Supporting Information for

Cu-Catalyzed Alkynylation of Thiosulfonate-Based Peptide: An Efficient Approach to S-Alkynyl-Containing Cyclic Peptides

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1. General Information

General information: unless otherwise stated, all reactions were set up under inert (N_2) atmosphere. Starting materials were purchased from commercial suppliers (Sigma Aldrich, Energy Chemical, Bidepharm, Tansoole) and used without further purifications unless otherwise stated. Basified silica gel was obtained by immersing silica in the 5% Et_3N/pentane overnight, and then the solvent was removed in vacuo. All solvents were dried according to standard procedures or purchased from commercial suppliers. Reactions were monitored using thin-layer chromatography (TLC) on *Merck silica gel aluminium plates* with *F254 indicator*. Visualization of the developed plates was performed under UV light (254 nm) or $KMnO_4$ stain (1.5 g $KMnO_4$, 1.25 mL 10% NaOH, 10 g K_2CO_3, 200 mL H_2O).

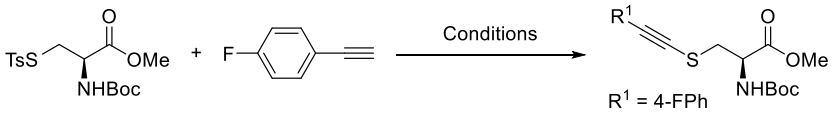
^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AVIII 400 spectrometer. ^1H NMR and ^{13}C NMR chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as the external standard and low field is positive. Coupling constants (*J*) are reported in Hertz (Hz). The residual solvent peak was used as an internal reference: ^1H NMR ($CDCl_3$ δ 7.26 ppm), ^{13}C NMR ($CDCl_3$ δ 77.16 ppm), ^1H NMR (DMSO-d_6 δ 2.50 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded using Nicolet iS50 spectrometer. HRMS data was recorded using HRMR Exactive Plus instrument. Melting point was measured using SGW X-4A instrument.

2. General Procedure for Reaction Optimization

2.1 Optimization for the S-alkynylation of S-tosyl-protected cysteine (Tables S1-S5)

In a glove box filled with nitrogen, to an oven-dried 10 mL tube equipped with a stirring bar were added methyl *N*-(*tert*-butoxycarbonyl)-*S*-tosyl-*L*-cysteinate **1a** (0.1 mmol, 1.0 equiv.), 4-fluorophenylacetylene **2a** (0.2 mmol, 2.0 equiv.), Cu catalyst, ligand, base, solvent. The tube was sealed with a Teflon screw cap and the mixture was stirred at an indicated temperature. Upon completion, the yield was determined by ^{19}F NMR spectroscopy with fluorobenzene as an internal standard.

Table S1: Catalyst screening

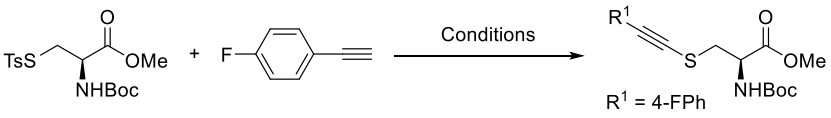


1a **2a** **3a**

Entry	Catalyst	Yield (%)[a]
1	Cu	trace
2	CuI	36
3	CuCl	25
4	$Cu(OTf)_2$	**77**
5	$CuBr_2$	19
6	$Cu(OAc)_2$	trace
7	$Cu(acac)_2$	9
8	$CuPF_6(CH_3CN)_4$	71
9	Copper hydroxyquinolate	N.P.

Reaction conditions: 0.1 M solution of the **1a** (0.1 mmol) and **2a** (1.2 equiv.), K_2CO_3 (2.0 equiv.), Catalyst (20 mol%), Xantphos (20 mol%) in anhydrous DMSO under N_2 atmosphere at 30 °C for 1.5 h. [a]Yields were determined by crude ^{19}F NMR spectra analysis using fluorobenzene as an internal standard.

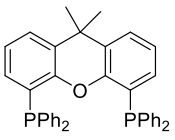
Table S2: Ligand screening



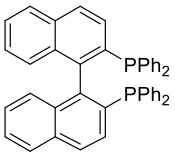
1a **2a** **3a**

Entry	Ligand	Yield (%)[a]
1	Xantphos	77
2	BINAP	21
3	DPPP	8
4	DPEphos	24
5	DPPPy	N.P.
6	PPh_3	7
7	Sphos	15

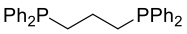
Reaction conditions: 0.1 M solution of the **1a** (0.1 mmol) and **2a** (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Cu(OTf)_2$ (20 mol%), ligand (20 mol%) in anhydrous DMSO under N_2 atmosphere at 30 ^oC for 1.5 h. [a]Yields were determined by crude ^{19}F NMR spectra analysis using fluorobenzene as an internal standard.



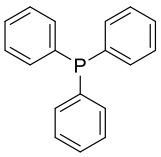
Xantphos



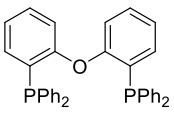
BINAP



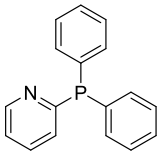
DPPP



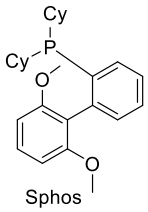
PPh_3



DPEphos

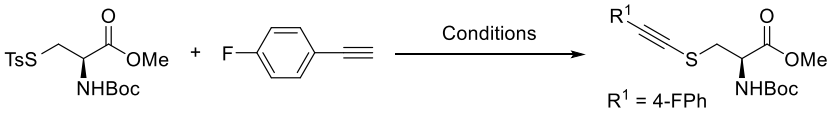


DPPPy



Sphos

Table S3: Investigation of equivalent of catalyst and ligand

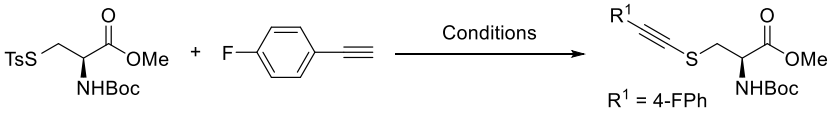


1a **2a** **3a**

Entry	Catalyst (equiv.)	Ligand (equiv.)	Yield (%)[a]
1	20 mol%	20 mol%	77
2	20 mol%	10 mol%	36
3	10 mol%	12 mol%	36
4	5 mol%	6 mol%	11

Reaction conditions: 0.1 M solution of the **1a** (0.1 mmol) and **2a** (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Cu(OTf)_2$ (x mol%), Xantphos (y mol%) in anhydrous DMSO under N_2 atmosphere at 30 °C for 1.5 h. [a]Yields were determined by crude ^{19}F NMR spectra analysis using fluorobenzene as an internal standard.

Table S4: Base screening

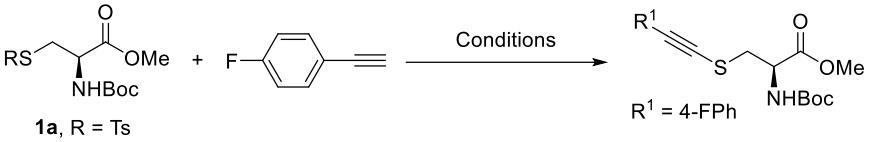


1a **2a** **3a**

Entry	Base	Yield (%)[a]
1	K_2CO_3	76
2	$NaHCO_3$	40
3	$CsCO_3$	N.P.
4	K_3PO_4	46
5	NaOH	25
6	Et_3N	N.P.
7	CH_3COONa	N.P.
8	K_2CO_3	85[b]

Reaction conditions: 0.1 M solution of the **1a** (0.1 mmol) and **2a** (1.2 equiv.), base (2.0 equiv.), $Cu(OTf)_2$ (20 mol%), Xantphos (20 mol%) in anhydrous DMSO under N_2 atmosphere at 30 °C for 1.5 h. [a]Yields were determined by crude ^{19}F NMR spectra analysis using fluorobenzene as an internal standard. [b]35 °C.

Table S5: Control experiments



1a, R = Ts
1a', R = SO_2Ph

2a

3a

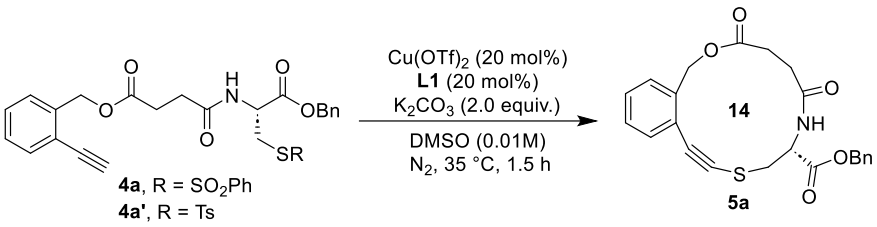
Entry	Deviation from standard condition	Yield (%)[a]
1	none	85
2	1 equiv. Base	72
3	2 equiv. **2a**	98
4	no Ligand	33
5	no Catalyst	N.P.
6	no Base	trace
7	ambient atmosphere	N.P.
8	0.2M **1a**	85
9[b]	**1a'** instead of **1a**	98
10[b]	**1a''** (R = H) instead of **1a**, under N_2 or air	0 (N_2), 56 (air)

Reaction conditions: 0.1 M solution of the **1a** (0.1 mmol) and **2a** (1.2 equiv.), base (2.0 equiv.), $Cu(OTf)_2$ (20 mol%), Xantphos (20 mol%) in anhydrous DMSO under N_2 atmosphere at 35 ^oC for 1.5 h. [a]Yields were determined by crude ^{19}F NMR spectra analysis using fluorobenzene as an internal standard. [b]**2a** (2.0 equiv.).

2.1 Optimization for the S-alkynyl-containing cyclic peptides (Table S6)

In a glove box filled with nitrogen, to an oven-dried 10 mL tube equipped with a stirring bar were added peptide **4a** (0.03 mmol), $Cu(OTf)_2$ (20 mol%, 2.2 mg), **L1** (20 mol%, 3.5 mg), K_2CO_3 (0.06 mmol, 8.3 mg) and DMSO. The tube was sealed with a Teflon screw cap and the mixture was stirred at 35 °C. Upon completion, the product was isolated.

Table S6: Investigation of concentration and protecting group

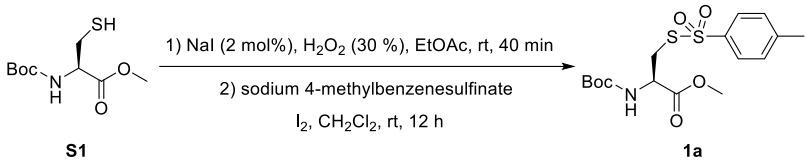


Entry	Deviation from standard condition	Yield (%)[a]
1	none	79
2	0.1 M	44
3	0.05 M	41
4	**4a'** instead of **4a**	50

Standard conditions: peptide **4a** (0.03 mmol), K_2CO_3 (2.0 equiv.), $Cu(OTf)_2$ (20 mol%), **L1** (20 mol%) in DMSO (0.01) under N_2 atmosphere at 35 °C for 1.5 h. [a]Isolated yield.

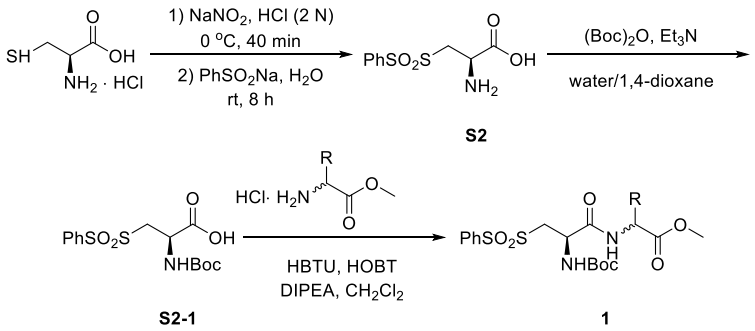
3. Procedure for the Synthesis of Starting Materials

3.1 General procedure (A) for the synthesis of S-tosyl-protected cysteine (1a)



To a stirred solution of a *N*-Boc-*L*-Cys-OMe (2 mmol, 470.6 mg) in ethyl acetate (6 mL) was added NaI (6 mg, 2 mol%) and 30% H_2O_2 (2 mmol, 0.22 mL) and the mixture was stirred at rt for 40 min. The solvent was removed under reduced pressure and the residue was directly used for the next step without further purification. To the mixture of sodium *p*-toluenesulfonate (3.2 mmol, 570 mg) and obtained crude disulfide in CH_2Cl_2 (6 mL) was added I_2 (2 mmol, 507.6 mg), and the mixture was stirred overnight. CH_2Cl_2 (50 mL) was added, followed by the addition of aq. $Na_2S_2O_3$ (1 M) with stirring until the I_2 color disappeared. The mixture was washed with H_2O (2×50 mL). The organic layers were dried over anhydrous Na_2SO_4, followed by evaporation of solvent under vacuum. The resulting residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate as eluent to give the targeted product.[1]

3.2 General procedure (B) for the synthesis of dipeptides (1r-1u)

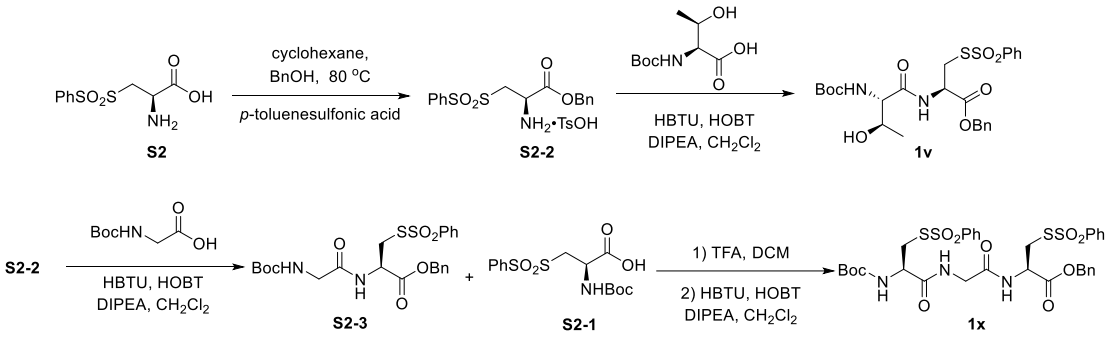


***S*-(phenylsulfonyl)-*L*-cysteine (S2)**: *L*-Cysteine monohydrochloride (6 mmol, 945.6 mg) was dissolved in 6 mL of 2 N HCl then cooled to 0 °C with ice-water bath. A solution of sodium nitrite (6 mmol, 414 mg) in 4 mL of deionized water was added dropwise and the resulted deep red solution was stirred for 40 min under air atmosphere, solution of sodium 4-methylbenzenesulfinate (6 mmol, 1.97 g) in 4 mL deionized water was added dropwise with stirring. Precipitation of solids was observed immediately. The solution was warmed to room temperature to disperse solids (the product began collecting on the magnetic stirrer). Stirring was continued at rt about 8 h. The suspension was briefly cooled in an ice bath, then filtered, and washed with approximately 6 mL each of DI water, and diethyl ether to afford the target compound **S2** as a white solid (1.143 g, 4.4 mmol, 73%).[2] **S2** was directly used for the next step without further purification. ***N*-(*tert*-butoxycarbonyl)-*S*-(phenylsulfonyl)-*L*-cysteine**

(S2-1): To a solution of *S*-(phenylsulfonyl)-*L*-cysteine **S2** (2 mmol, 522.6 mg) in 4 mL of a mixture of water/dioxane (2 mL/2 mL, v/v). The mixture was added $(Boc)_2O$ (2 mmol, 436.6 mg) and Et_3N (1.6 equiv., 0.44 mL), stirred overnight. After 12 h, the dioxane was removed under vacuum and the resulting aqueous layers was acidified to pH 6 and extracted with ethyl acetate for three times and was dried over Na_2SO_4. The resulting was concentrated under vacuum and was purified by column chromatography on silica-gel to afford the desired product as a pale yellow solid (363.5 mg, 1 mmol, 50%).[3]

Dipeptide 1: To a 0.1 M solution of the *N*-Boc-*S*-(phenylsulfonyl)-*L*-Cys **S2-1** and methyl amino acids (1.1 equiv.) in anhydrous CH_2Cl_2 were added HBTU (1.1 equiv.), HOBT (0.37 equiv.) and DIPEA (2.0 equiv.). The reaction was monitored by analytical TLC. When **S2-1** was consumed, the solution was removed under vacuum and the resulting was dissolved in ethyl acetate. Organic layer was washed with saturated $NaHCO_3$ and NaCl aqueous, and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica-gel to afford the desired product.[4]

3.3 General procedure (C) for the synthesis of dipeptide (1v, 1x)



Benzyl *S*-(phenylsulfonyl)-*L*-cysteinate (S2-2): A mixture of *S*-(phenylsulfonyl)-*L*-cysteine **S2** (2 mmol, 522.6 mg), benzyl alcohol (10 mmol, 1.03 mL), *p*-toluene sulfonic acid monohydrate (2.4 mmol, 413.3 mg) and cyclohexane (20 mL) was refluxed at 80 °C for 4 h using a Dean-Stark apparatus to separate water that was azeotroped out as it formed. The reaction mixture was cooled to room temperature and ethyl acetate (50 mL) was added. After stirring for 1 h, the precipitate was collected by filtration and dried to give the corresponding benzyl ester *p*-toluenesulfonate as a white solid. The crude product was used for next step without further purification.

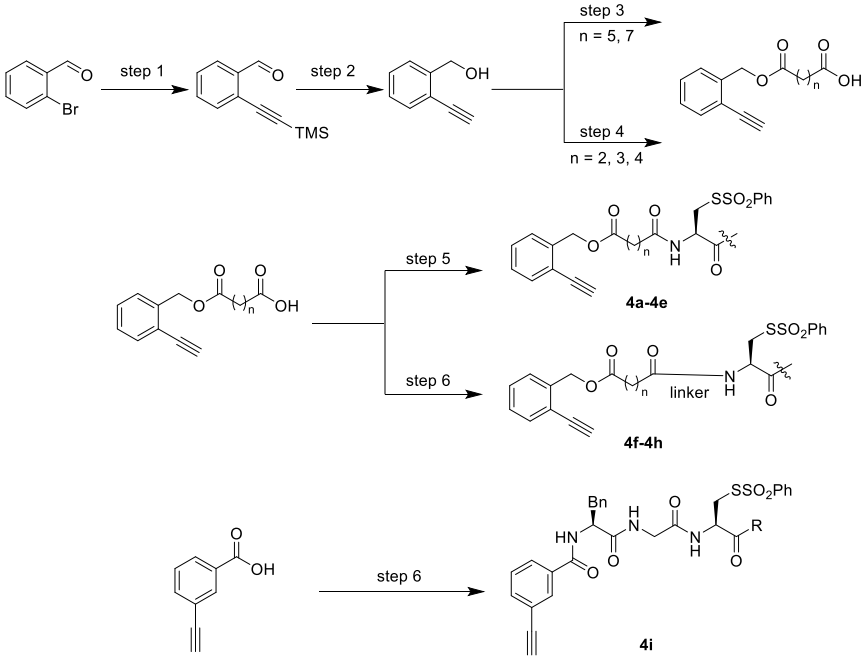
To a 0.1 M solution of the benzyl *S*-(phenylsulfonyl)-*L*-cysteinate **S2-2** (1.1 equiv.) and *L*-threonine (1.0 equiv.) in anhydrous CH_2Cl_2 were added HBTU (1.1 equiv.), HOBT (0.37 equiv.) and DIPEA (2.0 equiv.). Reaction monitored by analytical TLC. When material was consumed, the solvent was removed under vacuum and the resulting was dissolved in ethyl acetate. Organic layer was washed with saturated $NaHCO_3$×1, NaCl×2, and dried over anhydrous Na_2SO_4. After filtration, the organic solvent was removed under vacuum and the residue was purified by column chromatography on silica-gel to afford

the desired product.[5]

Protected amino acids (0.55 mmol, 1.1 equiv.) was dissolved in 5 mL of dichloromethane, and TFA (2.0 mL) was added dropwise. After 1 h, solvent was removed under reduced pressure. The resulting residue as a brown yellow liquid for next step without further purification.

Tripeptide: The residue and 0.1 M solution of acid **S2-1** (0.5 mmol) in 5 mL of anhydrous CH_2Cl_2 were added HBTU (0.55 mmol, 1.1 equiv.), HOBT (0.18 mmol, 0.37 equiv.) and DIPEA (1.0 mmol, 2.0 equiv.). The reaction was monitored by analytical TLC. When starting material was consumed, the solution was removed under vacuum and the resulting was dissolved in ethyl acetate. Organic layer was washed with saturated $NaHCO_3$ and NaCl aqueous, and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica-gel to afford the desired product.

3.4 General procedure (D) for the synthesis of substrates for cyclic peptide (4a-4j)



Step 1: To a stirred solution of 2-bromobenzaldehyde (10 mmol, 1.85 g, 1 equiv.), TMS-acetylene (13 mmol, 1.28 g, 1.3 equiv.), bis(triphenylphosphine)palladium(II) chloride (0.2 mmol, 140 mg, 0.02 equiv.), cuprous iodide(0.4 mmol, 76 mg, 0.04 equiv.), and triethylamine (15.5 mmol, 2.16 mL, 1.55 equiv.) in tetrahydrofuran (20 mL) at room temperature under N_2 atmosphere. After stirring for 4 h, the organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel to afford the desired product.[6]

Step 2: To a stirred solution of 2-((trimethylsilyl)ethynyl)benzaldehyde (2.04 g, 10 mmol, 1.0 equiv.) in MeOH (40 mL) at 0 ºC. Added sodium borohydride (189 mg, 5 mmol, 0.5 equiv.) slowly, and the mixture was stirred at 0 ºC for 4 h, then reacted at room temperature. Upon complete conversion of the starting material (detected by TLC). The aqueous layer was extracted with DCM×3 and the combined organic layer was dried $NaSO_4$, filtered and concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired product.[6]

Step 3: To a stirred solution of 2-ethynylbenzyl alcohol (132.2 g, 1 mmol, 1.0 equiv.) and azelaic acid (2 mmol, 2.0 equiv.) in dry dichloromethane (10 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (DCC, 227 mg, 1.1 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (DMAP, 134 mg, 1.1 mmol, 1.1 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 1 h. Upon complete conversion of the starting material, the crude reaction mixture was placed in a freezer for 5 hours to induce the precipitation of the urea, which was subsequently removed by filtration. The filtrate was concentrated under vacuum to provide the crude reaction mixture which was purified by flash column chromatography on silica gel to afford the pure desired product.[7]

Step 4: To a stirred solution of 2-ethynylbenzyl alcohol (132.2 g, 1 mmol, 1.0 equiv.) (0.200 g, 0.525 mmol, 1.0 equiv.) and anhydrides (1.3 mmol, 1.3 equiv.) in dry dichloromethane (10 mL) was added

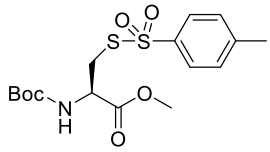
Et_3N (202.4 mg, 2 mmol, 2,0 equiv.) at room temperature for 4 h. Upon complete conversion of the starting material, 1M HCl was added dropwise until an acid pH was obtained. Dichloromethane was added to the mixture and following extraction, the combined organic phases were dried $NaSO_4$, organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel to afford the desired product.[8]

Step 5: To a 0.1 M solution of the **step 3** or **step 4** product (0.5 mmol) and protected amino acids **S2-2** (0.55 mmol, 1.1 equiv.) in anhydrous CH_2Cl_2 were added HBTU (0.55 mmol, 1.1 equiv.), HOBT (0.18 mmol, 0.37 equiv.) and DIPEA (1.0 mmol, 2.0 equiv.). The reaction was monitored by analytical TLC. When starting material was consumed, the solution was removed under vacuum and the resulting was dissolved in ethyl acetate. Organic layer was washed with saturated $NaHCO_3$ and NaCl aqueous, and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica-gel to afford the desired product.[5]

Step 6: Protected amino acids (0.55 mmol, 1.1 equiv.) was dissolved in 5 mL of dichloromethane, and TFA (2.0 mL) was added dropwise. After 1 h, solvent was removed under reduced pressure. The resulting residue as a brown yellow liquid for next step without further purification.

The residue and 0.1 M solution of acid (0.5 mmol) in 5 mL of anhydrous CH_2Cl_2 were added HBTU (0.55 mmol, 1.1 equiv.), HOBT (0.18 mmol, 0.37 equiv.) and DIPEA (1.0 mmol, 2.0 equiv.). The reaction was monitored by analytical TLC. When starting material was consumed, the solution was removed under vacuum and the resulting was dissolved in ethyl acetate. Organic layer was washed with saturated $NaHCO_3$ and NaCl aqueous, and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica-gel to afford the desired product.

Characterization data

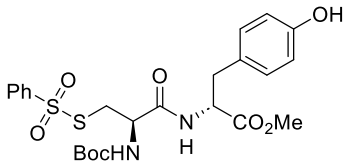


1a

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-tosyl-*L*-cysteinate (1a)

The title compound was synthesized according to general procedure A. The residue was purified by flash column chromatography to afford the pure desired product **1a** (682.4 mg, 1.755 mmol, 88% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.33 (d, *J* = 7.6 Hz, 1H), 4.58-4.55 (m, 1H), 3.74 (s, 3H), 3.51 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.40 (dd, *J* = 14.2, 5.6 Hz, 1H), 2.45 (s, 3H), 1.43 (s, 9H) ppm. The data is in accordance to the literature.[1]



1r

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(phenylsulfonyl)-*L*-cysteinyl-*D*-tyrosinate (1r)

The title compound was synthesized according to general procedure B with 0.3 mmol of *N*-(*tert*-butoxycarbonyl)-*S*-tosyl-*L*-cysteine for 11 h. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1) as eluent to afford the pure desired product **1r** (138.5 mg, 86% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.62-7.58 (m, 1H), 7.53-7.50 (m, 2H), 7.06-7.01 (m, 1H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 2H), 5.59 (d, *J* = 8.4 Hz, 1H), 4.78-4.70 (m, 1H), 4.47-4.41 (m, 1H), 3.68 (s, 3H), 3.34-3.17 (m, 2H), 3.03 (dd, *J* = 14.1, 5.3 Hz, 1H), 2.96 (dd, *J* = 14.0, 6.3 Hz, 1H), 1.42 (s, 9H) ppm.

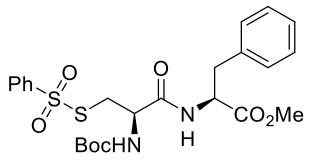
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 169.6, 155.7, 155.6, 143.9, 134.1, 130.1, 129.6, 127.1, 126.8, 115.7, 81.1, 53.7, 53.4, 52.5, 37.0, 28.3 ppm.

IR (thin film, cm^{-1}): 3346, 2958, 2926, 1666, 1614, 1515, 1446, 1367, 1324, 1257, 1216, 1161, 1142, 1077, 1018, 795, 756, 715, 684, 597, 537.

$[\alpha]_D^{25}$ = -33.0 (*c* = 0.44, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{24}H_{30}N_2NaO_8S_2$ ($M+Na^+$): 561.1336, found 561.1343.

M.p.: 85.8-87.4 °C.



1s

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(phenylsulfonyl)-*L*-cysteinyl-*L*-phenylalaninate (1s)

The title compound was synthesized according to general procedure B with 0.3 mmol of *N*-(*tert*-butoxycarbonyl)-*S*-tosyl-*L*-cysteine for 19 h. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **1s** (108 mg, 69% yield) as a pale yellow syrup.

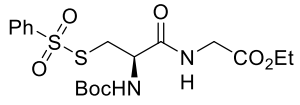
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.65-7.61 (m, 1H), 7.56-7.52 (m, 2H), 7.31-7.20 (m, 3H), 7.12 (d, *J* = 6.4 Hz, 2H), 7.01-6.98 (m, 1H), 5.49 (d, *J* = 8.2 Hz, 1H), 4.83-4.76 (m, 1H), 4.51-4.45 (m, 1H), 3.35-3.31 (m, 1H), 3.25-3.18 (m, 1H), 3.16-3.11 (m, 1H), 3.07-3.02 (m, 1H), 1.45 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 169.4, 155.5, 143.9, 135.6, 134.1, 129.5, 129.3, 128.7, 127.2, 127.1, 80.8, 53.5, 53.4, 52.4, 37.8, 36.9, 28.3 ppm.

IR (thin film, cm^{-1}): 3312, 2959, 2926, 2649, 2323, 2287, 2049, 1979, 1741, 1665, 1512, 1446, 1367, 1326, 1259, 1143, 1079, 1018, 863, 796, 715, 686, 600, 537, 417.

$[\alpha]_D^{25}$ = -30.2 (*c* = 0.44, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{24}H_{30}N_2NaO_7S_2$ ($M+Na^+$): 545.1387, found 545.1392.



1t

Ethyl *N*-(*tert*-butoxycarbonyl)-*S*-(phenylsulfonyl)-*L*-cysteinylglycinate (1t)

The title compound was synthesized according to general procedure B with 0.5 mmol of *N*-(*tert*-butoxycarbonyl)-*S*-tosyl-*L*-cysteine for 12 h. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as eluent to afford the pure desired product **1t** (192.6 mg, 86% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.64-7.60 (m, 1H), 7.55-7.51 (m, 2H), 7.13 (t, *J* = 5.4 Hz, 1H), 5.63 (d, *J* = 8.4 Hz, 1H), 4.59-4.51 (m, 1H), 4.21-4.16 (m, 2H), 4.04-3.90 (m, 2H), 3.40-3.24 (m, 2H), 1.42 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm.

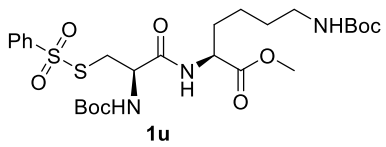
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.3, 155.6, 143.9, 134.0, 129.5, 127.2, 80.8, 61.6, 53.2, 41.4, 37.1, 28.3, 14.1 ppm.

IR (thin film, cm^{-1}): 3308, 2961, 2926, 2162, 1979, 1674, 1512, 1367, 1326, 1259, 1143, 1078, 1019, 863, 798, 716, 686, 600, 537, 457.

[α]$_D^{25}$ = -36.9 (*c* = 0.52, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{18}H_{26}N_2NaO_7S_2$ ($M+Na^+$): 469.1074, found 469.1075.

M.p.: 114.5-116.1 °C.



1u

Methyl *N*^{6}-(*tert*-butoxycarbonyl)-*N*^{2}-(*N*-(*tert*-butoxycarbonyl)-*S*-(phenylsulfonyl)-*L*-cysteinyl)-*L*-lysinate (1u)

The title compound was synthesized according to general procedure B with 0.5 mmol of *N*-(*tert*-butoxycarbonyl)-*S*-tosyl-*L*-cysteine for 11 h. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **1u** (259.7 mg, 86% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.7 Hz, 2H), 7.59-7.57 (m, 1H), 7.51-7.48 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 5.71 (d, *J* = 6.5 Hz, 1H), 4.81-4.77 (m, 1H), 4.48-4.41 (m, 1H), 3.66 (s, 3H), 3.34-3.27 (m, 2H), 3.05-3.00 (m, 2H), 1.84-1.73 (m, 1H), 1.68-1.56 (m, 1H), 1.46-1.32 (m, 20H), 1.30-1.22 (m, 2H) ppm.

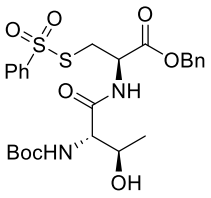
^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3, 172.1, 169.7, 156.0, 155.5, 143.9, 133.9, 129.4, 127.1, 80.6, 78.9, 52.4, 52.1, 40.1, 36.9, 31.7, 29.2, 28.4, 28.2, 22.3 ppm.

IR (thin film, cm^{-1}): 3332, 3019, 2962, 1694, 1508, 1367, 1260, 1214, 1144, 1094, 1013, 805, 747, 684, 665, 600, 537.

[α]$_D^{25}$ = -38.6 (*c* = 0.85, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{26}H_{41}N_3NaO_9S_2$ ($M+Na^+$): 626.2176, found 626.2181.

M.p.: 144.5-146 °C.



1v

Benzyl *N*-((*tert*-butoxycarbonyl)-*L*-threonyl)-*S*-(phenylsulfonyl)-*L*-cysteinate (1v)

The title compound was synthesized according to general procedure C with 0.5 mmol of benzyl *S*-(phenylsulfonyl)-*L*-cysteinate for 14 h. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **1v** (213.8 mg, 77% yield) as a yellow-green syrup.

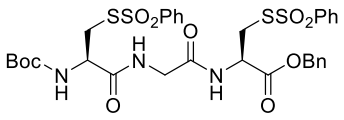
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.62-7.58 (m, 1H), 7.50-7.47 (m, 2H), 7.37-7.27 (m, 5H), 5.73 (d, *J* = 7.7 Hz, 1H), 5.13 (s, 2H), 4.88-4.81 (m, 1H), 4.31 (d, *J* = 6.3 Hz, 1H), 4.17 (d, *J* = 7.9 Hz, 1H), 3.73 (s, 1H), 3.56-3.52 (m, 1H), 3.47-3.42 (m, 1H), 1.44 (s, 9H), 1.15 (d, *J* = 5.7 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 168.9, 156.1, 143.8, 134.6, 133.9, 129.4, 128.5, 128.3, 126.9, 80.2, 67.9, 66.9, 58.8, 51.9, 36.6, 28.2, 18.3 ppm.

IR (thin film, cm^{-1}): 3348, 2961, 2926, 2035, 1978, 1667, 1497, 1447, 1367, 1326, 1258, 1163, 1143, 1077, 1018, 874, 796, 752, 715, 697, 684, 597, 536.

$[\alpha]_D^{25}$ = -51.2 (*c* = 0.43, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{25}H_{32}N_2NaO_8S_2$ ($M+Na^+$): 575.1492, found 575.1492.



1x

benzyl (*tert*-butoxycarbonyl)(phenoxysulfonothioyl)-*D*-alanylglycyl(phenoxysulfonothioyl)-*D*-alaninate (1x)

The title compound was synthesized according to general procedure C with 0.5 mmol of (*tert*-butoxycarbonyl)((phenylthio)sulfonyl)-*D*-alanine for 4 h. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1) as eluent to afford the pure desired product **1x** (264.4 mg, 70% yield) as a white solid.

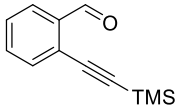
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.66-7.62 (m, 2H), 7.60-7.49 (m, 4H), 7.36-7.30 (m, 5H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.17 (d, *J* = 5.6 Hz, 1H), 5.63 (d, *J* = 7.2 Hz, 1H), 5.20-5.10 (m, 2H), 4.89-4.85 (m, 1H), 4.57-4.54 (m, 1H), 4.04-3.93 (m, 2H), 3.51-3.41 (m, 2H), 3.38-3.29 (m, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.1, 168.8, 155.8, 144.0, 143.9, 134.8, 134.3, 134.2, 129.7, 129.6, 128.8, 128.6, 127.3, 81.2, 68.2, 60.5, 53.6, 52.1, 43.2, 38.7, 37.1, 36.8, 28.4 ppm.

$[\alpha]_D^{25}$ = -24.6 (*c* = 0.13, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{32}H_{38}N_3O_{10}S_4$ ($M+H^+$): 752.1435, found 752.1418.

M.p.: 94.9-96.4°C.

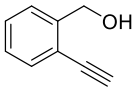


2-((trimethylsilyl)ethynyl)benzaldehyde

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (50:1) as eluent to afford

the pure desired product (2.0 g, quant. yield) as a brown yellow solid.

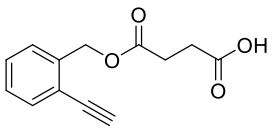
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.58-7.50 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 0.28 (s, 9H) ppm. The data is in accordance to the literature.[6]



(2-ethynylphenyl)methanol

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (15:1) as eluent to afford the pure desired product (1.06 g, 80% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.40-7.32 (m, 1H), 7.30-7.26 (t, *J* = 7.8 Hz, 1H), 4.84 (s, 2H), 3.34 (s, 1H) ppm. The data is in accordance to the literature.[6]



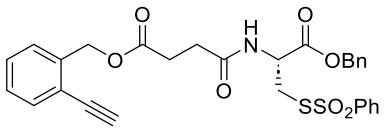
4-((2-ethynylbenzyl)oxy)-4-oxobutanoic acid

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford the pure desired product (201.9 mg, 87% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.9 Hz, 1H), 7.42-7.33 (m, 2H), 7.31-7.29 (m, 1H), 5.32 (s, 2H), 3.31 (s, 1H), 2.72 (t, *J* = 2.2 Hz, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 171.9, 137.8, 132.8, 129.0, 128.2, 128.1, 121.4, 82.4, 80.7, 64.9, 28.9, 28.7 ppm.

HRMS (ESI-TOF): calculated for $C_{13}H_{12}NaO_4$ ($M+Na^+$): 255.0628, found 255.0625.



4a

2-ethynylbenzyl (*R*)-4-((1-(benzyloxy)-1-oxo-3-((phenylsulfonyl)thio)propan-2-yl)amino)-4-oxobutanoate (4a)

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford

the pure desired product **4a** (184.5 mg, 65% yield) as yellow-green syrup.

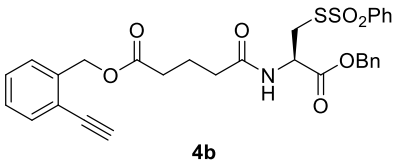
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.63-7.59 (m, 1H), 7.55-7.47 (m, 3H), 7.42-7.30 (m, 7H), 7.30-7.23 (m, 1H), 5.30 (s, 2H), 5.16 (s, 2H), 4.91-4.82 (m, 1H), 3.50 (dd, *J* = 14.5, 4.7 Hz, 1H), 3.44 (dd, *J* = 14.5, 5.4 Hz, 1H), 3.33 (s, 1H), 2.75-2.69 (m, 2H), 2.60-2.54 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 171.6, 169.3, 144.0, 138.1, 134.8, 134.1, 132.9, 129.5, 129.1, 128.7, 128.6, 128.2, 128.1, 127.2, 121.4, 82.5, 80.8, 68.4, 64.8, 51.9, 37.1, 30.6, 29.2 ppm.

IR (thin film, cm^{-1}): 3283, 2922, 2854, 1736, 1670, 1527, 1450, 1380, 1325, 1256, 1144, 1075, 1020, 799, 756, 713, 687, 596, 536.

$[\alpha]_D^{25}$ = -11.3 (*c* = 0.47, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{29}H_{27}NNaO_7S_2$ ($M+Na^+$): 588.1121, found 588.1116.



4b

2-ethynylbenzyl 5-(((2*R*)-1-(benzyloxy)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-5-oxopentanoate (4b)

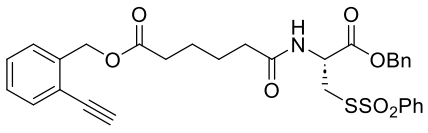
The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **4b** (143.4 mg, 50% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.65-7.63 (m, 1H), 7,56-7.50 (m, 3H), 7.42-7.32 (m, 7H), 7.30 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.3 Hz, 1H), 5.29 (s, 2H), 5.17 (s, 2H), 4.89-4.84 (m, 1H), 3.49-3.47 (m, 2H), 3.33 (s, 1H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.01-1.94 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 172.4, 169.4, 144.2, 138.3, 134.9, 134.2, 133.1, 129.6, 129.2, 128.8, 128.7, 128.5, 128.2, 127.3, 121.6, 82.4, 81.0, 68.2, 64.7, 51.8, 37.2, 35.1, 33.3, 20.7 ppm.

$[\alpha]_D^{25}$ = +4 (*c* = 0.10, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{30}H_{30}NO_7S_2$ ($M+H^+$): 580.1458, found 580.1447.



4c

2-ethynylbenzyl 6-(((2R)-1-(benzyloxy)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-6-oxohexanoate (4c)

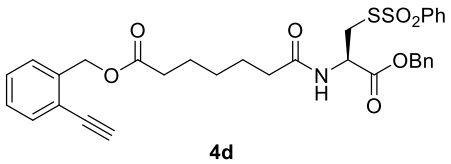
The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **4c** (195.5 mg, 65% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 2H), 7.66-7.61 (m, 1H), 7.56-7.50 (m, 3H), 7.40-7.32 (m, 7H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 1H), 5.28 (s, 2H), 5.17 (s, 2H), 4.90-4.85 (m, 2H), 3.53-3.43 (m, 2H), 3.33 (s, 1H), 2.42-2.36 (m, 2H), 2.28-2.25 (m, 2H), 1.71-1.65 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 172.8, 169.5, 144.2, 138.4, 134.9, 134.2, 133.0, 129.6, 129.2, 128.8, 128.7, 128.5, 128.2, 127.3, 121.7, 82.4, 80.9, 68.2, 64.6, 51.8, 37.3, 35.9, 33.9, 24.8, 24.5 ppm.

$[\alpha]_D^{25}$ = -1.4 (*c* = 0.14, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{31}H_{32}NO_7S_2$ ($M+H^+$): 594.1615, found 594.1605.



4d

2-ethynylbenzyl 7-(((2*R*)-1-(benzyloxy)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-7-oxoheptanoate (4d)

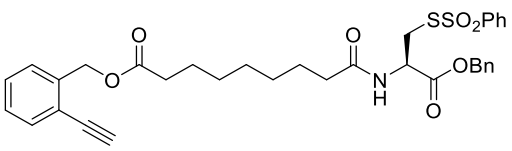
The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford the pure desired product **4d** (207 mg, 69% yield) as yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.65-7.62 (m, 1H), 7.55-7.50 (m, 3H), 7.41-7.31 (m, 7H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 7.3 Hz, 1H), 5.28 (s, 2H), 5.17 (s, 2H), 4.92-4.85 (m, 1H), 3.55-3.42 (m, 2H), 3.32 (s, 1H), 2.42-2.37 (m, 2H), 2.27-2.22 (m, 2H), 1.69-1.63 (m, 4H), 1.40-1.32 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.1, 169.5, 144.2, 138.4, 134.9, 134.2, 133.0, 129.6, 129.2, 128.8, 128.6, 128.4, 128.1, 127.3, 121.6, 82.3, 80.9, 68.2, 64.5, 51.8, 37.3, 36.1, 34.1, 28.7, 25.0, 24.7 ppm.

$[\alpha]_D^{25}$ = -21.0 (*c* = 0.11, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{32}H_{34}NO_7S_2$ ($M+H^+$): 608.1771, found 608.1758.



4e

2-ethynylbenzyl (*R*)-9-((1-(benzyloxy)-1-oxo-3-((phenylsulfonyl)thio)propan-2-yl)amino)-9-

oxononanoate (4e)

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1) as eluent to afford the pure desired product **4e** (106.1 mg, 33% yield) as a yellow-green syrup.[7]

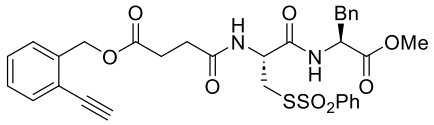
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.3 Hz, 2H), 7.65-7.60 (m, 1H), 7.54-7.50 (m, 3H), 7.40-7.31 (m, 7H), 7.30-7.25 (m, 1H), 6.56 (d, *J* = 7.4 Hz, 1H), 5.28 (s, 2H), 5.16 (s, 2H), 4.92-4.83 (m, 1H), 3.52 (dd, *J* = 14.4, 4.6 Hz, 1H), 3.46 (dd, *J* = 14.4, 5.7 Hz, 1H), 3.33 (s, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 7.6 Hz, 2H), 1.68-1.56 (m, 4H), 1.35-1.27 (m, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 173.4, 169.5, 144.1, 138.4, 134.9, 134.1, 132.9, 129.5, 129.1, 128.7, 128.5, 128.3, 128.0, 127.1, 121.5, 82.3, 80.9, 68.0, 64.4, 51.7, 37.2, 36.2, 34.2, 33.9, 28.9, 28.8, 25.3, 24.6 ppm.

IR (thin film, cm^{-1}): 3283, 2924, 2855, 1734, 1660, 1529, 1451, 1378, 1325, 1255, 1143, 1078, 1017, 796, 756, 714, 687, 597, 536.

$[\alpha]_D^{25}$ = -7.0 (*c* = 0.30, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{34}H_{37}NNaO_7S_2$ ($M+Na^+$): 658.1898, found 658.1904.



4f

2-ethynylbenzyl 4-(((2*R*)-1-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-4-oxobutanoate (4f)

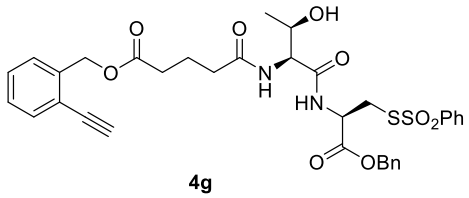
The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (3:2) as eluent to afford the pure desired product **4f** (206.4 mg, 65% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 2H), 7.68-7.64 (m, 1H), 7.59-7.55 (m, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.42-7.39 (m, 2H), 7.32-7.27 (m, 3H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.19-7.16 (m, 3H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.31 (s, 2H), 4.84-4.78 (m, 2H), 3.70 (s, 3H), 3.42 (dd, *J* = 15.0, 5.7 Hz, 1H), 3.32 (s, 1H), 3.19 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.11-3.07 (m, 1H), 3.06-3.01 (m, 1H), 2.88-2.81 (m, 1H), 2.77-2.69 (m, 1H), 2.58-2.52 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 172.3, 171.5, 169.2, 143.6, 138.0, 136.1, 134.3, 133.1, 129.7, 129.4, 129.2, 128.8, 128.4, 128.3, 127.4, 127.3, 121.5, 82.5, 80.9, 65.1, 53.7, 52.6, 52.2, 37.7, 36.3, 30.9, 29.4 ppm.

$[\alpha]_D^{25}$ = -16.7 (*c* = 0.12, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{32}H_{33}N_2O_8S_2$ ($M+H^+$): 637.1673, found 637.1661.



4g

2-ethynylbenzyl 5-(((2*S*,3*R*)-1-(((2*R*)-1-(benzyloxy)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-3-hydroxy-1-oxobutan-2-yl)amino)-5-oxopentanoate (4g)

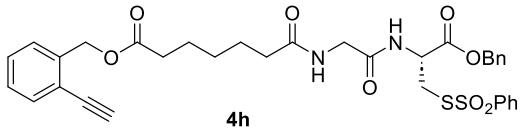
The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **4g** (189.6 mg, 56% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 2H), 7.65-7.61 (m, 2H), 7.54-7.49 (m, 3H), 7.41-7.33 (m, 5H), 7.32-7.27 (m, 3H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 2H), 5.14 (s, 2H), 4.83 (d, *J* = 5.4 Hz, 1H), 4.47-4.44 (m, 2H), 4.02 (s, 1H), 3.55 (dd, *J* = 14.6, 3.9 Hz, 1H), 3.44 (dd, *J* = 14.7, 6.2 Hz, 1H), 3.34 (s, 1H), 2.47-2.43 (m, 2H), 2.37-2.34 (m, 2H), 2.04-1.99 (m, 2H), 1.14 (d, *J* = 6.2 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 173.1, 171.5, 169.0, 144.1, 138.2, 134.8, 134.3, 133.1, 129.6, 129.2, 128.9, 128.8, 128.7, 128.5, 128.2, 127.2, 121.6, 82.5, 80.9, 68.2, 66.5, 64.8, 57.3, 52.2, 36.9, 35.2, 33.4, 20.9, 18.5 ppm.

$[\alpha]_D^{25}$ = -14.5 (*c* = 0.11, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{34}H_{37}N_2O_9S_2$ ($M+H^+$): 681.1935, found 681.1918.



4h

2-ethynylbenzyl 7-((2-(((2*R*)-1-(benzyloxy)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-2-oxoethyl)amino)-7-oxoheptanoate (4h)

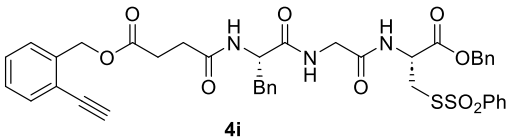
The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **4h** (218.3 mg, 66% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.64-7.62 (m, 1H), 7.54-7.48 (m, 3H), 7.38-7.31 (m, 5H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.24 (s, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 6.30 (s, 1H), 5.25 (s, 2H), 5.14 (s, 2H), 4.87 (d, *J* = 5.7 Hz, 1H), 4.06 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.91 (dd, *J* = 16.8, 4.7 Hz, 1H), 3.52-3.39 (m, 2H), 3.30 (s, 1H), 2.38-2.34 (m, 2H), 2.25-2.20 (m, 2H), 1.67-1.62 (m, 4H), 1.40-1.32 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 173.6, 169.6, 169.0, 143.9, 138.4, 134.8, 134.3, 133.0, 129.6, 129.1, 128.9, 128.8, 128.6, 128.4, 128.1, 127.3, 121.6, 82.4, 80.9, 68.2, 64.5, 51.9, 43.2, 36.9, 36.2, 34.1, 28.8, 25.2, 24.7 ppm.

[α]$_D^{25}$ = -15.8 (*c* = 0.12, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{34}H_{37}N_2O_8S_2$ ($M+H^+$): 665.1986, found 665.1975.



4i

2-ethynylbenzyl 4-(((2*S*)-1-((2-(((2*R*)-1-(benzyloxy)-1-oxo-3-(phenoxysulfonothioyl)propan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanoate (4i)

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **4i** (128.9 mg, 34% yield) as a white solid.

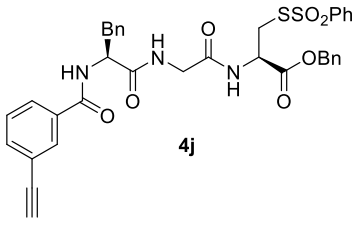
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 2H), 7.64-7.60 (m, 1H), 7.50-7.46 (m, 3H), 7.35-7.28 (m, 8H), 7.24-7.22 (m, 2H), 7.21-7.14 (m, 3H), 7.09 (s, 1H), 6.32 (d, *J* = 6.5 Hz, 1H), 5.27-5.23 (m, 2H), 5.13-5.08 (m, 2H), 4.76 (d, *J* = 5.8 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 3.99 (dd, *J* = 16.8, 6.1 Hz, 1H), 3.83 (dd, *J* = 16.9, 5.2 Hz, 1H), 3.42 (d, *J* = 5.0 Hz, 2H), 3.30 (s, 1H), 3.21 (dd, *J* = 14.2, 5.4 Hz, 1H), 3.02 (dd, *J* = 13.7, 8.4 Hz, 1H), 2.83-2.77 (m, 2H), 2.67-2.58 (m, 1H), 2.42-2.38 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 172.6, 171.5, 169.4, 169.2, 143.9, 137.9, 136.6, 134.9, 134.3, 133.0, 129.6, 129.3, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.4, 127.3, 121.6, 82.6, 80.9, 68.0, 65.2, 55.2, 51.9, 43.2, 37.2, 36.9, 30.9, 29.5 ppm.

[α]$_D^{25}$ = -18.7 (*c* = 0.23, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{40}H_{40}N_3O_9S_2$ ($M+H^+$): 770.2200, found 770.2183.

M.p.: 102.8-103.4°C.



4j

benzyl (3-ethynylbenzoyl)-*L*-phenylalanylglycyl(phenoxysulfonothioyl)-*D*-alaninate (4j)

The title compound was synthesized according to general procedure D. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1) as eluent to afford the pure desired product **4j** (131.8 mg, 39% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.77 (m, 3H), 7.65-7.53 (m, 3H), 7.48-7.44 (m, 2H), 7.33-7.26 (m, 8H), 7.24-7.19 (m, 4H), 6.92 (d, *J* = 6.6 Hz, 1H), 6.79 (s, 1H), 5.16-5.07 (m, 2H), 4.84-4.78 (m, 2H), 4.04 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.89 (dd, *J* = 17.1, 5.1 Hz, 1H), 3.48-3.36 (m, 2H), 3.26-3.20 (m, 1H),

3.19-3.12 (m, 1H), 3.08 (s, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 169.2, 169.1, 166.9, 143.8, 136.4, 135.4, 134.8, 134.3, 133.8, 130.9, 129.6, 129.4, 129.0, 128.8, 128.6, 127.7, 127.4, 127.3, 122.8, 82.7, 78.5, 68.2, 55.6, 52.1, 43.1, 38.1, 36.7 ppm.

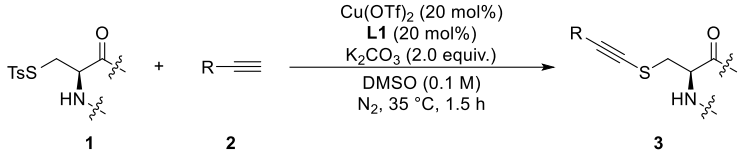
$[\alpha]_D^{25}$ = -44.2 (*c* = 0.19, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{36}H_{34}N_3O_7S_2$ ($M+H^+$): 684.1833, found 684.1820.

M.p.: 96.2-97.6°C.

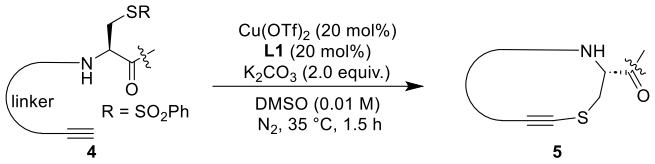
4. General Procedure for S-alkynylation

4.1 General procedure (E) for copper-catalyzed S-alkynylation (3a-3x)



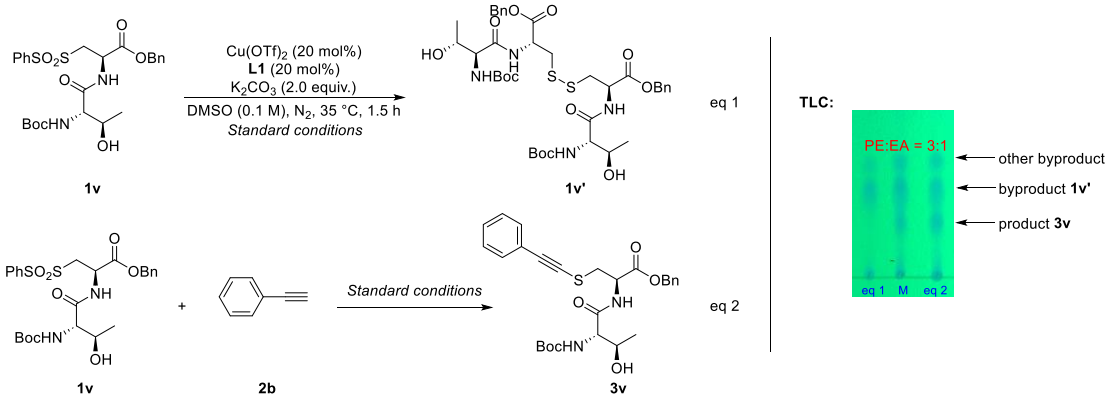
The mixture of **1** (0.1 mmol), **2** (0.2 mmol, 2.0 equiv.), K_2CO_3 (0.2 mmol, 2.0 equiv., 27.6 mg), $Cu(OTf)_2$ (20 mol%, 7.2 mg), **L1** (20 mol%, 11.6 mg) in 1 mL of dry DMSO was stirred at 35 °C under N_2 atmosphere. After 1.5 h, CH_2Cl_2 was added to dilute the reaction mixture. Then organic layer was washed with saturated NaCl aqueous (×3), and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel to afford the desired product.

