Supplementary Information

Click and Photo-unclick Chemistry of Aminoacrylate for Visible Light-triggered Drug Release

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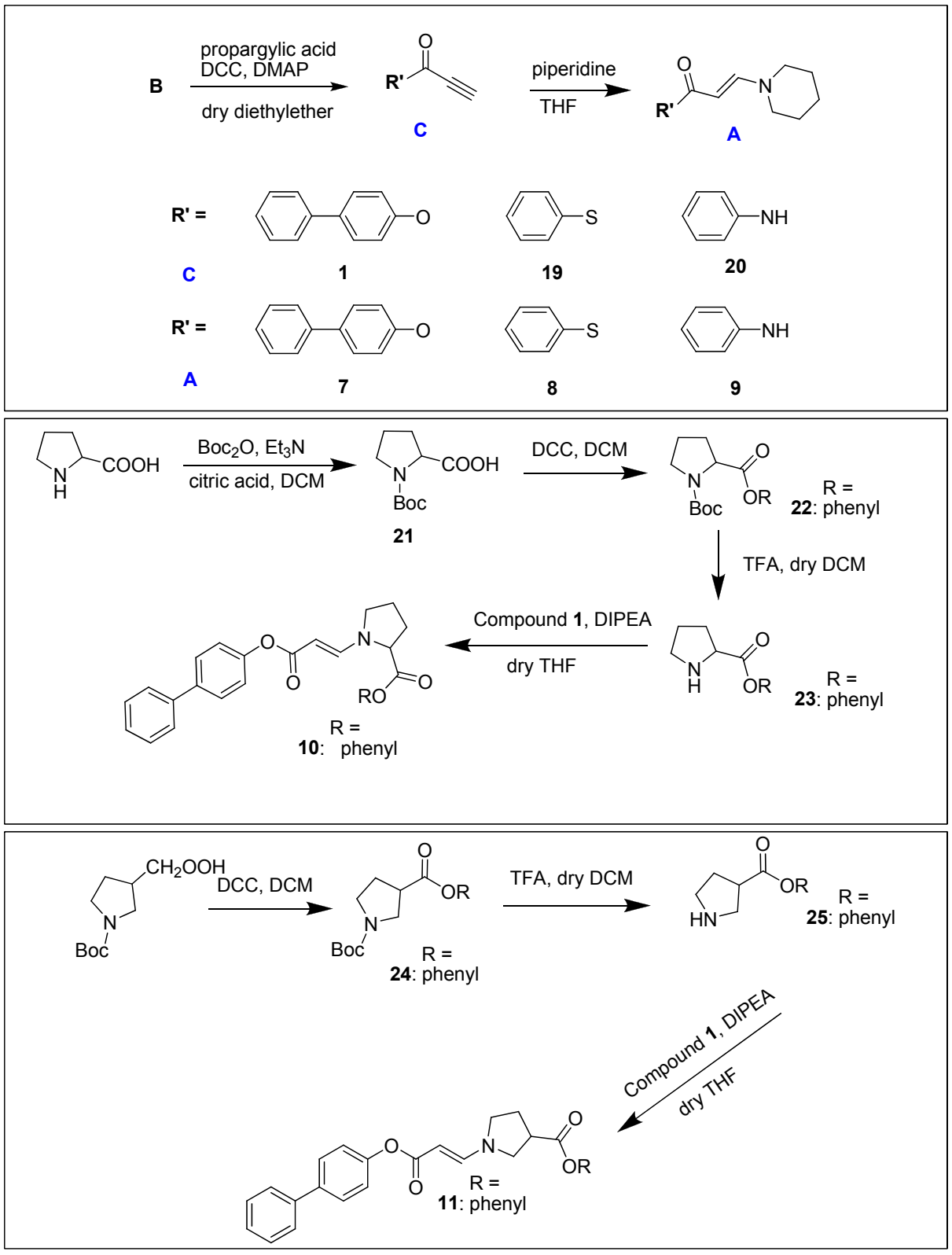
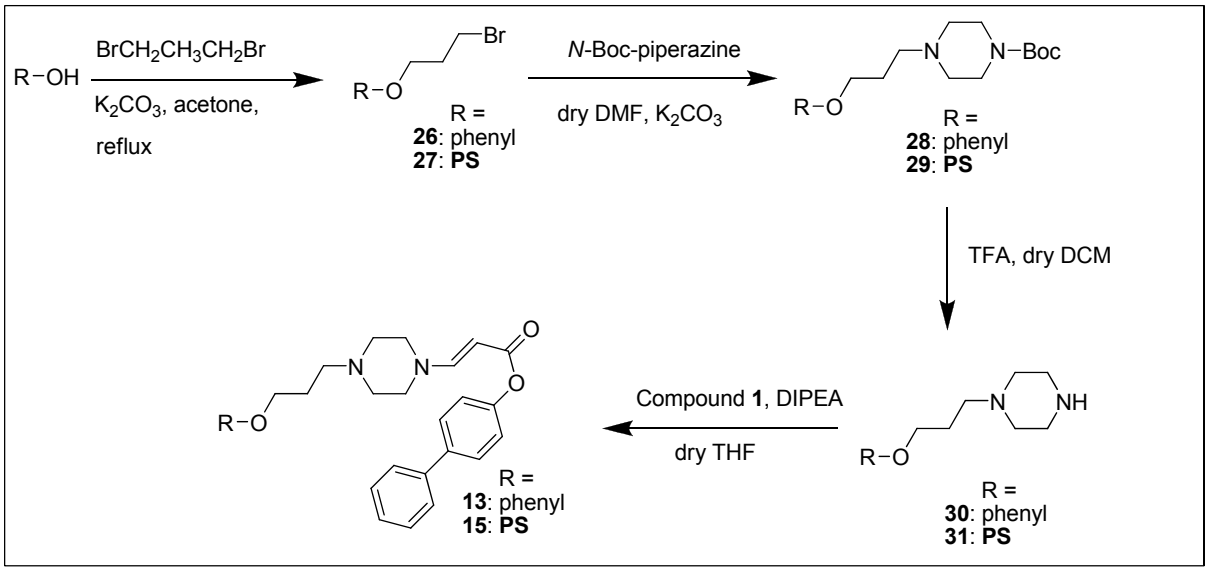
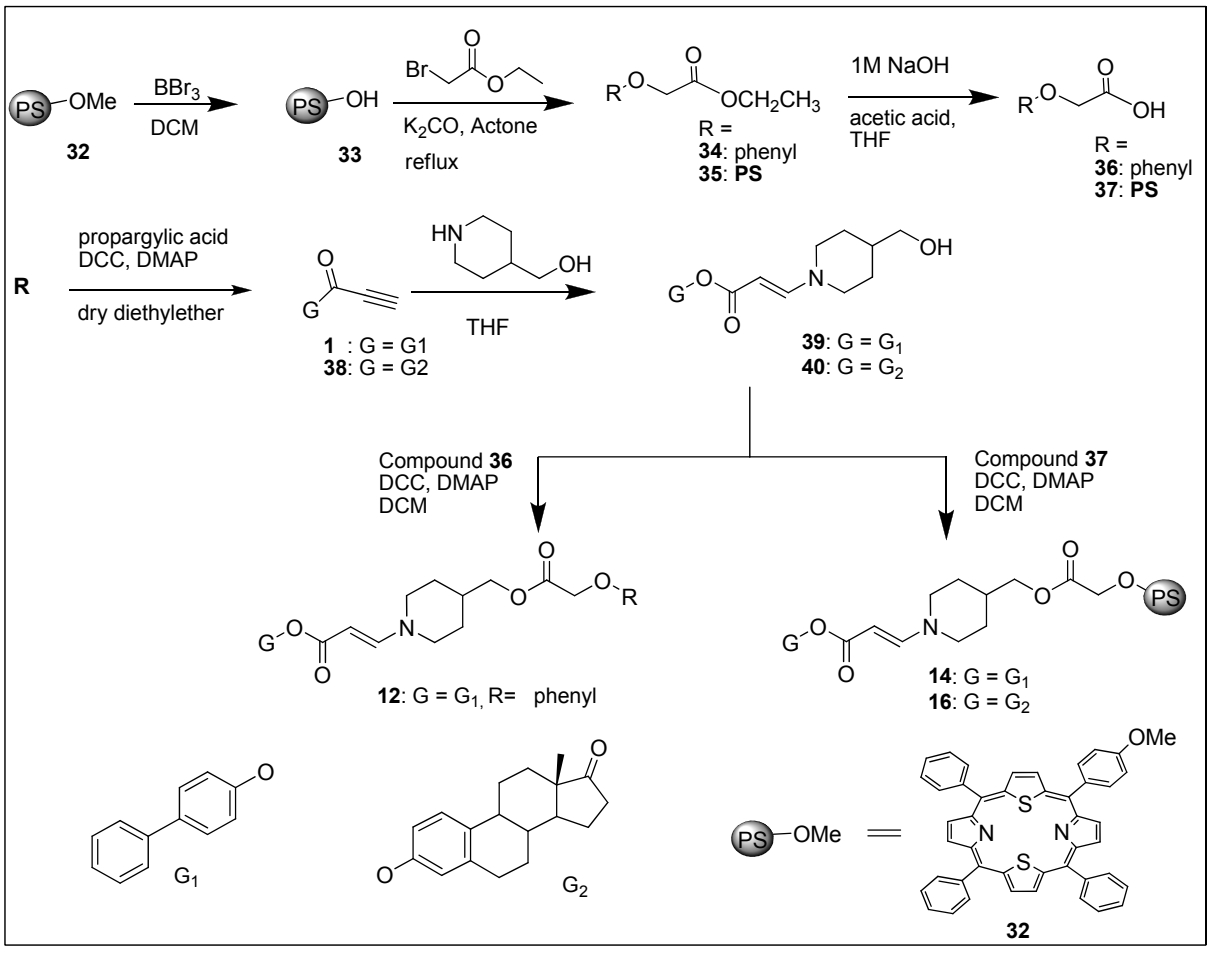
Experimental Section

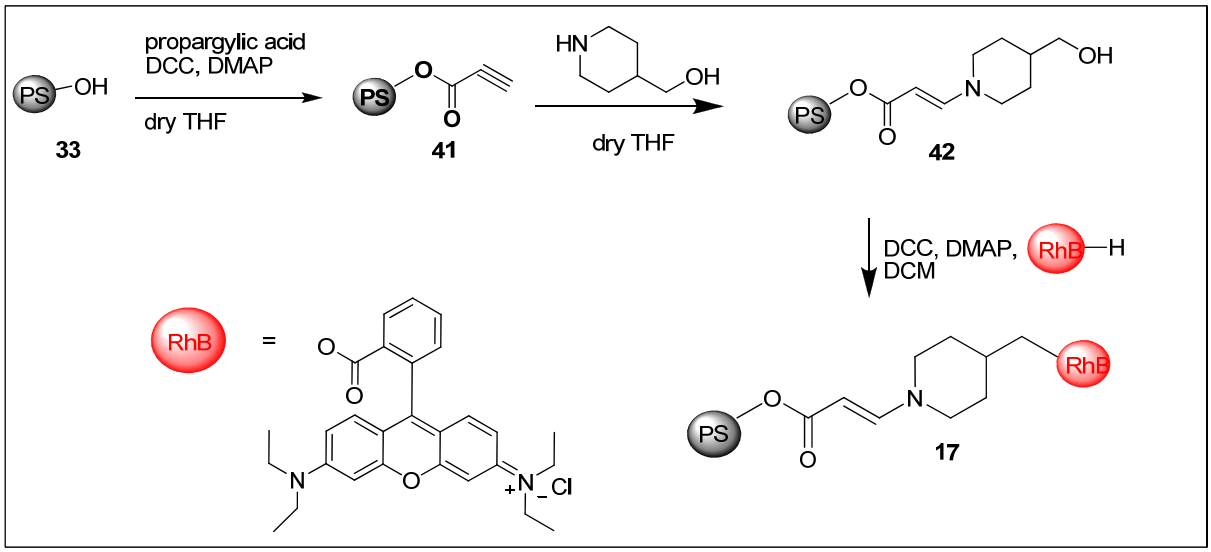
Synthesis

All solvents and reagents were used as obtained from Sigma Aldrich and Thermo Fisher Scientific unless otherwise stated. All reactions were monitored by GC-MS and/or TLC using 5-17 μm silica gel plates with fluorescent indicators from Sigma-Aldrich. All column chromatography was done using 40-63 μm silica gel from Sorbent Technologies. NMR spectra were recorded at 25 ºC using a 400 or 300 MHz Spectrometer. NMR solvents with residual solvent signals were used as internal standards. ESI mass spectral data were collected at facilities at South Dakota State University, University of Oklahoma, or University of Buffalo. GC-MS analyses were performed with HP/agilent 6890A gas chromatograph with an HP/agilent 5973C MSD with EI ion source at the Mass Spectrometry Facility at the University of Oklahoma. UV-Vis and fluorescence data were obtained using Perkin Elmer LAMBDA 25 and LS45 Fluorescence Spectrometer, respectively.









Scheme S1. Synthetic routes of the substrates

Sodium benzenethiolate (43). A solution of thiophenol (4.3 g, 39 mmol) in 5mL of dry diethyl ether was added to a stirring suspension of sodium (0.45 g, 19.5 mmol) in 20 mL of diethyl ether. Stirring was continued until sodium could no longer be seen. The white solid product was filtered and washed with hexane to remove thiophenol and air dried in a desiccator to give compound **43** (2.31 g, 90 %).

(Z)-1,2-Bis(phenylthio) ethene (control). A solution of (*Z*)-1,2-dichloroethene (0.49 g, 5.04 mmol) and compound **43** (2.0 g, 15.15 mmol) in HMPA (10 mL) was stirred under nitrogen for 1 h. The solvent was removed under reduced pressure to give the crude product that was then purified by column chromatography using 100 % hexane as a solvent to give control (1.04 g, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 2H), 7.29 (m, 2H), 7.35 (t, J = 7.7 Hz, 4H), 7.43 (s, 2H), 7.44 (m, 2H). HRMS ESI (m/z): Calculated for $C_{14}H_{12}S_2$ $[M]^+$: 244.0380; found: 244.0377.

Biphenyl-4-yl propiolate (1). To an ice cooled and stirred solution of propargylic acid (285 mg, 4.01 mmol) and 4-phenylphenol (693 mg, 4.07 mmol) in dry diethyl ether was added dropwise a solution of *N,N'*-dicyclohexylcarbodiimide (DCC, 840 mg, 4.07 mmol) and 4-dimethylaminopyridine (DMAP, 3.2 mg, 0.03 mmol) in dry diethyl ether (10 mL) during 2 h under nitrogen atmosphere. Reaction mixture was then stirred at room temperature for 10 h, filtered and the solid was washed with diethyl ether. Then, the combined filtrate was washed with 1 N HCl solution followed by washing with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product that was then purified by column chromatography using ethyl acetate: hexane (1:9) as an eluant to give compound **1** (0.81 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (s, 1H), 7.24 (s, 1H), 7.26 (s, 1H), 7.38 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.57 (s, 1H), 7.59 (s, 1H), 7.62 (s, 1H), 7.64 (s, 1H). HRMS ESI (m/z): Calculated for $C_{15}H_{10}O_2$ ($[M+H]^+$): 223.0681; found: 223.0734.

Biphenyl-4-yl 3-(diethylamino)acrylate (2). Diethylamine (66 mg, 0.89 mmol) and compound **1** (200 mg, 0.89 mmol) were dissolved in dry THF (20 mL), and the solution was stirred at RT for 15 min. The solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography using ethyl acetate:hexane (7:3) to give compound **2** (237 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 6H), 3.28 (br. s , 4H), 4.79 (d, *J* = 13.0 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.62 (m, 4H), 7.63 (d, *J* = 13.0 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{19}H_{21}NO_2$ ($[M+H]^+$): 296.1572; found: 296.1647.

Biphenyl-4-yl 3-(piperidin-1-yl)acrylate (3). The compound **3** was prepared according to the method described for compound **2** employing piperidine (77 mg, 0.89 mmol) and compound **1** (200 mg, 0.89 mmol) to give white solid compound **3** (221 mg, 80%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.67 (br s, 6H), 3.30 (s (b), 4H), 4.83 (d, *J* = 13.1 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.59 (m, 5H). HRMS ESI (m/z): Calculated for $C_{20}H_{21}NO_2$ ($[M+H]^+$): 308.1572; found: 308.1646.

