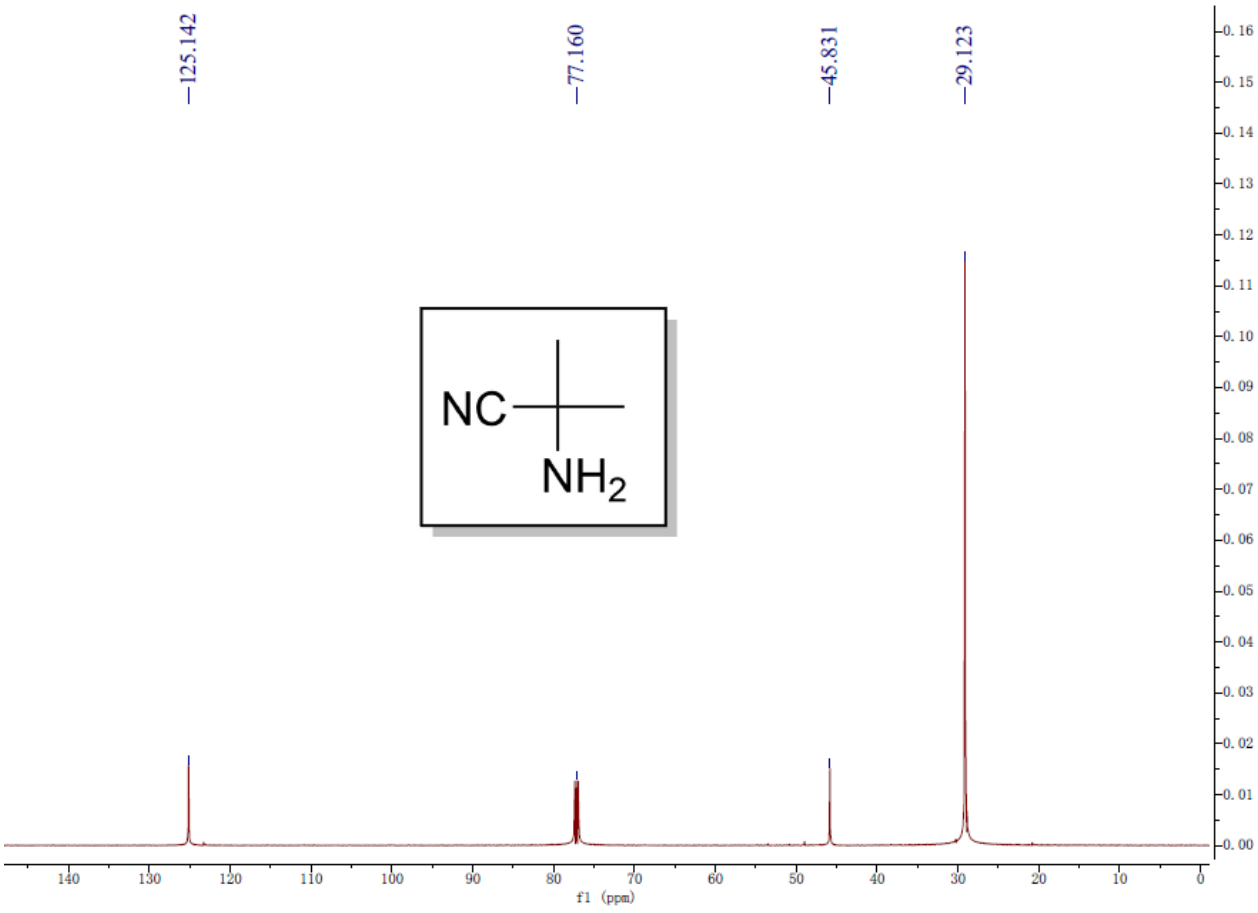




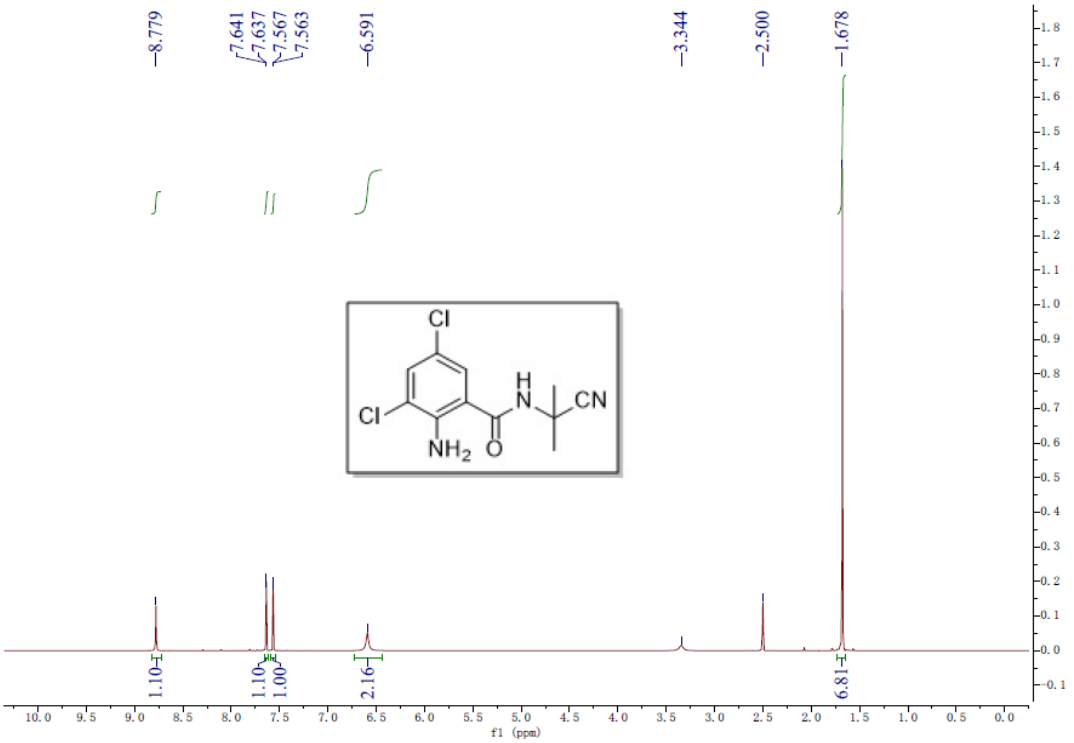


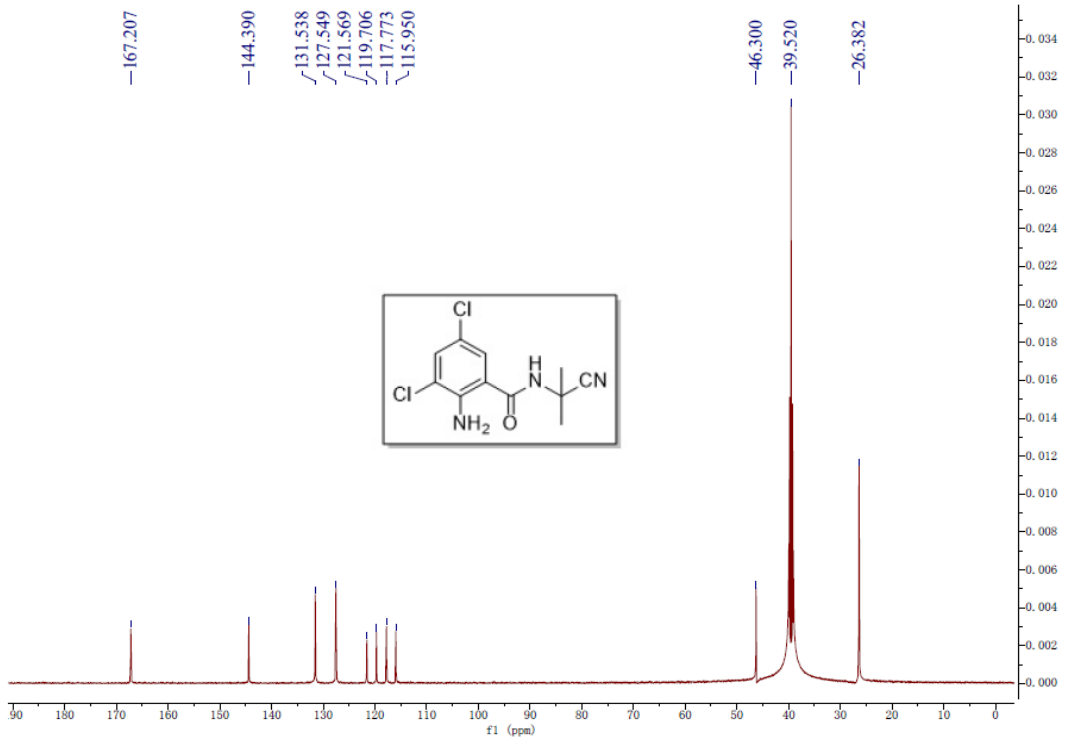
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) spectra of compound **5**

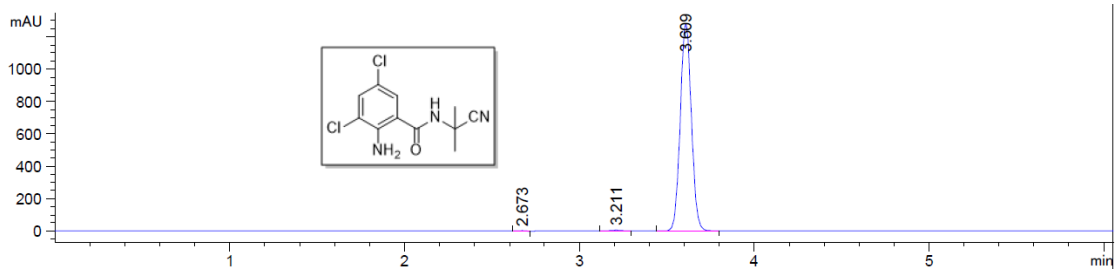




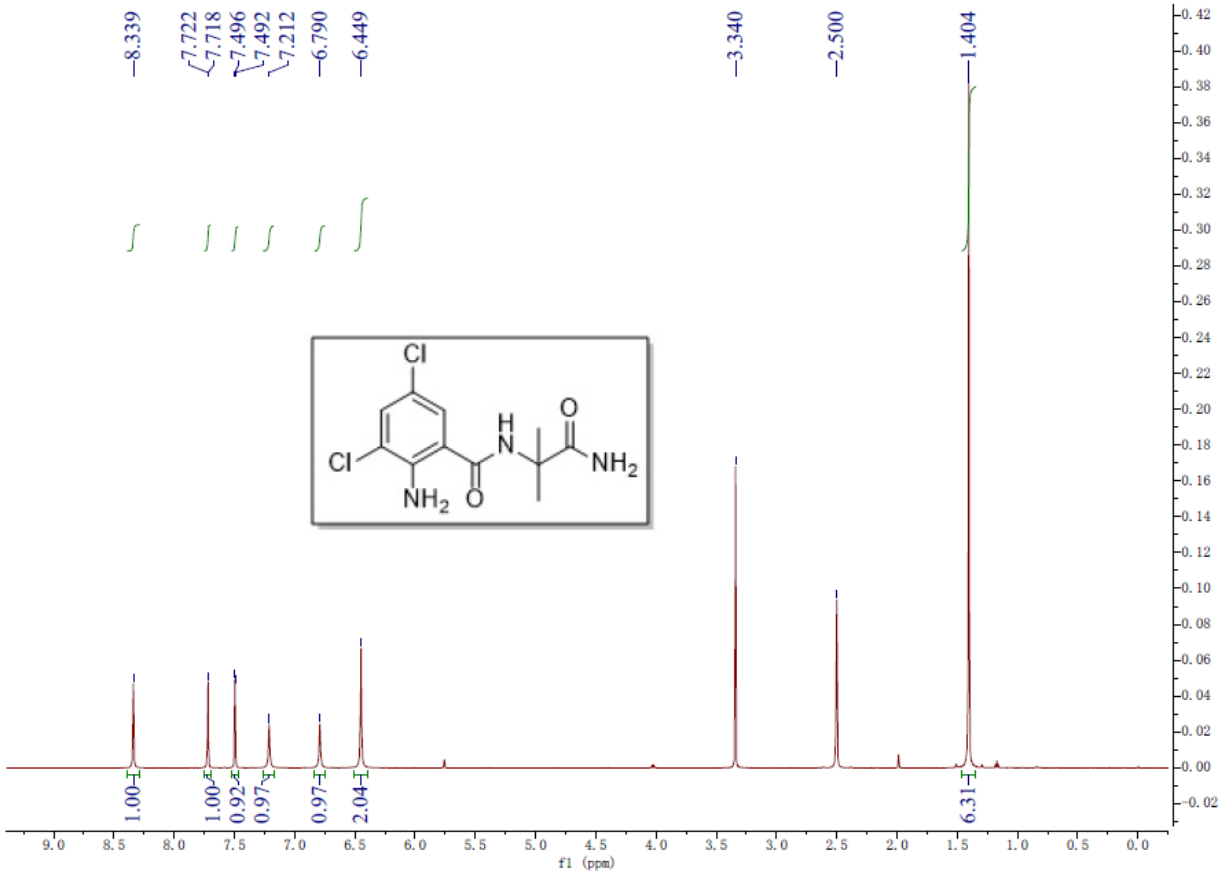
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **6**

