

Supporting Information

Design and Synthesis of Novel Pyrazolo[4,3-*d*]pyrimidines as Potential Therapeutic Agents for Acute Lung Injury

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PART 1. General procedure for the synthesis of intermediates C1~C4

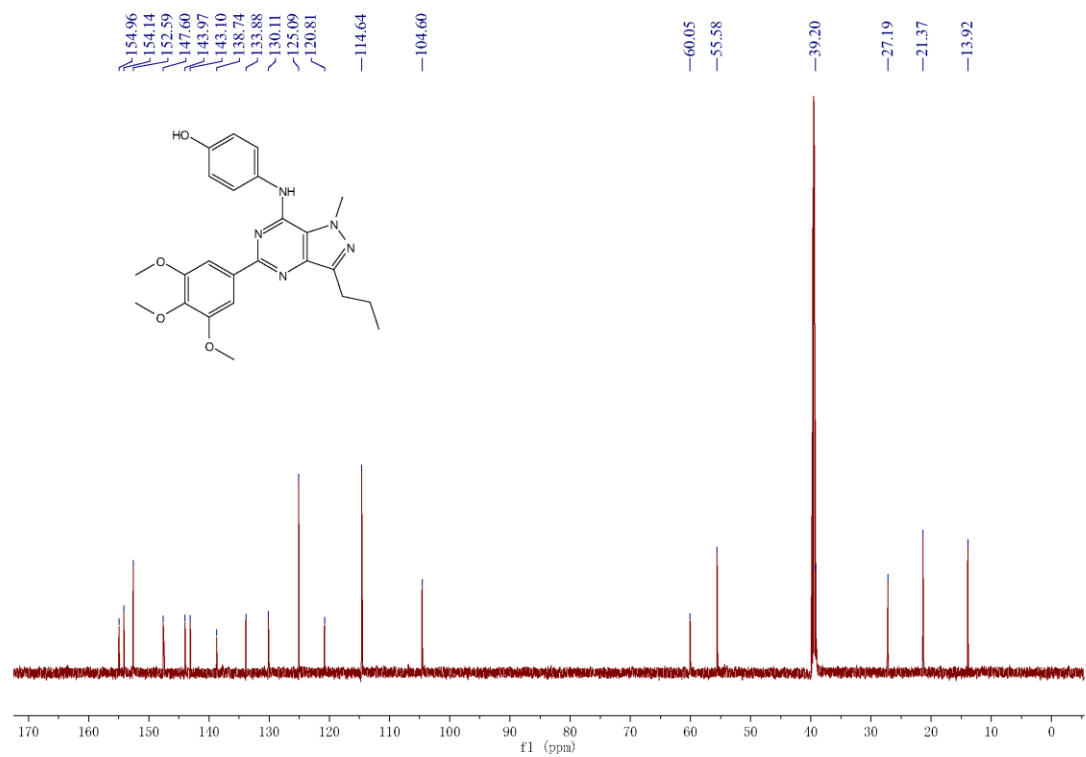
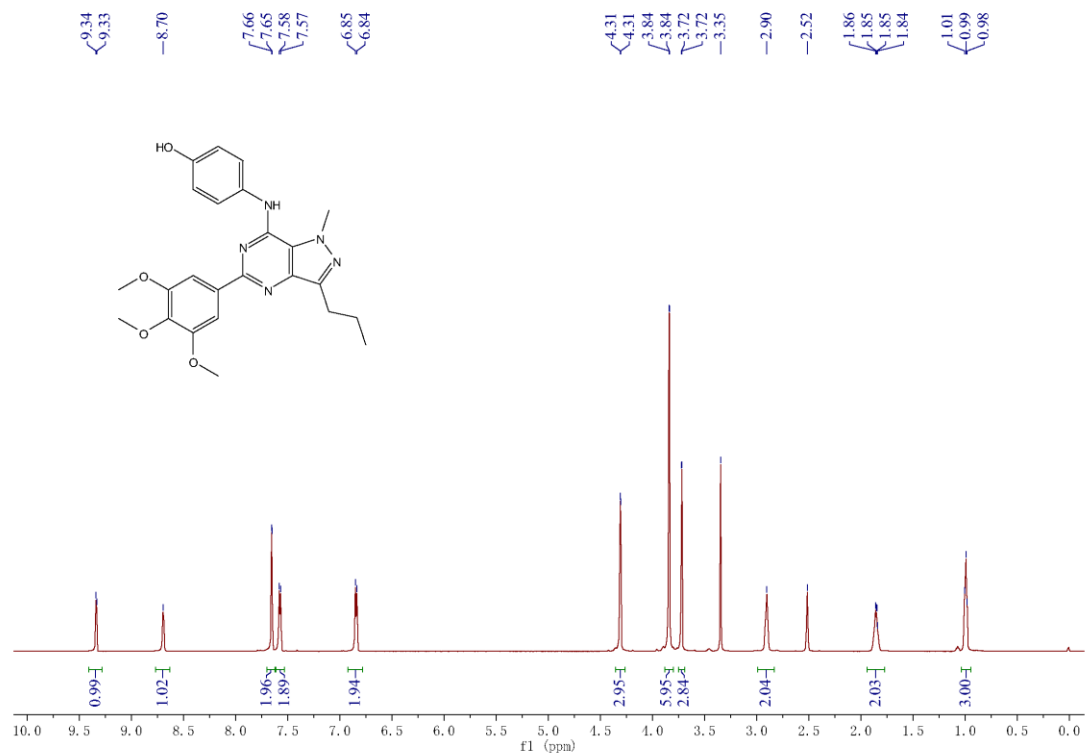
3,4,5-trimethoxybenzoic acid (1.06 g, 5 mmol), EDCI (1.438 g, 7.5 mmol), HOBT (1.013 g, 7.5 mmol), 4-amino-1-methyl-3-propyl-5-pyrazolecarboxamide (**SM**) (0.922 g, 5 mmol) and TEA (0.94 mL, 0.75 mmol) were dissolved in dry DCM (20 mL), and the mixture was stirred at room temperature for 18~20 h. DCM was removed under reduced pressure after the reaction was completed. Residue and sufficient water are mixed at room temperature, the intermediate **A1** was obtained as white solid by suction filtration. And intermediates **A2~A4** were obtained using the same procedure as intermediate **A1**.

To a solution of the sodium ethoxide (0.340 g, 5 mmol) was dissolved in ethanol (20 mL) and added intermediate **A1** (1.88 g, 5 mmol), and the reaction mixture were stirred at refluxed for 8~12 h. The resulting solution was concentrated under reduced pressure and the residue was acidified with hydrochloric acid (15%, v/v) to pH 7. The intermediate **B1** was obtained as white solid by suction filtration. And intermediate **B2~B4** were obtained using the same procedure as intermediate **B1**.

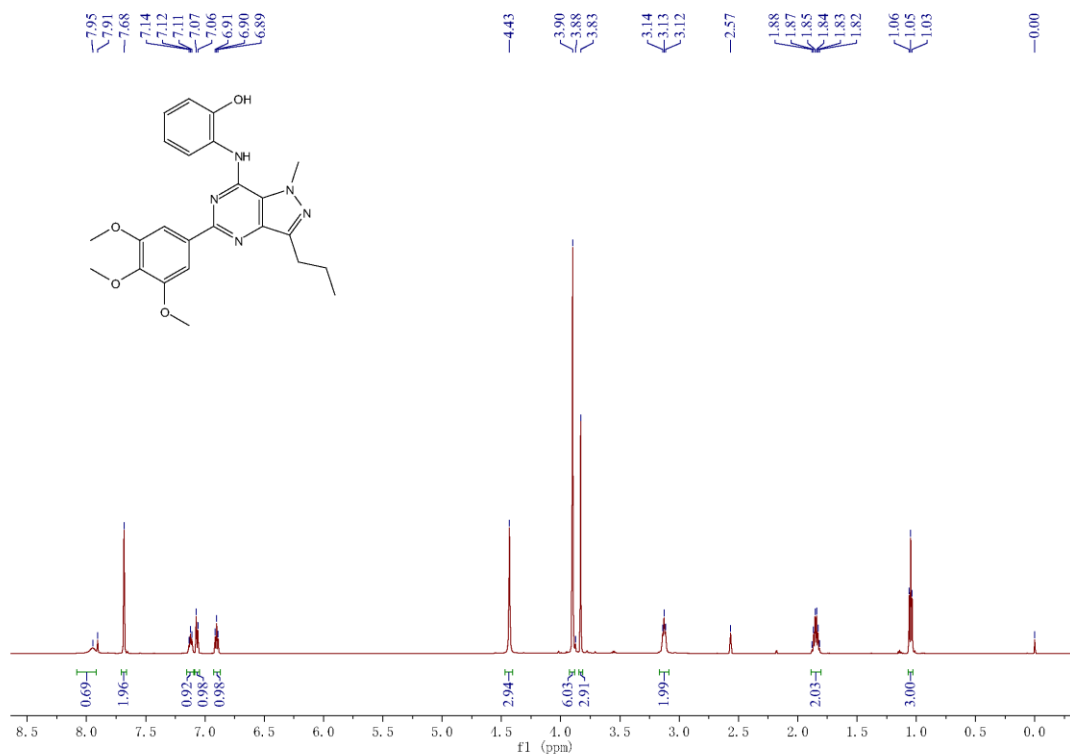
To a solution of intermediate **B1** (1.79 g, 5 mmol) were dissolved in phosphorus oxychloride (POCl₃, 15 mL), and the reaction mixture were stirred at 95 °C, for 10~12 h under N₂ atmosphere. The excess POCl₃ was removed under reduced pressure after the reaction was completed. Slowly pour the oily residue into ice water and mix quickly and extracted with DCM (50 mL×3). The organic layer was washed with saturated NaHCO₃ solution and saturated brine solution, dried over Na₂SO₄, and concentrated under reduced pressure. The intermediate **C1** was obtained as yellow solid. And intermediates **C2~C4** were obtained using the same procedure as intermediate **C1**.

PART 2. ¹H NMR and ¹³C NMR data of 1a~1j, 2a~2g, 3a~3g and 4a~4k.

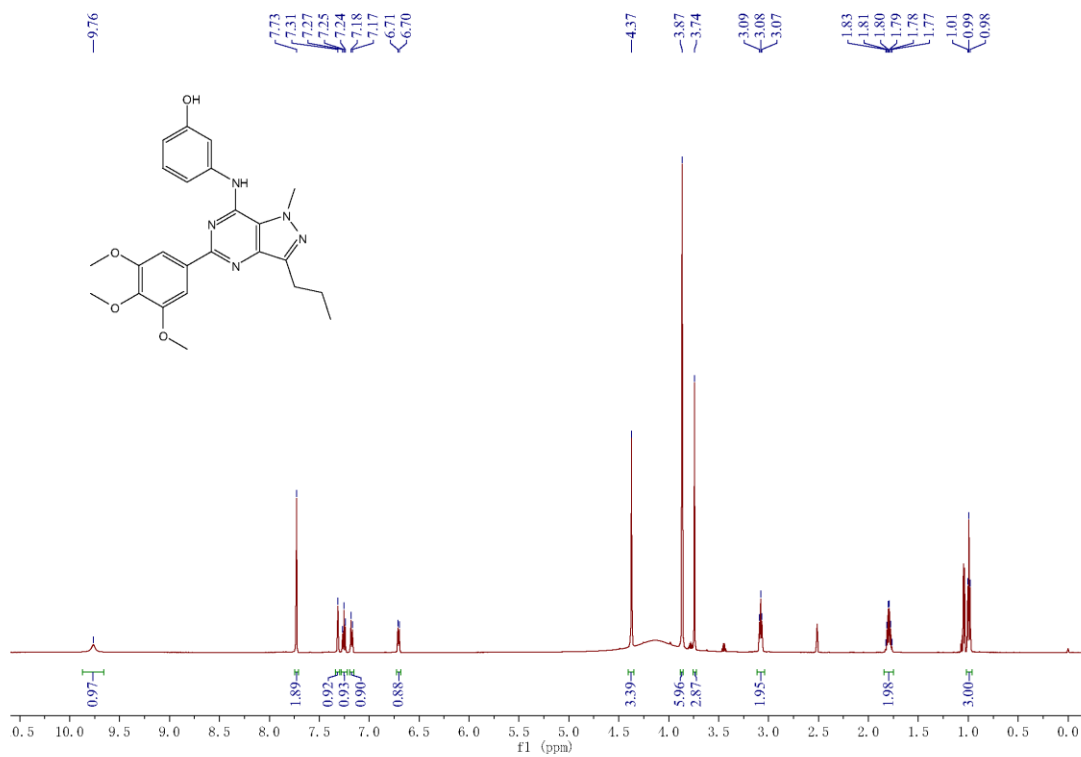
¹H NMR and ¹³C NMR for 1a

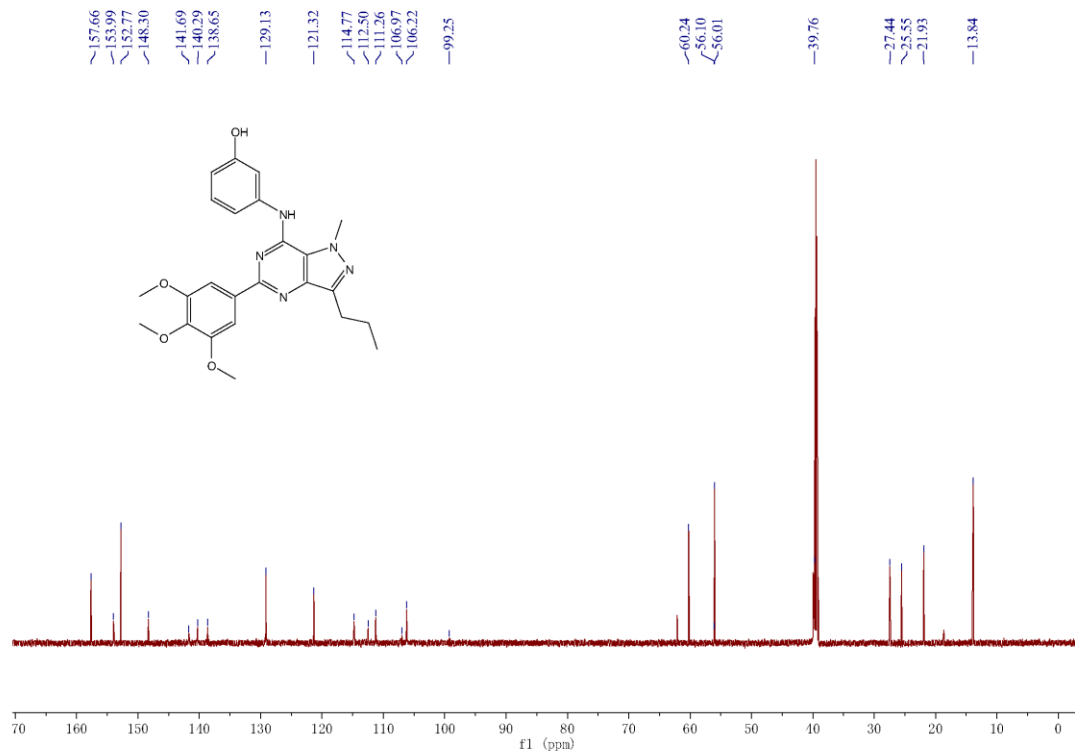


^1H NMR for *1b*

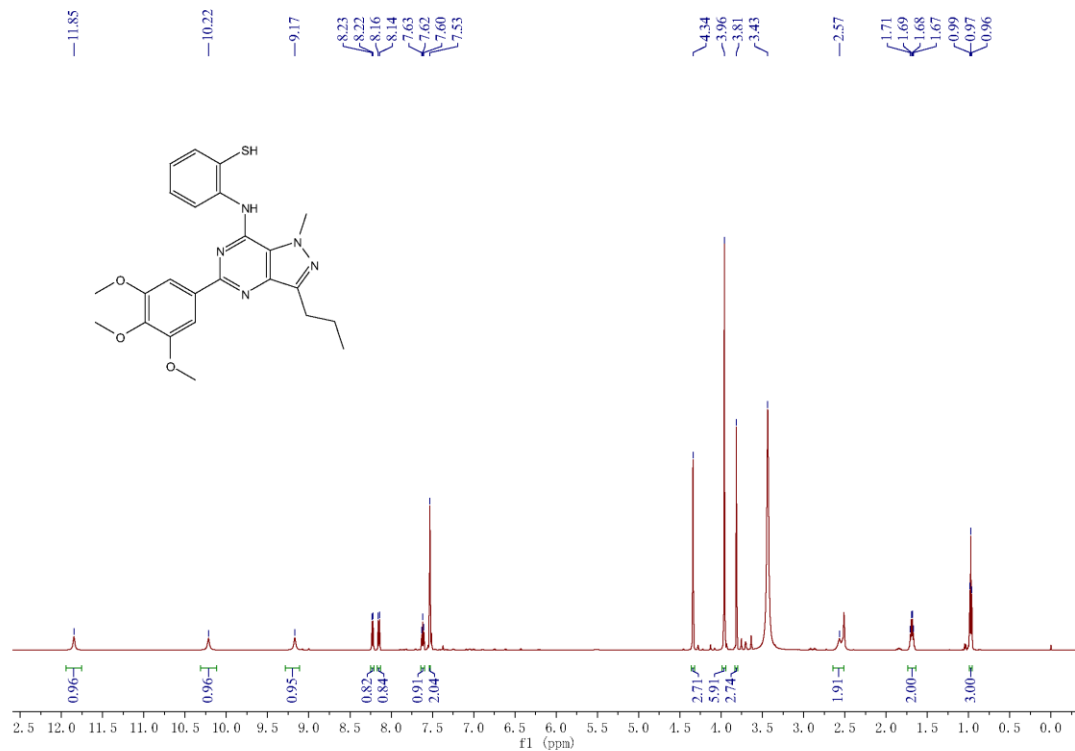


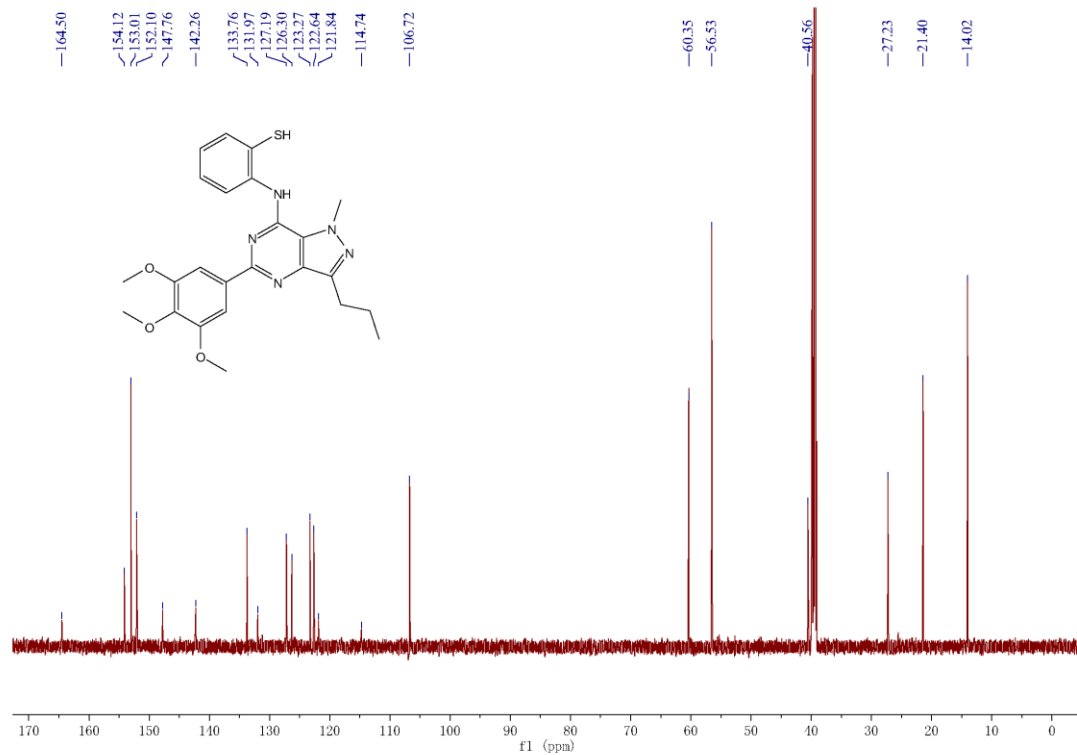
^1H NMR and ^{13}C NMR for *1c*



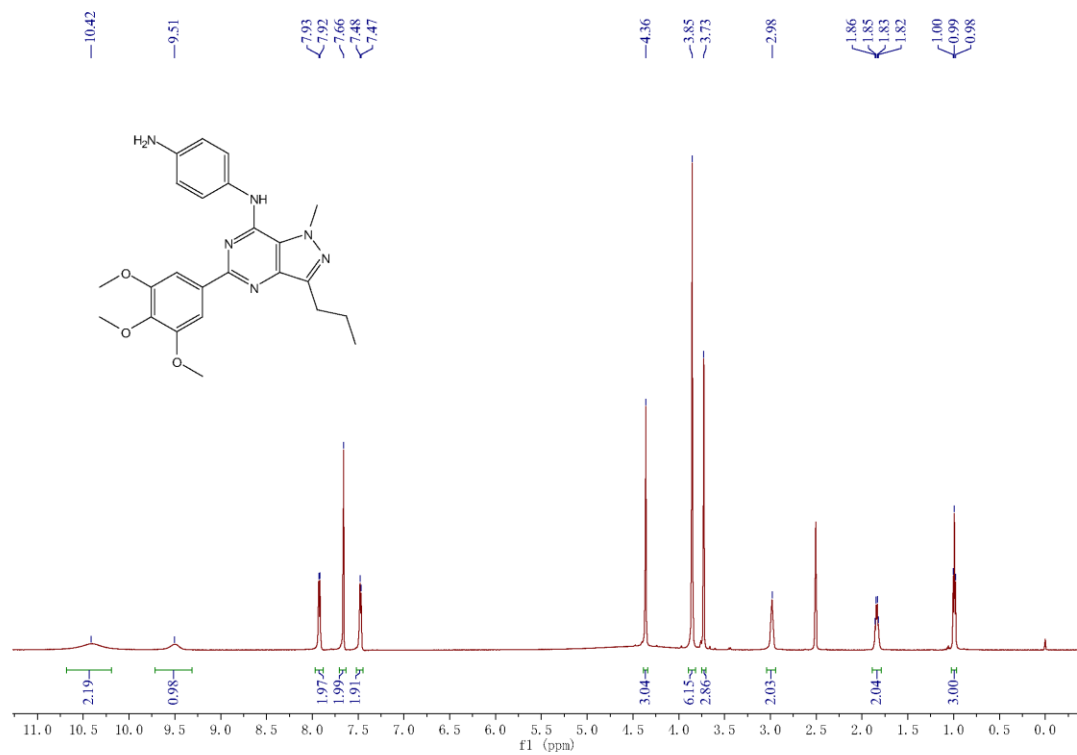


¹H NMR and ¹³C NMR for 1d

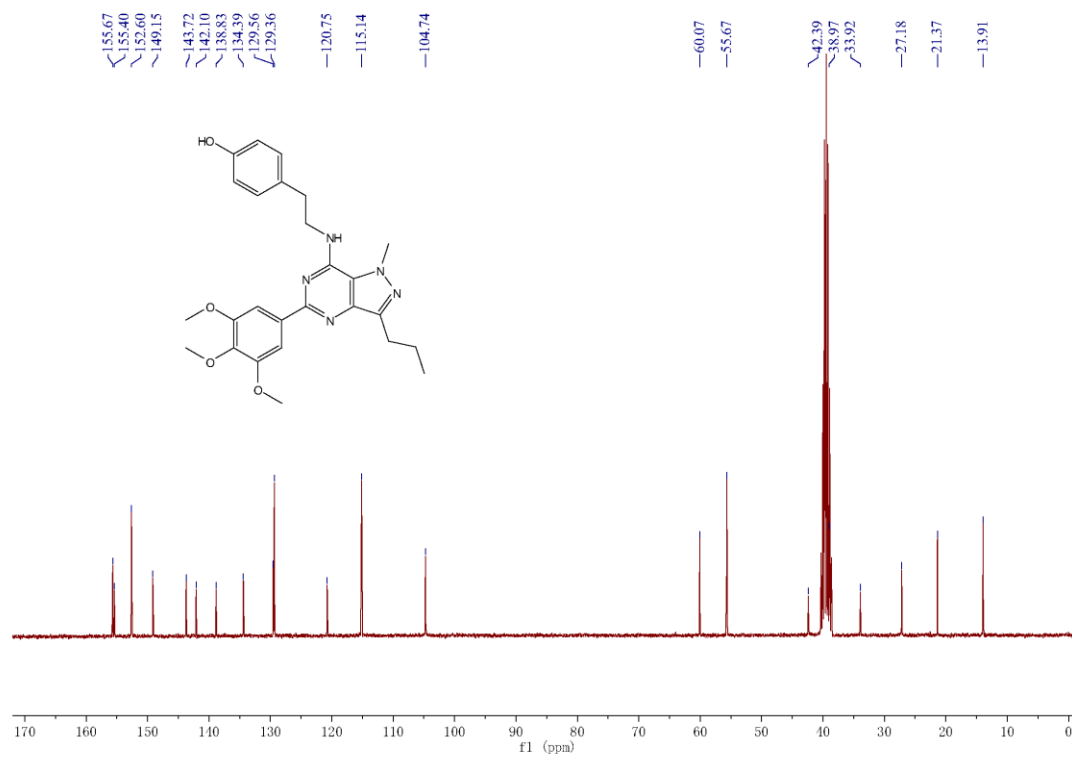
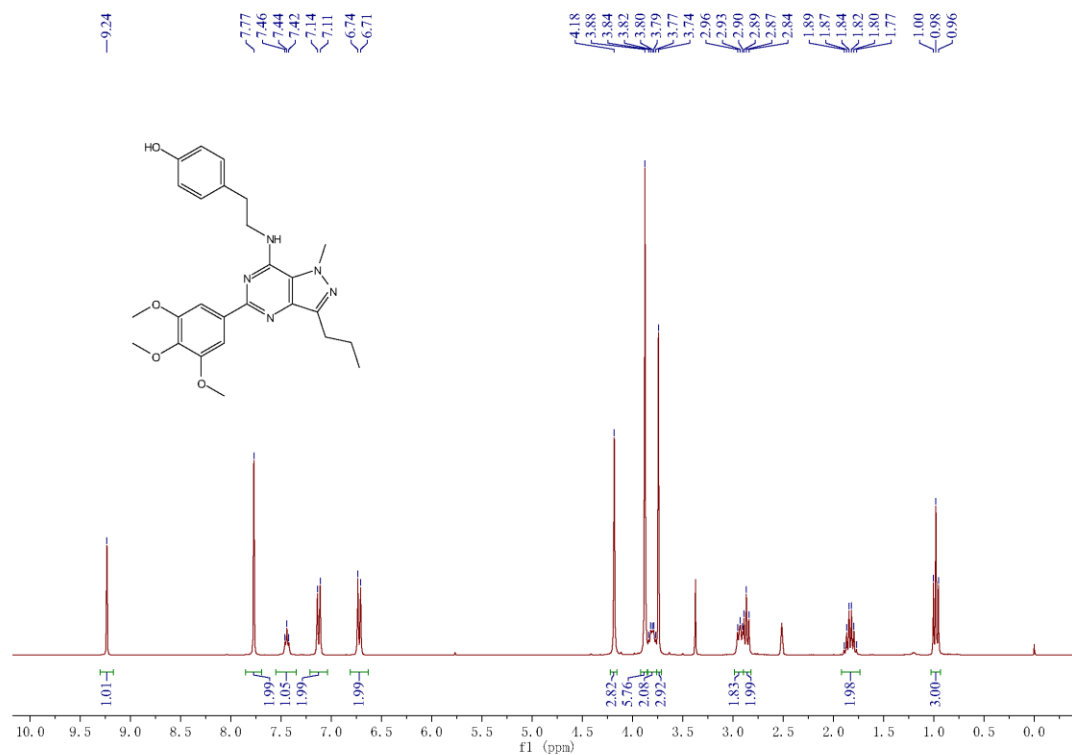