Biphenyl-4-yl 3-(phenylthio)acrylate (4). To a stirred solution of 1,4-diazabicyclo[2.2.2]octane (DABCO, 10 mg, 0.89 mmol) and thiophenol (99 mg, 0.89 mmol) in dry THF (20 mL) at RT was added compound **1** (200 mg, 0.89) dissolved in dry THF (2 mL) through a syringe over 12 min. The reaction mixture was further stirred for 20 min. 10% $NaOH_{(aq)}$ was added. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed by evaporation. The crude product was purified by column chromatography using ethyl acetate:hexane (2:8) as an eluent to give compound **4** (254 mg, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, *J* = 15.0 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.46 (m, 6H), 7.58 (m, 6H), 8.05 (d, *J* = 15.0 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{21}H_{16}O_2S$ ($[M+H]^+$): 333.0871; found: 333.0852.

Biphenyl-4-yl 3-(benzylthio)acrylate (5). The compound **5** was prepared according to the method described for compound **4** employing compound **1** (200 mg, 0.89 mmol) and benzylthiol (112 mg, 0.89 mmol) to give white solid compound **5** (284 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 2H), 6.02 (d, *J* = 15.1 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.39 (m, 8H), 7.57 (t, *J* = 5.9 Hz, 4H), 7.94 (d, *J* = 15.1 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{22}H_{18}O_2S$ ($[M+H]^+$): 347.1028; found: 347.1101.

Biphenyl-4-yl 3-phenoxyacrylate (6). The compound **6** was prepared according to the method described for compound **4** employing compound **1** (435 mg, 2.15 mmol) and phenol (223 mg, 2.36 mmol) to give white solid compound **6** (510 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67

(d, *J* = 12.2 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.33 (q, *J* = 7.9 Hz, 5H), 7.49 (t, *J* = 7.0 Hz, 5H), 7.92 (d, *J* = 12.2 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{21}H_{I6}O_3$ ($[M+H]^+$): 317.1099; found: 317.1175.

Biphenyl-4-yl 3-(benzyloxy)acrylate (7). The compound **7** was prepared according to the method described for compound **4** employing compound **1** (300 mg, 1.34 mmol) and benzylalcohol (161 mg, 1.48 mmol) to give white solid compound **7** (419 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 2H), 5.53 (d, *J* = 12.5 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.39 (m, 8H), 7.57 (t, *J* = 4.8 Hz, 4H), 7.88 (d, *J* = 12.5 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{22}H_{18}O_3$ ($[M+H]^+$): 331.1256; found: 331.1332

(E)-S-Phenyl 3-(piperidin-1-yl)prop-2-enethioate (8). The compound **8** was prepared according to the method described for compound **3** employing piperidine (184 mg, 2.18 mmol) and compound **19** (350 mg, 2.18 mmol) to give pale red solid compound **8** (507 mg, 95%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.64 (s, 6H), 3.27 (s, 4H), 5.11 (d, *J* = 12.6 Hz, 1H), 7.38 (s, 3H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.48 (d, *J* = 12.6 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{14}H_{17}NOS$ ($[M+H]^+$): 248.1031; found: 248.1125.

(E)-N-Phenyl-3-(piperidin-1-yl)acrylamide (9). The compound **9** was prepared according to the method described for compound **3** employing piperidine (211 mg, 2.48 mmol) and compound **20** (360 mg, 2.48 mmol) to give brown solid compound **9** (497 mg, 87 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.62 (s, 6H), 3.20 (s, 4H), 4.73 (d, *J* = 12.6 Hz, 1H), 6.89 (s, 1H), 7.00 (t, *J* = 6.2 Hz, 1H), 7.27 (t, *J* = 6.9 Hz, 2H), 7.43 (d, *J* = 12.6 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 2H). HRMS ESI (m/z): Calculated for $C_{14}H_{18}N_2O$ ($[M+H]^+$): 231.1419; found: 231.1512.

Phenyl 1-(3-(biphenyl-4-yloxy)-3-oxoprop-1-enyl)pyrrolidine-2-carboxylate (10). The compound **10** was prepared according to the method described for compound **13** employing compound **23** (112 mg, 0.36 mmol), compound **1** (82 mg, 0.36 mmol) and 0.06 ml of N, N–diisopropylethylamine to give solid compound **10 (**129 mg, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (m, 2H, pro), 2.38 (br. s, 2H, pro), 3.28-3.83 (m, 2H, pro) 4.49 (br. s, 1H, pro), 4.87 (d, *J* = 12.0 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.31 (m, 2H), 7.41 (q, *J* = 7.5 Hz, 4H), 7.58 (s, 2H), 7.64 (s, 2H), 7.86 (d, *J* = 12.0 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{26}H_{23}NO_4$ ($[M+H]^+$): 414.1627; found: 414.1697.

Phenyl 1-(3-(biphenyl-4-yloxy)-3-oxoprop-1-enyl)pyrrolidine-3-carboxylate (11). The compound **11** was prepared following all the steps described for compound **10** (137 mg, 90 %**).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.71 (m, 1H, pro), 2.45 (br. s, 2H, pro), 3.40-3.95 (m, 4H, pro), 4.78 (d, *J* = 13.0 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.35 (s, 1H), 7.44 (q, *J* = 7.6 Hz, 4H), 7.58 (s, 2H), 7.60 (s, 2H), 7.83 (d, *J* = 13.0 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{26}H_{23}NO_4$ ($[M+H]^+$): 414.1627; found: 414.1700.

(E)-Biphenyl-4-yl 3-(4-((2-phenoxyacetoxy)methyl)piperidin-1-yl)acrylate (12). To a stirred solution of compound **36** (75 mg, 0.49 mmol) and compound **39** (250 mg, 0.74 mmol) in dry dichloromethane (DCM) was added dropwise a solution of DCC (407 mg, 1.98 mmol) and DMAP (60 mg, 0.49 mmol) in dry DCM (15 mL). Reaction mixture was then stirred at room temperature for 24 h. The solvent was removed under reduced pressure to give the crude product that was then purified by column chromatography using ethyl acetate: hexane (6:4) as an eluant to give a white solid compound **12** (279 mg, 80 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.11 (m, 1H), 1.33 (m, 2H), 1.72 (t, *J* = 12.9 Hz, 2H), 1.90 (d, *J* = 9.9 Hz, 1H), 3.05 (br s, 1H), 3.58 (m, 2H), 4.09 (d, *J* = 5.9, 2H), 4.68 (s, 2H), 4.83 (d, *J* = 13.0 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 2H), 7.02

(t, *J* = 7.2, 1H), 7.15 (d, *J* = 8.3, 2H), 7.33 (m, 2H), 7.45 (t, *J* = 7.50, 2H), 7.59 (br s, 5H). HRMS ESI (m/z): Calculated for $C_{29}H_{29}NO_5$ ($[M+H]^+$):472.2046 ; found: 472.2118.

Biphenyl-4-yl 3-(4-(3-phenoxypropyl)piperazin-1-yl)acrylate (13). Compound **30** (150 mg, 0.45 mmol) was dissolved in dry THF (20 mL) with stirring under nitrogen. *N*,*N*-diisopropylethylamine (0.08 mL) was added drop wise and then compound **1** (100 mg, 0.45 mmol) dissolved in dry THF (5 mL) was added. The reaction mixture was stirred at RT for 15 min. After the reaction was completed, solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography using ethyl acetate:hexane (4:6) to give product **13** (173 mg, 87 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.94 (m, 2H), 2.51 (m, 6H), 3.31 (s, 4H), 4.01 (t, *J* = 6.1 Hz, 2H), 4.80 (d, *J* = 13.0 Hz, 1H), 6.89 (m, 3), 7.12 (d, *J* = 8.2 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H) 7.32 (d, *J* = 6.2 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.56 (m, 4H). HRMS ESI (m/z): Calculated for $C_{28}H_{30}N_2O_3$ ($[M+H]^+$): 443.2256; found: 443.2333.

***(E)-Biphenyl-4-yl 3-(4-((2-phenoxy-10,15,20-triphenyl-21,23-dithiaporphyrin acetoxy)methyl)piperidin-1-yl)acrylate* (*14*).** The compound **14** was prepared according to the method described for compound **12** employing compound **37** (80 mg, 0.11 mmol), compound **39** (56 mg, 0.17 mmol), DCC (45 mg, 0.22 mmol) and DMAP (13 mg, 0.11 mmol) to give a solid red purple compound **14** (128 mg, 74%).^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.01 (m, 2H), 1.24 (m, 2H), 1.60 (m, 2H), 1.80 (d, *J* = 12.2 Hz, 2H), 3.34 (m, 1H), 3.97 (br s, 1H), 4.14 (d, *J* = 5.9, 2H), 4.72 (d, *J* = 12.9 Hz, 1H), 4.88 (s, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 7.32 (m, 3H), 7.45 (m, 5H), 7.74 (br s, 9H), 8.16 (m, 8H), 8.62 (m, 4H), 9.64 (m, 4H). HRMS ESI (m/z): Calculated for $C_{67}H_{51}N_3O_5S_2$ ($[M+H]^+$): 1042.3270; found:1042.3343 .

Biphenyl-4-yl 3-(4-(3-(5-(4-phenoxy-10,15,20-triphenyl-21,23-dithiaporphyrin propyl)piperazin-1-yl)acrylate (15). The compound **15** was prepared following all the steps described for compound **13** (39 mg, 65 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (br. s, 2H), 2.52 (br. s, 4H), 2.66 (br. s, 2H), 3.33 (br. s, 2H), 4.15 (br. s, 4H), 4.80 (d, *J* = 13.3 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.17 (s, 1H), 7.26 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.49 (s, 2H), 7.52 (s, 2H), 7.72 (s, 11H) 8.08 (d, *J* = 8.6 Hz, 2H), 8.17 (s, 6H), 8.61 (s, 4H), 9.61 (s, 4H). HRMS ESI (m/z): Calculated for $C_{66}H_{52}N_4O_3S_2$ ($[M+H]^+$): 1013.35; found: 1013.3565.

(E)-((13S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)3-(4-((2-phenoxy-10,15,20-triphenyl-21,23-dithiaporphyrin acetoxy)methyl)piperidin-1-yl)acrylate (16). The compound **16** was prepared according to the method described for compound **12** employing compound **37** (120 mg, 0.17 mmol), compound **40** (108 mg, 0.25 mmol), DCC (68 mg, 0.33 mmol) and DMAP (20 mg, 0.17 mmol) to give a solid red purple compound **16** (211 mg, 75%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.77 (s, 3H), 1.95-1.08 (m, 3H), 1.18-1.39 (m, 7H), 1.55-1.64 (m, 2H), 1.75-1.80 (m, 2H) 1.88-2.08 (m, 2H), 2.18-2.41 (m, 1H), 2.72 (m, 2H), 3.00 (br s, 1H), 3.33 (m, 1H), 3.53 (m, 2H), 3.96 (m, 1H), 4.13 (d, *J* = 6.1 Hz, 2H), 4.69 (d, *J* = 13.3 Hz, 1H), 4.87 (s, 2H), 6.62 (s, 2H), 7.07 (d, *J* = 8.6, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 13.3 Hz, 1H), 7.74 (br s, 9H), 8.12 (d, *J* = 8.6, 2H), 8.16 (m, 6H), 8.63 (m, 4H), 9.64 (m, 4H). HRMS ESI (m/z): Calculated for $C_{73}H_{63}N_3O_6S_2$ ($[M+H]^+$): 1142.4158; found:1142.4233.

PS-L-Rh (17). The compound **17** was prepared according to the method described for compound **12** employing compound **42** (100 mg, 0.12 mmol), Rhodamine B (58 mg, 0.12 mmol), DCC (99 mg, 0.48 mmol) and DMAP (13 mg, 0.01 mmol) to give a solid red purple compound **17** (101 mg, 65%).^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.14 (m, 6H), 1.36 (m, 3H), 1.65 (m, 3H), 1.89 (m,

2H), 2.13 (s, 1H) 2.83 (s, 2H), 2.91 (s, 2H), 3.18(s, 1H), 3.22 (s, 1H), 3.44 (m, 4H), 3.56 (m, 1H), 3.65 (s, 1H), 4.07 (s, 4H), 4.99 (d, J = 13.0 Hz, 1H), 6.65 (s, 4H), 7.13 (d, J = 9.1Hz, 1H) , 7.58 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 13.0 Hz, 1H), 7.84 (s, 10H), 7.97 (s, 1H), 8.13 (d, J = 6.6 Hz, 1H), 8.27 (m, 9H), 8.52 (d, J = 8.2 Hz, 1H) 8.71 (s, 3H), 8.76 (s, 1H), 9.73 (s, 3H), 9.79 (s, 1H). HRMS ESI (m/z): Calculated for $C_{81}H_{70}ClN_5O_5S_2$ ($[M+H]^+$-Cl): 1256.998; found: 1256.4790

S-Phenyl prop-2-ynethioate (19). The compound **19** was prepared according to the method described for compound **1** employing thiophenol (1g, 9.07 mmol), propargylic acid (0.64 g, 9.07 mmol), DCC (1.87g, 9.07 mmol) and DMAP (7.3 mg, 0.06 mmol) to give brownish liquid compound **19** (1.24 g, 84%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.40 (s, 1H), 7.46 (s, 5H).

N-Phenylpropiolamide (20). The compound **20** was prepared according to the method described for compound **1** employing aniline (1g, 0.01mol), propargylic acid (0.76g, 0.01 mol), DCC (2.2g, 0.01) and DMAP (8.6 mg, 0.07 mmol) to give brown solid compound **20** (1.35 g, 87 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.93 (s, 1H), 7.15 (t, J = 6.9 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.52 (t, J = 7.4 Hz, 2H), 7.79 (br s, 1H).

1-(tert-Butoxycarbonyl)pyrrolidine-2-carboxylic acid (21). (*S*)-Proline (2.3 g, 20 mmol) was dissolved in 40 mL of DCM. To the solution, triethylamine (3.73 mL, 26 mmol) and di-*tert*-butyl dicarbonate (6.3 g, 28.9 mmol) dissolved in DCM (5 mL) were added. The mixture was stirred at RT for 2.5 h. Then, the reaction was quenched with saturated aqueous citric acid solution (15 mL), washed with brine (30 mL) and water (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed by evaporation. The white crystallized solid formed

was washed with hexane to obtain compound **21** (3.85 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 2H), 1.75 – 2.39 (m, 4H), 3.22 – 3.54 (m, 2H), 4.21 – 4.39 (m, 1H).

1-tert-Butyl 2-phenyl pyrrolidine-1,2-dicarboxylate (22). Compound **21** (500 mg, 2.32 mmol) and DCC (523 mg, 2.53 mmol) in DCM (12 mL) were stirred at 0 ^{o}C for 30 min under argon atmosphere. To the solution, phenol (199 mg, 2.12 mmol) was added and stirred at RT for 24 h. The reaction mixture was diluted with ethyl acetate (30 mL) and filtered. The combined organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed by evaporation. The crude product was purified by column chromatography using ethyl acetate–hexane (4:6) to give compound **22** as a white solid (492 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.89 – 2.43 (m, 4H), 3.40 – 3.66 (m, 2H), 4.41 – 4.55 (m, 1H), 7.09 (m, 2H), 7.22 (m, 1H), 7.37 (m, 2H).

Phenyl pyrrolidine-2-carboxylate (23). Compound **22** (500 mg, 1.71 mmol) was dissolved in dry DCM (6 mL). Trifluoroacetic acid (0.66 mL, 8.58 mmol) was then added to the solution at 0 ^{0}C and stirred under nitrogen for 1 h. The reaction mixture was then concentrated under vacuum and used directly in the next step without further purification.

1-*tert*-Butyl 3-phenyl pyrrolidine-1,3-dicarboxylate (24) The compound **24** was prepared according to the method described for compound **22** employing1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid (500 mg, 2.32 mmol), phenol (198 mg, 2.12 mmol) and DCC (522 mg, 2.53) to give pale white solid compound **24** (510 mg, 83 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.84 – 1.57 (m, 1H), 2.21(m, 2H), 3.17-3.70 (m, 4H), 7.00 (s, 1H), 7.02 (s, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H).

Phenyl pyrrolidine-3-carboxylate (25).

The compound **25** was prepared according to the method described for compound **23** employing TFA (0.66 mL, 8.58 mmol) and compound **24**(500 mg, 1.71 mmol) to give white solid compound. Compound was used without further purification after solvent removal.

(3-Bromopropoxy)benzene (26). Phenol (1.0 g, 10.6 mmol) was dissolved in acetone (20 mL). Anhydrous potassium carbonate (7.34 g, 53.1 mmol) and 1,3-dibromopropane (8.58 g, 42.5 mmol) was added to the solution. The reaction mixture was refluxed in an oil bath for 12 h. After the reaction, the potassium carbonate was removed by suction filtration and solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography using ethyl acetate:hexane (3:7) to give product **26** (2.05 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (m, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 4.03 (t, *J* = 5.8 Hz, 2H), 6.86 (m, 3H), 7.21 (m, 2H).

