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General Information

Reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased from Innochem and stored under a nitrogen atmosphere with activated molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were measured on Varian Mercury 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), Varian Mercury 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or Varian INOVA 600 (^{1}H, 600 MHz; ^{13}C, 150 MHz) spectrometers. Chemical shifts were given in ppm. Coupling constants were given in Hertz. High-resolution mass spectra for verification of synthesized small molecules were carried out on a Thermo Exactive Plus spectrometer. The ionization method was ESI and the mass analyzer type was orbitrap.

Cell Culture and Lysate Preparation

Human brain astroblastoma cells (U87MG) were maintained in DMEM with 10% (vol/vol) fetal bovine serum (FBS) in a humidified atmosphere at 37 °C with 5% CO_2. Cells were harvested and resuspended in 0.1% NP-40/phosphate-buffered saline (PBS) buffer containing an ethylenediaminetetraacetic acid (EDTA)-free Pierce Halt protease inhibitor cocktail. The cells were first lysed by sonication on ice for 10 s and then lysed on ice for

another 30 min. The cell lysates were collected by centrifugation (15,000 rpm, 20 min) at 4 °C to remove the debris. The whole proteome was transferred to a separate microfuge tube, and the protein concentration was determined by using the BCA protein assay kit.

The Binding Assay of BME with Electrophiles

50 μL solution of electrophiles in 40% DMSO/PBS (400 μM) were treated with 50 μL PBS or 50 μL solution of BME in PBS (100 mM) for 10 min. Then UV-visible absorption spectra were recorded. Each reaction was then diluted 10-fold by PBS or a solution of BME in PBS (50 mM) as indicated, and the absorption spectra were recorded after 10 min again.

The Binding Assay of BSA with III-8

50 μL solution of electrophiles in 40% DMSO/PBS (400 μM) were treated with 50 μL PBS or 50 μL solution of BSA in PBS (1 or 2 mM) for 30 min. Then UV-visible absorption spectra were recorded. Each reaction was then diluted 10-fold by PBS and the absorption spectra were recorded after 30 min again.

Click free probe DbGGI and DbG'G'I concentration-Dependent Gel-Base ABPP

Each sample was normalized to 2 mg/mL in a volume of 190 μL, followed by incubating with 2 μL of different concentrations of DbGGI or DbG'G'I at 37 °C for 1 h. The resulting lysates were precipitated by 500 μL of ice acetone at −20 °C overnight. The precipitated proteins were centrifuged at 5500 rpm for 5 min at 4 °C, washed three times with 500 μL of cold methanol, and resuspended in 200 μL of 1.2% sodium dodecyl sulfate (SDS)/PBS, followed by diluting to 0.4% SDS/PBS. Next, 100 μL of streptavidin beads was washed three times with 1 mL of PBS and deionized water, separately, and added to the above proteomes. The beads were incubated with the protein solution for 4 h at room temperature. The beads were washed 3 times with 6 M urea, 3 times with PBS, and 3 times with deionized H_2O. To obtain the proteins from the beads by heating, to the samples were added 40 μL of 0.4% SDS/PBS and 10 μL of 5× SDS loading buffer, followed by heating at 95 °C for 10 min. Next, 25 μL of supernatant of each sample was loaded and resolved on a 10% sodium dodecyl sulfatepolyacrylamide gel electrophoresis gel. The gels were stained by Coomassie brilliant blue.

Chemoproteomic Experiments with the DbGGI Tags to Investigate the Accuracy of Quantification

Two samples of 1.5 mL BSA or freshly prepared lysate of U87MG cells were incubated with 15 μL of 10 mM light DbGGI or heavy DbG'G'I in DMSO, each, and incubated at room temperature for 1 h. After incubation, the light-/heavy-probe-labeled samples were combined into 8 mL of cold acetone in order to precipitate all proteins. For the experiments, to determine the accuracy of quantification, either 500 μL of the light- and heavy-labeled samples, each, were combined (1:1) or 800 μL light- and 200 μL heavy-probe-labeled sample were combined (4:1). The resulting lysates were precipitated by 500 μL of ice acetone at −20 °C overnight.

Comparison between Click Free Probe (DbGGI) and it's Corresponding Clickable Probe

For Click free probe (DbGGI) group, each sample was normalized to 2 mg/mL in a volume of 190 μL, followed by incubating with 2 μL of different concentrations of DbGGI at 37 °C for 1 h.The resulting lysates were precipitated by 500 μL of ice acetone at −20 °C overnight.

For Clickable probe group, each sample was normalized to 2 mg/mL in a volume of 190 μL, followed by incubating with 2 μL of different concentrations of IAA at 37 °C for 1 h. Then each sample was added 20 μL click buffer, including 2 μL $CuSO_4$ (100 mM in H_2O), 2 μL TBTA (10 mM in DMSO) and 2 μL TCEP (100 mM in H_2O), 4 μL Db-N_3 (10 mM in DMSO). The mixture was then incubated at 37 °C for 1 h. The resulting lysates were precipitated by 500 μL of ice acetone at −20 °C overnight.

The precipitated proteins were centrifuged at 5500 rpm for 5 min at 4 °C, washed three times with 500 μL of cold methanol, and resuspended in 200 μL of 1.2% SDS/PBS, followed by diluting to 0.4% SDS/PBS. Next, 100 μL of streptavidin beads was washed three times with 1 mL of PBS and deionized water, separately, and added to the above proteomes. The beads were incubated with the protein solution for 4 h at room temperature. The beads were washed 3 times with 6 M urea, 3 times with PBS, and 3 times with deionized H_2O.

To obtain the proteins from the beads by heating, to the samples were added 40 μL of 0.4% SDS/PBS and 10 μL of 5× SDS loading buffer, followed by heating at 95 °C for 10 min. Next, 25 μL of supernatant of each sample was loaded and resolved on a 10% sodium dodecyl sulfatepolyacrylamide gel electrophoresis gel. The gels were stained by Coomassie brilliant blue.

Competitive Chemoproteomic Experiments with the DbGGI/DbG'G'I Tags

For competitive experiments, 500 μL freshly-prepared lysate of U87MG cells were incubated with the electrophile in DMSO (5 μL, 10 mM stock for 100 μM final concentration) at room temperature for 1 h. Another 500 μL sample of lysate was incubated with 5 μL of DMSO. After incubation, DbGGI and 5 mM DbG'G'I in DMSO (5 μL, 5 mM) were separately added to the lysate with or without the electrophile and incubated at room temperature for 1 h. After incubation, the light-/heavy-probe-labeled samples were combined into 1.2 mL of cold acetone in order to precipitate all proteins. Precipitates were stored at −20 °C overnight.

MS Sample Preparation

For all types of experiments, protein precipitates were centrifuged at 5500 rpm for 5 min at 4 °C, washed three times with 500 μL of cold methanol, and resuspended in 200 μL of 1.2% SDS/PBS, followed by diluting to 0.4% SDS/PBS. For enrichment, the whole proteome was incubated with 100 μL of streptavidin agarose resin (washed with 1 mL of PBS× 3, deionized water× 3 before usage) for 4 h at room temperature. The beads were then washed 3 times with 500 μL of 6 M urea, 3 times with 500 μL of PBS, and 3 times with 500 μL of deionized H_2O. The supernatant was removed, and the beads were resuspended in 500 μL 6 M urea. 25 μL 200 mM DTT/H_2O were added and the beads incubated at 37°C with shaking at 800 rpm for 60 min. Free thiol groups were modified by adding 25 μL of 400 mM iodoacetamide/H_2O and

incubation at 37°C with shaking at 800 rpm for 30 min. Remaining iodoacetamide was quenched by adding 950 μL H_2O and the supernatant was removed. The enriched proteins were then digested on beads by 4 μL of 0.5 mg/mL trypsin in 200 μL of 2M urea/PBS and 2 μL of 100 mM $CaCl_2$ for 12−16 h at 37 °C. After trypsin digestion, samples were centrifuged and the supernatant was removed. For binding site analysis, the beads were washed with 50% acetonitrile with 0.1% FA at 24 °C for 10 min twice. The eluted peptides were combined and dried. The digested peptide samples were both desalted through Pierce C18 Tips before MS analysis. Samples were stored at −20 °C until measurement.

Sample Analysis by LC-MS/MS

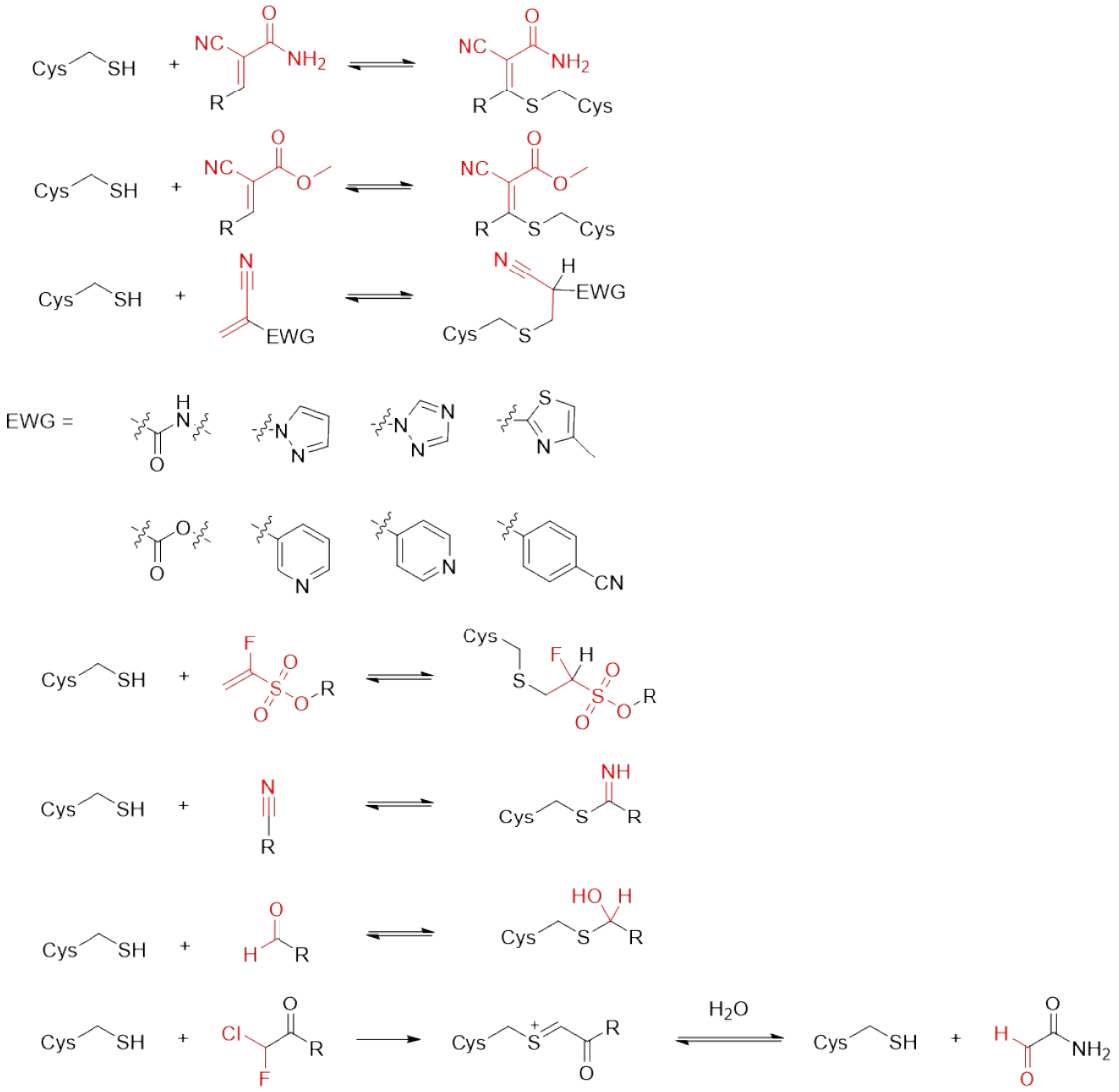
All of the LC−MS/MS analysis was performed on an Orbitrap Fusion Lumos Tribrid mass spectrometer (Thermo Fisher Scientific) in line with an Ultimate 3000 LC system. Samples for the proteome analysis were resuspended in water containing 0.1% formic acid and centrifuged at 4 °C /15,000 rpm for 30 min. The peptides were loaded on a trap column (0.3 mm × 5 mm, C18, 5 μm, 100 Å, 160,454) and washed at a flow rate of 10 μL/min in 100% loading buffer with 0.1% formic acid for 10 min. The samples were then transferred to an analytical column (Acclaim PepMap RSLC 75 μm × 15 cm, nanoViper C18, 2 μm, 100 Å) at a flow rate of 0.3 μL/min. A 90 min gradient was used for separtion (buffer A: 0.1% formic acid, HPLC-grade water; buffer B: 0.08% formic acid, 80% acetonitrile; 10 min of 4% B, 60 min of 4−30% B, 5 min of 30−80% B, 5 min of 80% B, 5 min of 80−4% B, 5 min of 4% B). The peptides were ionized using a spray voltage of 2.4 kV and an ion transfer tube temperature of 320 °C. The Orbitrap Fusion Lumos Tribrid mass spectrometer switched automatically between MS and MS2 scans in the data-dependent mode with a 25 s-exclusion duration. The MS spectra were acquired at a resolution of 60,000 with a maximum injection time of 50 ms and an automatic gain control (AGC) target value of 4×10^5 charges. The scanning range of full-scan MS spectra was from 350 to 1500 (m/z). Higher-energy collision dissociation (HCD) with the normalized energy of 30% was applied for peptide fragmentation. MS2 spectra were acquired at a resolution of 15,000 with a maximum injection time of 35 ms and an AGC target value of 1×10^4. Only precursors with charge states ranging from 2 to 7 were chosen for fragmentation. The isolation window was 1.6 m/z.

Data Evaluation using MsFragger

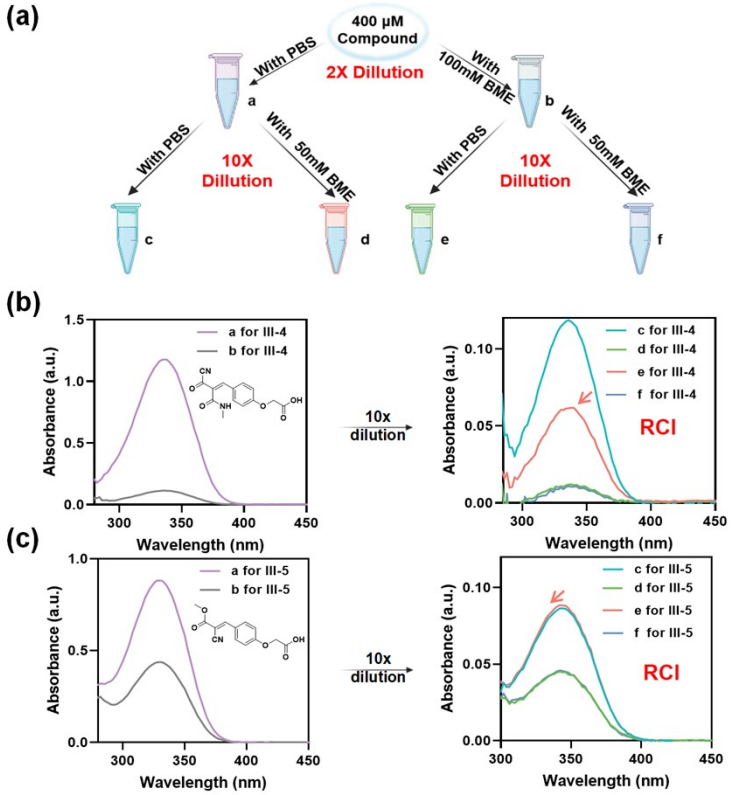
MS raw data were analyzed using MsFragger software (version 17.1). With the use of default parameters of fixed modification of cysteine (+57.0215 Da) variable oxidation modification of methionine (+15.9949 Da). A human fasta file (ipi.HUMAN.v.3.68.fasta) was employed as the database for protein identification. The resulting data were further analyzed using Perseus software (v1.6.15.0). Cysteine residues were searched with a variable modification with either the light or heavy DbGGI tags (+353.2063 or +359.2138, respectively). Peptides were required to be fully tryptic peptides. Light versus heavy isotopic probe-modified peptide ratios are calculated by taking the mean of the ratios of each replicate paired light versus heavy precursor abundance for all peptide-spectral matches associated with a peptide. The paired abundances were also used to calculate a paired sample t-test *P* value in an effort to estimate constancy in paired abundances and significance in change between treatment and control. *P* values were corrected using the *Benjamini*–*Hochberg*

method.

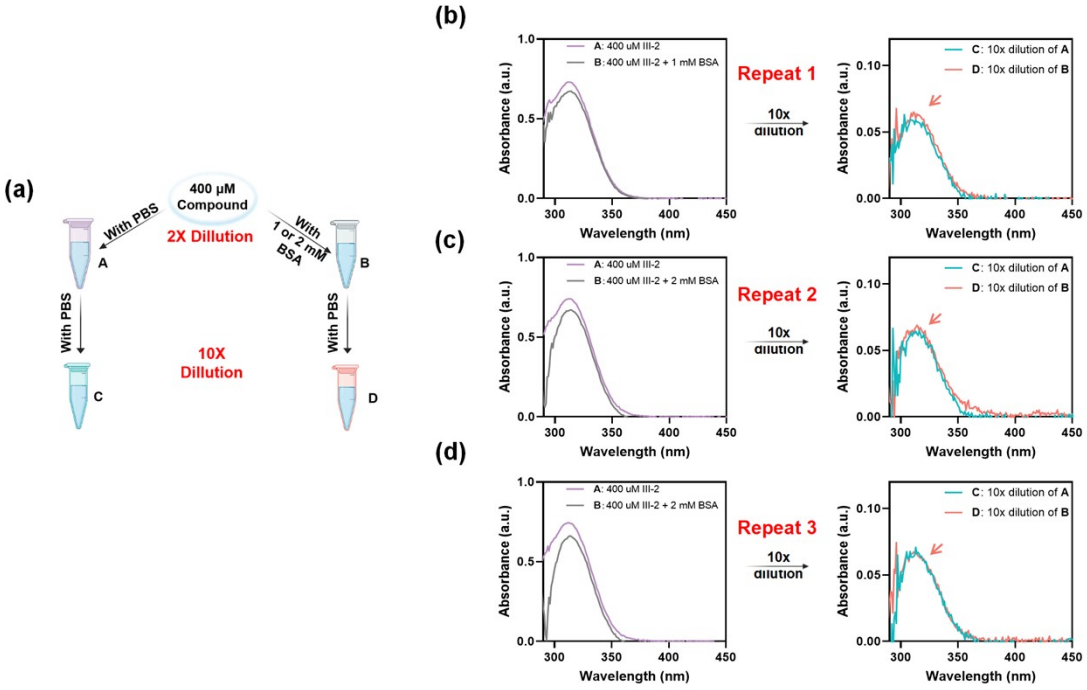
Supplementary Figure



Supplementary Figure 1: Previously-reported representative covalent reversible groups targeting cysteine. The electrophilic warheads are highlighted in red.

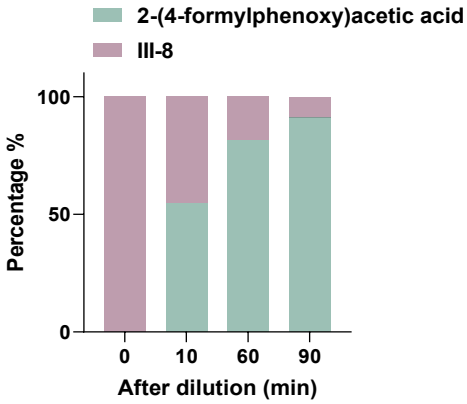


Supplementary Figure 2: The binding assay of thiol and compounds III-4 or III-5 *in vitro*. (a) The workflow for studying the reversibility of reactions between model molecules (III-4 and III-5) and BME. (b)~(c) The UV-visible absorption spectra of reaction mixture before and after dilution.

