Supporting Information

Photoinduced synthesis of methylated marine cyclopeptide Galaxamide analogs with isoindolinone as anticancer agents

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Contents

1. **Table S1**. The absolute configurations, relative free energies and populations of the conformations as determined in methanol

Compounds	Stable conformers*	ΔG**	P%***	Determined absolute configuration of C-3
1	1S	0	100	***S***
2	2S-1	0	50.5	***S***
	3S-2	0.01	49.5	
3	3S-1	0	98.7	***S***
	3S-2	2.55	1.3	
4	4R-1	0	69.0	***R***
	4R-2	0.48	31.0	
5	5R-1	0	99.8	***R***
	5R-2	3.61	0.2	
6	6R-1	0.00	91.3	***R***
	6R-2	1.39	83.7	
7	7R-1	0	70.0	***R***
	7R-2	0.59	25.7	
	7R-3	1.65	4.3	
8	8R-1	0	8.03	***R***
	8R-2	0.83	19.7	

*See Fig.S1 for the structures of the most stable conformers.

**The unit for ΔG is kcal mol^{-1}.

***Populations are based on ΔG values.

2. The most stable conformers of the prepared compounds in methanol

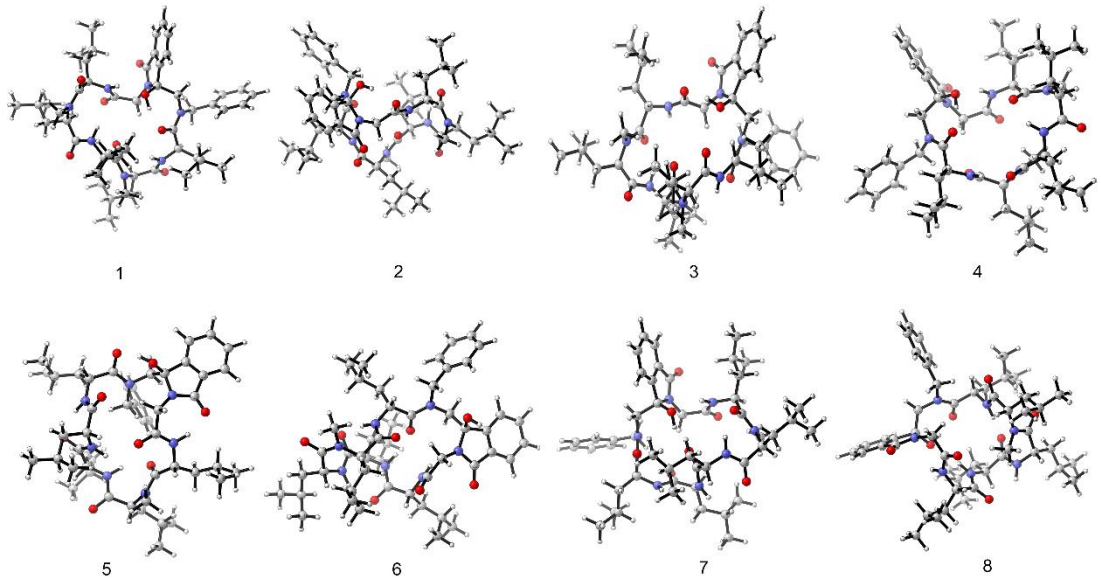


Fig. S1. The most stable low energy conformers of cyclic compounds in methanol (DFT/B3LYP/6-31G**).

3. Computational details

Conformational analysis was performed by fixing the absolute configuration of C-3 with the MMFF94 method. The obtained conformers were optimized at the DFT/B3LYP/6-31G(d,p) level by Gaussian 09 (Gaussian 09, Revision C.01; Gaussian, Inc.: Wallingford, CT, 2010.). The excitation energy (denoted by wavelength in nm) and rotatory strength R of the lowest energy conformations (>5% population) were calculated at the level of TDDFT/ωB97XD/cc-PVDZ using polarizable continuum model (PCM) to consider the solvent effect. ECD curves were obtained based on rotatory strengths using half bandwidth of 0.30~0.40 eV by Specdis 1.71(T. Bruhn, et. al. *Chirality*, 2013, **25**, 243). UV correction was used to facilitate comparison between the calculated and experimental data.

Docking experiments were performed by AutoDock 4.26 (ADT). The structure of target protein MDM2 was downloaded from the RCSB protein database (RCSB PDB, http://www.pdb.org/), and the modified ligand and water were separated using PyMol software. The cyclic structure was based on the optimized structure at the level of DFT/B3LYP/6-31G(d,p). The hydrogen was added and charge calculated by AutoDock Tools 1.5.6 software, and the docking results were processed by Discovery Studio 2019 Client. The docking parameters were shown in supplements Table S1 and S2.

Table S2. Docking process parameter settings for those with relative high binding energy.

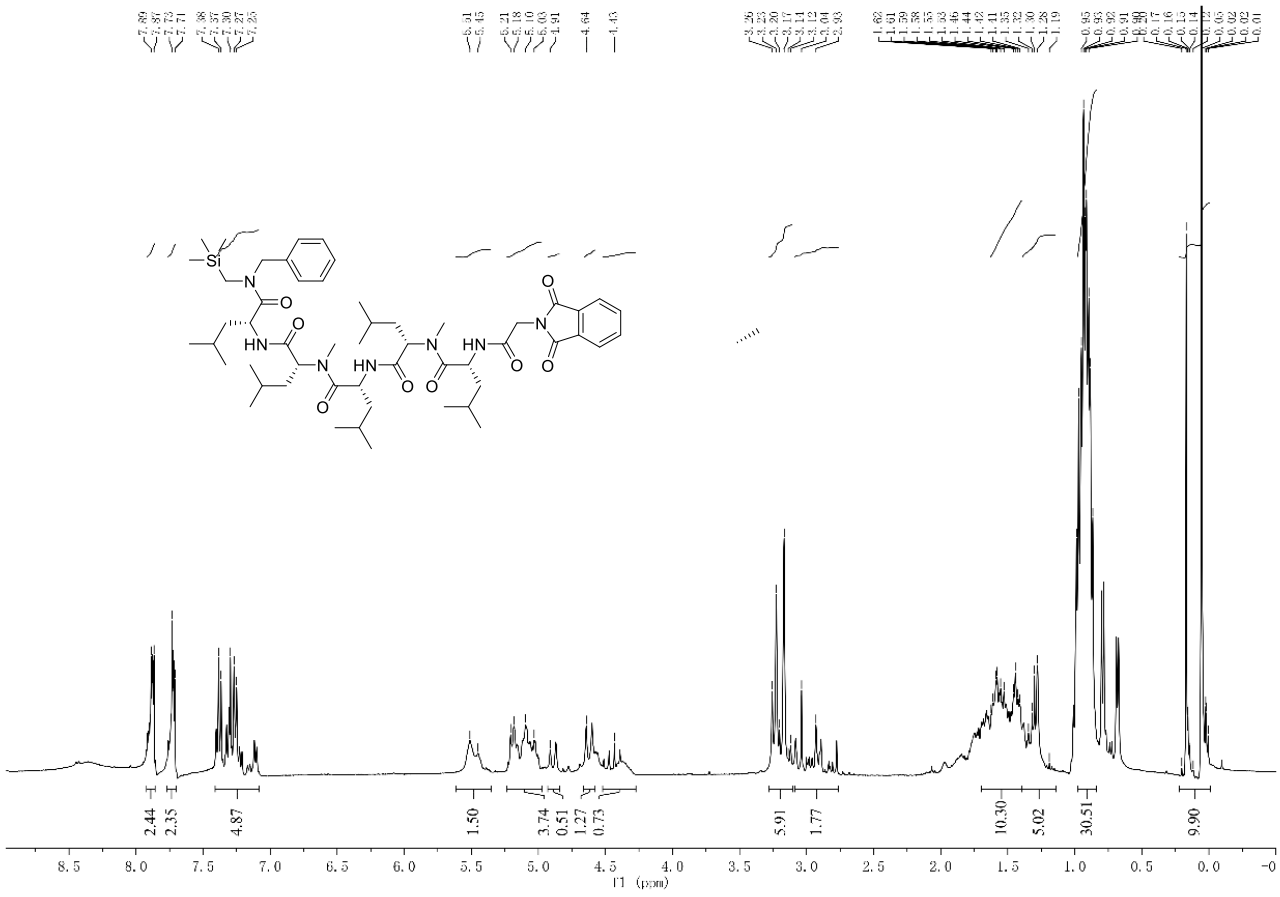
Parameter	4R	8R
Grid box (nm)	60 × 60 × 60	60 × 60 × 60
spacing	0.375	0.375
grid center x	-7.442	-7.442
grid center y	0.621	0.621
grid center z	6.892	6.892
GA runs	20	20
population size	150	150

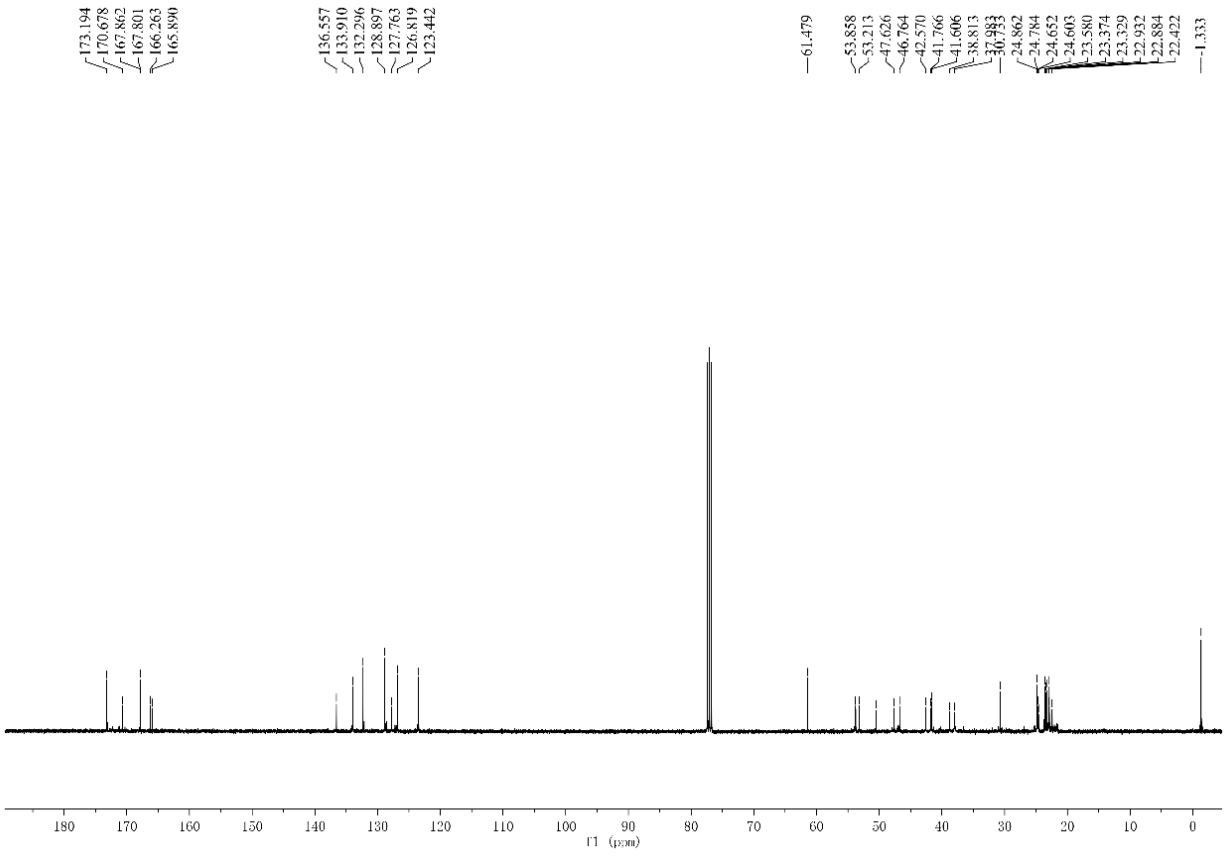
Table S3. The forces between compound **4**, compound **8** and MDM2 protein obtained by molecular docking.

Compounds	Vander Waals	Conventional H-bond	Carbon H-bond	Alkyl, π-Alkyl	π-Sigma,	Amide-Pi Stacked
4	Leu^{54}, Leu^{57}, Gly^{58}, Gln^{72}, His^{73}, Val^{75}, Phe^{86}, Ile^{103}		Gly^{58}	Phe^{55}, Ile^{61}, Met^{62}, Val^{93} , Ile^{99}	Tyr^{67}, His^{96}	
8	Lys^{51}, Phe^{55}, Gly^{58}, Gln^{72}, Phe^{91}, Tyr^{100}, Ile^{103}	His^{96}	His^{73}	Leu^{57}, Val^{57}, Ile^{61}, Met^{62}, Tyr^{67}, Val^{93}, Ile^{99}	Val^{93}	Leu^{54}

4. ^{1}H, ^{13}C-NMR and HRMS of linear peptides.

(1) ^{1}H, ^{13}C-NMR and HRMS of **9.**





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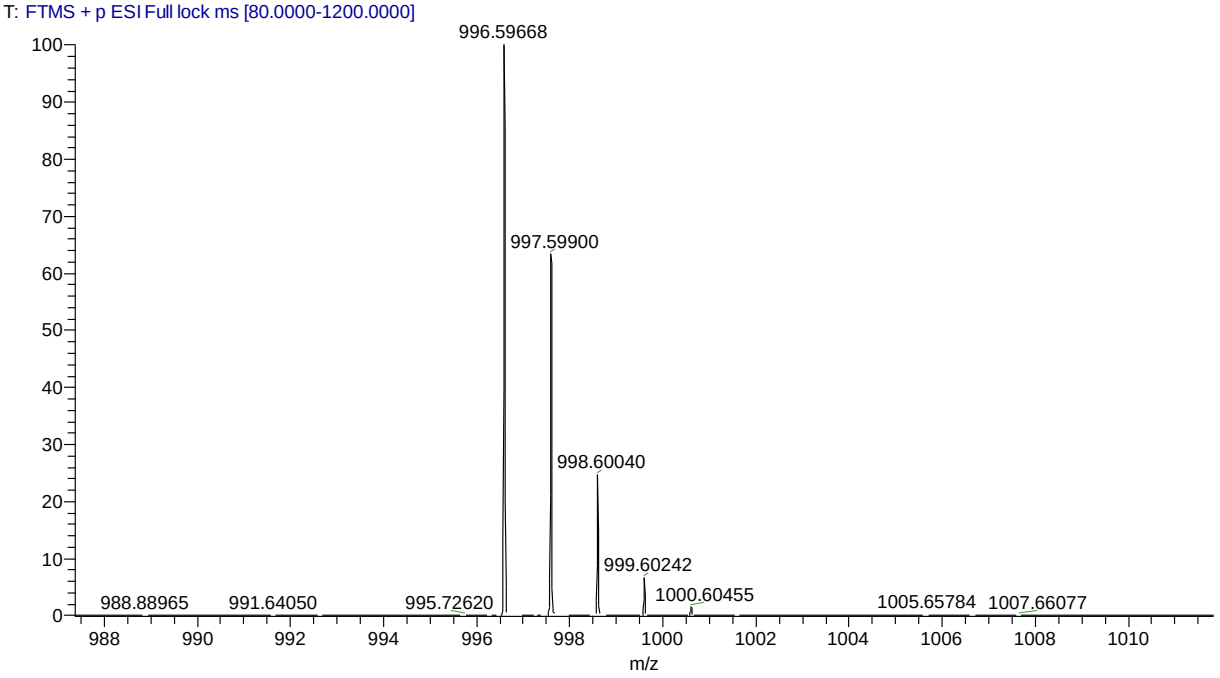

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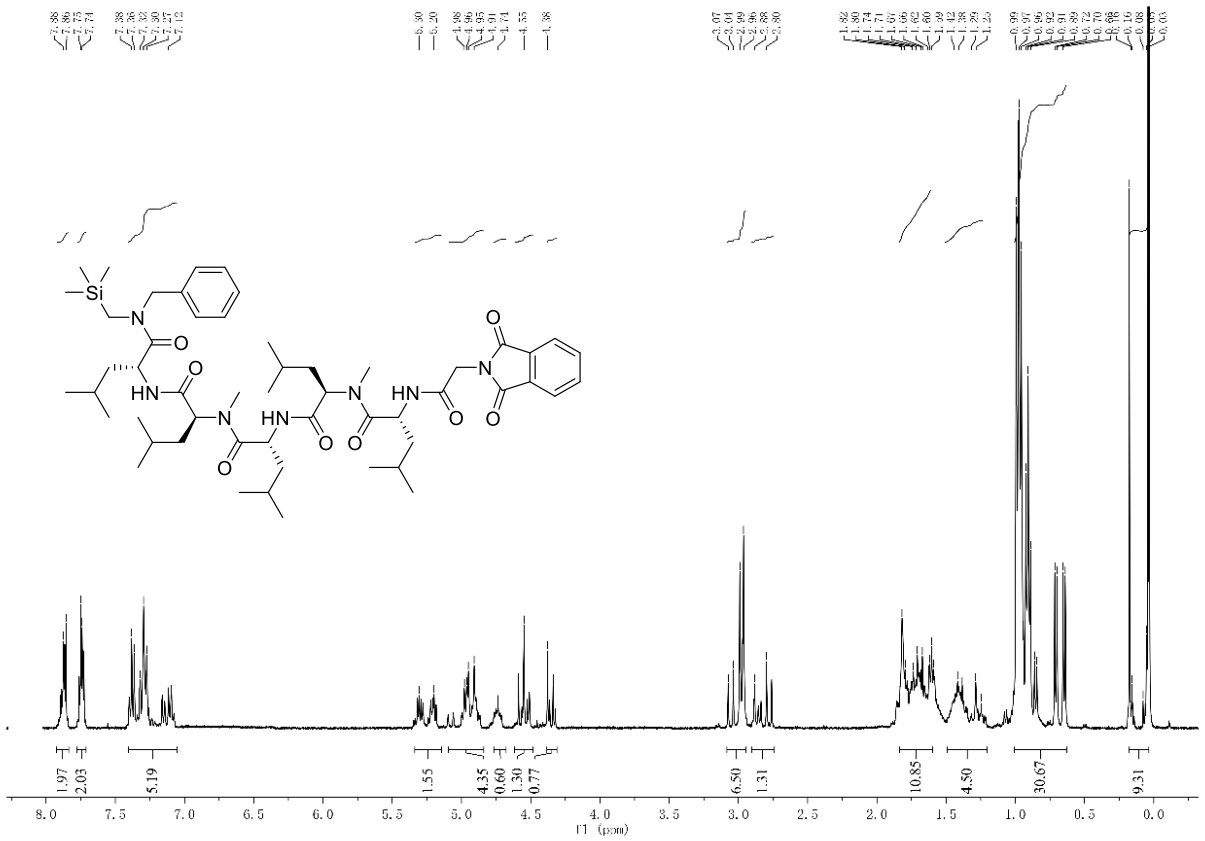

