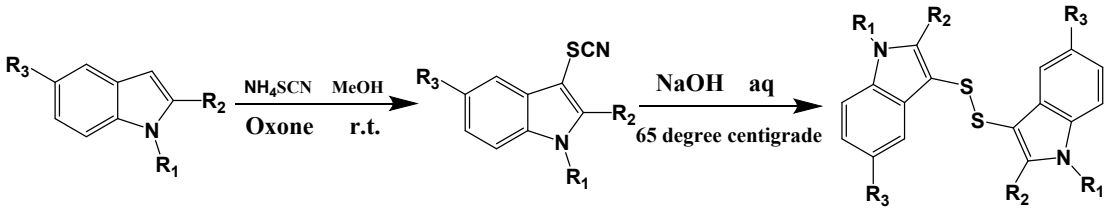
Electronic Supplementary Material (ESI) for RSC Advances.

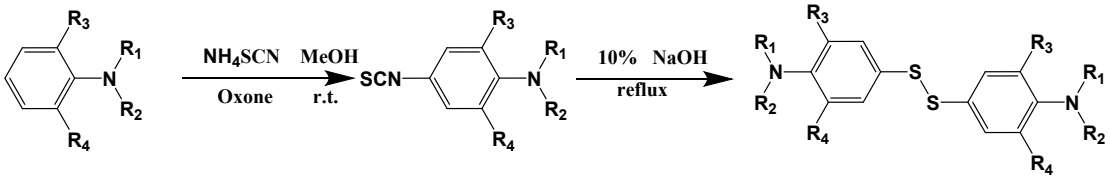
SupplementaryMaterial

The synthetic pathway of indoles disulfide compounds and IPA-3 is shown in Scheme 1[1-4]. Indole or indol derivates reacted with ammonium thiocyanate in the solution with the addition of potassiumperoxymonisulfate (oxone), giving the 3- thiocyano substituted indoles. The resulting crystal was refluxed in 10% aqueous solution of NaOH to give the products.



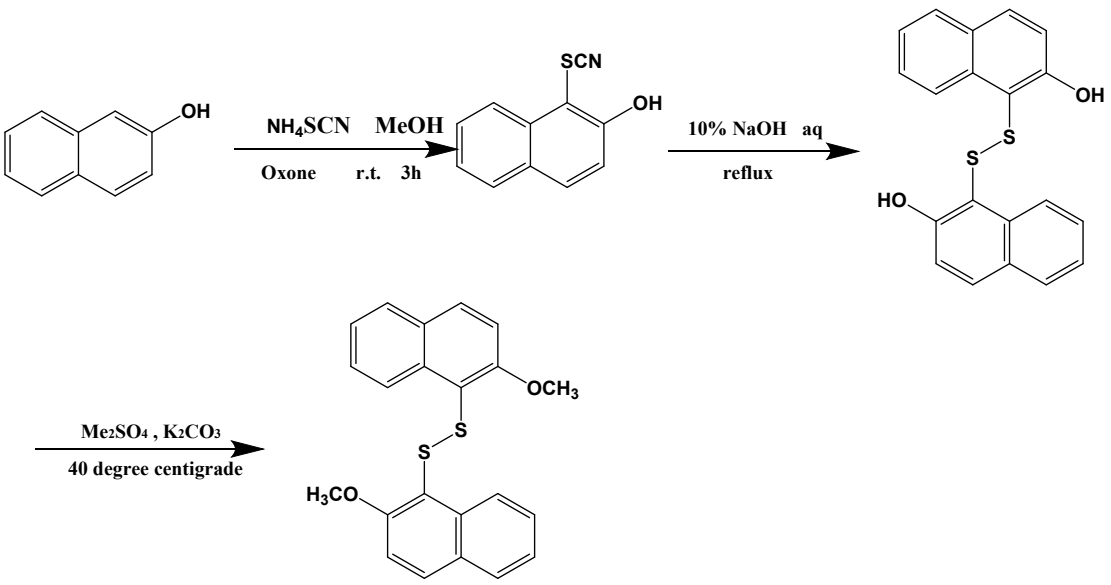
Scheme 1 The synthetic route of indole disulfide compounds

The synthetic pathway of aniline disulfide compounds is shown in Scheme 2[1-4]**.** Aniline disulfide compounds reacted with ammonium thiocyanate in the solution with the addition of oxone, giving 4- thiocyanate substituted aniline disulfide compounds. The resulting crystal was refluxed in 10% aqueous solution of sodium hydroxide to give products.



Scheme 2 The synthetic route of aniline disulfide compounds

The synthetic pathway of bis (Naphthol 2- methoxyradica) sulfide compounds (Na01) is shown in Scheme 3[5, 6]. β-naphthol was mixed with ammonium thiocyanate and Oxone, followed by reflux in 10% aqueous solution of sodium hydroxide to yield IPA-3. The methylation of IPA-3 gave Na01.



Scheme 3 The synthetic route of Na-01

3-thiocyanate-5-bromoindole (1). Compound **1** was prepared according to the reported procedure in REF 4.

1-benzyl-5- bromoindole (2). Compound **2** was prepared according to the reported procedure in REF 7.

1-methyl-5- bromoindole (3). Compound **3** was prepared according to the reported procedure in REF 4.

4-thiocyanate- N,N-dimethylformamide (4). Compound **4** was prepared according to the reported procedure in REF 4. The product was used without purification.

1-Thiocyanate-2 naphthol (5).To a solution of β-naphthol(7.2g, 50 mmol) in ethanol (70mL) was added ammonium thiocyanate (5.7g, 75mmol). After ammonium thiocyanate was completely dissolved, Oxone (46.1g, 75mmol) was added and the resulting mixture was stirred for 3h at room temperature. The reaction mixture was

then quenched by water (30 mL), extracted with CH_2Cl_2 (60mL×3), dried with Na_2SO_4 and concentrated via rotary evaporation togive the titled compound as a yellow solid (8.6g). The product was used without purification.

2,2'-dihydroxy-1,10-dinaphthyldisulfide (IPA-3, 6).Compound **5** (5.6g, 28mmol) was dissolved in 10% aqNaOH (45mL) and refluxed for 3h. After the mixture was cooled to room temperature, the pH was adjusted to 6 using 6N sulfuric acid and yellow precipitation was observed. After leaching, drying at room temperature and purification via column chromatography (petroleum ether/EtOAc 20:1), the titled compound was given as a yellow solid (3.8g, 79.1%). Melting point was 171.0~172.5℃. ^{1}H NMR (DMSO-d6) δ: 10.0 (s, 2H, -OH), 7.03~7.19 (m, 6H), 7.82~7.79 (d, 2H, J=8.91Hz), 7.70~7.75 (t, 4H, J=7.43Hz). **^{13}C-NMR (151 MHz, DMSO-d6) δ 156.56 (s, 2C), 135.24 (s, 2C), 130.26 (s, 2C), 128.62 (s, 2C), 128.36 (s, 2C), 126.78 (s, 2C), 124.52 (s, 2C), 122.88 (s, 2C), 118.01 (s, 2C), 112.29 (s, 2C). The ^{1}H NMR of IPA-3 was shown in figure S1, and the ^{13}C-NMR was shown in figure S15.**

Bis (2-methoxynaphthalenyl) disulfide (Na01,7).To a yellow solution of Compound **6** (2g, 5.7mmol) in acetone (30mL) was added K_2CO_3 (2.3g, 17mmol). After the mixture was stirred for 0.5h, dimethyl sulfate (1.6mL, 17mmol) was added, and the resulting mixture was heated and refluxed for 4h. The reaction mixture was then cooledto room temperature, washed with water (30 mL), extracted with EtOAc (60mL×3), dried with Na_2SO_4, and purified with column chromatography (petroleum ether/EtOAc 60:1) to give white crystal (1.2g, 60.1%). Melting point was 118.3~119.6℃. ^{1}H NMR (DMSO-d6) δ: 3.87 (s, 6H, -CH_3), 7.14~7.48 (m, 6H), **13C NMR (151 MHz, DMSO-d6) δ 157.47 (s, 2C), 129.98 (s, 4C), 128.95 (s, 2C), 128.12 (s, 2C), 126.70 (s, 2C), 126.47 (s, 2C), 124.35 (s, 2C), 117.91 (s, 2C), 113.94**

(s, 2C), 56.46 (s, 2C). The ^{1}H NMR of Na01 was shown in figure S2 and the ^{13}C-NMR was shown in figure S16.

Bis (5-bromo-1-methyl-1H-indol-3-yl) disulfide (In01,8). N-methyl-3-thiocyanate-5-bromoindole (1g, 4mmol) was dissolved in 10% aqNaOH (30mL), heated to 60℃, and the solution was stirred for 4h. After being cooled to room temperature, the solution was acidified with 2N aqHCl (pH=6) and yellow solid precipitated out. The resulting crystal was washed with water, leached, dried (Na_2SO_4) and purified by column chromatography (petroleum ether/EtOAc=20:1) to gave **8** as a yellow solid (0.2g, 41.7%). Melting point was 189.0~201.8℃. ^{1}H- NMR (DMSO-d6) δ: 3.78 (s, 6H, -CH_3), 7.15~7.16 (d, 2H, J=1.74Hz), 7.32~7.35 (dd, 2H, J_{12}=1.77Hz, J_{13}=8.67Hz), 7.50~7.52 (m, 4H). **^{13}C NMR (151 MHz, DMSO-d_6) δ 137.07(s, 2C), 135.75(s, 2C), 130.48(s, 2C), 124.65(s, 2C), 120.88(s, 2C), 113.12(s, 2C), 112.70(s, 2C), 104.31(s, 2C), 32.87 (s, 2C). The^{1}H- NMR of In01 was shown in figure S3 and the ^{13}C-NMR was shown in figure S17**