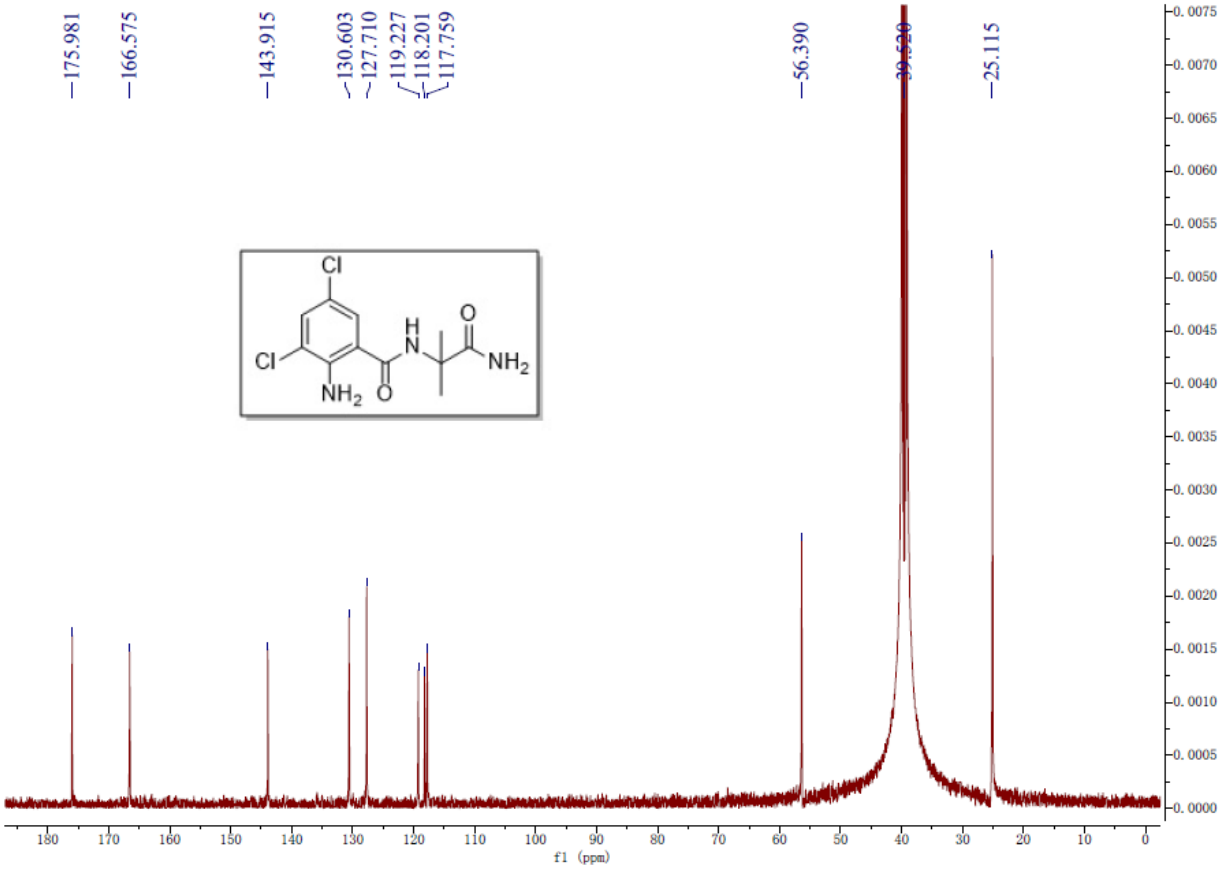


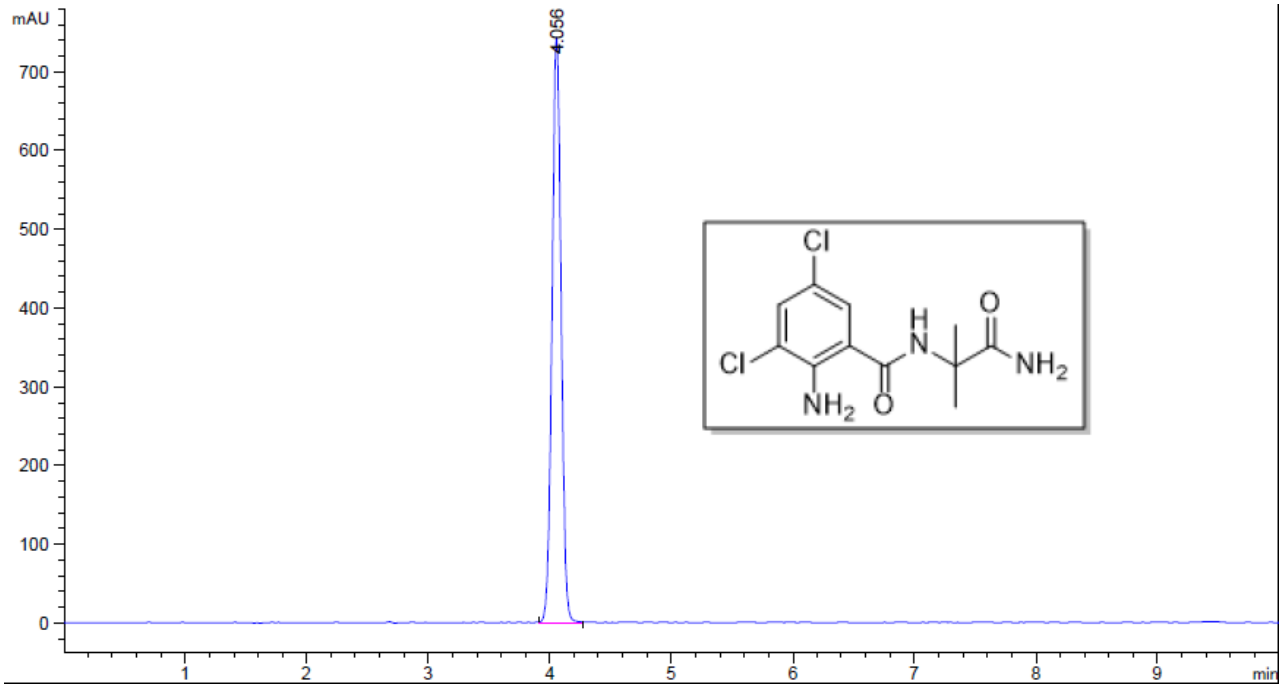




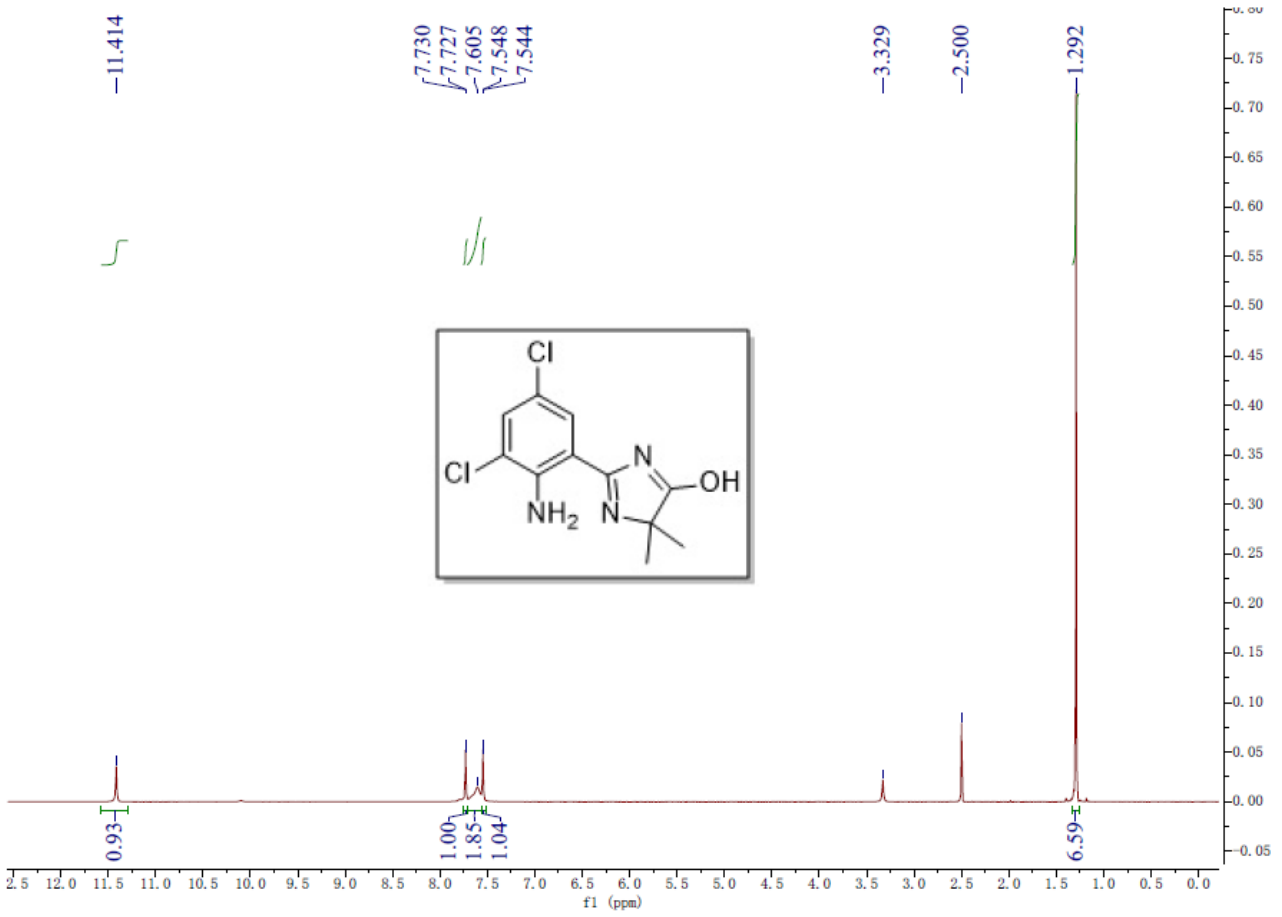
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **7**

