Electronic Supplementary Material (ESI) for ChemComm.

Controlled release of hydrogen sulfide significantly reduces ROS stress and increases dopamine levels in transgenic *C. elegans*.

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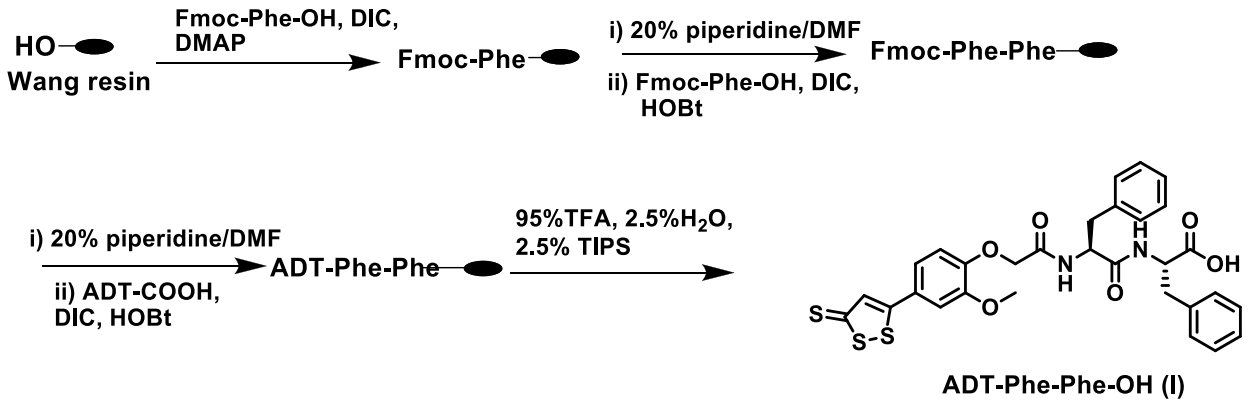
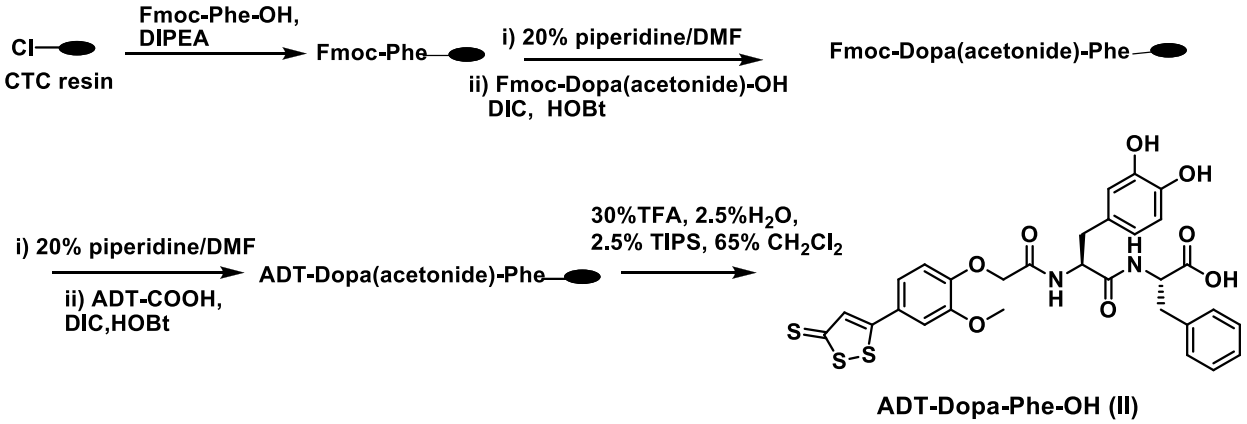
1) General Information:

Benzyl bromide, *N*, *N'*-Diisopropylcarbodiimide (DIC) and 4-Dimethylaminopyridine were obtained from Spectrochem (Mumbai, India). 1-Hydroxybenzotriazole, Sulphur powder was purchased from Finar chemicals. Triisopropylsilane (TIPS) was purchased from sigma aldrich. Methylbromoacetate, Piperidine and Trifluoroacetic acid (TFA) were purchased from Avra synthesis Pvt. Ltd. (Hyderabad, India). Palladium on 10% activated carbon was purchased from Alfa Aesar. Fmoc-Phe-OH, Fmoc-Trp(Boc)-OH, Wang resin and 2-Chlorotritylchloride (CTC) resin were purchased from Novabiochem. Eugenol was purchased from S. D. Fine-Chem Pvt. Ltd. Dichloromethane (DCM), and methanol (MeOH) were distilled according to standard procedures prior to use. Dry *N*, *N*-dimethylformamide (DMF) was purchased from Finar chemicals and used as such. Reactions were monitored by thin layer chromatography (TLC) carried out on readymade TLC silica gel $60F_{254}$ plates (Merck, Dermstadt, Germany) and compounds were visualized with UV light at 254 nm. 100−200 mesh silica gel (S. D. Fine-Chem Pvt. Ltd.) was used for chromatographic separation. IR spectra were recorded as neat liquids or KBr pellets on PerkinElmer Spectrum Version 10.03.06 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on JEOL-JNM spectrometer operating at 400 or 500 MHz at 25 °C using 2- 10 mM concentration in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts (*δ)* are shown in ppm scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), td (triplet of a doublet), dd (doublet of doublet), dt (doublet of a triplet) and m (multiplet, for unresolved lines). ^{13}C NMR spectra were recorded at 100 or 125 MHz with complete proton decoupling. HRMS spectra were recorded on Waters, Q-Tof Premier Micromass HAB 213 mass spectrometer using capillary voltage 2.6-3.2 Kv. UV-Vis absorption spectra were recorded on Varian CARY 100 Bio UV-Vis spectrophotometer with 10 mm quartz cell at 25 °C.

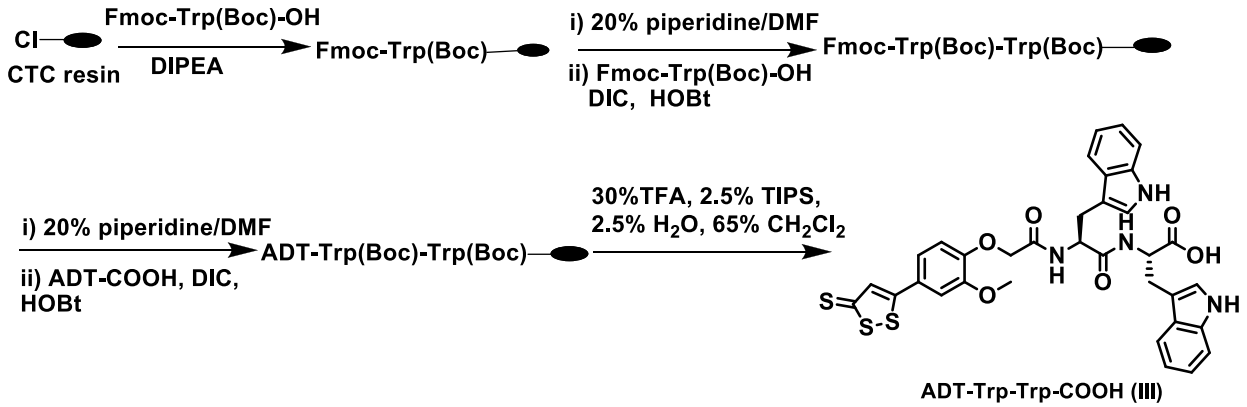
2) Synthetic schemes for conjugates I, II and III:



Scheme S1: Synthesis of ADT-Phe-Phe-OH (Conjugate **I**)



Scheme S2: Synthesis of ADT-Dopa-Phe-OH (Conjugate **II**)



Scheme S3: Synthesis of ADT-Trp-Trp-OH (Conjugate **III**)

3) General experimental procedure and spectral data of compounds:

Synthesis of Methyl 2-(4-allyl-2-methoxyphenoxy) acetate: To a solution of Sodium hydroxide (1.48 gm, 37.04 mmol) in methanol (40 mL), Eugenol (6 gm, 5.6 mL, 36.54 mmol) was added under nitrogen atmosphere and the reaction was left for stirring for ten minutes. After that methyl bromoacetate (7.48 gm, 4.50 mL, 48.88 mmol) was added to the reaction mixture and was heated at 55 °C for two hours. After completion of the reaction, the solvent was evaporated and cold solution of 0.1 N NaOH was added to the residual white solid and the mixture is extracted with diethyl ether. Afterwards the organic layer was washed with cold water followed by drying of the organic phase on anhydrous sodium sulphate. The organic phase was evaporated under reduced pressure and the crude compound was purified by silica gel chromatography using 40% methylene chloride/hexane. Yield (4.0 gm, 16.93 mmol, 46.33%); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.90 – 6.52 (m, 3H), 6.35 – 5.72 (m, 1H), 5.09-5.04 (m, 2H), 4.65 (s, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.32 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm =

169.72, 149.59, 145.58, 137.49, 134.62, 120.47, 115.88, 114.52, 112.57, 66.70, 55.89, 52.24, 39.89; FTIR (neat) 3549, 3003, 2953, 2842, 1760, 1638, 1593, 1513, 1435, 1260, 1204, 1145, 1035, 805, 749 cm^{-1}; ESI-HRMS, $[M+H]^+$, Calculated for $C_{13}H_{17}O_4^+$ = 237.1121, Found = 237.1127.

Methyl 2-2-methoxy-4-(3-thioxo-3H-1,2-dithiol-5-yl)phenoxy] acetate: Elemental Sulphur (2.06 gm, 64.44 mL) was melted in a round bottom flask by heating at 146 °C with constant stirring. Methyl 2-(4-allyl-2-methoxyphenoxy) acetate (2.06 gm, 8.72 mmol) which was prepared in previous step was added to the molten sulphur and the mixture were heated at 220 °C for two hours under constant stirring condition. After this the reaction mixture is allowed to cool to room temperature followed by the addition of toluene (2.5 mL) and acetone (5 mL). The suspension was stirred overnight at room temperature and the excess sulphur was filtered and washed with acetone. The filtrate was evaporated to dryness and the crude compound was pure by silica gel column chromatography using 98% methylene chloride/hexane to give the target compound as red solid powder. Yield (0.9 gm, 2.74 mmol, 31.42%); Red colour soli; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.87 (s, 1H), 7.48-7.39 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.92 (s, 2H), 3.89 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 215.45, 174.35, 169.29, 151.15, 149.79, 135.29, 125.17, 120.81, 113.94, 111.29, 65.49, 56.54, 52.46; FTIR (KBr) 3430, 2951, 1727, 1483, 1266, 1154, 1028, 954, 803, 658 cm^{-1}; ESI-HRMS, $[M+H]^+$, Calculated for $C_{13}H_{13}O_4S_3^+$= 328.9970, Found = 328.9979.

2-(2-methoxy-4-(5-thioxo-5H-1,2-dithiol-3-yl)phenoxy) acetic acid (ADT-COOH): A suspension of methyl 2-[2-methoxy-4-(3-thioxo-3H-1,2-dithiol-5-yl) phenoxy] acetate (587 mg; 1.79 mmol) in acetic acid (25 mL) and 50% sulphuric acid (4 mL) was stirred for 1.5 hours at 100 ºC. After complete hydrolysis the reaction mixture was cooled on an ice bath and the precipitate was filtered and washed with water and diethyl ether to give the desired compound as brown powder. Yield (350 mg, 1.11 mmol, 62.2 %); Brown colour solid; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 7.87 (s, 1H), 7.68 – 7.29 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.80 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm = 215.37, 174.47, 170.22, 151.37, 149.70, 135.17, 124.83, 120.84, 113.62, 111.13, 65.27, 56.47; FTIR (KBr) 3557, 3471, 3073, 2932, 1752, 1524, 1477, 1274, 1152, 1019, 950, 769, 632; ESI-HRMS: $[M-H]^-$, Calculated for $C_{12}H_9O_4S_3^-$ = 312.9668, Found= 312.9669.

