Supporting Information

Cleavable and Tunable Cysteine-Specific Arylation Modification by Aryl Thioethers

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1. General information

1.1 Reagents

Commercial available reagents and solvents were purchased from Energy Chemical, J&K Chemical, Innochem or Bidepharm and all these reagents were used directly without further purification unless otherwise noted. RP-HPLC solvents were purchased as HPLC grade from Energy Chemical.

Fmoc-amino acids for solid phase peptide synthesis (SPPS) were used with the following side-chain protection: Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(*t*Bu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(*t*Bu)-OH, Fmoc-His(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(*t*Bu)-OH, FmocThr(*t*Bu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(*t*Bu)-OH.

1.2 Instruments

NMR spectra were recorded on a Bruker AVANCE AV 400 or 500 instruments and all NMR experiments were reported in units, parts per million (ppm), using TMS as internal reference. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, and br = broad signal), Coupling constants (*J*) were reported as Hertz (Hz). HRMS spectra were recorded with a LCMS-IT-TOF mass spectrometer, equipped with an ESI source. LC-MS spectra were performed on an Agilent Technologies 1260 Infinity Ⅱ HPLC system, connected to an Agilent G6125B LC/MSD, equipped with an Agilent ZORBAX SB-C18 column, 2.1 × 50 mm, 1.8 μm). Preparative RP-HPLC were performed on Hanbon Sci. &Tech. Newstyle HPLC systems equipped with NP7000 serials pump, NU3000 serials UV/VIS detector and DM-A dynamic mixer, using the following column: Dubhe C18 D18122010.25 column, 12 nm, 10 μm, 20 x 250 mm. TLC analysis was visualized by fluorescence quenching under UV light (254 nm and 365 nm), or developing the plates with I_2, phosphomolybdic acid (PMA), permanganate. Flash chromatography purifications were performed on silica gel GF254 (200-300 mesh) purchased from Qingdao Haiyang Chemical.

2. LC-MS and preparative HPLC information

2.1 LC-MS analysis

LC-MS measurements were performed on an Agilent Technologies 1260 Infinity Ⅱ HPLC system with a G7129A 1260 Vislsampler, a G7111B 1260 Quat Pump and a G7114A 1260 VWD detector, connected to an Agilent G6125B LC/MSD, equipped with an Agilent ZORBAX SB-C18 column, 2.1 × 50 mm, 1.8 μm). Water (solvent A) and acetonitrile (solvent B), each containing 0.1% formic acid, were used as the mobile phase. Low-resolution mass spectrometric measurements were acquired using the following parameters: positive electrospray ionization (ESI), temperature of drying gas = 350 °C, flow rate of drying gas = 12 L/min, pressure of nebulizer gas = 60 psi, capillary voltage = 4000 V and fragmentor voltage = 70 V.

Following LC methods were used:

Method A (Column: Agilent ZORBAX SB-C18 column, 2.1 × 50 mm, 1.8 µm, flow rate 0.3 mL / min)

Time (min)	H_2O (%)	Acetonitrile (%)
0	95	5
2	95	5
17	70	30
18	0	100
24	0	100

Method B (Column: Agilent ZORBAX SB-C18 column, 2.1 × 50 mm, 1.8 µm, flow rate 0.3 mL / min)

Time (min)	H_2O (%)	Acetonitrile (%)
0	100	0
2	100	0
17	70	30
18	0	100
24	0	100

Method C (Column: Agilent Poroshell SB-C18 column, 3 × 100 mm, 2.7 µm, flow rate 0.6 mL / min)

Time (min)	H_2O (%)	Acetonitrile (%)
0	95	5
2	95	5
10	70	30
18	5	95
24	5	95

Method D (Column: Agilent Poroshell SB-C18 column, 3 × 100 mm, 2.7 µm, flow rate 0.6 mL / min)

Time (min)	H_2O (%)	Acetonitrile (%)
0	95	5
2	95	5
17	70	30
18	0	100
24	0	100

All reported LC-MS yields were determined by integrating TIC spectra. The peak areas for all relevant peptide-containing species on the chromatogram were integrated using Agilent software package. The yields were determined as follows: %yield = $S_{product}/S_{total}$, where $S_{product}$ is the peak area of the product and S_{total} is the peak area of combined peptide-containing species (product, starting material and byproduct).

2.2 Preparative HPLC

Preparative RP-HPLC was performed on a Hanbon Sci.&Tech. Newstyle HPLC system with a NU3000 serials UV/VIS detector, a NP7000 serials pump, a DM-A dynamic mixer and a collector, coupled with a Dubhe C18 column (30 x 250 mm, 10 μm). Water (solvent A) and acetonitrile (solvent B), each containing 0.1% TFA, were used as the mobile phase.

Following LC method was used:

Method E (Column: Dubhe C18 column, 30 x 250 mm, 10 μm, flow rate 20 mL / min)

Time (min)	H_2O (%)	Acetonitrile (%)
0	95	5
5	95	5
35	60	40
45	0	100
60	0	100

3. Solid phase peptide synthesis (SPPS) and purification

Peptide synthesis was carried out manually using standard Fmoc SPPS-chemistry and 2-Chloro-trityl chloride (2-CTC) resin (0.98 mmol/g resin, 0.2 mmol) or Rink amide resin (0.61 mmol/g resin, 0.2 mmol). Peptides **1m**/**1n** were made via Rink amide resin and other peptides were made via 2-chloro-trityl chloride resin.

Preloading 2-chloro-trityl chloride resin: 2-CTC resin was swollen in anhydrous DCM for 10 min, then washed with DCM (3 × 5 mL). A solution of Fmoc-AA-OH (4 equiv.) and DIPEA (8 equiv.) in anhydrous DCM (4 mL) was added to the resin and the suspension was shaken at room temperature for 2 hours. The resin was washed with DCM (3 × 5 mL), DMF (3 × 5 mL) and DCM (3 × 5 mL). The resin was capped with a solution of DCM/MeOH/DIPEA (17/2/1, v/v/v, 4 mL) for 30 min and washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL).

Preloading Rink amide resin: Rink amide resin was swollen in anhydrous DCM for 10 min, then washed with DCM (3 × 5 mL) and DMF (3 × 5 mL). Then the resin was treated with piperidine/DMF (1/4, v/v, 2 × 4 mL, 2 × 5 min) at room temperature and washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL). A solution of Fmoc-AA-OH (4 equiv.), HOBT (4 equiv.) and collidine (8 equiv.) in anhydrous DMF (4 mL) was added to the resin and the suspension was shaken at room temperature for 2 hours. The resin was washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL). The resin was capped with acetic anhydride/pyridine (1/9, v/v) (30 min) and washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL).

Fmoc-deprotection: The washed resin was treated with piperidine/DMF (1/4, v/v, 2 × 4 mL, 2 × 5 min) at room temperature and then washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL).

Amino acid coupling and Fmoc-deprotection: A solution of protected amino acid (4 equiv.),

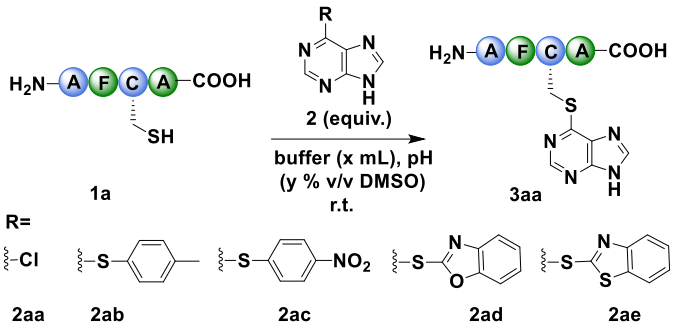
HATU (4 equiv.), HOBT (4 equiv.) and collidine (8 equiv.) in DMF (4 mL) was added to the resin. The reaction mixture was agitated at room temperature for 2 hours. After the reaction was completed, the resin-bound peptide was washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL). Then the washed resin was treated with piperidine/DMF (1/4, v/v, 2 × 4 mL, 2 × 5 min) at room temperature and then washed with DMF (3 × 5 mL), MeOH (3 × 5 mL) and DCM (3 × 5 mL).

Peptide cleavage and deprotection: Peptides were deprotected and cleaved from the resin under reducing conditions, by treatment with 2.5% v/v water, 2.5% v/v *i*-Pr_3SiH, 2.5% v/v ethanethiol and 2.5% v/v thioanisole in neat trifluoroacetic acid (4 mL). The resulting mixture was shaken for 1 hours at room temperature. The resin was removed by filtration and washed with TFA (2 × 3 mL). The combined cleavage solutions were concentrated in vacum.

Peptide purification and analysis: Peptides were dissolved in water with a minimum amount of organic co-solvent (acetonitrile). Then purified by preparative RP-HPLC (Method D). Fractions containing the desired peptide were lyophilized. The purity was assessed by analyzing a peptide water solution by LC-MS. At the same time, low-resolution mass spectrometric measurements were also acquired.

5. Optimization of reaction conditions for cysteine arylation

Table S1: Optimization of reaction conditions for cysteine arylation[a]



Entry	**2** (eq.)	buffer	pH	x	y	Yield (%)[b]
1	**2aa** (1.5 eq.)	100 mM PBS	8.0	0.5	10	n.d.
2	**2ab** (1.5 eq.)	100 mM PBS	8.0	0.5	10	n.d.
3	**2ac** (1.5 eq.)	100 mM PBS	8.0	0.5	10	n.d.
4	**2ad** (1.5 eq.)	100 mM PBS	8.0	0.5	10	43
5	**2ae** (1.5 eq.)	100 mM PBS	8.0	0.5	10	17
6	**2ad** (1.5 eq.)	100 mM HEPES	8.0	0.5	10	41
7	**2ad** (1.5 eq.)	100 mM Tris	8.0	0.5	10	47
8	**2ad** (1.5 eq.)	100 mM Tris	7.4	0.5	10	35
9	**2ad** (1.5 eq.)	100 mM Tris	7.6	0.5	10	39
10	**2ad** (1.5 eq.)	100 mM Tris	7.8	0.5	10	43
11	**2ad** (1.5 eq.)	100 mM Tris	8.2	0.5	10	47
12	**2ad** (1.5 eq.)	100 mM Tris	8.4	0.5	10	46
13	**2ad** (1.5 eq.)	200 mM Tris	8.0	0.5	10	46
14	**2ad** (2.0 eq.)	100 mM Tris	8.0	0.5	10	55
15	**2ad** (3.0 eq.)	100 mM Tris	8.0	0.5	10	64 (85)
16	**2ad** (3.0 eq.)	100 mM Tris	8.0	0.5	5	62 (87)
17	**2ad** (3.0 eq.)	100 mM Tris	8.0	1.0	5	54 (82)
18	**2ad** (3.0 eq.)	100 mM Tris	8.0	0.5	2	53 (79)
19	**2ad** (3.0 eq.)	100 mM Tris	8.0	1.0	2	57 (89)
20	**2ad** (3.0 eq.)	100 mM Tris	8.0	0.5	1	45 (80)
21	**2ad** (3.0 eq.)	100 mM Tris	8.0	1.0	1	59 (90, 83[c])

a) Reaction conditions: 1.0 µmol **1a** and **2** (eq.) in non-degassed buffer at room tempeture for 1 h. b) Reported yields are LC-MS yields after 1 h (The yields in parentheses correspond to the yields after 5 h of reaction). c) Isolated yield.

6. Chemoselectivity determination of arylation modification

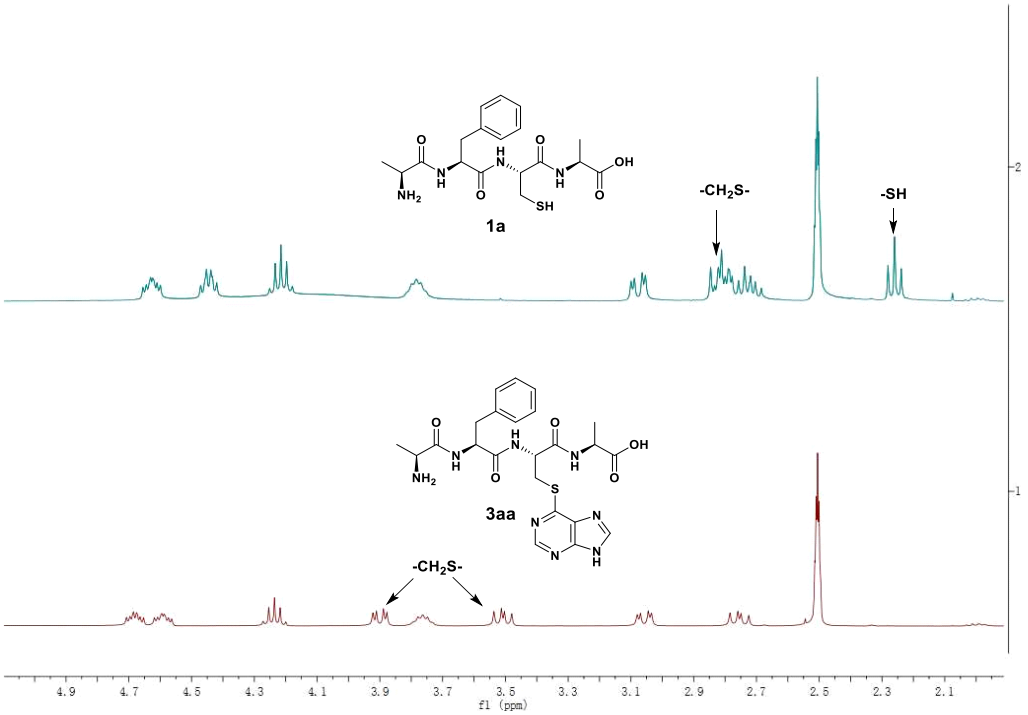


Figure S1. Comparison of 1D ^{1}H NMR spectra of peptides **1a** and **3aa**.

7. Synthesis and characterization of aryl thioethers

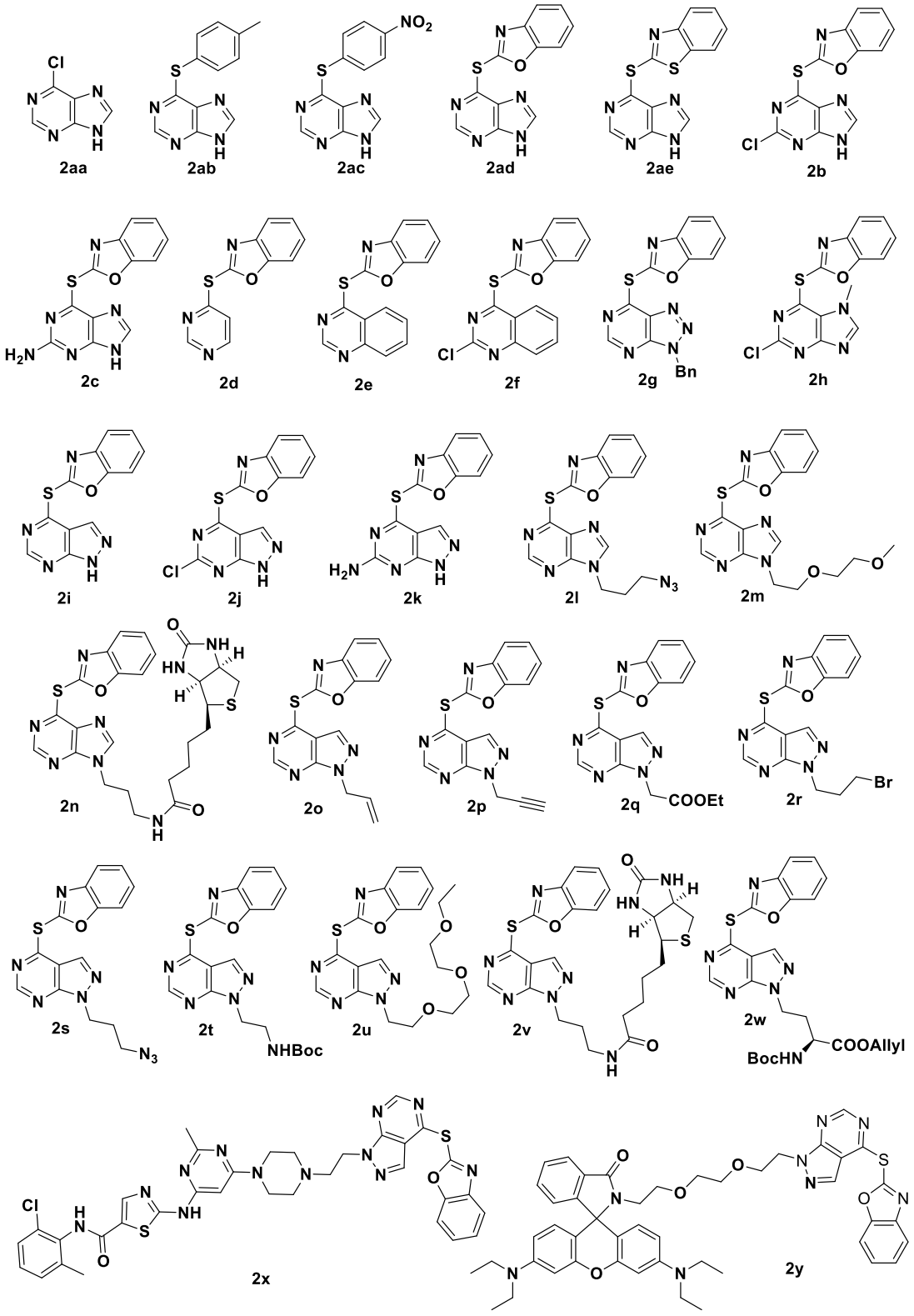
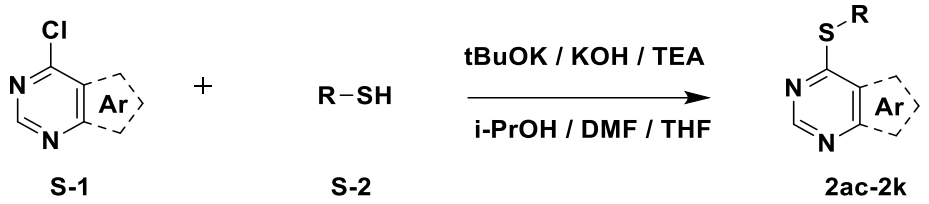


Figure S2. Structure of aryl thioethers

Compound **2aa** is commercial available. Compound **2ab**[1], **2g**[2] were synthesized according to reported literature.

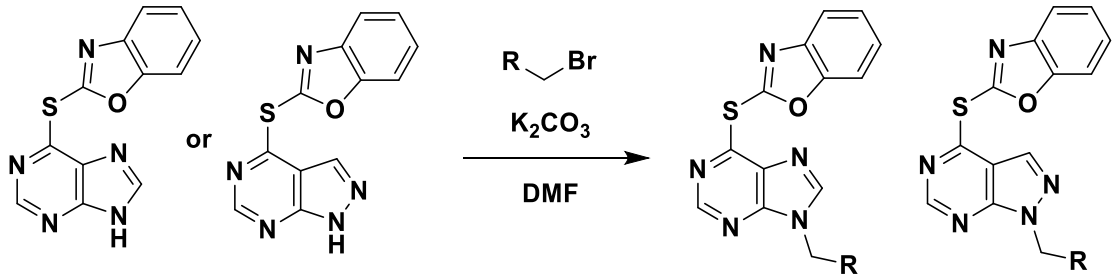
General procedure for **2ac-2k**:



S-1 **S-2** **2ac-2k**

The starting chloro compound (**S-1**) in solvent was heated under reflux with aryl mercaptan (**S-2**, 1.5 eq.) in the presence of base (1.5 eq.), monitored by TLC until reaction completion. Cooled down to room temperature, concentrated in vacuo, and the residue was purified by silica gel (200−300 mesh) column chromatography to afford the desired compound.

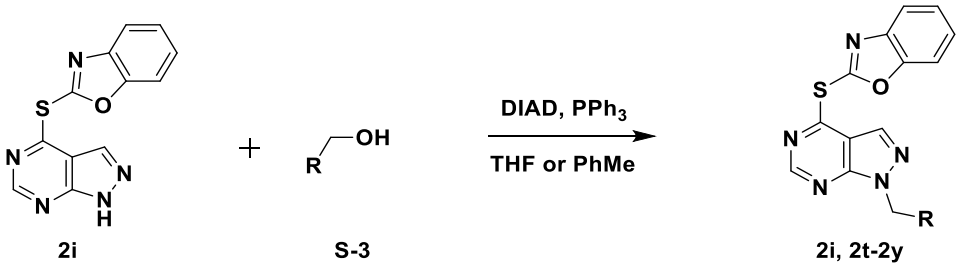
General procedure for **S-4, S-5, 2m, 2o-2q**:



2ad **2i** **S-4, S-5, 2m** **2o-2q**

The starting compound (**2ad** or **2i**, 0.2 mmol) and K_2CO_3 (1.2 eq.) were dissolved in DMF (2 mL). Then corresponding bromo compound (1.2 eq.) was added and the reaction mixture was stirred at room temperature until reaction completion. The suspension was diluted with EtOAc (20 mL) and washed successively with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel (200−300 mesh) column chromatography to afford the desired compound.

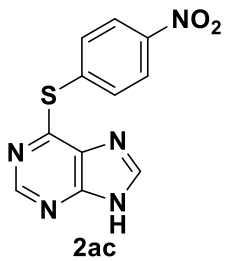
General procedure for **2r, 2t-2z**:



2i **S-3** **2i, 2t-2y**

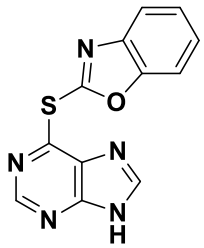
2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)benzo[d]oxazole (**2i**, 0.2 mmol) and triphenylphosphine (PPh_3, 1.5 eq.) were dissolved in dry THF (2 mL) under N_2 and cooled to 0 °C. The alcohol (1.5 eq.) was added immediately followed by dropwise addition of diisopropyl azodiformate (DIAD, 1.5 eq.). Stirring at room temperature or 60 °C until reaction completion. The reaction mixture was evaporated in vacuo and purified by silica gel (200−300 mesh)

column chromatography to afford the desired compound.



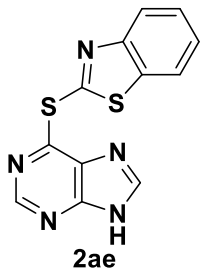
2ac

6-((4-nitrophenyl)thio)-9*H*-purine (2ac): According to the general procedure, using *i*-PrOH as solvent and $(CH_3)_3COK$ as base, affording the **2ac** as a yellow solid. 86% yield. ^{1}H NMR (500 MHz, DMSO) δ 13.72 (s, 1H), 8.65 (s, 1H), 8.59 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO) δ 152.08, 148.01, 137.25, 135.60, 124.37. HRMS (ESI) m/z calcd for $C_{11}H_8N_5O_2S^+$ $[M+H]^+$ 274.0393, found 270.0389.



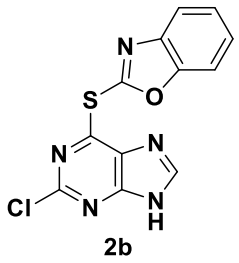
2ad

2-((9*H*-purin-6-yl)thio)benzo[*d*]oxazole (2ad): According to the general procedure, using *i*-PrOH as solvent and $(CH_3)_3COK$ as base, affording the **2ad** as a white solid. 86% yield. ^{1}H NMR (400 MHz, DMSO) δ 13.85 (s, 1H), 8.71 (s, 1H), 8.59 (s, 1H), 7.86 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.79 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.55 – 7.44 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 155.99, 152.62, 152.21, 145.74, 141.83, 126.84, 125.50, 120.50, 111.55.HRMS (ESI) m/z calcd for $C_{12}H_8N_5OS^+$ $[M+H]^+$ 270.0444, found 270.0441.



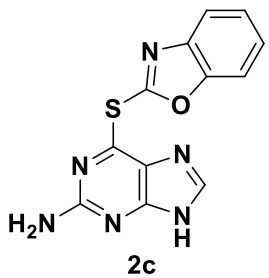
2ae

2-((9*H*-purin-6-yl)thio)benzo[*d*]thiazole (2ae): According to the general procedure, using *i*-PrOH as solvent and $(CH_3)_3COK$ as base, affording the **2ae** as a white solid. 76% yield. ^{1}H NMR (400 MHz, DMSO) δ 8.87 (s, 1H), 8.65 (s, 1H), 8.17 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.53 – 7.48 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 158.54, 151.74, 151.68, 145.56, 136.56, 126.97, 125.98, 122.73, 122.32. HRMS (ESI) m/z calcd for $C_{12}H_8N_5S_2^+$ $[M+H]^+$ 286.0216, found 286.0209.



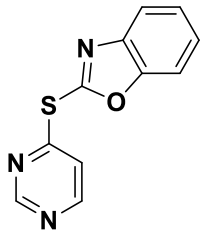
2b

2-((2-chloro-9H-purin-6-yl)thio)benzo[d]oxazole (2b): According to the general procedure, using *i*-PrOH as solvent and $(CH_3)_3COK$ as base, affording the **2b** as a white solid. 64% yield. ^{1}H NMR (400 MHz, DMSO) δ 14.02 (s, 1H), 8.60 (s, 1H), 7.91 – 7.85 (m, 1H), 7.84 – 7.79 (m, 1H), 7.58 – 7.44 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 155.19, 152.60, 152.08, 141.74, 127.03, 125.60, 120.61, 111.60. HRMS (ESI) m/z calcd for $C_{12}H_7ClN_5OS^+$ $[M+H]^+$ 304.0054, found 304.0054.



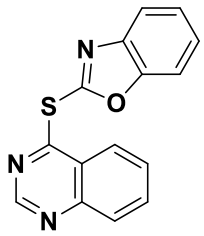
2c

6-(benzo[*d*]oxazol-2-ylthio)-9*H*-purin-2-amine (2c): According to the general procedure, using DMF as solvent and $(CH_3)_3COK$ as base, affording the **2c** as a white solid. 50% yield. ^{1}H NMR (400 MHz, DMSO) δ 12.74 (s, 1H), 7.95 (s, 1H), 7.81 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.74 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.50 – 7.38 (m, 2H), 6.53 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 160.27, 152.55, 141.91, 141.33, 126.50, 125.31, 120.29, 111.46. HRMS (ESI) m/z calcd for $C_{12}H_9N_6OS^+$ $[M+H]^+$ 285.0553, found 285.0546.



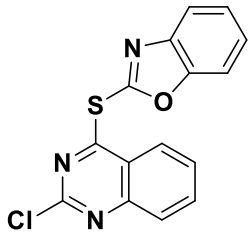
2d

2-(pyrimidin-4-ylthio)benzo[*d*]oxazole (2d): According to the general procedure, using EtOH as solvent and triethylamine as base, affording the **2d** as a white solid. 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.62 (d, *J* = 5.6 Hz, 1H), 7.84 – 7.72 (m, 2H), 7.62 – 7.53 (m, 1H), 7.45 – 7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.89, 158.47, 156.84, 156.54, 152.01, 141.53, 126.13, 125.09, 120.18, 119.92, 110.74. HRMS (ESI) m/z calcd for $C_{11}H_8N_3OS^+$ $[M+H]^+$ 230.0383, found 230.0379.



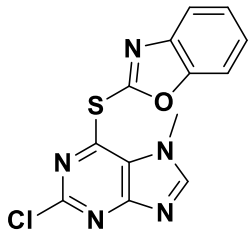
2e

2-(quinazolin-4-ylthio)benzo[*d*]oxazole (2e): According to the general procedure, using EtOH as solvent and KOH as base, affording the **2e** as a white solid. 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.12 (dd, *J* = 8.4, 0.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.99 – 7.91 (m, 1H), 7.86 – 7.81 (m, 1H), 7.74 – 7.67 (m, 1H), 7.63 – 7.57 (m, 1H), 7.49 – 7.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.63, 155.03, 153.88, 153.06, 149.17, 141.98, 134.68, 129.20, 128.41, 126.33, 124.91, 123.86, 123.54, 120.65, 110.96. HRMS (ESI) m/z calcd for $C_{15}H_{10}N_3OS^+$ $[M+H]^+$ 280.0539, found 280.0529.



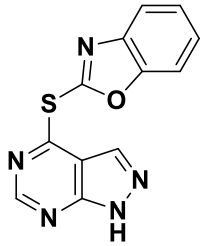
2f

2-((2-chloroquinazolin-4-yl)thio)benzo[*d*]oxazole (2f): According to the general procedure, using THF as solvent and triethylamine as base, affording the **2f** as a white solid. 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.24, 155.90, 153.85, 153.08, 150.67, 141.84, 135.78, 128.56, 128.39, 126.56, 125.02, 123.93, 121.72, 120.69, 111.00. HRMS (ESI) m/z calcd for $C_{15}H_9ClN_3OS^+$ $[M+H]^+$ 314.0149, found 314.0135.



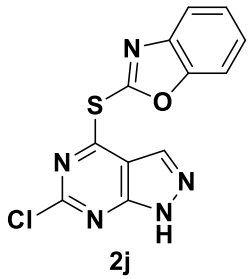
2h

2-((2-chloro-7-methyl-7*H*-purin-6-yl)thio)benzo[*d*]oxazole (2h): According to the general procedure, using DMF as solvent and KOH as base, affording the **2h** as a white solid. 30% yield. ^{1}H NMR (400 MHz, DMSO) δ 8.81 (s, 1H), 7.94 – 7.70 (m, 2H), 7.60 – 7.33 (m, 2H), 4.12 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 162.58, 156.29, 153.30, 152.49, 152.04, 148.04, 141.55, 126.86, 125.68, 125.00, 120.40, 111.51, 34.77. HRMS (ESI) m/z calcd for $C_{13}H_9ClN_5OS^+$ $[M+H]^+$ 318.0211, found 318.0204.



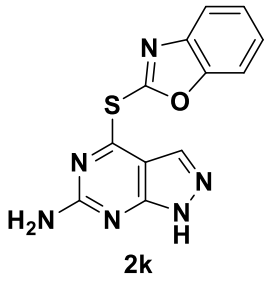
2i

2-((1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio)benzo[*d*]oxazole (2i): According to the general procedure, using THF as solvent and triethylamine as base, affording the **2i** as a white solid. 51% yield. ^{1}H NMR (400 MHz, DMSO) δ 14.41 (s, 1H), 8.74 (s, 1H), 8.11 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.37 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 155.15, 154.77, 152.61, 141.67, 127.32, 125.81, 120.78, 111.77. HRMS (ESI) m/z calcd for $C_{12}H_8N_5OS^+$ $[M+H]^+$ 270.0444, found 270.0432.



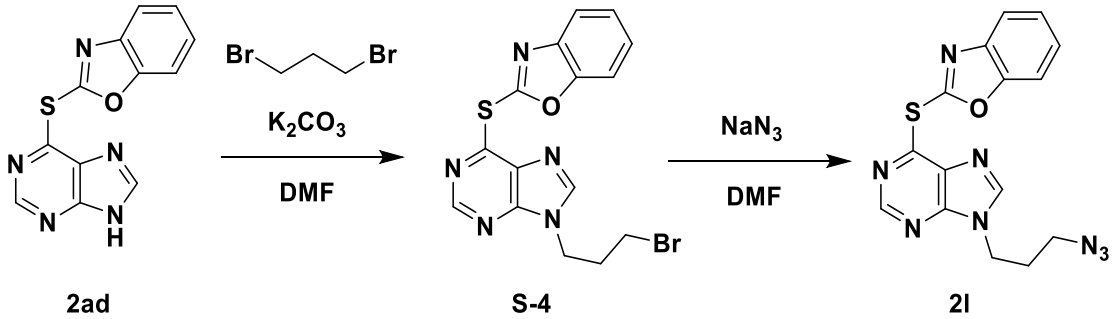
2j

2-((6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio)benzo[*d*] oxazole (2j): According to the general procedure, using THF as solvent and triethylamine as base, reacted in -20 °C affording the **2j** as a white solid. 24% yield. ^{1}H NMR (400 MHz, DMSO) δ 14.56 (s, 1H), 8.08 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.47 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 162.40, 155.77, 154.92, 154.33, 152.58, 141.55, 133.21, 127.54, 125.92, 120.90, 111.80, 111.00. HRMS (ESI) m/z calcd for $C_{12}H_7ClN_5OS^+$ $[M+H]^+$ 304.0054, found 304.0054.

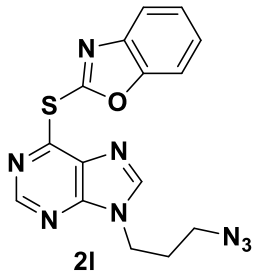


2k

4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine (2k): According to the general procedure, using THF as solvent and triethylamine as base, affording the **2k** as a white solid. 48% yield. ^{1}H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.45 (m, 2H), 7.30 (s, 1H), 6.95 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 161.46, 159.54, 156.97, 156.13, 152.46, 141.64, 132.23, 127.15, 125.76, 120.64, 111.73, 105.90. HRMS (ESI) m/z calcd for $C_{12}H_9N_6OS^+$ $[M+H]^+$ 285.0553, found 285.0548.



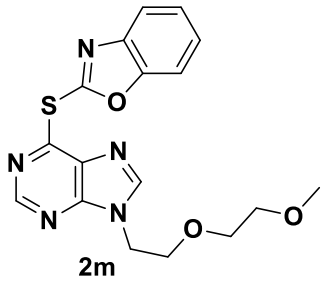
2ad **S-4** **2l**



2l

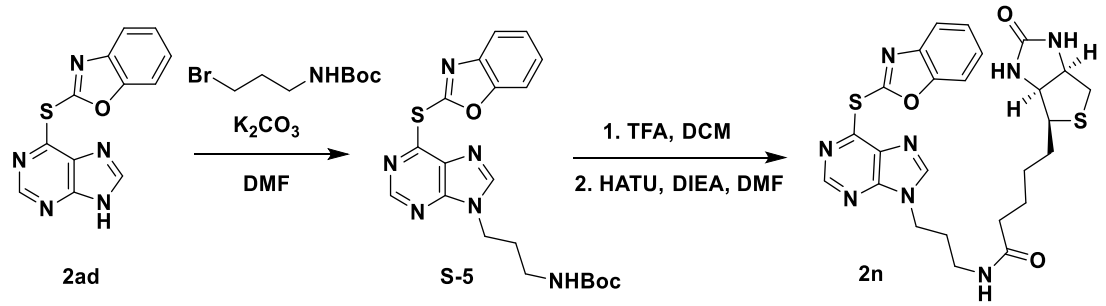
2-((9-(3-azidopropyl)-9*H*-purin-6-yl)thio)benzo[*d*]oxazole (2l): **S-4** was synthesized according to the general procedure. Then **S-4** (69.3 mg, 1.8 mmol) and NaN_3 (1.1 eq) was stirred in DMF (2 mL) at room temperature until reaction completion. The suspension was diluted with EtOAc (20 mL) and washed successively with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel (200−300 mesh) column chromatography to afford the desired compound **2l** as a white solid. 38% yield for two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.99 (s, 1H), 7.86 – 7.76 (m, 1H), 7.60 – 7.50 (m, 1H), 7.47 – 7.34 (m, 2H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 2.24 – 2.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.06, 155.76, 152.76, 152.22, 150.25, 144.36, 141.98, 131.78, 126.07, 124.77, 120.49, 110.84, 48.11, 41.43, 28.89. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_8OS^+$ $[M+H]^+$ 353.0928, found 353.0922.

2-((9-(2-(2-methoxyethoxy)ethyl)-9*H*-purin-6-yl)thio) benzo[*d*]oxazole (2m): According to

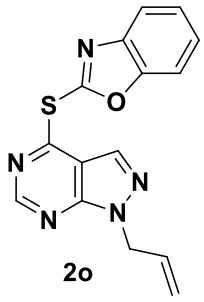


2m

the general procedure affording the **2m** as a white solid. 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.21 (s, 1H), 7.84 – 7.77 (m, 1H), 7.59 – 7.51 (m, 1H), 7.45 – 7.34 (m, 2H), 4.46 (t, *J* = 4.8 Hz, 2H), 3.84 (t, *J* = 4.8 Hz, 2H), 3.63 – 3.56 (m, 2H), 3.52 – 3.44 (m, 2H), 3.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.02, 155.38, 152.75, 151.99, 150.18, 145.67, 141.99, 131.62, 125.97, 124.71, 120.45, 110.80, 71.77, 70.57, 68.93, 59.01, 43.84. HRMS (ESI) m/z calcd for $C_{17}H_{18}N_5O_3S^+$ $[M+H]^+$ 372.1125, found 372.1109.

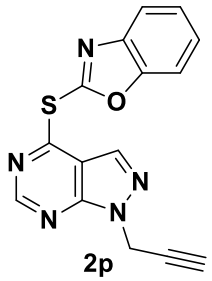


N-(3-(6-(benzo[*d*]oxazol-2-ylthio)-9*H*-purin-9-yl)propyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (2n): S-5 was synthesized according to the general procedure. Then **S-5** (85.3 mg, 0.2 mmol) was dissolved in DCM (3 mL), added with TFA (1 mL) and the reactant stirred in room temperature for 1h. Reaction mixture concentrated under reduced pressure without further purification. The residue dissolved in DMF (2 mL), followed by adding with DIEA (3 eq), D-biotin (1.2 eq) and HATU (1.2 eq), the reactant stirred in room temperature for 2h. The reactant was diluted with water (20 mL) and extracted by DCM (3 × 20 mL). The combine organic phase was concentrated under reduced pressure and purified by silica gel (200−300 mesh) column chromatography to afford the desired compound **2n** as a white solid. 56% yield for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.25 (s, 1H), 7.81 – 7.71 (m, 1H), 7.59 – 7.51 (m, 1H), 7.45 – 7.33 (m, 2H), 7.23 (t, *J* = 5.6 Hz, 1H), 6.91 (s, 1H), 6.12 (s, 1H), 4.54 – 4.41 (m, 1H), 4.35 – 4.24 (m, 3H), 3.30 – 3.16 (m, 2H), 3.14 – 3.06 (m, 1H), 2.86 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.67 (d, *J* = 12.8 Hz, 1H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.78 – 1.53 (m, 2H), 1.44 – 1.34 (m, 2H), 1.33 – 1.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.87, 164.39, 155.71, 155.50, 152.71, 151.93, 150.30, 145.36, 141.82, 131.69, 126.19, 124.87, 120.35, 110.91, 61.83, 60.17, 55.87, 41.88, 40.66, 36.11, 35.89, 29.93, 28.27, 28.03, 25.67. HRMS (ESI) m/z calcd for $C_{25}H_{29}N_8O_3S_2^+$ $[M+H]^+$ 553.1799, found 553.1800.

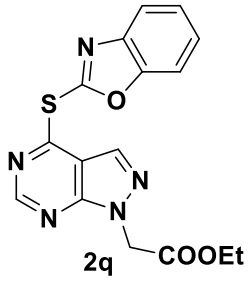


2o

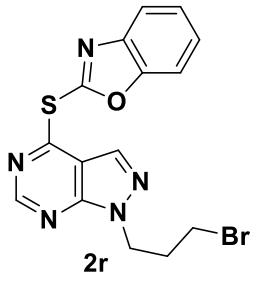
2-((1-allyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio)benzo[*d*] oxazole (2o): According to the general procedure affording the **2m** as a white solid. 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.93 – 7.78 (m, 1H), 7.65 (s, 1H), 7.62 – 7.54 (m, 1H), 7.52 – 7.34 (m, 2H), 6.25 – 5.94 (m, 1H), 5.33 – 5.16 (m, 2H), 5.12 – 5.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.83, 155.02, 154.29, 152.60, 151.87, 141.75, 131.70, 131.50, 126.63, 125.21, 120.73, 118.93, 112.58, 111.02, 49.80. HRMS (ESI) m/z calcd for $C_{15}H_{12}N_5OS^+$ $[M+H]^+$ 310.0757, found 310.0746.



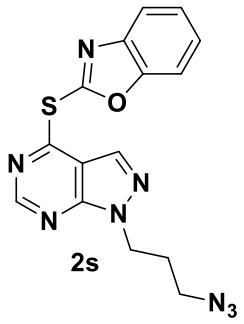
2-((1-(prop-2-yn-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio) benzo[*d*]oxazole (2p): According to the general procedure affording the **2p** as a white solid. 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.84 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.68 (s, 1H), 7.59 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.51 – 7.40 (m, 2H), 5.27 (d, *J* = 2.8 Hz, 2H), 2.41 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.18, 154.81, 154.56, 152.61, 151.89, 141.71, 132.18, 126.73, 125.28, 120.77, 112.70, 111.07, 76.29, 73.78, 36.95. HRMS (ESI) m/z calcd for $C_{15}H_{10}N_5OS^+$ $[M+H]^+$ 308.0601, found 308.0597.



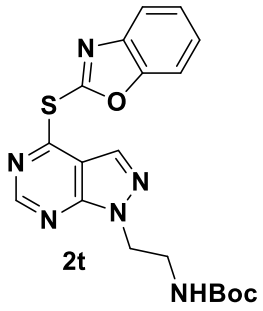
Ethyl 2-(4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo[3,4-*d*] pyrimidin-1-yl)acetate (2q): According to the general procedure affording the **2q** as a white solid. 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.88 – 7.81 (m, 1H), 7.72 (s, 1H), 7.63 – 7.56 (m, 1H), 7.49 – 7.38 (m, 2H), 5.24 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.98, 161.08, 154.84, 154.59, 152.85, 152.63, 141.75, 132.26, 126.66, 125.22, 120.75, 112.68, 111.05, 62.14, 48.44, 14.09. HRMS (ESI) m/z calcd for $C_{16}H_{14}N_5O_3S^+$ $[M+H]^+$ 356.0812, found 356.0803.



2-((1-(3-bromopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio) benzo[*d*]oxazole (2r): According to the general procedure affording the **2r** as a white solid. 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.86 – 7.80 (m, 1H), 7.64 (s, 1H), 7.63 – 7.56 (m, 1H), 7.50 – 7.40 (m, 2H), 4.65 (t, *J* = 6.4 Hz, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 2.50 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.94, 154.95, 154.32, 152.60, 152.12, 141.72, 131.52, 126.69, 125.26, 120.76, 112.55, 111.05, 45.72, 32.24, 29.59. HRMS (ESI) m/z calcd for $C_{15}H_{13}BrN_5OS^+$ $[M+H]^+$ 390.0019, found 390.0017.

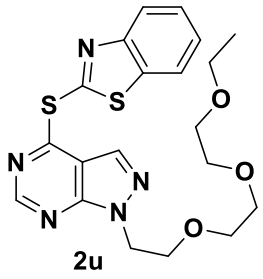


2-((1-(3-azidopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio) benzo[*d*]oxazole (2s): According to the general procedure affording the **2s** as a white solid. 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.93 – 7.76 (m, 1H), 7.65 (s, 1H), 7.62 – 7.54 (m, 1H), 7.53 – 7.37 (m, 2H), 4.58 (t, *J* = 6.8 Hz, 2H), 3.34 (t, *J* = 6.8 Hz, 2H), 2.19 (p, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.92, 154.96, 154.32, 152.60, 152.09, 141.74, 131.48, 126.66, 125.24, 120.74, 112.53, 111.03, 48.54, 44.58, 28.79. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_8O_3S^+$ $[M+H]^+$ 353.0928, found 353.0925.

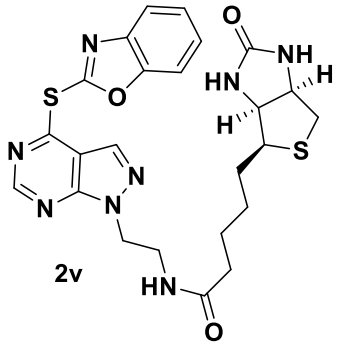


***tert*-Butyl (2-(4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)carbamate (2t):** According to the general procedure affording the **2t** as a white solid. 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.90 – 7.79 (m, 1H), 7.65 (s, 1H), 7.62 – 7.56 (m, 1H), 7.50 – 7.40 (m, 2H), 4.97 (s, 1H), 4.80 – 4.46 (t, *J* = 5.2 Hz, 2H), 3.75 – 3.57 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.81, 155.65, 154.95, 154.29, 152.57, 152.45, 141.69, 131.58,

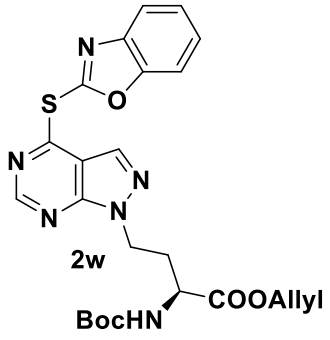
126.66, 125.23, 120.72, 112.54, 111.03, 79.62, 47.44, 40.16, 28.29 (s). HRMS (ESI) m/z calcd for $C_{19}H_{21}N_6O_3S^+$ $[M+H]^+$ 413.1390, found 413.1374.



2-((1-(2-(2-(2-ethoxyethoxy)ethoxy)ethyl)-1*H*-pyrazolo[3,4-*d*] pyrimidin-4-yl)thio)benzo[*d*]thiazole (2u): According to the general procedure affording the **2u** as a white solid. 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.91 – 7.77 (m, 1H), 7.65 (s, 1H), 7.62 – 7.55 (m, 1H), 7.50 – 7.37 (m, 2H), 4.66 (t, *J* = 5.6 Hz, 2H), 3.98 (t, *J* = 5.6 Hz, 2H), 3.63 – 3.58 (m, 2H), 3.57 – 3.44 (m, 8H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.62, 155.04, 154.19, 152.59, 152.45, 141.73, 131.37, 126.62, 125.20, 120.72, 112.55, 111.03, 70.65, 70.50, 70.42, 69.75, 68.87, 66.62, 47.13, 15.16. HRMS (ESI) m/z calcd for $C_{20}H_{24}N_5O_4S^+$ $[M+H]^+$ 430.1544, found 430.1542.

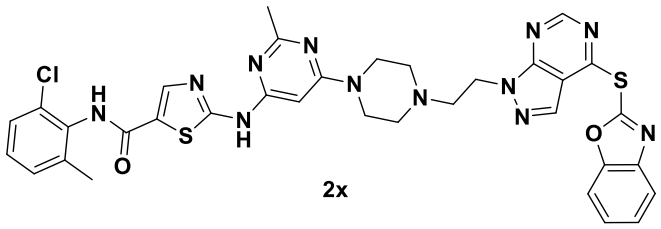


***N*-(2-(4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo[3,4-*d*] pyrimidin-1-yl)ethyl)-5-((3aS,4S,6aR)-2-oxohexahydro -1H-thieno[3,4-*d*]imidazol-4-yl)pentanamide (2v):** According to the general procedure affording the **2v** as a white solid. 39% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.88 – 7.82 (m, 1H), 7.68 (s, 1H), 7.64 – 7.56 (m, 1H), 7.53 – 7.39 (m, 2H), 6.72 (s, 1H), 6.56 (s, 1H), 6.19 (s, 1H), 4.65 – 4.48 (m, 3ZH), 4.43 – 4.36 (m, 1H), 3.29 – 3.05 (m, 3H), 2.93 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.76 (d, *J* = 12.8 Hz, 1H), 2.36 – 2.22 (m, 2H), 2.17 – 2.06 (m, 2H), 1.84 – 1.63 (m, 2H), 1.55 – 1.39 (m, 2H), 1.36 – 1.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.87, 164.69, 161.26, 154.77, 154.25, 152.61, 151.94, 141.62, 131.56, 126.80, 125.34, 120.72, 112.46, 111.09, 62.29, 60.69, 55.16, 44.79, 40.39, 36.39, 35.75, 28.94, 27.88, 27.80, 25.36. HRMS (ESI) m/z calcd for $C_{25}H_{29}N_8O_3S_2^+$ $[M+H]^+$ 553.1799, found 553.1803.



Allyl (S)-4-(4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo [3,4-*d*]pyrimidin-1-yl)-2-((*tert*-butoxycarbonyl)amino) butanoate (2w): According to the general procedure affording the **2w** as a white solid. 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.87 – 7.80 (m, 1H), 7.62 (s, 1H), 7.61 – 7.55 (m, 1H), 7.51 – 7.39 (m, 2H), 5.91 – 5.75 (m, 1H), 5.39 – 5.18 (m, 3H), 4.59 (t, *J* = 6.8 Hz, 2H), 4.53 – 4.46 (m, 2H), 4.44 – 4.33 (m, 1H), 2.60 – 2.46 (m, 1H), 2.44 – 2.28 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.30, 160.80, 155.31, 154.97, 154.20, 152.57, 152.01, 141.71, 131.45, 131.30, 126.64, 125.21, 120.71, 119.02, 112.57, 111.01, 80.17, 66.14, 51.36, 43.83, 31.73, 28.28. HRMS (ESI) m/z calcd for $C_{24}H_{27}N_6O_5S_2^+$ $[M+H]^+$ 511.1758, found 511.1746.

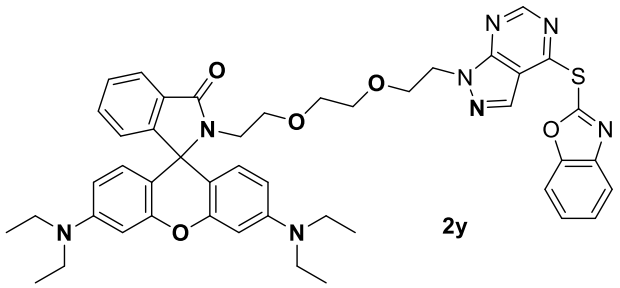
2-((6-(4-(2-(4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl) piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl) thiazole-5-carboxamide (2x):



2x

According to the general procedure affording the **2x** as a white solid. 58% yield. ^{1}H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 9.93 (s, 1H), 8.82 (s, 1H), 8.27 (s, 1H), 8.25 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.38 – 7.26 (m, 2H), 6.06 (s, 1H), 4.66 (t, *J* = 5.6 Hz, 2H), 3.47 – 3.40 (m, 4H), 2.90 (t, *J* = 5.6 Hz, 2H), 2.55 (s, 4H), 2.44 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 165.61, 163.01, 162.77, 160.50, 160.39, 157.38, 155.00, 154.69, 152.62, 152.14, 141.67, 141.30, 139.29, 133.99, 132.90, 131.98, 129.50, 128.64, 127.48, 127.34, 126.17, 125.82, 120.80, 112.09, 111.76, 83.10, 56.71, 52.37, 44.83, 43.94, 26.04, 18.78. HRMS (ESI) m/z calcd for $C_{34}H_{31}ClN_{12}O_2S_2^+$ $[M+H]^+$ 739.1896, found 739.1925.

2-(2-(2-(2-(4-(benzo[*d*]oxazol-2-ylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethoxy) ethoxy)ethyl)-3',6'-bis(diethylamino)spiro[isoindoline-1,9'-xanthen]-3-one (2y):

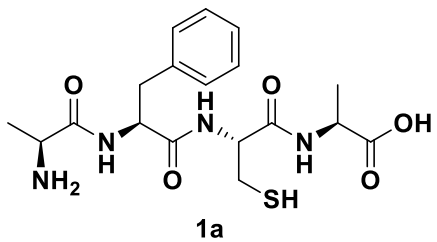


2y

According to the general procedure affording the **2x** as a pink solid. 52% yied. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.93 – 7.86 (m, 1H), 7.85 – 7.78 (m, 1H), 7.61 (s, 1H), 7.60 – 7.54 (m, 1H), 7.49 – 7.35 (m, 4ZH), 7.09 – 7.01 (m, 1H), 6.45 – 6.34 (m, 4H), 6.24 (dd, *J* = 8.8, 2.4 Hz, 2H), 4.59 (t, *J* = 5.7 Hz, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.46 – 3.41 (m, 2H), 3.36 – 3.24 (m, 12H), 3.11 (t, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.28, 160.47, 155.18, 154.16, 153.78, 153.25, 152.59, 152.39, 148.77, 141.75, 132.36, 131.33, 130.95, 128.84, 127.95, 126.57, 125.16, 123.76, 122.76, 120.67, 112.60, 111.03, 108.09 , 105.56, 97.82, 70.11, 69.94, 68.85, 67.84, 64.85, 47.09, 44.36, 39.27, 12.60. HRMS (ESI) m/z calcd for $C_{46}H_{49}N_8O_5S^+$ $[M+H]^+$ 824.3541, found 825.3559.

8. Arylation of cysteine-containing peptides/proteins

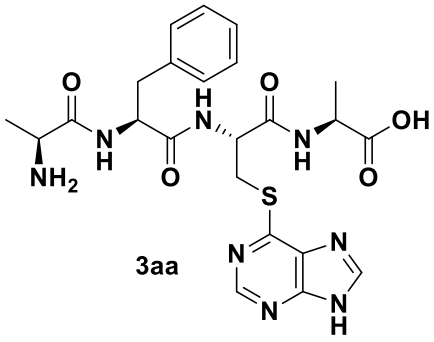
General procedure for arylation of cysteine-containing peptides: 1.0 μmol peptide (**1**) was dissolved in 990 μL non-degassed Tris buffer (100 mM, pH 8.0). Then, aryl thioether (**2**, 3.0 μmol) in DMSO was added. The resulting solution was vortexed and shaking at room temperature for 1h. After this time, the reaction was analyzed by HPLC-MS.



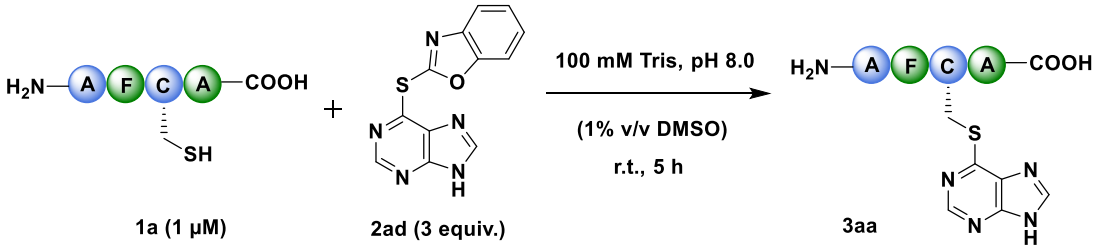
1a

According to the general procedure for peptide synthesis affording **1a** as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 8.60 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 7.2 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.33 – 7.17 (m, 5H), 4.67 – 4.55 (m, 1H), 4.49 – 4.39 (m, 1H), 4.27 – 4.12 (m, 1H), 3.82 – 3.68 (m, 1H), 3.07 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.88 – 2.65 (m, 3H), 2.25 (t, *J* = 8.4 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz,

DMSO) δ 174.15, 171.34, 169.87, 169.82, 137.73, 129.56, 128.72, 127.04, 54.74, 52.20, 48.23, 48.10, 40.47, 37.56, 17.46, 17.36. HRMS (ESI) m/z calcd for $C_{18}H_{27}N_4O_5S^+$ $[M+H]^+$ 411.1697, found 411.1679.



According to the general procedure for arylation of cysteine containing peptides affording **3aa** as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 8.71 (s, 1H), 8.60 (d, *J* = 8.0 Hz, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.46 (s, 1H), 8.33 (d, *J* = 7.2 Hz, 1H), 8.01 (d, *J* = 4.4 Hz, 2H), 7.33 – 7.11 (m, 5H), 4.75 – 4.64 (m, 1H), 4.63 – 4.54 (m, 1H), 4.30 – 4.15 (m, 1H), 3.90 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.81 – 3.71 (m, 1H), 3.51 (dd, *J* = 13.2, 9.2 Hz, 1H), 3.06 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.75 (dd, *J* = 14.0, 9.6 Hz, 1H), 1.32 (d, *J* = 4.8 Hz, 3H), 1.30 (d, *J* = 5.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 174.17, 171.27, 169.99, 169.73, 158.83, 158.48, 151.94, 143.85, 137.99, 129.61, 128.63, 126.89, 117.98, 54.72, 52.29, 48.43, 48.21, 37.70, 30.81, 17.68. HRMS (ESI) m/z calcd for $C_{23}H_{29}N_8O_5S^+$ $[M+H]^+$ 529.1976, found 529.1992.



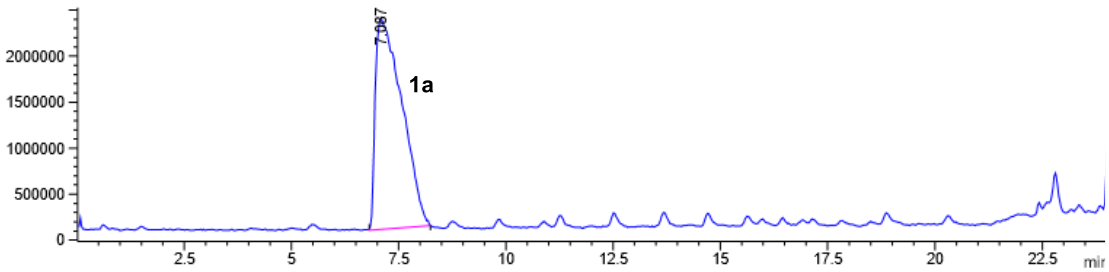


Figure S3. LC-MS TIC curve of peptide **1a**. Gradient used： Method A

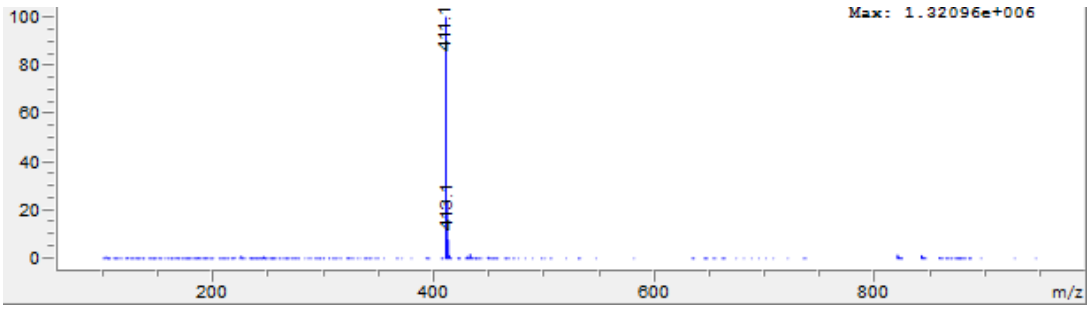


Figure S4. ESI Mass spectrum of peptide **1a**. Calculated Mass $[M+H]^+$: 411.2; Mass Found (ESI+); $[M+H]^+$: 411.1.

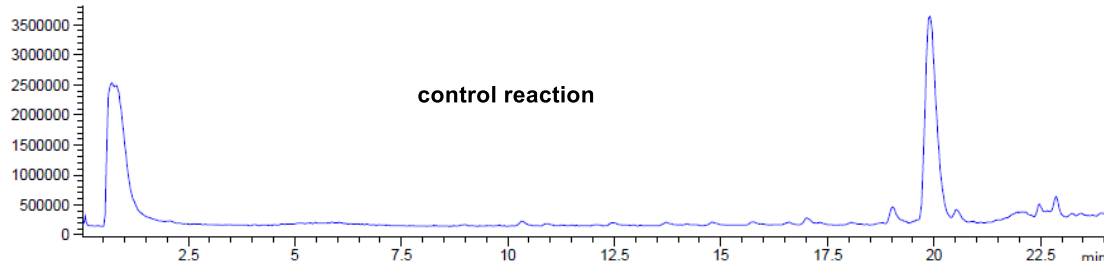


Figure S5. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

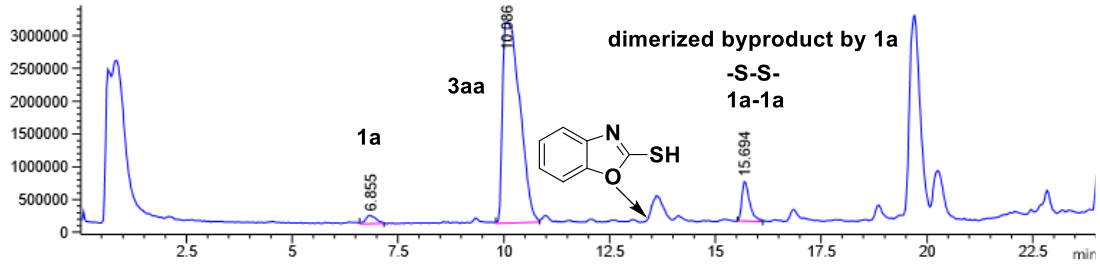


Figure S6. LC-MS TIC curve of reaction mixture. Gradient used： Method A

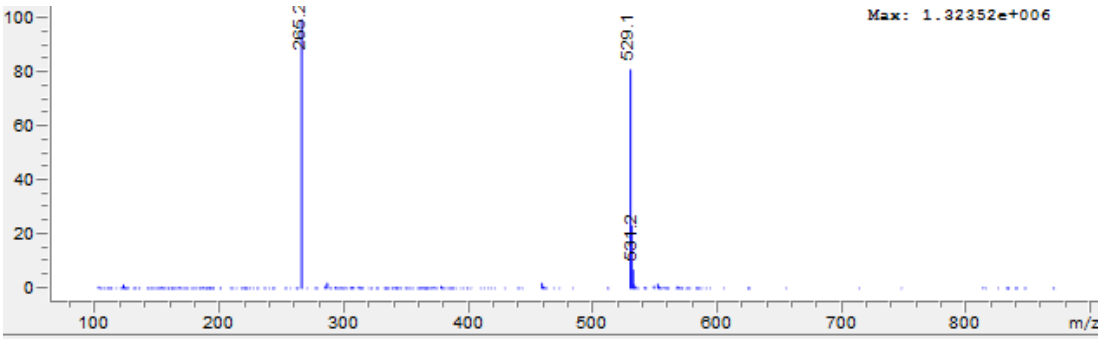


Figure S7. ESI Mass spectrum of modified product **3aa**. Calculated Mass $[M+H]^+$: 529.2; $[M+2H]^{2+}$: 265.1; Mass Found (ESI+); $[M+H]^+$: 529.1; $[M+2H]^{2+}$: 265.1.

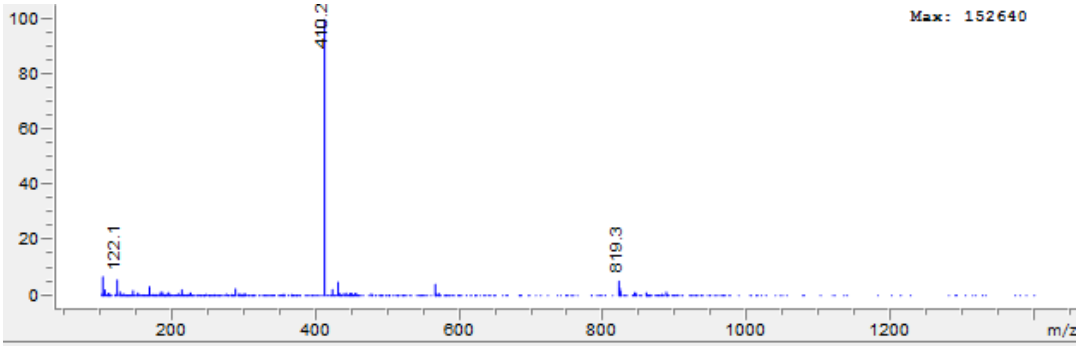
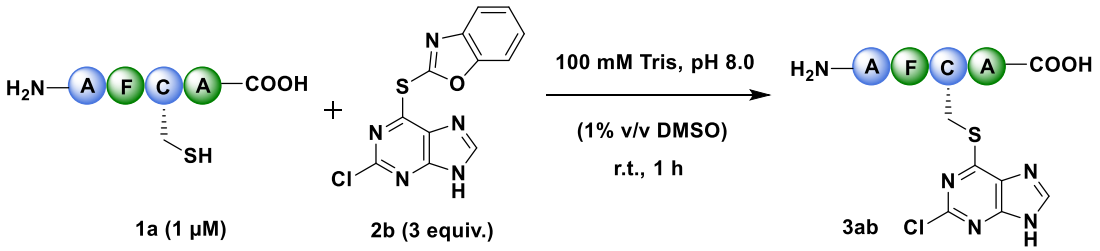


Figure S8. ESI Mass spectrum of dimerized byproduct by peptide **1a**. Calculated Mass $[M+H]^+$: 819.3; $[M+2H]^{2+}$: 410.2; Mass Found (ESI+); $[M+H]^+$: 819.3; $[M+2H]^{2+}$: 410.2.



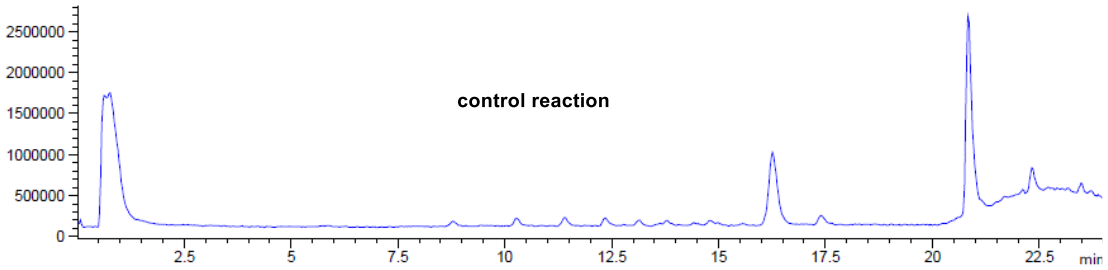


Figure S9. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

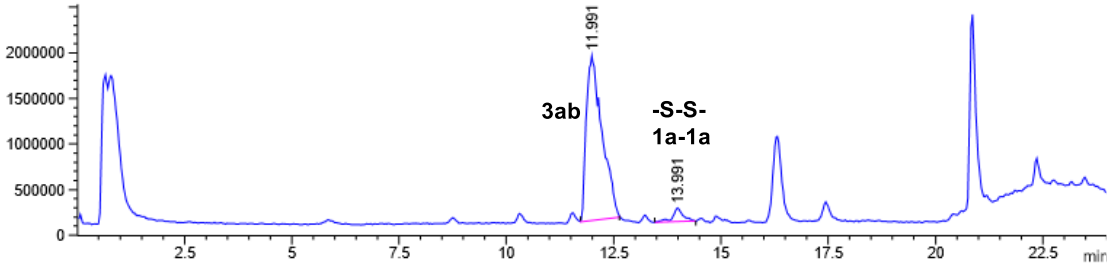


Figure S10. LC-MS TIC curve of reaction mixture. Gradient used： Method A

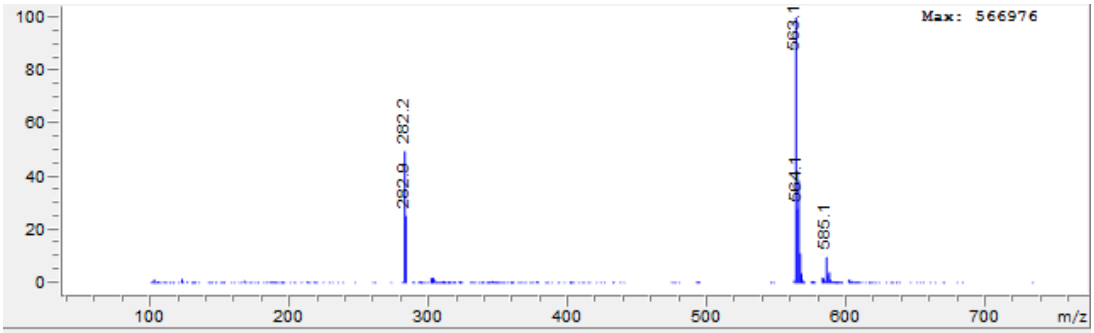
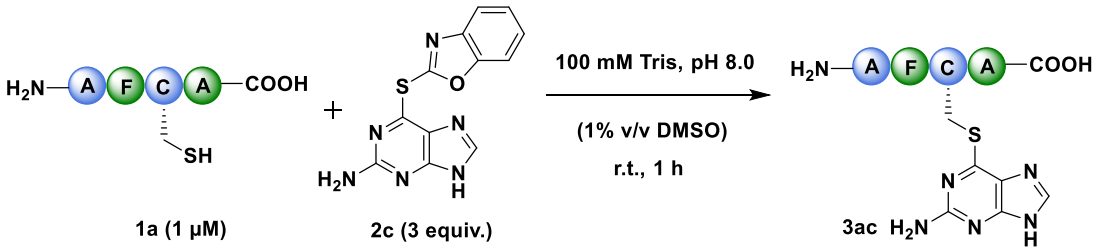


Figure S11. ESI Mass spectrum of modified product **3ab**. Calculated Mass $[M+H]^+$: 563.2; $[M+2H]^{2+}$: 282.1; Mass Found (ESI+); $[M+H]^+$: 563.1; $[M+2H]^{2+}$: 282.2.



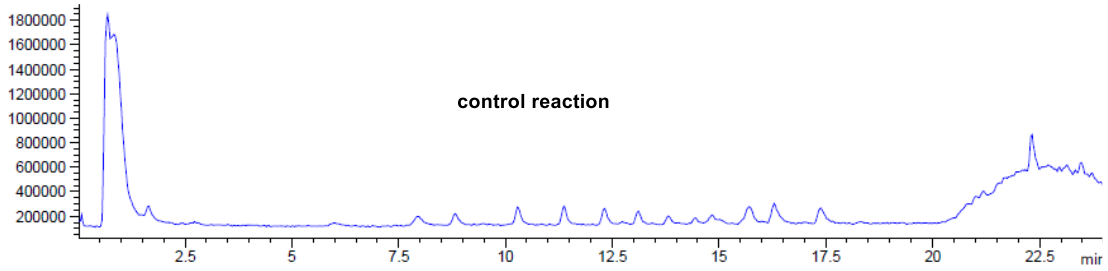


Figure S12. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

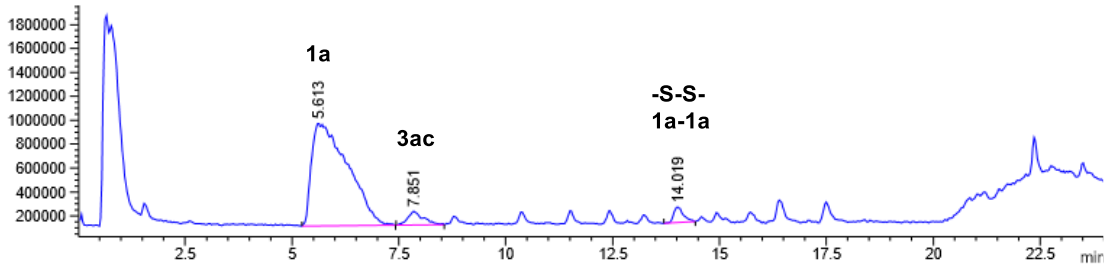


Figure S13. LC-MS TIC curve of reaction mixture. Gradient used： Method A

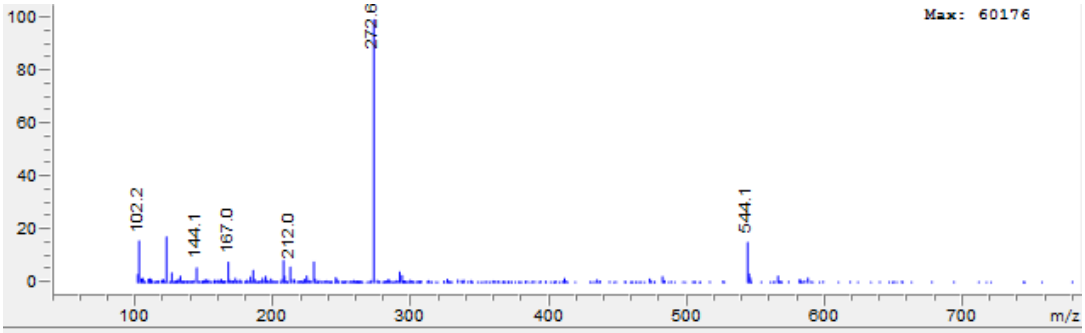
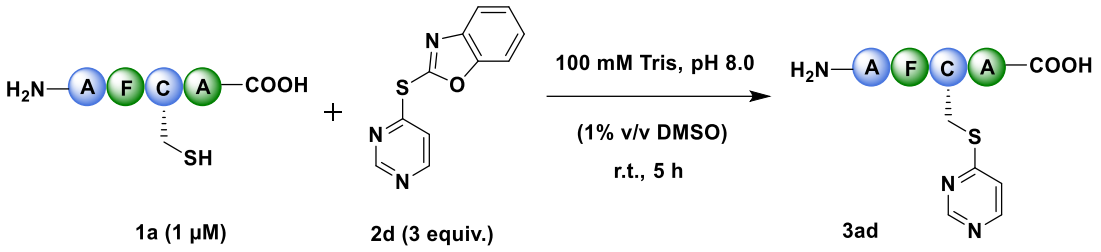


Figure S14. ESI Mass spectrum of modified product **3ac**. Calculated Mass $[M+H]^+$: 544.2; $[M+2H]^{2+}$: 272.6; Mass Found (ESI+); $[M+H]^+$: 544.1; $[M+2H]^{2+}$: 272.6.



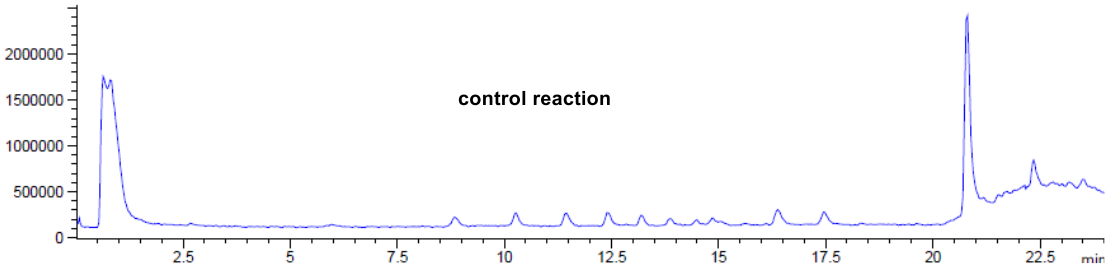


Figure S15. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

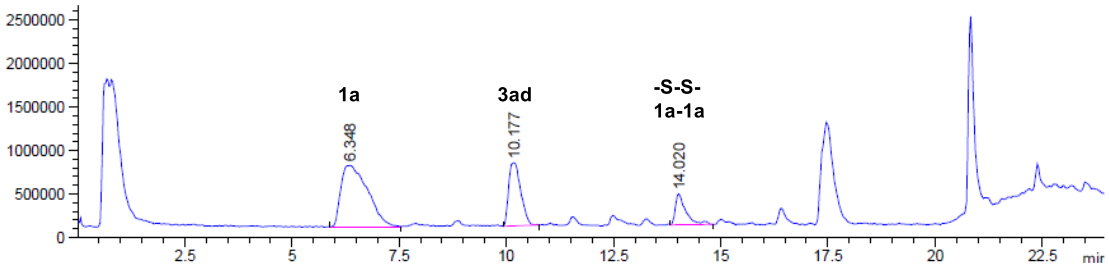


Figure S16. LC-MS TIC curve of reaction mixture. Gradient used： Method A

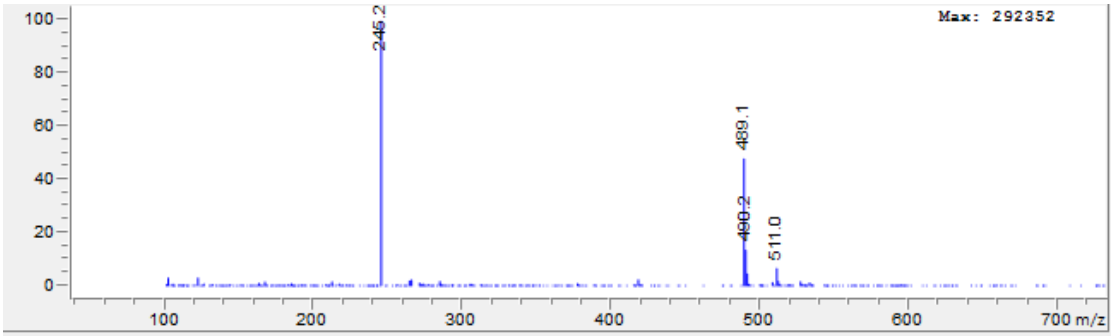
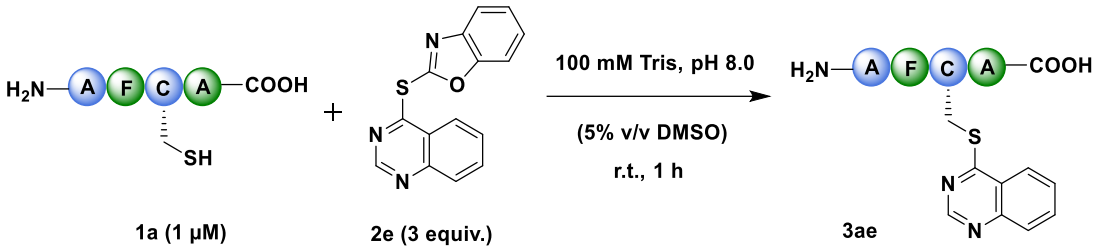


Figure S17. ESI Mass spectrum of modified product **3ad**. Calculated Mass $[M+H]^+$: 489.2; $[M+2H]^{2+}$: 245.1; Mass Found (ESI+); $[M+H]^+$: 489.1; $[M+2H]^{2+}$: 245.2.



