Supporting Information

Organocatalytic asymmetric synthesis of multifunctionalized α-carboline-spirooxindole hybrids that suppressed proliferation in colorectal cancer cell lines

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1. General methods and materials

Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 or $CDCl_3$ on Bruker 600, 700 MHz, or JEOL 600 NMR instrument (at 600 or 700 MHz for ^1H, and at 150, or 175 MHz for ^{13}C). The ^1H NMR chemical shifts are reported in ppm, and are referenced using residual protium in the NMR solvent ($CDCl_3$: δ = 7.26 ppm ($CHCl_3$), DMSO-d_6: δ = 2.49 ppm (DMSO)). The ^{13}C NMR chemical shifts were given using DMSO-d_6 or $CDCl_3$ as the internal standard (DMSO-d_6: δ = 39.52 ppm; $CDCl_3$: δ = 77.00 ppm). Enantiomeric ratio (er) was determined by comparing HPLC analyses of products on chiral columns with results obtained using authentic racemates. Enantiomeric ratio (er) was determined by comparing HPLC analyses of products on chiral columns with results obtained using authentic racemates. The following Daicel Chiralpak columns were used: IA (250 x 4.6 mm), IC (250 x 4.6 mm) or IE (250 x 4.6 mm). UV detection was performed at 254 nm. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at 25 °C. High-resolution mass spectra (HRMS) were obtained using Agilent P/N G1969-90010. High-resolution mass spectra were reported for the molecular ion $[M+H]^+$ or $[M+Na]^+$. Melting points were recorded on BUCHI Melting Point M-565 instrument. X-ray diffraction experiment was carried out on an Agilent Gemini and the data obtained were deposited at the Cambridge Crystallographic Data Centre. UV detection was performed at 254 nm. TLC was performed on glass-backed silica plates; products were visualized using UV light. Column chromatography was performed on silica gel (400–500 mesh) using an eluent of ethyl acetate and petroleum ether. All reagents and solvents were obtained from commercial sources and used without further purification. isatin-derived MBH carbonates **1**[1], indolin-2-imines **2**[2] and catalysts[3] were prepared according to the literature procedures.

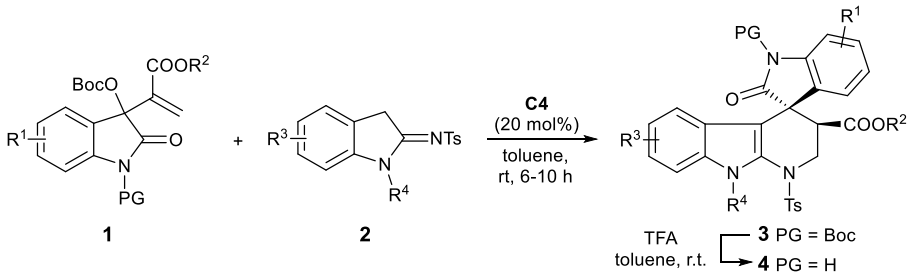
Reference:

1. J. Peng, X. Huang, H.-L. Cui, Y. -C. Chen, Organocatalytic and Electrophilic Approach to Oxindoles with C3-Quaternary Stereocenters. *Org. Lett*., 2010, **12**, 4260.

2. (a) K. S, K. C. K. Swamy, Transition-Metal-Free, Brønsted Acid-Mediated Cascade Sequence in the Reaction of Propargyl Alcohols with Sulfonamido-indoles/-indolines: Highly Substituted δ-and α-Carbolines. *J. Org. Chem*., 2018, **83**, 15043; (b) H. Liu, A. M. Z. Slawin, A. D. Smith, Isothiourea-Catalyzed Enantioselective Synthesis of Tetrahydro-α-carbolinones, *Org. Lett*., 2020, **22**, 1301.

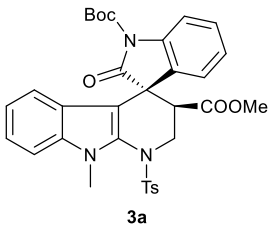
3. H. Waldmann, V. Khedkar, H. Dückert, M. Schürmann, I. Oppel, K. Kumar, Asymmetric Synthesis of Natural Product Inspired Tricyclic Benzopyrones by an Organocatalyzed Annulation Reaction. *Angew. Chem. Int. Ed*., 2008, **47**, 6869.

2. General procedure for the synthesis of 4



A mixture of **1** (0.1 mmol) and **2** (0.12 mmol, 1.2 equiv.) was added **C4** (0.02 mmol, 20 mol%) in toluene (1.0 mL) at room temperature for 6-10 hours until the complete consumption of **1** (monitored by TLC). The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether /ethyl acetate = 15:1 to 10:1) to give the protected spirooxindole-α-carboline derivative **3**. To a solution of **3** in toluene (1.0 mL) was added TEA (20.0 mg) at room temperature for about 1 h. After the reaction was completed (monitored by TLC), the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether /ethyl acetate = 5:1 to 3:1) to give the deprotected spirooxindole-α-carboline derivative **4**, which was dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR, HPLC and high-resolution mass spectrometry.

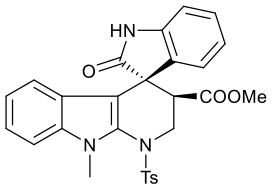
1-(tert-butyl) 3'-methyl (3*S*,3'*R*)-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-1,3'-dicarboxylate 3a：



3a

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol,) was added **C4** (6.5 mg, 0.02 mmol, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3a**: 52.2 mg, as a white solid, 85% yield, 93:7 er, >20:1 dr; m.p. 190–192 °C, $[\alpha]_D^{25}$ = 89.6 (c 0.67, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IE, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.73 min, t_{minor} = 20.54 min). **^{1}H NMR (700 MHz, $CDCl_3$)**: δ = 7.90 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.25–7.23 (m, 1H), 7.16–7.14 (m, 1H), 6.88–6.86 (m, 1H), 6.83–6.82 (m, 1H), 6.83–6.82 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.51 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.89–3.85 (m, 4H), 3.15 (s, 3H), 3.00 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 2.45 (s, 3H), 1.64 (s, 9H) ppm; **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)**: δ = 175.27, 169.48, 149.34, 145.20, 139.32, 136.71, 134.25, 133.80, 130.47 (2C), 129.66, 128.94 (2C), 128.30, 124.69, 123.70, 123.36, 122.42, 120.50, 117.76, 114.82, 110.07, 101.89, 84.32, 51.64, 49.88, 46.96, 44.85, 32.90, 28.07, 21.75 ppm. HRMS (ESI-TOF) Calcd. For $C_{33}H_{33}N_3O_7S$ $[M+Na]^+$: 638.1937; found 638.1936.

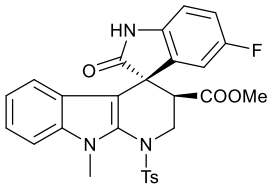
methyl (3*S*,3'*R*)-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4a):



4a

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3a**. To a solution of **3a** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4a**: 43.5 mg, as a white solid, 84% yield, 92:8 er, >20:1 dr; m.p. 259–261 °C, $[\alpha]_D^{25}$ = 135.8 (c 0.75, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 32.02 min, t_{minor} = 19.83 min). **^{1}H NMR (600 MHz, DMSO-*d*$_6$)**: δ = 10.79 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.17 (dd, J_1 = 14.4 Hz, J_2 = 3.6 Hz, 1H), 3.98 (dd, J_1 = 15.0 Hz, J_2 = 12.0 Hz, 1H), 3.76 (s, 3H), 3.38 (dd, J_1 = 12.0 Hz, J_2 = 3.6 Hz, 1H), 3.12 (s, 3H), 2.44 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$):** δ = 178.51, 170.00, 145.56, 142.49, 136.26, 134.58, 133.88, 131.34, 130.93 (2C), 129.21, 128.53 (2C), 124.88, 123.54, 122.42, 121.98, 120.35, 117.74, 110.74, 109.74, 102.43, 51.79, 49.70, 47.02, 44.79, 32.46, 21.68 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{25}N_3O_5S$ $[M+Na]^+$: 538.1413; found 538.1411.

methyl (3*S*,3'*R*)-5-fluoro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4b):

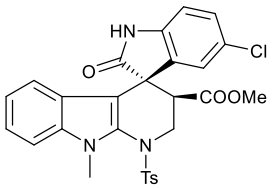


4b

A mixture of **1b** (45.1 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3b**. To a solution of **3b** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4b**: 40.7 mg, as a white solid, 76% yield, 90:10 er, >20:1 dr; m.p. 234–235 °C, $[\alpha]_D^{25}$ = 109.4 (c 0.65, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 Ml/min, λ = 254 nm, t_{major} = 23.21 min, t_{minor} = 8.54 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.82 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.15–7.12 (m, 1H), 7.03–6.97 (m, 2H), 6.95–6.94 (m, 1H), 6.89–6.86 (m, 1H), 6.68–6.65 (m, 1H), 4.15 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H),

3.98 (dd, J_1 = 14.7 Hz, J_2 = 12.6 Hz, 1H), 3.77 (s, 3H), 3.38 (dd, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 1H), 3.18 (s, 3H), 2.45 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$)**: δ = 177.99, 169.42, 157.79 (d, J_{CF} = 235.4 Hz), 145.12, 138.31, 135.80, 134.08, 133.60, 132.55 (d, J = 8.1 Hz), 130.47 (2C), 128.06 (2C), 122.97, 122.01, 120.01, 117.04, 115.07 (d, J = 23.3 Hz), 112.44 (d, J = 24.7 Hz), 110.37, 110.04 (d, J = 7.7 Hz), 101.39, 51.47, 49.73, 46.26, 44.21, 32.03, 21.21 ppm; **^{19}F NMR (658 MHz, DMSO-*d*$_6$)**: δ = -121.57 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}FN_3O_5S$ [M+Na]$^+$: 556.1318; found 556.1316.

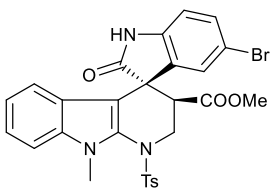
methyl (3*S*,3'*R*)-5-chloro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4c):



4c

A mixture of **1c** (46.8 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3c**. To a solution of **3c** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4c**: 43.6 mg, as a white solid, 79% yield, 89:11 er, >20:1 dr; m.p. 204–206 °C, $[\alpha]_D^{25}$ = 85.6 (c 0.82, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 23.06 min, t_{minor} = 7.95 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.86 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.16 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 7.08–7.05 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H); 6.81 (t, J = 8.4 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 4.08 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 4.02–3.98 (m, 1H), 3.70 (s,3H), 3.31–3.28 (m, 1H), 3.12 (s,3H), 2.37 (s,3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.24, 169.86, 145.57, 141.49, 136.27, 134.57, 134.19, 133.36, 130.93 (2C), 129.20, 128.50 (2C), 126.09, 125.06, 123.40, 122.49, 120.52, 117.44, 111.20, 110.88, 101.68, 51.98, 49.98, 46.74, 44.72, 32.52, 21.67 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}ClN_3O_5S$ [M+Na]$^+$: 572.1023; found 572.1023.

methyl (3*S*,3'*R*)-5-bromo-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4d):

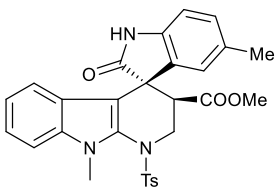


4d

A mixture of **1d** (51.2 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3d**. To a solution of **3d** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for

1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4d**: 45.8 mg, as a white solid, 77% yield, 90:10 er, >20:1 dr; m.p. 263–264 ℃, $[\alpha]_D^{25}$ = 110.4 (c 0.60, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IE, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 34.52 min, t_{minor} = 19.52 min). **^{1}H NMR (600 MHz, *d*-DMSO)**: δ = 10.94 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 4.14 (dd, J_1 = 15.0 Hz, J_2 = 3.6 Hz, 1H), 4.06 (dd, J_1 = 15.0 Hz, J_2 = 12.0 Hz, 1H), 3.76 (s,3H), 3.37-3.34 (m, 1H), 3.18 (s, 3H), 2.44 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d_6*)**: δ = 178.19, 169.92, 145.62, 141.96, 136.33, 134.66, 134.27, 133.79, 132.15, 130.99 (2C), 128.55 (2C), 127.73, 123.47, 122.55, 120.60, 117.50, 113.89, 111.79, 110.96, 101.71, 52.05, 50.00, 46.80, 44.83, 32.59, 21.73 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}{}^{79}BrN_3O_5S$ $[M+Na]^+$: 616.0518; found 616.0518; Calcd. For $C_{28}H_{24}{}^{81}BrN_3O_5S$ $[M+Na]^+$: 618.0497; found 618.0502.

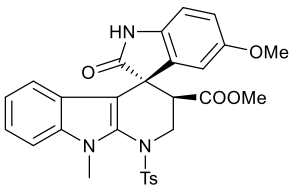
<u>methyl (3*S*,3'*R*)-5,9'-dimethyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido-[2,3-b]indole]-3'-carboxylate (4e):</u>



4e

A mixture of **1e** (44.8 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 9 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3e**. To a solution of **3e** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4e**: 46.2 mg, as a white solid, 87% yield, 87:13 er, >20:1 dr; m.p. 247–249 ℃, $[\alpha]_D^{25}$ = 83.5 (c 0.40, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 27.05 min, t_{minor} = 13.82 min). **^{1}H NMR (700 MHz, DMSO-*d_6*)**: δ = 10.67 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.12–7.09 (m, 1H), 6.97–6.95 (m, 1H), 6.85–6.83 (m, 2H), 6.82–6.79 (m, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.16 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.97 (dd, J_1 = 14.7 Hz, J_2 = 12.6 Hz, 1H), 3.75 (s, 3H), 3.36-3.35 (m, 1H), 3.13 (s, 3H), 2.43 (s, 3H), 2.03 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d_6*)**: δ = 178.01, 169.56, 145.06, 139.58, 135.80, 134.15, 133.36, 130.93 (2C), 130.45, 130.30, 129.00 (2C), 128.03, 124.84, 123.12, 121.92, 119.87, 117.37, 110.26, 109.01, 102.09, 51.33, 49.26, 46.58, 44.28, 32.03, 21.20, 20.49 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_5S$ $[M+Na]^+$: 552.1569; found 552.1569.

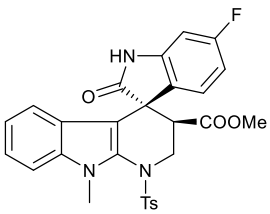
methyl (3*S*,3'*R*)-5-methoxy-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4f):



4f

A mixture of **1f** (46.4 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 10 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) gave the protected product **3f**. To a solution of **3f** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 4/1) gave the deprotected product **4f**: 48.6 mg, as a white solid, 89% yield, 88:12 er, >20:1 dr; m.p. 226–227 ℃, $[\alpha]_D^{25}$ = 80.9 (c 0.74, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 36.90 min, t_{minor} = 10.92 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.59 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.12–7.09 (m, 1H), 6.84 (t, *J* = 7.7 Hz, 2H), 6.73 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.59–6.58 (m 1H), 4.14–4.11 (m, 1H), 4.04–4.00 (m, 1H), 3.75 (s, 3H), 3.52 (s, 3H), 3.39–3.37 (m, 1H), 3.14 (s, 3H), 2.43 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 177.90, 169.56, 154.63, 145.04, 135.78, 135.36, 134.20, 133.42, 132.18, 130.44 (2C), 128.03 (2C), 123.13, 121.89, 119.86, 117.33, 113.01, 111.81, 110.24, 109.53, 101.95, 55.40, 51.35, 49.67, 46.44, 44.32, 32.00, 21.20 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_6S$ $[M+Na]^+$: 568.1518; found 568.1521.

methyl (3S,3'R)-6-fluoro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido-[2,3-b]indole]-3'-carboxylate (4g):

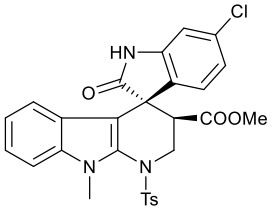


4g

A mixture of **1g** (45.1 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3g**. To a solution of **3g** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4g**: 42.3 mg, as a white solid, 79% yield, 95:5 er, >20:1 dr; m.p. 237–239 ℃, $[\alpha]_D^{25}$ = 126.7 (c 0.78, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 45.00 min, t_{minor} = 29.55 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.96 (s, 1H), 7.87–7.85 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.15–7.12 (m, 1H), 7.01 (dd, J_1 = 8.4 Hz, J_2 = 5.6 Hz, 1H), 6.89–6.87 (m, 1H), 6.78 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 1H), 6.66–6.64 (m, 1H), 6.56–

6.53 (m, 1H), 4.17 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.99 (dd, J_1 = 15.4 Hz, J_2 = 12.6 Hz, 1H), 3.76 (s, 3H), 3.34–3.33 (m, 1H), 3.18 (s, 3H), 2.45 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.87, 169.90, 162.78 (d, *J* = 241.2 Hz), 145.59, 144.19 (d, *J* = 12.3 Hz), 136.28, 134.52, 133.99, 130.94 (2C), 128.53 (2C), 127.24, 126.44 (d, *J* = 9.8 Hz), 123.42, 122.49, 120.49, 117.55, 110.84, 108.08 (d, *J* = 22.1 Hz), 102.12, 98.03 (d, *J* = 26.8 Hz), 51.93, 49.32, 46.87, 44.83, 32.49, 21.67 ppm; **^{19}F NMR (658 MHz, DMSO-*d*$_6$)**: δ = -111.80 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}FN_3O_5S$ [M+Na]$^+$: 556.1318; found 556.1318.

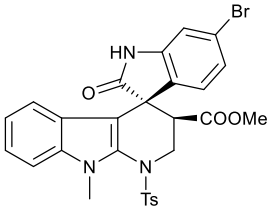
methyl (3*S*,3'*R*)-6-chloro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4h):



4h

A mixture of **1h** (46.8 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3h**. To a solution of **3h** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4h**: 40.6 mg, as a white solid, 74% yield, 88:12 er, >20:1 dr; m.p. 233–234 ℃, $[\alpha]_D^{25}$ = 77.5 (c 0.85, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 47.06 min, t_{minor} = 37.73 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.93 (s, 1H), 7.82–7.80 (m, 2H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.97–6.96 (m, 1H), 6.94 (t, *J* = 9.1 Hz, 1H), 6.85 (t, J_1 = 7.0 Hz, 1H), 6.76–6.74 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.15–4.12 (m, 1H), 3.96–3.92 (m, 1H), 3.72 (s, 3H), 3.32–3.30 (m, 1H), 3.15 (s, 3H), 2.39 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.49, 169.83, 145.62, 144.05, 136.26, 134.48, 134.02, 133.44, 130.94 (2C), 130.28, 128.52 (2C), 126.38, 123.36, 122.53, 121.74, 120.58, 117.50, 110.87, 109.93, 101.80, 52.01, 49.42, 46.85, 44.73, 32.50, 21.67 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}ClN_3O_5S$ [M+Na]$^+$: 572.1023; found 572.1024.

methyl (3*S*,3'*R*)-6-bromo-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4i):

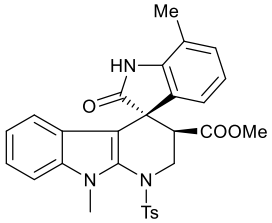


4i

A mixture of **1i** (51.2 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3i**. To a solution of **3i** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for

1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4i**: 46.8 mg, as a white solid, 79% yield, 86:14 er, >20:1 dr; m.p. 234–236 ℃, $[\alpha]_D^{25}$ = 96.6 (c 0.80, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 46.35 min, t_{minor} = 40.26 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.95 (s, 1H), 7.86-7.84 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.14-7.12 (m, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.96-6.92 (m, 1H), 6.90-6.88 (m, 1H), 6.90-6.88 (m, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.17 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.98 (dd, J_1 = 14.7 Hz, J_2 =4.9 Hz, 1H), 3.76 (s, 3H), 3.36-3.35 (m, 1H), 3.19 (s, 3H), 2.44 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.35, 169.81, 169.81, 145.62, 144.22, 136.25, 134.48, 134.02, 130.95 (2C), 130.72, 128.53 (2C), 126.74, 124.63, 123.35, 122.53, 121.81, 120.59, 117.50, 112.65, 110.87, 101.72, 52.02, 49.48, 46.85, 44.66, 32.51, 21.67 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}{}^{79}BrN_3O_5S$ $[M+Na]^+$: 616.0518; found 616.0518; Calcd. For $C_{28}H_{24}{}^{81}BrN_3O_5S$ $[M+Na]^+$: 618.0497; found 618.0503.

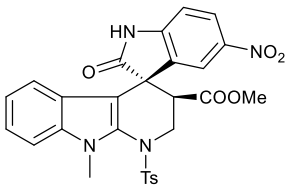
<u>methyl (3*S*,3'*R*)-7,9'-dimethyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido-[2,3-b]indole]-3'-carboxylate (4j):</u>



4j

A mixture of **1j** (44.8 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3j**. To a solution of **3j** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4j**: 47.6 mg, as a white solid, 90% yield, 96:4 er, >20:1 dr; m.p. 260–261 ℃, $[\alpha]_D^{25}$ = 129.4 (c 0.68, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 20.04 min, t_{minor} = 16.93 min). **^{1}H NMR** (700 MHz, DMSO-*d*$_6$): δ = 10.82 (s, 1H), 7.88-7.86 (m, 2H), 7.51-7.49 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.11-7.09 (m, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.83 (t, *J* = 7.7 Hz 1H), 6.75 (d, *J* = 7.0 Hz 1H), 6.64-6.62 (m, 2H), 4.13 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.93 (dd, J_1 = 14.7 Hz, J_2 = 11.9 Hz, 1H),3.74 (s, 3H), 3.40-3.39 (m, 1H), 3.09 (s, 3H), 2.43 (s, 3H), 2.29 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 179.08, 170.01, 145.56, 141.05, 136.23, 134.60, 133.79, 130.96 (2C), 130.94, 130.33, 128.52 (2C), 123.59, 122.40, 122.13, 121.90, 120.35, 119.05, 117.86, 110.68, 102.55, 51.68, 49.94, 46.97, 45.00, 32.39, 21.66, 16.99 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_5S$ $[M+Na]^+$: 552.1569; found 552.1569.

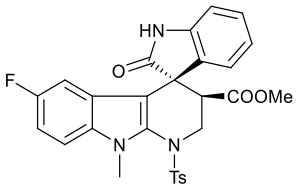
methyl (3S,3'R)-9'-methyl-5-nitro-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4k):



4k

A mixture of **1k** (47.8 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 6 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 8/1) gave the protected product **3k**. To a solution of **3k** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 3/1) gave the deprotected product **4k**: 42.5 mg, as a white solid, 76% yield, 88:12 er, >20:1 dr; m.p. 257–259 ℃, $[\alpha]_D^{25}$ = 89.4 (c 0.69, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 32.62 min, t_{minor} = 45.30 min). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ = 9.27 (s, 1H), 8.12–8.10 (m, 1H), 7.80–7.77 (m, 2H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.41–7.39 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.50 (dd, J_1 = 15.0 Hz, J_2 = 3.6 Hz, 1H), 3.91 (s, 3H), 3.89–3.86 (m, 1H), 3.38 (dd, J_1 = 12.6 Hz, J_2 = 3.6 Hz, 1H), 3.28 (s, 3H), 2.48 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$):** δ = 179.73, 169.35, 146.67, 145.55, 143.47, 136.66, 134.37, 134.16, 132.41, 130.53 (2C), 128.50 (2C), 126.14, 123.01, 122.87, 120.84, 120.09, 117.27, 110.48, 109.69, 99.93, 52.16, 49.88, 46.95, 44.53, 32.88, 21.94 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}N_4O_7S$ $[M+Na]^+$: 583.1263; found 583.1262.

methyl (3*S*,3'*R*)-6'-fluoro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4l):

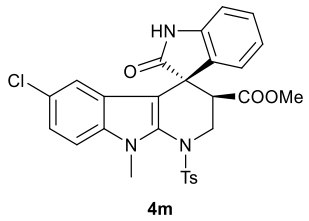


4l

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2b** (38.2 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3l**. To a solution of **3l** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4l**: 44.4 mg, as a white solid, 83% yield, 92:8 er, >20:1 dr; m.p. 243–245 ℃, $[\alpha]_D^{25}$ = 104.8 (c 0.91, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.05 min, t_{minor} = 25.69 min). **^{1}H NMR (700 MHz, $CDCl_3$)**: δ = 8.58 (s, 1H), 7.72–7.70 (m, 2H), 7.38–7.37 (m, 2H), 7.21 (dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, 1H), 7.18–7.16 (m, 1H), 6.93–6.82 (m, 4H), 6.43 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 1H), 4.48 (dd, J_1 = 15.4 Hz, J_2 = 4.2 Hz, 1H), 3.90–3.86 (m, 4H),

3.13 (s, 3H), 2.98 (dd, J_1 = 15.4 Hz, J_2 = 3.5 Hz, 1H), 2.45 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$)**: δ = 179.07, 169.71, 158.02 (d, *J* = 234.5 Hz), 145.34, 140.41, 135.56, 133.97, 133.28, 130.68 (2C), 130.41, 129.07, 128.54 (2C), 124.26, 123.66 (d, *J* = 10.5 Hz), 123.00, 110.89 (d, *J* = 8.8 Hz), 110.61 (d, *J* = 24.2 Hz), 109.68, 103.25 (d, *J* = 24.2 Hz), 101.36 (d, *J* = 4.4 Hz), 51.57, 49.69, 47.02, 43.87, 33.12, 21.82 ppm; **^{19}F NMR (658 MHz, DMSO-*d*$_6$)**: δ = -123.14 ppm. For $C_{28}H_{24}FN_3O_5S$ $[M+Na]^+$: 556.1318; found 556.1315.

