Discovery of novel coumarin amphiphiles: dual-action antimicrobials with bacteria-mediated biofilm disruption and host-directed immunomodulation

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General procedure for preparation of target compound 2

A solution of **1** in CH_2Cl_2 (25 mL) was treated with a solution of 1.0 M BBr_3 in CH_2Cl_2. The solution was stirred for 1 hour at room temperature and then hydrolyzed with water (30 mL). After stirring for 30 minutes, the precipitate formed was filtered. Separation of the organic layer The organic layer was separated, dried over Na_2SO_4 and then the organic solvent was evaporated in vacuum to obtain the residue. The crude product was finally purified by column chromatography to give compound **2**.

General procedure for preparation of target compound 6

A mixture of 2-hydroxybenzaldehyde (18.1 mmol) and (triphenylphosphoranylidene) ethyl acetate (7.6 g, 21.7 mmol) in N,N-diethylaniline (50 mL) was refluxed under N_2. The reaction mixture was diluted with 5% aqueous solution. HCl solution, extracted with Et_2O and concentrated in vacuum. The residue was purified with (petroleum ether/Et_2O).

General procedure for preparation of target compound 10

10 Properly substituted resorcinol (100 mmol) was dissolved in dioxane (100 mL) and ethylpropiolate (100 mmol), and dried zinc chloride (100 mmol) was added. The mixture was refluxed for 24 h. After cooling to room temperature, 100 mL of 5% HCl was added slowly. After addition, the mixture was concentrated to half volume and kept at 4℃. The precipitate was filtered and dried at room temperature.

General procedure for preparation of target compound 13

Properly substituted resorcinol (100 mmol) was dissolved in dioxane (100 ml) and ethylpropiolate (100 mmol), and dried zinc chloride (100 mmol) was added. The mixture was refluxed for 24 h. After cooling to room temperature, 100 ml of 5% HCl was added slowly. After addition, the mixture was concentrated to half volume and kept at 4℃. The precipitate was filtered and dried at room temperature. The product was recrystallised from ethanol. Compound **13** was obtained.

General procedure for preparation of target compound 3, 7, 11 and 14

The appropriate dibromoalkane (1.5 mmol) was added to a solution of hydroxycoumarin (1.5 mmol) and potassium carbonate (3 mmol) in acetone (50 mL) with stirring. The mixture was heated at refluxed and the reaction was monitored by TLC. After cooling, the mixture was separated and the solvent was evaporated. The crude product was Purification by column chromatography to yield compounds **3**, **7**, **11** and **14**.

General procedure for preparation of target compound 4, 8, 12 and 15

The appropriate Amino group (1.5 mmol) was added to a solution of coumarin derivatives (1.5 mmol) and potassium carbonate (3 mmol) in acetone (50 mL) with stirring. The mixture was heated at refluxed and the reaction was monitored by TLC. After cooling, the mixture was separated and the solvent was evaporated. The crude product was Purification by column chromatography to yield compounds **4**, **8**, **12** and **15**.

3-hydroxy-2H-chromen-2-one (**2**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.43 – 7.23 (m, 3H), 7.12 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.32, 149.07, 141.63, 127.64, 126.36, 124.59, 120.57, 115.61, 114.92. TOF-MS, m/z: [M+H$^+$] calculated for $C_9H_7O_3$, 163.0317, found: 163.0322.

3-((10-bromodecyl)oxy)-2H-chromen-2-one (**3a**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 6.8 Hz, 1H), 7.46 – 7.25 (m, 5H), 7.12 (s, 1H), 4.01 (t, J = 6.5 Hz, 2H), 3.51 (t, J = 6.7 Hz, 2H), 1.90 – 1.67 (m, 5H), 1.57 – 1.17 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.59, 149.00, 143.19, 128.25, 126.84, 124.67, 115.64, 113.81, 68.81, 60.71, 39.52, 35.20, 32.24, 28.86, 28.81, 28.62, 28.13, 28.07, 27.51, 25.51, 25.40. TOF-MS, m/z: [M+H$^+$] calculated for $C_{19}H_{26}BrO_3$, 381.1065, found: 381.1069.

3-((12-bromododecyl)oxy)-2H-chromen-2-one (**3b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 8.5 Hz, 1H), 7.47 – 7.26 (m, 2H), 4.26 (t, J = 6.6 Hz, 1H), 4.03 (q, J = 7.2 Hz, 3H), 3.51 (t, J = 6.7 Hz, 6H), 1.87 – 1.66 (m, 7H), 1.45 – 1.32 (m, 8H), 1.18 (t, J = 7.1 Hz, 22H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 128.25, 126.86, 124.66, 115.63, 113.83, 68.83, 59.75, 39.52, 35.17, 32.57, 32.26, 29.13, 29.00, 28.88, 28.69, 28.16, 28.13, 27.53, 25.53, 20.77, 14.09. TOF-MS, m/z: [M+H$^+$] calculated for $C_{21}H_{30}BrO_3$, 409.1305, found: 409.1308.

3-((10-(diethylamino)decyl)oxy)-2H-chromen-2-one (**4a**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 8.1 Hz, 1H), 7.50 – 7.27 (m, 3H), 5.75 (s, 1H), 4.02 (t, J = 6.4 Hz, 2H), 3.03 (dd, J = 43.5, 7.8 Hz, 5H), 1.85 – 1.71 (m, 2H), 1.68 – 1.55 (m, 2H), 1.50 – 1.11 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.62, 149.00, 143.19, 128.31, 126.86, 124.71, 119.90, 115.67, 113.85, 68.83, 54.92, 50.87, 46.26, 28.94 – 28.60 (m), 28.51, 28.15, 26.02, 25.45, 8.59. TOF-MS, m/z: [M+H$^+$] calculated for $C_{23}H_{36}NO_3$, 374.2617, found: 374.2622.

3-((12-(diethylamino)dodecyl)oxy)-2H-chromen-2-one (**4b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 7.6 Hz, 1H), 7.50 – 7.22 (m, 3H), 4.02 (t, J = 6.5 Hz, 2H), 3.51 (t, J = 6.7 Hz, 1H), 3.11 (q, J = 7.2 Hz, 5H), 3.05 – 2.95 (m, 3H), 1.81 – 1.71 (m, 3H), 1.61 (s, 3H), 1.45 – 1.14 (m, 29H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 124.66, 115.61, 113.85, 68.83, 50.73, 46.18, 39.52, 28.96, 28.68, 28.52, 28.14, 28.09, 27.49, 26.02, 25.42, 23.04, 8.48. TOF-MS, m/z: [M+H$^+$] calculated for $C_{25}H_{40}NO_3$, 402.2930, found: 402.2933.

6-hydroxy-2H-chromen-2-one (**6**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 9.5 Hz, 1H), 7.22 (d, J = 9.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 2H), 6.42 (d, J = 9.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.95, 191.45, 184.46, 181.78, 157.49, 156.94, 154.81, 153.93, 150.16, 77.16. TOF-MS, m/z: [M+H$^+$] calculated for $C_9H_7O_3$, 163.0317, found: 163.0321.

6-((10-bromodecyl)oxy)-2H-chromen-2-one (**7a**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 9.6 Hz, 1H), 7.40 – 7.09 (m, 3H), 6.47 (d, J = 9.6 Hz, 1H), 3.98 (t, J = 6.4 Hz, 2H), 3.50 (t, J = 6.7 Hz, 2H), 1.75 (dq, J = 22.5, 7.0 Hz, 3H), 1.50 – 1.18 (m, 11H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.08, 119.80, 119.20, 116.51, 111.30, 68.10, 60.71, 39.52, 32.55, 32.24, 28.88, 28.82, 28.70, 28.58, 28.09, 27.51, 25.45. TOF-MS, m/z: [M+H$^+$] calculated for $C_{19}H_{26}BrO_3$, 381.0987, found: 381.0991.

6-((12-bromododecyl)oxy)-2H-chromen-2-one (**7b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 9.6 Hz, 1H), 7.35 – 7.23 (m, 2H), 7.17 (d, J = 11.9 Hz, 1H), 6.47 (d, J = 9.6 Hz, 1H), 3.98 (t, J = 6.5 Hz, 2H), 3.50 (t, J = 6.7 Hz, 4H), 1.75 (tt, J = 14.9, 6.9 Hz, 5H), 1.46 – 1.20 (m, 22H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.74, 144.08, 119.79, 117.28, 116.50, 111.30, 39.52, 35.12, 32.56, 32.26, 29.02, 29.00, 28.96, 28.94, 28.90, 28.76, 28.60, 28.13, 27.53. TOF-MS, m/z: [M+H$^+$] calculated for $C_{21}H_{30}BrO_3$, 409.1300, found: 409.1303.

6-((10-(diethylamino)decyl)oxy)-2H-chromen-2-one (**8a**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 9.6 Hz, 1H), 7.39 – 7.11 (m, 2H), 6.49 (d, J = 9.5 Hz, 1H), 4.00 (t, J = 6.5 Hz, 2H), 3.16 – 2.91 (m, 4H), 1.66 (dt, J = 55.1, 7.0 Hz, 3H), 1.53 – 1.09 (m, 13H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 197.78, 192.63, 185.38, 181.74, 157.45, 156.86, 154.97, 154.19, 148.97, 105.75, 88.42, 83.87, 77.16, 66.52, 66.42, 66.36, 66.21, 66.15, 63.65, 63.11, 60.77, 46.19. TOF-MS, m/z: [M+H$^+$] calculated for $C_{23}H_{36}NO_3$, 374.2617, found: 374.2619.

6-((12-(diethylamino)dodecyl)oxy)-2H-chromen-2-one (**8b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 9.6 Hz, 1H), 7.37 – 7.07 (m, 2H), 6.47 (d, J = 9.5 Hz, 1H), 3.98 (t, J = 6.5 Hz, 1H), 2.72 (dd, J = 45.7, 7.2 Hz, 4H), 1.82 – 1.64 (m, 2H), 1.52 – 1.17 (m, 12H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 197.78, 192.63, 185.38, 181.74, 157.45, 156.86, 154.97, 154.19, 148.97, 105.75, 88.42, 83.87, 77.16, 66.52, 66.42, 66.36, 66.21, 66.15, 63.65, 63.11, 60.77, 46.19. TOF-MS, m/z: [M+H$^+$] calculated for $C_{21}H_{30}BrO_3$, 402.2930, found: 402.2933.

7-hydroxy-2H-chromen-2-one (**10**)

^{1}H NMR (400 MHz, DMSO-d6) δ = 10.54 (s, 1H), 7.91 (d, J = 9.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 6.78 (dd, J = 8.5, 2.3 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 6.19 (d, J = 9.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.12, 160.27, 155.33, 144.34, 129.53, 112.94, 101.99. TOF-MS, m/z: [M+H$^+$] calculated for $C_9H_7O_3$, 163.0395, found: 163.0399.

7-((12-bromododecyl)oxy)-2H-chromen-2-one (**11**)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 − 7.60 (d, J = 6 Hz, 1H), 7.35 − 7.33 (d, 1H), 6.83 – 6.78 (m, 2H), 6.23 – 6.21 (d, J = 8 Hz, 1H), 4.01 – 3.98 (t, J = 8 Hz, 2H), 3.41 – 3.37 (t, J = 8 Hz, 2H), 1.87 – 1.76 (m, 4H), 1.47 – 1.28 (m, 16H). ^{13}C NMR (100 MHz, DMSO) δ = 162.40, 161.18, 155.89, 144.18, 128.63, 112.93, 112.33, 101.32, 68.63, 33.93, 32.79, 29.44, 29.36, 29.25, 28.93, 28.70, 28.12, 25.89. TOF-MS, m/z: [M+H$^+$] calculated for $C_{21}H_{29}BrO_3$, 408.1300, found: 409.1377.

7-((12-(piperidin-1-yl)dodecyl)oxy)-2H-chromen-2-one (**12a**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.92 – 6.74 (m, 2H), 6.24 (d, *J* = 9.5 Hz, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 2.61 – 2.32 (m, 6H), 1.87 – 1.21 (m, 24H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.59, 161.44, 156.08, 143.59, 128.82, 113.15, 112.51, 101.49, 68.83, 59.45, 54.52, 29.69, 29.46, 29.11, 27.76, 26.09, 25.45, 24.20. TOF-MS, m/z: [M+H^{+}] calculated for $C_{26}H_{40}NO_3$, 414.2930, found: 414.2933.

7-((12-(4-methylpiperazin-1-yl)dodecyl)oxy)-2H-chromen-2-one (**12b**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 9.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 6.86 – 6.73 (m, 2H), 6.21 (d, *J* = 9.5 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 2.50 – 2.34 (m, 6H), 2.27 (d, *J* = 14.4 Hz, 6H), 1.82 – 1.72 (m, 2H), 1.52 – 1.39 (m, 5H), 1.25 (s, 14H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.53, 161.35, 156.02, 143.52, 128.76, 113.08, 112.45, 101.42, 68.76, 58.94, 55.26, 53.36, 46.16, 29.68, 29.07, 27.73, 27.02, 26.05. TOF-MS, m/z: [M+H^{+}] calculated for $C_{26}H_{41}N_2O_3$, 429.3039, found: 429.3043.

7-((12-morpholinododecyl)oxy)-2H-chromen-2-one (**12c**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 9.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.88 – 6.72 (m, 2H), 6.22 (d, *J* = 9.5 Hz, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.81 – 3.65 (m, 5H), 2.55 – 2.23 (m, 7H), 1.79 (dt, *J* = 14.4, 6.6 Hz, 2H), 1.54 – 1.19 (m, 18H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.54, 161.38, 156.04, 143.55, 128.79, 113.10, 112.47, 101.43, 68.78, 67.08, 59.36, 53.90, 29.68, 29.64, 29.44, 29.08, 27.64, 26.64, 26.06. TOF-MS, m/z: [M+H^{+}] calculated for $C_{25}H_{38}NO_4$, 416.2723, found: 416.2725.

7-((12-thiomorpholinododecyl)oxy)-2H-chromen-2-one (**12d**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 9.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.90 – 6.73 (m, 2H), 6.24 (d, *J* = 9.5 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 2.44 – 2.24 (m, 4H), 1.91 – 1.74 (m, 2H), 1.36 (d, *J* = 75.8 Hz, 25H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.57, 161.40, 156.08, 143.56, 128.81, 113.14, 112.51, 101.47, 68.82, 59.66, 55.19, 29.72, 29.48, 28.13, 27.71, 26.62, 26.10. TOF-MS, m/z: [M+H^{+}] calculated for $C_{25}H_{38}NO_3S$, 432.2494, found: 432.2499.

7-((12-(4-methylpiperazin-1-yl)dodecyl)oxy)-2H-chromen-2-one (**13**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 7.54 (d, J = 8.6 Hz, 1H), 6.85 – 6.62 (m, 2H), 6.08 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.97, 154.65, 126.35, 112.65, 110.07, 101.99, 17.91. TOF-MS, m/z: [M+H$^+$] calculated for $C_{10}H_9O_3$, 177.0551, found: 177.0554.

7-((12-bromododecyl)oxy)-4-methyl-2H-chromen-2-one (**14**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, J = 8.8 Hz, 1H), 6.88 – 6.72 (m, 2H), 6.11 (s, 1H), 4.00 (t, J = 6.5 Hz, 2H), 3.40 (t, J = 6.9 Hz, 2H), 2.38 (s, 3H), 1.89 – 1.76 (m, 4H), 1.49 – 1.25 (m, 18H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.34, 161.47, 152.69, 125.56, 112.77, 111.90, 101.43, 68.71 , 34.18, 32.93, 29.61, 29.52, 29.43, 29.09, 28.86, 28.27, 26.06, 18.79. TOF-MS, m/z: [M+H$^+$] calculated for $C_{22}H_{32}BrO_3$, 423.1457, found: 423.1459.

