Supporting Information

Activity-based Protein Profiling Reveals Secondary-carbon-Centered Radicals of Synthetic 1,2,4-Trioxolanes are Predominately Responsible for Modification of Protein Targets in Malaria Parasites

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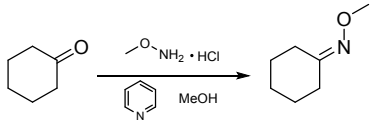
Synthesis of compound 3 and probes ZJH-1, ZJH-2

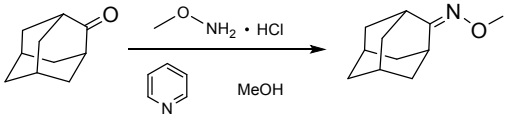
Synthesis of compound 2 (cyclohexanone O-methyl oxime)



1

To a solution of cyclohexanone (2.0 g, 20.4 mmol) in methanol (20 mL), anhydrous pyridine (2.5 mL, 30.6 mmol) and methoxyammonium chloride (2.3 g, 30.6 mmol) were added. The reaction mixture was allowed to stir under nitrogen for 12 h, and monitored by TLC. After completion, the mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with 1M HCl (2 x 50 mL) and saturated NaCl (30 mL) and dried with Na_2SO_4. Solvent was removed by concentration under reduced pressure. The crude product was purified by column chromatography to yield compound 1 (2.1 g, (81 %)) as colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.82 (s, 3H), 2.45 (t, 2H), 2.21 (m, 2H), 1.68 (t, 2H) , 1.60 (s, 4H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 160.54, 61.29, 32.53, 27.37, 26.18, 26.10, 25.49. MS (ESI) calcd. for $[M+H]^+$: 128.1075, found: 128.1069.

Synthesis of compound 1 (adamantan-2-one O-methyl oxime)

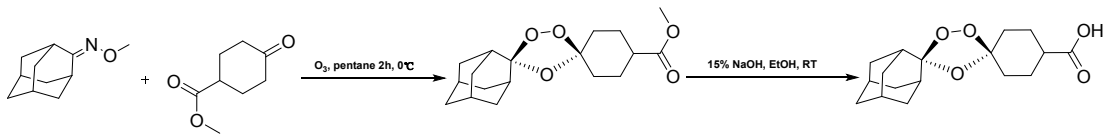


2

To a solution of 2-adamantanone (3.0 g, 20 mmol) in methanol (20 mL), anhydrous pyridine (2.4 mL, 30 mmol) and methoxyammonium chloride (2.5 g, 30 mmol) were added. The reaction mixture was allowed to stir under nitrogen for 8 h,

diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with 1M HCl (50 mL) and saturated NaCl (30 mL) and dried with Na_2SO_4. Solvent was removed by concentration under reduced pressure. The crude product was purified by column chromatography to yield compound **2** (2.1 g, 59 %) as colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.80 (s, 3H), 3.45 (s, 1H), 2.53 (s, 1H), 1.99-1.93 (m, 4H), 1.93-1.71 (m, 8H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 166.60, 60.83, 38.89, 37.50, 36.38, 36.10, 29.39, 27.72. MS (ESI) calcd. for $[M+H]^+$: 180.1388, found: 180.1379.

Synthesis of compound 3 (methyl dispiro [adamantane- 2,3'-[1,2,4] trioxolane- 5',1''-cyclohexane]-4''- carboxylate) and 3-1(dispiro[adamantane- 2,3'-[1,2,4]trioxolane-5',1''-cyclohexane]-4''- carboxylic acid)

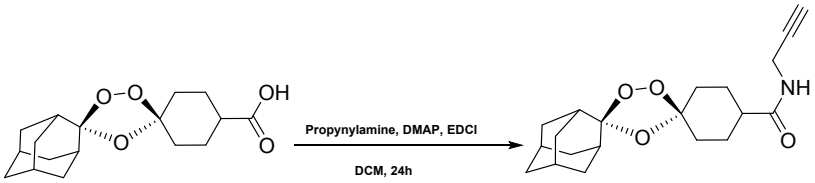


2 3 3-1

Ozone (3-4 %) was produced with an ozone generator, first passed through dried CH_2Cl_2 (80 mL, -78°C), then bubbled through a solution of Compound **2** (1.0 g, 5.59 mmol) and methyl 4-oxocyclohexane-1-carboxylate (0.58 g, 3.73 mmol) in pentane (120 mL). The reaction was left for 0.5 h. After completion, the solution was flushed with nitrogen for 15 min then concentrated in vacuo. The residue was purified by column chromatography to give compound **3** (0.46 g, 30 %) as colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 3.66 (d, J = 8.1 Hz, 3H), 2.39-2.27 (m, 1H), 2.10-1.91 (m, 12H), 1.74-1.61 (m, 10H). ^{13}C NMR (125 MHz, Chloroform-d) δ 175.49, 111.67, 108.07, 51.86, 47.17, 41.47, 39.45, 36.97, 36.57, 35.01, 34.96, 33.53, 33.31, 27.07, 26.66, 26.40.

To a solution of **3** (0.1 g, 1.8 mmol) in 95 % ethanol (5 mL), 15 % aq. NaOH (2 mL) was added. The mixture was allowed to stir for 3 h and acidified with 3 M HCl (2 mL). Water (10 mL) and EtOAc (10 mL) were added to the solution and the aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and concentrated to give compound **3-1** (73 mg, 76%) as white powder. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.27 (s, 1H), 2.18-1.58 (m, 23H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 111.68, 108.55, 37.33, 36.87, 35.29, 34.05, 27.42, 27.03; MS (ESI) calcd. for $[M-H]^-$: 307.1545,found: 307.1587.

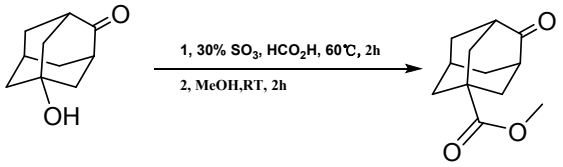
Synthesis of probe ZJH-1 (N-(prop-2-yn-1-yl) dispiro[adamantine-2,3'-[1,2,4]trioxolane -5',1''- cyclohexane]-4''- carboxamide)



3-1 ZJH-1

To a stirring solution of carboxylic acid **3-1**(50 mg, 0.15 mmol) in CH_2Cl_2 (10 mL), EDC·HCl (50 mg, 0.24 mmol) and DMAP (19 mg, 0.17 mmol) were added. After activating for 1 h, amine alkyne (11 mg, 0.2 mmol) in CH_2Cl_2 was added to the solution. After 24 h, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give desired product **ZJH-1** (42 mg, 73 %) as white powder. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.63 (s, 1H), 4.12 -3.96 (m, 2H), 2.23 (s, 1H), 2.14 (d, J=4.1 Hz, 1H), 2.08-1.88 (m, 11H), 1.70 (q, J = 14.5, 13.5 Hz, 10H).^{13}C NMR (125 MHz, Chloroform-*d*) δ 174.63, 112.04, 108.23, 80.00, 72.22, 43.86, 37.26, 36.86, 35.29, 35.25, 34.06, 30.18, 29.70, 27.35, 26.94. MS (ESI) calcd. for $[M+Na]^+$: 368.1838, found: 368.1826.

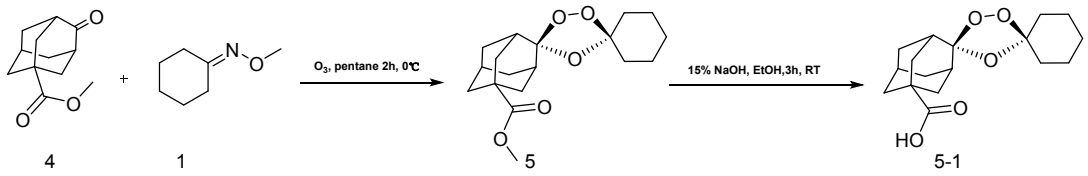
Synthesis of compound 4 (methyl -4-oxoadamantane-1-carboxylate)



4

To a solution of oleum (30 % SO_3, 48 mL, 100 mmol) at 60 ºC, 5-hydoxy-2-adamantanone (2.0 g, 12 mmol) in formic acid (99 %, 12 mL, 0.32 mmol) was added dropwise and stirred vigorously for 0.5 h. Then the solution was allowed to stir for a further 1 h. The residue was then cautiously poured into vigorously stirred methanol (100 mL) at 0 °C. After 2 h at room temperature, the residue was concentrated and poured over ice. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL) and the combined organic fractions were washed with brine (2 x 50 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography to yield compound **4** (1.3 g, (52 %)) as a white crystalline solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.66 (s, 3H), 2.56 (s, 2H), 2.20-1.94 (m, 12H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 216.75, 176.45, 52.29, 46.11, 40.66, 40.46, 38.64, 38.16, 27.60.MS (ESI) calcd. for $[M+H]^+$: 209.1, found: 209.1.