Bis (1H-indol-3-yl) disulfide (In02, 9). Compound **9** was prepared using the same method as**8** and given as a pink solid (yield = 81.6%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc10:3) gave compound 9 as a white solid (yield 69.2%).** Melting point was 209~210℃. ^{1}H-NMR (DMSO-d6) δ: 11.54 (m, 2H, -NH), 7.28~7.29 (d, 2H, J=3.0Hz), 7.38~7.39 (d, 2H, J_{12}=8.4Hz), 7.03~7.05 (t, 2H, J=7.5Hz), 7.15~7.17 (t, 2H, J=7.5Hz), 7.42~7.44 (d, 2H, J=8.4Hz). **^{13}C NMR (151 MHz, DMSO-d6) δ 136.55 (s, 2C), 131.94(s, 2C), 128.40 (s, 2C), 122.14 (s, 2C), 119.98 (s, 2C), 118.76 (s, 2C), 112.18 (s, 2C), 105.84 (s, 2C). The ^{1}H NMR of In02 was shown in figure S4 and the ^{13}C-NMR was shown in figure S18.**

Bis (2-methyl-1H-indol-3-yl) disulfide (In03, 10).Compound **10** was prepared using the same method as**8** and given as a white solid (yield = 41.7%). **Purification by**

column chromatography on silica gel (petroleum ether/EtOAc100: 1→10: 3) gave compound 10 as a brown solid (yield 75.4%). Melting point was 170.8~175.2℃. ^{1}H-NMR (DMSO-d6) δ: 1.73 (m, 6H, -CH_3), 11.43 (m, 2H, -NH), 6.99~7.02 (t, 2H, J=7.4Hz), 7.07~7.09 (t, 2H, J=7.5Hz), 7.29~7.32 (m, 4H). **^{13}C NMR (151 MHz, DMSO-d6) δ 142.73 (s, 2C), 135.36 (s, 2C), 129.25 (s, 2C), 121.32 (s, 2C), 119.68 (s, 2C), 117.83 (s, 2C), 110.95 (s, 2C), 102.26 (s, 2C), 10.54 (s, 2C). The ^{1}H NMR of In03 was shown in figure S5 and the ^{13}C-NMR was shown in figure S19.**

Bis (1-methy-1H-indol-3-yl) disulfide (In04, 11). Compound **11** was prepared using the same method as**8** and given as a pink solid (yield =53.6%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc 10:1) gave compound 11 as abrownsolid (yield82.3%).** Melting point was 134~136℃. ^{1}H-NMR (DMSO-d6) δ: 3.76(s, 6H, -CH_3), 7.34~7.37 (m, 4H), 7.06~7.11 (t, 2H, J=7.4Hz), 7.22~7.27 (t, 2H, J=7.56Hz), 7.50~7.52 (d, 2H, J=8.16Hz). **^{13}C NMR (151 MHz, DMSO-d6) δ 137.03 (s, 2C), 135.70 (s, 2C), 128.67 (s, 2C), 122.10 (s, 2C), 120.03 (s, 2C), 118.79 (s, 2C), 110.39 (s, 2C), 104.60 (s, 2C), 32.58 (s, 2C).The ^{1}H NMR of In04 was shown in figure S6 and the ^{13}C-NMR was shown in figure S20.**

Bis (5-bromo-1H-indol-3-yl) disulfide (In05, 12).Compound **12** was prepared using the same method as**8** and given as a yellow solid (yield =30.7%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc 2:1) gave compound 12 as ayellow solid (yield 77.8%).** Melting point was 249.5~250.4℃. ^{1}H-NMR (DMSO-d6) δ: 11.79(s, 2H), 7.25~7.28 (m, 4H), 7.40~7.45 (m, 4H). **13C NMR (151 MHz, DMSO-d6) δ 135.14 (s, 2C), 133.39 (s, 2C), 130.12 (s, 2C), 124.65 (s, 2C), 120.80 (s, 2C), 114.17 (s, 2C), 112.83 (s, 2C), 105.32 (s, 2C). The ^{1}H NMR of In05 was shown in figure S7 and the ^{13}C-NMR was shown in figure S21.**

Bis (1-benzyl-5-bromo-1H-indol-3-yl) disulfide (In06, 13).Compound **13** was prepared using the same method as**8** and given as a yellow solid (yield =40.1%). **Purification by column chromatography on silica gel (petroleum ether/EtOAce100: 1→10: 1) gave compound 13 as a white solid (yield 63.5%).** Melting point was 111.7~115.3℃. ^{1}H-NMR (DMSO-d6) δ: 5.5(s, 4H, -CH_2), 7.25~7.32 (m, 10H, -C_6H_5), 8.27(s, 2H), 7.82~7.83 (d, 2H, J=1.68Hz), 7.41~7.44 (dd, 2H, J_{12}=1.8Hz, J_{13}=8.76Hz), 7.61~7.64 (d, 2H, J=8.79Hz). **13C NMR (151 MHz, DMSO-d6) δ 137.28 (s, 2C), 136.68 (s, 2C), 134.92 (s, 2C), 129.64 (s, 2C), 128.62 (s, 4C), 127.71 (s, 2C), 127.17 (s, 4C), 125.69 (s, 2C), 120.28 (s, 2C), 114.16 (s, 2C), 113.80 (s, 2C), 111.98 (s, 2C), 49.73 (s, 2C). The ^{1}H NMR of In06 was shown in figure S8 and the ^{13}C-NMR was shown in figure S22.**

Bis (4-dimethylaminophenyl) disulfide (Ph01, 14).Compound**4** (1.8g, 10mmol) was dissolved in 10% aqNaOH (25mL) and the solution was refluxed for 2.5 h, cooled to room temperature, and acidified to pH 6with 6N aq H_2SO_4 to precipitate the crude product. The resulting crystal was leached, dried at room temperature and purified by column chromatography (petroleum ether/EtOAc= 25:1) to give **14**as a yellow solid (1.9g, 62.5%). Melting point was 118~119℃. ^{1}H-NMR (DMSO-d6) δ: 6.65~6.68(d, 4H, J=8.85Hz), 7.22~7.25 (dd, 4H, J_{12}=1.83Hz, J_{13}=6.96Hz), 2.92 (s, 12H, -CH_3). **13C NMR (151 MHz, DMSO-d6) δ 150.04 (s, 2C), 133.08 (s, 4C), 120.68 (s, 2C), 111.88 (s, 4C), 41.92(s, 4C). The ^{1}H NMR of Ph01 was shown in figure S9 and the ^{13}C-NMR was shown in figure S23.**

Bis (4-amino-3,5-dimethylphenyl)disulfide (Ph02, 15).Compound **15** was prepared using the same method as14 and given as a yellow solid (yield = 30.3%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc5:2) gave compound 15 as a yellow solid (yield71.7%).** ^{1}H-NMR (DMSO-d6) δ: 2.05(m, 12H,

-CH_3), 4.94 (s, 4H, -NH_2), 6.89 (s, 4H). **^{13}C NMR (151 MHz, DMSO-d6) δ 145.42 (s, 2C), 132.95, 132.61 (s, 4C), 121.13 (s, 4C), 17.55 (s, 4C). The ^{1}H NMR of Ph02 was shown in figure S10 and the ^{13}C-NMR was shown in figure S24.**

Bis (4-amino-3-chloro-5-methylphenyl) disulfide (Ph03, 16). Compound **16** was prepared using the same method as**1**4 and given as a yellow solid (yield = 71.3%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc100: 1→10: 3) gave compound 16 as a yellow solid (yield 79.4%).** Melting point was 148.1~150.3℃. ^{1}H-NMR (DMSO-d6) δ: 2.11(s, 6H, -CH_3), 7.0~7.1 (m, 4H). **13C NMR (151 MHz, DMSO-d6) δ 143.91 (s, 2C), 133.30 (s, 2C), 130.82 (s, 2C), 123.74 (s, 2C), 121.30 (s, 2C), 116.71 (s, 2C), 18.03 (s, 2C). The ^{1}H NMR of Ph03 was shown in figure S11 and the ^{13}C-NMR was shown in figure S25.**

Bis-(4-chloroactanmido-3-3-chloro-5-methylphenyl) disulfide (Ph04, 17).To a solution of Compound **16** (0.33g, 1mmol) in CH_2Cl_2 (10mL) was added pyridine (0.13mL, 2mmol). The mixture was cooled by ice bath and chloroacetyl chloride (0.2mL, 2.5mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3h. The resulting crystal was washed by water, extracted with CH_2Cl_2 (30mL×3), dried with Na_2SO_4, and concentrated via rotary evaporation togive the titled compound as a yellow solid (0.13g, 20.2%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc10:3) gave compound 17 as a yellow solid (yield 73.5%).** Melting point was 155.4~156.7℃. ^{1}H-NMR (DMSO-d6) δ: 2.16(s, 6H, -CH_3), 4.29 (s, 4H, -CH_2), 7.43~7.44 (d, 2H, J=1.57Hz), 7.51~7.52 (d, 2H, J=1.8Hz), 9.95 (s, 2H, -NH-). **^{13}C NMR (151 MHz, DMSO-d6) δ 164.84 (s, 2C), 139.27 (s, 2C), 135.08 (s, 2C), 132.55 (s, 2C), 131.41 (s, 2C), 127.34 (s, 2C),**

124.86 (s, 2C), 42.33 (s, 2C), 18.54 (s, 2C). The ^{1}H NMR of Ph04 was shown in figure S12 and the ^{13}C-NMR was shown in figure S26.

