Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supplementary Information

Serendipitous discovery of an efficient method for the synthesis of Dimeric-RGD analogues using a DMAP-photoirradiation

Ruiping Zhang,[*#a] Yao Sun,[# b] Ying Qiao,[a] Jian-Ding Li,[a] and Jun Xie,[c]

Table of Contents

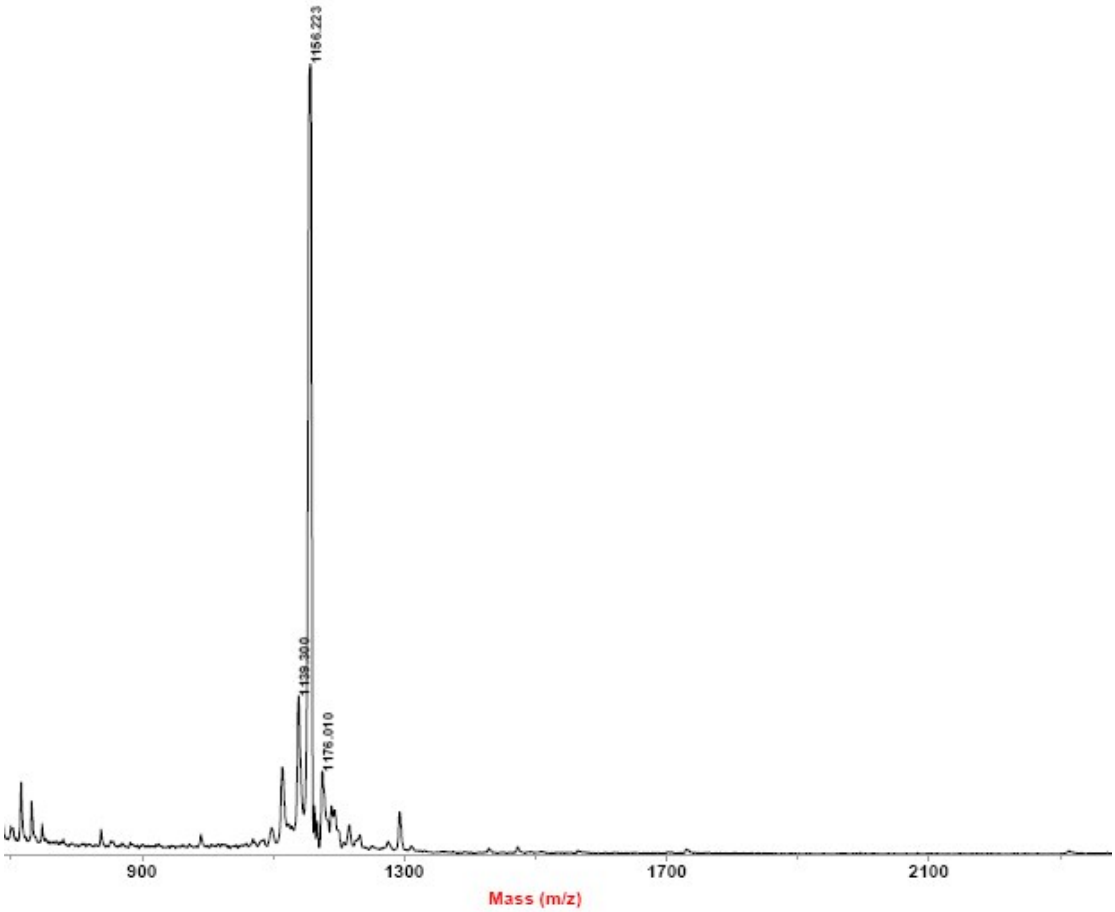


Figure S1. MALDI-TOF-MS of dimmer-RGD

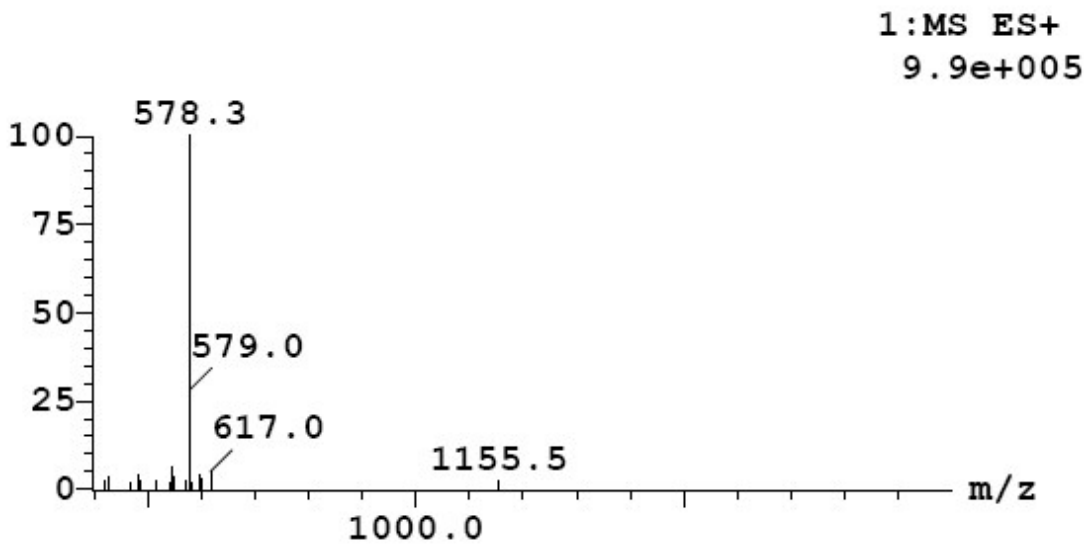


Figure S2. ESI-MS of dimmer-RGD

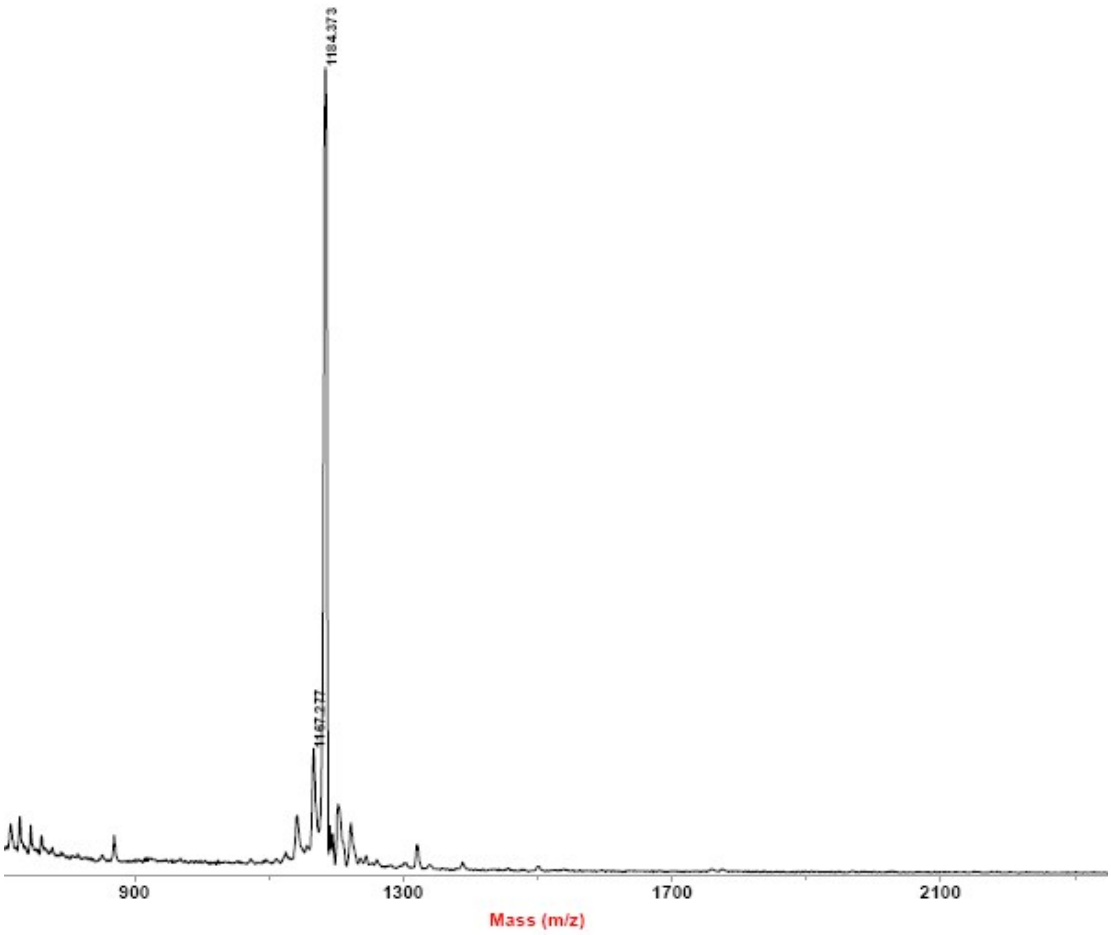


Figure S3. MALDI-TOF-MS of dimmer-RAD

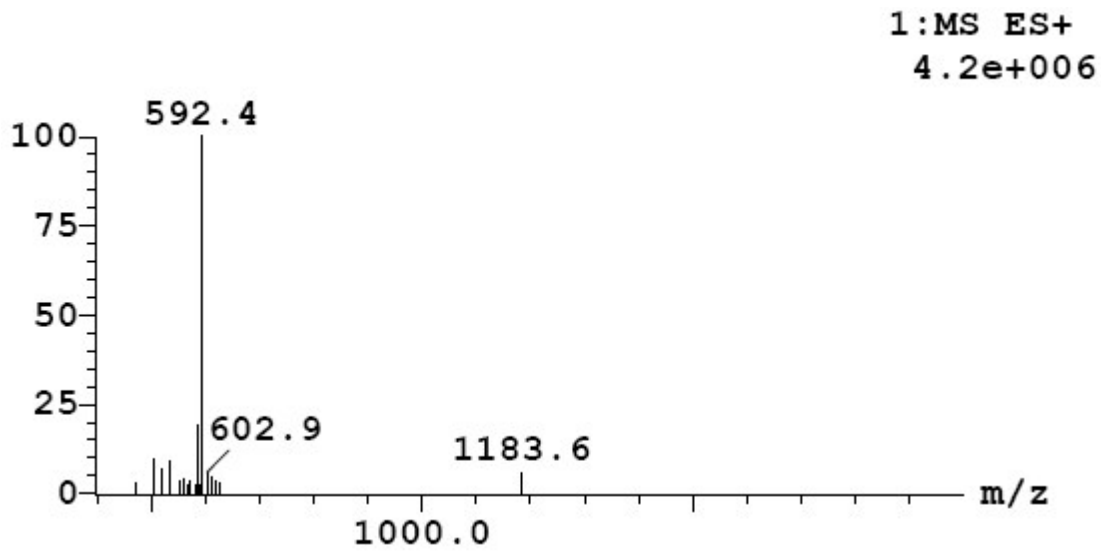


Figure S4. ESI-MS of dimmer-RAD

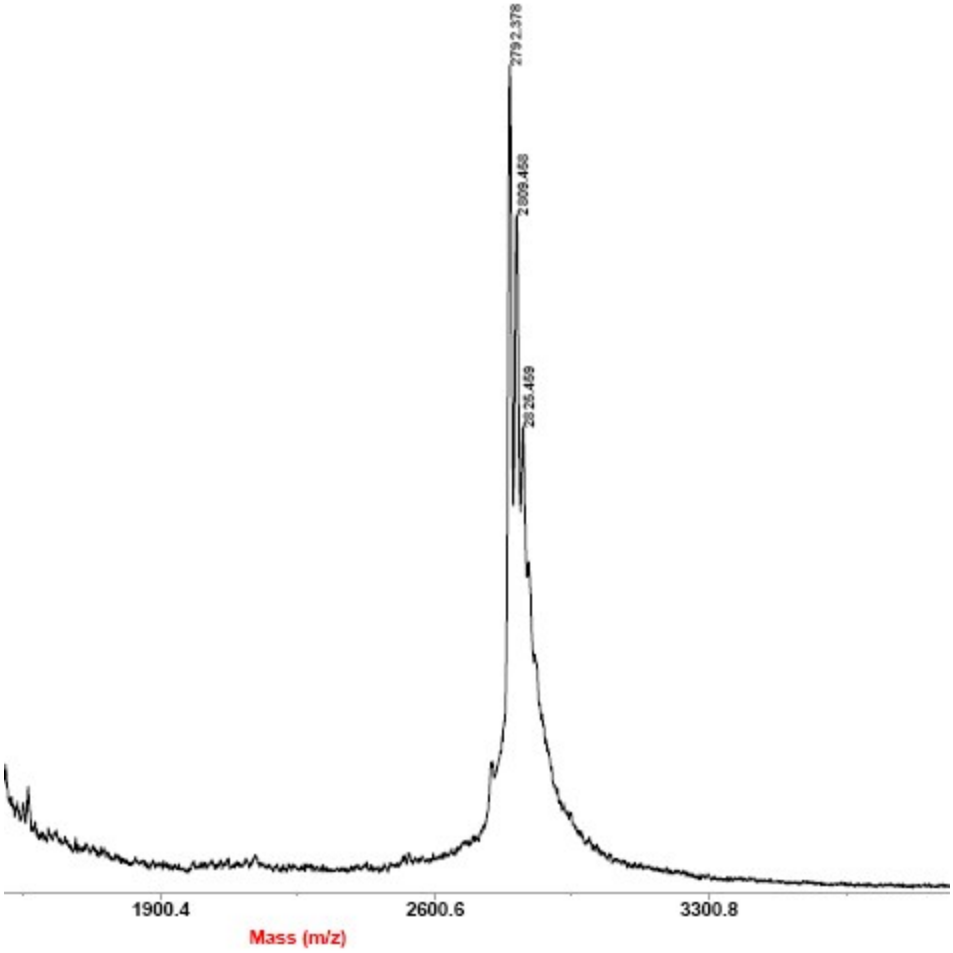


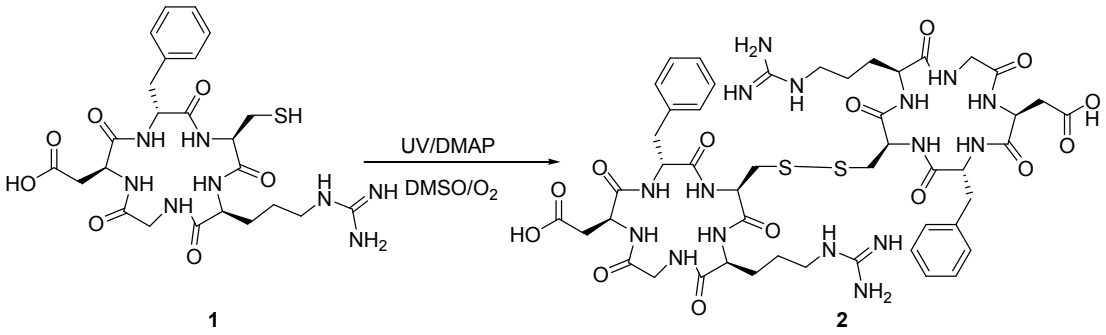
Figure S5. MALDI-TOF-MS of dimmer-AE105

General methods

All chemicals were purchased from commercial sources (such as Aldrich, AREVA Med and peptide international). The ^{1}H and ^{13}C NMR spectra were acquired on a Bruker 400 MHz magnetic resonance spectrometer. Data for ^{1}H NMR spectra are reported as follows: chemical shifts are reported as δ in units of parts per million (ppm) relative to chloroform-d (δ 7.26, s); multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), or br (broadened); coupling constants are reported as a *J* value in Hertz (Hz); the number of protons (n) for a given resonance is indicated nH, and based on the spectral integration values. MALDI-MS spectrometric analyses were performed at the Mass Spectrometry Facility of Stanford University. HPLC was performed on a Dionex HPLC System (Dionex Corporation) equipped with a GP50 gradient pump and an in-line diode array UV-Vis detector. A reversed-phase C18 (Phenomenax, 5 μm, 4.6 × 250 mm, 5 μm, 10 × 250 mm or 21.2 × 250 mm) column was used for analysis and semi-preparation.

