Electronic Supplementary Material (ESI) for Analyst.

Supporting Information for

A Lysosome-Locating and Acidic pH-Activatable Fluorescent Probe for Visualizing Endogenous H_2O_2 in Lysosomes

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Synthesis of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic Acid (DHBA)

A solution of 3-diethylamino phenol (1.0 equiv) and phthalic anhydride (1.0 equiv) in toluene was refluxed under N_2 for 6 h and then allowed to 65℃ within 2 h. The 35% aqueous NaOH was added to the reaction mixture at 90℃ for 16 h. The resulting mixture was poured into distilled water, acidified with HCl at 0 ℃, and allowed to stir at room temperature for 4 h. The suspension was then filtered. The residue was purified by column chromatography on silica gel (EA/PE, 2:1 vol/vol) to give DHBA (2.2g) as a pink solid. Yield: 67%.

Synthesis of L1

A solution of compound DHBA (0.6 g, 2.0 mmol) and Naphthalene-1,8-diol (0.32 g, 2.0 mmol) in 10 mL TFA (trifluoroacetic acid) was heated under at 90 ℃ for 10 h. The cooled mixture was then poured into 20 mL of ice water, neutralized with saturated aqueous Na_2CO_3, and finally filtered. The solution was evaporated under pressure to give a red powder, which was dried and purified by column chromatography on silica to afford compound L1 (0.33 g) with a yield of 54.6% (methanol:dichloromethane= 1:10). ^{1}H NMR (500 MHz, DMSO) δ 9.78 (s, 1H), 8.04 (d, J=7.6 Hz, 1H), 7.80 (t, J=7.4 Hz, 1H), 7.74 (t, J=7.5 Hz, 1H), 7.47 (d, J=3.8 Hz, 1H), 7.45 (t, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.30 (d, J=7.6 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 6.72 (s, 1H), 6.62 (d, J=8.7 Hz, 1H), 6.54 (t, 2H), 3.39 (q, J=6.9 Hz, 4H), 1.13 (t, J=7.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 169.30, 154.98, 153.34, 152.12, 149.68, 148.71, 137.00, 136.10, 130.58, 129.26, 128.85, 126.71, 125.11, 124.63, 124.36, 124.00, 119.32, 114.28, 112.92, 112.37, 109.72, 104.50, 97.89, 84.40, 60.24, 44.27, 12.83 ppm. ESI-MS: m/z calcd for $[C_{28}H_{23}NO_4]^+$, 437.16; found, 437.8 $(M)^+$.

Synthesis of L2

A solution of compound DHBA (0.6 g, 2.0 mmol) and 1,6-Naphthalenediol (0.32 g, 2.0 mmol) in 10 mL TFA (trifluoroacetic acid) was heated under at 90 ℃ for 10 h. The cooled mixture was then poured into 20mL of ice water, neutralized with saturated aqueous Na_2CO_3, and finally filtered. The solution was evaporated under pressure to give a red powder, which was dried and purified by column chromatography on silica to afford compound L1 (0.36 g) with a yield of 56.1% (methanol:dichloromethane= 1:8). ^{1}H NMR (500 MHz, DMSO) δ 10.36 (s, 1H), 8.05 (t, J=7.7 Hz, 2H), 7.79 (t, J=7.5 Hz, 1H), 7.74 (t, J=7.4 Hz, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.06 (d, J=7.6 Hz, 1H), 6.75 (s, 1H), 6.66 (d, J=8.9 Hz, 1H), 6.57 (d, J=8.9 Hz, 1H), 6.53 (d, J=2.2 Hz, 2H), 3.39 (q, 4H), 1.13 (t, J=7.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 170.79, 169.36, 153.87, 153.42, 152.39, 149.79, 146.90, 136.07, 130.56, 129.06, 127.98, 126.65, 125.54, 125.13, 125.09, 124.57, 122.54, 118.04, 113.29, 112.79, 110.92, 109.57, 104.84, 97.70, 84.19, 60.22, 44.25, 12.84 ppm. ESI-MS: m/z calcd for $[C_{28}H_{23}NO_4]^+$, 437.16; found, 437.9 $(M)^+$.

Synthesis of L3

A solution of compound DHBA (0.6 g, 2.0 mmol) and 1,5-Naphthalenediol (0.32 g, 2.0 mmol) in 10 mL TFA (trifluoroacetic acid) was heated under at 90 ℃ for 10 h. The cooled mixture was then poured into 20 mL of ice water, neutralized with saturated aqueous Na_2CO_3, and finally filtered. The solution was evaporated under pressure to give a red powder, which was dried and purified by column chromatography on silica to afford compound L1 (0.44 g) with a yield of 63% (methanol:dichloromethane= 1:9). ^{1}H NMR (500 MHz, DMSO) δ 10.50 (s, 1H), 8.11 (d, J=7.3 Hz, 2H), 7.85 (t, 2H), 7.82 (d, J=7.4 Hz, 1H), 7.77 (t, J=7.5 Hz, 1H), 7.57 (t, J=8.8 Hz, 1H), 7.34 (d, J=7.3 Hz, 1H), 7.20 (t, J=7.9 Hz, 1H), 7.11 (d, J=7.3 Hz, 1H), 6.83 (d, J=7.4 Hz, 1H), 6.74 (d, J=6.5 Hz,

1H), 4.03 (dd, J=14.2, 7.1 Hz, 4H), 1.17 (t, 6H). ^{13}C NMR (126 MHz, DMSO) δ 170.80, 169.37, 158.84, 157.68, 153.37, 152.39, 149.73, 147.35, 136.33, 136.00, 130.49, 130.16, 129.08, 126.79, 125.02, 124.53, 124.20, 122.25, 119.37, 117.70, 110.17, 109.77, 109.47, 105.05, 97.70, 84.50, 60.22, 44.26, 12.85 ppm. ESI-MS: m/z calcd for $[C_{28}H_{23}NO_4]^+$, 437.16; found, 437.7 $(M)^+$.

Synthesis of Lyso-L1

Compound L1 (220 mg, 0.5 mmol) and 4-(2-aminoethyl)-morpholine (130 mg, 1 mmol) were dissolved in ethanol (15 mL), and the reaction mixture was refluxed with stirring for 6 h and then evaporated in vacuo. The residue was puried by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1 vol/vol) to give Lyso-L1 (160 mg) as a faint yellow powder. Yield: 62%. ^{1}H NMR (500 MHz, DMSO) δ 9.66 (s, 1H), 7.87 (d, J=6.7 Hz, 1H), 7.51 (s, 2H), 7.36 (t, J=8.5 Hz, 2H), 7.27 (d, J=8.0 Hz, 1H), 7.05 (d, J=7.1 Hz, 2H), 7.00 (d, J=7.6 Hz, 1H), 6.74 (d, J=1.9 Hz, 1H), 6.49 (d, J=8.7 Hz, 1H), 6.41 (d, J=1.7 Hz, 1H), 6.39 (d, J=8.9 Hz, 1H), 4.02 (q, J=7.1 Hz, 1H), 3.33 (t, 4H), 3.18 (t, J=6.9 Hz, 2H), 2.01 (s, 2H), 1.98 (s, 2H), 1.93 (s, 2H), 1.16 (t, J=7.1 Hz, 2H), 1.08 (t, J = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 170.88, 168.05, 167.42, 156.60, 156.33, 153.72, 152.70, 149.78, 148.84, 148.79, 146.48, 135.06, 134.76, 134.43, 128.53, 128.23, 126.16, 125.86, 115.24, 83.99, 74.02, 63.21, 60.26, 53.34, 25.39, 25.13, 14.54 ppm. ESI-MS: m/z calcd for $[C_{34}H_{35}N_3O_4]^+$, 549.26; found, 550.0 $(M)^+$.

Synthesis of Lyso-L2

Compound L1 (220 mg, 0.5 mmol) and 4-(2-aminoethyl)-morpholine (130 mg, 1 mmol) were dissolved in ethanol (15 mL), and the reaction mixture was refluxed with stirring for 6 h and then evaporated in vacuo. The residue was puried by column chromatography on silica gel (CH_2Cl_2/ MeOH, 10:1 vol/vol) to give Lyso-L1 (153 mg) as a faint yellow

powder. Yield: 59%. ^{1}H NMR (500 MHz, DMSO) δ 10.29 (s, 1H), 7.97 (d, J=8.1 Hz, 2H), 7.85 (t, 1H), 7.70 (d, J=8.9 Hz, 2H), 7.54 (t, 2H), 7.47 (t, J=8.0 Hz, 2H), 7.35 (d, J=.4 Hz, 2H), 7.01 (d, J=7.6 Hz, 2H), 6.80 (d, J=9.1 Hz, 1H), 6.51 (d, J=8.9 Hz, 2H), 6.07 (d, J=2.3 Hz, 2H), 3.45 (dd, J=14.0, 7.0 Hz, 2H), 3.34 (t, 4H), 3.14 (t, J=6.5 Hz, 2H), 1.99 (d, J=1.5 Hz, 2H), 1.91 (t, 6H). ^{13}C NMR (126 MHz, DMSO) δ 167.50, 165.09, 153.79, 153.42, 152.63, 149.05, 147.67, 147.14, 141.90, 140.50, 134.70, 133.35, 130.91, 130.29, 129.78, 128.03, 125.25, 123.00, 122.94, 113.78, 113.07, 104.40, 97.94, 96.78, 66.36, 64.66, 53.33, 44.48, 44.16, 21.24, 12.89 ppm. ESI-MS: m/z calcd for $[C_{34}H_{35}N_3O_4]^+$, 549.26; found, 550.1 $(M)^+$.