4.2 General procedure (F) for synthesis of cyclic peptides (5a-5j)



The mixture of **4** (0.03 mmol), K_2CO_3 (0.06 mmol, 8.3 mg), $Cu(OTf)_2$ (20 mol%, 2.2 mg), **L1** (20 mol%, 3.5 mg) in 3 mL of dry DMSO was stirred at 35 °C under N_2 atmosphere. After 1.5 h, CH_2Cl_2 was added to dilute the reaction mixture. Then organic layer was washed with saturated NaCl aqueous (×3), and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel to afford the desired product.

4.3 Byproduct analysis for S-alkynylation (3v-3x, 5f-5j)



Eq 1: The mixture of **1v** (0.1 mmol, 55.2 mg), K_2CO_3 (0.2 mmol, 2.0 equiv., 27.6 mg), $Cu(OTf)_2$ (20 mol%, 7.2 mg), **L1** (20 mol%, 11.6 mg) in 1 mL of dry DMSO was stirred at 35 °C under N_2 atmosphere. After 1.5 h, CH_2Cl_2 was added to dilute the reaction mixture. Then organic layer was washed with

saturated NaCl aqueous (×3), and dried over anhydrous Na_2SO_4 to afford a residue. The crude ^1H NMR spectrum was listed in Figure S1 (bottom).

Eq 2: The mixture of **1v** (0.1 mmol, 55.2 mg), **2b** (0.2 mmol, 2.0 equiv.), K_2CO_3 (0.2 mmol, 2.0 equiv., 27.6 mg), $Cu(OTf)_2$ (20 mol%, 7.2 mg), **L1** (20 mol%, 11.6 mg) in 1 mL of dry DMSO was stirred at 35 ^oC under N_2 atmosphere. After 1.5 h, CH_2Cl_2 was added to dilute the reaction mixture. Then organic layer was washed with saturated NaCl aqueous (×3), and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel to afford the desired product. The ^1H NMR spectrum was listed in Figure S1 (up).

The chemical shifts of main peaks for two ^1H NMR spectra were consistent with each other.

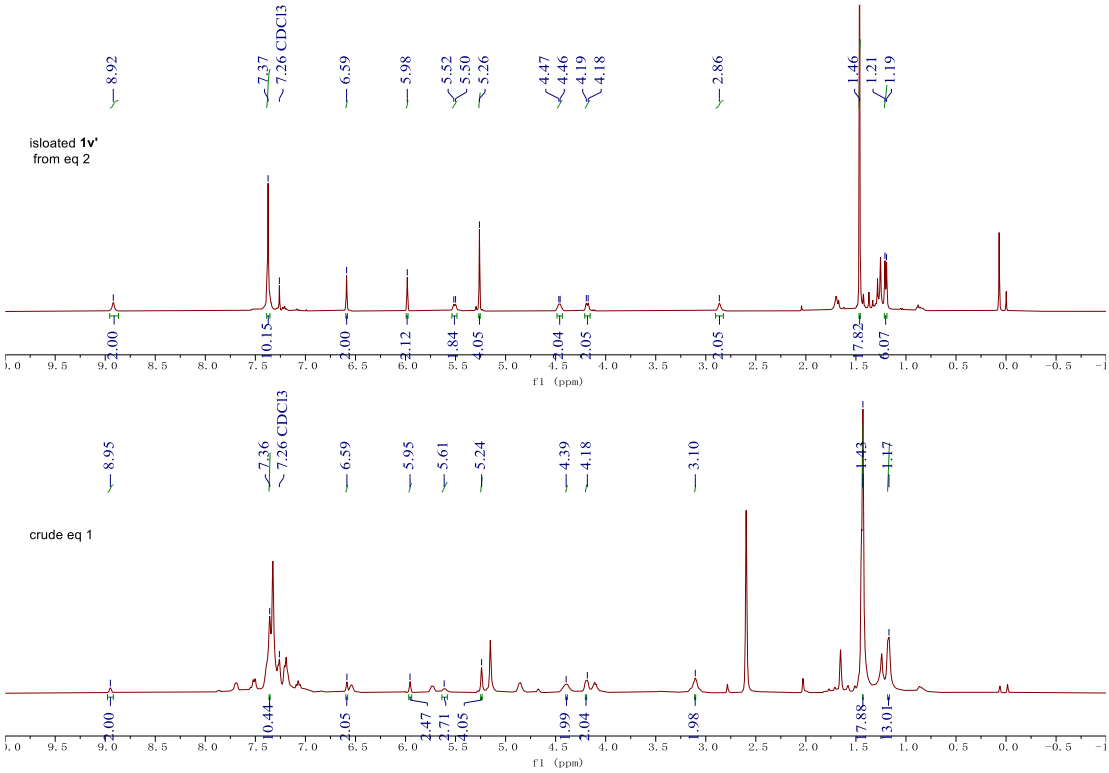


Figure S1. ^1H NMR analysis for byproduct 1v'

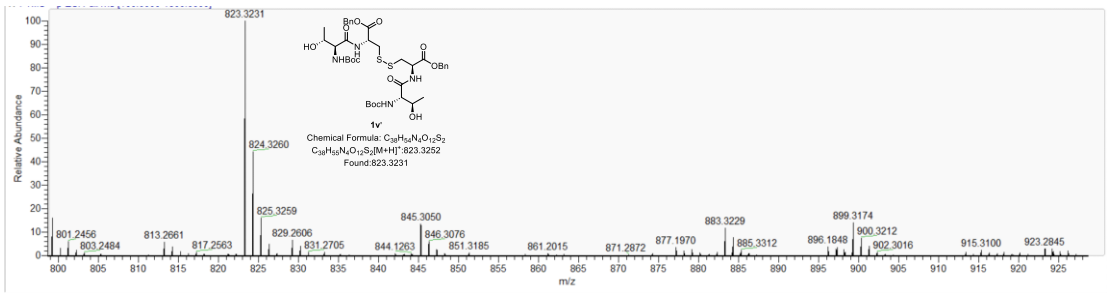
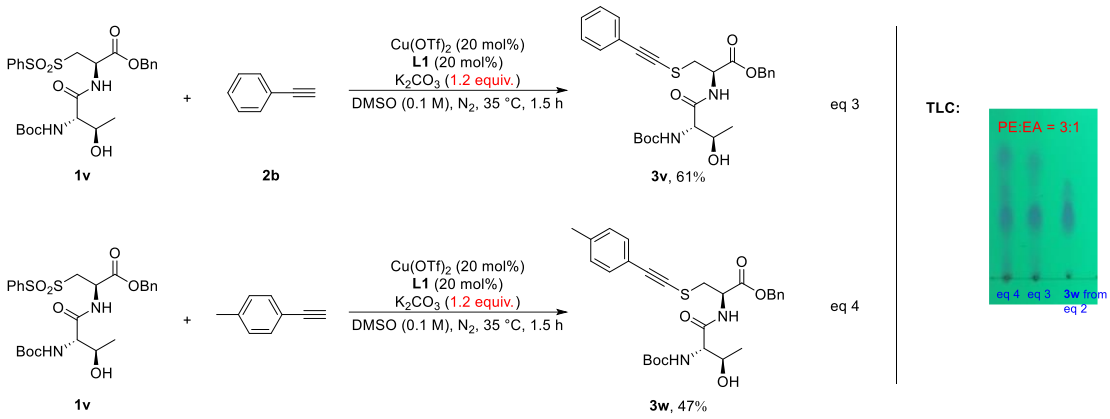
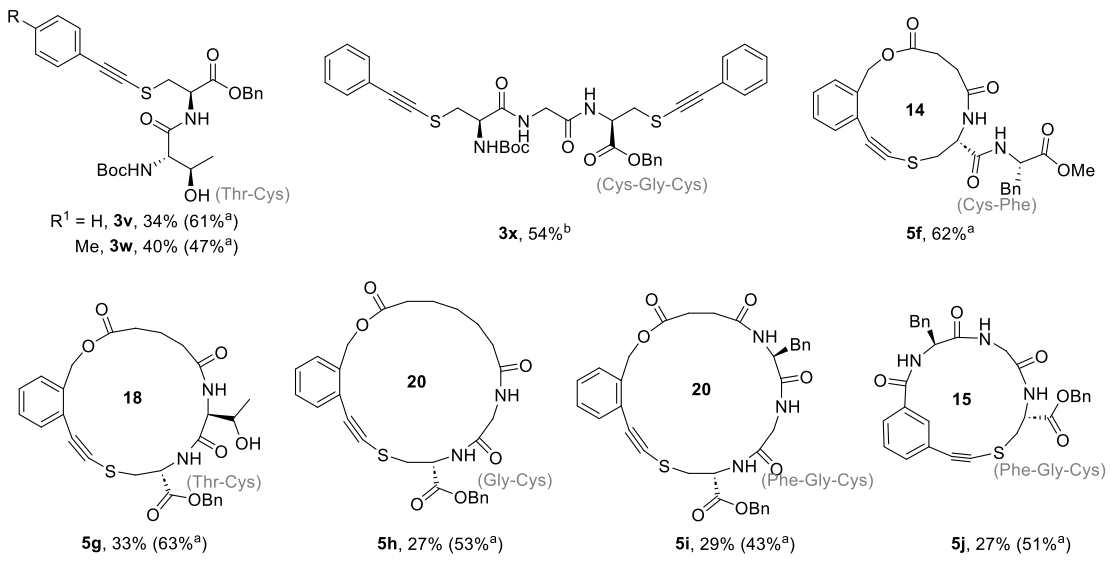


Figure S2. HMRS analysis for byproduct 1v' from reaction eq 2



Eq 3 and eq 4: The mixture of **1v** (0.1 mmol, 38.9 mg), **2** (0.2 mmol, 2.0 equiv.), K_2CO_3 (0.12 mmol, 1.2 equiv., 16.5 mg), $Cu(OTf)_2$ (20 mol%, 7.2 mg), **L1** (20 mol%, 11.6 mg) in 1 mL of dry DMSO was stirred at 35 °C under N_2 atmosphere. After 1.5 h, CH_2Cl_2 was added to dilute the reaction mixture. Then organic layer was washed with saturated NaCl aqueous (×3), and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel to afford the desired product.

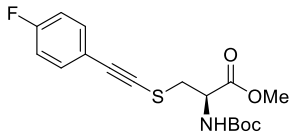
Reducing the amount of K_2CO_3 to 1.2 equivalents further improved the yield of the desired products (**3v-3x**). This modified condition was used in the synthesis of cyclic peptides **5f-5j**.



Standard conditions: peptide **1** or **4** , K_2CO_3 (2.0 equiv.), $Cu(OTf)_2$ (20 mol%), **L1** (20 mol%) in DMSO under N_2 atmosphere at 35 °C for 1.5 h. Isolated yield. [a] K_2CO_3 (1.2 equiv.) was used. [b] $Cu(OTf)_2$ (40 mol%), **L1** (40 mol%), **2a** (4.0 equiv.) and K_2CO_3 (2.4 equiv.)

Figure S3. The effect of the amount of base

Characterization data



3a

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-fluorophenyl)ethynyl)-*L*-cysteinate (3a)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3a** (31.1 mg, 88% yield) as a brown-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 5.58 (d, *J* = 8.1Hz, 1H), 4.80-4.66 (m, 1H), 3.71 (s, 3H), 3.25 (d, *J* = 4.7 Hz, 2H), 1.41 (s, 9H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.17 (m, 1F) ppm.

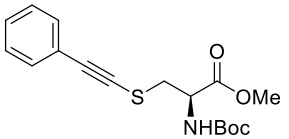
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 162.7 (d, *J* = 250.1 Hz), 155.1, 133.9 (d, *J* = 8.4 Hz), 119.2 (d, *J* = 3.4 Hz), 115.7 (d, *J* = 22.1 Hz), 91.9, 80.4, 77.9, 53.6, 52.8, 37.9, 28.3 ppm.

IR (thin film, cm^{-1}): 3350, 2955, 2924, 2855, 1712, 1649, 1503, 1230, 1162, 951, 868, 838, 798, 655, 531.

$[\alpha]_D^{25}$ = +46.0 (*c* = 0.47, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{20}FNNaO_4S$ ($M+Na^+$): 376.0989, found 376.0989.

M.p.: 98.8-99.4 °C.



3b

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(phenylethynyl)-*L*-cysteinate (3b)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3b** (26.8 mg, 80% yield) as a yellow syrup.

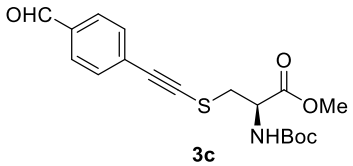
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.31-7.27 (m, 3H), 5.60 (d, *J* = 8.1 Hz, 1H), 4.79-4.70 (m, 1H), 3.73 (s, 3H), 3.34-3.21 (m, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.1, 131.8, 128.6, 128.4, 123.1, 93.1, 80.5, 78.1, 53.7, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 3364, 2955, 2292, 2854, 1715, 1666, 1635, 1499, 1458, 1365, 1258, 1163, 1060, 1019, 875, 801, 756, 692, 531.

$[\alpha]_D^{25}$ = +52.5 (*c* = 0.20, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{21}NNaO_4S$ ($M+Na^+$): 358.1084, found 358.1082.



3c

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-formylphenyl)ethynyl)-*L*-cysteinate (3c)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3c** (13.8 mg, 38% yield) as a yellow syrup.

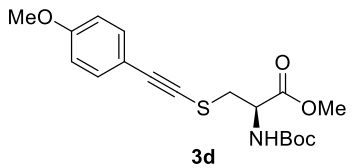
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 5.55 (d, *J* = 8.0Hz, 1H), 4.81-4.72 (m, 1H), 3.76 (s, 3H), 3.38-3.24 (m, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 170.6, 155.1, 135.4, 131.7, 129.7, 129.4, 92.7, 83.8, 80.6, 53.7, 53.0, 38.2, 28.4 ppm.

IR (thin film, cm^{-1}): 3351, 2954, 2921, 2853, 1700, 1599, 1499, 1459, 1371, 1258, 1209, 1164, 1018, 867, 800, 511.

$[\alpha]_D^{25}$ = +43.1 (*c* = 0.16, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{18}H_{21}NNaO_5S$ ($M+Na^+$): 386.1033, found 386.1032.



3d

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-methoxyphenyl)ethynyl)-*L*-cysteinate (3d)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3d** (32.7 mg, 90% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.61 (d, *J* = 8.2 Hz, 1H), 4.76-4.67 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.28 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.21 (dd, *J* = 13.8, 4.6 Hz, 1H), 1.42 (s, 9H) ppm.

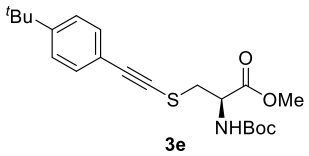
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 160.0, 155.1, 133.8, 115.1, 114.1, 93.0, 80.4, 76.2, 55.4, 53.6, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 3386, 2954, 2921, 2853, 1715, 1604, 1505, 1459, 1370, 1254, 1166, 1018, 795, 695, 536.

$[\alpha]_D^{25}$ = +54.5 (*c* = 0.22, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{18}H_{23}NNaO_5S$ ($M+Na^+$): 388.1189, found 388.1189.

M.p.: 95.3-96.7 °C.



3e

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-(*tert*-butyl)phenyl)ethynyl)-*L*-cysteinate (3e)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3e** (32.4 mg, 83% yield) as a yellow syrup.

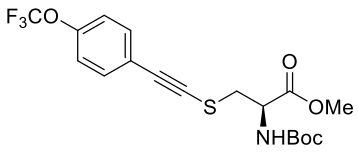
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.61 (d, *J* = 8.2 Hz, 1H), 4.77-4.69 (m, 1H), 3.74 (s, 3H), 3.33-3.19 (m, 2H), 1.42 (s, 9H), 1.29 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 155.1, 151.9, 131.7, 125.4, 120.0, 93.3, 80.4, 53.6, 52.9, 38.1, 34.9, 31.2, 28.4 ppm.

IR (thin film, cm^{-1}): 3368, 2956, 2923, 2862, 1716, 1501, 1459, 1364, 1255, 1213, 1164, 1057, 1017, 833, 800, 560.

$[\alpha]_D^{25}$ = +48.8 (*c* = 0.43, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{21}H_{29}NNaO_4S$ ($M+Na^+$): 414.1710, found 414.1710.



3f

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-(trifluoromethoxy)phenyl)ethynyl)-*L*-cysteinate (3f)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3f** (20.5 mg, 49% yield) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.56 (d, *J* = 8.1 Hz, 1H), 4.79-4.70 (m, 1H), 3.74 (s, 3H), 3.27 (d, *J* = 4.7 Hz, 2H), 1.42 (s, 9H) ppm.

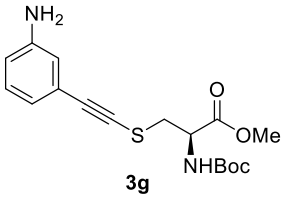
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.82 (s, 3F) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.1, 149.1, 133.3, 121.9, 120.9, 120.5 (q, *J* = 257.8 Hz), 91.7, 80.5, 79.5, 53.6, 52.9, 38.0, 28.4 ppm.

IR (thin film, cm^{-1}): 3365, 2955, 2921, 2854, 1714, 1502, 1458, 1367, 1256, 1211, 1163, 1016, 848, 797, 537.

$[\alpha]_D^{25}$ = +45.1 (*c* = 0.45, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{18}H_{20}F_3NNaO_5S$ ($M+Na^+$): 442.0906, found 442.0905.



3g

Methyl *S*-((3-aminophenyl)ethynyl)-*N*-(*tert*-butoxycarbonyl)-*L*-cysteinate (3g)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **3g** (25 mg, 71% yield) as a yellow syrup.

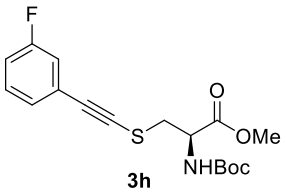
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-7.04 (m, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.73 (s, 1H), 6.62 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.58 (d, *J* = 8.2 Hz, 1H), 4.75-4.69 (m, 1H), 3.73 (s, 3H), 3.67 (s, 2H), 3.29 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.23 (dd, *J* = 13.8, 4.7 Hz, 1H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 155.1, 146.4, 129.4, 123.7, 122.3, 117.9, 115.6, 93.4, 80.5, 53.5, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 3366, 2953, 2922, 2853, 1704, 1625, 1598, 1498, 1455, 1366, 1219, 1164, 856, 780, 685, 464.

$[\alpha]_D^{25}$ = +68.8 (*c* = 0.17, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{22}N_2NaO_4S$ ($M+Na^+$): 373.1192, found 373.1189.



3h

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((3-fluorophenyl)ethynyl)-*L*-cysteinate (3h)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3h** (22.2 mg, 63% yield) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.22 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 9.4 Hz, 1H), 7.01 (t, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 8.1 Hz, 1H), 4.78-4.72 (m, 1H), 3.75 (s, 3H), 3.28 (d, *J* = 4.6 Hz, 2H), 1.44 (s, 9H) ppm.

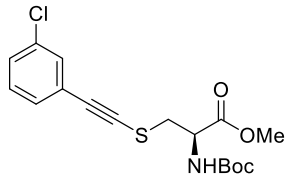
^{19}F NMR (376 MHz, $CDCl_3$) δ -112.78 (m, 1F) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 162.5 (d, *J* = 246.9 Hz), 155.1, 130.0 (d, *J* = 8.6 Hz), 127.5, 124.9 (d, *J* = 9.4 Hz), 118.4 (d, *J* = 22.7 Hz), 115.9 (d, *J* = 21.2 Hz), 91.9, 80.6, 79.8, 53.7, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 3356, 2954, 2921, 2853, 1713, 1495, 1459, 1368, 1259, 1163, 1015, 789, 680, 461.

[α]$_D^{25}$ = +53.5 (*c* = 0.31, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{20}FNNaO_4S$ ($M+Na^+$): 376.0989, found 376.0988.



3i

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((3-chlorophenyl)ethynyl)-*L*-cysteinate (3i)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3i** (14.9 mg, 41% yield) as a yellow syrup.

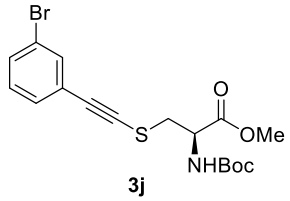
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 1.9 Hz, 1H), 7.31-7.27 (m, 2H), 7.25-7.20 (m, 1H), 5.55 (d, *J* = 8.0 Hz, 1H), 4.79-4.71 (m, 1H), 3.75 (s, 3H), 3.28 (d, *J* = 4.4 Hz, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 155.1, 134.3, 131.5, 129.8, 129.7, 128.8, 124.8, 91.8, 80.6, 80.1, 53.8, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 2954, 2921, 2853, 1716, 1460, 1370, 1258, 1163, 1015, 860, 793, 684, 492.

[α]$_D^{25}$ = +34.7 (*c* = 0.15, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{20}ClNNaO_4S$ ($M+Na^+$): 392.0694, found 392.0690.



3j

Methyl *S*-((3-bromophenyl)ethynyl)-*N*-(*tert*-butoxycarbonyl)-*L*-cysteinate (3j)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3j** (15.2 mg, 37% yield) as a yellow-green syrup.

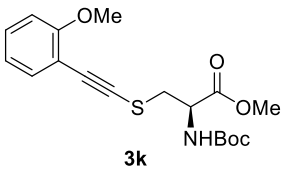
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 1H), 7.46-7.39 (m, 1H), 7.37-7.31 (m, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 5.55 (d, *J* = 8.1Hz, 1H), 4.78-4.70 (m, 1H), 3.75 (s, 3H), 3.28 (d, *J* = 4.7 Hz, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.1, 134.3, 131.7, 130.2, 129.9, 125.1, 122.3, 91.6, 80.6, 80.2, 53.7, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 3343, 3166, 2955, 2923, 2854, 1661, 1583, 1504, 1461, 1368, 1258, 1163, 1088, 875, 744, 531.

[α]$_D^{25}$ = +36.0 (c = 0.15, $CHCl_3$)

HRMS (ESI-TOF): calculated for $C_{17}H_{20}BrNNaO_4S$ ($M+Na^+$): 436.0189, found 436.0189.



3k

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((2-methoxyphenyl)ethynyl)-*L*-cysteinate (3k)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **3k** (27.2 mg, 75% yield) as a yellow-green syrup.

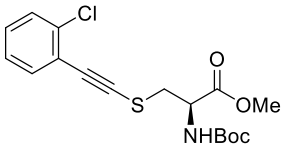
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 1H), 7.29-7.25 (m, 1H), 6.91-6.81 (m, 2H), 5.76 (d, *J* = 8.3 Hz, 1H), 4.78-4.71 (m, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.34-3.19 (m, 2H), 1.40 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 160.5, 155.2, 133.6, 129.9, 120.5, 112.3, 110.6, 89.6, 81.9, 80.2, 55.8, 53.9, 52.7, 37.9, 28.3 ppm.

IR (thin film, cm^{-1}): 3370, 2954, 2920, 2852, 1712, 1595, 1492, 1459, 1367, 1256, 1162, 1017, 861, 795, 754, 694, 504.

$[\alpha]_D^{25}$ = +42.8 (*c* = 0.32, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{18}H_{23}NNaO_5S$ ($M+Na^+$): 388.1189, found 388.1189.



3l

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((2-chlorophenyl)ethynyl)-*L*-cysteinate (3l)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3l** (18.3 mg, 49% yield) as a brown yellow syrup.

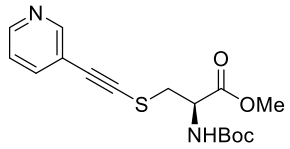
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25-7.16 (m, 2H), 5.56 (d, *J* = 6.2 Hz, 1H), 4.81-4.71 (m, 1H), 3.75 (s, 3H), 3.38-3.25 (m, 2H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.2, 135.9, 133.3, 129.4, 126.6, 123.1, 89.9, 84.2, 80.5, 53.8, 52.9, 38.4, 28.4 ppm.

IR (thin film, cm^{-1}): 3352, 2926, 2855, 1715, 1501, 1468, 1437, 1362, 1309, 1216, 1165, 1058, 1021, 755, 456.

$[\alpha]_D^{25}$ = +32.4 (*c* = 0.34, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{20}ClNNaO_4S$ ($M+Na^+$): 392.0694, found 392.0691.



3m

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(pyridin-3-ylethynyl)-*L*-cysteinate (3m)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3m** (17.4 mg, 52% yield) as a yellow syrup.

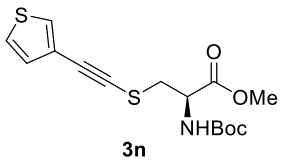
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.51 (d, *J* = 5.0 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 7.9, 4.9 Hz, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 4.78-4.72 (m, 1H), 3.78 (s, 3H), 3.35-3.24 (m, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 155.1, 152.3, 148.7, 138.6, 123.1, 120.4, 89.8, 82.5, 80.6, 53.64, 52.9, 38.1, 28.4 ppm.

IR (thin film, cm^{-1}): 3352, 2922, 2854, 1712, 1459, 1366, 1256, 1165, 1016, 795, 701, 537.

$[\alpha]_D^{25}$ = +43.6 (*c* = 0.55, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{16}H_{21}N_2NaO_4S$ ($M+H^+$): 337.1217, found 337.1215.



3n

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(thiophen-3-ylethynyl)-*L*-cysteinate (3n)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3n** (27.6 mg, 81% yield) as a brown yellow syrup.

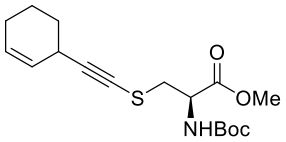
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.4 Hz, 1H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 5.57 (d, *J* = 8.1 Hz, 1H), 4.75-4.68 (m, 1H), 3.73 (s, 3H), 3.32-3.20 (m, 2H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.1, 130.2, 129.9, 125.4, 122.2, 88.1, 80.5, 53.6, 52.9, 38.0, 28.4 ppm.

IR (thin film, cm^{-1}): 3364, 2953, 2921, 2853, 1713, 1501, 1458, 1365, 1256, 1215, 1164, 1017, 791, 624, 490.

$[\alpha]_D^{25}$ = +60.8 (*c* = 0.24, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{15}H_{19}NNaO_4S_2$ ($M+Na^+$): 364.0648, found 364.0643.



3o

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(cyclohex-2-en-1-ylethynyl)-*L*-cysteinate (3o)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3o** (26.4 mg, 78% yield) as a yellow syrup.

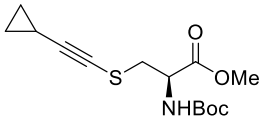
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14-6.07 (m, 1H), 5.55 (d, *J* = 8.3 Hz, 1H), 4.72-4.63 (m, 1H), 3.76 (s, 3H), 3.16 (d, *J* = 4.8 Hz, 2H), 2.12-2.01 (m, 4H), 1.65-1.51 (m, 4H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 155.2, 136.0, 120.9, 80.4, 74.8, 53.8, 52.8, 38.1, 29.8, 29.1, 28.4, 25.8, 22.4, 21.6 ppm.

IR (thin film, cm^{-1}): 3362, 2922, 2854, 1719, 1498, 1458, 1370, 1258, 1216, 1165, 1017, 798, 694.

$[\alpha]_D^{25}$ = +26.2 (*c* = 0.13, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{25}NNaO_4S$ ($M+Na^+$): 362.1397, found 362.1394.



3p

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(cyclopropylethynyl)-*L*-cysteinate (3p)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3p** (13 mg, 43% yield) as a yellow syrup.

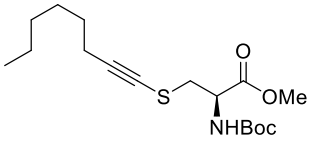
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (d, *J* = 8.2 Hz, 1H), 4.69-4.61 (m, 1H), 3.78 (s, 3H), 3.17-3.02 (m, 2H), 1.43 (s, 9H), 1.35-1.26 (m, 1H), 0.82-0.70 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 155.2, 98.8, 80.3, 63.0, 53.6, 52.7, 37.7, 28.4, 9.0, 0.9 ppm.

IR (thin film, cm^{-1}): 3368, 2954, 2922, 2854, 1716, 1500, 1457, 1364, 1257, 1215, 1164, 1053, 1018, 798, 694.

$[\alpha]_D^{25}$ = +31.1 (*c* = 0.36, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{14}H_{21}NNaO_4S$ ($M+Na^+$): 322.1084, found 322.1081.



3q

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(oct-1-yn-1-yl)-*L*-cysteinate (3q)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent to afford the pure desired product **3q** (14 mg, 41% yield) as a colorless syrup.

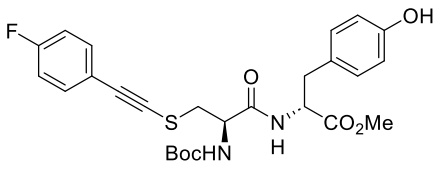
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (d, *J* = 8.2 Hz, 1H), 4.65 (d, *J* = 8.2 Hz, 1H), 3.76 (s, 3H), 3.11 (d, *J* = 4.8 Hz, 2H), 2.26 (t, *J* = 7.2 Hz, 2H), 1.54-1.46 (m, 2H), 1.44 (s, 9H), 1.39-1.22 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 155.2, 95.1, 80.3, 67.0, 53.6, 52.7, 37.7, 31.4, 28.7, 28.7, 28.4, 22.6, 20.3, 14.2 ppm.

IR (thin film, cm^{-1}): 2953, 2923, 2855, 1720, 1499, 1459, 1368, 1258, 1165, 1018, 798.

$[\alpha]_D^{25}$ = +6.5 (*c* = 0.26, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{17}H_{29}NNaO_4S$ ($M+Na^+$): 366.1710, found 366.1705.



3r

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-fluorophenyl)ethynyl)-*L*-cysteinyl-*D*-tyrosinate (3r)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **3r** (35.8 mg, 69% yield) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.98-6.88 (m, 4H), 6.66 (d, *J* = 7.9 Hz, 2H), 6.56 (s, 1H), 5.56 (d, *J* = 9.3 Hz, 1H), 4.87-4.78 (m, 1H), 4.55 (d, *J* = 7.9 Hz, 1H), 3.14 (d, *J* = 6.0 Hz, 1H), 3.04 (dd, *J* = 8.6, 5.5 Hz, 1H), 3.18-2.97 (m, 3H), 1.88 (s, 1H), 1.43 (s, 9H) ppm.

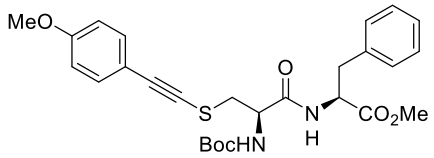
^{19}F NMR (376 MHz, $CDCl_3$) δ -110.22 (m, 1F) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 169.7, 162.7 (d, *J* = 249.9 Hz), 155.6, 155.3, 133.9 (d, *J* = 8.4 Hz), 130.6, 127.2, 119.1 (d, *J* = 3.4 Hz), 115.7 (d, *J* = 22.1 Hz), 115.7, 92.7, 81.1, 53.8, 52.6, 37.2, 31.7, 28.4, 22.8, 14.2 ppm.

IR (thin film, cm^{-1}): 3328, 2954, 2923, 2854, 1666, 1507, 1454, 1369, 1229, 1164, 1019, 836, 796, 534.

$[\alpha]_D^{25}$ = -23.7 (*c* = 0.19, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{26}H_{29}FN_2NaO_6S$ ($M+Na^+$): 539.1623, found 539.1623.



3s

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-methoxyphenyl)ethynyl)-*L*-cysteinyl-*L*-phenylalaninate (3s)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford the pure desired product **3s** (46.8 mg, 91% yield) as a yellow syrup.

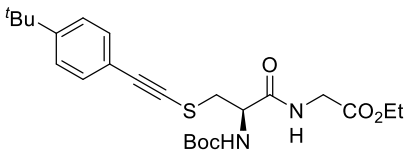
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz, 2H), 7.30-7.21 (m, 3H), 7.13 (d, *J* = 6.5 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.58 (d, *J* = 7.7 Hz, 1H), 4.91-4.82 (m, 1H), 4.58-4.54 (m, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.21-3.06 (m, 4H), 1.41 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 169.6, 159.9, 155.4, 135.7, 133.7, 129.5, 128.7, 127.2, 114.9, 114.0, 93.6, 80.8, 76.6, 55.4, 55.0, 53.5, 52.4, 38.0, 37.2, 28.3 ppm.

IR (thin film, cm^{-1}): 3321, 2954, 2921, 2853, 1666, 1604, 1505, 1458, 1371, 1253, 1168, 1087, 1018, 795, 697, 538.

$[\alpha]_D^{25}$ = -19.2 (*c* = 0.24, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{27}H_{32}N_2NaO_6S$ ($M+Na^+$): 535.1873, found 535.1874.



3t

Ethyl *N*-(*tert*-butoxycarbonyl)-*S*-((4-(*tert*-butyl)phenyl)ethynyl)-*L*-cysteinylglycinate (3t)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **3t** (41.3 mg, 89% yield) as a colorless syrup.

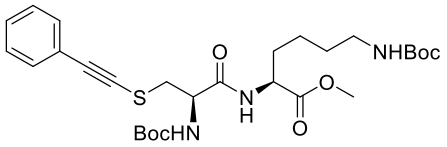
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.97 (s, 1H), 5.60 (d, *J* = 7.7 Hz, 1H), 4.62 (d, *J* = 8.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.12-3.94 (m, 2H), 3.31-3.12 (m, 2H), 1.43 (s, 9H), 1.29 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.5, 155.6, 152.0, 131.7, 125.4, 119.9, 93.9, 80.9, 61.7, 54.8, 41.7, 37.4, 34.9, 31.3, 28.4, 14.2 ppm.

IR (thin film, cm^{-1}): 2921, 2855, 1739, 1458, 1374, 1256, 1090, 1016, 794, 695, 480.

$[\alpha]_D^{25}$ = -5.7 (*c* = 0.14, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{24}H_{34}N_2NaO_5S$ ($M+Na^+$): 485.2081, found 485.2089.



3u

Methyl N_6-(*tert*-butoxycarbonyl)-N_2-(*N*-(*tert*-butoxycarbonyl)-*S*-(phenylethynyl)-*L*-cysteinyl)-*L*-lysinate (3u)

The title compound was synthesized according to general procedure E. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **3u** (51.2 mg, 91% yield) as a yellow syrup.

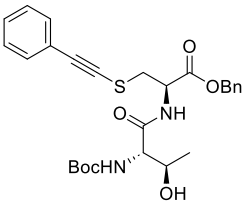
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.33-7.27 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.65 (s, 1H), 4.69-4.52 (m, 3H), 3.72 (s, 3H), 3.31-3.15 (m, 2H), 3.11-3.03 (m, 2H), 1.94-1.81 (m, 1H), 1.72-1.64 (m, 3H), 1.46-1.41 (m, 18H) 1.38-1.29 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.9, 156.2, 155.6, 131.7, 128.9, 128.5, 122.9, 93.7, 80.9, 79.3, 78.5, 55.0, 52.6, 52.2, 40.3, 37.1, 32.3, 29.3, 28.6, 28.4, 22.4 ppm.

IR (thin film, cm^{-1}): 3330, 2953, 2922, 2854, 1689, 1502, 1458, 1368, 1254, 1167, 1091, 1018, 861, 795, 757, 690, 528.

$[\alpha]_D^{25}$ = -49.3 (*c* = 0.14, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{28}H_{41}N_3NaO_7S$ ($M+Na^+$): 586.2557, found 586.2557.



3v

Benzyl *N*-((*tert*-butoxycarbonyl)-*L*-threonyl)-*S*-(phenylethynyl)-*L*-cysteinate (3v)

The title compound was synthesized according to general procedure E (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as eluent to afford the pure desired product **3v** (31 mg, 61% yield) as a yellow solid.

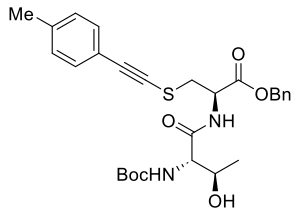
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.1 Hz, 1H), 7.42-7.39 (m, 2H), 7.33 (d, *J* = 5.2 Hz, 3H), 7.29-7.26 (m, 5H), 5.47 (d, *J* = 7.5 Hz, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 4.99-4.93 (m, 1H), 4.34 (s, 1H), 4.15 (d, *J* = 7.2 Hz, 1H), 3.32 (d, *J* = 5.0 Hz, 2H), 2.99 (s, 1H), 1.45 (s, 9H), 1.16 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 169.6, 156.5, 134.9, 131.9, 128.8, 128.7, 128.5, 128.5, 122.9, 93.7, 80.6, 68.0, 67.0, 58.3, 52.2, 37.4, 28.4, 18.3 ppm.

$[\alpha]_D^{25}$ = -7.3 (*c* = 0.11, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{27}H_{33}N_2O_6S$ ($M+H^+$): 513.2054, found 513.2047.

M.p.: 82.1-83.5°C.



3w

Benzyl *N*-((*tert*-butoxycarbonyl)-*L*-threonyl)-*S*-(*p*-tolylethynyl)-*L*-cysteinate (3w)

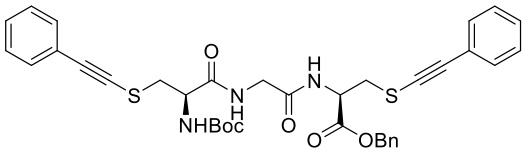
The title compound was synthesized according to general procedure E (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as eluent to afford the pure desired product **3w** (24.7 mg, 47% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 1H), 7.42-7.38 (m, 1H), 7.35-7.30 (m, 3H), 7.30-7.28 (m, 2H), 7.24-7.19 (m, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 5.46 (d, *J* = 7.4 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 4.98-4.92 (m, 1H), 4.36-4.32 (m, 1H), 4.14 (d, *J* = 7.2 Hz, 1H), 3.31 (d, *J* = 5.0 Hz, 2H), 2.95 (s, 1H), 2.33 (s, 3H), 1.46 (s, 9H), 1.16 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 169.7, 156.5, 139.1, 134.9, 133.9, 132.0, 129.3, 128.8, 128.7, 128.5, 119.9, 93.9, 80.6, 68.0, 67.1, 58.3, 52.2, 37.4, 28.4, 21.6, 18.3 ppm.

$[\alpha]_D^{25}$ = -2.0 (*c* = 0.10, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{28}H_{35}N_2O_6S$ ($M+H^+$): 527.2210, found 527.2201.



3x

benzyl *N*-*N*-(*tert*-butoxycarbonyl)-*S*-(phenylethynyl)-*L*-cysteinylglycyl-*S*-(phenylethynyl)-*L*-cysteinate (3x)

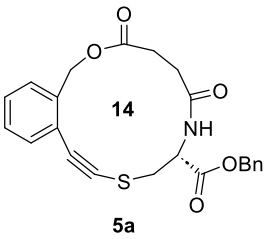
The title compound was synthesized according to general procedure E (**1x** 75.1 mg, **2a** 4.0 equiv. 41 mg, $Cu(OTf)_2$ 14.4 mg, K_2CO_3 2.4 equiv. 33.1 mg, Xantphos 23.2 mg). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **3x** (36.3 mg, 54% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 2H), 7.42-7.36 (m, 2H), 7.34-7.31 (m, 3H), 7.30-7.26 (m, 8H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.11-7.07 (m, 1H), 5.64-5.58 (m, 1H), 5.21-5.08 (m, 2H), 5.01-4.97 (m, 1H), 4.61-4.55 (m, 1H), 4.10-3.93 (m, 2H), 3.36-3.27 (m, 2H), 3.23-3.13 (m, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.6, 168.5, 155.6, 134.9, 131.9, 131.8, 128.8, 128.7, 128.6, 128.5, 128.4, 123.0, 122.9, 93.9, 93.4, 81.1, 78.3, 78.1, 68.0, 52.4, 43.3, 37.4, 32.1, 29.8, 28.4 ppm.

$[\alpha]_D^{25}$ = -34.0 (*c* = 0.10, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{36}H_{38}N_3O_6S_2$ ($M+H^+$): 672.2196, found 672.2181.



5a

The title compound was synthesized according to general procedure F. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford the pure desired product **5a** (10.0 mg, 79% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 7H), 7.32-7.27 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.45 (d, *J* = 11.1 Hz, 1H), 5.29-5.20 (m, 3H), 4.90 (d, *J* = 11.1 Hz, 1H), 3.42 (dd, *J* = 14.4, 2.8 Hz, 1H), 3.23 (dd, *J* = 14.4, 4.1 Hz, 1H), 3.04-2.93 (m, 1H), 2.54-2.45 (m, 2H), 2.43-2.35 (m, 1H) ppm.

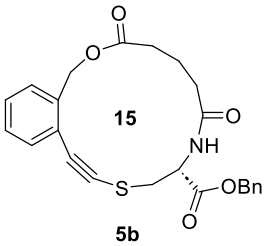
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 171.1, 169.5, 136.5, 134.9, 132.0, 131.1, 129.1, 128.9, 128.9, 128.7, 128.3, 124.5, 90.9, 83.8, 68.1, 65.6, 53.9, 37.9, 31.4, 30.7 ppm.

IR (thin film, cm^{-1}): 3315, 2953, 2921, 2853, 1731, 1647, 1532, 1459, 1405, 1376, 1318, 1261, 1216, 1089, 1015, 798, 755, 697, 565.

$[\alpha]_D^{25}$ = +4.5 (*c* = 0.11, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{23}H_{22}NO_5S$ ($M+H^+$): 424.1213, found 424.1217.

M.p.: 143.3-144.5°C.



5b

The title compound was synthesized according to general procedure F. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford the pure desired product **5b** (9.0 mg, 69% yield) as a yellow solid.

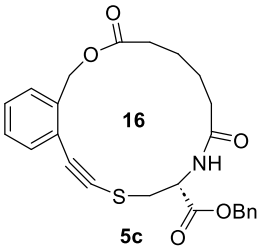
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (m, *J* = 6.6 Hz, 2H), 7.38-7.32 (m, 5H), 7.23-7.17 (m, 2H), 6.56 (dd, *J* = 7.4, 3.4 Hz, 1H), 5.30-5.26 (m, 2H), 5.25 (s, 1H), 5.21 (d, *J* = 7.4 Hz, 1H), 5.17-5.12 (m, 1H), 3.33-3.22 (m, 2H), 2.57-2.29 (m, 1H), 2.36-2.29 (m, 1H), 2.13-2.02 (m, 2H), 1.90-1.83 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 172.0, 169.6, 138.4, 135.1, 133.9, 131.9, 129.9, 129.6, 129.2, 128.8, 128.7, 123.4, 91.3, 83.2, 67.9, 65.7, 54.0, 37.2, 34.5, 32.2, 21.9 ppm.

[α]$_D^{25}$ = -60 (*c* = 0.16, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{24}H_{24}NO_5S$ ($M+H^+$): 438.1370, found 438.1361.

M.p.: 162.4-163.6°C.



5c

The title compound was synthesized according to general procedure F. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **5c** (6.8 mg, 50% yield) as a white solid.

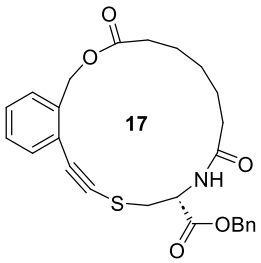
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 1H), 7.42-7.35 (m, 4H), 7.33-7.30 (m, 4H), 6.64 (d, *J* = 7.5 Hz, 1H), 5.27-5.20 (m, 2H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.09-5.02 (m, 2H), 3.36-3.30 (m, 2H), 2.36-2.22 (m, 4H), 1.74-1.69 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 172.8, 169.9, 137.1, 135.1, 133.4, 131.3, 129.0, 128.9, 128.8, 128.8, 128.6, 123.9, 91.2, 82.7, 67.9, 65.4, 52.6, 37.9, 36.2, 34.3, 25.1, 24.4 ppm.

[α]$_D^{25}$ = -29.4 (*c* = 0.17, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{25}H_{26}NO_5S$ ($M+H^+$): 452.1526, found 452.1518.

M.p.: 158.2-159.7°C.



5d

The title compound was synthesized according to general procedure F. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (5:2) as eluent to afford the pure desired product **5d** (10.2 mg, 73% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 1H), 7.44-7.41 (m, 1H), 7.37-7.33 (m, 4H), 7.33-7.29 (m, 3H), 6.71 (d, *J* = 7.6 Hz, 1H), 5.27 (d, *J* = 11.3 Hz, 1H), 5.22-5.14 (m, 2H), 5.11 (d, *J* = 11.3 Hz, 1H), 5.04-4.99 (m, 1H), 3.42 (dd, *J* = 13.6, 4.3 Hz, 1H), 3.30 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.35-2.30 (m, 2H), 2.29-2.24 (m, 1H), 2.18-2.09 (m, 1H), 1.69-1.64 (m, 2H), 1.63-1.56 (m, 2H), 1.34-1.27 (m, 2H)

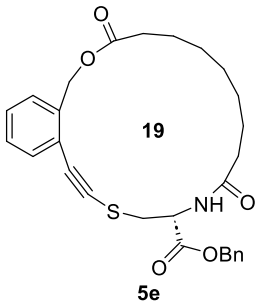
ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 173.1, 169.9, 137.6, 135.1, 132.9, 131.3, 128.9, 128.9, 128.8, 128.7, 128.5, 123.9, 91.3, 82.7, 67.9, 65.2, 52.5, 37.2, 36.0, 33.9, 27.6, 24.8, 23.9 ppm.

$[\alpha]_D^{25}$ = +4 (*c* = 0.10, $CHCl_3$).

H**RMS** (ESI-TOF): calculated for $C_{26}H_{28}NO_5S$ ($M+H^+$): 466.1683, found 366.1676.

M.p.: 202.1-203.4°C.



5e

The title compound was synthesized according to general procedure F. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the pure desired product **5e** (9.1 mg, 62% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.25 (m, 9H), 6.63 (d, *J* = 7.3 Hz, 1H), 5.26 (d, *J* = 11.7 Hz, 1H), 5.18 (s, 2H), 5.09 (d, *J* = 11.7 Hz, 1H), 4.98-4.92 (m, 1H), 3.47 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.33 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.38-2.20 (m, 4H), 1.77-1.65 (m, 4H), 1.44-1.27 (m, 6H) ppm.

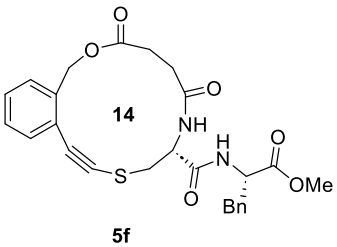
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 173.3, 170.1, 137.3, 135.0, 132.3, 130.5, 128.8, 128.8, 128.6, 128.5, 123.7, 91.5, 82.7, 67.9, 65.1, 52.1, 37.2, 36.3, 34.4, 28.0, 27.9, 27.4, 25.2, 24.4 ppm.

IR (thin film, cm^{-1}): 3283, 2924, 2855, 1734, 1660, 1529, 1451, 1378, 1325, 1255, 1143, 1078, 1017, 796, 756, 714, 687, 597, 536.

$[\alpha]_D^{25}$ = -3.8 (*c* = 0.13, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{28}H_{32}NO_5S$ ($M+H^+$): 494.1996, found 494.1990.

M.p.: 195.1-196.7°C.



5f

The title compound was synthesized according to general procedure F (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1) as

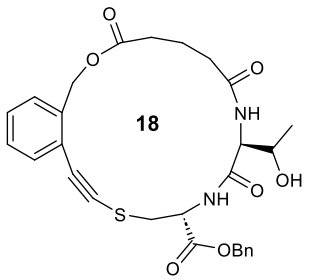
eluent to afford the pure desired product **5f** (9.2 mg, 62% yield) as a yellow-green syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.25-7.21 (m, 3H), 7.09 (d, *J* = 7.0 Hz, 2H), 6.97 (d, *J* = 7.7 Hz, 1H), 5.13 (dd, *J* = 10.9, 4.8 Hz, 1H), 4.87-4.81 (m, 1H), 4.76 (d, *J* = 12.5 Hz, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 3.73 (s, 3H), 3.71-3.65 (m, 1H), 3.44 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.16 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.06 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.70-2.62 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 171.8, 166.6, 142.5, 135.9, 132.2, 129.5, 128.9, 128.7, 128.6, 127.9, 127.3, 122.0, 92.6, 81.6, 64.2, 54.3, 53.5, 52.6, 37.7, 33.4, 29.8, 28.2 ppm.

$[\alpha]_D^{25}$ = -6.7 (*c* = 0.12, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{26}H_{27}N_2O_6S$ ($M+H^+$): 495.1584, found 495.1578.



5g

The title compound was synthesized according to general procedure F (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **5g** (10.2 mg, 63% yield) as a white solid.

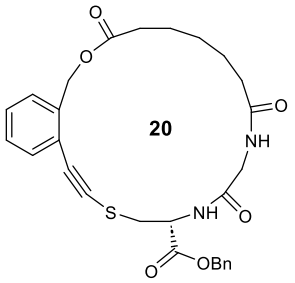
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 6.6 Hz, 1H), 7.40 (s, 1H), 7.36-7.34 (m, 4H), 7.31-7.28 (m, 3H), 6.39 (d, *J* = 8.4 Hz, 1H), 5.31 (d, *J* = 11.8 Hz, 1H), 5.21-5.11 (m, 3H), 5.04 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 5.8 Hz, 1H), 4.45 (d, *J* = 8.6 Hz, 2H), 3.47 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.28 (dd, *J* = 13.6, 7.5 Hz, 1H), 3.15 (s, 1H), 2.59-2.55 (m, 1H), 2.34 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.19-2.14 (m, 2H), 2.03-1.89 (m, 2H), 1.14 (d, *J* = 6.2 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 173.5, 172.0, 169.4, 137.4, 134.9, 132.4, 130.4, 128.9, 128.8, 128.8, 128.7, 128.6, 123.4, 91.5, 82.8, 67.9, 66.1, 65.4, 56.9, 52.5, 36.4, 34.6, 32.8, 20.9, 18.7 ppm.

$[\alpha]_D^{25}$ = -29 (*c* = 0.10, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{28}H_{31}N_2O_7S$ ($M+H^+$): 539.1846, found 539.1837.

M.p.: 184.8-185.2°C.



5h

The title compound was synthesized according to general procedure F (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **5h** (8.3 mg, 53% yield) as a white solid.

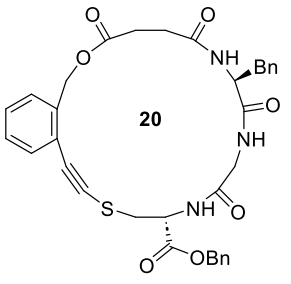
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 9H), 6.47 (s, 1H), 5.27 (d, *J* = 6.4 Hz, 1H), 5.23 (s, 1H), 5.17-5.09 (m, 2H), 5.00-4.95 (m, 1H), 4.11 (dd, *J* = 16.6, 5.9 Hz, 1H), 3.98 (s, 1H), 3.87-3.80 (m, 1H), 3.32-3.27 (m, 2H), 2.40-2.23 (m, 4H), 1.71-1.65 (m, 2H), 1.46 (d, *J* = 7.0 Hz, 2H), 1.38-1.33 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 174.2, 169.7, 169.6, 138.2, 134.9, 132.7, 129.5, 129.0, 128.8, 128.7, 128.7, 128.6, 128.4, 128.4, 122.9, 90.7, 82.5, 67.9, 65.3, 51.7, 43.7, 37.2, 35.6, 33.3, 27.5, 24.8, 23.5 ppm.

$[\alpha]_D^{25}$ = -36.4 (*c* = 0.11, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{28}H_{31}N_2O_6S$ ($M+H^+$): 523.1897, found 523.1881.

M.p.: 187.2-183.5°C.



5i

The title compound was synthesized according to general procedure F (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **5i** (8.1 mg, 43% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 9H), 7.25-7.18 (m, 4H), 7.13 (s, 1H), 7.08 (d, *J* = 7.0 Hz, 2H), 5.16 (s, 2H), 5.00 (d, *J* = 4.9 Hz, 1H), 4.91 (dd, *J* = 10.9, 5.5 Hz, 1H), 4.71 (s, 2H), 4.09 (dd, *J* = 17.2, 5.6 Hz, 1H), 3.74 (dd, *J* = 16.9, 4.1 Hz, 1H), 3.56 (s, 1H), 3.48-3.37 (m, 2H), 3.34-3.26 (m, 1H), 3.16 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.51-2.37 (m, 4H) ppm.

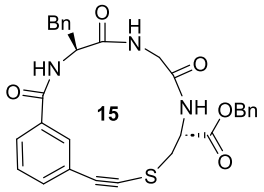
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 169.9, 169.6, 168.6, 142.9, 136.4, 134.9, 132.5, 129.1, 129.0,

128.9, 128.8, 128.7, 128.6, 128.4, 127.9, 127.2, 121.8, 91.4, 82.4, 68.1, 63.8, 55.3, 52.7, 43.0, 36.9, 33.8, 29.8, 28.1 ppm.

$[\alpha]_D^{25}$ = -2.5 (*c* = 0.24, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{34}H_{34}N_3O_7S$ ($M+H^+$): 628.2112, found 628.2098.

M.p.: 217.7-218.9°C.



5j

The title compound was synthesized according to general procedure F (K_2CO_3 1.2 equiv.). The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as eluent to afford the pure desired product **5j** (8.3 mg, 51% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.62-7.56 (m, 3H), 7.36-7.28 (m, 7H), 7.23-7.19 (m, 3H), 7.10 (s, 1H), 5.13 (s, 2H), 4.87 (d, *J* = 7.1 Hz, 1H), 4.80 (s, 1H), 4.13 (dd, *J* = 17.0, 5.7 Hz, 1H), 3.70 (d, *J* = 14.4 Hz, 1H), 3.16-3.14 (m 3H), 3.09 (s, 1H), 2.81-2.73 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.4, 168.8, 166.9, 136.5, 135.6, 135.1, 133.5, 131.3, 129.3, 128.9, 128.8, 128.7, 128.4, 127.7, 127.4, 122.9, 82.7, 78.7, 67.8, 55.9, 52.9, 43.4, 40.8, 38.4 ppm.

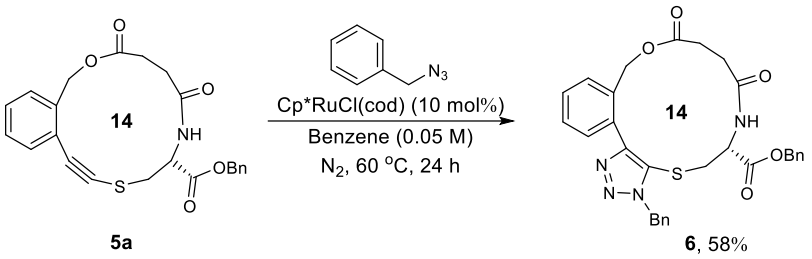
$[\alpha]_D^{25}$ = -5.7 (*c* = 0.14, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{30}H_{28}N_3O_5S$ ($M+H^+$): 542.1744, found 542.1726.