Bis (4-acetamido-3-chloro-5-methylphenyl) disulfide (Ph05, 18).Compound **18** was prepared using the same method as**17** and given as a yellow solid (yield = 46.3%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc 5:1) gave compound 18 as a white solid (yield68.6%).** Melting point was 147.4~151.5℃. ^{1}H-NMR (DMSO-d6) δ: 9.5(s, 2H, -NH-), 7.12~7.45 (m, 4H), 2.04~2.16 (m, 12H, -CH_3). **^{13}C NMR (151 MHz, DMSO-d6) δ 167.34(s, 2C), 140.12(s, 2C), 135.93(s, 2C), 132.95(s, 2C), 131.31(s, 2C), 127.13(s, 2C), 124.26(s, 2C), 25.36(s, 2C), 18.62(s, 2C). The ^{1}H NMR of Ph05 was shown in figure S13 and the ^{13}C-NMR was shown in figure S27.**

Bis (4-benzamido-3-chloro-5-methylpheny) disulfide (Ph06, 19).Compound **19** was prepared using the same method as**17** and given as a yellow solid (yield = 33.3%). **Purification by column chromatography on silica gel (petroleum ether/EtOAc100: 1→5: 1) gave compound 19 as a white solid (yield 75.4%).** Melting point was 148~149℃. ^{1}H-NMR (DMSO-d6) δ: 2.2(s, 6H, -CH_3), 7.49~7.59 (m, 10H, -C_6H_5), 7.9~8.0 (m, 4H), 10.1 (s, 2H, -NH-). **^{13}C NMR (151 MHz, DMSO-d6) δ 165.07 (s, 2C), 133.65 (s, 2C), 133.45 (s, 2C), 133.25 (s, 2C), 131.77 (s, 2C), 131.56 (s, 2C), 131.41 (s, 2C), 128.54 (s, 2C), 128.42 (s, 4C), 127.48 (s, 4C), 124.99 (s, 2C), 18.25 (s, 2C). The ^{1}H NMR of Ph06 was shown in figure S14 and the ^{13}C-NMR was shown in figure S28.**

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Table S1 The Field Similarity for template molecules

Template	IPA-3	PIR-3.1	PIR-3.2	Similarity	Field Similarity	Field score
1	109	1	70	0.827552	0.804304	-70.3667
2	110	2	69	0.827483	0.804514	-70.3868
3	186	2	18	0.813706	0.763314	-66.0783
4	186	2	18	0.813698	0.772880	-66.8999
5	185	1	17	0.813171	0.763067	-66.054
6	135	3	40	0.810888	0.771752	-63.5742
7	200	1	17	0.810348	0.759186	-68.5881
8	136	4	39	0.809992	0.765898	-63.1079
9	199	2	18	0.809601	0.760031	-68.6595
10	185	1	17	0.809130	0.780548	-67.5363
11	154	3	66	0.808880	0.765617	-66.3258
12	199	2	18	0.808584	0.757613	-68.4563
13	153	4	65	0.808382	0.763628	-66.1613

14	145	3	104	0.808263	0.767546	-62.6144
15	153	4	94	0.806973	0.752086	-65.7594
16	154	3	93	0.806915	0.754017	-65.9109
17	199	3	93	0.804640	0.749901	-67.434
18	200	4	94	0.804551	0.748723	-67.3341
19	199	5	18	0.799864	0.747472	-65.0213
20	199	2	52	0.798403	0.745201	-67.6319
21	200	6	17	0.798142	0.746033	-64.9018
22	200	6	17	0.798103	0.745238	-64.8267
23	199	5	18	0.797704	0.745677	-64.8742
24	200	1	51	0.797673	0.746901	-67.7923
25	199	2	52	0.796482	0.741219	-67.2767
26	200	1	51	0.795201	0.740589	-67.2284
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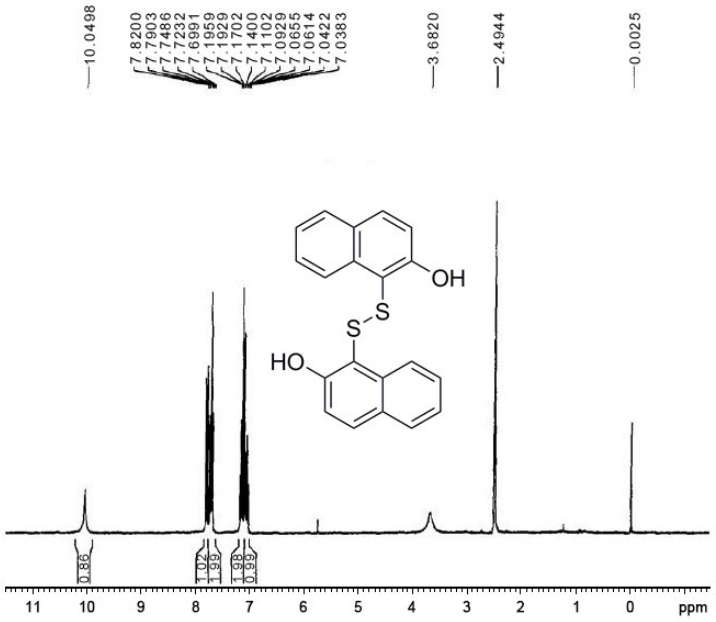

