Electronic Supporting Information

An in-tether sulfilimine chiral center induces helicity in short peptides

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General information

For peptide synthesis, Fmoc-protected amino acids Fmoc-Ala-OH, Fmoc-Gly-OH, Fmoc-Phe-OH, Fmoc-Ile-OH, Fmoc-Val-OH, Fmoc-Leu-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asn(Trt)-OH and Fmoc-D-Ala-OH were purchased from GL Biochem. 2-chlorotritylchloride resin (loading value ~0.65 mmol/g) was purchased from Nankai Synthesis. N-methylpyrolidone (NMP), dichloromethane (DCM), dimethylformamide (DMF), diisopropylethylamine (DIPEA), trifluoroacetic acid (TFA), triisopropylsilane (TIPS) were purchased from Energy Chemical. 2,2-dimethoxy-2-phenylacetophenone (DMPA) were purchased from Aladdin Chemical. Other solvents and reagents were purchased from Energy Chemical and J&K without further purification.

The reverse phase high performance liquid chromatography (HPLC) was performed on Shimadzu prominence LC-20AT instrument equipped with C18 column and acetonitrile /water as the eluent condition. ^{1}H-NMR spectra were recorded on Bruker Avance-III 400MHz. LC-MS was recorded on Shimadzu LCMS 2020 equipped with electrospray ionization. Circular dichroism spectra were recorded on Applied photophysics chirascan instrument. In serum digestion two-month-old mice were purchased from Guangdong medical laboratory animal center.

Synthesis of unnatural amino acids (S_3~S_6)

The synthesis of S_5 was showed as an example, and S_3, S_4, S_6 were synthesized in the similar route.

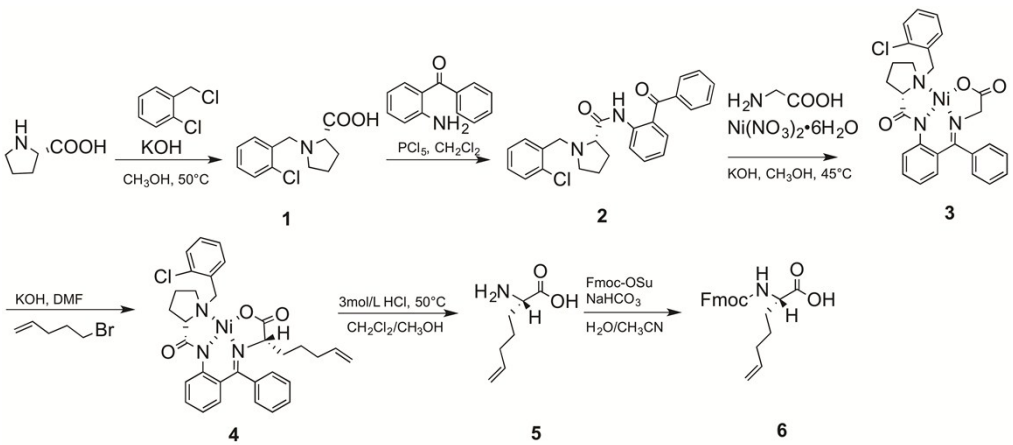


Figure S1 The synthetic route of S_5

Compound 1:

Potassium hydroxide (76.8 g, 1.4 mol) was dissolved in anhydrous methanol (250 ml) and heated to 60℃, then L-proline (46 g, 0.4 mol) was added into the mixture. After complete dissolution, 2-chlorobenzyl chloride (65.7 ml, 0.52 mol) was added dropwise. After 24h, CH_2Cl_2 (200 ml) was added and the reaction mixture stood for 4h. Then the mixture was filtered out and the residue was washed by CH_2Cl_2 twice. The filtrate was gathered, concentrated and crystallized in acetone to obtain compound 1 (80.6 g, yield: 82%).

Compound 2:

Compound 1 (24.8 g, 0.1 mol) was added into CH_2Cl_2 (200 ml) and the mixture was cooled to 0℃. Phosphorus pentachloride (30.2 g, 0.15 mol) was added dropwise and stirred for 1h, followed by the addition of 2-aminobenzophenone (20.0 g, 0.1 mol). The reaction was stirred at r.t. for 4h. CH_2Cl_2 was removed under vacuum and acetone was added for crystallization to obtain compound 2 (23.5 g, yield: 56%).

Compound 3:

Compound 2 (25.0 g, 0.065 mol), nickel (II) nitrate hexahydrate (31.6 g, 0.11 mol) and glycine (20.5 g, 0.27 mol) were dissolved in anhydrous methanol (300 ml) and heated to 50℃. The potassium hydroxide (25.0 g, 0.47 mol) in methanol (150 ml) solution was added dropwise. After 4h, acetic acid was added. Methanol was removed and followed by the addition of water (800 ml), and stirred at r.t. overnight to promote the precipitation. The mixture was filtered out and residue was gathered to obtain red solid compound 3 (22 g, yield: 75%).

Compound 4

Under N_2 atmosphere, compound 3 (20.0 g, 0.04 mol) was dissolved in DMF (200 ml), followed by the addition of powdered potassium hydroxide (21.1 g, 0.4 mol) and the reaction mixture was stirred at r.t. for 1h. Under the condition of ice bath, 5-bromo-1-pentene (4.7 ml, 0.042 mol) was added dropwise. Then the reaction was gradually warmed to r.t. and stirred for 4h before the addition of 5% v/v acetic acid in water. The reaction continued to be stirred for 6h to promote the precipitation and filtered out. The residue was gathered and washed by water for three times to obtain compound 4 (19.7 g, yield: 87%).

Compound 5

Compound 4 (19.7 g, 0.035 mol) was dissolved in methanol/CH_2Cl_2 (v/v = 50 ml/100 ml), and 3M hydrochloric acid (100 ml) was added into the mixture. The reaction was heated to 60℃ and stirred overnight until yellow/green color change was observed. Then the solvent was removed in vacuo and chloroform was used for

extraction for three times to recover the ligand. The amino acid aqueous fraction was used for the next step without further purification.

Compound 6 (S_5)

Sodium bicarbonate (16.8 g, 0.2 mol) and EDTA-Na (18.6 g, 0.05 mol) were added into the aqueous fraction to remove residual nickel. After stirring for 20 minutes, sodium bicarbonate was added again to make pH value of the mixture stay at 7-8. Then the mixture was cooled to 0℃ with ice bath. 9-fluorenylmethyl succinimidyl carbonate (11.7 g, 0.035 mol) was dissolved in 1,4-dioxane (50 ml) and added dropwise into the aqueous solution. The reaction was gradually warmed to r.t. and stirred for 12h. 1,4-dioxane was removed in vacuo and citric acid was added to make pH value of the mixture stay at 2-3. The reaction was extracted with ethyl acetate for three times. The organic layers were gathered, dried with Na_2SO_4 and concentrated in vacuo. The final product S_5 was obtained after the purification of flash chromatography (CH_2Cl_2:H_2O = 20:1) (4.9 g, yield: 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (td, *J* = 7.4, 0.9 Hz, 2H), 5.75 (s, 1H), 5.57 (s, 1H), 4.98 (dd, *J* = 27.6, 13.4 Hz, 2H), 4.40 (s, 2H), 4.21 (t, *J* = 6.5 Hz, 1H), 2.34 – 2.16 (m, 1H), 2.00 (d, *J* = 35.3 Hz, 3H), 1.62 (s, 2H).

Preparation of cyclic pentapeptide sulfides before oxidation

The synthesis of cyclic pentapeptide sulfide Ac-(cyclo-1,5)-[S_5AAAC]-NH_2 was showed as an example, and other peptide sulfides were synthesized in the similar route. All peptides were prepared by standard Fmoc solid-phase synthesis on 2-chlorotritylchloride resin.

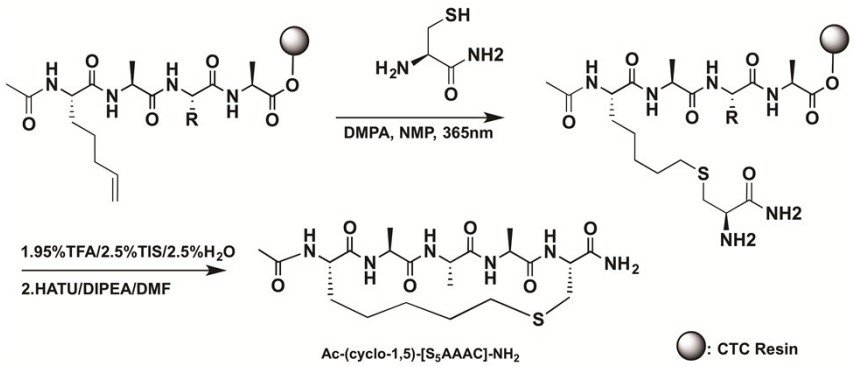


Figure S2 The synthetic route of cyclic peptide sulfide

Step 1: swelling

The required resin was put into the tube and placed on the vacuum manifold. NMP (5 ml) was added and the resin was bubbled with N_2 for 15 minutes.

Step 2: coupling of the first Ala

Fmoc-Ala-OH (5 eq.) and DIPEA (10 eq.) were dissolved in NMP (5 ml) and added to the resin. The reaction mixture was bubbled with N_2 for 3h.

Step 3: washing

Coupling reagents were drained, and the resin was washed by CH_2Cl_2 and NMP (3 × 5 ml)

Step 4: deprotection

50% morpholine in NMP was added and the resin was bubbled with N_2 (2 × 30 min).

Step 5: coupling of Fmoc-Ala-OH with HCTU

Ala (3 eq.), HCTU (2.94 eq.) and DIPEA (6 eq.) were dissolved in NMP (5 ml) and added to the resin. The reaction mixture was bubbled with N_2 for 2h. Then washing, deprotection and coupling of the another Ala and S_5 were followed in the similar procedure.

Step 6: N-terminal acetylation

Acetic anhydride (1 ml) and DIPEA (3 ml) were dissolved in NMP (16 ml) and added to the resin. The reaction mixture was bubbled with N_2 (2 × 1 h).

Step 7: intermolecular thiol-ene reaction

The resin was swelled in NMP (5 ml), followed by the addition of Cys (1 eq.) and DMPA (1 eq.) under N_2 atmosphere. Then the flask was put under the UV lamp at 365 nm and reacted for 2h. The resulting resin was washed by CH_2Cl_2 (3 × 10ml).

Step 8: macrocyclization

The crude peptide was cleaved from the resin by agitation with cleavage cocktail (TFA: TIPS: H_2O=95:2.5:2.5, v/v/v) for 2h. Then Et_2O was added for precipitation of peptides and removed after centrifugation. The precipitate peptide was dissolved in anhydrous DMF (50 ml), and the mixture was cooled to 0℃ with ice bath. HATU (1 eq.) and DIPEA (1 eq.) were added into the mixture under N_2 atmosphere. The reaction was gradually warmed to r.t. and stirred for 24h. Then DMF was removed under vacuum and the crude was dissolved in H_2O/CH_3CN for further HPLC purification.

Preparation of cyclic pentapeptide sulfilimines

Cyclic pentapeptide sulfide (1 eq.) and chloramine-T (1.2 eq.) were dissolved in CH_3CN (5 ml), and the reaction was stirred at r.t. for 24h. Then CH_3CN was removed under vacuum and H_2O/CH_3CN were added to dissolve the crude for HPLC purification.

Circular dichroism spectroscopy

All peptide samples were dissolved in deionized H_2O for CD measurements. CD scans were performed at wavelength from 190 nm to 250 nm with the 0.1 cm path

length for twice. Variable temperature CD scans for peptide **3B** were collected from 25℃ to 70℃ at 5℃ intervals.

Guanidine·HCl denaturation experiment

Cyclic pentapeptide sulfilimine **12B** (~1 mg) was added into varied concentration of guanidine·HCl (0.5 ml) 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 7.0 M. The helicity was monitored by molar ellipticity at 215 nm.

Serum stability

The *in vitro* serum stability assay was performed on the basis of the procedure of the following literature. Standard solution of the sulfilimine peptide **11B**, termed as Ac-(cyclo-1,5)-[S_5ALAC(NTs)]-NH_2 and its linear analog, termed as Ac-S_5ALAC(SH)-NH_2, were prepared in water. Each peptide was added to the murine serum (800 uL) and incubated at 37°C at a final concentration of 100 μM (25% serum). Aliquots (5 μL) were taken periodically at 0 to 18 h, and then 100 μl 12% trichloroacetic acid in H_2O/CH_3CN (1:3) was added and cooled to 4 °C for 30 min to precipitate serum proteins. Samples were then centrifuged at 14000 rpm for 10 min. The standard supernatant was analyzed by LC/MS with a grace smart C18 250× 4.6mm column, using a 3% per minute linear gradient from 20% to 80% acetonitrile over 20min. The amount of starting material left in each sample was quantified by LC/MS-based peak detection at 220 nm.

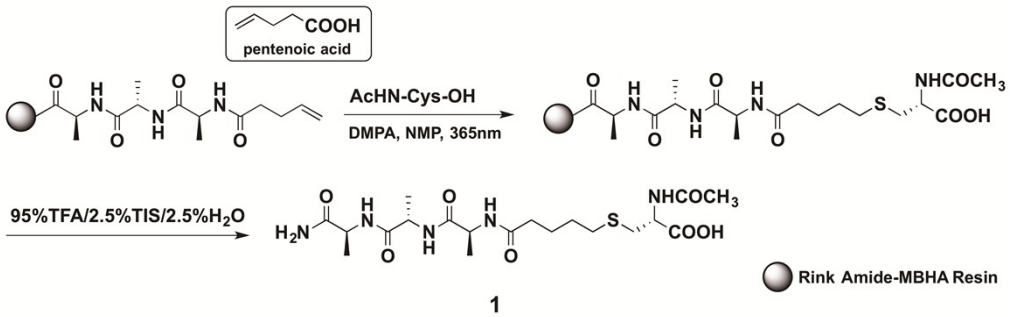
Reference

N. E. Shepherd, H. N. Hoang, G. Abbenante, D. P. Fairlie, *J. Am. Chem. Soc.*, 2005, **127**, 2974.

Condition screening for synthesis of peptide sulfilimines

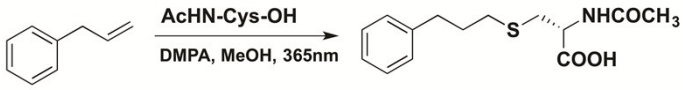
Preparation of model substrate **1**, **2** and **3**

Substrates **1**, **2** and **3** were synthesized for screening the optimal condition of sulfilimine synthesis. Synthetic routes of **1**, **2** and **3** were shown below.



1

Figure S3 The synthetic route of substrate **1**

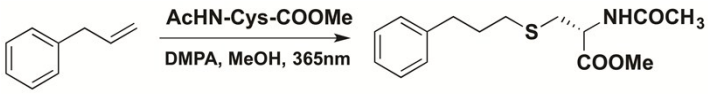


2

Figure S4 The synthetic route of substrate **2**

Propenylbenzene (0.89 g, 7.5 mmol), Cys (1.23 g, 7.5 mmol) and DMPA (1.94 g, 7.5 mmol) were added into the flask purged of air, followed by the addition of methanol (20 ml). Under N_2 atmosphere, the reaction was stirred by UV irradiation at 365 nm for 3h. Then methanol was removed under vacuum, and the crude was purified by flash chromatography (CH_2Cl_2: methanol = 100:1) to obtain substrate **2** (1.73 g, yield: 81%).

^{1}H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.20 – 7.15 (m, 3H), 4.35 (td, *J* = 8.1, 5.1 Hz, 1H), 2.87 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.72 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.67 – 2.20 (m, 4H), 1.84 (s, 3H), 1.78 (dd, *J* = 14.8, 7.4 Hz, 2H).



3

Figure S5 The synthetic route of substrate **3**

The preparation procedure of substrate **3** was similar with **2**.

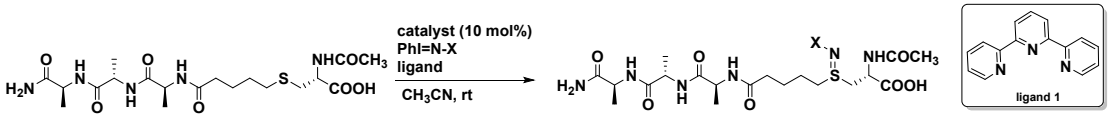
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.24 – 7.14 (m, 3H), 6.27 (d, *J* = 7.1 Hz, 1H), 4.82 (dt, *J* = 7.6, 4.9 Hz, 1H), 3.74 (s, 3H), 3.05 – 2.94 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.52 (dd, *J* = 15.2, 8.0 Hz, 2H), 2.02 (s, 3H), 1.95 – 1.83 (m, 2H).

Condition screening for sulfilimine synthesis with PhI=NTs as the nitrogen source

We utilized **1**, **2**, and **3** as substrate models to investigate the optimal condition of sulfilimine synthesis. The first method was based on the nitrogen source PhI=NTs. The results were summarized in table S1. Different metal catalysts were tested, but no corresponding peptide sulfilimines were observed.

(Abbreviation: Ts, *p*-tolylsulfonyl group ; Ns, *p*-nitrobenzolsulfonyl group)

Table S1 Reactions of substrate **1** with PhI=NTs[a]



entry	catalyst	ligand	X	yield (%)[b]
1	$Fe(OTf)_2$	--	Ts	NR

2 [c]	$AgNO_3$	1	Ts	NR
3	CuOTf	--	Ts	NR
4[d]	CuOTf	--	Ts	NR
5	$Fe(acac)_3$	--	Ts	NR
6	$Fe(OTf)_2$	--	Ns	NR
7 [e]	$Rh_2(OAc)_4$	--	Ts	NR

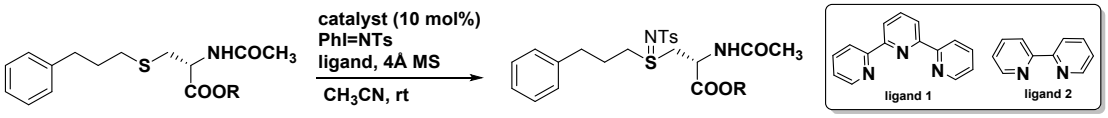
[a] Reaction conditions: peptide substrate (1.0 equiv), PhI=N-X (1.2 equiv) in CH_3CN at r.t., 24 h.

[b] Yield after HPLC purification. [c] Ligand 1(8 mol%) was used. [d] 4Å MS was used.

[e] CH_2Cl_2 was used as a solvent.

Then we tested the reactivity of substrate **2** and **3** with PhI=NTs under different conditions. The results were summarized in table S2. However, the conversions were not satisfactory. It was worth mentioning that the carboxyl group was harmful to produce sulfilimines as entry 8 showed.

Table S2 Reactions of substrate **2, 3** with PhI=NTs[a]



entry	R	catalyst	ligand	yield (%)[b]
1	H	CuOTf	--	10
2	H	CuOTf	1	11
3	H	CuOTf	2	12
4[c]	H	CuOTf	--	11
5	H	AgOTf	--	17
6	H	AgOTf	1	19
7	H	AgOTf	2	10
8	Me	CuOTf	--	30

[a] Reaction conditions: sulfide (1.0 equiv), PhI=NTs (1.2 equiv) in CH_3CN at r.t., 24 h.

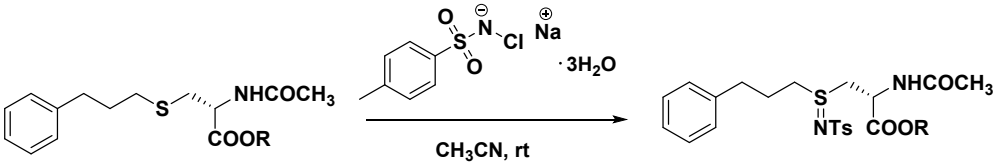
[b] Yield after columm chromatography. [c] Reaction was performed at 50℃.