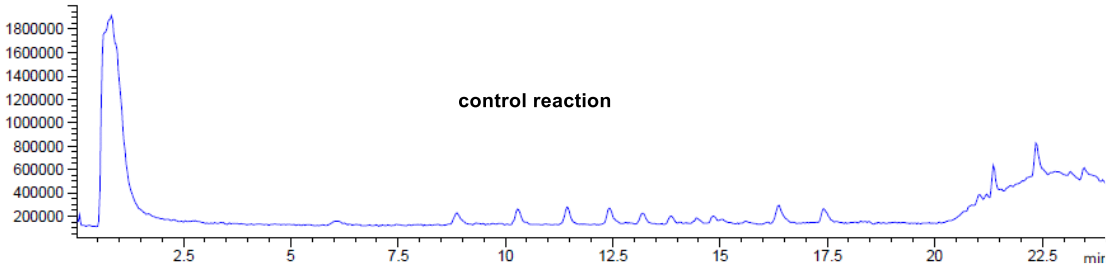


Figure S18. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

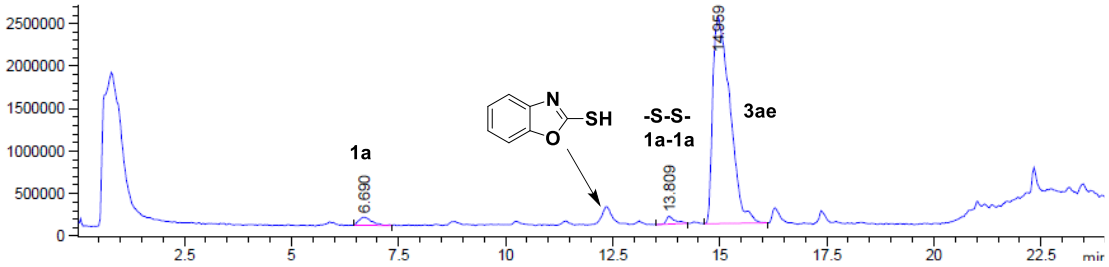


Figure S19. LC-MS TIC curve of reaction mixture. Gradient used： Method A

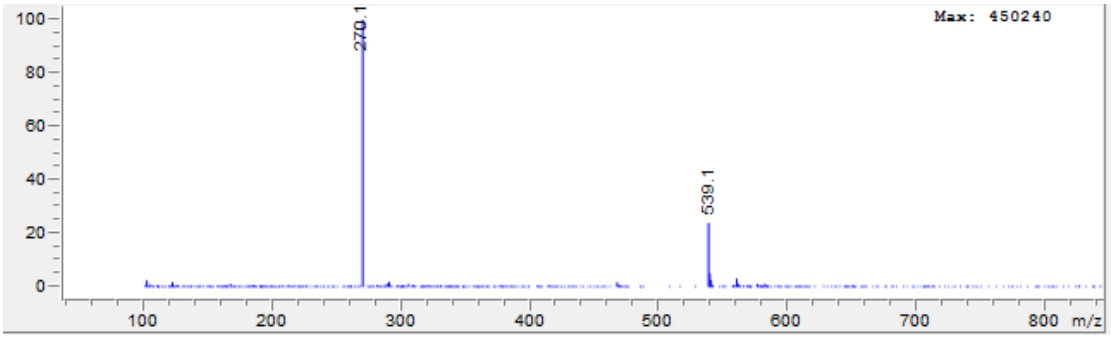
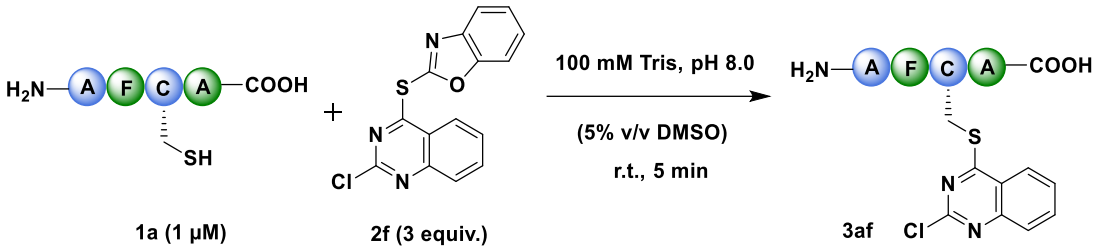


Figure S20. ESI Mass spectrum of modified product **3ae**. Calculated Mass $[M+H]^+$: 539.2; $[M+2H]^{2+}$: 270.1; Mass Found (ESI+); $[M+H]^+$: 539.1; $[M+2H]^{2+}$: 270.1.



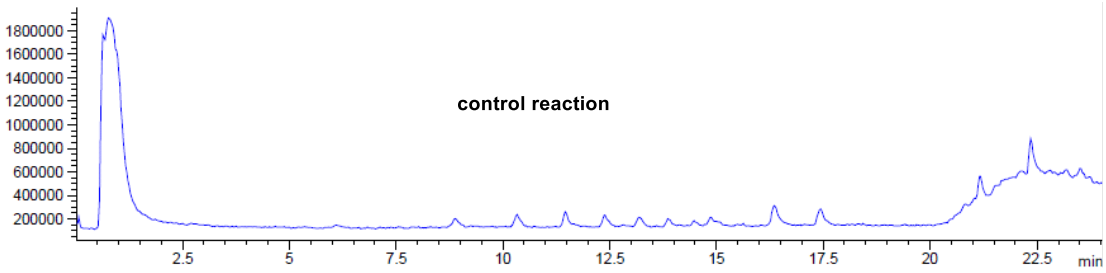


Figure S21. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

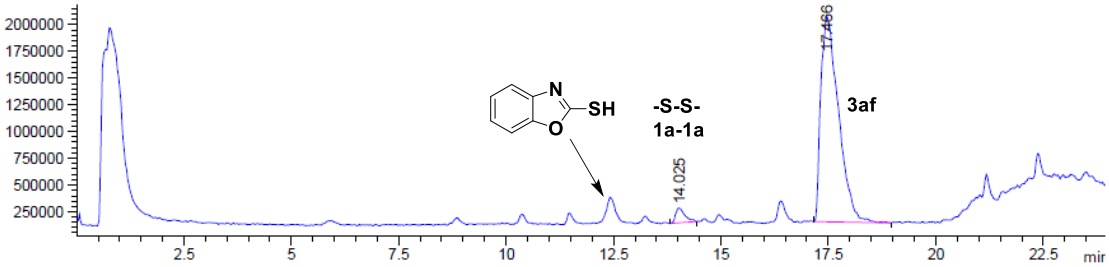


Figure S22. LC-MS TIC curve of reaction mixture. Gradient used： Method A

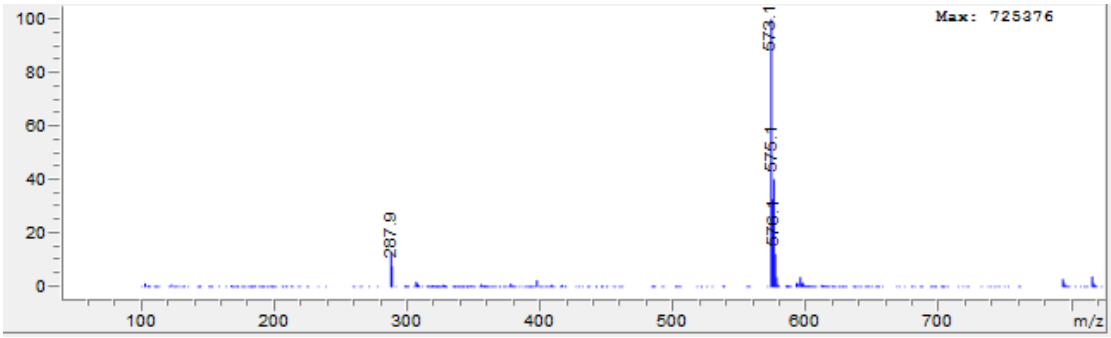


Figure S23. ESI Mass spectrum of modified product **3af**. Calculated Mass $[M+H]^+$: 573.2; $[M+H]^+$: 573.1.

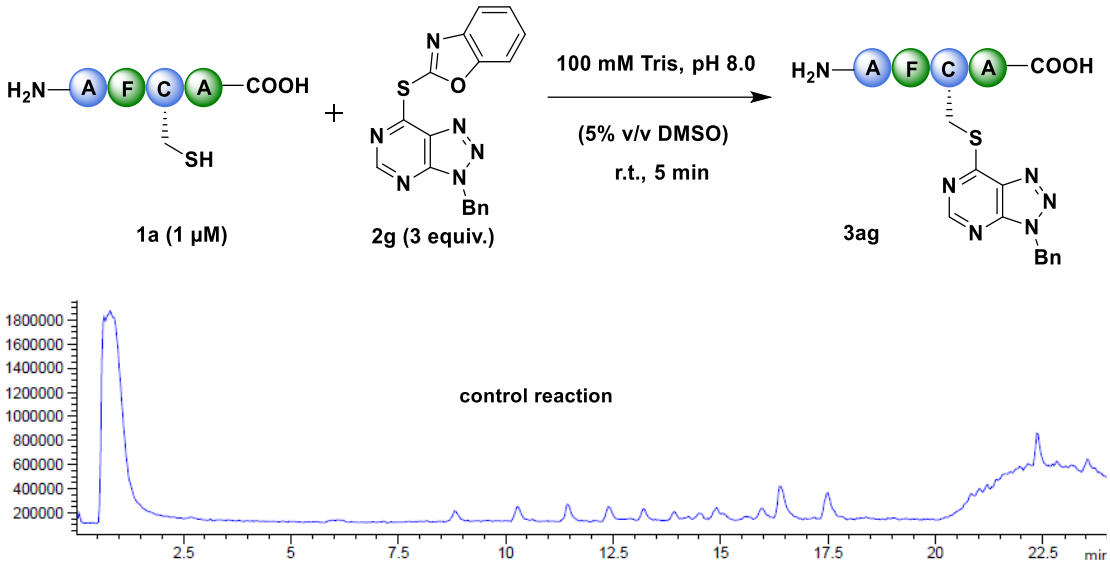


Figure S24. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

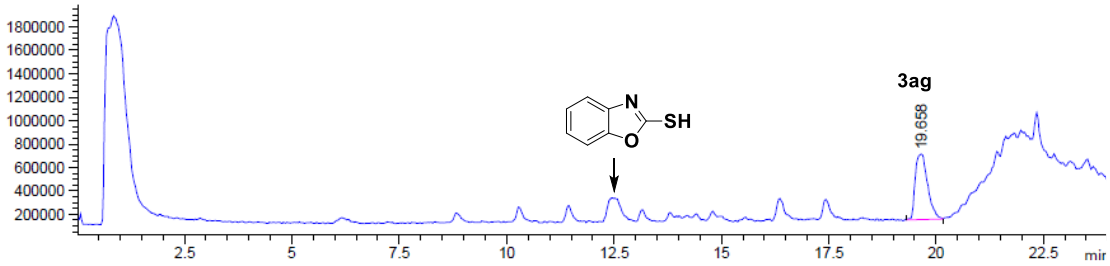


Figure S25. LC-MS TIC curve of reaction mixture. Gradient used： Method A

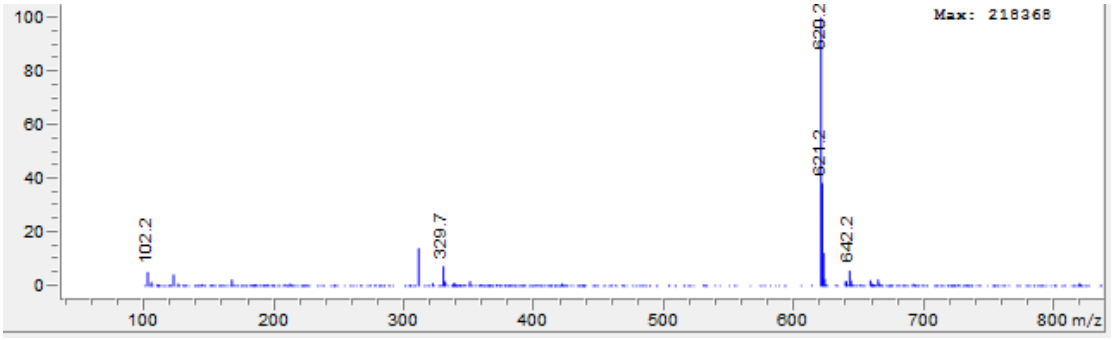
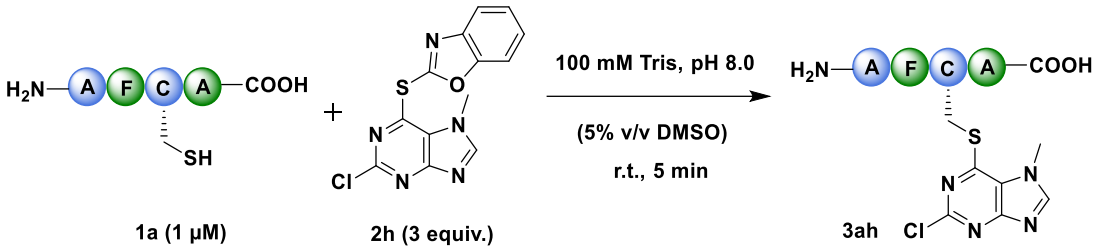


Figure S26. ESI Mass spectrum of modified product **3ag**. Calculated Mass $[M+H]^+$: 620.2; Mass Found (ESI+); $[M+H]^+$: 620.2.



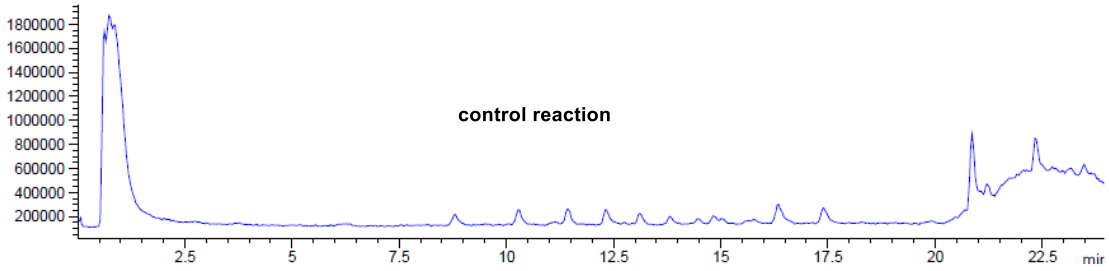


Figure S27. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

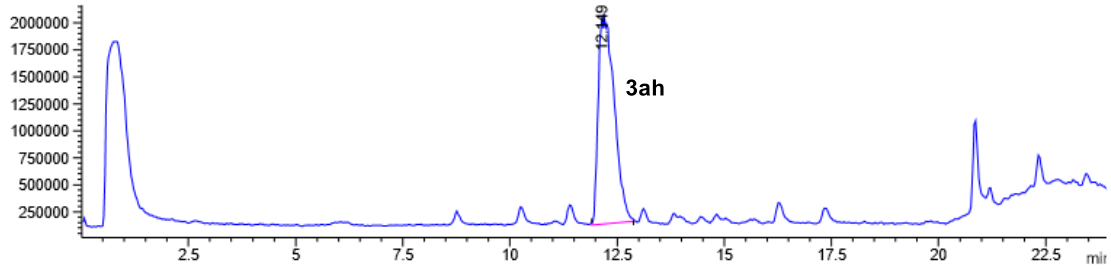


Figure S28. LC-MS TIC curve of reaction mixture. Gradient used： Method A

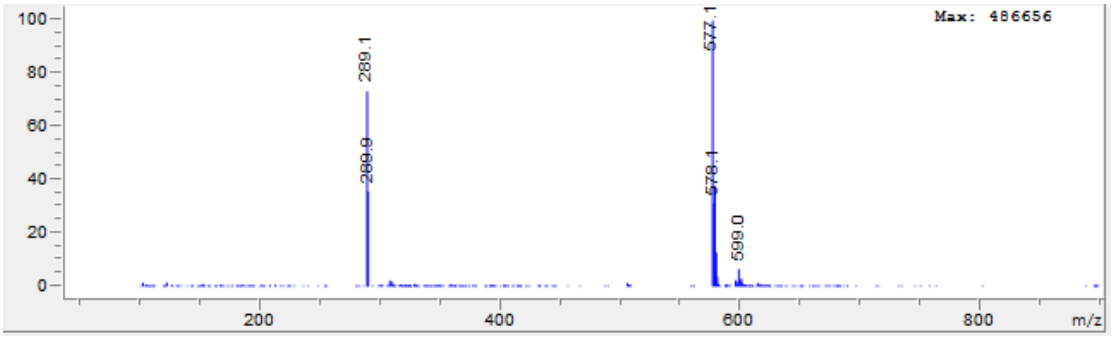
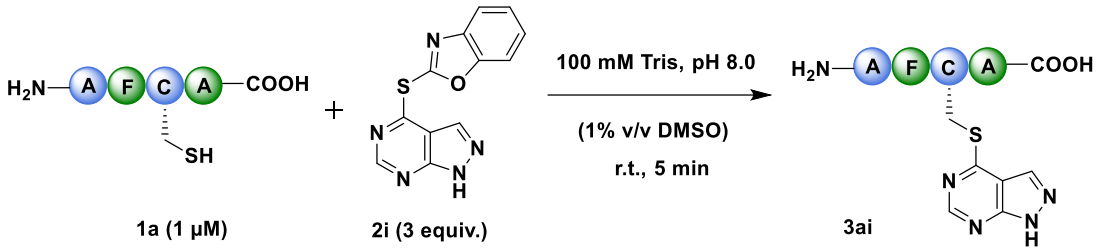


Figure S29. ESI Mass spectrum of modified product **3ah**. Calculated Mass $[M+H]^+$: 577.2; $[M+2H]^{2+}$: 289.1; Mass Found (ESI+); $[M+H]^+$: 577.1; $[M+2H]^{2+}$: 289.1.



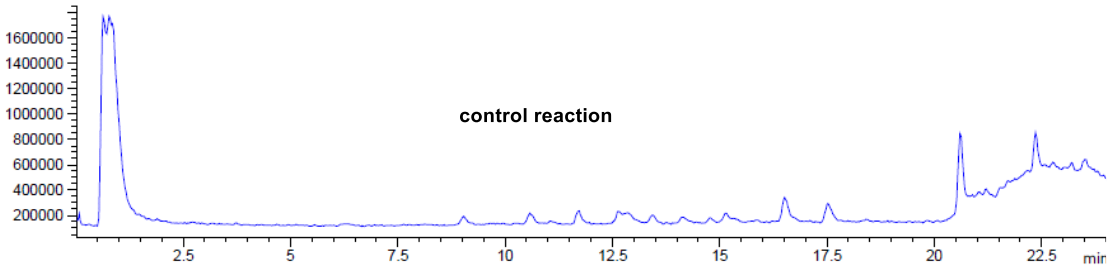


Figure S30. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

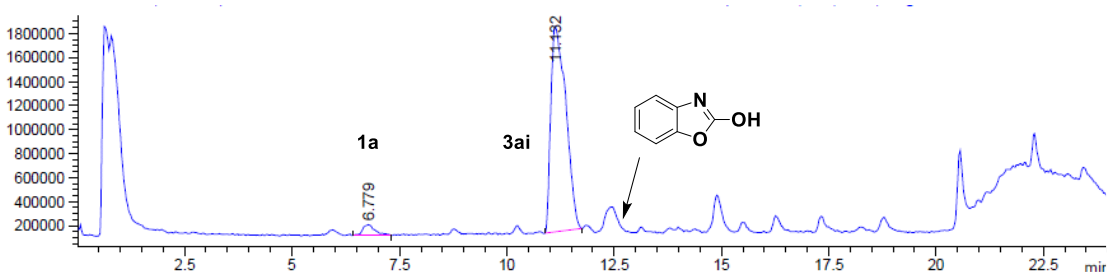


Figure S31. LC-MS TIC curve of reaction mixture. Gradient used： Method A

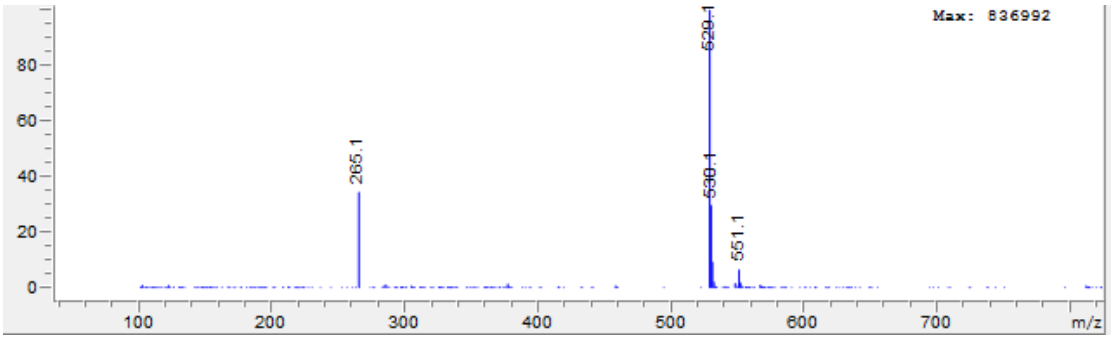
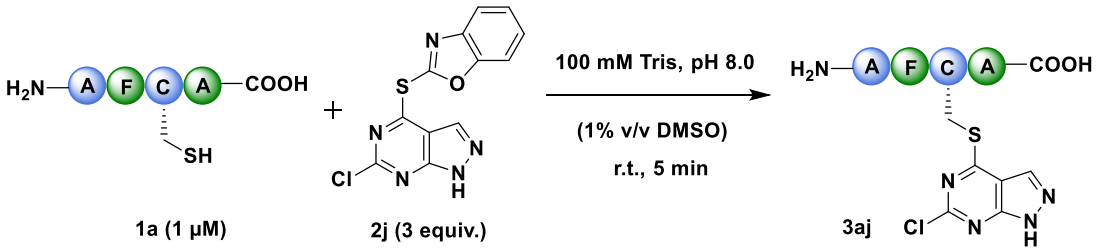


Figure S32. ESI Mass spectrum of modified product **3ai**. Calculated Mass $[M+H]^+$: 529.2; $[M+2H]^{2+}$: 265.1; Mass Found (ESI+); $[M+H]^+$: 529.1; $[M+2H]^{2+}$: 265.1.



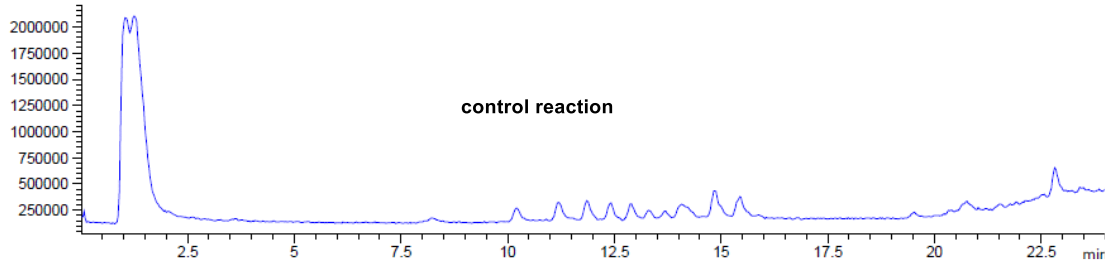


Figure S33. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

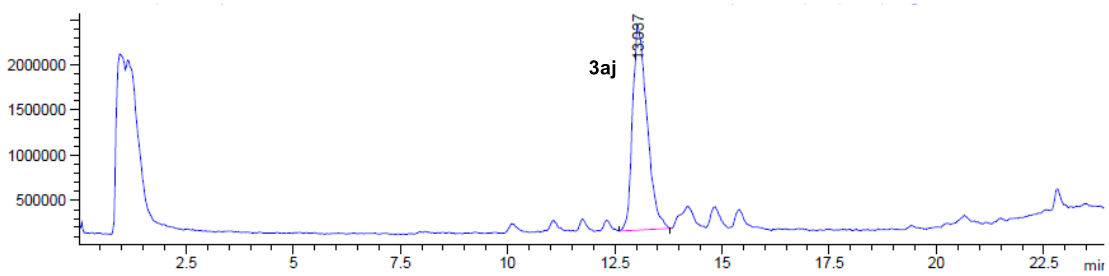


Figure S34. LC-MS TIC curve of reaction mixture. Gradient used： Method A

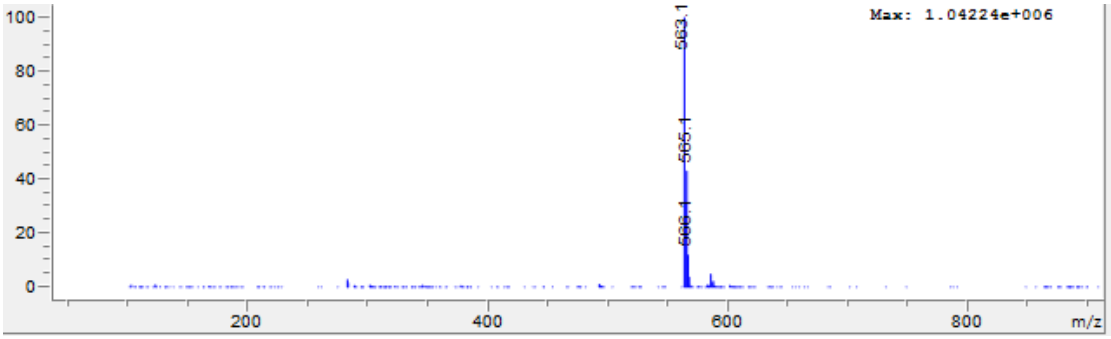
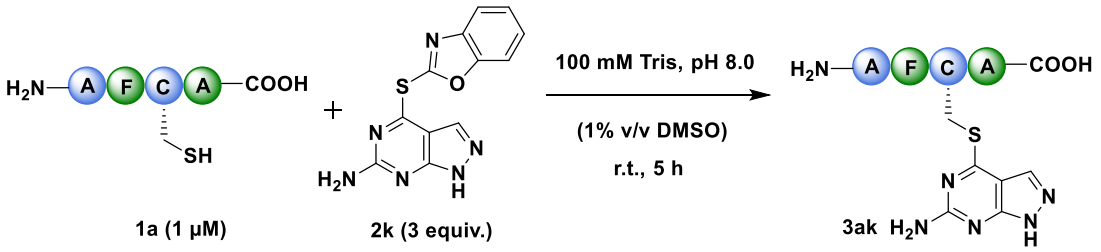


Figure S35. ESI Mass spectrum of modified product **3aj**. Calculated Mass $[M+H]^+$: 563.2; Mass Found (ESI+); $[M+H]^+$: 563.1.



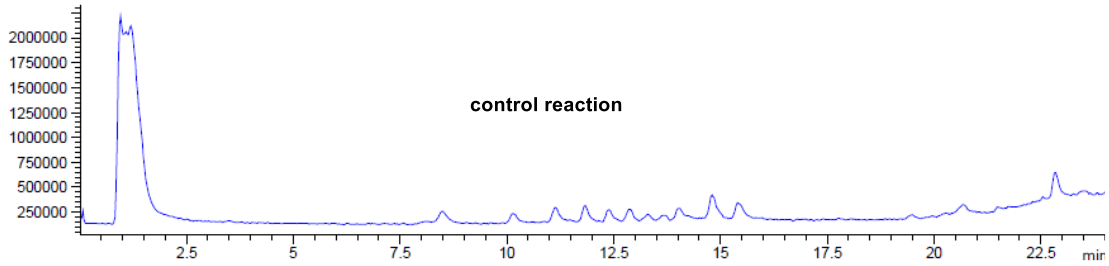


Figure S36. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

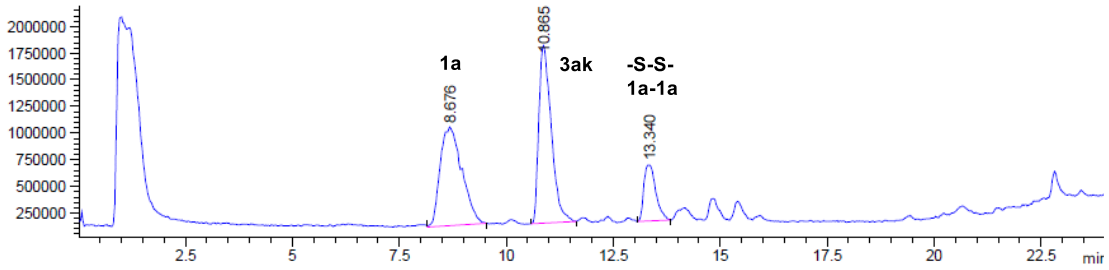


Figure S37. LC-MS TIC curve of reaction mixture. Gradient used： Method A

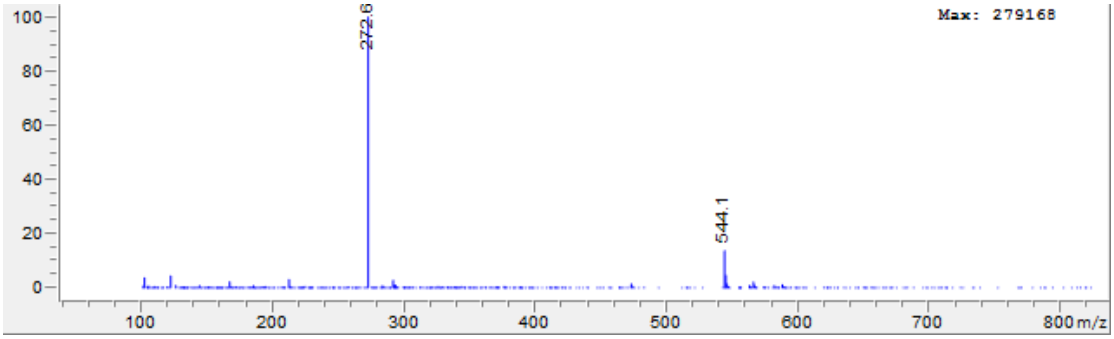
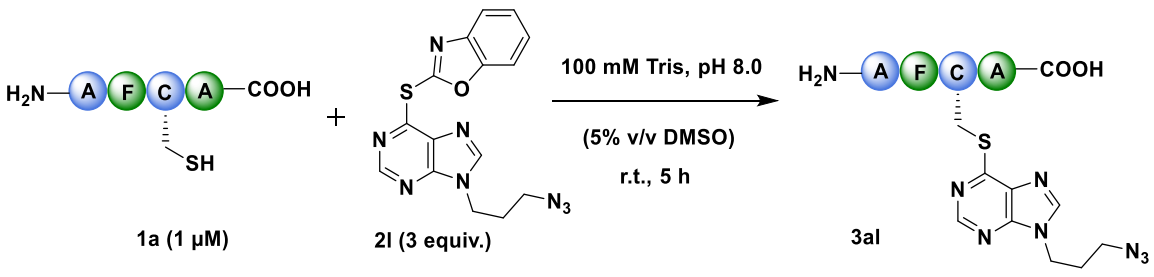


Figure S38. ESI Mass spectrum of modified product **3ak**. Calculated Mass $[M+H]^+$: 544.2; $[M+2H]^{2+}$: 272.6; Mass Found (ESI+); $[M+H]^+$: 544.1; $[M+2H]^{2+}$: 272.6.



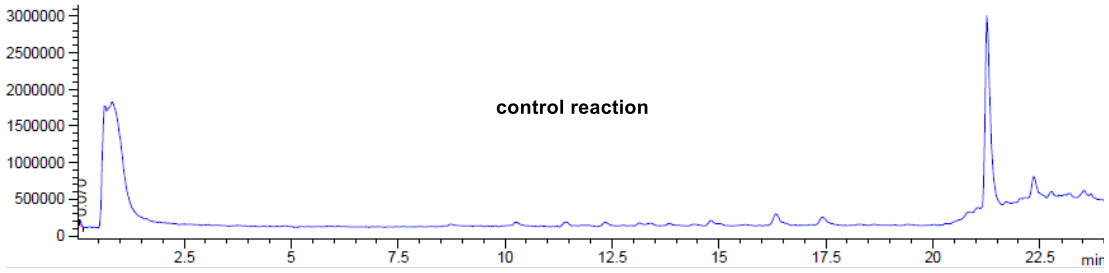


Figure S39. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

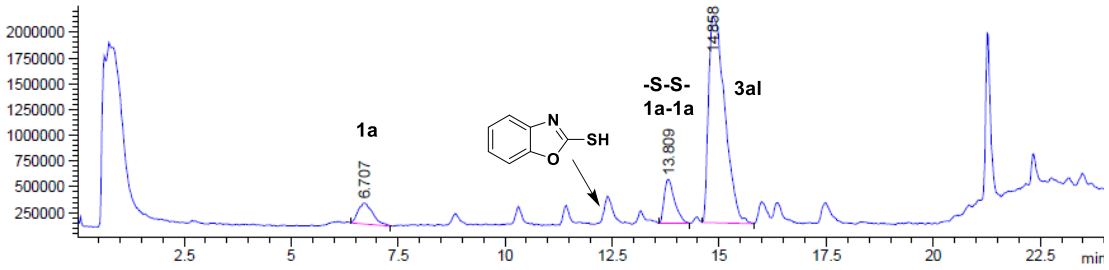


Figure S40. LC-MS TIC curve of reaction mixture. Gradient used： Method A

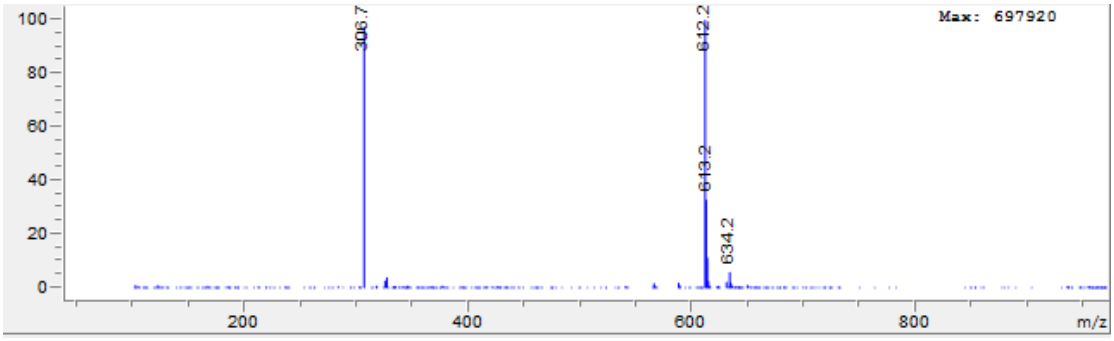
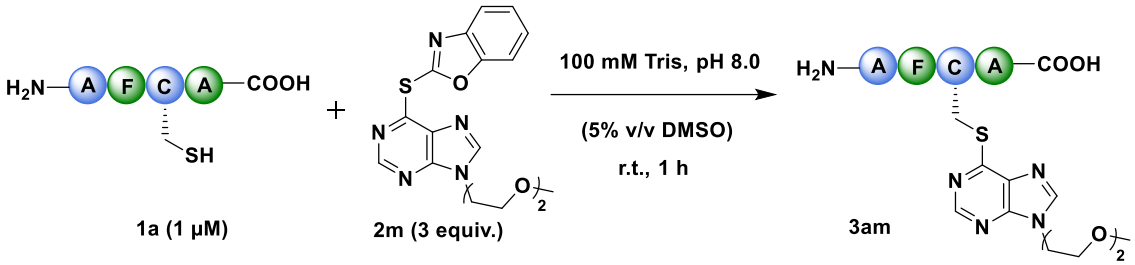


Figure S41. ESI Mass spectrum of modified product **3al**. Calculated Mass $[M+H]^+$: 612.2; $[M+2H]^{2+}$: 306.6; Mass Found (ESI+); $[M+H]^+$: 612.2; $[M+2H]^{2+}$: 306.7.



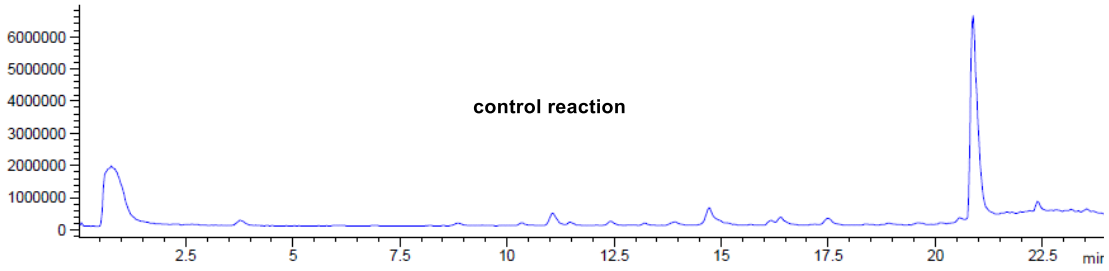


Figure S42. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

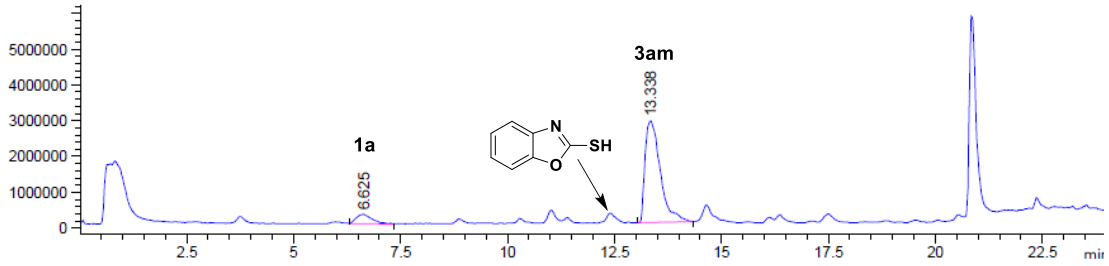


Figure S43. LC-MS TIC curve of reaction mixture. Gradient used： Method A

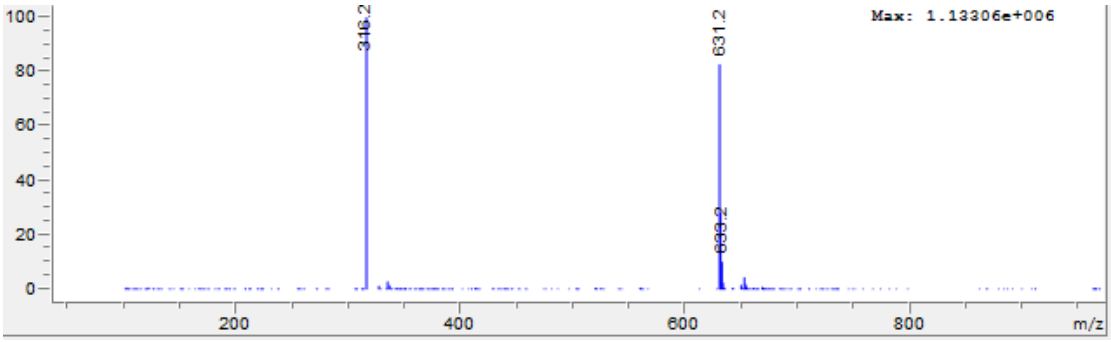
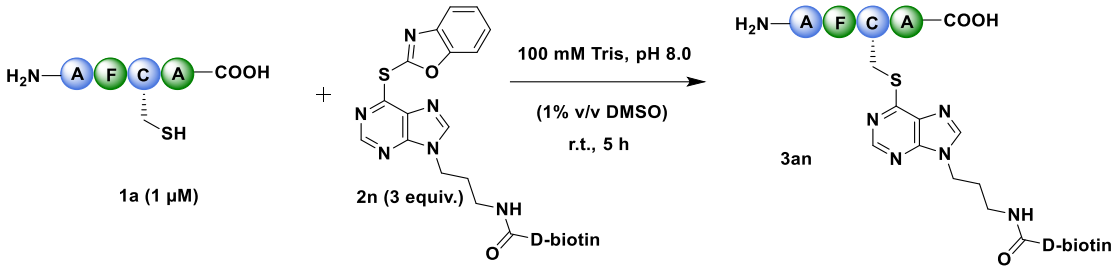


Figure S44. ESI Mass spectrum of modified product **3am**. Calculated Mass $[M+H]^+$: 631.3; $[M+2H]^{2+}$: 316.1; Mass Found (ESI+); $[M+H]^+$: 631.2; $[M+2H]^{2+}$: 316.2.



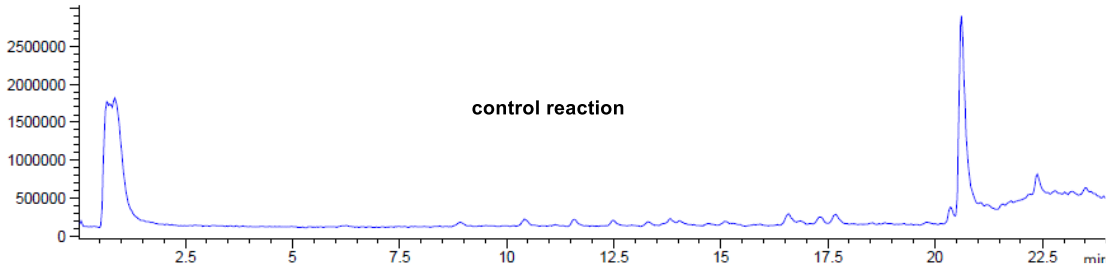


Figure S45. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

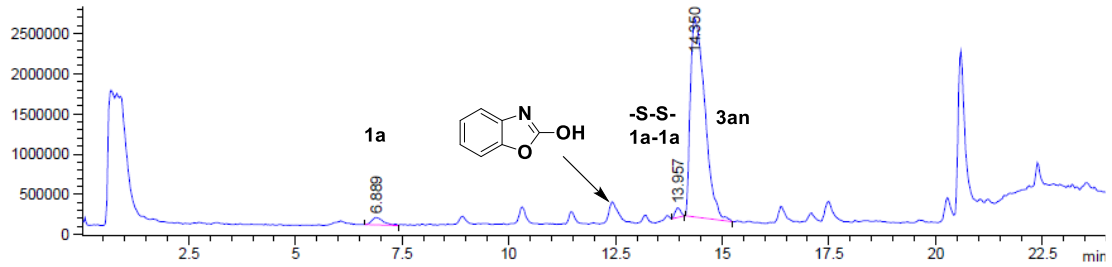


Figure S46. LC-MS TIC curve of reaction mixture. Gradient used： Method A

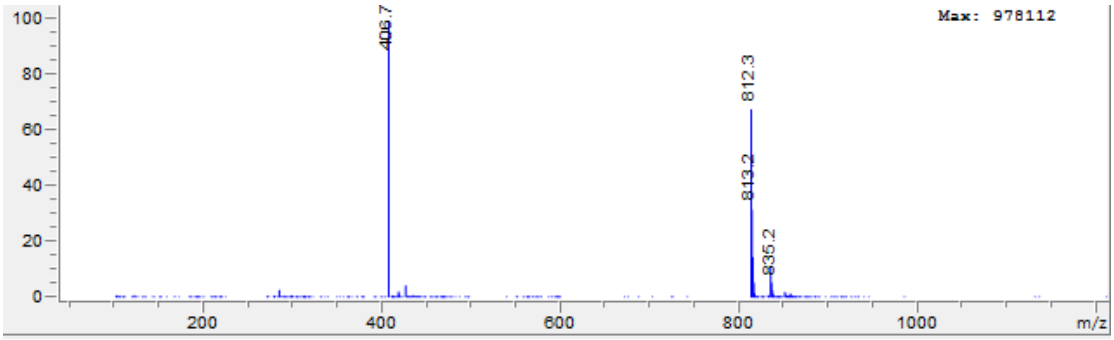
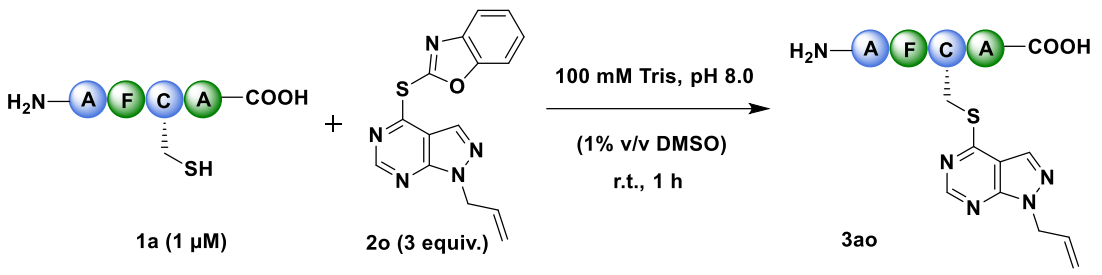


Figure S47. ESI Mass spectrum of modified product **3an**. Calculated Mass $[M+H]^+$: 812.3; $[M+2H]^{2+}$: 406.7; Mass Found (ESI+); $[M+H]^+$: 812.3; $[M+2H]^{2+}$: 406.7.



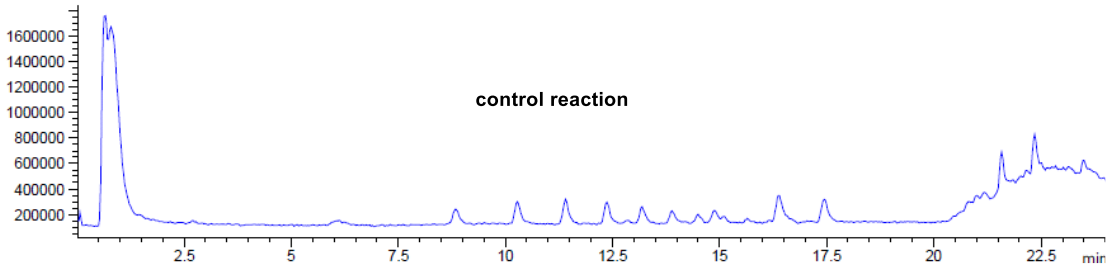


Figure S48. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

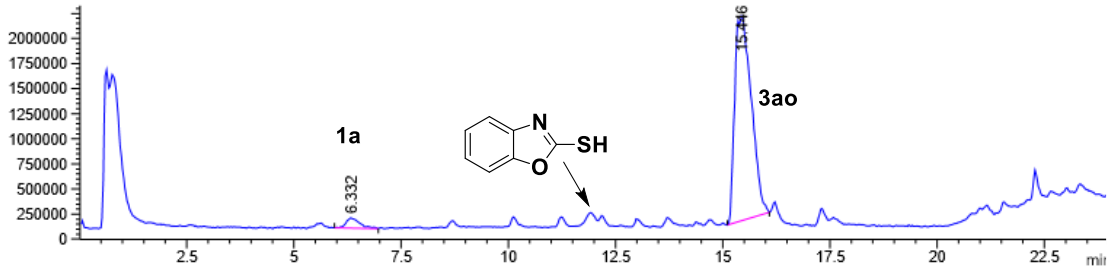


Figure S49. LC-MS TIC curve of reaction mixture. Gradient used： Method A

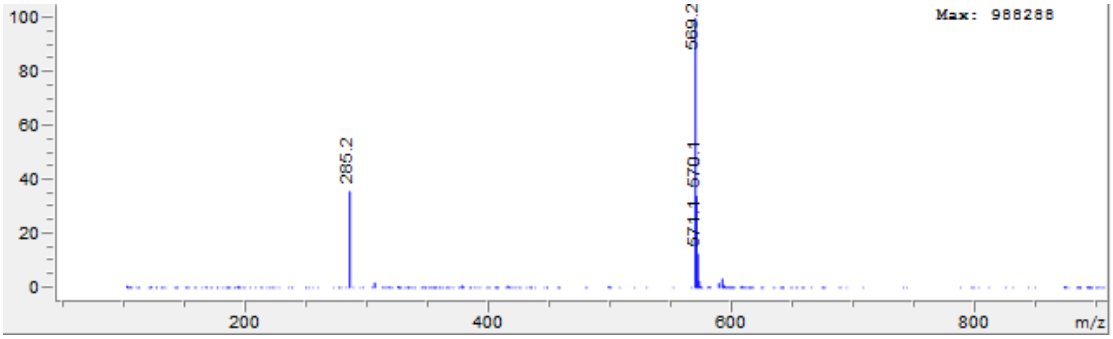
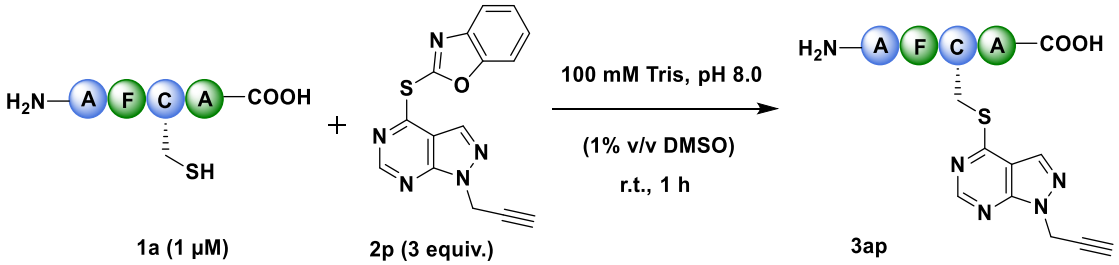


Figure S50. ESI Mass spectrum of modified product **3ao**. Calculated Mass $[M+H]^+$: 569.2; $[M+2H]^{2+}$: 285.1; Mass Found (ESI+); $[M+H]^+$: 569.2; $[M+2H]^{2+}$: 285.2.



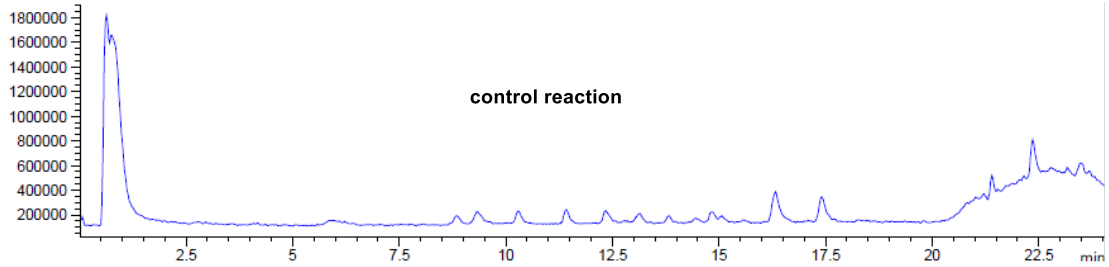


Figure S51. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

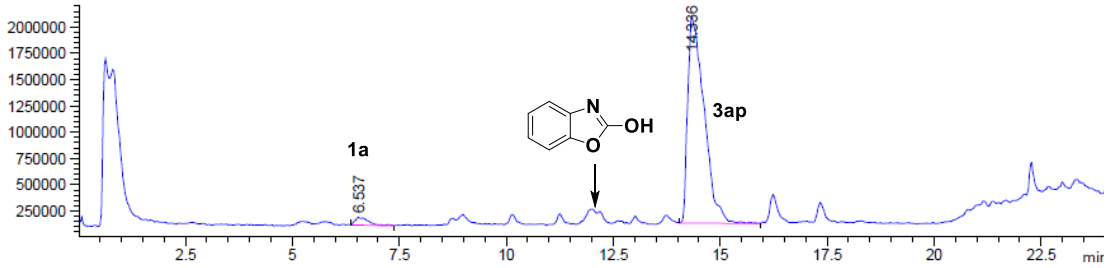


Figure S52. LC-MS TIC curve of reaction mixture. Gradient used： Method A

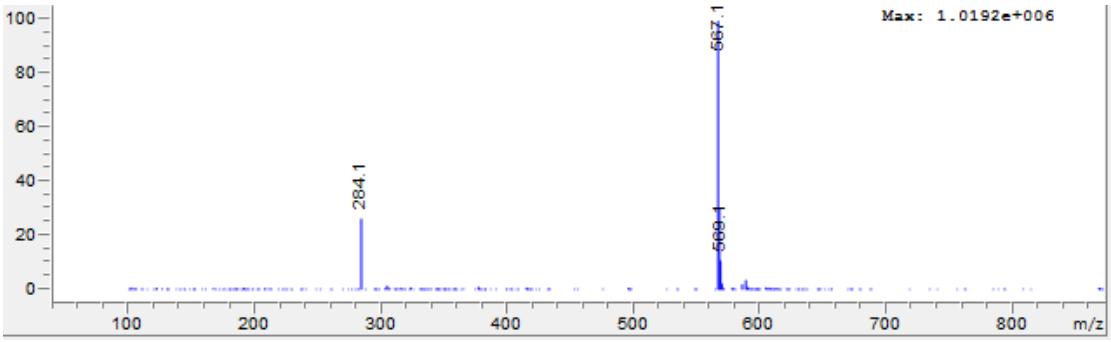
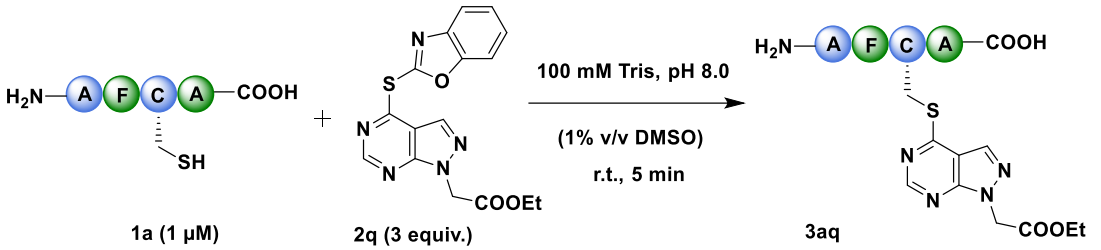


Figure S53. ESI Mass spectrum of modified product **3ap**. Calculated Mass $[M+H]^+$: 567.2; $[M+2H]^{2+}$: 284.1; Mass Found (ESI+); $[M+H]^+$: 567.1; $[M+2H]^{2+}$: 284.1.



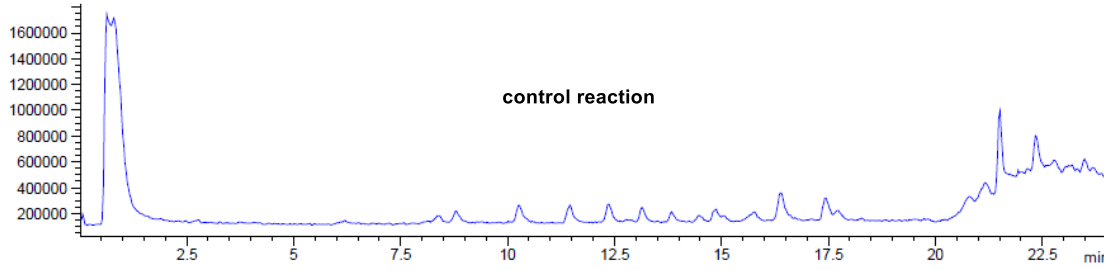


Figure S54. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

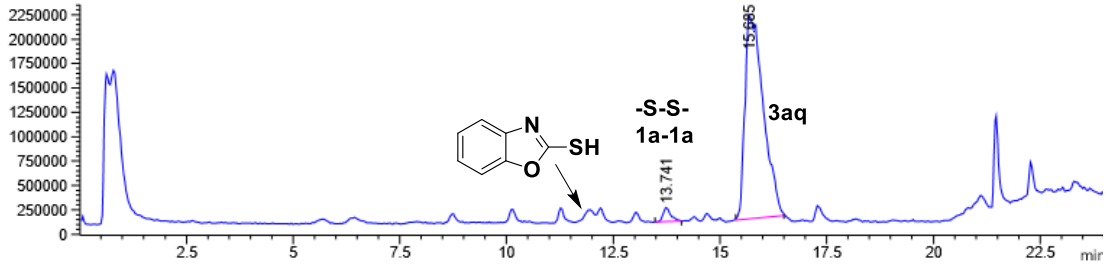


Figure S55. LC-MS TIC curve of reaction mixture. Gradient used： Method A

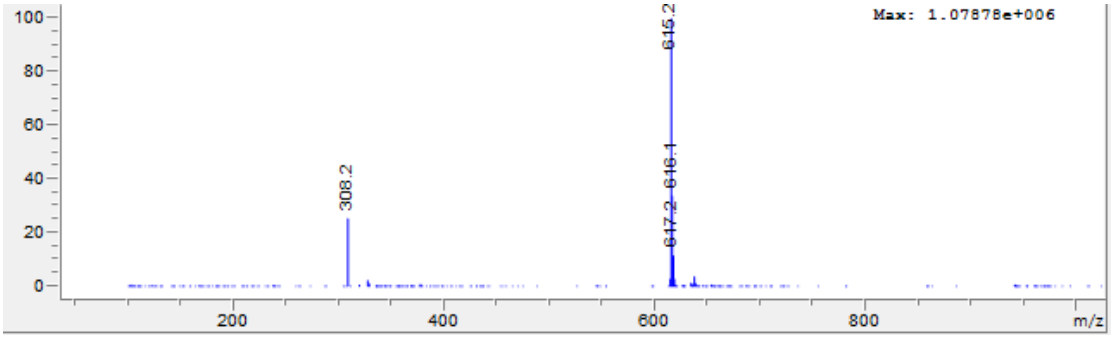
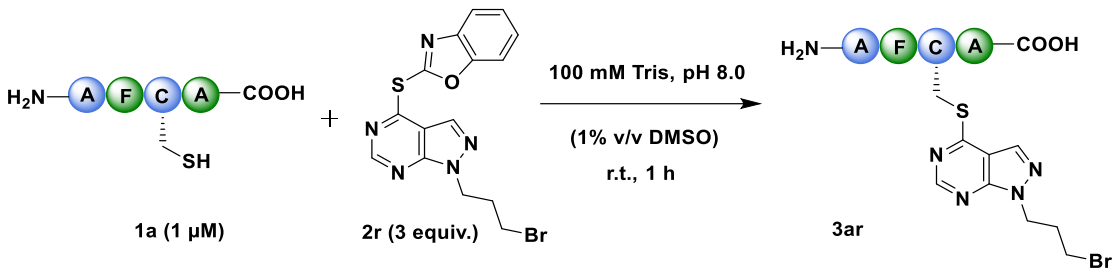


Figure S56. ESI Mass spectrum of modified product **3aq**. Calculated Mass $[M+H]^+$: 615.2; $[M+2H]^{2+}$: 308.1; Mass Found (ESI+); $[M+H]^+$: 615.2; $[M+2H]^{2+}$: 308.2.



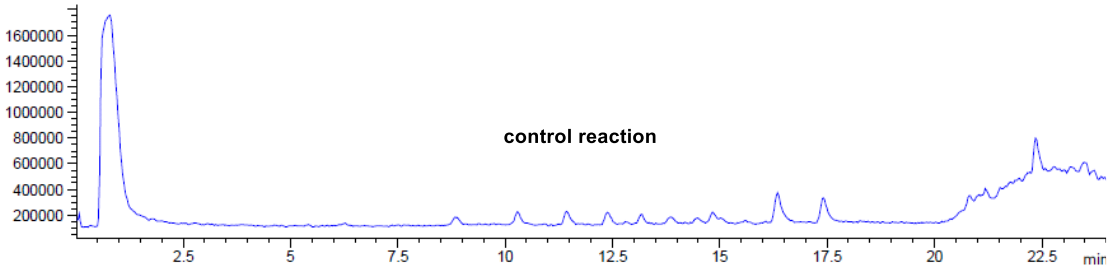


Figure S57. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

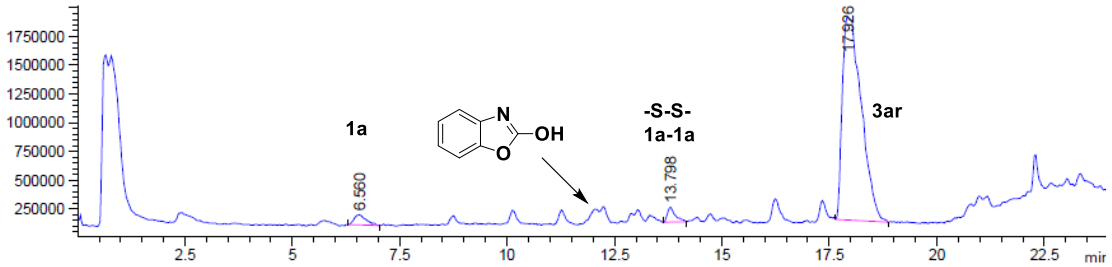


Figure S58. LC-MS TIC curve of reaction mixture. Gradient used： Method A

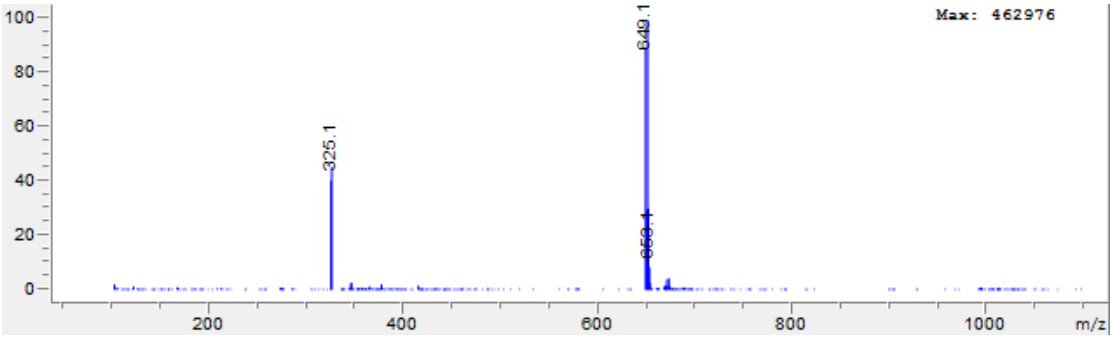
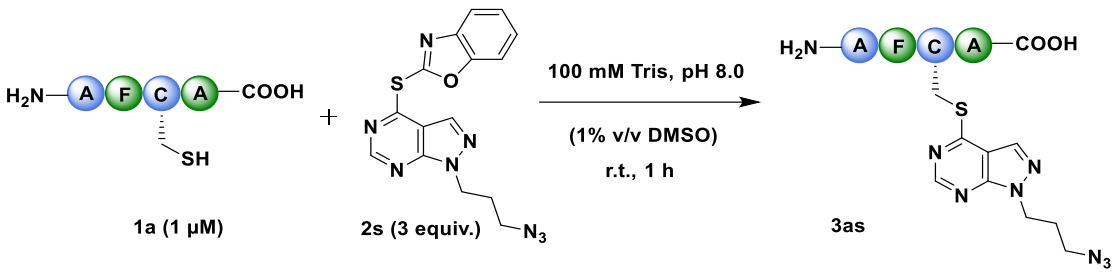


Figure S59. ESI Mass spectrum of modified product **3ar**. Calculated Mass $[M+H]^+$: 649.2; $[M+2H]^{2+}$: 325.1; Mass Found (ESI+); $[M+H]^+$: 649.1; $[M+2H]^{2+}$: 325.1.



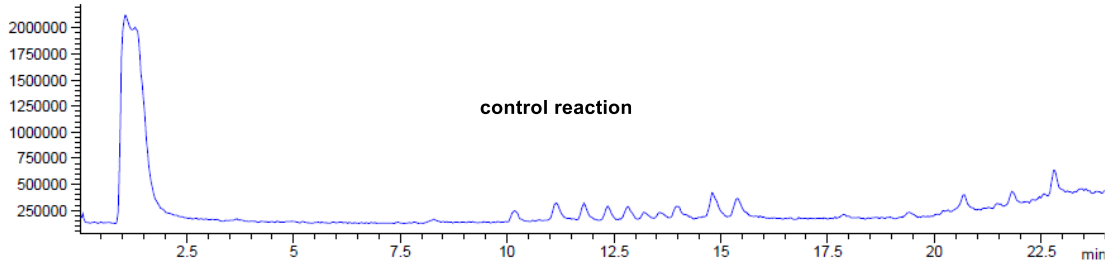


Figure S60. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

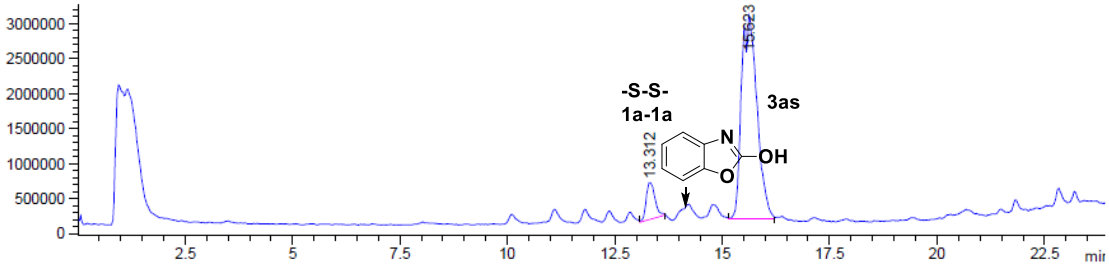


Figure S61. LC-MS TIC curve of reaction mixture. Gradient used： Method A

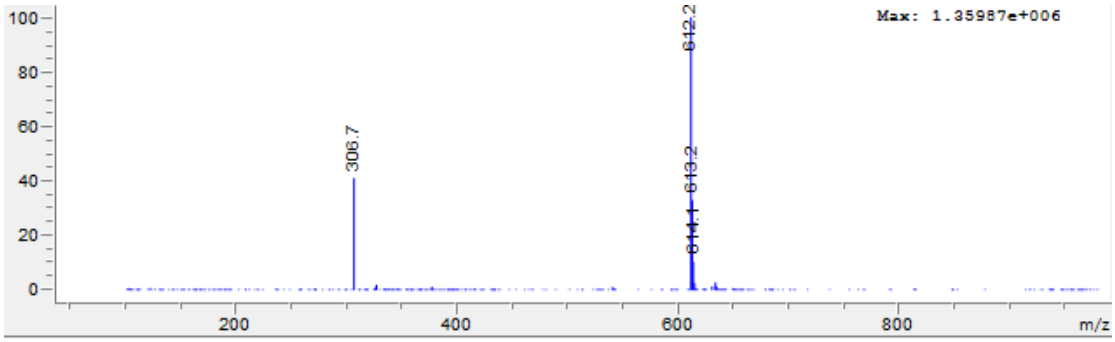
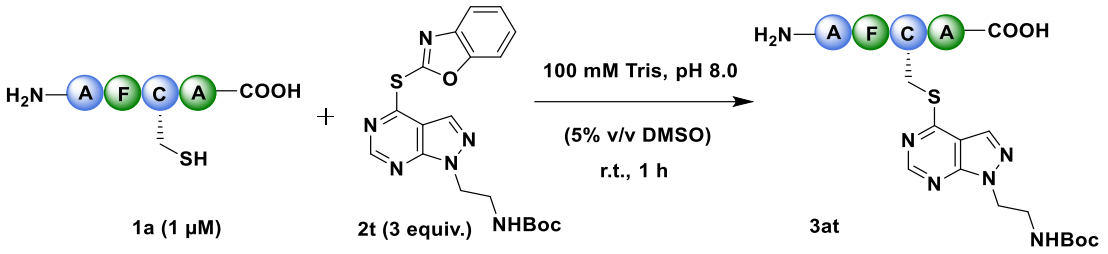


Figure S62. ESI Mass spectrum of modified product **3as**. Calculated Mass $[M+H]^+$: 612.2; $[M+2H]^{2+}$: 306.6; Mass Found (ESI+); $[M+H]^+$: 612.2; $[M+2H]^{2+}$: 306.7.



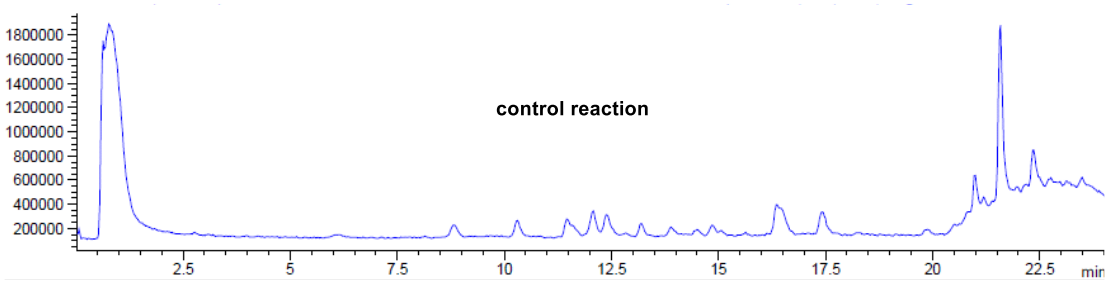


Figure S63. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

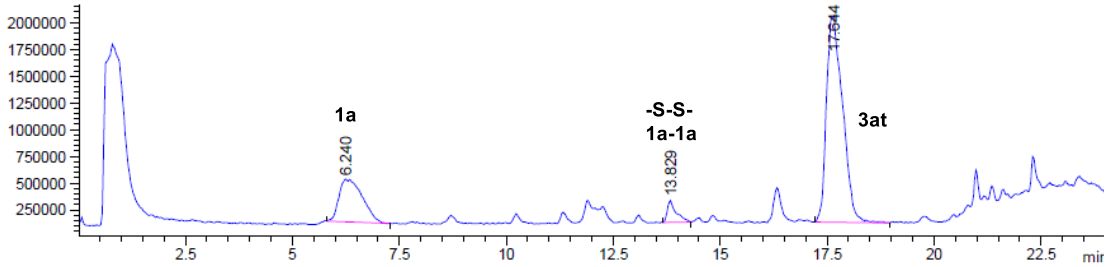


Figure S64. LC-MS TIC curve of reaction mixture. Gradient used： Method A

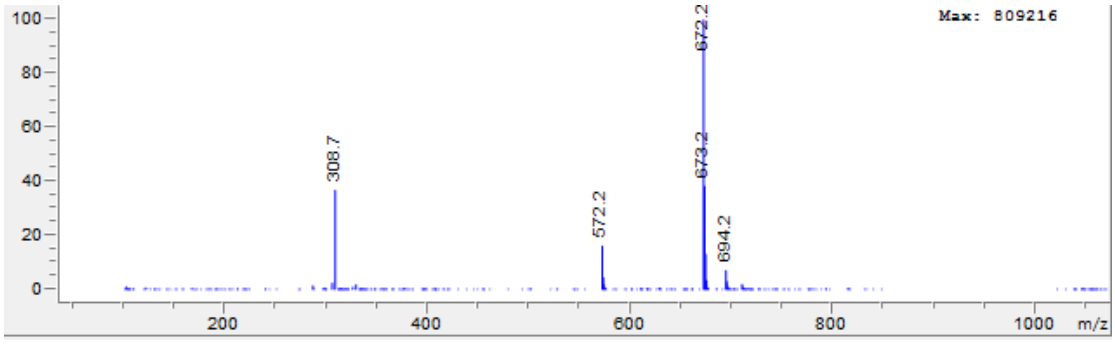
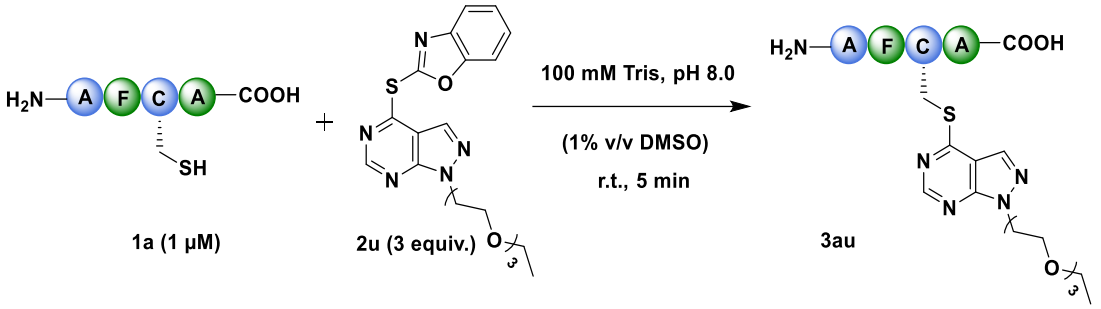


Figure S65. ESI Mass spectrum of modified product **3at**. Calculated Mass $[M+H]^+$: 672.3; Mass Found (ESI+); $[M+H]^+$: 672.2.



