

## Supplementary Information

### Bioisosteric Replacement Driven Lead Optimization of Tyclopyrazoflor

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21    **Contents**

22    1.    General Synthetic procedure for intermediates **2** and **9**.

23    2.    Copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of target compounds.

24

## 1. General Synthetic procedure for intermediates 2 and 9

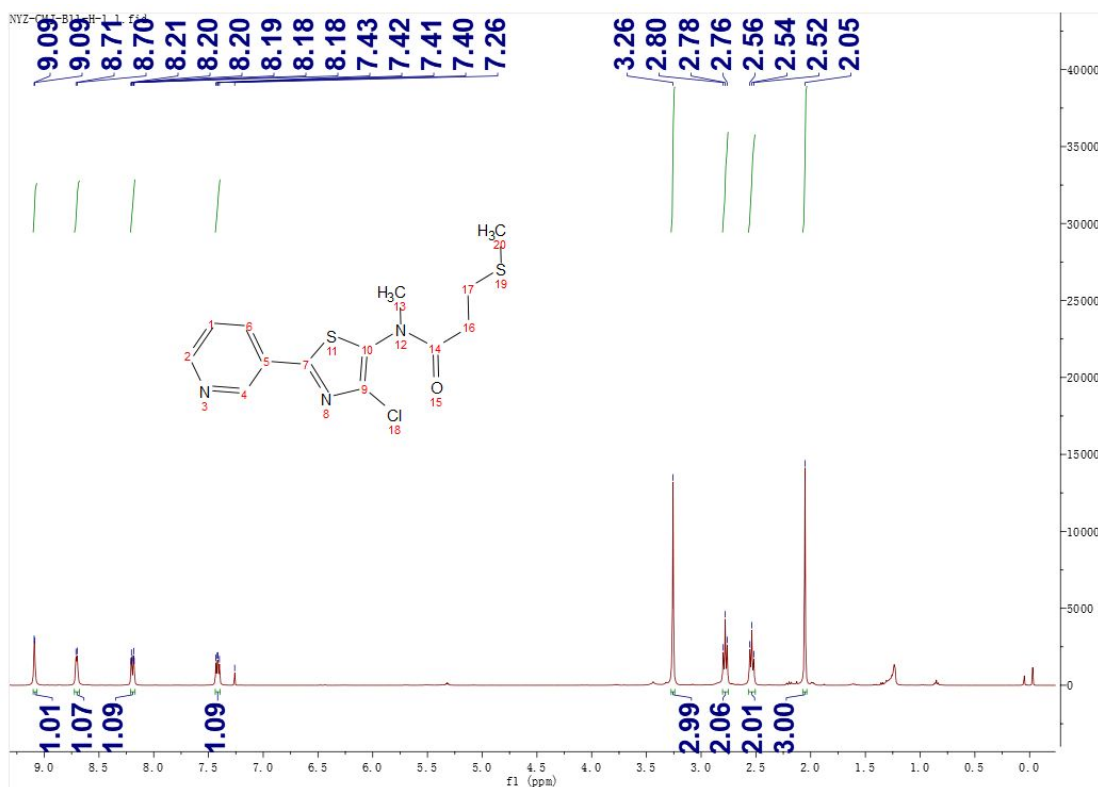
### *Synthesis of tert-butyl N-(2-bromo-1,3-thiazol-5-yl) carbamate (2)*

To a stirred solution of 2-Bromo-5-thiazolecarboxylic acid **1** (5 g, 24 mmol) in t-butanol (40 mL) was added Et<sub>3</sub>N (3.3 mL, 26.4 mmol). After 10 min, diphenylphosphoryl azide (5.7 mL, 24 mmol) was added and the reaction was heated at 80°C for 16 h. The reaction mixture was then concentrated, diluted with water (60 mL) and extracted with ethyl acetate (60 mL x 2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give residue, which was purified by flash column chromatography (0-100% petroleum ether/ethyl acetate) to afford tert-butyl N-(2-bromo-1,3-thiazol-5-yl) carbamate **2** (60% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.94 (s, 1H), 7.11 (s, 1H), 1.46 (s, 9H) ppm.

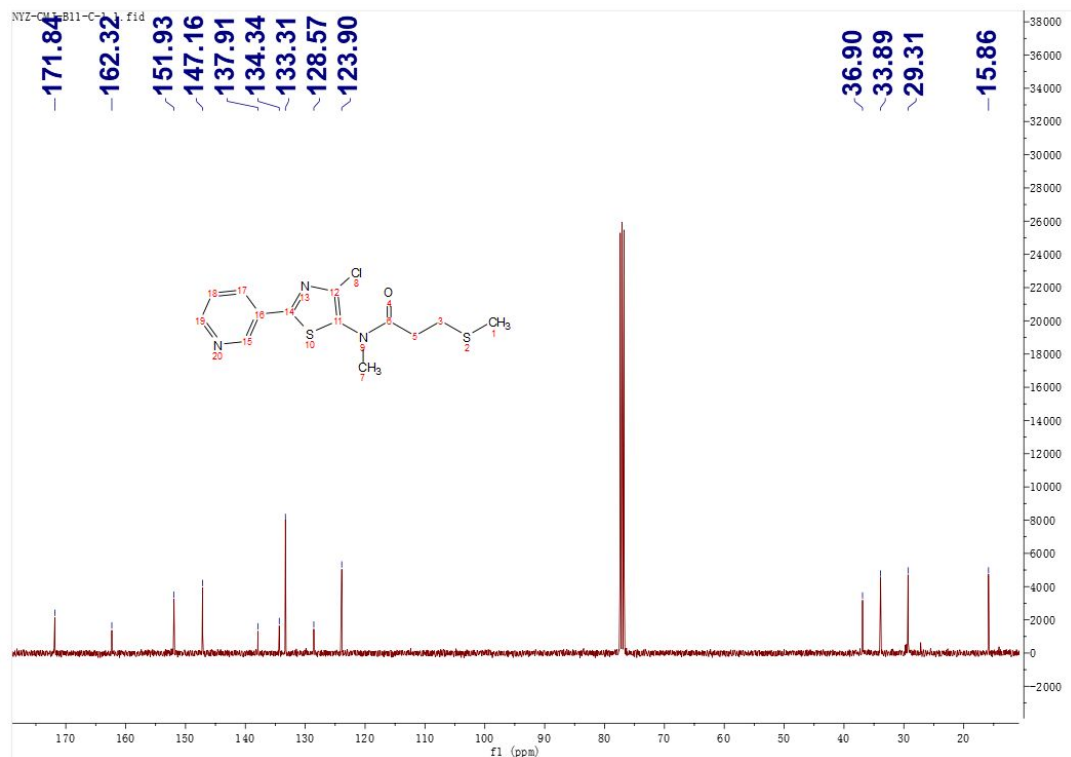
### *Synthesis of methyl (pyridazine-4-carbonyl)glycinate (9)*

A mixture of pyridazine-4-carboxylic acid **7** (2.5 g, 20 mmol), p-toluenesulfonyl chloride (4.2 g, 22 mmol), benzyltriethylammonium chloride (0.5 g, 8.1 mmol), and K<sub>2</sub>CO<sub>3</sub> (11.3 g, 80 mmol) in CHCl<sub>3</sub> (125 mL) was stirred at 40°C for 1 h. Glycine methyl ester hydrochloride **8** (2.6 g, 20 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.8 g, 20 mmol) were then added and stirred at 50°C for 90 min. The reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (7% ethyl acetate/methanol) to give methyl (pyridazine-4-carbonyl)glycinate **9** (49% yield) as an orange gum which solidified upon standing at room temperature. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.57 (dt, *J* = 2.4, 1.0 Hz, 1H), 9.54 (d, *J* = 6.0 Hz, 1H), 9.48 (dt, *J* = 5.2, 1.0 Hz, 1H), 8.03 (dd, *J* = 5.2, 2.4 Hz, 1H), 4.11 (d, *J* = 6.0 Hz, 2H), 3.68 (s, 3H) ppm.

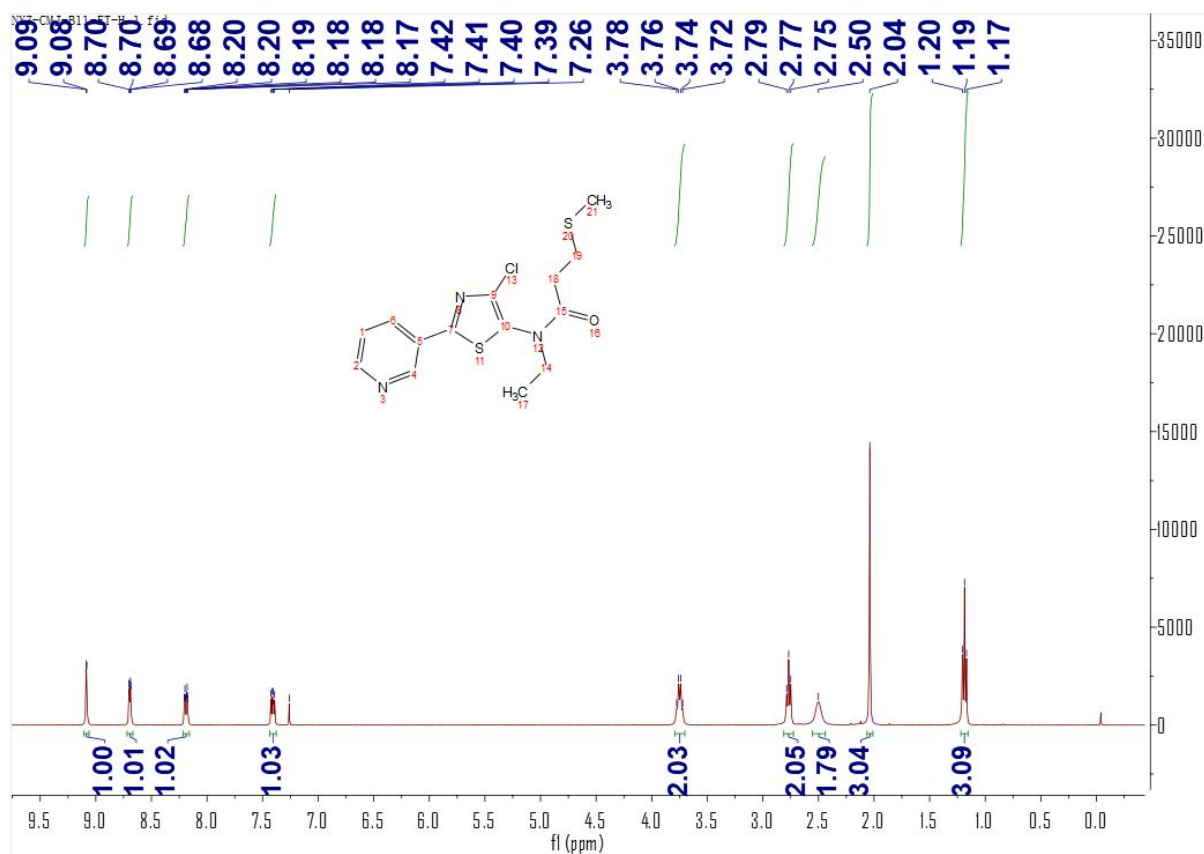
47 2. Copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of target compounds



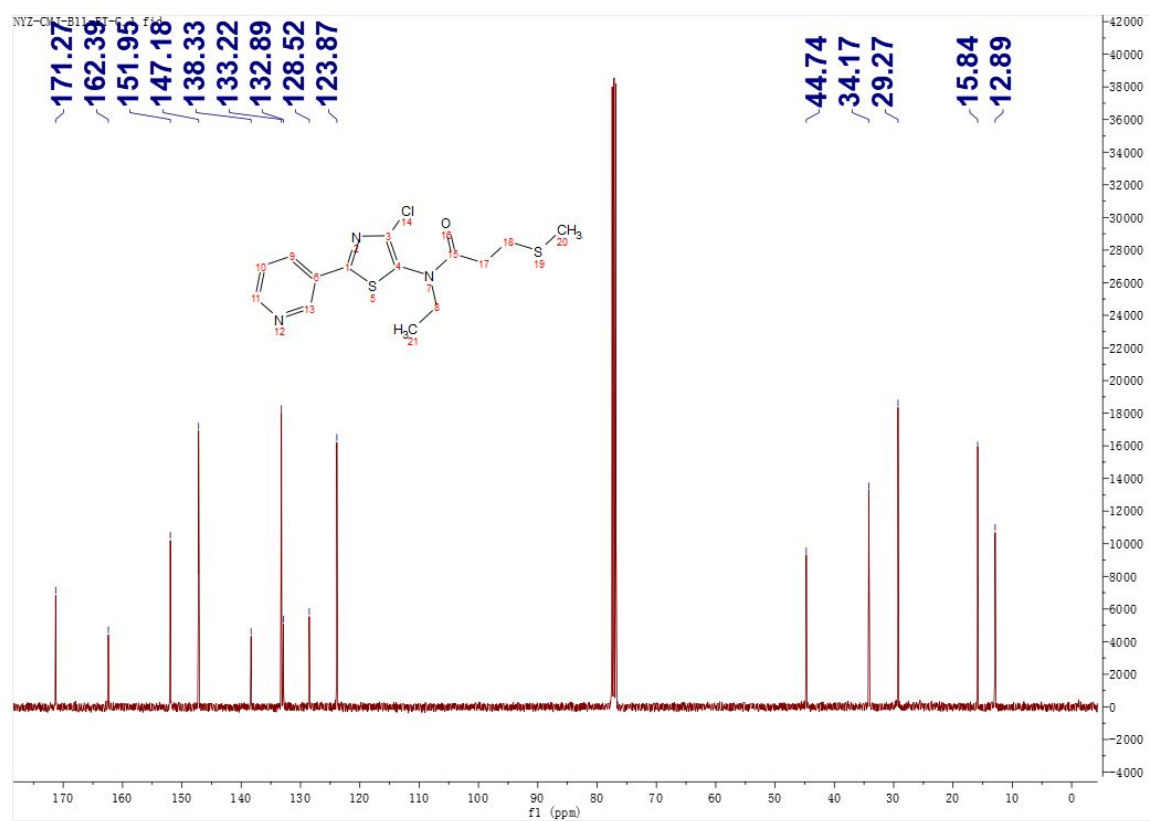
49 The  $^1\text{H}$  NMR spectrum of compound I-1



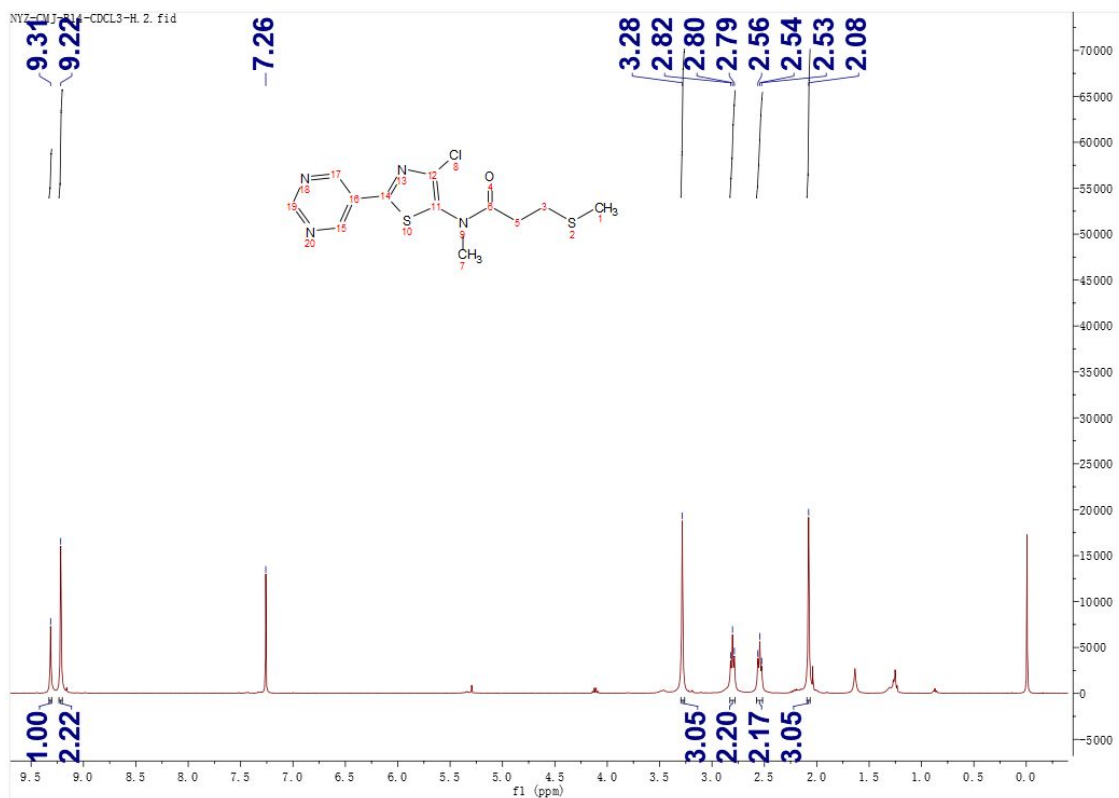
51 The  $^{13}\text{C}$  NMR spectrum of compound I-1