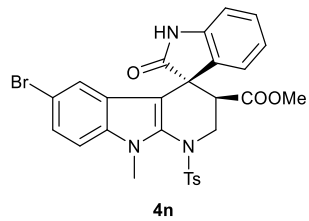
methyl (3S,3'R)-6'-chloro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4m):



4m

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2c** (40.2 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3m**. To a solution of **3m** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4m**: 46.8 mg, as a white solid, 85% yield, 93:7 er, >20:1 dr; m.p. 254–256 °C, $[\alpha]_D^{25}$ = 90.5 (c 0.84, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 13.68 min, t_{minor} = 25.95 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.84 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 8.4 Hz, 3H), 7.19 (td, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.12 (dd, J_1 = 9.1 Hz, J_2 = 2.1 Hz, 1H), 6.98-6.97 (m, 2H), 6.77–6.75 (m, 1H), 6.58 (d, *J* = 2.1 Hz 1H), 4.16 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.98 (dd, J_1 = 14.7 Hz, J_2 = 12.6 Hz, 1H),3.75 (s, 3H), 3.36-3.33 (m, 1H), 3.11 (s, 3H), 2.43 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 177.74, 169.35, 145.24, 141.87, 134.85, 134.30, 133.96, 130.50 (2C), 130.47, 129.02, 128.06 (2C), 124.46, 124.42, 124.00, 121.84, 121.75, 116.22, 112.21, 109.35, 101.72, 51.38, 49.03, 46.49, 44.18, 32.28, 21.20 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}ClN_3O_5S$ $[M+Na]^+$: 572.1023; found 572.1017.

methyl (3*S*,3'*R*)-6'-bromo-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4n):

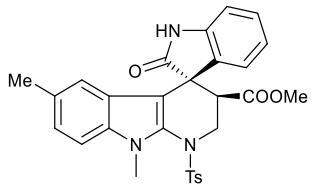


4n

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2d** (45.5 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3n**. To a solution of **3n** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel

(petroleum ether/EtOAc = 5/1) gave the deprotected product **4n**: 46.3 mg, as a white solid, 78% yield, 96:4 er, >20:1 dr; m.p. 257–259 ℃, $[\alpha]_D^{25}$ = 87.2 (c 0.83, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 13.49 min, t_{minor} = 26.79 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.86 (s, 1H), 7.88–7.86 (m, 2H), 7.52–7.50 (m, 1H), 7.45 (d, *J* = 9.1 Hz, 1H), 7.25 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 7.22–7.20 (m, 1H), 7.00–6.98 (m, 2H), 6.79–6.75 (m, 2H), 4.18 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 4.00 (dd, J_1 = 14.7 Hz, J_2 =12.6 Hz, 1H), 3.76 (s, 3H), 3.38–3.36 (m, 1H), 3.13 (s, 3H), 2.45 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 177.73, 169.34, 145.25, 141.87, 134.68, 134.54, 133.94, 130.50 (2C), 130.47, 129.02, 128.05 (2C), 124.66, 124.46, 124.41, 121.76, 119.26, 112.63, 112.38, 109.33, 101.61, 51.38, 49.03, 46.48, 44.16, 32.27, 21.21 ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}{}^{79}BrN_3O_5S$ $[M+Na]^+$: 616.0518; found 616.0518; Calcd. For $C_{28}H_{24}{}^{81}BrN_3O_5S$ $[M+Na]^+$: 618.0497; found 618.0502.

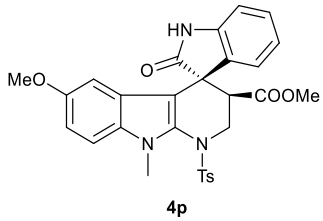
<u>methyl (3*S*,3'*R*)-6',9'-dimethyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4o):</u>



4o

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2e** (37.7 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3o**. To a solution of **3o** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4o**: 38.1 mg, as a white solid, 72% yield, 93:7 er, >20:1 dr; m.p. 232–233 ℃, $[\alpha]_D^{25}$ = 114.9 (c 0.71, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.80 min, t_{minor} = 27.84 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.74 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.16 (td, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 6.93 (td, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 3H), 6.73–6.71 (m, 1H), 6.44 (s, 1H), 4.16-4.13 (m, 1H), 3.97–3.93 (m, 1H),3.71 (s, 3H), 3.30–3.29 (m, 1H), 3.10 (s, 3H), 2.42 (s, 3H), 2.13 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.04, 169.53, 145.04, 142.02, 134.26, 134.11, 133.33, 130.85 (2C), 130.44, 128.74 (2C), 128.32, 128.01, 124.36, 123.38, 123.27, 121.52, 117.00, 110.05, 109.18, 101.45, 51.31, 49.21, 46.50, 44.22, 32.03, 21.25, 21.20 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_5S$ $[M+Na]^+$: 552.1569; found 552.1569.

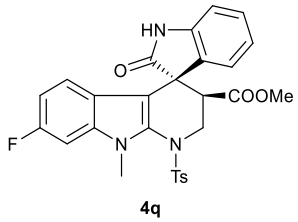
methyl (3S,3'R)-6'-methoxy-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4p):



4p

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2f** (39.7 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 9 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) gave the protected product **3p**. To a solution of **3p** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 3/1) gave the deprotected product **4p**: 38.7 mg, as a white solid, 71% yield, 94:6 er, >20:1 dr; m.p. 259–261 °C, $[\alpha]_D^{25}$ = 109.7 (c 0.92, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IE, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 80.95 min, t_{minor} = 48.32 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.78 (s, 1H), 7.84 (d, *J* =7.7 Hz, 2H), 7.50 (d, *J* =8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.19–7.17 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.78–6.74 (m, 2H), 6.14 (d, *J* = 2.8 Hz 1H), 4.18 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.97 (dd, J_1 = 15.4 Hz, J_2 = 5.6 Hz, 1H), 3.72 (s, 3H), 3.51 (s, 3H), 3.36–3.35 (m, 1H), 3.14 (s, 3H), 2.44 (s, 3H)ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.31, 170.03, 154.09, 145.51, 142.56, 134.59, 134.22, 131.53, 131.22, 130.92 (2C), 129.19, 128.50 (2C), 124.90, 123.93, 122.06, 111.52, 111.07, 109.55, 102.16, 100.83, 55.51, 51.79, 49.69, 47.05, 44.56, 32.55, 21.67 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_6S$ $[M+Na]^+$: 568.1518; found 568.1520.

methyl (3*S*,3'*R*)-7'-fluoro-9'-dimethyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4q):

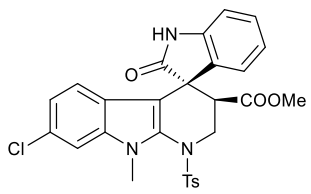


4q

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2g** (38.2 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3q**. To a solution of **3q** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4q**: 42.1 mg, as a white solid, 79% yield, 89:11 er, >20:1 dr; m.p. 229–231 °C, $[\alpha]_D^{25}$ = 115.4 (c 0.76, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.99 min, t_{minor} = 23.01 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.82 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4Hz, 2H), 7.36 (dd, J_1 = 9.8 Hz, J_2 = 2.1 Hz, 1H), 7.18 (td, J_1 = 7.7 Hz, J_2 = 0.7 Hz, 1H), 6.96 (dd, J_1 = 15.3 Hz, J_2 = 7.7 Hz, 1H), 6.76–6.74 (m, 2H), 6.61 (dd, J_1 = 9.1 Hz, J_2 =

5.6 Hz, 1H), 4.15 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.97 (dd, J_1 = 14.7 Hz, J_2 = 12.6 Hz, 1H), 3.74 (s, 3H), 3.39 (dd, J_1 = 11.9 Hz, J_2 = 3.5 Hz, 1H), 3.12 (s, 3H), 2.45 (s, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.37, 169.92, 159.59 (d, J = 234.9 Hz), 145.62, 142.42, 136.46 (d, J = 12.4 Hz), 134.36, 134.34, 131.18, 130.95 (2C), 129.32, 128.56 (2C), 124.89, 122.07, 120.14, 118.73 (d, J = 10.0 Hz), 109.83, 108.69 (d, J = 24.3 Hz), 102.71, 97.65 (d, J = 25.7 Hz), 51.81, 49.61, 46.99, 44.75, 32.68, 21.67 ppm; **^{19}F NMR (658 MHz, DMSO-*d*$_6$)**: δ = -119.47 ppm. HRMS (ESI-TOF) For $C_{28}H_{24}FN_3O_5S$ $[M+Na]^+$: 556.1318; found 556.1314.

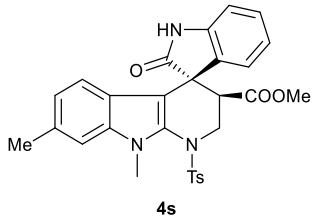
<u>methyl (3*S*,3'*R*)-7'-chloro-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4r):</u>



4r

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2h** (40.2 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3r**. To a solution of **3r** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4r**: 44.7 mg, as a white solid, 81% yield, 93:7 er, >20:1 dr; m.p. 229–230 ℃, $[\alpha]_D^{25}$ = 71.54 (c 0.74, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.07 min, t_{minor} = 23.83 min). **^{1}H NMR (600 MHz, DMSO-*d*$_6$)**: δ = 10.83 (s, 1H), 7.88–7.86 (m, 2H), 7.60 (d, J =7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.18 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.95 (dd, J_1 = 13.8 Hz, J_2 = 7.2 Hz, 2H), 6.90 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 6.74 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.15 (dd, J_1 = 15.0 Hz, J_2 = 3.6 Hz, 1H), 3.97 (dd, J_1 = 15.0 Hz, J_2 = 12.0 Hz, 1H), 3.75 (s, 3H), 3.39-3.38 (m, 1H), 3.12 (s,3H), 2.44 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$)**: δ = 178.37, 169.94, 145.75, 142.46, 136.79, 134.84, 134.53, 131.17, 131.03 (2C), 129.42, 128.61 (2C), 127.35, 124.97, 122.27, 122.15, 120.77, 118.97, 110.94, 109.93, 102.82, 51.89, 49.62, 47.05, 44.84, 32.74, 21.74. ppm. HRMS (ESI-TOF) Calcd. For $C_{28}H_{24}ClN_3O_5S$ $[M+Na]^+$: 572.1023; found 572.1018.

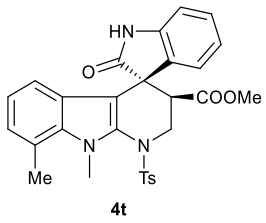
methyl (3*S*,3'*R*)-7',9'-dimethyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4s):



4s

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2i** (37.7 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 9 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3s**. To a solution of **3s** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4s**: 36.7 mg, as a white solid, 69% yield, 91:9 er, >20:1 dr; m.p. 202–204 ℃, $[\alpha]_D^{25}$ = 79.9 (c 0.79, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IE, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 63.60 min, t_{minor} = 37.77 min). **^{1}H NMR (600 MHz, *d*-DMSO)**: δ = 10.76 (s, 1H), 7.85–7.83 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.22 (s, 1H), 7.15 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.72 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.67 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 4.15 (dd, J_1 = 15.0 Hz, J_2 = 3.6 Hz, 1H), 3.95 (dd, J_1 = 15.0 Hz, J_2 = 12.0 Hz, 1H), 3.72 (s,3H), 3.37-3.36 (m, 1H), 3.11 (s, 3H), 2.44 (s, 3H), 2.33 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$)**: δ = 178.59, 170.11, 145.57, 142.52, 136.69, 134.65, 133.25, 131.86, 131.50, 130.98 (2C), 129.21, 128.57 (2C), 124.88, 122.01, 121.95, 121.44, 117.60, 110.64, 109.76, 102.48, 51.84, 49.75, 47.10, 44.74, 32.41, 21.94, 21.73 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_5S$ $[M+Na]^+$: 552.1569; found 552.1568.

methyl (3S,3'R)-8',9'-dimethyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4t)：

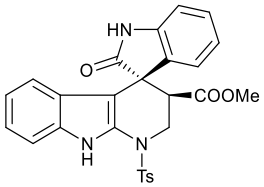


4t

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2j** (37.7 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3t**. To a solution of **3t** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4t**: 39.4 mg, as a white solid, 74% yield, 92:8 er, >20:1 dr; m.p. 235–237 ℃, $[\alpha]_D^{25}$ = 135.8 (c 0.68, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 14.33 min, t_{minor} = 20.56 min). **^{1}H NMR (700 MHz, DMSO-*d*$_6$)**: δ = 10.82 (s, 1H), 7.87 (d, *J* = 8.4Hz, 2H), 7.50 (d, *J* = 8.4Hz, 2H), 7.41 (d, *J* = 8.4Hz, 1H), 7.11–7.09 (m, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.83

(t, *J*= 7.7 Hz, 1H), 6.75 (d, *J* = 7.7 Hz 1H), 6.64–6.62 (m, 2H), 4.13 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.93 (dd, J_1 = 15.4 Hz, J_2 = 12.6 Hz, 1H), 3.74 (s, 3H), 3.38 (dd, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 1H), 3.09 (s, 3H), 2.43 (s, 3H), 2.29 (s, 3H)) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.60, 169.54, 145.08, 140.58, 135.76, 134.13, 133.32, 130.49 (2C), 130.47, 129.86, 128.05 (2C), 123.12, 121.92, 121.66, 121.43, 119.88, 118.57, 117.38, 110.21, 102.07, 51.21, 49.47, 46.50, 44.53, 31.92, 21.19, 16.52. ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_5S$ $[M+Na]^+$: 552.1569; found 552.1562.

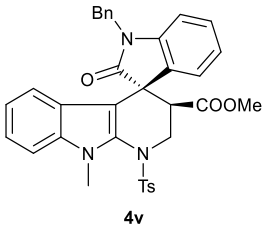
methyl (3*S*,3'*R*)-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4u):



4u

A mixture of **1a** (43.4 mg, 0.1 mmol) and **2k** (34.4 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3u**. To a solution of **3u** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4u**: 36.3 mg, as a white solid, 72% yield, 81:19 er, >20:1 dr; m.p. 279–280 ℃, $[\alpha]_D^{25}$ = 79.6 (c 0.54, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 15.16 min, t_{minor} = 16.88 min). **^{1}H NMR (600 MHz, DMSO-*d*$_6$)**: δ = 11.14 (s, 1H), 10.74 (s, 1H), 7.74–7.71 (m, 2H), 7.44–7.42 (m, 3H), 7.16 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.99–6.96 (m, 1H), 6.93–6.90 (m, 2H), 6.78-6.73 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.43 (dd, J_1 = 14.4 Hz, J_2 = 3.6 Hz, 1H), 3.98 (dd, J_1 = 14.4 Hz, J_2 = 12.6 Hz, 1H), 3.17 (s, 3H), 2.90 (dd, J_1 = 13.2 Hz, J_2 = 3.6 Hz, 1H), 2.38 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$)**: δ = 177.81, 169.08, 144.76, 141.96, 133.86, 133.68, 131.82, 130.47, 130.38 (2C), 128.64, 127.19 (2C), 124.40, 123.44, 121.48, 121.06, 119.42, 116.57, 111.97, 109.34, 98.23, 59.77, 51.43, 48.87, 44.66, 21.13 ppm. HRMS (ESI-TOF) Calcd. For $C_{27}H_{23}N_3O_5S$ $[M+Na]^+$: 524.1256; found 524.1253.

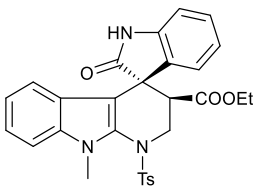
methyl (3S,3'R)-1-benzyl-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4v):



4v

A mixture of **1l** (42.4 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 6 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **4v**: 55.1 mg, as a white solid, 91% yield, 94:6 er, >20:1 dr; m.p. 237–239 ℃, $[\alpha]_D^{25}$ = 107.4 (c 1.03, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IE, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 23.57 min, t_{minor} = 65.54 min). **^{1}H NMR (600 MHz, DMSO-*d*$_6$)**: δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.43–7.41 (m, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.31–7.25 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.08–7.05 (m, 2H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.77–6.72 (m, 2H), 6.69–6.66 (m, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 4.91 (dd, J_1 = 18.6 Hz, J_2 = 15.0 Hz, 2H), 4.39 (dd, J_1 = 15.0 Hz, J_2 = 3.6 Hz, 1H), 3.84–3.79 (m, 4H), 2.97 (dd, J_1 = 12.6 Hz, J_2 = 3.6 Hz, 1H), 2.88 (s, 3H), 2.42 (s, 3H) ppm; **^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$)**: δ = 177.22, 170.03, 142.88, 136.76, 136.15, 134.47, 134.14, 130.81, 130.53 (2C), 128.78 (2C), 128.68 (2C), 128.65 (2C), 127.99, 124.15, 123.54, 122.86, 122.36, 120.25, 118.22, 110.04, 108.62, 101.76, 51.48, 49.43, 47.31, 44.86, 44.20, 32.90, 21.90. ppm. HRMS (ESI-TOF) Calcd. For $C_{35}H_{31}N_3O_5S$ $[M+Na]^+$: 628.1882; found 628.1880.

ethyl (3S,3'R)-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4w):

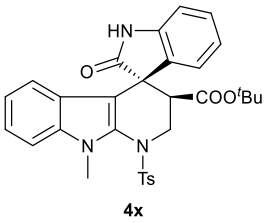


4w

A mixture of **1m** (44.8 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3w**. To a solution of **3w** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4w**: 46.5 mg, as a white solid, 88% yield, 94:6 er, >20:1 dr; m.p. 232–234 ℃, $[\alpha]_D^{25}$ = 91.7 (c 0.87, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 42.94 min, t_{minor} = 17.69 min). **^{1}H NMR (700 MHz, *d*-DMSO)**: δ = 10.78 (s, 1H), 7.86 (d, *J* = 8.4Hz, 2H), 7.51–7.49 (m, 2H), 7.41 (d, *J* = 8.4Hz, 1H), 7.16 (td, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.11–7.09 (m, 1H), 6.94 (dd, J_1 = 14.7 Hz, J_2 = 7.7 Hz, 2H), 6.83 (t, *J* = 7.0 Hz, 1H); 6.72 (t, *J* = 7.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.12 (dd, J_1 = 14.7 Hz, J_2 = 3.5 Hz, 1H), 3.95 (dd, J_1 = 15.4 Hz, J_2 = 3.5 Hz,

1H), 3.74 (s, 3H), 3.64–3.56 (m, 2H), 3.35 (dd, J_1 = 10.5 Hz, J_2 = 11.2 Hz, 1H), 2.43 (s, 3H), 0.69–0.67 (m, 3H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.10, 169.11, 145.09, 142.31, 135.78, 134.14, 133.37, 130.87 (2C), 130.48, 128.72 (2C), 128.05, 124.43, 123.04, 121.92, 121.50, 119.87, 117.29, 110.25, 109.35, 102.06, 60.26, 54.92, 49.18, 46.63, 43.94, 31.95, 21.20, 13.11 ppm. HRMS (ESI-TOF) Calcd. For $C_{29}H_{27}N_3O_5S$ [M+Na]$^+$: 552.1569; found 552.1569.

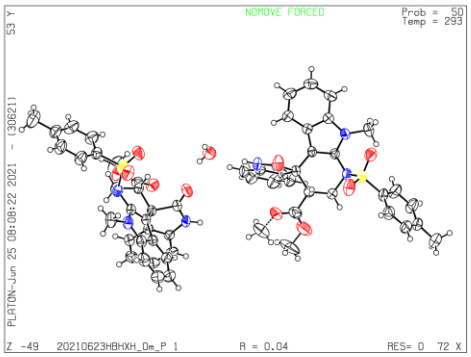
tert-butyl (3*S*,3'*R*)-9'-methyl-2-oxo-1'-tosyl-1',2',3',9'-tetrahydrospiro[indoline-3,4'-pyrido[2,3-b]indole]-3'-carboxylate (4x)



4x

A mixture of **1n** (47.6 mg, 0.1 mmol) and **2a** (36.1 mg, 0.12 mmol) was added **C4** (6.5 mg, 20 mol%) in toluene (1.0 mL) at room temperature for 8 hours. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 12/1) gave the protected product **3x**. To a solution of **3x** in toluene (1.0 mL) was added TFA (20.0 mg) at room temperature for 1 hour. After completion, purification by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) gave the deprotected product **4x**: 45.3 mg, as a white solid, 81% yield, 91:9 er, >20:1 dr; m.p. 235–237 ℃, $[\alpha]_D^{25}$ = 70.4 (c 0.67, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IA, 2-propanol/*n*-hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 71.05 min, t_{minor} = 18.37 min). **^{1}H NMR (600 MHz, DMSO-*d*$_6$)**: δ = 10.81 (s, 1H), 7.91–7.90 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4Hz, 1H), 7.19 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.12–7.09 (m, 1H), 6.99–6.97 (m, 2H), 6.86–6.83 (m, 1H), 6.75–6.70 (m, 2H), 4.06 (dd, J_1 = 14.4 Hz, J_2 = 3.6 Hz, 1H), 3.87 (dd, J_1 = 15.0 Hz, J_2 = 12.6 Hz, 1H), 3.74 (s, 3H), 3.27 (dd, J_1 = 12.6 Hz, J_2 = 3.0 Hz, 1H), 2.45 (s, 3H), 0.95 (s, 9H) ppm; **^{13}C{^{1}H} NMR (175 MHz, DMSO-*d*$_6$)**: δ = 178.20, 168.35, 145.11, 142.62, 135.69, 134.20, 133.33, 131.25, 130.51 (2C), 128.65, 128.02 (2C), 124.39, 123.00, 121.86, 121.53, 119.83, 117.32, 110.18, 109.35, 102.20, 81.11, 49.09, 46.74, 44.41, 31.80, 26.77, 21.18 ppm. HRMS (ESI-TOF) Calcd. For $C_{31}H_{31}N_3O_5S$ [M+Na]$^+$: 580.1882; found 580.1881.