Figure S1

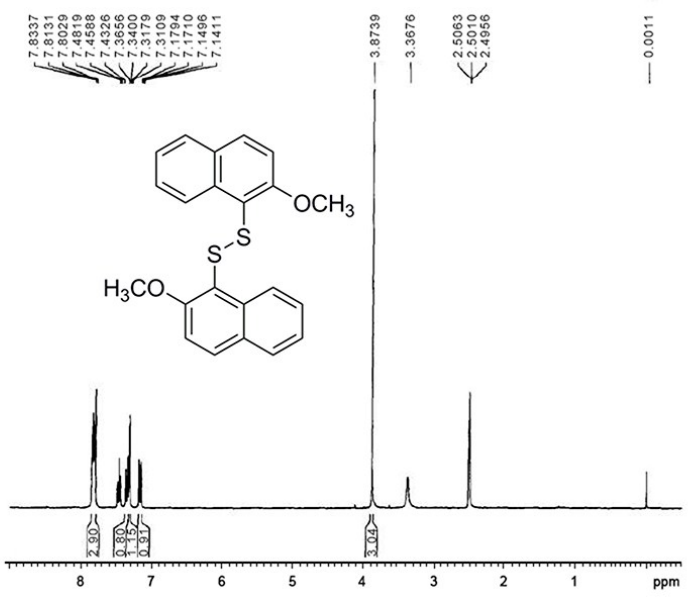

Figure S2

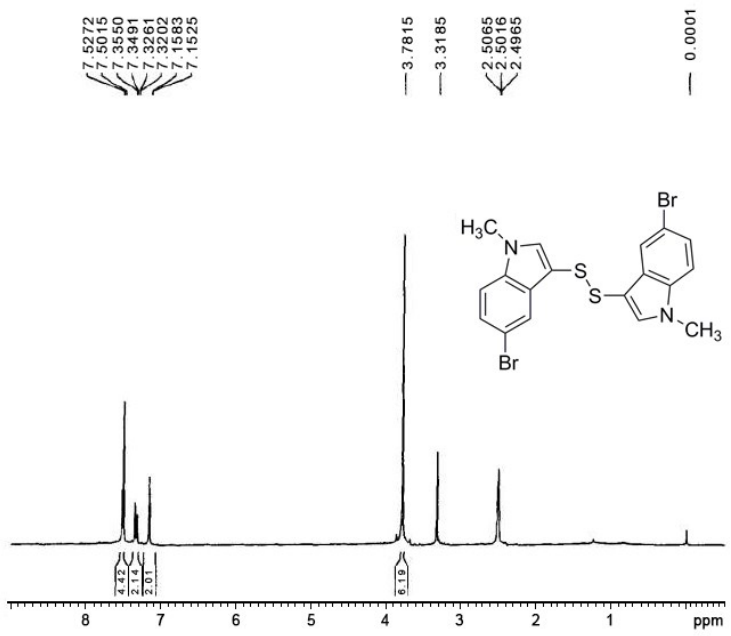

Figure S3

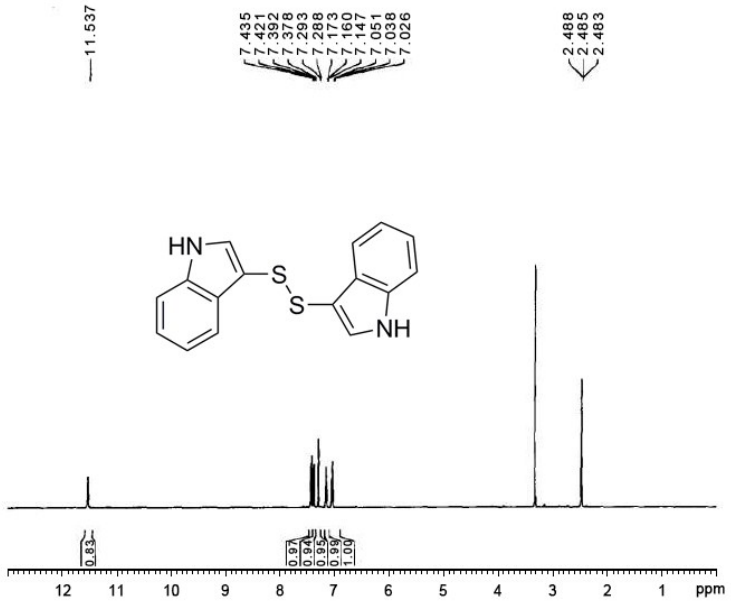

Figure S4

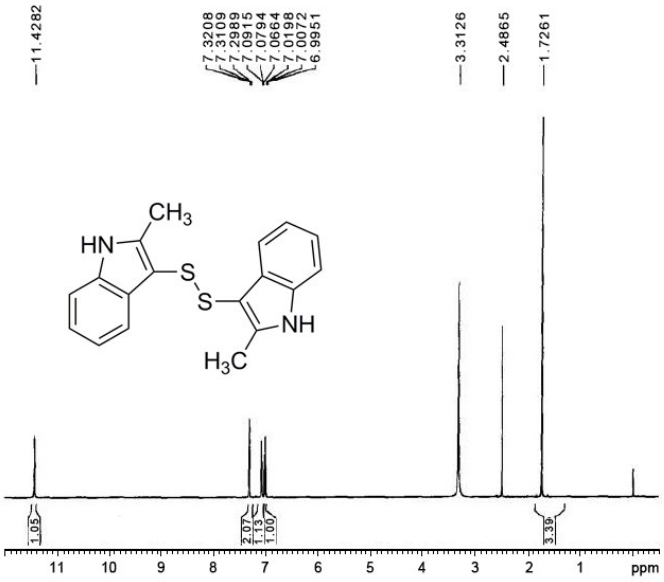

Figure S5

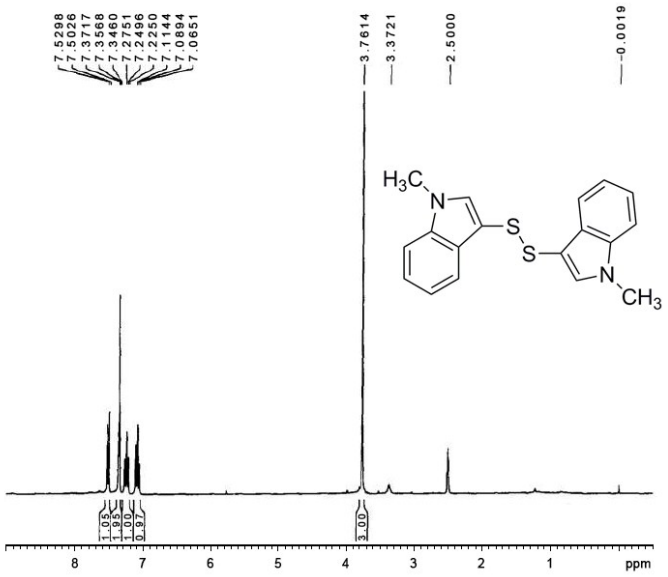

Figure S6