Synthesis of Lyso-L3

Compound L1 (220 mg, 0.5 mmol) and 4-(2-aminoethyl)-morpholine (130 mg, 1 mmol) were dissolved in ethanol (15 mL), and the reaction mixture was refluxed with stirring for 6 h and then evaporated in vacuo. The residue was puried by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1 vol/vol) to give Lyso-L1 (146 mg) as a faint yellow powder. Yield: 55.2%. ^{1}H NMR (500 MHz, DMSO) δ 12.59 (s, 1H), 8.40 (d, J=9.0 Hz, 2H), 7.96 (d, J=7.6 Hz, 2H), 7.68 (t, J=7.1 Hz, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.37 (d, J=7.3 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 6.80 (d, J=9.1 Hz, 1H), 6.45 (d, J=8.8 Hz, 1H), 6.20 (d, J=.4 Hz, 1H), 6.07 (d, J=2.4 Hz, 1H), 4.04 (q, J=7.1 Hz, 4H), 3.13 (t, 2H), 2.43 (t, 2H), 2.00 (s, 2H), 1.90 (t, 2H), 1.24 (s, 2H), 1.18 (t, J=7.1 Hz, 2H), 1.11 (t, 6H). ^{13}C NMR (126 MHz, DMSO) δ 167.42, 157.25, 153.53, 152.65, 149.00, 147.51, 135.90, 133.29, 130.99, 129.09, 129.01, 125.00, 124.31, 123.91, 122.88, 121.90, 119.03, 117.89, 110.48, 109.69, 109.29, 104.95, 97.94, 66.37, 64.63, 56.13, 53.34, 44.17, 37.19, 12.89 ppm. ESI-MS: m/z calcd for $[C_{34}H_{35}N_3O_4]^+$, 549.26; found, 550.0 $(M)^+$.

Synthesis of Lyso-B-L1

A mixture of Lyso-L1 (110 mg, 0.2 mmol), 4-(bromomethyl)benzeneboronic acid pinacol ester (75 mg, 0.25 mmol), and Cs_2CO_3 (98 mg, 0.3 mmol) in N,N-dimethylformamide (DMF; 10 mL) was heated at 80℃ for 8 h. After cooling, 30 mL water was added into the mixture and extracted with CH_2Cl_2 (10 mL×3). The organic solutions were combined, washed with water and brine, and dried with Na_2SO_4. The solvents were evaporated to give the crude product, which was purified by flash chromatography (silica gel, dichloromethane/ 0-10% methanol) to give the desired products as a pale solid (100 mg). Yield: 49%. ^{1}H NMR (500 MHz, DMSO) δ 7.84 (t, J=7.1 Hz, 2H), 7.71 (d, J=7.9 Hz, 2H), 7.66 (d, J=7.8 Hz, 1H), 7.48 (t, 2H), 7.41 (t, 1H), 7.34 (d, J=7.9 Hz, 1H), 7.24 (d, J=7.9 Hz, 2H), 7.13 (d, J=8.4 Hz, 1H), 7.03 (d, J=7.3 Hz, 1H), 6.73 (d, J=8.4 Hz, 2H), 6.54 (d, J=8.7 Hz, 1H), 6.34 (s, 2H), 4.39 (d, J=5.1 Hz, 2H), 3.96 (s, 4H), 3.34 (s, 2H), 3.09 (d, J=6.9 Hz, 2H), 1.99 (s, 2H), 1.88 (t, J=7.1 Hz, 2H), 1.16 (t, 2H), 1.10 (s, 12H), 0.90 (t, J=7.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 167.50, 165.09, 153.79, 153.42, 152.63, 149.05, 147.67, 147.14, 141.90, 140.50, 134.70, 133.35, 130.91, 130.29, 129.78, 128.03, 125.25, 123.00, 122.94, 113.78, 113.07, 104.40, 97.94, 96.78, 66.36, 64.66, 60.24, 56.13, 53.33, 44.48, 44.16, 21.24, 12.94, 12.89 ppm. ESI-MS: m/z calcd for $[C_{47}H_{52}BN_3O_6]^+$, 765.39; found, 766.5 $(M)^+$.

Synthesis of Lyso-B-L2

A mixture of Lyso-L2 (110 mg, 0.2 mmol), 4-(bromomethyl)benzeneboronic acid pinacol ester (75 mg, 0.25 mmol), and Cs_2CO_3 (98 mg, 0.3 mmol) in N,N-dimethylformamide (DMF; 10 mL) was heated at 80℃ for 8 h. After cooling, 30 mL water was added into the mixture and extracted with CH_2Cl_2 (10 mL×3). The organic solutions were combined, washed with water and brine, and dried with Na_2SO_4. The solvents were evaporated to give the crude product, which was purified by flash chromatography (silica gel,

dichloromethane/ 0-10% methanol) to give the desired products as a pale solid (110 mg). Yield: 52.4%. ^{1}H NMR (500 MHz, DMSO) δ 7.83 (t, 2H), 7.74 (d, J=7.8 Hz, 2H), 7.64 (d, J=7.9 Hz, 2H), 7.54 (t, 1H), 7.45 (t, 1H), 7.33 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 7.07 (d, J=1.9 Hz, 2H), 6.54 (d, J=8.7 Hz, 1H), 6.35 (t, J=10.4 Hz, 2H), 5.28 (t, 2H), 4.53 (d, J=5.5 Hz, 2H), 4.03 (q, J=7.1 Hz, 4H), 3.97 (s, 2H), 3.35 (t, 2H), 3.09 (t, 2H), 1.88 (t, J=7.3 Hz, 2H), 1.34 (s, 2H), 1.08 (s, 12H), 0.91 (t, J=7.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 170.74, 167.39, 156.66, 156.36, 153.76, 152.73, 148.77, 146.47, 140.72, 136.76, 135.05, 134.77, 133.23, 133.19, 130.83, 128.50, 128.12, 126.10, 115.25, 113.92, 104.47, 97.79, 84.11, 74.03, 66.36, 64.88, 63.30, 53.34, 43.76, 25.38, 25.12, 12.53 ppm. ESI-MS: m/z calcd for $[C_{47}H_{52}BN_3O_6]^+$, 765.39; found, 766.3 $(M)^+$.

Synthesis of Lyso-B-L3

A mixture of Lyso-L3 (110 mg, 0.2 mmol), 4-(bromomethyl)benzeneboronic acid pinacol ester (75 mg, 0.25 mmol), and Cs_2CO_3 (98 mg, 0.3 mmol) in N,N-dimethylformamide (DMF; 10 mL) was heated at 80℃ for 8 h. After cooling, 30 mL water was added into the mixture and extracted with CH_2Cl_2 (10 mL×3). The organic solutions were combined, washed with water and brine, and dried with Na_2SO_4. The solvents were evaporated to give the crude product, which was purified by flash chromatography (silica gel, dichloromethane/ 0-10% methanol) to give the desired products as a pale solid (118 mg). Yield: 54%. 1H NMR (500 MHz, DMSO) δ 7.94 (d, J=7.6 Hz, 2H), 7.80 (d, J=7.7 Hz, 2H), 7.72 (d, J=7.5 Hz, 2H), 7.45 (d, J=5.0 Hz, 1H), 7.36 (d, J=7.6 Hz, 2H), 7.28 (d, J=7.0 Hz, 1H), 7.20 (d, J=7.7 Hz, 2H), 7.12 (d, J=7.7 Hz, 1H), 7.06 (d, J=7.4 Hz, 1H), 6.63 (d, J=8.6 Hz, 1H), 6.45 (d, J=8.8 Hz, 2H), 6.27 (t, J=7.0 Hz, 1H), 5.28 (s, 1H), 3.70 (t, 1H), 3.50 (t, 4H), 3.13 (d, J=7.0 Hz, 2H), 2.76 (t, J=6.0 Hz, 2H), 2.39 (d, J=6.0 Hz, 2H), 2.18 (s, 2H), 1.38 (s, 2H), 1.34 (s, 12H), 0.99 (t, J=7.0 Hz, 6H). ^{13}C NMR (126 MHz,

DMSO) δ 167.55, 165.07, 157.25, 153.91, 152.65, 149.02, 140.47, 140.46, 135.90, 135.82, 134.70, 134.64, 132.22, 130.34, 130.29, 129.78, 128.00, 124.30, 110.46, 109.83, 104.90, 104.40, 97.93, 96.76, 66.61, 66.35, 60.26, 53.55, 53.32, 44.48, 44.17, 21.23, 12.92 ppm. ESI-MS: m/z calcd for $[C_{47}H_{52}BN_3O_6]^+$, 765.39; found, 766.1 $(M)^+$.