5-(3-Bromopropoxy)phenyl-10,15,20-triphenyl-21,13-dithiaporphyrin (27). Compound **27** was prepared according to the method described for compound **26** employing 5-(4-hydroxyphenyl)-10,15,20-triphenyl-21,23dithiaporphyrin (300 mg, 0.45 mmol), 1,3-dibromopropane (364 mg, 1.81 mmol) and potassium carbonate (311 mg, 2.26) to give pale red solid compound **27** (301 mg, 85 %).^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (m, 2H), 3.79 (t, *J* = 6.3 Hz, 2H), 4.41 (t, *J* = 5.6 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.81 (s, 9H), 8.19 (d, *J* = 8.3 Hz, 2H), 8.26 (d, *J* = 3.6 Hz, 6H), 8.68 (s, 3H), 8.70 (s, 1H), 9.70 (s, 3H), 9.73 (s, 1H)

tert-Butyl 4-(3-phenoxypropyl)piperazine-1-carboxylate (28). To a solution of *n*-Boc-piperazine (1.08 g, 5.80 mmol) in dry DMF (10 mL) were added anhydrous potassium carbonate (4.01 g, 29.04 mmol) and compound **26** (1.5 g, 6.97 mmol). The reaction mixture was stirred at RT for 8

h. The potassium carbonate was removed by suction filtration and the solvent was removed under reduced pressure. The residue was dissolved with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed by evaporation. The crude product was purified by column chromatography using ethyl acetate:hexane (8:2) to give compound **28** (1.58 g, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.92 (s, 2H), 2.36 (s, 4H), 2.48 (s, 2H), 3.39 (s, 4), 3.95 (m, 2), 6.83 (m, 2H), 7.19 (m, 3H).

tert-Butyl 4-(5-(3-phenyl-10,15,20-triphenyl-21,13-dithiaporphyrinoxypropyl)piperazine-1-carboxylate (29). The compound **29** was prepared according to the method described for compound **28** employing compound **27** (150 mg, 0.19 mmol), *n*-Boc-piperazine (29 mg, 0.16 mmol) and potassium carbonate (110 mg, 0.80) to give pale red solid compound **29** (128 mg, 75 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.25 (br s, 2H), 2.60 (br s, 4H), 2.77 (br s, 2H), 3.59 (br s, 4H), 4.33(br s, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.80 (s, 9H), 8.16 (d, J = 8.3 Hz, 2H), 8.24 (d, J = 4.0, 6H), 8.68 (s, 4H), 9.68 (s, 4H).

1-(3-Phenoxypropyl)piperazine (30). The compound **30** was prepared according to the method described for compound **23** employing TFA (6 mL) and compound **28**(550 mg, 1.72 mmol) to give white solid compound. Compound was used without further purification after solvent removal

***1-3(-(5-(4-Phenyl)-10,15,20-triphenyl-21,23dithiaporphyrin)oxypropylpiperazine* (31).** Compound **29** (70 mg, 0.09 mmol) was dissolved in dry DCM (6 mL). After trifluoroacetic acid (0.03 mL) was added to the solution at 0 ^{0}C, it was stirred under nitrogen for 1 h. The reaction mixture was then concentrated under vacuum and then used directly in the next step.

5-(4-Methoxyphenyl)-10,15,20-triphenyl-21-23-dithiaporphyrin (32). Compound **32** was prepared following reference.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 3H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 9H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.16 (m, 6H), 8.63 (m, 4H), 9.64 (m, 4H). HRMS ESI (m/z): Calculated for $C_{45}H_{30}N_2OS_2$ ($[M+H]^+$): 679.1878; found: 679.186.

5-(4-Hydroxyphenyl)-10,15,20-triphenyl-21,23dithiaporphyrin (33). Compound **33** was prepared following reference.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 9H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.16 (m, 6H), 8.63 (m, 4H), 9.64 (m, 4H). HRMS ESI (m/z): Calculated for $C_{44}H_{28}N_2OS_2$ ($[M+H]^+$): 665.1721; found: 665.1708.

Ethyl 2-phenoxyacetate (34). The compound **34** was prepared according to the method described for compound **26** employing phenol (4.5 g, 0.05 mol), ethyl bromoacetate (31 g, 0.19 mol) and potassium carbonate (33 g, 0.24 mol) to give a colorless oily compound **34** (6.9 g, 81 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.30 (t, *J* = 7.0 Hz, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 4.62 (s, 2H), 6.91 (d, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 7.0 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H).

Ethyl 5,10,15-triphenyl-20-(4-carboxylatomethoxy)phenyl-21,23-dithiaporphyrin (35). The compound **35** was prepared according to the method described for compound **26** employing compound **33** (0.25 g, 0.38 mol), ethyl bromoacetate (2.1 mL, 19 mmol) and potassium carbonate (2.6 g, 19 mmol) to give purple solid compound **35** (0.22 g, 78 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.42 (t, *J* = 7.0 Hz, 3H), 4.42 (q, *J* = 7.0 Hz, 2H), 4.92 (s, 2H), 7.37 (d, *J* = 8.2,

2H), 7.81 (br s, 9H), 8.19 (d, *J* = 8.2, 2H), 8.26 (m, 6H), 8.69 (m, 4H), 9.70 (m, 4H). HRMS ESI (m/z): Calculated for $C_{48}H_{34}N_2O_3S_2$ ($[M+H]^+$): 751.2011; found:751.2065 .

2-Phenoxyacetic acid (36). Compound **34** (2 g, 0.011 mol) was dissolved in 100 mL of THF, and 1 M NaOH (110 mL, 0.11 mol) was added. The reaction mixture was stirred at RT for 24 h. The solution was then acidified by the addition of 40 mL of acetic acid. The reaction mixture was diluted with 150 mL of H_2O and the product was extracted with ethyl acetate. The organic extracts was dried over magnesium sulfate and concentrated. The crude product was washed several times with hexane:ethylacetate (9:1) to give a pale white solid (1.58 g, 94 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 4.69 (s, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 7.03 (t, *J* = 7.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H),

5,10,15-Triphenyl-20-(4-carboxylatomethoxy)phenyl-21,23-dithiaporphyrin **(37)**.The compound **37** was prepared according to the method described for compound **36** employing compound **35** (0.18 g, 0.24 mmol), 1 M NaOH (20 mL, 20 mmol) and 8 mL of acetic acid to a purple solid compound **37** (0.16 g, 92 %). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 5.00 (s, 2H), 7.42 (d, *J* = 7.8, 2H), 7.80 (br s, 9H), 8.21 (br s, 8H), 8.67 (s, 4H), 9.70 (s, 4H).

(13S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-ylpropiolate (38). The compound **38** was prepared according to the method described for compound **1** employing estrone (500 mg, 1.85 mmol), propargylic acid (262 mg, 3.69 mmol), DCC (763 mg, 3.69 mmol) and DMAP (2.98 mg, 0.03 mmol) and dry DMF (10 mL) to give white solid compound **38** (417 mg, 70%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.84 (s, 3H), 1.52 (m, 5H), 1.85-2.51 (m, 8H), 2.84 (s, 2H), 2.99 (s, 1H), 6.81 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.24 (d,

J = 8.9 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{21}H_{22}O_3$ ($[M+H]^+$): 323.1569; found: 323.1660.

(E)-Biphenyl-4-yl 3-(4-(hydroxymethyl)piperidin-1-yl)acrylate (39). The compound **39** was prepared according to the method described for compound **2** employing piperidin-4-ylmethanol (900 mg, 4.05mmol) and compound **1** (466 mg, 4.05 mmol) to give white solid compound **39** (1.15 g, 84%).^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.29 (m, 1H), 1.80 (m, 2H), 3.08 (br s, 1H), 3.51 (s, 2H), 3.62 (d, *J* = 9.9 Hz, 2H), 4.82 (d, *J* = 13.0 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.35 (m, 1H), 7.45 (t, *J* = 7.0 Hz, 2H), 7.60 (br s, 5H). HRMS ESI (m/z): Calculated for $C_{21}H_{23}NO_3$ ($[M+Na]^+$):338.1678 ; found: 338.1751.

(E)-((13S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl) 3-(4-(hydroxymethyl)piperidin-1-yl)acrylate (40) The compound **40** was prepared according to the method described for compound **2** employing piperidin-4-ylmethanol (61 mg, 0.53 mmol) and compound **38** (170 mg, 0.53 mmol) to give white solid compound **40** (212 mg, 92%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.91 (s, 3H), 1.20-1.37 (m, 3H), 1.46 (s, 2H), 1.50 (s, 2H), 1.57-1.74 (m, 4H) 1.79 (s, 1H), 1.83 (s, 1H), 1.91 (d, *J* = 11.4 Hz, 1H), 1.98-2.17 (m, 3H), 2.24-2.54 (m, 3H), 2.90 (m, 2H), 3.01(s, 1H), 3.50(s, 2H), 3.60 (d, *J* = 11.1, 2H), 4.78 (d, *J* = 12.9 Hz, 1H), 6.79 (s, 2H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 12.9 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{27}H_{35}NO_4$ ($[M+Na]^+$): 460.2566; found: 460.2452.

Compound 41. The compound **41** was prepared according to the method described for compound **1** employing compound **33** (600 mg, 0.902 mmol), propargylic acid (320 mg, 4.51 mmol), DCC (930 mg, .4.51 mmol) and DMAP (11 mg, 0.09 mmol) and dry THF (10 mL) to give red purple solid compound **41** (400 mg, 70%). **.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.1 (s, 1),

4.89 (d, *J* = 12.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H) , 7.64 (d, *J* = 12.8 Hz, 1H), 7.75 (m, 9H), 8.17 (m, 8H), 8.61 (m, 3H), 8.67 (d, *J* = 4.5 Hz, 1H) 9.63 (m, 3H) 9.71 (d, *J* = 4.5 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{47}H_{28}N_2O_2S_2$ ($[M+H]^+$): 717.1592; found: 717.1591

Compound 42. The compound **42** was prepared according to the method described for compound **2** employing piperidin-4-ylmethanol (64 mg, 0.56mmol) and compound **41** (400 mg, 0.56 mmol) to give red purple solid compound **42** (395 mg, 85%).^{1}H NMR (300 MHz, CD_2Cl_2) δ1.02 (m, 2H), 1.26 (m, 2H), 1.59 (m, 2H), 1.79 (m, 2H), 3.34 (m, 1H) 3.45 (m, 1H), 3.95 (s, 1), 4.89 (d, *J* = 12.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H) , 7.64 (d, *J* = 12.8 Hz, 1H), 7.75 (m, 9H), 8.17 (m, 8H), 8.61 (m, 3H), 8.67 (d, *J* = 4.5 Hz, 1H) 9.63 (m, 3H) 9.71 (d, *J* = 4.5 Hz, 1H). HRMS ESI (m/z): Calculated for $C_{53}H_{41}N_3O_3S_2$ ($[M+H]^+$): 832.2589; found: 832.2683.

General photooxygenation procedure. In a NMR tube, an olefin (0.0048 mmol) was dissolved in $CDCl_3$ (0.5 mL). The photosensitizer compound (**32)**, 3 mg, 0.0048 mmol] was added to this solution. Then, the reaction mixture was irradiated for 25 min using a diode laser (690 nm, 200 mW/cm^2). The reaction of olefins with singlet oxygen was monitored by the decrease of olefinic peaks in ^{1}H-NMR spectra. In the case of compound **14**, **15** and **16** no photosensitizer was added,

Procedure for monitoring the cleavage of the linker (PS-L-Rh) by fluorescence emission intensity affected by FRET

Stock solutions of compound **17** (2 mM) was prepared in DMSO. 50 µl of stock solutions was then diluted with 950 µl either chloroform or Dulbecco's Modified Eagle Medium with 5% fetal bovine serum to give 100 µM solutions. The resulting solution was irradiated using a diode laser (690 nm, 200 mW/cm^2). 10 µl was taken every 10 min and 990 µl of chloroform was added. The solutions were excited at 525 nm and the fluorescence measured from 550 nm to 750 nm.

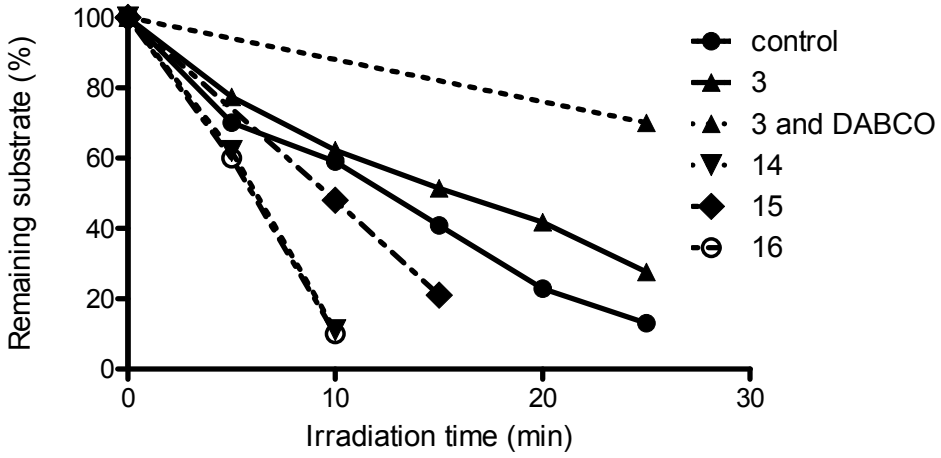
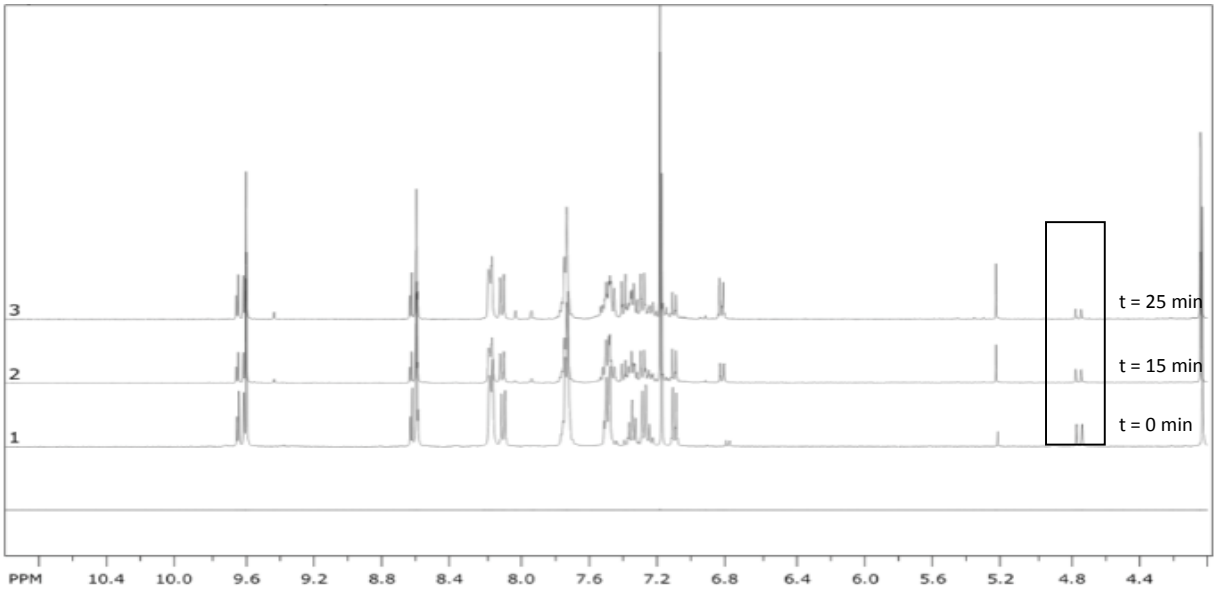


Figure S1. Time-dependent photo-oxidation of model compounds [control = (*Z*)-1,2-Bis(phenylthio)ethylene].