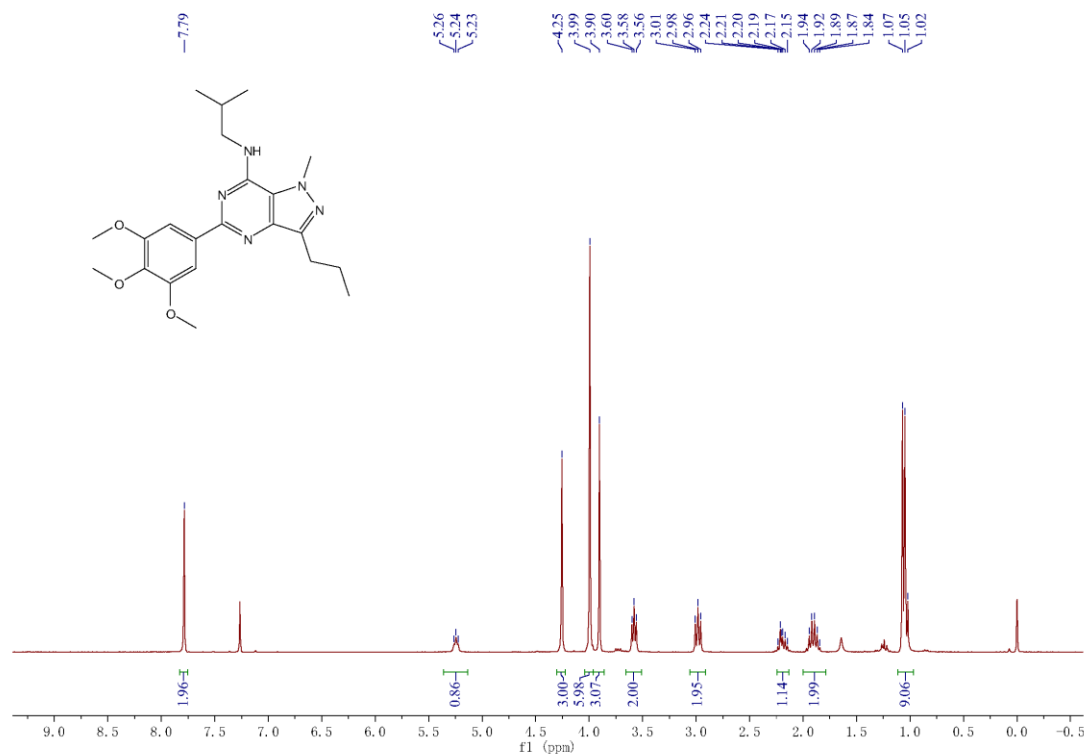
¹H NMR for 1e



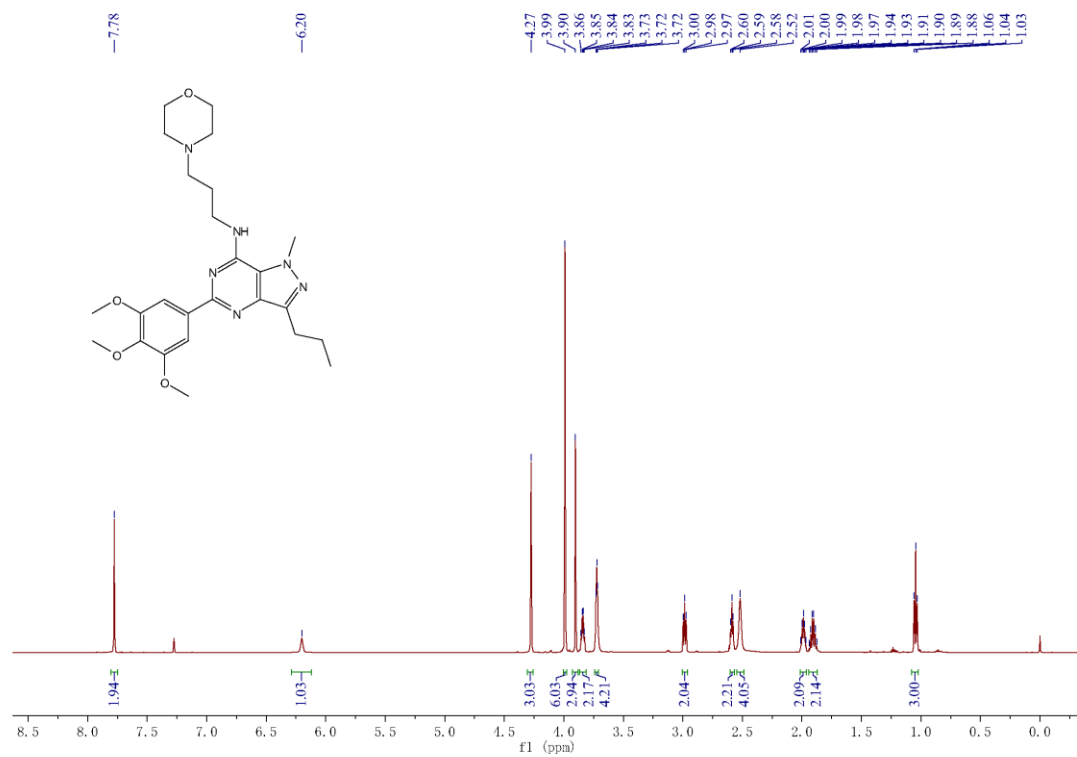
^1H NMR and ^{13}C NMR for *1f*

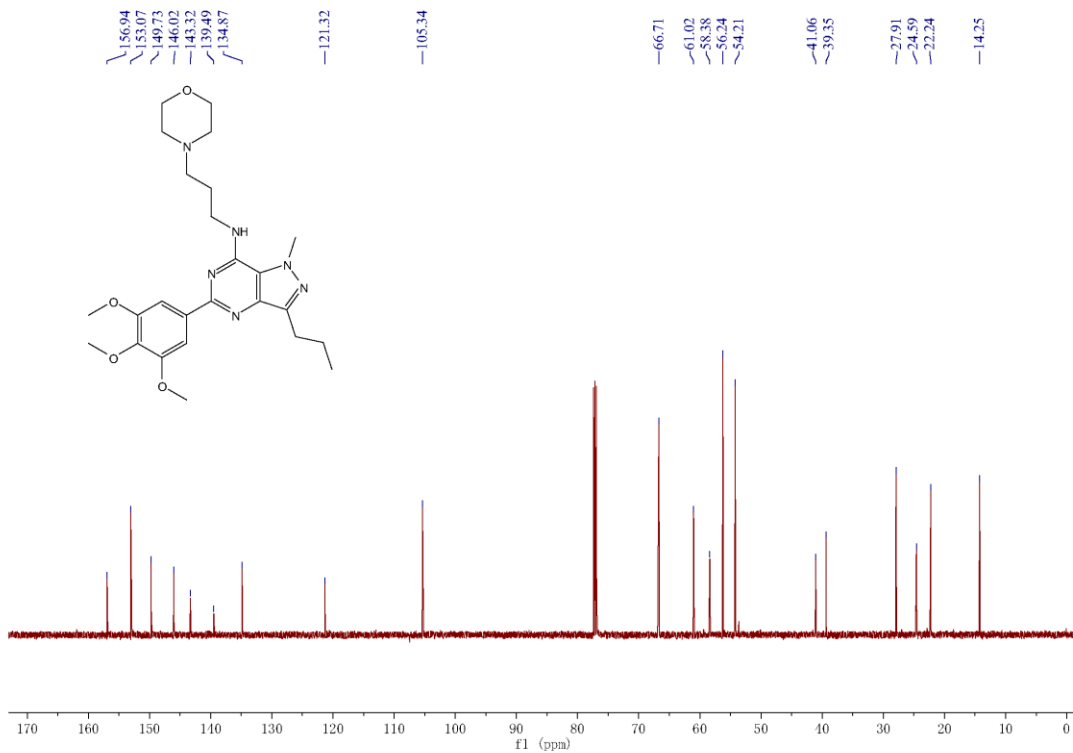


^1H NMR for *1g*

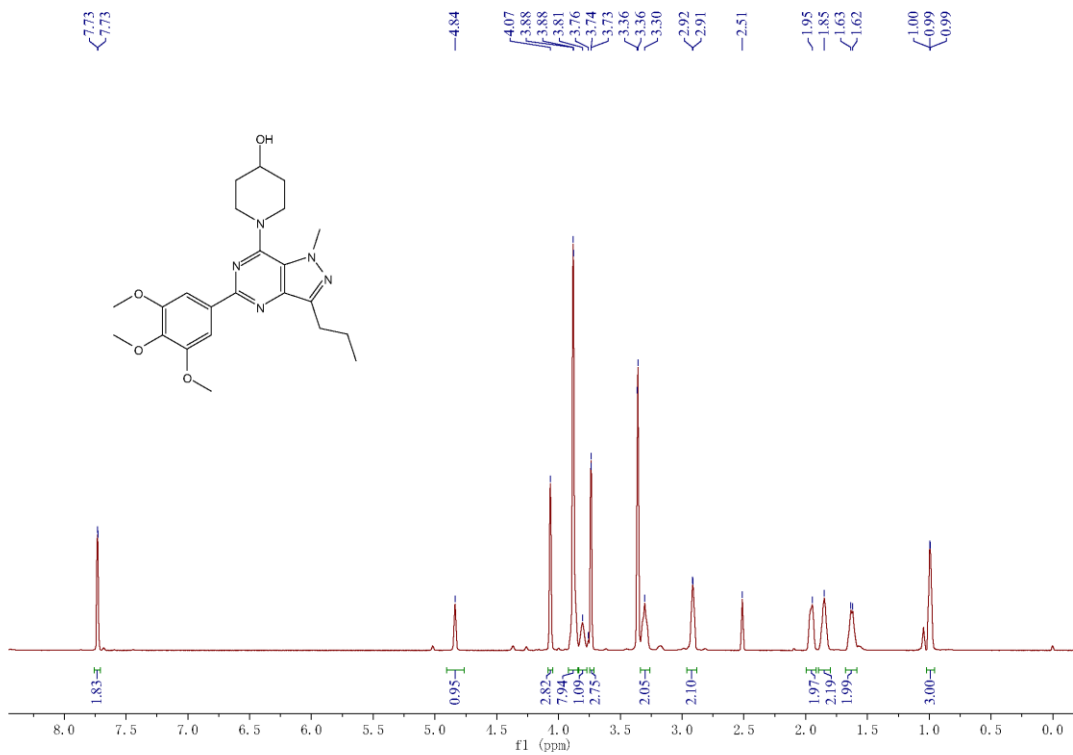


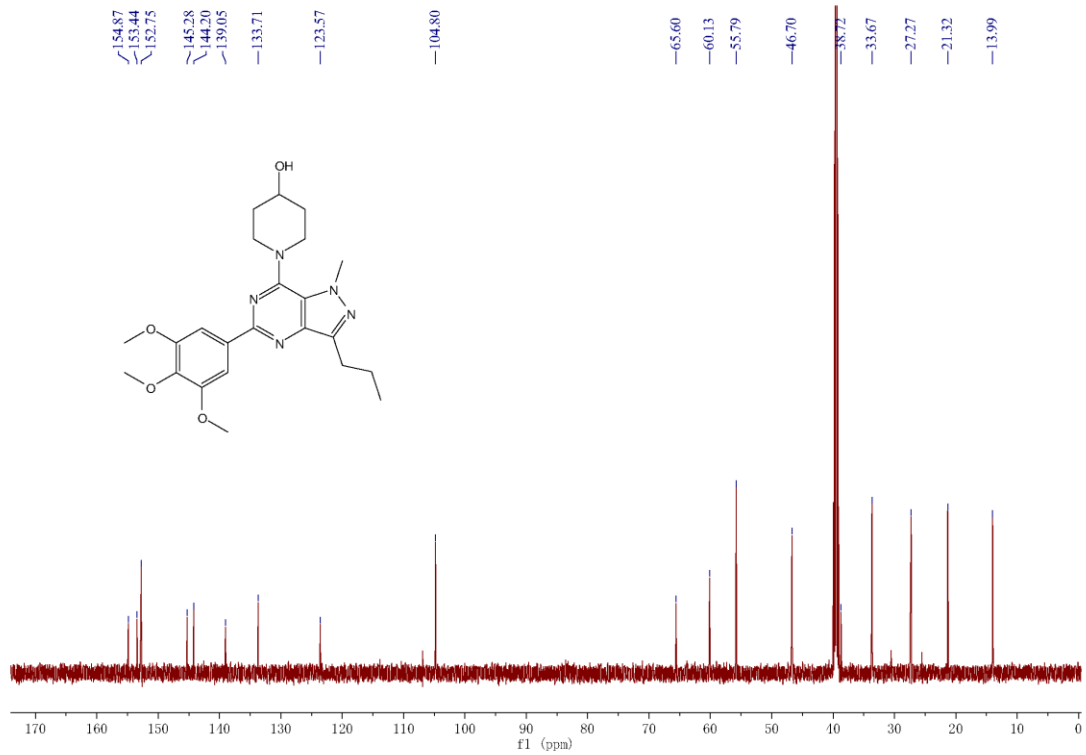
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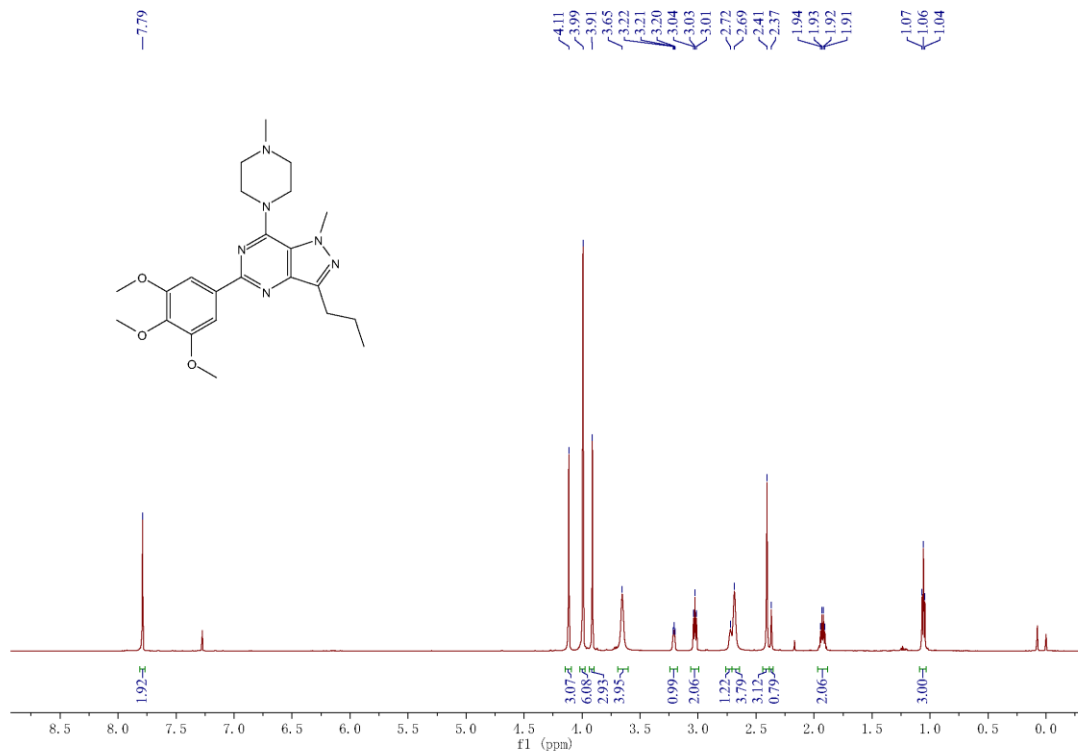


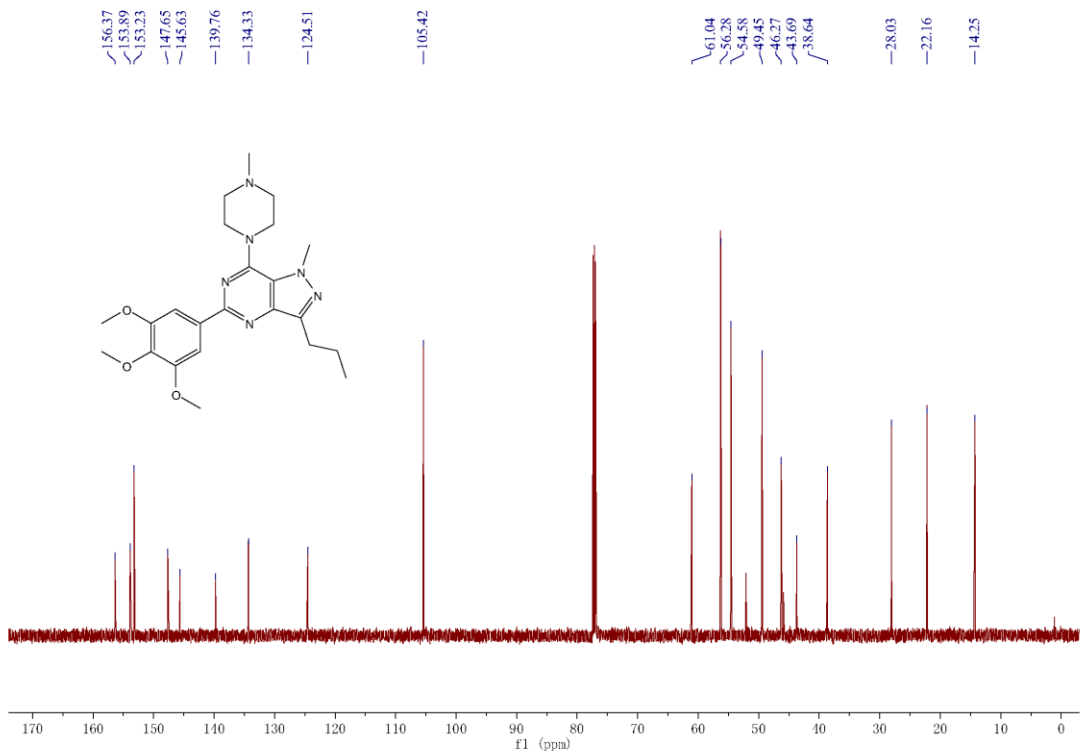
¹H NMR and ¹³C NMR for **1i**



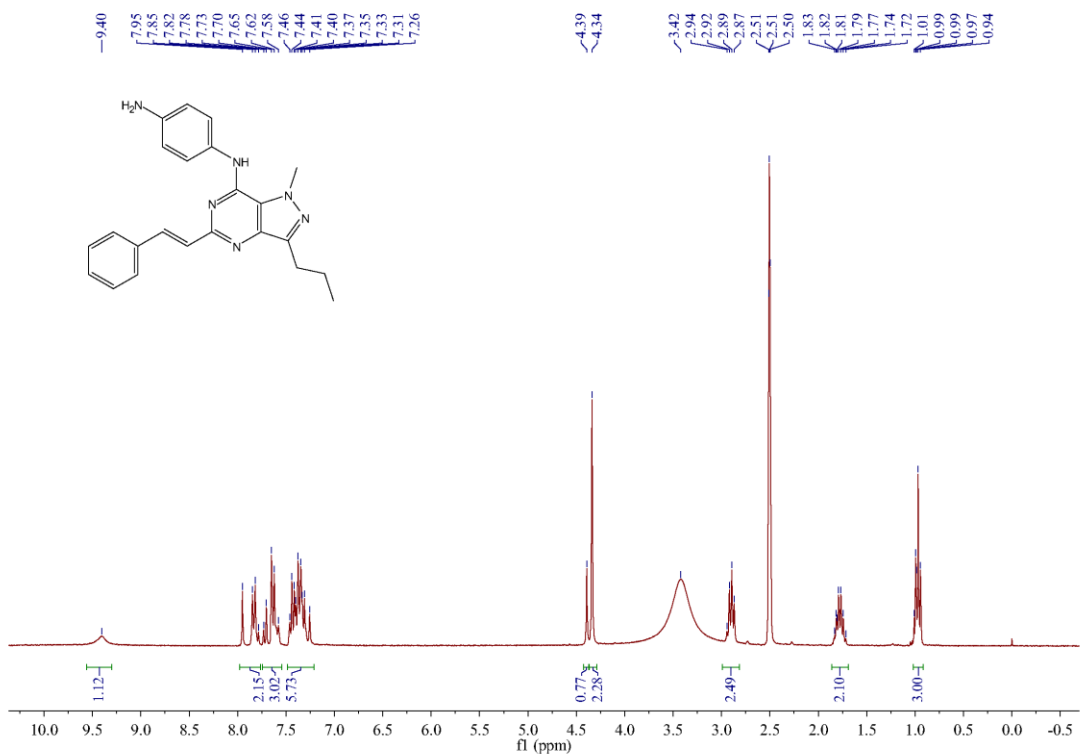


¹H NMR and ¹³C NMR for **1j**

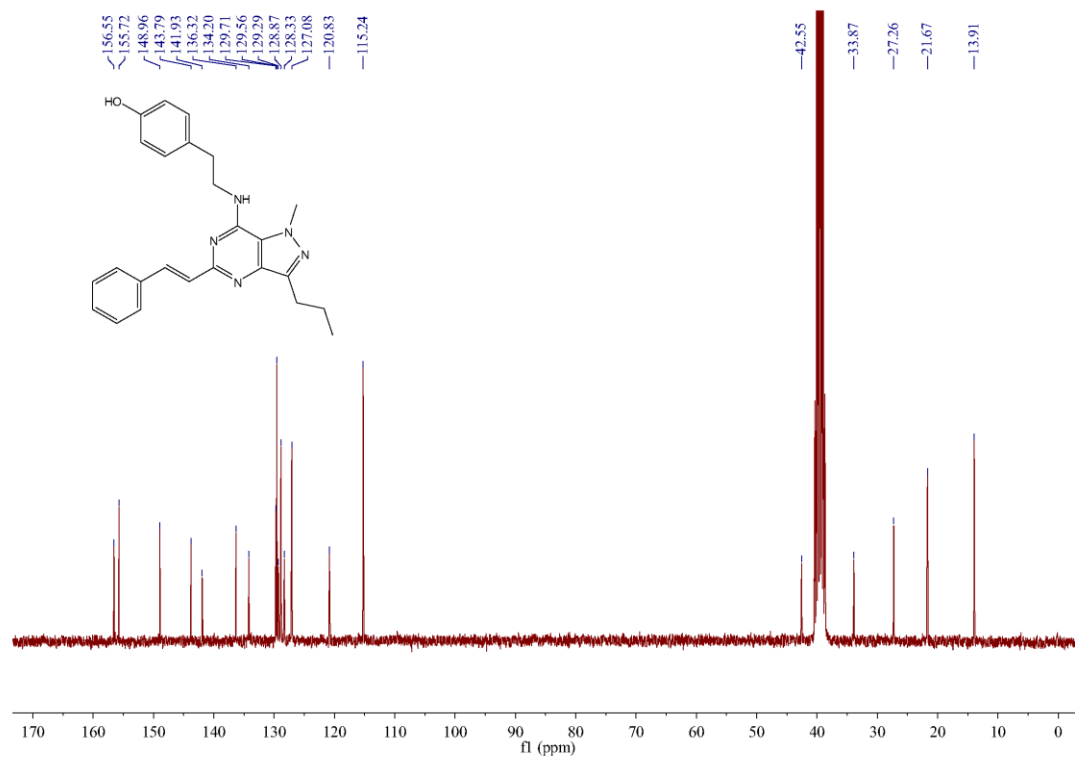
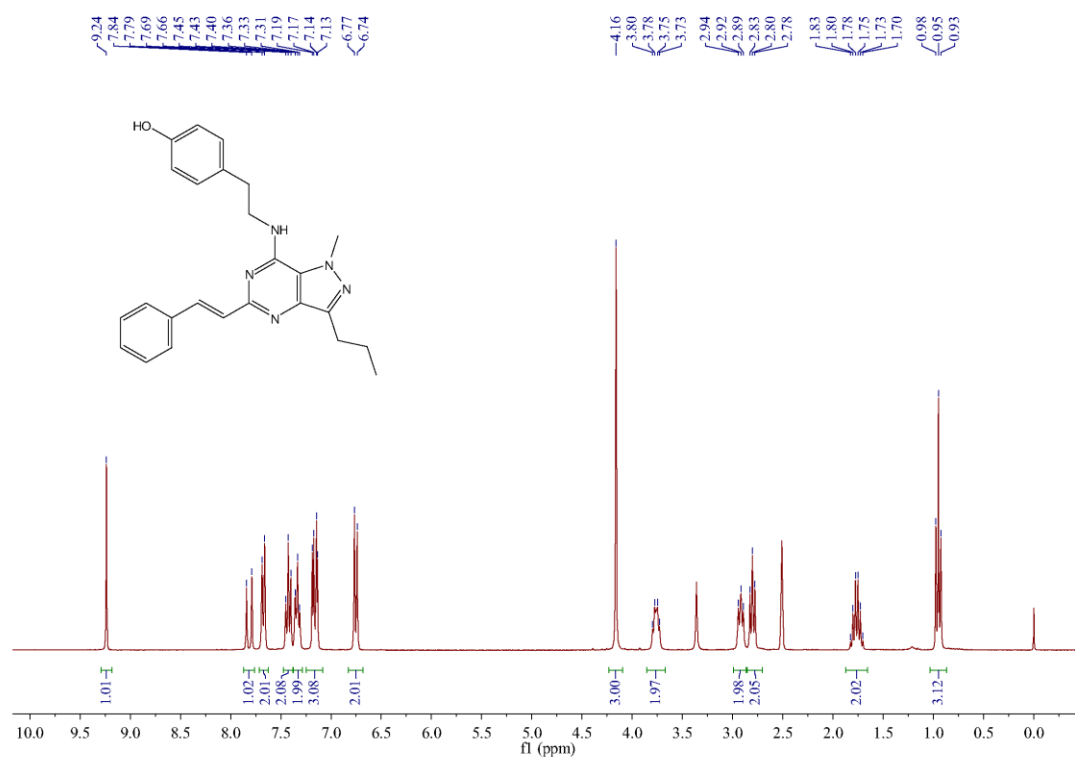




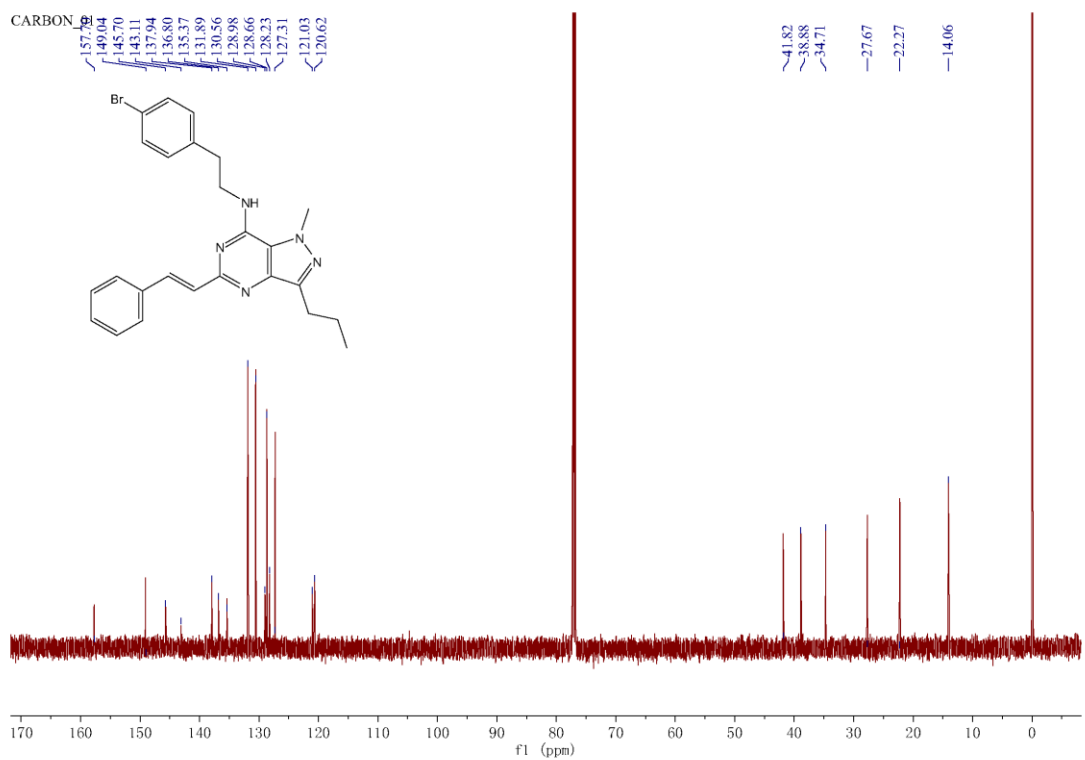
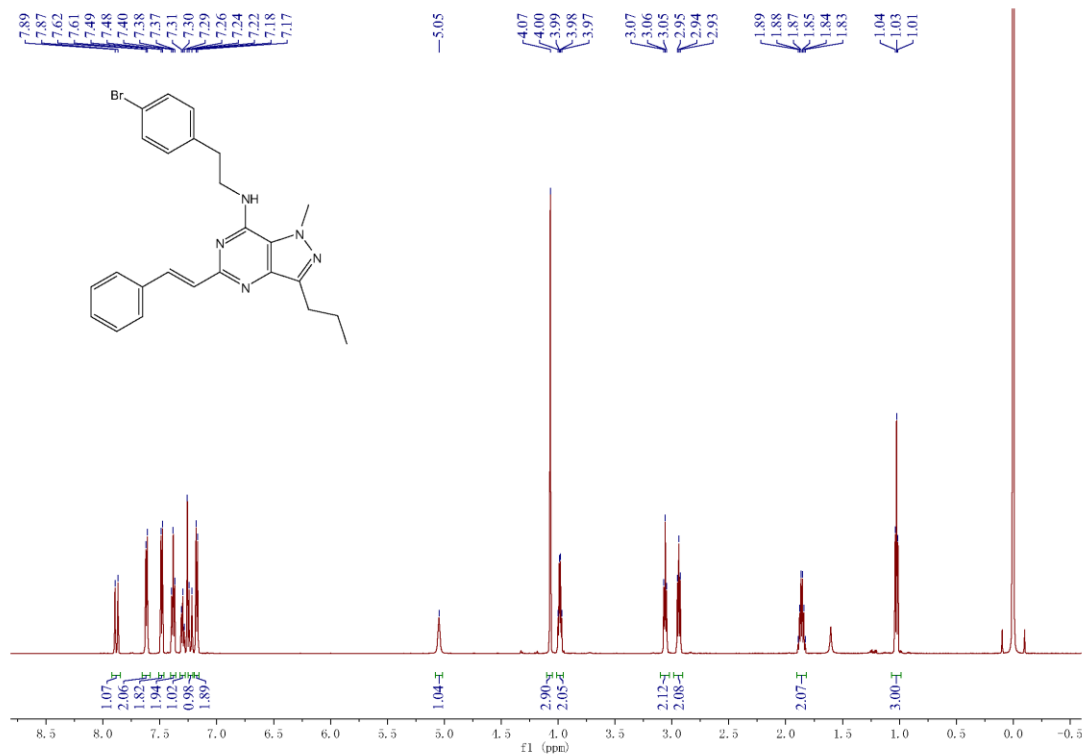
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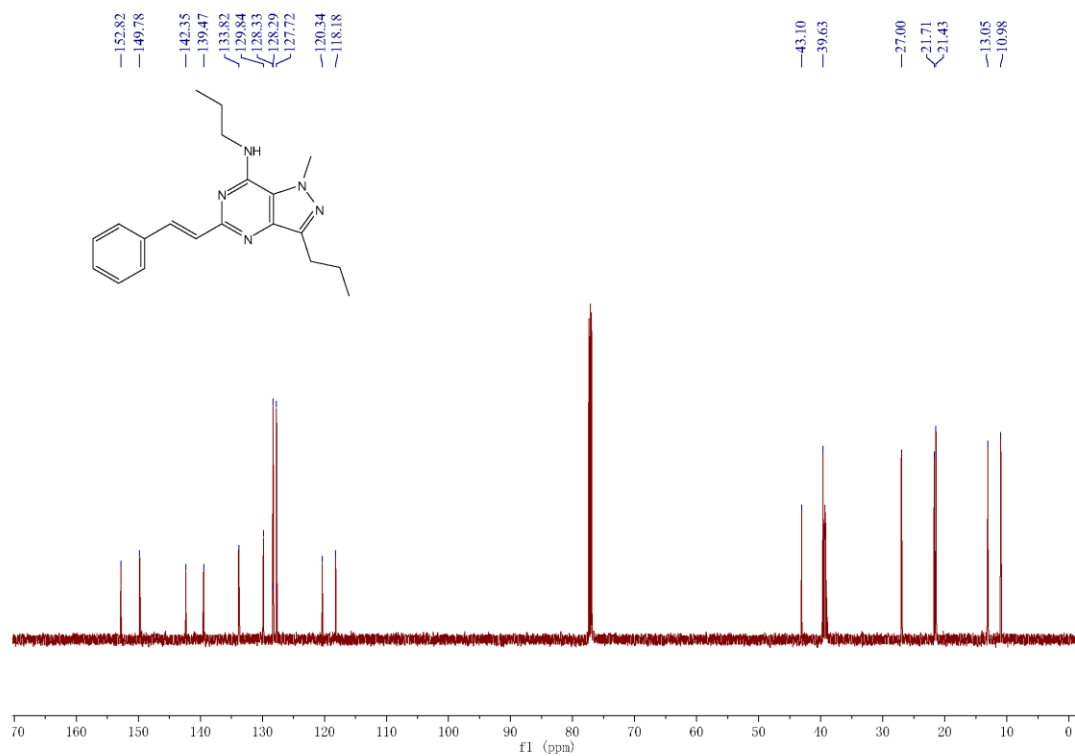
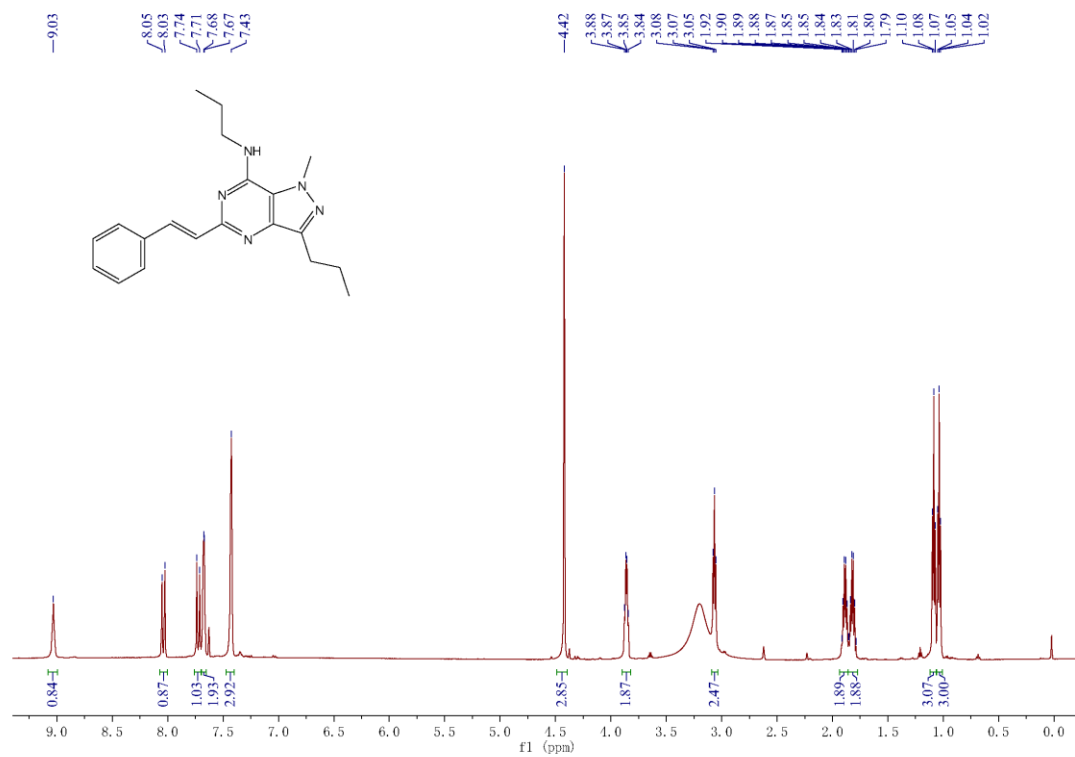
^1H NMR and ^{13}C NMR for **2b**