3. X-ray crystal structure of 4a



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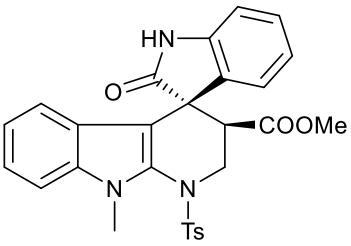
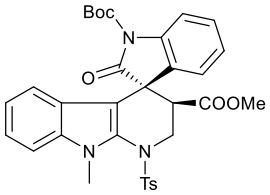


4a, CCDC 2100825

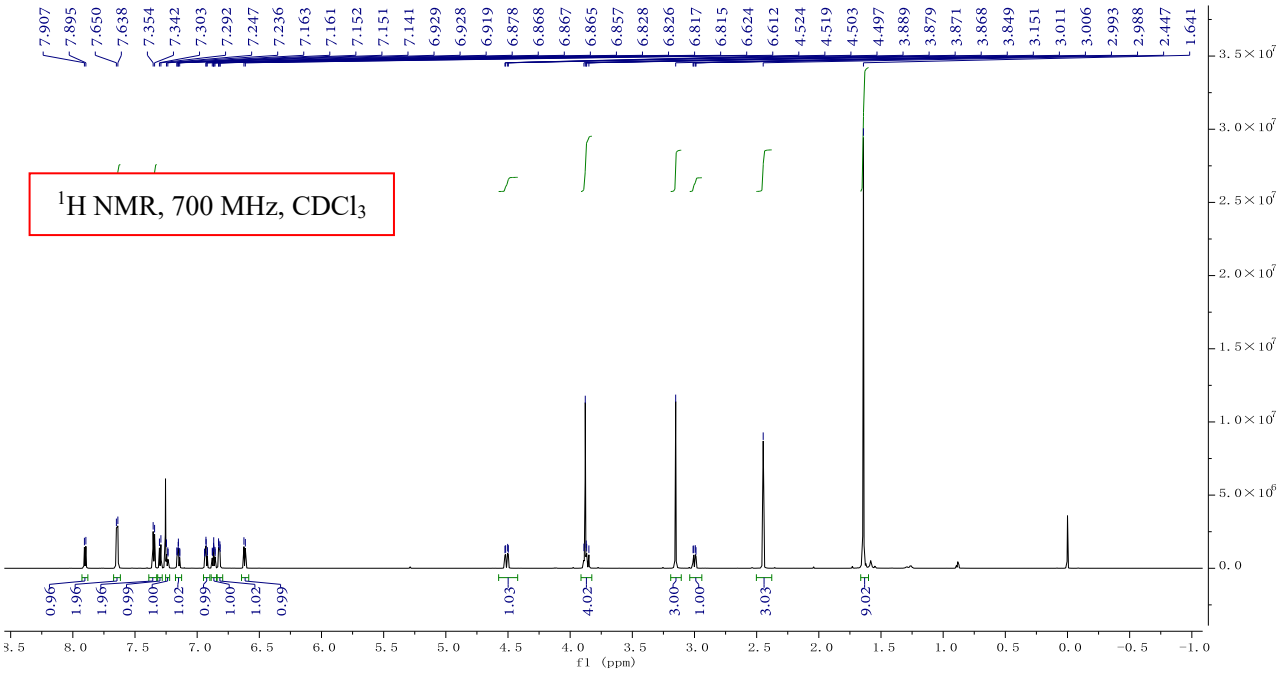
(dimer, connection with a H_2O molecule)

Theta range for data collection	3.10 to 68.53°
Index ranges	-9<=h<=9, -13<=k<=13, -16<=l<=17
Reflections collected	43996
Independent reflections	9179 [R(int) = 0.0432]
Coverage of independent reflections	99.6%
Absorption correction	Multi-Scan
Structure solution technique	direct methods
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2016/6 (Sheldrick, 2016)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	9179 / 3 / 705
Goodness-of-fit on F^2	1.076
Δ/σ_{max}	0.003
Final R indices	8600 data; I>2σ(I) R1 = 0.0356, wR2 = 0.0886
	all data R1 = 0.0382, wR2 = 0.0908
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0466P)^2+0.1655P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.027(6)
Largest diff. peak and hole	0.393 and -0.255 eÅ^{-3}
R.M.S. deviation from mean	0.041 eÅ^{-3}

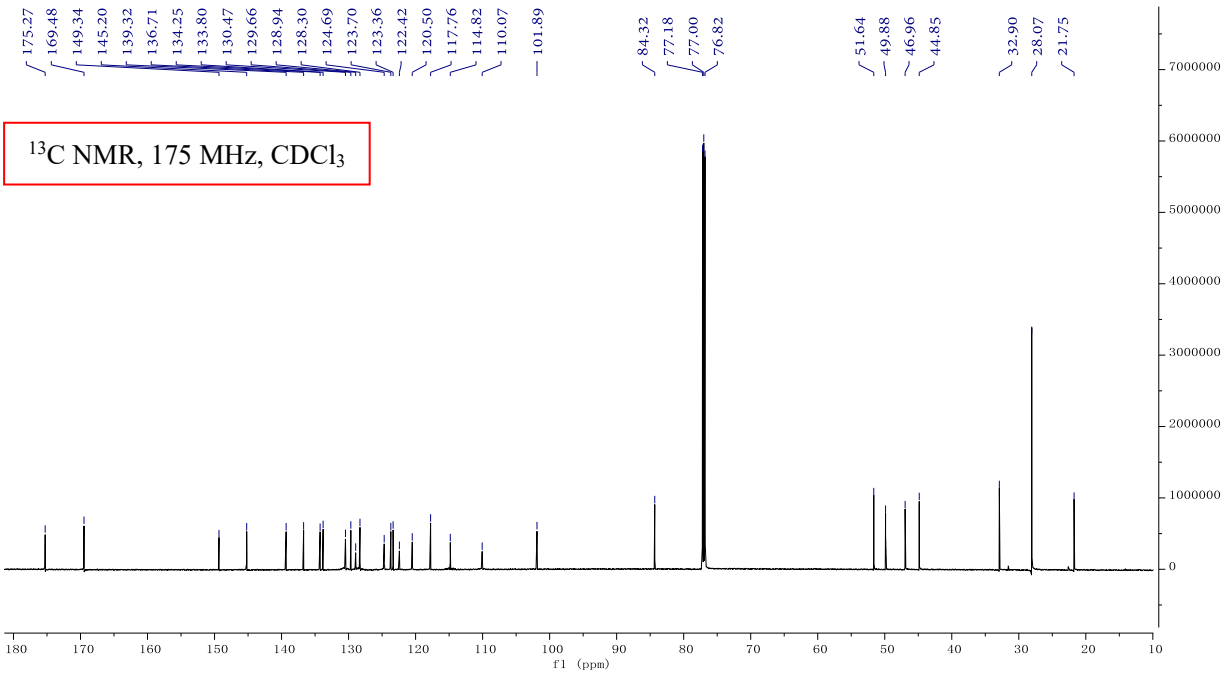
4. NMR and HPLC spectra



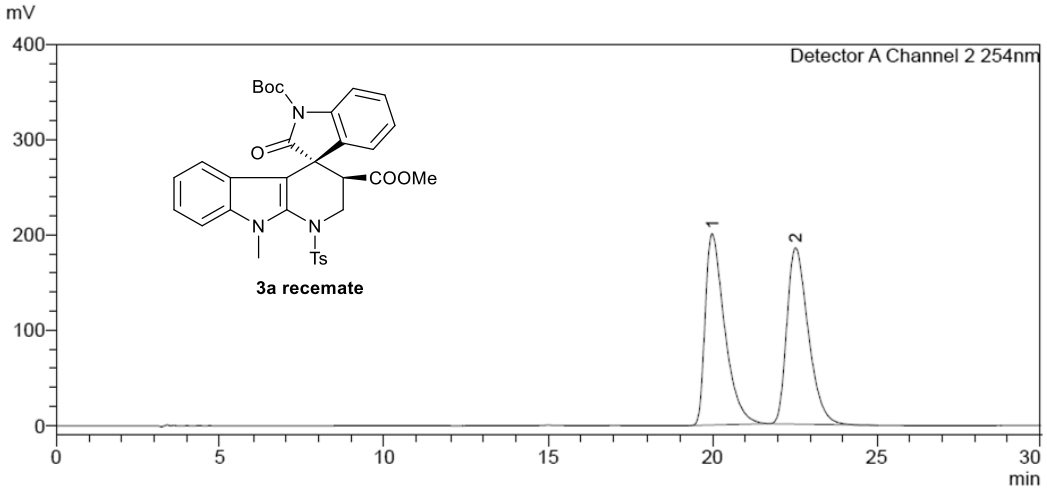
3a



^{1}H NMR, 700 MHz, $CDCl_3$



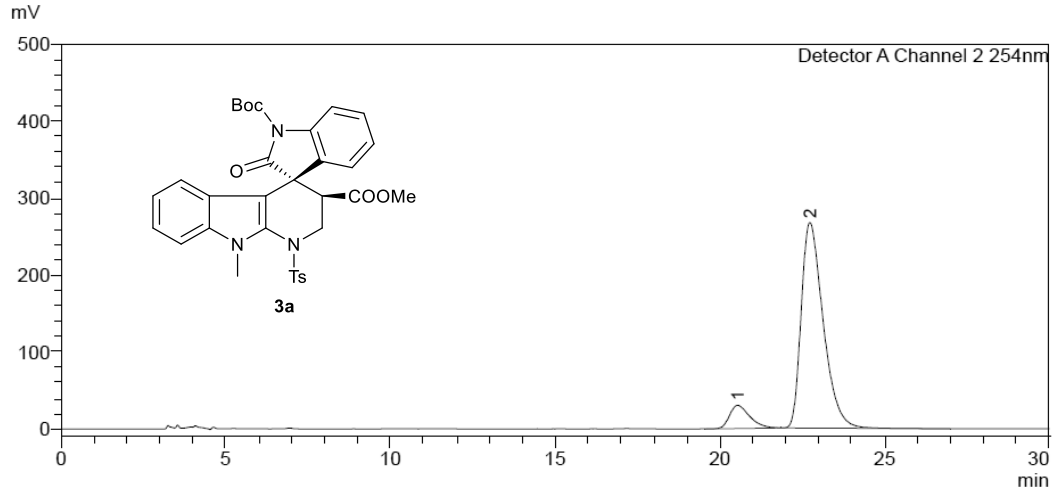
^{13}C NMR, 175 MHz, $CDCl_3$



Peak Analysis Report

Detector A Channel 2 254nm

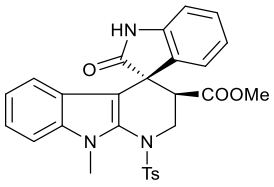
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	19.990	200604	8279841	49.647
2	22.532	185033	8397592	50.353
Total		385637	16677433	100.000



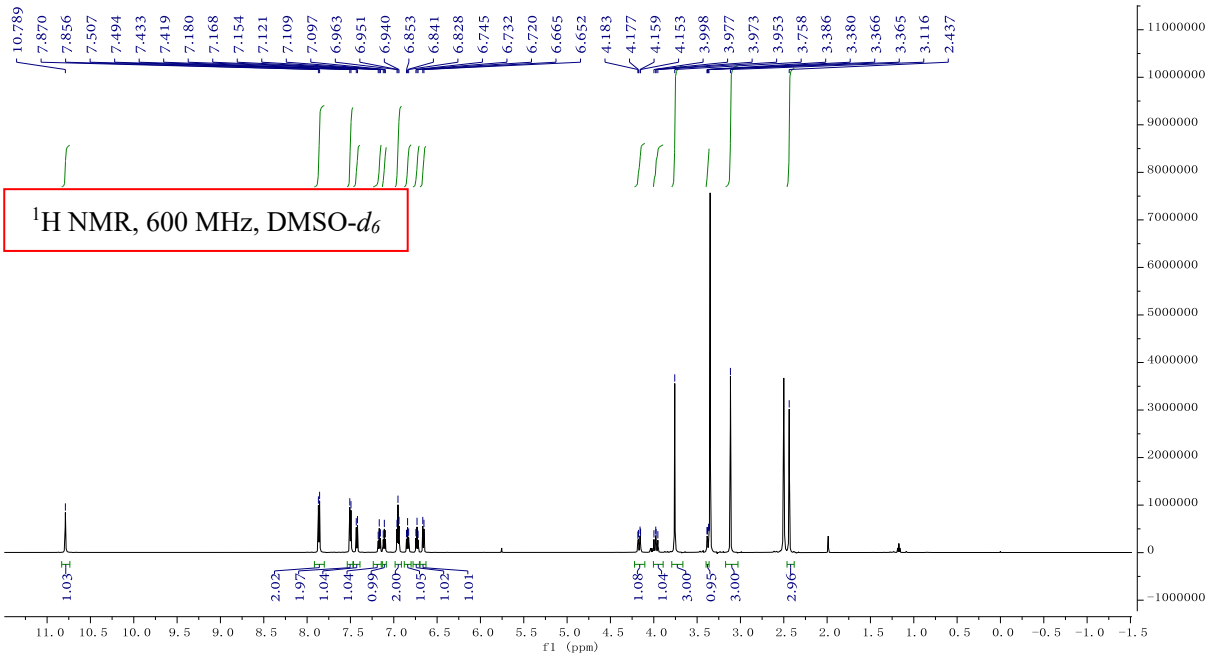
Peak Analysis Report

Detector A Channel 2 254nm

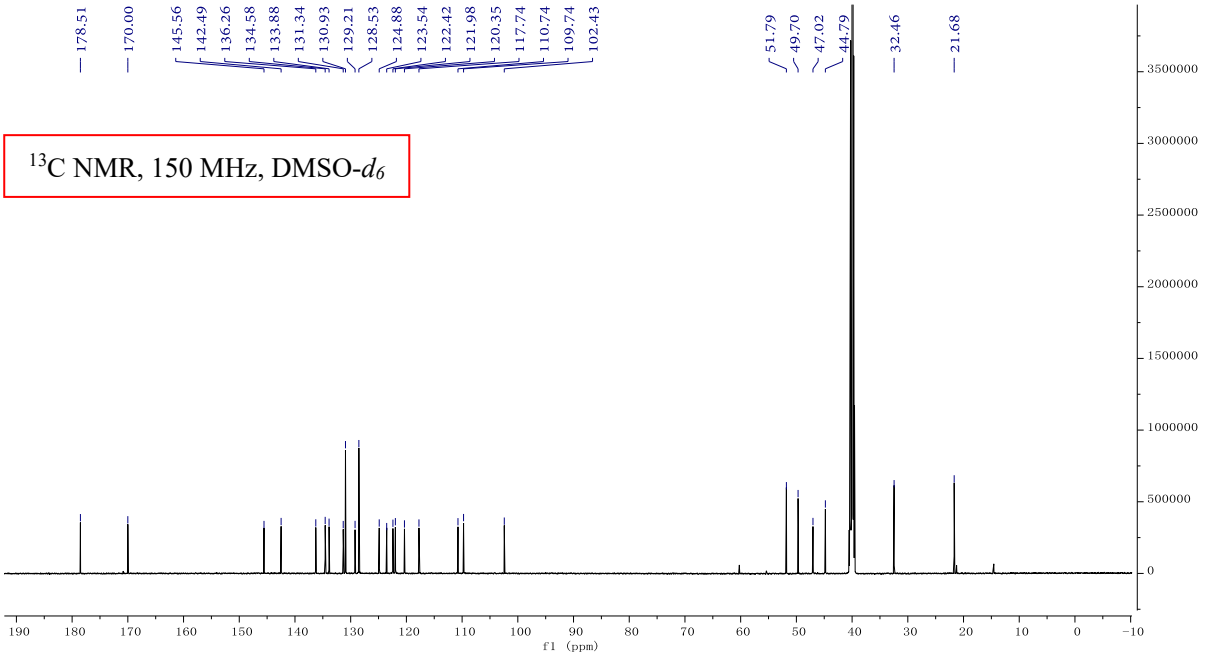
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	20.539	25869	902084	6.838
2	22.730	266584	12290576	93.162
Total		292453	13192660	100.00



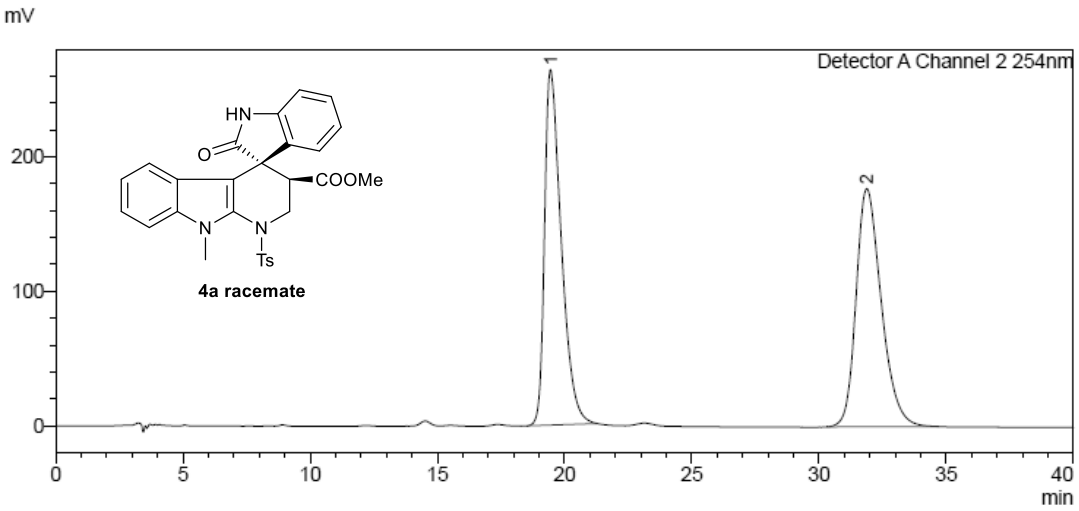
4a



^{1}H NMR, 600 MHz, DMSO-*d*$_6$



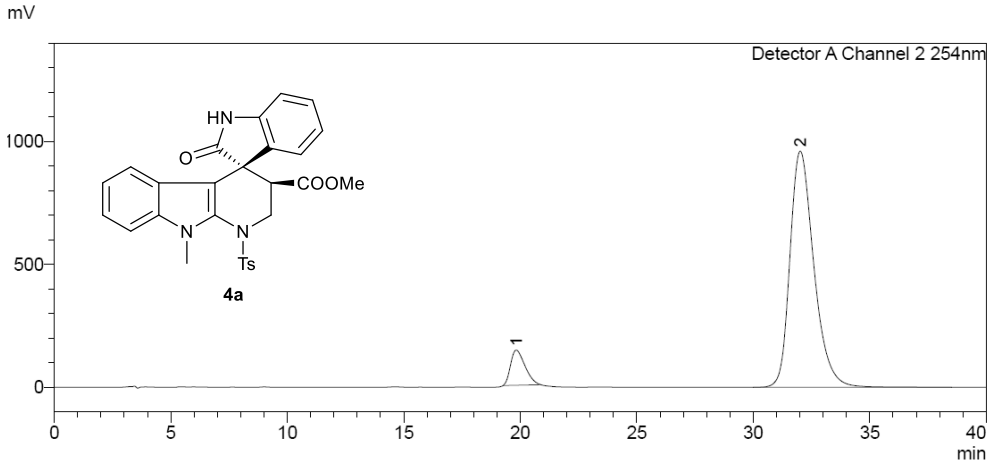
^{13}C NMR, 150 MHz, DMSO-*d*$_6$



Peak Analysis Report

Detector A Channel 2 254nm

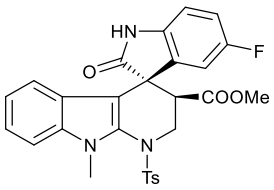
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	19.447	263886	12044923	49.732
2	31.877	176780	12174704	50.268
Total		440666	24219627	100.000



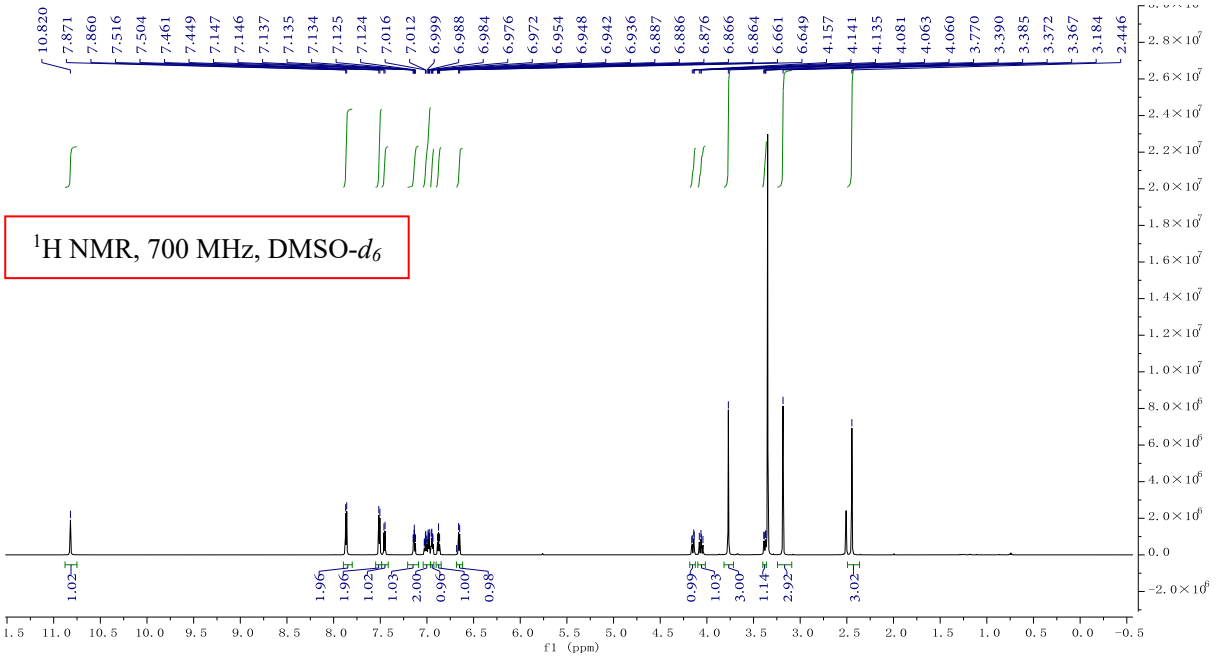
Peak Analysis Report

Detector A Channel 2 254nm

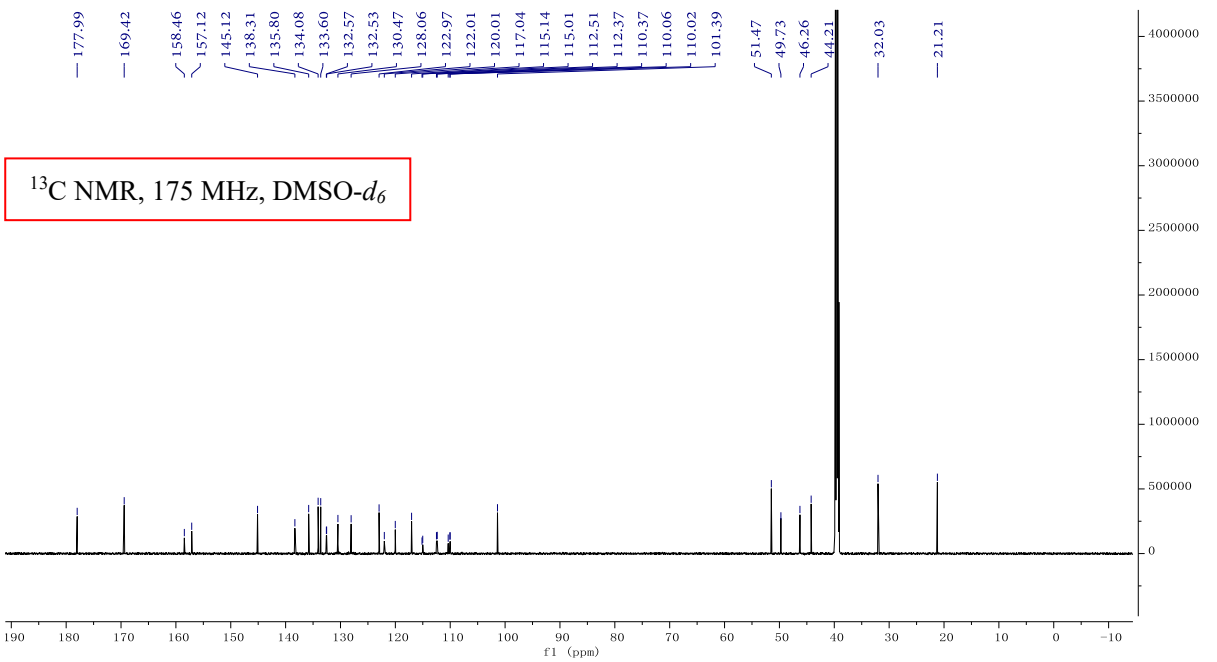
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	19.827	143208	6151922	8.220
2	32.017	961463	68693431	91.780
Total		1104671	74845353	100.000