Condition screening for sulfilimine synthesis with chloramine-T as the nitrogen

source

Then we turned to the second method based on chloramine-T nitrogen source. Substrate **2** and **3** were utilized to react with chloramine-T, and results were summarized in table S3. We found chloramine-T was the more suitable reagent to convert sulfides to sulfilimines.

Table S3 Reactions of substrate **2, 3** with chloramine-T[a]



entry	R	chloramine-T (equiv)	yield (%)[b]
1	H	1.2	37
2	H	3.0	30
3[c]	H	3.0	35
4	Me	1.2	75

[a] Reaction conditions: sulfide (1.0 equiv), chloramine-T (1.2 equiv) in CH_3CN at r.t., 24 h.

[b] Yield after columm chromatography. [c] Reaction was performed at 50℃.

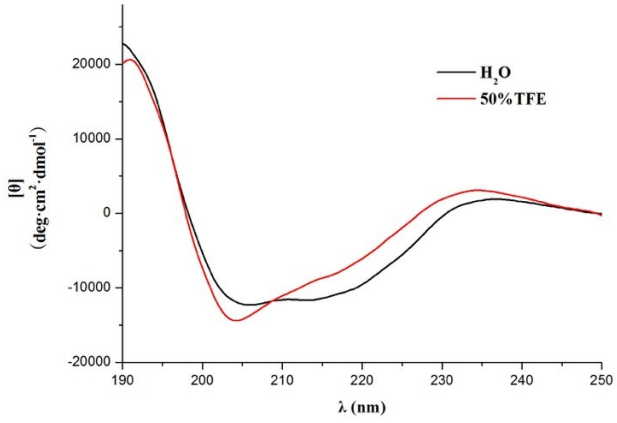


Figure S6 CD spectra of peptide sulfilimine **3B** in H_2O and 50% TFE.

Table S4 Reactions of peptide sulfides with chloramine-T to generate **1~14**[a]

peptide	conversion (%)[b]
Ac-(cyclo-1,5)-[S_3AAAC(NTs)]-NH_2 (**1**)	69
Ac-(cyclo-1,5)-[S_4AAAC(NTs)]-NH_2 (**2**)	53
Ac-(cyclo-1,5)-[S_5AAAC(NTs)]-NH_2 (**3**)	60
Ac-(cyclo-1,5)-[S_6AAAC(NTs)]-NH_2 (**4**)	56
Ac-(cyclo-1,5)-[C(NTs)AAAS_5]-NH_2 (**5**)	81
Ac-(cyclo-1,5)-[homoC(NTs)AAAS_4]-NH_2 (**6**)	85
Ac-(cyclo-1,5)-[S_4AAAhomoC(NTs)]-NH_2 (**7**)	65
Ac-(cyclo-1,5)-[S_5AGAC(NTs)]-NH_2 (**8**)	83
Ac-(cyclo-1,5)-[S_5AFAC(NTs)]-NH_2 (**9**)	53
Ac-(cyclo-1,5)-[S_5AIAC(NTs)]-NH_2 (**10**)	46[c]
Ac-(cyclo-1,5)-[S_5ALAC(NTs)]-NH_2 (**11**)	90
Ac-(cyclo-1,5)-[S_5AVAC(NTs)]-NH_2 (**12**)	57[c]
Ac-(cyclo-1,5)-[S_5AQAC(NTs)]-NH_2 (**13**)	59
Ac-(cyclo-1,5)-[S_5ANAC(NTs)]-NH_2 (**14**)	53

[a] Reaction conditions: peptide sulfide (1.0 equiv), chloramine-T (1.2 equiv) in CH_3CN at r.t., 24 h.

[b] Yield after HPLC purification and identified by 1,3,5-tribromobenzene as internal standard.

[c] Yield after isolation.

Table S5 Amide coupling constants $^3J_{NH\text{-}CH\alpha}$ and temperature coefficients ($\Delta\delta/T$) of peptide **12B** at 288K, 293K, 298K, 303K, 308K and 313K.

peptide	$^3J_{NH\text{-}CH\alpha}$ (Hz)					Δδ/*T* (ppb/K)				
	S_5	Ala	Val	Ala	Cys	S_5	Ala	Val	Ala	Cys
12B	1.9	3.7	6.5	3.9	7.0	-6.3	-4.3	-9.5	-4.7	-3.5

Table S6 Amide NH chemical shift of peptide **12B** at 288K, 293K, 298K, 303K, 308K and 313K.

K	S_5	Ala	Val	Ala	Cys
	HN	HN	HN	HN	HN
288	8.383	8.543	7.663	8.243	8.003
293	8.342	8.522	7.612	8.212	7.982

298	8.315	8.505	7.565	8.185	7.965
303	8.292	8.482	7.512	8.172	7.942
308	8.258	8.458	7.468	8.148	7.938
313	8.225	8.435	7.425	8.125	7.915
Jahnh	1.9Hz	3.7Hz	6.5Hz	3.9Hz	7.0Hz

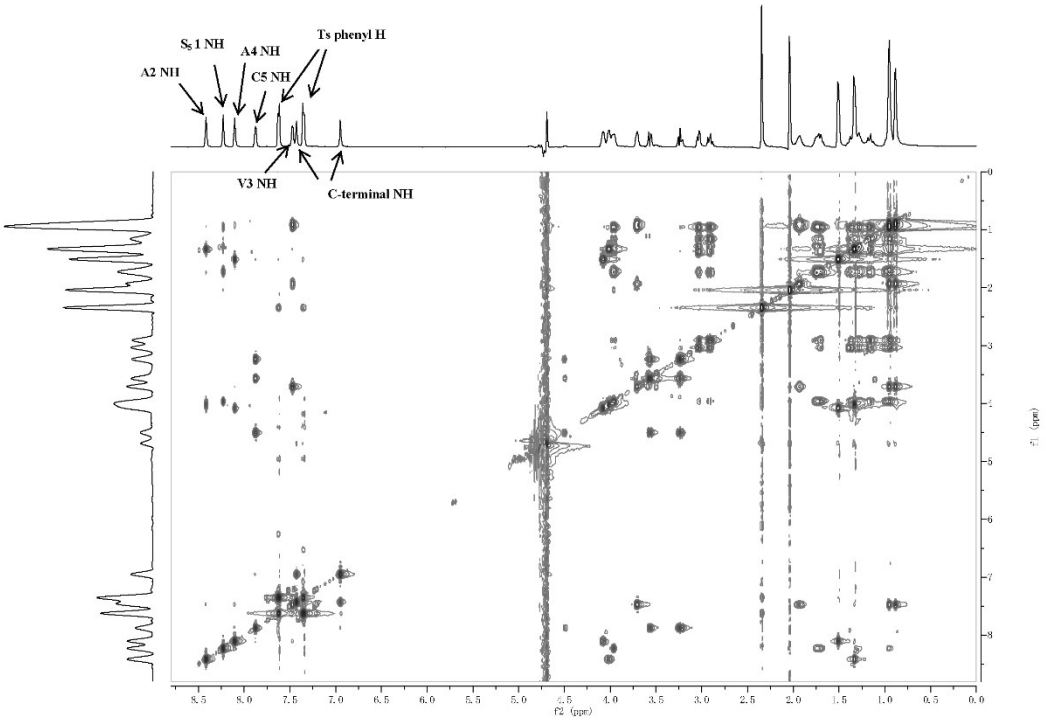


Figure S7 The ROESY spectrum for peptide **12B** (H_2O:D_2O=9:1, 288K, 600 MHz). The amide protons were indicated and labelled by one letter amino acid codes and their sequential numbers from N-terminal to C-terminal in **12B**.

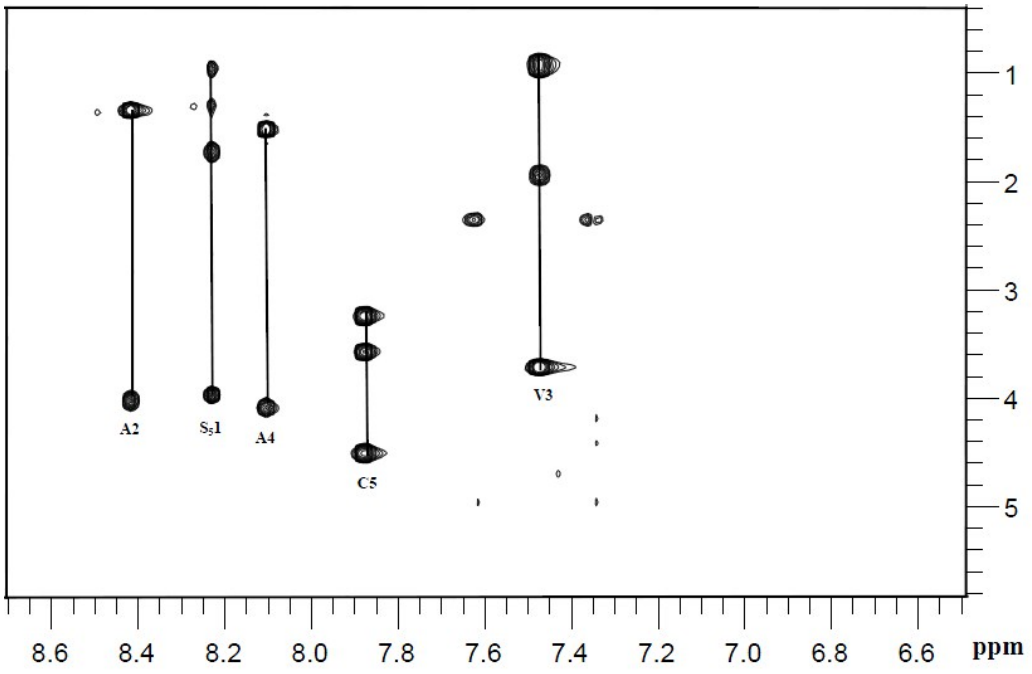


Figure S8 Section from the TOCSY spectrum for peptide **12B** (H_2O:D_2O=9:1, 288K, 600 MHz). Spin systems were indicated and labelled by one letter amino acid codes and their sequential numbers from N-terminal to C-terminal in **12B**.

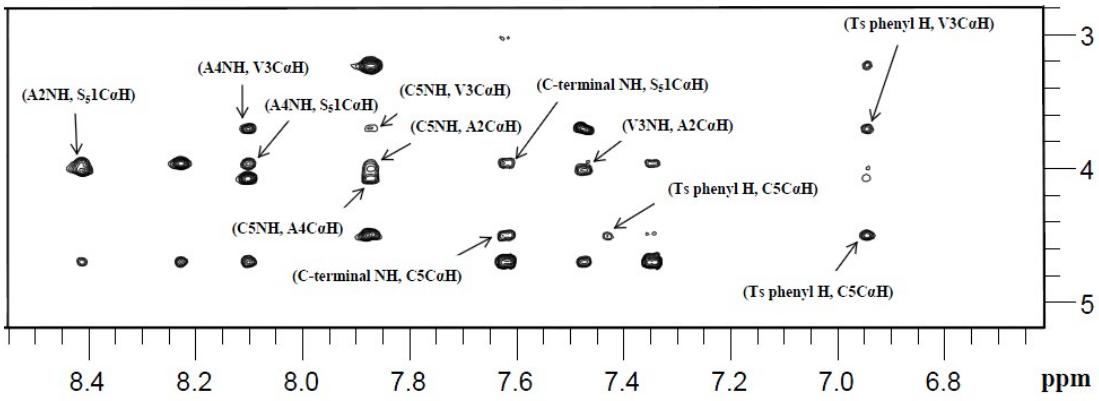


Figure S9 Section from the ROESY spectrum for peptide **12B** (H_2O:D_2O=9:1, 288K, 600 MHz). Residue amide NH-CαH connectivity was indicated and labelled by one letter amino acid codes and their sequential numbers from N-terminal to C-terminal in **12B**.

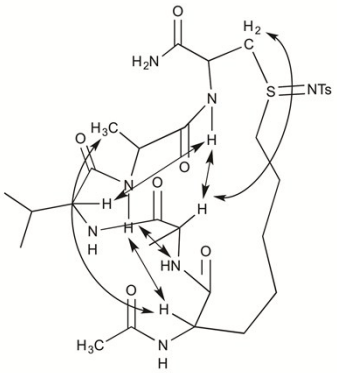


Figure S10 Region of 600-MHz NOESY spectrum of peptide **12B** in H_2O solution

Table S7 MS data for peptides **1~14**.

peptide	$[M+H]^+$ (m/z)	
	calculated	observed
1A	642.2	642.3
1B	642.2	642.3
2A	656.2	656.3
2B	656.2	656.3
3A	670.3	670.4
3B	670.3	670.4
4A	684.3	684.4
4B	684.3	684.4
5A	670.3	670.4
5B	670.3	670.4
6A	670.3	670.4
6B	670.3	670.4
7A	670.3	670.4
7B	670.3	670.4
8A	656.3	656.3
8B	656.3	656.3
9A	746.3	746.4
9B	746.3	746.4
10A	712.3	712.4
10B	712.3	712.4
11A	712.3	712.4
11B	712.3	712.5
12A	698.3	698.4
12B	698.3	698.3
13A	727.3	727.4
13B	727.3	727.4
14A	713.3	713.4
14B	713.3	713.3