7-((12-(diethylamino)dodecyl)oxy)-4-methyl-2H-chromen-2-one (**15**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, J = 8.8 Hz, 1H), 6.92 – 6.70 (m, 2H), 6.10 (s, 1H), 3.99 (t, J = 6.5 Hz, 2H), 2.80 (q, J = 7.2 Hz, 4H), 2.70 – 2.61 (m, 2H), 2.38 (s, 3H), 1.85 – 1.74 (m, 2H), 1.67 – 1.54 (m, 2H), 1.49 – 1.16 (m, 22H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.34, 161.49, 155.39, 152.73, 125.58, 112.76, 113.49, 111.87, 101.45, 68.71, 52.28, 46.85, 29.59, 29.43, 29.40, 29.06, 27.43, 26.03, 25.24, 18.78, 10.31. TOF-MS, m/z: [M+H$^+$] calculated for $C_{26}H_{42}NO_3$, 416.3086, found: 416.3089.

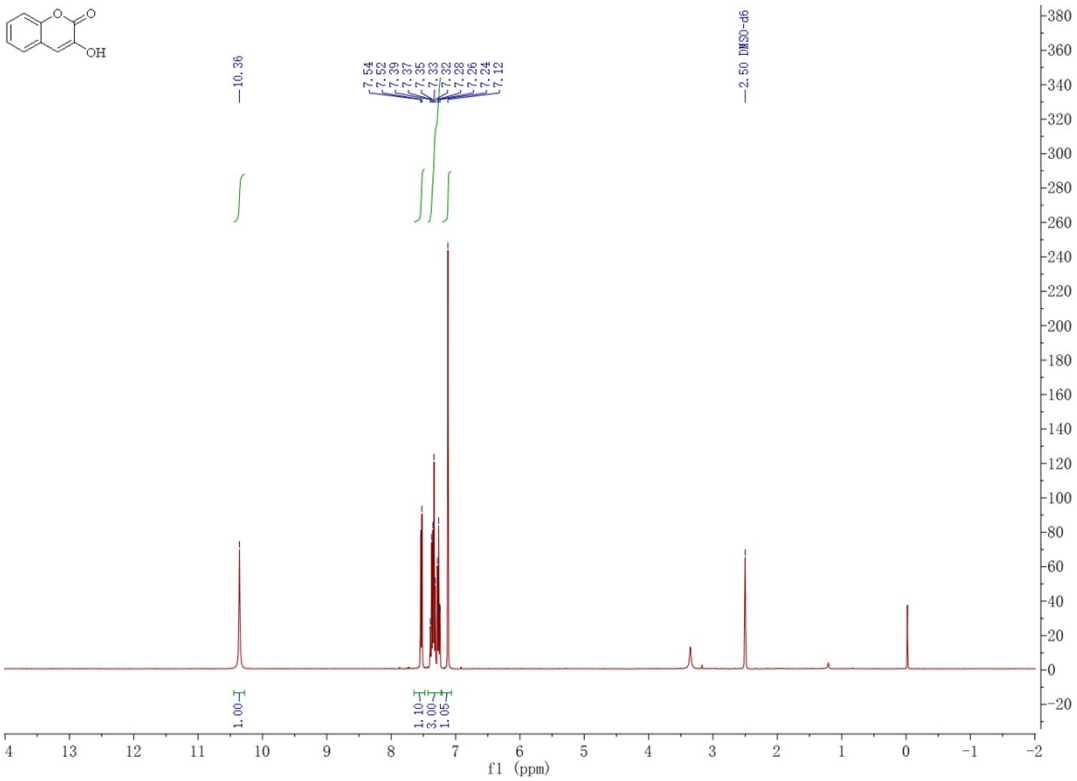

Fig.S1 *[1]H NMR of* **2** (400 MHz, DMSO)

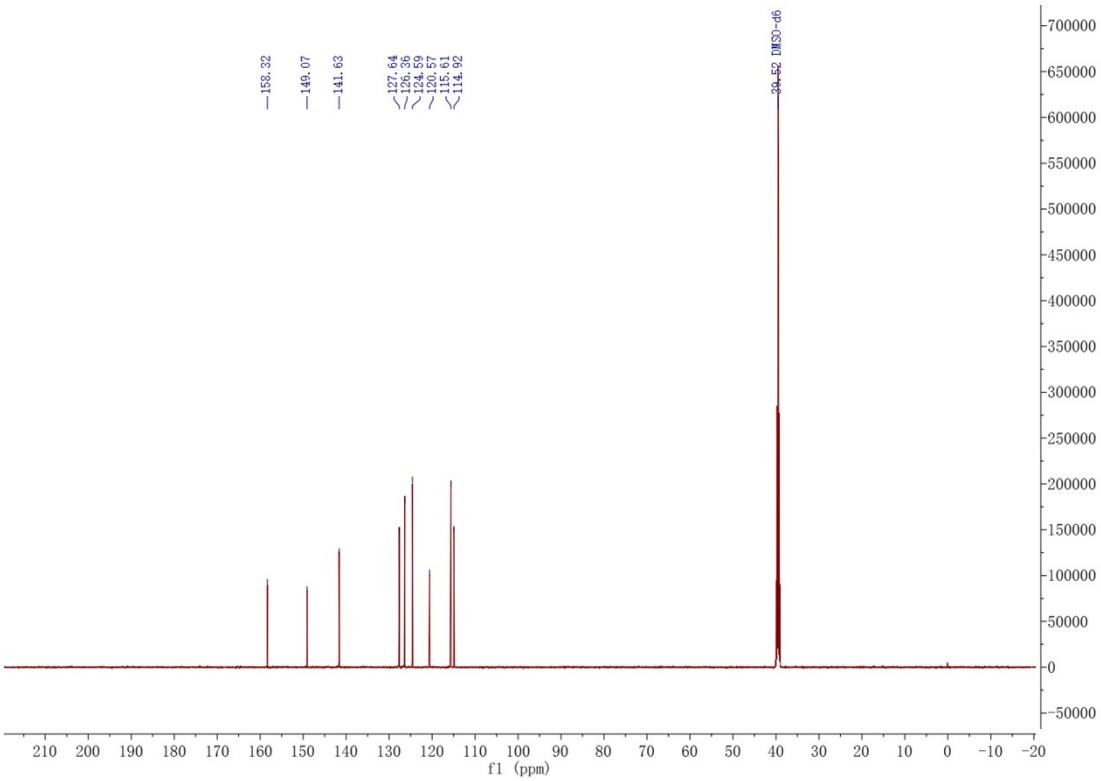

Fig.S2 *[13]C NMR of* **2** (100 MHz, DMSO)

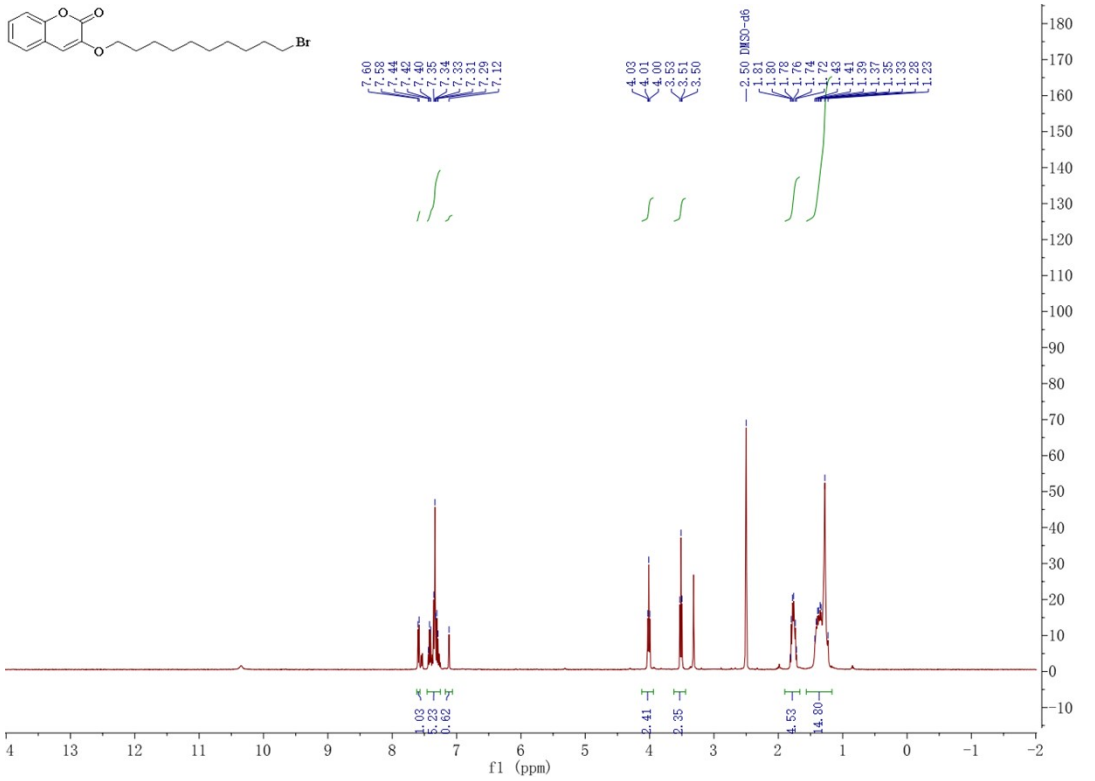

Fig.S3 *[1]H NMR of* **3a** (400 MHz, DMSO)

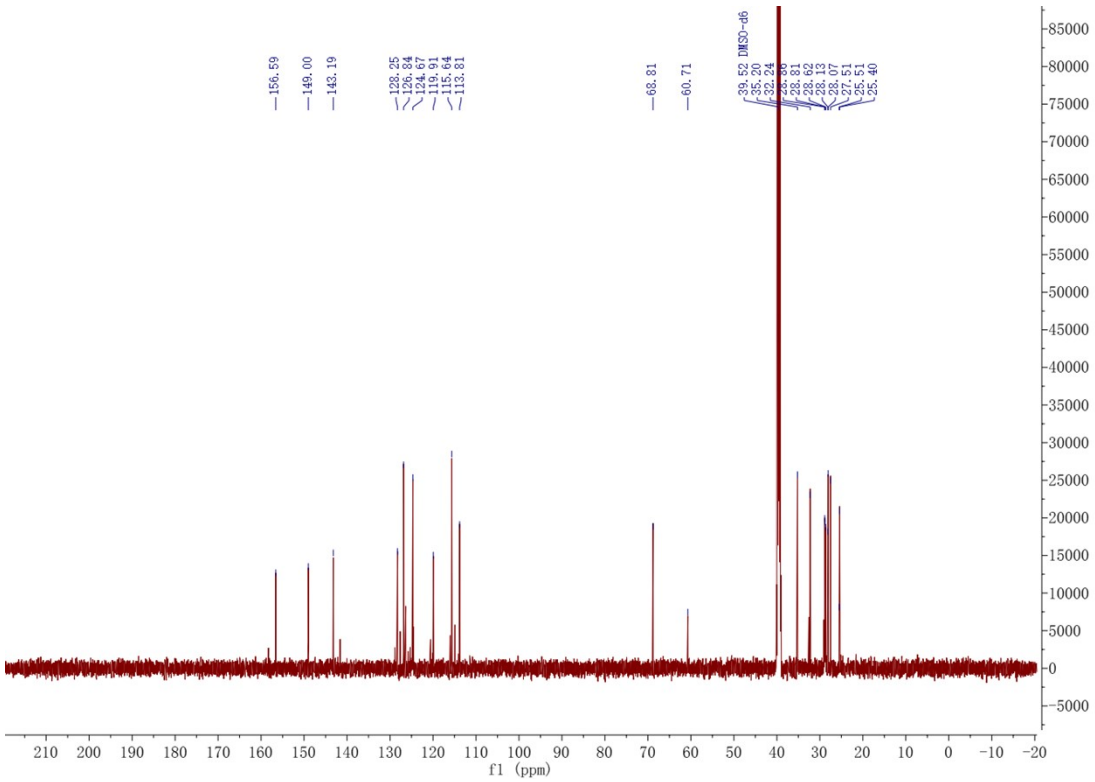

Fig.S4 *[13]C NMR of* **3a** (100 MHz, DMSO)

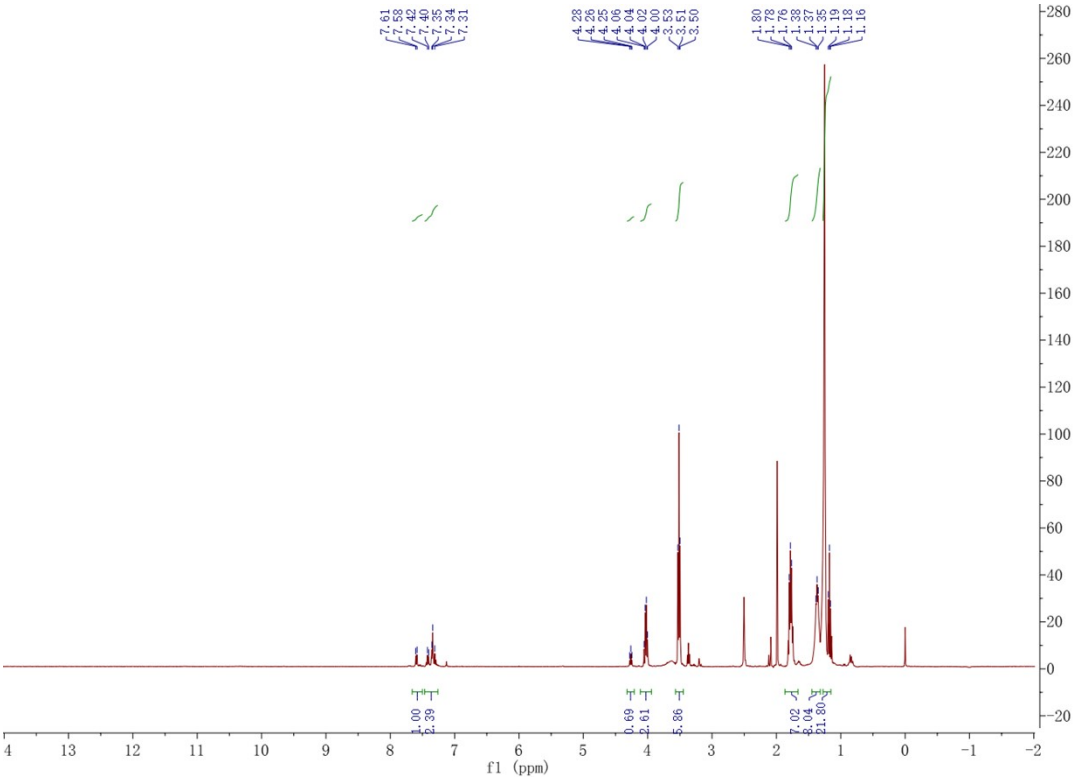

Fig.S5 *[1]H NMR of* **3b** (400 MHz, DMSO)