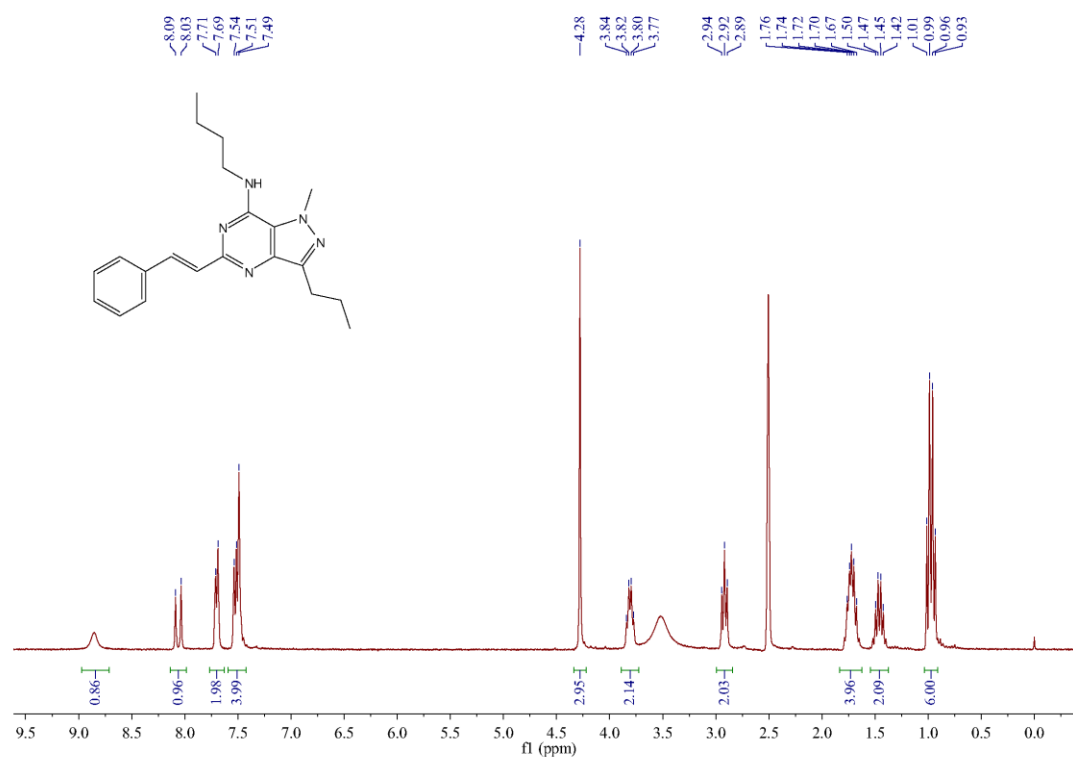
^1H NMR and ^{13}C NMR for 2c



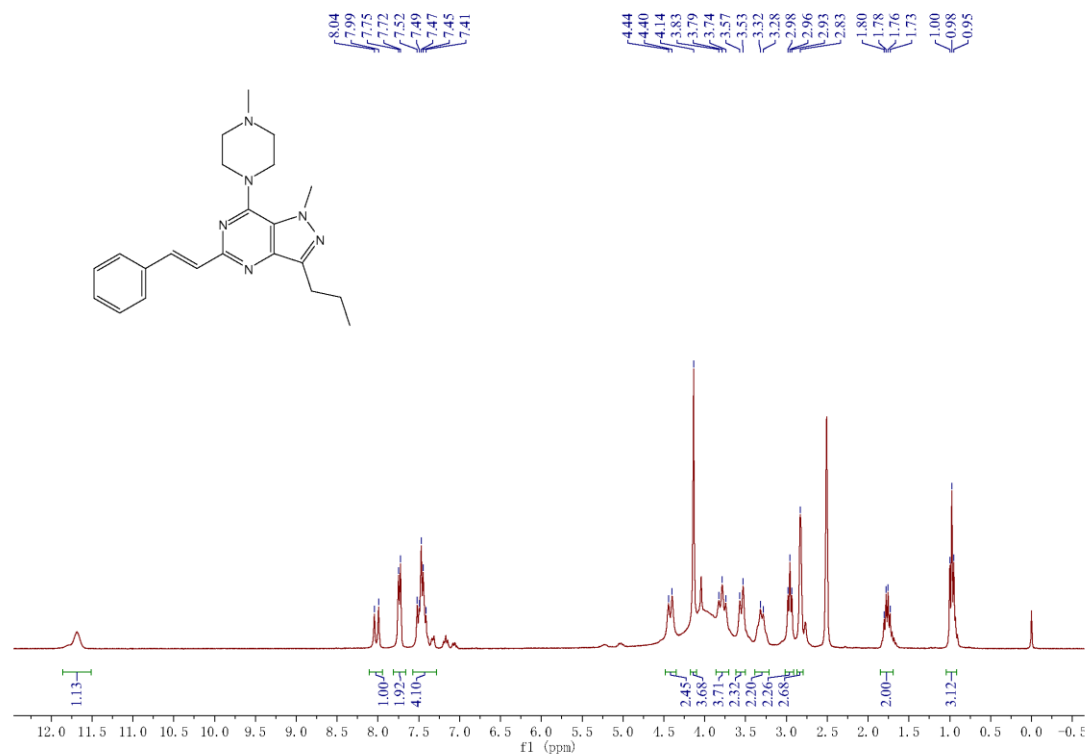
^1H NMR and ^{13}C NMR for *2d*



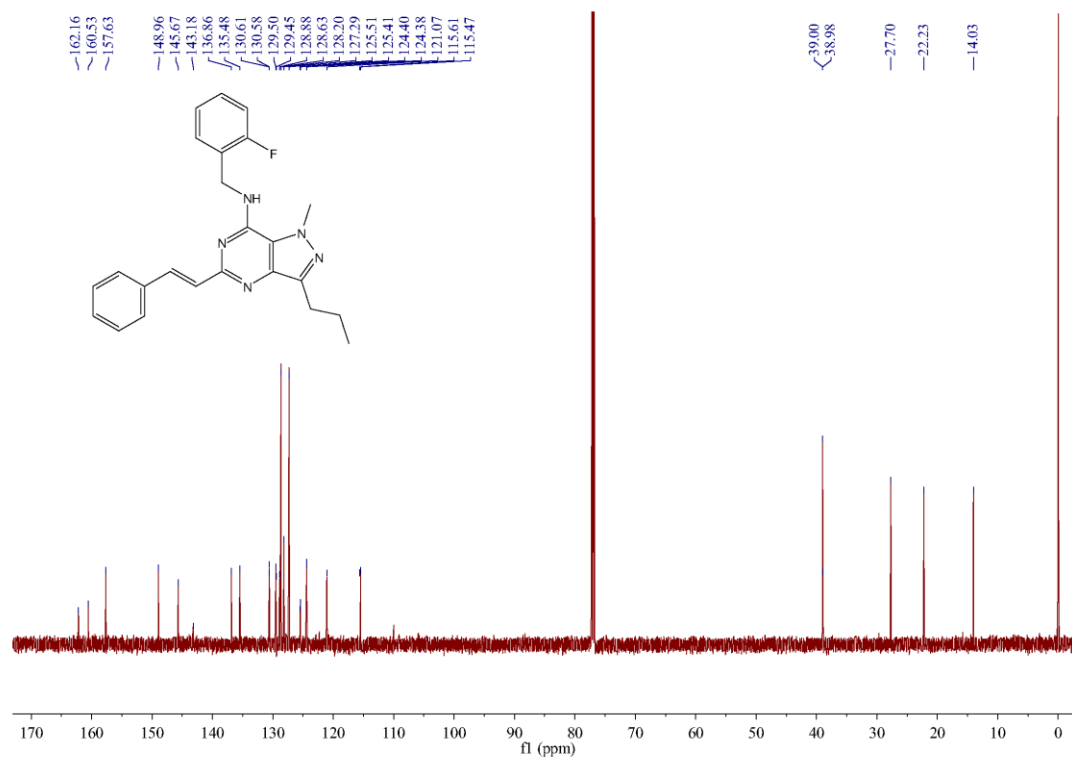
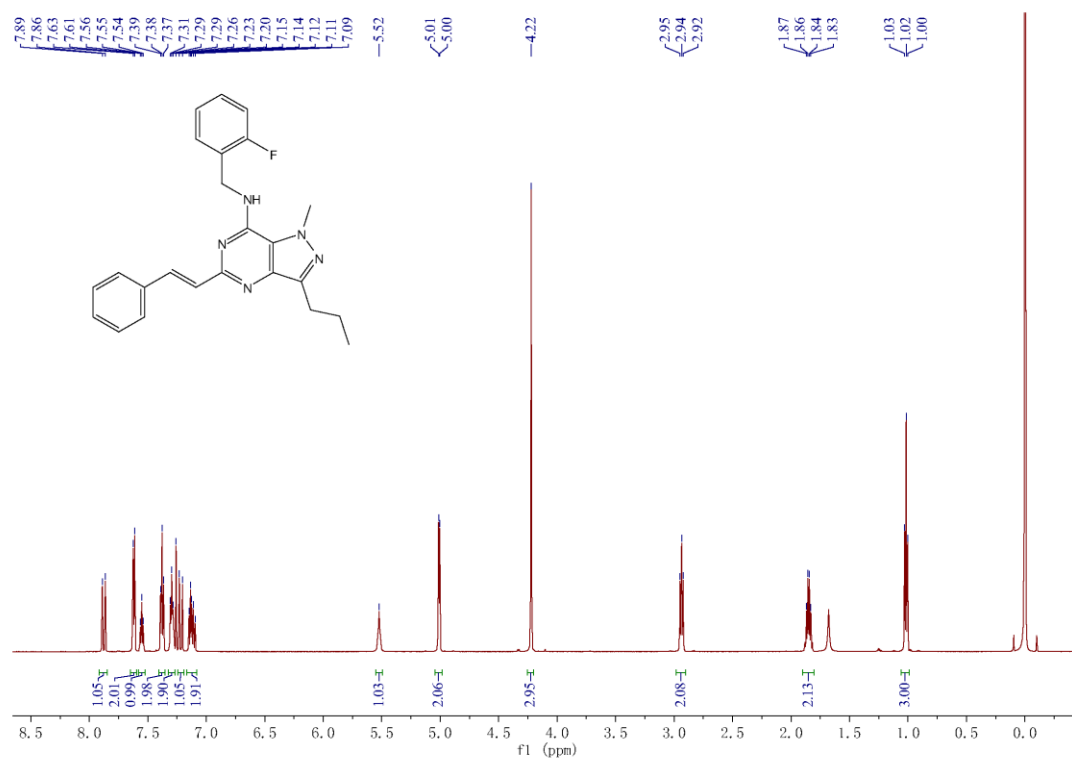
¹H NMR for 2e



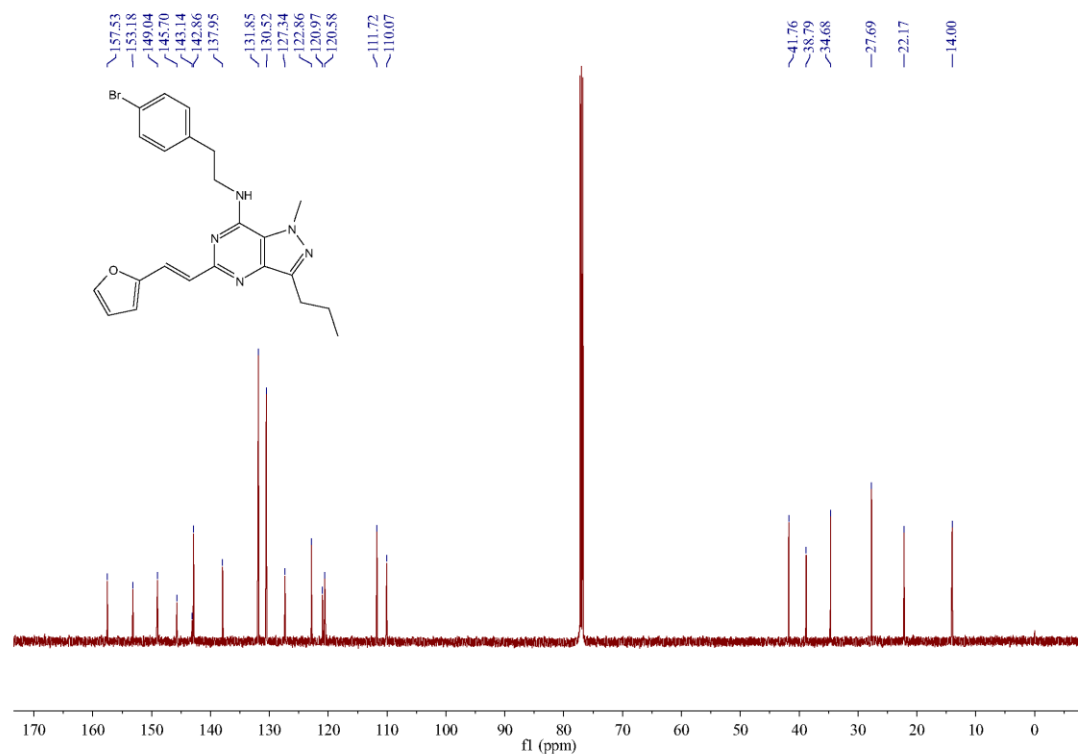
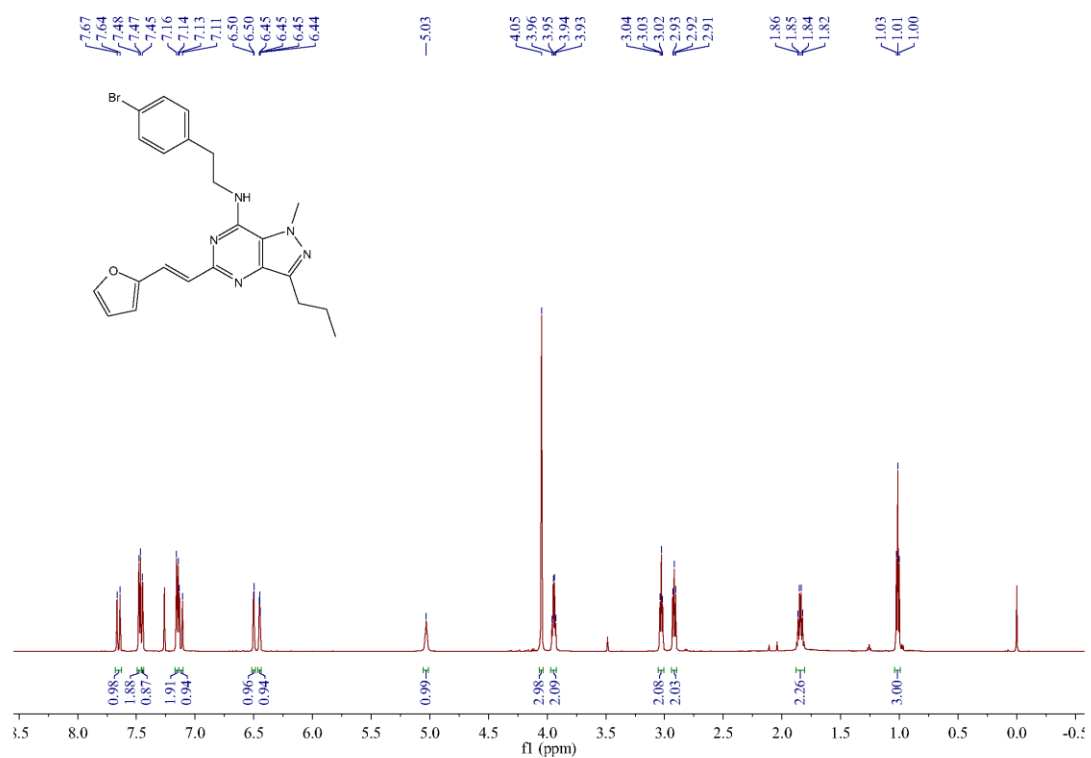
¹H NMR for 2f



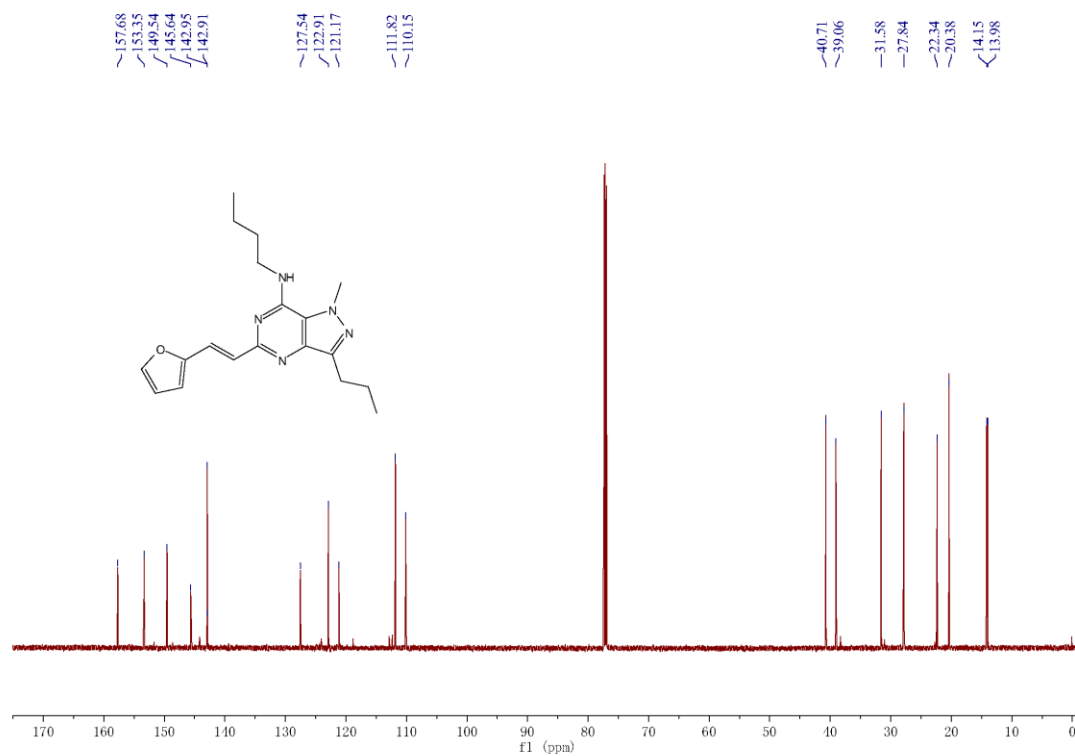
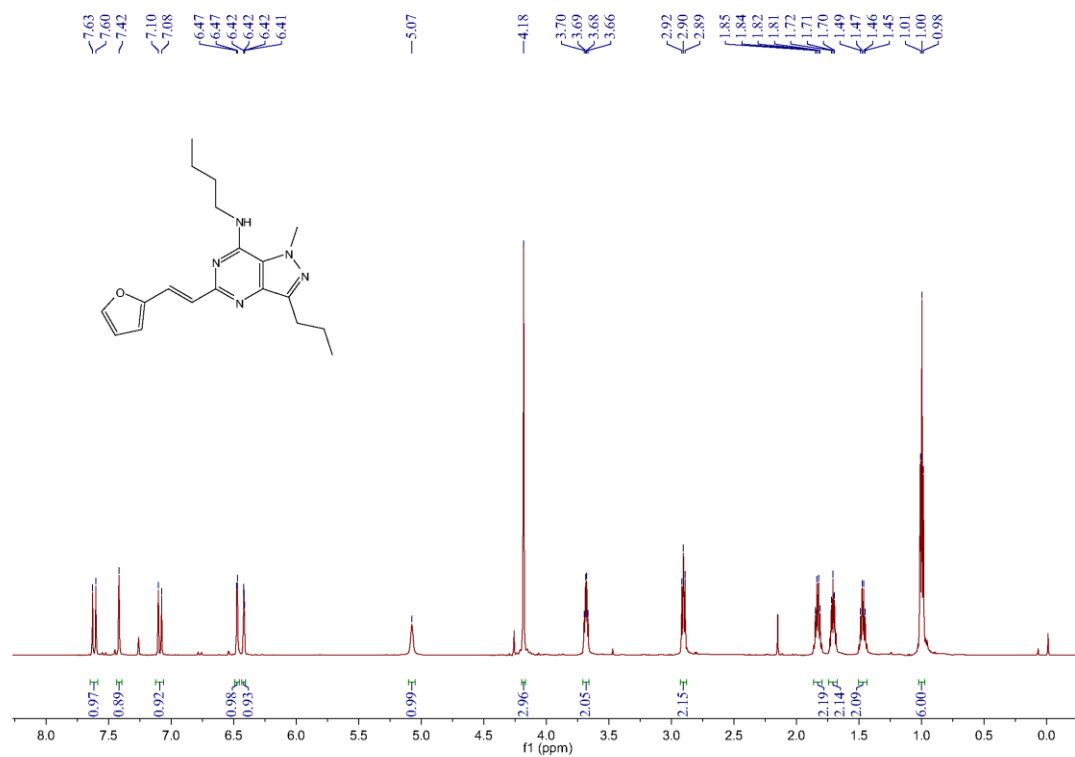
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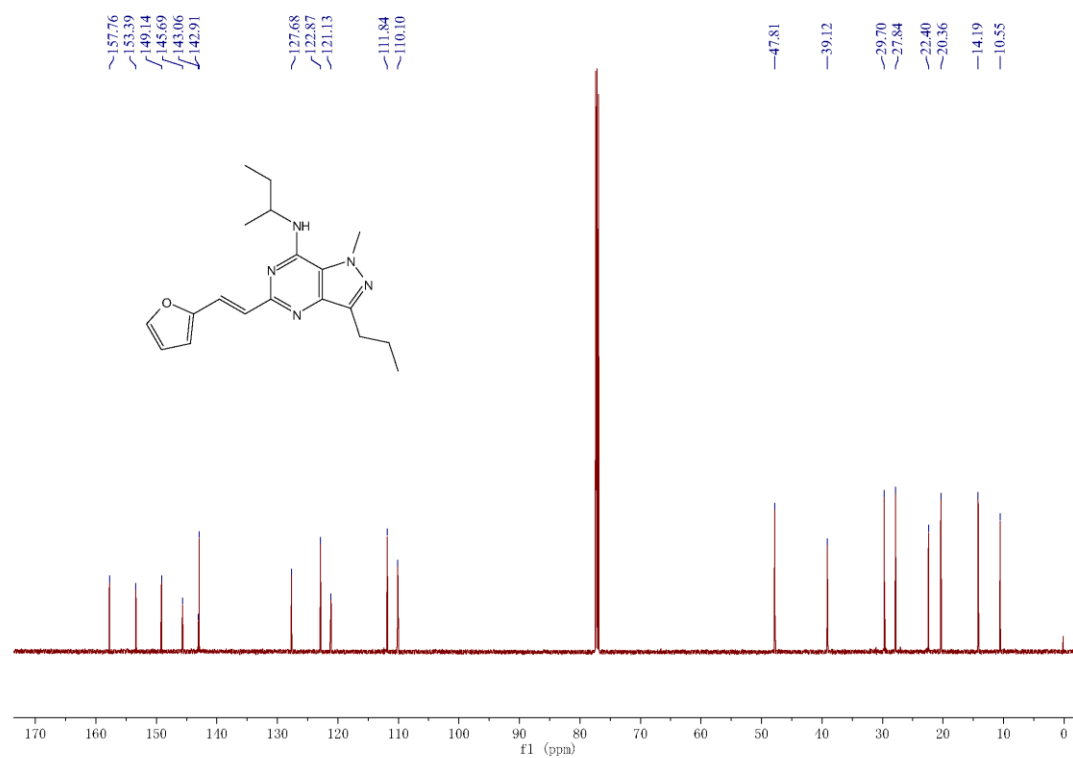
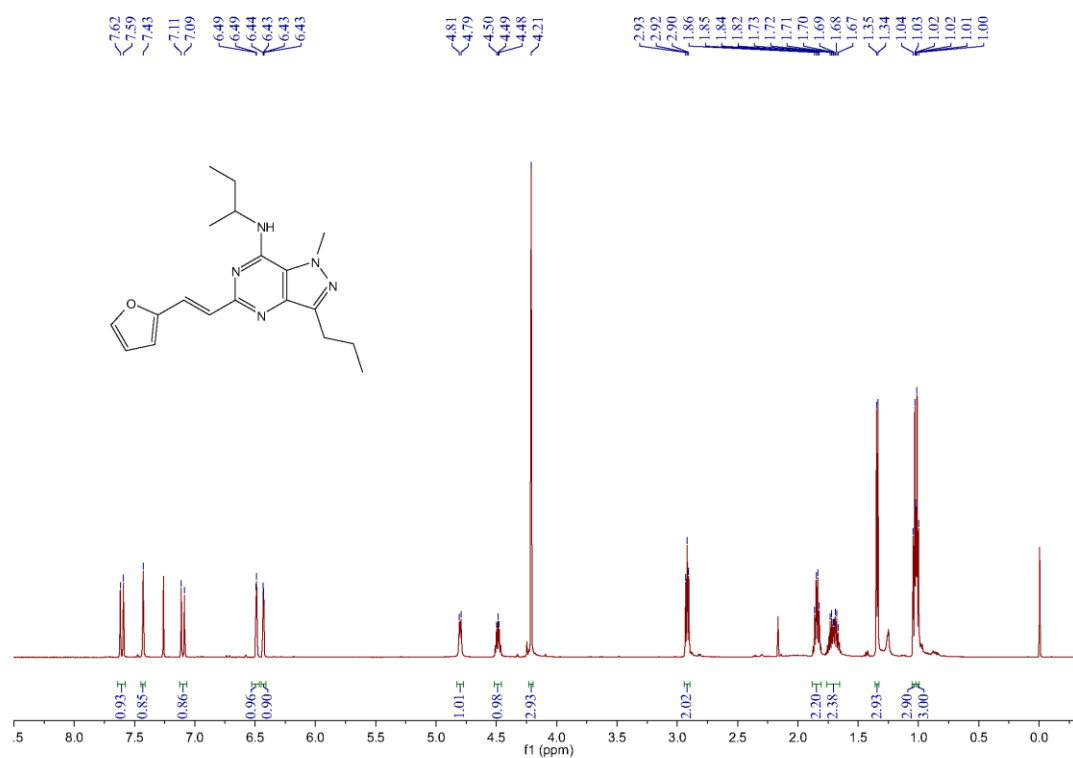
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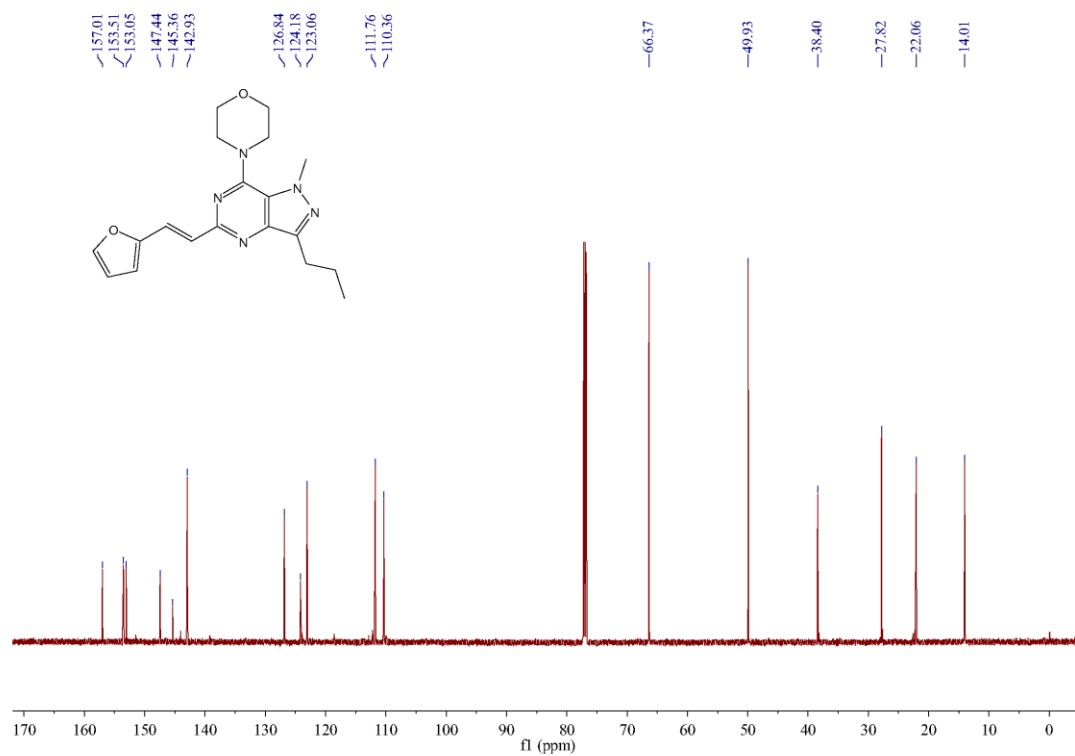
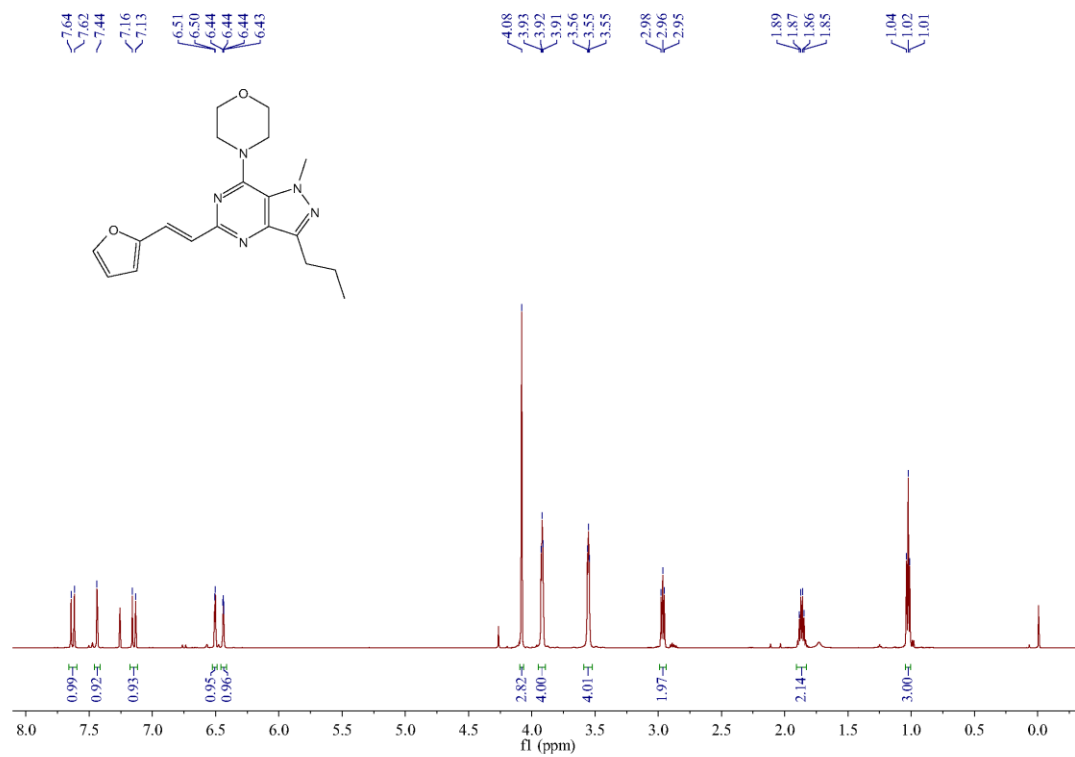
^1H NMR and ^{13}C NMR for **3b**