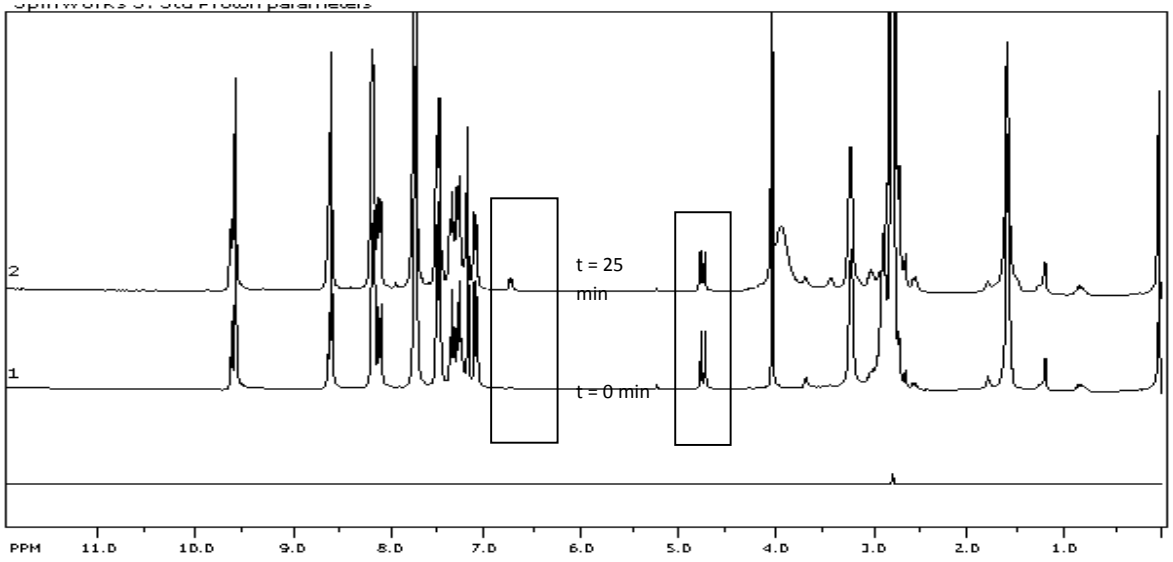
Table S1. Percentile of remaning compounds 2-16 at different time point during irradiation (690 nm diode laser, 200 mW/cm^2; *: not determined)

	0 min	**5 mim**	**10 min**	**15 min**	**20 min**	**25 min**
control	100	70	59	41	23	13
2	100	83	69	58	51	38
3	100	77	62	51	42	28
4	100	-*	-	-	-	100
5	100	-	-	-	-	100
6	100	-	-	-	-	100
7	100	-	-	-	-	100
8	100	-	-	-	-	40
9	100	-	-	-	-	0
10	100	-	-	-	-	60
11	100	-	-	-	-	38
12	100	-	-	-	-	41
13	100	-	-	-	-	50
14	100	62	11	-	-	-
15	100	-	48	21	-	-
16	100	60	10	-	-	-

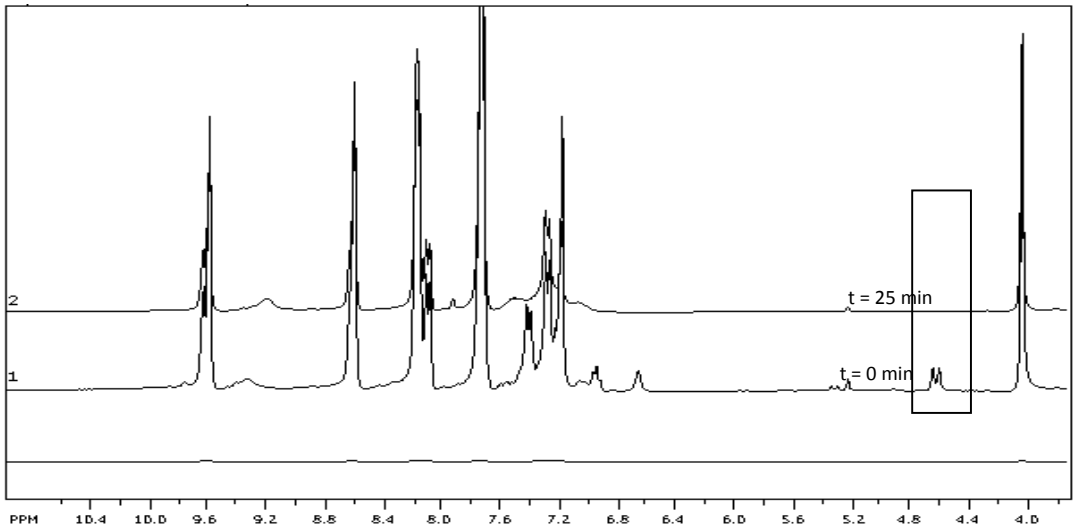
^{1}H-NMR spectra of the photo-oxidation of 3



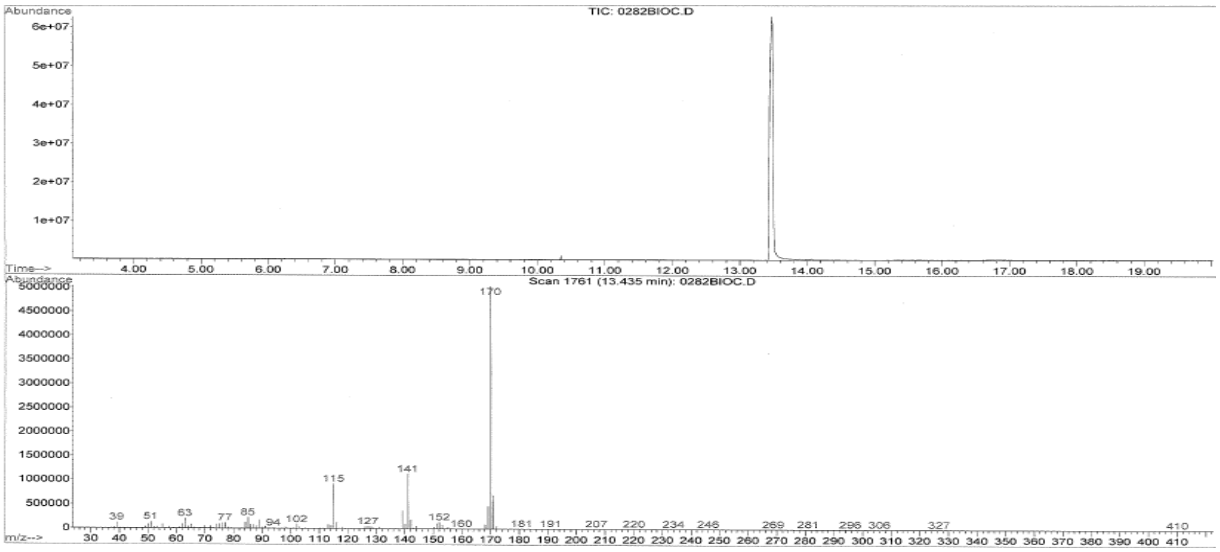
^{1}H-NMR spectra of the photo-oxidation of 3a



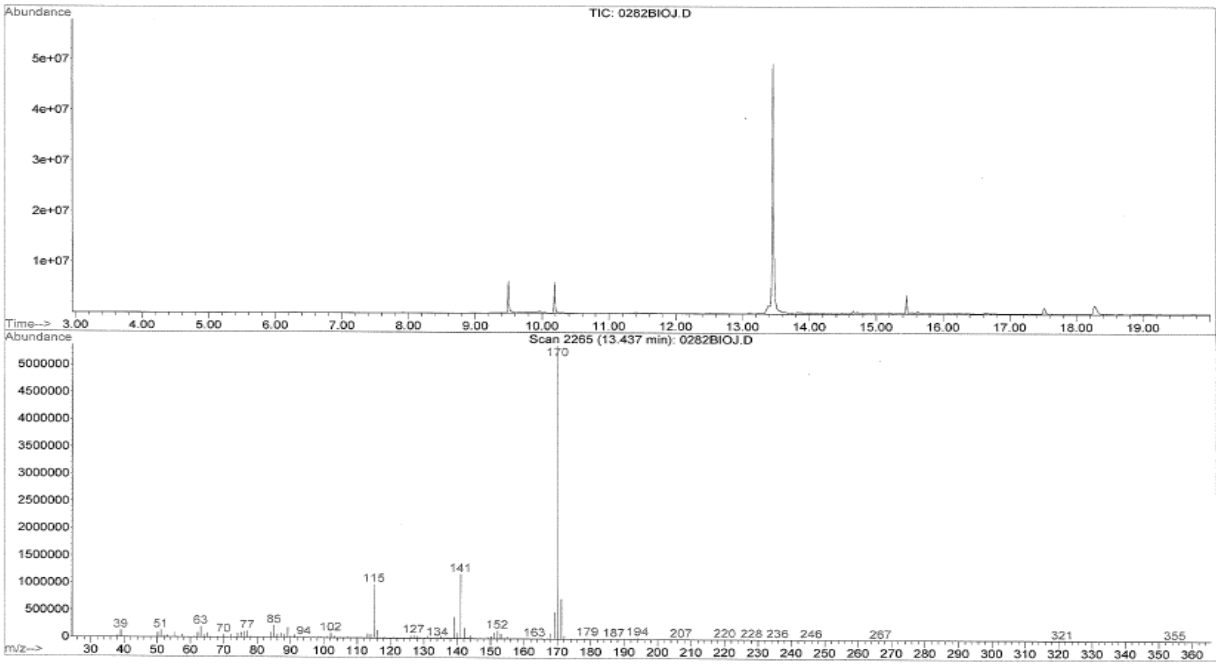
^{1}H-NMR spectra of the photo-oxidation of 9



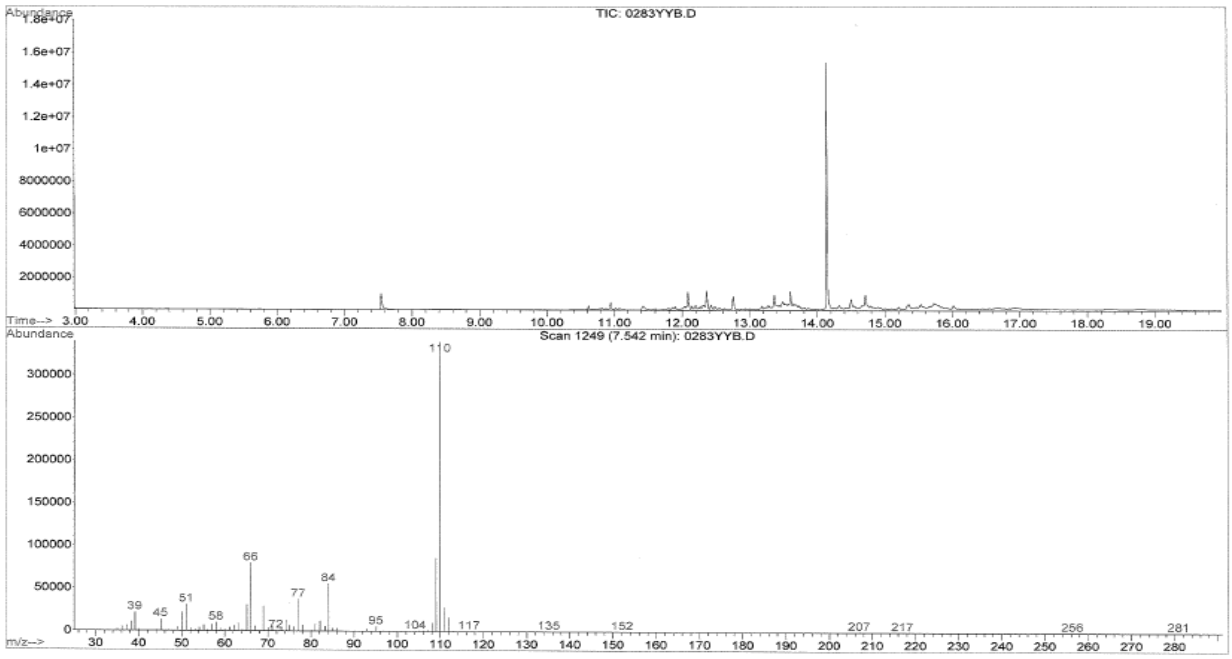
GC-MS data of 4-phenylphenol standard sample (retention time = 13.43 min, MW = 170)



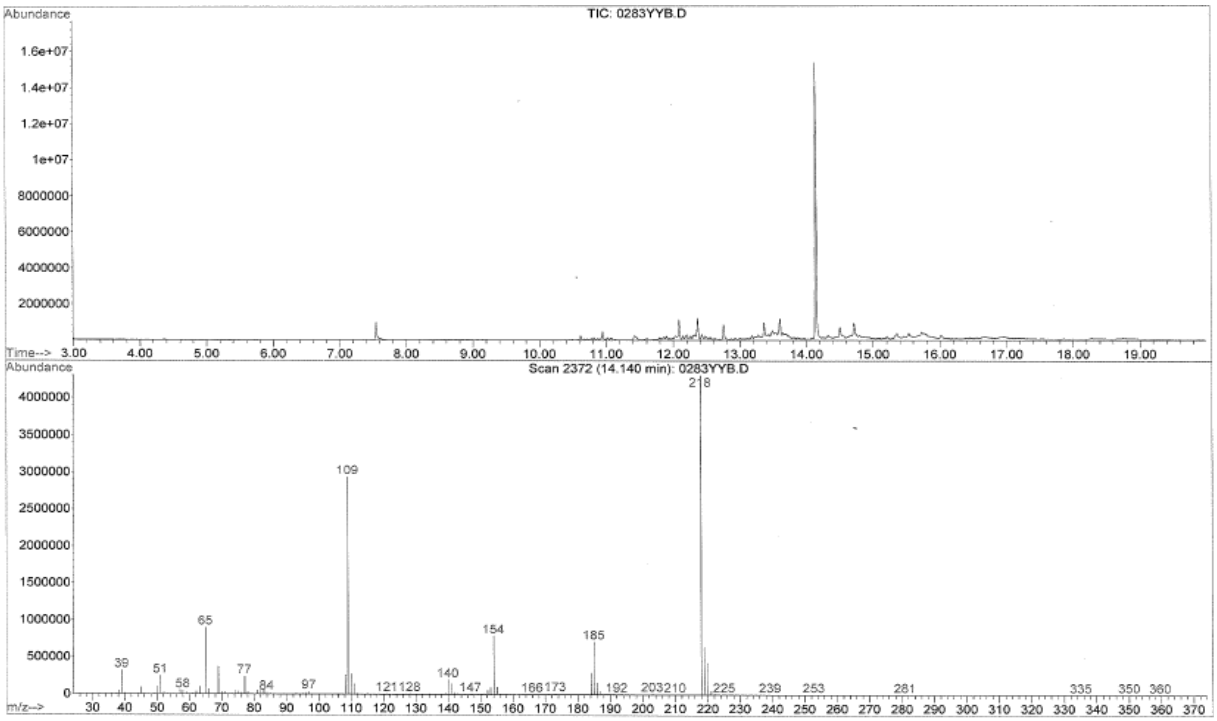
GC-MS data of cleavage mixture of compound 3 (4-phenylphenol peak observed: retention time = 13.43 min, MW = 170)



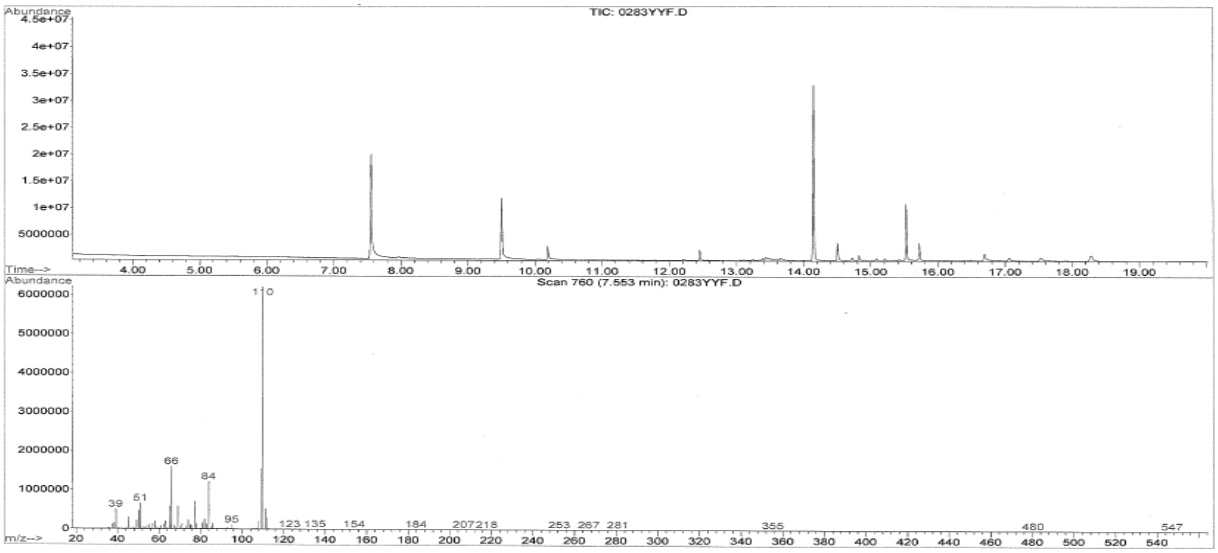
GC-MS data of thiophenol standard sample (retention time = 7.54 min, MW = 110)