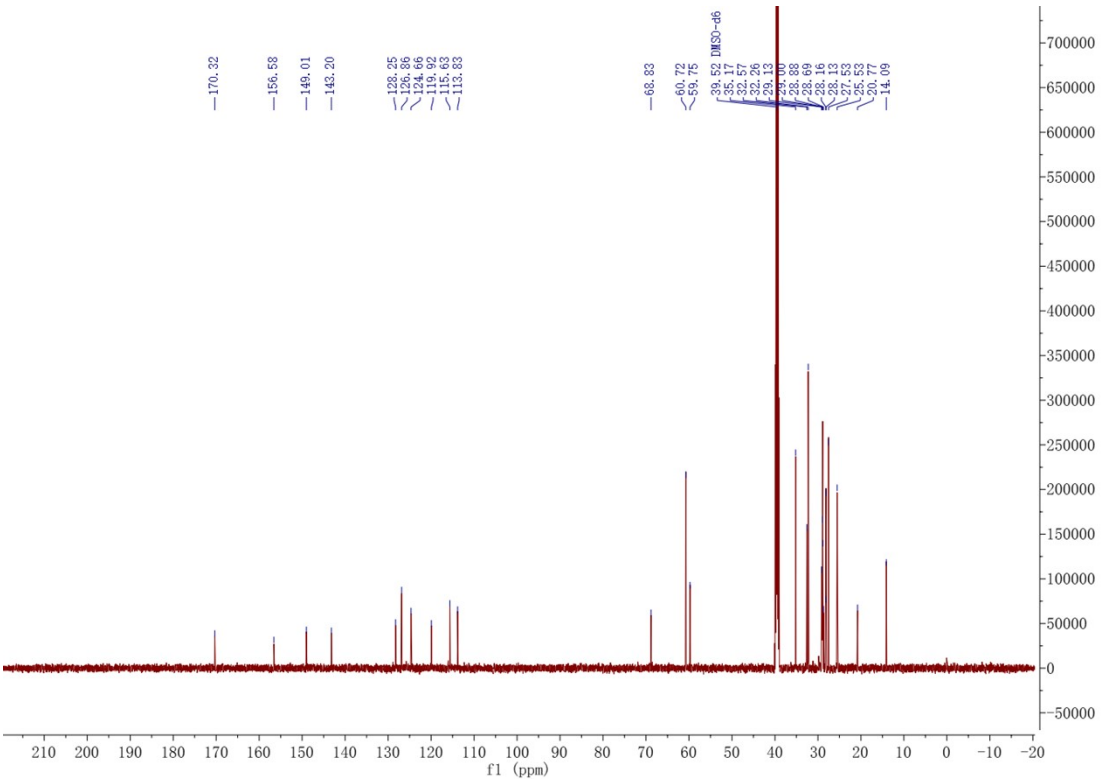

Fig.S6 *[13]C NMR of* **3b** (100 MHz, DMSO)

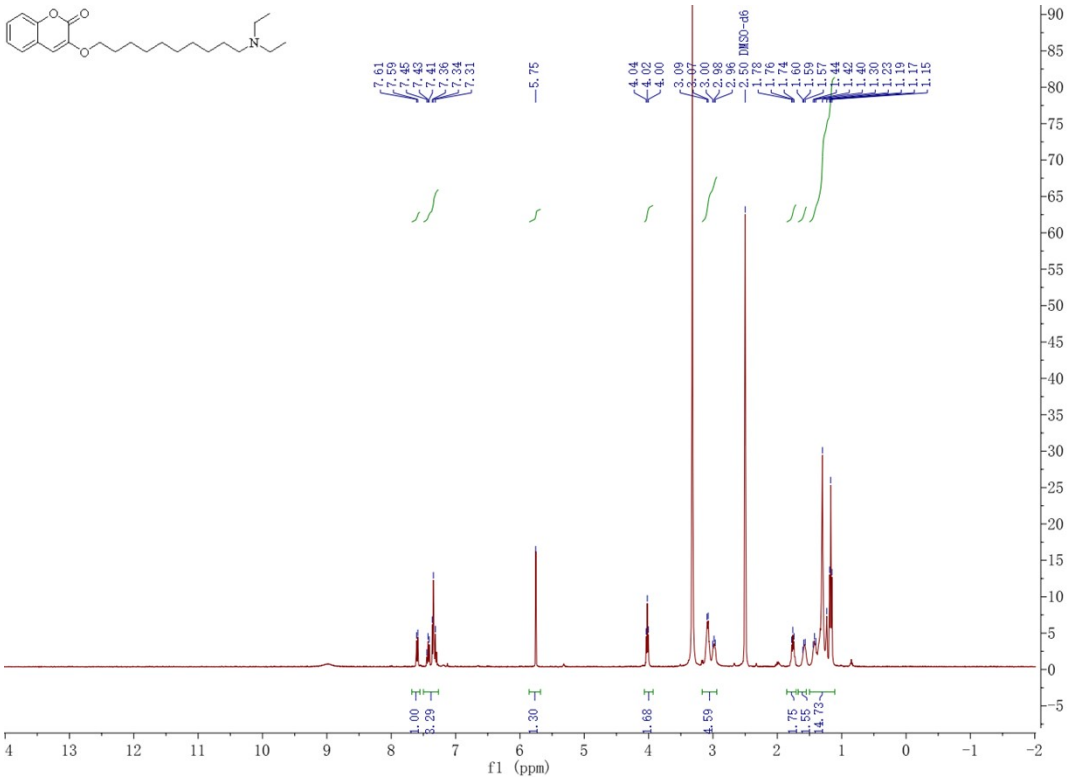

Fig.S7 *[1]H NMR of* **4a** (400 MHz, DMSO)

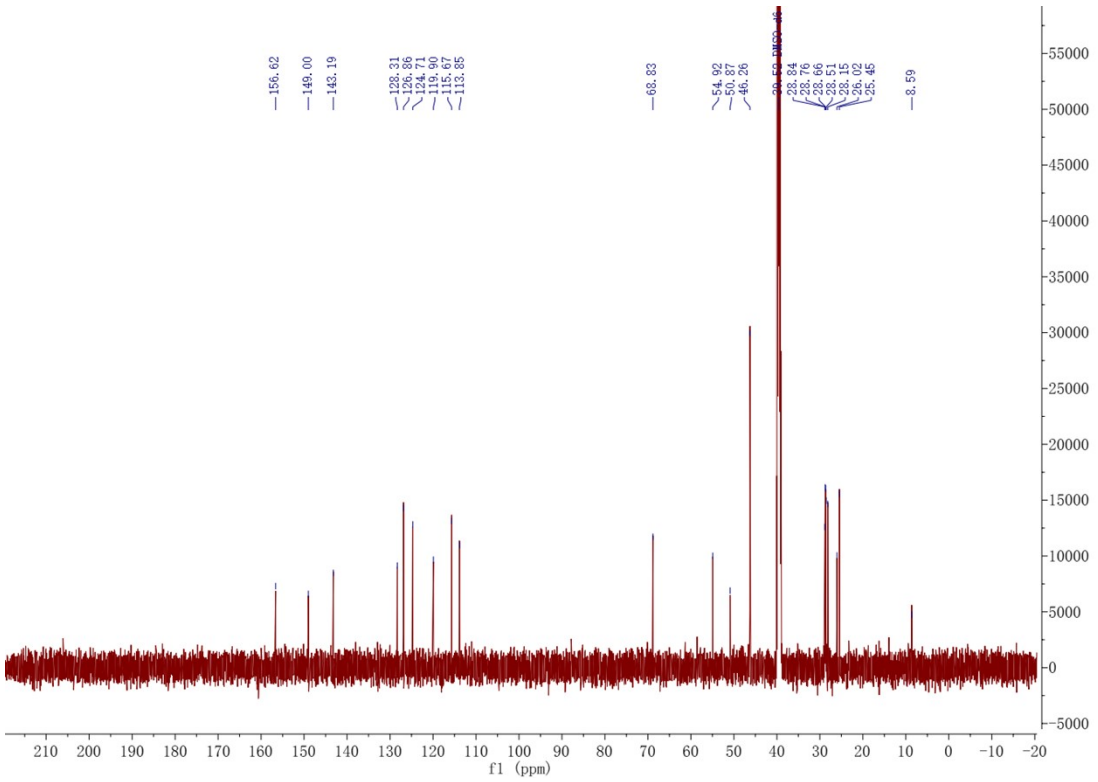

Fig.S8 *[13]C NMR of* **4a** (101 MHz, DMSO)

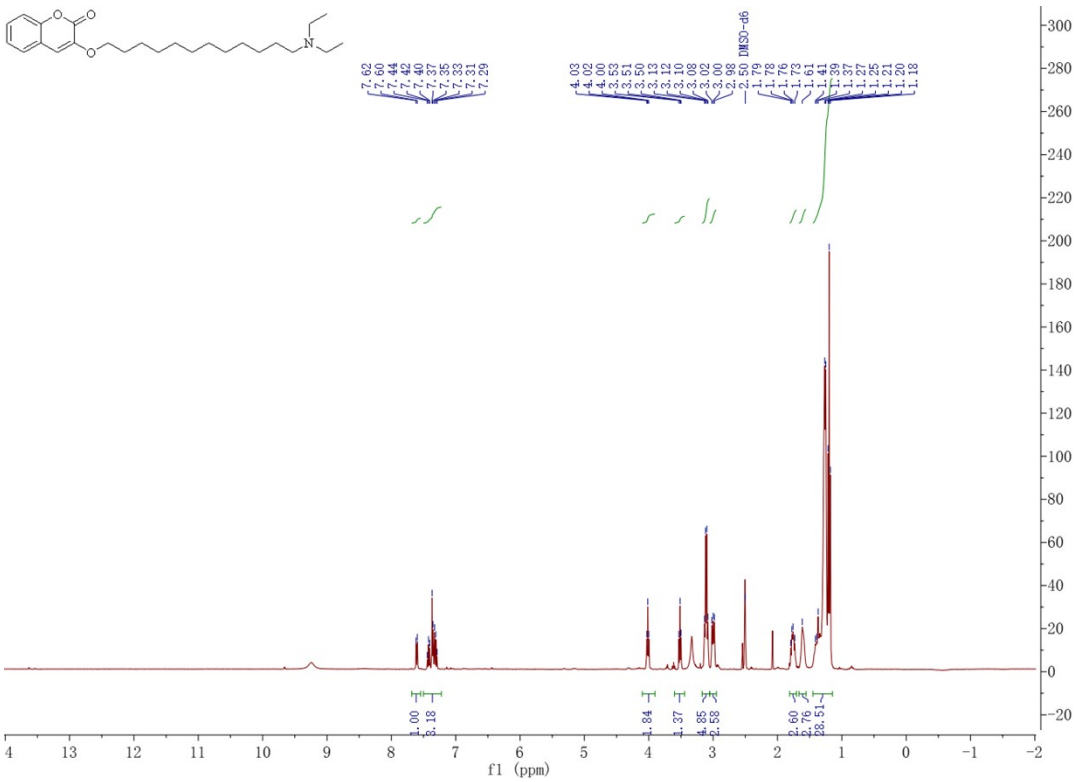

Fig.S9 *[1]H NMR of* **4b** (400 MHz, DMSO)

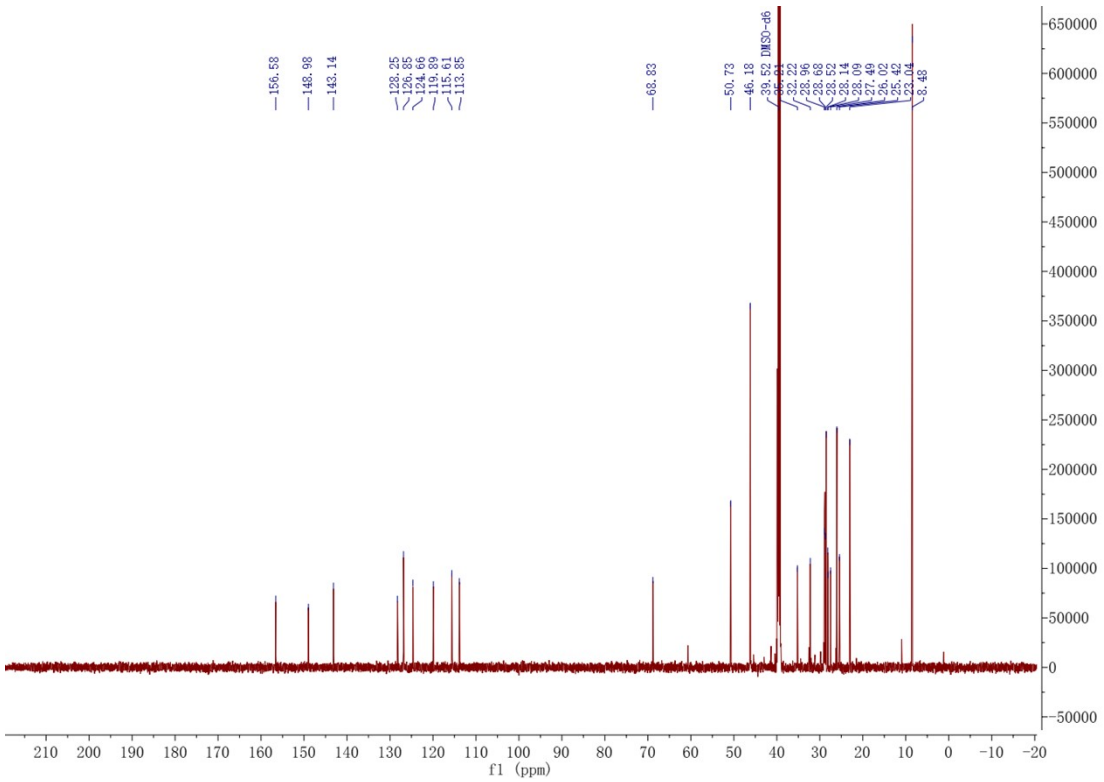

Fig.S10 *[13]C NMR of* **4b** (101 MHz, DMSO)

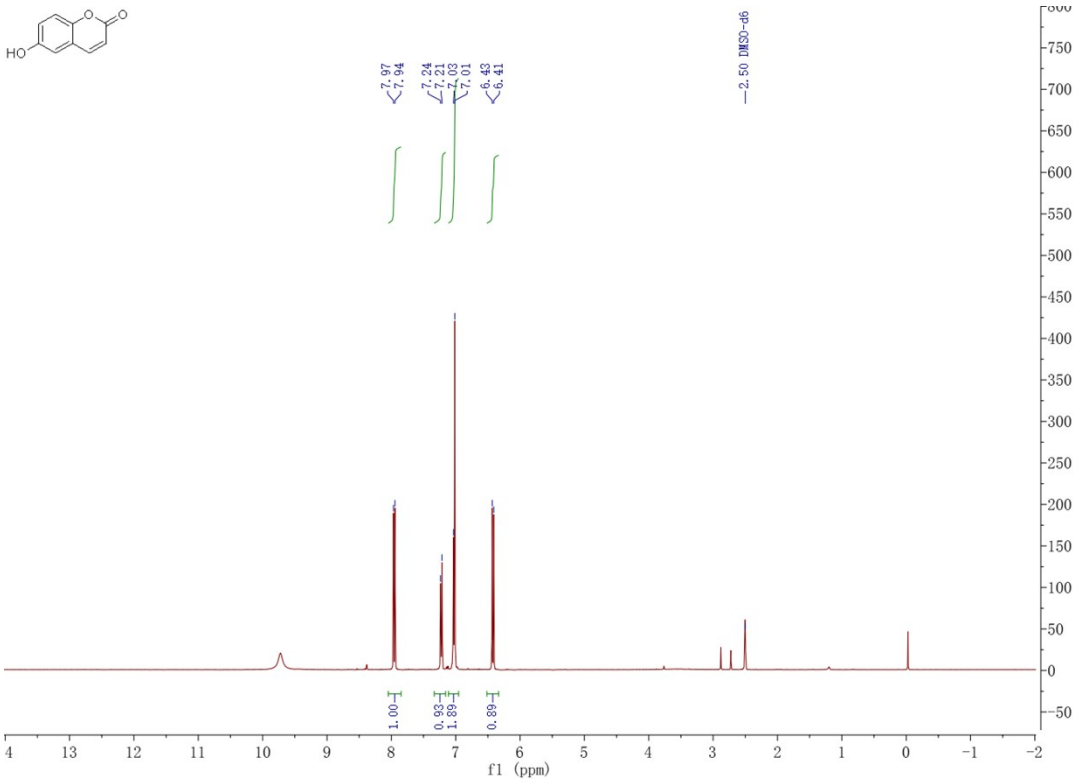

Fig.S11 *[1]H NMR of* **6** (400 MHz, DMSO)