Synthesis of Fmoc-Dopa (Acetonide)-OH: It was synthesize using previously reported method.[1] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ/ppm = 7.75 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.32-7.28 (m, 2H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.59-6.42 (m, 2H), 5.25 (d, *J* = 7.8 Hz, 1H), 4.64 (q, *J* =7.1 Hz, 1H), 4.51-4.30 (m, 2H), 4.21 (t, *J* = 6.9 Hz, 1H), 3.23-2.89 (m, 2H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm = 175.64, 155.92, 147.79, 146.76, 143.75, 141.39, 127.81, 127.18, 125.16, 121.99, 120.08, 118.11, 109.48, 108.33, 76.78, 67.20, 54.80, 47.21, 37.52, 25.94; FTIR (KBr) 3405, 2988, 2938, 1715, 1496, 1448, 1254, 1235, 980, 759, 740 cm^{-1}.

Synthesis of ADT-Phe-Phe-COOH (conjugate I):

Preparation of Fmoc-Phe-Resin: Wang resin having substitution 0.83 mmol/gm (241 mg, 0.2 mmol) was transferred to the reaction vessel. Resin was washed with DMF (3 x 3 mL) and swollen for 30 minute in DCM (3 mL). Resin was washed with DMF (3x3 mL). Solution of Fmoc–Phe-OH (232 mg, 0.6 mmol) and DMAP (7.3 mg, 0.06 mmol) dissolved in 4 mL of DMF was added to the resin and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 3 h under nitrogen. After that, the resin was then washed with DMF (3x3 mL) and DCM (3x3 mL). The resin obtained was dried under vacuum. Loading of amino acid on resin is tested by measuring the increased weight of resin. We get 351.5 mg of Fmoc-Phe-resin (100 % loading)

Preparation of ADT-Phe-Phe-Resin: Fmoc-Phe-resin was washed with DMF (3x3 mL) and swollen for 30 minute in DCM (3 mL). Resin was washed with DMF (3x3 mL). The resin was then treated with 20% piperidine in DMF (3 mL) and stirred for 5 minute and filtered. The resin was again treated with 20% piperidine in DMF (5 mL) and stirred for 25 minutes under nitrogen and filtered. The resin was washed with DMF (3x3 mL). To this resin a solution of Fmoc-Phe-OH (232 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) dissolved in 4 mL of DMF was added and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 3 h under nitrogen. Sample of resin was tested for monitoring the coupling by Kaiser's test. If the test is found positive, stirring was continued till Kaiser's test is negative. After complete reaction, the resin was then washed with DMF (3x3 mL). The resin after proper washing was treated with 20% piperidine in DMF (3 mL) and stirred for 5 minute and filtered. The resin was again treated with 20% piperidine in DMF (5 mL) and stirred for 20 minutes under nitrogen and filtered. The resin was washed with DMF (3x3 mL). To this resin a solution of ADT-COOH (188.6 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) dissolved in 4 mL of DMF was added and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 4 h under nitrogen. Sample of resin was tested for monitoring the coupling by Kaiser's test. If the test is found positive, stirring was continued till Kaiser's test is negative. After completion of reaction, the resin was then washed with DMF (3x3 mL) and DCM (3x3 mL). The resin obtained was then dried under vacuum

*Preparation of ADT-Phe-Phe-OH (**I**):* The above resin was then treated with 10 mL mixture of TFA:TIPS:water (95:2.5:2.5 %) and the reaction mixture was stirred for 2 h. The resin was removed by filtration and the filtrate was reduced to half by evaporation under reduced pressure below 45 °C. Peptide was precipitated with diethyl ether. Precipitate obtained was filtered and further washed three times with diethyl ether. Precipitate obtained was dried under vacuum to give crude peptide which was purified by silica gel chromatography using 5% MeOH/DCM. yield (80 mg, 0.13 mmol, 65.6%); Yellow colour solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.28 (d, *J* = 6.2 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.34-7.03 (m, 11H), 6.69 (d, *J* = 8.5 Hz, 1H), 4.66-4.55 (m, 1H), 4.53 (s, 2H), 4.41-4.34 (m, 1H), 3.85 (s, 3H), 3.18-2.85 (m, 3H), 2.79-2.73 (m, 1H); ^{13}C NMR (100 MHz,

DMSO-d_6): δ/ppm = 215.43, 174.38, 170.91, 167.21, 151.39, 149.81, 138.01, 135.21, 129.79, 128.56, 126.76, 125.03, 120.81, 114.12, 111.09, 67.74, 56.51, 54.57, 53.56, 37.88, 37.41; FTIR (KBr) 3428, 3273, 3082, 2922, 1650, 1594, 1492, 1415, 1152, 1018, 700 cm^{-1}; ESI-HRMS: $[M+H]^+$ Calculated for $C_{30}H_{29}N_2O_6S_3^+$ =609.1182, Found = 609.1182.

Synthesis of ADT-Dopa-Phe-COOH (conjugate II):

Preparation of ADT-Dopa(acetonide)-Phe-Resin: 2-Chlorotrityl chloride (CTC) resin having substitution 1.32 mmol/gm (152 mg, 0.2 mmol) was transferred to the reaction vessel. Resin was swollen for 30 minute in dry DCM (3 mL). Resin was washed with dry DCM (3x3 mL). Solution of Fmoc–Phe-OH (232 mg, 0.6 mmol) and DIPEA (209 µL, 1.2 mmol) dissolved in 4 mL of dry DCM was added to the resin and reaction mixture was stirred by purging nitrogen gas for 3 h under nitrogen. To endcap the reactive group on resin 1 mL of HPLC grade methanol was added to the solution and stirred for 15 minutes. After that, the resin was washed with DMF (3x3 mL) and DCM (3x3 mL). The resin was then treated with 20% piperidine in DMF (3 mL) and stirred for 5 minute and filtered. The resin was again treated with 20% piperidine in DMF (5 mL) and stirred for 25 minutes under nitrogen and filtered. The resin was washed with DMF (3x3 mL). To this resin a solution of Fmoc-Dopa(acetonide)-OH (275 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) dissolved in 4 mL of DMF was added and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 3 h under nitrogen. Sample of resin was tested for monitoring the coupling by Kaiser's test. If the test is found positive, stirring was continued till Kaiser's test is negative. After complete reaction, the resin was then washed with DMF (3x3 mL). The resin after proper washing was treated with 20% piperidine in DMF (3 mL) and stirred for 5 minute and filtered. The resin was again treated with 20% piperidine in DMF (5 mL) and stirred for 20 minutes under nitrogen and filtered. The resin was washed with DMF (3x3 mL). To this resin a solution of ADT-COOH (188.6 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) dissolved in 4 mL of DMF was added and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 4 h under nitrogen. Sample of resin was tested for monitoring the coupling by Kaiser's test. If the test is found positive, stirring was continued till Kaiser's test is negative. After completion of reaction, the resin was then washed with DMF (3x3 mL) and DCM (3x3 mL). The resin obtained was then dried under vacuum

*Preparation of ADT-Dopa-Phe-OH (**II**):* The above resin was then treated with 10 mL mixture of TFA:TIPS:water:DCM (30:2.5:2.5:65%) and the reaction mixture was stirred for 2 h. The resin was removed by filtration and the filtrate was reduced to half by evaporation under reduced pressure below 45 °C. Peptide was precipitated with diethyl ether. Precipitate obtained was filtered and further washed three times with diethyl ether. Precipitate obtained was dried under vacuum to give crude peptide which was purified by silica gel chromatography using 5% MeOH/DCM plus 1% acetic acid. Yield (75 mg, 0.12 mmol, 58.4%); Yellow colour solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.70 (s, 2H), 8.33 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H),

7.37 (d, *J* = 2.1 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.26-7.09 (m, 5H), 6.69-6.50 (m, 3H), 6.41 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.70-4.22 (m, 4H), 3.82 (s, 3H), 3.10-2.76 (m, 3H), 2.58-2.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm = 215.33, 174.56, 173.36, 171.43, 167.07, 151.46, 149.76, 145.37, 144.32, 138.14, 135.16, 129.71, 128.65, 126.88, 124.99, 120.86, 120.62, 117.22, 115.70, 114.14, 111.03, 67.53, 56.50, 54.22, 54.05, 37.82, 37.25; FTIR (KBr) 3400, 3058, 2933, 1732, 1636, 1532, 1492, 1445, 1265, 1192, 1150, 1033, 629 cm^{-1}; ESI-HRMS; $[M+H]^+$ Calculated for $C_{30}H_{29}N_2O_8S_3^+$ = 641.1081, Found= 641.1088.

Synthesis of ADT-Trp-Trp-COOH (conjugate III):

Preparation of ADT-Trp(Boc)-Trp(Boc)-Resin: 2-Chlorotrityl chloride (CTC) resin having substitution 1.32 mmol/gm (152 mg, 0.2 mmol) was transferred to the reaction vessel. Resin was swollen for 30 minute in dry DCM (3 mL). Resin was washed with dry DCM (3x3 mL). Solution of Fmoc–Trp(Boc)-OH (316 mg, 0.6 mmol) and DIPEA (209 µL, 1.2 mmol) dissolved in 4 mL of dry DCM was added to the resin and reaction mixture was stirred by purging nitrogen gas for 3 h under nitrogen. To endcap the reactive group on resin 1 mL of HPLC grade methanol was added to the solution and stirred for 15 minutes. After that, the resin was washed with DMF (3x3 mL) and DCM (3x3 mL). The resin was then treated with 20% piperidine in DMF (3 mL) and stirred for 5 minute and filtered. The resin was again treated with 20% piperidine in DMF (5 mL) and stirred for 25 minutes under nitrogen and filtered. The resin was washed with DMF (3x3 mL). To this resin a solution of Fmoc-Trp(Boc)-OH (316 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) dissolved in 4 mL of DMF was added and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 3 h under nitrogen. Sample of resin was tested for monitoring the coupling by Kaiser's test. If the test is found positive, stirring was continued till Kaiser's test is negative. After complete reaction, the resin was then washed with DMF (3x3 mL). The resin after proper washing was treated with 20% piperidine in DMF (3 mL) and stirred for 5 minute and filtered. The resin was again treated with 20% piperidine in DMF (5 mL) and stirred for 20 minutes under nitrogen and filtered. The resin was washed with DMF (3x3 mL). To this resin a solution of ADT-COOH (188.6 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) dissolved in 4 mL of DMF was added and reaction mixture was stirred by purging nitrogen gas followed by addition of DIC (94 µL, 0.6 mmol) and the reaction mixture was stirred by purging nitrogen gas for 4 h under nitrogen. Sample of resin was tested for monitoring the coupling by Kaiser's test. If the test is found positive, stirring was continued till Kaiser's test is negative. After completion of reaction, the resin was then washed with DMF (3x3 mL) and DCM (3x3 mL). The resin obtained was then dried under vacuum

*Preparation of ADT-Trp-Trp-OH (**III**):* The above resin was then treated with 10 mL mixture of TFA:TIPS:water:DCM (30:2.5:2.5:65%) and the reaction mixture was stirred for 2 h. The resin was removed by filtration and the filtrate was reduced to half by evaporation under reduced pressure below 45 °C. Peptide was precipitated with diethyl ether. Precipitate obtained was filtered and further washed three times with diethyl ether. Precipitate obtained was dried under vacuum to give crude peptide which was purified by silica gel chromatography using 4% MeOH/DCM plus 1% acetic acid. Yield (100 mg, 0.14 mmol, 72.8 %); Yellow colour solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 10.86 (s, 2H), 8.46 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.83 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.42-7.29 (m, 3H), 7.21 – 6.85 (m, 7H), 6.53 (d, *J* = 8.5 Hz, 1H), 4.72-4.63 (m, 1H), 4.61-4.41 (m, 3H), 3.82 (s, 3H), 3.28-3.04 (m, 3H), 2.98-2.92 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm = 215.33, 174.43, 173.84, 171.68, 167.21, 151.30, 149.72, 136.57, 135.19, 127.91, 127.78, 124.96, 124.38, 124.11, 121.39, 120.72, 118.72, 113.97, 111.88, 110.97, 110.15, 67.67, 56.45, 53.66, 53.25, 28.46, 27.59; FTIR (KBr) 3403, 3054, 2927, 1649, 1598, 1486, 1457, 1438, 1264, 1149, 1023, 744 cm^{-1}; ESI-HRMS: $[M+H]^+$ Calculated for $C_{34}H_{31}N_4O_6S_3^+$ = 687.1400, Found = 687.1409.