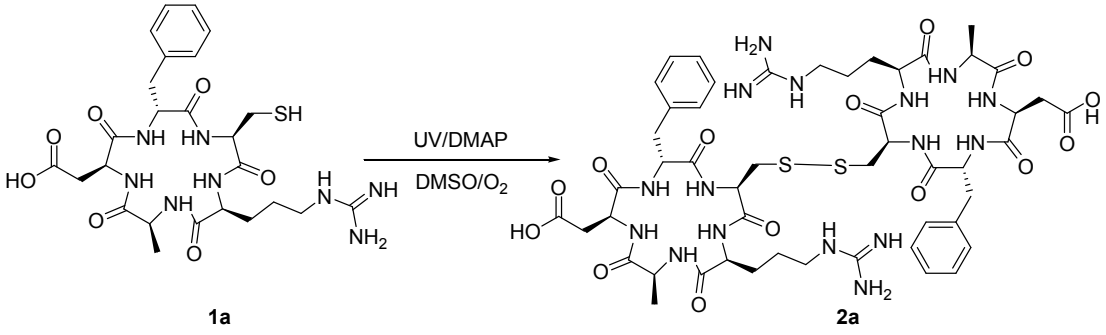
Cell line. U87MG glioblastoma cells were obtained from the American Type Culture Collection (Manassas, VA, USA) and culture media was obtained from Invitrogen Co. (Carlsbad, CA, USA). The cells were cultured in Dulbecco's modified Eagle's medium (DMEM)supplemented with 10% (v/v) fetal bovine serum and 1% (v/v) penicillin at 37°C and 5% CO_2.

Chemical synthesis and characterization



1 2

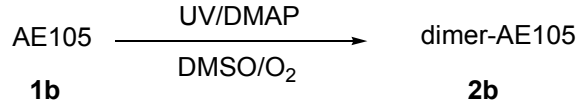
Synthesis of **2**: To a solution of compound **1** (2.89 mg, 0.005 mmol) and DMAP (0.61 mg, 0.005 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 3 h. The crude product was purified by HPLC. Lyophilization of the purified material gave **2**. (78 %) ESI-MS Calcd for: $C_{48}H_{67}N_{16}O14S_2^+$ ($[M+H]^+$): 1155.4, found: 1155.5, MALDI-MS: m/z 1556.223.



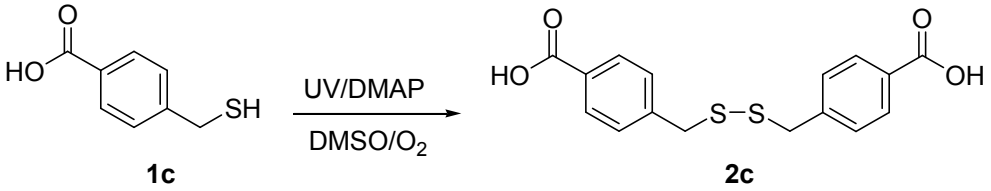
1a 2a

Synthesis of **2a**: To a solution of compound **1a** (2.96 mg, 0.005 mmol) and DMAP (0.61 mg, 0.005 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 3 h. The crude product was purified by HPLC. Lyophilization of the purified material gave **2a**. (75 %) ESI-MS Calcd for: $C_{50}H_{71}N_{16}O14S_2^+$ ($[M+H]^+$):

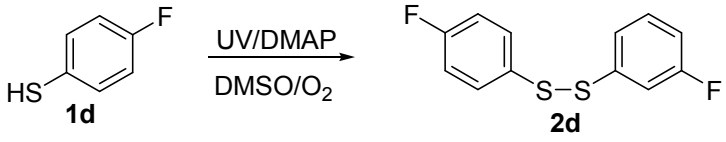
1183.4, found: 1183.6, MALDI-MS: m/z 1184.336.



Synthesis of **2b**: To a solution of compound **1b** (1.40 mg, 0.001 mmol) and DMAP (0.112 mg, 0.001 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 5 h. The crude product was purified by HPLC. Lyophilization of the purified material gave **2b**. (54 %)MS Calcd for: $C_{132}H_{183}N_{32}O_{32}S_2^+$ ($[M+H]^+$): 2792.3, found: MALDI-MS: m/z 2792.376.

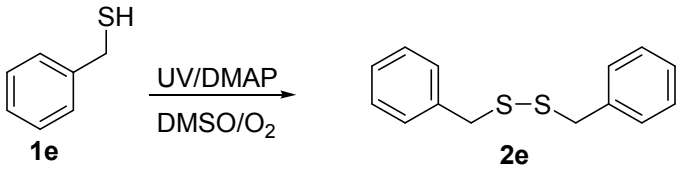


Synthesis of **2c**: To a solution of compound **1c** (16.8 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by flash chromatography affording the desired products. (80 %) ^{1}H NMR (400 MHz, MeOD): δ = 7.45 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.58 (s, 2H); ^{13}C NMR (101 MHz, MeOD) δ = 173.74, 135.23, 134.30, 129.88, 127.69, 39.85; HRMS (ESI) Calcd for: $C_{16}H_{15}O_4S_2^+$ ($[M+H]^+$): 335.0406, found: 335.0401.



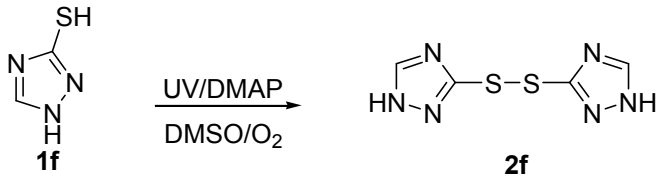
Synthesis of **2d**: To a solution of compound **1d** (12.8 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by flash chromatography

affording the desired products. (82 %) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.23 (m, 2H), 6.95-6.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.76, 160.38, 131.97, 125.05, 116.29, 116.07; HRMS (ESI) Calcd for: $C_{12}H_9F_2S_2^+$ ($[M+H]^+$): 255.0108, found: 255.0112.



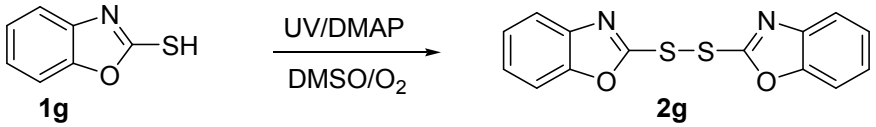
1e **2e**

Synthesis of **2e**: To a solution of compound **1e** (12.4 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by flash chromatography affording the desired products. (87 %) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.27 (m, 4H), 7.22-7.18 (m, 1H), 3.69 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.26, 128.78, 128.14, 127.14, 29.08; HRMS (ESI) Calcd for: $C_{14}H_{15}S_2^+$ ($[M+H]^+$): 247.0615, found: 247.0612.