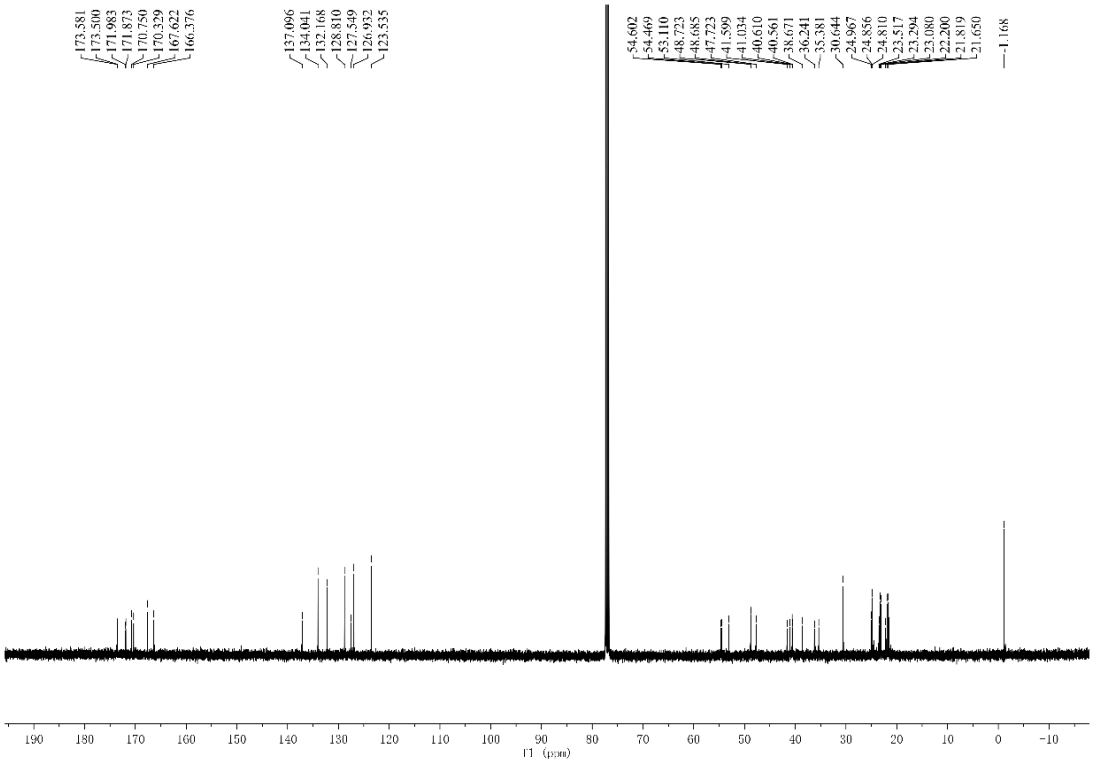

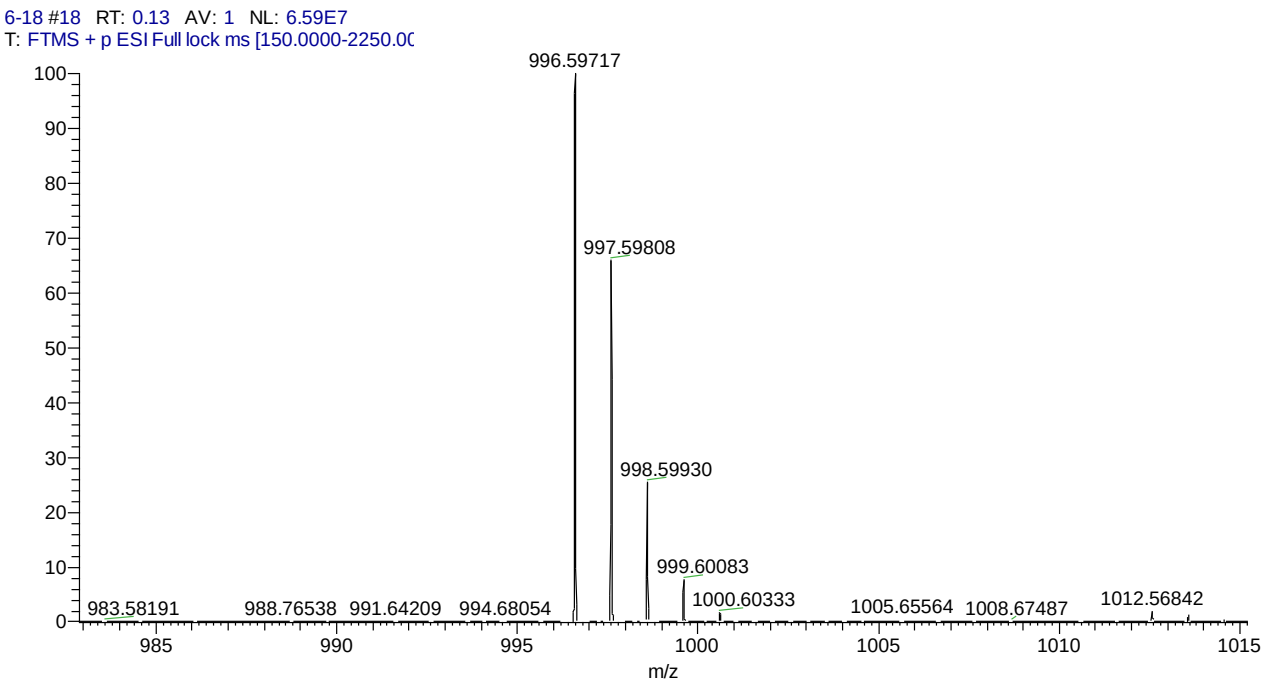

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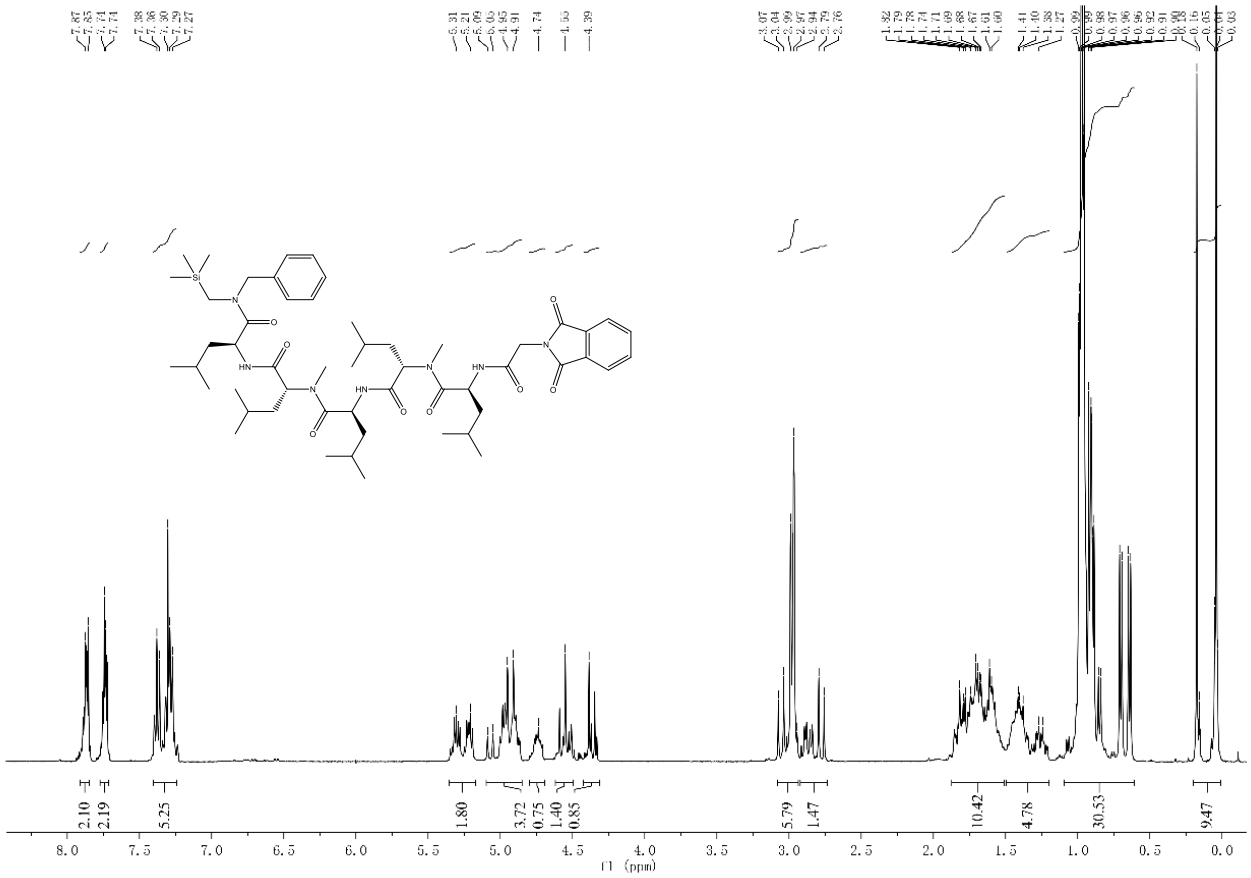

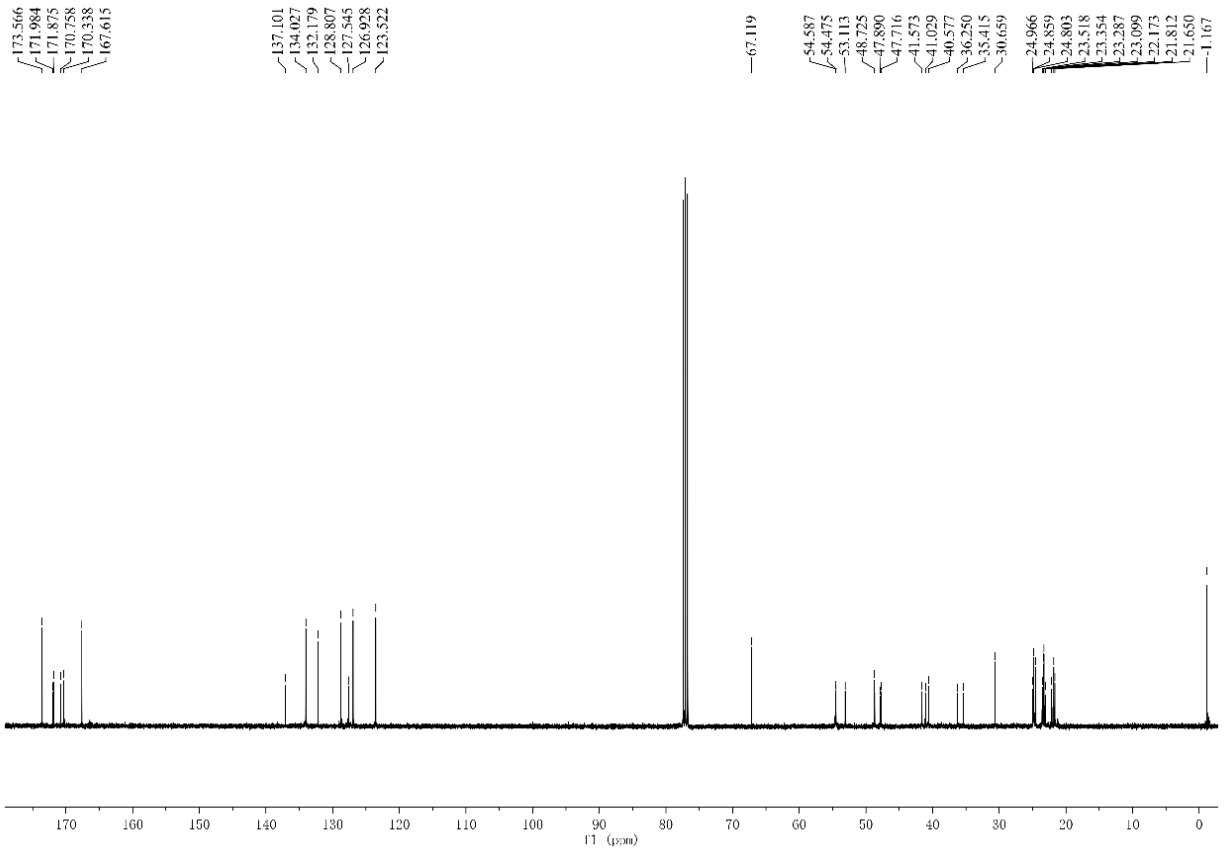

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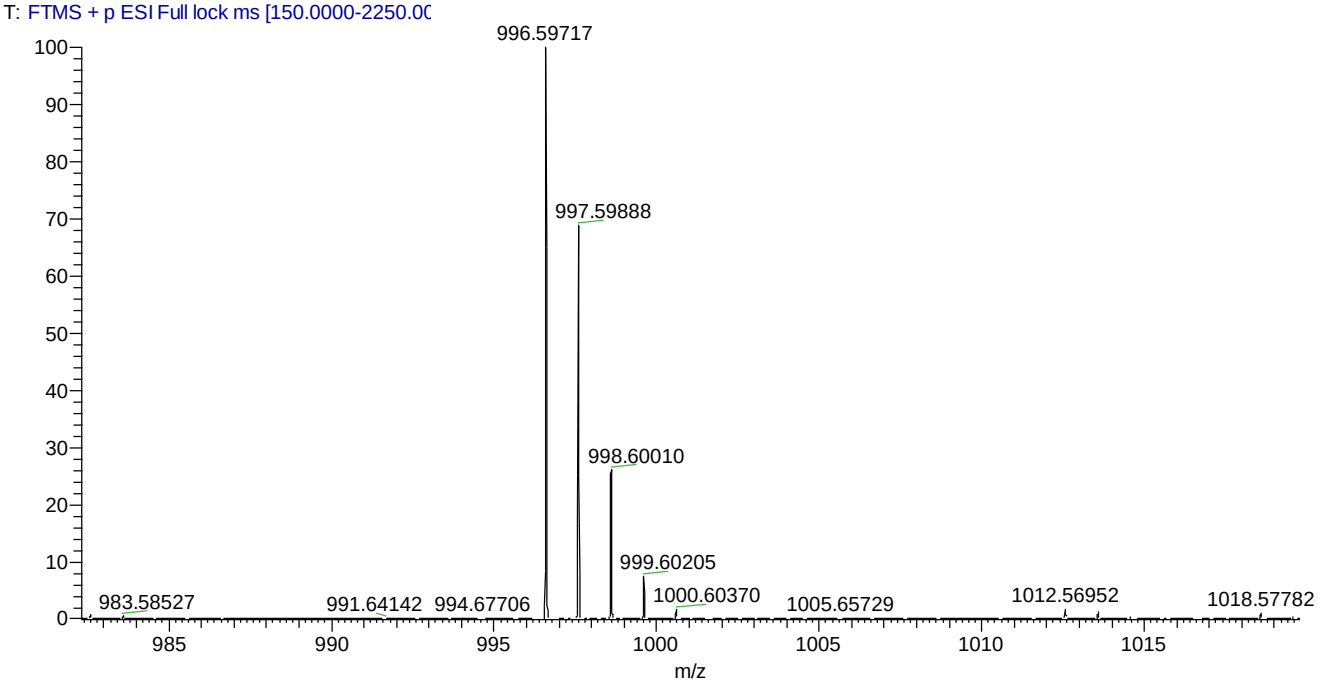

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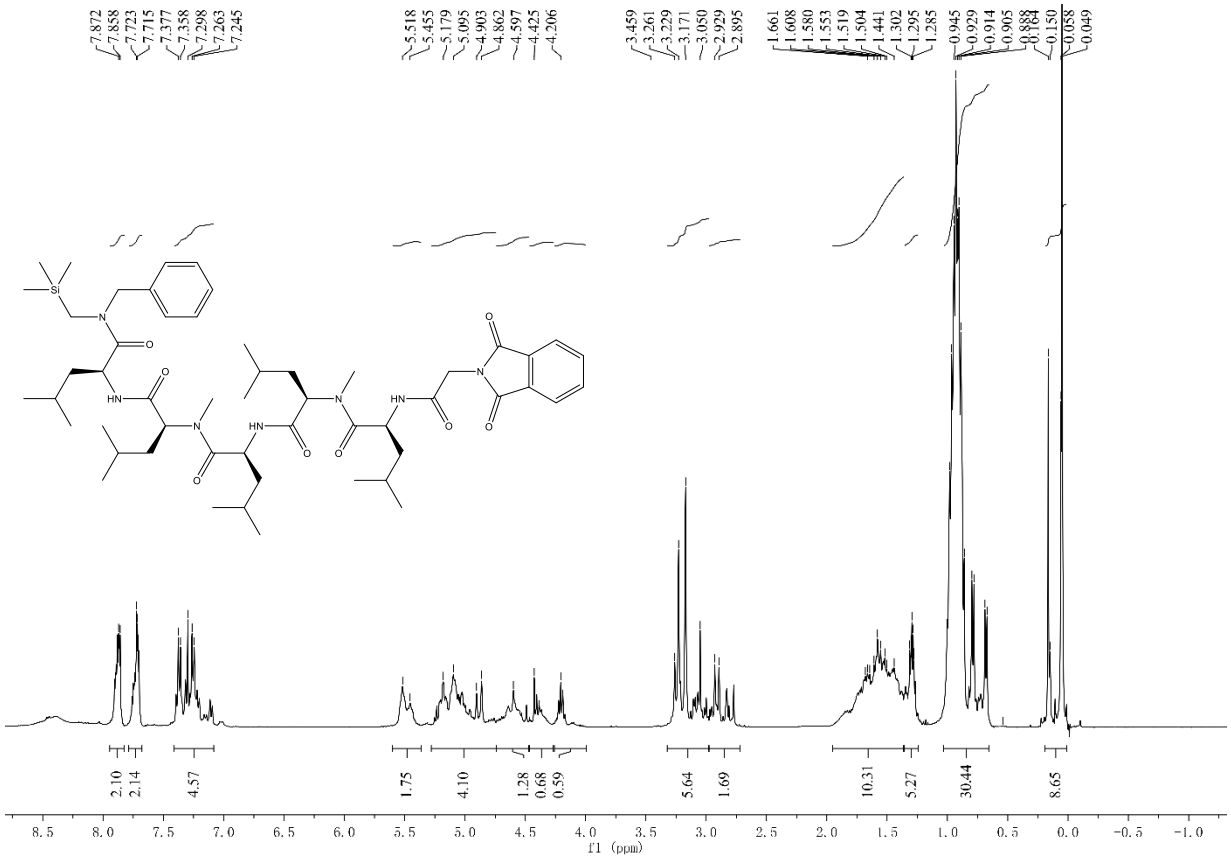