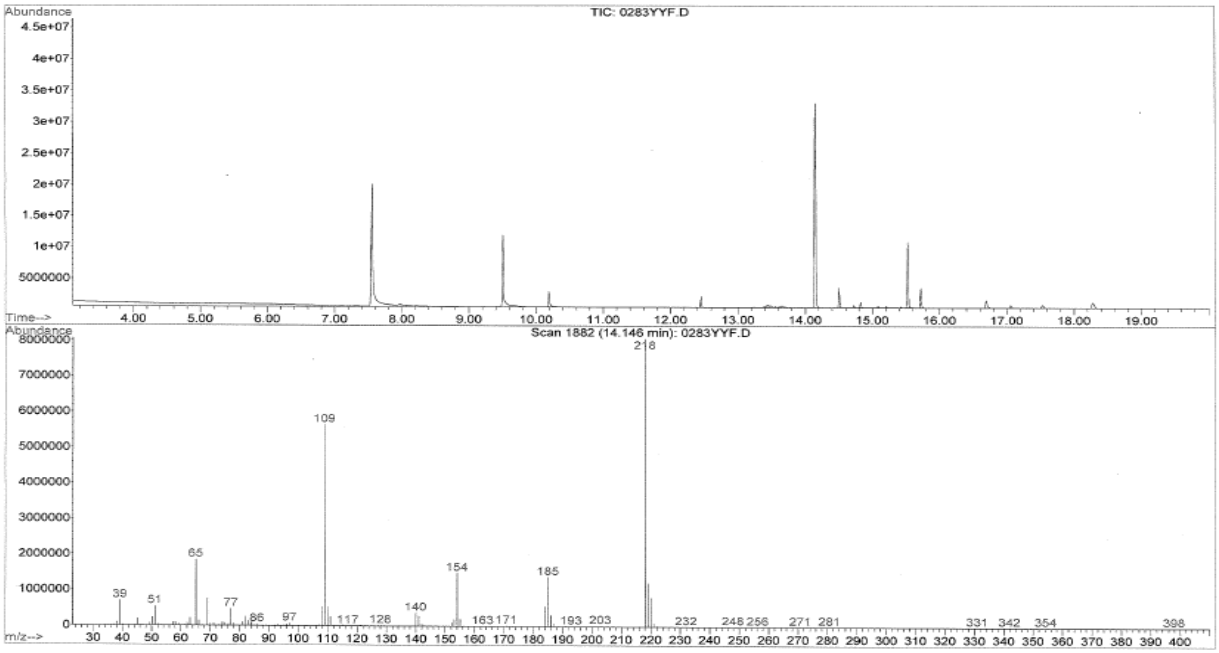
GC-MS data of thiophenol standard sample (diphenyl disulfide observed, retention time = 14.14 min, MW = 218)



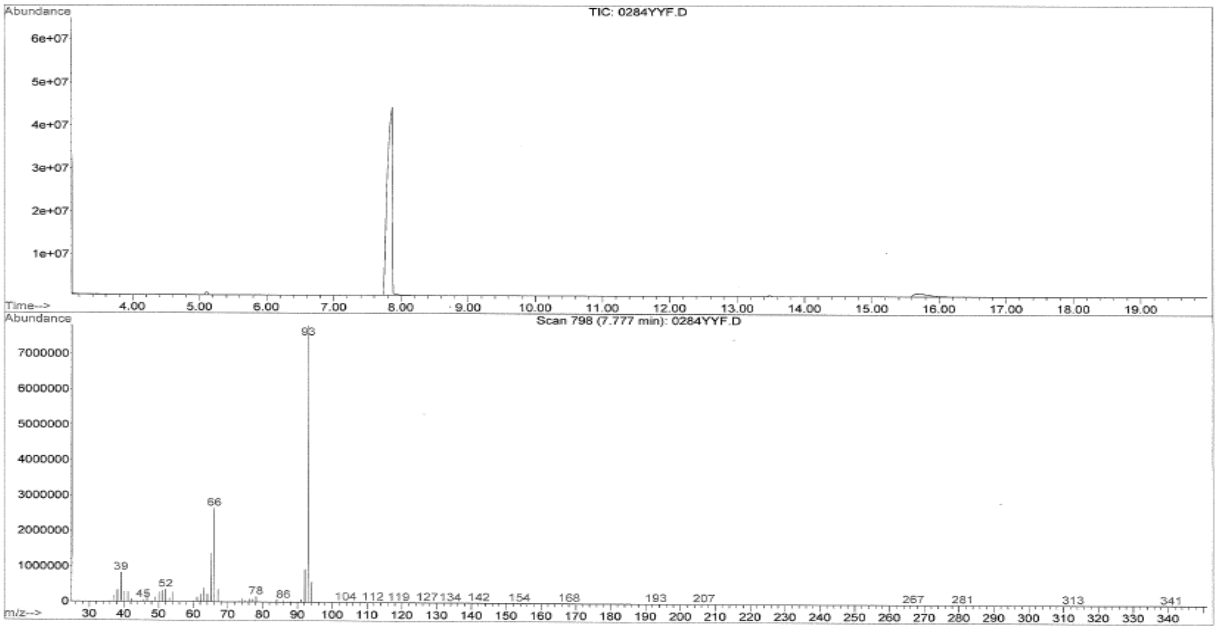
GC-MS data of the cleavage mixture of 8 (thiophenol observed: retention time = 7.55 min, MW = 110)



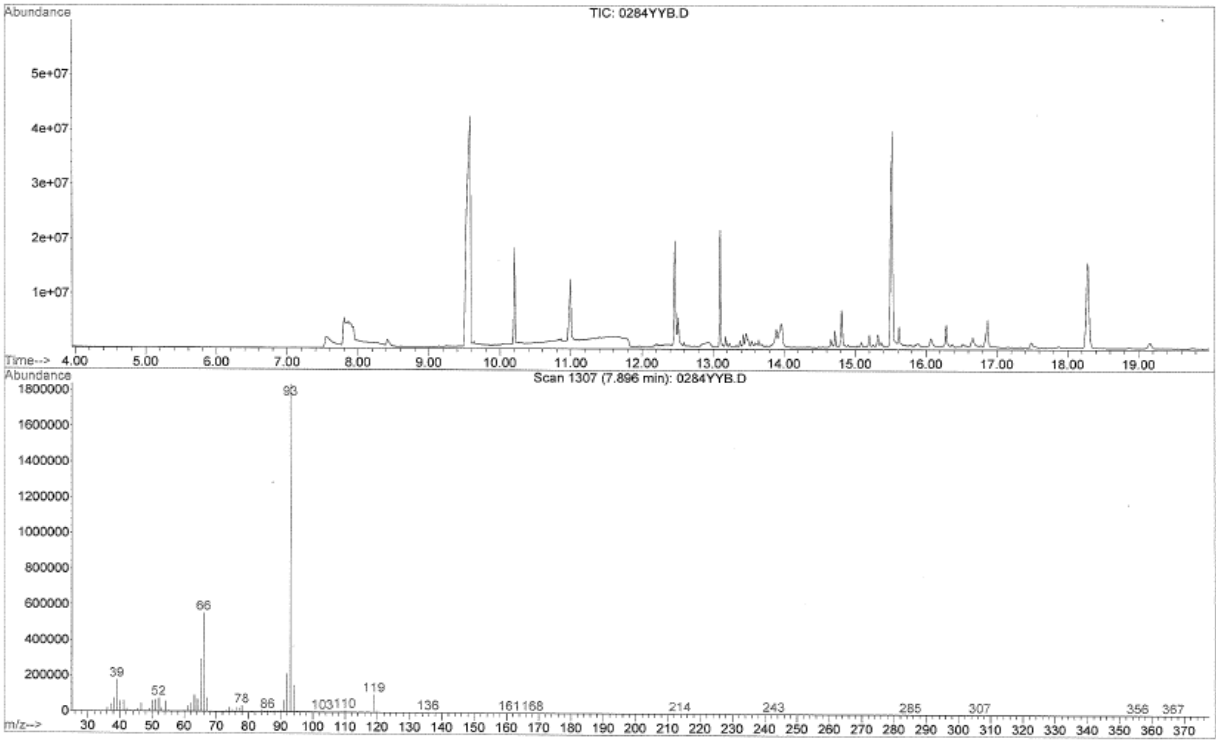
GC-MS data of the cleavage mixture of 8 (diphenyl disulfide observed: retention time = 14.14 min, MW = 218)



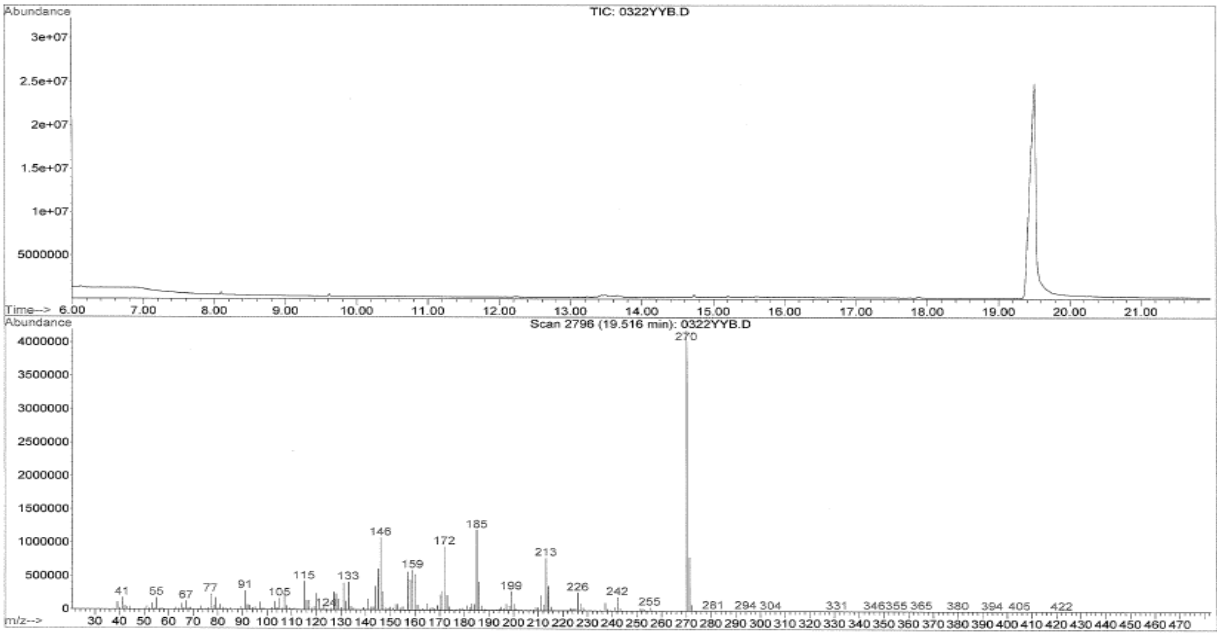
GC-MS data of aniline standard sample (retention time =7.77 min, MW = 93)



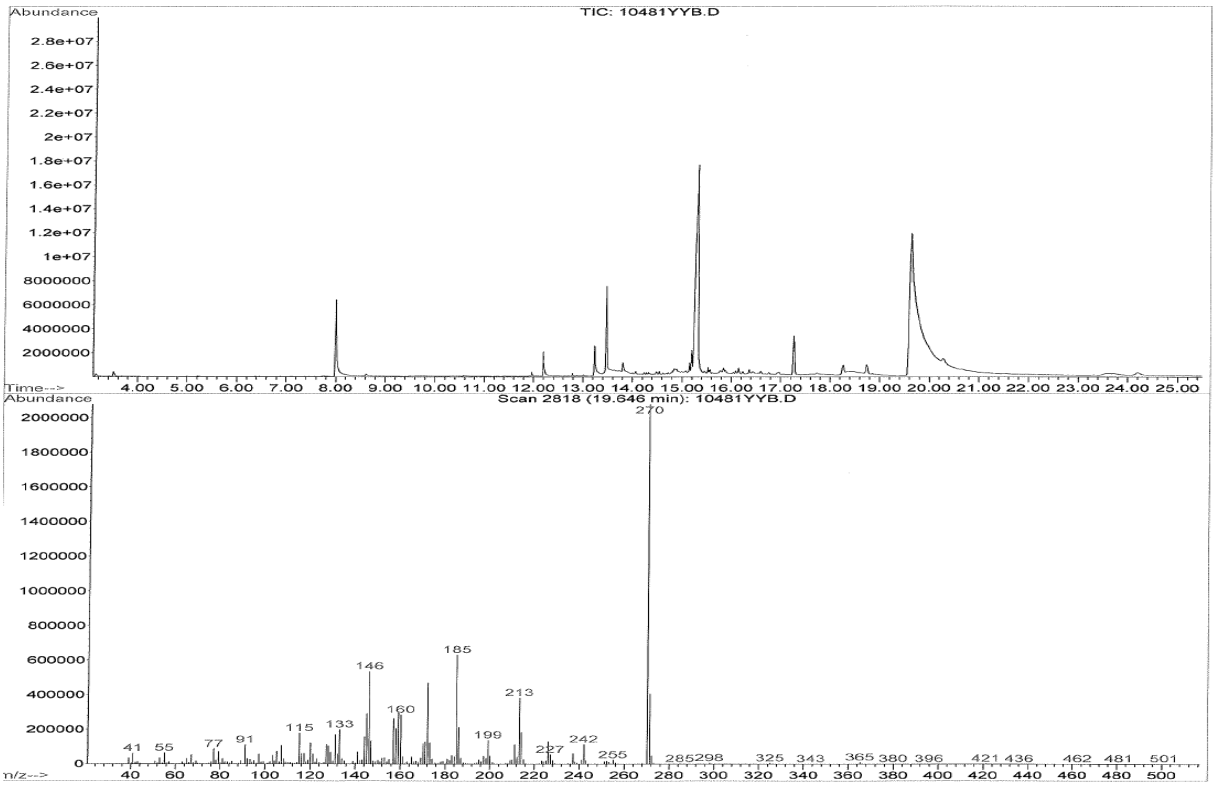
GC-MS data of the cleavage mixture of 9 (aniline observed: retention time = 7.89 min, MW = 93)



GC-MS data of Estrone standard sample (retention time = 19.51 min, MW = 270)

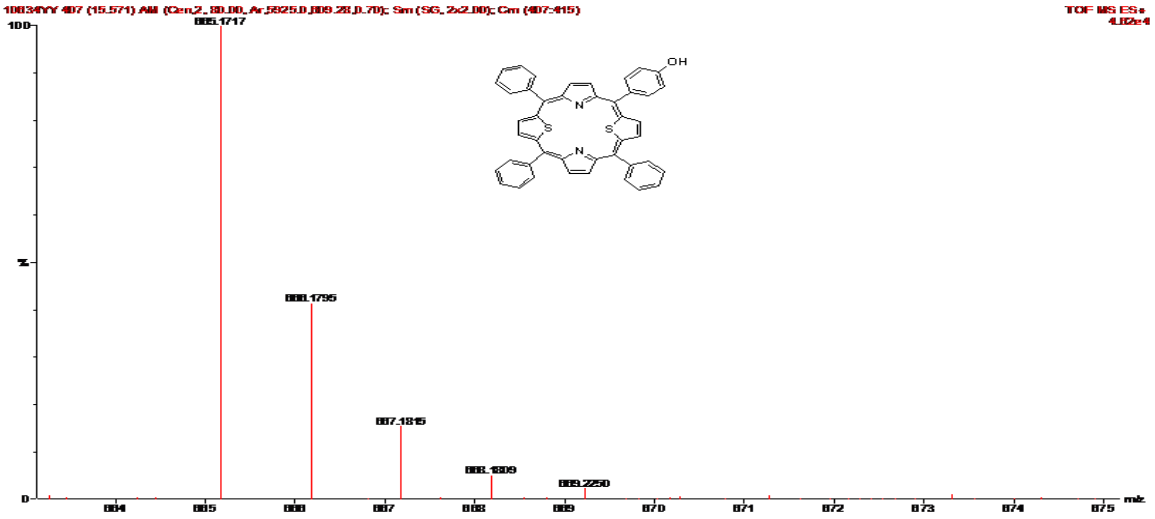


GC-MS data of the cleavage mixture of 16 (Estrone observed: retention time = 19.6min, MW = 270)