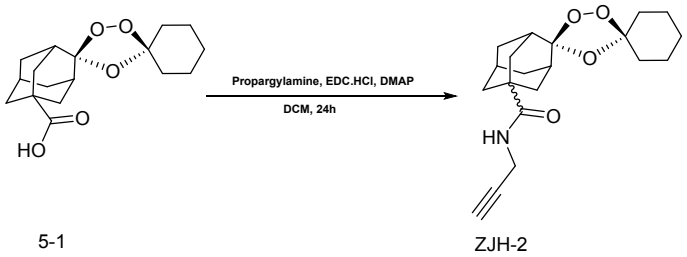
Synthesis of compound 5(methyl –dispiro[adamantine-2,3'- [1,2,4]trioxolane-5',1''-cyclohexane]-5- carboxylate) and compound 5-1 (dispiro[adamantine-2,3'- [1,2,4]trioxolane-5',1''- cyclohexane]-5-carboxylic acid)



Ozone (3-4 %) was produced with an ozone generator, first passed through dried CH_2Cl_2 (80 mL, -78°C), then bubbled through a solution of compounds 1 (0.50 g, 2.4 mmol) and 4 (0.46 g, 3.6 mmol) in pentane (100 mL). The reaction was left for 0.5 h. After completion, the solution was flushed with nitrogen for 15 min and then concentrated in vacuo. The residue was purified by column chromatography to give compound**5** (0.22 g, 23 %) as colorless oil. MS (ESI) calcd. for $[M+Na]^+$: 345.1678, found: 345.2839.

To a solution of **5** (0.15 g, 0.47 mmol) in 95 % ethanol (8 mL), 15 % aq. NaOH (5 mL) was added. The mixture was allowed to stir for 5 h and acidified with 3 M HCl (5 mL). Water (10 mL) and EtOAc (20 mL) were added to the solution and the aqueous layer was washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (30 mL), saturated brine (20 mL), dried with Na_2SO_4, filtered and concentrated to give compound **5-1** (110 mg, 76 %) as fine white powder. MS (ESI) calcd. for $[M-H]^-$: 307.1545,found: 307.1588 $[M-H]^-$.

Synthesis of probe ZJH-2 (N-(prop-2-yn-1-yl)dispiro [adamantine-2,3'- [1,2,4]trioxolane-5',1''- cyclohexane]-5- carboxamide)



To a stirring solution of carboxylic acid **5-1** (50 mg, 0.16 mmol) in CH_2Cl_2 (10 mL), EDC·HCl (50 mg, 0.24 mmol), and DMAP (19 mg, 0.17 mmol) were added. After activating for 1 h, amine alkyne (11 mg, 0.2 mmol) in CH_2Cl_2 was added to the solution. After 24 h the solvent was removed under reduced pressure, the crude product was purified by column chromatography to yield compound **ZJH-2** (44 mg,77%) as white powder. ^{1}H NMR (500 MHz, Chloroform-d) δ 5.68 (s, 1H), 4.12-3.94 (m, 2H), 2.23-1.57 (m, 23H).^{13}C NMR (125 MHz, Chloroform-d) δ 176.79,

109.92, 72.20, 38.75, 37.09, 36.99, 36.66, 36.49, 35.17, 34.17, 34.09, 29.79, 27.16, 26.78, 25.40, 24.31. HRMS (ESI) calcd. for $[M+H]^+$: 346.2018, found: 346.2020.

Parasite culture and synchronization

P. falciparum strain 3D7 was cultured at 37 °C in 5 % O_2 and 5 % CO_2 in N_2, essentially as previously described by Trager and Jensen[1] with modifications. Briefly, parasites were incubated in petri dishes at 37 °C using 5 % haematocrit of human red blood cells with RPMI Medium1640, supplemented with 25 mM HEPES, 10mg/L Glucose, 0.5 % Albumax II, 0.3 g/L L-Glutamine, 0.015 % Hypoxanthine, 0.125 g/L gentamicin, and 25mM sodium bicarbonate. Synchronization of parasite cultures with 5 % (w/v) D-sorbitol was performed as previously described[2]. To obtain highly synchronized ring-stage parasite cultures, two rounds of 5 % (w/v) D-sorbitol treatment were performed. Parasitaemia and parasite stages were determined by Giemsa-stained thin blood smears.

***In vitro* Drug Sensitivity Assay**

The parasite sensitivity to compound 3, ZJH-1 and ZJH-2 was measured by a fluorescent SYBR Green Ibased 96 microplate assay as described previously with modifications[3, 4]. In brief, highly synchronized ring-stage parasite cultures were diluted with fresh erythrocytes and complete medium to 0.5 % parasitaemia and 2% haematocrit. The cultures were incubated with compound 3, ZJH-1 and ZJH-2at different concentrations according to a 2-fold serially dilution for 72h. Then the cultures were stained with SYBR Green I (Invitrogen) in lysis buffer for 45min at 37 ^oC in the dark. The fluorescence was measured using Synergy H1 Hybrid Multi-Mode Microplate Reader (BioTek) with excitation and emission wavelength bands centered at 485 and 528 nm, respectively. At least three biological replicates, each in triplicate technical replicates, were carried out. The half-maximal inhibitory concentration (IC_{50}) of compound 3, ZJH-1 and ZJH-2 against *P. falciparum* 3D7 were calculated and plotting of the sigmoidal dose–response curve was performed using the software GraphPad Prism 5.

In situ* labelling of *P. falciparum

The mixed stage *P. falciparum* parasites were prepared in a 6-well plate with 2.5 % haematocrit and 5 % parasitemia in the gassed incubator. 30 μL of diluted probes ZJH-1 and ZJH-2 were dispensed into each well to obtain increasing concentrations (2 μM, 5 μM, 10 μM, 20 μM) and incubated with the cultures for 4 h at 37 ^oC. An equal volume of 0.1 % DMSO was used as negative control. After incubation, the cultures were harvested and were incubated with 0.1 % saponin for 5 min on ice to lysis the

red blood cell. Then the released parasites were pelleted down by centrifugation at 6000 rpm for 4 min and washed three times with ice-cold PI-PBS (protease inhibitors in phosphate buffered saline). Total parasite proteins from each sample were extracted by sonication on ice at 31 % amplification for 2 min (2 s on, 2 s off)[5]and 176 µL clear protein extracts were obtained by centrifugation at 12000 rpm for 5 min.

Fractions were supplemented with 0.20 mM rhodamine-azide (10 mM stock in DMSO; *Clickchemistrytools*; Rh-N_3), 1.0 mM TCEP (52 mM stock in ddH_2O; *Sigma-Aldrich*) and 0.10 mM TBTA ligand (1.667 mM stockin DMSO; *Sigma-Aldrich*). Samples were gently pipetted and the cycloaddition was initiated by the addition of 1.0 mM $CuSO_4$ (50 mM stock in ddH_2O). After incubation at 37 °C for 1 h, 25 µL 5× SDS loading buffer were added and the samples heated for 10 min at 100 °C.

For gel electrophoresis, 20 µL were applied per gel-lane on a SDS-PAGE gel (10% acrylamide). Fluorescence was recorded using a *GE* Typhoon FLA9500 luminescent image analyser with $\lambda_{ex/em}$= *532nm/596nm* at 560V.

Preparative *in situ* label-free ABPP and Quantification

Twelve milliliters of mixed stage *P. falciparum* parasites were cultured in 100 mm×20 mm petri dishes (Corning) with 2.5%haematocritand 5% parasitemia in the gassed incubator. Probes ZJH-1 and ZJH-2 were dispensed to the cultures and incubated with the parasites for 4 h at 37 ^oC. The final incubation concentration of ZJH-1 and ZJH-2 are 20 µM and 2 µM, respectively. An equal volume of 0.1 % DMSO was used as negative control. All the experiments using ZJH-1, ZJH-2 and DMSO were run in triplicate. After incubation, the procedures were similar to that in the above *in situ* labelling of *P. falciparum*, except in the parasite proteins were extracted in 400 µL PBS and sonicated on ice for 4 min.

Protein concentrations were measured using a BCA assay (*Thermo Fisher*) and equal protein amounts were pooled and adjusted to a final volume of 376 µL. The lysates were supplemented with 0.20 mMazide-PEG3-biotin conjugate (10 mM stock in DMSO; *Sigma-Aldrich*), 0.52 mM TCEP (52 mM stock in ddH_2O) and 0.050 mM TBTA ligand (1.67 mM stock in DMSO). Samples were gently pipetted and the cycloaddition was initiated by the addition of 0.50 mM $CuSO_4$ (50 mM stock in ddH_2O). The reaction mixtures were incubated at 37 °C for 1 h. Proteins were precipitated by the addition of a 4-fold volume excess of methanol (3.2 mL)and incubated over night at -20 °C. The samples were centrifuged at 16k rcf for 15 min at 4 °C. The supernatant was discarded and the pellet washed two times with 2 mL of pre-chilled methanol. Subsequently, the pellet was dissolved in 0.5 mL of PBS with 0.4 % SDS by sonication and incubated under gentle mixing with 80 µL of prewashed streptavidin-agarose beads (*Thermo Fisher*) at room temperature for 3 h. The beads were washed three times with 1 mL of PBS with 0.4 % SDS, twice with 1 mL of 6 M

urea and three times with 1 mL of PBS.