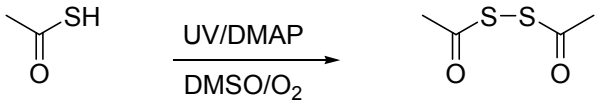
1f **2f**

Synthesis of **2f**: To a solution of compound **1f** (10.1 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by flash chromatography affording the desired products. (88 %) ^{1}H NMR (400 MHz, MeOD): δ = 8.01 (s, 1H); ^{13}C NMR (101 MHz, MeOD) δ = 167.03, 141.51; HRMS (ESI) Calcd for: $C_4H_5N_6S_2^+$ ($[M+H]^+$): 201.0012, found: 201.0007.



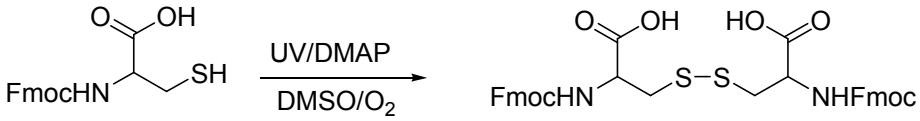
1g **2g**

Synthesis of **2g**: To a solution of compound **1g** (15.1 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by flash chromatography affording the desired products. (82 %) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.36 (m, 2H), 7.28-7.23 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.88, 125.42, 124.53, 110.61, 110.27; HRMS (ESI) Calcd for: $C_{14}H_9N_2O_2S_2^+$ ([M+H]$^+$): 301.0100, found: 301.0093.



1h **2h**

Synthesis of **2h**: To a solution of compound **1h** (7.6 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by HPLC. Lyophilization of the purified material gave **2h**. (78 %) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 194.20, 32.59; HRMS (ESI) Calcd for: $C_4H_7O_2S_2^+$ ([M+H]$^+$): 150.9882, found: 150.9891.



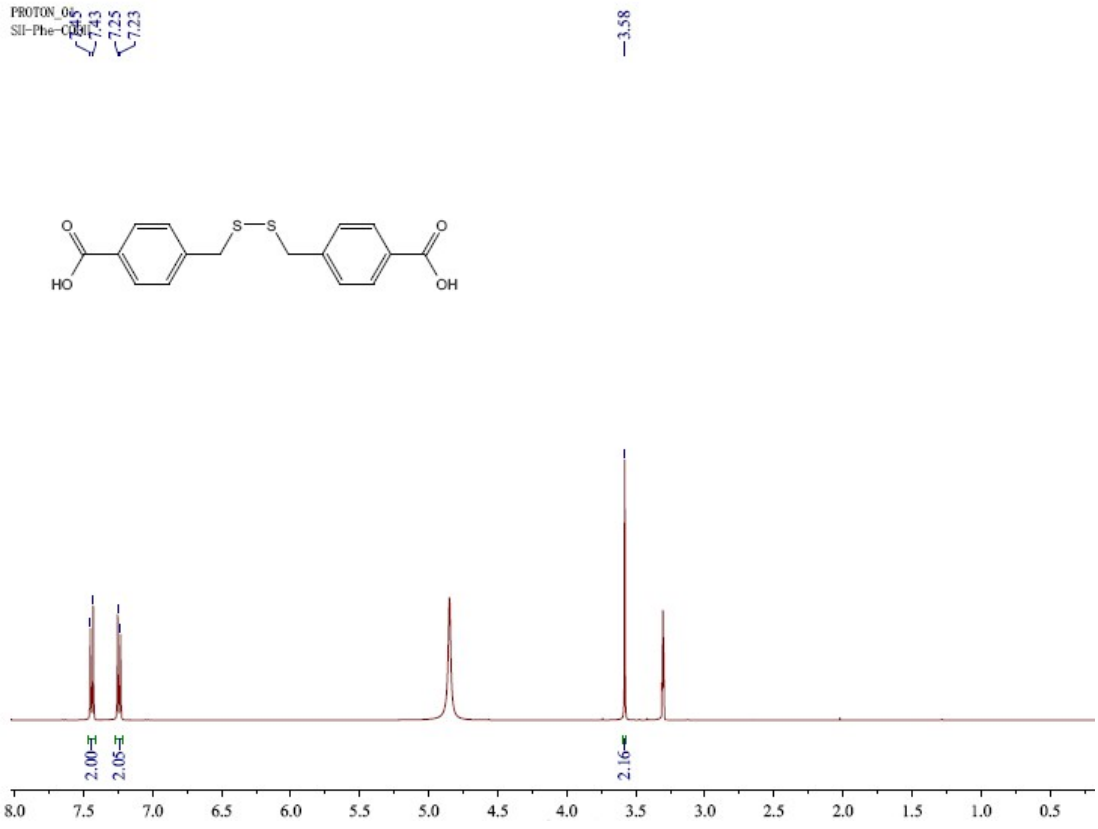
1i **2i**

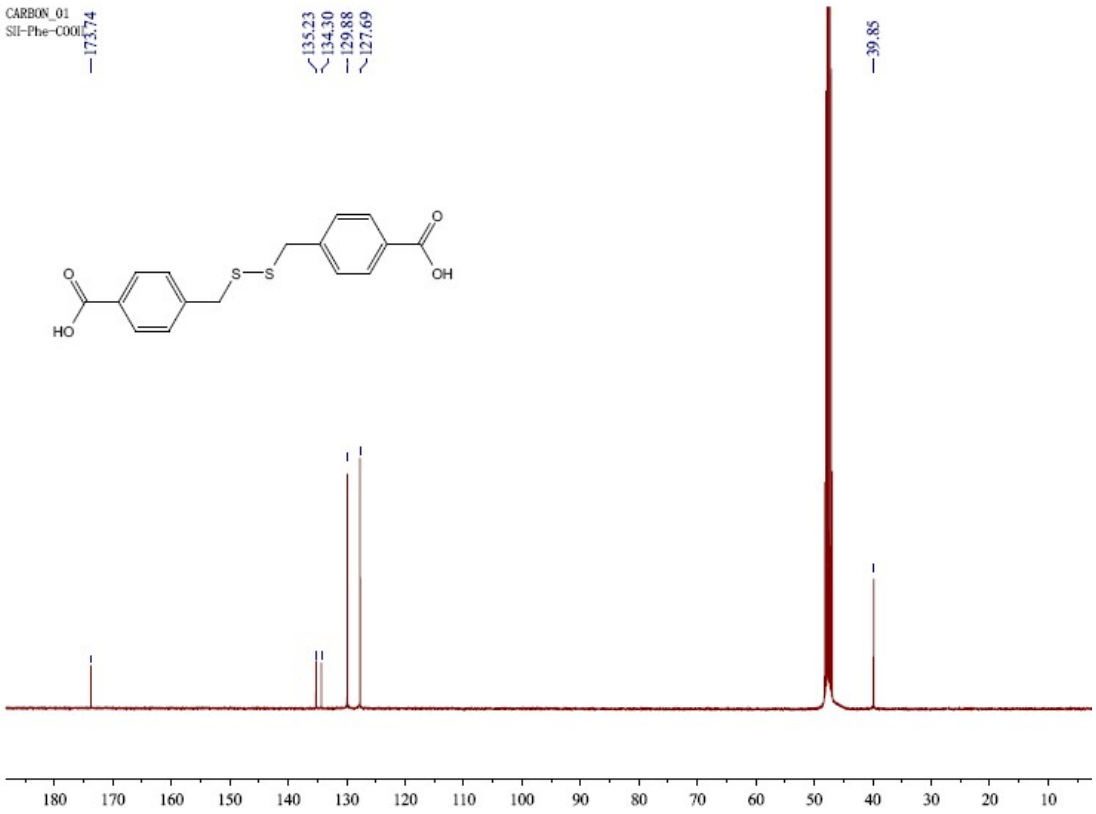
Synthesis of **2i**: To a solution of compound **1i** (34.3 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol, 1.0 equiv) in DMSO (c=0.2 M) at room temperature under UV lamp and molecular oxygen (4W, 365 nm). The reaction mixture was stirred at room temperature for 0.5 h. The crude product was purified by flash chromatography

affording the desired products. (42 %) ^{1}H NMR (400 MHz, MeOD): δ = 7.80 (d, *J* = 8.0 Hz, 2H), 7.69-7.66 (m, 2H), 7.40-7.37 (m, 2H), 7.32-7.29 (m, 2H), 4.38 (d, *J* = 12.0 Hz, 2H), 4.25-4.22 (m, 1H), 2.98-2.93 (m, 1H), 2.88-2.83 (m, 1H); ^{13}C NMR (101 MHz, MeOD) δ = 172.02, 157.06, 143.87, 143.73, 141.17, 127.37, 126.74, 124.84, 119.54, 66.63, 56.28, 25.48; HRMS (ESI) Calcd for: $C_{36}H_{33}N_2O_8S_2^+$ ($[M+H]^+$): 685.1673, found: 685.1682.