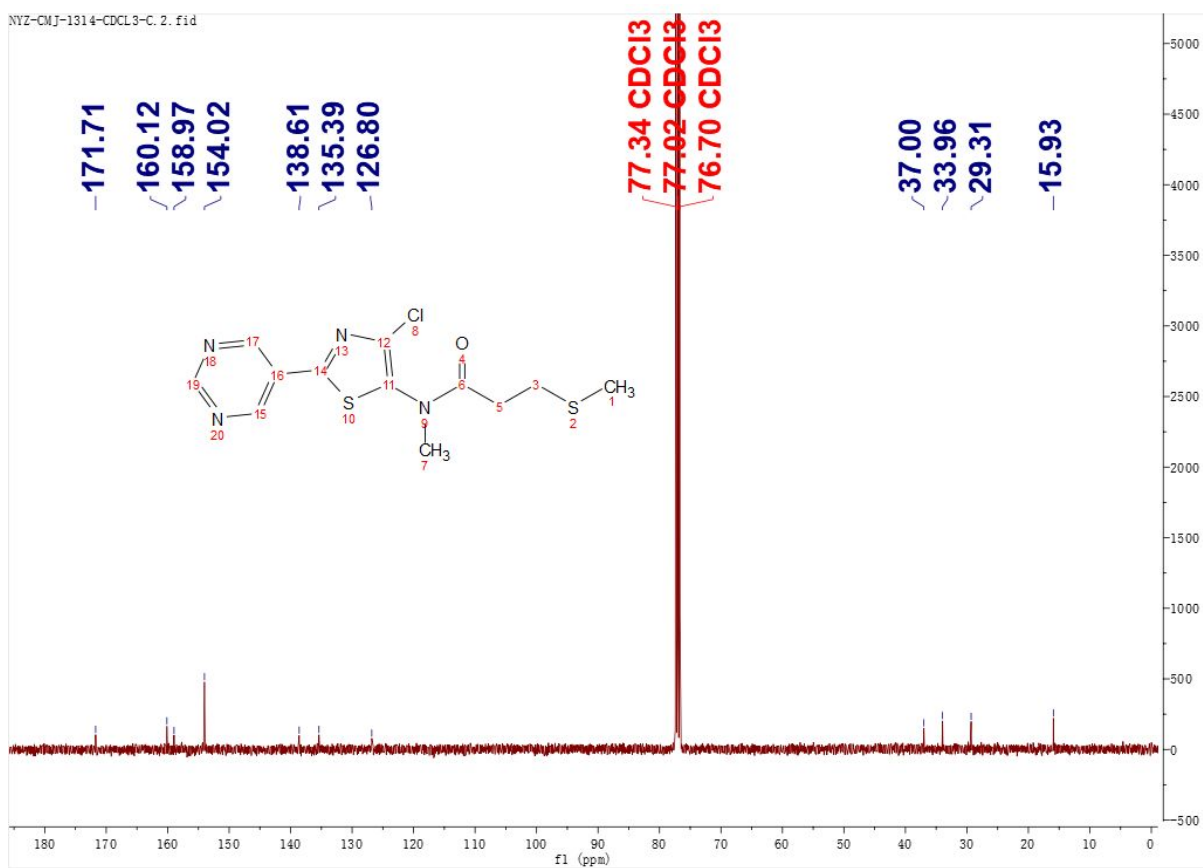
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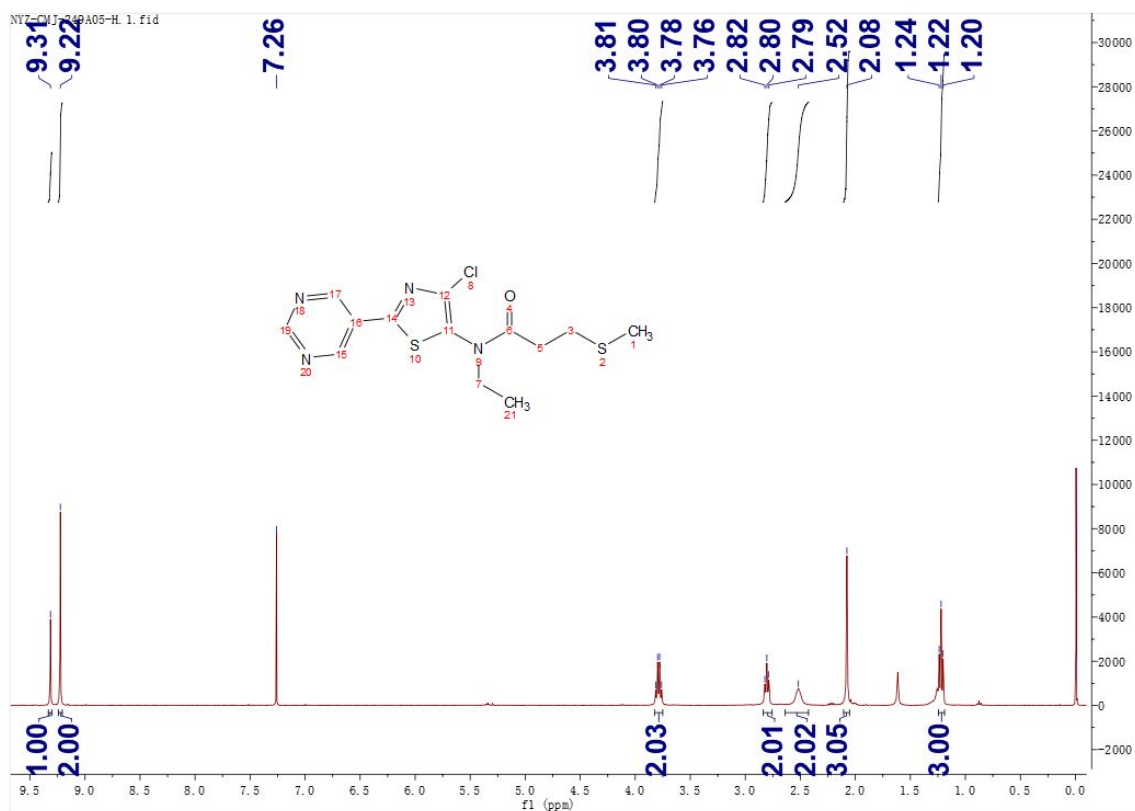
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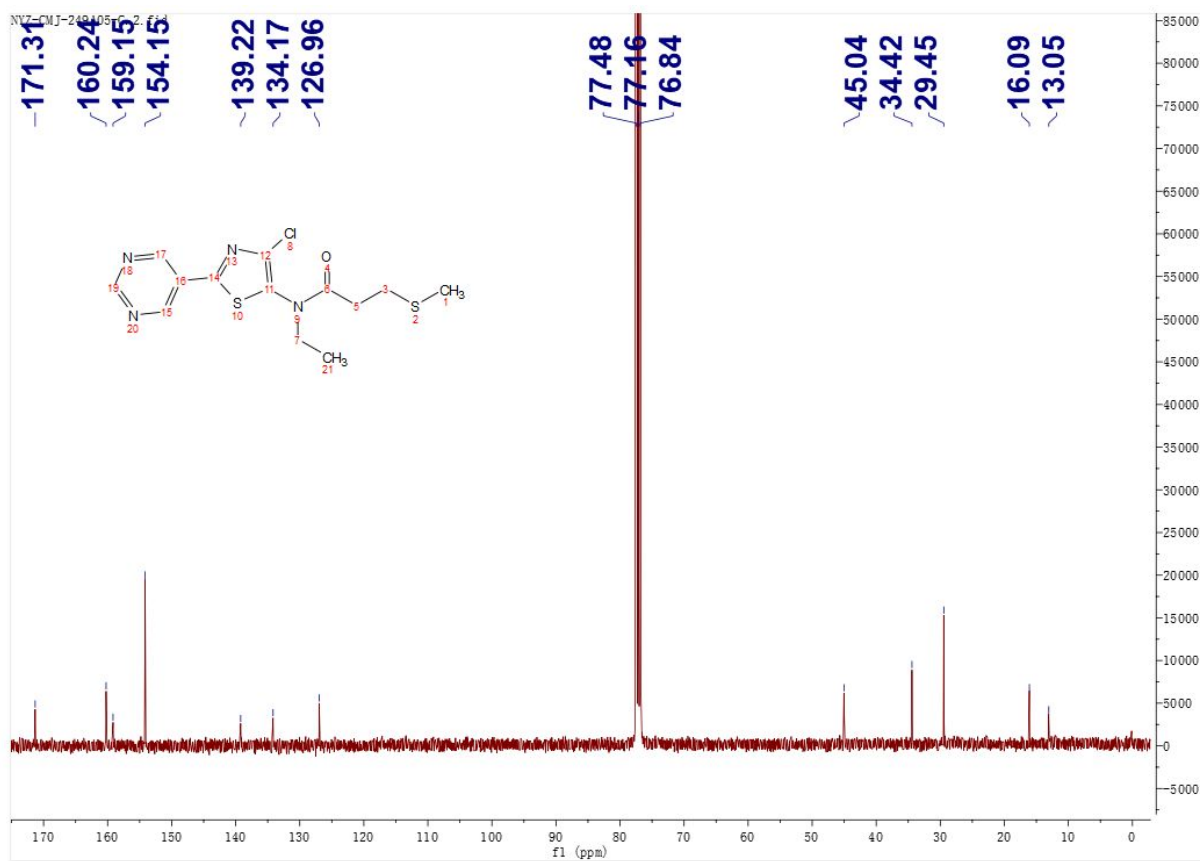
The <sup>1</sup>H NMR spectrum of compound I-4



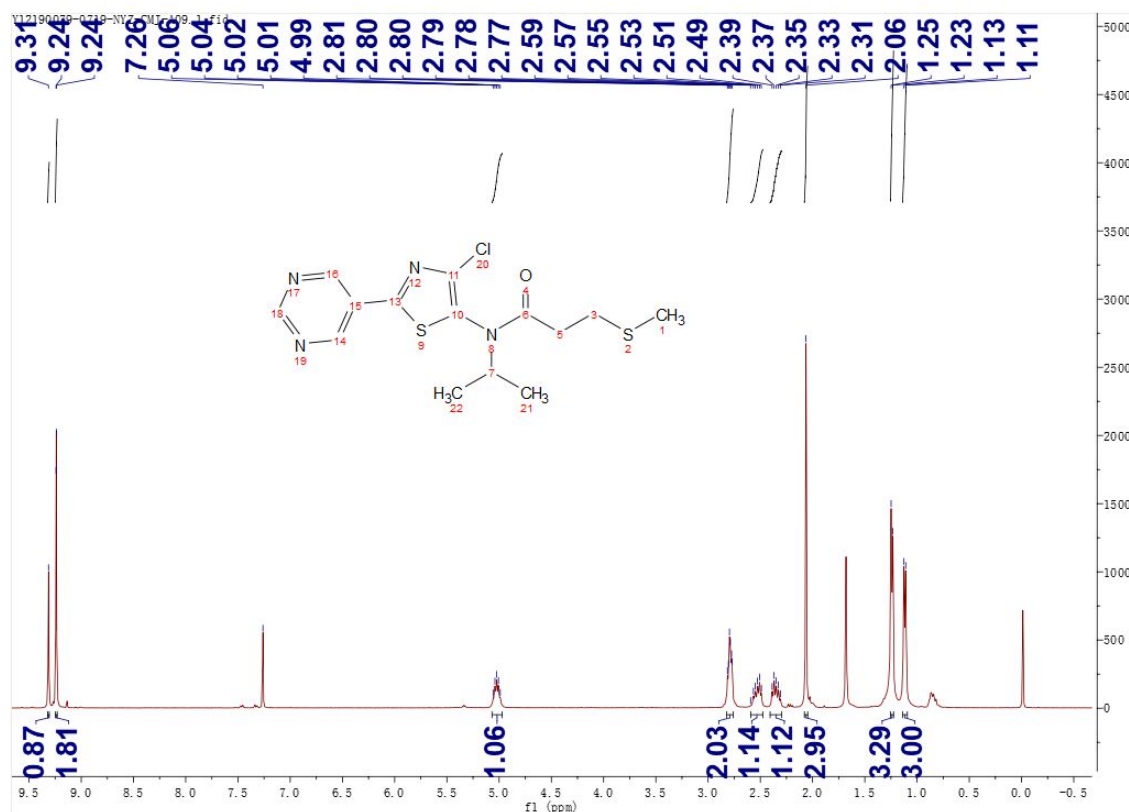
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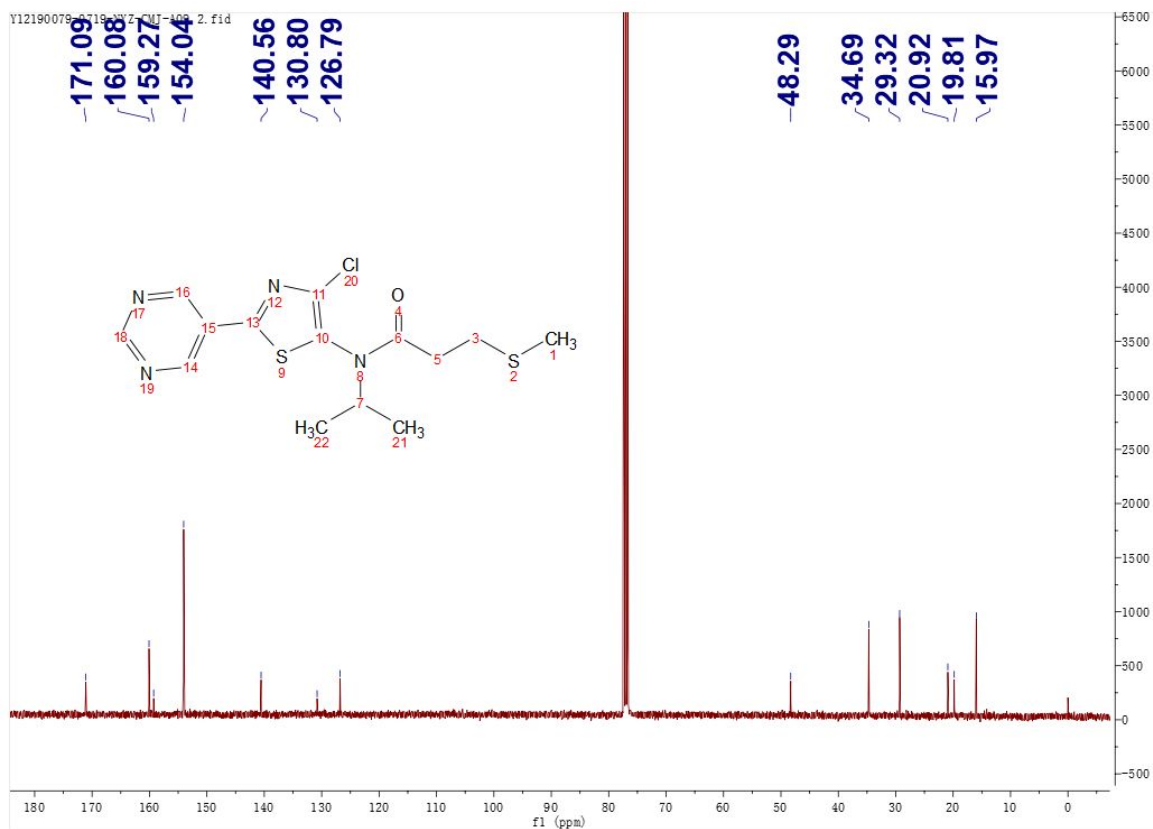
The  $^1\text{H}$  NMR spectrum of compound I-5