HPLC analyses of formation of peptides 1~15

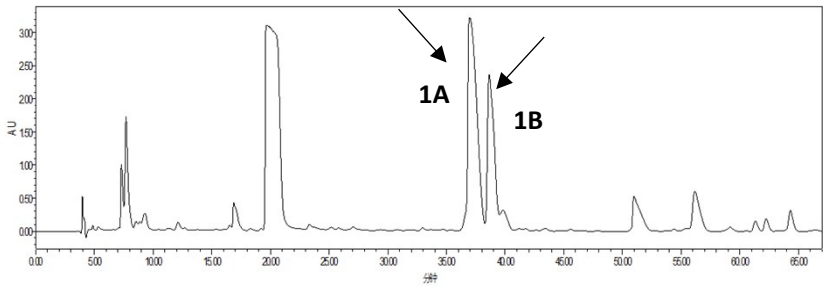


Figure S11 HPLC separation spectrum of sulfilimine **1A** and **1B**

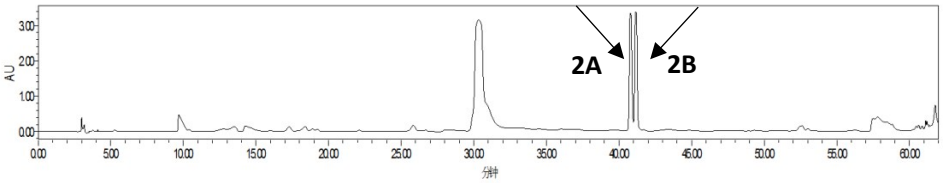


Figure S12 HPLC separation spectrum of sulfilimine **2A** and **2B**

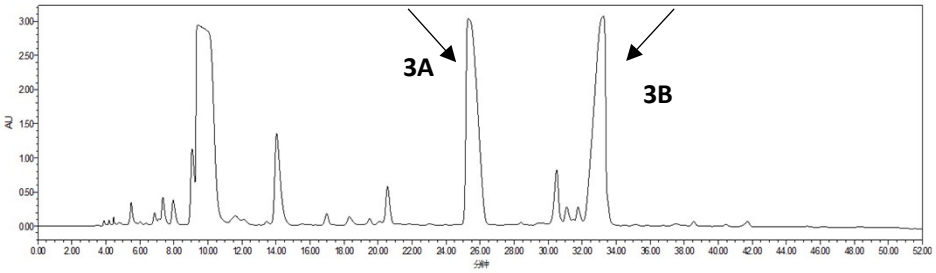


Figure S13 HPLC separation spectrum of sulfilimine **3A** and **3B**

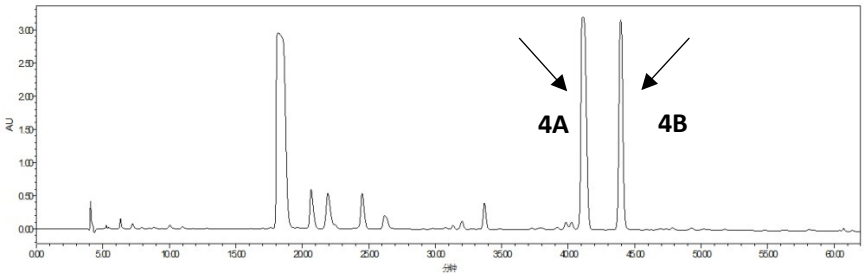


Figure S14 HPLC separation spectrum of sulfilimine **4A** and **4B**

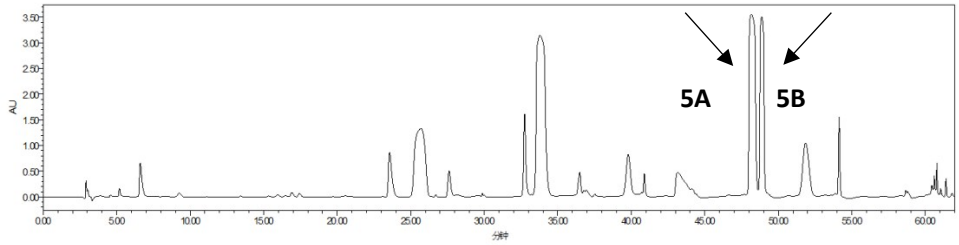


Figure S15 HPLC separation spectrum of sulfilimine **5A** and **5B**

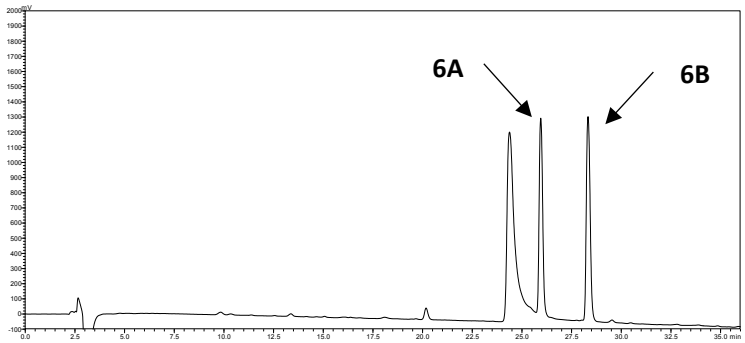


Figure S16 HPLC separation spectrum of sulfilimine **6A** and **6B**

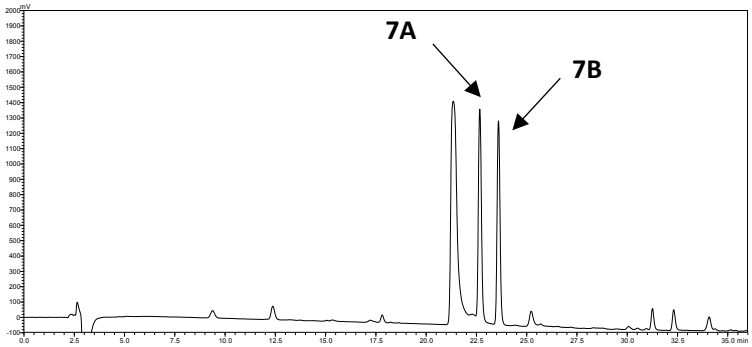


Figure S17 HPLC separation spectrum of sulfilimine **7A** and **7B**

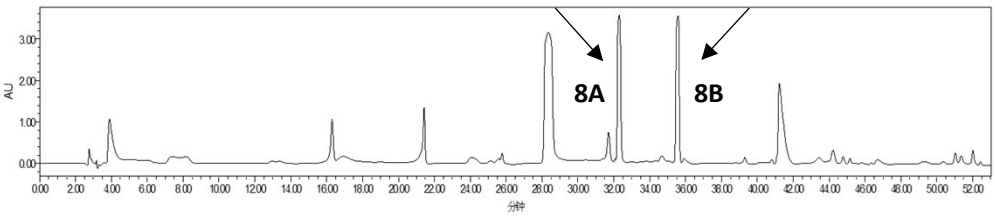


Figure S18 HPLC separation spectrum of sulfilimine **8A** and **8B**

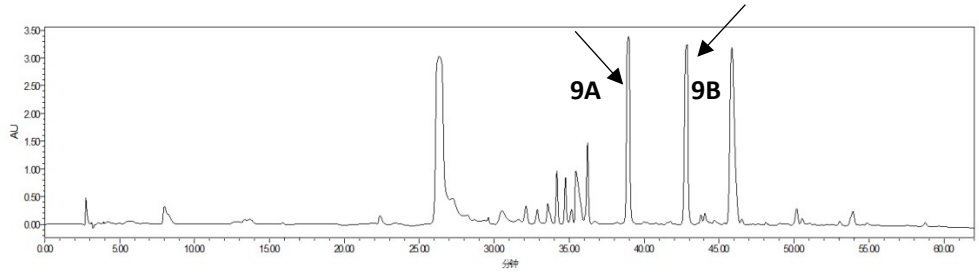


Figure S19 HPLC separation spectrum of sulfilimine **9A** and **9B**

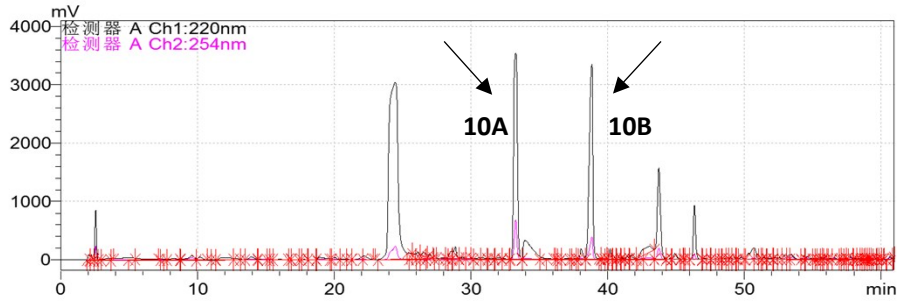


Figure S20 HPLC separation spectrum of sulfilimine **10A** and **10B**

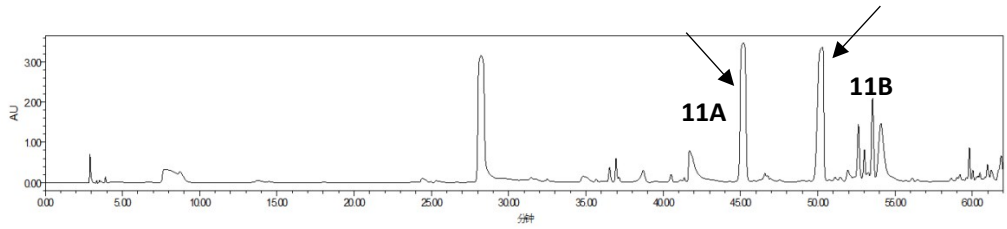


Figure S21 HPLC separation spectrum of sulfilimine **11A** and **11B**

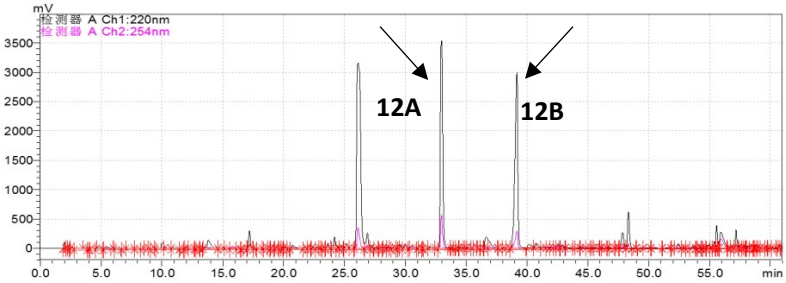


Figure S22 HPLC separation spectrum of sulfilimine **12A** and **12B**

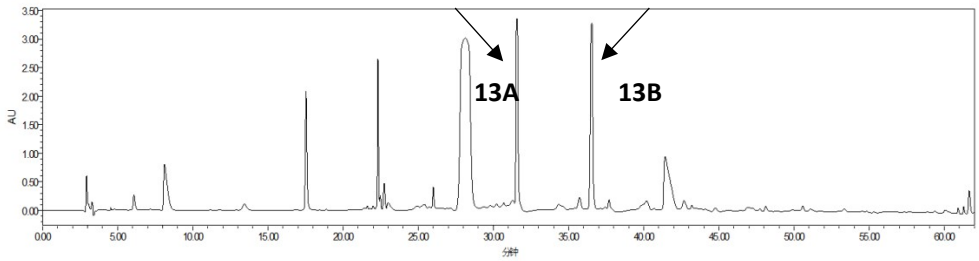


Figure S23 HPLC separation spectrum of sulfilimine **13A** and **13B**

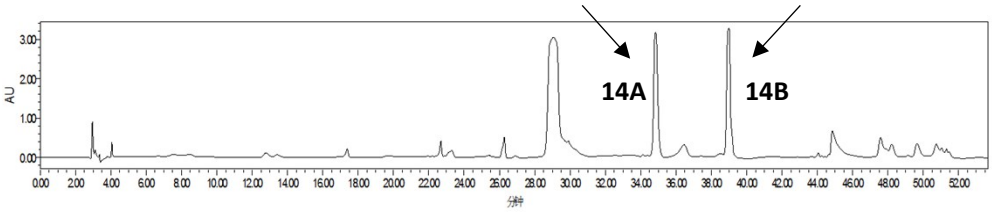


Figure S24 HPLC separation spectrum of sulfilimine **14A** and **14B**

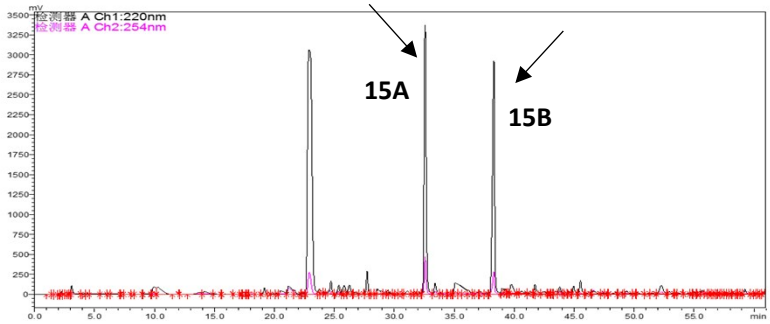
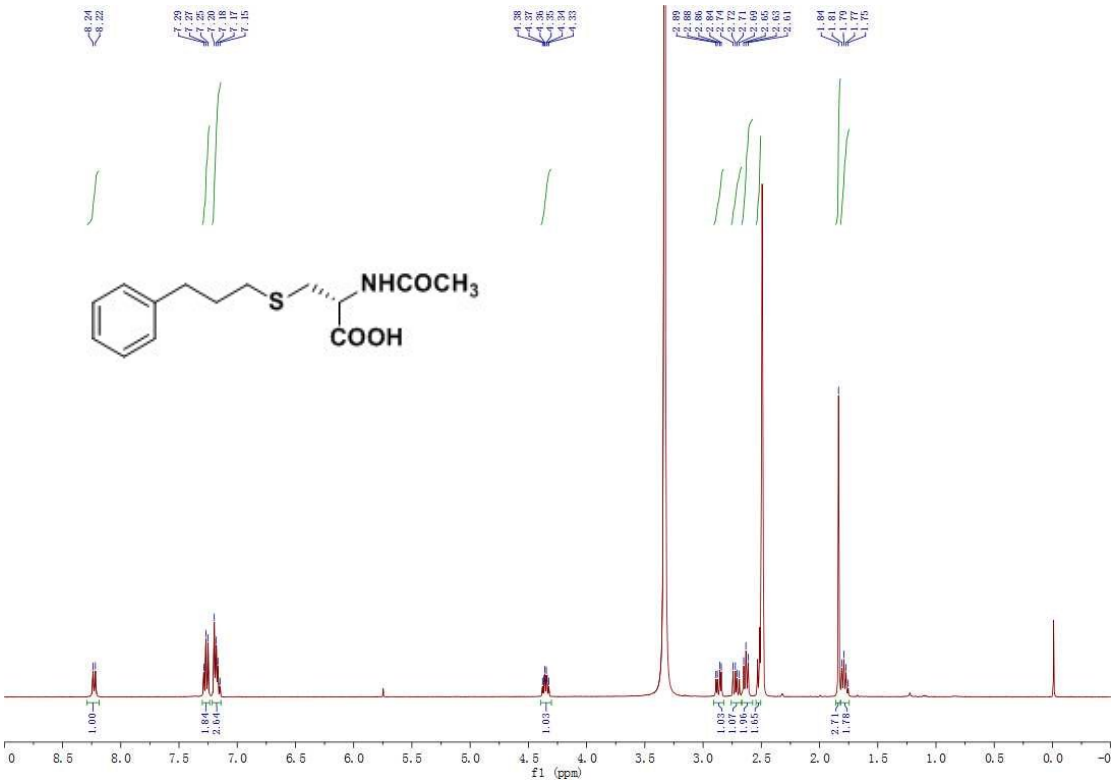


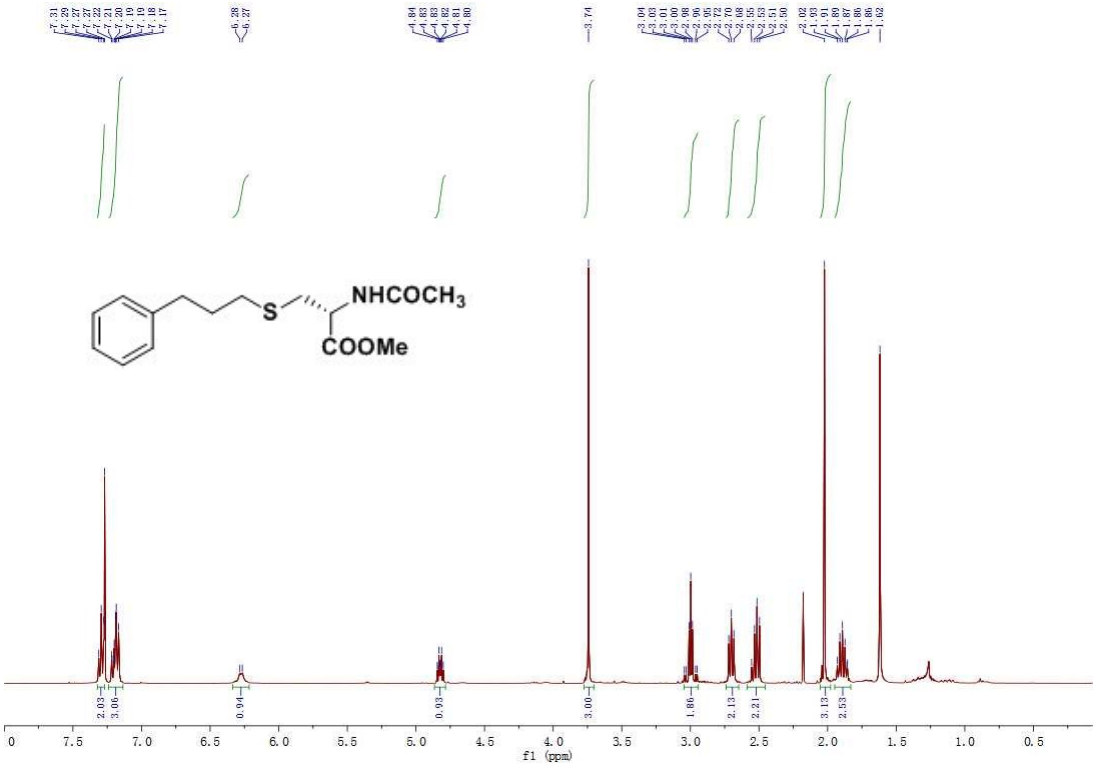
Figure S25 HPLC separation spectrum of sulfilimine **15A** and **15B**

^{1}H NMR spectra

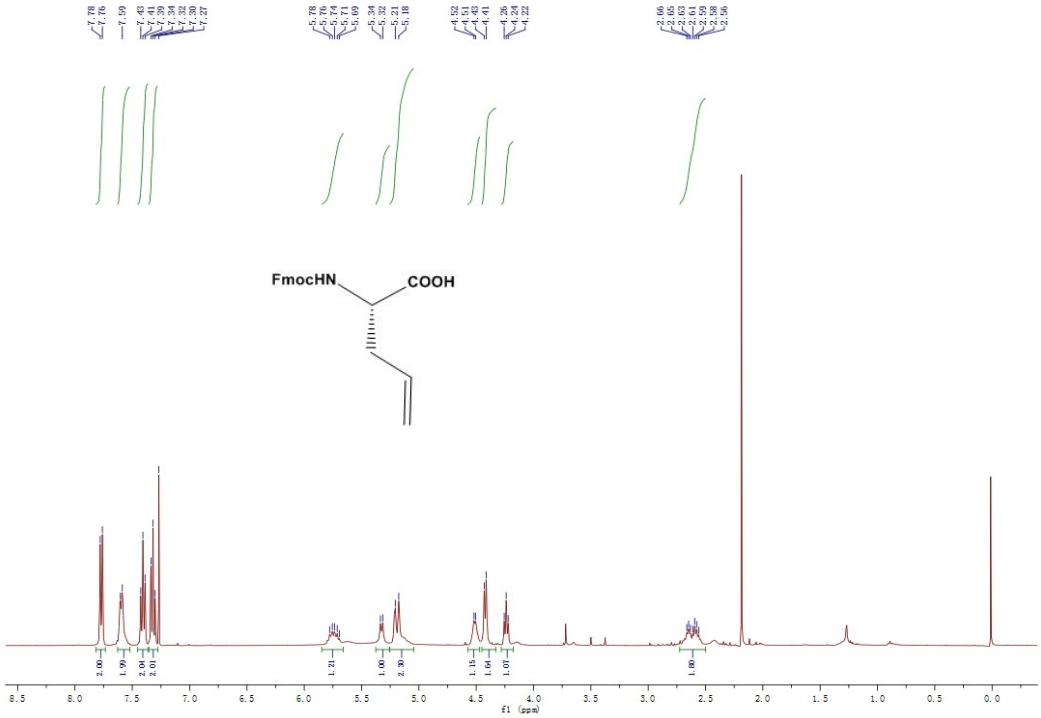
N-acetyl-S-(3-phenylpropyl)-L-cysteine



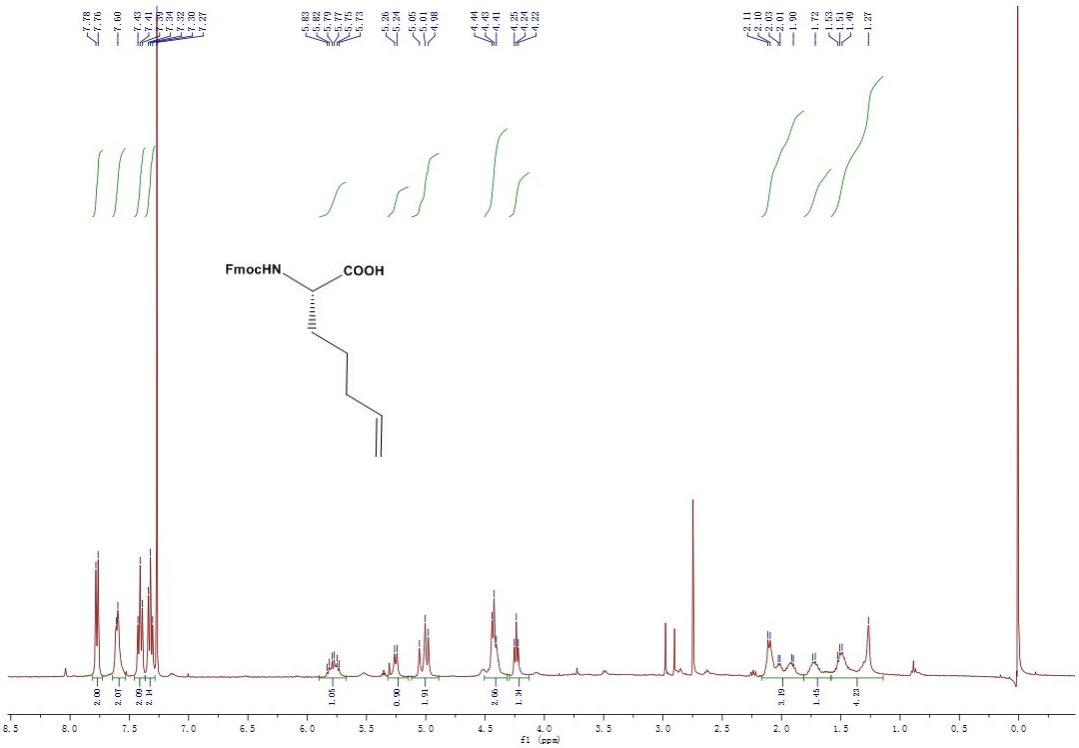
methyl N-acetyl-S-(3-phenylpropyl)-L-cysteinate



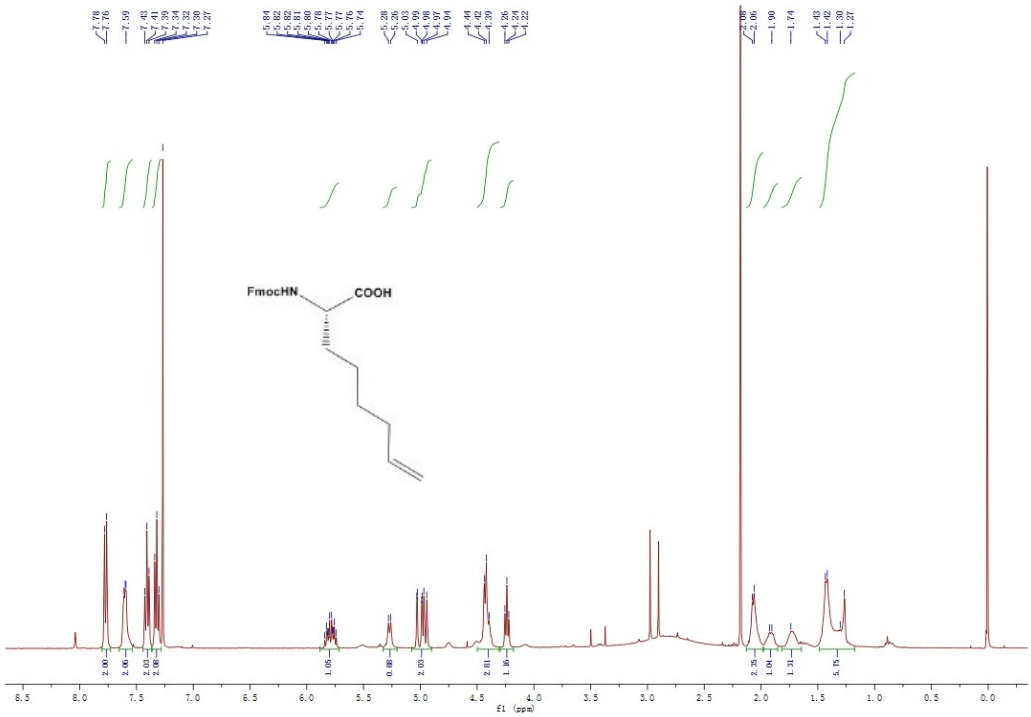
(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoic acid