The proteins were reduced, alkylated and trypsin digested on the beads. Therefore, 200 µLNH_4HCO_3 (50 mM) was added to the beads and centrifuged at 8k rcf for 5 min at 4 °C, and repeated once. Then, 100 µL reduction buffer (50 mM NH_4HCO_3, 10 mM DTT) was added to the beads, followed by incubation at 37 °C for 3 h. Iodoacetamide was added to a final concentration of 50 mM, followed by reactionin dark at 25 °C for 40 min and then centrifuged at 8k rcf for 5 min at 4 °C. After the beads were washed with 50 mM NH_4HCO_3 twice, 1 µg trypsin was added to 100 µL 50 mM NH_4HCO_3 to digestion at 37 °C. The resulting peptides were desalted and concentrated using Sep-Pak C18.The beads were pelleted and the peptide solution loaded to the cartridges. The peptides were dried at 45 °C and stored at -80 °C.

Mass Spectrometry

Prior to LC-MS/MS measurements all peptide samples were reconstituted in 2 % MeCN /0.1 % FA ddH_2O and centrifuged at 13k rcf for 10 min at 4 °C.

Nanoflow LC-MS/MS analysis was performed with an Easy-nLC1000 system (*Thermo Scientific*) coupled to an Orbitrap Fusion™ Lumos™ Tribrid™ Mass Spectrometer (*Thermo Scientific*). Peptides were loaded on a trap column (300 µm i.d.×5mm, packed with Acclaim PepMap RPLC C_{18}, 5µm, 100Å), then transferred to an analytical column(75µmi.d.×150mm, packed with Acclaim PepMap RPLC C18, 3 µm, 100 Å) and separated using a gradient from 4% to 10 % B for 5 min, from 10 % to 22 % B for 80 min, from 22 % to 40 % B for 25 min, from 40 % to 95 % B for 5 min and from 95 % to 95 % B for 5 min at a flow rate of 600 nL/min. (Mobile phase: A: 0.1 % formic acid in water; B: 0.1 % formic acid in acetonitrile).

Parameter Value:

Scan range (m/z): 350-1800

MS1 AGC-Target:4e6

MS2 AGC-Target:2e4

Max. MS1 injection time: 50 ms

Max. MS2 injection time:80 ms

Data analysis

The raw MS files were analyzed and searched against protein database based on the species of the samples using uniprot-Plasmodium falciparum. The parameters were set as follows: the protein modifications were carbamidomethylation (C) (fixed), oxidation (M) (variable); the enzyme specificity was set to trypsin; the maximum missed cleavages were set to 2; the precursor ion mass tolerance was set to 10 ppm, and MS/MS tolerance was 0.6 Da. Only high confident identified peptides were chosen for downstream protein identification analysis.

References:

1. W. Trager, J. B. Jensen,*Science*. 1976,**193**,673-675.
2. C. Lambros, J. P.Vanderberg,*J Parasitol*. 1979,**65**,418-20.
3. T. N. Bennett, M Paguio, B.Gligorijevic, C.Seudieu, A. D.Kosar, E. Davidson, P. D. Roepe,*Antimicrob Agents Chemother*, 2004,**48**,1807-1810.
4. M.Smilkstein, N.Sriwilaijaroen, J. X. Kelly, P.Wilairat, M.Riscoe,*Antimicrob Agents Chemother*, 2004,**48**,1803-1806.
5. J. Wang, C.-J. Zhang, W. N. Chia, C. C. Y. Loh, Z. Li, Y. M. Lee, Y. He, L.-X. Yuan, T. K. Lim, M. Liu, C. X. Liew, Y. Q. Lee, J. Zhang, N. Lu, C. T. Lim, Z.-C. Hua, H.-M. Shen, K. S. W. Tan, Q. Lin, *Nat Commun*, 2015, **6**, 10111.