The  $^{13}\text{C}$  NMR spectrum of compound I-5

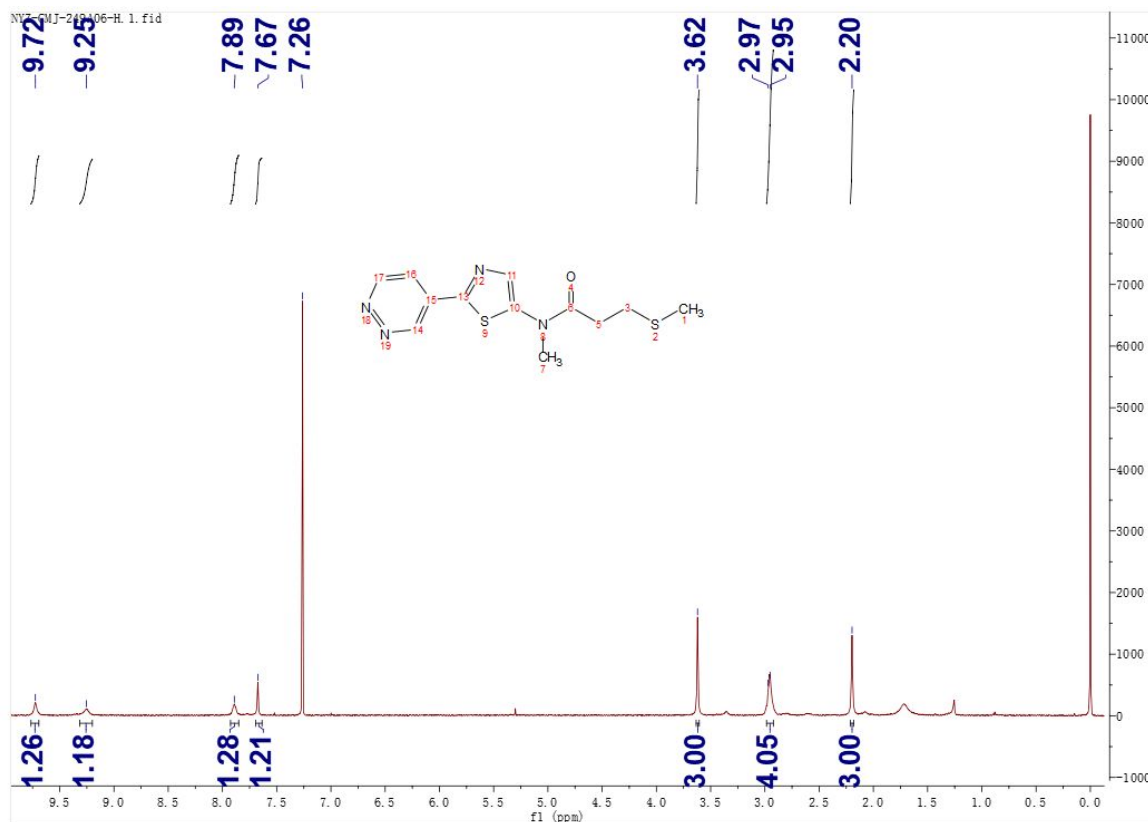


The <sup>1</sup>H NMR spectrum of compound I-6

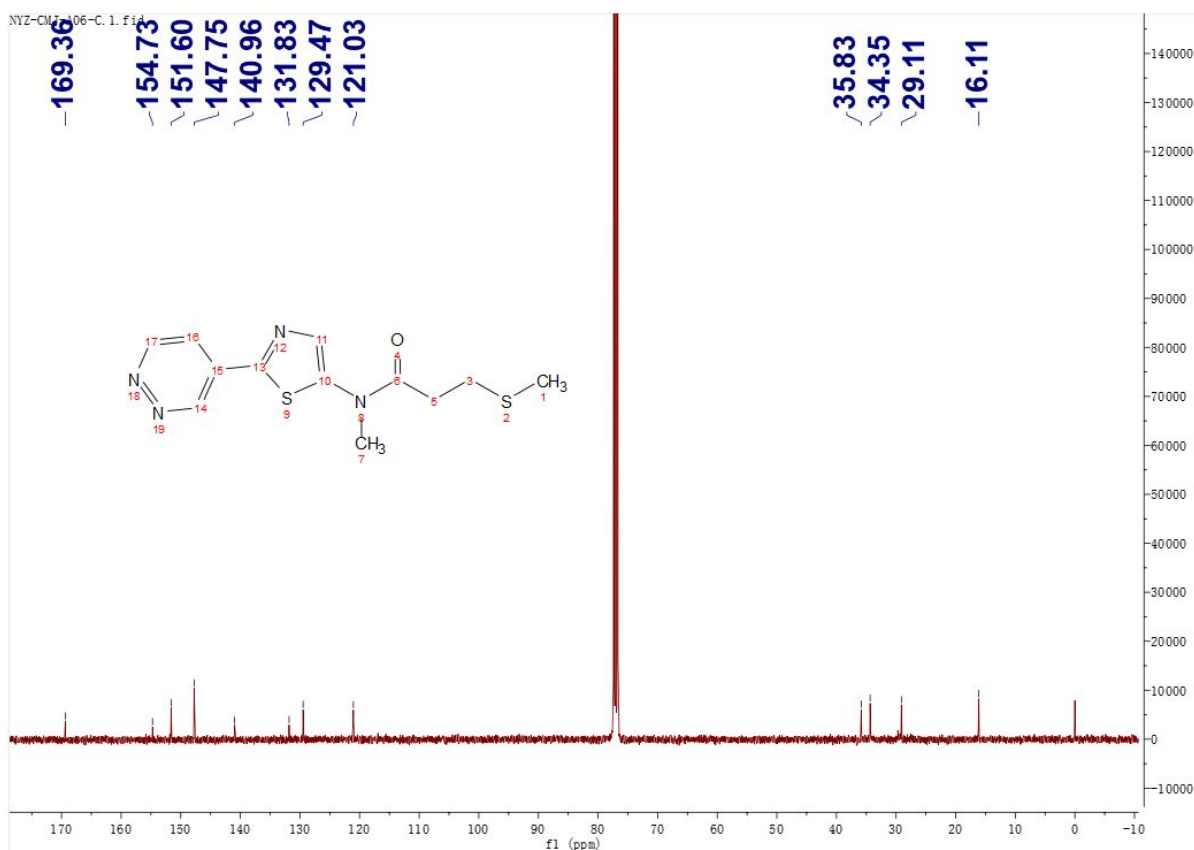


The <sup>13</sup>C NMR spectrum of compound I-6

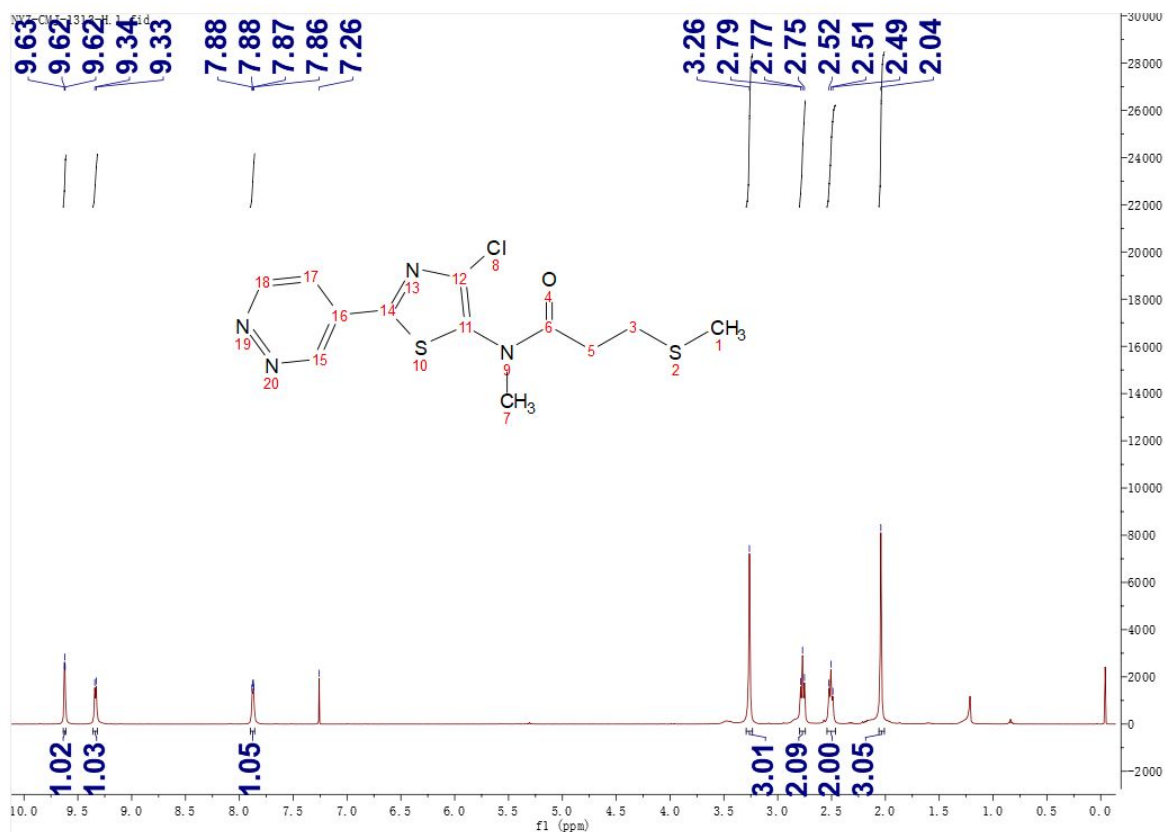




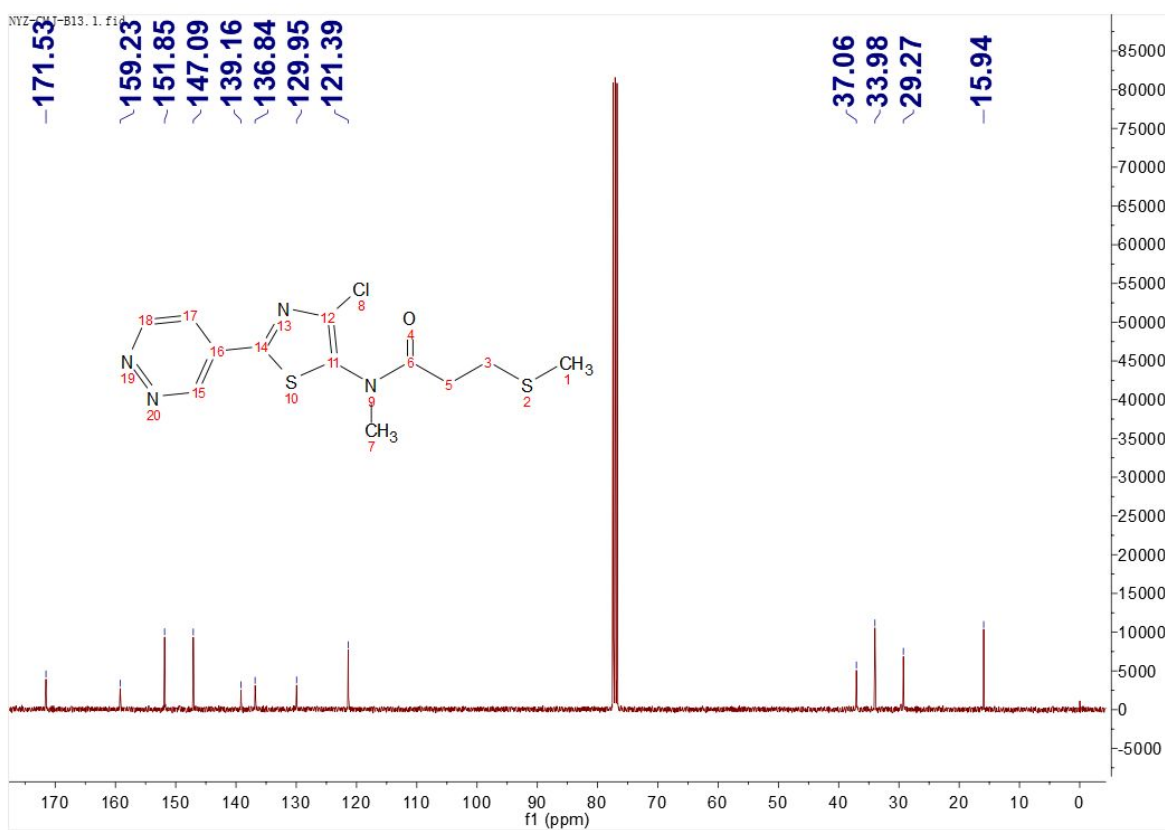
The  $^1\text{H}$  NMR spectrum of compound I-7



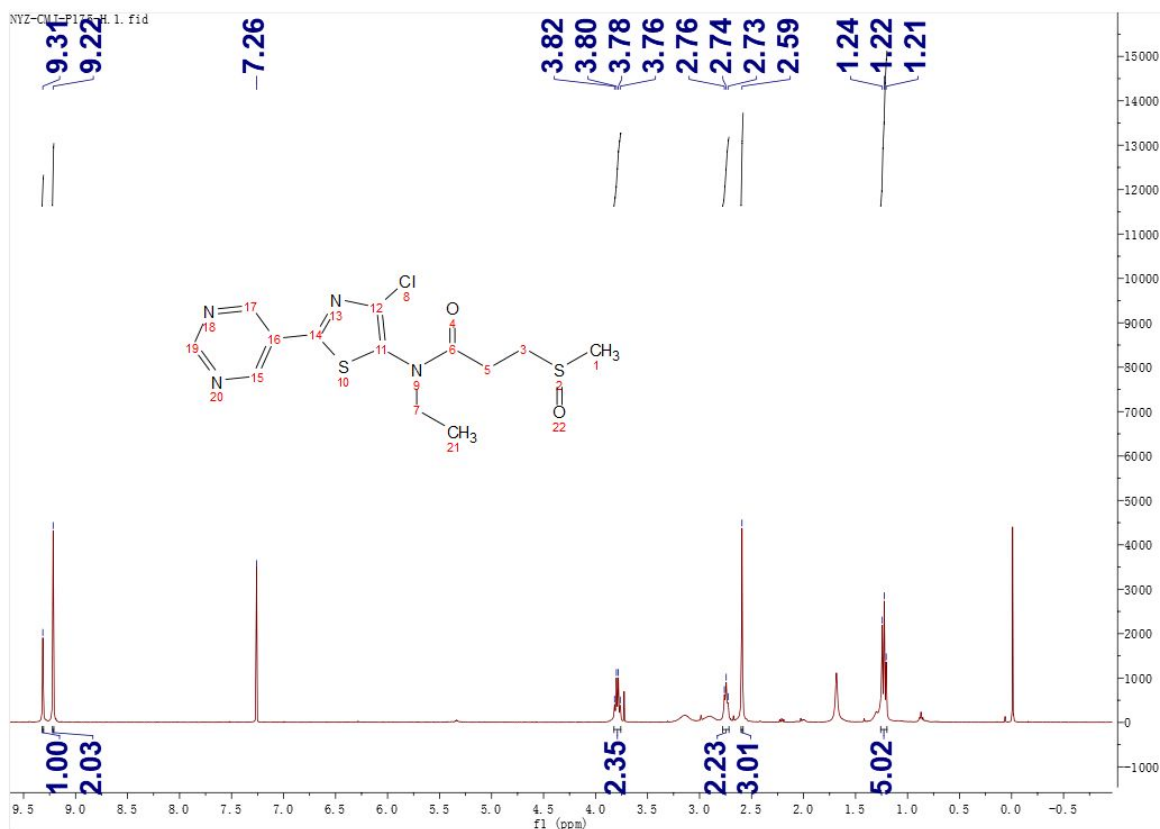
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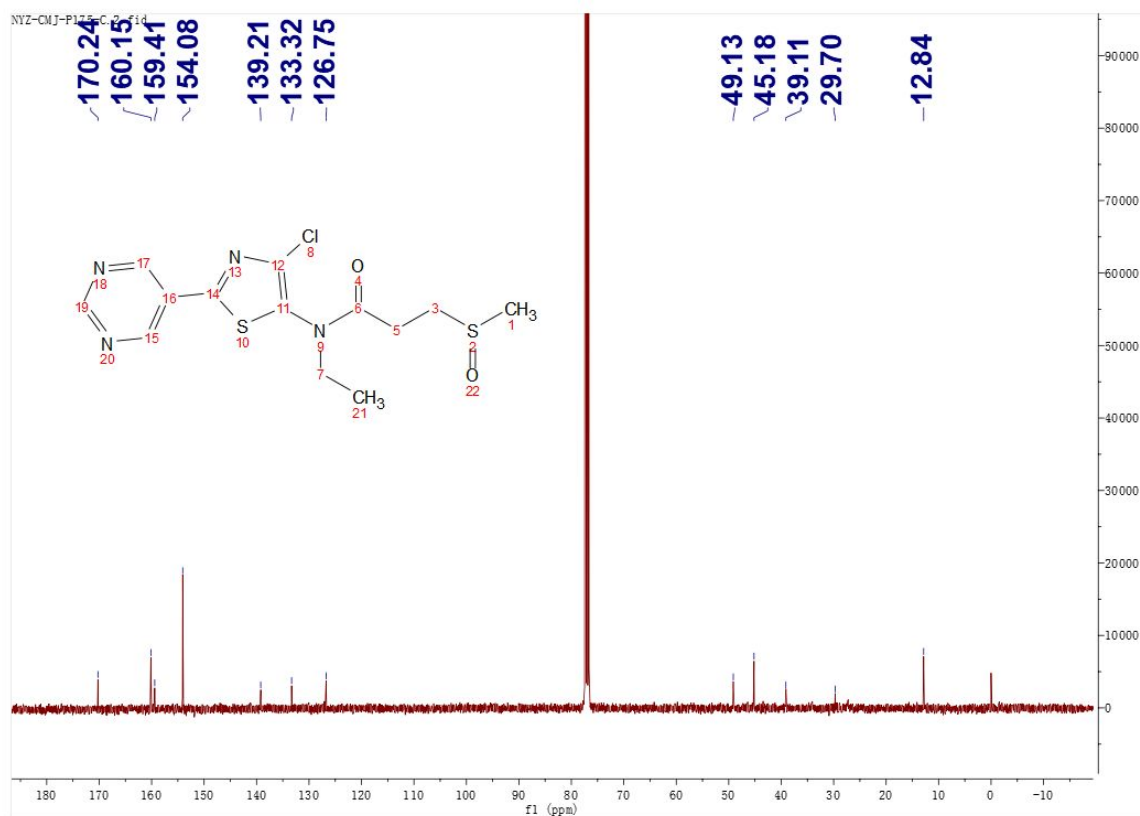
The <sup>1</sup>H NMR spectrum of compound I-8