(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)hept-6-enoic acid

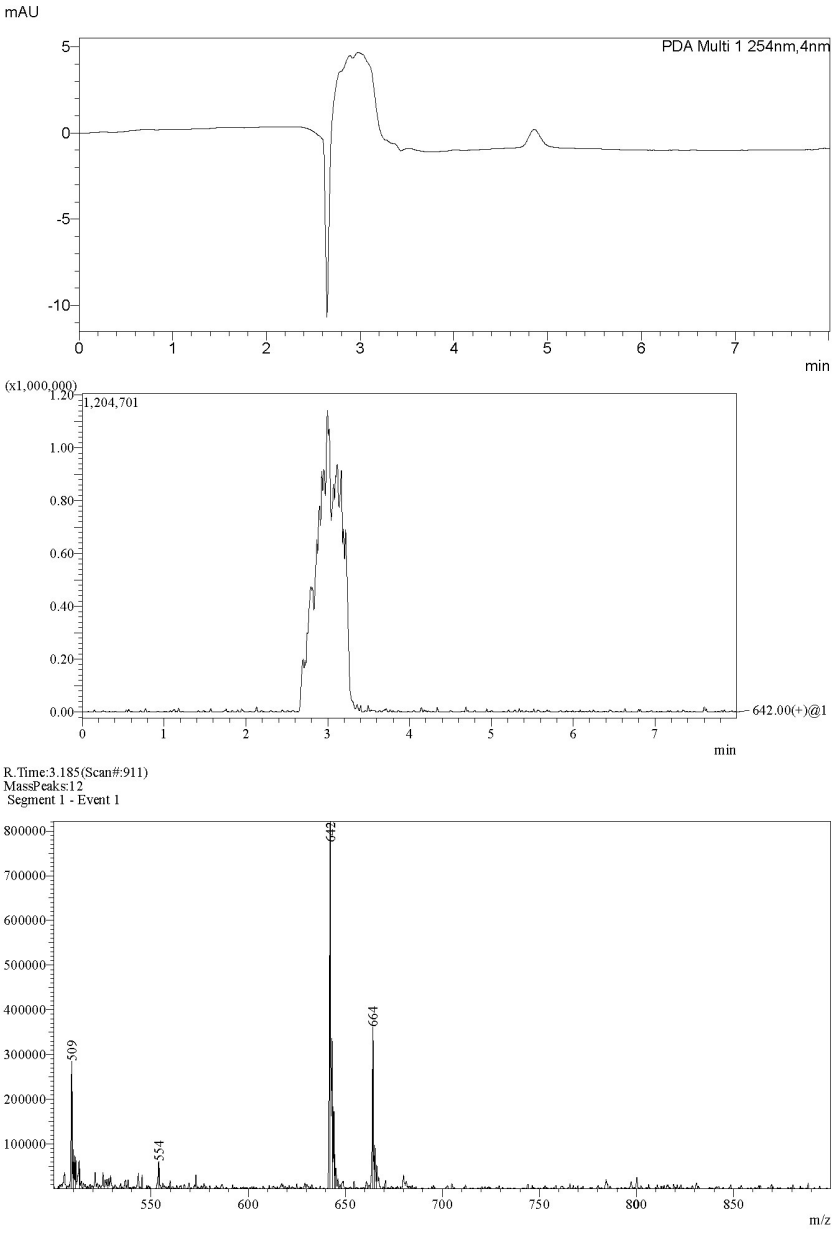


(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)oct-7-enoic acid

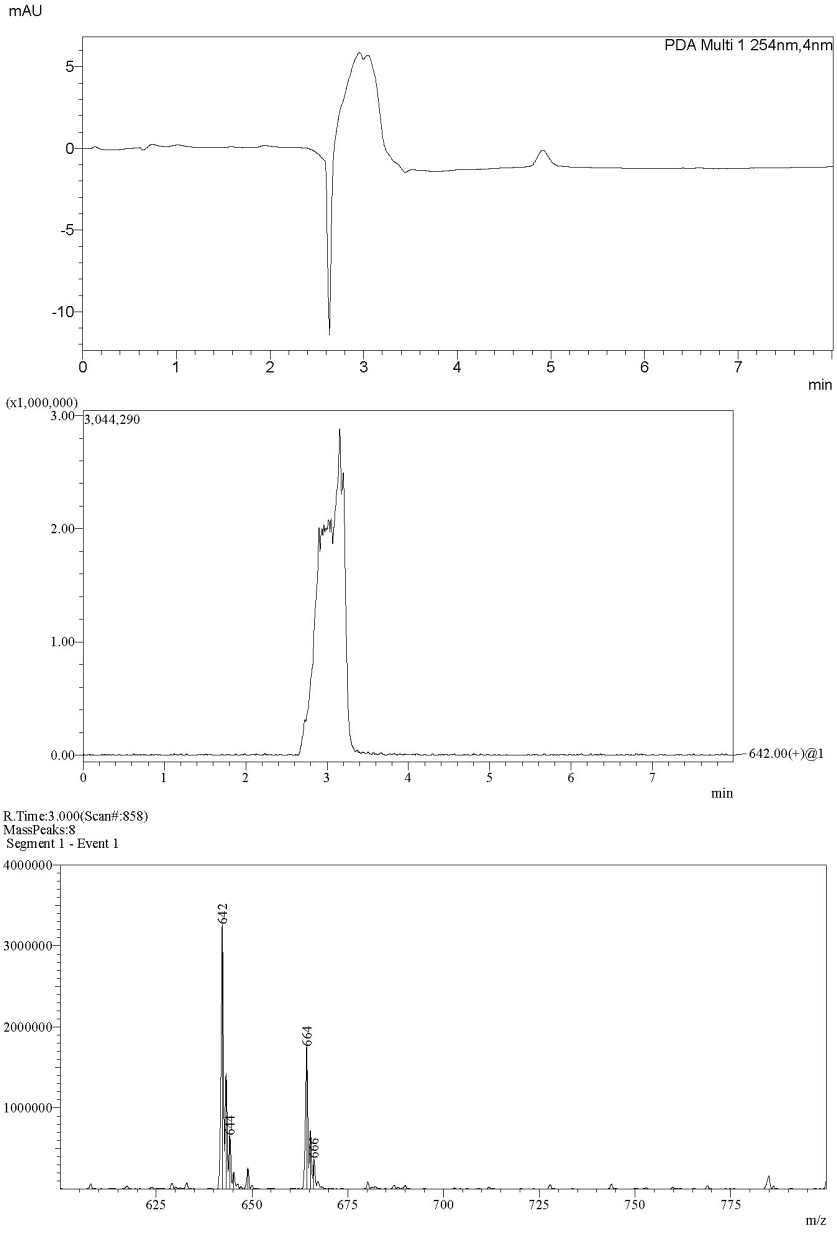


LC-MS spectra of peptides 1~15

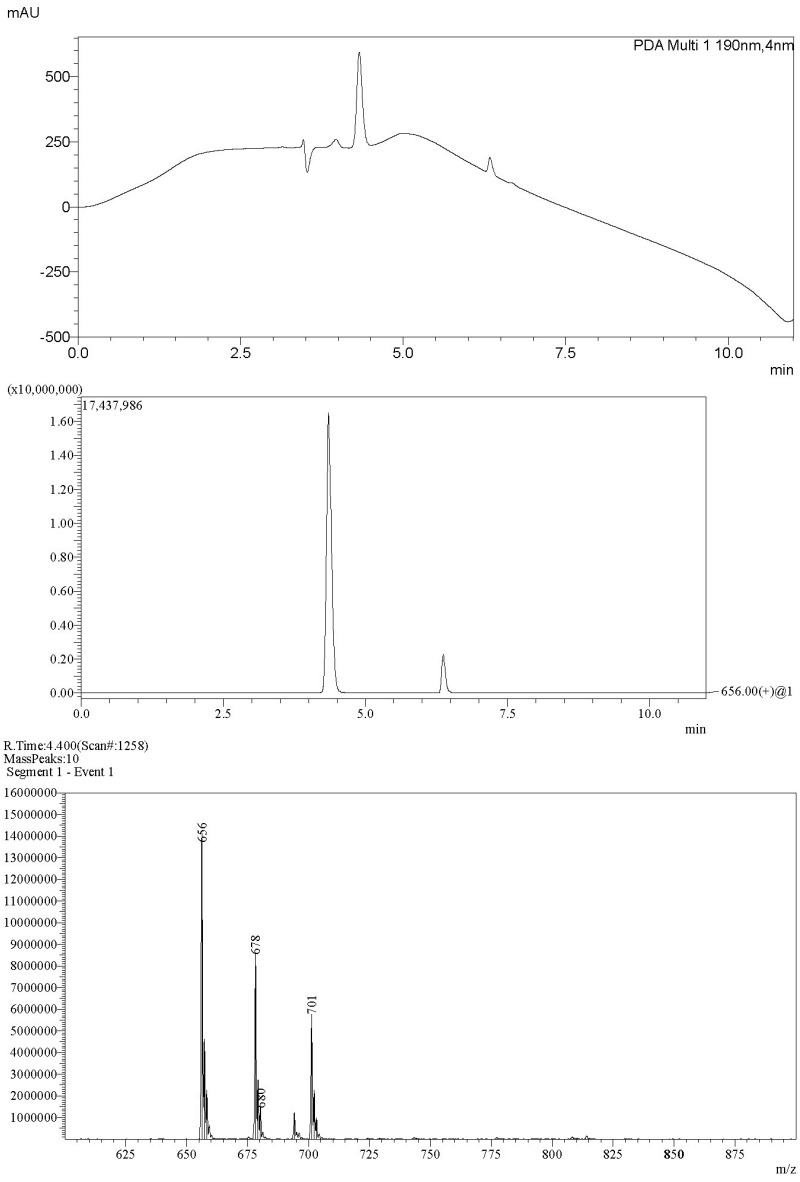
Ac-(cyclo-1,5)-[S_3AAAC(NTs)]-NH_2 **1A**



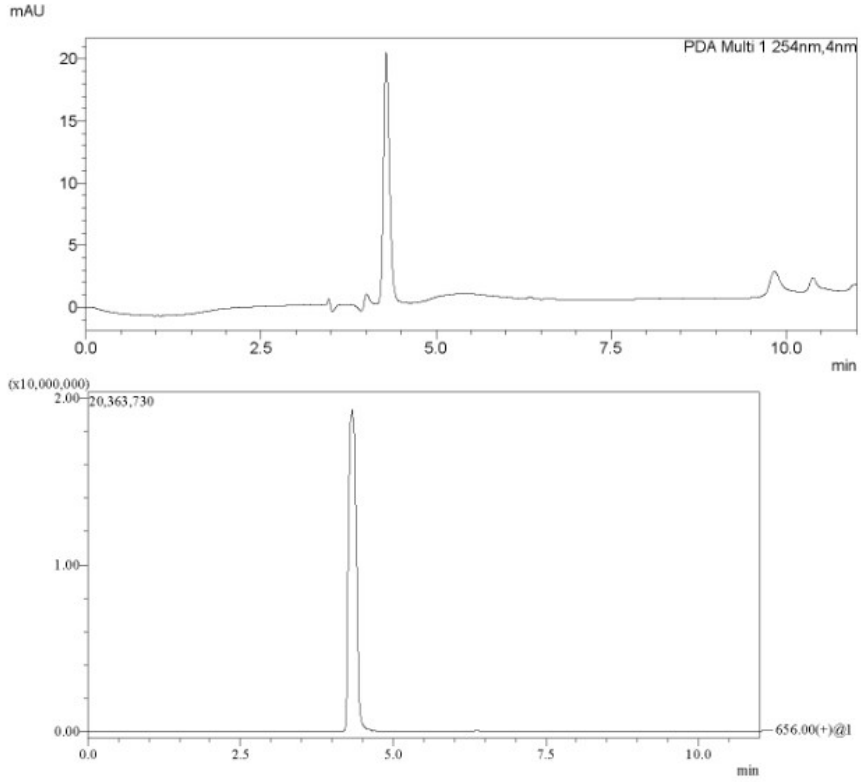
Ac-(cyclo-1,5)-[S_3AAAC(NTs)]-NH_2 **1B**