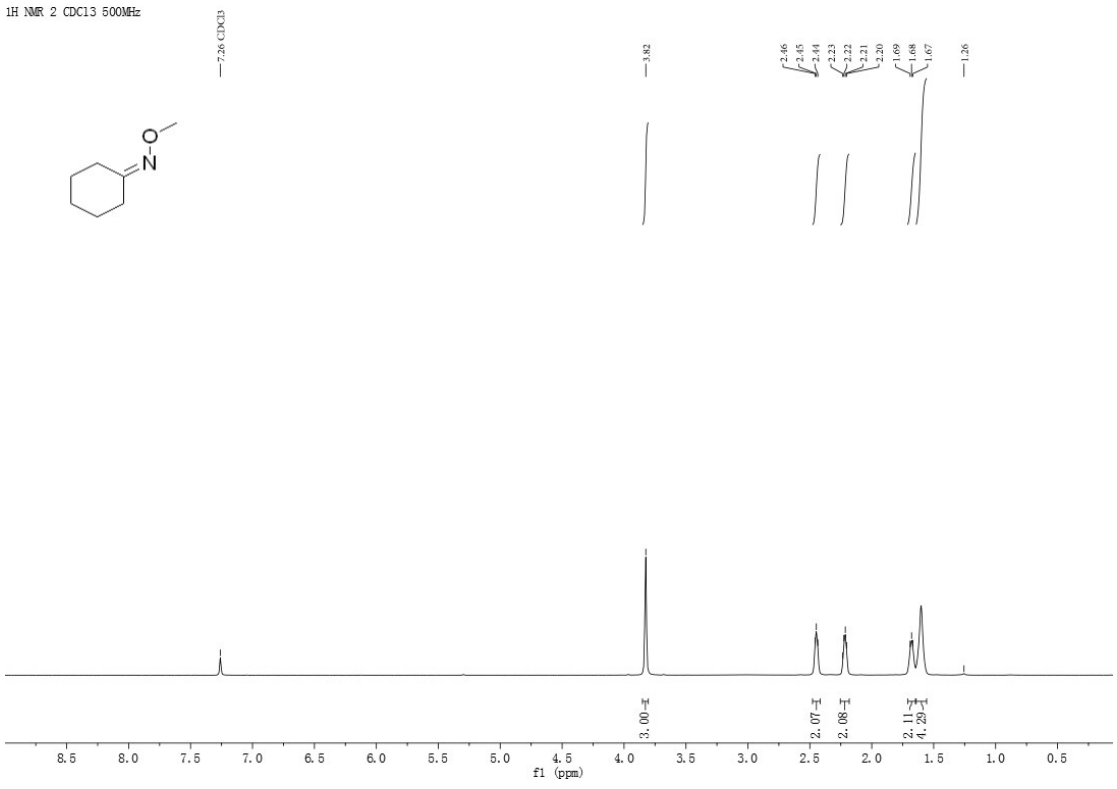


Figure S1. ^{1}H NMR spectrum of Compound **1** in $CDCl_3$

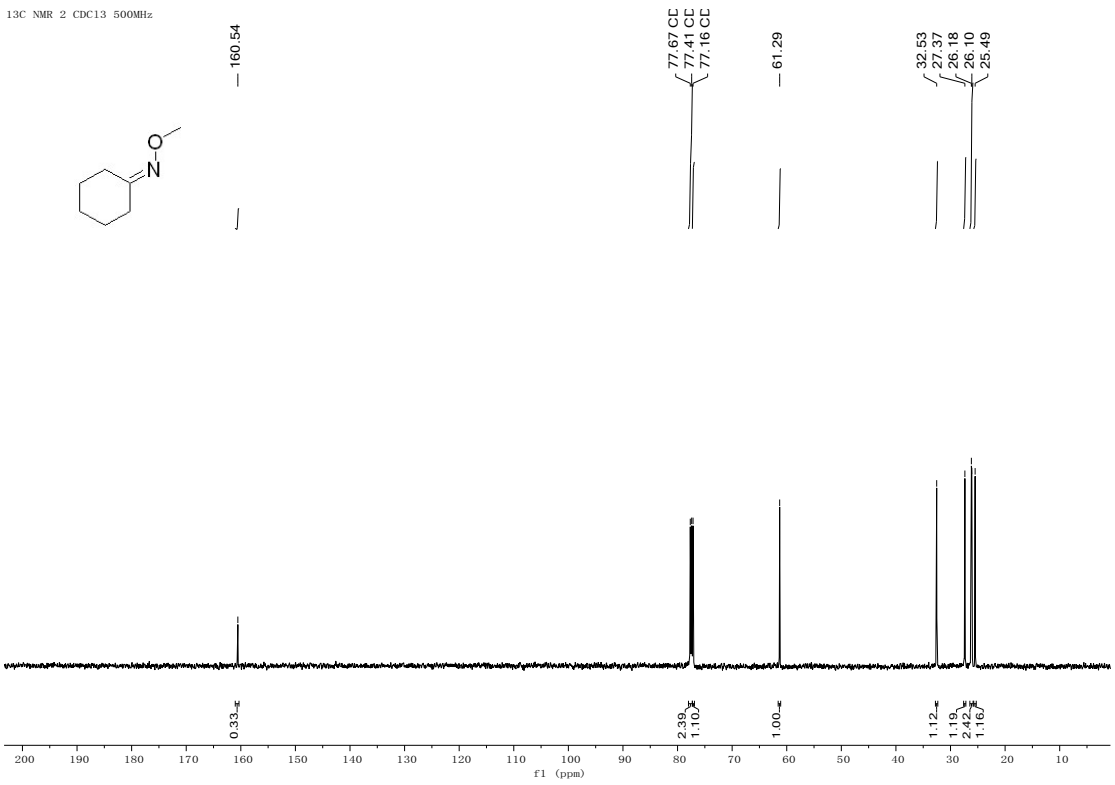


Figure S2. ^{13}C NMR spectrum of Compound **1** in $CDCl_3$

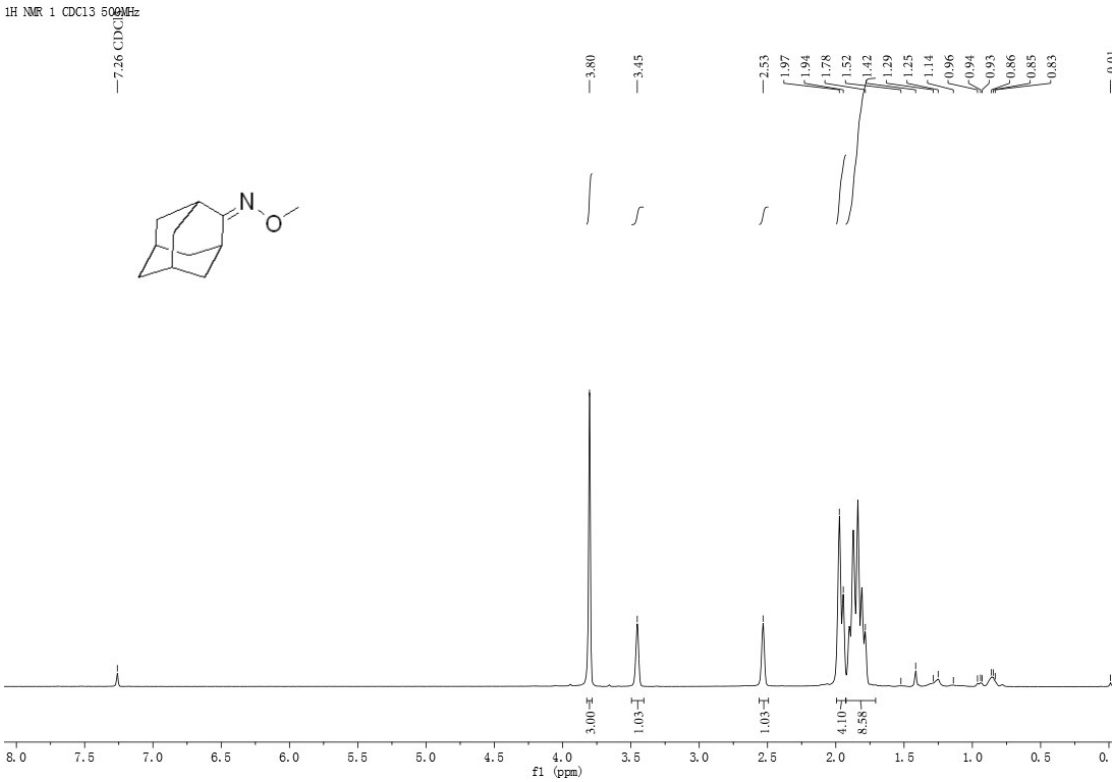


Figure S3. ^{1}H NMR spectrum of Compound **2** in $CDCl_3$

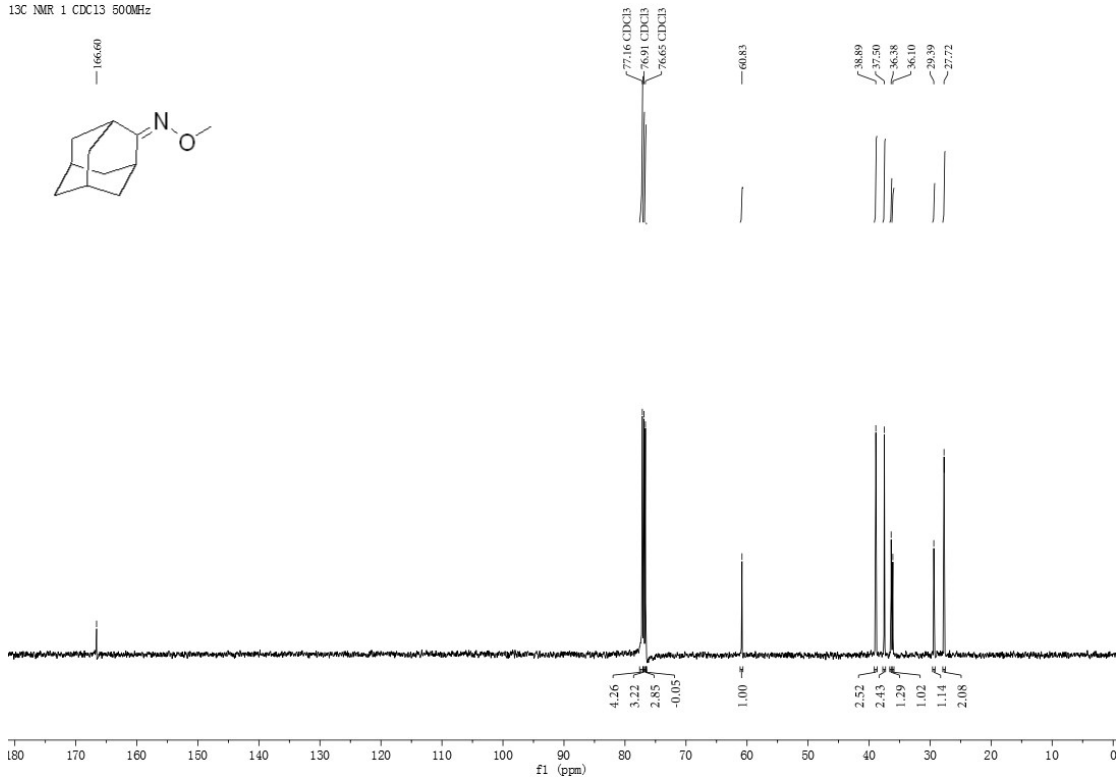


Figure S4. ^{13}C NMR spectrum of Compound **2** in $CDCl_3$

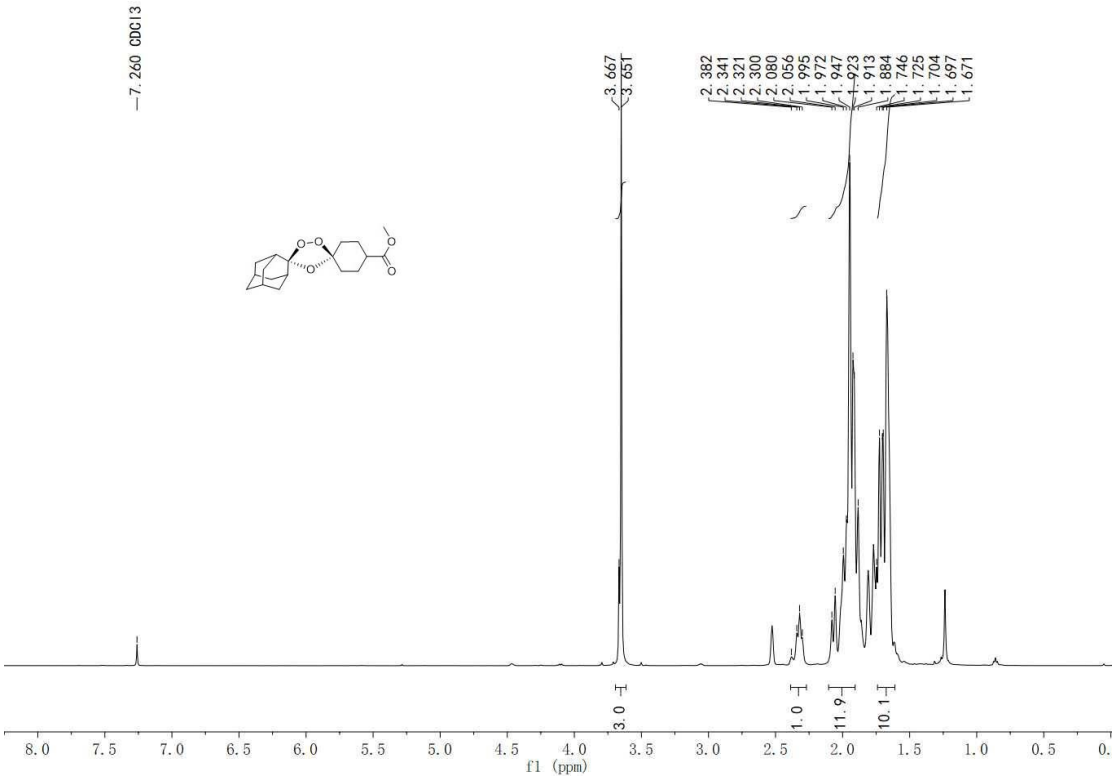