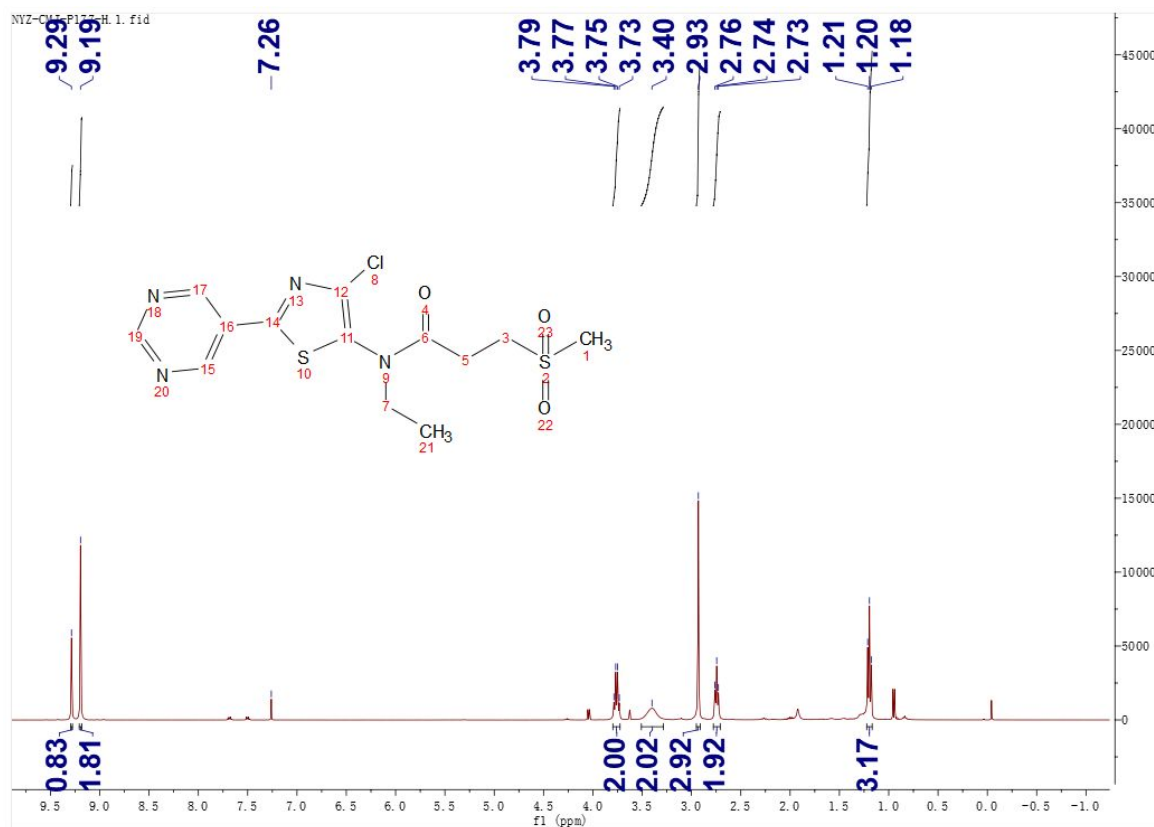
The <sup>13</sup>C NMR spectrum of compound I-8



The <sup>1</sup>H NMR spectrum of compound II-1



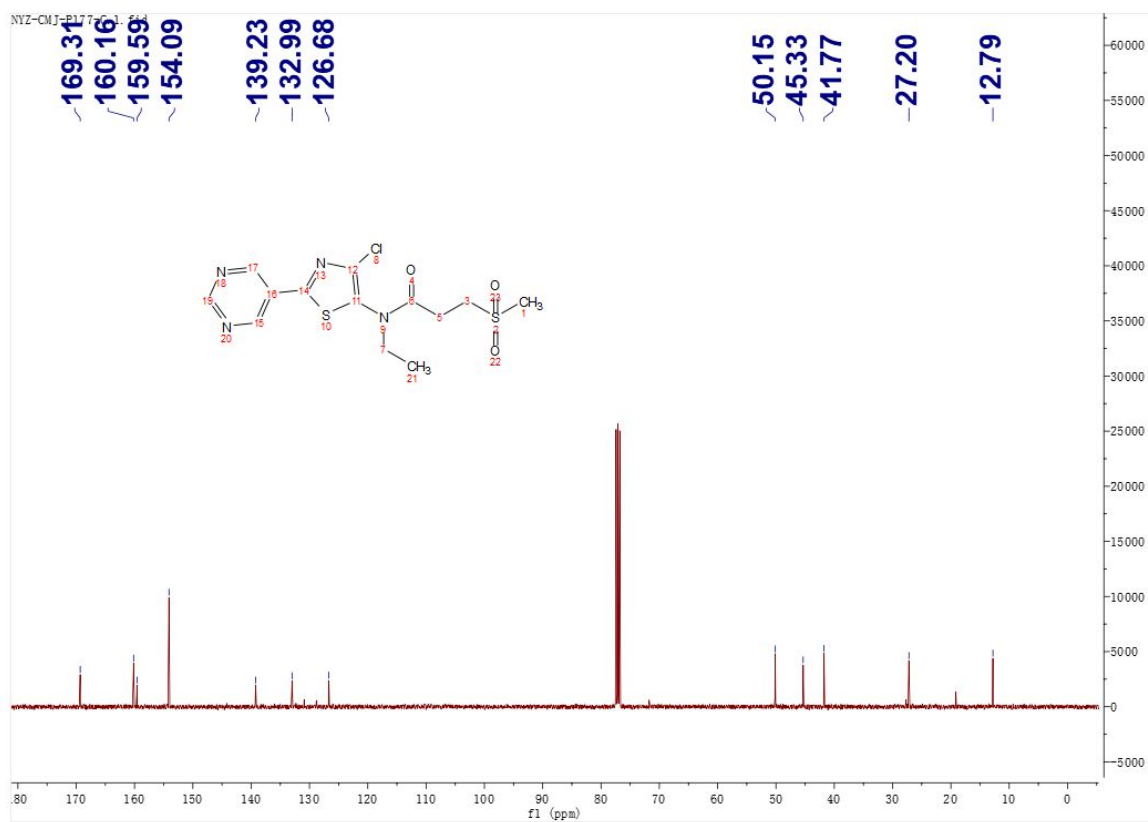
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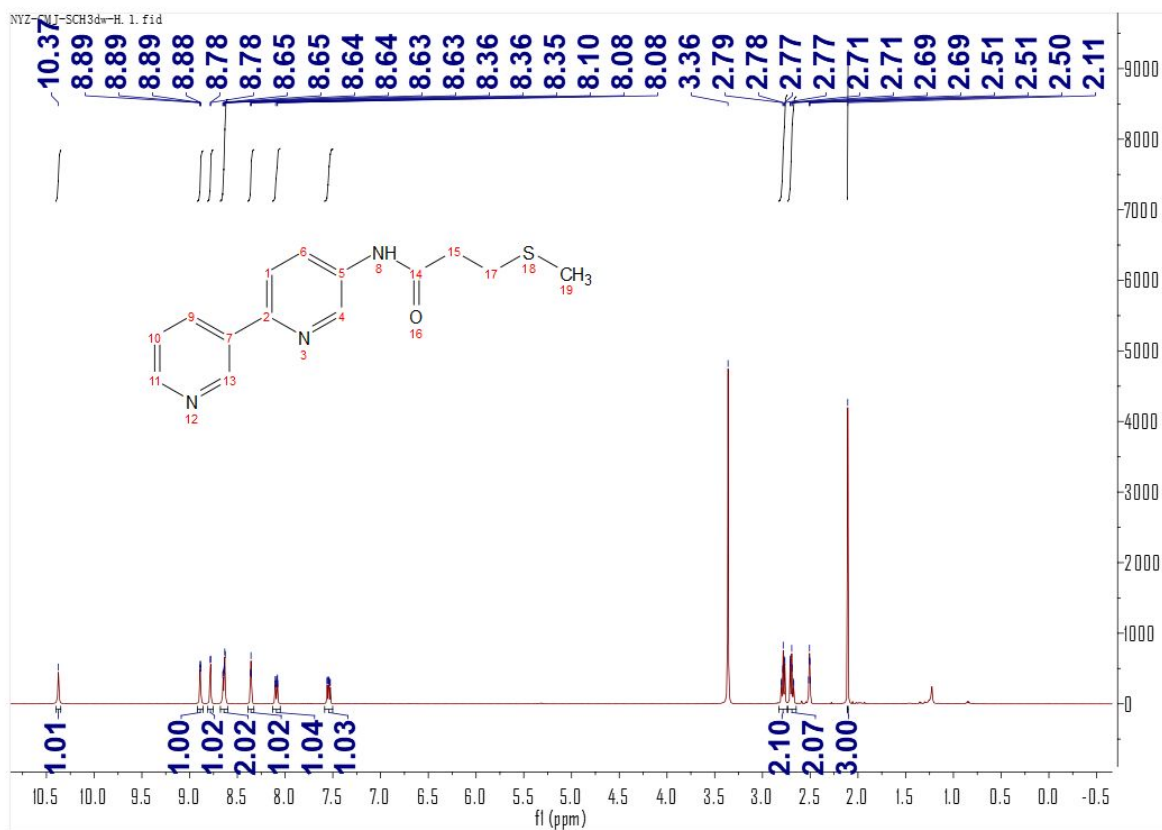
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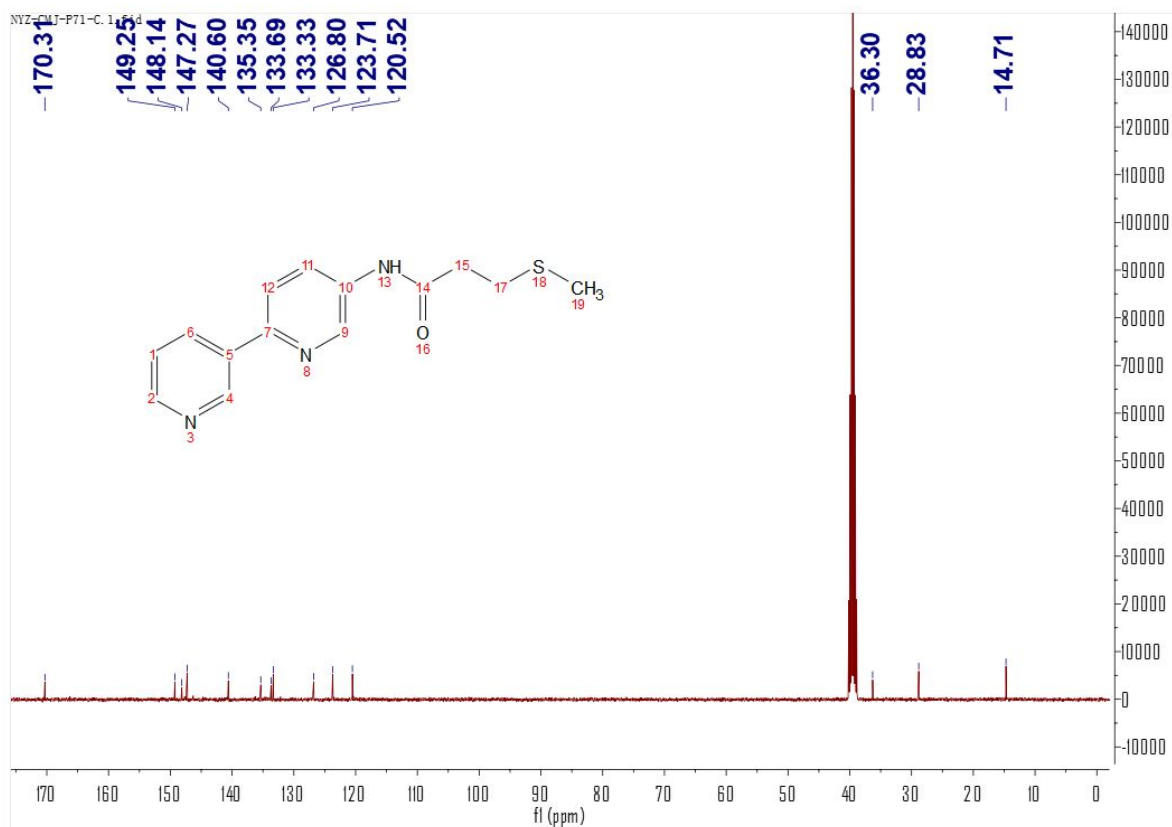
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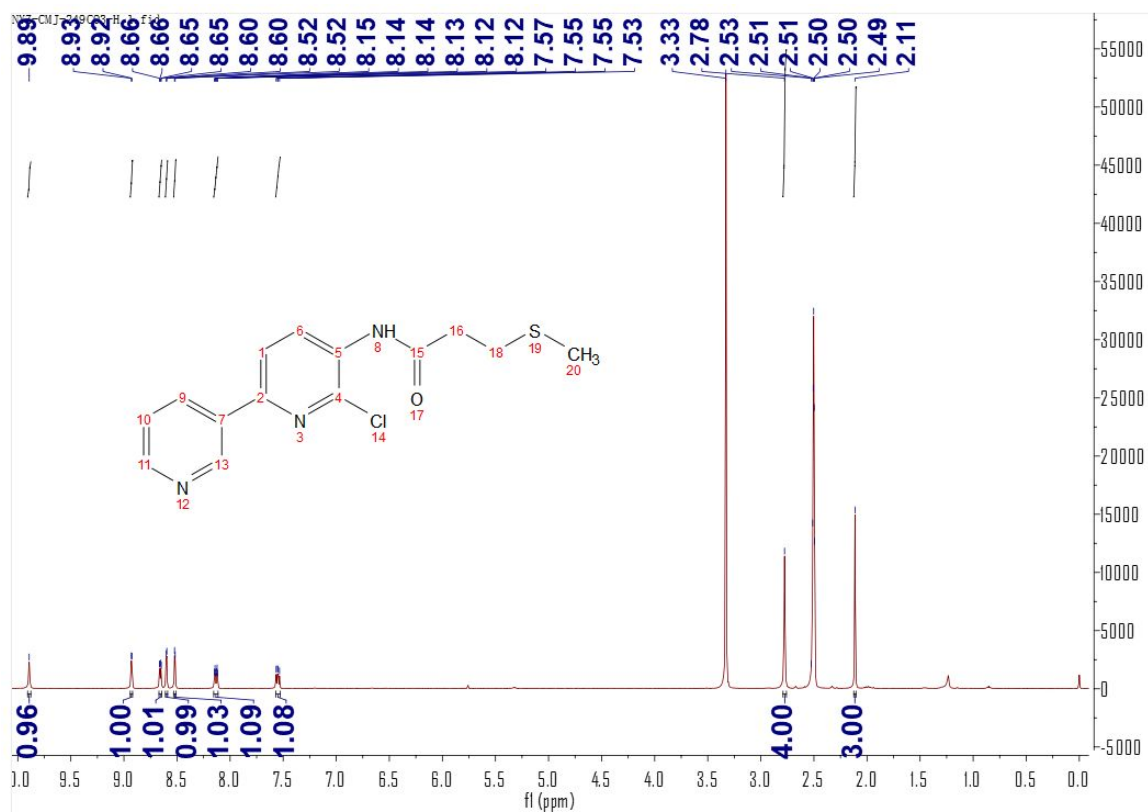
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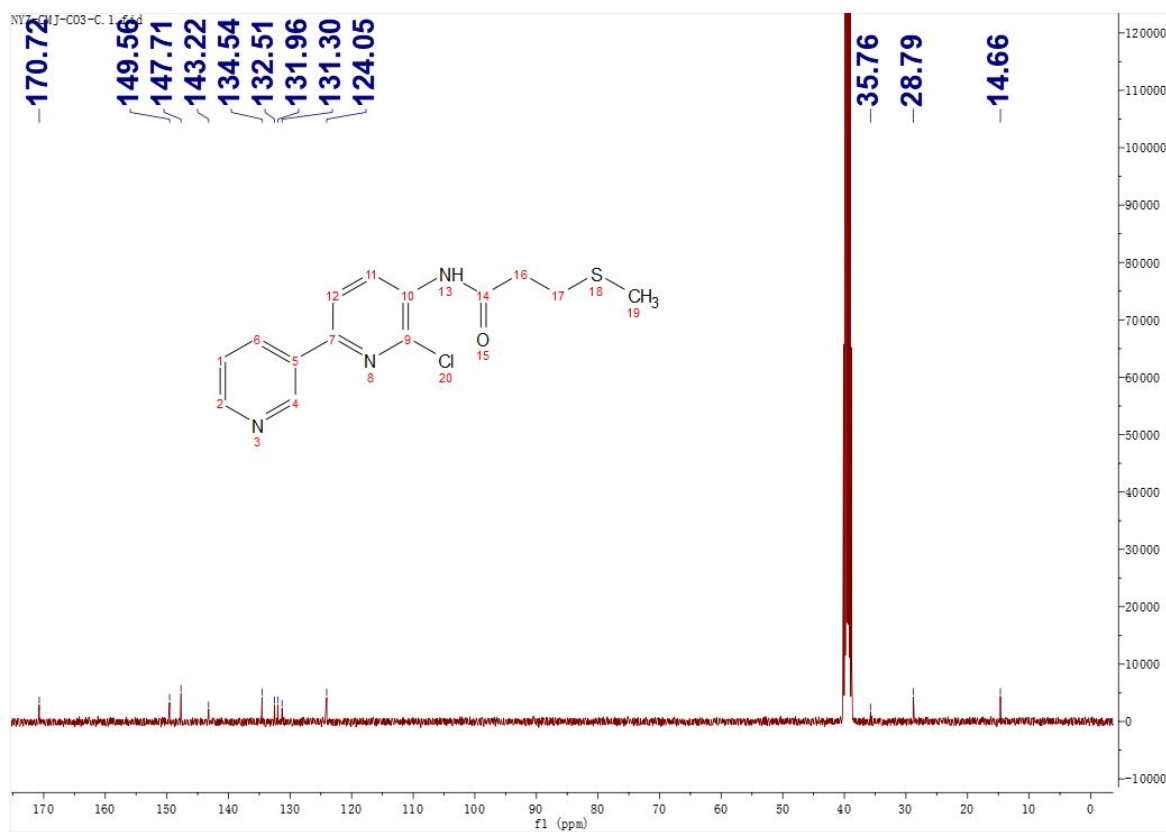
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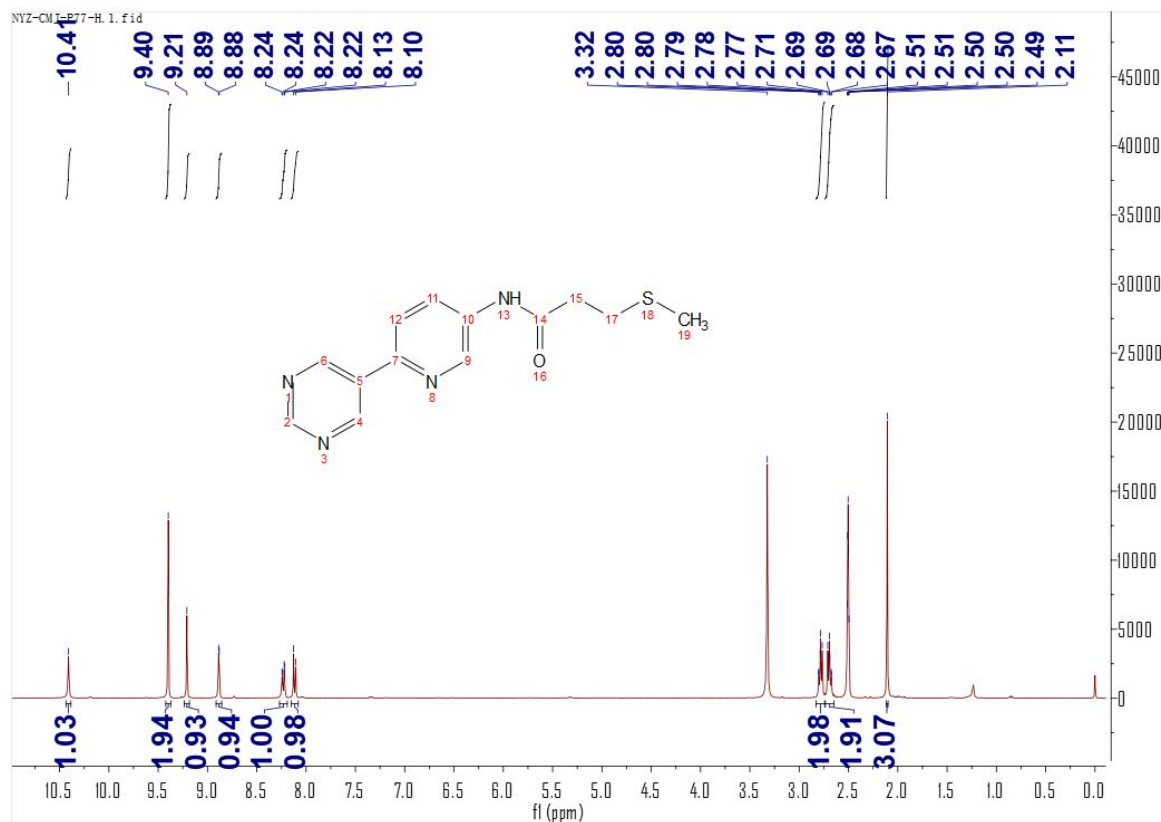
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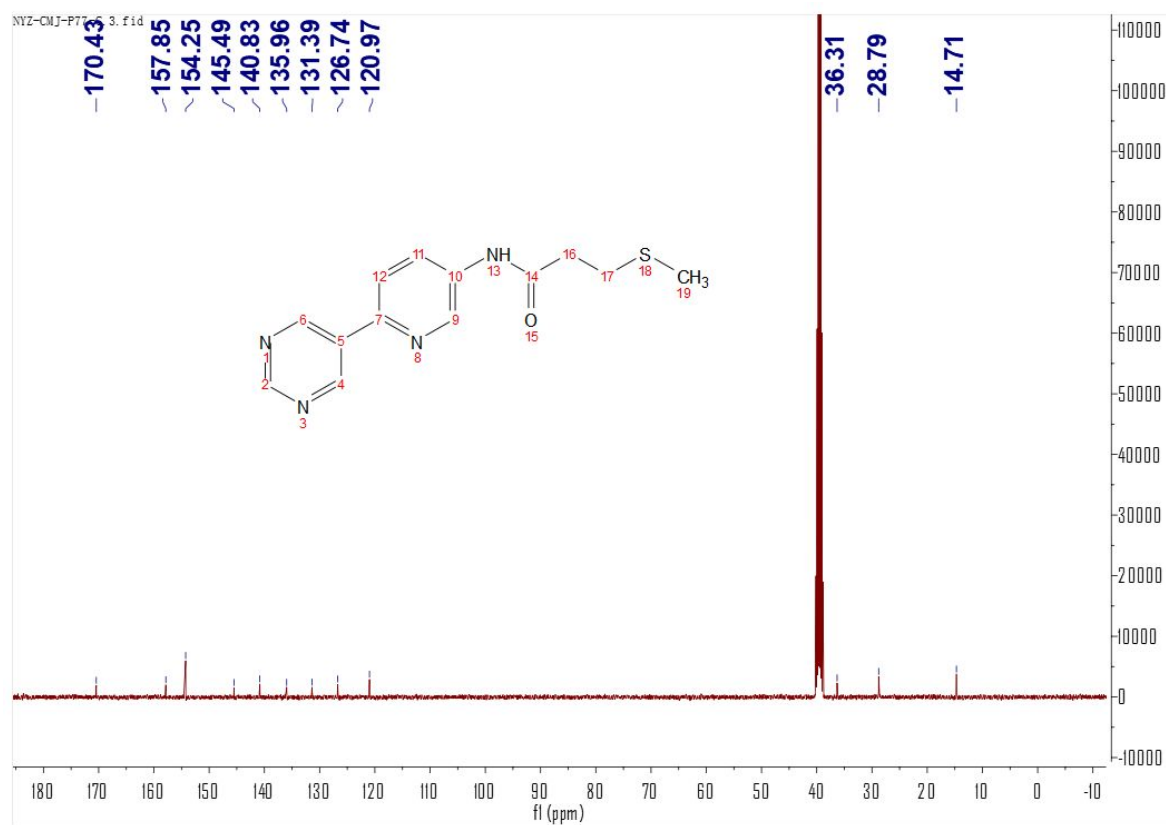
The <sup>1</sup>H NMR spectrum of compound III-2