4) High performance liquid chromatography (HPLC) analysis:

HPLC analysis were performed with a HPLC system (Agilent technologies 1260 infinity) equipped with a quaternary pump (G1311B), auto liquid sampler (G1329B), Diode array detector (G1315D) and analytical scale-fraction collector (G1364C). Instrument control, data acquisition and data analyses were performed using a ChemStation software (Agilent Technologies, Workingham, UK). A ZORBAX Eclipse plus C 18 (250 x 4.6 mm) column with 5 µ particle size at room temperature was used. Mobile phase consisted of solvent A (0.1% TFA in water) and solvent B (0.1% TFA in acetonitrile) and the flow rate was 1.0 mL/min.

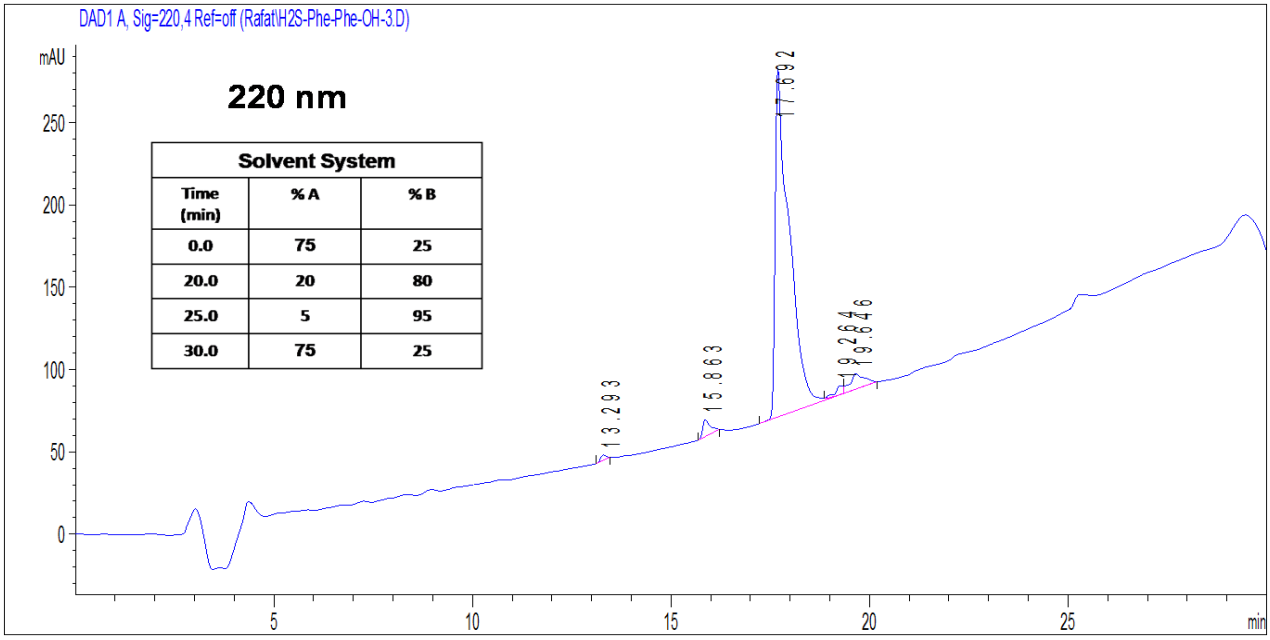


Figure S1: Analytical HPLC chromatogram of conjugate **I** at wavelength 220 nm

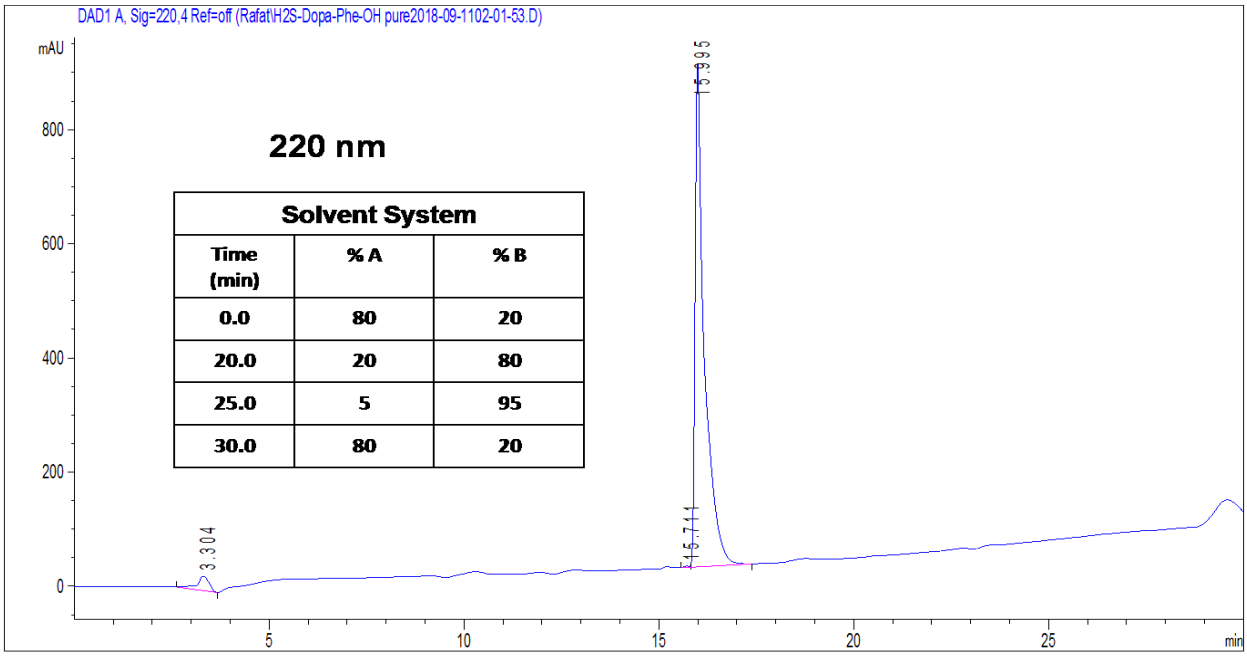


Figure S2: Analytical HPLC chromatogram of conjugate **II** at wavelength 220 nm

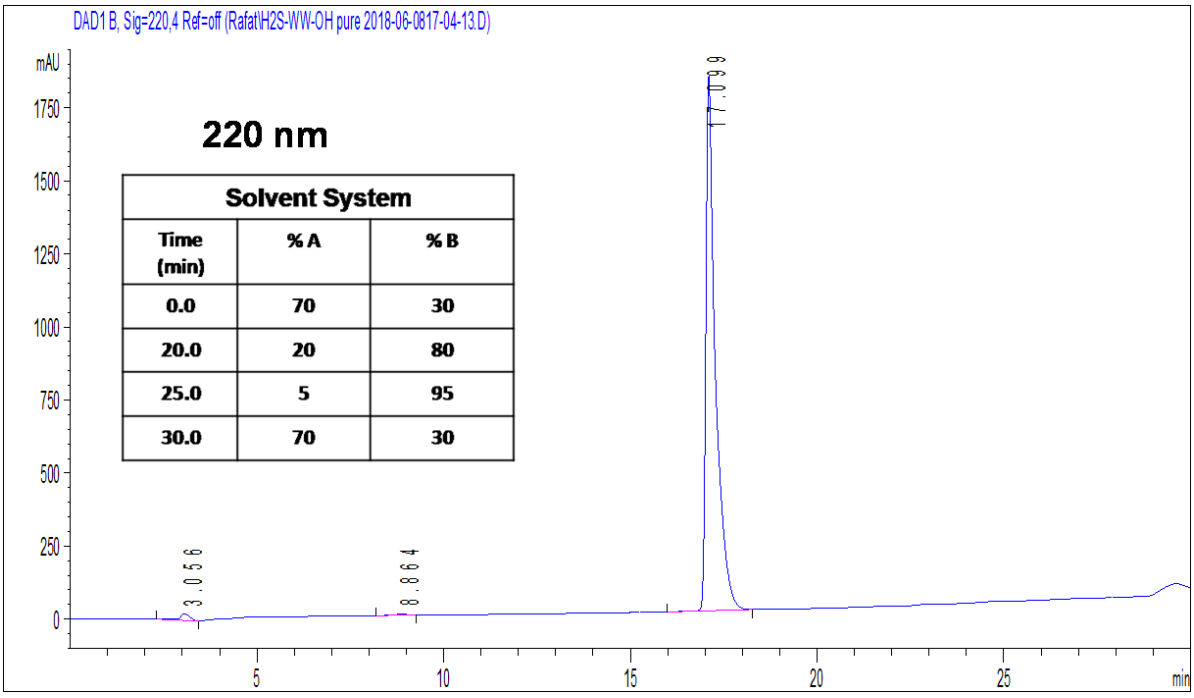


Figure S3: Analytical HPLC chromatogram of conjugate **III** at wavelength 220 nm

5) Atomic Force Microscopy (AFM):

From the stock solution of Conjugate **I**, **II** and **III** (1 mM in 10% Acetone/water), 15 µL were drop casted on silicon wafer or copper surface at room temperature. All the three samples were allowed to air dry at room temperature

for overnight followed by subsequent drying under vacuum for 30 minutes prior to scanning. The samples were scanned with an atomic force microscope (Asylum Research, Oxford Instruments, MFP-3D Origin) at room temperature. Scanning was carried out under tapping mode with a force constant of 21 N/m. Silicon nitride cantilever from Nanosensors with following features was used; Resonance frequency: 170 kHz, Thickness :7.0 µm, length :225 µm, width: 38 µm.

