Supplemental Information

Pd/NHC sequentially catalyzed atroposelective synthesis of planar-chiral macrocycles

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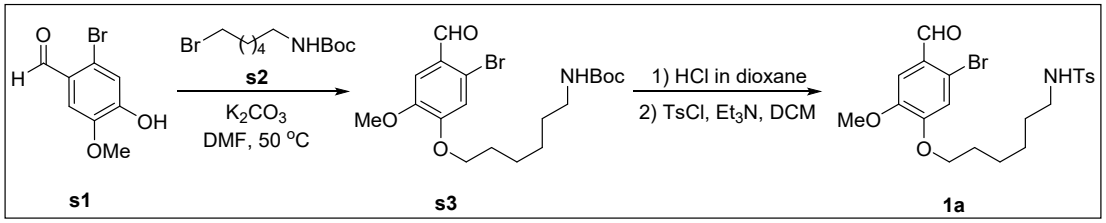
General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF400 (400 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in EI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

General Procedure for the Synthesis of Substrates



Note: All of the aryl aldehydes[1] and *tert*-butyl-bromohexyl-carbamate[2] were synthesized according to the reported methods.

The mixture of 2-bromo-4-hydroxy-5-methoxybenzaldehyde (**s1)** (5 mmol, 1.0 equiv.), tert-butyl (6-bromohexyl) carbamate (**s2**) (6 mmol, 1.0 equiv.), K_2CO_3 (15 mmol, 3 equiv.), DMF (10 mL), were heated 50 °C for 6 h under argon atmosphere.

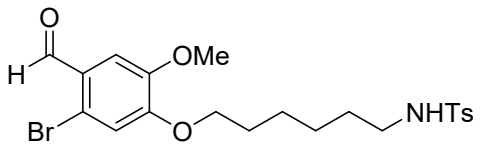
After cooling to room temperature, the reaction was quenched by H_2O, The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2/1) to give **s3** as colorless oil (2.07 g, 96%yield).

To a solution of obtained **s3** (4.8 mmol, 1.0 equiv.) in EtOAc, then the mixture was cooled to 0 °C, and HCl in dioxane (4 equiv. 4.0 M) added slowly. After that, the mixture was allowed warmed to room temperature and stirred for about 3 h (then the white solid was formed). Then the mixture was concentrated in vacuo. Lastly, the obtained crud product was dissolved in CH_2Cl_2/pyridine (v:v = 2/l, 15 mL) at 0 °C, then TsCl (5.76 mmol, 1.2 equiv.) in CH_2Cl_2 (5 mL) was added dropwise. After that, the mixture was warmed to room temperature and stirred for 12 h. Then the reaction was quenched by H_2O, and neutralized with 1 N HCl aqueous solution and extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2/1) to give **1a** as a white solid (3.2 g, 86% yield in total).

***Note*:** All of the vinyl ethylene carbonates (VECs) are known compounds and were synthesized according to the previously reported procedures and all characterization data are in accordance with the literature.[3]

Characterization Data

N-(6-(5-bromo-4-formyl-2-methoxyphenoxy)hexyl)-4-methylbenzenesulfonamide (1a)

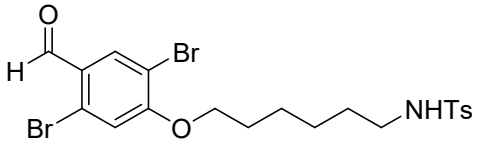


1a

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (3.2 g, 86% yield) as White solid.

R_f (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.19 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.42 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.03 (s, 1H), 4.65 (t, *J* = 6.2 Hz, 1H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.90 (s, 3H), 2.97 (q, *J* = 6.7 Hz, 2H), 2.44 (s, 3H), 1.83 (p, *J* = 6.7 Hz, 2H), 1.51 (q, *J* = 7.3 Hz, 2H), 1.47 – 1.25 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 190.8, 154.1, 149.1, 143.3, 137.0, 129.7, 127.1, 126.3, 120.3, 116.3, 110.7, 69.3, 56.2, 43.1, 29.5, 28.6, 26.2, 25.4, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{21}H_{27}BrNO_5S$: $[M + H]^+$ 484.0788, found: 484.0795.

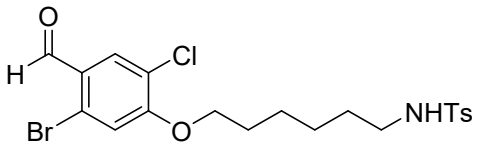
***N*-(6-(2,5-dibromo-4-formylphenoxy)hexyl)-4-methylbenzenesulfonamide (1b)**



1b

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (420 mg, 78% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.16 (s, 1H), 8.12 (s, 1H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.07 (s, 1H), 4.57 (t, *J* = 6.2 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 2H), 2.98 (q, *J* = 6.7 Hz, 2H), 2.45 (s, 3H), 1.89 – 1.78 (m, 2H), 1.56 – 1.46 (m, 4H), 1.44 – 1.36 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 189.4, 160.1, 143.4, 137.0, 134.1, 129.7, 127.4, 127.3, 127.1, 116.9, 112.3, 69.8, 43.1, 29.5, 28.5, 26.1, 25.4, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{20}H_{24}Br_2NO_4S$: $[M + H]^+$ 533.9767, found: 533.9776.

***N*-(6-(5-bromo-2-chloro-4-formylphenoxy)hexyl)-4-methylbenzenesulfonamide (1c)**

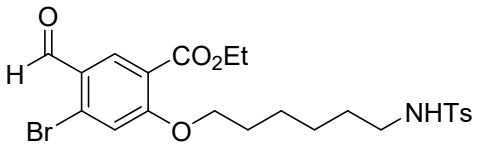


1c

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (385 mg, 79% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.17

(s, 1H), 7.95 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.11 (s, 1H), 4.44 (t, *J* = 6.2 Hz, 1H), 4.09 (t, *J* = 6.3 Hz, 2H), 2.98 (q, *J* = 6.7 Hz, 2H), 2.45 (s, 3H), 1.90 – 1.78 (m, 2H), 1.58 – 1.47 (m, 4H), 1.44 – 1.36 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 189.6, 159.2, 143.4, 137.0, 130.9, 129.7, 127.1, 127.0, 126.5, 123.5, 117.1, 69.7, 43.1, 29.5, 28.5, 26.1, 25.4, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{20}H_{24}BrClNO_4S$: $[M + H]^+$ 488.0293, found: 488.0301.

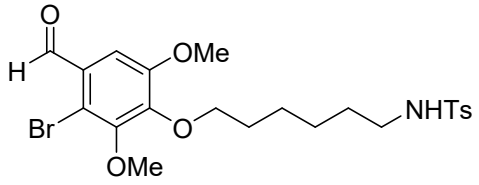
Ethyl 4-bromo-5-formyl-2-((6-((4-methylphenyl)sulfonamido)hexyl)oxy)benzoate (1d)



1d

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (426 mg, 81% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.21 (s, 1H), 8.35 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.17 (s, 1H), 4.81 (t, *J* = 6.2 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 2.96 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 1.88 – 1.78 (m, 2H), 1.55 – 1.44 (m, 4H), 1.41 – 1.34 (m, 5H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 189.7, 164.5, 162.6, 143.3, 137.2, 133.4, 132.0, 129.7, 127.1, 126.2, 120.7, 117.5, 69.6, 61.4, 43.0, 29.4, 28.5, 26.0, 25.4, 21.49, 14.3; **HRMS** (ESI): *m/z*: calculated for $C_{23}H_{29}BrNO_6S$: $[M + H]^+$ 526.0894, found: 526.0900.

***N*-(6-(3-bromo-4-formyl-2,6-dimethoxyphenoxy)hexyl)-4-methylbenzenesulfonamide (1e)**

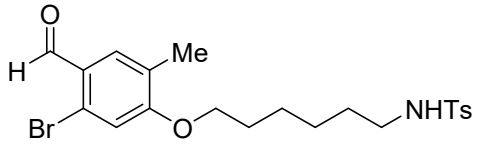


1e

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (387 mg, 75% yield) as White

solid. **R_f** (pentane:EtOAc = 2:1) = 0.20; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.32 (s, 1H), 7.79 – 7.74 (m, 2H), 7.33 (t, *J* = 4.0 Hz, 3H), 4.39 (q, *J* = 9.3, 6.3 Hz, 1H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.91 (s, 6H), 2.97 (p, *J* = 6.3 Hz, 2H), 2.45 (s, 3H), 1.81 – 1.69 (m, 2H), 1.56 – 1.44 (m, 4H), 1.42 – 1.34 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 191.1, 153.3, 148.1, 143.4, 137.0, 129.7, 128.8, 127.1, 115.6, 107.6, 73.9, 61.2, 56.2, 43.1, 29.9, 29.6, 26.2, 25.3, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{22}H_{29}BrNO_6S$: $[M + H]^+$ 514.0894, found: 514.0901.

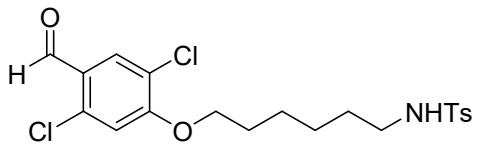
***N*-(6-(5-bromo-4-formyl-2-methylphenoxy)hexyl)-4-methylbenzenesulfonamide (1f)**



1f

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (400 mg, 85% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.68 (d, J = 1.7 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.47 (t, J = 5.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 4.09 (t, J = 6.4 Hz, 2H), 2.71 (q, J = 6.6 Hz, 2H), 2.38 (s, 3H), 2.18 – 2.08 (m, 3H), 1.75 – 1.62 (m, 2H), 1.41 – 1.23 (m, 6H). **^{13}C NMR** (100 MHz, DMSO-d6) δ 190.6, 142.9, 138.2, 131.5, 130.0, 127.04, 126.95, 126.1, 116.2, 69.1, 42.9, 29.3, 28.7, 26.1, 25.3, 21.4, 15.9; **HRMS** (ESI): *m/z*: calculated for $C_{21}H_{27}BrNO_4S$: $[M + H]^+$ 468.0839, found: 468.0844.

***N*-(6-(2,5-dichloro-4-formylphenoxy)hexyl)-4-methylbenzenesulfonamide (1g)**

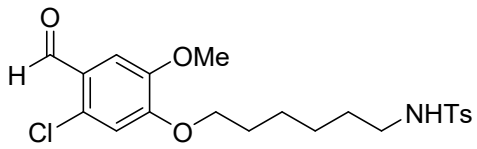


1g

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (343 mg, 77% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.29

(s, 1H), 7.95 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 1H), 4.53 (t, *J* = 6.3 Hz, 1H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.98 (q, *J* = 6.7 Hz, 2H), 2.45 (s, 3H), 1.90 – 1.80 (m, 2H), 1.58 – 1.45 (m, 4H), 1.45 – 1.35 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 187.5, 159.2, 143.4, 137.8, 137.0, 130.5, 129.7, 127.1, 125.9, 122.8, 113.9, 69.7, 43.0, 29.5, 28.5, 26.1, 25.4, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{20}H_{24}Cl_2NO_4S$: $[M + H]^+$ 444.0798, found: 444.0805.

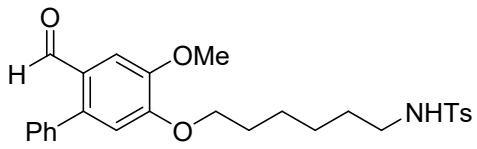
***N*-(6-(5-chloro-4-formyl-2-methoxyphenoxy)hexyl)-4-methylbenzenesulfonamide (1h)**



1h

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (352 mg, 80% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.33 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.40 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 1H), 4.51 (t, *J* = 6.3 Hz, 1H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.91 (s, 3H), 2.97 (q, *J* = 6.7 Hz, 2H), 2.44 (s, 3H), 1.90 – 1.80 (m, 2H), 1.55 – 1.36 (m, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 188.7, 154.1, 148.6, 143.4, 137.1, 131.9, 129.7, 127.1, 125.3, 113.2, 110.0, 69.3, 56.2, 43.1, 29.5, 28.6, 26.2, 25.4, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{21}H_{27}ClNO_5S$: $[M + H]^+$ 440.1293, found: 440.1299.

***N*-(6-((6-formyl-4-methoxy-[1,1'-biphenyl]-3-yl)oxy)hexyl)-4-methylbenzenesulfonamide (1i)**

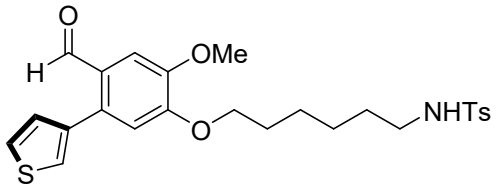


1i

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (405 mg, 84% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.83 (s,

1H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.55 (s, 1H), 7.51 – 7.43 (m, 3H), 7.42 – 7.36 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.84 (s, 1H), 4.60 (t, *J* = 6.2 Hz, 1H), 4.08 (t, *J* = 6.6 Hz, 2H), 3.97 (s, 3H), 2.96 (q, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.90 – 1.79 (m, 2H), 1.57 – 1.42 (m, 4H), 1.41 – 1.33 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 191.2, 153.0, 149.0, 143.3, 141.4, 137.7, 137.0, 130.2, 129.7, 128.3, 128.0, 127.1, 126.7, 113.6, 108.9, 68.9, 56.1, 43.1, 29.5, 28.7, 26.2, 25.5, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{27}H_{32}NO_5S$: $[M + H]^+$ 482.1996, found: 482.2000.

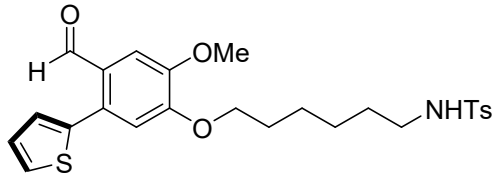
***N*-(6-(4-formyl-2-methoxy-5-(thiophen-3-yl)phenoxy)hexyl)-4-methylbenzenesulfonamide (1j)**



1j

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (395 mg, 81% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.95 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.52 (s, 1H), 7.45 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.19 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.86 (s, 1H), 4.54 (t, *J* = 6.2 Hz, 1H), 4.08 (t, *J* = 6.6 Hz, 2H), 3.96 (s, 3H), 2.96 (q, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.90 – 1.79 (m, 2H), 1.54 – 1.35 (m, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 191.0, 153.1, 149.0, 143.3, 138.1, 137.1, 135.9, 129.7, 129.5, 127.2, 127.1, 126.0, 124.7, 113.4, 108.9, 68.9, 56.1, 43.1, 29.5, 28.7, 26.2, 25.5, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{25}H_{30}NO_5S_2$: $[M + H]^+$ 488.1560, found: 488.1569.

***N*-(6-(4-formyl-2-methoxy-5-(thiophen-2-yl)phenoxy)hexyl)-4-methylbenzenesulfonamide (1k)**

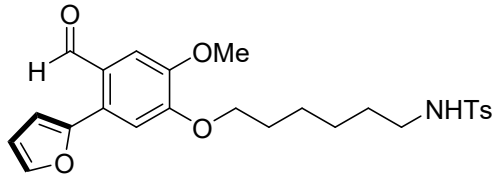


1k

Following the general procedure, the crude product was purified by column

chromatography on a silica gel to afford the product (389 mg, 80% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.04 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.52 (s, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 7.07 (s, 1H), 6.92 (s, 1H), 4.62 (t, *J* = 6.2 Hz, 1H), 4.08 (t, *J* = 6.6 Hz, 2H), 3.96 (s, 3H), 2.96 (q, *J* = 6.8 Hz, 2H), 2.43 (s, 3H), 1.90 – 1.79 (m, 2H), 1.56 – 1.33 (m, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 190.8, 152.9, 149.4, 143.4, 138.7, 137.0, 133.2, 129.7, 129.3, 127.6, 127.5, 127.1, 126.9, 114.1, 109.0, 67.0, 56.2, 43.1, 29.5, 28.7, 26.2, 25.5, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{25}H_{30}NO_5S_2$: $[M + H]^+$ 488.1560, found: 488.1567.

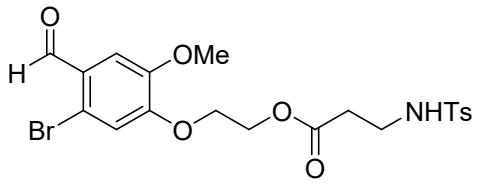
***N*-(6-(4-formyl-5-(furan-2-yl)-2-methoxyphenoxy)hexyl)-4-methylbenzenesulfonamide (1l)**



1l

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (365 mg, 77% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.24 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.60 (s, 1H), 7.51 (s, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.07 (s, 1H), 6.55 (d, *J* = 4.5 Hz, 2H), 4.53 (t, *J* = 6.2 Hz, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.95 (s, 3H), 2.97 (q, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.91 – 1.81 (m, 2H), 1.55 – 1.36 (m, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 190.8, 153.1, 150.5, 149.3, 143.5, 143.4, 137.0, 129.7, 128.9, 127.1, 126.6, 111.8, 111.3, 111.1, 109.1, 67.0, 56.1, 43.1, 29.5, 28.7, 26.2, 25.5, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{25}H_{30}NO_6S$: $[M + H]^+$ 472.1789, found: 472.1794.

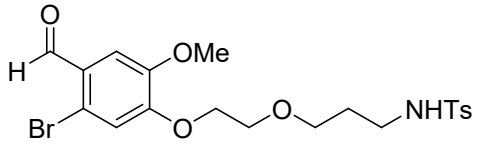
2-(5-bromo-4-formyl-2-methoxyphenoxy)ethyl3-((4-methylphenyl)sulfonamido)propanoate (1m)



1m

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (340 mg, 68% yield) as White solid. $\mathbf{R_f}$ (pentane:EtOAc = 1:1) = 0.30; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.72 – 7.63 (m, 3H), 7.43 – 7.33 (m, 4H), 4.34 (s, 4H), 3.82 (s, 3H), 3.01 – 2.92 (m, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.38 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 190.7, 171.1, 149.1, 143.2, 137.7, 130.1, 127.0, 126.5, 119.6, 117.4, 111.4, 67.7, 62.8, 56.2, 38.8, 34.4, 21.4; **HRMS** (ESI): *m/z*: calculated for $C_{20}H_{23}BrNO_7S$: $[M + H]^+$ 500.0374, found: 500.0381.

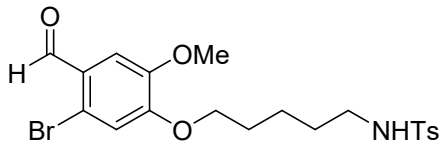
***N*-(3-(2-(5-bromo-4-formyl-2-methoxyphenoxy)ethoxy)propyl)-4-methylbenzenesulfonamide (1n)**



1n

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (317 mg, 65% yield) as White solid. $\mathbf{R_f}$ (pentane:EtOAc = 1:1) = 0.30; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.49 (t, J = 5.9 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.34 (s, 2H), 4.25 – 4.18 (m, 2H), 3.81 (s, 3H), 3.70 – 3.63 (m, 2H), 3.43 (t, J = 6.2 Hz, 2H), 2.77 (q, J = 6.8 Hz, 2H), 2.38 (s, 3H), 1.61 (q, J = 6.6 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 190.7, 154.3, 149.1, 143.0, 138.1, 130.0, 127.0, 126.3, 119.6, 117.3, 111.3, 69.1, 68.7, 68.0, 56.2, 29.8, 21.4; **HRMS** (ESI): *m/z*: calculated for $C_{20}H_{25}BrNO_6S$: $[M + H]^+$ 486.0581, found: 486.0590.

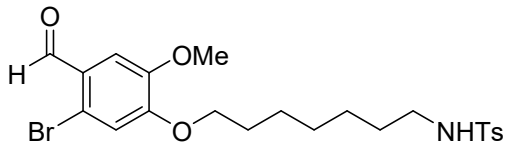
***N*-(5-(5-bromo-4-formyl-2-methoxyphenoxy)pentyl)-4-methylbenzenesulfonamide (1o)**



1o

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (373 mg, 79% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.30; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.72 – 7.64 (m, 2H), 7.51 (t, *J* = 5.9 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 13.0 Hz, 2H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.82 (s, 3H), 2.72 (q, *J* = 6.4 Hz, 2H), 2.37 (s, 3H), 1.67 (p, *J* = 6.8 Hz, 2H), 1.47 – 1.34 (m, 4H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 190.7, 154.4, 149.1, 142.9, 138.2, 130.0, 127.0, 126.1, 119.8, 117.0, 111.1, 69.4, 56.2, 42.8, 29.0, 28.3, 23.0, 21.4; **HRMS** (ESI): *m/z*: calculated for $C_{20}H_{25}BrNO_5S$: $[M + H]^+$ 470.0632, found: 470.0638.

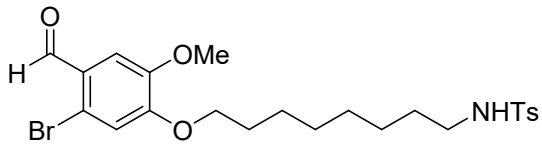
***N*-(7-(5-bromo-4-formyl-2-methoxyphenoxy)heptyl)-4-methylbenzenesulfonamide (1p)**



1p

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (420 mg, 84% yield) as White solid. **R_f** (pentane:EtOAc = 2:1) = 0.30; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.70 – 7.65 (m, 2H), 7.48 (t, J = 5.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 4.08 (t, J = 6.5 Hz, 2H), 3.82 (s, 3H), 2.69 (dq, J = 12.1, 6.8 Hz, 2H), 2.38 (s, 3H), 1.70 (p, J = 6.8 Hz, 2H), 1.33 (p, J = 7.2 Hz, 4H), 1.27 – 1.19 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.6, 154.5, 149.1, 142.9, 138.3, 130.0, 126.9, 126.1, 119.8, 117.0, 111.2, 69.5, 56.2, 42.9, 29.3, 28.7, 28.6, 26.4, 25.7, 21.4; **HRMS** (ESI): *m/z*: calculated for $C_{22}H_{29}BrNO_5S$: $[M + H]^+$ 498.0945, found: 498.0952.

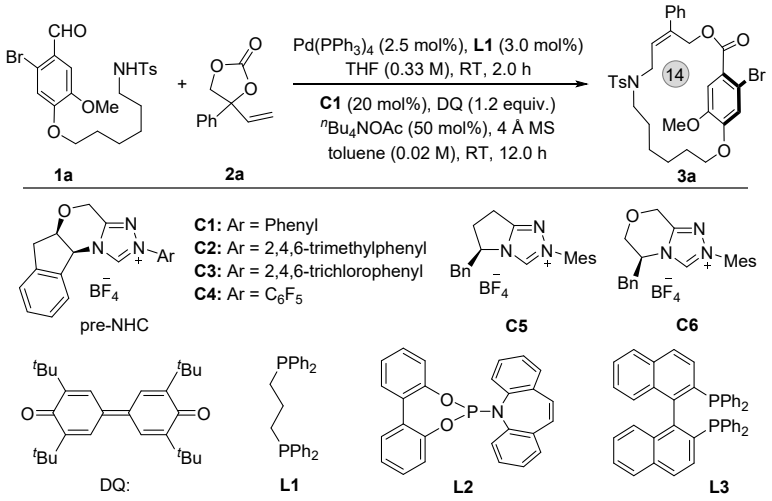
***N*-(8-(5-bromo-4-formyl-2-methoxyphenoxy)octyl)-4-methylbenzenesulfonamide (1q)**



1q

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product (437 mg, 85% yield) as White solid. $\mathbf{R_f}$ (pentane:EtOAc = 2:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.20 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.43 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.05 (s, 1H), 4.30 (d, *J* = 6.1 Hz, 1H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.92 (s, 3H), 2.96 (q, *J* = 6.7 Hz, 2H), 2.45 (s, 3H), 1.92 – 1.82 (m, 2H), 1.51 – 1.42 (m, 4H), 1.35 – 1.27 (m, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 190.8, 154.2, 149.1, 143.3, 137.1, 129.7, 127.1, 126.3, 120.3, 116.3, 110.7, 69.5, 56.2, 43.2, 29.6, 29.1, 28.9, 28.7, 26.4, 25.7, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{23}H_{31}BrNO_5S$: $[M + H]^+$ 512.1101, found: 512.1120.

Reaction Condition Optimization

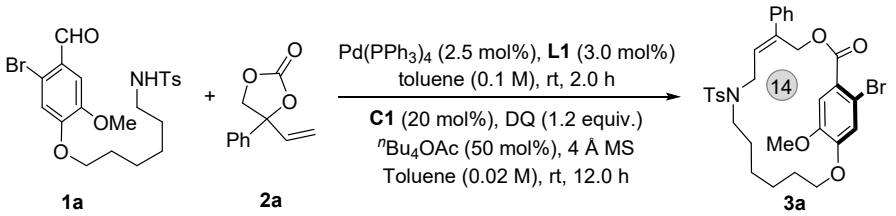


Entry[a]	Variation of standard conditions	Yield (%)[b]	ee (%)[c]
1	none	72	96
2	**C2** instead of **C1**	65	30
3	**C3** or **C4** instead of **C1**	< 5	-
4	**C5** instead of **C1**	30	-16
5	**C6** instead of **C1**	46	-22

6	**L2** instead of **L1**	60	96
7	**L3** instead of **L1**	65	96
8	without of **L1**	68	96
9	K_2CO_3 instead of $^nBu_4NOAc$	28	94
10	KOAc instead of $^nBu_4NOAc$	35	96
11	Et_3N instead of $^nBu_4NOAc$	30	92
12	THF instead of toluene	52	90
13	CH_2Cl_2 instead of toluene	68	93
14	without 4 Å MS	67	96
15	toluene (0.1 M) was used	62	96

[a] Conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $Pd(PPh_3)_4$ (2.5 mol%) and **L1** (3.0 mol%) in 0.3 mL of THF were allowed to stir at room temperature for 2 h. The solution was then transferred into a mixture of pre-NHC catalyst **C1** (20 mol%), $^nBu_4NOAc$ (50 mol%), DQ (0.12 mmol) and 4Å MS 50 mg in toluene (5.0 mL). The reaction mixture was allowed to stir at room temperature for another 12 h under Ar. [b] Isolated yield after flash column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase.

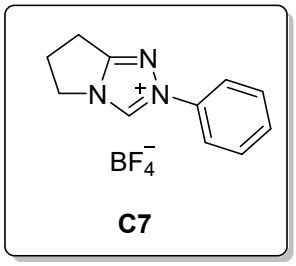
General Procedure for Atroposelective Intermolecular Macrocyclization



To a flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added the catalyst $Pd(PPh_3)_4$ (2.9 mg, 0.025 mmol), **L1** (1.3 mg, 0.03 mmol), toluene (1.0 mL) was added. The mixture was then stirred at room temperature for 0.5 h. After that, **1a** (48.4 mg, 0.1 mmol) and **2a** (28.5 mg, 0.15 mmol) were added sequentially under Ar. The reaction mixture was then stirred at room temperature for 2 h. Then the solution was transferred into a mixture of pre-NHC catalyst **C1** (20 mol%), $^nBu_4NOAc$ (50 mol%), DQ (0.12 mmol) and 4Å MS 50 mg in toluene (4.0 mL) and stirred at room temperature for another 12 h (monitored by TLC). After the reaction was completed, the reaction mixture was filtered and concentrated. The residue was purified by a silica gel flash chromatography (Hexane/EtOAc = 5:1) to

afford the desired product **3a** in 72% yield with 96% ee.

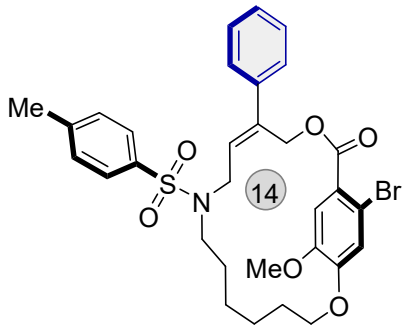
Note: Racemic samples for the standard of chiral HPLC spectra were prepared using **C7** as catalyst.



C7

Characterization Data of Planar Chiral Products

(R_p,*Z*)-1^5-bromo-1^2-methoxy-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3a)

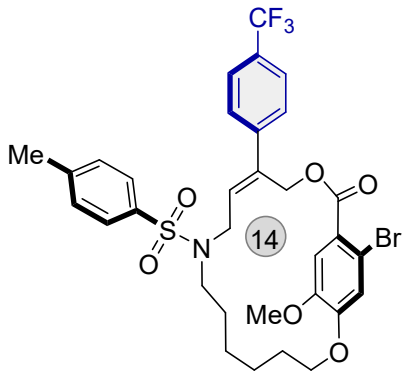


3a

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3a** (45.2 mg, 72% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.28 (m, 8H), 7.25 (s, 1H), 5.68 (t, *J* = 5.9 Hz, 1H), 5.20 (d, *J* = 13.2 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 4.45 – 4.28 (m, 2H), 4.03 (qd, *J* = 17.6, 5.9 Hz, 2H), 3.89 (s, 3H), 3.05 (ddd, *J* = 14.6, 10.3, 4.9 Hz, 1H), 2.87 (ddd, *J* = 14.5, 10.8, 4.3 Hz, 1H), 2.46 (s, 3H), 1.83 – 1.68 (m, 1H), 1.68 – 1.49 (m, 1H), 1.26 – 1.13 (m, 1H), 1.12 – 0.98 (m, 1H), 0.96 – 0.67 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.9, 151.8, 150.4, 143.2, 140.4, 137.9, 136.6, 131.3, 129.7, 128.5, 127.8, 127.2, 126.3, 126.3, 124.8, 114.3, 111.9, 70.6, 63.5, 56.3, 48.3, 46.2, 29.4, 29.1,

25.2, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{21}H_{35}BrNO_6S$: $[M + H]^+$ 628.1363, found: 628.1369; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 26.2 min, t_R (minor) = 20.3 min, 96% ee; $[\alpha]^{25}_D$ = - 63.8 (*c* = 0.2, $CHCl_3$).

(R_p,*Z*)-1^5-bromo-1^2-methoxy-9-tosyl-12-(4-(trifluoromethyl)phenyl)-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3b)

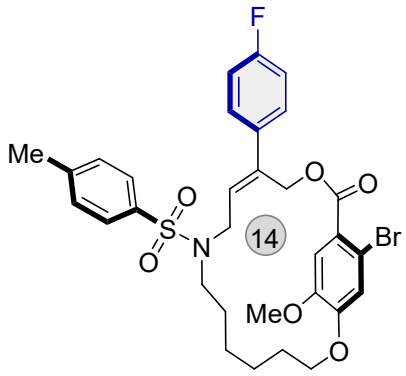


3b

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3b** (49.3 mg, 71% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.28; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.30 (m, 3H), 7.26 (s, 1H), 5.81 (t, *J* = 5.8 Hz, 1H), 5.20 (d, *J* = 13.3 Hz, 1H), 5.10 (d, *J* = 13.3 Hz, 1H), 4.42 – 4.33 (m, 2H), 4.12 – 3.93 (m, 2H), 3.89 (s, 3H), 3.07 (ddd, *J* = 15.1, 10.7, 5.4 Hz, 1H), 2.85 (ddd, *J* = 14.5, 11.4, 3.9 Hz, 1H), 2.46 (s, 3H), 1.84 – 1.72 (m, 1H), 1.58 (q, *J* = 6.0, 5.2 Hz, 1H), 1.27 – 1.15 (m, 1H), 1.10 – 0.98 (m, 1H), 0.94 – 0.74 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 151.9, 150.4, 143.9, 143.4, 137.6, 135.6, 133. 8, 129.8, 127.2, 126.7, 125.8, 125.5 (q, *J* = 3.8 Hz), 124.7, 114.4, 112.0, 70.5, 63.1, 56.3, 48.6, 46.2, 29.3, 29.0, 25.1, 25.0, 21.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.57; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{34}BrF_3NO_6S$: $[M + H]^+$ 696.1237, found: 696.1244; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 21.8 min, t_R (minor) = 15.9 min, 98% ee; $[\alpha]^{25}_D$ = - 72.5 (*c* = 0.2, $CHCl_3$).

(R_p,*Z*)-1^5-bromo-1^2-(4-fluorophenyl)-12-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-

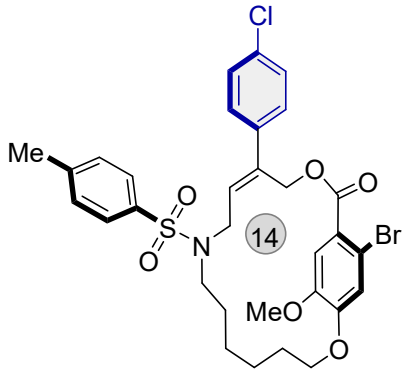
benzenacyclopentadecaphan-11-en-15-one (3c)



3c

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3c** (45.3 mg, 70% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.30 (m, 5H), 7.26 (s, 1H), 7.03 (t, *J* = 8.7 Hz, 2H), 5.65 (t, *J* = 5.8 Hz, 1H), 5.17 (d, *J* = 13.3 Hz, 1H), 5.06 (d, *J* = 13.3 Hz, 1H), 4.42 – 4.34 (m, 2H), 4.13 – 3.90 (m, 2H), 3.89 (s, 3H), 3.13 – 2.96 (m, 1H), 2.86 (ddd, *J* = 14.5, 11.0, 4.1 Hz, 1H), 2.46 (s, 3H), 1.86 – 1.70 (m, 1H), 1.66 – 1.50 (m, 1H), 1.30 – 1.17 (m, 1H), 1.15 – 0.99 (m, 1H), 0.96 – 0.74 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 162.5 (d, *J* = 247.3 Hz), 151.8, 150.37, 143.3, 137.8, 136.5 (d, *J* = 3.3 Hz), 135.7, 131.3, 129.7, 128.2, 128.1, 127.2, 126.0, 124.8, 115.5, 115.3, 114.4, 112.0, 70.6, 63.5, 56.3, 48.4, 46.2, 29.3, 29.0, 25.1, 25.0, 21.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -114.33; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{34}BrFNO_6S$: $[M + H]^+$ 646.1269, found: 646.1274; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 21.8 min, t_R (minor) = 16.9 min, 99% ee; $[\alpha]^{25}_D$ = - 61.8 (*c* = 0.2, $CHCl_3$).

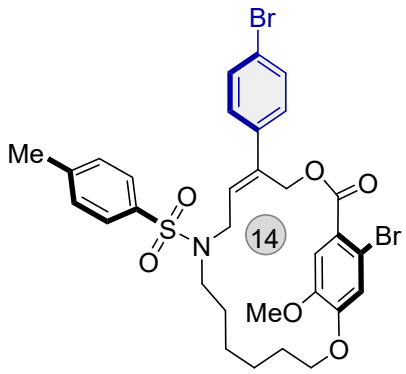
(*R*$_p$,*Z*)-1^5-bromo-1^2-(4-chlorophenyl)-12-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3d)



3d

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3d** (47.6 mg, 72% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 7H), 7.25 (s, 1H), 5.70 (t, *J* = 5.8 Hz, 1H), 5.16 (d, *J* = 13.2 Hz, 1H), 5.06 (d, *J* = 13.2 Hz, 1H), 4.37 (q, *J* = 4.3, 3.2 Hz, 2H), 4.09 – 3.91 (m, 2H), 3.89 (s, 3H), 3.05 (ddd, *J* = 14.6, 10.6, 5.4 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.46 (s, 3H), 1.77 (dt, *J* = 13.7, 6.2 Hz, 1H), 1.59 (d, *J* = 8.5 Hz, 1H), 1.23 (t, *J* = 13.8 Hz, 1H), 1.10 – 0.98 (m, 1H), 0.95 – 0.70 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 151.8, 150.4, 143.3, 138.8, 137.7, 135.6, 133.8, 132.0, 129.7, 128.7, 127.7, 127.2, 126.0, 124.7, 114.4, 112.0, 70.6, 63.3, 56.3, 48.4, 46.2, 29.3, 29.0, 25.1, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{34}BrClNO_6S$: $[M + H]^+$ 662.0974, found: 626.0982; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 25.5 min, t_R (minor) = 18.8 min, 98% ee; $[\alpha]^{25}_D$ = - 43.1 (*c* = 0.1, $CHCl_3$).

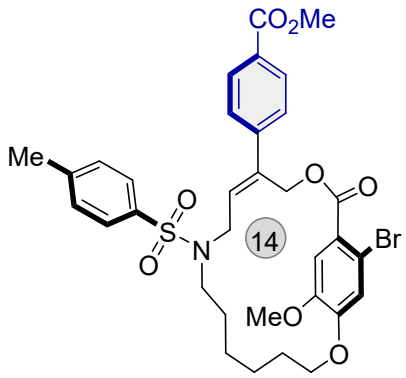
(*R*$_p$,*Z*)-1^5-bromo-1^2-(4-bromophenyl)-12-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3e)



3e

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3e** (51.8 mg, 73% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.30 (s, 1H), 7.27 (s, 1H), 7.25 (s, 2H), 5.70 (t, *J* = 5.8 Hz, 1H), 5.16 (d, *J* = 13.3 Hz, 1H), 5.05 (d, *J* = 13.2 Hz, 1H), 4.42 – 4.32 (m, 2H), 4.09 – 3.90 (m, 2H), 3.89 (s, 3H), 3.10 – 2.98 (m, 1H), 2.84 (ddd, *J* = 14.5, 11.0, 4.0 Hz, 1H), 2.46 (s, 3H), 1.84 – 1.71 (m, 1H), 1.61 – 1.51 (m, 1H), 1.27 – 1.15 (m, 1H), 1.07 – 0.98 (m, 1H), 0.92 – 0.72 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 151.9, 150.4, 143.3, 139.3, 137.7, 135.7, 132.1, 131.6, 129.7, 128.0, 127.2, 125.9, 124.7, 121.9, 114.4, 112.0, 70.6, 63.2, 56.3, 48.5, 46.2, 29.3, 29.0, 25.1, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{34}Br_2NO_6S$: $[M + H]^+$ 708.0448, found: 708.0455; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 30.5 min, t_R (minor) = 22.1 min, 98% ee; $[\alpha]^{25}_D$ = - 70.6 (*c* = 0.2, $CHCl_3$).

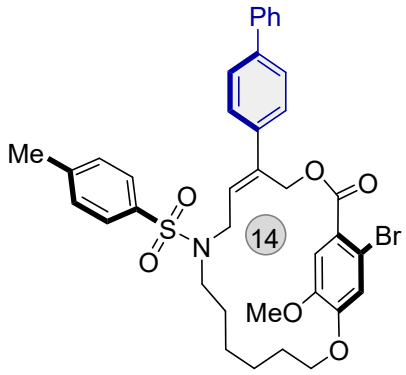
(*R*$_p$,*Z*)methyl-4-(1^5-bromo-1^2-methoxy-15-oxo-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-12-yl)benzoate (3f)



3f

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3f** (48.2 mg, 70% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.26 (s, 1H), 5.81 (t, *J* = 5.8 Hz, 1H), 5.20 (d, *J* = 13.2 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 4.37 (t, *J* = 5.0 Hz, 2H), 4.12 – 3.98 (m, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.07 (ddd, *J* = 14.6, 5.8 Hz, 1H), 2.86 (ddd, *J* = 14.6, 11.1, 3.9 Hz, 1H), 2.46 (s, 3H), 1.83 – 1.71 (m, 1H), 1.64 – 1.53 (m, 1H), 1.25 – 1.17 (m, 1H), 1.10 – 0.98 (m, 1H), 0.94 – 0.72 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.7, 165.8, 151.9, 150.4, 144.7, 143.4, 137.7, 135.9, 133.5, 129.9, 129.8, 129.4, 127.2, 126.3, 125.9, 124.7, 114.4, 112.0, 70.6, 63.1, 56.3, 52.2, 48.5, 46.2, 29.3, 29.1, 25.1, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{33}H_{37}BrNO_8S$: $[M + H]^+$ 686.1418, found: 686.1412; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 46.5 min, t_R (minor) = 35.0 min, 98% ee; $[\alpha]^{25}_D$ = - 57.3 (*c* = 0.2, $CHCl_3$).

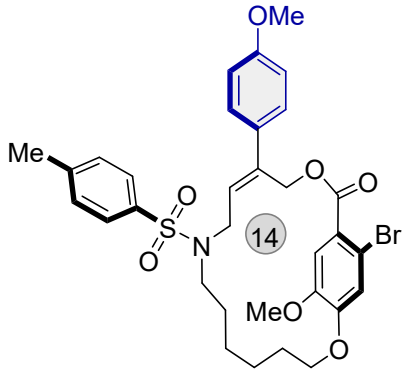
(*R*$_p$,*Z*)-12-([1,1'-biphenyl]-4-yl)-15-bromo-12-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3g)



3g

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3g** (48.7 mg, 69% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.61 (ddd, *J* = 11.0, 7.7, 1.7 Hz, 4H), 7.52 – 7.43 (m, 4H), 7.43 – 7.29 (m, 4H), 7.27 (s, 1H), 5.76 (t, *J* = 5.9 Hz, 1H), 5.24 (d, *J* = 13.2 Hz, 1H), 5.14 (d, *J* = 13.2 Hz, 1H), 4.37 (q, *J* = 4.6, 3.9 Hz, 2H), 4.06 (qd, *J* = 17.6, 5.9 Hz, 2H), 3.90 (s, 3H), 3.07 (ddd, *J* = 14.5, 11.0, 4.8 Hz, 1H), 2.88 (ddd, *J* = 14.5, 10.9, 4.3 Hz, 1H), 2.47 (s, 3H), 1.91 – 1.70 (m, 1H), 1.59 (s, 1H), 1.34 – 1.16 (m, 1H), 1.13 – 1.01 (m, 1H), 0.97 – 0.74 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.9, 151.8, 150.4, 143.3, 140.7, 140.5, 139.2, 137.9, 136.2, 131.3, 129.7, 128.8, 127.5, 127.23, 127.19, 127.0, 126.7, 126.3, 124.9, 114.4, 111.9, 70.64, 63.4, 56.3, 48.3, 46.2, 29.4, 29.2, 25.2, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{37}H_{39}BrNO_6S$: $[M + H]^+$ 704.1676, found: 704.1681; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 38.5 min, t_R (minor) = 28.1 min, 98% ee; $[\alpha]^{25}_D$ = - 70.5 (*c* = 0.2, $CHCl_3$).

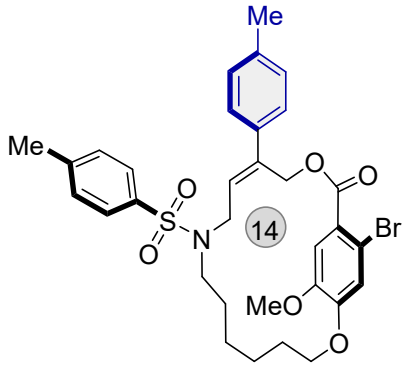
(R_p,*Z*)-1^5-bromo-1^2-methoxy-12-(4-methoxyphenyl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3h)



3h

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3h** (45.2 mg, 68% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.29 (m, 5H), 7.24 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.58 (t, *J* = 5.9 Hz, 1H), 5.23 – 4.98 (m, 2H), 4.36 (q, *J* = 4.6, 4.1 Hz, 2H), 4.12 – 3.92 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.04 (ddd, *J* = 14.8, 10.6, 4.9 Hz, 1H), 2.86 (ddd, *J* = 14.6, 10.9, 4.5 Hz, 1H), 2.46 (s, 3H), 1.82 – 1.66 (m, 1H), 1.59 (ddd, *J* = 14.5, 7.5, 3.6 Hz, 1H), 1.27 – 1.15 (m, 1H), 1.12 – 0.98 (m, 1H), 0.96 – 0.71 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.0, 159.4, 151.7, 150.4, 143.2, 137.9, 136.1, 132.8, 129.7, 129.5, 127.6, 127.2, 126.4, 124.8, 114.3, 113.9, 111.9, 70.7, 63.5, 56.3, 55.3, 48.2, 46.2, 29.4, 29.2, 25.2, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_7S$: $[M + H]^+$ 658.1469, found: 658.1477; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 33.7 min, t_R (minor) = 26.6 min, 97% ee; $[\alpha]^{25}_D$ = - 33.9 (*c* = 0.1, $CHCl_3$).

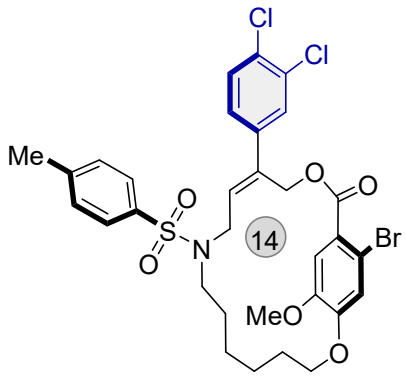
(*R*$_p$,*Z*)-1^5-bromo-1^2-methoxy-12-(p-tolyl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3i)



3i

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3i** (44.1 mg, 69% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.28 (s, 1H), 7.25 (d, *J* = 5.7 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.63 (t, *J* = 6.0 Hz, 1H), 5.18 (d, *J* = 13.1 Hz, 1H), 5.08 (d, *J* = 13.1 Hz, 1H), 4.36 (dt, *J* = 7.9, 4.1 Hz, 2H), 4.11 – 3.93 (m, 2H), 3.89 (s, 3H), 3.04 (ddd, *J* = 14.7, 10.5, 4.9 Hz, 1H), 2.86 (ddd, *J* = 14.5, 10.8, 4.4 Hz, 1H), 2.46 (s, 3H), 2.37 (s, 3H), 1.84 – 1.69 (m, 1H), 1.59 (q, *J* = 6.6 Hz, 1H), 1.27 – 1.15 (m, 1H), 1.12 – 0.98 (m, 1H), 0.94 – 0.73 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.0, 151.7, 150.4, 143.2, 137.9, 137.7, 137.5, 136.4, 130.4, 129.7, 129.2, 127.2, 126.4, 126.2, 124.9, 114.3, 111.9, 70.7, 63.5, 56.3, 48.2, 46.1, 29.41, 29.2, 25.2, 25.0, 21.5, 21.1; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_6S$: $[M + H]^+$ 642.1520, found: 642.1514; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 22.9 min, t_R (minor) = 18.2 min, 97% ee; $[\alpha]^{25}_D$ = - 58.7 (*c* = 0.2, $CHCl_3$).

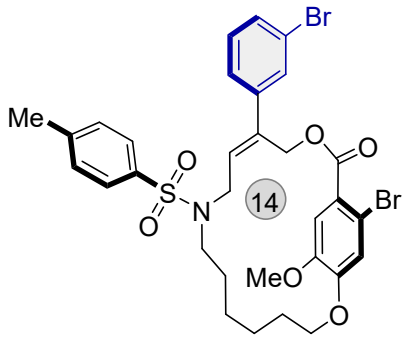
(*R*$_p$,*Z*)-15-bromo-12-(3,4-dichlorophenyl)-12-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3j)



3j

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3j** (50.3 mg, 72% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.22 (s, 1H), 7.20 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.15 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.75 (t, *J* = 6.1 Hz, 1H), 5.22 (d, *J* = 13.2 Hz, 1H), 5.11 (d, *J* = 13.2 Hz, 1H), 4.46 – 4.32 (m, 2H), 4.05 (dd, *J* = 6.1, 1.8 Hz, 2H), 3.88 (s, 3H), 3.00 (ddd, *J* = 14.1, 11.1, 5.0 Hz, 1H), 2.87 (ddd, *J* = 14.1, 10.9, 5.2 Hz, 1H), 2.46 (s, 3H), 1.74 (dt, *J* = 13.0, 7.5 Hz, 1H), 1.61 (ddd, *J* = 14.0, 7.4, 3.6 Hz, 1H), 1.22 (dt, *J* = 14.5, 7.1 Hz, 1H), 1.13 – 1.00 (m, 1H), 0.90 (dt, *J* = 14.0, 6.6 Hz, 2H), 0.84 – 0.71 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 151.8, 150.4, 143.6, 143.3, 137.8, 130.5, 129.8, 128.8, 127.7, 127.1, 126.3, 124.9, 124.9, 124.1, 114.3, 111.8, 70.7, 62.8, 56.3, 48.3, 45.9, 29.4, 29.3, 25.3, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{33}BrCl_2NO_6S$: $[M + H]^+$ 696.0584, found: 696.0593; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 29.2 min, t_R (minor) = 19.1 min, >99% ee; $[\alpha]^{25}_D$ = - 69.6 (*c* = 0.2, $CHCl_3$).

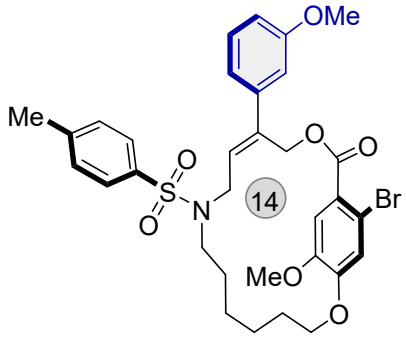
(*R*$_p$,*Z*)-1^5-bromo-12-(3-bromophenyl)-1^2-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3k)



3k

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3k** (49.8 mg, 71% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.36 (t, *J* = 8.3 Hz, 3H), 7.31 (s, 1H), 7.27 (s, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 5.64 (t, *J* = 5.8 Hz, 1H), 5.15 (d, *J* = 13.3 Hz, 1H), 5.05 (d, *J* = 13.3 Hz, 1H), 4.42 – 4.33 (m, 2H), 4.13 – 3.92 (m, 2H), 3.90 (s, 3H), 3.04 (ddd, *J* = 14.5, 10.2, 5.1 Hz, 1H), 2.92 – 2.79 (m, 1H), 2.47 (s, 3H), 1.86 – 1.71 (m, 1H), 1.64 – 1.57 (m, 1H), 1.30 – 1.17 (m, 1H), 1.12 – 1.00 (m, 1H), 0.96 – 0.71 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 151.8, 150.4, 143.4, 142.4, 137.8, 135.6, 132.4, 130.8, 130.0, 129.8, 129.4, 127.1, 125.9, 124.97, 124.8, 122.7, 114.4, 112.0, 70.6, 63.2, 56.3, 48.4, 46.1, 29.2, 29.1, 25.1, 25.0, 21.6; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{33}Br_2NO_6S$: $[M + H]^+$ 707.0375, found: 707.0381; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 24.7 min, t_R (minor) = 17.9 min, 97% ee; $[\alpha]^{25}_D$ = - 51.8 (*c* = 0.2, $CHCl_3$).

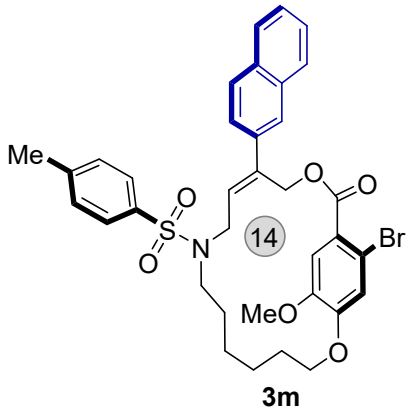
(*R*$_p$,*Z*)-1^5-bromo-1^2-methoxy-12-(3-methoxyphenyl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3l)



3l

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3l** (43.8 mg, 67% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.29 – 7.23 (m, 2H), 6.97 (dt, *J* = 7.9, 1.1 Hz, 1H), 6.91 (t, *J* = 2.1 Hz, 1H), 6.88 – 6.82 (m, 1H), 5.80 – 5.59 (m, 1H), 5.18 (d, *J* = 13.1 Hz, 1H), 5.08 (d, *J* = 13.1 Hz, 1H), 4.37 (dt, *J* = 8.1, 4.1 Hz, 2H), 4.14 – 3.94 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.12 – 3.00 (m, 1H), 2.86 (ddd, *J* = 14.5, 10.8, 4.3 Hz, 1H), 2.45 (s, 3H), 1.87 – 1.71 (m, 1H), 1.65 – 1.51 (m, 1H), 1.27 – 1.15 (m, 1H), 1.07 (dd, *J* = 10.6, 5.9 Hz, 1H), 0.92 – 0.71 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.9, 159.7, 151.8, 150.4, 143.3, 141.9, 137.9, 136.6, 131.4, 129.7, 129.5, 127.1, 126.3, 124.9, 118.8, 114.3, 113.2, 112.1, 111.9, 70.7, 63.5, 56.3, 55.3, 48.2, 46.1, 29.4, 29.2, 25.2, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_7S$: $[M + H]^+$ 658.1469, found: 658.1462; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 28.2 min, t_R (minor) = 21.7 min, 96% ee; $[\alpha]^{25}_D$ = - 70.1 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-15-bromo-12-methoxy-12-(naphthalen-2-yl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3m)

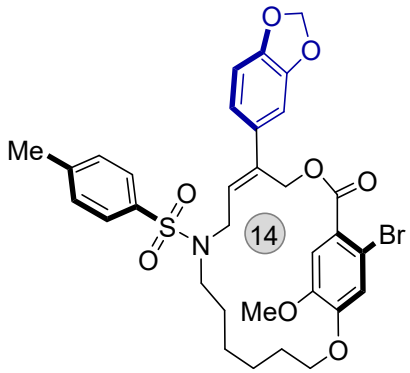


3m

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3m** (49.8 mg, 71% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 – 7.80 (m, 4H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.48 (m, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.32 (s, 1H), 7.28 (s, 1H), 5.83 (t, *J* = 5.9 Hz, 1H), 5.31 (d, *J* = 13.2 Hz, 1H),

5.22 (d, J = 13.2 Hz, 1H), 4.37 (q, J = 4.5 Hz, 2H), 4.19 – 3.99 (m, 2H), 3.89 (s, 3H), 3.09 (ddd, J = 14.6, 10.5, 4.8 Hz, 1H), 2.90 (ddd, J = 14.6, 10.8, 4.4 Hz, 1H), 2.46 (s, 3H), 1.85 – 1.70 (m, 1H), 1.70 – 1.53 (m, 1H), 1.27 – 1.16 (m, 1H), 1.14 – 1.00 (m, 1H), 0.94 – 0.75 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.0, 151.8, 150.4, 143.23, 137.9, 137.6, 136.5, 133.3, 132.8, 131.7, 129.8, 128.19, 128.16, 127.6, 127.2, 126.4, 126.3, 126.2, 125.2, 124.9, 124.4, 114.4, 111.9, 70.6, 63.5, 56.3, 48.3, 46.3, 29.4, 29.1, 25.2, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{35}H_{37}BrNO_6S$: $[M + H]^+$ 678.1520, found: 678.1525; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 32.6 min, t_R (minor) = 23.7 min, 96% ee; $[\alpha]^{25}_D$ = - 67.4 (*c* = 0.2, $CHCl_3$).

(R_p,*Z*)-12-(benzo[d][1,3]dioxol-5-yl)-1^5-bromo-1^2-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3n)

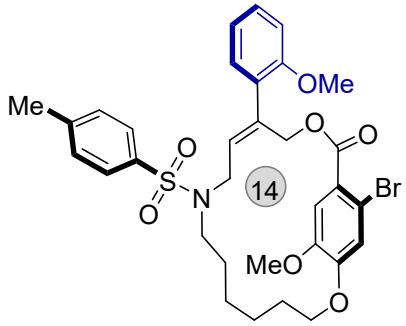


3n

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3n** (47.3 mg, 70% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.30 (s, 1H), 7.25 (s, 1H), 6.88 (dd, J = 8.1, 1.9 Hz, 1H), 6.82 – 6.76 (m, 2H), 5.98 (s, 2H), 5.52 (t, J = 5.9 Hz, 1H), 5.13 (d, J = 13.2 Hz, 1H), 5.03 (d, J = 13.2 Hz, 1H), 4.41 – 4.33 (m, 2H), 4.09 – 3.90 (m, 2H), 3.89 (s, 3H), 3.04 (ddd, J = 14.7, 10.3, 5.0 Hz, 1H), 2.86 (ddd, J = 14.5, 10.8, 4.4 Hz, 1H), 2.46 (s, 3H), 1.82 – 1.71 (m, 1H), 1.64 – 1.54 (m, 1H), 1.22 (q, J = 5.1 Hz, 1H), 1.11 – 1.00 (m, 1H), 0.97 – 0.73 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.9, 151.8, 150.4, 147.9, 147.4, 143.3, 137.9, 136.3, 134.6, 129.9, 129.7, 127.2,

126.2, 124.8, 120.1, 114.4, 111.9, 108.2, 107.0, 101.2, 70.65, 63.6, 56.3, 48.2, 46.1, 29.3, 29.2, 25.2, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{35}BrNO_8S$: $[M + H]^+$ 672.1262, found: 672.1268; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 44.0 min, t_R (minor) = 31.6 min, 98% ee; $[\alpha]^{25}_D$ = - 72.1 (*c* = 0.2, $CHCl_3$).

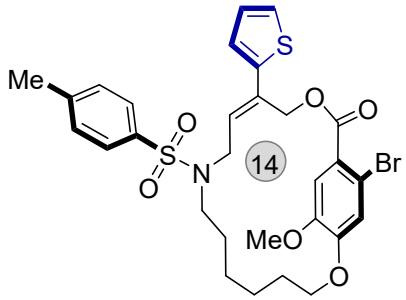
(*R*$_p$,*Z*)-1^5-bromo-1^2-methoxy-12-(2-methoxyphenyl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3o)



3o

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3o** (43.1 mg, 66% yield) as colorless oil. **R$_f$** (pentane:EtOAc = 4:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.24 (m, 5H), 7.08 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.96 – 6.82 (m, 2H), 5.61 (t, *J* = 6.1 Hz, 1H), 5.17 – 4.95 (m, 2H), 4.44 – 4.25 (m, 2H), 4.09 – 3.93 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.10 (td, *J* = 10.5, 5.3 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.41 (s, 3H), 1.77 (q, *J* = 6.8 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.19 (dd, *J* = 10.3, 6.1 Hz, 1H), 1.12 – 1.00 (m, 1H), 0.94 – 0.76 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.2, 156.4, 151.5, 150.4, 143.1, 137.9, 136.0, 132.6, 130.7, 129.9, 129.6, 129.2, 127.18, 127.15, 124.8, 120.7, 114.0, 111.5, 110.5, 70.5, 63.9, 56.3, 55.4, 48.1, 45.8, 29.6, 29.1, 25.3, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_7S$: $[M + H]^+$ 658.1469, found: 658.1477; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 18.5 min, t_R (minor) = 16.5 min, 96% ee; $[\alpha]^{25}_D$ = - 51.8 (*c* = 0.2, $CHCl_3$).

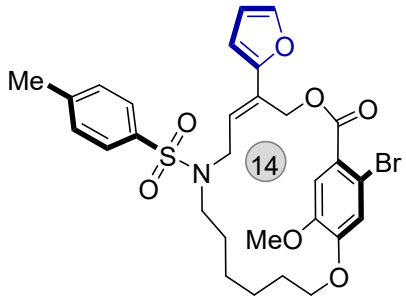
(*R*$_p$,*E*)-1^5-bromo-1^2-methoxy-12-(thiophen-2-yl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3p)



3p

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3p** (44.8 mg, 71% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.22 (s, 1H), 7.20 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.15 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.75 (t, *J* = 6.1 Hz, 1H), 5.22 (d, *J* = 13.2 Hz, 1H), 5.11 (d, *J* = 13.2 Hz, 1H), 4.46 – 4.32 (m, 2H), 4.05 (dd, *J* = 6.1, 1.8 Hz, 2H), 3.88 (s, 3H), 3.00 (ddd, *J* = 14.1, 11.1, 5.0 Hz, 1H), 2.87 (ddd, *J* = 14.1, 10.9, 5.2 Hz, 1H), 2.46 (s, 3H), 1.74 (dt, *J* = 13.0, 7.5 Hz, 1H), 1.61 (ddd, *J* = 14.0, 7.4, 3.6 Hz, 1H), 1.22 (dt, *J* = 14.5, 7.1 Hz, 1H), 1.13 – 1.00 (m, 1H), 0.90 (dt, *J* = 14.0, 6.6 Hz, 2H), 0.84 – 0.71 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 151.8, 150.4, 143.6, 143.3, 137.8, 130.5, 129.8, 128.8, 127.7, 127.1, 126.3, 124.89, 124.85, 124.1, 114.3, 111.8, 70.7, 62.8, 56.3, 48.3, 45.9, 29.4, 29.3, 25.3, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{29}H_{33}BrNO_6S_2$: $[M + H]^+$ 634.0928, found: 634.0935; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 18.5 min, t_R (minor) = 16.5 min, 96% ee; $[\alpha]^{25}_D$ = - 48.2 (*c* = 0.2, $CHCl_3$).

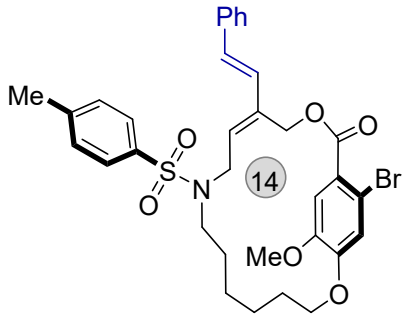
(*R*$_p$,*E*)-1^5-bromo-1^2-(furan-2-yl)-12-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3q)



3q

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3q** (42.7 mg, 70% yield) as white solid. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.30 (m, 4H), 7.18 (s, 1H), 6.49 – 6.40 (m, 2H), 6.03 (t, *J* = 6.3 Hz, 1H), 5.15 (d, *J* = 13.0 Hz, 1H), 5.02 (d, *J* = 13.0 Hz, 1H), 4.42 – 4.31 (m, 2H), 4.04 (d, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.00 (ddd, *J* = 15.9, 11.3, 4.9 Hz, 1H), 2.87 (ddd, *J* = 14.1, 11.1, 5.1 Hz, 1H), 2.46 (s, 3H), 1.81 – 1.68 (m, 1H), 1.66 – 1.58 (m, 1H), 1.24 – 1.12 (m, 1H), 1.11 – 0.99 (m, 1H), 0.95 – 0.84 (m, 3H), 0.82 – 0.74 (m, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.9, 152.5, 151.7, 150.4, 143.2, 142.5, 137.7, 129.7, 127.18, 127.15, 126.5, 126.1, 124.8, 114.15, 111.7, 111.5, 106.6, 70.7, 60.6, 56.3, 48.3, 45.8, 29.6, 29.2, 25.3, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{29}H_{33}BrNO_7S$: $[M + H]^+$ 618.1156, found: 618.1161; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 31.8 min, t_R (minor) = 26.8 min, 97% ee; $[\alpha]^{25}_D$ = - 55.3 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^5-bromo-1^2-methoxy-12-((*E*)-styryl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3r)

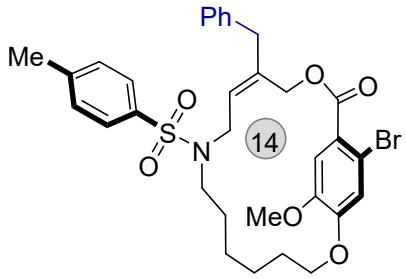


3r

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3r** (40.8 mg, 62% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.39 – 7.31 (m, 4H), 7.28 (d, *J* = 4.7 Hz, 2H), 7.20 (s, 1H), 6.75 – 6.58 (m, 2H), 5.69 (t, *J* = 6.2 Hz, 1H), 5.14 (d, *J* = 13.1 Hz, 1H), 5.04 (d, *J* = 13.1 Hz, 1H), 4.38 – 4.31 (m, 2H), 4.00 (d, *J* = 6.2 Hz, 2H), 3.88 (s, 3H), 3.04 (ddd, *J* = 14.9, 10.6, 4.8 Hz, 1H), 2.88 (ddd, *J* = 14.6, 10.9, 4.5 Hz, 1H), 2.46 (s, 3H), 1.80 – 1.68 (m, 1H), 1.62 – 1.51 (m, 1H), 1.24 – 1.13 (m, 1H), 1.09 –

0.97 (m, 1H), 0.92 – 0.81 (m, 2H), 0.82 – 0.73 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.0, 151.6, 150.4, 143.2, 137.6, 136.9, 134.1, 133.7, 129.7, 129.4, 128.7, 128.1, 127.8, 127.2, 126.6, 126.5, 124.8, 114.1, 111.7, 70.6, 59.9, 56.3, 48.4, 46.0, 29.5, 28.9, 25.3, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{33}H_{37}BrNO_6S$: $[M + H]^+$ 654.1520, found: 654.1527; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 42.1 min, t_R (minor) = 34.2 min, 96% ee; $[\alpha]^{25}_D$ = - 41.7 (*c* = 0.2, $CHCl_3$).

(R_p,*Z*)-12-benzyl-1^5-bromo-1^2-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (3s)

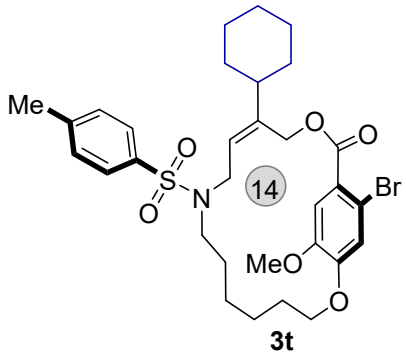


3s

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3s** (37.2 mg, 57% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.35; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.23 (m, 5H), 7.19 – 7.15 (m, 2H), 7.11 (s, 1H), 5.37 (t, *J* = 6.1 Hz, 1H), 4.69 (d, *J* = 12.9 Hz, 1H), 4.60 (d, *J* = 12.9 Hz, 1H), 4.42 – 4.29 (m, 2H), 3.94 – 3.87 (m, 5H), 3.43 (d, *J* = 3.0 Hz, 2H), 3.00 (ddd, *J* = 15.1, 10.6, 4.9 Hz, 1H), 2.83 (ddd, *J* = 14.7, 10.8, 4.7 Hz, 1H), 2.44 (s, 3H), 1.82 – 1.70 (m, 1H), 1.65 – 1.58 (m, 1H), 1.24 – 1.13 (m, 1H), 1.09 – 0.97 (m, 1H), 0.94 – 0.82 (m, 2H), 0.81 – 0.70 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.0, 151.7, 150.4, 143.0, 138.2, 137.9, 135.7, 129.6, 129.4, 129.0, 128.5, 127.1, 126.60, 126.56, 124.9, 114.1, 111.7, 70.8, 63.0, 56.3, 48.0, 45.5, 44.0, 29.5, 29.1, 25.3, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_6S$: $[M + H]^+$ 642.1520, found: 642.1529; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 9.3 min, t_R (minor) = 8.9 min, 97% ee; $[\alpha]^{25}_D$ = - 36.4 (*c* = 0.2, $CHCl_3$).

(R_p,*Z*)-1^5-bromo-12-cyclohexyl-1^2-methoxy-9-tosyl-2,14-dioxa-9-aza-1(1,4)-

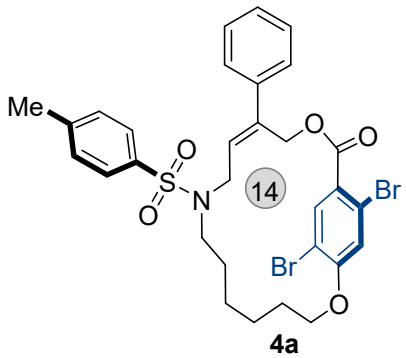
benzenacyclopentadecaphan-11-en-15-one (3t)



3t

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3t** (35.8 mg, 56% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.35; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 3H), 7.16 (s, 1H), 5.15 (t, *J* = 6.0 Hz, 1H), 4.70 (q, *J* = 12.9 Hz, 2H), 4.44 – 4.27 (m, 2H), 3.96 – 3.83 (m, 4H), 3.76 (dd, *J* = 16.9, 6.7 Hz, 1H), 3.09 – 2.94 (m, 1H), 2.83 (t, *J* = 11.4 Hz, 1H), 2.44 (s, 3H), 1.92 (t, *J* = 12.1 Hz, 1H), 1.74 (dd, *J* = 26.8, 12.2 Hz, 6H), 1.63 – 1.54 (m, 1H), 1.39 – 1.21 (m, 2H), 1.15 (t, *J* = 12.5 Hz, 2H), 1.09 – 0.95 (m, 3H), 0.93 – 0.66 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.2, 151.6, 150.4, 143.0, 141.4, 138.2, 129.6, 127.1, 126.9, 125.8, 124.9, 114.1, 111.5, 70.6, 62.9, 56.27, 47.8, 45.6, 45.3, 31.8, 31.6, 29.6, 29.2, 26.5, 26.4, 26.1, 25.2, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{41}BrNO_6S$: $[M + H]^+$ 634.1833, found: 634.1835; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 19.4 min, t_R (minor) = 16.1 min, 97% ee; $[\alpha]^{25}_D$ = - 50.3 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^2,1^5-dibromo-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4a)

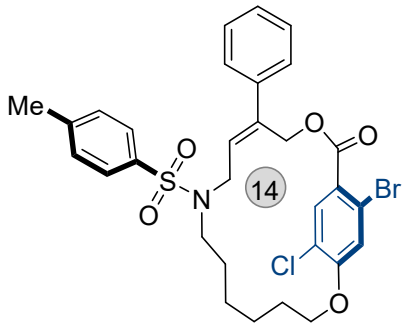


4a

Following the general procedure, the crude product was purified by column

chromatography on a silica gel to afford the product **4a** (47.2 mg, 70% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.31 (m, 8H), 5.73 (dd, *J* = 6.8, 5.1 Hz, 1H), 5.21 – 5.06 (m, 2H), 4.53 – 4.35 (m, 2H), 4.09 – 3.86 (m, 2H), 3.10 (ddd, *J* = 14.7, 10.7, 4.5 Hz, 1H), 2.86 (ddd, *J* = 13.7, 11.0, 4.5 Hz, 1H), 2.46 (s, 3H), 1.95 – 1.81 (m, 1H), 1.61 – 1.52 (m, 1H), 1.32 – 1.23 (m, 1H), 1.11 – 1.00 (m, 1H), 0.92 – 0.74 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 164.8, 159.1, 143.3, 140.3, 137.7, 136.3, 135.0, 131.6, 129.7, 128.6, 127.8, 127.3, 127.2, 126.3, 123.8, 120.1, 113.7, 71.0, 63.7, 48.3, 46.2, 29.2, 29.0, 24.9, 24.9, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{30}H_{32}Br_2NO_5S$: $[M + H]^+$ 678.0342, found: 678.0350; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 25.3 min, t_R (minor) = 16.4 min, 92% ee; $[\alpha]^{25}_D$ = - 58.3 (*c* = 0.2, $CHCl_3$).