Synthesis of L1-B

A mixture of L1 (220 mg, 0.5 mmol), 4-(bromomethyl)benzeneboronic acid pinacol ester (178 mg, 0.6 mmol), and Cs_2CO_3 (245 mg, 0.75 mmol) in N,N-dimethylformamide (DMF; 10 mL) was heated at 80℃ for 8 h. After cooling, 30 mL water was added into the mixture and extracted with CH_2Cl_2 (10 mL×3). The organic solutions were combined, washed with water and brine, and dried with Na_2SO_4. The solvents were evaporated to give the crude product, which was purified by flash chromatography (silica gel, dichloromethane/ 0-10% methanol) to give the desired products as a pale solid (230 mg). Yield: 58%. ^{1}H NMR (500 MHz, DMSO) δ 7.84 (t, J=7.1 Hz, 2H), 7.71 (d, J=7.9 Hz, 2H), 7.66 (d, J=7.8 Hz, 1H), 7.48 (t, 2H), 7.34 (d, J=7.9 Hz, 1H), 7.24 (d, J=7.9 Hz, 1H), 7.13 (d, J=8.4 Hz, 2H), 7.03 (d, J=7.3 Hz, 1H), 6.73 (d, J=8.4 Hz, 1H), 6.54 (d, J=8.7 Hz, 1H), 6.34 (s, 2H), 5.24 (s, 2H), 3.96 (s, 4H), 1.10 (s, 12H), 0.90 (t, J=7.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 167.42, 157.25, 153.53, 152.65, 149.00, 147.51, 135.90, 133.29, 130.99, 129.09, 129.01, 125.00, 124.31, 123.91, 122.88, 121.90, 119.03, 117.89, 110.48, 109.69, 109.29, 104.95, 97.94, 66.37, 53.34, 44.17, 12.89 ppm. ESI-MS: m/z calcd for $[C_{41}H_{40}BNO_6]^+$, 653.29; found, 653.9 $(M)^+$.

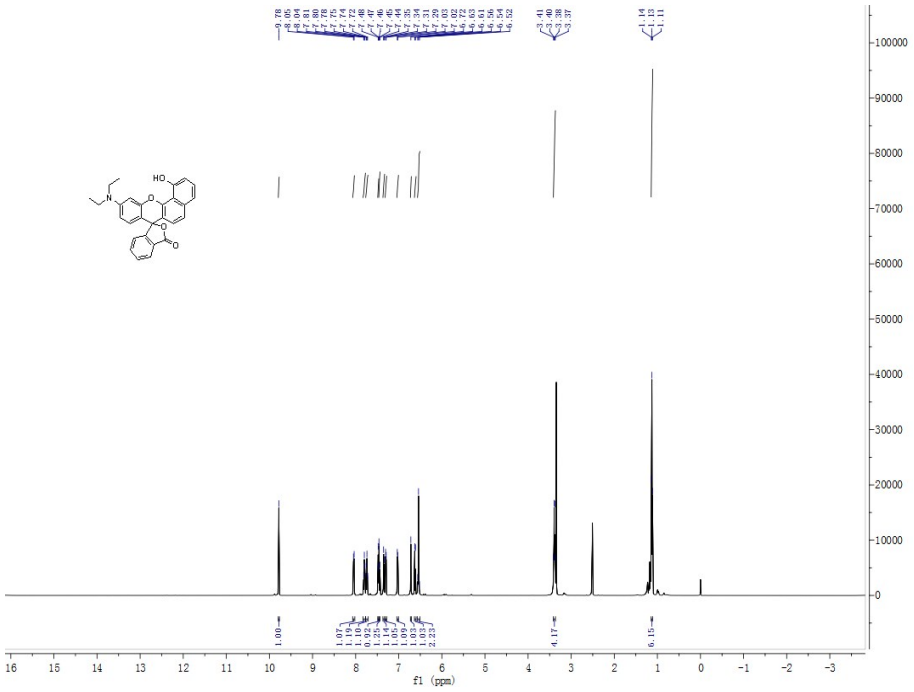

Figure. S1. ^{1}H NMR of compound **L1**.

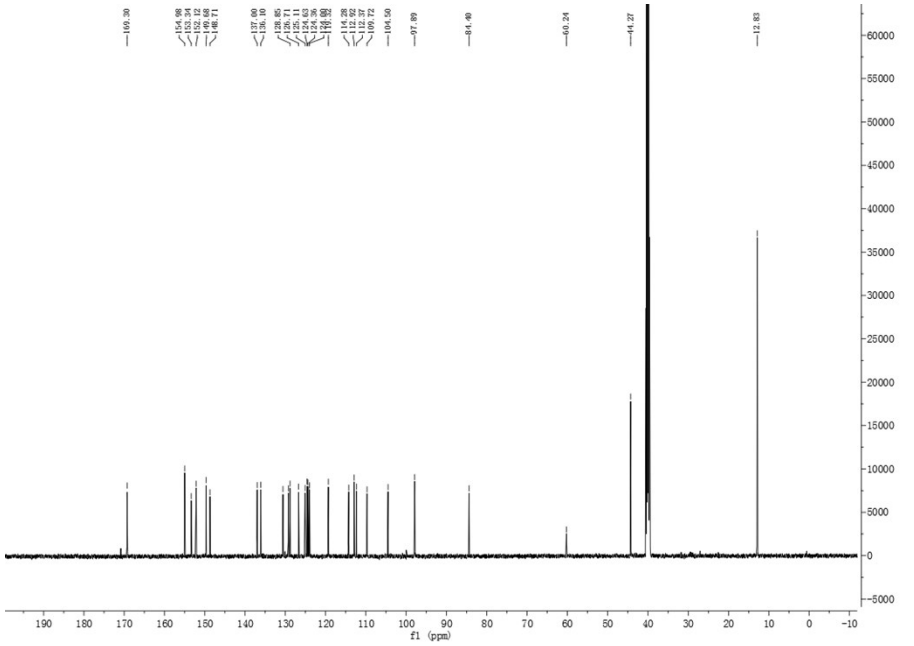

Figure. S2. ^{13}C NMR of compound **L1**.

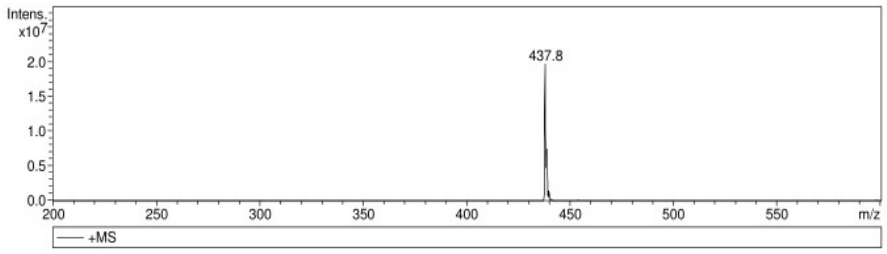

Figure. S3. Mass spectrum of compound **L1**.

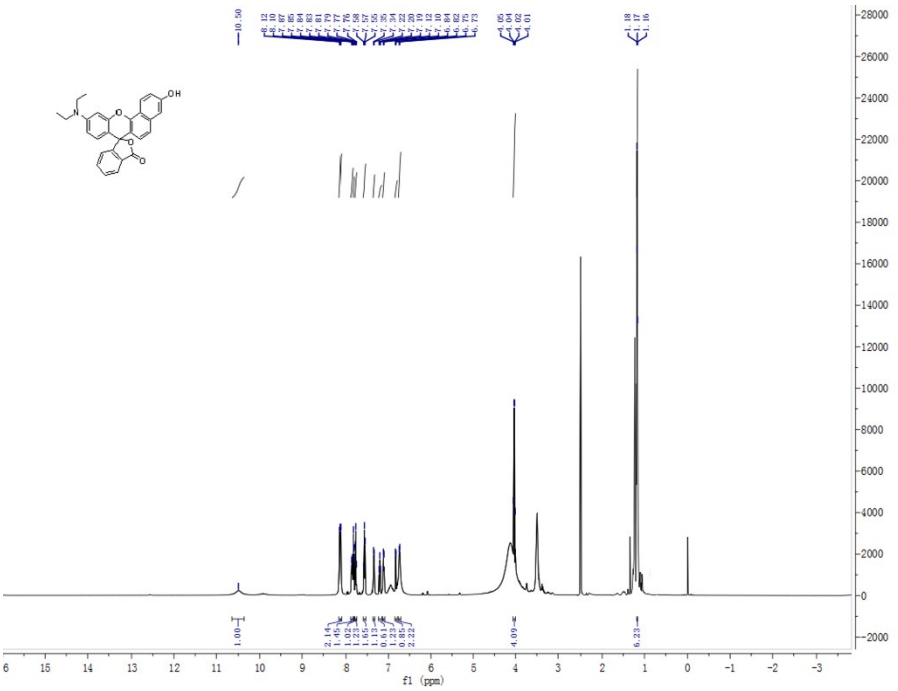

Figure. S4. ^{1}H NMR of compound **L2**.