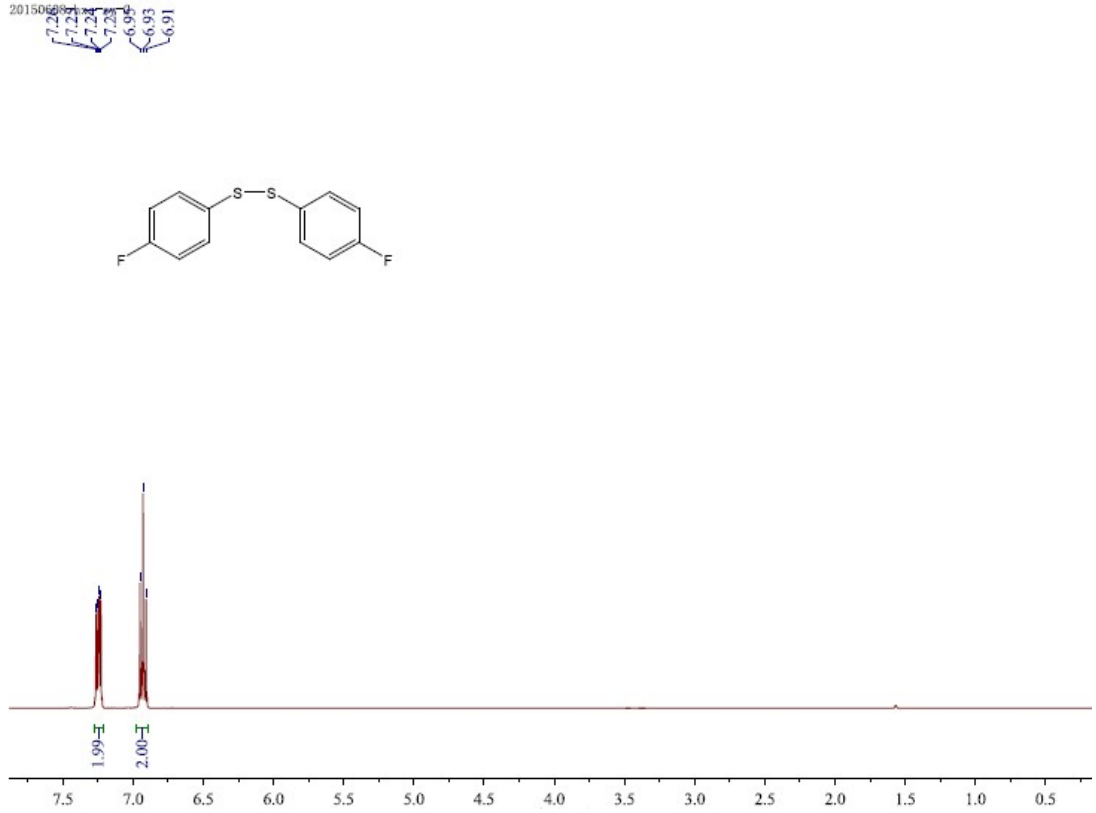
NMR Spectra

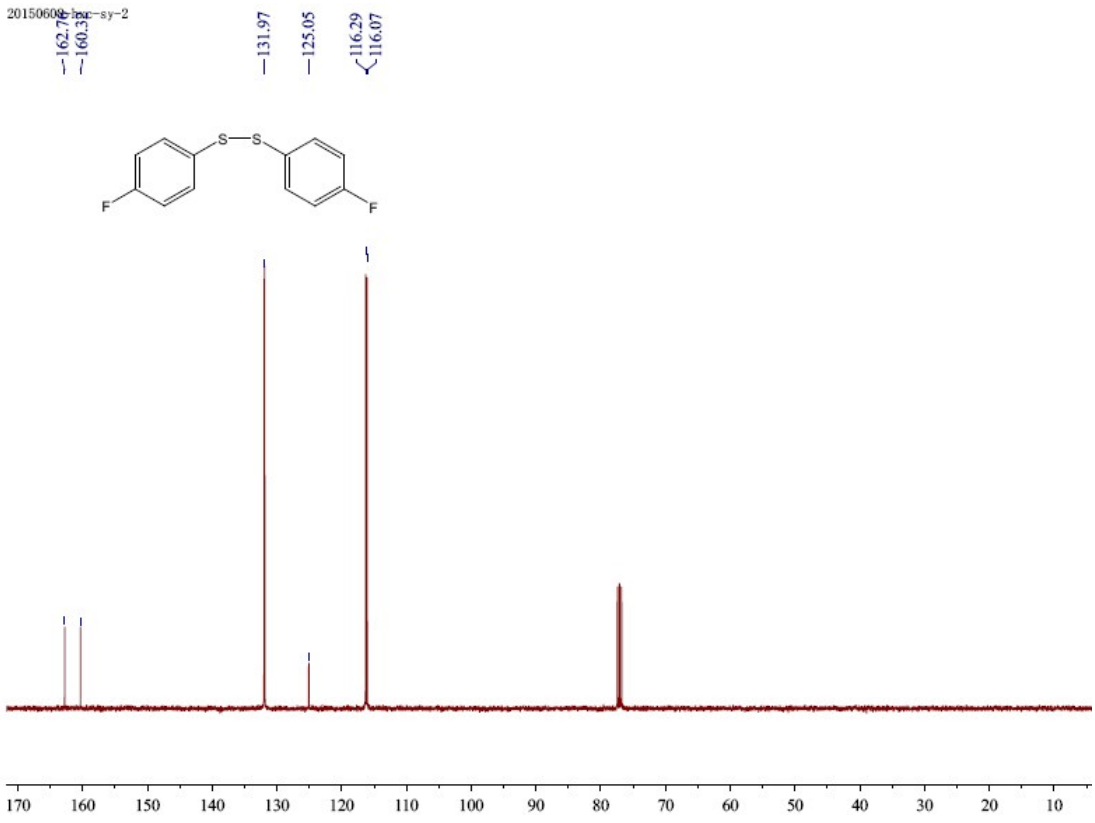
(a). ^{1}H NMR and ^{13}C NMR for 2c