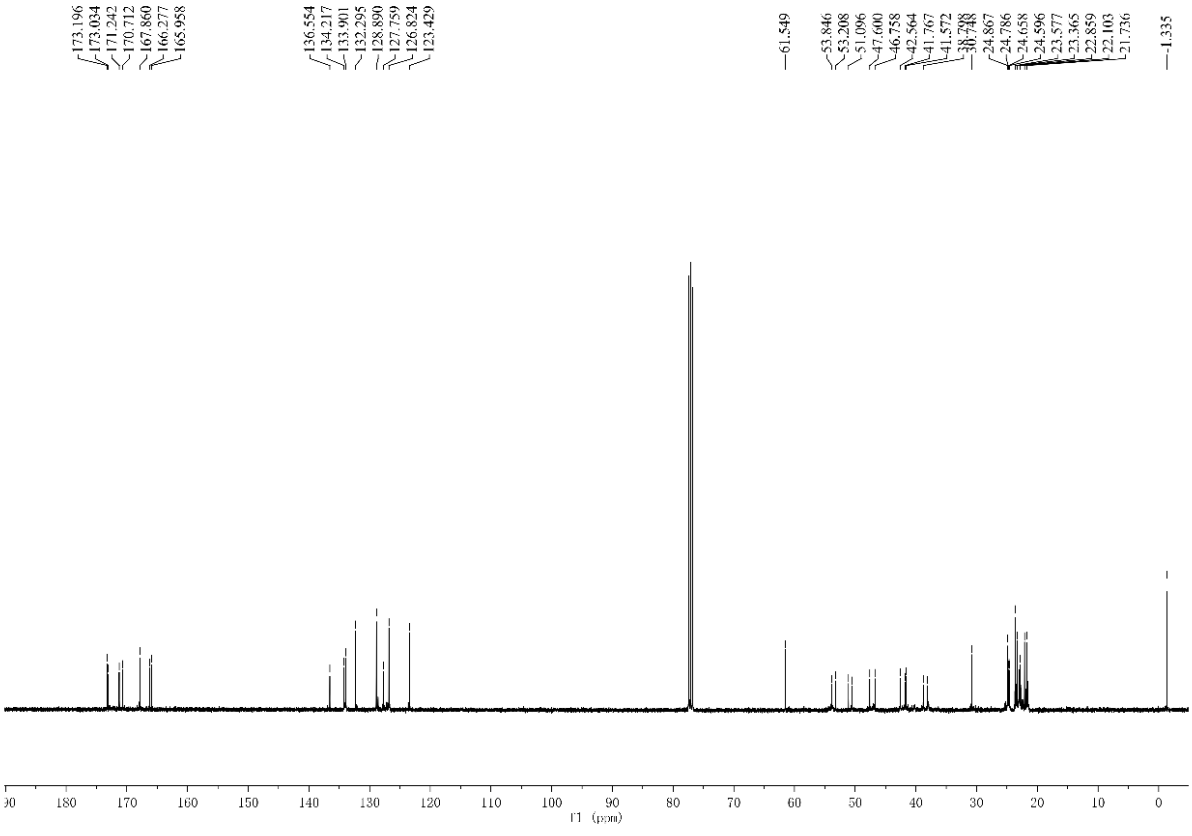

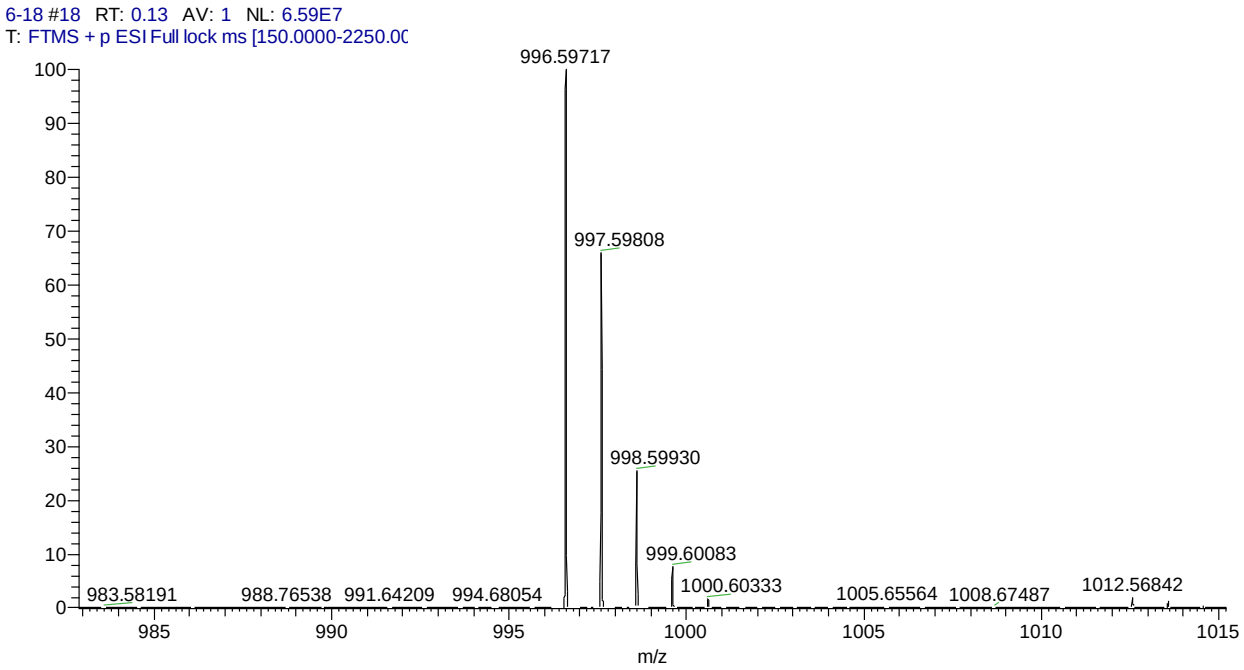

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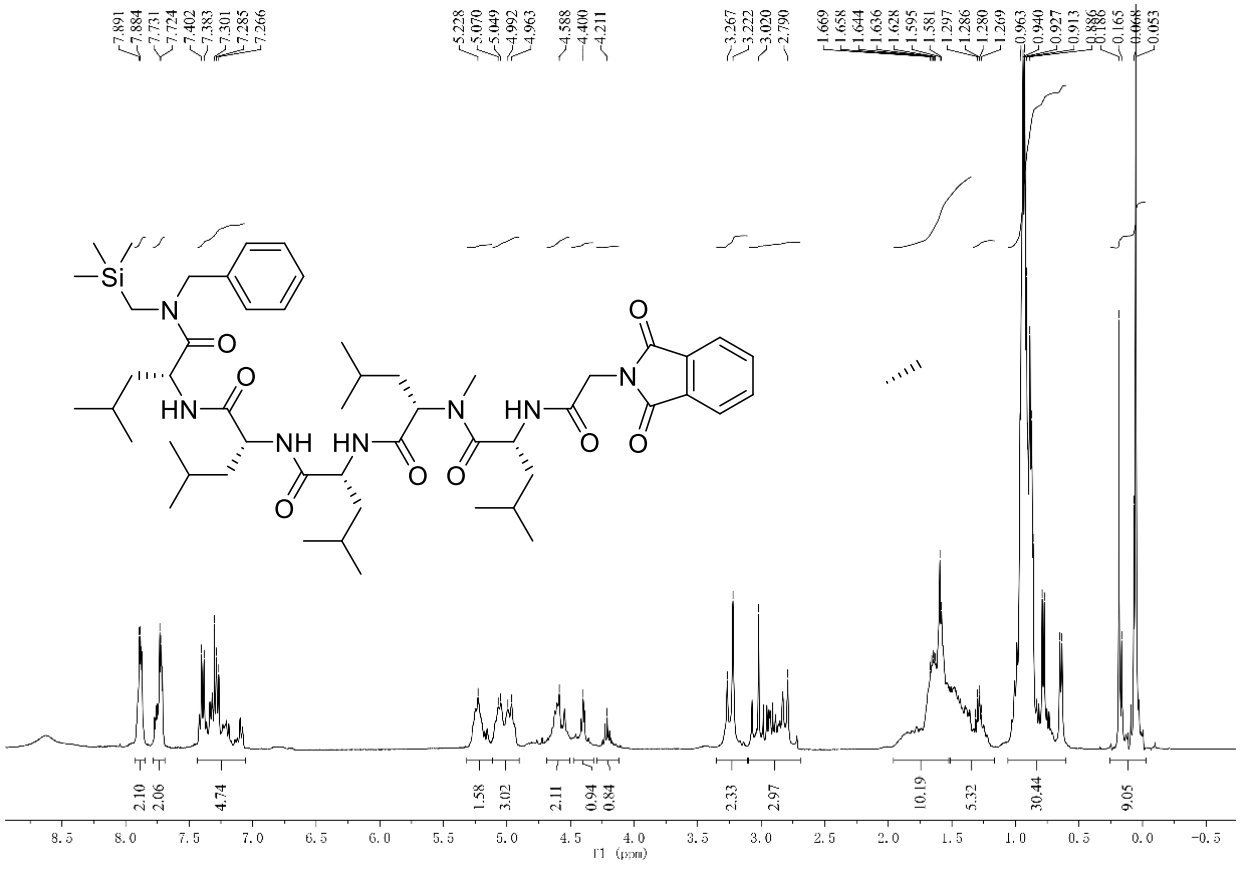

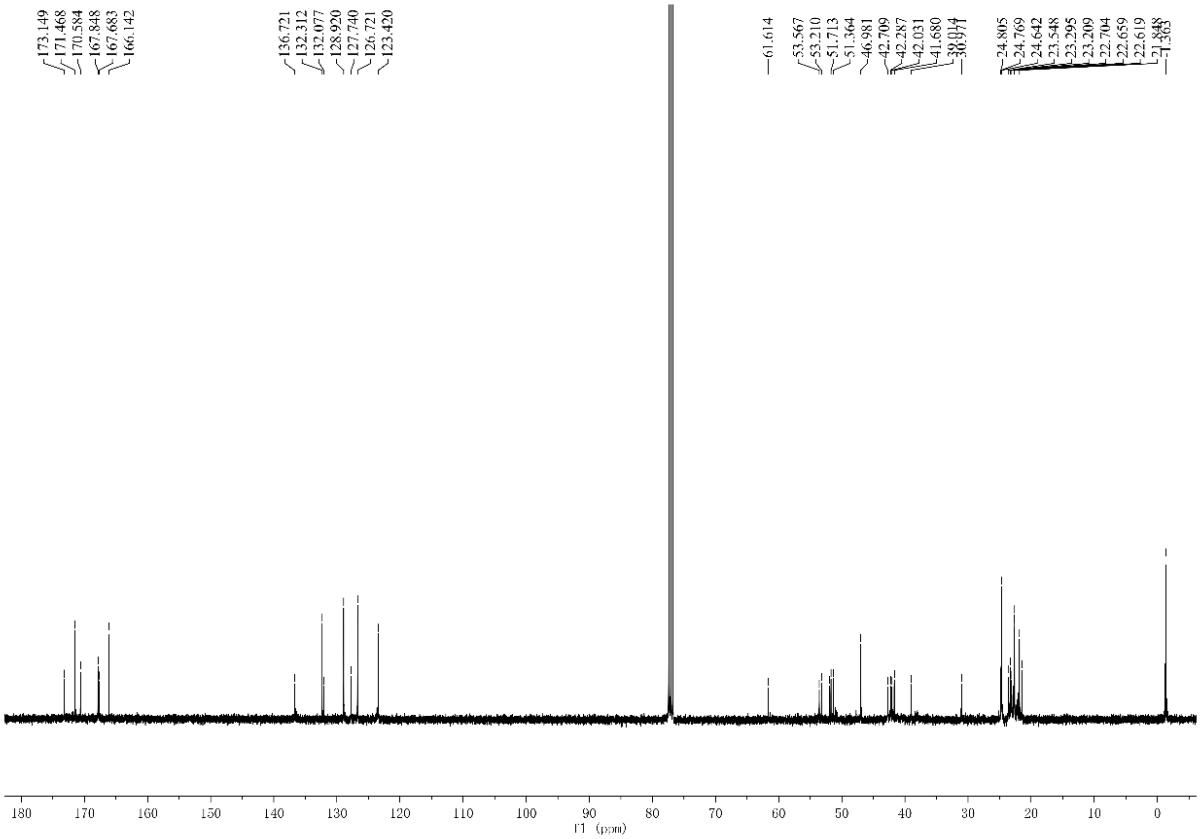

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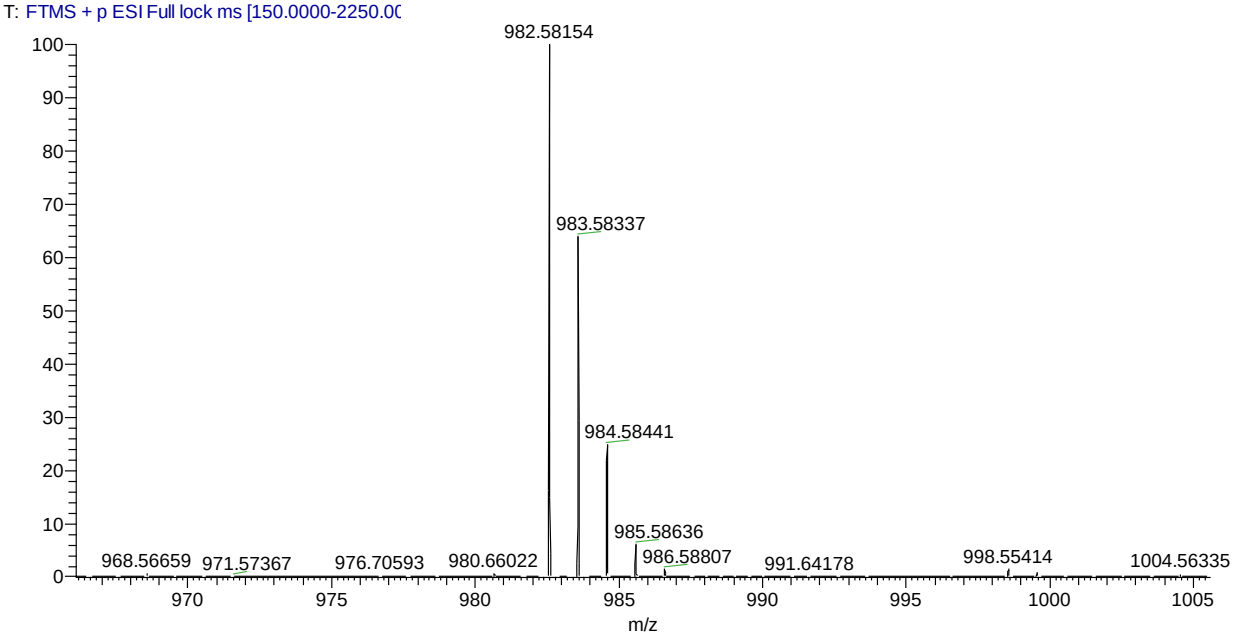
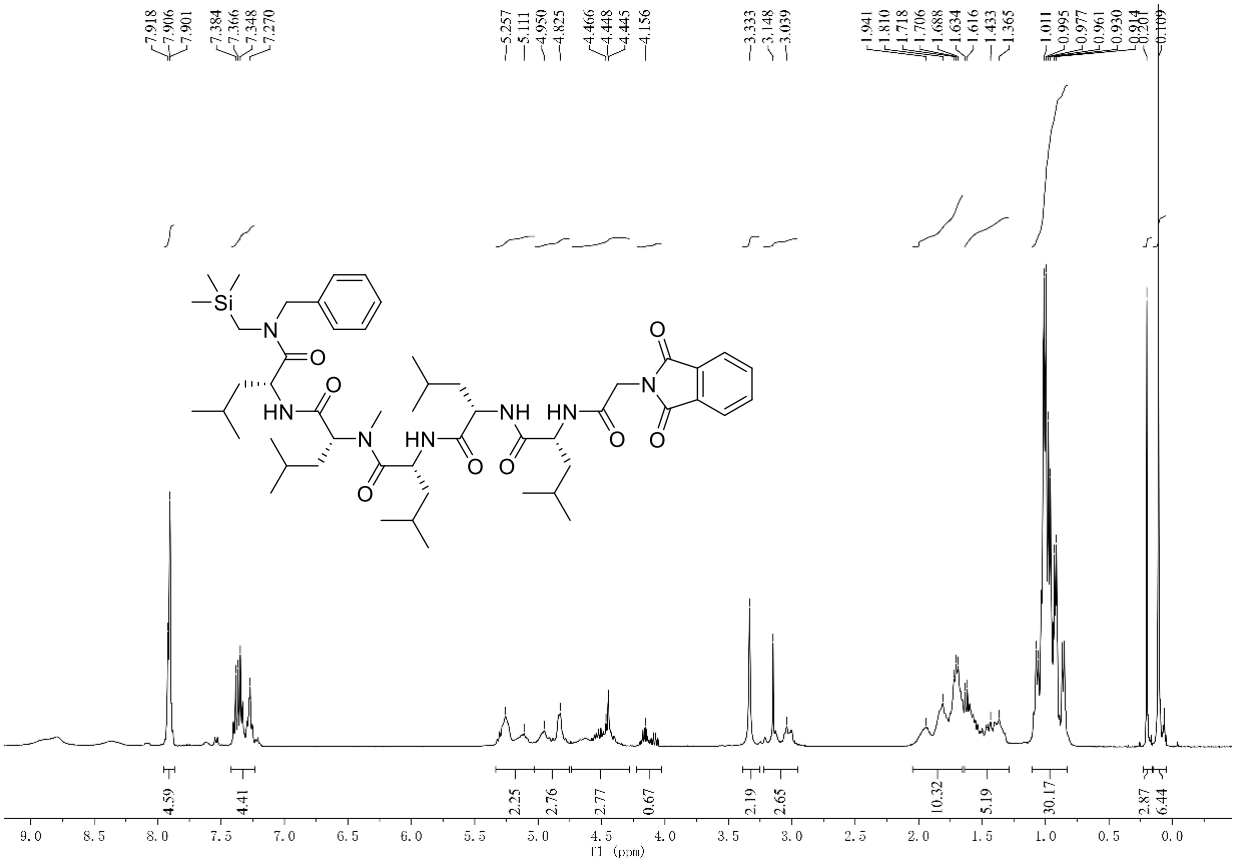
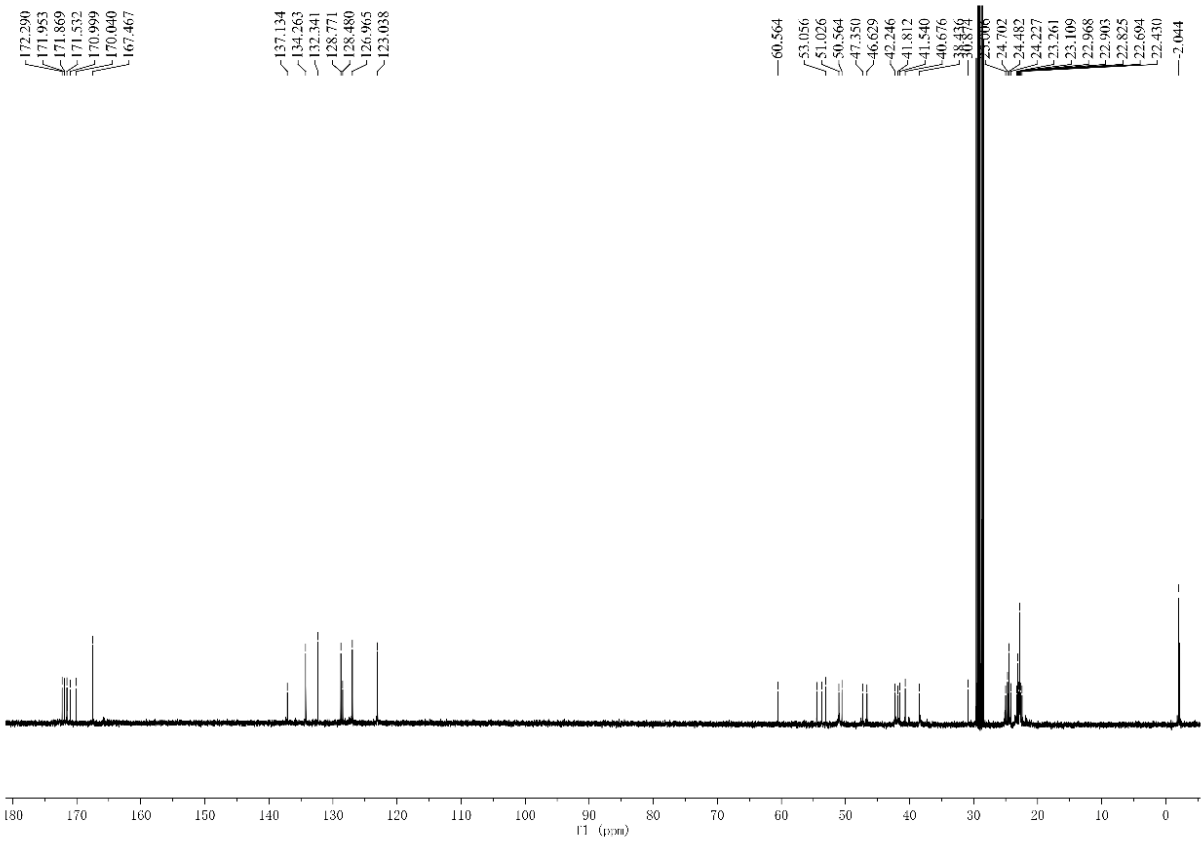
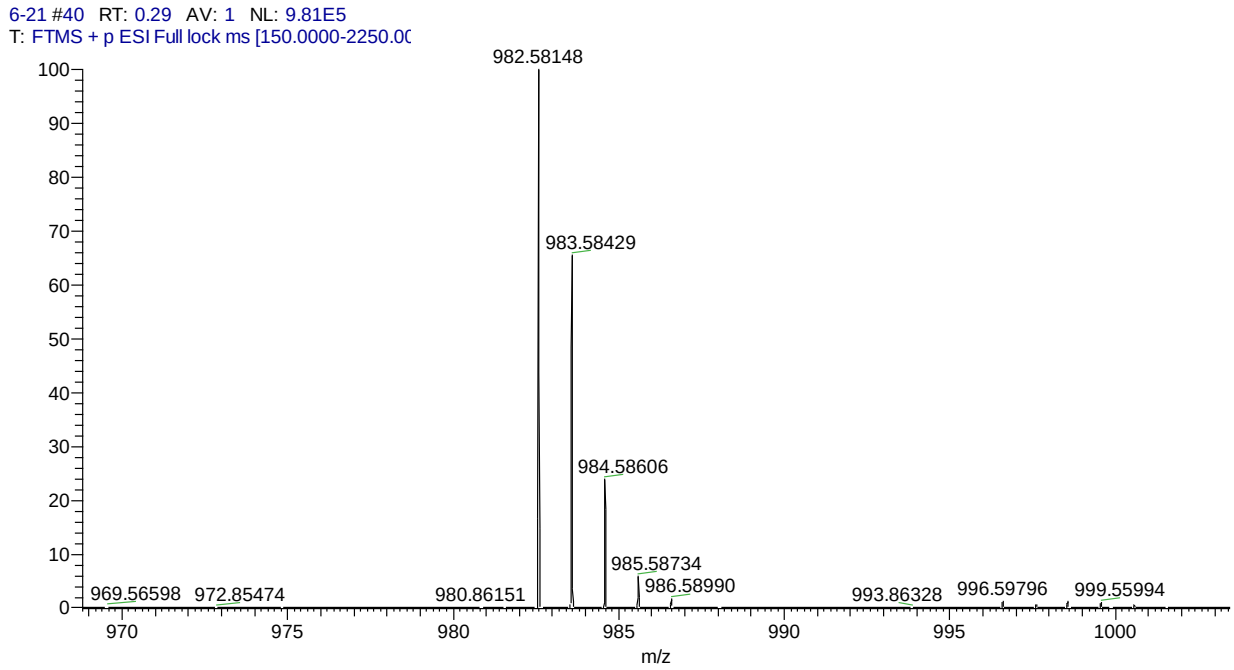


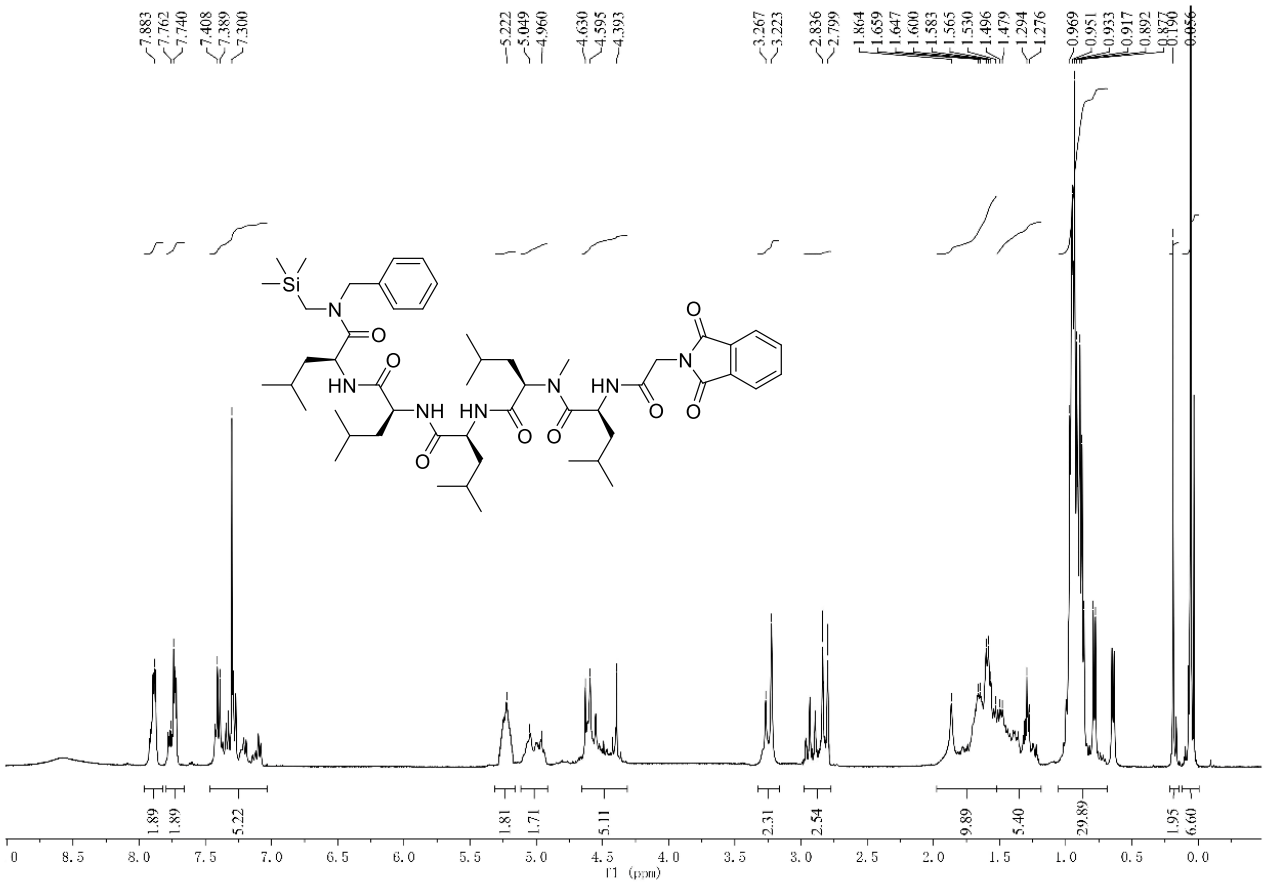
(6) ^{1}H, ^{13}C-NMR and HRMS of **14**.