The <sup>13</sup>C NMR spectrum of compound III-2

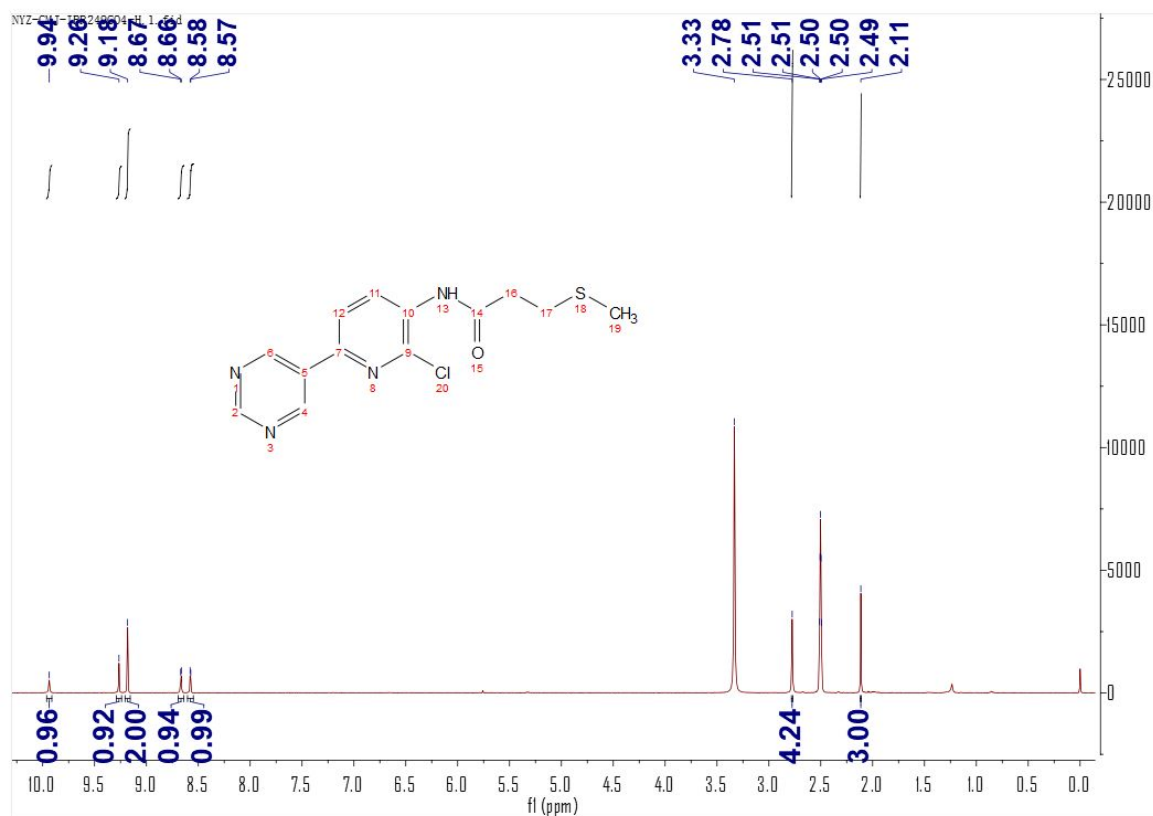


The <sup>1</sup>H NMR spectrum of compound **III-3**

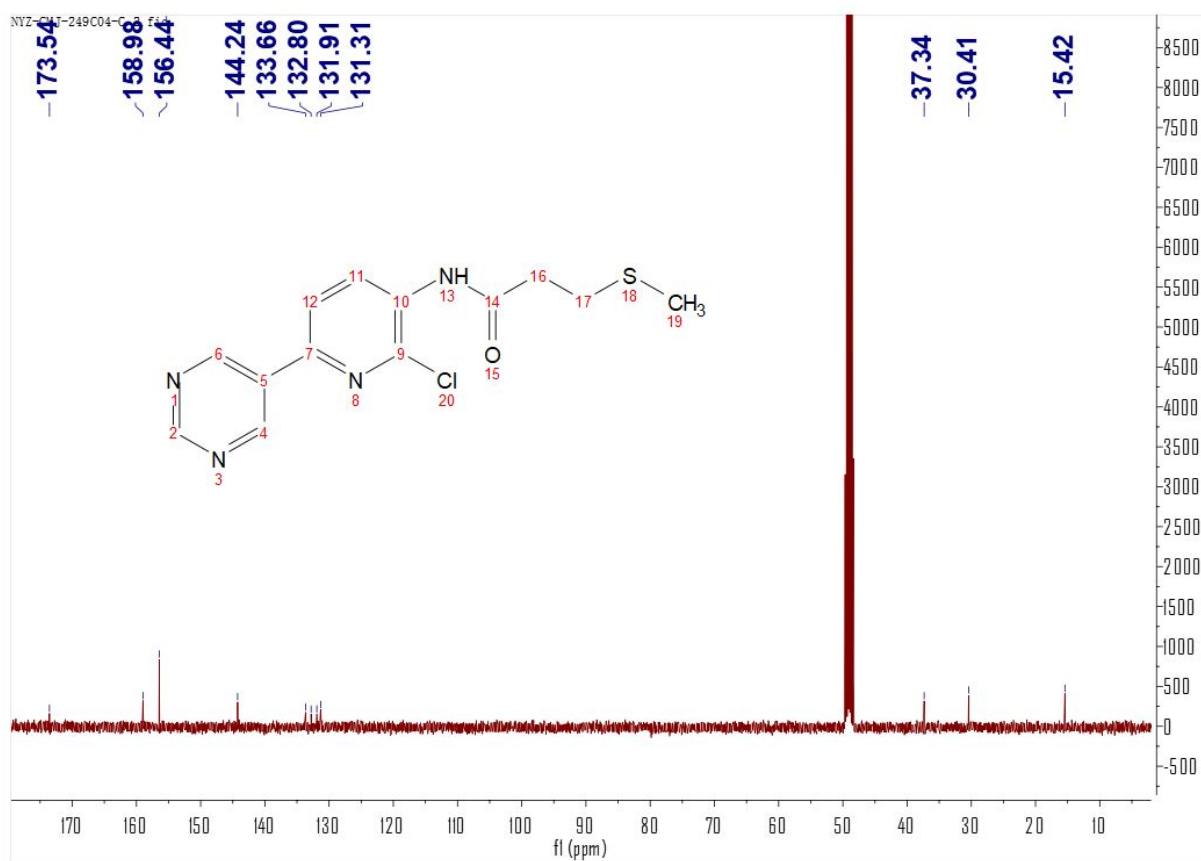


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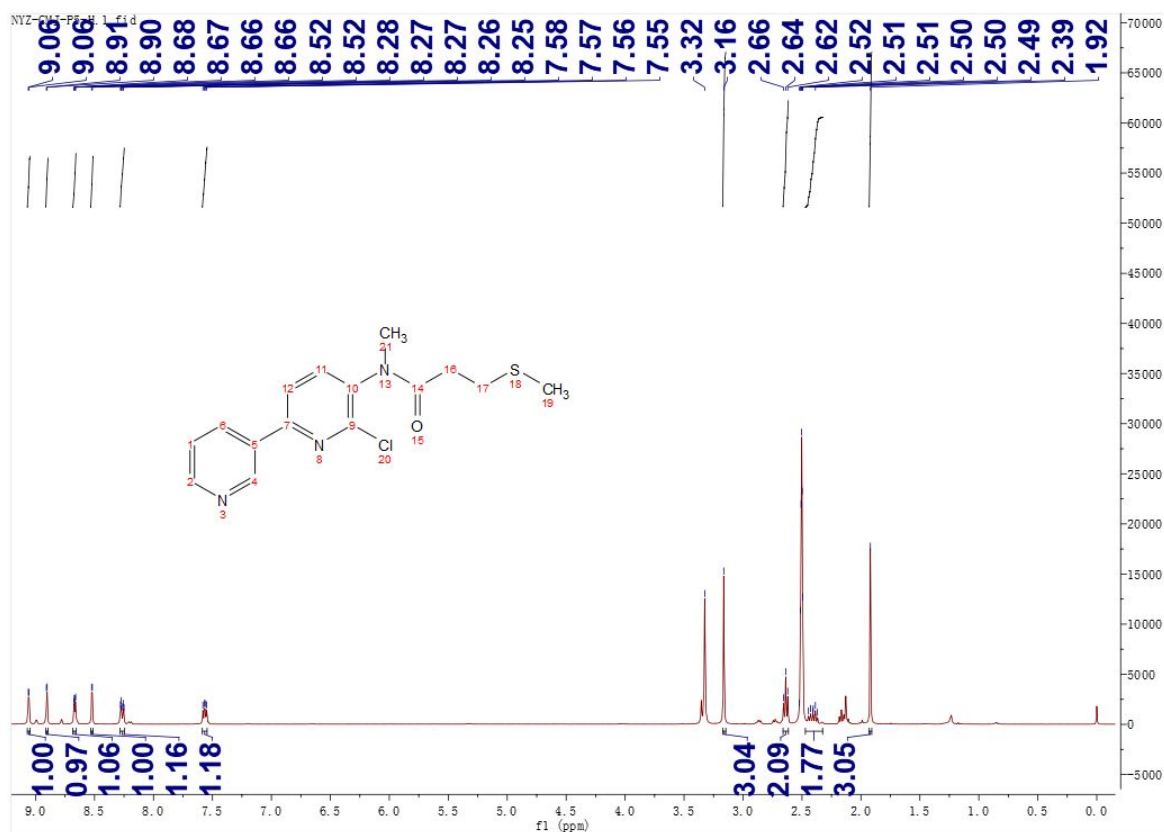