M.p.: 176.5-178.1°C.

5. Further Derivatization of Cyclic Peptides

5.1 [3+2] cycloaddition with benzyl azide



5a **6**, 58%

Cp*RuCl(cod) (1.9 mg, 10 mol%) was dissolved in dry benzene (1 mL) and **5a** (21.2 mg, 0.05 mmol) and benzyl azide (6.7 mg, 0.05 mmol, 1.0 equiv.) were then added. The reaction mixture was purged with nitrogen for 10 minutes. The mixture was stirred at 60 °C for 24 h.[7] The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:2) as eluent to afford the desired product **6** (16.1 mg, 58% yield) as a yellow-green syrup.

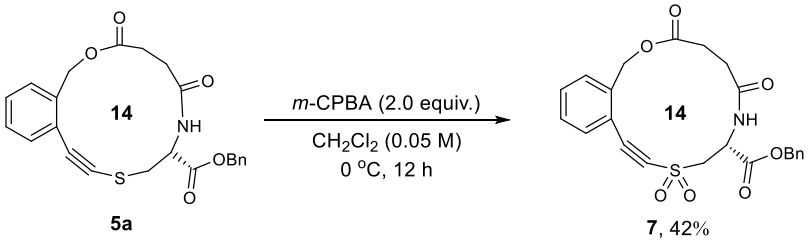
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.39-7.36 (m, 5H), 7.36-7.34 (m, 4H), 7.34-7.29 (m, 4H), 6.04 (s, 1H), 5.65 (d, *J* = 14.8 Hz, 1H), 5.59 (d, *J* = 14.8 Hz, 1H), 5.51-5.33 (m, 3H), 5.21-5.16 (m, 1H), 4.81 (s, 1H), 3.04 (s, 1H), 2.91 (d, *J* = 13.2 Hz, 1H), 2.71 (s, 1H), 2.27 (s, 1H), 1.98 (d, *J* = 15.3 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 173.3, 170.1, 137.3, 135.0, 132.3, 130.5, 128.8, 128.8, 128.6, 128.5, 123.7, 91.5, 82.7, 67.9, 65.1, 52.1, 37.2, 36.3, 34.4, 28.0, 27.9, 27.4, 25.2, 24.4 ppm.

$[\alpha]_D^{25}$ = -56.7 (*c* = 0.12, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{30}H_{29}N_4O_5S$ ($M+H^+$): 557.1853, found 557.1848.

5.2 Oxidation to sulfone or sulfoxide



5a **7**, 42%

5a (21.2 mg, 0.05 mmol) was dissolved in dry dichloromethane (1 mL) and *m*-CPBA (17.3 mg, 0.1 mmol, 2.0 equiv.) was then added. The mixture was stirred at 0 °C for 12 h.[7] The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to afford the desired product **7** (9.5 mg, 42% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.52-7.41 (m, 4H), 7.38-7.35 (m, 4H), 6.76 (d, *J* = 6.3 Hz, 1H), 5.35 (d, *J* = 11.6 Hz, 1H), 5.31-5.17 (m, 2H), 5.00-4.93 (m, 2H), 4.19 (dd, *J* = 15.7,

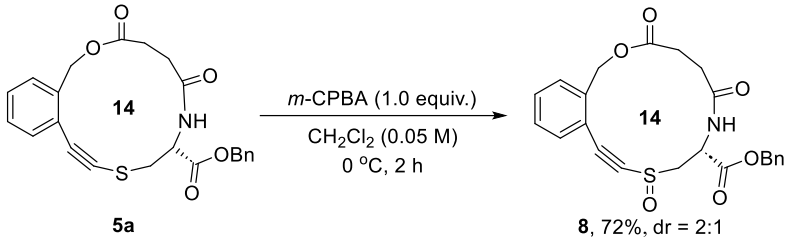
3.9 Hz, 1H), 4.00 (dd, *J* = 15.7, 5.1 Hz, 1H), 2.95-2.85 (m, 1H), 2.61-2.50 (m, 2H), 2.49-2.40 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.8, 168.5, 138.5, 134.7, 134.6, 132.1, 131.4, 129.5, 128.9, 128.9, 128.8, 118.8, 91.1, 88.2, 68.8, 64.9, 58.4, 49.8, 30.7, 29.7 ppm.

$[\alpha]_D^{25}$ = +49.2 (*c* = 0.14, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{23}H_{22}NO_7S$ ($M+H^+$): 456.1111, found 456.1108.

M.p.: 183.1-184.9°C.



5a **8**, 72%, dr = 2:1

5a (21.2 mg, 0.05 mmol) was dissolved in dry dichloromethane (1 mL) and *m*-CPBA (8.6 mg, 0.05 mmol, 1.0 equiv.) was then added. The mixture was stirred at 0 °C for 2 h.[7] The organic solvent was removed under vacuum and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (1:1) as eluent to afford the desired product **8** (15.8 mg, 72% yield, diastereomeric ratio of 2:1) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.60 (m, 3H), 7.45-7.40 (m, 9H), 7.39-7.34 (m, 15H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.60 (d, *J* = 7.0 Hz, 1H), 5.40 (d, *J* = 11.5 Hz, 2H), 5.32-5.29 (m, 2H), 5.28-5.24 (m, 3H), 5.21-5.16 (m, 4H), 5.04 (d, *J* = 11.5 Hz, 2H), 5.00-4.95 (m, 1H), 4.87 (d, *J* = 11.5 Hz, 2H), 4.17-4.10 (m, 3H), 3.71 (dd, *J* = 14.1, 9.1 Hz, 1H), 3.56 (dd, *J* = 14.0, 4.4 Hz, 2H), 3.05-2.96 (m, 3H), 2.66-2.58 (m, 3H), 2.49-2.46 (m, 3H), 2.45-2.42 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.8, 171.0, 170.9, 169.8, 169.4, 137.5, 137.4, 135.1, 135.0, 134.7, 133.8, 133.7, 133.6, 131.3, 131.1, 131.0, 130.3, 129.9, 129.4, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 120.8, 103.9, 88.7, 68.3, 68.3, 65.1, 65.0, 53.5, 48.3, 46.4, 30.9, 30.9, 29.9, 29.8, 29.7, 29.5 ppm.

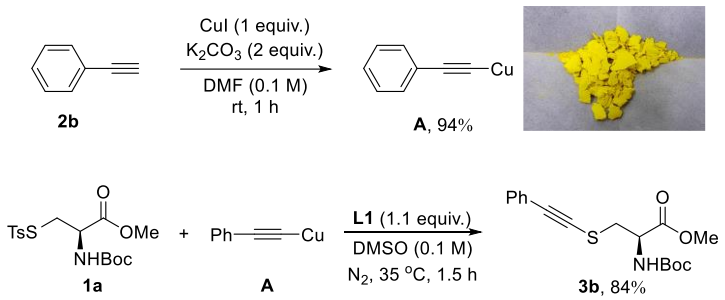
$[\alpha]_D^{25}$ = -263.6 (*c* = 0.14, $CHCl_3$).

HRMS (ESI-TOF): calculated for $C_{23}H_{22}NO_6S$ ($M+H^+$): 440.1162, found 440.1155.

M.p.: 152.1-153.8°C.

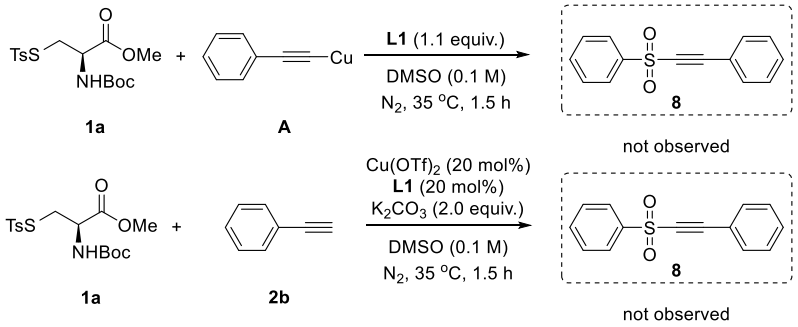
6. Mechanistic Studies

6.1 Investigation for intermediate alkynylated copper A



Alkynylated copper species **A** was synthesized according to the standard literature procedures[9] with 1 mmol ethynylbenzene **2b** and the precipitate was filtered out and washed with water, ethanol, and diethyl ether, three times each. The solid was vacuum-dried, and 153 mg (94% yield) of a bright yellow solid was obtained. Following the reaction of *S*-tosyl-protected cysteine **1a** (14.5 mg, 0.05 mmol), alkynylated copper species **A** (8.2 mg, 0.05 mmol), Xantphos (31.8 mg, 0.055 mmol, 1.1 equiv.) and DMSO (0.5 mL) at 35 °C for 1.5 h, product **3b** was obtained in an excellent yield of 84% (14.1 mg). Alkynylated copper species **A** maybe a key intermediates for this reaction.[10]

6.2 HRMS analysis of potential byproduct



A reaction of *S*-tosyl-protected cysteine **1a** (14.5 mg, 0.05 mmol) with **2b** (22 mg, 0.10 mmol) following general procedure E, and **1a** (14.5 mg, 0.05 mmol) with alkynylated copper species **A**, Xantphos (31.8 mg, 0.055 mmol, 1.1 equiv.) and DMSO (0.5 mL) at 35 °C for 1.5 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated NaCl aqueous. Then the combined organic phase was dried over anhydrous Na_2SO_4, then removed in vacuo. The resulting residue was directly subjected for HRMS analysis. The potential byproduct alkynyl aryl sulfone **8** was not detected, possibly ruling out the path b in Figure S7.

A reaction of *S*-tosyl-protected cysteine **1a** (14.5 mg, 0.05 mmol) with **2b** (22 mg, 0.10 mmol) following general procedure E, and **1a** (14.5 mg, 0.05 mmol) with alkynylated copper species **A**, xantphos (31.8 mg, 0.055 mmol, 1.1 equiv.) and DMSO (0.5 mL) at 35 ºC for 1.5 h. Upon completion, the reaction mixture was filtration and subjected for HRMS analysis. The Ts-CuLn after reductive elimination or sigma-bond metathesis leads to the formation potassium 4-methylbenzenesulfinate in Figure S4.

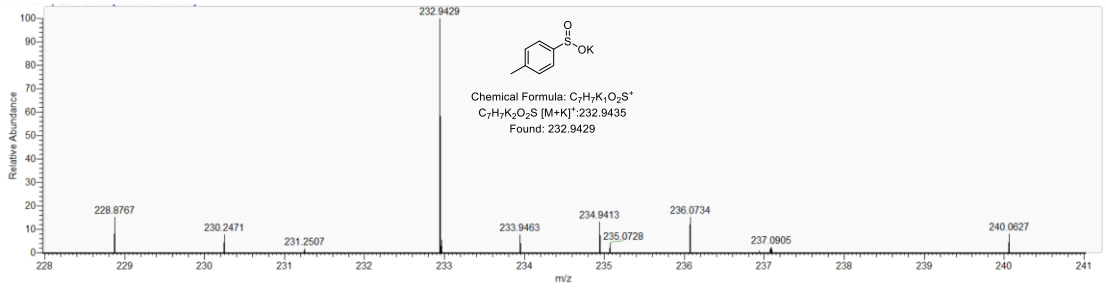
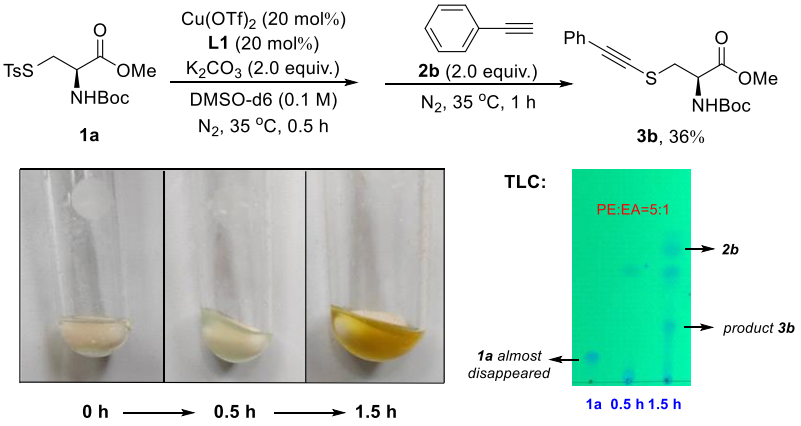


Figure S4. Crude HRMS analysis for the reaction

6.3 Investigaiton of the pathway via oxidative addition of catalyst with 1a



S-tosyl-protected cysteine **1a** (14.5 mg, 0.05 mmol), K_2CO_3 (0.1 mmol, 2 equiv., 13.8 mg), $Cu(OTf)_2$ (20 mol%, 3.6 mg), **L1** (20 mol%, 5.8 mg) was dissolved in DMSO-d6 (0.5 mL) stirred at 35 °C for 0.5 h, then added **2b** (22 mg, 0.10 mmol) for 1 h.

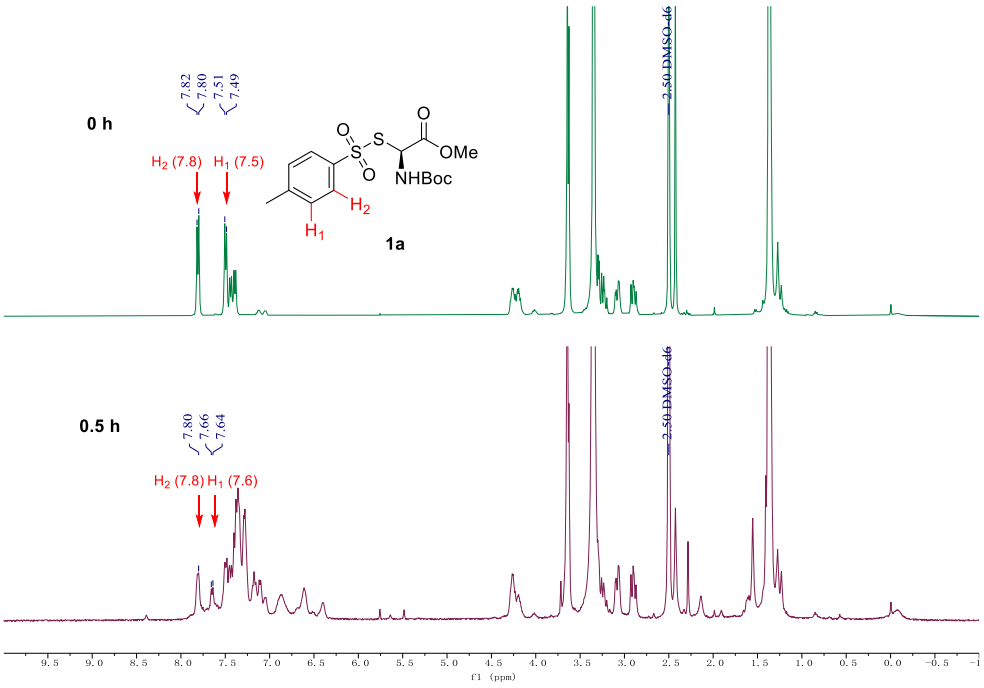


Figure S5. ^{1}H NMR analysis for the reaction of copper complex with 1a

The comparison of in situ ^{1}H NMR spectrum and pure starting material (Figure S5), and the TLC analysis (page S50) collectively demonstrated almost full conversion of **1a**. A new spot was observed at the baseline of the TLC plate, indicating the formation of a new species, which was subsequently converted to product **3b** (36%, 6.0 mg) (Figure S6).

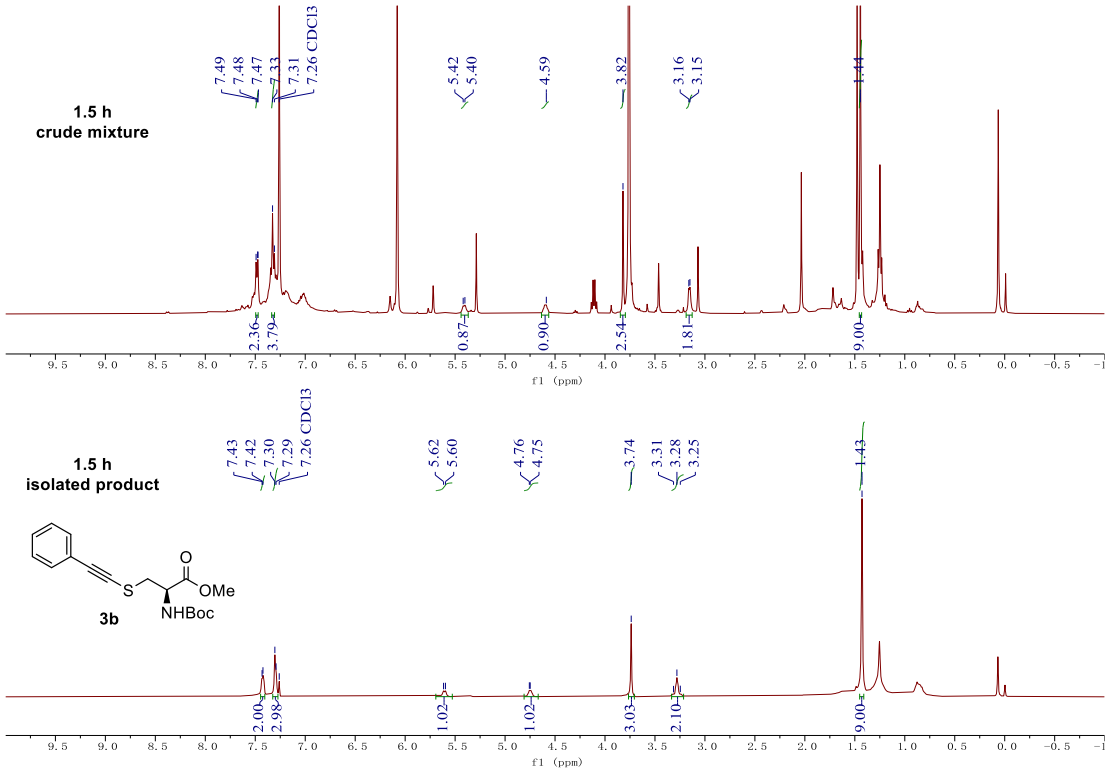
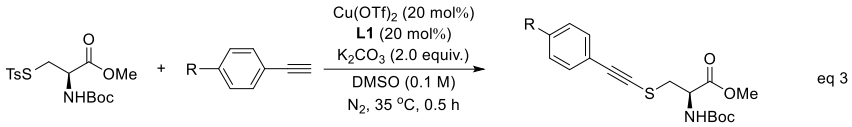
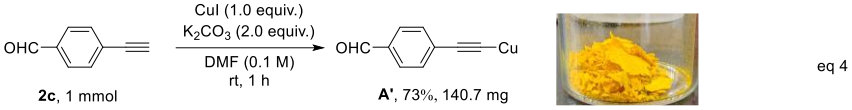


Figure S6. ^{1}H NMR analysis for the ligand exchange with alkyne

6.4 Rate-determining step (RDS) analysis



eq 3



eq 4

A competition experiment, using equimolar amounts of two alkynes, **2a** and **2c**, revealed that alkyne **2a** reacts at a significantly faster rate compared to **2c** (eq 3) (yield determined by crude ^{1}H NMR spectra analysis using 1,3,5-Trimethoxybenzene as an internal standard). Furthermore, when the preformed alkynylated copper complex **A'** was employed, the reaction yielded a result comparable to that in eq 1 but with a significantly higher yield than the catalytic reaction (isolated yield 66% vs 38%) (eq 4). These findings suggest that the formation of the intermediate alkynylated copper species **A'** is likely the rate-determining step in this transformation.