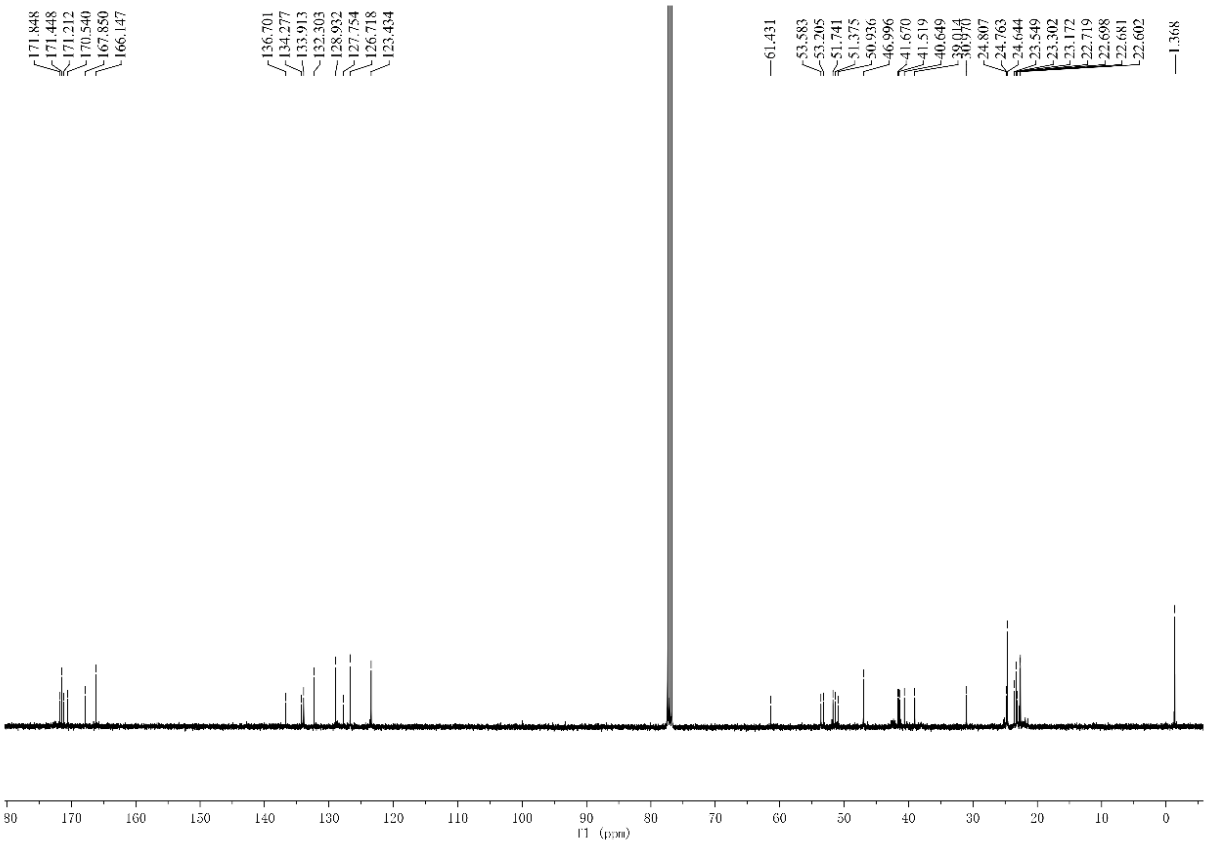






(7) ^{1}H, ^{13}C-NMR and HRMS of **15**.





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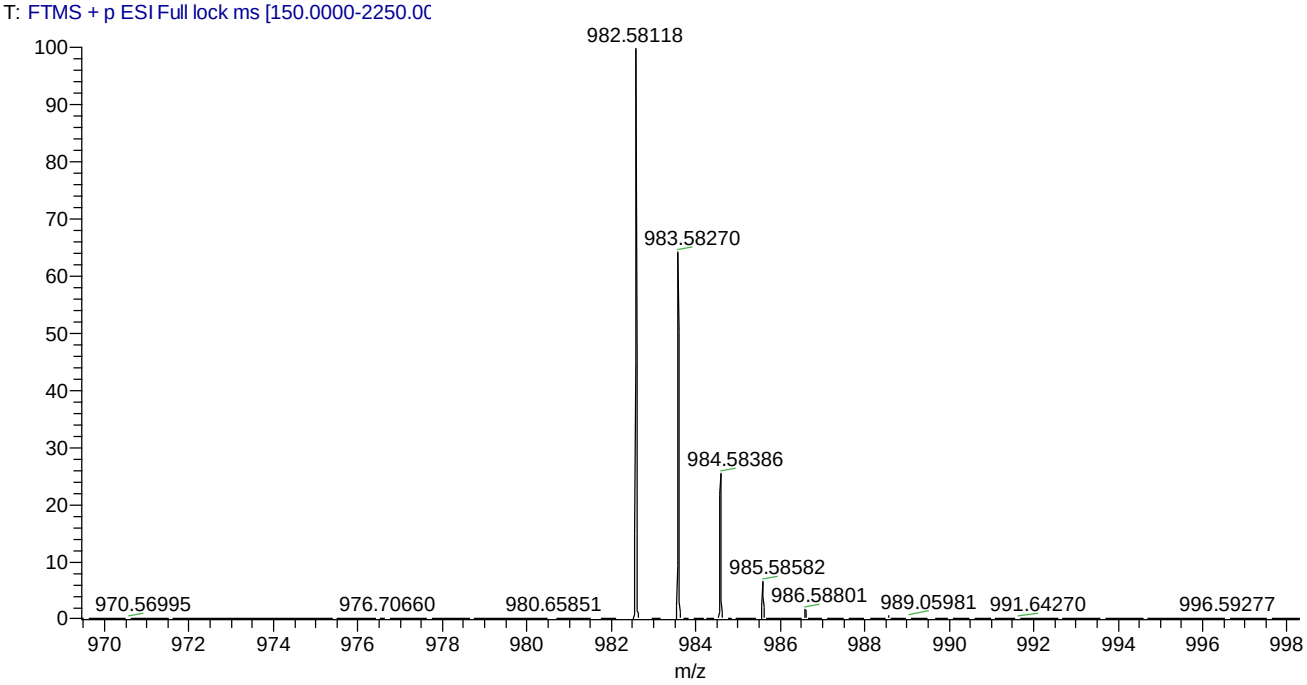
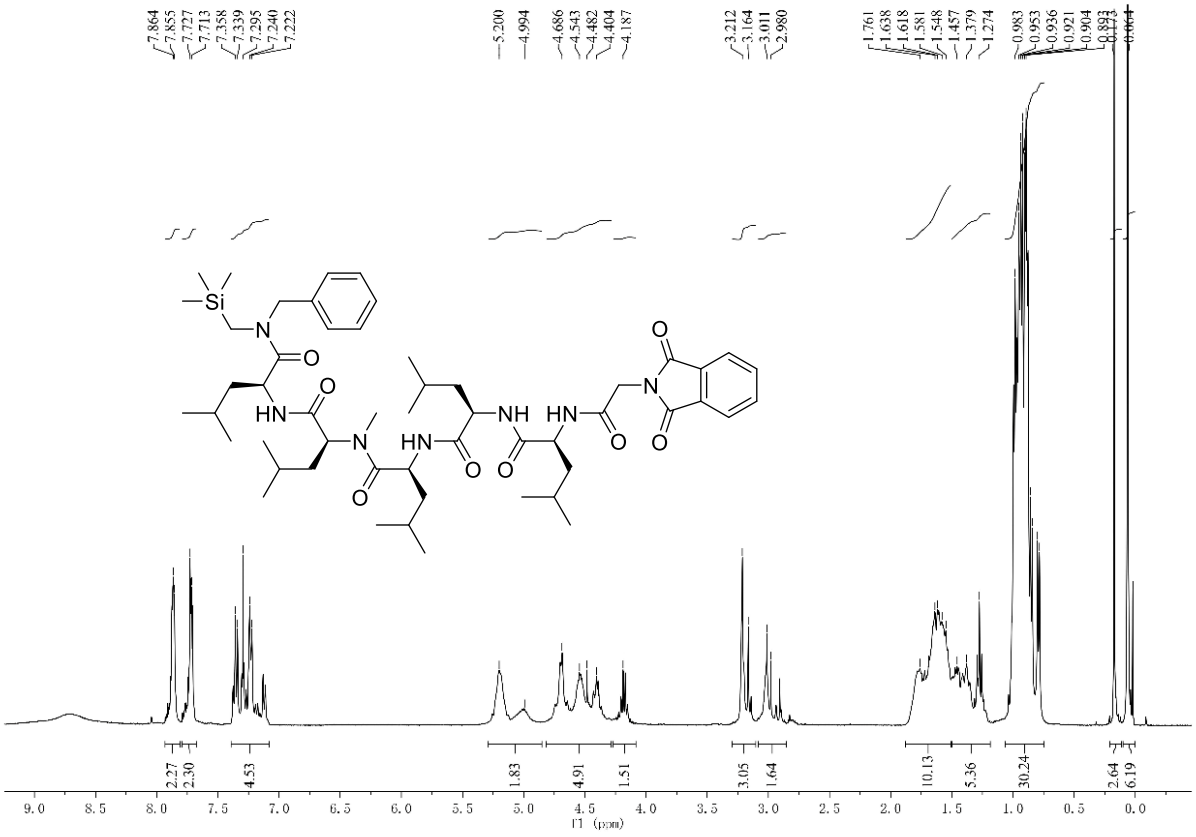
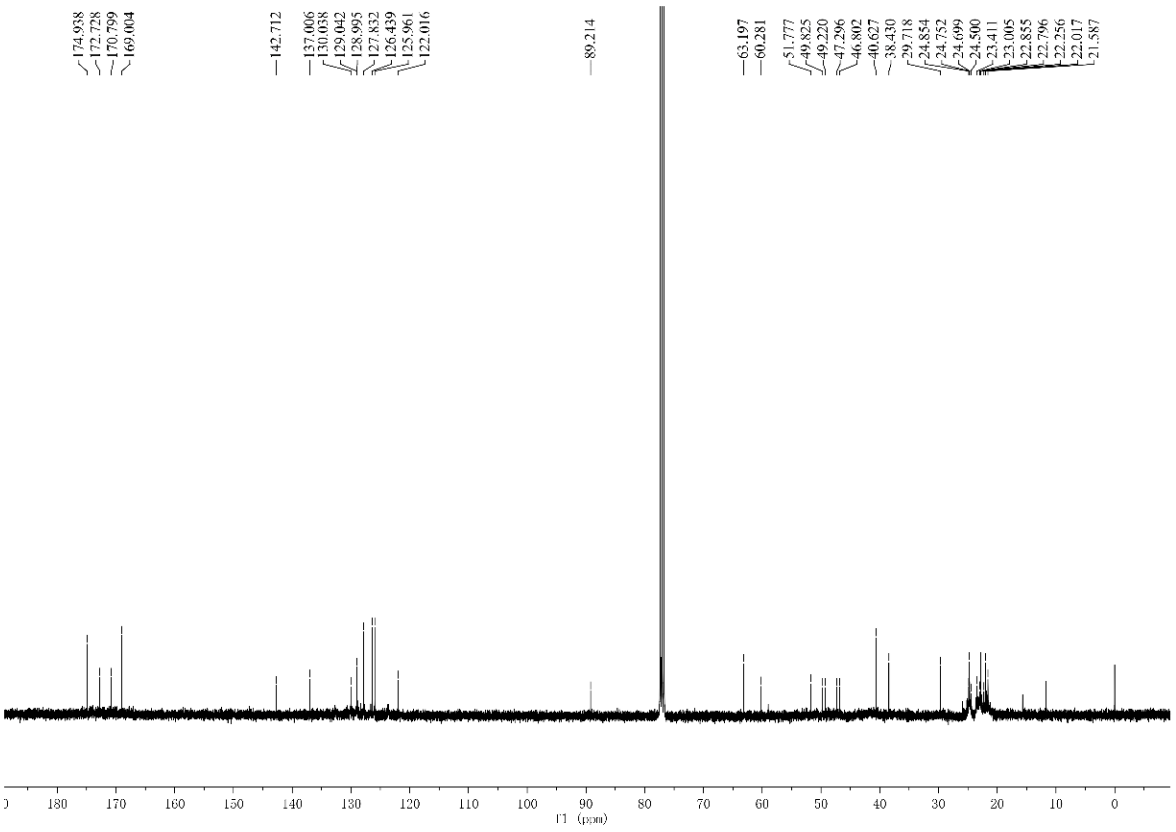
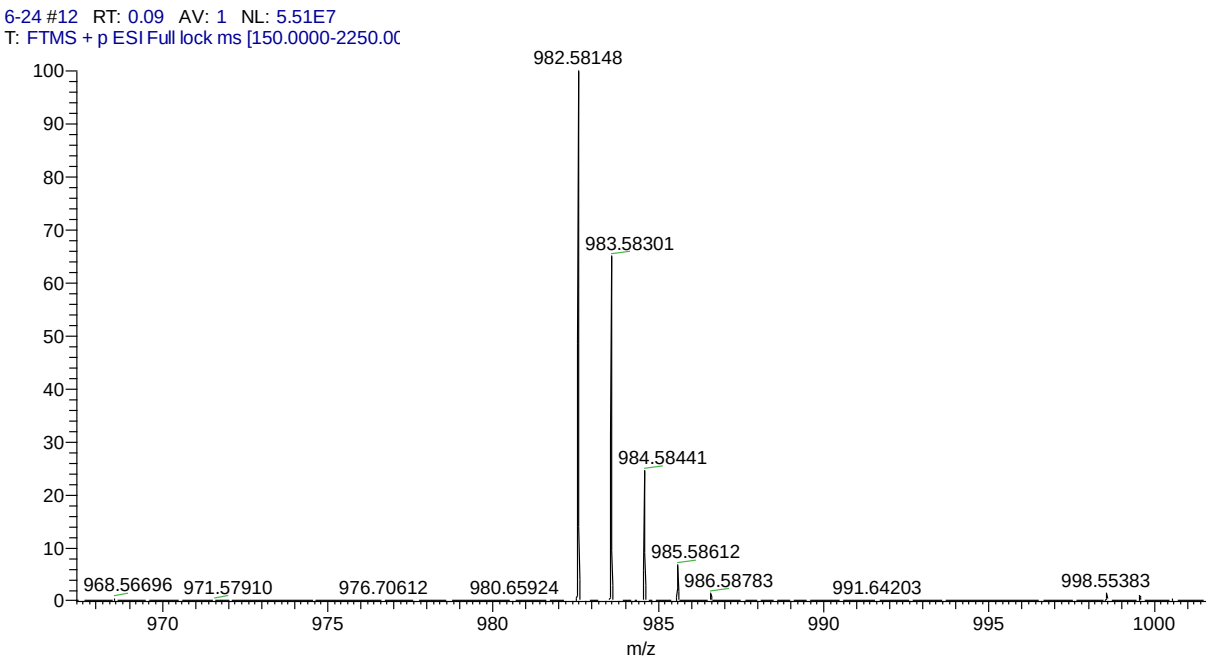


(8) ^{1}H, ^{13}C-NMR and HRMS of **16**.

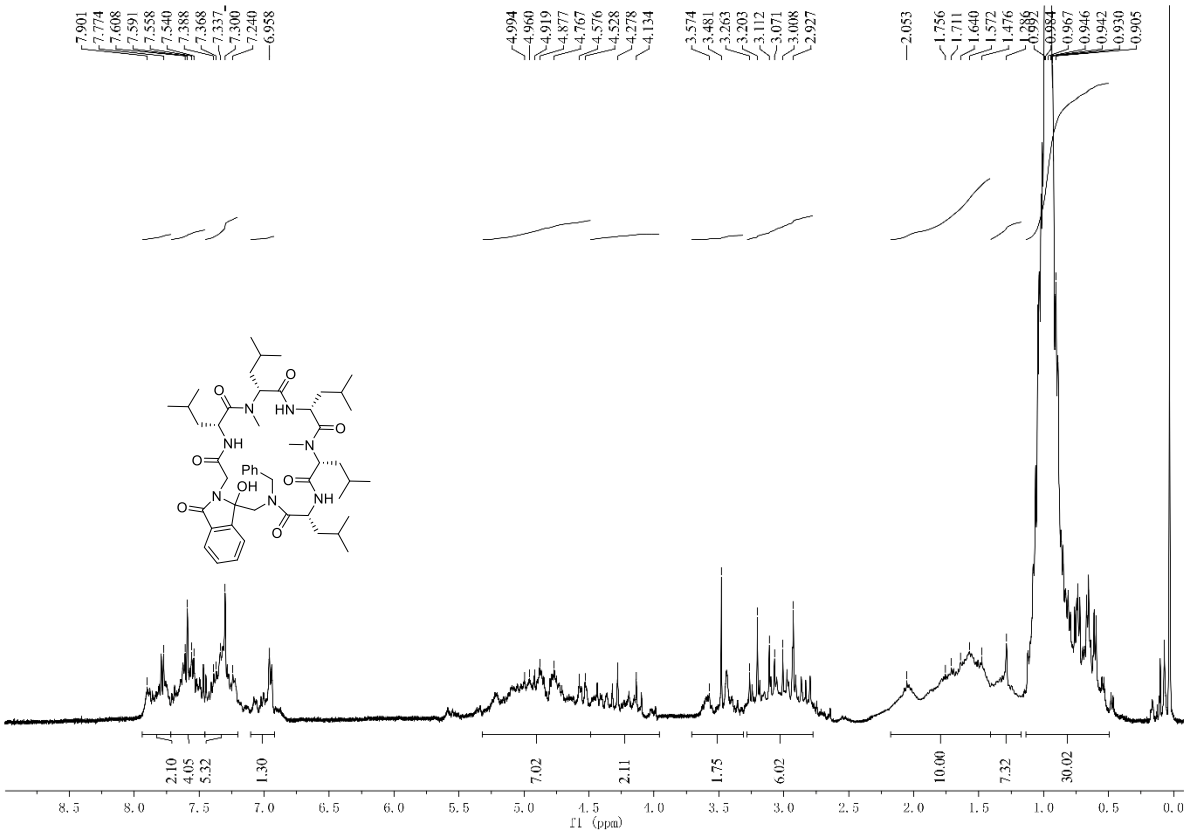


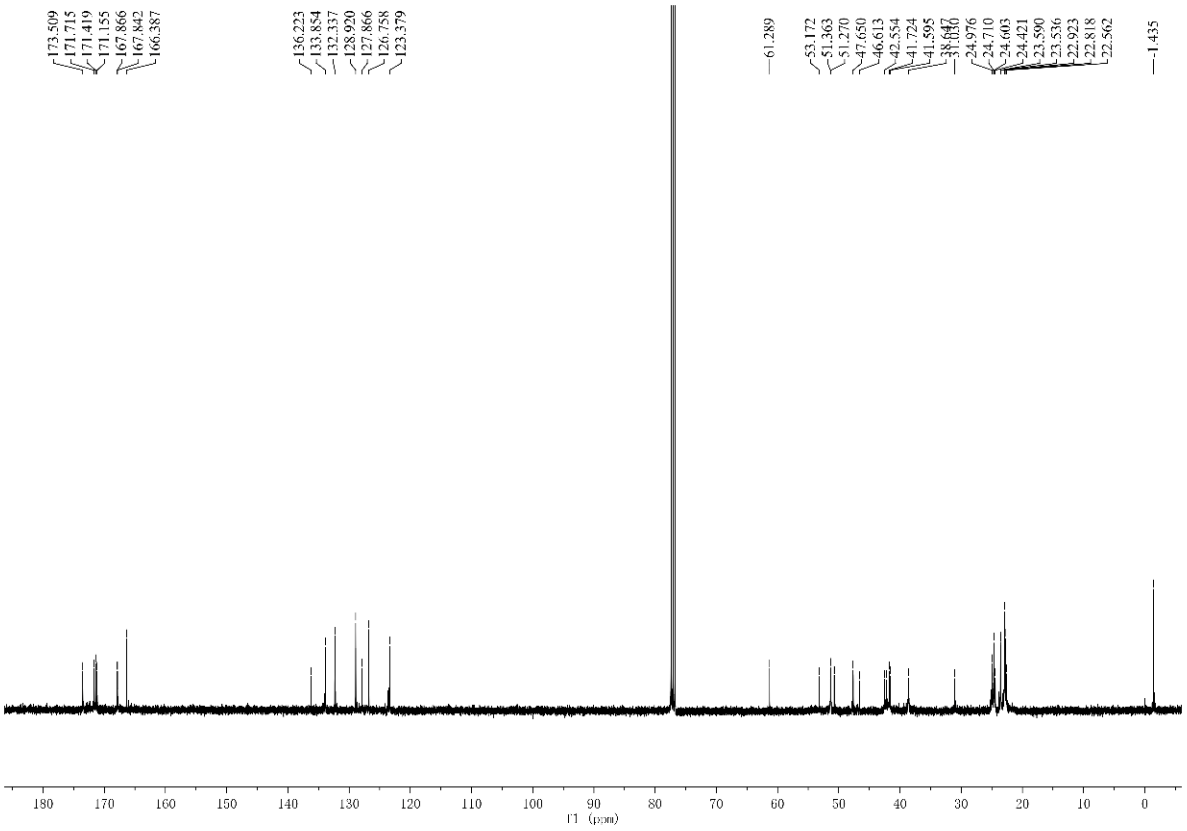




5. ^{1}H, ^{13}C-NMR, HRMS and HPLC of cyclic peptides.