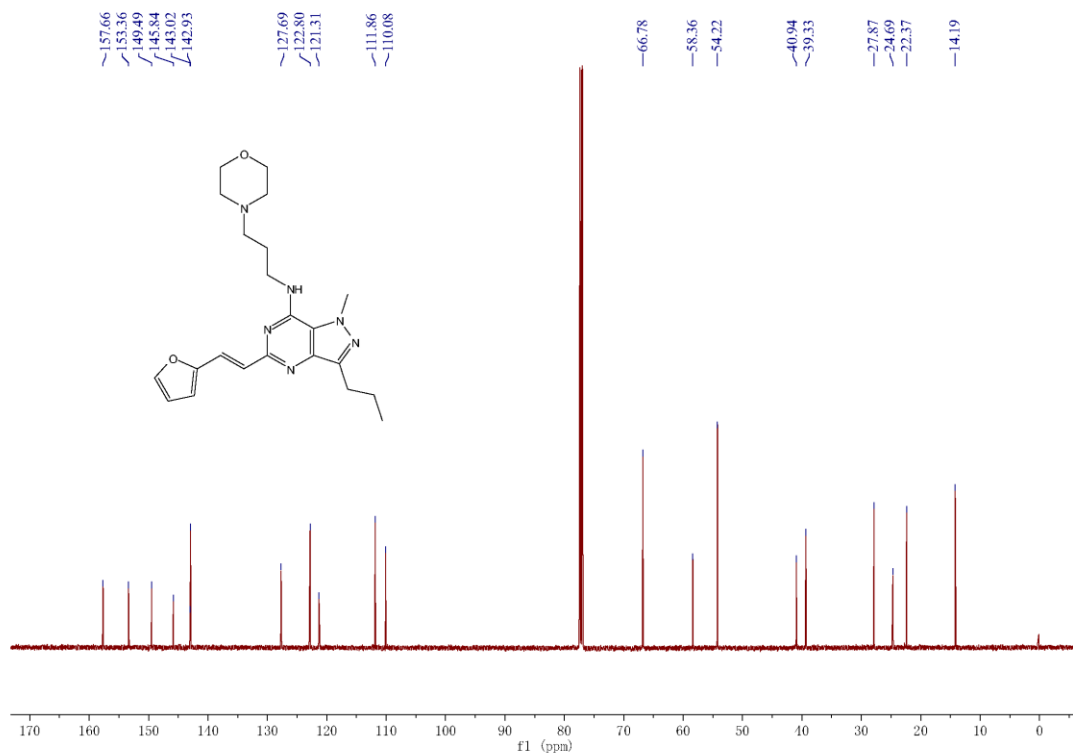
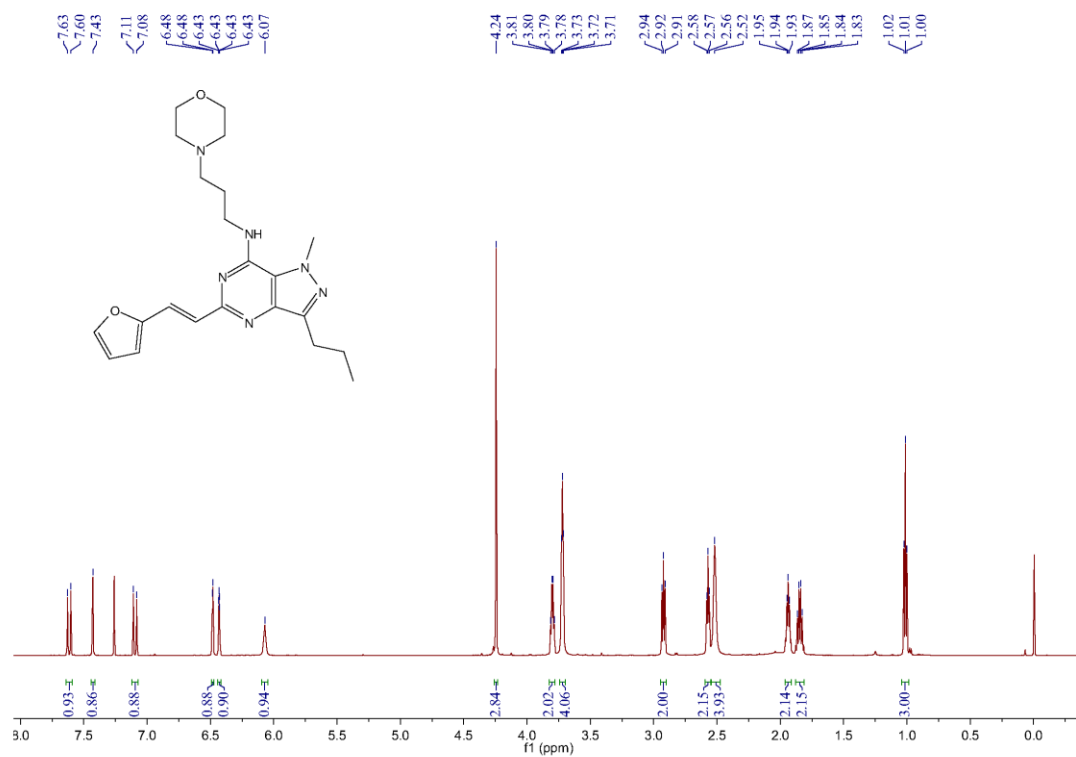
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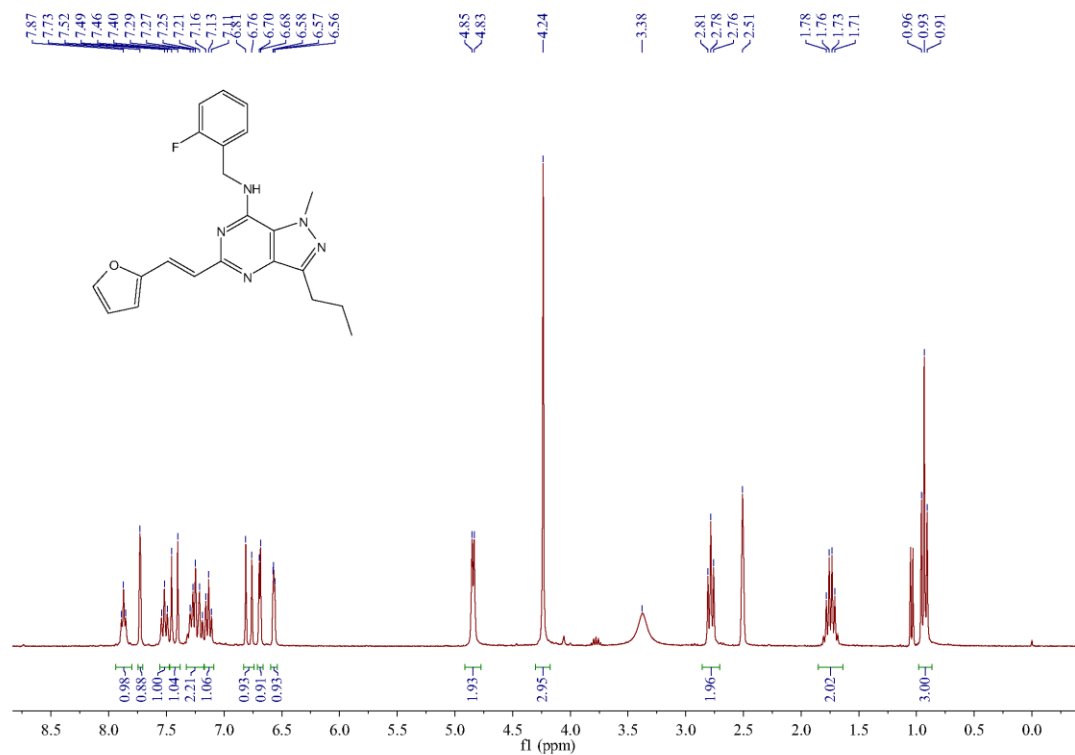
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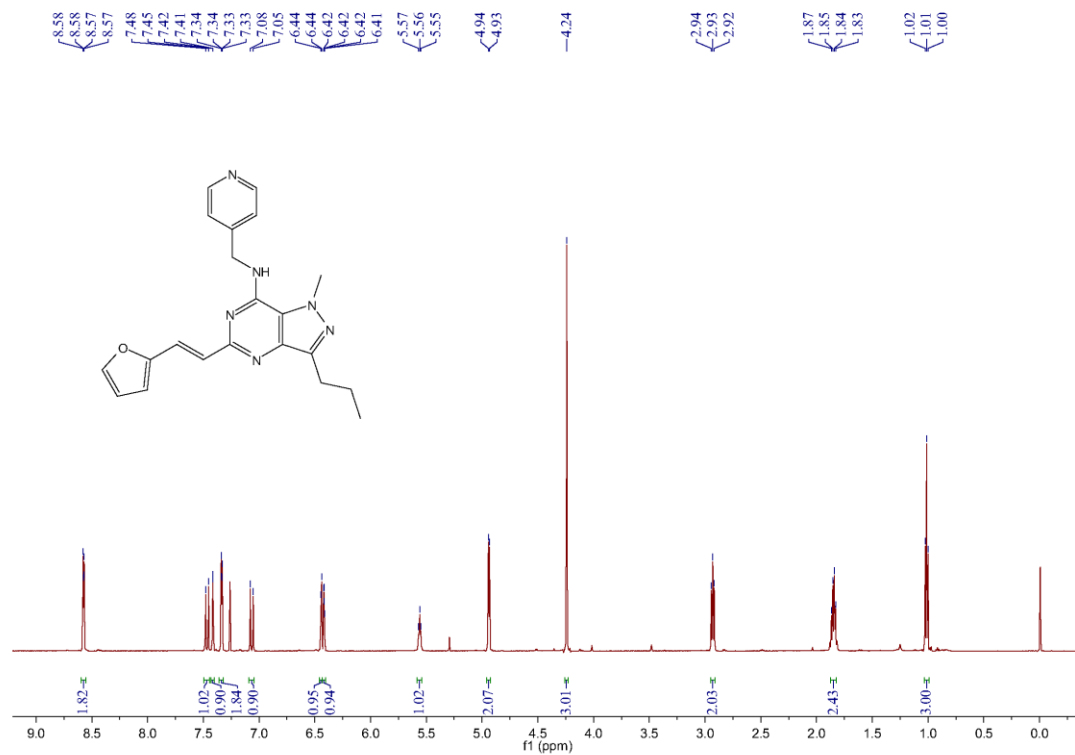
^1H NMR and ^{13}C NMR for **3e**