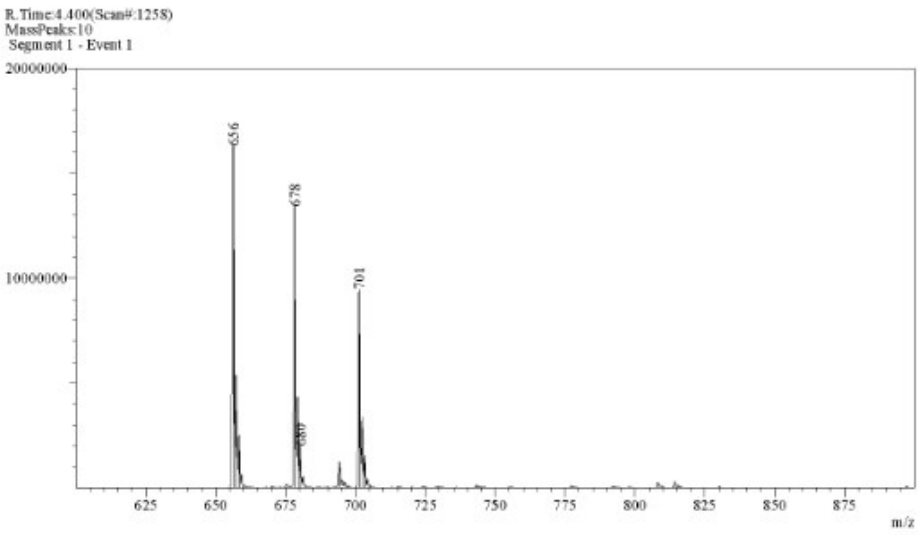


Ac-(cyclo-1,5)-[S_4AAAC(NTs)]-NH_2 **2A**

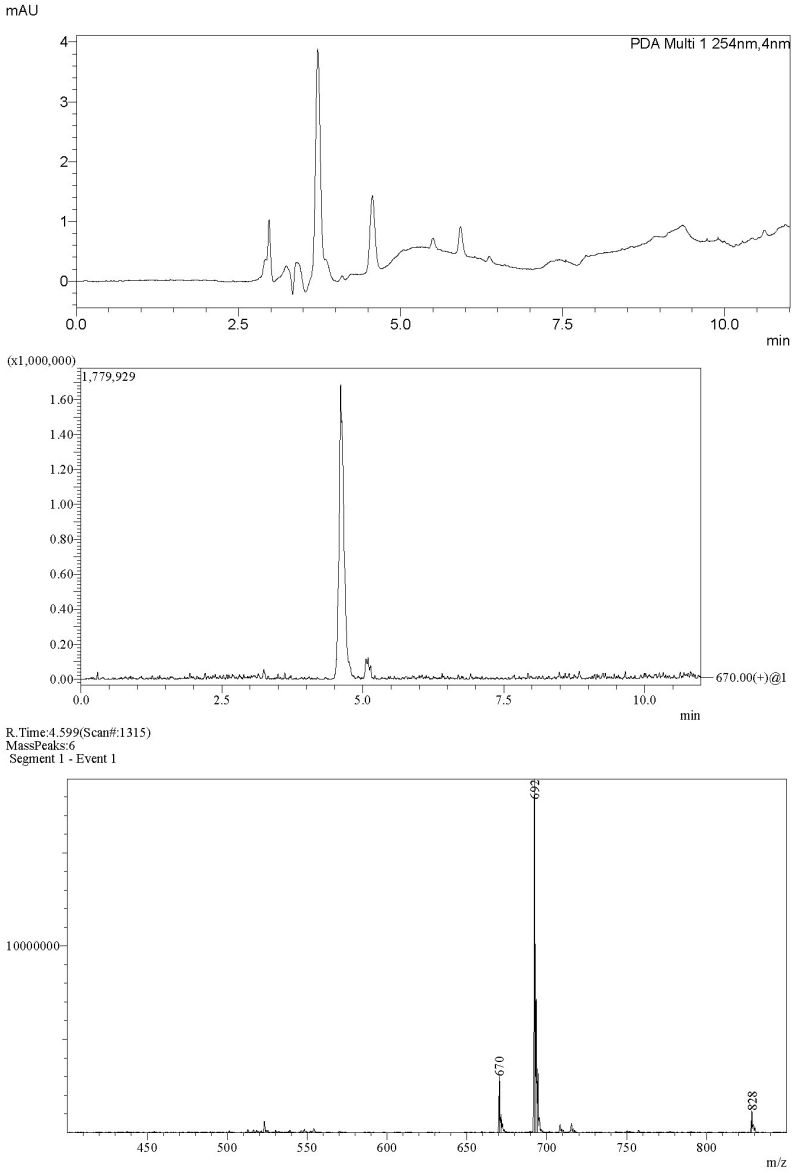


Ac-(cyclo-1,5)-[S_4AAAC(NTs)]-NH_2 **2B**

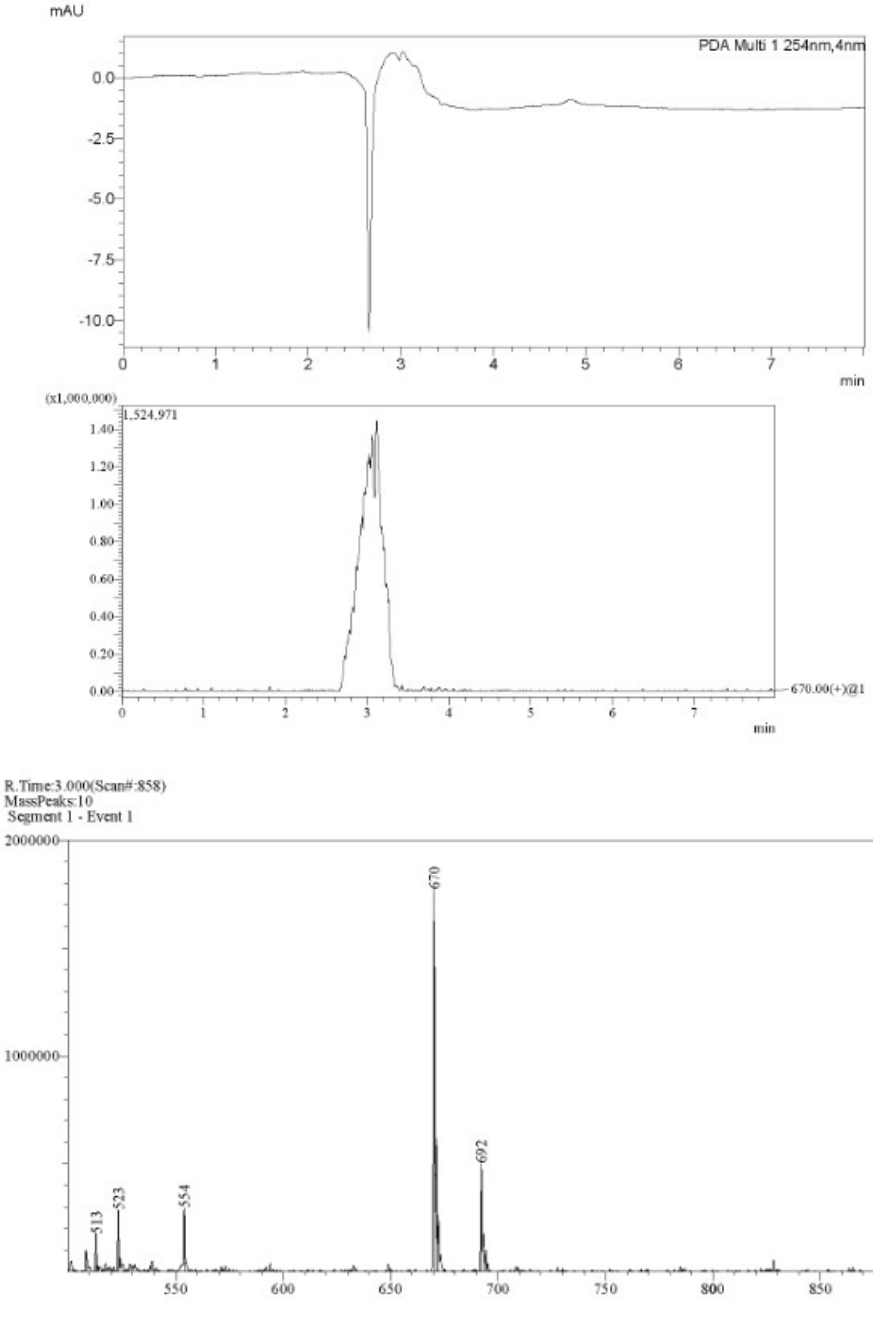




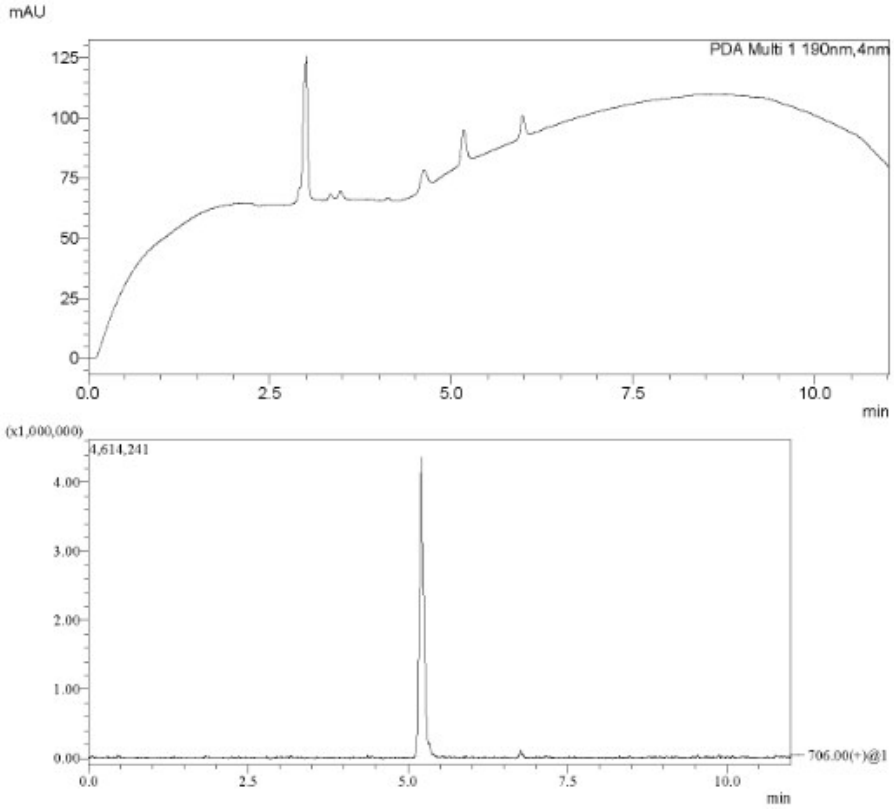
Ac-(cyclo-1,5)-[S_5AAAC(NTs)]-NH_2 **3A**

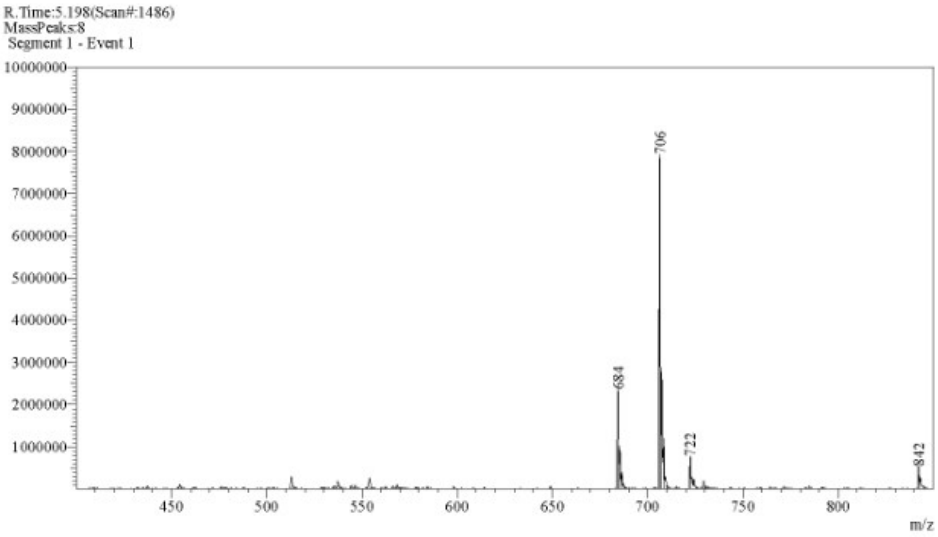


Ac-(cyclo-1,5)-[S_5AAAC(NTs)]-NH_2 **3B**

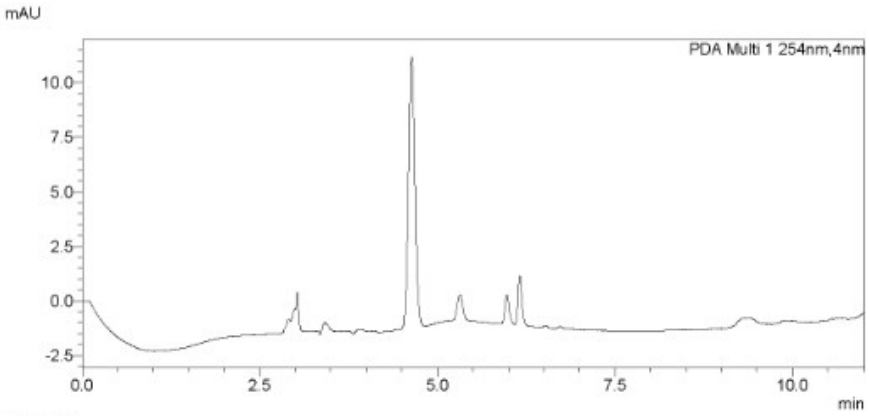


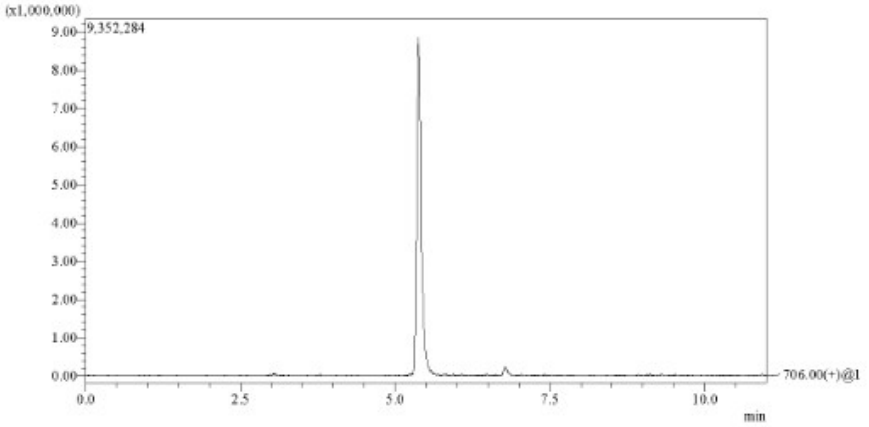
Ac-(cyclo-1,5)-[S_6AAAC(NTs)]-NH_2 **4A**

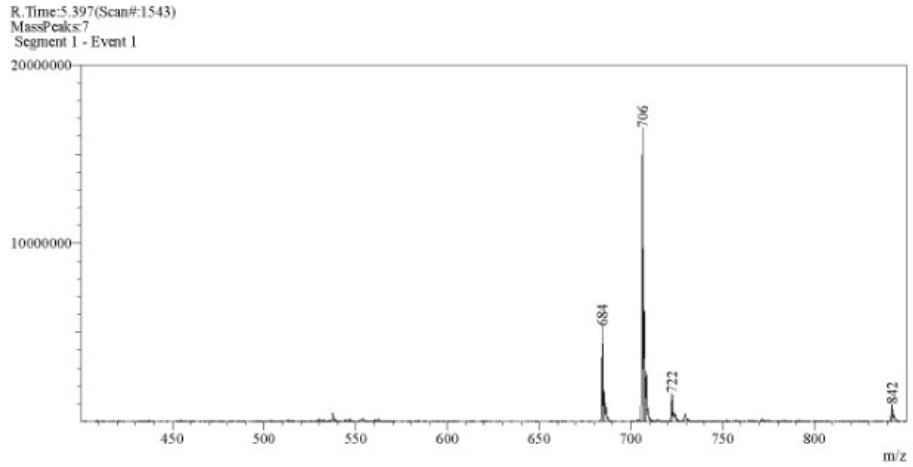




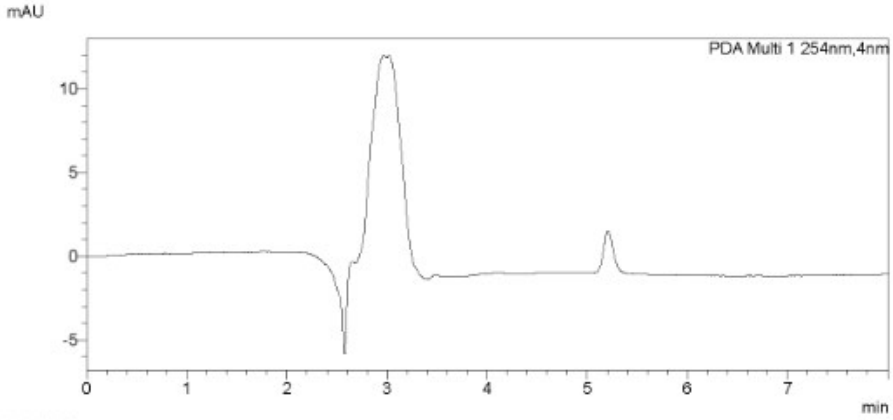
Ac-(cyclo-1,5)-[S_6AAAC(NTs)]-NH_2 **4B**

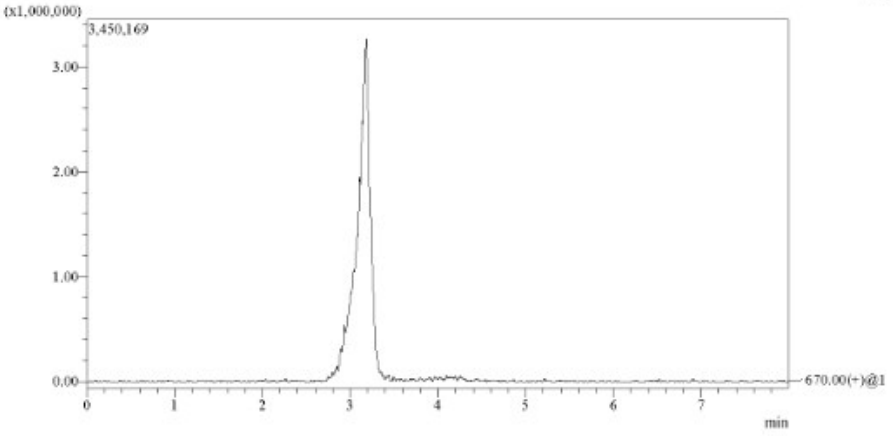


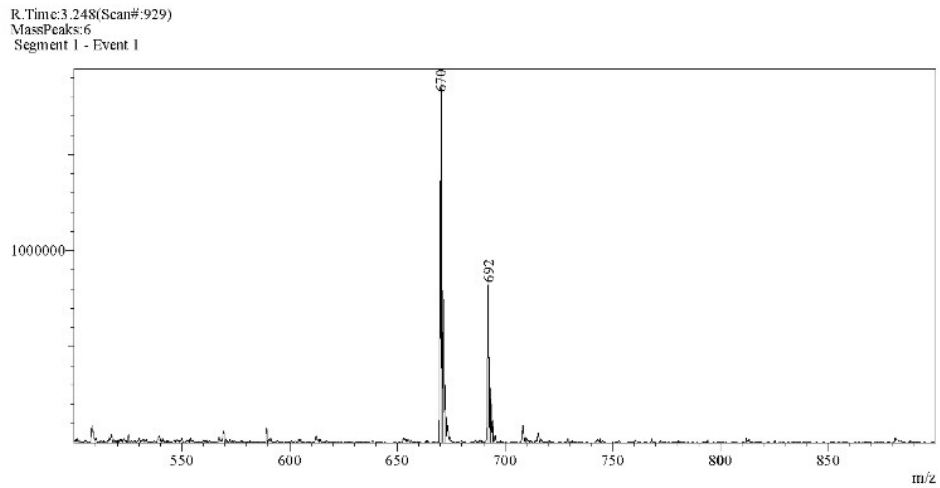




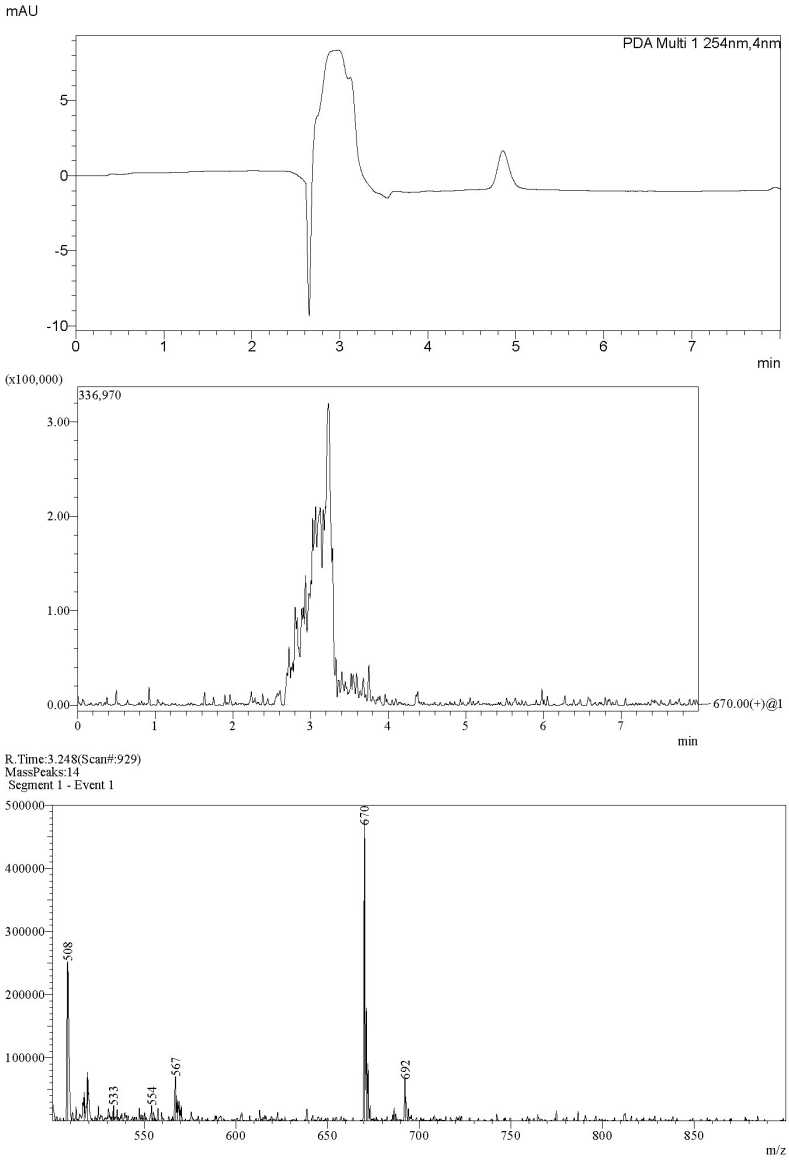
Ac-(cyclo-1,5)-[C(NTs)AAAS$_5$]-NH$_2$ **5A**



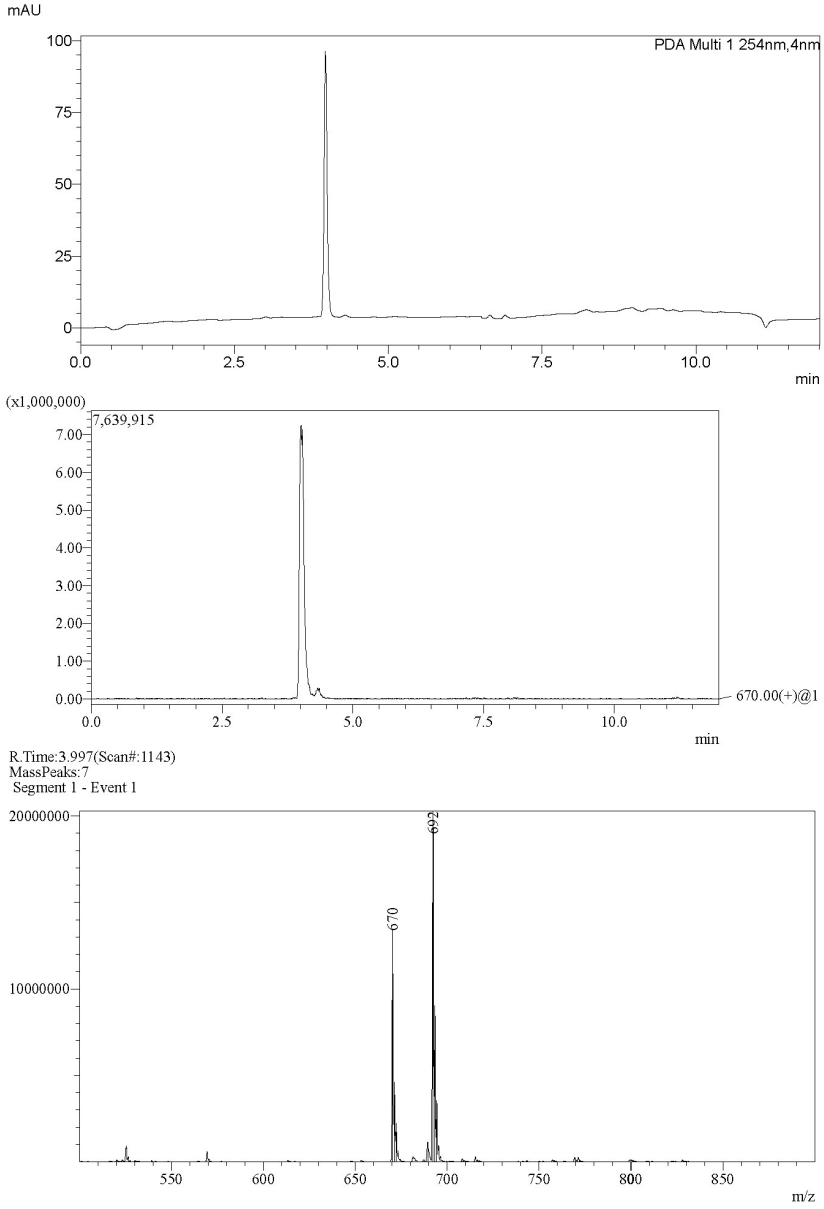




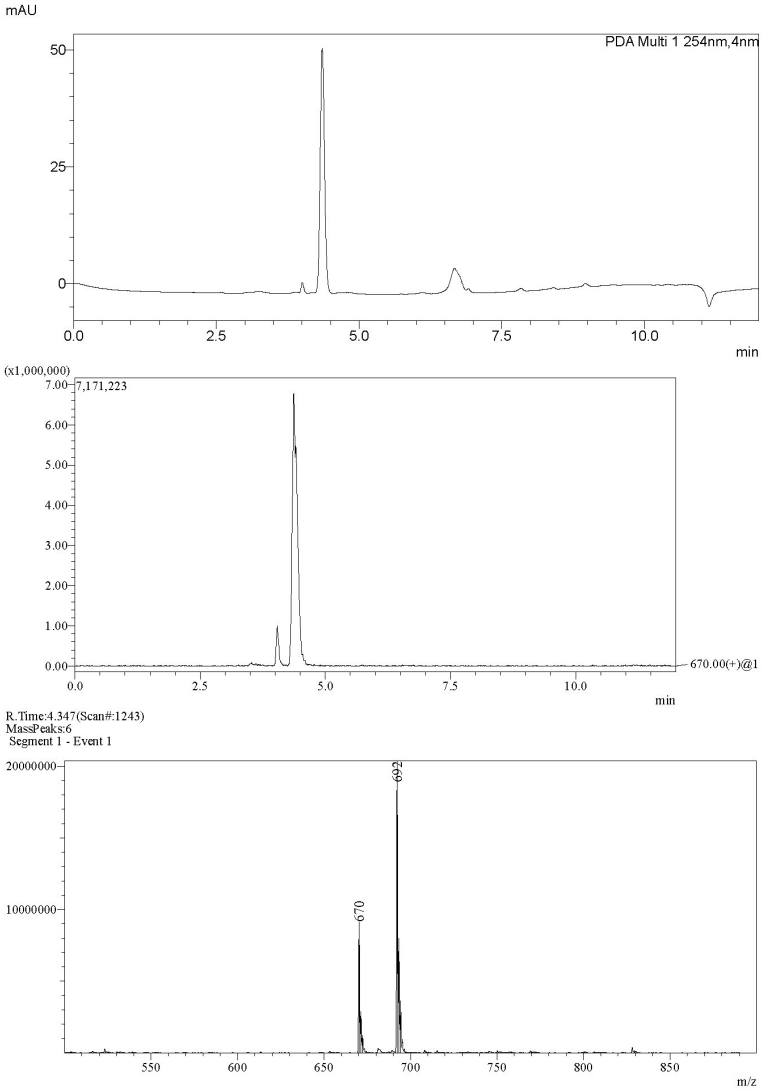
Ac-(cyclo-1,5)-[C(NTs)AAAS$_5$]-NH$_2$ **5B**