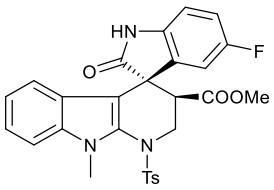
4b



^{1}H NMR, 700 MHz, DMSO-d_6

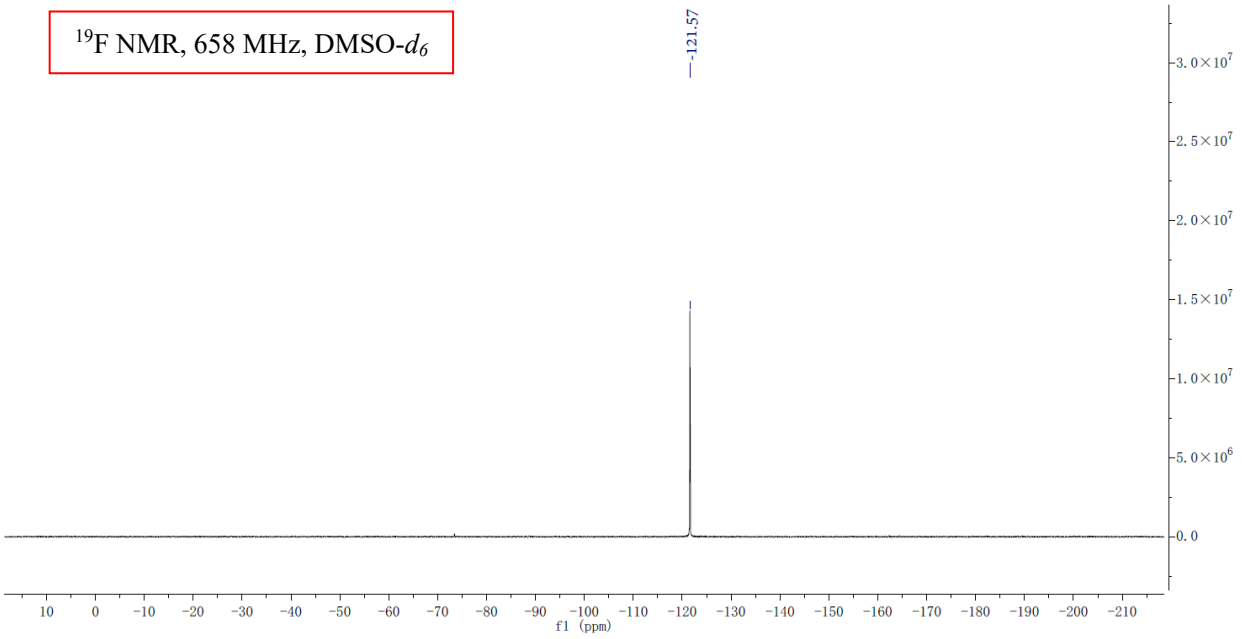


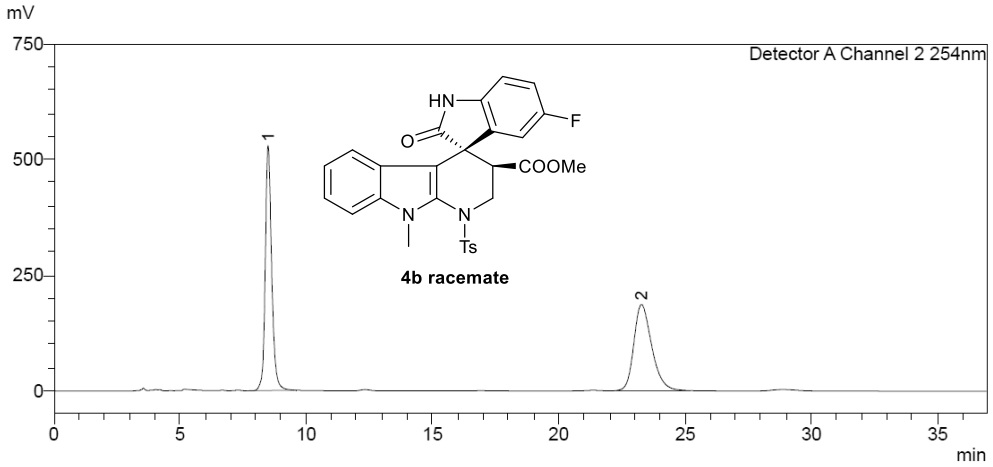
^{13}C NMR, 175 MHz, DMSO-d_6



4b

^{19}F NMR, 658 MHz, DMSO-d_6

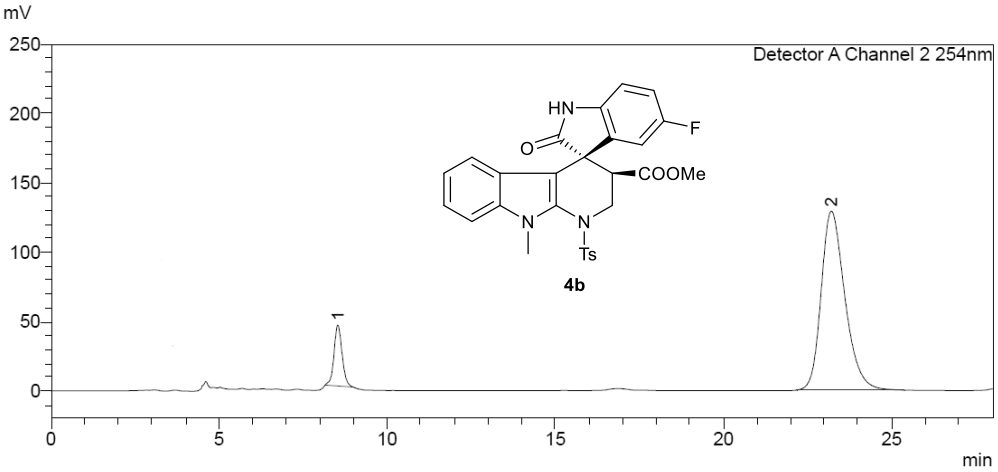




Peak Analysis Report

Detector A Channel 2 254nm

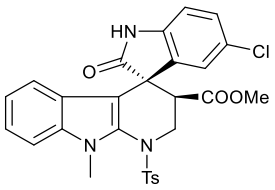
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	8.491	528749	9332048	50.583
2	23.274	185858	9117023	49.417
Total		714607	18449071	100.000



Peak Analysis Report

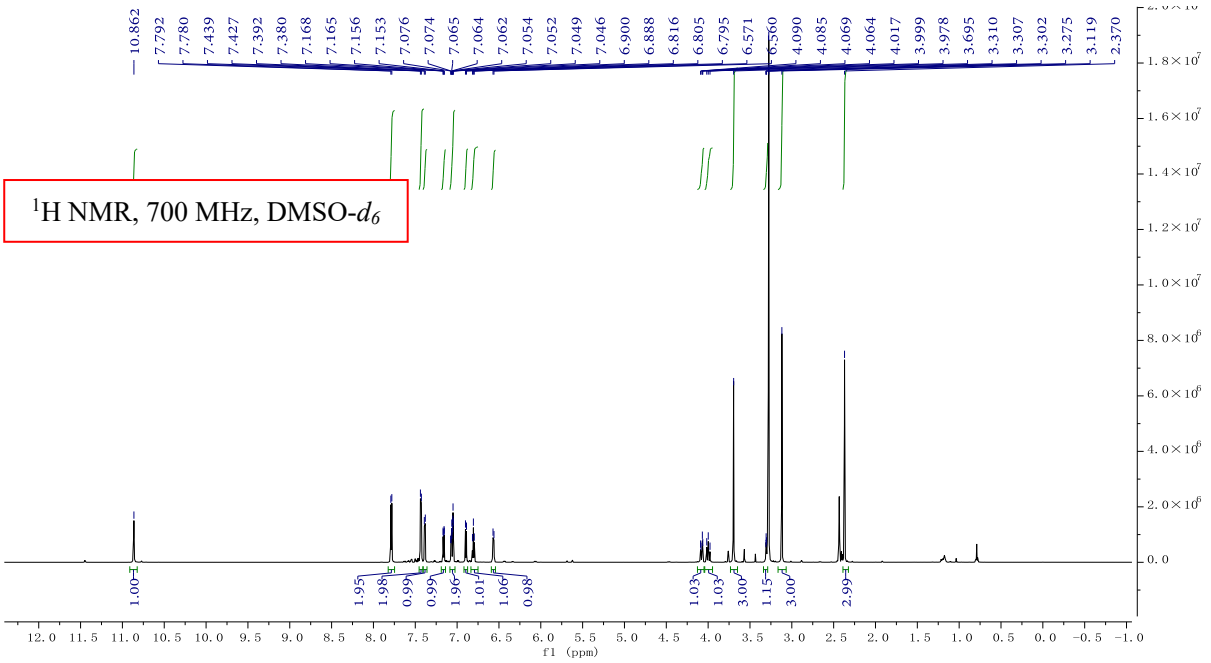
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	8.535	43921	738244	10.432
2	23.210	129101	6338574	89.568
Total		173022	7076819	100.000

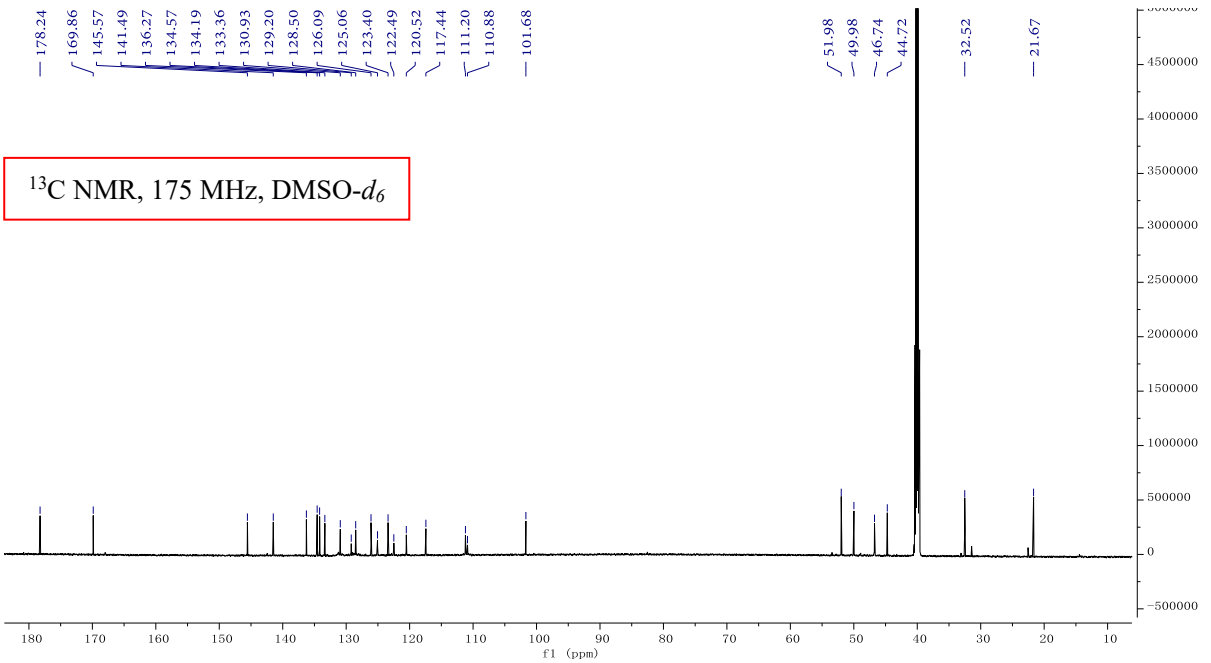


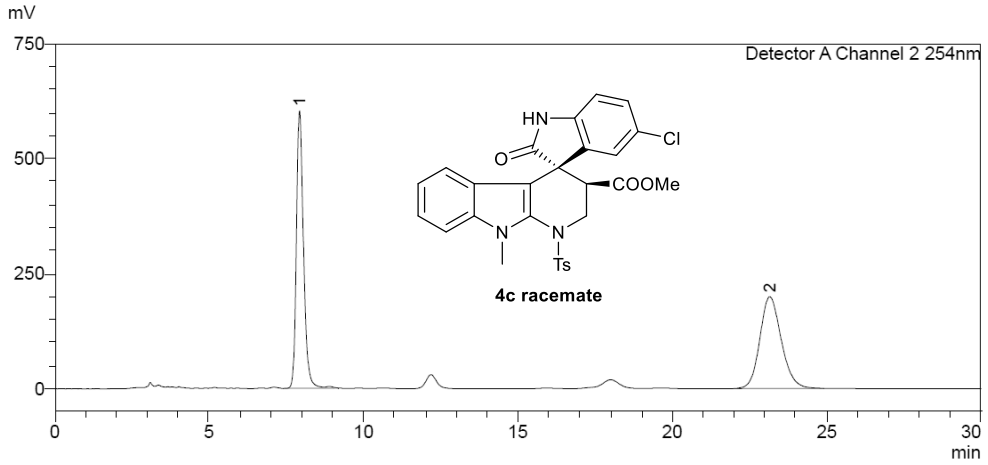
4c

^{1}H NMR, 700 MHz, DMSO-d_6



^{13}C NMR, 175 MHz, DMSO-d_6

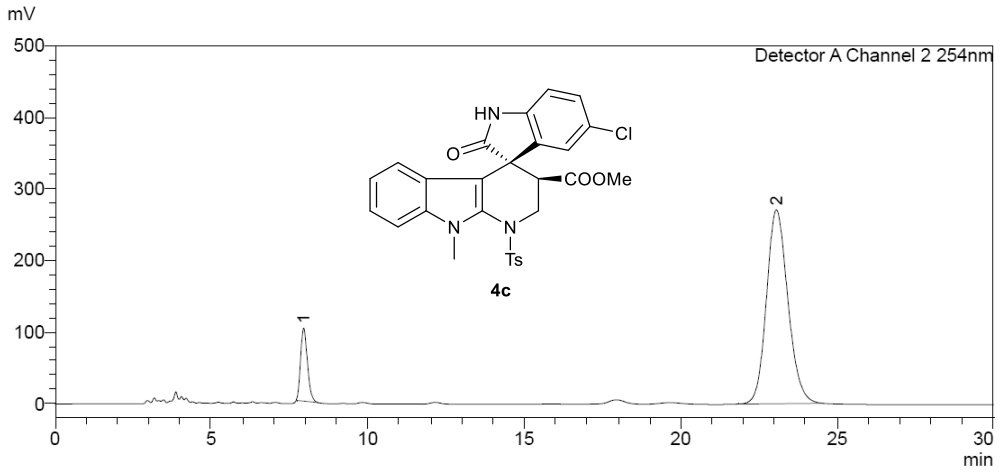




Peak Analysis Report

Detector A Channel 2 254nm

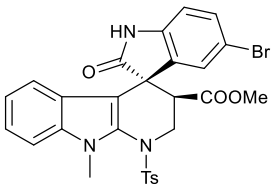
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	7.930	602765	9693426	50.269
2	23.154	199301	9589829	49.731
Total		802066	19283255	100.000



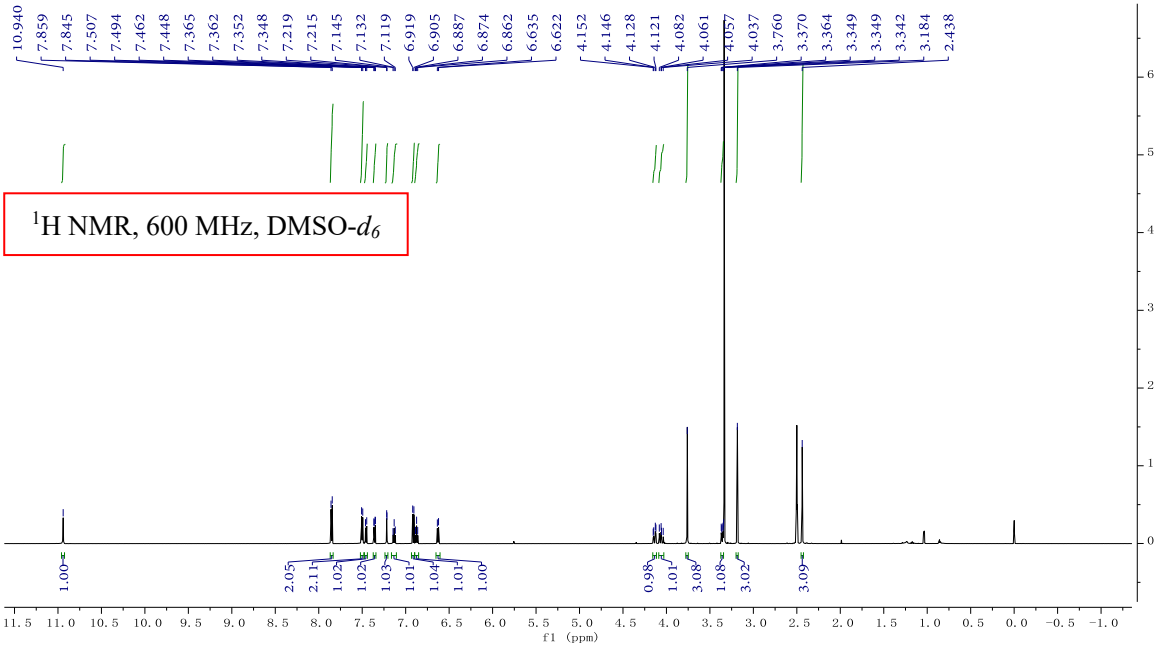
Peak Analysis Report

Detector A Channel 2 254nm

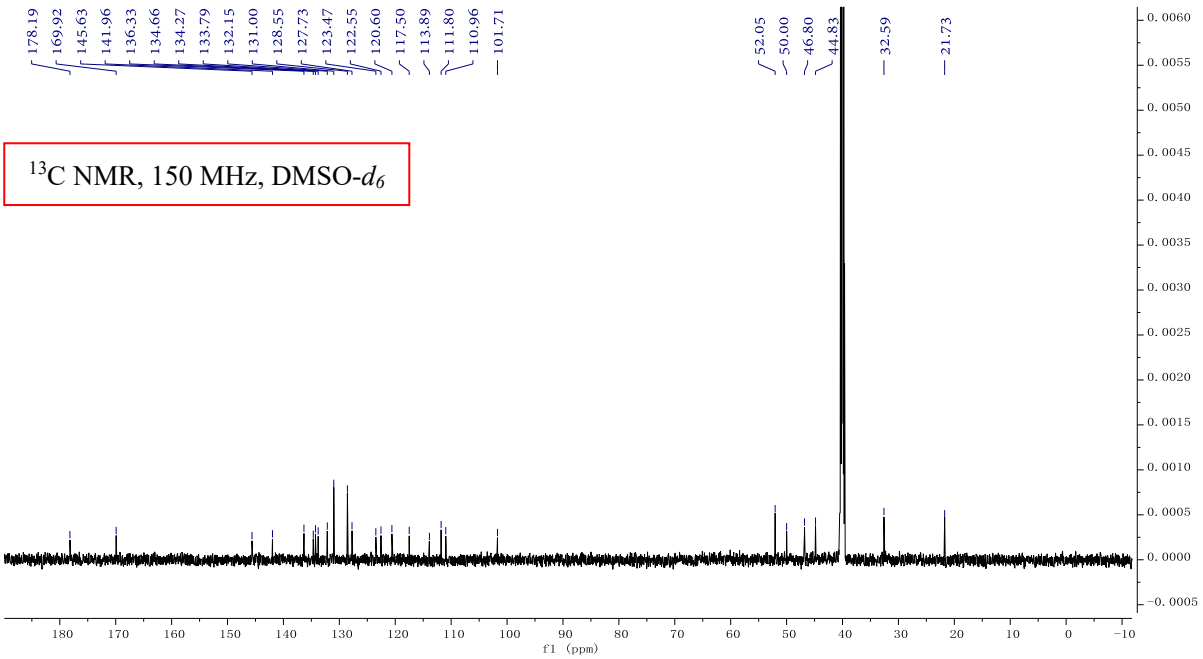
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	7.953	101668	1542757	10.695
2	23.059	270140	12882223	89.305
Total		371808	14424980	100.000



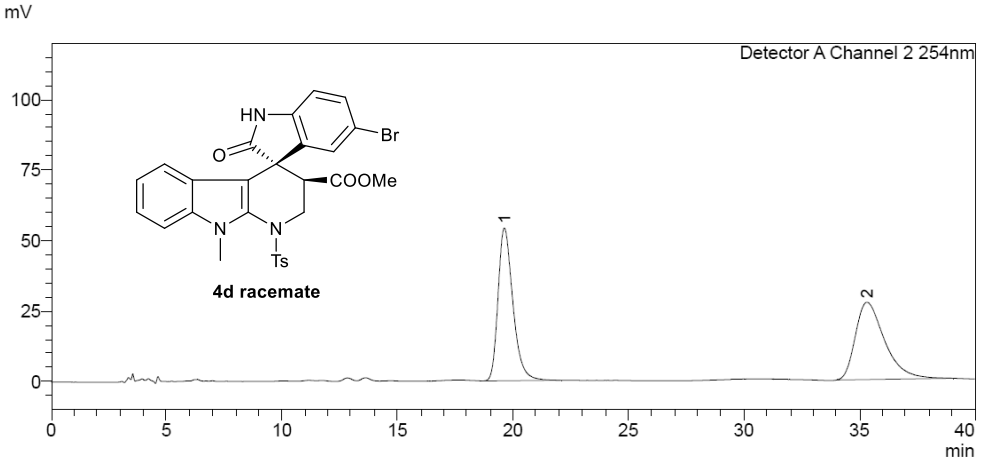
4d



^{1}H NMR, 600 MHz, DMSO-d_6



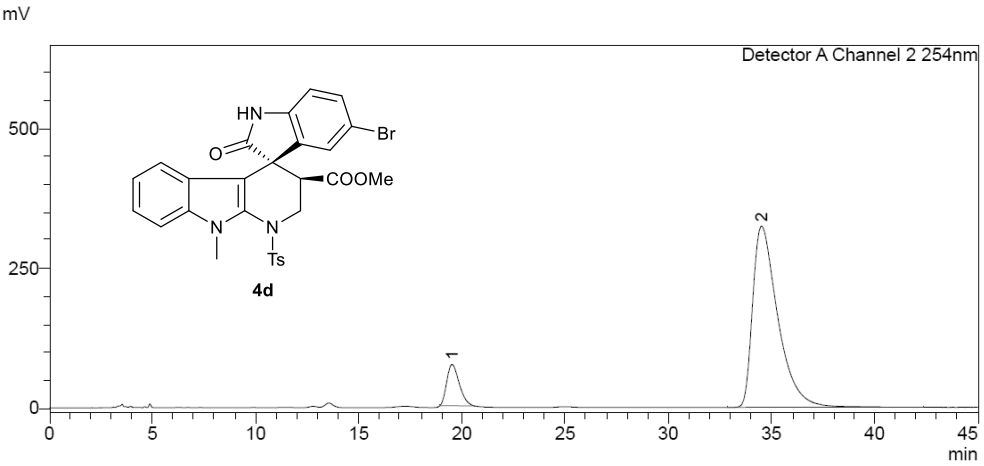
^{13}C NMR, 150 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

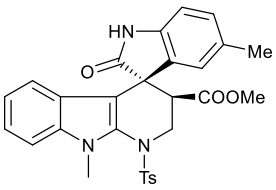
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	19.635	54060	2414371	50.049
2	35.342	27359	2409669	49.951
Total		81420	4824040	100.000