6.5 Proposed mechanism

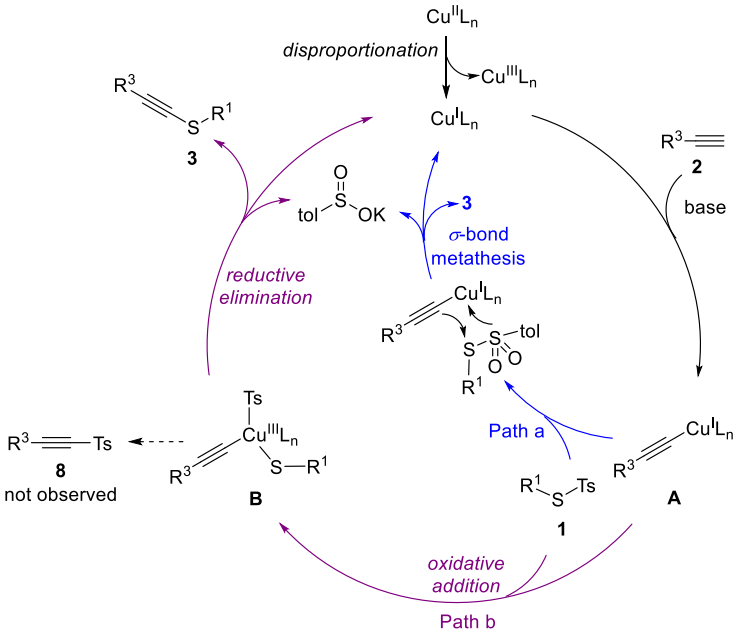


Figure S7. Proposed mechanism for σ-bond metathesis process

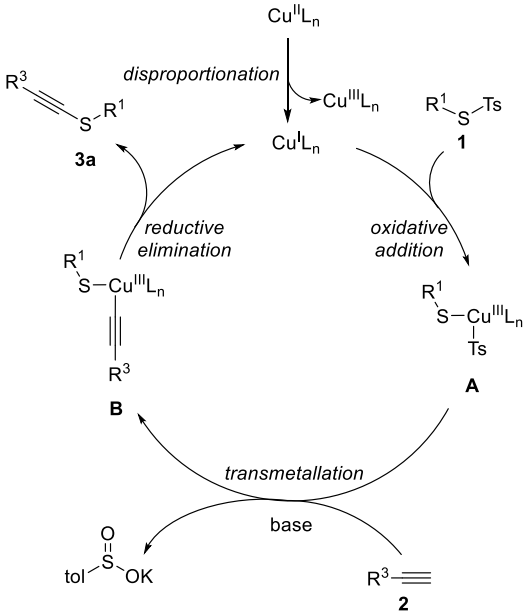


Figure S8. Proposed mechanism for oxidative addition of Cu(I) species with 1

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8. Copies of NMR Spectra

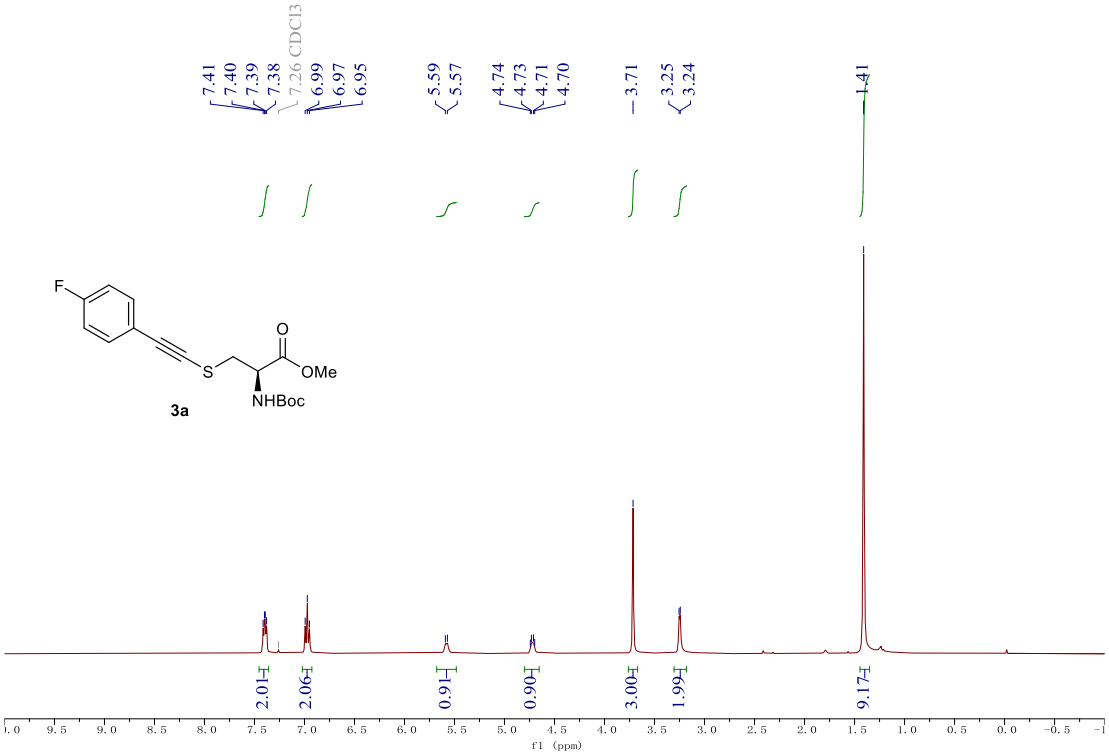

Figure S9. ^{1}H NMR (400 MHz, $CDCl_3$) spectra for compound 3a

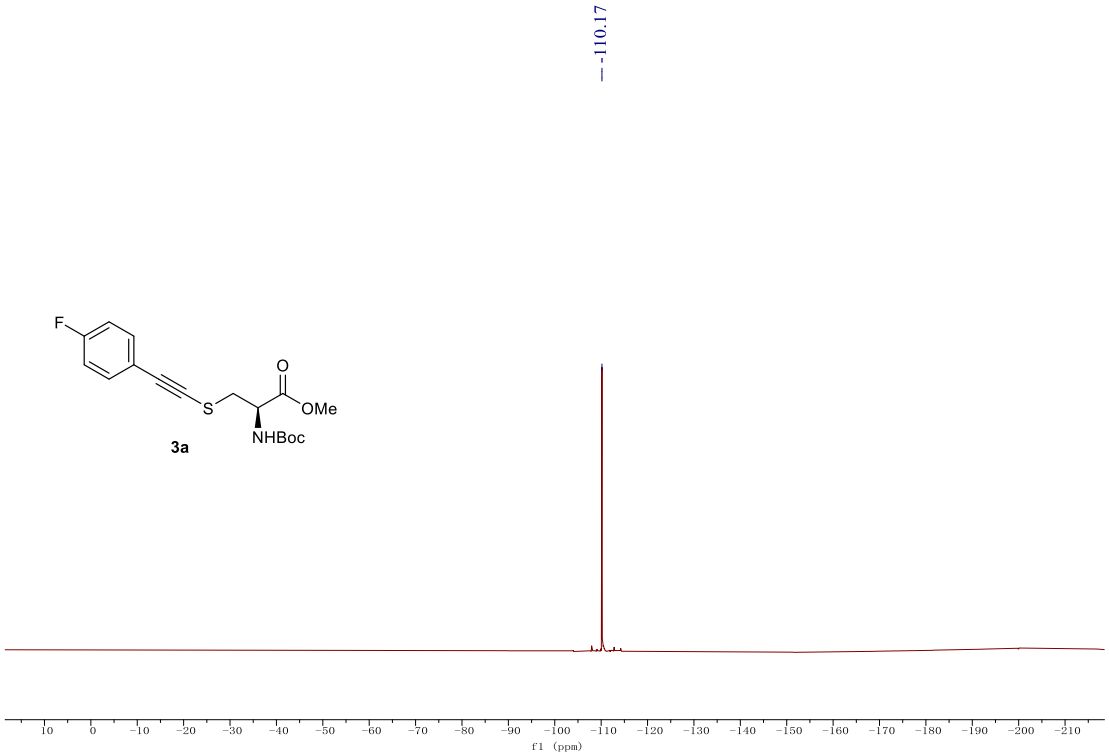

Figure S10. ^{19}F NMR (376 MHz $CDCl_3$) spectra for compound 3a

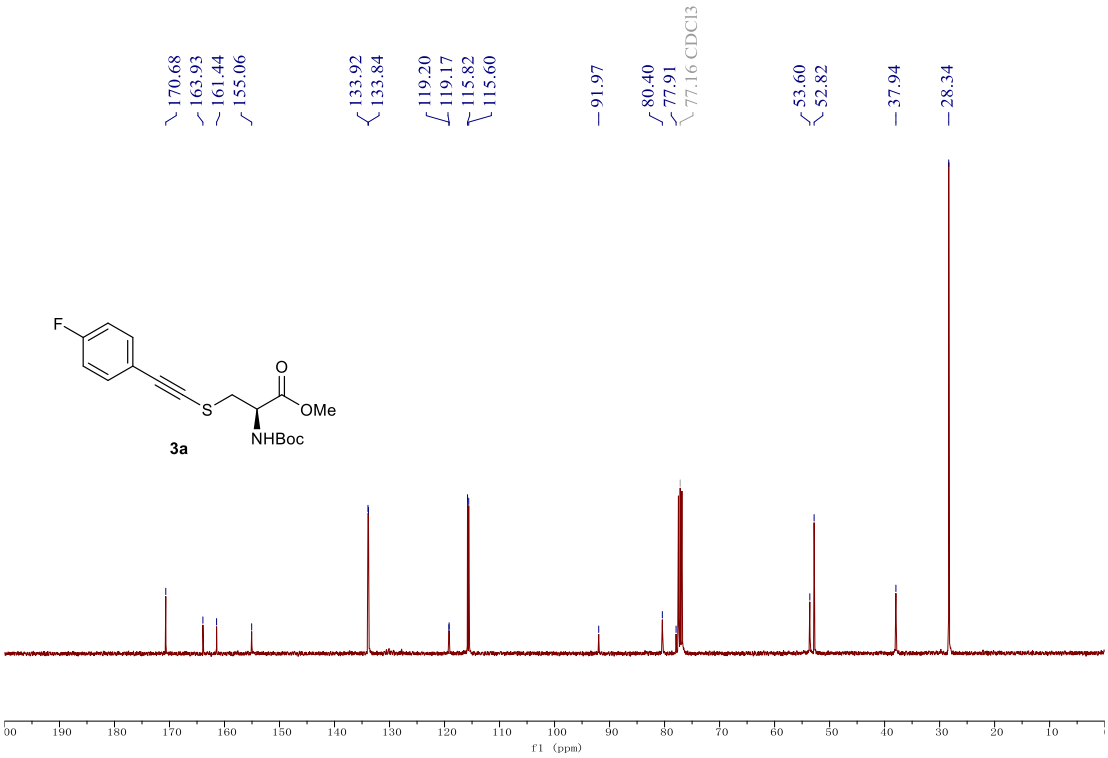

Figure S11. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3a

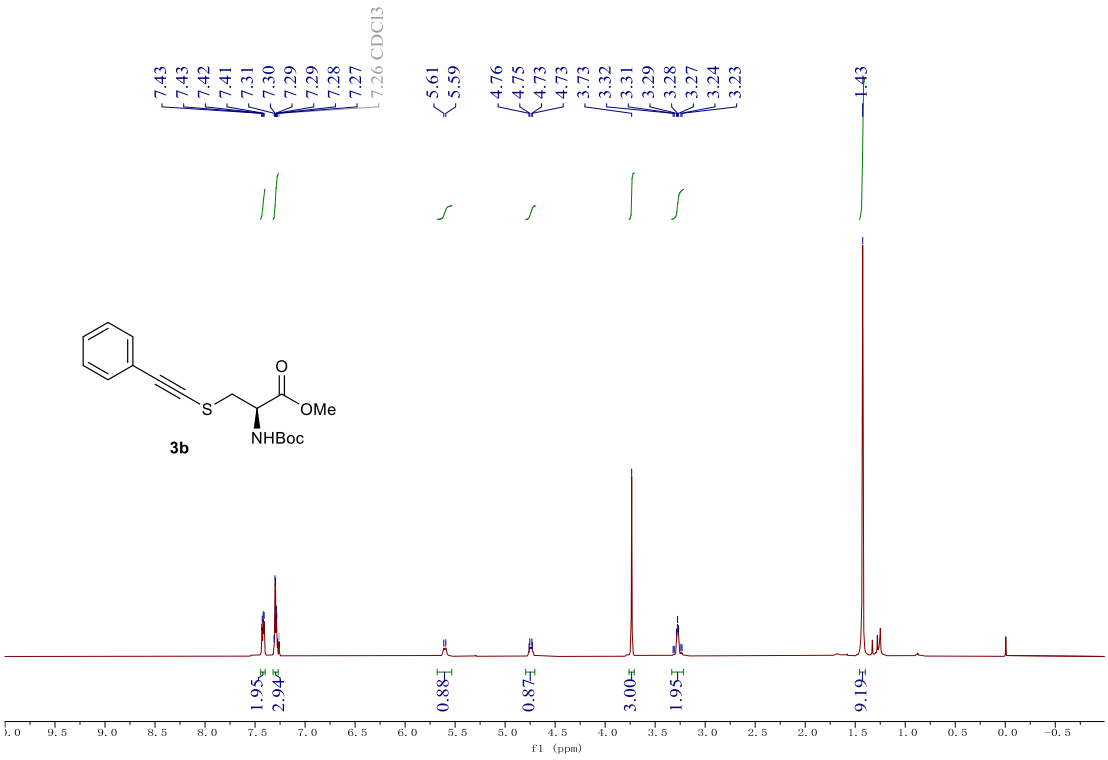

Figure S12. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3b

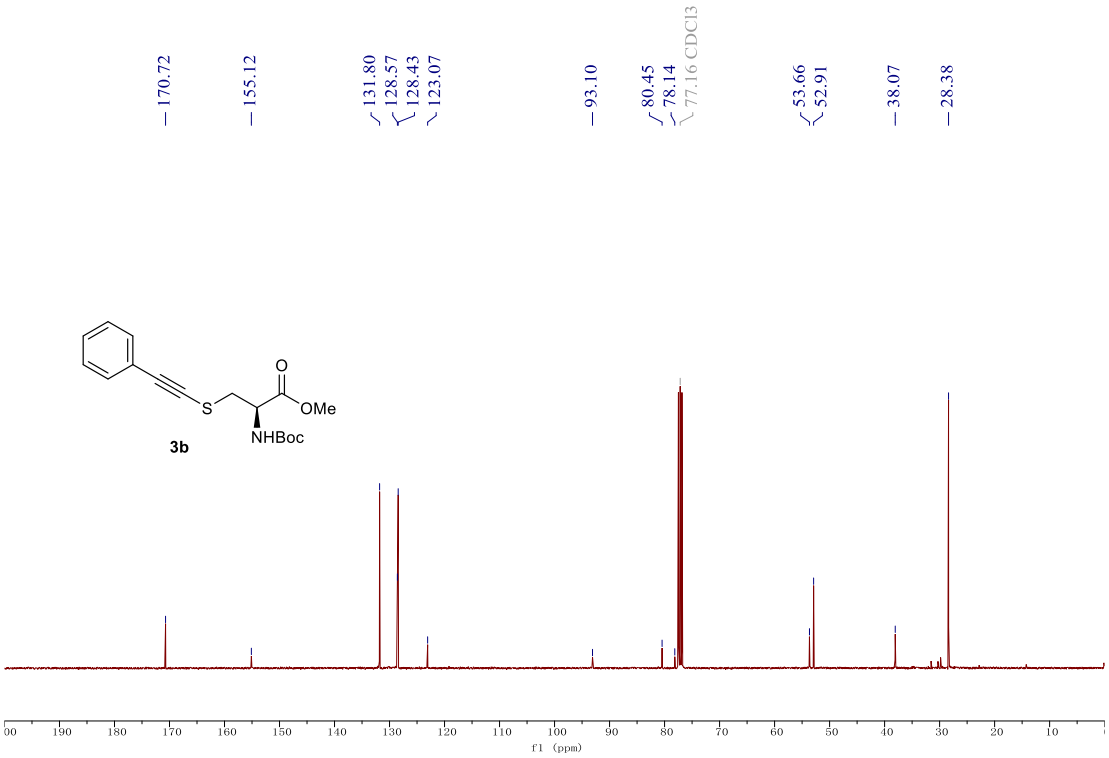

Figure S13. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3b

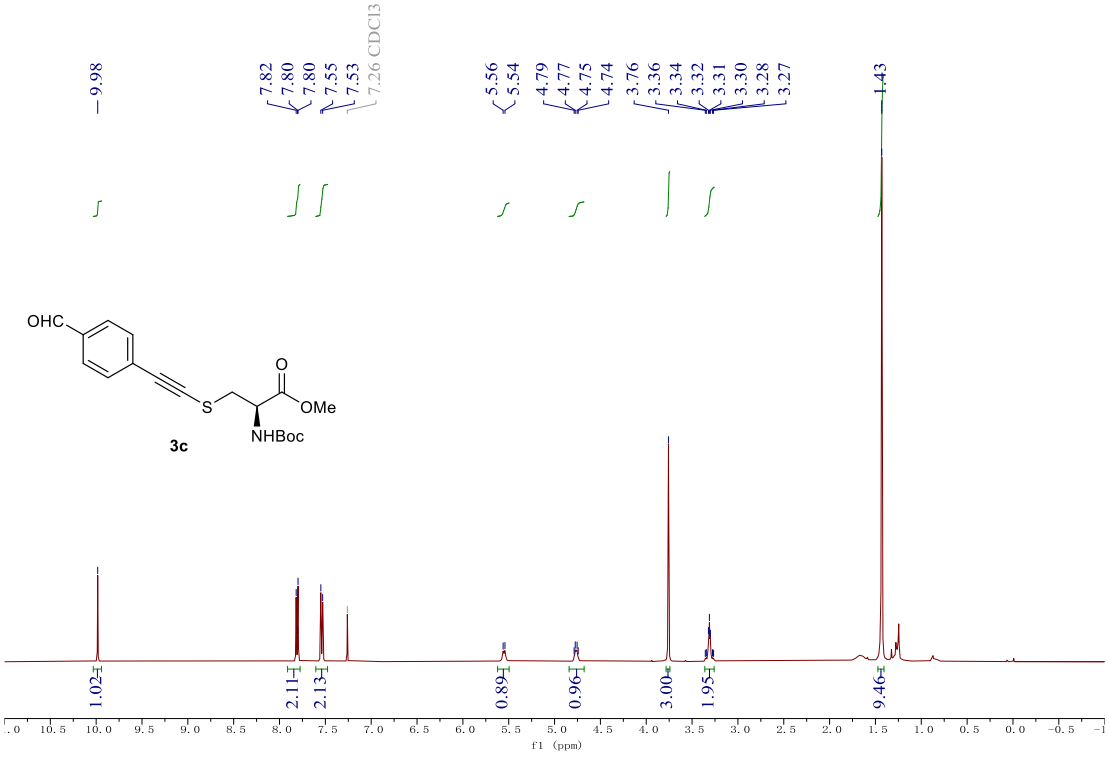

Figure S14. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3c

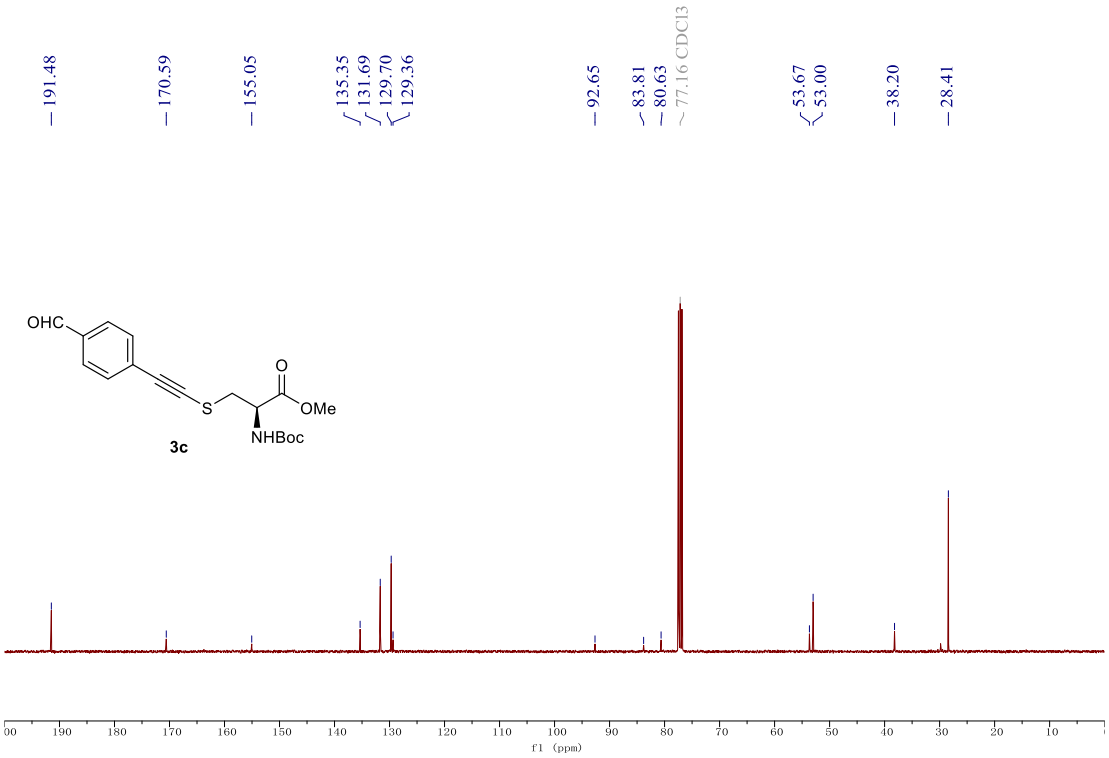

Figure S15. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3c

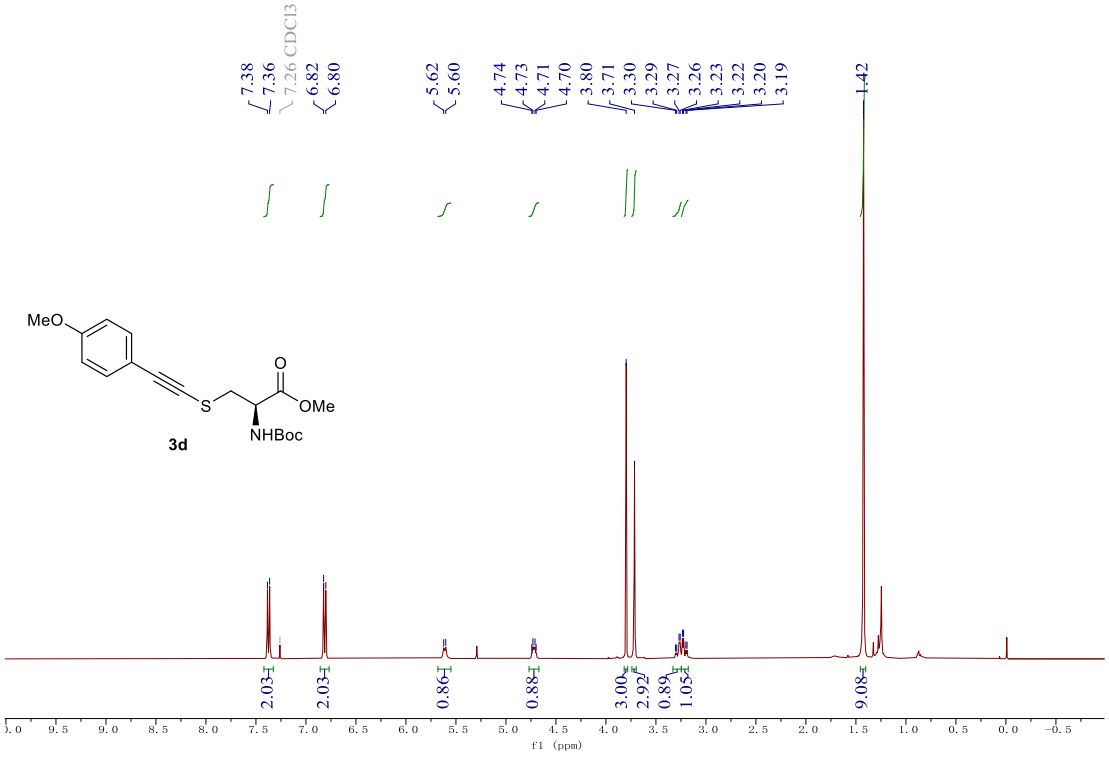

Figure S16. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3d

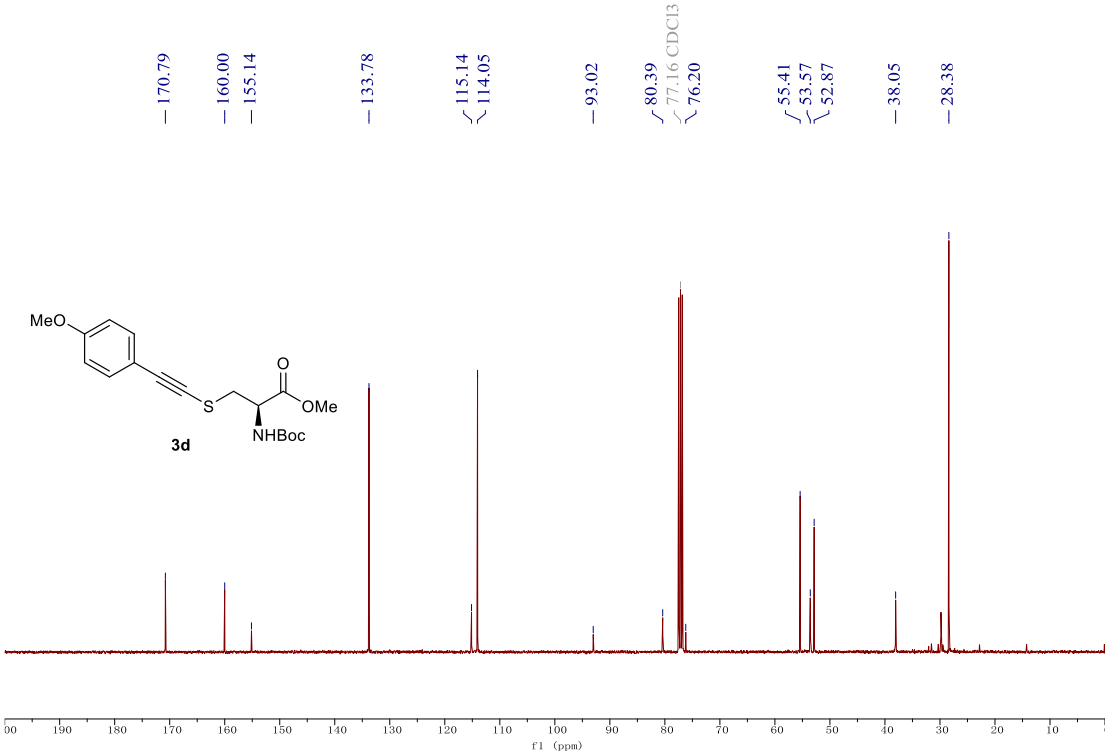

Figure S17. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3d

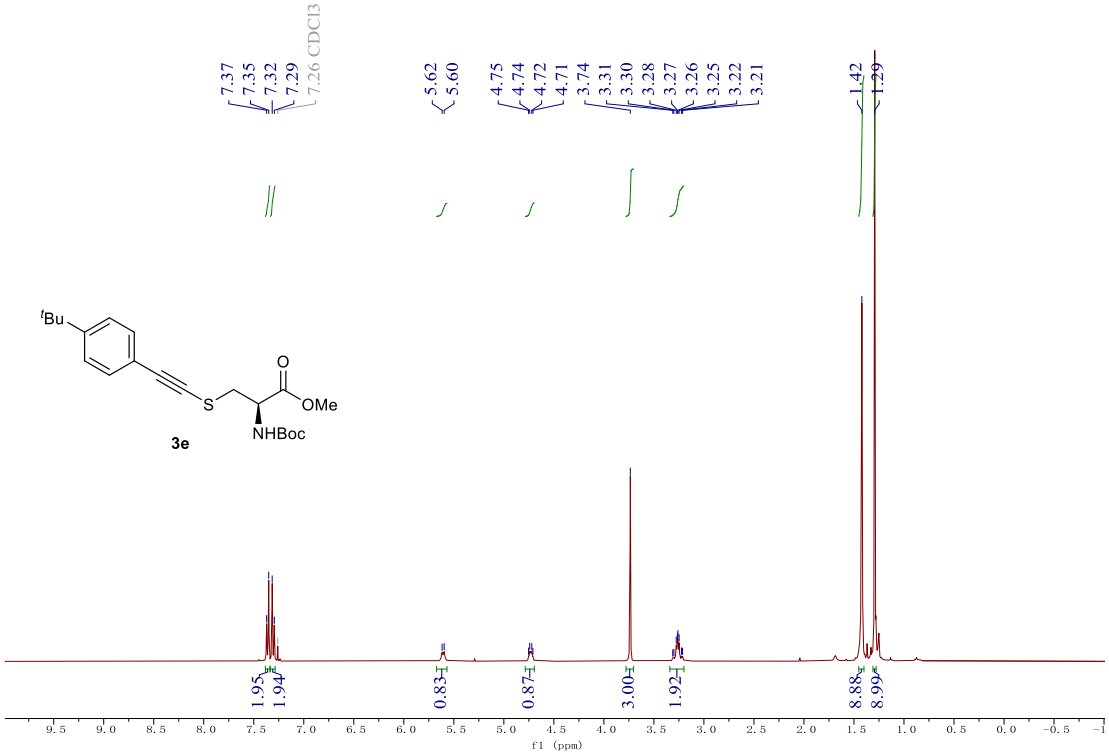

Figure S18. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3e

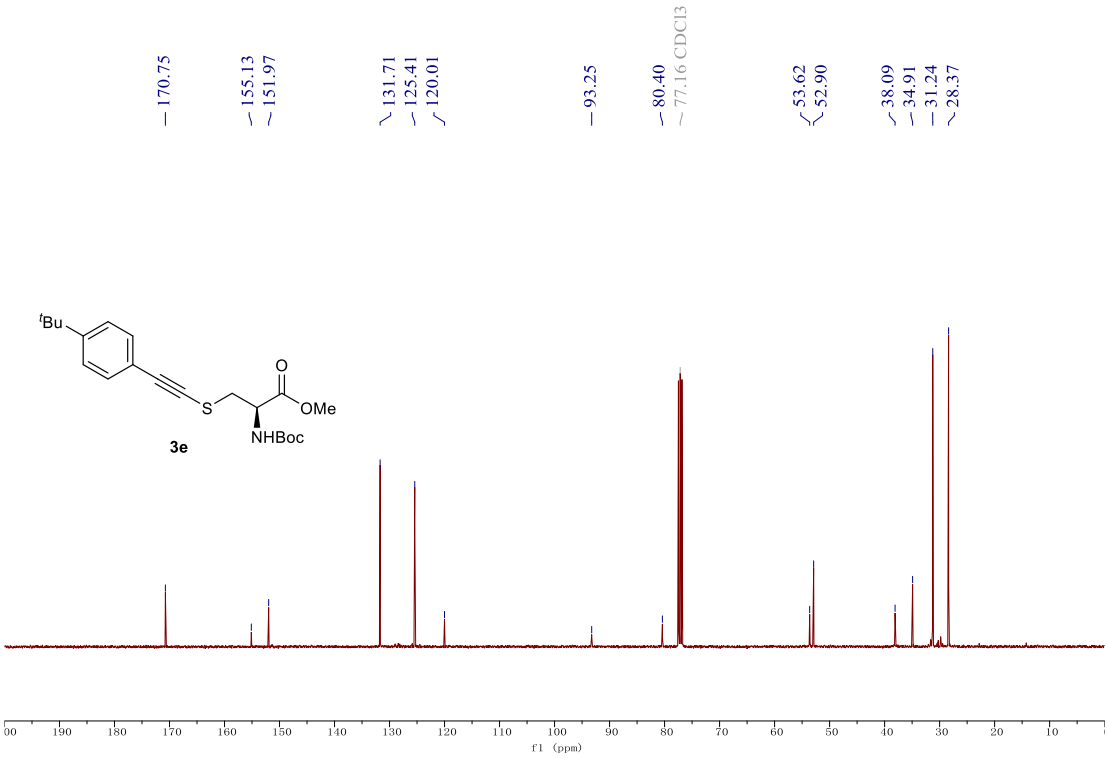

Figure S19. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3e

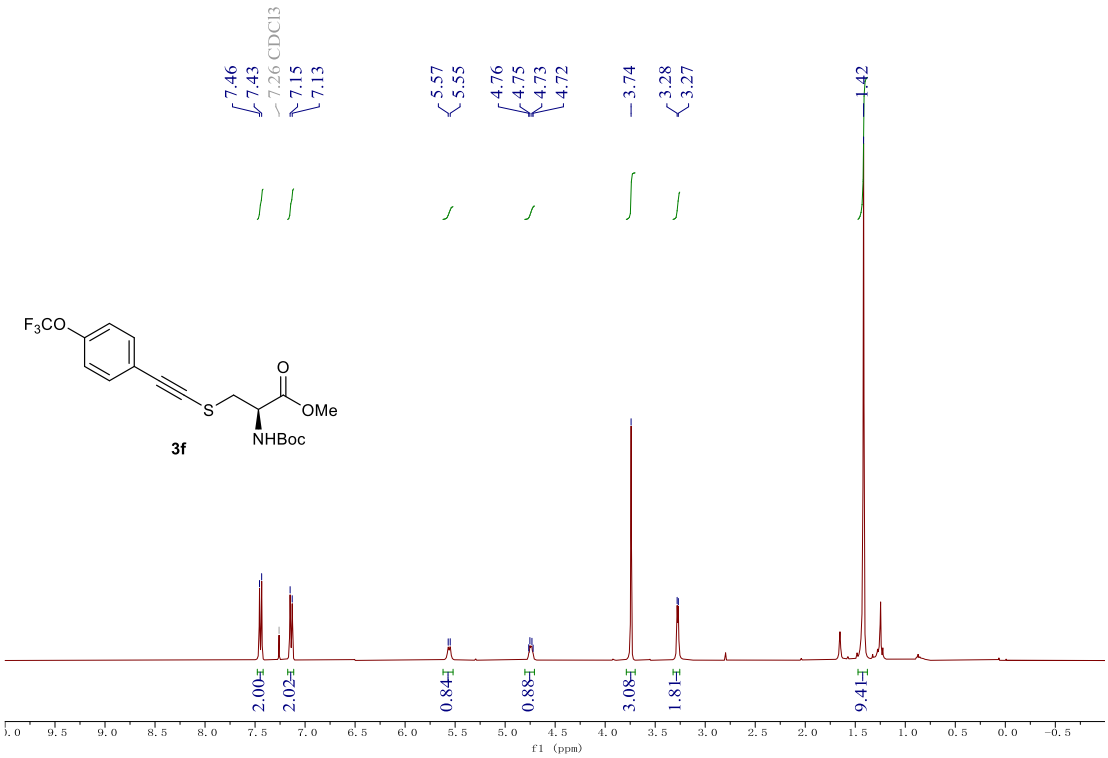

Figure S20. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3f

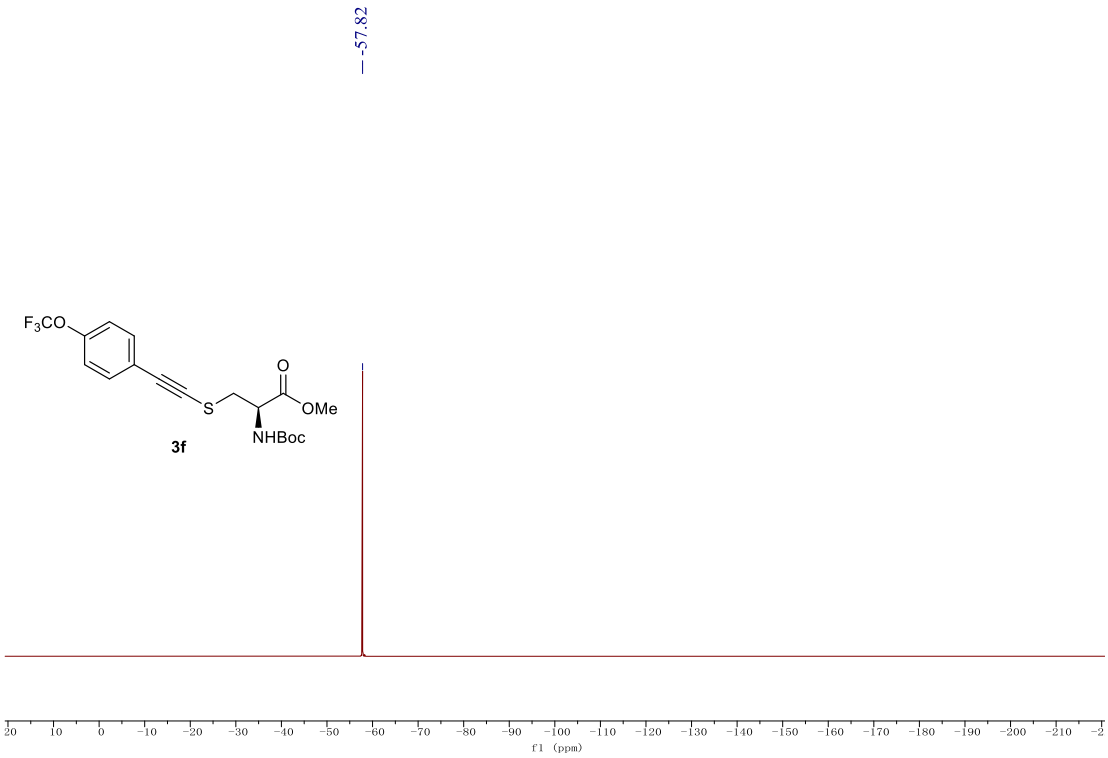

Figure S21. ^{19}F NMR (376 MHz $CDCl_3$) spectra for compound 3f

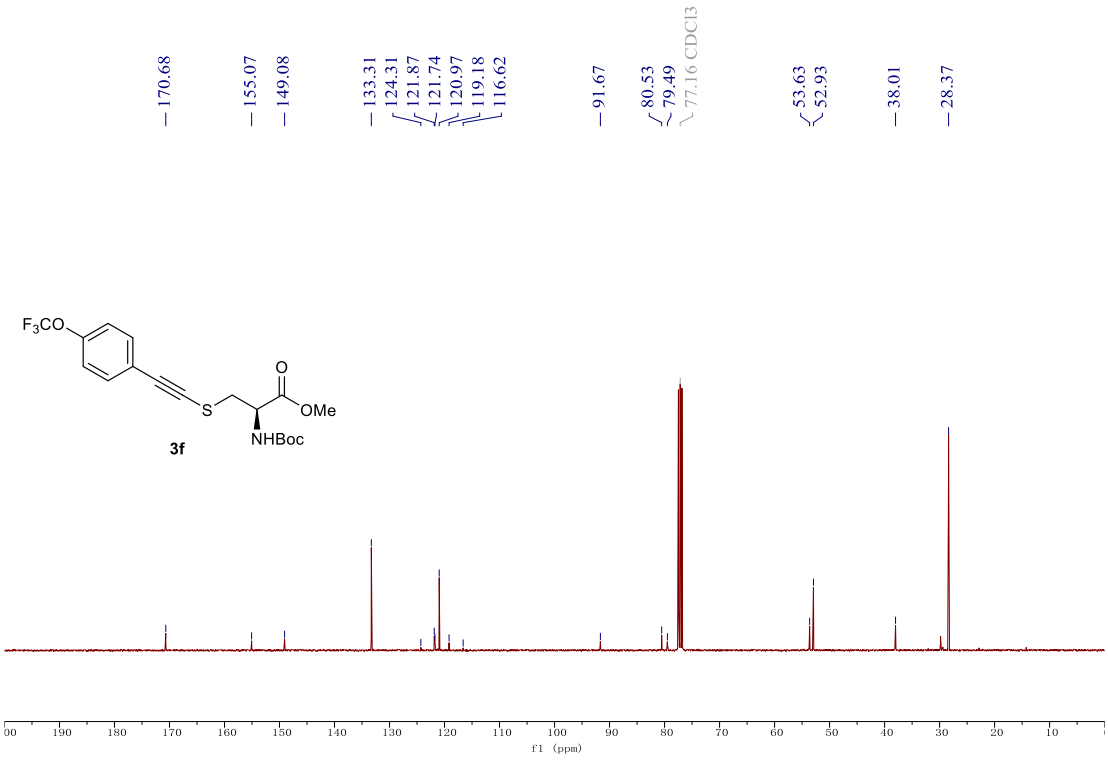

Figure S22. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3f

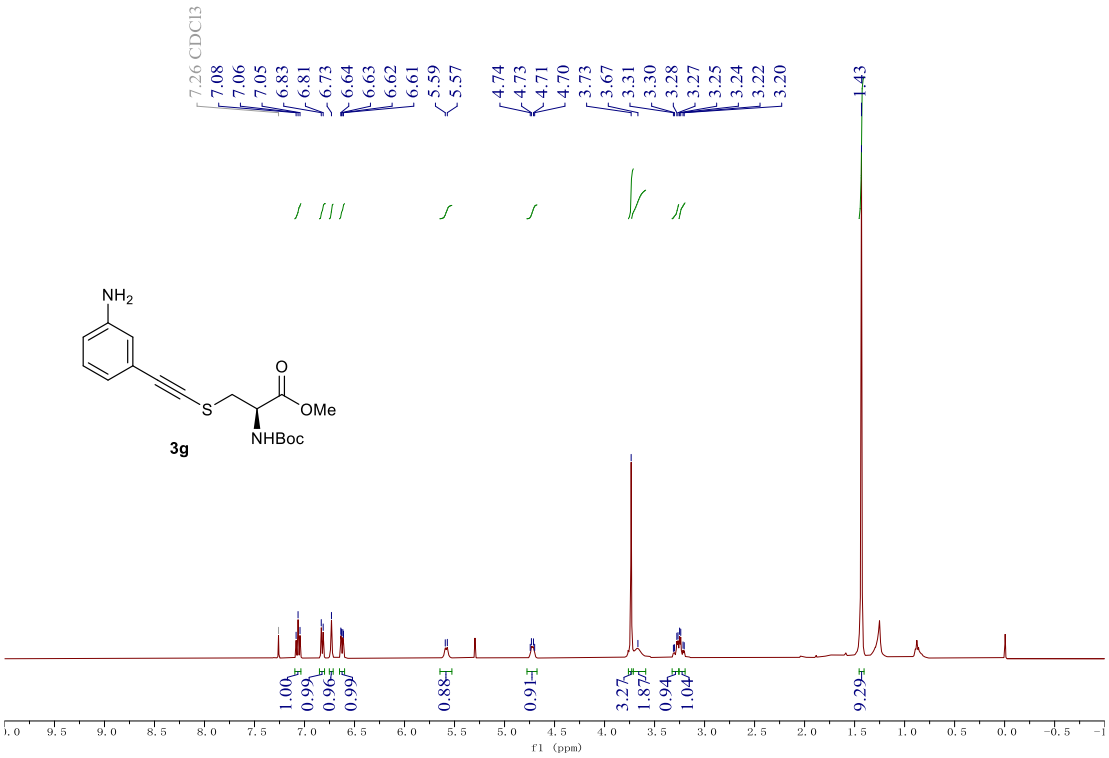

Figure S23. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3g

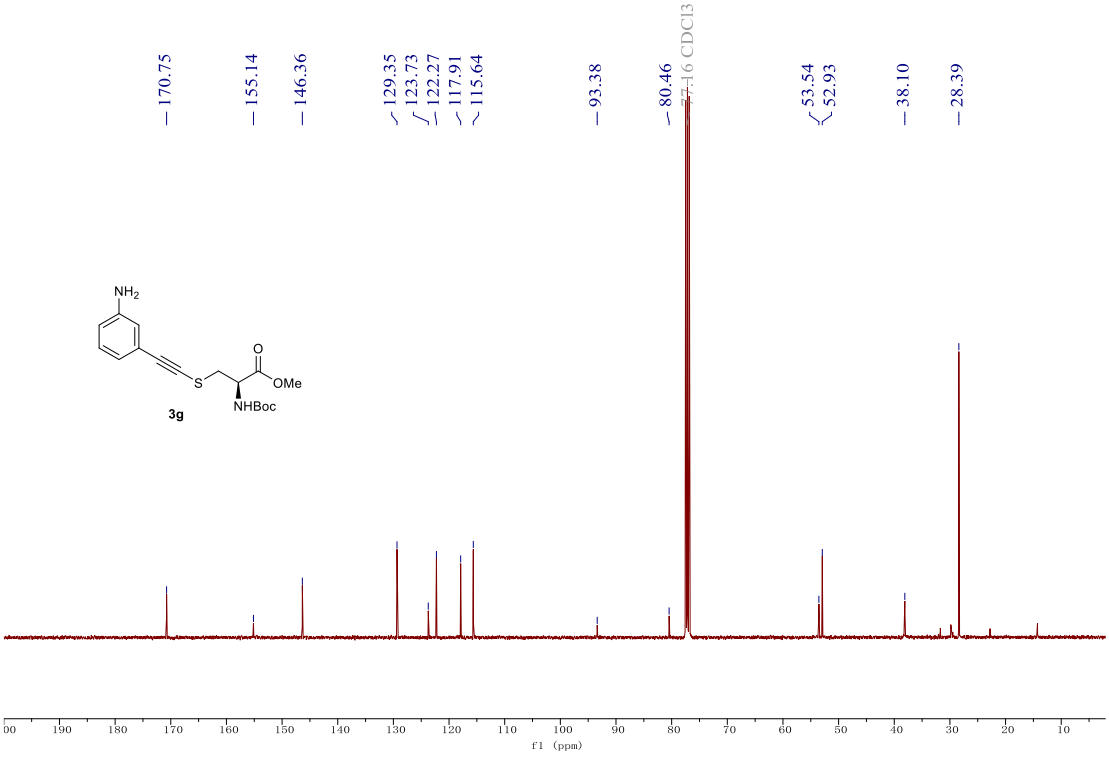

Figure S24. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3g

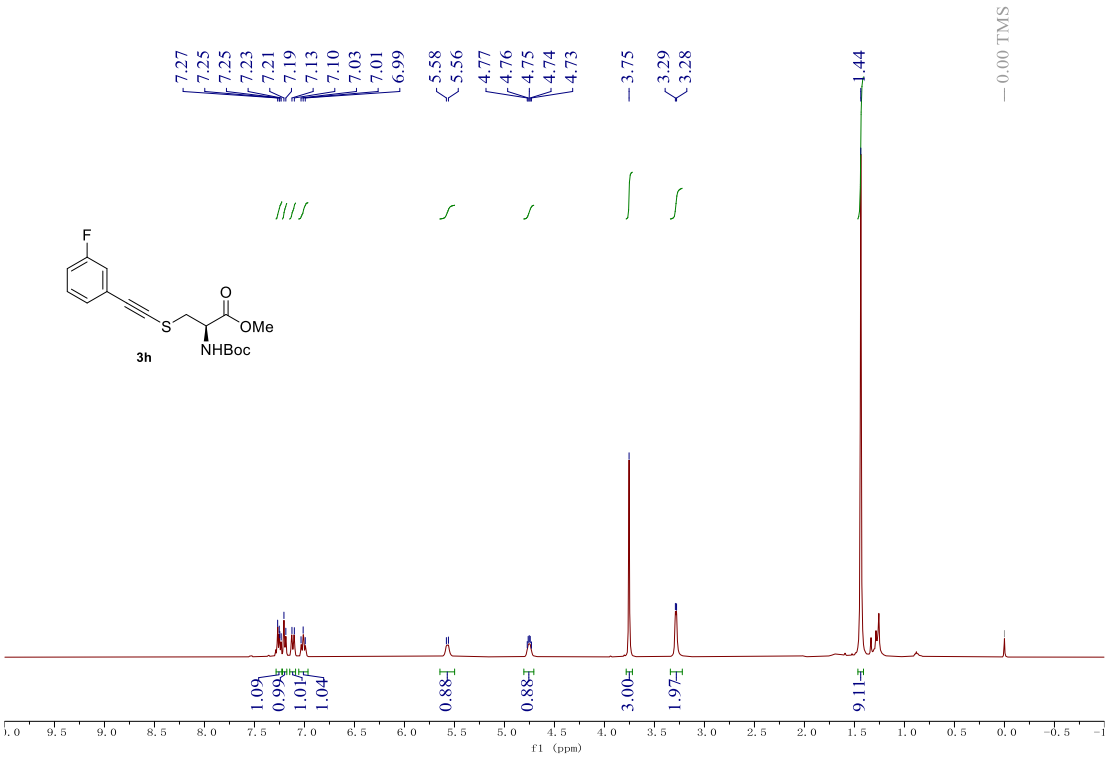

Figure S25. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3h

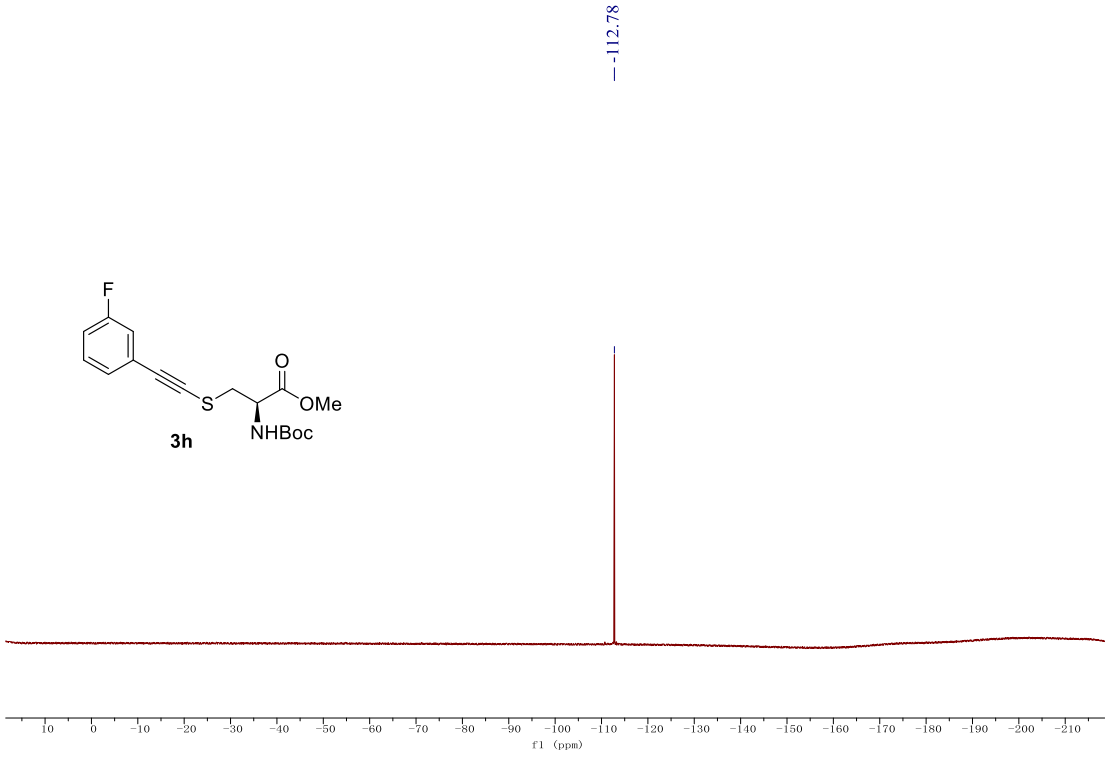

Figure S26. ^{19}F NMR (376 MHz $CDCl_3$) spectra for compound 3h

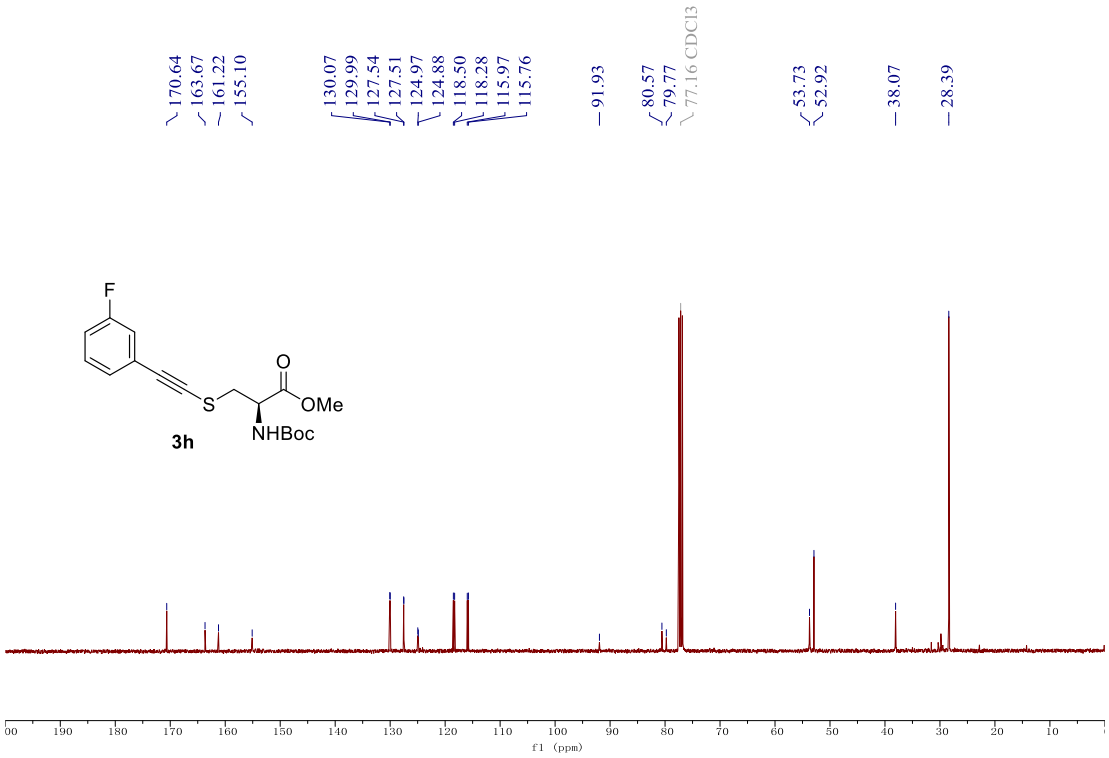

Figure S27. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3h

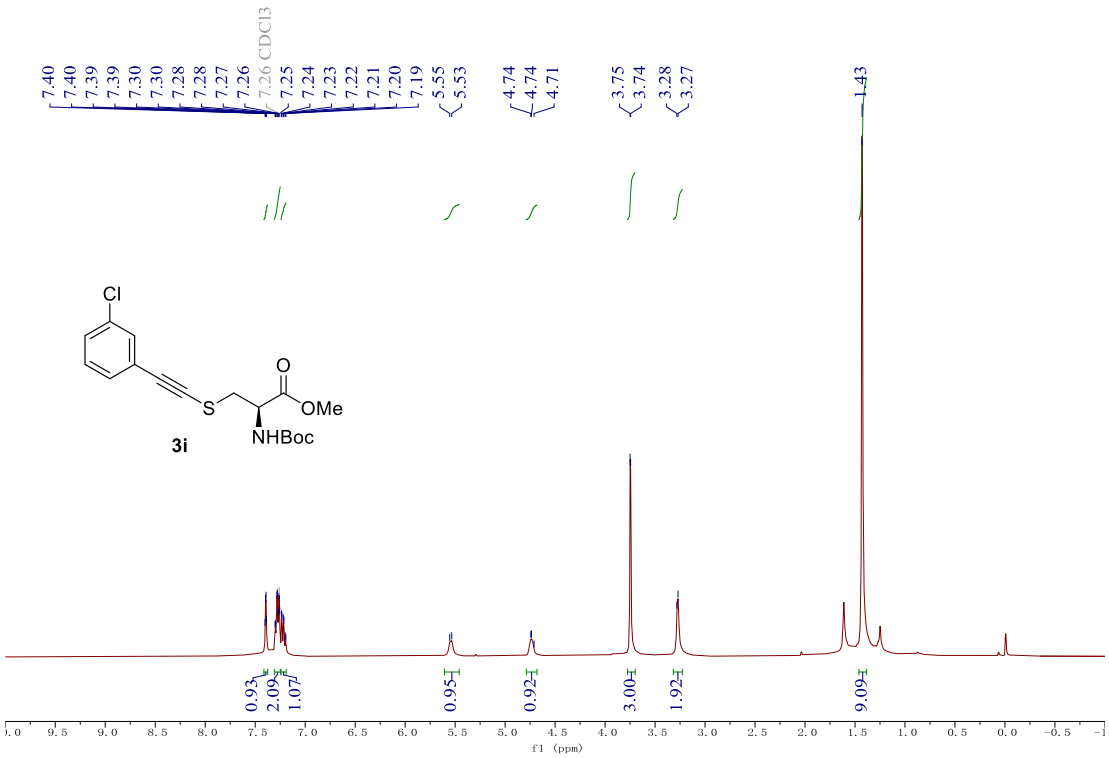

Figure S28. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3i

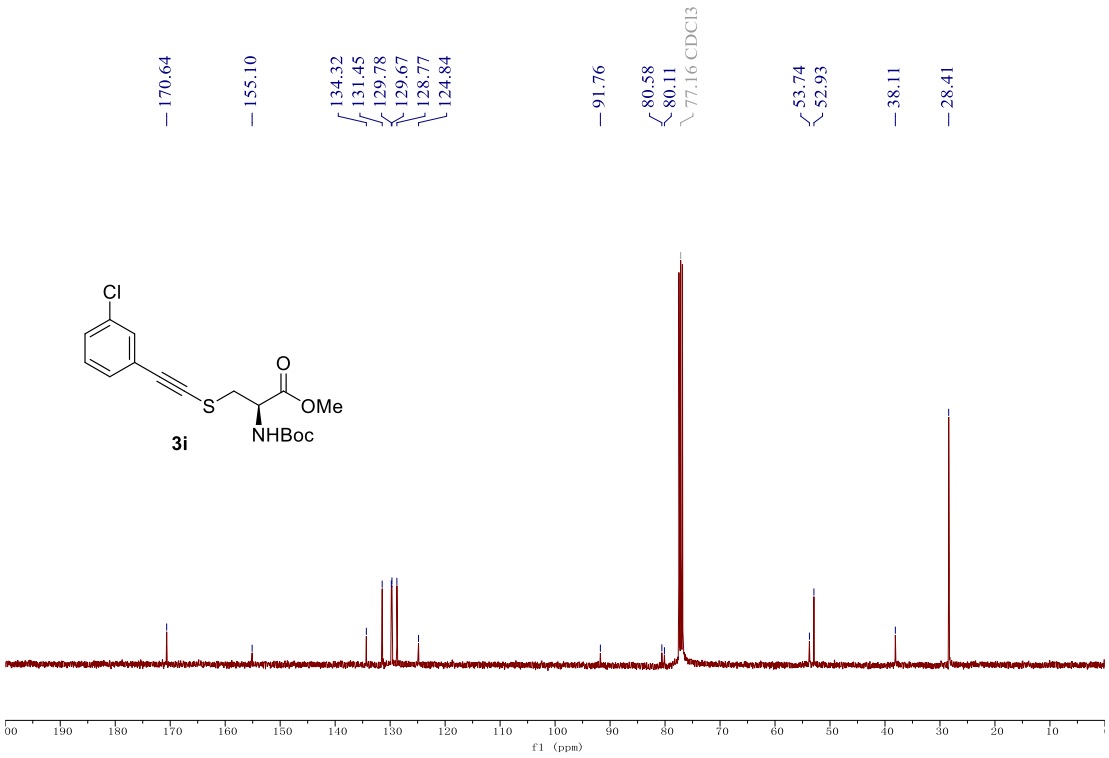

Figure S29. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3i

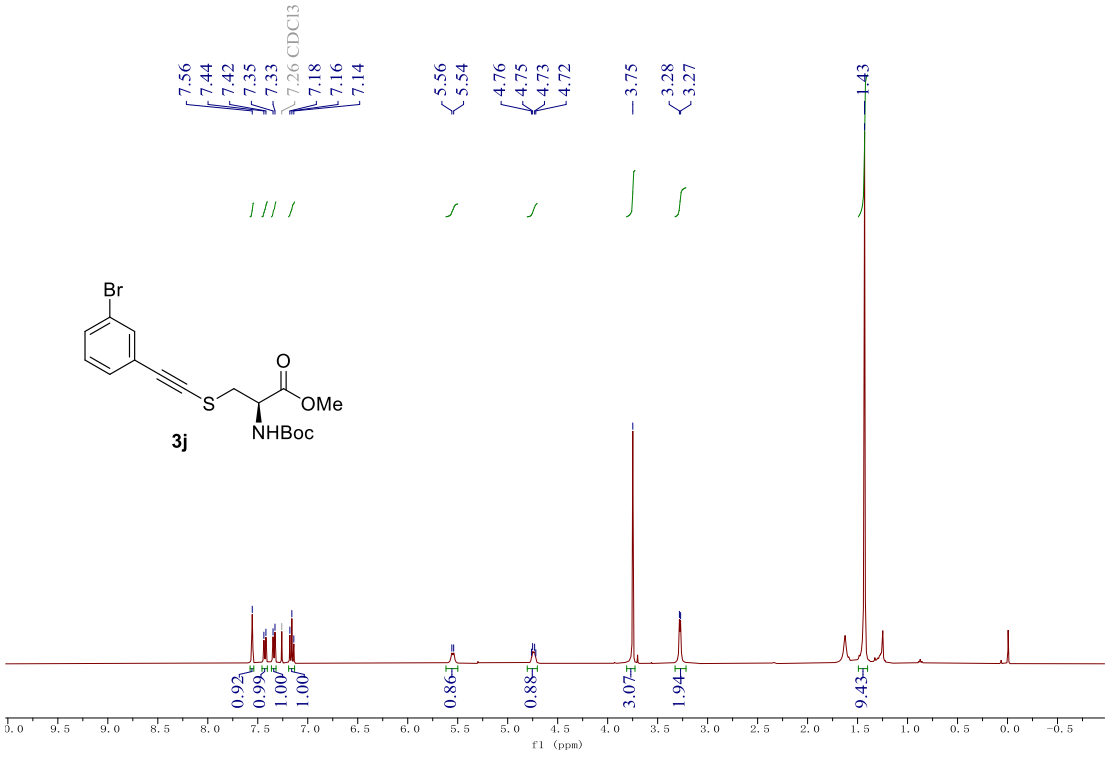