(R_p,*Z*)-15-bromo-12-chloro-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4b)

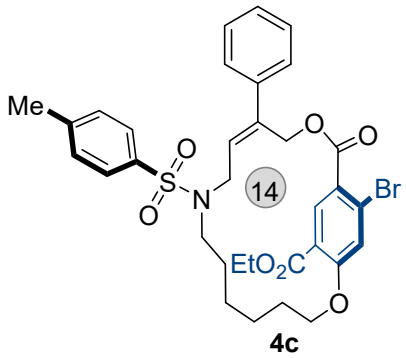


4b

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4b** (44.8 mg, 71% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.6 Hz, 3H), 7.41 – 7.30 (m, 8H), 5.79 – 5.66 (m, 1H), 5.22 – 5.05 (m, 2H), 4.53 – 4.35 (m, 2H), 4.09 – 3.84 (m, 2H), 3.09 (ddd, *J* = 14.9, 10.8, 4.6 Hz, 1H), 2.85 (ddd, *J* = 14.6, 11.1, 4.2 Hz, 1H), 2.46 (s, 3H), 1.85 (ddd, *J* = 14.6, 10.3, 5.7 Hz, 1H), 1.62 – 1.51 (m, 1H), 1.32 – 1.21 (m, 1H), 1.11 – 0.98 (m, 1H), 0.94 – 0.70 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 164.9, 158.1, 143.3, 140.3, 137.7, 136.4, 132.1, 131.6, 129.7, 128.6, 127.9, 127.2, 127.0, 126.3, 124.8, 124.3, 119.3, 71.1, 63.7, 48.3, 46.2, 29.2, 29.0, 25.0, 24.8, 21.5; **HRMS** (ESI): *m/z*: calculated for

$C_{30}H_{32}BrClNO_5S$: $[M + H]^+$ 632.0868, found: 632.0874; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 22.6 min, t_R (minor) = 16.4 min, 92% ee; $[\alpha]^{25}_D$ = - 52.4 (*c* = 0.2, $CHCl_3$).

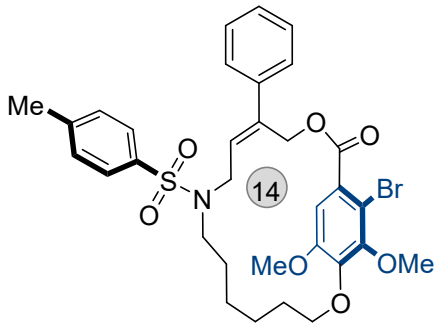
(R_p)-ethyl(Z)-1^5-bromo-15-oxo-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-ene-1^2-carboxylate (4c)



4c

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4c** (45.1 mg, 67% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.44 (s, 1H), 7.39 – 7.30 (m, 7H), 5.72 (dd, *J* = 6.7, 5.2 Hz, 1H), 5.22 – 5.07 (m, 2H), 4.51 (ddd, *J* = 12.1, 9.0, 2.8 Hz, 1H), 4.44 – 4.30 (m, 3H), 4.12 – 3.90 (m, 2H), 3.07 (ddd, *J* = 14.6, 10.8, 4.6 Hz, 1H), 2.88 (ddd, *J* = 14.5, 11.0, 4.4 Hz, 1H), 2.46 (s, 3H), 1.92 – 1.77 (m, 1H), 1.67 – 1.50 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.16 (m, 1H), 1.14 – 0.96 (m, 1H), 0.97 – 0.69 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.2, 164.3, 162.2, 143.3, 140.3, 137.9, 136.4, 133.7, 131.7, 129.7, 128.5, 127.8, 127.1, 126.3, 126.1, 125.2, 124.7, 122.2, 71.2, 63.5, 61.5, 48.2, 46.2, 29.5, 29.2, 25.1, 24.8, 21.5, 14.2; **HRMS** (ESI): *m/z*: calculated for $C_{33}H_{37}BrNO_7S$: $[M + H]^+$ 670.1469, found: 670.1478; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 31.3 min, t_R (minor) = 24.0 min, 90% ee; $[\alpha]^{25}_D$ = - 46.7 (*c* = 0.2, $CHCl_3$).

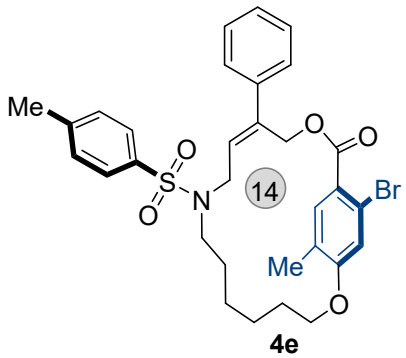
(R_p,*Z*)-1^3-bromo-1^2,1^6-dimethoxy-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4d)



4d

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4d** (47.8 mg, 73% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 7.9 Hz, 2H), 7.34 (dd, *J* = 16.1, 6.9 Hz, 7H), 6.98 (s, 1H), 5.72 (t, *J* = 6.2 Hz, 1H), 5.20 (d, *J* = 13.0 Hz, 1H), 5.10 (d, *J* = 13.0 Hz, 1H), 4.43 (ddd, *J* = 11.3, 8.0, 2.7 Hz, 1H), 4.29 (ddd, *J* = 11.6, 7.1, 3.0 Hz, 1H), 4.06 (qd, *J* = 17.2, 6.3 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.06 (ddd, *J* = 15.6, 11.0, 5.2 Hz, 1H), 2.85 (ddd, *J* = 14.5, 10.7, 5.2 Hz, 1H), 2.45 (s, 3H), 1.75 – 1.62 (m, 1H), 1.62 – 1.50 (m, 1H), 1.13 – 0.99 (m, 2H), 1.00 – 0.86 (m, 1H), 0.86 – 0.58 (m, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.4, 153.0, 151.5, 144.4, 143.2, 140.4, 137.8, 136.5, 131.6, 129.7, 128.5, 128.3, 127.8, 127.1, 126.2, 108.8, 107.9, 71.0, 63.3, 60.9, 56.4, 48.0, 46.1, 29.8, 29.0, 26.1, 25.3, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_7S$: $[M + H]^+$ 658.1469, found: 658.1475; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 18.2 min, t_R (minor) = 16.3 min, 94% ee; $[\alpha]^{25}_D$ = - 40.2 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^5-bromo-1^2-methyl-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4e)

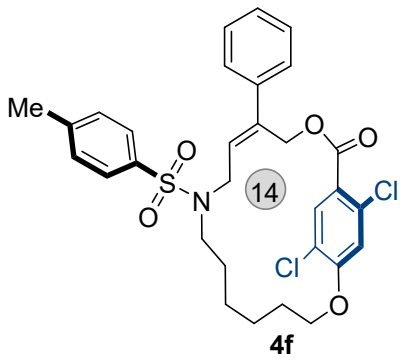


4e

Following the general procedure, the crude product was purified by column

chromatography on a silica gel to afford the product **4e** (42.7 mg, 71% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.35; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.50 (s, 1H), 7.42 – 7.30 (m, 7H), 7.25 (s, 1H), 5.71 (dd, *J* = 6.7, 5.1 Hz, 1H), 5.17 (d, *J* = 13.1 Hz, 1H), 5.07 (d, *J* = 13.1 Hz, 1H), 4.45 (ddd, *J* = 12.4, 9.5, 2.8 Hz, 1H), 4.28 (dt, *J* = 12.4, 4.7 Hz, 1H), 4.12 – 3.85 (m, 2H), 3.10 (ddd, *J* = 15.0, 10.9, 4.4 Hz, 1H), 2.83 (ddd, *J* = 13.4, 10.9, 4.5 Hz, 1H), 2.46 (s, 3H), 2.21 (s, 3H), 1.79 (ddd, *J* = 14.7, 9.9, 4.9 Hz, 1H), 1.61 – 1.49 (m, 1H), 1.34 – 1.18 (m, 1H), 1.03 (ddd, *J* = 15.3, 8.3, 4.3 Hz, 1H), 0.89 – 0.70 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.2, 160.8, 143.2, 140.5, 137.8, 136.5, 133.0, 131.5, 129.7, 128.5, 128.3, 127.7, 127.2, 126.3, 125.5, 121.9, 118.4, 69.5, 63.3, 48.4, 46.3, 29.5, 29.1, 24.9, 24.9, 21.5, 15.7; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{35}BrNO_5S$: $[M + H]^+$ 612.1414, found: 612.1419; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 23.1 min, t_R (minor) = 15.3 min, 97% ee; $[\alpha]^{25}_D$ = - 63.7 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^2,1^5-dichloro-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4f)

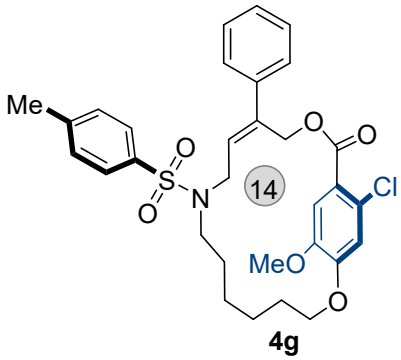


4f

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4f** (38.6 mg, 66% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.30 (m, 7H), 7.19 (s, 1H), 5.70 (dd, *J* = 6.6, 5.1 Hz, 1H), 5.19 (d, *J* = 13.2 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 4.44 (dt, *J* = 10.1, 3.9 Hz, 2H), 3.97 (qd, *J* = 17.7, 5.9 Hz, 2H), 3.06 (ddd, *J* = 14.7, 10.6, 4.5 Hz, 1H), 2.84 (ddd, *J* = 13.7, 10.9, 4.4 Hz, 1H), 2.46 (s, 3H), 1.95 – 1.78 (m, 1H), 1.65 – 1.50 (m, 1H), 1.36 – 1.21 (m, 1H), 1.14 – 0.98 (m, 1H), 0.95 – 0.69 (m, 4H). **^{13}C**

NMR (100 MHz, Chloroform-*d*) δ 164.5, 158.2, 143.3, 140.3, 137.7, 136.5, 132.3, 132.1, 131.4, 129.8, 128.6, 127.9, 127.2, 126.3, 124.7, 124.1, 121.0, 71.0, 63.8, 48.3, 46.2, 29.1, 28.9, 24.9, 24.8, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{30}H_{32}Cl_2NO_5S$: $[M + H]^+$ 588.1373, found: 588.1380; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 19.6 min, t_R (minor) = 14.8 min, 97% ee; $[\alpha]^{25}_D$ = - 59.7 (*c* = 0.2, $CHCl_3$).

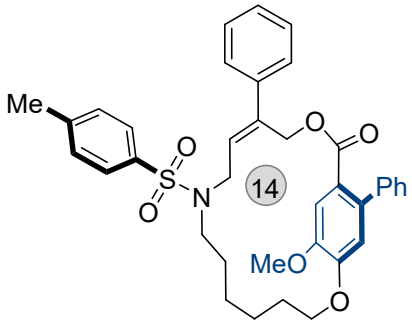
(*R*$_p$,*Z*)-15-chloro-12-methoxy-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4g)



4g

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4g** (41.1 mg, 70% yield) as colorless oil. **R$_f$** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.28 (m, 8H), 7.12 (s, 1H), 5.66 (t, *J* = 5.8 Hz, 1H), 5.23 (d, *J* = 13.2 Hz, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 4.42 – 4.27 (m, 2H), 4.02 (qd, *J* = 17.8, 5.9 Hz, 2H), 3.89 (s, 3H), 3.03 (ddd, *J* = 14.5, 10.1, 5.1 Hz, 1H), 2.86 (ddd, *J* = 14.6, 10.8, 4.3 Hz, 1H), 2.46 (s, 3H), 1.83 – 1.69 (m, 1H), 1.65 – 1.47 (m, 1H), 1.27 – 1.13 (m, 1H), 1.12 – 0.97 (m, 1H), 0.96 – 0.69 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.5, 151.9, 149.9, 143.2, 140.4, 137.8, 136.8, 131.1, 129.7, 128.5, 127.8, 127.2, 126.4, 125.2, 123.9, 121.6, 114.2, 70.6, 63.6, 56.3, 48.3, 46.1, 29.3, 29.1, 25.1, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{35}ClNO_6S$: $[M + H]^+$ 584.1869, found: 584.1977; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 21.2 min, t_R (minor) = 17.4 min, 96% ee; $[\alpha]^{25}_D$ = - 60.4 (*c* = 0.2, $CHCl_3$).

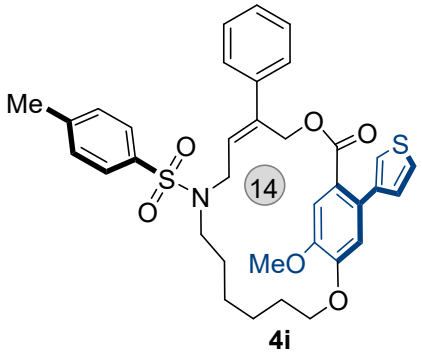
(*R*$_p$,*Z*)-12-methoxy-15,12-diphenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4h)



4h

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4h** (46.0 mg, 74% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 7.9 Hz, 2H), 7.39 – 7.29 (m, 8H), 7.25 – 7.19 (m, 3H), 7.16 (s, 1H), 6.84 (dd, *J* = 7.3, 2.3 Hz, 2H), 5.41 (dd, *J* = 7.7, 4.3 Hz, 1H), 5.08 (d, *J* = 13.0 Hz, 1H), 4.44 (t, *J* = 4.8 Hz, 2H), 4.32 (d, *J* = 13.0 Hz, 1H), 3.96 (s, 3H), 3.95 – 3.87 (m, 1H), 3.62 (dd, *J* = 17.5, 7.7 Hz, 1H), 3.04 – 2.89 (m, 1H), 2.74 (ddd, *J* = 14.3, 11.1, 4.2 Hz, 1H), 2.45 (s, 3H), 1.96 – 1.83 (m, 1H), 1.69 – 1.55 (m, 1H), 1.36 – 1.23 (m, 1H), 1.07 (ddd, *J* = 18.6, 10.2, 5.9 Hz, 2H), 0.94 – 0.78 (m, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.9, 151.1, 150.1, 143.2, 140.8, 140.4, 137.9, 136.9, 135.9, 130.6, 129.7, 128.5, 128.2, 128.2, 127.5, 127.3, 127.1, 126.1, 124.7, 121.4, 113.7, 70.5, 62.9, 56.2, 47.8, 45.9, 29.7, 29.3, 25.2, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{37}H_{40}NO_6S$: $[M + H]^+$ 626.2571, found: 626.2577; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 33.0 min, t_R (minor) = 18.5 min, >99% ee; $[\alpha]^{25}_D$ = - 72.3 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^2-methoxy-12-phenyl-1^5-(thiophen-3-yl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4i)

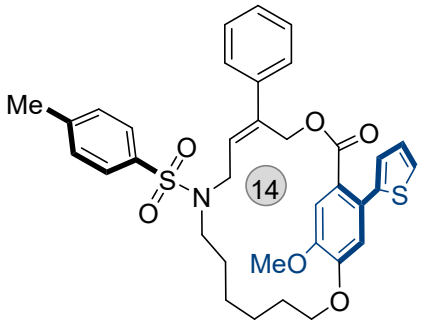


4i

Following the general procedure, the crude product was purified by column

chromatography on a silica gel to afford the product **4i** (47.8 mg, 76% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.26 (dd, *J* = 6.0, 4.2 Hz, 5H), 7.17 (d, *J* = 2.8 Hz, 2H), 7.07 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.05 – 7.00 (m, 2H), 5.46 (dd, *J* = 7.3, 4.8 Hz, 1H), 5.13 (d, *J* = 13.1 Hz, 1H), 4.49 (d, *J* = 13.1 Hz, 1H), 4.44 – 4.37 (m, 2H), 3.94 (s, 3H), 3.89 (dd, *J* = 17.6, 4.7 Hz, 1H), 3.69 (dd, *J* = 17.5, 7.3 Hz, 1H), 2.96 (ddd, *J* = 14.5, 10.1, 5.0 Hz, 1H), 2.85 – 2.69 (m, 1H), 2.46 (s, 3H), 1.93 – 1.76 (m, 1H), 1.63 (ddd, *J* = 19.5, 9.3, 5.1 Hz, 1H), 1.35 – 1.21 (m, 1H), 1.15 – 0.97 (m, 2H), 0.95 – 0.74 (m, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.8, 151.0, 150.2, 143.2, 141.1, 140.3, 137.9, 136.8, 130.7, 130.0, 129.7, 128.3, 128.1, 127.6, 127.1, 126.1, 125.7, 124.8, 121.8, 121.1, 113.4, 70.4, 63.0, 56.2, 47.9, 45.8, 29.6, 29.2, 25.2, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{35}H_{38}NO_6S_2$: $[M + H]^+$ 632.2136, found: 632.2141; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 55.4 min, t_R (minor) = 20.7 min, 98% ee; $[\alpha]^{25}_D$ = - 69.3 (*c* = 0.2, $CHCl_3$).

(*R_p*,*Z*)-1^2-methoxy-12-phenyl-1^5-(thiophen-2-yl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4j)

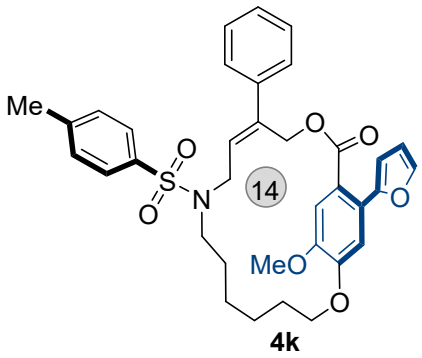


4j

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4j** (47.1 mg, 75% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.26 (dd, *J* = 5.6, 2.9 Hz, 4H), 7.23 – 7.19 (m, 2H), 7.06 – 7.00 (m, 2H), 7.00 – 6.94 (m, 2H), 5.50 (dd, *J* = 7.6, 4.7 Hz, 1H), 5.11 (d, *J* = 12.9 Hz, 1H), 4.52 (d, *J* = 12.9 Hz, 1H), 4.42 (q, *J* = 5.2, 4.4 Hz, 2H), 3.95 (s, 4H), 3.70 (dd, *J* = 17.4, 7.6 Hz, 1H), 3.01 (ddd, *J* = 14.6, 10.3, 4.9 Hz, 1H),

2.84 – 2.72 (m, 1H), 2.46 (s, 3H), 1.91 – 1.78 (m, 1H), 1.63 (ddd, *J* = 10.7, 7.4, 3.7 Hz, 1H), 1.34 – 1.21 (m, 1H), 1.17 – 1.05 (m, 1H), 0.98 (ddd, *J* = 18.0, 9.0, 4.8 Hz, 1H), 0.94 – 0.74 (m, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.7, 150.9, 150.6, 143.1, 142.1, 140.4, 137.9, 136.6, 131.0, 129.7, 128.3, 127.6, 127.6, 127.1, 126.2, 126.0, 125.6, 125.4, 121.5, 113.3, 70.4, 63.1, 56.3, 47.9, 45.9, 29.7, 29.3, 25.2, 25.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{35}H_{38}NO_6S_2$: $[M + H]^+$ 632.2136, found: 632.2143; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 44.7 min, t_R (minor) = 21.1 min, 98% ee; $[\alpha]^{25}_D$ = - 64.8 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^5-(furan-2-yl)-1^2-methoxy-12-phenyl-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4k)

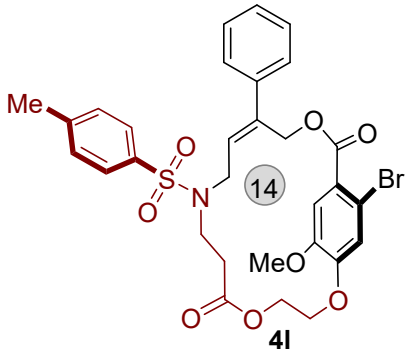


4k

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4k** (44.8 mg, 73% yield) as colorless oil. **R$_f$** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.29 (m, 7H), 7.23 – 7.16 (m, 3H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.35 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.57 (dd, *J* = 6.8, 5.3 Hz, 1H), 5.21 (d, *J* = 13.1 Hz, 1H), 4.72 (d, *J* = 13.1 Hz, 1H), 4.49 – 4.33 (m, 2H), 3.93 (s, 3H), 3.86 (dd, *J* = 17.6, 5.4 Hz, 1H), 3.73 (dd, *J* = 17.5, 6.9 Hz, 1H), 2.99 (ddd, *J* = 14.5, 10.4, 4.6 Hz, 1H), 2.80 – 2.68 (m, 1H), 2.45 (s, 3H), 1.88 – 1.76 (m, 1H), 1.67 – 1.59 (m, 1H), 1.33 – 1.21 (m, 1H), 1.12 – 1.02 (m, 1H), 0.98 – 0.78 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.6, 152.2, 150.8, 150.5, 143.1, 142.4, 140.2, 137.8, 136.2, 131.1, 129.6, 128.4, 127.7, 127.2, 126.2, 123.7, 123.6, 118.4, 113.0, 111.5, 107.3, 70.1, 63.1, 56.2, 48.0, 45.8, 29.6, 29.0, 25.1, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{35}H_{38}NO_7S$: $[M + H]^+$ 616.2364, found: 616.2373; HPLC (Chiralpak IF, *i*-

propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 38.6 min, t_R (minor) = 23.6 min, 92% ee; $[\alpha]^{25}_D$ = - 57.3 (*c* = 0.2, $CHCl_3$).

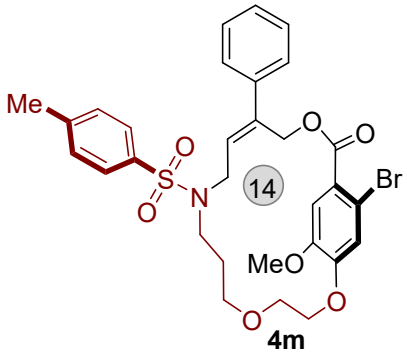
(R_p,*Z*)-1^5-bromo-1^2-methoxy-12-phenyl-9-tosyl-2,5,14-trioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-ene-6,15-dione (4l)



4l

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4l** (52.3 mg, 81% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.25; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.29 (m, 8H), 7.19 (s, 1H), 5.62 (t, *J* = 6.7 Hz, 1H), 5.23 (d, *J* = 12.7 Hz, 1H), 5.06 (d, *J* = 12.8 Hz, 1H), 4.59 – 4.51 (m, 1H), 4.51 – 4.41 (m, 2H), 4.39 – 4.30 (m, 1H), 4.14 (qd, *J* = 16.9, 6.8 Hz, 2H), 3.88 (s, 3H), 3.29 – 3.09 (m, 2H), 2.45 (s, 3H), 2.26 – 2.04 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 169.9, 165.9, 151.0, 150.5, 143.6, 140.3, 137.8, 137.4, 130.6, 129.9, 128.6, 128.0, 127.7, 127.1, 126.2, 126.1, 114.0, 111.1, 69.1, 64.9, 62.9, 56.3, 46.6, 42.6, 32.7, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{30}H_{31}BrNO_8S$: $[M + H]^+$ 644.0949, found: 644.0954; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 61.9 min, t_R (minor) = 48.3 min, 90% ee; $[\alpha]^{25}_D$ = - 55.8 (*c* = 0.2, $CHCl_3$).

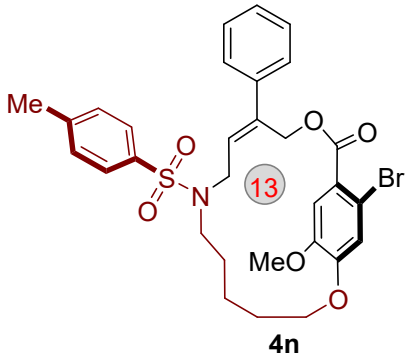
(R_p,*Z*)-1^5-bromo-1^2-methoxy-12-phenyl-9-tosyl-2,5,14-trioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (4m)



4m

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4m** (50.5 mg, 80% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.20; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.30 (m, 8H), 7.21 (s, 1H), 5.76 (t, *J* = 6.1 Hz, 1H), 5.22 (d, *J* = 13.2 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 4.47 (dd, *J* = 13.3, 5.7 Hz, 1H), 4.29 (dd, *J* = 13.0, 6.0 Hz, 1H), 4.11 – 3.93 (m, 2H), 3.87 (s, 3H), 3.66 (dd, *J* = 11.8, 6.0 Hz, 1H), 3.58 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.11 – 2.76 (m, 4H), 2.46 (s, 3H), 1.42 – 1.30 (m, 1H), 1.32 – 1.13 (m, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.1, 151.6, 151.2, 143.4, 140.4, 137.2, 136.9, 131.2, 129.8, 128.6, 127.9, 127.2, 127.0, 126.6, 126.4, 114.0, 111.3, 72.0, 70.8, 68.1, 63.5, 56.2, 46.3, 45.1, 28.8, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{30}H_{33}BrNO_7S$: $[M + H]^+$ 630.1156, found: 630.1163; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 31.3 min, t_R (minor) = 22.9 min, 96% ee; $[\alpha]^{25}_D$ = - 63.4 (*c* = 0.2, $CHCl_3$).

(*R*$_p$,*Z*)-1^5-bromo-1^2-methoxy-11-phenyl-8-tosyl-2,13-dioxa-8-aza-1(1,4)-benzenacyclotetradecaphan-10-en-14-one (4n)

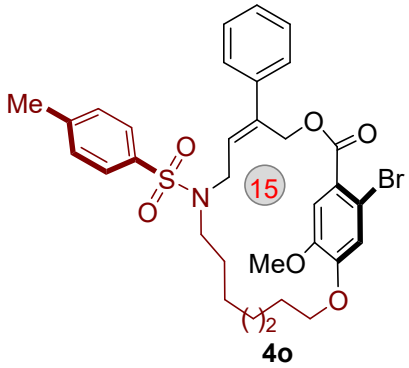


4n

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4n** (34.2 mg, 56% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ

7.72 (d, J = 8.3 Hz, 2H), 7.37 (s, 1H), 7.31 (dd, J = 8.0, 1.8 Hz, 5H), 7.28 – 7.24 (m, 2H), 7.22 (s, 1H), 5.35 (d, J = 14.1 Hz, 1H), 5.27 (t, J = 5.5 Hz, 1H), 5.05 (dd, J = 14.1, 1.7 Hz, 1H), 4.42 (ddd, J = 12.3, 5.7, 3.3 Hz, 1H), 4.29 (ddd, J = 12.0, 9.2, 2.2 Hz, 1H), 4.04 (dd, J = 18.5, 4.8 Hz, 1H), 3.89 (s, 3H), 3.83 (dd, J = 18.7, 6.1 Hz, 1H), 3.01 (ddd, J = 14.8, 9.6, 5.5 Hz, 1H), 2.57 (ddd, J = 14.8, 9.7, 5.5 Hz, 1H), 2.46 (s, 3H), 1.92 – 1.79 (m, 0H), 1.65 – 1.51 (m, 1H), 1.27 – 1.19 (m, 1H), 1.19 – 1.08 (m, 1H), 1.05 – 0.88 (m, 1H), 0.82 – 0.68 (m, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.9, 152.2, 150.9, 143.2, 139.9, 138.4, 137.8, 129.7, 129.7, 128.4, 127.9, 127.2, 126.7, 125.9, 114.6, 111.9, 72.0, 64.5, 56.4, 49.1, 47.3, 30.6, 28.7, 23.6, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{30}H_{33}BrNO_6S$: $[M + H]^+$ 614.1207, found: 614.1215; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 19.6 min, t_R (minor) = 14.8 min, 99% ee; $[\alpha]^{25}_D$ = - 67.4 (c = 0.2, $CHCl_3$).

(R_p,*Z*)-1^5-bromo-1^2-methoxy-13-phenyl-10-tosyl-2,15-dioxa-10-aza-1(1,4)-benzenacyclohexadecaphan-12-en-16-one (4o)

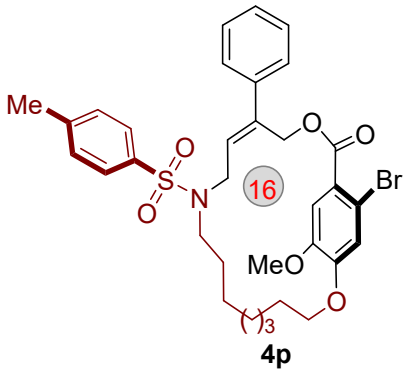


4o

Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4o** (47.7 mg, 74% yield) as colorless oil. **R_f** (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.74 (d, J = 8.3 Hz, 2H), 7.36 – 7.30 (m, 8H), 7.28 (s, 1H), 5.49 (t, J = 5.9 Hz, 1H), 5.23 – 5.11 (m, 2H), 4.42 (dt, J = 6.5, 4.5 Hz, 2H), 4.21 (dd, J = 18.0, 6.3 Hz, 1H), 4.09 (dd, J = 17.7, 5.9 Hz, 1H), 3.90 (s, 3H), 3.10 (ddd, J = 14.7, 9.4, 5.5 Hz, 1H), 2.95 (ddd, J = 14.5, 9.3, 5.8 Hz, 1H), 2.46 (s, 3H), 1.77 – 1.62 (m, 2H), 1.31 – 1.13 (m, 3H), 1.13 – 1.05 (m, 1H), 1.03 – 0.92 (m, 2H), 0.87 – 0.77 (m, 1H), 0.77 – 0.66 (m, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.6, 151.5, 149.8, 143.2, 140.3,

138.1, 137.4, 130.2, 129.7, 128.5, 127.8, 127.2, 126.3, 124.7, 123.1, 114.4, 112.5, 70.2, 63.4, 56.2, 47.8, 46.1, 28.5, 28.3, 27.7, 26.6, 25.0, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{32}H_{37}BrNO_6S$: $[M + H]^+$ 642.1520, found: 642.1526; HPLC (Chiralpak IF, *i*-propanol/hexane = 28/52, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 25.9 min, t_R (minor) = 22.8 min, 98% ee; $[\alpha]^{25}_D$ = - 60.8 (*c* = 0.2, $CHCl_3$).

(*Z*)-15-bromo-12-methoxy-14-phenyl-11-tosyl-2,16-dioxa-11-aza-1(1,4)-benzenacycloheptadecaphan-13-en-17-one (4p)



4p

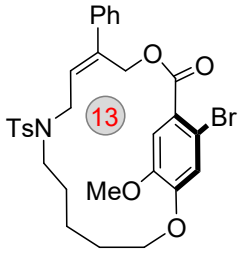
Following the general procedure, the crude product was purified by column chromatography on a silica gel to afford the product **4p** (48.2 mg, 73% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.31 (m, 7H), 7.30 (s, 1H), 7.22 (s, 1H), 5.82 (t, *J* = 6.6 Hz, 1H), 5.21 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 4.42 (ddd, *J* = 12.0, 6.9, 4.2 Hz, 2H), 4.13 (d, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.13 – 2.92 (m, 2H), 2.46 (s, 3H), 1.80 – 1.68 (m, 1H), 1.68 – 1.59 (m, 1H), 1.26 (ddd, *J* = 26.8, 11.3, 6.9 Hz, 4H), 1.15 – 1.00 (m, 1H), 0.85 – 0.73 (m, 2H), 0.74 – 0.57 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.6, 151.1, 149.5, 143.2, 140.2, 137.7, 136.6, 131.1, 129.8, 128.6, 127.9, 127.1, 126.1, 123.8, 122.1, 114.5, 113.0, 69.6, 62.1, 56.1, 47.9, 46.1, 29.0, 28.8, 27.6, 26.9, 26.7, 24.1, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{33}H_{39}BrNO_6S$: $[M + H]^+$ 656.1676, found: 656.1685.

Investigations on the Thermal Stability of the Planar-Chirality

Dependence of Thermal Stability on Temperature[4]

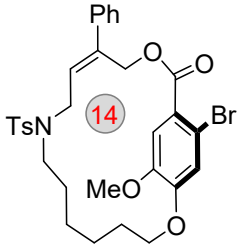
3a/4n/4o (10 mg) was dissolved in toluene (5 mL) in a Schlenk tube. Then the solution was allowed to stir at 40 °C. After 2 h, a small amount of sample (20 µL) was taken out from solution and diluted by *i*-propanol/hexane (38/42, 0.5 mL), then the ee values of the sample was determined using HPLC. Then the temperature was increased by 10 °C and allowed to stir for two more hours and checked the ee values, and same procedure was repeated up to 140 °C.

The variation of enantiomeric excess *vs* temperature is given below:



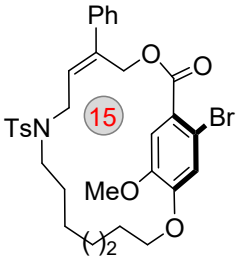
4n, 99% ee

No racemization at
140 °C for 2 h in toluene



3a, 96% ee

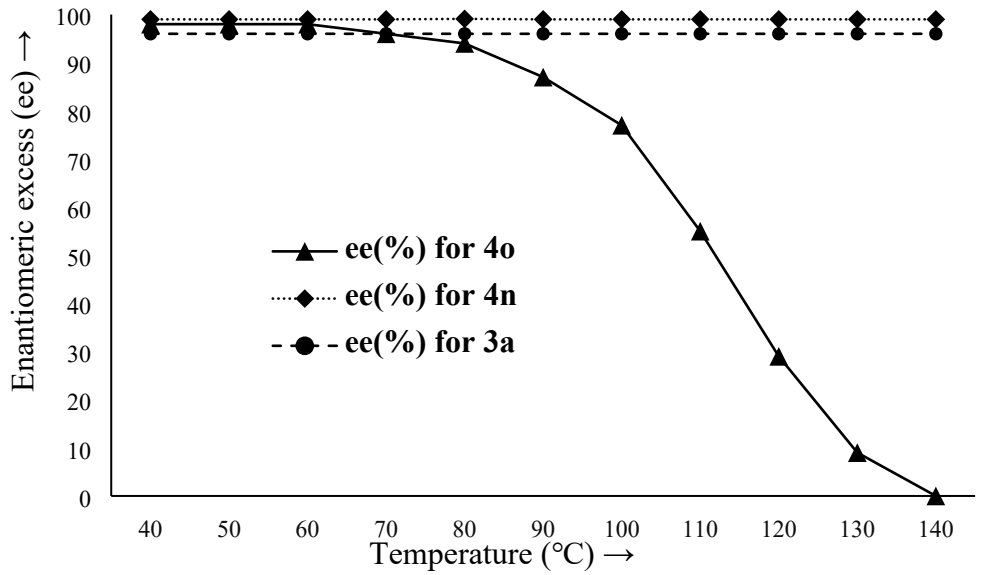
No racemization at
140 °C for 2 h in toluene



4o, 98% ee

$\Delta G_{rot}^{\ddagger}$: 31.1 kcal/mol
$t_{1/2}$ (25 °C): 33.5 years

Temperature (°C)	ee(%) for 4n	ee(%) for 3a	ee(%) for 4o
40	99	96	98
50	99	96	98
60	99	96	98
70	99	96	96
80	99	96	94
90	99	96	87
100	99	96	77
110	99	96	55
120	99	96	29
130	99	96	9
140	99	96	0



In this experiment, the planar-chiral macrocycle **3a** or **4n** was heated in toluene under sealed conditions at 140 °C, no racemization of them was observed after 2 h. For compound **4o**, the ee value remained up to 60 °C demonstrating the restricted rotation of the *ansa* chain. These results demonstrated the good thermal stability of the macrocyclic planar-chiral products.

Experimental Determination of Rotation Barrier of 4o[5]

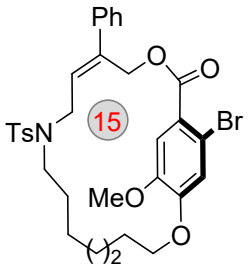
The rotation barriers were obtained by racemization experiments of an enantiomer via chiral HPLC analysis. The racemization constant was obtained from the slope of the first-order kinetic line (kracemization = 2 ×kenantiomerzation). Rotation barrier ($\Delta G^{\ddagger}$) was obtained from the eyring equation. (R = 8.31451 $J \cdot K^{-1} \cdot mol^{-1}$, h = 6.62608 $\times 10^{-34}$ J·s and k_B = 1.38066 10^{-23} $J \cdot K^{-1}$).

Eyring Equation:

$$k_{enantiomerization} = \frac{k_B * T}{h} * e^{\frac{-\Delta G^{\ddagger}}{RT}}$$

Half-life time:

$$t_{1/2} = \frac{\ln 2}{k_{racemetization}}$$



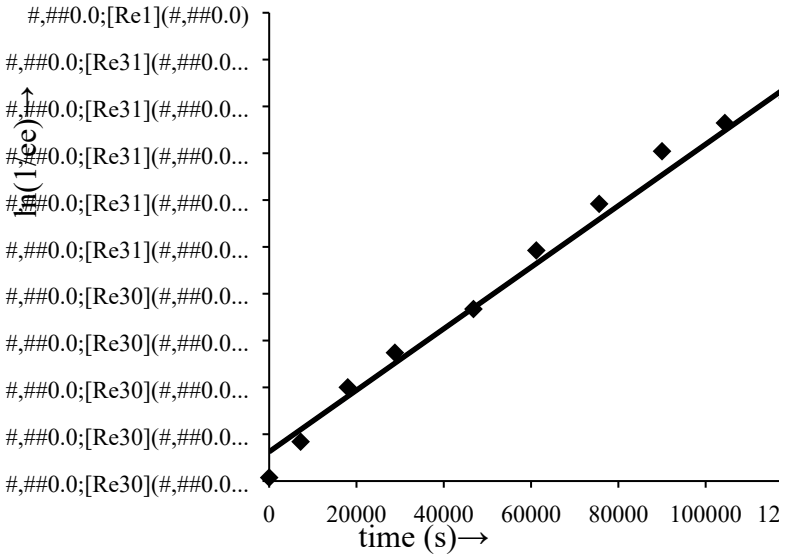
4o, 98% ee

Rotation barrier for 4o: (10 mg) was dissolved in toluene (5 mL) and stirred at 100 °C for about 37 h. A small amount of sample (20 µL) was taken out from solution and diluted by *i*-propanol/hexane (38/42, 0.5 mL), then the ee values of the sample was determined using HPLC to monitor the percentage decrease of the second eluted enantiomer over time.

The variation of enantiomeric excess *vs* time is given below:

Time (s)	% of major enantiomer (M)	% of minor enantiomer (m)	ln [(M+m)/(M-m)]
0	97.953	2.047	0.0148
7200	92.265	7.735	0.1681
18000	83.505	16.495	0.4003
28800	78.901	21.099	0.5481
46800	73.982	26.018	0.7347
61200	68.674	31.326	0.9849
75600	65.306	34.649	1.1838
90000	62.224	37.776	1.4086
104400	60.834	39.166	1.5293
118800	59.739	40.261	1.6359
133200	58.680	41.320	1.7510

The plot on variation of ee values with time for **4o** is presented below:



$k_{racemization}$ (100 °C) = 1.0×10^{-5} s^{-1}

$k_{enantiomerization}$ (100 °C) = 0.5×10^{-5} s^{-1}

$t_{1/2}^{rac}$ (100 °C) = ln(2)/$k_{racemization}$ = 69315 s = 19.3 h

Employing the Eyring equation:

$\Delta G^{\neq} = RT \ln(kB\times T/ k_{racemization}\times h)$

$\Delta G^{\neq} = 8.314\ J\cdot mol^{-1}\cdot K^{-1}\times 373.15\ K \times \ln(1.38\times10^{-23}\ J\cdot K^{-1}\times 373.15K/0.5\times10^{-5}\ s^{-1}\times6.626\times10^{-34}\ Js)$

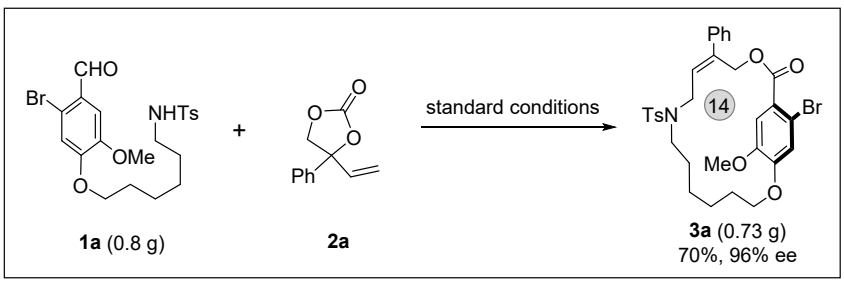
$\Delta G^{\neq}$ = 129.95 *KJ·mol*$^{-1}$ = 31.1 *kcal· mol*$^{-1}$

$k_{racemization}$ (25 °C) = 6.57×10^{-10} s^{-1}

$t_{1/2}^{rac}$ (25 °C) = ln(2)/$k_{racemization}$ (25 °C) = 1.06×10^{9} s = 33.5 years

Gram-Scale Synthesis and Synthetic Transformations

Gram-Scale Synthesis of 3a

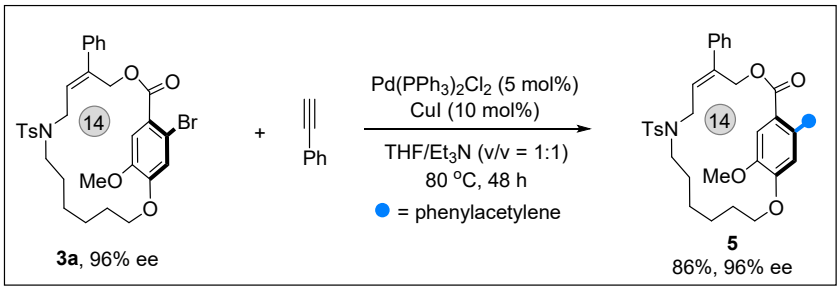


To a flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was

added the catalyst $Pd(PPh_3)_4$ (47.8 mg, 2.5 mol%), **L1** (21.5 mg, 3 mol%), toluene (1.5 mL) was added. The mixture was then stirred at room temperature for 0.5 h. After that, **1a** (0.8 g, 1.0 equiv.) and **2a** (0.47 g, 1.5 equiv.) were added sequentially under Ar. The reaction mixture was then stirred at room temperature for 2 h. Then the solution was transferred into a mixture of pre-NHC catalyst **C1** (20 mol%), $^{n}Bu_4NOAc$ (50 mol%), DQ (0.12 mmol) and 4Å MS 50 mg in toluene (80.0 mL) and stirred at room temperature for another 12 h (monitored by TLC). After the reaction was completed, the reaction mixture was filtered and concentrated. The residue was purified by a silica gel flash chromatography (Hexane/EtOAc = 5:1) to afford the desired product **3a** in 70% yield (0.73 g) with 96% ee.

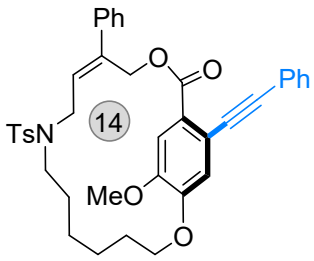
Synthetic Transformations of 3a

Sonogashira coupling



To a solution of **3a** (62.8 mg, 0.1 mmol) and ethynylbenzene (30.6 mg, 3.0 equiv) in THF/Et_3N (v/v = 1:1, 2.0 mL) was added $Pd(PPh_3)_2Cl_2$ (3.5.0 mg, 5 mol%) and CuI (1.5 mg, 10 mol%). The flask was flushed with nitrogen gas. The resulting mixture was stirred at 80 °C for 48 h. Then the reaction mixture was concentrated and the residue was purified by a silica gel column chromatography to give **5** in 86% yield without compromising the ee values (96% ee).

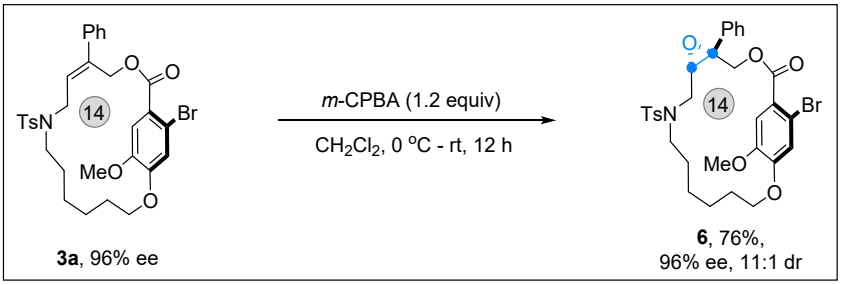
(*R*,*Z*)-1^2-methoxy-12-phenyl-1^5-(phenylethynyl)-9-tosyl-2,14-dioxa-9-aza-1(1,4)-benzenacyclopentadecaphan-11-en-15-one (5)



5

Following the above procedure, the crude product was purified by column chromatography on a silica gel to afford the product **5** (56.1 mg, 86% yield) as colorless oil. $\mathbf{R_f}$ (pentane:EtOAc = 4:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.44 (s, 1H), 7.42 – 7.36 (m, 4H), 7.35 – 7.29 (m, 2H), 7.28 – 7.21 (m, 7H), 5.73 (t, *J* = 5.6 Hz, 1H), 5.36 (d, *J* = 13.3 Hz, 1H), 5.06 (d, *J* = 13.3 Hz, 1H), 4.41 (dddd, *J* = 18.0, 12.3, 8.9, 3.7 Hz, 2H), 4.15 (dd, *J* = 18.1, 5.4 Hz, 1H), 4.00 (dd, *J* = 18.1, 6.1 Hz, 1H), 3.94 (s, 3H), 3.08 (ddd, *J* = 15.1, 10.6, 5.0 Hz, 1H), 2.89 (ddd, *J* = 13.5, 11.1, 4.0 Hz, 1H), 2.42 (s, 3H), 1.85 – 1.73 (m, 1H), 1.67 – 1.52 (m, 1H), 1.38 – 1.18 (m, 1H), 1.13 – 0.99 (m, 1H), 0.89 – 0.72 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.2, 151.4, 151.0, 143.1, 140.4, 137.7, 136.7, 131.5, 131.4, 129.6, 128.41, 128.35, 128.3, 127.7, 127.1, 126.4, 126.4, 123.7, 123.0, 116.3, 113.7, 93.0, 87.7, 70.0, 63.6, 56.2, 48.8, 46.4, 29.4, 29.1, 25.0, 24.9, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{39}H_{40}NO_6S$: $[M + H]^+$ 650.2571, found: 650.2578; HPLC (Chiralpak IF, *i*-propanol/hexane = 30/50, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 31.4 min, t_R (minor) = 28.1 min, 96% ee; $[\alpha]^{25}_D$ = - 63.8 (*c* = 0.2, $CHCl_3$).

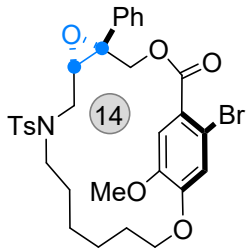
Expoidation



A solution of **3a** (62.8 mg, 0.1 mmol, 1.0 equiv.) in dichloromethane (2 mL) was cooled by an ice bath and added *m*-CPBA (34.5 mg, 70% w/w, 0.15 mmol, 2.0 equiv) portion wise. The reaction mixture was allowed to warm to room temperature slowly

and stir for 12 h. The reaction was then quenched with saturated $Na_2S_2O_3$ solution. The organic phase was filtered and the solvent was removed by rotary evaporation. The residue was purified by a silica gel flash chromatography (pentane/CH_2Cl_2 = 2:1) to afford the desired product **6** (48.8 mg, 76%, 96% ee, 11:1 dr).

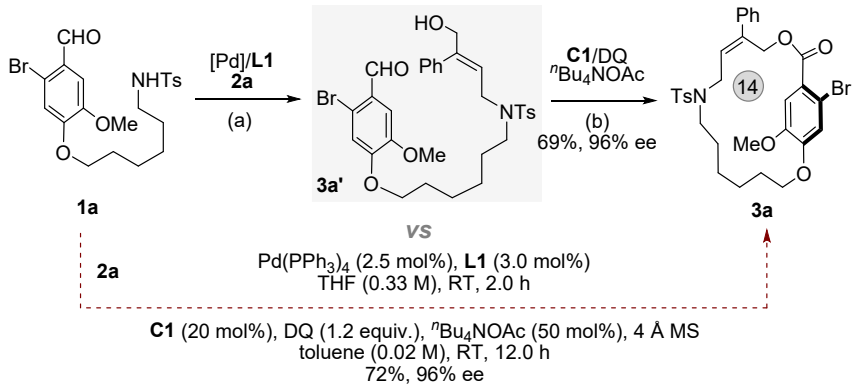
5^2-bromo-5^5-methoxy-1^2-phenyl-13-tosyl-3,6-dioxa-13-aza-1(2,3)-oxirana-5(1,4)-benzenacyclotetradecaphan-4-one (6)



6

Following the above procedure, the crude product was purified by column chromatography on a silica gel to afford the product **6** (48.8 mg, 76% yield) as colorless oil. **R_f** (pentane/CH_2Cl_2 = 2:1) = 0.30; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.35 (m, 6H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.23 (s, 1H), 5.18 (d, *J* = 12.6 Hz, 1H), 4.70 (d, *J* = 12.7 Hz, 1H), 4.39 – 4.29 (m, 2H), 4.05 (d, *J* = 16.0 Hz, 1H), 3.93 (s, 3H), 3.22 – 3.04 (m, 3H), 2.90 (ddd, *J* = 14.5, 9.5, 4.9 Hz, 1H), 2.43 (s, 3H), 1.63 (q, *J* = 6.0 Hz, 2H), 1.35 – 1.19 (m, 1H), 1.06 (dd, *J* = 14.2, 6.7 Hz, 1H), 0.95 – 0.76 (m, 3H), 0.76 – 0.56 (m, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.7, 151.3, 150.0, 143.3, 137.8, 137.6, 129.7, 128.6, 128.5, 127.1, 126.0, 125.8, 123.7, 115.5, 111.1, 69.9, 64.1, 61.9, 60.6, 56.3, 49.0, 46.0, 28.1, 27.8, 24.9, 24.8, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{35}BrNO_7S$: $[M + H]^+$ 644.1313, found: 644.1322; HPLC (Chiralpak IF, *i*-propanol/hexane = 38/42, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 31.8 min, t_R (minor) = 22.4 min, 98% ee; $[\alpha]^{25}_D$ = - 46.2 (*c* = 0.2, $CHCl_3$).

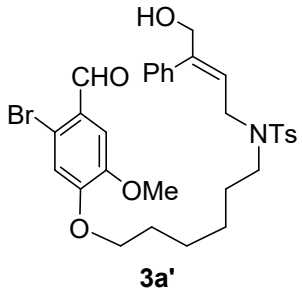
Control Experiments



To a flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added the catalyst $Pd(PPh_3)_4$ (2.9 mg, 0.025 mmol), **L1** (1.3 mg, 0.03 mmol), toluene (1.0 mL) was added. The mixture was then stirred at room temperature for 0.5 h. After that, **1a** (48.4 mg, 0.1 mmol) and **2a** (28.5 mg, 0.15 mmol) were added sequentially under Ar. The reaction mixture was then stirred at room temperature for 2 h. Then the mixture was purified by a silica gel flash chromatography (pentane/EtOAc = 2:1) directly to afford the desired product **3a'** (60.5 mg, 96%).

To a solution of pre-NHC catalyst **C1** (20 mol%), $^{n}Bu_4NOAc$ (50 mol%), DQ (0.12 mmol) and 4Å MS 50 mg in toluene (4.0 mL), the obtained 3a' (60.5 mg) was added and stirred at room temperature for another 12 h (monitored by TLC). After the reaction was completed, the reaction mixture was filtered and concentrated. The residue was purified by a silica gel flash chromatography (Hexane/EtOAc = 5:1) to afford the desired product **3a** in 72% yield (43.2 mg) in total and with 96% ee.

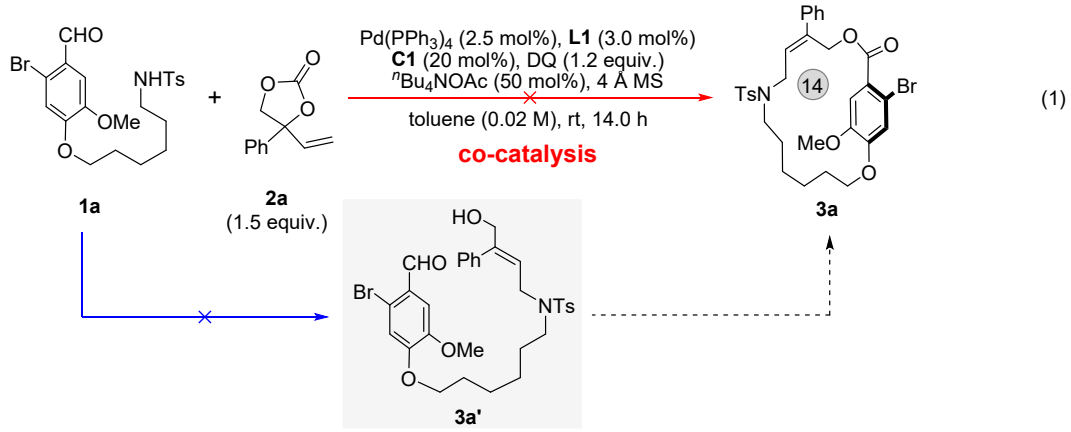
(*E*)-N-(6-(5-bromo-4-formyl-2-methoxyphenoxy)hexyl)-N-(4-hydroxy-3-phenylbut-2-en-1-yl)-4-methylbenzenesulfonamide (3a')



Following the above procedure, the crude product was purified by column chromatography on a silica gel to afford the product **3a'** (60.5 mg, 96% yield) as colorless oil. $\mathbf{R_f}$ (pentane/EtOAc = 2:1) = 0.20; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ

10.20 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.42 (s, 1H), 7.37 – 7.29 (m, 7H), 7.04 (s, 1H), 5.71 (t, J = 7.1 Hz, 1H), 4.57 (s, 2H), 4.09 (d, J = 7.1 Hz, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.90 (s, 3H), 3.22 (t, J = 7.4 Hz, 2H), 2.43 (s, 3H), 1.87 (p, J = 6.8 Hz, 2H), 1.66 (p, J = 7.4 Hz, 2H), 1.50 (dt, J = 14.7, 7.0 Hz, 2H), 1.42 (dd, J = 14.5, 7.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 190.8, 154.2, 149.1, 143.3, 141.9, 140.1, 137.0, 129.7, 128.5, 127.8, 127.2, 126.3, 126.3, 126.2, 120.4, 116.3, 110.7, 69.3, 59.6, 56.1, 48.2, 45.7, 28.7, 28.5, 26.3, 25.5, 21.5; **HRMS** (ESI): *m/z*: calculated for $C_{31}H_{37}BrNO_6S$: $[M + H]^+$ 630.1520, found: 630.1526.

Mechanistic Studies



(1)

The result of equation (1) indicates that the co-catalytic process is impermissible, and the Pd-catalyzed process is prohibited by some factor. Therefore, control experiments were performed as bellow.

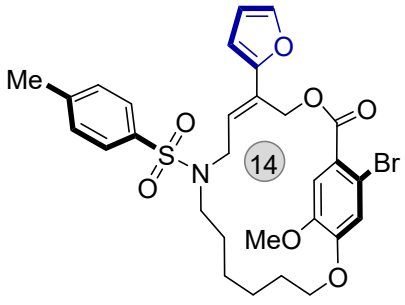
entry	conditions	yield (%)
1	$Pd(PPh_3)_4$ (2.5 mol%), **L1** (3 mol%)	96
2	$Pd(PPh_3)_4$ (2.5 mol%), **L1** (3 mol%), DQ (1.2 equiv.)	92
3	$Pd(PPh_3)_4$ (2.5 mol%), **L1** (3 mol%), DQ (1.2 equiv.), ^{n}Bu$_4$NOAc (50 mol%)	93

4	$Pd(PPh_3)_4$ (2.5 mol%), **L1** (3 mol%), DQ (1.2 equiv.), $^nBu_4NOAc$ (50 mol%), **C1** (20 mol)	no product
5	$Pd(PPh_3)_4$ (2.5 mol%), $^nBu_4NOAc$ (50 mol%), **C1** (20 mol)	no product

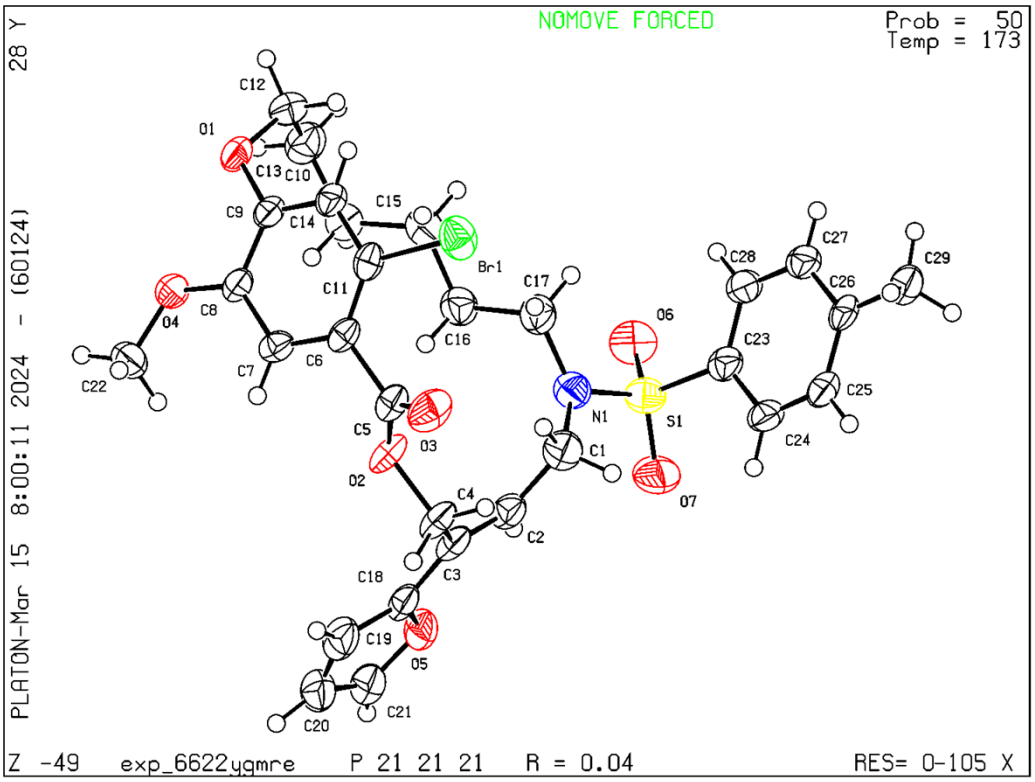
Above results shows that the **C1** affects the Pd-catalyzed process. **According the literature,[6] the probable reason is that there are formed a stable complex between generated free carbebe and palladium, which is consistent with the nature of the strong coordination between palladium and free carbene.**

Crystal Structure of 3q

Single crystals of **3q** (50 mg) were grown in CH_2Cl_2/hexane = 10:1 (1.5 mL). The 1.5 mL vial was capped and placed at room temperature in the experimental cabinet for 5 days, whereupon crystals formed. A clear light colorless block shaped crystal of **3q** was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 173 K, on an AtlasS2 diffractometer. The crystal data of **3q** have been deposited in CCDC and have been displayed at 50% ellipsoid contour probability level.