Peak Analysis Report

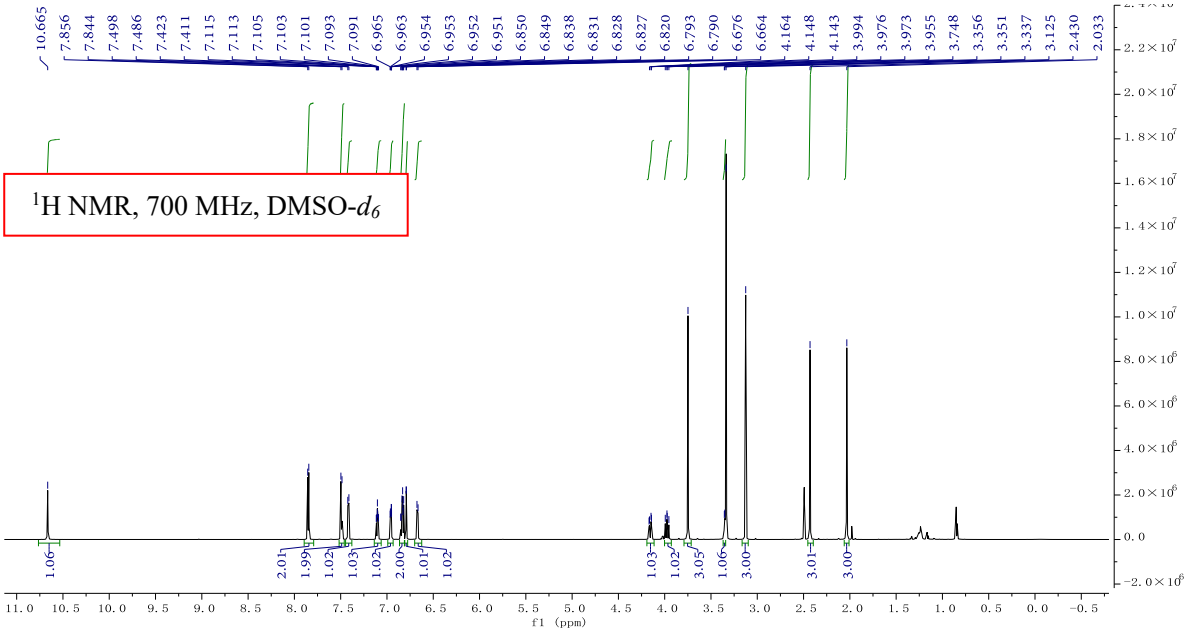
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	19.523	74005	3119485	10.185
2	34.523	324506	27509592	89.815
Total		398511	30629076	100.000

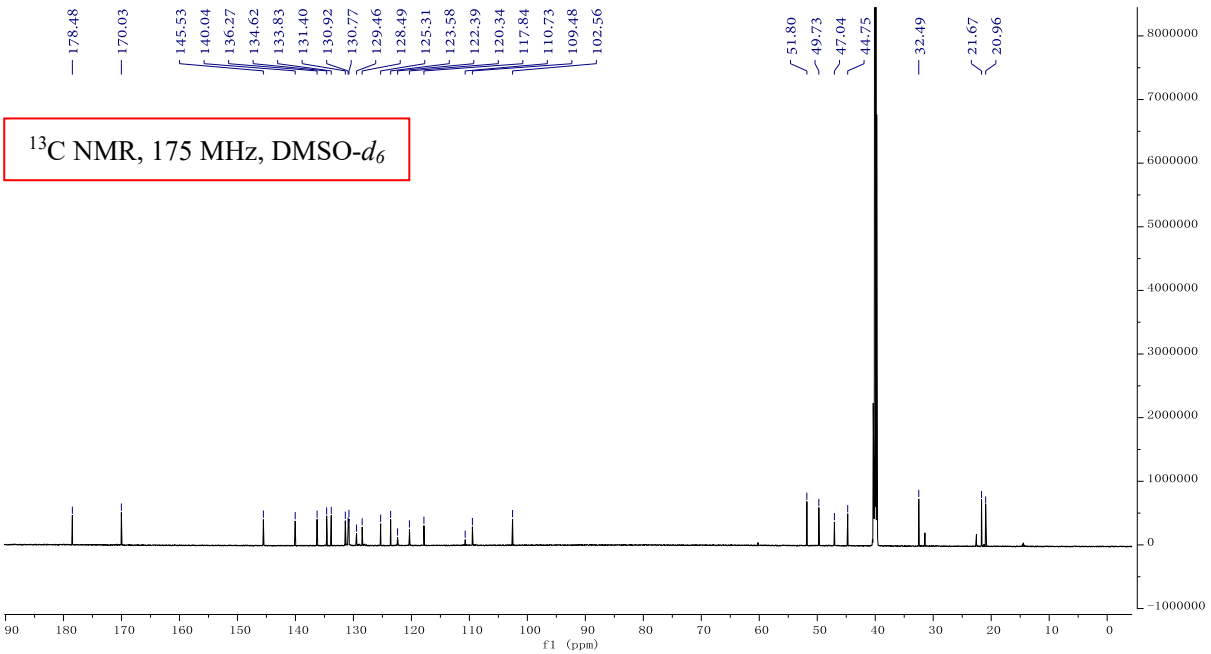


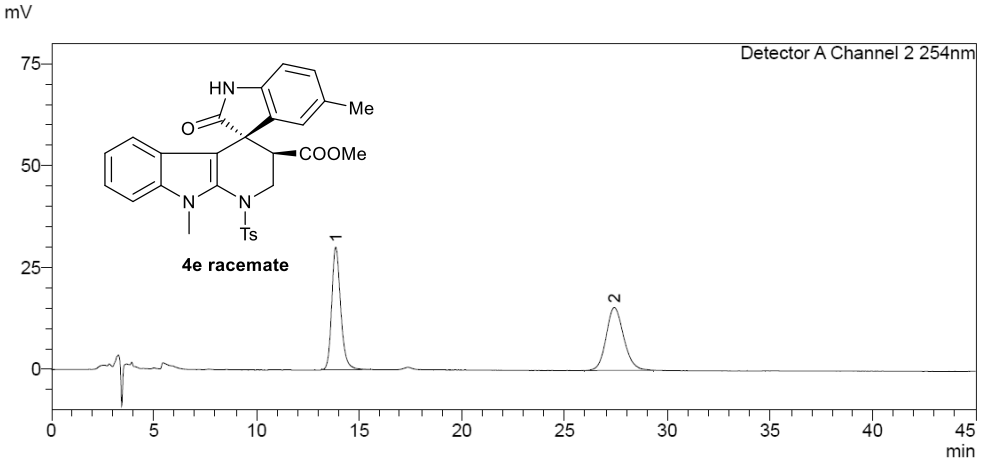
4e

^{1}H NMR, 700 MHz, DMSO-d_6



^{13}C NMR, 175 MHz, DMSO-d_6

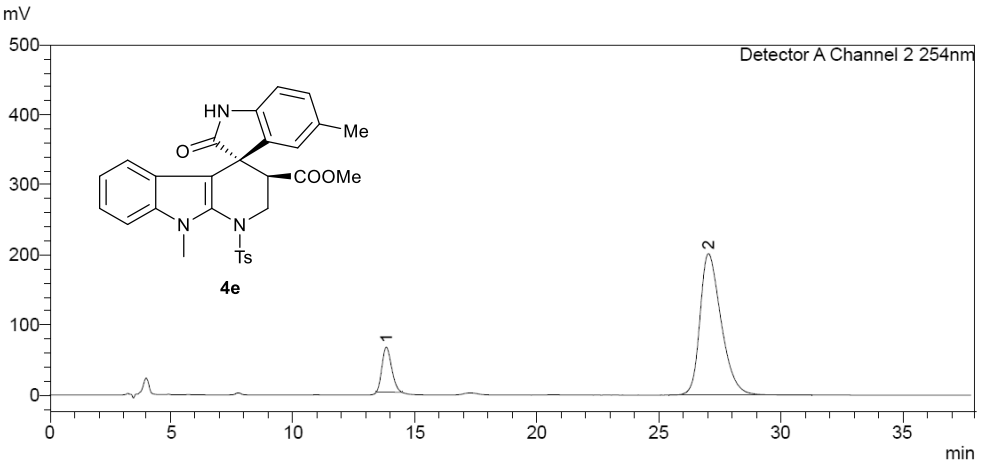




Peak Analysis Report

Detector A Channel 2 254nm

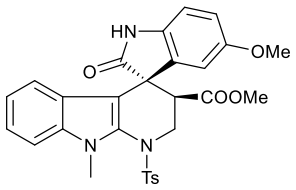
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.858	30052	912642	50.032
2	27.422	15398	911479	49.968
Total		45450	1824121	100.000



Peak Analysis Report

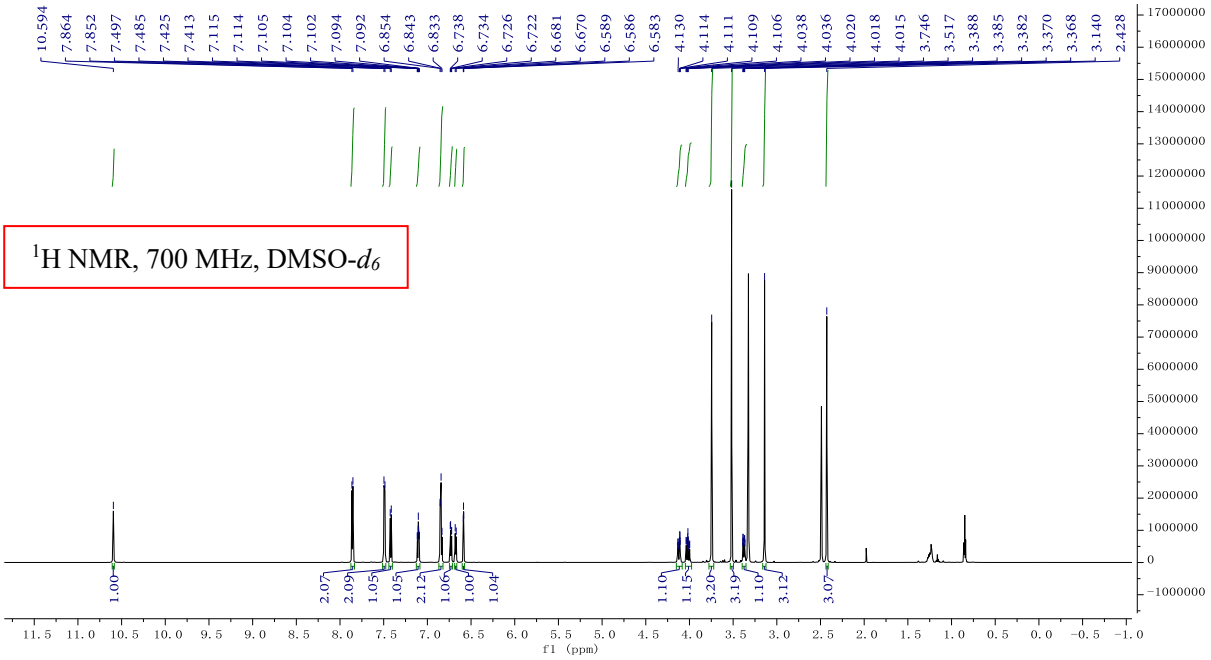
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.823	64052	1751166	12.559
2	27.047	201736	12192562	87.441
Total		265788	13943728	100.000

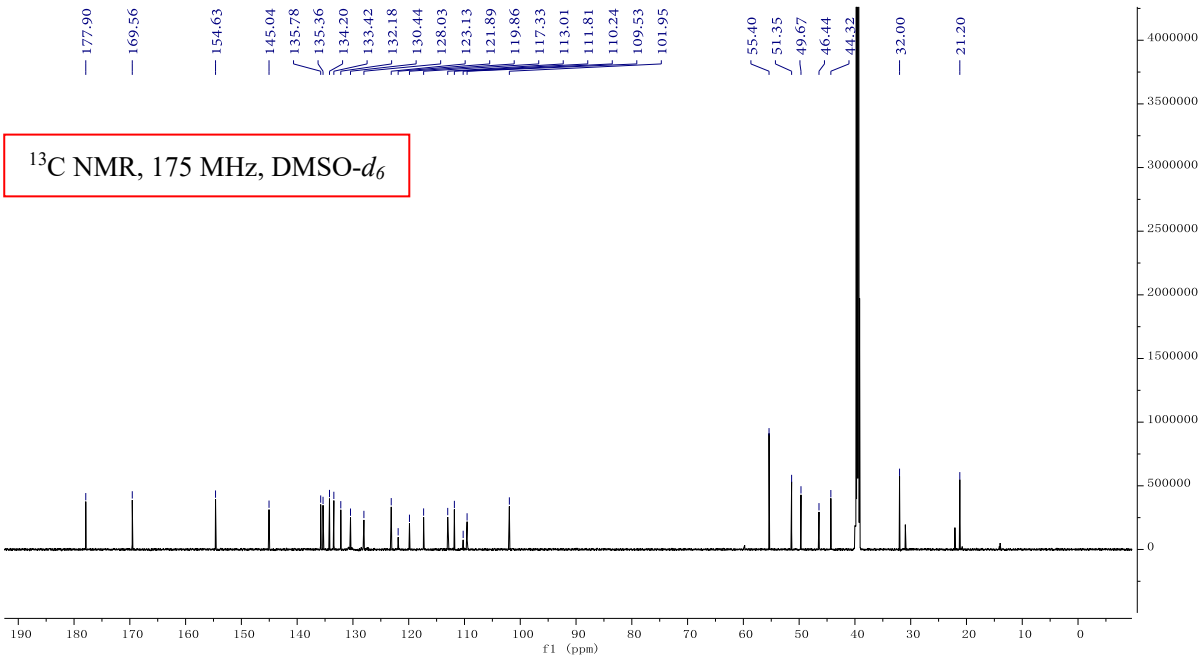


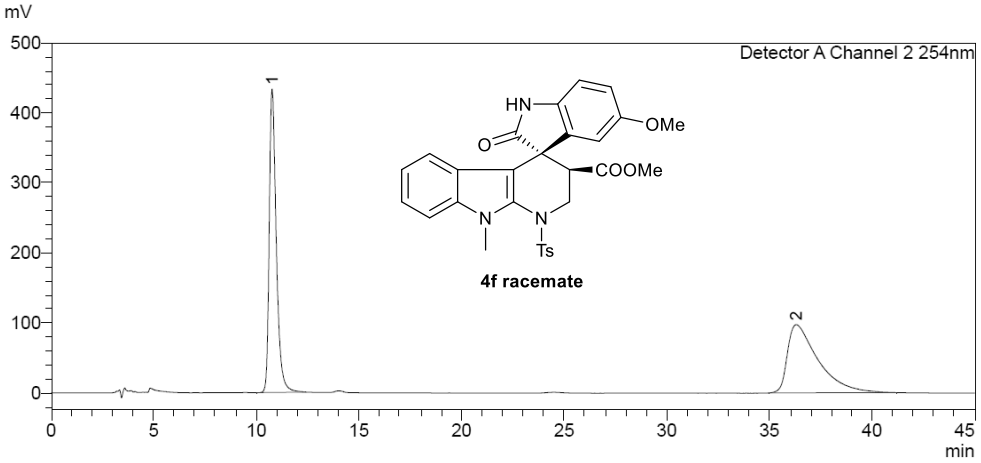
4f

^{1}H NMR, 700 MHz, DMSO-d_6



^{13}C NMR, 175 MHz, DMSO-d_6

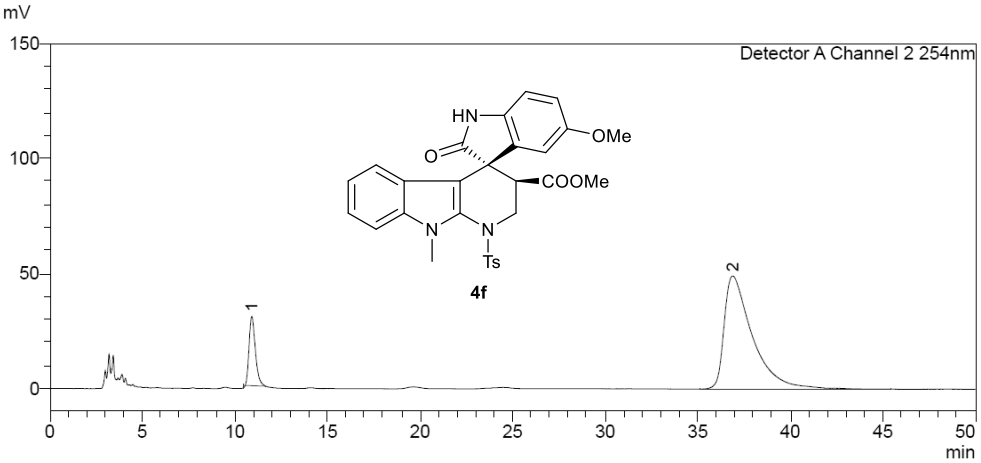




Peak Analysis Report

Detector A Channel 2 254nm

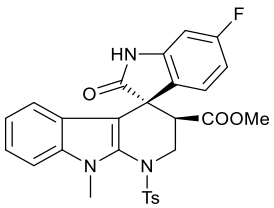
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.773	432753	10337899	50.635
2	36.308	97294	10078628	49.365
Total		530047	20416526	100.000



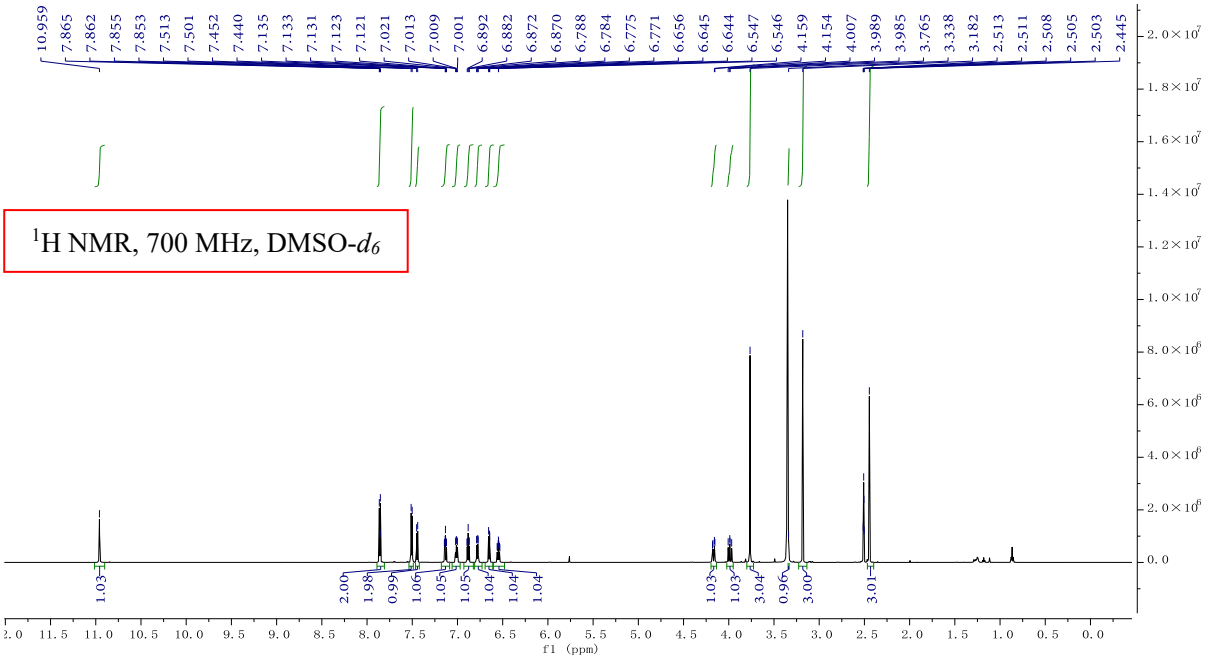
Peak Analysis Report

Detector A Channel 2 254nm

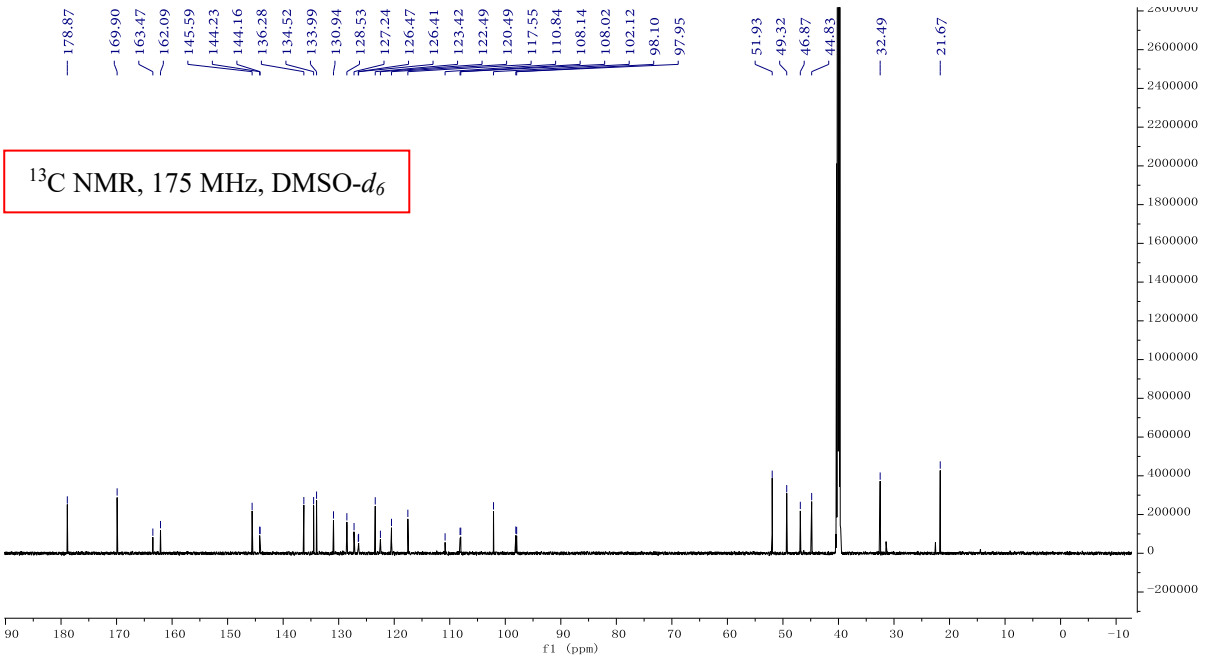
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.922	30117	710330	11.969
2	36.894	49172	5224595	88.031
Total		79289	5934925	100.000