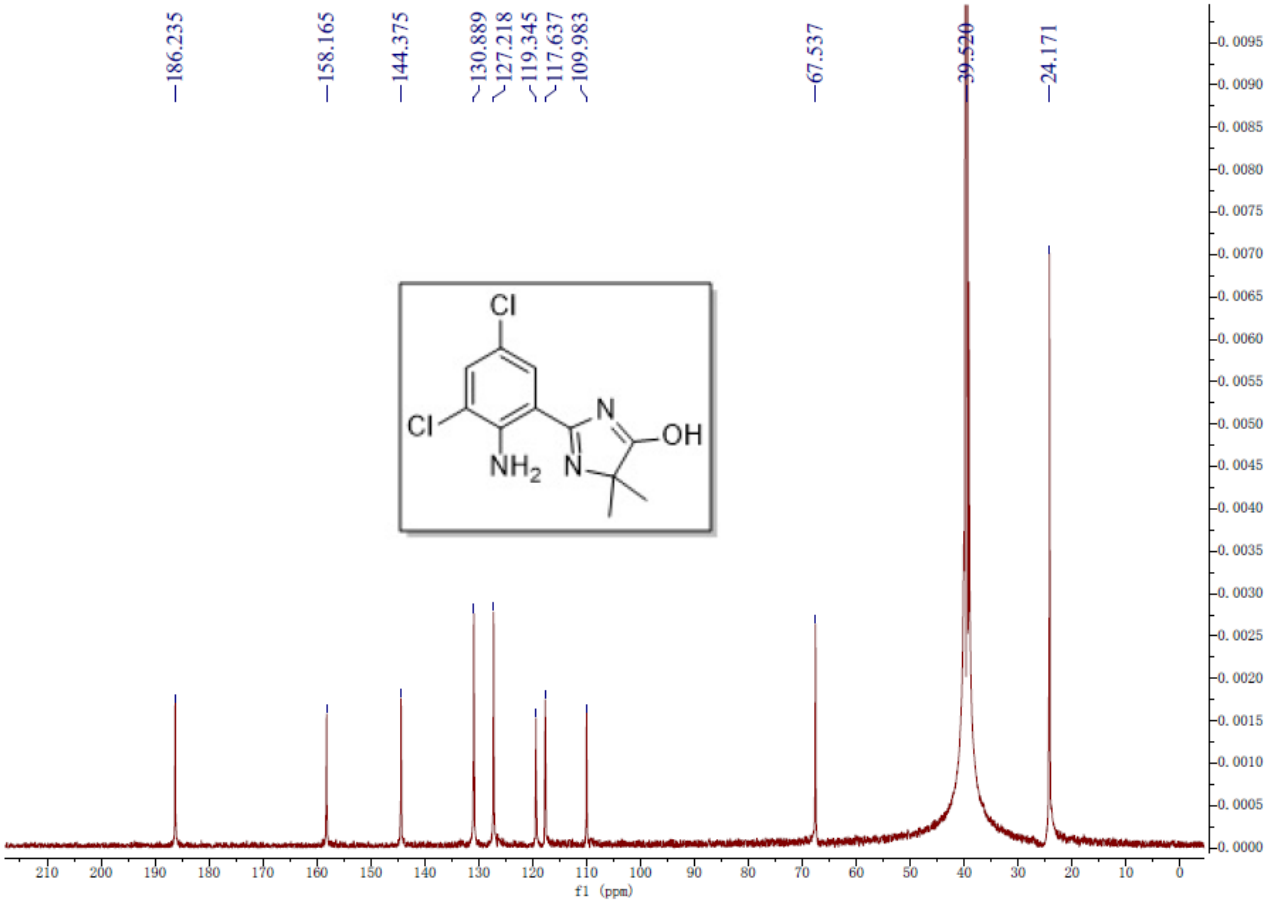


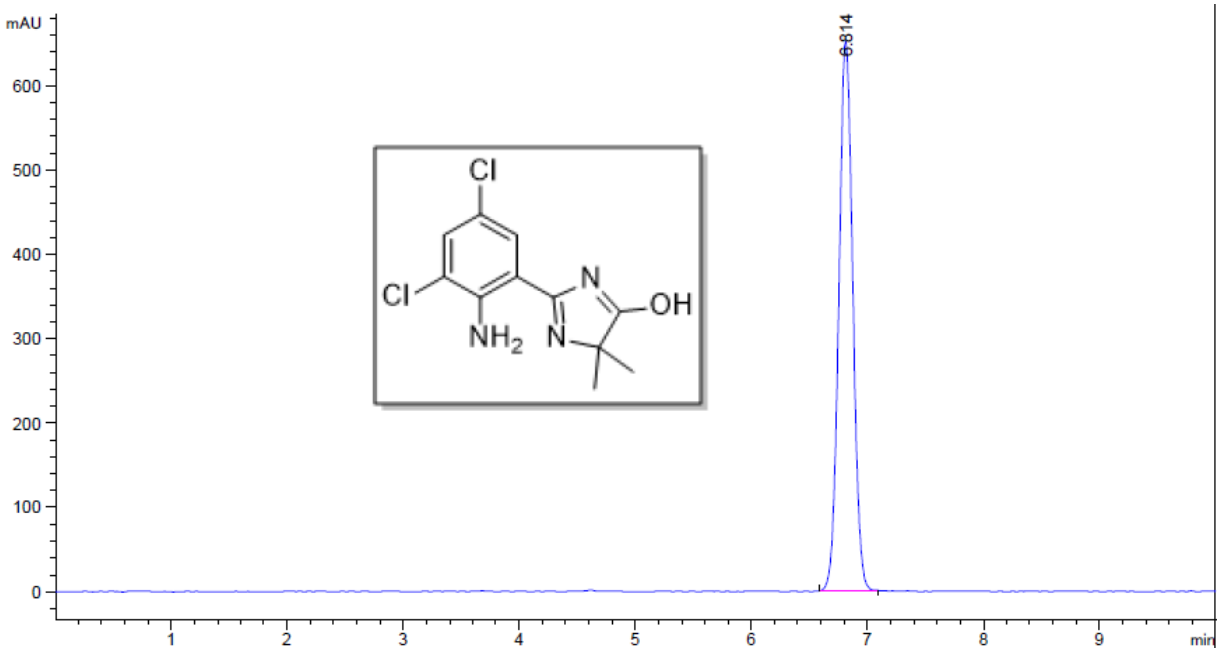




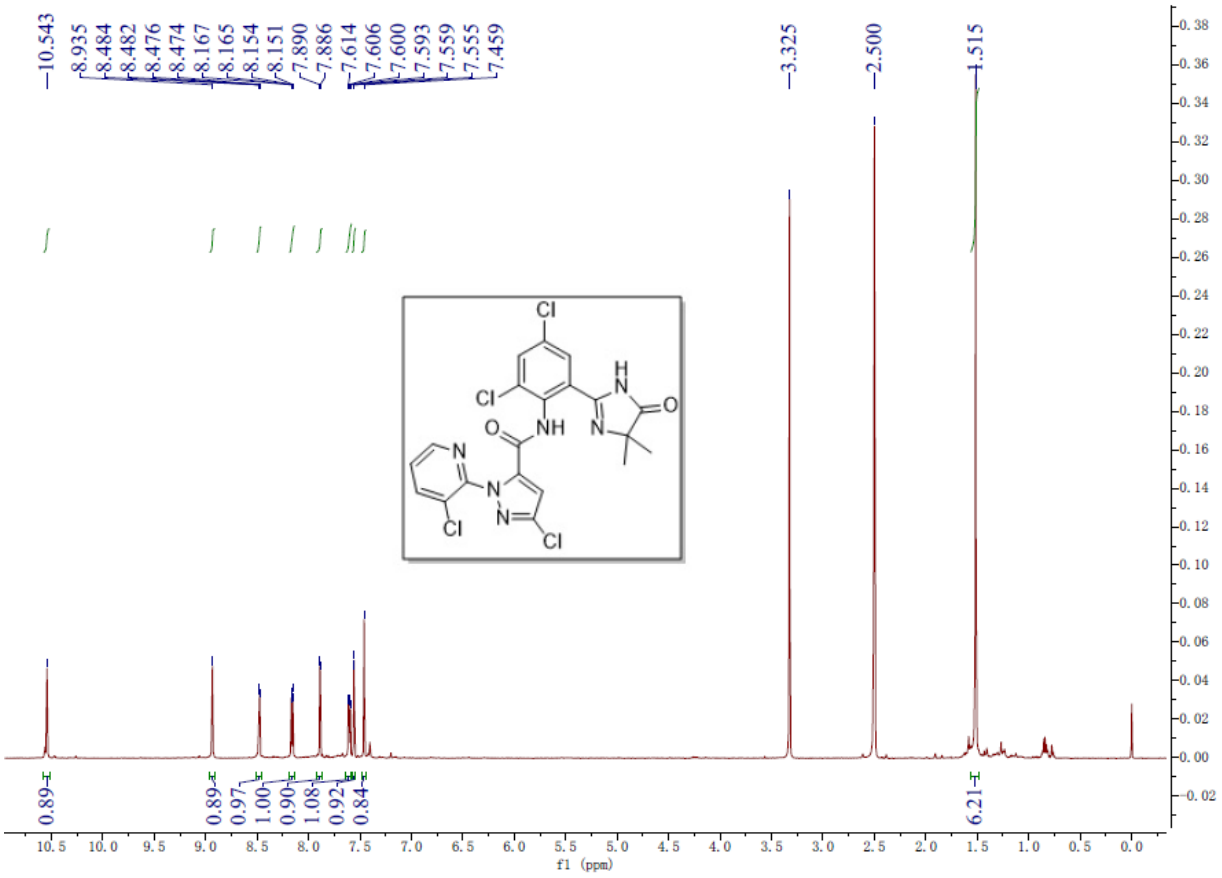
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **10**