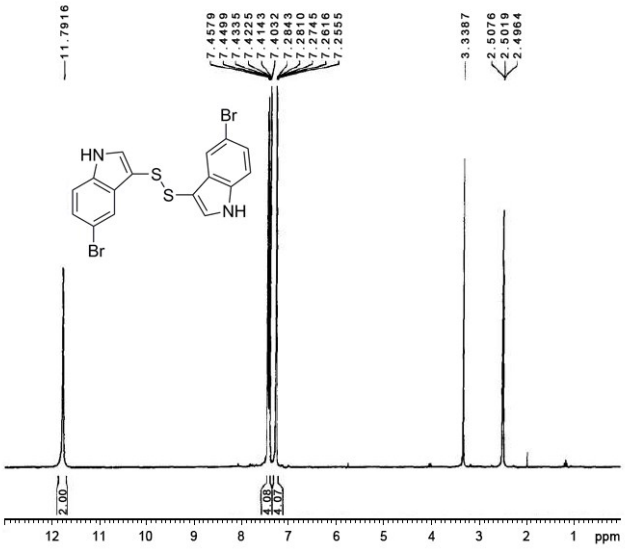

Figure S7

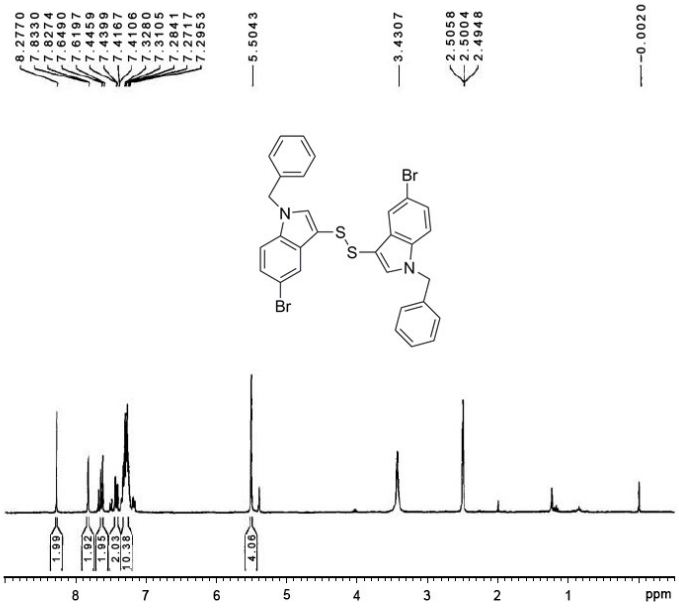

Figure S8

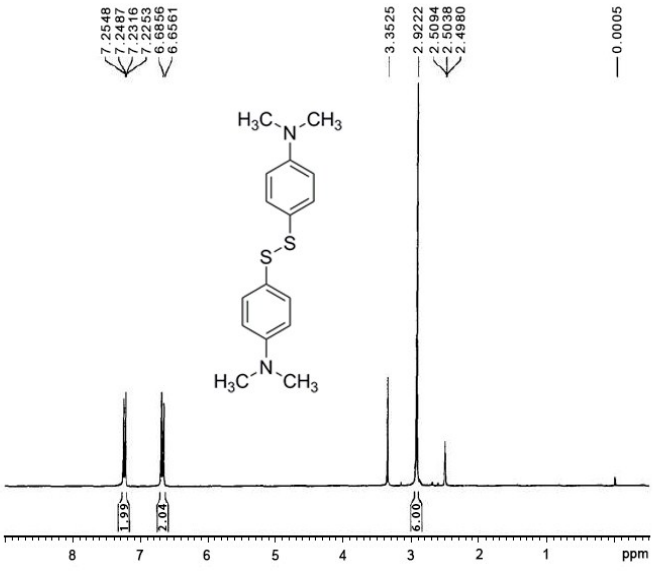

Figure S9

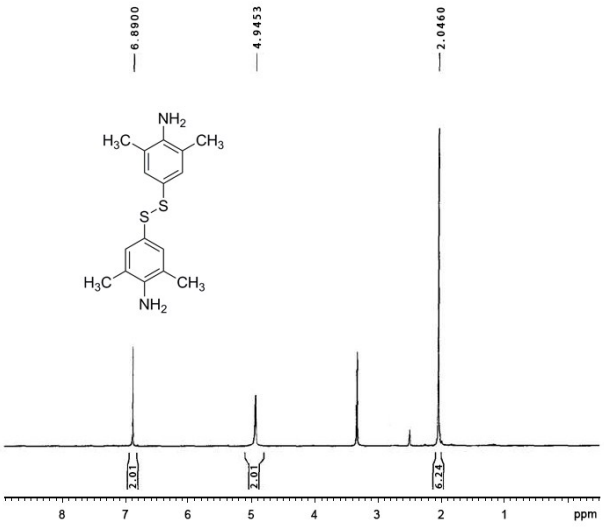

Figure S10

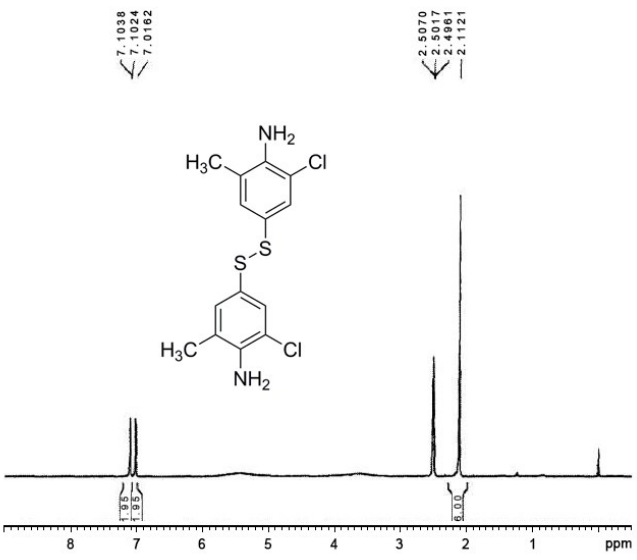

Figure S11

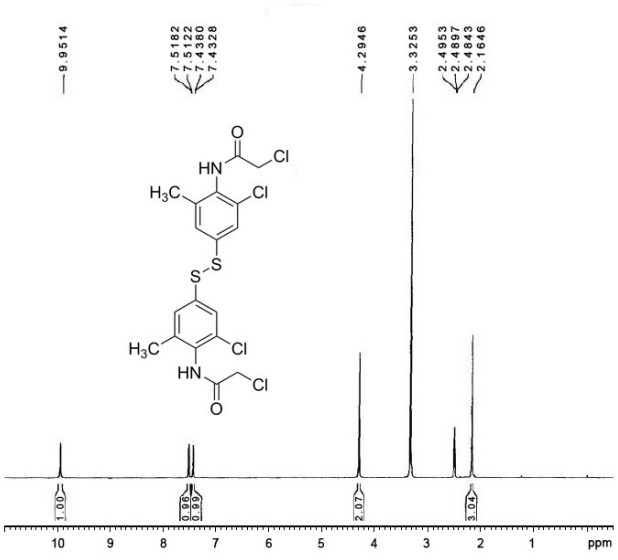