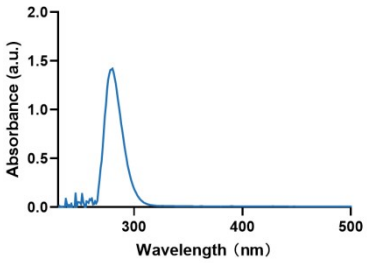


Supplementary Figure 3: The reversibility study of products fromed between BSA and compounds III-2 *in vitro*. (a) The workflow for studying the reversibility of BSA

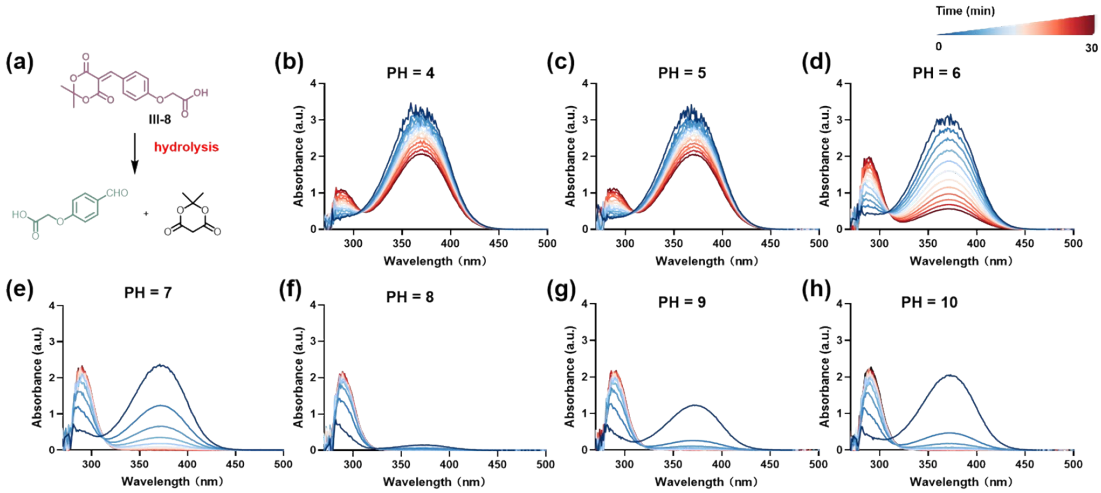
to III-2. (b)-(d) The UV-visible absorption spectra of reaction mixtures of III-2, showing the results from three repeated experiments.



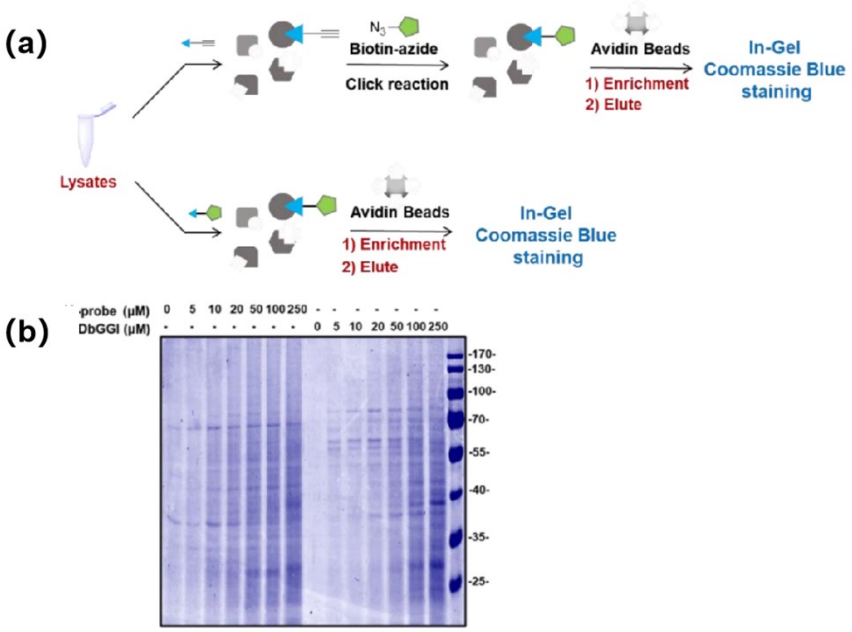
Supplementary Figure 4: The ratio of III-8 and its hydrolized product (2-(4-formylphenoxy)acetic acid) after dilution in water (PH=7.3).



Supplementary Figure 5: The UV Absorption Spectra of 2-(4-formylphenoxy)acetic acid (200 μM) in water (PH=7.35).

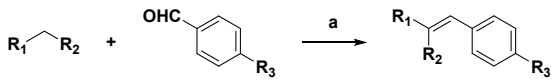


Supplementary Figure 6: The stability assay of compound III-8 at different pHs. (a) The hydrolysis reaction equation of III-8 in aqueous solution. (b)-(h) The UV-Vis absorption spectra of compound III-8 at different pHs (4-10).



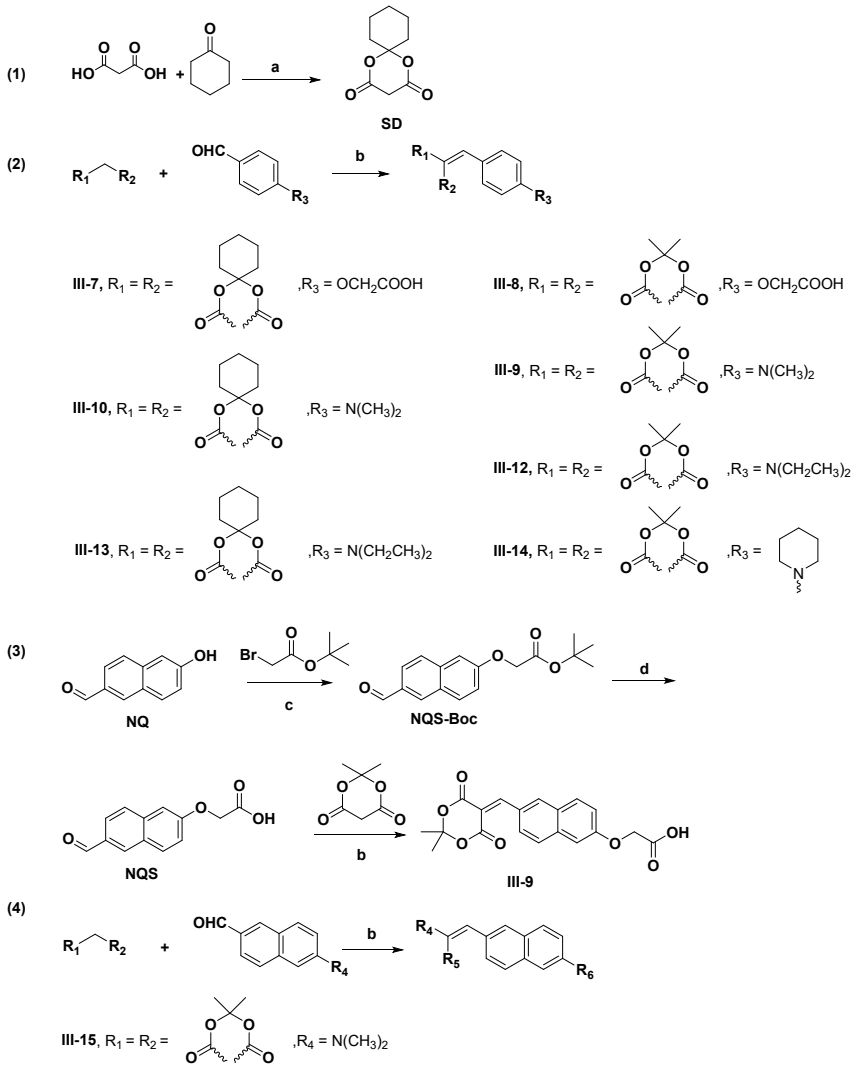
Supplementary Figure 7: The background protein labeling with click-free probe (DbGGI) is much less than that with its corresponding clickable probe (IA-probe) in the process of target identification. (a) The workflow of comparing DbGGI with IA-probe. (b) SDS-PAGE gel of label proteome with DbGGI and IA-probe.

Supplementary Scheme

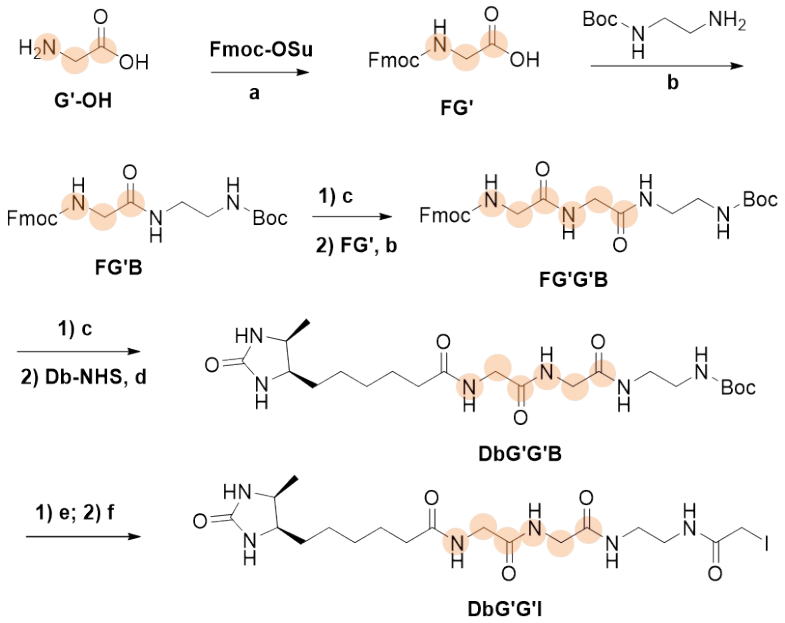


III-1, $R_1 = COOCH_3$, $R_2 = COOCH_3$, $R_3 = OCH_2COOH$
III-2, $R_1 = CONH_2$, $R_2 = CONH_2$, $R_3 = OCH_3$
III-3, $R_1 = COOCH_3$, $R_2 = CONH_2$, $R_3 = OCH_2COOH$
III-4, $R_1 = CONHCH_3$, $R_2 = CN$, $R_3 = OCH_2COOH$
III-5, $R_1 = COOCH_3$, $R_2 = CN$, $R_3 = OCH_2COOH$
III-6, $R_1 = CN$, $R_2 = CN$, $R_3 = OCH_2COOH$

Supplementary Scheme S1: Synthesis of III-1~III-6. Reagents and conditions: (a) piperidine, acetic acid, toluene, 120 ℃, reflux, 12-16 h or MeOH / water, reflex, 2 h.

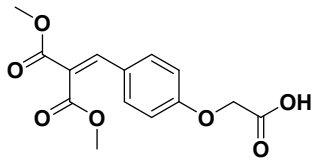


Supplementary Scheme S2: Synthesis of III-7~III-15. Reagents and conditions: (a) P-toluenesulfonic acid, cyclohexanone, 28-30℃, 3 h; (b) piperidine, acetic acid, toluene, 120 ℃, reflux, 12-16 h or MeOH / water, reflex, 2 h; (c) potassium carbonate, 60 ℃, 1 h; (d) trifluoroacetic acid, DCM, r.t., 2 h.



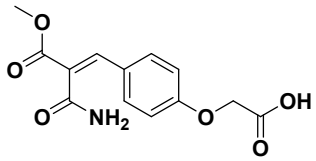
Supplementary Scheme S3: Synthesis of DbG'G'I. Reagents and conditions: (a) NaHCO3, acetone/water, r.t.; (b) 4-Methylmorpholine, HATU, DMF, r.t., overnight; (c) 40% diethylamine / DMF, r.t., 2 h; (d) Triethylamine, DMF, overnight; (e) 20% TFA/DCM (v/v), r.t., 2 h; (f) Iodoacetic anhydride, DIPEA, DCM/DMF (1/2, v/v), 0 °C, argon, in the dark.

Chemical synthesis



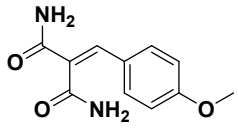
Synthesis of III-1

Dimethyl malonate (1.25 eq, 1.8 mmol, 205 μL), 4-Formylphenoxyacetic acid (1.0 eq, 1.44 mmol, 260 mg), piperidine (0.14 eq, 0.2 mmol, 20 μ L), acetic acid (0.32 eq, 0.46 mmol, 26 μL) were added to 10 mL of toluene and reflux at 120 ℃ until the raw material is consumed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (s, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.76 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H). HRMS (ESI) calculated for $C_{14}H_{14}O_7Na[M+Na]^+$ 317.0637, found 317.0624.



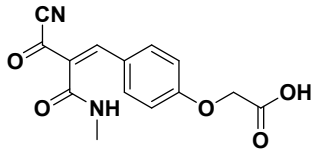
Synthesis of III-2

Methylmalondimide (1.25 eq, 2.5 mmol, 245 mg), 4-formylphenoxyacetic acid (1.0 eq, 2.0 mmol, 360 mg), piperidine (0.14 eq, 0.28 mmol, 29 μL) acetic acid (0.42 eq, 0.83 mmol, 47 μL) were added to 10 mL of toluene and reflux at 120 ℃ until the raw material is consumed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 2.2 Hz, 1H), 7.46 (s, 1H), 6.96 (d, J = 9.0 Hz, 2H), 4.74 (s, 2H), 3.73 (s, 3H). HRMS (ESI) calculated for $C_{13}H_{13}NO_6Na[M+Na]^+$ 302.0641, found 302.0620.



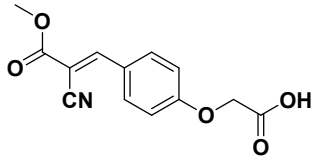
Synthesis of III-3

Malondimide (1.2 eq, 2.4 mmol, 244.8 mg), p-neneneba methoxy Benzaldehyde (1.0 eq, 2.0 mmol, 243 μL) Piperidine (0.14 eq, 0.28 mmol, 29 μL) Acetic acid (0.42 eq, 0.83 mmol, 47 μL) were added to 10 mL of toluene and reflux at 120 ℃ until the raw material is consumed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.46 (s, 1H), 7.25 (s, 1H), 7.23 (s, 1H), 6.96 (d, J = 8.9 Hz, 2H), 3.78 (s, 3H).



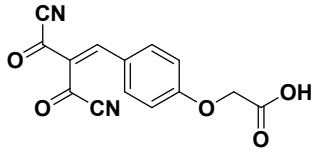
Synthesis of III-4

2-Cyano-N-methylacetamide (1.25 eq, 2.5 mmol, 245 mg), 4-formylphenoxyacetic acid (1.0 eq, 2.0 mmol, 360 mg), piperidine (0.14 eq, 0.28 mmol, 29 μL) acetic acid (0.42 eq, 0.83 mmol, 47 μL) were added to 10 mL of toluene and reflux at 120 ℃ until the raw material is consumed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford light yellow solid (495.5mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 4.6 Hz, 1H), 8.10 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 4.81 (s, 2H), 2.75 (d, J = 4.5 Hz, 3H). HRMS (ESI) calculated for $C_{13}H_{13}N_2O_4$[M+H]$^+$ 261.0875, found 261.0871.



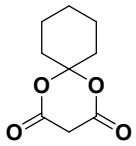
Synthesis of III-5

Methyl cyanoacetate (1.25 eq, 2.5 mmol, 247.5 mg), 4-formylphenoxyacetic acid (1.0 eq, 2.0 mmol, 360 mg), piperidine (0.14 eq, 0.28 mmol, 29 μL) acetic acid (0.42 eq, 0.83 mmol, 47 μL) were added to 10 mL of toluene and reflux at 120 ℃ until the raw material is consumed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 4.64 (s, 2H), 3.83 (s, 3H). HRMS (ESI) calculated for $C_{13}H_{11}NO_5Na$[M+Na]$^+$ 284.0535, found 284.2946.



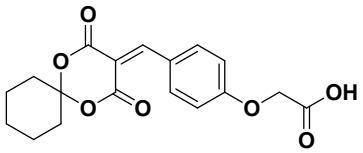
Synthesis of III-6

Malononitrile (1.05 eq, 2.1 mmol, 138.6 mg), 4-formylphenoxyacetic acid (1 eq, 2.0 mmol, 360 mg), piperidine (0.14 eq, 0.28 mmol, 29 μL) acetic acid (0.42 eq, 0.83 mmol, 47 μL) were added to 10 mL of toluene and reflux at 120 ℃ until the raw material is consumed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford light yellow solid (84.6 mg, 18.6%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 4.59 (s, 2H). HRMS (ESI) calculated for $C_{12}H_9N_2O_3$[M+H]$^+$ 229.0613, found 229.1411.



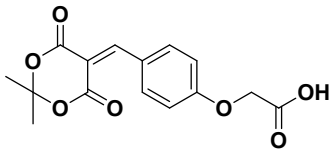
Synthesis of SD

Malonic acid (1.0 eq, 6 mmol, 624 mg), p-toluenesulfonic acid (0.02 eq, 1.6 mmol, 17.2 mg), cyclohexanone (1.0 eq, 6 mmol, 618 μL), and 2 mL acetic anhydride were added into a 25 mL round-bottom flask. The reaction was stirred at 30 ℃ for 3 hours. The reaction solution was stopped by adding 30 ml saturated Na_2CO_3 solution and washed with 20 mL DCM for 3 times. The combined organic layers were washed by aqueous saturated NaCl solution (20 mL), then dried over sodium sulfate, filtered, and the solvent was evaporated. The crude product was purified by column chromatography white solid 331.8 mg was obtained by silica gel column chromatography [petroleum ether/ethyl acetate = 15:1 (v/v)] to afford white solid (331.8 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 2H), 2.01 (m, 4H), 1.78 (s, 4H), 1.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.90, 107.13, 99.91, 36.44, 23.98, 22.13.



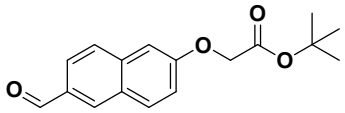
Synthesis of III-7

4-formylphenoxyacetic acid (1.0 eq, 1 mmol, 144 mg) was added to 5 mL of water. The reaction was refluxed at 80 ℃, and then SD (1.0 eq, 1 mmol, 184 mg) was added and stirred for 2 hours. The reaction was monitored by TLC until it was completed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid (331.8 mg, 69.4%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.19 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 4.85 (s, 2H), 1.98 (t, J = 6.1 Hz, 4H), 1.64-1.56 (m, 4H), 1.48-1.42 (m, 2H). HRMS (ESI) calculated for $C_{18}H_{18}O_7Na$ $[M+Na]^+$ 369.0950, found 369.0965



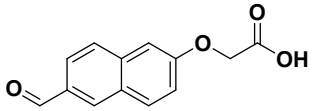
Synthesis of III-8

4-formylphenoxyacetic acid (1.0 eq, 2.5 mmol, 450 mg) was added to 10 mL of water. The reaction was refluxed at 80 ℃, and then cycloisopropyl malonic acid (1.0 eq, 2.5 mmol, 360 mg) was added and stirred for 2 hours. The reaction was monitored by TLC until it was completed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid (540 mg, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.20 (d, J = 9.1 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 4.85 (s, 2H), 1.74 (s, 6H). HRMS (ESI) calculated for $C_{15}H_{14}O_7Na$ $[M+Na]^+$ 329.0637, found 329.0646.



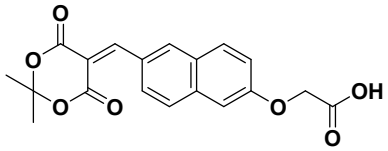
Synthesis of NQS-Boc

6-hydroxy-2-naphthaldehyde (1.0 eq, 1 mmol, 172 mg), K_2CO_3 (5.0 eq, 5 mmol, 690 mg) and tert-butyl Bromoacetic acid (1.0 eq, 1 mmol, 145 μL) were added in 5 mL DMF and stirred at 60 ℃ for 1 h. The reaction was cooled to room temperature and diluted with 10 mL of water, followed by extracting twice with 20 mL of ethyl acetate. The combined organic layers were washed by aqueous saturated NaCl solution (20 mL), then dried over sodium sulfate, filtered, and the solvent was evaporated. The crude product was purified by column chromatography [petroleum ether/ethyl acetate = 10:1 (v/v)] to obtain white solid (272.7 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.26 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.5 Hz, 1H), 7.31 (dd, J = 8.9, 2.5 Hz, 1H), 4.67 (s, 2H), 1.50 (s, 9H).



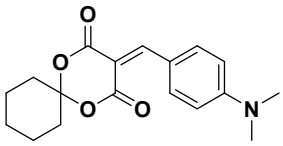
Synthesis of NQS

NQS-Boc (0.3 mmol, 100 mg) was dissolved in 7.5 ml of 20% TFA/DCM and stirred at room temperature for 2 hours to obtain a gray white solid solution. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.50 (s, 1H), 8.10 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 8.5, 1.7 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.34 (dd, J = 8.9, 2.5 Hz, 1H), 4.87 (s, 2H).