3q



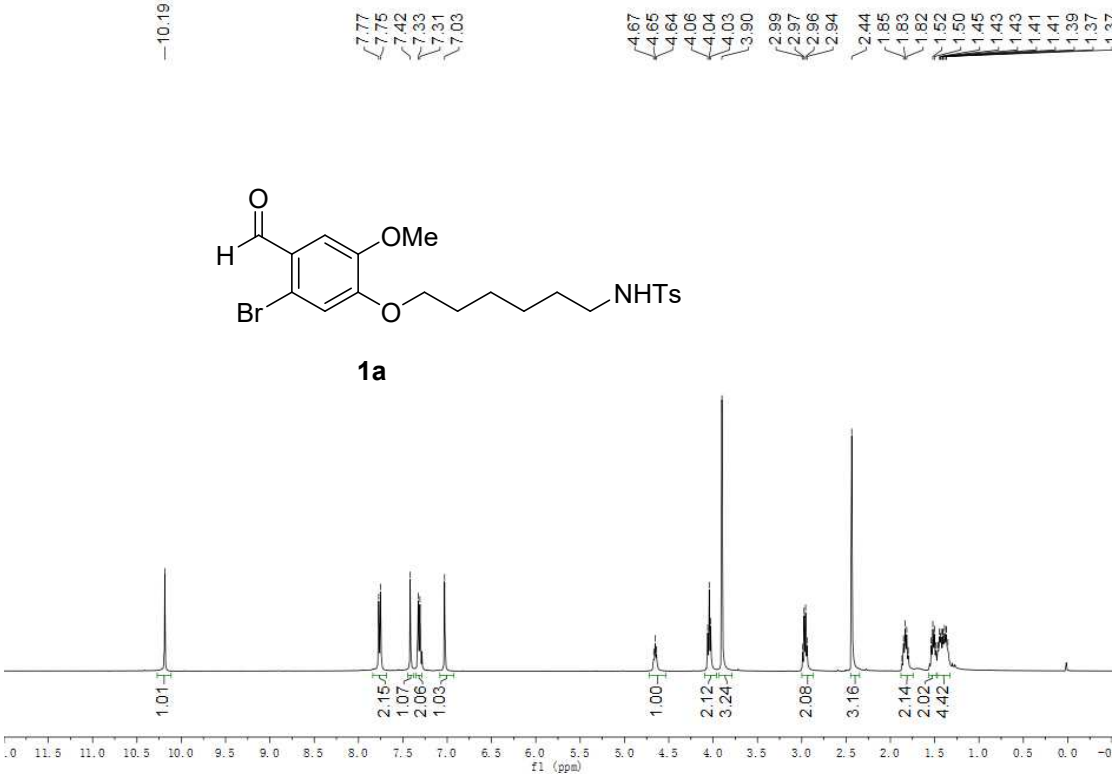
Crystal data and structure refinement for exp_6622YGMre

Identification code	exp_6622YGMre
Empirical formula	$C_{29}H_{32}BrNO_7S$
Formula weight	618.53
Temperature / K	172.99(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a / Å, b / Å, c / Å	9.65444(8), 11.52287(10), 25.33694(19)
α/°, β/°, γ/°	90.00, 90.00, 90.00
Volume / Å^3	2818.65(4)
Z	4
ρ_{calc} / mg mm^{-3}	1.458
μ / mm^{-1}	3.079
F(000)	1280
Crystal size / mm^3	0.2 × 0.1 × 0.1
2Θ range for data collection	6.98 to 133.48°
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $-30 \le l \le 30$
Reflections collected	80404
Independent reflections	4948[R(int) = 0.1334]
Data/restraints/parameters	4948/0/355

Goodness-of-fit on F^2	1.082
Final R indexes [I>2σ (I) i.e. F_o>4σ (F_o)]	R_1 = 0.0447, wR_2 = 0.1203
Final R indexes [all data]	R_1 = 0.0448, wR_2 = 0.1204
Largest diff. peak/hole / e $Å^{-3}$	0.673/-0.583
Flack Parameters	-0.003(18)
Completeness	0.9851

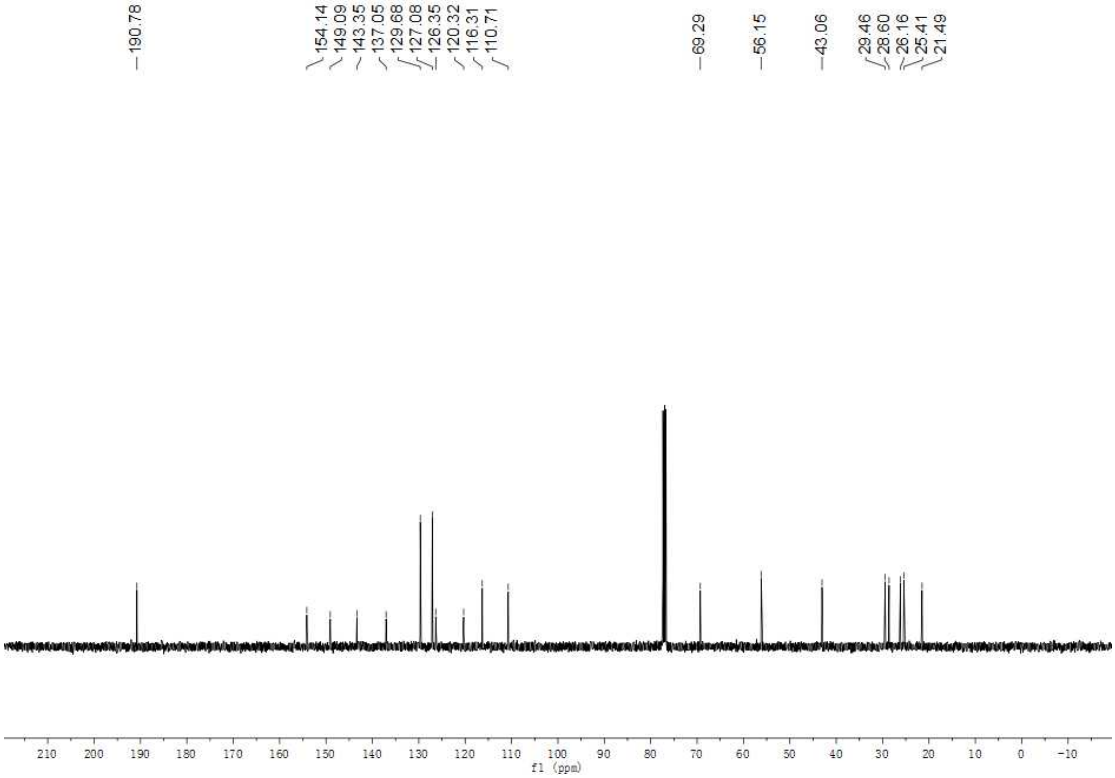
NMR Spectra

^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1a

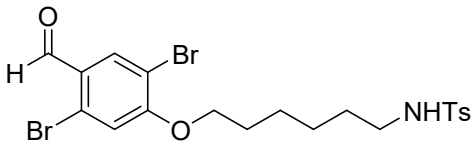


1a

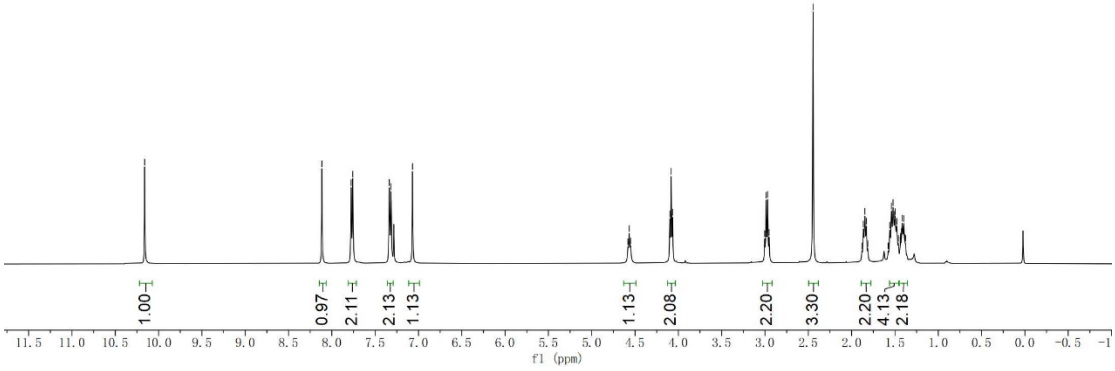
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1a



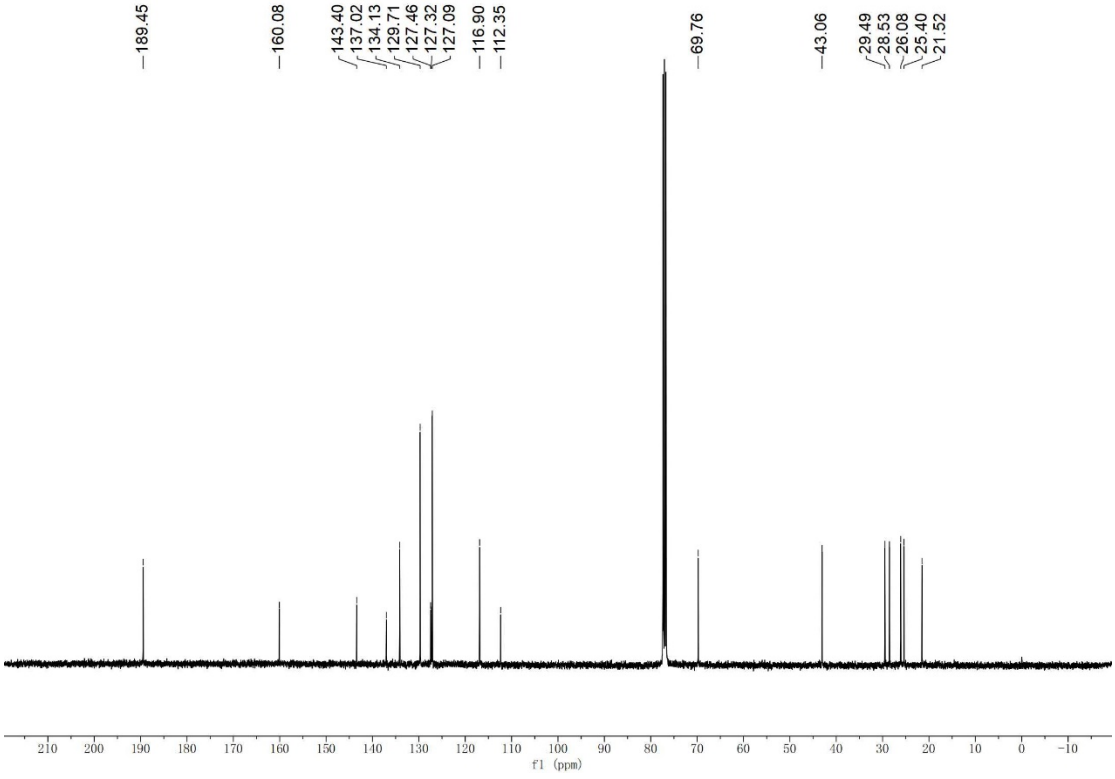
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1b



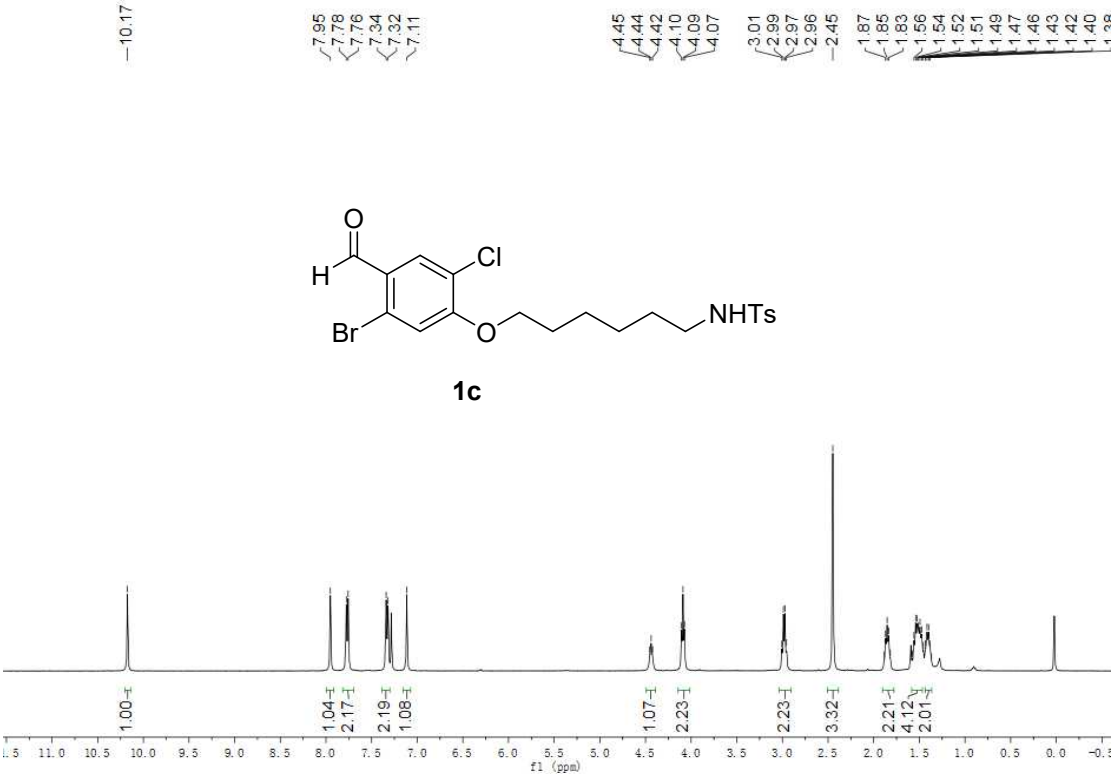
1b



^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1b

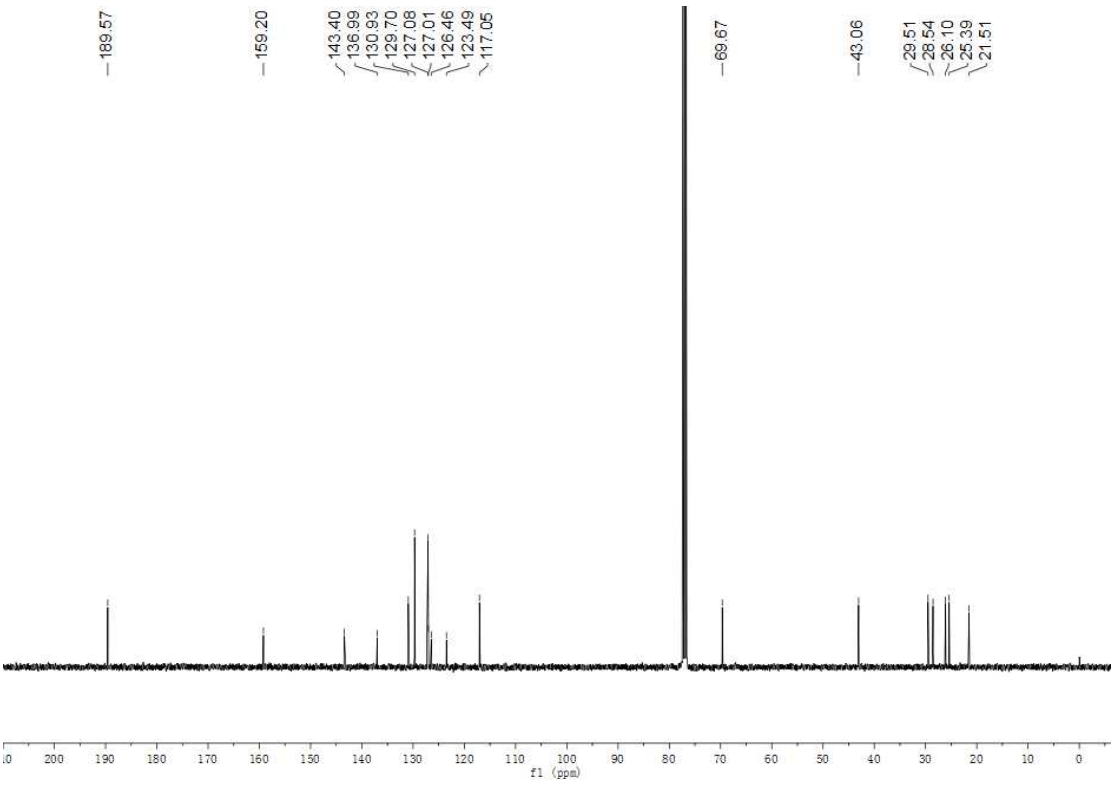


^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1c

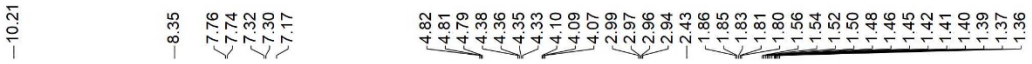


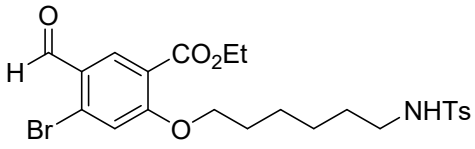
1c

^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1c

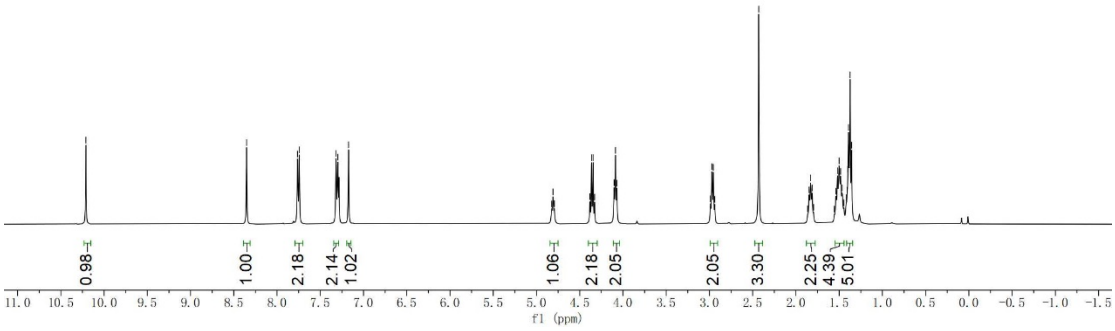


^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1d

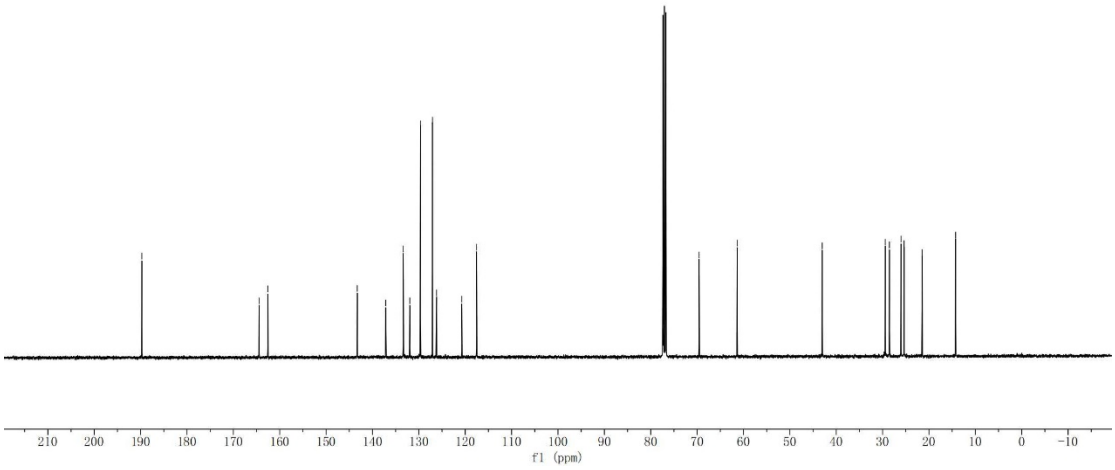




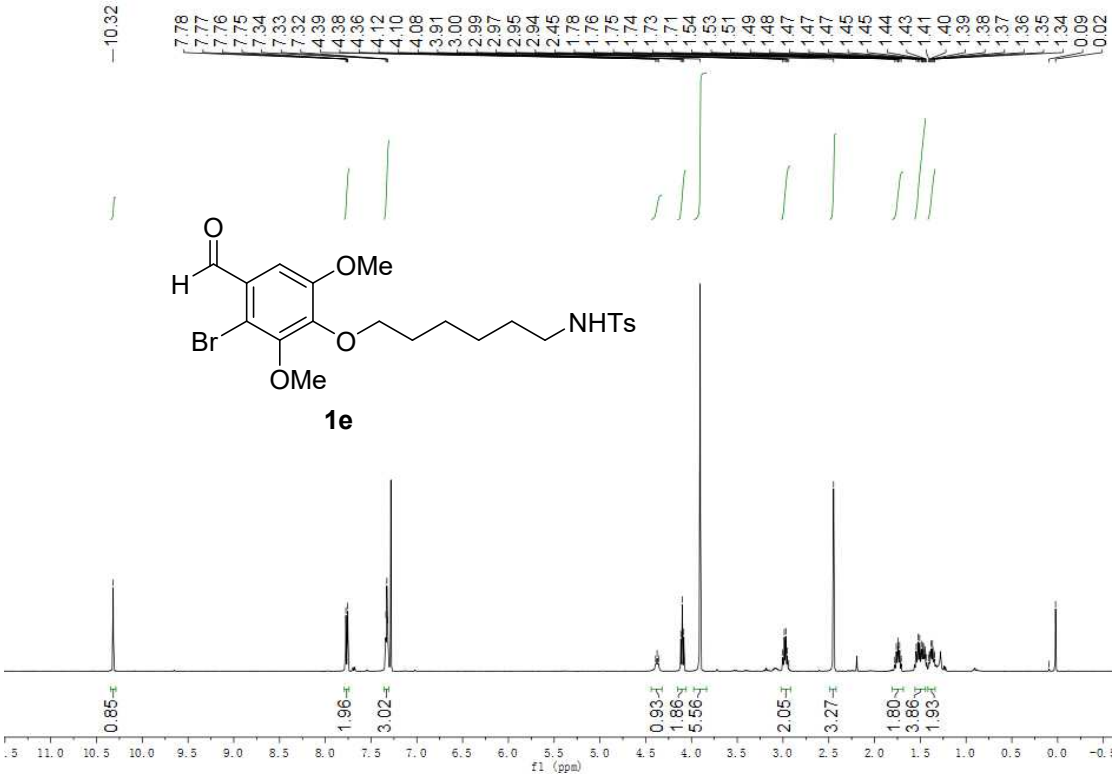
1d



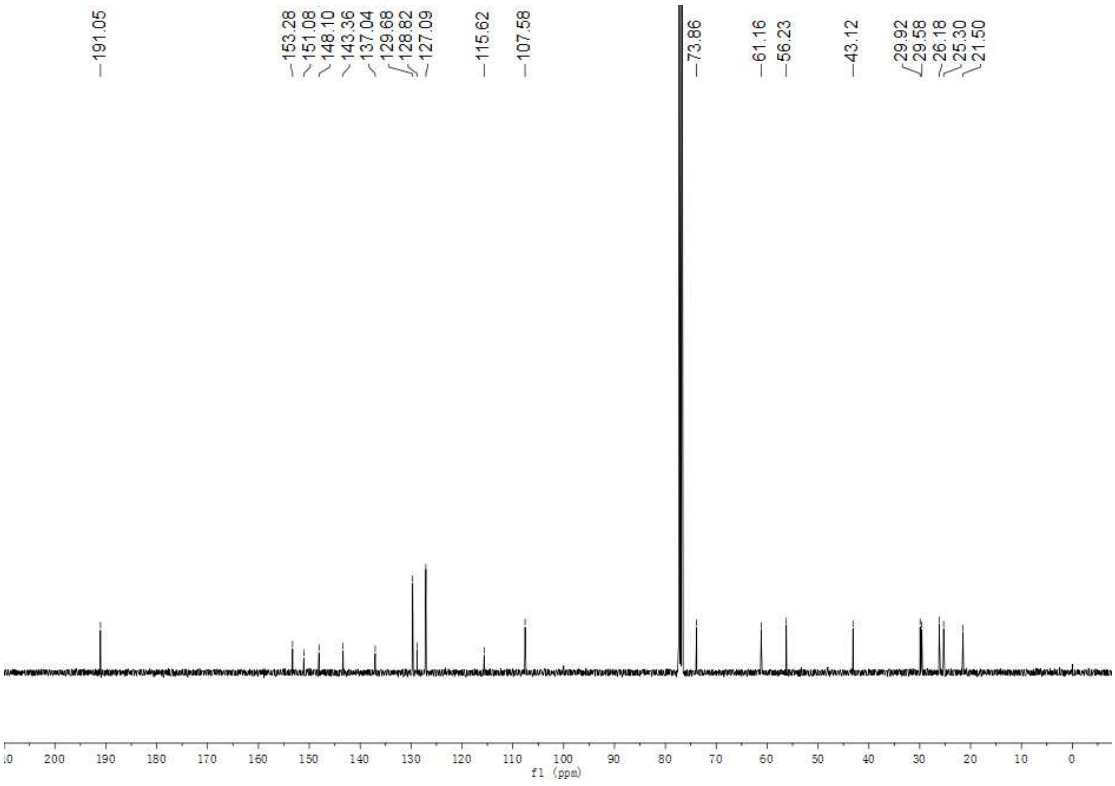
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1d



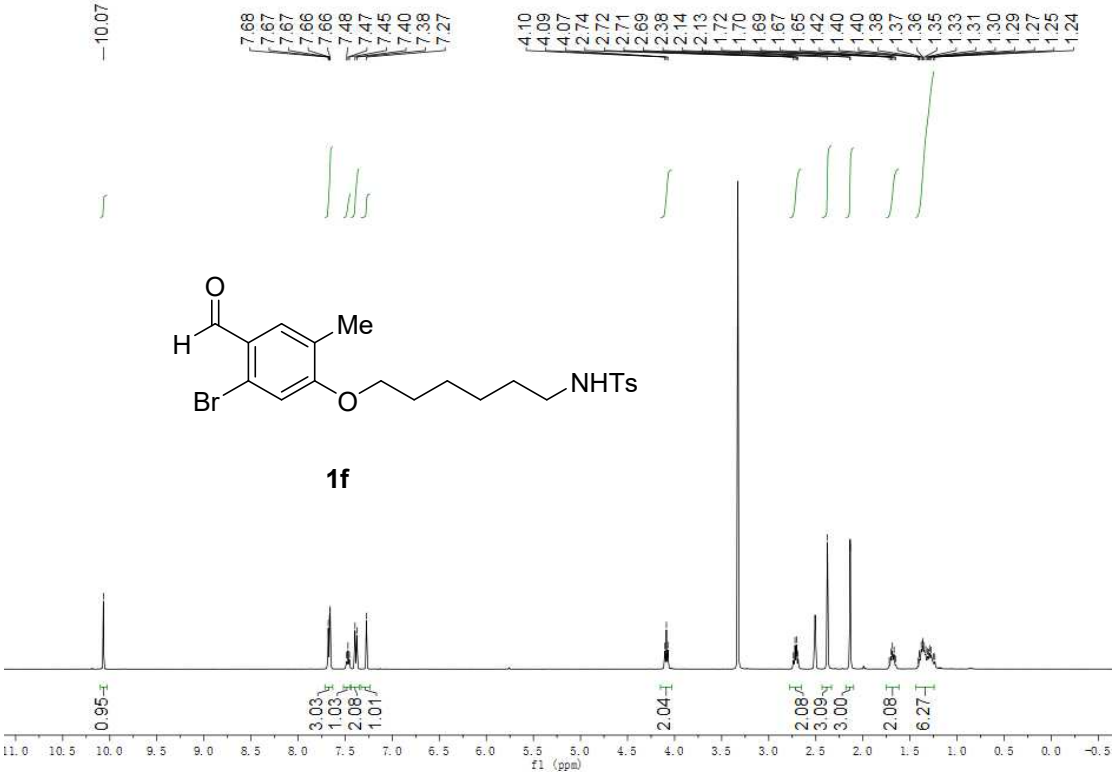
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1e



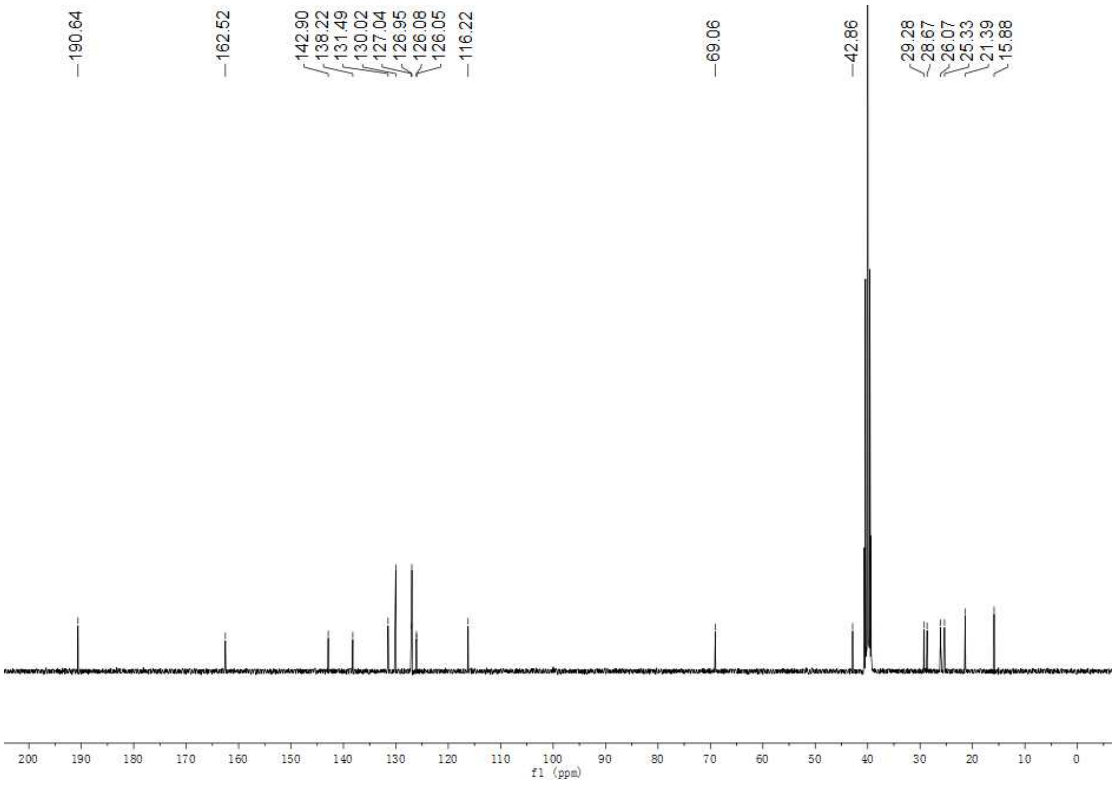
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1e



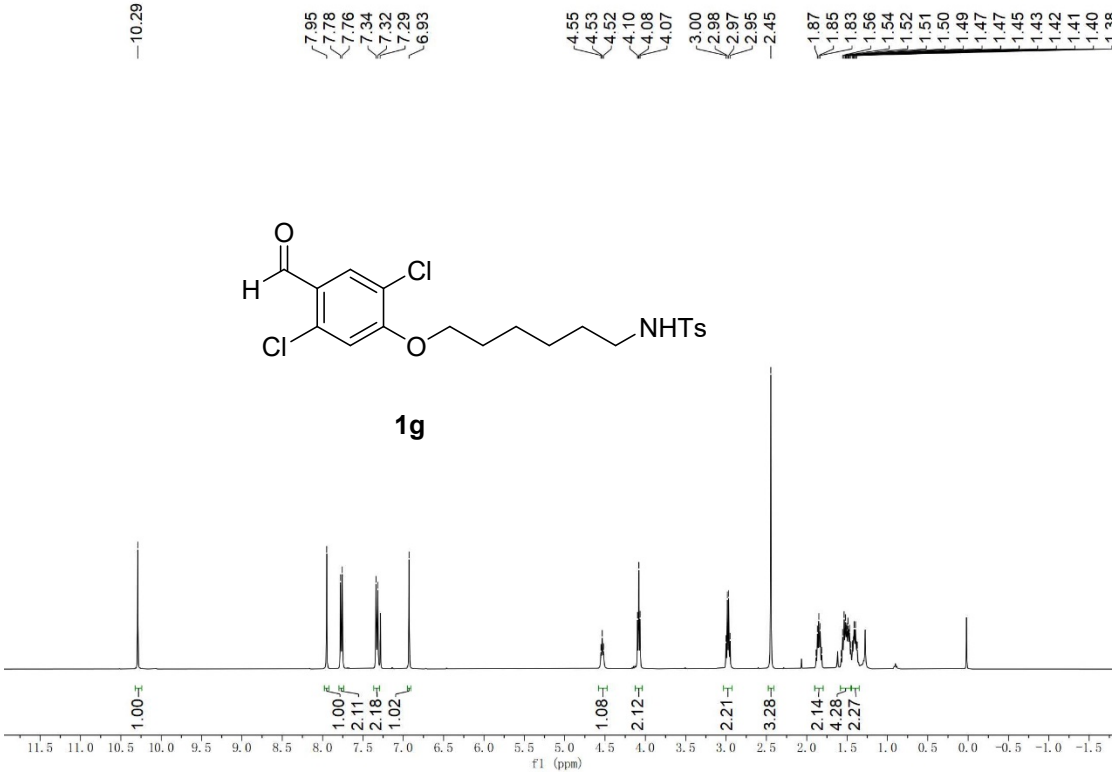
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1f



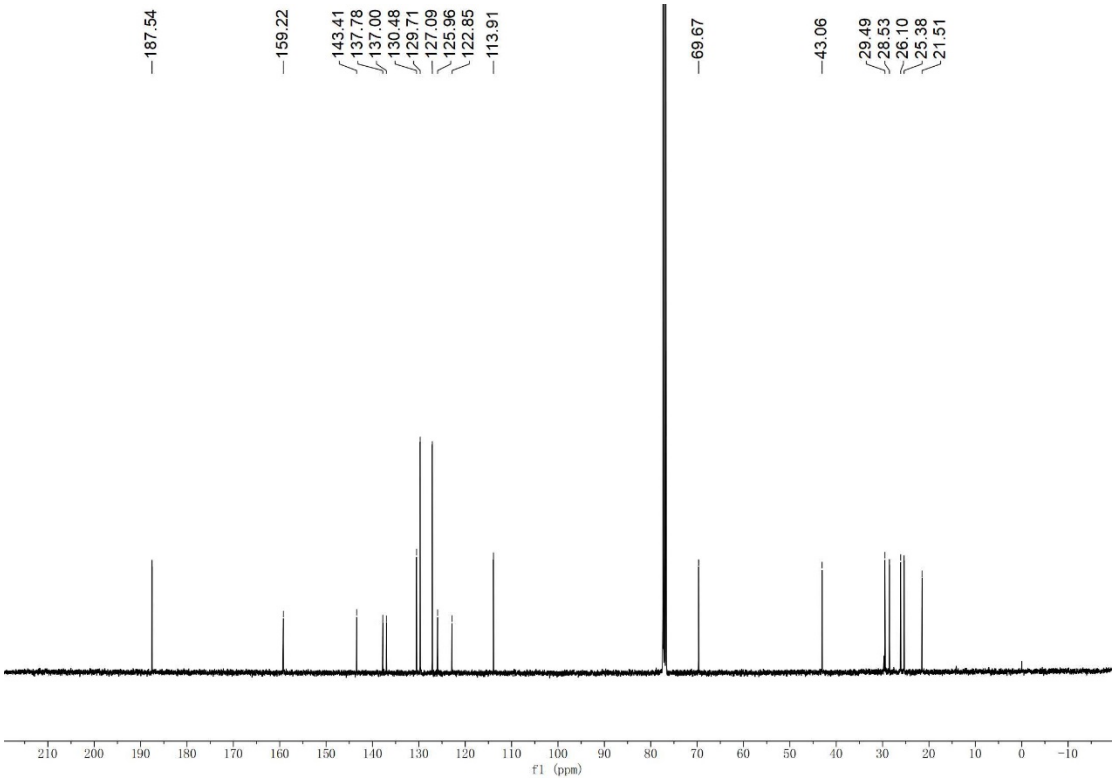
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1f



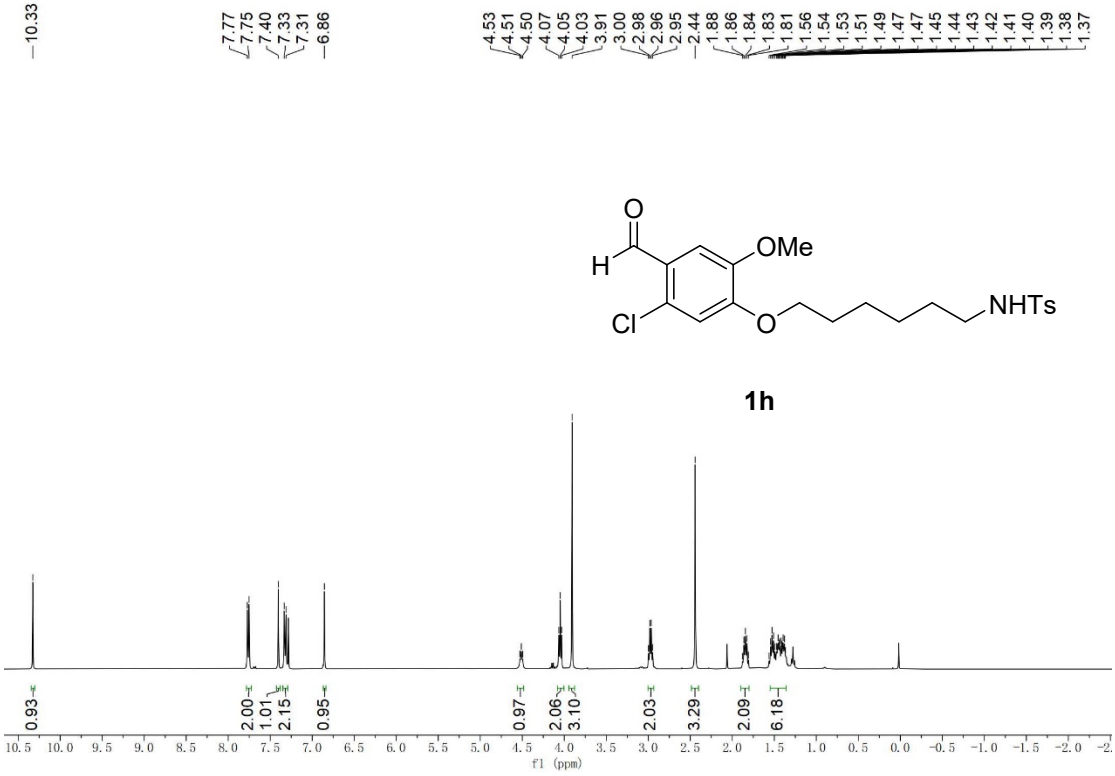
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1g



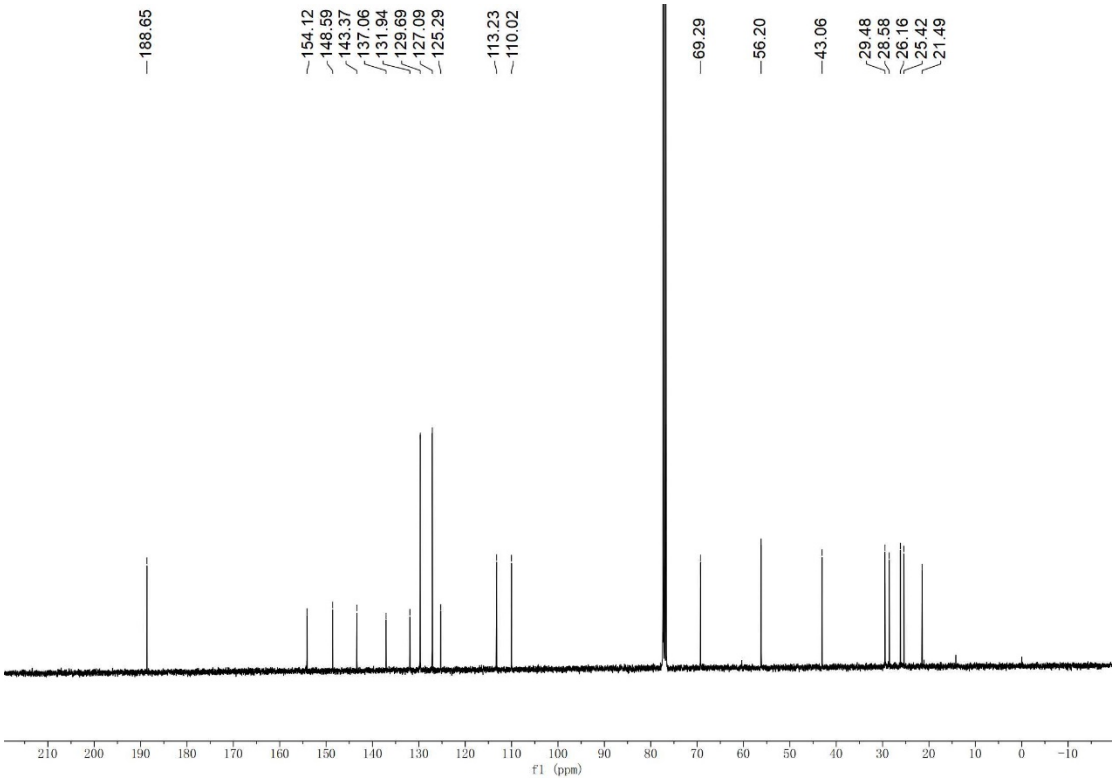
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1g



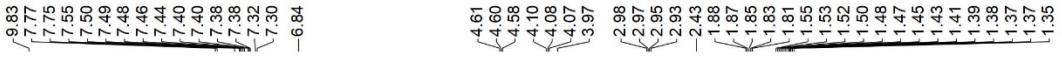
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1h

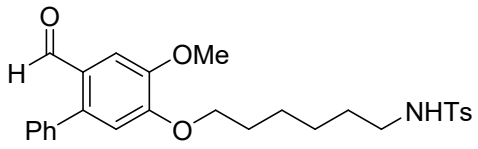


^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1h

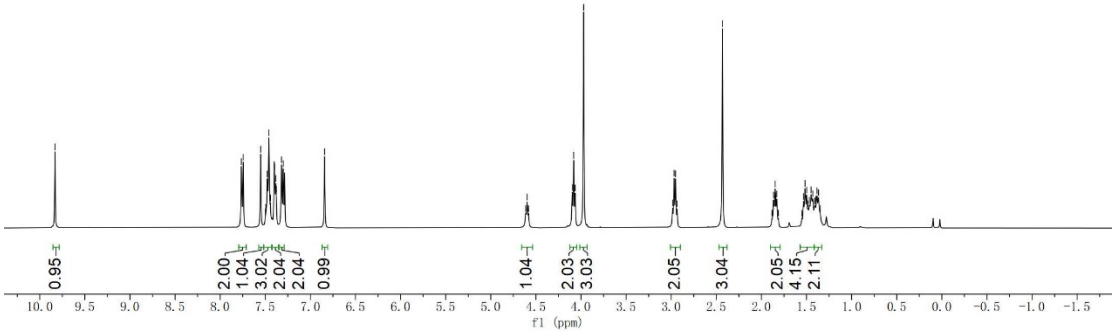


^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1i

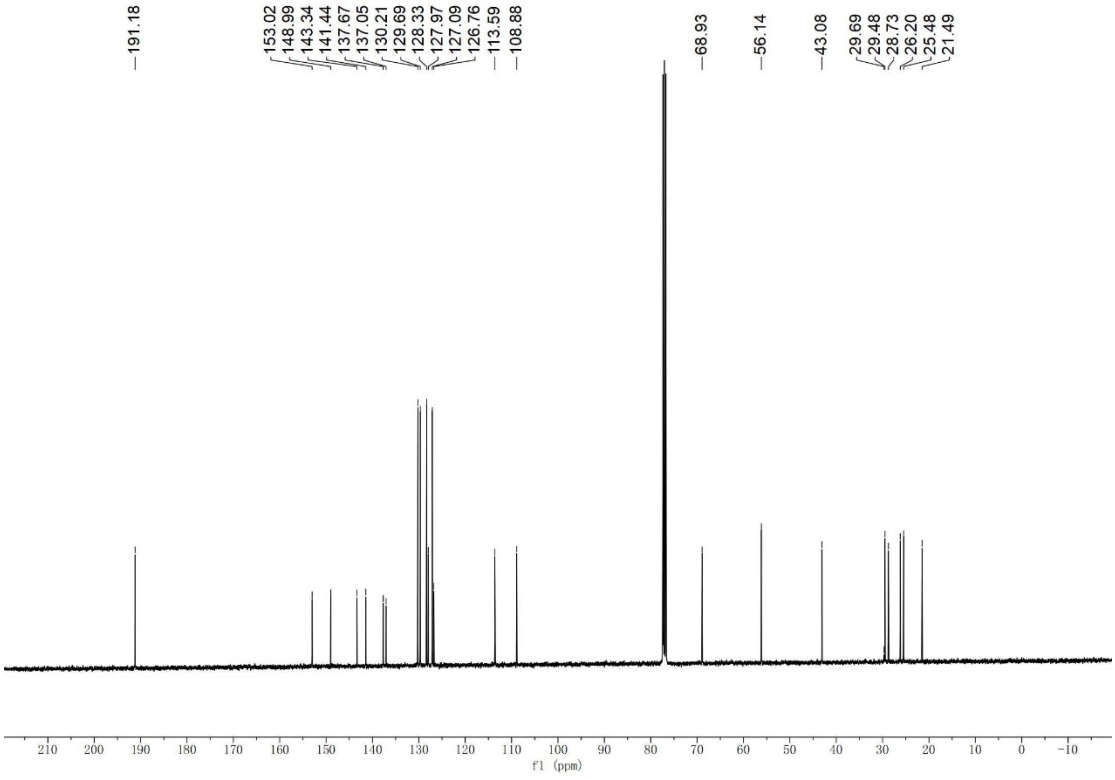




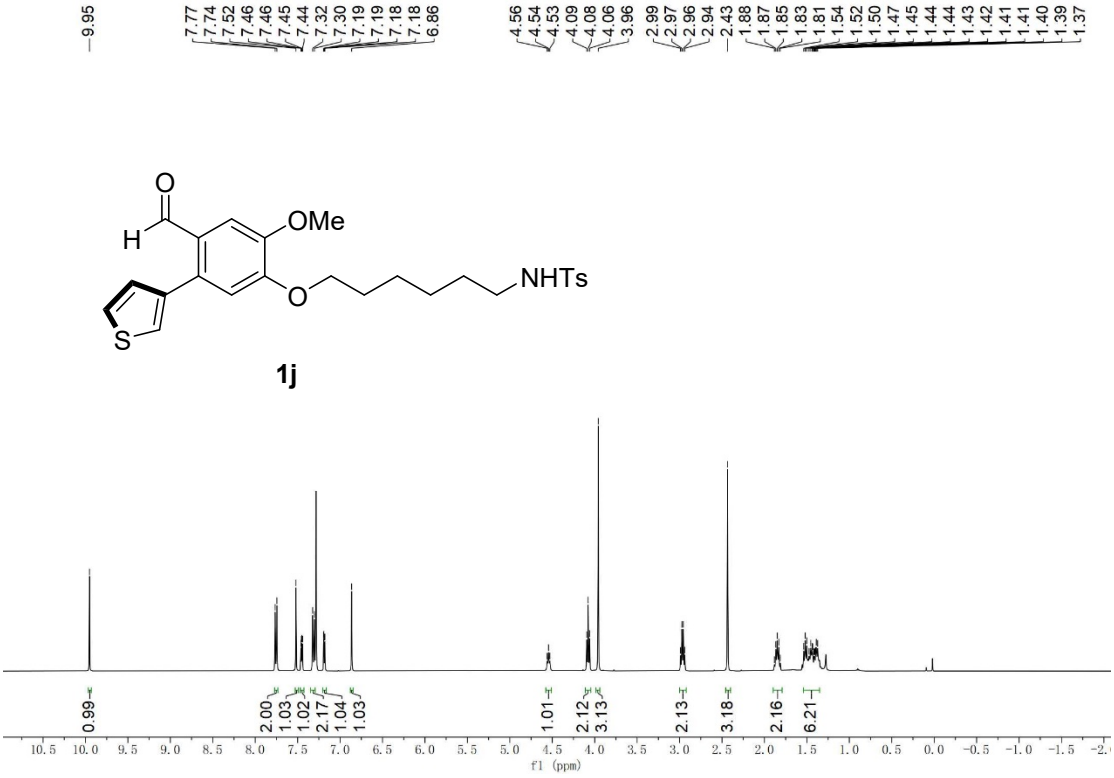
1i



^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1i

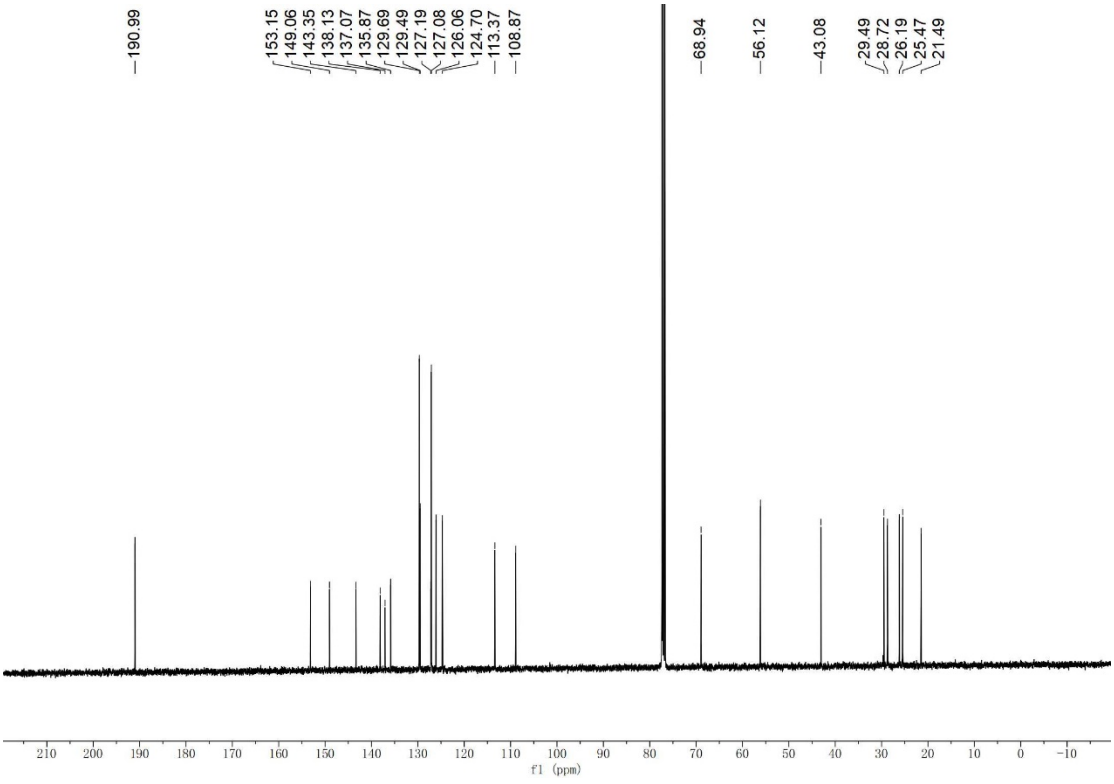


^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1j

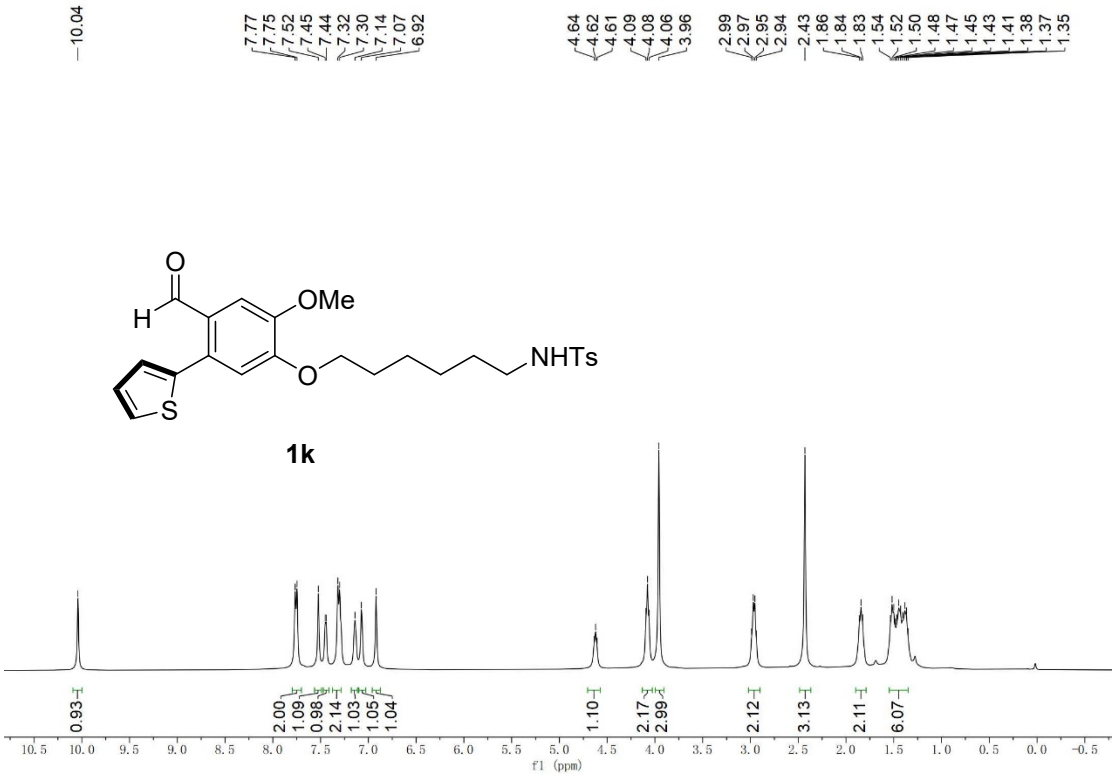


1j

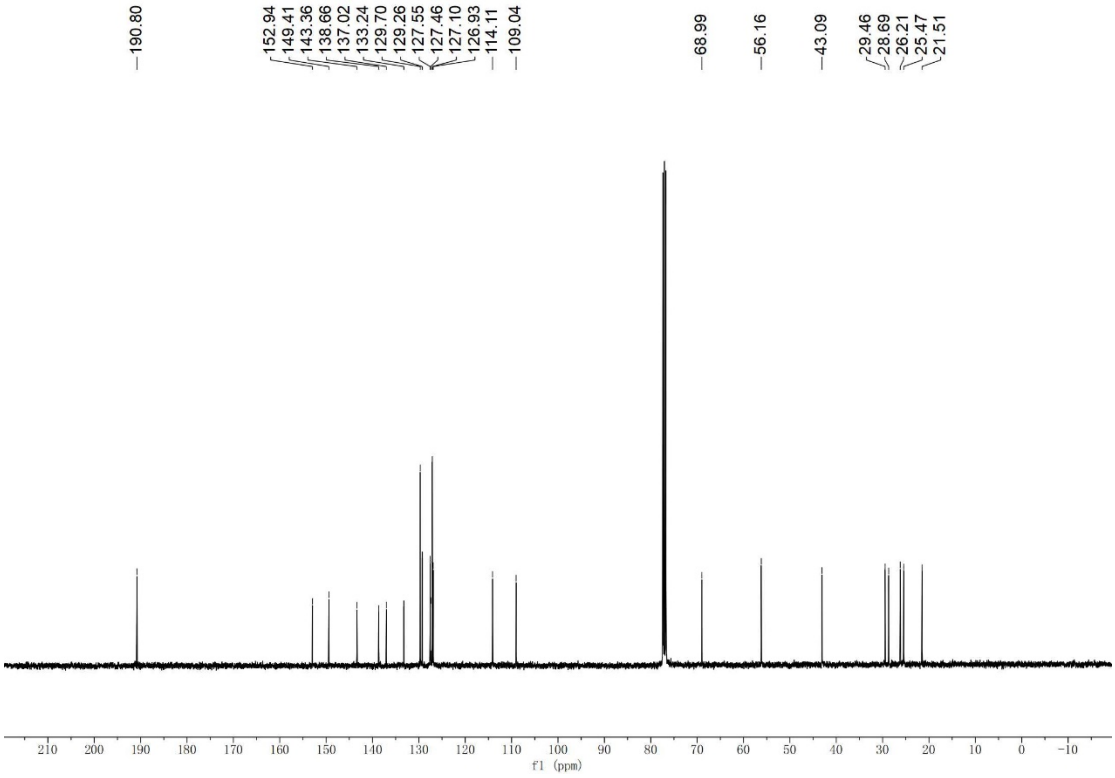
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1j



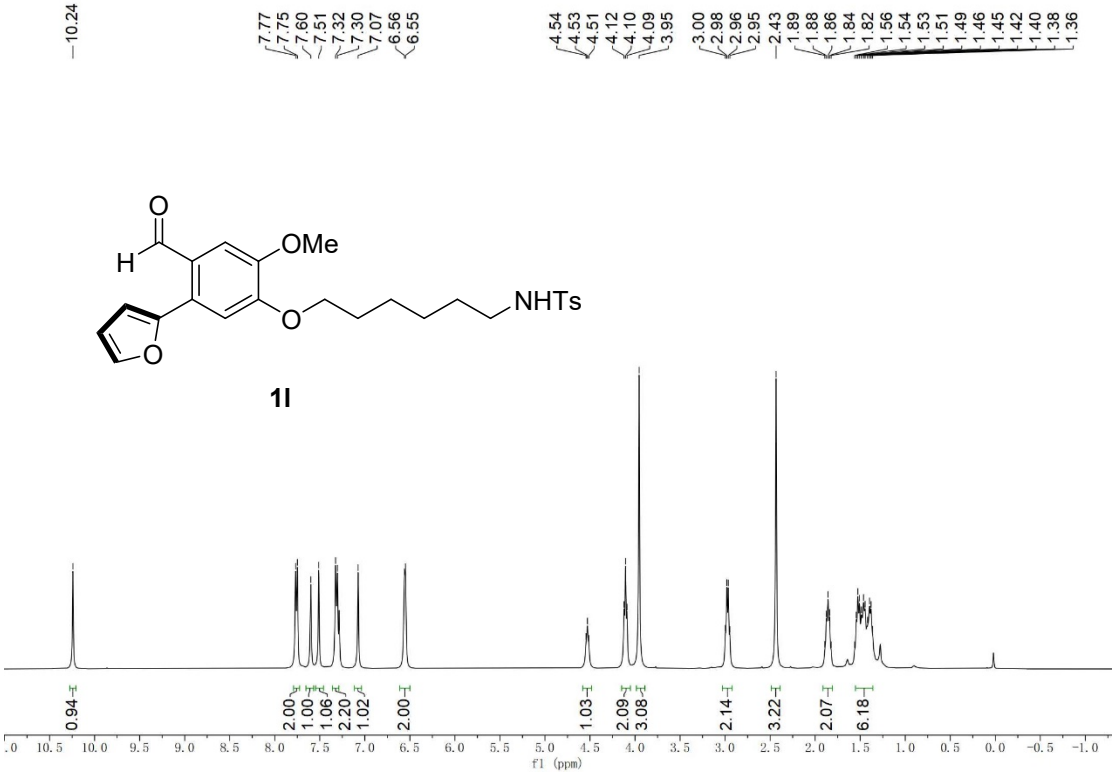
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1k



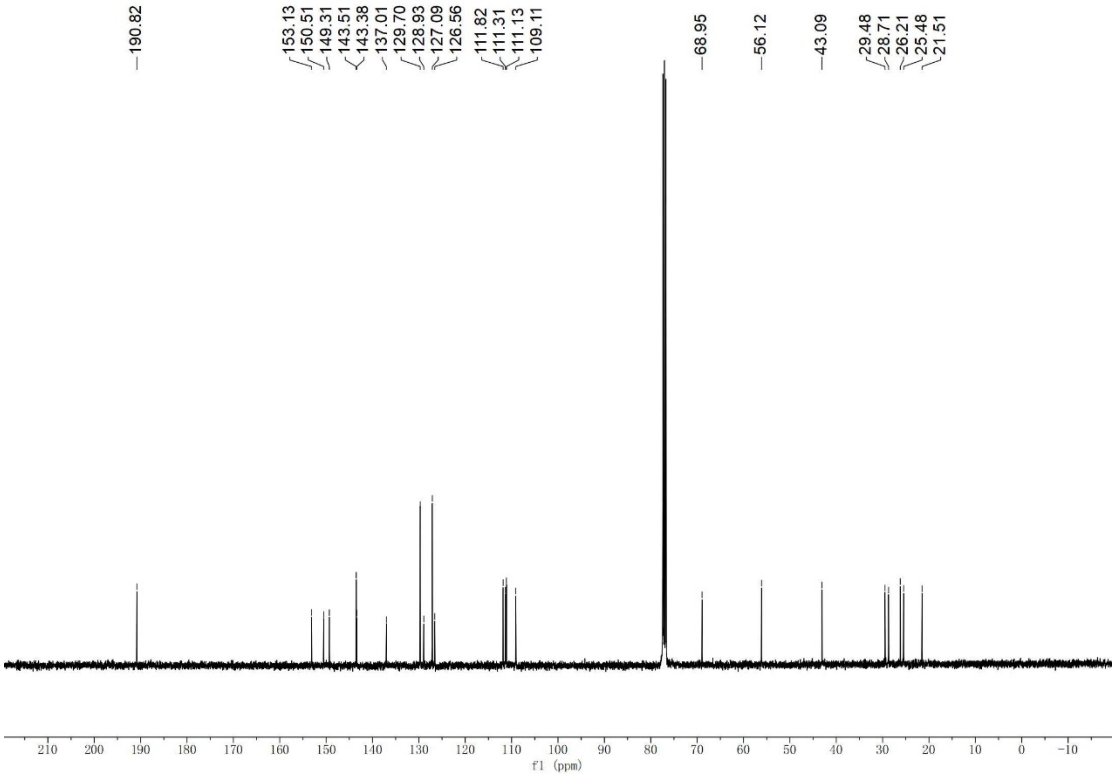
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1k



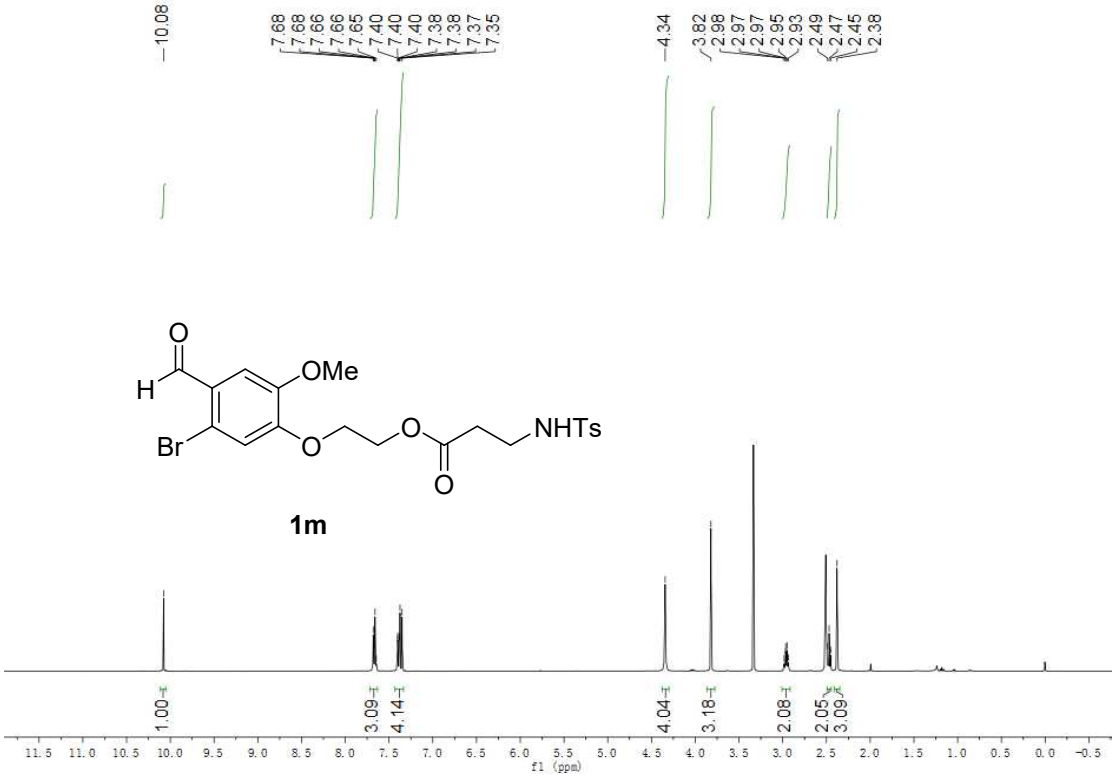
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1l



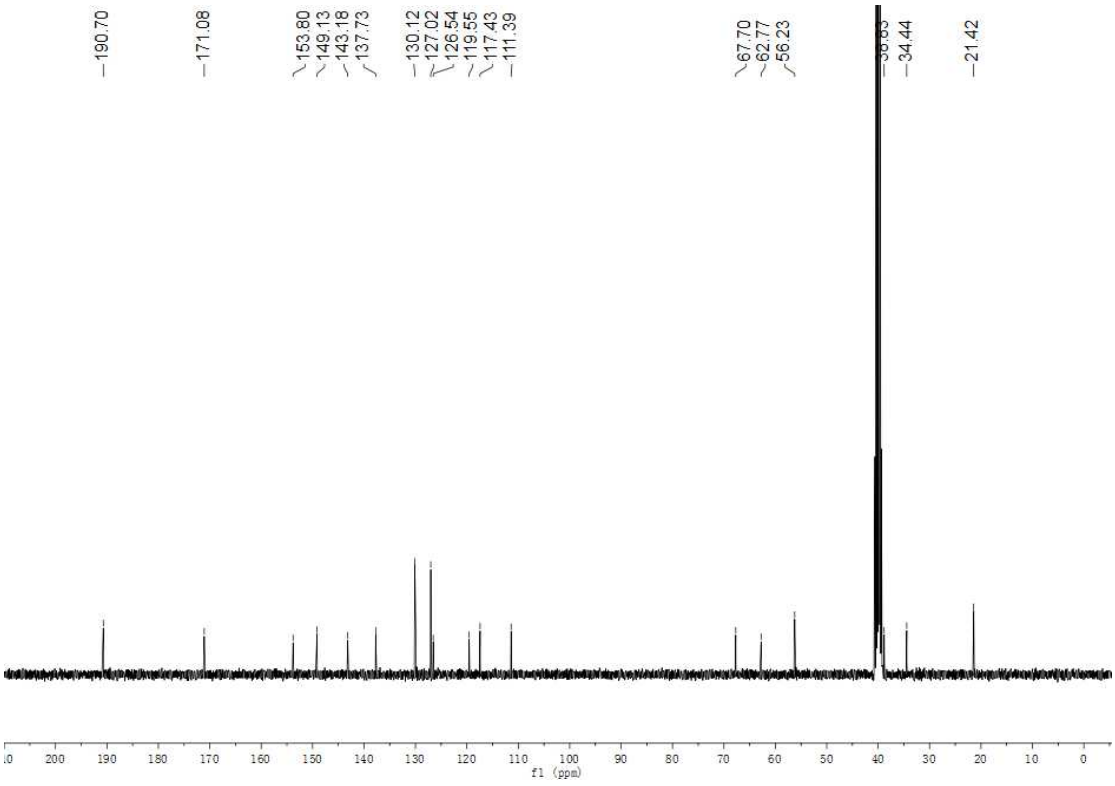
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1l



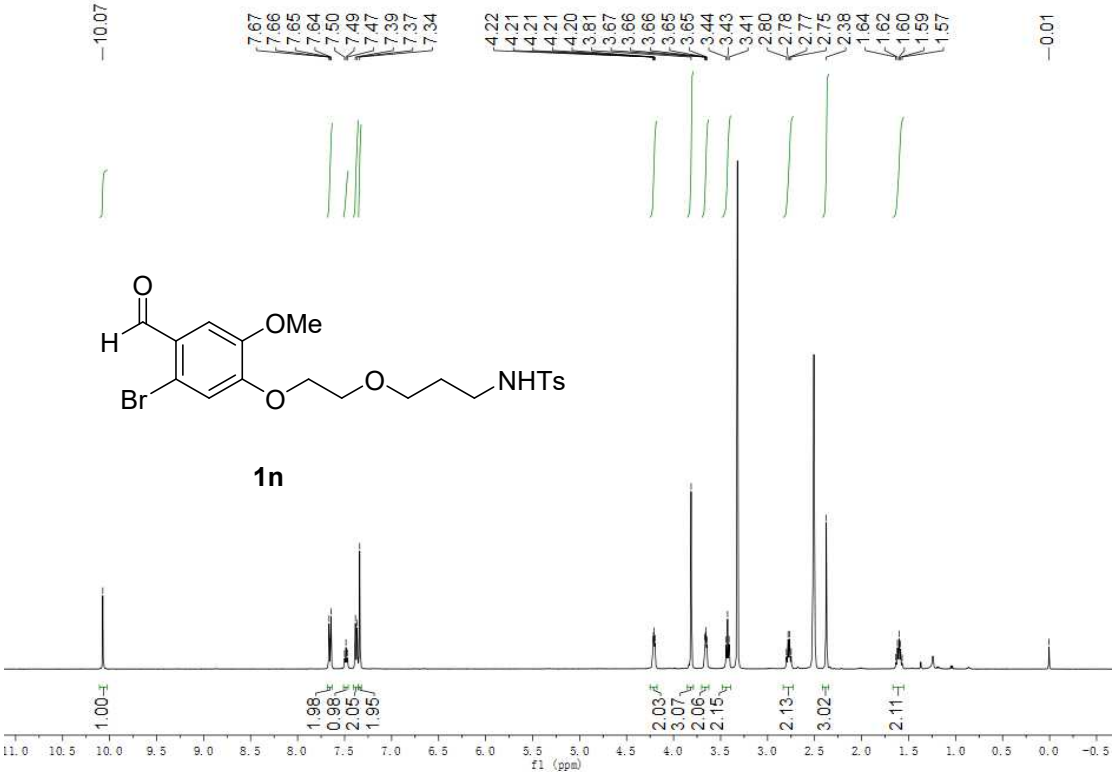
^{1}H NMR (400 MHz, DMSO-d_6) spectra of 1m



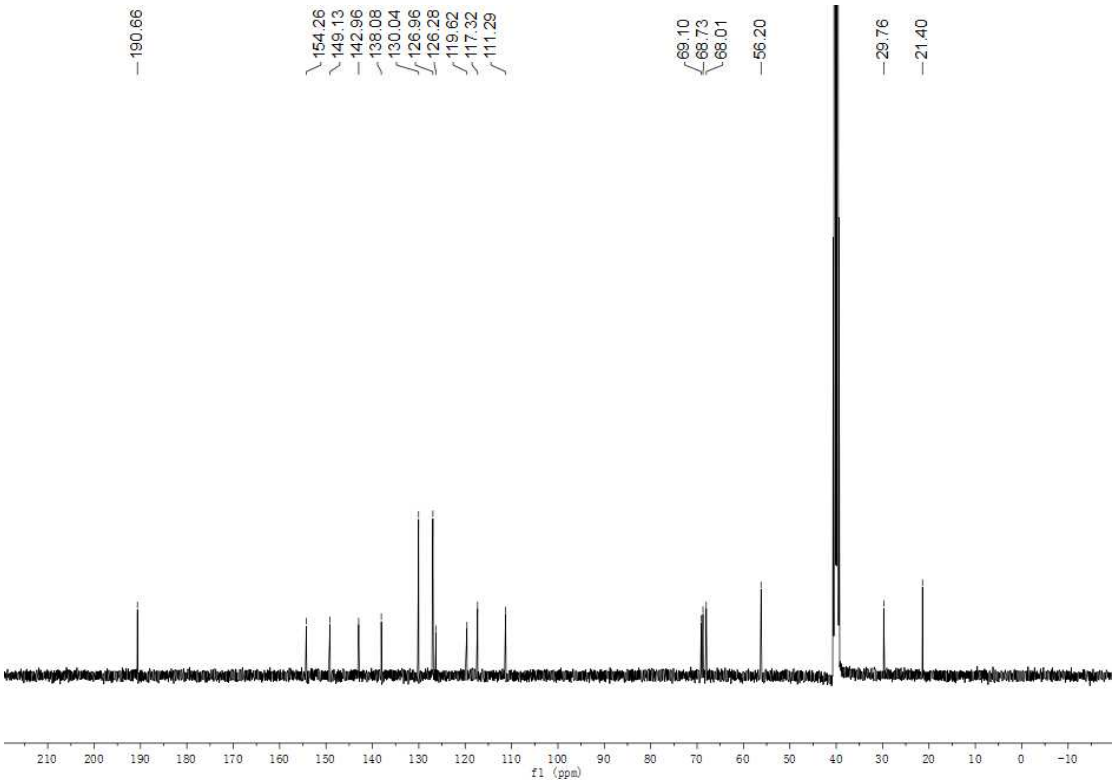
^{13}C NMR (100 MHz, DMSO-d_6) spectra of 1m



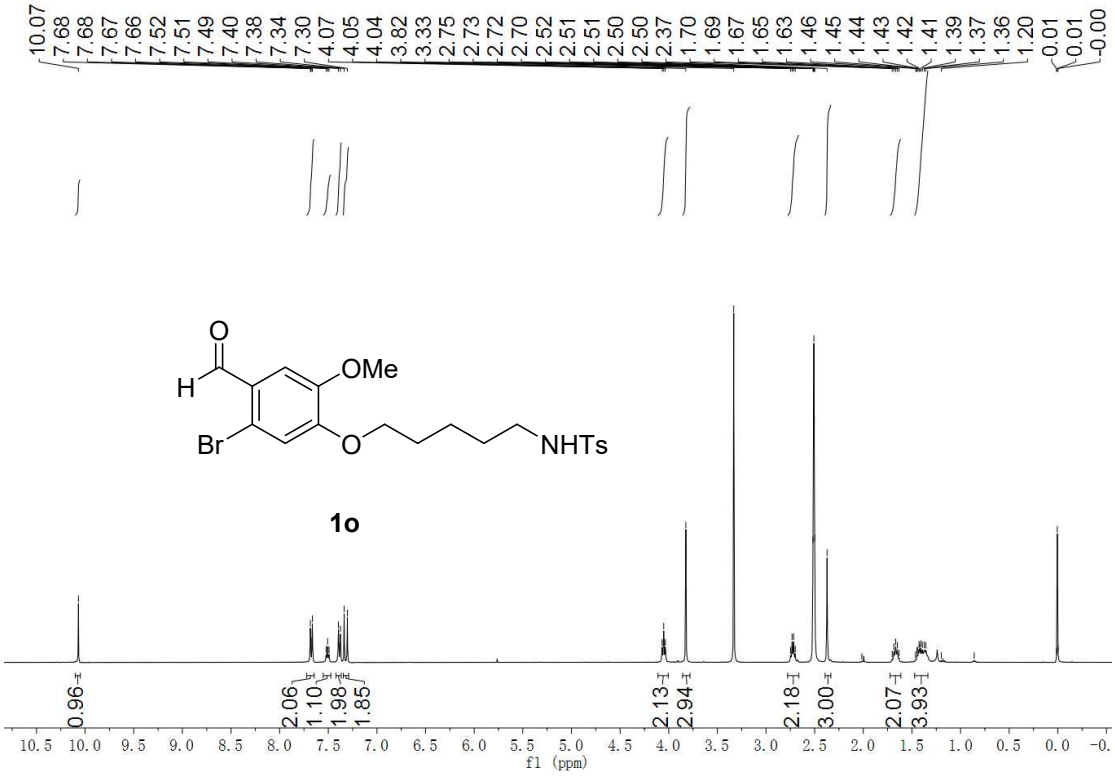
^{1}H NMR (400 MHz, DMSO-d_6) spectra of 1n



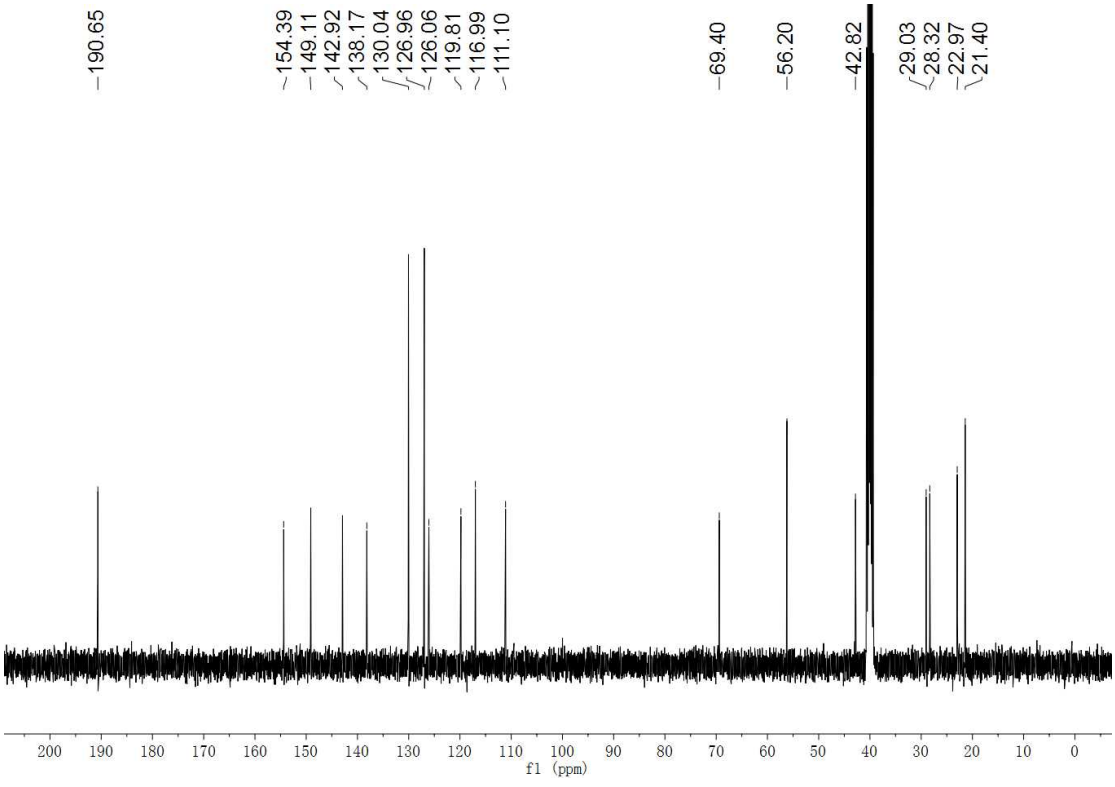
^{13}C NMR (100 MHz, DMSO-d_6) spectra of 1n