Figure S30. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3j

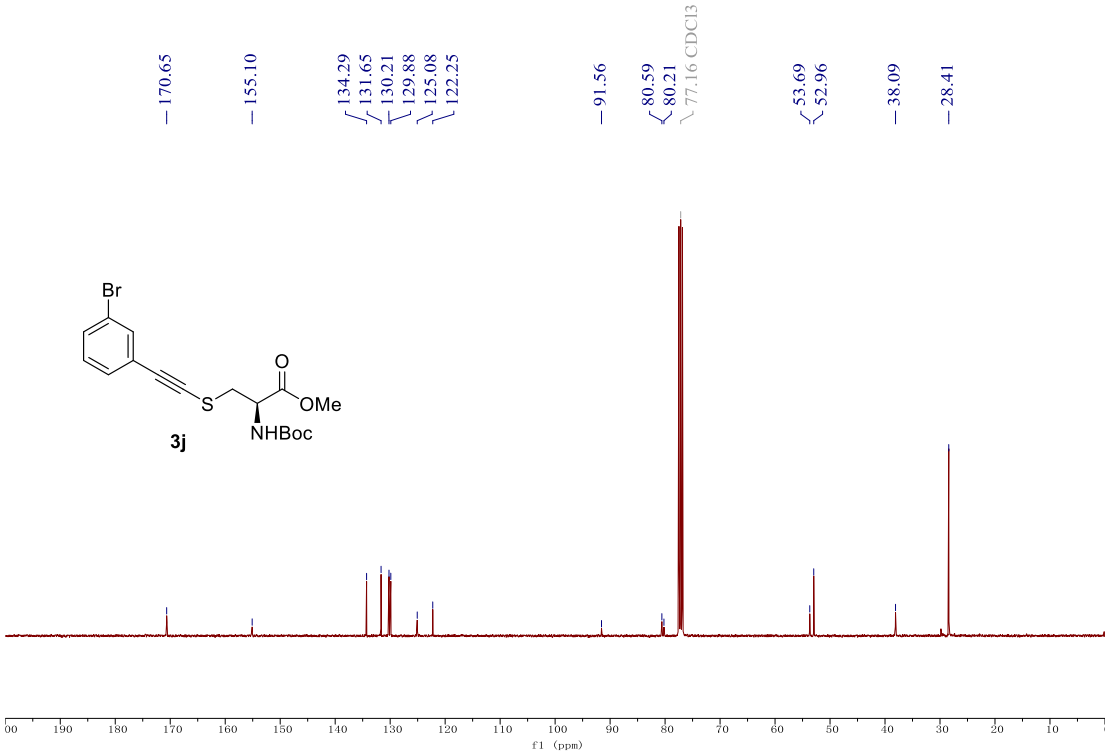

Figure S31. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3j

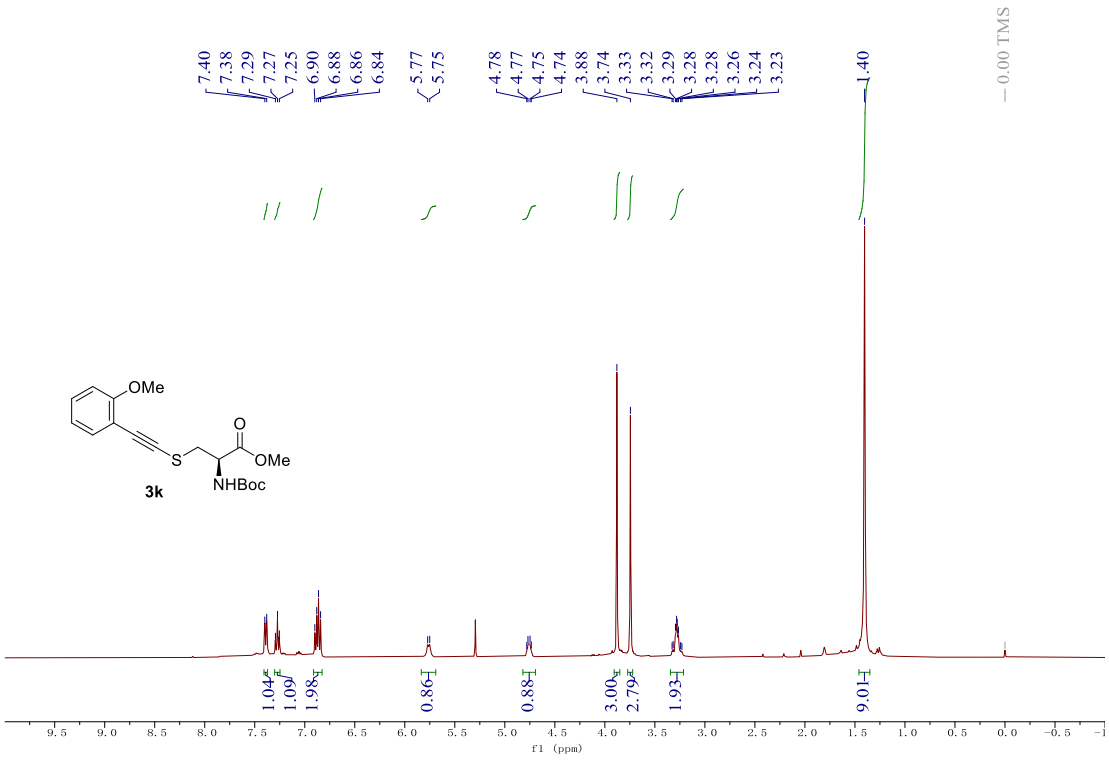

Figure S32. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3k

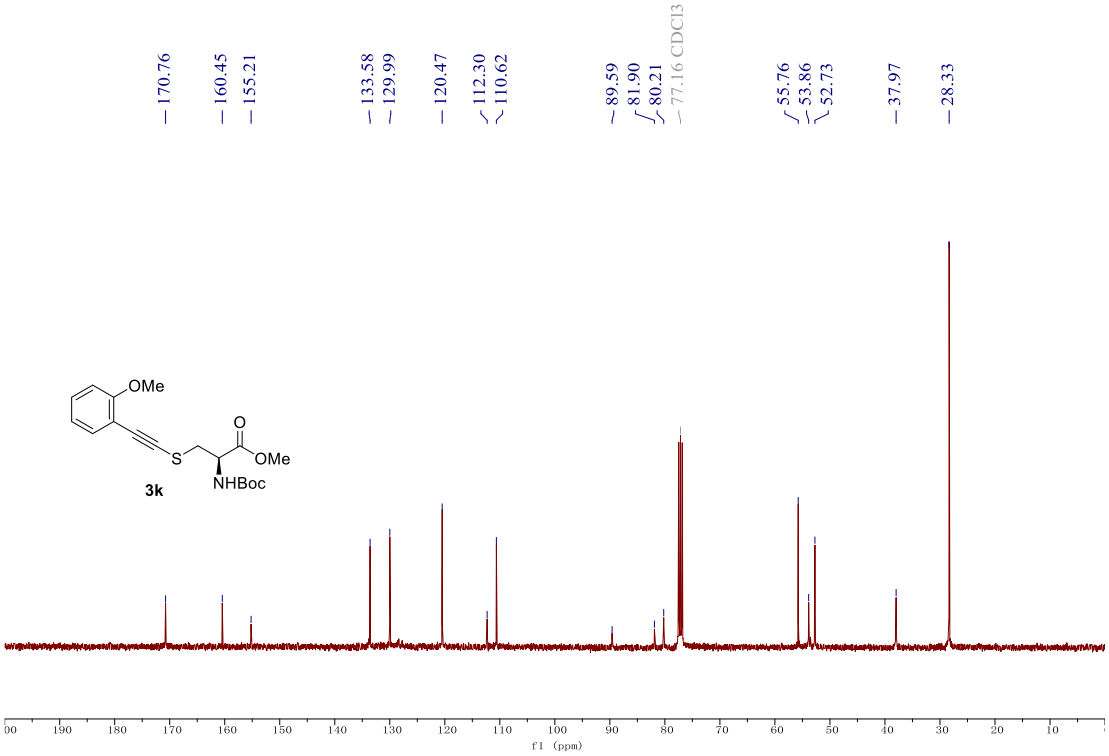

Figure S33. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3k

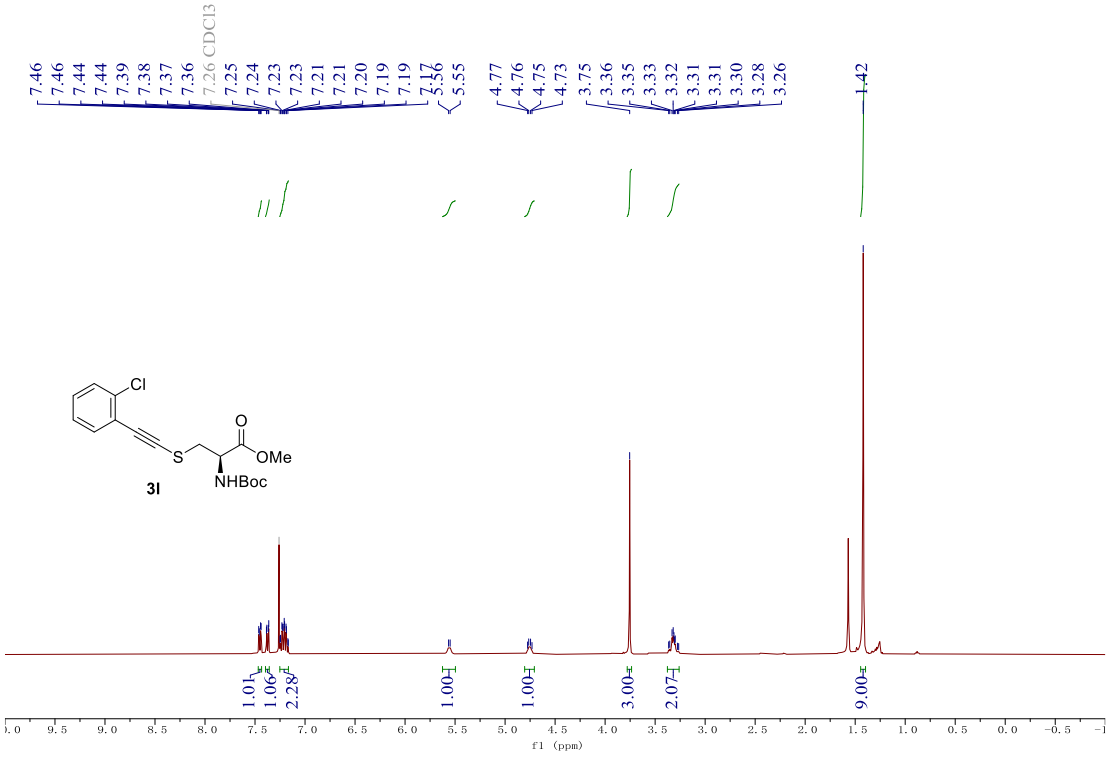

Figure S34. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3l

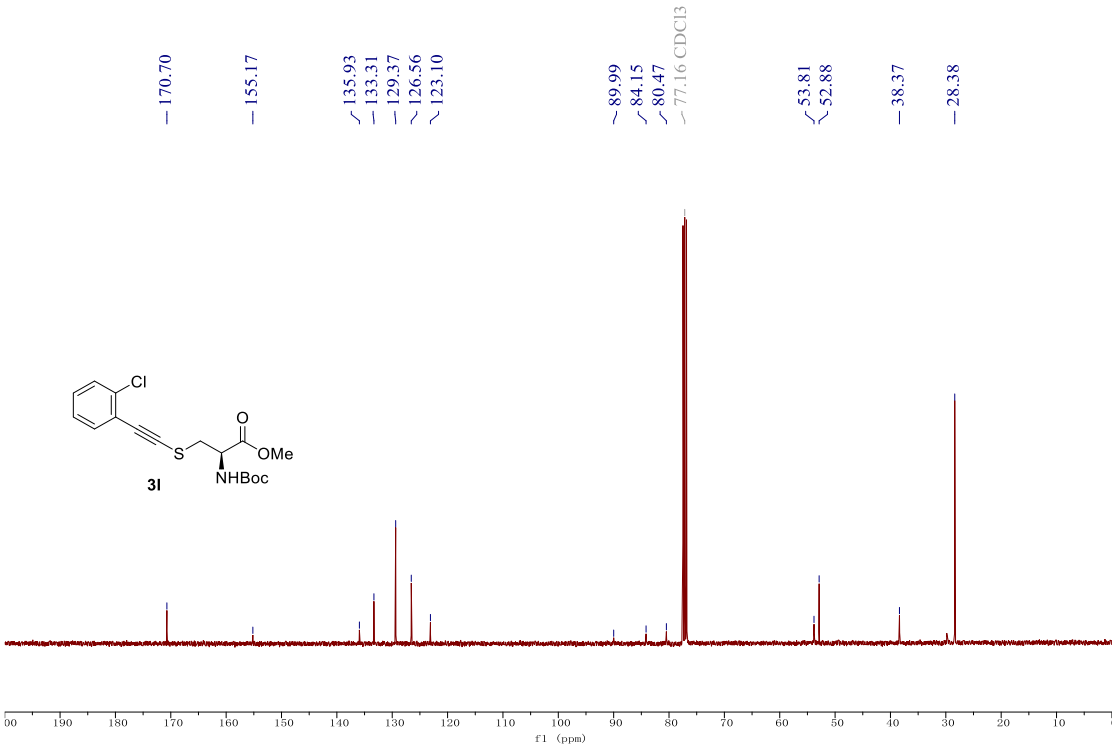

Figure S35. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3l

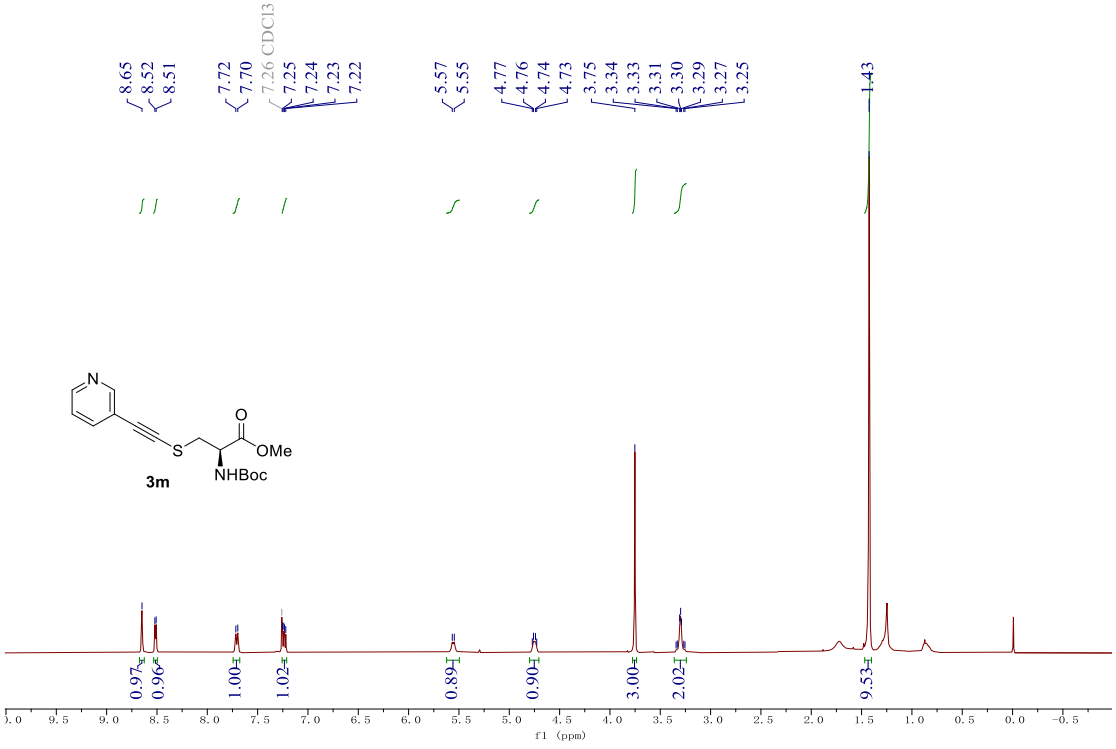

Figure S36. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3m

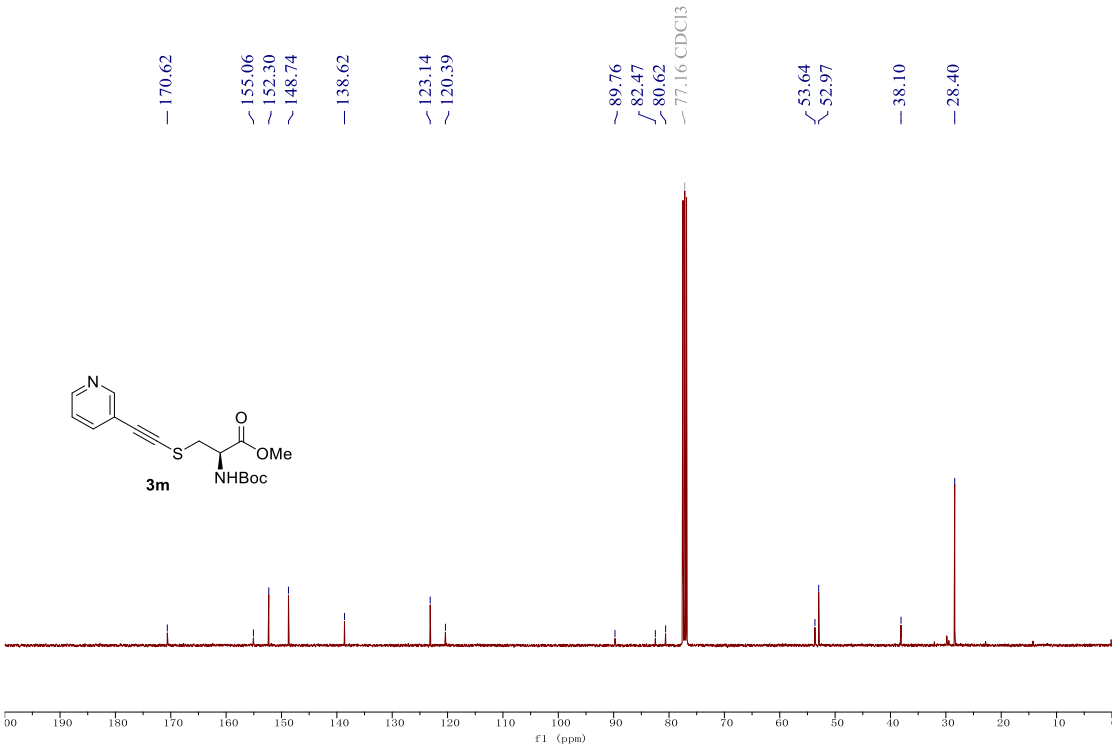

Figure S37. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3m

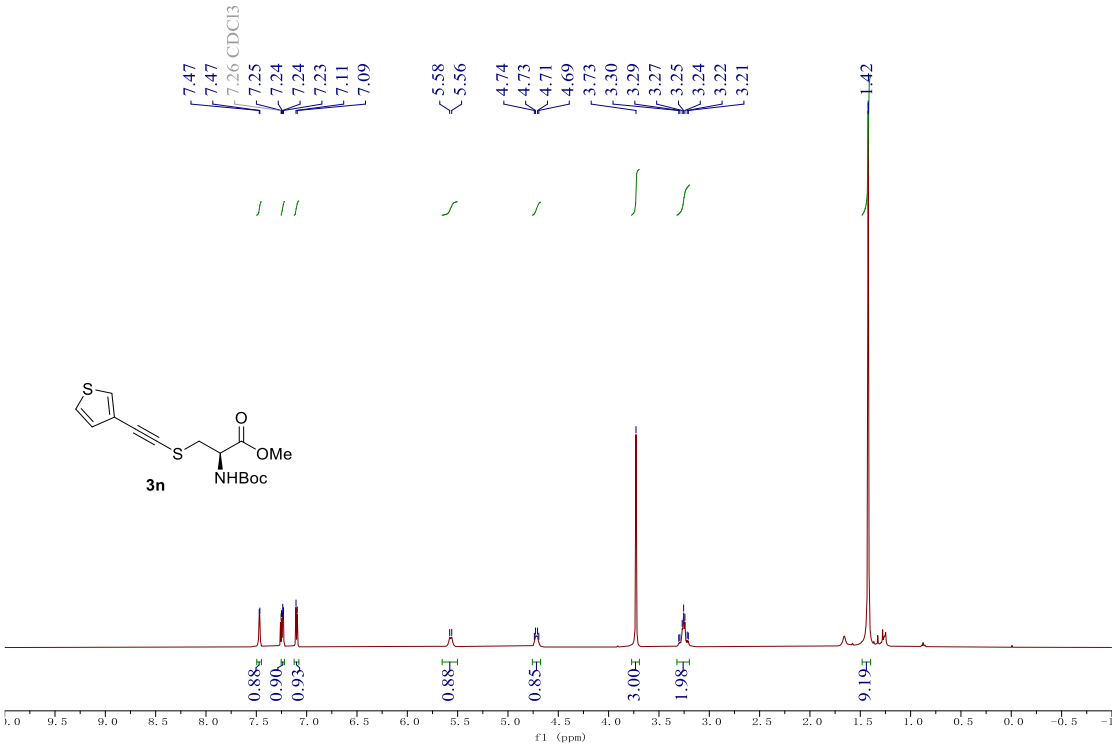

Figure S38. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3n

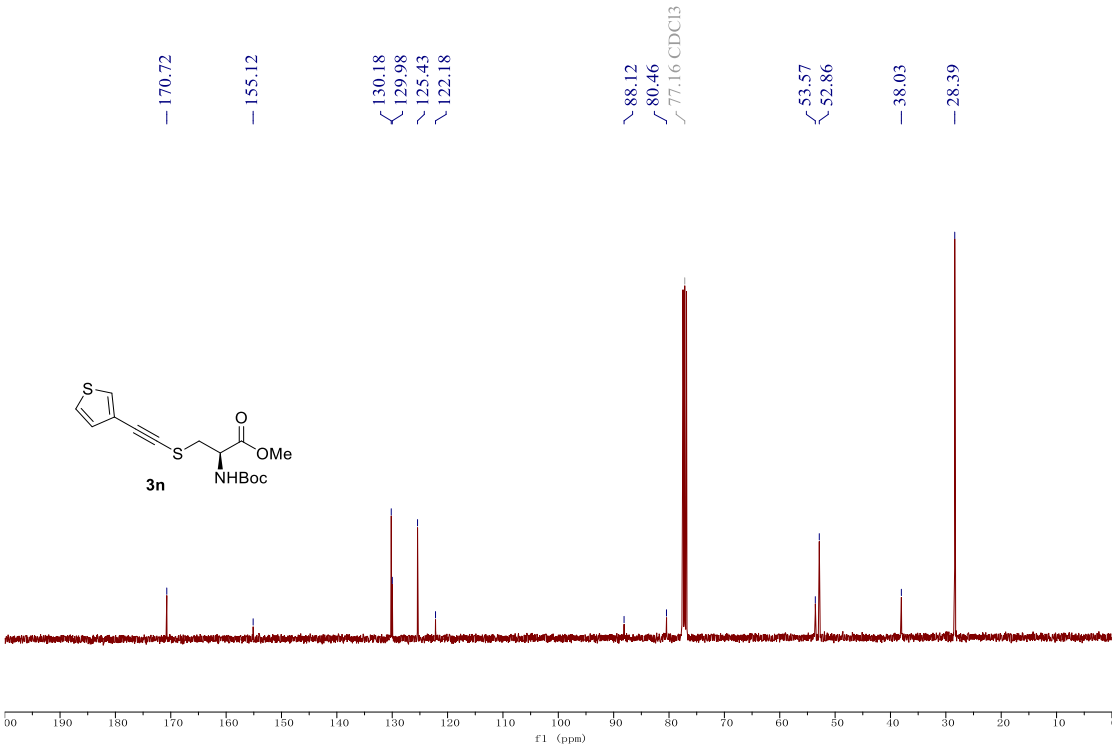

Figure S39. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3n

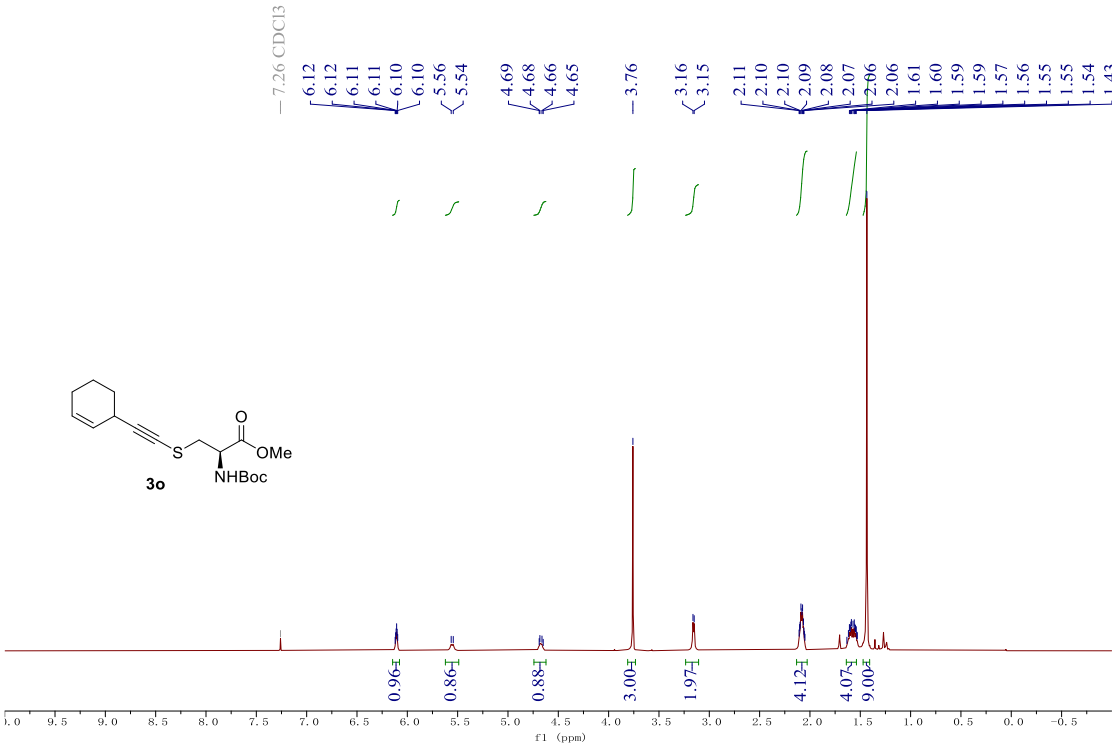

Figure S40. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3o

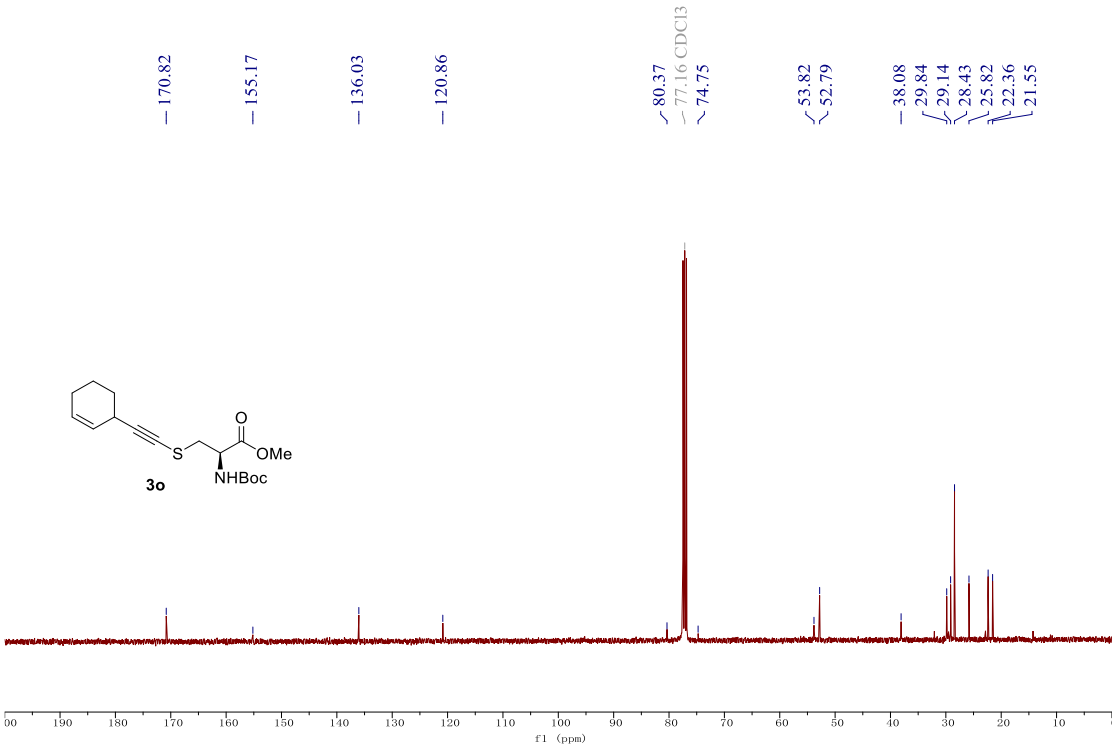

Figure S41. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3o

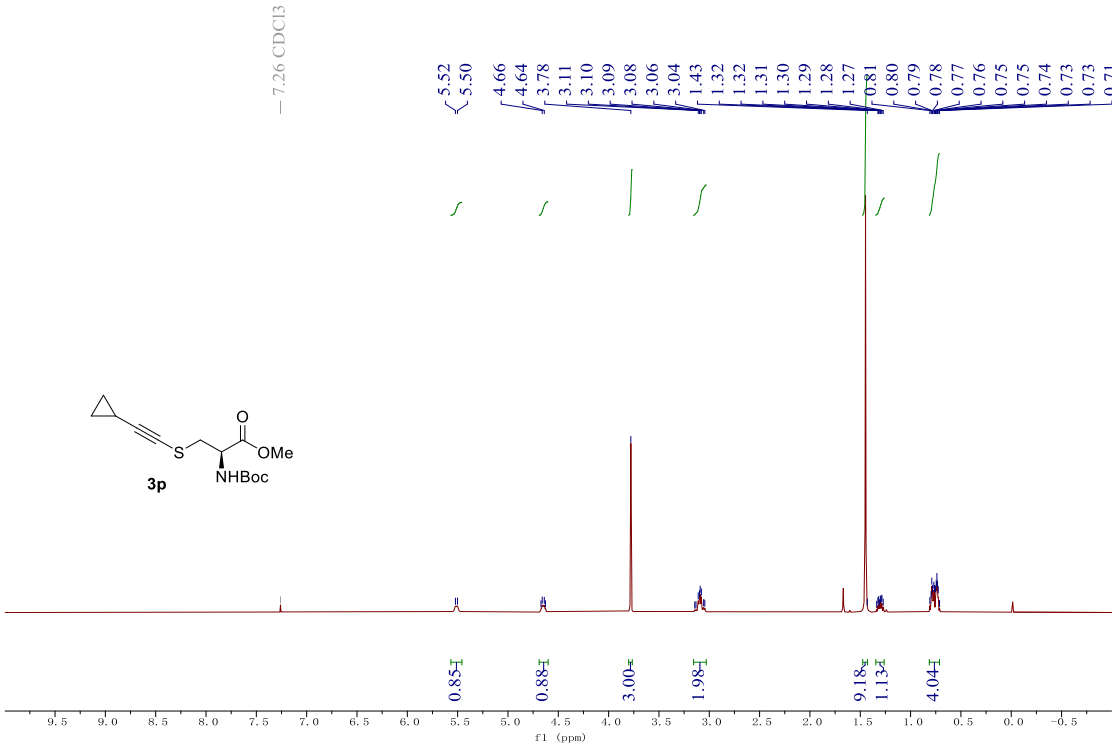

Figure S42. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3p

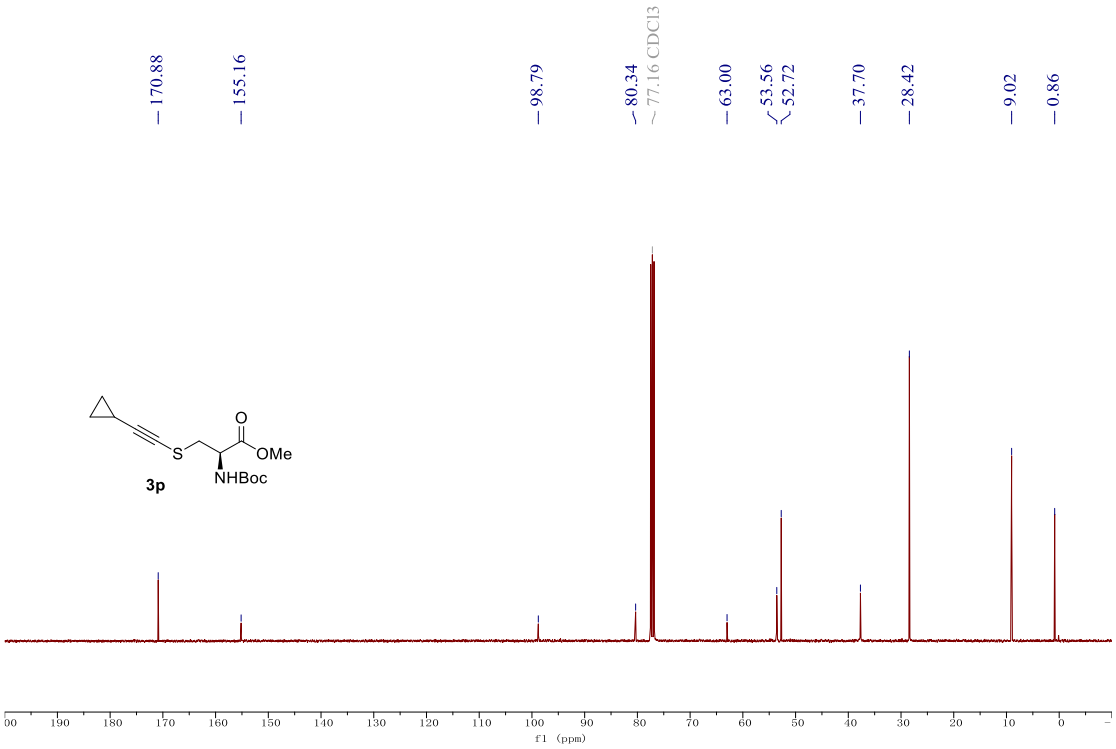

Figure S43. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3p

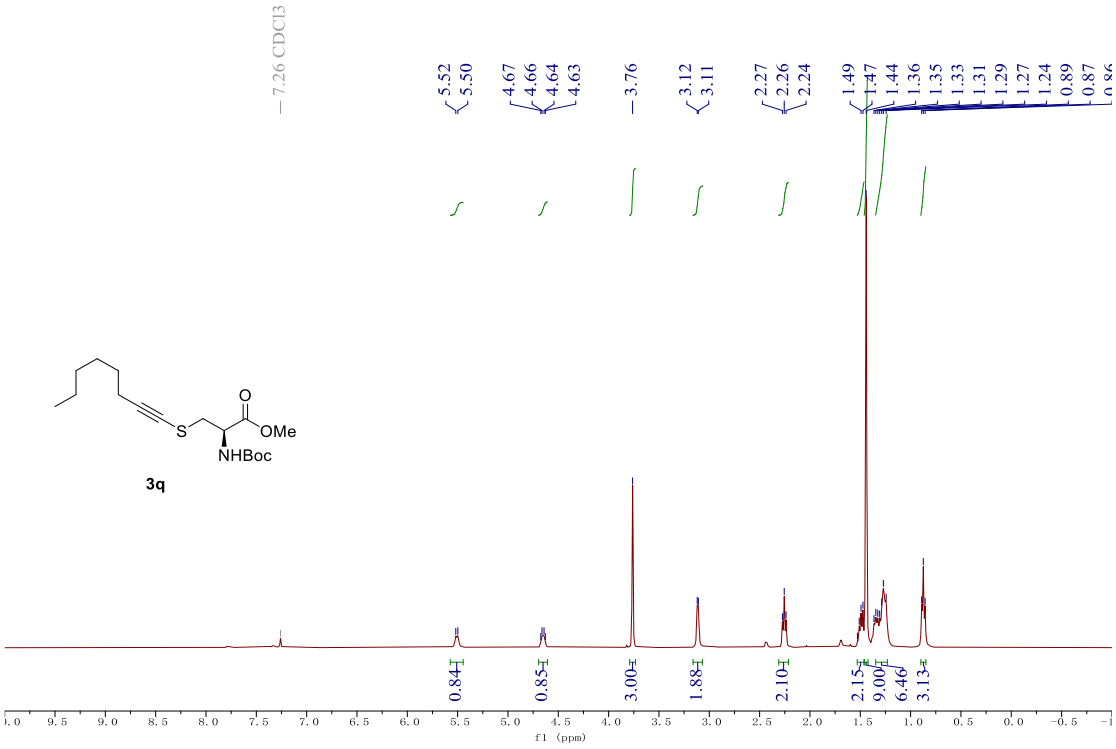

Figure S44. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3q

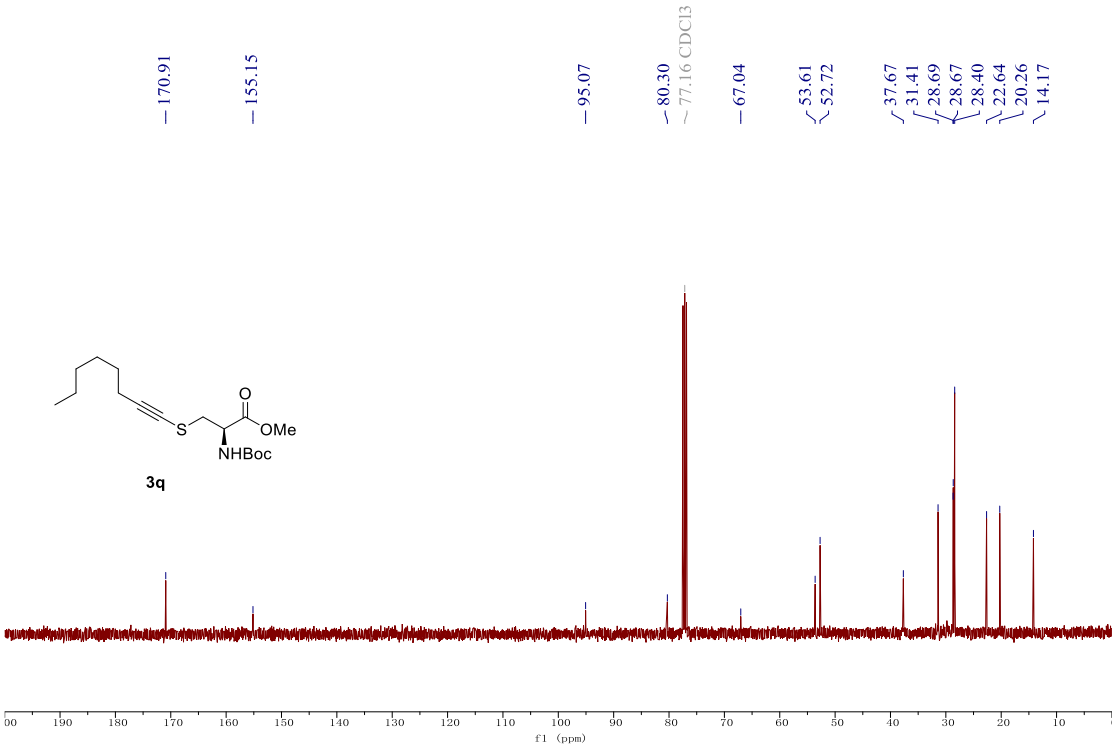

Figure S45. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3q

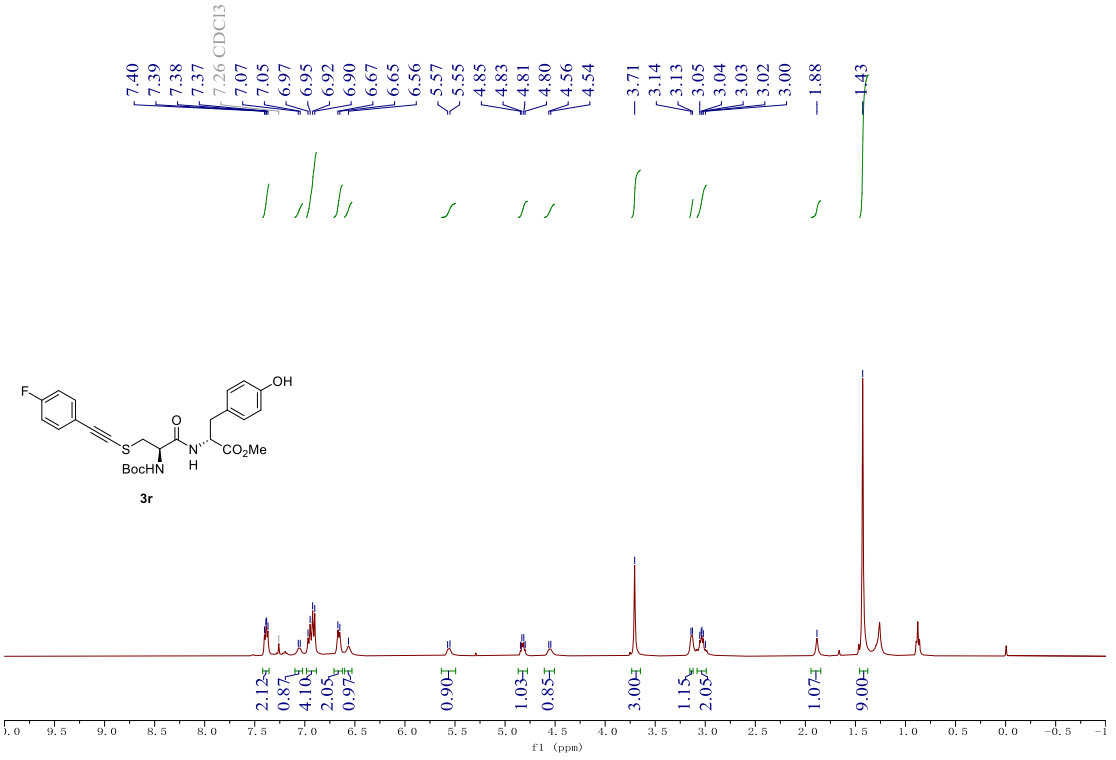

Figure S46. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3r

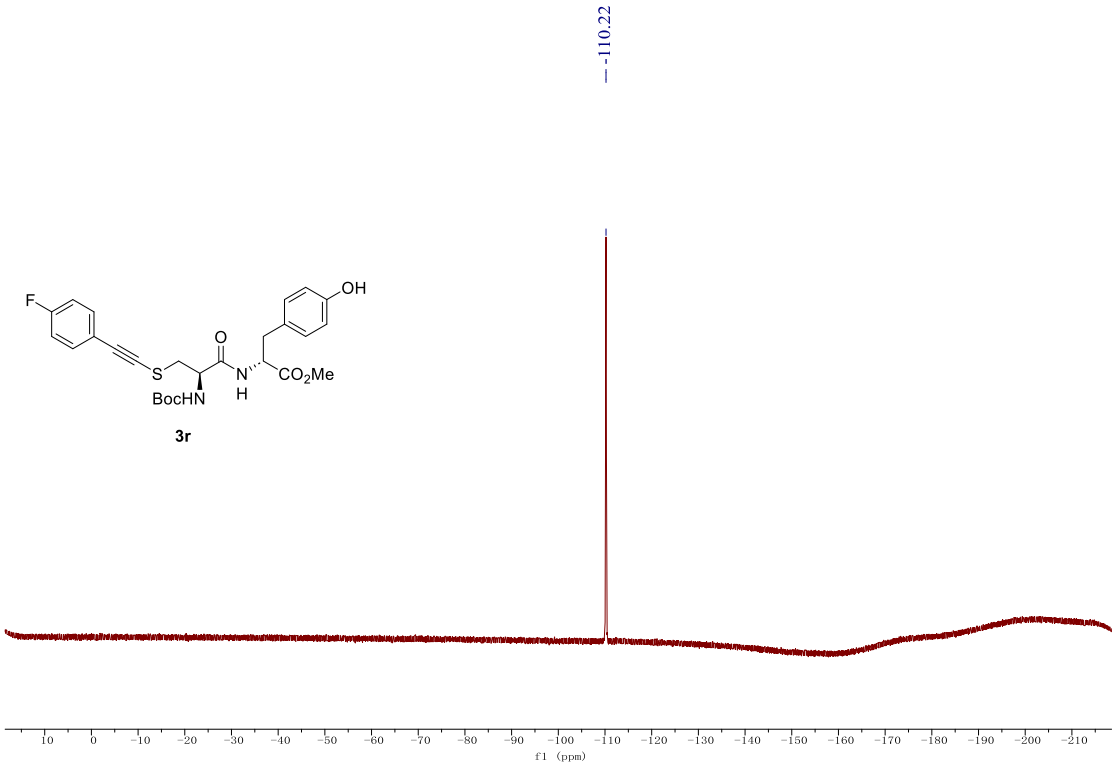

Figure S47. ^{19}F NMR (376 MHz $CDCl_3$) spectra for compound 3r

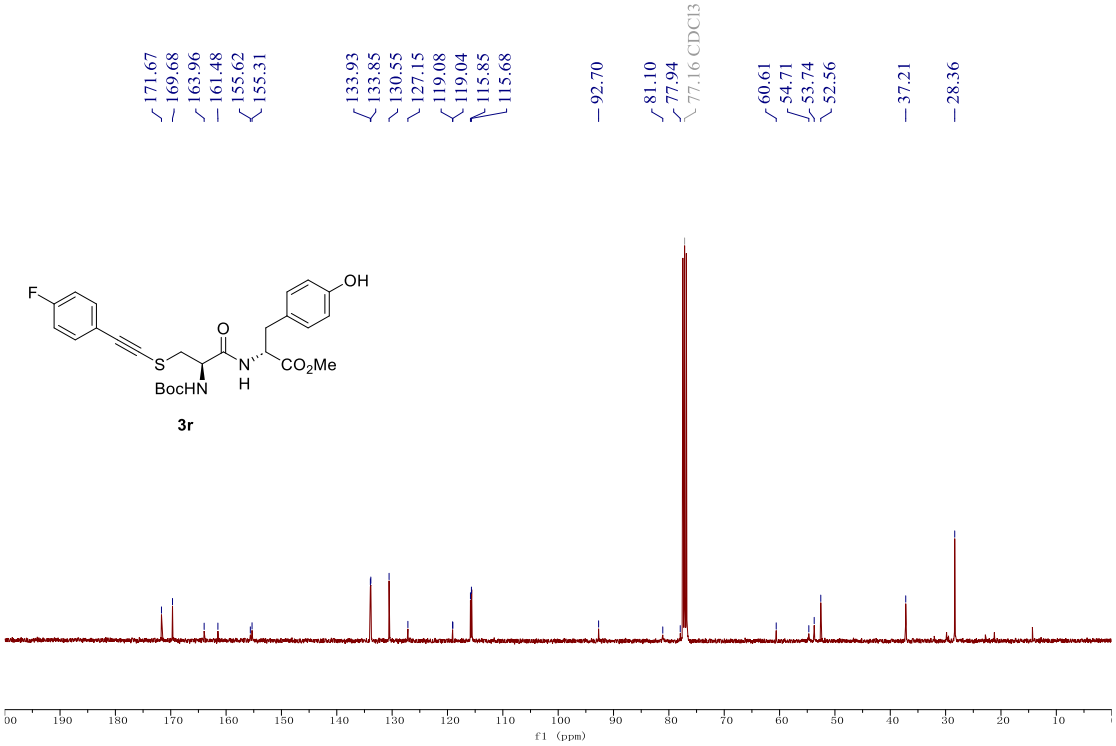

Figure S48. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3r

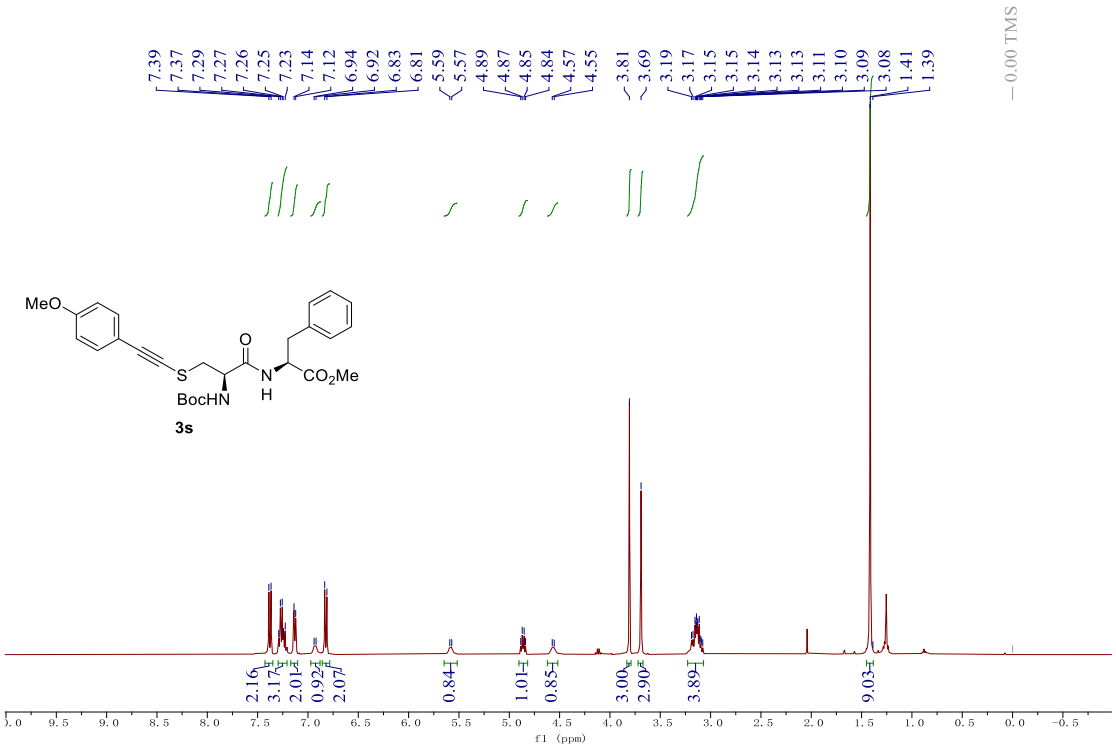

Figure S49. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3s

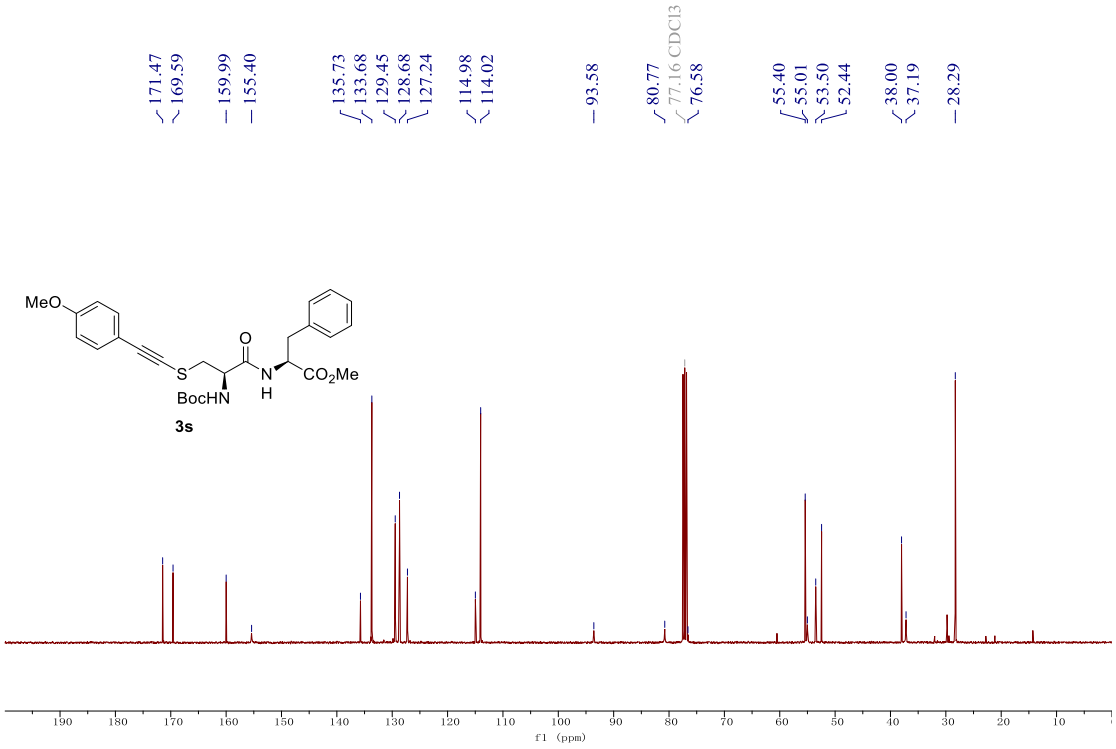

Figure S50. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3s

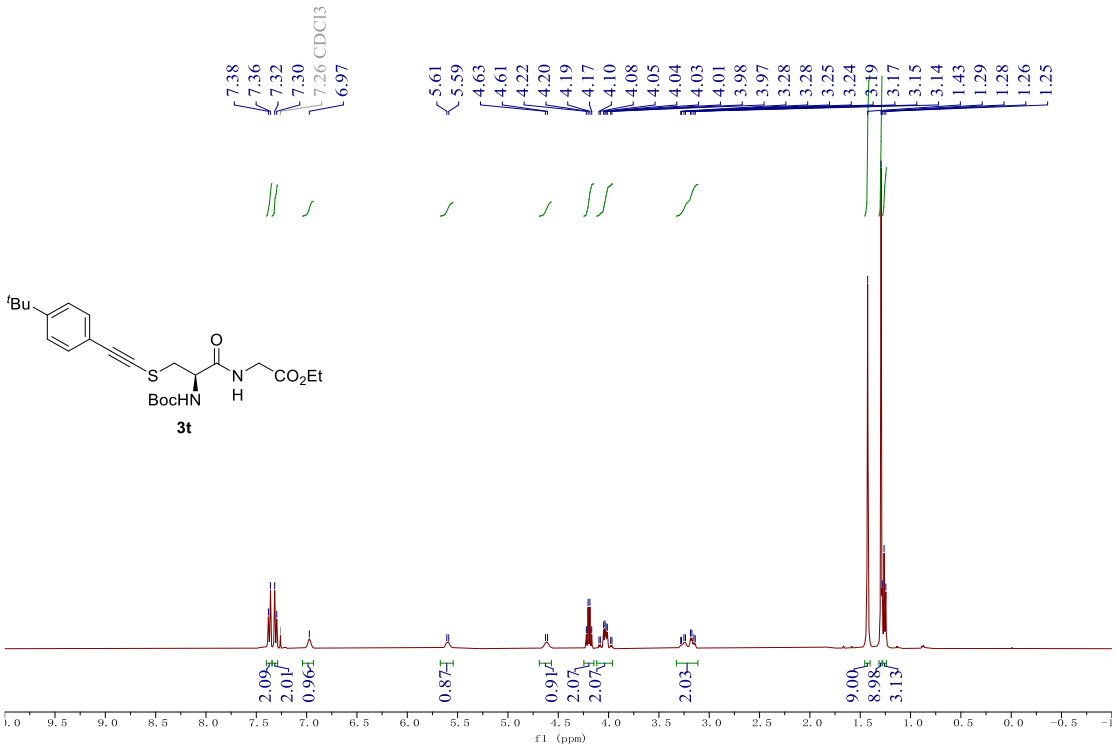

Figure S51. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3t

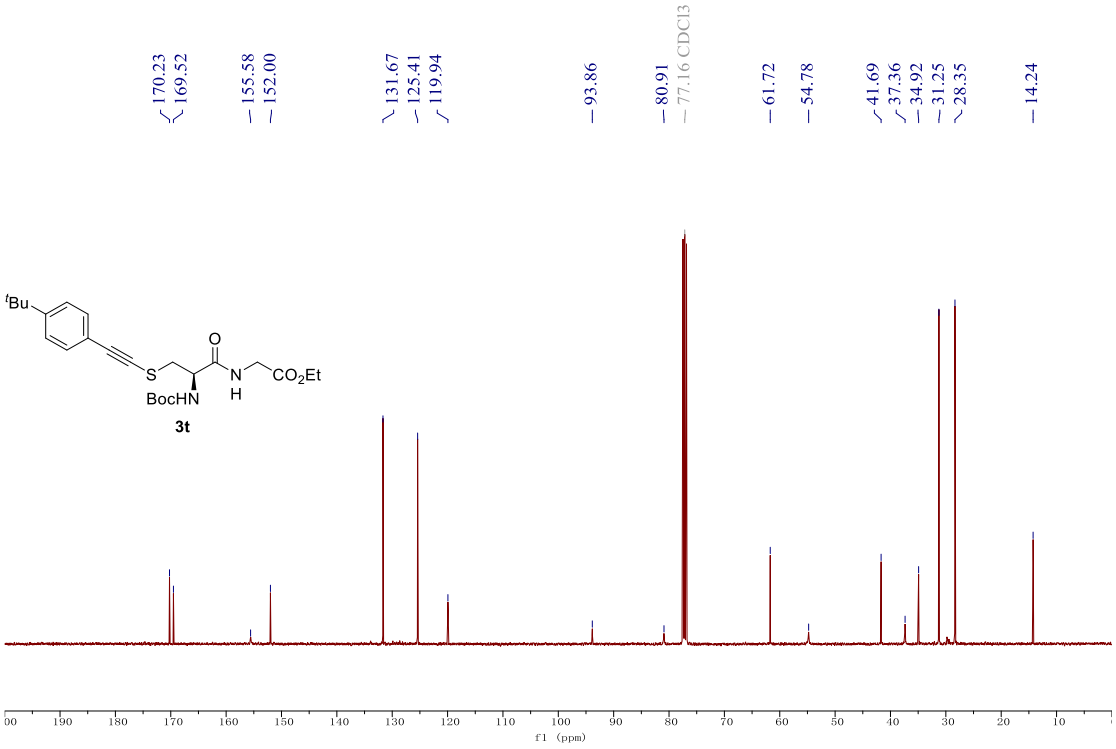

Figure S52. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3t

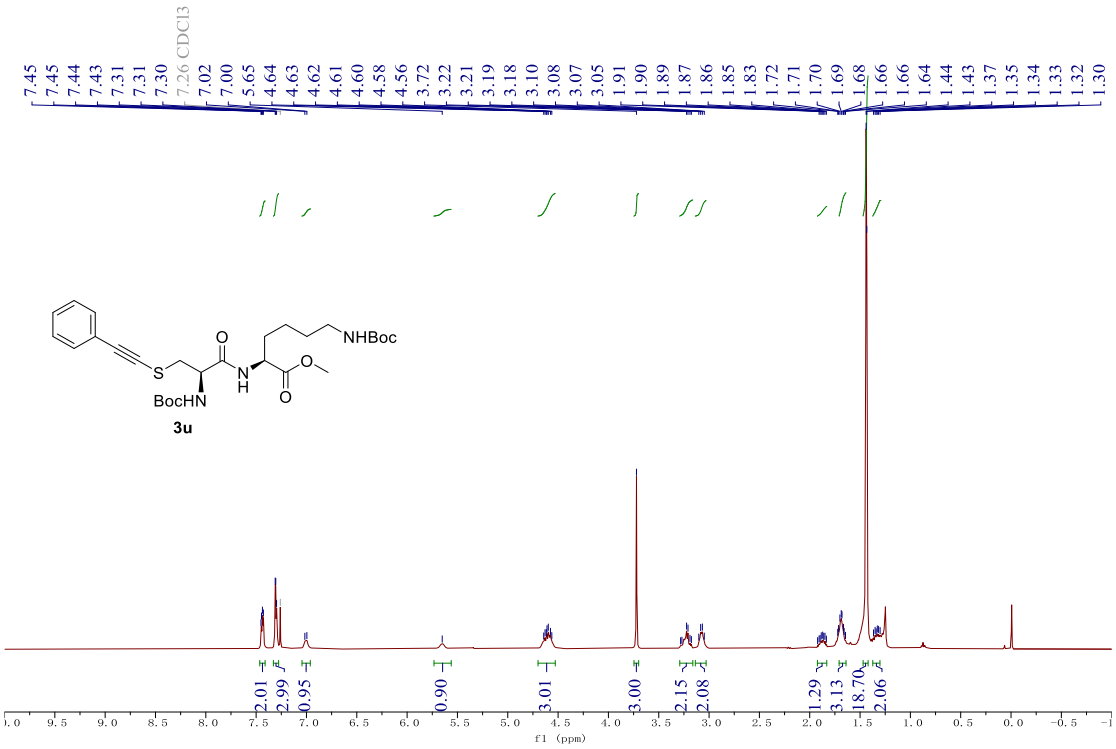

Figure S53. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3u

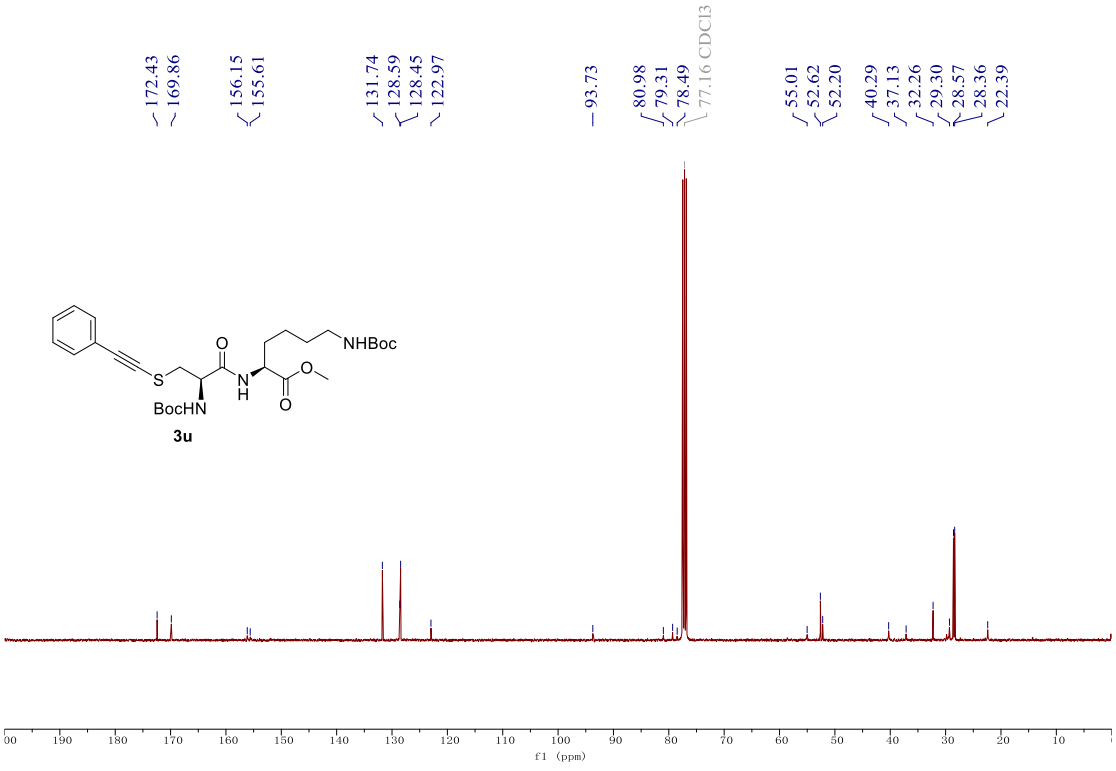

Figure S54. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3u