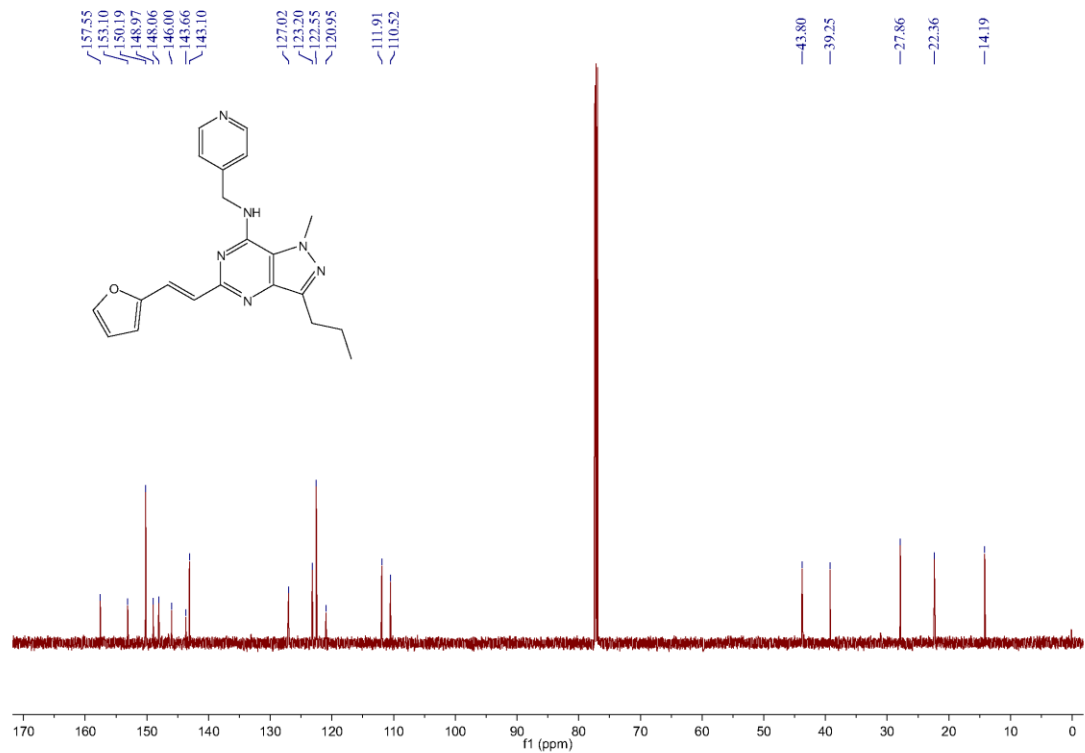


^1H NMR and ^{13}C NMR for 3f

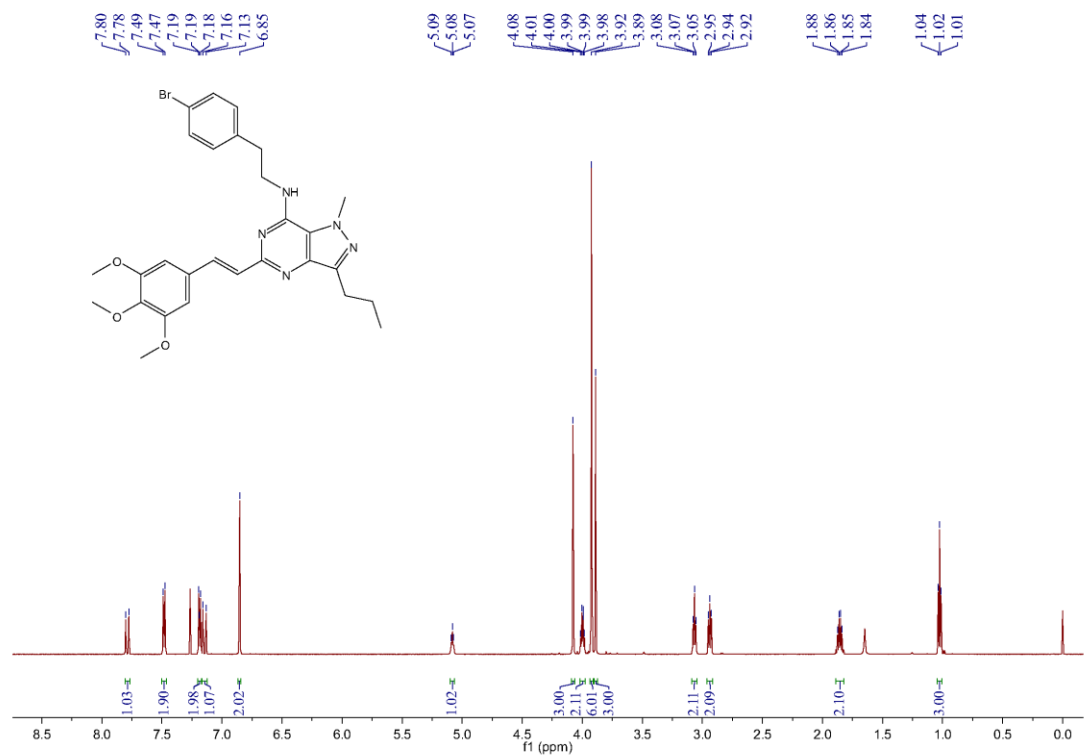


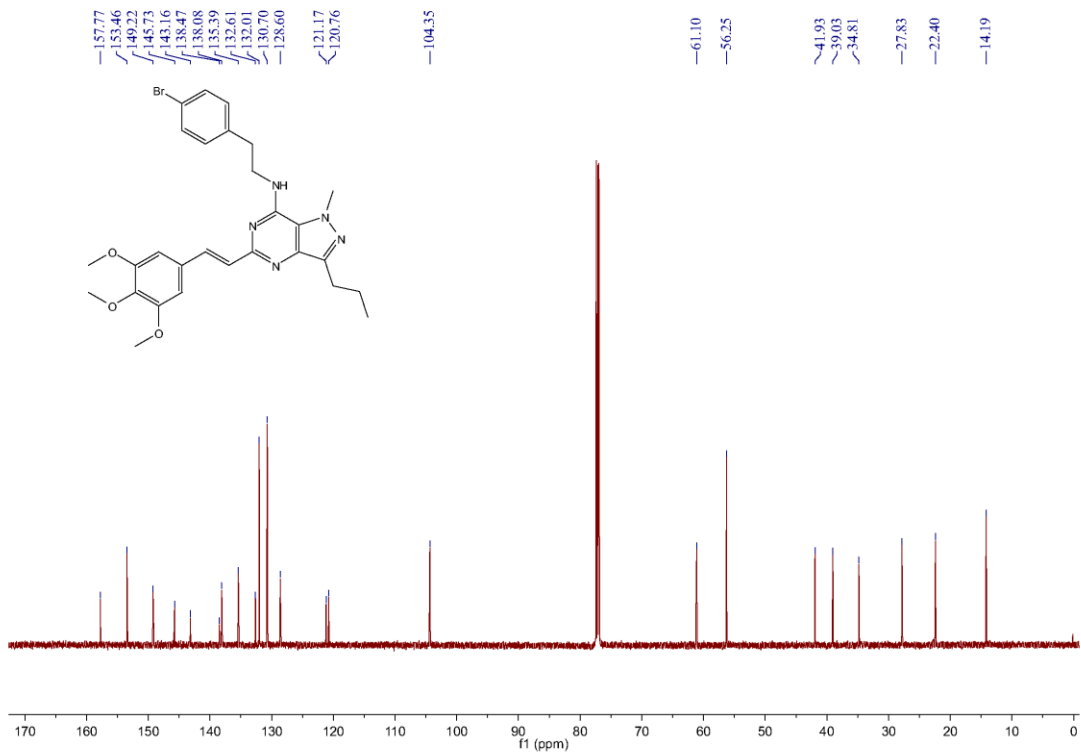
^1H NMR and ^{13}C NMR for 3g



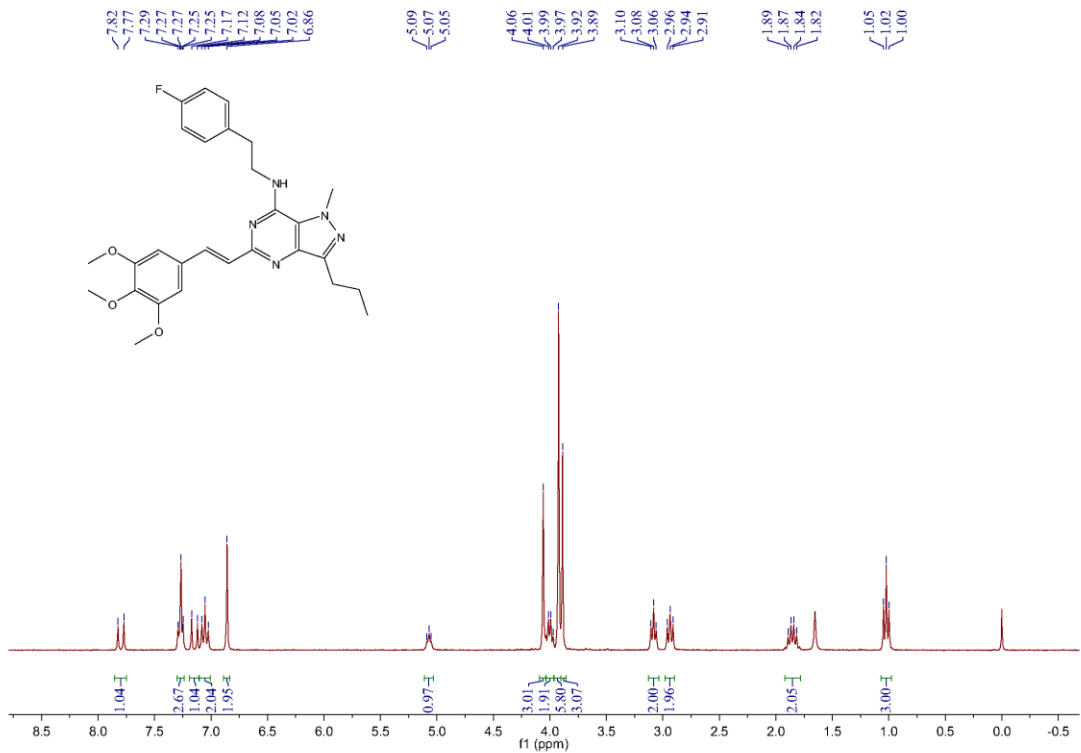


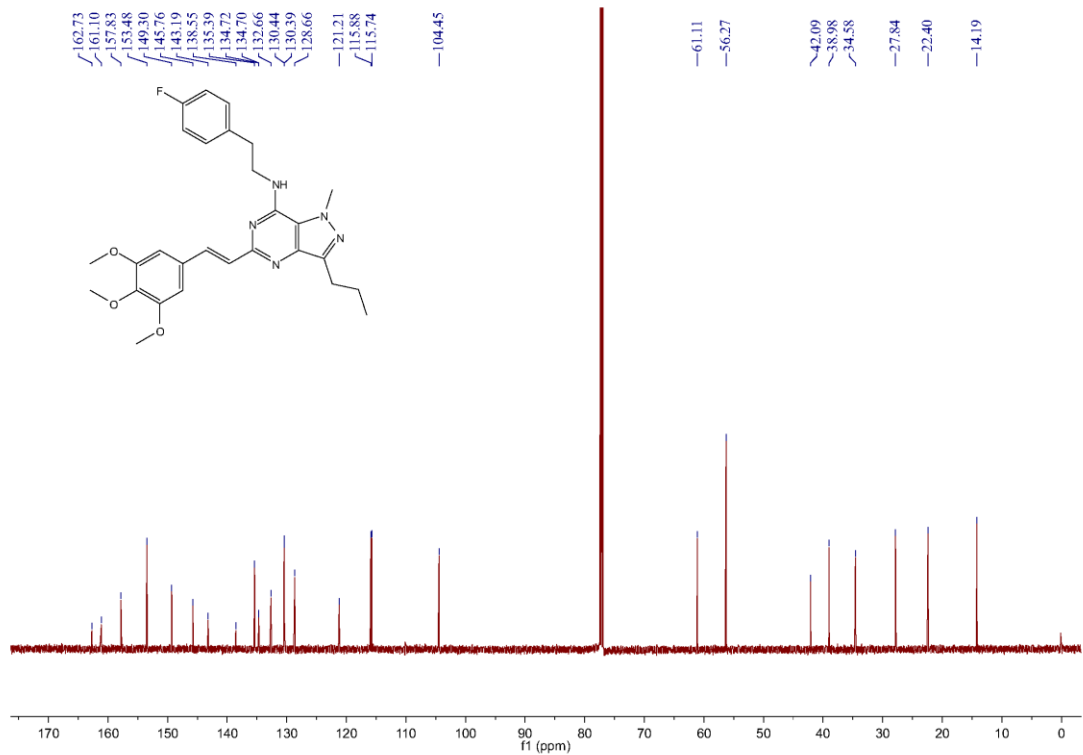
¹H NMR and ¹³C NMR for 4a



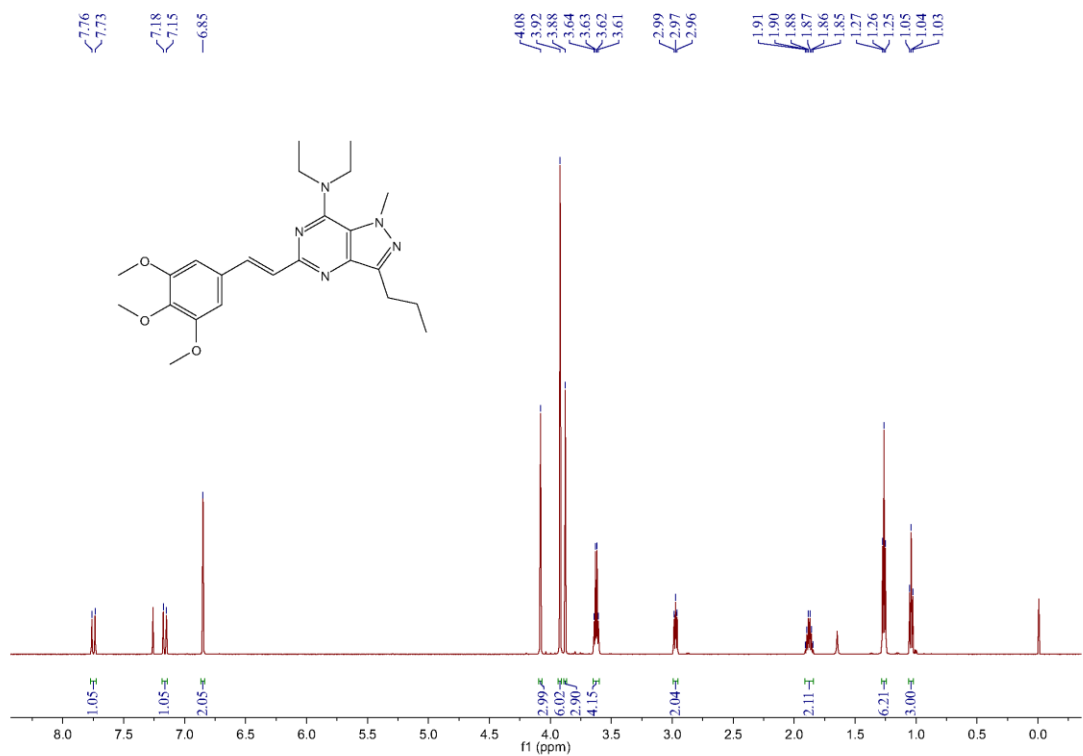


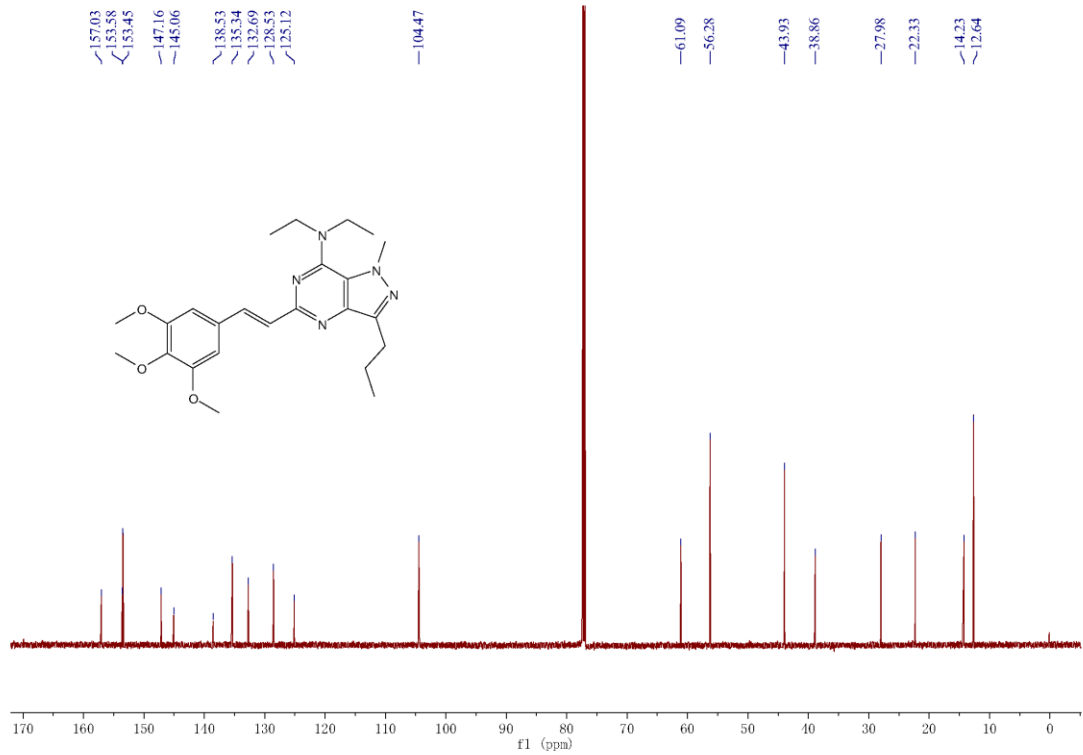
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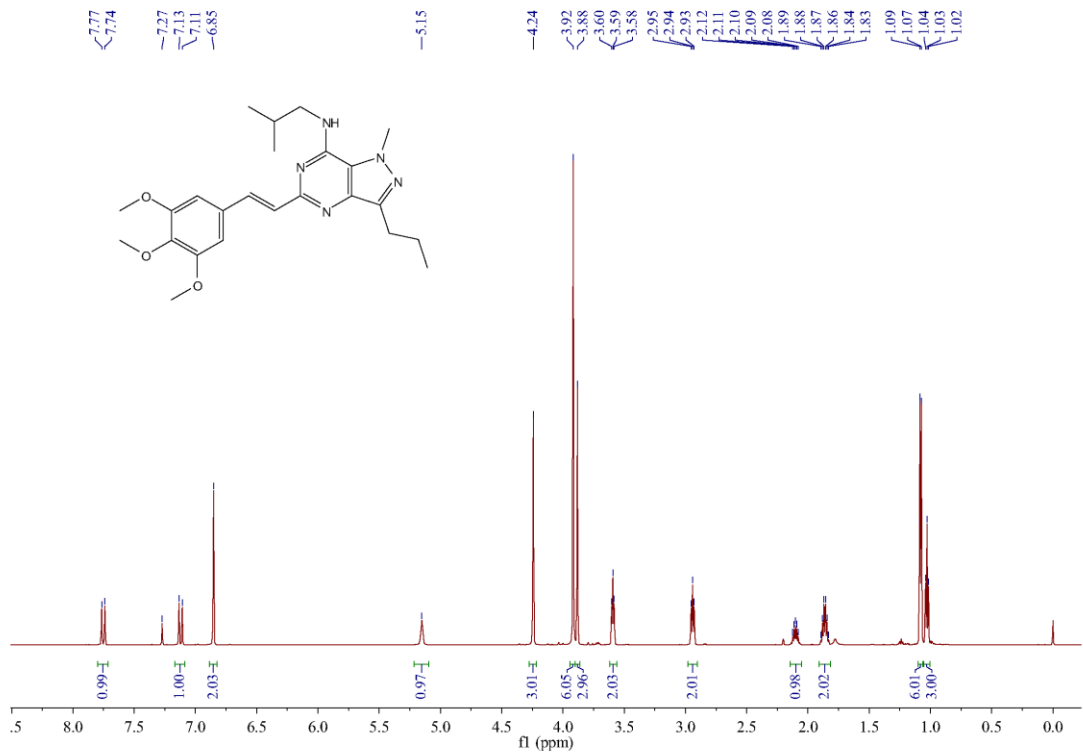


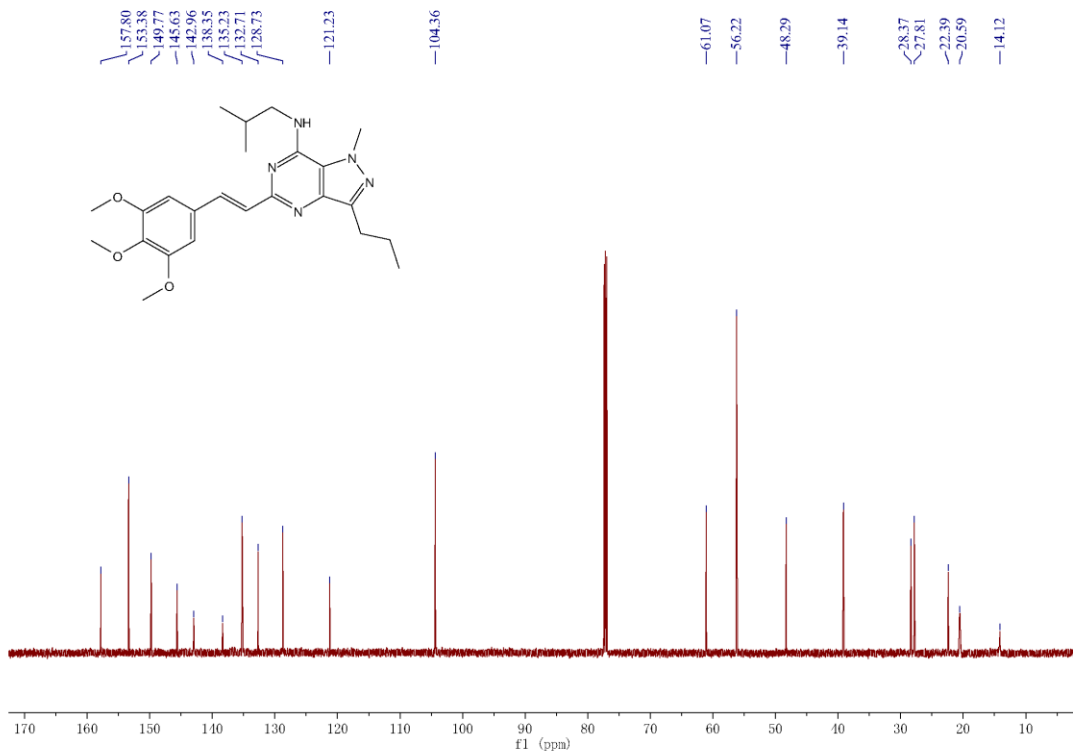
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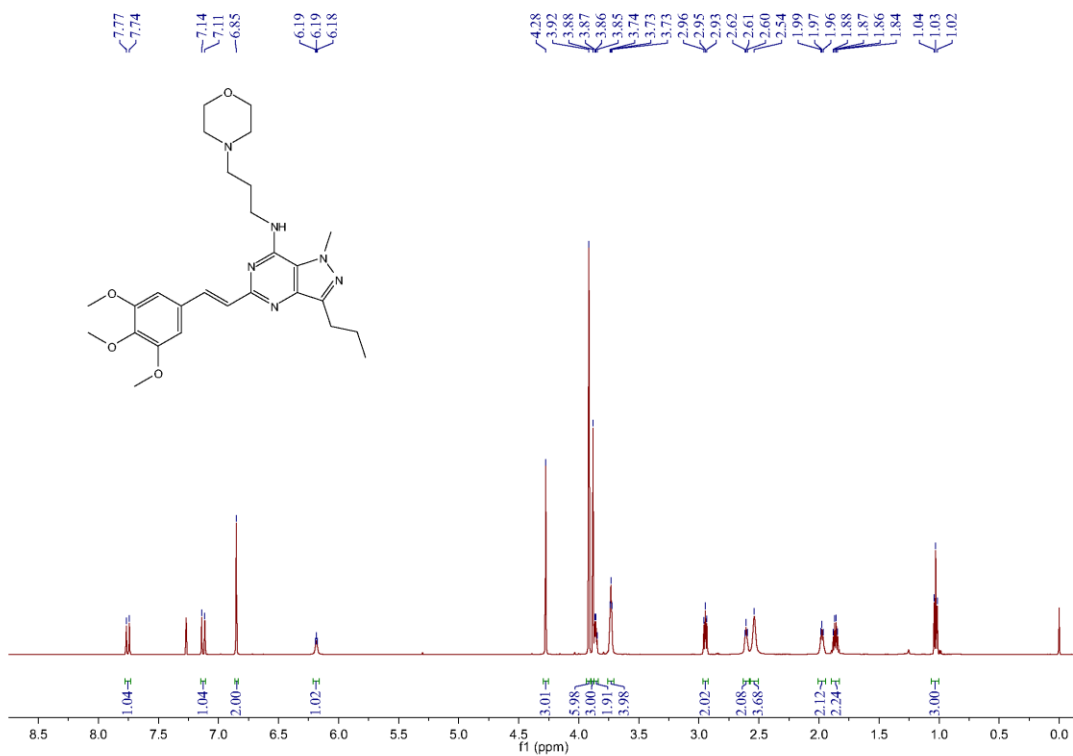


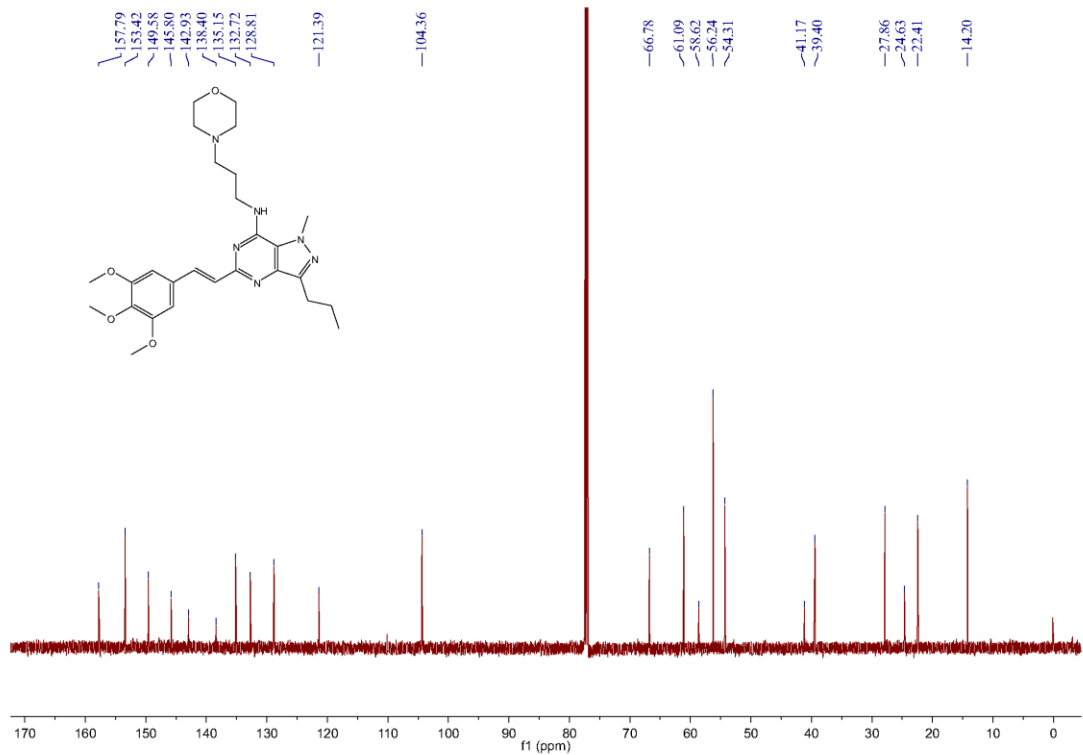
¹H NMR and ¹³C NMR for 4d



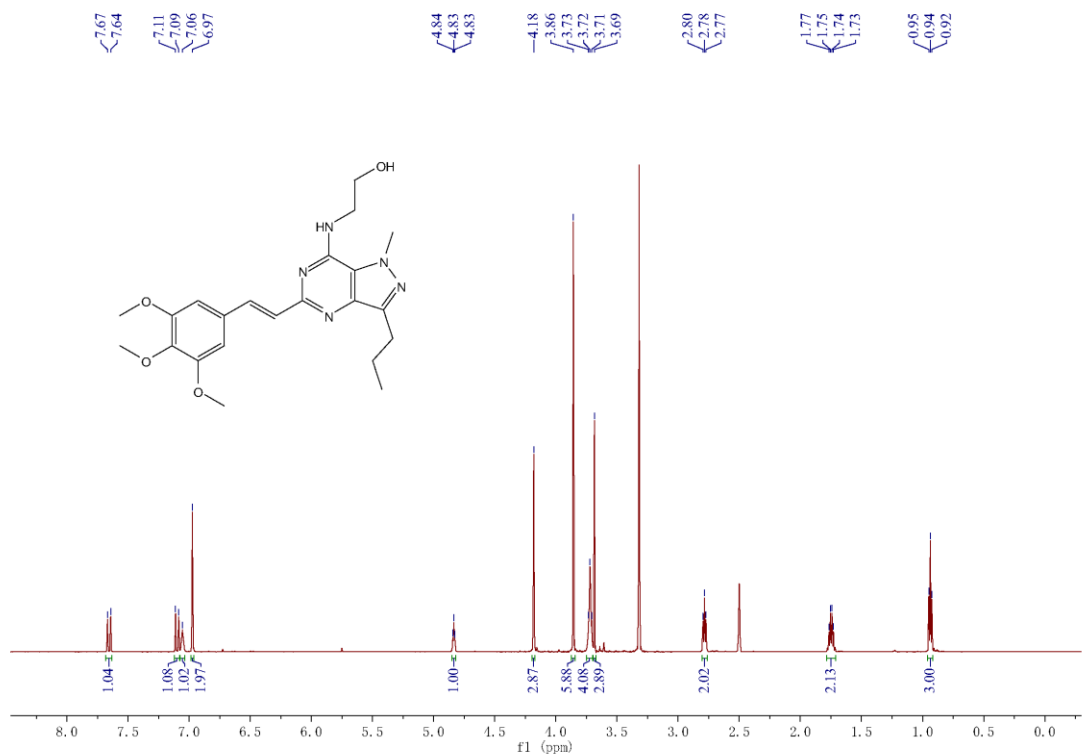


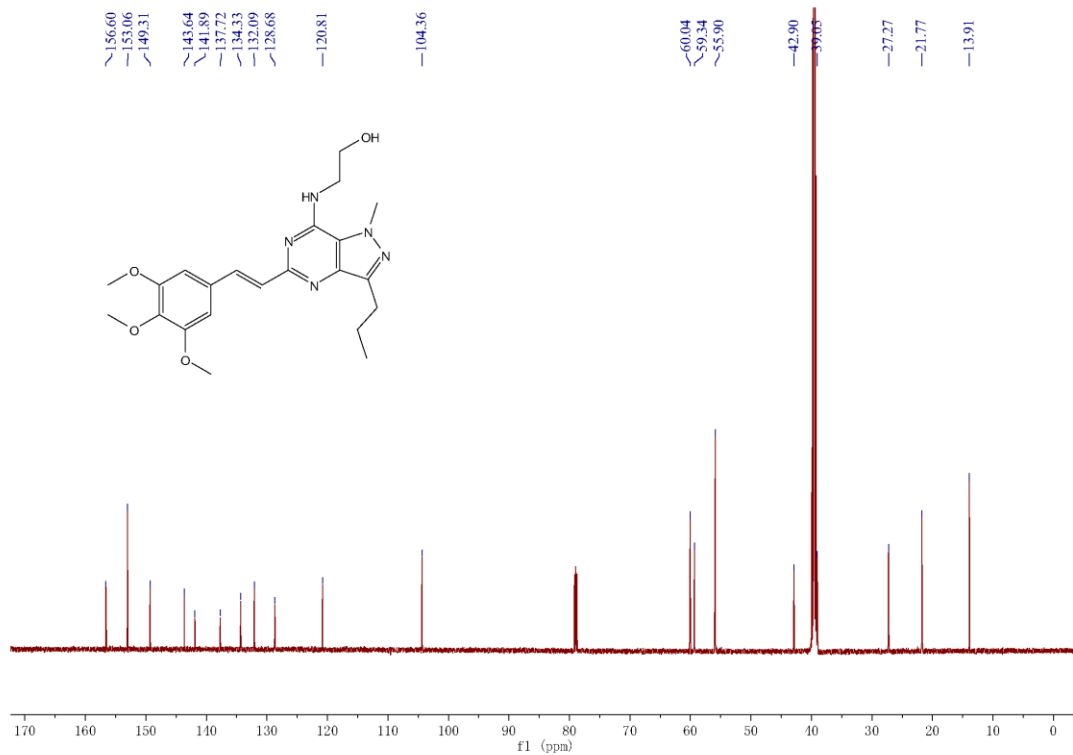
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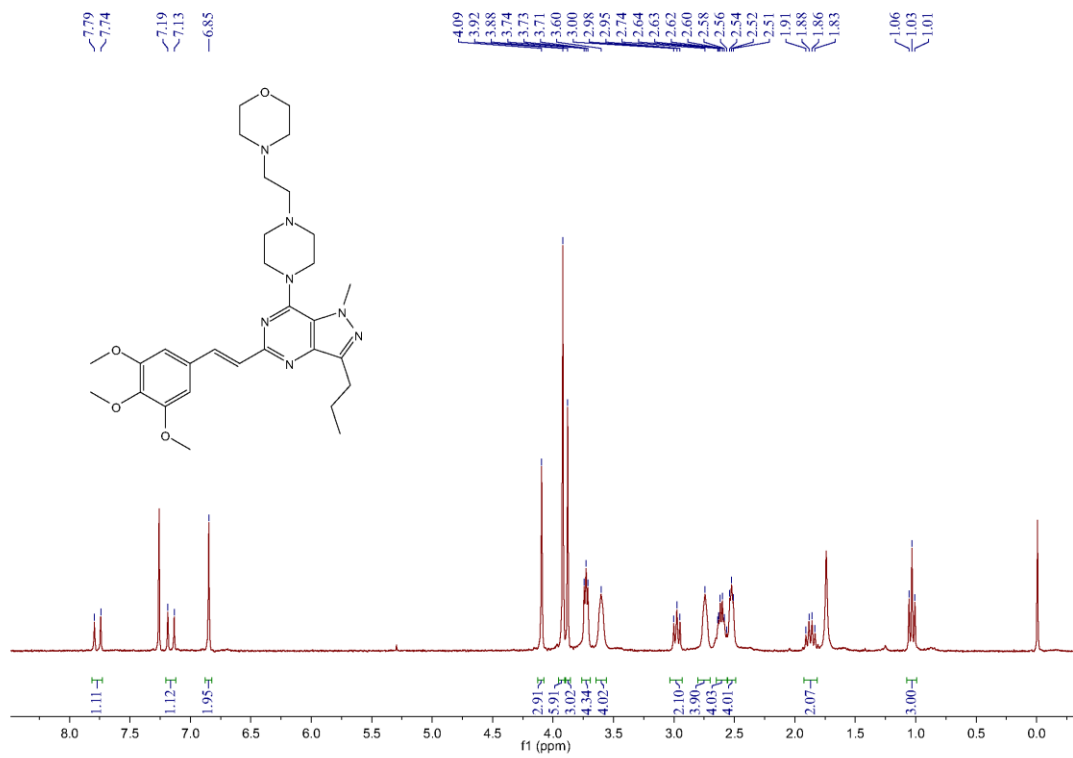


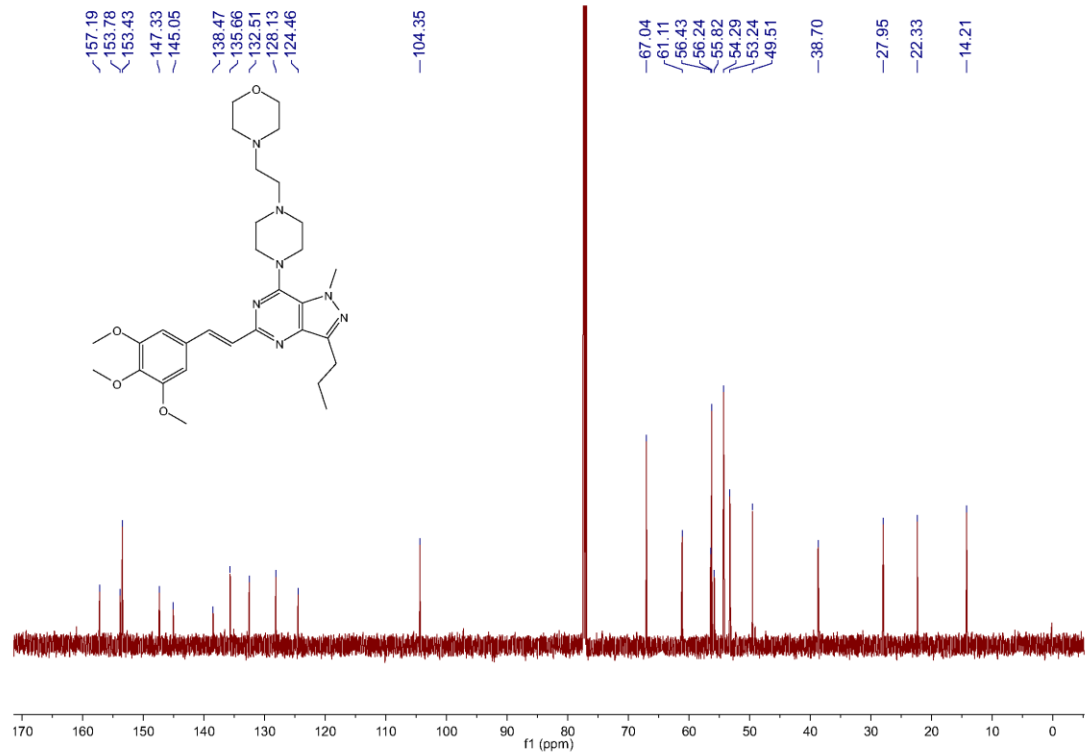
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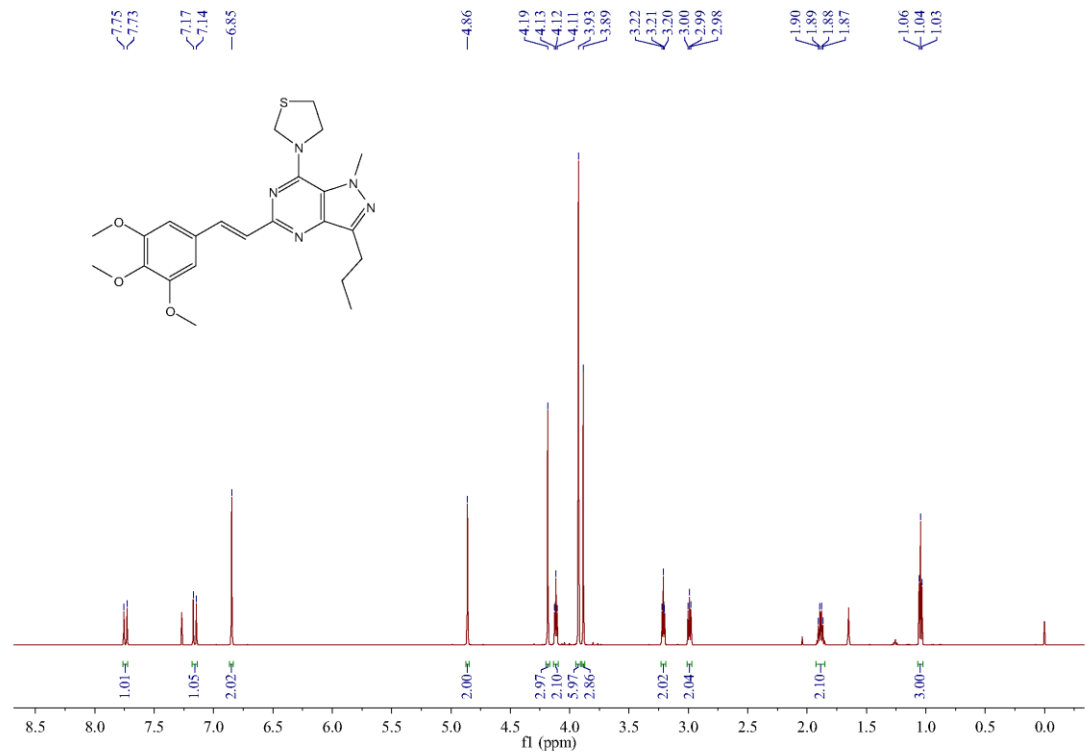


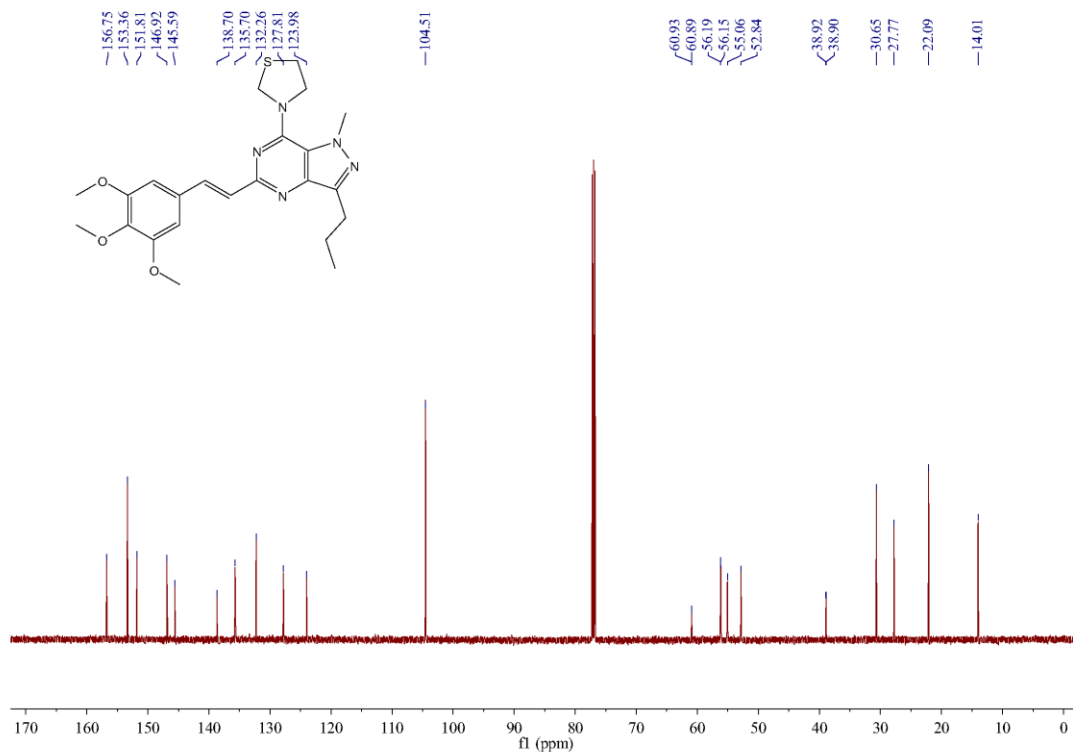
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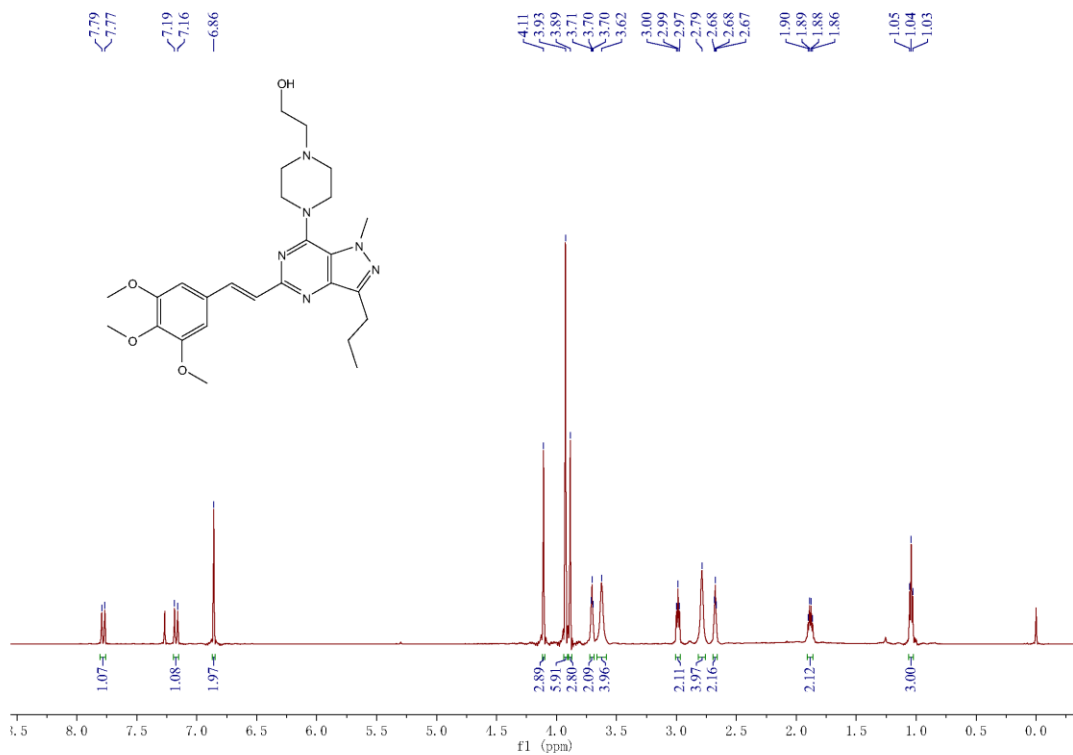