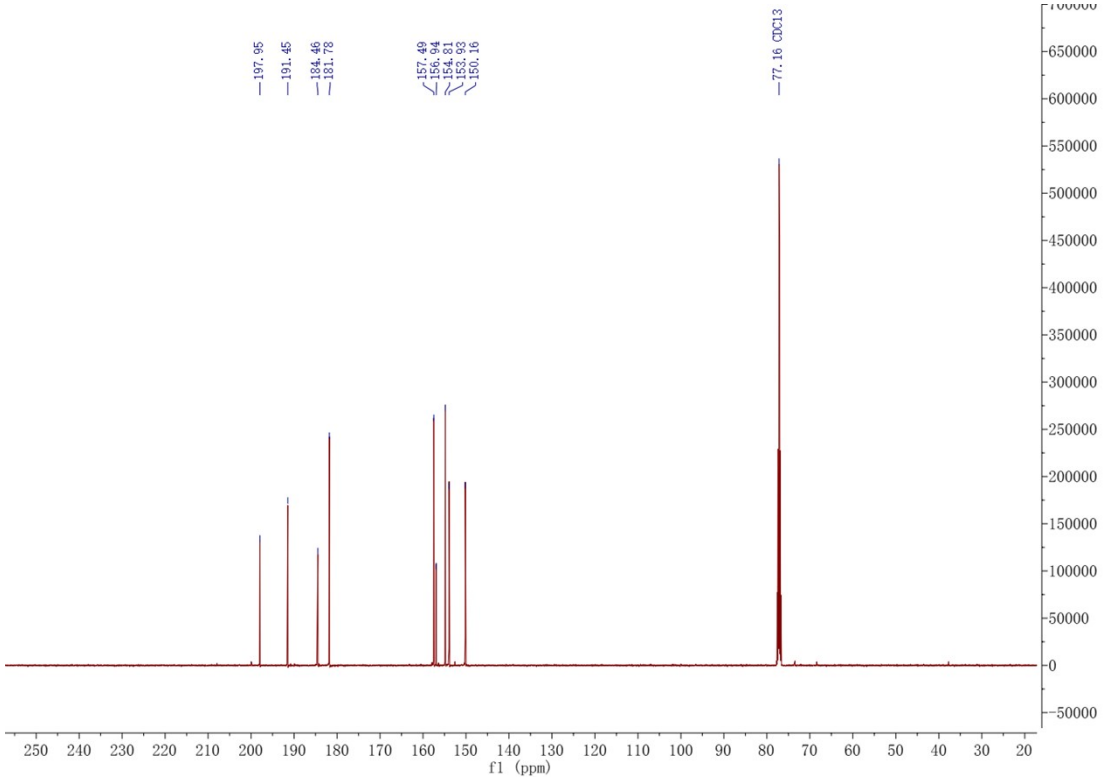

Fig.S12 *[13]C NMR of* **6** (101 MHz, DMSO)

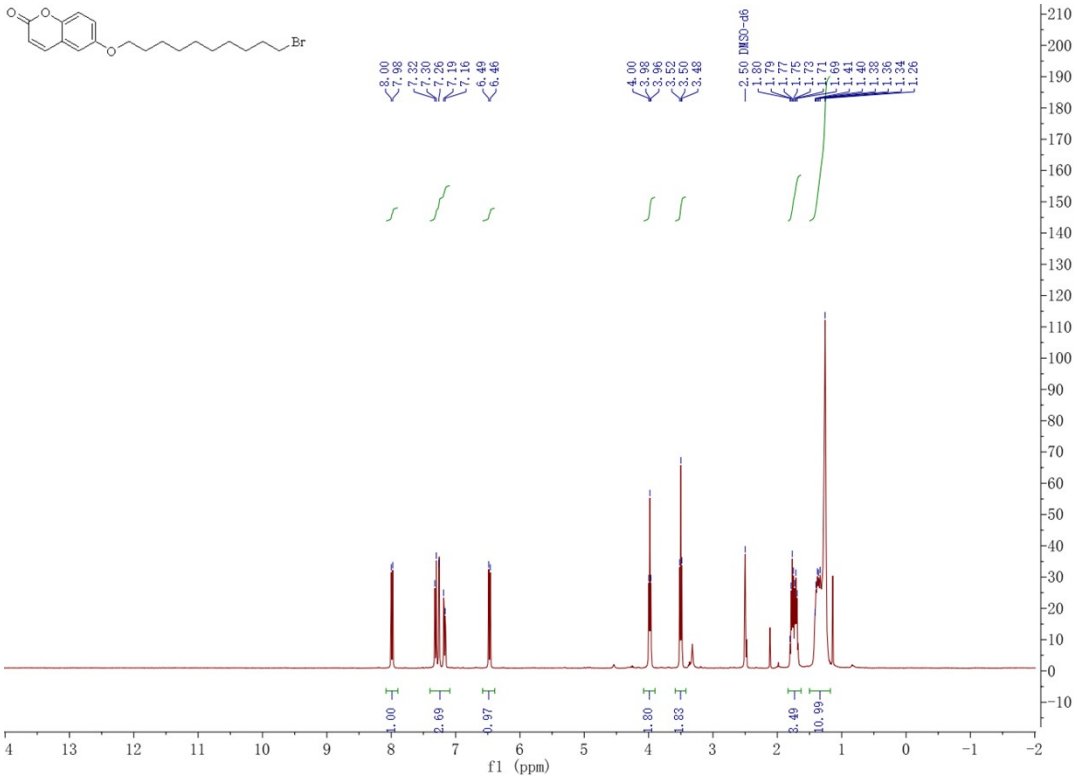

Fig.S13 *[1]H NMR of* **7a** (400 MHz, DMSO)

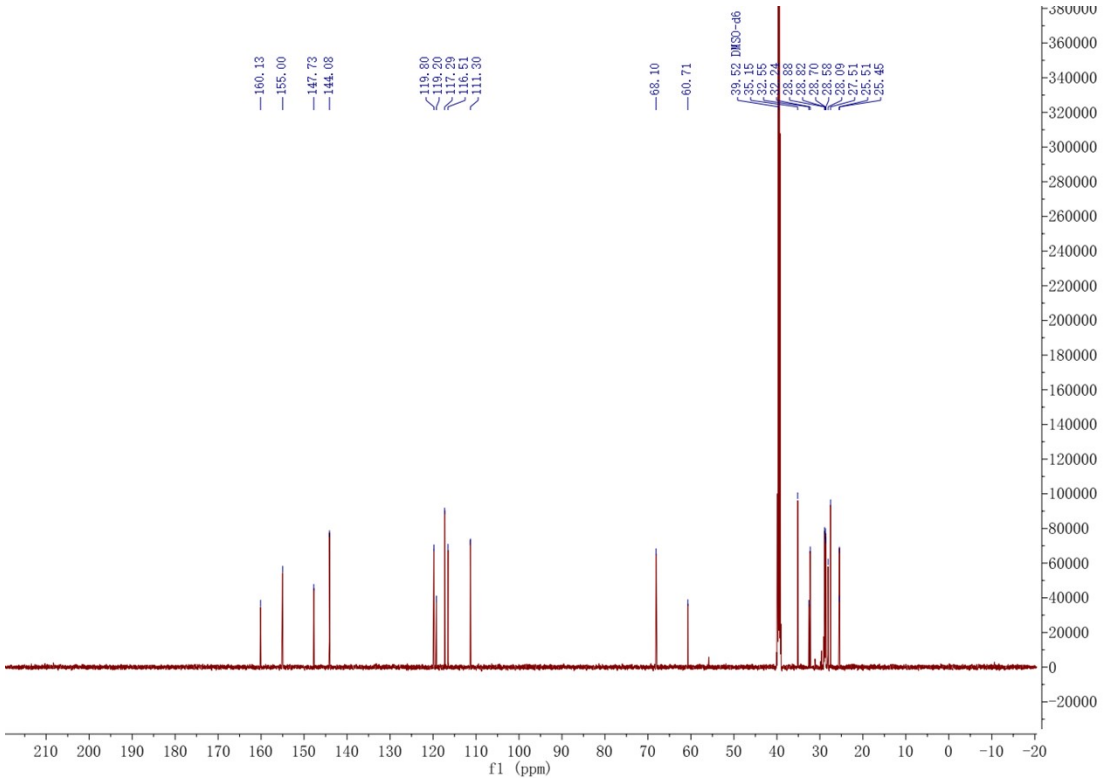

Fig.S14 *[13]C NMR of* **7a** (101 MHz, DMSO)

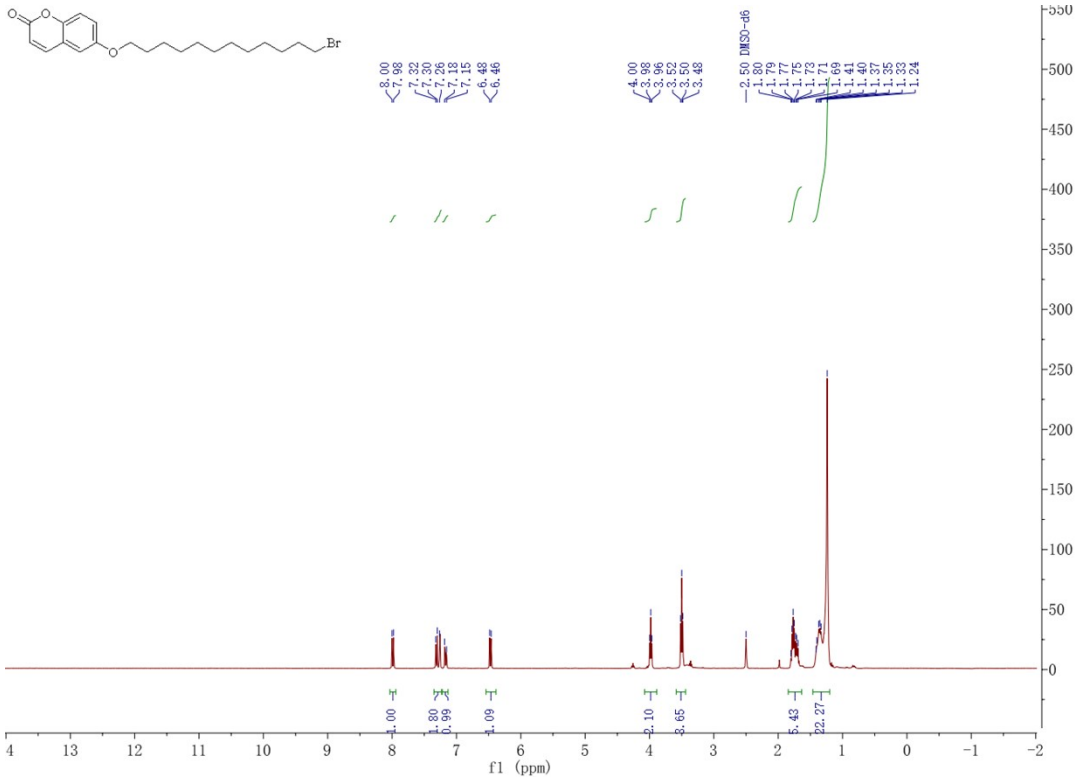

Fig.S15 *[1]H NMR of* **7b** (400 MHz, DMSO)

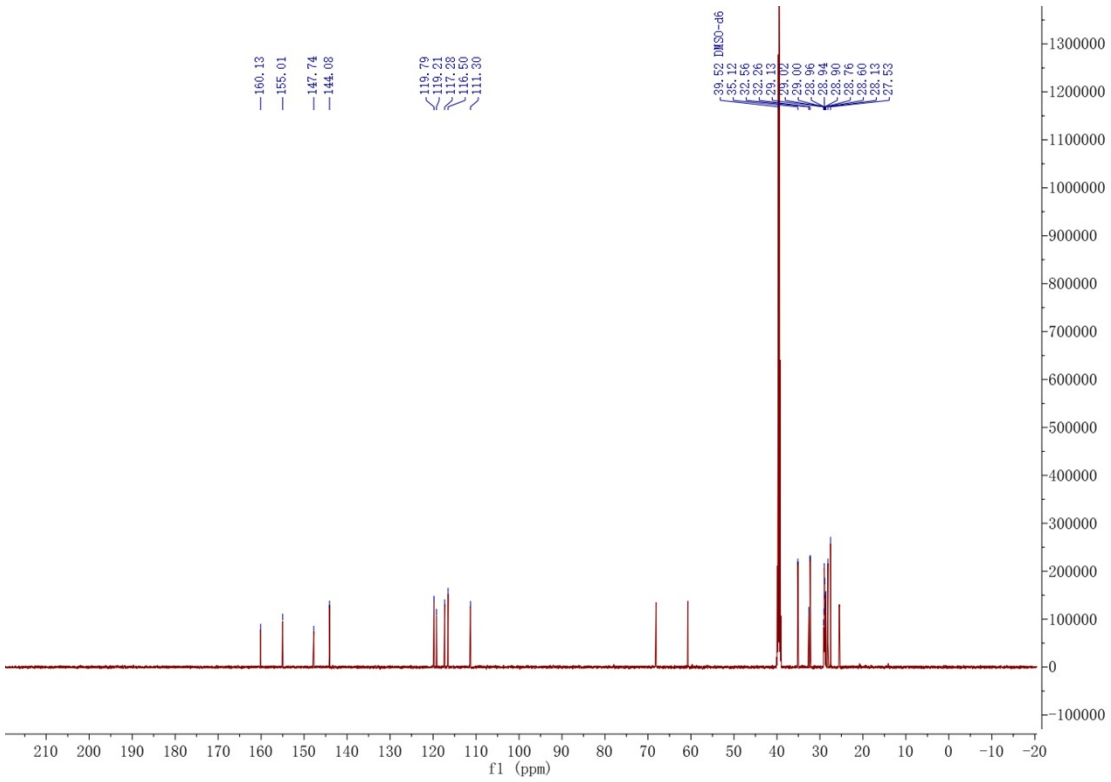

Fig.S16 *[13]C NMR of* **7b** (101 MHz, DMSO)