(1) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **1**.





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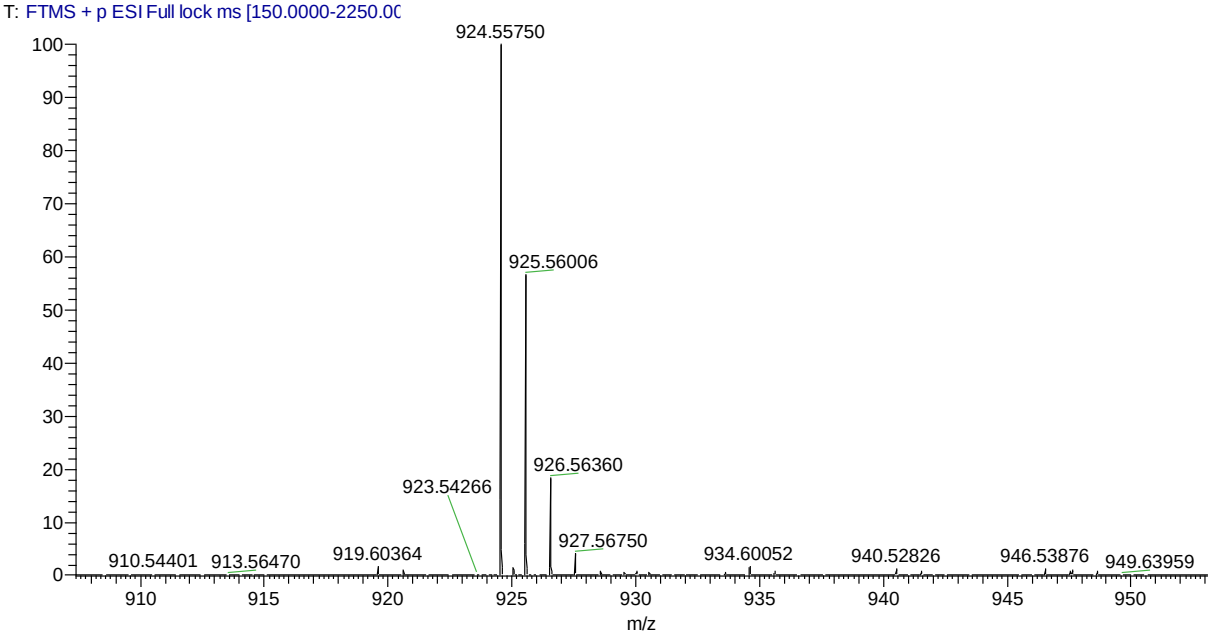
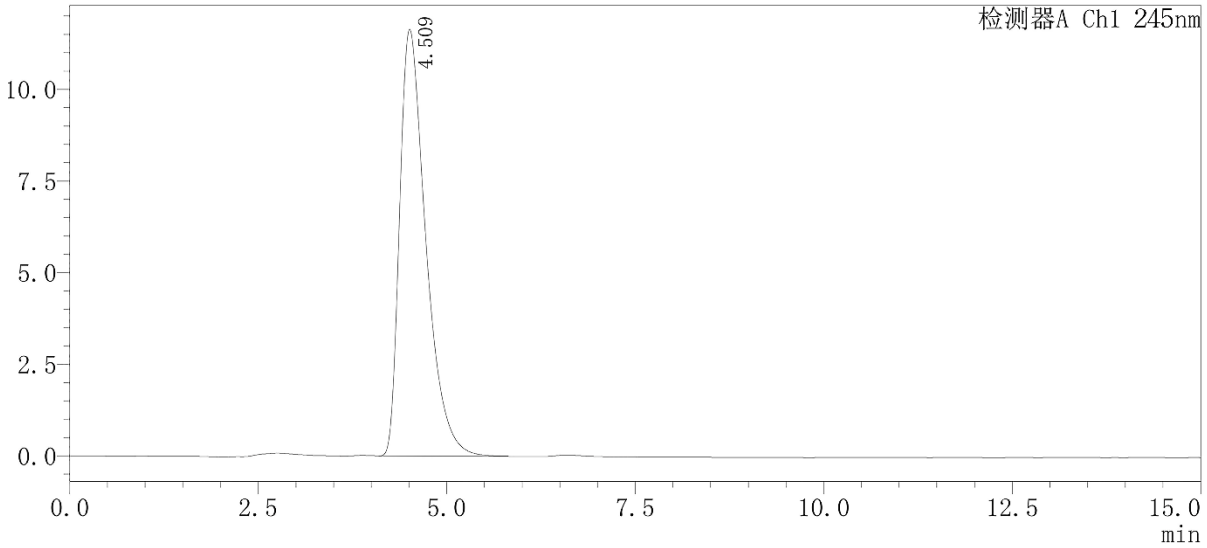
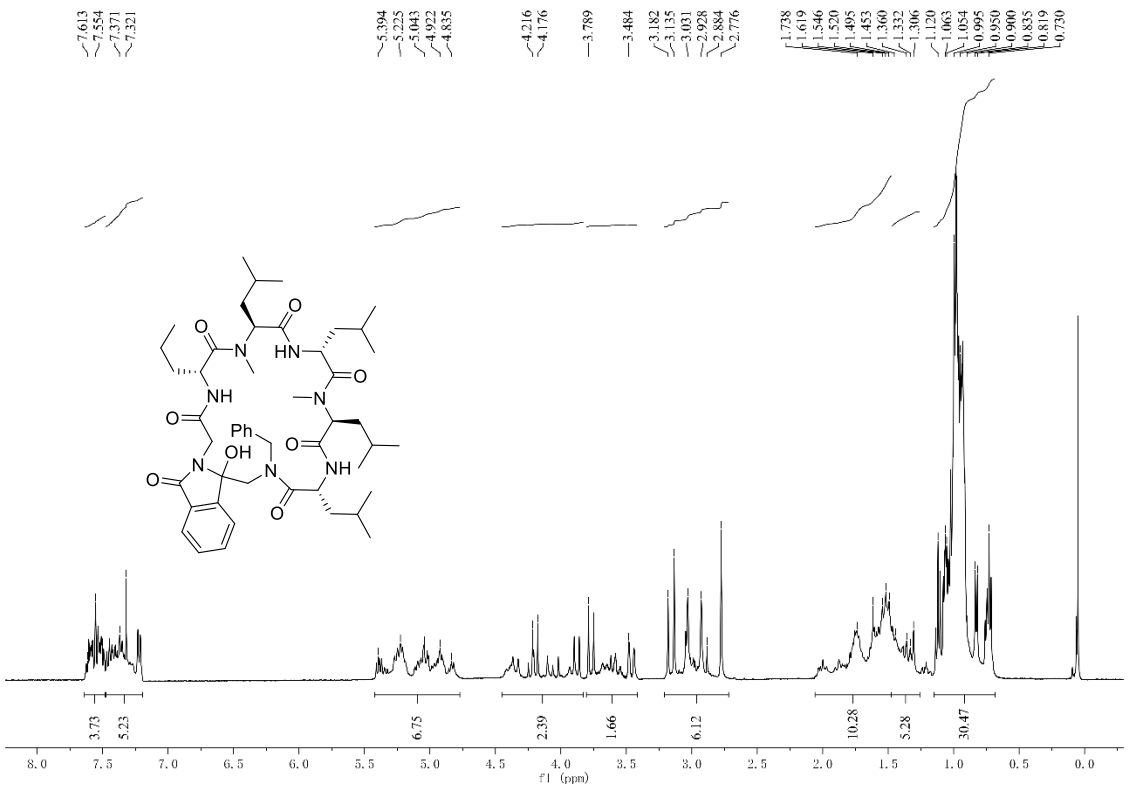
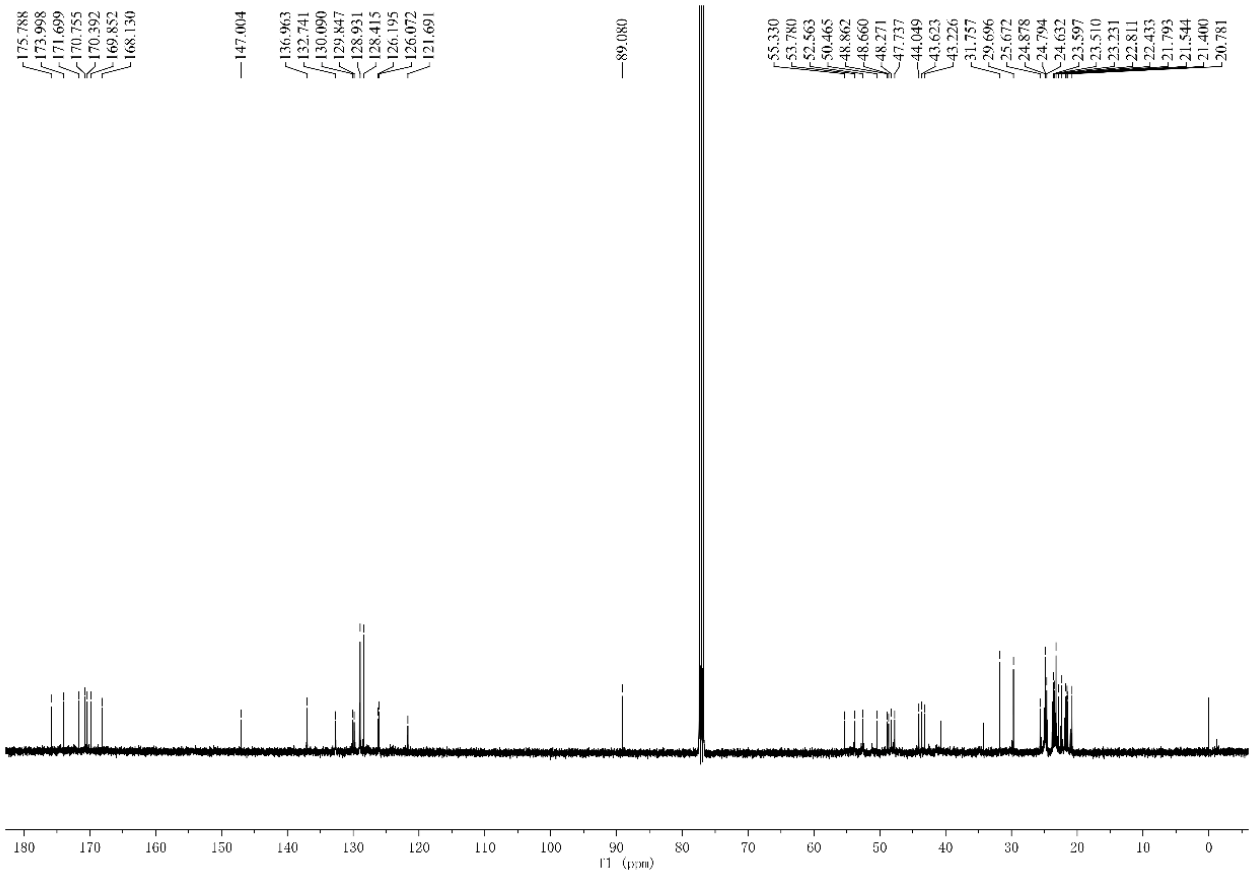




HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

(2) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **2**.





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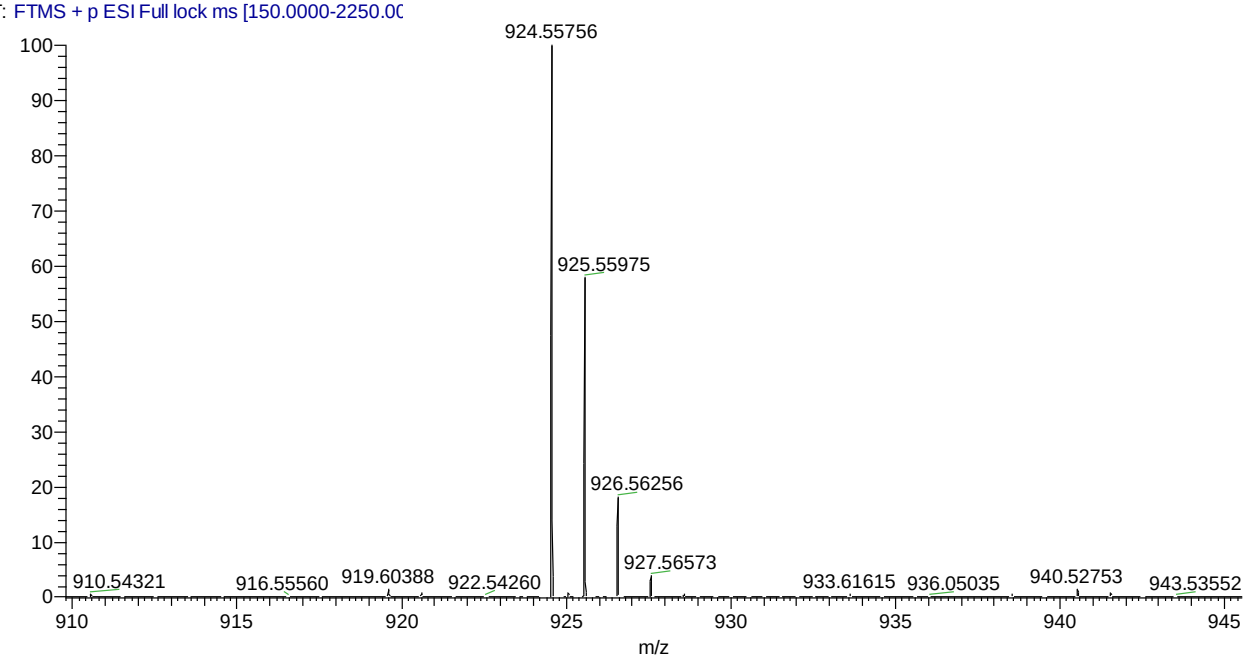
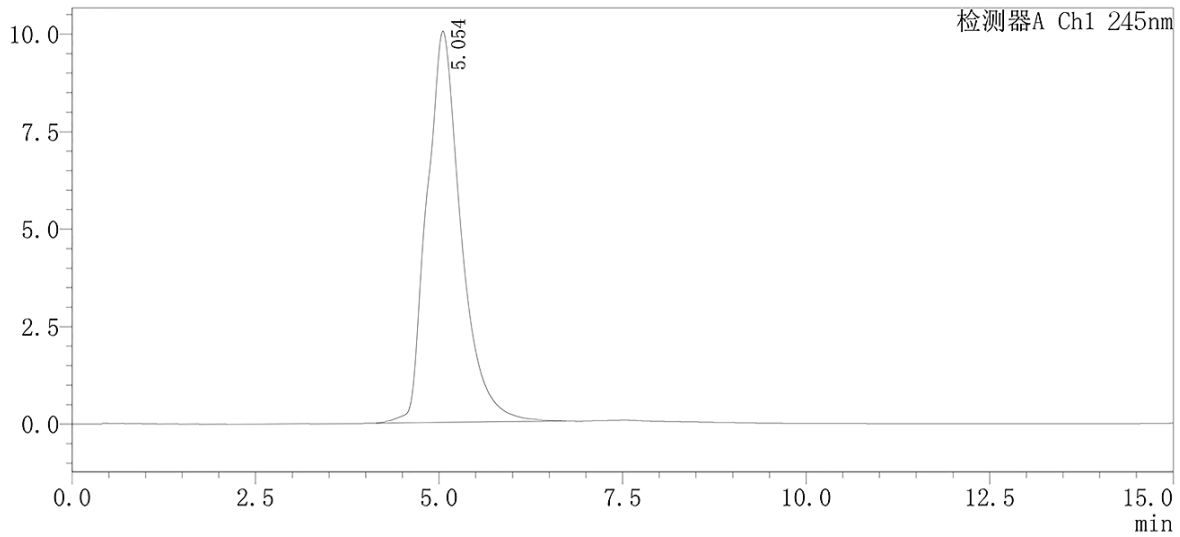
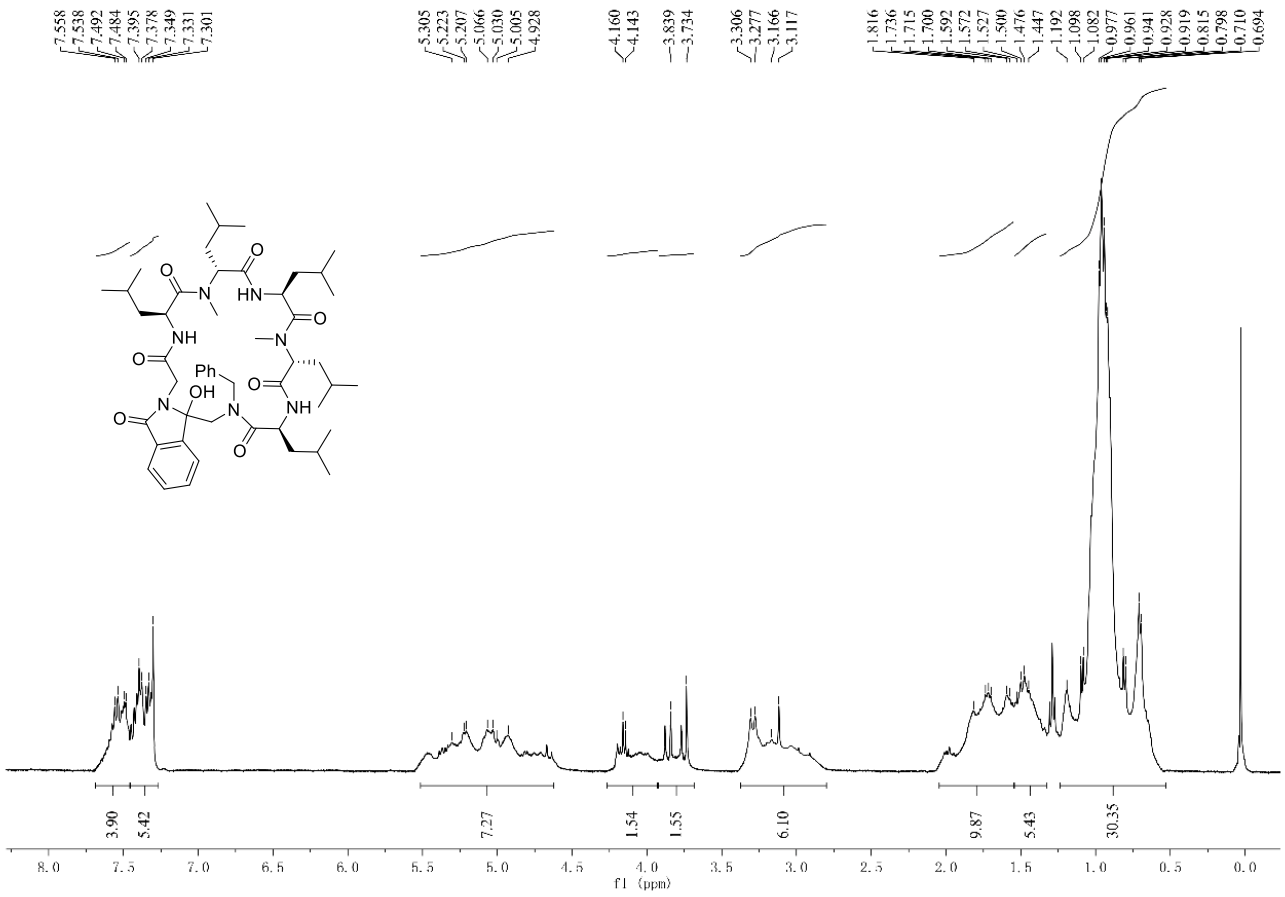
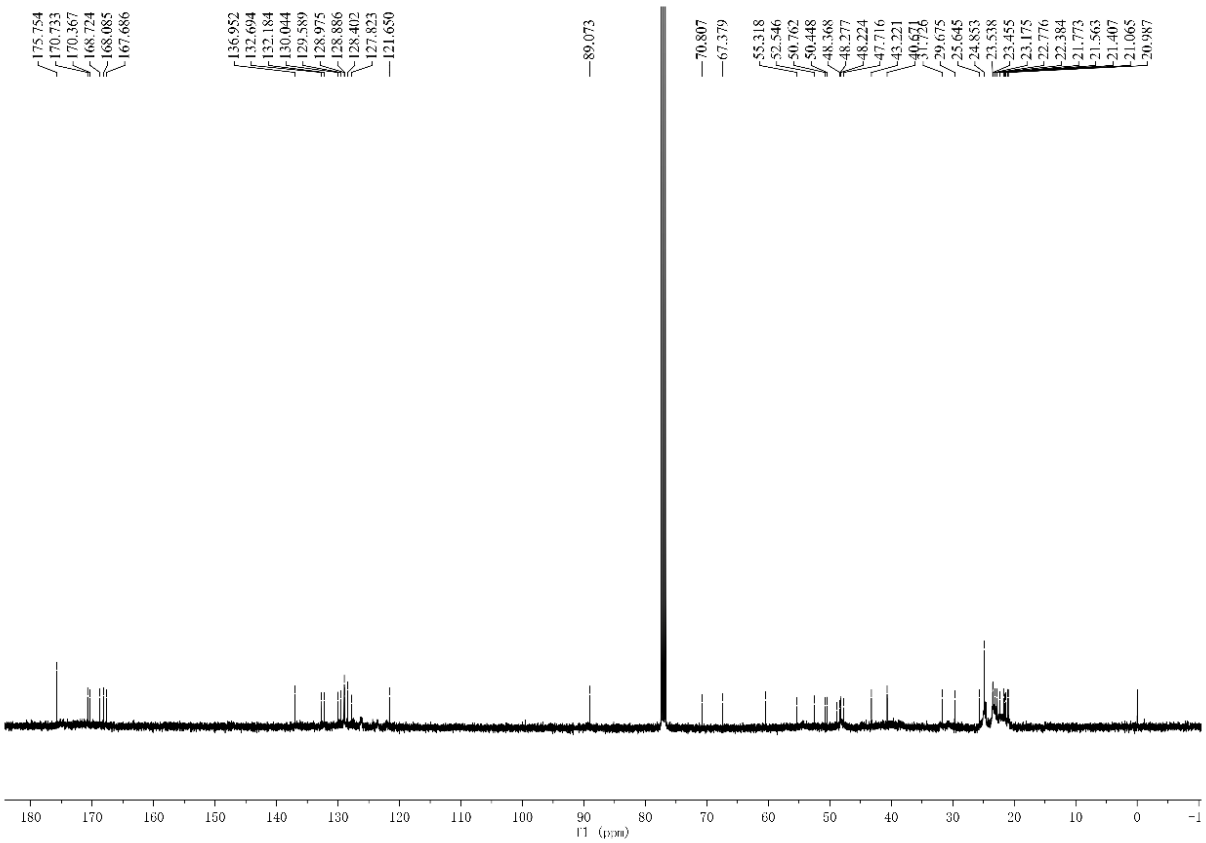




HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

(3) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **3**.