Synthesis of III-9

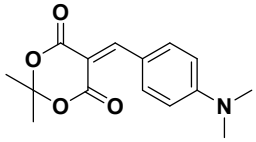
NQS (1.0 eq, 1 mmol, 230 mg) and cycloisopropyl malonic acid (2.0 eq, 2 mmol, 288 mg) was added into 6 mL of methanol and stirred for 2 hours. The reaction was monitored by TLC (PE: EA: FA=4:1:1 drop) until it was completed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid ethanol to obtain yellow solids (140 mg, 39%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.48 (s, 1H), 8.13 (dd, J = 8.8, 1.9 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 9.0, 2.5 Hz, 1H), 4.88 (s, 2H), 1.78 (s, 6H). HRMS (ESI) calculated for $C_{19}H_{17}O_7$ $[M+H]^+$ 357.0974, found 357.0975.



Synthesis of III-10

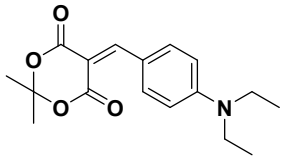
p-dimethylamine benzaldehyde (1.0 eq, 1 mmol, 149 mg) and SD (1.0 eq, 1 mmol, 184 mg) were added in 2 mL methanol and stirred at room temperature. The reaction

was monitored by TLC (PE: EA=4:1) until it was completed. The solid was filtered and washed with water for 2-3 times, and the dried, recrystallized with hot ethanol to afford yellow solid ethanol to obtain orange solids (286 mg, 90%).^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 8.9 Hz, 2H), 8.14 (s, 1H), 6.81 (d, J = 9.0 Hz, 2H), 3.13 (s, 6H), 1.93 (s, 4H), 1.60-1.57 (m, 4H), 1.44-1.42 (m, 2H). HRMS (ESI) calculated for $C_{18}H_{22}NO_4$ $[M+H]^+$ 316.1549, found 316.1561.



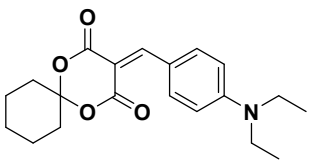
Synthesis of III-11

p-dimethylamine benzaldehyde (1.0 eq, 1 mmol, 149 mg) and Cycloisopropyl malonic acid (1.0 eq, 1 mmol, 144 mg) were added in 2 mL methanol and stirred at room temperature. The reaction was monitored by TLC (PE: EA=4:1) until it was completed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid ethanol to obtain orange solids (224 mg, 81.5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (d, J = 9.1 Hz, 2H), 8.16 (s, 1H), 6.85-6.74 (m, 2H), 3.13 (s, 6H), 1.69 (s, 6H). HRMS (ESI) calculated for $C_{15}H_{18}NO_4$ $[M+H]^+$ 276.1236, found 276.1245.



Synthesis of III-12

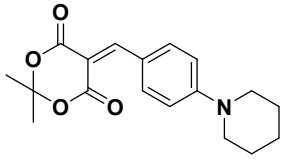
p-Diethylamino benzaldehyde (1.0 eq, 1 mmol, 177 mg) and Cycloisopropyl malonic acid (1.0 eq, 1 mmol, 144 mg) were added in 2 mL methanol and stirred at room temperature. The reaction was monitored by TLC (PE: EA=4:1) until it was completed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid ethanol to obtain orange solids (245 mg, 80.9%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 8.9 Hz, 2H), 8.12 (s, 1H), 6.80 (d, J = 8.9 Hz, 2H), 3.51 (q, J = 7.0 Hz, 4H), 1.68 (s, 6H), 1.14 (t, J = 7.0 Hz, 6H). HRMS (ESI) calculated for $C_{17}H_{22}NO_4$ $[M+H]^+$ 304.1549, found 304.1562.



Synthesis of III-13

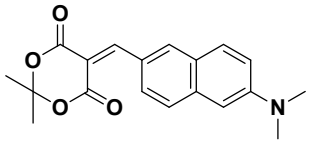
p-Diethylamino benzaldehyde (1.0 eq, 1 mmol, 177 mg) and Cycloisopropyl SD (1.0 eq, 1 mmol, 184 mg) were added in 2 mL methanol and stirred at room temperature.

The reaction was monitored by TLC (PE: EA=4:1) until it was completed. The solid was filtered and washed with water for 3 times, and the dried, recrystallized with hot ethanol to afford yellow solid ethanol to obtain orange solids. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 8.9 Hz, 2H), 8.11 (s, 1H), 6.80 (d, J = 9.0 Hz, 2H), 3.51 (q, J = 7.1 Hz, 4H), 1.92 (t, J = 5.9 Hz, 4H), 1.58 (p, J = 6.4, 5.9 Hz, 4H), 1.44 (q, J = 6.3, 5.8 Hz, 2H), 1.14 (t, J = 7.0 Hz, 6H). HRMS (ESI) calculated for $C_{20}H_{26}NO_4$ $[M+H]^+$ 344.1862, found 344.1878.



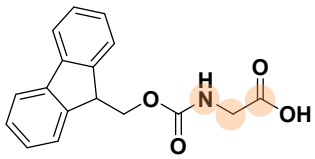
Synthesis of III-14

4-piperidine-1-yl benzaldehyde (1.0 eq, 1.0 mmol, 189 mg) was added into 5mL of water and refluxed at 80 ℃ until it was dissolved to colorless clear solution. Then cyclic (iminous) isopropyl malonic acid (1 eq, 1.0 mmol, 144 mg) was added and reacted for 4h. The reaction was washed with 20 mL EA and 20 mL saturated sodium chloride, and dry with anhydrous sodium sulfate. The crude product was purified by column chromatography [petroleum ether/ethyl acetate = 10:1 (v/v)] to obtain yellow solid (80 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.52 (s, 4H), 1.76 (s, 6H), 1.73-1.65 (m, 6H). HRMS (ESI) calculated for $C_{18}H_{22}NO_4$ $[M+H]^+$ 316.1549, found 316.1575.



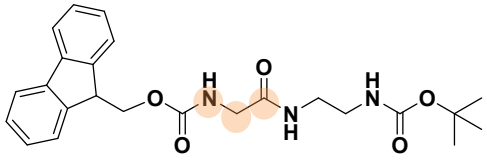
Synthesis of III-15

6-(dimethylamino)-2-naphthenal (1.0 eq, 0.25 mmol, 50.0 mg) and Cycloisopropyl malonic acid (1.0 eq, 0.25 mmol, 36.0 mg) were added in 4 mL methanol at dark and stirred at room temperature. The reaction was monitored by TLC (PE: EA=4:1) until it was completed. The solid was filtered and washed with water for 2-3 times, and the dried, recrystallized with hot ethanol to afford yellow solid ethanol to obtain reddish brown solids (60.0 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.50 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.16 (dd, J = 9.1, 2.6 Hz, 1H), 6.89 (s, 1H), 3.17 (s, 6H), 1.81 (s, 6H). HRMS (ESI) calculated for $C_{19}H_{20}NO_4$ $[M+H]^+$ 326.1392, found 326.1418.



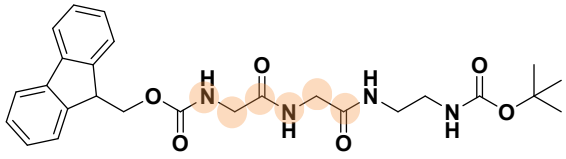
Synthesis of FG*

N-(9-Fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu, 1.1 eq, 2.2 mmol, 741.4 mg), Glysine-$^{13}C_2$,^{15}N (G′-OH, 1.0 eq, 2.0 mmol, 156.0 mg), sodium bicarbonate (1.0 eq, 2.0 mmol, 168.0 mg) were dissolved in a mixture of 15 mL water and 15 mL acetone and stirred at room temperature until the system was clear. 30 mL saturated potassium hydrogen sulfate solution was added and filtered. The residue was washed with 50 mL water for 4-5 times, dried. The solid was dissolved in ethyl acetate, filtered. Part of the filtrate was spin-dried and recrystallized by petroleum ether to obtain white solid (570.0 mg, 95.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.33 (td, J = 7.4, 1.2 Hz, 2H), 4.30 (d, J = 6.4 Hz, 2H), 4.23 (dd, J = 9.0, 4.8 Hz, 1H), 3.83 (t, J = 5.8 Hz, 1H), 3.48 (t, J = 5.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.58 (dd, J = 59.0, 24.8 Hz), 156.61, 143.84, 127.64, 127.09, 125.22, 120.13, 65.68, 46.61, 42.08 (dd, J =58.9, 13.3 Hz). HRMS (ESI) calculated for $C_{15}{}^{13}C_2H_{15}{}^{15}NO_4$ $[M+H]^+$ 301.1117, found 301.1109.



Synthesis of FG*B

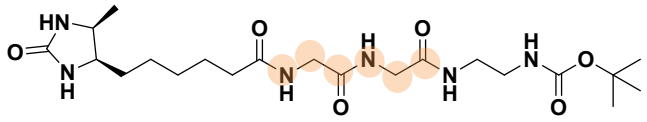
FG' (0.9 eq, 2.0 mmol, 600.0 mg), 4-Methylmorpholine (1.1 eq, 2.4 mmol, 264 μL), 2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (1.0 eq, 2.2 mmol, 836.0 mg) were added into 10 mL DMF. The reactive mixture was stirred under ice bath for 1-2 h. Then N-Boc-Ethylenediamine (1.0 eq, 2.2 mmol, 348.0 μL) was added and stirred for 1 h. The reaction solution was reacted overnight and washed with 100 mL ethyl acetate for four times. The combined organic layers were washed by aqueous saturated 30 mL NaCl solution, then dried over sodium sulfate, filtered, and the solvent was evaporated. The crude product was purified by column chromatography [petroleum ether/ethyl acetate = 1:1 (v/v)] to afford white solid (625.4 mg, 69.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, J = 7.6, 1.0 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.31 (dt, J = 7.5, 1.2 Hz, 2H), 6.98 (s, 1H), 5.61 (m, 2H), 4.43 (d, J = 7.0 Hz, 2H), 4.22 (t, J = 6.9 Hz, 1H), 4.05 (s, 1H), 3.71 (s, 1H), 3.38 (s, 2H), 3.32 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.87, 170.88 (d, J = 52.3 Hz), 157.35, 143.83, 141.48, 127.97, 127.28, 125.21, 120.21, 80.16, 67.55, 47.24, 44.57 (dd, J = 52.0, 13.7 Hz), 41.25, 40.14, 28.47. HRMS (ESI) calculated for $C_{22}{}^{13}C_2H_{30}N_2{}^{15}NO_5$ $[M+H]^+$ 443.2223, found 443.2207.



Synthesis of FG*G*B

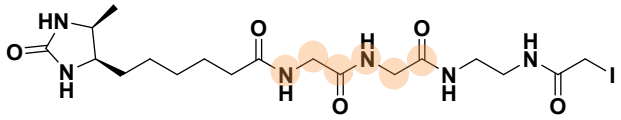
FG'B (1.0 eq, 1.4 mmol, 623.2 mg) was dissolved in a solution of 6 mL 40% diethylamine / DMF and stirred at room temperature for 2 h until the reaction was completed monitored by TLC. Diethylamine was removed to get solution A. FG' (0.9 eq, 1.3 mmol, 380.7 mg), NMM (1.1 eq, 1.6 mmol, 170.6 μL), HATU (1.0 eq, 1.4

mmol, 536.2 mg) in 5mL DMF was stirred under ice bath for 1 h to obtain solution B. Solution A was added into solution B to react for 1 h at 0 ℃. The reaction solution was reacted overnight and washed with 100 mL ethyl acetate for four times. The combined organic layers were washed by aqueous saturated 30 mL NaCl solution , then dried over sodium sulfate, filtered, and the solvent was evaporated. The crude product was purified by column chromatography [ethyl acetate/methanol = 40:1 (v/v)] to afford white solid (498.5 mg, 77.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.5 Hz, 2H), 7.82 (m, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.52 Hz, 2H), 7.33 (t, J = 7.38 Hz, 2H), 6.79 (m, 1H), 4.30 (d, J = 7.0 Hz, 2H), 4.23 (t, J = 7.0 Hz, 1H), 3.88 – 3.80 (m, 2H), 3.51-3.47 (m, 2H), 3.10-3.06 (m, 2H), 3.00-2.95 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.89, 169.36 (dd, J = 52.7, 14.9 Hz), 168.82 (dd, J = 52.5, 9.7 Hz), 155.62, 143.84, 140.74, 127.64, 127.09, 125.26, 120.12, 77.72, 65.76, 46.64, 43.54 (dt, J = 52.8, 11.8 Hz), 41.98 (dd, J = 52.5, 12.3 Hz), 40.02, 38.75, 28.22. HRMS (ESI) calculated for $C_{22}{}^{13}C_4H_{32}N_2{}^{15}N_2O_6$ $[M+H]^+$ 503.2475, found 503.2459.



Synthesis of DbG'G'B

FG'G'B (1.0 eq, 0.3 mmol, 131.0 mg) was dissolved in a solution A of 3 mL 40% diethylamine / DMF and stirred at room temperature for 2 h until the reaction was completed monitored by TLC. Diethylamine was removed. Triethylamine (5.0 eq, 1.5 mmol, 208.5 μL) was then added and reacted for 15 min under a nitrogen atmosphere followed by adding desthiobiotin N-hydroxysuccinimidyl ester (Db-NHS, 1.0 eq, 0.3 mmol, 93.4 mg). The reaction mixture was stirred overnight, evaporated to dryness and separated by RP-HPLC (Thermo Hypersil GOLD C18, 150 × 50 mm, 28% acetonitrile (0.1% TFA) in water (0.1% TFA) in an isogradient, 3 mL/min)). The product fraction was lyophilized to afford white solid (86.1 mg, 60.3%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 – 8.13 (m, 1H), 8.08 – 7.95 (m, 1H), 7.79 (d, J = 5.0 Hz, 1H), 6.78 (t, J = 5.7 Hz, 1H), 3.87 – 3.75 (m, 2H), 3.61 (m, 1H), 3.52 (m, 3H), 3.12 – 3.03 (m, 2H), 2.97 (m, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.50 (t, J = 7.4 Hz, 2H), 1.36 (s, 9H), 1.34 – 1.11 (m, 6H), 0.95 (d, J = 6.4 Hz, 3H). [DMF solvent residual peak: 7.94 (s), 2.88 (s), 2.72 (s)]. ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.11 (d, J = 13.1 Hz), 169.48 (dd, J = 52.9 Hz, 14.8 Hz), 168.98 (d, J = 52.8 Hz), 77.78, 55.13, 50.40, 42.30 (dt, J = 52.9, 11.1 Hz), 42.08 (dd, J = 52.2, 12.4 Hz), 40.40, 38.90, 35.19, 29.56, 28.80, 28.26, 25.68, 25.07, 15.51. [DMF solvent residual peak: 163.03]. HRMS (ESI) calculated for $C_{17}{}^{13}C_4H_{38}N_4{}^{15}N_2O_6$ $[M+H]^+$ 477.3006, found 477.2994.



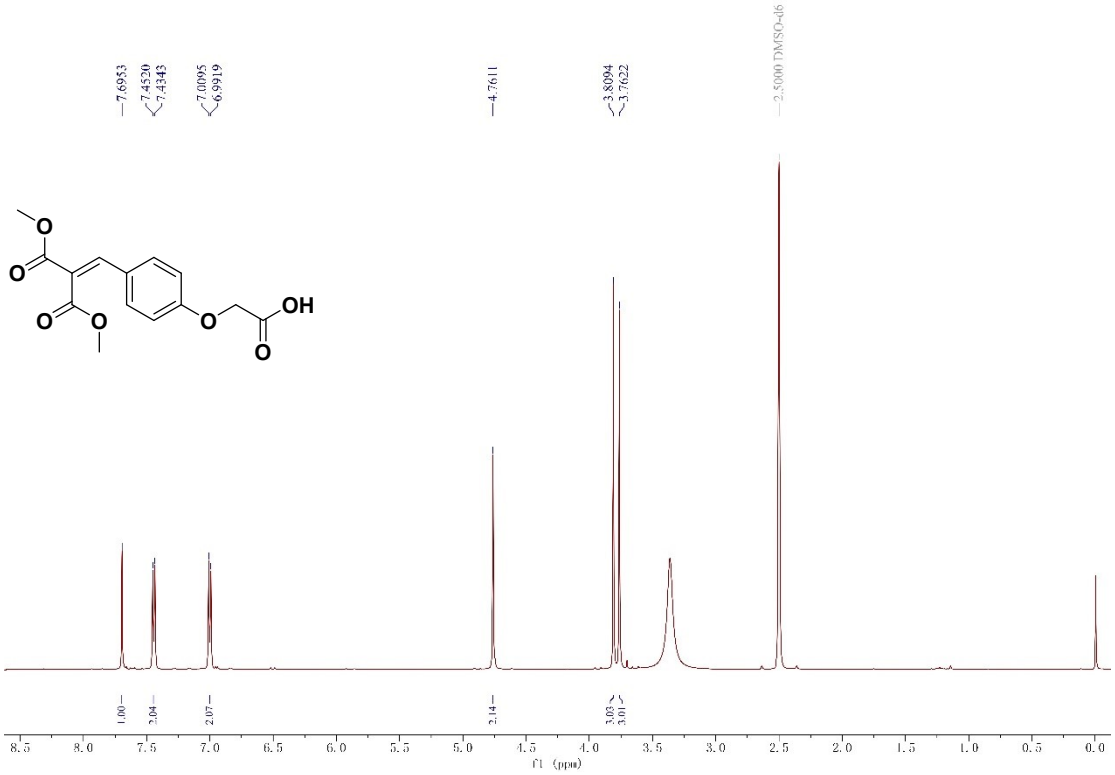
Synthesis of DbG'G'I

DbG'G'B (1.0 eq, 0.18 mmol, 86.5 mg) was dissolved in 8 mL 20% TFA/DCM (v/v) and stirred for 2 h at room temperature. TFA and DCM were then removed under reduced pressure. DIPEA was used to adjust pH to 8-9. Iodoacetic anhydride (1.2 eq,

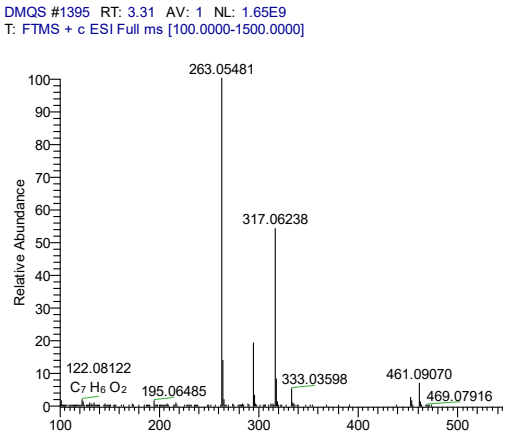
0.22 mmol, 77.9 mg) and DIEPA (1.6 eq, 0.29 mmol, 47.8 μL) were added to a solution of 3 mL DCM and 6 mL DMF at 0 ℃ under argon protection. The reaction was stirred in the dark until it was completed detected by RP-HPLC (Thermo Hypersil GOLD C18, 150 × 50 mm, 5-95% acetonitrile (0.1% TFA) in water (0.1% TFA) in a linear gradient over 30 min, 3 mL/min, t_R = 9.47 min). The reaction mixture was evaporated to dryness and separated by RP-HPLC (Thermo Hypersil GOLD C18, 150 × 50 mm, 21% acetonitrile (0.1% TFA) in water (0.1% TFA) in an isogradient, 3 mL/min)). The product fraction was lyophilized to afford white solid (50.0 mg, 51.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (m, 1H), 8.19 (m, 1H), 7.96 (m, 1H), 7.85-7.80 (m, 1H), 3.89-3.81 (m, 2H), 3.62 (s, 2H), 3.54-3.46 (m, 4H), 3.10 (m, 4H), 2.13 (t, J = 7.4 Hz, 2H), 1.50 (p, J = 7.4 Hz, 2H), 1.38-1.20 (m, 6H), 0.95 (d, J = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.58 (dd, J = 209.61, 59.04 Hz), 169.23 (dd, J = 209.61, 59.10 Hz), 168.91 (d, J = 208.74 Hz), 167.88, 162.81, 54.97, 50.22, 42.24 (m), 41.89 (m), 38.67, 38.03, 35.06, 29.52, 28.74, 25.61, 25.01, 15.52, 0.72. HRMS (ESI) calculated for $C_{14}{}^{13}C_4H_{31}IN_4{}^{15}N_2O_5$ $[M+H]^+$ 545.1554, found 545.1550.