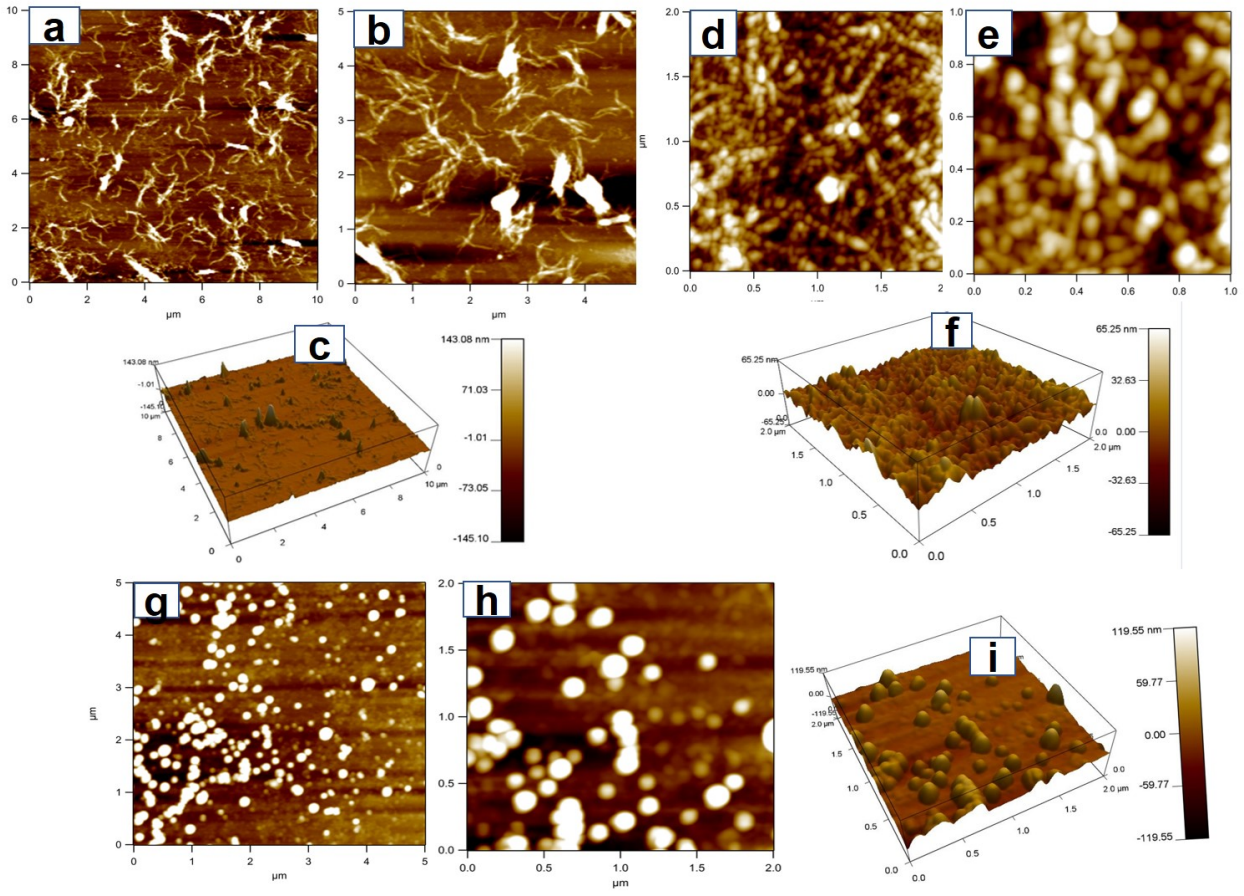


Figure S4: AFM micrographs of conjugate **I** (a, b, c), conjugate **II** (d, e, f) and **III** (g, h, i)

6) Scanning Electron Microscopy (SEM):

Field emission scanning electron microscopy (FESEM) images were acquired on FEI QUANTA 200 microscope, equipped with a tungsten filament gun, operating at working distance 3.88 mm and 10 kV. 15 µL aliquots of freshly prepared solutions of conjugates **I**, **II** and **III** (1 mM in water/Acetone, 50:50) were deposited on copper stubs and were allowed to dry at room temperature for overnight followed by drying under high vacuum for another 30 minutes. The samples were gold coated for 1 min and then imaged with FESEM.

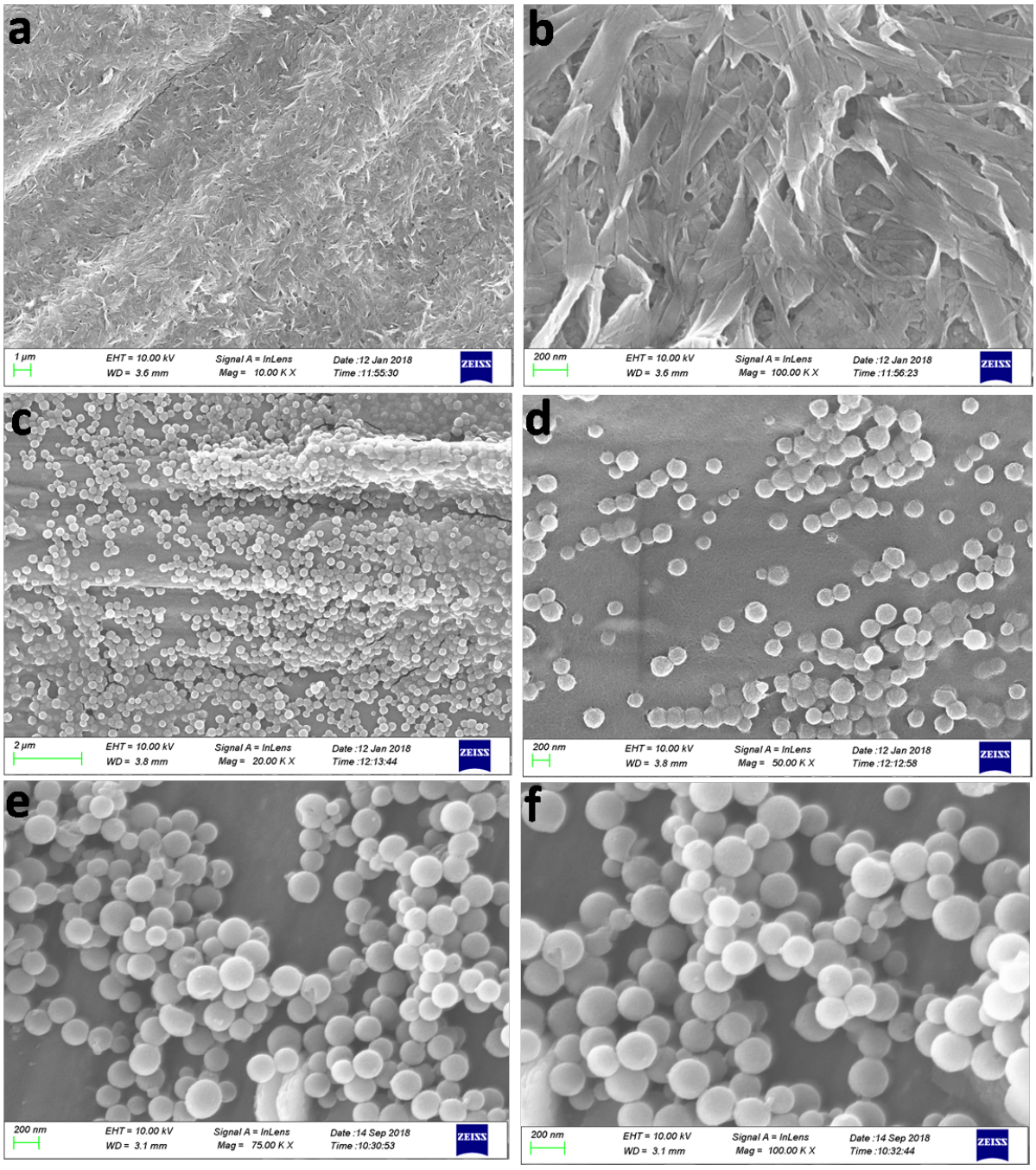


Figure S5: SEM micrographs of conjugate **I** (a, b), **II** (c, d) and **III** (e,f).

7) Dynamic Light Scattering (DLS): Dynamic light scattering (DLS) for Particle size distribution was done using Delsa^{TM} Nano from Beckman Coulter India.

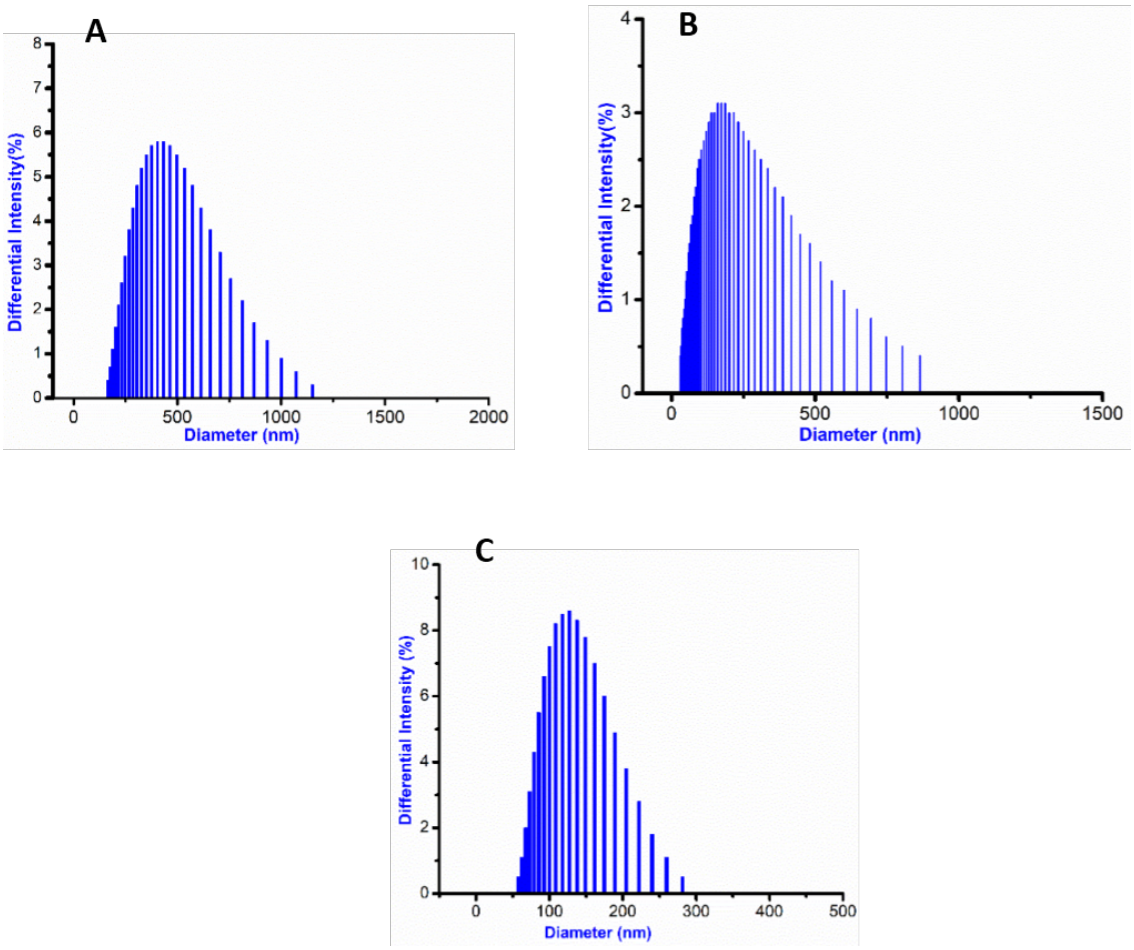


Figure S6: Dynamic light scattering measurement for observing size distribution of conjugate **I** (A), **II** (B) and **III** (C); (500 µM, 5% Acetone/Water).

8) Hydrogen sulfide release experiment:

The previously described protocol was adopted for studying release kinetics.[2] The 5mM stock solution of sodium sulfide ($Na_2S.9H_2O$) in sodium phosphate buffer (20 mM, pH 7.4) was prepared. From the stock solution aliquots of 50, 100, 200, 400, 600, 800, 1000, 1500 mL were added into a 50 mL volumetric flask and dissolved in sodium phosphate buffer to obtain the working solutions of 5, 10, 20, 40, 60, 80, 100, 150 mM concentrations, respectively. 1 mL aliquot of the respective solution was reacted with the methylene blue (MB^+) cocktail: 30 mM FeCl3 in 1.2 M HCl (200 µL), 20 mM of *N*, *N*-dimethyl-1, 4-phenylenediamine sulfate in 7.2 M HCl (200 µL), 1%w/v of $Zn(OAc)_2$ in water (100 µL) at room temperature for at least 15 min (each reaction was performed in triplicate). The absorbance of methylene blue was measured at 670 nm in UV-Vis spectrophotometer and from these values standard Na_2S concentration-absorbance calibration curve were plot which is used for calculating H_2S concentration of the conjugates.