Figure S12

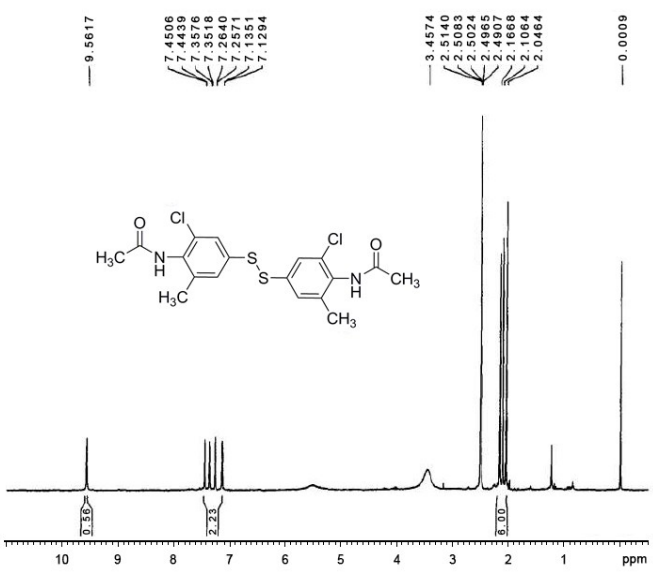

Figure S13

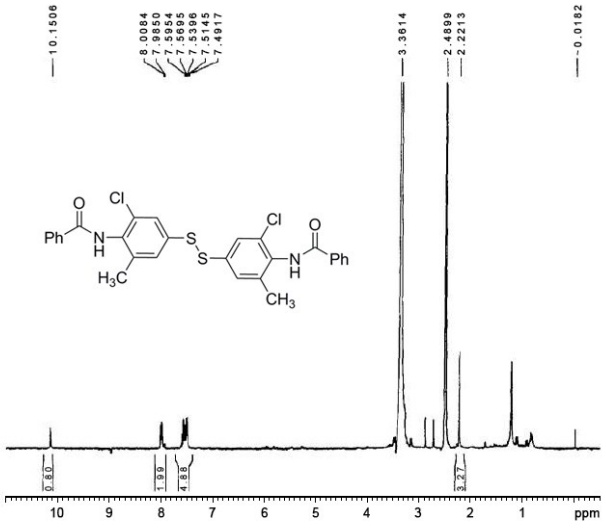

Figure S14

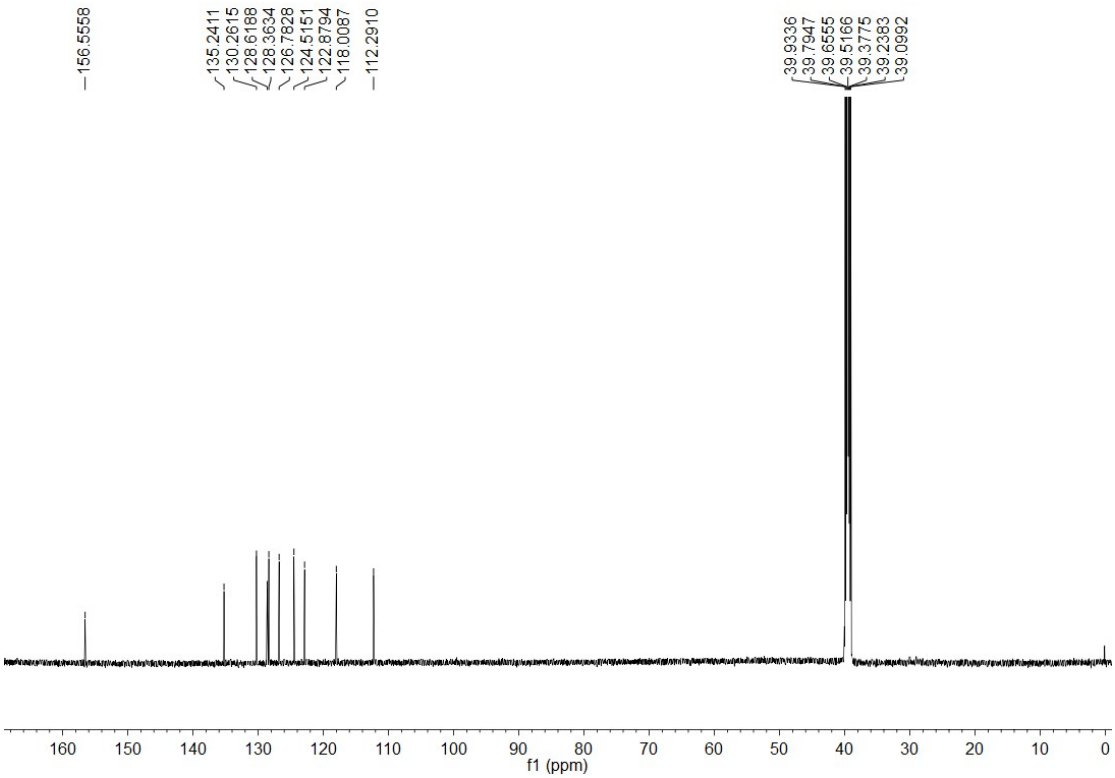

Figure S15

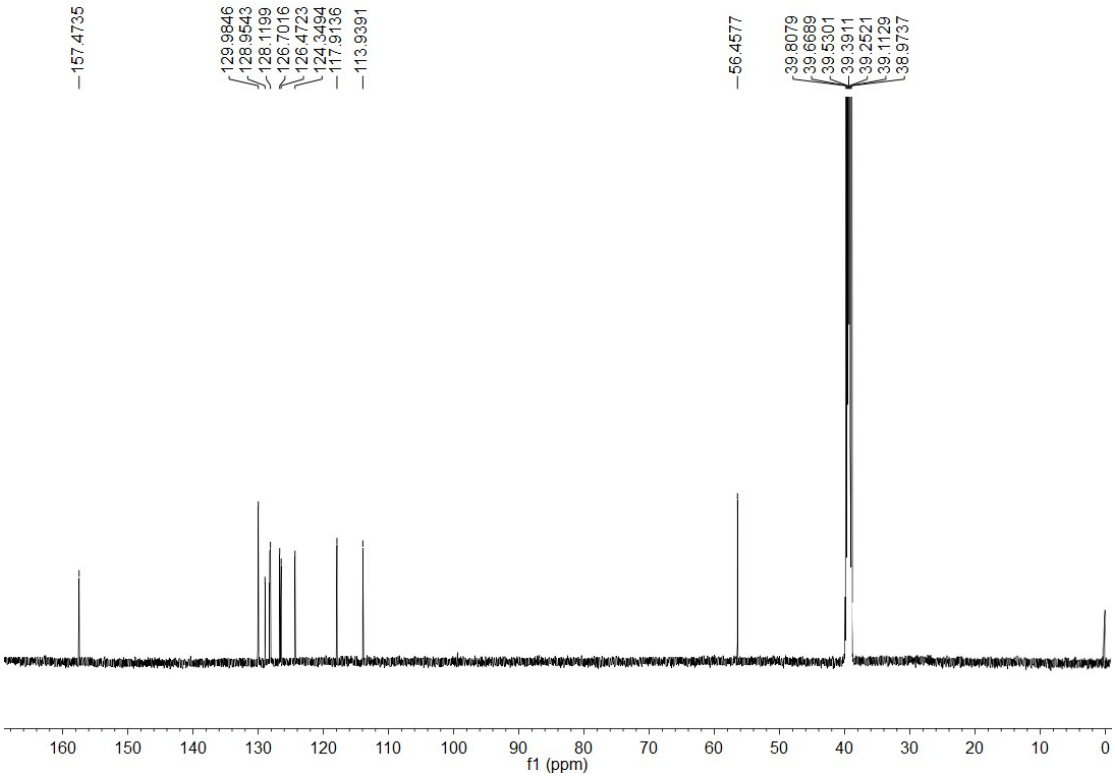

Figure S16

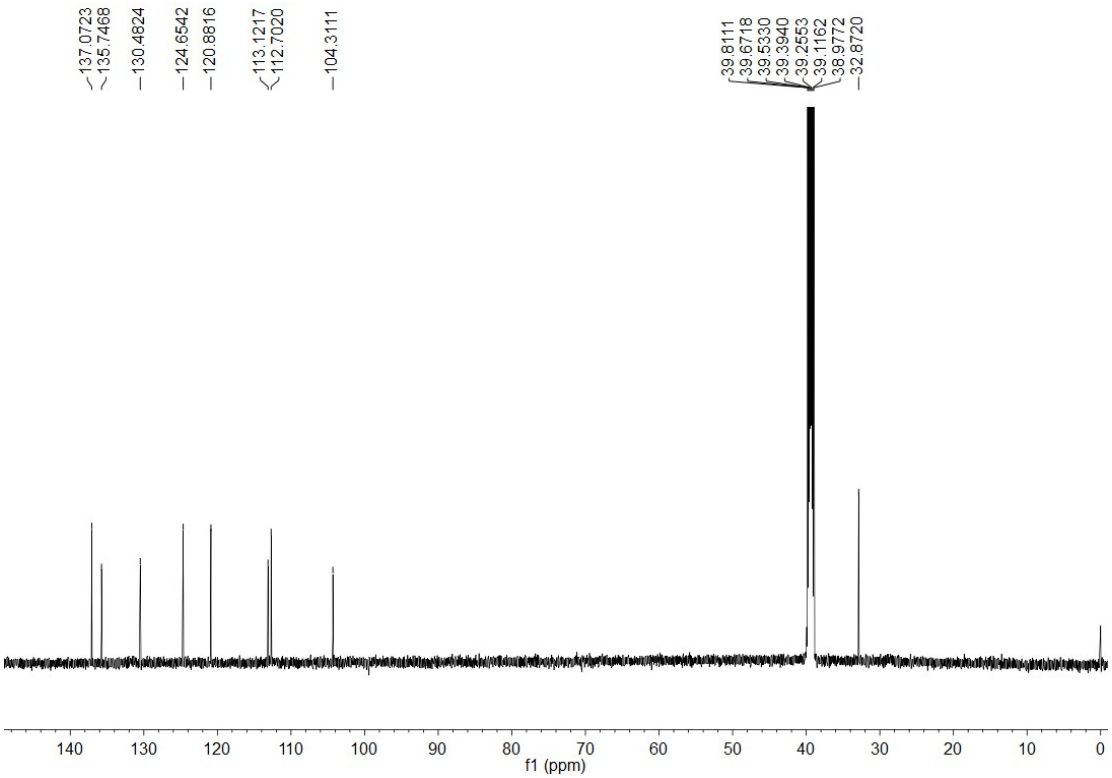

Figure S17