Appendix

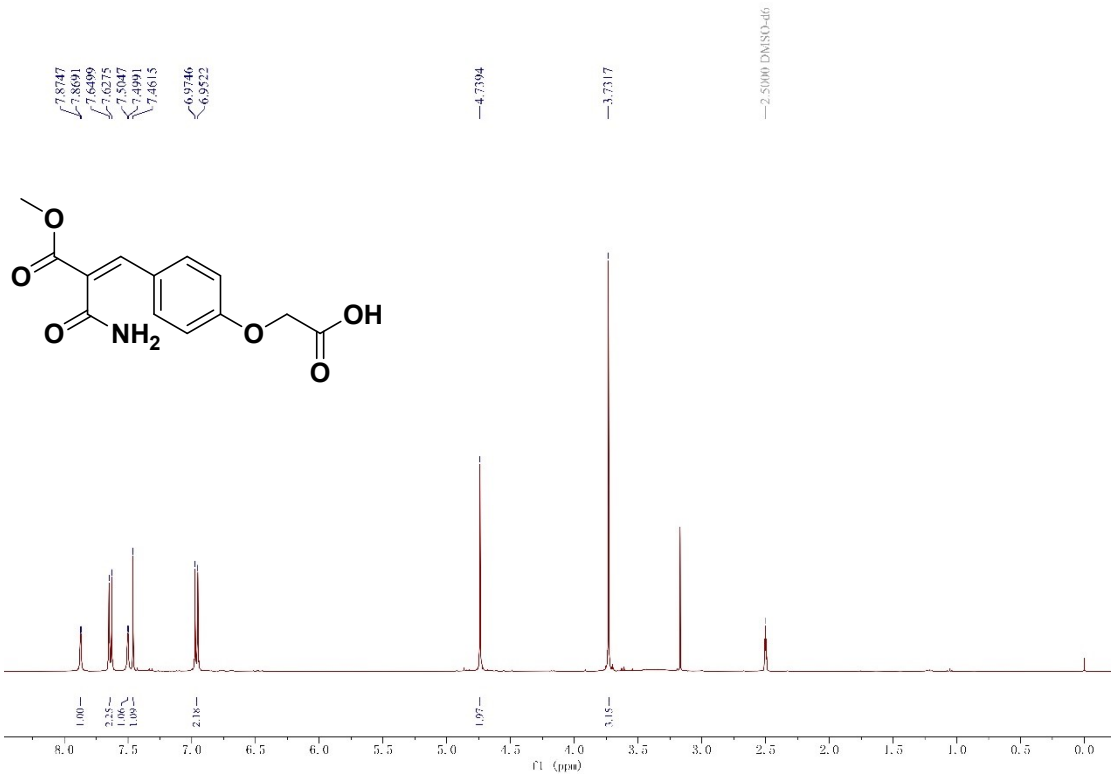
NMR Spectra and ESI/HRMS



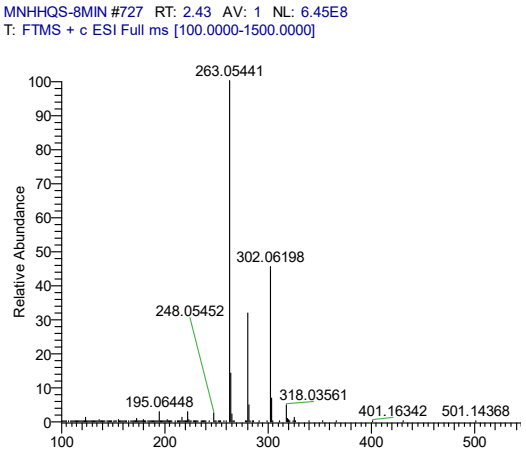
^{1}H NMR spectrum of **III-1** in DMSO-d_6



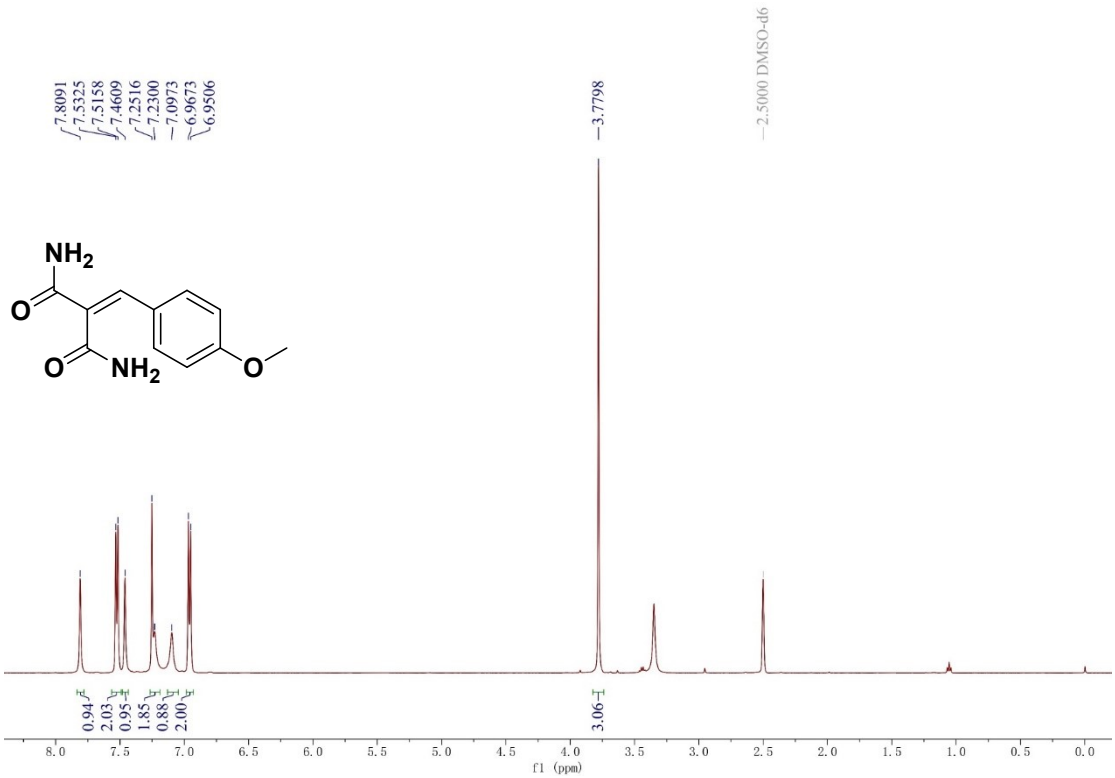
ESI/HRMS spectrum of **III-1**



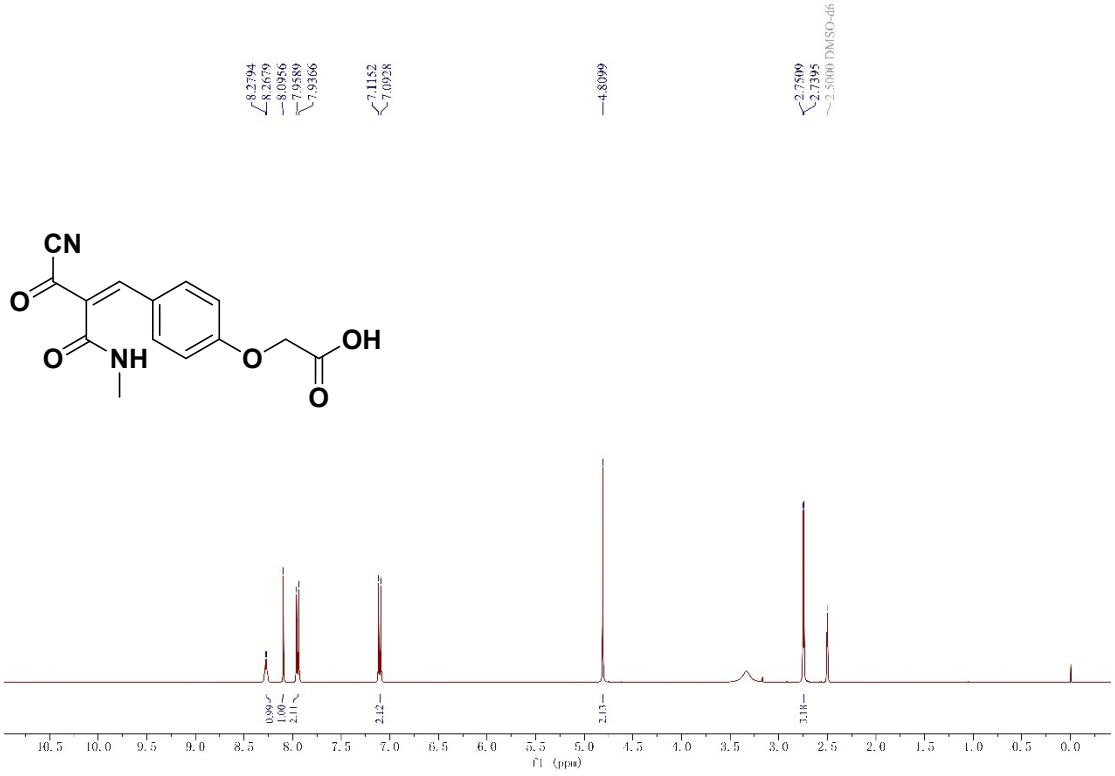
^{1}H NMR spectrum of **III-2** in DMSO-d_6



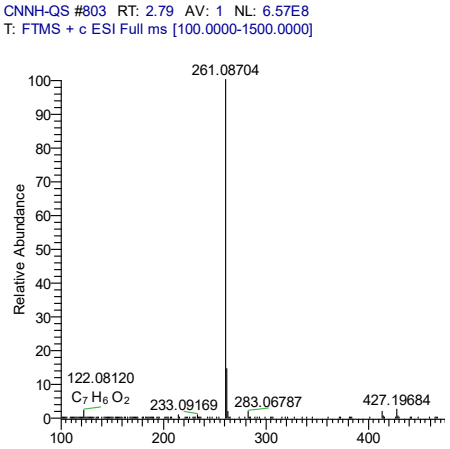
ESI/HRMS spectrum of **III-2**



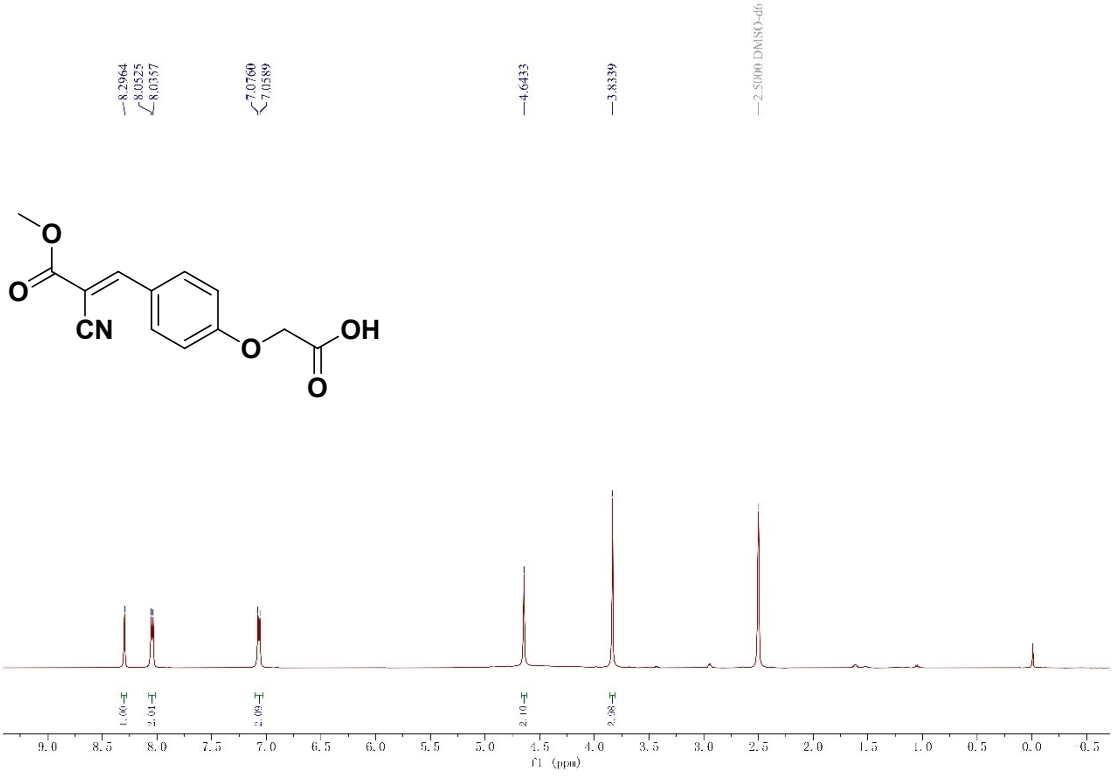
^{1}H NMR spectrum of **III-3** in DMSO-d_6



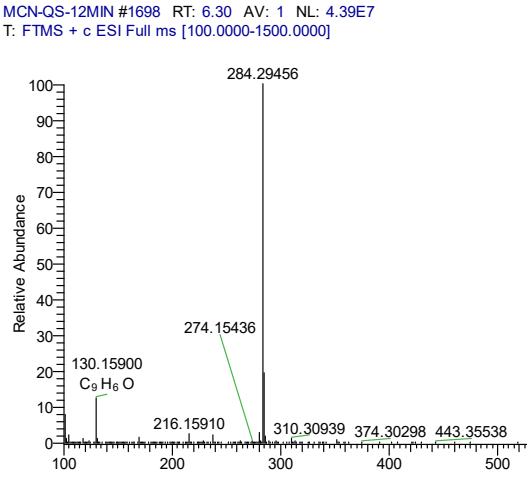
^{1}H NMR spectrum of **III-4** in DMSO-d_6



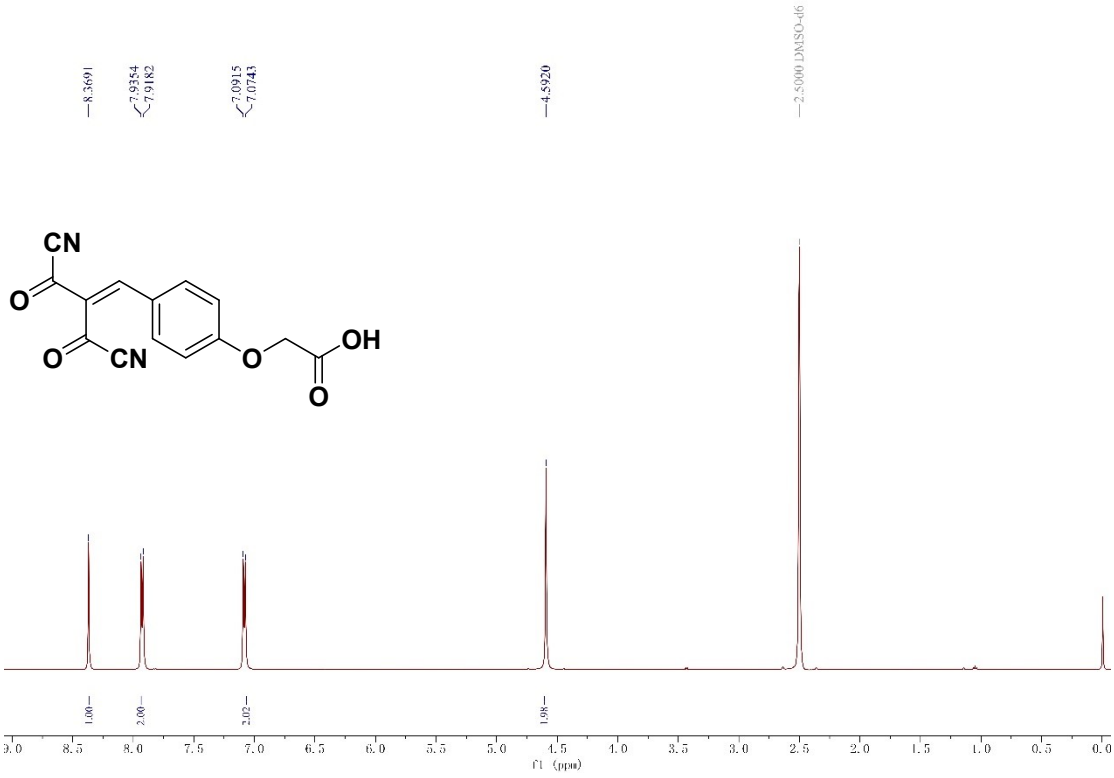
ESI/HRMS spectrum of **III-4**



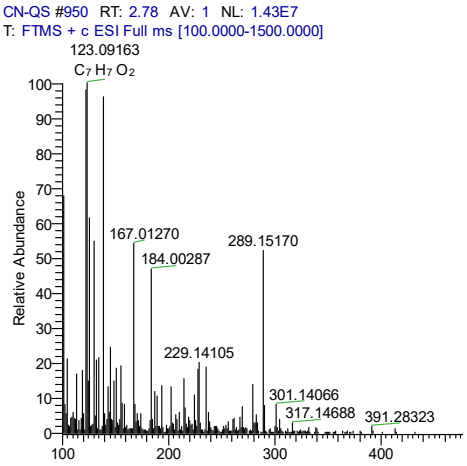
^{1}H NMR spectrum of **III-5** in DMSO-d_6



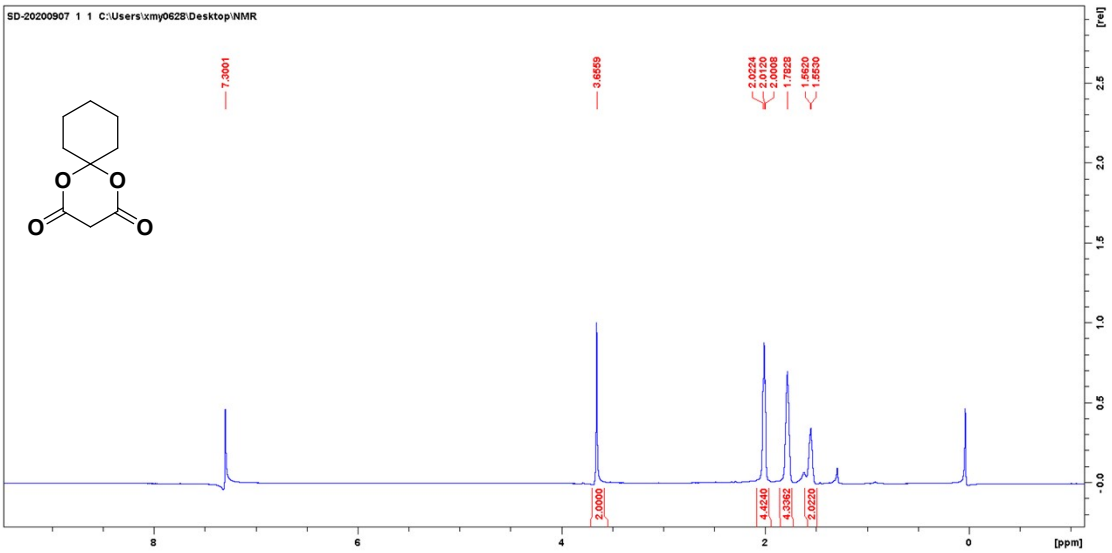
ESI/HRMS spectrum of **III-5**



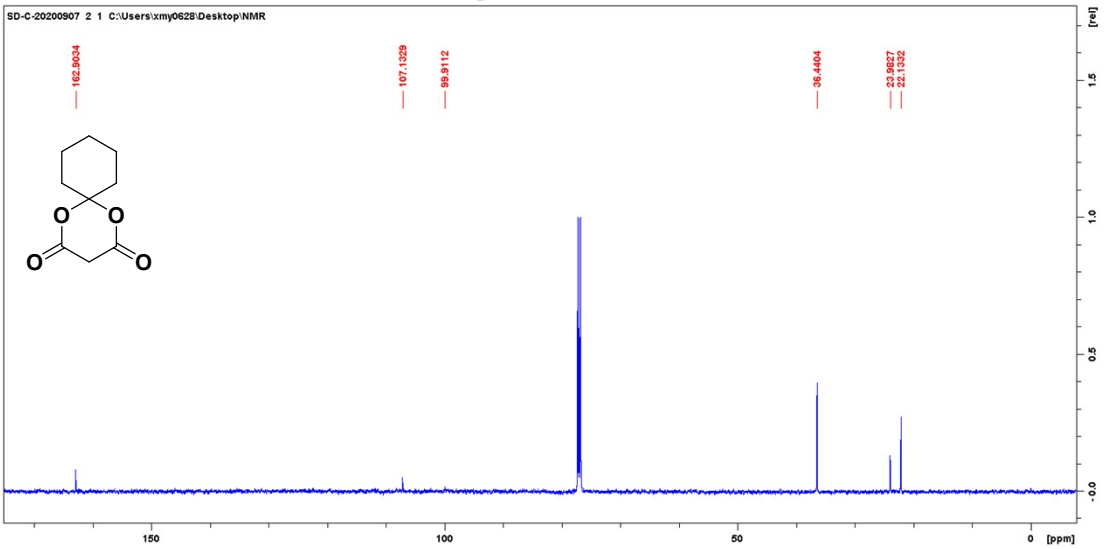
^{1}H NMR spectrum of **III-6** in DMSO-d_6