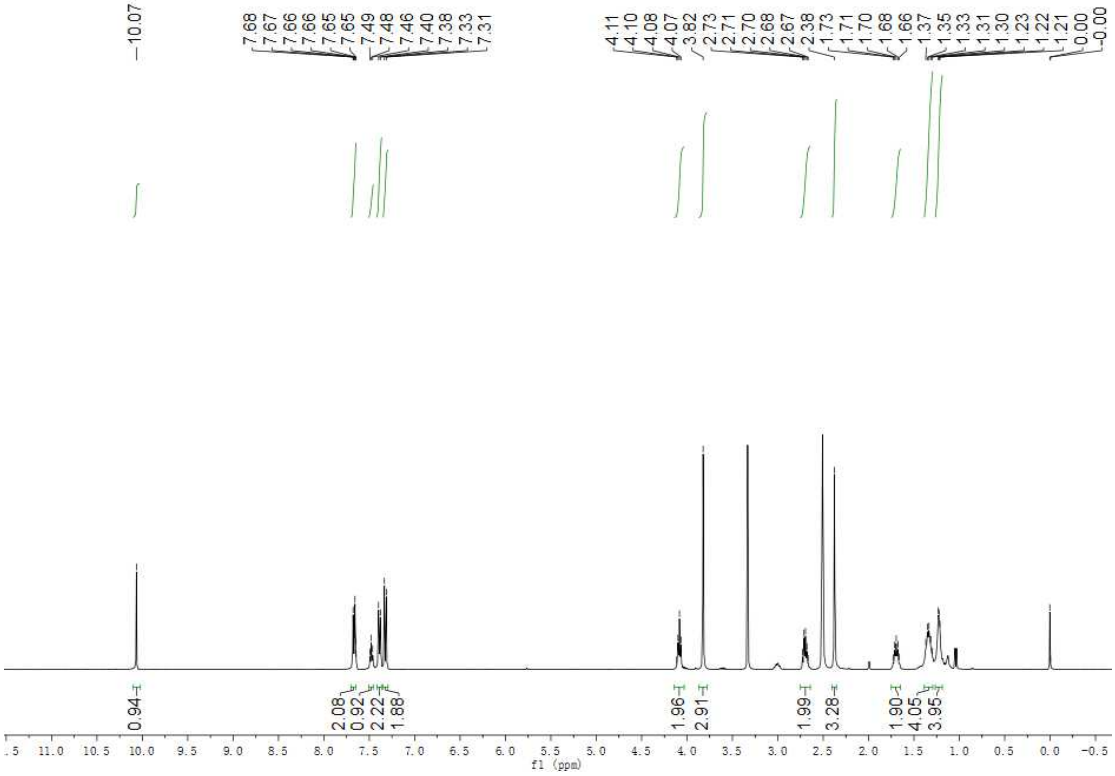
^{1}H NMR (400 MHz, DMSO-d_6) spectra of 1o



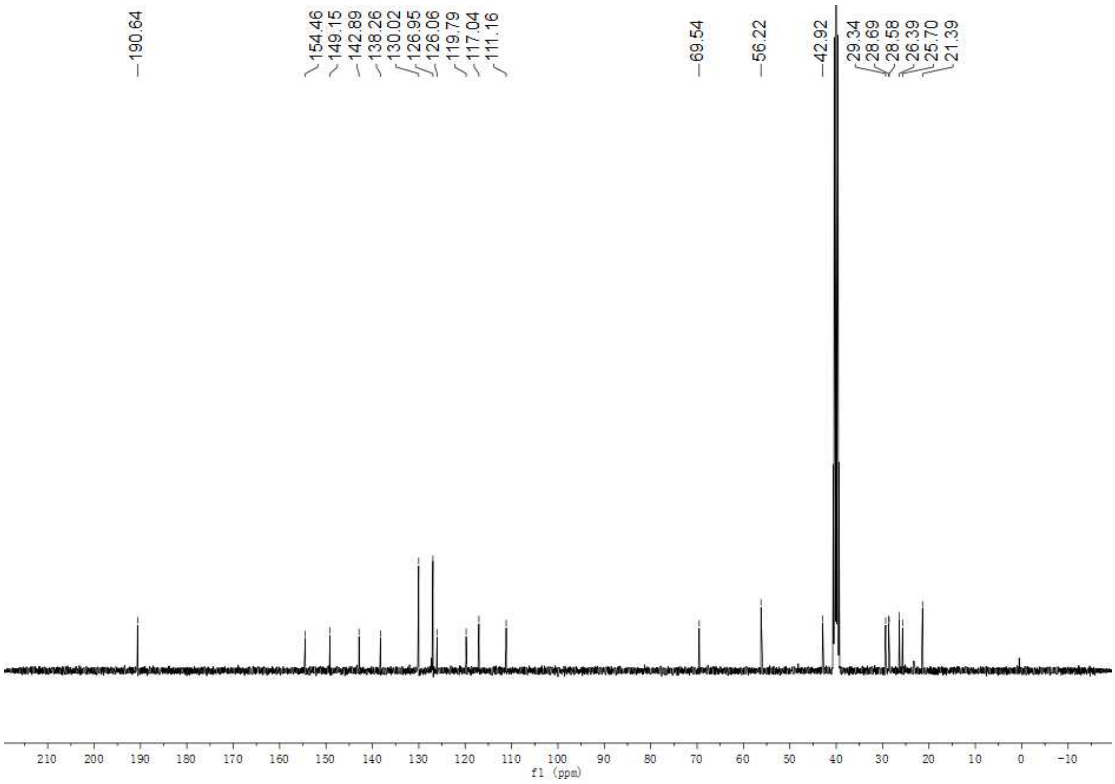
^{13}C NMR (100 MHz, DMSO-d_6) spectra of 1o



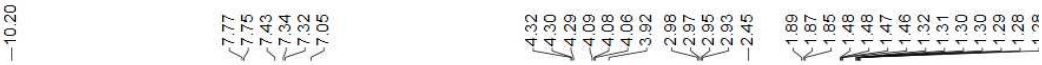
^{1}H NMR (400 MHz, DMSO-d_6) spectra of 1p

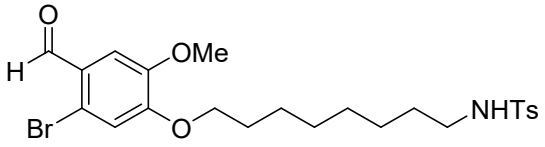


^{13}C NMR (100 MHz, DMSO-d_6) spectra of 1p

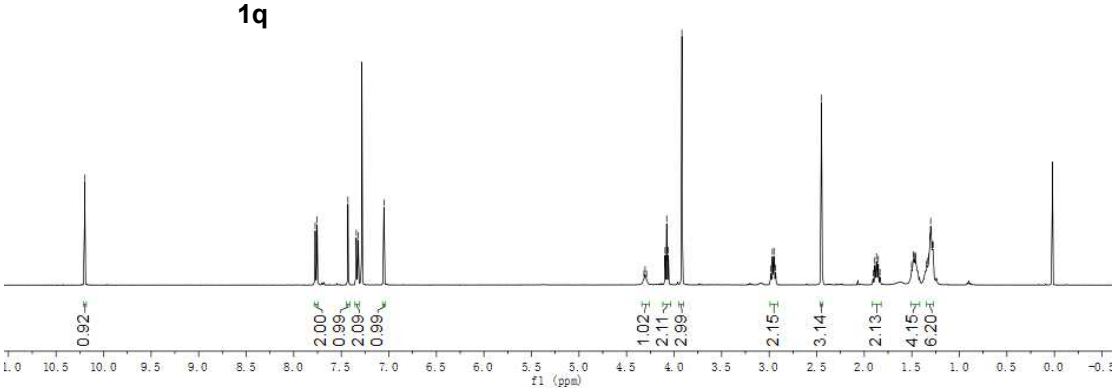


^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1q

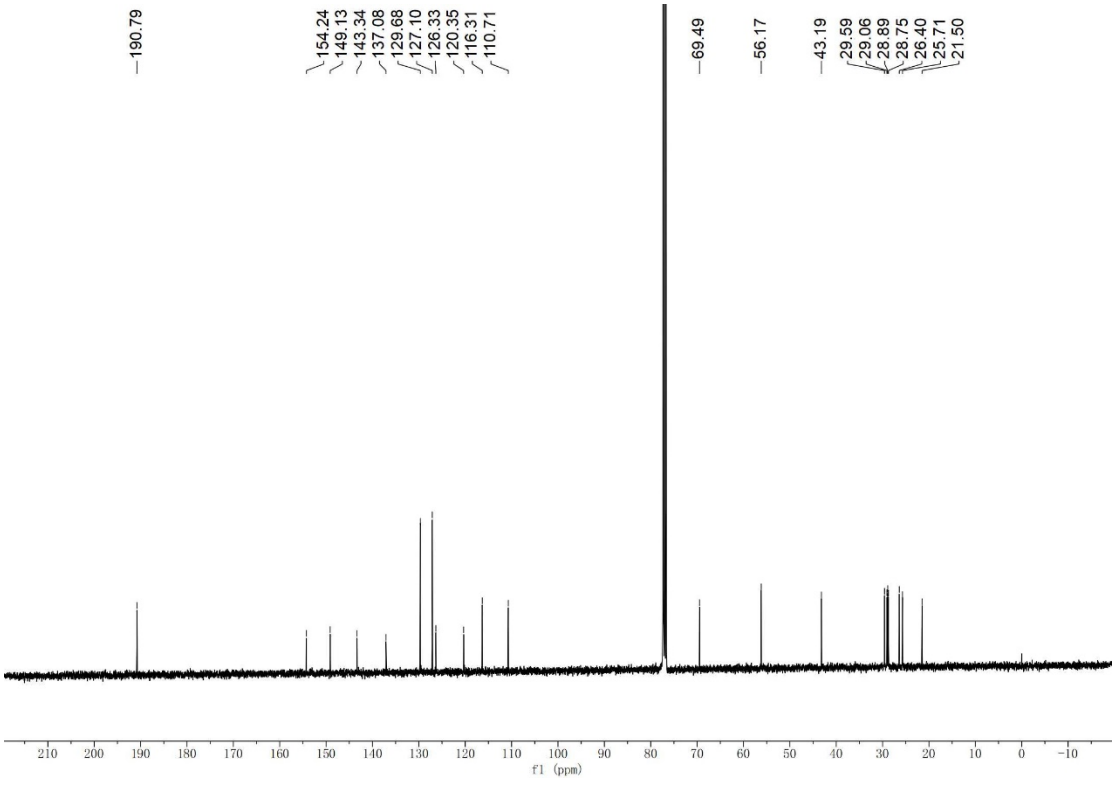




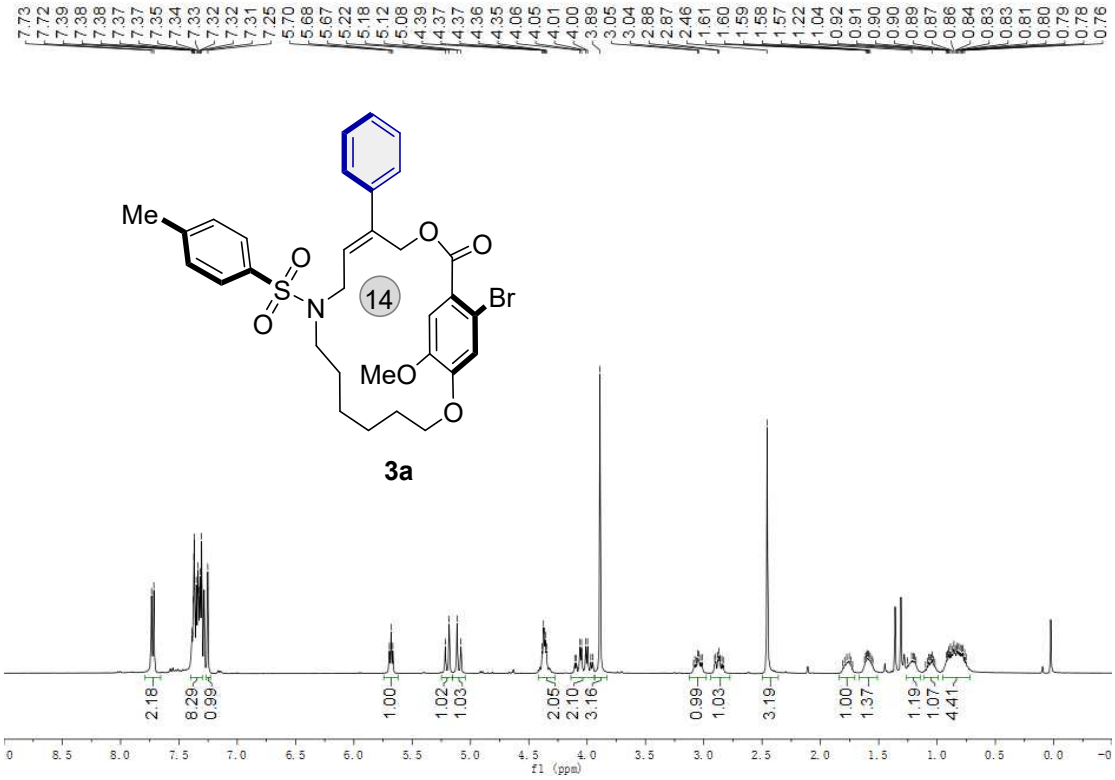
1q



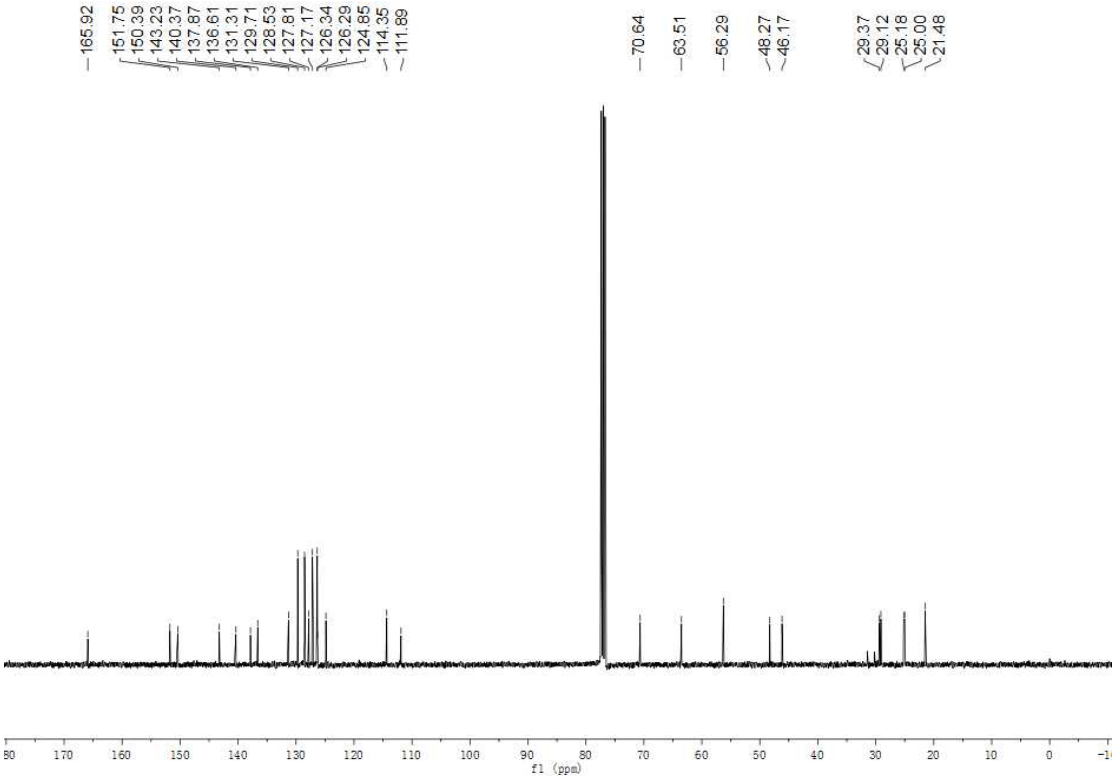
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 1q



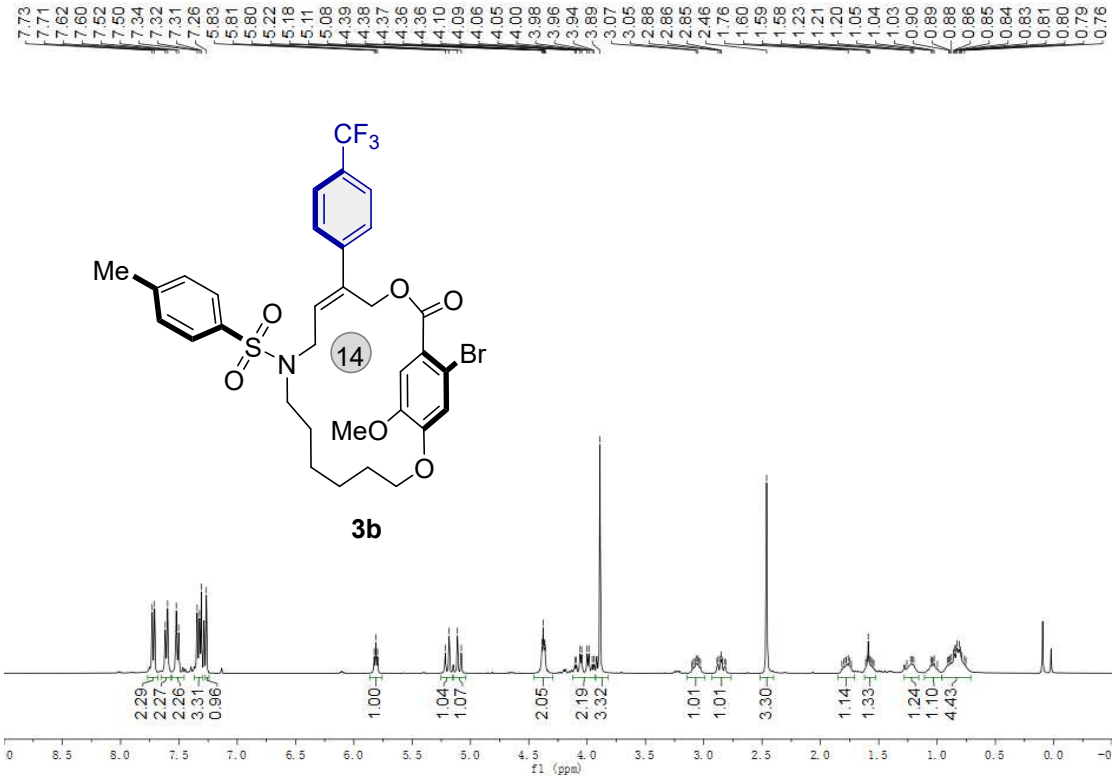
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3a



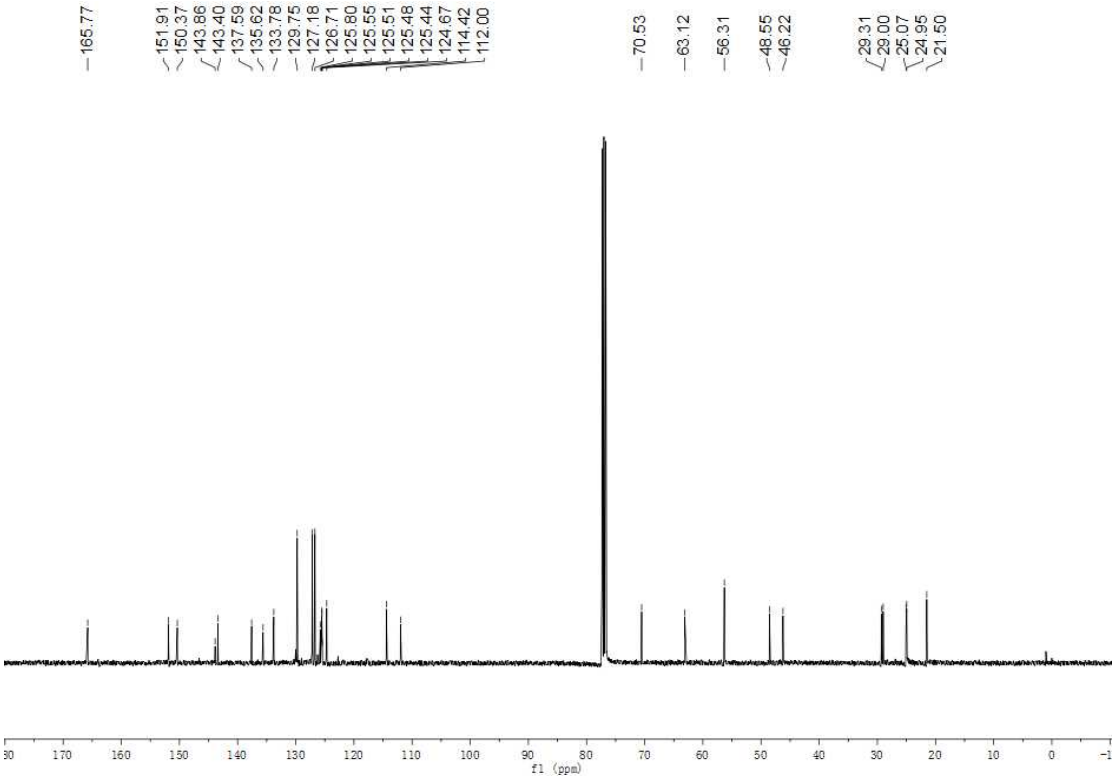
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3a



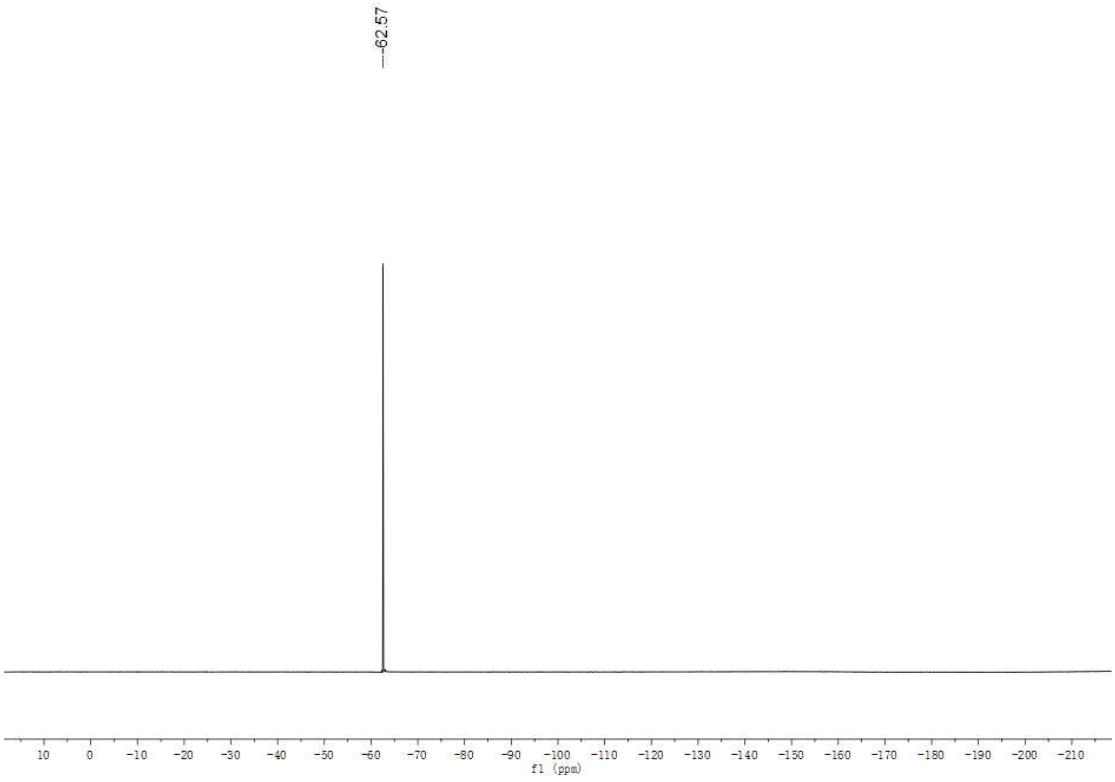
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3b



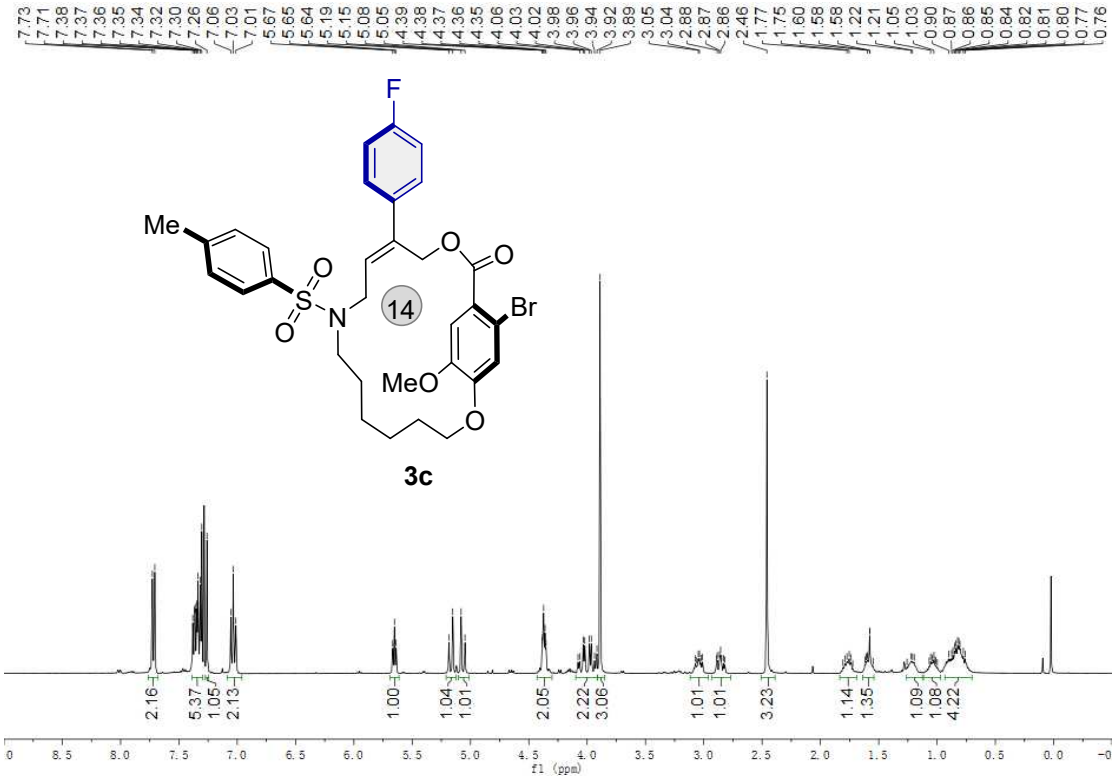
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3b



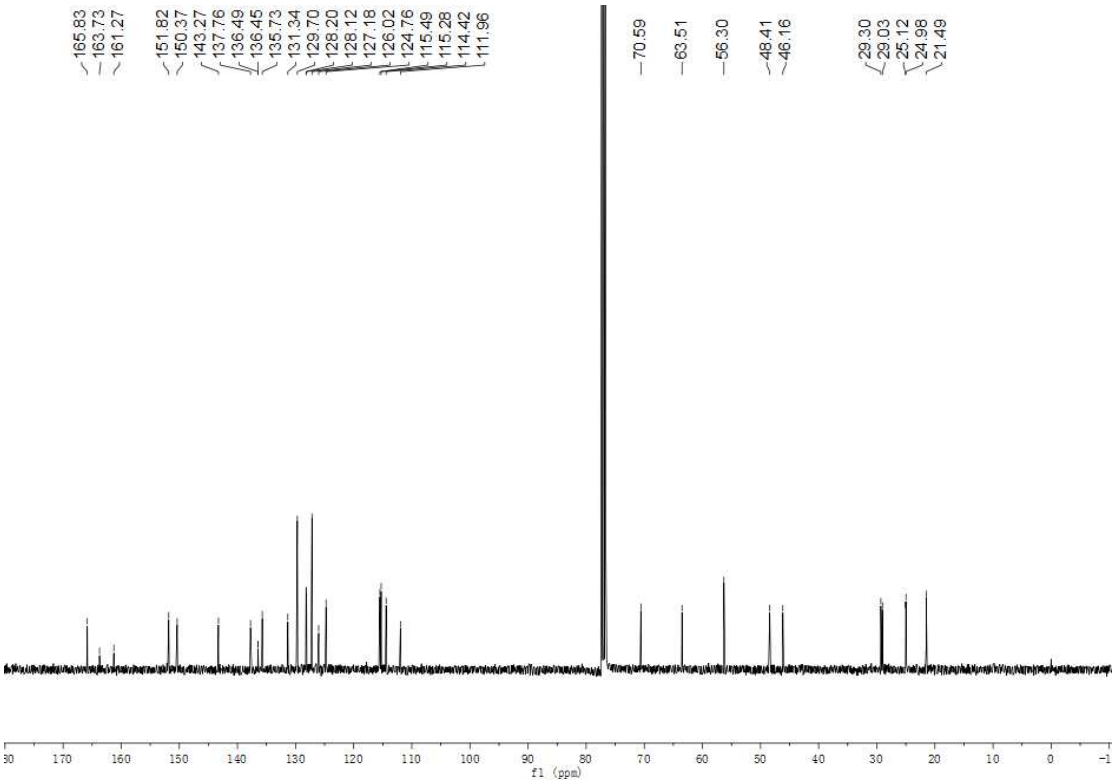
^{19}F NMR (376 MHz, $CDCl_3$) spectra of 3b



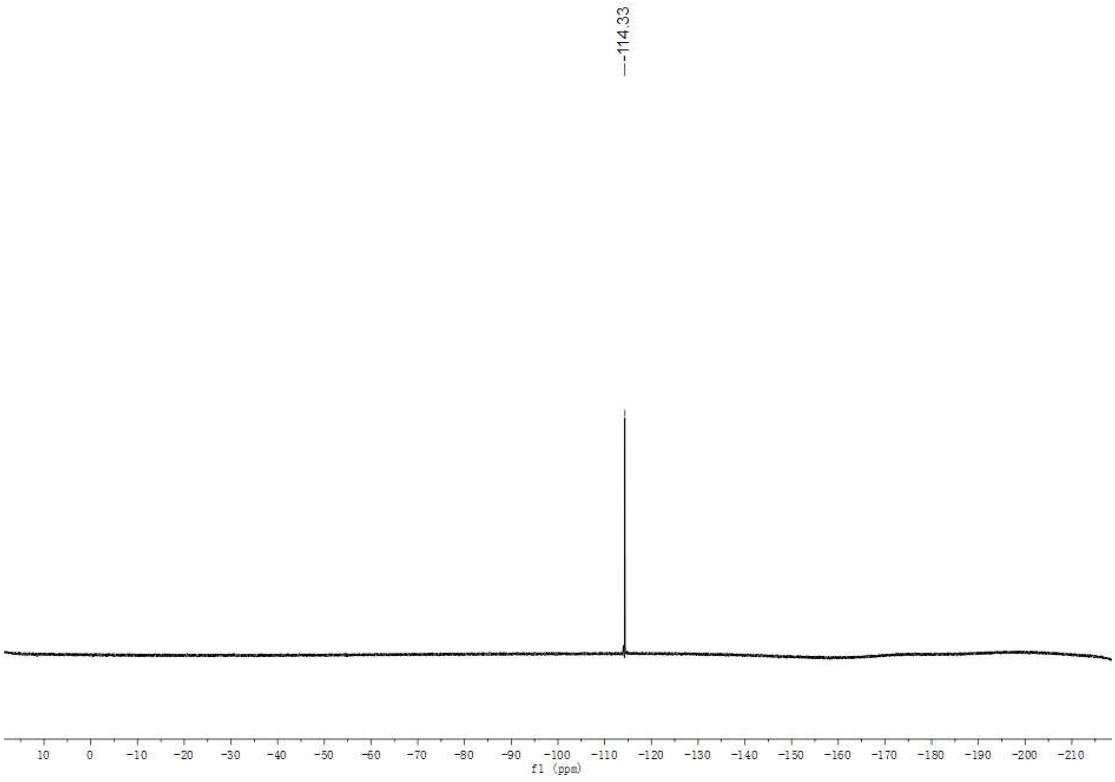
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3c



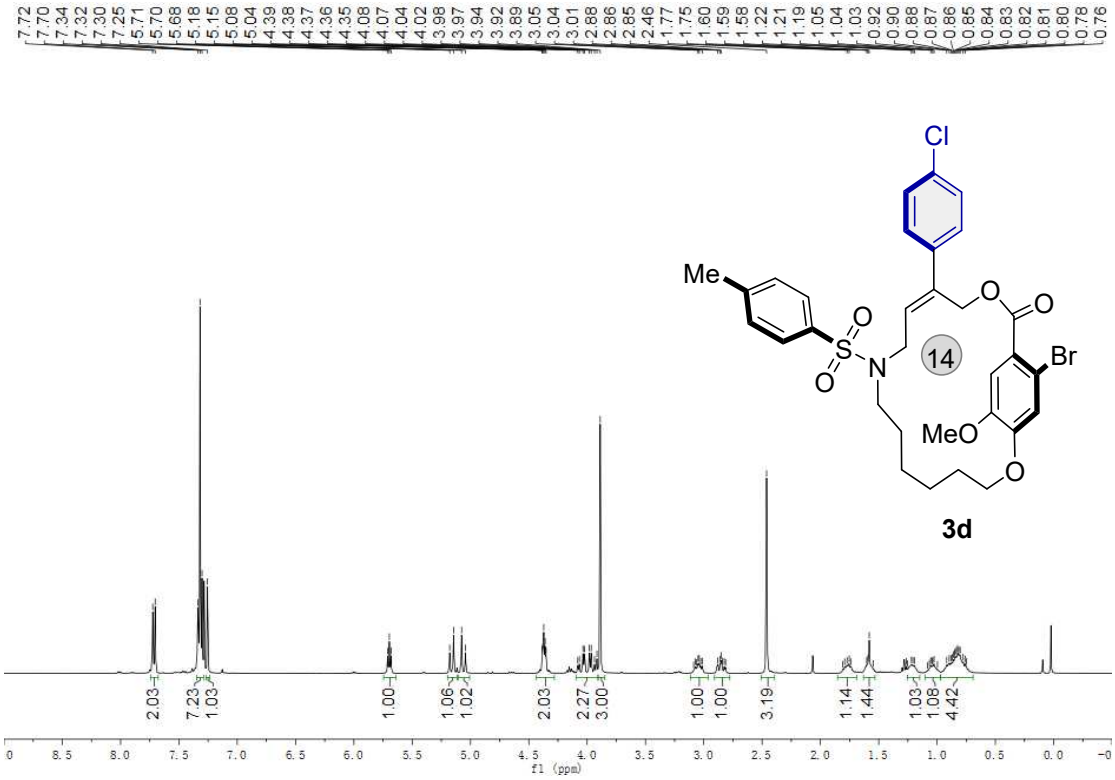
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3c



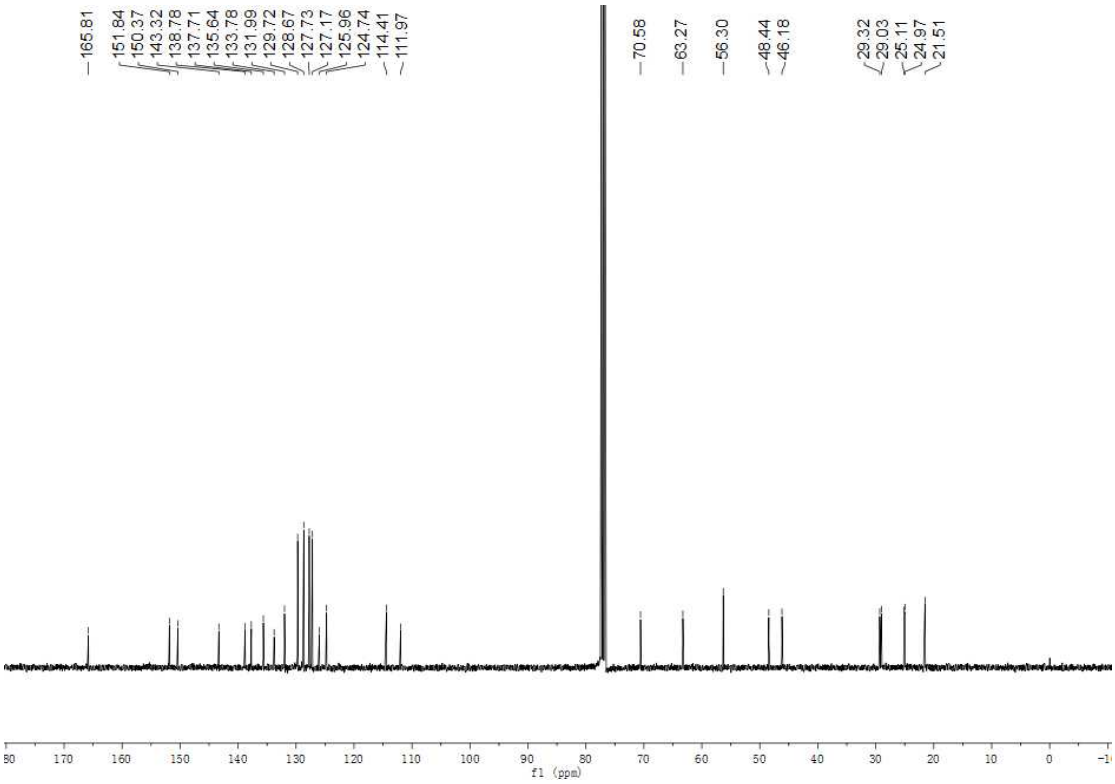
^{19}F NMR (376 MHz, $CDCl_3$) spectra of 3c



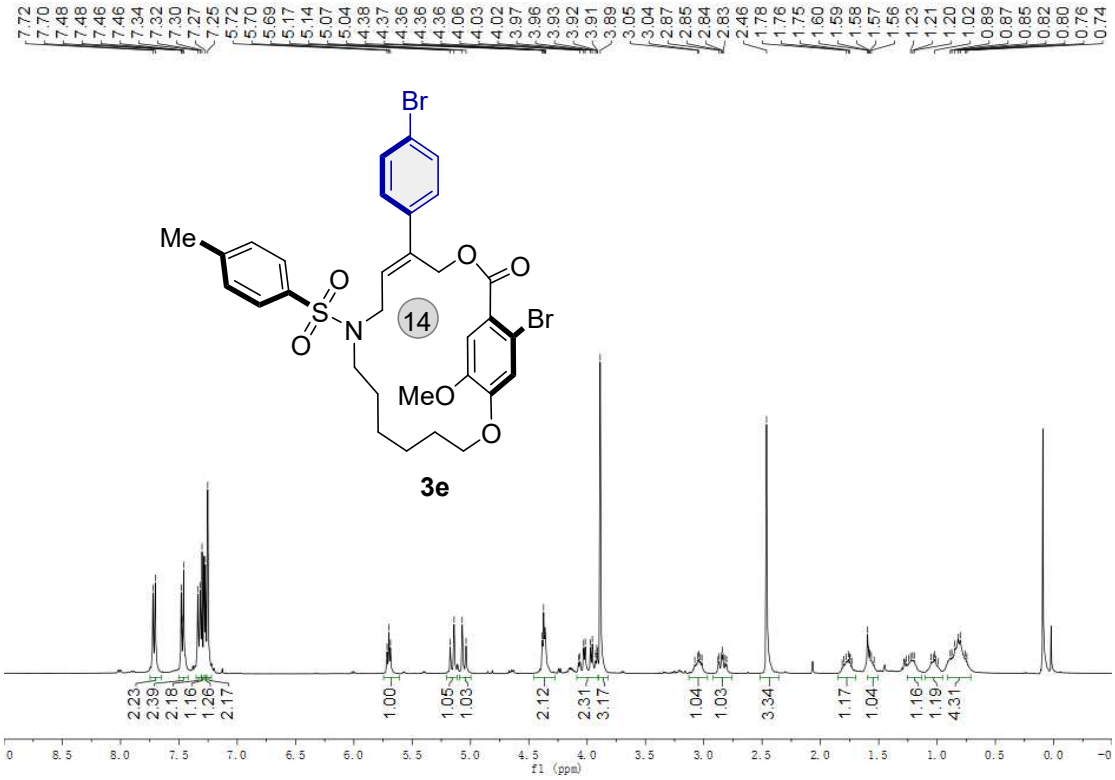
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3d



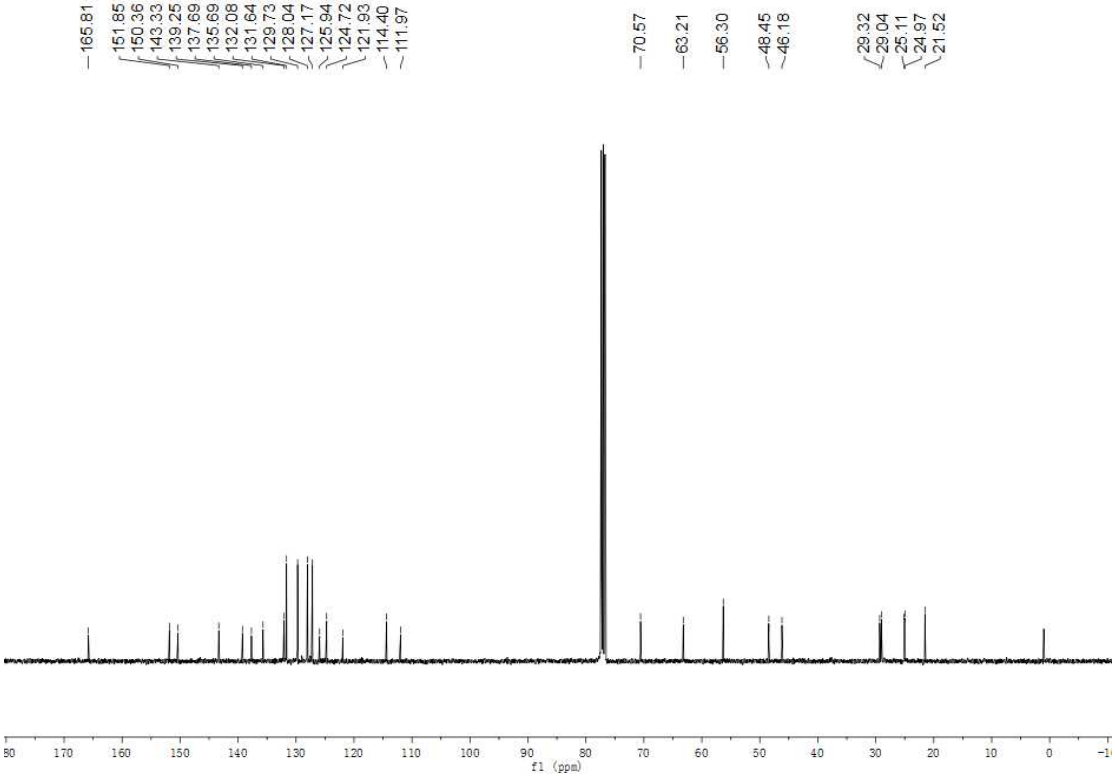
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3d



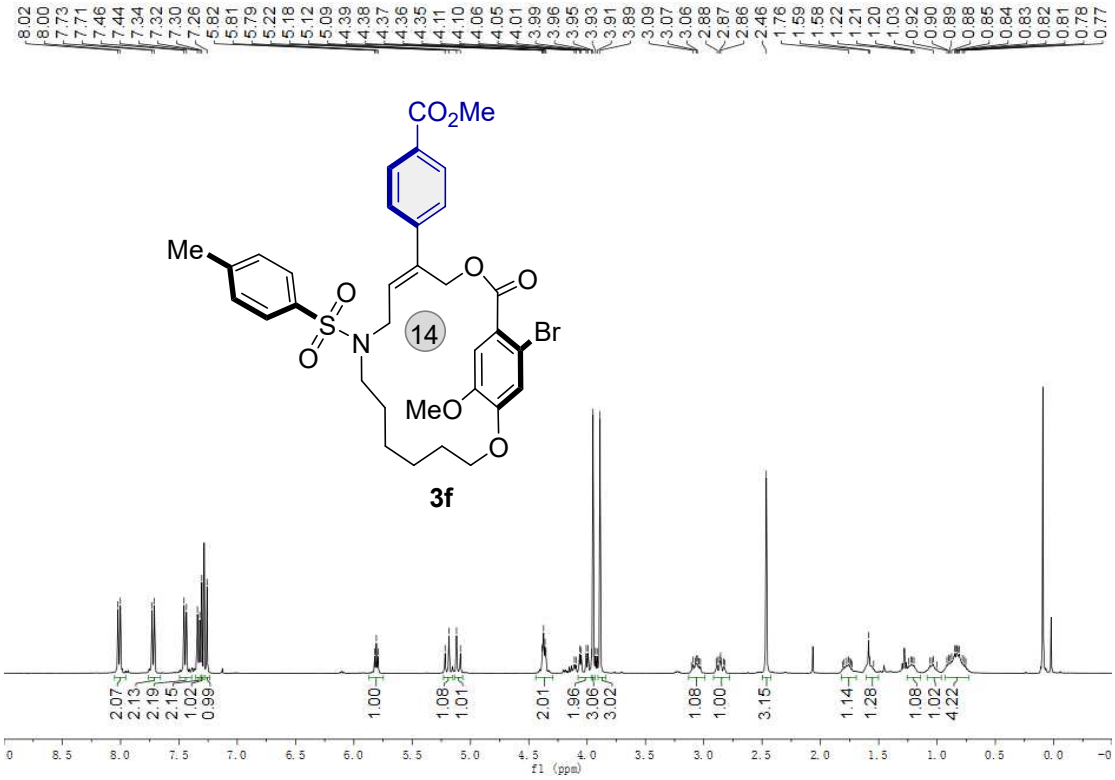
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3e



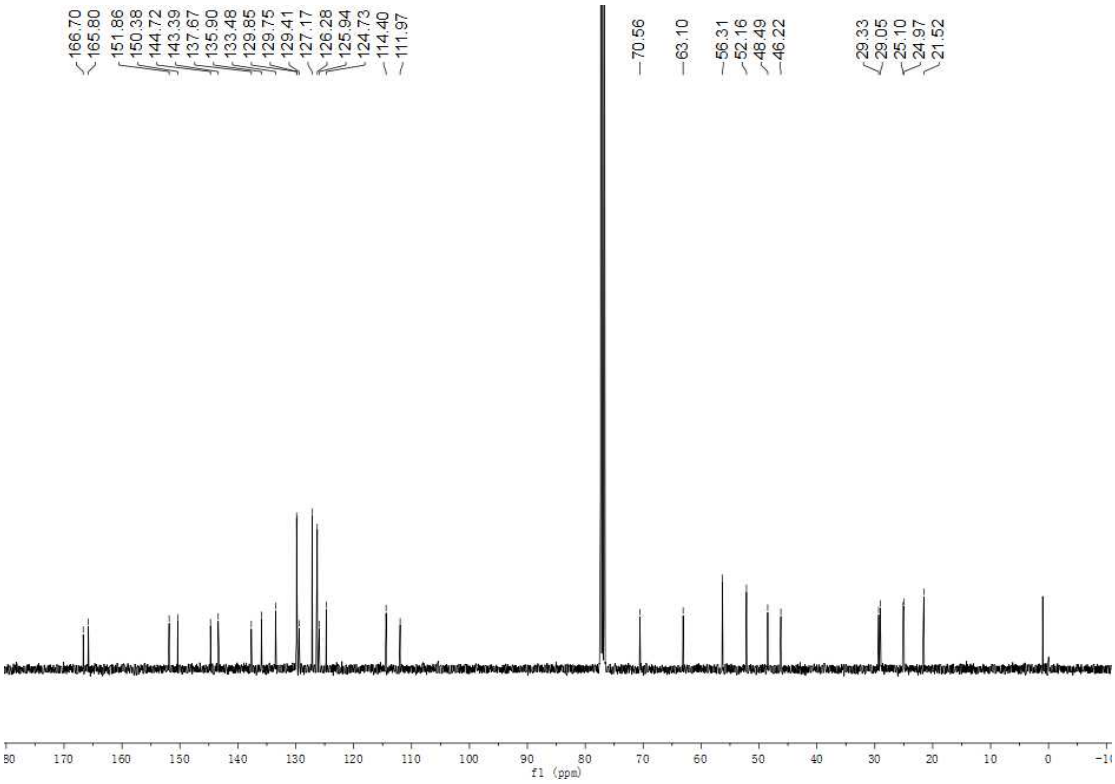
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3e



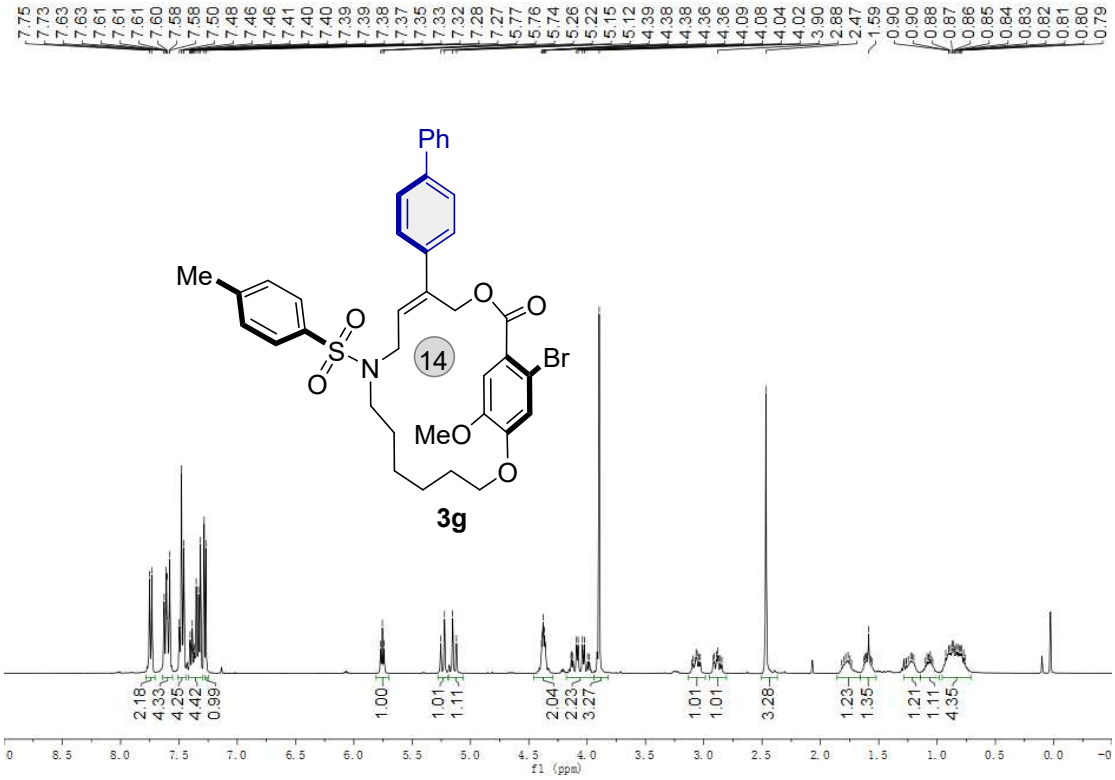
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3f



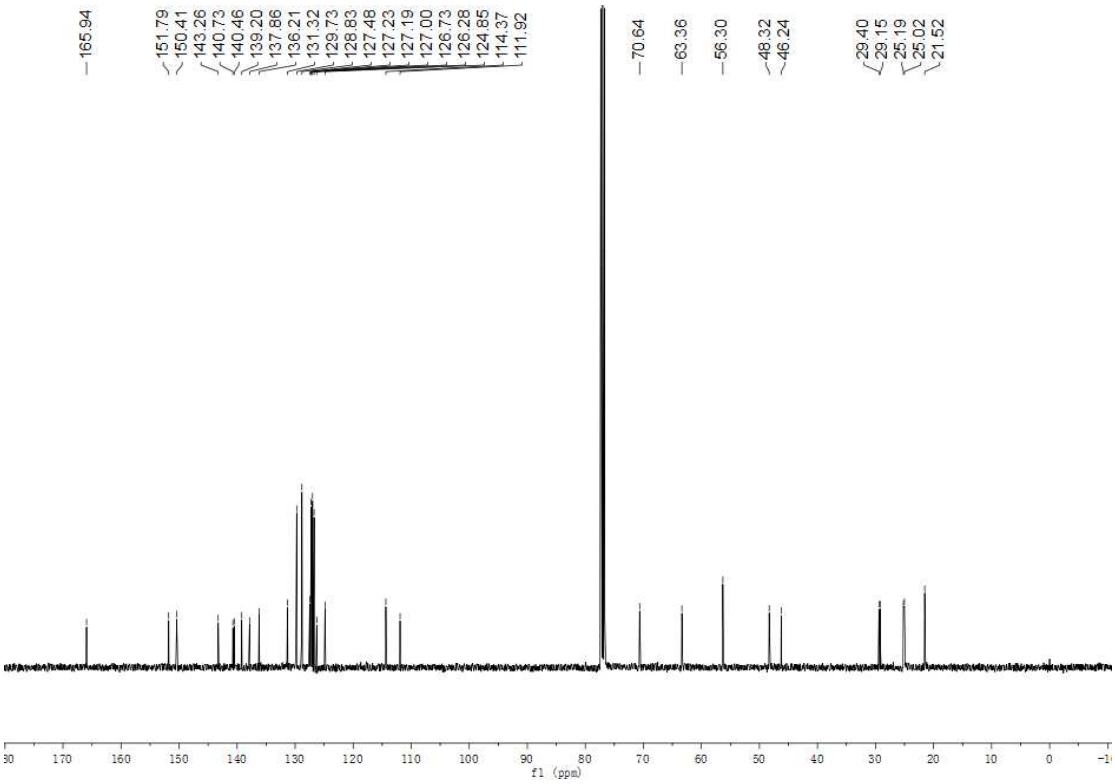
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3f



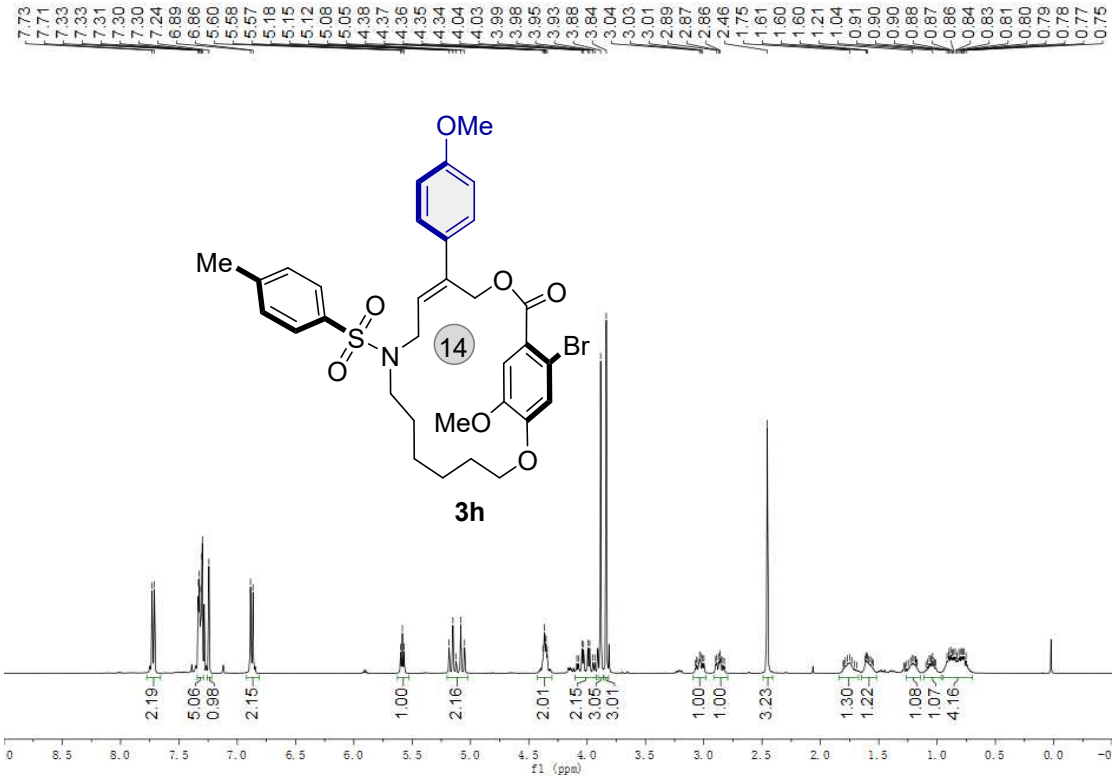
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3g



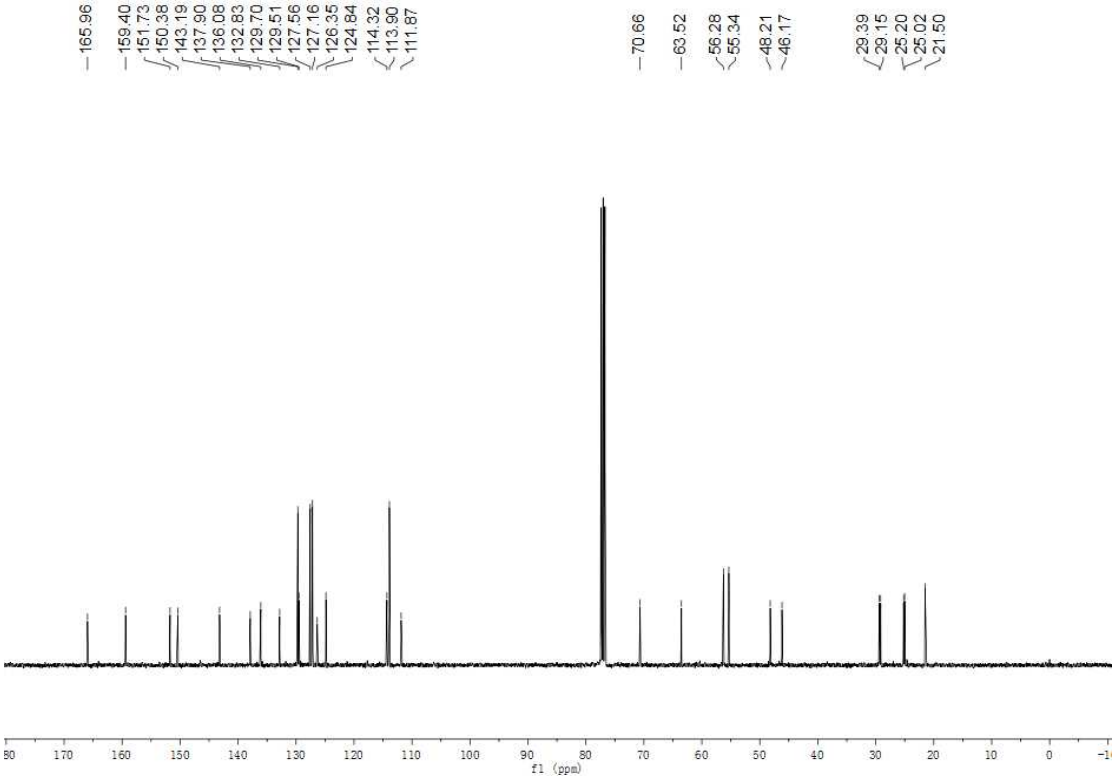
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3g



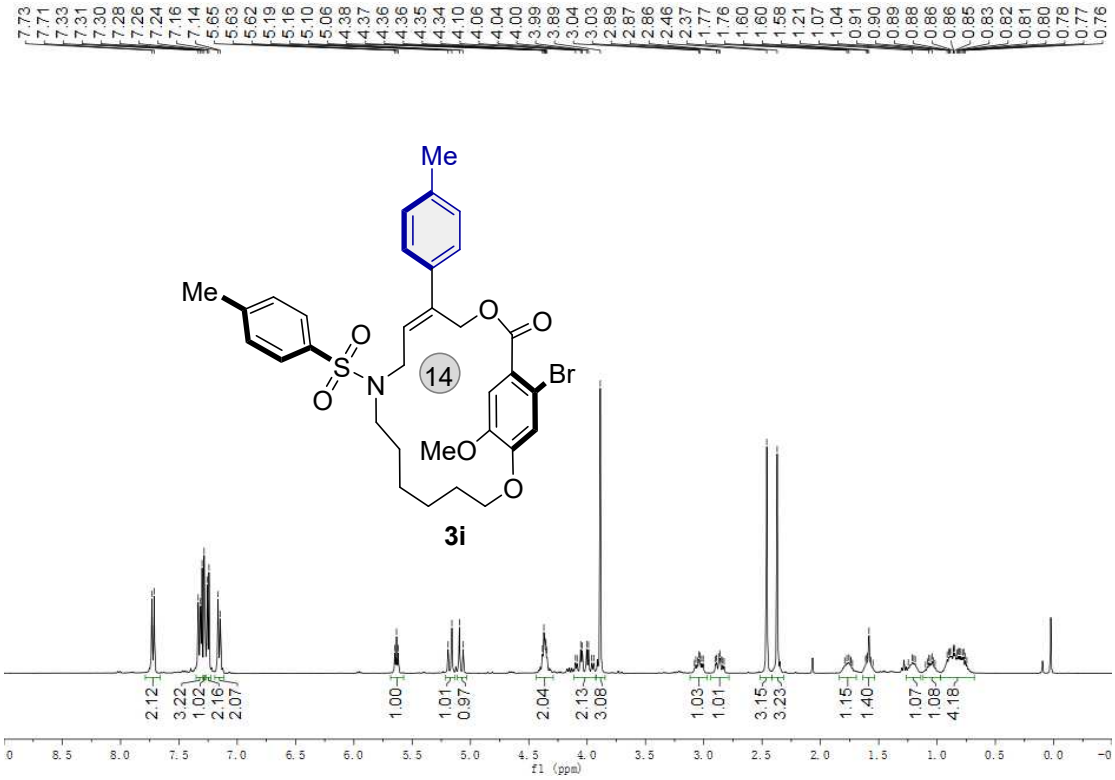
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3h



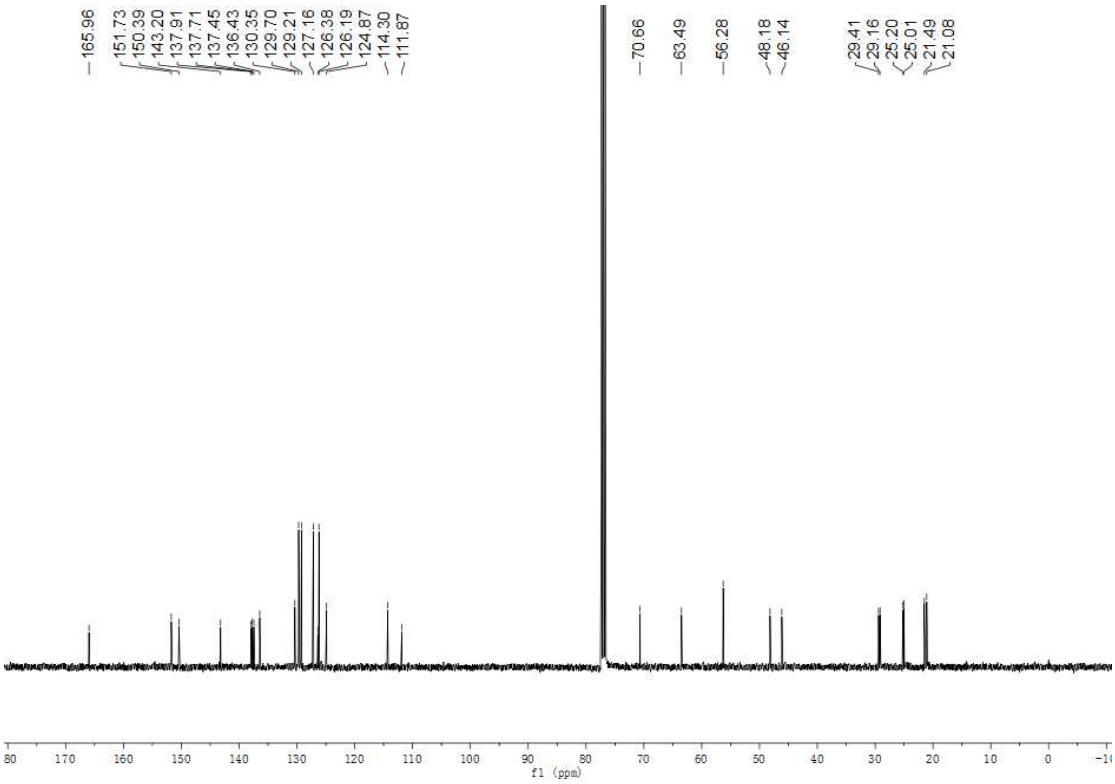
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3h



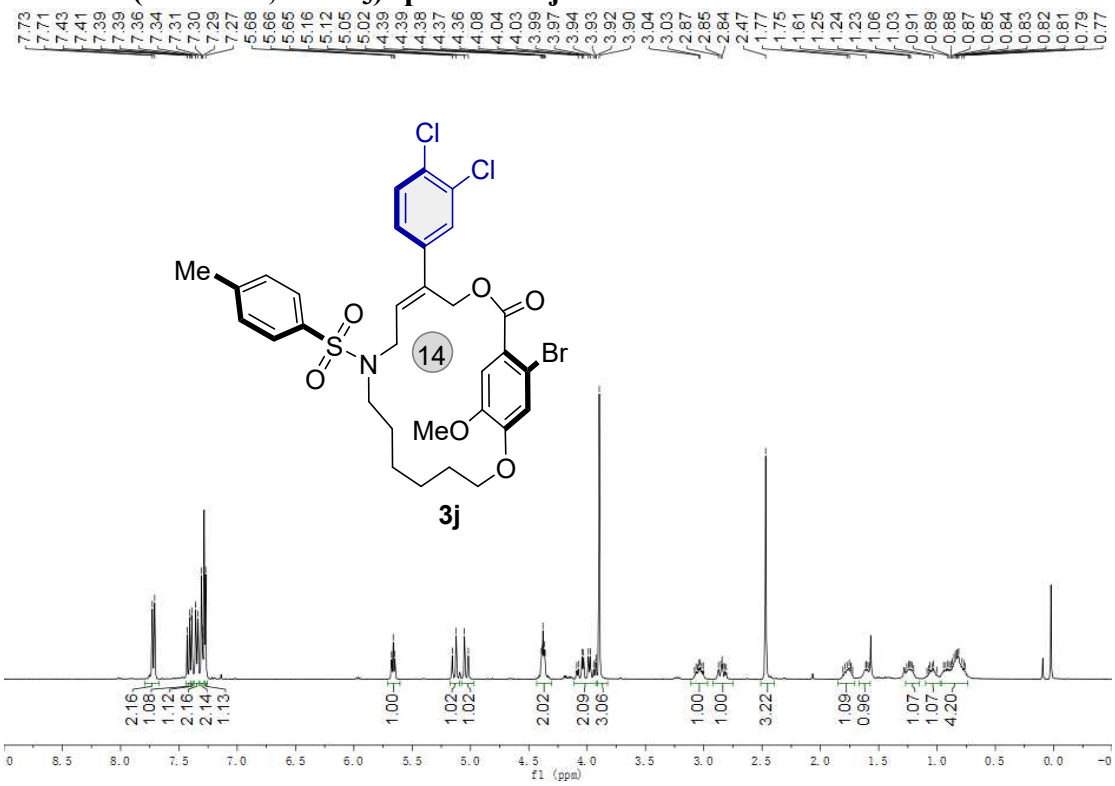
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3i