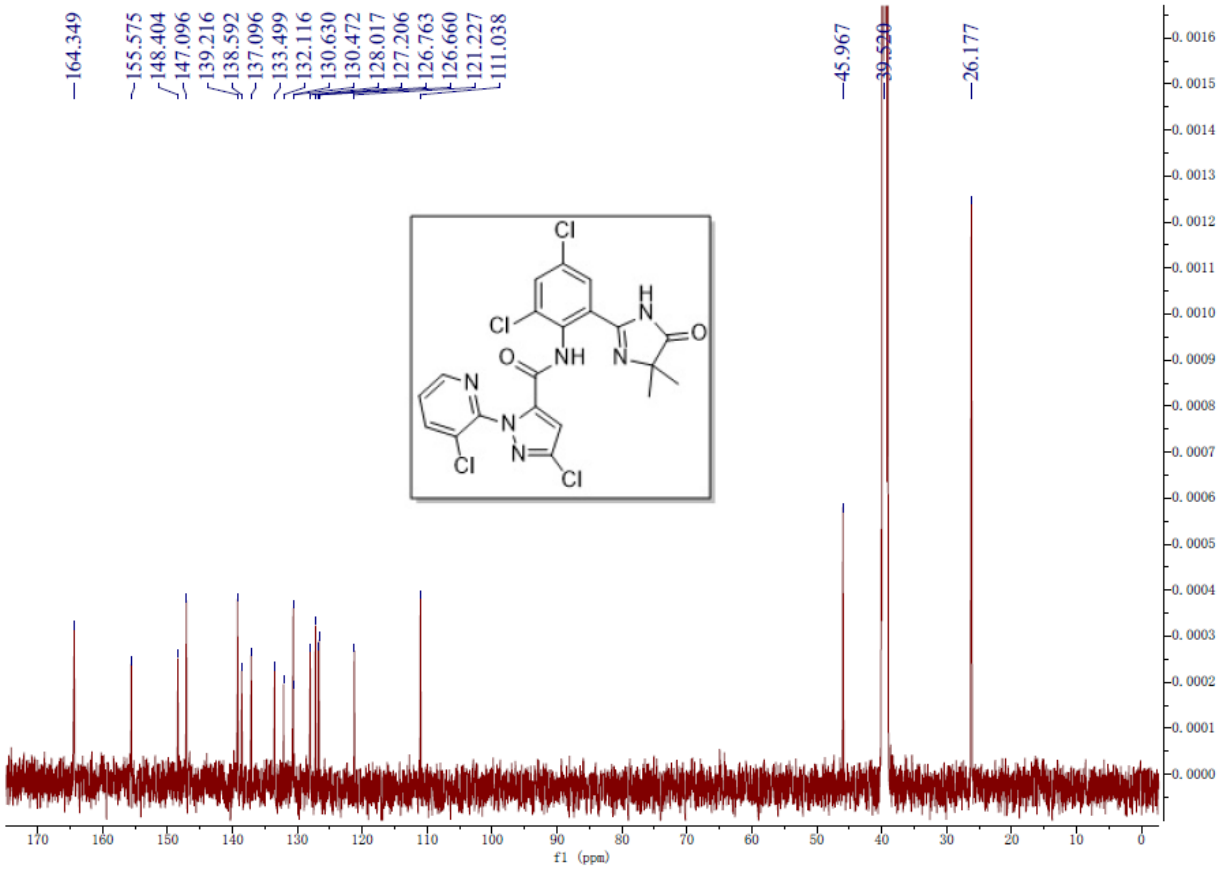


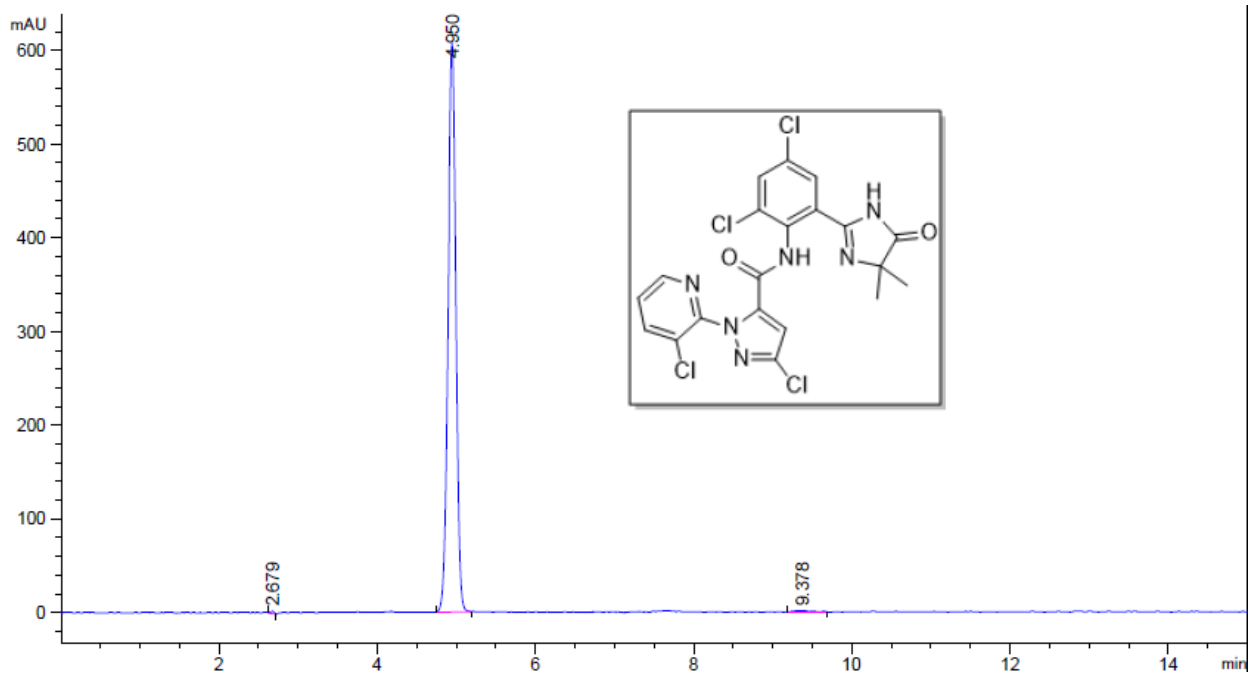

186.235
158.165
144.375
130.889
127.218
119.345
117.637
109.983
67.537
39.520
24.171
Cl
Cl
NH2
N
N
OH
f1 (ppm)


mAU
6.814
Cl
Cl
NH2
N
N
OH
min

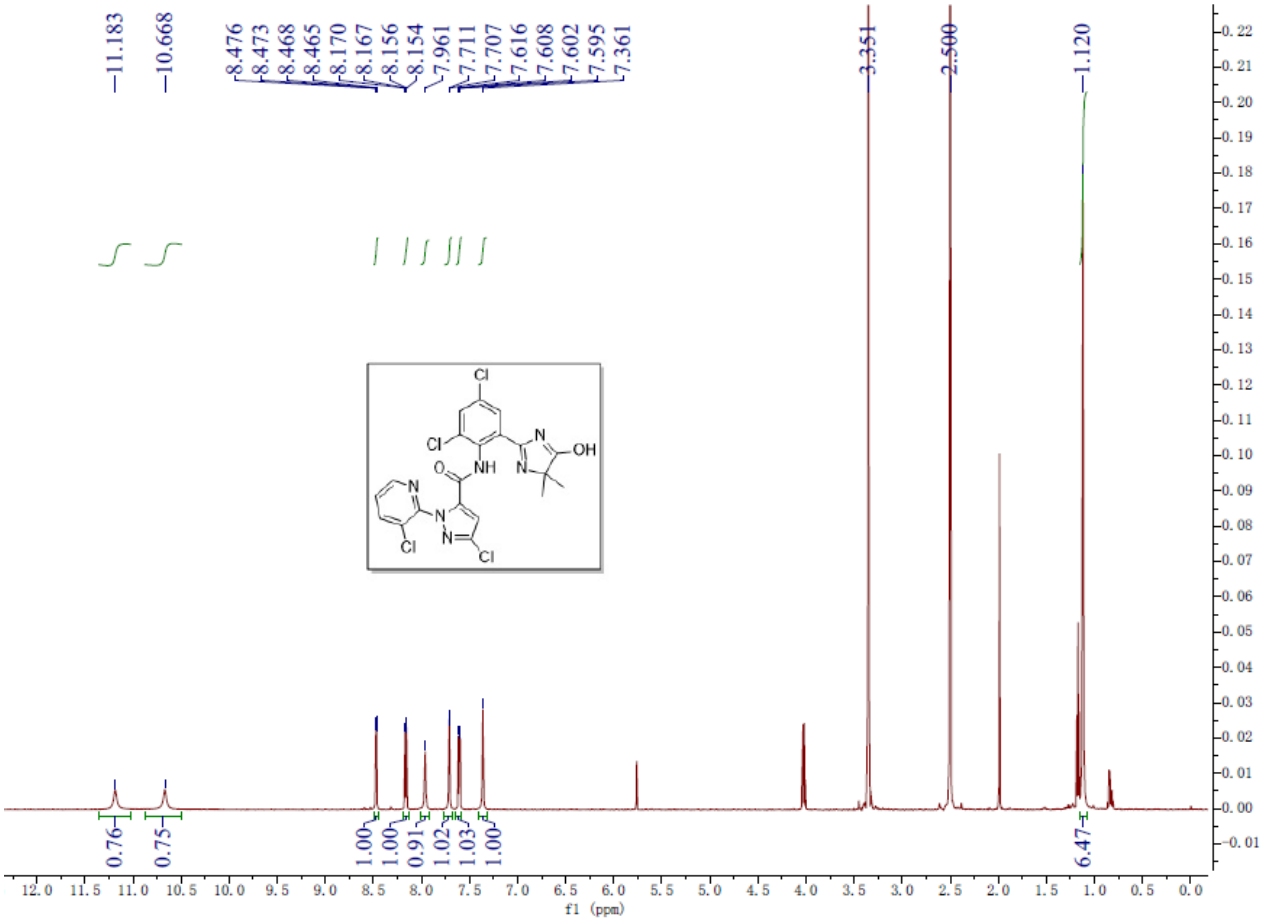
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **12a**