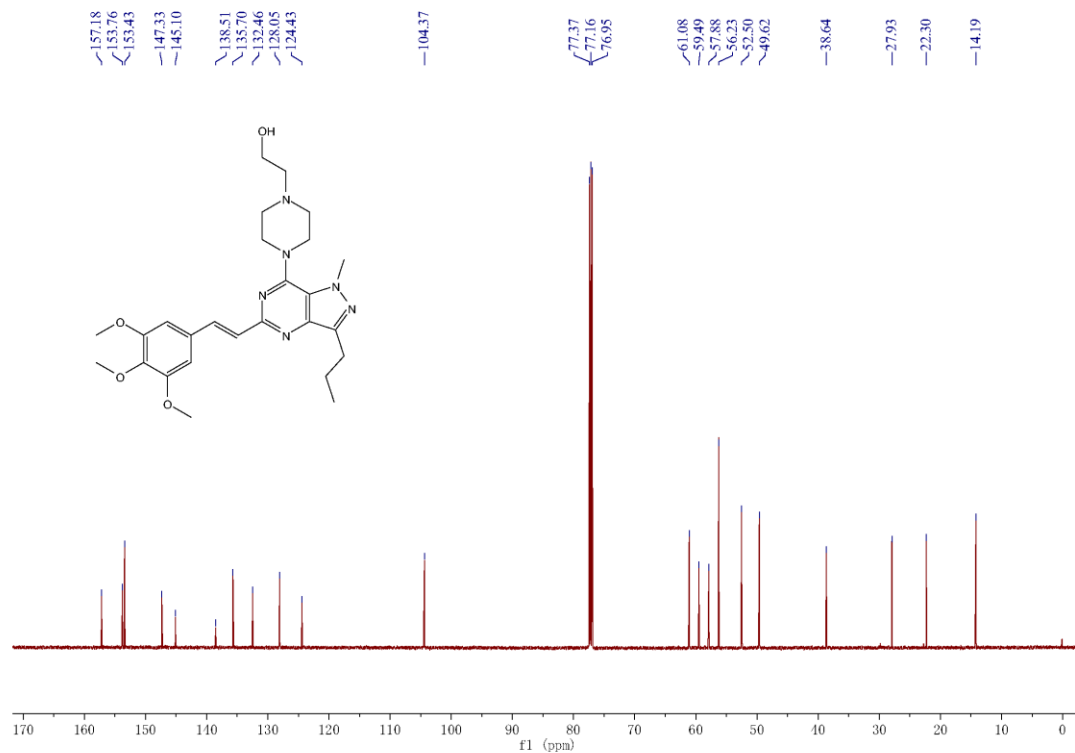
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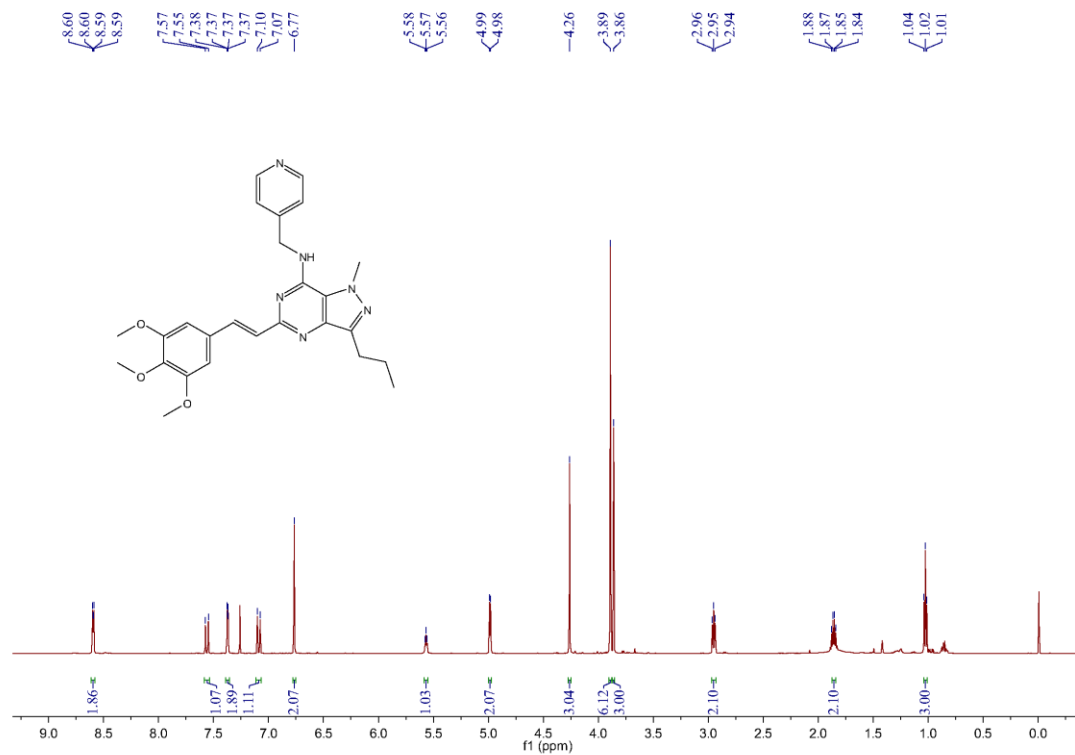


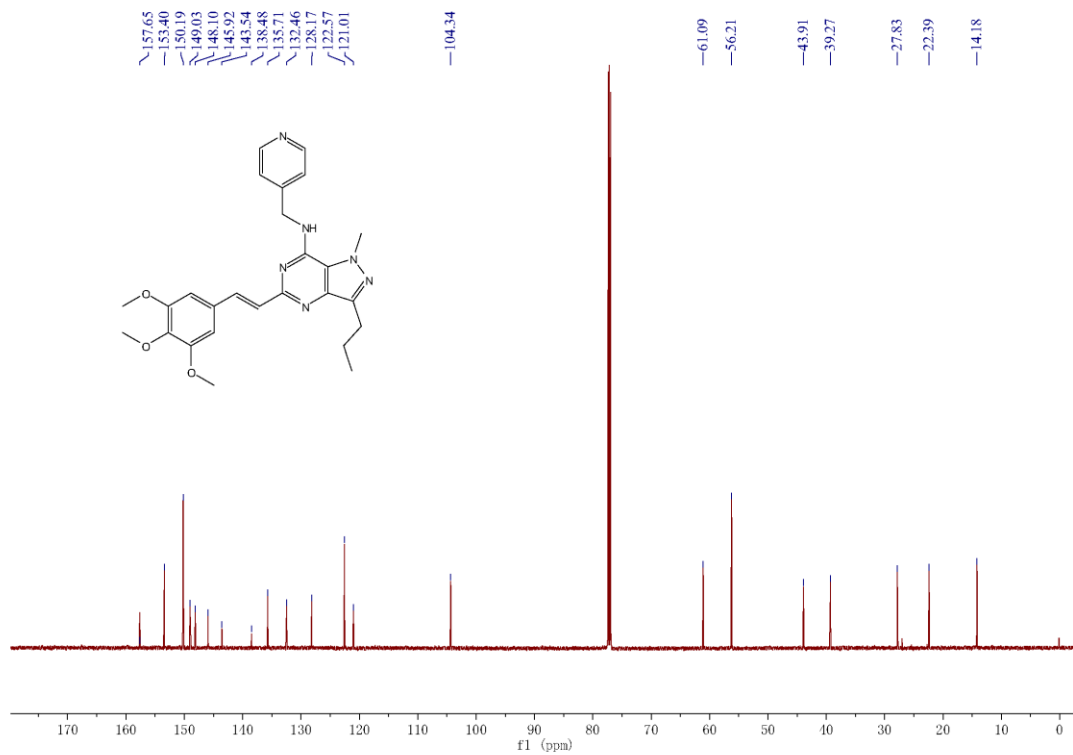
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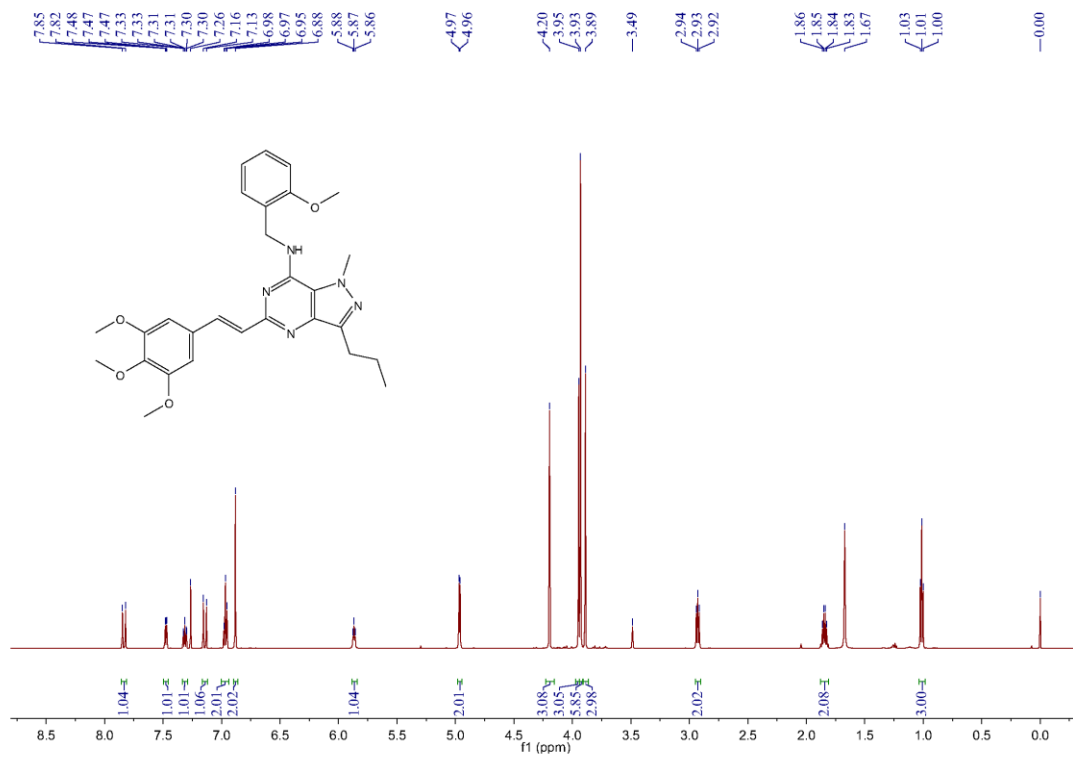


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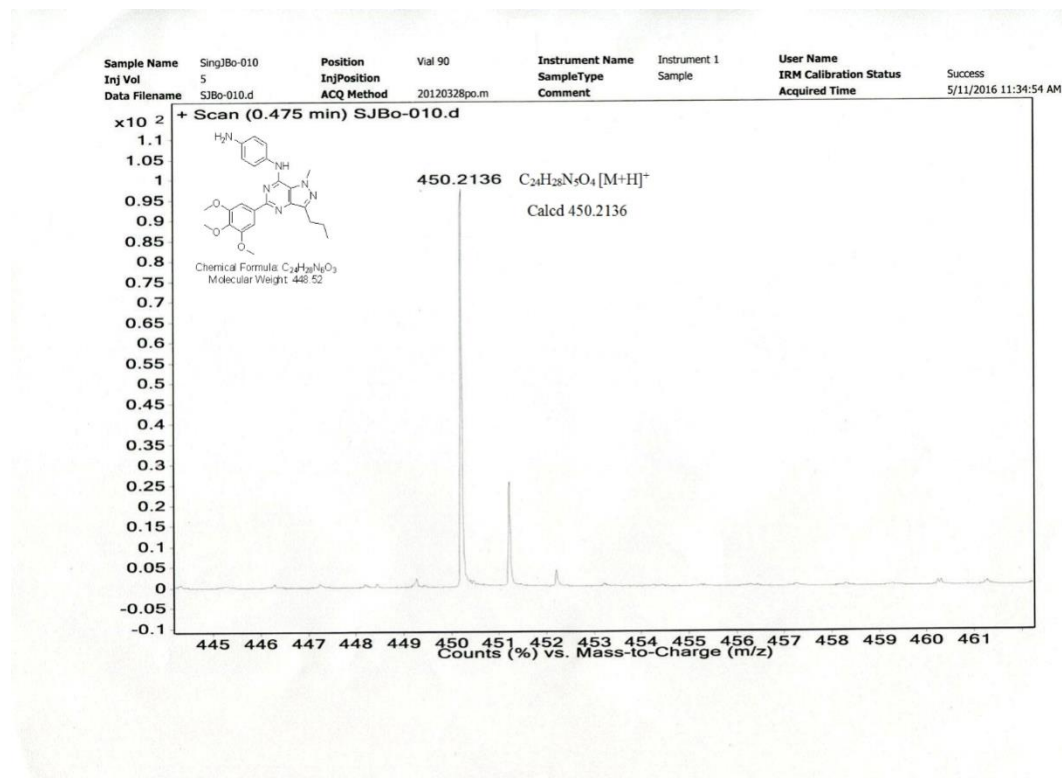


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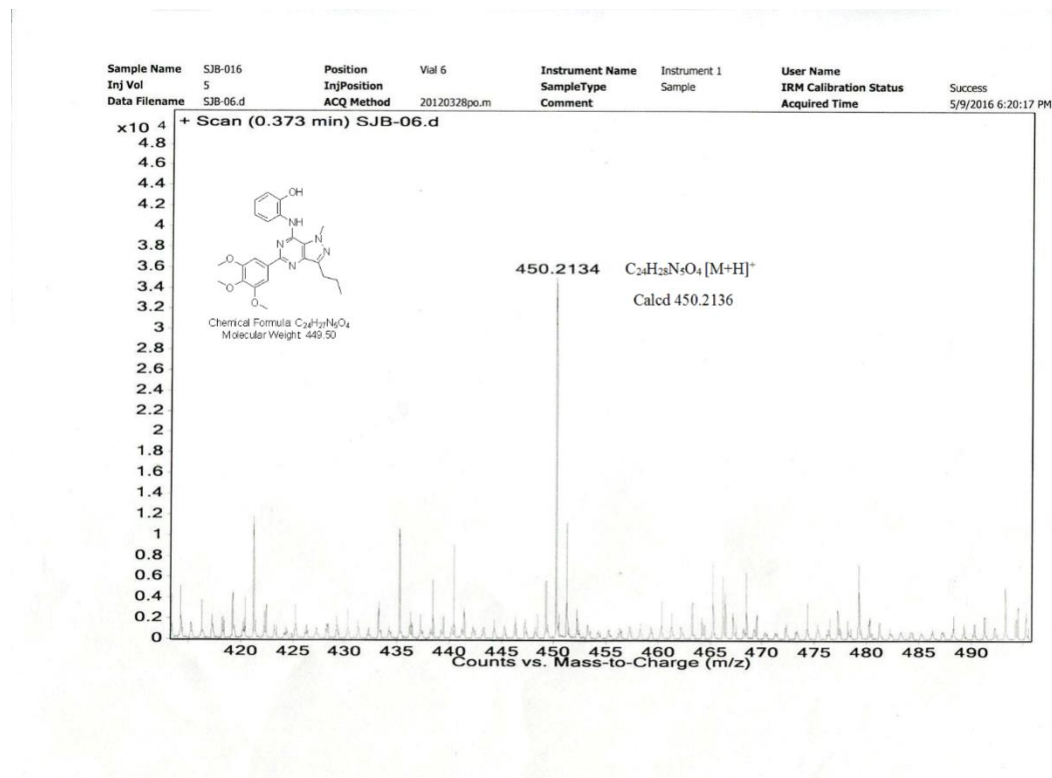


PART 3. HR-MS data of 1a~1j, 2a~2g, 3a~3g and 4a~4k.