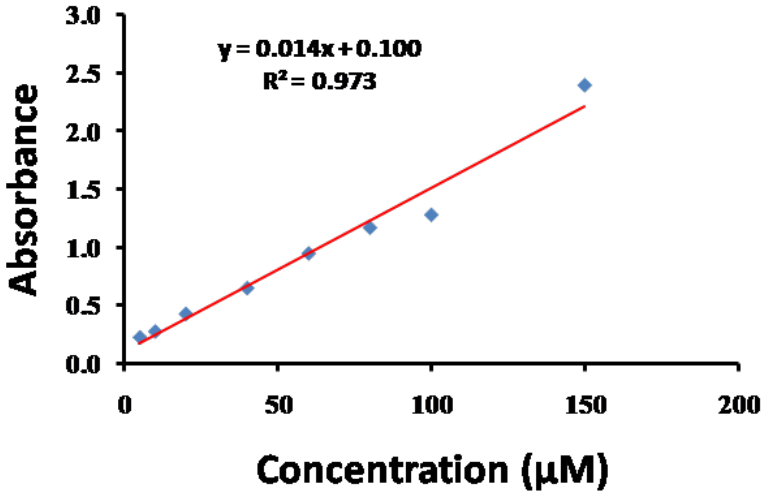


Figure S7: Standard Na_2S Absorption vs concentration calibration curve

The 40 mM stock solution of conjugates **I-III** was prepared in tetrahydrofuran. The reactions was started by taking 75 µL from the stock solution and add into phosphate buffer (pH 7.4, 30 mL) containing accelerator Tris (2-carboxyethyl) phosphine (1.0 mM) so that the final concentration of conjugates was 100 µM. Then 1.0 mL of reaction aliquots were periodically taken and was added to methylene blue cocktail containing 30 mM FeCl3 in 1.2 M HCl (200 µL), 20 mM of *N*, *N*-dimethyl-1, 4-phenylenediamine sulfate in 7.2 M HCl (200 µL), 1%w/v of $Zn(OAc)_2$ in water (100 µL). The absorbance at 670 nm of the resulted solution was determined after 15 minute using UV-Vis spectrophotometer. The concentration of the H_2S is calculated by converting absorbance readings to H_2S concentration from standard calibration curve of H_2S. The H_2S releasing curve was obtained by plotting H_2S concentration versus time. All experiments were repeated thrice.

9) Estimation for Reactive oxygen Species (ROS):

To determine the effect of compounds on reactive oxygen species (ROS) levels in *C. elegans* worms, we employed 2, 7-dichlorodihydrofluorescein-diacetate (H2-DCFDA) assay. Briefly H_2-DCFDA dye diffuses inside the living cells where diacetate cleaved by intracellular esterase converts into H_2-DCA, this is in turn oxidized by host cell reactive oxygen species into 2, 7- DCF, that exhibits florescence at excitation/emission of 495/512-527 nm. *C. elegans* N2 strain (Wild type) was used in this assay, worms were treated with 20 mM H_2O_2 (Sigma cat: 32 338-1) as positive control (OP50 + H_2O_2) concentration for 1 hour at 22 ^{0}C then washed with M9 buffer once followed by three washes with PBS.[3] Hundred worms were taken from each treatment group and transferred into 96 well plate with three replicates of each sample. 100 µL of H_2-DCFDA dye having 100 µM concentration was added to each well, fluorescence was measured at excitation of 495 nm and emission at 512-527 nm. Basal fluorescence was measured immediately and second observation was recorded just after addition of dye; final observation was recorded after 1 hour of incubation. Fluorescence per worm was calculated after subtracting initial to zero hour fluorescence.

10) Dopamine content analysis using LC-MS/MS:

Dopamine content was estimated in untreated (control) as well as in worms treated with ADT-COOH, conjugates **I**, **II** and **III** using LC-MS/MS after 48 hour treatment in NL5901 strain of *C. elegans*. Worms were washed thrice with M9 buffer to remove adhering bacteria. For dopamine estimation 5000 worms were collected, worm pellet was sonicated in 500 uL MilliQ water at 25 % amplitude for 3 min (pulse rate 15 sec on/off). Sonicated samples were centrifuged at 13000 rpm at 4°C for 20 min. Supernatant was used directly for analysis of dopamine concentration. The LC consists of WATERS Delta 600 binary pump (Manchester, UK) equipped with 2707 autosampler and in-line degasser AF was coupled to API 3200 triple quadruple mass spectrometer (ABI SCIEX, ON, Canada). The samples were processed by using simple protein precipitation technique using acetonitrile in ratio 1:3 of sample/acetonitrile, centrifuged at 14,000 rpm for 20 minute and 20 µL of supernatant was injected into LC-MS/MS. The separation was achieved on the Thermo Fischer scientific Accucore AQ column (150×4.6 mm, 2.6 µm) with the mobile phase composition of acetonitrile: 0.1% formic acid in water (35:65) at a flow rate of 0.6 mL/min. The total run time for sample was 4.00 min. The ionization of dopamine was performed in positive MRM mode at transition of 154.00/137.2. Analytical data was integrated by Analyst software 1.6 versions (AB SCIEX, ON, Canada).

11) Copies of ^{1}H and ^{13}C NMR spectra:

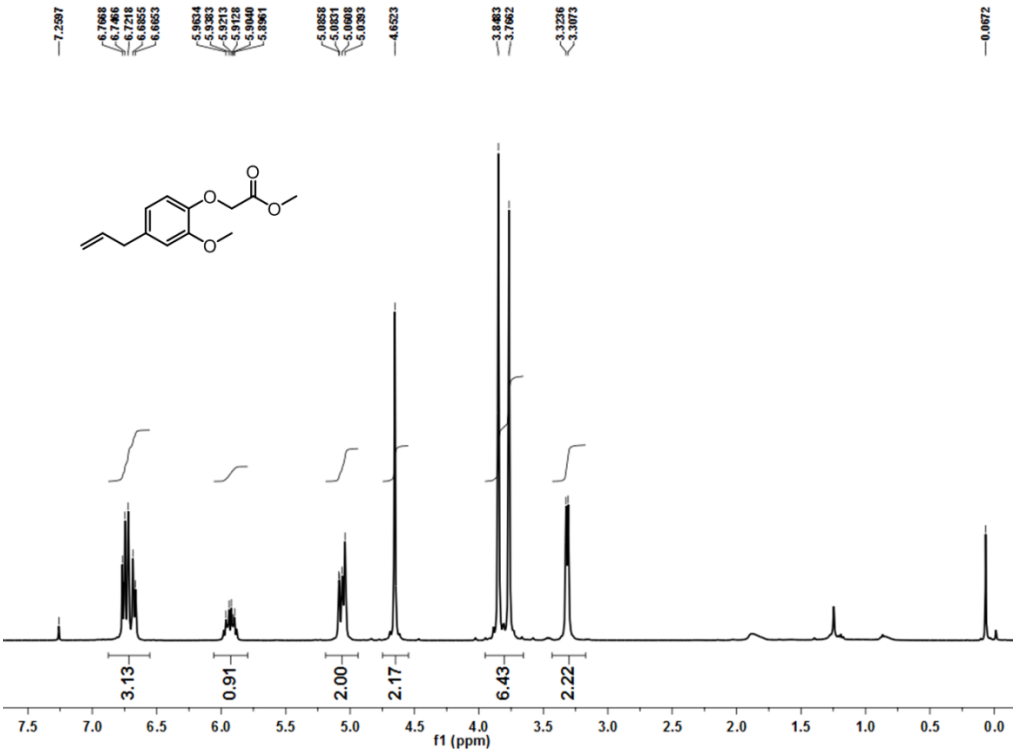


Figure S8: ^{1}H NMR spectrum of **Methyl 2-(4-allyl-2-methoxyphenoxy) acetate** (400 MHz, $CDCl_3$)

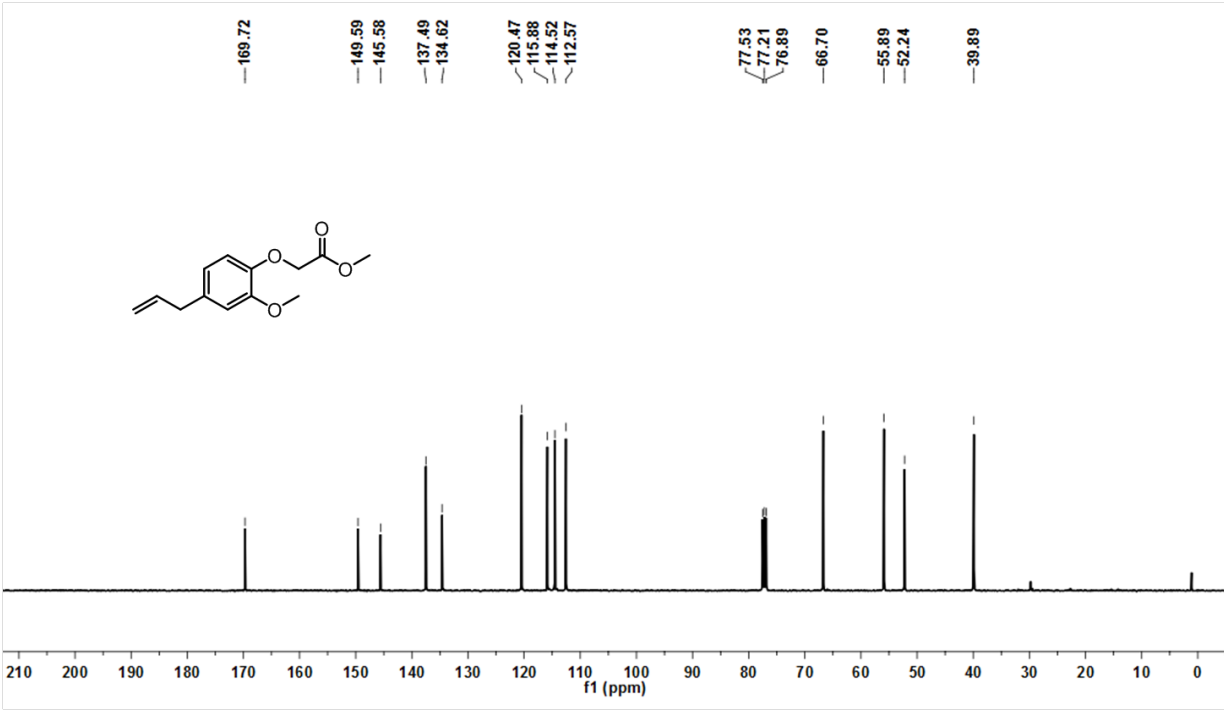


Figure S9: ^{13}C NMR spectrum of **Methyl 2-(4-allyl-2-methoxyphenoxy) acetate** (100 MHz, $CDCl_3$)