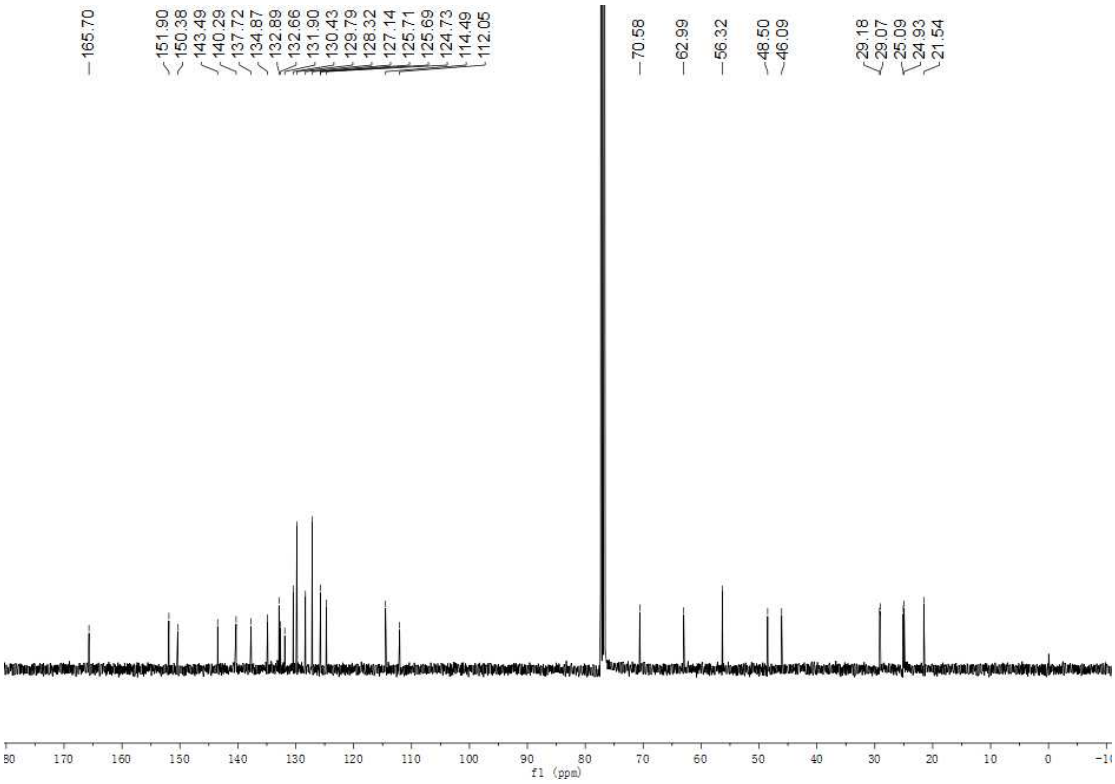
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3i



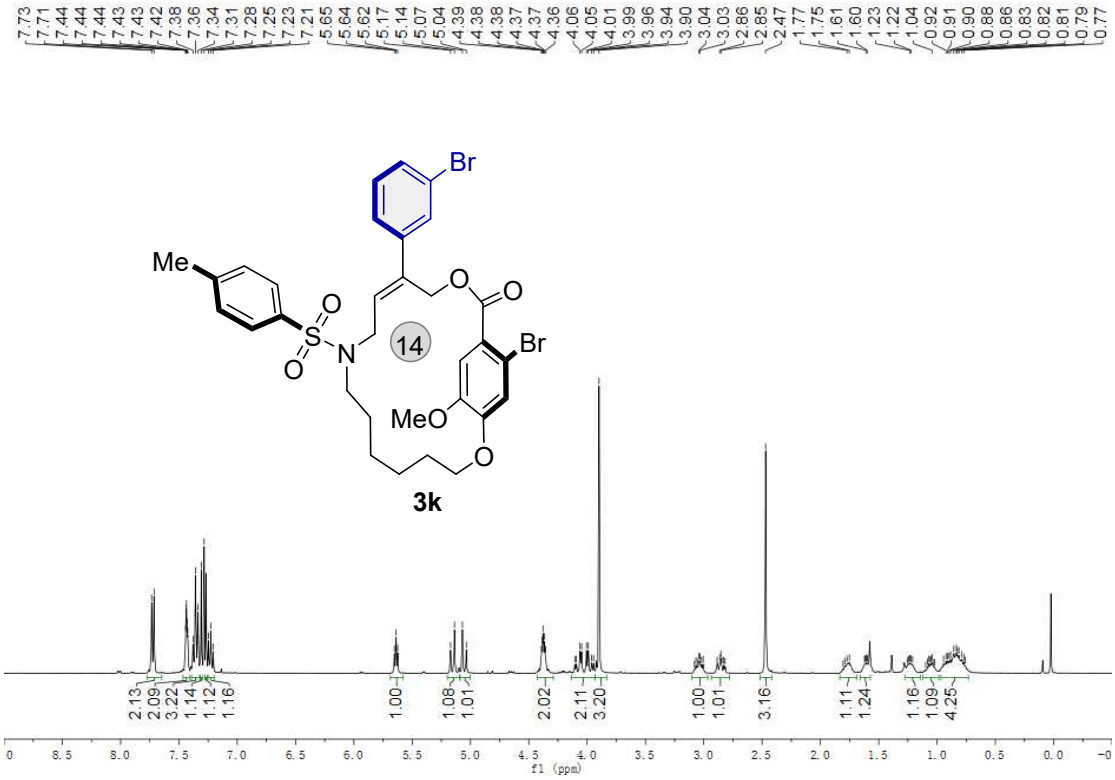
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3j



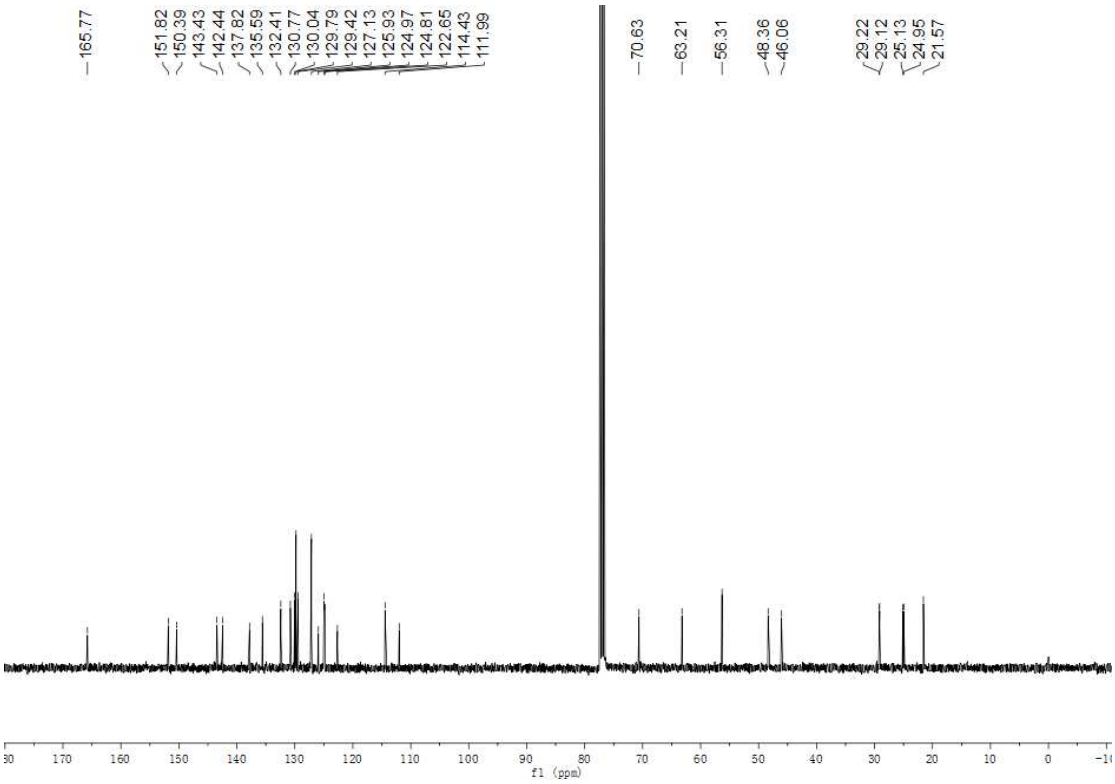
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3j



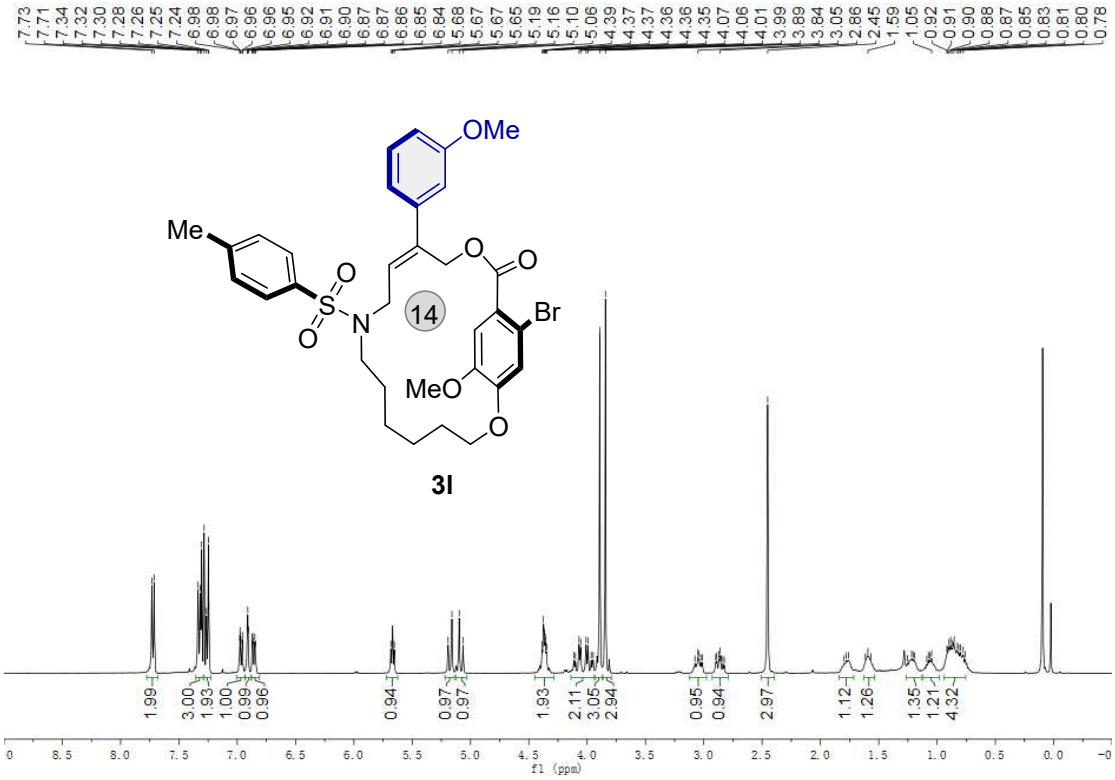
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3k



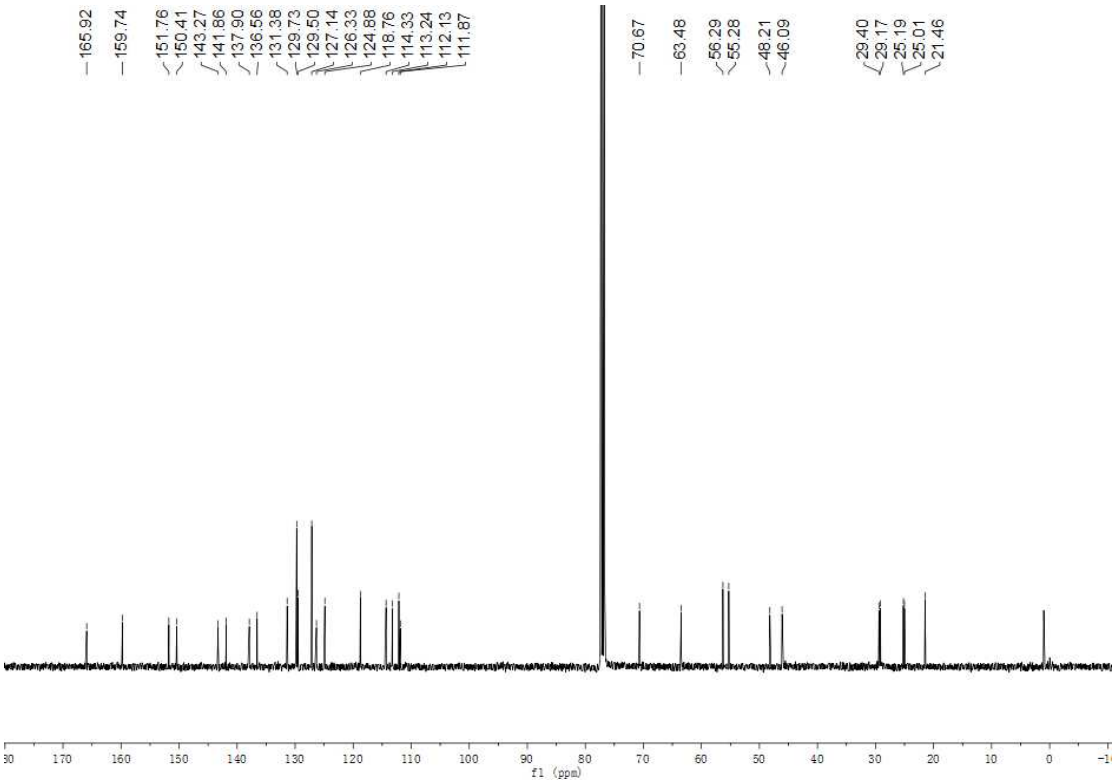
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3k



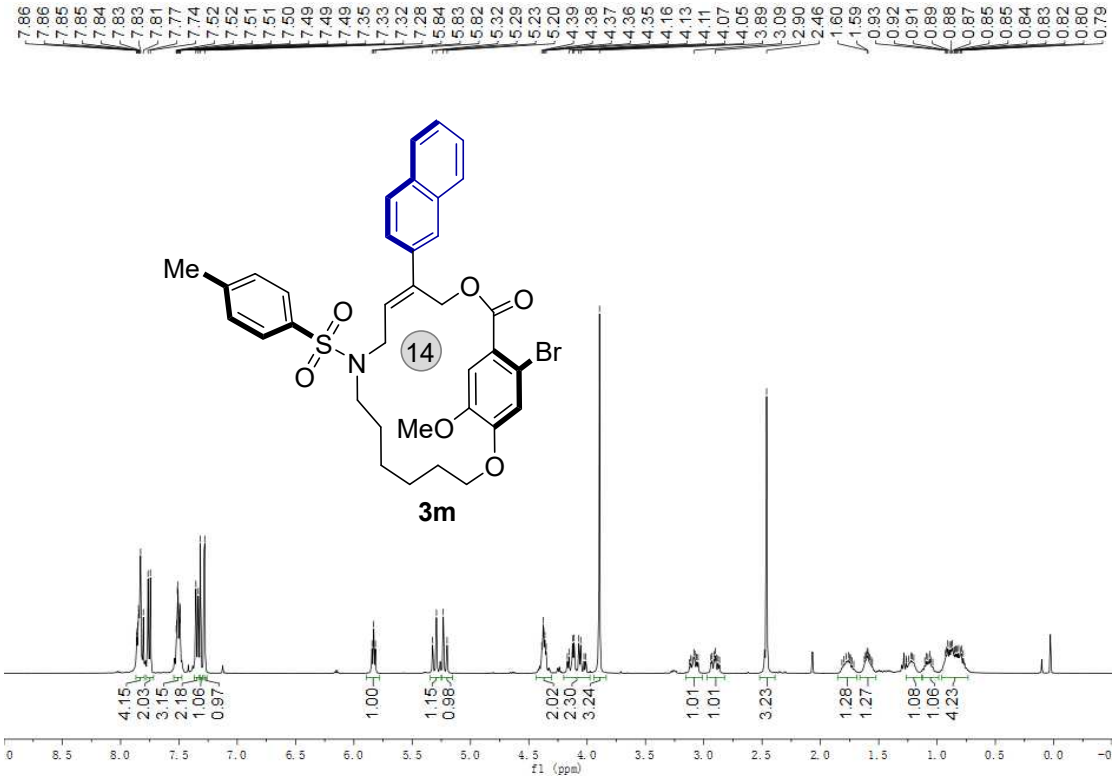
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3l



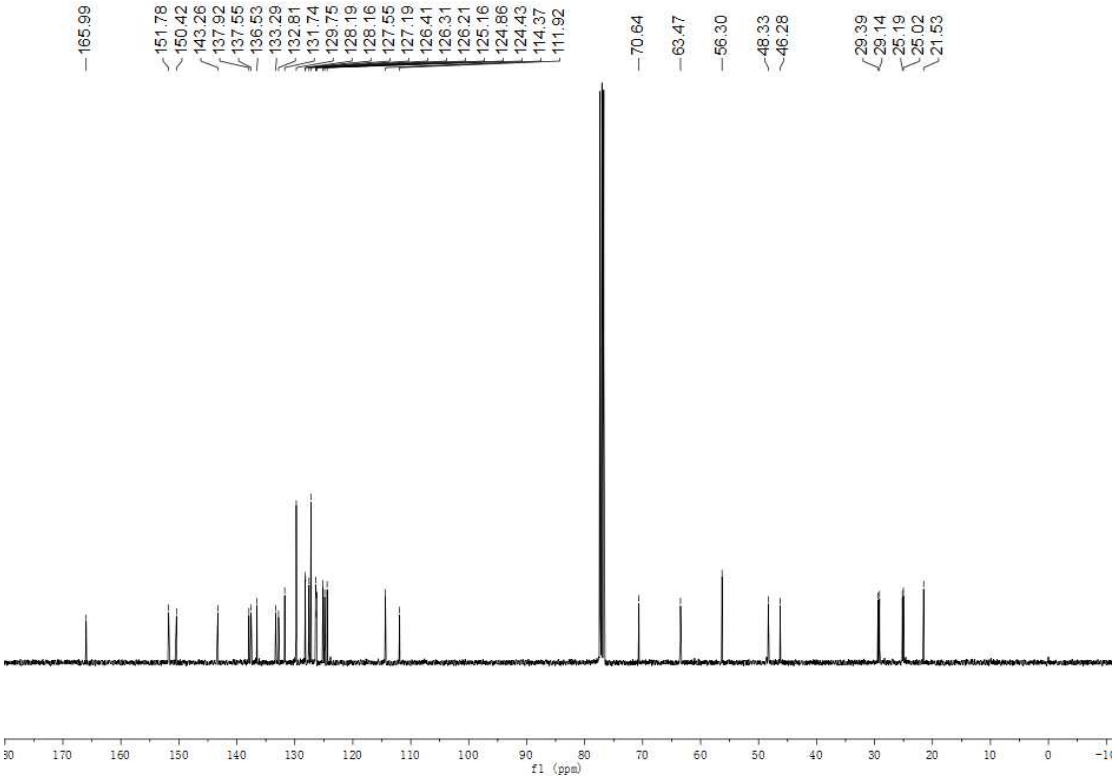
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3l



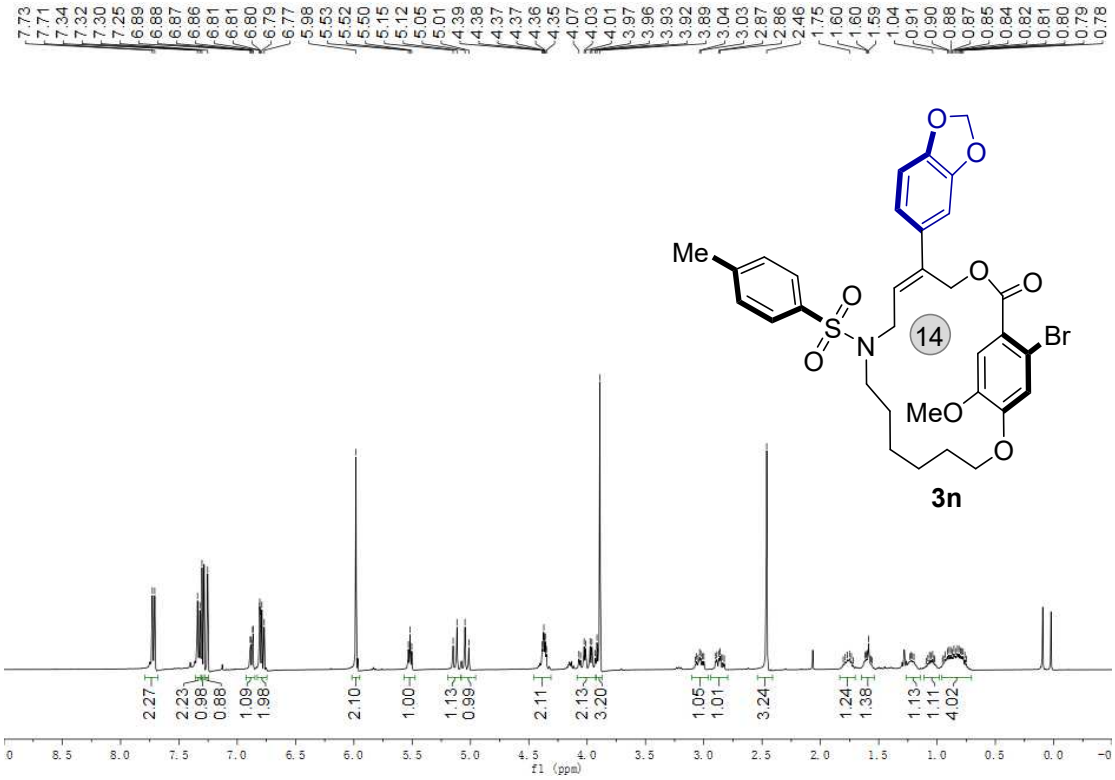
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3m



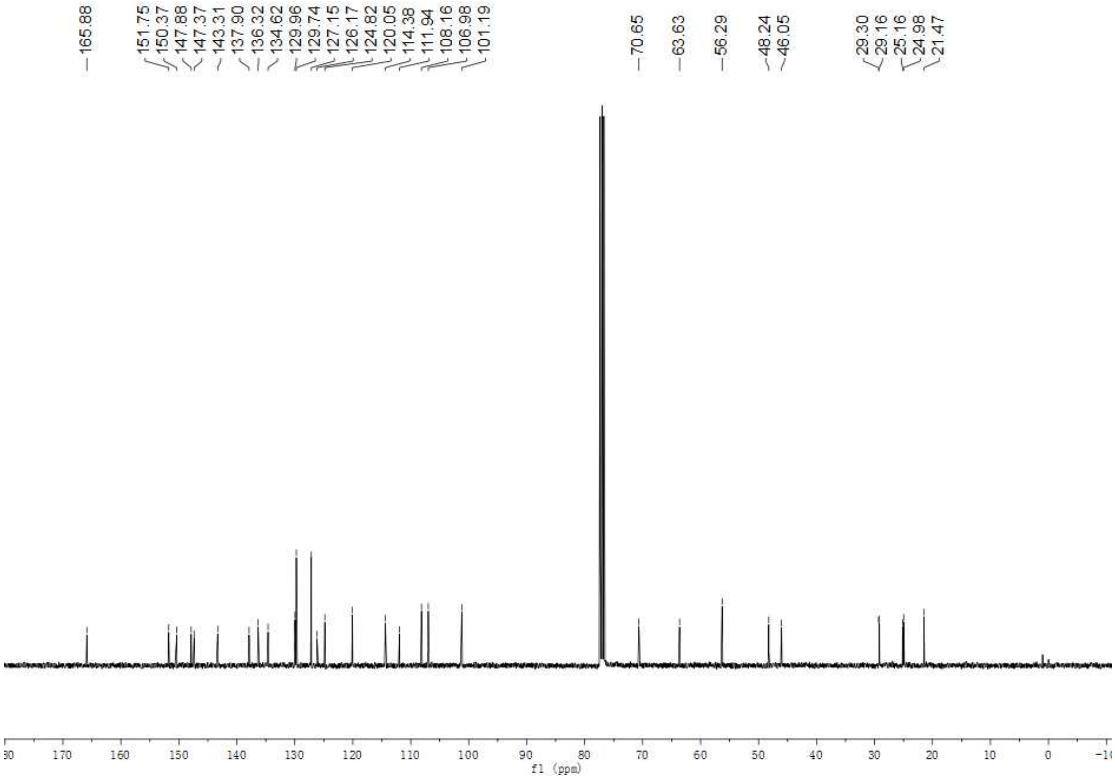
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3m



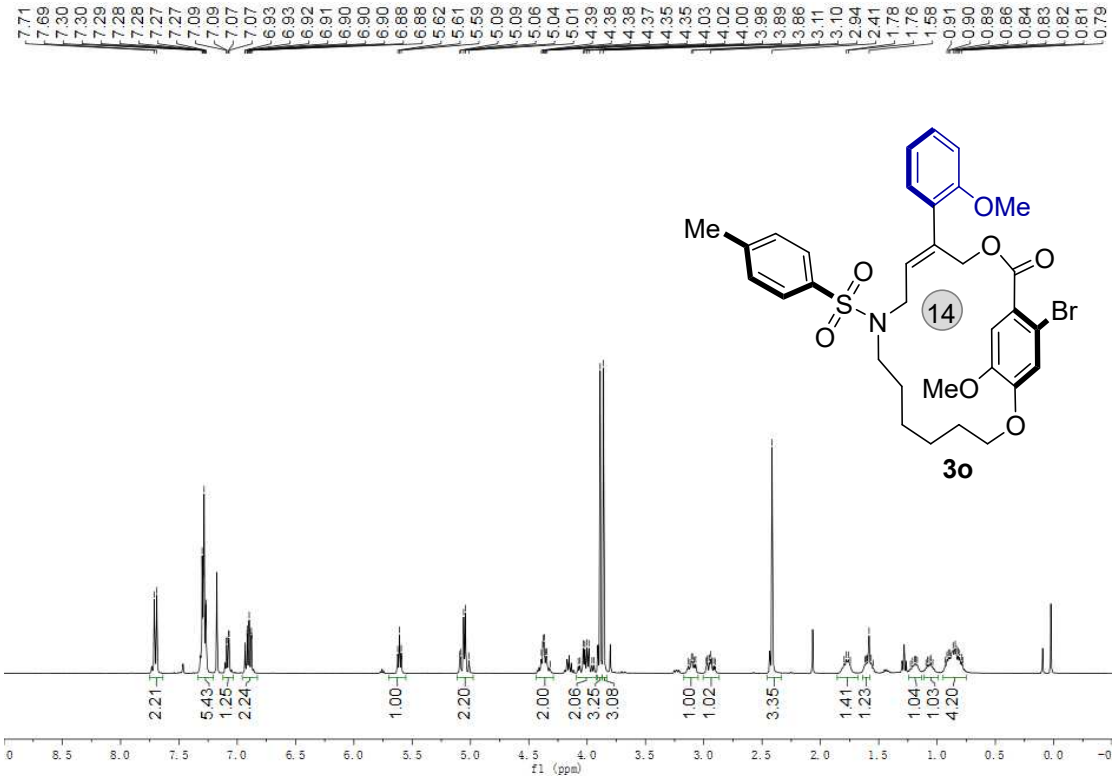
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3n



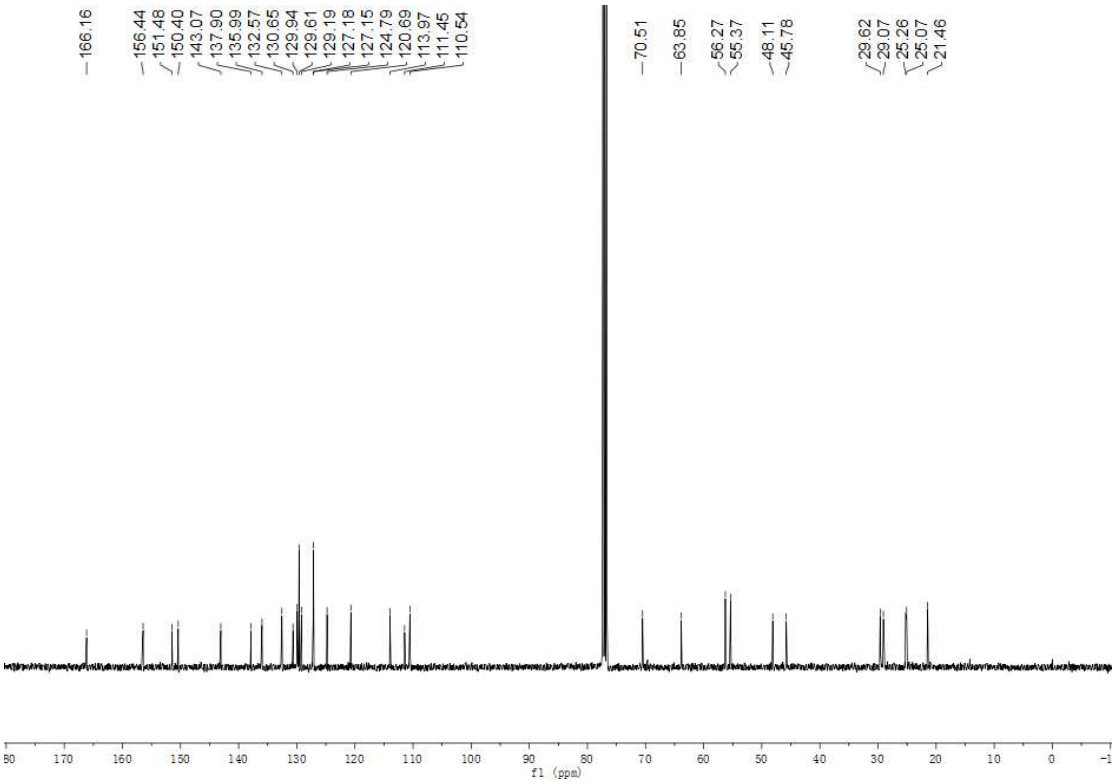
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3n



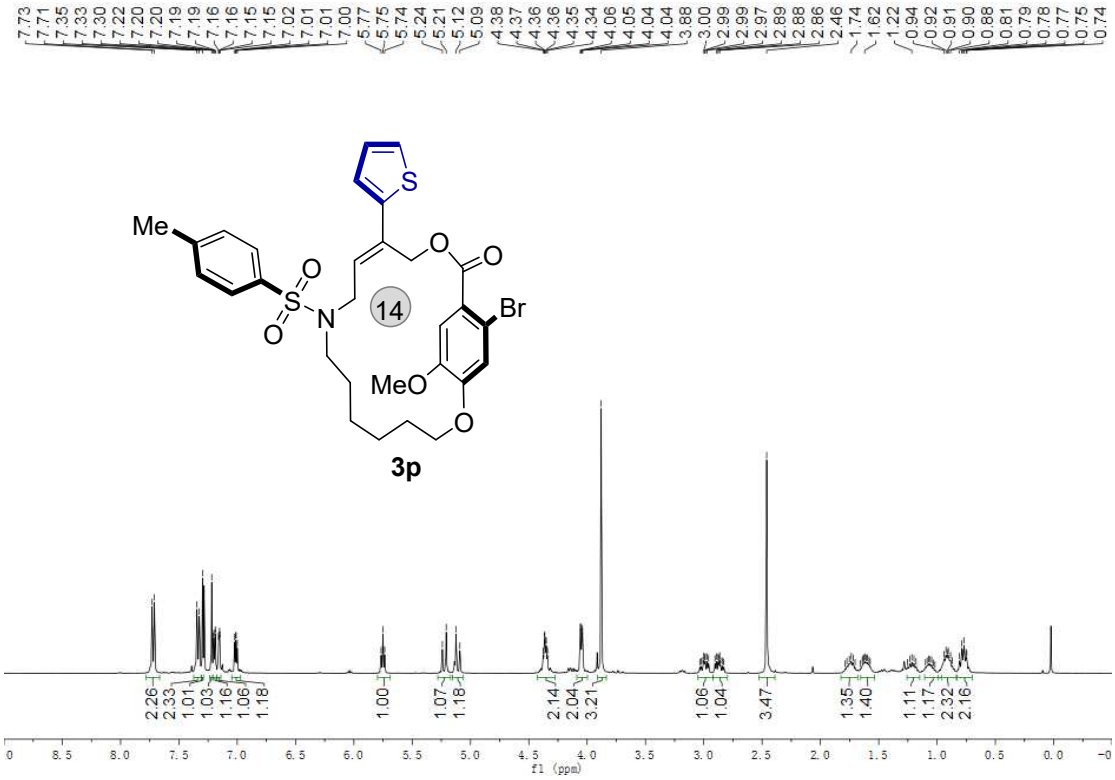
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3o



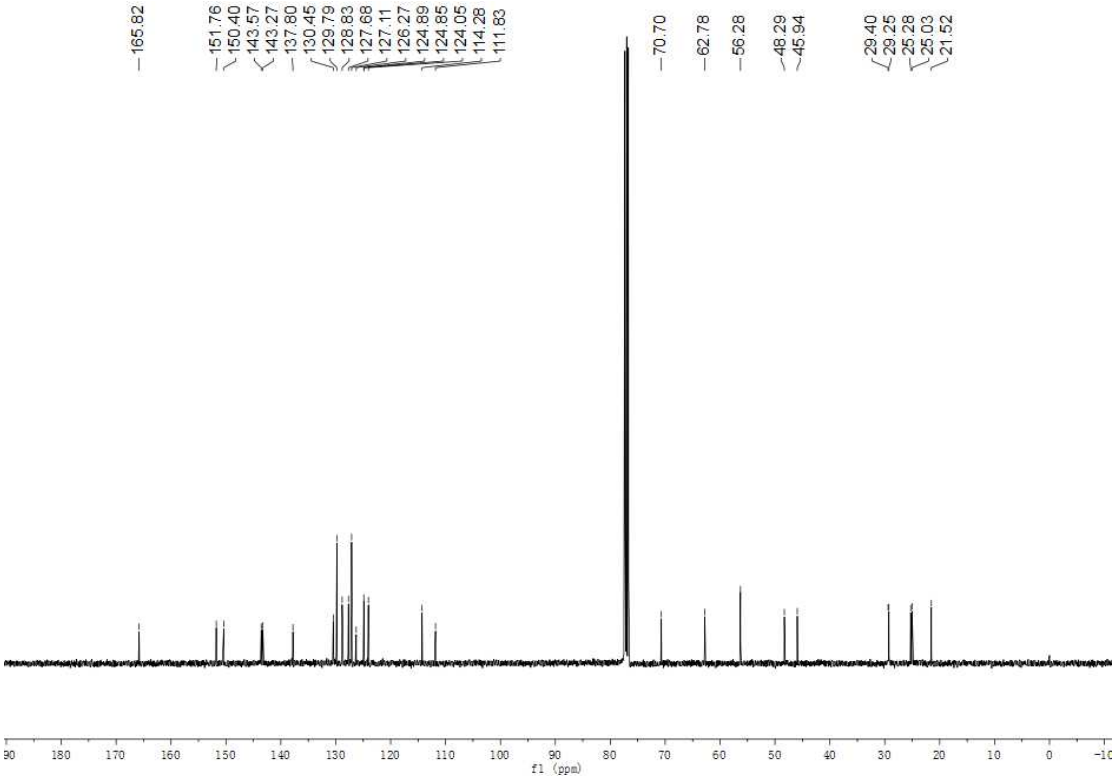
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3o



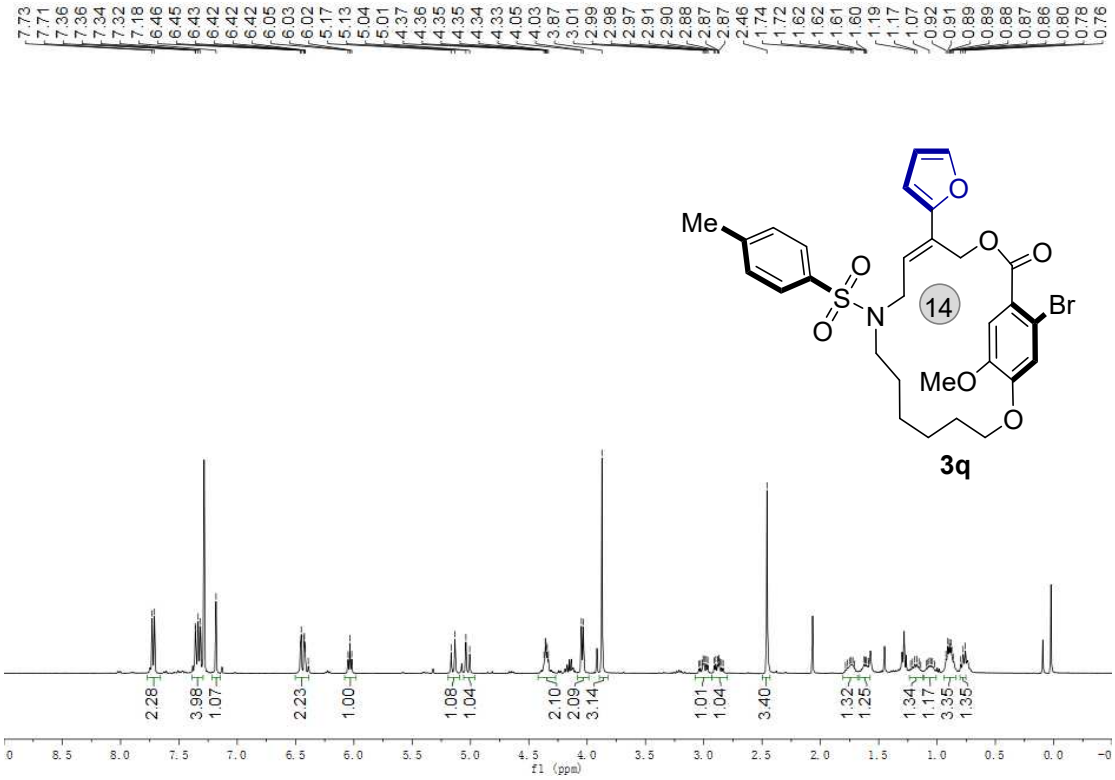
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3p



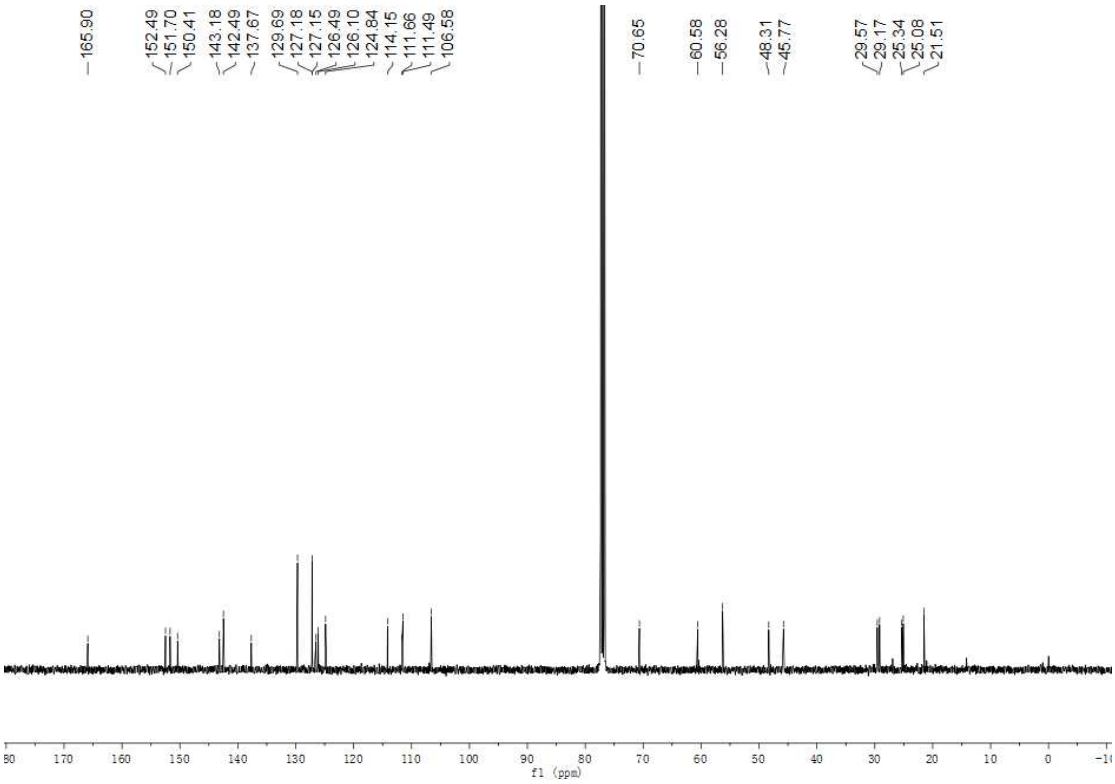
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3p



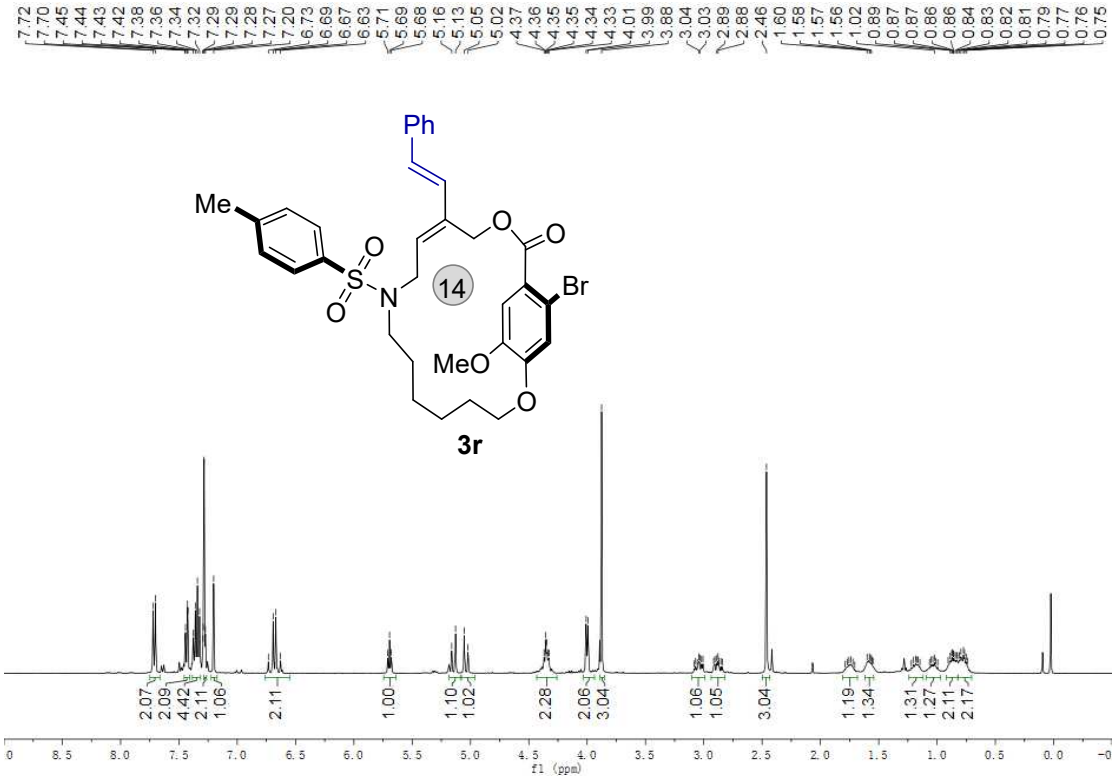
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3q



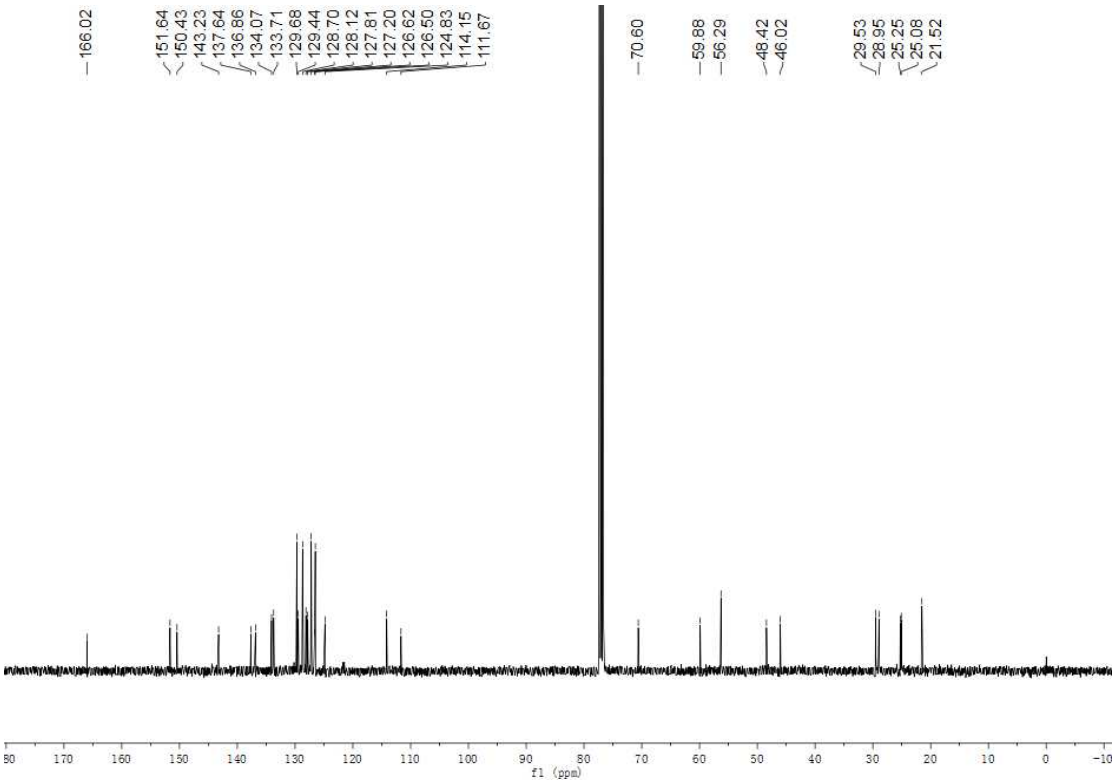
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3q



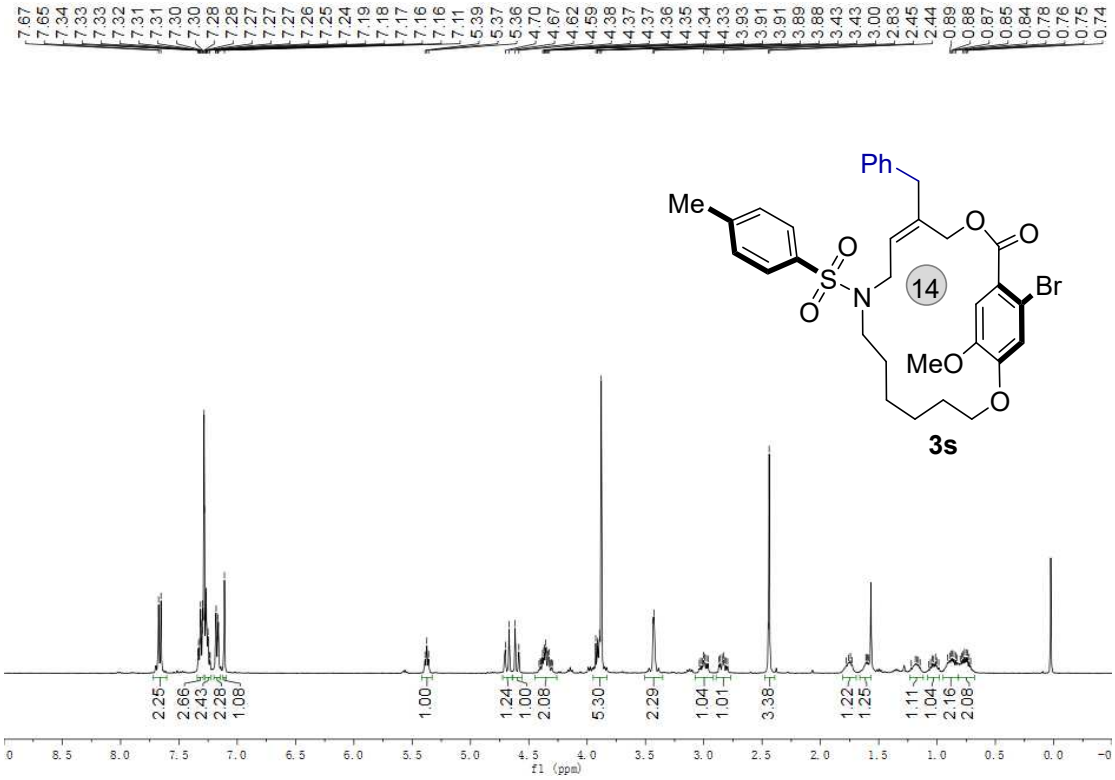
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3r



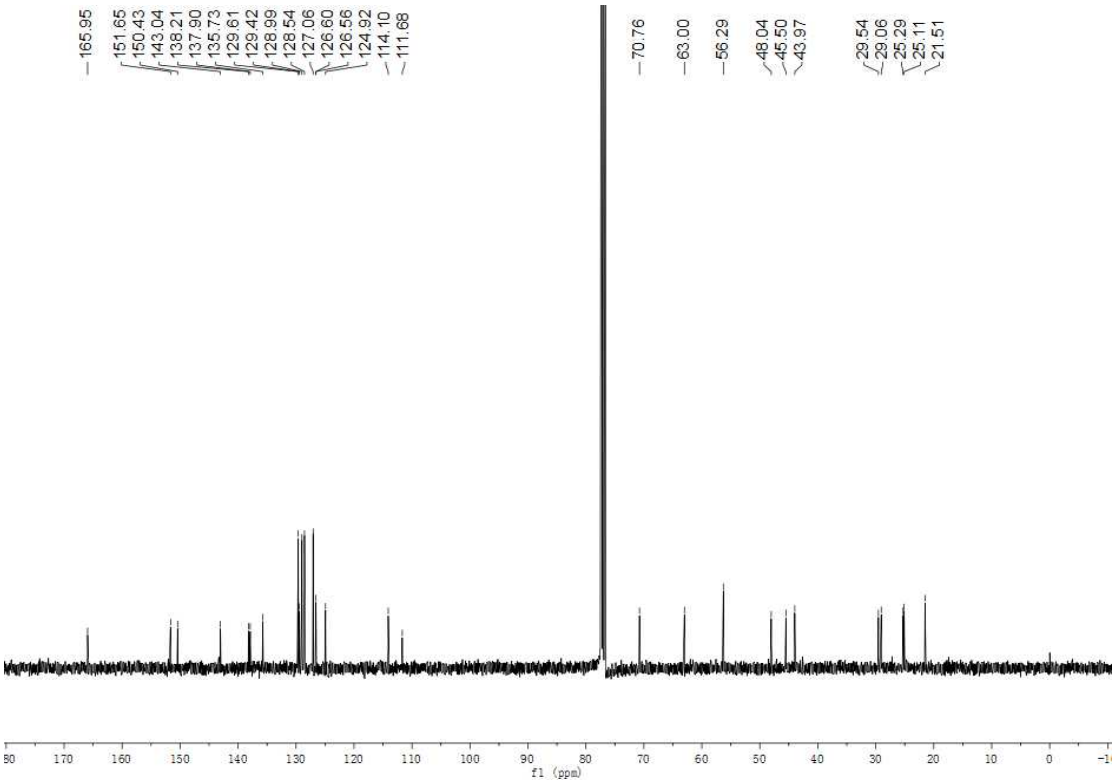
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3r



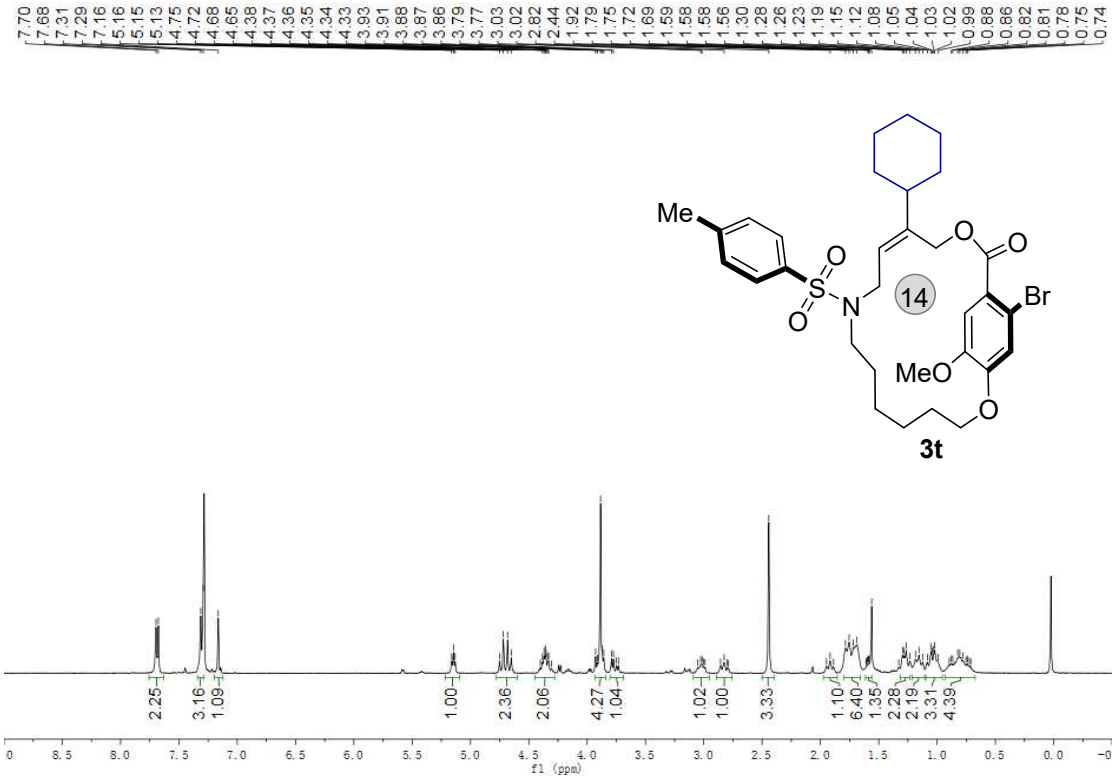
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3s



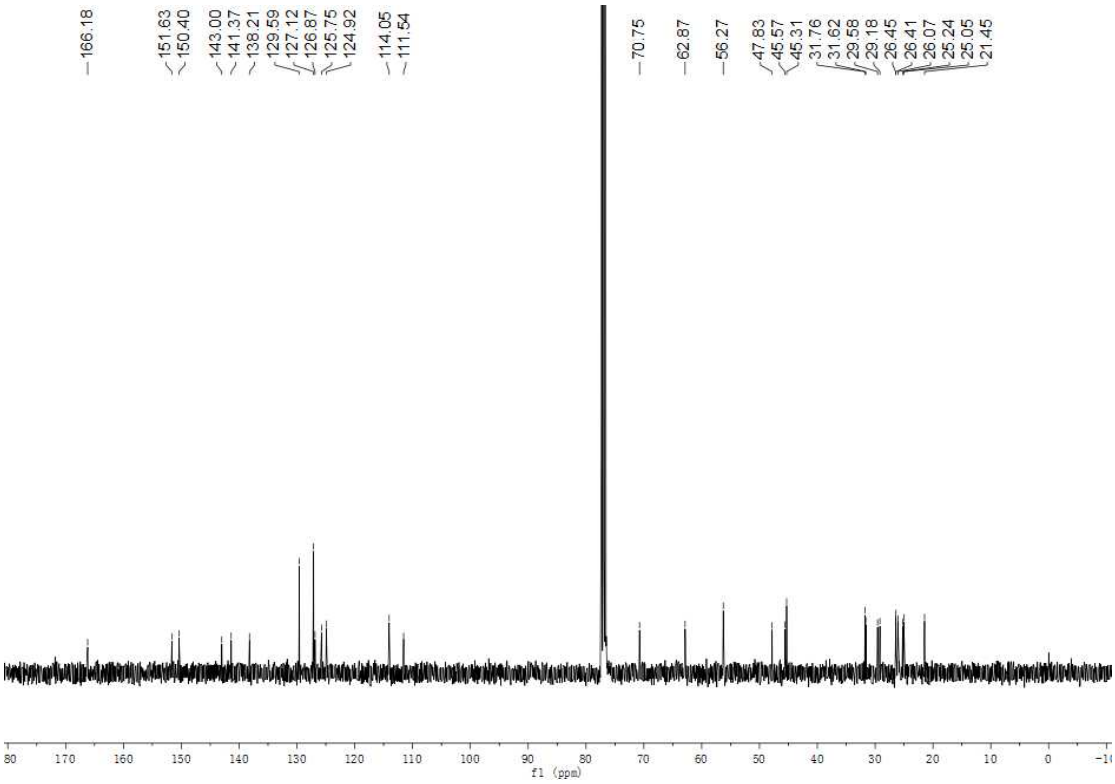
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3s



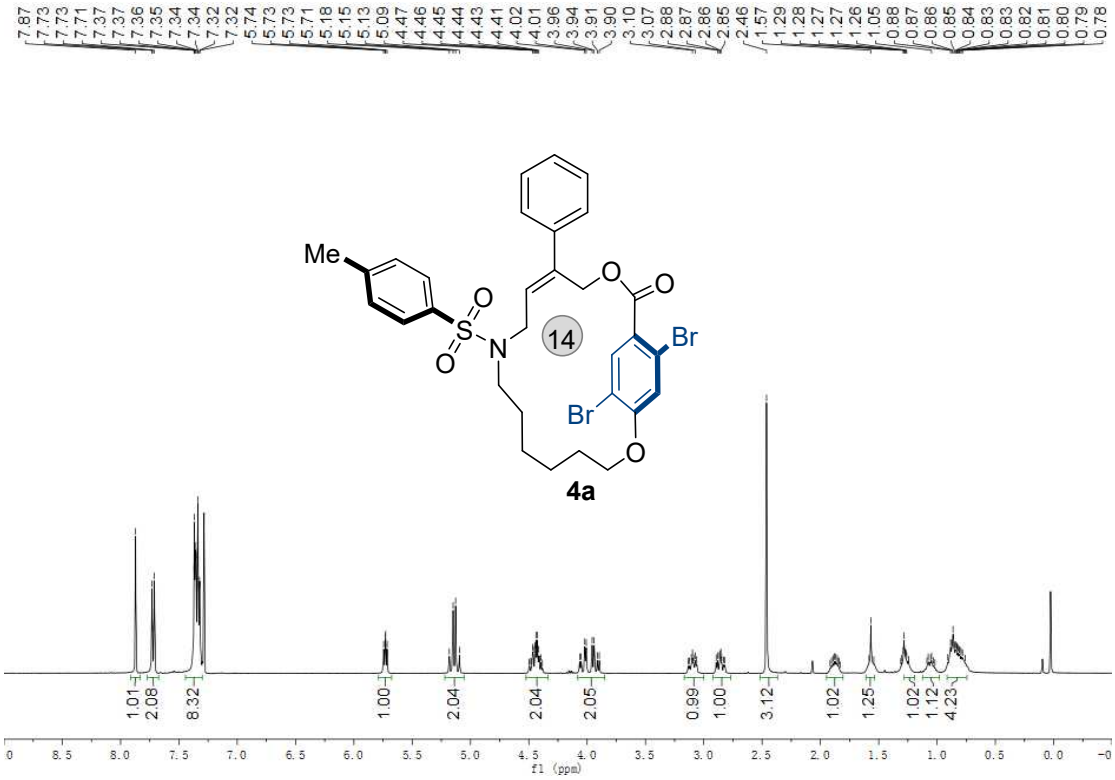
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3t



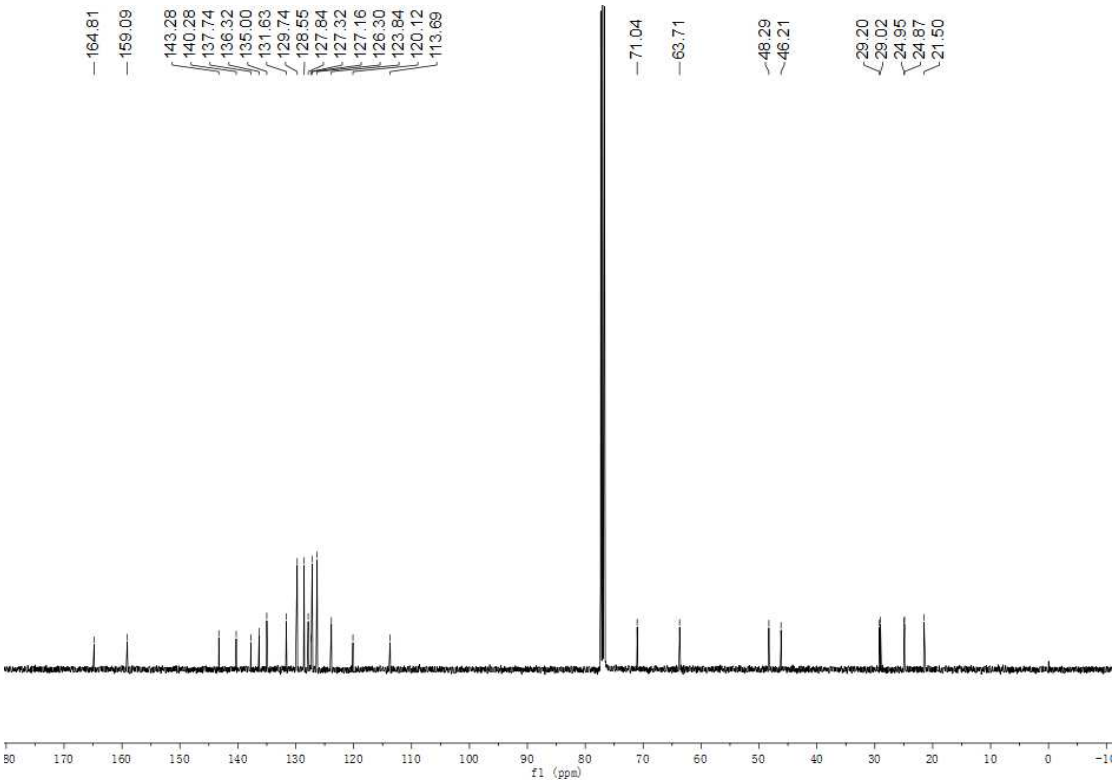
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3t



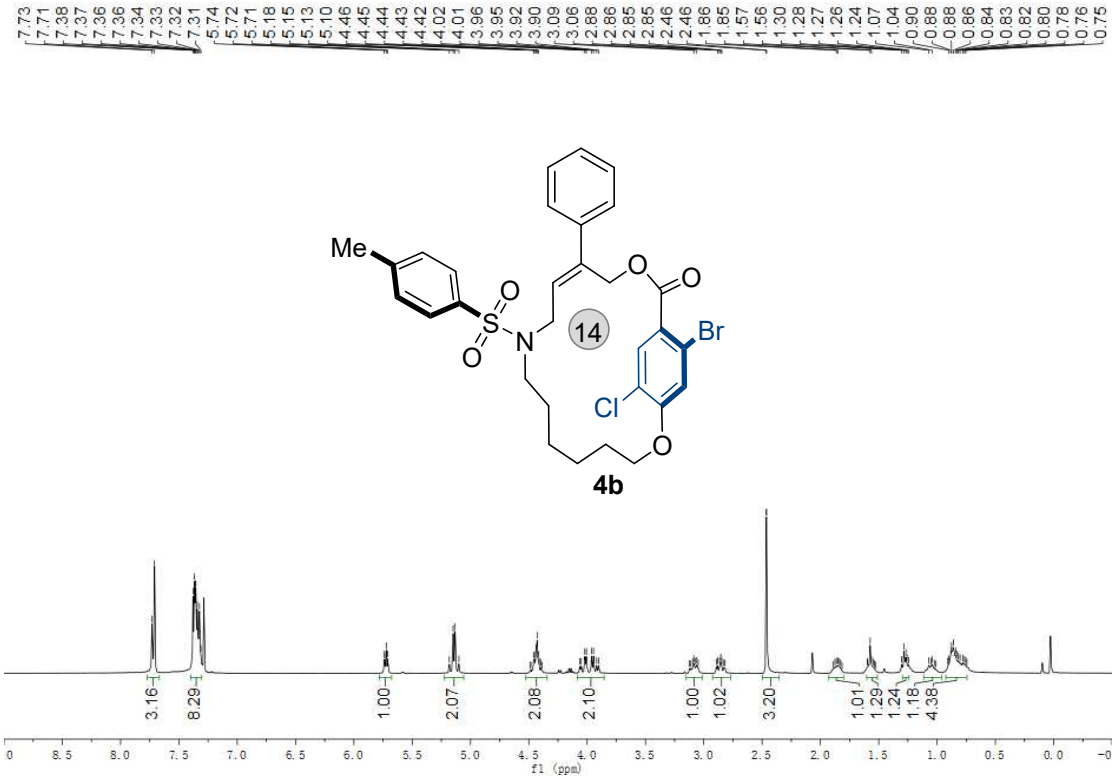
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4a



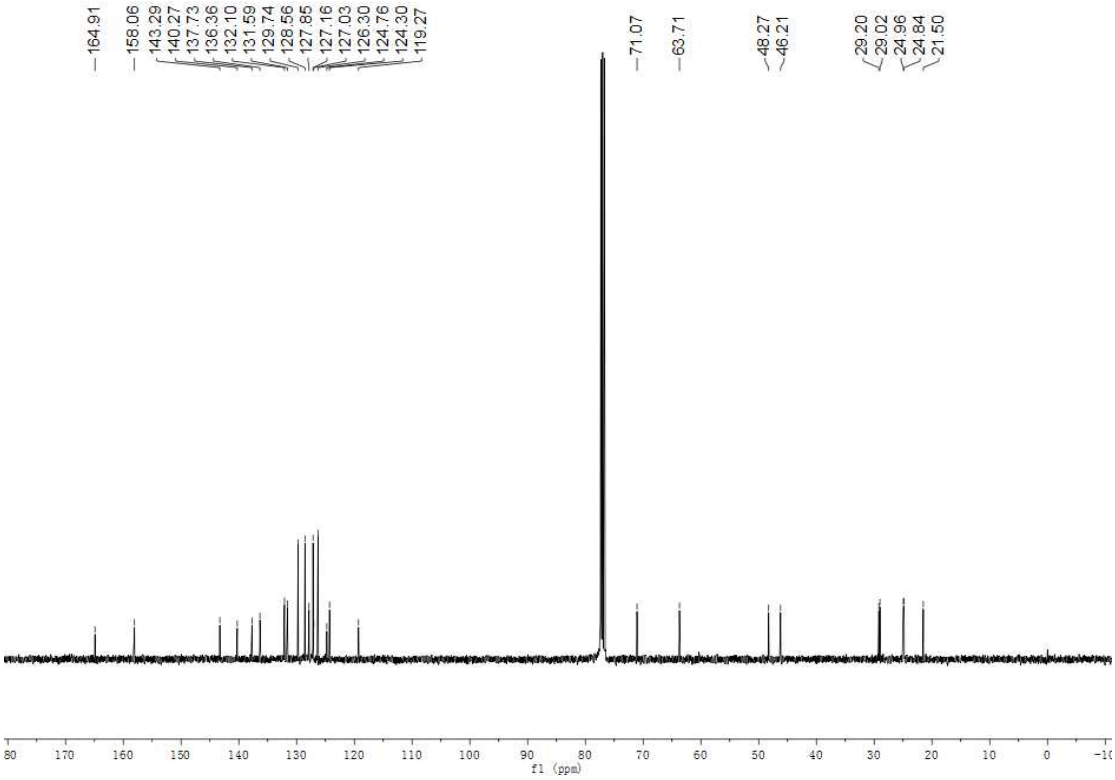
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4a



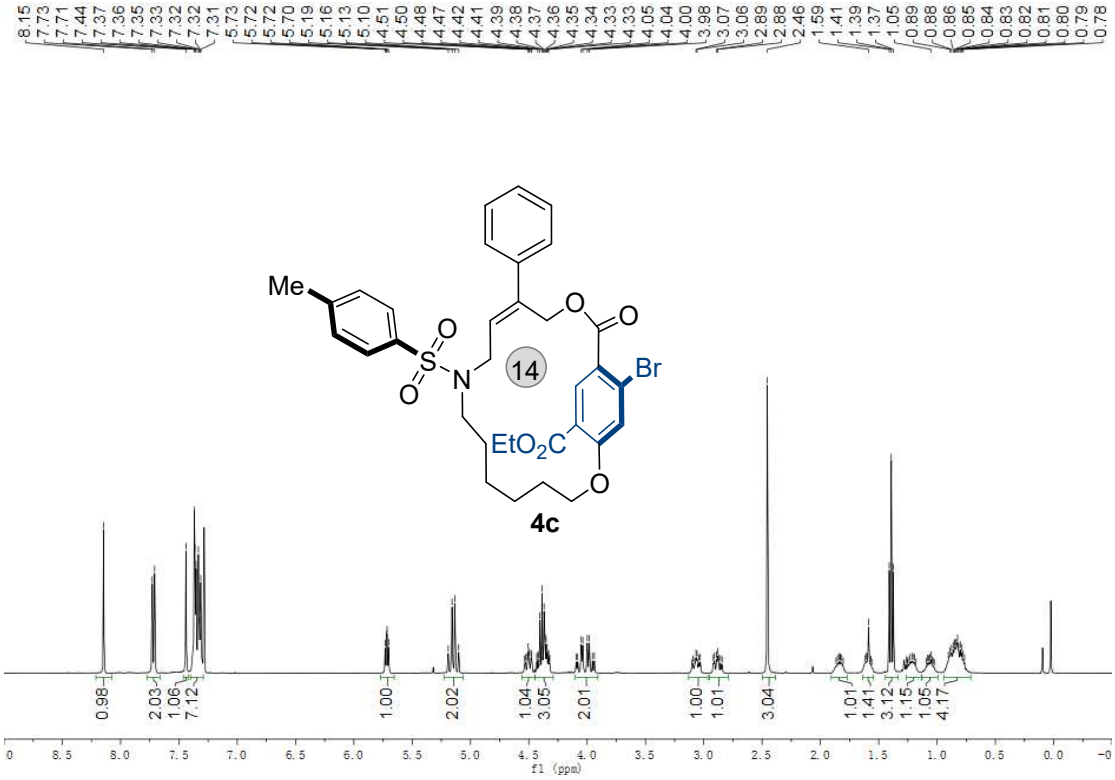
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4b