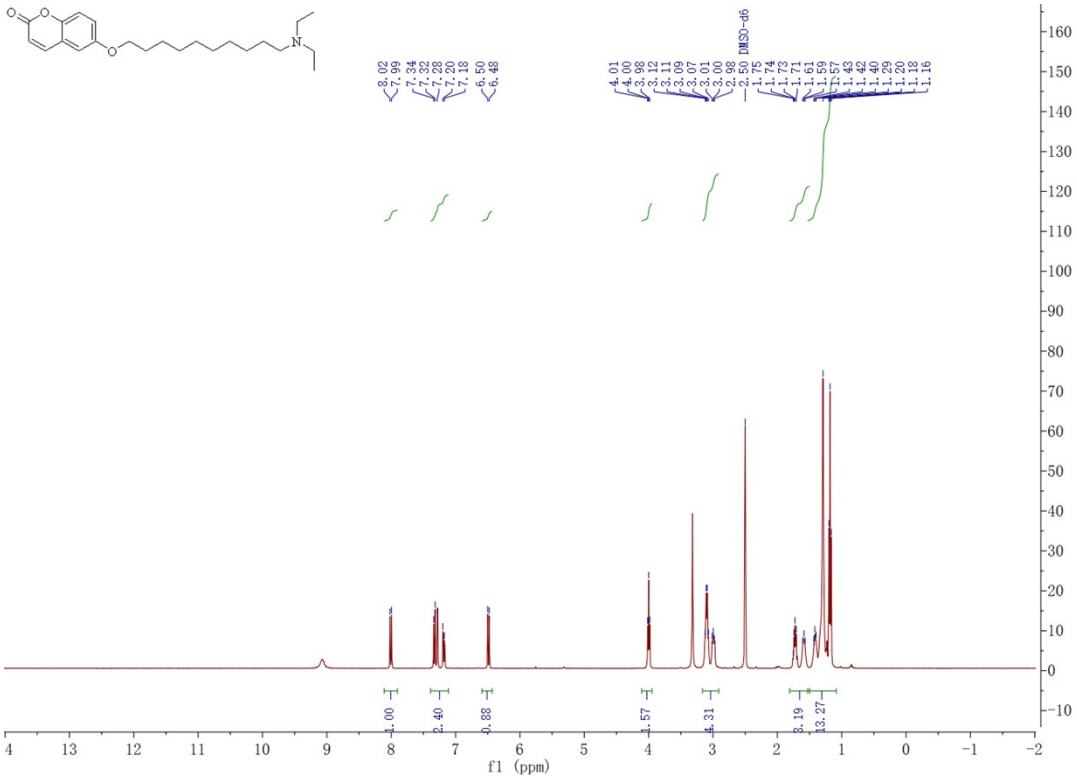

Fig.S17 *[1]H NMR of* **8a** (400 MHz, DMSO)

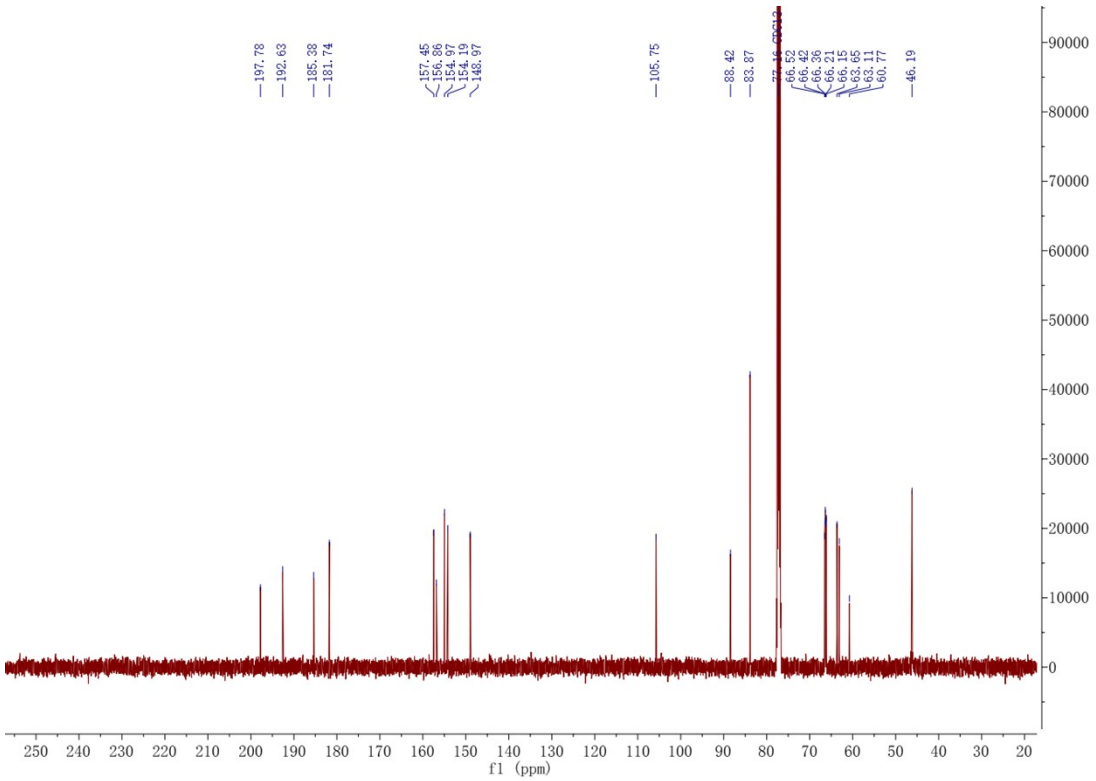

Fig.S18 *[13]C NMR of* **8a** (101 MHz, DMSO)

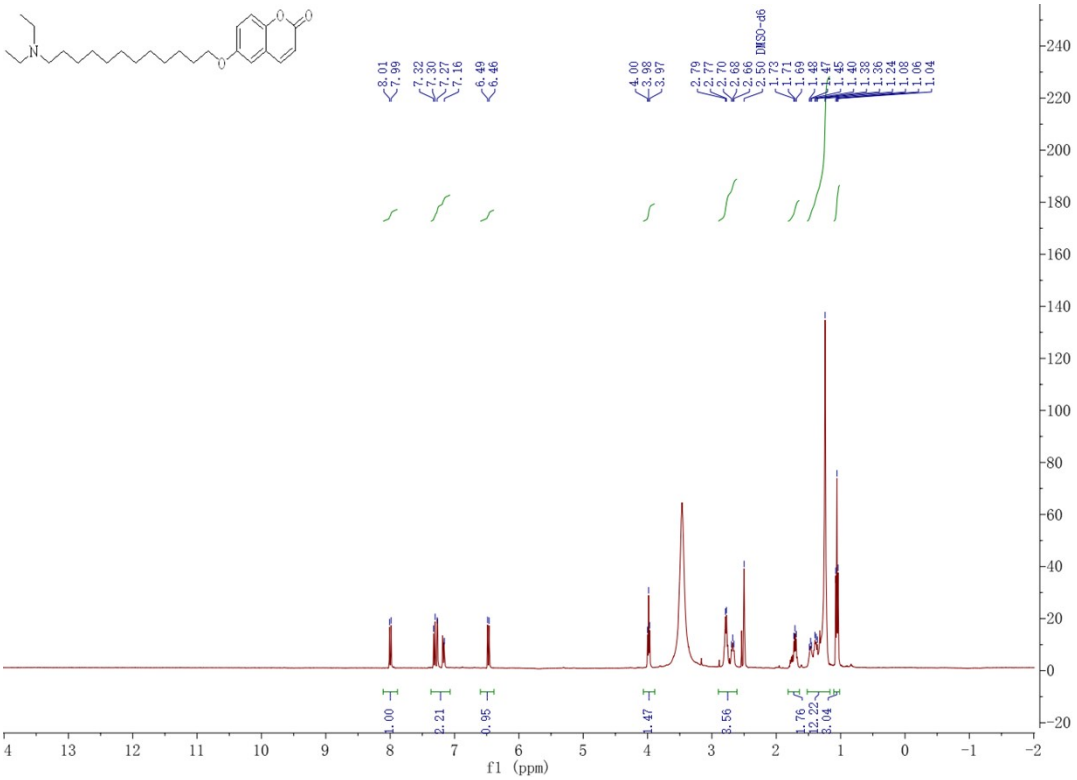

Fig.S19 *[1]H NMR of* **8b** (400 MHz, DMSO)

Fig.S20 *[13]C NMR of* **8b** (101 MHz, DMSO)

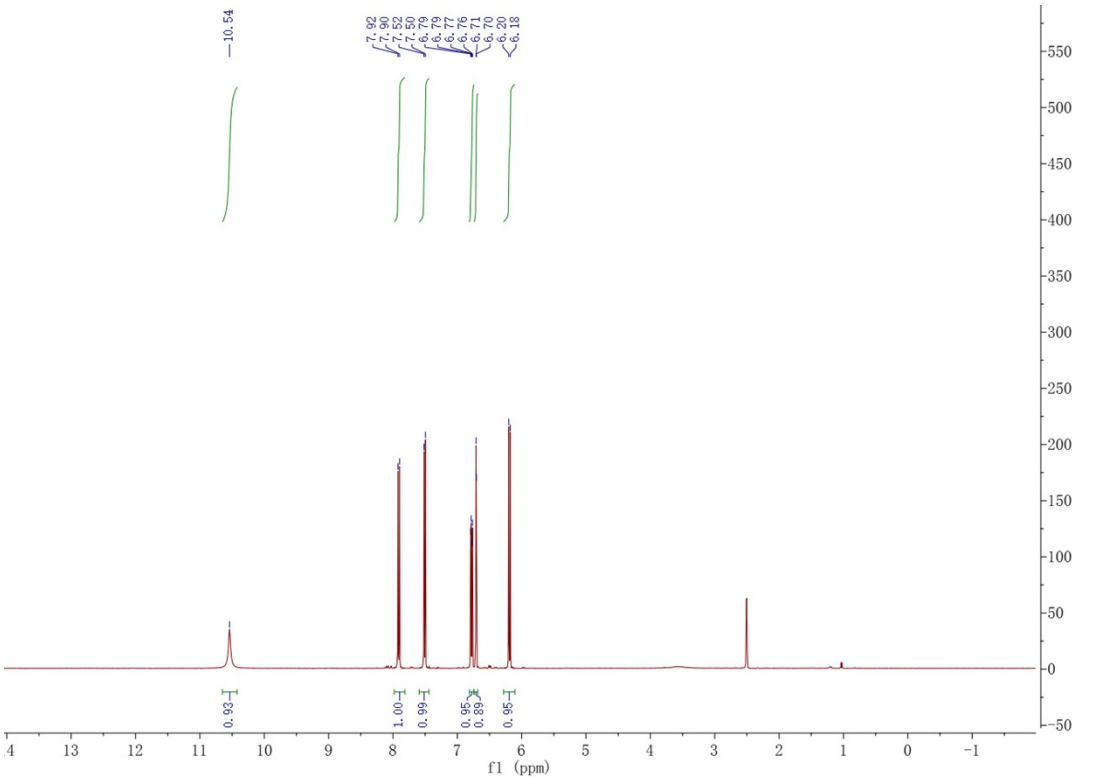

Fig.S21 *[1]H NMR of* **10** (400 MHz, DMSO)

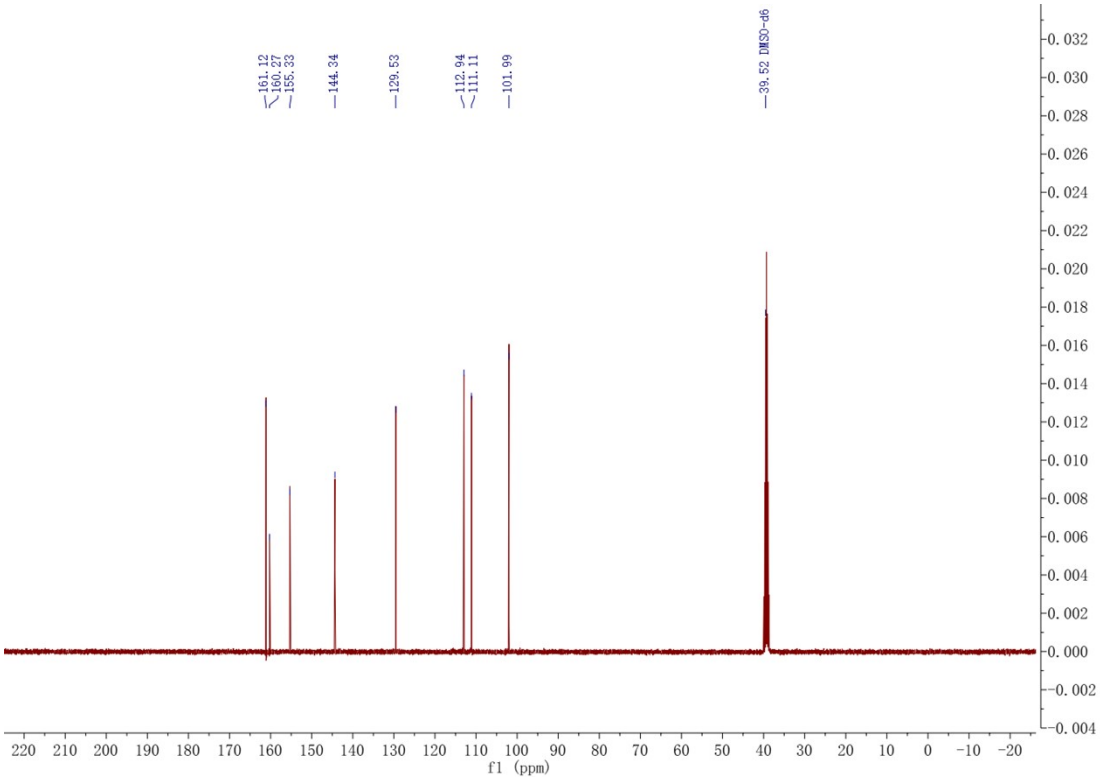

Fig.S22 *[13]C NMR of* **10** (101 MHz, DMSO)

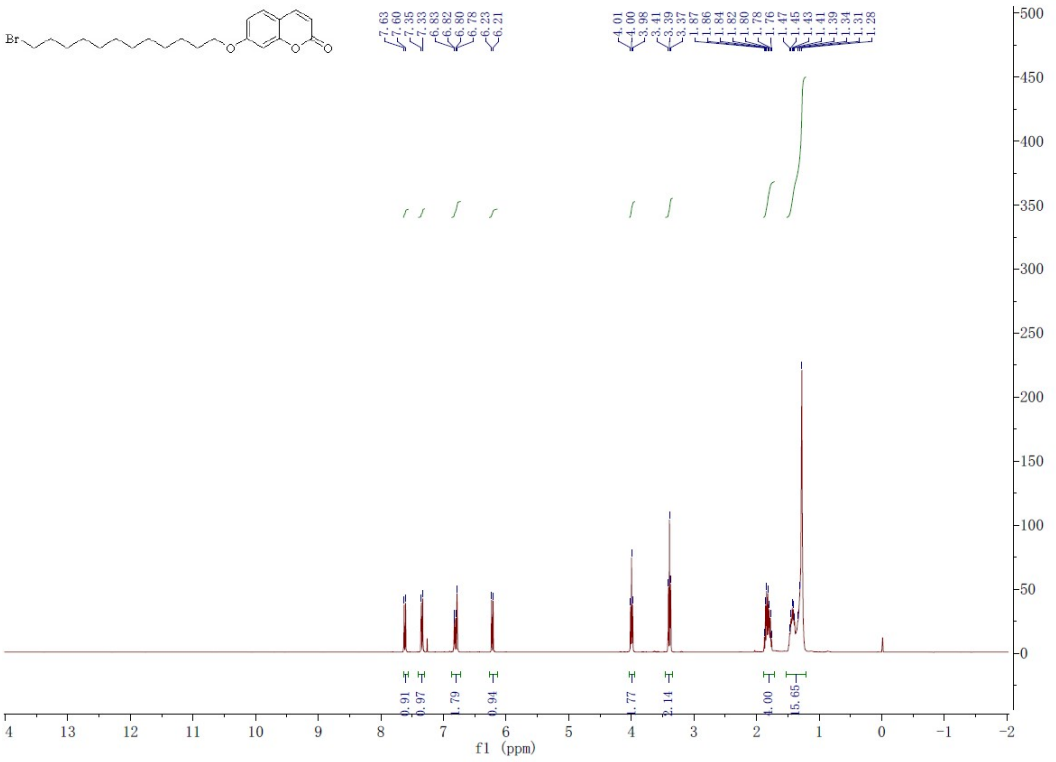

Fig.S23 *[1]H NMR of* **11** (400 MHz, $CDCl_3$)