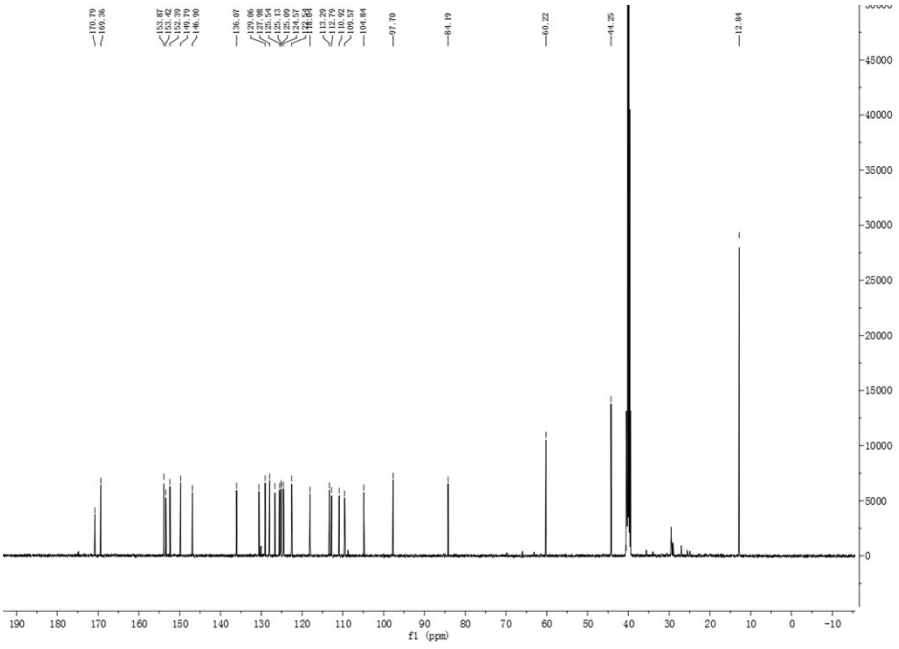

Figure. S5. ^{13}C NMR of compound **L2**.

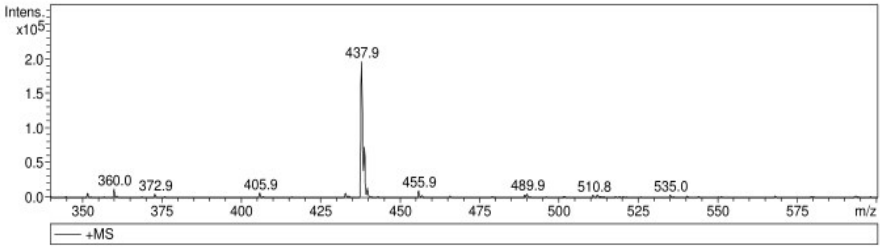

Figure. S6. Mass spectrum of compound **L2**.

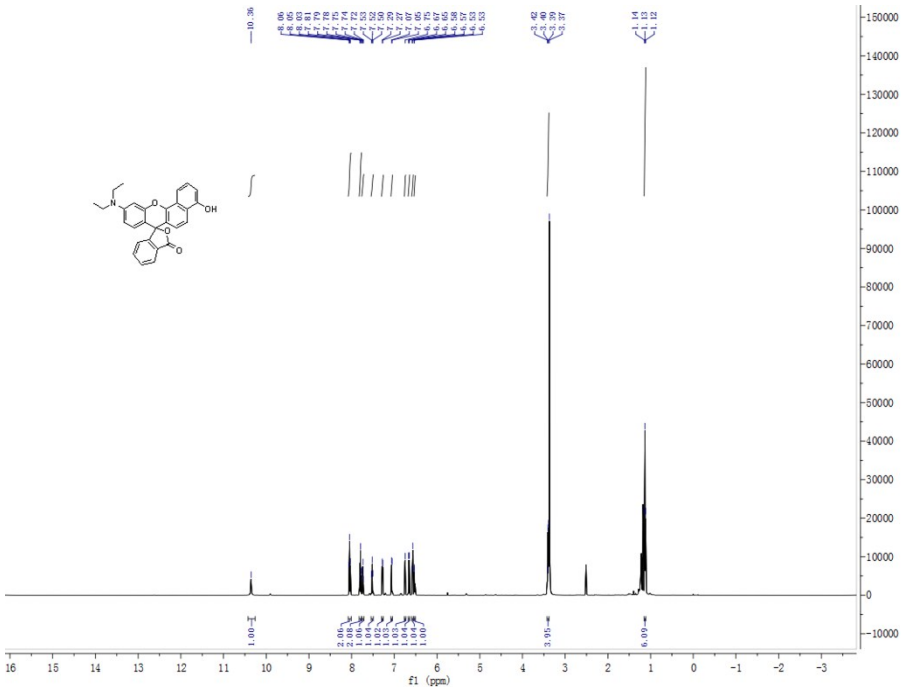

Figure. S7. ^{1}H NMR of compound **L3**.

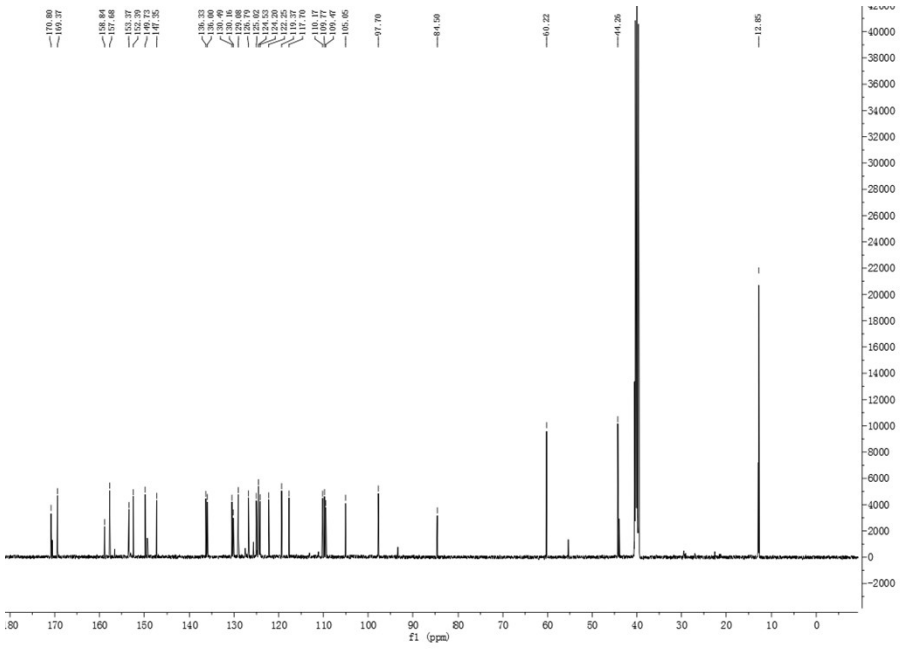

Figure. S8. ^{13}C NMR of compound **L3**.

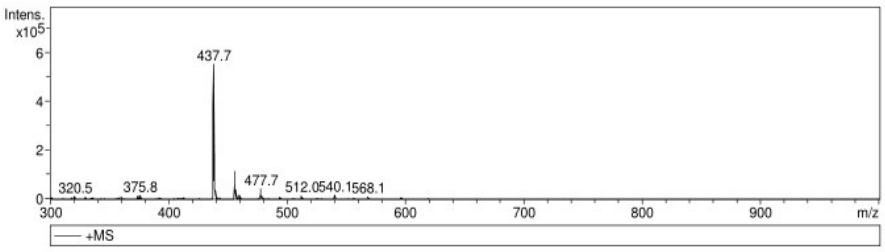

Figure. S9. Mass spectrum of compound **L3**.