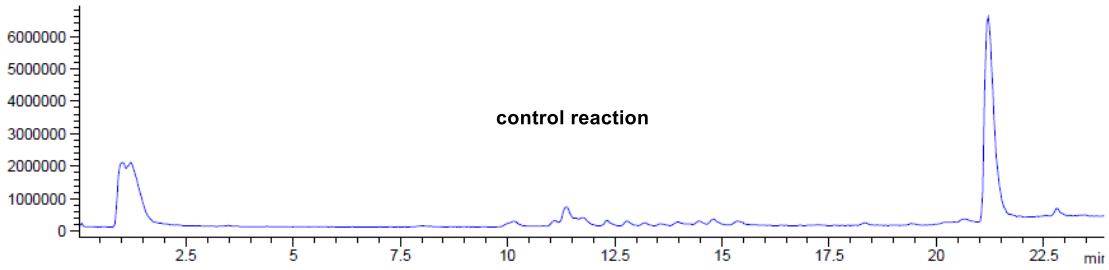


Figure S66. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

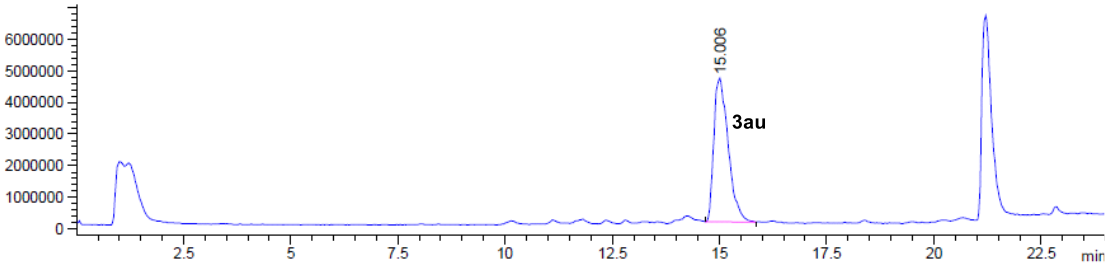


Figure S67. LC-MS TIC curve of reaction mixture. Gradient used： Method A

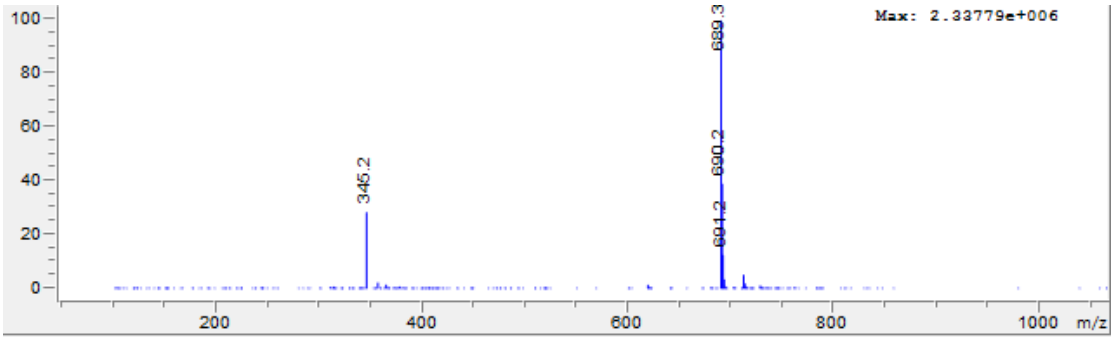


Figure S68. ESI Mass spectrum of modified product **3au**. Calculated Mass $[M+H]^+$: 689.3; $[M+2H]^{2+}$: 345.2; Mass Found (ESI+); $[M+H]^+$: 688.3; $[M+2H]^{2+}$: 345.2.

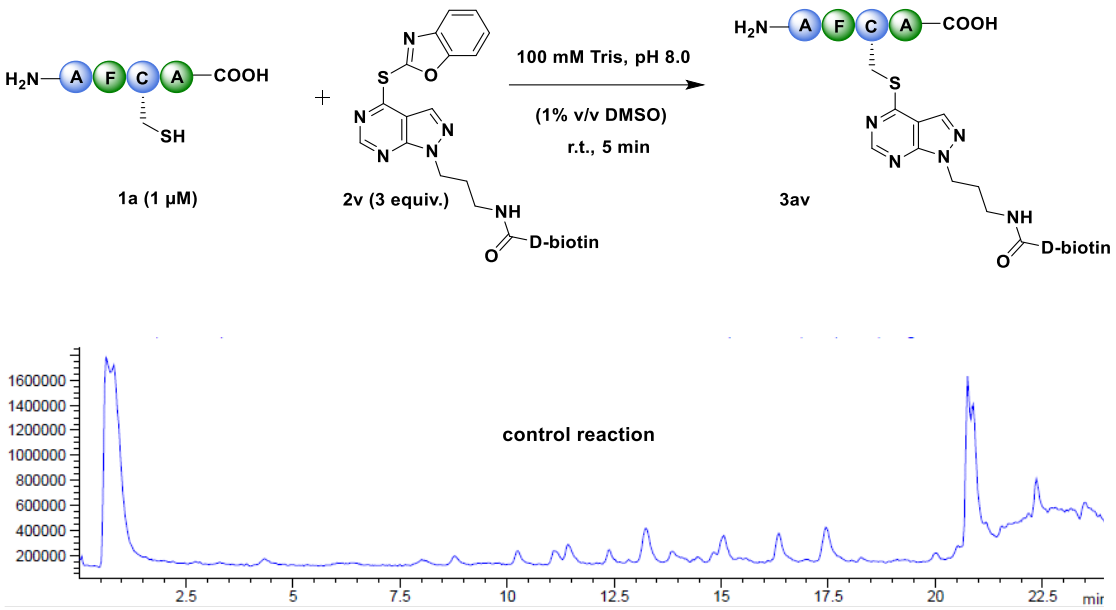


Figure S69. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

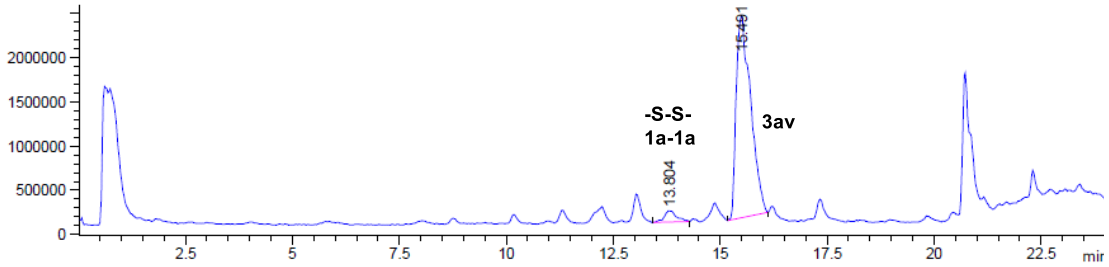


Figure S70. LC-MS TIC curve of reaction mixture. Gradient used： Method A

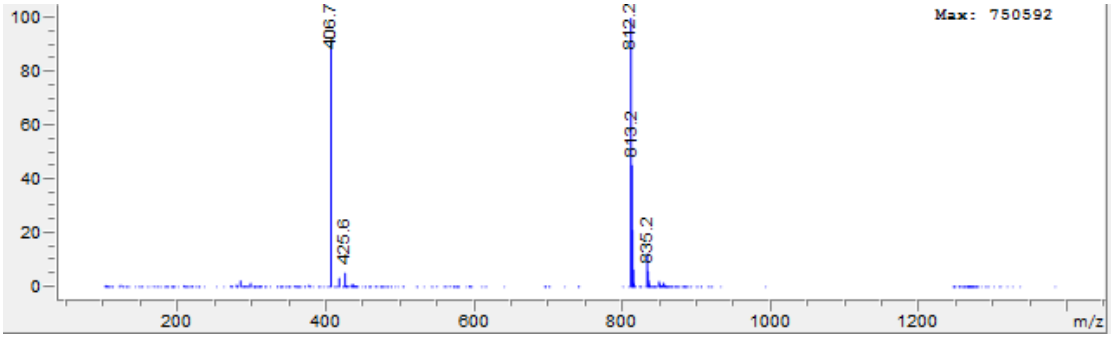


Figure S71. ESI Mass spectrum of modified product **3av**. Calculated Mass $[M+H]^+$: 812.3; $[M+2H]^{2+}$: 406.7; Mass Found (ESI+); $[M+H]^+$: 812.2; $[M+2H]^{2+}$: 406.7.

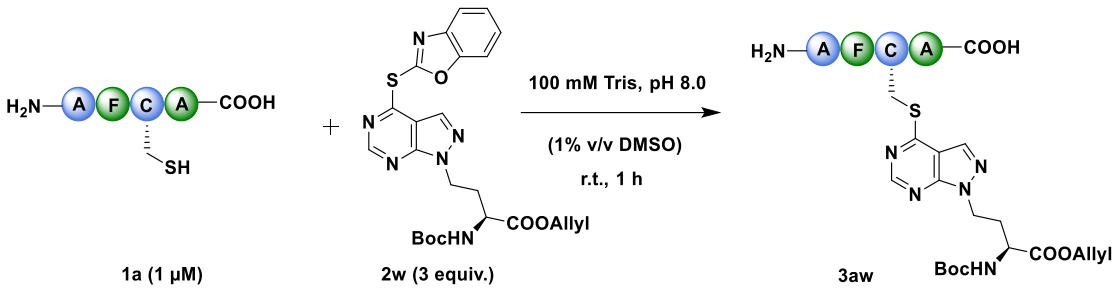


Figure S72. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method A

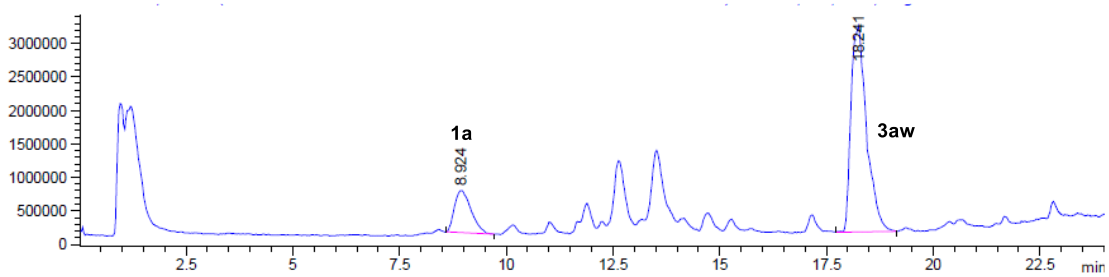


Figure S73. LC-MS TIC curve of reaction mixture. Gradient used： Method A

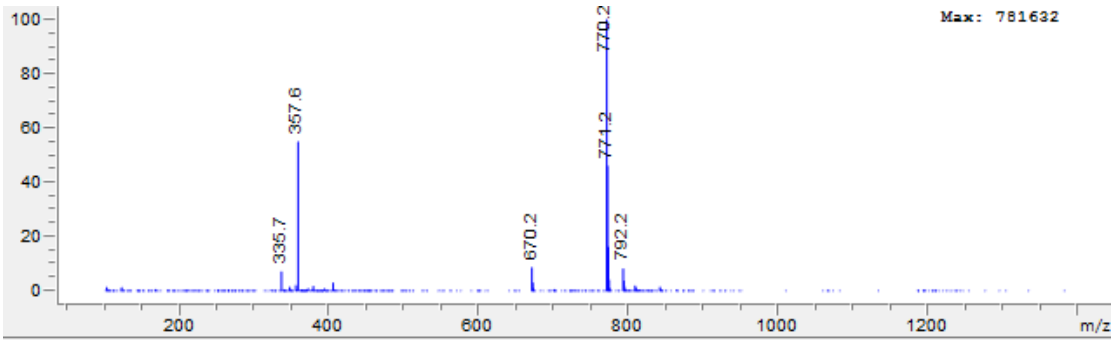
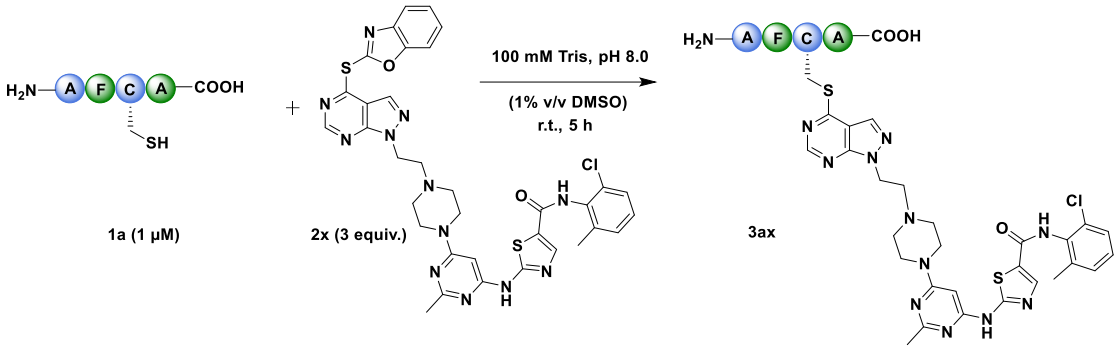


Figure S74. ESI Mass spectrum of modified product **3aw**. Calculated Mass $[M+H]^+$: 770.3; Mass Found (ESI+); $[M+H]^+$: 770.2.



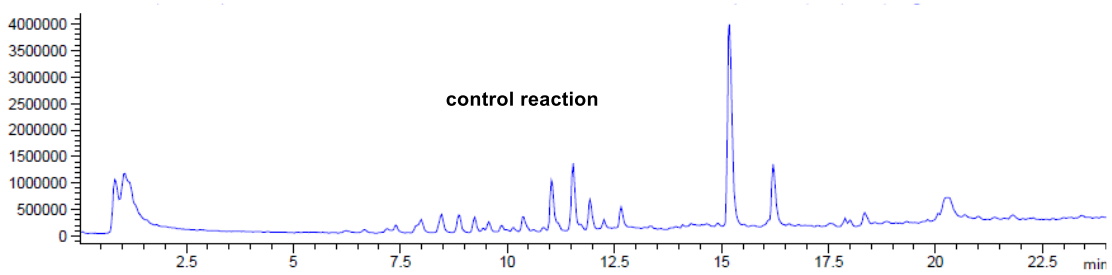


Figure S75. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

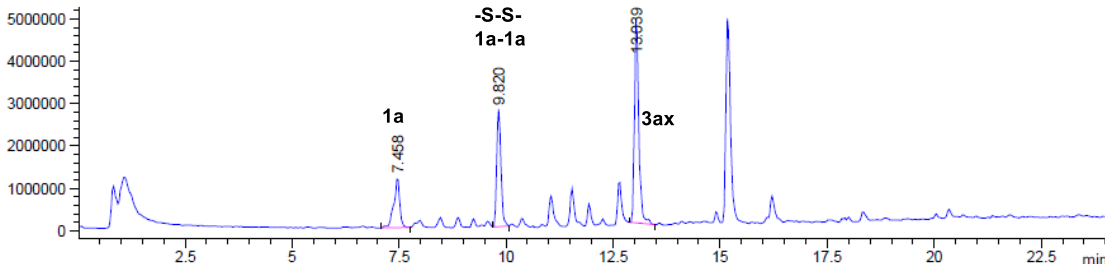


Figure S76. LC-MS TIC curve of reaction mixture. Gradient used： Method C

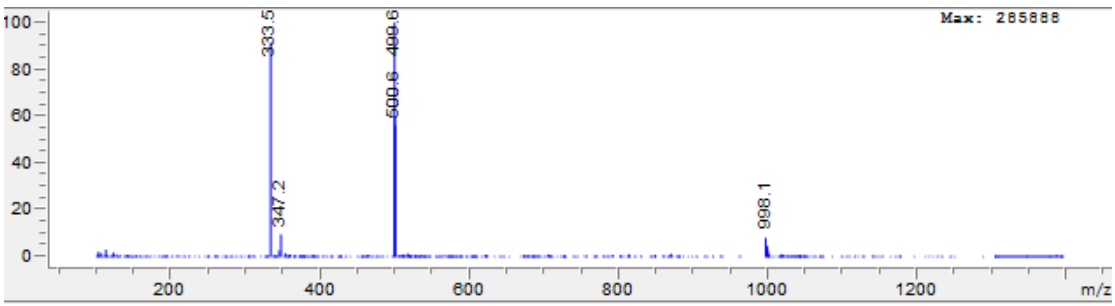
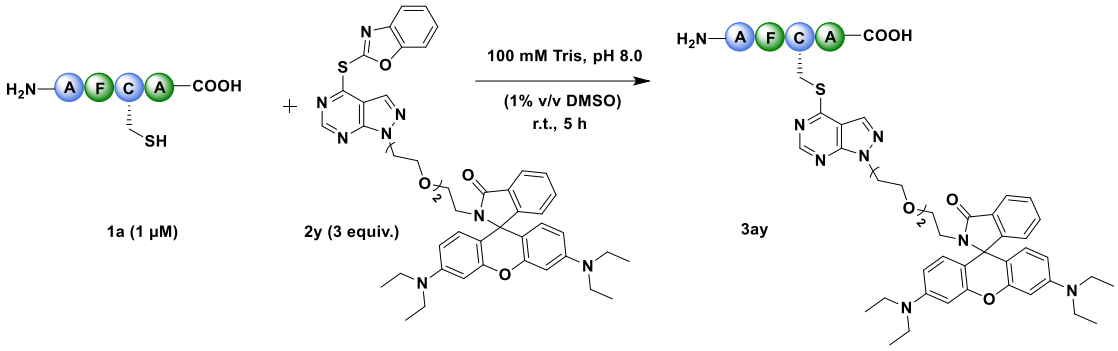


Figure S77. ESI Mass spectrum of modified product **3ax**. Calculated Mass $[M+H]^{+}$: 998.3; $[M+2H]^{2+}$: 499.7; $[M+3H]^{3+}$: 333.5; Mass Found (ESI+); $[M+H]^{+}$: 998.1; $[M+2H]^{2+}$: 499.6; $[M+3H]^{3+}$: 333.5.



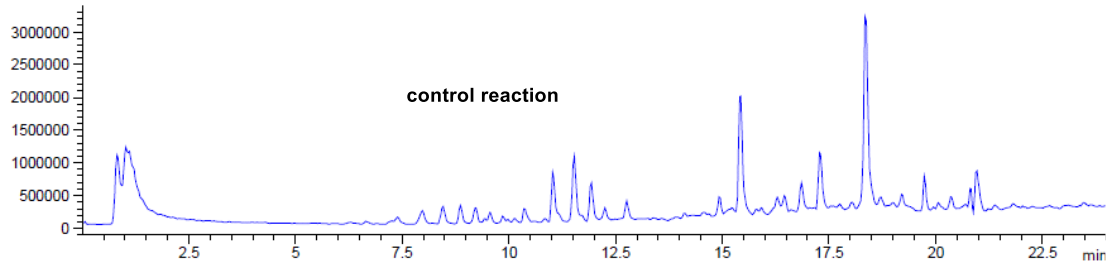


Figure S78. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

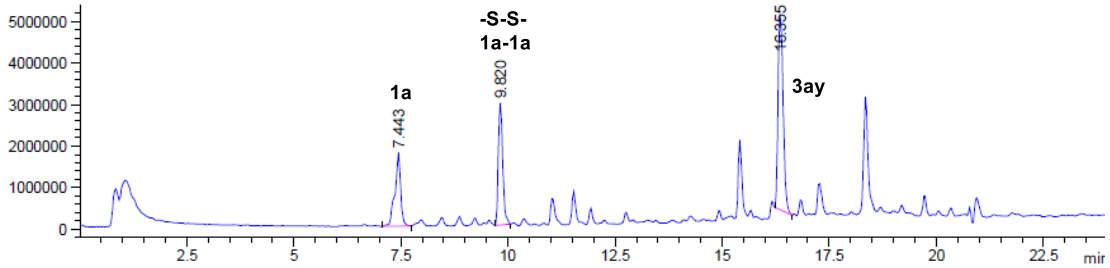


Figure S79. LC-MS TIC curve of reaction mixture. Gradient used： Method C

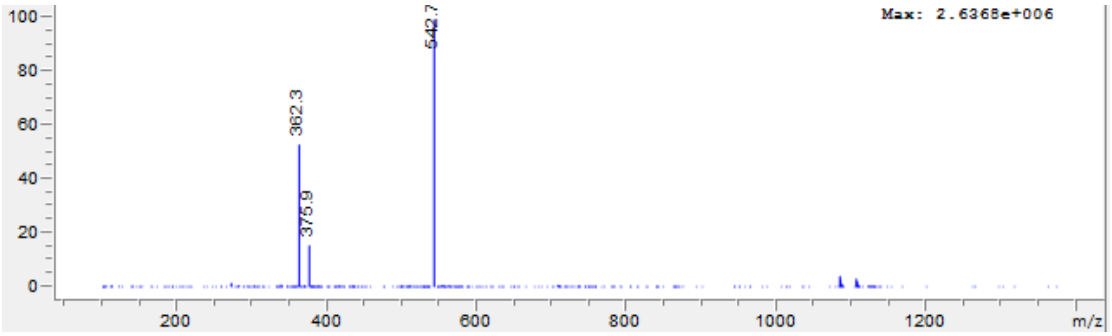
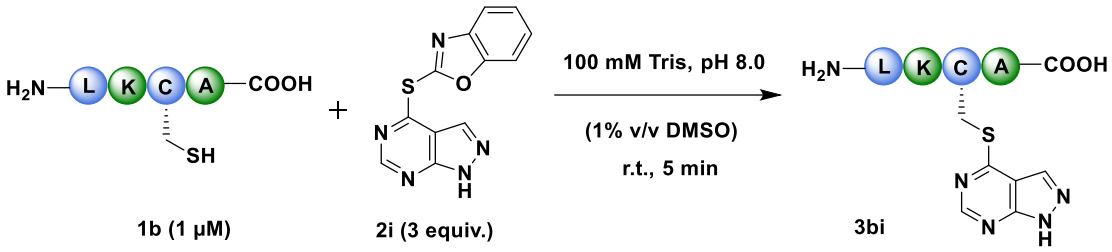


Figure S80. ESI Mass spectrum of modified product **3ay**. Calculated Mass $[M+2H]^{2+}$: 542.8; $[M+3H]^{3+}$: 362.2; Mass Found (ESI+); $[M+2H]^{2+}$: 542.7; $[M+3H]^{3+}$: 362.3.



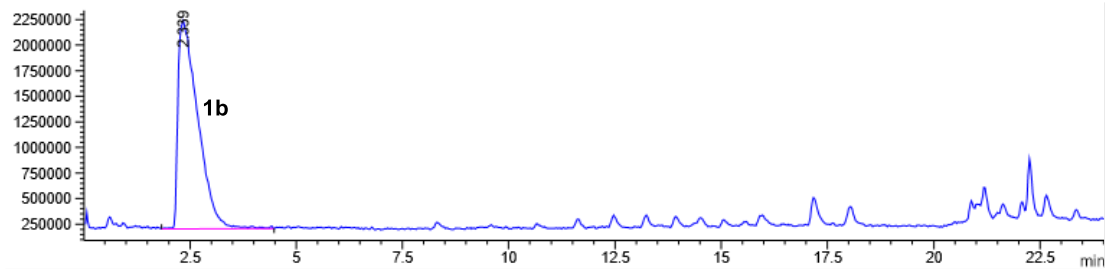


Figure S81. LC-MS TIC curve of peptide **1b**. Gradient used： Method B

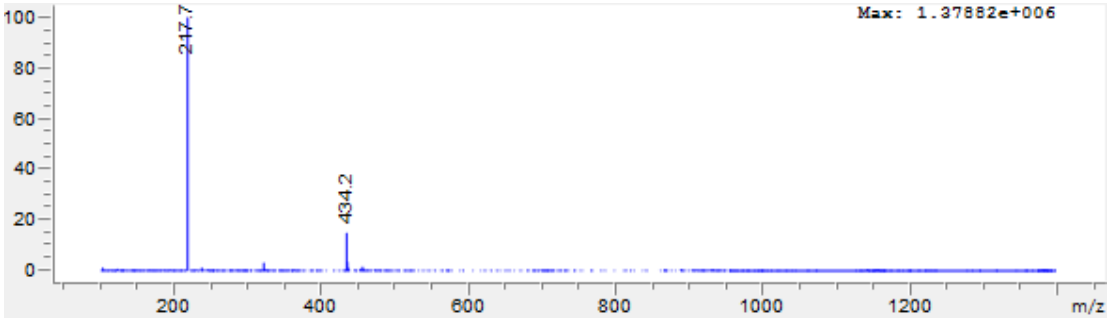


Figure S82. ESI Mass spectrum of peptide **1b**. Calculated Mass $[M+H]^+$: 434.2; Mass Found (ESI+); $[M+H]^+$: 434.2.

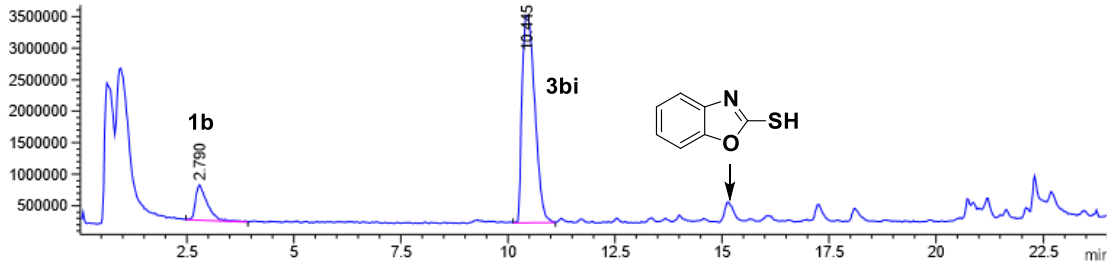


Figure S83. LC-MS TIC curve of reaction mixture. Gradient used： Method B

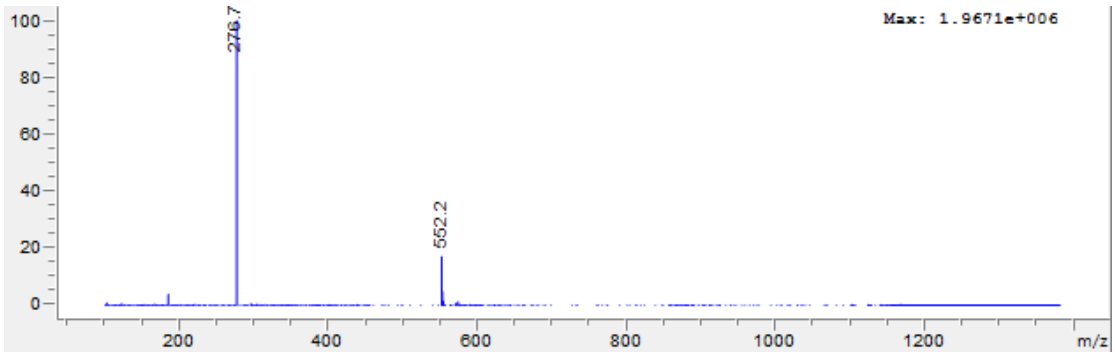
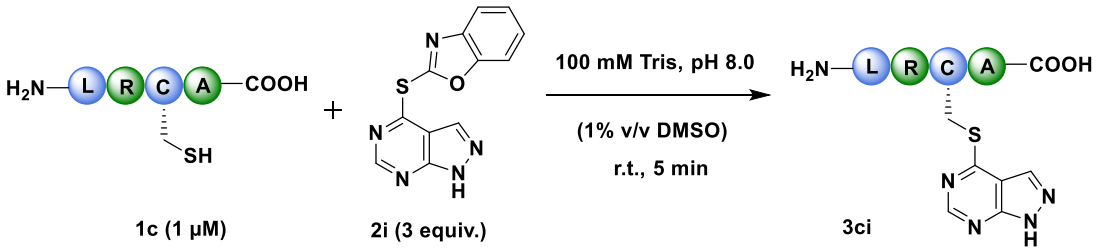


Figure S84. ESI Mass spectrum of modified product **3bi**. Calculated Mass $[M+H]^+$: 552.3; $[M+2H]^{2+}$: 276.6; Mass Found (ESI+); $[M+H]^+$: 552.2; $[M+2H]^{2+}$: 276.7.



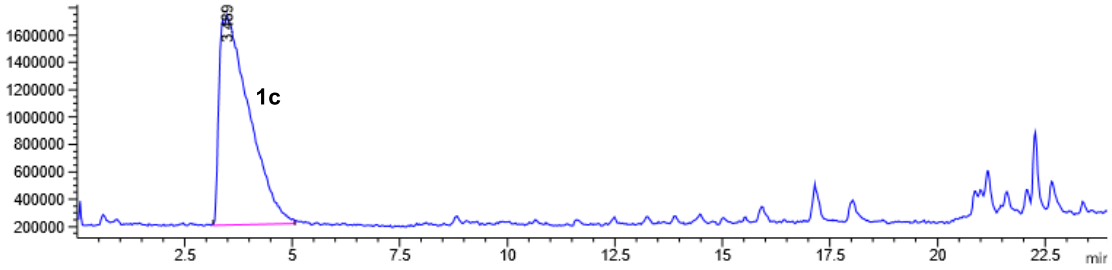


Figure S85. LC-MS TIC curve of peptide **1c**. Gradient used： Method B

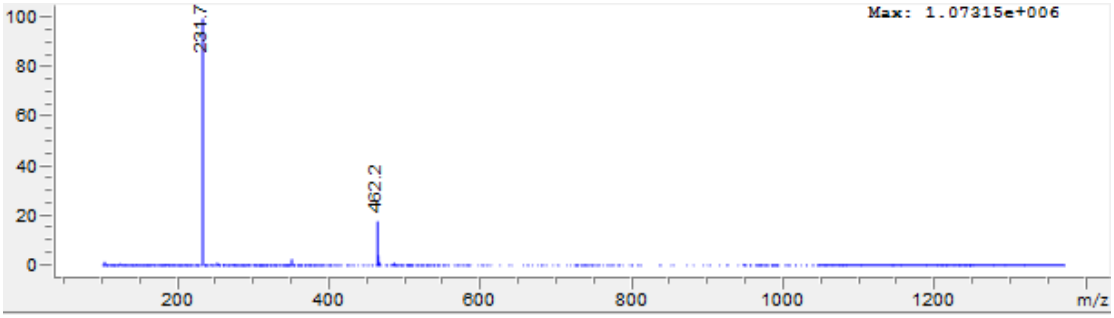


Figure S86. ESI Mass spectrum of peptide **1c**. Calculated Mass $[M+H]^+$: 462.2; Mass Found (ESI+); $[M+H]^+$: 462.2.

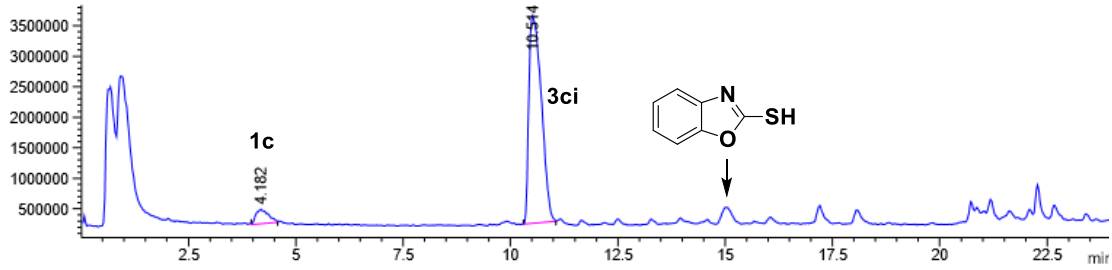


Figure S87. LC-MS TIC curve of reaction mixture. Gradient used： Method B

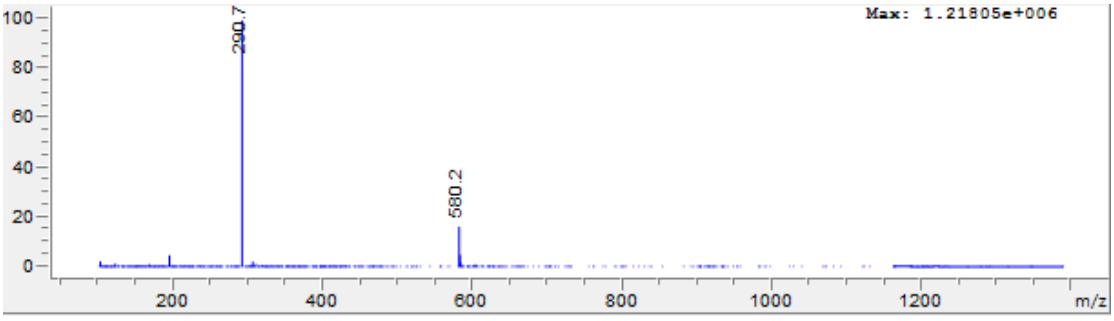
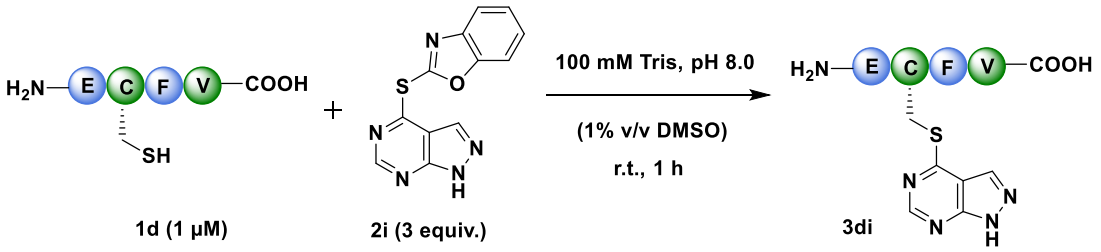


Figure S88. ESI Mass spectrum of modified product **3ci**. Calculated Mass $[M+H]^+$: 580.3; $[M+2H]^{2+}$: 290.6; Mass Found (ESI+); $[M+H]^+$: 580.2; $[M+2H]^{2+}$: 290.7.



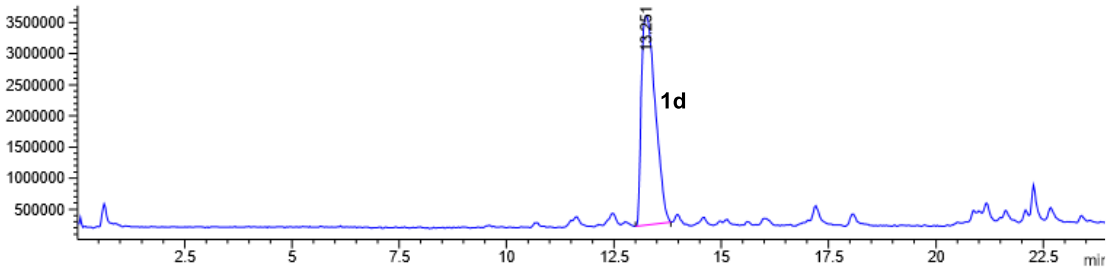


Figure S89. LC-MS TIC curve of peptide **1d**. Gradient used： Method B

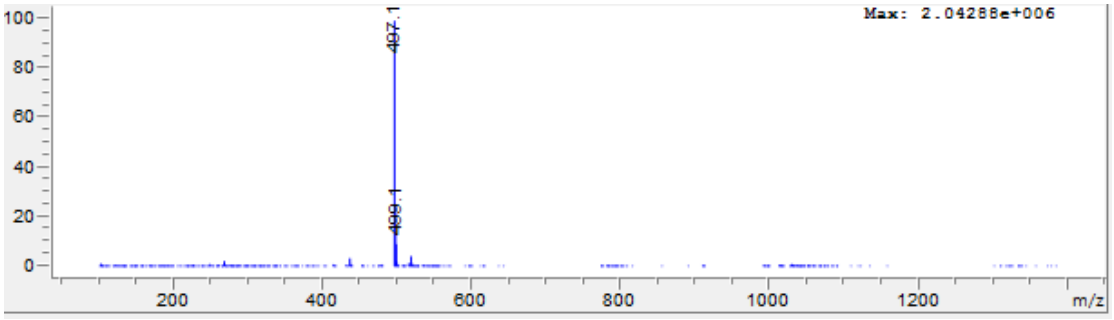


Figure S90. ESI Mass spectrum of peptide **1d**. Calculated Mass $[M+H]^+$: 497.2; Mass Found (ESI+); $[M+H]^+$: 497.1.

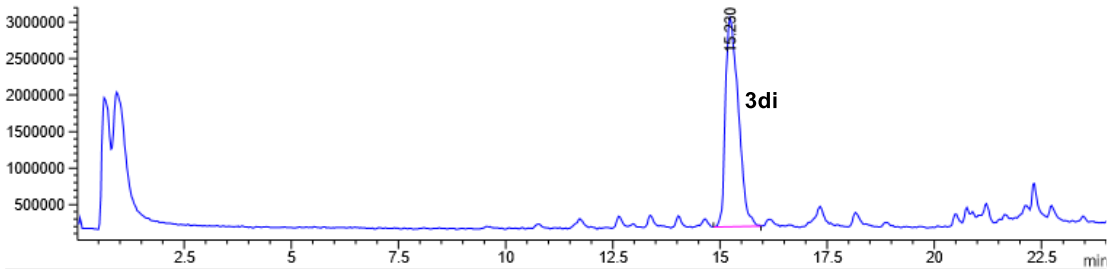


Figure S91. LC-MS TIC curve of reaction mixture. Gradient used： Method B

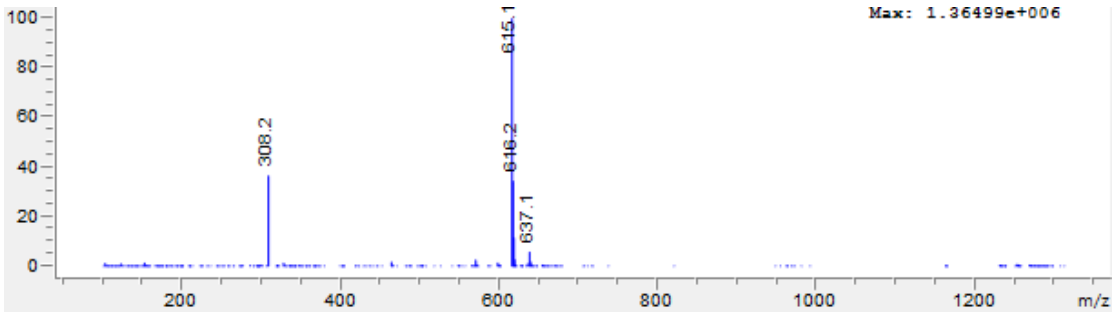
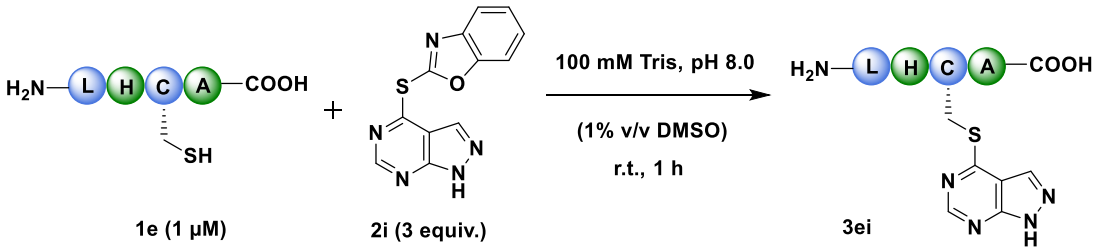


Figure S92. ESI Mass spectrum of modified product **3di**. Calculated Mass $[M+H]^+$: 615.2; $[M+2H]^{2+}$: 308.1; Mass Found (ESI+); $[M+H]^+$: 615.1; $[M+2H]^{2+}$: 308.2.



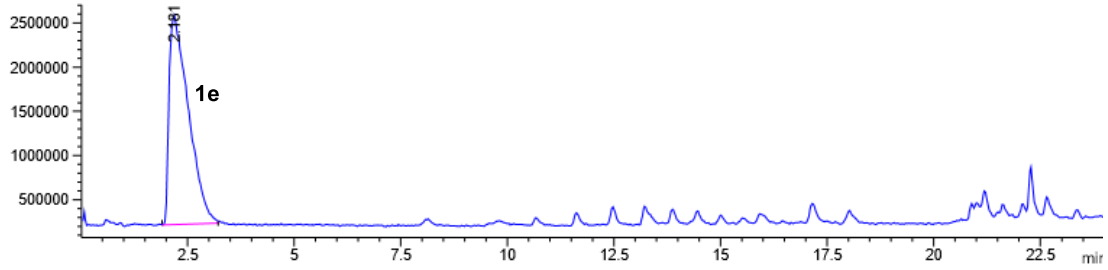


Figure S93. LC-MS TIC curve of peptide **1e**. Gradient used： Method B

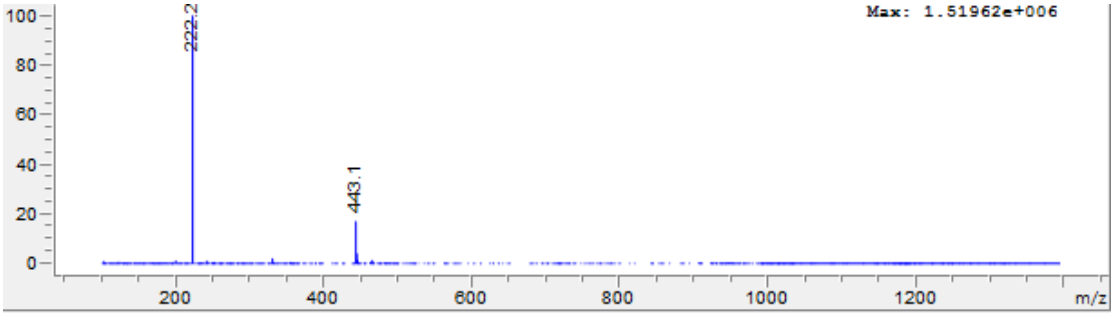


Figure S94. ESI Mass spectrum of peptide **1e**. Calculated Mass $[M+H]^{+}$: 443.2; $[M+2H]^{2+}$: 222.1; Mass Found (ESI+); $[M+H]^{+}$: 443.1; $[M+2H]^{2+}$: 222.2.

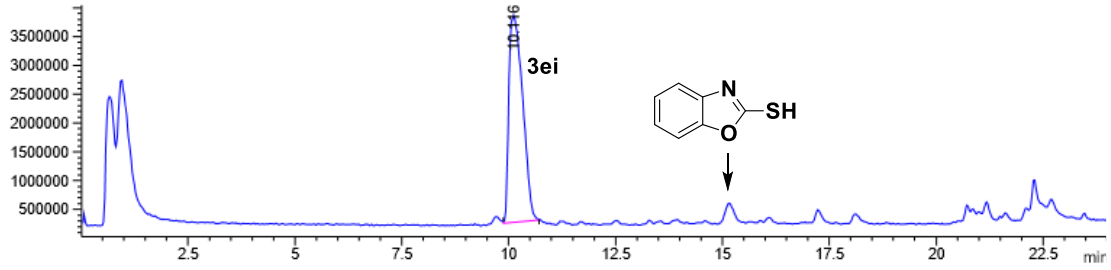


Figure S95. LC-MS TIC curve of reaction mixture. Gradient used： Method B

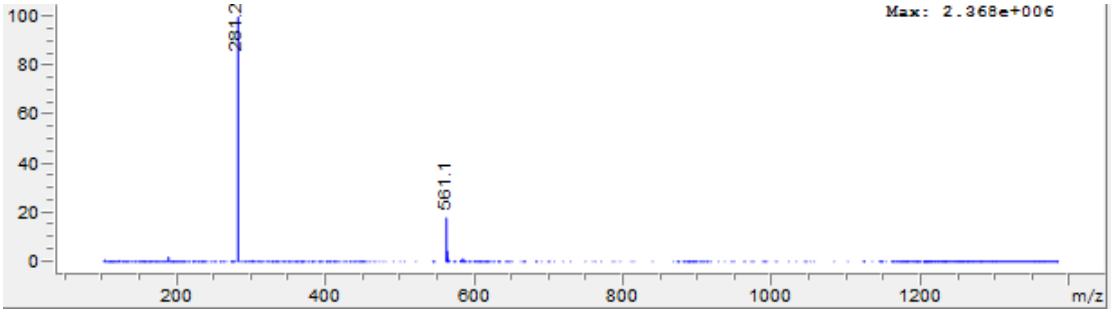
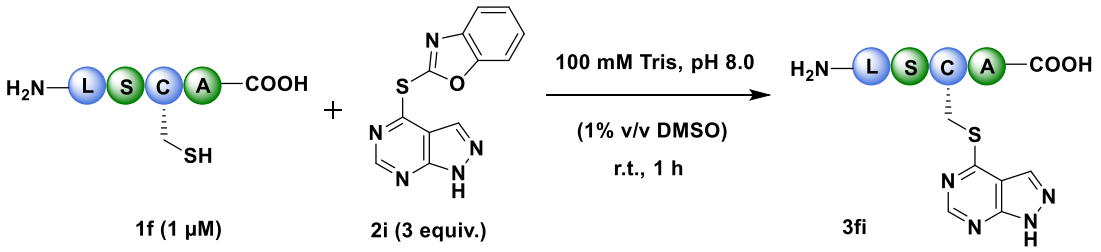


Figure S96. ESI Mass spectrum of modified product **3ei**. Calculated Mass $[M+H]^{+}$: 561.2; $[M+2H]^{2+}$: 281.2; Mass Found (ESI+); $[M+H]^{+}$: 561.1; $[M+2H]^{2+}$: 281.2.



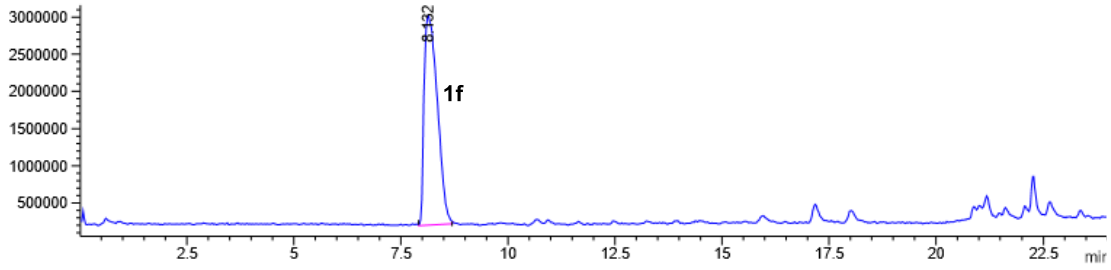


Figure S97. LC-MS TIC curve of peptide **1f**. Gradient used： Method B

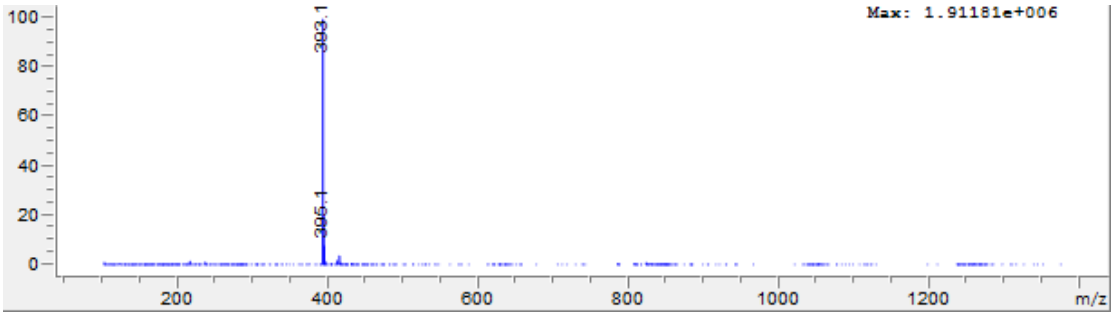


Figure S98. ESI Mass spectrum of peptide **1f**. Calculated Mass $[M+H]^+$: 393.2; Mass Found (ESI+); $[M+H]^+$: 393.1.

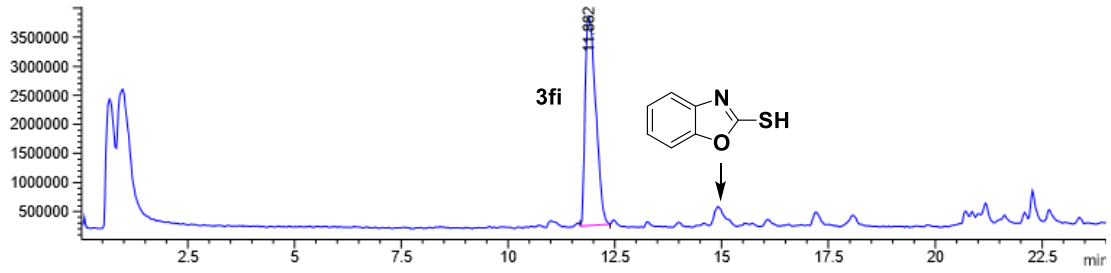


Figure S99. LC-MS TIC curve of reaction mixture. Gradient used： Method B

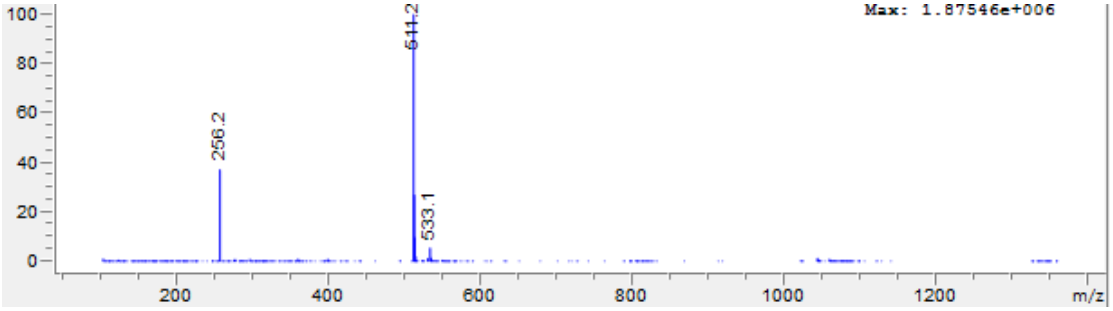
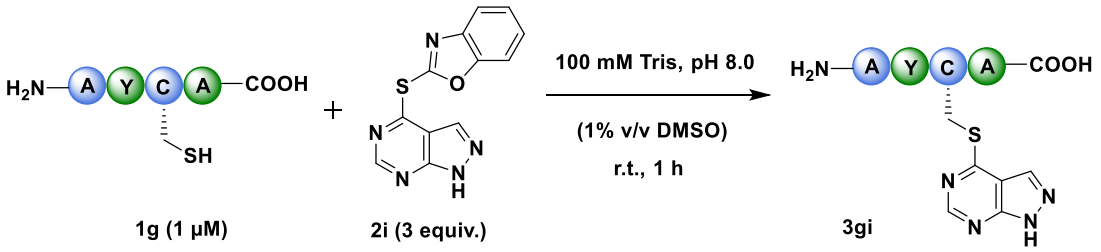


Figure S100. ESI Mass spectrum of modified product **3fi**. Calculated Mass $[M+H]^+$: 511.2; $[M+2H]^{2+}$: 256.1; Mass Found (ESI+); $[M+H]^+$: 511.2; $[M+2H]^{2+}$: 256.2.



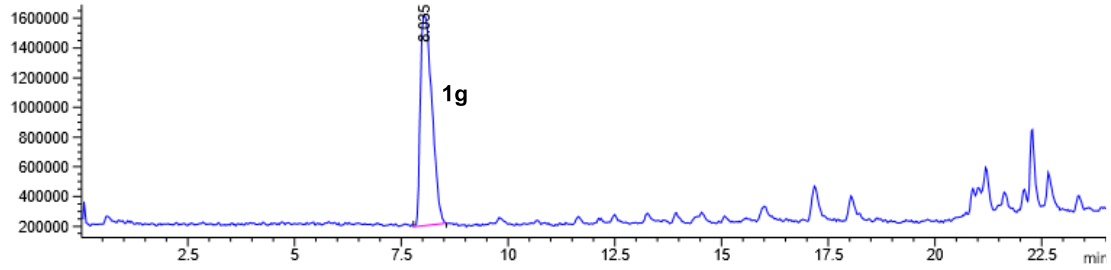


Figure S101. LC-MS TIC curve of peptide **1g**. Gradient used： Method B

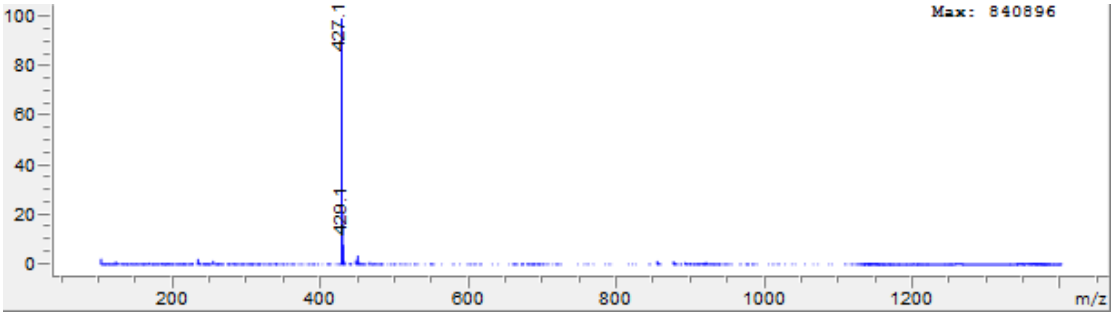


Figure S102. ESI Mass spectrum of peptide **1g**. Calculated Mass $[M+H]^+$: 427.2; Mass Found (ESI+); $[M+H]^+$: 427.1.

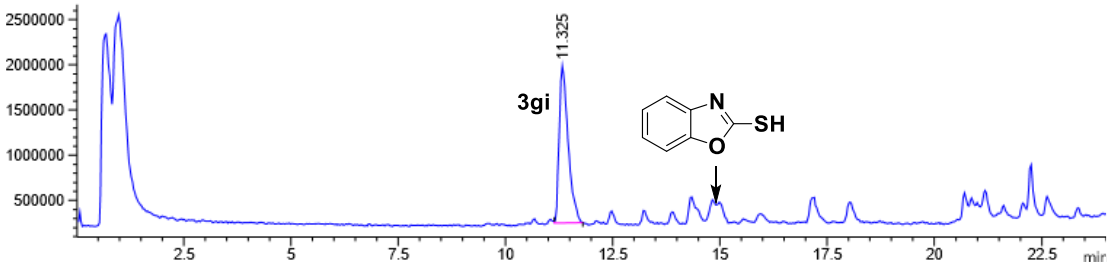


Figure S103. LC-MS TIC curve of reaction mixture. Gradient used： Method B

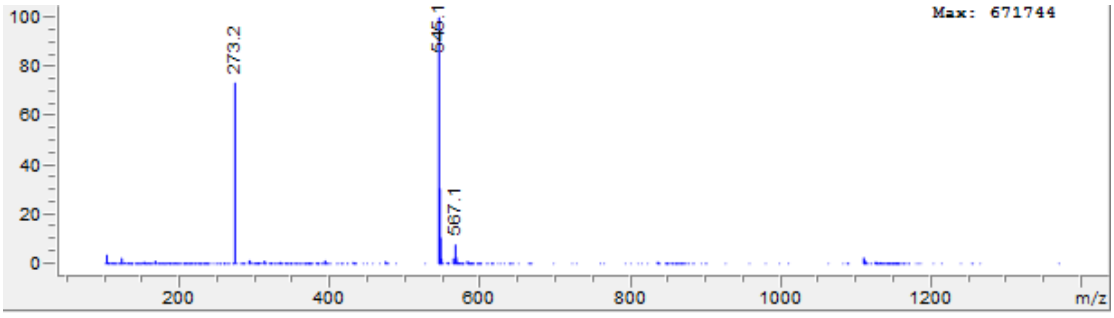
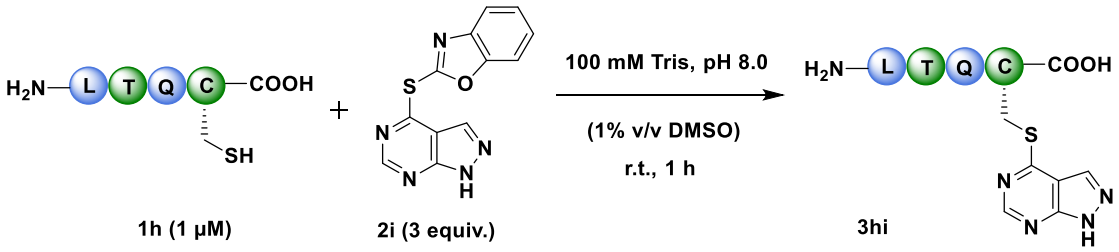


Figure S104. ESI Mass spectrum of modified product **3gi**. Calculated Mass $[M+H]^+$: 545.2; $[M+2H]^{2+}$: 273.1; Mass Found (ESI+); $[M+H]^+$: 545.1; $[M+2H]^{2+}$: 273.2.



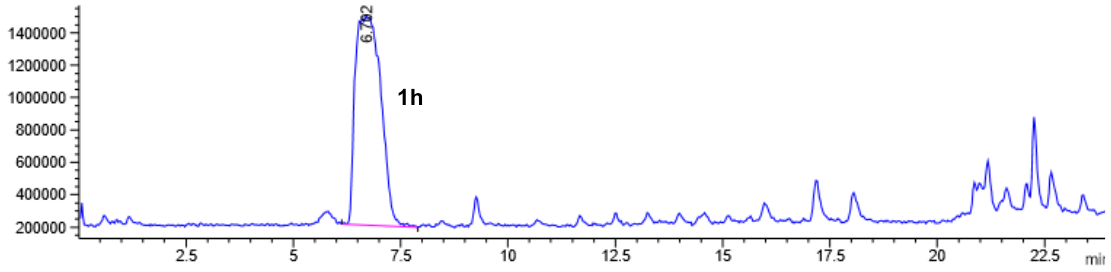


Figure S105. LC-MS TIC curve of peptide **1h**. Gradient used： Method B

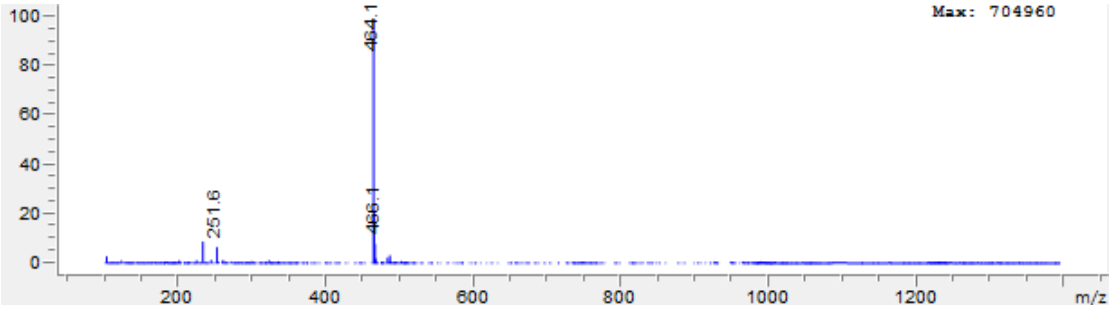


Figure S106. ESI Mass spectrum of peptide **1h**. Calculated Mass $[M+H]^+$: 464.2; Mass Found (ESI+); $[M+H]^+$: 464.1.

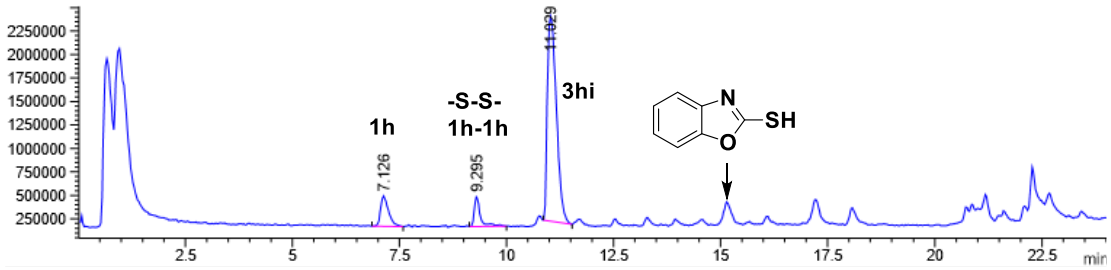


Figure S107. LC-MS TIC curve of reaction mixture. Gradient used： Method B

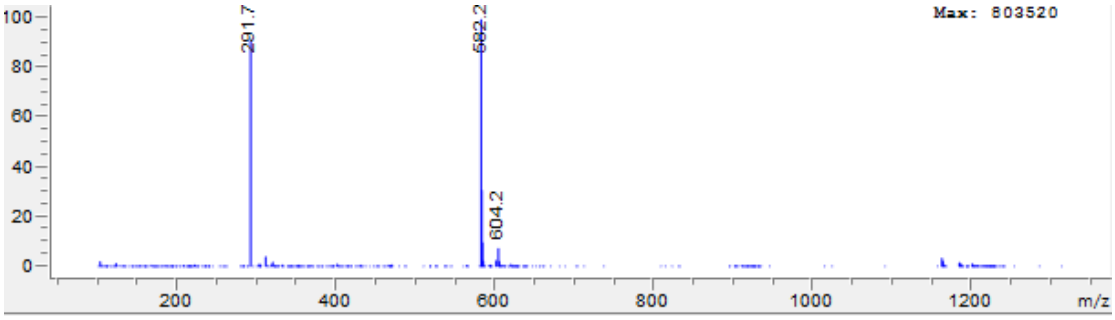


Figure S108. ESI Mass spectrum of modified product **3hi**. Calculated Mass $[M+H]^+$: 582.2; $[M+2H]^{2+}$: 291.6; Mass Found (ESI+); $[M+H]^+$: 582.2; $[M+2H]^{2+}$: 291.7.

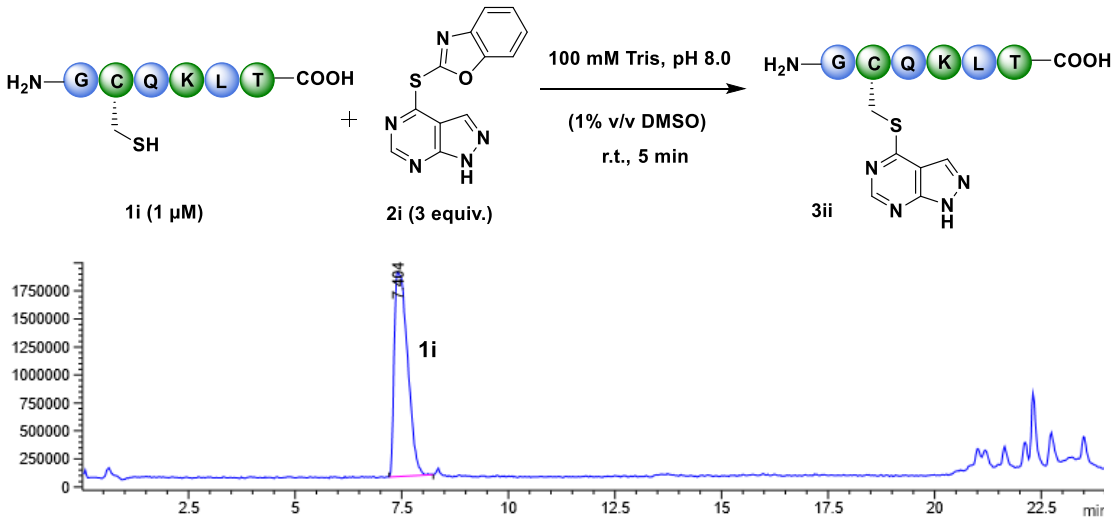


Figure S109. LC-MS TIC curve of peptide **1i**. Gradient used： Method B

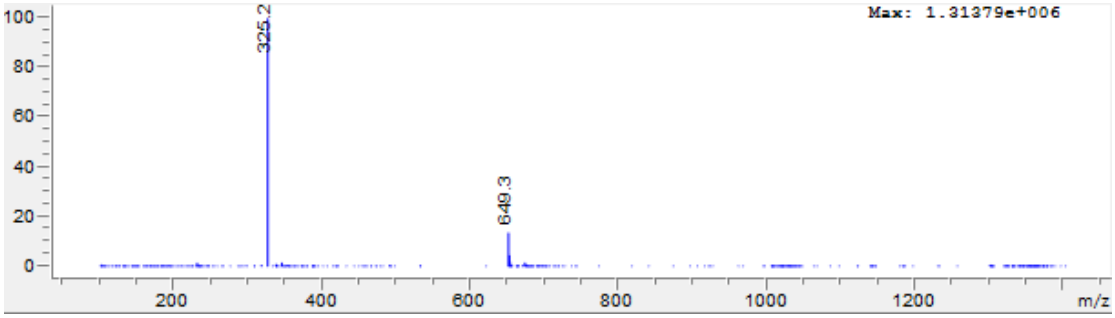


Figure S110. ESI Mass spectrum of peptide **1i**. Calculated Mass $[M+H]^{+}$: 649.3; $[M+2H]^{2+}$: 325.2; Mass Found (ESI+); $[M+H]^{+}$: 649.3; $[M+2H]^{2+}$: 325.2.

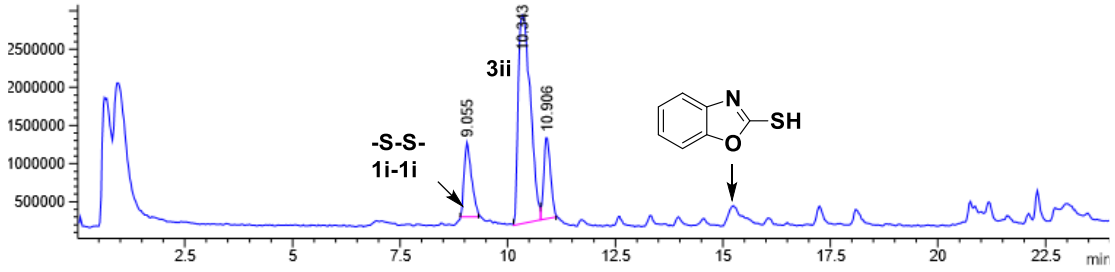


Figure S111. LC-MS TIC curve of reaction mixture. Gradient used： Method B

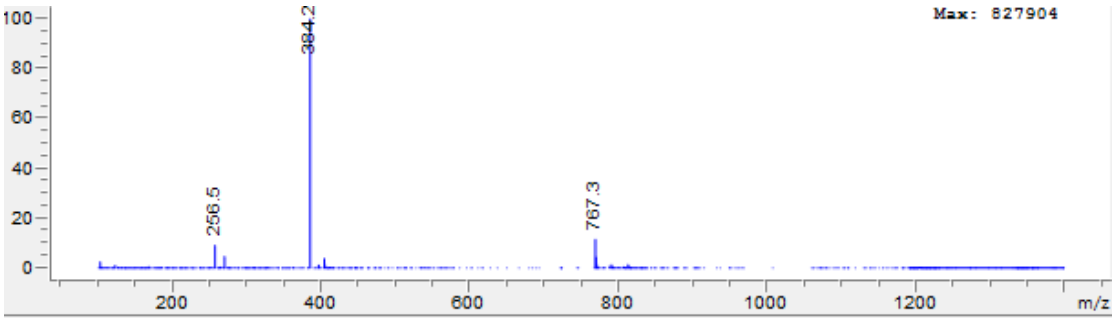


Figure S112. ESI Mass spectrum of modified product **3ii**. Calculated Mass $[M+H]^{+}$: 767.4; $[M+2H]^{2+}$: 384.2; Mass Found (ESI+); $[M+H]^{+}$: 767.3; $[M+2H]^{2+}$: 384.2.

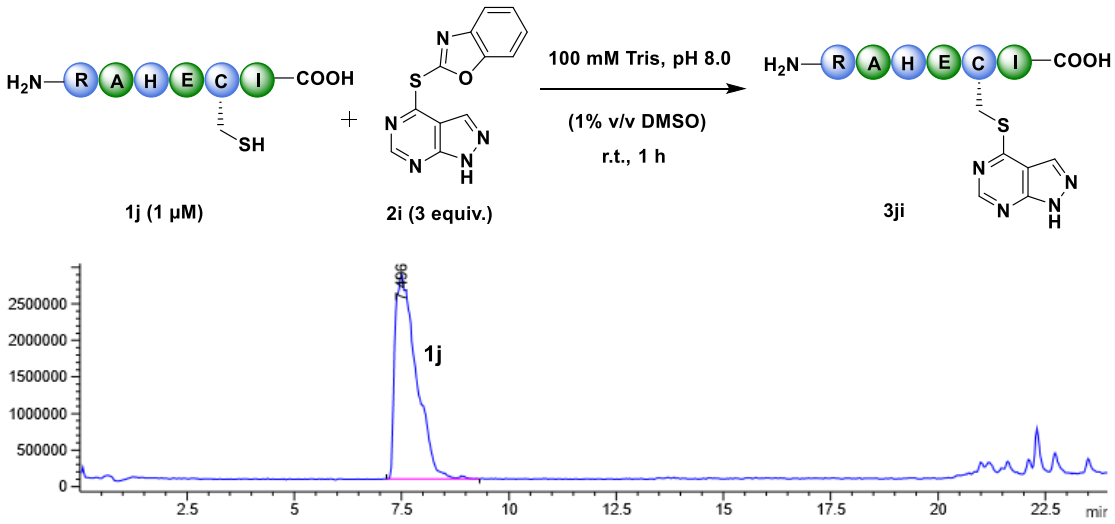


Figure S113. LC-MS TIC curve of peptide **1j**. Gradient used： Method B

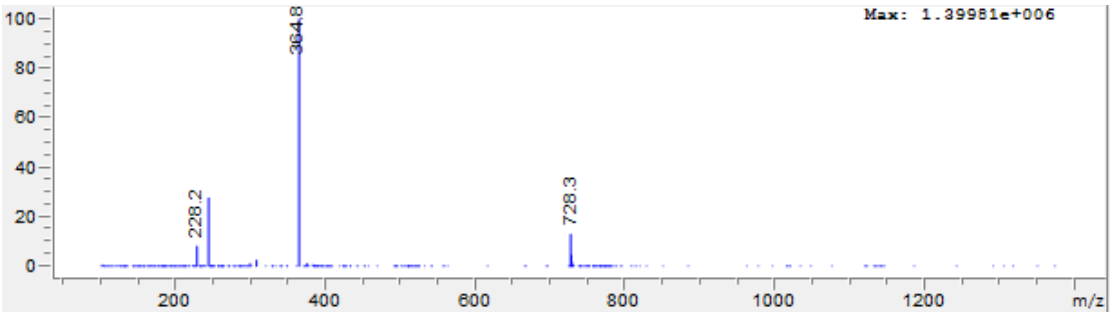


Figure S114. ESI Mass spectrum of peptide **1j**. Calculated Mass $[M+H]^{+}$: 728.4; $[M+2H]^{2+}$: 364.7; Mass Found (ESI+); $[M+H]^{+}$: 728.3; $[M+2H]^{2+}$: 364.8.

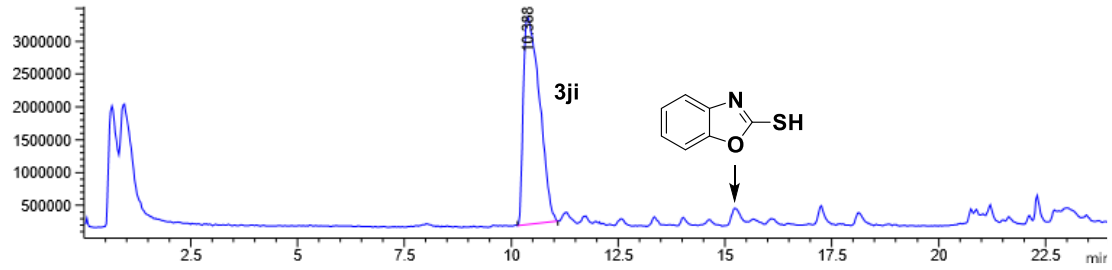


Figure S115. LC-MS TIC curve of reaction mixture. Gradient used： Method B

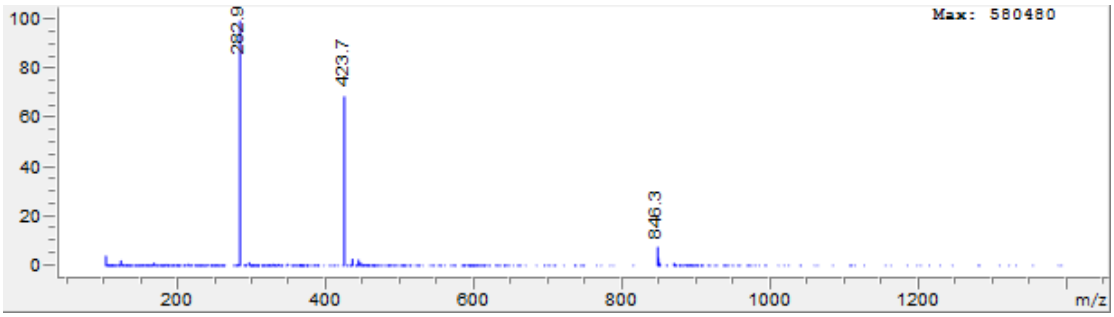


Figure S116. ESI Mass spectrum of modified product **3ji**. Calculated Mass $[M+H]^{+}$: 846.4; $[M+2H]^{2+}$: 423.7; $[M+3H]^{3+}$: 282.8; Mass Found (ESI+); $[M+H]^{+}$: 846.3; $[M+2H]^{2+}$: 423.7; $[M+3H]^{3+}$: 282.9.

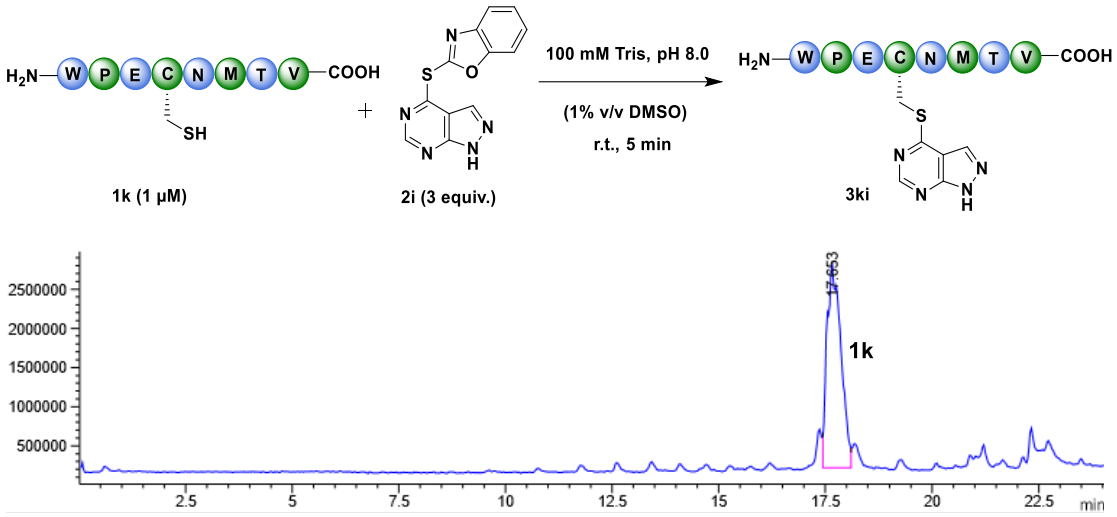


Figure S117. LC-MS TIC curve of peptide **1k**. Gradient used： Method B

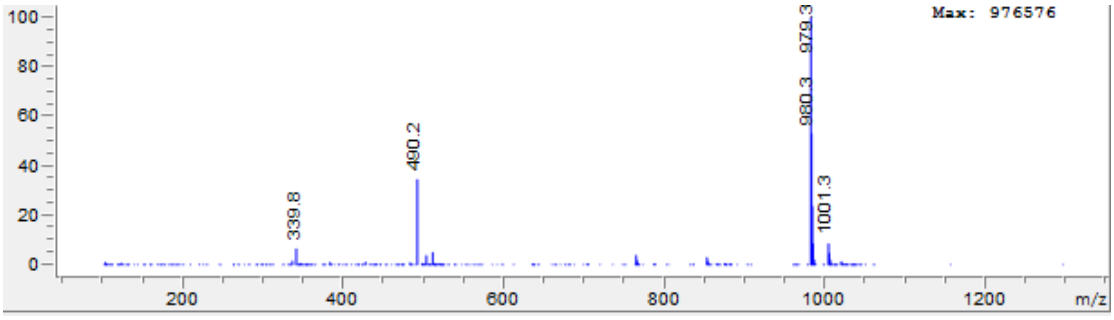


Figure S118. ESI Mass spectrum of peptide **1k**. Calculated Mass $[M+H]^+$: 979.4; $[M+2H]^{2+}$: 490.2; Mass Found (ESI+); $[M+H]^+$: 979.3; $[M+2H]^{2+}$: 490.2.