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180
170
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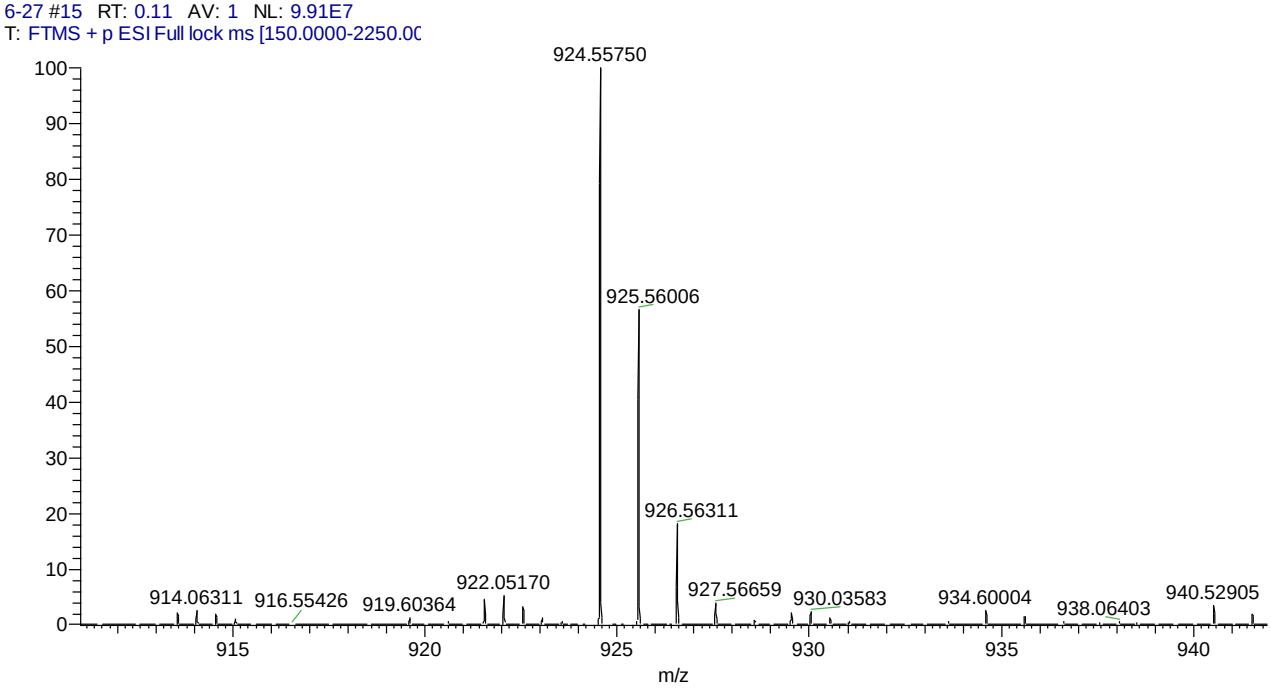
0
-1
f1 (ppm)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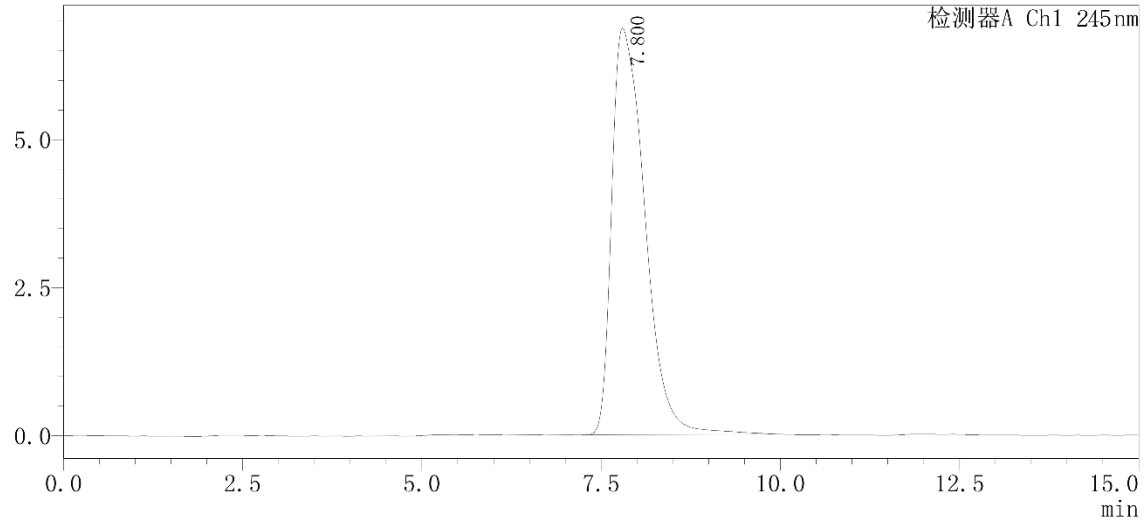
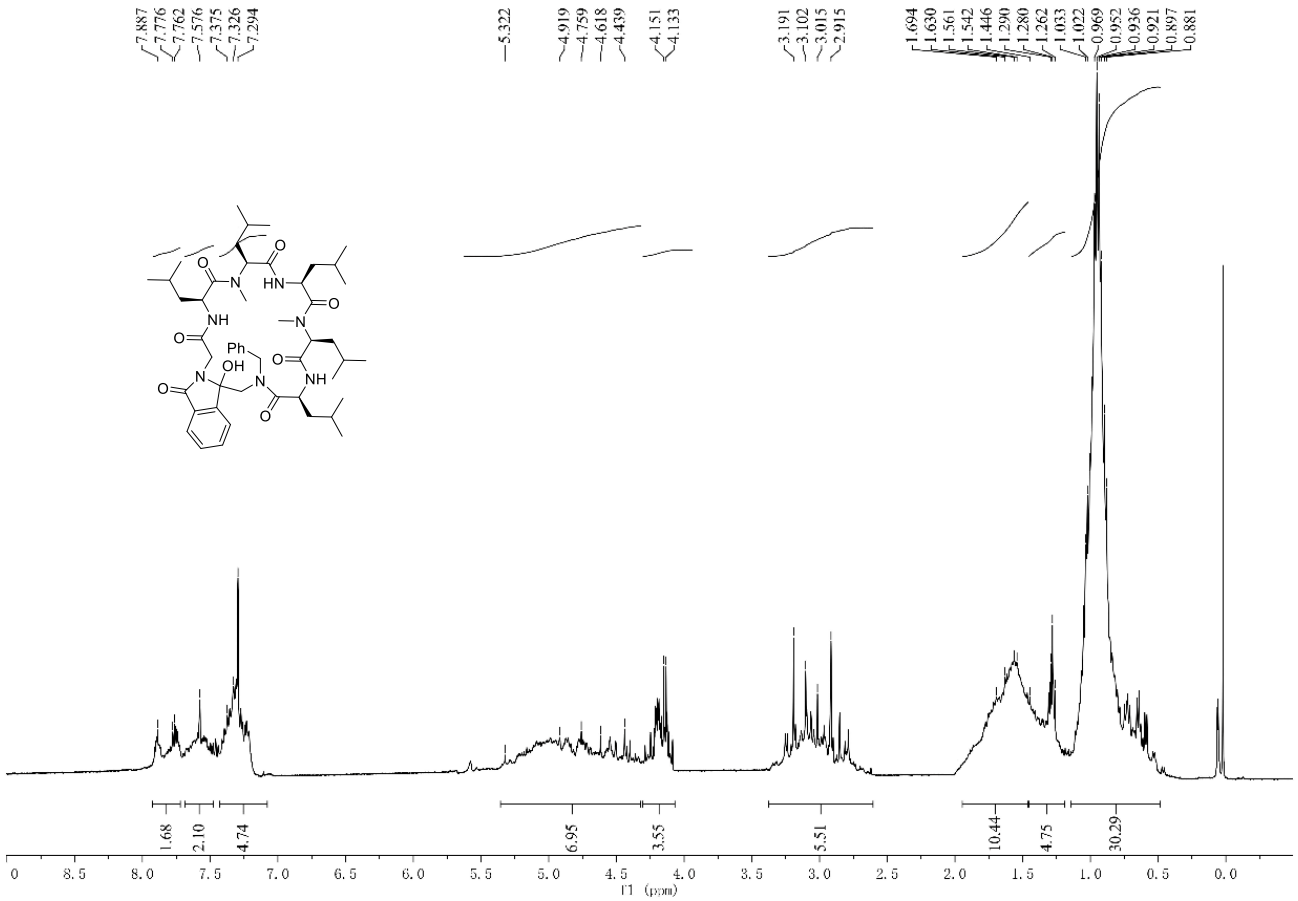
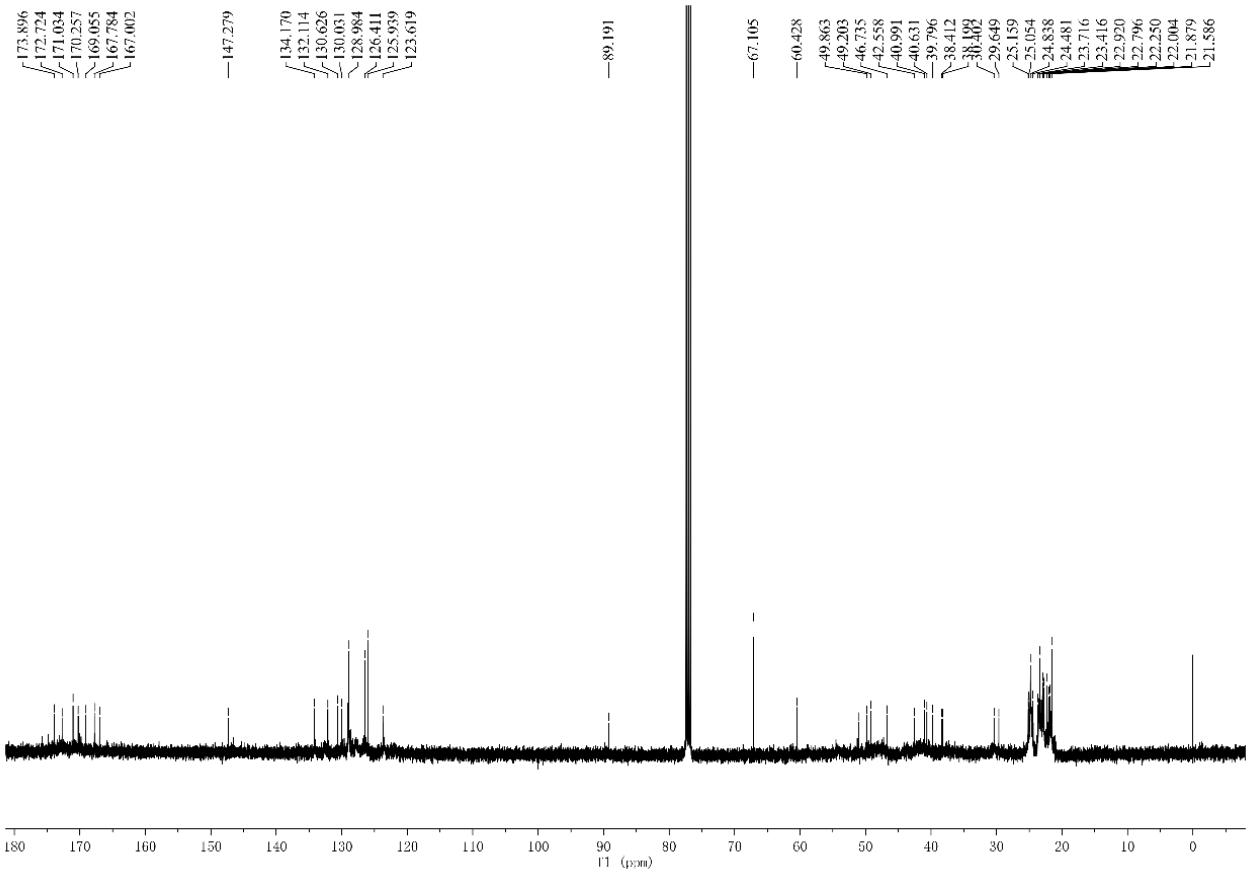


HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

(4) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **4**.





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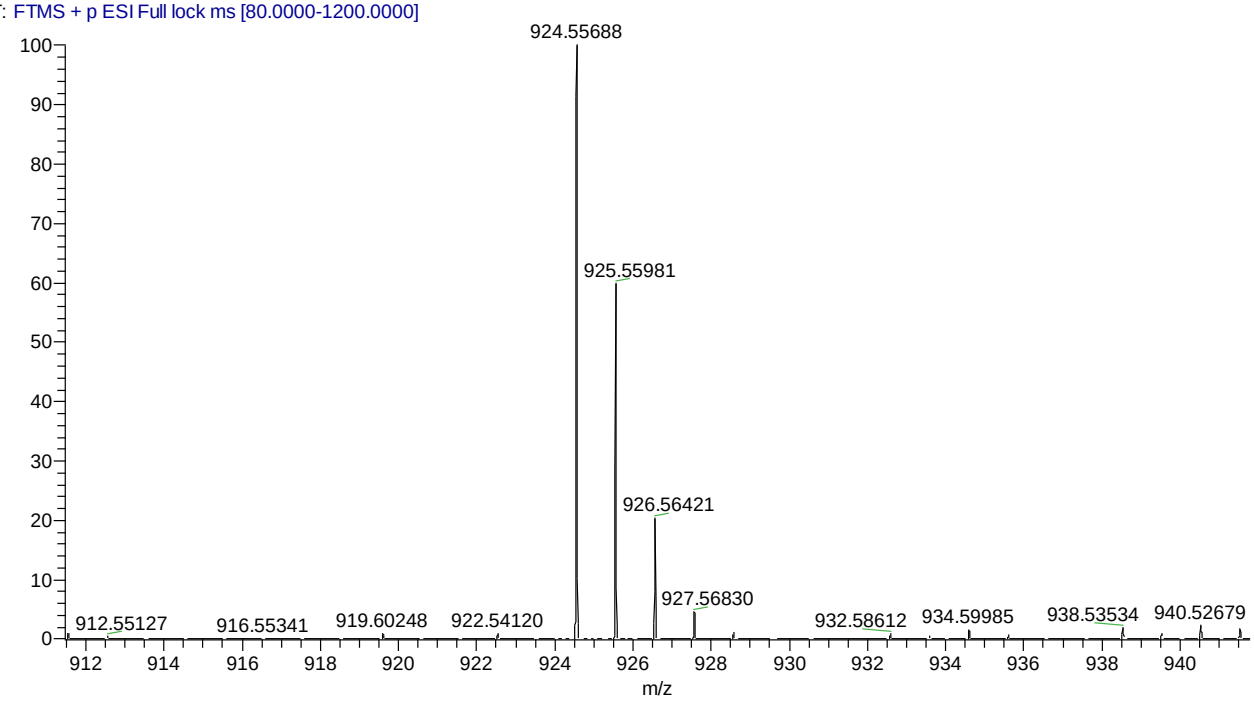
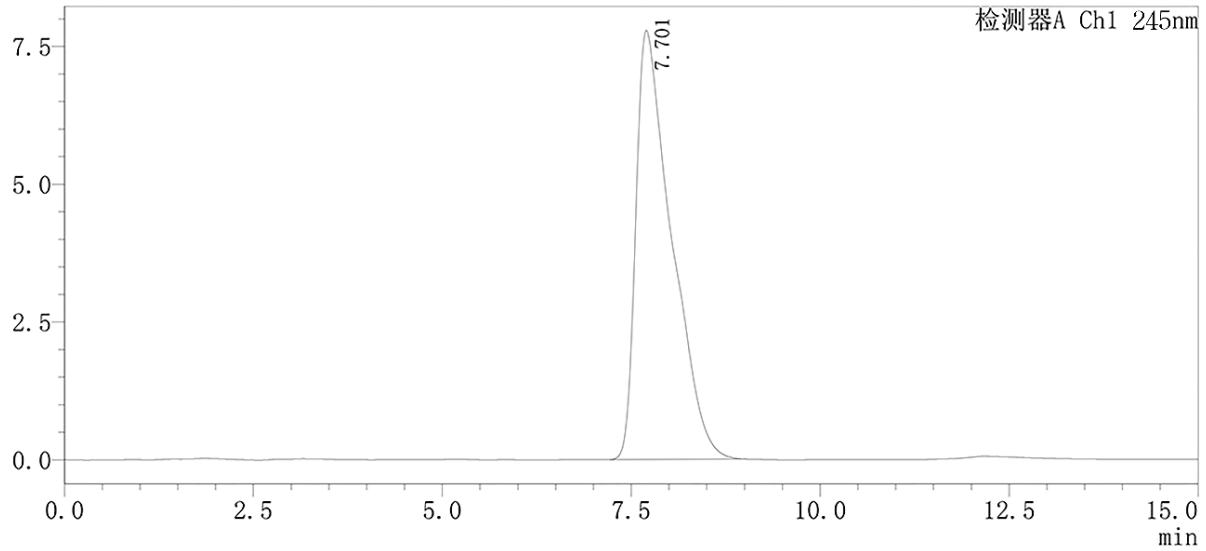
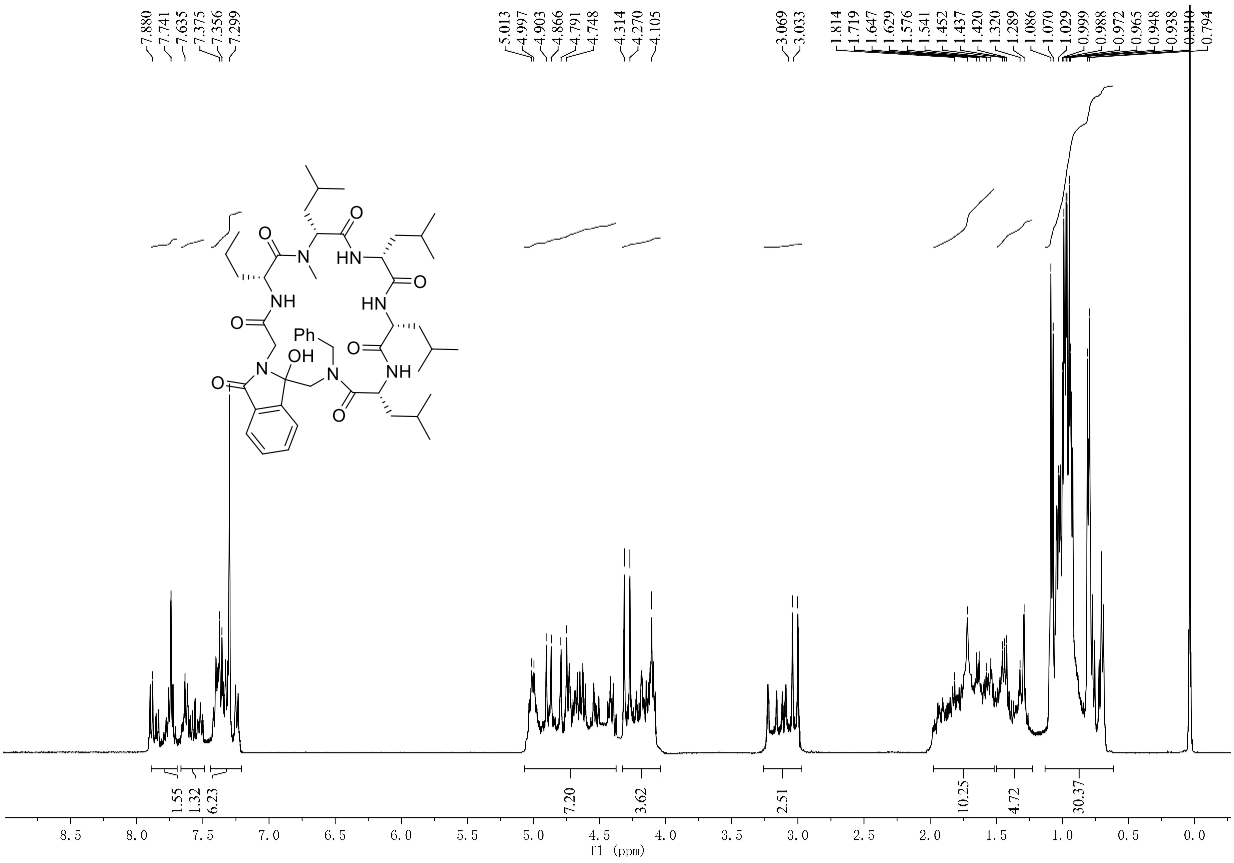
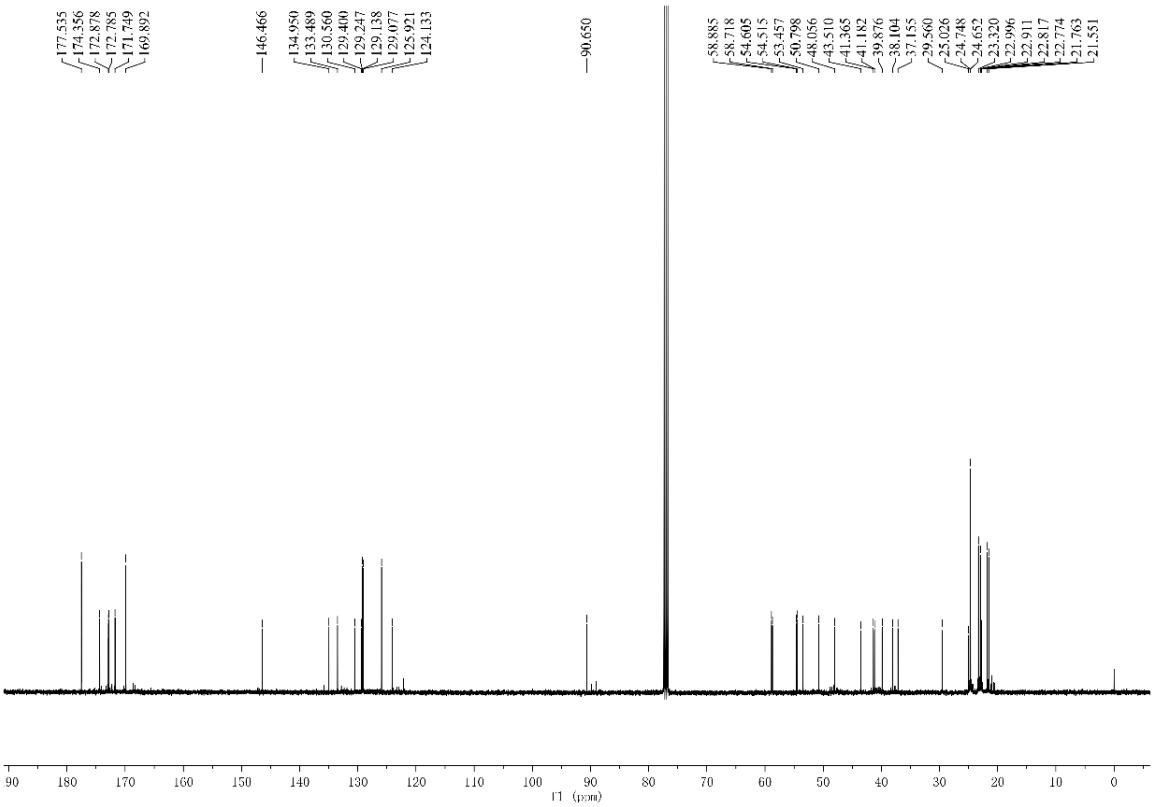