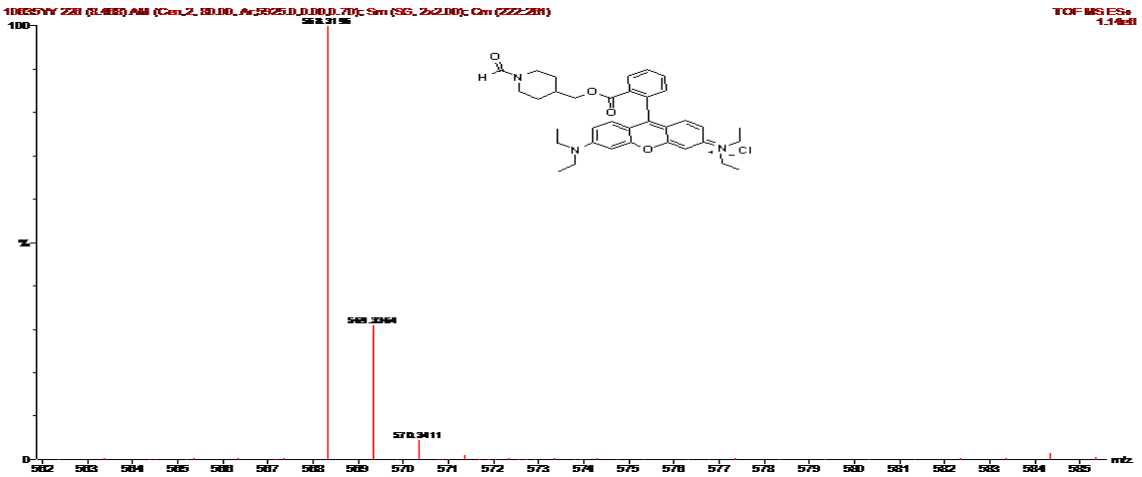
Mass data of isolated cleaved product 5-(4-Hydroxyphenyl)-10,15,20-triphenyl-21,23-dithiaporphyrin form the oxidation of **17**

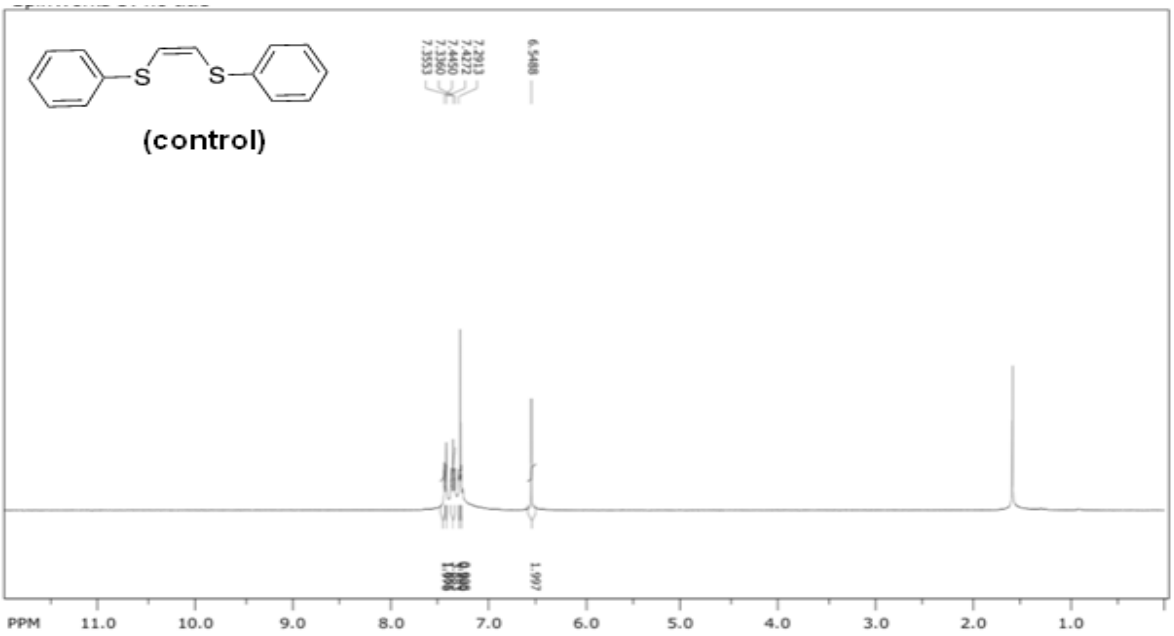
Calculated for $C_{44}H_{28}N_2OS_2$ ($[M+H]^+$):665.1643 ; found: 665.1717

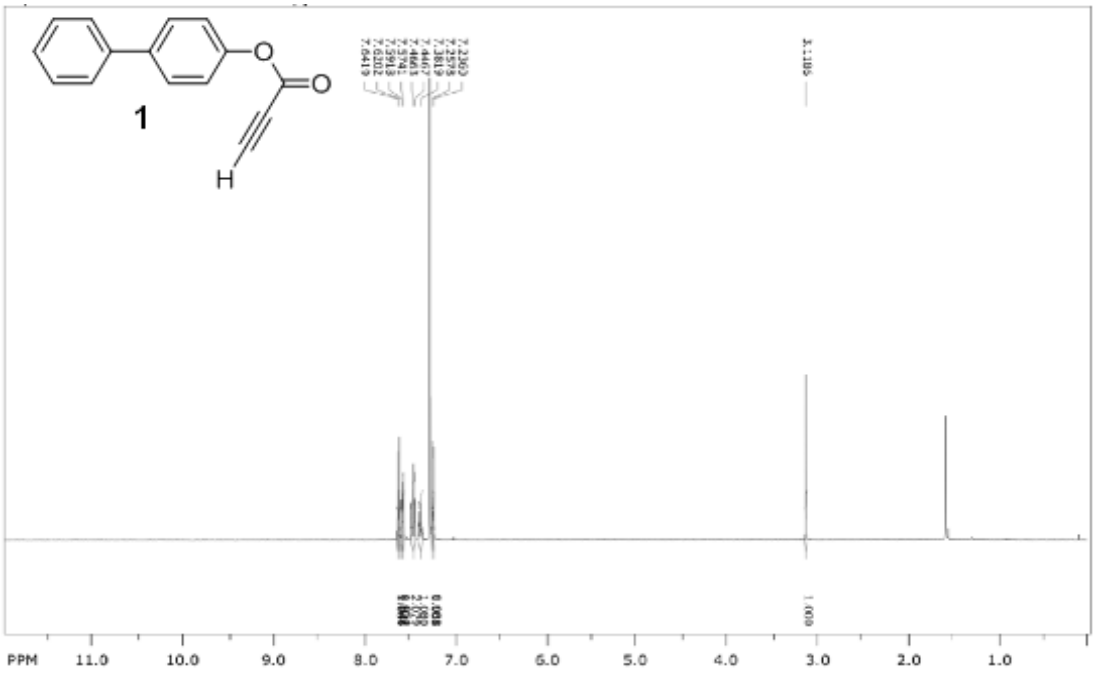


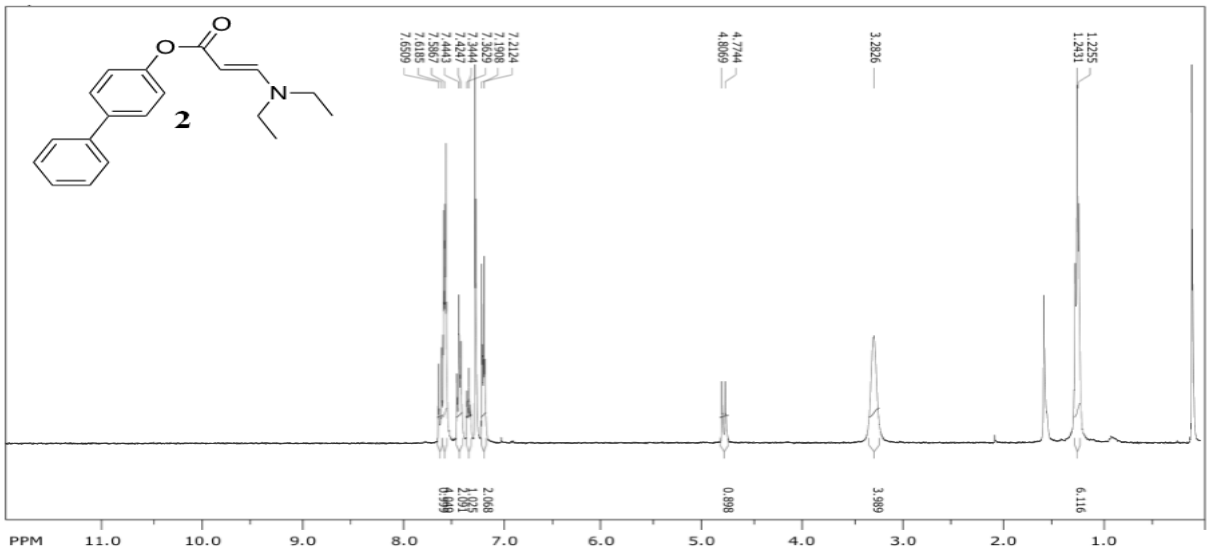
Mass data of isolated cleaved product N-(6-(diethylamino)-9-(2-(((1-formylpiperidin-4-yl)methoxy)carbonyl)phenyl)-3H-xanthem-3-ylidene)-N-ethylethanaminium chloride from the oxidation of **17.**

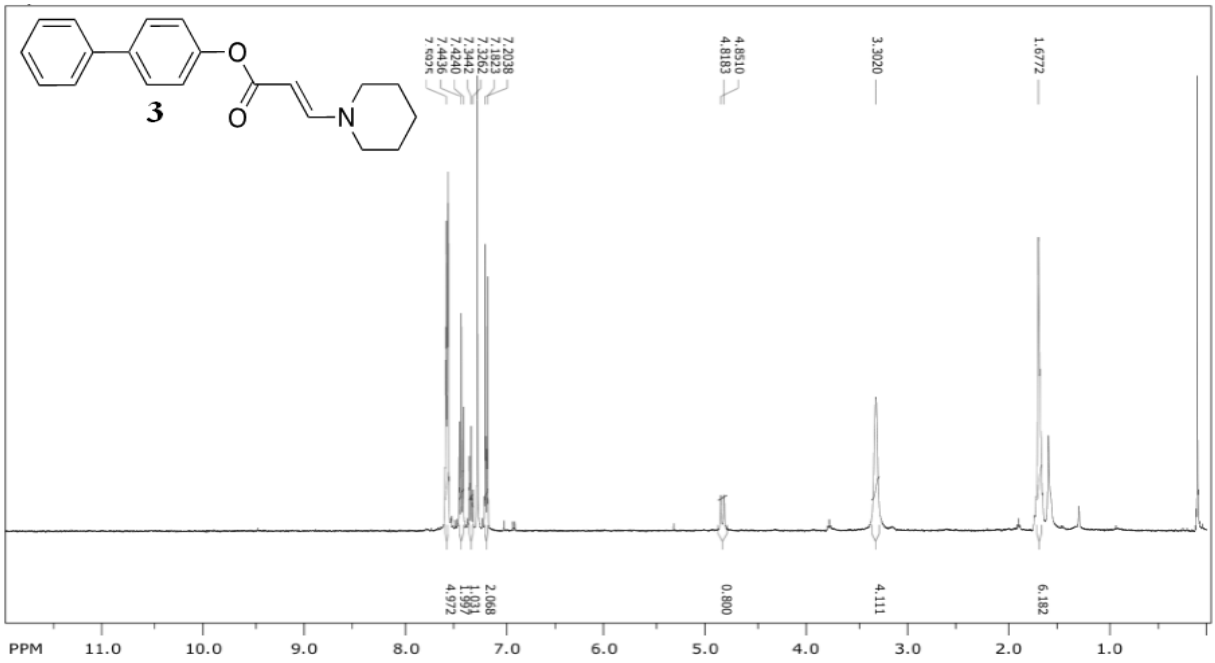
Calculated for $C_{35}H_{42}ClN_3O_4$ ($[M+H]^+$-Cl):568.833 ; found: 568.3196