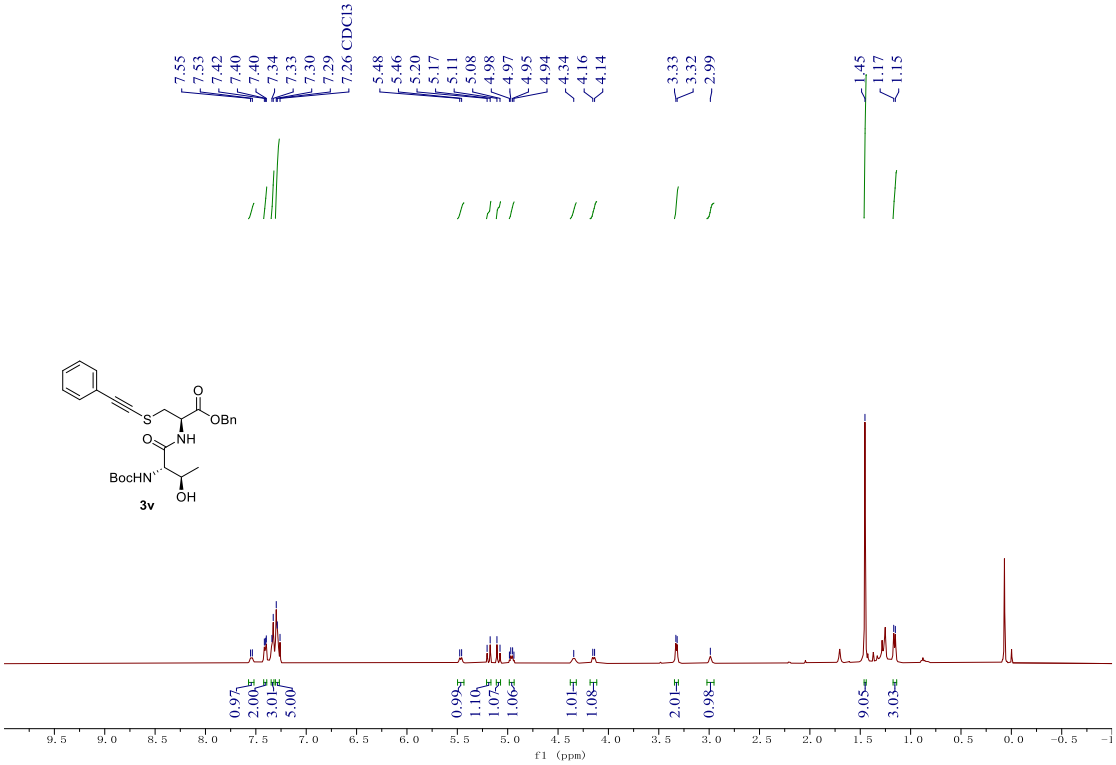

Figure S55. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3v

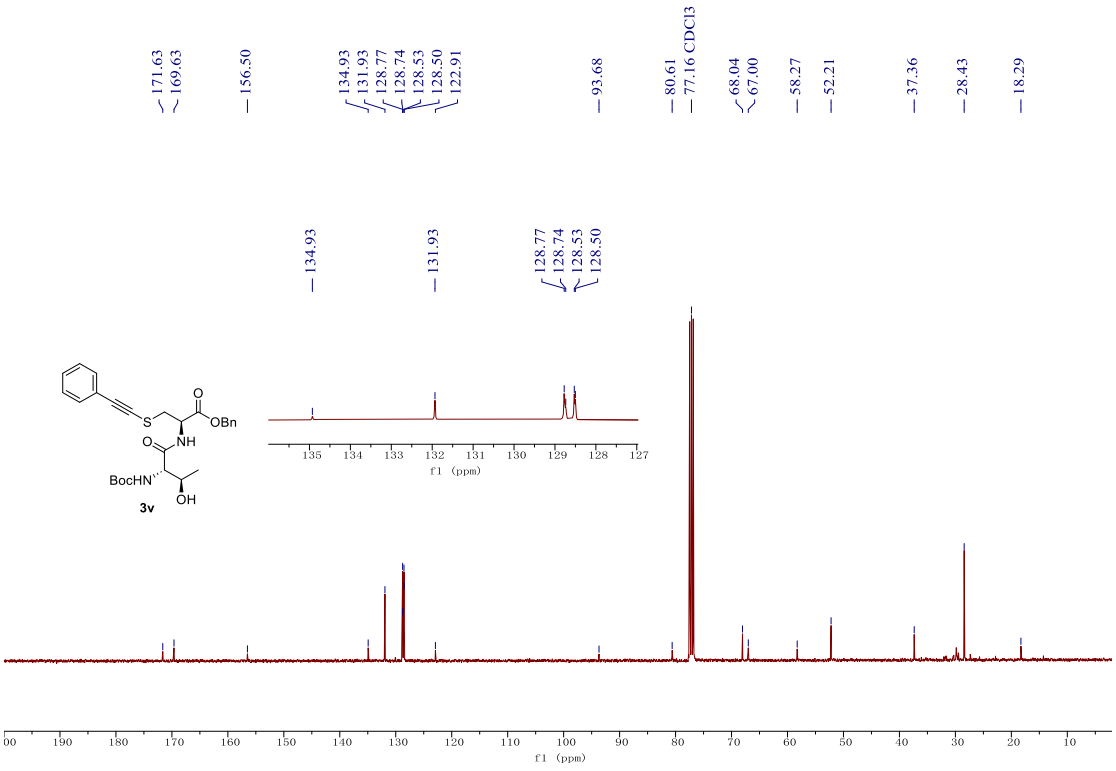

Figure S56. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3v

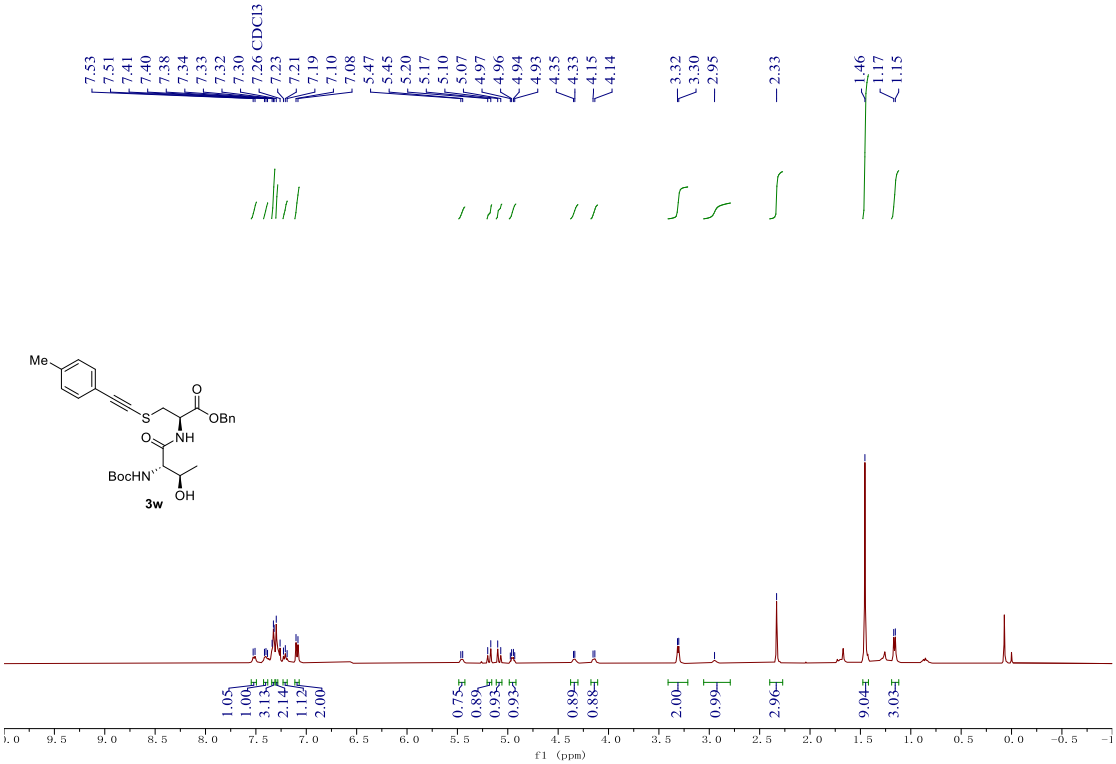

Figure S57. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3w

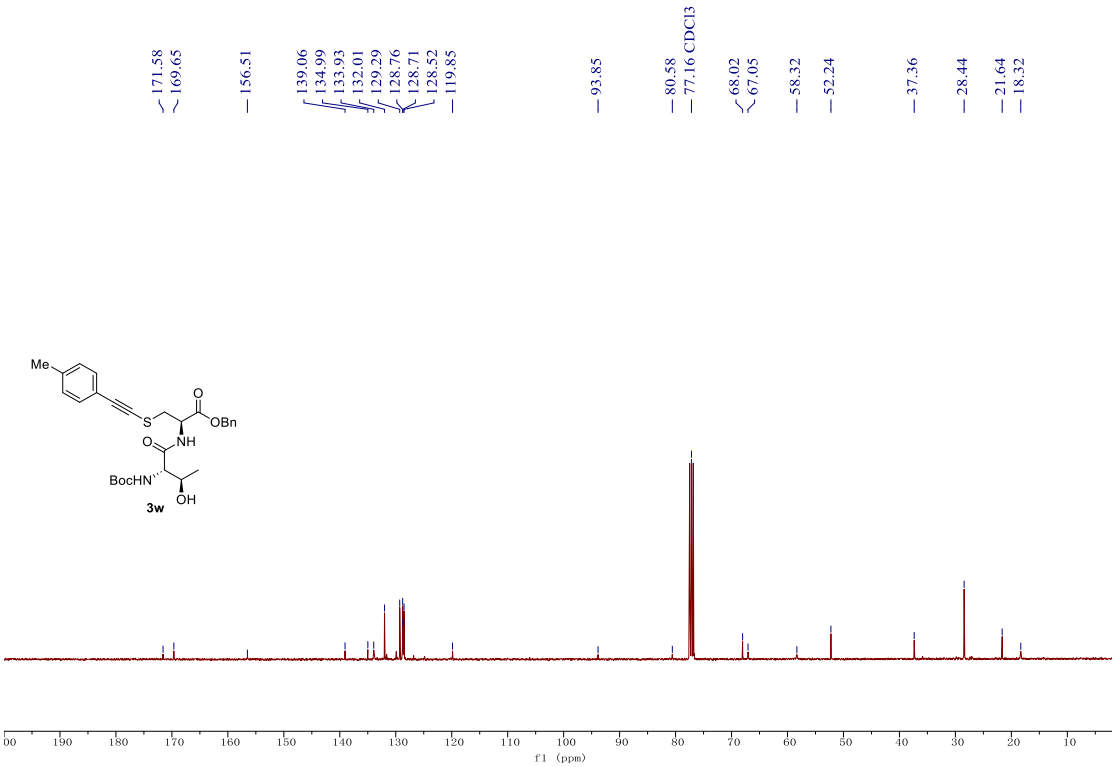

Figure S58. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3w

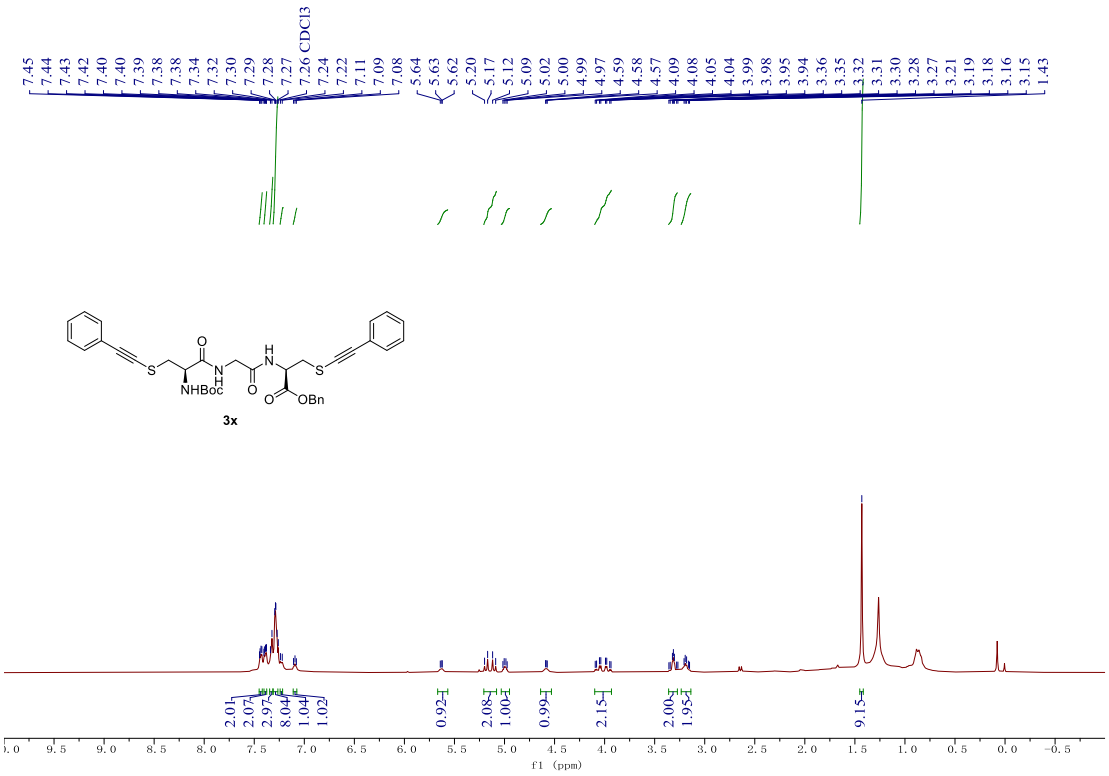

Figure S59. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 3x

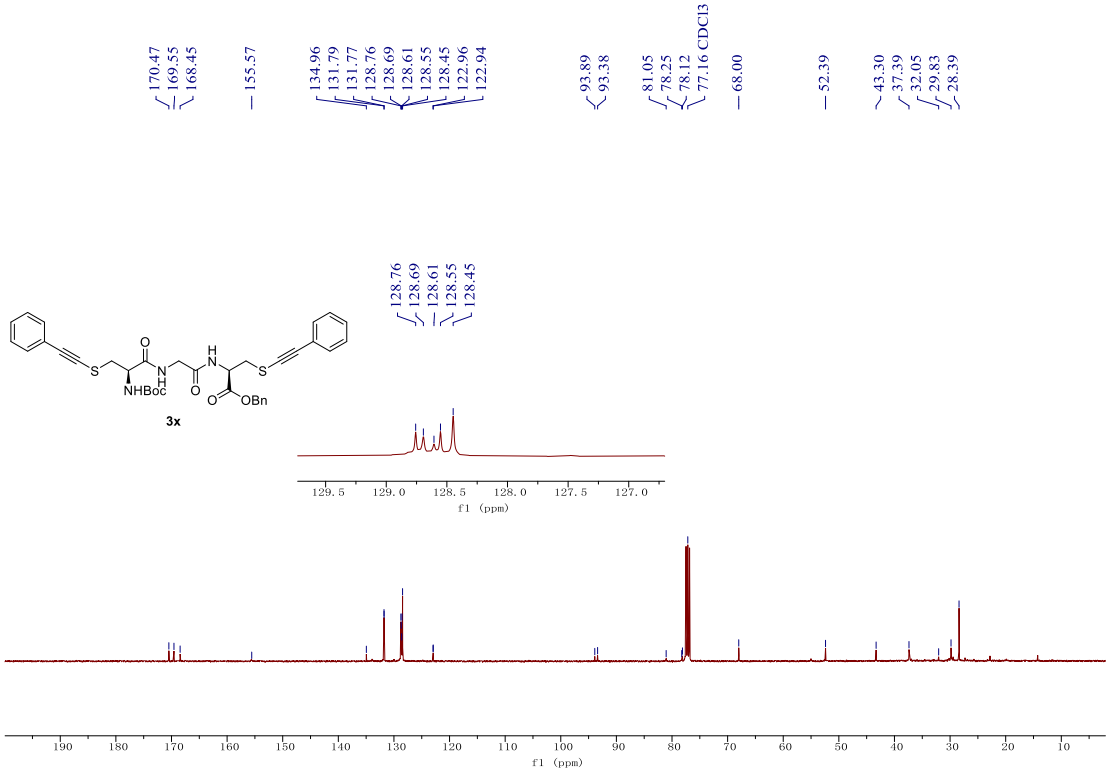

Figure S60. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 3x

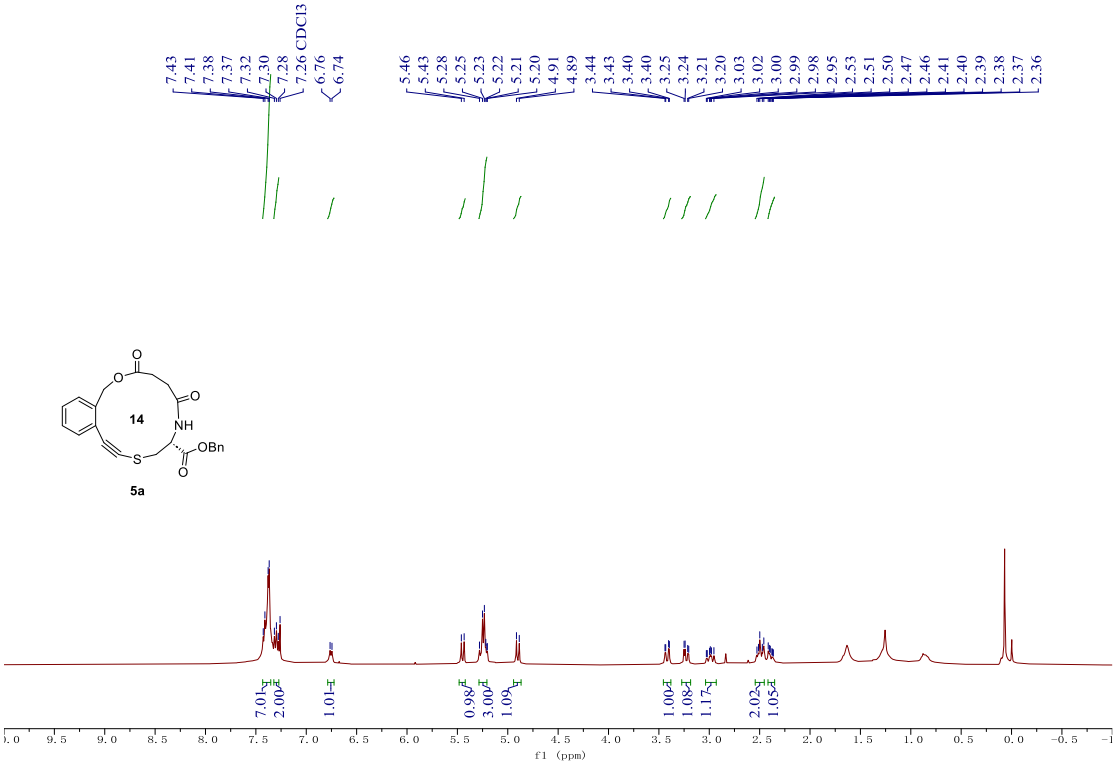

Figure S61. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5a

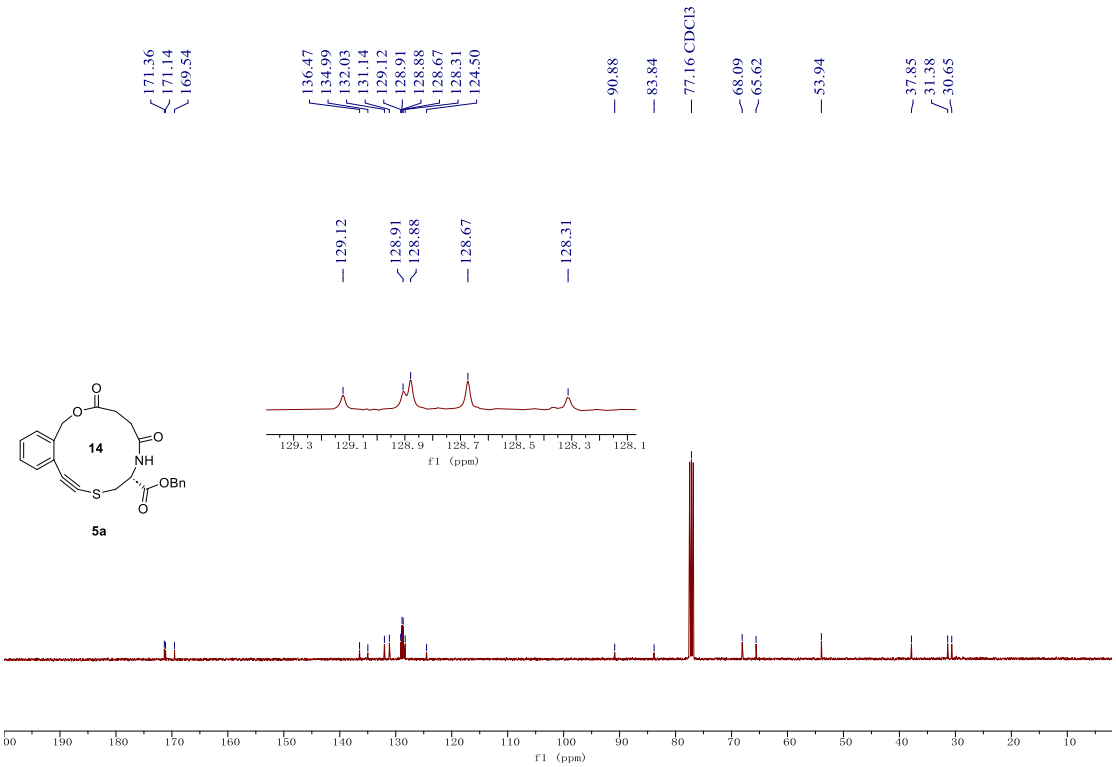

Figure S62. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5a

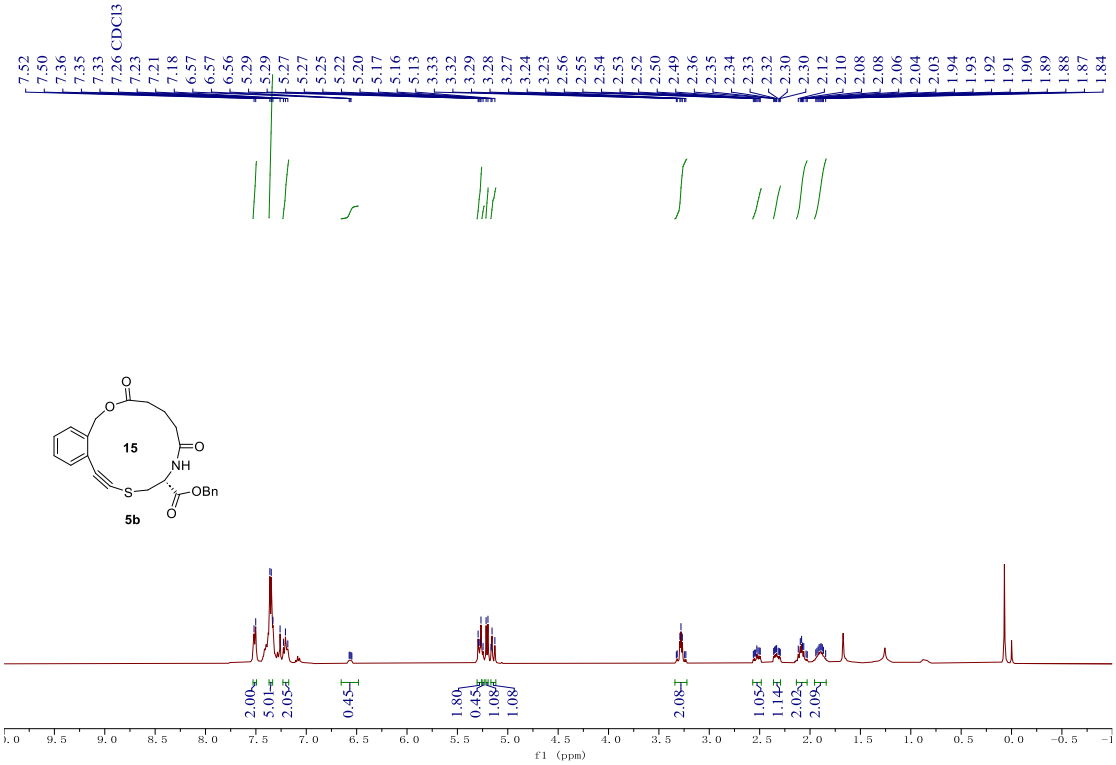

Figure S63. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5b

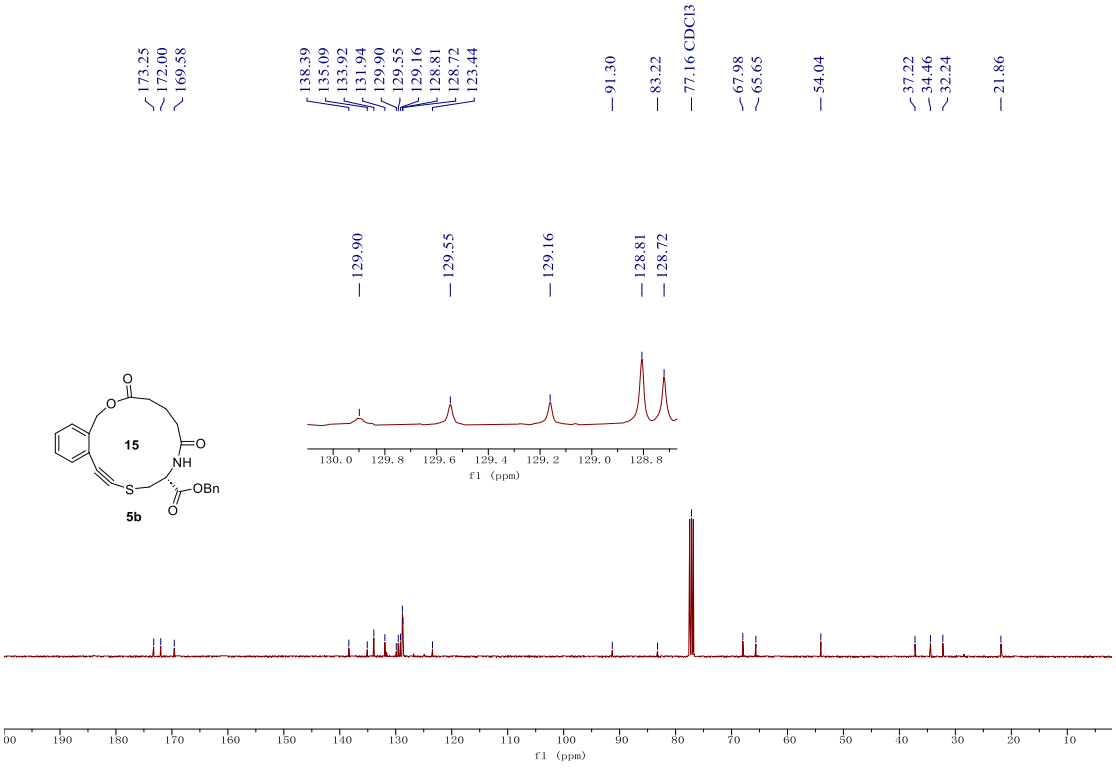

Figure S64. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5b

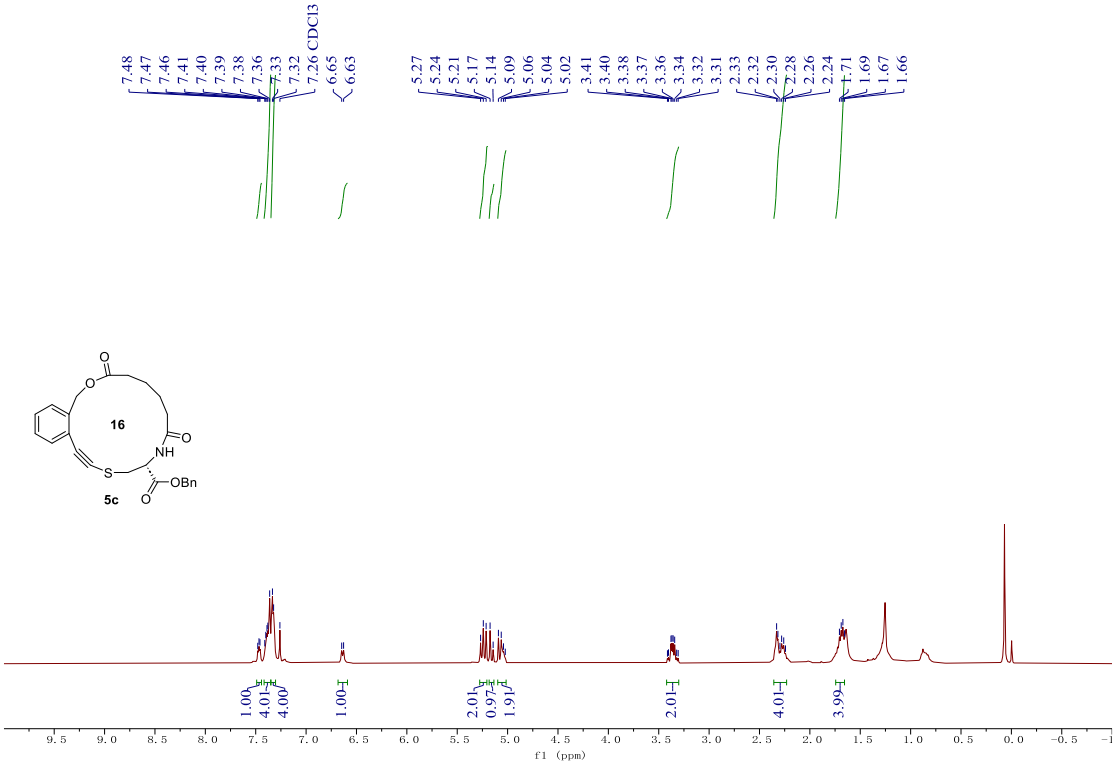

Figure S65. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5c

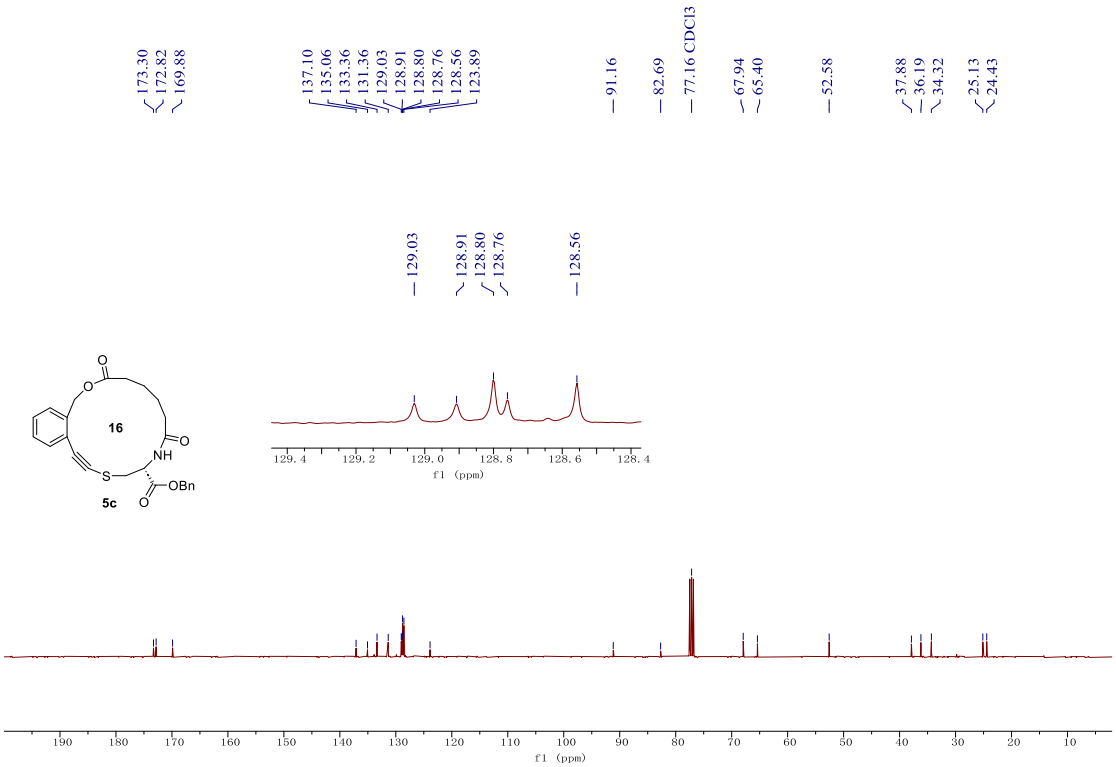

Figure S66. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5c

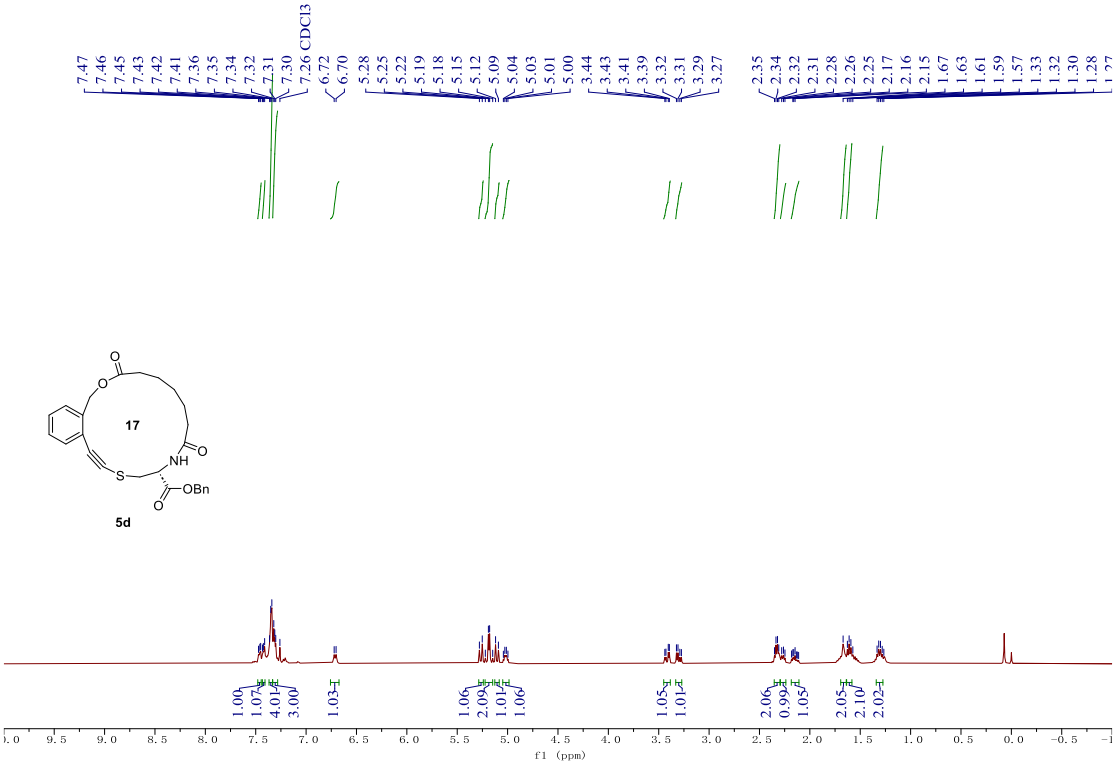

Figure S67. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5d

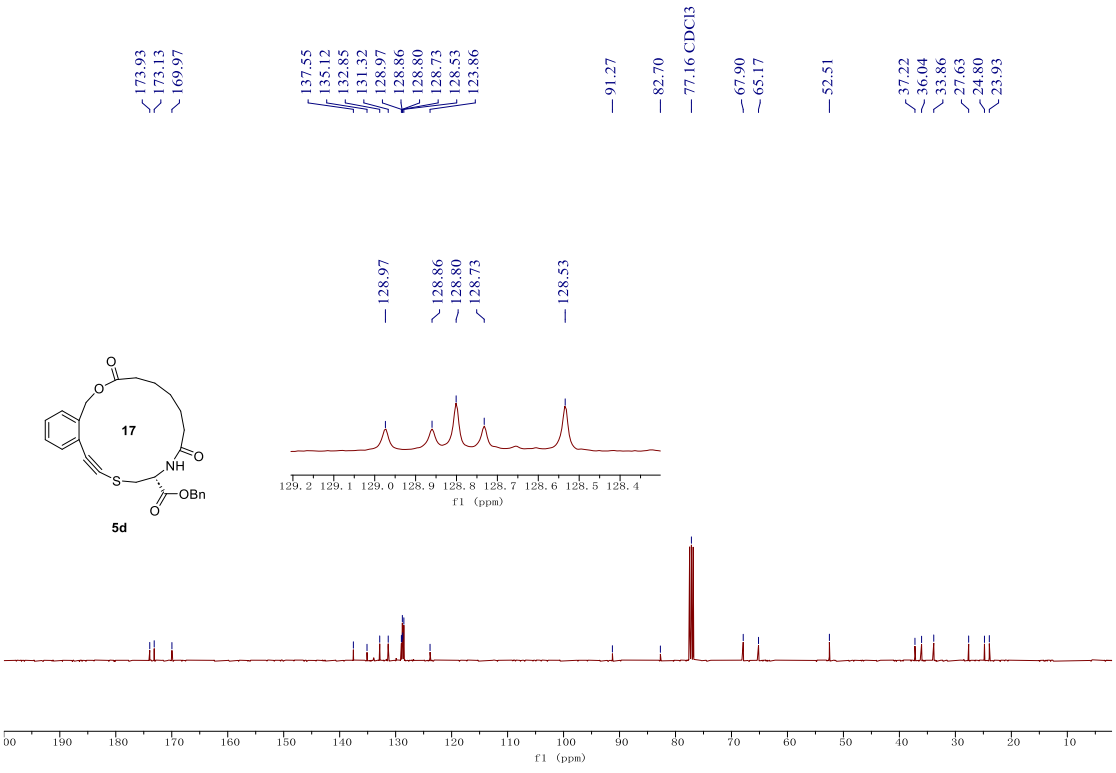

Figure S68. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5d

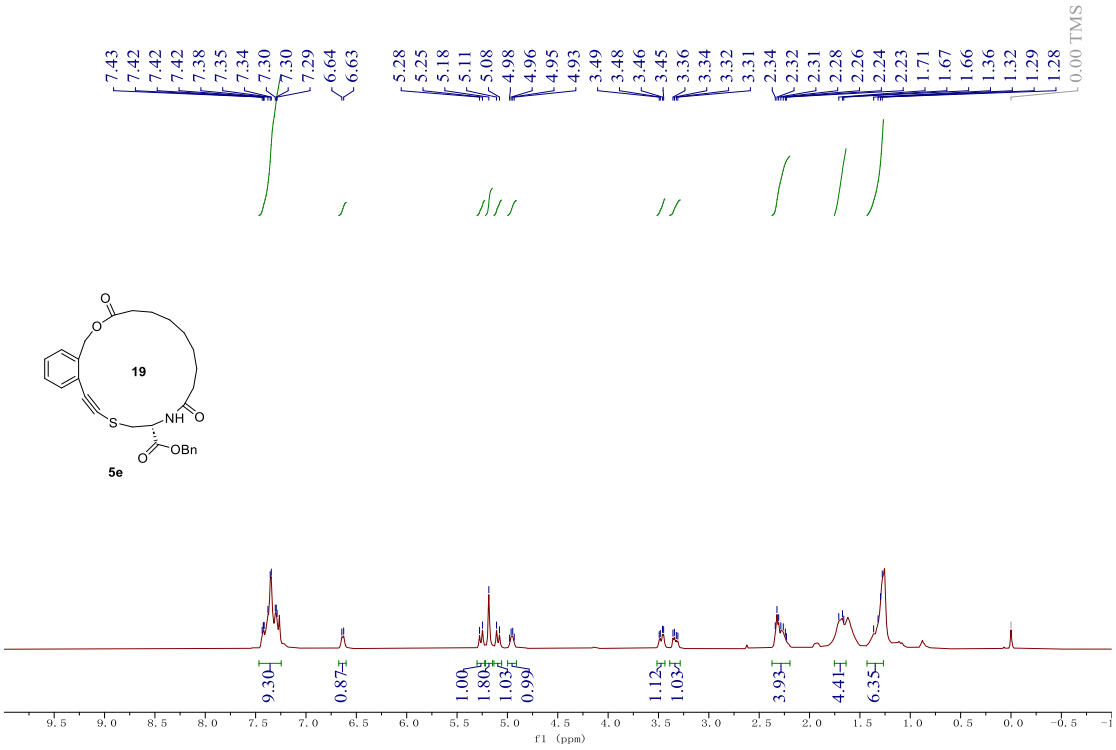

Figure S69. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5e

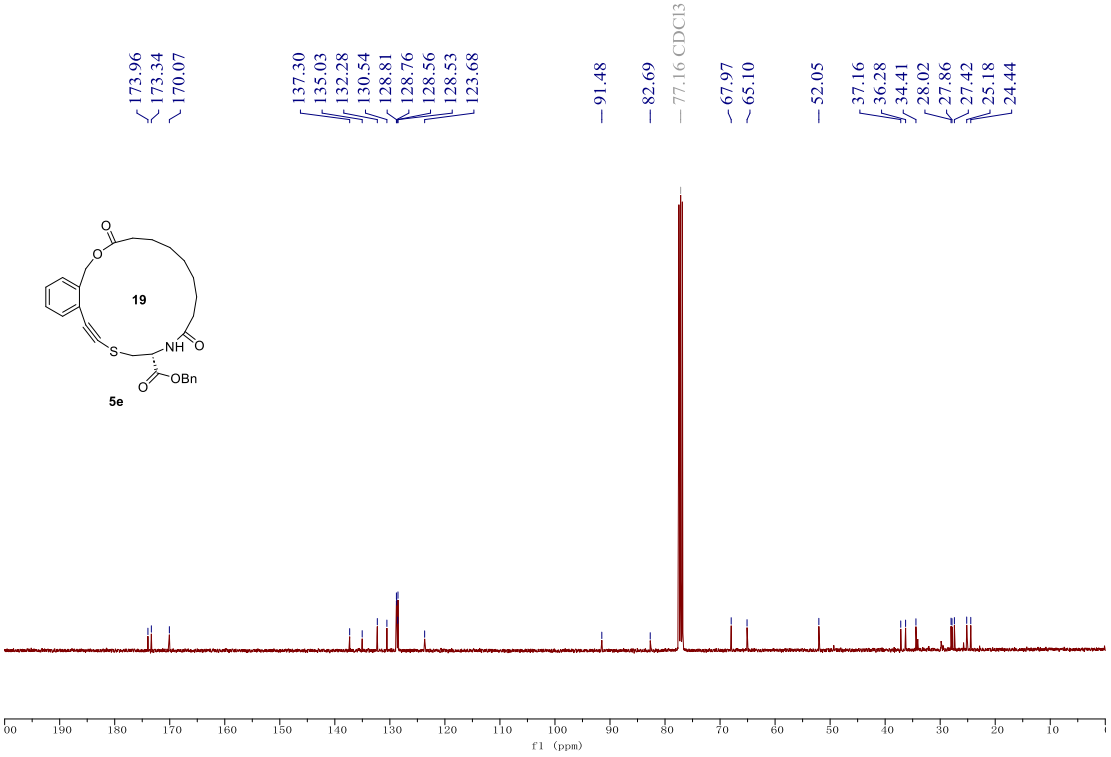

Figure S70. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5e

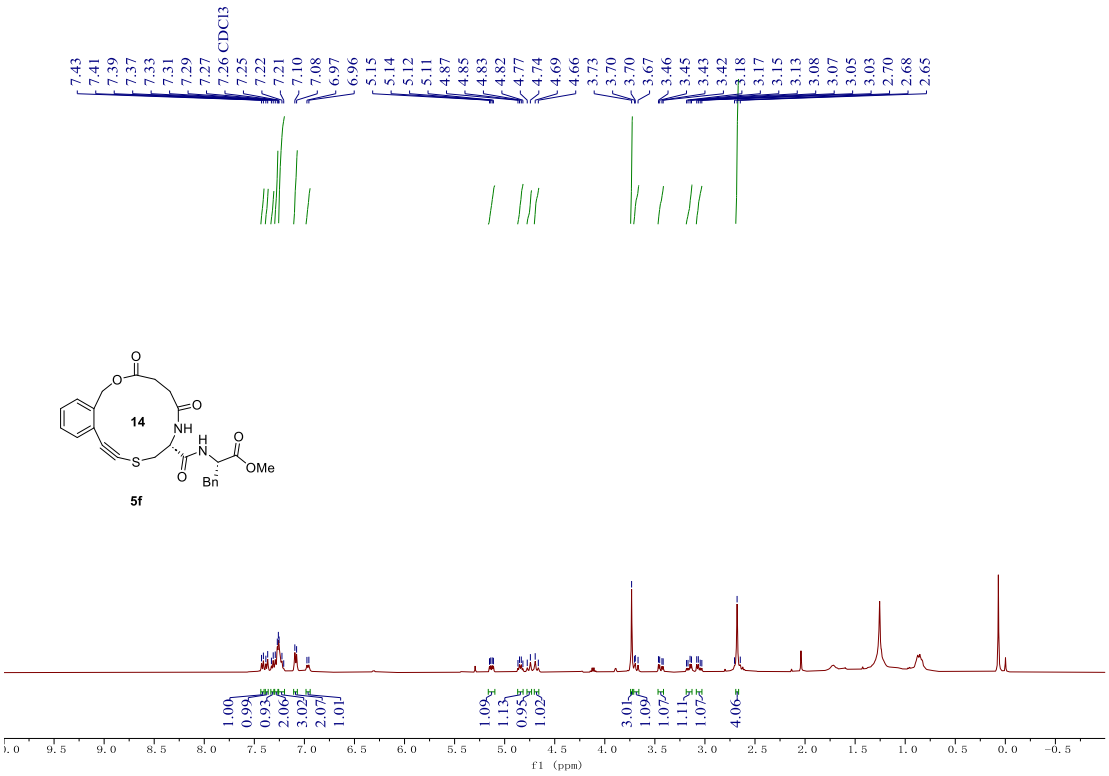

Figure S71. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5f

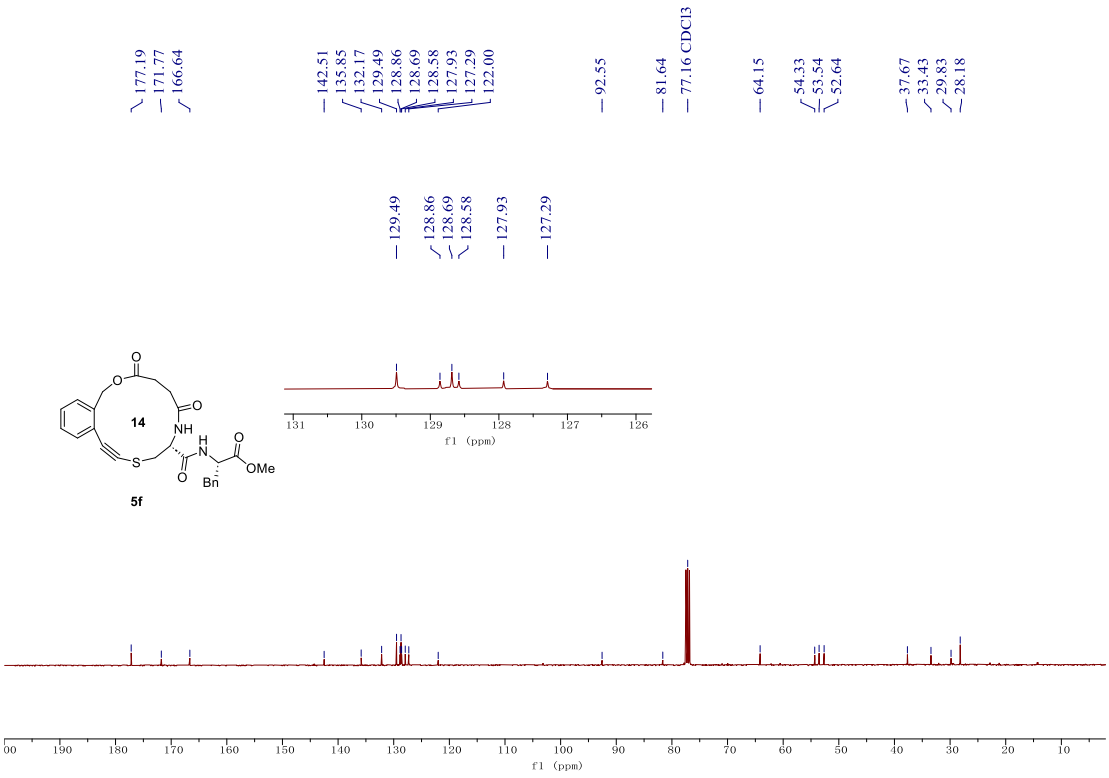

Figure S72. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5f

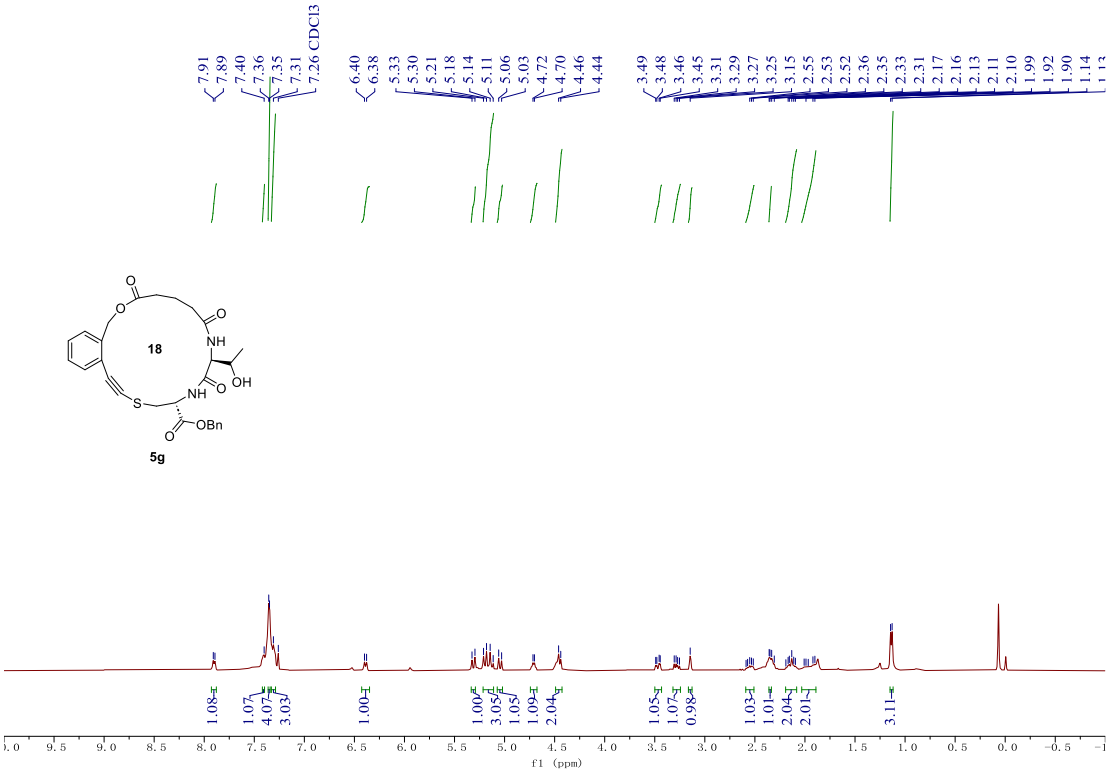

Figure S73. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5g

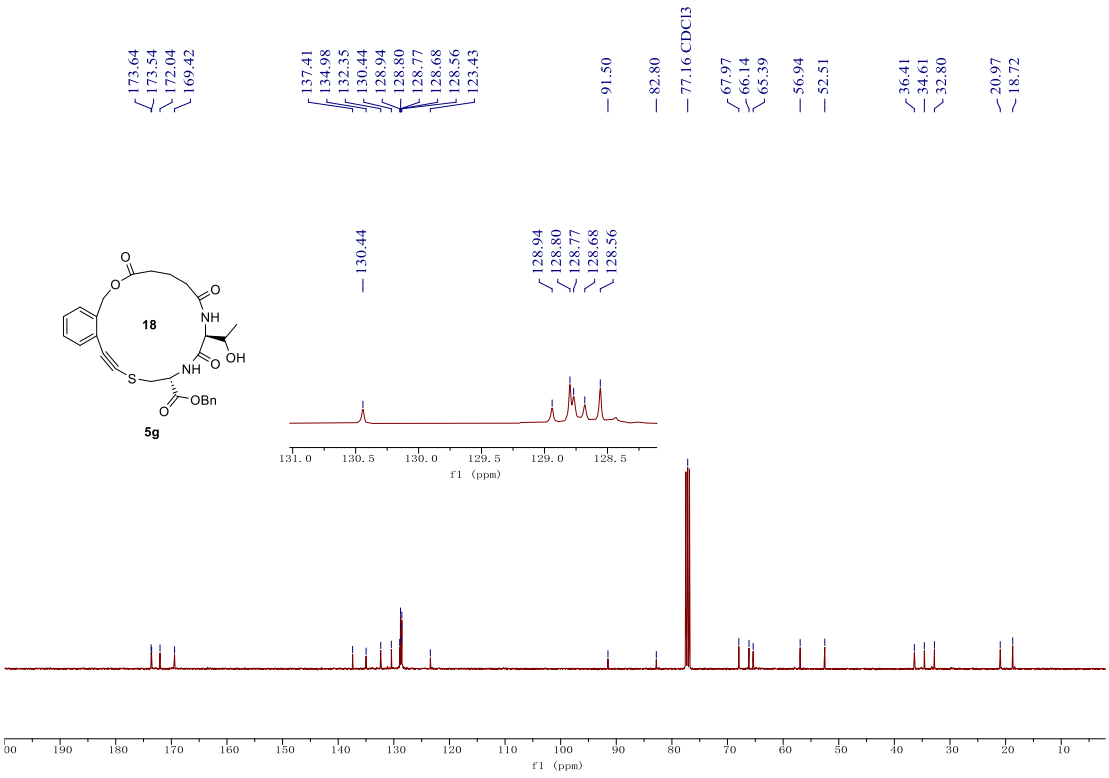

Figure S74. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5g

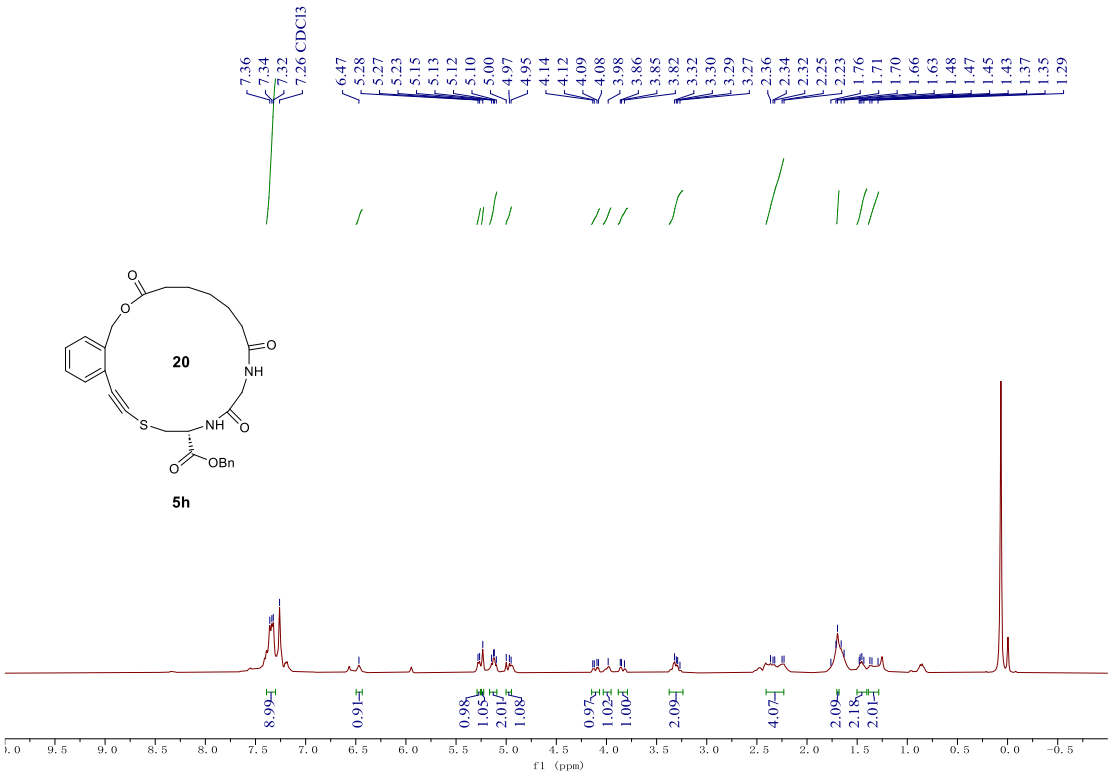

Figure S75. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5h

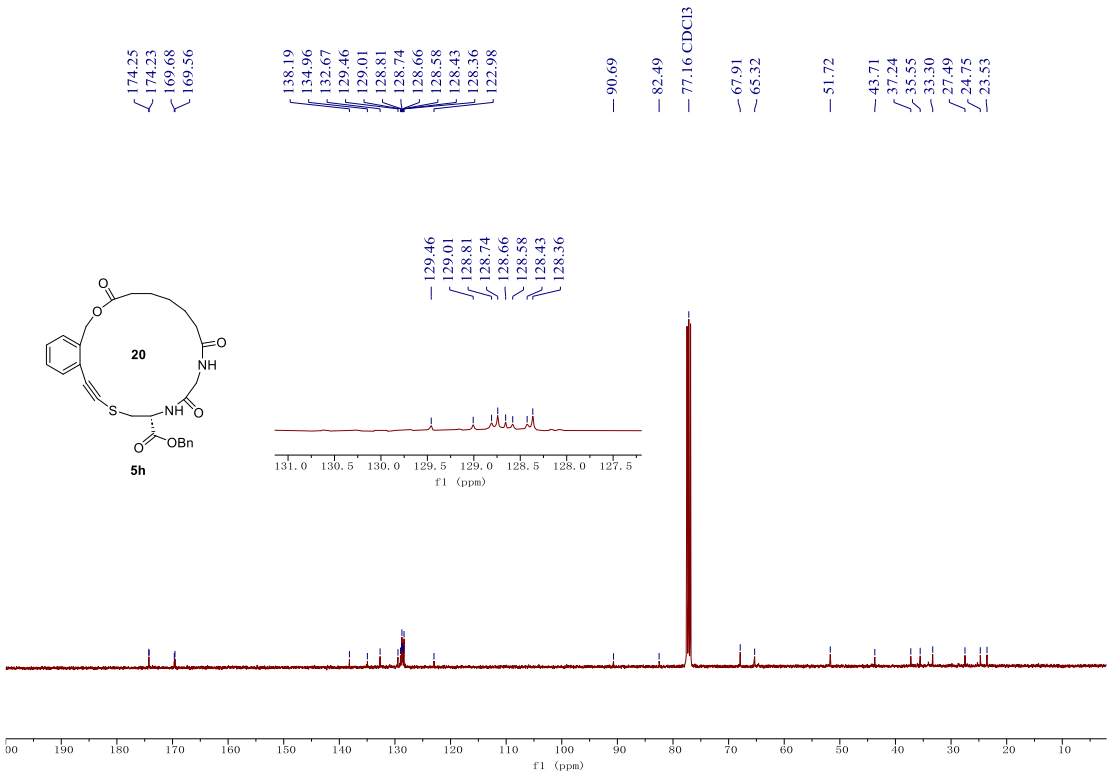

Figure S76. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5h

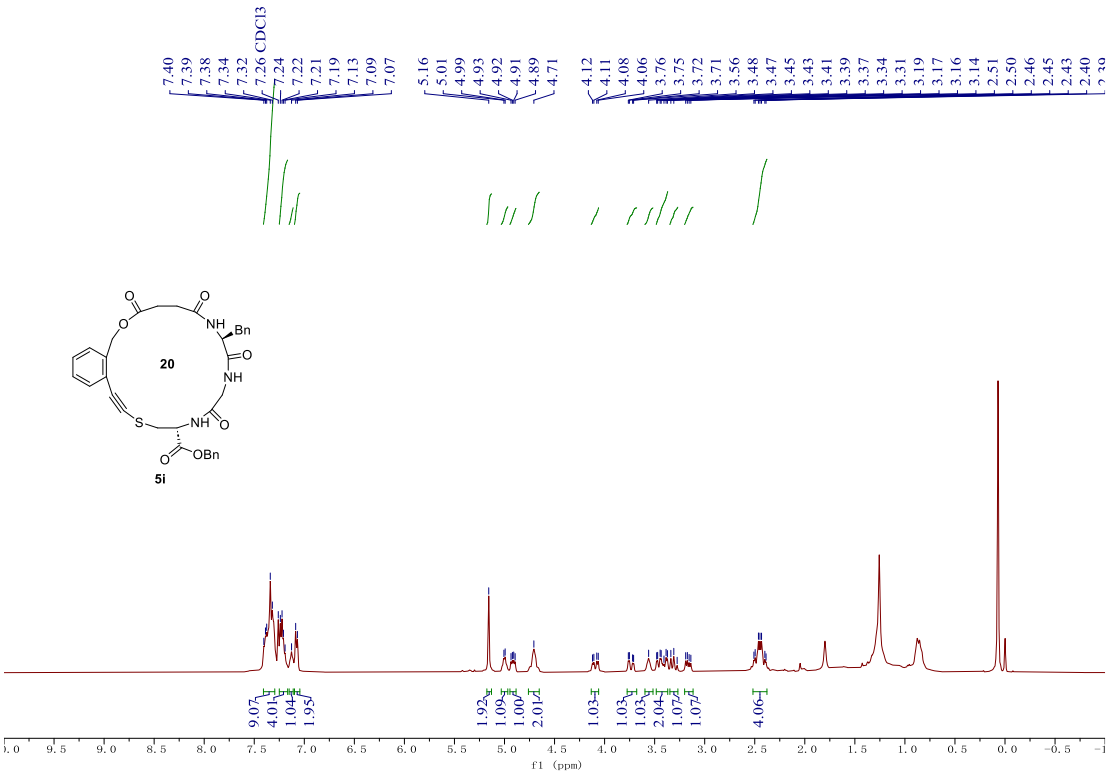

Figure S77. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5i

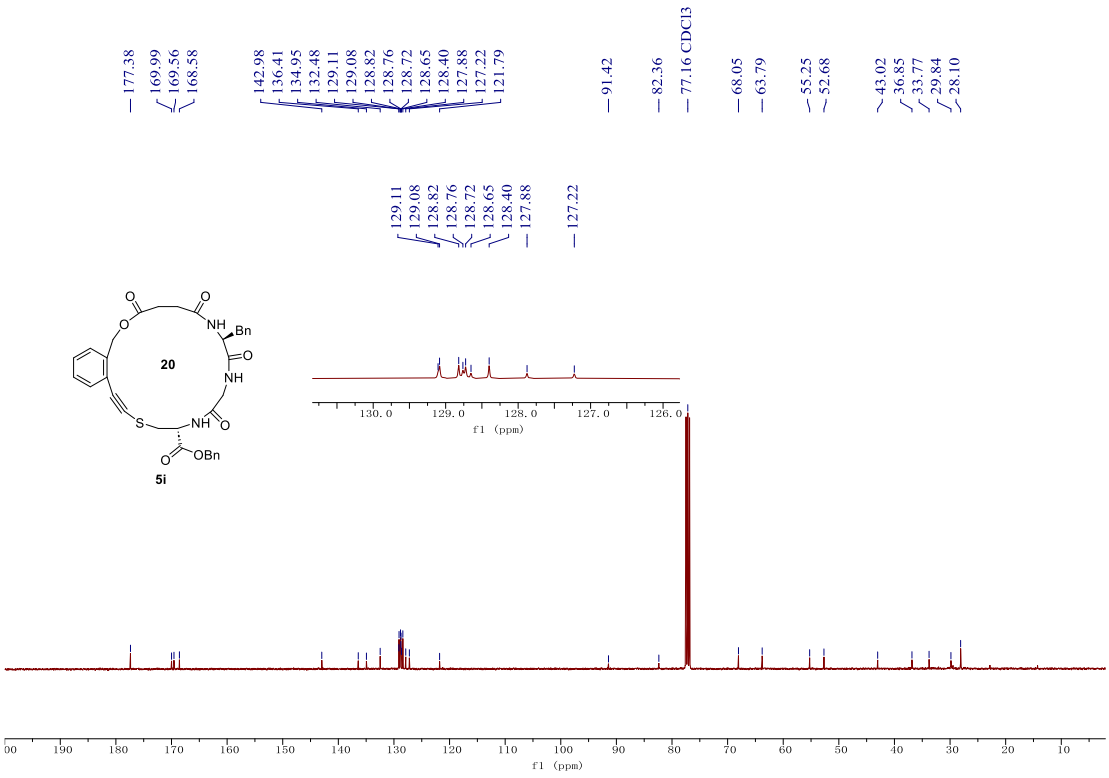

Figure S78. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5i

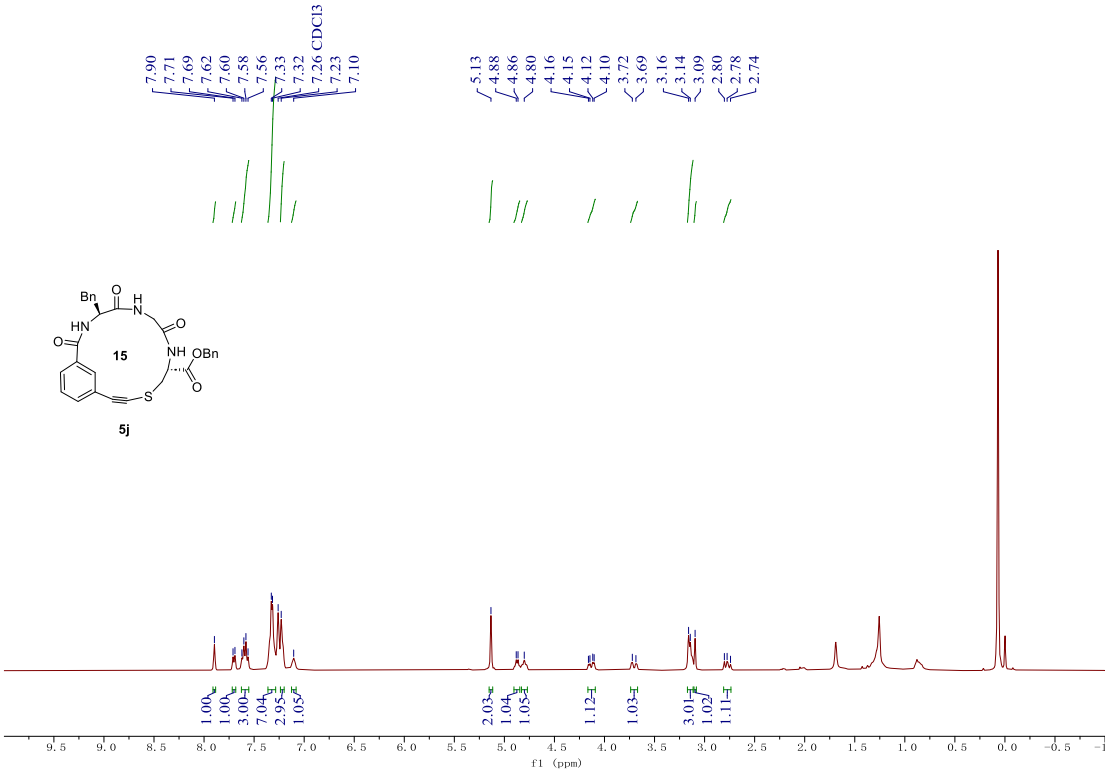