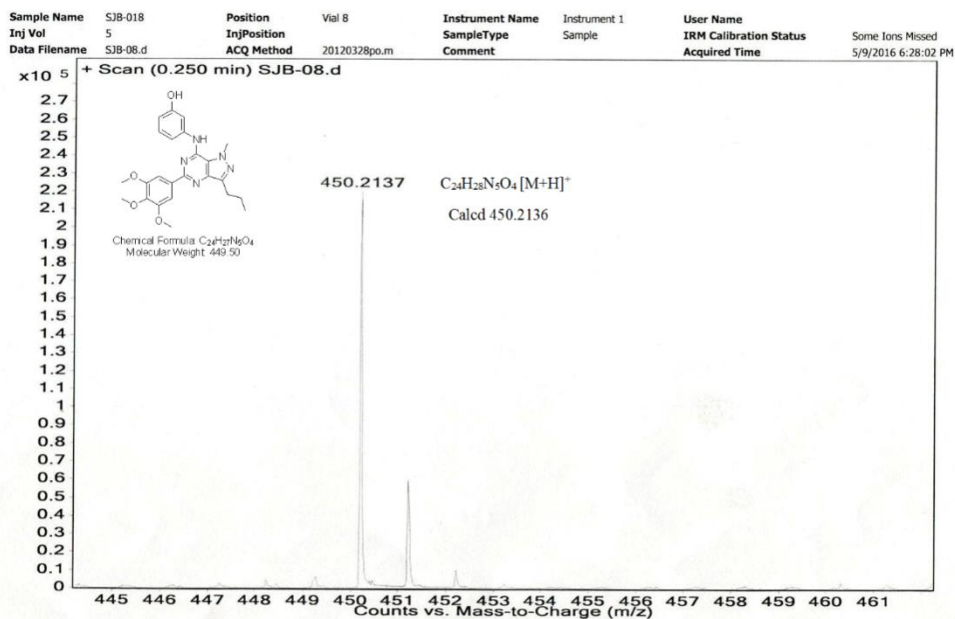
HR-MS data for 1a



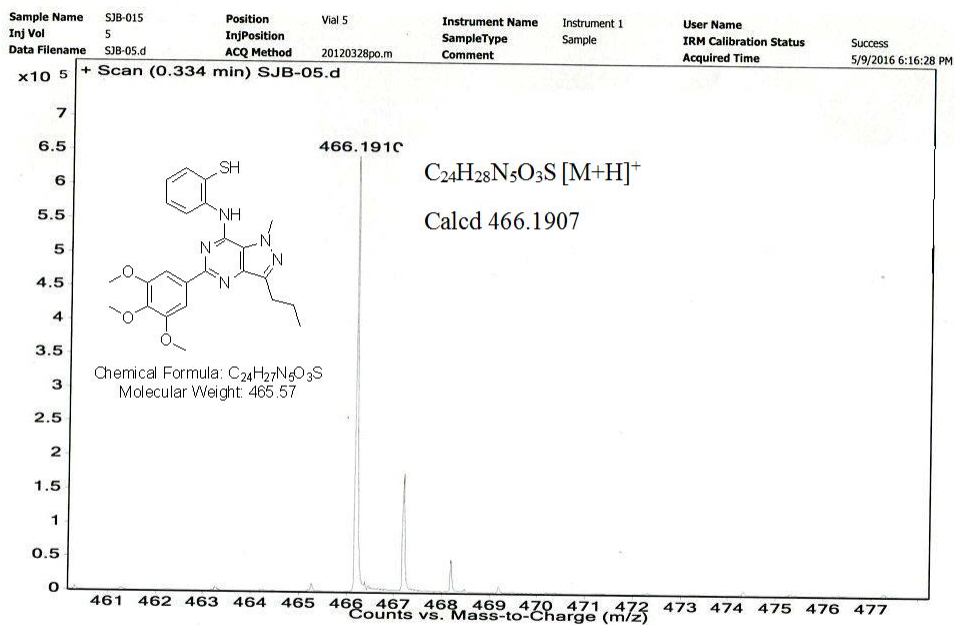
HR-MS data for 1b



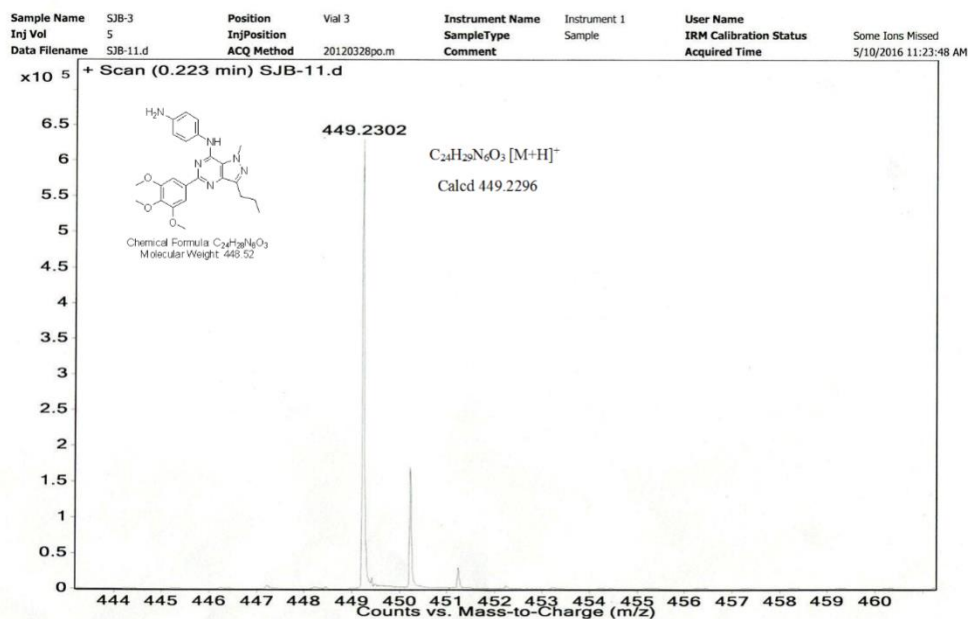
HR-MS data for *1c*



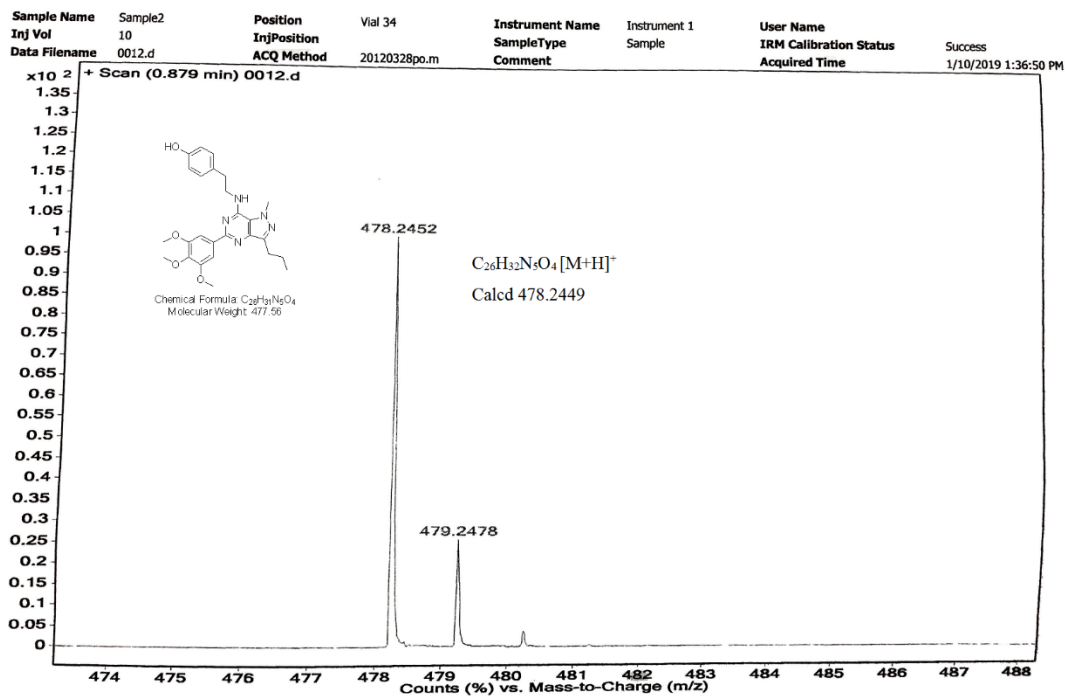
HR-MS data for *1d*



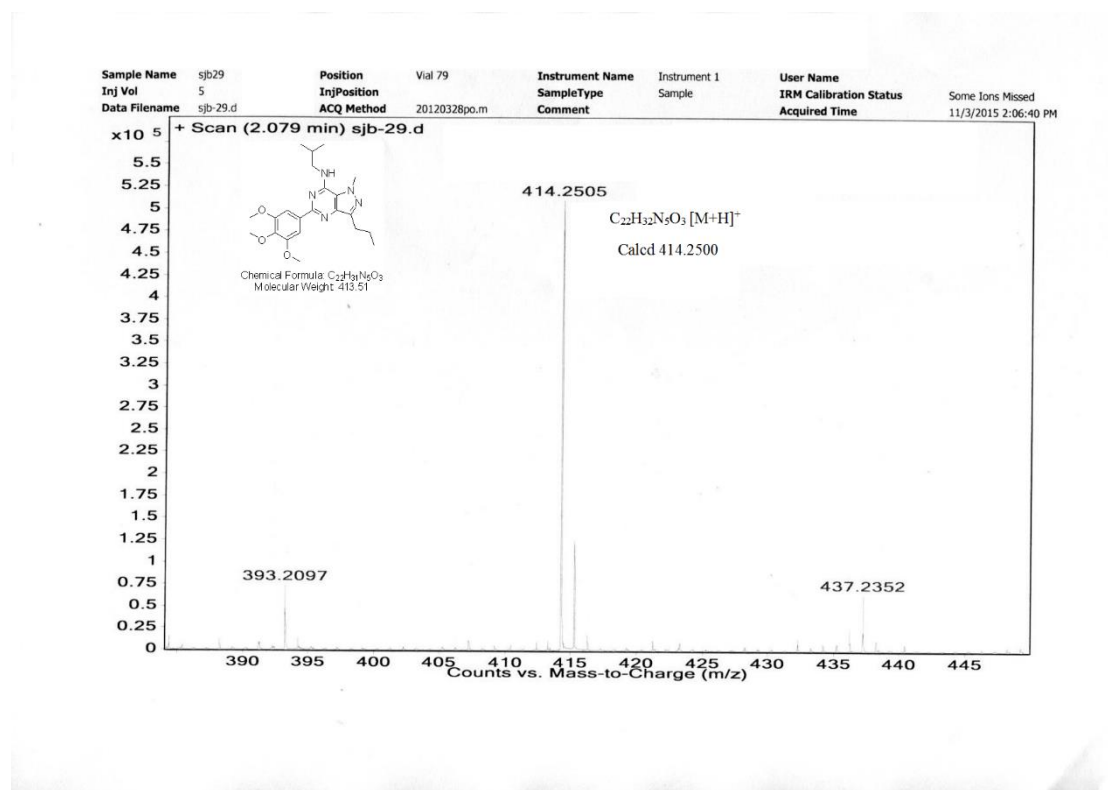
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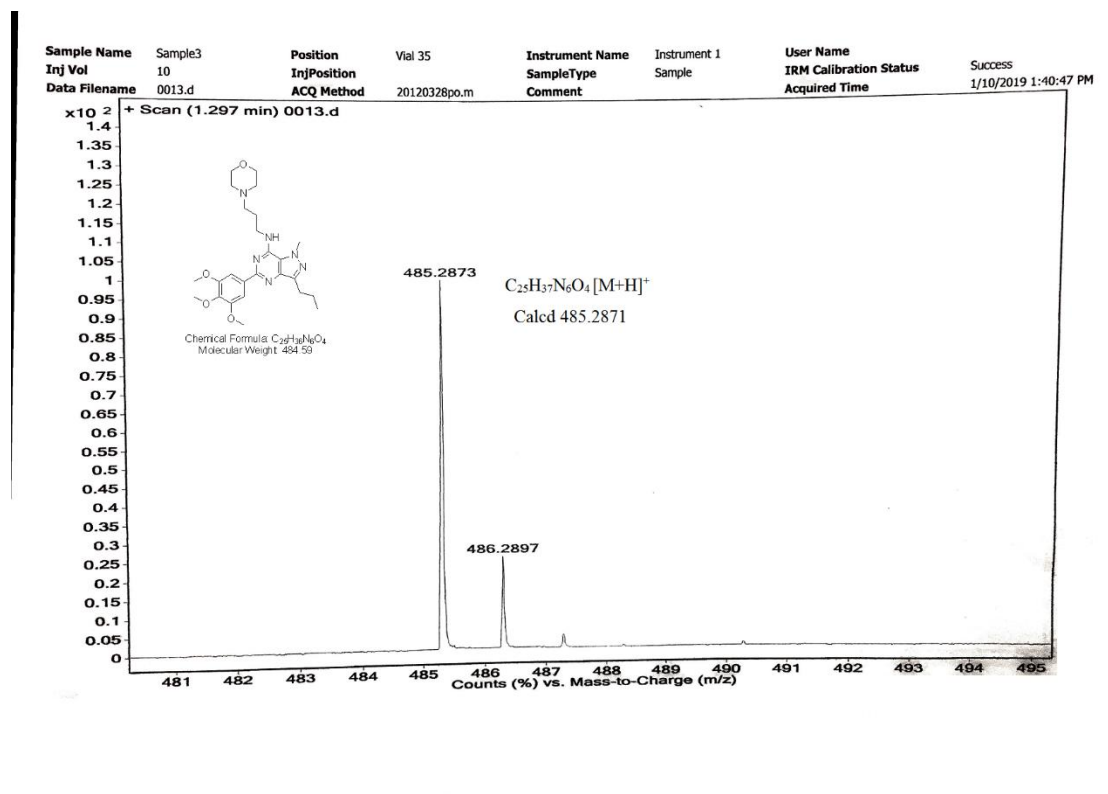
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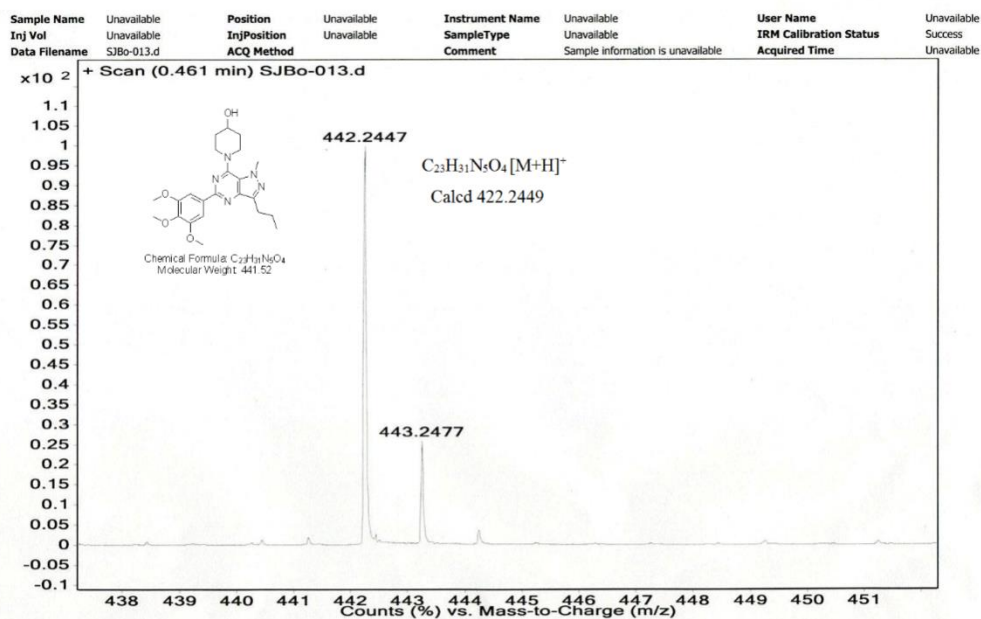
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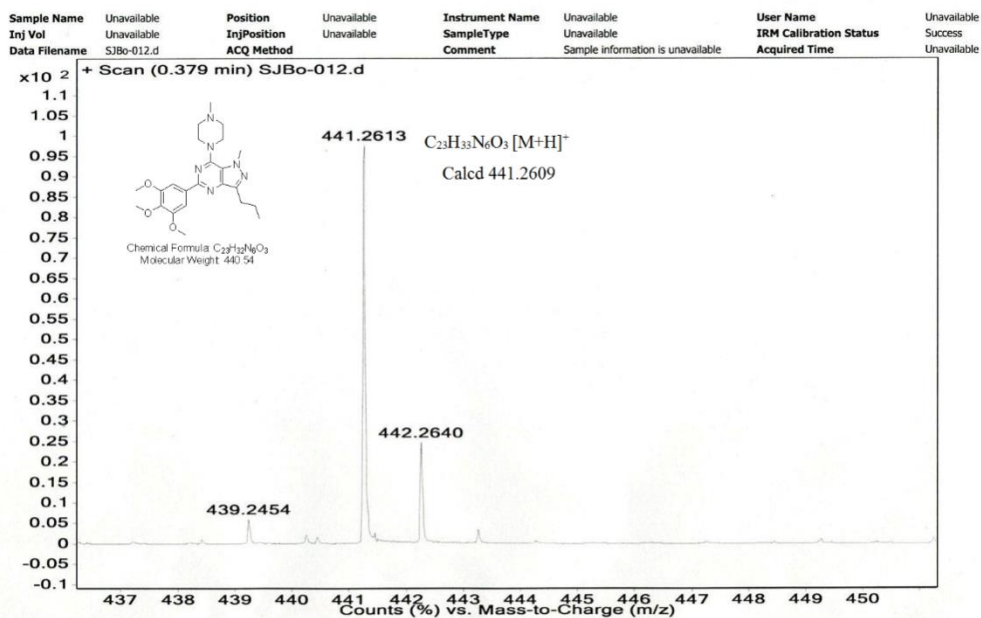
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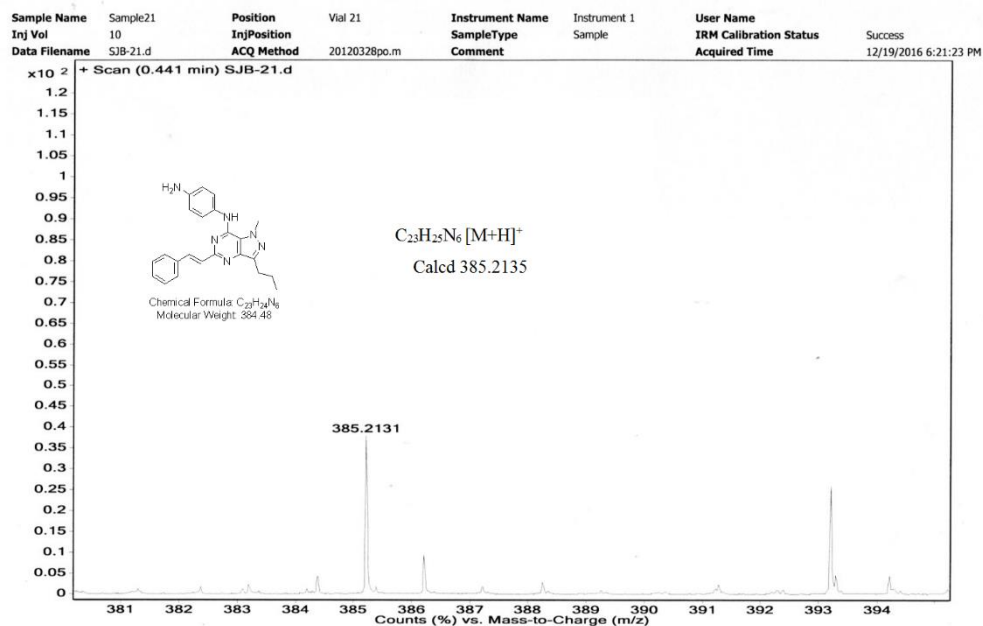
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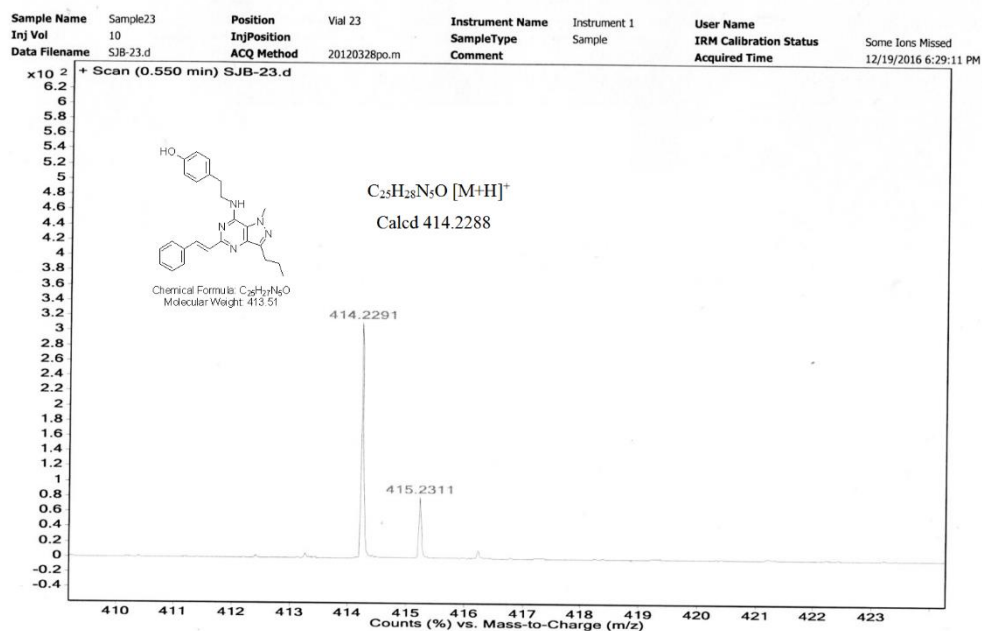
HR-MS data for *lj*



HR-MS data for 2a

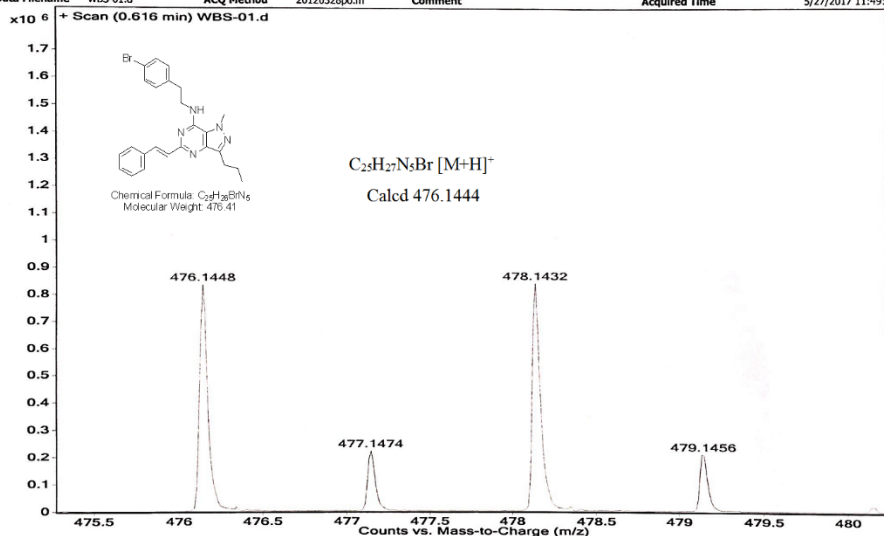


HR-MS data for 2b



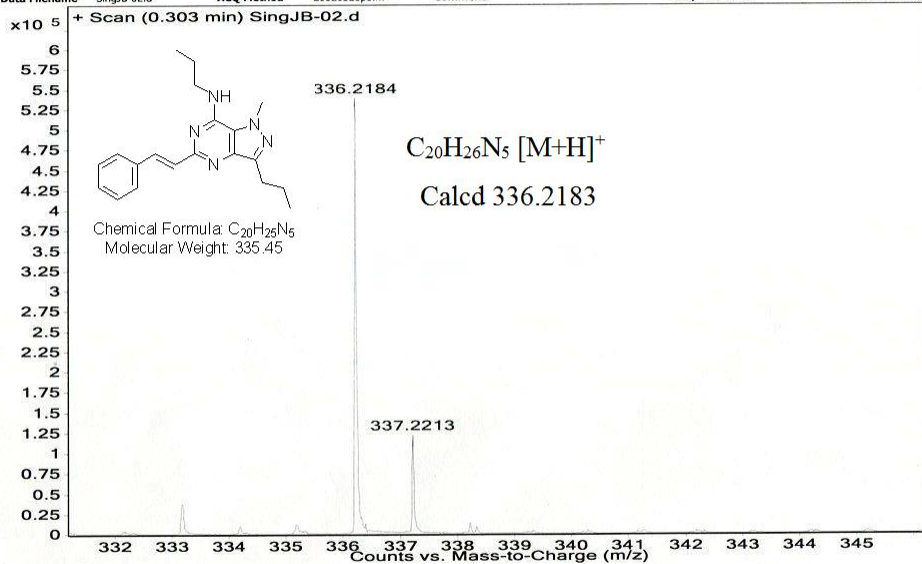
HR-MS data for 2c

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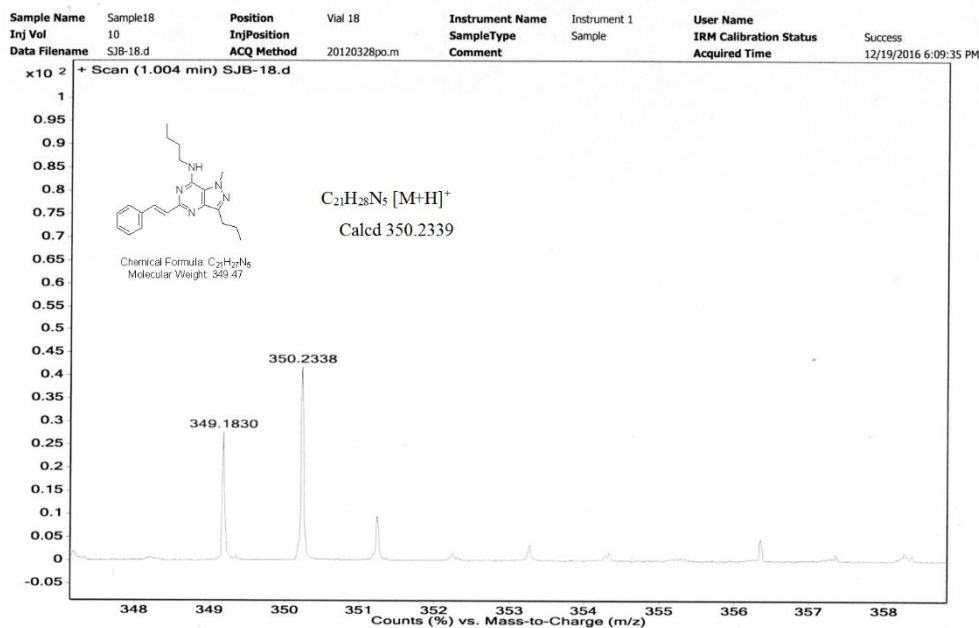


HR-MS data for 2d

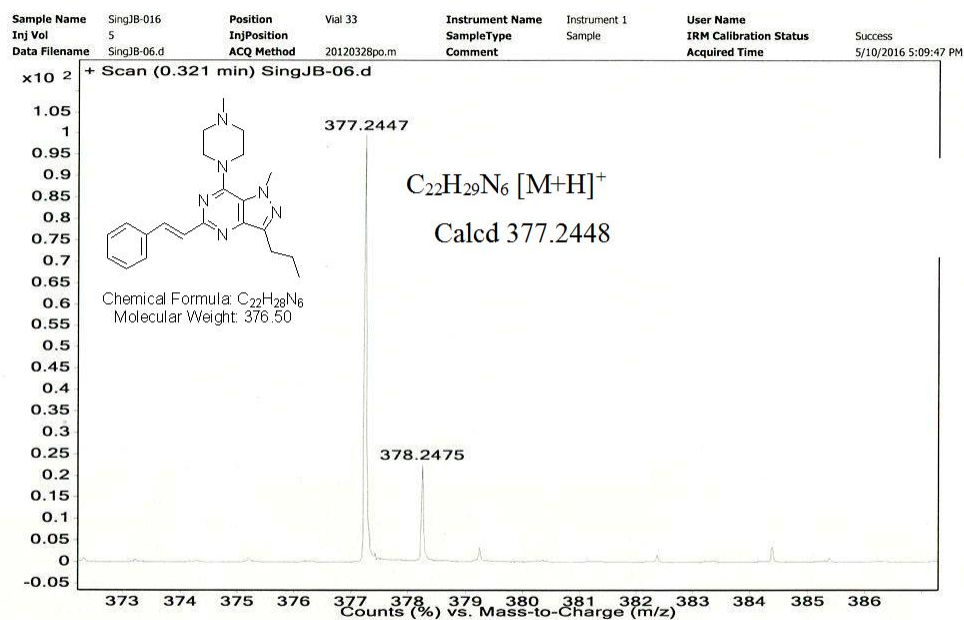
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Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Success
Data Filename	SingJB-02.d	ACQ Method	20120328po.m	Comment		Acquired Time	5/10/2016 4:54:18 PM