Figure S5. ^{1}H NMR spectrum of Compound **3** in $CDCl_3$

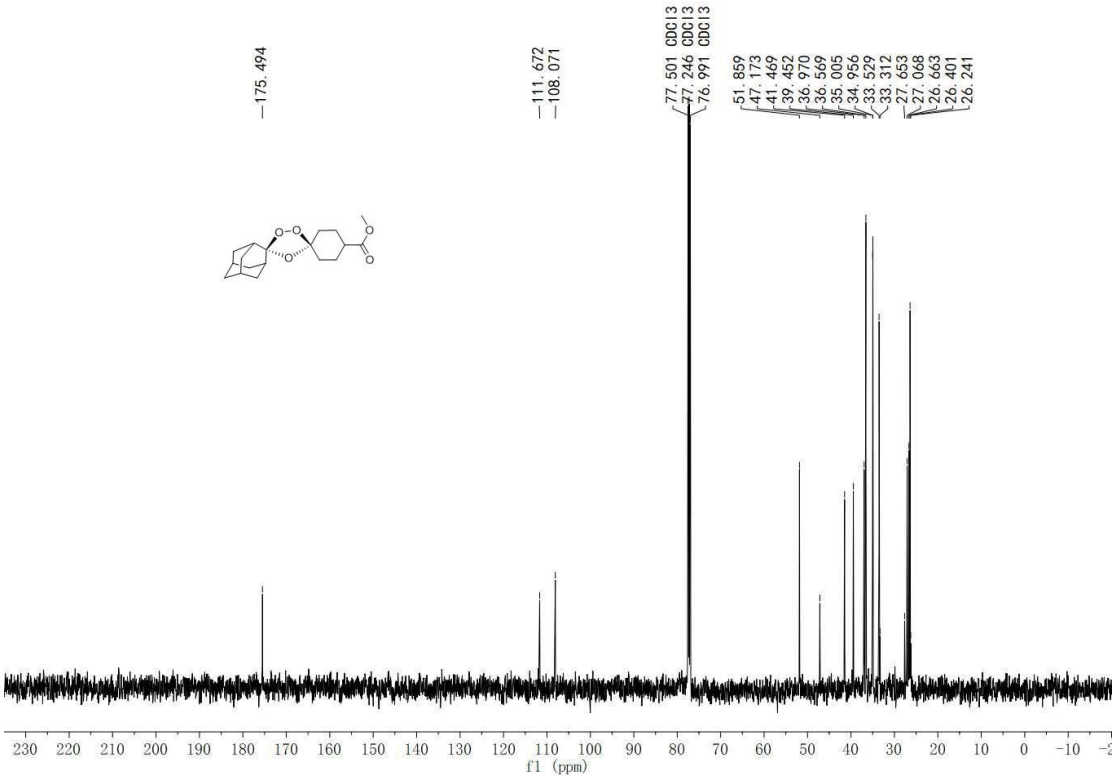


Figure S6. ^{13}C NMR spectrum of Compound **3** in $CDCl_3$

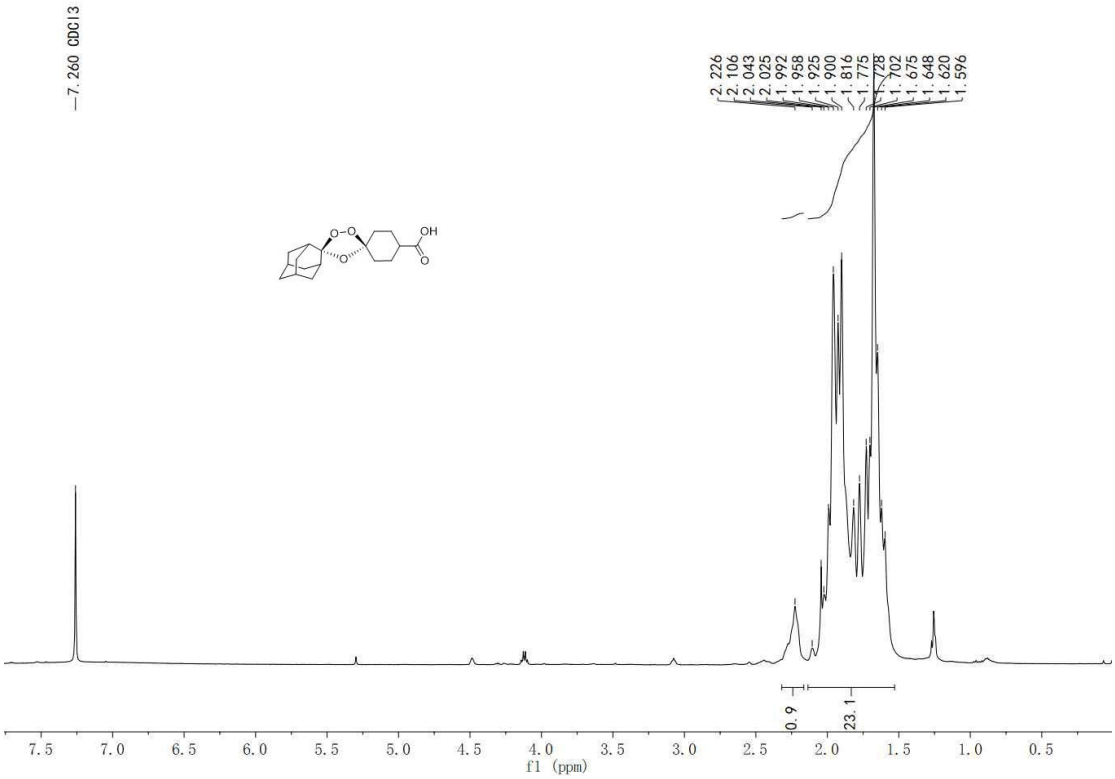


Figure S7. ^{1}H NMR spectrum of Compound **3-1** in $CDCl_3$

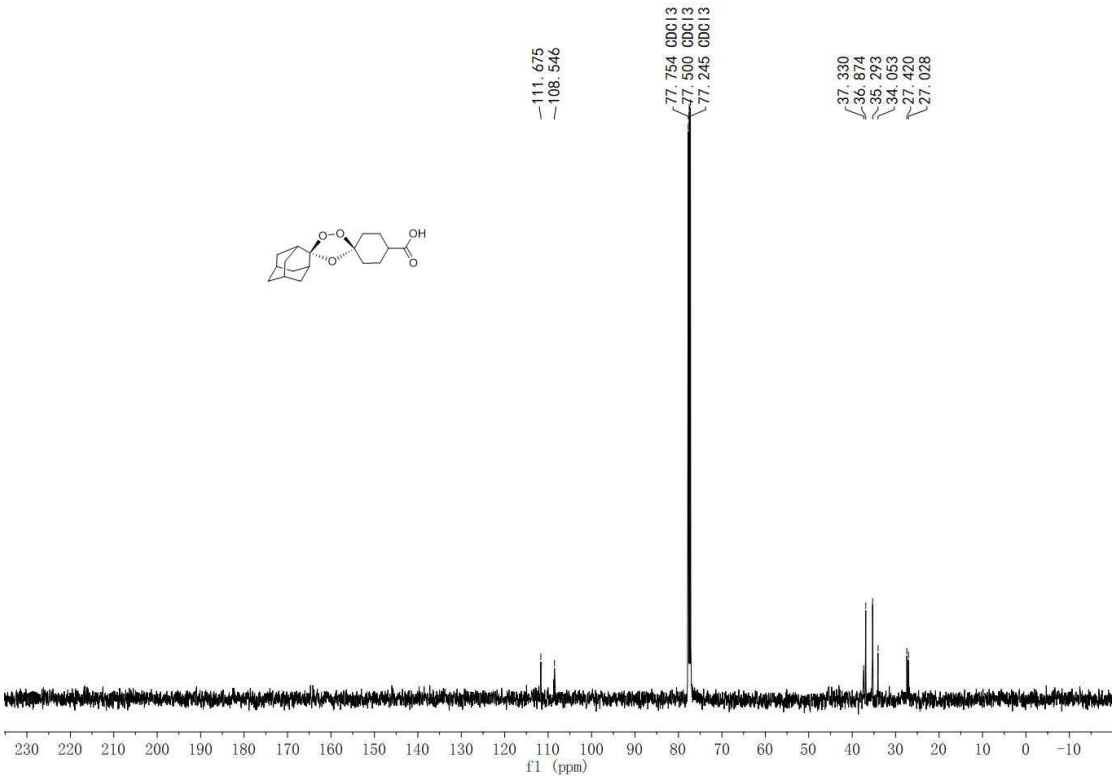


Figure S8. ^{13}C NMR spectrum of Compound **3-1** in $CDCl_3$

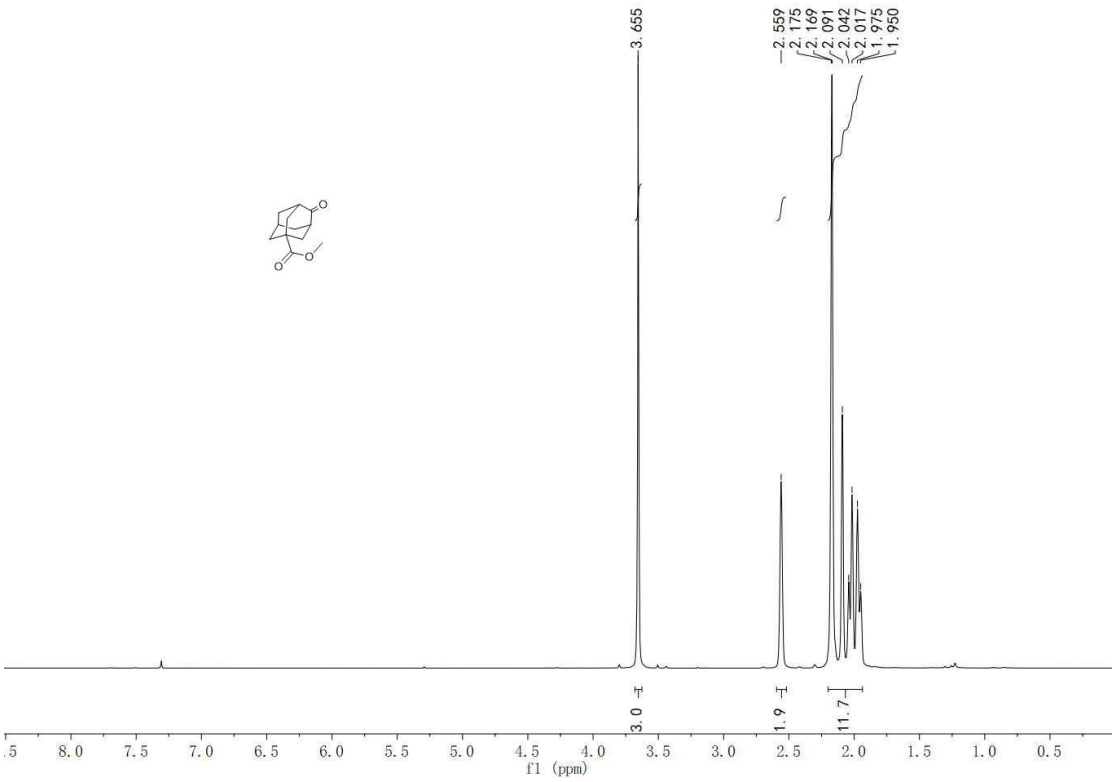