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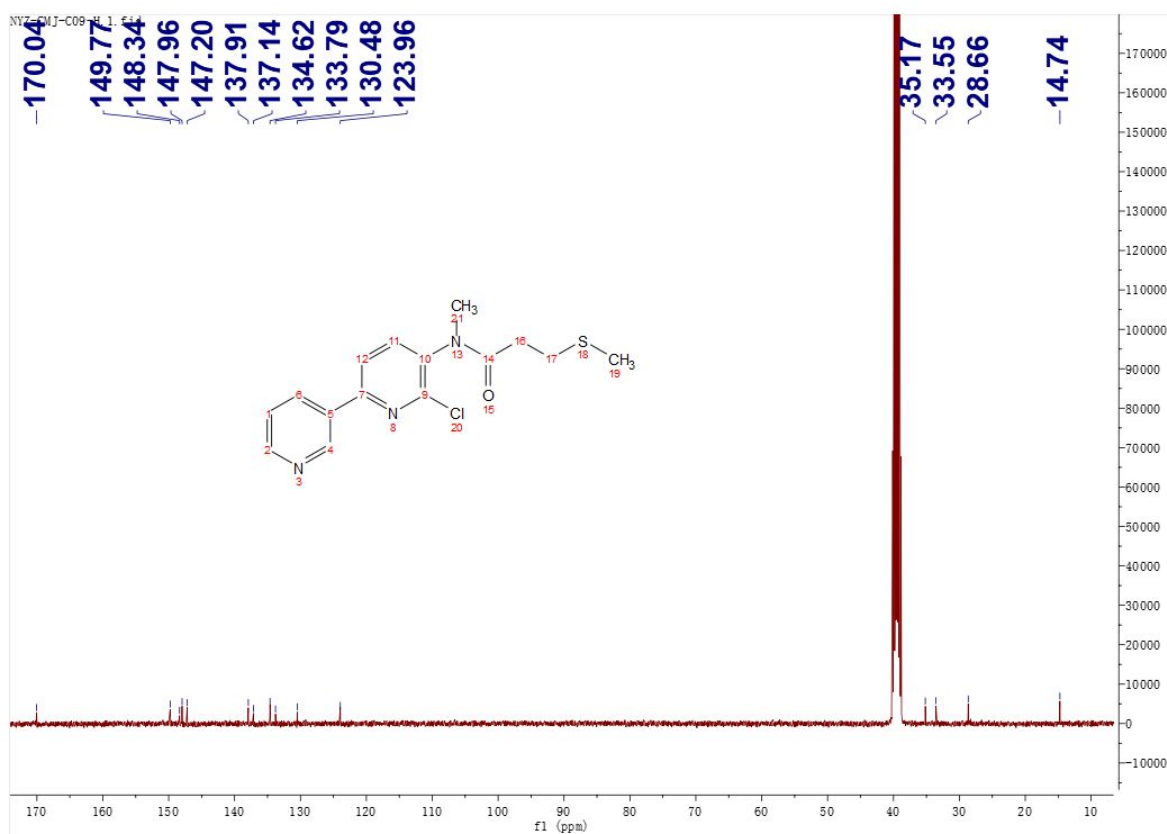


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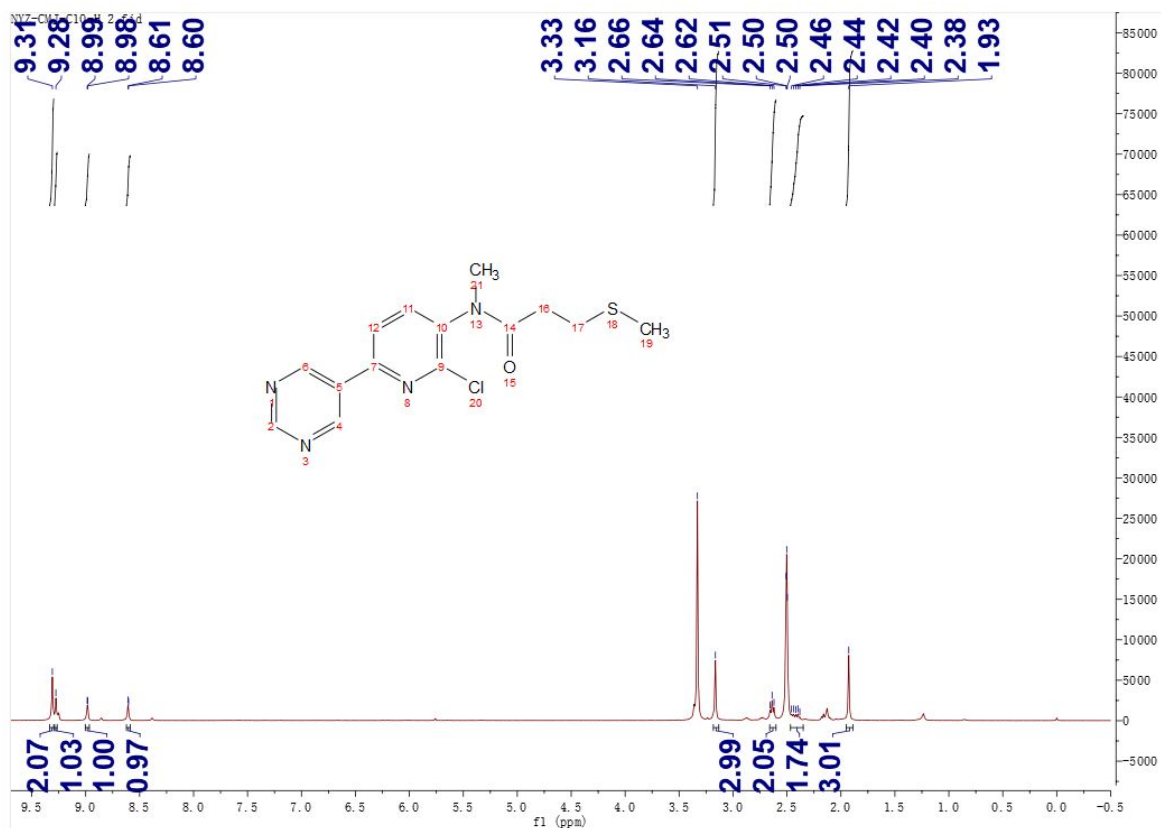




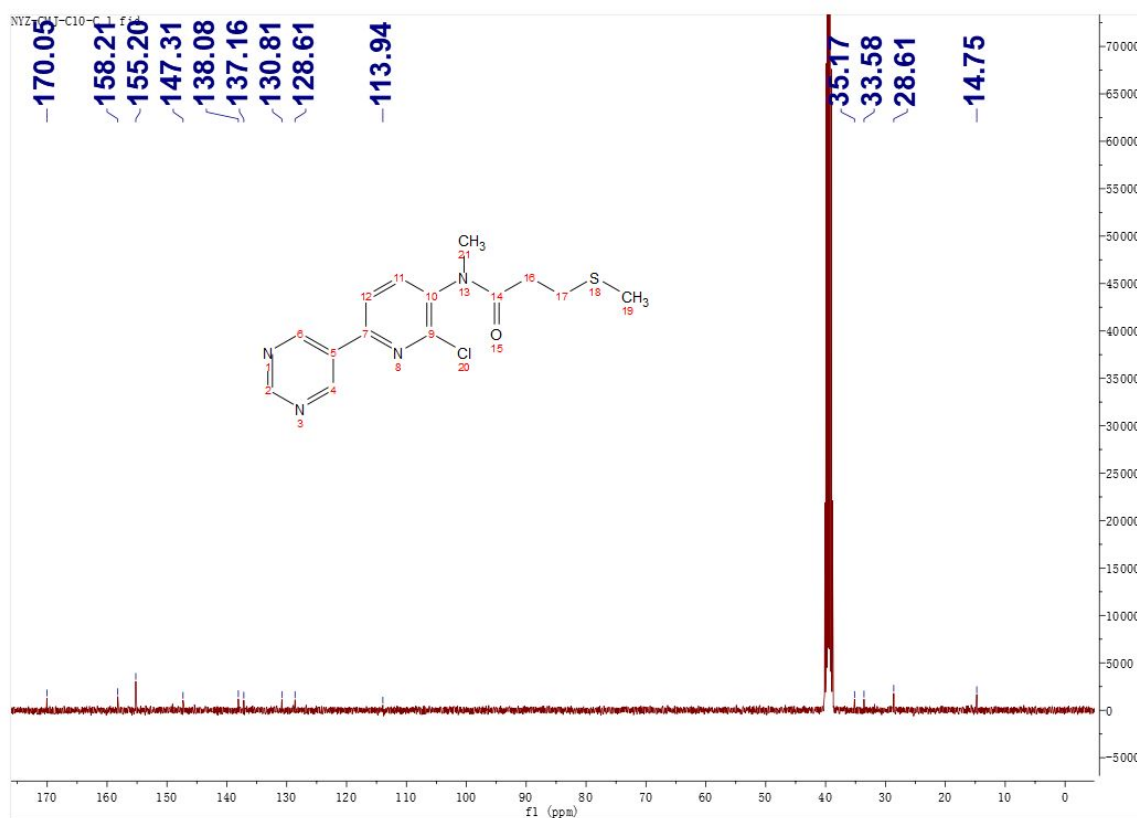
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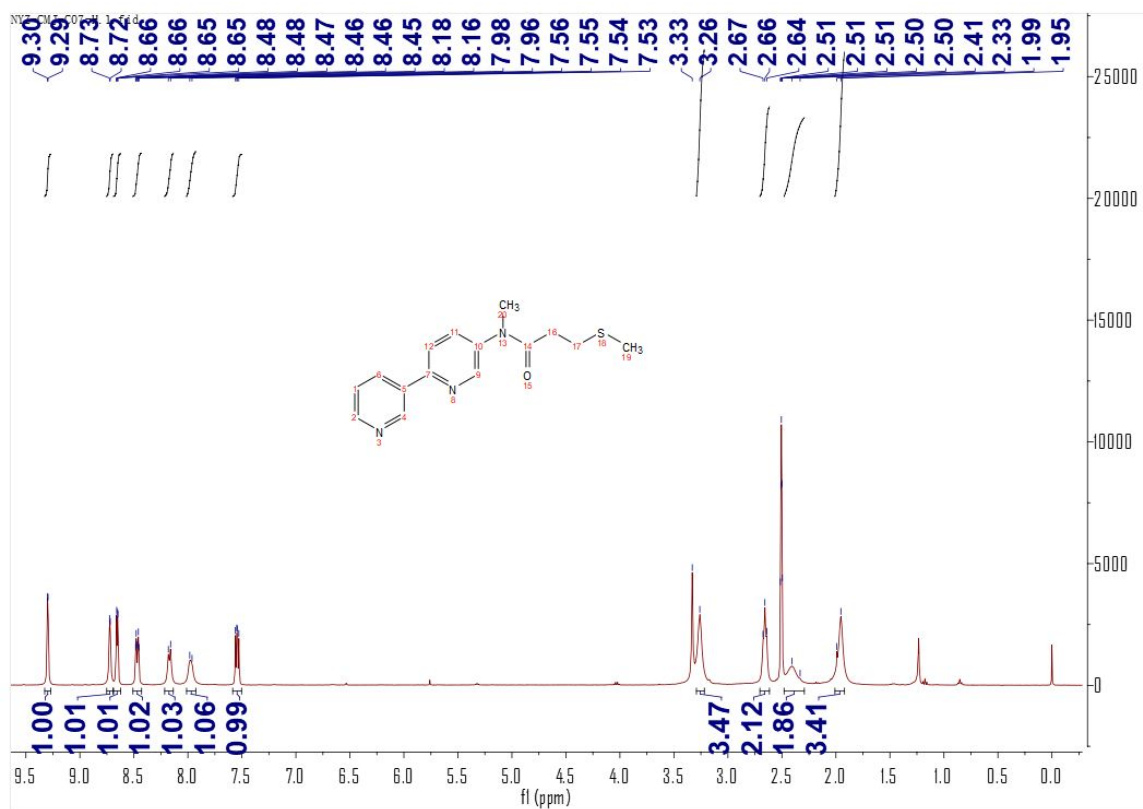
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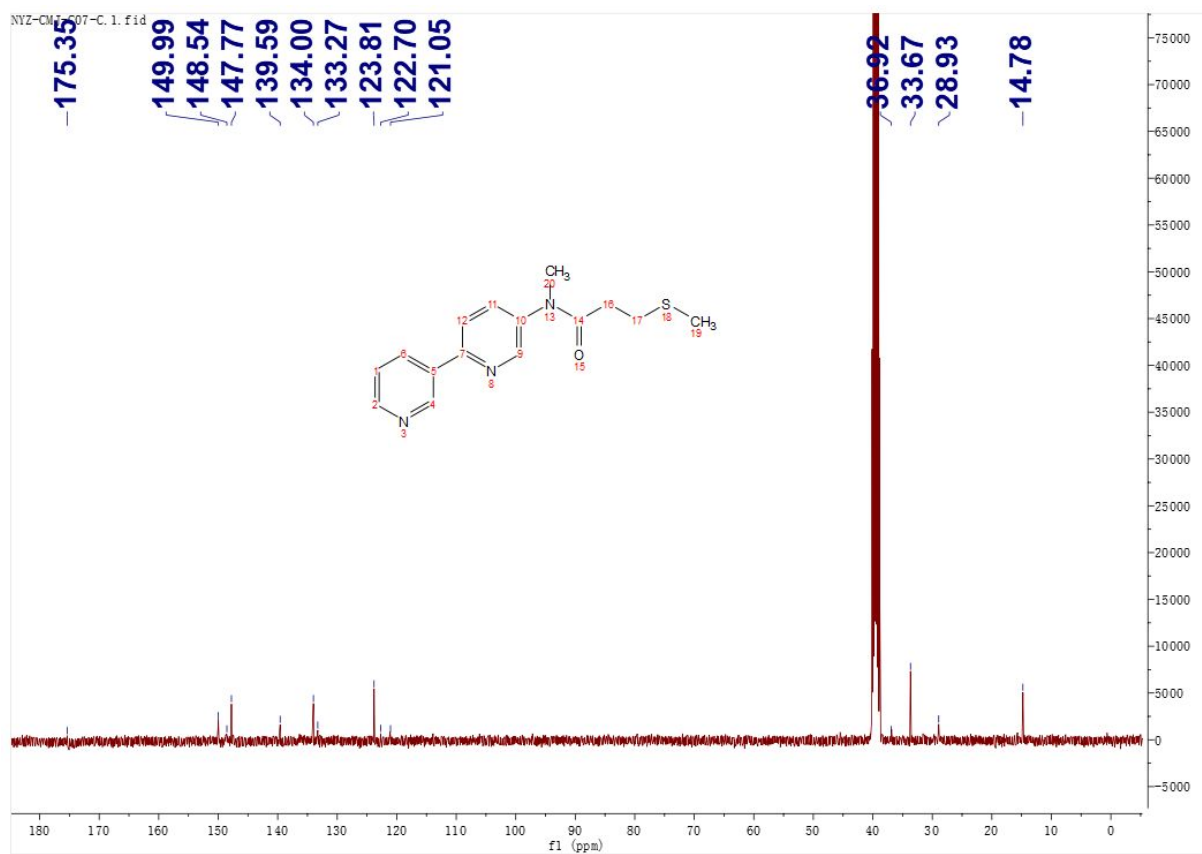
105 The <sup>1</sup>H NMR spectrum of compound III-7