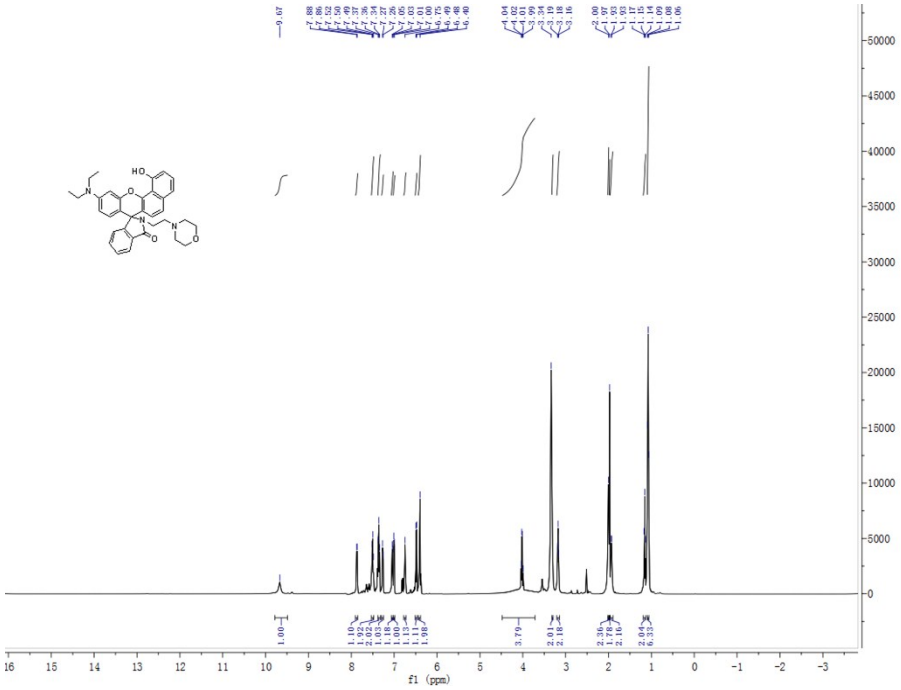

Figure. S10. ^{1}H NMR of compound **Lyso-L1**.

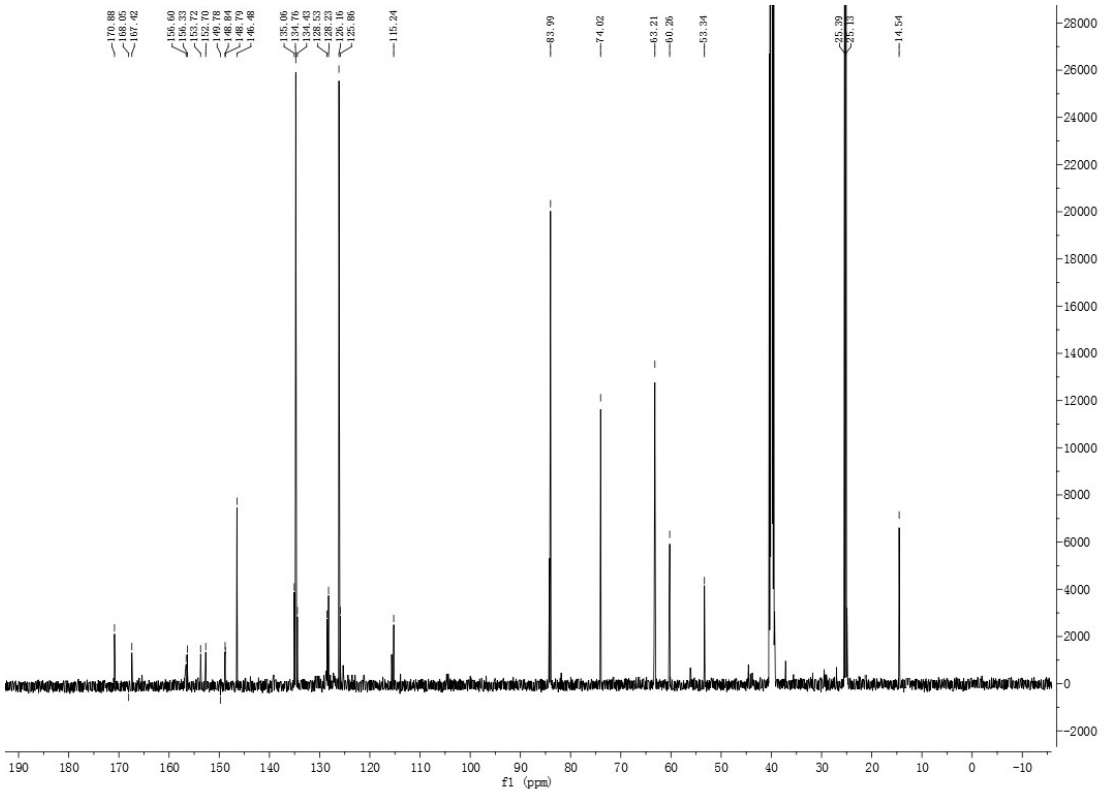

Figure. S11. ^{1}H NMR of compound **Lyso-L1**.

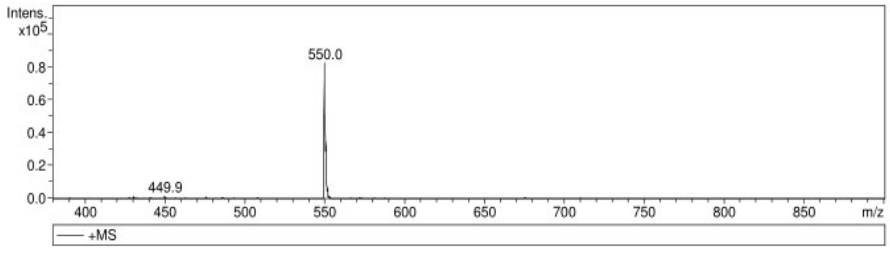

Figure. S12. Mass spectrum of compound **Lyso-L1**.

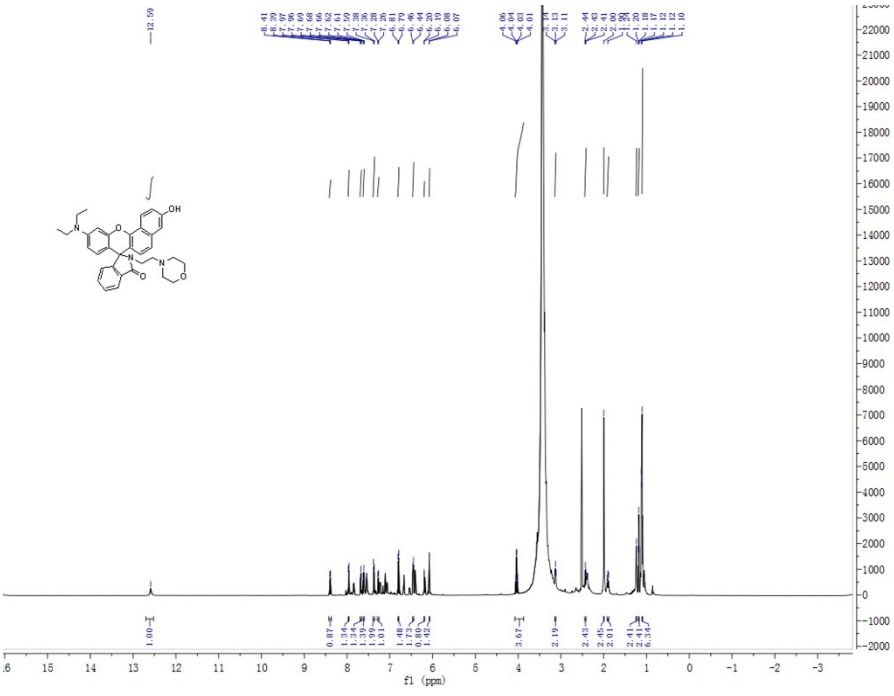

Figure. S13. ^{1}H NMR of compound **Lyso-L2**.

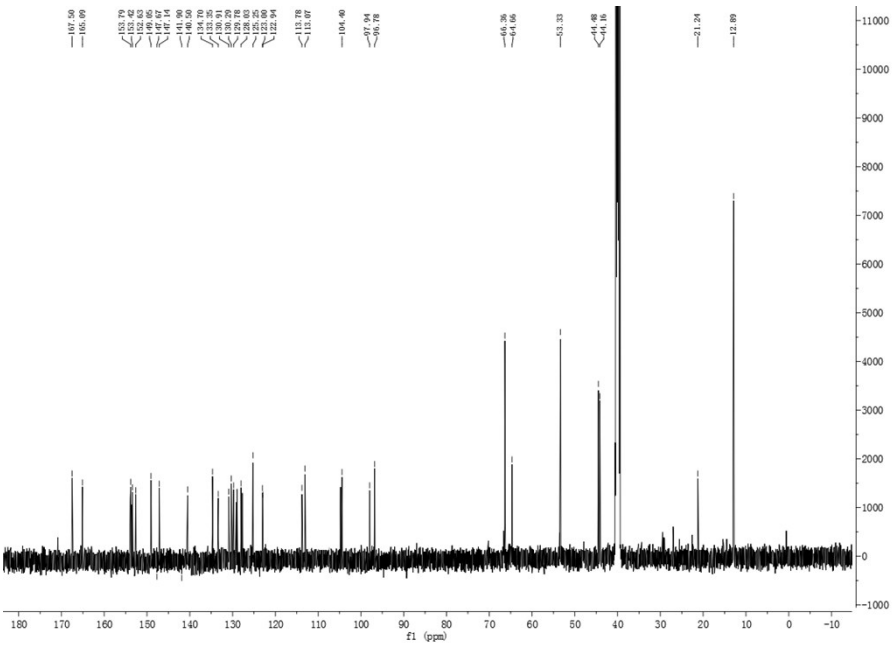

Figure. S14. ^{13}C NMR of compound **Lyso-L2**.