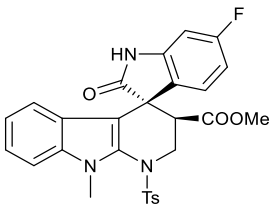
4g



^{1}H NMR, 700 MHz, DMSO-*d*$_6$

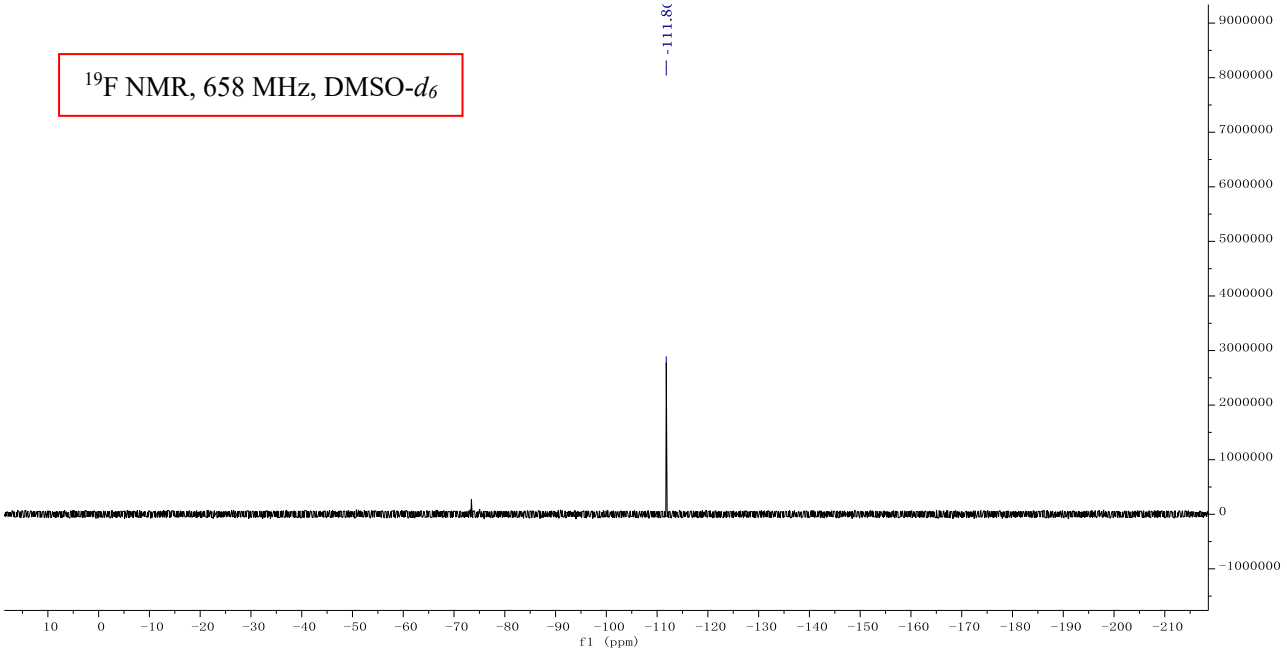


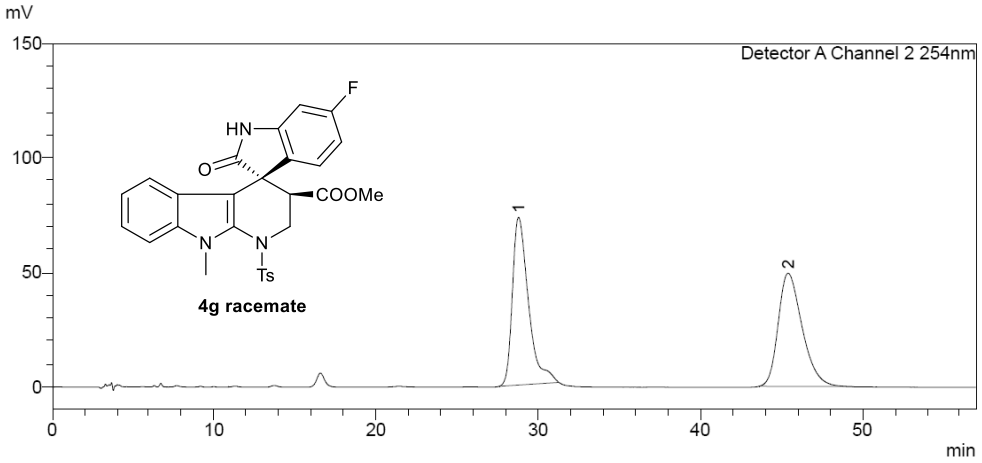
^{13}C NMR, 175 MHz, DMSO-*d*$_6$



4g

^{19}F NMR, 658 MHz, DMSO-*d*$_6$

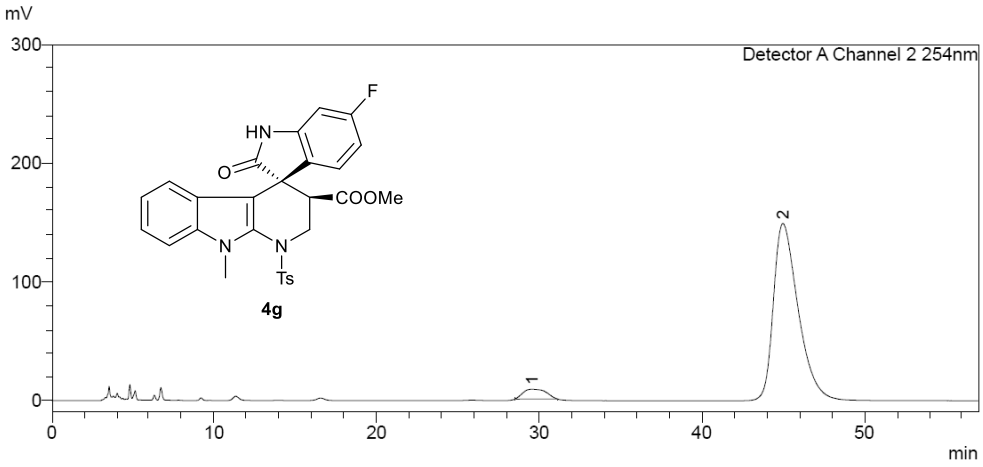




Peak Analysis Report

Detector A Channel 2 254nm

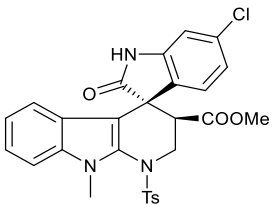
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	28.794	73223	5059270	49.918
2	45.428	49440	5075886	50.082
Total		122663	10135156	100.000



Peak Analysis Report

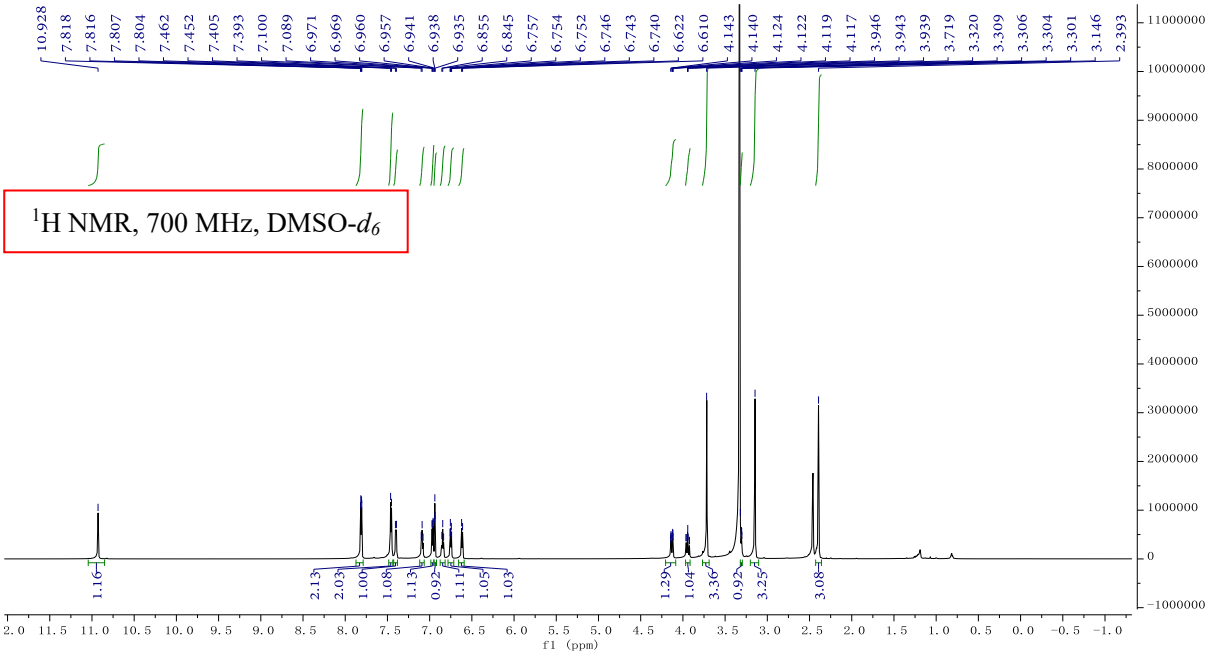
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	29.554	8333	816749	4.869
2	44.998	149327	15958786	95.131
Total		157660	16775534	100.000

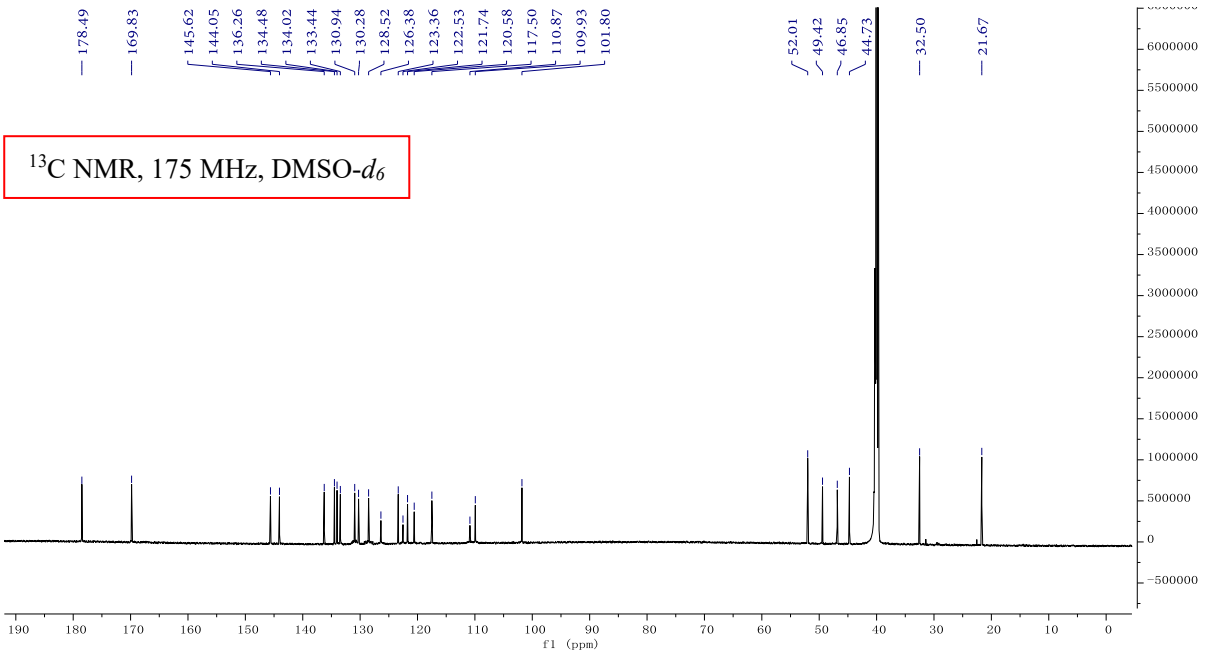


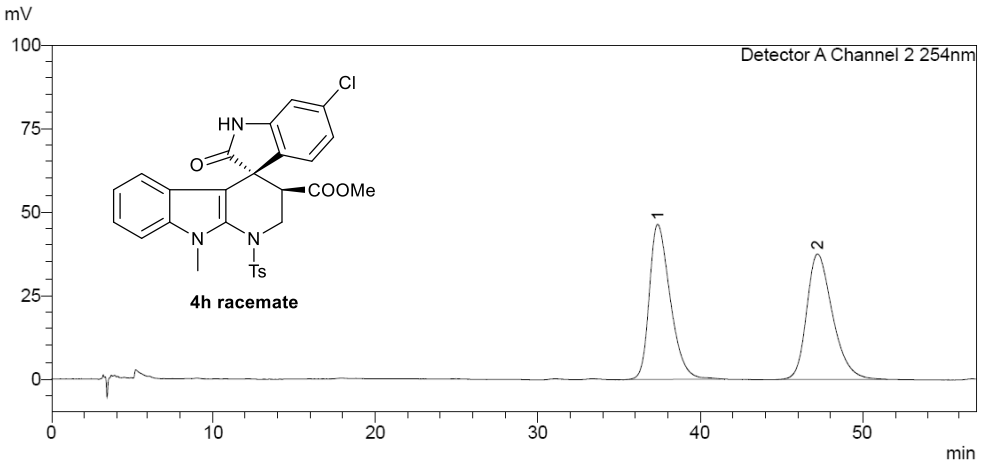
4h

^{1}H NMR, 700 MHz, DMSO-d_6



^{13}C NMR, 175 MHz, DMSO-d_6

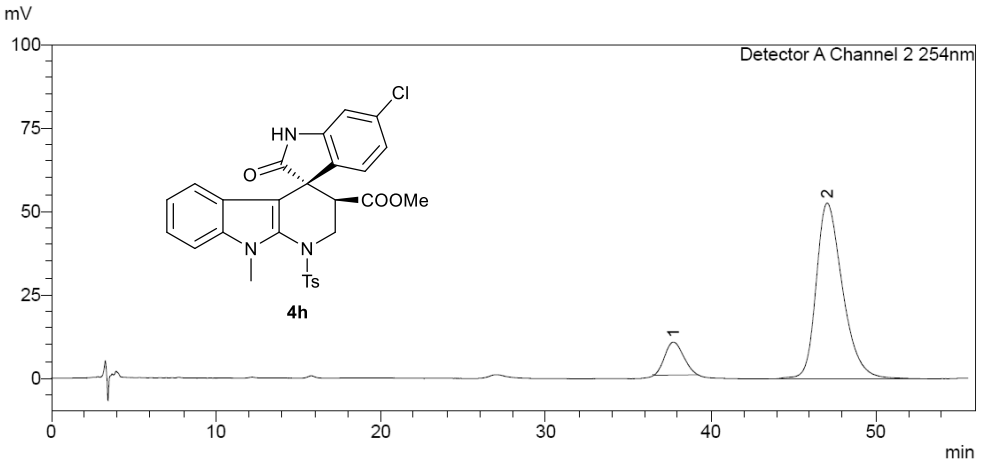




Peak Analysis Report

Detector A Channel 2 254nm

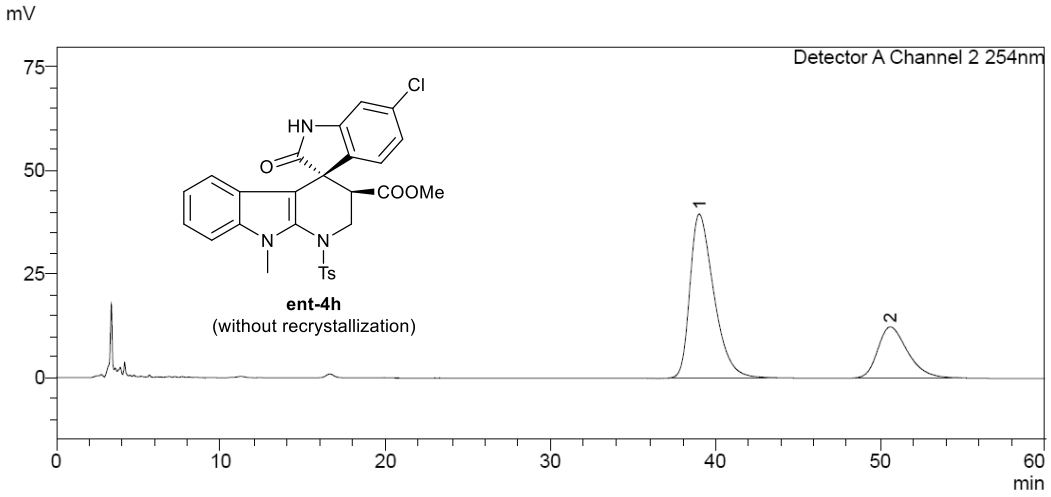
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	37.392	46431	4171393	50.106
2	47.252	37527	4153792	49.894
Total		83959	8325185	100.000



Peak Analysis Report

Detector A Channel 2 254nm

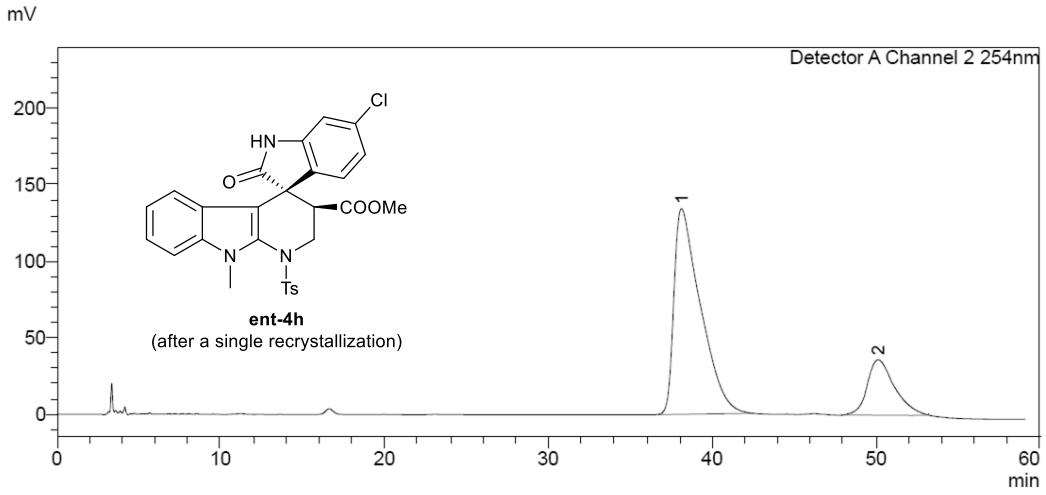
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	37.734	9921	778510	11.724
2	47.060	52648	5861764	88.276
Total		62568	6640274	100.000



Peak Analysis Report

Detector A Channel 2 254nm

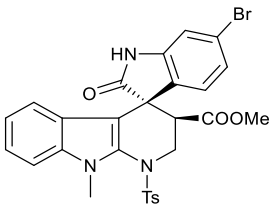
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	39.024	39623	3992585	71.961
2	50.600	12377	1555690	28.039
Total		52000	5548275	100.000



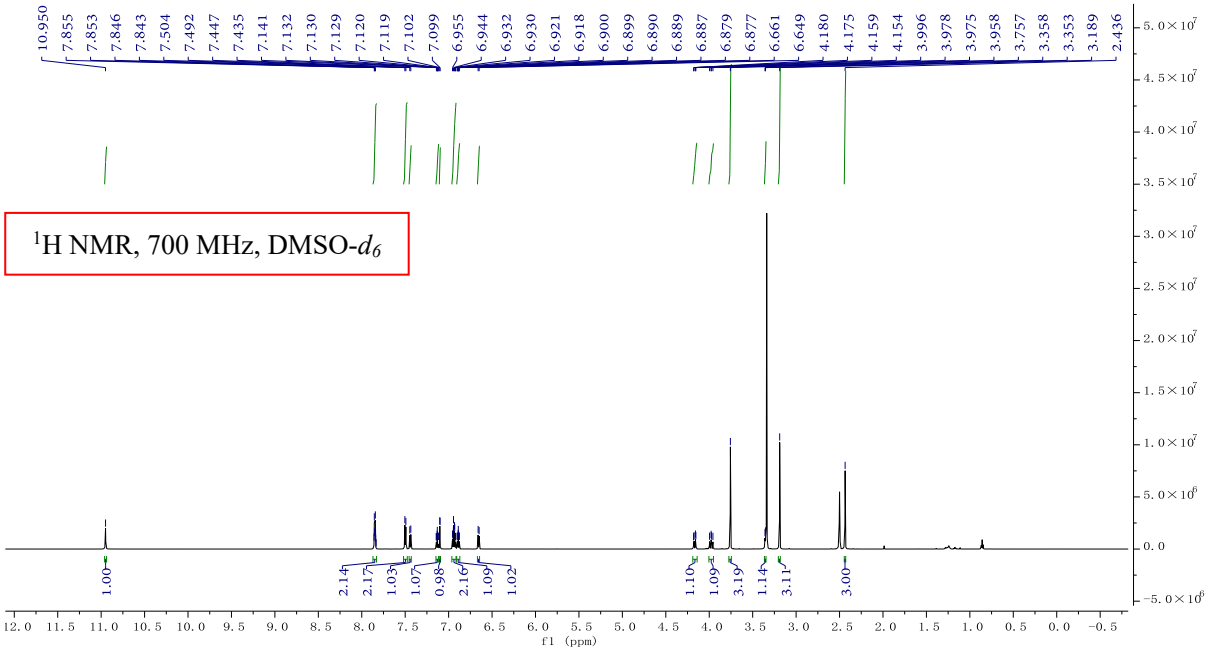
Peak Analysis Report

Detector A Channel 2 254nm

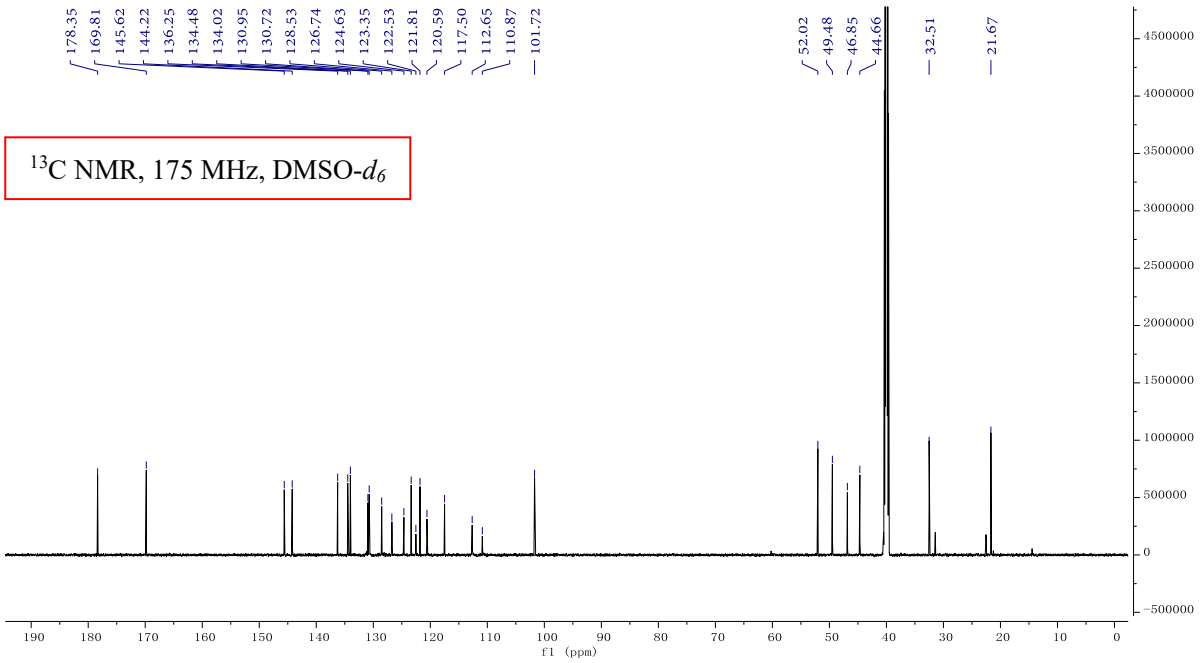
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	38.127	134271	15130694	81.194
2	50.299	34781	3504592	18.806
Total		169052	18635286	100.000



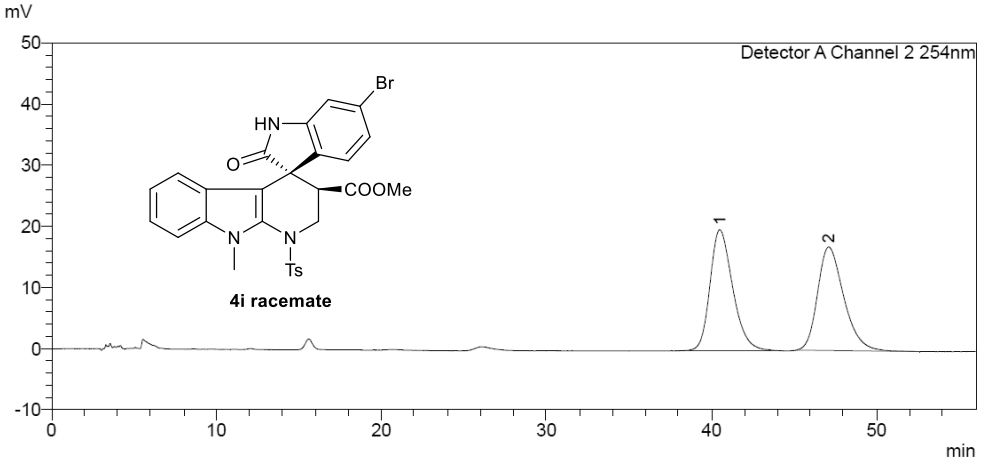
4i



^{1}H NMR, 700 MHz, DMSO-d_6



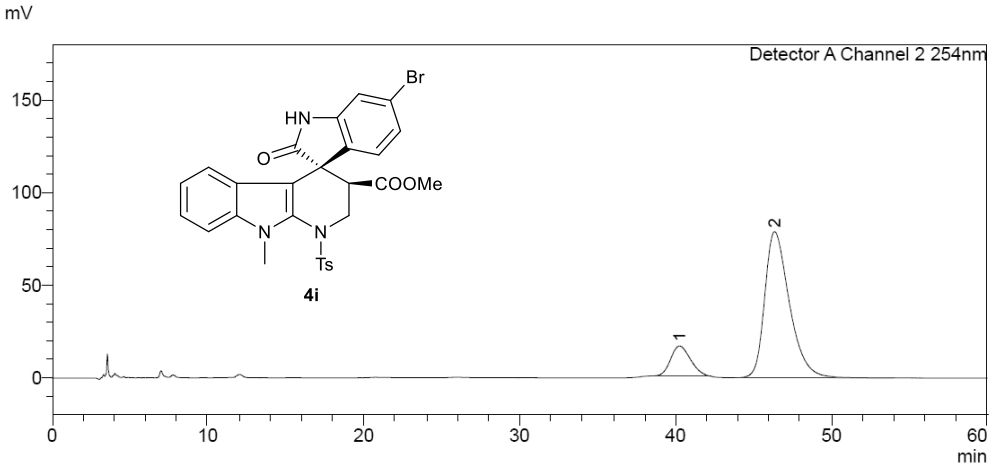
^{13}C NMR, 175 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