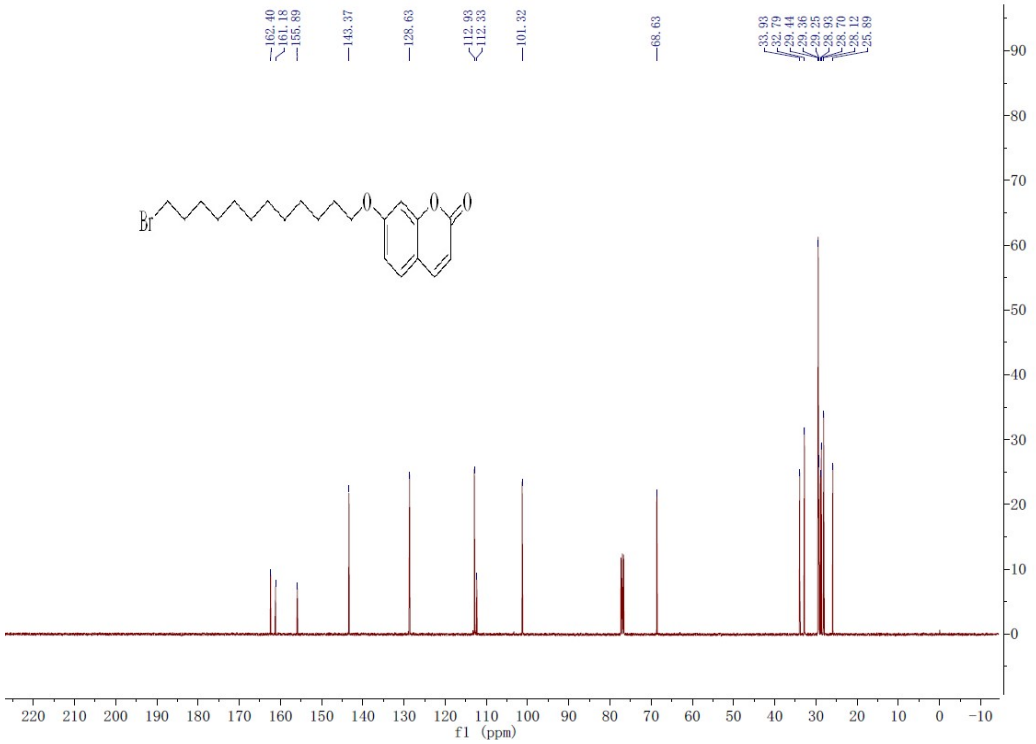

Fig.S24 *[13]C NMR of* **11** (100 MHz, $CDCl_3$)

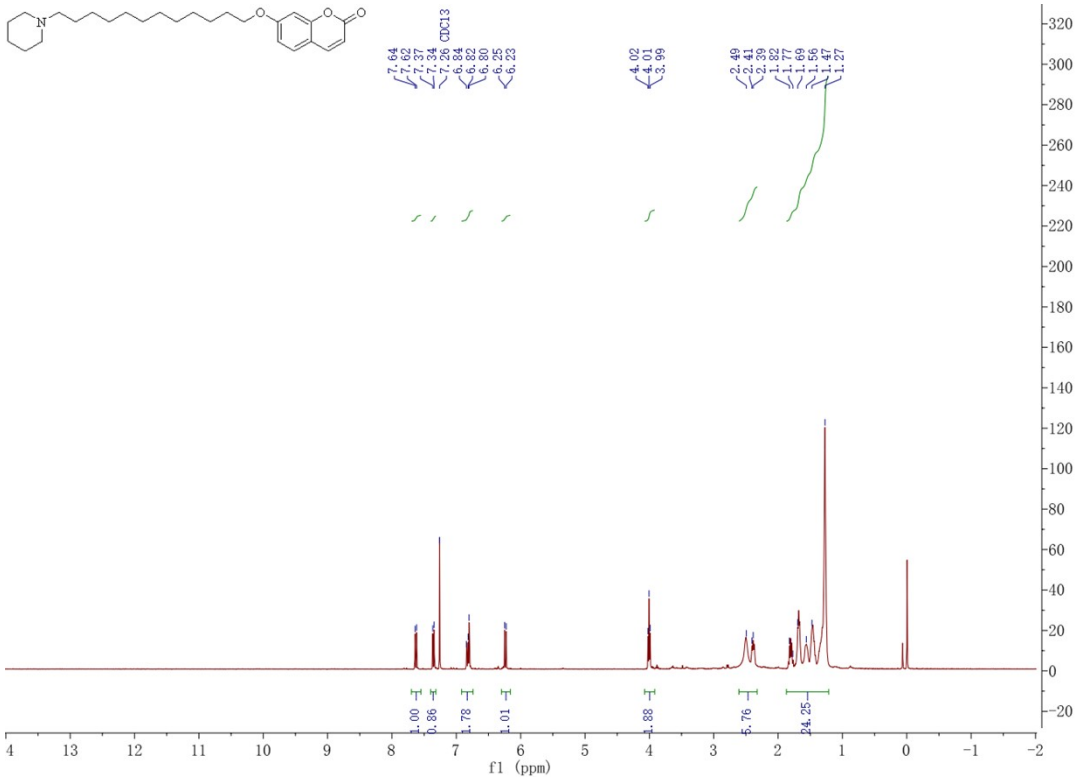

Fig.S25 *[1]H NMR of* **12a** (400 MHz, $CDCl_3$)

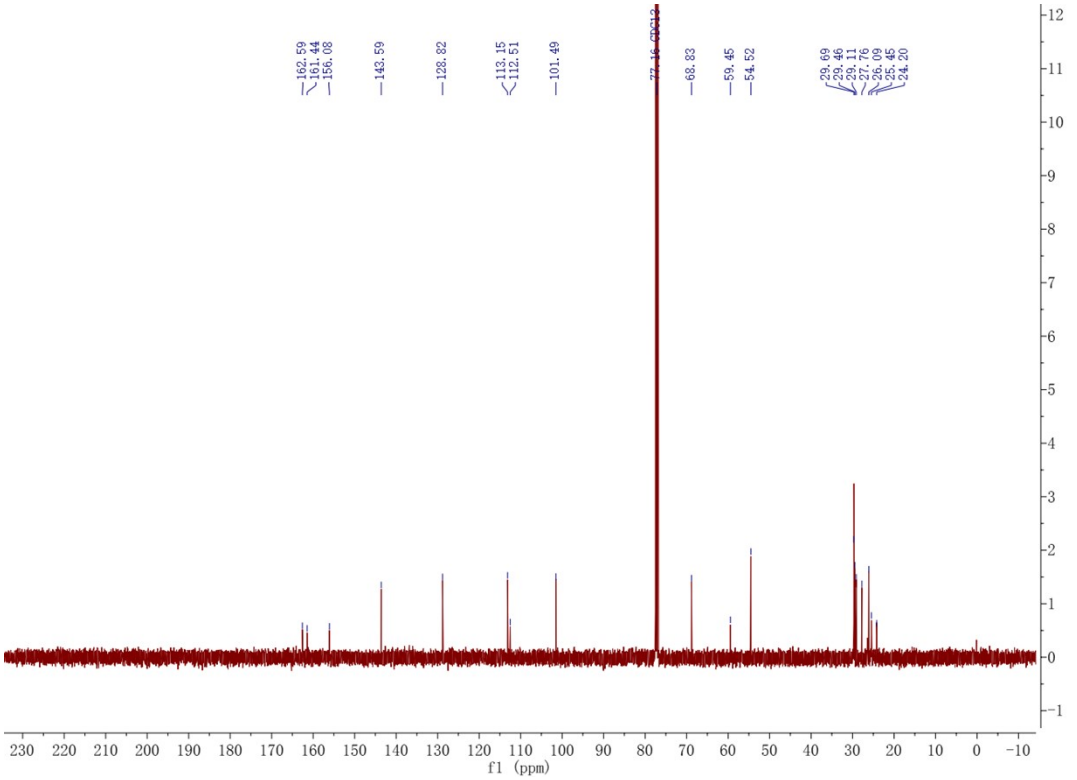

Fig.S26 *[13]C NMR of* **12a** (400 MHz, $CDCl_3$)

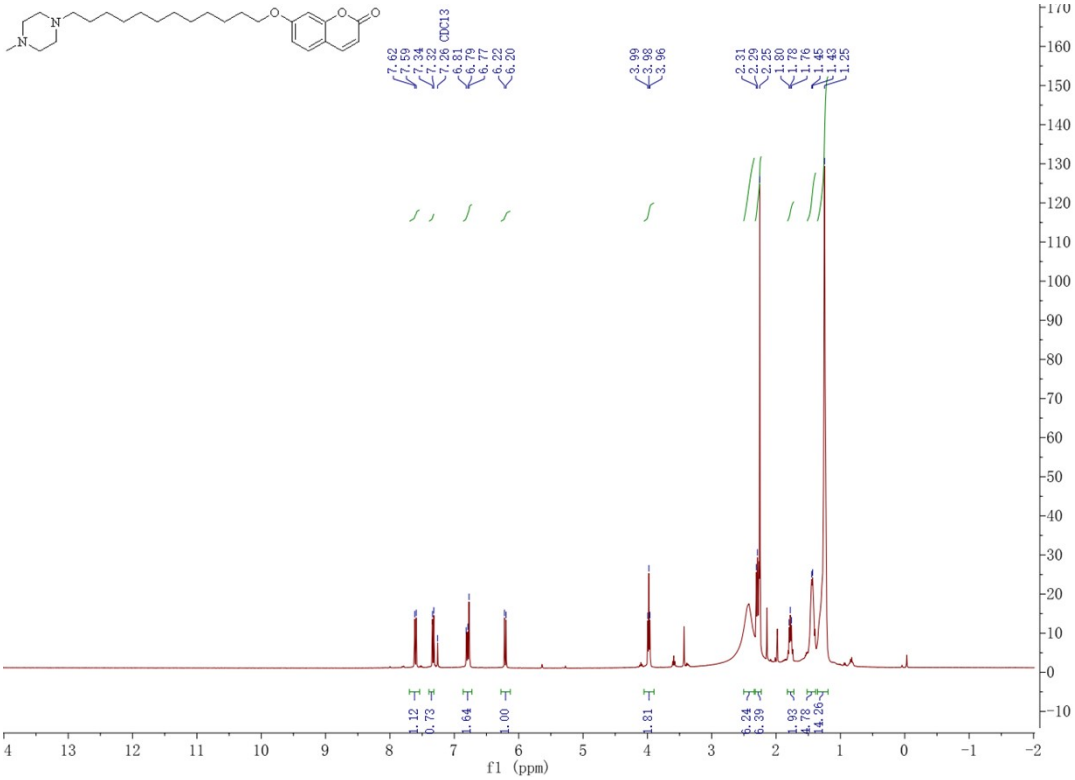

Fig.S27 *[1]H NMR of* **12b** (400 MHz, $CDCl_3$)

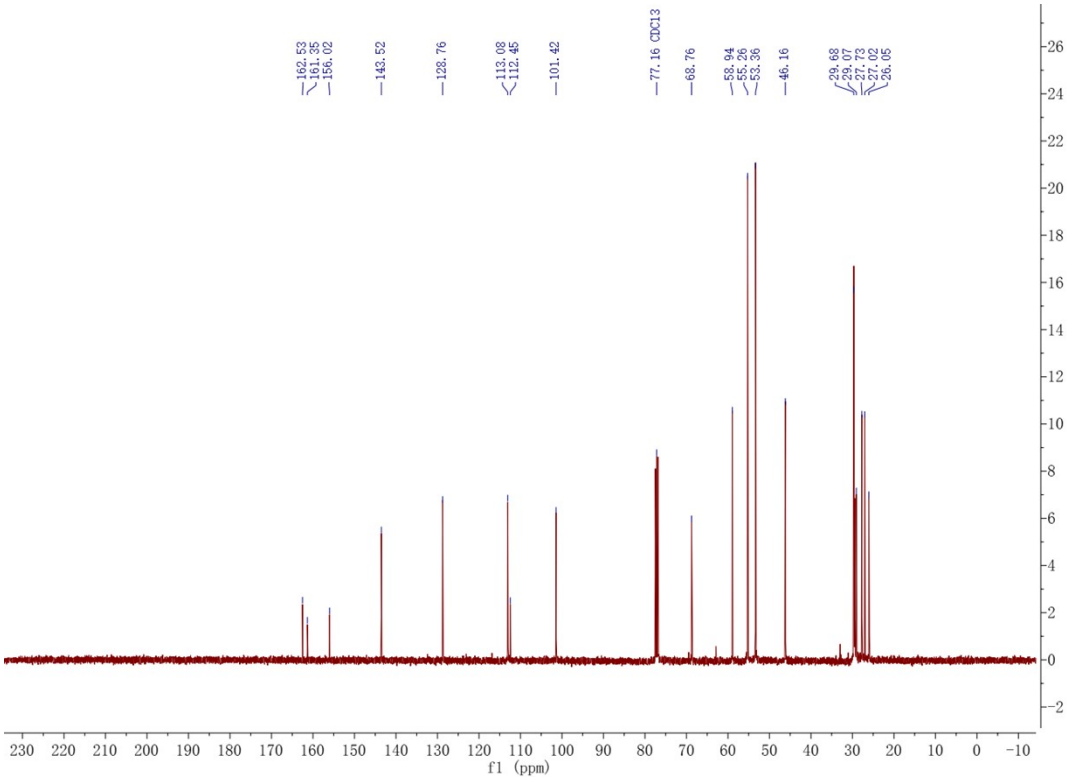

Fig.S28 *[13]C NMR of* **12b** (400 MHz, $CDCl_3$)