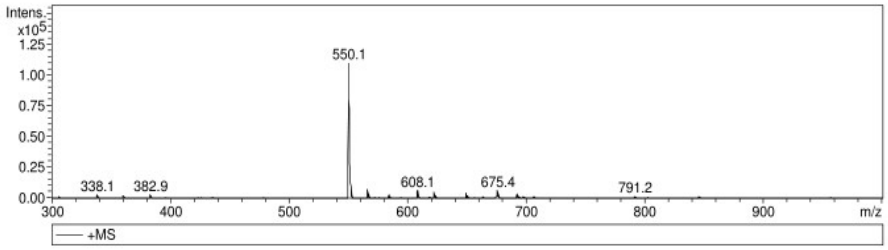

Figure. S15. Mass spectrum of compound **Lyso-L2**.

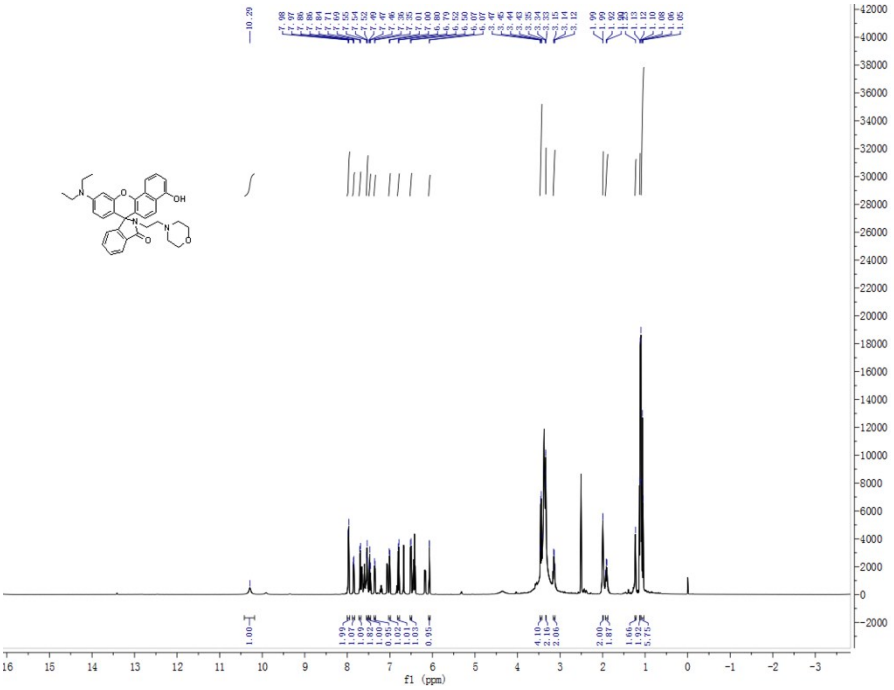

Figure. S16. ^{1}H NMR of compound **Lyso-L3**.

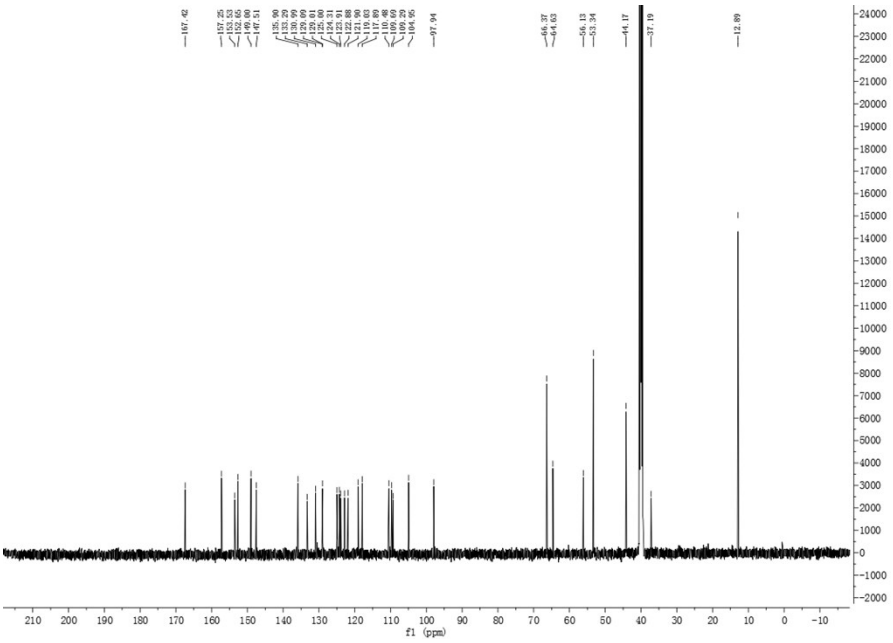

Figure. S17. ^{13}C NMR of compound **Lyso-L3**.

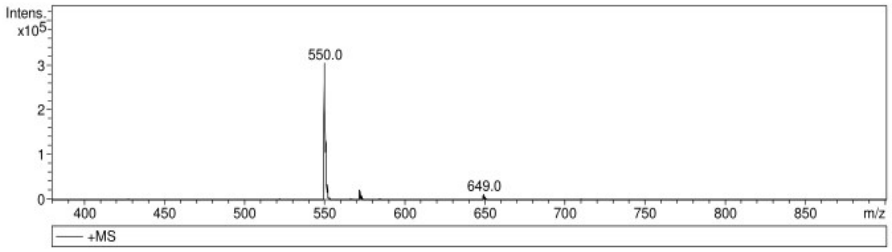

Figure. S18. Mass spectrum of compound **Lyso-L3**.

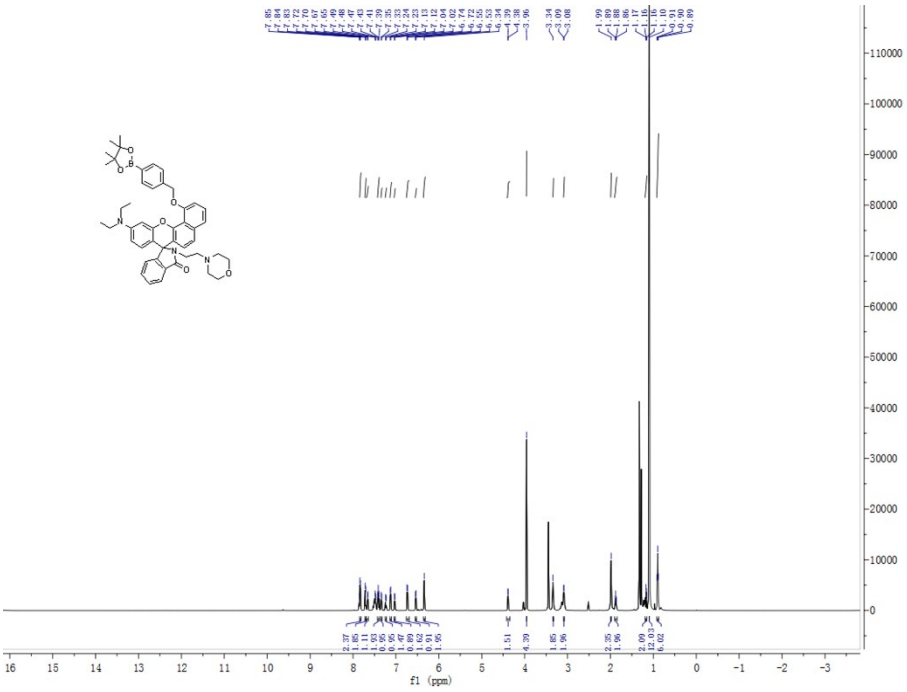

Figure. S19. ^{1}H NMR of compound **Lyso-B-L1**.

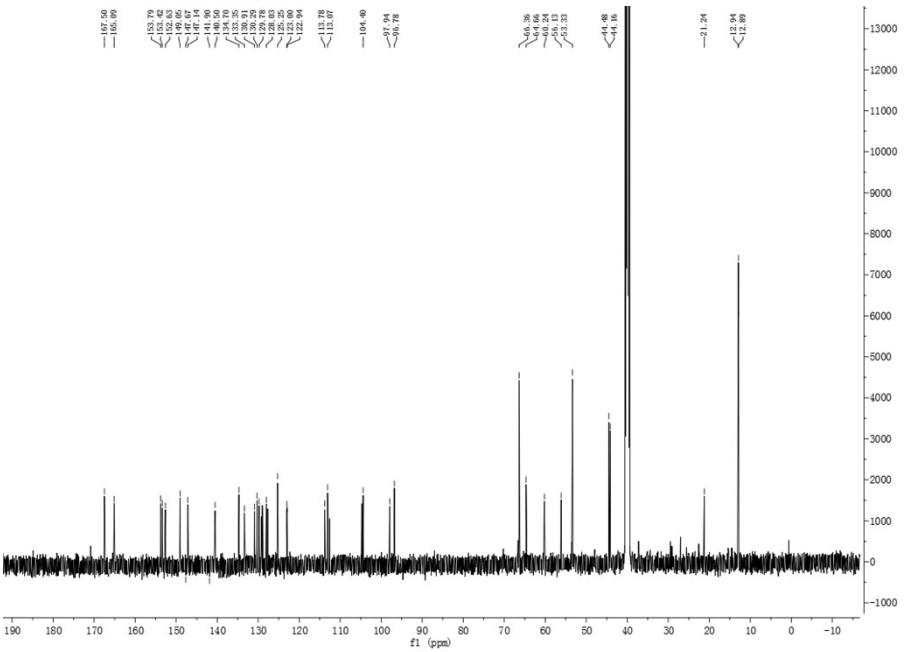

Figure. S20. ^{13}C NMR of compound **Lyso-B-L1**.