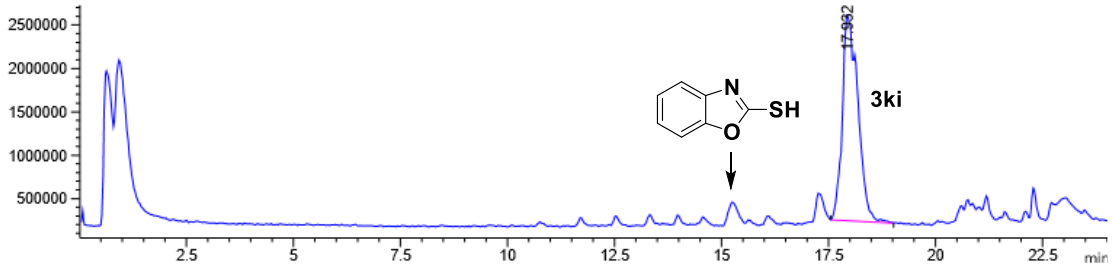


Figure S119. LC-MS TIC curve of reaction mixture. Gradient used： Method B

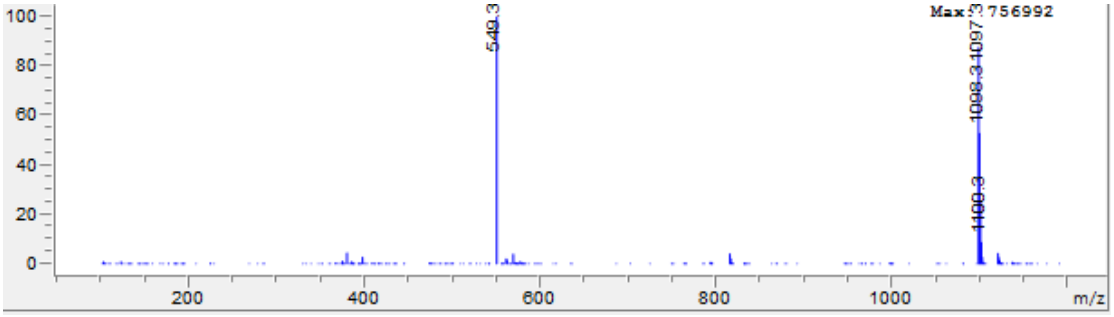


Figure S120. ESI Mass spectrum of modified product **3ki**. Calculated Mass $[M+H]^+$: 1097.4; $[M+2H]^{2+}$: 549.2; Mass Found (ESI+); $[M+H]^+$: 1097.3; $[M+2H]^{2+}$: 549.3.

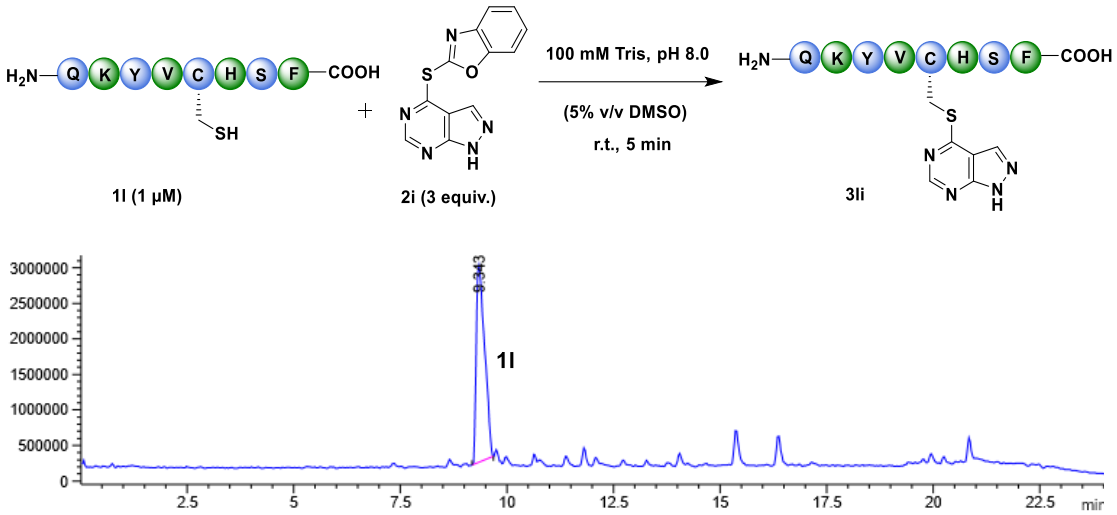


Figure S121. LC-MS TIC curve of peptide **1l**. Gradient used： Method C

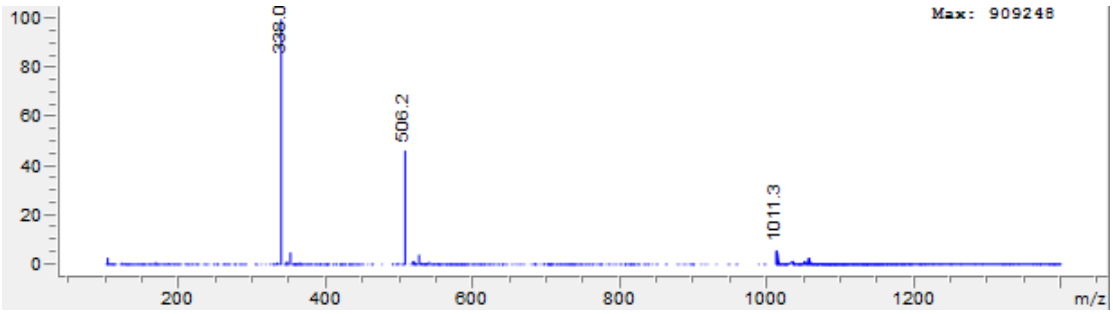


Figure S122. ESI Mass spectrum of peptide **1l**. Calculated Mass $[M+H]^{+}$: 1011.5; $[M+2H]^{2+}$: 506.2; $[M+3H]^{3+}$: 337.8; Mass Found (ESI+); $[M+H]^{+}$: 1011.3; $[M+2H]^{2+}$: 506.2; $[M+3H]^{3+}$: 338.0.

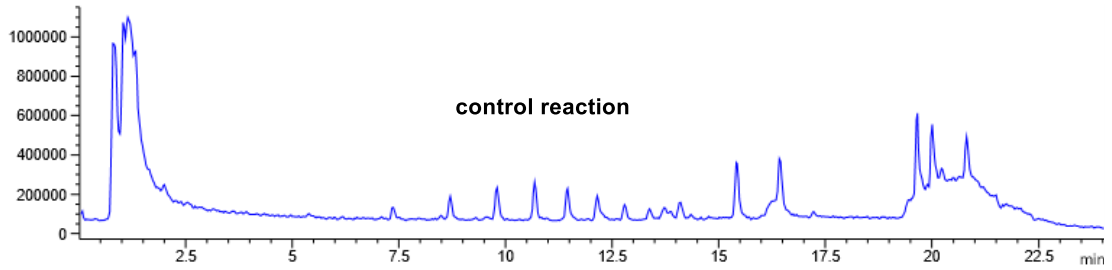


Figure S123. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

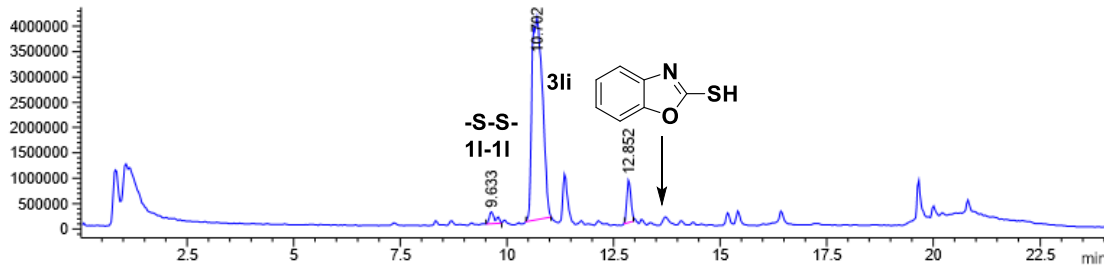


Figure S124. LC-MS TIC curve of reaction mixture. Gradient used： Method C

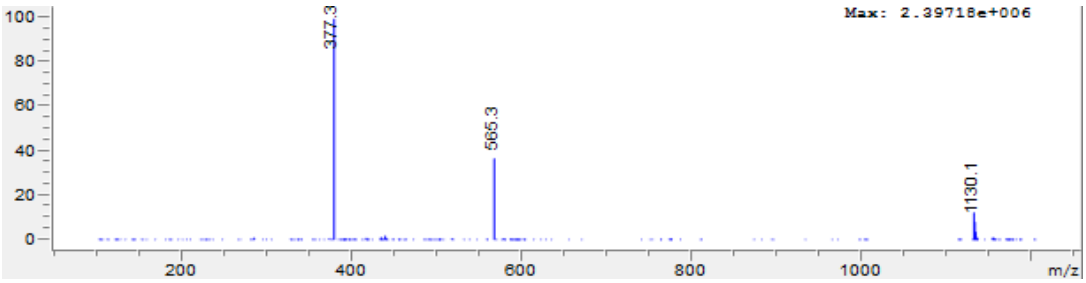


Figure S125. ESI Mass spectrum of modified product **3li**. Calculated Mass $[M+H]^{+}$: 1129.5; $[M+2H]^{2+}$: 565.3; $[M+3H]^{3+}$: 377.2; Mass Found (ESI+); $[M+H]^{+}$: 1130.1; $[M+2H]^{2+}$: 565.3; $[M+3H]^{3+}$: 377.3.

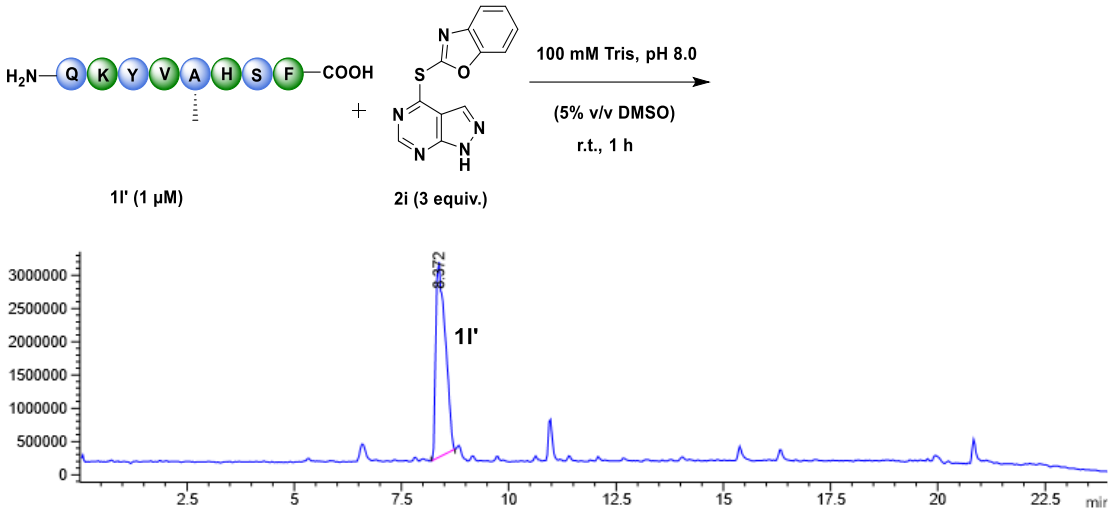


Figure S126. LC-MS TIC curve of peptide **1l'**. Gradient used： Method D

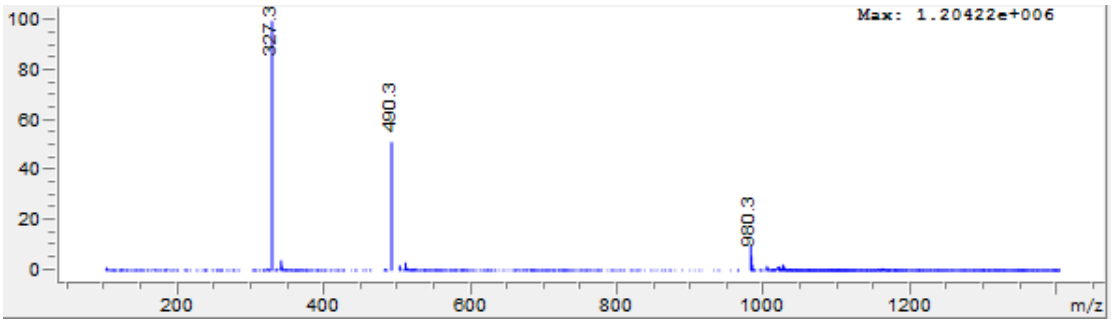


Figure S127. ESI Mass spectrum of peptide **1l'**. Calculated Mass $[M+H]^{+}$: 979.5; $[M+2H]^{2+}$: 490.3; $[M+3H]^{3+}$: 327.3; Mass Found (ESI+); $[M+H]^{+}$: 980.3; $[M+2H]^{2+}$: 490.3; $[M+3H]^{3+}$: 327.2.

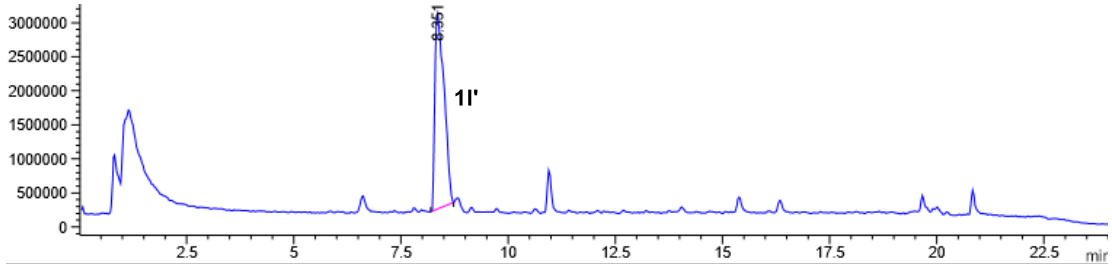


Figure S128. LC-MS TIC curve of reaction mixture. Gradient used： Method D

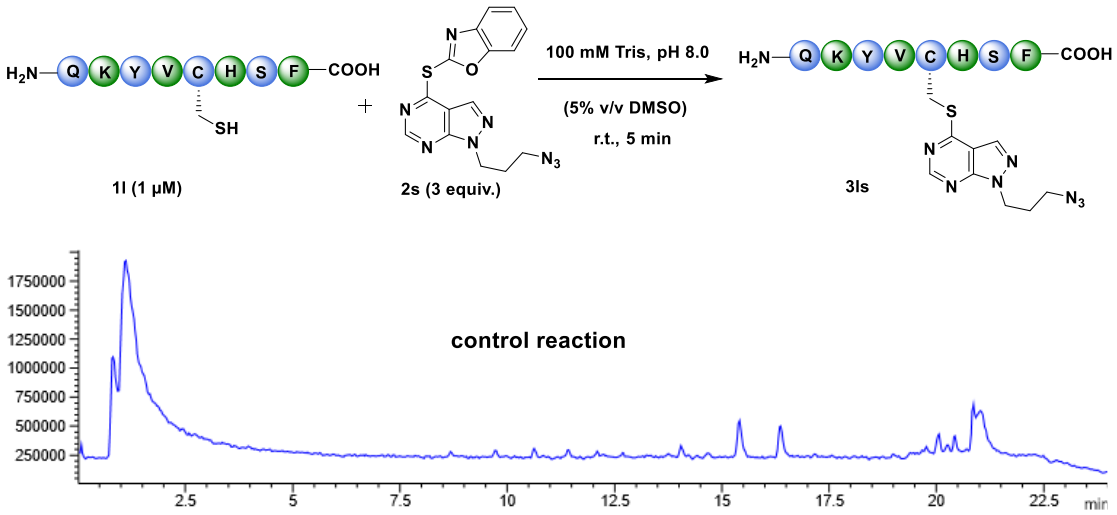


Figure S129. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

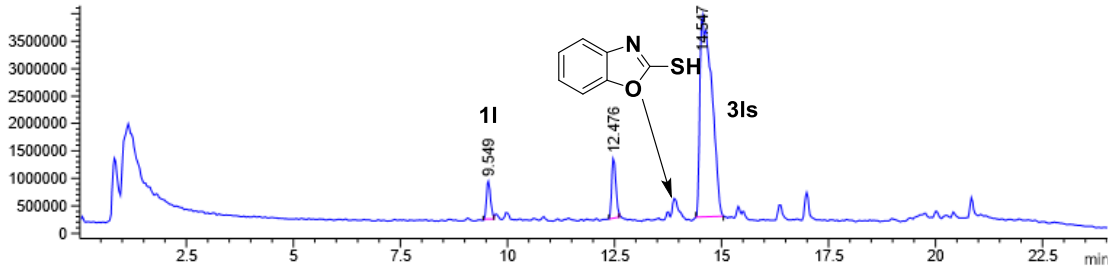


Figure S130. LC-MS TIC curve of reaction mixture. Gradient used： Method C

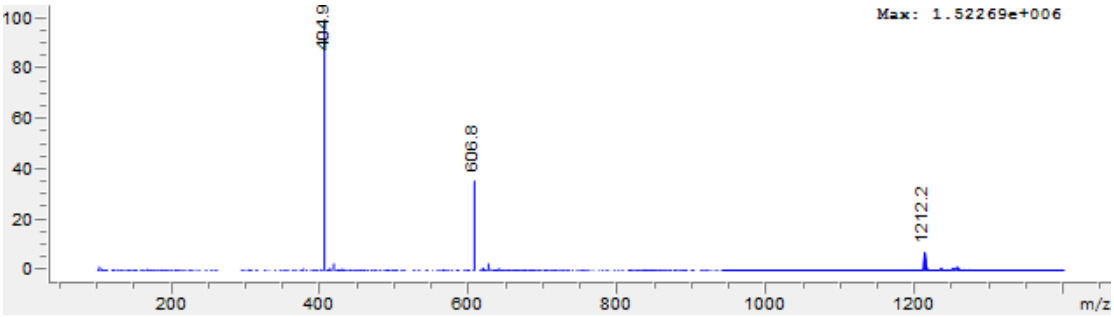
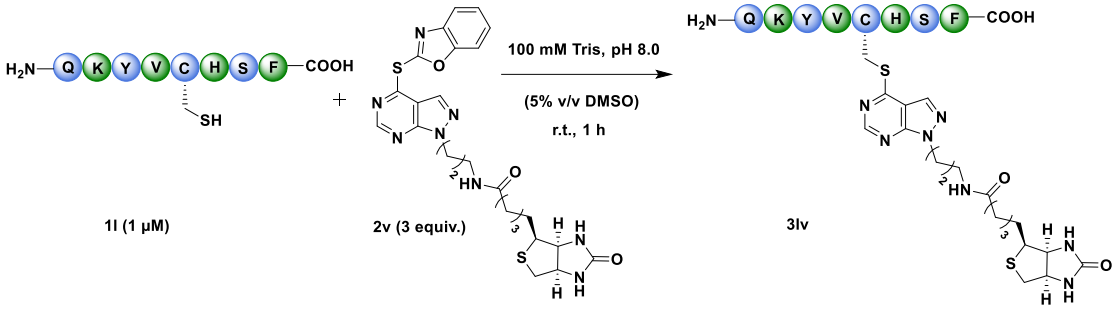


Figure S131. ESI Mass spectrum of modified product **3ls**. Calculated Mass $[M+H]^{+}$: 1212.5; $[M+2H]^{2+}$: 606.8; $[M+3H]^{3+}$: 404.9; Mass Found (ESI+); $[M+H]^{+}$: 1212.2; $[M+2H]^{2+}$: 606.8; $[M+3H]^{3+}$: 404.9.



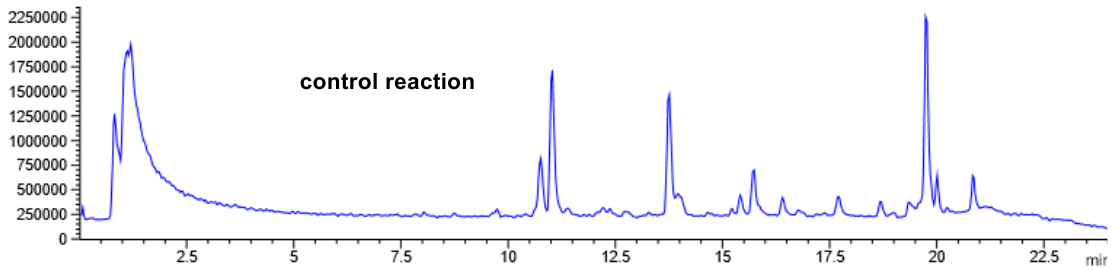


Figure S132. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

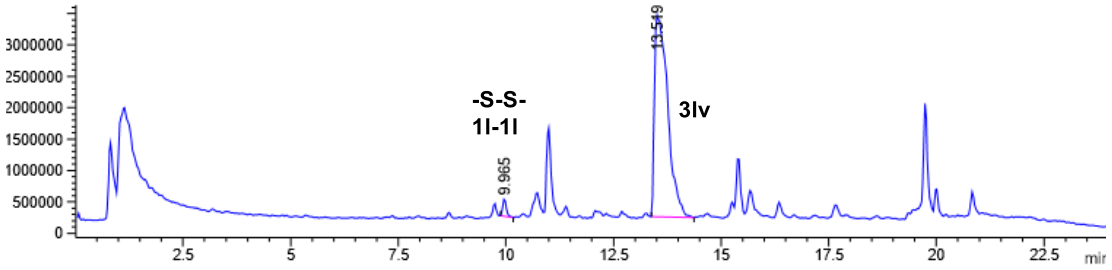


Figure S133. LC-MS TIC curve of reaction mixture. Gradient used： Method C

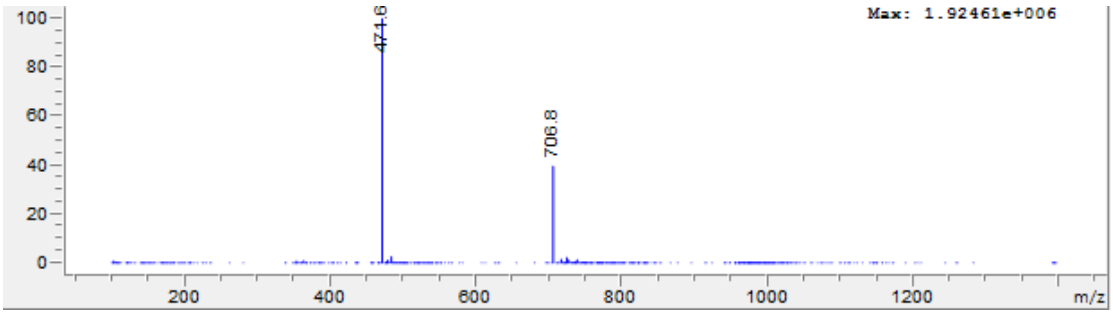
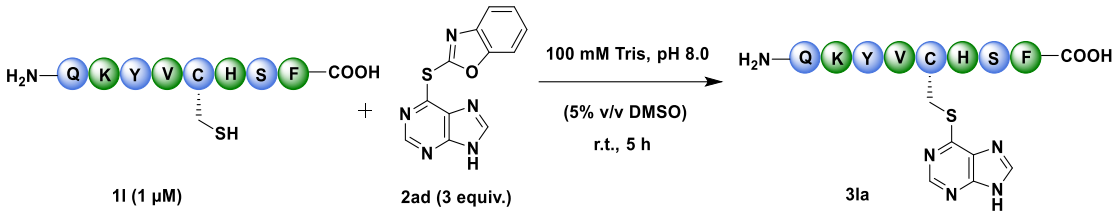


Figure S134. ESI Mass spectrum of modified product **3lv**. Calculated Mass $[M+2H]^{2+}$: 706.8; $[M+3H]^{3+}$: 471.6; Mass Found (ESI+); $[M+2H]^{2+}$: 706.8; $[M+3H]^{3+}$: 471.6.



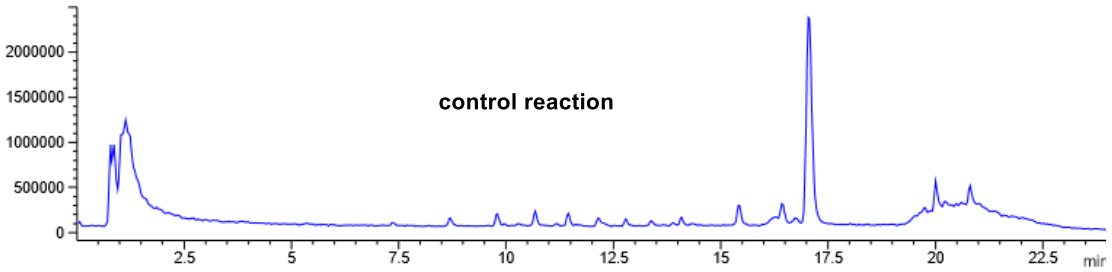


Figure S135. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

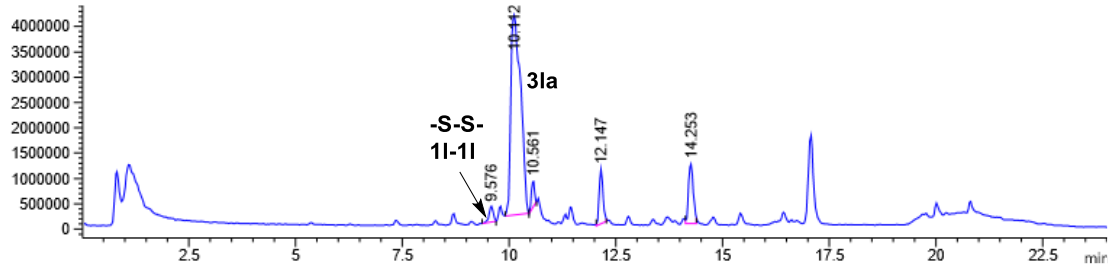


Figure S136. LC-MS TIC curve of reaction mixture. Gradient used： Method C

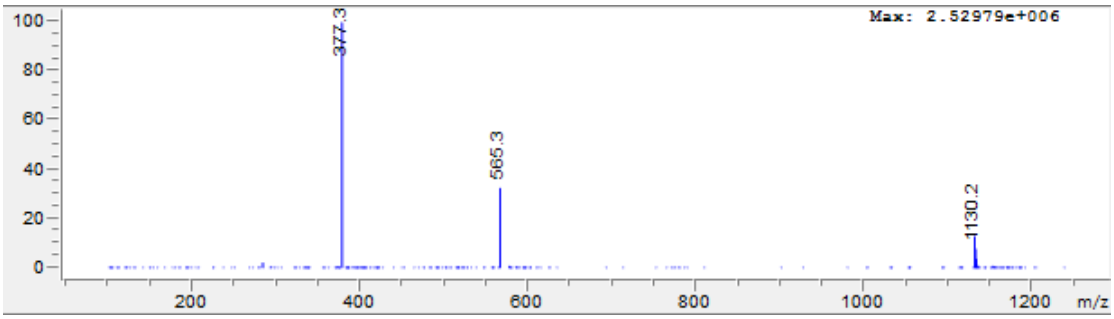


Figure S137. ESI Mass spectrum of modified product **3la**. Calculated Mass $[M+H]^+$: 1129.5; $[M+2H]^{2+}$: 565.3; $[M+3H]^{3+}$: 377.2; Mass Found (ESI+); $[M+H]^+$: 1130.2; $[M+2H]^{2+}$: 565.3; $[M+3H]^{3+}$: 377.3.

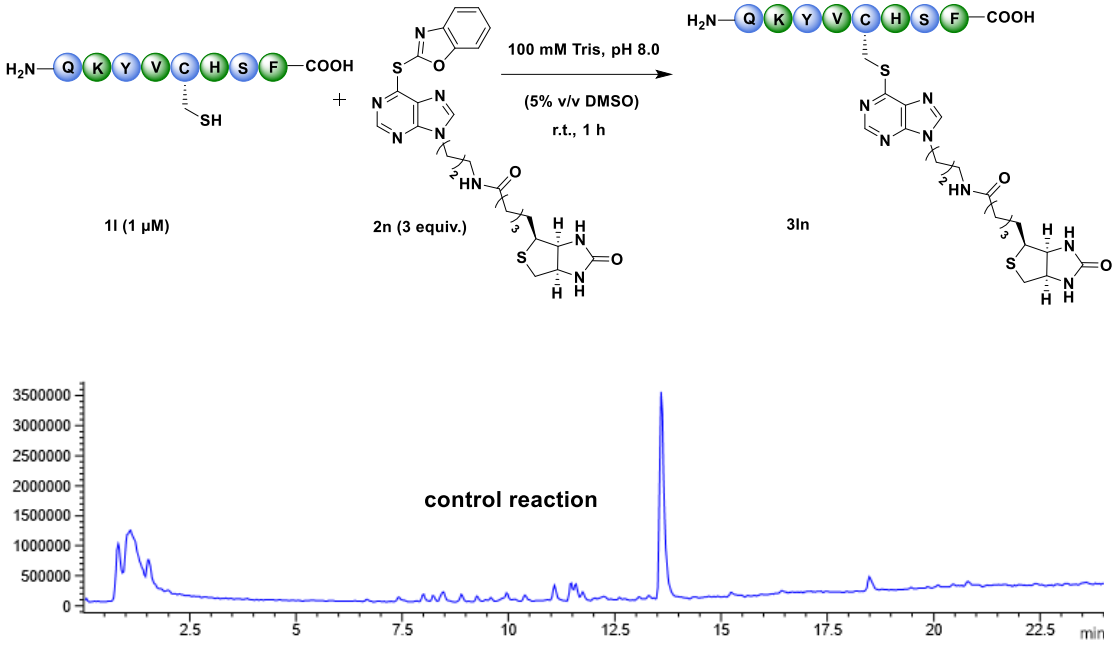


Figure S138. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method C

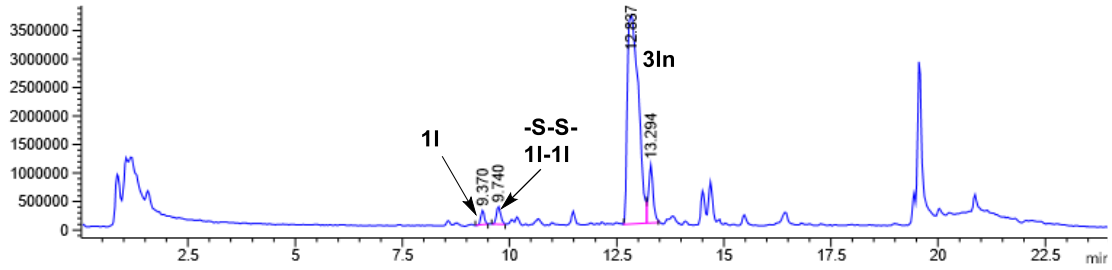


Figure S139. LC-MS TIC curve of reaction mixture. Gradient used： Method C

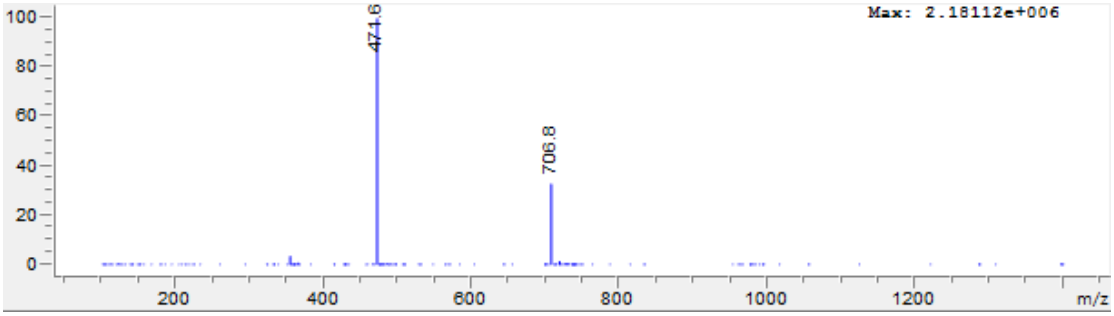


Figure S140. ESI Mass spectrum of modified product **3ln**. Calculated Mass $[M+2H]^{2+}$: 706.8; $[M+3H]^{3+}$: 471.6; Mass Found (ESI+); $[M+2H]^{2+}$: 706.8; $[M+3H]^{3+}$: 471.6.

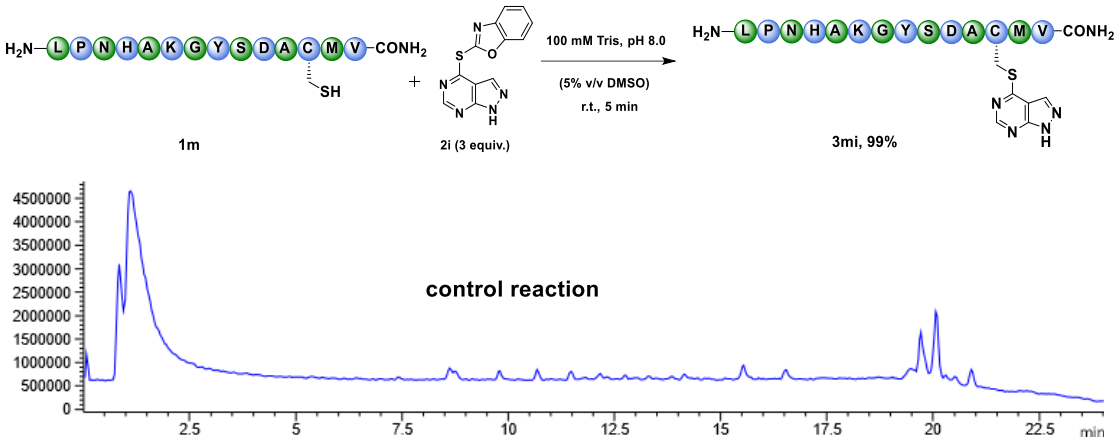


Figure S141. LC-MS TIC curve of control reaction (without peptide). Gradient used： Method D

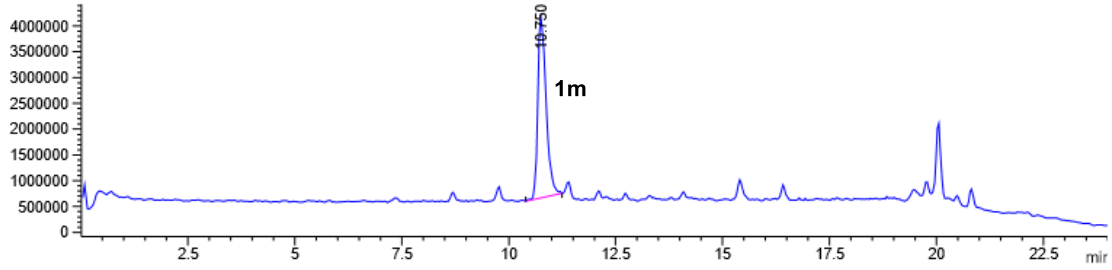


Figure S142. LC-MS TIC curve of peptide **1m**. Gradient used： Method D

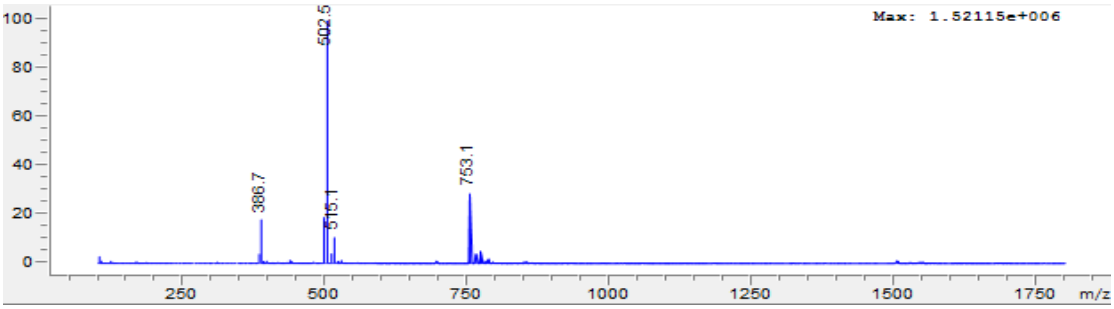


Figure S143. ESI Mass spectrum of peptide **1m**. Calculated Mass $[M+2H]^{2+}$: 752.9; $[M+3H]^{3+}$: 502.2; Mass Found (ESI+); $[M+2H]^{2+}$: 753.1; $[M+3H]^{3+}$: 502.5.

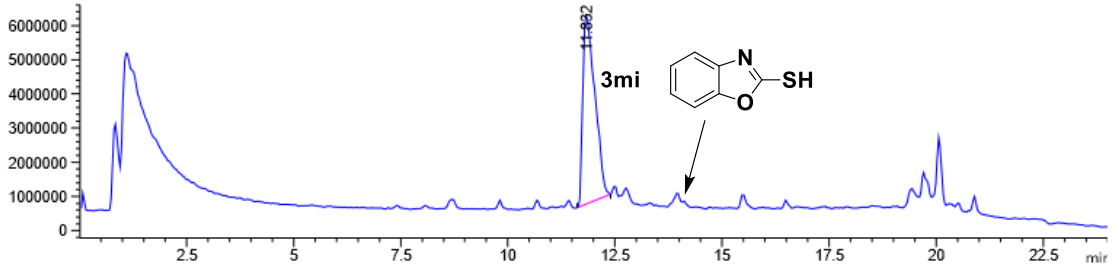


Figure S144. LC-MS TIC curve of reaction mixture. Gradient used： Method D

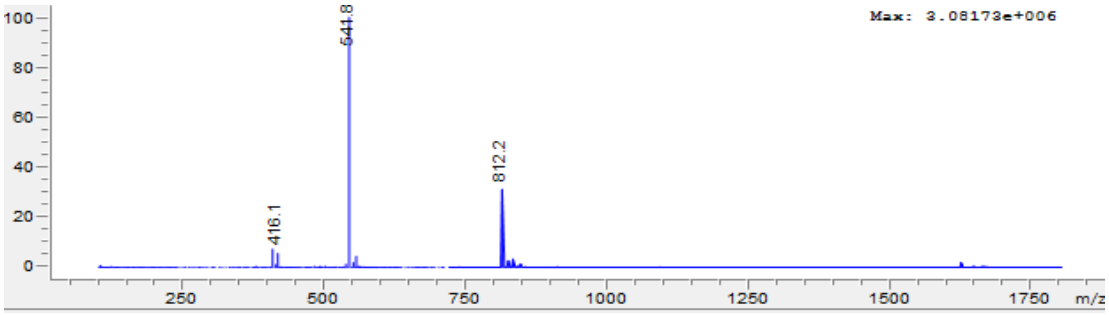


Figure S145. ESI Mass spectrum of modified product **3mi**. Calculated Mass $[M+2H]^{2+}$: 811.9; $[M+3H]^{3+}$: 541.6; Mass Found (ESI+); $[M+2H]^{2+}$: 812.2; $[M+3H]^{3+}$: 541.8.

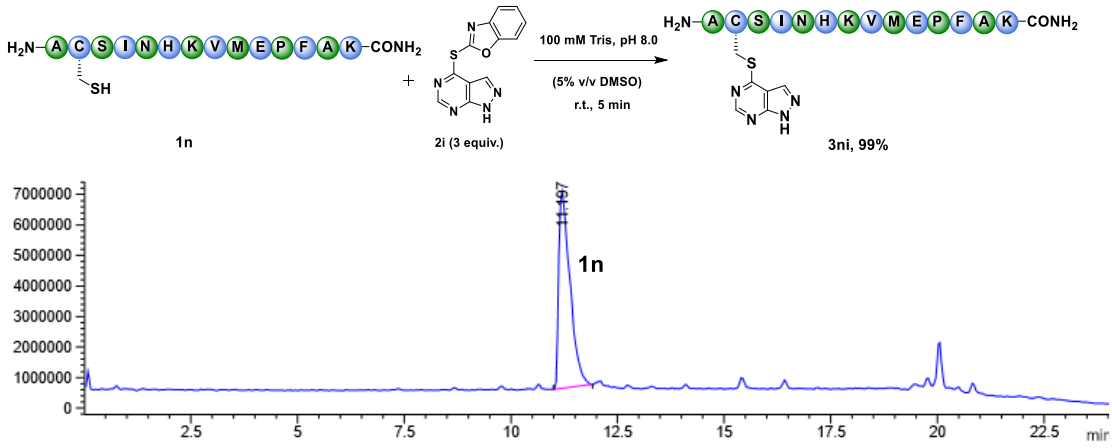


Figure S146. LC-MS TIC curve of peptide **1n**. Gradient used： Method D

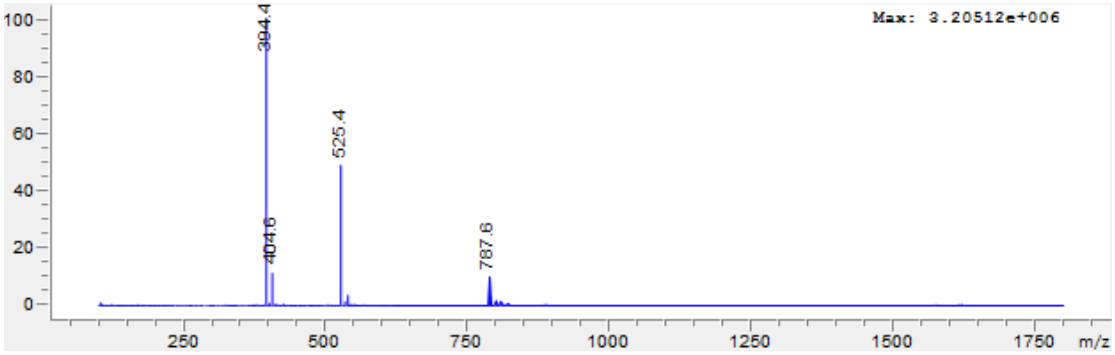


Figure S147. ESI Mass spectrum of peptide **1n**. Calculated Mass $[M+2H]^{2+}$: 787.4; $[M+3H]^{3+}$: 525.3; $[M+4H]^{4+}$: 394.2; Mass Found (ESI+); $[M+2H]^{2+}$: 787.6; $[M+3H]^{3+}$: 525.4; $[M+4H]^{4+}$: 394.4.

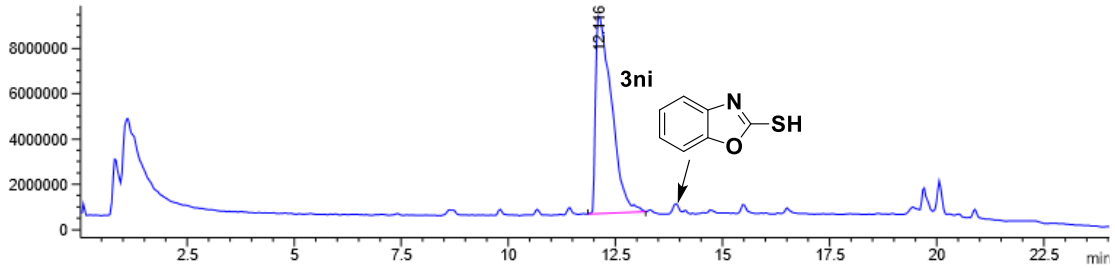


Figure S148. LC-MS TIC curve of reaction mixture. Gradient used： Method D

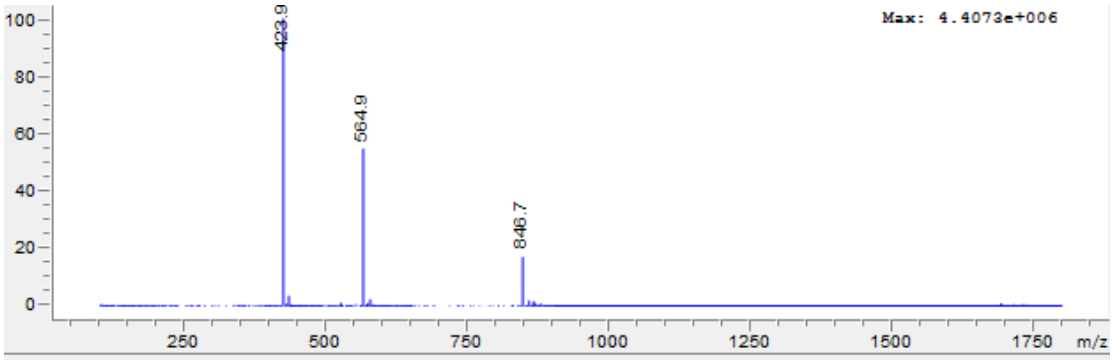


Figure S149. ESI Mass spectrum of modified peptide **1ni**. Calculated Mass $[M+2H]^{2+}$: 846.4; $[M+3H]^{3+}$: 564.6; $[M+4H]^{4+}$: 423.7; Mass Found (ESI+); $[M+2H]^{2+}$: 846.7; $[M+3H]^{3+}$: 546.9; $[M+4H]^{4+}$: 423.9.

9. Stability evaluation of modified peptide

Peptide conjugates were pre-dissolved in water to afford the 1.11 mM stock solution. K_2CO_3 and H_5IO_6 were dissolved in water to afford 50 mM K_2CO_3 and 5 mM H_5IO_6 solutions. Glutathione (GSH) and 2-mercaptoethanol (βME) were dissolved in Tris buffer (100 mM, pH 8.0) to afford external thiol test solutions.

Acidic conditions (pH 4.0 AcOH)

Peptide conjugates were dissolved in pH 4.0 AcOH buffeer to afford the 1 mM peptide solutions. Then these samples left at room temperature and analyzed by LC-MS at corresponding time.

Basic conditions (5 mM K_2CO_3)

Corresponding cysteine conjugates (1.11 mM; 450 µL) and K_2CO_3 solution (50 µL, 50 mM in H_2O) were combined in a plastic Eppendorf and left at room temperature and analyzed by LC-MS at corresponding time.

Oxidation conditions (5 mM H_5IO_6)

Corresponding cysteine conjugates (1.11 mM; 450 µL) and H_5IO_6 solution (50 µL, 50 mM in H_2O) were combined in a plastic Eppendorf and left at room temperature and analyzed by LC-MS at corresponding time.

External thiol nucleophiles (GSH and βME)

Peptide conjugates were dissolved in GSH (100 mM in Tris) orβME (100 mM in Tris) to afford the 1 mM peptide solutions. Then these samples left at room temperature and analyzed by LC-MS at corresponding time.

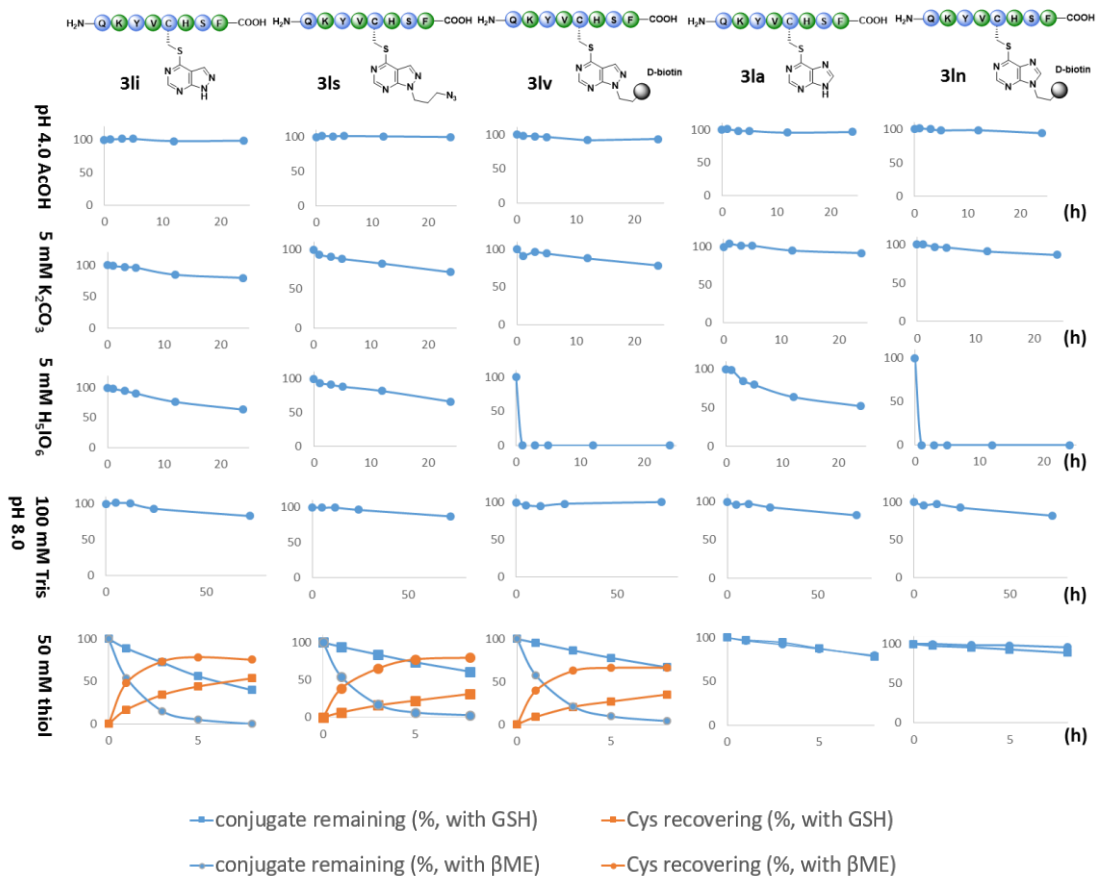
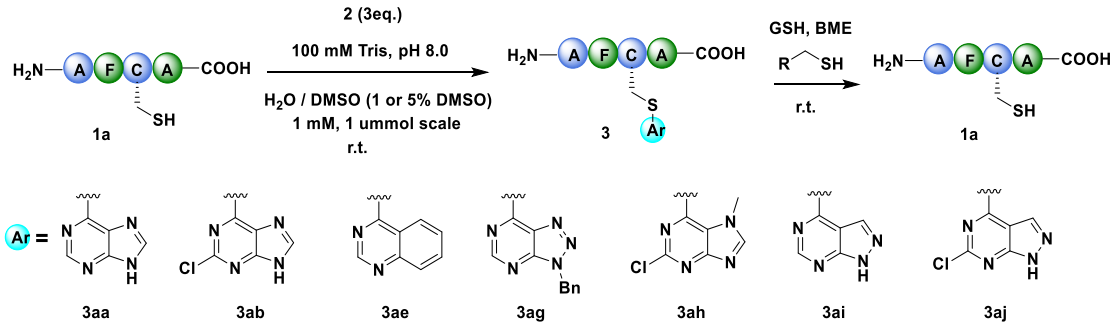
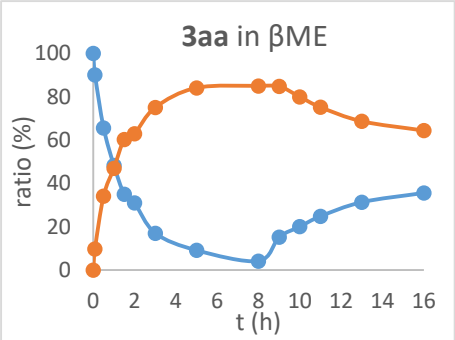


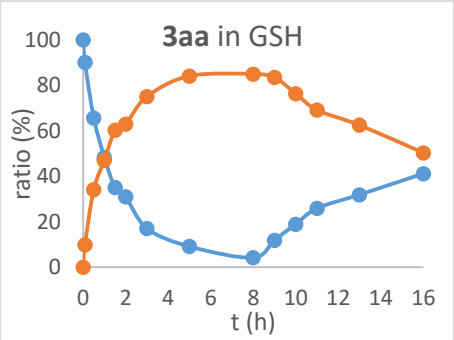
Figure S150. Stability of modified peptides **3li**, **3ls**, **3lv**, **3la** and **3ln**.

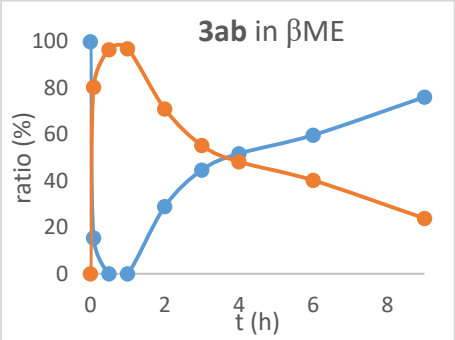
10.Regeneration activity evaluation of modified peptides

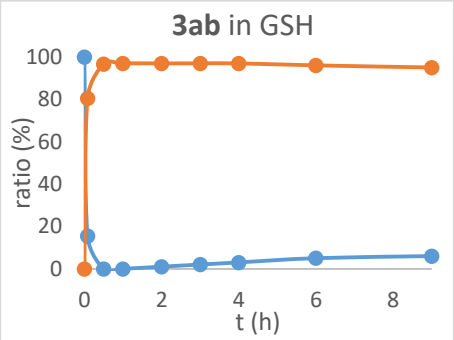
General procedure: Firstly, according the general procedure for arylation of cysteine-containing peptides to afford the modified peptide **3**. After reaction finished, 1 mL 100 mM mercaptoethanol (βME) or glutathione (GSH) Tris (100 mM, pH 8.0) solution was added to reaction mixture respectively, then monitored by LC-MS to determine the ratio of **3** and **1a** in peptide species. %ratio = $S_{desired}/S_{total}$, where $S_{desired}$ is the peak area of **3** or **1a** and S_{total} is the peak area of combined peptide-containing species (**3**, **1a** and byproduct). The blue curve represent the ratio of **3** and the orange represent **1a**.

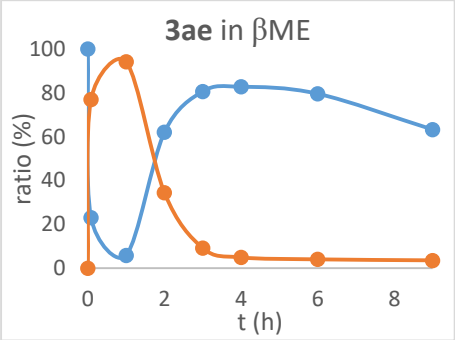


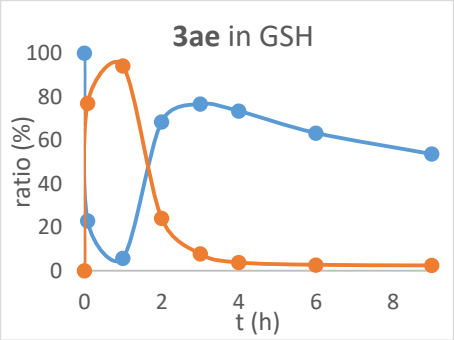

3aa in βME
ratio (%)
t (h)

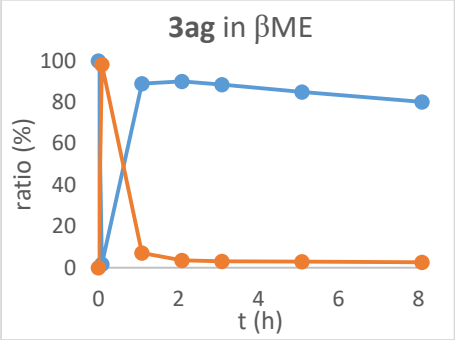

3aa in GSH
ratio (%)
t (h)

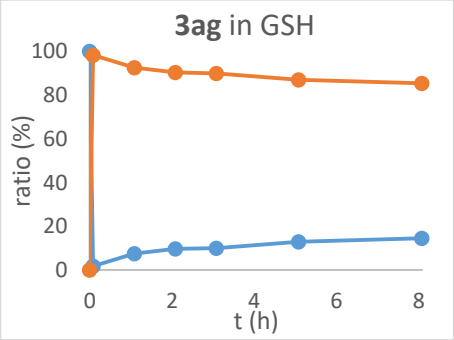

3ab in βME
ratio (%)
t (h)

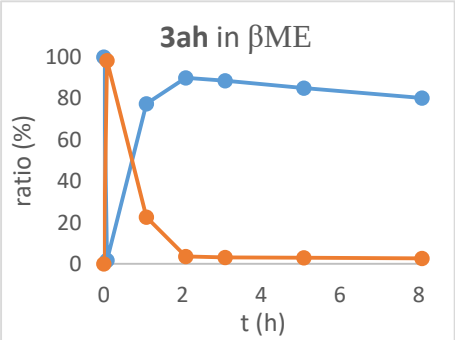

3ab in GSH
ratio (%)
t (h)

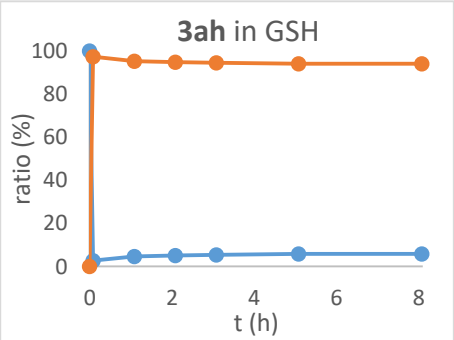

3ae in βME
ratio (%)
t (h)


3ae in GSH
ratio (%)
t (h)


3ag in βME
ratio (%)
t (h)


3ag in GSH
ratio (%)
t (h)


3ah in βME
ratio (%)
t (h)


3ah in GSH
ratio (%)
t (h)

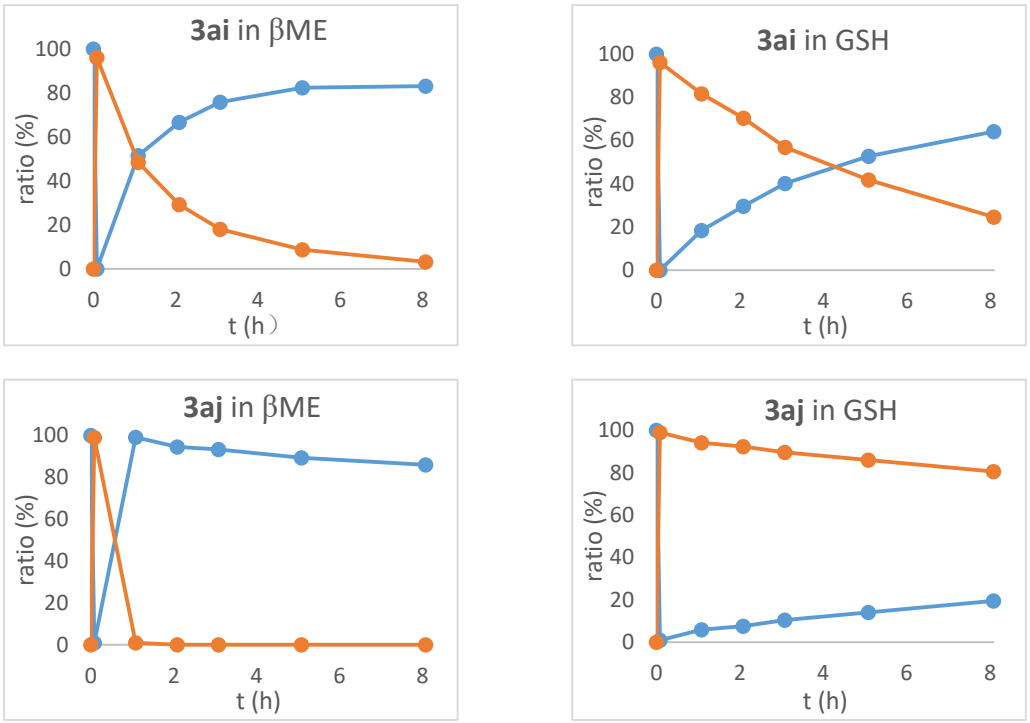


Figure 151. Regeneration activity evaluation of modified peptides.

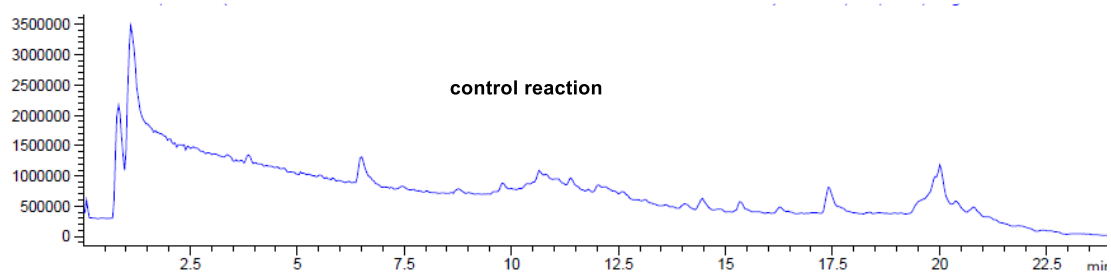
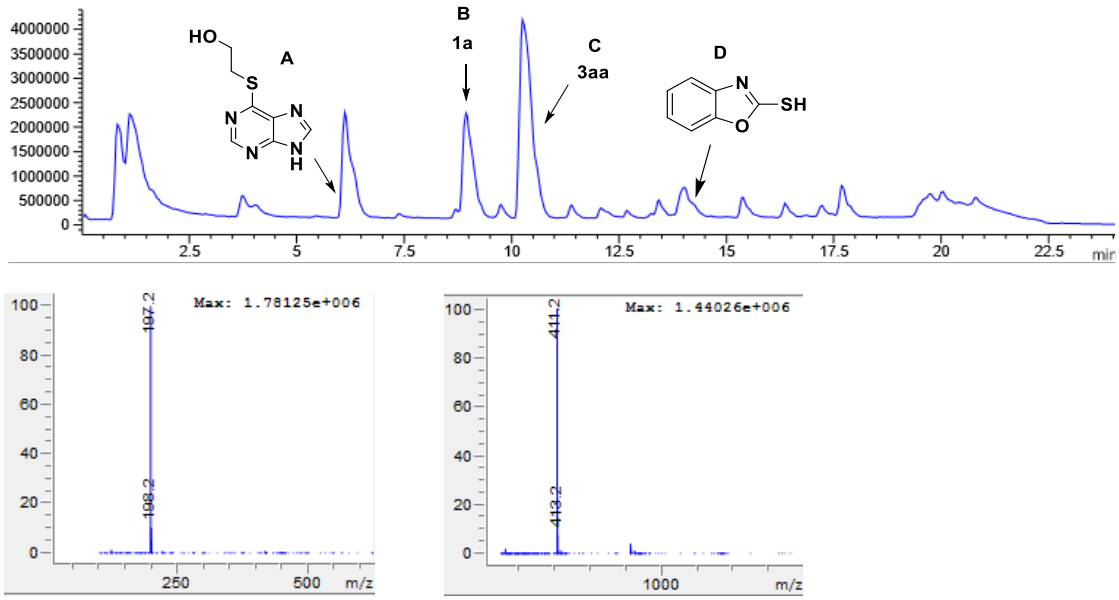
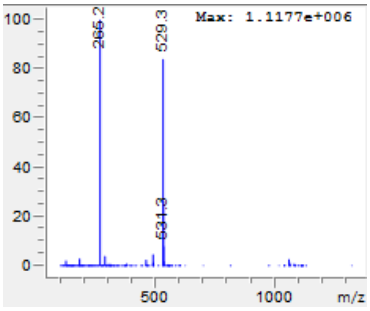


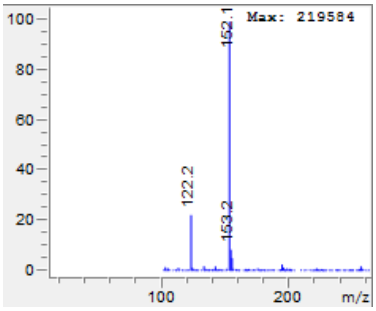
Figure S152. LC-MS TIC curve of control reaction for the whole process with **2ad** and βME (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A



ESI Mass spectrum of peak B



ESI Mass spectrum of peak C

ESI Mass spectrum of peak D

Figure S153. LC-MS TIC curve of reaction mixture of **3aa** and corresponding ESI mass spectrum after added βME for 8h. Gradient used： Method D

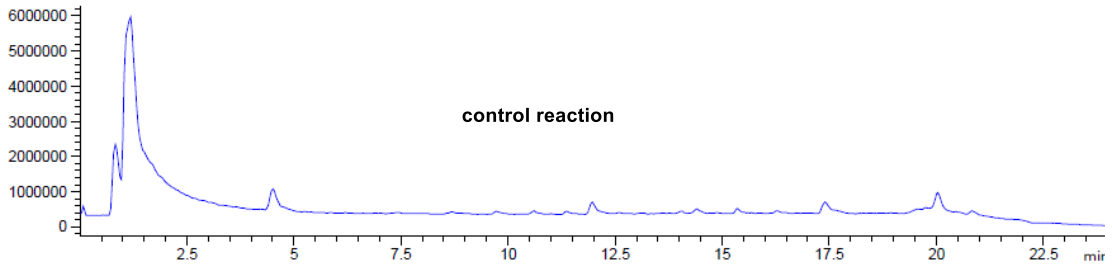
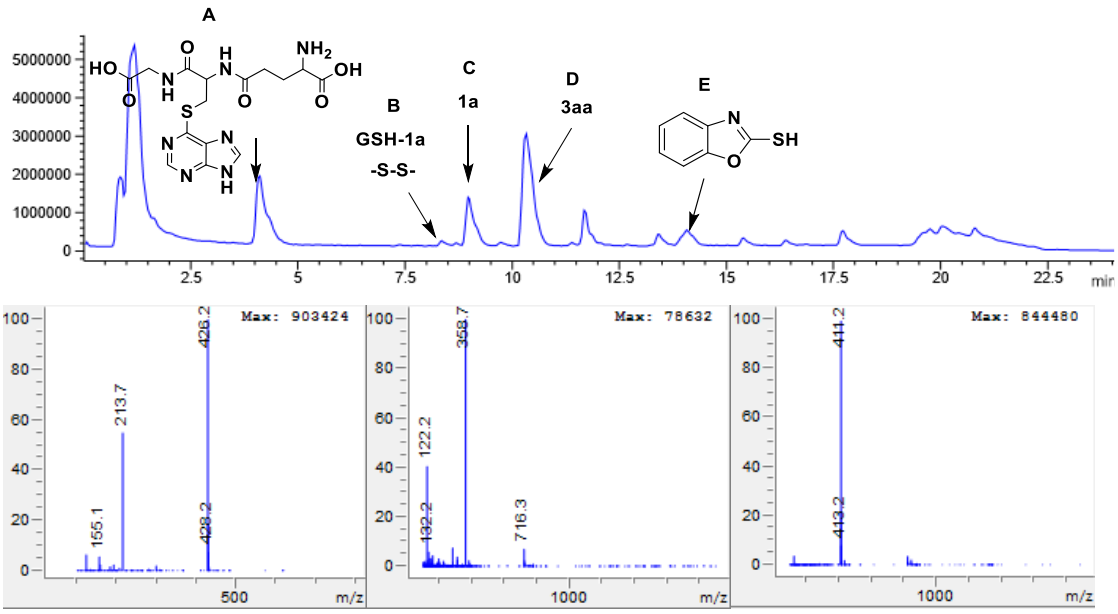


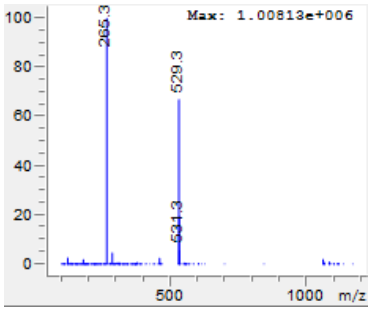
Figure S154. LC-MS TIC curve of control reaction for the whole process with **2ad** and GSH (without peptide). Gradient used： Method D

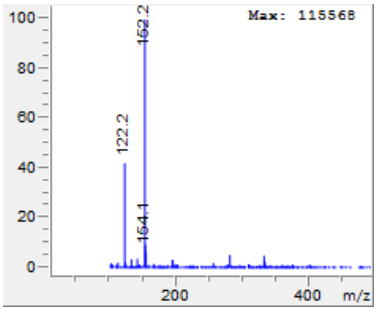


ESI Mass spectrum of peak A

ESI Mass spectrum of peak B

ESI Mass spectrum of peak C





ESI Mass spectrum of peak D ESI Mass spectrum of peak E

Figure S155. LC-MS TIC curve of reaction mixture of **3aa** and corresponding ESI mass spectrum after added GSH for 8h. Gradient used： Method D

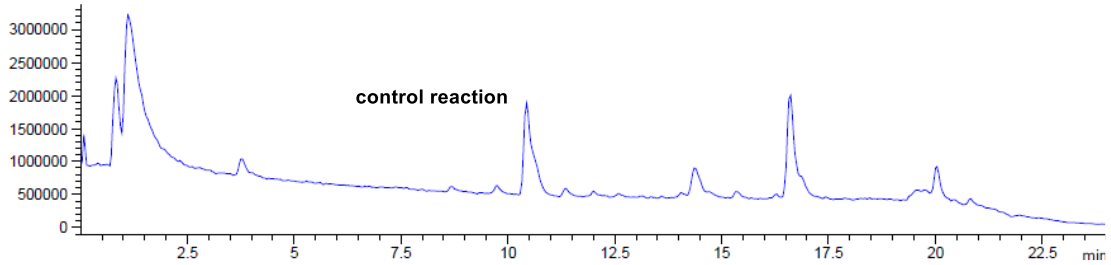
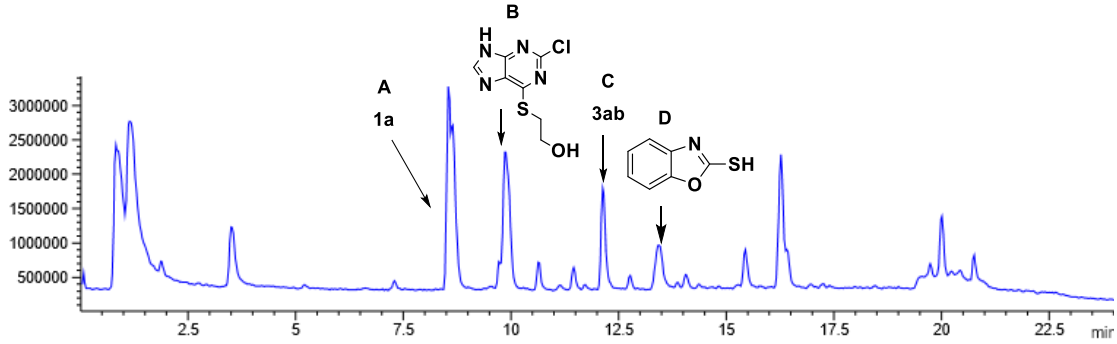
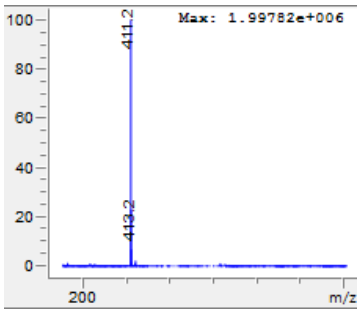
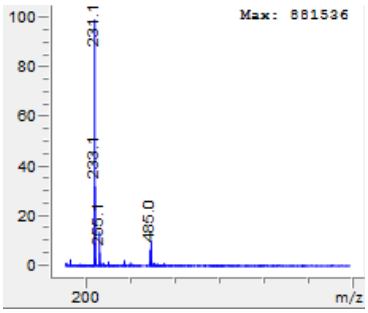


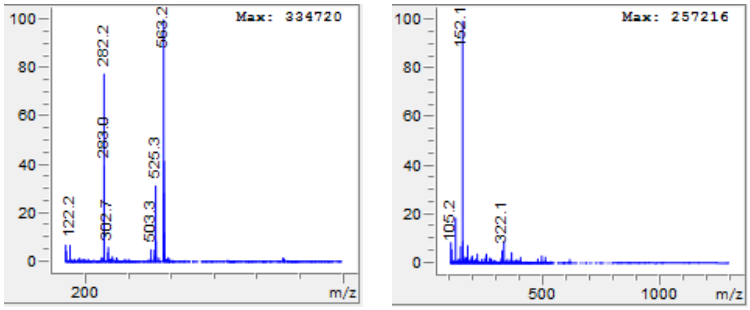
Figure S156. LC-MS TIC curve of control reaction for the whole process with **2b** and βME (without peptide). Gradient used： Method D







ESI Mass spectrum of peak A ESI Mass spectrum of peak B



ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S157. LC-MS TIC curve of reaction mixture of **3ab** and corresponding ESI mass spectrum after added βME for 8h. Gradient used： Method D

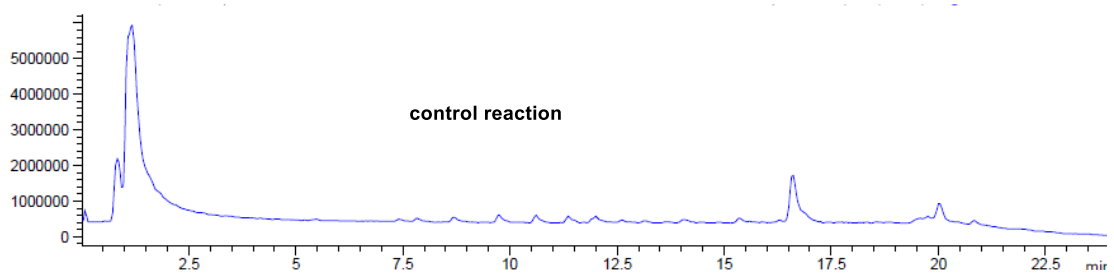
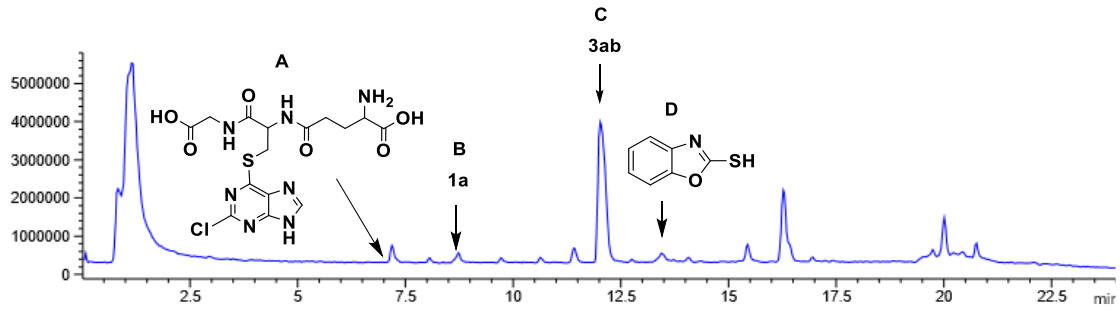
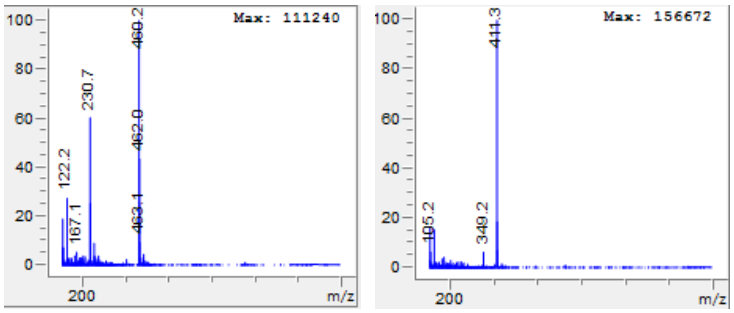
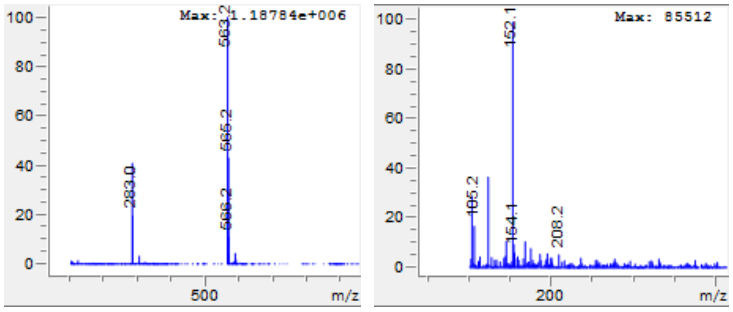