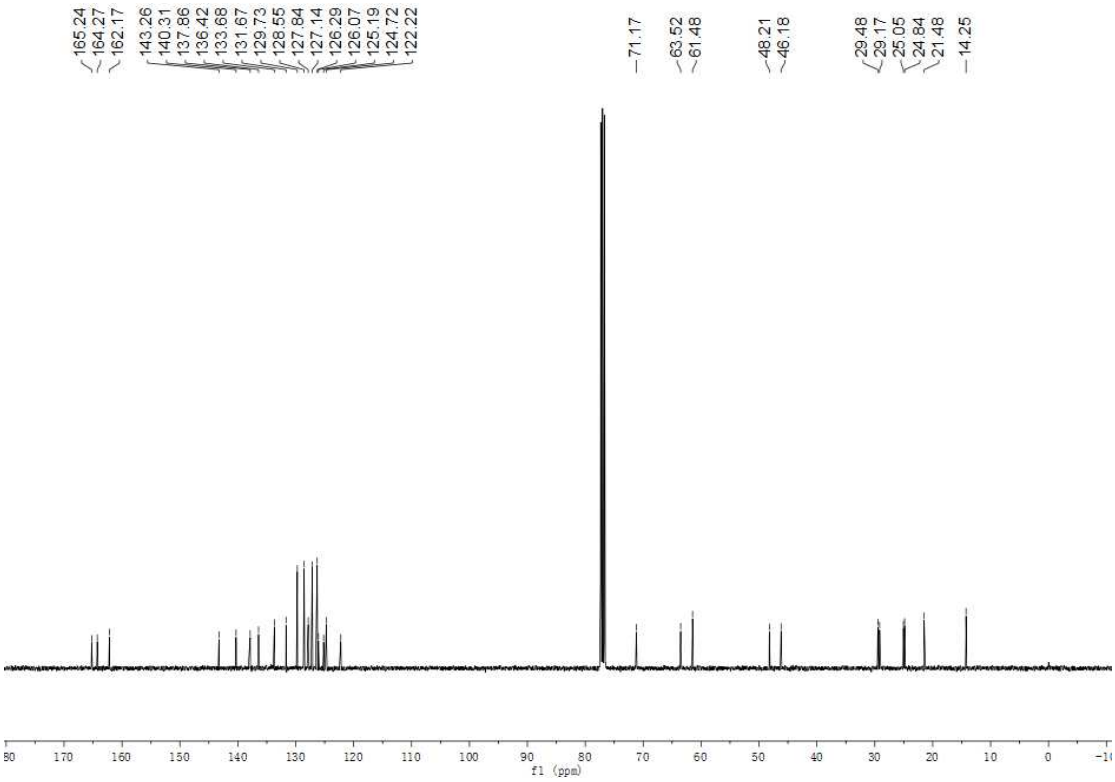
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4b



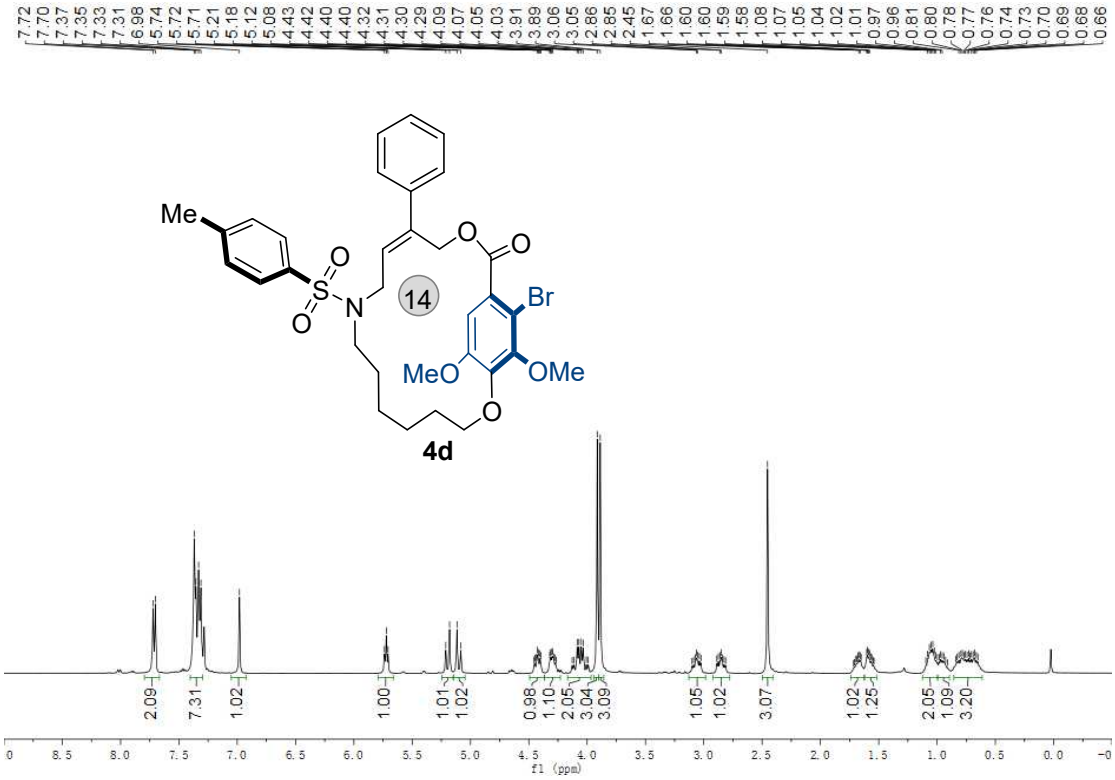
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4c



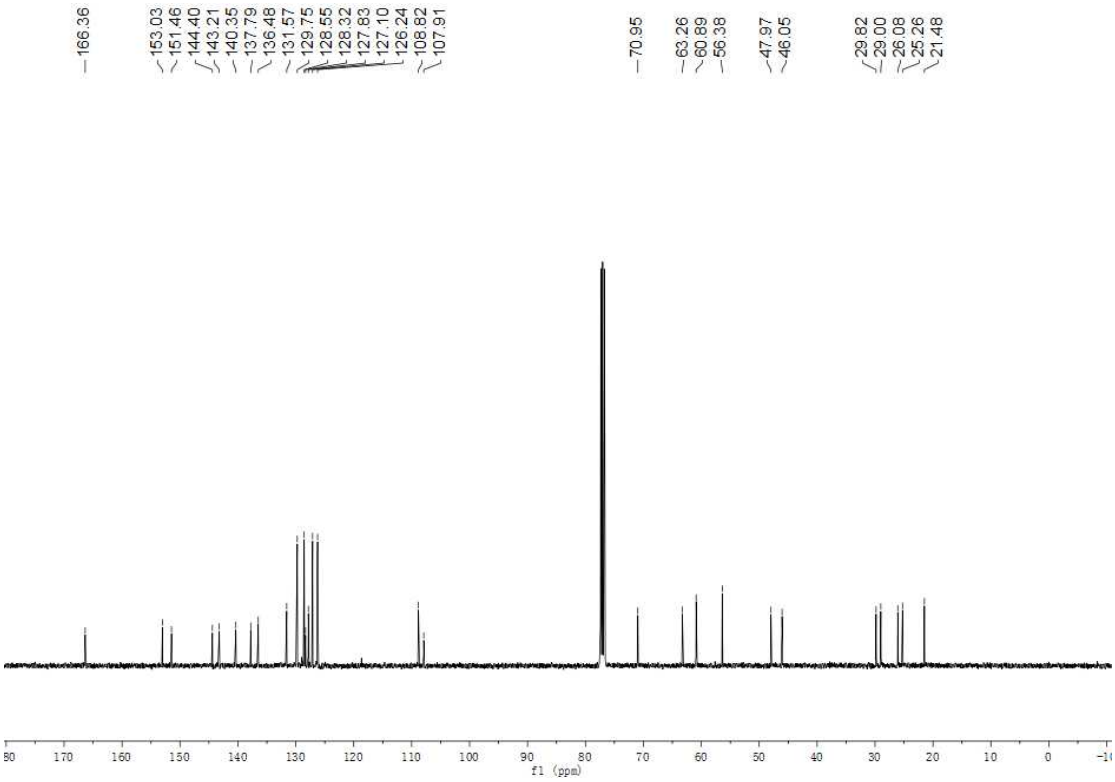
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4c



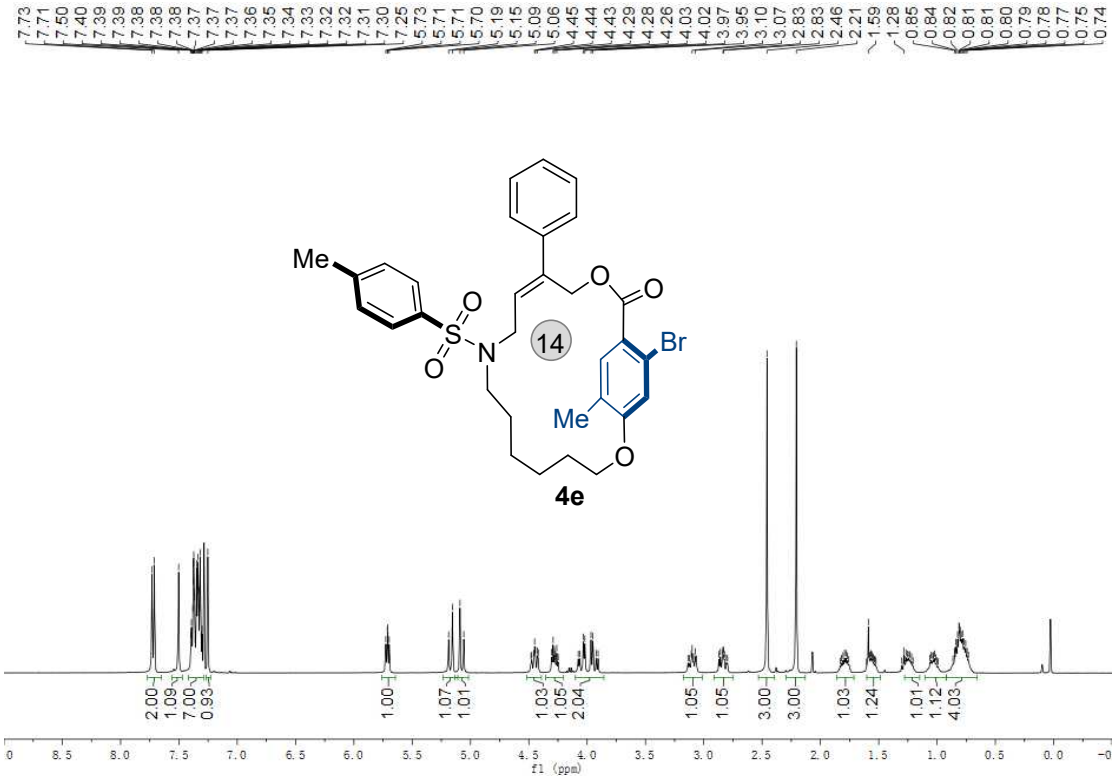
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4d



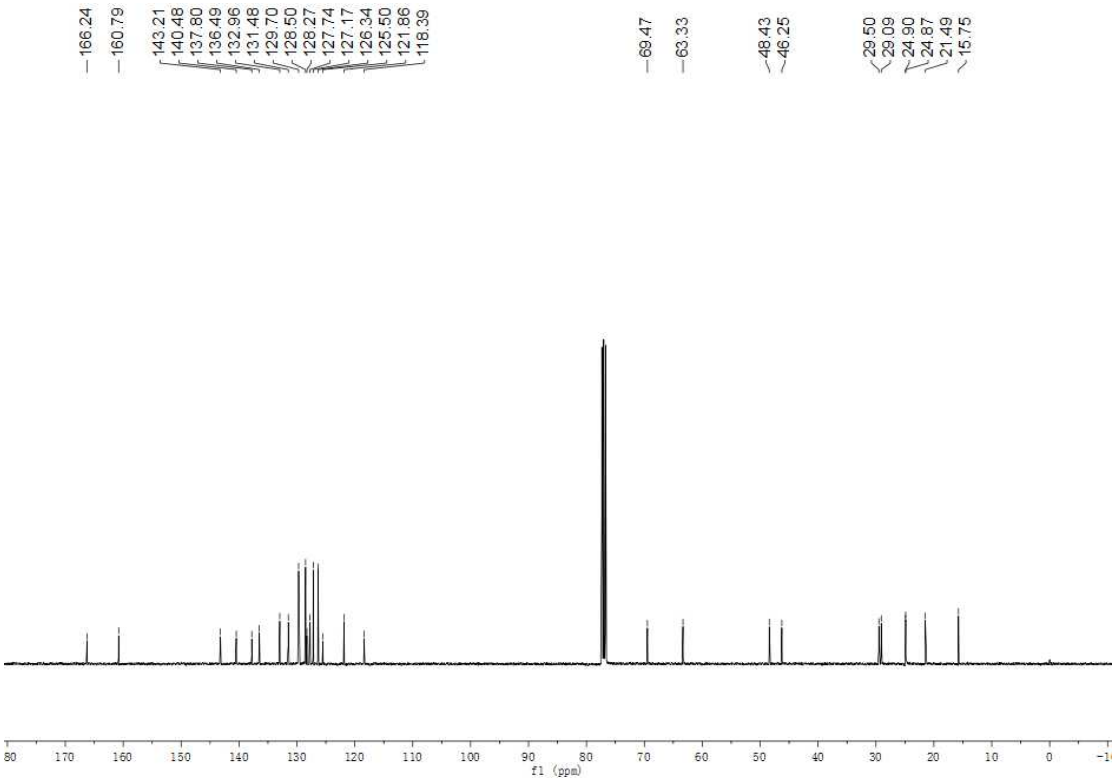
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4d



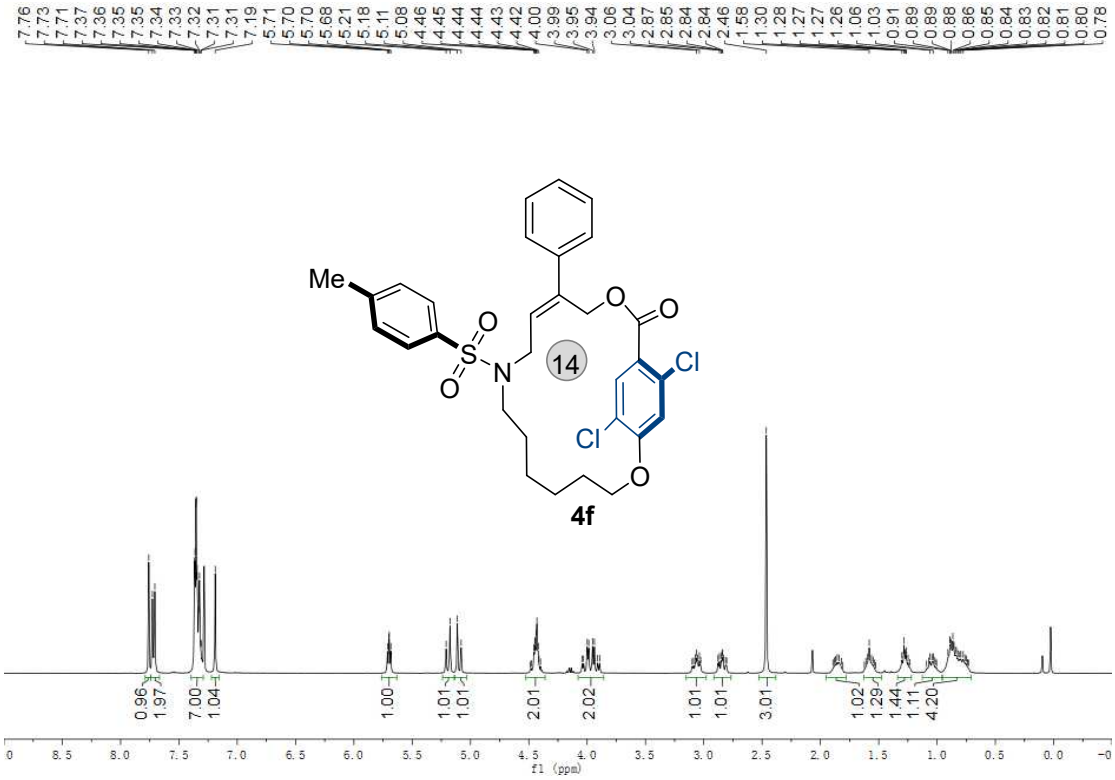
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4e



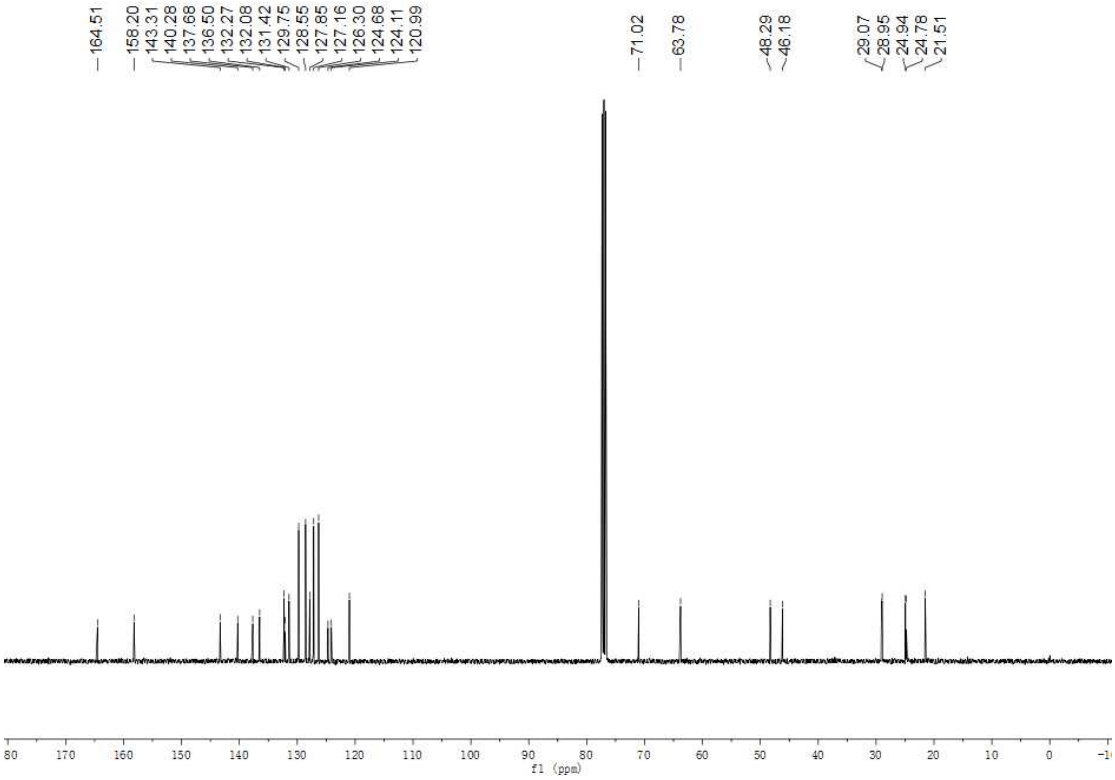
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4e



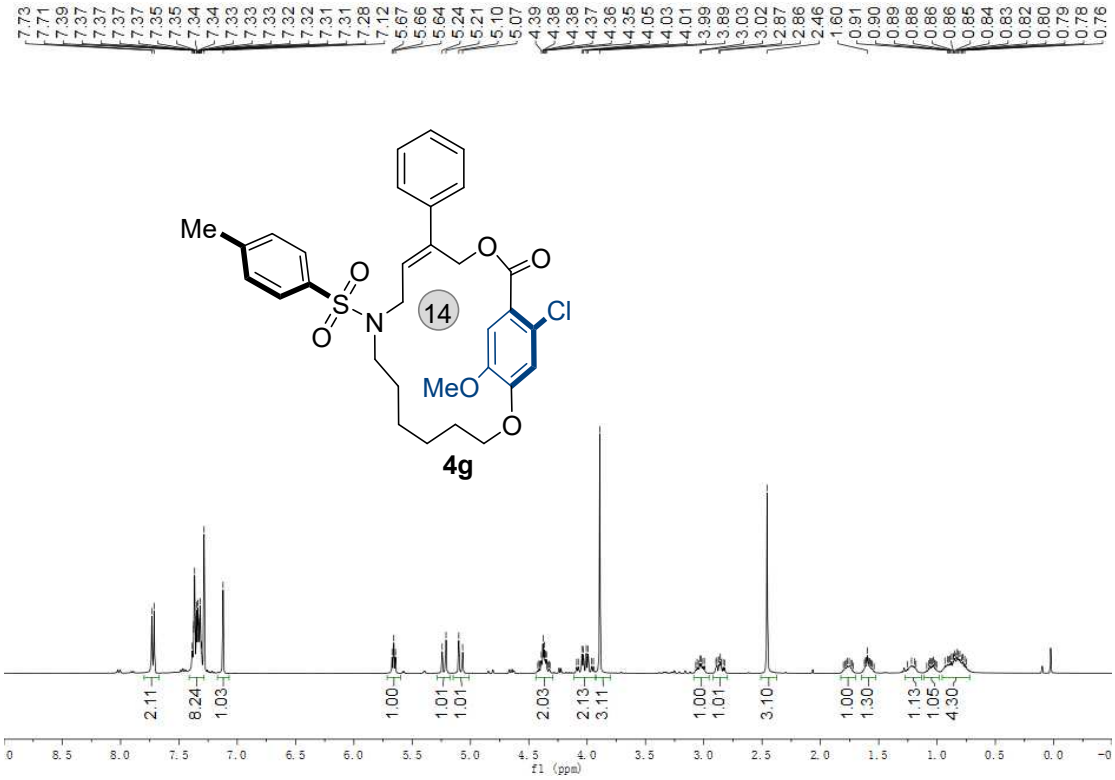
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4f



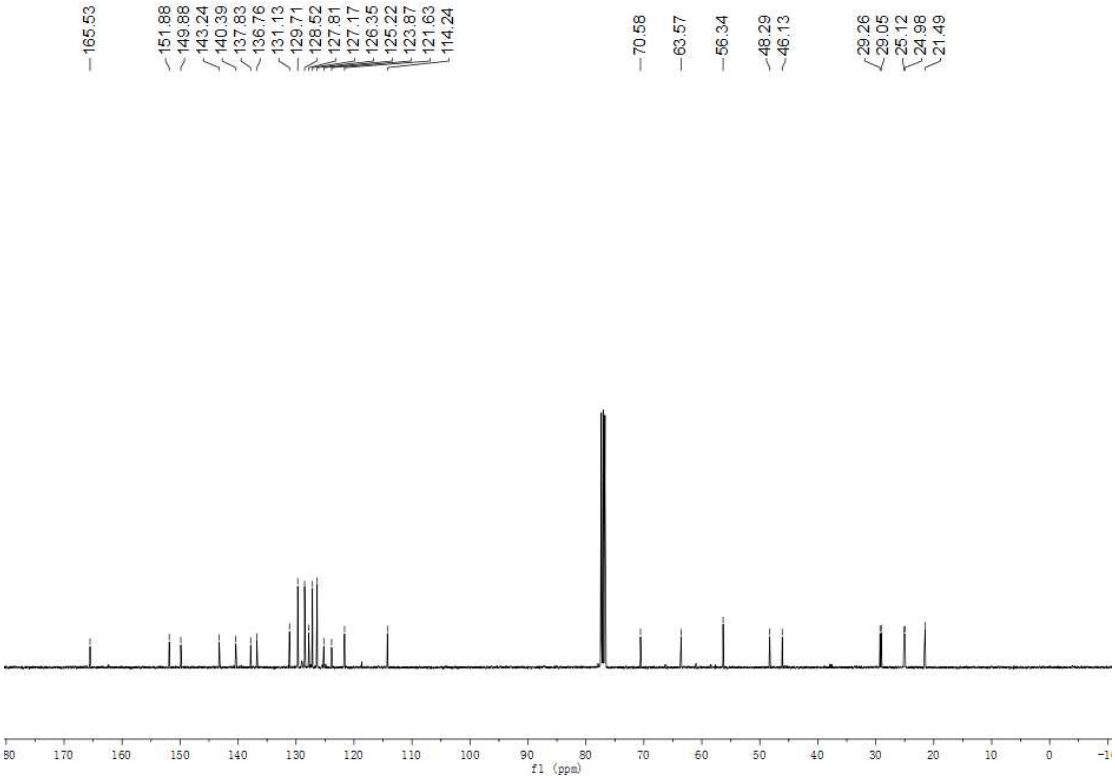
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4f



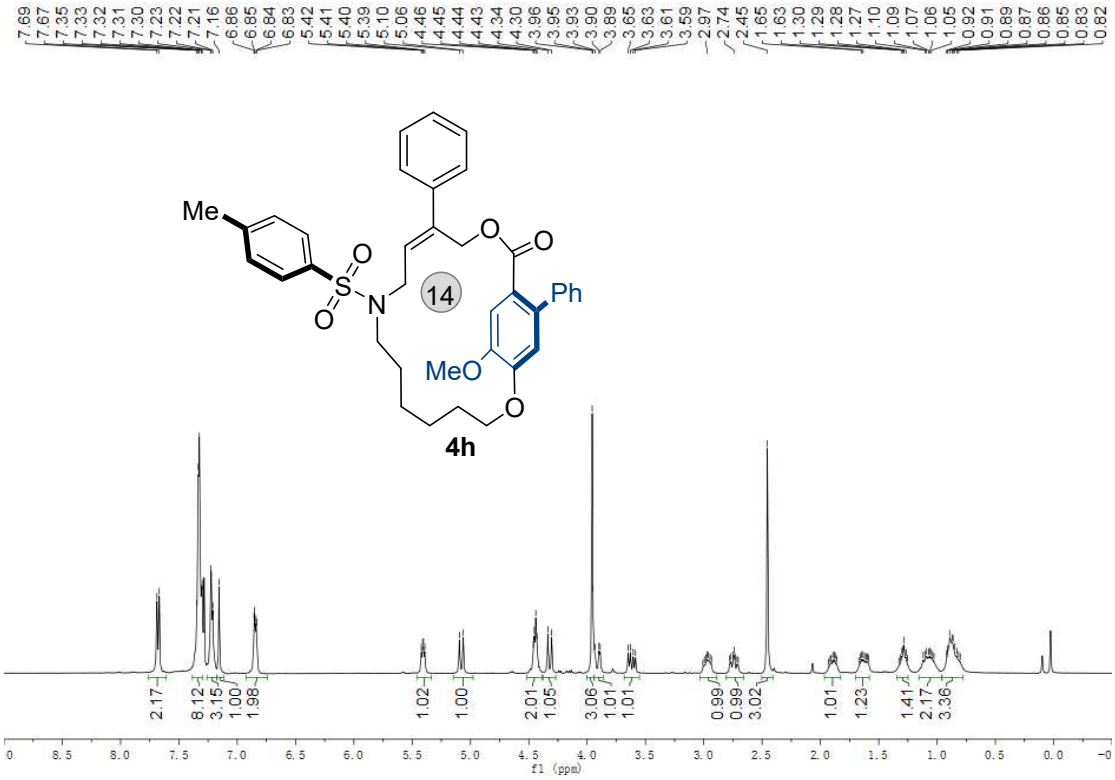
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4g



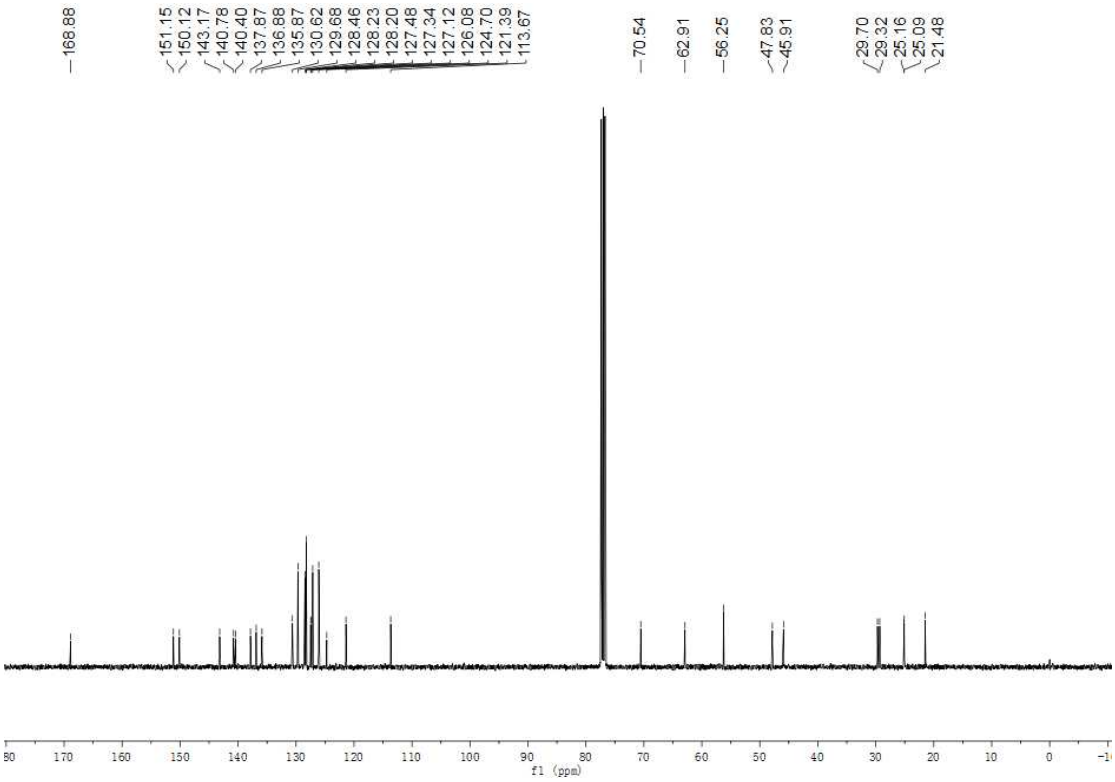
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4g



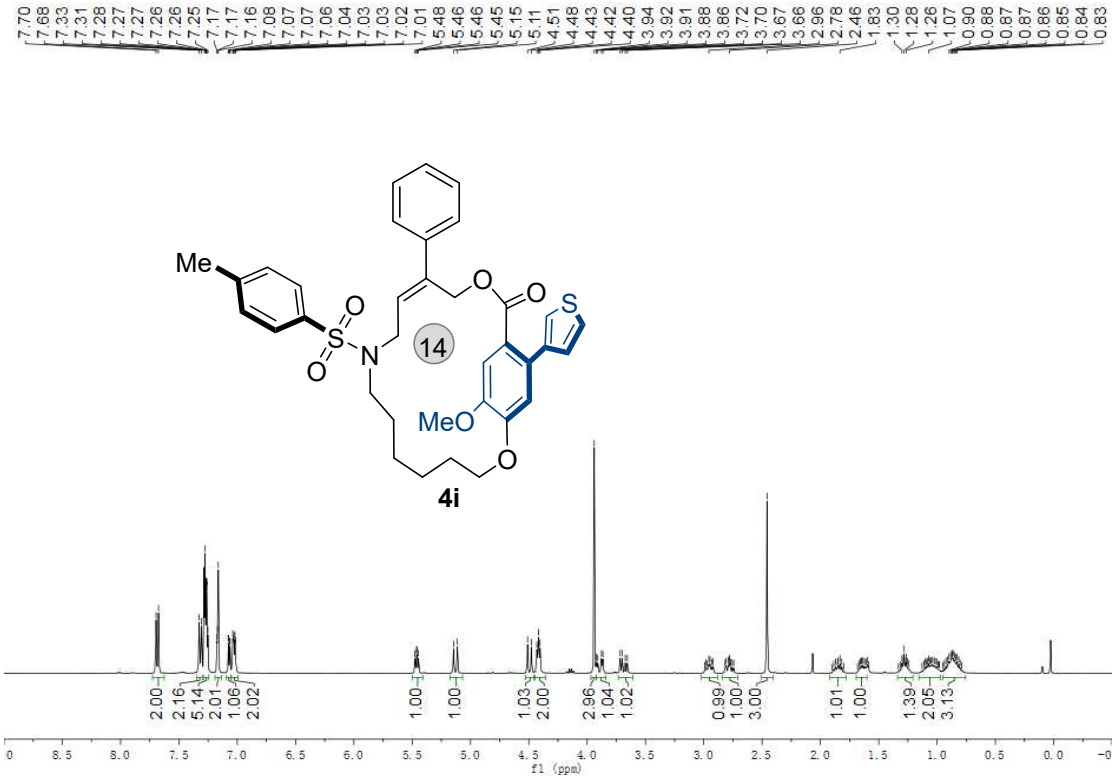
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4h



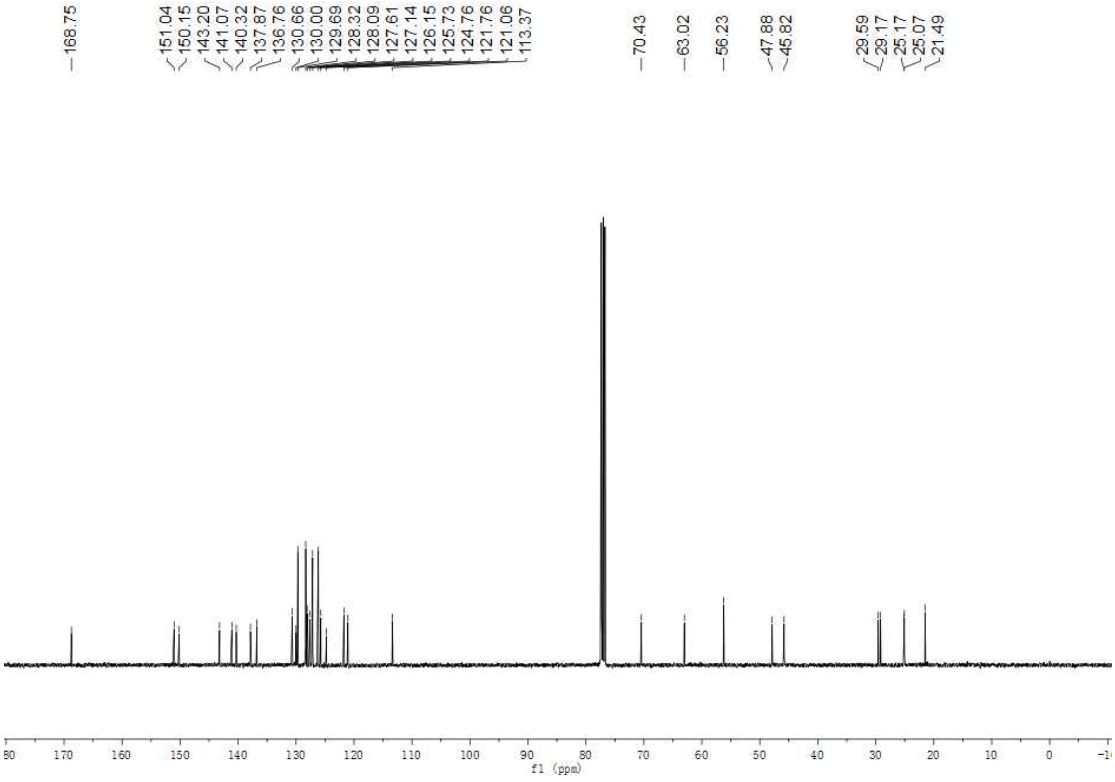
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4h



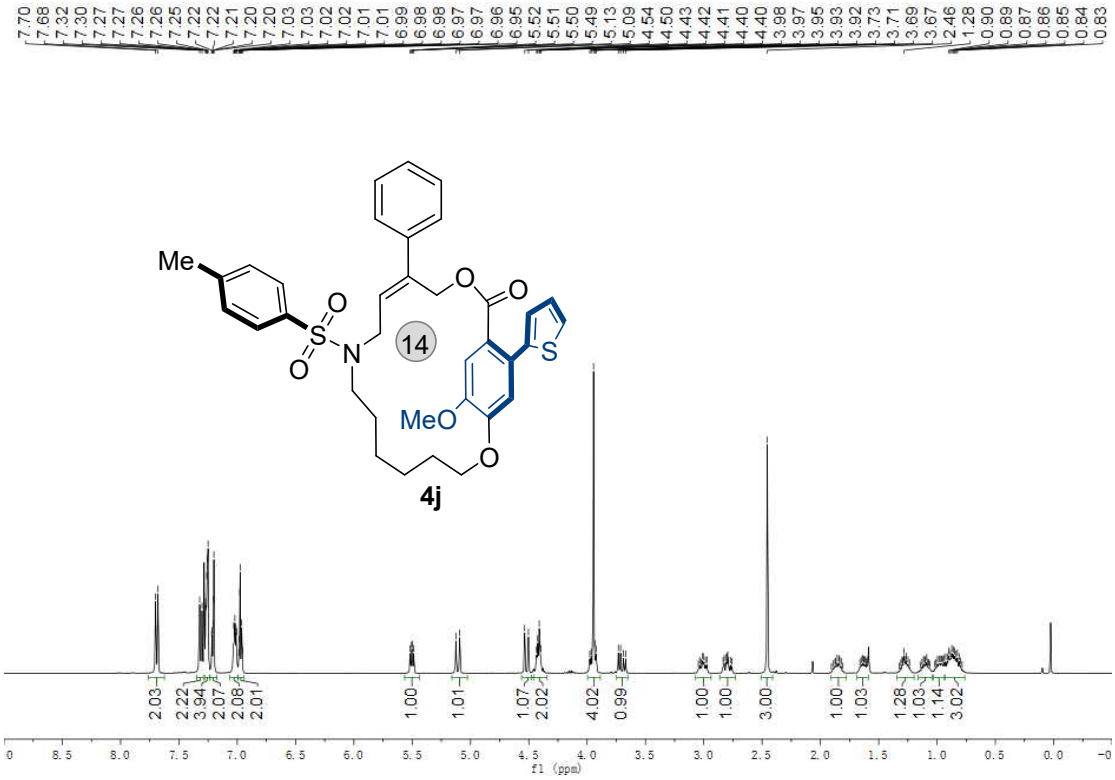
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4i



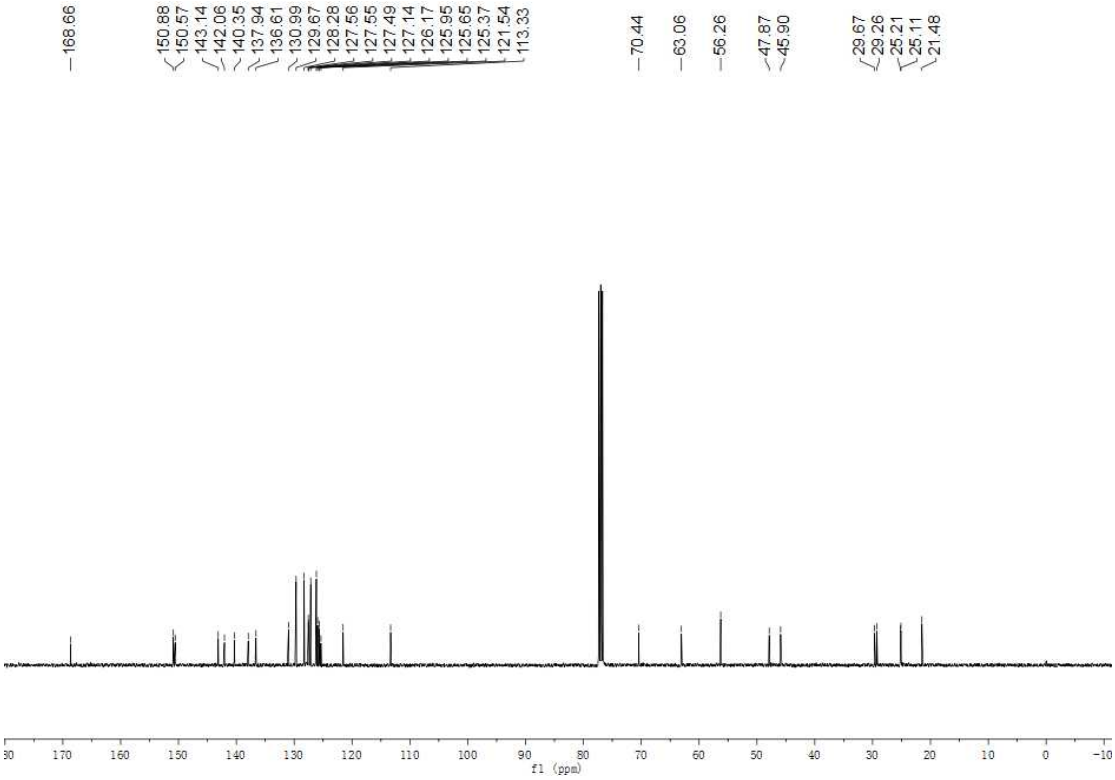
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4i



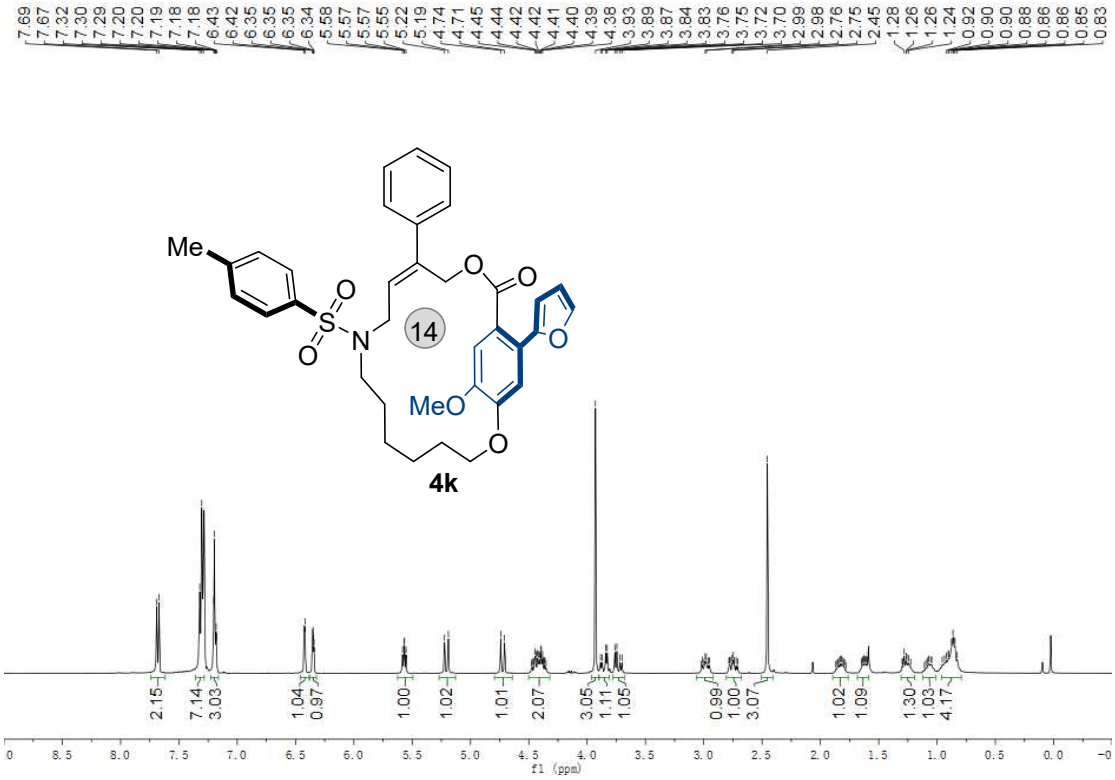
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4j



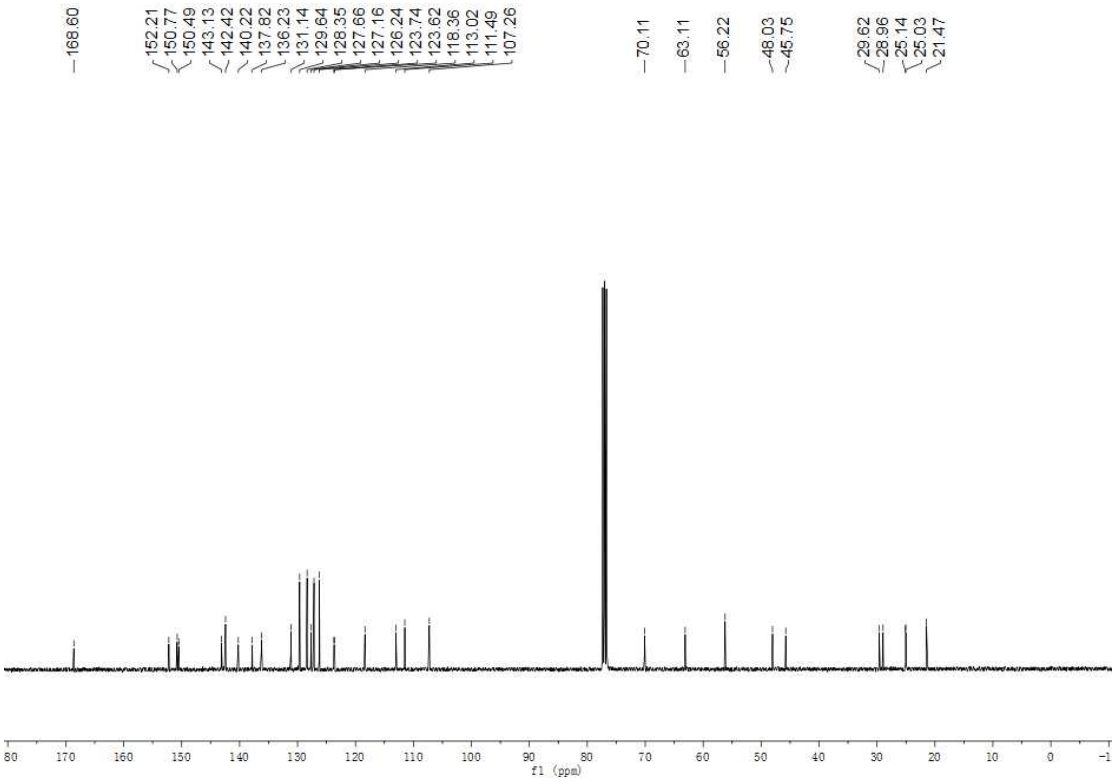
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4j



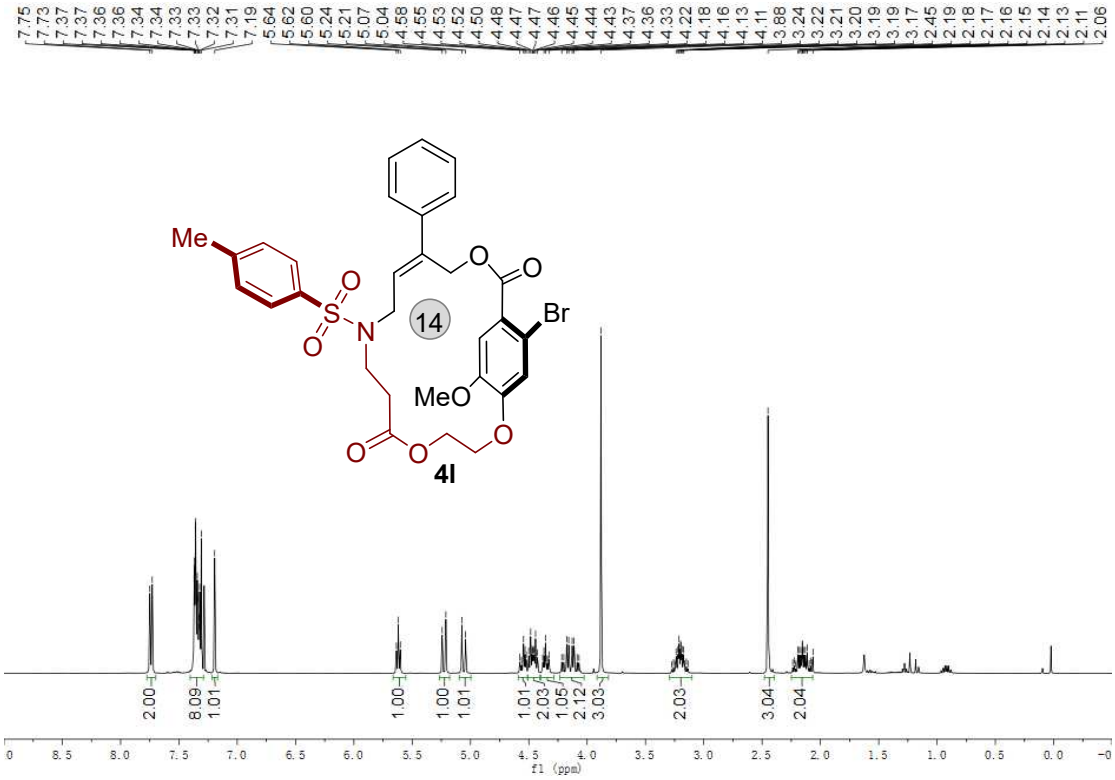
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4k



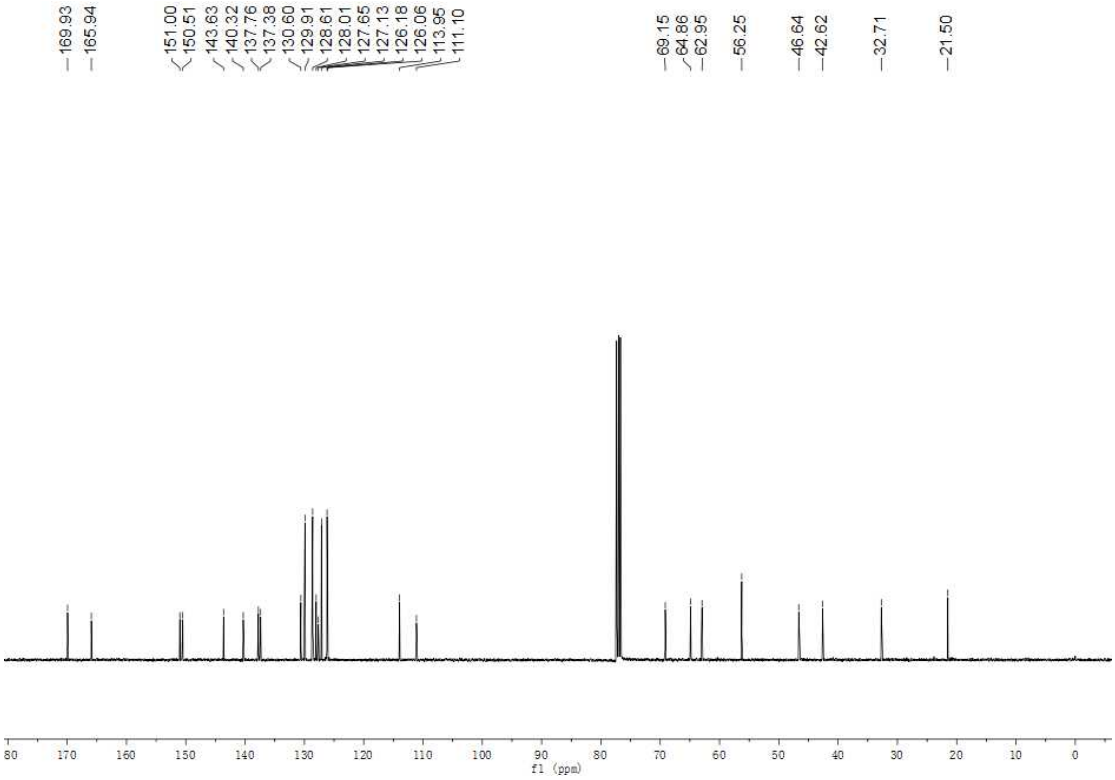
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4k



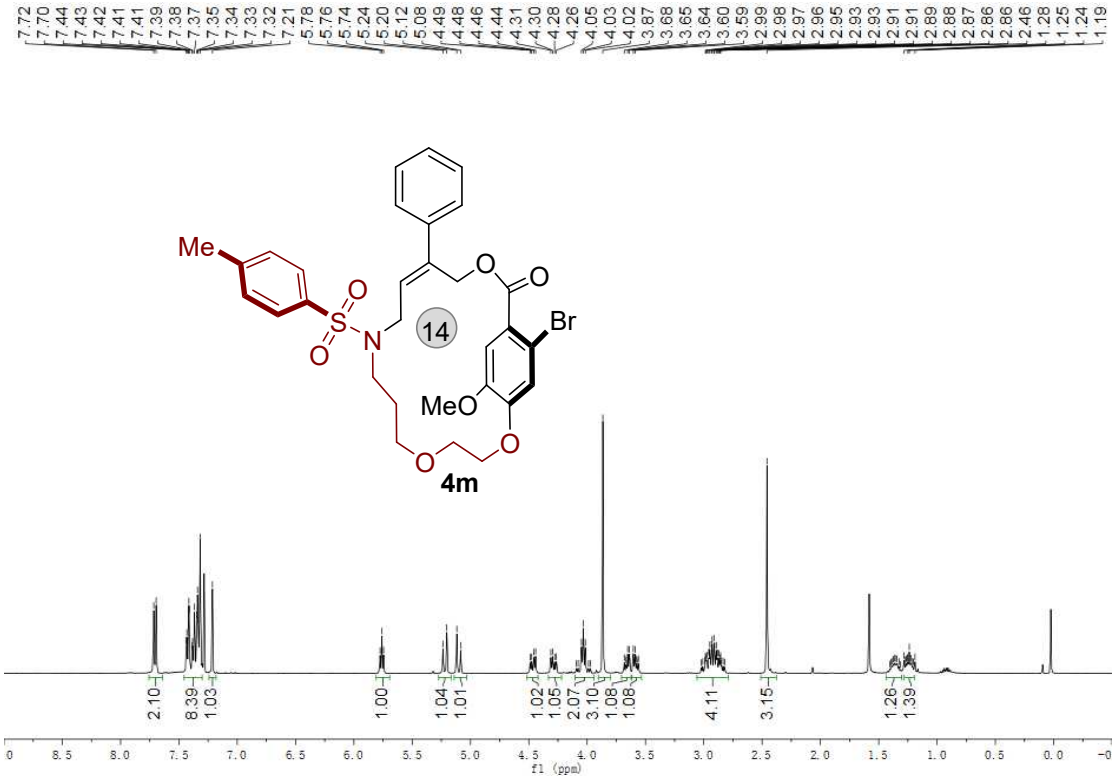
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4l



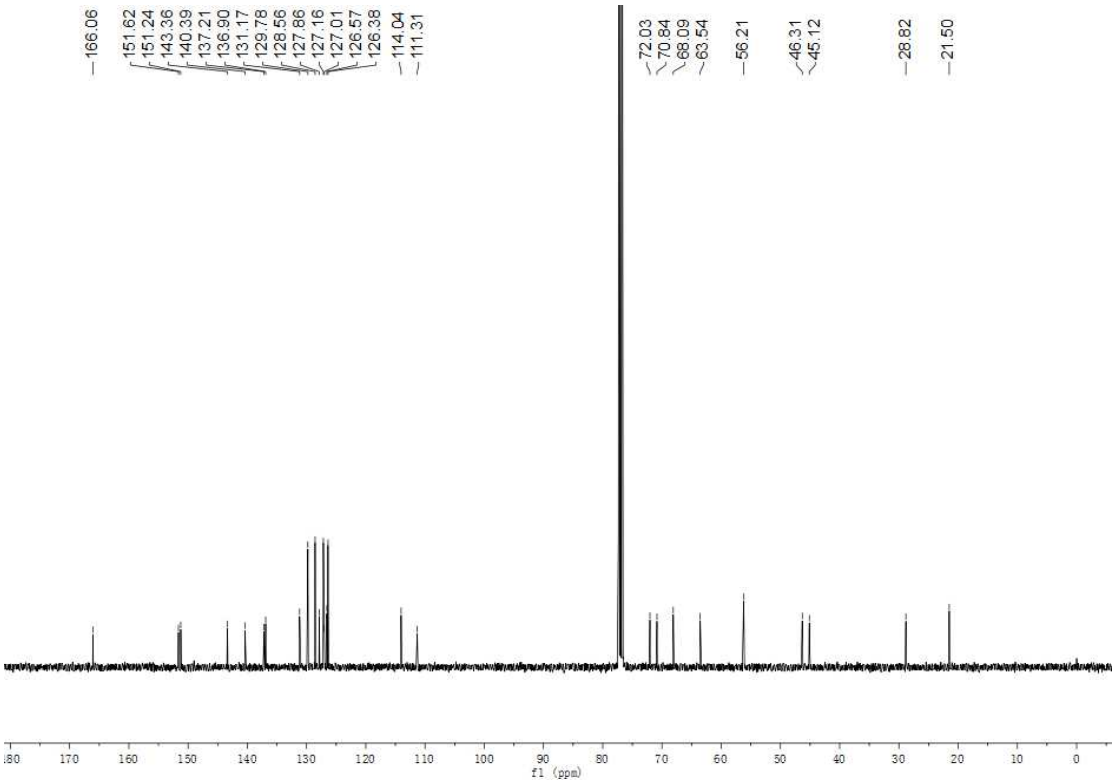
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4l



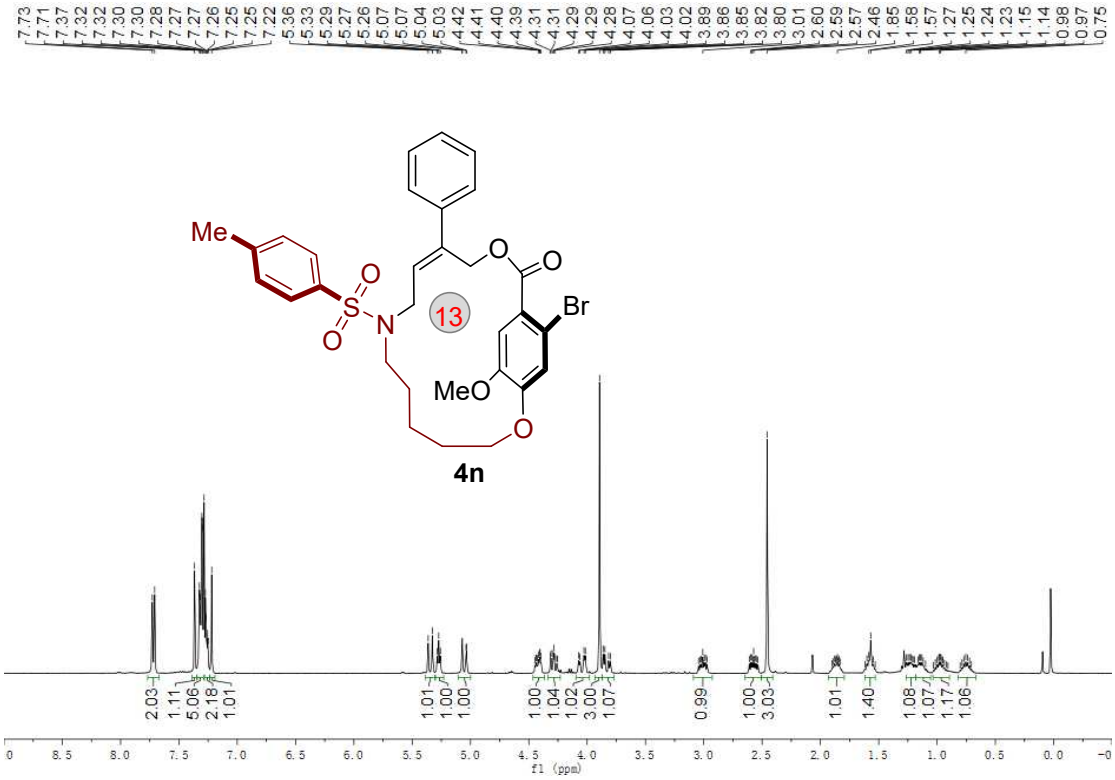
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4m



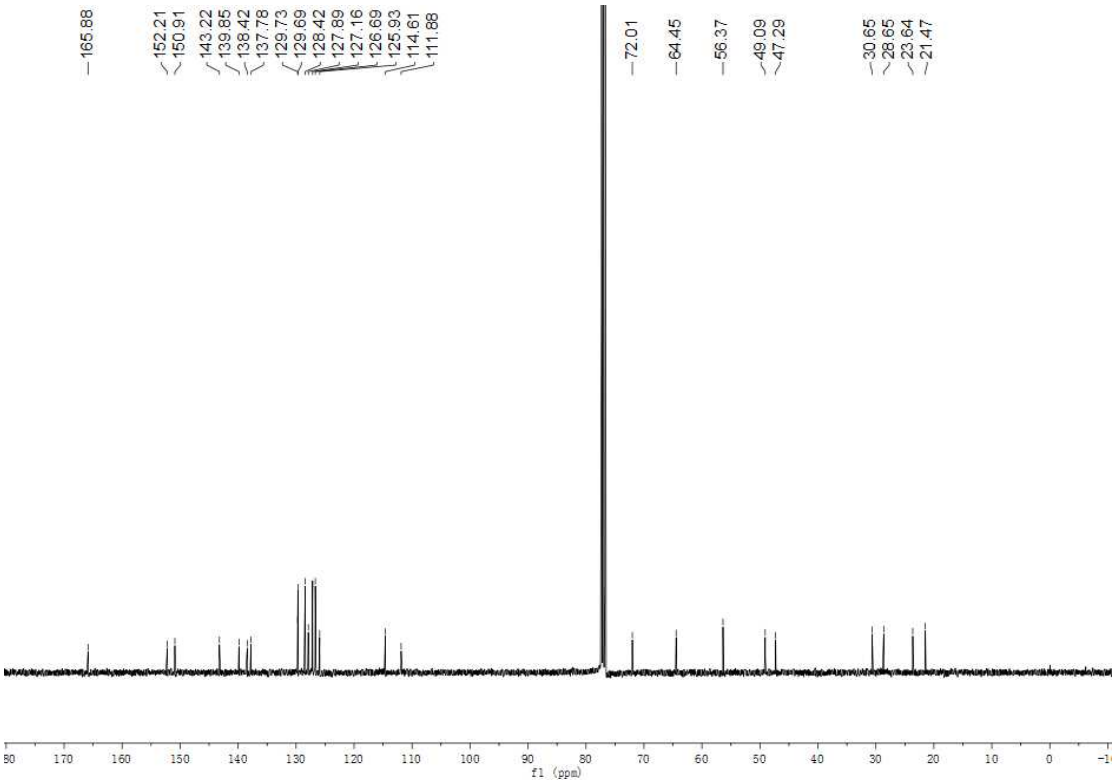
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4m



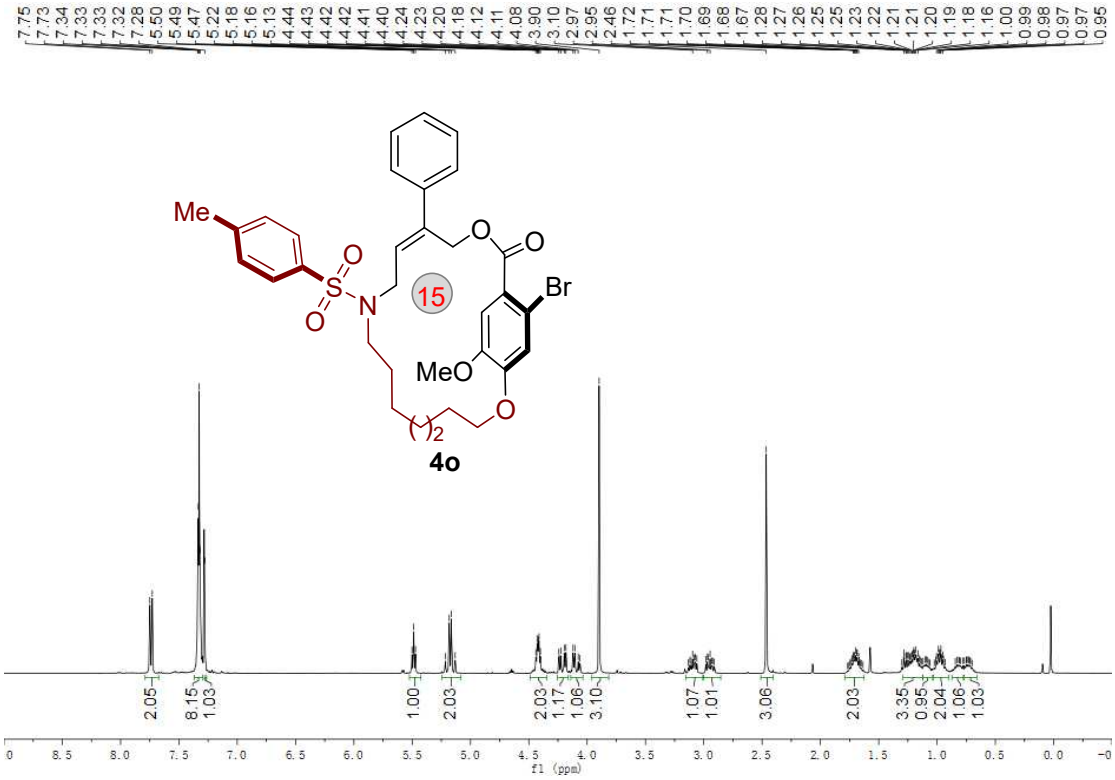
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4n



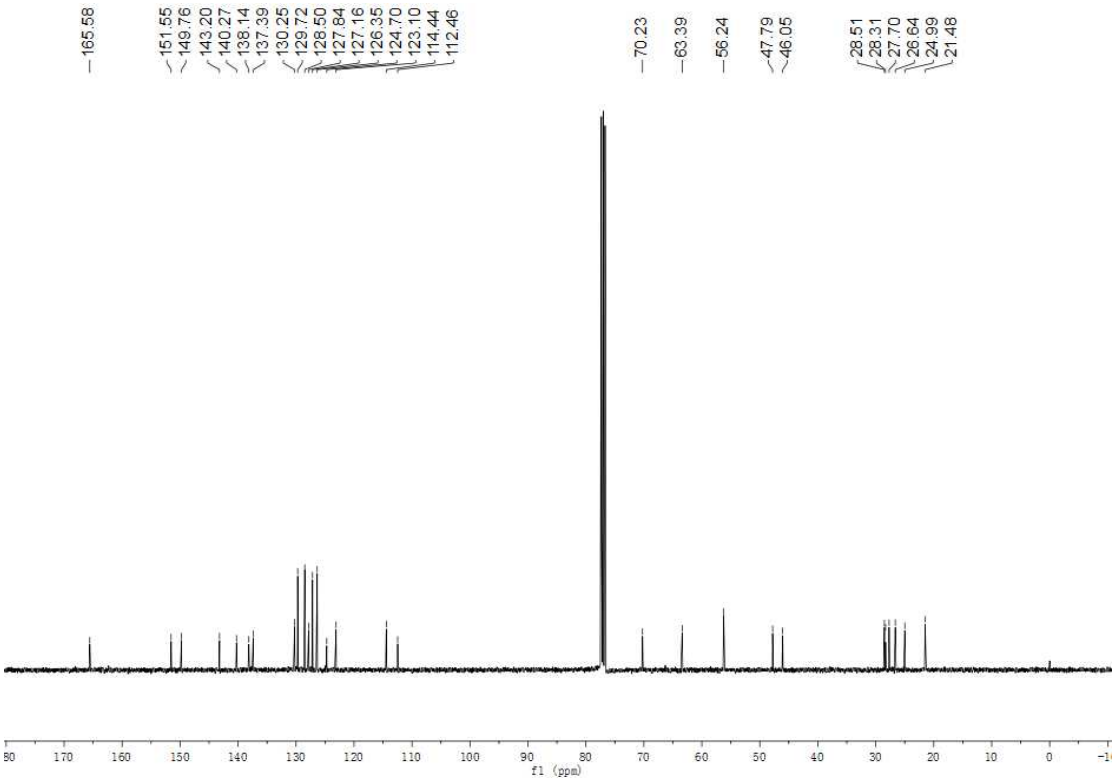
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4n