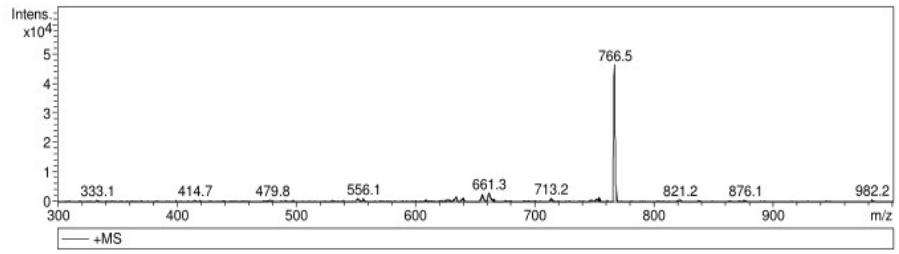

Figure. S21. Mass spectrum of compound **Lyso-B-L1**.

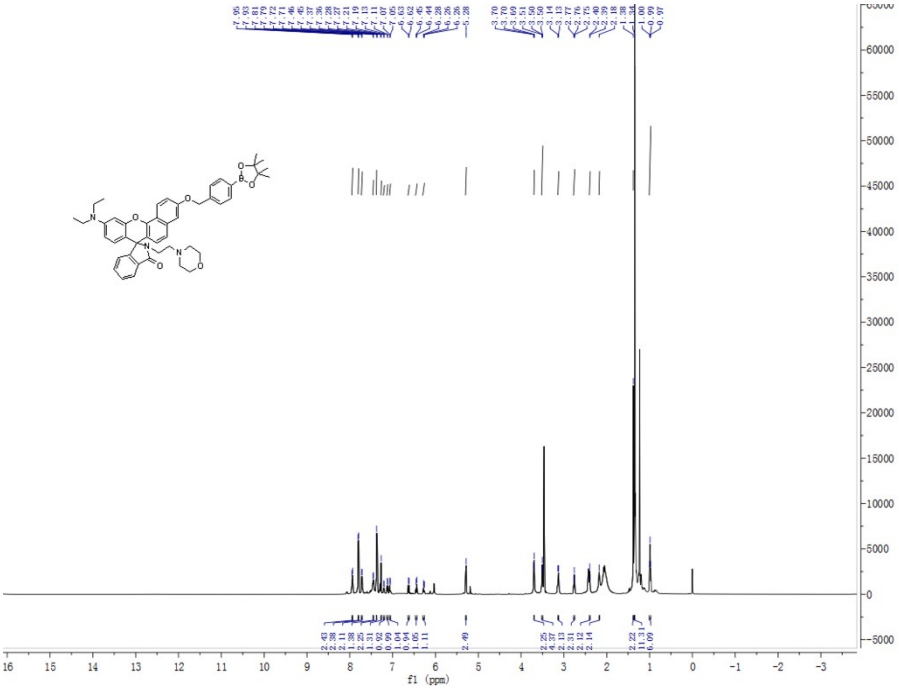

Figure. S22. ^{1}H NMR of compound **Lyso-B-L2**.

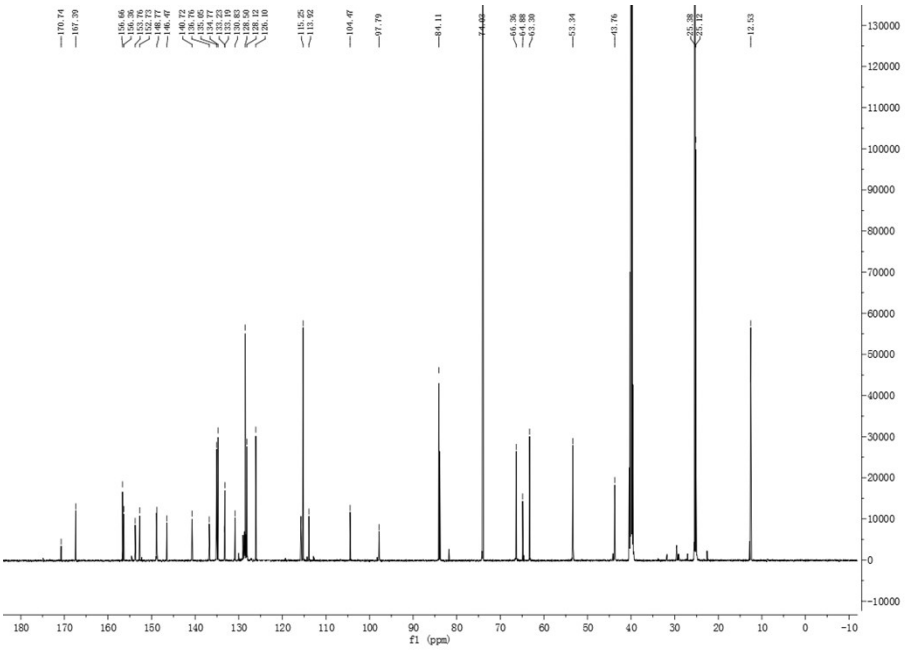

Figure. S23. ^{1}H NMR of compound **Lyso-B-L2**.

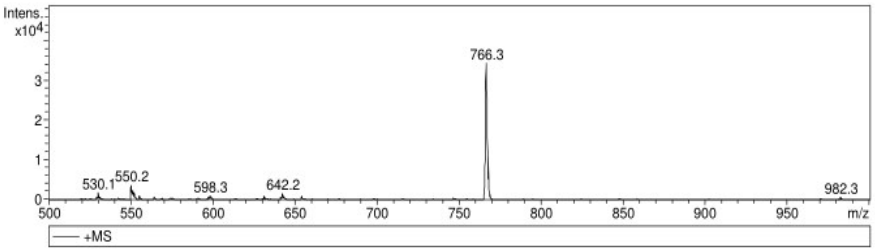

Figure. S24. Mass spectrum of compound **Lyso-B-L2**.

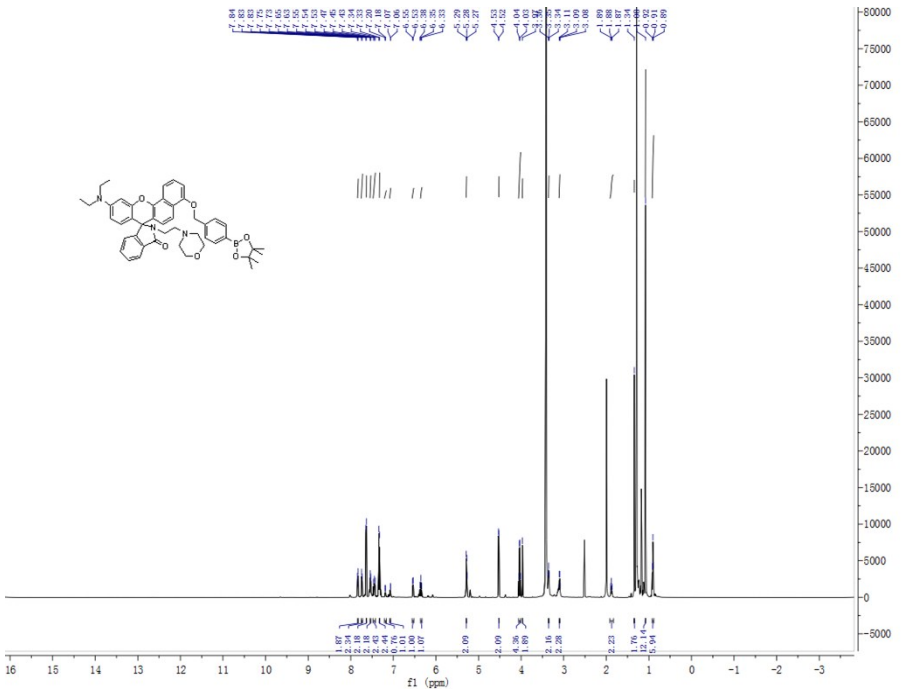

Figure. S25. ^{1}H NMR of compound **Lyso-B-L3**.