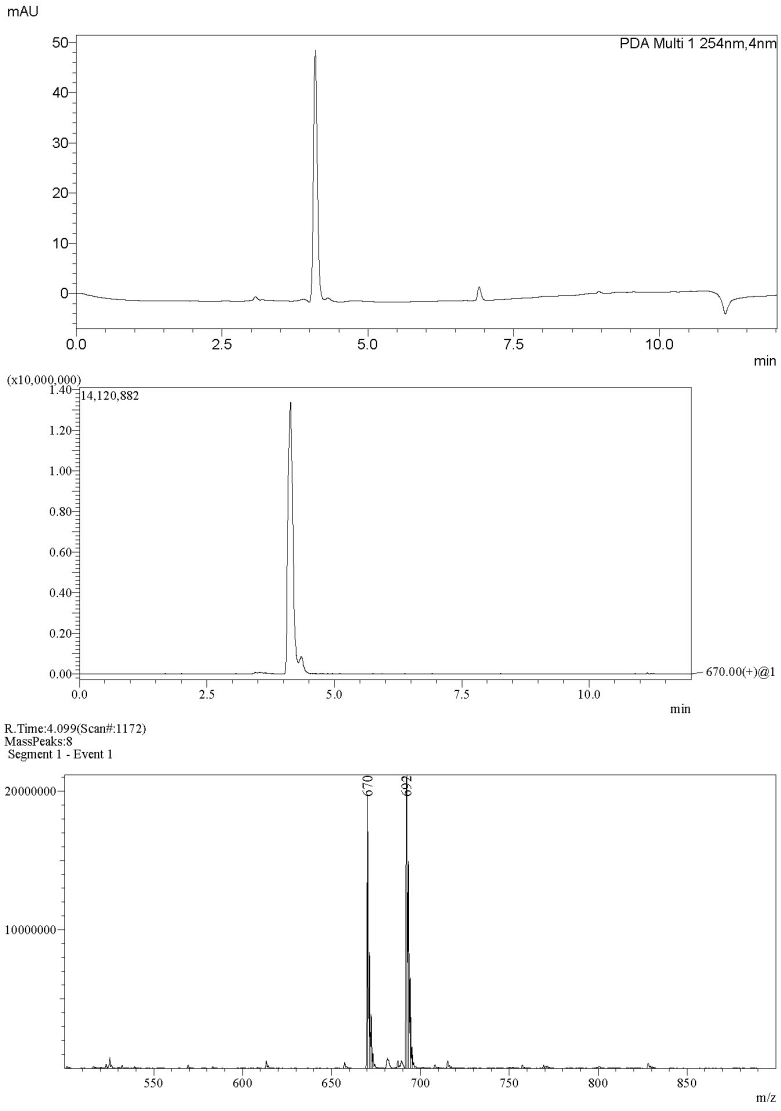
Ac-(cyclo-1,5)-[homoC(NTs)AAAS$_4$]-NH$_2$ **6A**



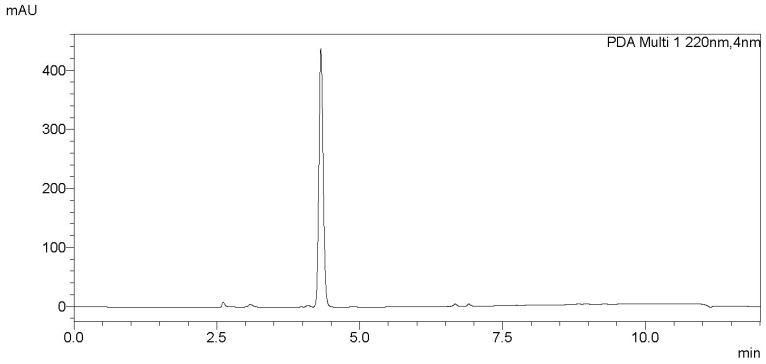
Ac-(cyclo-1,5)-[homoC(NTs)AAAS$_4$]-NH$_2$ **6B**

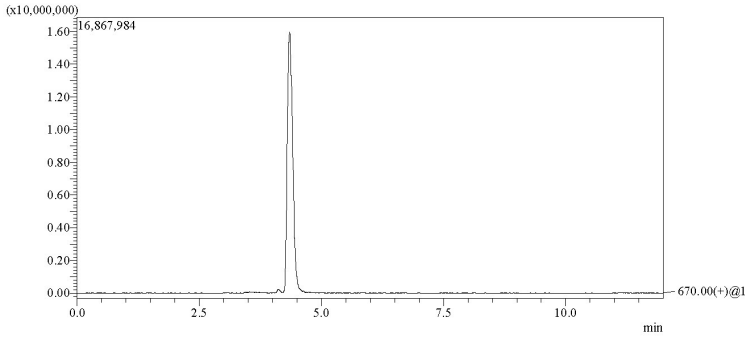


Ac-(cyclo-1,5)-[S_4AAAhomoC(NTs)]-NH_2 **7A**



Ac-(cyclo-1,5)-[S_4AAAhomoC(NTs)]-NH_2 **7B**





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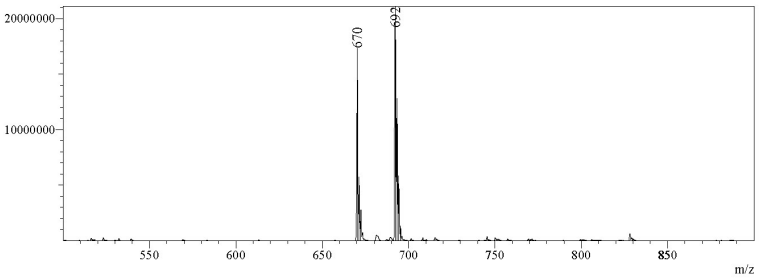
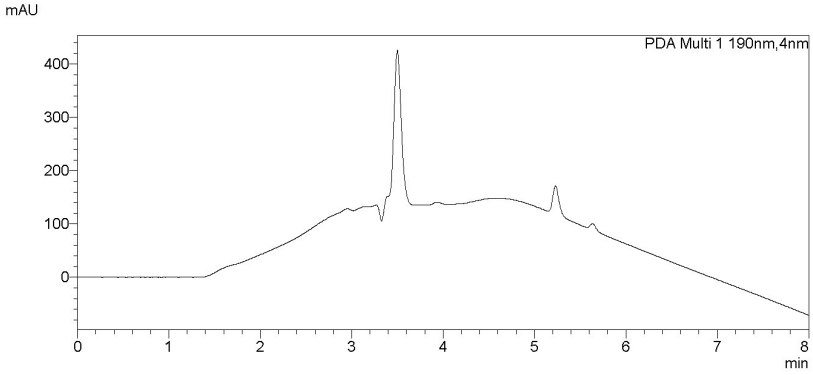
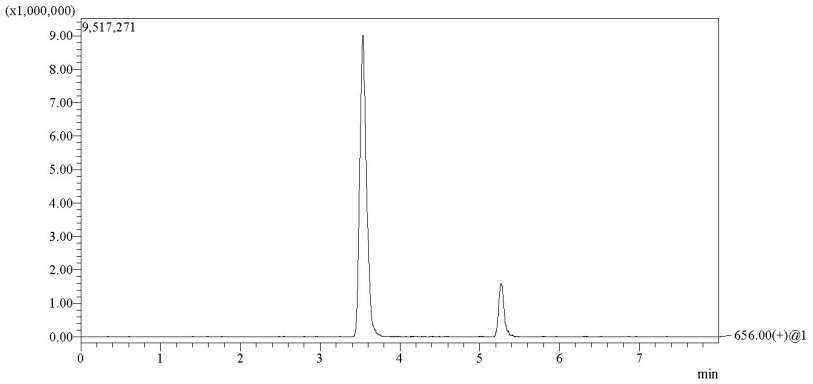
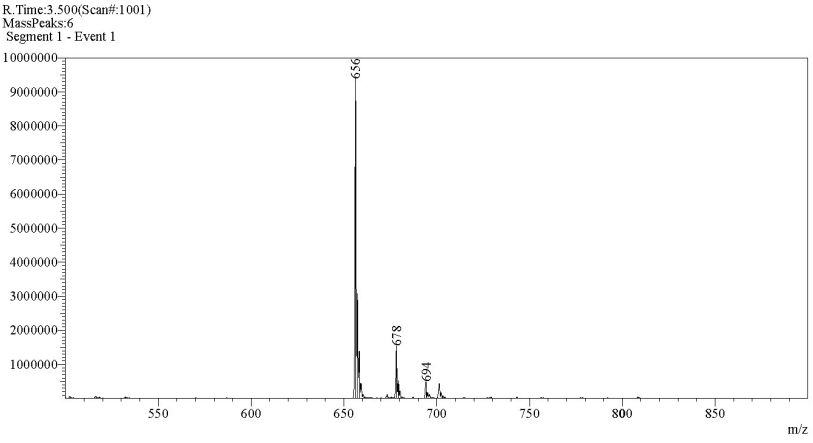


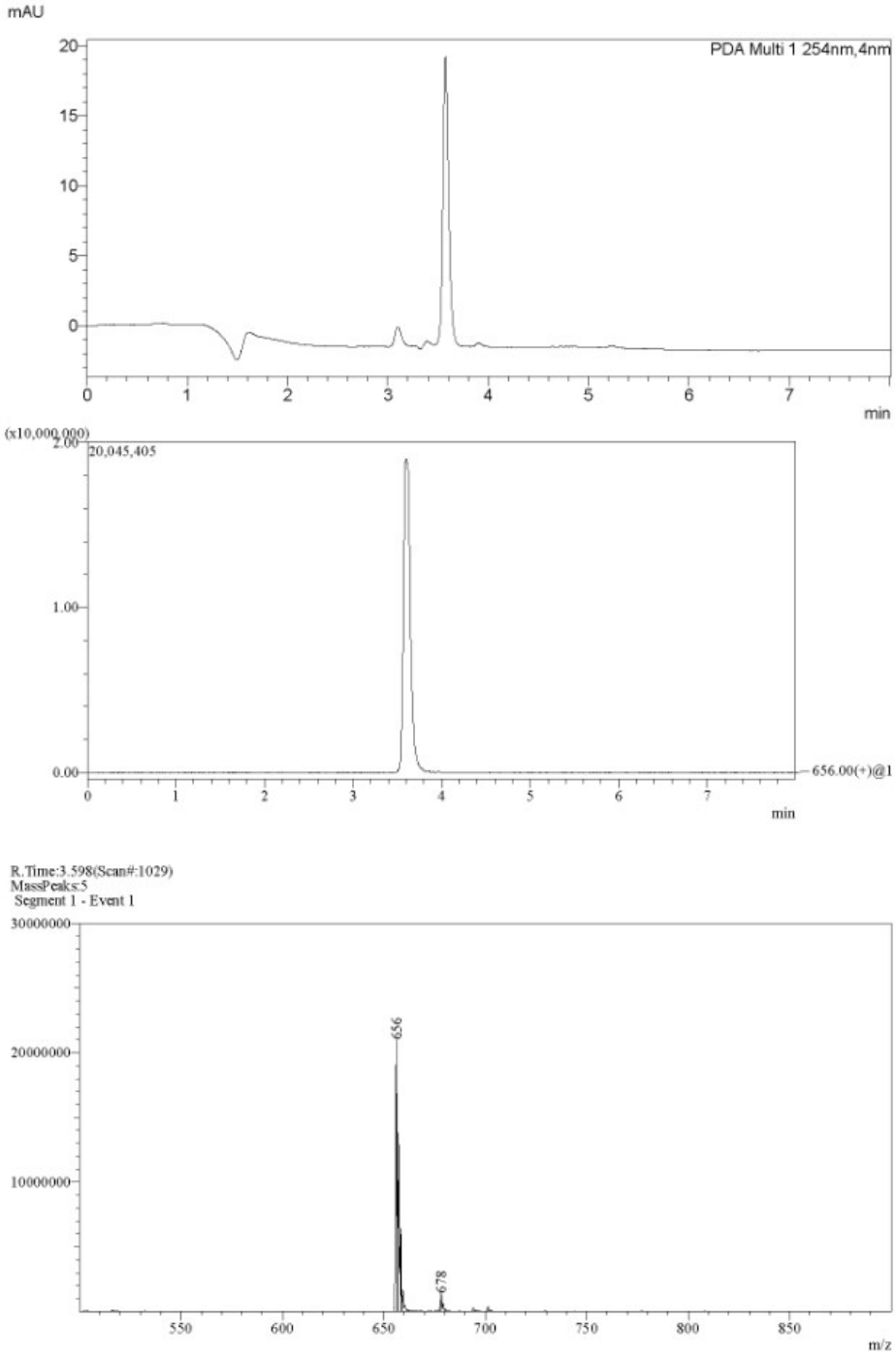
Ac-(cyclo-1,5)-[S_5AGAC(NTs)]-NH_2 **8A**



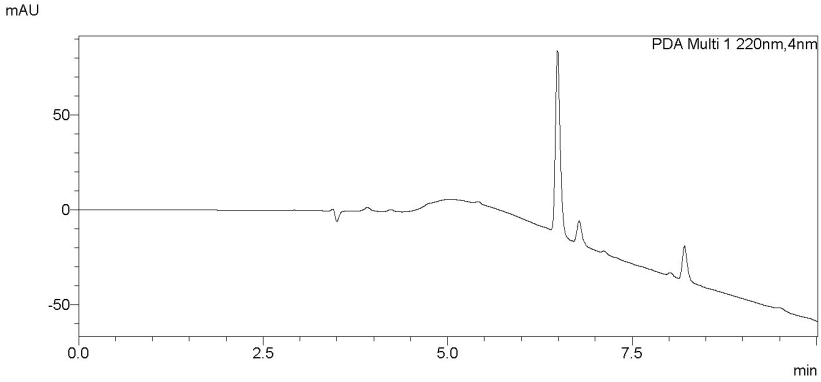


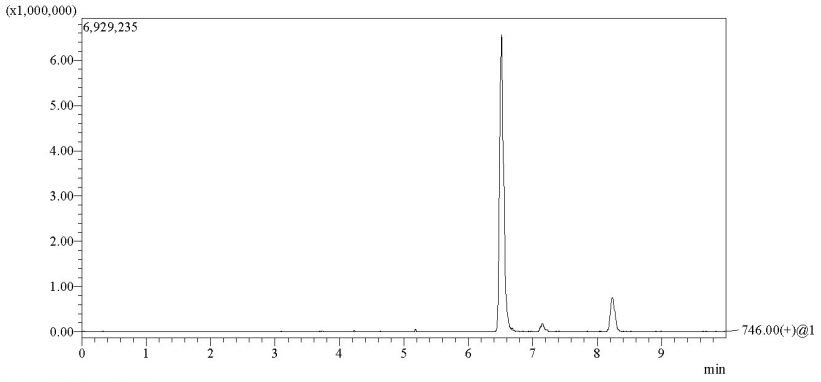


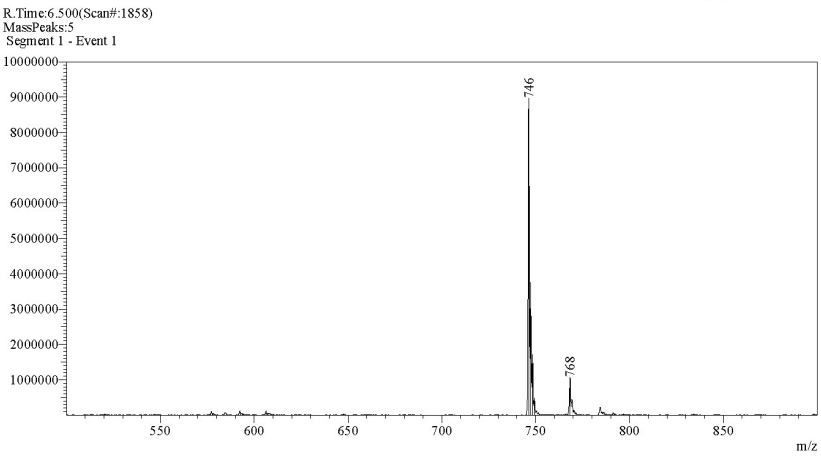
Ac-(cyclo-1,5)-[S_5AGAC(NTs)]-NH_2 **8B**