Figure S158. LC-MS TIC curve of control reaction for the whole process with **2b** and GSH (without peptide). Gradient used： Method D





ESI Mass spectrum of peak A ESI Mass spectrum of peak B



ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S159. LC-MS TIC curve of reaction mixture of **3ab** and corresponding ESI mass spectrum after added GSH for 8h. Gradient used： Method D

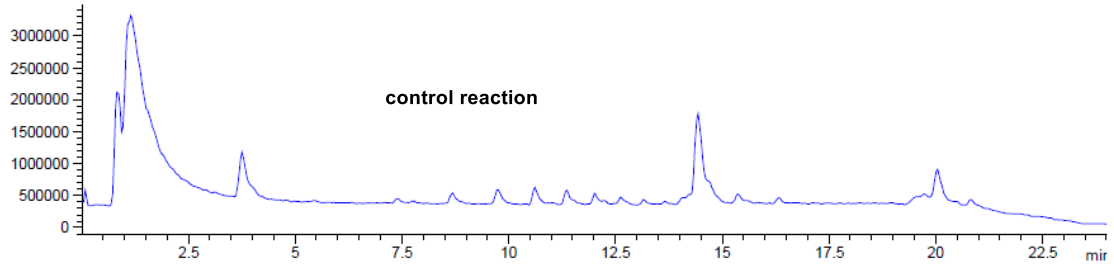
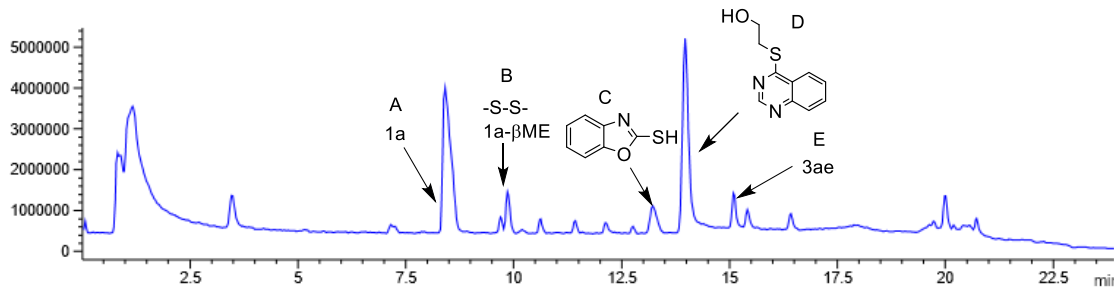
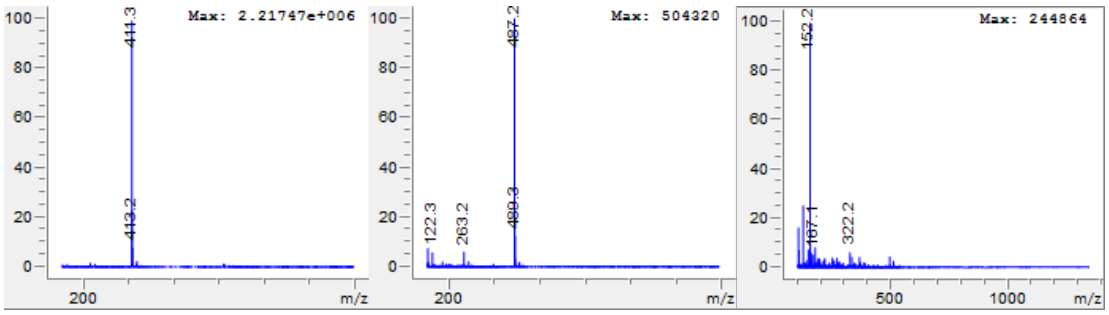
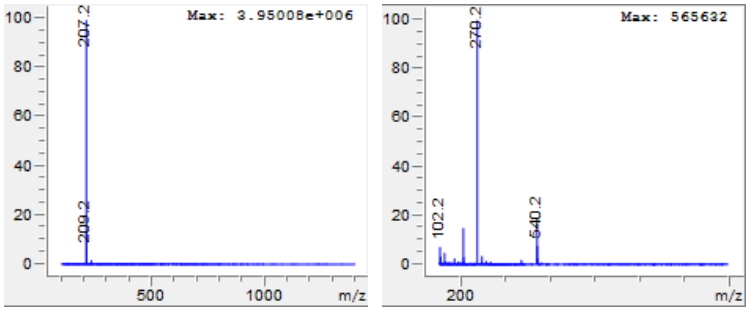


Figure S160. LC-MS TIC curve of control reaction for the whole process with **2e** and βME (without peptide). Gradient used： Method D





ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C



ESI Mass spectrum of peak D ESI Mass spectrum of peak E

Figure S161. LC-MS TIC curve of reaction mixture of **3ae** and corresponding ESI mass spectrum after added βME for 2h. Gradient used： Method D

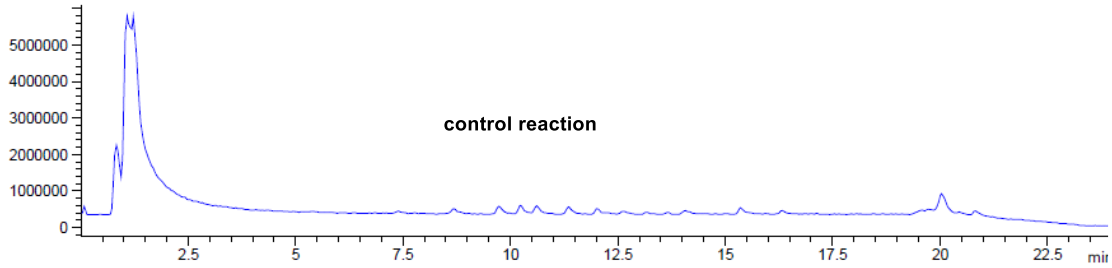
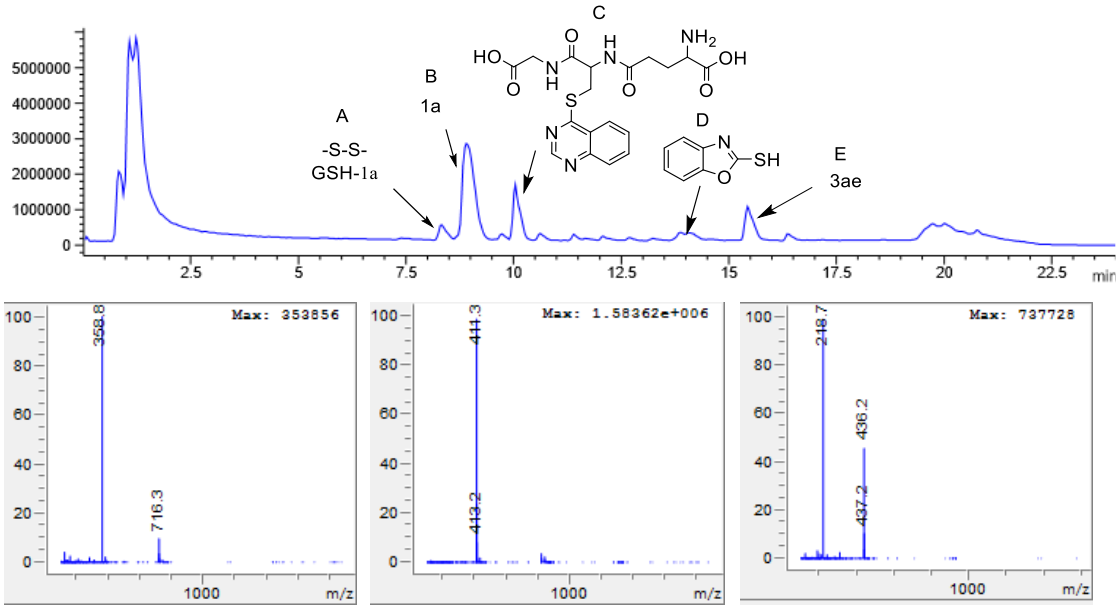
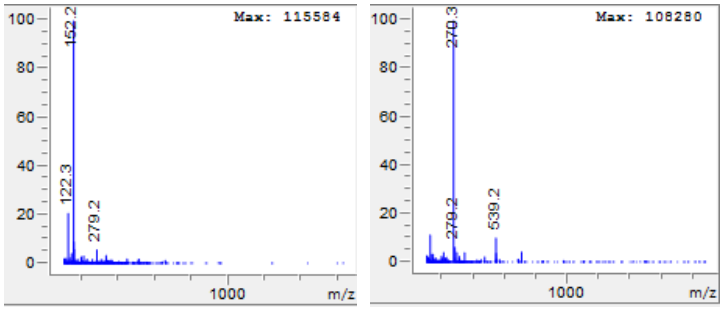


Figure S162. LC-MS TIC curve of control reaction for the whole process with **2e** and GSH (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C



ESI Mass spectrum of peak D ESI Mass spectrum of peak E

Figure S163. LC-MS TIC curve of reaction mixture of **3ae** and corresponding ESI mass spectrum after added GSH for 3h. Gradient used： Method D

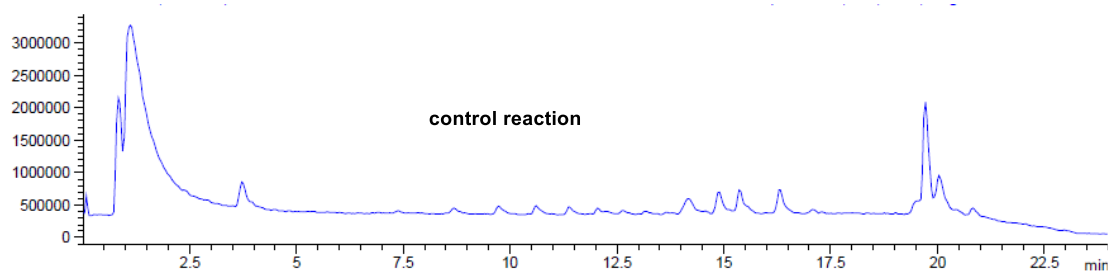
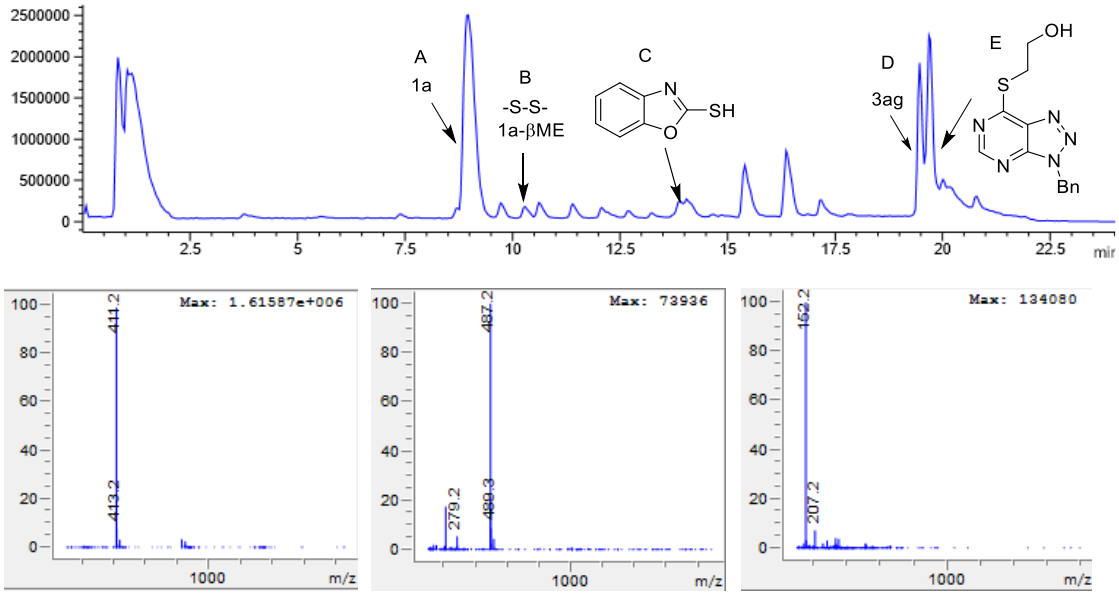
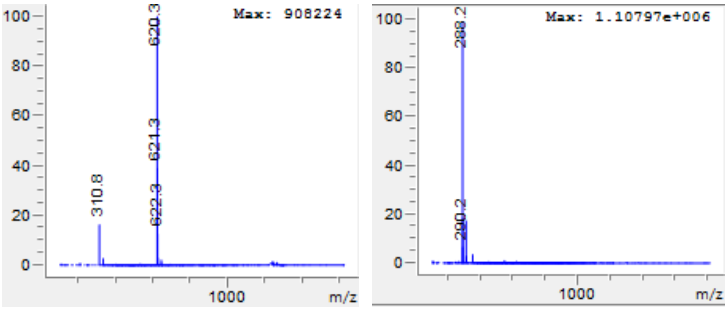


Figure S164. LC-MS TIC curve of control reaction for the whole process with **2g** and βME (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C



ESI Mass spectrum of peak D ESI Mass spectrum of peak E

Figure S165. LC-MS TIC curve of reaction mixture of **3ag** and corresponding ESI mass spectrum after added βME for 1h. Gradient used： Method D

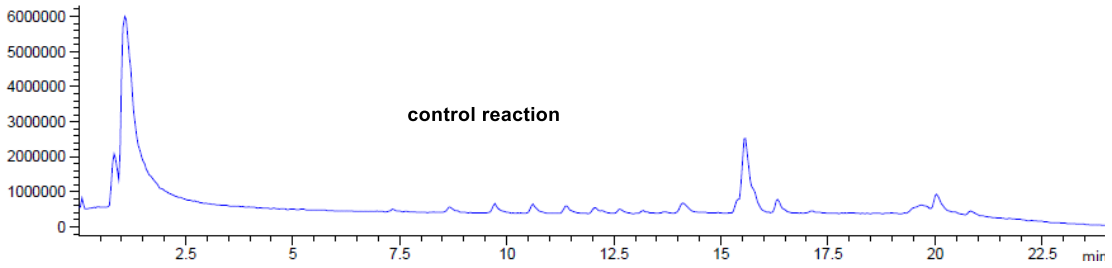
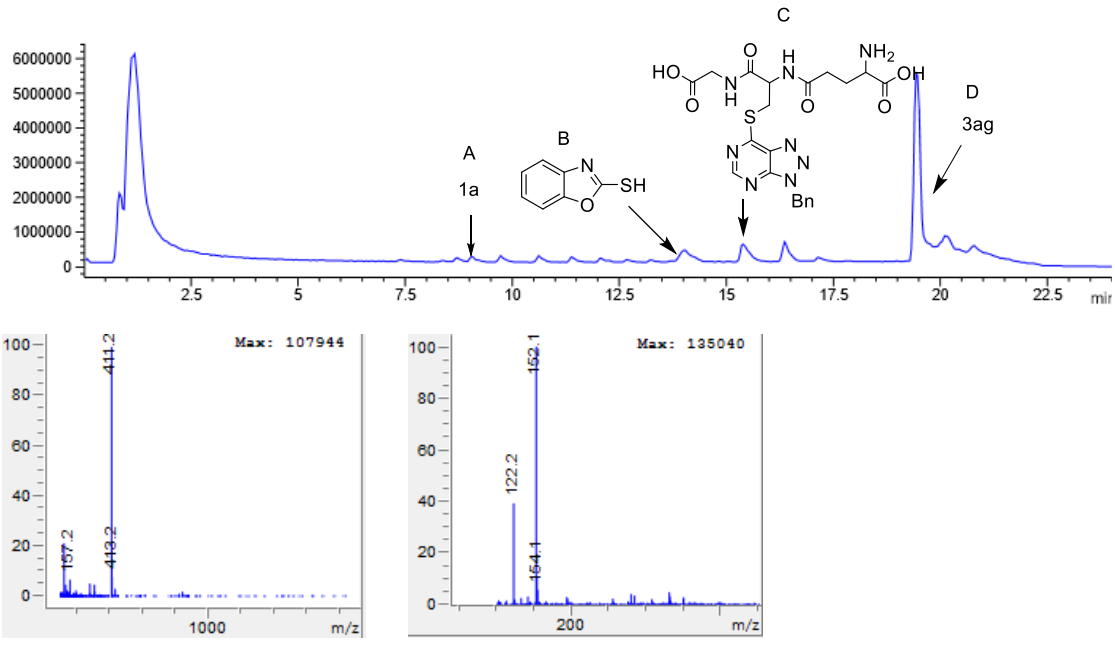
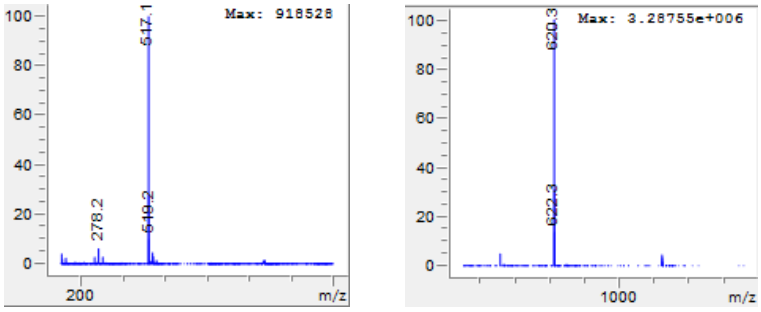


Figure S166. LC-MS TIC curve of control reaction for the whole process with **2g** and GSH (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A ESI Mass spectrum of peak B



ESI Mass spectrum of peak D ESI Mass spectrum of peak E

Figure S167. LC-MS TIC curve of reaction mixture of **3ag** and corresponding ESI mass spectrum after added GSH for 8h. Gradient used： Method D

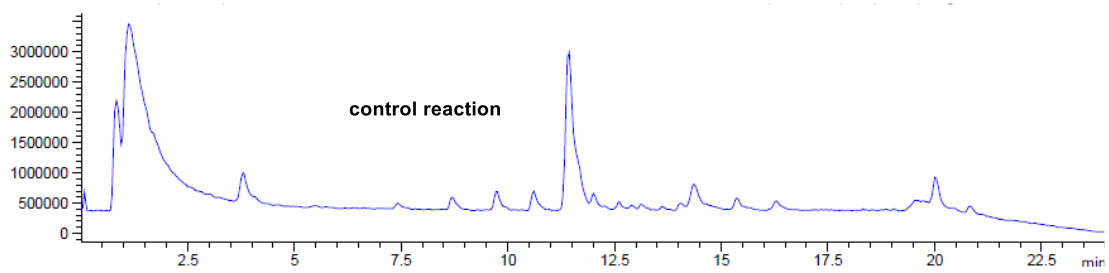
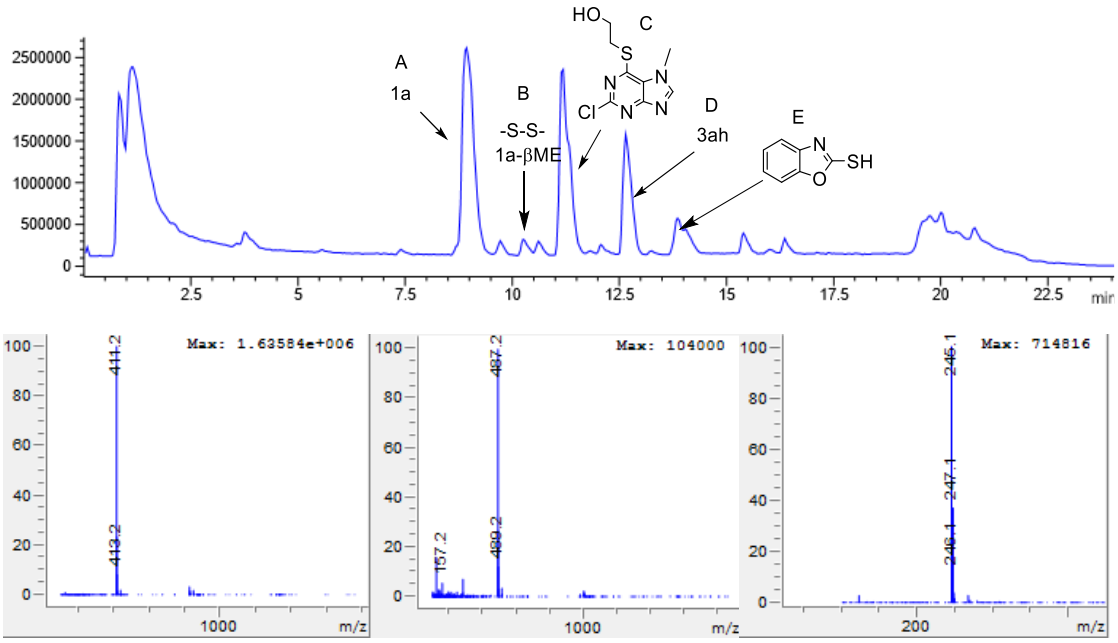
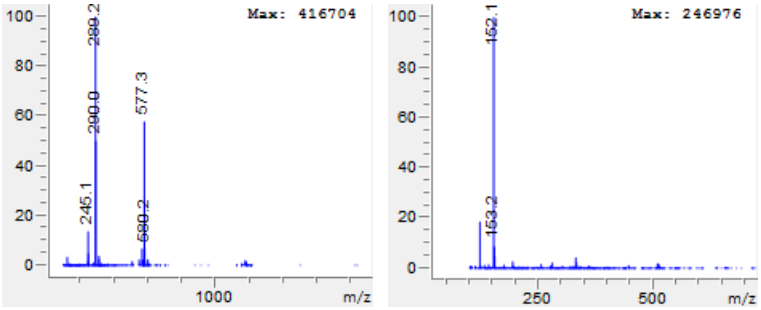


Figure S168. LC-MS TIC curve of control reaction for the whole process with **2h** and βME (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C



ESI Mass spectrum of peak D ESI Mass spectrum of peak E

Figure S169. LC-MS TIC curve of reaction mixture of **3ah** and corresponding ESI mass spectrum after added βME for 1h. Gradient used： Method D

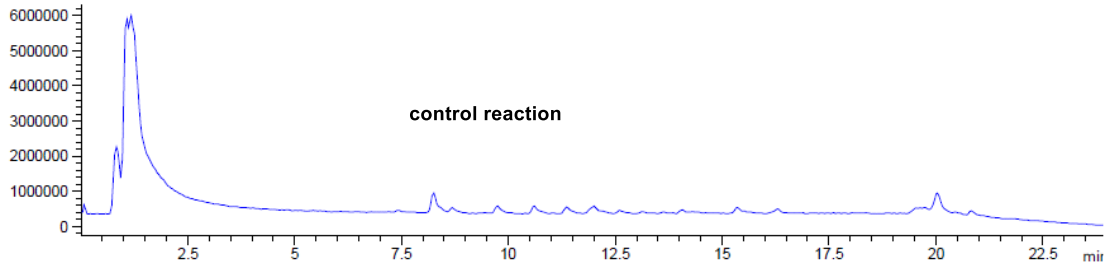
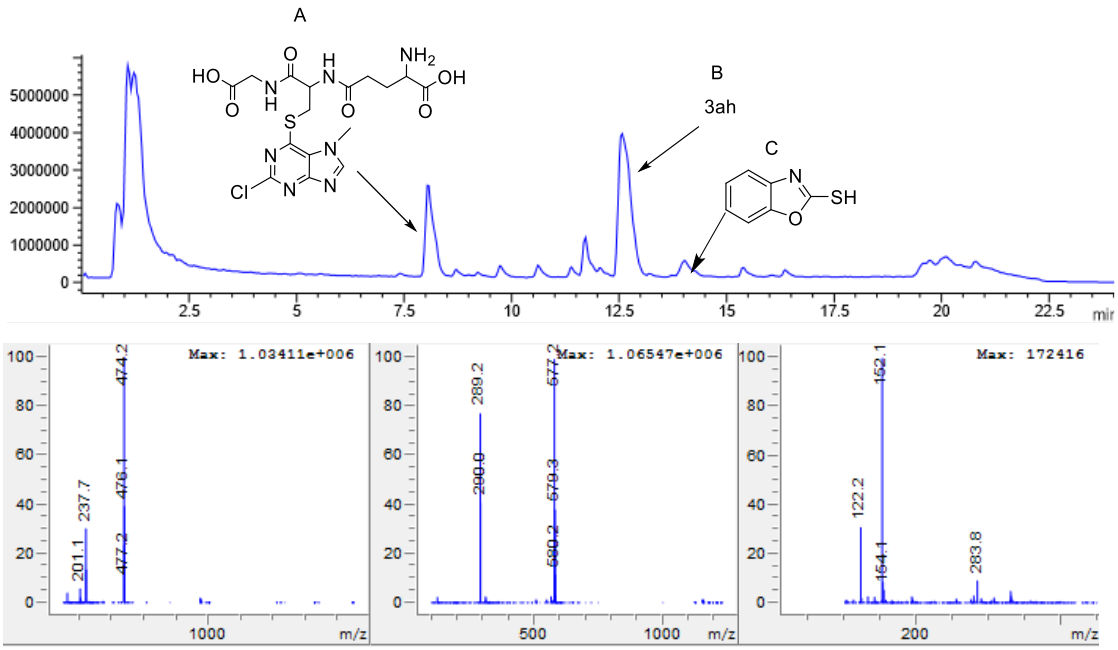


Figure S170. LC-MS TIC curve of control reaction for the whole process with **2h** and GSH (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C

Figure S171. LC-MS TIC curve of reaction mixture of **3ah** and corresponding ESI mass spectrum after added GSH for 8h. Gradient used： Method D

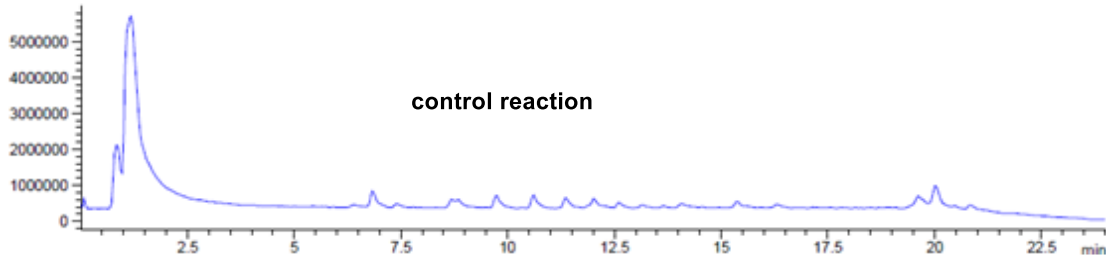
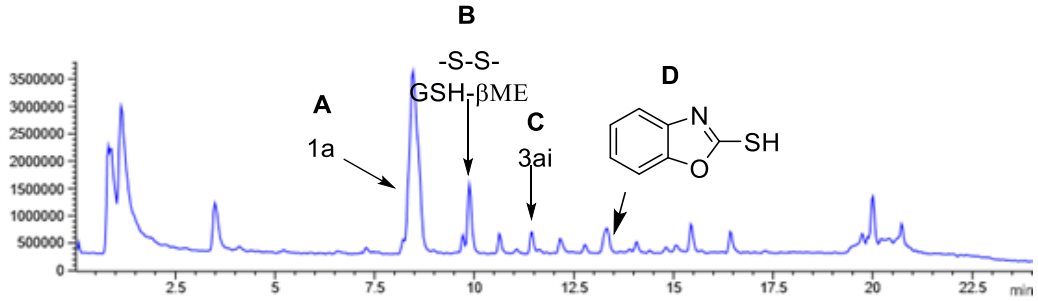
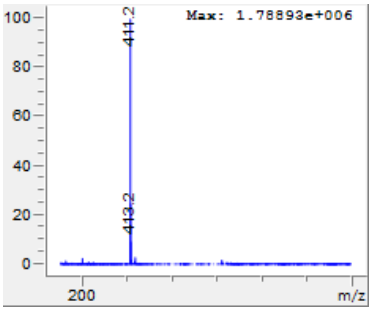
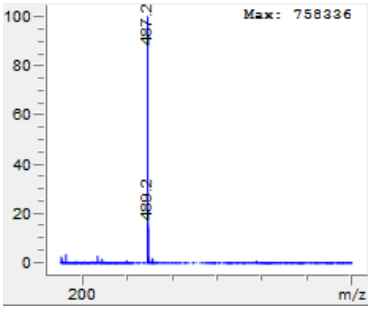


Figure S172. LC-MS TIC curve of control reaction for the whole process with **2i** and βME (without peptide). Gradient used： Method D

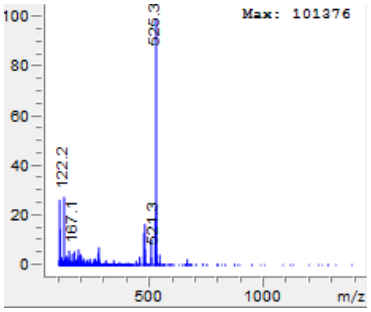




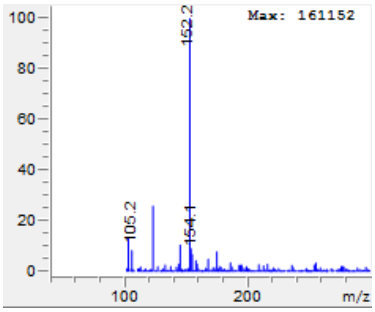
ESI Mass spectrum of peak A



ESI Mass spectrum of peak B



ESI Mass spectrum of peak C



ESI Mass spectrum of peak D

Figure S173. LC-MS TIC curve of reaction mixture of **3ai** and corresponding ESI mass spectrum after added βME for 8h. Gradient used： Method D

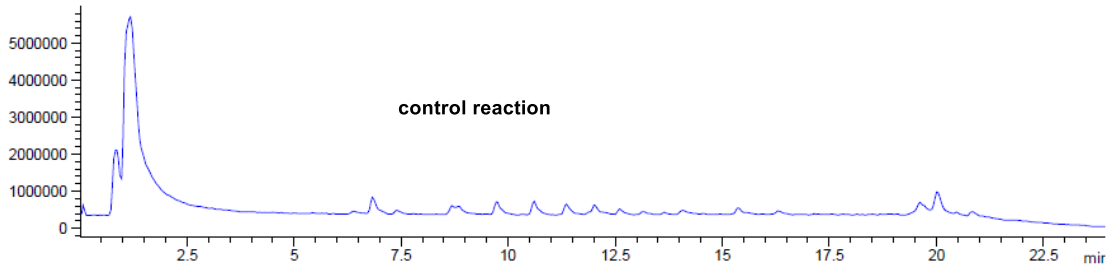
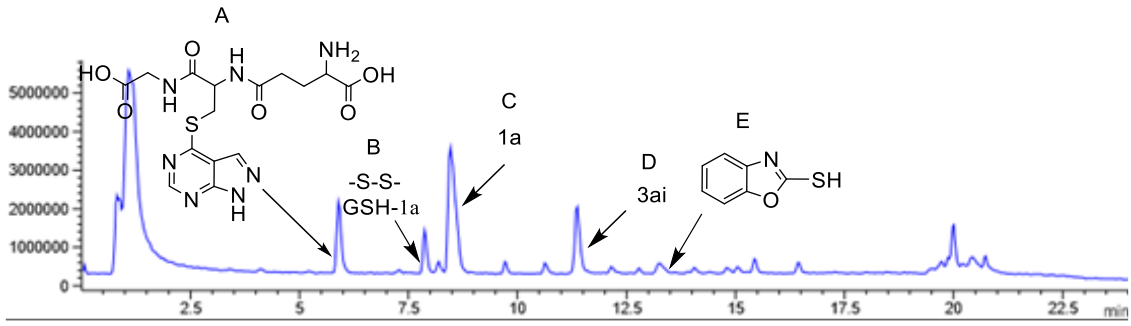
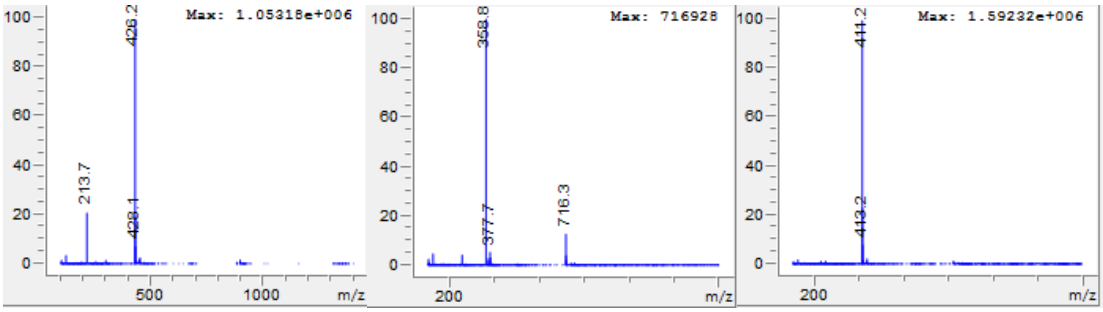
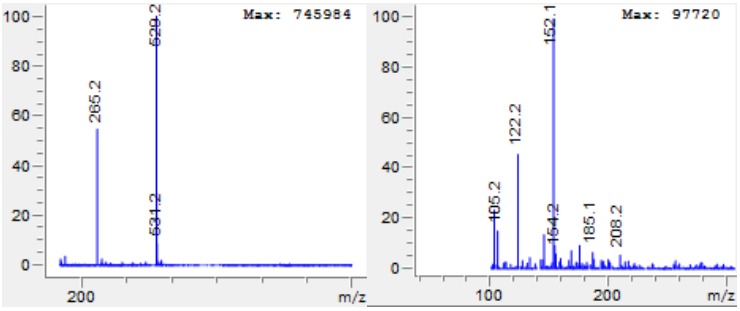


Figure S174. LC-MS TIC curve of control reaction for the whole process with **2i** and GSH (without peptide). Gradient used： Method D





ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C



ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S175. LC-MS TIC curve of reaction mixture of **3ai** and corresponding ESI mass spectrum after added GSH for 8h. Gradient used： Method D

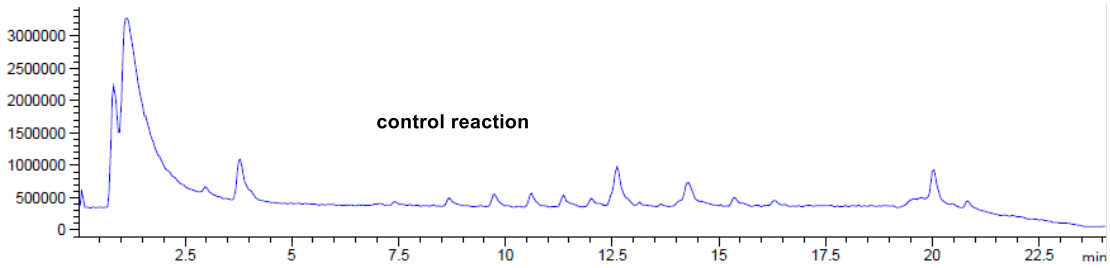
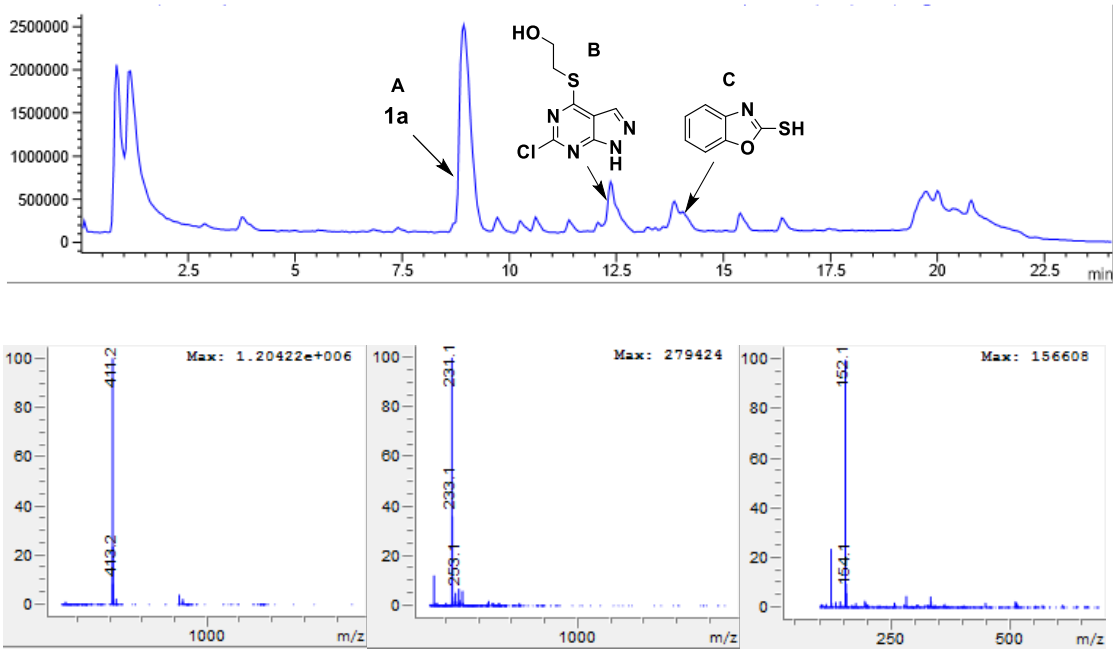


Figure S176. LC-MS TIC curve of control reaction for the whole process with **2j** and βME (without peptide). Gradient used： Method D



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C

Figure S177. LC-MS TIC curve of reaction mixture of **3aj** and corresponding ESI mass spectrum after added βME for 1h. Gradient used： Method D

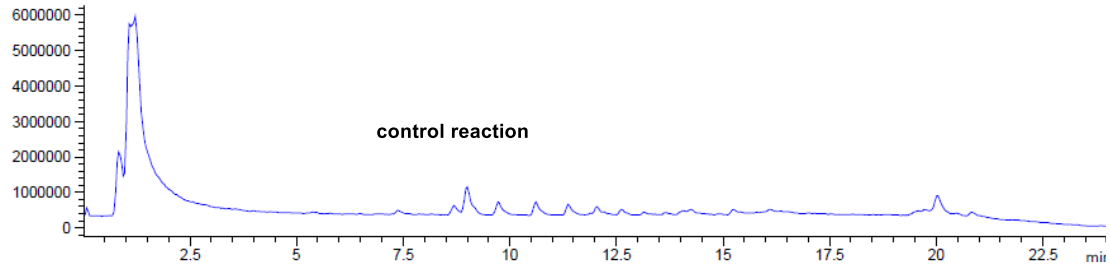
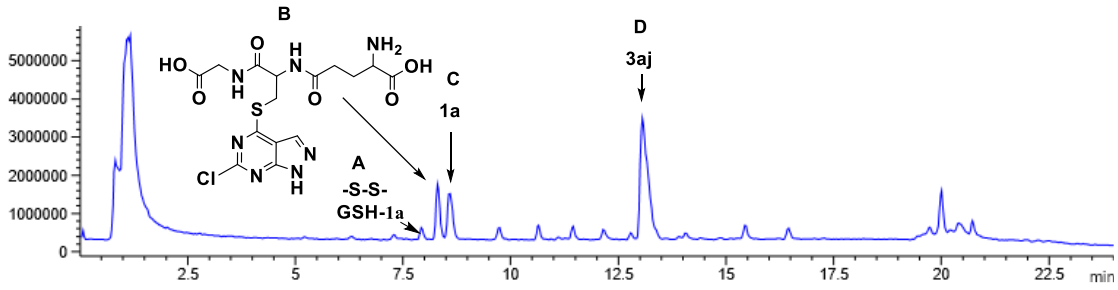
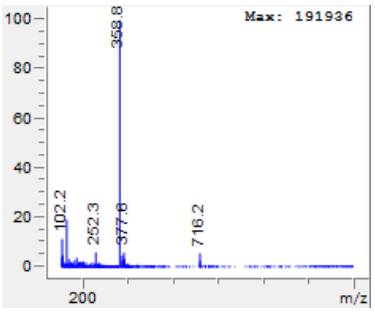
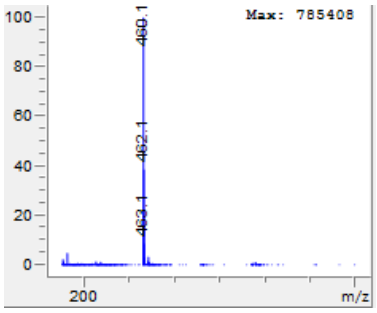


Figure S178. LC-MS TIC curve of control reaction for the whole process with **2j** and GSH (without peptide). Gradient used： Method D

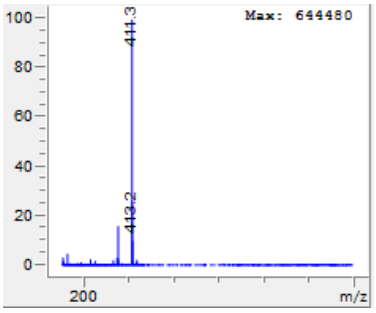




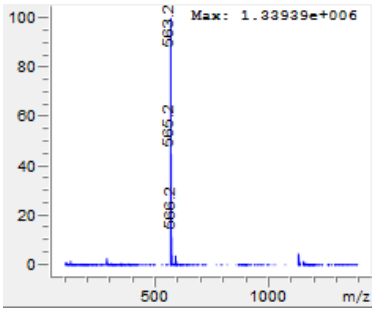
ESI Mass spectrum of peak A



ESI Mass spectrum of peak B

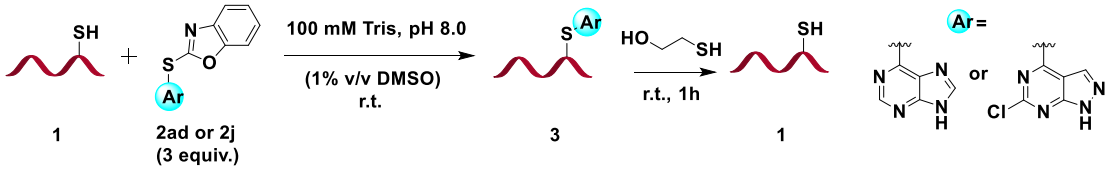


ESI Mass spectrum of peak C



ESI Mass spectrum of peak D

Figure S179. LC-MS TIC curve of reaction mixture of **3aj** and corresponding ESI mass spectrum after added GSH for 8h. Gradient used： Method D



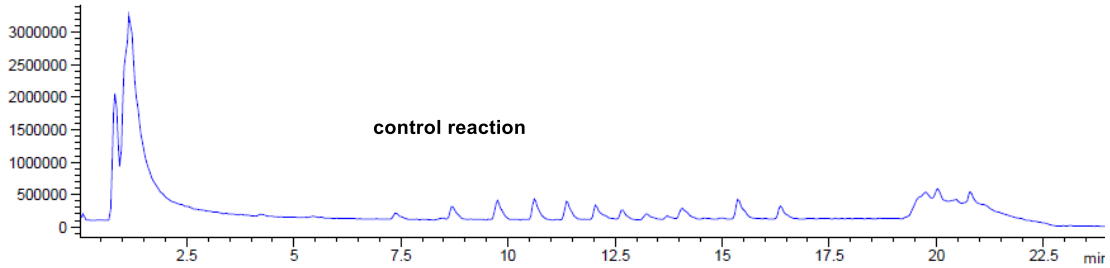


Figure S180. LC-MS TIC curve of control reaction (without peptide) for the first step with **2j**. Gradient used： Method D

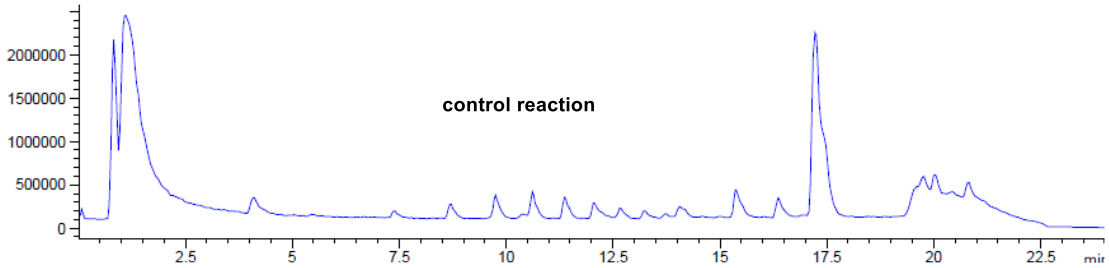


Figure S181. LC-MS TIC curve of control reaction (without peptide) for the first step with **2ad**. Gradient used： Method D

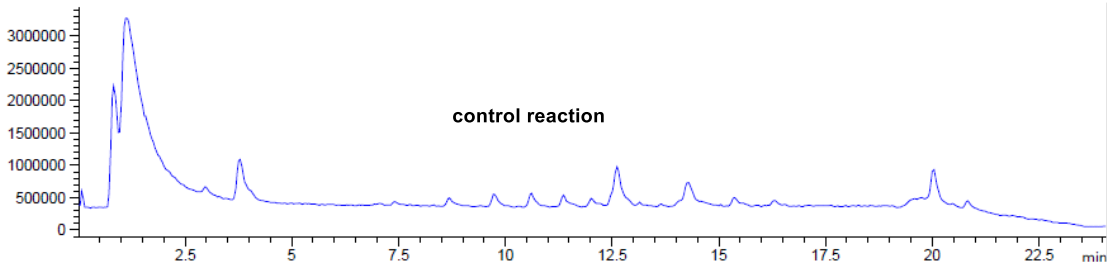


Figure S182. LC-MS TIC curve of control reaction for the whole process with **2j** and βME (without peptide). Gradient used： Method D

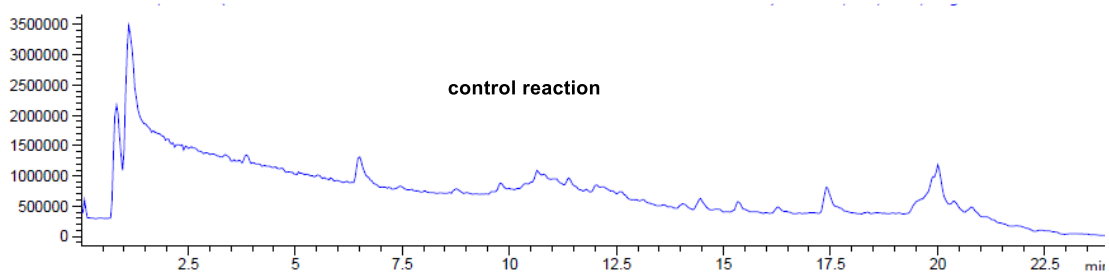


Figure S183. LC-MS TIC curve of control reaction for the whole process with **2ad** and βME (without peptide). Gradient used： Method D

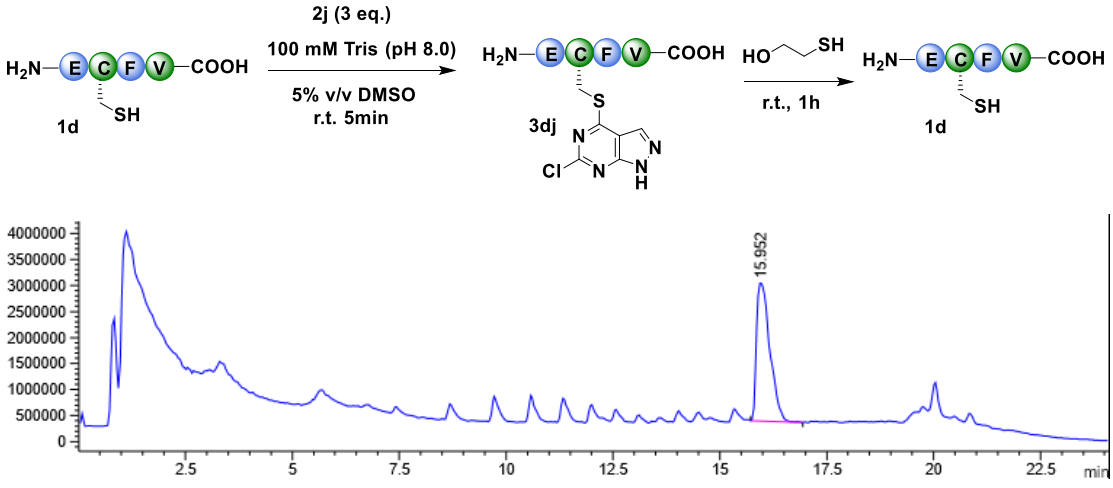


Figure S184. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

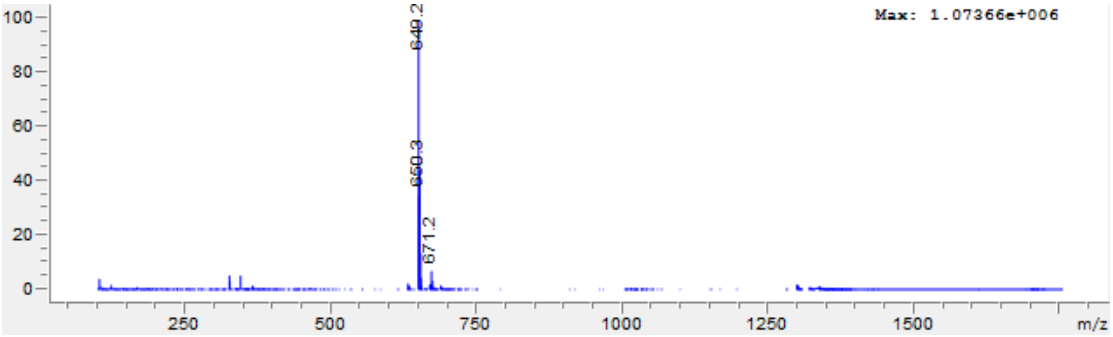
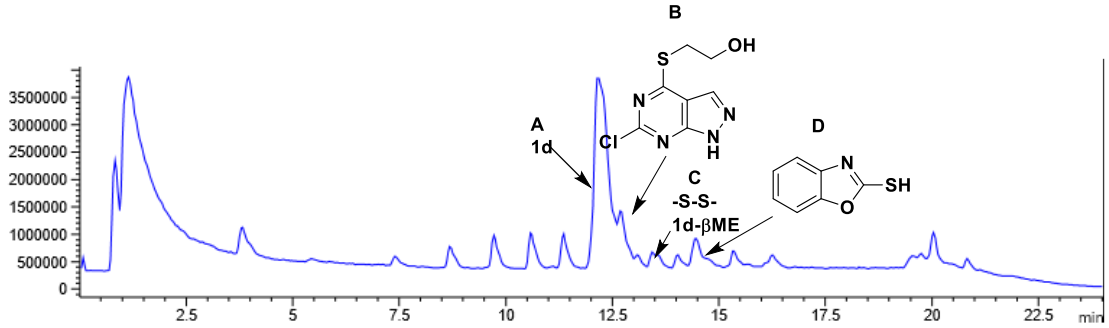
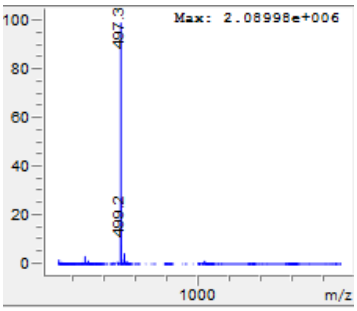
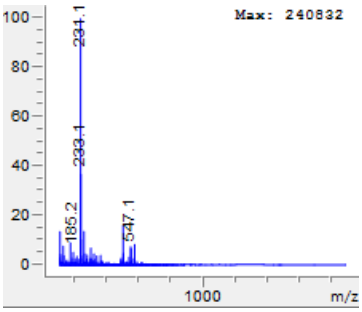


Figure S185. ESI Mass spectrum of modified product **3di**. Calculated Mass $[M+H]^+$: 649.2; Mass Found (ESI+); $[M+H]^+$: 649.2.

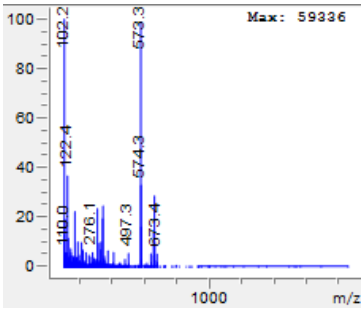




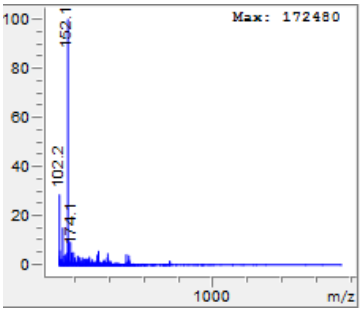
ESI Mass spectrum of peak A



ESI Mass spectrum of peak B



ESI Mass spectrum of peak C



ESI Mass spectrum of peak D

Figure S186. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

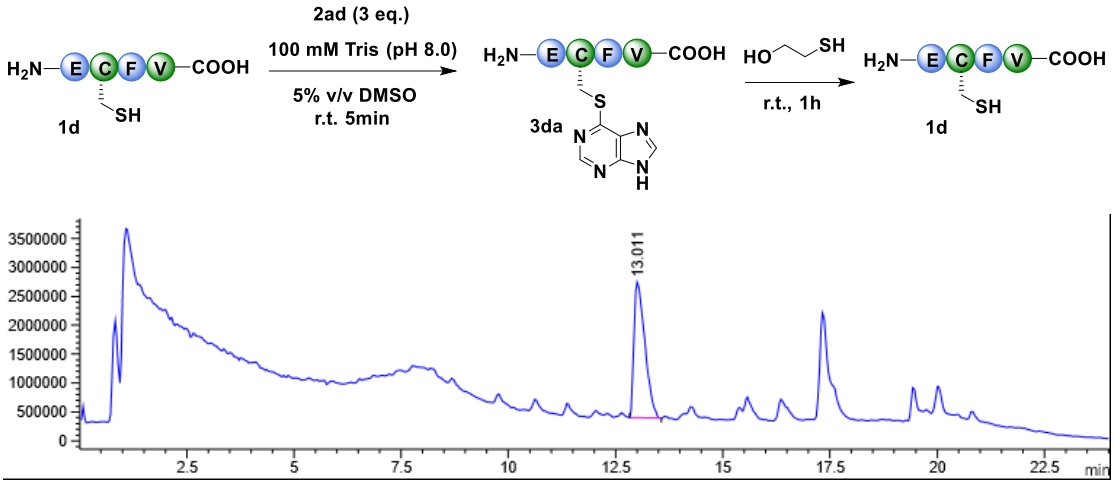


Figure S187. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

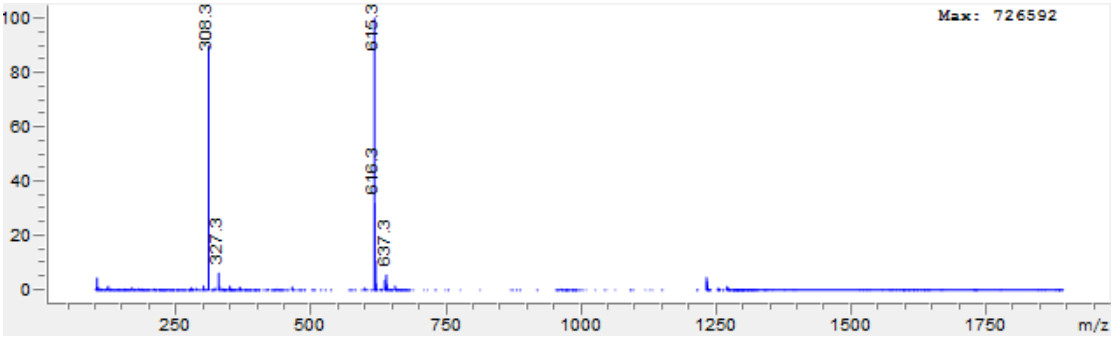
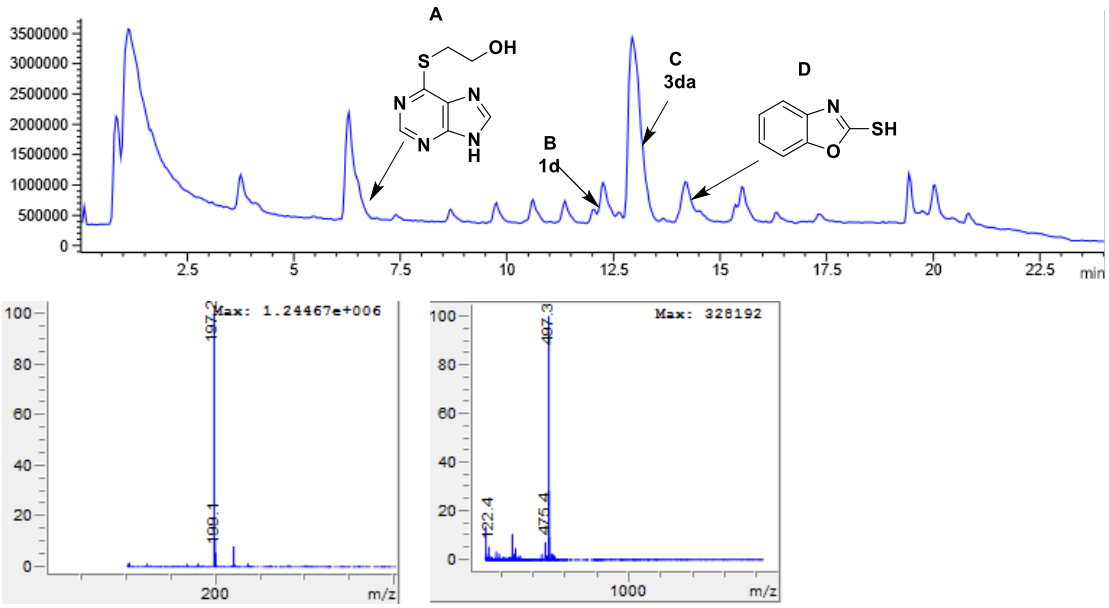
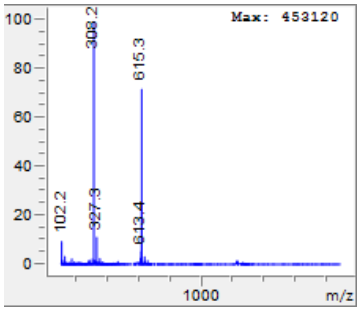
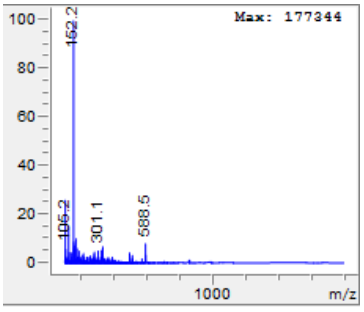


Figure S188. ESI Mass spectrum of modified product **3da**. Calculated Mass $[M+H]^+$: 615.2; $[M+2H]^{2+}$: 308.1; Mass Found (ESI+); $[M+H]^+$: 615.3; $[M+2H]^{2+}$: 308.3.



ESI Mass spectrum of peak A ESI Mass spectrum of peak B





ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S189. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

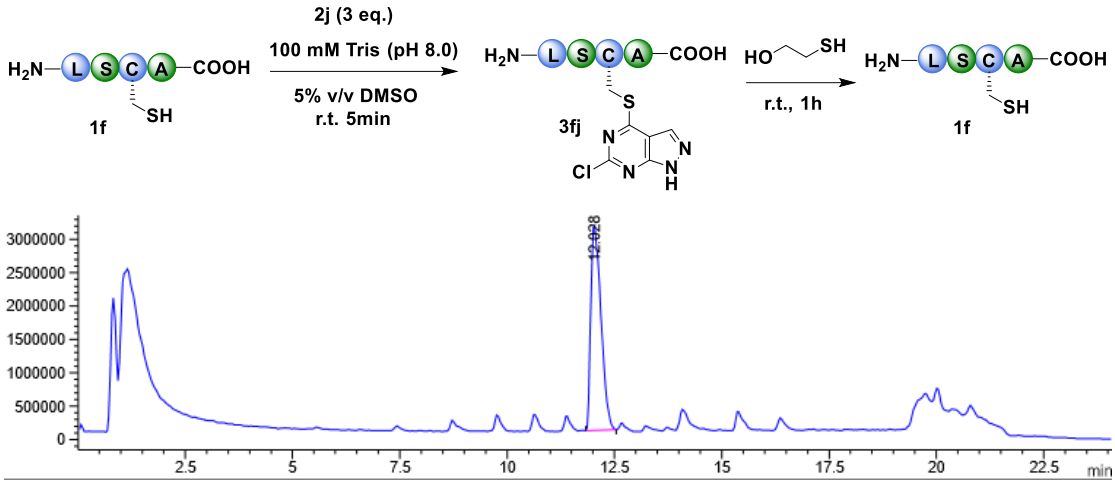


Figure S190. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

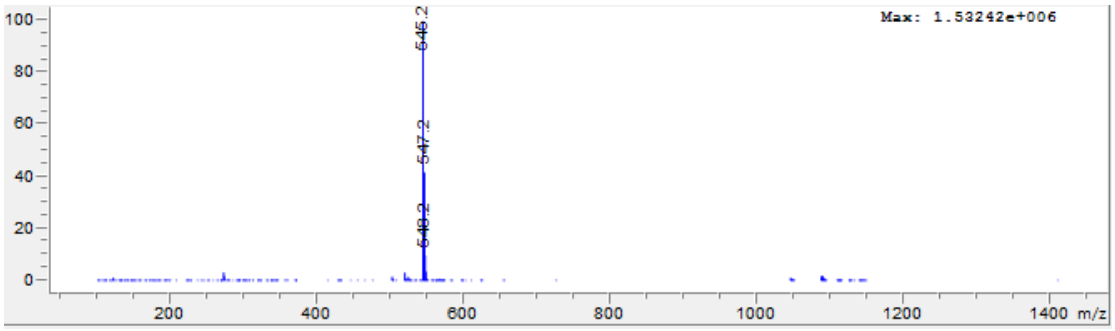
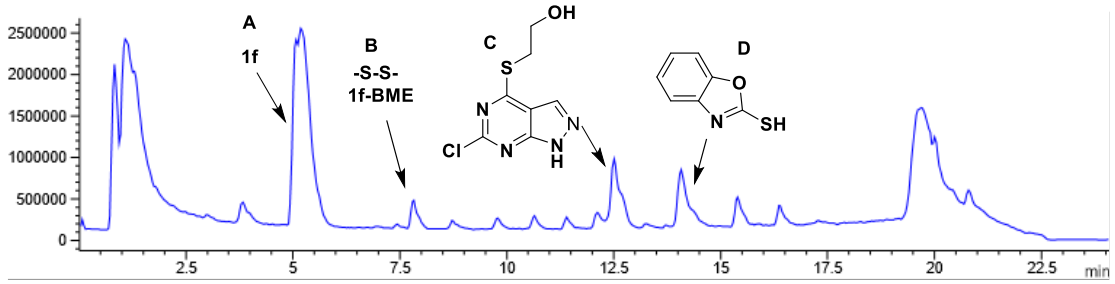
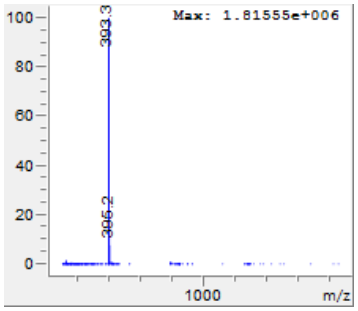
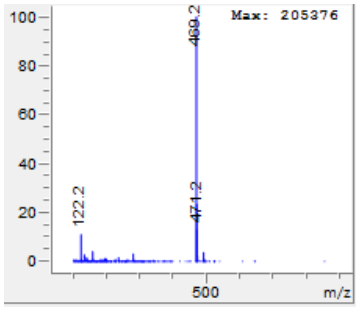


Figure S191. ESI Mass spectrum of modified product **3fj**. Calculated Mass $[M+H]^+$: 545.2; Mass Found (ESI+); $[M+H]^+$: 545.2.

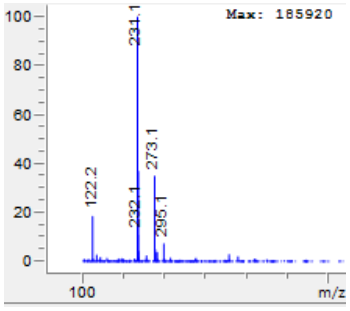




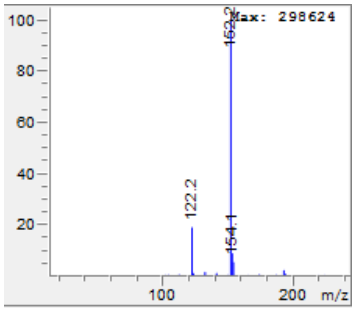
ESI Mass spectrum of peak A



ESI Mass spectrum of peak B

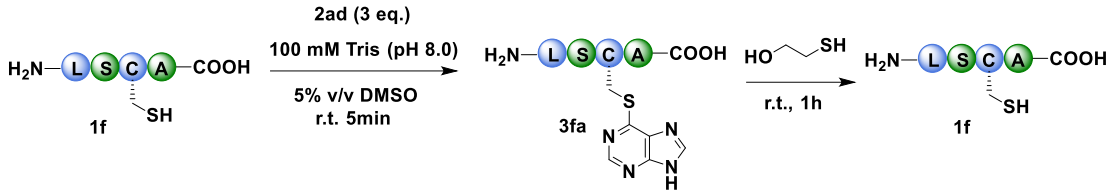


ESI Mass spectrum of peak C



ESI Mass spectrum of peak D

Figure S192. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D



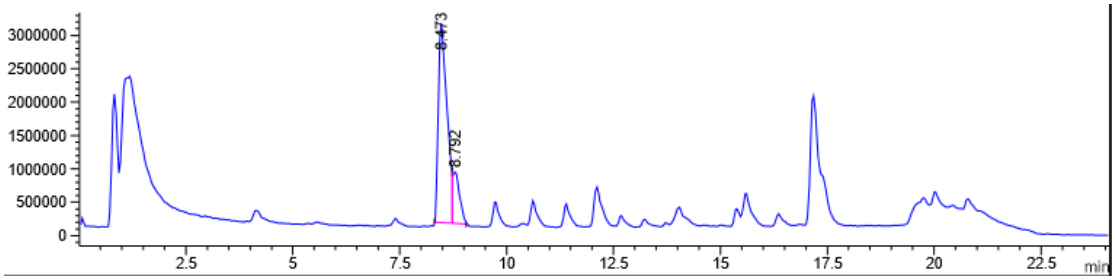


Figure S193. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

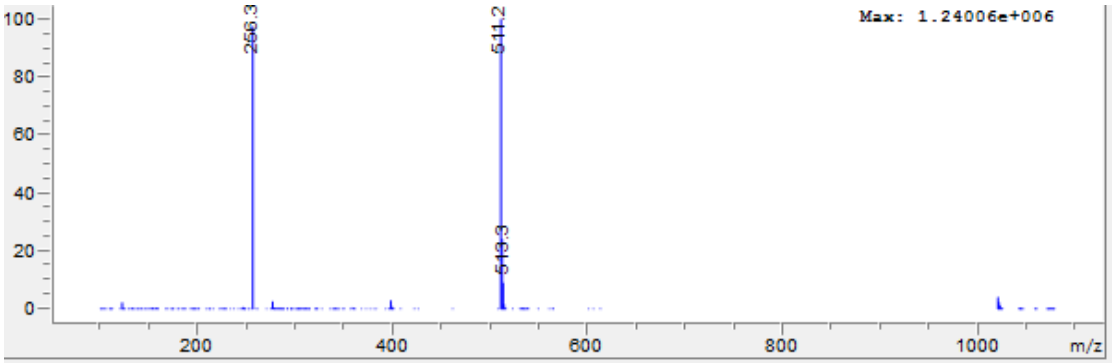
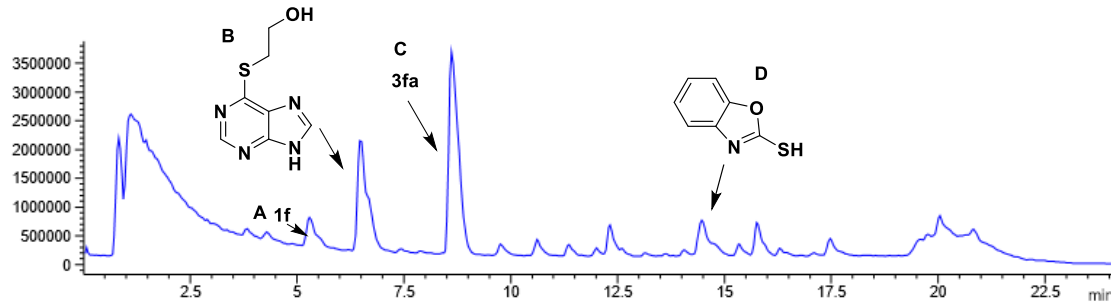
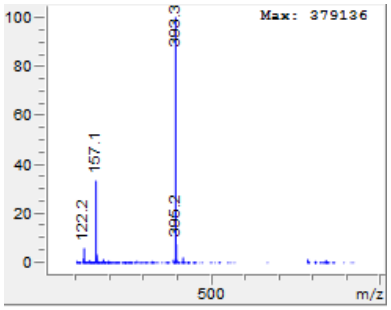
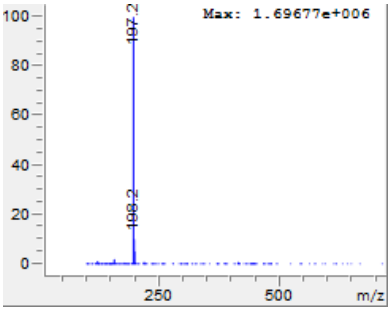


Figure S194. ESI Mass spectrum of modified product **3fa**. Calculated Mass $[M+H]^+$: 511.2;

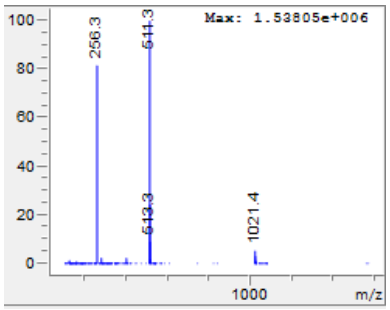
$[M+2H]^{2+}$: 256.1; Mass Found (ESI+); $[M+H]^{+}$: 511.2; $[M+2H]^{2+}$: 256.3.

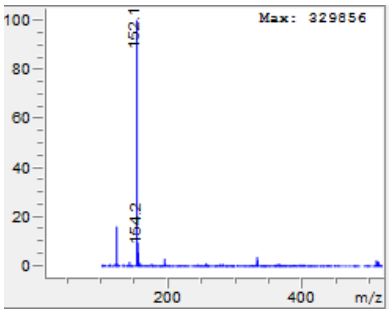






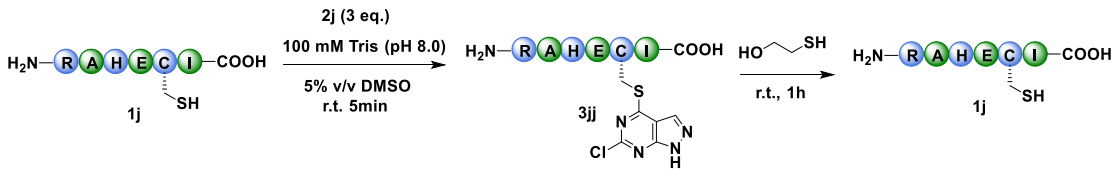
ESI Mass spectrum of peak A ESI Mass spectrum of peak B





ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S195. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D



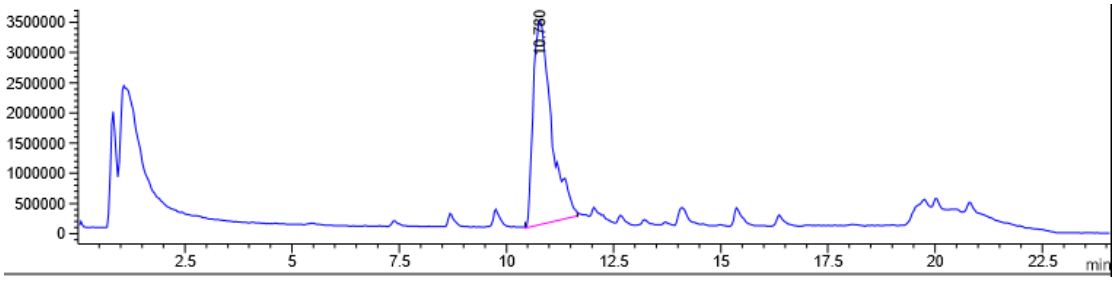


Figure S196. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

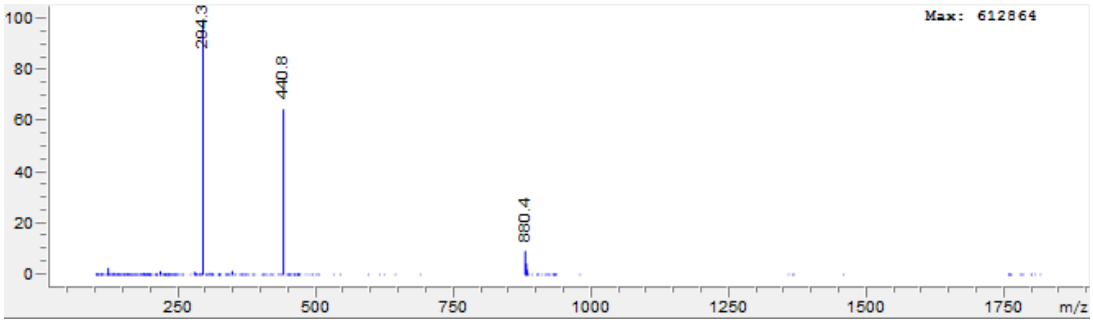
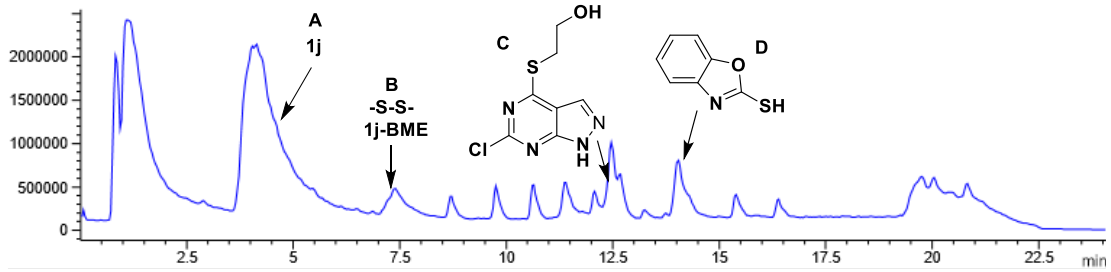
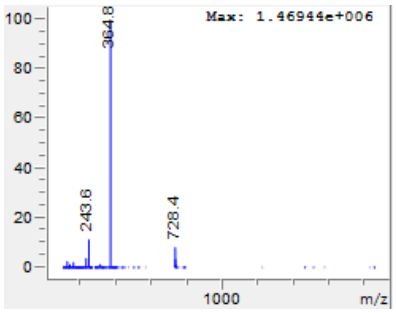
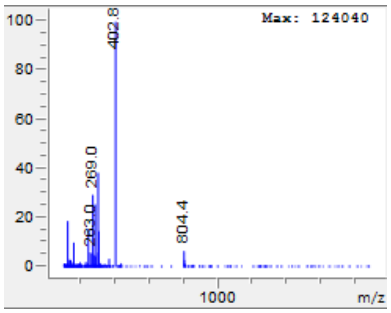


Figure S197. ESI Mass spectrum of modified product **3jj**. Calculated Mass $[M+H]^{+}$: 880.3; $[M+2H]^{2+}$: 440.7; $[M+3H]^{3+}$: 294.1; Mass Found (ESI+); $[M+H]^{+}$: 880.4; $[M+2H]^{2+}$: 440.8; $[M+3H]^{3+}$: 294.3.