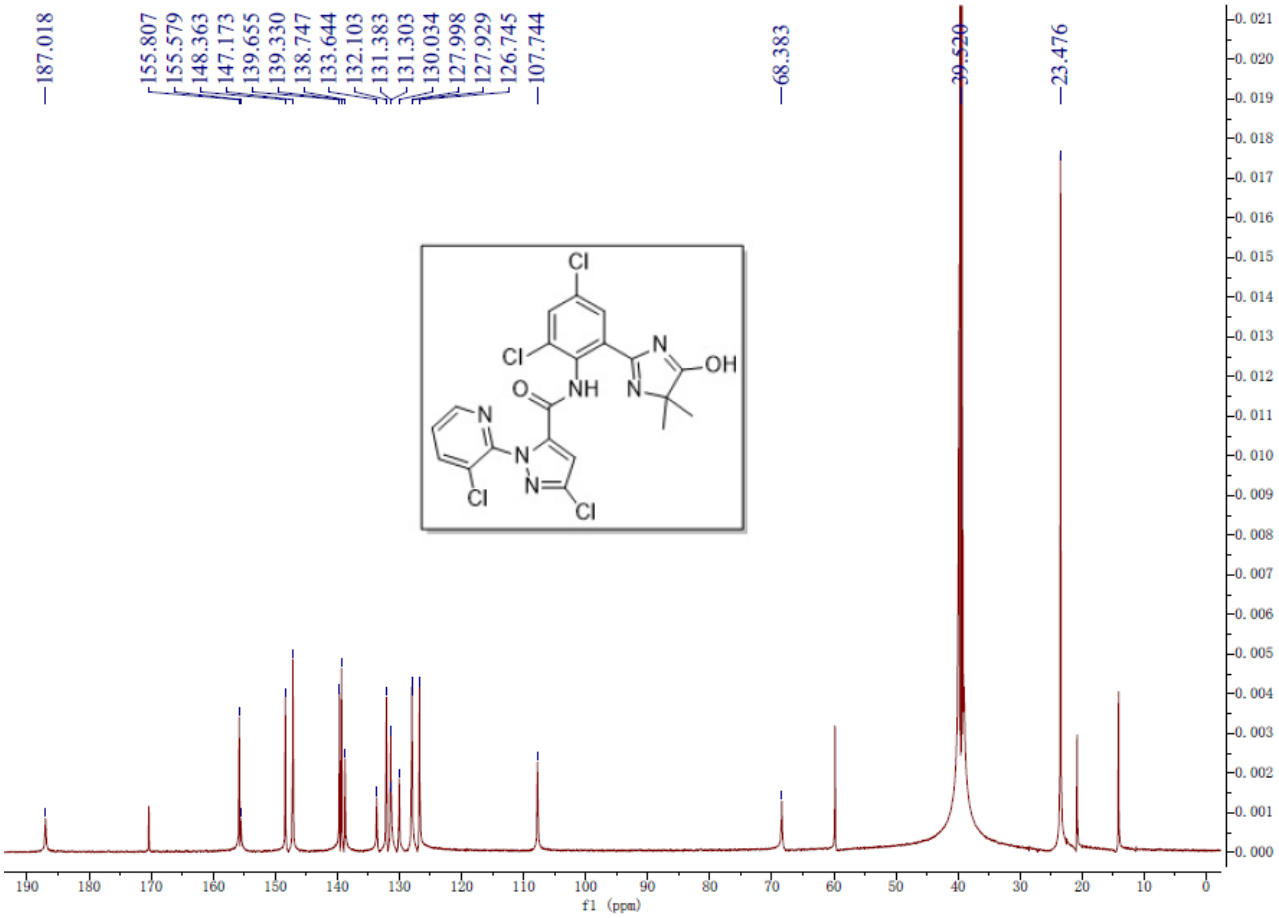


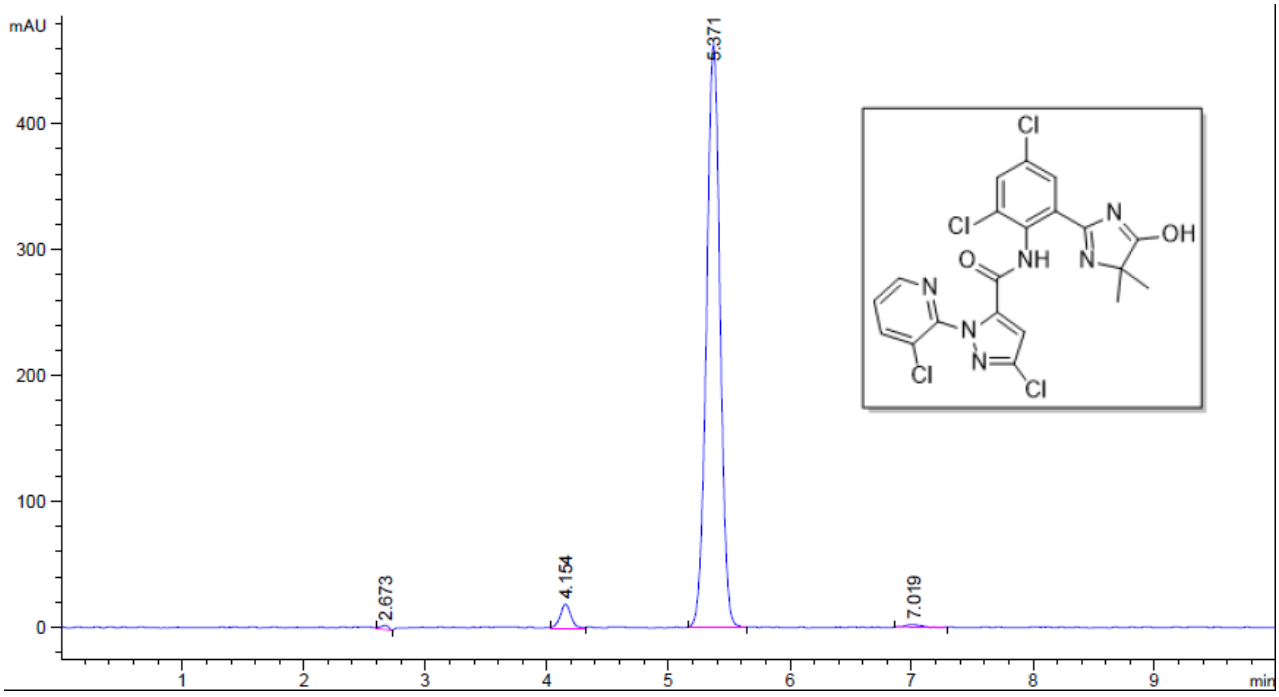




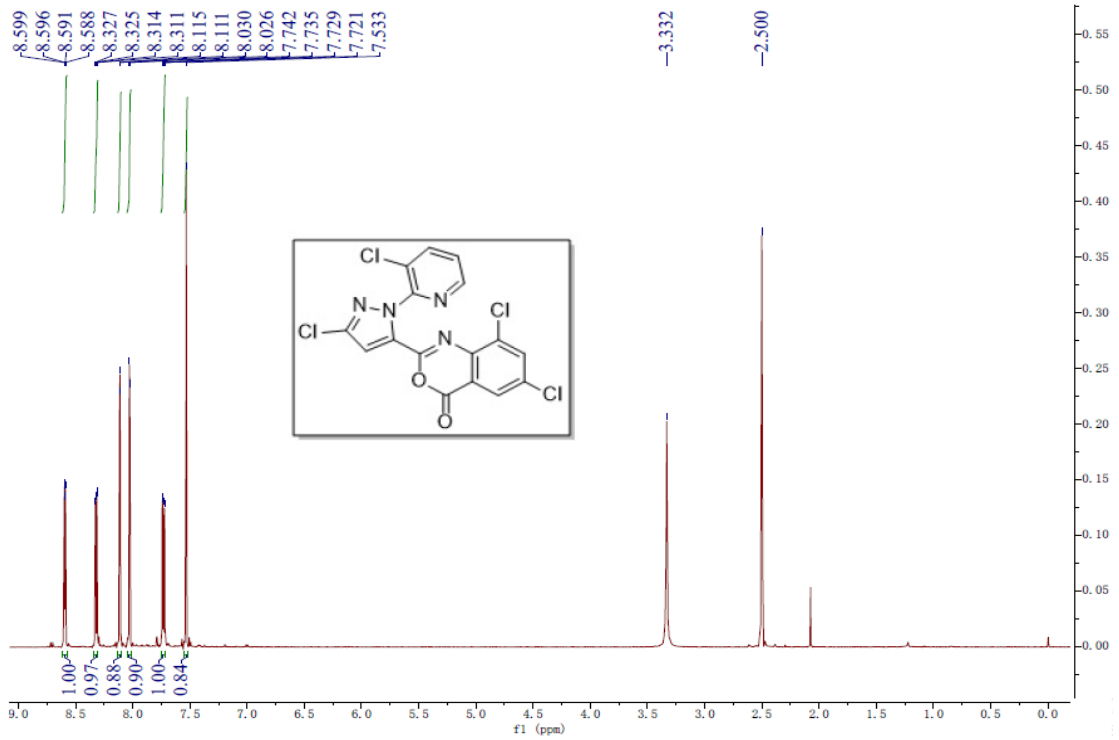
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **12b**

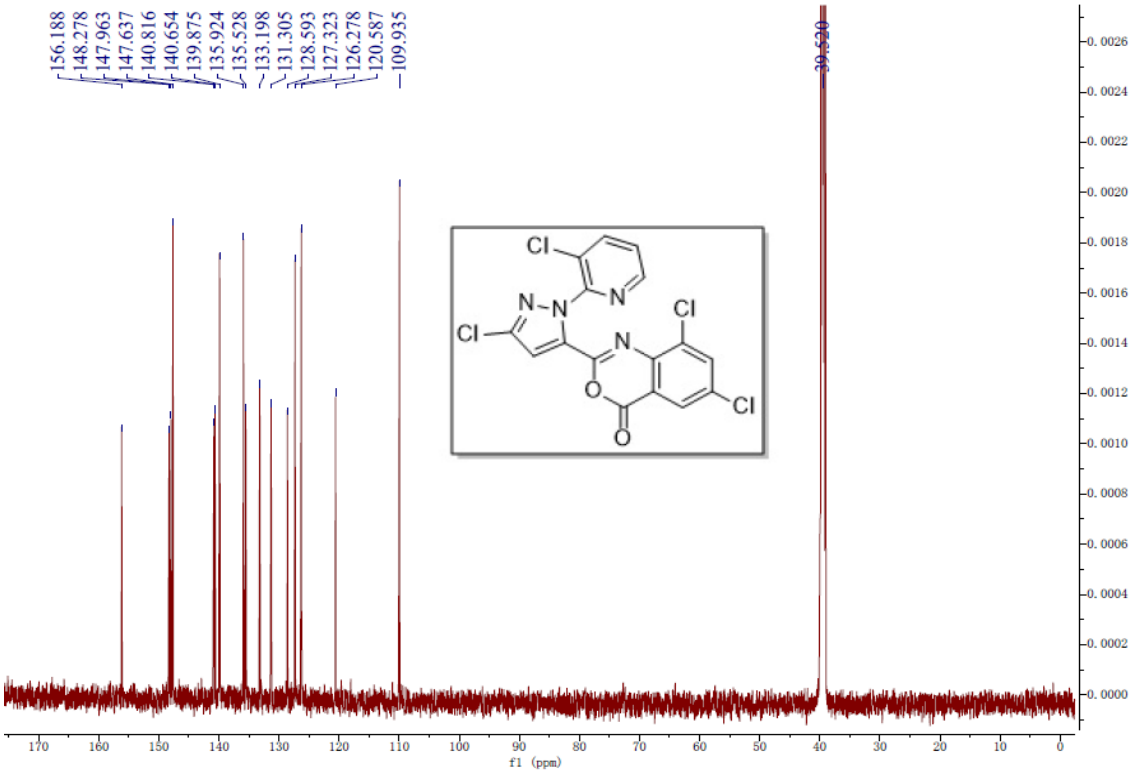


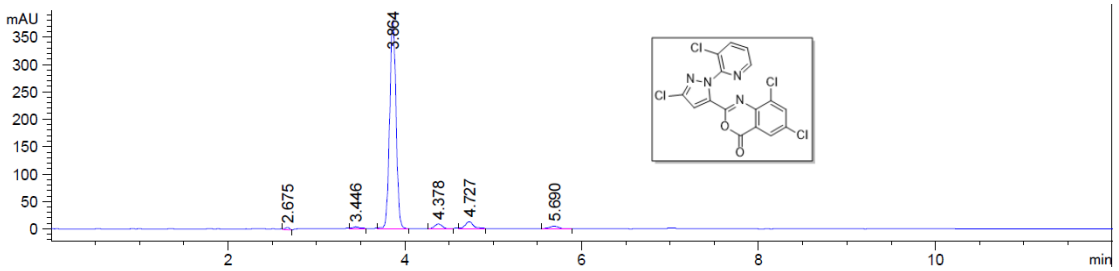

187.018
155.807
155.579
148.363
147.173
139.655
139.330
138.747
133.644
132.103
131.383
131.303
130.034
127.998
127.929
126.745
107.744
68.383
39.520
23.476
f1 (ppm)


mAU
5.371
2.673
4.154
7.019
min

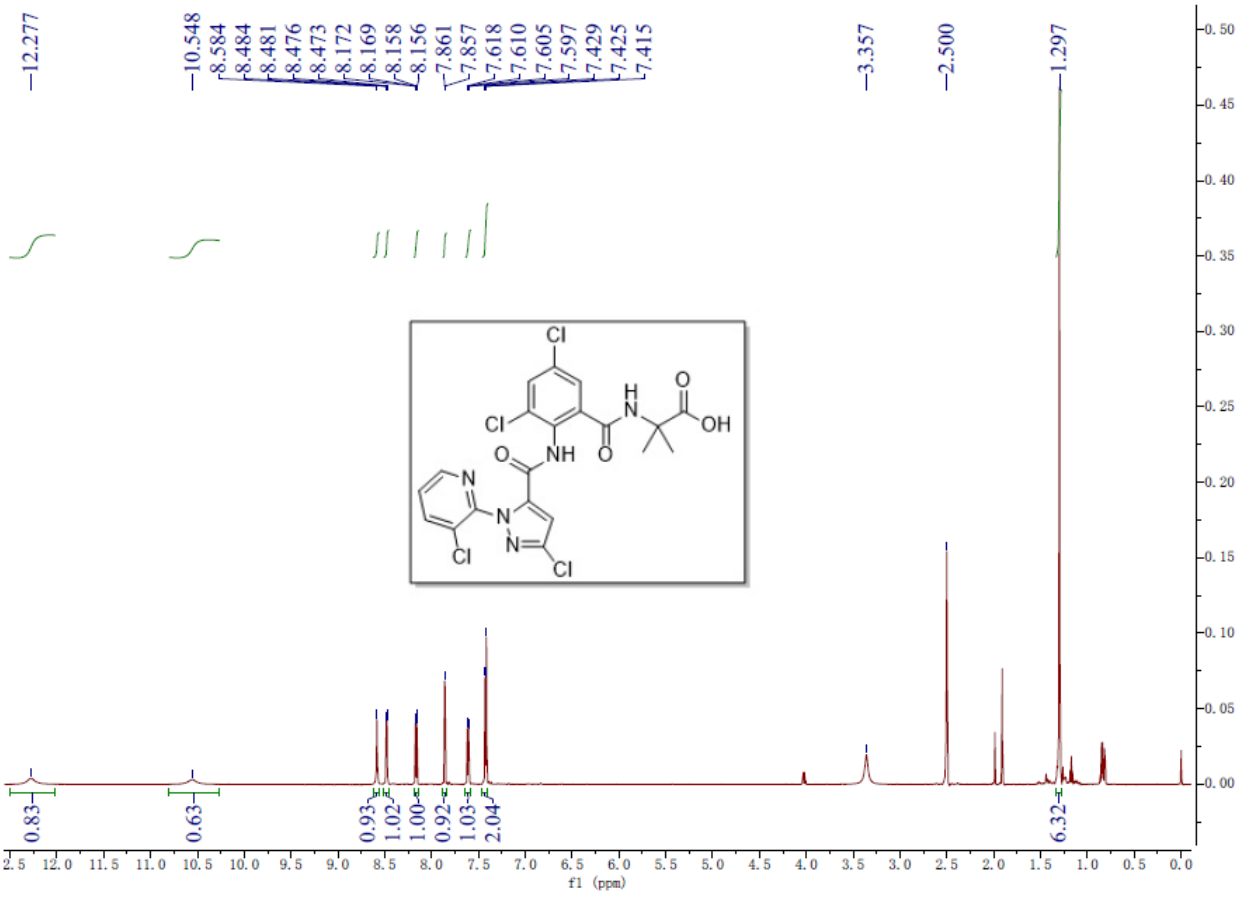
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **13**