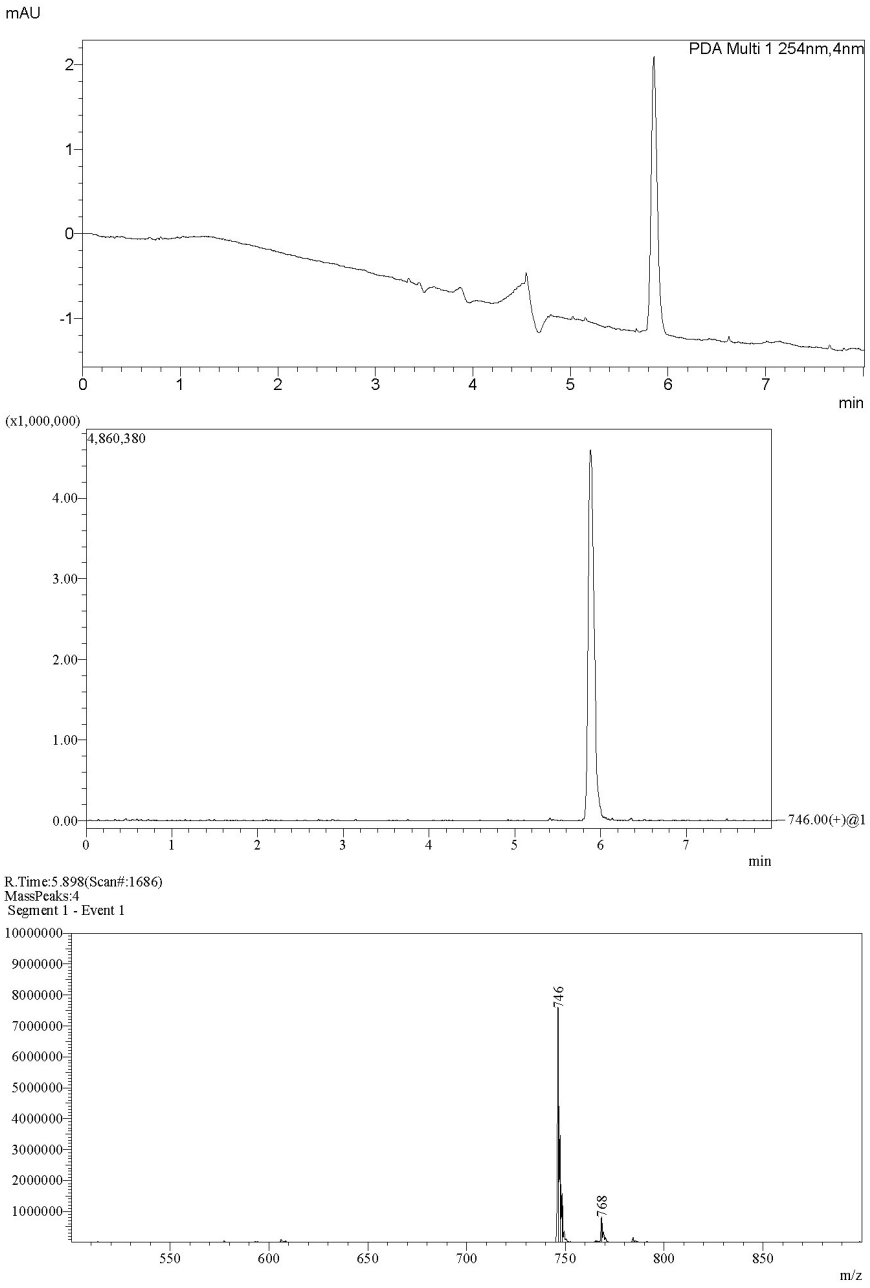
Ac-(cyclo-1,5)-[S_5AFAC(NTs)]-NH_2 **9A**



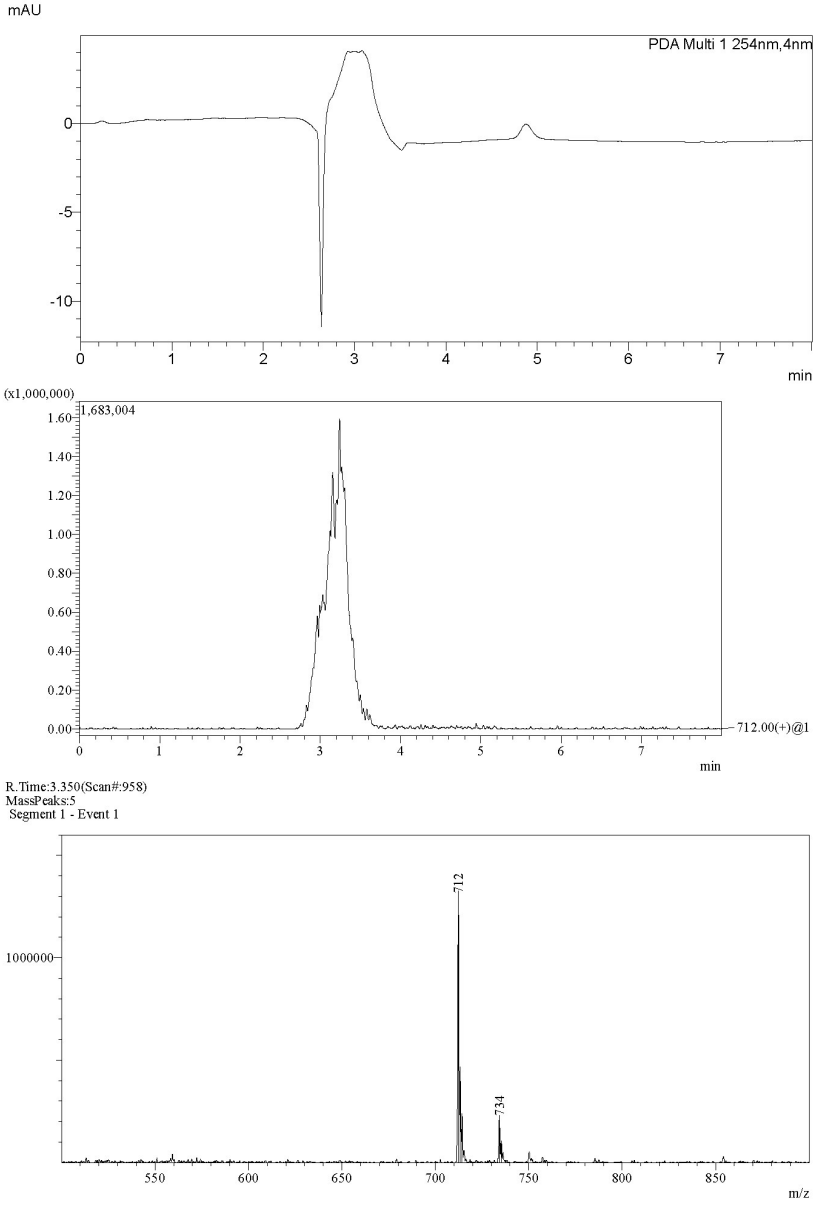




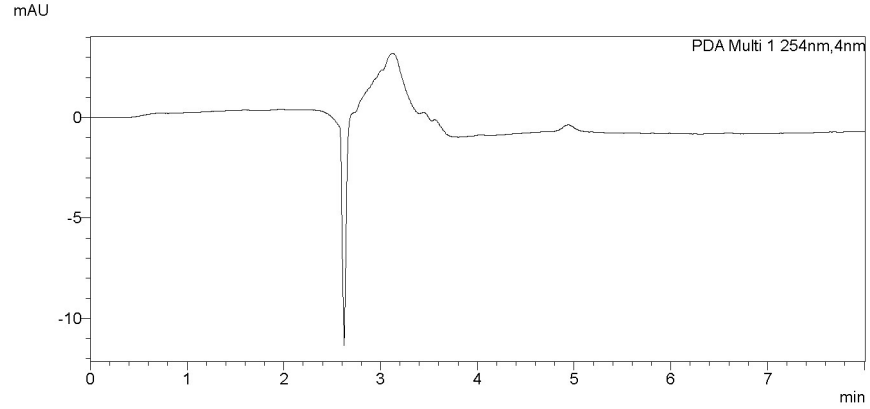
Ac-(cyclo-1,5)-[S_5AFAC(NTs)]-NH_2 **9B**

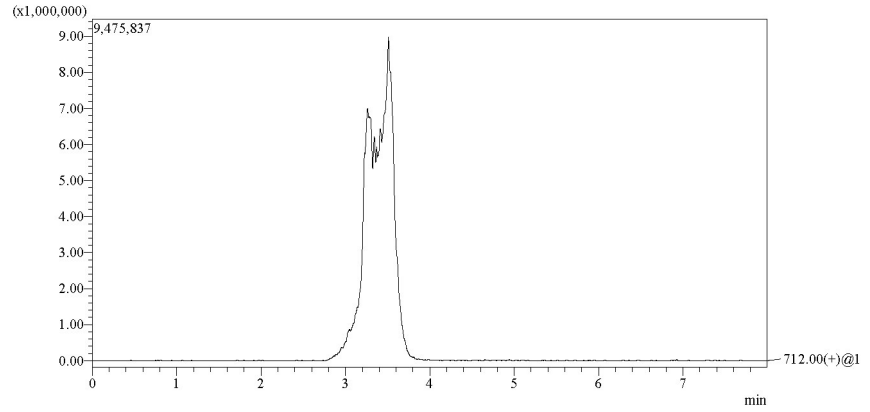


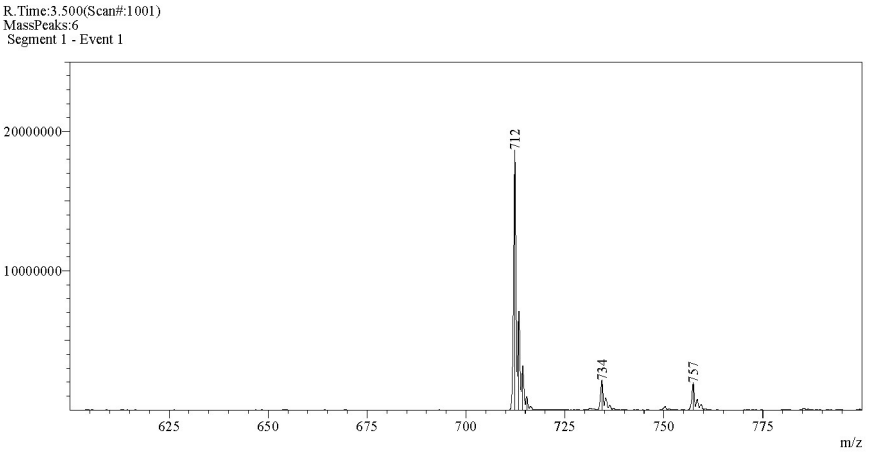
Ac-(cyclo-1,5)-[S_5AIAC(NTs)]-NH_2 **10A**



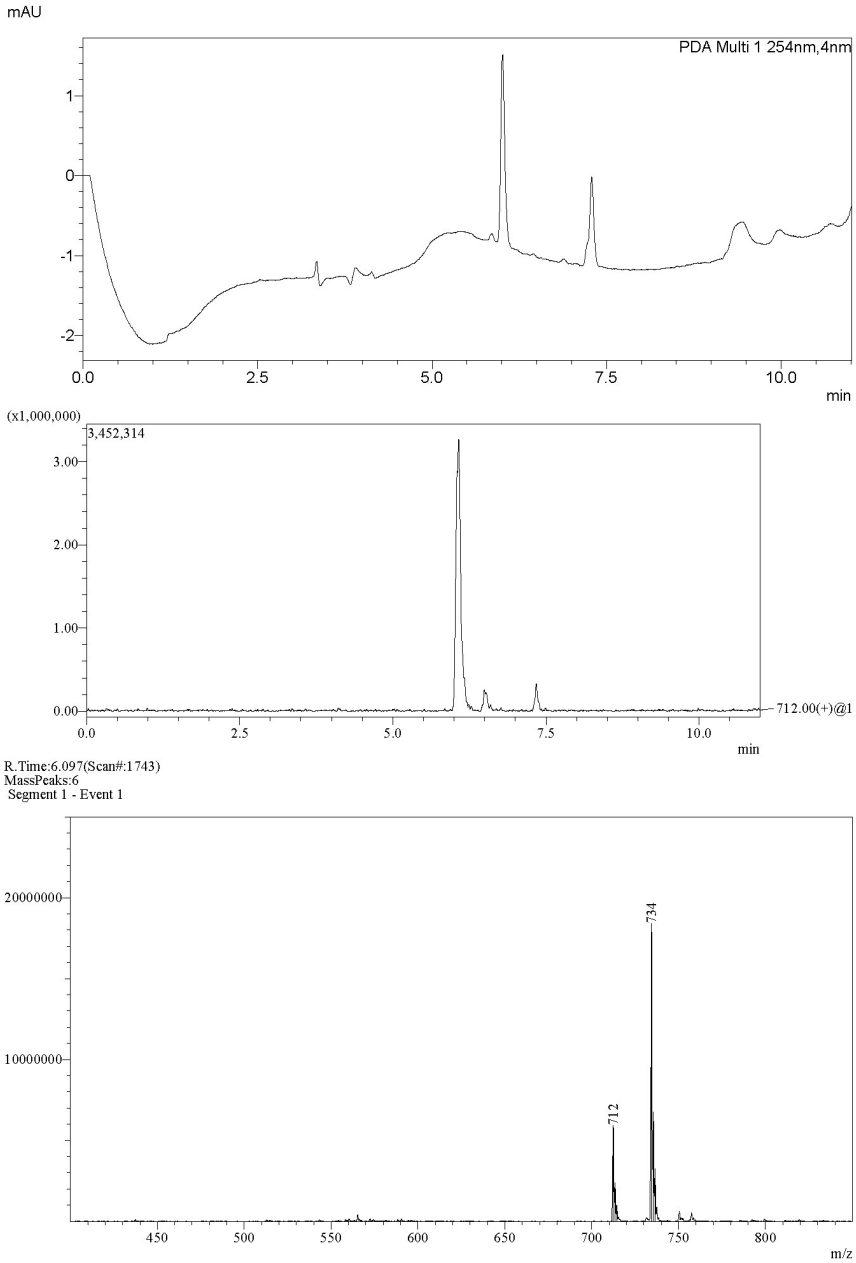
Ac-(cyclo-1,5)-[S_5AIAC(NTs)]-NH_2 **10B**



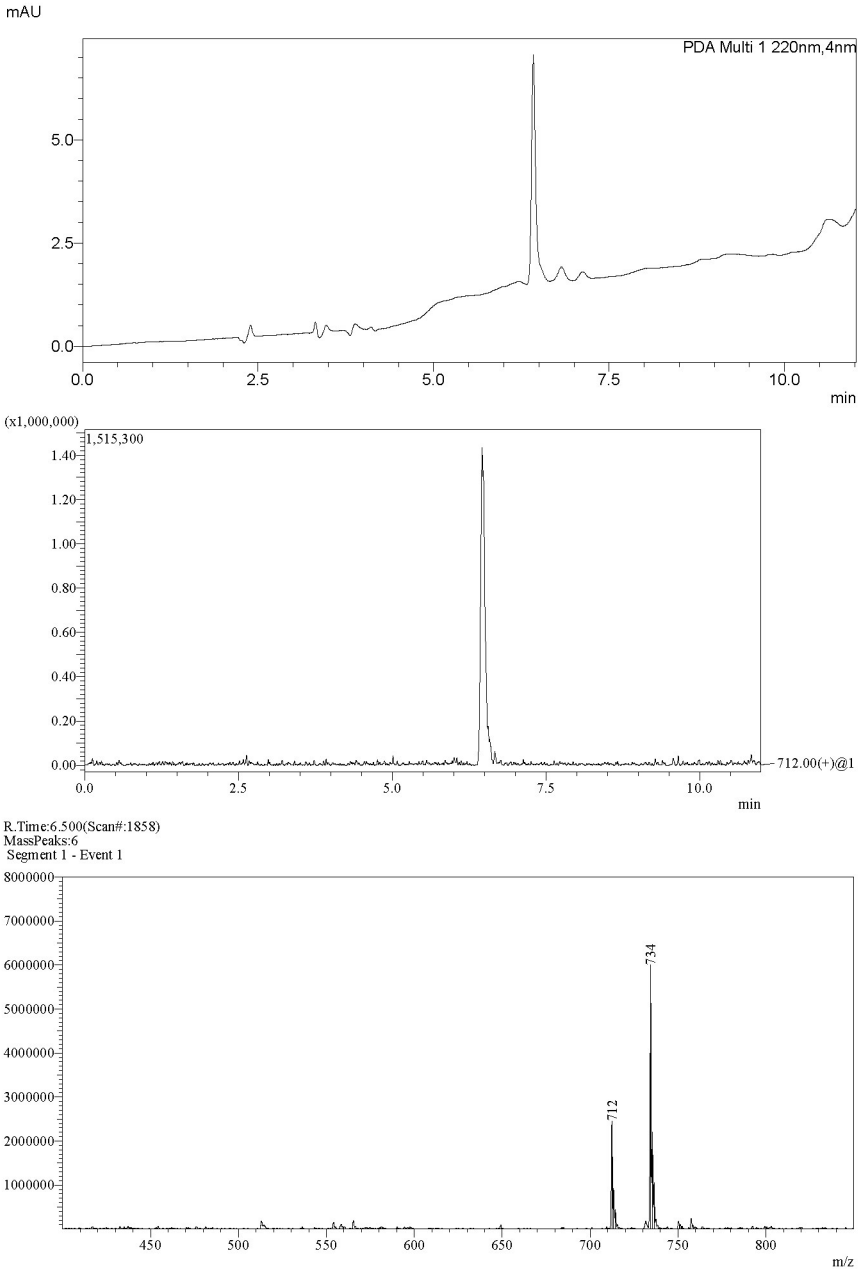




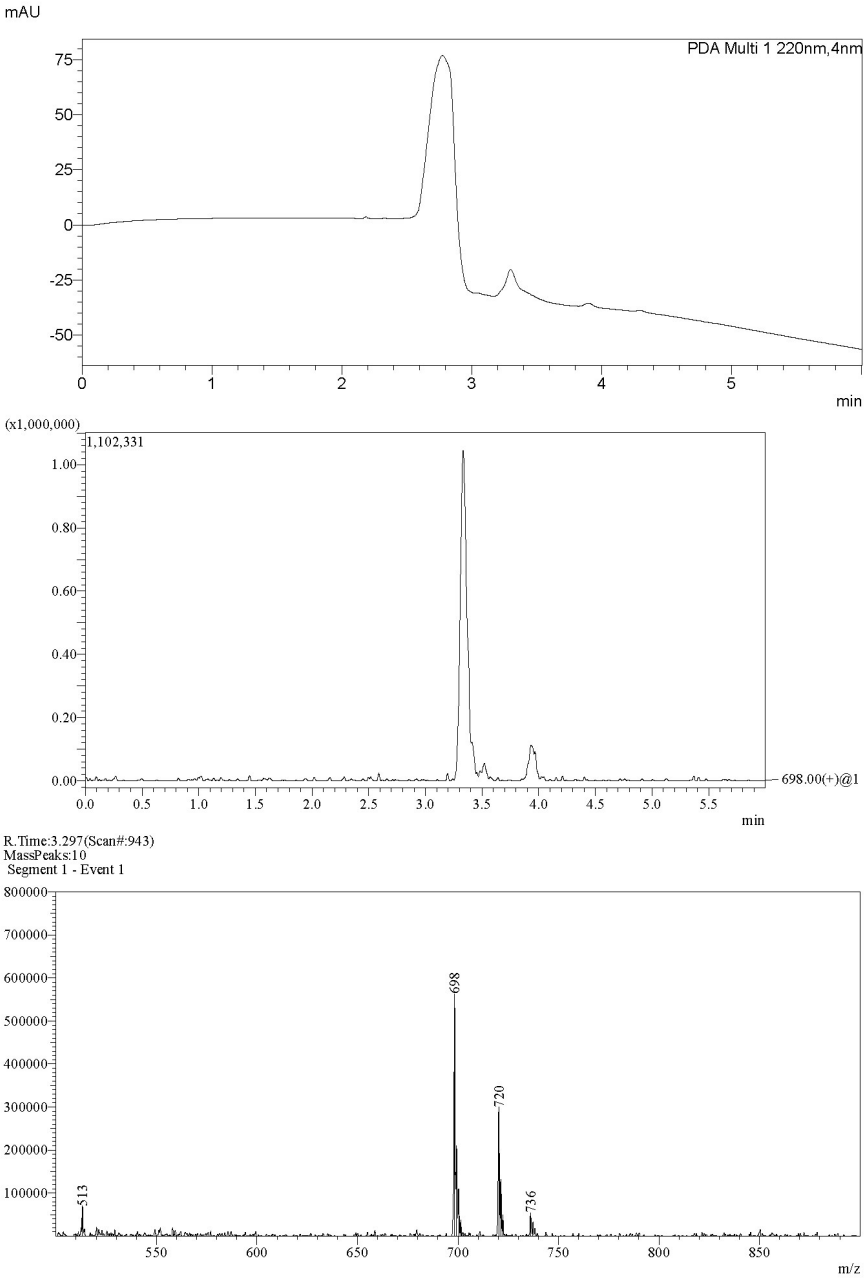
Ac-(cyclo-1,5)-[S_5ALAC(NTs)]-NH_2 **11A**