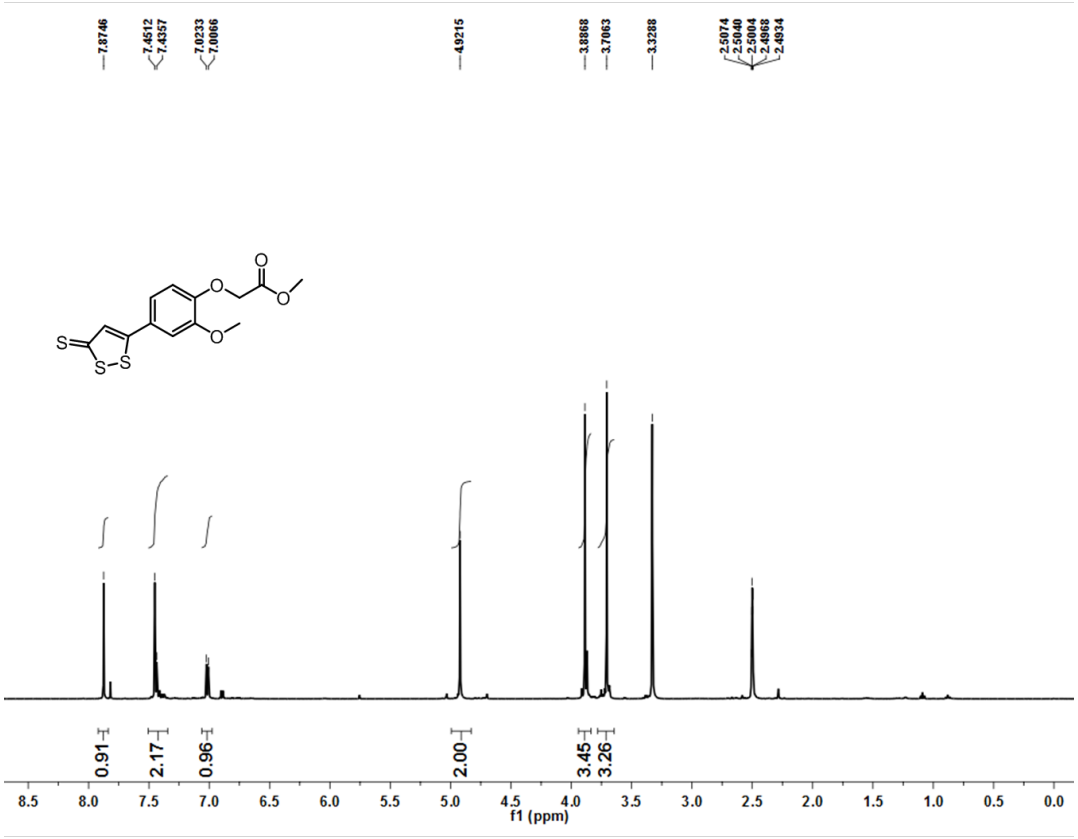


Figure S10: ^{1}H NMR spectrum of **Methyl 2-2-methoxy-4-(3-thioxo-3H-1,2-dithiol-5-yl)phenoxy] acetate** (500 MHz, DMSO-d_6)

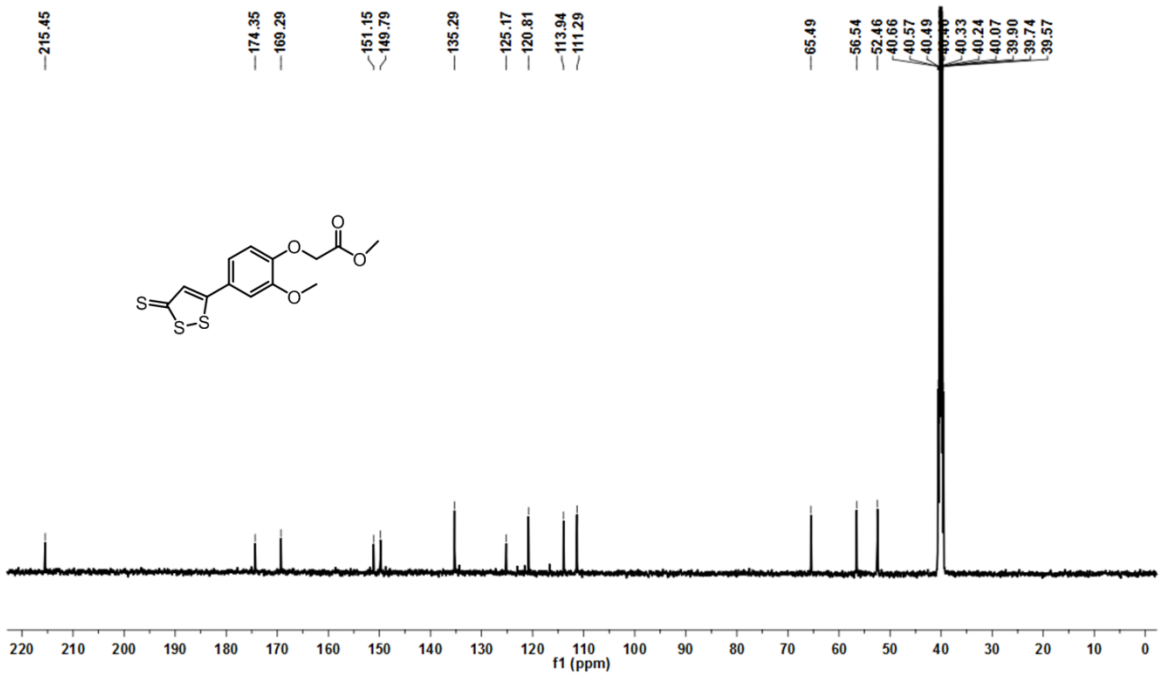


Figure S11: ^{13}C NMR spectrum of **Methyl 2-2-methoxy-4-(3-thioxo-3H-1,2-dithiol-5-yl)phenoxy] acetate** (125 MHz, DMSO-d_6)

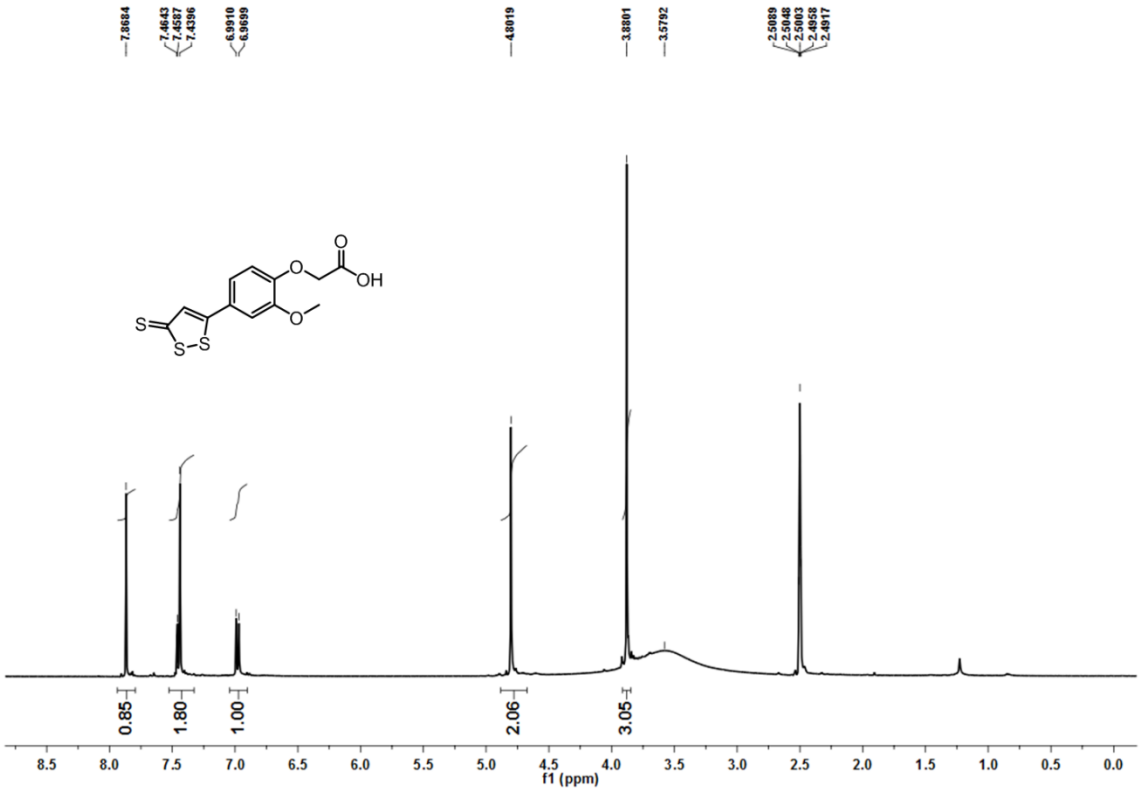


Figure S12: ^{1}H NMR spectrum of **ADT-COOH** (400 MHz, DMSO-d_6)

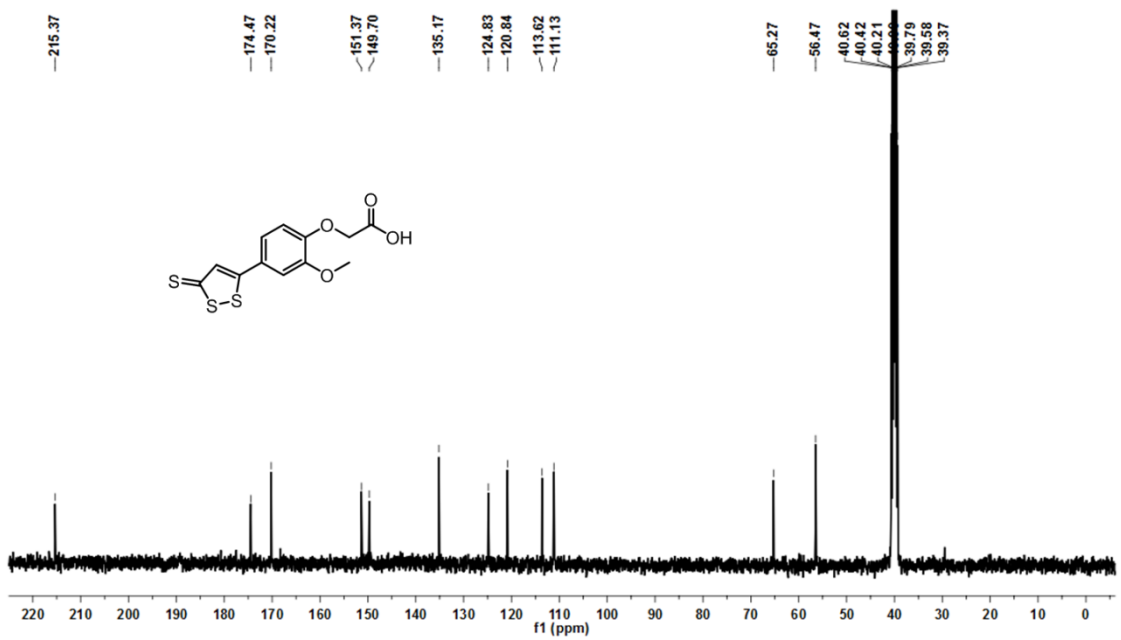


Figure S13: ^{13}C NMR spectrum of **ADT-COOH** (100 MHz, DMSO-d_6)