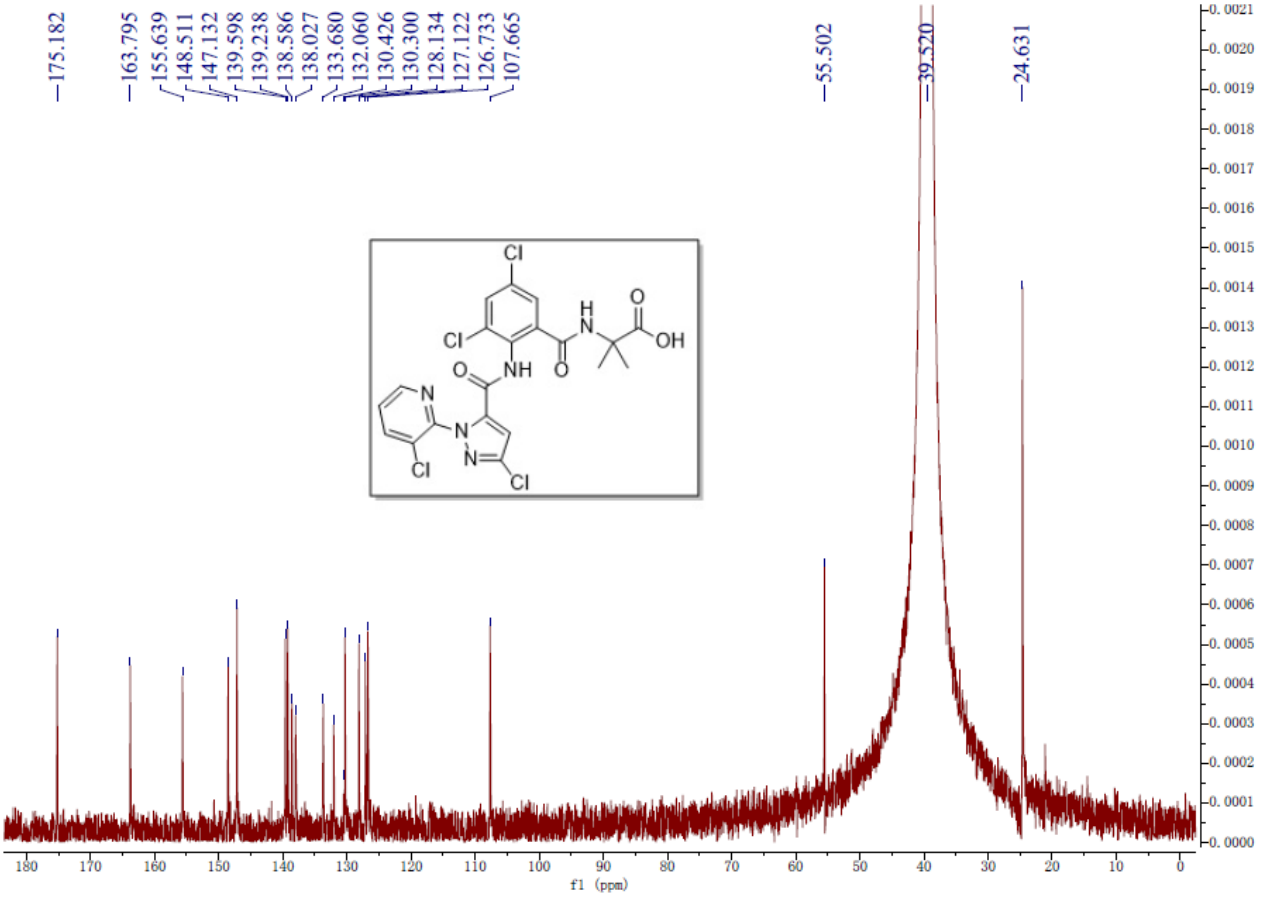


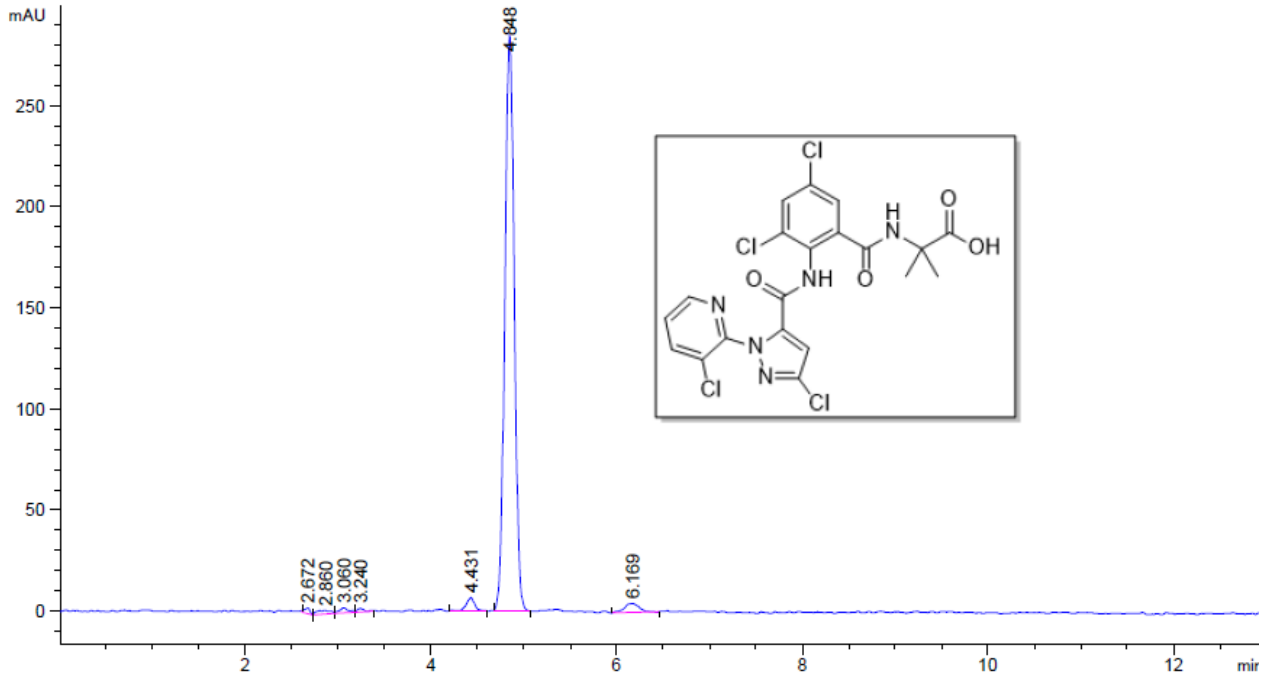




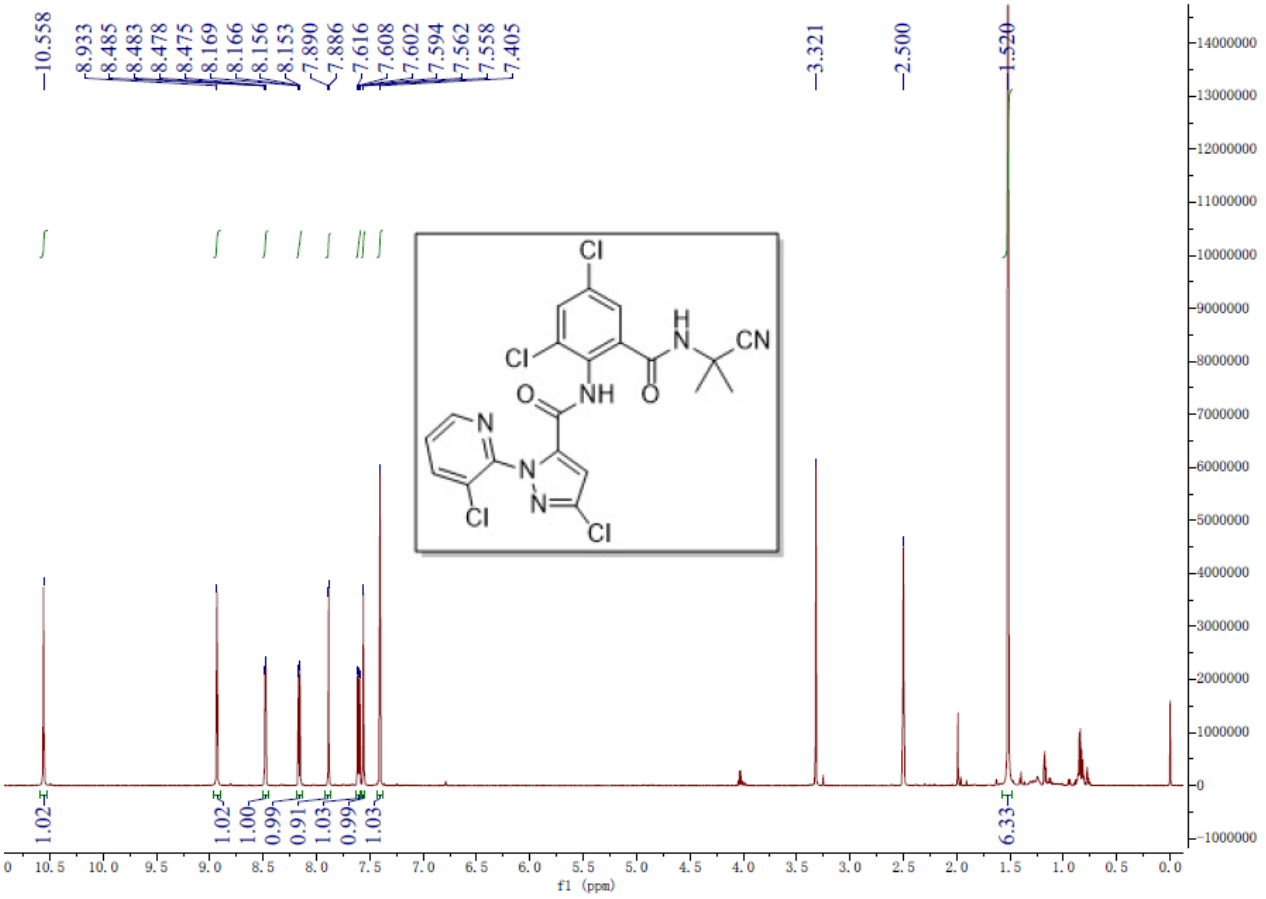
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **14**