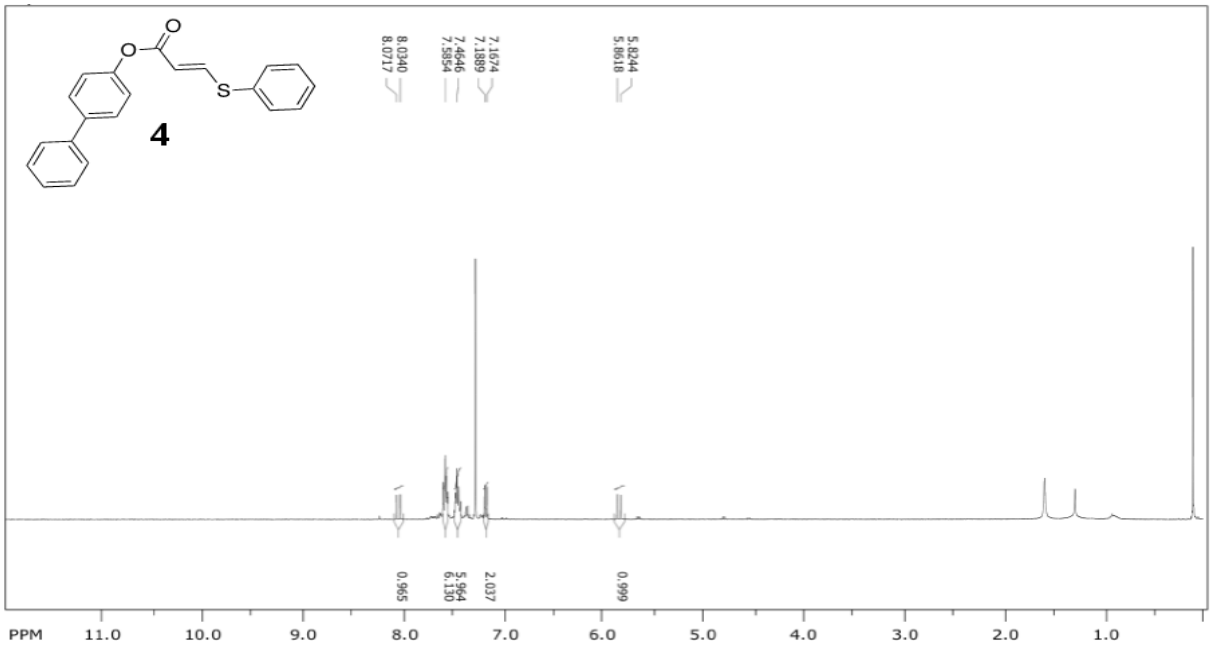


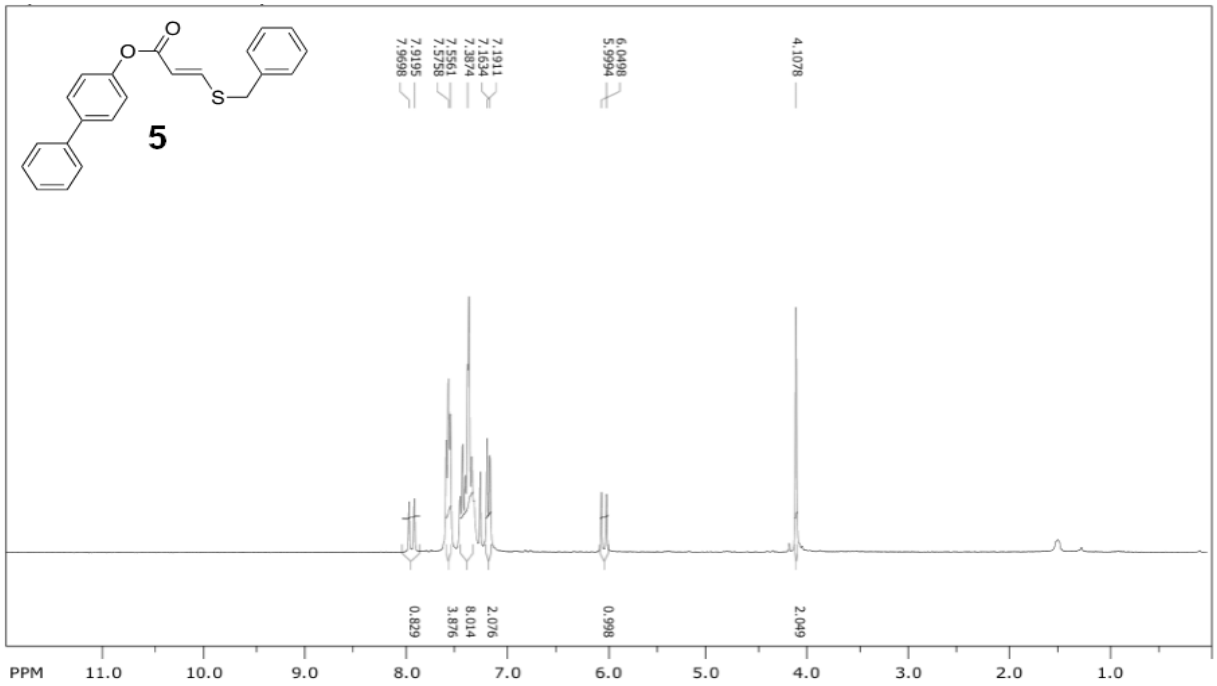


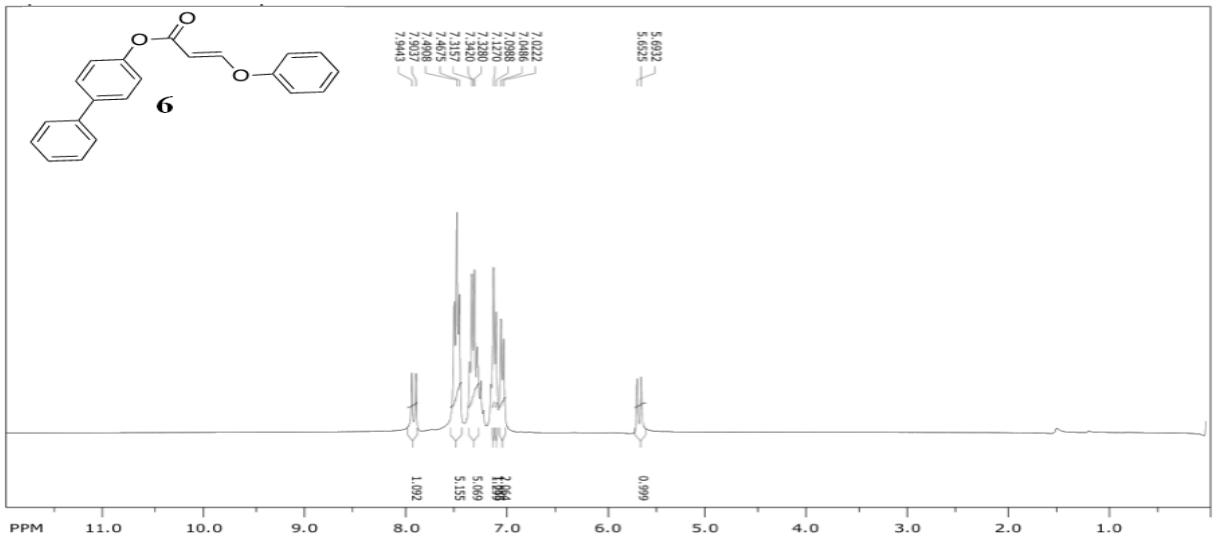


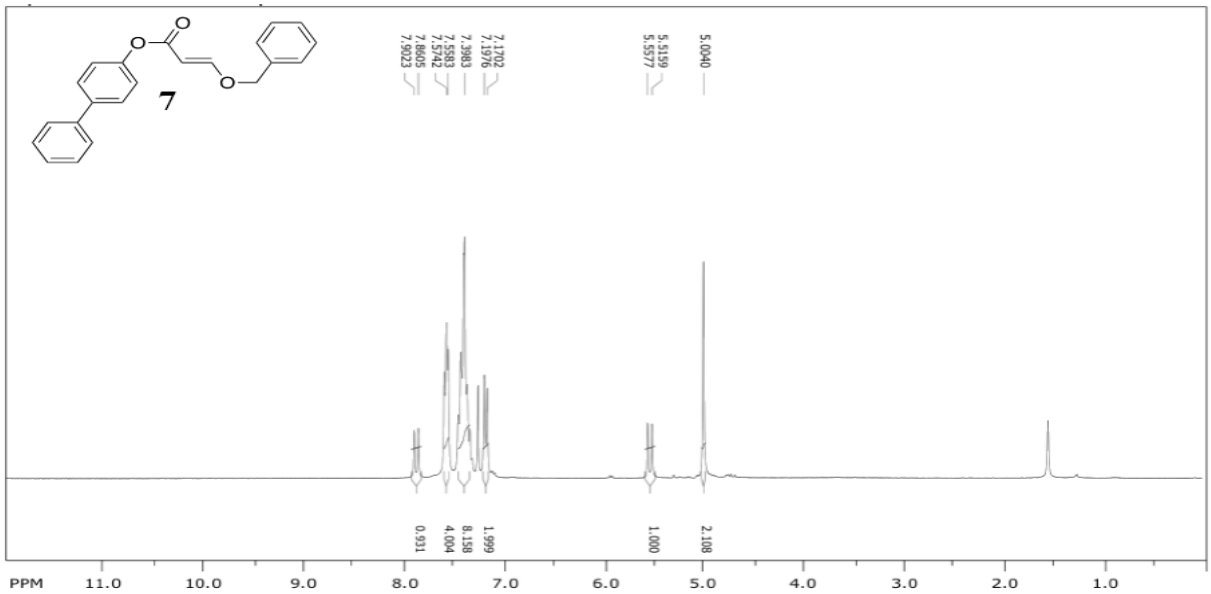


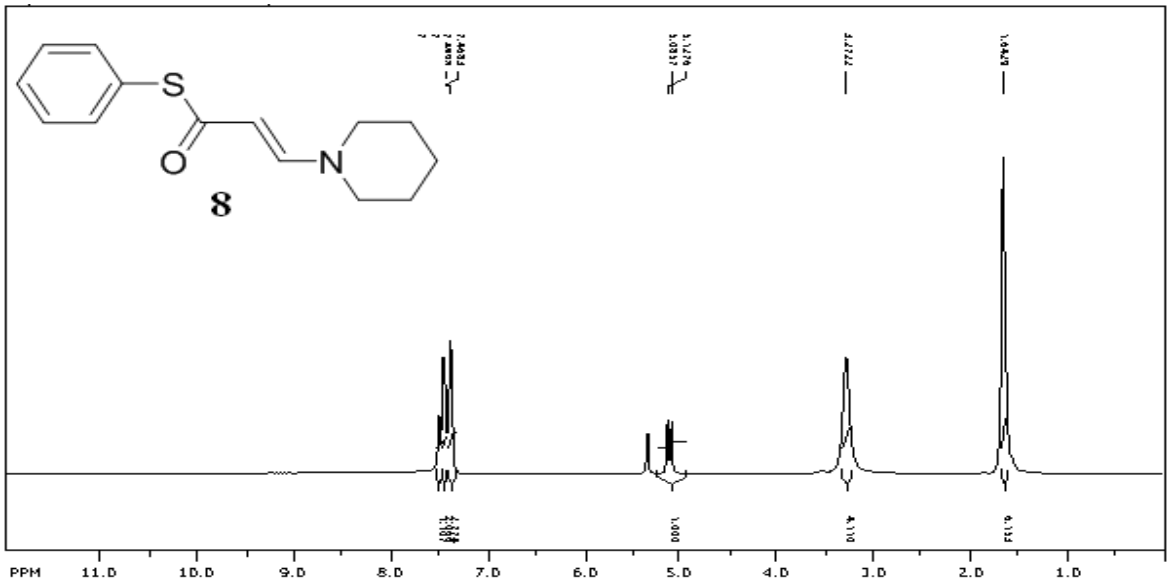


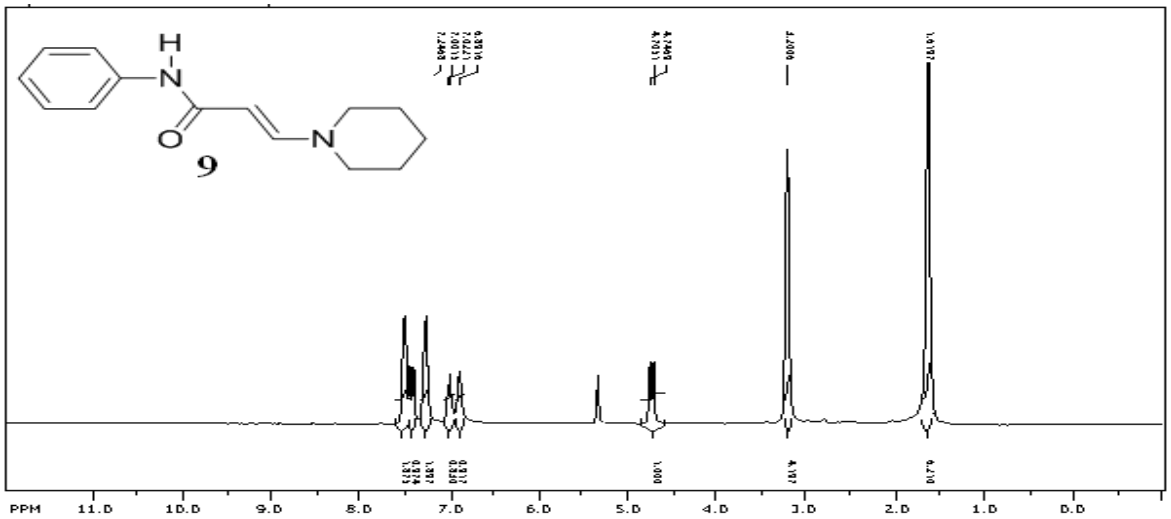


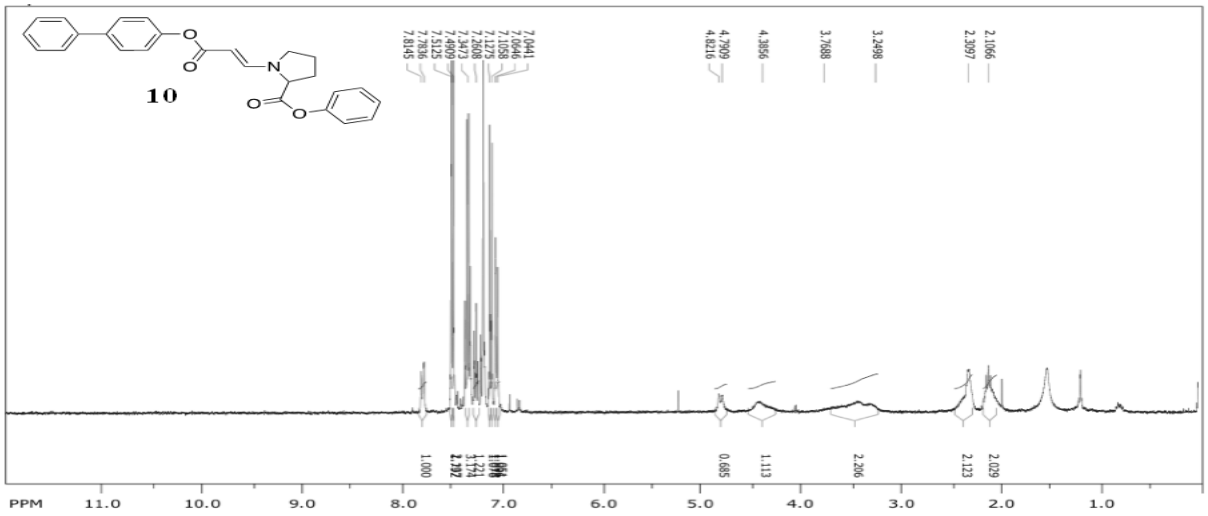








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7.0046
4.7709
4.6816
4.3856
3.7688
3.2498
2.3997
2.1066
1.000
0.685
1.113
2.286
2.123
2.029
PPM
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10.0
9.0
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6.0
5.0
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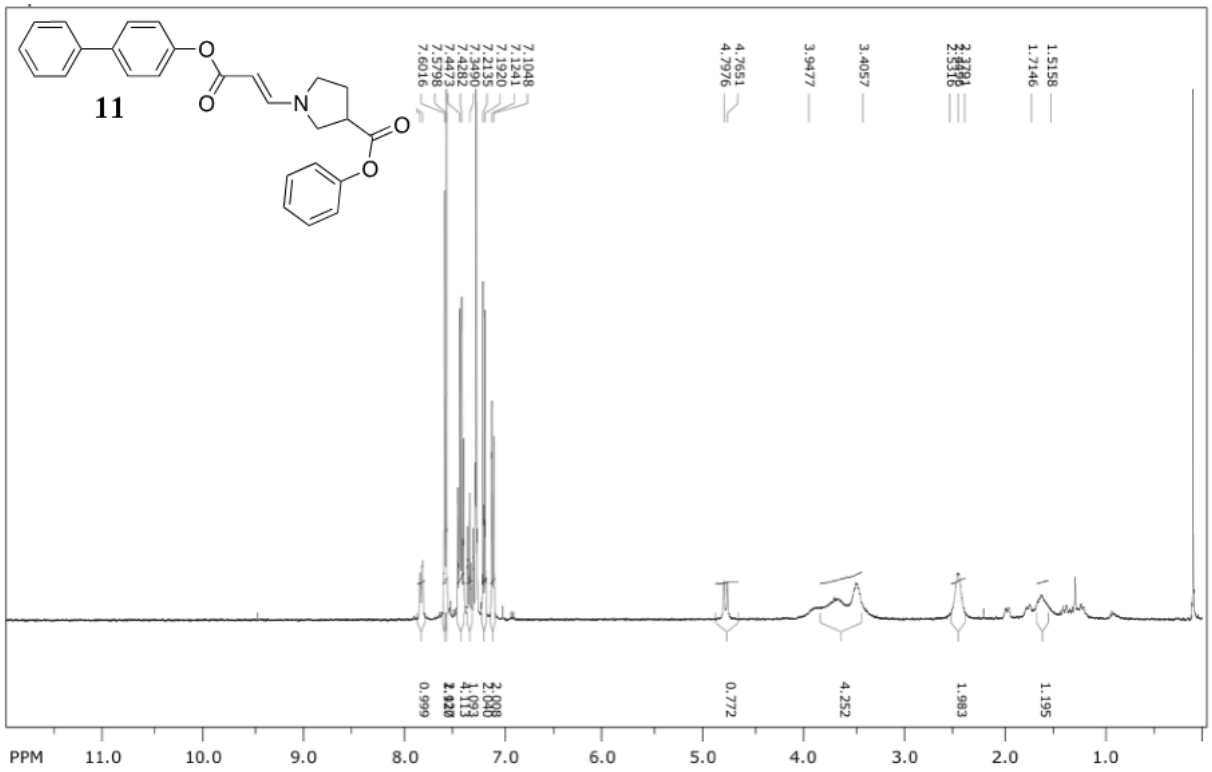
2.0
1.0