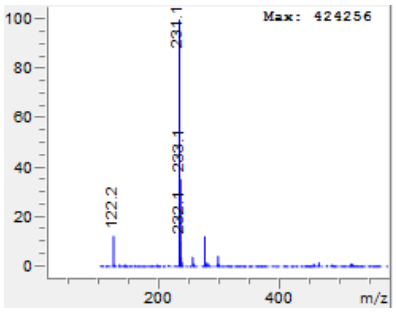




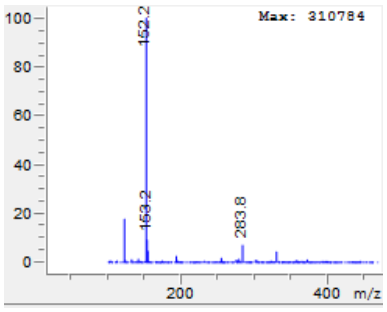
ESI Mass spectrum of peak A



ESI Mass spectrum of peak B



ESI Mass spectrum of peak C



ESI Mass spectrum of peak D

Figure S198. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

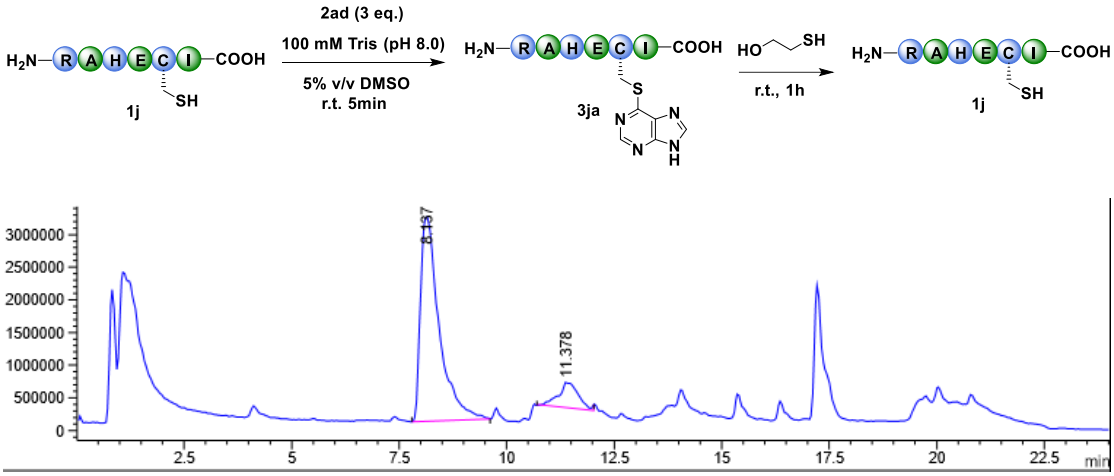


Figure S199. LC-MS TIC curve of reaction mixture for the first step. Gradient used：Method D

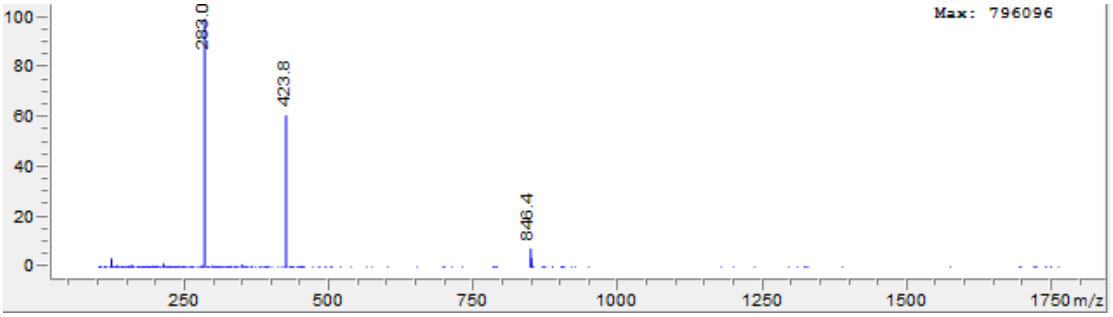
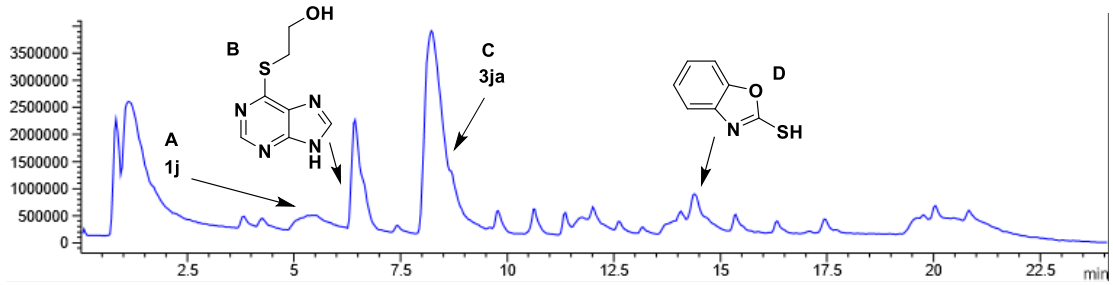
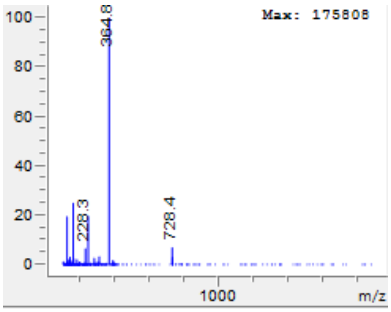
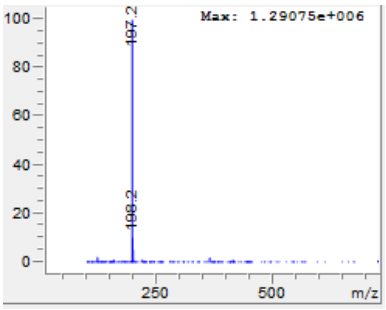


Figure S200. ESI Mass spectrum of modified product **3ja**. Calculated Mass $[M+H]^{+}$: 846.4; $[M+2H]^{2+}$: 423.7; $[M+3H]^{3+}$: 282.8; Mass Found (ESI+); $[M+H]^{+}$: 846.4; $[M+2H]^{2+}$: 423.8; $[M+3H]^{3+}$: 283.0.

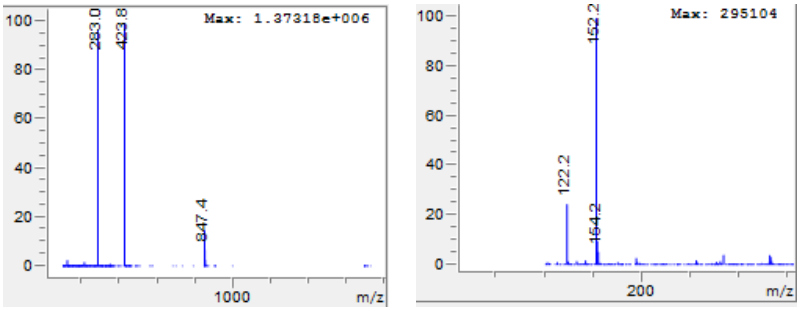




ESI Mass spectrum of peak A



ESI Mass spectrum of peak B



ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S201. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

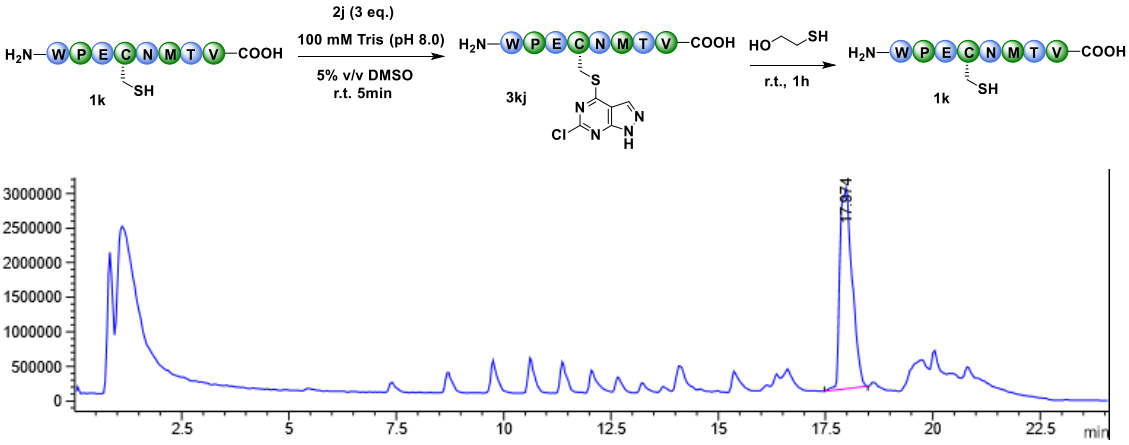


Figure S202. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

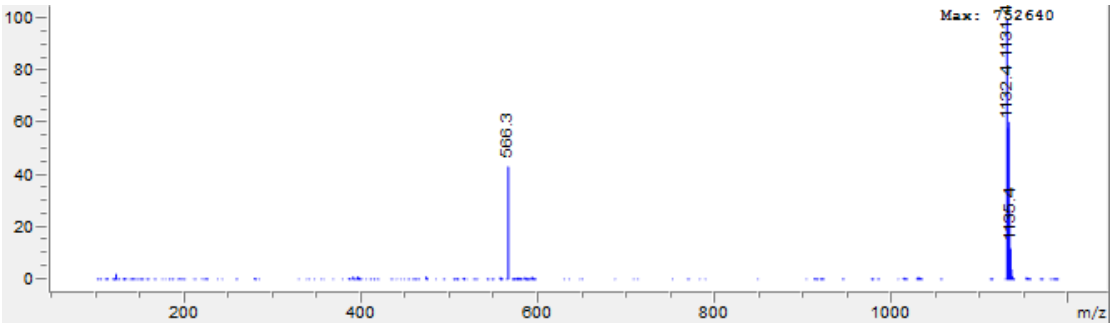
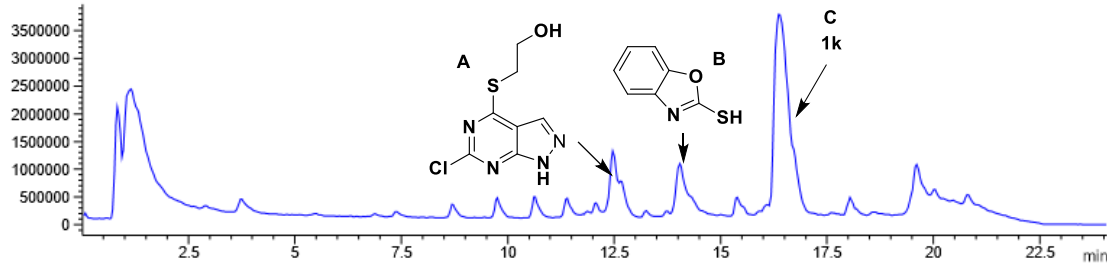
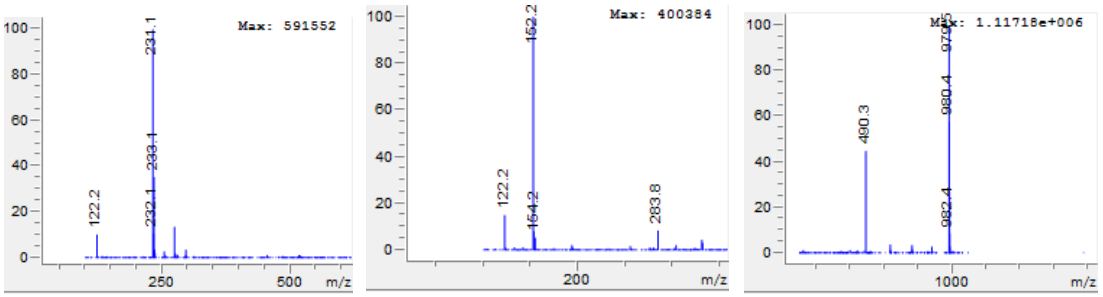


Figure S203. ESI Mass spectrum of modified product **3kj**. Calculated Mass $[M+H]^+$: 1131.4; $[M+2H]^{2+}$: 566.2; Mass Found (ESI+); $[M+H]^+$: 1131.4; $[M+2H]^{2+}$: 566.3.





ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C

Figure S204. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

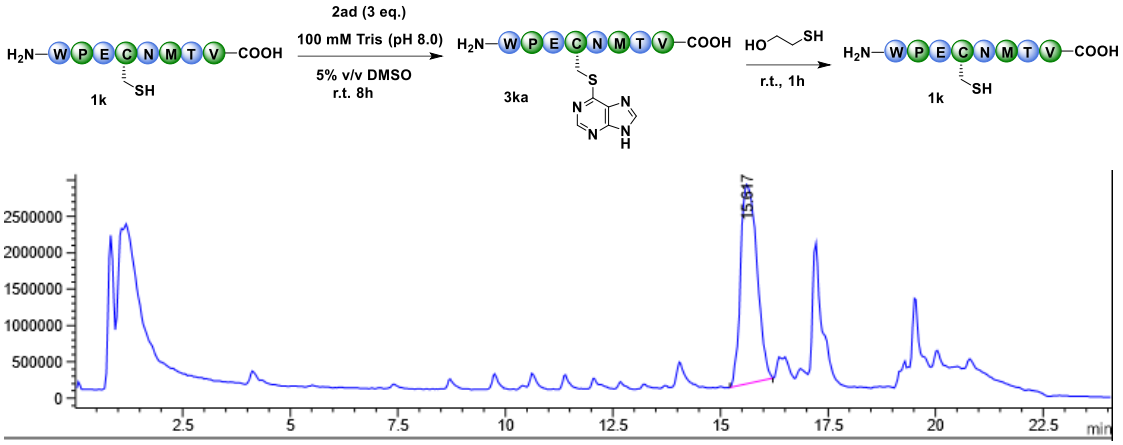


Figure S205. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

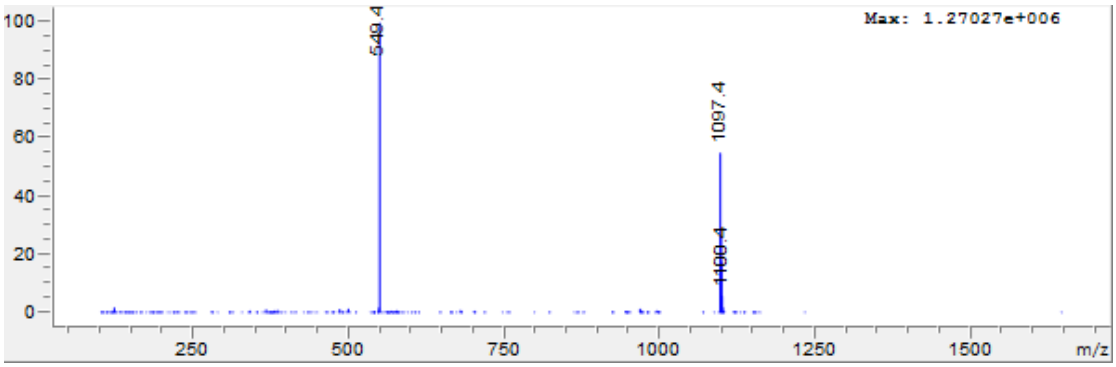
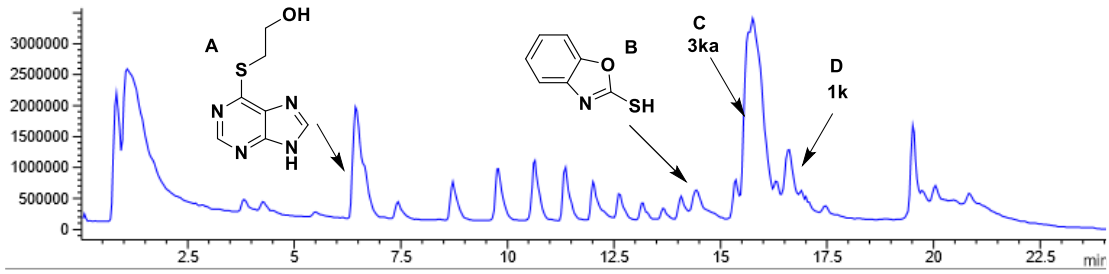
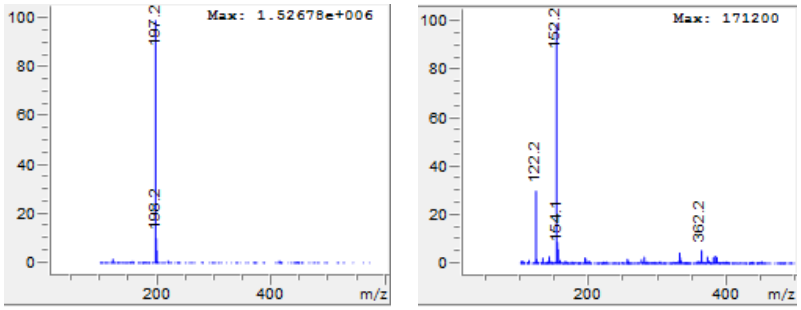
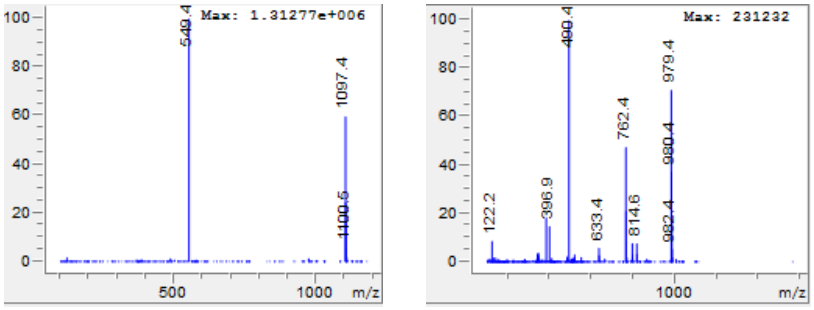


Figure S206. ESI Mass spectrum of modified product **3ka**. Calculated Mass $[M+H]^+$: 1097.4; $[M+2H]^{2+}$: 549.2; Mass Found (ESI+); $[M+H]^+$: 1097.4; $[M+2H]^{2+}$: 549.4.





ESI Mass spectrum of peak A ESI Mass spectrum of peak B



ESI Mass spectrum of peak C ESI Mass spectrum of peak D

Figure S207. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

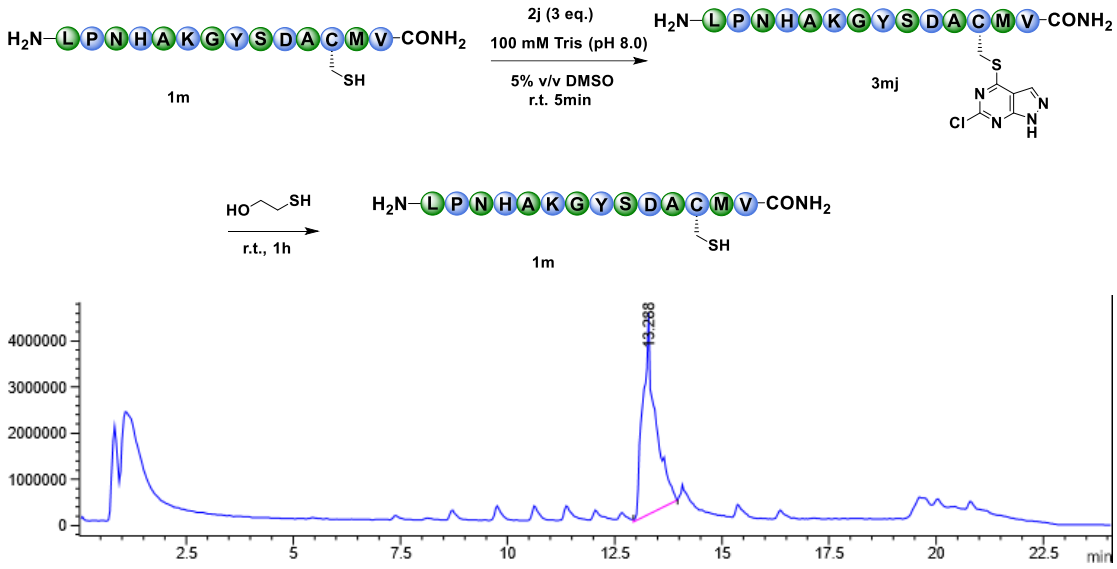


Figure S208. LC-MS TIC curve of reaction mixture for the first step. Gradient used： Method D

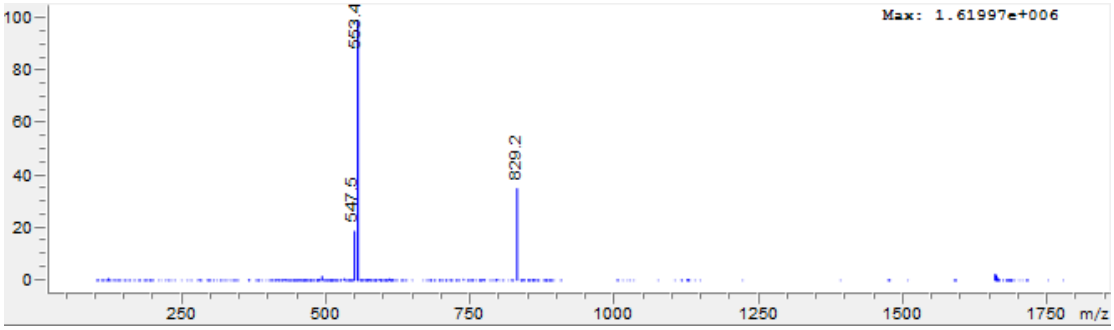
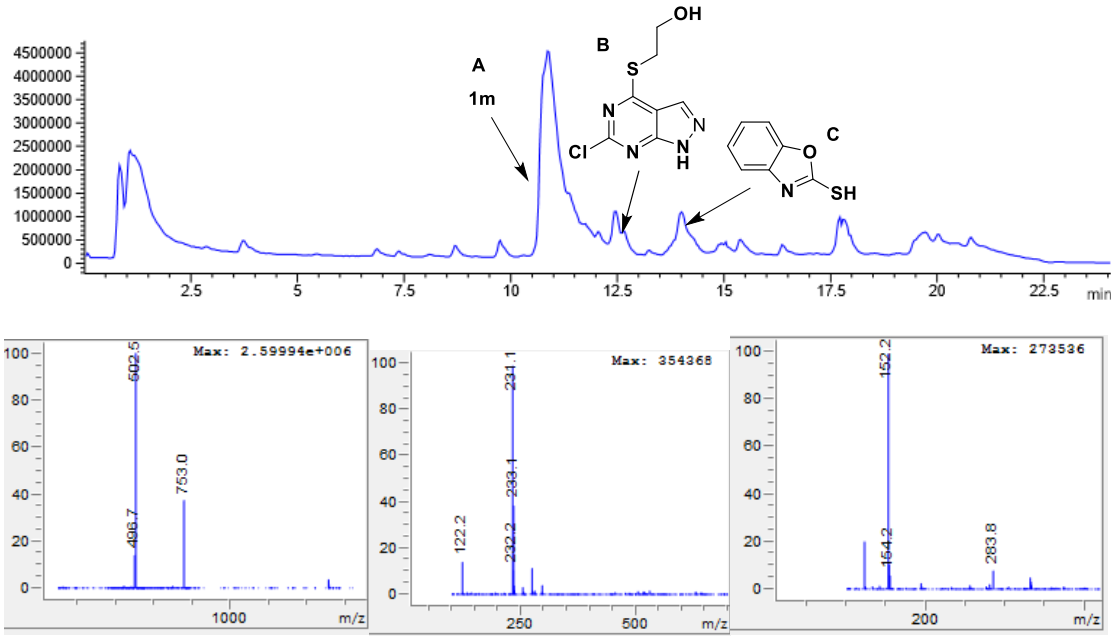


Figure S209. ESI Mass spectrum of modified product **3mj**. Calculated Mass $[M+2H]^{2+}$: 829.3; $[M+3H]^{3+}$: 553.2; Mass Found (ESI+); $[M+2H]^{2+}$: 829.2; $[M+3H]^{3+}$: 553.4.



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C

Figure S210. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

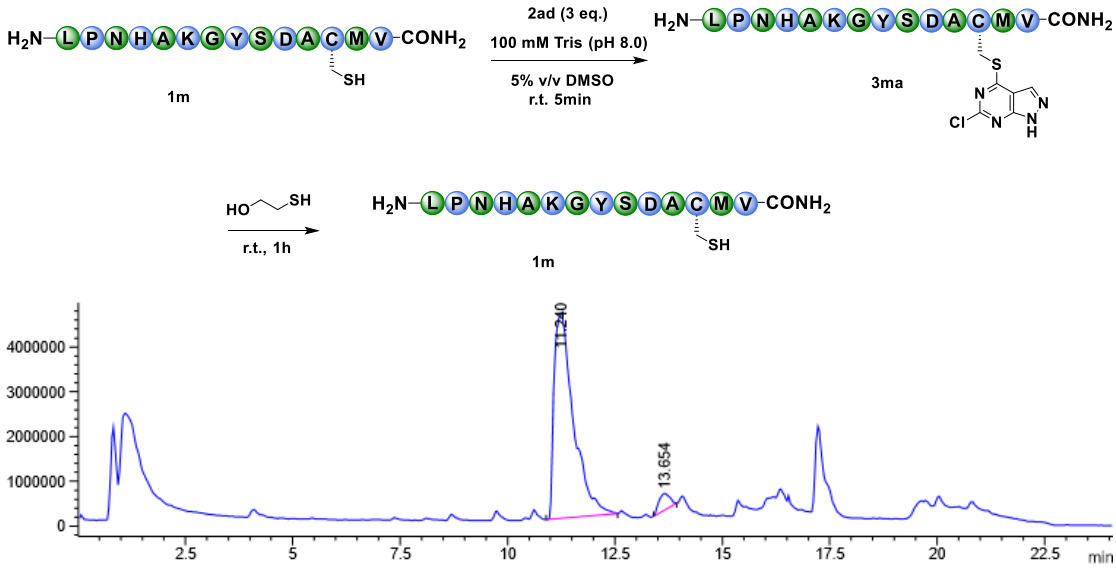


Figure S212. LC-MS TIC curve of reaction mixture for the first step. Gradient used：Method D

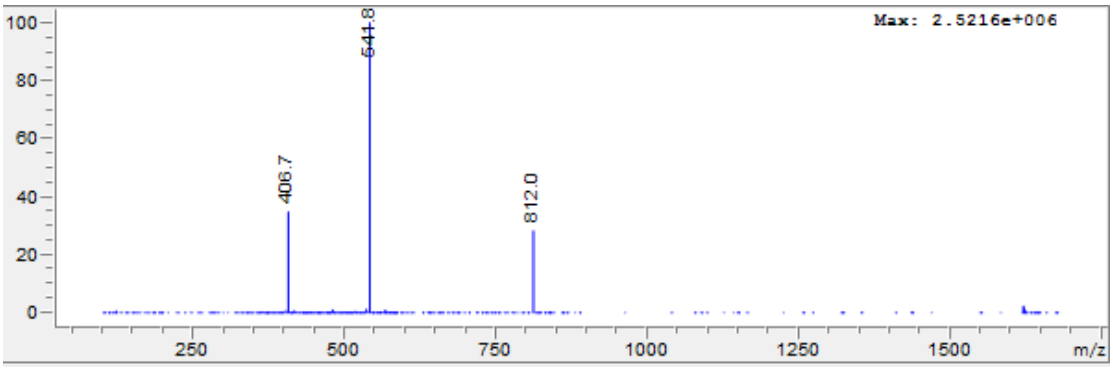
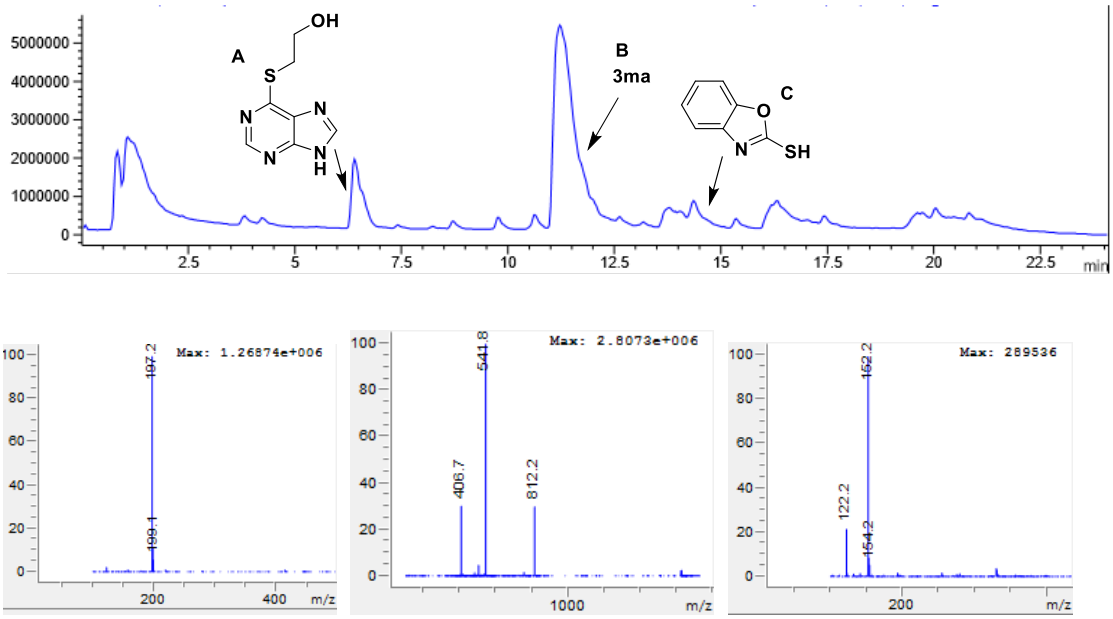


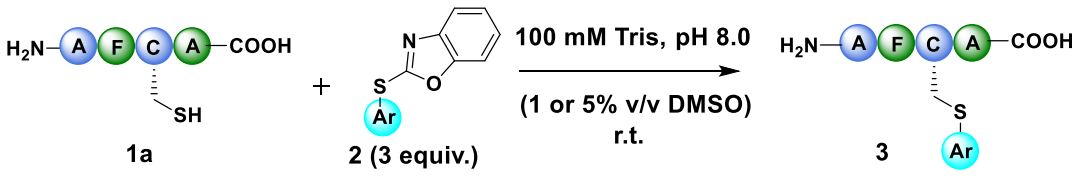
Figure S213. ESI Mass spectrum of modified product **3ma**. Calculated Mass $[M+2H]^{2+}$: 811.9; $[M+3H]^{3+}$: 541.6; $[M+4H]^{4+}$: 406.7; Mass Found (ESI+); $[M+2H]^{2+}$: 812.0; $[M+3H]^{3+}$: 541.8; $[M+4H]^{4+}$: 406.7.



ESI Mass spectrum of peak A ESI Mass spectrum of peak B ESI Mass spectrum of peak C

Figure S214. LC-MS TIC curve of reaction mixture for the whole process and corresponding ESI mass spectrum. Gradient used: Method D

11.Evaluation of Reaction Kinetics



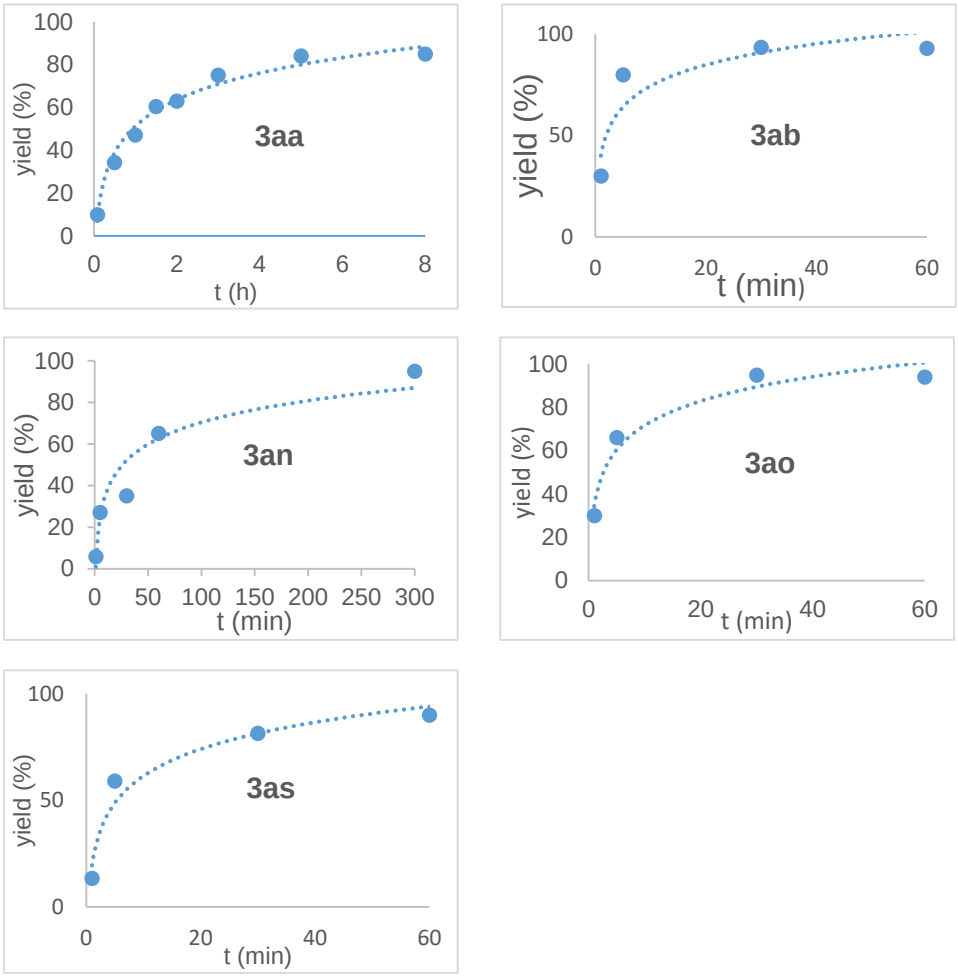
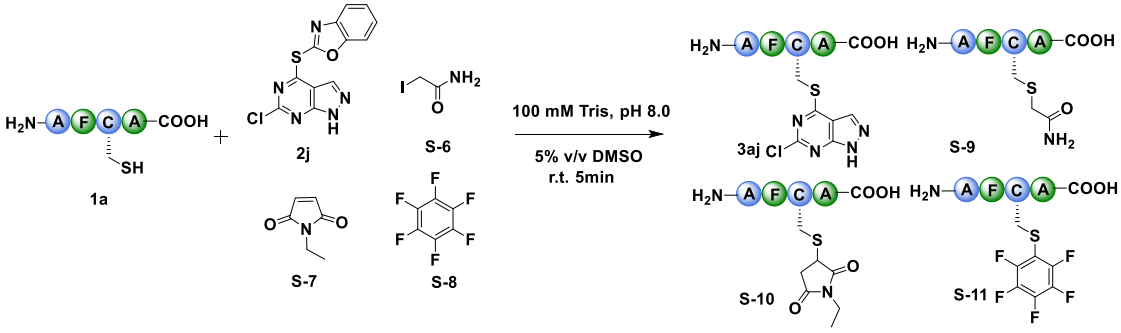


Figure S215. Time-course analysis of Cys arylation between **1a** and **2**.

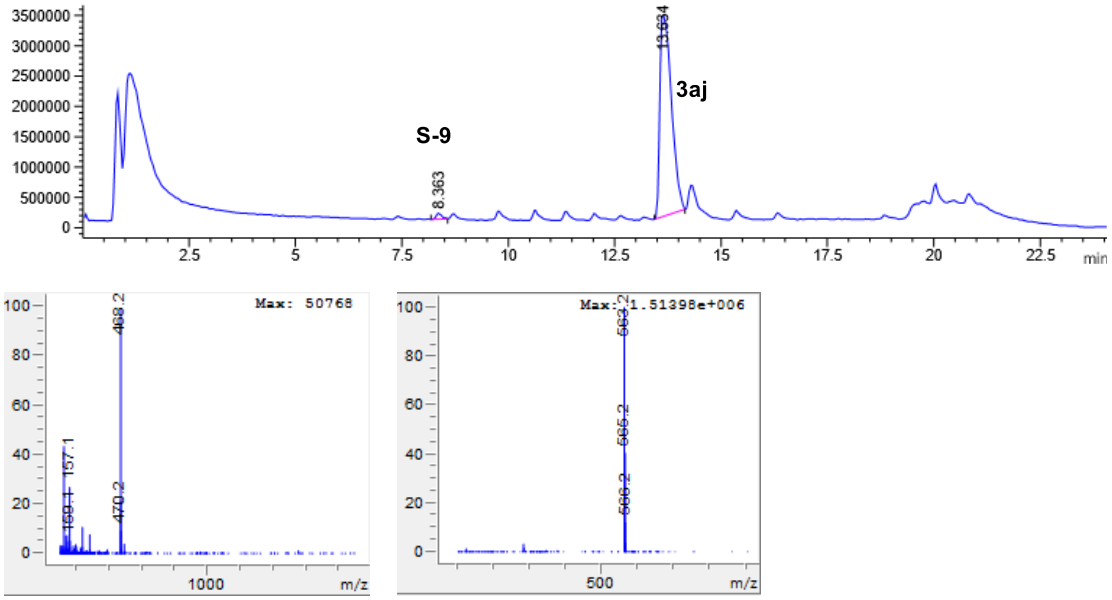
Table S2. Competition experiments



Entry	Condition	Results
1	**2j** (3eq.), **S-6** (3eq.)	**3aj : S-9** = 99:1
2	**2j** (3eq.), **S-7** (3eq.)	**3aj : S-10** = 5:95
3	**2j** (3eq.), **S-8** (3eq.)	**3aj : S-11** > 99:1

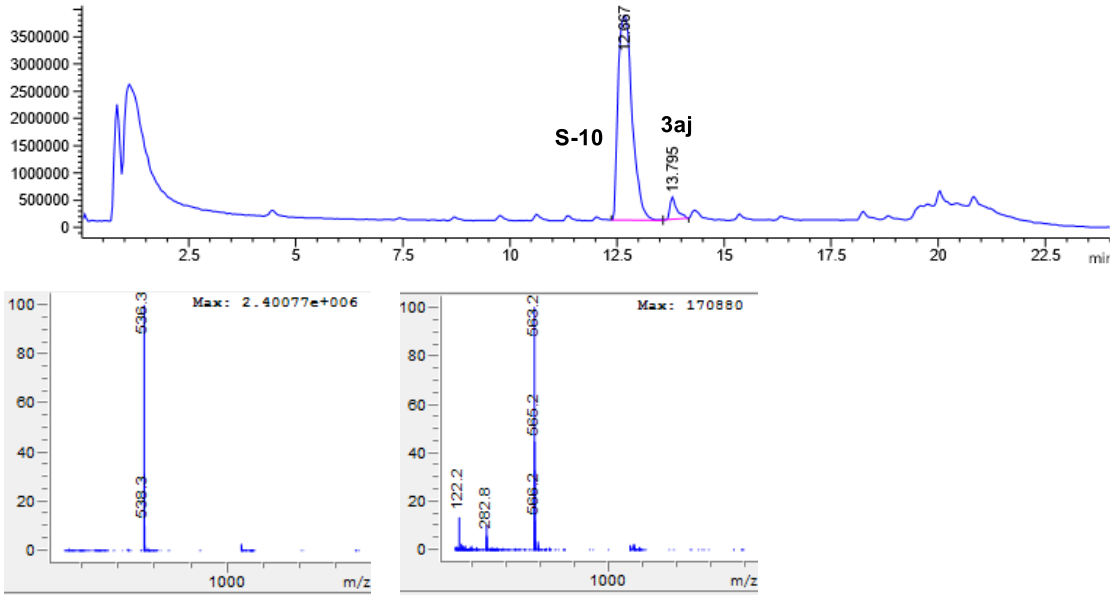
General procedure for competition experiments: 1.0 μmol peptide (**1a**) was dissolved in 950 μL non-degassed Tris buffer (100 mM, pH 8.0). Then, 3.0 μmol aryl thioether **2j** (reach reaction completion less than 30s) and 3.0 μmol **S-6** (or **S-7**, or **S-8**) in 50 μL DMSO was added. The

resulting solution was vortexed and shaking at room temperature for 5 min. After this time, the reaction was analyzed by HPLC-MS.



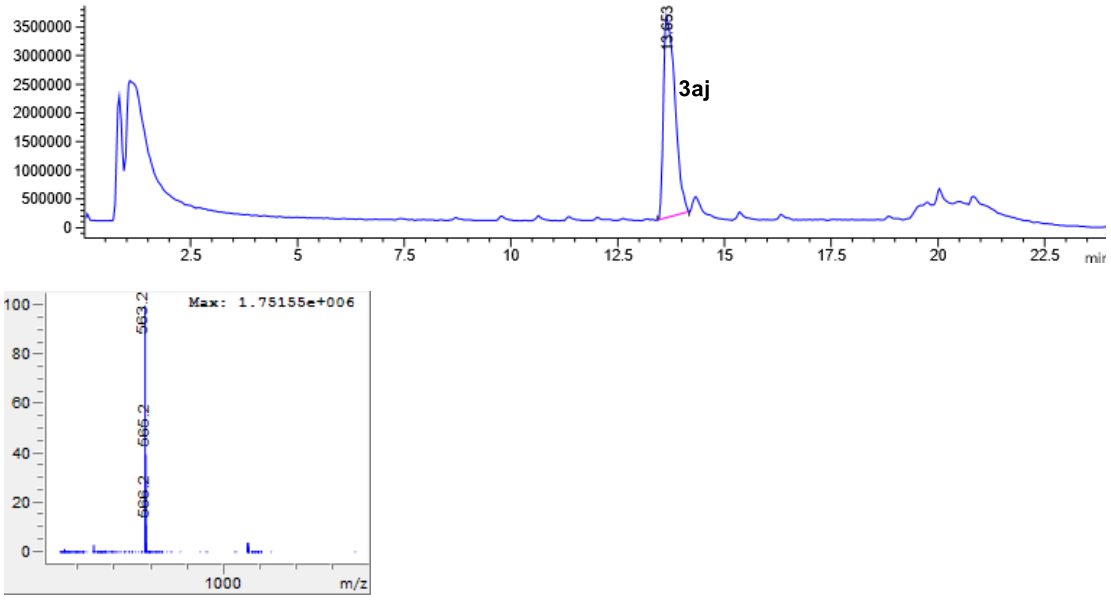
ESI Mass spectrum of **S-9** ESI Mass spectrum of **3aj**

Figure S216. LC-MS TIC curve of reaction mixture modified by **2j** and **S-6** and corresponding ESI mass spectrum. Gradient used： Method D



ESI Mass spectrum of **S-10** ESI Mass spectrum of **3aj**

Figure S217. LC-MS TIC curve of reaction mixture modified by **2j** and **S-7** and corresponding ESI mass spectrum. Gradient used： Method D



ESI Mass spectrum of **3aj**

Figure S217. LC-MS TIC curve of reaction mixture modified by **2j** and **S-8** and corresponding ESI mass spectrum. Gradient used： Method D

12.BSA modification by 2v

Bovine serum albumin (BSA) was purchased from Sigma and used without further purification. BSA is composed of 583 amino acids and contains one free cysteine Cys34 (35 Cys residues in total, and 34 cysteine residues are in the form of disulfide bonds) and 59 lysines. Calculated M.W. (average): 66429.98 Da

Sequence:

DTHKSEIAHRFKDLGEEHFKGLVLIAFSQYLQQC[34]PFDEHVKLVNELTEFAKTCVADESHAGCEKSLHTLF
GDELCKVASLRETYGDMADCCEKQEPERNECFLSHKDDSPDLPKLKPDPNTLCDEFKADEKKFWGKYLYEI
ARRHPYFYAPELLYYANKYNGVFQECCQAEDKGACLLPKIETMREKVLTSSARQRLRCASIQKFGERALKA
WSVARLSQKFPKAEFVEVTKLVTDLTKVHKECCHGDLLECADDRADLAKYICDNQDTISSKLKECCDKPLLE
KSHCIAEVEKDAIPENLPPLTADFAEDKDVCKNYQEAKDAFLGSFLYEYSRRHPEYAVSVLLRLAKEYEATLEE
CCAKDDPHACYSTVFDKLKHLVDEPQNLIKQNCDQFEKLGEYGFQNALIVRYTRKVPQVSTPTLVEVSRSL
GKVGTRCCTKPESERMPCTEDYLSLILNRLCVLHEKTPVSEKVTKCCTESLVNRRPCFSALTPDETYVPKAFD
EKLFTFHADICTLPDTEKQIKKQTALVELLKHKPKATEEQLKTVMENFVAFVDKCCAADDKEACFAVEGPKL
VV STQTALA

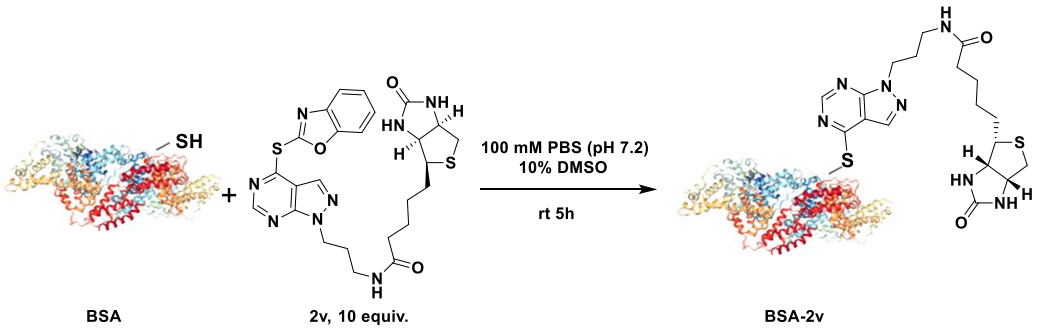


Figure S218. BSA modification by **2v**

In a 1.5 mL eppendorf tube, bovine serum albumin (BSA) solution in 100 mM PBS buffer (pH = 7.2) (10 nmmol, 0.9 mL), 2v (100 equiv in DMSO) was added to BSA solution and shaking at room temperature for 5 h. The sample was lyophilized and analyzed by electrospray ionization mass spectrometry (ESI-MS). The lyophilized protein samples were first dissolved in Milli-Q water and buffer-exchanged with 10 mM ammonium acetate (AA) at a concentration of 50 µM using Amicon centrifugal filters (Merck Millipore, Darmstadt, Germany) with a molecular weight cutoff of 30 k. For denatured nanoESI-MS analysis, the desalted protein samples were further diluted with 49.5/49.5/1 (v/v/v) methanol/water/formic acid mixture solution to a concentration of 3 µM. BSA protein aliquots (3 µL) were analyzed using a quadrupole ion mobility time-of-flight mass spectrometer (Synapt G2-Si HDMS, Waters, UK) in the positive ion mode according to the previously described method.[4] Briefly, BSA protein ions were generated by nano-ESI from a homemade borosilicate capillary emitter (1.0 mm o.d./0.58 mm i.d., Sutter Instruments, Novato, CA, USA) with a tip i.d. of ~1 µm pulled using a P-97 puller (Sutter Instruments, Novato, CA, USA). The detailed instrumental parameters were as follows: capillary voltage 0.7 kV, sampling cone 100 V, extraction cone 80 V, and source temperature 30 °C.

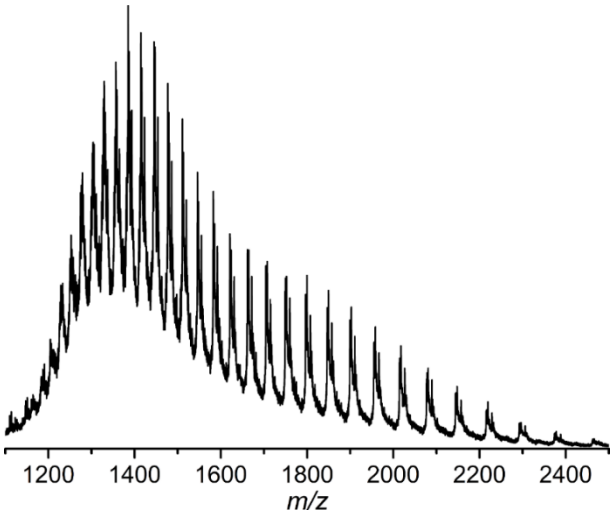


Figure S219. Ion series of BSA modification by **2v**

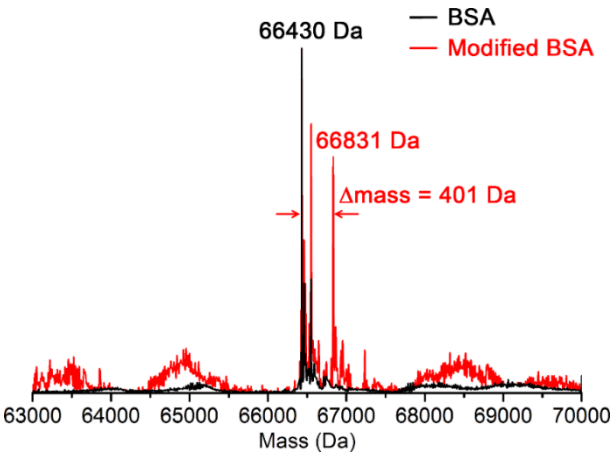


Figure S220. ESI-MS spectra of native BSA and modified BSA-**2v** protein.

13.Secondary labeling of modified peptide

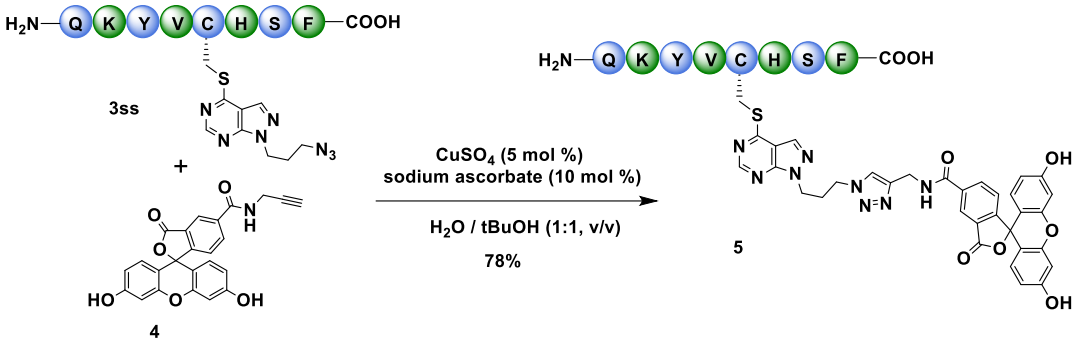


Figure S221. Secondary labeling of modified peptide **3ss** via click reaction

3ss (1.31 mg, 1 μmol, 1 equiv.) in water (480 μL) was added to the solution of **4** (20 equiv.) in *t*BuOH (500 μL). CuSO4·5H_2O (5 mol%) and sodium ascorbate (10 mol%) in water (20 μL) were added under vigorously stirring. The mixture was stirred at room temperature for 12 hours under Ar atmosphere. Then the crude mixture was filtered, and analyzed by LC-MS.

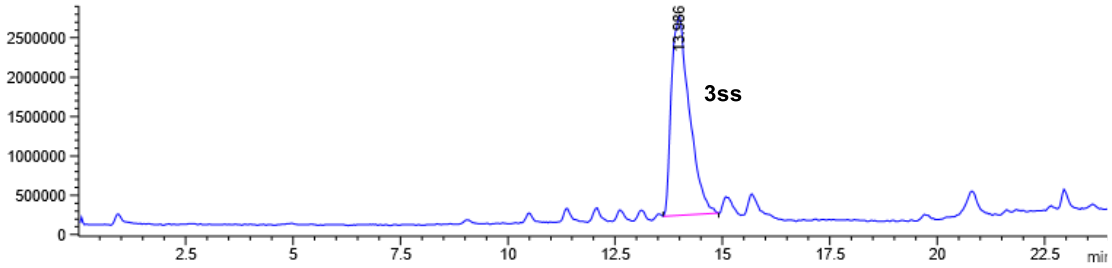


Figure S222. LC-MS TIC curve of **3ss**. Gradient used： Method A

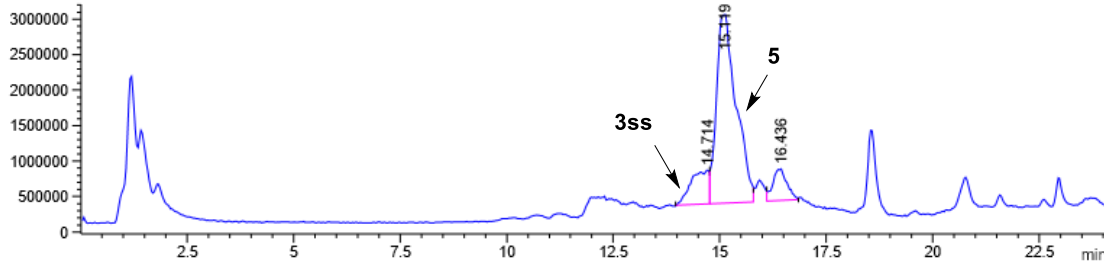


Figure S223. LC-MS TIC curve of reaction mixture. Gradient used： Method A

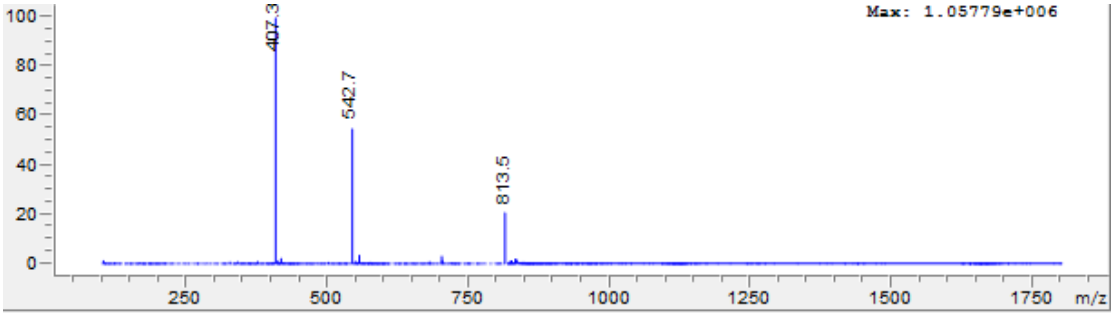
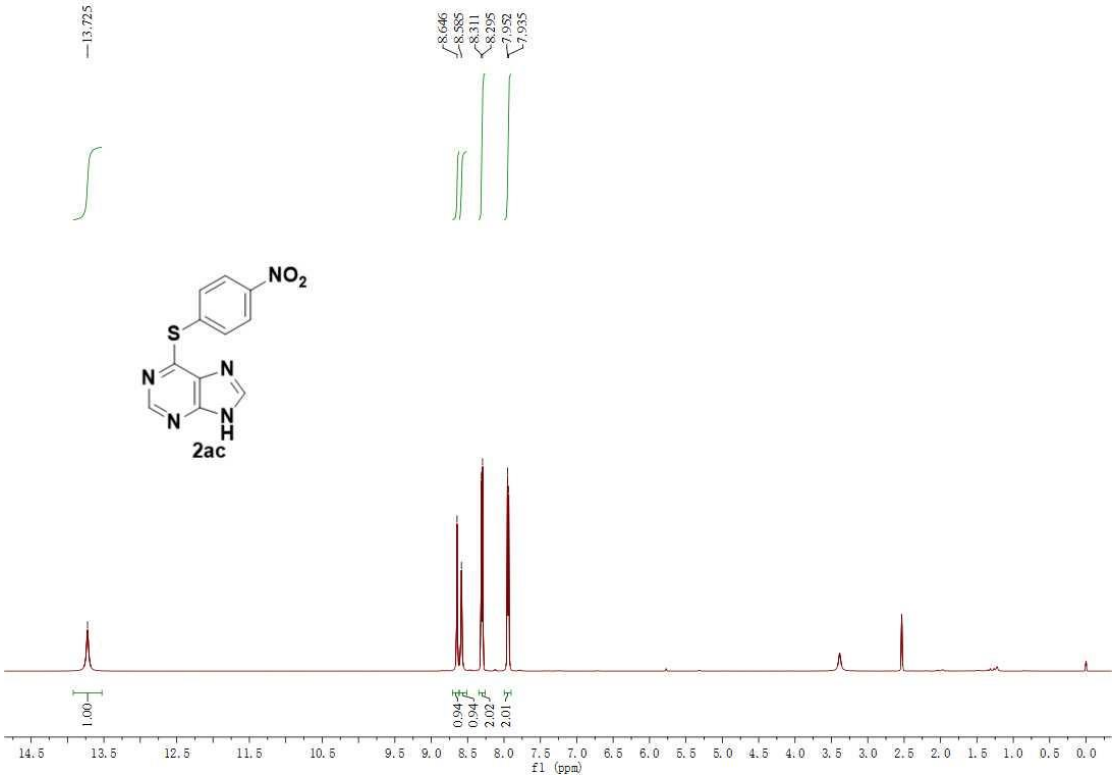
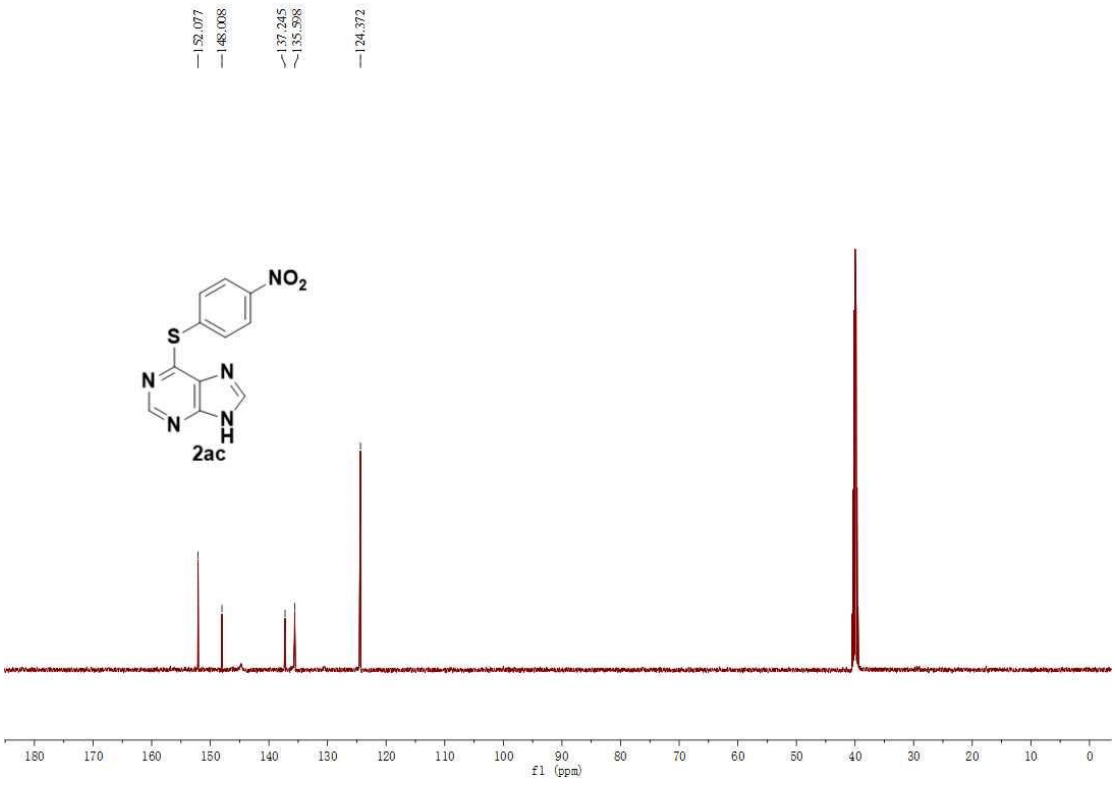
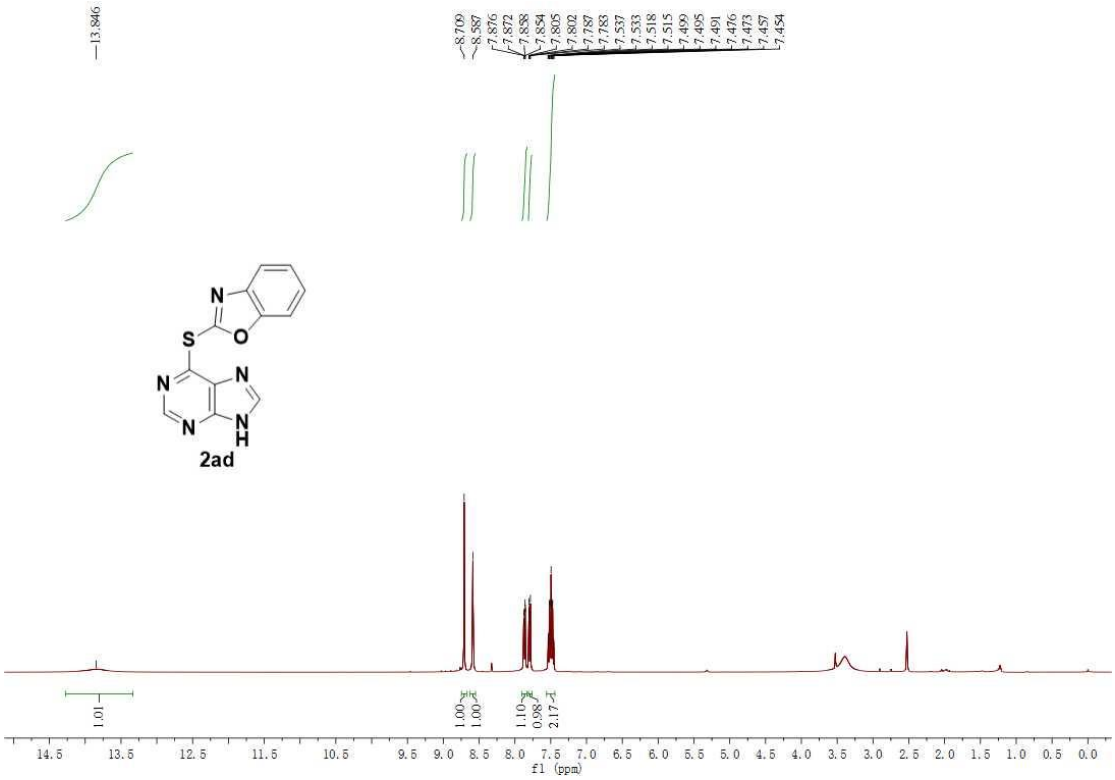


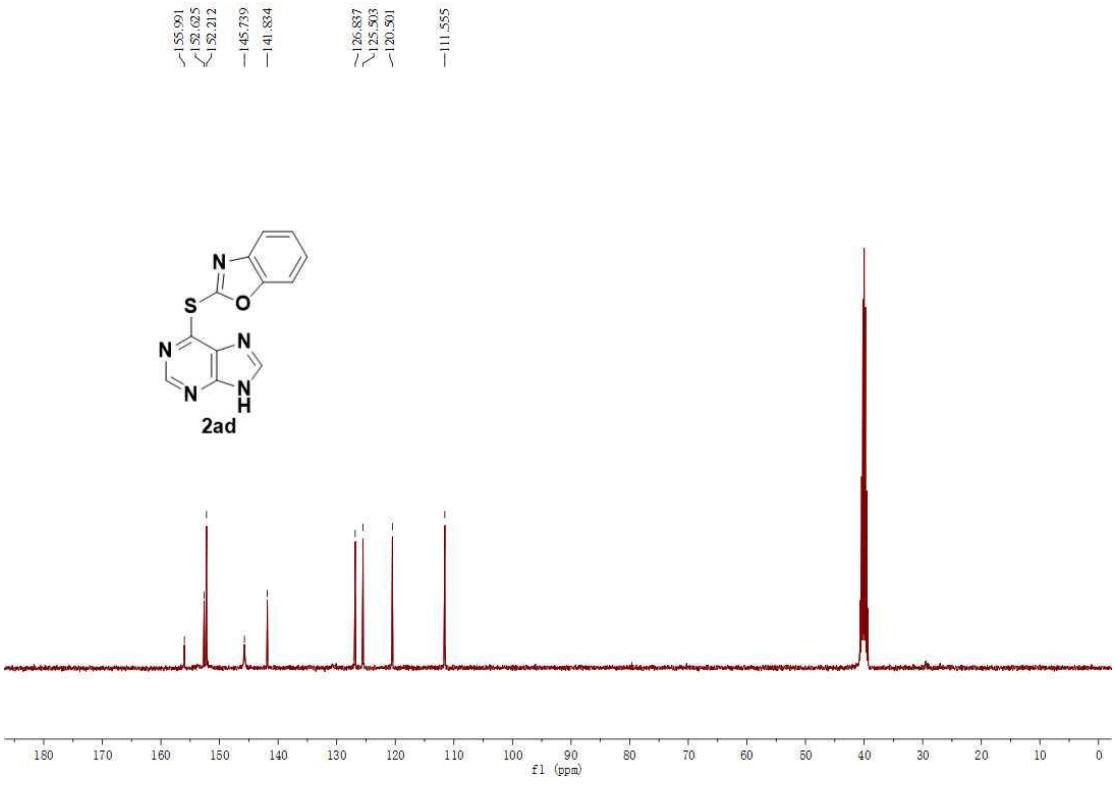
Figure S224. ESI Mass spectrum of product **5**. Calculated Mass $[M+2H]^{+}$: 813.3; $[M+3H]^{3+}$: 542.6; $[M+4H]^{4+}$: 407.2;Mass Found (ESI+); $[M+2H]^{+}$: 813.5; $[M+3H]^{3+}$: 542.7; $[M+4H]^{4+}$: 407.3.