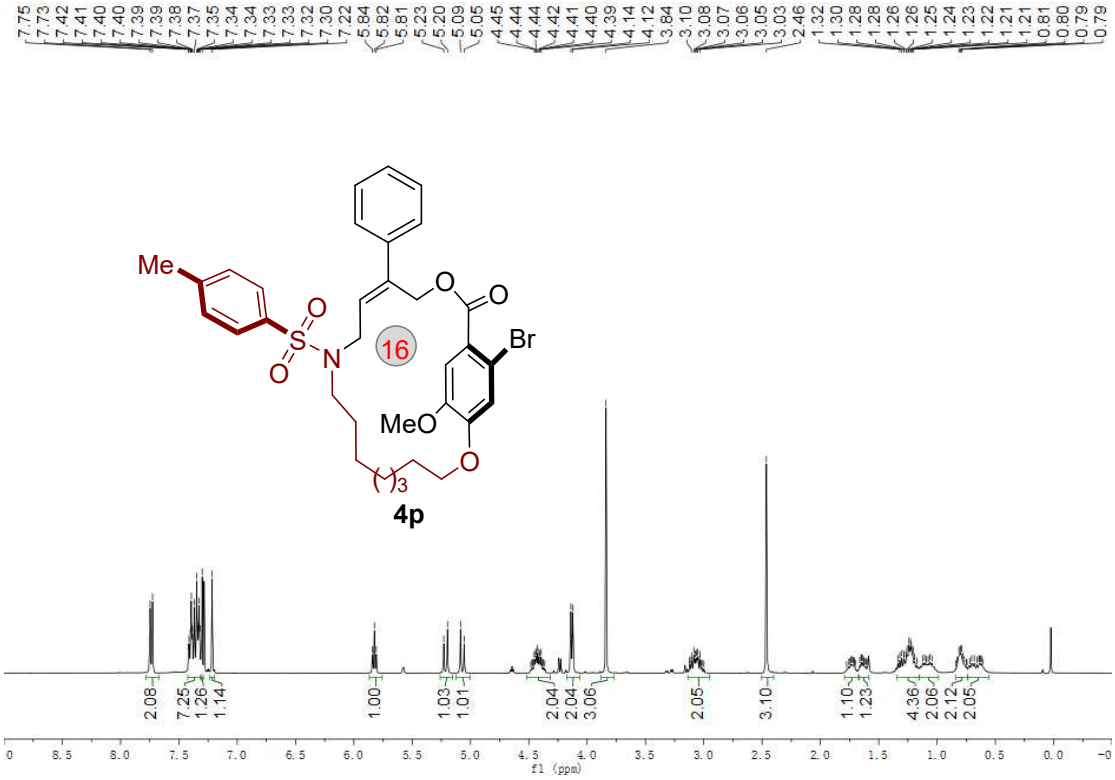
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4o



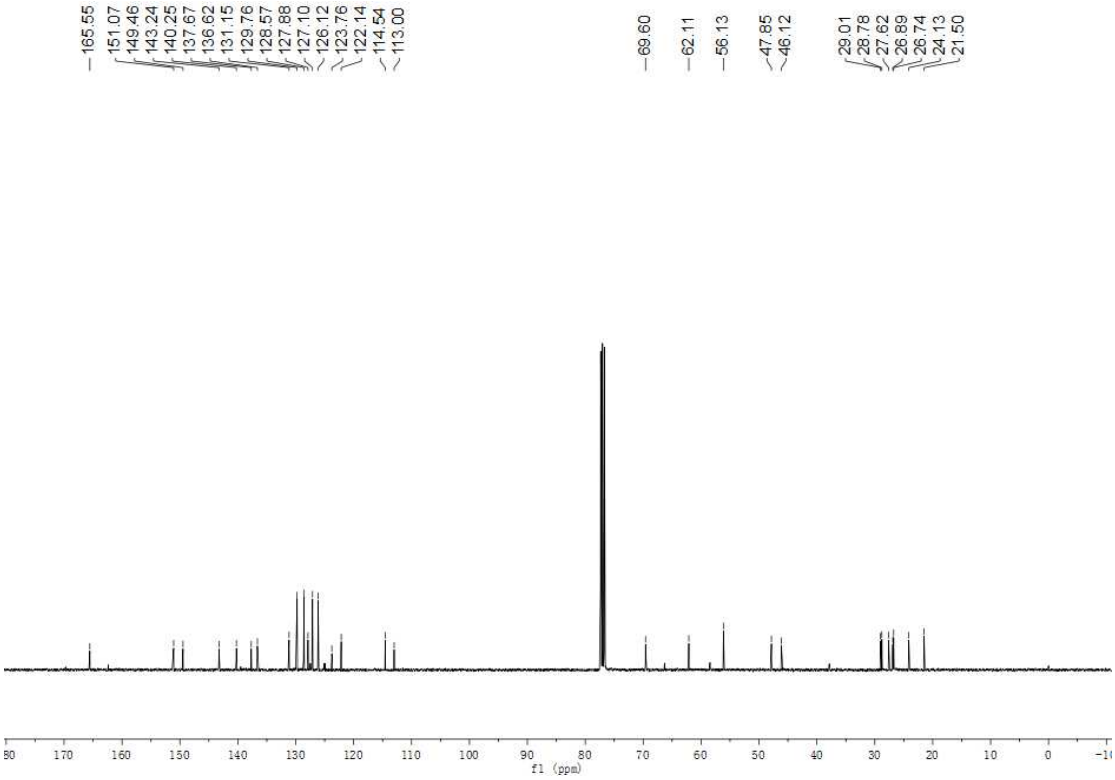
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4o



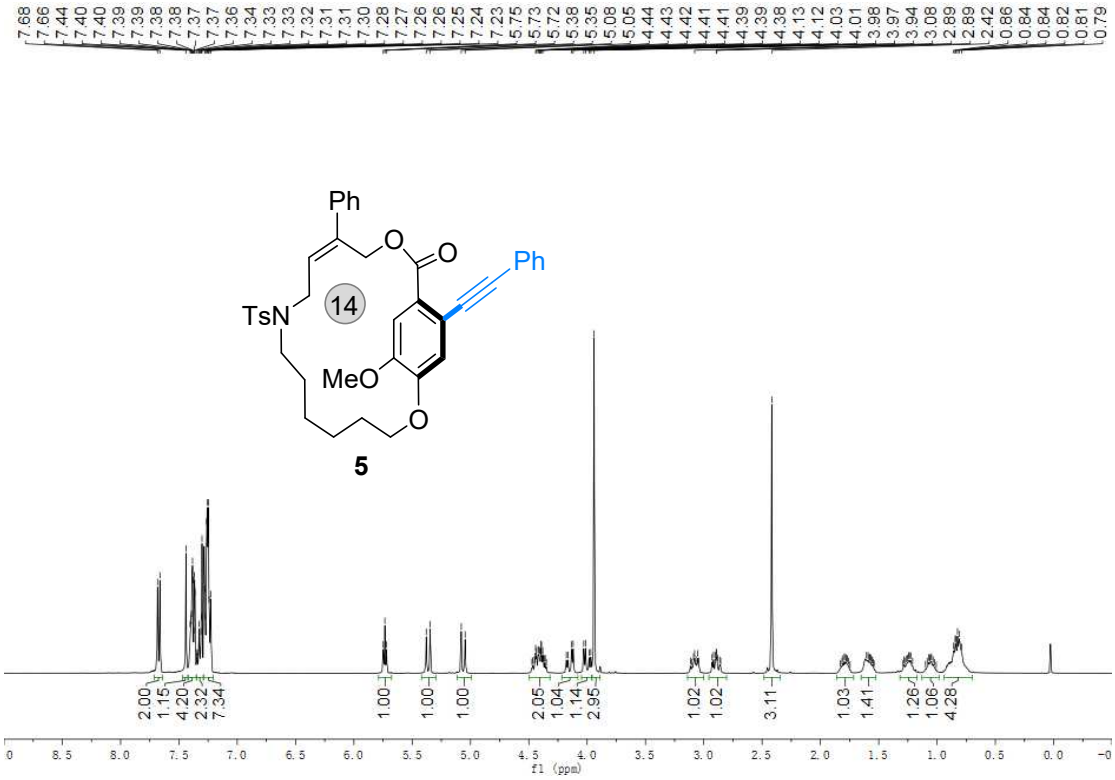
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 4p



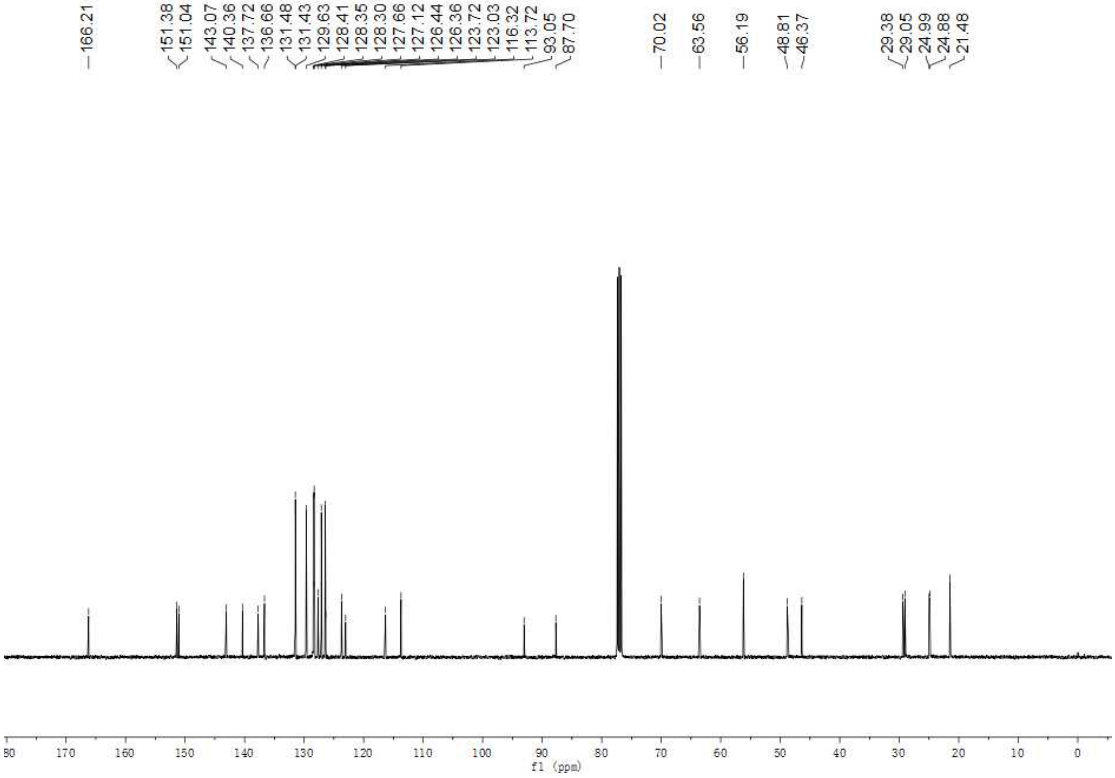
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 4p



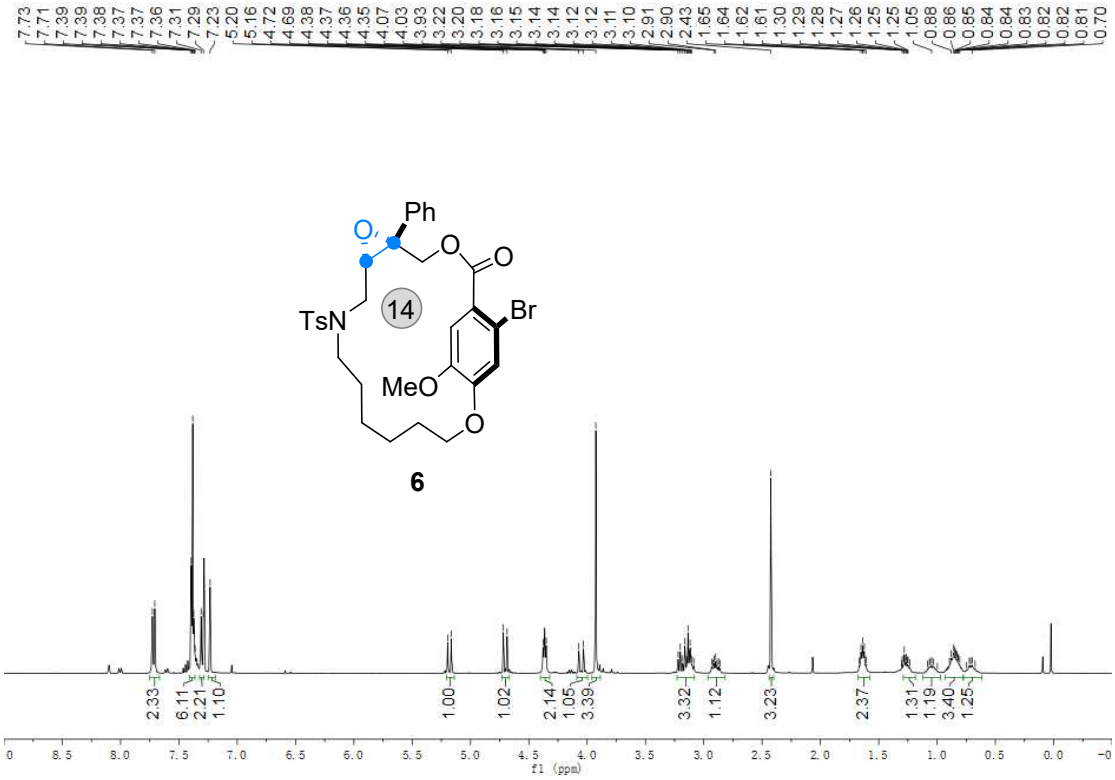
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 5



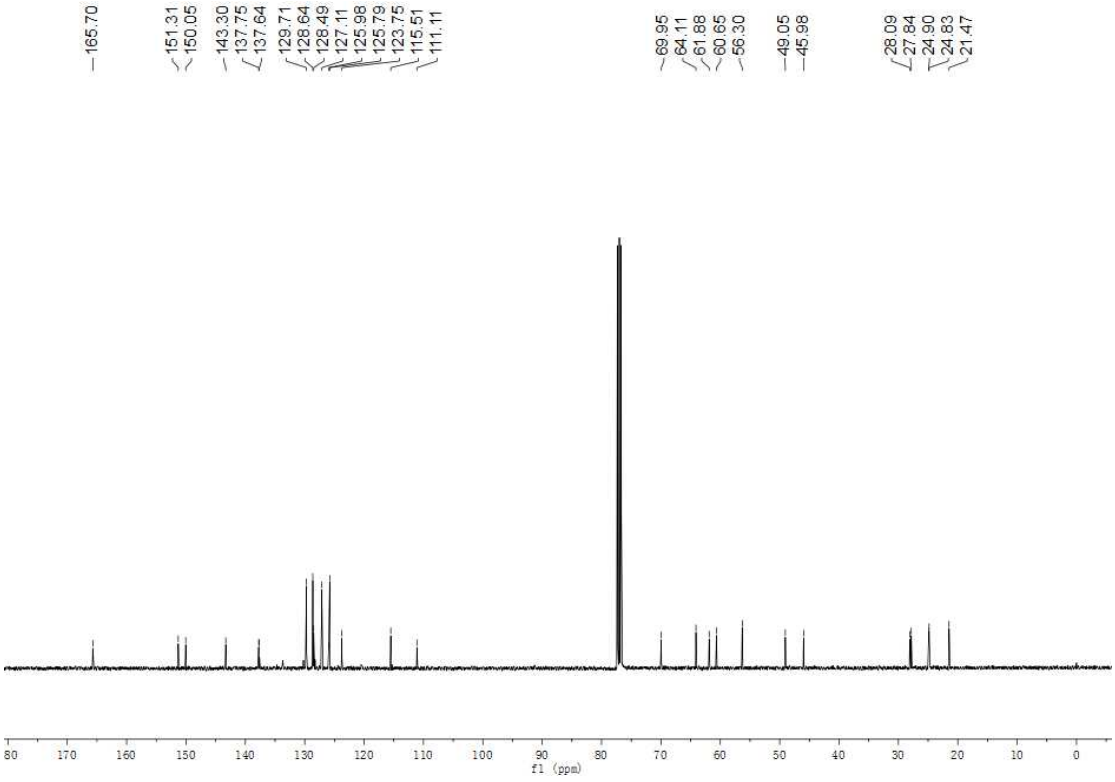
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 5



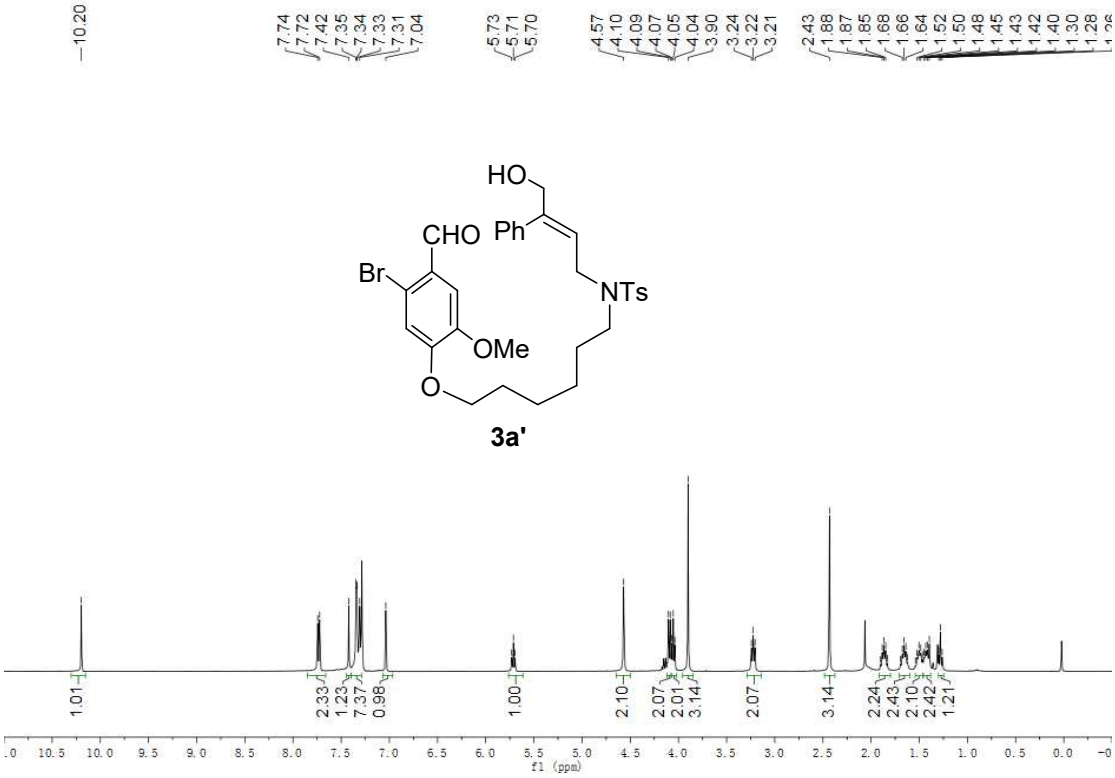
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 6



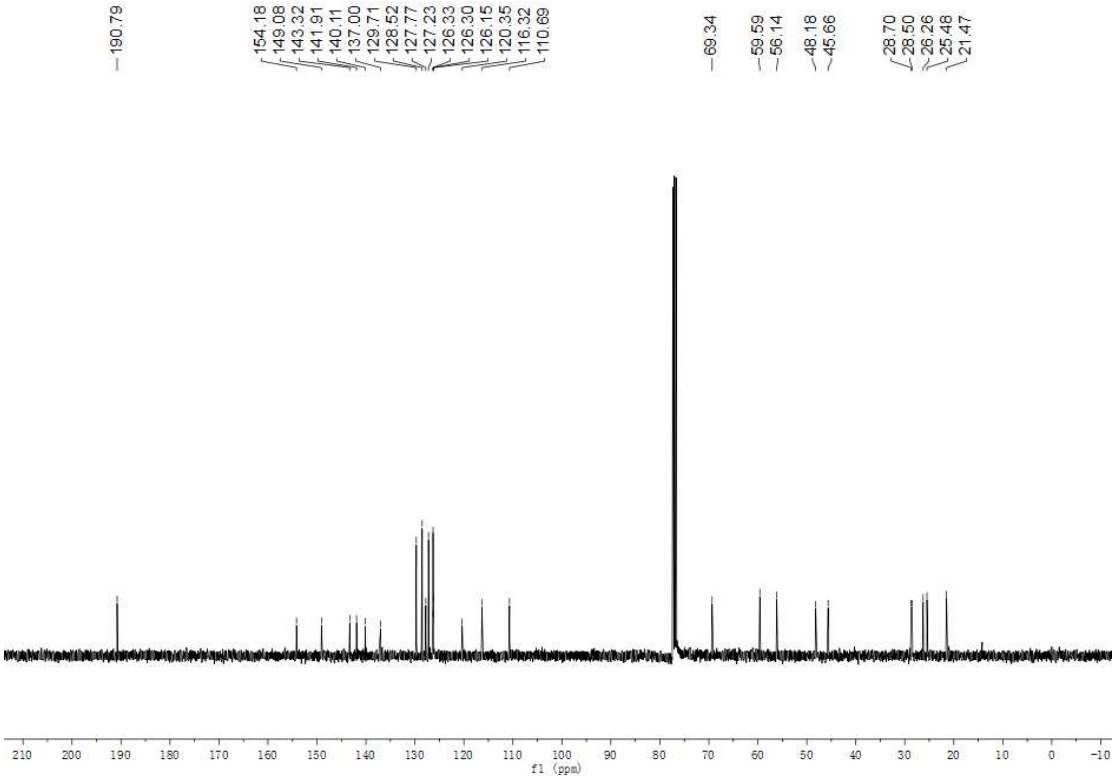
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 6



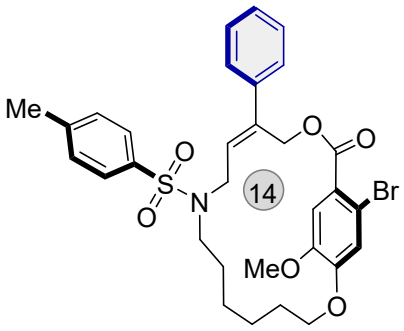
^{1}H NMR (400 MHz, $CDCl_3$) spectra of 3a'



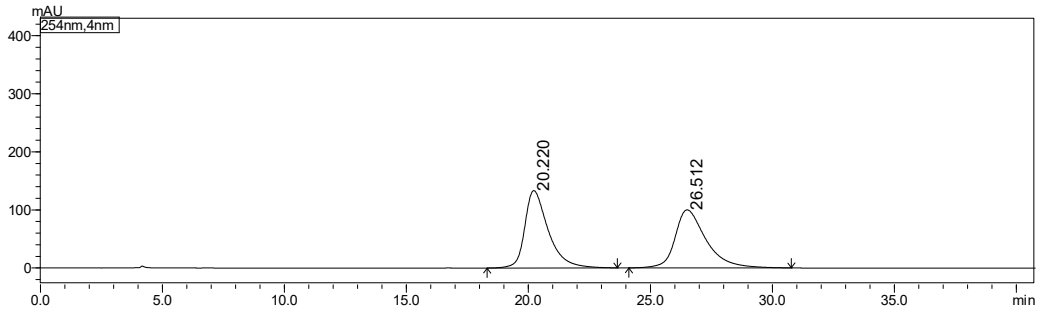
^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3a'



HPLC Spectra

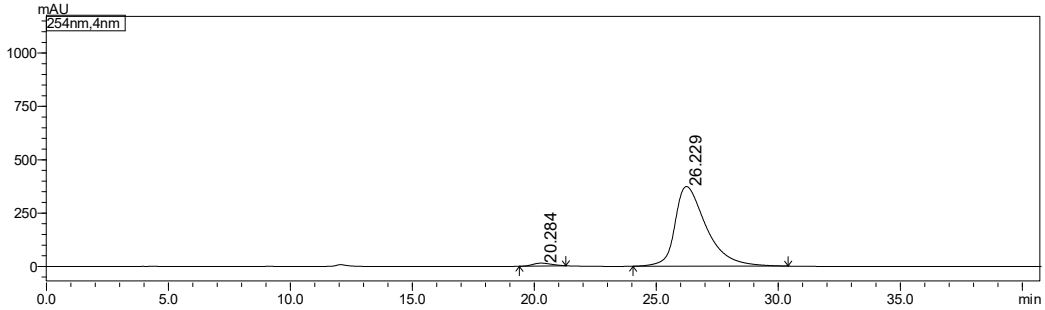


3a



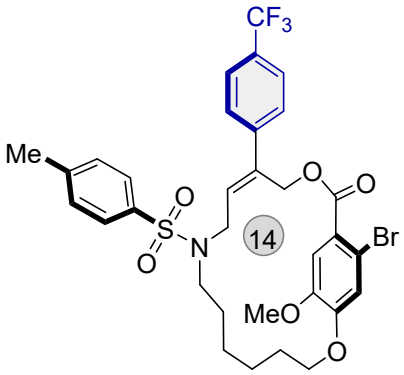
Peak	Ret. time	Area	Height	Area%	Height%
1	20.220	8949225	133289	50.257	57.142
2	26.512	8857723	99972	49.743	42.858
Total		17806948	233261	100.000	100.000

HPLC Spectrum of racemic 3a.

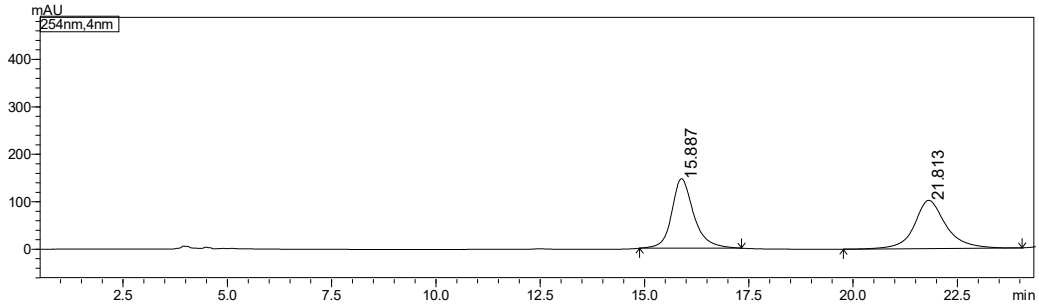


Peak	Ret. time	Area	Height	Area%	Height%
1	20.284	732864	13664	2.146	3.531
2	26.229	33416664	373351	97.854	96.469
Total		34149528	387014	100.000	100.000

HPLC Spectrum of enantioenriched 3a.

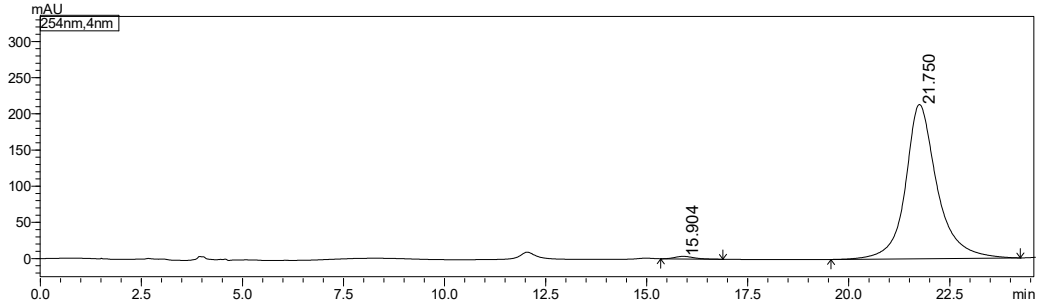


3b



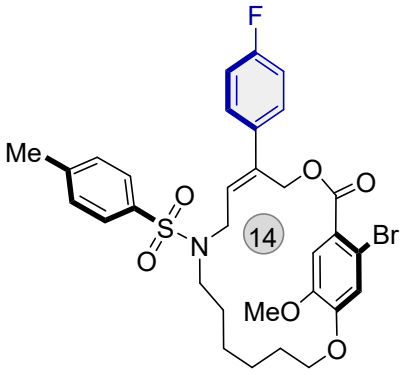
Peak	Ret. time	Area	Height	Area%	Height%
1	15.887	5399469	146268	50.120	59.009
2	21.813	5373681	101604	49.880	40.991
Total		10773150	247872	100.000	100.000

HPLC Spectrum of racemic 3b.

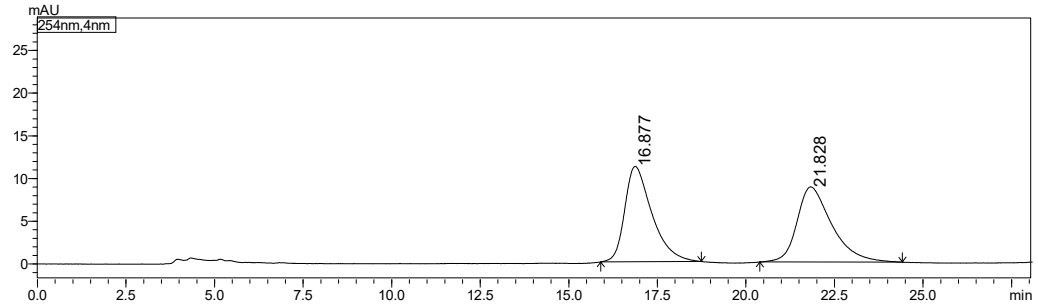


Peak	Ret. time	Area	Height	Area%	Height%
1	15.904	117525	3596	1.001	1.659
2	21.750	11623985	213182	98.999	98.341
Total		11741510	216778	100.000	100.000

HPLC Spectrum of enantioenriched 3b.

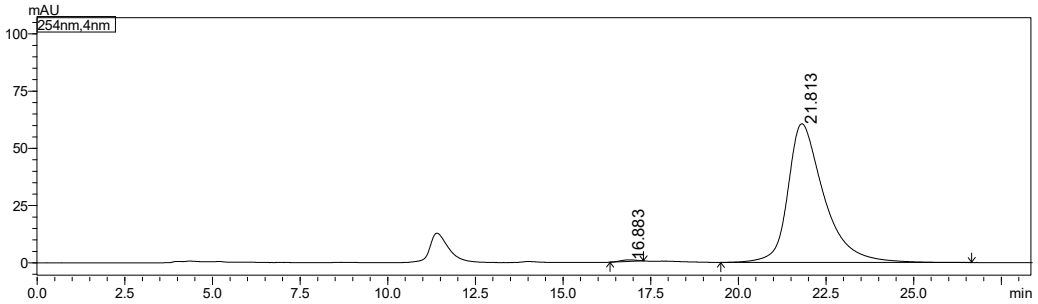


3c



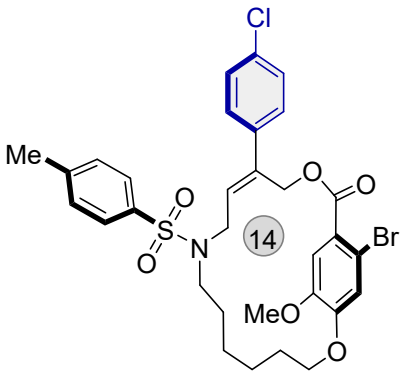
Peak	Ret. time	Area	Height	Area%	Height%
1	16.877	596505	11173	49.780	55.949
2	21.828	601789	8797	50.220	44.051
Total		1198293	19970	100.000	100.000

HPLC Spectrum of racemic 3c.

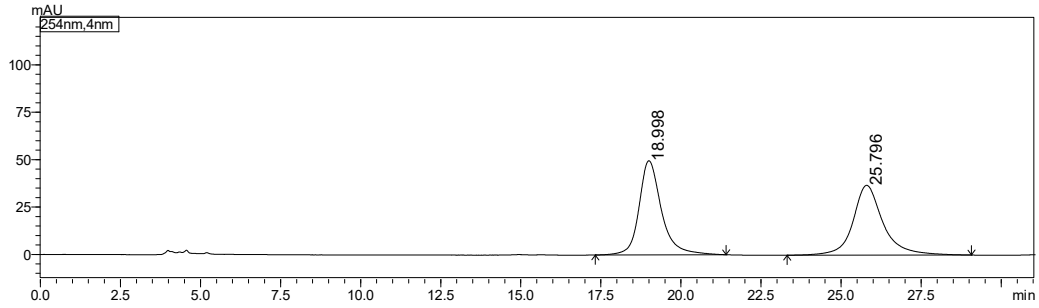


Peak	Ret. time	Area	Height	Area%	Height%
1	16.883	22087	700	0.507	1.142
2	21.813	4337467	60594	99.493	98.858
Total		4359554	61294	100.000	100.000

HPLC Spectrum of enantioenriched 3c.

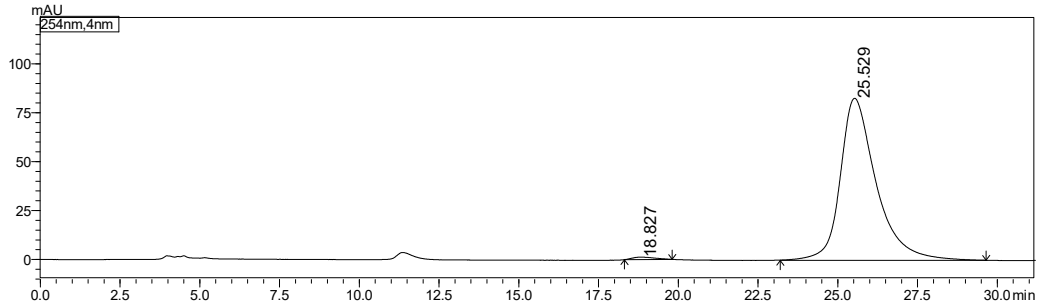


3d



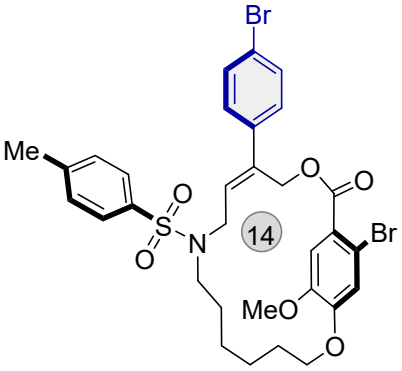
Peak	Ret. time	Area	Height	Area%	Height%
1	18.998	2424528	49675	50.134	57.404
2	25.796	2411532	36861	49.866	42.596
Total		4836060	86537	100.000	100.000

HPLC Spectrum of racemic 3d.

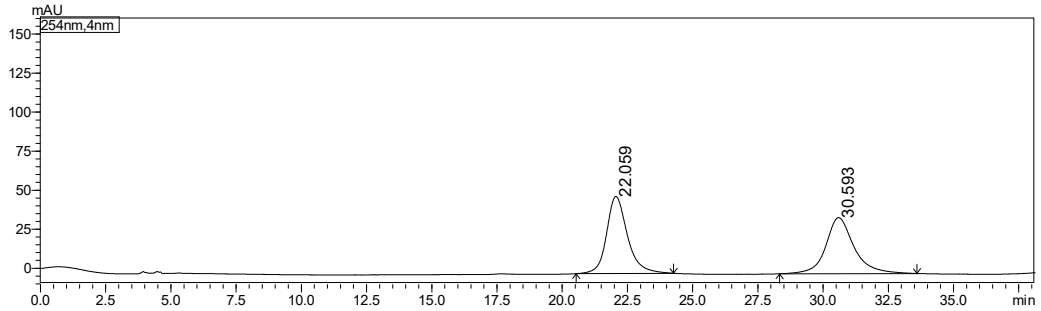


Peak	Ret. time	Area	Height	Area%	Height%
1	18.827	59199	1242	0.903	1.478
2	25.529	6498239	82807	99.097	98.522
Total		6557438	84050	100.000	100.000

HPLC Spectrum of enantioenriched 3d.

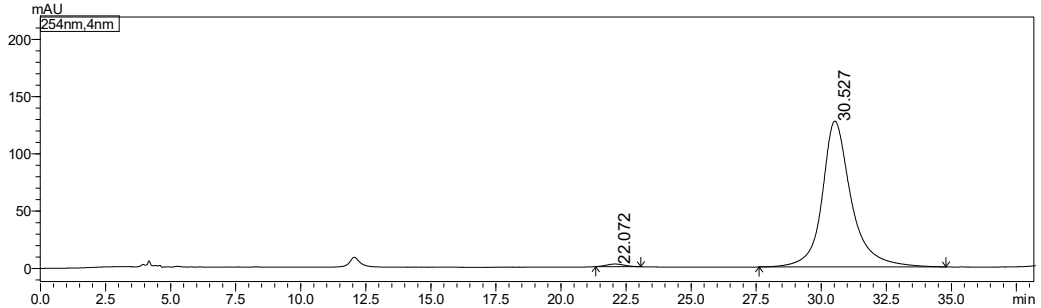


3e



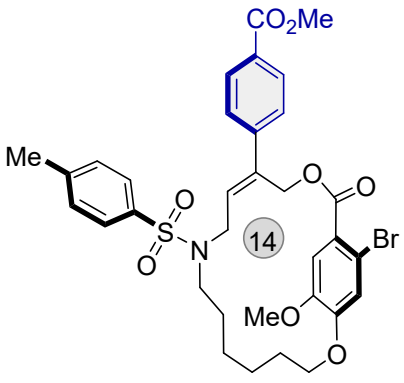
Peak	Ret. time	Area	Height	Area%	Height%
1	22.059	2755230	49385	50.351	57.882
2	30.593	2716819	35935	49.649	42.118
Total		5472049	85319	100.000	100.000

HPLC Spectrum of racemic 3e.

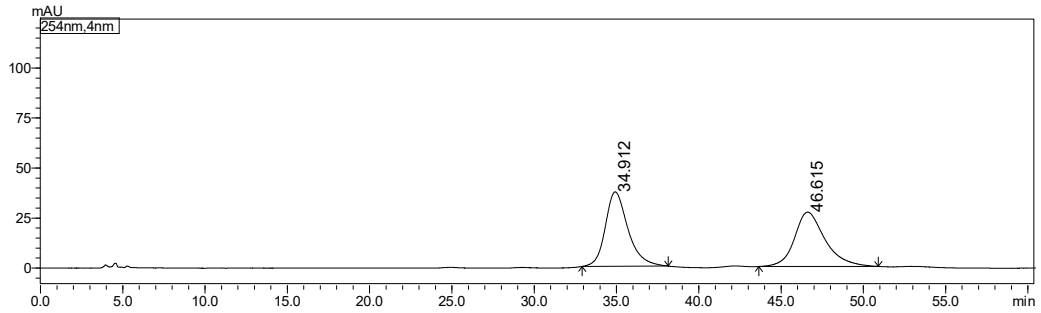


Peak	Ret. time	Area	Height	Area%	Height%
1	22.072	112150	2317	1.114	1.785
2	30.527	9952176	127461	98.886	98.215
Total		10064326	129778	100.000	100.000

HPLC Spectrum of enantioenriched 3e.

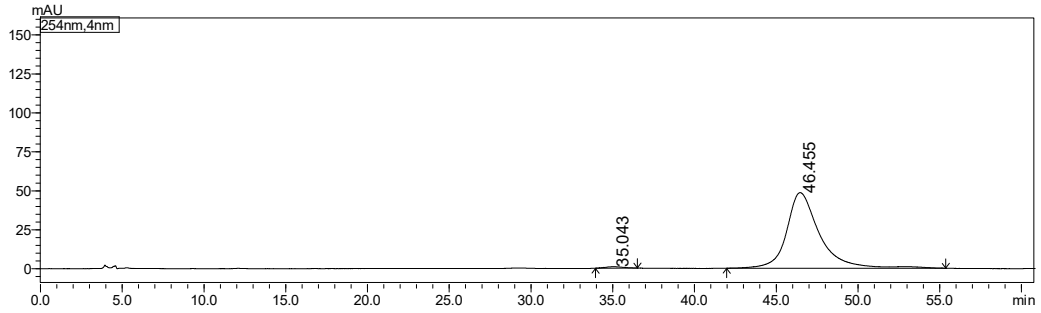


3f



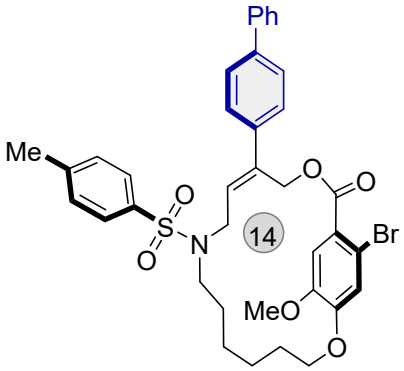
Peak	Ret. time	Area	Height	Area%	Height%
1	34.912	3570614	37218	50.295	57.776
2	46.615	3528744	27200	49.705	42.224
Total		7099358	64418	100.000	100.000

HPLC Spectrum of racemic 3f.

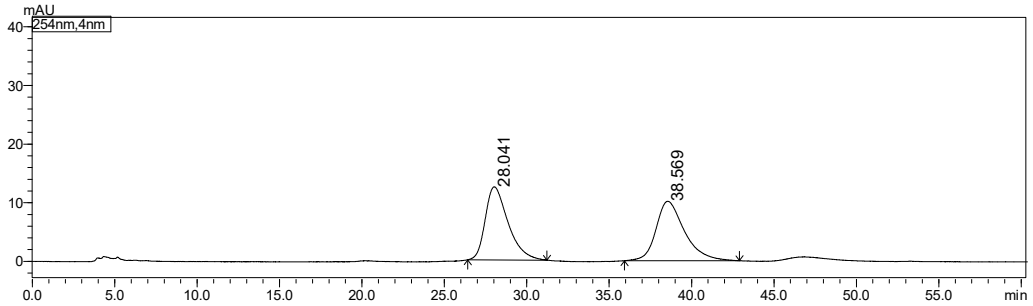


Peak	Ret. time	Area	Height	Area%	Height%
1	35.043	69895	959	1.016	1.938
2	46.455	6808898	48516	98.984	98.062
Total		6878793	49475	100.000	100.000

HPLC Spectrum of enantioenriched 3f.

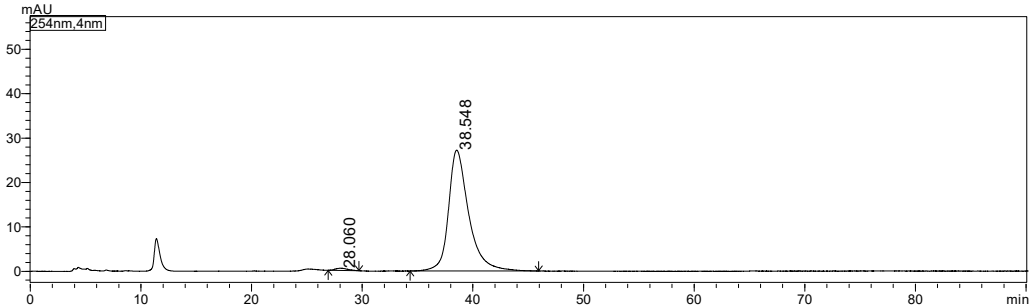


3g



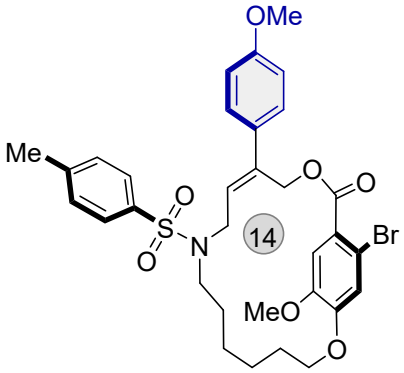
Peak	Ret. time	Area	Height	Area%	Height%
1	28.041	1204770	12476	49.743	55.164
2	38.569	1217225	10140	50.257	44.836
Total		2421995	22616	100.000	100.000

HPLC Spectrum of racemic 3g.

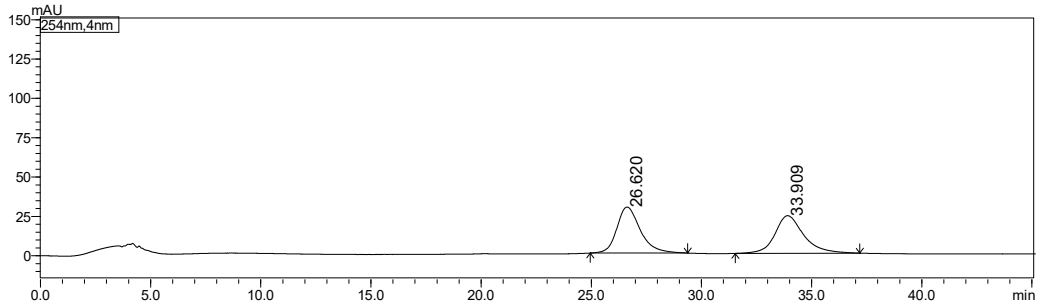


Peak	Ret. time	Area	Height	Area%	Height%
1	28.060	39747	510	1.136	1.838
2	38.548	3457612	27227	98.864	98.162
Total		3497358	27736	100.000	100.000

HPLC Spectrum of enantioenriched 3g.

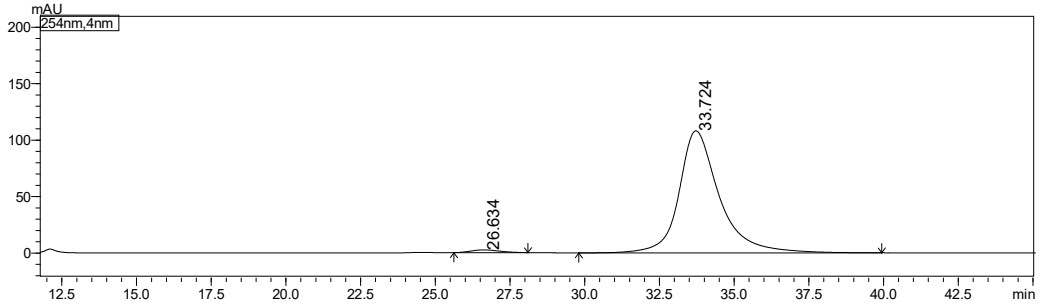


3h



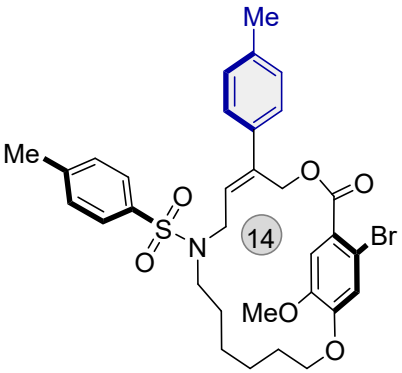
Peak	Ret. time	Area	Height	Area%	Height%
1	26.620	2174360	29245	49.894	54.990
2	33.909	2183604	23937	50.106	45.010
Total		4357964	53183	100.000	100.000

HPLC Spectrum of racemic 3h.

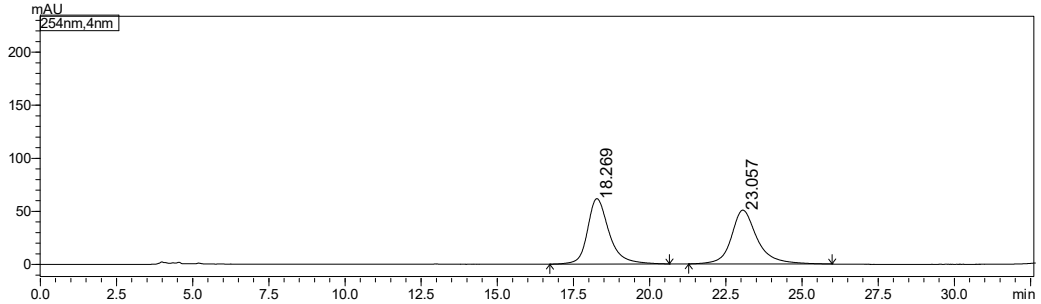


Peak	Ret. time	Area	Height	Area%	Height%
1	26.634	164651	2461	1.594	2.228
2	33.724	10164911	108027	98.406	97.772
Total		10329562	110489	100.000	100.000

HPLC Spectrum of enantioenriched 3h.

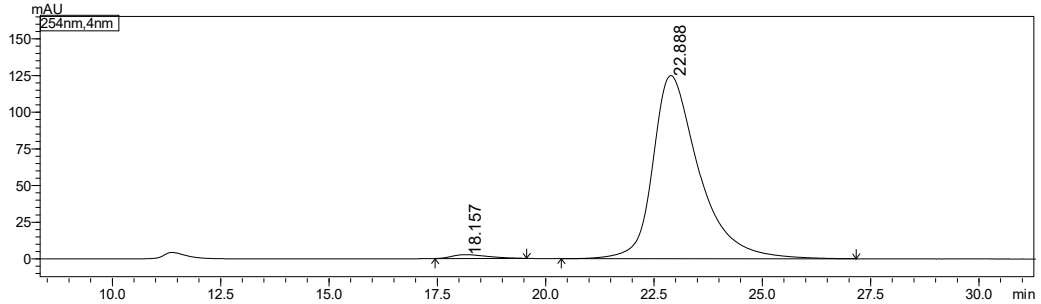


3i



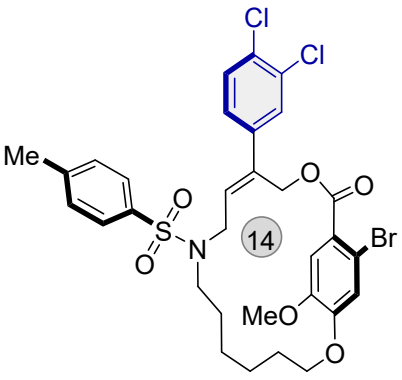
Peak	Ret. time	Area	Height	Area%	Height%
1	18.269	3045431	61647	50.207	54.835
2	23.057	3020273	50777	49.793	45.165
Total		6065704	112424	100.000	100.000

HPLC Spectrum of racemic 3i.

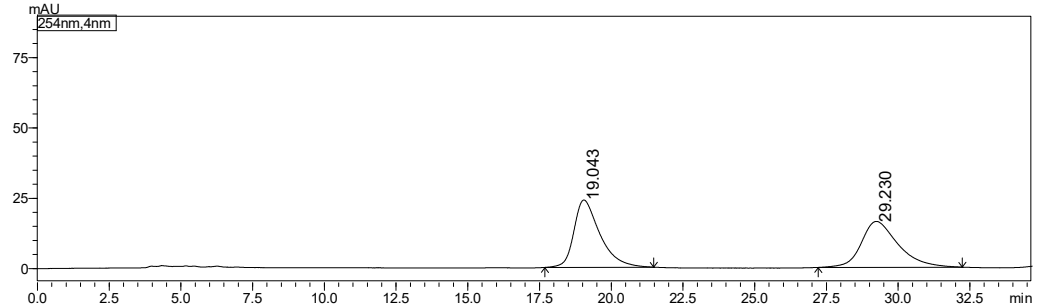


Peak	Ret. time	Area	Height	Area%	Height%
1	18.157	148458	2618	1.579	2.054
2	22.888	9256306	124855	98.421	97.946
Total		9404765	127473	100.000	100.000

HPLC Spectrum of enantioenriched 3i.

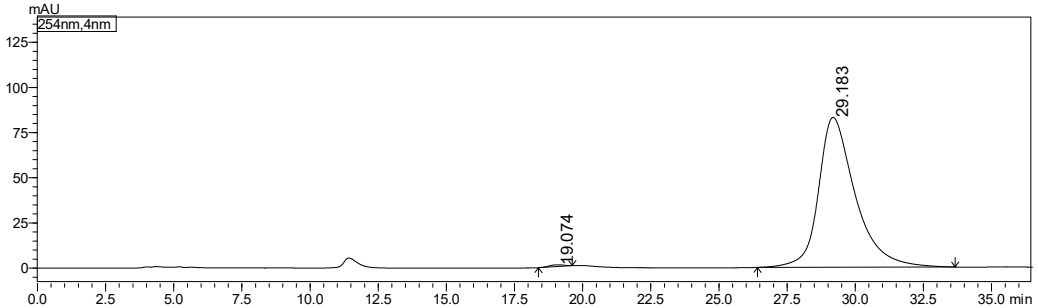


3j



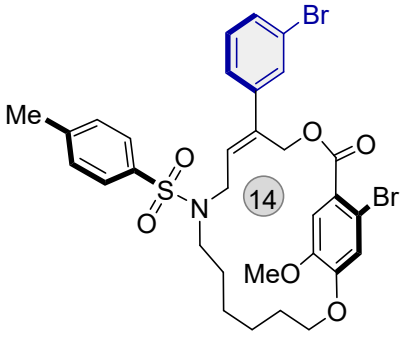
Peak	Ret. time	Area	Height	Area%	Height%
1	19.043	1510707	23942	50.808	59.473
2	29.230	1462652	16315	49.192	40.527
Total		2973360	40256	100.000	100.000

HPLC Spectrum of racemic 3j.

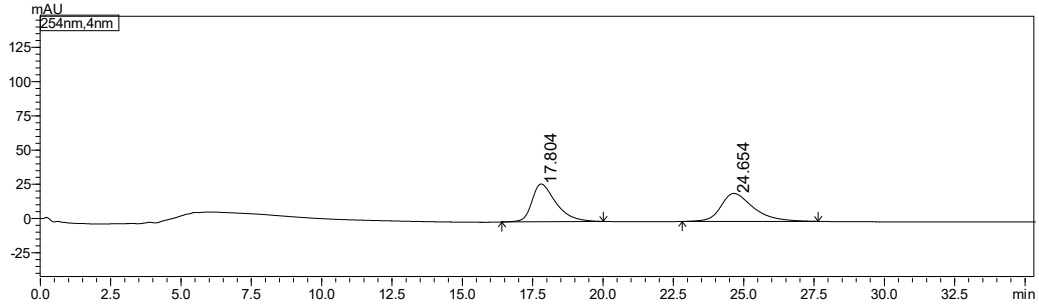


Peak	Ret. time	Area	Height	Area%	Height%
1	19.074	38147	995	0.487	1.185
2	29.183	7793299	82956	99.513	98.815
Total		7831446	83950	100.000	100.000

HPLC Spectrum of enantioenriched 3j.

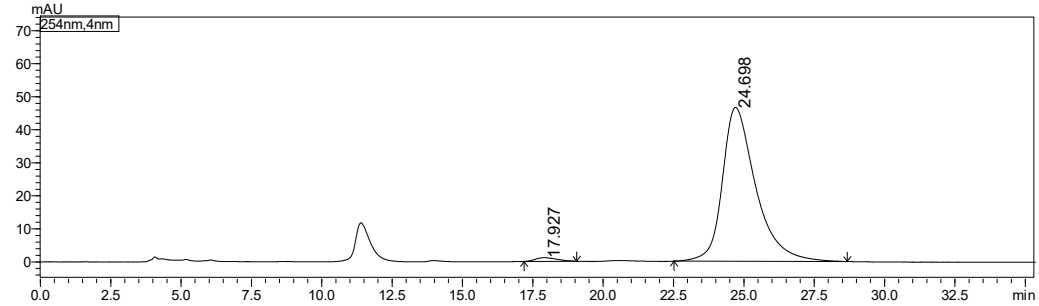


3k



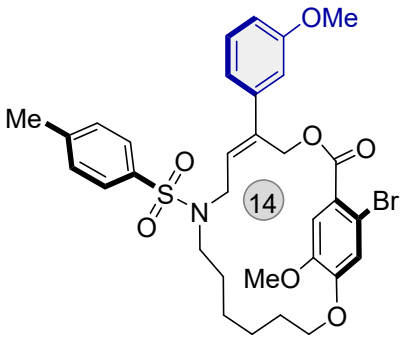
Peak	Ret. time	Area	Height	Area%	Height%
1	17.804	1648188	27621	49.819	57.436
2	24.654	1660189	20469	50.181	42.564
Total		3308376	48090	100.000	100.000

HPLC Spectrum of racemic 3k.

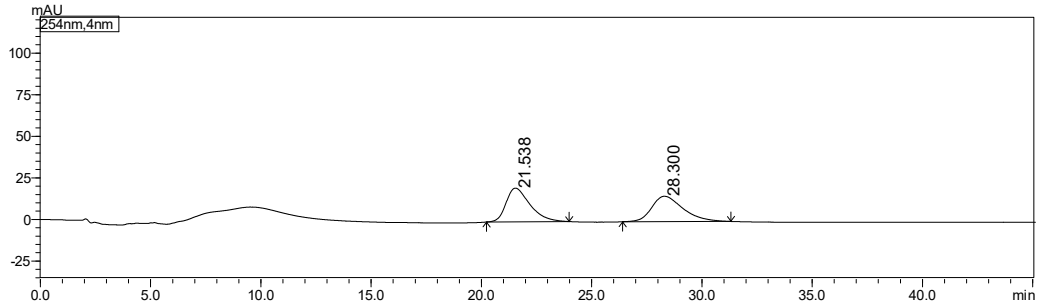


Peak	Ret. time	Area	Height	Area%	Height%
1	17.927	59370	1121	1.520	2.351
2	24.698	3847650	46571	98.480	97.649
Total		3907020	47692	100.000	100.000

HPLC Spectrum of enantioenriched 3k.

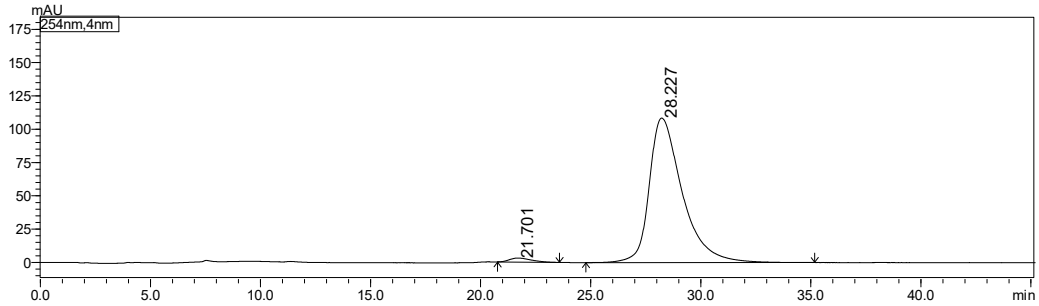


3l



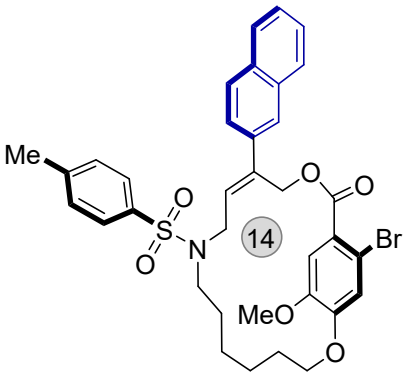
Peak	Ret. time	Area	Height	Area%	Height%
1	21.538	1531254	20288	50.248	57.038
2	28.300	1516141	15281	49.752	42.962
Total		3047395	35569	100.000	100.000

HPLC Spectrum of racemic 3l.

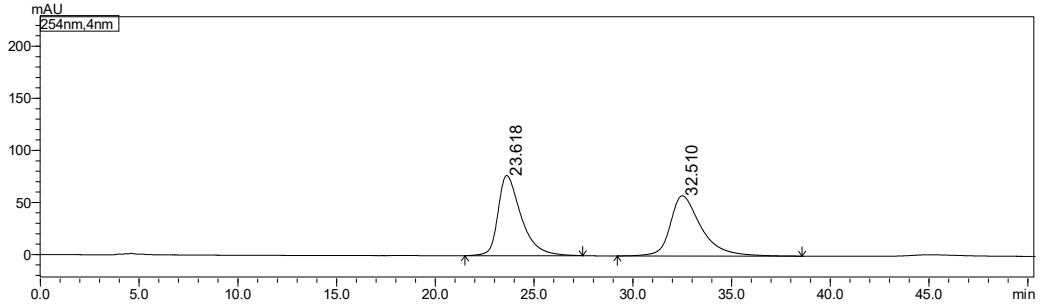


Peak	Ret. time	Area	Height	Area%	Height%
1	21.701	210686	3060	1.827	2.744
2	28.227	11323979	108437	98.173	97.256
Total		11534664	111497	100.000	100.000

HPLC Spectrum of enantioenriched 3l.

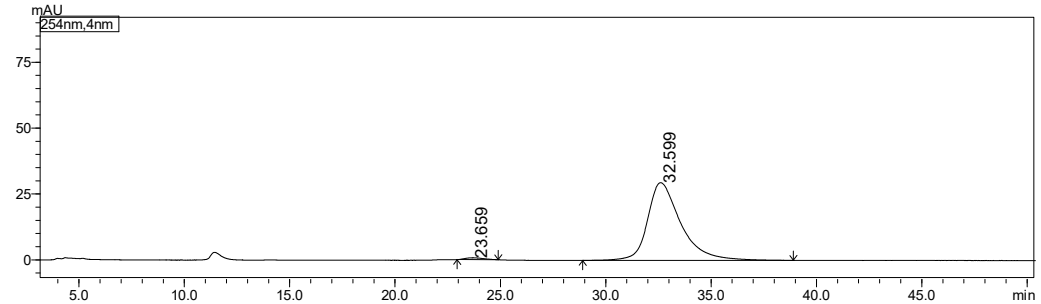


3m



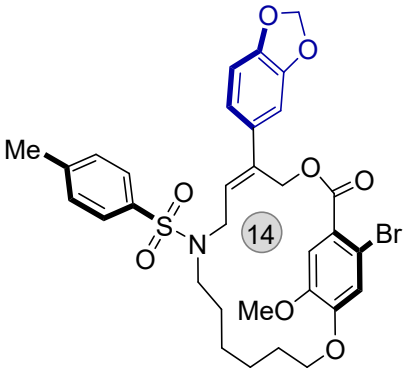
Peak	Ret. time	Area	Height	Area%	Height%
1	23.618	6280899	76947	49.950	57.111
2	32.510	6293533	57786	50.050	42.889
Total		12574432	134733	100.000	100.000

HPLC Spectrum of racemic 3m.

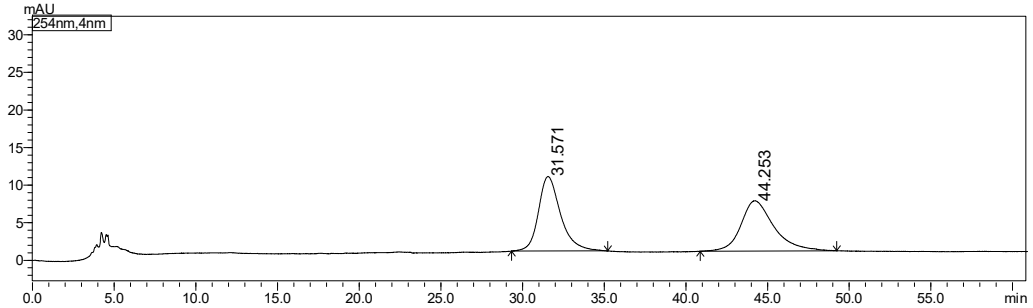


Peak	Ret. time	Area	Height	Area%	Height%
1	23.659	43042	713	1.310	2.362
2	32.599	3241804	29491	98.690	97.638
Total		3284846	30204	100.000	100.000

HPLC Spectrum of enantioenriched 3m.

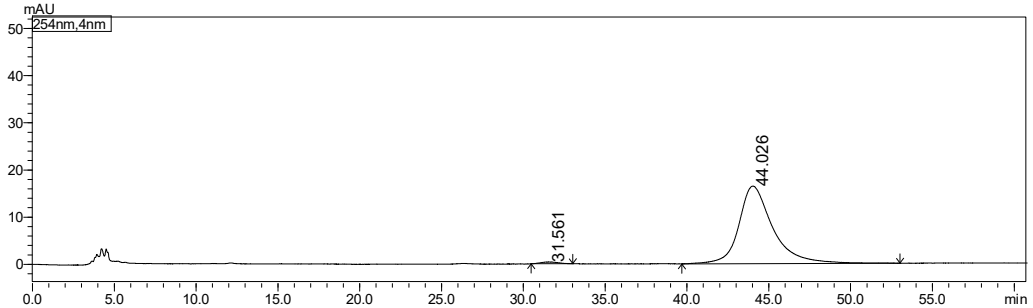


3n



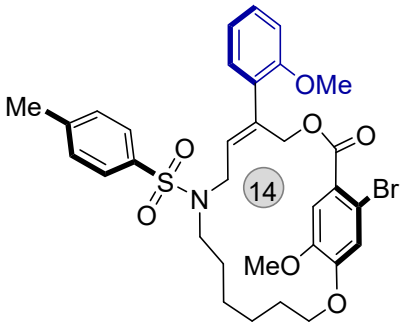
Peak	Ret. time	Area	Height	Area%	Height%
1	31.571	935113	9921	49.884	59.692
2	44.253	939460	6699	50.116	40.308
Total		1874574	16620	100.000	100.000

HPLC Spectrum of racemic 3n.

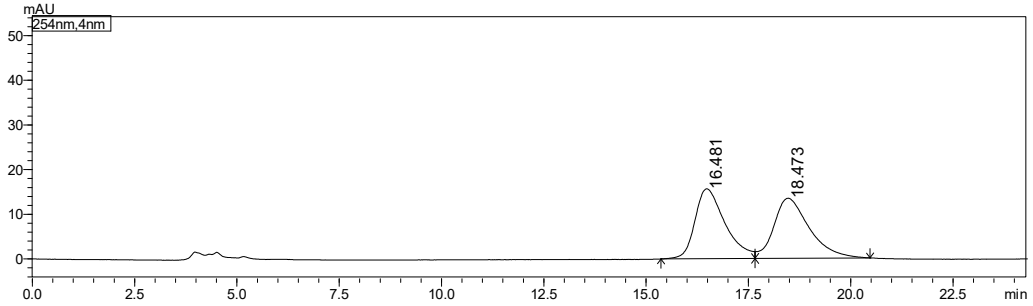


Peak	Ret. time	Area	Height	Area%	Height%
1	31.561	26190	376	1.093	2.235
2	44.026	2370282	16437	98.907	97.765
Total		2396472	16812	100.000	100.000

HPLC Spectrum of enantioenriched 3n.

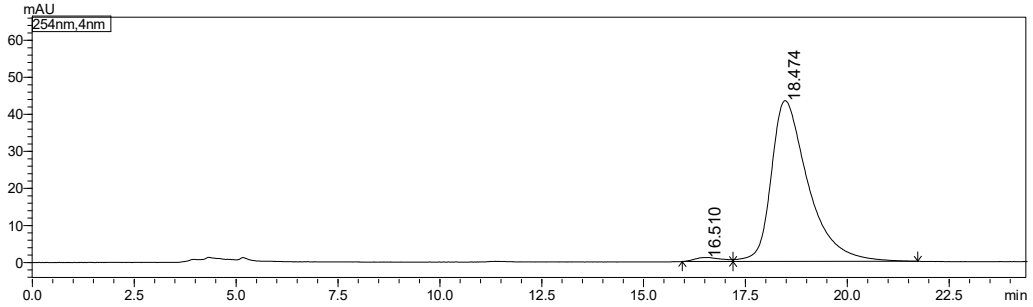


3o



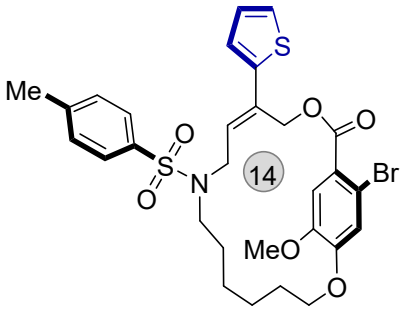
Peak	Ret. time	Area	Height	Area%	Height%
1	16.481	801210	15660	49.608	53.754
2	18.473	813884	13473	50.392	46.246
Total		1615094	29133	100.000	100.000

HPLC Spectrum of racemic 3o.

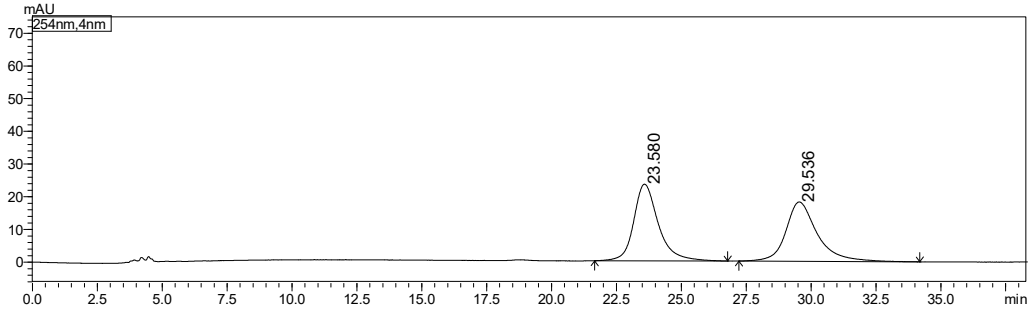


Peak	Ret. time	Area	Height	Area%	Height%
1	16.510	50061	1087	1.798	2.442
2	18.474	2733897	43417	98.202	97.558
Total		2783958	44504	100.000	100.000

HPLC Spectrum of enantioenriched 3o.

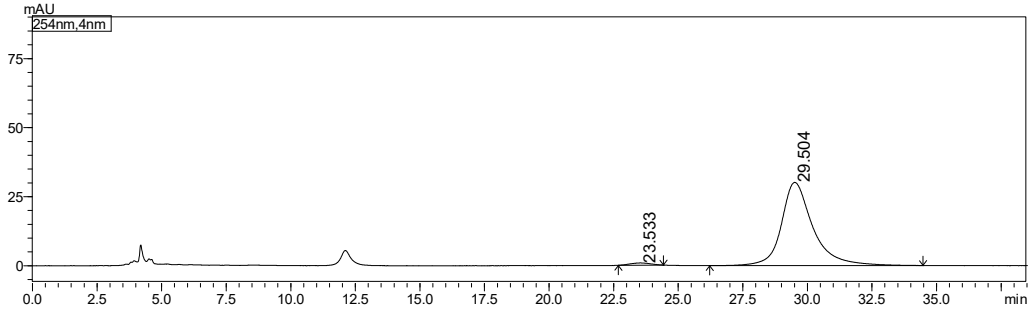


3p



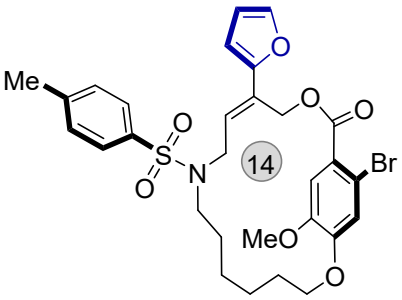
Peak	Ret. time	Area	Height	Area%	Height%
1	23.580	1551959	23456	50.291	56.360
2	29.536	1533995	18162	49.709	43.640
Total		3085954	41618	100.000	100.000

HPLC Spectrum of racemic 3p.