Figure S9. ^{1}H NMR spectrum of Compound **4** in $CDCl_3$

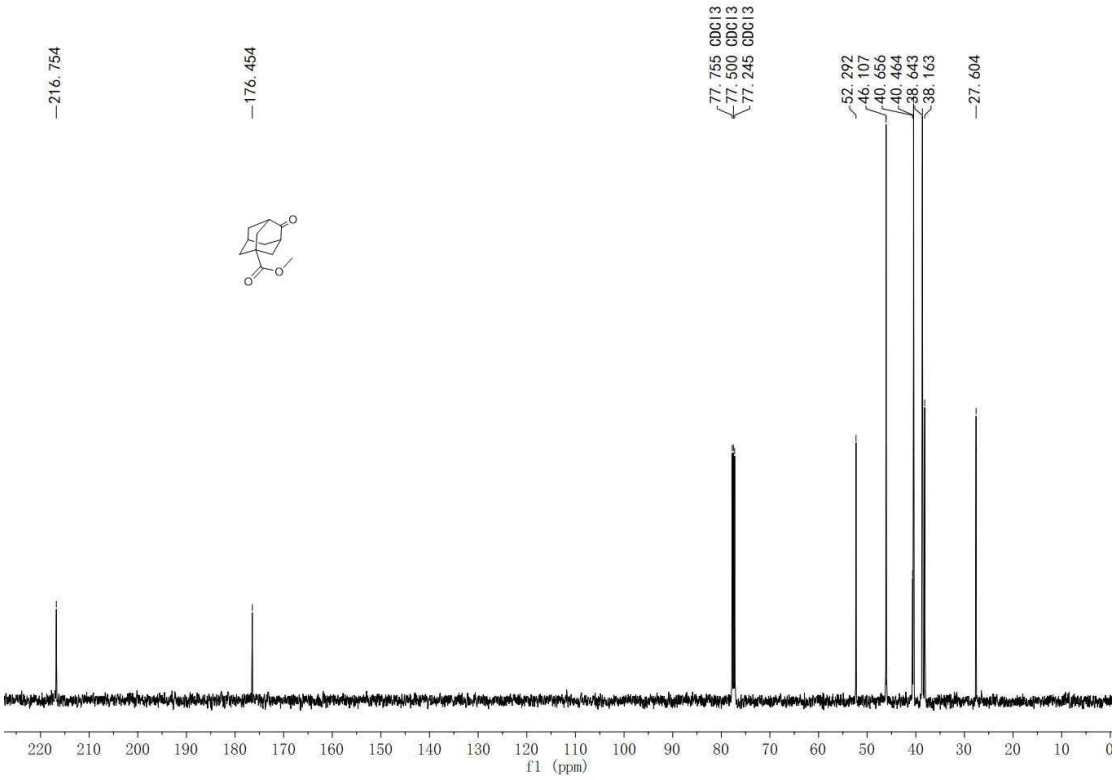


Figure S10. ^{13}C NMR spectrum of Compound **4** in $CDCl_3$

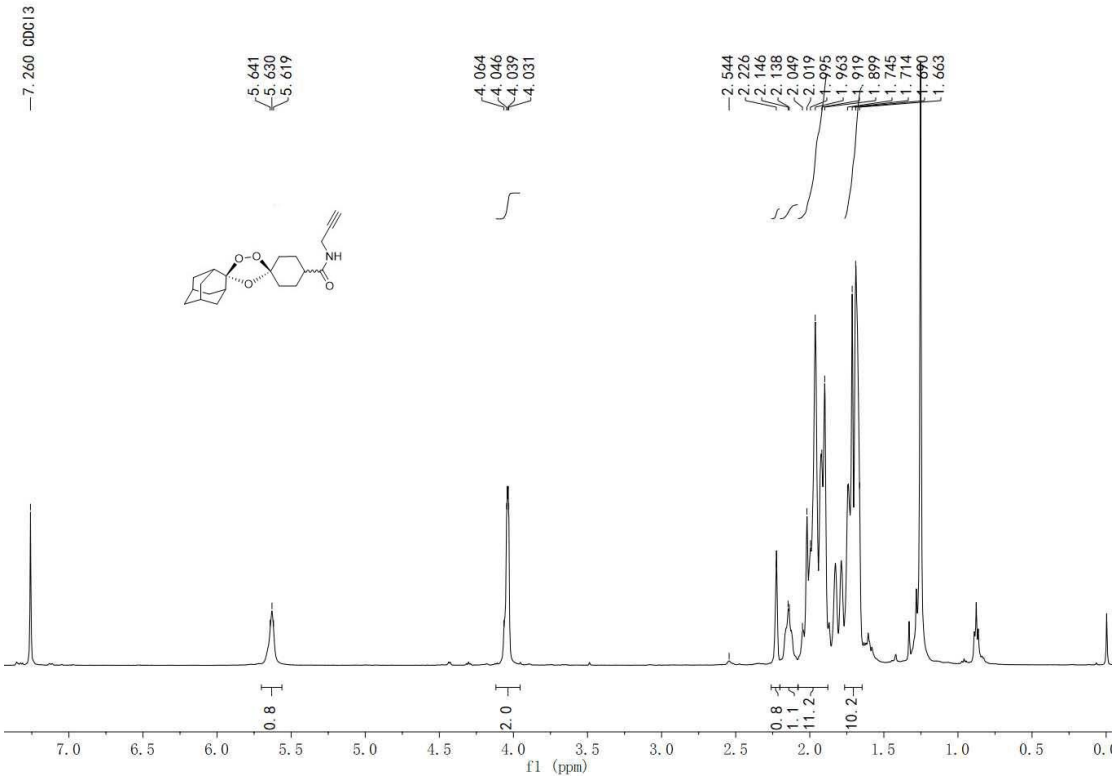


Figure S11. ^{1}H NMR spectrum of Compound **ZJH-1** in $CDCl_3$

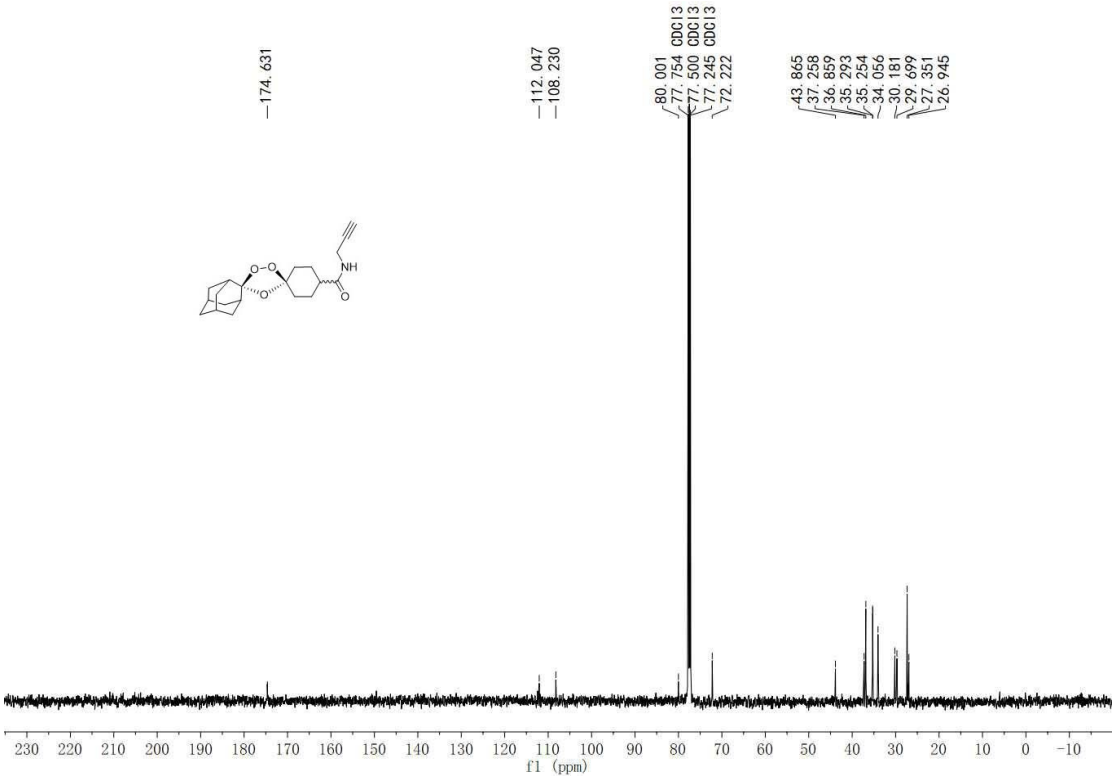


Figure S12. ^{13}C NMR spectrum of Compound **ZJH-1** in $CDCl_3$

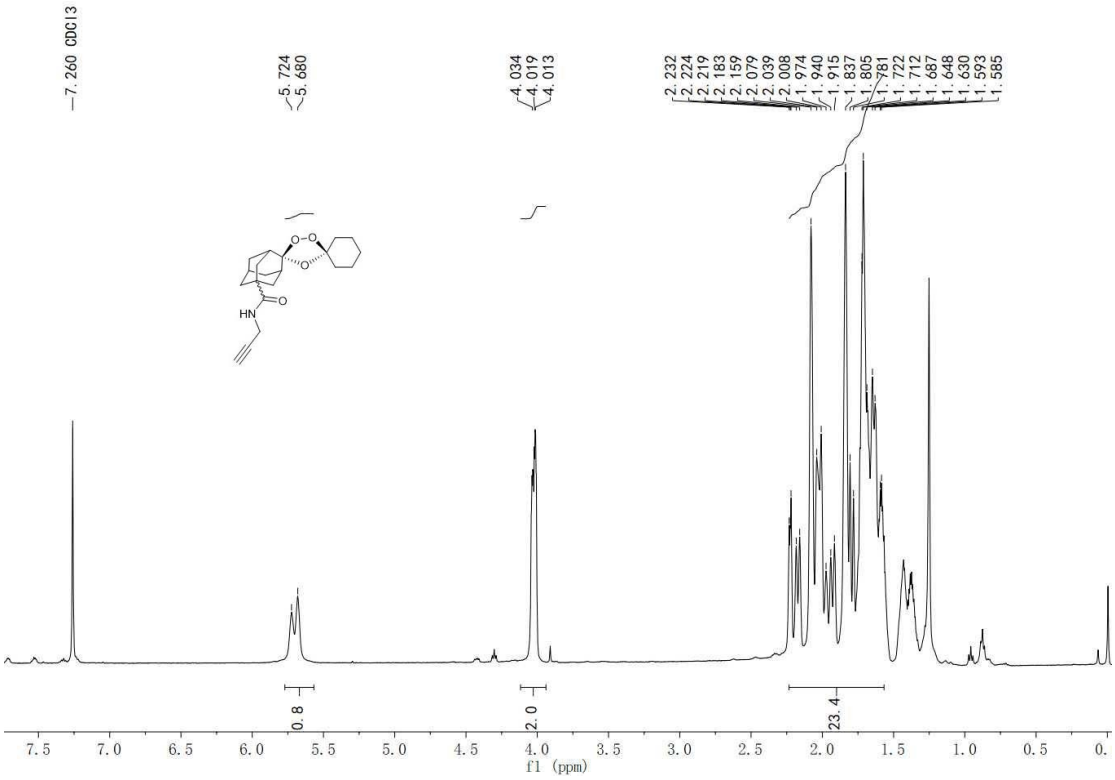