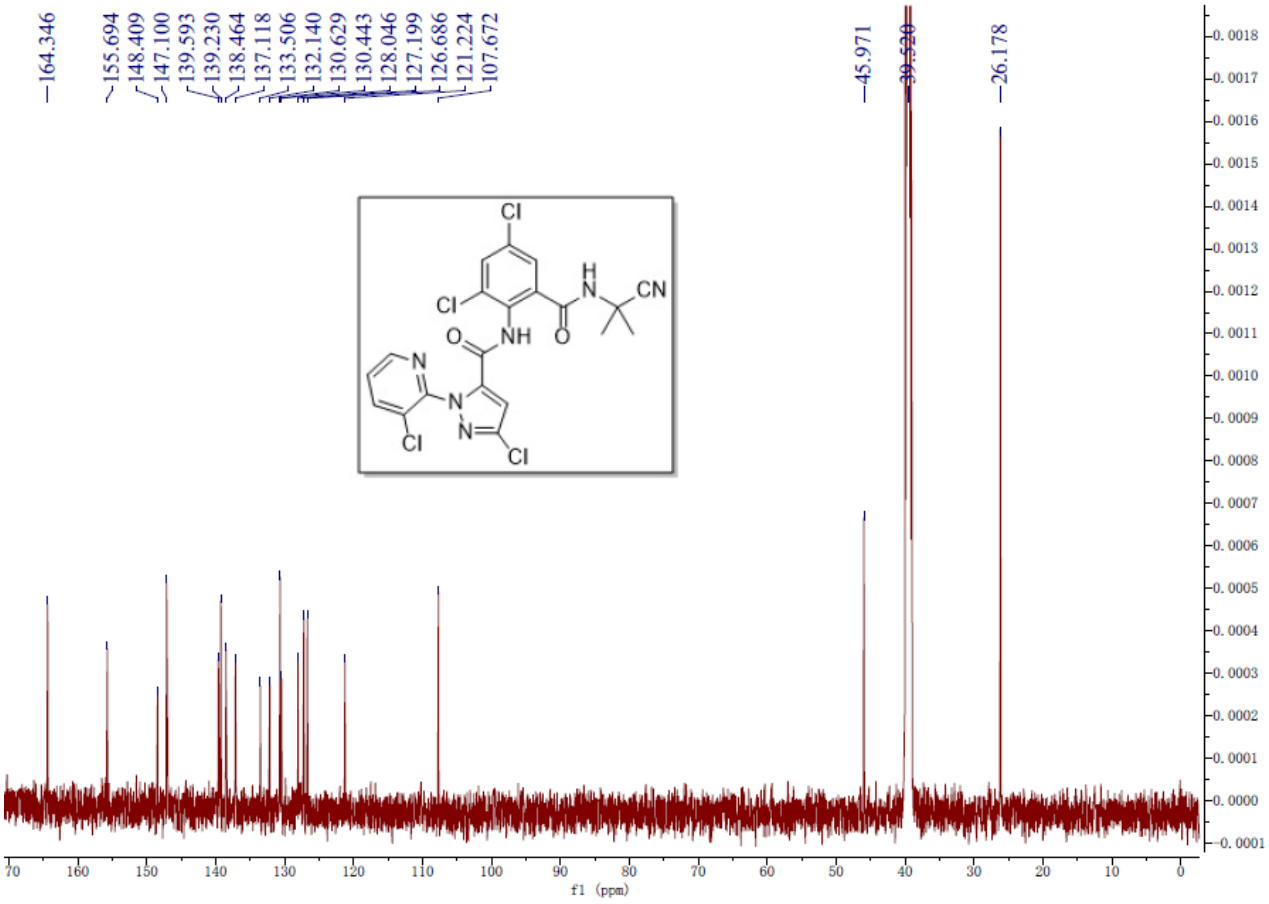


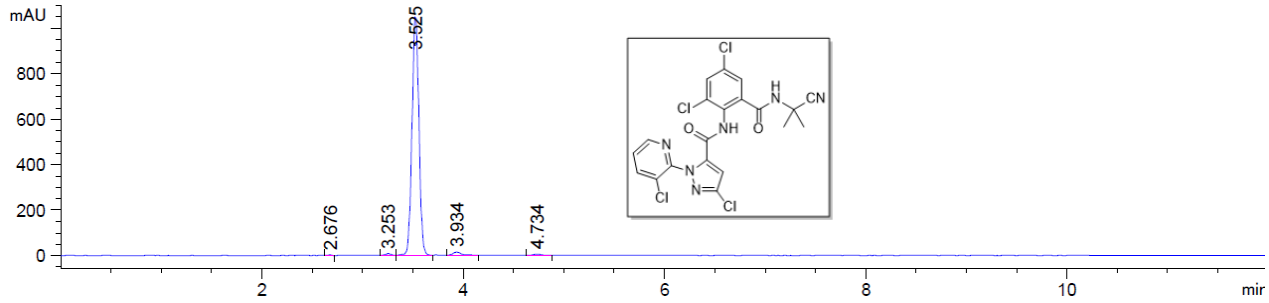




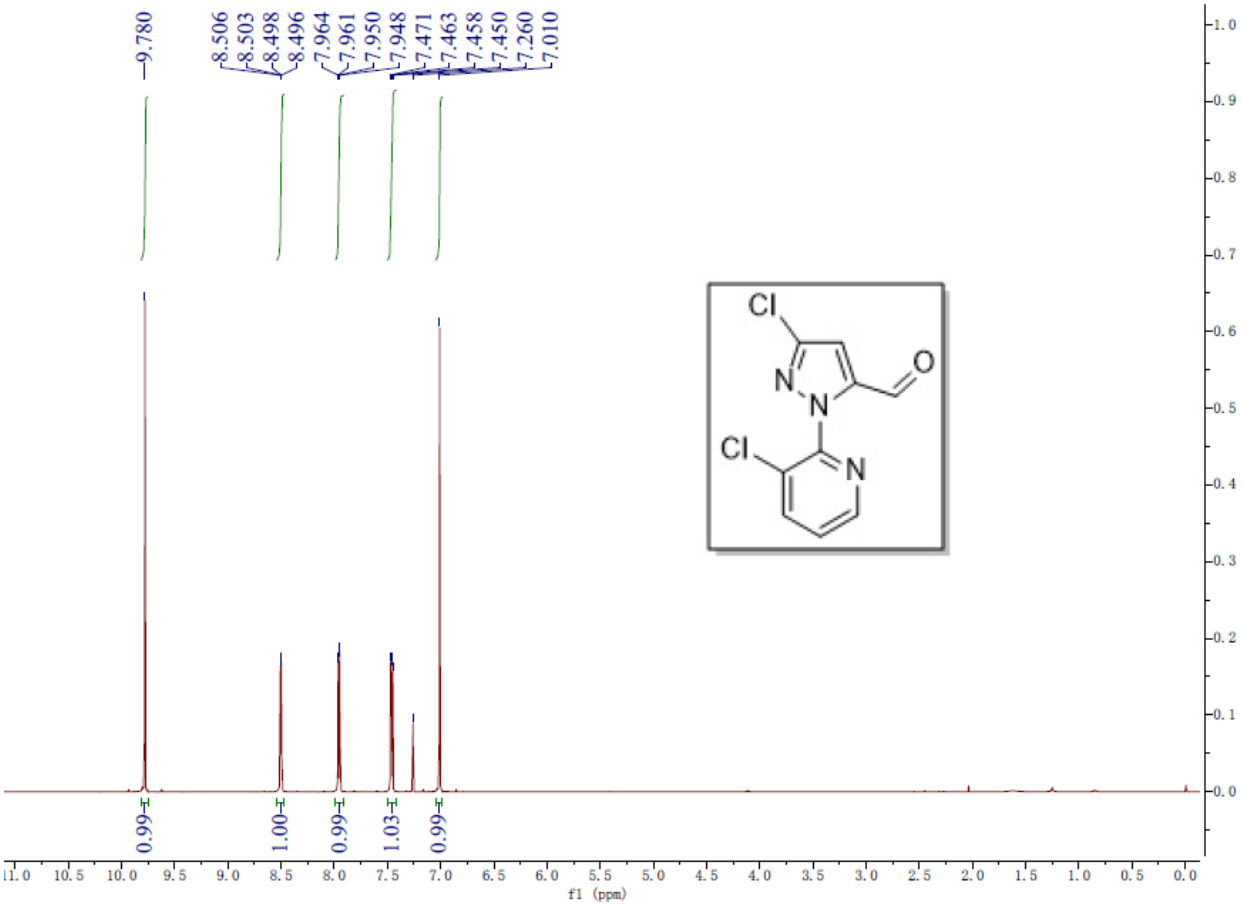
^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (150 MHz, DMSO-d_6) spectra and HPLC chromatogram of compound **16**