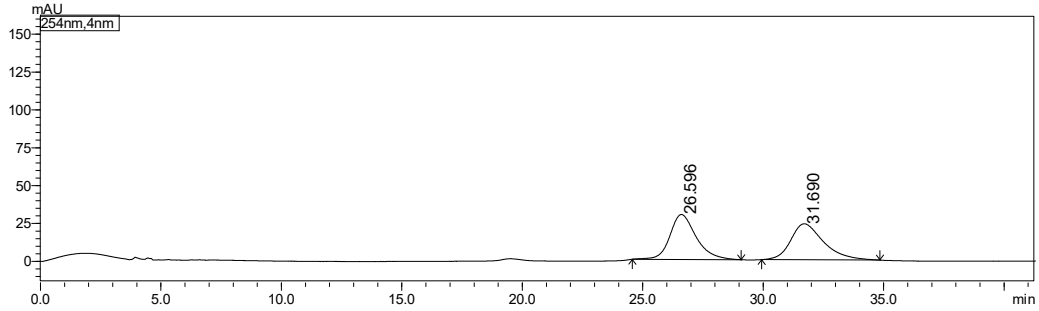


Peak	Ret. time	Area	Height	Area%	Height%
1	23.533	44550	820	1.711	2.651
2	29.504	2559817	30119	98.289	97.349
Total		2604367	30940	100.000	100.000

HPLC Spectrum of enantioenriched 3p.

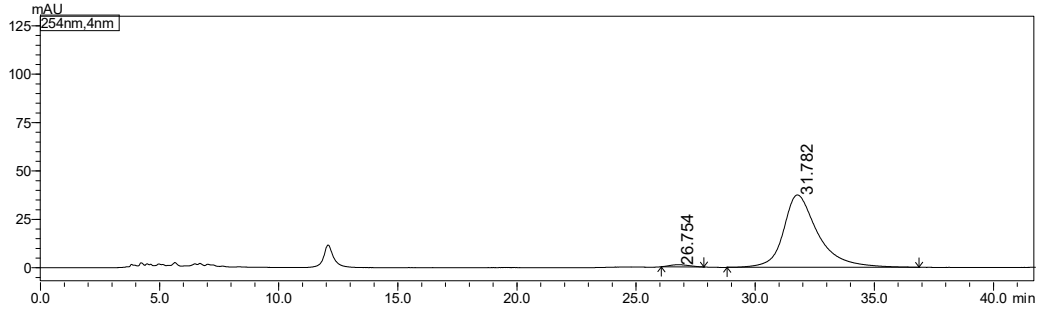


3q



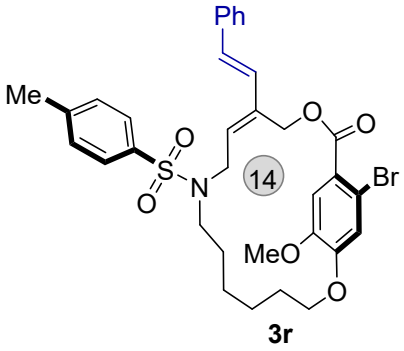
Peak	Ret. time	Area	Height	Area%	Height%
1	26.596	2262075	29718	49.999	55.585
2	31.690	2262151	23746	50.001	44.415
Total		4524226	53464	100.000	100.000

HPLC Spectrum of racemic 3q.

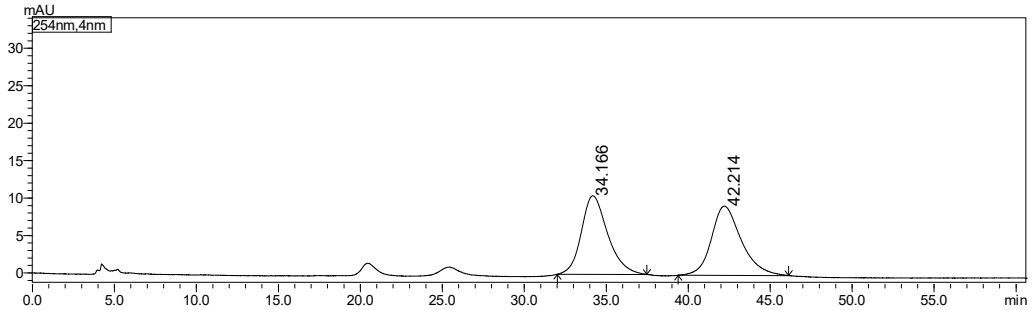


Peak	Ret. time	Area	Height	Area%	Height%
1	26.754	61828	1120	1.616	2.908
2	31.782	3763301	37404	98.384	97.092
Total		3825129	38525	100.000	100.000

HPLC Spectrum of enantioenriched 3q.

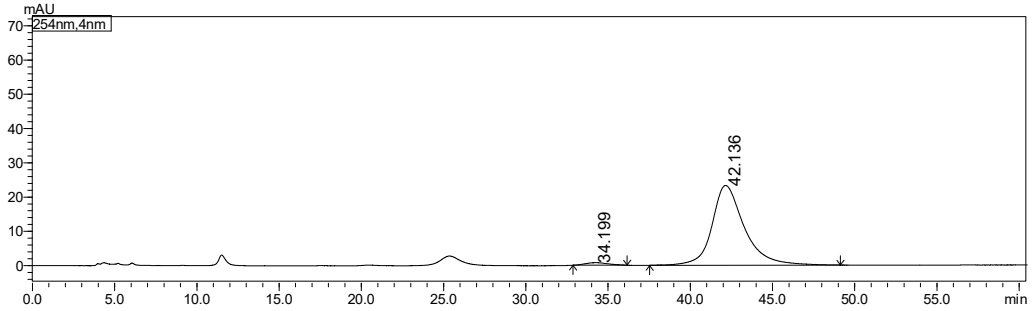


3r



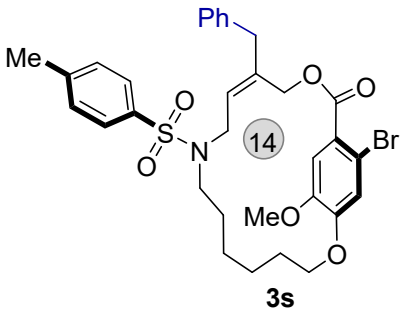
Peak	Ret. time	Area	Height	Area%	Height%
1	34.166	1174904	10488	49.920	53.140
2	42.214	1178678	9249	50.080	46.860
Total		2353582	19737	100.000	100.000

HPLC Spectrum of racemic 3r.

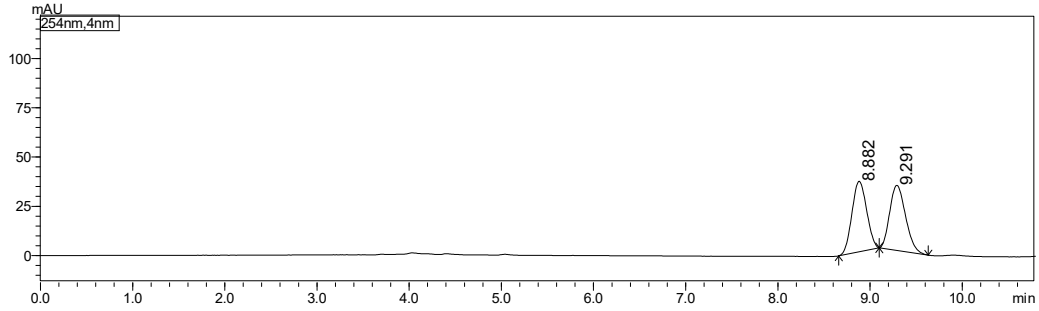


Peak	Ret. time	Area	Height	Area%	Height%
1	34.199	70756	759	2.171	3.157
2	42.136	3187911	23281	97.829	96.843
Total		3258667	24040	100.000	100.000

HPLC Spectrum of enantioenriched 3r.

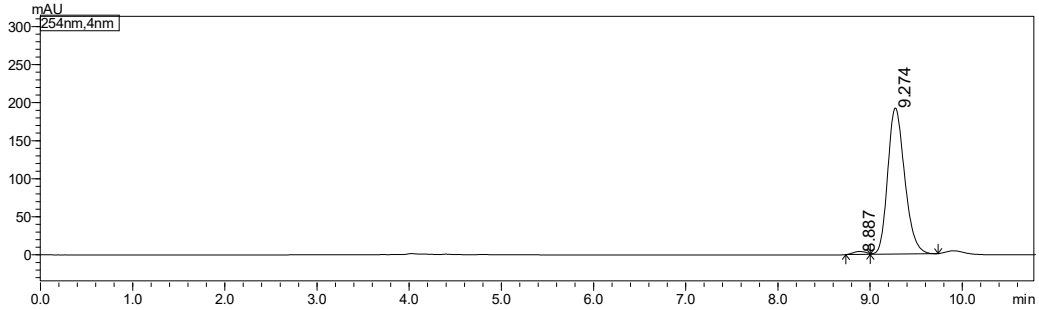


3s



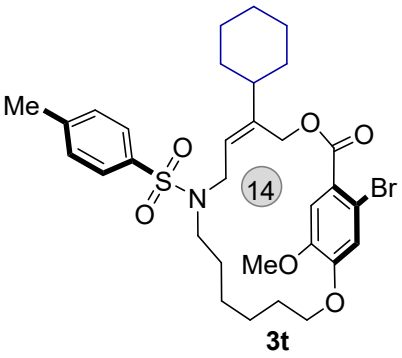
Peak	Ret. time	Area	Height	Area%	Height%
1	8.882	397804	35797	50.223	51.956
2	9.291	394266	33102	49.777	48.044
Total		792070	68898	100.000	100.000

HPLC Spectrum of racemic 3s.

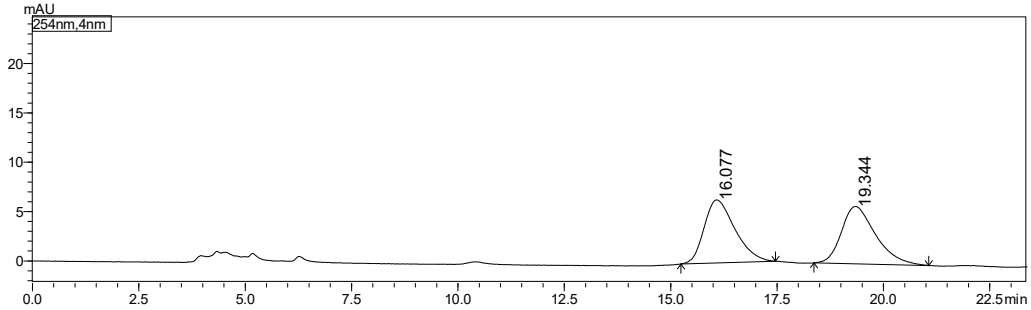


Peak	Ret. time	Area	Height	Area%	Height%
1	8.887	38289	3905	1.536	1.994
2	9.274	2454238	191962	98.464	98.006
Total		2492526	195867	100.000	100.000

HPLC Spectrum of enantioenriched 3s.

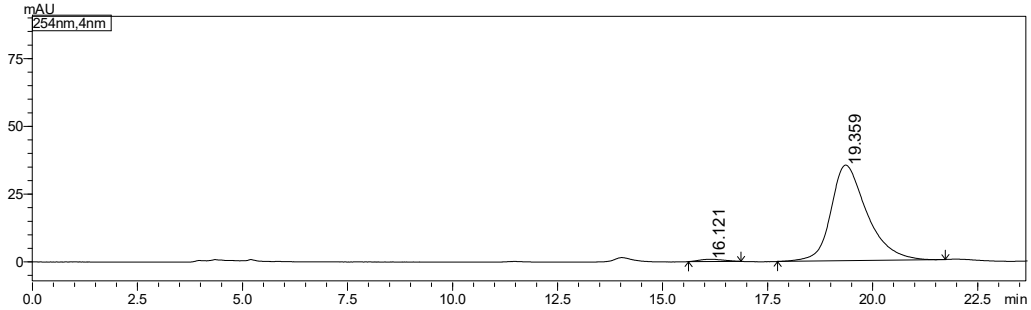


3t



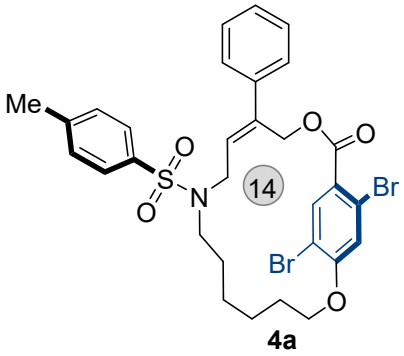
Peak	Ret. time	Area	Height	Area%	Height%
1	16.077	320879	6383	49.632	52.368
2	19.344	325633	5805	50.368	47.632
Total		646512	12188	100.000	100.000

HPLC Spectrum of racemic 3t.

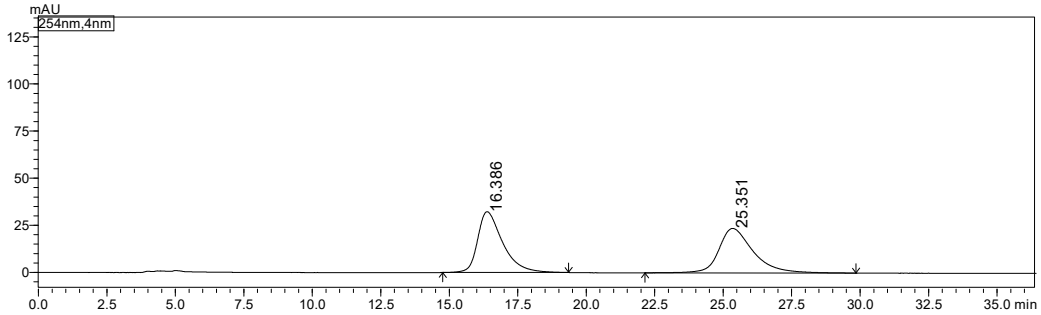


Peak	Ret. time	Area	Height	Area%	Height%
1	16.121	33006	823	1.551	2.281
2	19.359	2095556	35270	98.449	97.719
Total		2128563	36093	100.000	100.000

HPLC Spectrum of enantioenriched 3t.

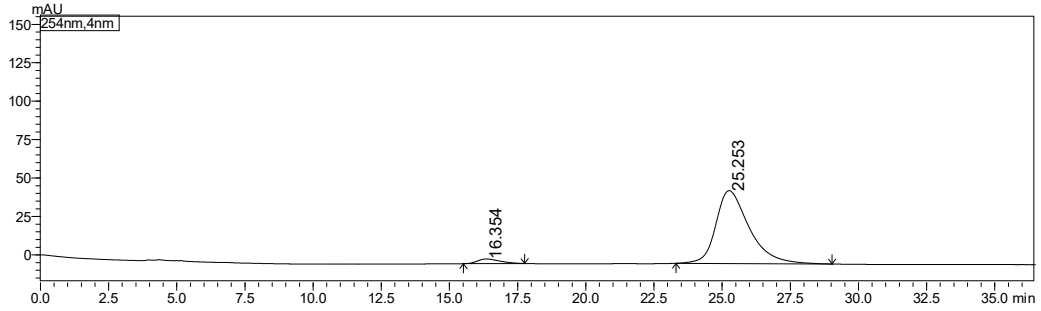


4a



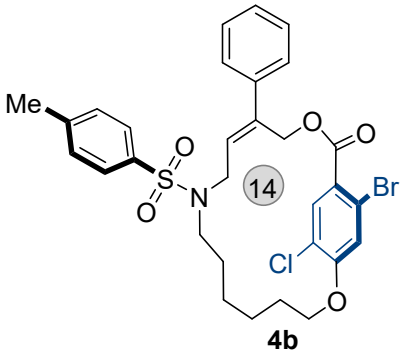
Peak	Ret. time	Area	Height	Area%	Height%
1	16.386	2056135	32276	49.910	57.748
2	25.351	2063570	23615	50.090	42.252
Total		4119705	55891	100.000	100.000

HPLC Spectrum of racemic 4a.

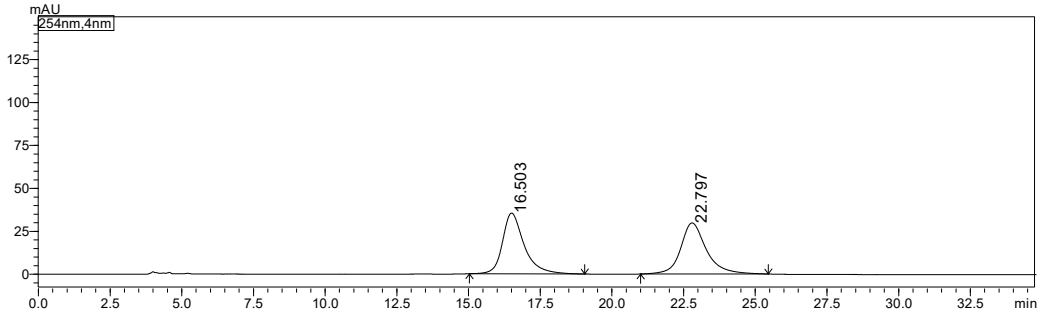


Peak	Ret. time	Area	Height	Area%	Height%
1	16.354	170606	3005	4.049	5.958
2	25.253	4042684	47424	95.951	94.042
Total		4213290	50429	100.000	100.000

HPLC Spectrum of enantioenriched 4a.

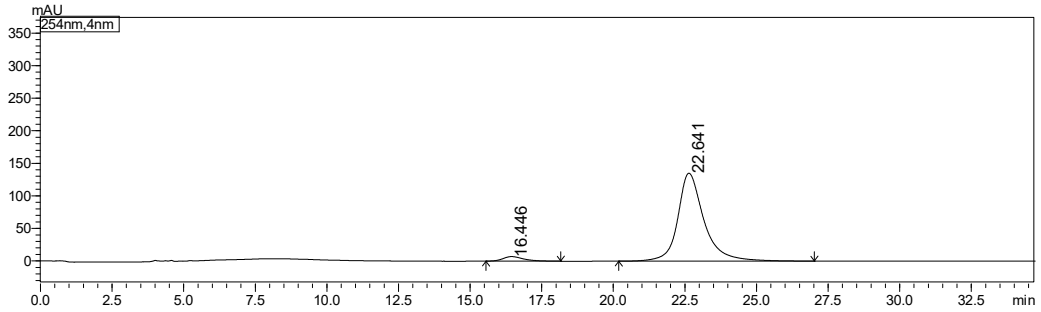


4b



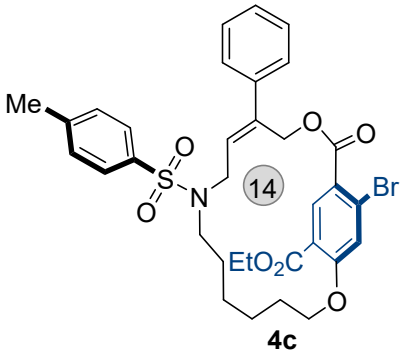
Peak	Ret. time	Area	Height	Area%	Height%
1	16.503	1867694	35416	50.150	54.344
2	22.797	1856499	29754	49.850	45.656
Total		3724192	65170	100.000	100.000

HPLC Spectrum of racemic 4b.

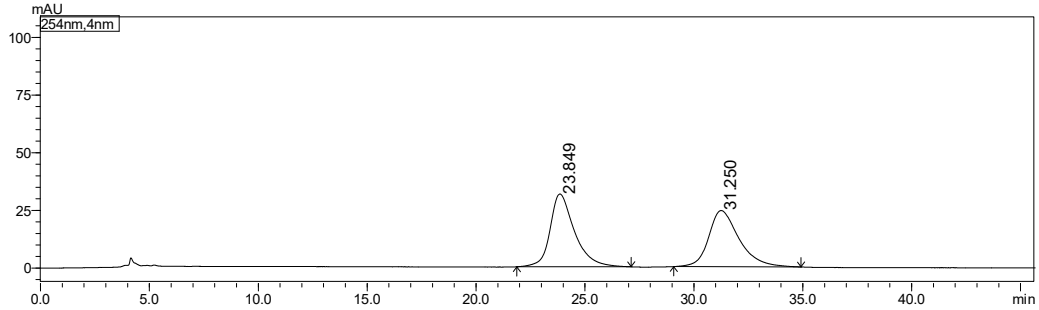


Peak	Ret. time	Area	Height	Area%	Height%
1	16.446	355083	7061	3.968	4.967
2	22.641	8593236	135080	96.032	95.033
Total		8948319	142141	100.000	100.000

HPLC Spectrum of enantioenriched 4b.

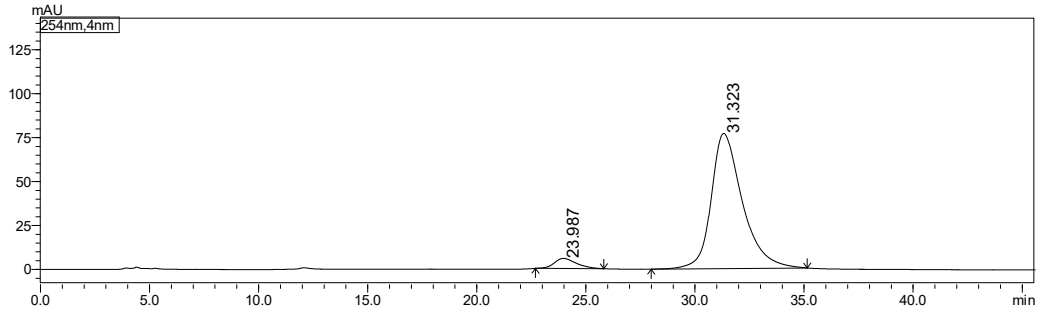


4c



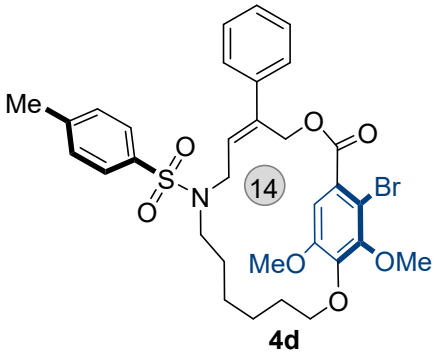
Peak	Ret. time	Area	Height	Area%	Height%
1	23.849	2461624	31553	50.939	56.431
2	31.250	2370914	24361	49.061	43.569
Total		4832539	55915	100.000	100.000

HPLC Spectrum of racemic 4c.

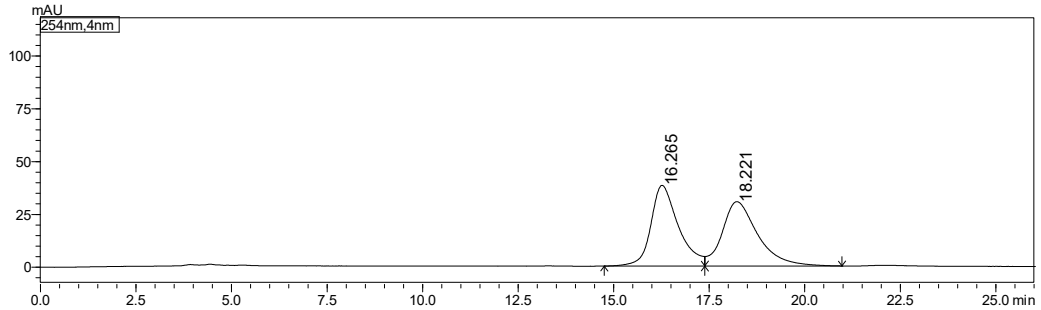


Peak	Ret. time	Area	Height	Area%	Height%
1	23.987	408000	5760	5.048	6.967
2	31.323	7674385	76915	94.952	93.033
Total		8082384	82675	100.000	100.000

HPLC Spectrum of enantioenriched 4c.

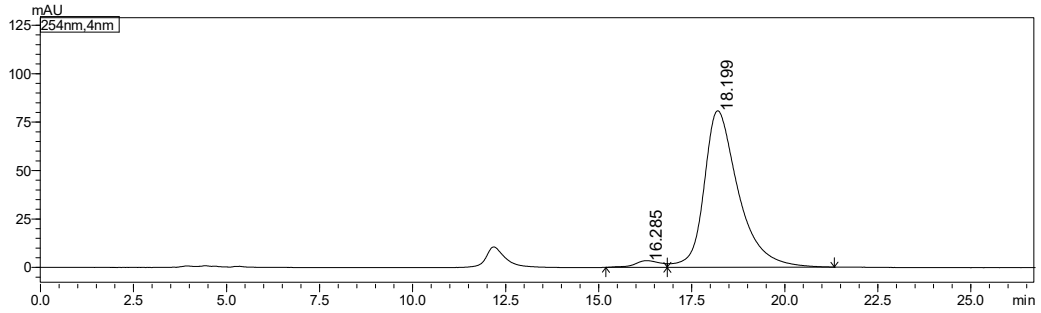


4d



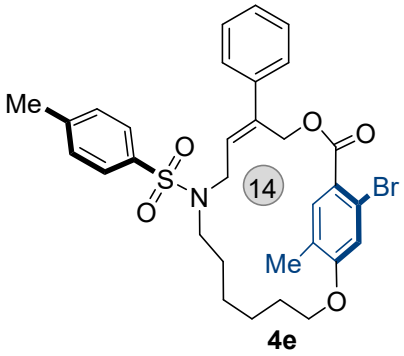
Peak	Ret. time	Area	Height	Area%	Height%
1	16.265	1916040	38200	49.343	55.637
2	18.221	1967093	30460	50.657	44.363
Total		3883134	68660	100.000	100.000

HPLC Spectrum of racemic 4d.

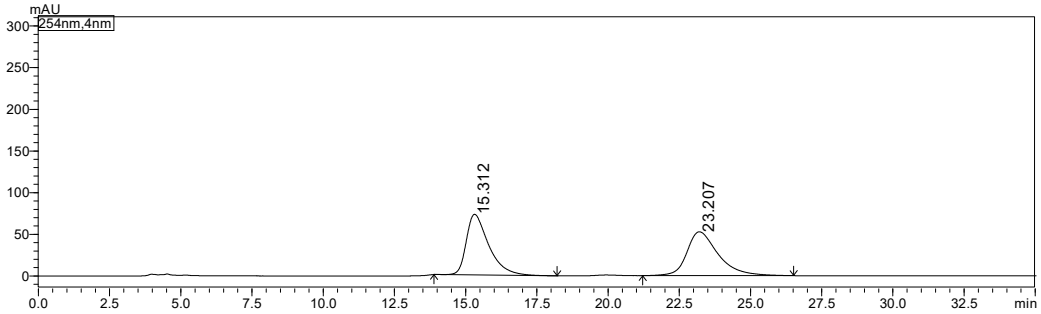


Peak	Ret. time	Area	Height	Area%	Height%
1	16.285	164443	3460	3.075	4.107
2	18.199	5183813	80790	96.925	95.893
Total		5348257	84250	100.000	100.000

HPLC Spectrum of enantioenriched 4d.

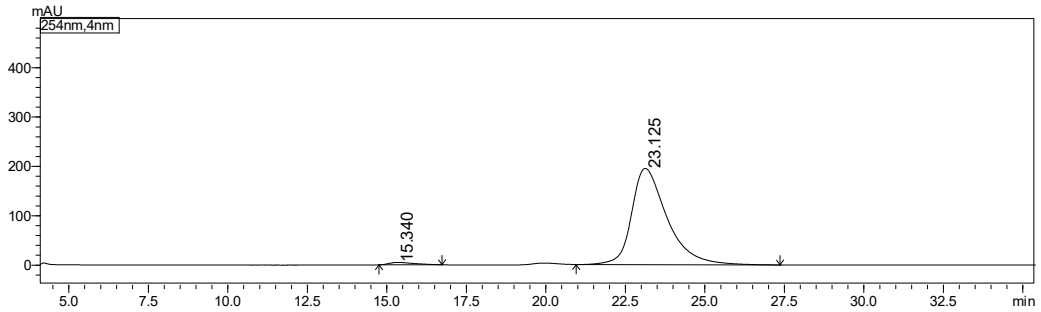


4e



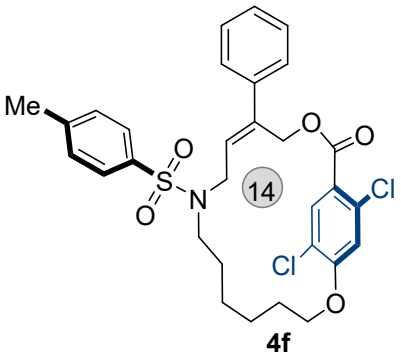
Peak	Ret. time	Area	Height	Area%	Height%
1	15.312	4000111	72756	49.707	58.014
2	23.207	4047212	52656	50.293	41.986
Total		8047324	125412	100.000	100.000

HPLC Spectrum of racemic 4e.

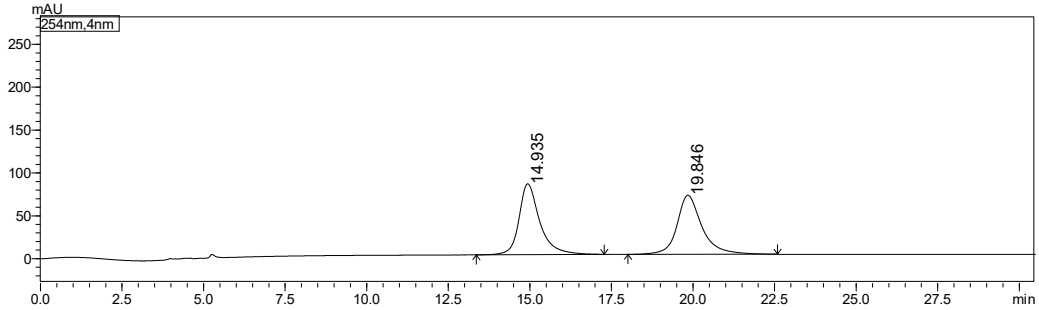


Peak	Ret. time	Area	Height	Area%	Height%
1	15.340	269993	4929	1.748	2.466
2	23.125	15175246	195001	98.252	97.534
Total		15445239	199930	100.000	100.000

HPLC Spectrum of enantioenriched 4e.

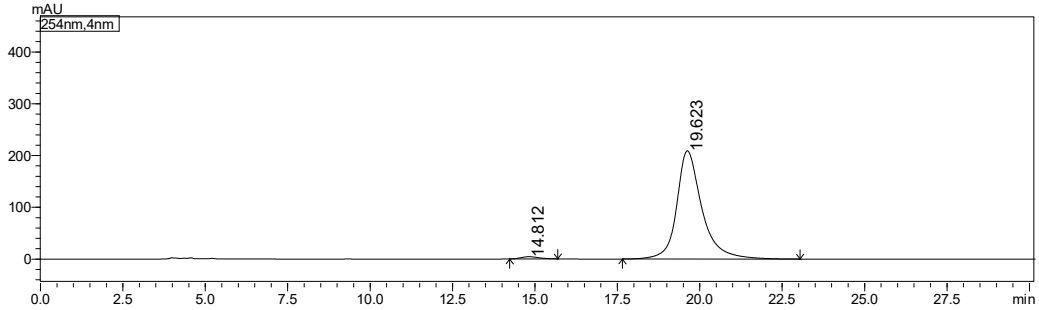


4f



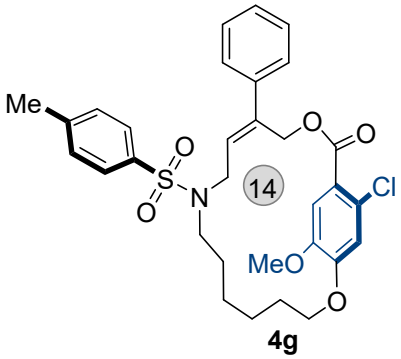
Peak	Ret. time	Area	Height	Area%	Height%
1	14.935	3673716	82683	49.967	54.535
2	19.846	3678567	68931	50.033	45.465
Total		7352283	151614	100.000	100.000

HPLC Spectrum of racemic 4f.

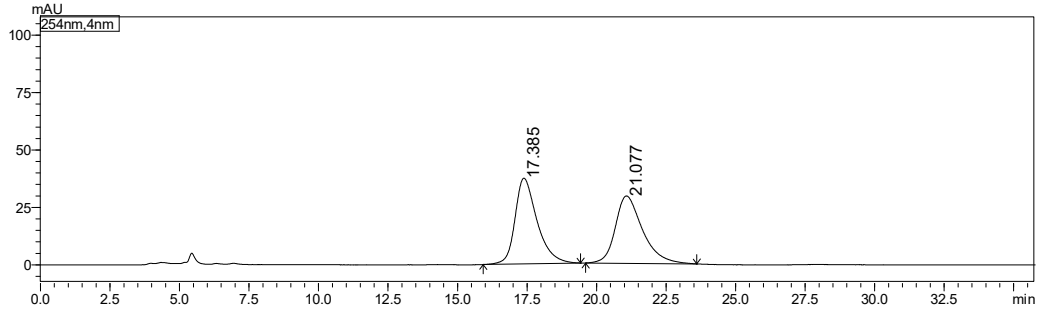


Peak	Ret. time	Area	Height	Area%	Height%
1	14.812	160368	4274	1.417	2.003
2	19.623	11160371	209174	98.583	97.997
Total		11320738	213448	100.000	100.000

HPLC Spectrum of enantioenriched 4f.

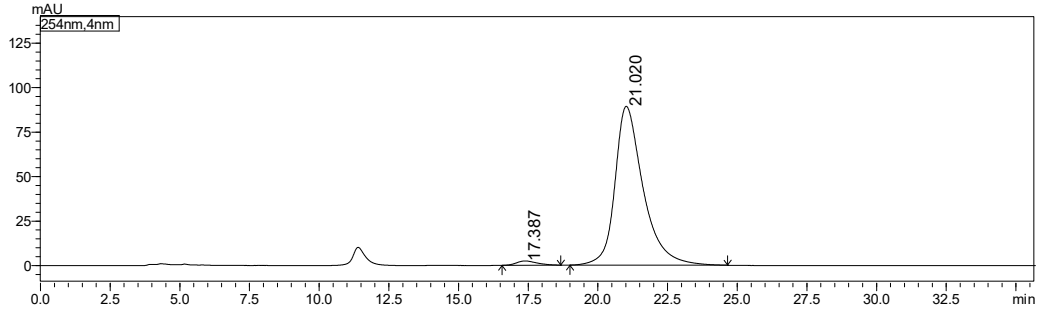


4g



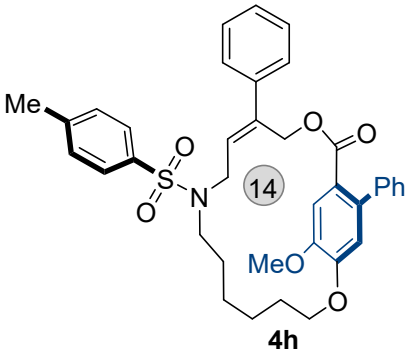
Peak	Ret. time	Area	Height	Area%	Height%
1	17.385	2058399	37320	50.716	55.977
2	21.077	2000310	29350	49.284	44.023
Total		4058709	66670	100.000	100.000

HPLC Spectrum of racemic 4g.

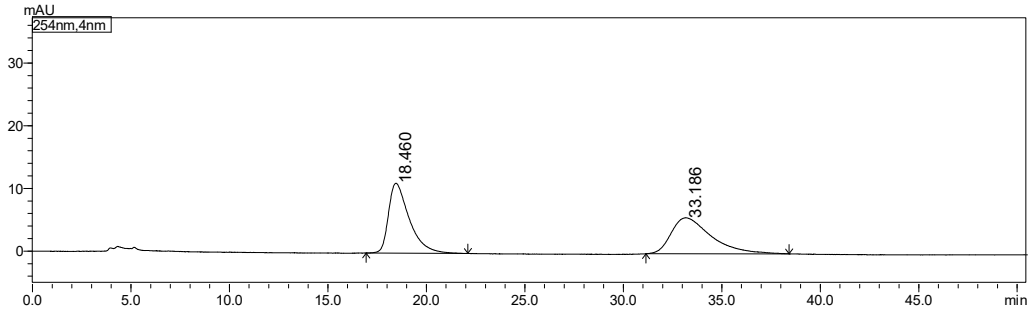


Peak	Ret. time	Area	Height	Area%	Height%
1	17.387	123455	2425	1.919	2.643
2	21.020	6308476	89298	98.081	97.357
Total		6431931	91722	100.000	100.000

HPLC Spectrum of enantioenriched 4g.

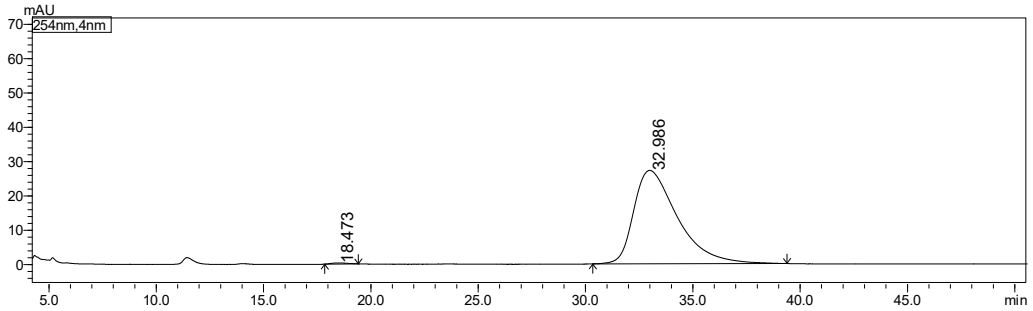


4h



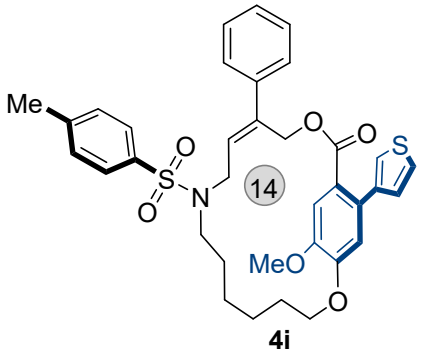
Peak	Ret. time	Area	Height	Area%	Height%
1	18.460	820392	11155	50.229	66.059
2	33.186	812912	5731	49.771	33.941
Total		1633305	16886	100.000	100.000

HPLC Spectrum of racemic 4h.

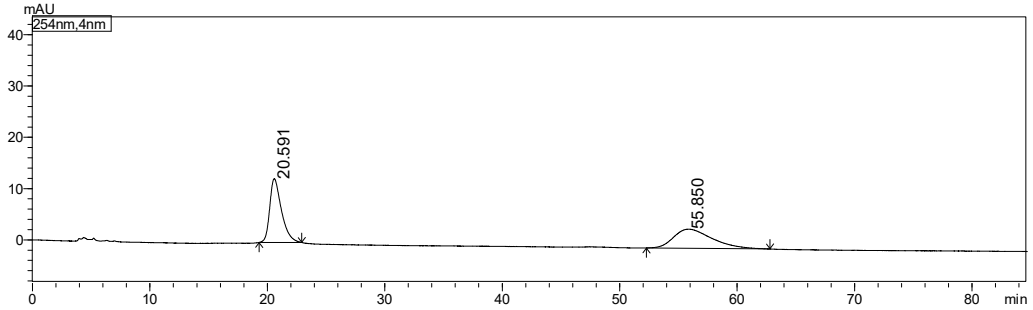


Peak	Ret. time	Area	Height	Area%	Height%
1	18.473	16492	321	0.426	1.165
2	32.986	3855793	27207	99.574	98.835
Total		3872286	27528	100.000	100.000

HPLC Spectrum of enantioenriched 4h.

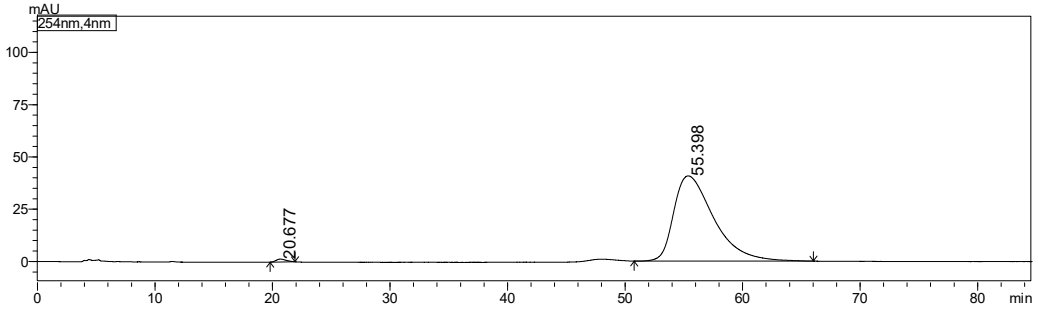


4i



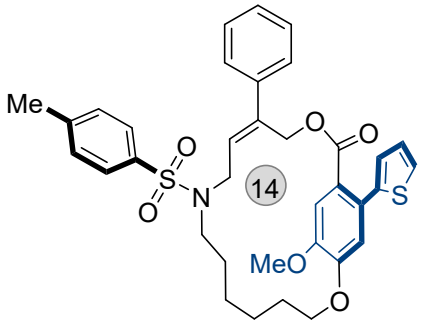
Peak	Ret. time	Area	Height	Area%	Height%
1	20.591	864170	12442	50.380	76.908
2	55.850	851135	3736	49.620	23.092
Total		1715305	16178	100.000	100.000

HPLC Spectrum of racemic 4i.

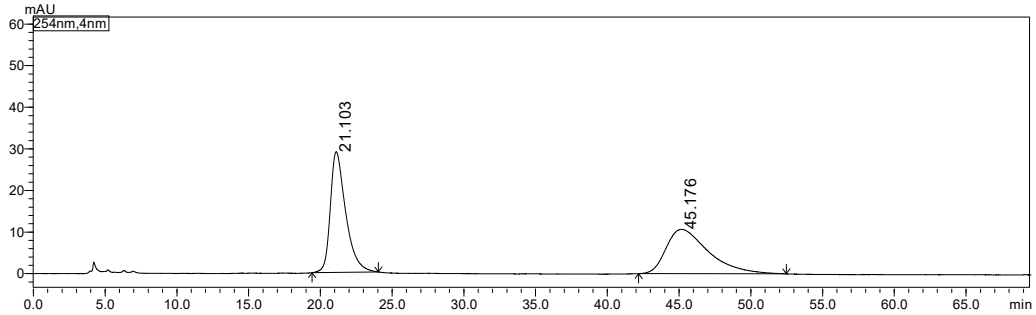


Peak	Ret. time	Area	Height	Area%	Height%
1	20.677	83370	1391	0.855	3.300
2	55.398	9663069	40768	99.145	96.700
Total		9746439	42159	100.000	100.000

HPLC Spectrum of enantioenriched 4i.

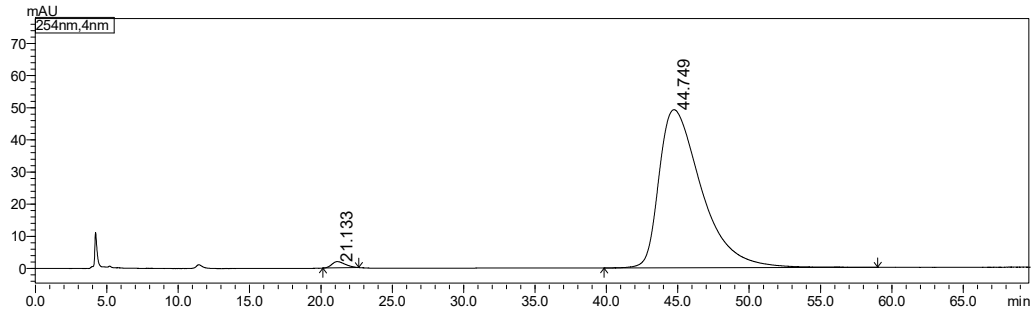


4j



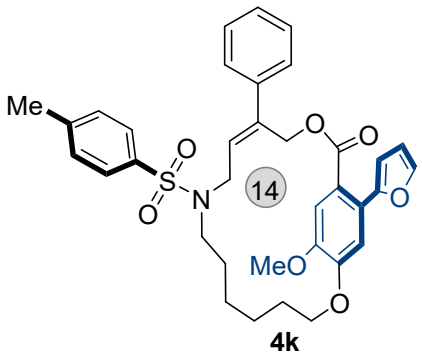
Peak	Ret. time	Area	Height	Area%	Height%
1	21.103	2170098	29045	49.745	73.112
2	45.176	2192357	10682	50.255	26.888
Total		4362456	39728	100.000	100.000

HPLC Spectrum of racemic 4j.

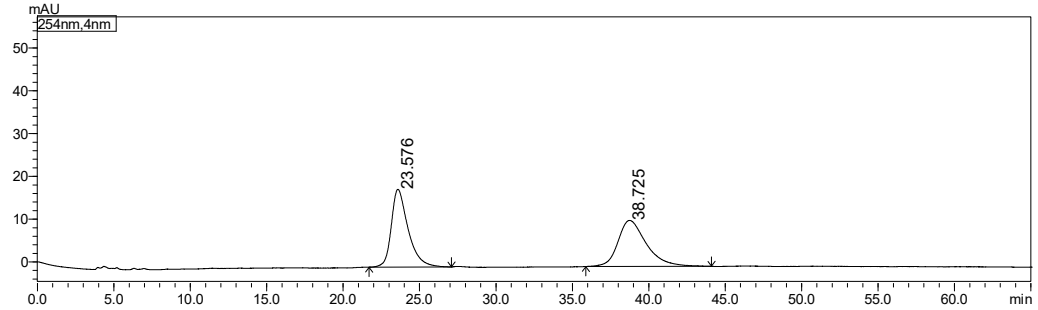


Peak	Ret. time	Area	Height	Area%	Height%
1	21.133	128731	1960	1.249	3.831
2	44.749	10181668	49200	98.751	96.169
Total		10310399	51160	100.000	100.000

HPLC Spectrum of enantioenriched 4j.

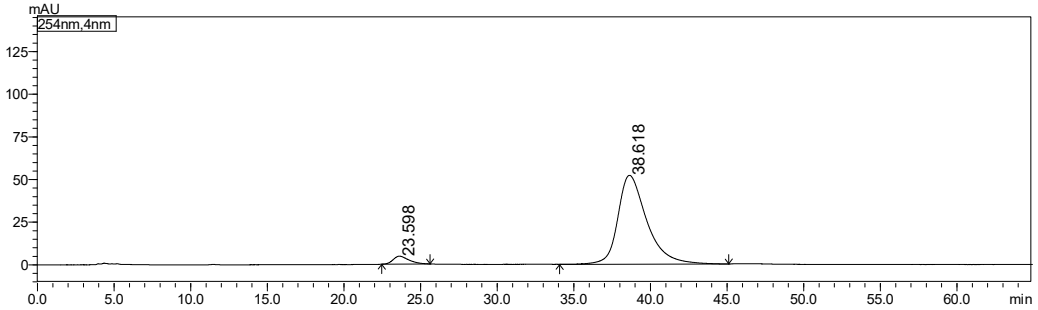


4k



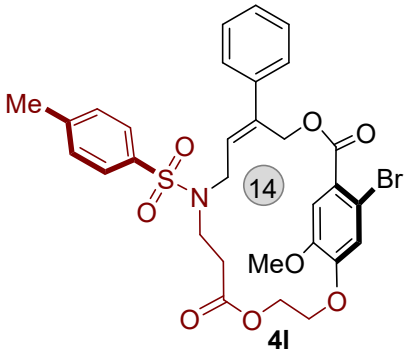
Peak	Ret. time	Area	Height	Area%	Height%
1	23.576	1390590	18161	49.981	62.759
2	38.725	1391640	10776	50.019	37.241
Total		2782230	28937	100.000	100.000

HPLC Spectrum of racemic 4k.

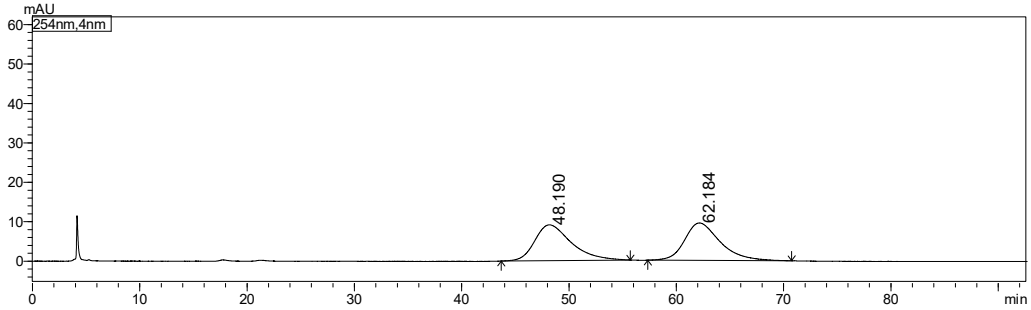


Peak	Ret. time	Area	Height	Area%	Height%
1	23.598	334754	4669	4.666	8.231
2	38.618	6839277	52054	95.334	91.769
Total		7174031	56723	100.000	100.000

HPLC Spectrum of enantioenriched 4k.

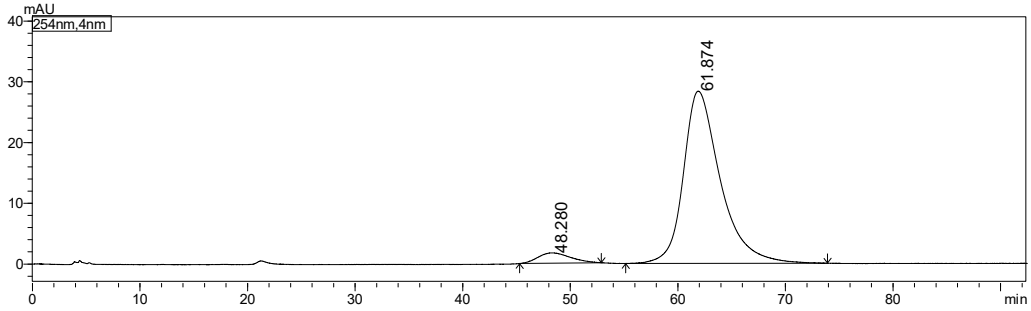


4l



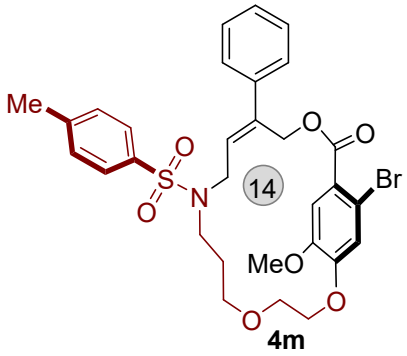
Peak	Ret. time	Area	Height	Area%	Height%
1	48.190	2147996	9085	49.464	48.843
2	62.184	2194562	9515	50.536	51.157
Total		4342558	18601	100.000	100.000

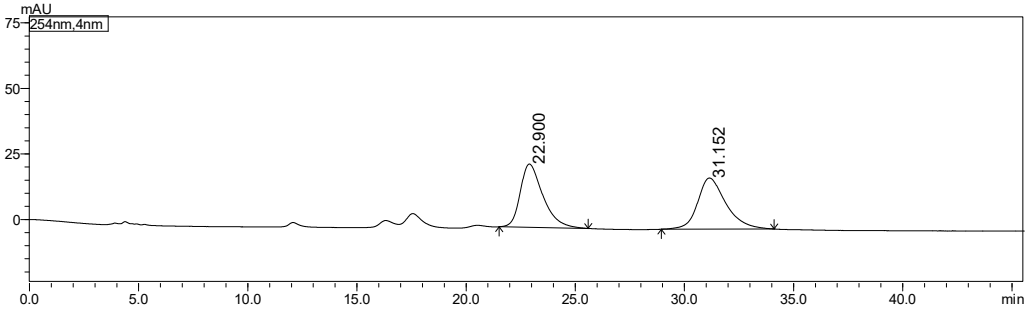
HPLC Spectrum of racemic 4l.



Peak	Ret. time	Area	Height	Area%	Height%
1	48.280	355424	1703	4.992	5.667
2	61.874	6764209	28355	95.008	94.333
Total		7119633	30058	100.000	100.000

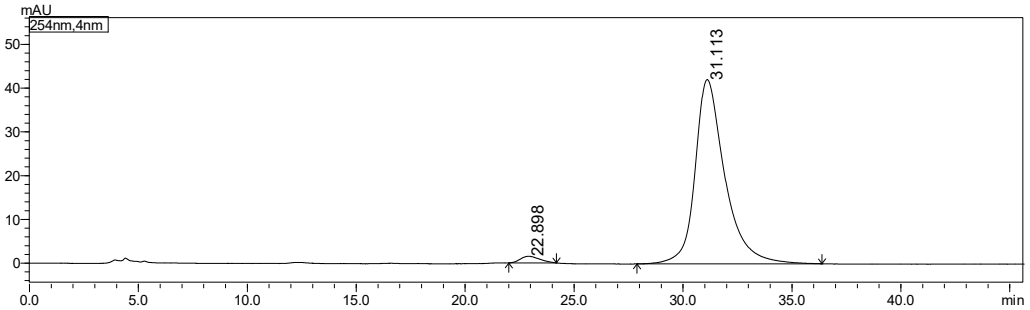
HPLC Spectrum of enantioenriched 4l.





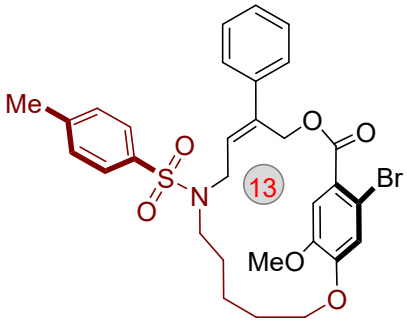
Peak	Ret. time	Area	Height	Area%	Height%
1	22.900	1748656	24155	49.761	55.328
2	31.152	1765463	19502	50.239	44.672
Total		3514118	43657	100.000	100.000

HPLC Spectrum of racemic 4m.

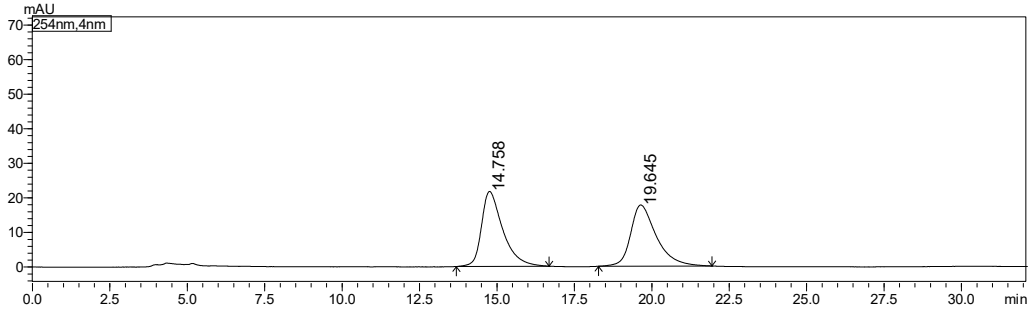


Peak	Ret. time	Area	Height	Area%	Height%
1	22.898	93645	1525	2.283	3.493
2	31.113	4008824	42124	97.717	96.507
Total		4102469	43649	100.000	100.000

HPLC Spectrum of enantioenriched 4m.

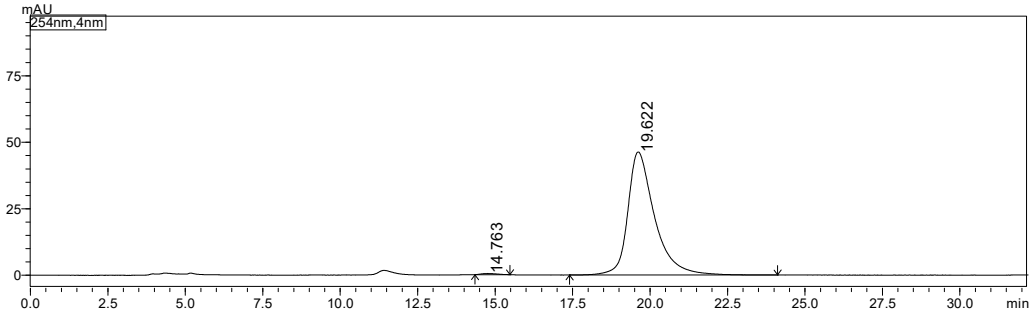


4n



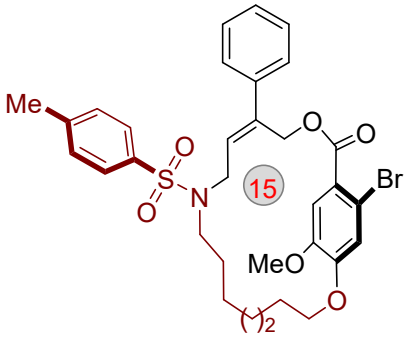
Peak	Ret. time	Area	Height	Area%	Height%
1	14.758	1036827	21677	50.241	55.026
2	19.645	1026872	17717	49.759	44.974
Total		2063699	39394	100.000	100.000

HPLC Spectrum of racemic 4n.

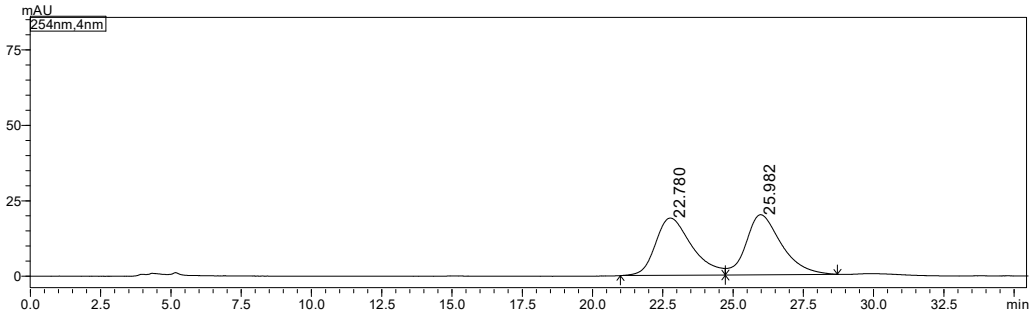


Peak	Ret. time	Area	Height	Area%	Height%
1	14.763	15793	456	0.564	0.977
2	19.622	2784765	46261	99.436	99.023
Total		2800558	46717	100.000	100.000

HPLC Spectrum of enantioenriched 4n.

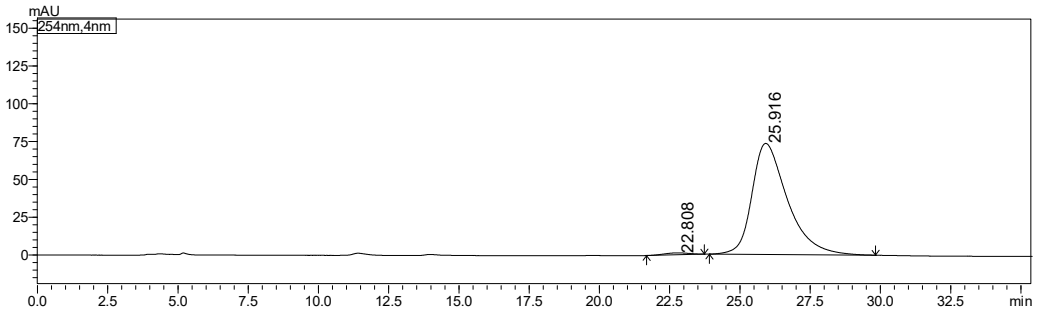


4o



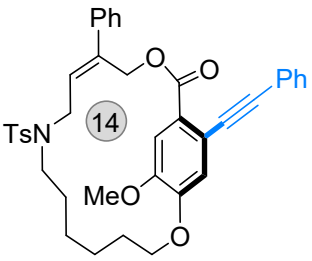
Peak	Ret. time	Area	Height	Area%	Height%
1	22.780	1708569	18981	49.497	48.799
2	25.982	1743303	19916	50.503	51.201
Total		3451872	38897	100.000	100.000

HPLC Spectrum of racemic 4o.

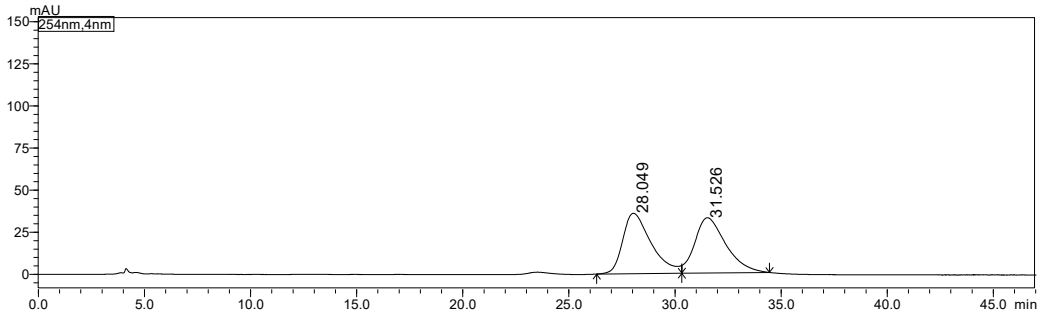


Peak	Ret. time	Area	Height	Area%	Height%
1	22.808	79481	1274	1.212	1.704
2	25.916	6476987	73461	98.788	98.296
Total		6556469	74735	100.000	100.000

HPLC Spectrum of enantioenriched 4o.

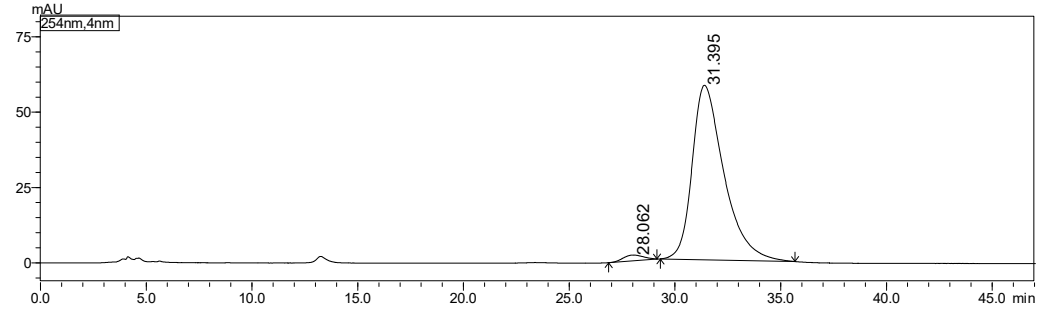


5



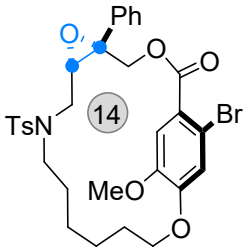
Peak	Ret. time	Area	Height	Area%	Height%
1	28.049	3363633	35882	50.142	52.207
2	31.526	3344565	32848	49.858	47.793
Total		6708197	68730	100.000	100.000

HPLC Spectrum of racemic 5.

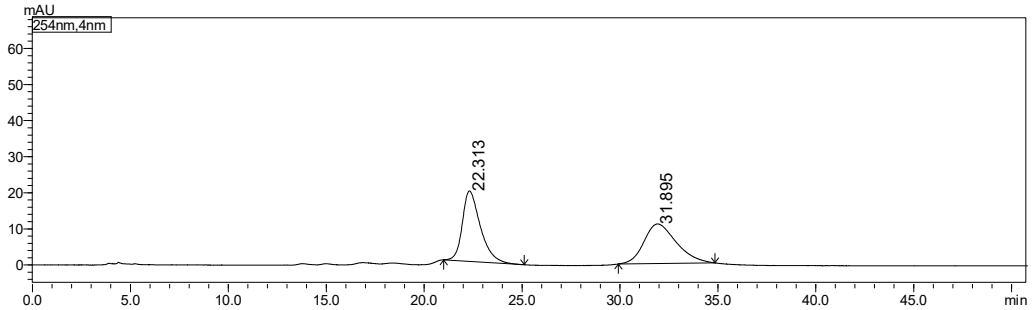


Peak	Ret. time	Area	Height	Area%	Height%
1	28.062	126995	1913	2.050	3.196
2	31.395	6067421	57929	97.950	96.804
Total		6194416	59842	100.000	100.000

HPLC Spectrum of enantioenriched 5.

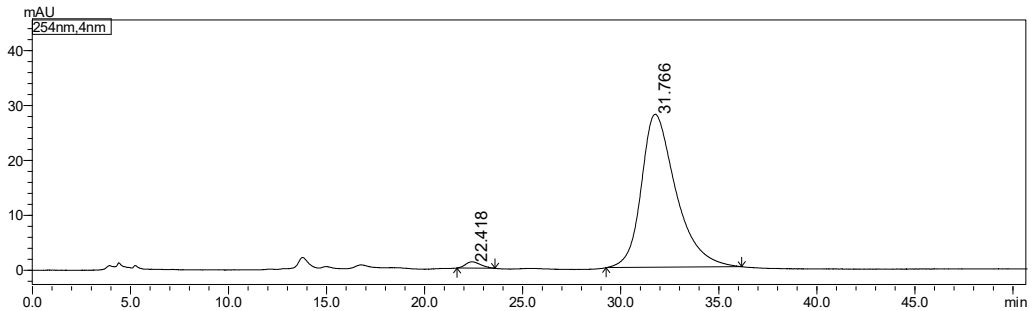


6



Peak	Ret. time	Area	Height	Area%	Height%
1	22.313	1252566	19496	49.758	64.012
2	31.895	1264765	10961	50.242	35.988
Total		2517331	30457	100.000	100.000

HPLC Spectrum of racemic 6.



Peak	Ret. time	Area	Height	Area%	Height%
1	22.418	61942	1156	1.776	3.978
2	31.766	3425970	27891	98.224	96.022
Total		3487913	29046	100.000	100.000

HPLC Spectrum of enantioenriched 6.

Supplementary References

1 (a) H. Chen, H. Long, X. Cui, J. Zhou, M. Xu, G. Yuan, *J. Am. Chem. Soc.* 2014, **136**, 2583-2591; (b) T. J. Doyon, J. C. Perkins, S. A. Baker Dockrey, E. O. Romero, K. C. Skinner, P. M. Zimmerman, A. R. H. Narayan, *J. Am. Chem. Soc.* 2019, **141**, 20269-20277; (c) T. Chen, N. W. Reich, N. Bell, P. D. Finn, D. Rodriguez, J. Kohler, K. Kozuka, L. He, A. G. Spencer, D. Charmot, M. Navre, C. W. Carreras, S. Koo-McCoy, J. Tabora, J. S. Caldwell, J. W. Jacobs, J. G. Lewis, *J. Med. Chem.* 2018, **61**, 7589-7613.

2 (a) K. Lee, J.-M. Rouillard, T. Pham, E. Gulari, J. Kim, *Angew. Chem. Int. Ed.* 2007, **46**, 4667-4670; (b) D. V. Hingorani, E. A. Randtke, M. D. Pagel, *J. Am. Chem. Soc.* 2013, **135**, 6396-6398; (c) T. Noguchi, B. Roy, D. Yoshihara, Y. Tsuchiya, T. Yamamoto, S. Shinkai, *Chem. Eur. J.* 2014, **20**, 13938-13944; (d) M. Takioku, Y. Takamura, M. Fujihara, M. Watanabe, S. Yamada, M. Kawasaki, S. Ito, S. Nakano, H. Kakuta, *ACS Med. Chem. Lett.* 2021, **12**, 1024-1029.

3 (a) A. Khan, R. Zheng, Y. Kan, J. Ye, J. Xing, Y. J. Zhang, *Angew. Chem. Int. Ed.* 2014, **53**, 6439-6442; (b) A. Khan, J. Xing, J. Zhao, Y. Kan, W. Zhang, Y. J. Zhang, *Chem. Eur. J.* 2015, **21**, 120-124; (c) W. Guo, L. Martínez-Rodríguez, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed.* 2016, **55**, 11037-11040; (d) A. Khan, S. Khan, I. Khan, C. Zhao, Y. Mao, Y. Chen, Y. J. Zhang, *J. Am. Chem. Soc.* 2017, **139**, 10733-10741; (e) S. Singha, T. Patra, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* 2018, **140**, 3551-3554.

4 (a) D. B. Guthrie, D. P. Curran, *Org. Lett.* 2009, **11**, 249-251; (b) S. Mondal, S. Mukherjee, *Org. Lett.* 2022, **24**, 8300-8304.

5 (a) G. Yang, S. Sun, Z. Li, Y. Liu, J. Wang, *Commun. Chem.* 2021, **4**, 144; (b) S. Shee, S. Shree Ranganathappa, M. S. Gadhave, R. Gogoi, A. T. Biju, *Angew. Chem. Int. Ed.* 2023, **62**, e202311709; (c) J. Wang, M. Wang, Y. Wen, P. Teng, C. Li, C. Zhao, *Org. Lett.* 2024, **26**, 1040-1045.

6 (a) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* 2016, **138**, 7840-7843; (b) L. Zhou, X. Wu, X. Yang, C. Mou, R. Song, S. Yu, H. Chai, L. Pan, Z. Jin, Y. R. Chi, *Angew. Chem. Int. Ed.* 2020, **59**, 1557-1561; (c) T. Fan, J. Song, L.-Z. Gong, *Angew. Chem. Int. Ed.* 2022, **61**, e202201678.