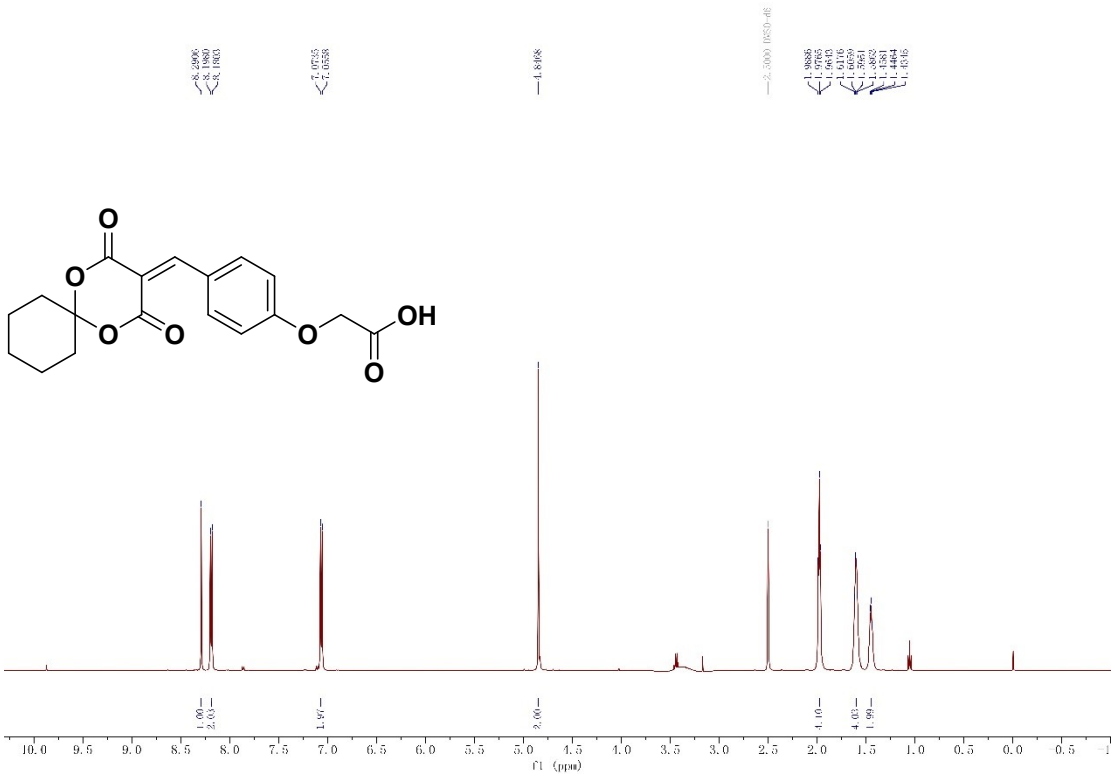
ESI/HRMS spectrum of **III-6**



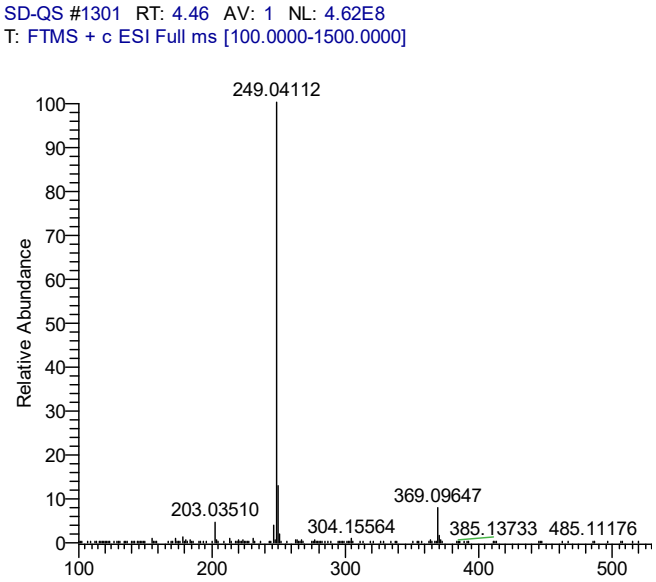
^{1}H NMR spectrum of **SD** in $CDCl_3$



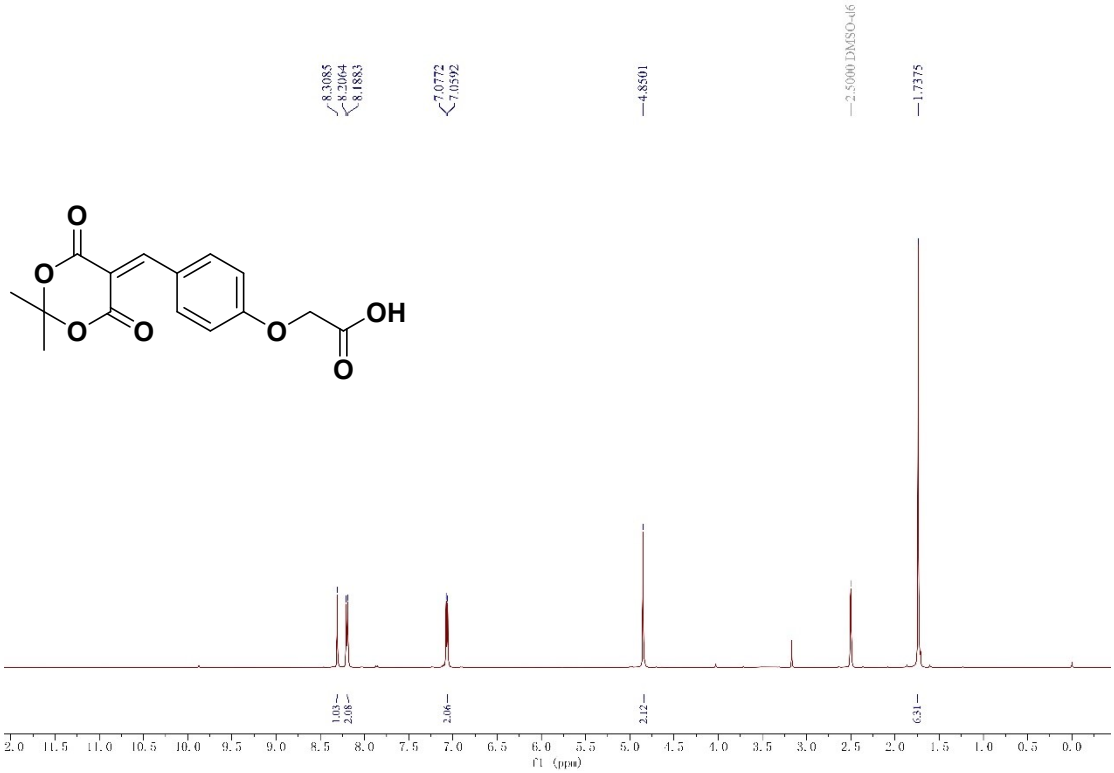
^{13}C NMR spectrum of **SD** in $CDCl_3$



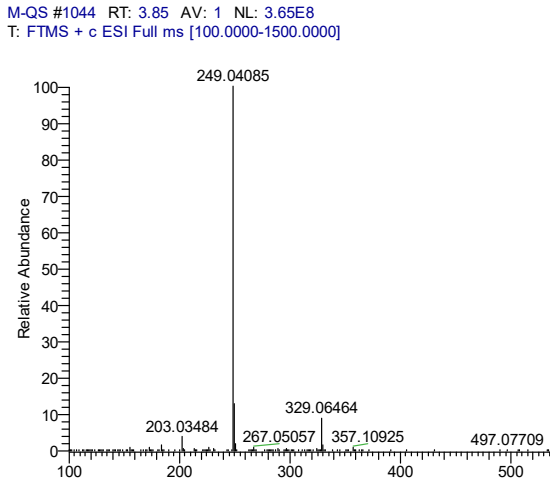
^{1}H NMR spectrum of **III-7** in DMSO-d_6



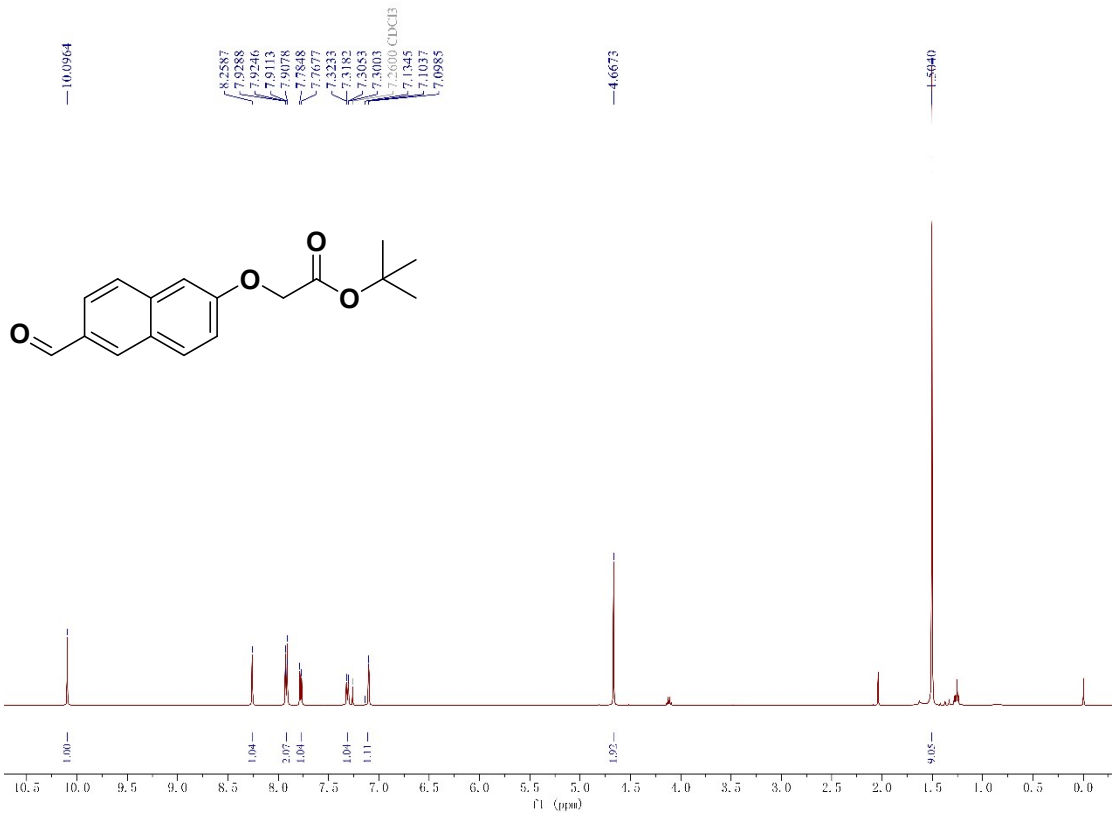
ESI/HRMS spectrum of **III-7**



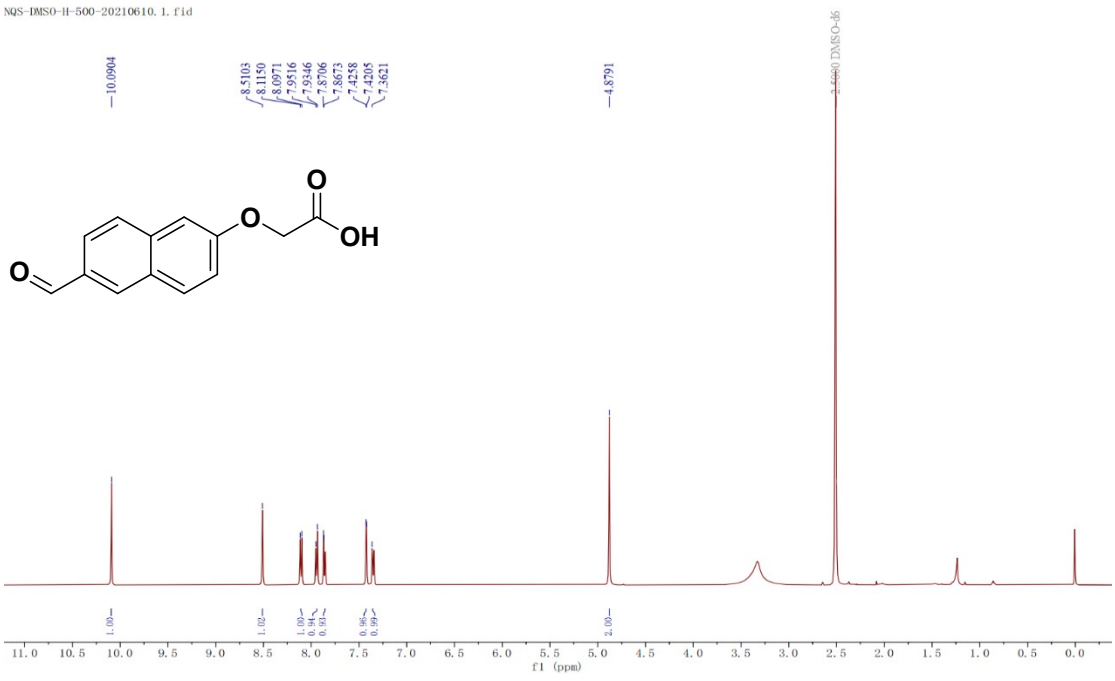
^{1}H NMR spectrum of **III-8** in DMSO-d_6



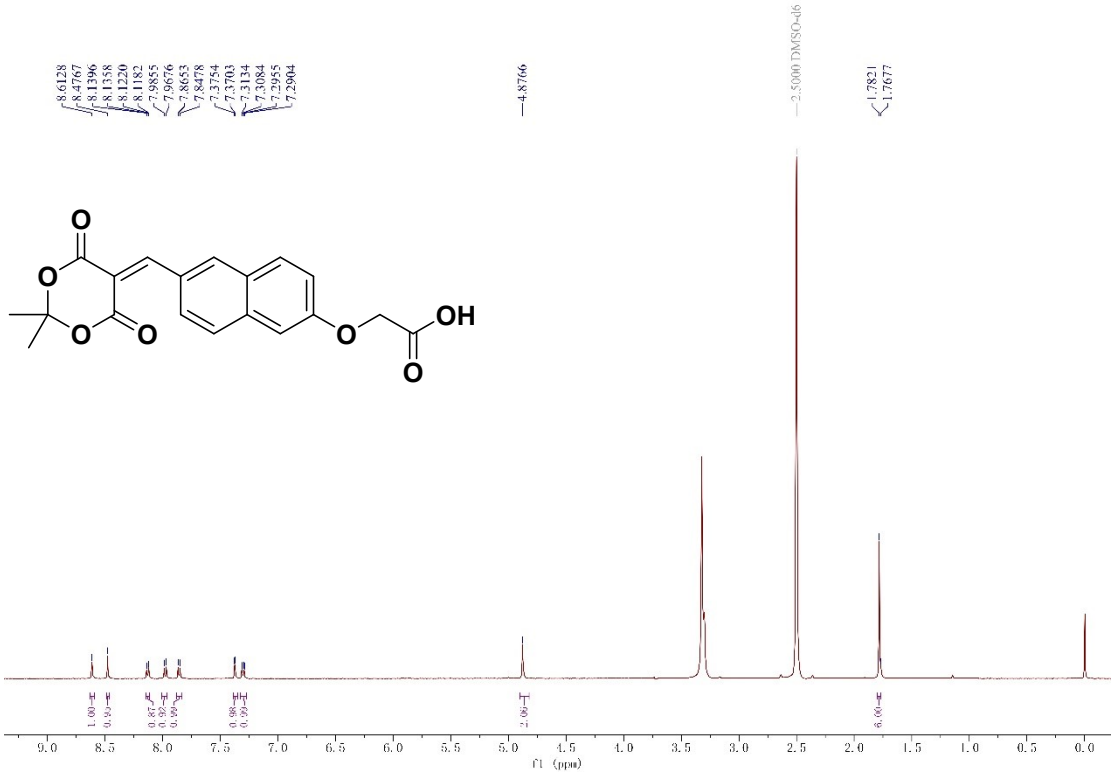
ESI/HRMS spectrum of **III-8**



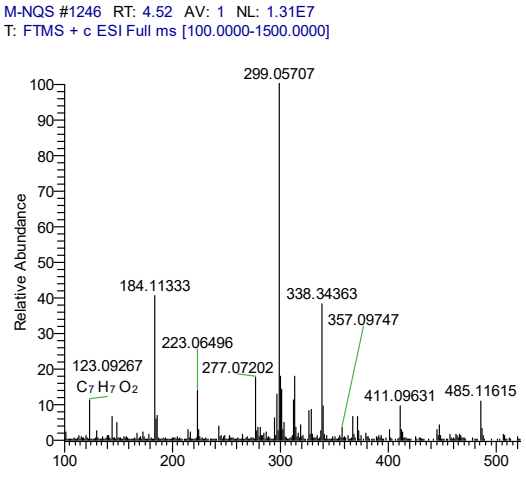
^{1}H NMR spectrum of **NQS-Boc** in $CDCl_3$



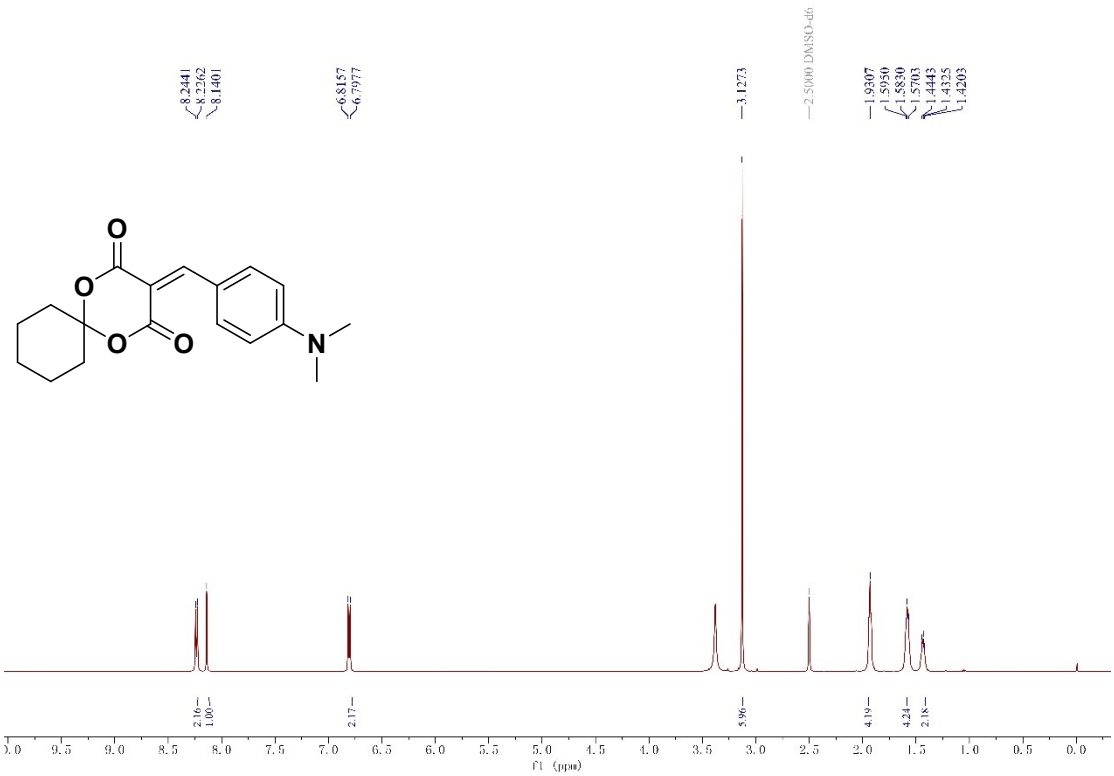
^{1}H NMR spectrum of **NQS** in DMSO-d_6