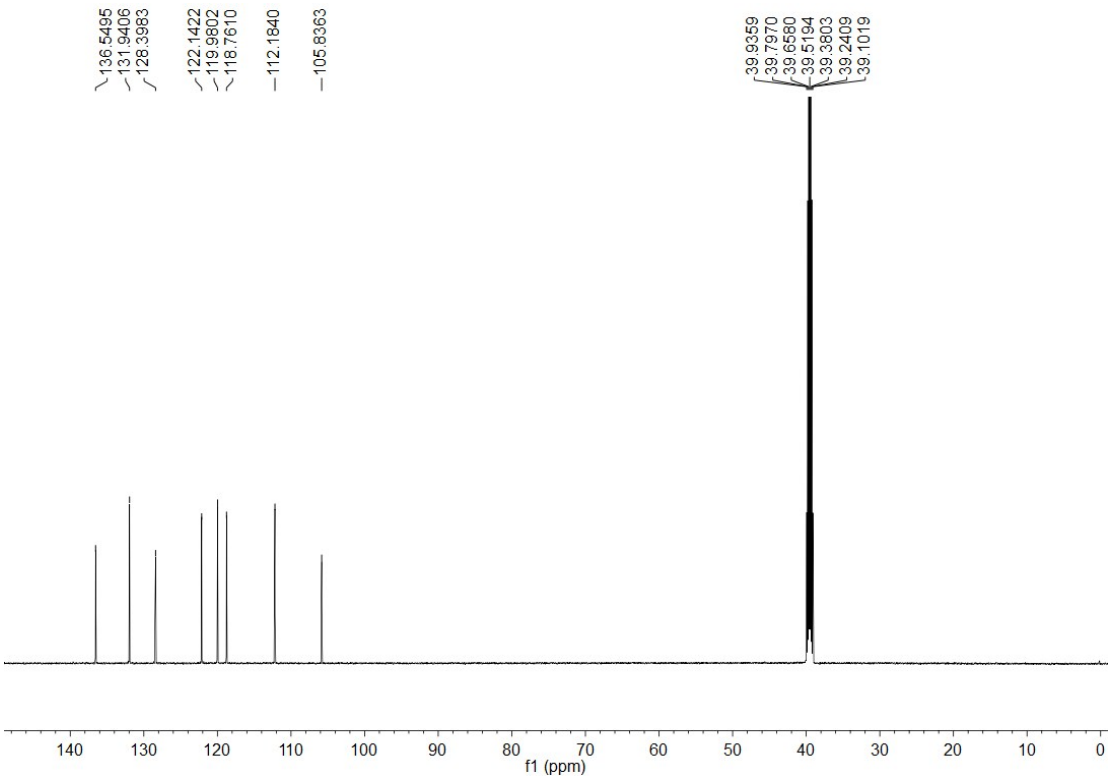

Figure S18

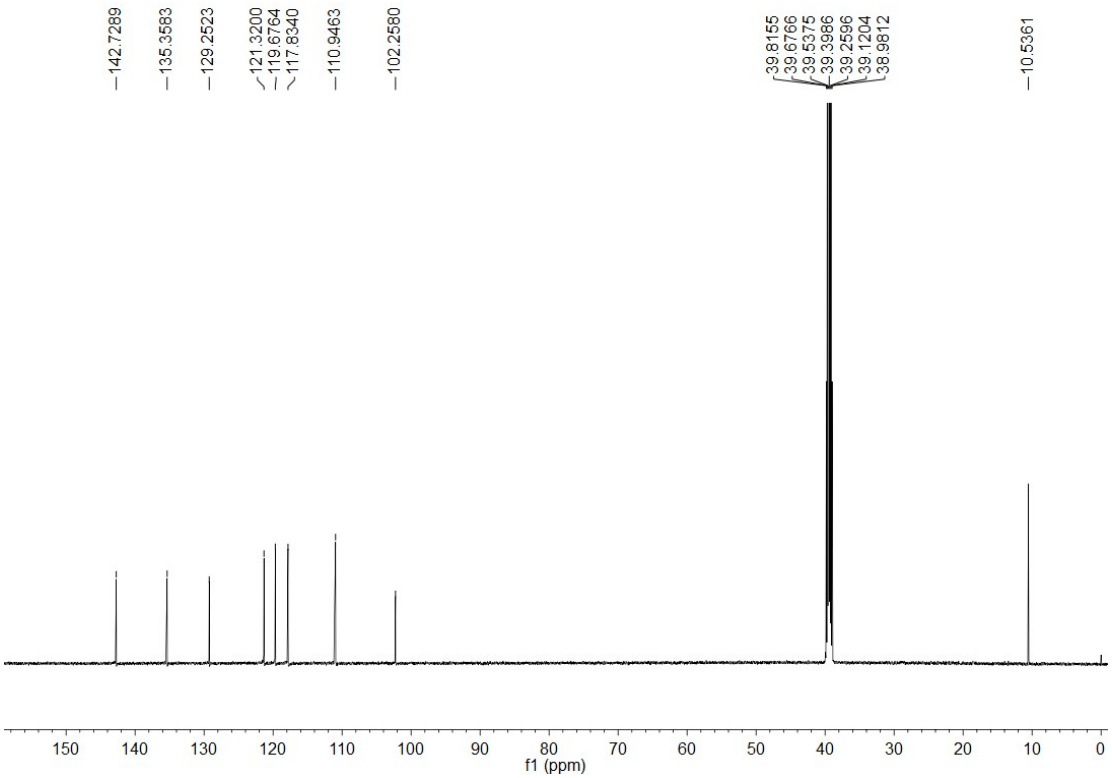

Figure S19

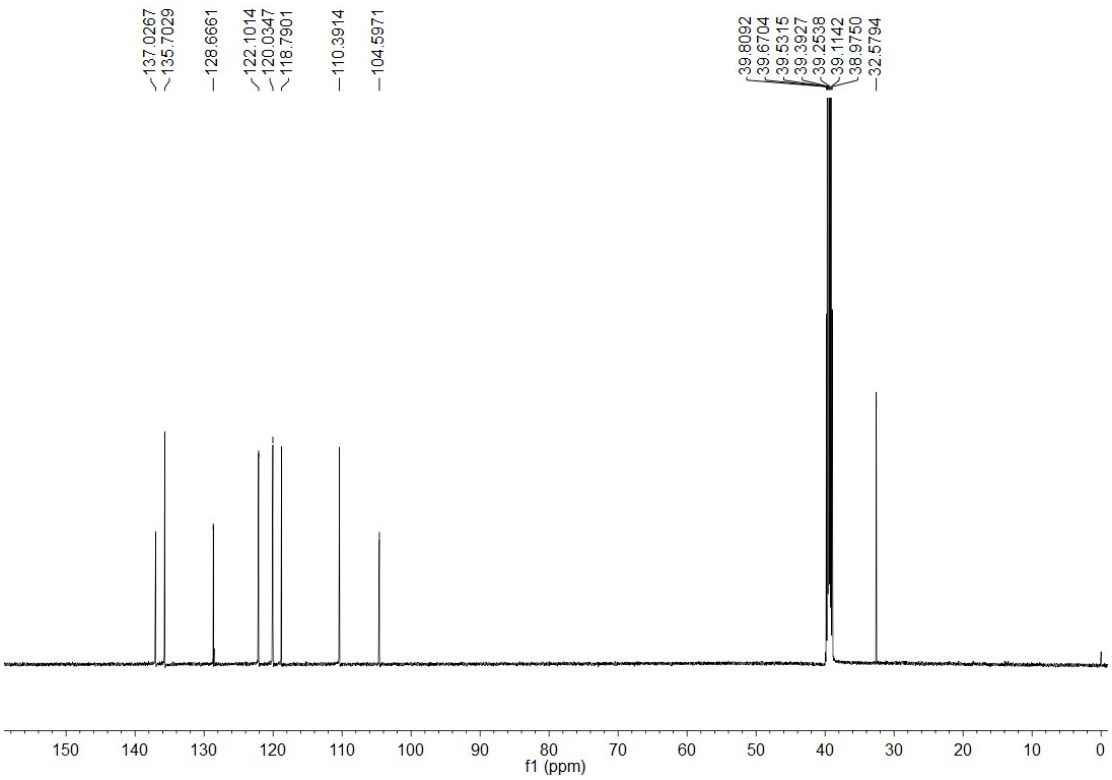

Figure S20

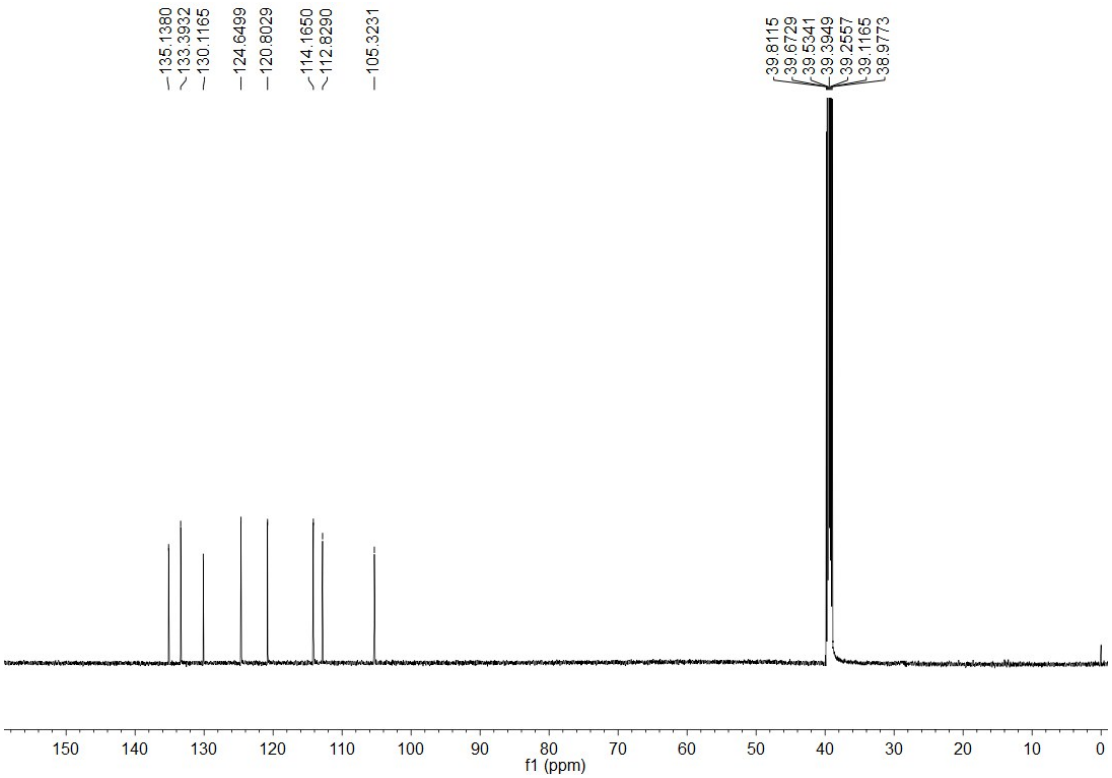

Figure S21

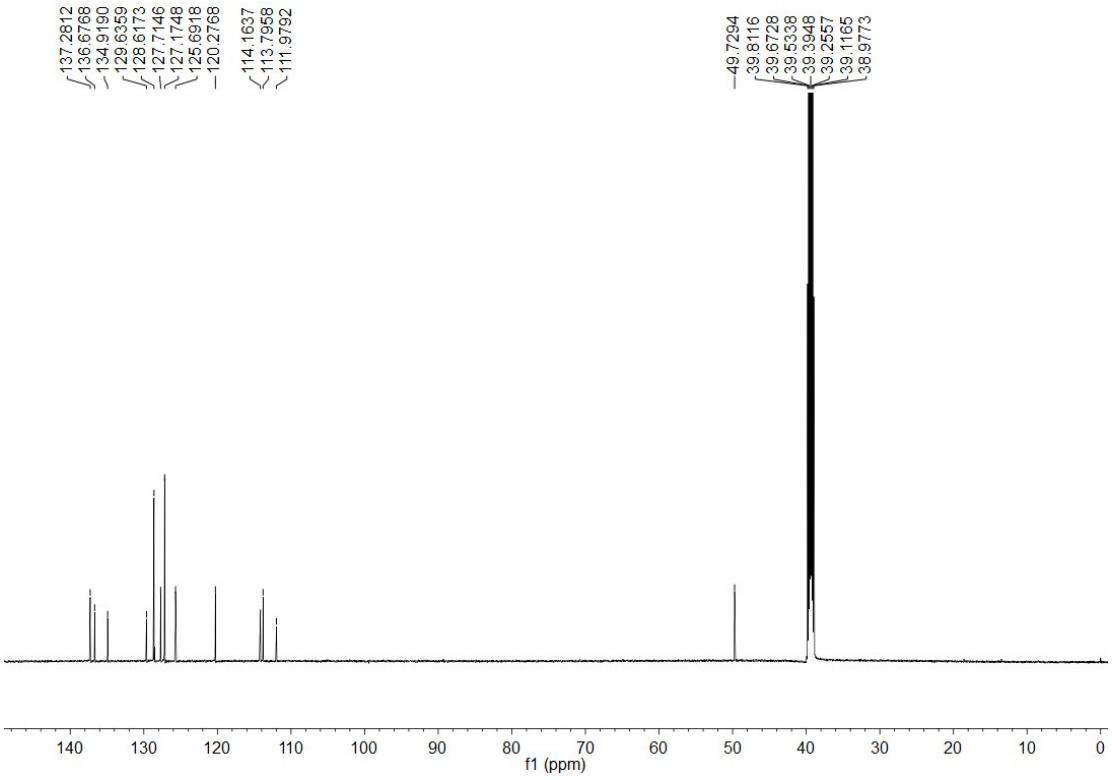

Figure S22

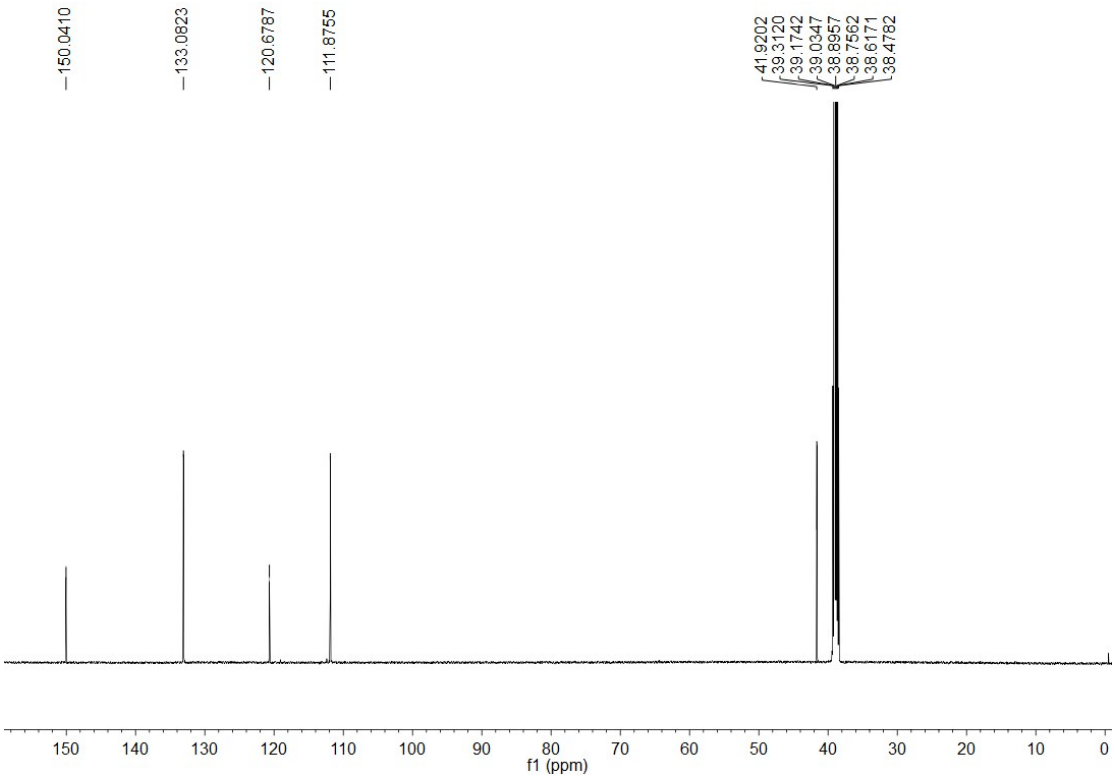