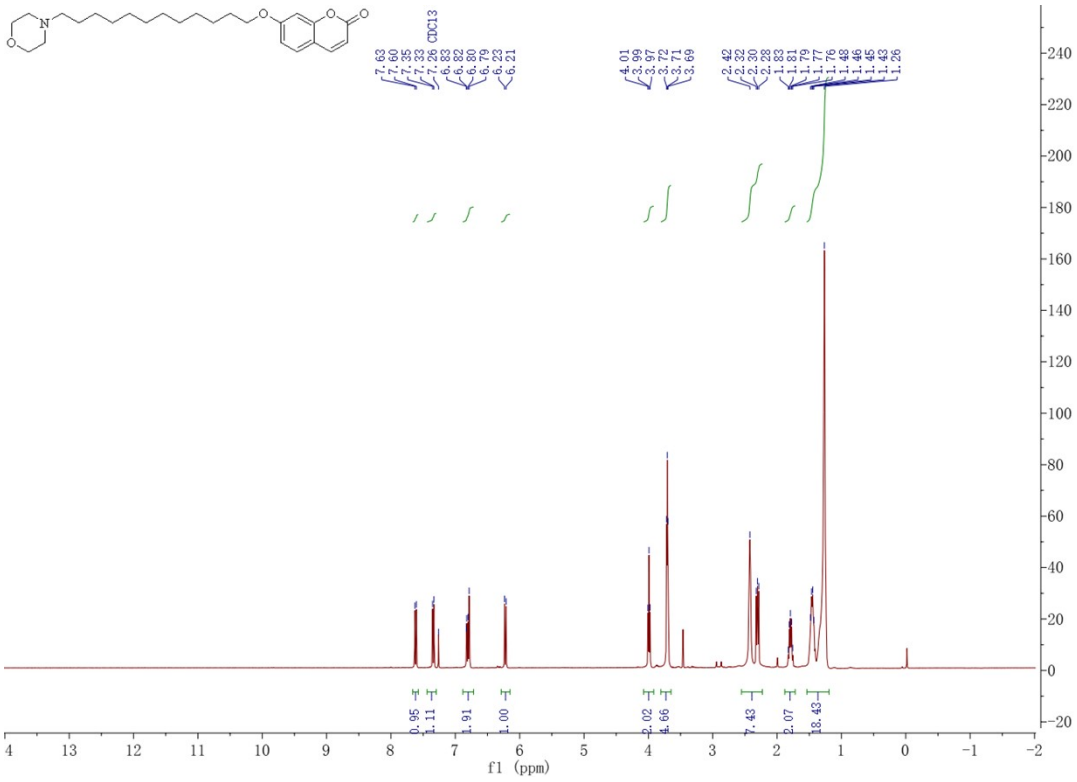

Fig.S29 *[1]H NMR of* **12c** (400 MHz, $CDCl_3$)

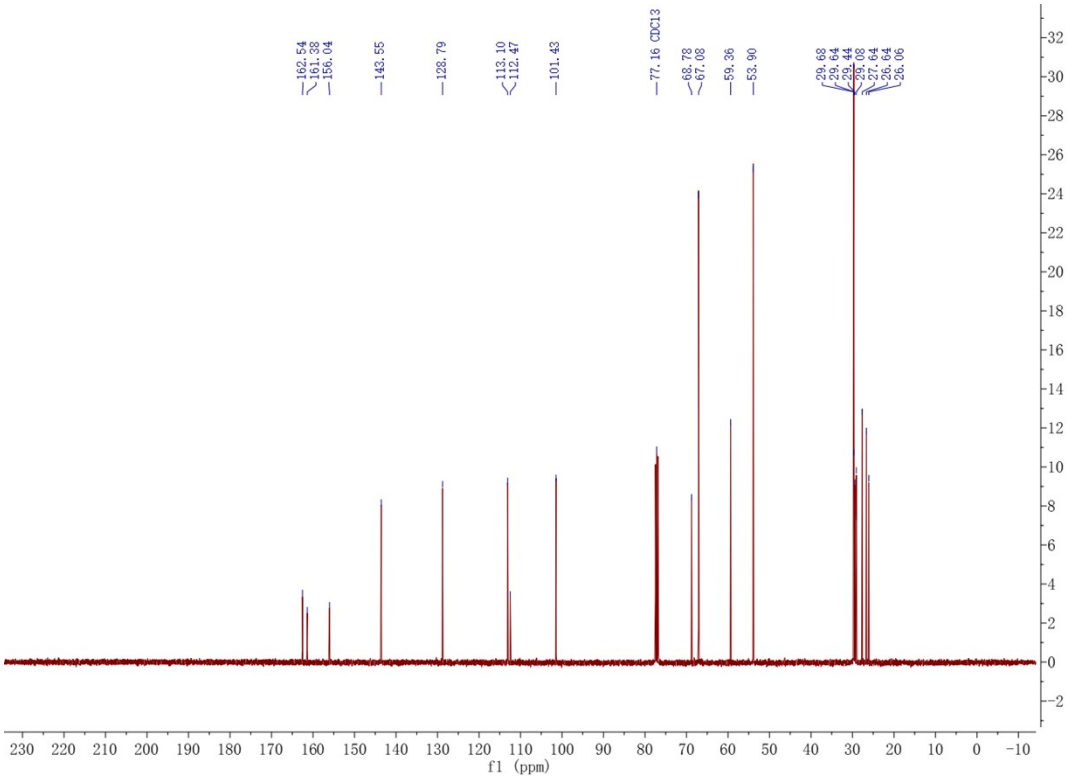

Fig.S30 *[13]C NMR of* **12c** (400 MHz, $CDCl_3$)

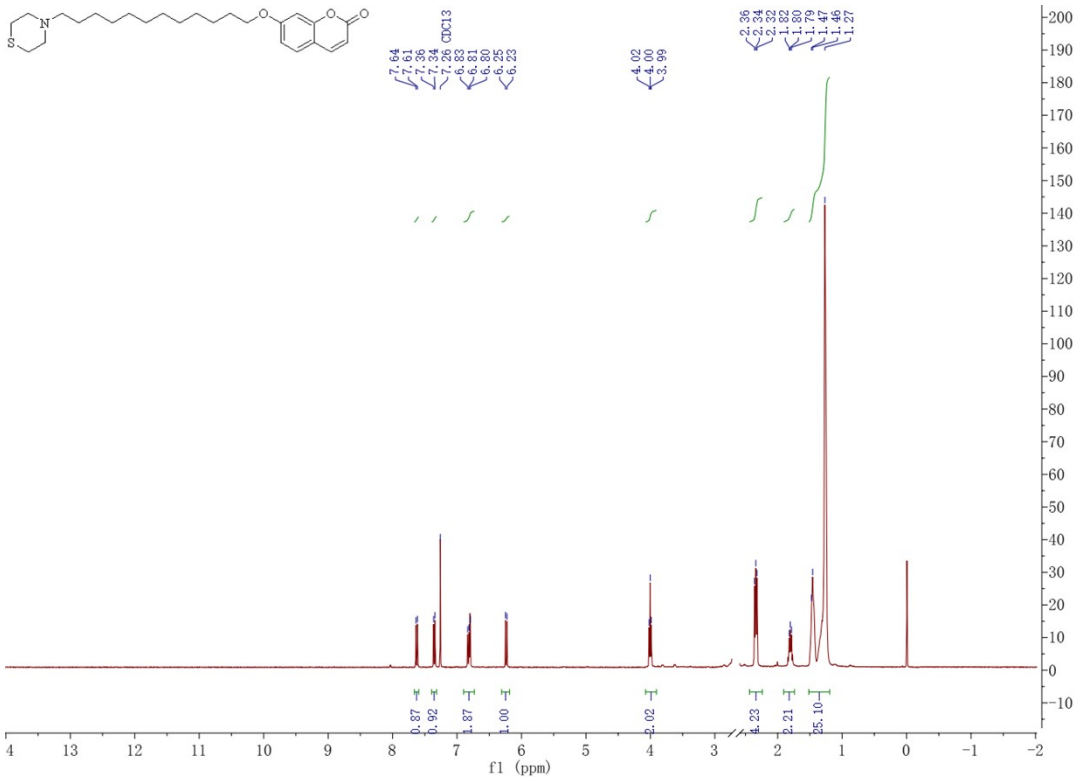

Fig.S31 *[1]H NMR of* **12d** (400 MHz, $CDCl_3$)

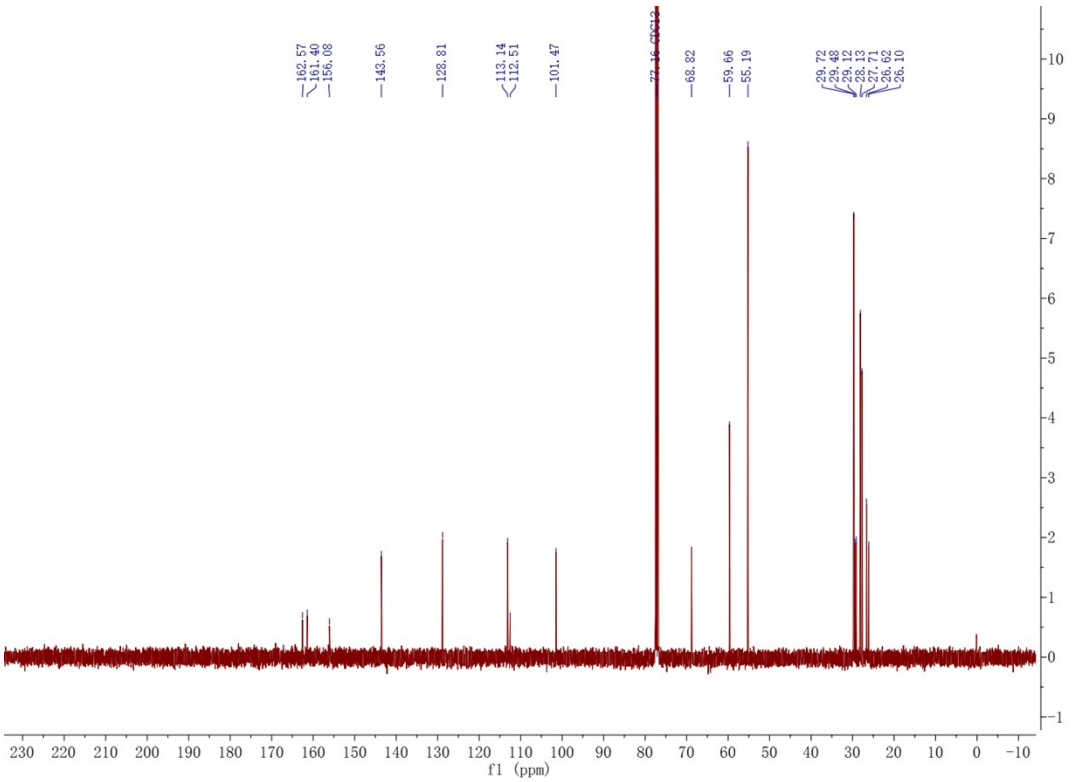

Fig.S32 *[13]C NMR of* **12d** (400 MHz, $CDCl_3$)

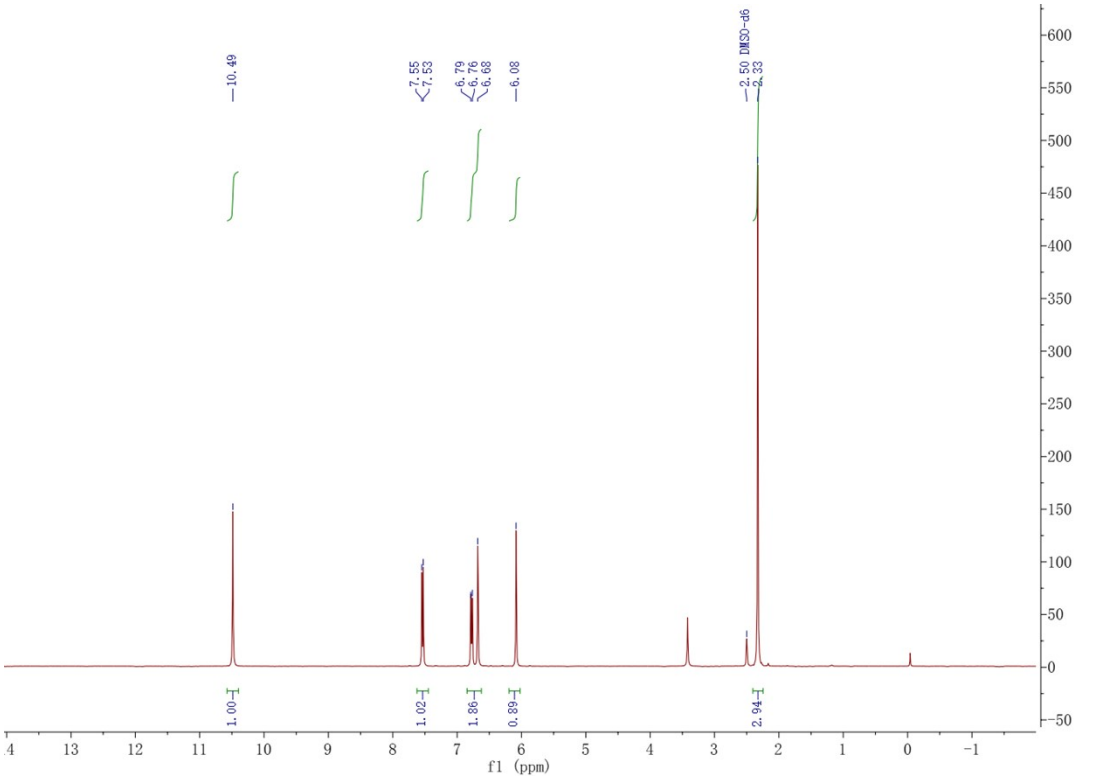

Fig.S33 *[1]H NMR of* **13** (400 MHz, DMSO)

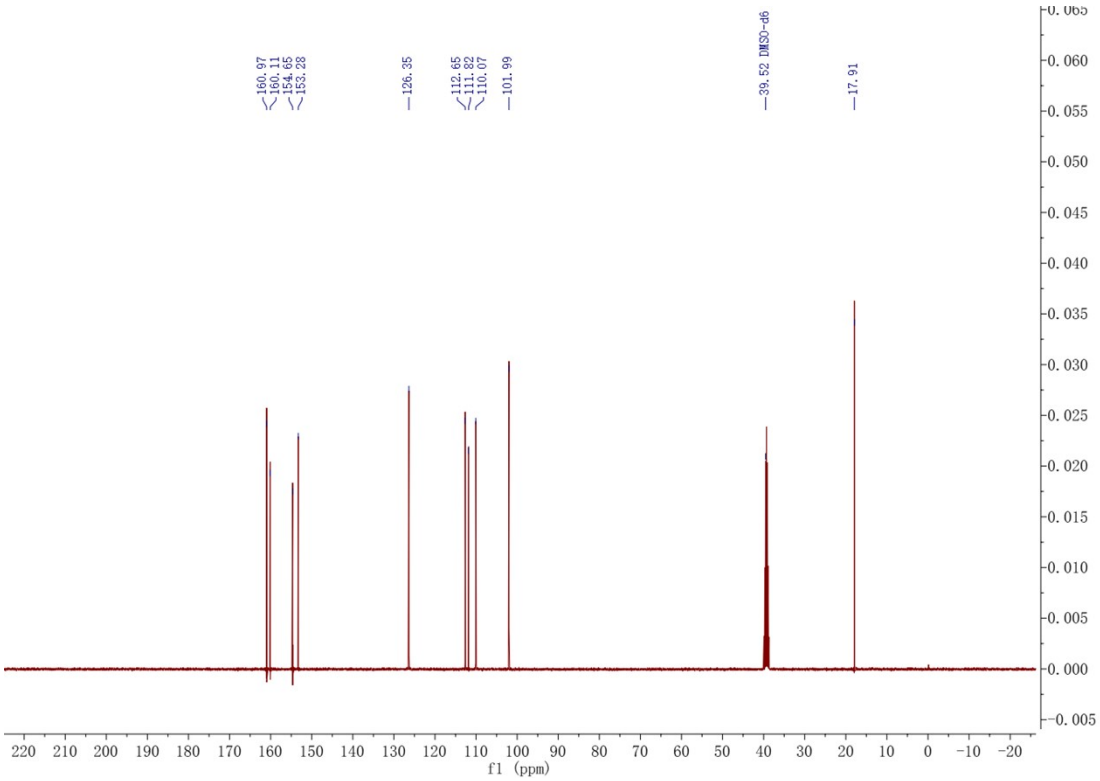

Fig.S34 *[13]C NMR of* **13** (400 MHz, DMSO)