Figure S13. ^{1}H NMR spectrum of Compound **ZJH-2** in $CDCl_3$

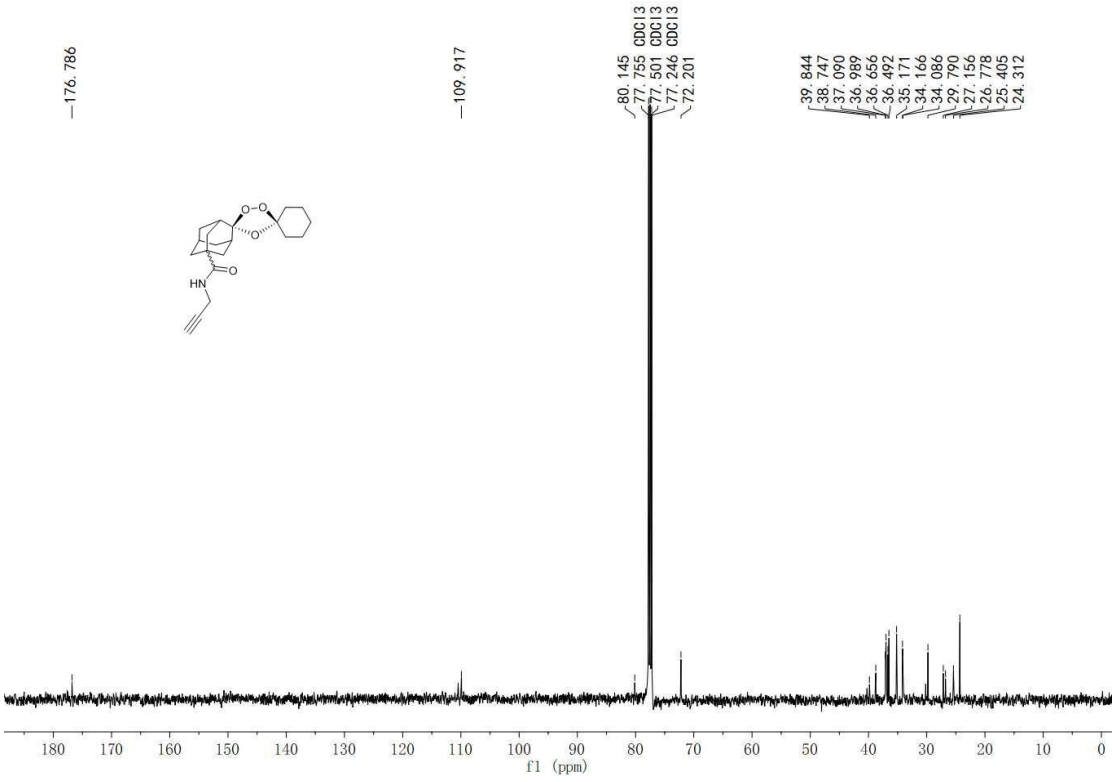


Figure S14. ^{13}C NMR spectrum of Compound **ZJH-2** in $CDCl_3$

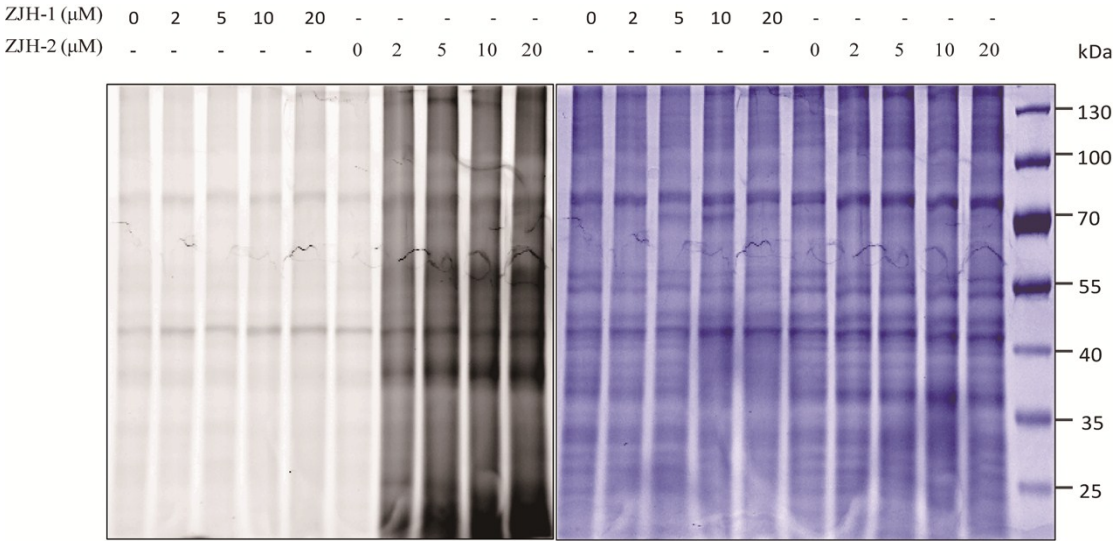


Figure S15. *In situ* labeling with different concentrations of probes ZJH-1 or ZJH-2 in malaria parasites. The image in black was the fluorescent scanning of probe-labelled proteome. The image in blue was the coomassie staining of total incubated proteome.