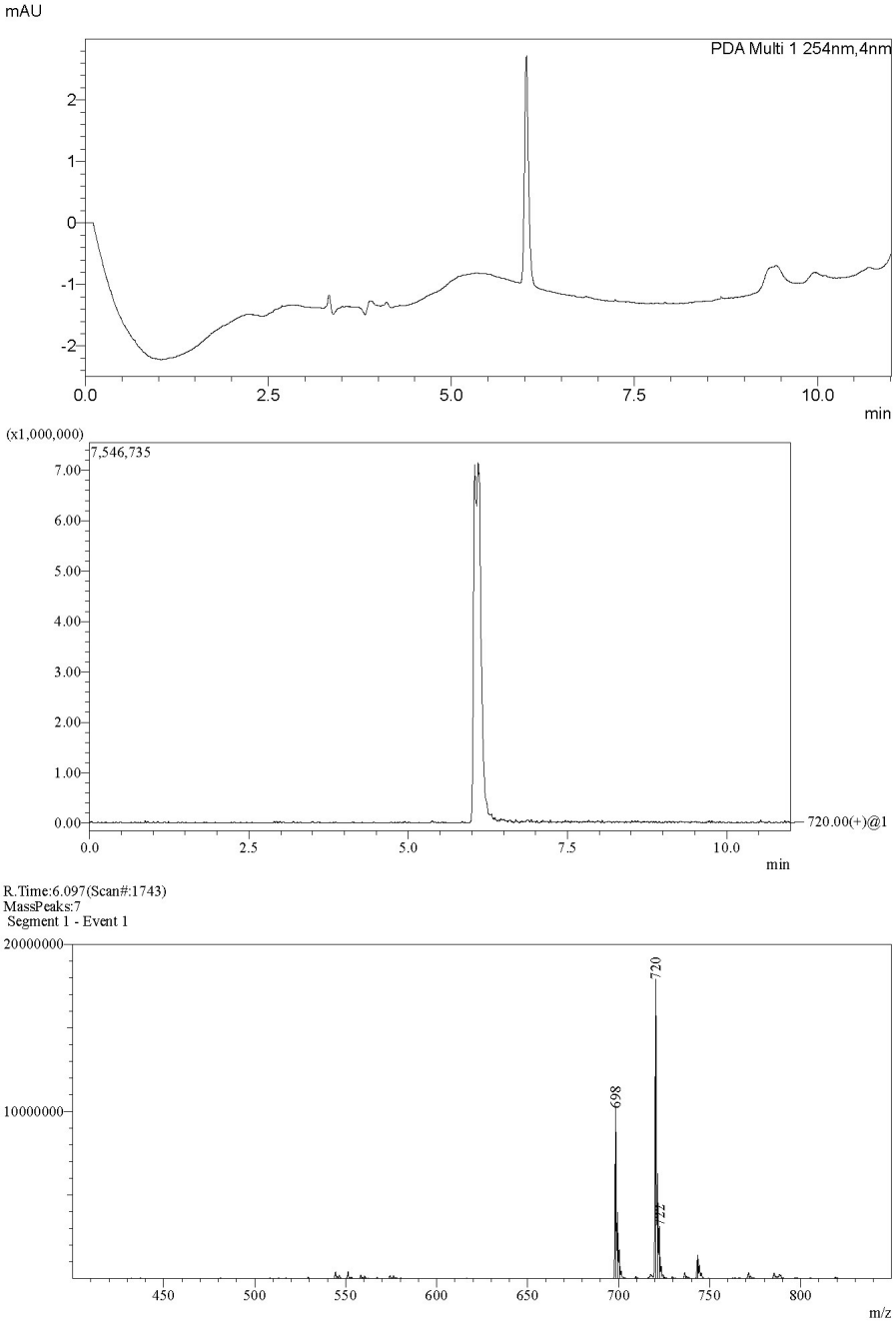
Ac-(cyclo-1,5)-[S_5ALAC(NTs)]-NH_2 **11B**



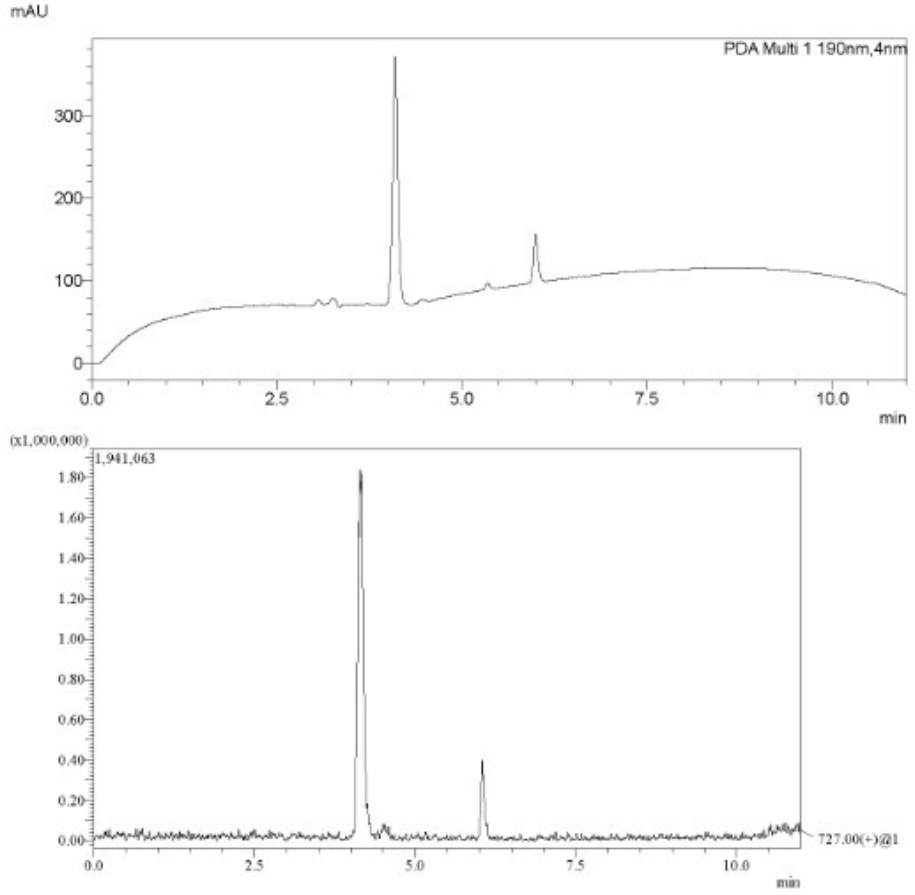
Ac-(cyclo-1,5)-[S_5AVAC(NTs)]-NH_2 **12A**

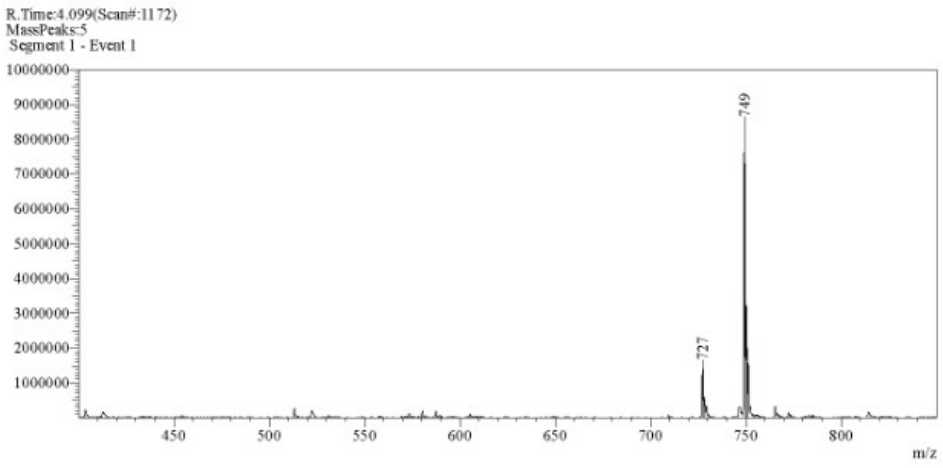


Ac-(cyclo-1,5)-[S_5AVAC(NTs)]-NH_2 **12B**

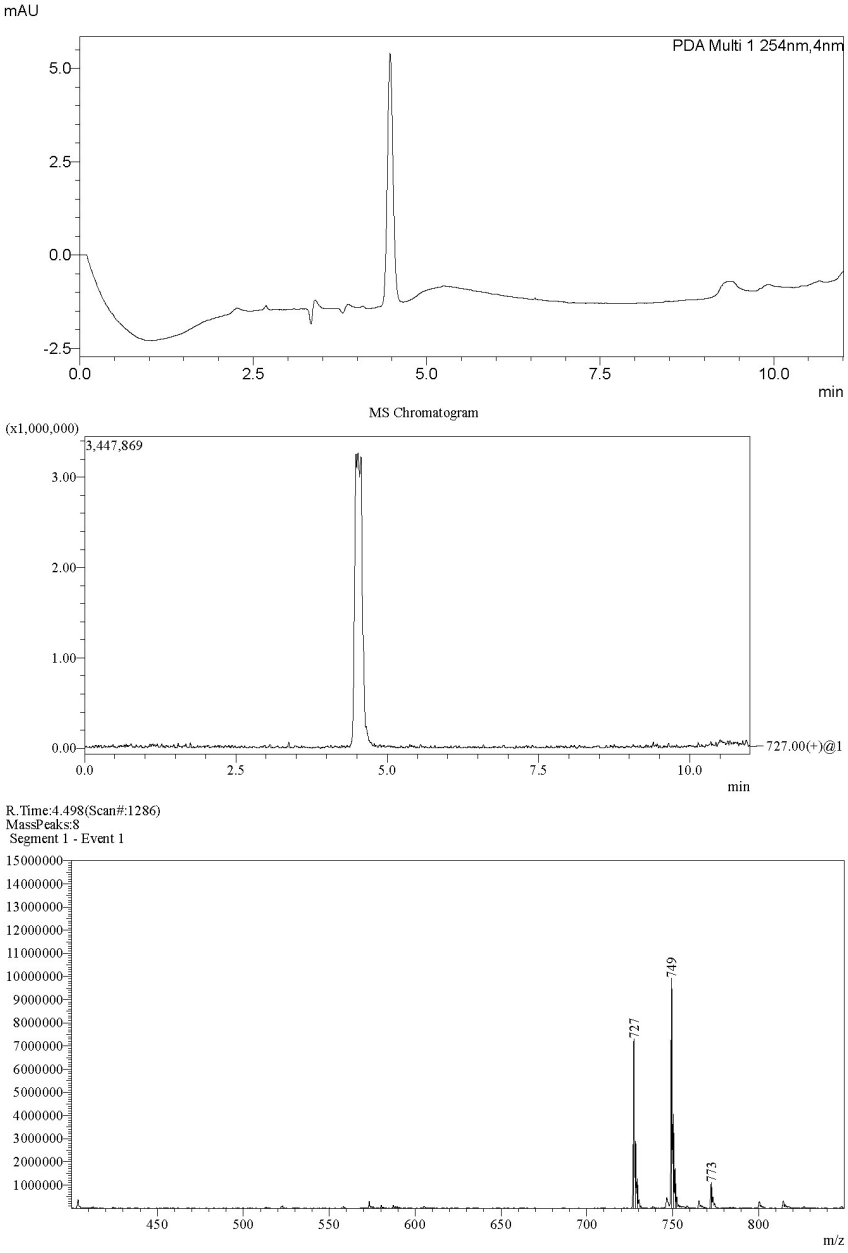


Ac-(cyclo-1,5)-[S_5AQAC(NTs)]-NH_2 **13A**

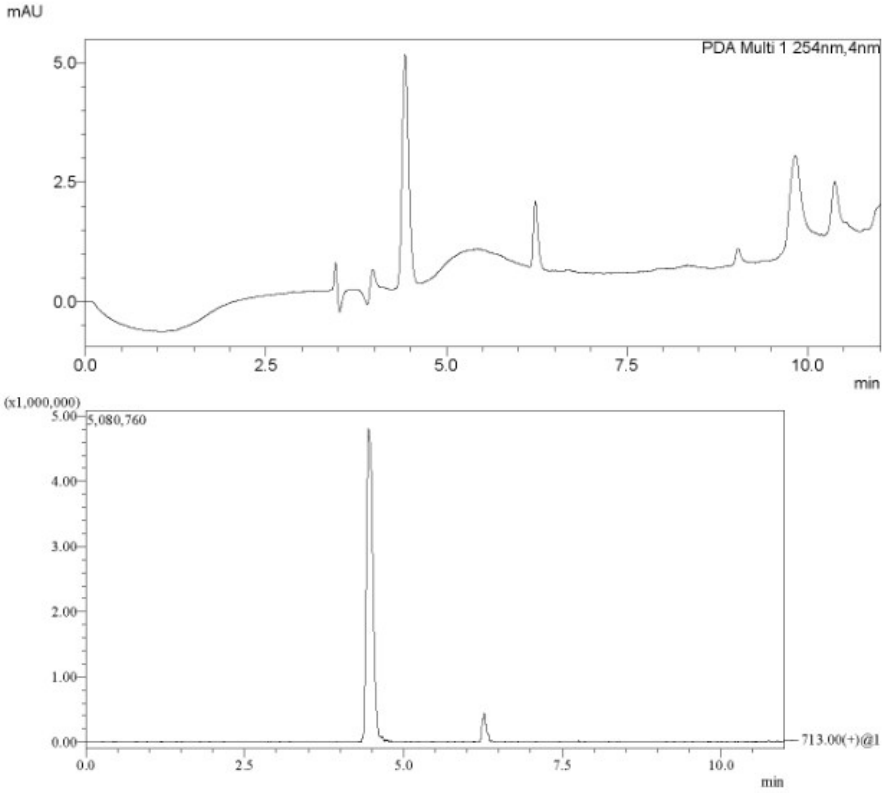


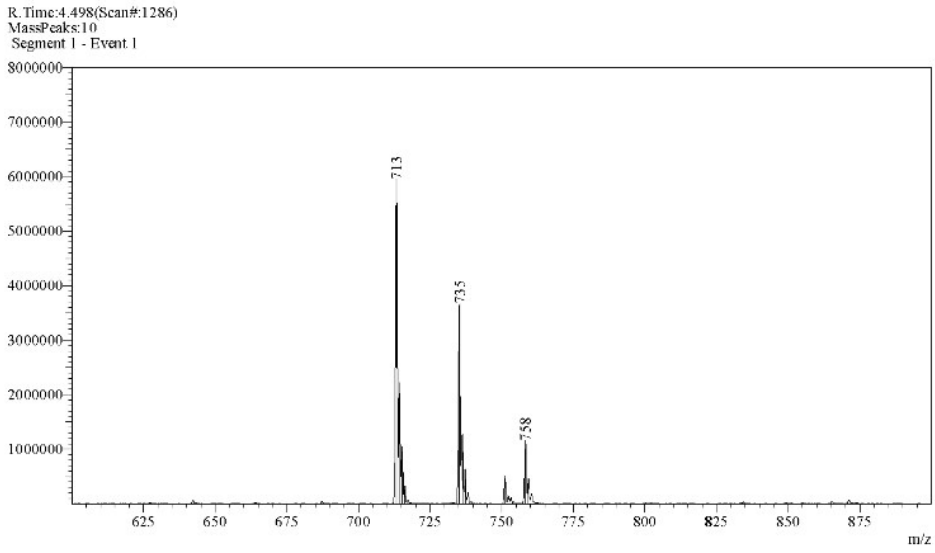


Ac-(cyclo-1,5)-[S_5AQAC(NTs)]-NH_2 **13B**

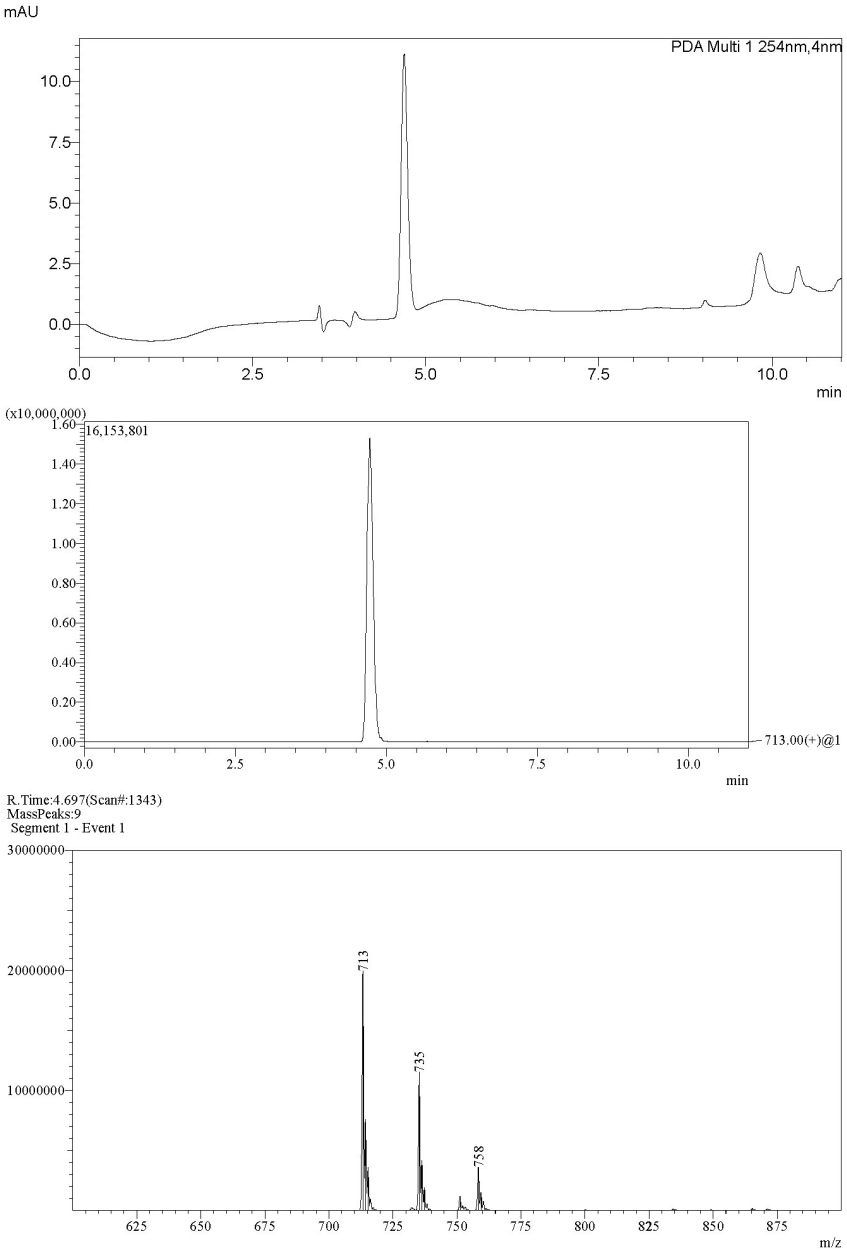


Ac-(cyclo-1,5)-[S_5ANAC(NTs)]-NH_2 **14A**





Ac-(cyclo-1,5)-[S_5ANAC(NTs)]-NH_2 **14B**



D-Ac-(cyclo-1,5)-[S_5AIAC(NTs)]-NH_2 **15B**