14. Spectra of new compounds






13.846
8.709
8.587
7.876
7.872
7.858
7.854
7.805
7.802
7.787
7.783
7.537
7.533
7.518
7.515
7.499
7.495
7.491
7.476
7.473
7.457
7.454
2ad
1.01
1.00
1.00
1.10
0.98
2.17
f1 (ppm)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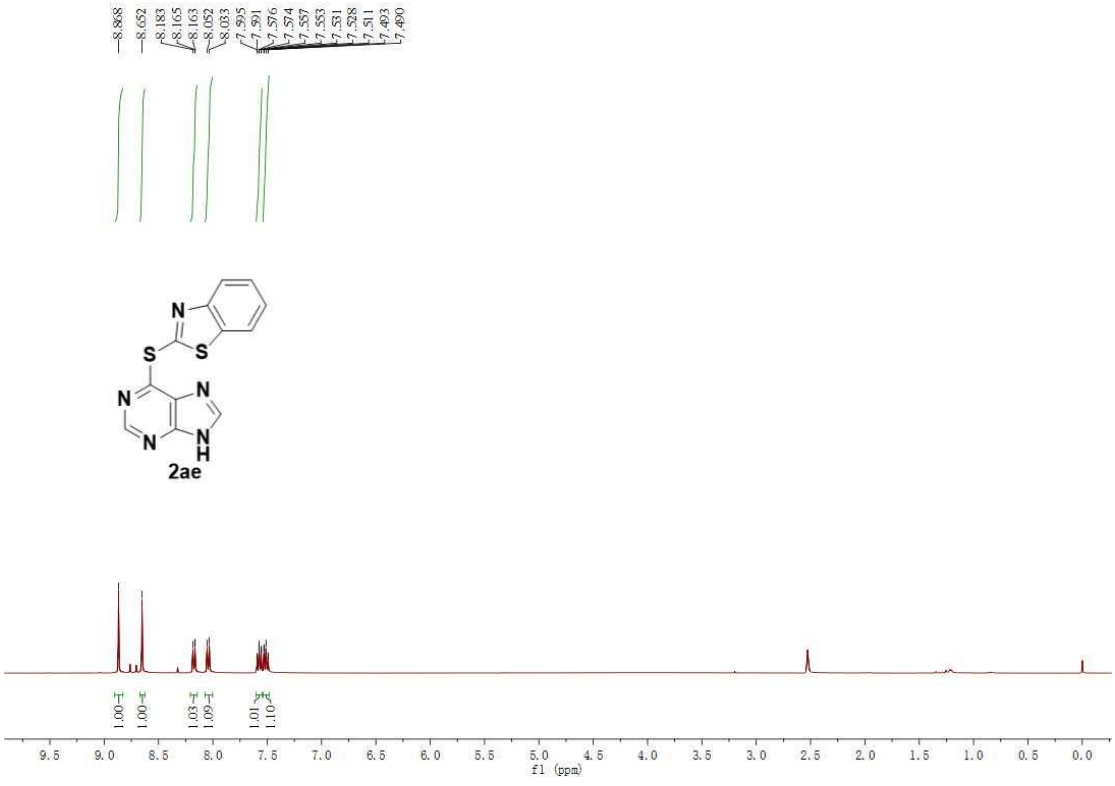
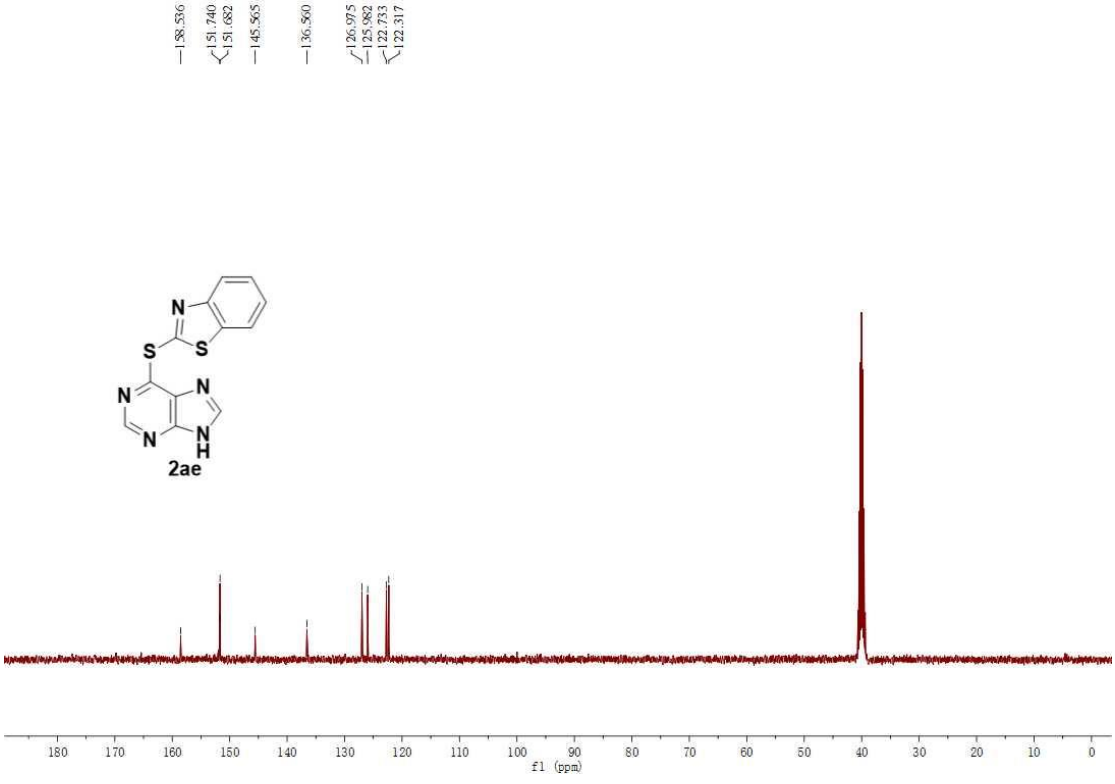
152.212
145.739
141.834
126.837
125.503
120.501
111.555
2ad
f1 (ppm)


8.868
8.652
8.183
8.165
8.163
8.052
8.033
7.595
7.591
7.576
7.574
7.557
7.553
7.531
7.528
7.511
7.493
7.490
2ae
1.00
1.00
1.03
1.09
1.01
1.10
f1 (ppm)


158.536
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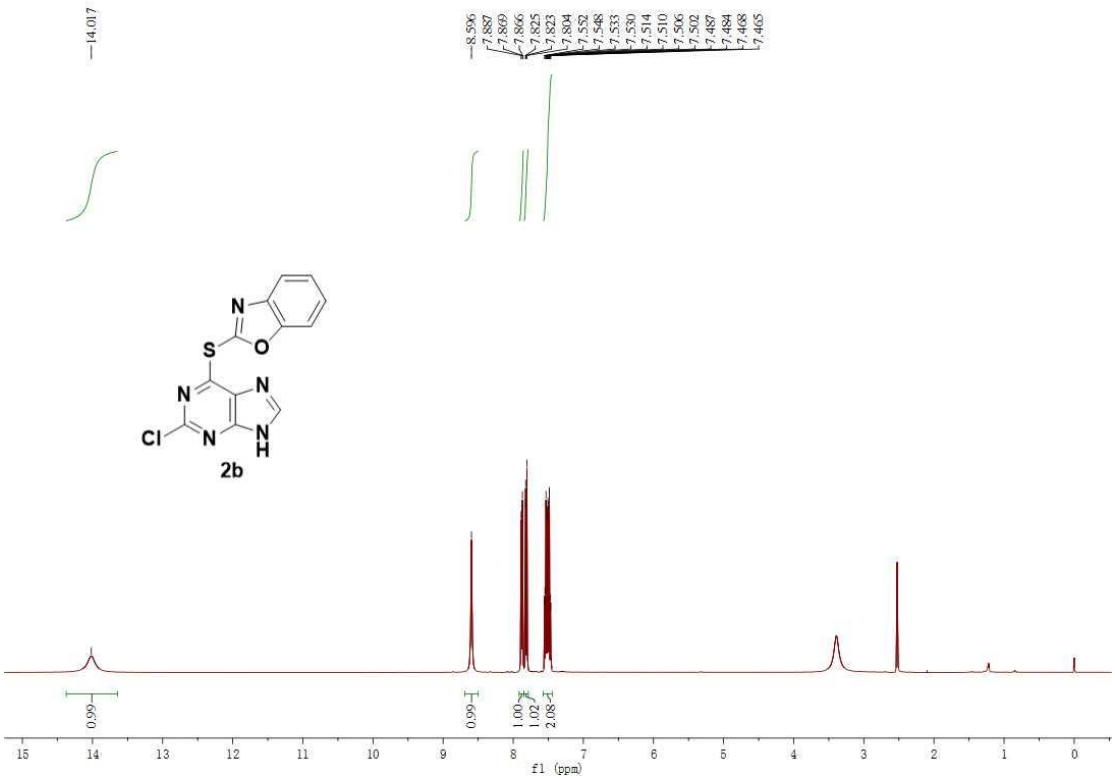
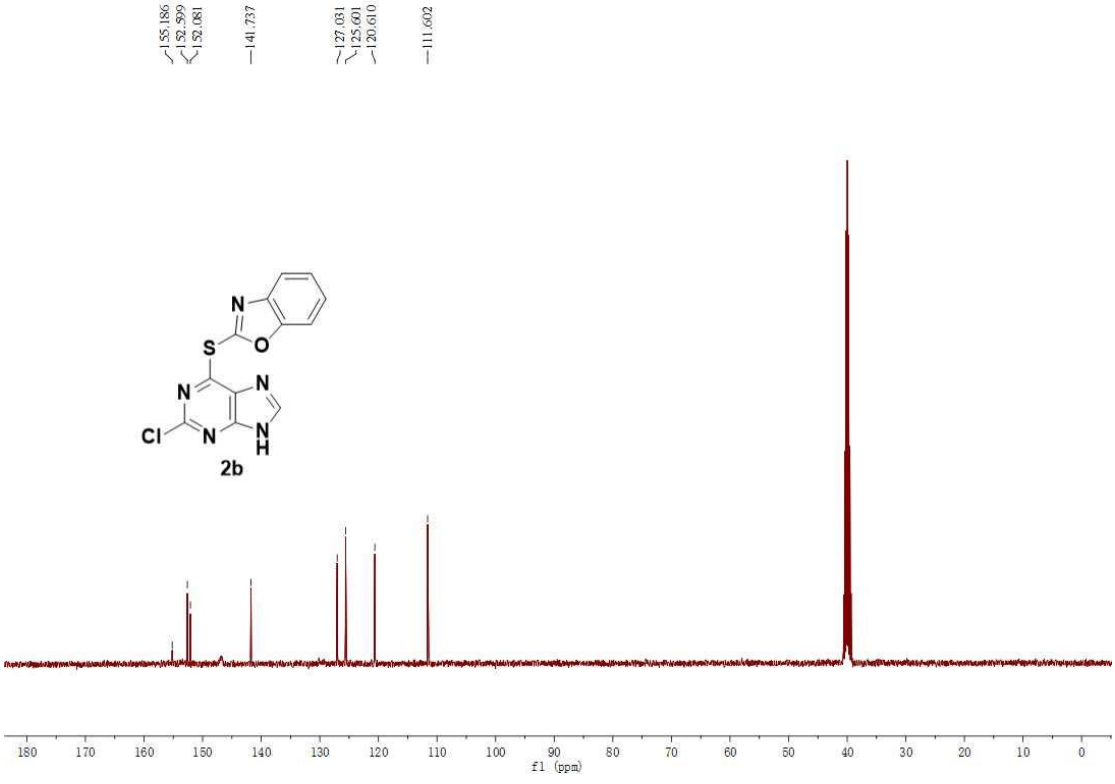
151.682
145.565
136.560
126.975
125.962
122.733
122.317
2ae
f1 (ppm)


14.017
8.596
7.887
7.869
7.866
7.825
7.823
7.804
7.552
7.548
7.533
7.530
7.514
7.510
7.506
7.502
7.487
7.484
7.468
7.465
2b
0.99
0.99
1.00
1.02
2.08
f1 (ppm)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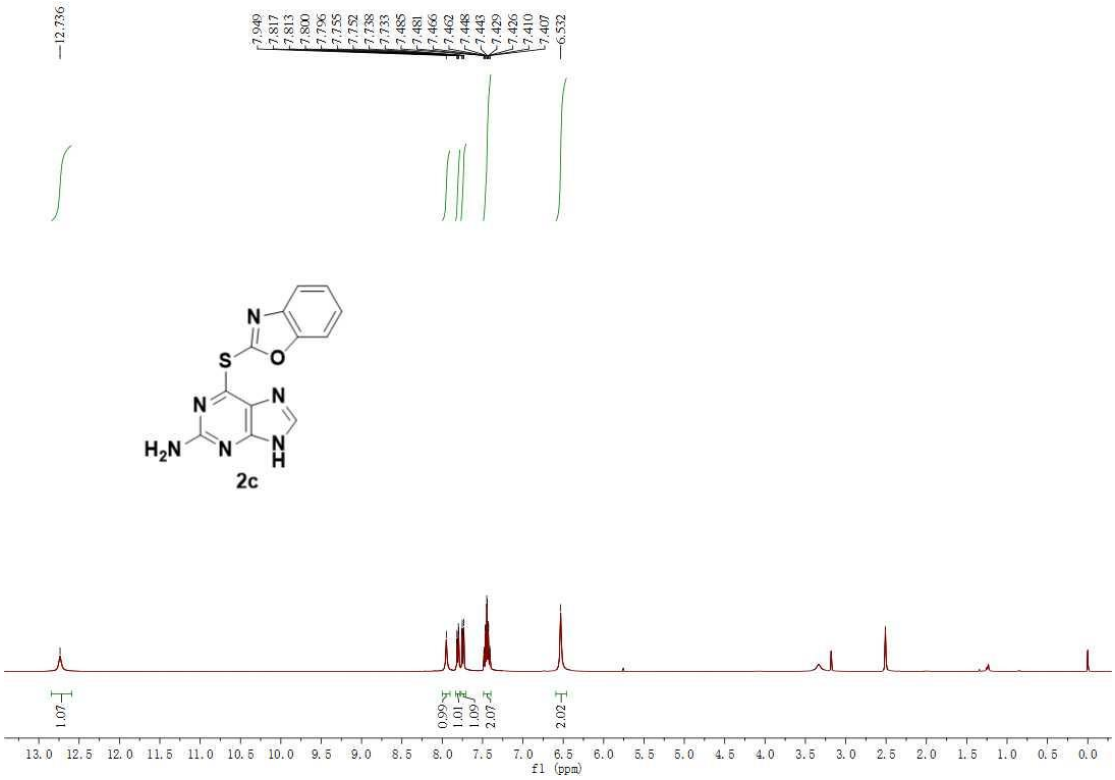
141.737
127.031
125.601
120.610
111.602
2b
f1 (ppm)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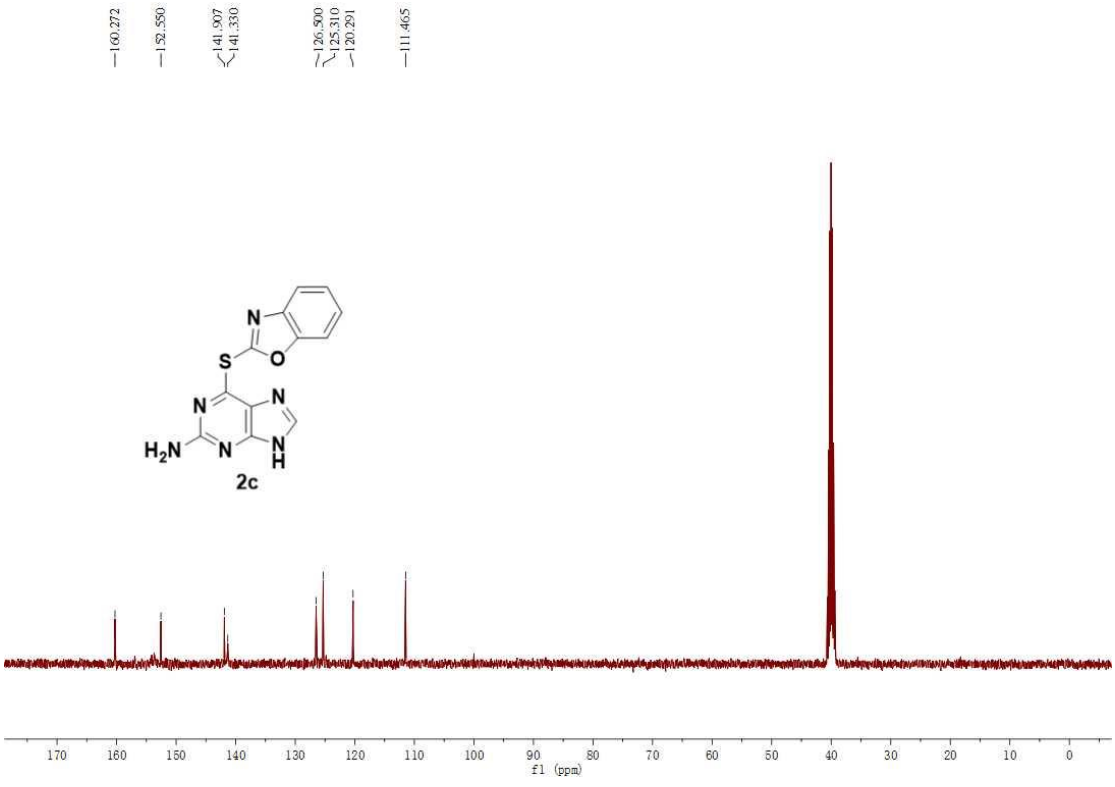
7.949
7.817
7.813
7.800
7.796
7.755
7.752
7.738
7.733
7.485
7.481
7.466
7.462
7.448
7.443
7.429
7.426
7.410
7.407
6.532
2c
1.07
0.99
1.01
1.09
2.07
2.02
f1 (ppm)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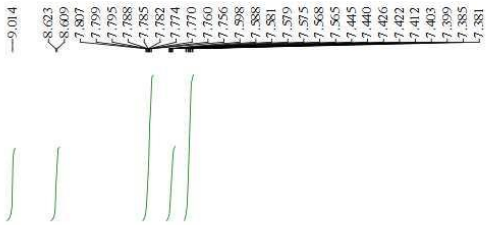
141.330
126.500
125.310
120.291
111.465
2c
f1 (ppm)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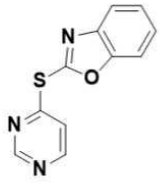
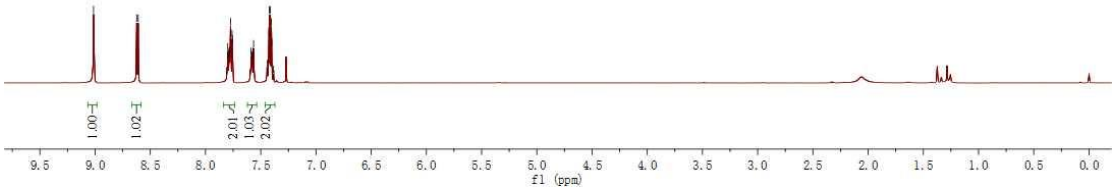
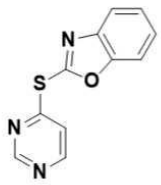
8.623
8.609
7.807
7.799
7.795
7.788
7.785
7.782
7.774
7.770
7.760
7.756
7.598
7.588
7.581
7.579
7.575
7.568
7.565
7.445
7.440
7.426
7.422
7.412
7.403
7.399
7.385
7.381



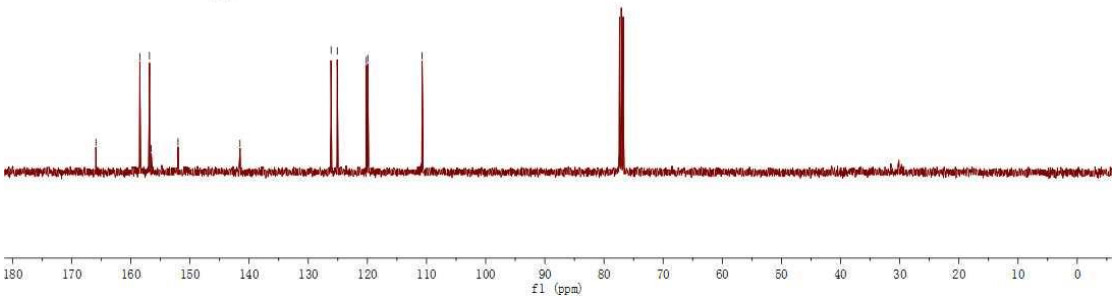
2d


1.00
1.02
2.01
1.03
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

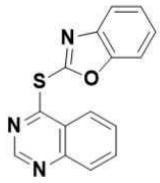

165.895
158.471
156.844
156.540
152.012
141.534
126.132
125.087
120.184
119.922
110.742



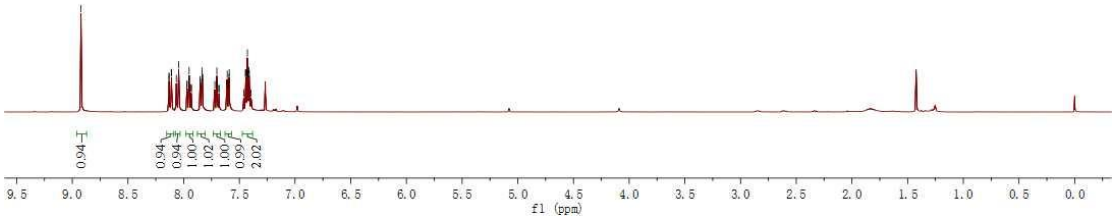
2d


180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.922
8.132
8.131
8.111
8.110
8.066
8.045
7.972
7.968
7.954
7.951
7.947
7.933
7.930
7.853
7.850
7.847
7.835
7.831
7.830
7.720
7.705
7.702
7.699
7.685
7.682
7.613
7.609
7.597
7.593
7.591
7.461
7.446
7.442
7.433
7.428
7.422
7.414
7.410
7.395



2e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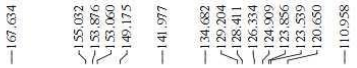
0.94
0.94
1.00
1.02
1.00
0.99
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


167.634
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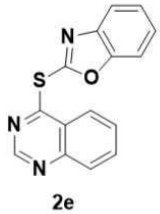
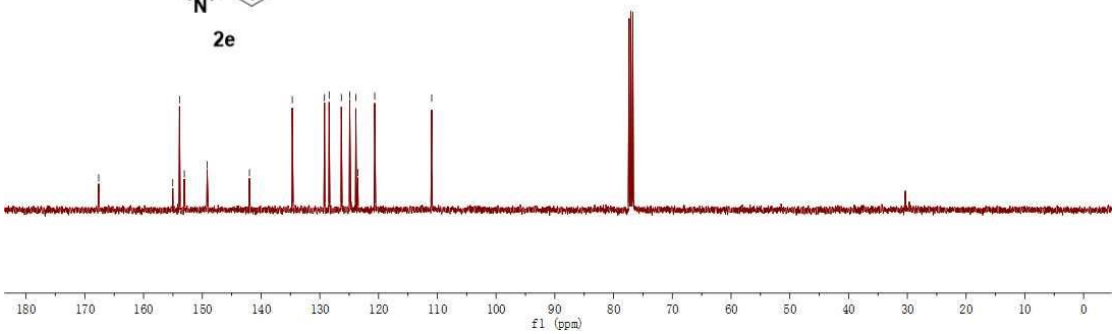
153.060
149.175
141.977
134.682
129.204
128.411
126.334
124.909
123.856
123.539
120.650
110.958



2e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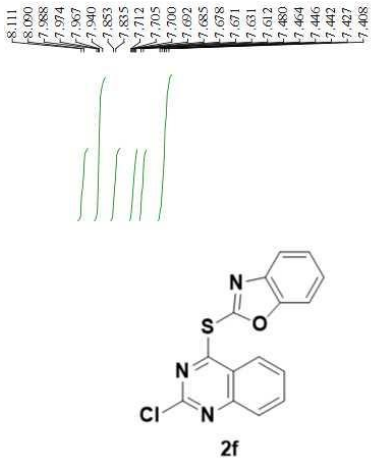
f1 (ppm)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8.090
7.988
7.974
7.967
7.940
7.853
7.835
7.712
7.705
7.700
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7.685
7.678
7.671
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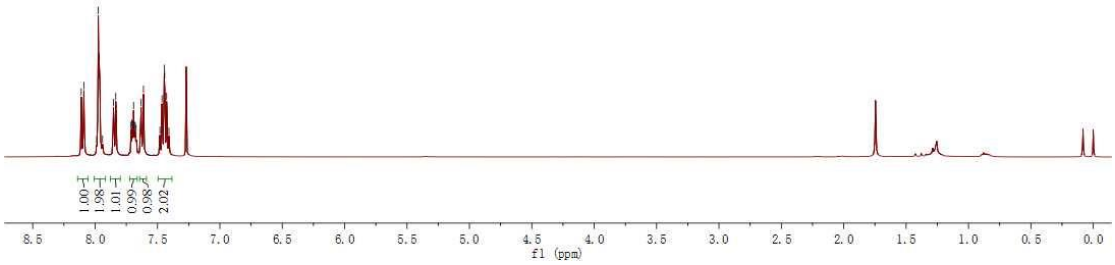
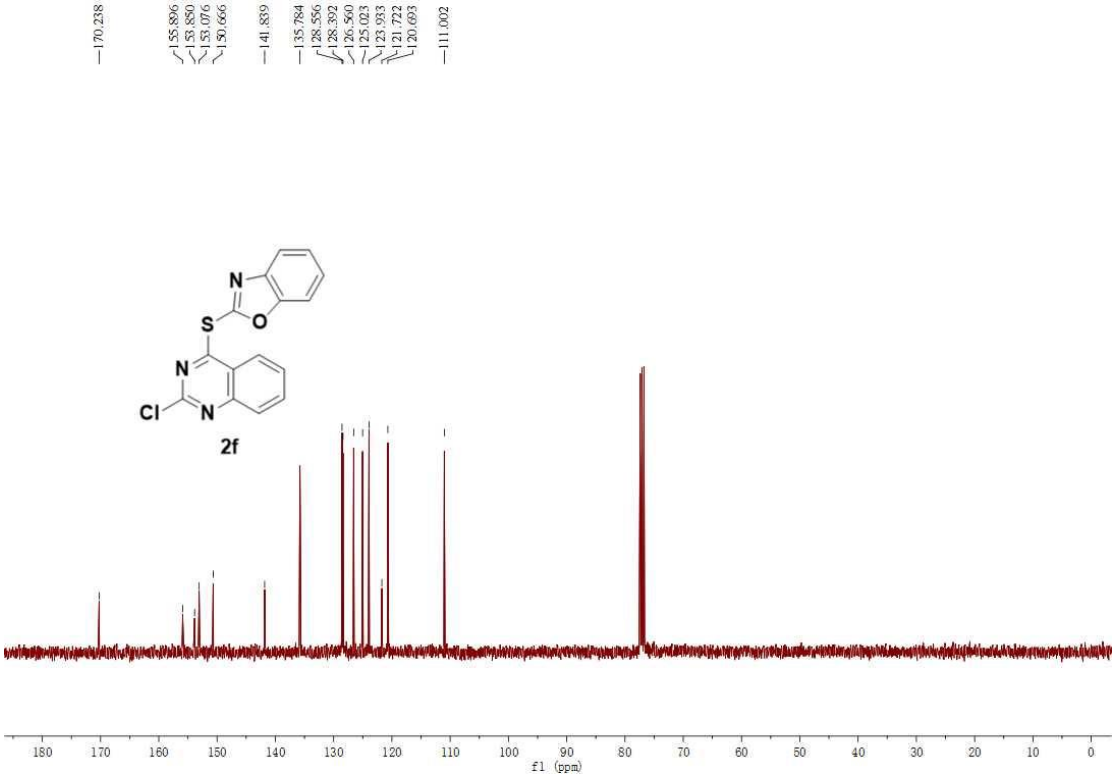
7.408
N
S
O
N
Cl
N
2f


1.00
1.98
1.01
0.99
0.98
2.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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153.850
153.076
150.666
141.839
135.784
128.556
128.392
126.560
125.023
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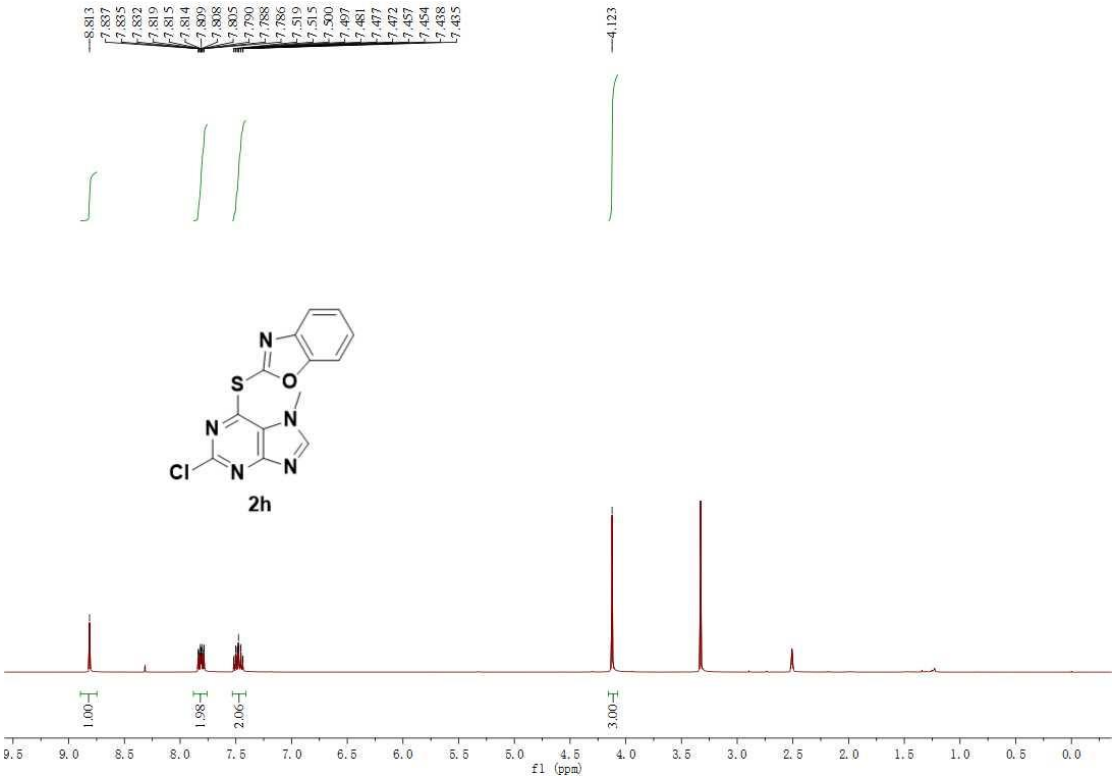
121.722
120.693
111.002
N
S
O
N
Cl
N
2f
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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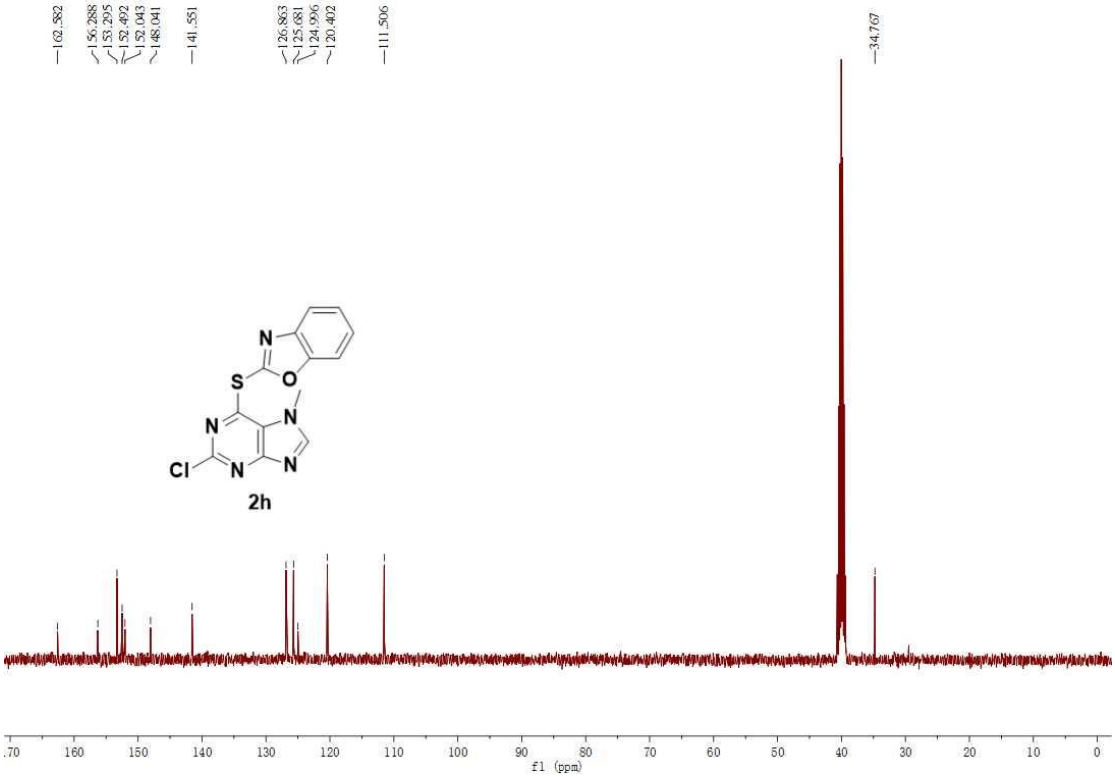
7.835
7.832
7.819
7.815
7.814
7.809
7.808
7.805
7.790
7.788
7.786
7.519
7.515
7.500
7.497
7.481
7.477
7.472
7.457
7.454
7.438
7.435
4.123
2h
1.00
1.98
2.06
3.00
f1 (ppm)


162.582
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153.295
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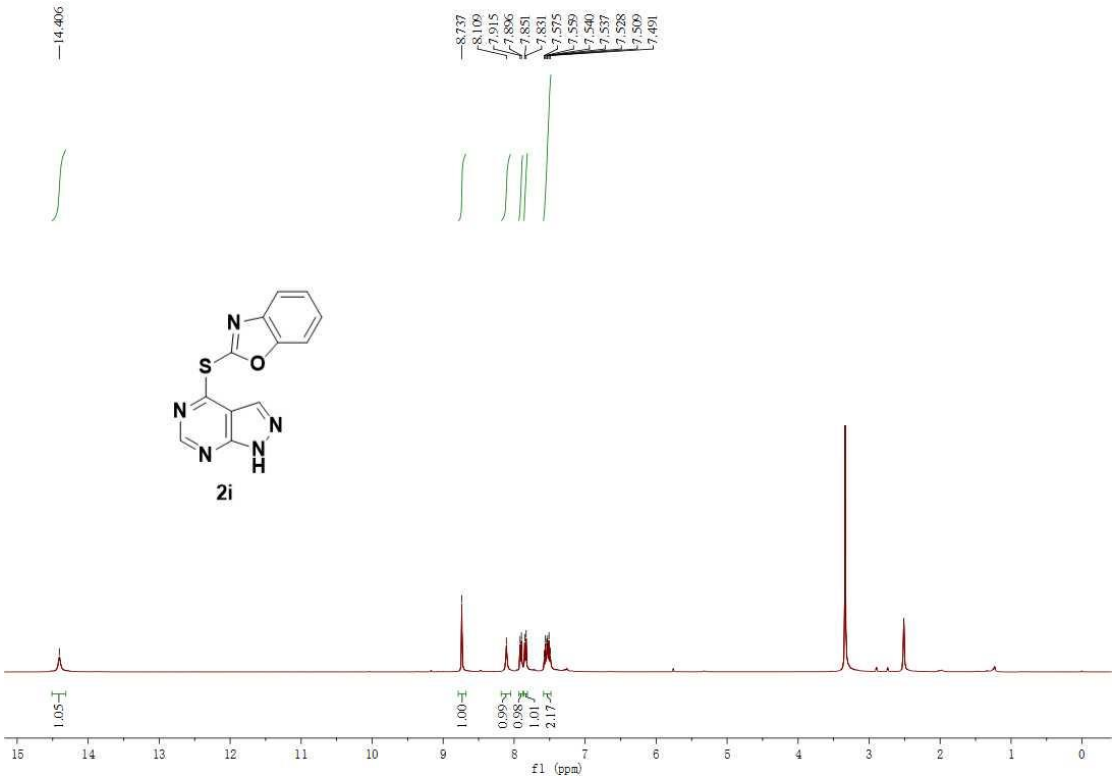
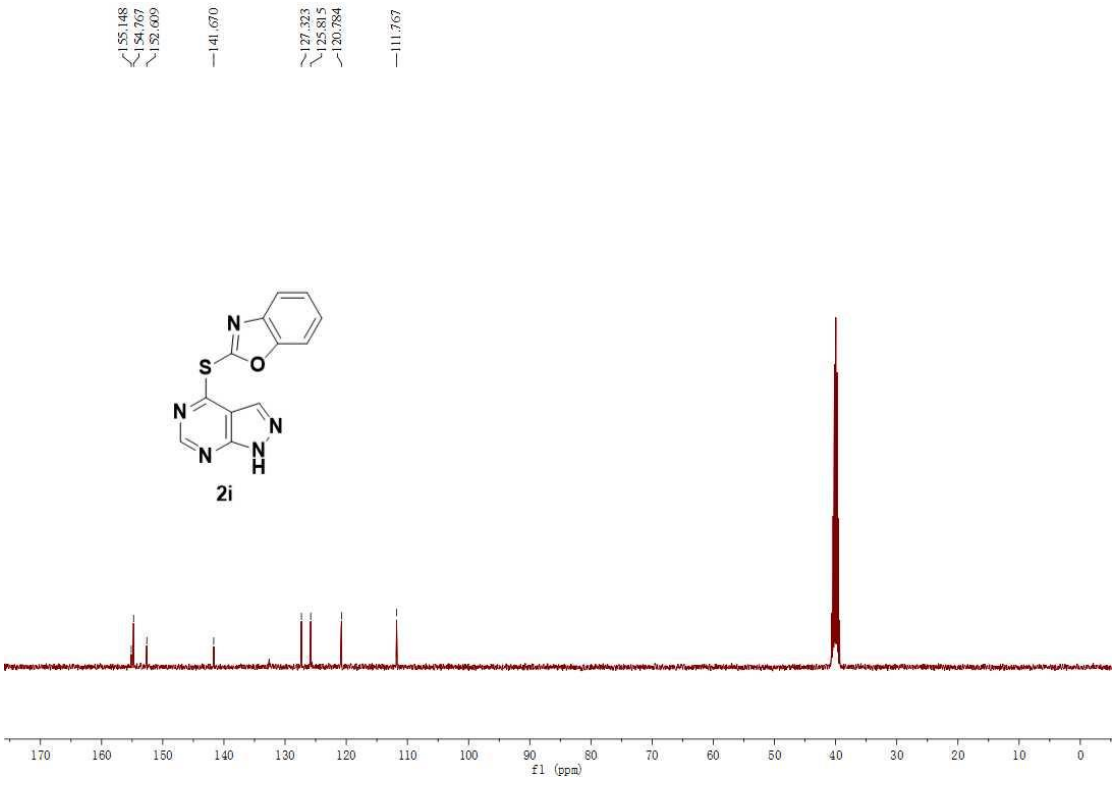
152.043
148.041
141.551
126.863
125.681
124.996
120.402
111.506
34.767
2h
f1 (ppm)


14.406
8.737
8.109
7.915
7.896
7.851
7.831
7.575
7.559
7.540
7.537
7.528
7.509
7.491
2i
1.05
1.00
0.99
0.98
1.01
2.17
f1 (ppm)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154.767
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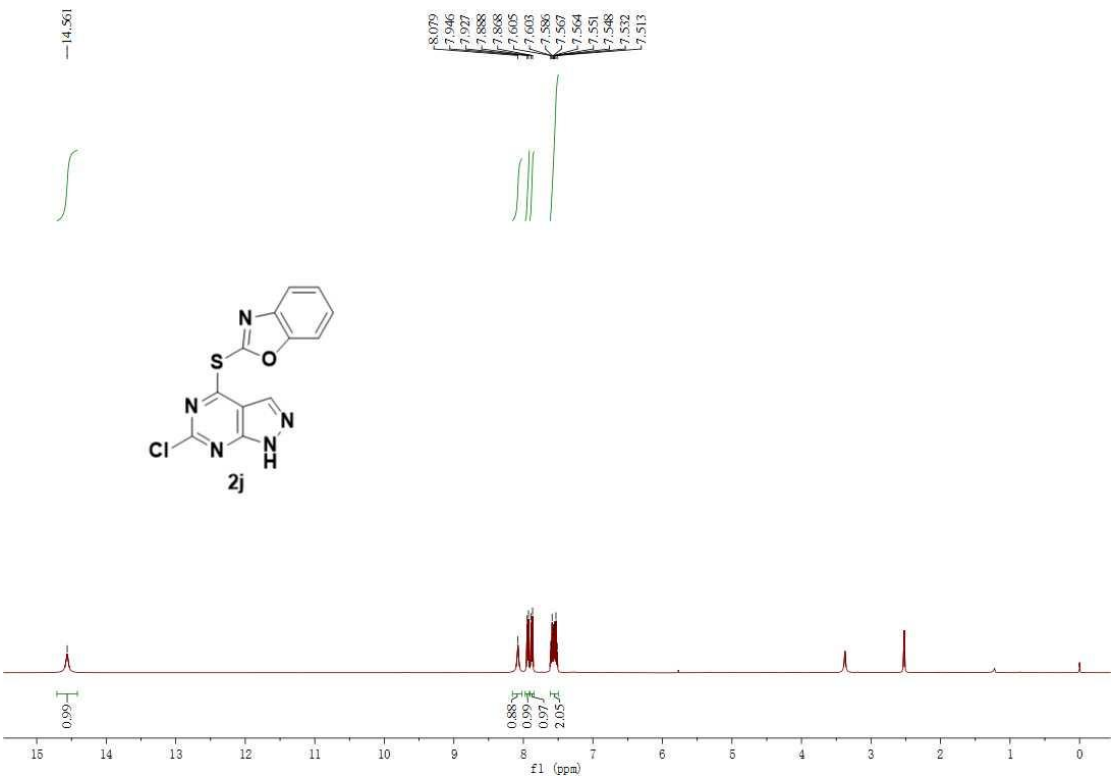
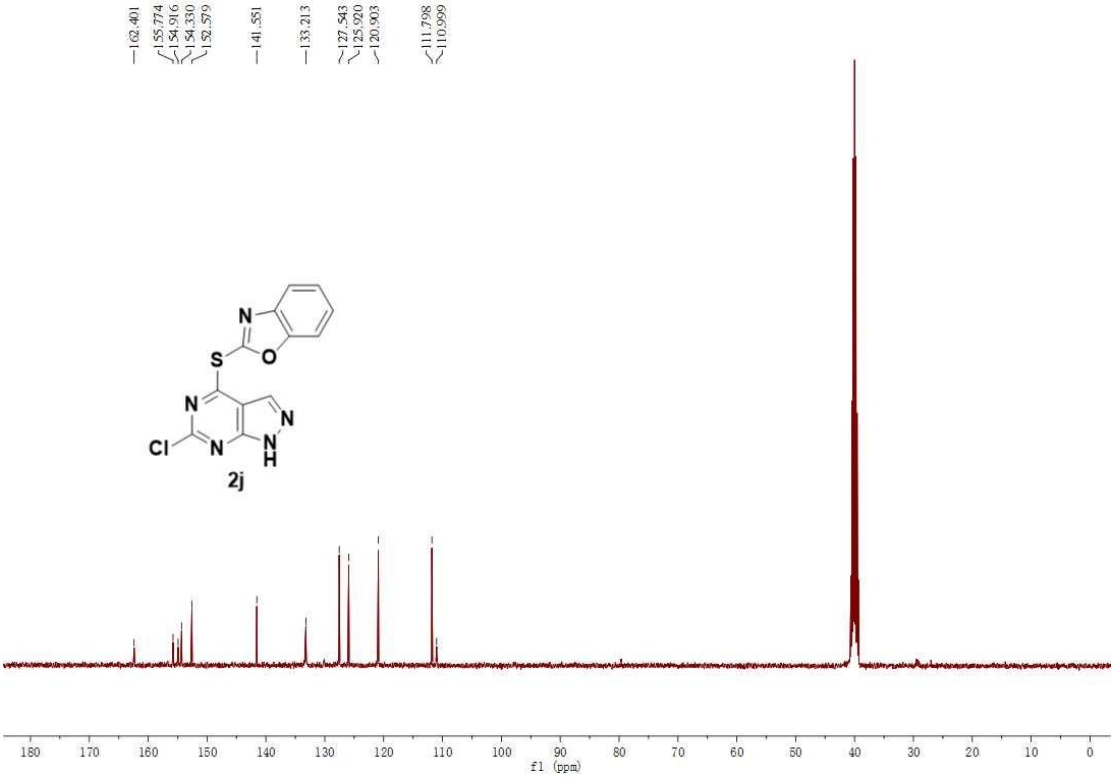
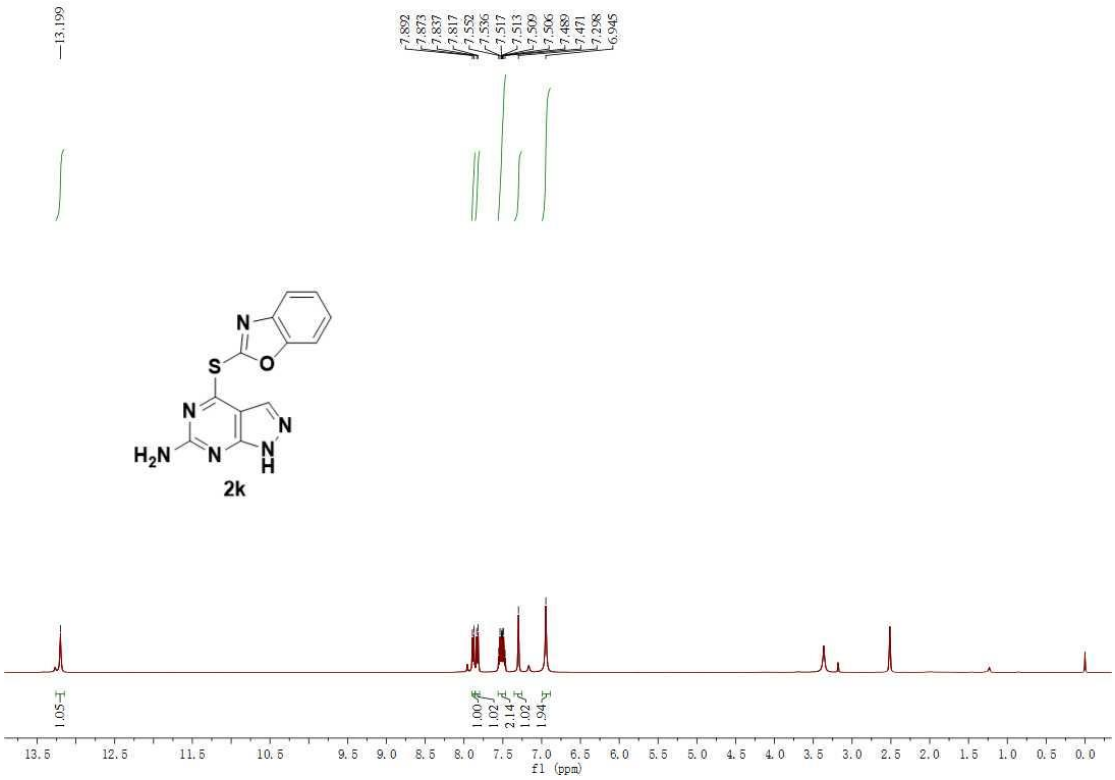
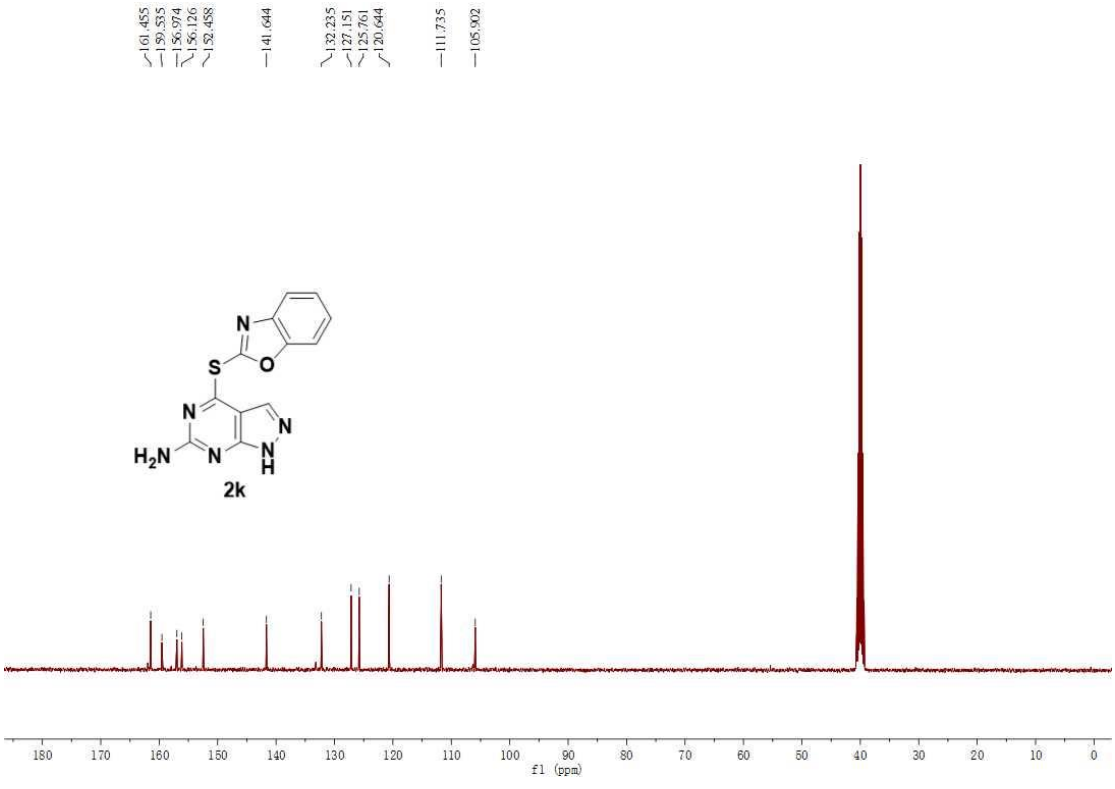
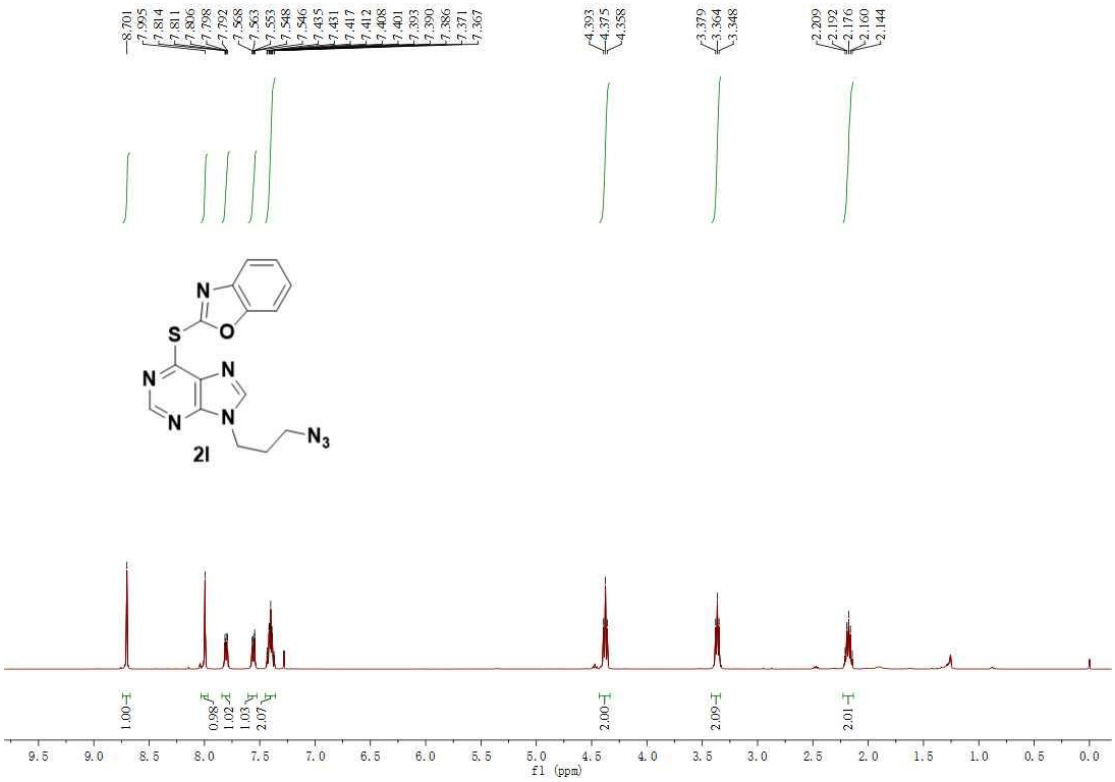
127.323
125.815
120.784
111.767
2i
f1 (ppm)

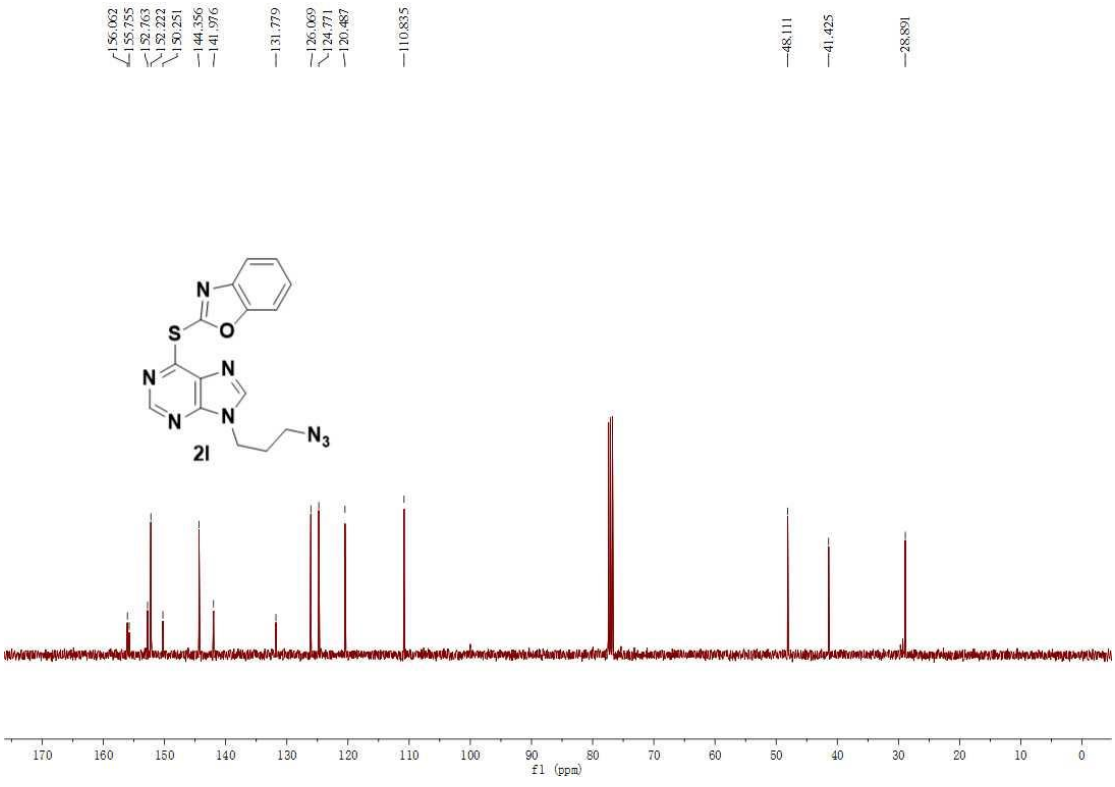

14.561
8.079
7.946
7.927
7.888
7.868
7.605
7.603
7.586
7.567
7.564
7.551
7.548
7.532
7.513
2j
0.99
0.88
0.99
0.97
2.05
f1 (ppm)

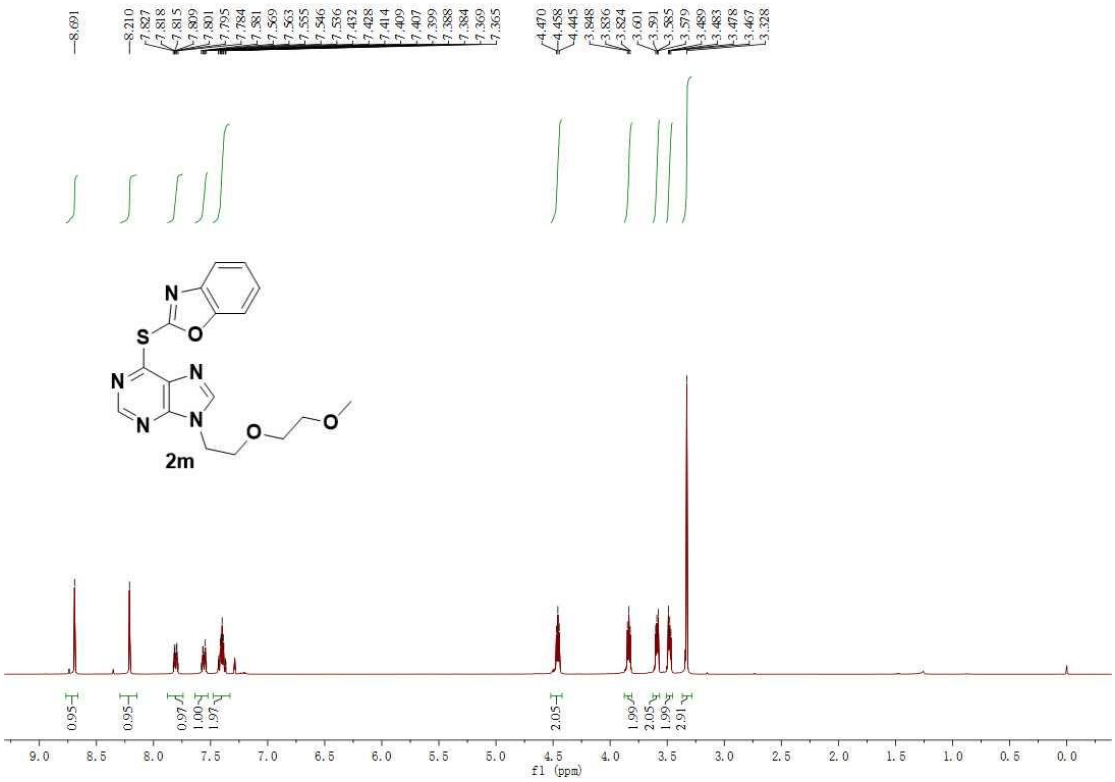

162.401
155.774
154.916
154.330
152.579
141.551
133.213
127.543
125.920
120.903
111.798
110.999
2j
f1 (ppm)


13.199
7.892
7.873
7.837
7.817
7.552
7.536
7.517
7.513
7.509
7.506
7.489
7.471
7.258
6.945
2k
1.05
1.00
1.02
2.14
1.02
1.94
f1 (ppm)


161.455
159.535
156.974
156.126
152.458
141.644
132.235
127.151
125.761
120.644
111.735
105.902
2k
f1 (ppm)


8.701
7.995
7.814
7.811
7.806
7.798
7.792
7.568
7.563
7.553
7.548
7.546
7.435
7.431
7.417
7.412
7.408
7.401
7.393
7.390
7.386
7.371
7.367
4.393
4.375
4.358
3.379
3.364
3.348
2.209
2.192
2.176
2.160
2.144
2l
1.00
0.98
1.02
1.03
2.07
2.00
2.09
2.01
f1 (ppm)


156.062
155.755
152.763
152.222
150.251
144.356
141.976
131.779
126.069
124.771
120.487
110.835
48.111
41.425
28.891
2l
f1 (ppm)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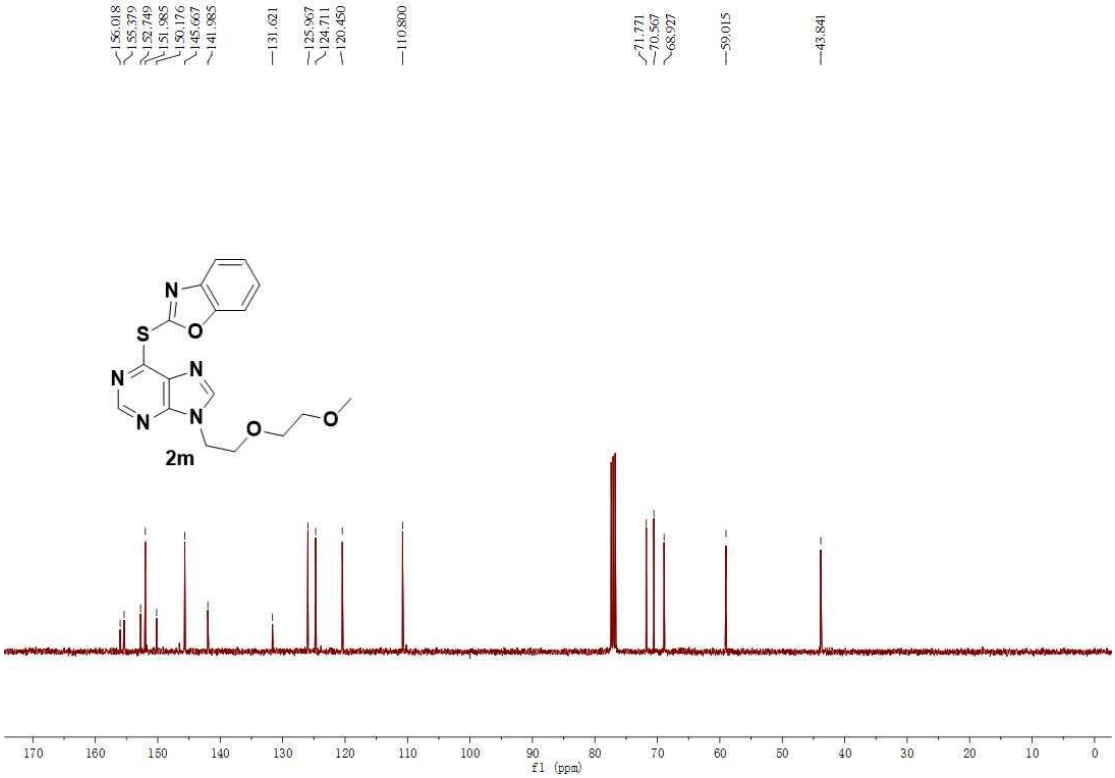
8.210
7.827
7.818
7.815
7.809
7.801
7.795
7.784
7.581
7.569
7.563
7.555
7.546
7.536
7.432
7.428
7.414
7.409
7.407
7.399
7.388
7.384
7.369
7.365
4.470
4.458
4.445
3.848
3.836
3.824
3.601
3.591
3.585
3.579
3.489
3.483
3.478
3.467
3.328
2m
0.95
0.95
0.97
1.00
1.97
2.05
1.99
2.05
1.99
2.91
f1 (ppm)


156.018
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152.749
151.985
150.176
145.667
141.985
131.621
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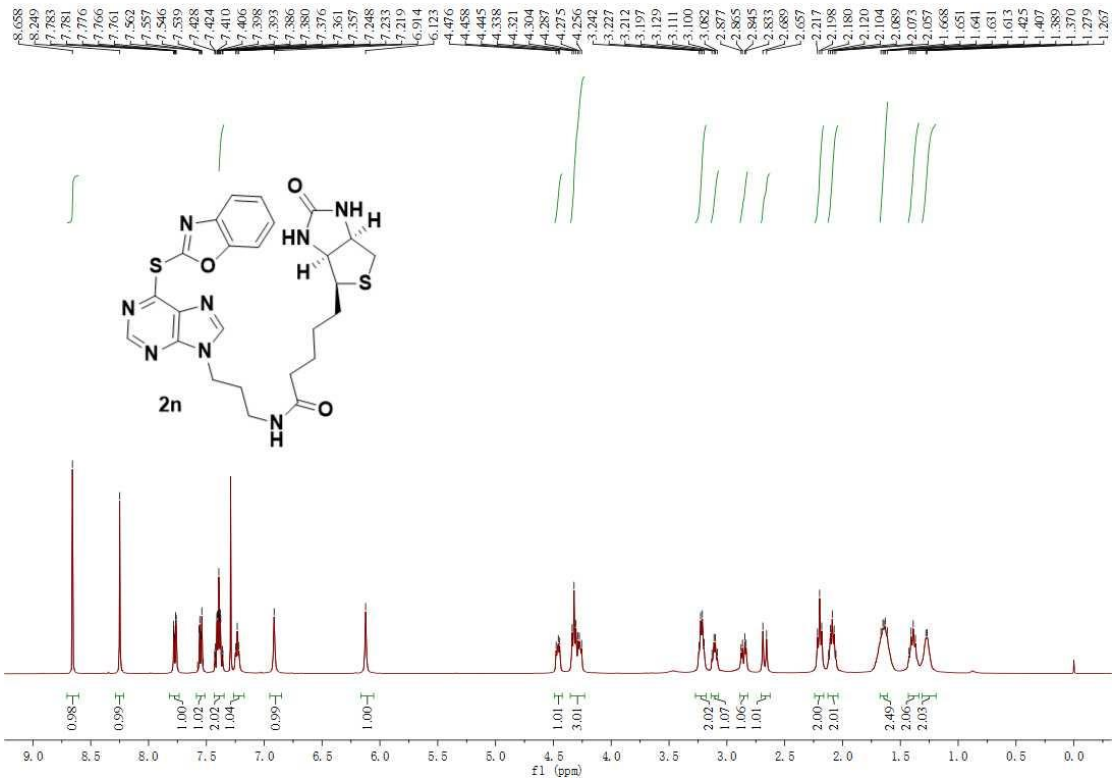
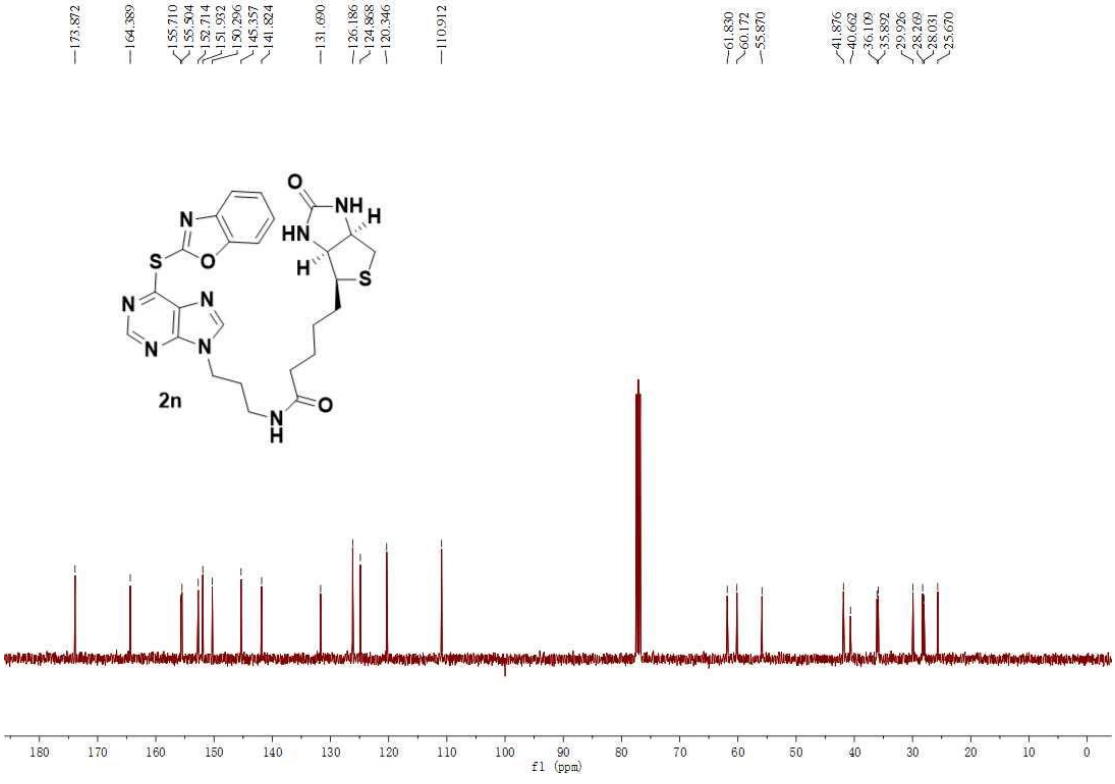
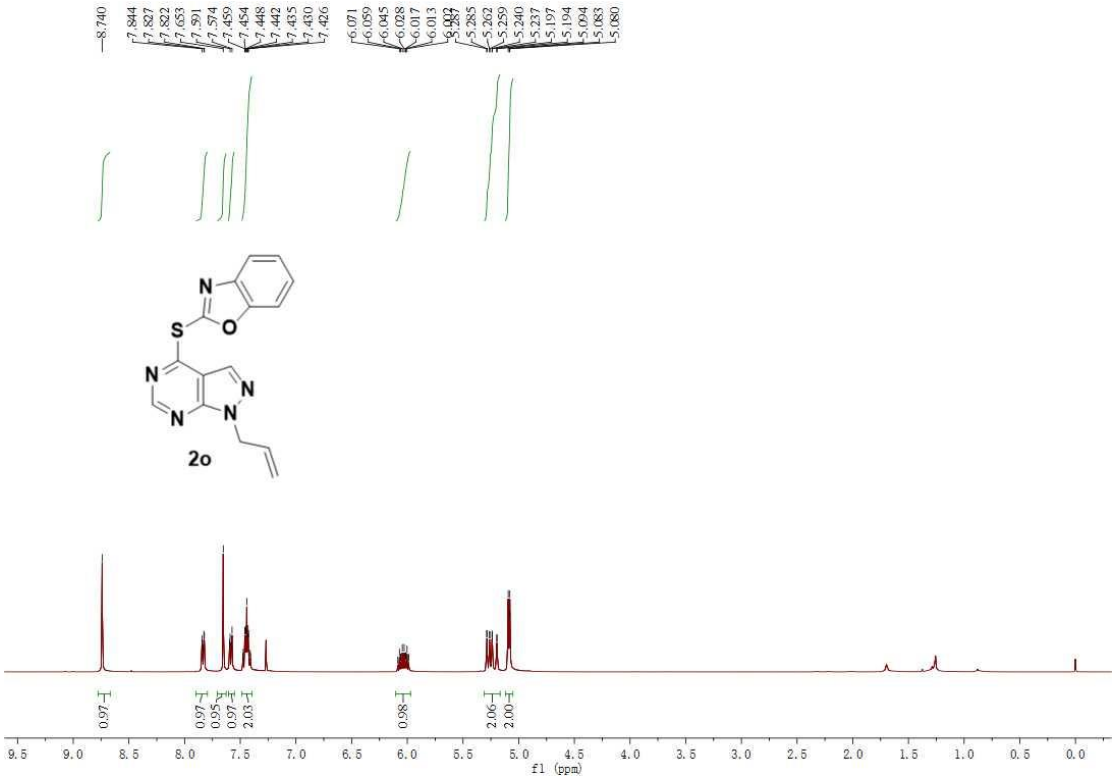
124.711
120.450
110.800
71.771
70.567
68.927
59.015
43.841
2m
f1 (ppm)


2n
f1 (ppm)


2n
f1 (ppm)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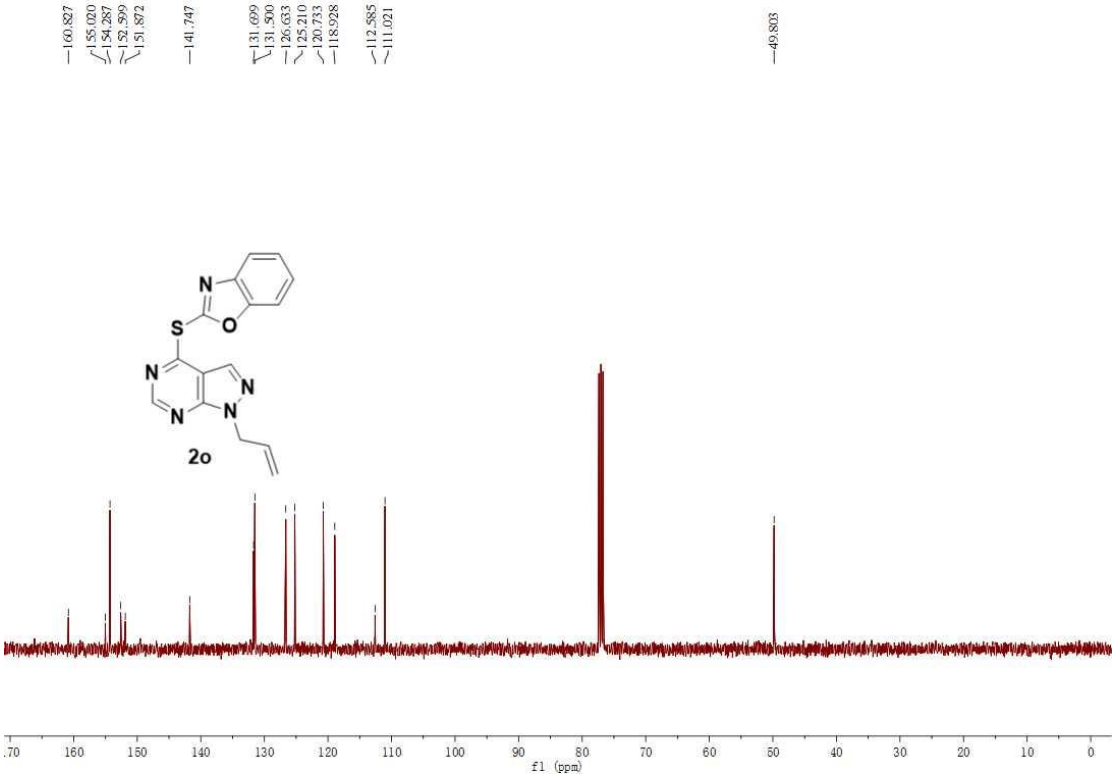
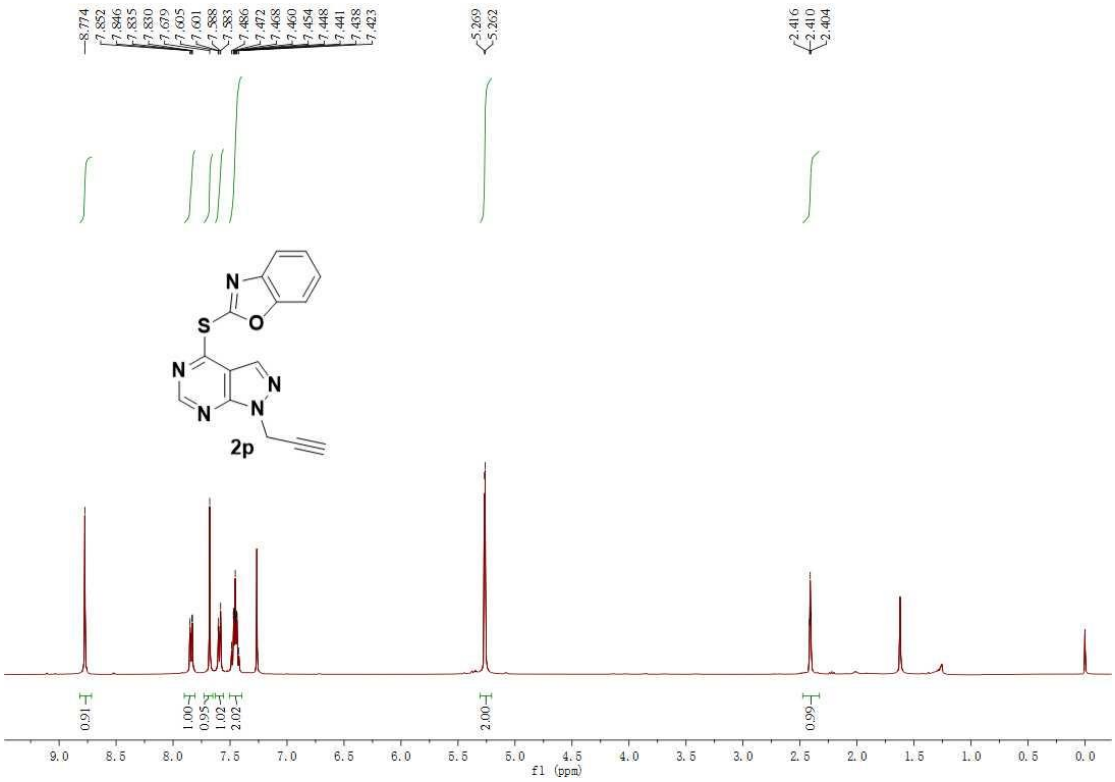
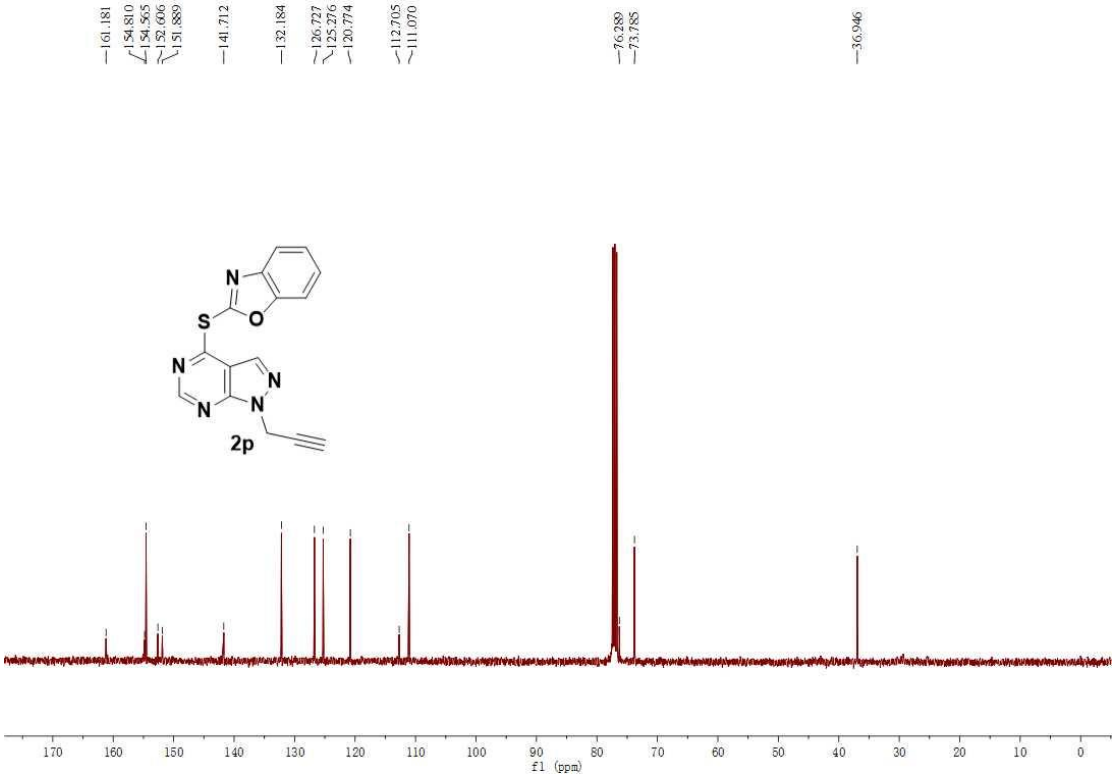
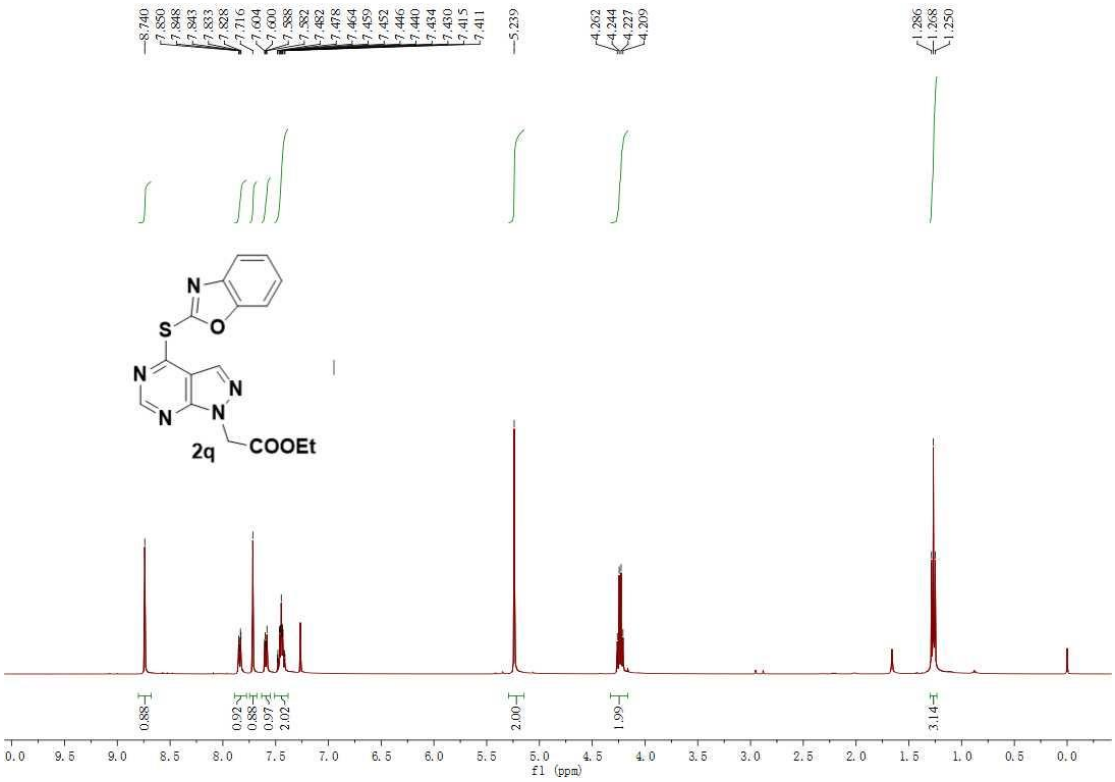
7.827
7.822
7.653
7.591
7.574
7.459
7.454
7.448
7.442
7.435
7.430
7.426
6.071
6.059
6.045
6.028
6.017
6.013
5.285
5.262
5.259
5.240
5.237
5.197
5.194
5.094
5.083
5.080
2o
0.97
0.97
0.95
0.97
2.03
0.98
2.06
2.00
f1 (ppm)


160.827
155.020
154.287
152.599
151.872
141.747
131.699
131.500
126.633
125.210
120.733
118.928
112.585
111.021
49.803
2o
f1 (ppm)


8.774
7.852
7.846
7.835
7.830
7.679
7.605
7.601
7.588
7.583
7.486
7.472
7.468
7.460
7.454
7.448
7.441
7.438
7.423
5.269
5.262
2.416
2.410
2.404
2p
0.91
1.00
0.95
1.02
2.02
2.00
0.99
f1 (ppm)