Figure S23

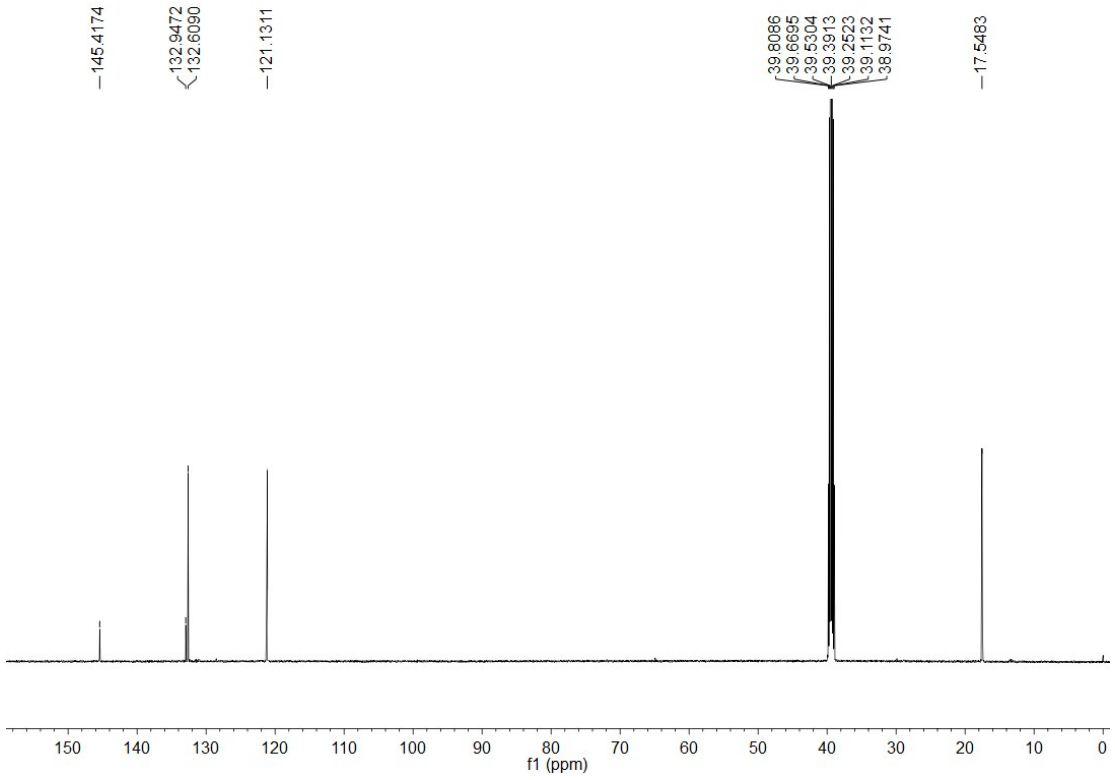

Figure S24

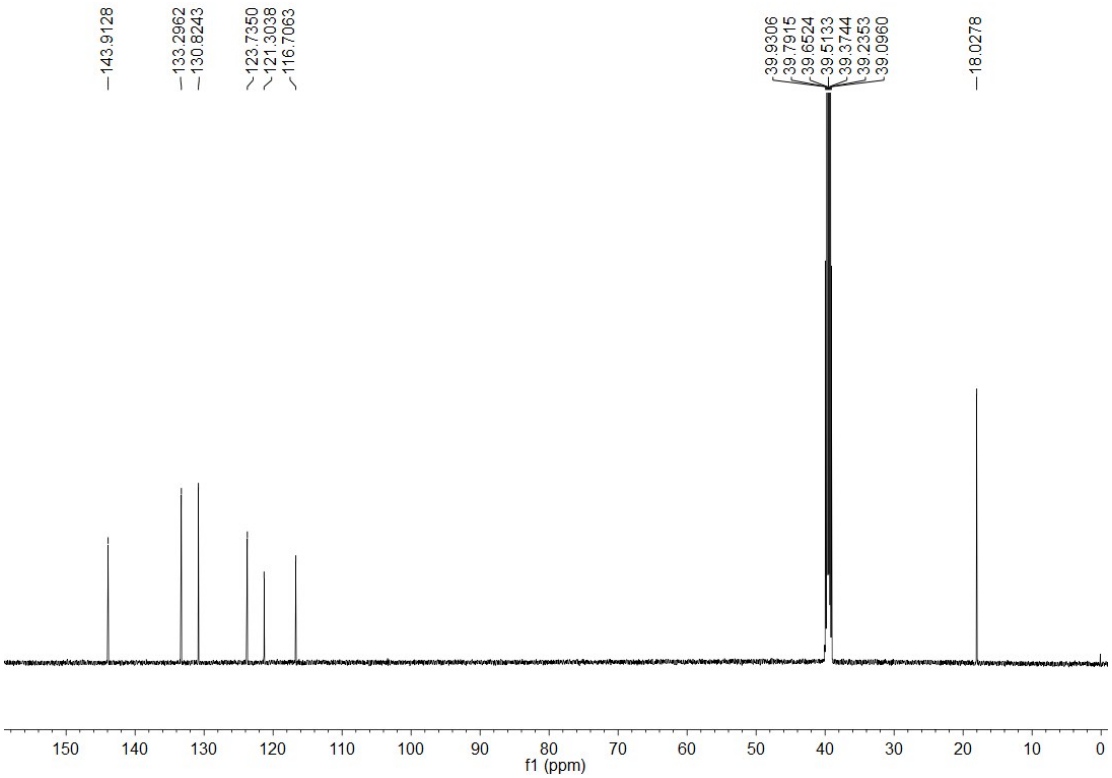

Figure S25

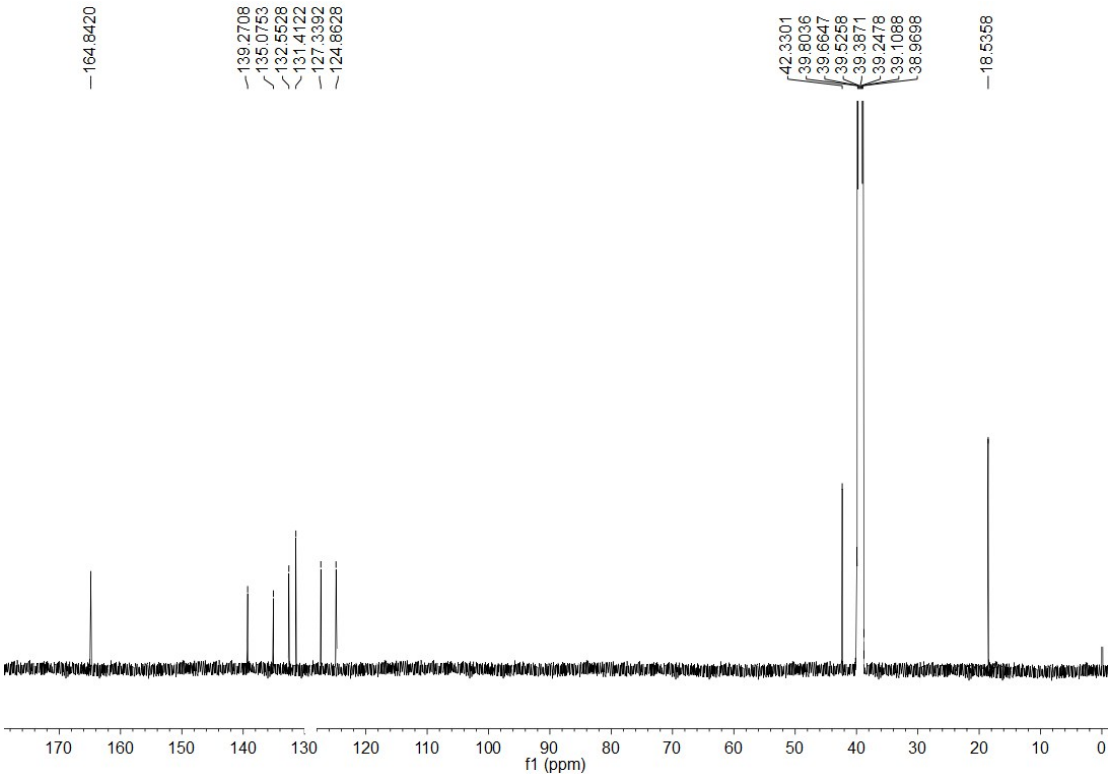

Figure S26

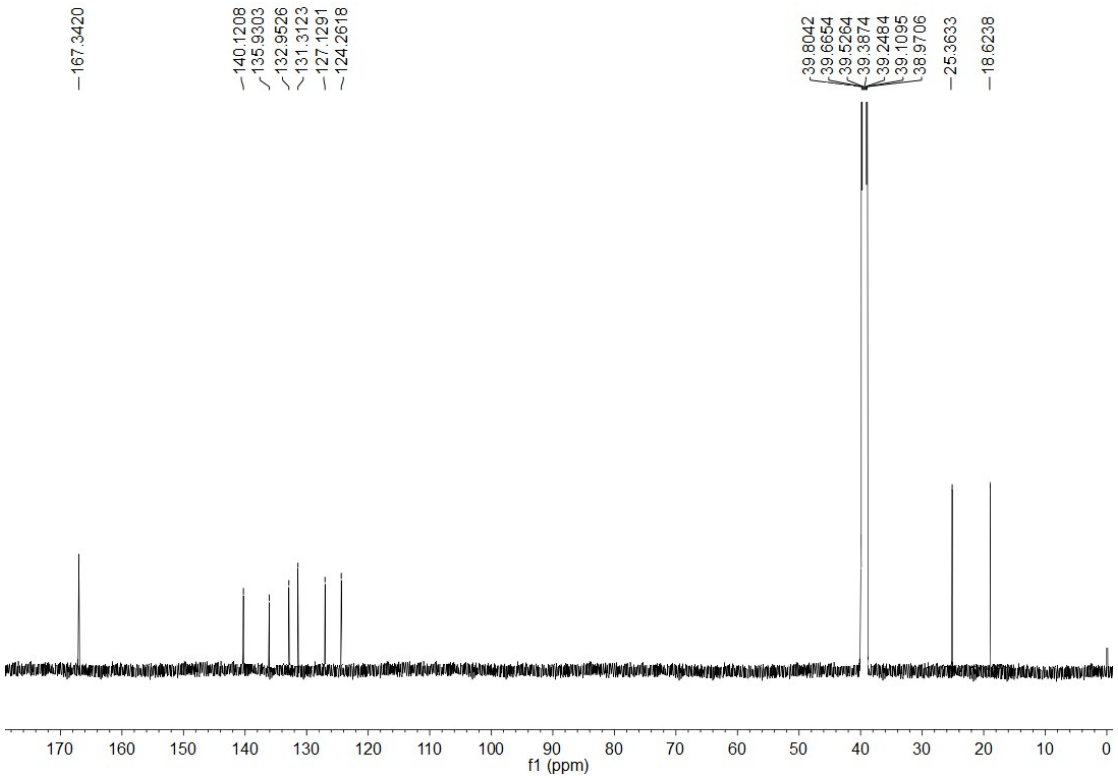

Figure S27

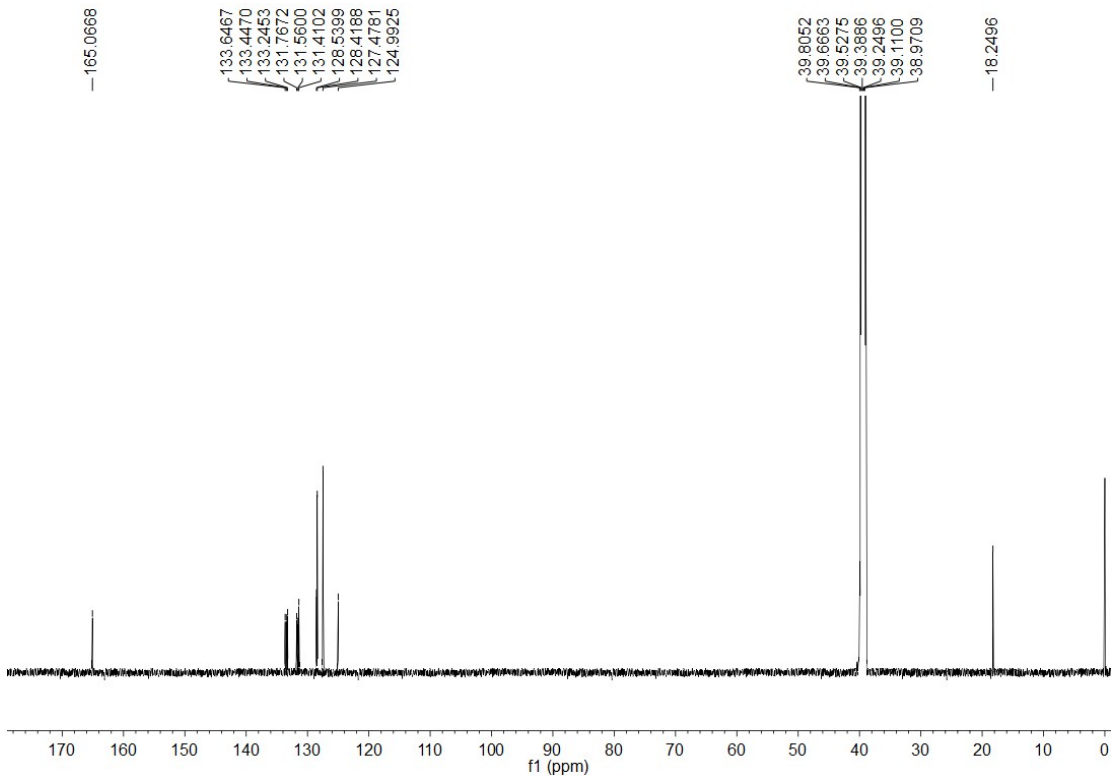

Figure S28