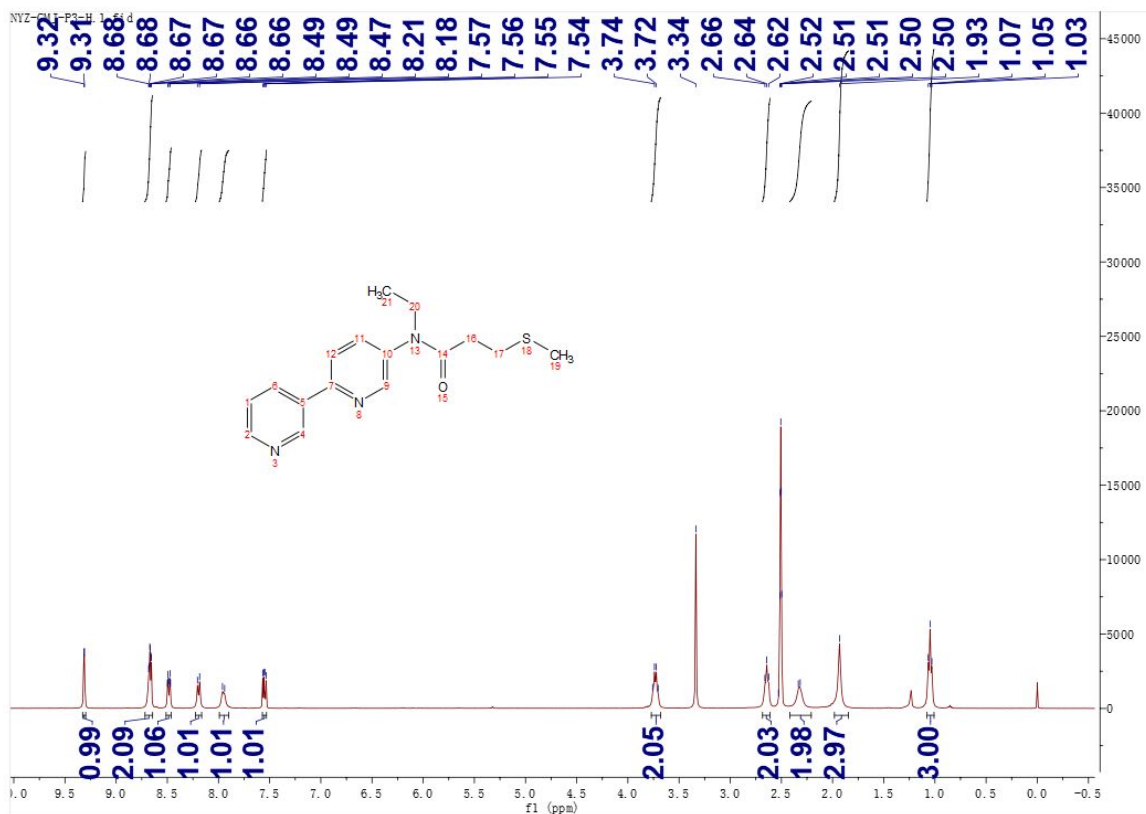
107 The <sup>13</sup>C NMR spectrum of compound III-7



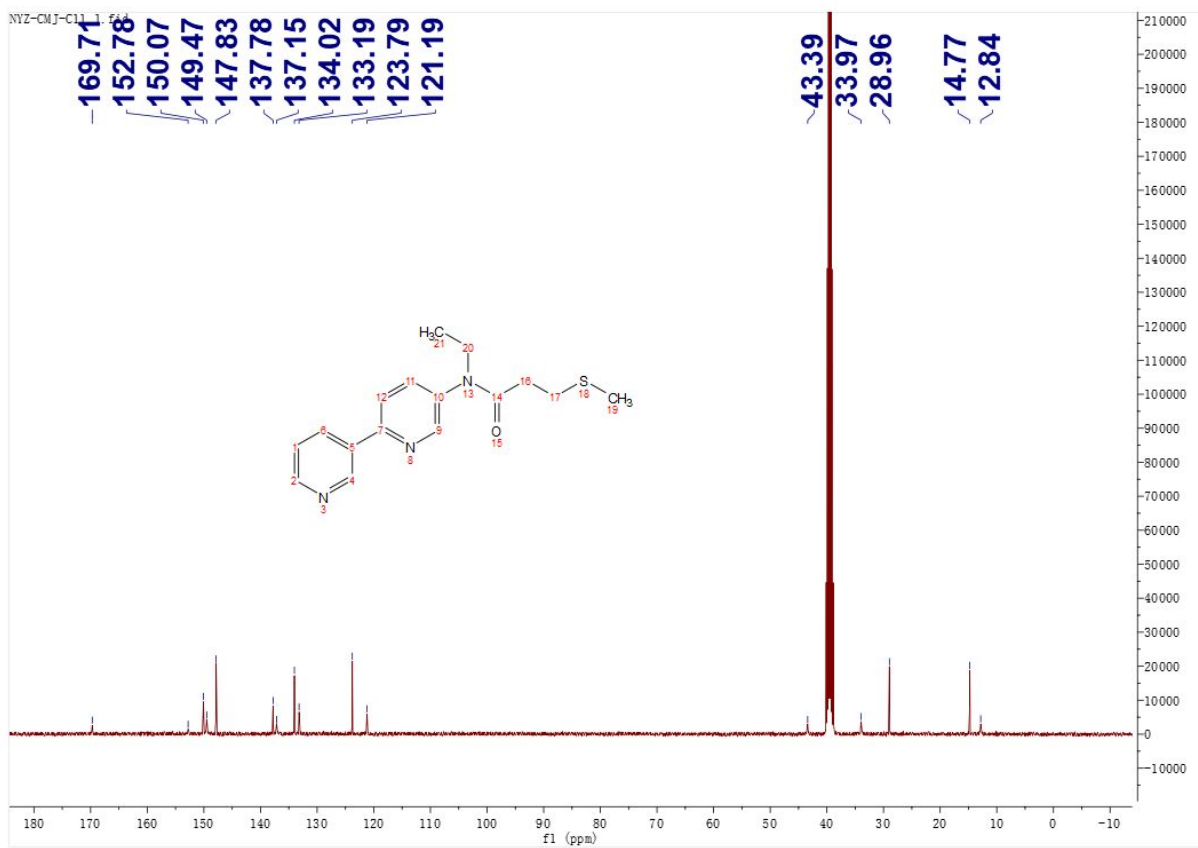
The  $^1\text{H}$  NMR spectrum of compound III-9



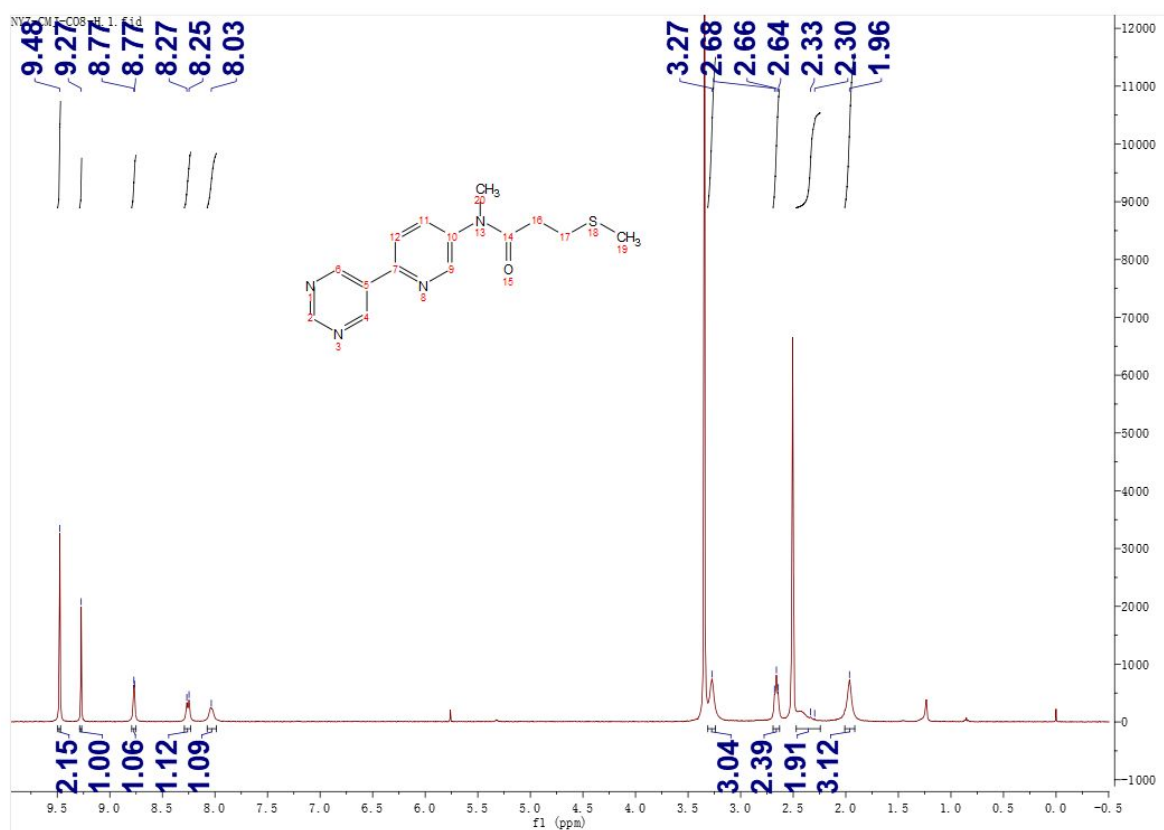
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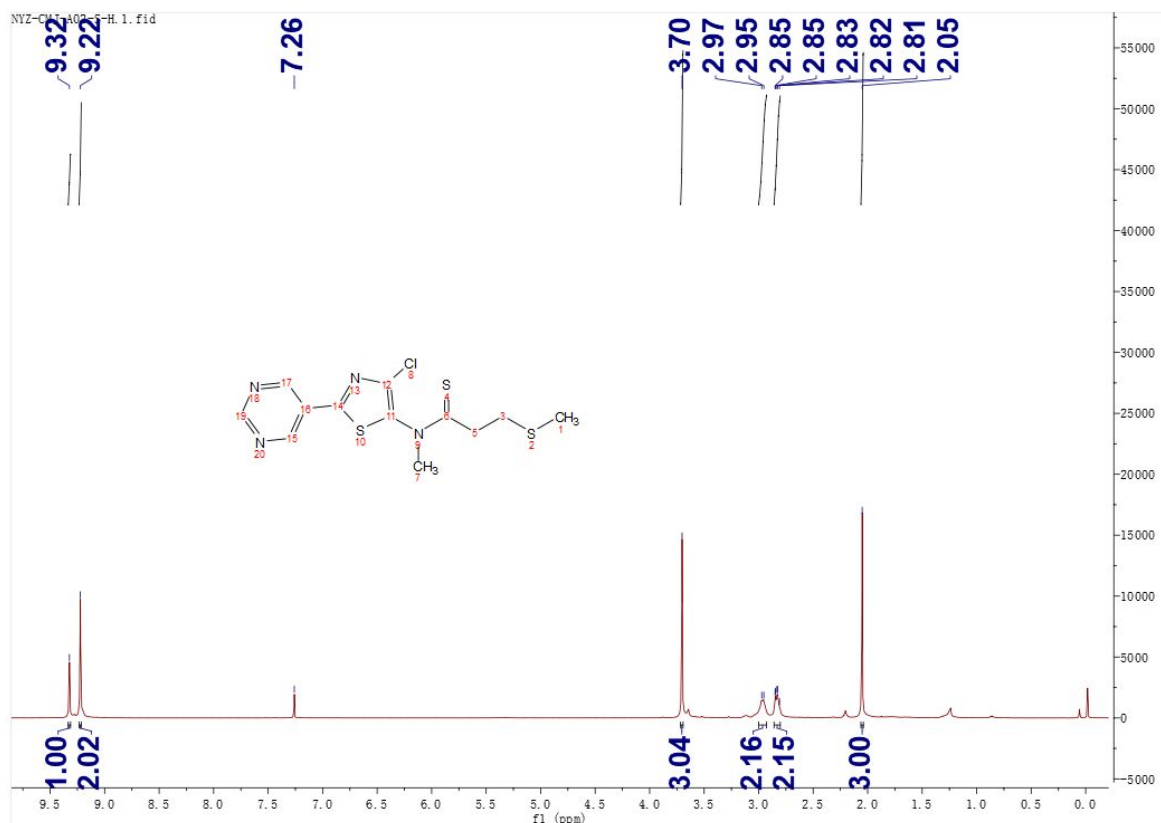
The <sup>1</sup>H NMR spectrum of compound **III-10**



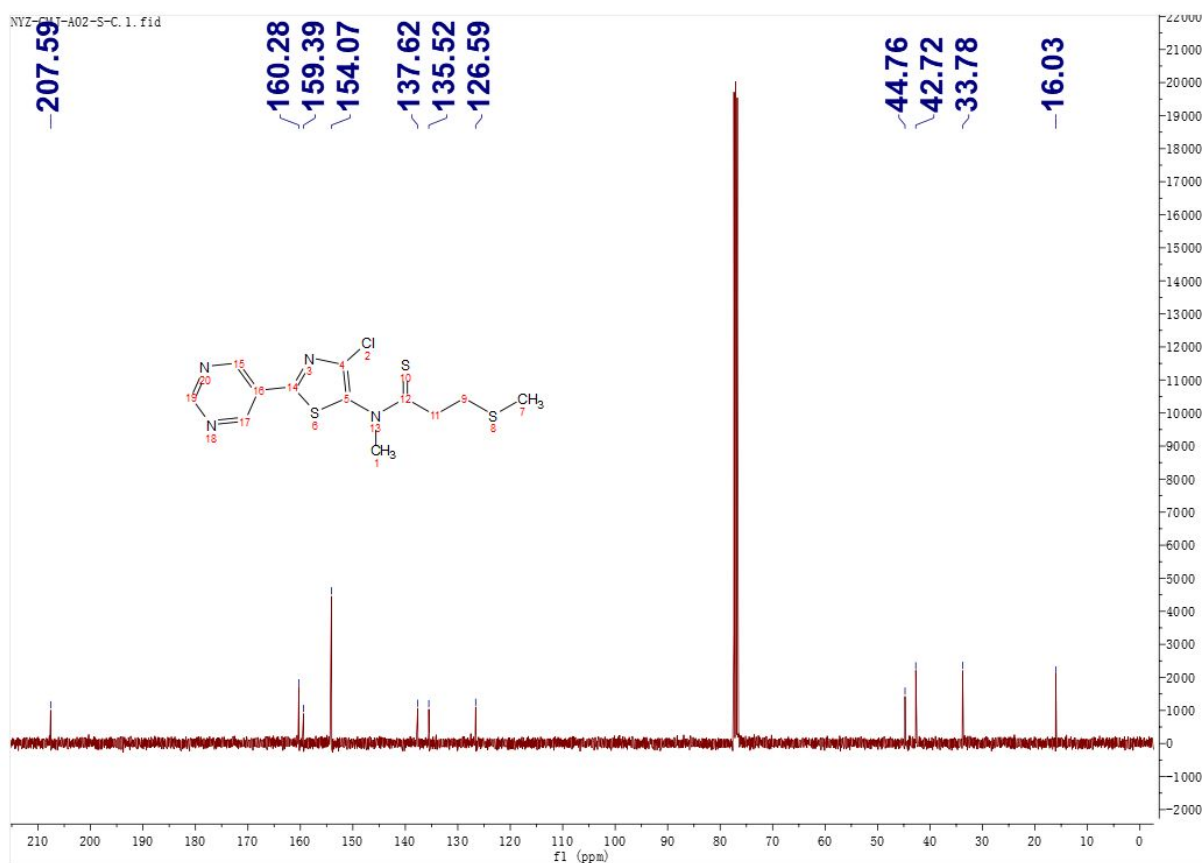
The <sup>13</sup>C NMR spectrum of compound **III-10**