11
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4.7651
3.9477
3.4057
1.7146
1.5158
0.999
0.772
4.252
1.983
1.195
PPM
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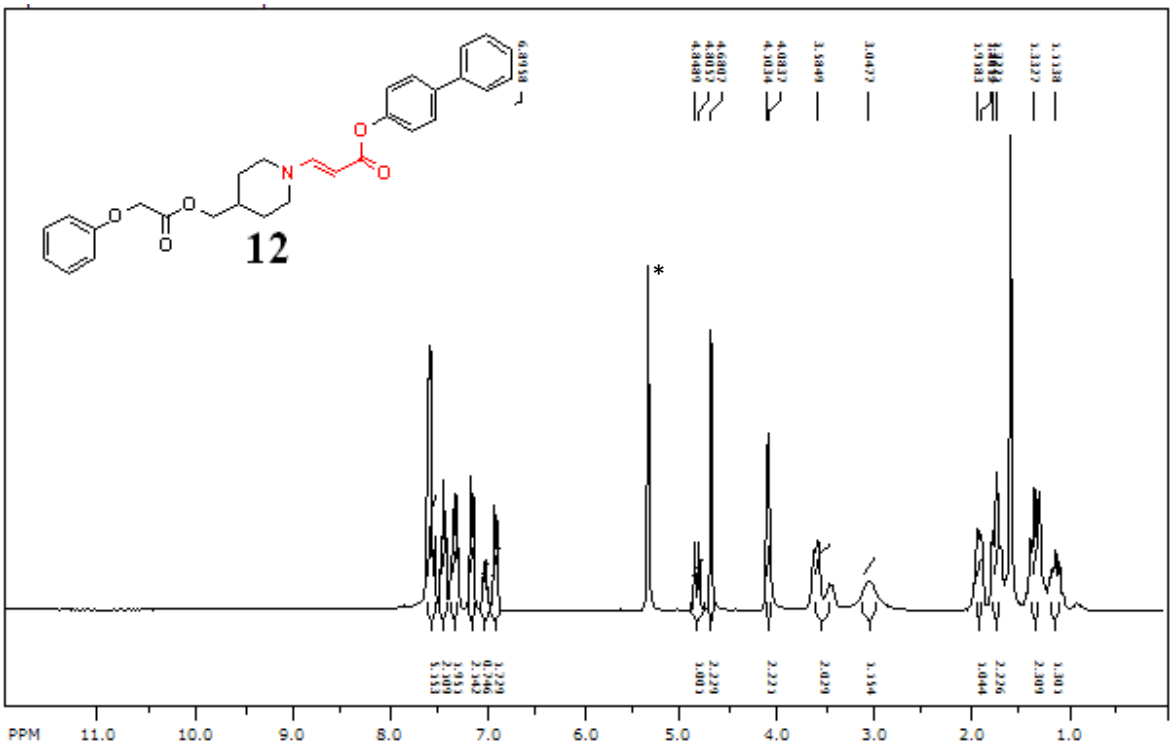
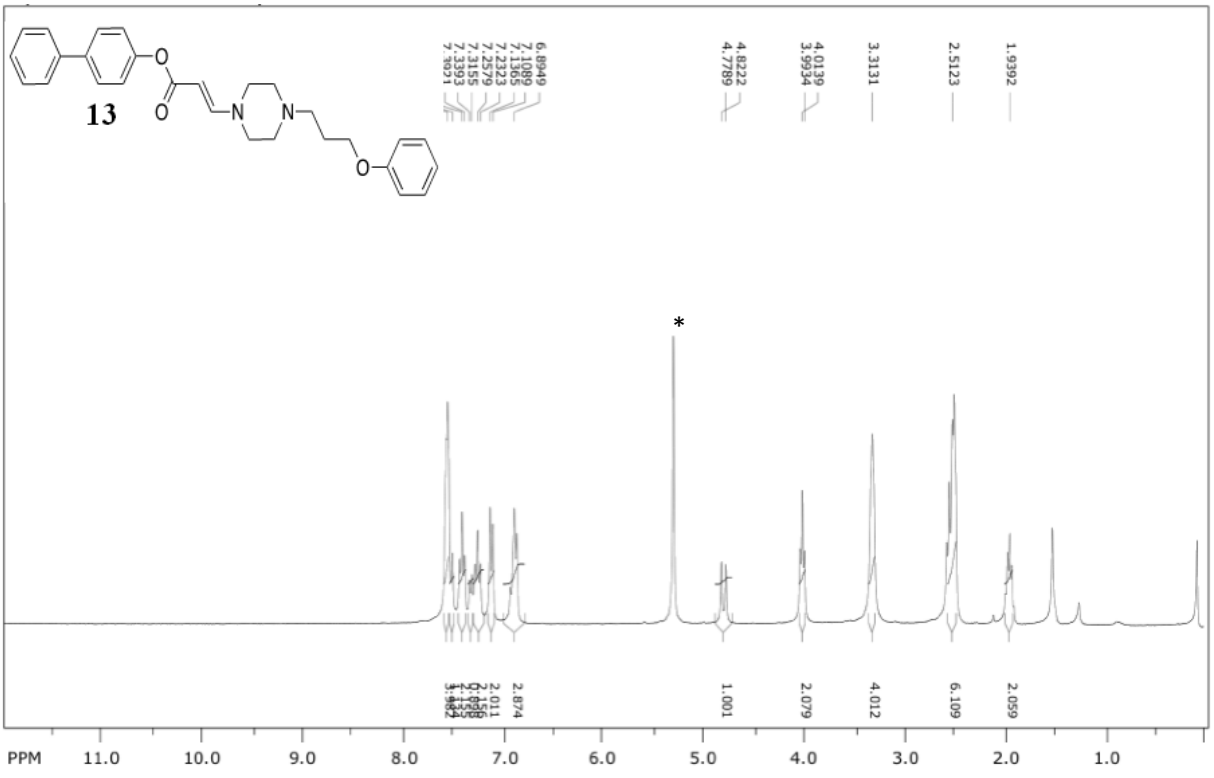
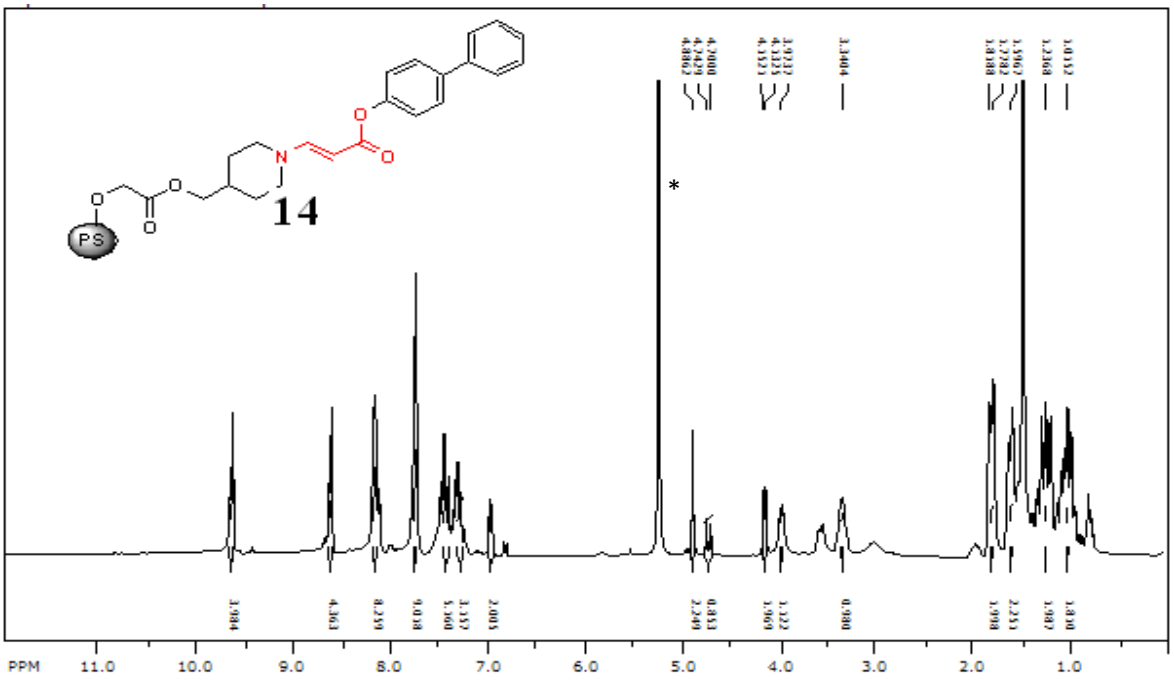
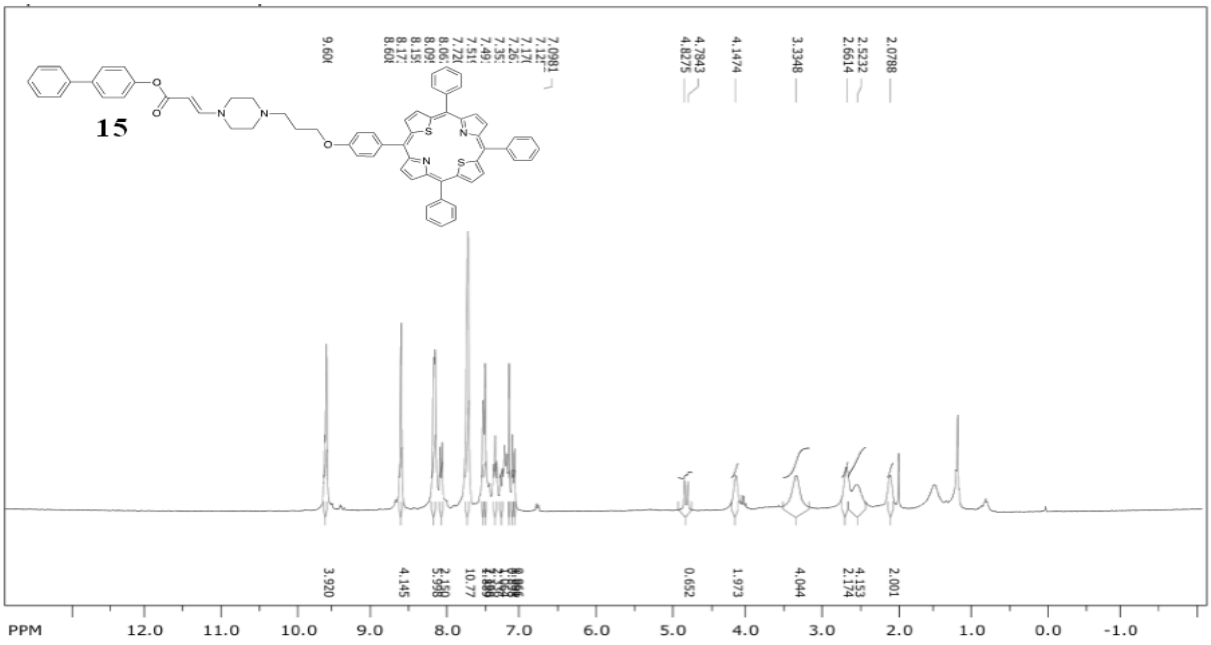
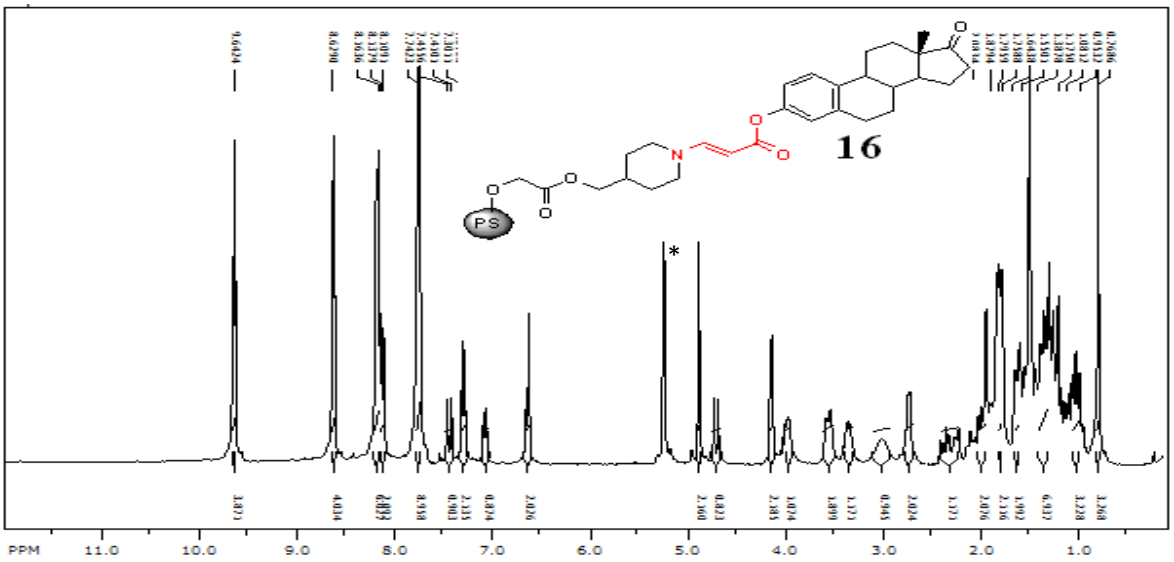
1.0

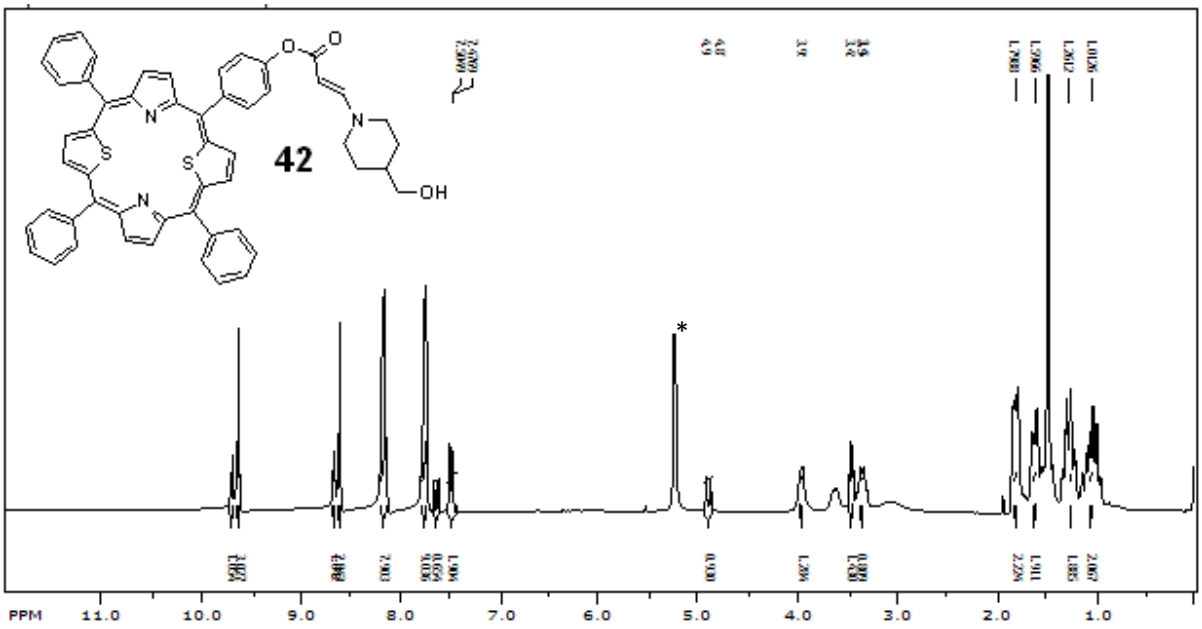


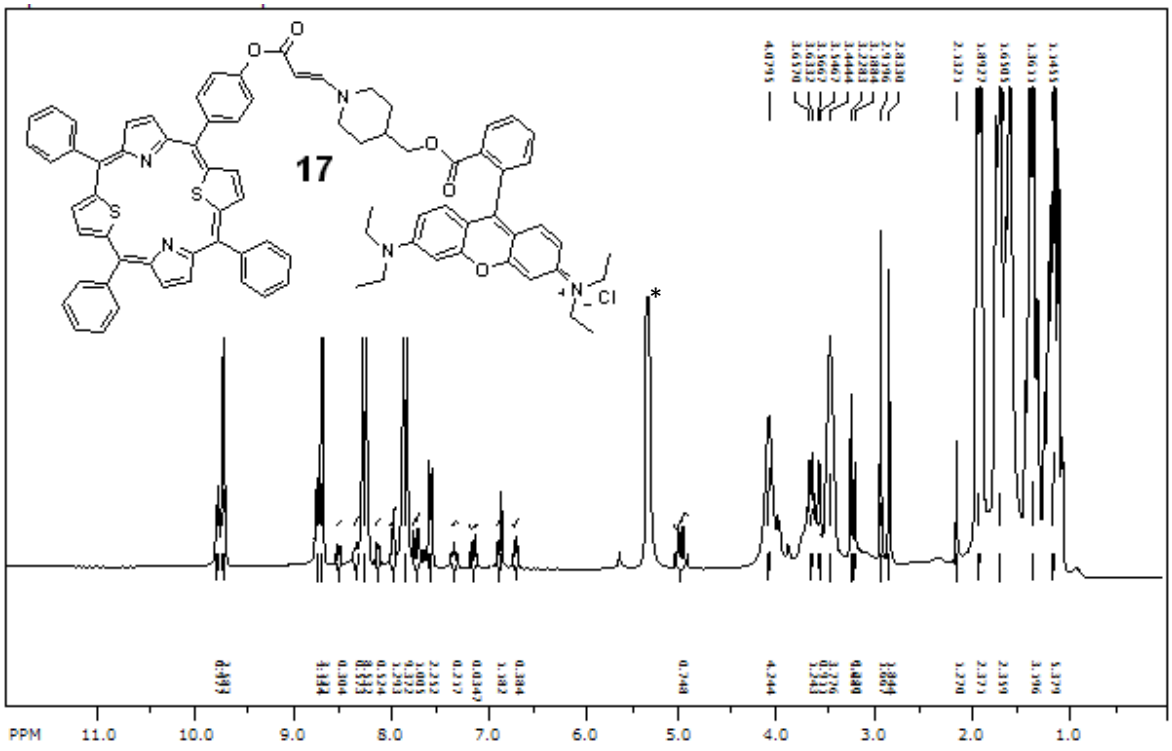












* *The peaks at 5.4 ppm were from a solvent: dichloromethane.*

References

1. You, Y., S. L. Gibson, R. Hilf, S. R. Davies, A. R. Oseroff, I. Roy, T. Y. Ohulchanskyy, E. J. Bergey and M. R. Detty Water soluble, core-modified porphyrins. Synthesis, photophysical properties, and in vitro studies of photosensitization, uptake, and localization with carboxylic acid-substituted derivatives. *J. Med. Chem.***2003** 46**,** 3734-47.