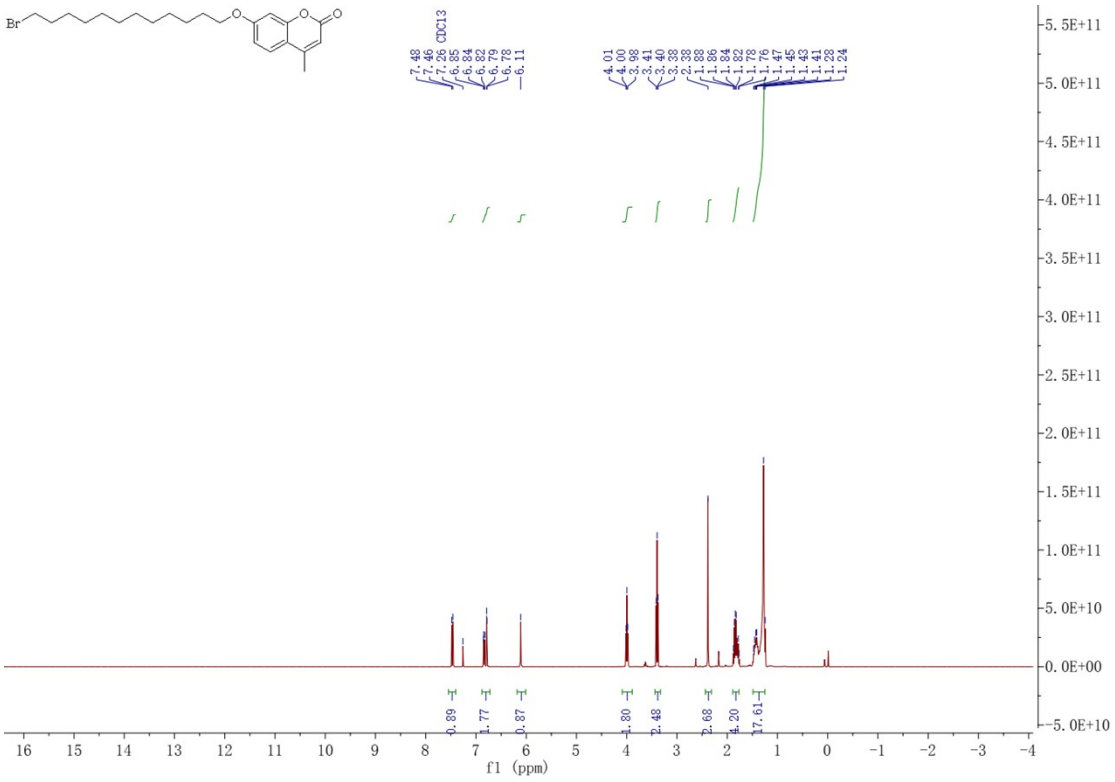

Fig.S35 *[1]H NMR of* **14** (400 MHz, DMSO)

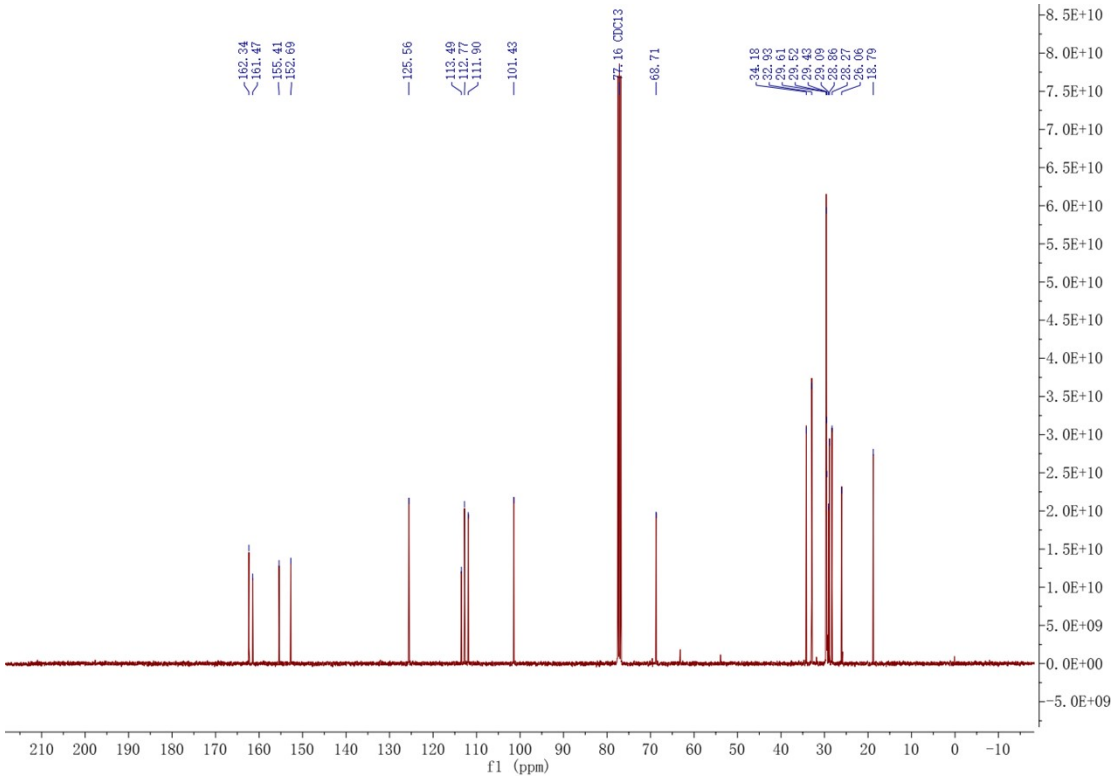

Fig.S36 *[13]C NMR of* **14** (400 MHz, DMSO)

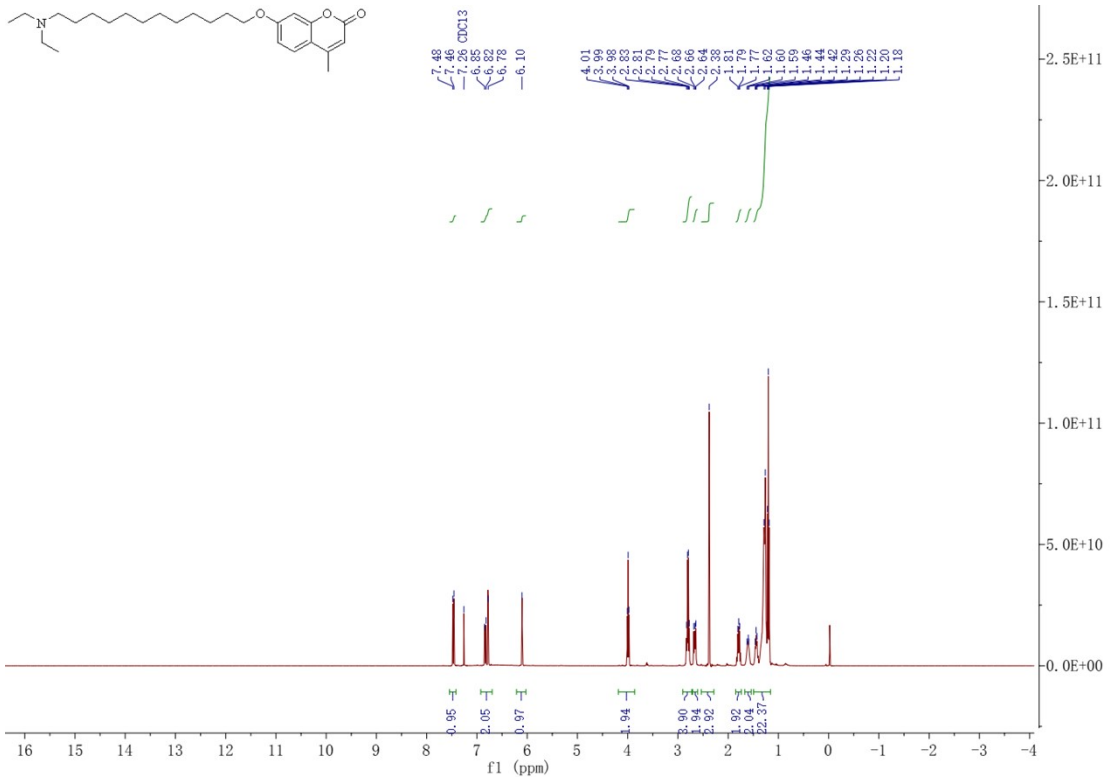

Fig.S37 *[1]H NMR of* **15** (400 MHz, DMSO)

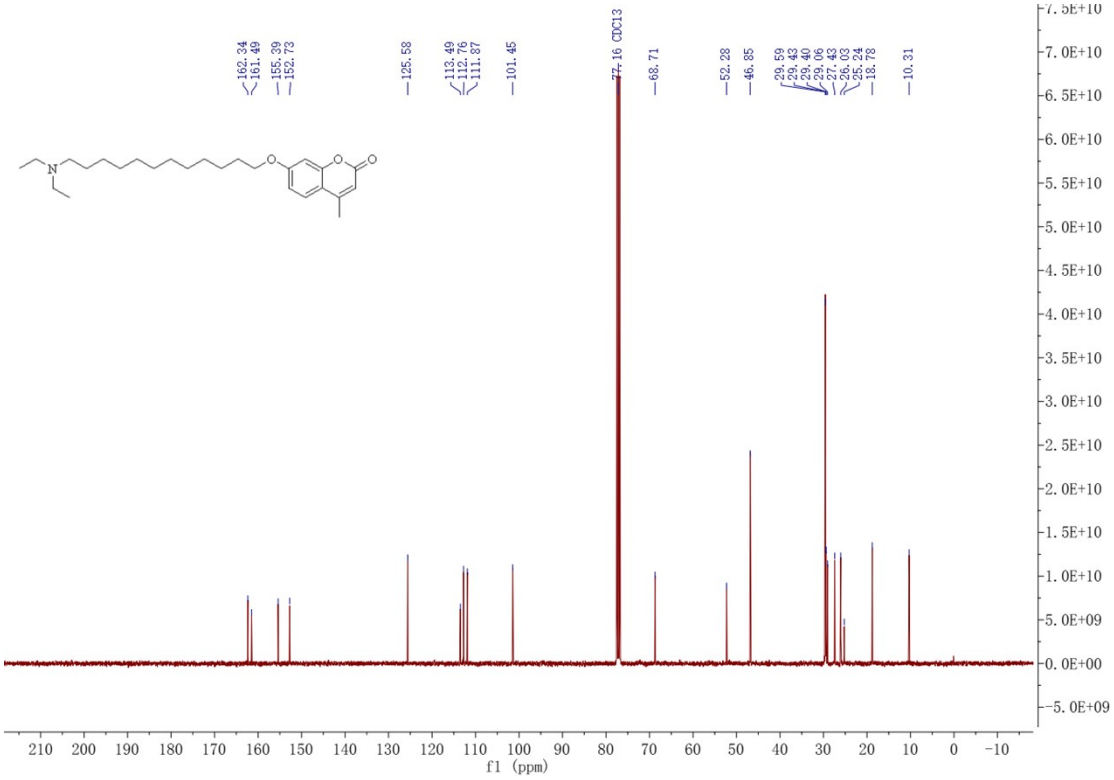

Fig.S38 *[13]C NMR of* **15** (400 MHz, DMSO)

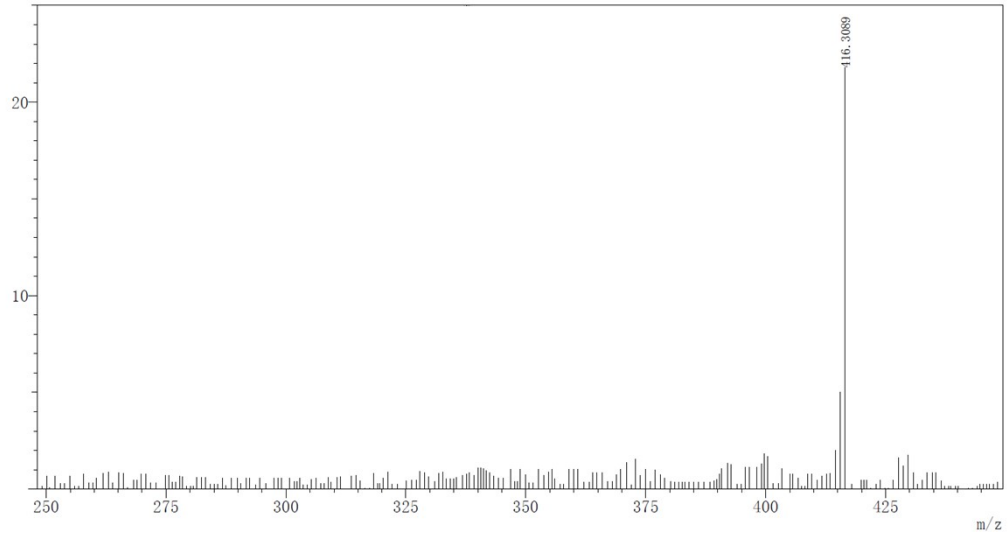

Fig. S39 *Mass spectrum of compound* **15**

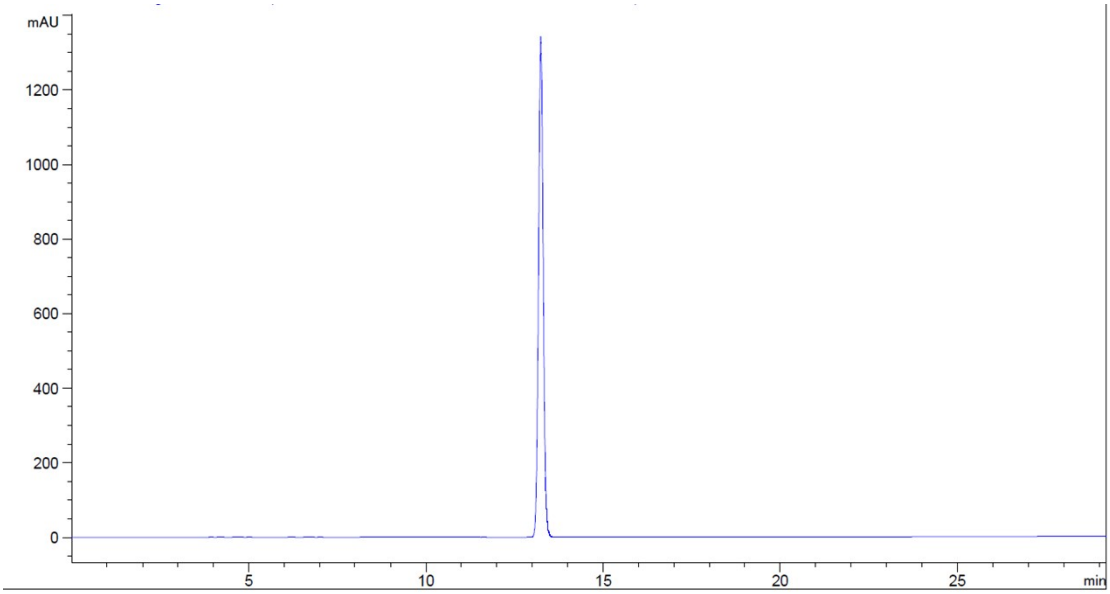

Fig. S40 *HPLC chromatograms compound* **15**