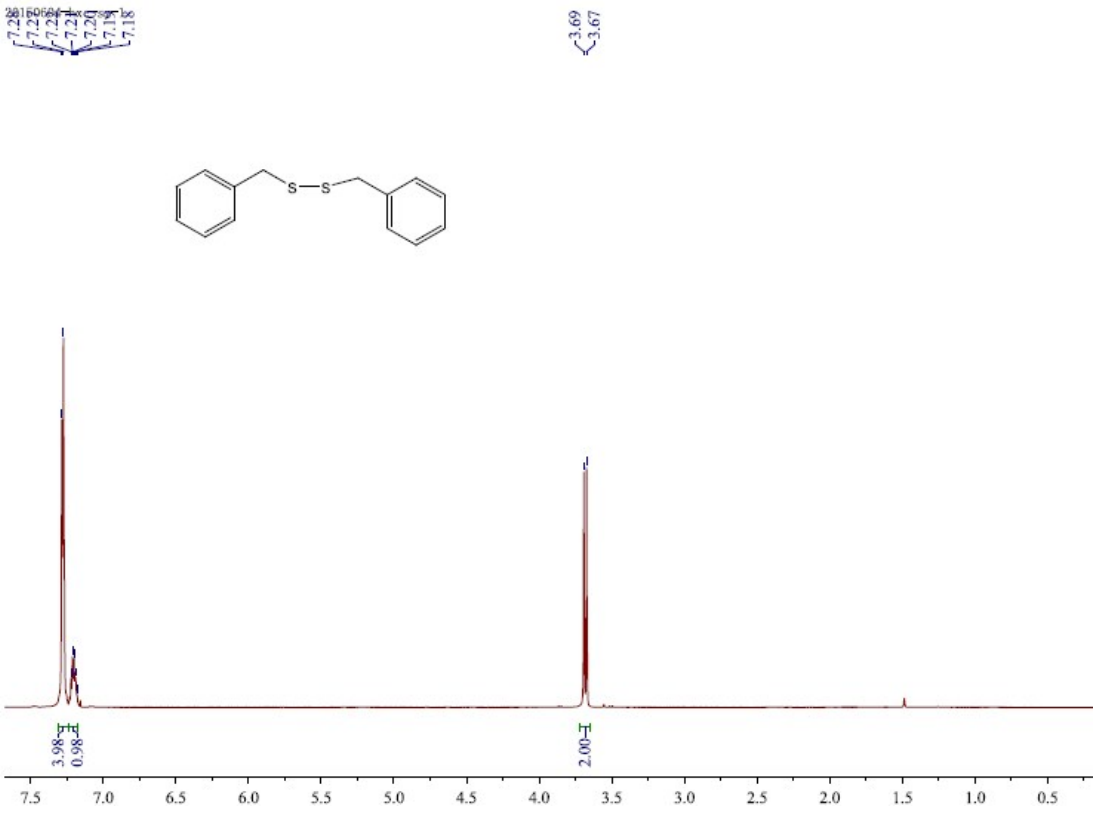


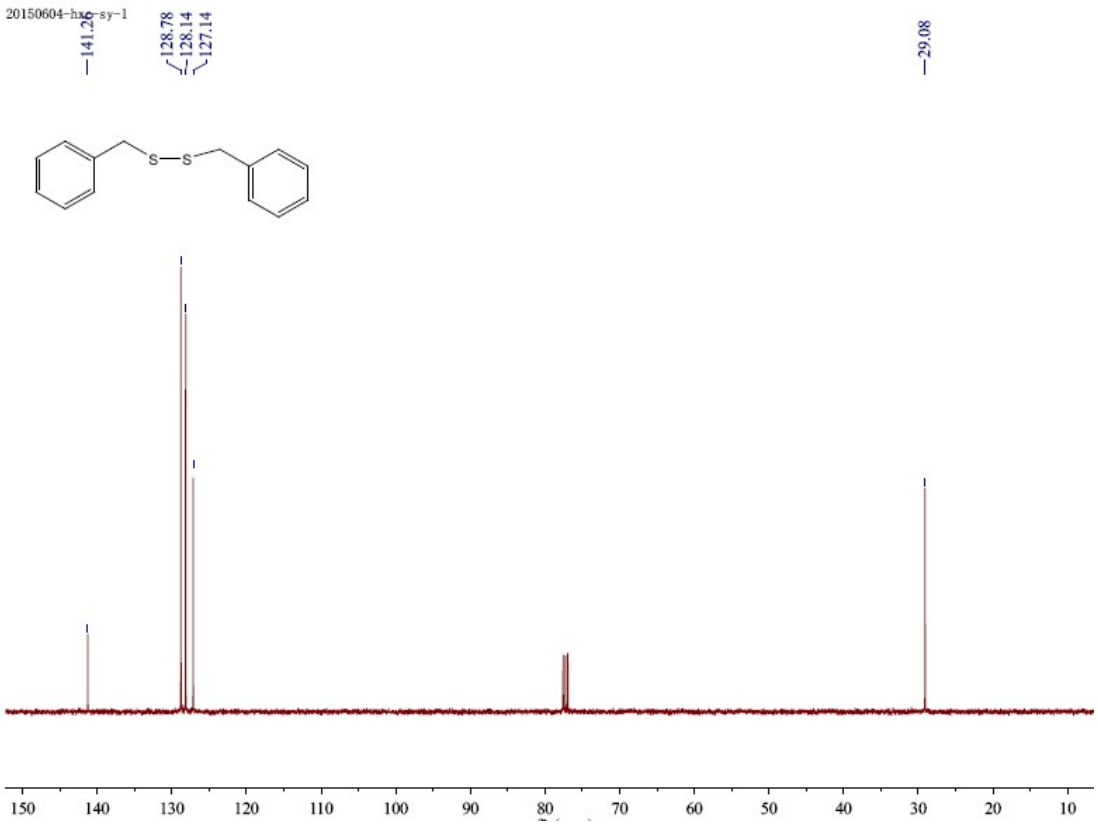
.**(b). ^{1}H NMR and ^{13}C NMR for 2d**