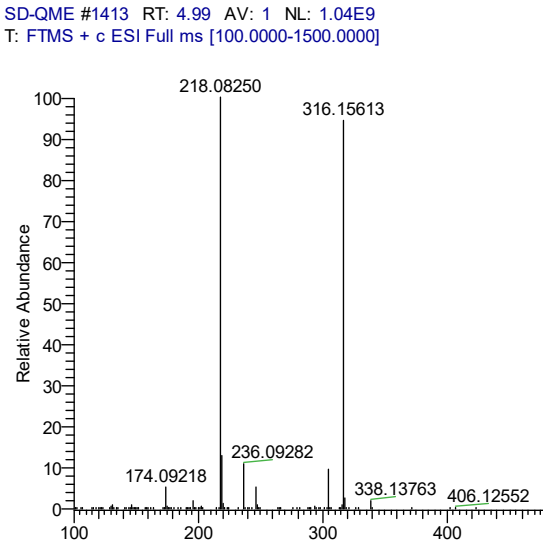
^{1}H NMR spectrum of **III-9** in DMSO-d_6



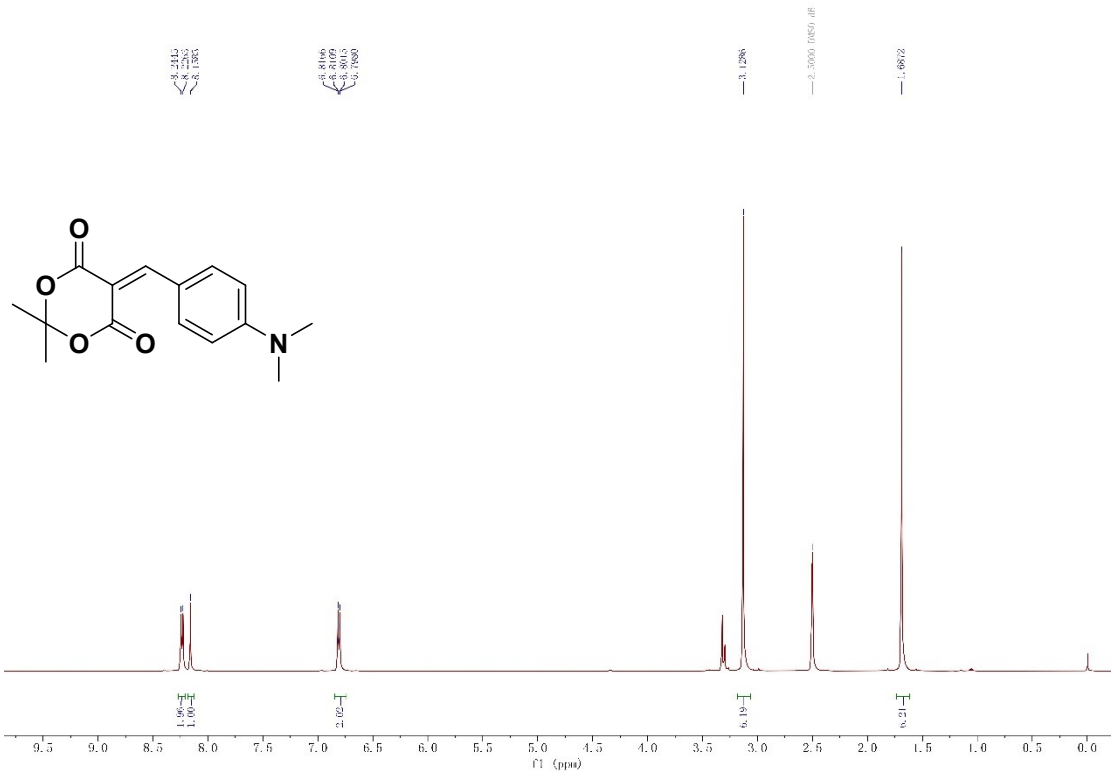
ESI/HRMS spectrum of **III-9**



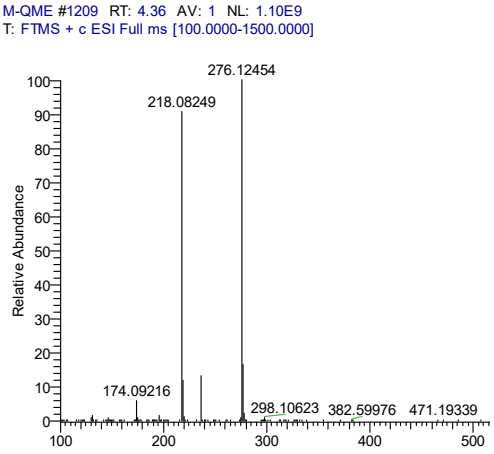
^{1}H NMR spectrum of **III-10** in DMSO-d_6



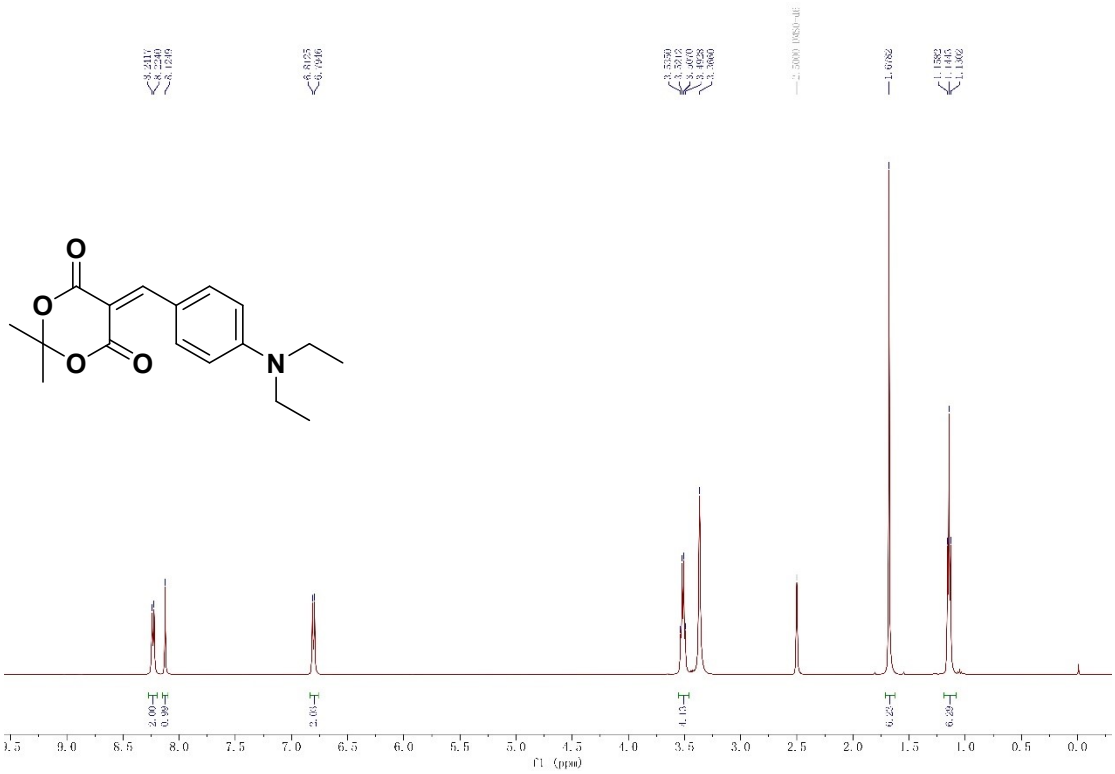
ESI/HRMS spectrum of **III-10**



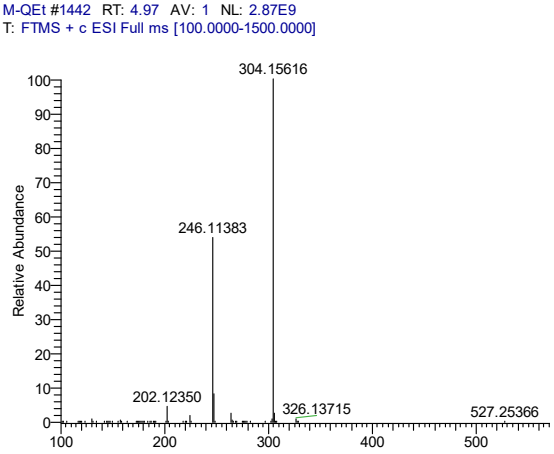
^{1}H NMR spectrum of **III-11** in DMSO-d_6



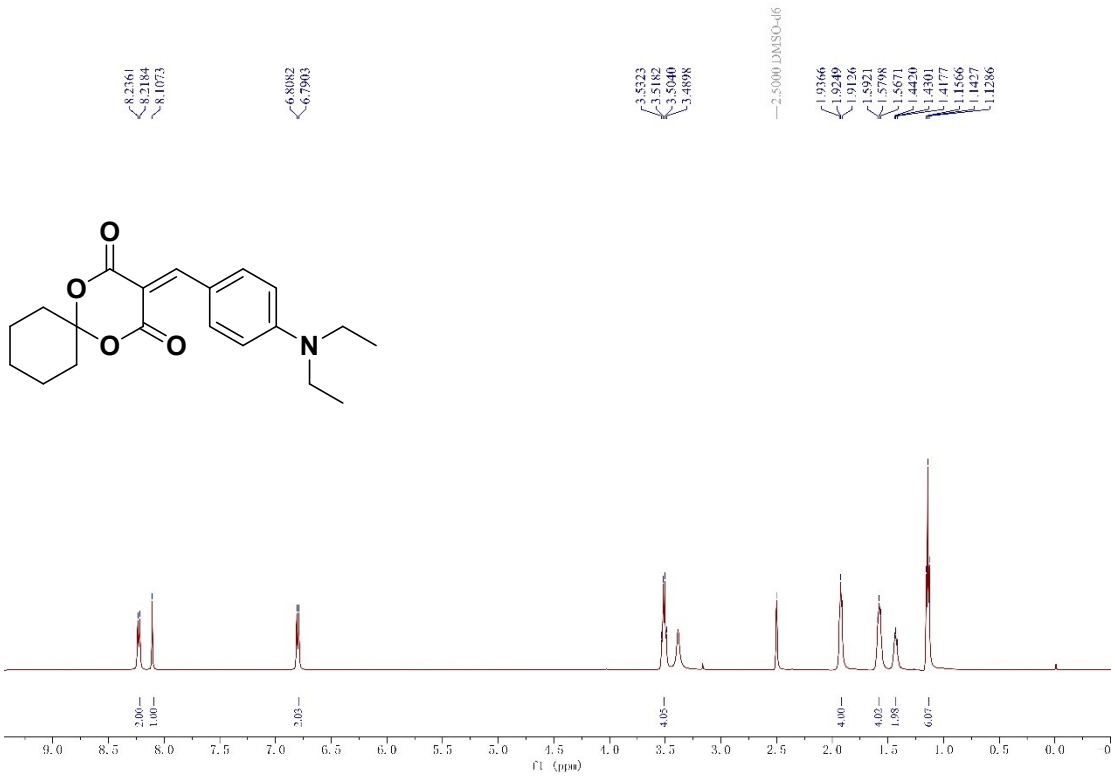
ESI/HRMS spectrum of **III-11**



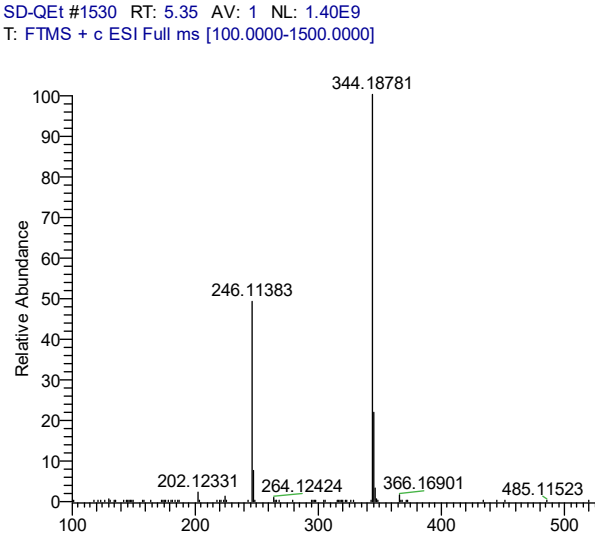
^{1}H NMR spectrum of **III-12** in DMSO-d_6



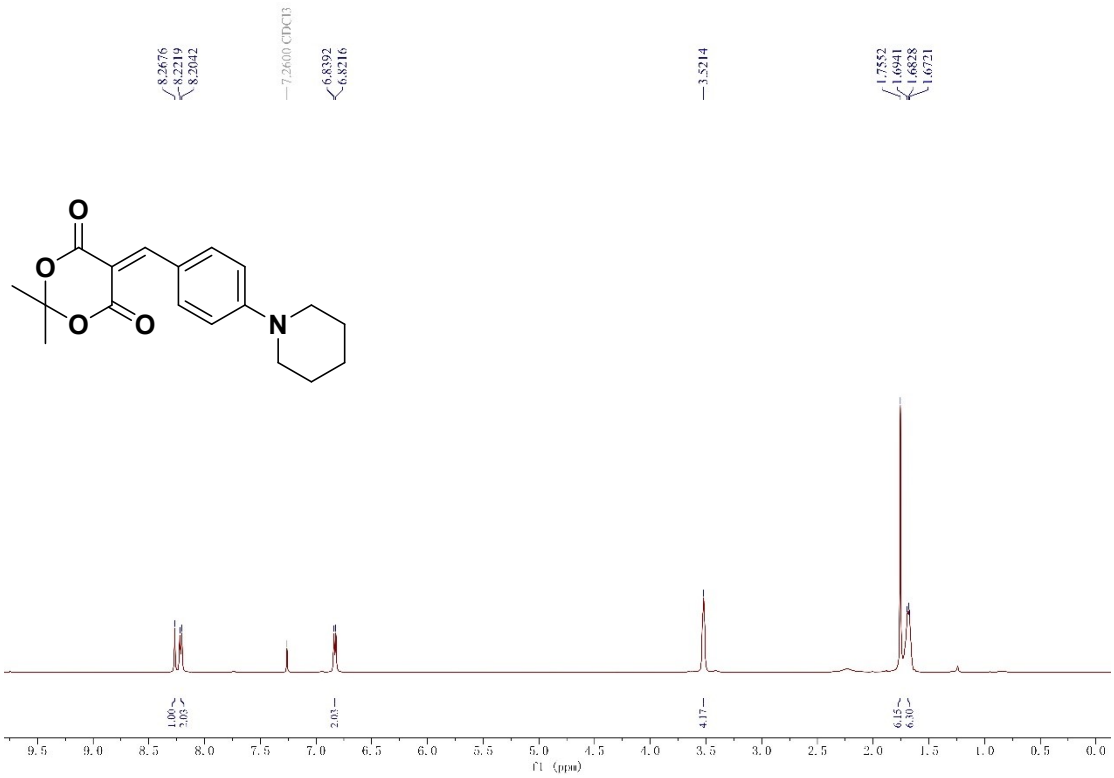
ESI/HRMS spectrum of **III-12**



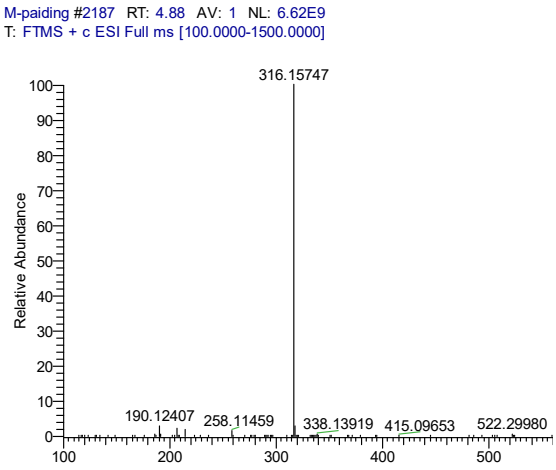
^{1}H NMR spectrum of **III-13** in DMSO-d_6



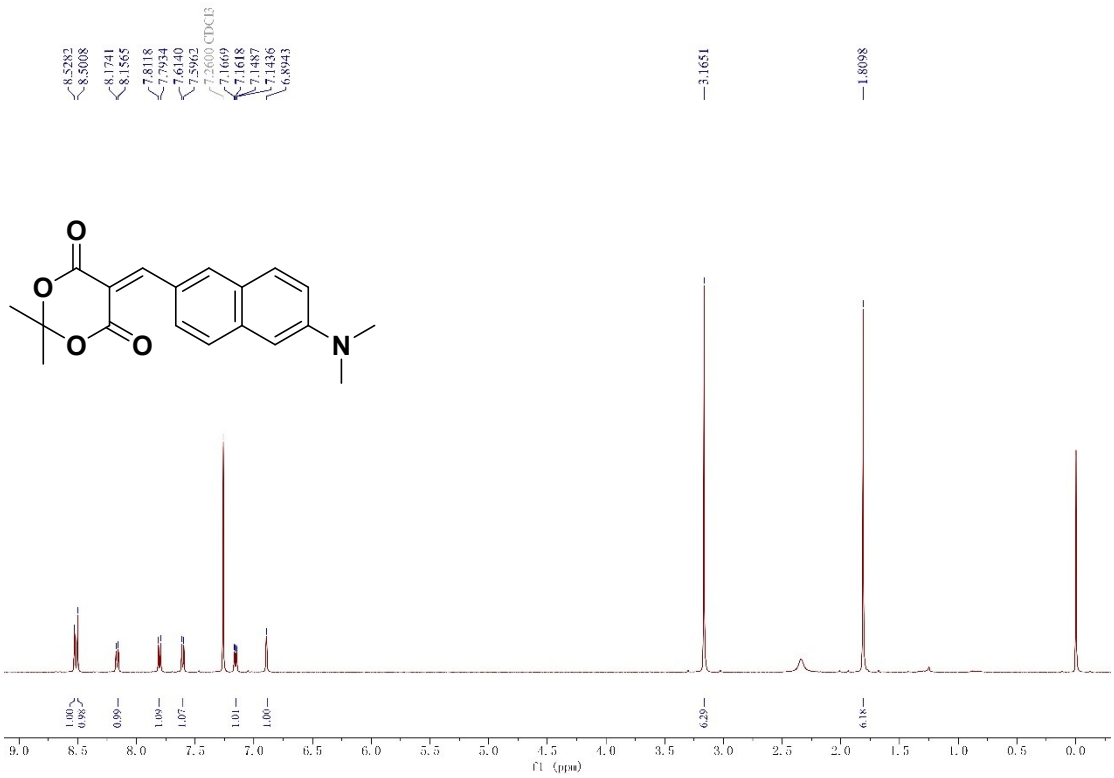
ESI/HRMS spectrum of **III-13**



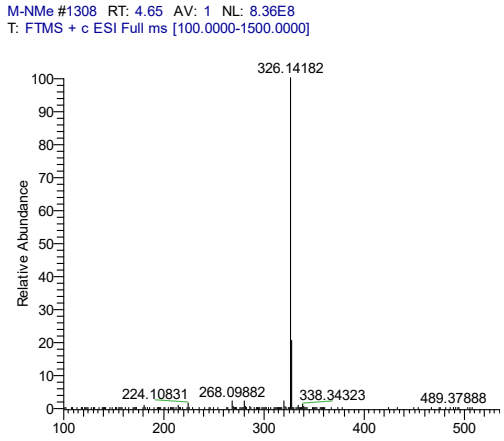
^{1}H NMR spectrum of **III-14** in $CDCl_3$