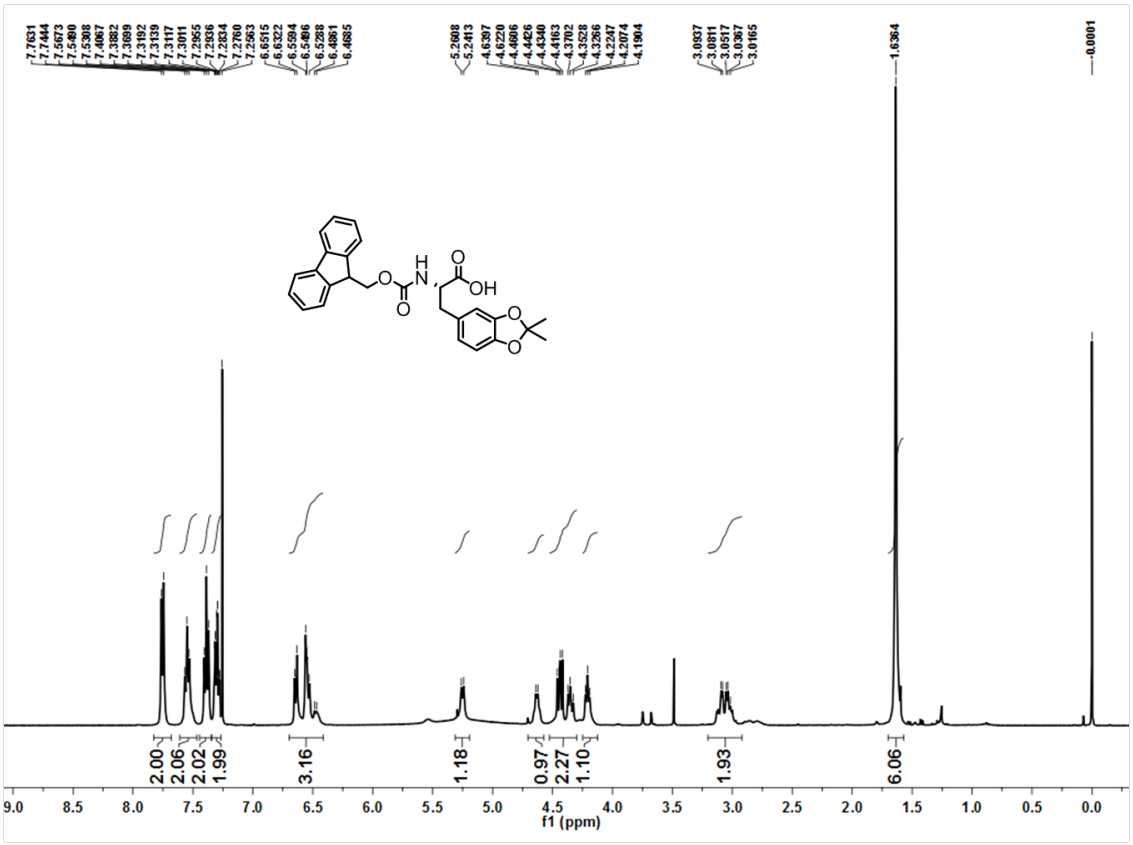


Figure S14: ^{1}H NMR spectrum of compound Fmoc-Dopa(acetonide)-OH (400 MHz, $CDCl_3$)

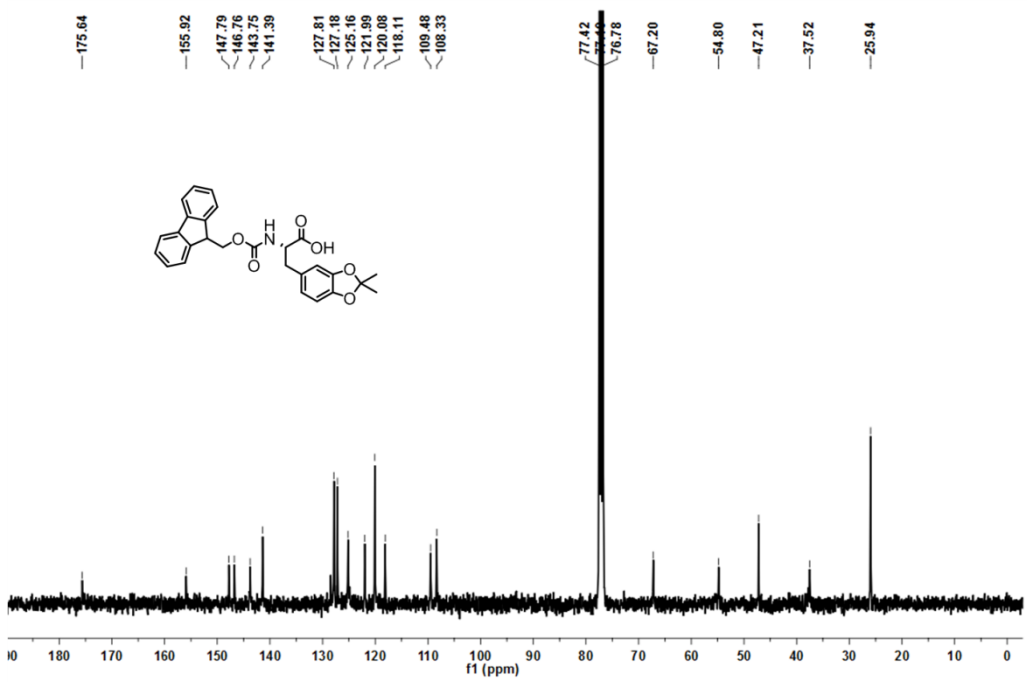


Figure S15: ^{13}C NMR spectrum of compound Fmoc-Dopa(acetonide)-OH (100 MHz, $CDCl_3$)

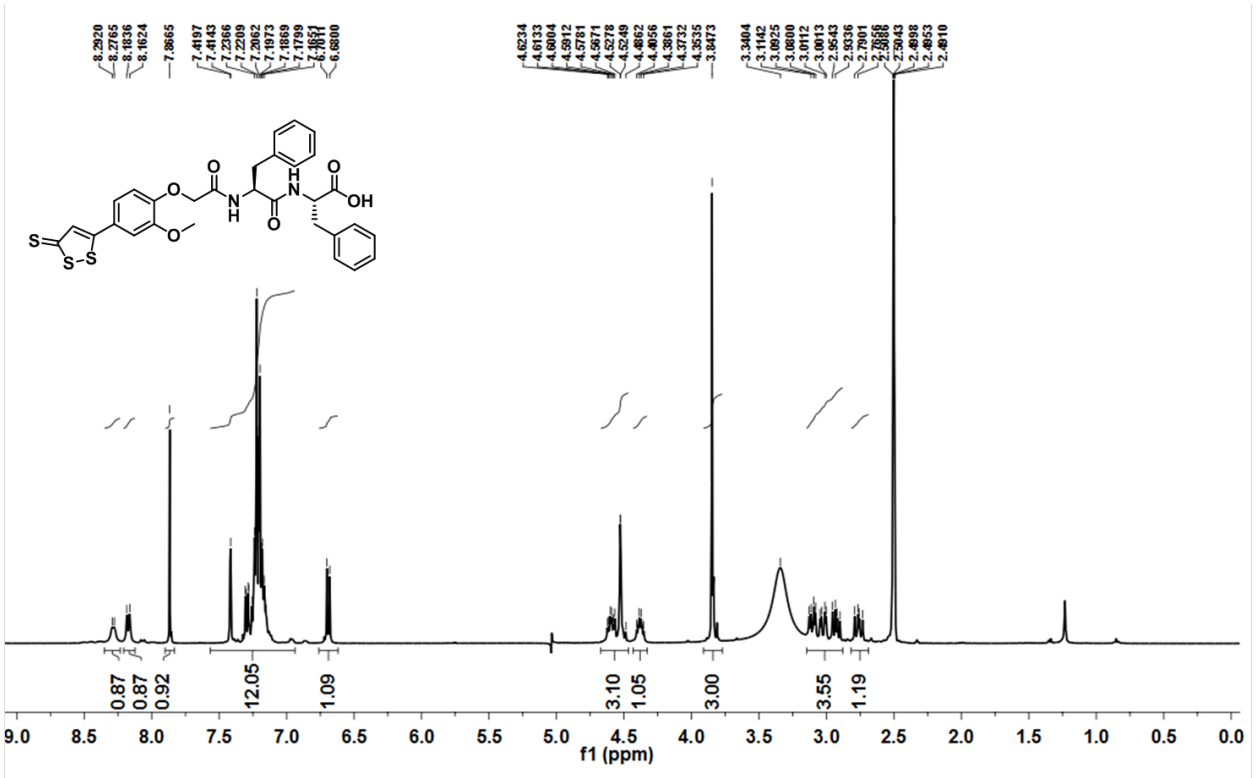


Figure S16: ^{1}H NMR spectrum of **conjugate I** (400 MHz, DMSO-d_6)

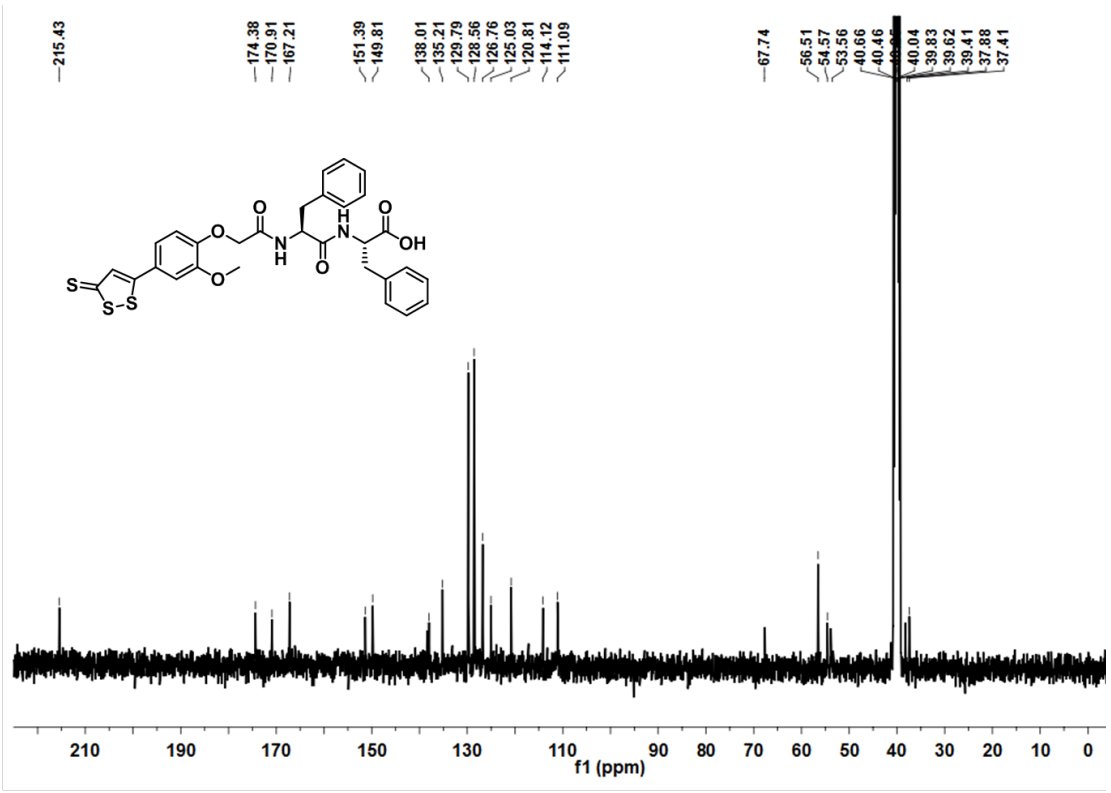


Figure S17: ^{13}C NMR spectrum of **conjugate I** (100 MHz, DMSO-d_6)