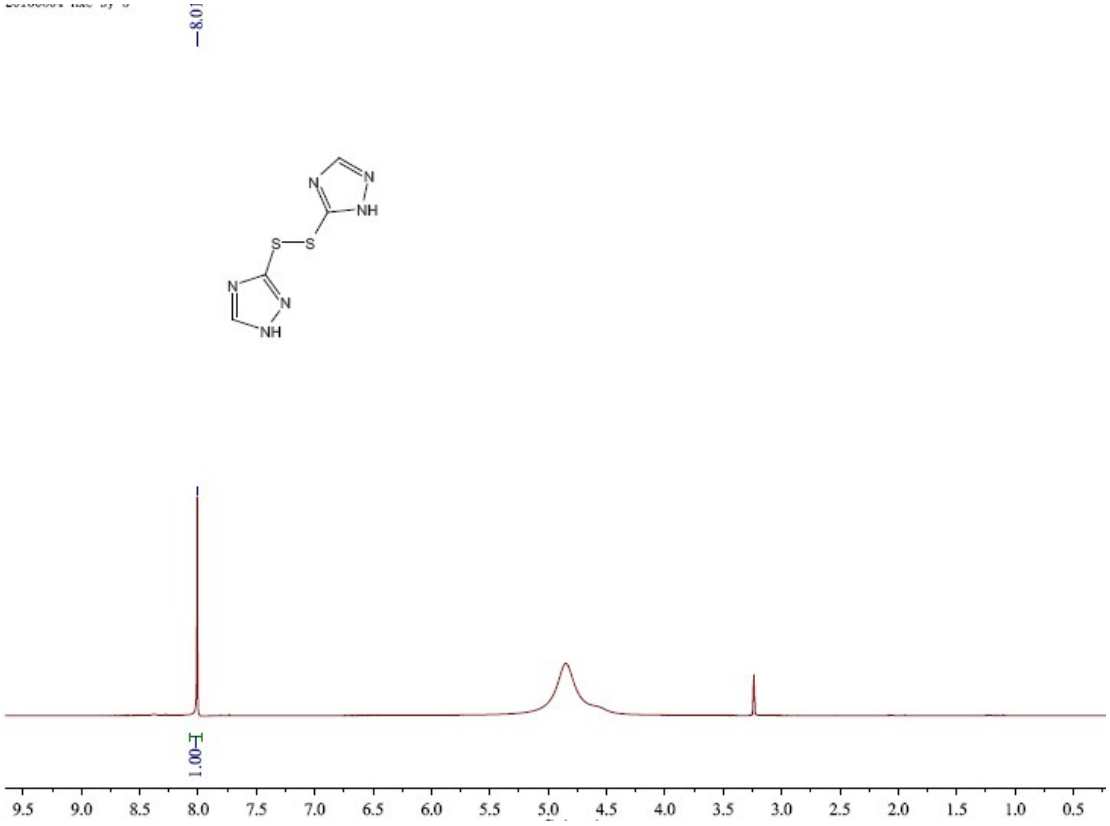


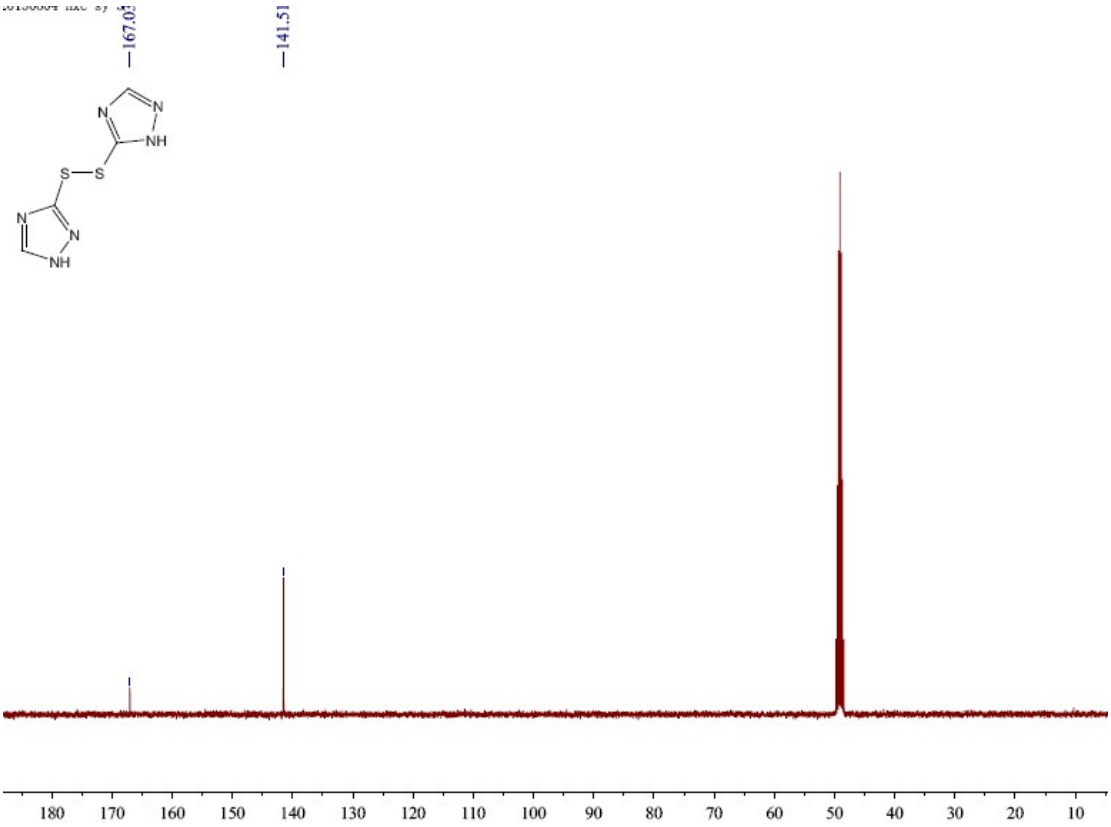
.(c). ^{1}H NMR and ^{13}C NMR for 2e



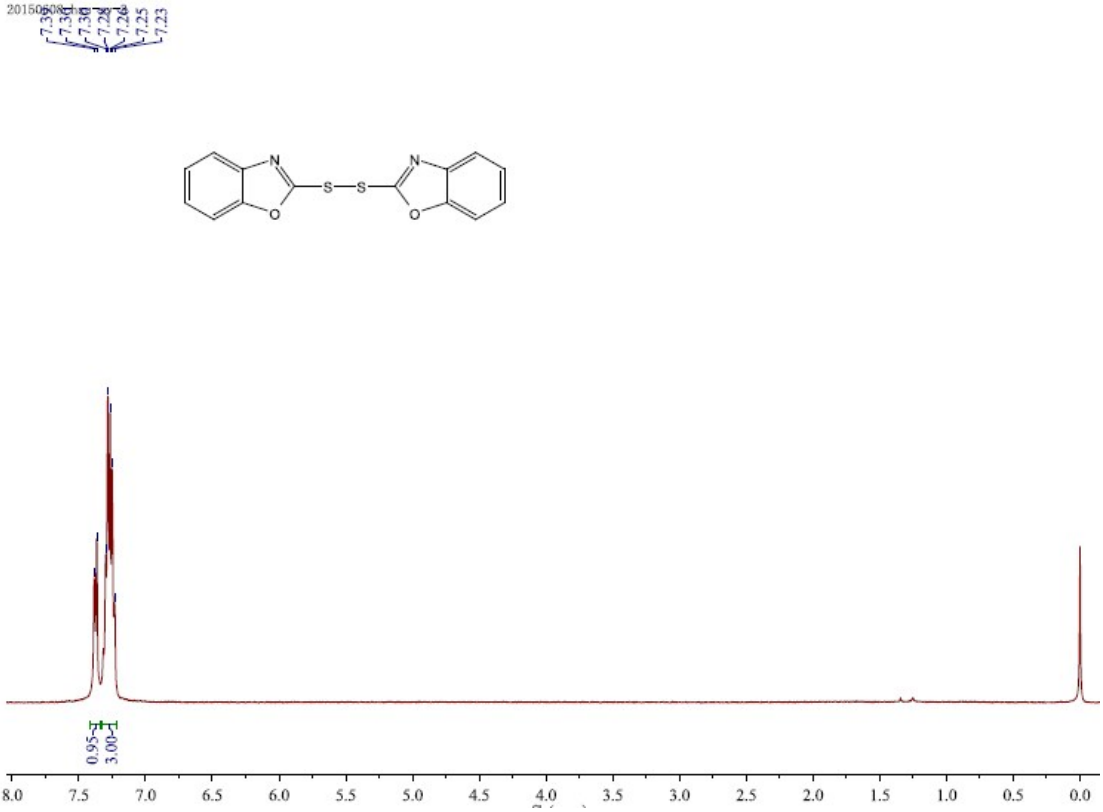


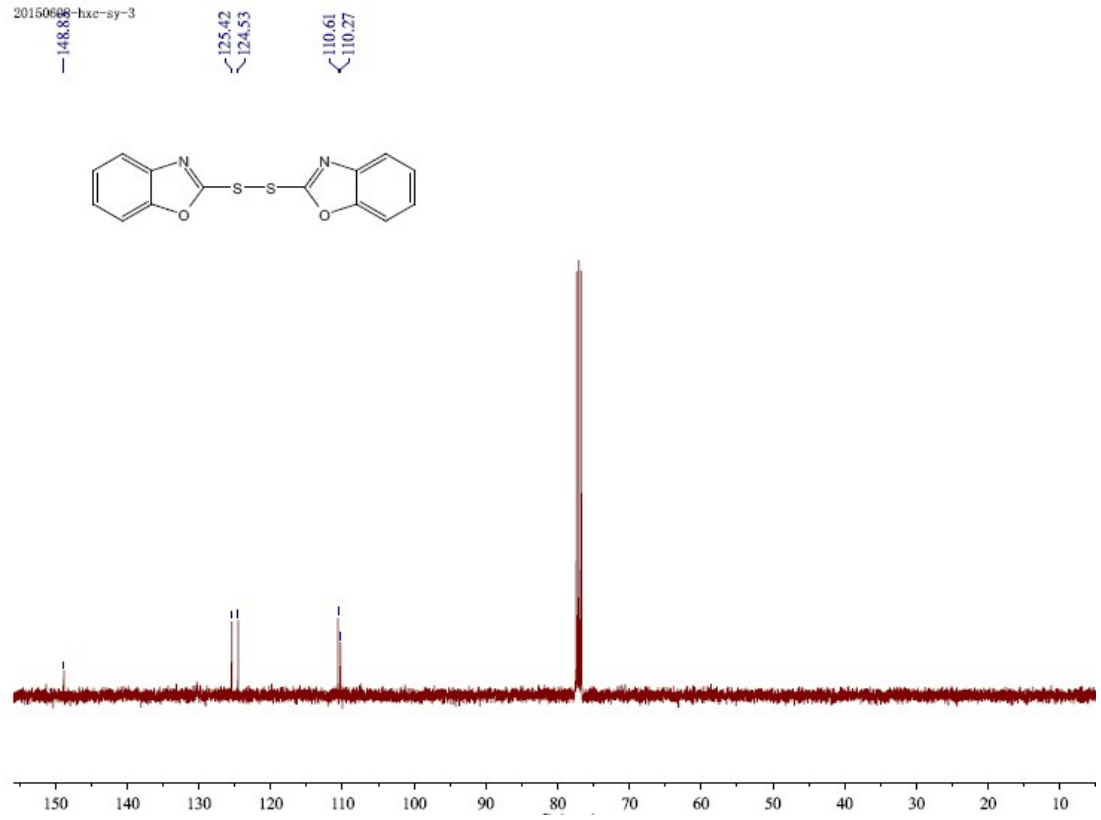
.(d). ^{1}H NMR and ^{13}C NMR for 2f



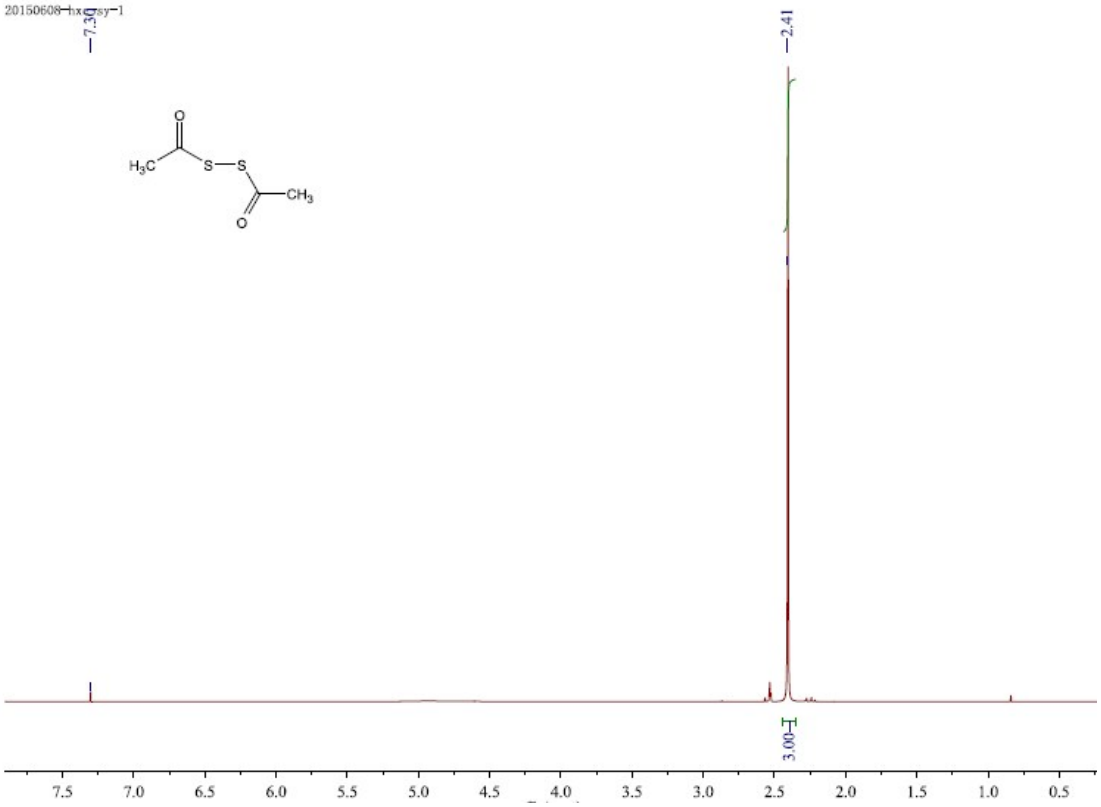