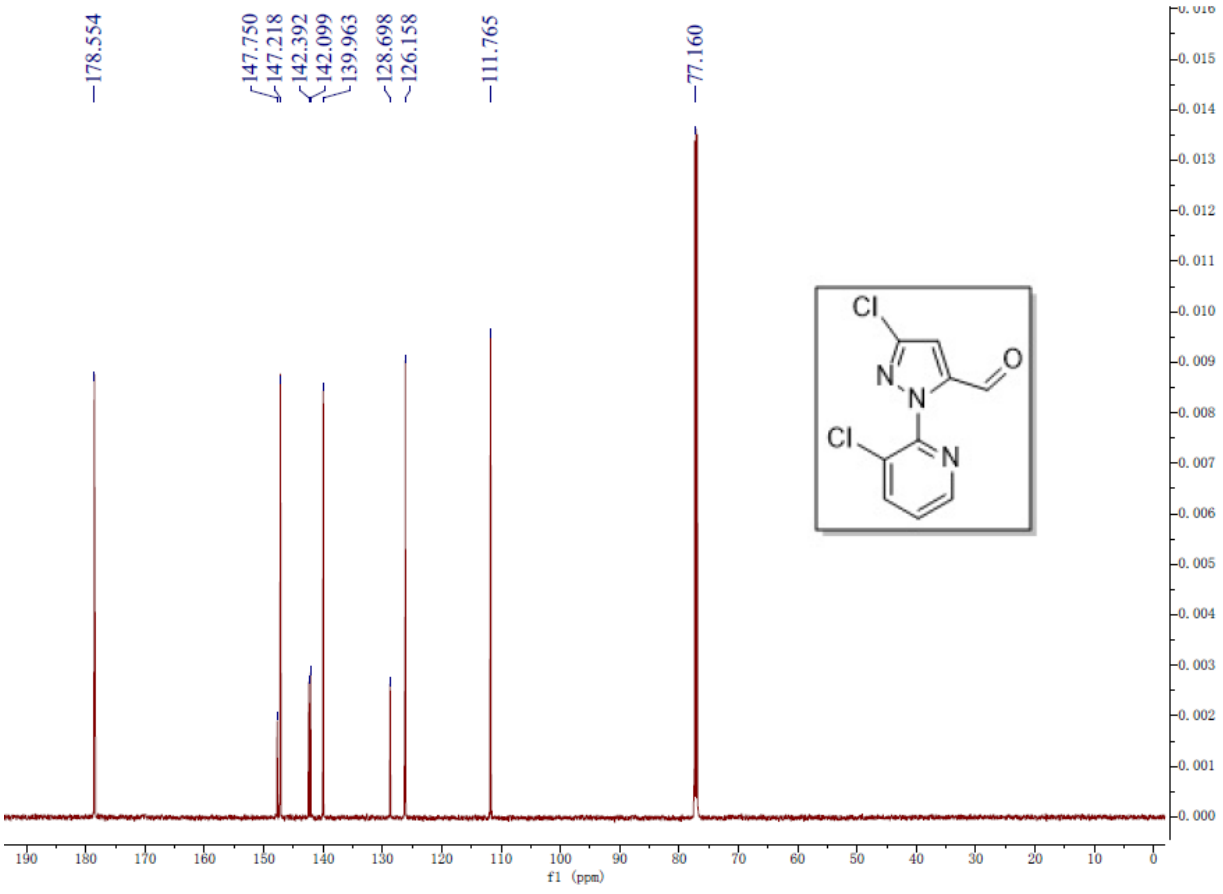


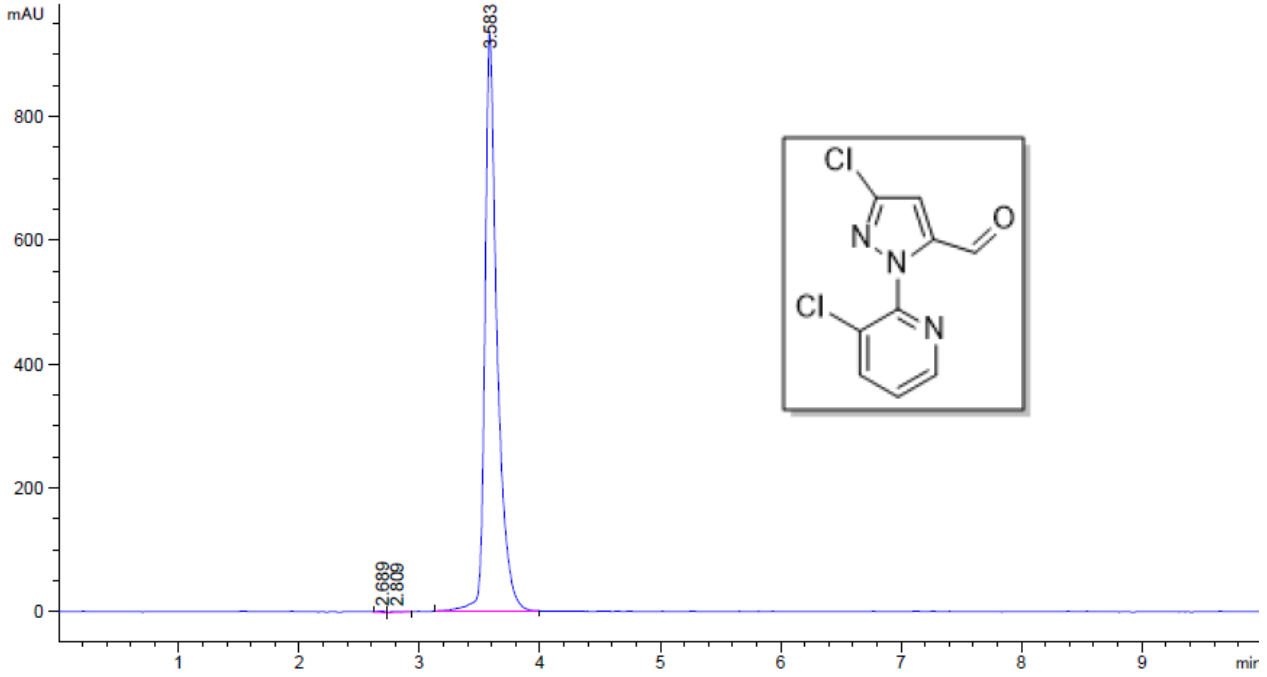

164.346
155.694
148.409
147.100
139.593
139.230
138.464
137.118
133.506
132.140
130.629
130.443
128.046
127.199
126.686
121.224
107.672
45.971
39.520
26.178
f1 (ppm)


mAU
3.525
2.676
3.253
3.934
4.734
min

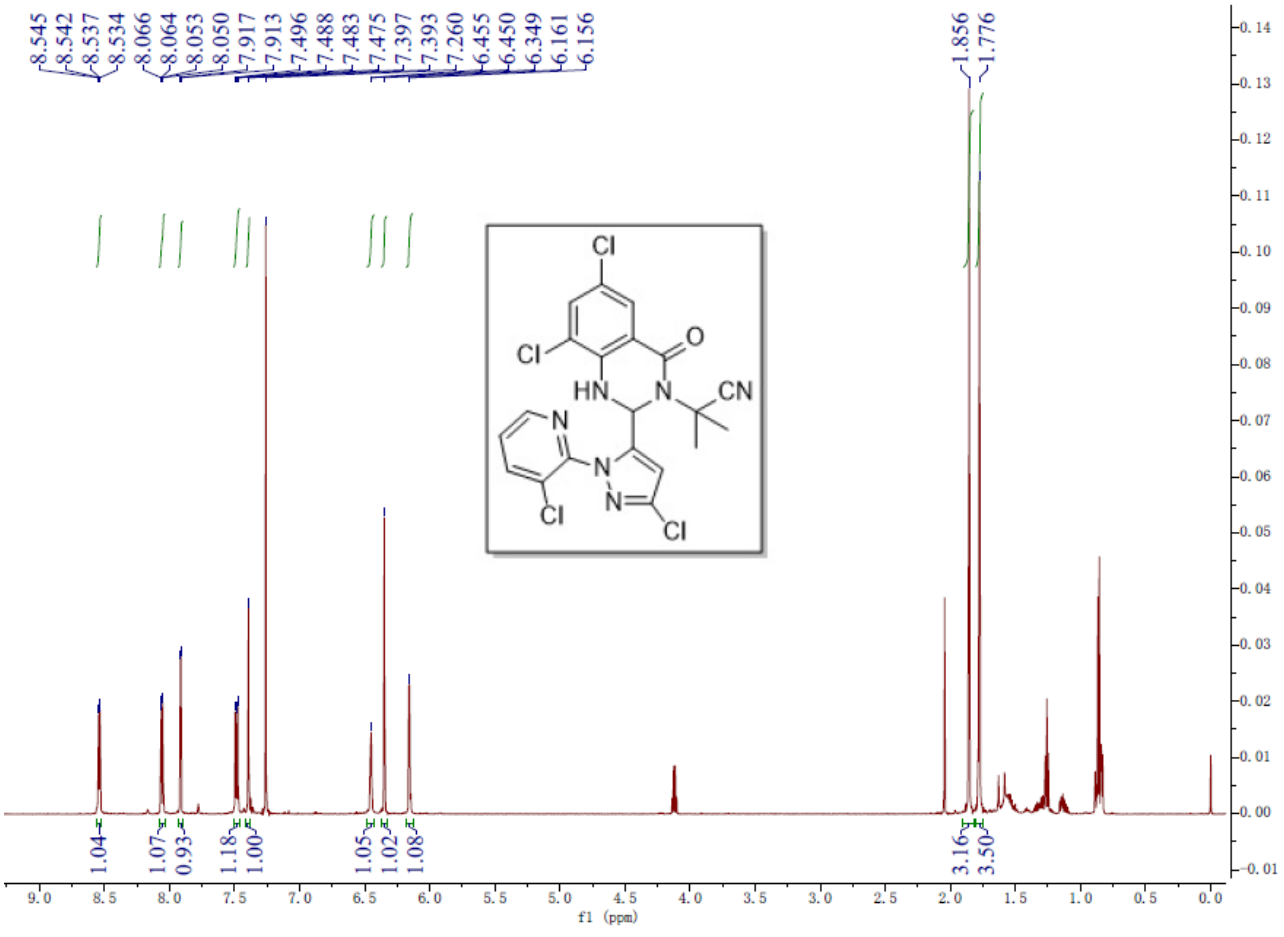
^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (150 MHz, $CDCl_3$) spectra and HPLC chromatogram of compound **17**

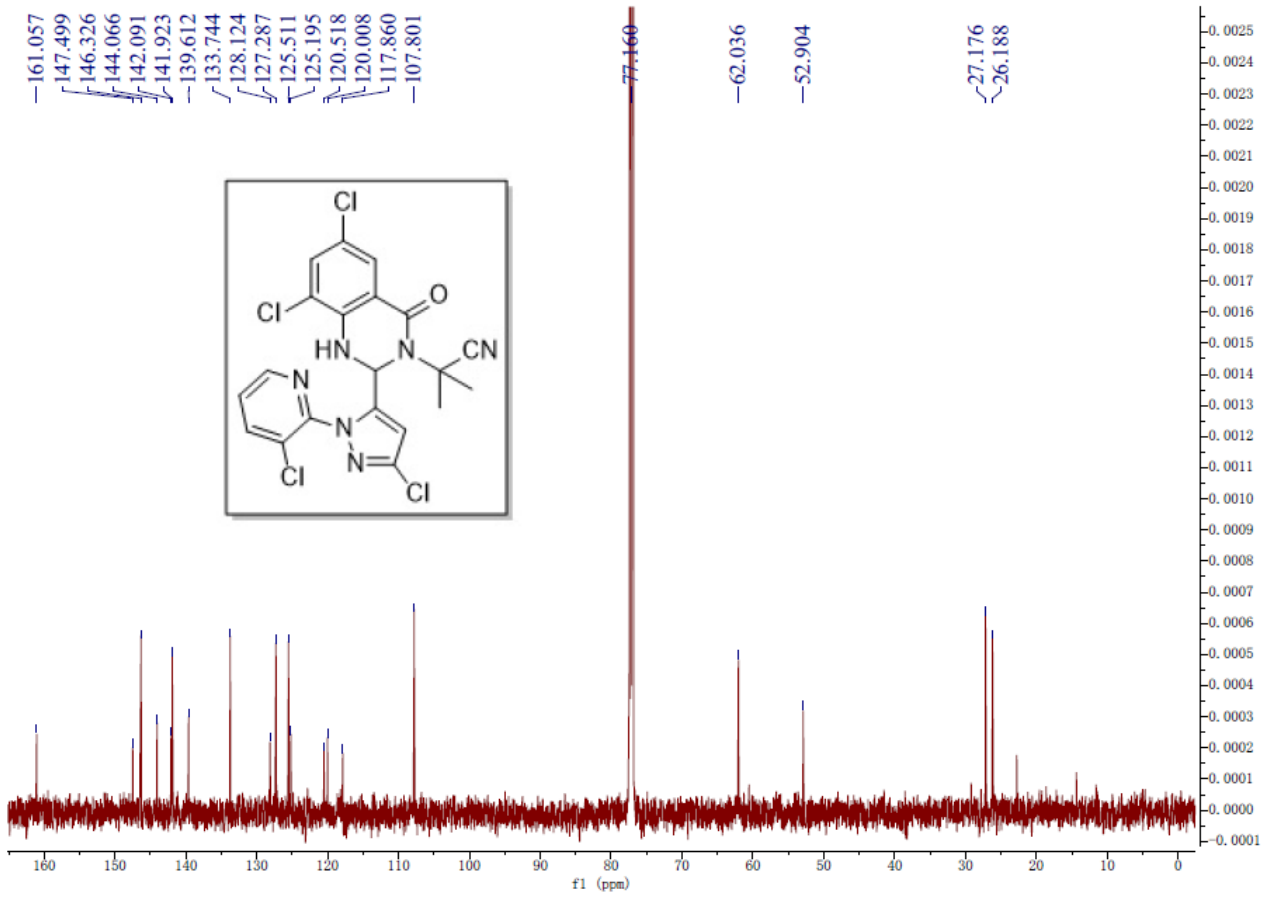


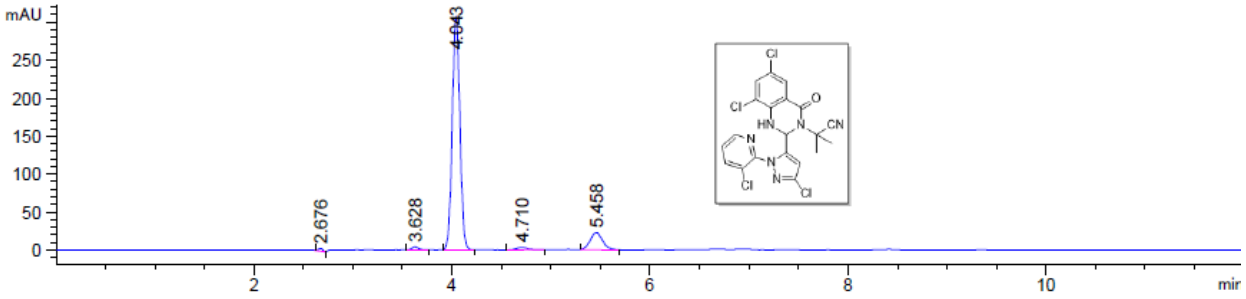




^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (150 MHz, $CDCl_3$) spectra and HPLC chromatogram of compound **18**




161.057
147.499
146.326
144.066
142.091
141.923
139.612
133.744
128.124
127.287
125.511
125.195
120.518
120.008
117.860
107.801
77.160
62.036
52.904
27.176
26.188
Cl
Cl
O
HN
N
CN
N
N
Cl
N
Cl
f1 (ppm)


mAU
4.043
2.676
3.628
4.710
5.458
min