161.181
154.810
154.565
152.606
151.889
141.712
132.184
126.727
125.276
120.774
112.705
111.070
76.289
73.785
36.946
2p
f1 (ppm)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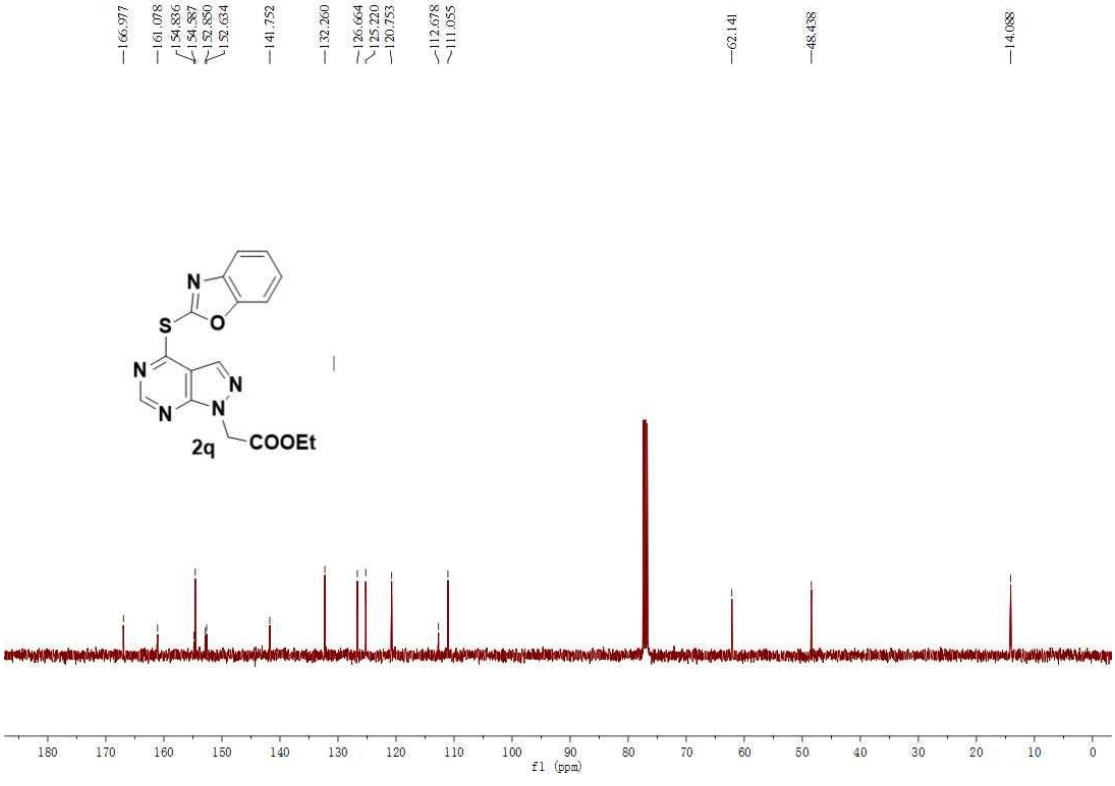
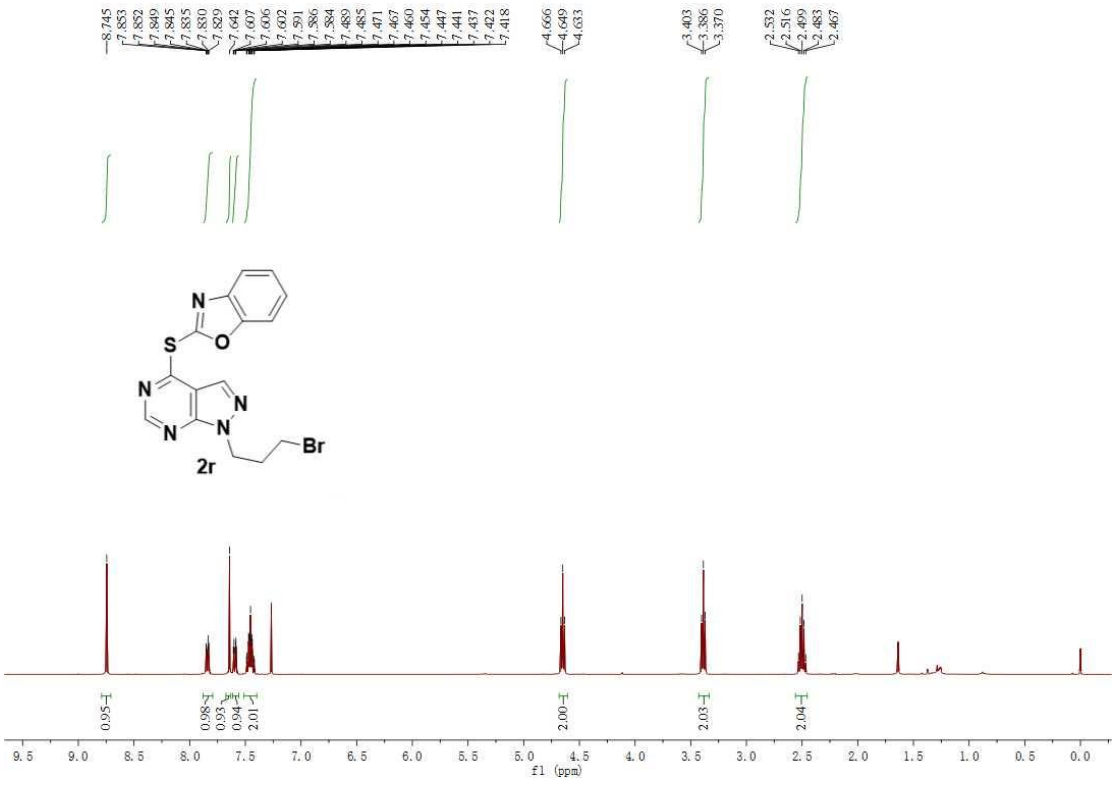
7.850
7.848
7.843
7.833
7.828
7.716
7.604
7.600
7.588
7.582
7.482
7.478
7.464
7.459
7.452
7.446
7.440
7.434
7.430
7.415
7.411
5.239
4.262
4.244
4.227
4.209
1.286
1.268
1.250
2q
COOEt
0.88
0.92
0.88
0.97
2.02
2.00
1.99
3.14
f1 (ppm)


166.977
161.078
154.836
154.587
152.850
152.634
141.752
132.260
126.664
125.220
120.753
112.678
111.055
62.141
48.438
14.088
2q
COOEt
f1 (ppm)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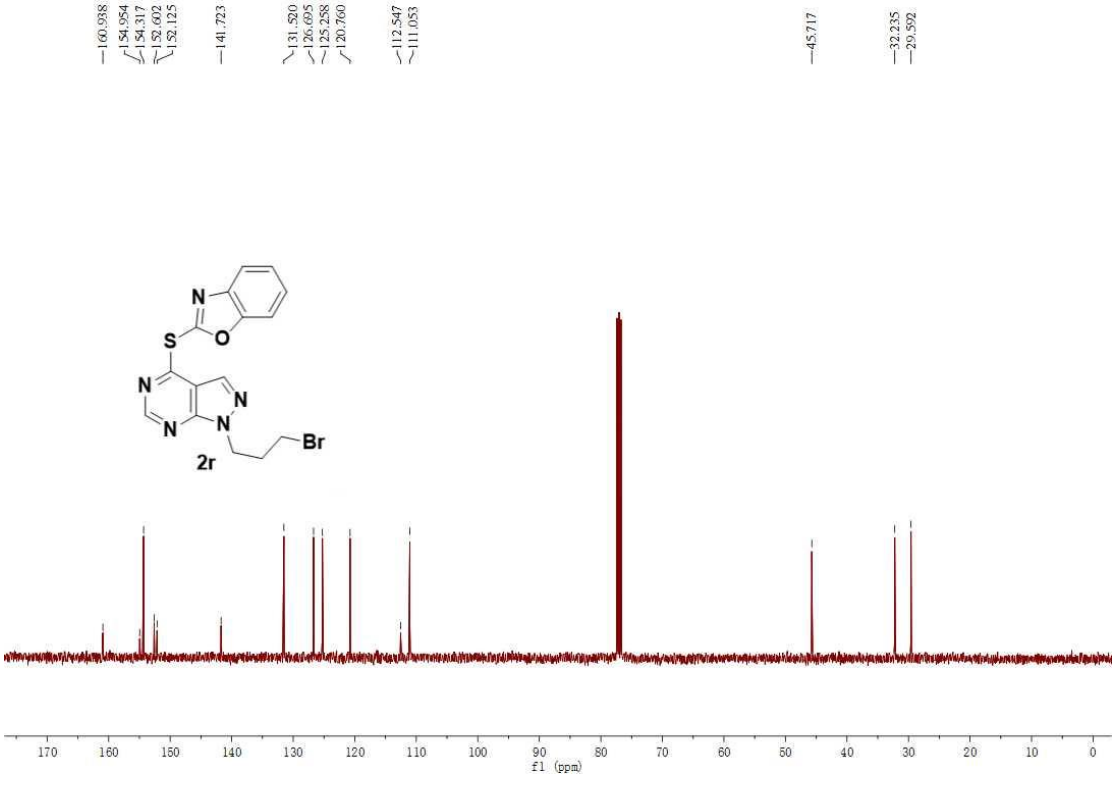
7.845
7.835
7.830
7.829
7.642
7.607
7.606
7.602
7.591
7.586
7.584
7.489
7.485
7.471
7.467
7.460
7.454
7.447
7.441
7.437
7.422
7.418
4.666
4.649
4.633
3.403
3.386
3.370
2.532
2.516
2.499
2.483
2.467
N
S
O
N
N
N
Br
2r
0.95
0.98
0.93
0.94
2.01
2.00
2.03
2.04
f1 (ppm)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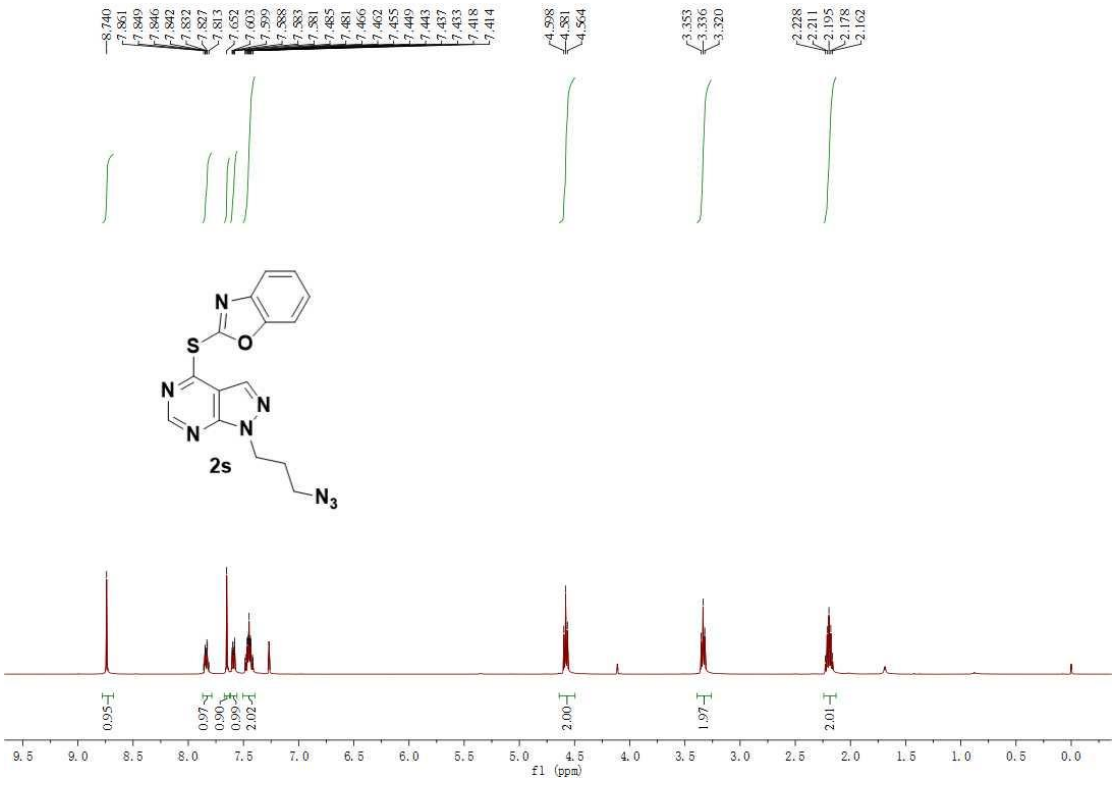
154.954
154.317
152.602
152.125
141.723
131.520
126.695
125.258
120.760
112.547
111.053
45.717
32.235
29.592
N
S
O
N
N
N
Br
2r
f1 (ppm)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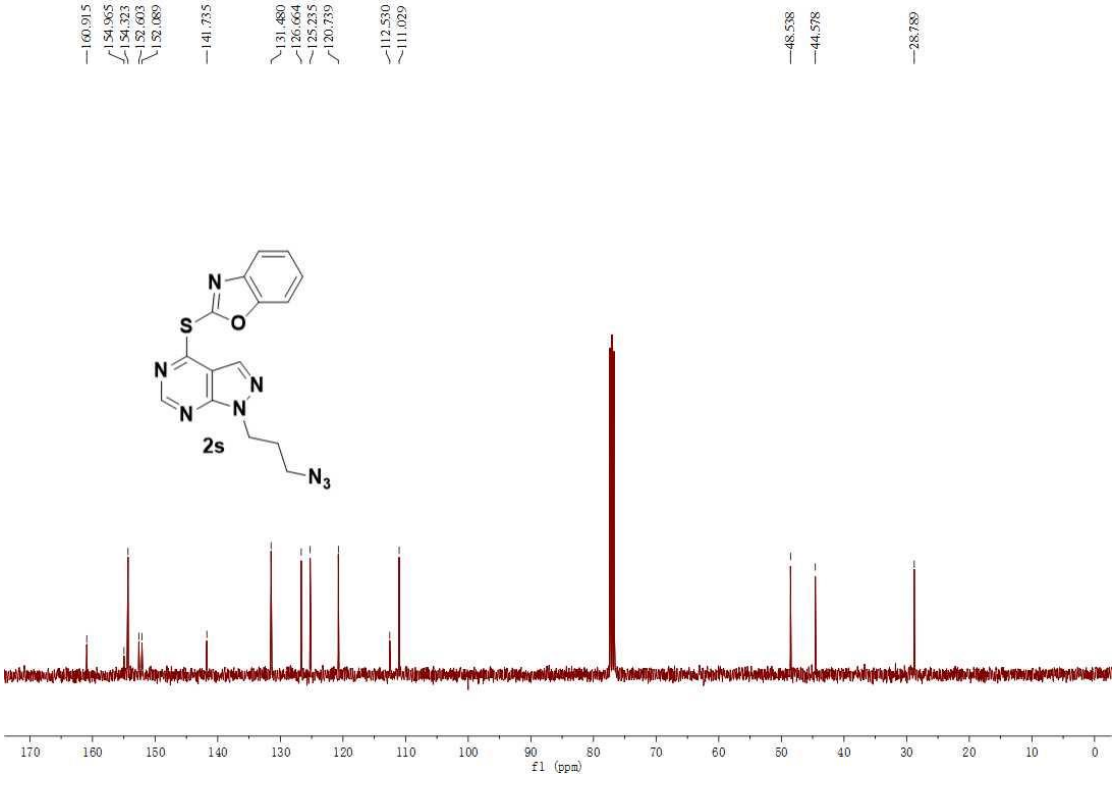
7.846
7.842
7.832
7.827
7.813
7.652
7.603
7.599
7.588
7.583
7.581
7.485
7.481
7.466
7.462
7.455
7.449
7.443
7.437
7.433
7.418
7.414
4.598
4.581
4.564
3.353
3.336
3.320
2.228
2.211
2.195
2.178
2.162
2s
0.95
0.97
0.90
0.99
2.02
2.00
1.97
2.01
f1 (ppm)


160.915
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154.323
152.603
152.089
141.735
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125.235
120.739
112.530
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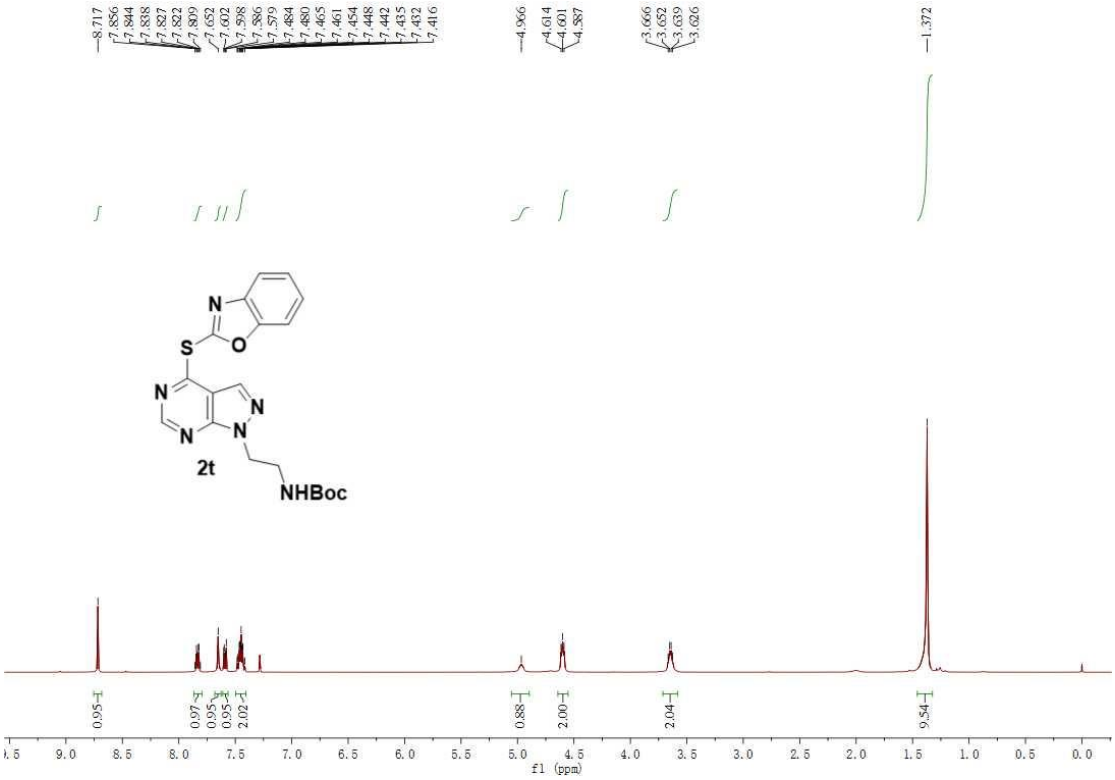
48.538
44.578
28.789
2s
f1 (ppm)


8.717
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7.652
7.602
7.598
7.586
7.579
7.484
7.480
7.465
7.461
7.454
7.448
7.442
7.435
7.432
7.416
4.966
4.614
4.601
4.587
3.666
3.652
3.639
3.626
1.372
2t
NHBoc
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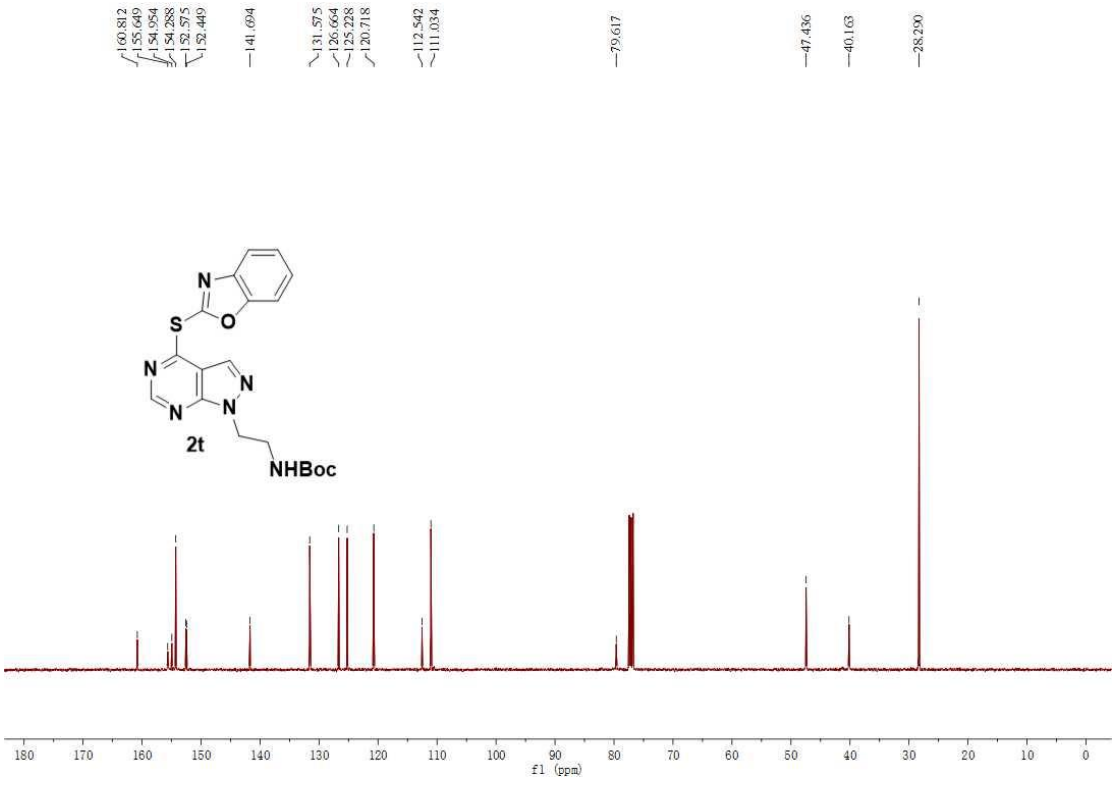
0.97
0.95
0.93
2.02
0.88
2.00
2.04
9.54
f1 (ppm)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154.268
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152.449
141.694
131.575
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120.718
112.542
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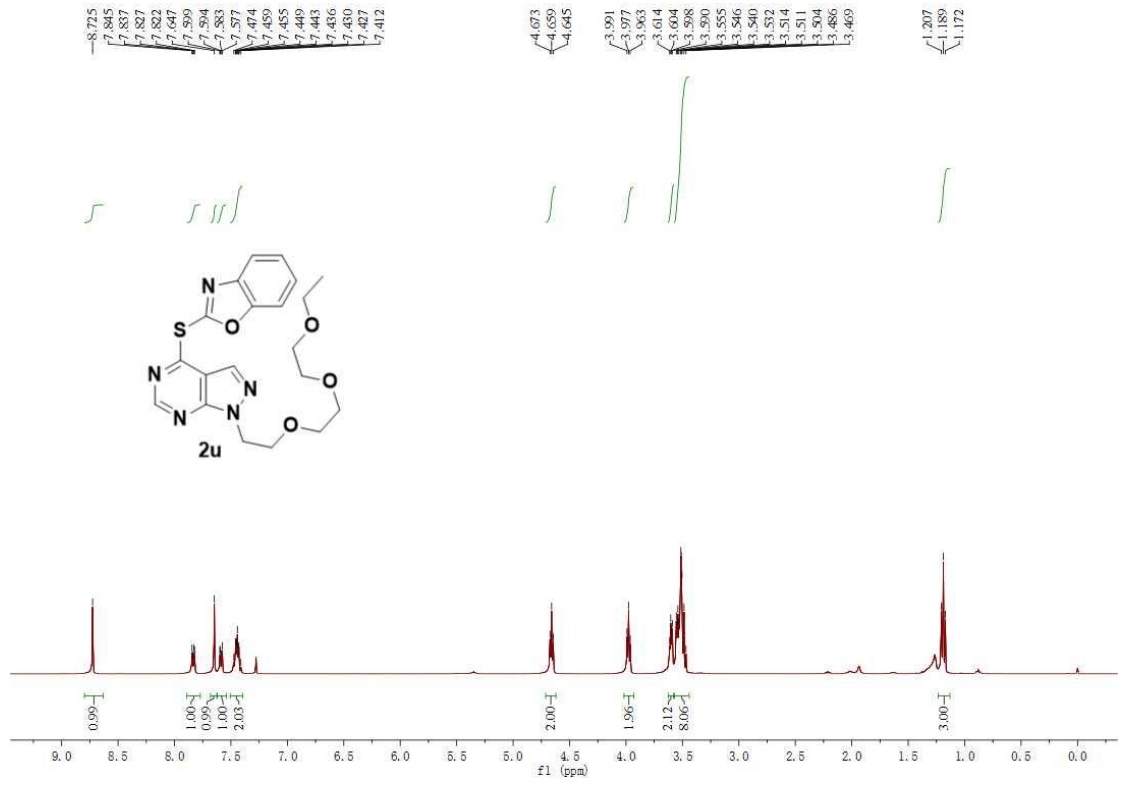
79.617
47.436
40.163
28.290
2t
NHBoc
f1 (ppm)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7.827
7.822
7.647
7.599
7.594
7.583
7.577
7.474
7.459
7.455
7.449
7.443
7.436
7.430
7.427
7.412
4.673
4.659
4.645
3.991
3.977
3.963
3.614
3.604
3.598
3.590
3.555
3.546
3.540
3.532
3.514
3.511
3.504
3.486
3.469
1.207
1.189
1.172
2u
0.99
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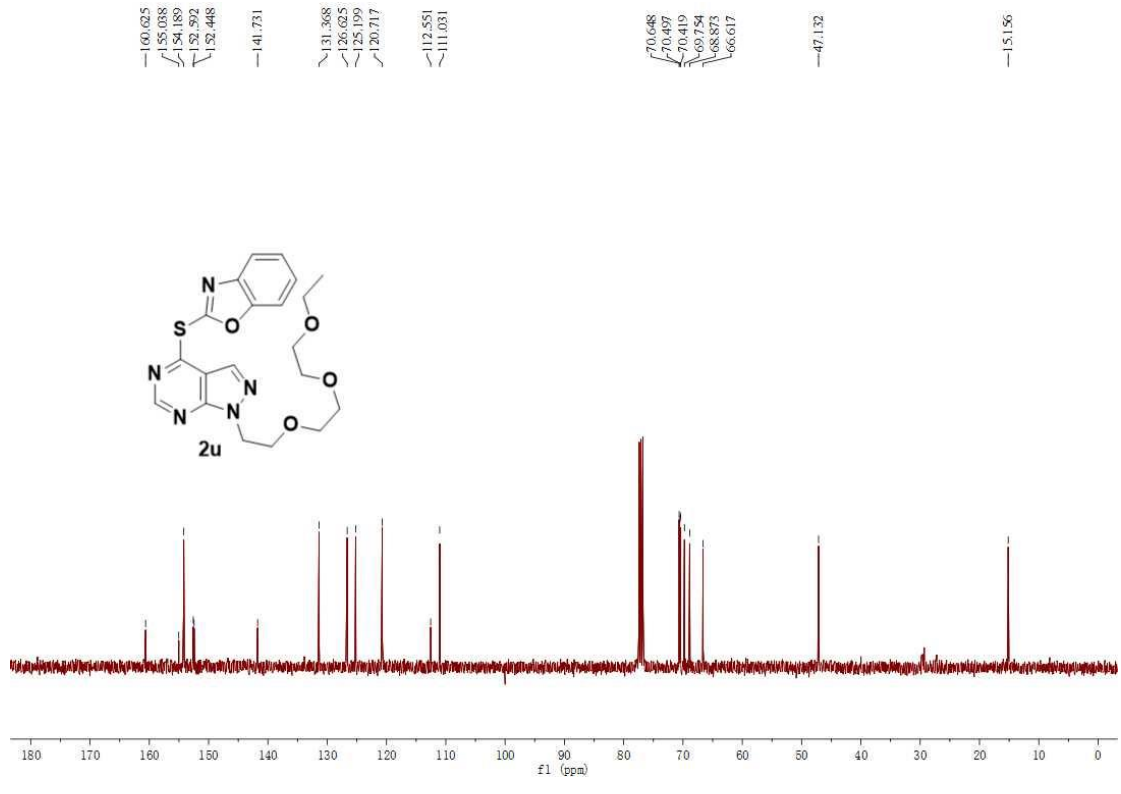
0.99
1.00
2.03
2.00
1.96
2.12
8.06
3.00
f1 (ppm)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125.199
120.717
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70.497
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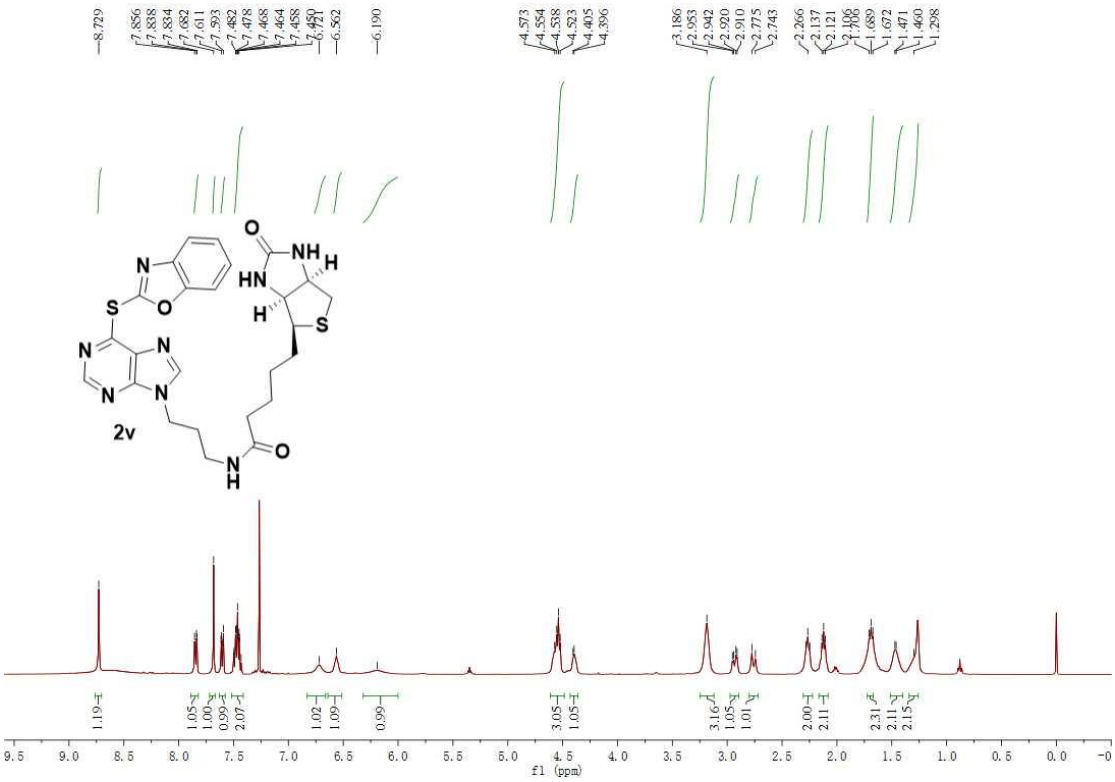
69.754
68.873
66.617
47.132
15.156
2u
f1 (ppm)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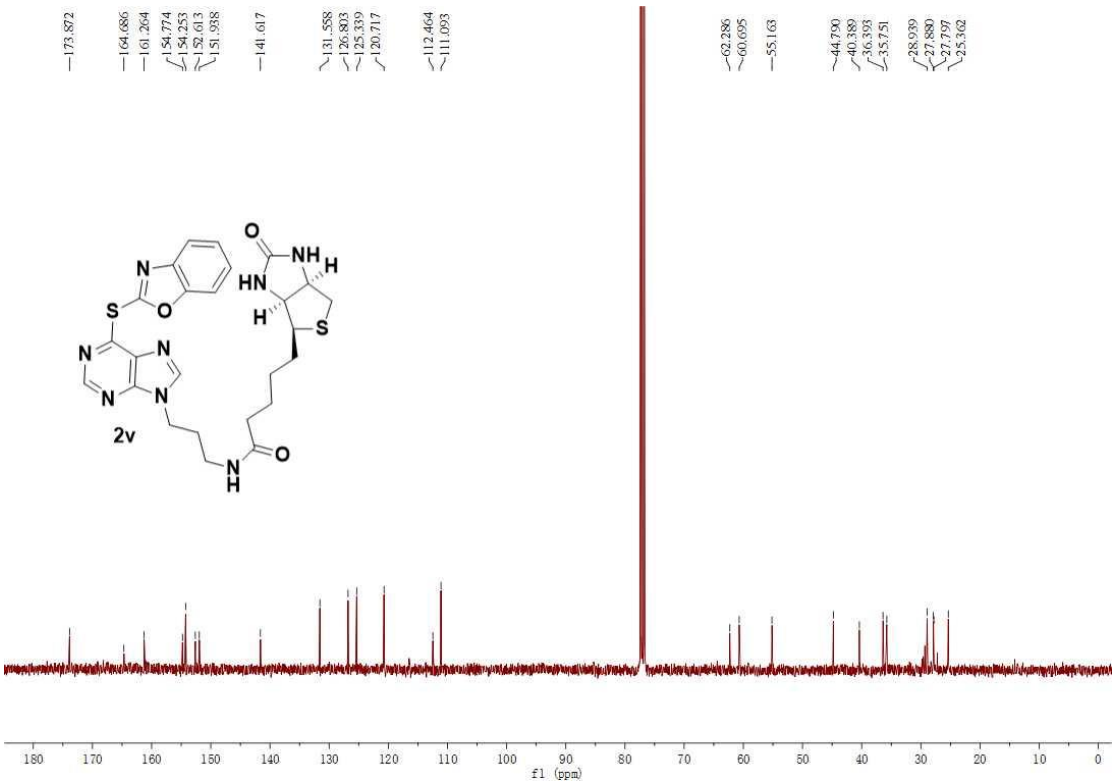
7.611
7.593
7.482
7.478
7.468
7.464
7.458
6.562
6.190
4.573
4.554
4.538
4.523
4.405
4.396
3.186
2.953
2.942
2.920
2.910
2.775
2.743
2.266
2.137
2.121
2.106
2.089
1.672
1.471
1.460
1.298
2v
f1 (ppm)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164.686
161.264
154.774
154.253
152.613
151.938
141.617
131.558
126.803
125.339
120.717
112.464
111.093
62.286
60.695
55.163
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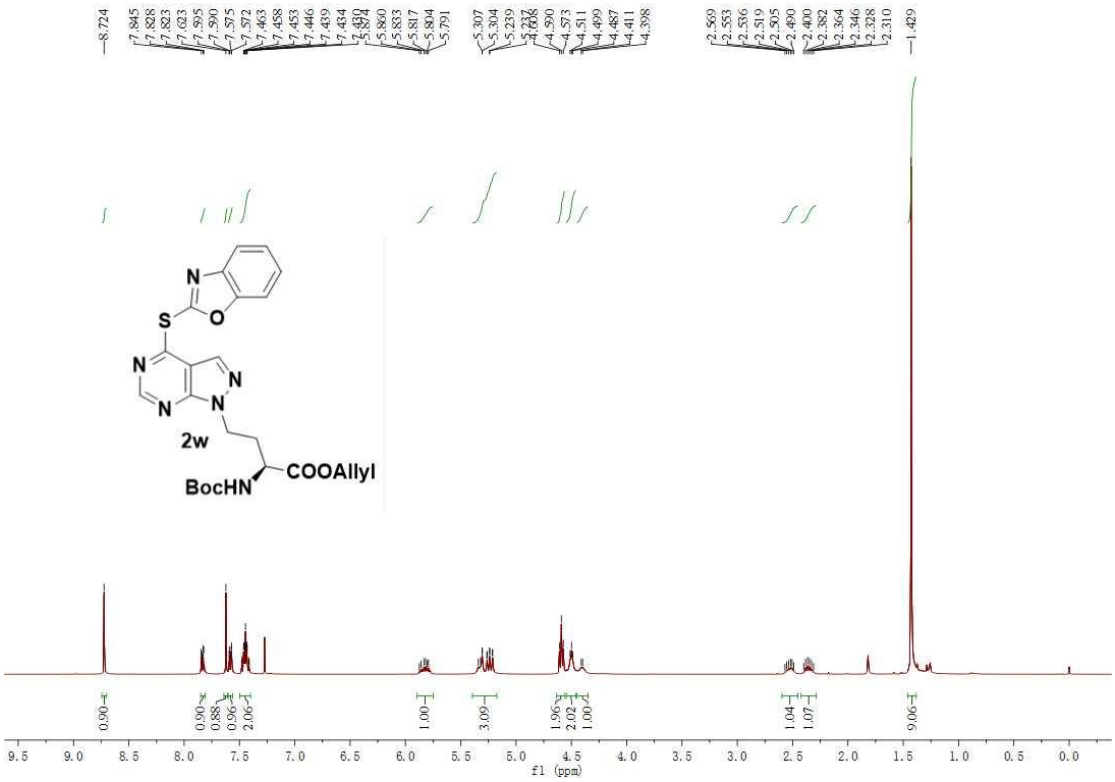
40.389
36.393
35.751
28.939
27.880
27.797
25.362
2v
f1 (ppm)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7.590
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7.572
7.463
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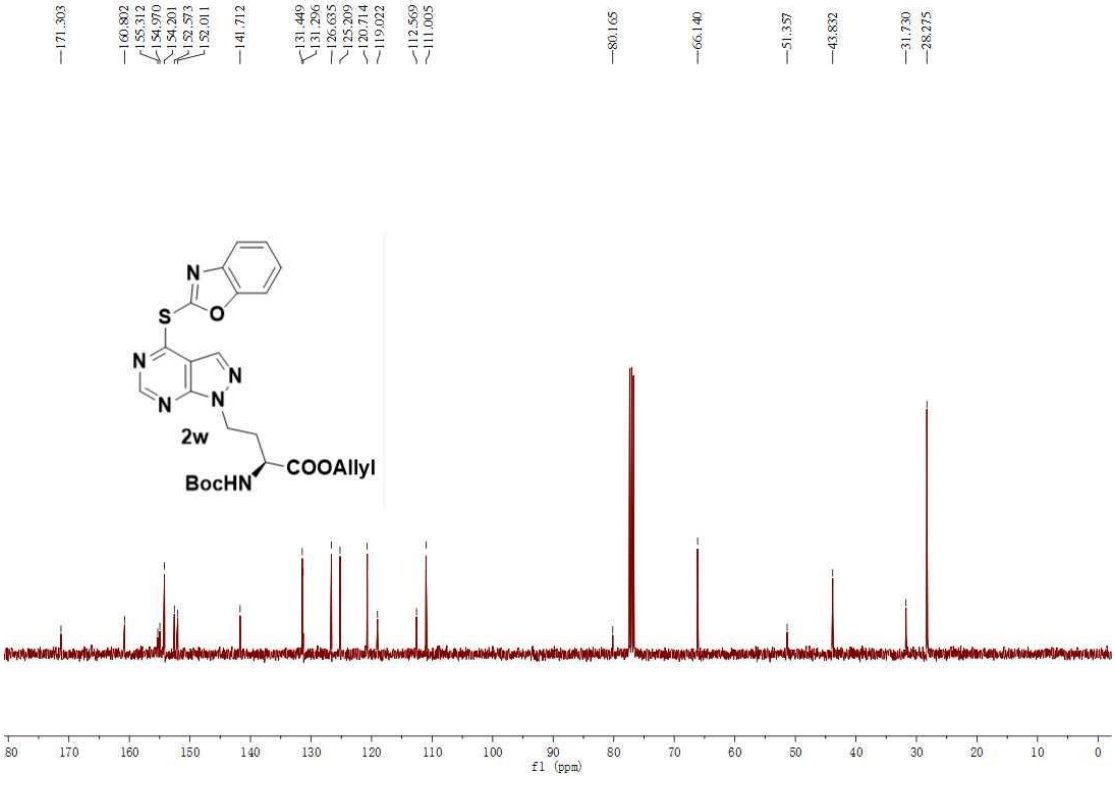
7.453
7.446
7.439
7.434
5.860
5.833
5.817
5.804
5.791
5.307
5.304
5.239
4.590
4.573
4.511
4.499
4.487
4.411
4.398
2.569
2.553
2.536
2.519
2.505
2.490
2.400
2.382
2.364
2.346
2.328
2.310
1.429
0.90
0.90
0.88
0.96
2.06
1.00
3.09
1.96
2.02
1.00
1.04
1.07
9.06
f1 (ppm)
2w
BocHN
COOAllyl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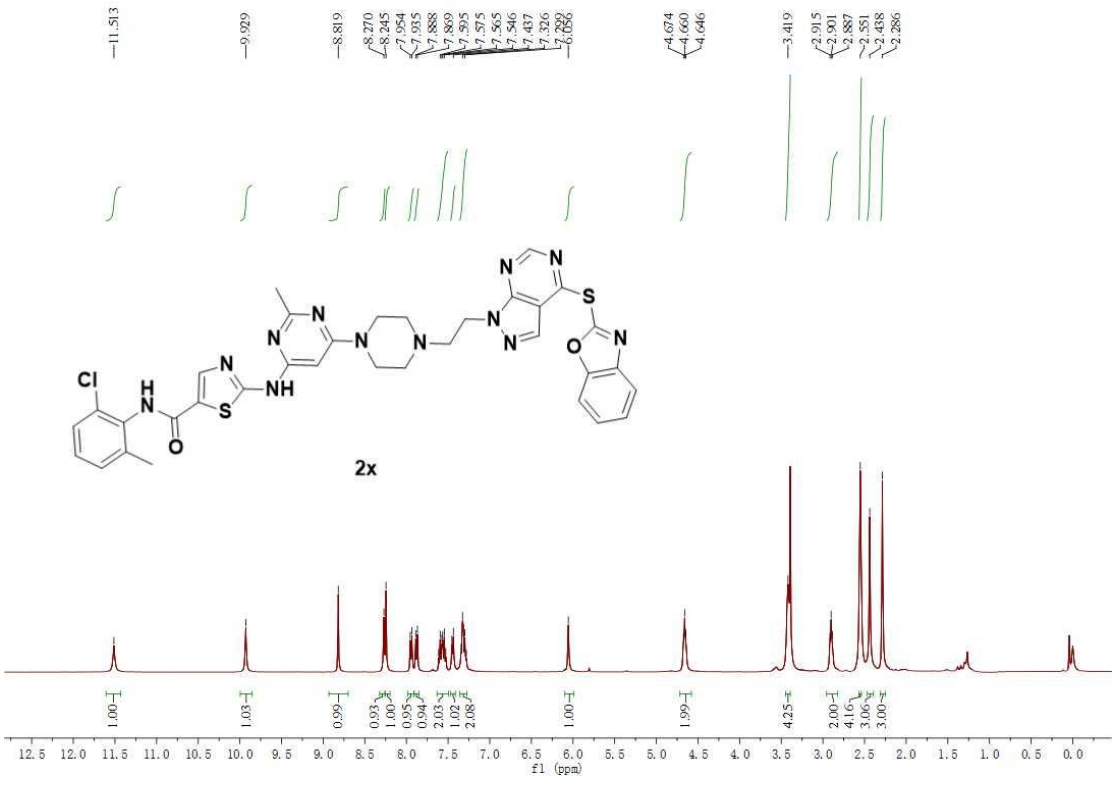
152.573
152.011
141.712
131.449
131.296
126.635
125.209
120.714
119.022
112.569
111.005
80.165
66.140
51.357
43.832
31.730
28.275
f1 (ppm)
2w
BocHN
COOAllyl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8.270
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7.935
7.888
7.869
7.595
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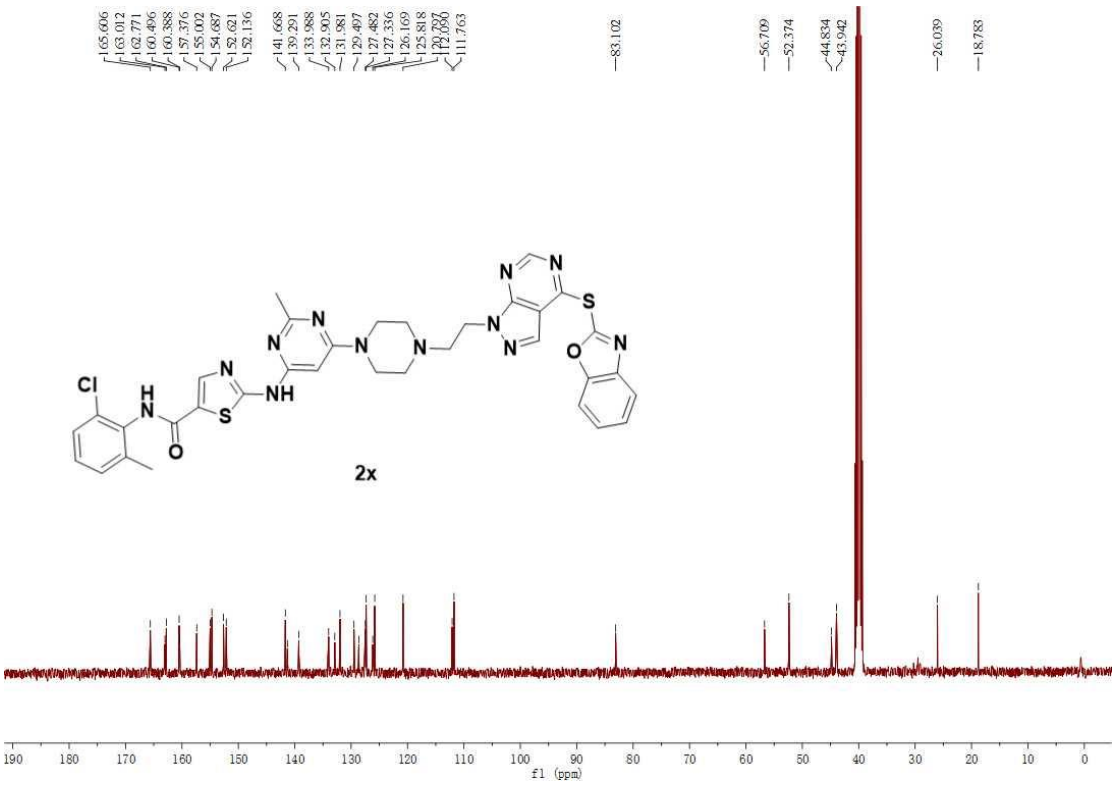
7.565
7.546
7.437
7.326
7.299
6.056
4.674
4.660
4.646
3.419
2.915
2.901
2.887
2.551
2.438
2.286
2x
1.00
1.03
0.99
0.93
1.00
0.95
0.94
2.03
1.02
2.08
1.00
1.99
4.25
2.00
4.16
3.06
3.00
f1 (ppm)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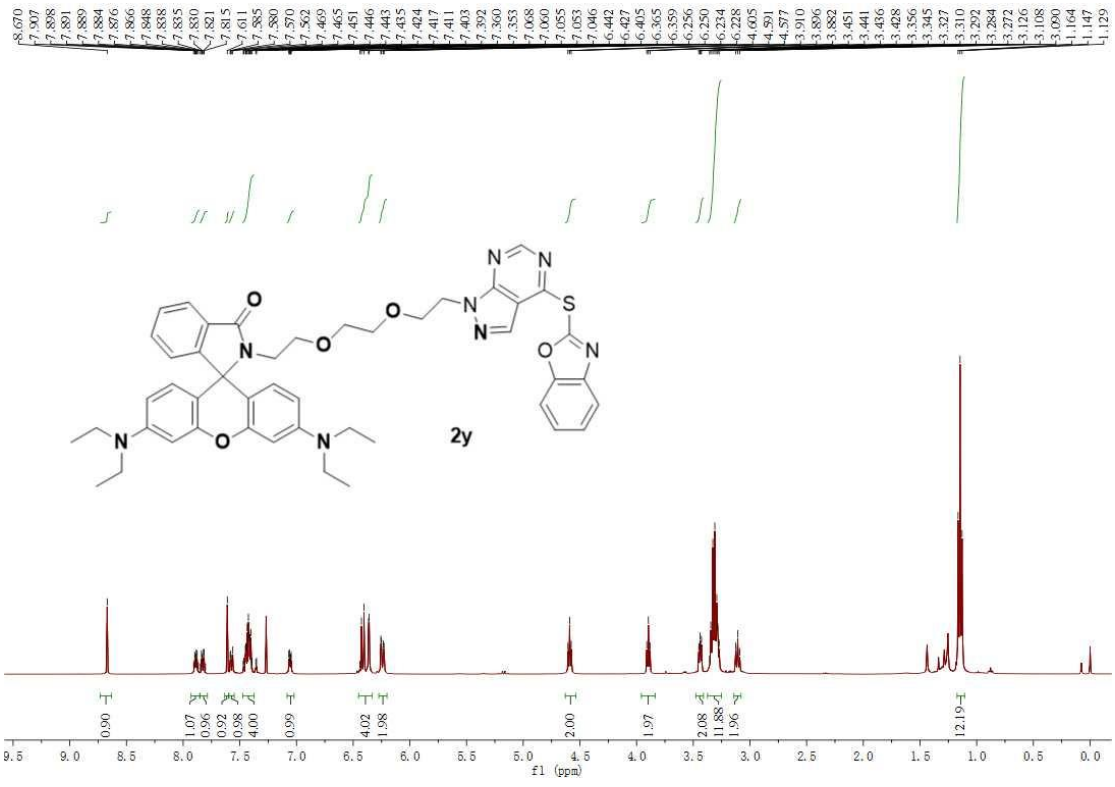
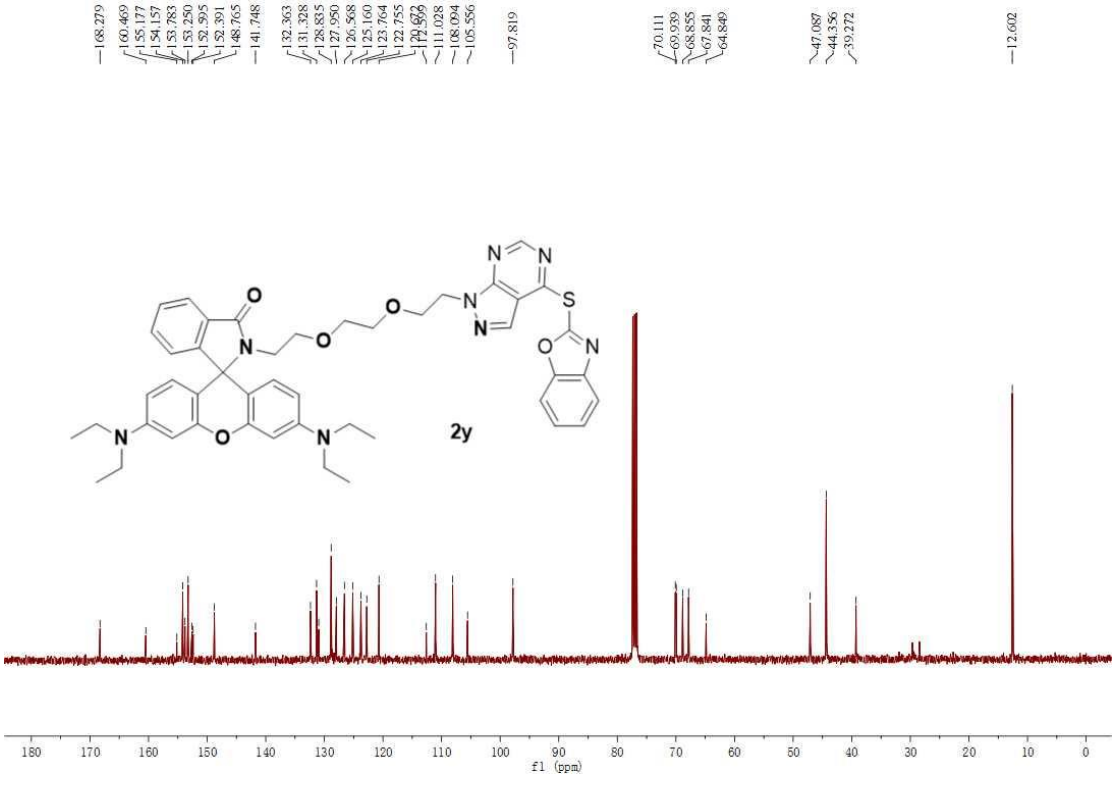
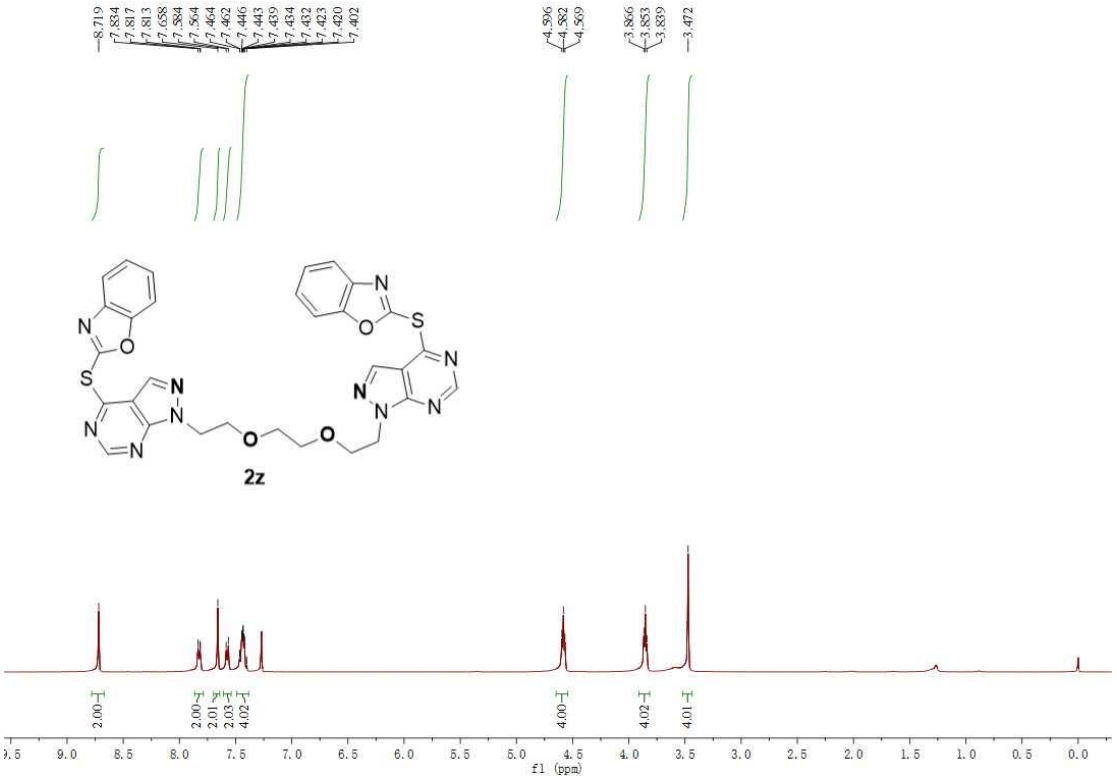
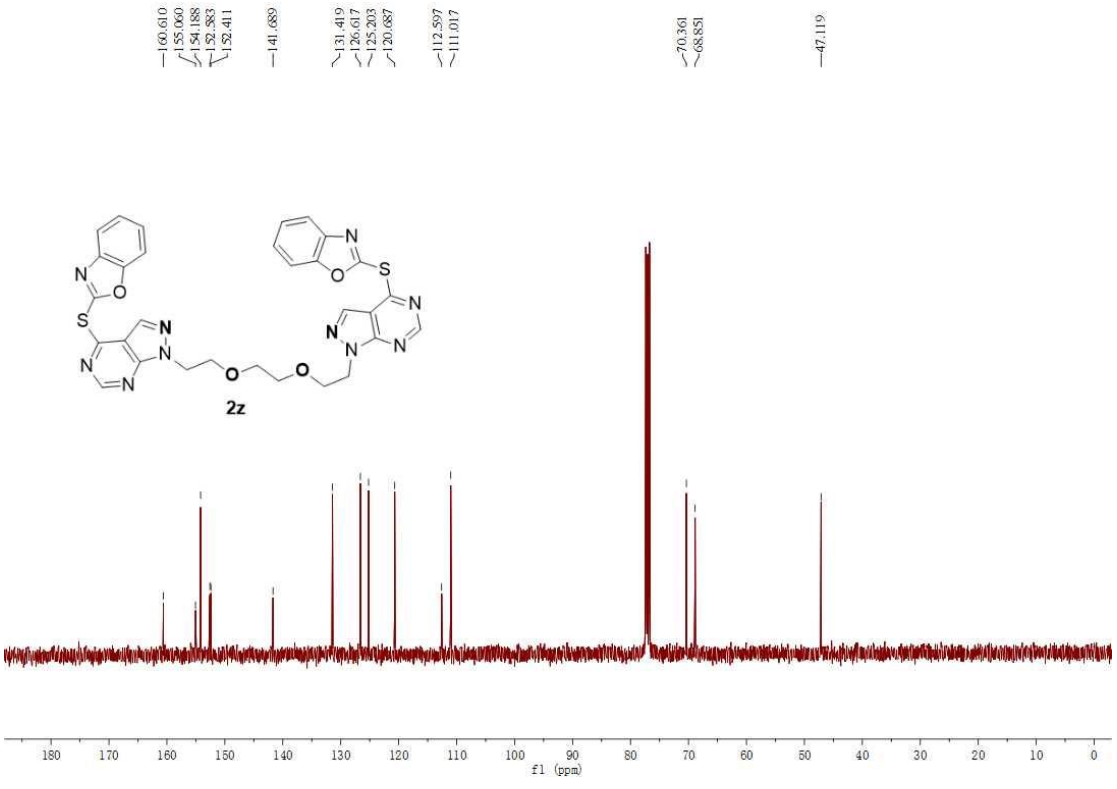
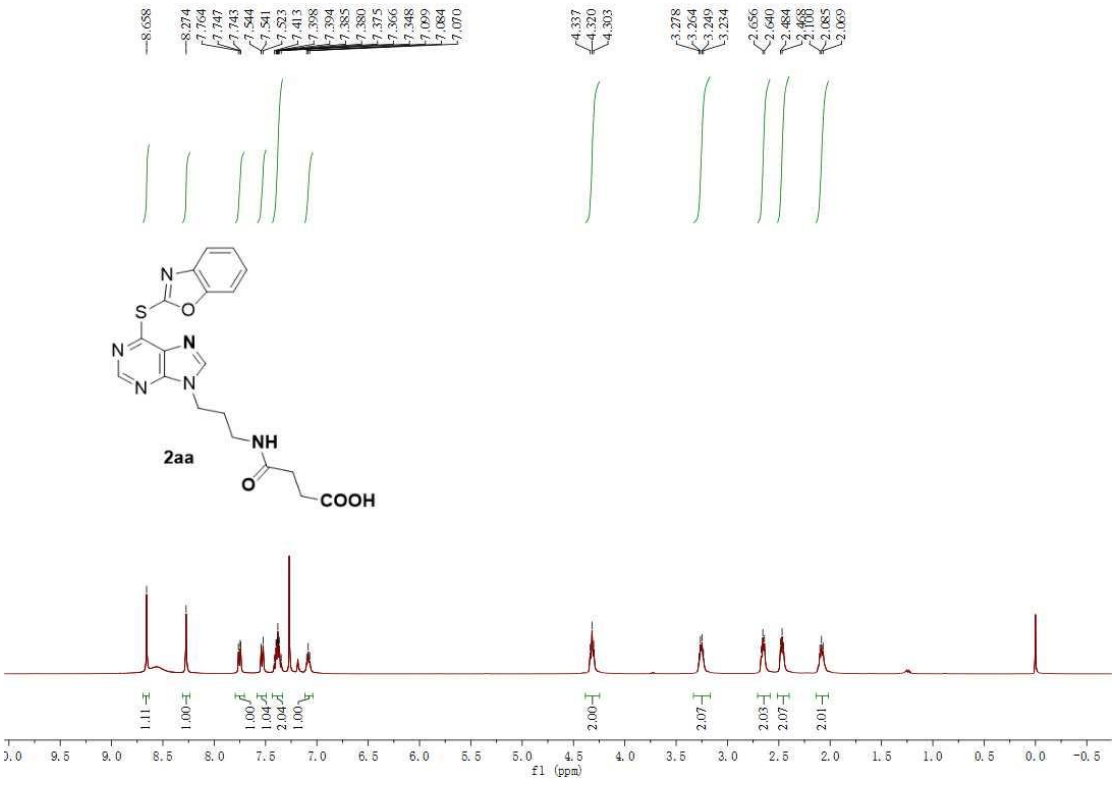
141.668
139.291
133.988
132.905
131.981
129.497
127.482
127.336
126.169
125.818
120.707
112.050
111.763
83.102
56.709
52.374
44.834
43.942
26.039
18.783
2x
f1 (ppm)

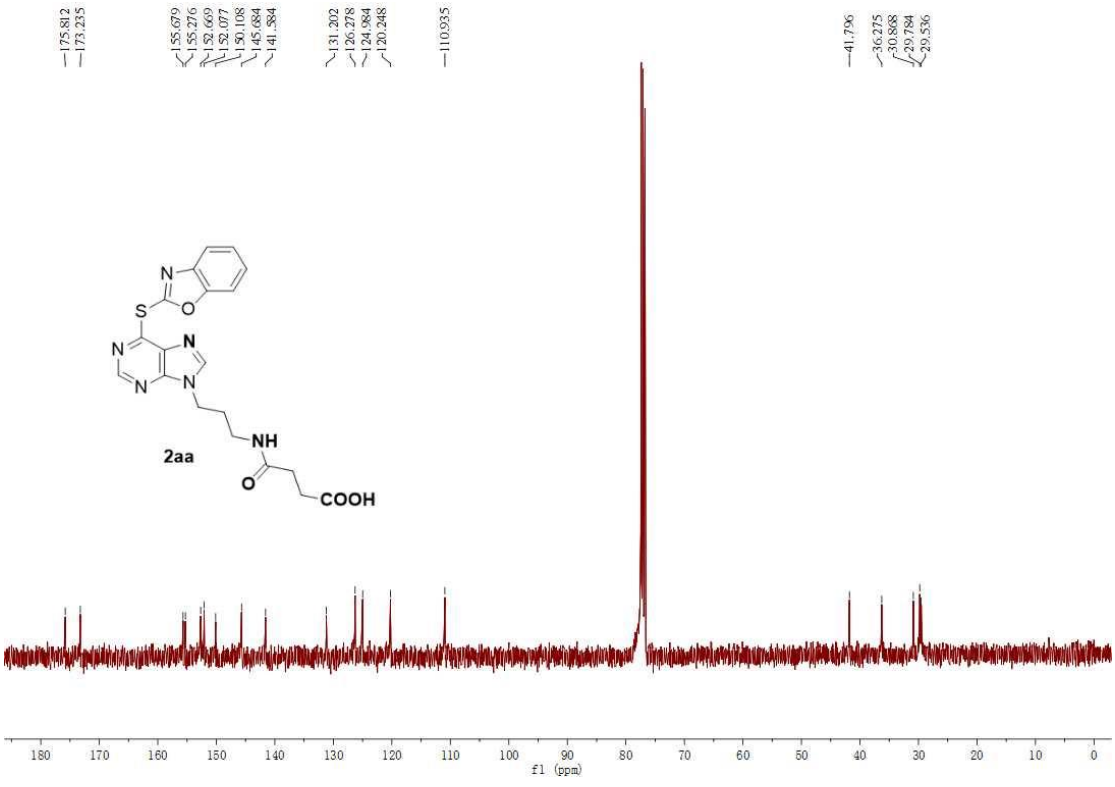

2y
f1 (ppm)

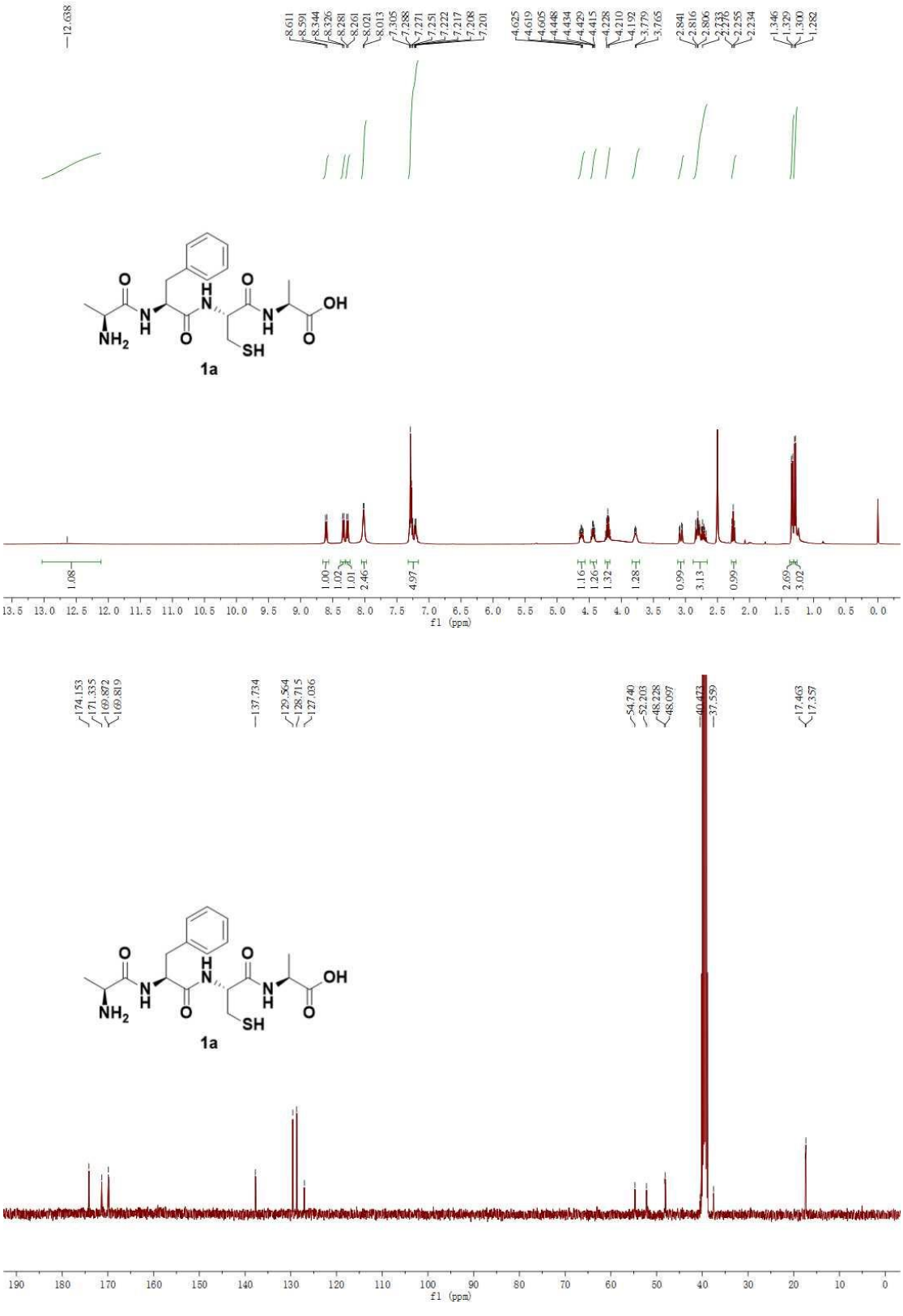

2y
f1 (ppm)

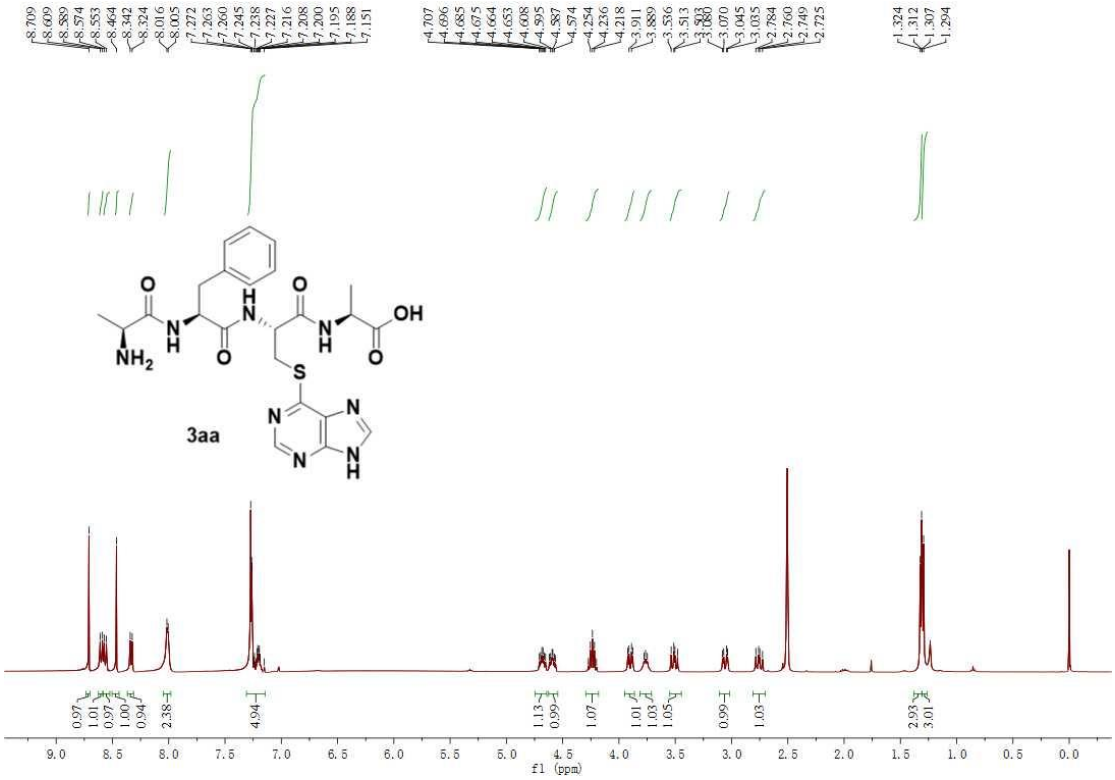

8.719
7.834
7.817
7.813
7.658
7.584
7.564
7.464
7.462
7.446
7.443
7.439
7.434
7.432
7.423
7.420
7.402
4.396
4.382
4.369
3.866
3.853
3.839
3.472
2z
2.00
2.00
2.01
2.03
4.02
4.00
4.02
4.01
f1 (ppm)

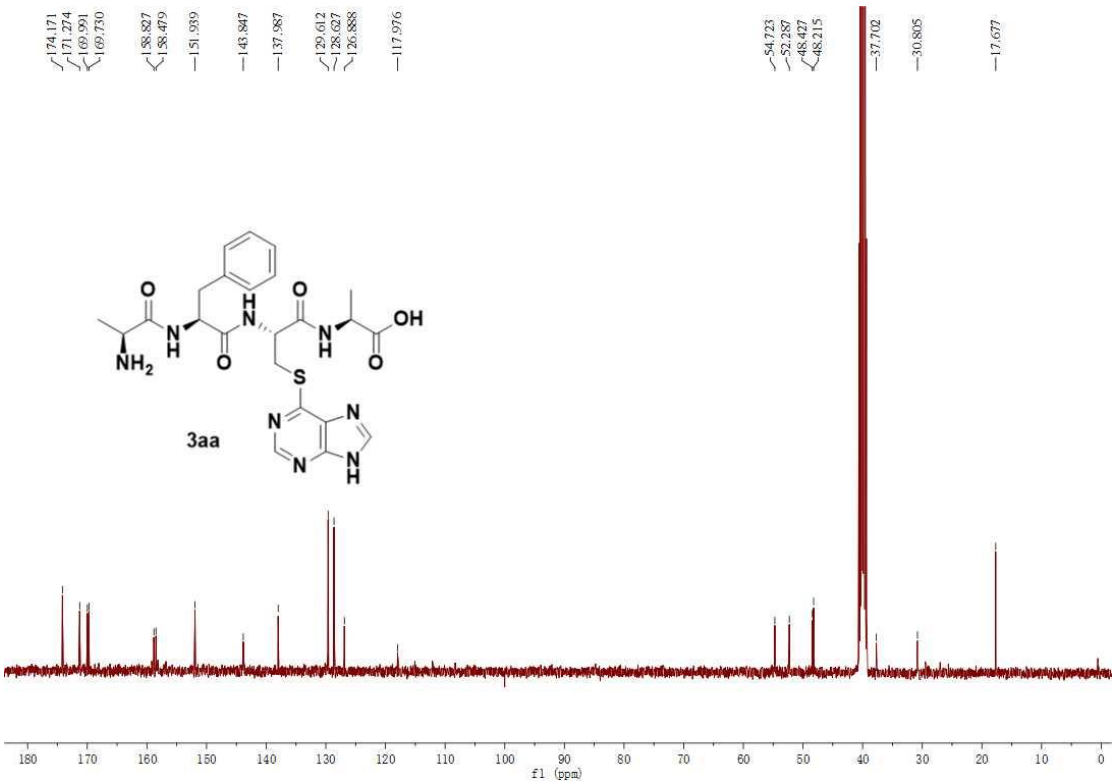

160.610
155.060
154.188
152.583
152.411
141.689
131.419
126.617
125.203
120.687
112.597
111.017
70.361
68.851
47.119
2z
f1 (ppm)


8.658
8.274
7.764
7.747
7.743
7.544
7.541
7.523
7.413
7.398
7.394
7.385
7.380
7.375
7.366
7.348
7.099
7.084
7.070
4.337
4.320
4.303
3.278
3.264
3.249
3.234
2.656
2.640
2.484
2.468
2.085
2.069
2aa
NH
O
COOH
1.11
1.00
1.00
1.04
2.04
1.00
2.00
2.07
2.03
2.07
2.01
f1 (ppm)


175.812
173.235
155.679
155.276
152.669
152.077
150.108
145.684
141.584
131.202
126.278
124.984
120.248
110.935
41.796
36.275
30.868
29.784
29.536
2aa
NH
O
COOH
f1 (ppm)


12.638
8.611
8.591
8.344
8.326
8.281
8.261
8.021
8.013
7.305
7.288
7.271
7.251
7.222
7.217
7.208
7.201
4.625
4.619
4.605
4.448
4.434
4.429
4.415
4.228
4.210
4.192
3.779
3.765
2.841
2.816
2.806
2.255
2.234
1.346
1.329
1.300
1.282
1a
1.08
1.00
1.02
1.01
2.46
4.97
1.16
1.26
1.32
1.28
0.99
3.13
0.99
2.69
3.02
f1 (ppm)
174.153
171.335
169.872
169.819
137.734
129.564
128.715
127.036
54.740
52.203
48.228
48.097
40.473
37.589
17.463
17.357
1a
f1 (ppm)


8.709
8.609
8.589
8.574
8.553
8.464
8.342
8.324
8.016
8.005
7.272
7.263
7.260
7.245
7.238
7.227
7.216
7.208
7.200
7.195
7.188
7.151
4.707
4.696
4.685
4.675
4.664
4.653
4.608
4.595
4.587
4.574
4.254
4.236
4.218
3.911
3.889
3.536
3.513
3.303
3.080
3.070
3.045
3.035
2.784
2.760
2.749
2.725
1.324
1.312
1.307
1.294
3aa
0.97
1.01
0.97
1.00
0.94
2.38
4.94
1.13
0.99
1.07
1.01
1.03
1.05
0.99
1.03
2.93
3.01
f1 (ppm)


174.171
171.274
169.991
169.730
158.827
158.479
151.939
143.847
137.987
129.612
128.627
126.888
117.976
54.723
52.287
48.427
48.215
37.702
30.805
17.677
3aa
f1 (ppm)

15. Reference

[1] A. K. Pathak, V. Pathak, L. E. Seitz, W. J. Suling, R. C. Reynolds, *J. Med. Chem.*, 2004, **47**, 273-276.
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