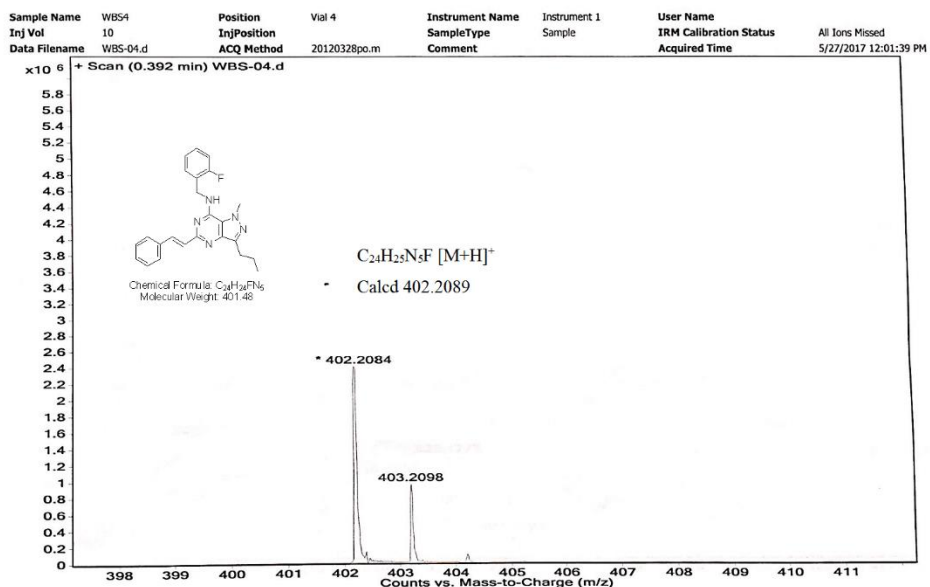
HR-MS data for 2e



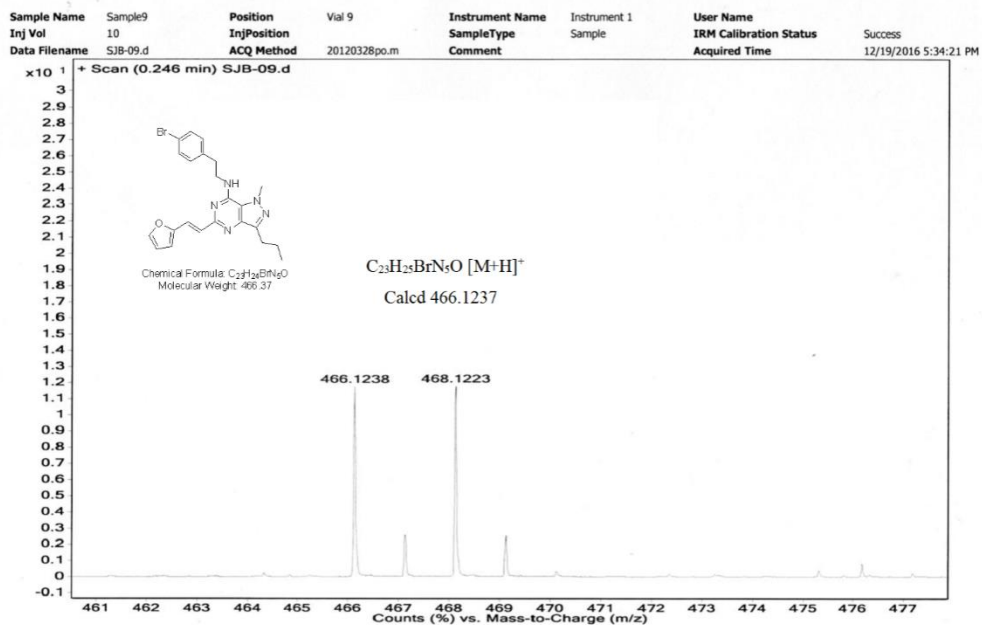
HR-MS data for 2f



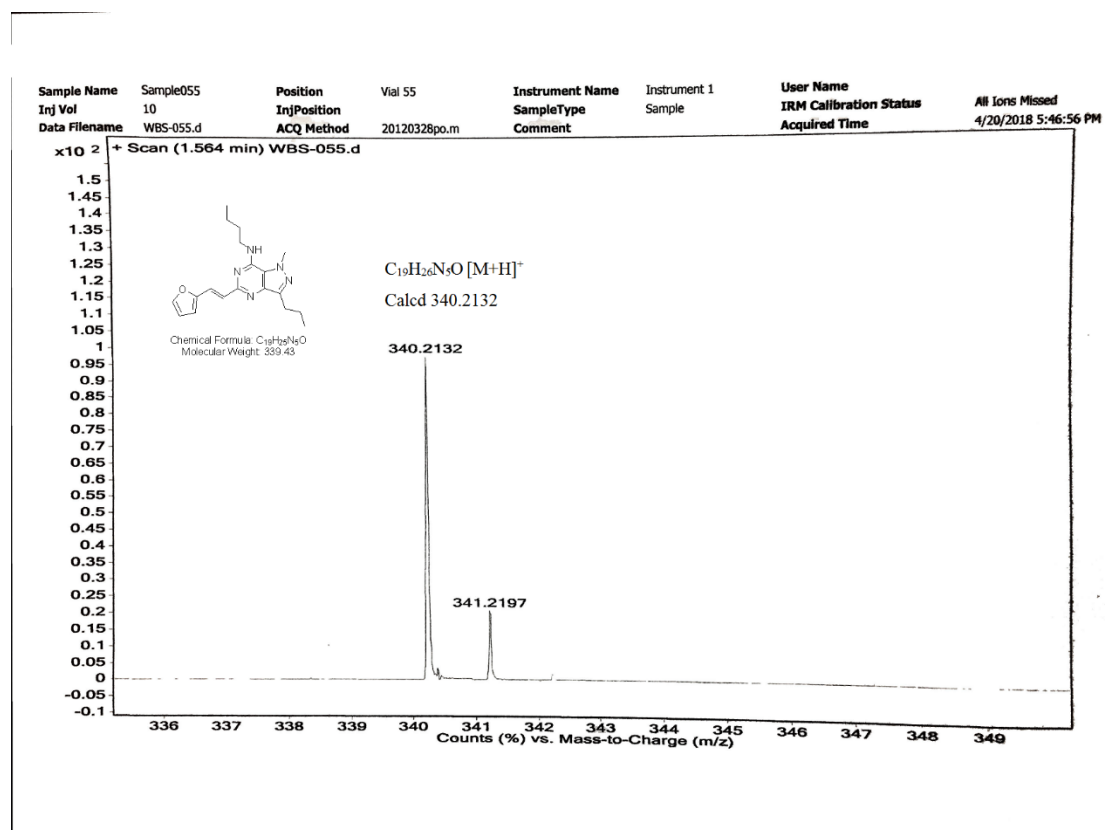
HR-MS data for 2g



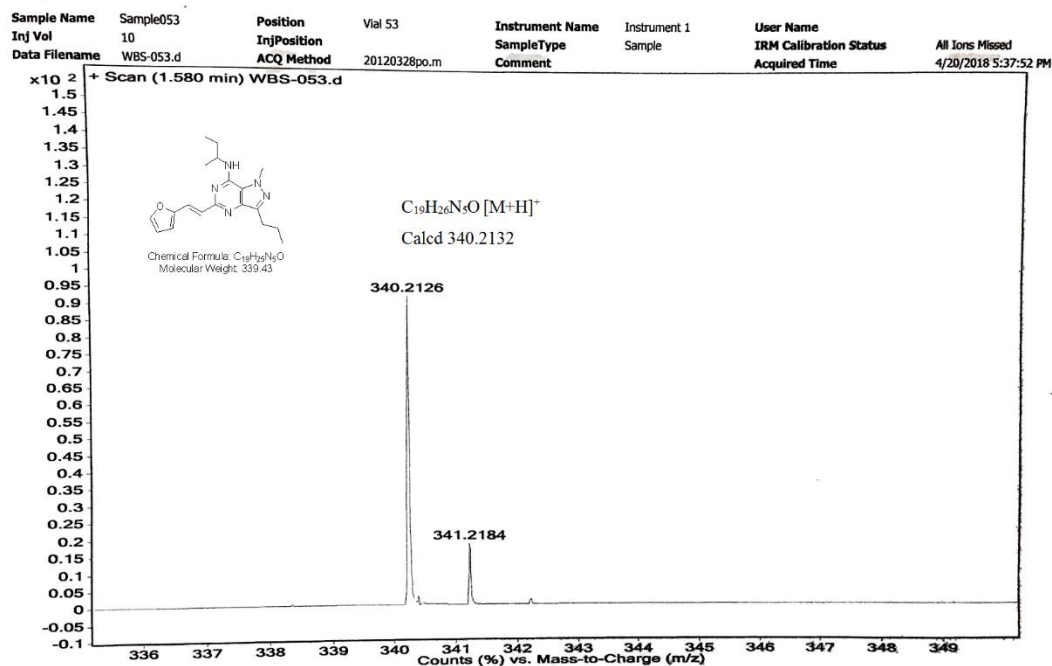
HR-MS data for 3a



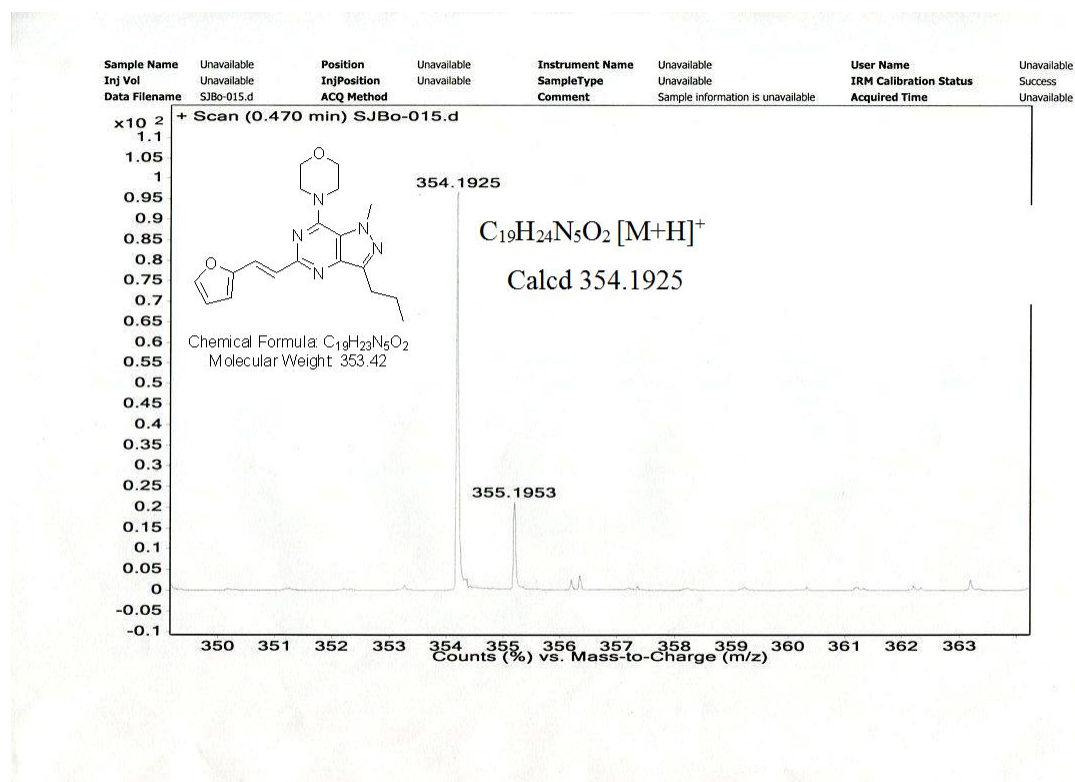
HR-MS data for 3b



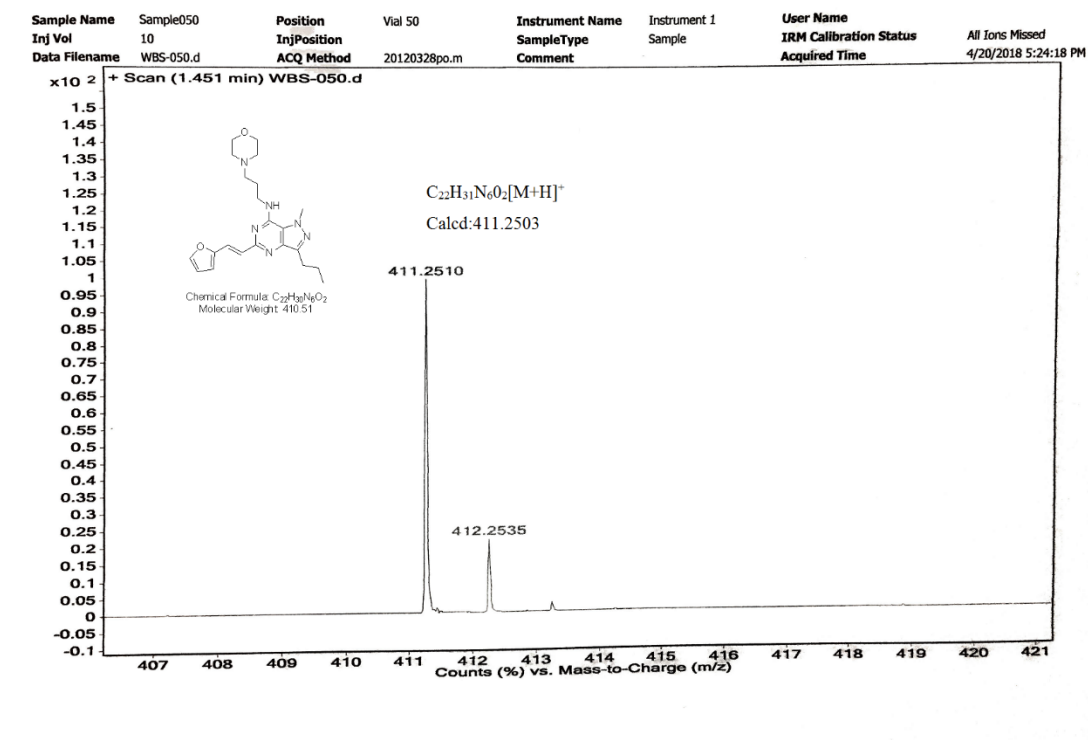
HR-MS data for 3c



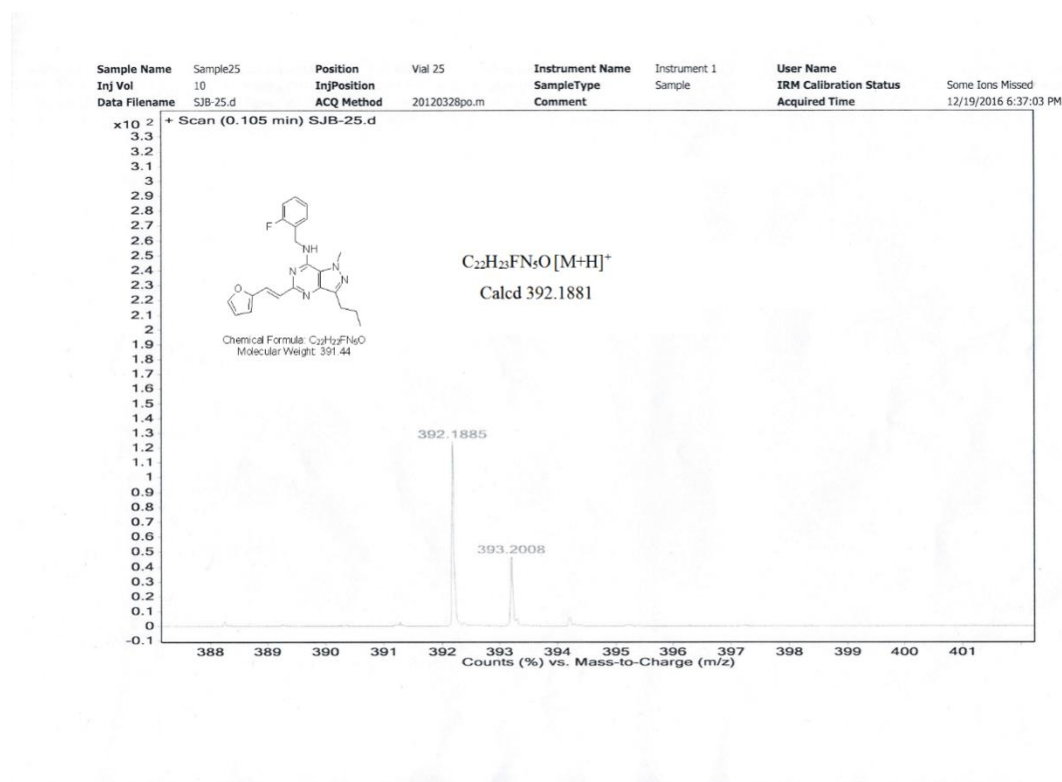
HR-MS data for 3d



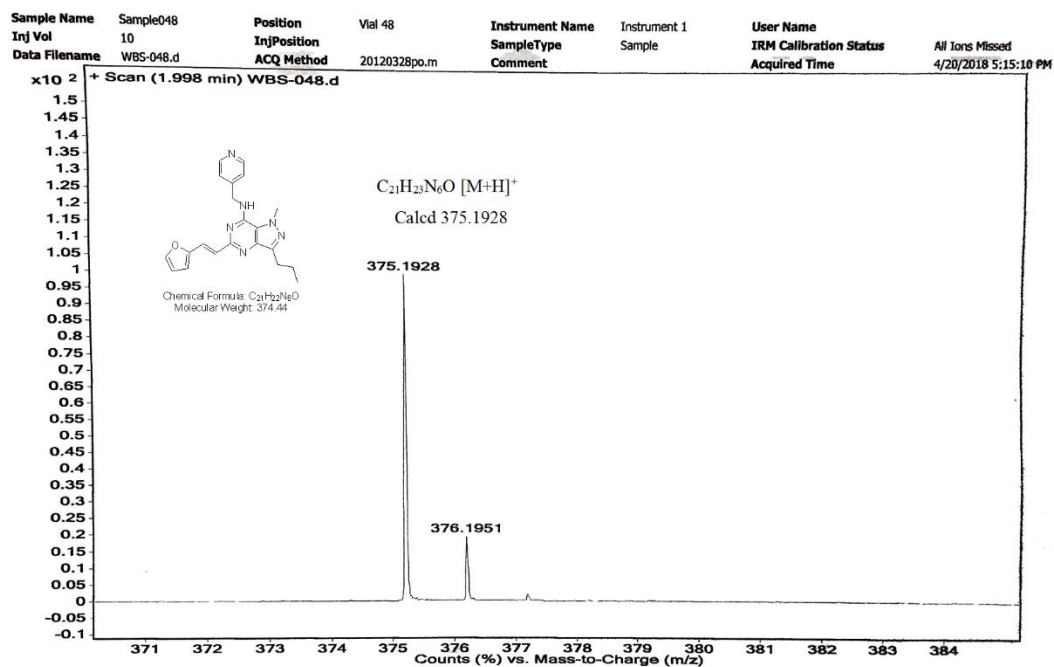
HR-MS data for 3e



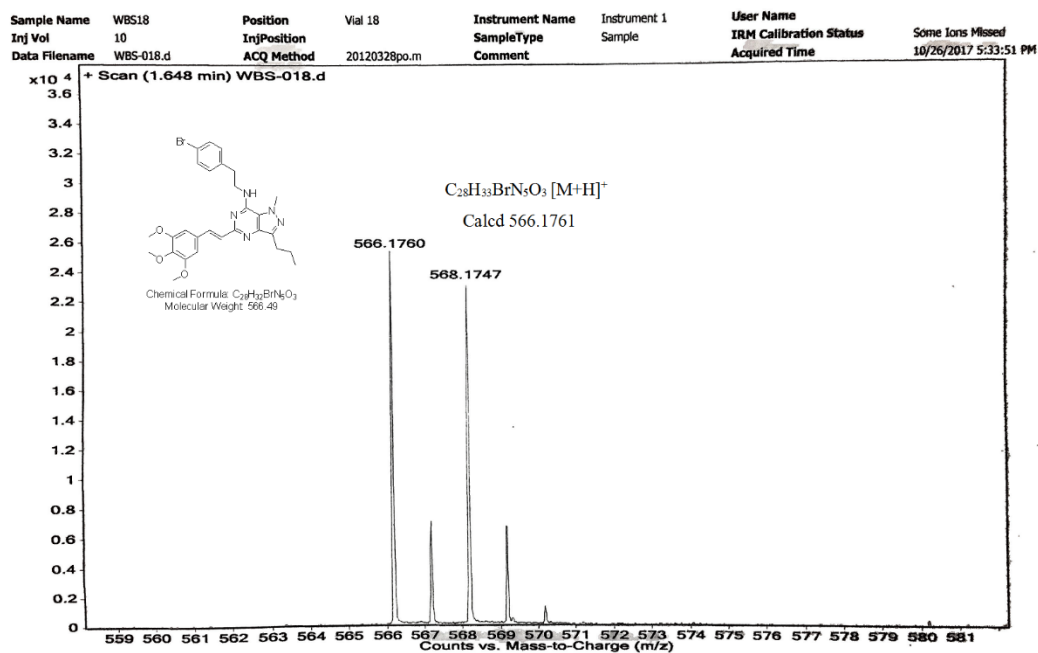
HR-MS data for 3f



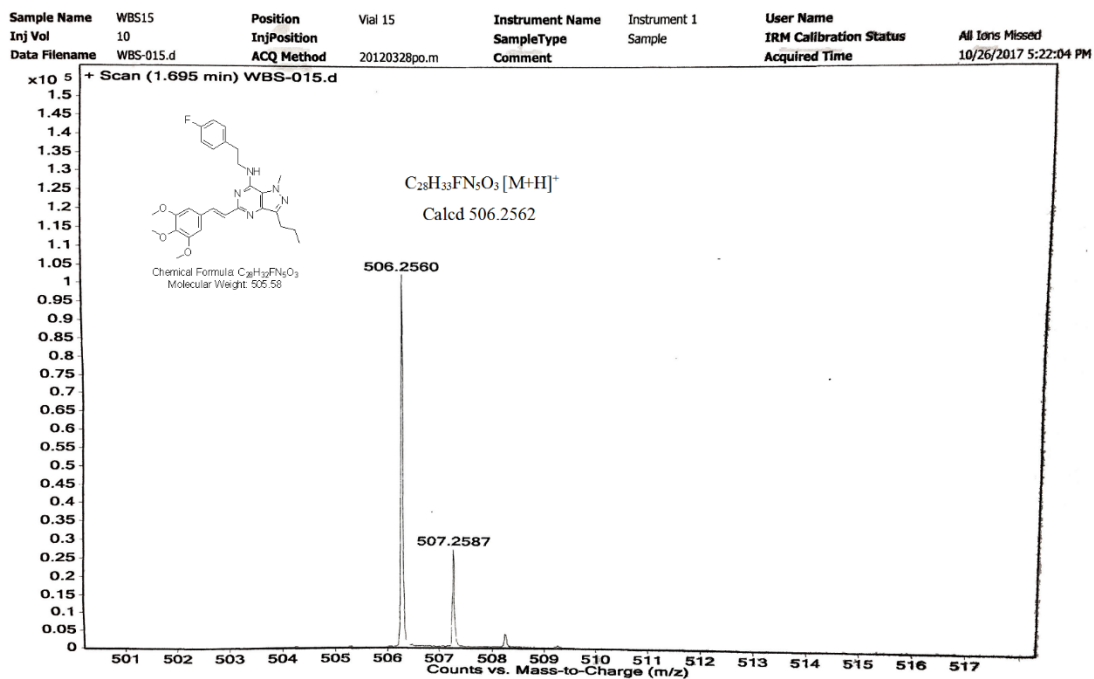
HR-MS data for 3g



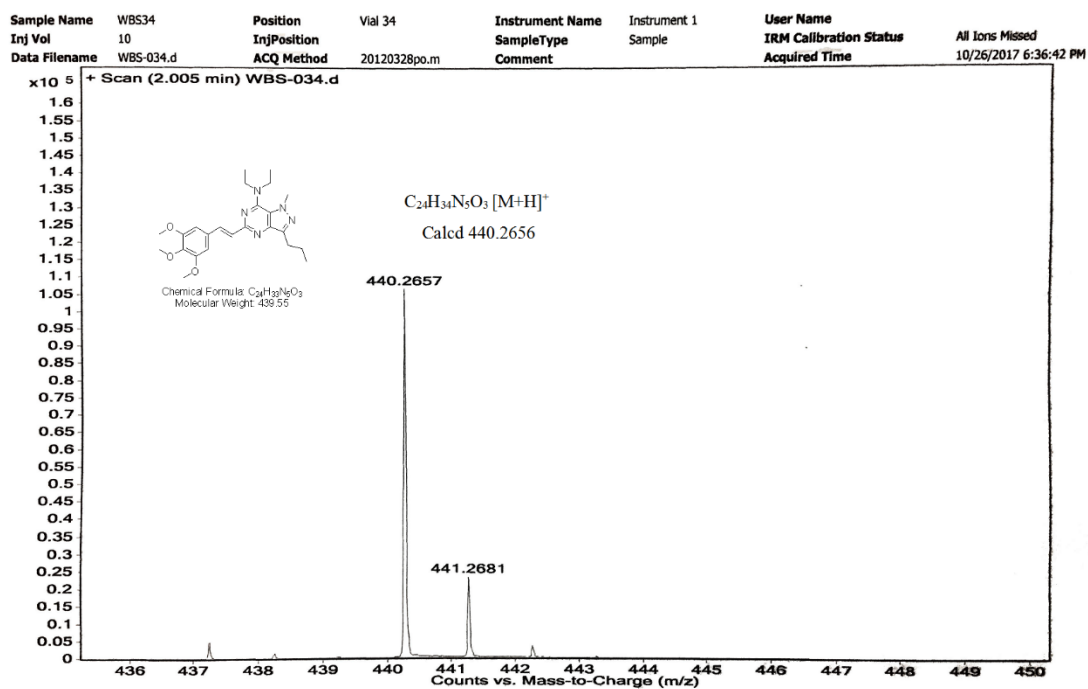
HR-MS data for 4a



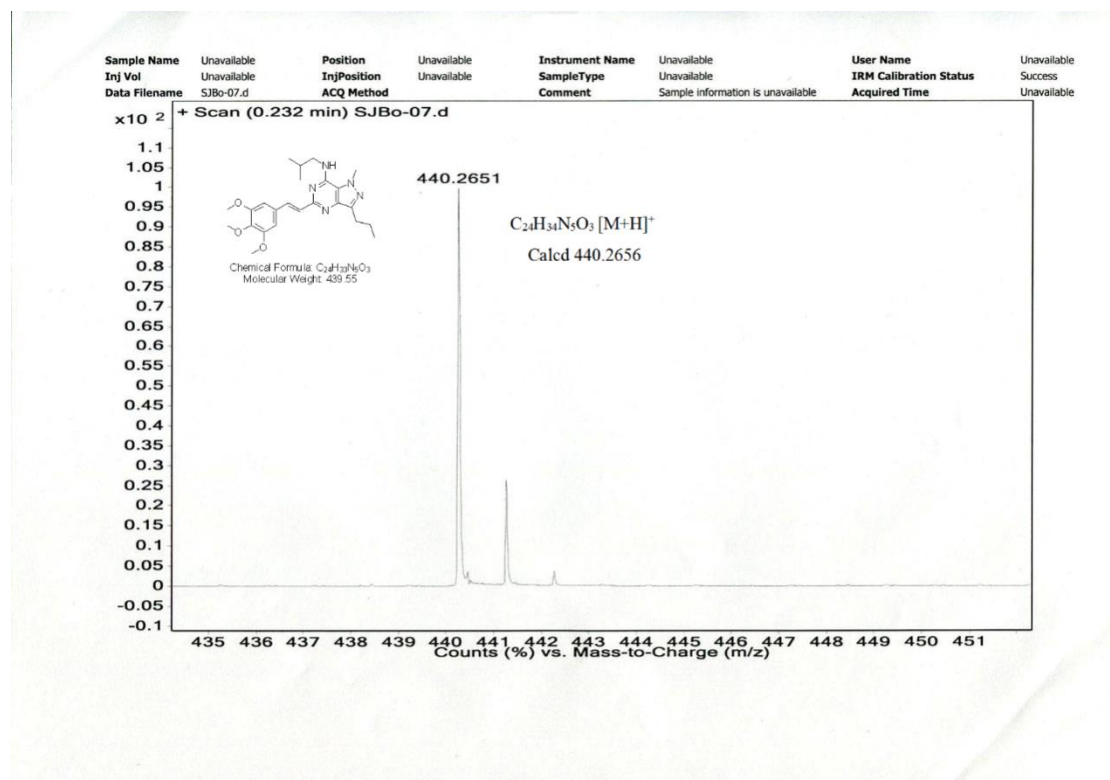
HR-MS data for 4b



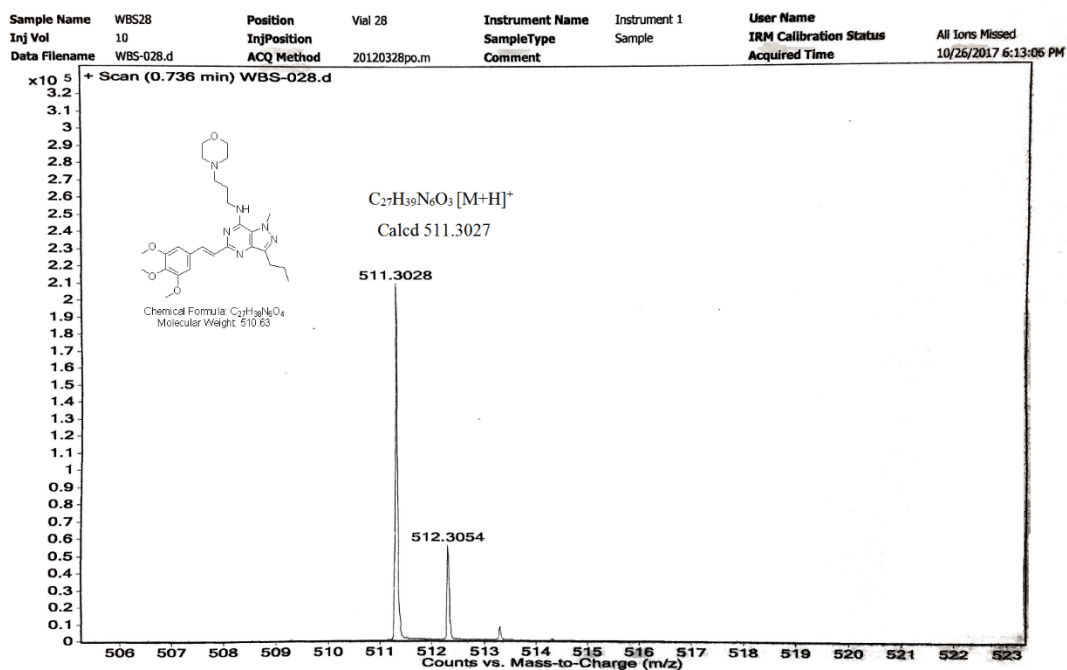
HR-MS data for 4c



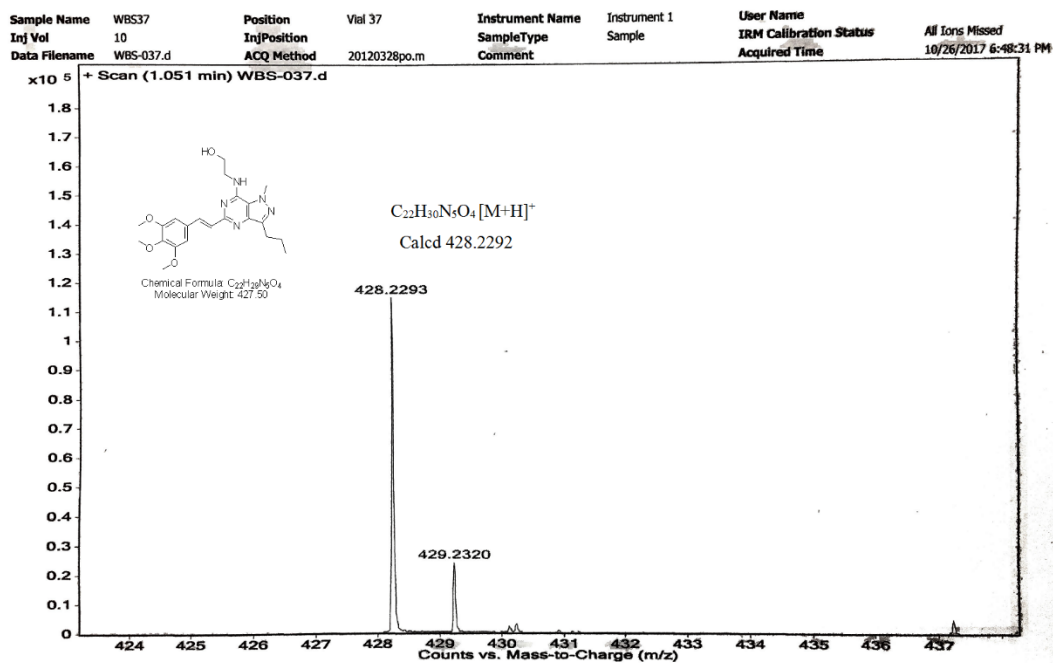
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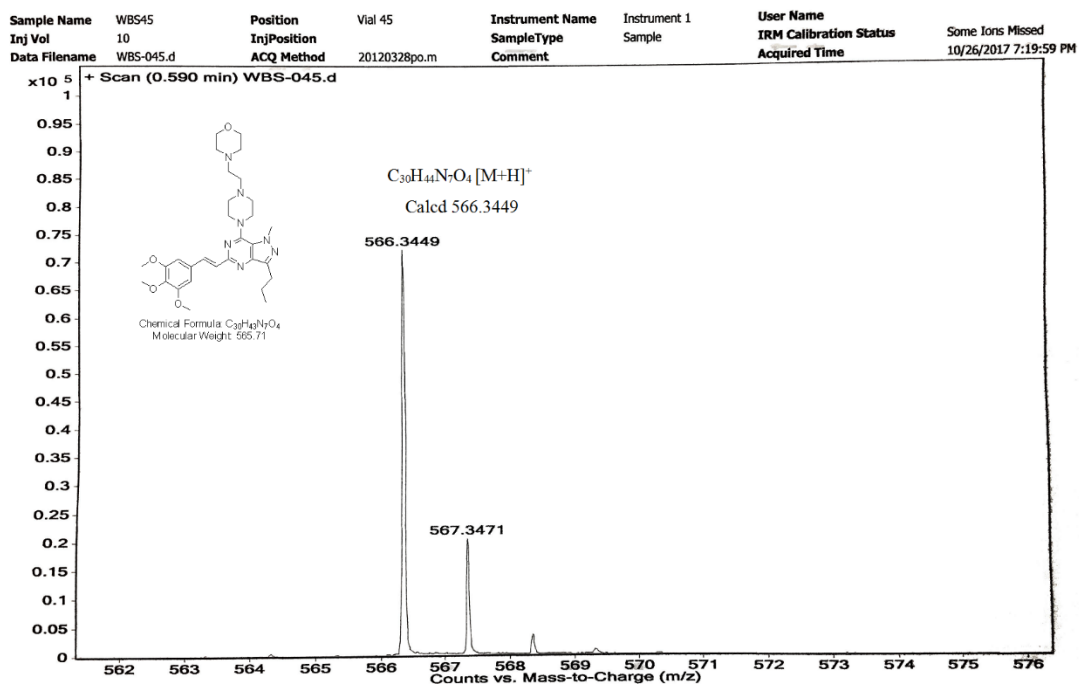
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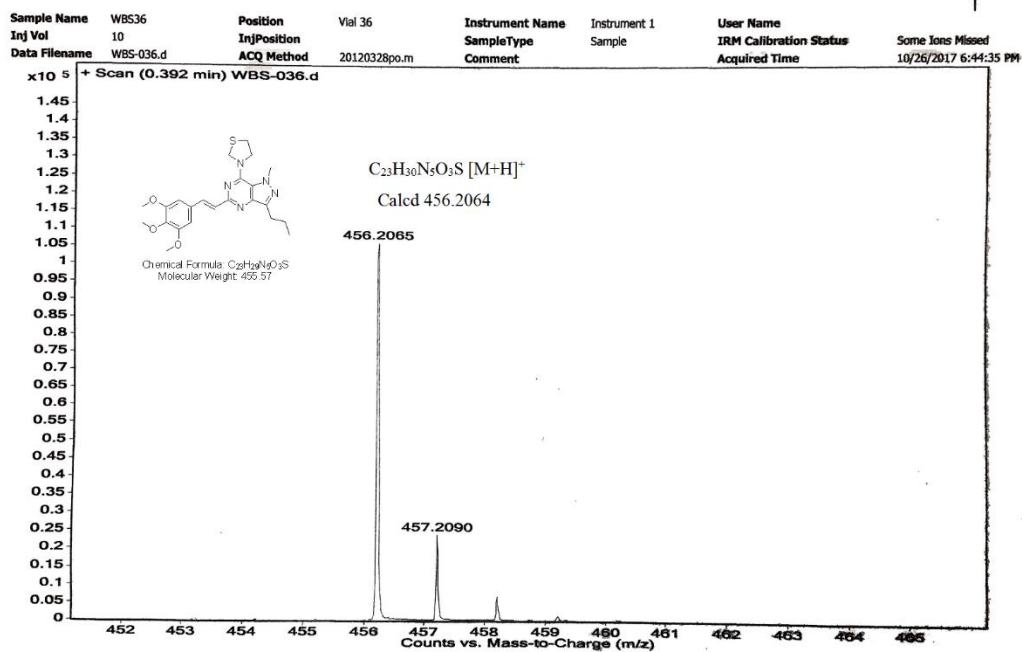
HR-MS data for 4f



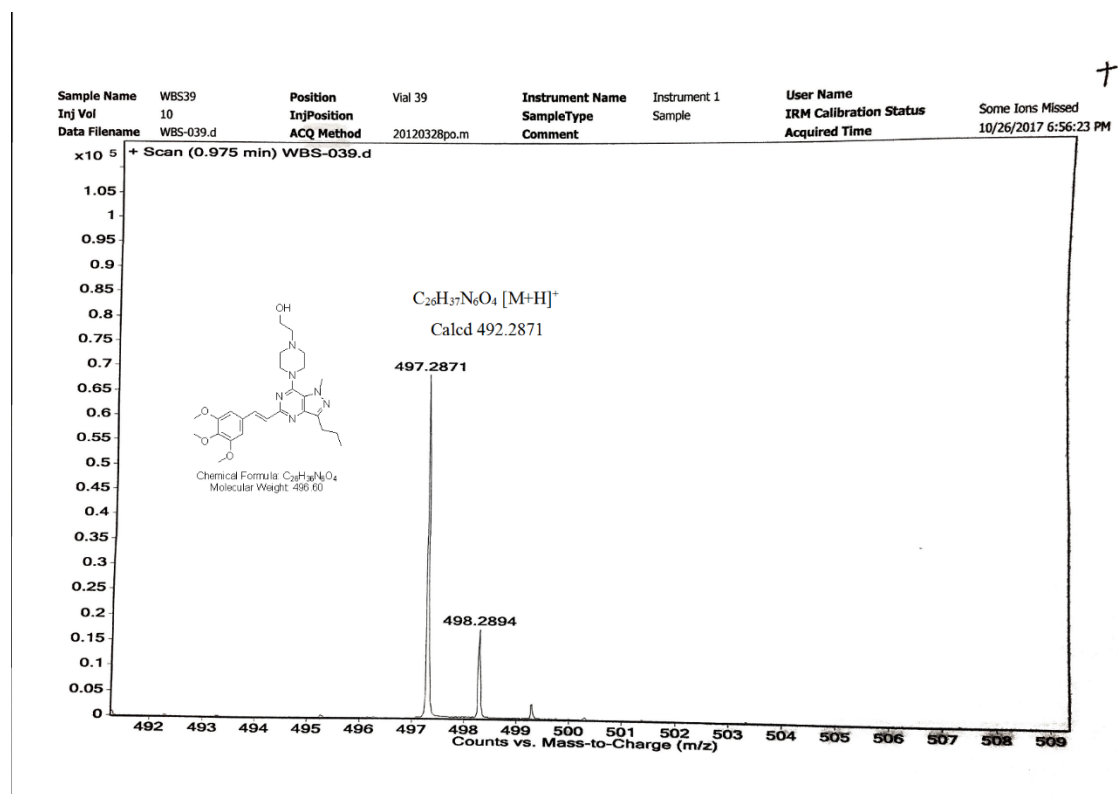
HR-MS data for 4g



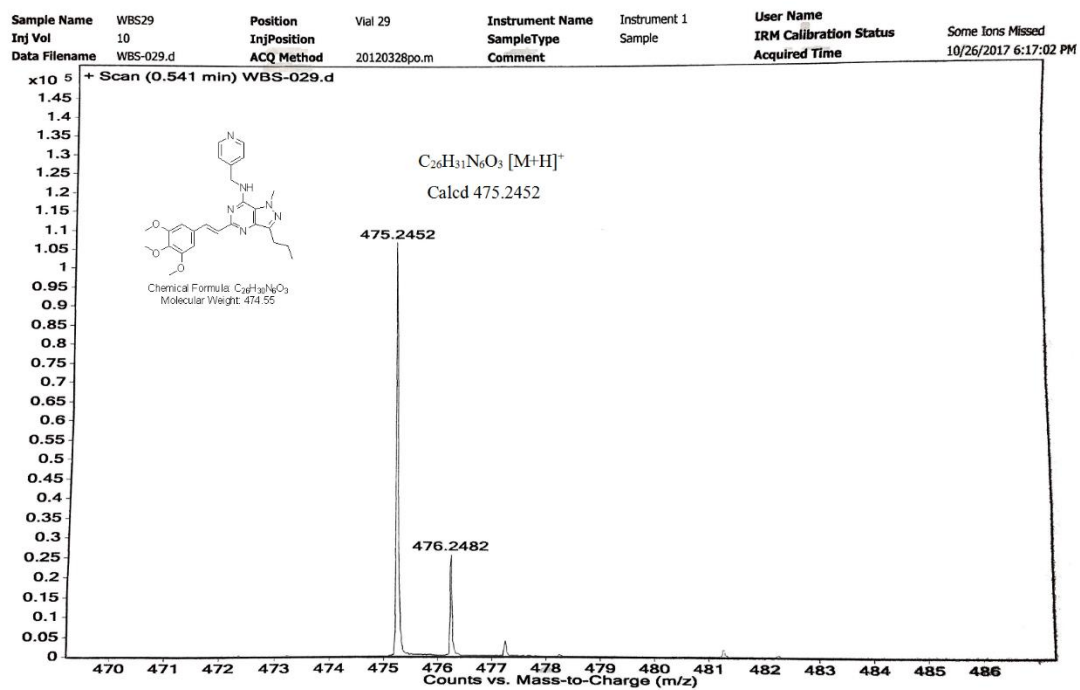
HR-MS data for 4h



HR-MS data for 4i



HR-MS data for 4j



HR-MS data for 4k

Sample Name	WBS8	Position	Vial 8	Instrument Name	Instrument 1	User Name	
Inj Vol	10	InjPosition		SampleType	Sample	IRM Calibration Status	Success
Data Filename	WBS-08.d	ACQ Method	20120328po.m	Comment		Acquired Time	10/26/2017 4:54:35 PM