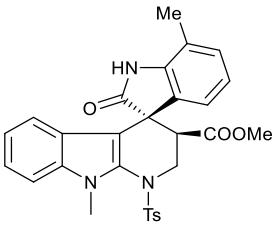
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	40.505	19681	1873612	50.183
2	47.093	16874	1859940	49.817
Total		36555	3733553	100.000



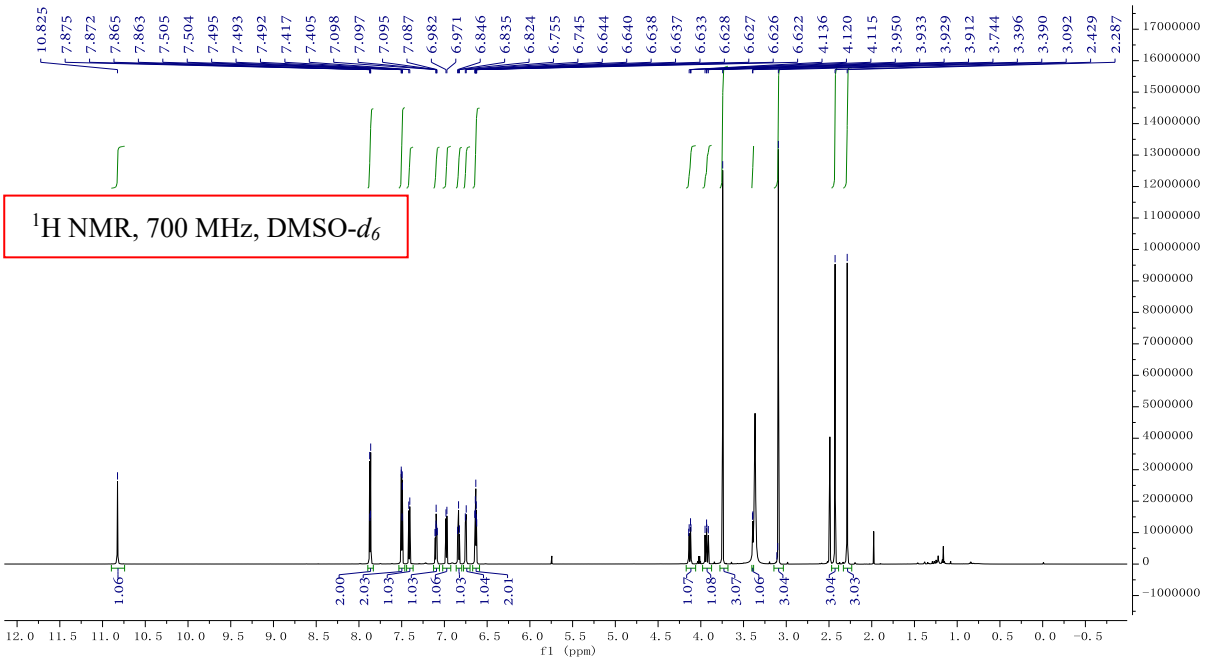
Peak Analysis Report

Detector A Channel 2 254nm

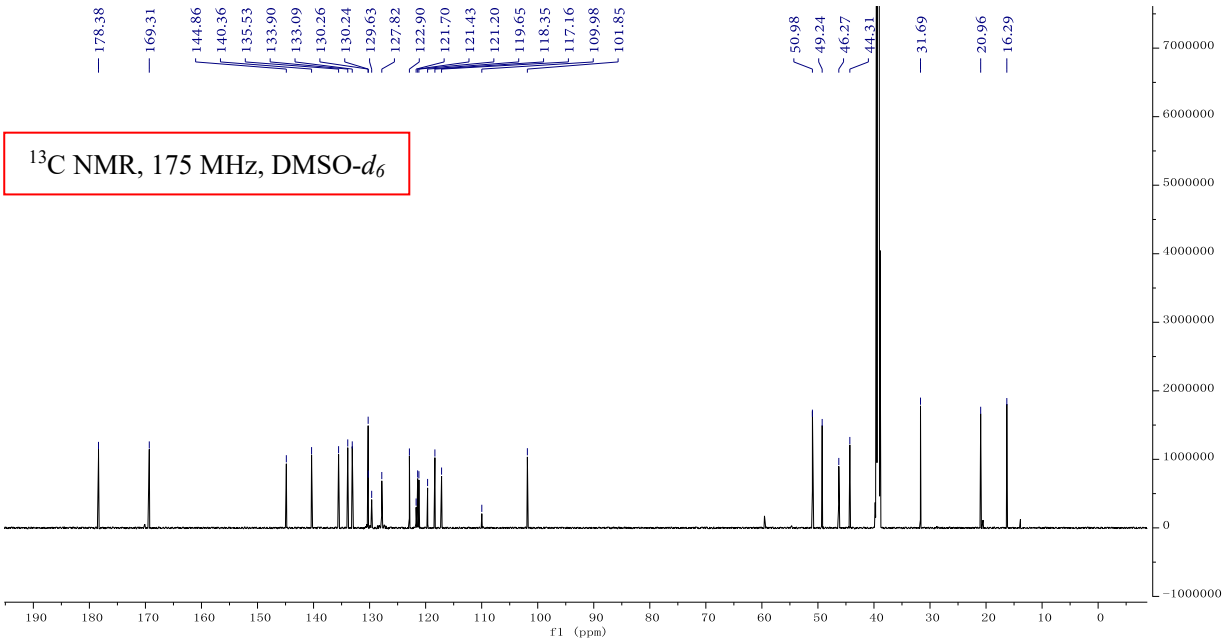
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	40.256	16214	1442166	14.266
2	46.353	78751	8667119	85.734
Total		94965	10109285	100.000



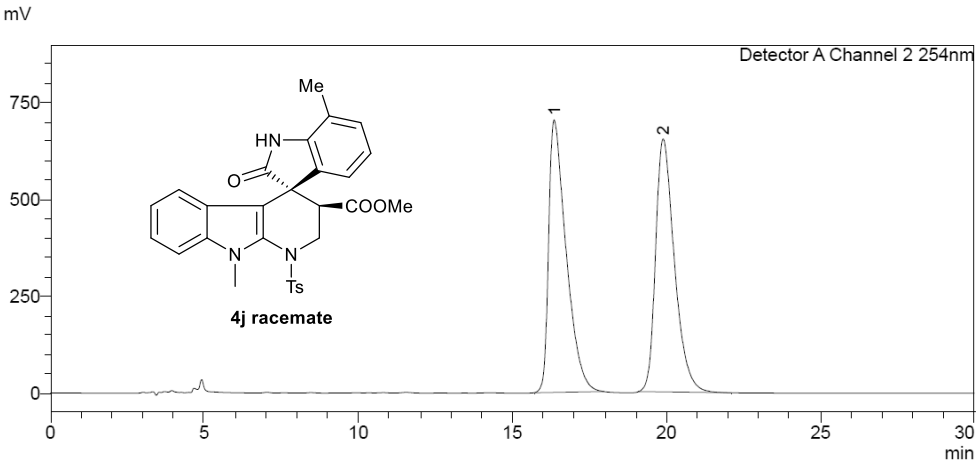
4j



^{1}H NMR, 700 MHz, DMSO-d_6



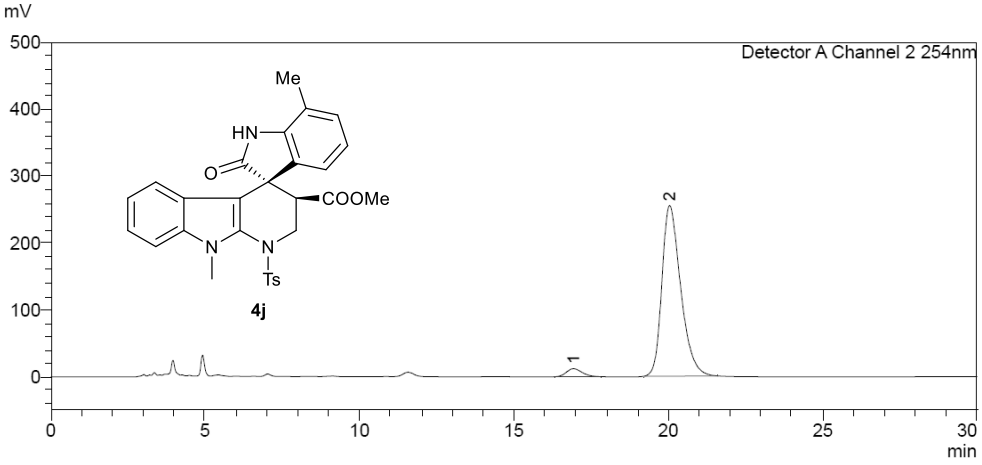
^{13}C NMR, 175 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

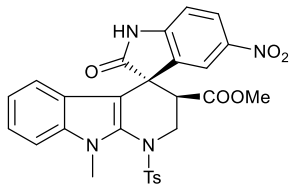
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.357	703763	27778193	49.945
2	19.894	653327	27839306	50.055
Total		1357090	55617499	100.000



Peak Analysis Report

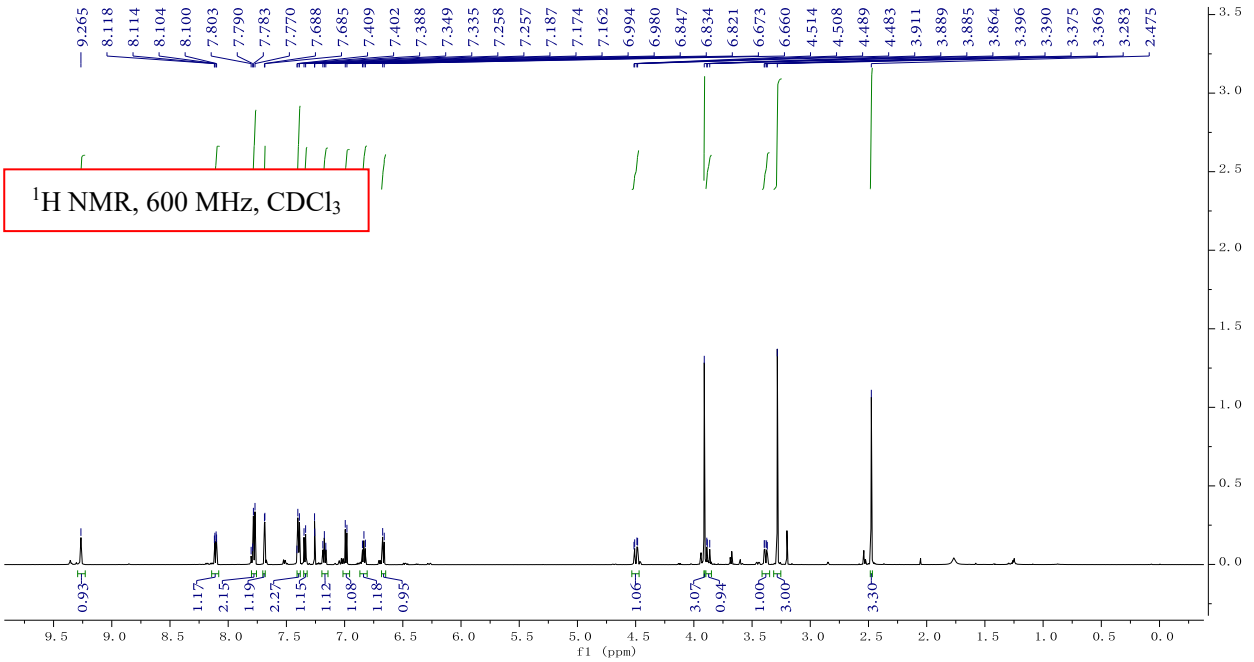
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.930	12067	429846	3.843
2	20.042	254555	10755694	96.157
Total		266621	11185540	100.000

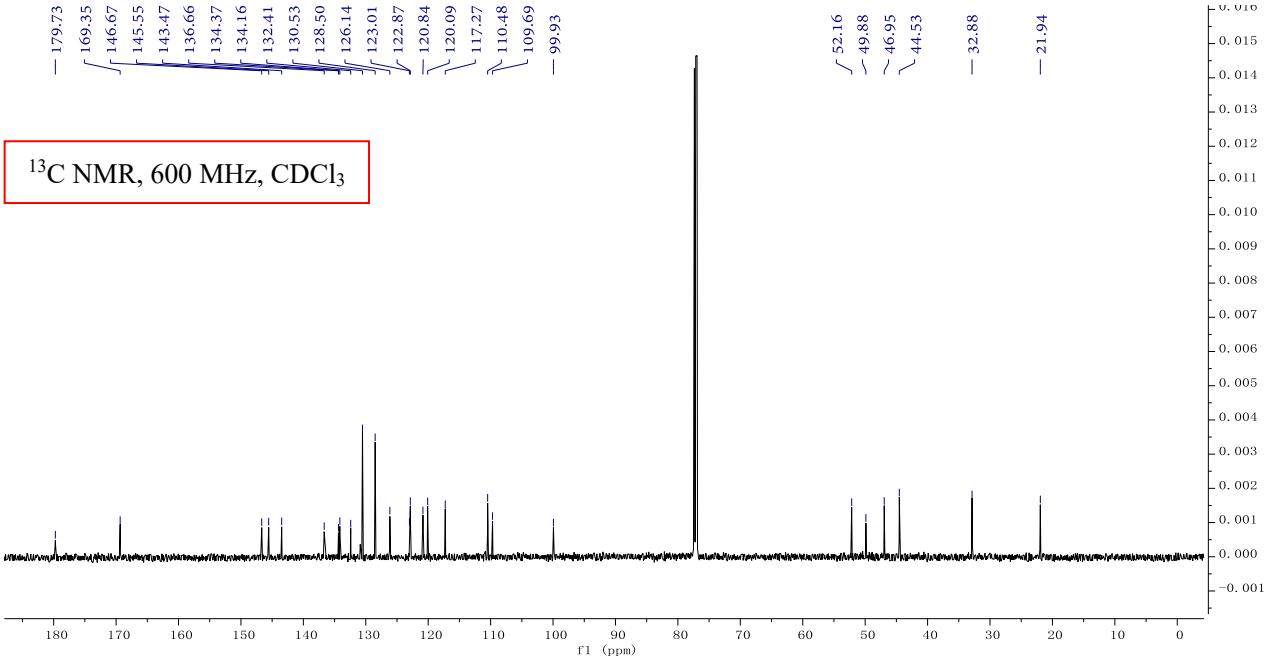


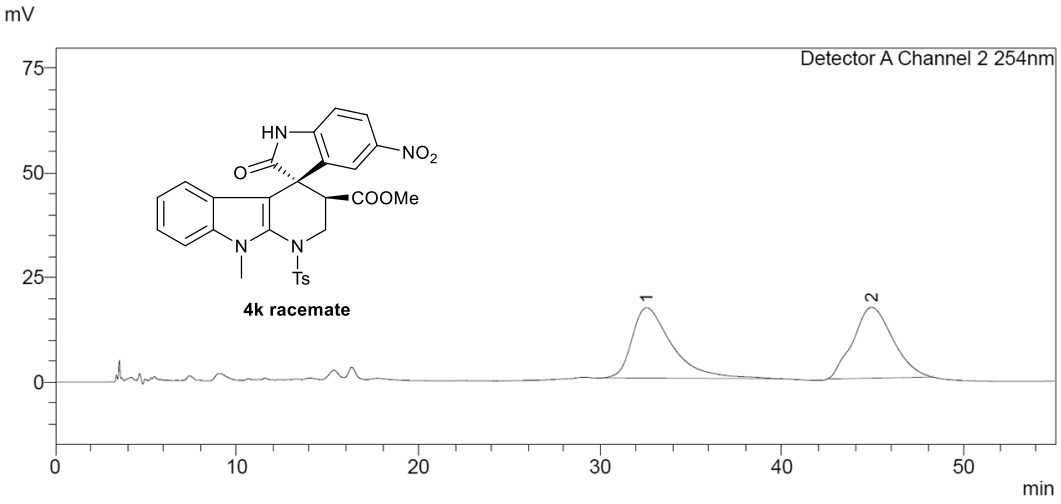
4k

^{1}H NMR, 600 MHz, $CDCl_3$



^{13}C NMR, 600 MHz, $CDCl_3$

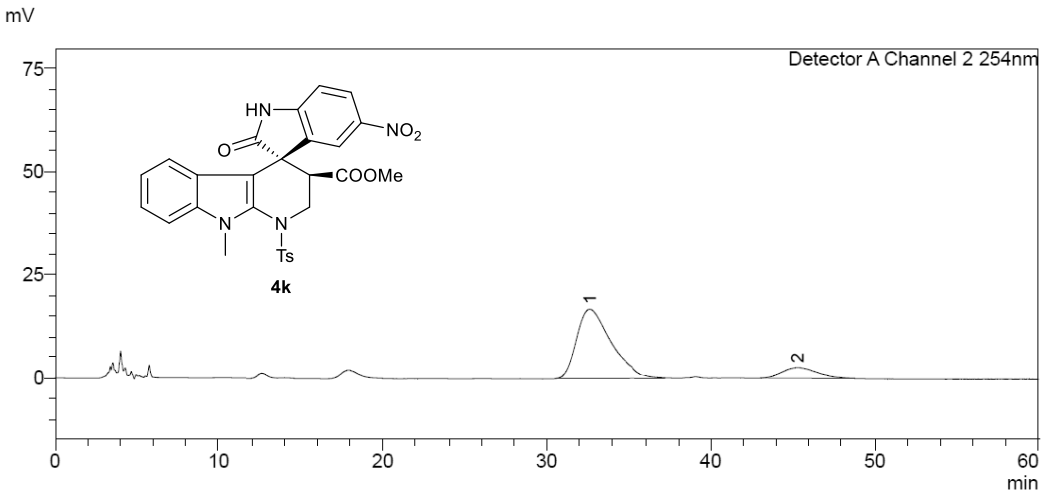




Peak Analysis Report

Detector A Channel 2 254nm

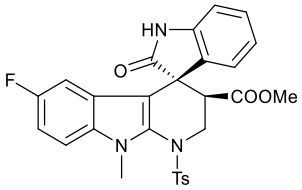
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	32.550	16841	2588131	50.078
2	44.934	16946	2580079	49.922
Total		33787	5168211	100.000



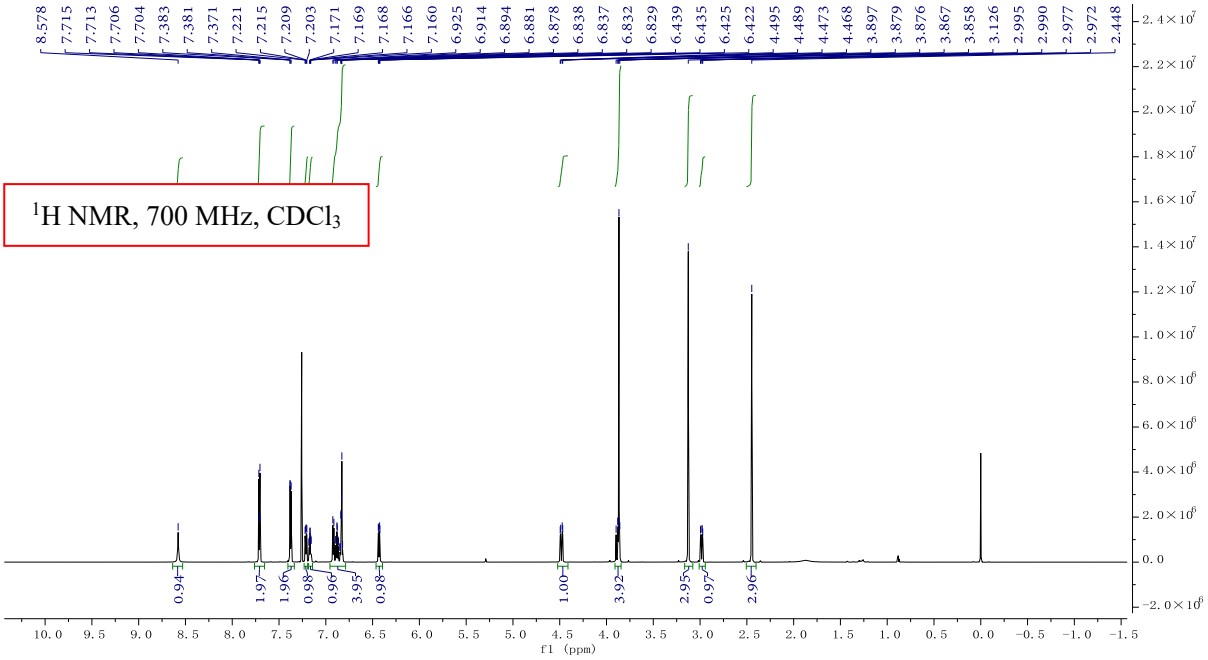
Peak Analysis Report

Detector A Channel 2 254nm

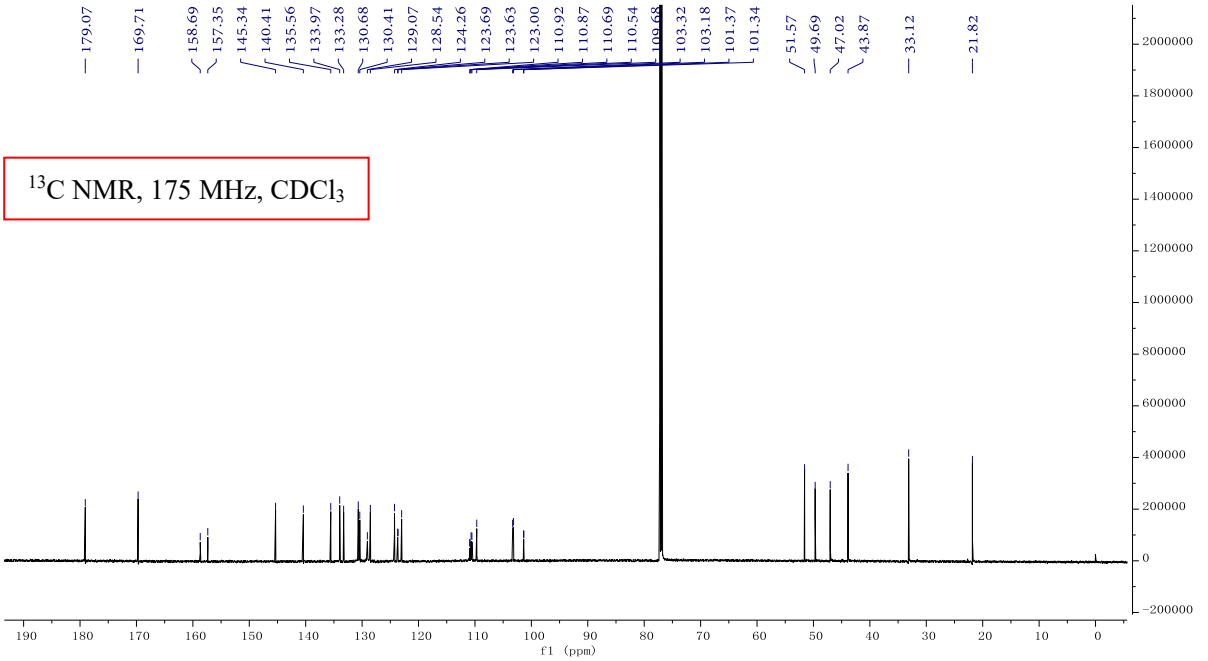
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	32.622	16753	2743309	88.076
2	45.300	2527	371391	11.924
Total		19280	3114700	100.000