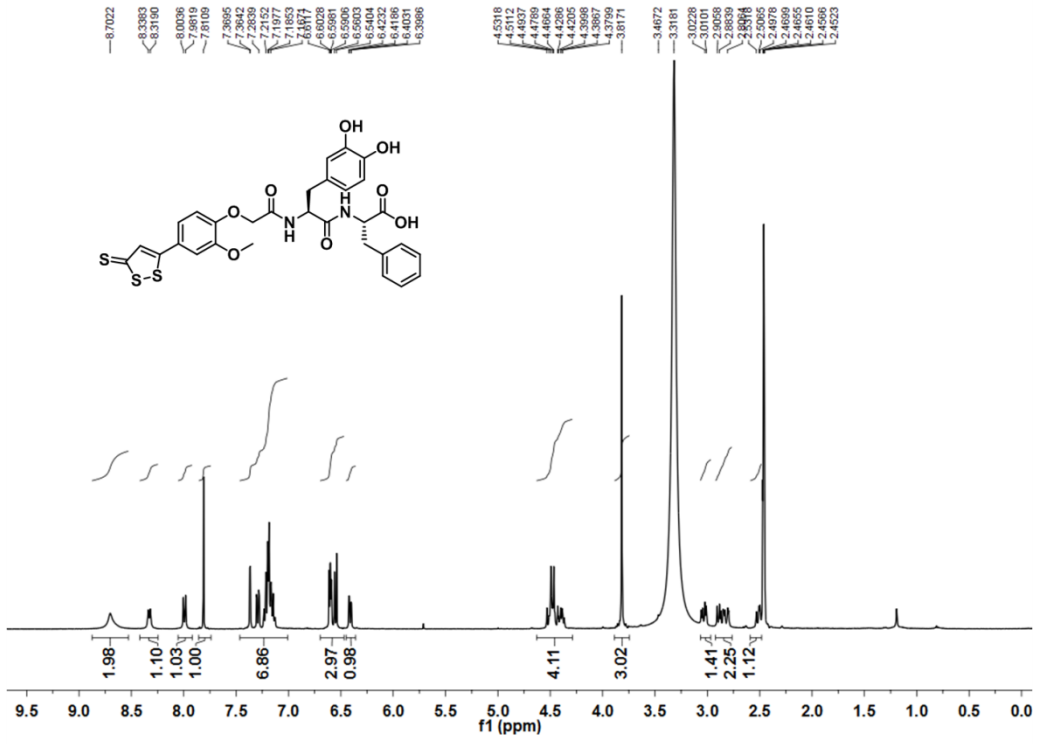


Figure S18: ^{1}H NMR spectrum of **conjugate II** (400 MHz, DMSO-d_6)

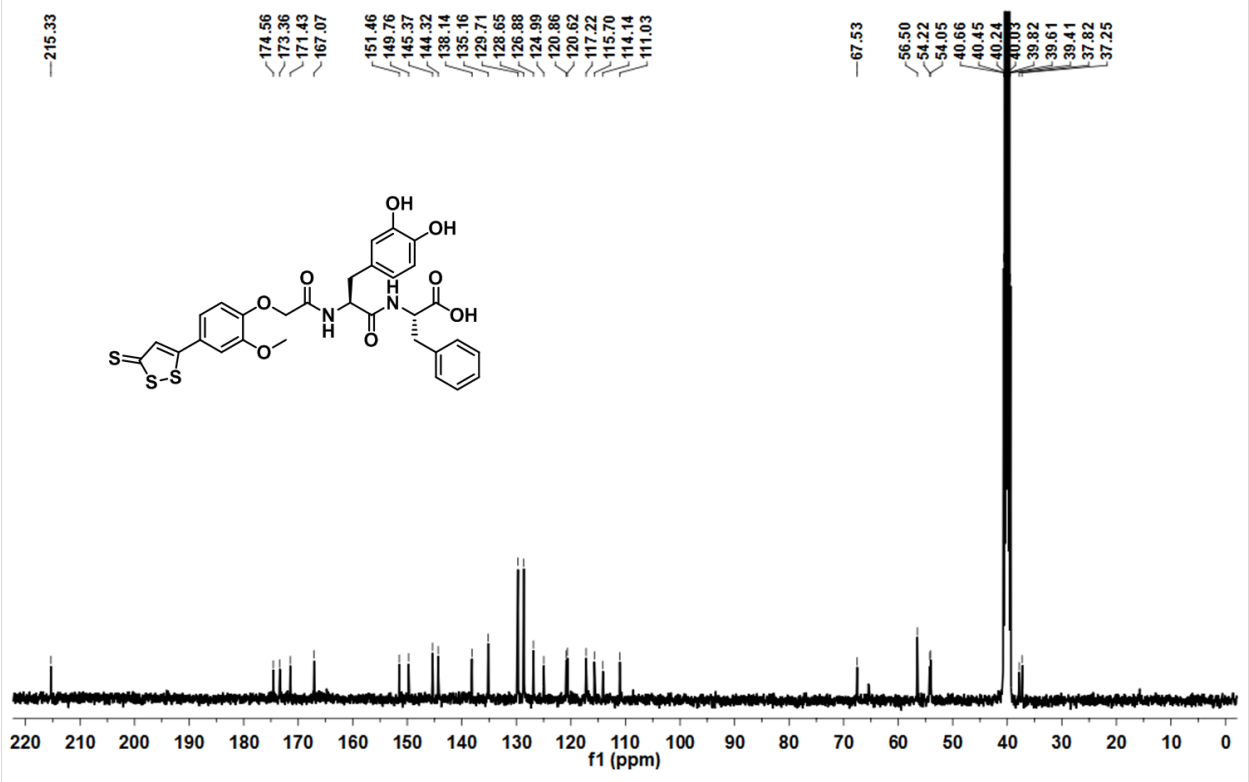


Figure S19: ^{13}C NMR spectrum of **conjugate II** (100 MHz, DMSO-d_6)

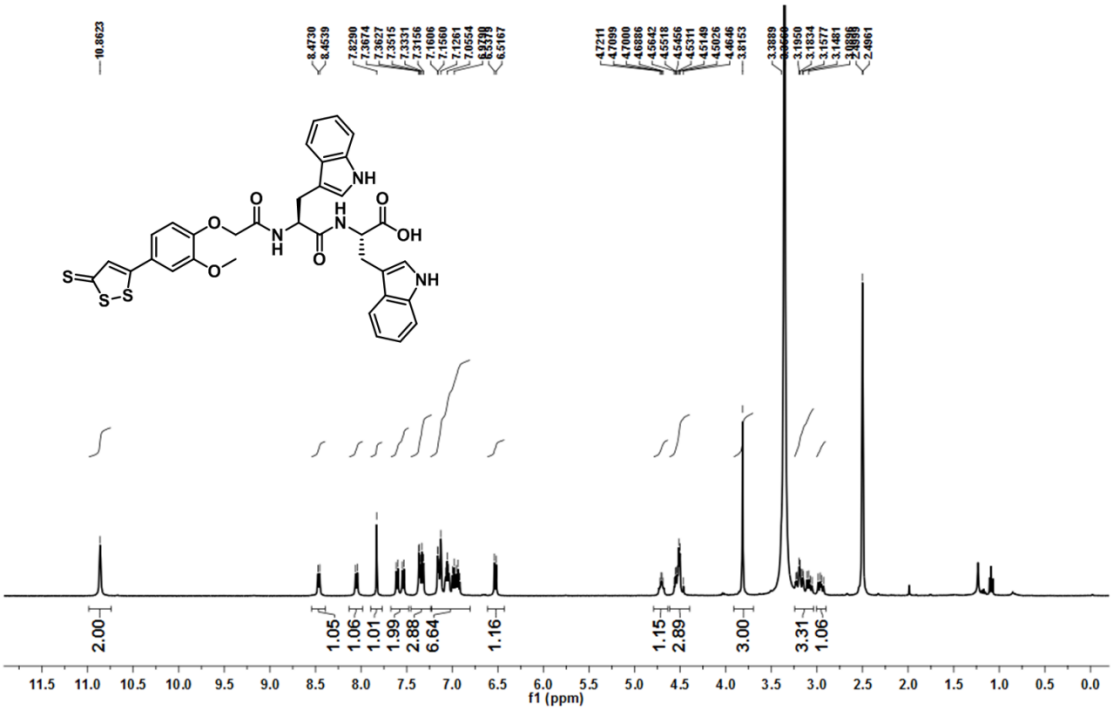


Figure S20: ^{1}H NMR spectrum of **conjugate III** (400 MHz, DMSO-d_6)

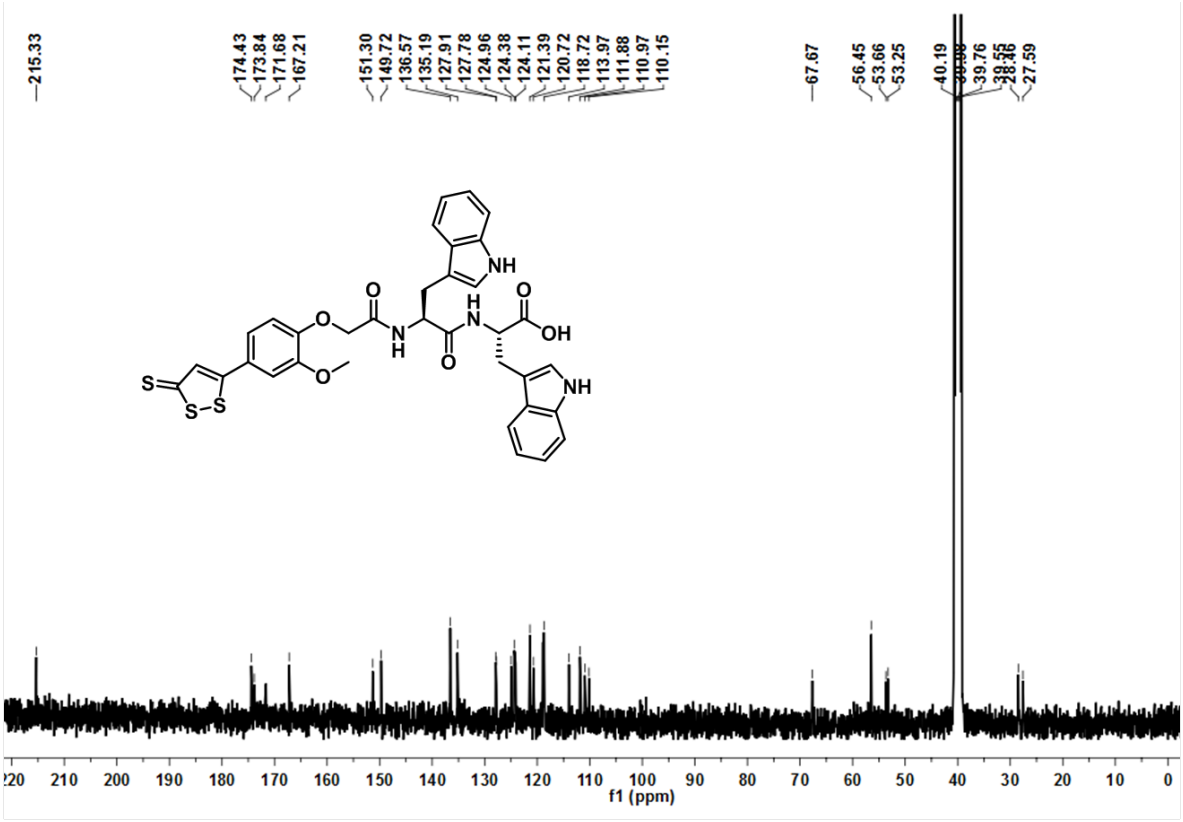


Figure S21: ^{13}C NMR spectrum of **conjugate III** (100 MHz, DMSO-d_6)

12) References:

1 S. P. Dion, R. J. Najmanovich, P.-L. Boudreault, É. Colombo, F. Béliveau, C. St-Georges, R. Leduc, A. Désilets, M. Ghinet and É. Marsault, *Eur. J. Med. Chem.*, 2017, **129**, 110–123.

2 M. Li, J. Li, T. Zhang, Q. Zhao, J. Cheng, B. Liu, Z. Wang, L. Zhao and C. Wang, *Eur. J. Med. Chem.*, 2017, **138**, 51–65.

3 S. L. Offenburger, X. Y. Ho, T. Tachie-Menson, S. Coakley, M. A. Hilliard and A. Gartner, *PLoS Genet.*, 2018, **14**, e1007125.