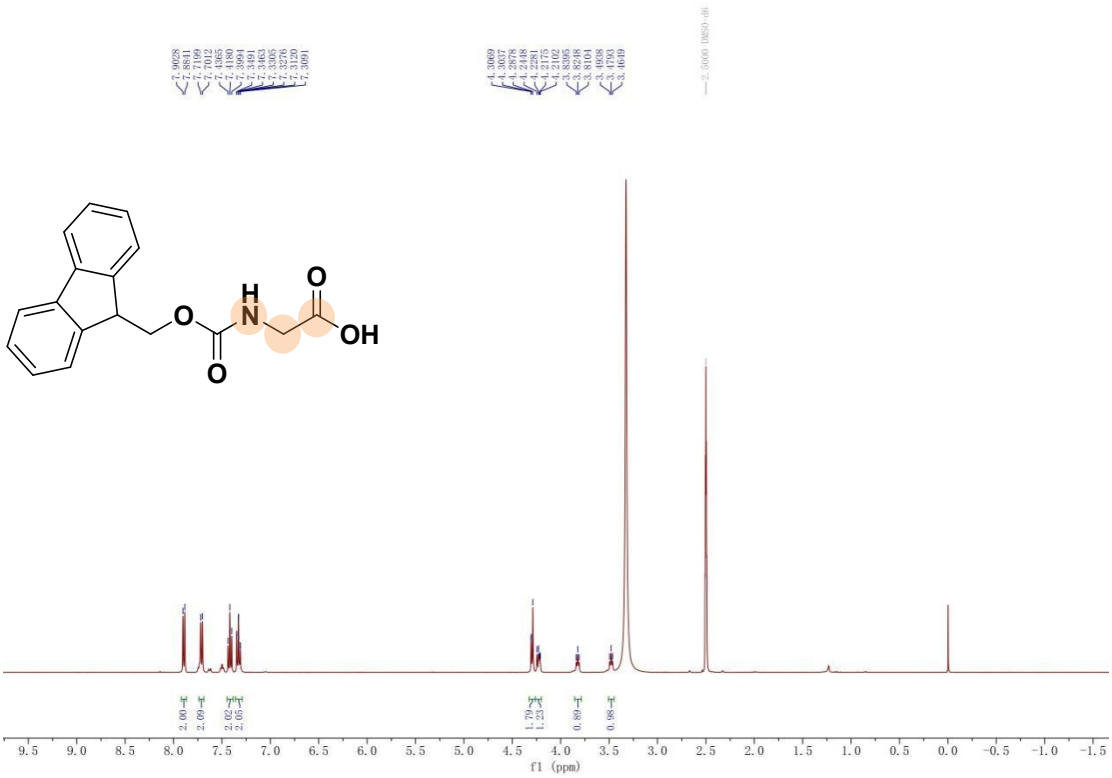
ESI/HRMS spectrum of **III-14**



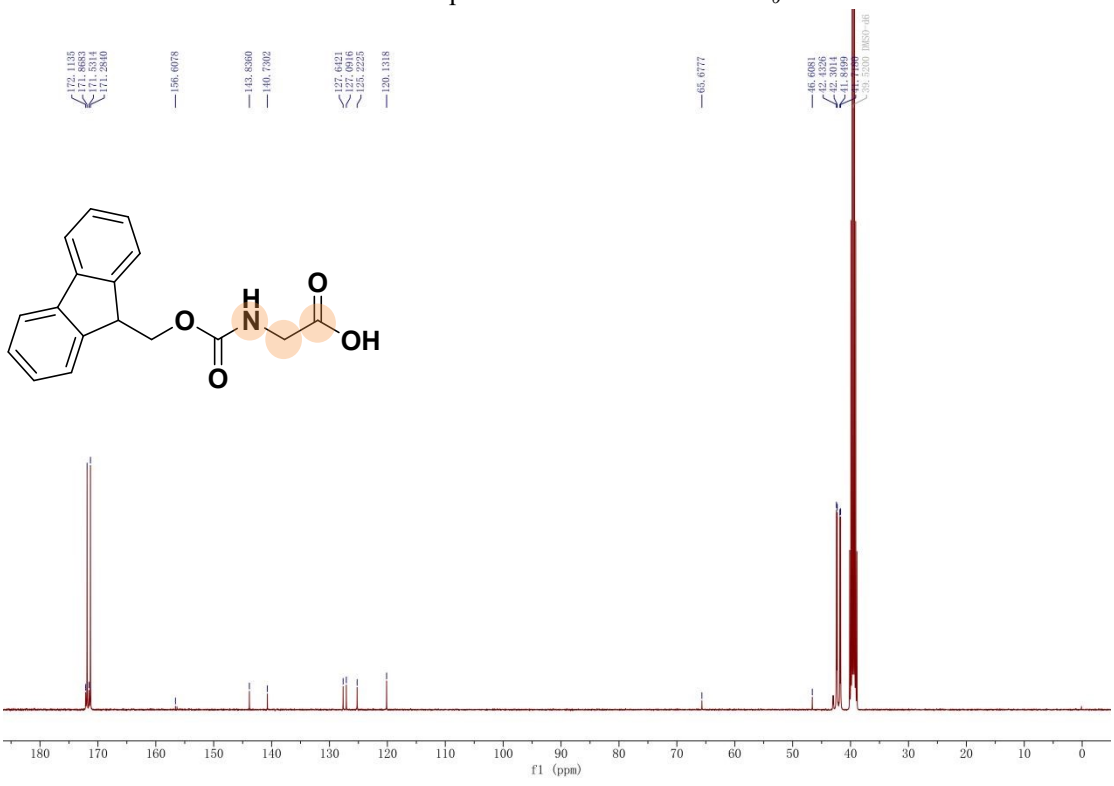
^{1}H NMR spectrum of **III-15** in $CDCl_3$



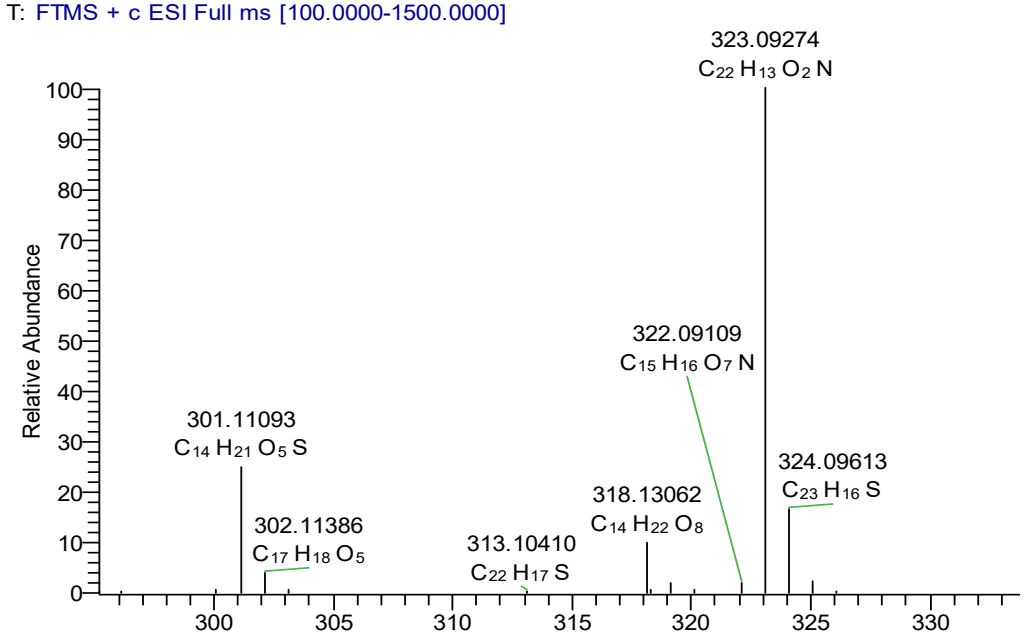
ESI/HRMS spectrum of **III-15**



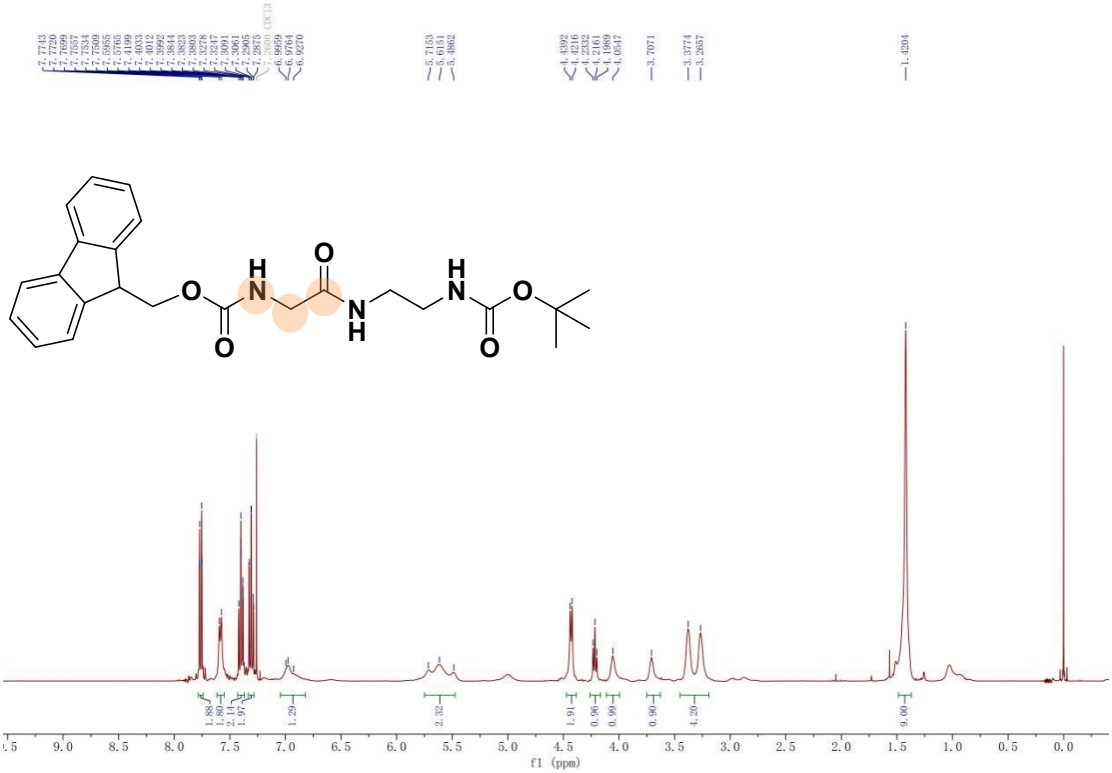
^{1}H NMR spectrum of **FG*** in DMSO-d_6



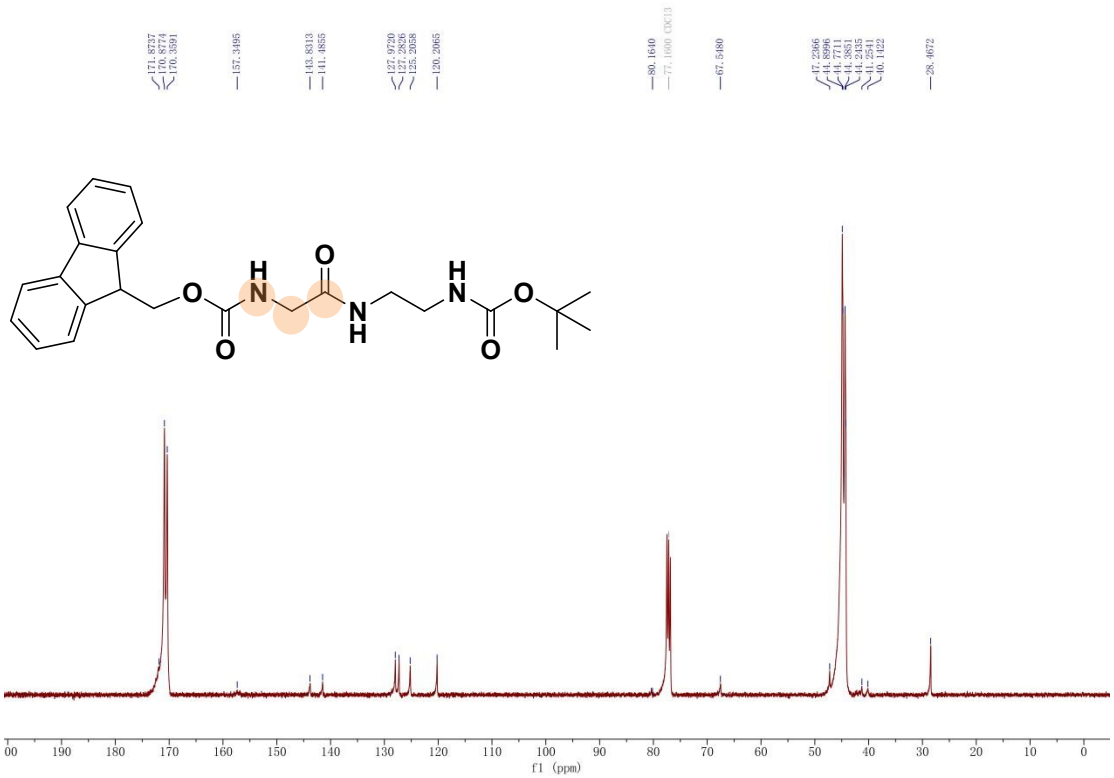
^{13}C NMR spectrum of **FG*** in DMSO-d_6



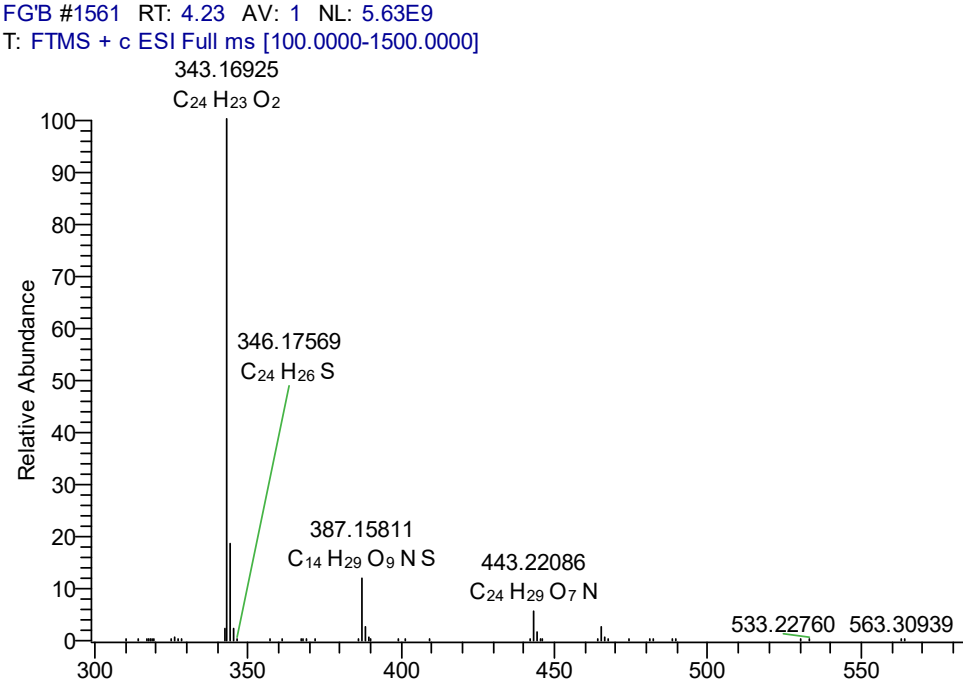
ESI/HRMS spectrum of **FG***



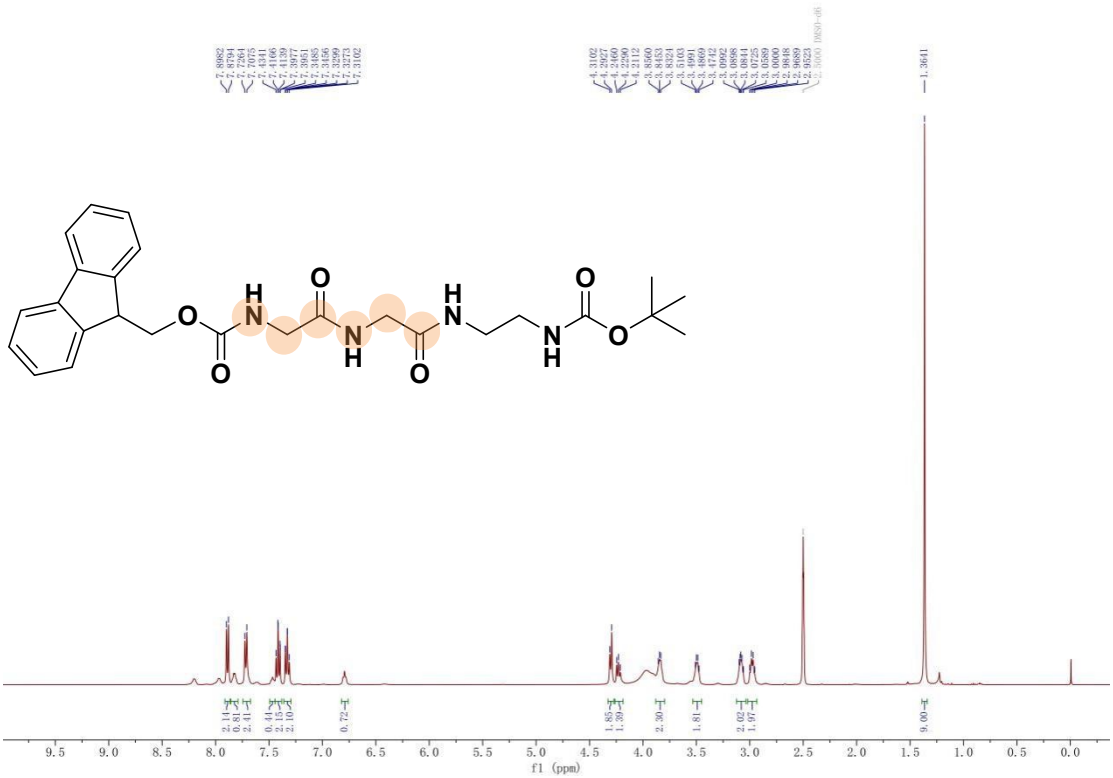
^{1}H NMR spectrum of **FG*B** in $CDCl_3$



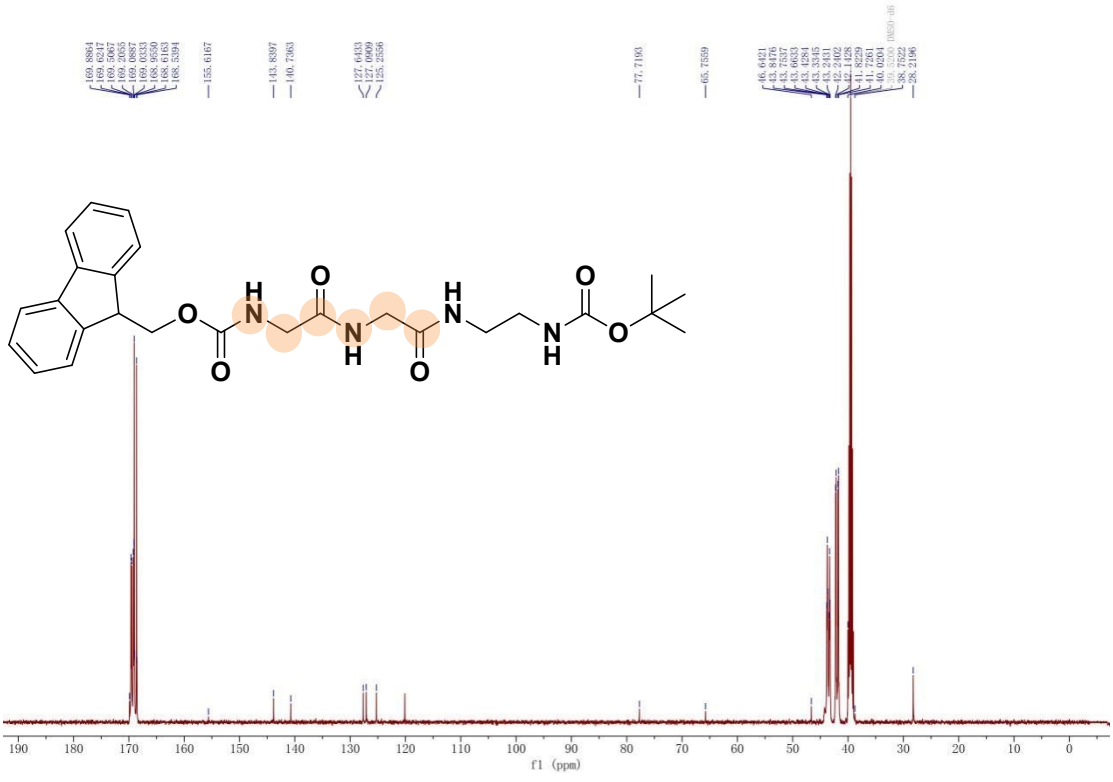
^{13}C NMR spectrum of **FG*B** in $CDCl_3$