Figure S79. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 5j

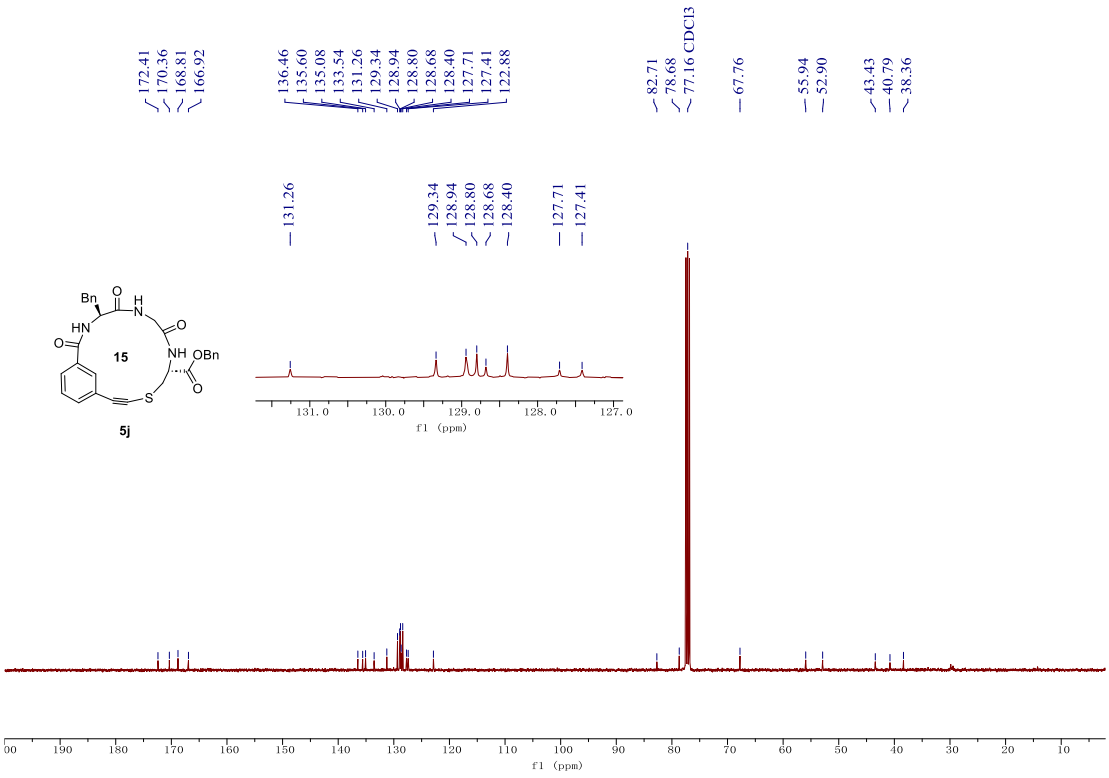

Figure S80. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 5j

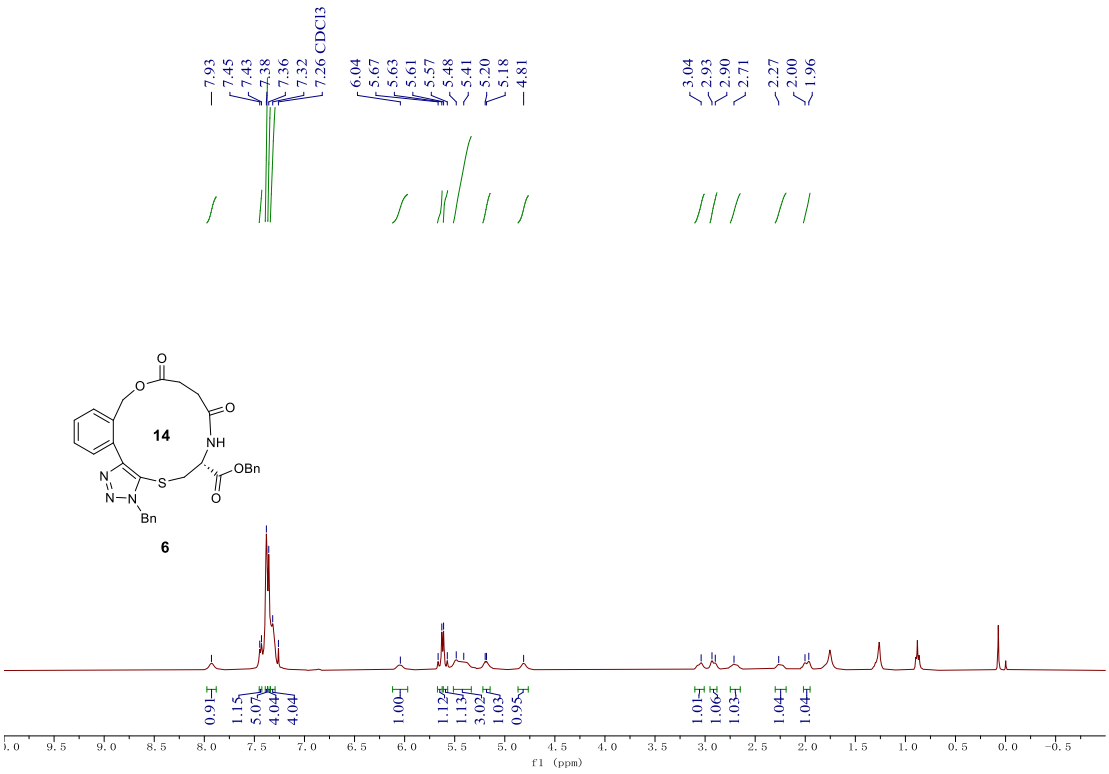

Figure S81. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 6

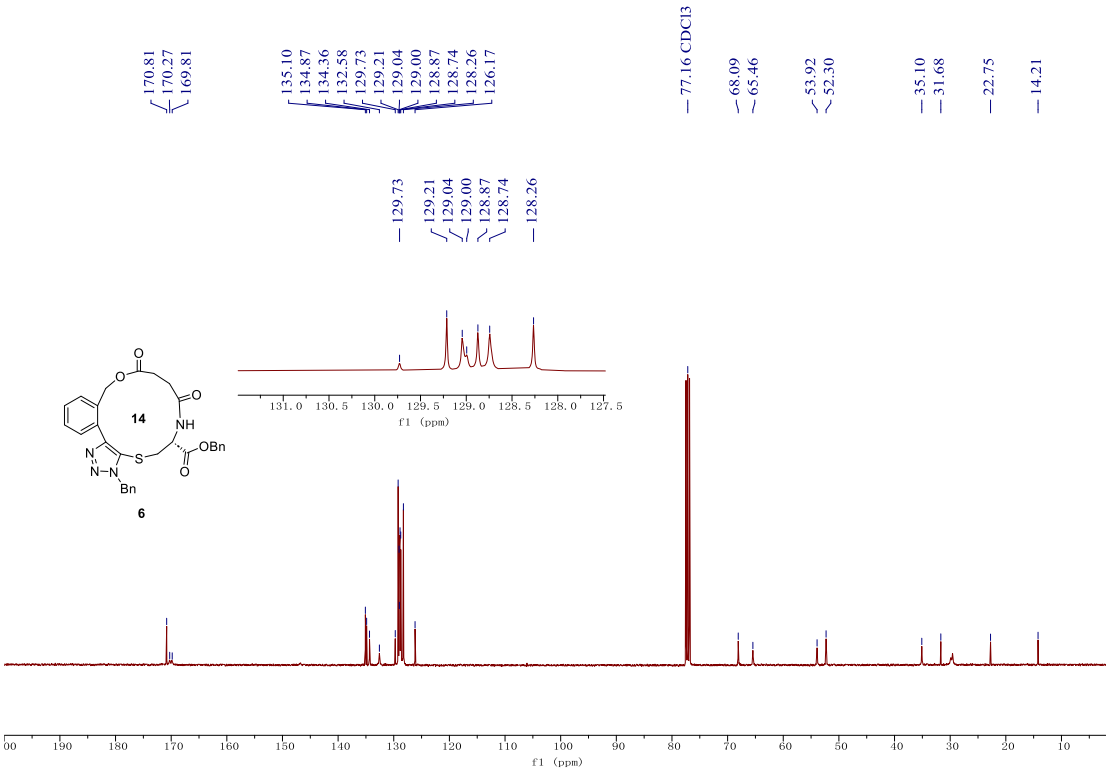

Figure S82. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 6

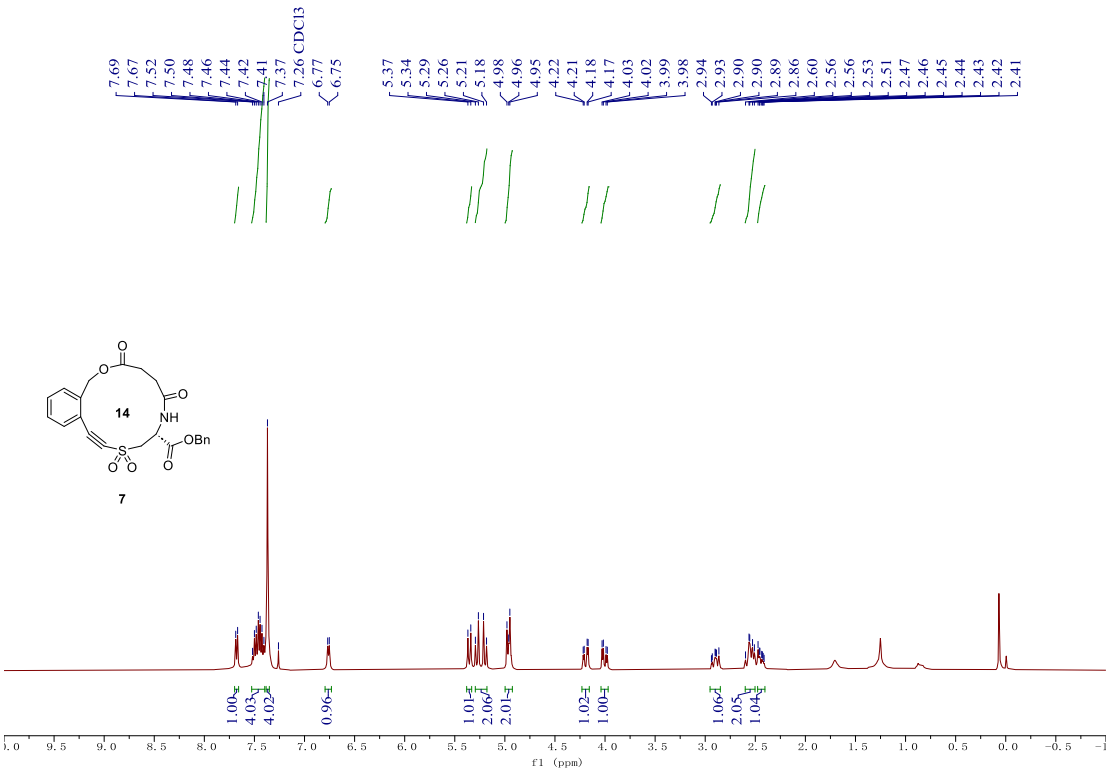

Figure S83. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 7

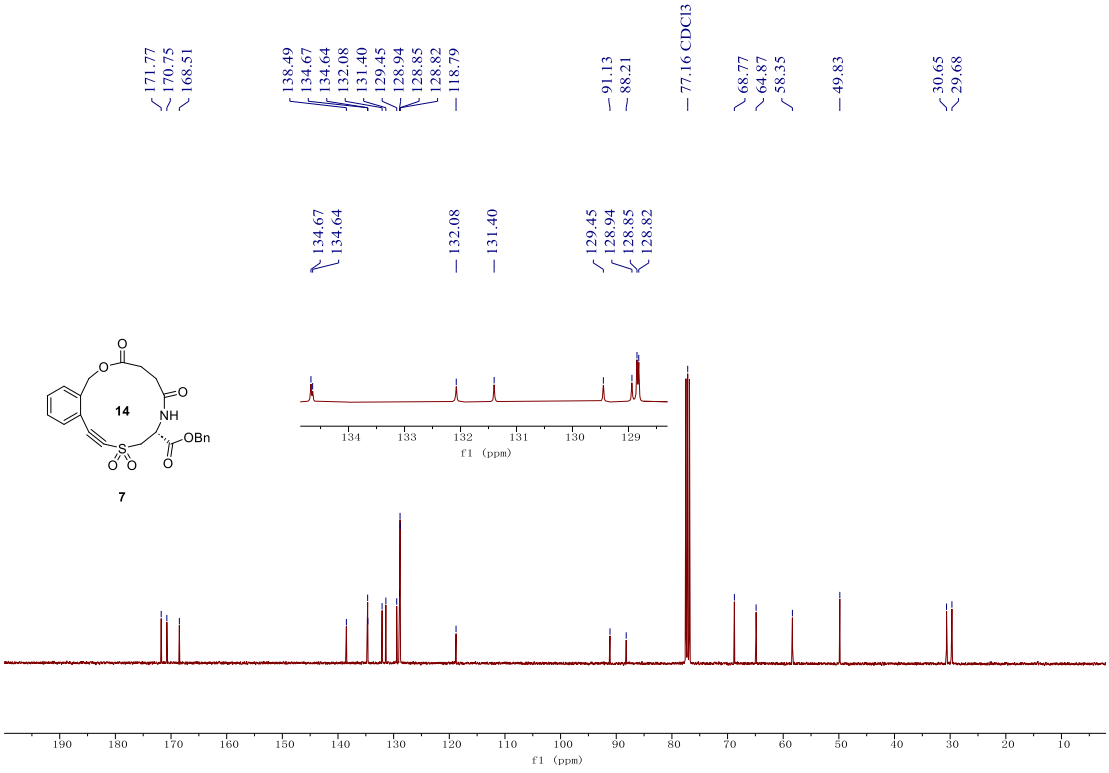

Figure S84. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 7

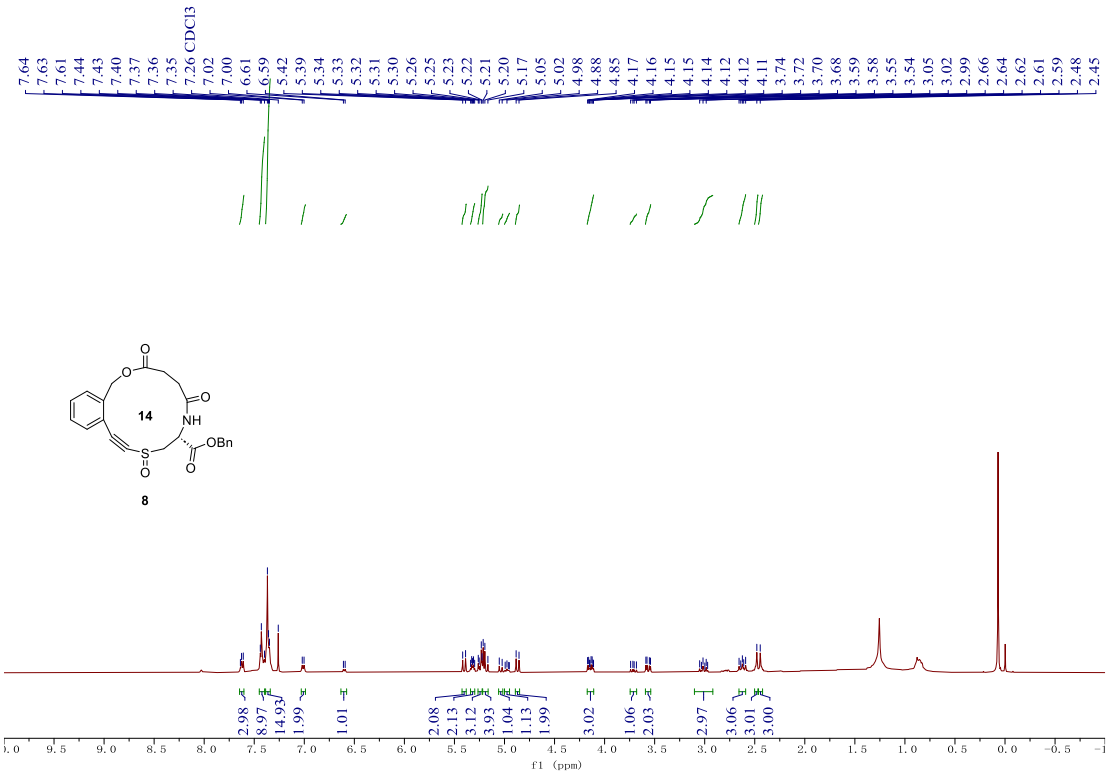

Figure S85. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 8

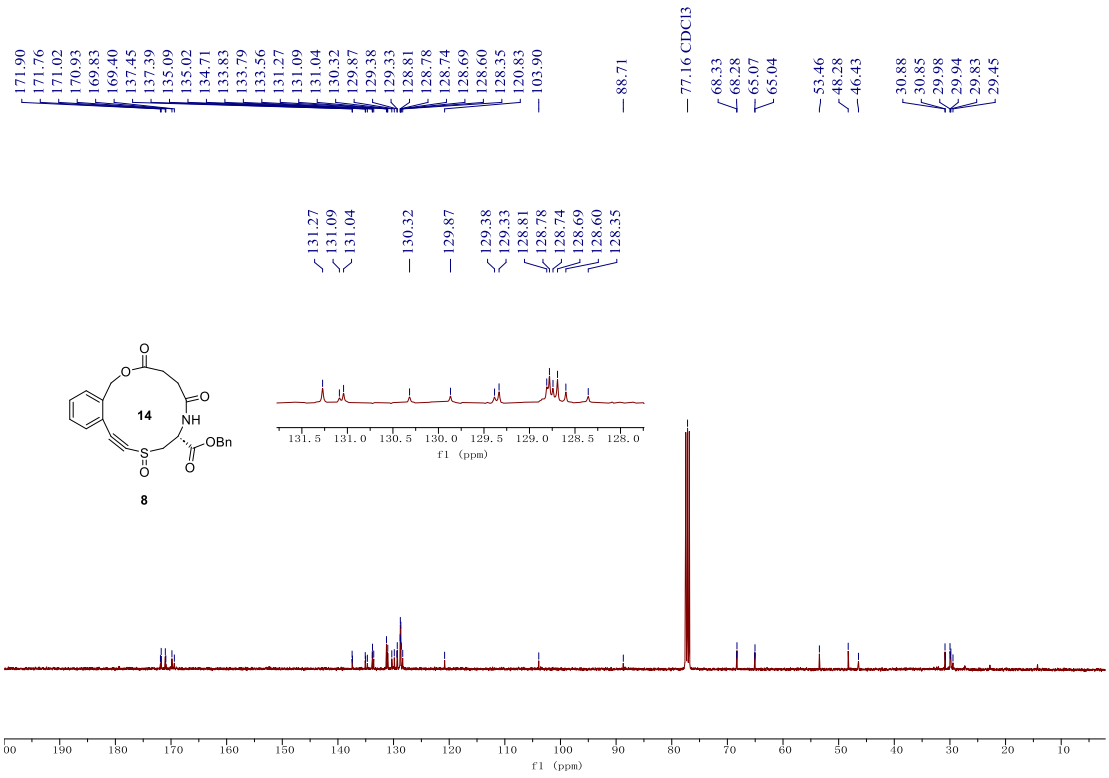

Figure S86. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 8

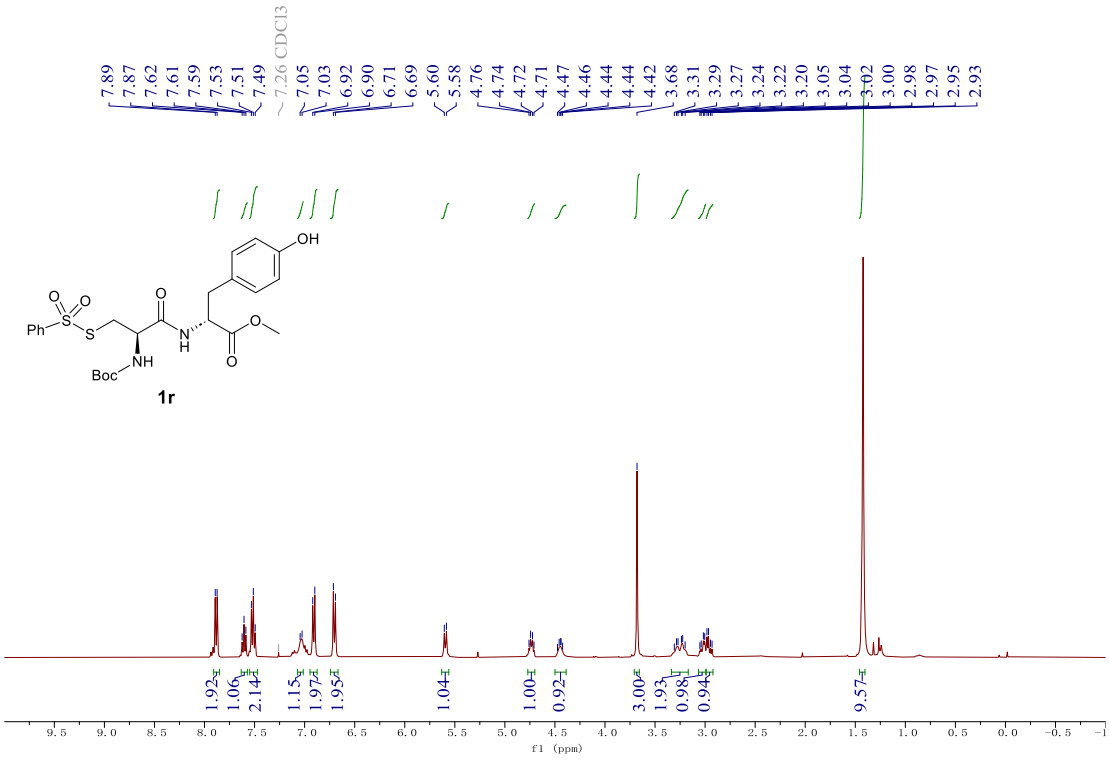

Figure S87. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 1r

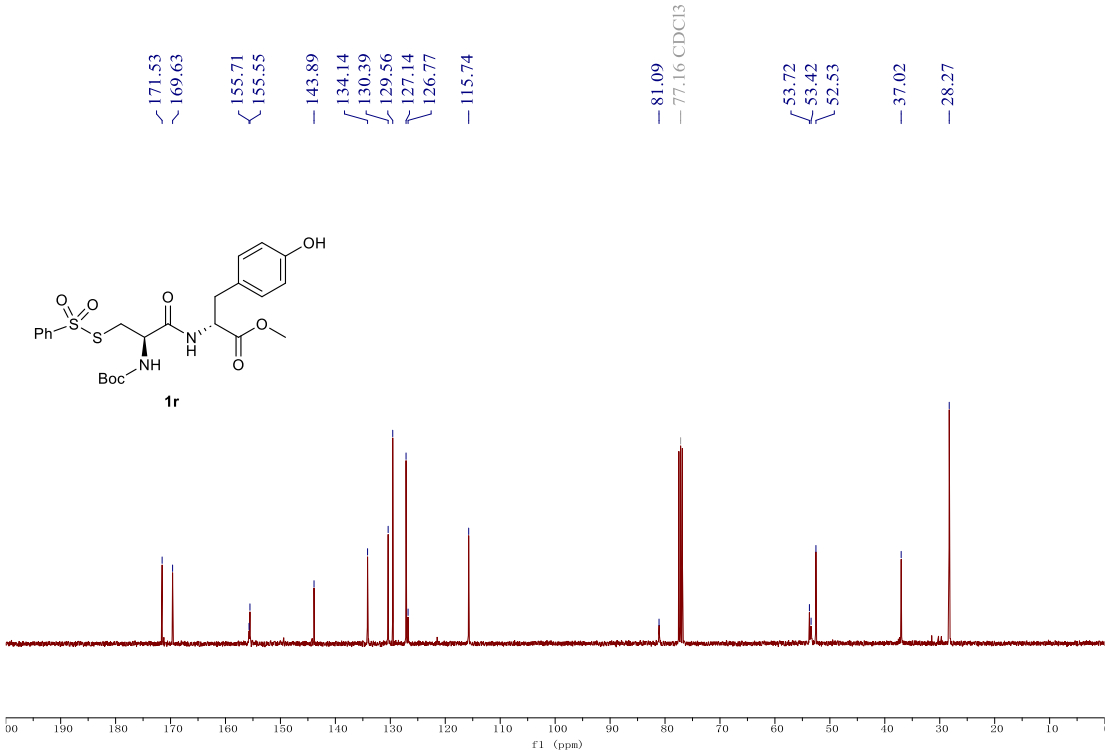

Figure S88. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 1r

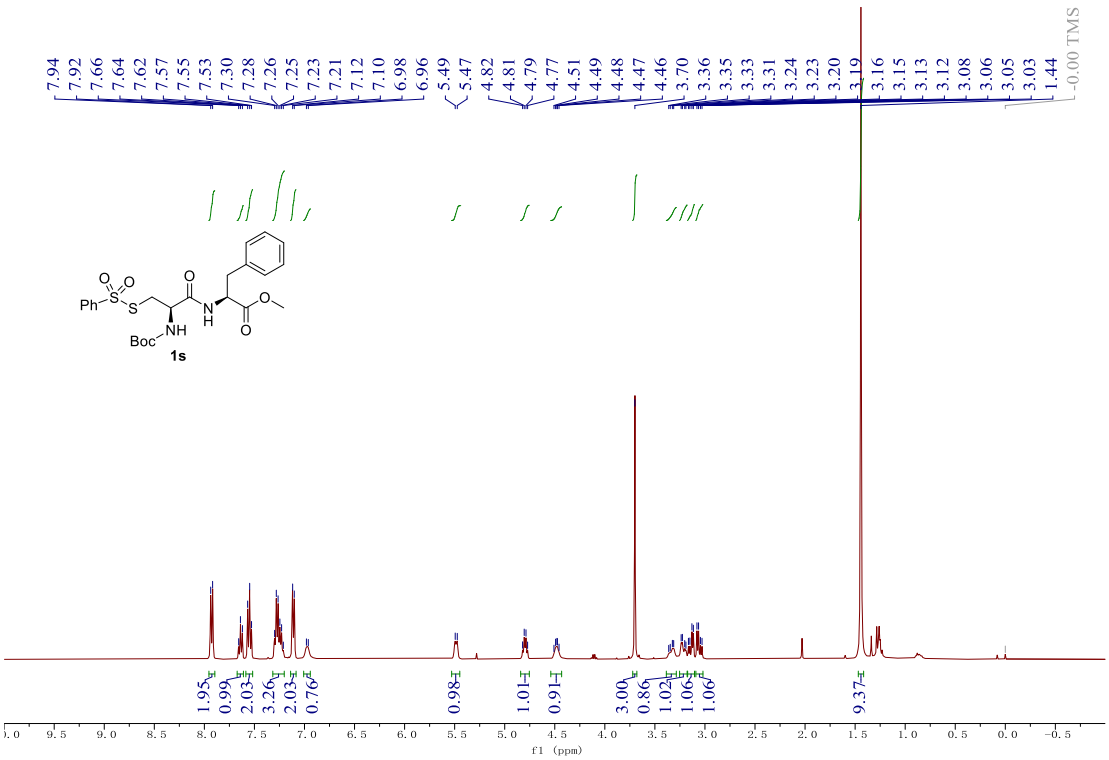

Figure S89. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 1s

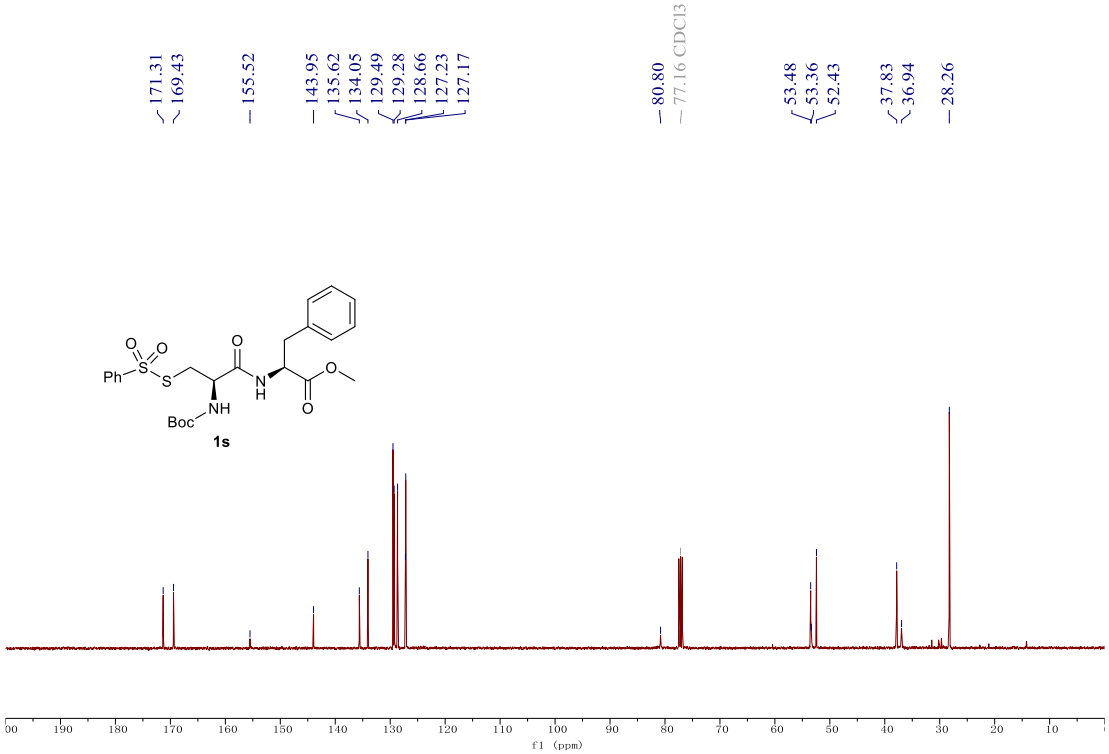

Figure S90. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 1s

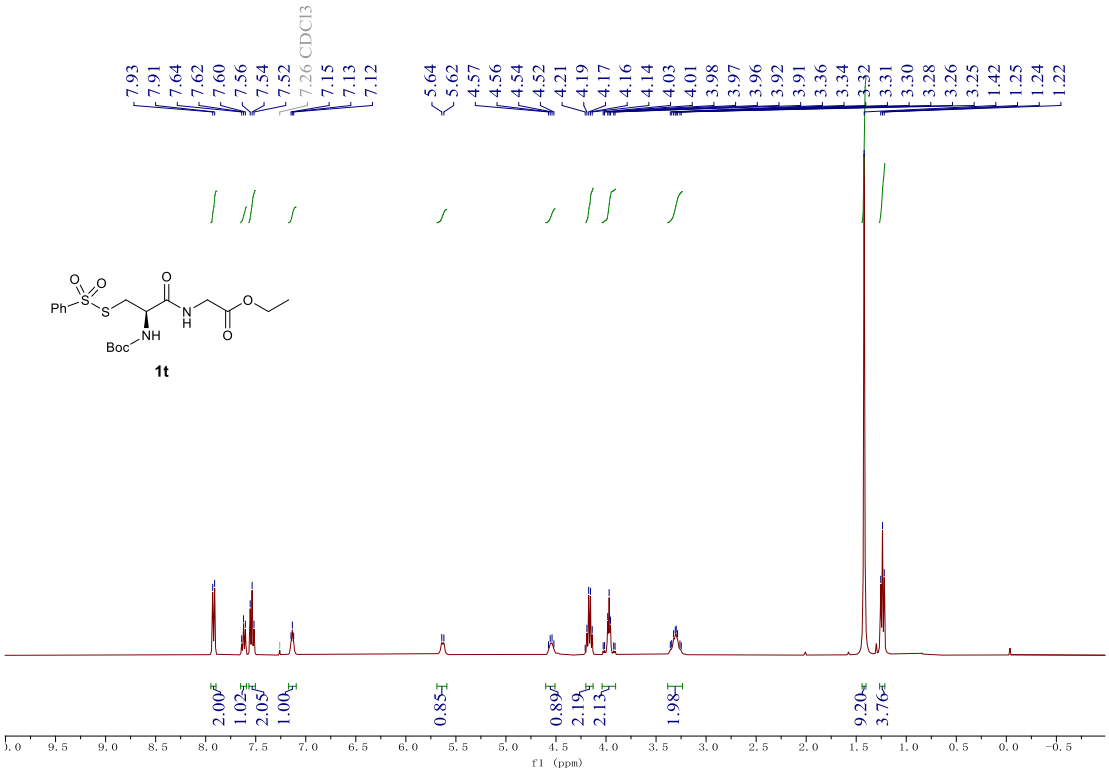

Figure S91. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 1t

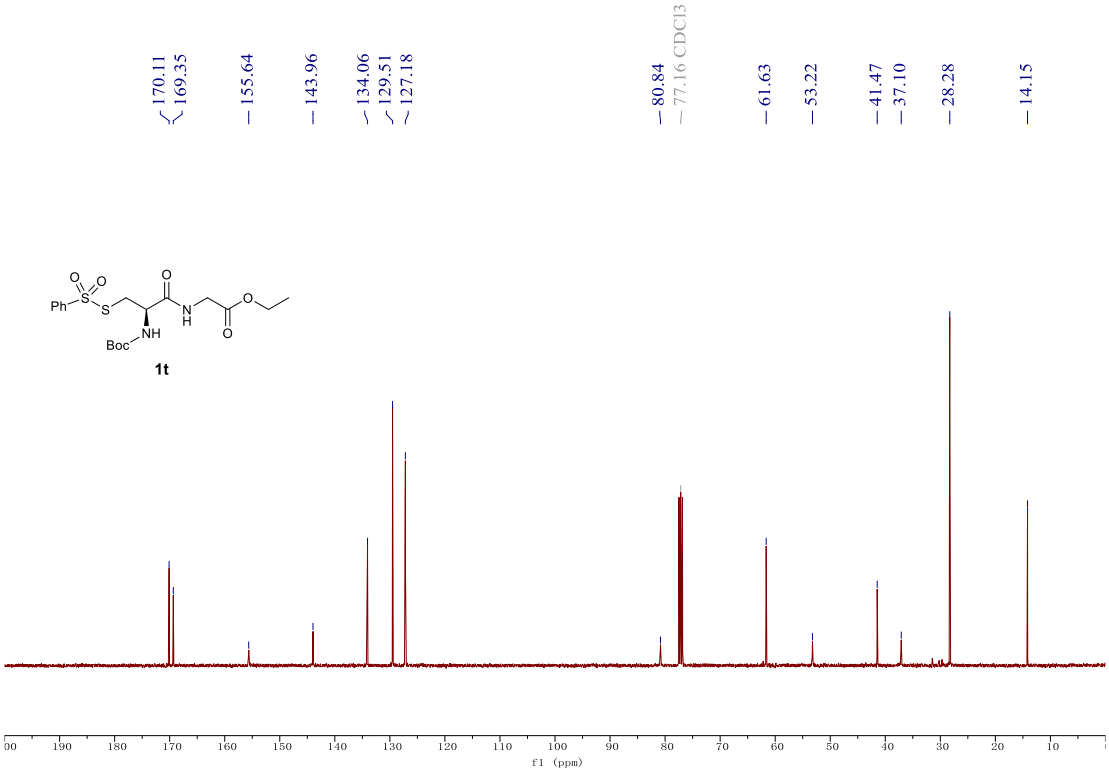

Figure S92. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 1t

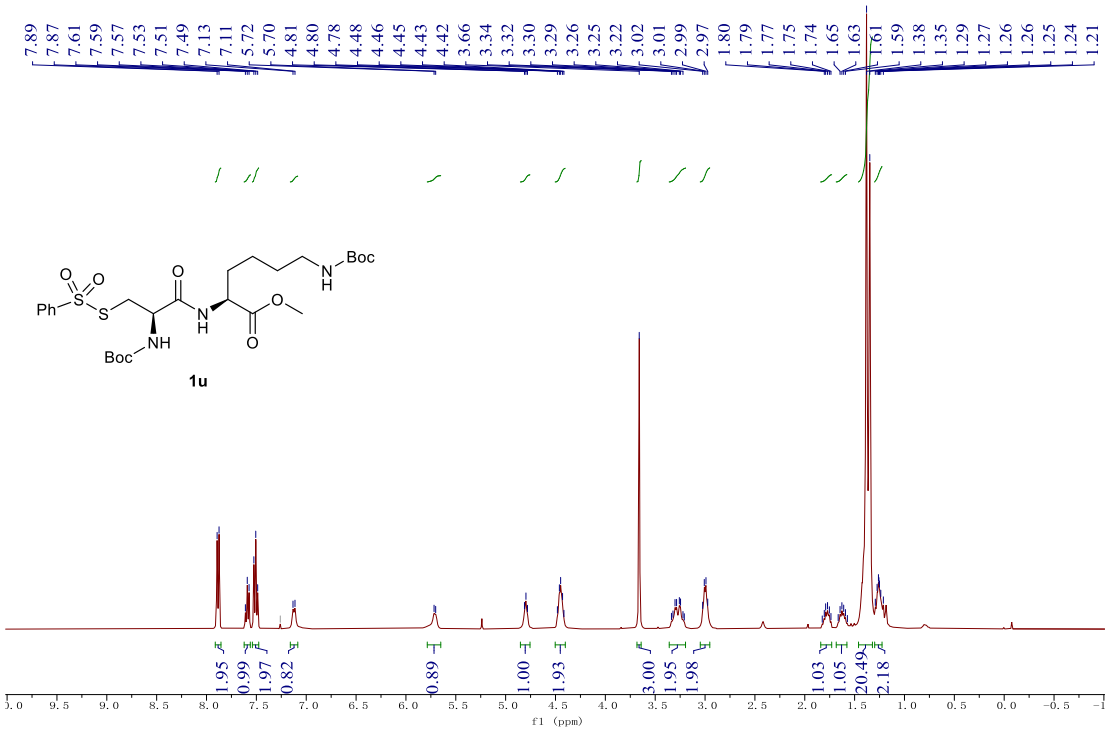

Figure S93. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 1u

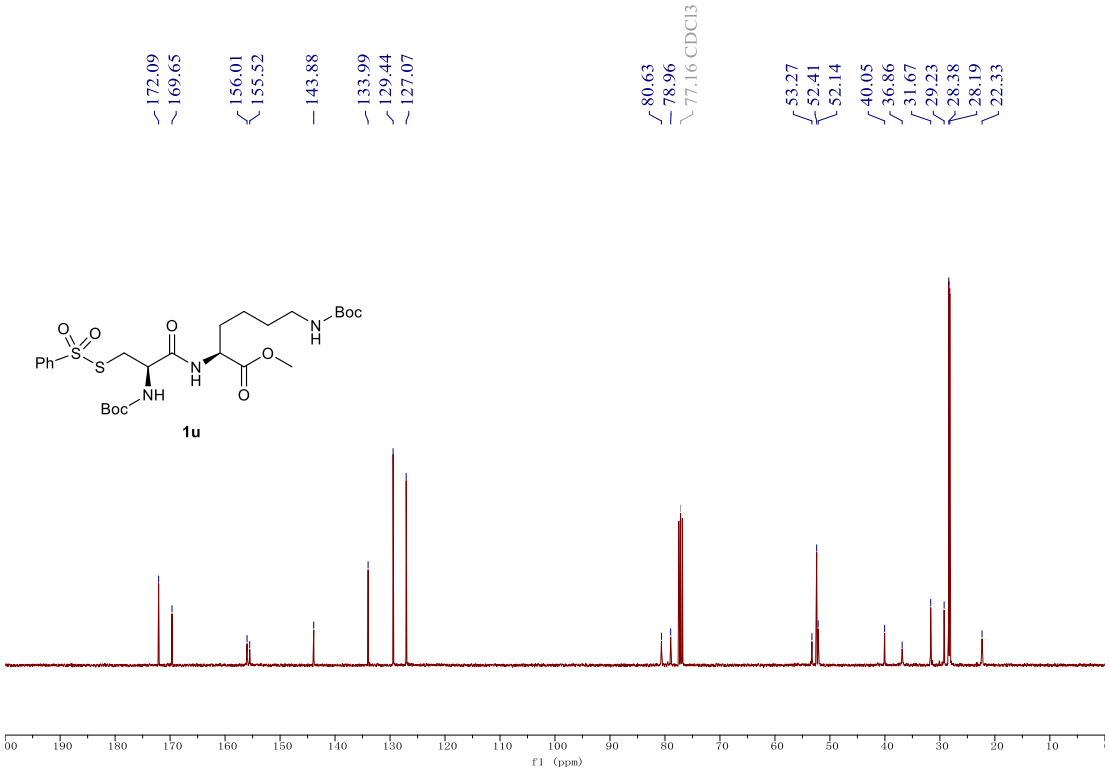

Figure S94. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 1u

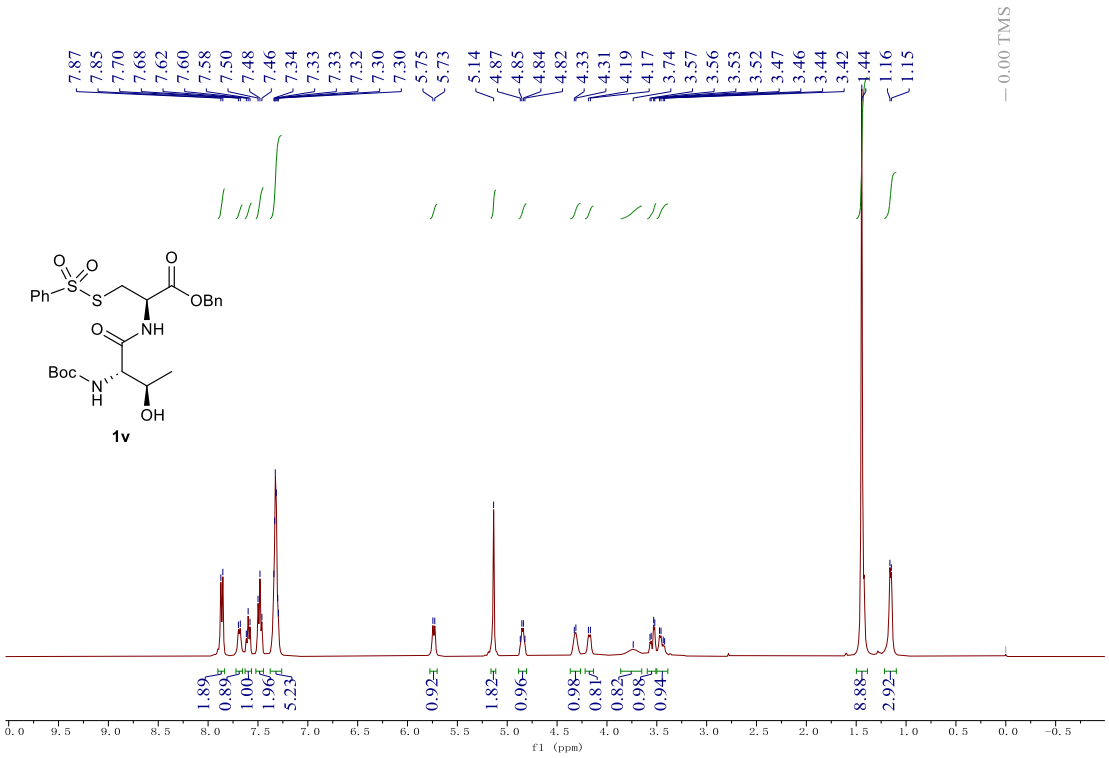

Figure S95. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 1v

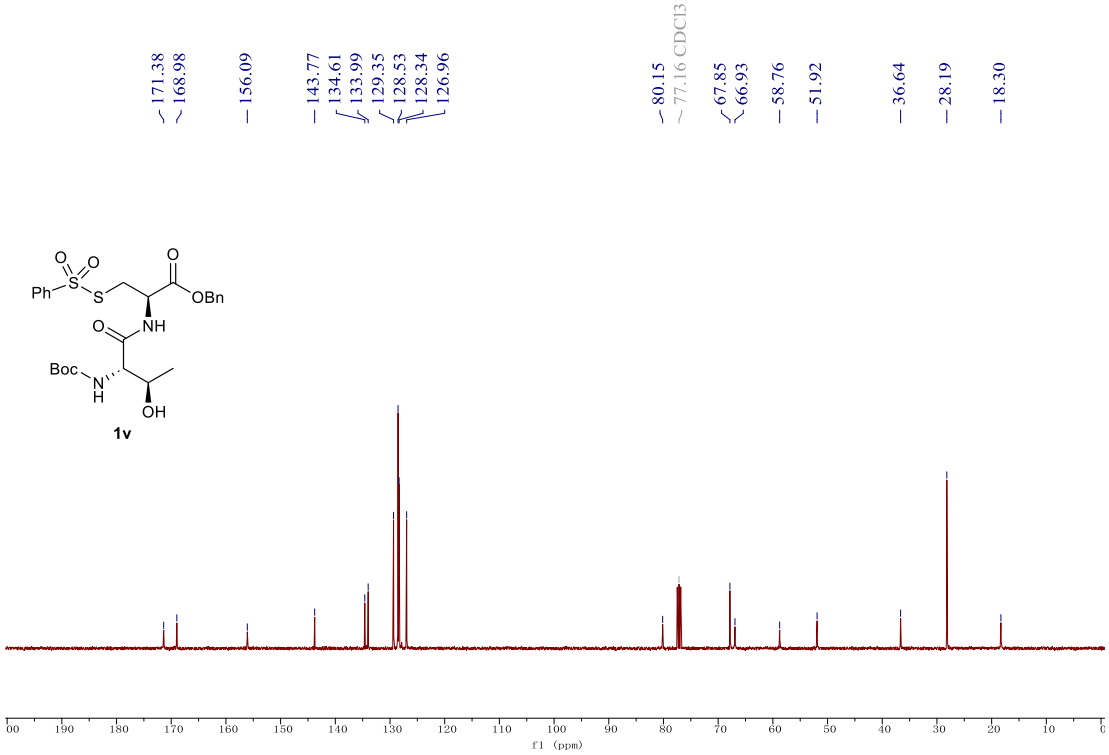

Figure S96. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 1v

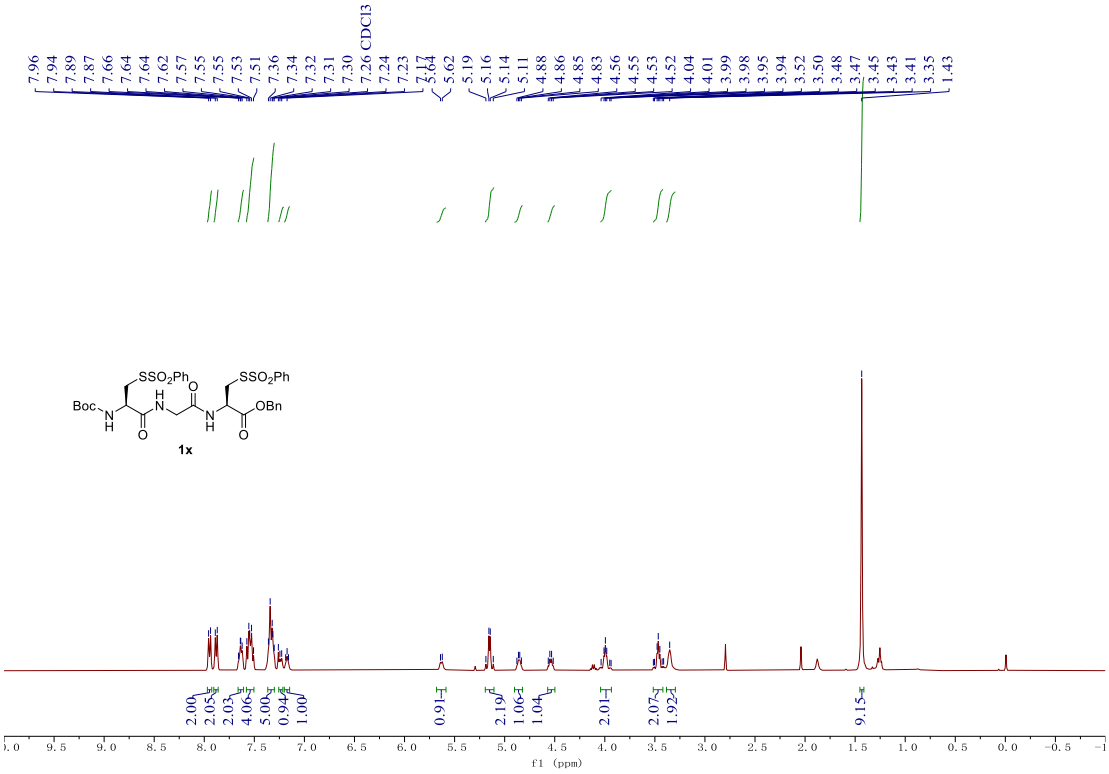

Figure S97. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 1x

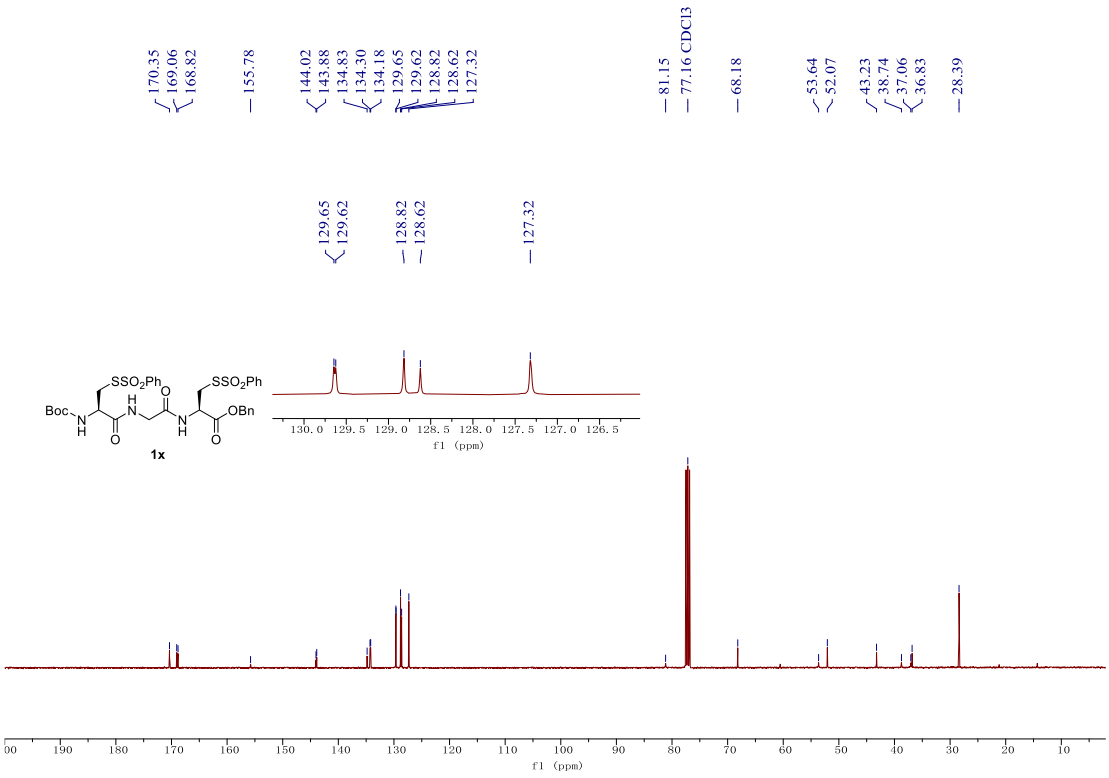

Figure S98. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 1x

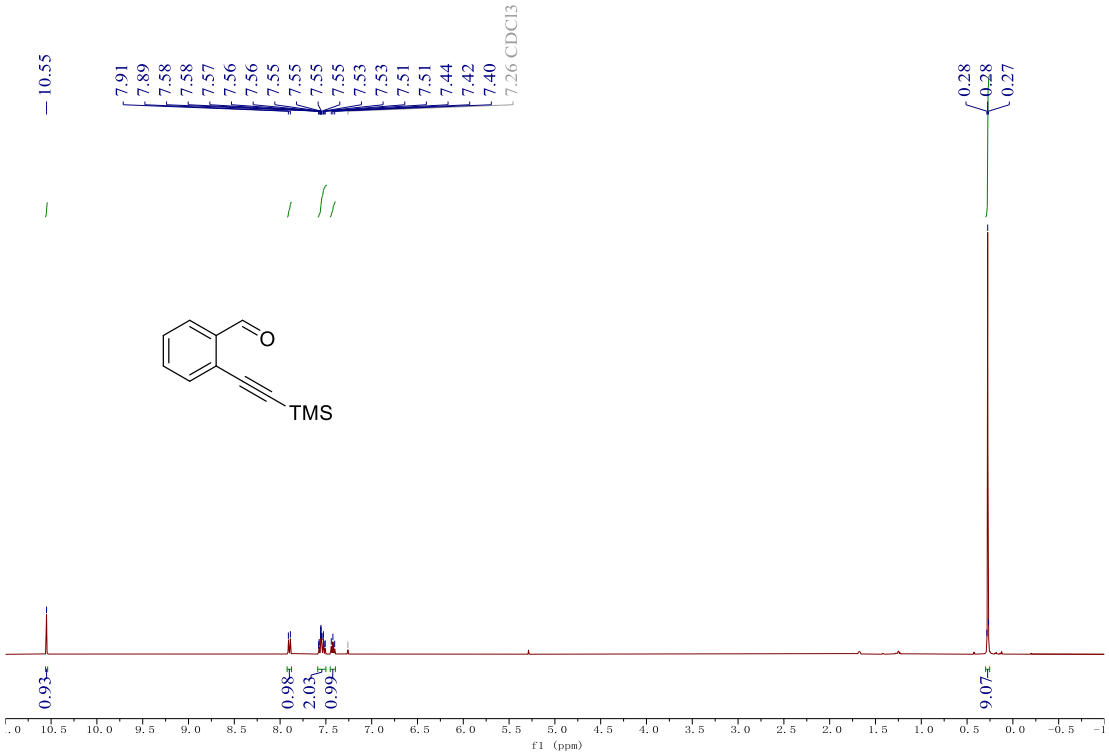

Figure S99. ^{1}H NMR (400 MHz $CDCl_3$) spectra for 2-((trimethylsilyl)ethynyl)benzaldehyde

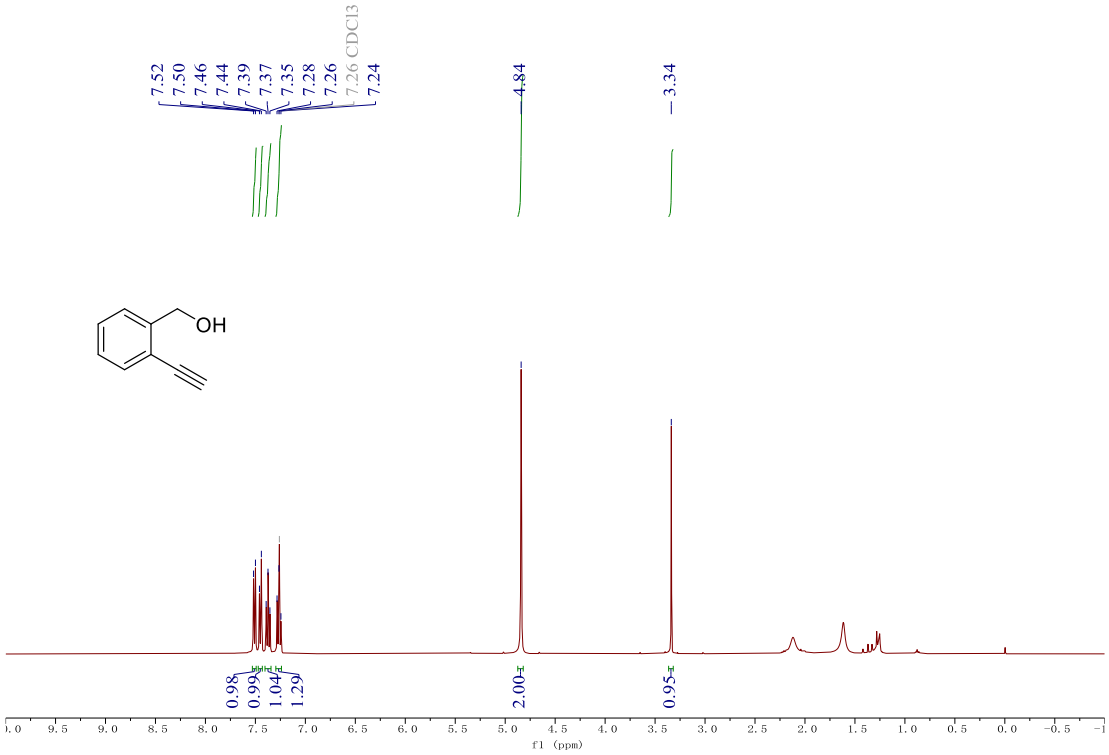

Figure S100. ^{1}H NMR (400 MHz $CDCl_3$) spectra for (2-ethynylphenyl)methanol

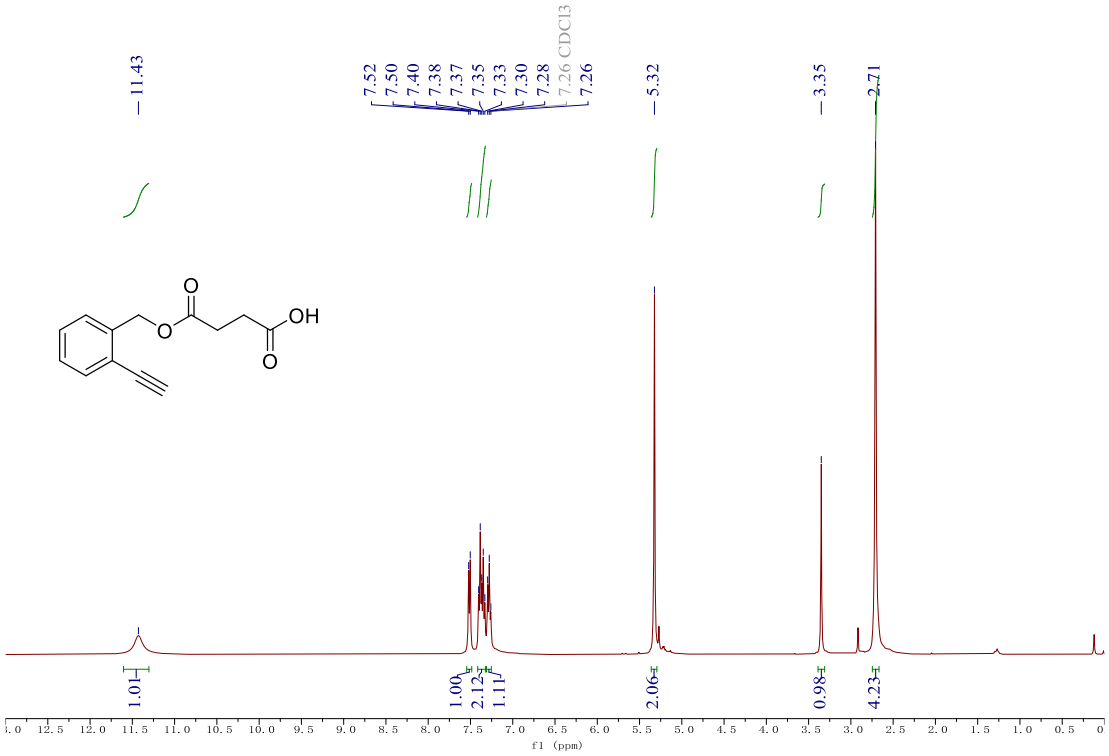

Figure S101. ^{1}H NMR (400 MHz $CDCl_3$) spectra for 4-((2-ethynylbenzyl)oxy)-4-oxobutanoic acid

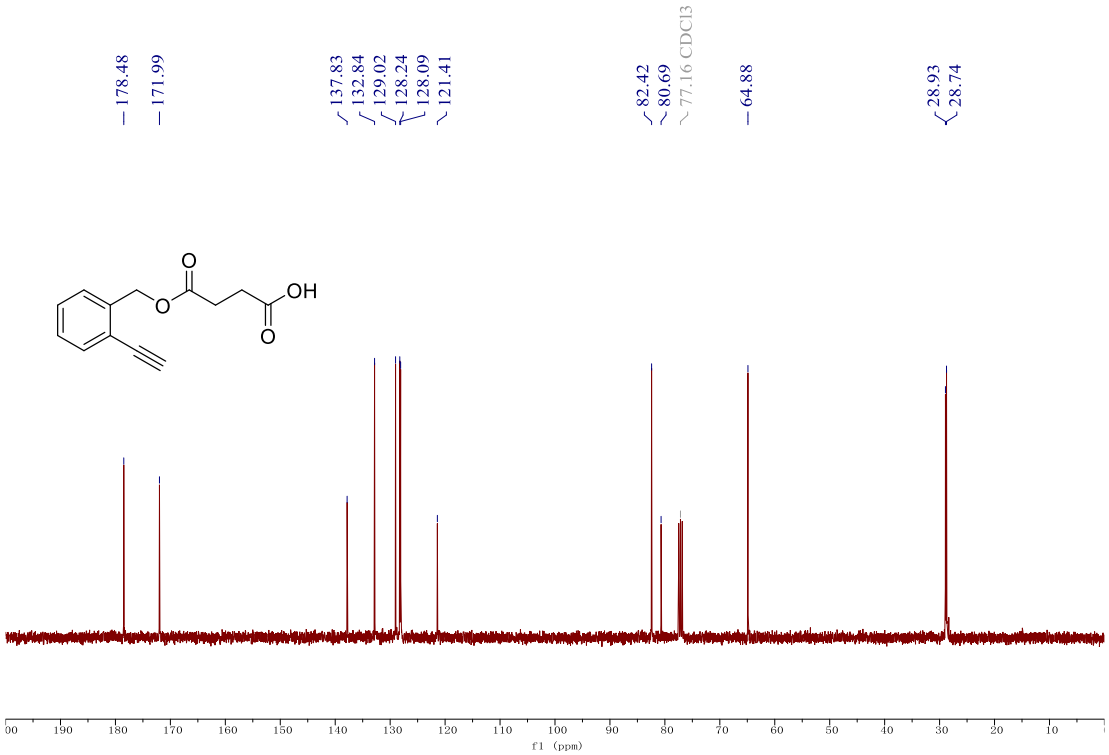

Figure S102. ^{13}C NMR (101 MHz $CDCl_3$) spectra for 4-((2-ethynylbenzyl)oxy)-4-oxobutanoic acid