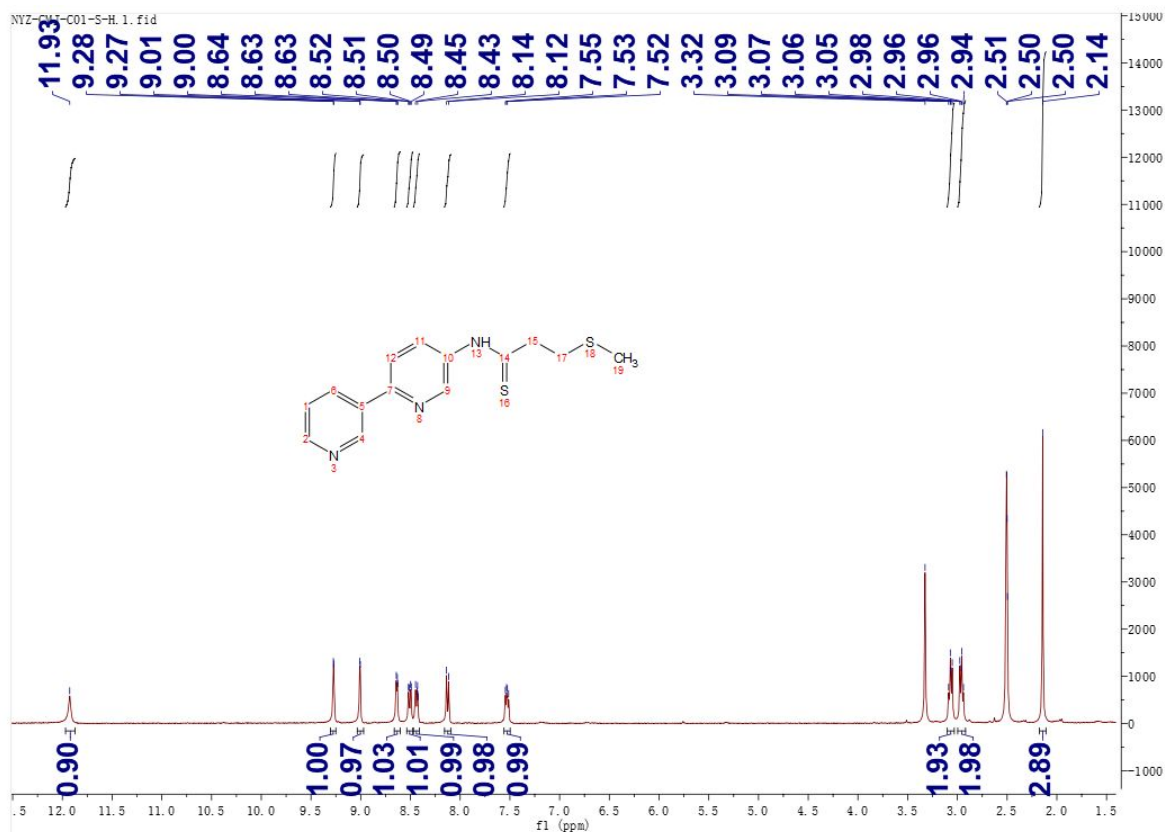
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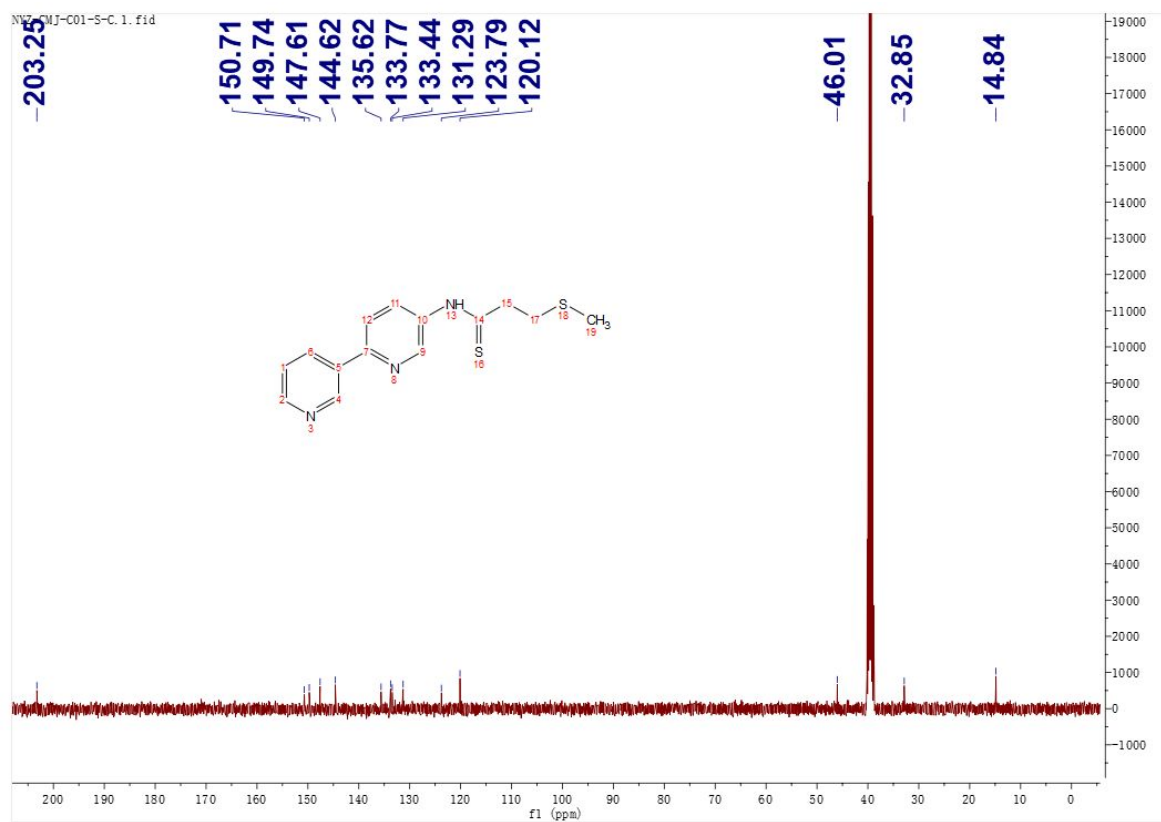
The  $^1\text{H}$  NMR spectrum of compound IV-1



The  $^{13}\text{C}$  NMR spectrum of compound IV-1

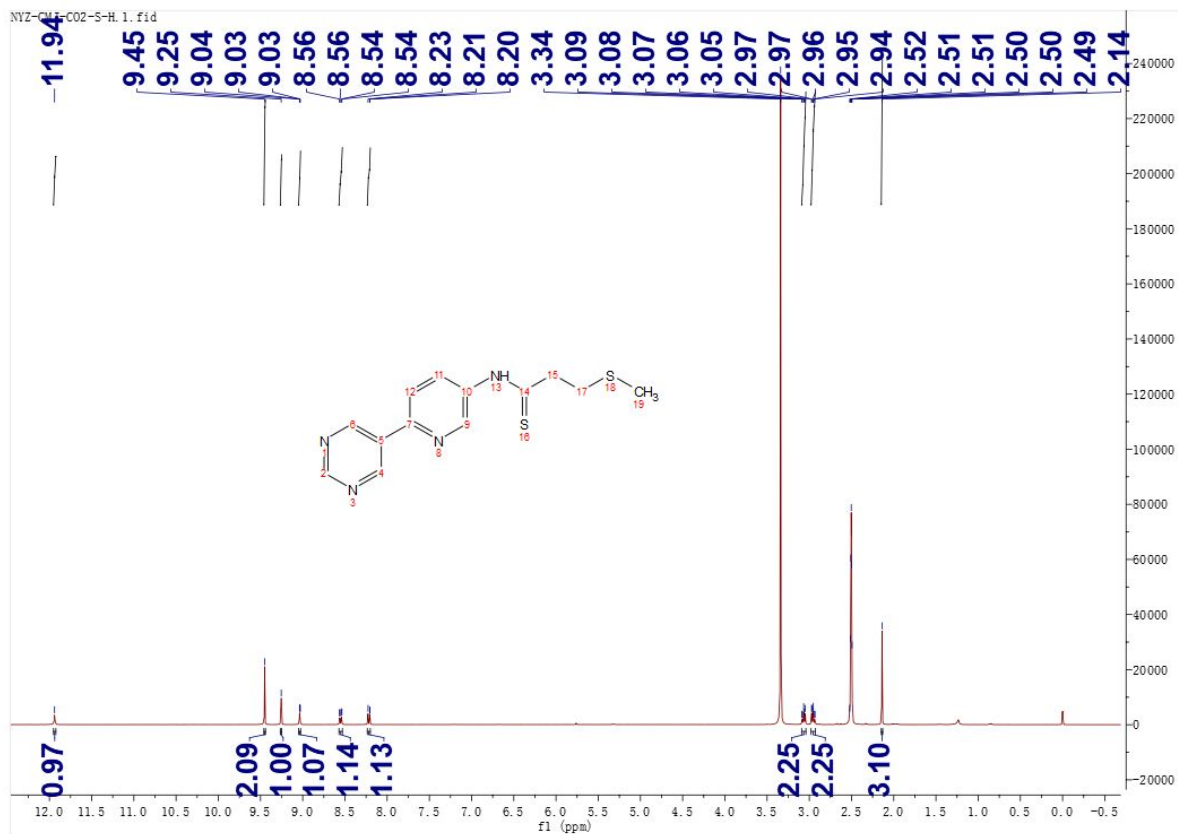


The  $^1\text{H}$  NMR spectrum of compound IV-2

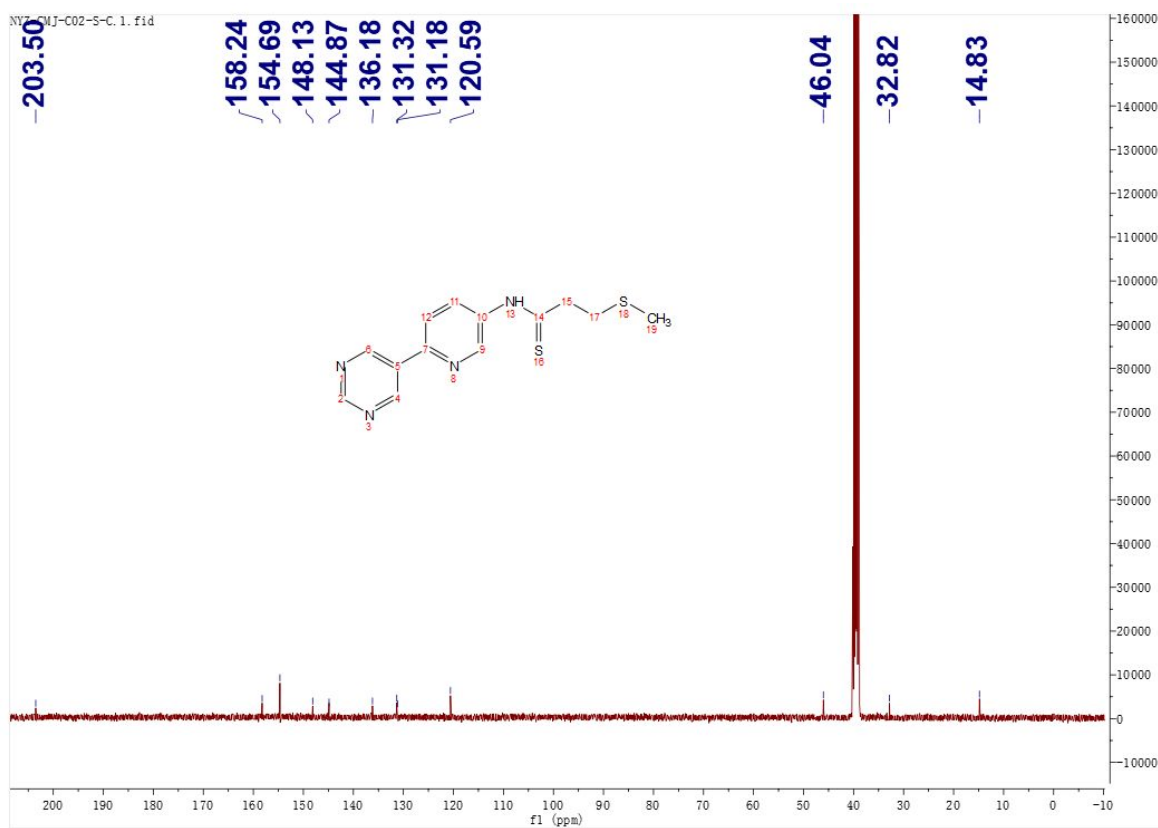


The  $^{13}\text{C}$  NMR spectrum of compound IV-2



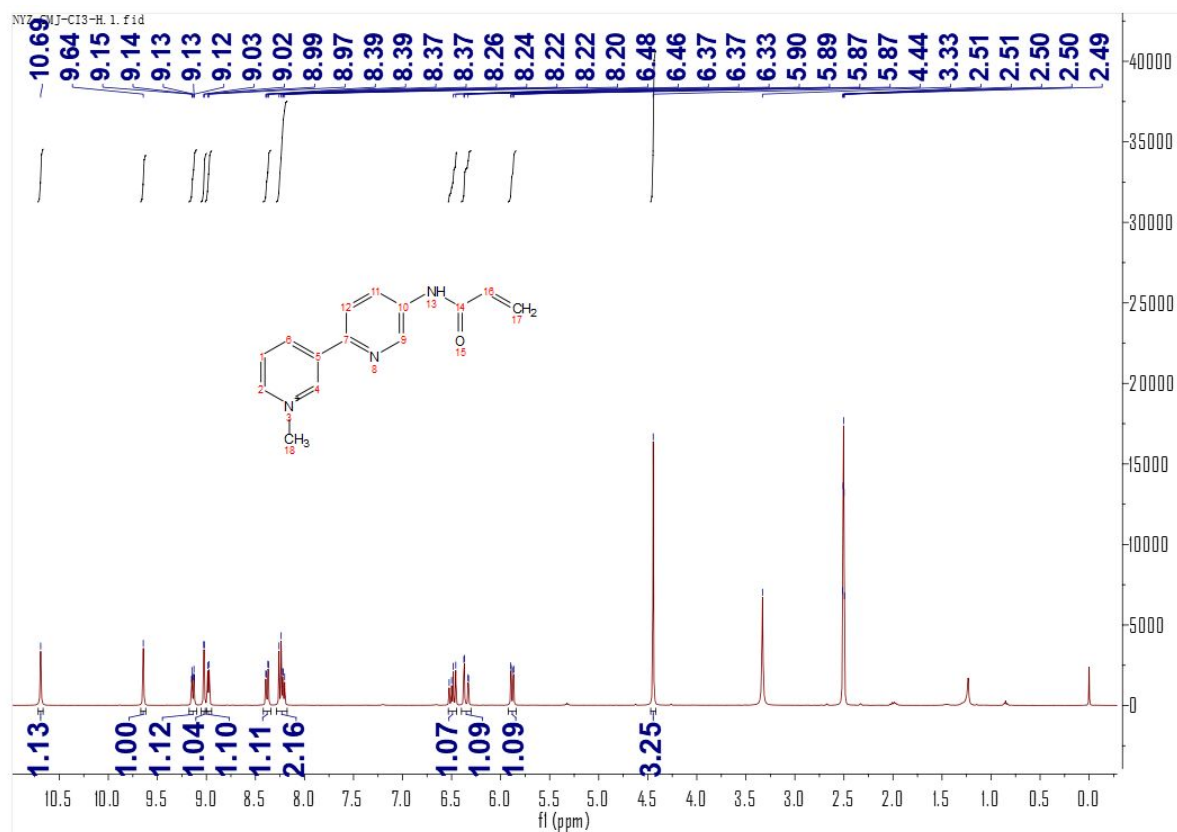


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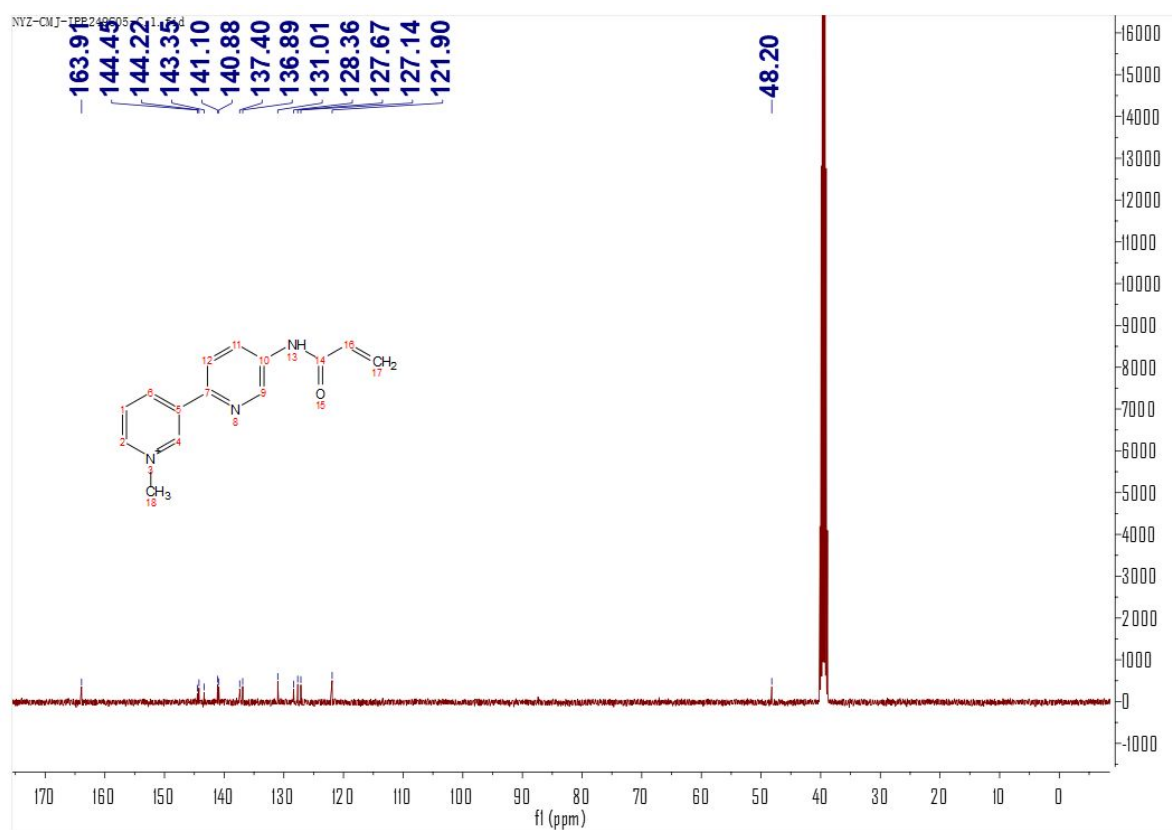


The  $^{13}\text{C}$  NMR spectrum of compound IV-3





The  $^1\text{H}$  NMR spectrum of compound V-1



The  $^{13}\text{C}$  NMR spectrum of compound V-1