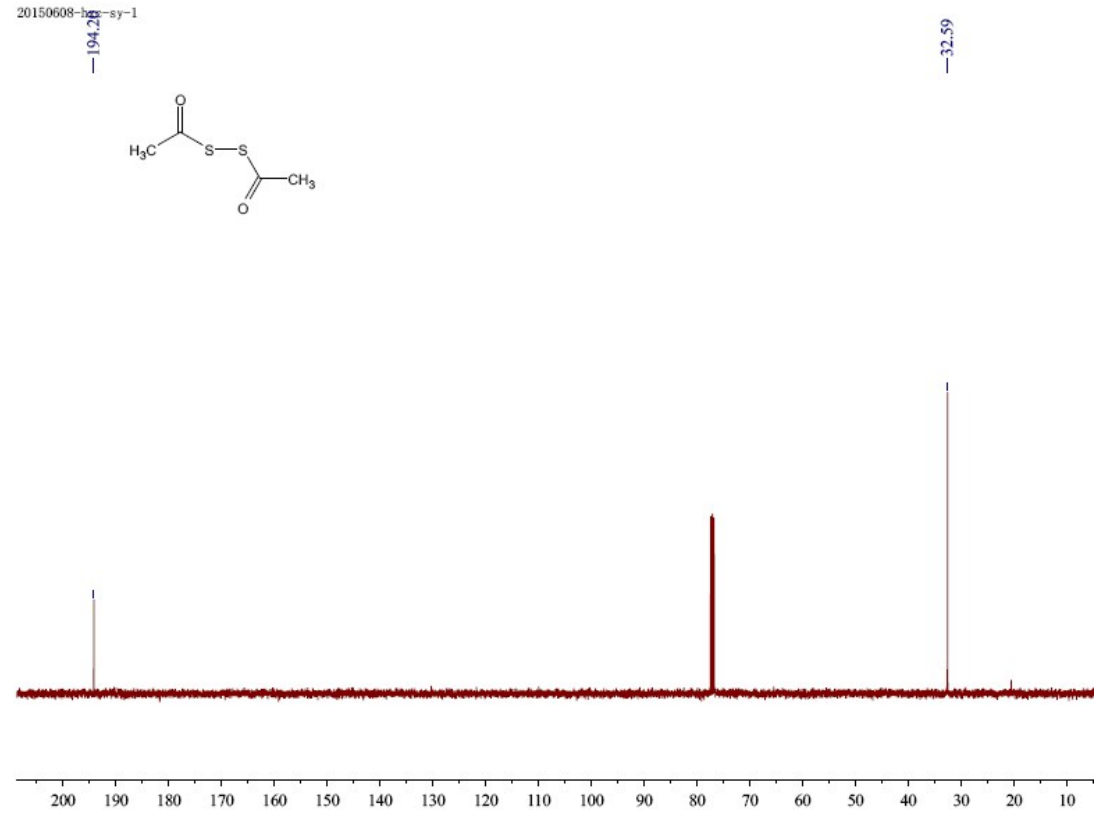
(e). ^{1}H NMR and ^{13}C NMR for 2g


7.36
7.26
7.25
7.23
0.95
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


148.88
125.42
124.53
110.61
110.27
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

(f). ^{1}H NMR and ^{13}C NMR for 2h





(g). ^{1}H NMR and ^{13}C NMR for 2i