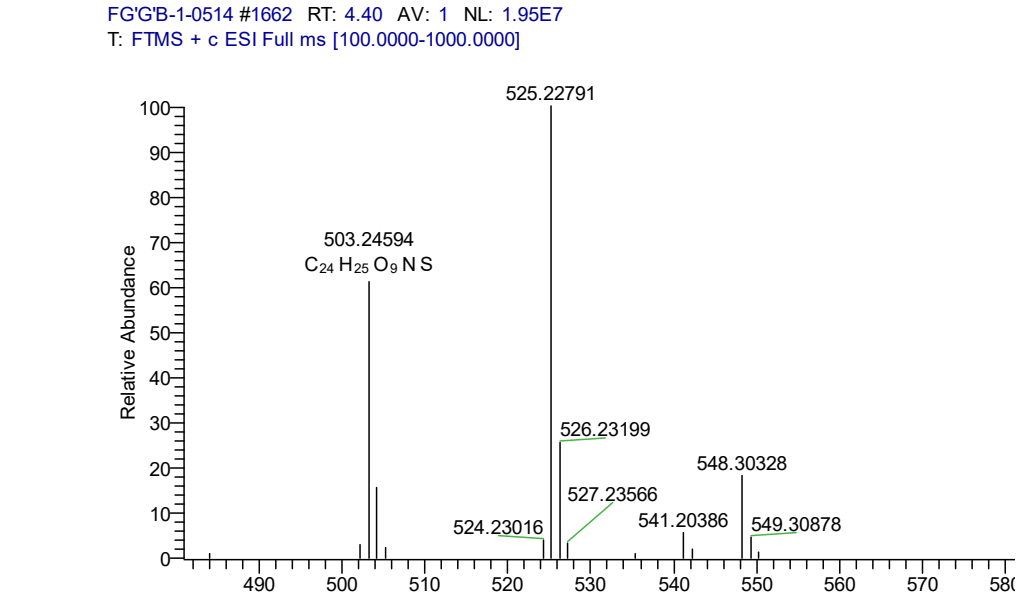
ESI/HRMS spectrum of **FG*B**



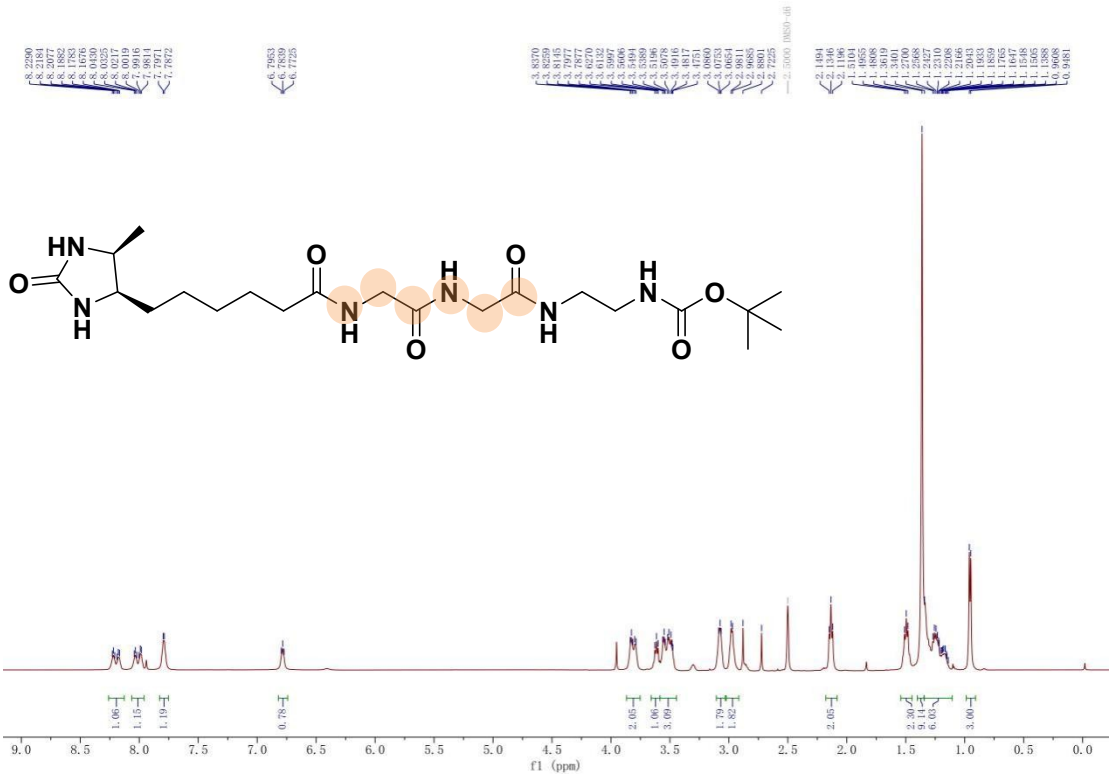
^{1}H NMR spectrum of **FG*G*B** in DMSO-d_6



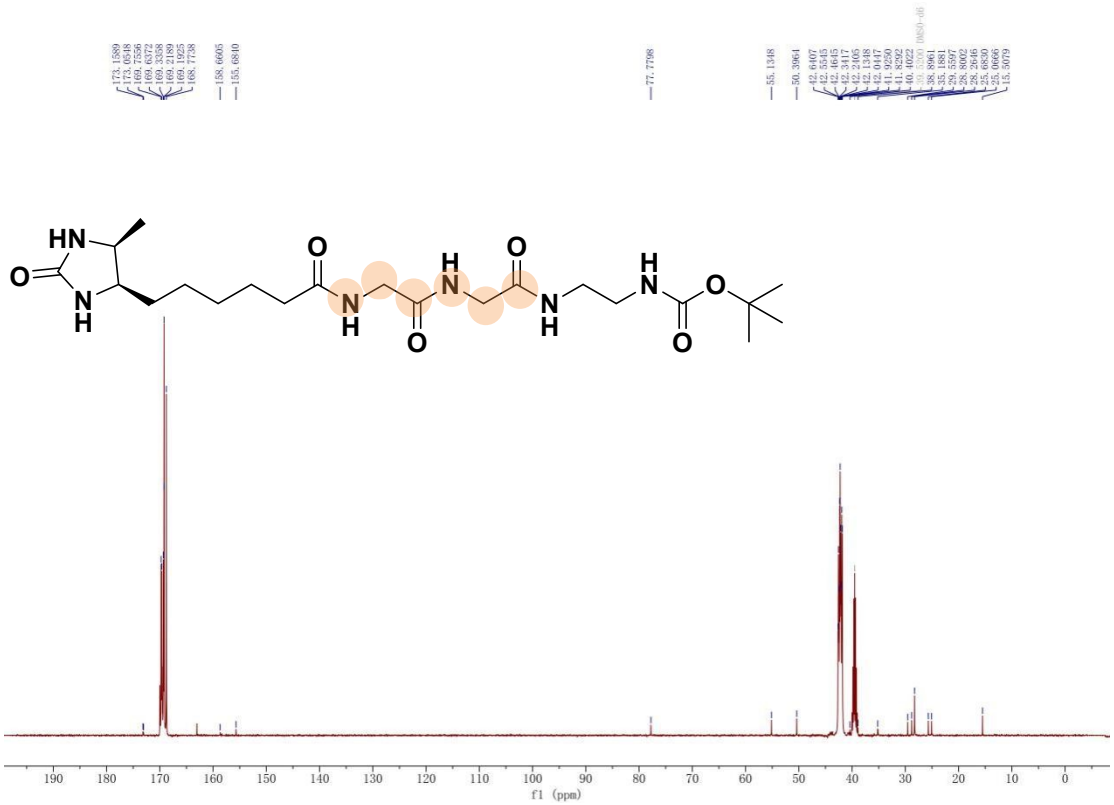
^{13}C NMR spectrum of **FG*G*B** in DMSO-d_6



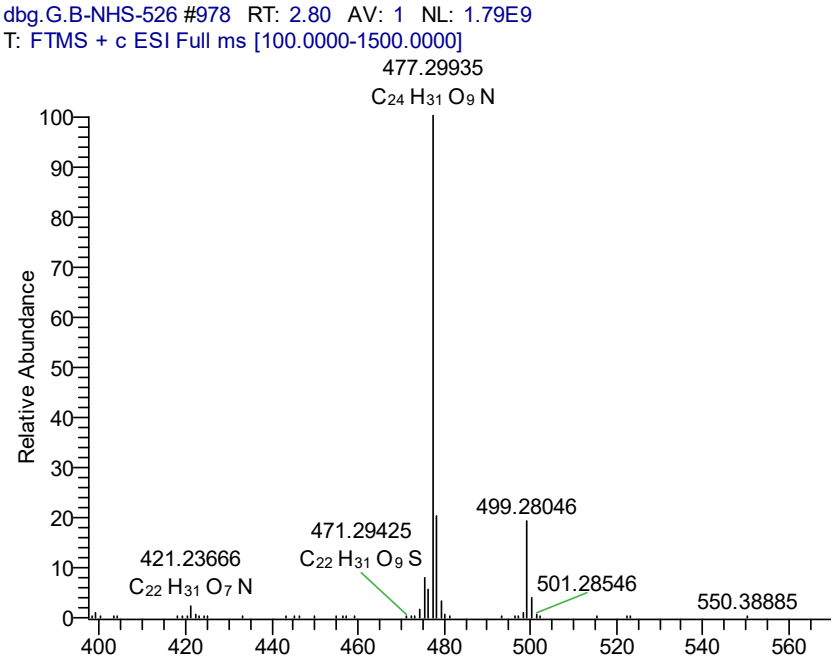
ESI/HRMS spectrum of **FG*G*B**



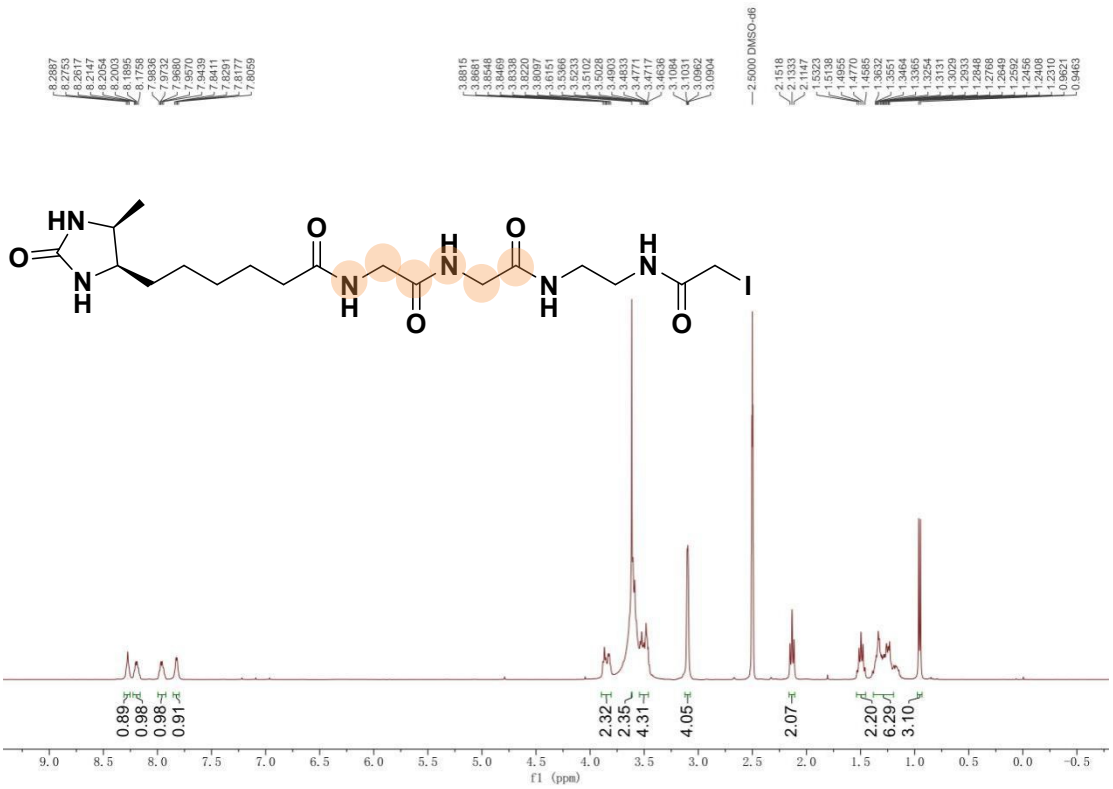
^{1}H NMR spectrum of **DbG'G'B** in DMSO-d_6



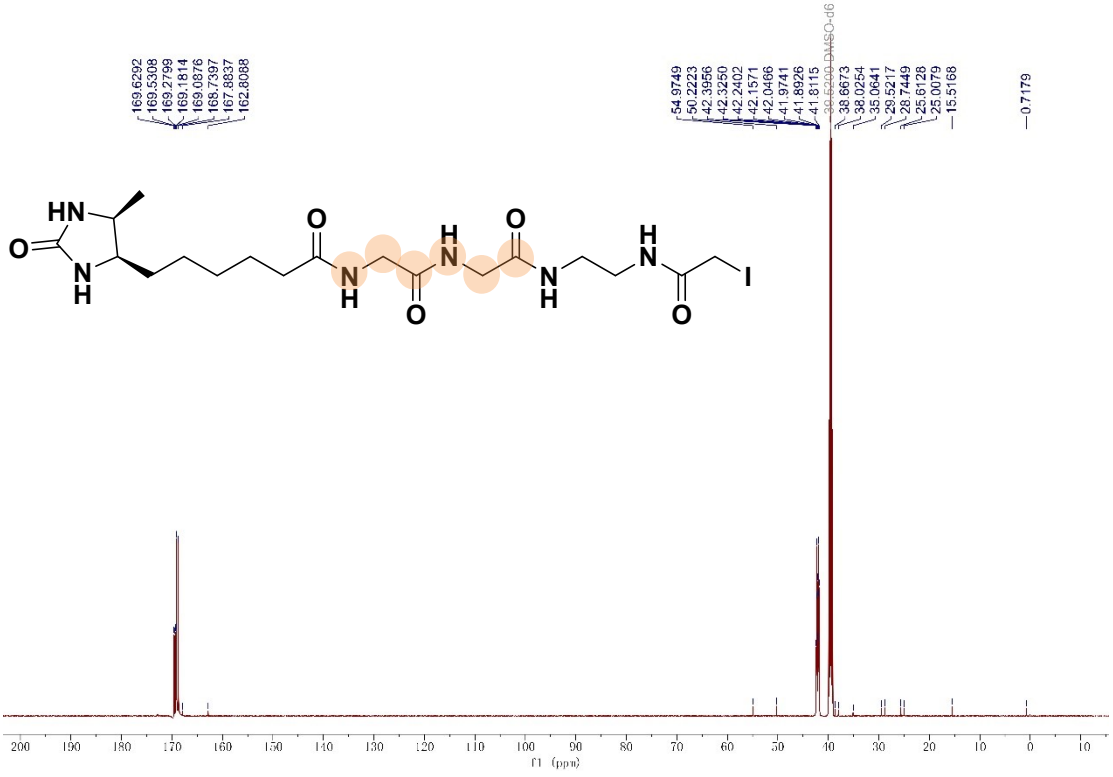
^{13}C NMR spectrum of **DbG'G'B** in DMSO-d_6



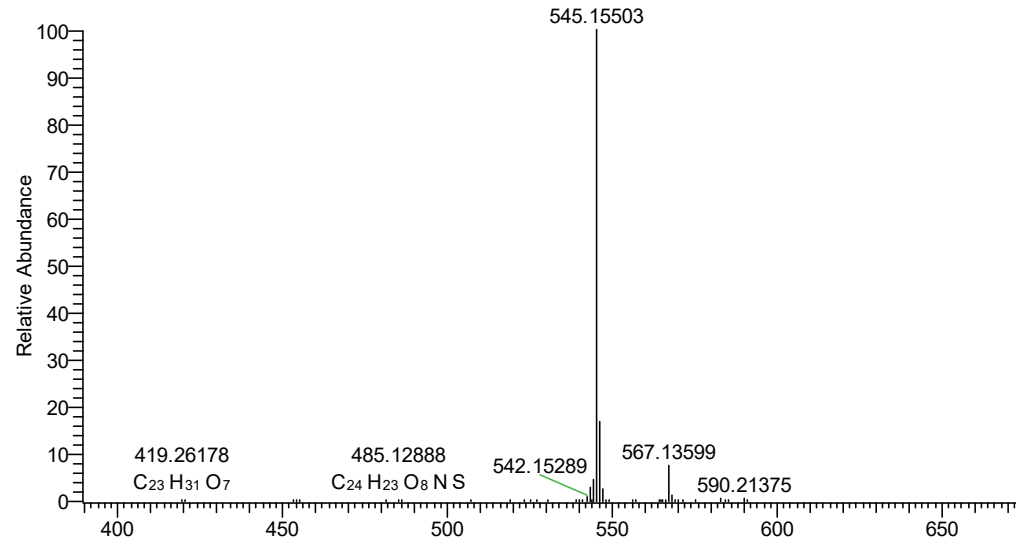
ESI/HRMS spectrum of **DbG'G'B**



^{1}H NMR spectrum of **DbG'G'I** in DMSO-d_6



^{13}C NMR spectrum of **DbG'G'I** in DMSO-d_6



ESI/HRMS spectrum of **DbG'G'I**

Supplementary Table S1: The list of targeted proteins of 100 μM III-2.

Protein ID	Gene	Protein Description	Media Log_2(R) 100 μM	ngtive $log_{10}(p)$
Q13263	TRIM28	Transcription intermediary factor 1-beta	1.03	1.39
O95671	ASMTL	Probable bifunctional dTTP/UTP pyrophosphatase /methyltransferase protein	1.61	1.38
Q8N6M3	FITM2	Fat storage-inducing transmembrane protein 2	4.91	1.82
Q86WR0	CCDC25	Coiled-coil domain-containing protein 25	1.23	2.82
Q99439	CNN2	Calponin-2	1.26	2.60
P02765	AHSG	Alpha-2-HS-glycoprotein	1.01	1.53
Q5MNZ6	WDR45B	WD repeat domain phosphoinositide-interacting protein 3	4.87	1.32
Q13795	ARFRP1	ADP-ribosylation factor-related protein 1	1.70	1.53
Q8N3F8	MICALL1	MICAL-like protein 1	1.91	1.48
O75934	BCAS2	Pre-mRNA-splicing factor SPF27	1.62	1.51
Q92685	ALG3	Dol-P-Man:Man(5)GlcNAc(2)-PP-Dol alpha-1,3-mannosyltransferase	1.26	1.53
Q9HB19	PLEKHA2	Pleckstrin homology domain-containing family A member 2	2.16	1.36
P13639	EEF2	Elongation factor 2	1.02	2.14
Q9UQ35	SRRM2	Serine/arginine repetitive matrix protein 2	1.23	1.43
Q6YN16	HSDL2	Hydroxysteroid dehydrogenase-like protein 2	1.28	1.45
O96008	TOMM40	Mitochondrial import receptor subunit TOM40 homolog	1.28	2.21
O14980	XPO1	Exportin-1	1.06	1.38
P14314	PRKCSH	Glucosidase 2 subunit beta	2.70	1.37
O60716	CTNND1	Catenin delta-1	2.00	1.82
Q05086	UBE3A	Ubiquitin-protein ligase E3A	2.71	1.49

Q9NP92	MRPS30	39S ribosomal protein S30, mitochondrial	1.68	1.33
Q9C0C2	TNKS1BP1	182 kDa tankyrase-1-binding protein	1.40	1.31
Q9BSJ8	ESYT1	Extended synaptotagmin-1	2.41	1.44
P17844	DDX5	Probable ATP-dependent RNA helicase DDX5	1.80	1.39
O96008	TOMM40	Mitochondrial import receptor subunit TOM40 homolog	1.43	1.41
P15121	AKR1B1	Aldo-keto reductase family 1 member B1	1.73	1.84

Supplementary Table S2: The list of targeted proteins of 100μM III-3.

Protein ID	Gene	Protein Description	Media Log_2(R) 100 μM	ngtive $log_{10}(p)$
Q9UBE0	SAE1	SUMO-activating enzyme subunit 1	4.71	1.41
Q07954	LRP1	Prolow-density lipoprotein receptor-related protein 1	2.72	1.41
P51159	RAB27A	Ras-related protein Rab-27A	2.65	1.54
P35998	PSMC2	26S proteasome regulatory subunit 7	2.28	1.58
Q9UEW8	STK39	STE20/SPS1-related proline-alanine-rich protein kinase	2.09	1.46
Q9NYP7	ELOVL5	Elongation of very long chain fatty acids protein 5	2.19	1.45
Q86W56	PARG	Poly(ADP-ribose) glycohydrolase	1.85	1.48
P04406	GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	1.89	1.74
Q03405	PLAUR	Urokinase plasminogen activator surface receptor	1.90	1.69
P35555	FBN1	Fibrillin-1	1.58	1.39
P12268	IMPDH2	Inosine-5'-monophosphate dehydrogenase 2	1.34	1.84
Q9Y2P8	RCL1	RNA 3'-terminal phosphate cyclase-like protein	1.40	1.51
P08754	GNAI3	Guanine nucleotide-binding protein G(i) subunit alpha	1.32	1.35
P68036	UBE2L3	Ubiquitin-conjugating enzyme E2 L3	1.19	1.50
Q15021	NCAPD2	Condensin complex subunit 1	1.12	1.34

P45880	VDAC2	Voltage-dependent anion-selective channel protein 2	1.04	1.32