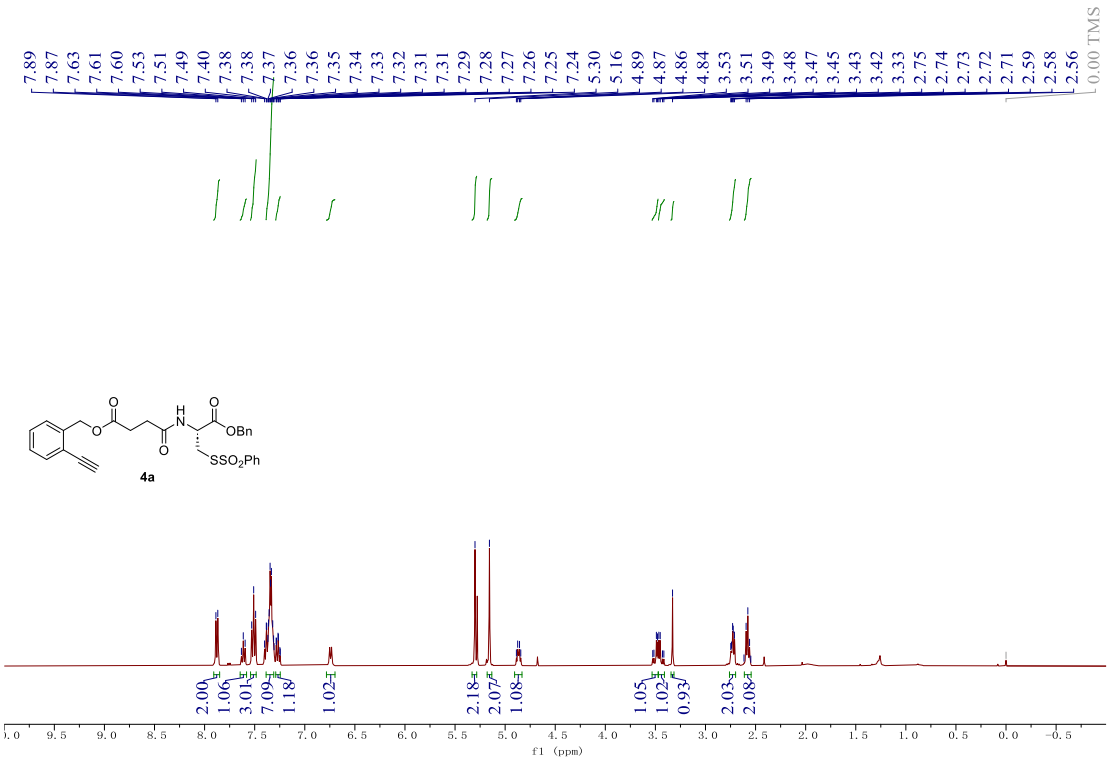

Figure S103. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4a

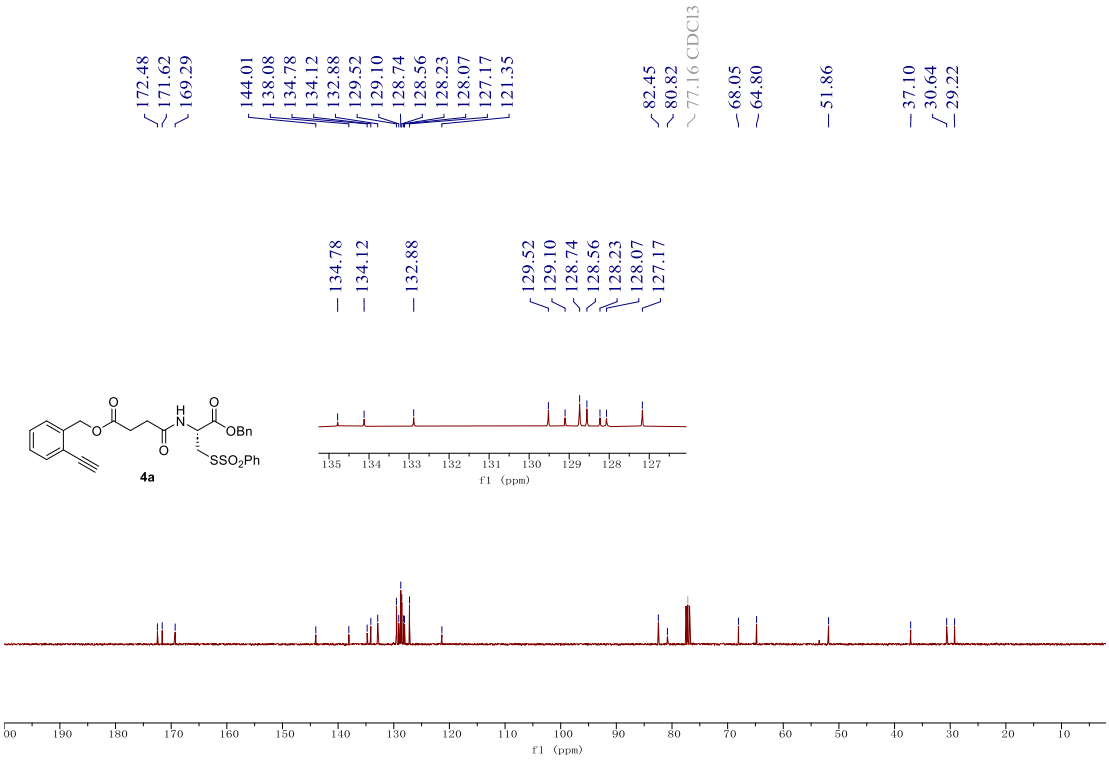

Figure S104. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4a

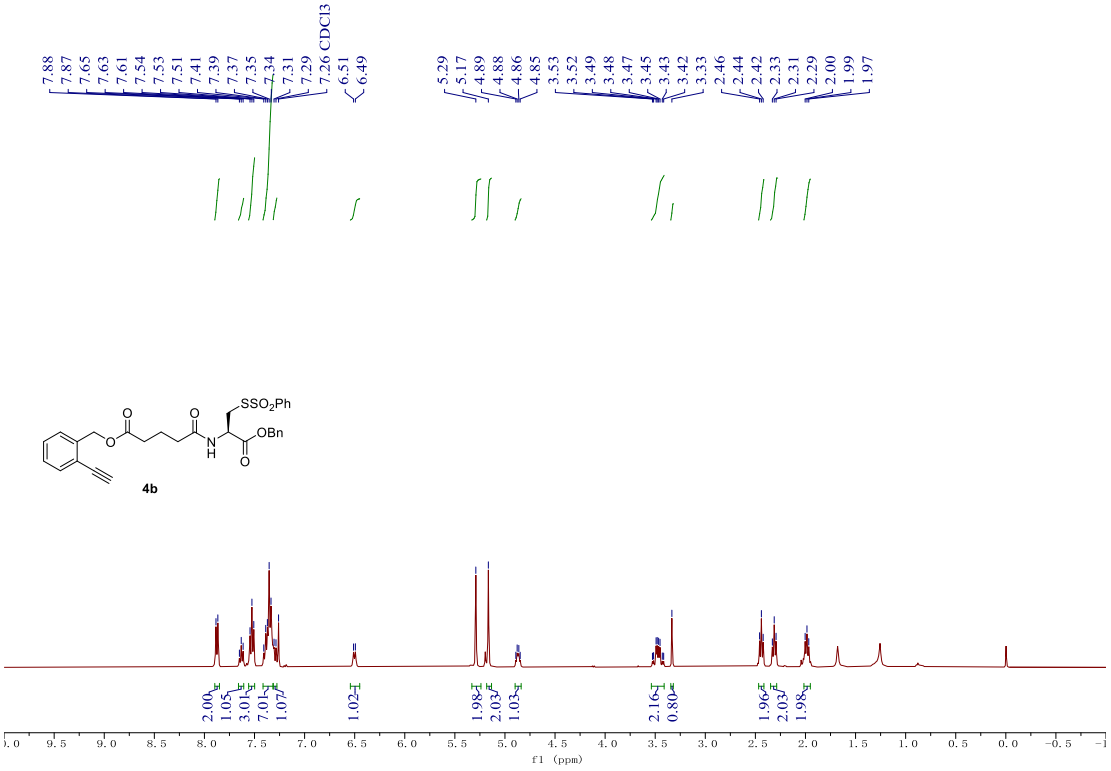

Figure S105. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4b

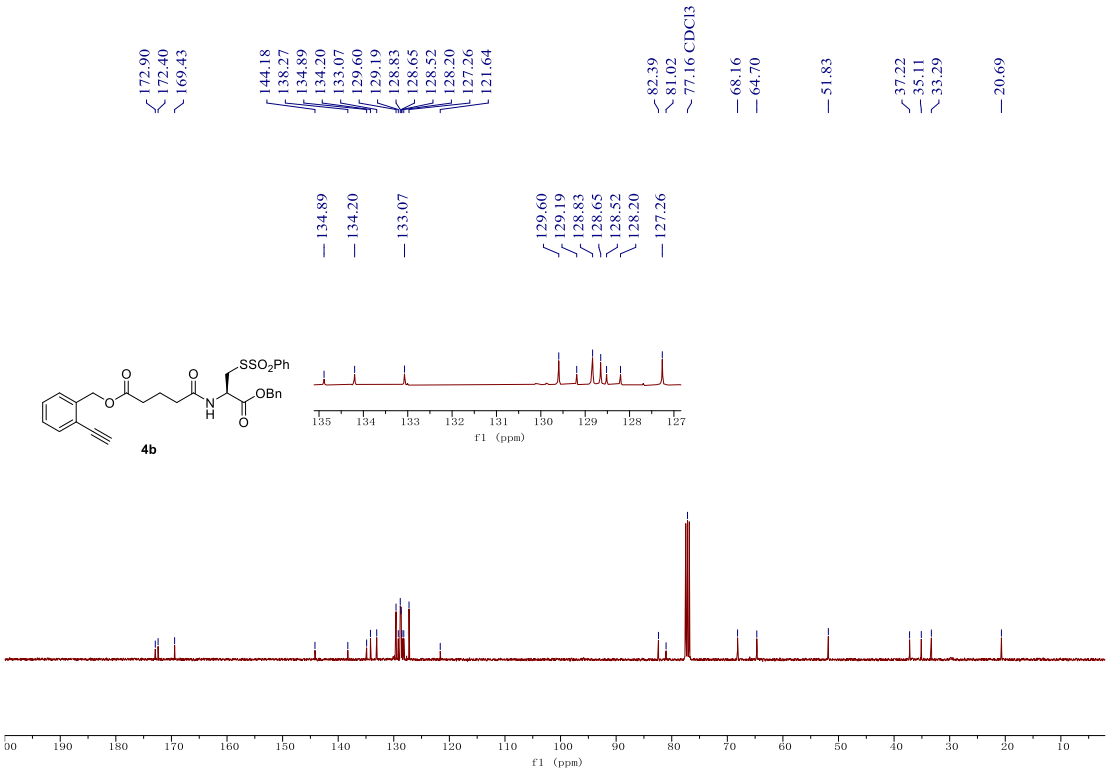

Figure S106. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4b

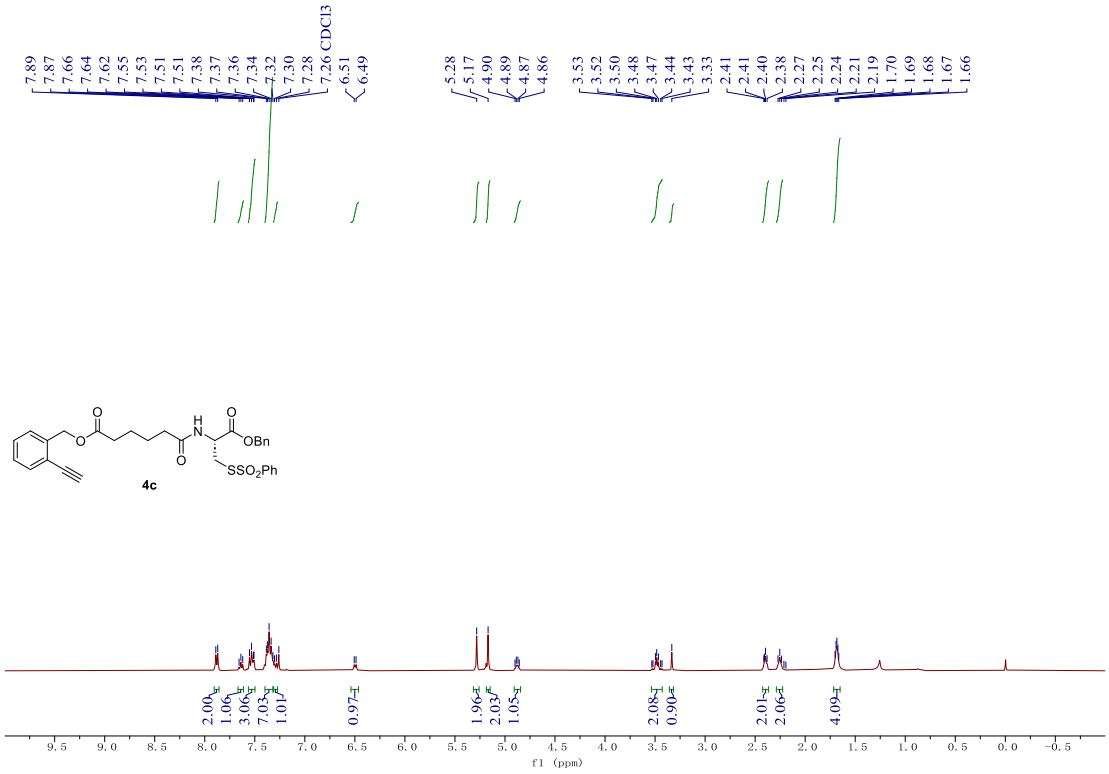

Figure S107. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4c

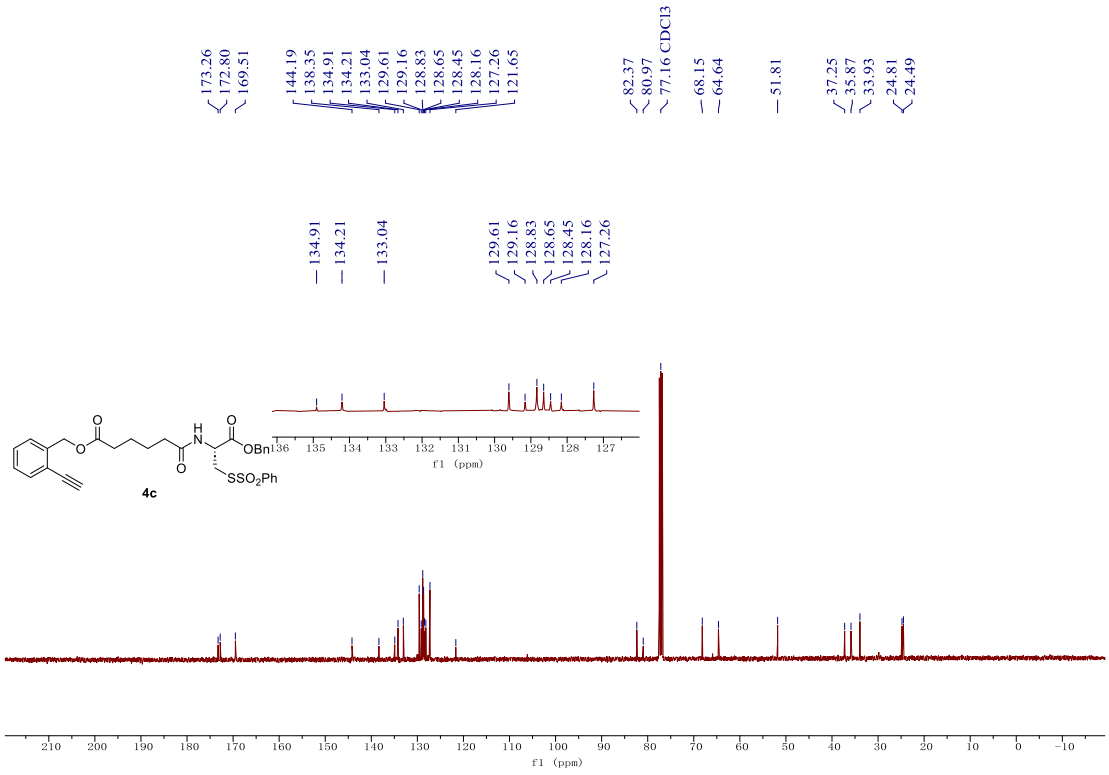

Figure S108. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4c

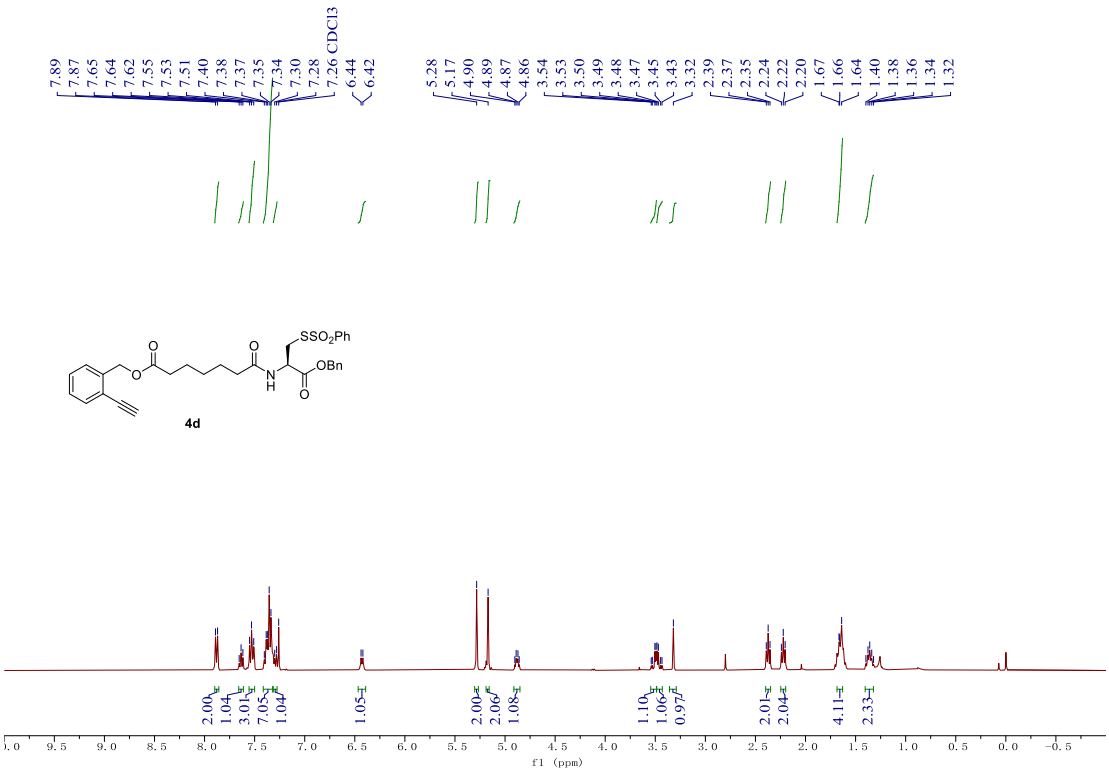

Figure S109. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4d

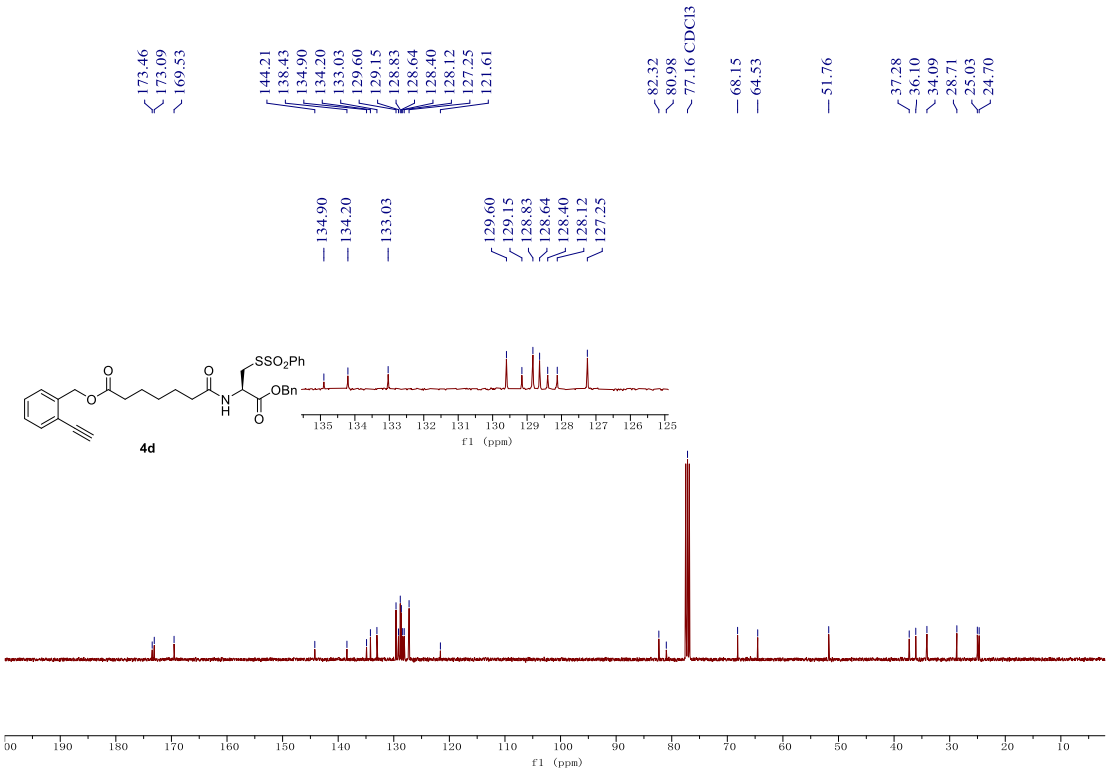

Figure S110. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4d

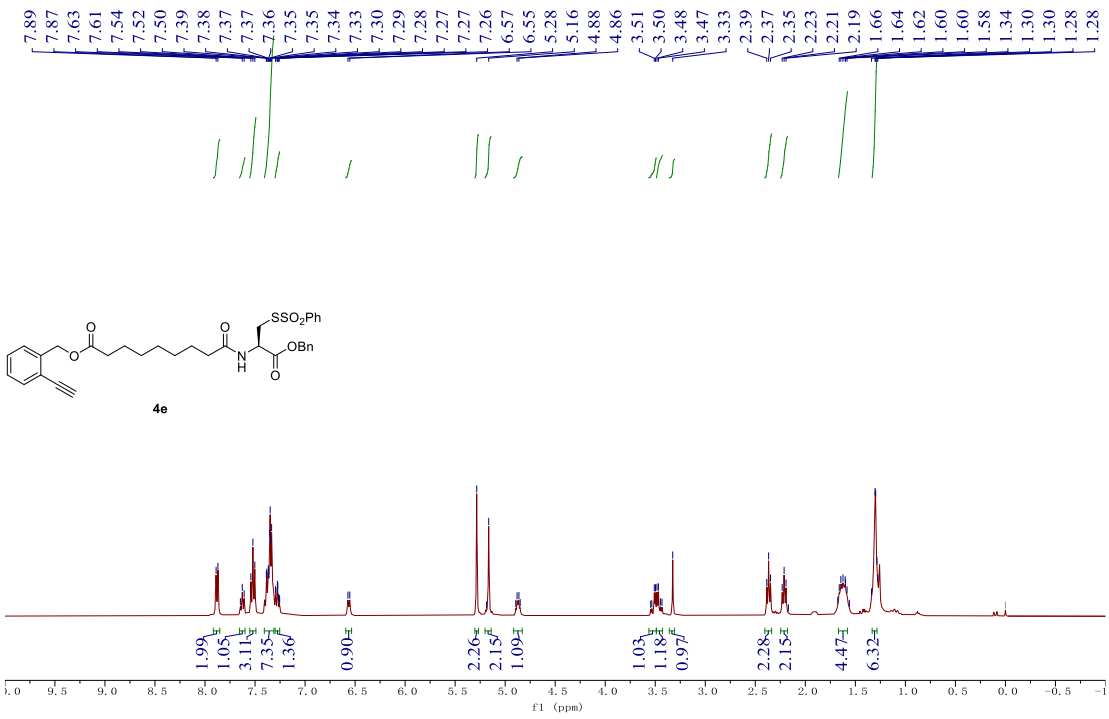

Figure S111. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4e

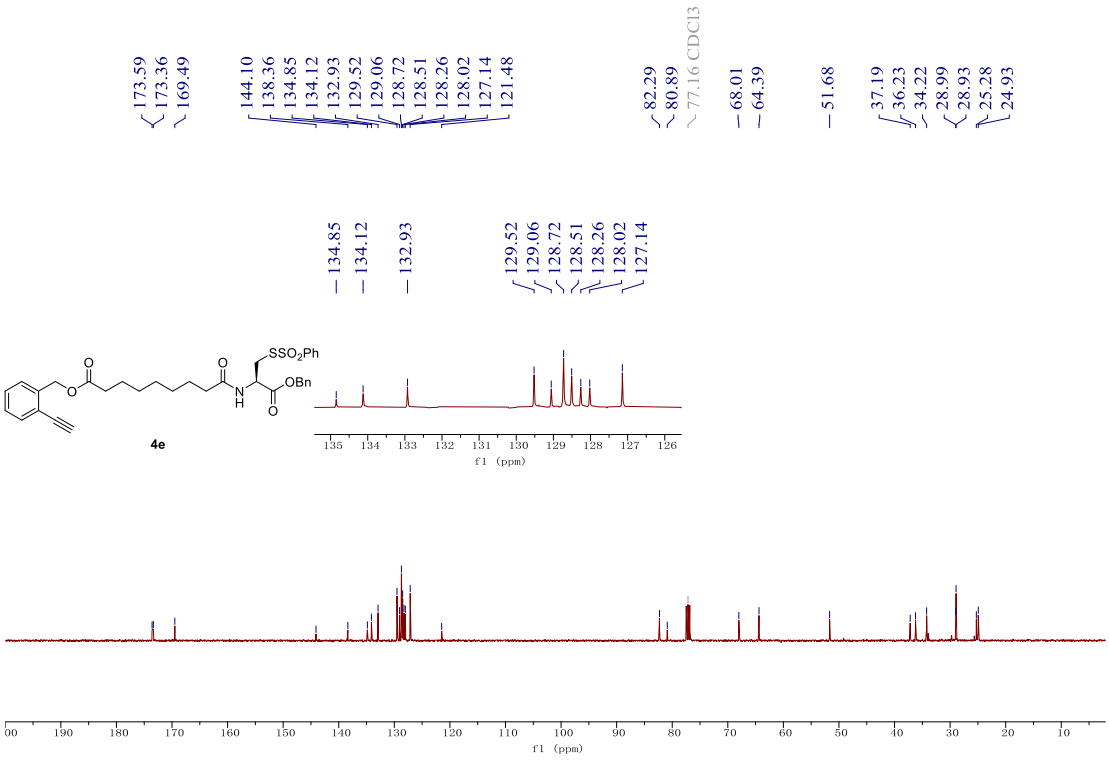

Figure S112. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4e

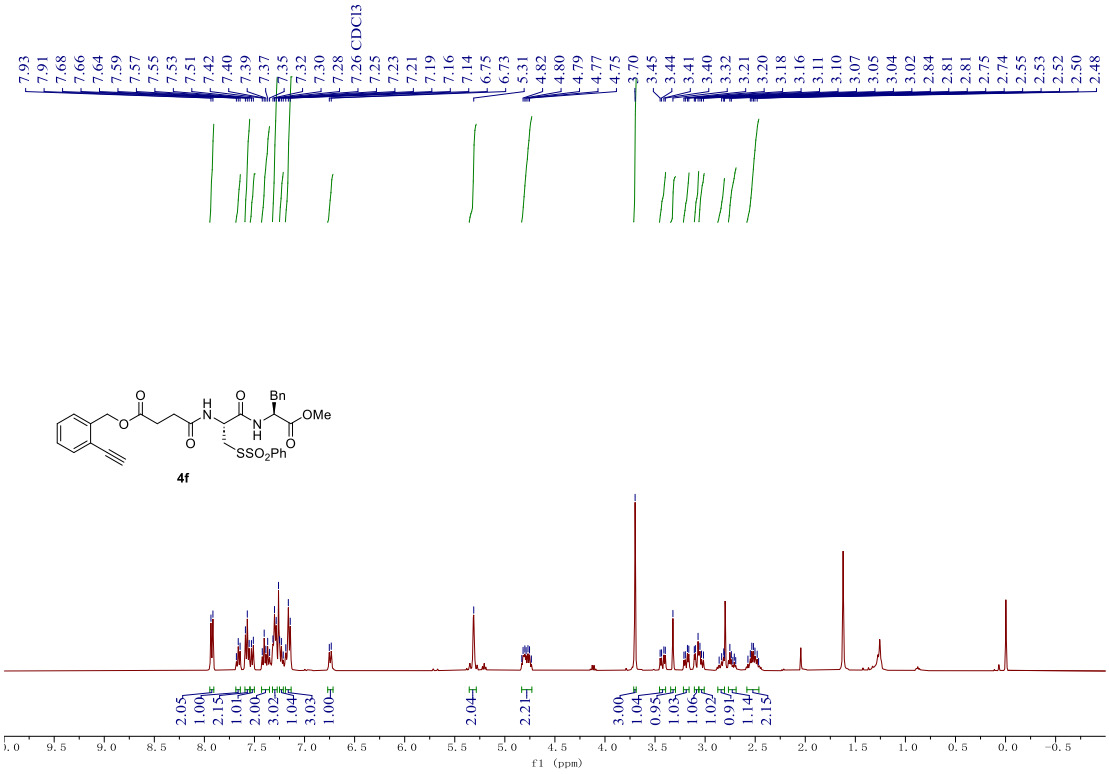

Figure S113. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4f

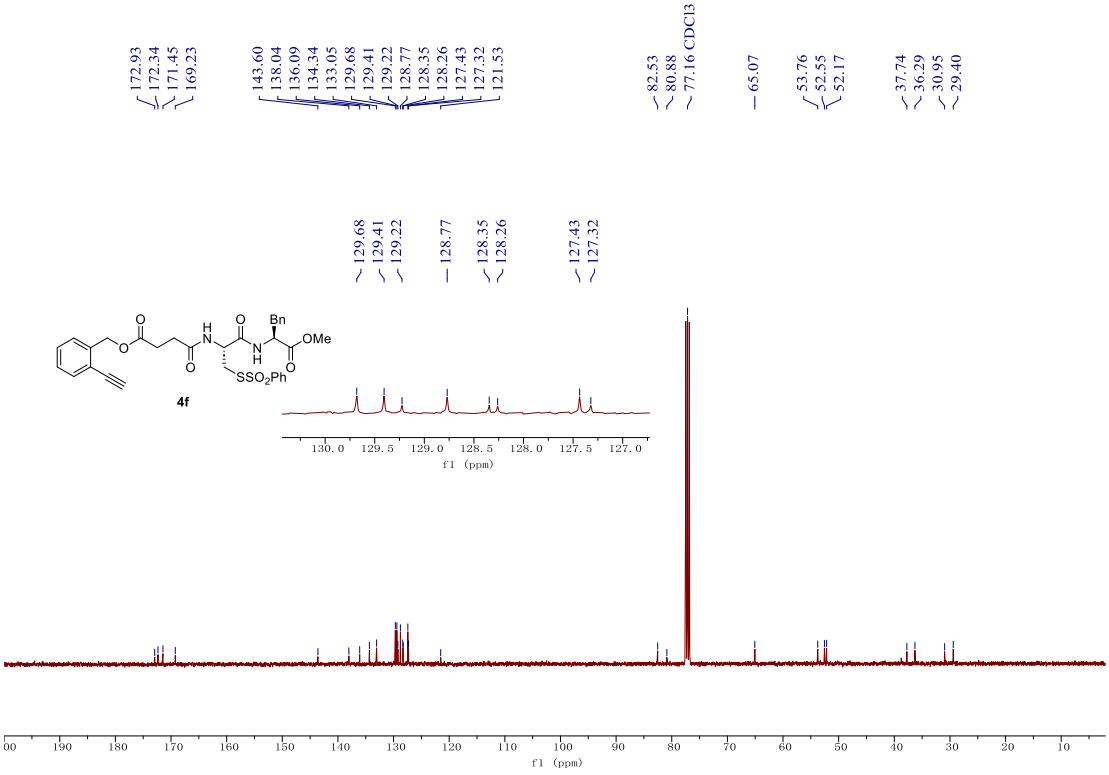

Figure S114. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4f

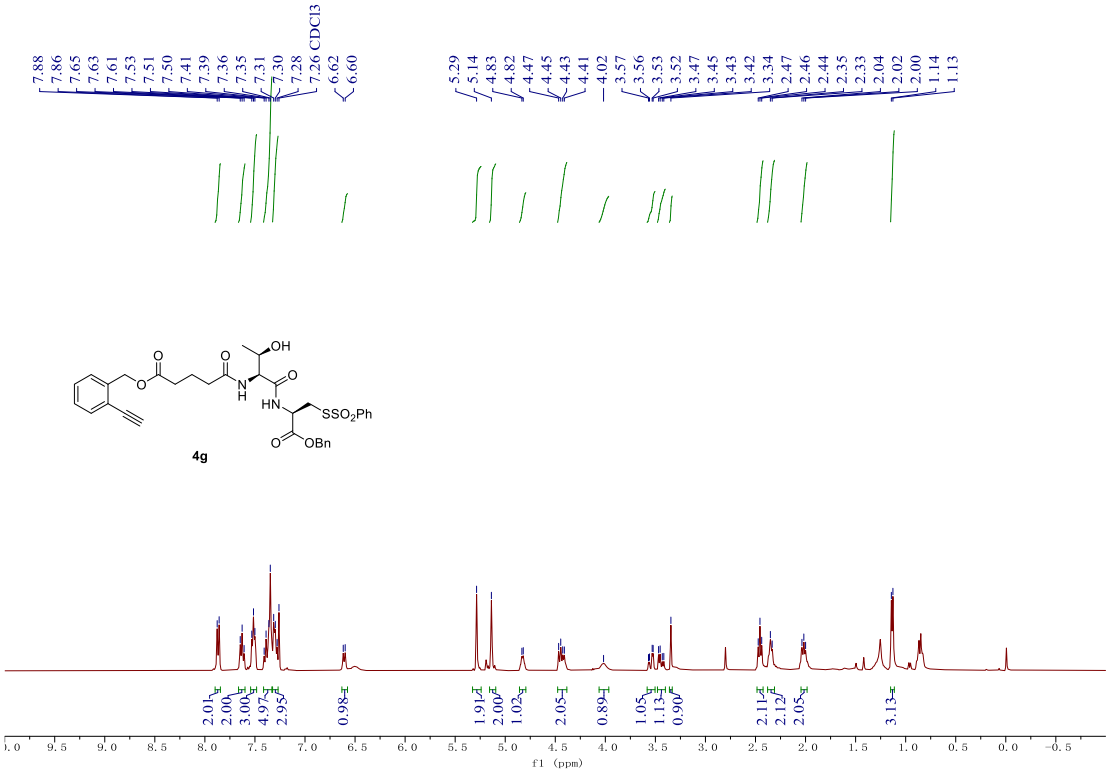

Figure S115. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4g

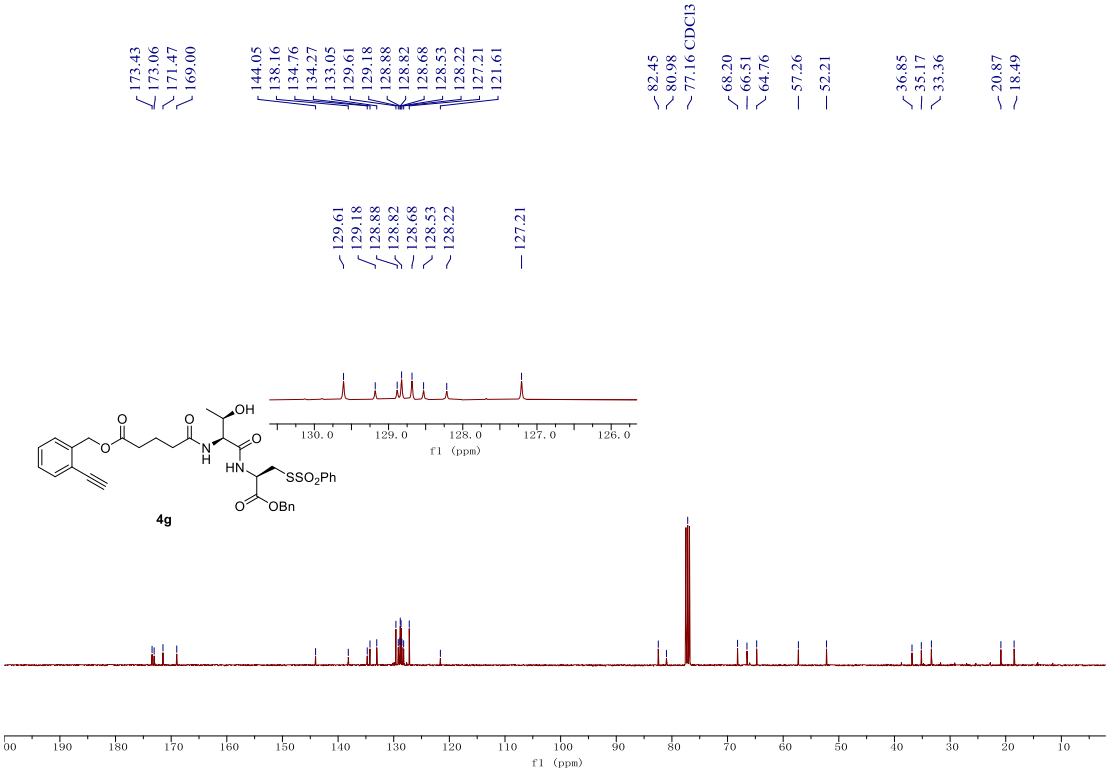

Figure S116. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4g

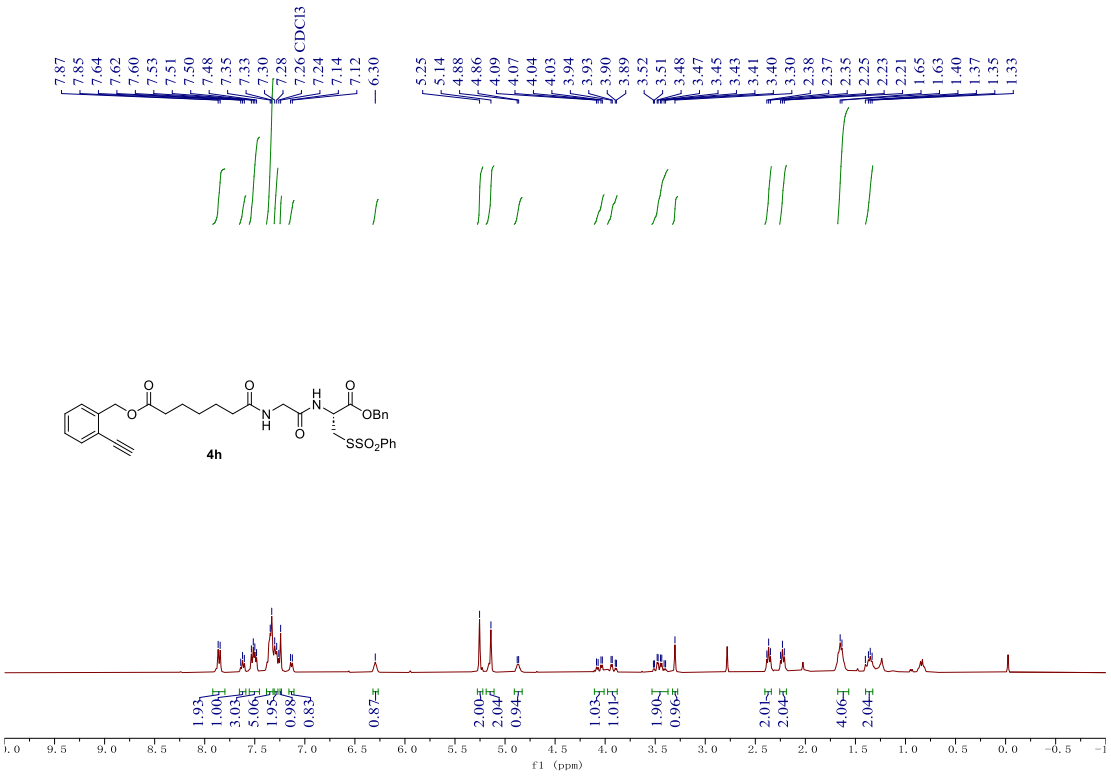

Figure S117. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4h

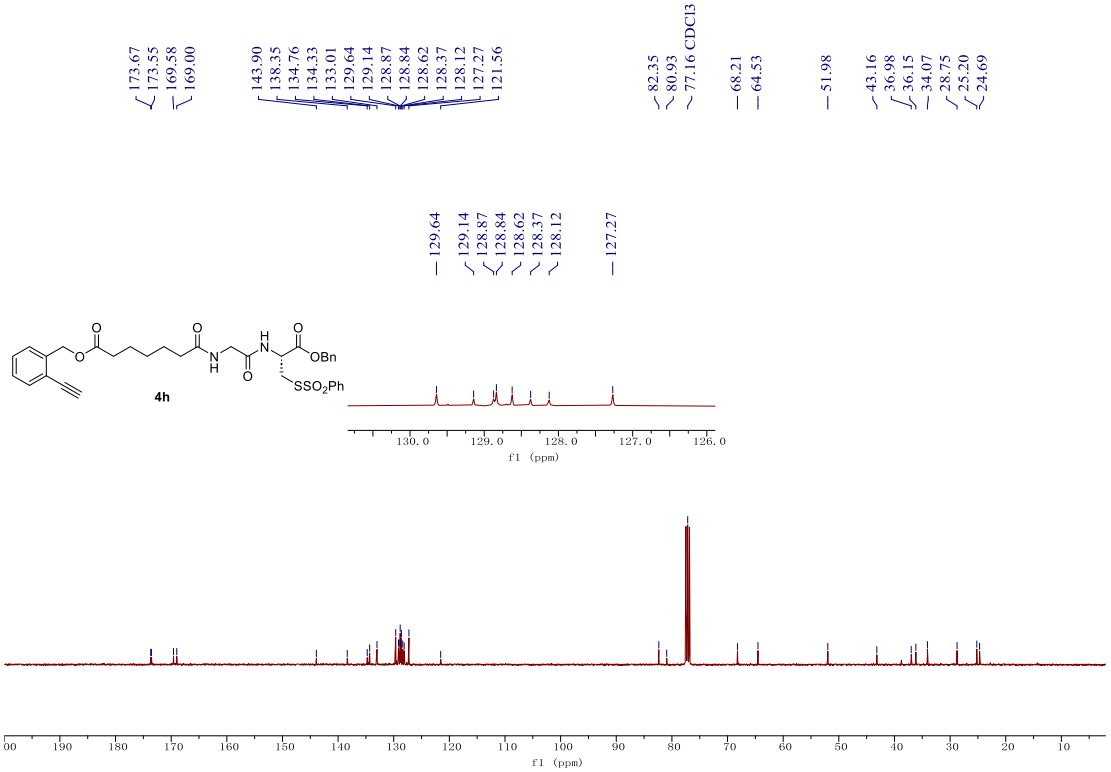

Figure S118. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4h

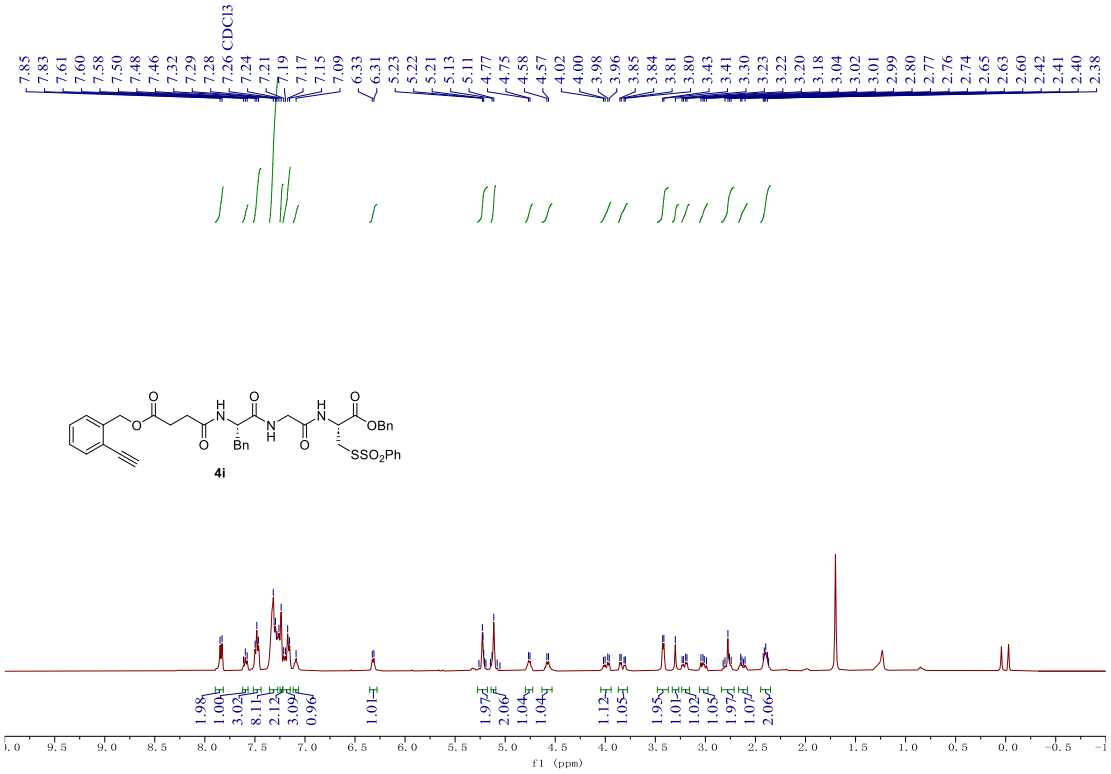

Figure S119. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4i

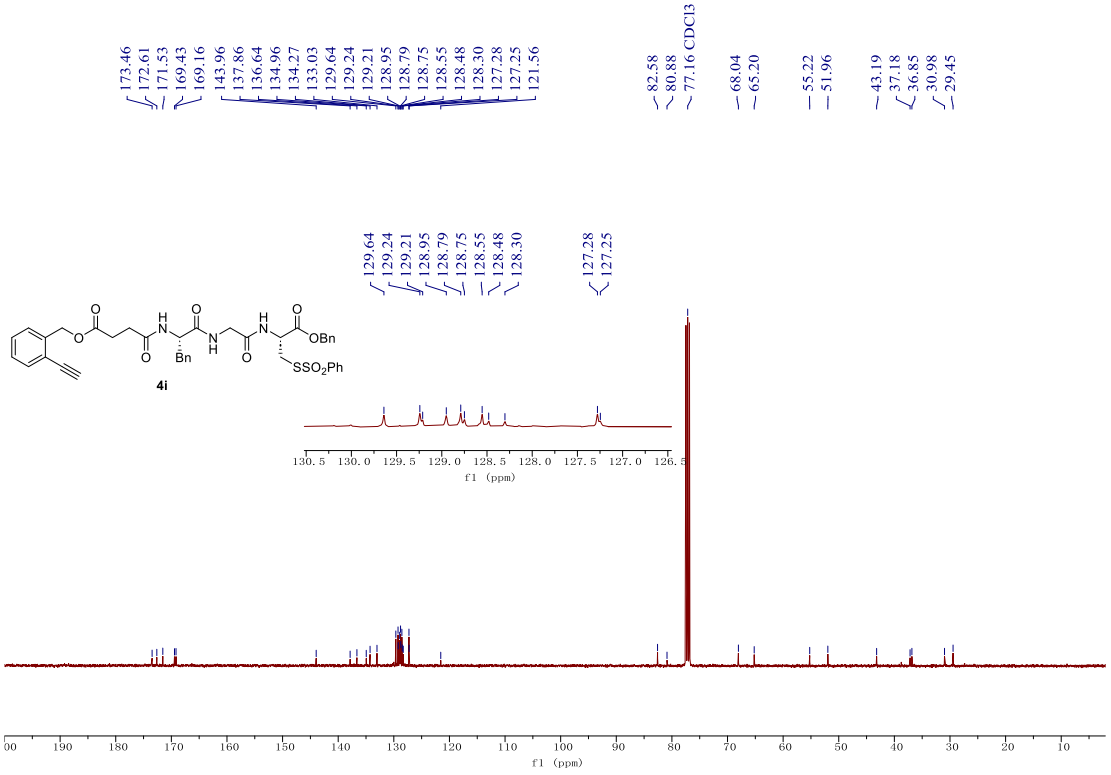

Figure S120. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4i

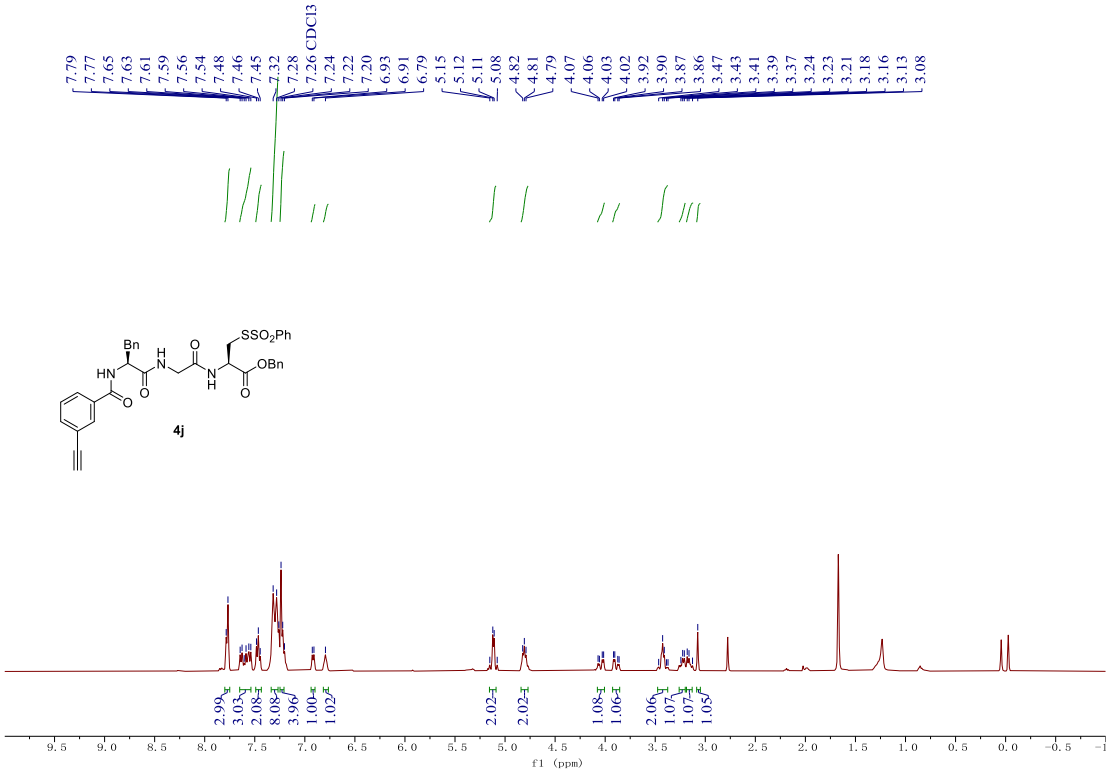

Figure S121. ^{1}H NMR (400 MHz $CDCl_3$) spectra for compound 4j

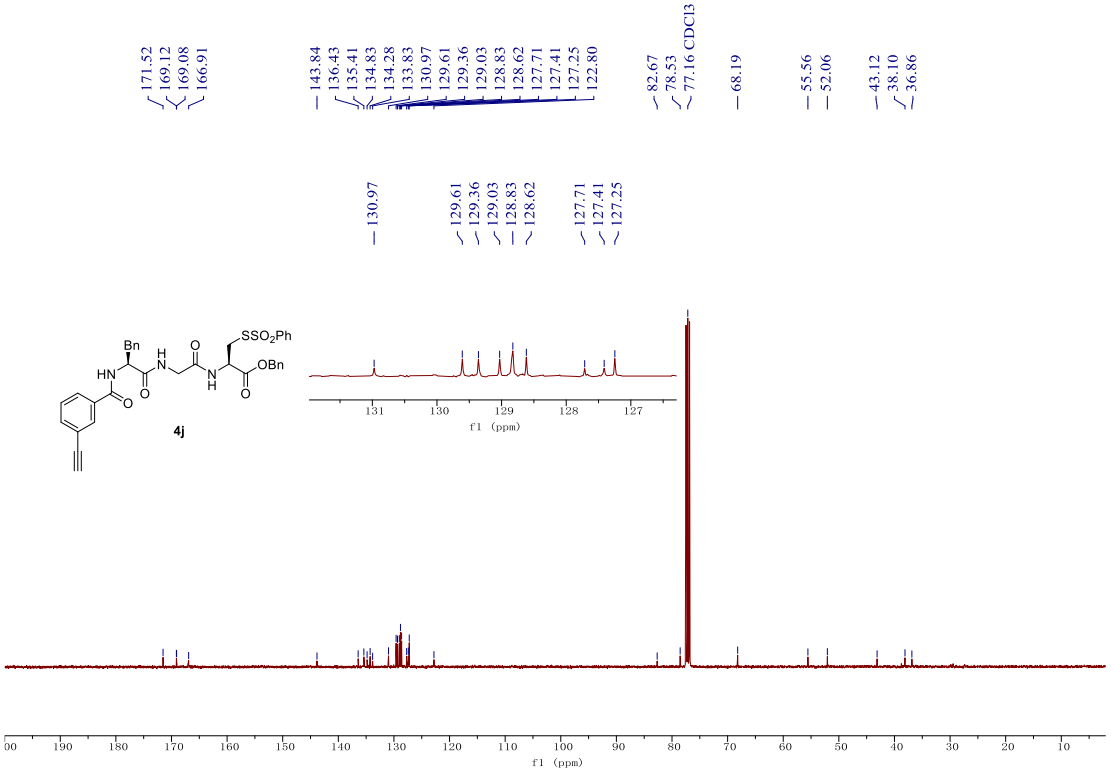

Figure S122. ^{13}C NMR (101 MHz $CDCl_3$) spectra for compound 4j