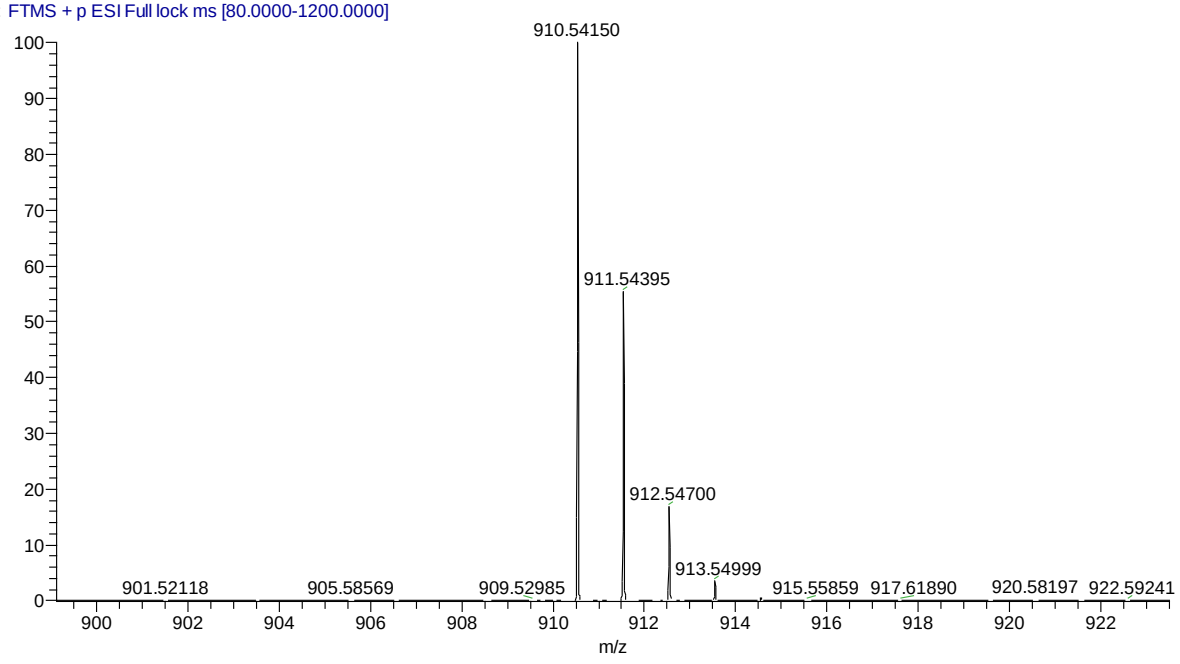
HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

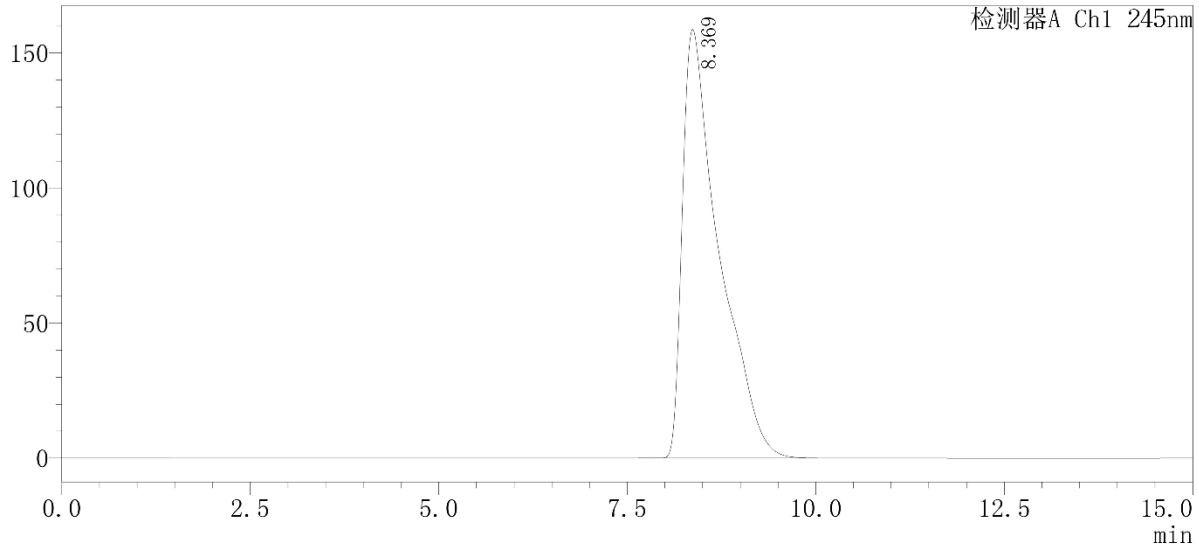
(5) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **5**.





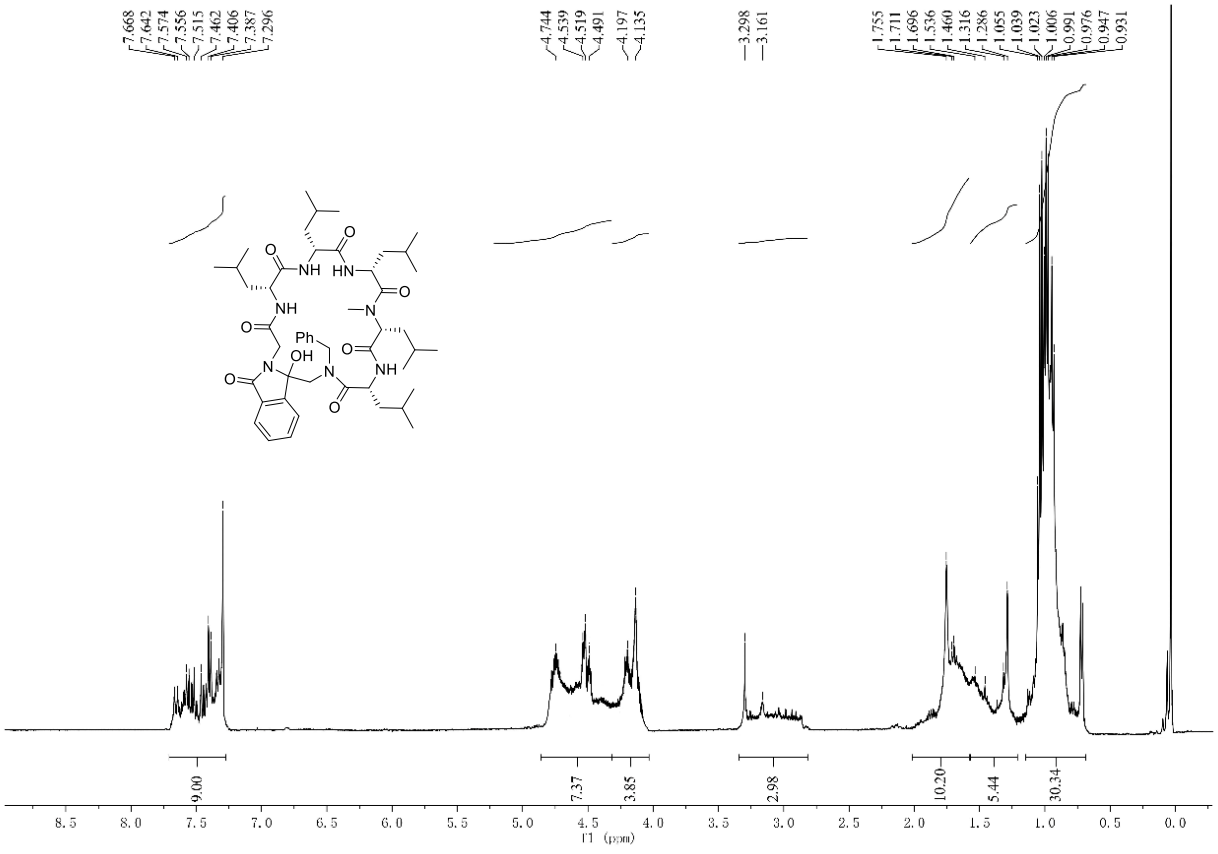
1-88 #9 RT: 0.10 AV: 1 NL: 2.98E7
T: FTMS + p ESI Full lock ms [80.0000-1200.0000]

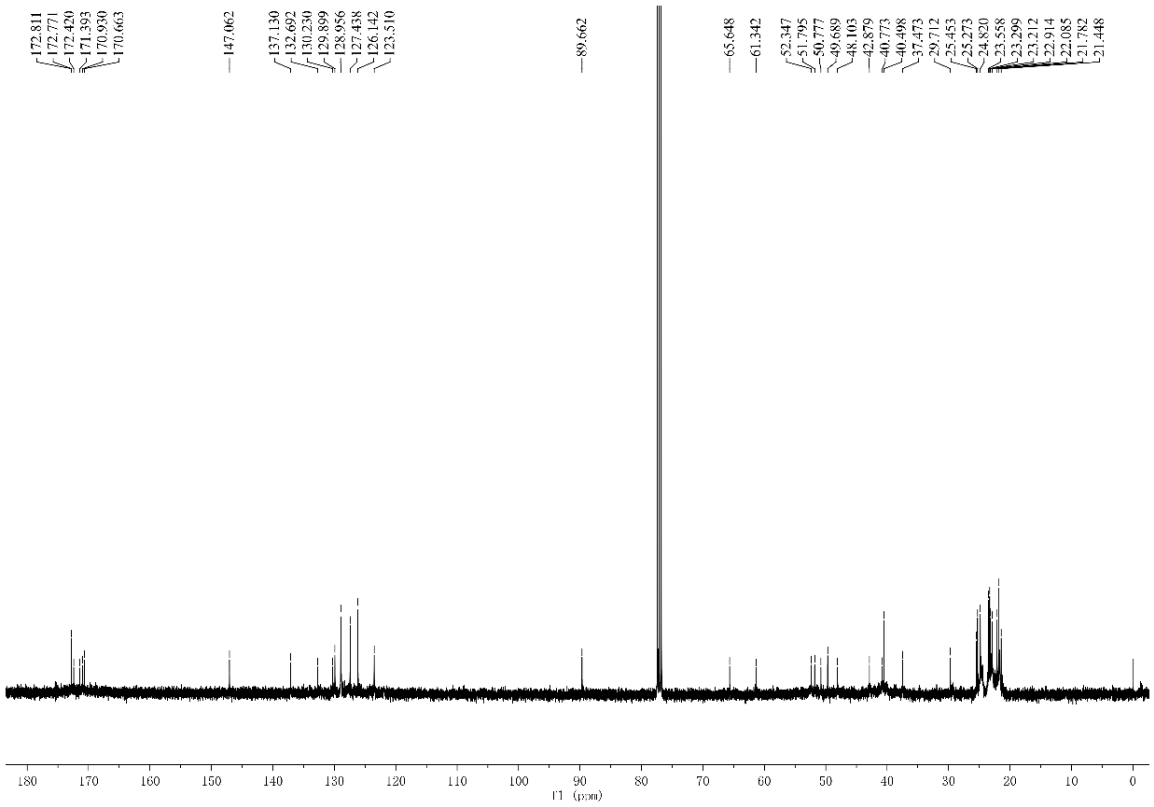




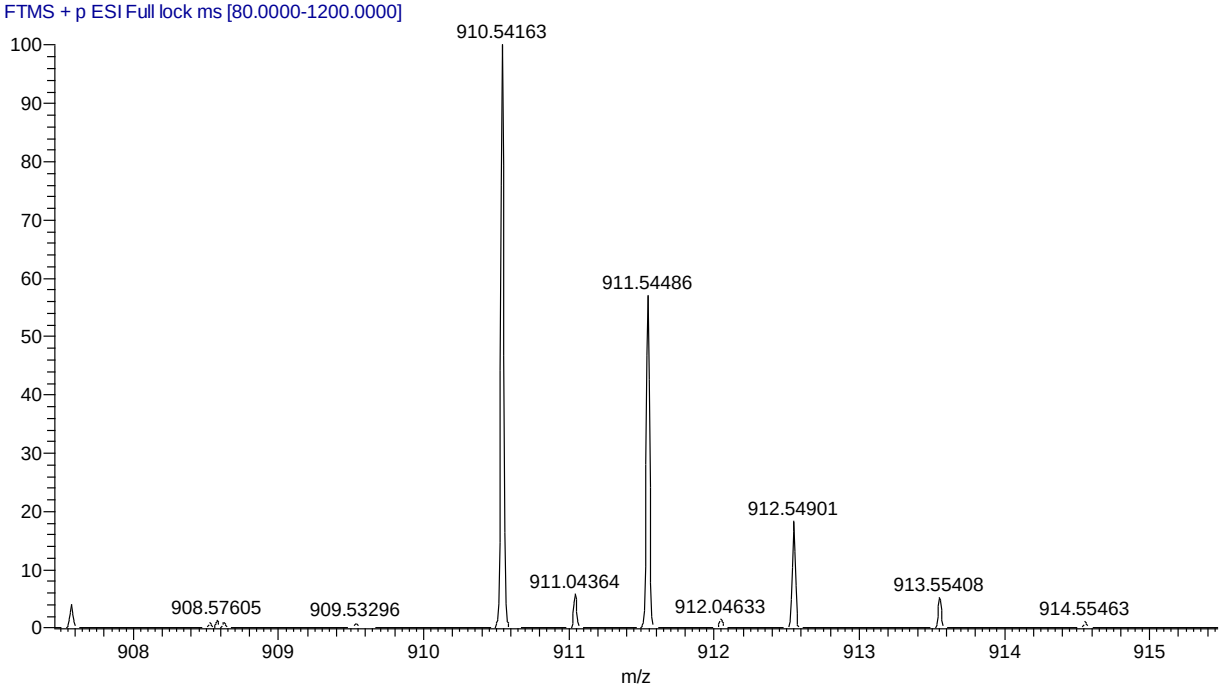
HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

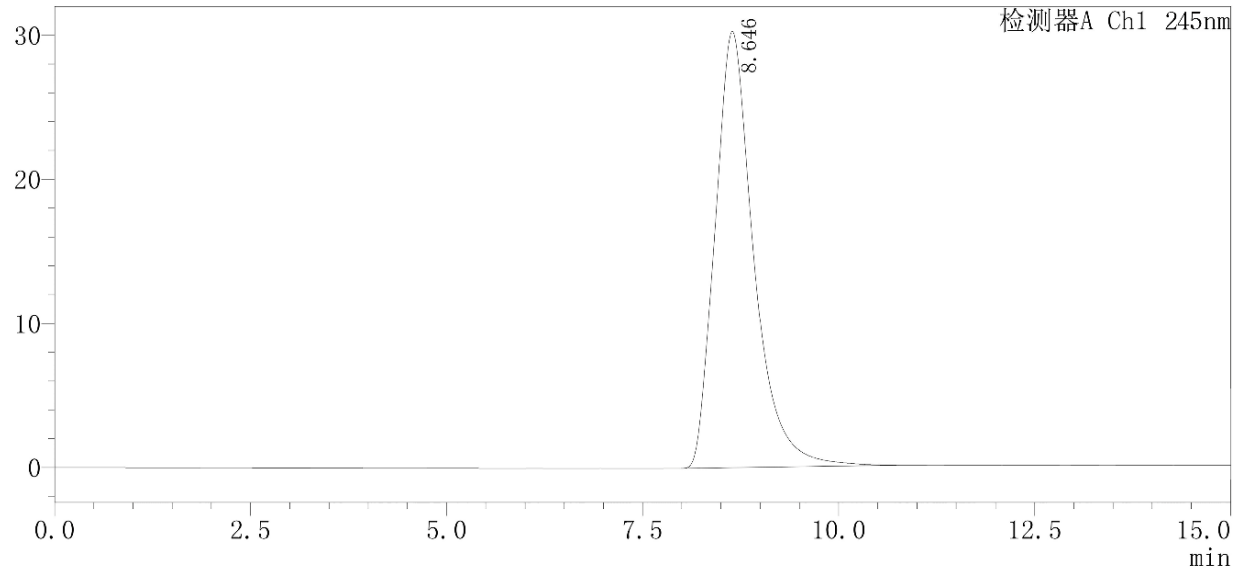
(6) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **6**.