Table S1 Fourteen proteins targeted by both ZJH-1 and ZJH-2

Protein IDs	Protein names	Gene names	Peptides	MW.kDa	Q-value	Score
C0H593	Uncharacterized protein	PF3D7_0937000	11	95.843	0	323.31
C0H4B1	memo-like protein	PF3D7_0417500.1	10	34.294	0	28.846
C0H5F2	Uncharacterized protein	PF3D7_1333400	7	28.084	0	323.31
C0H5H0	heat shock protein 110, putative	PF3D7_1344200	31	108.18	0	323.31
K7NTP5	Heat shock protein 70	PF3D7_0831700	14	75.052	0	143.26
Q76NM3	L-lactate dehydrogenase	PF3D7_1324900	19	34.107	0	323.31
Q8I2X4	heat shock protein 70	PF3D7_0917900	44	72.387	0	323.31
Q8I6T2	Isocitrate dehydrogenase [NADP]	PF3D7_1345700	17	53.593	0	140.7
Q8IBP8	Ferrodoxin reductase-like protein	PF3D7_0720400	15	72.721	0	259.22
Q8IBQ5	40S ribosomal protein S10, putative	PF3D7_0719700	4	16.478	0	323.31
Q8IIB6	GrpE protein homolog	PF3D7_1124700	15	35.042	0	323.31
Q8IJV6	Adenylate kinase	PF3D7_1008900	12	27.61	0	323.31
Q8ILK1	Protein arginine N-methyltransferase 1	PF3D7_1426200	11	47.446	0	98.58
Q8ILS0	H/ACA ribonucleoprotein complex subunit 4	PF3D7_1417500	8	52.941	0	65.624

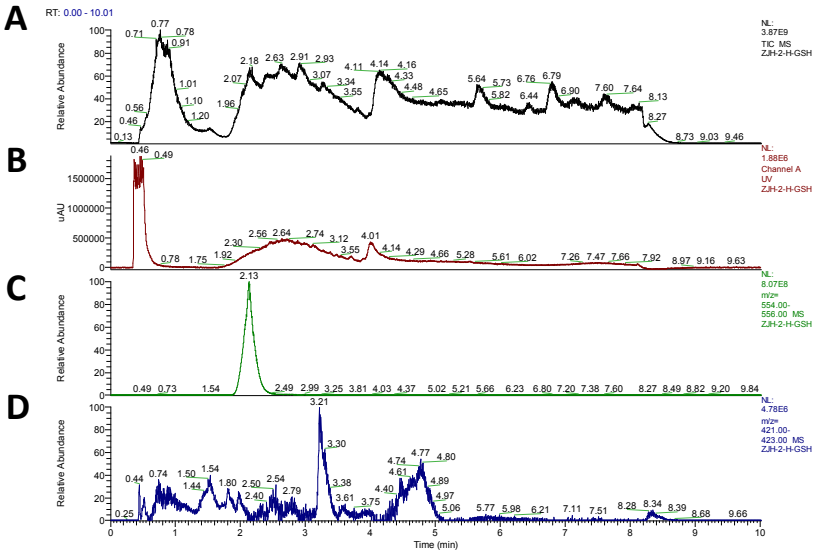


Figure S16. Reaction between ZJH-2 and GSH in presence of heme. A, The overall ion profile of the reaction mixture; B, The UV absorption profile of the reaction mixture; C, The extracted valve of m/z ranging from 554-556 for the product of ZJH-2-P-S; D, The extracted valve of m/z ranging from 421-423 for the product of ZJH-2-P-P.

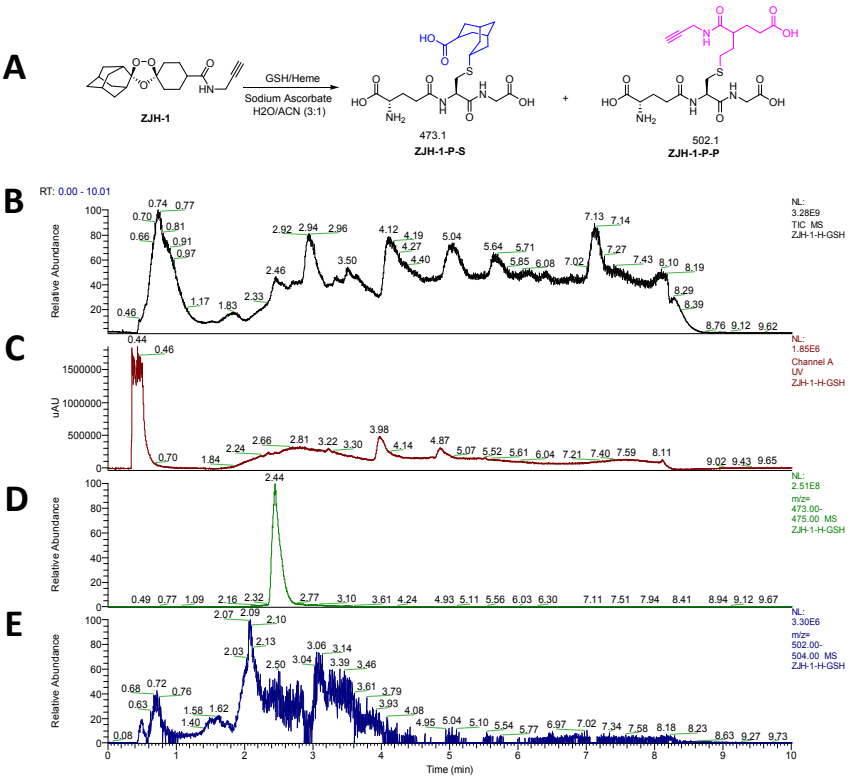


Figure S17. Reaction between ZJH-1 and GSH in presence of heme. A), Reaction scheme of ZJH-1 and GSH in presence of heme and sodium ascorbate; B-E) The reaction mixture was checked by LC-MS. B, The overall ion profile of the reaction

mixture; C, The UV absorption profile of the reaction mixture; D, The extracted valve of m/z ranging from 473-475 for the product of ZJH-1-P-S; E, The extracted valve of m/z ranging from 502-504 for the product of ZJH-1-P-P.

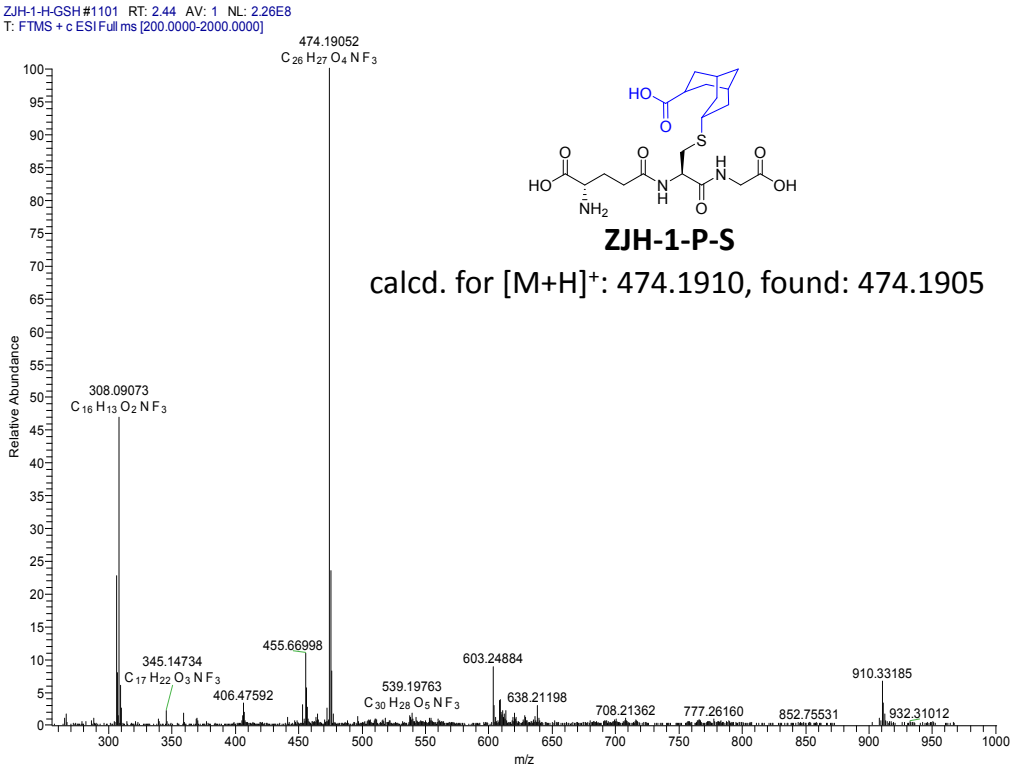


Figure S18. Mass spectrum of the main product of ZJH-1-P-S