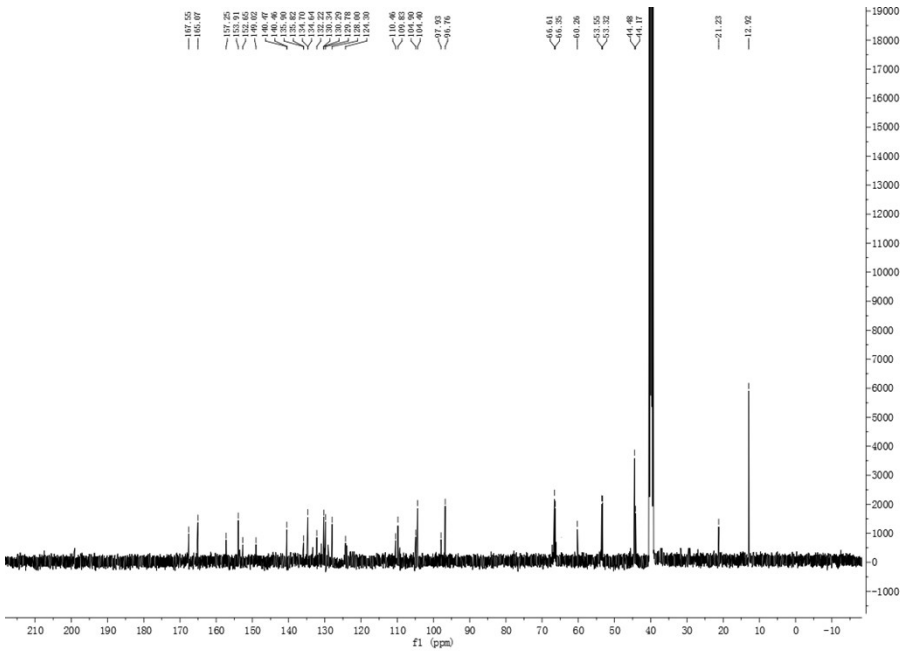

Figure. S26. ^{13}C NMR of compound **Lyso-B-L3**.

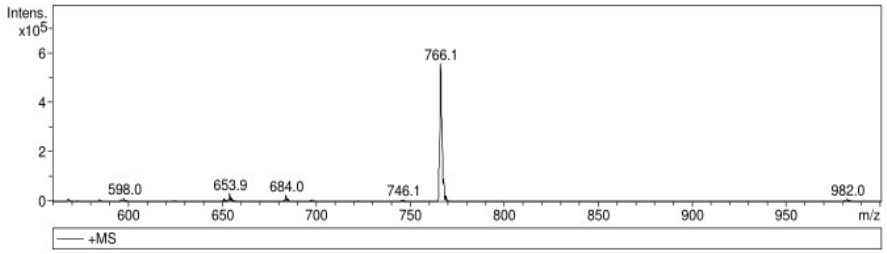

Figure. S27. Mass spectrum of compound **Lyso-B-L3**.

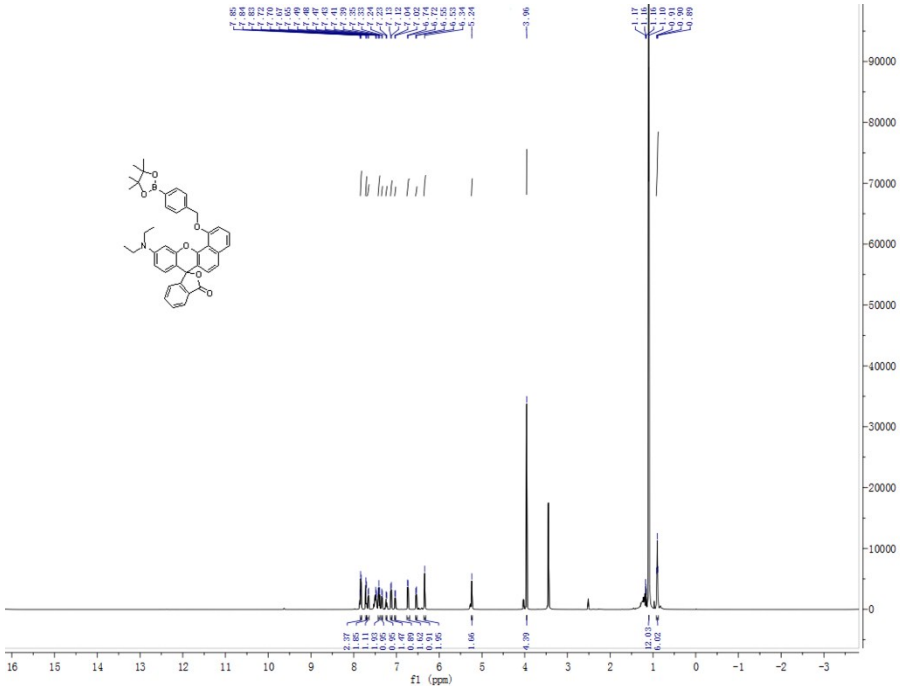

Figure. S28. ^{1}H NMR of compound **L1-B**.

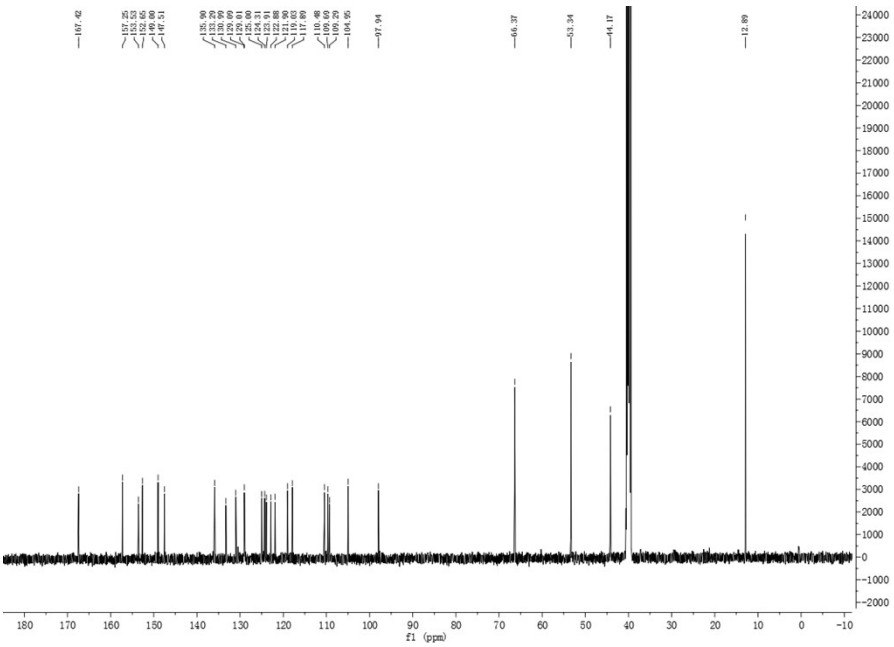

Figure. S29. ^{1}H NMR of compound **L1-B**.

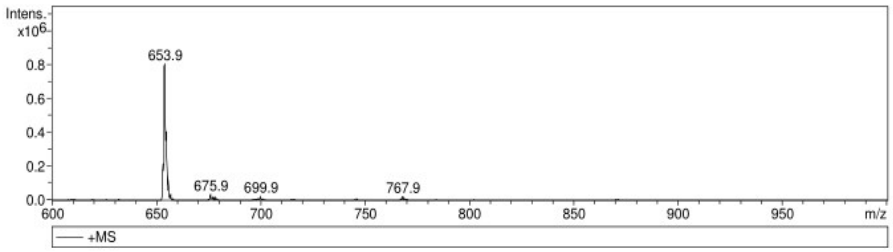

Figure. S30. Mass spectrum of compound **L1-B**.

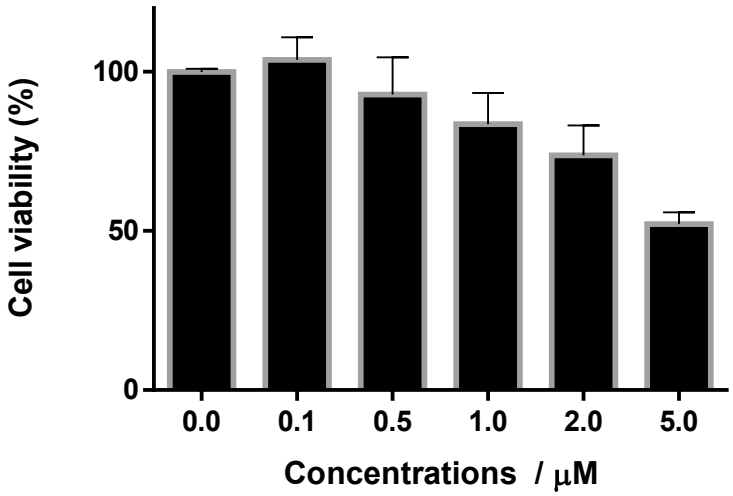

Figure. S31. Viability of HeLa cells after incubating with Lyso-L1-B of different concentrations in serum-free medium for 1 h determined by MTT assays. Data are presented as mean ± s.d. (n = 3). Lyso-L1-B is not toxic to HeLa cells under lower concentrations (0.1–1 uM), but under higher concentrations (e.g., 2 and 5 uM), it is moderately toxic.

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