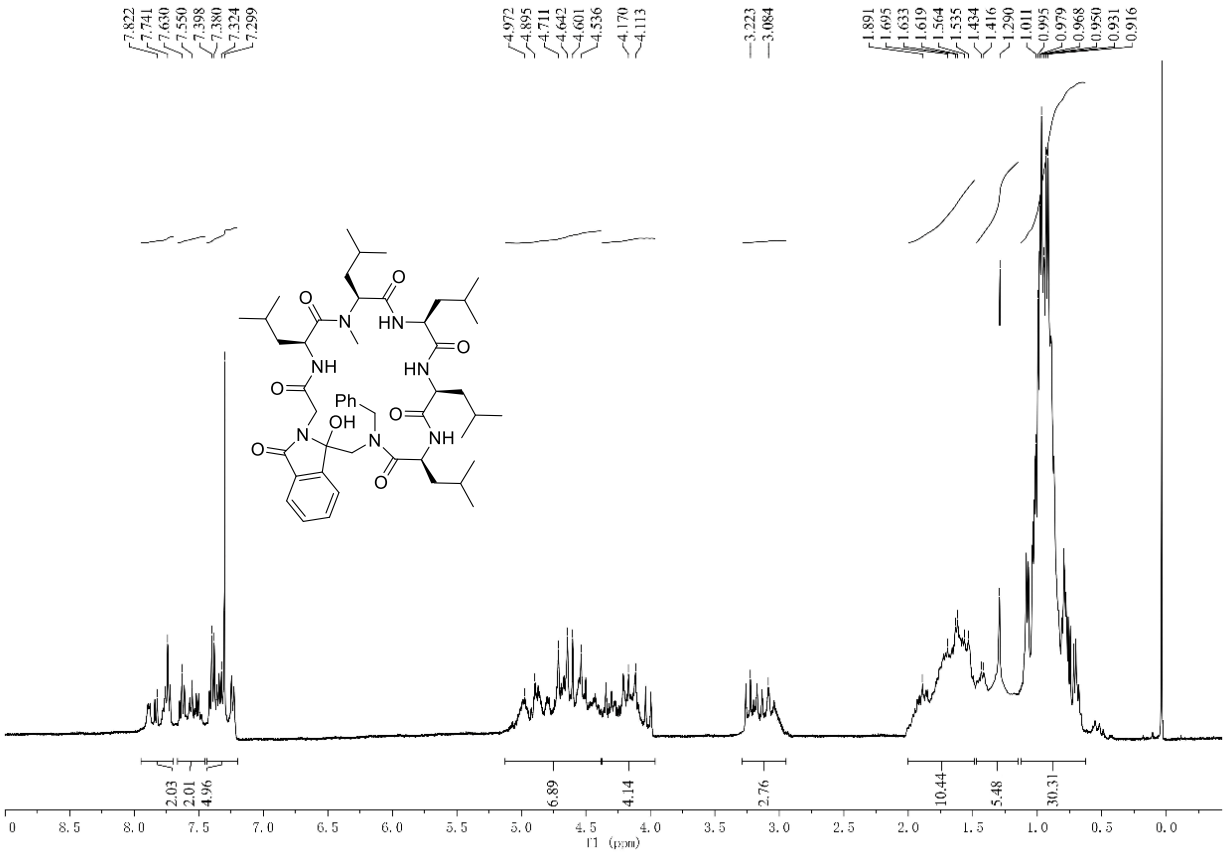
1-89 #9 RT: 0.10 AV: 1 NL: 2.61E6
T: FTMS + p ESI Full lock ms [80.0000-1200.0000]

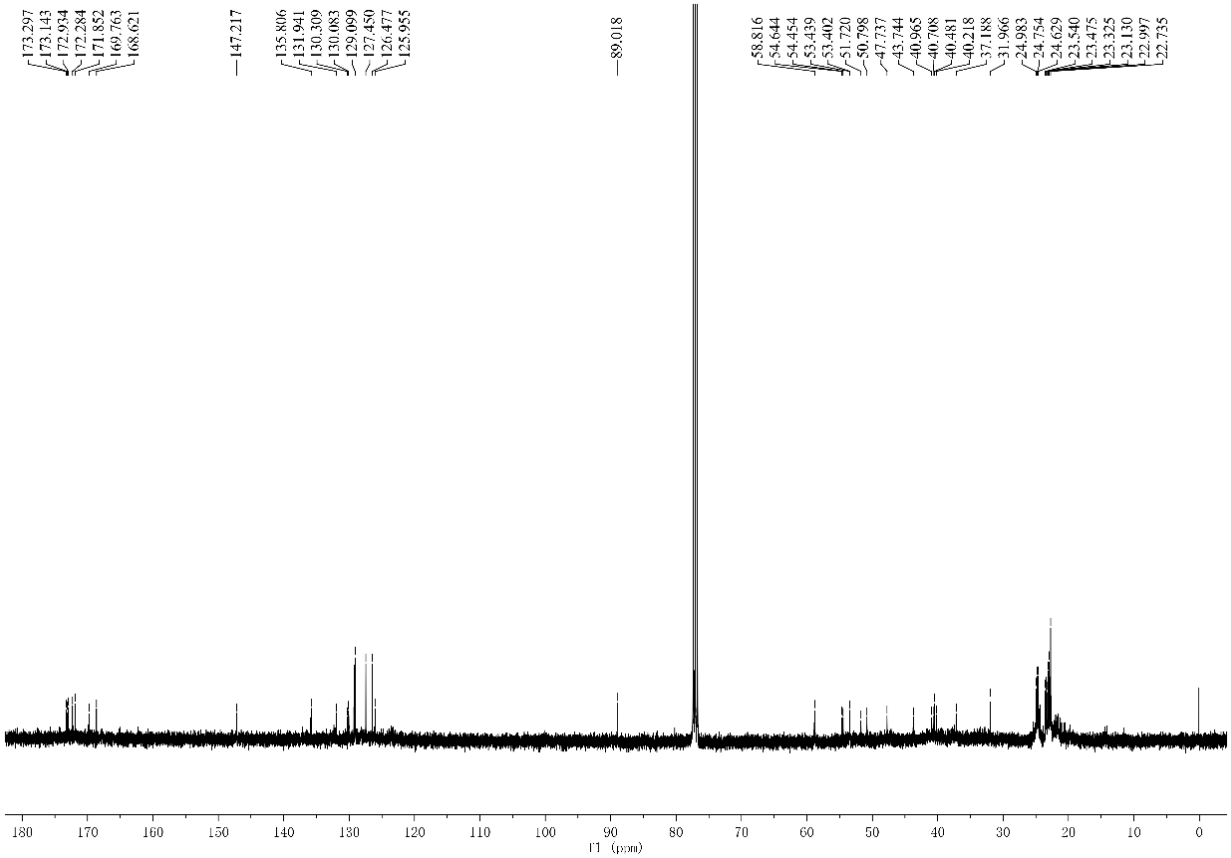




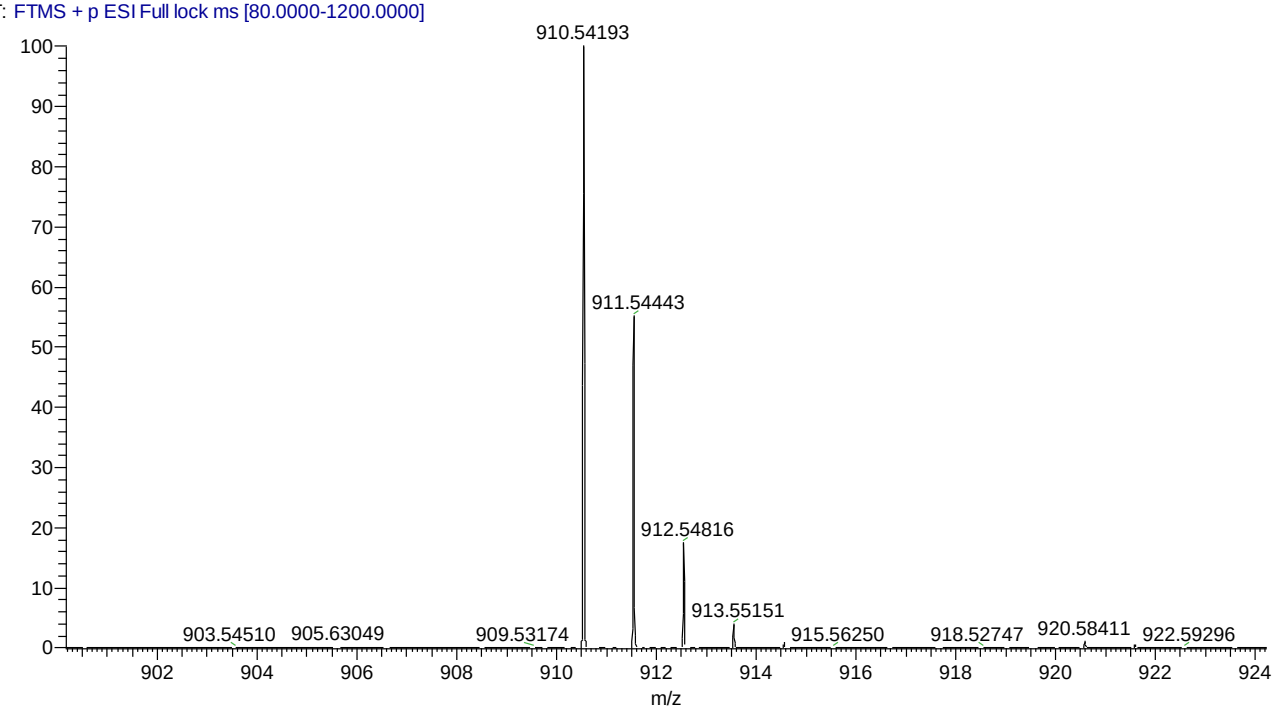
HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

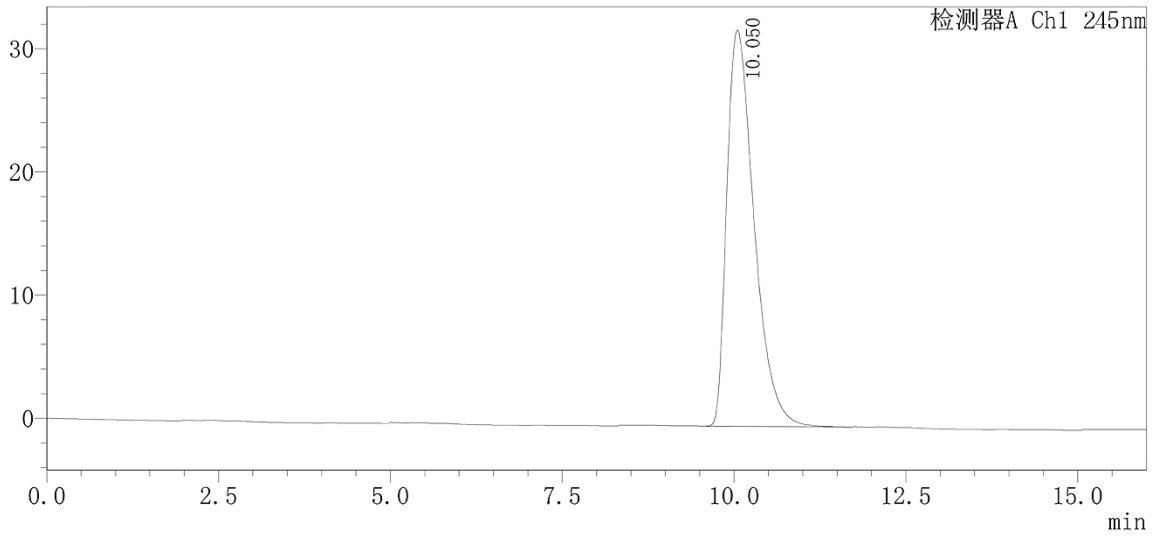
(7) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **7**.





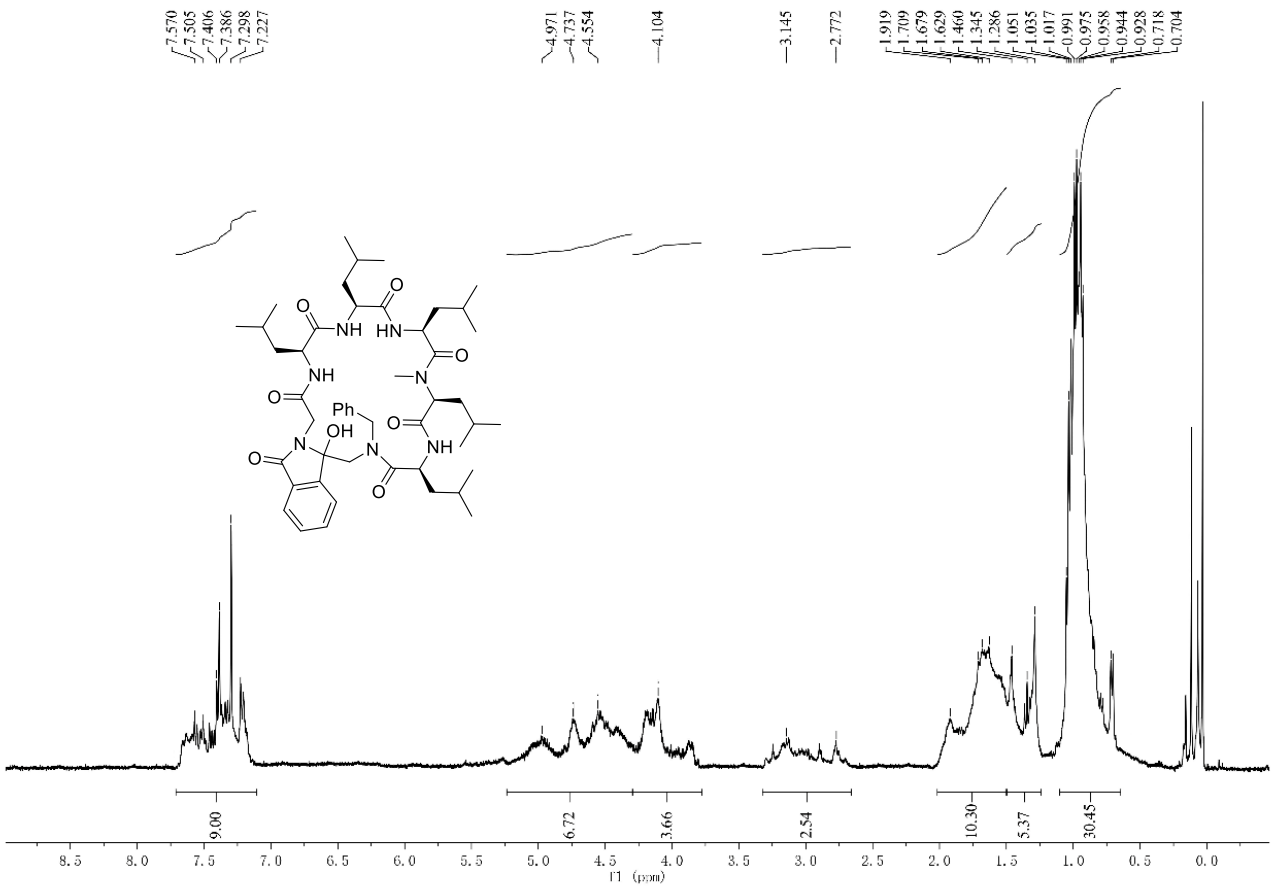
1-90 #9 RT: 0.10 AV: 1 NL: 8.93E6
T: FTMS + p ESI Full lock ms [80.0000-1200.0000]

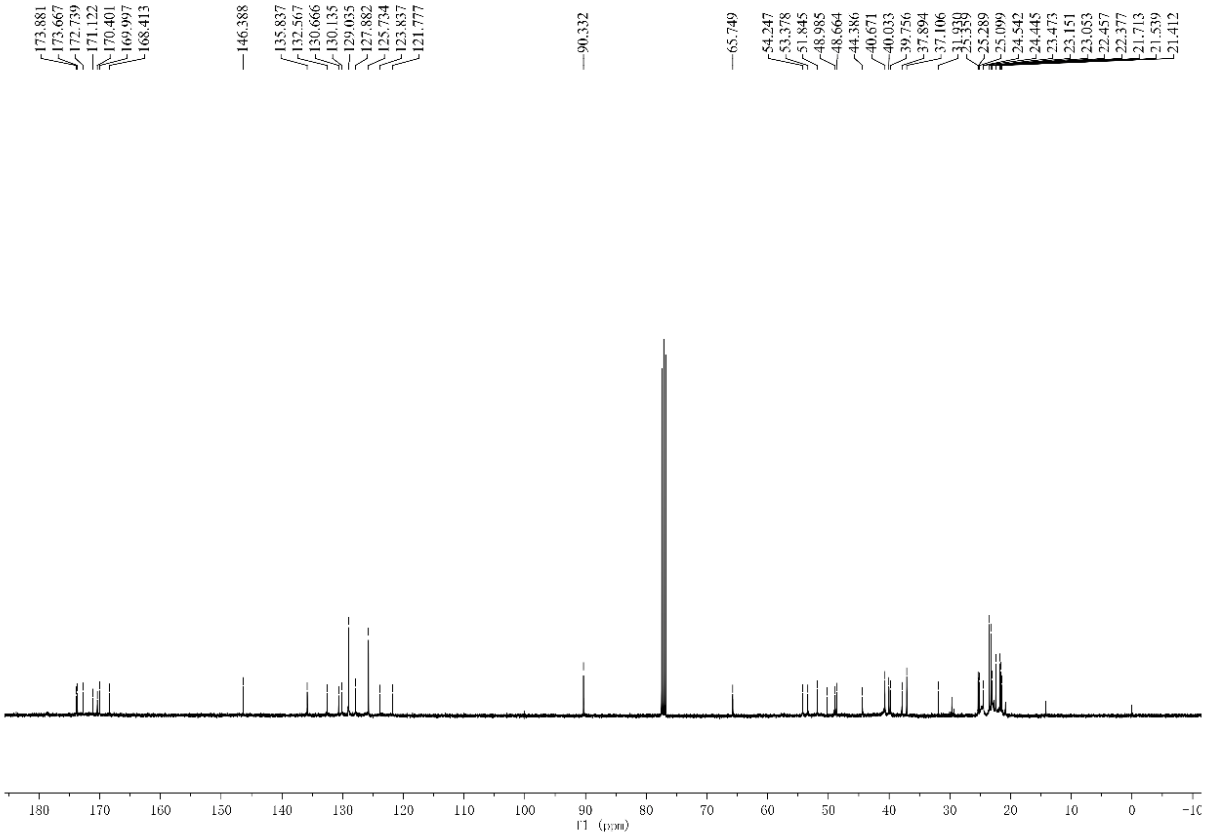




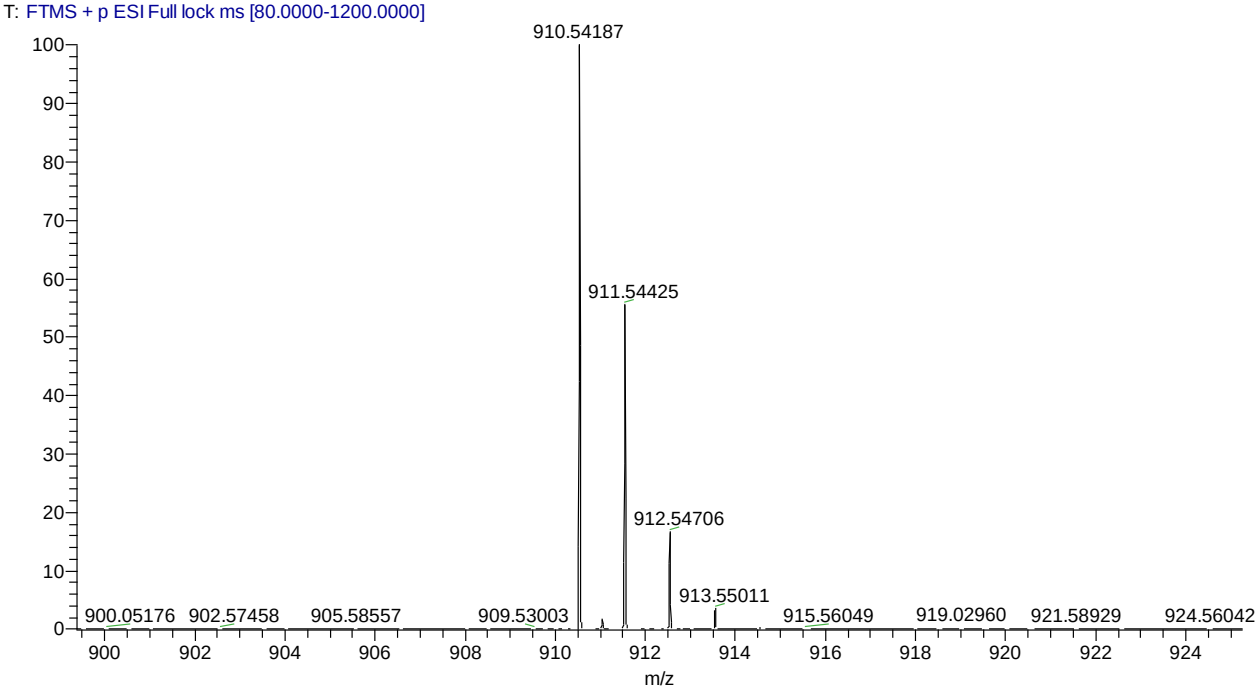
HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.

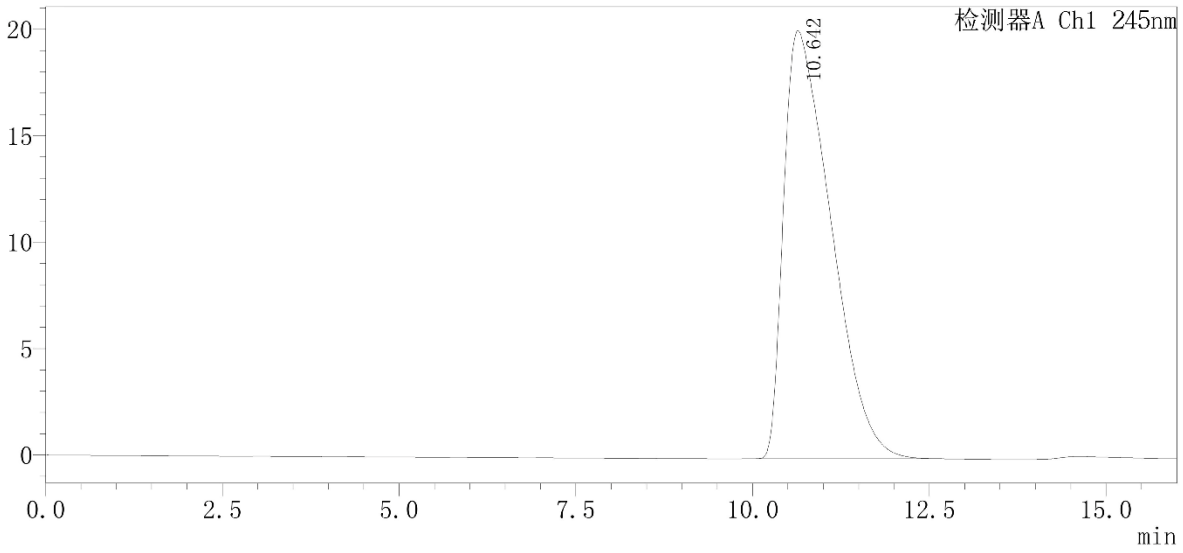
(8) ^{1}H, ^{13}C-NMR**,** HRMS and HPLC of **8**.





1-91 #9 RT: 0.10 AV: 1 NL: 1.36E7
T: FTMS + p ESI Full lock ms [80.0000-1200.0000]





HPLC conditions: Shiseido Capcell PAK C18 (150×4.0 mm, 5 μm) was used as the column at 30 ˚C, and the mobile phase flow rate was 1 mL/min. During the analytical run, the elution was carried out using mobile phases A (Ultrapure water) and B (acetonitrile), the percentage of mobile phases B was 30%, while the detection wavelength was 245 nm.