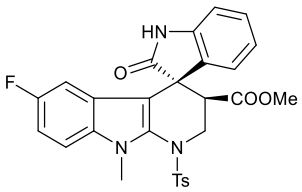
4l



^{1}H NMR, 700 MHz, $CDCl_3$

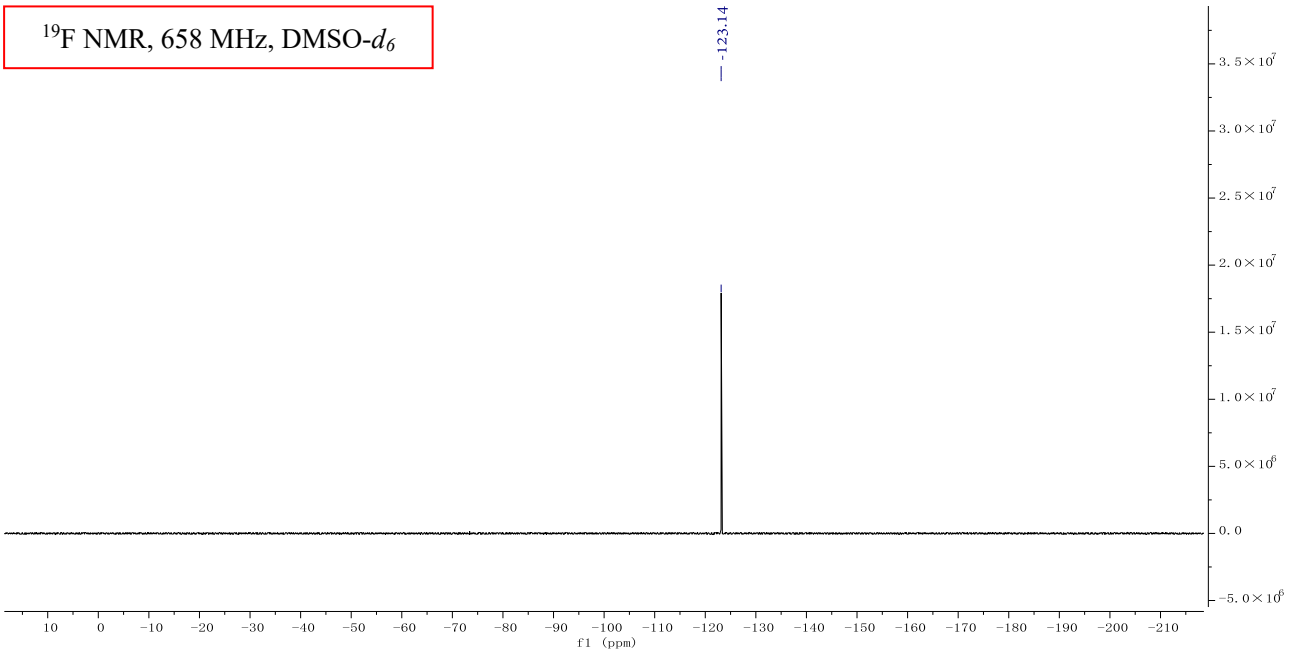


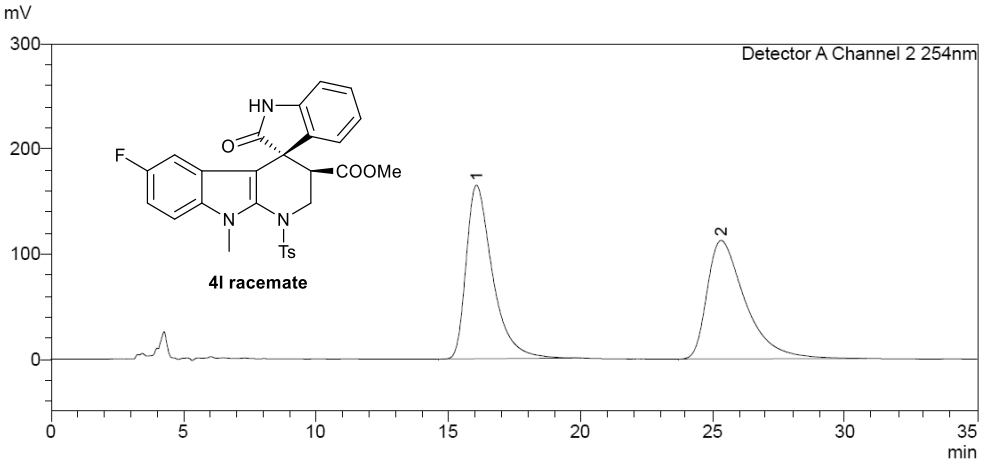
^{13}C NMR, 175 MHz, $CDCl_3$



4l

^{19}F NMR, 658 MHz, DMSO-d_6

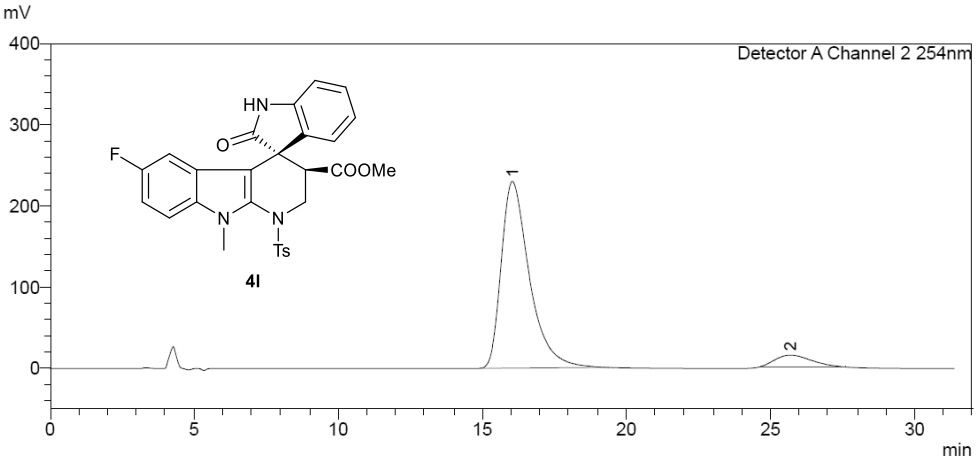




Peak Analysis Report

Detector A Channel 2 254nm

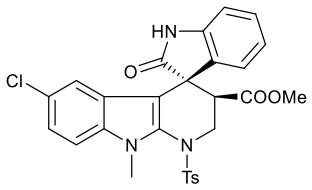
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.088	165206	11427945	50.260
2	25.329	112752	11309589	49.740
Total		277958	22737534	100.000



Peak Analysis Report

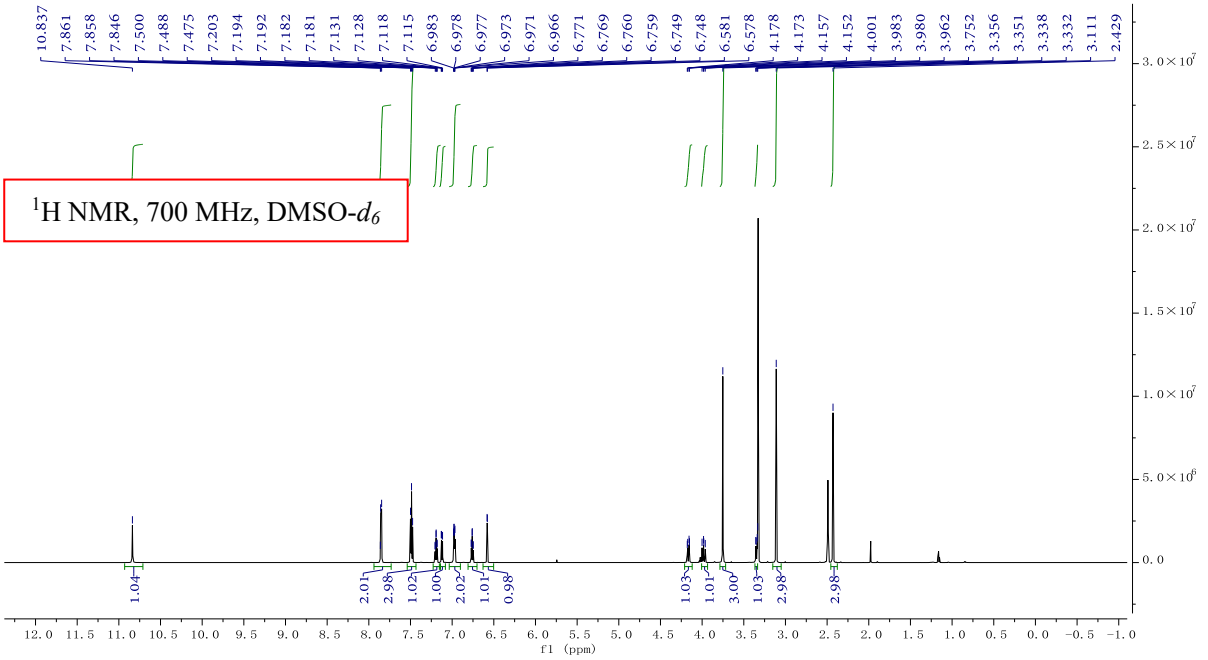
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.048	229414	15577984	92.438
2	25.691	14552	1274444	7.562
Total		243966	16852428	100.000

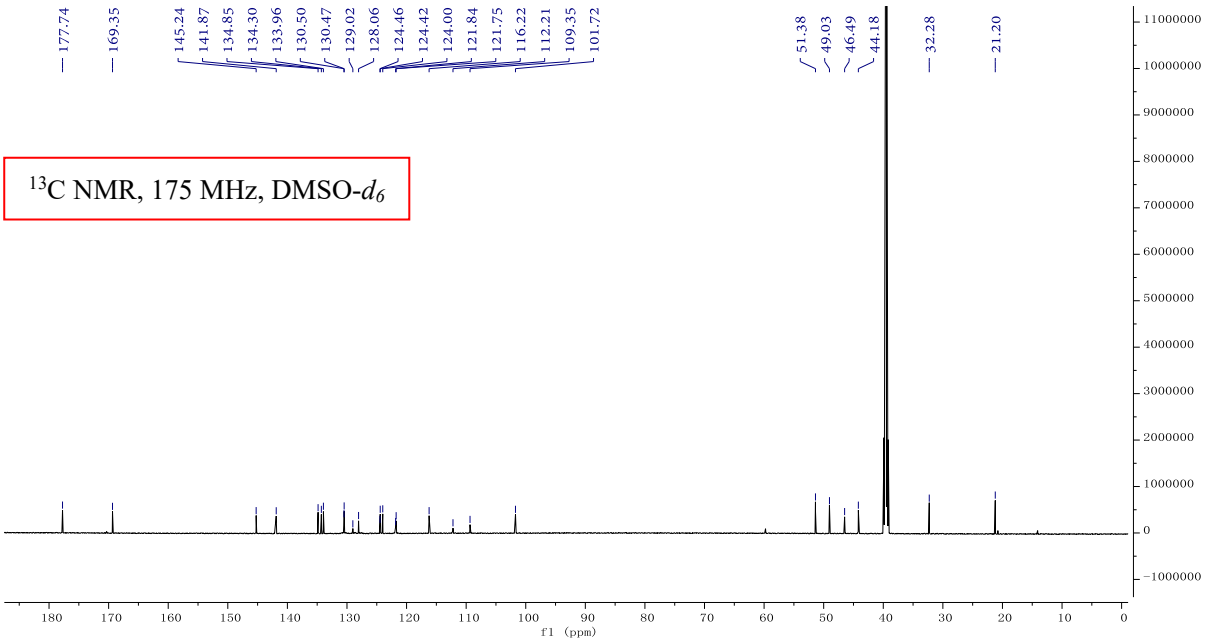


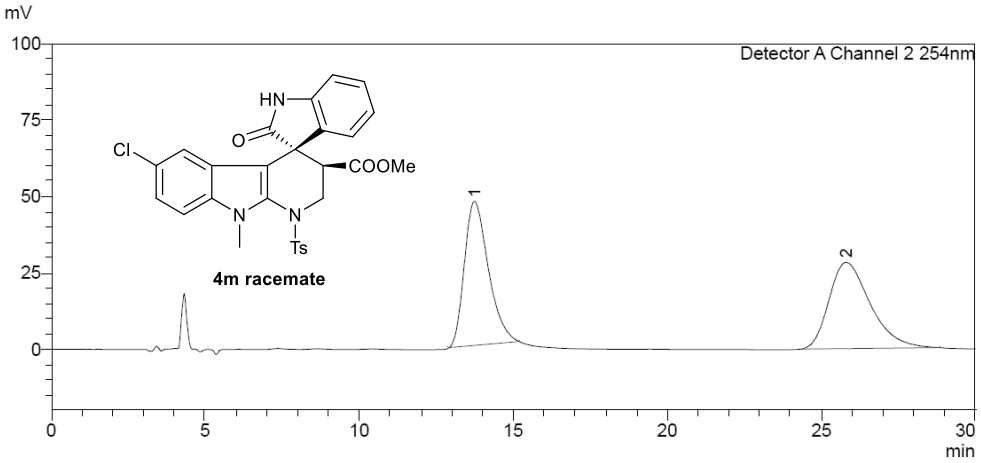
4m

^{1}H NMR, 700 MHz, DMSO-d_6



^{13}C NMR, 175 MHz, DMSO-d_6

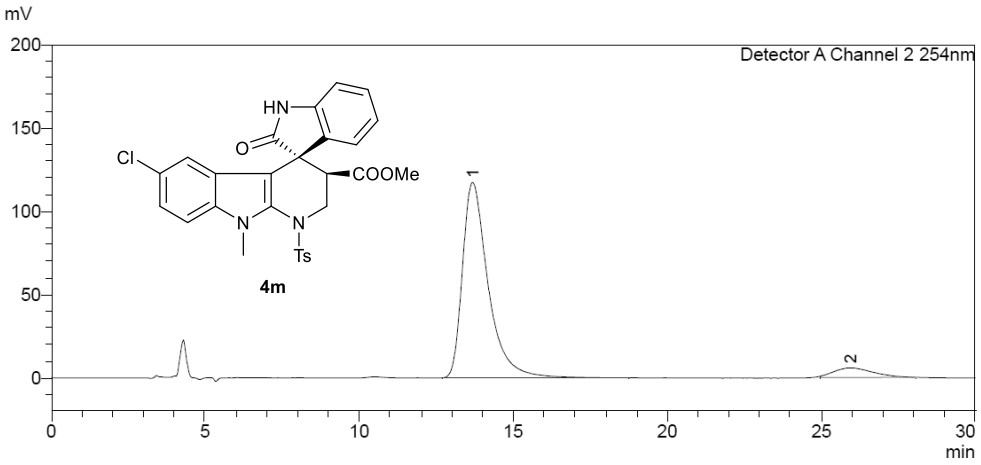




Peak Analysis Report

Detector A Channel 2 254nm

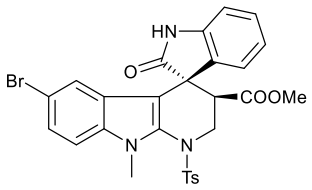
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.743	47091	2548343	49.317
2	25.799	28178	2618927	50.683
Total		75268	5167270	100.000



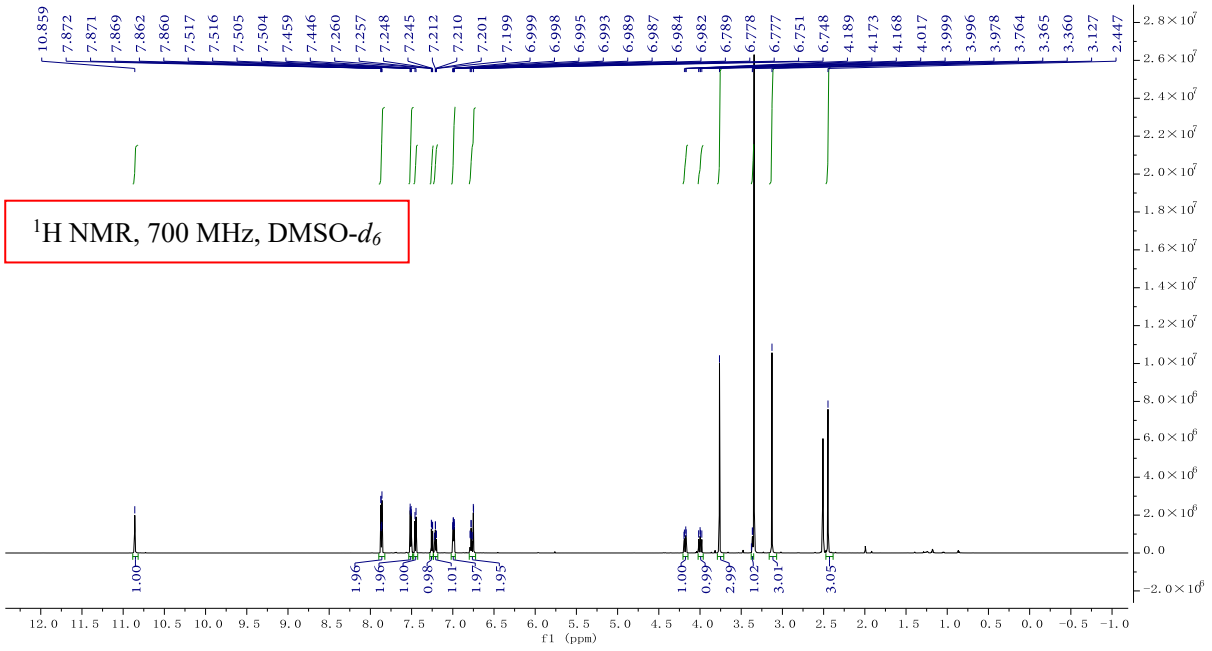
Peak Analysis Report

Detector A Channel 2 254nm

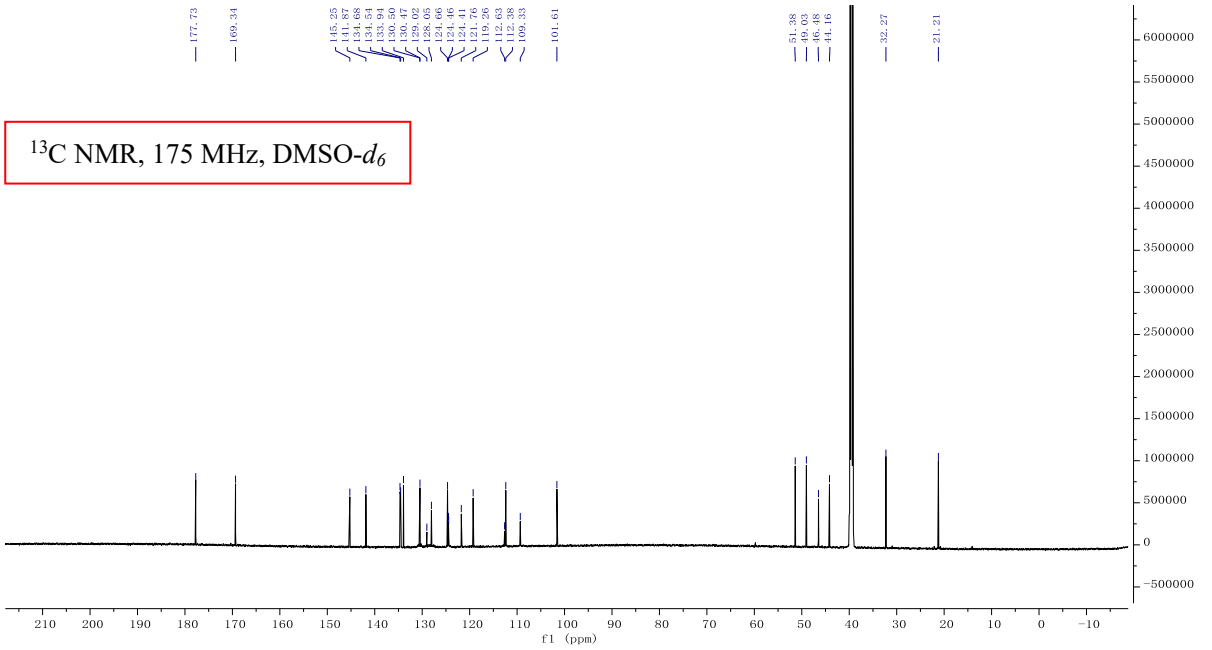
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.680	117334	6818709	93.061
2	25.953	5682	508397	6.939
Total		123016	7327106	100.000



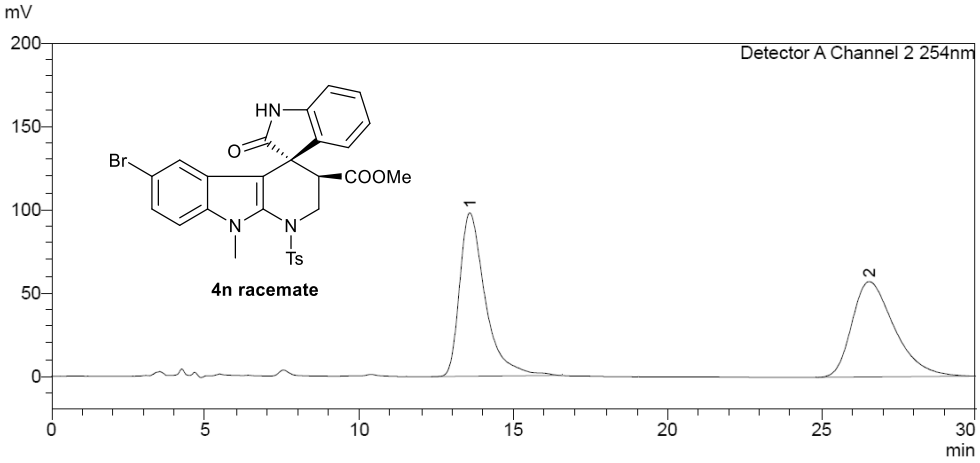
4n



^{1}H NMR, 700 MHz, DMSO-d_6



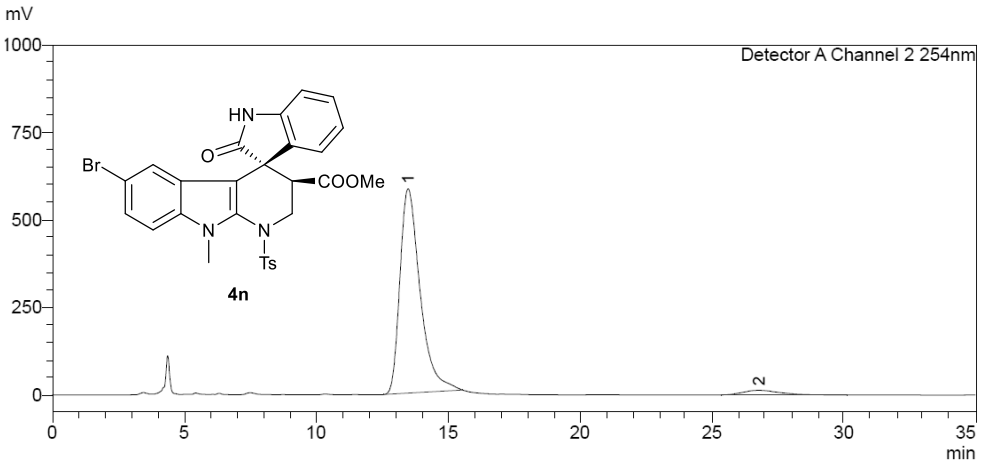
^{13}C NMR, 175 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

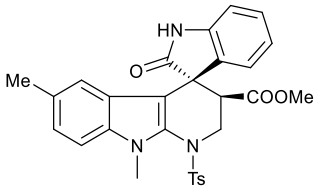
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.585	97936	5672297	50.833
2	26.549	57186	5486373	49.167
Total		155122	11158670	100.000



Peak Analysis Report

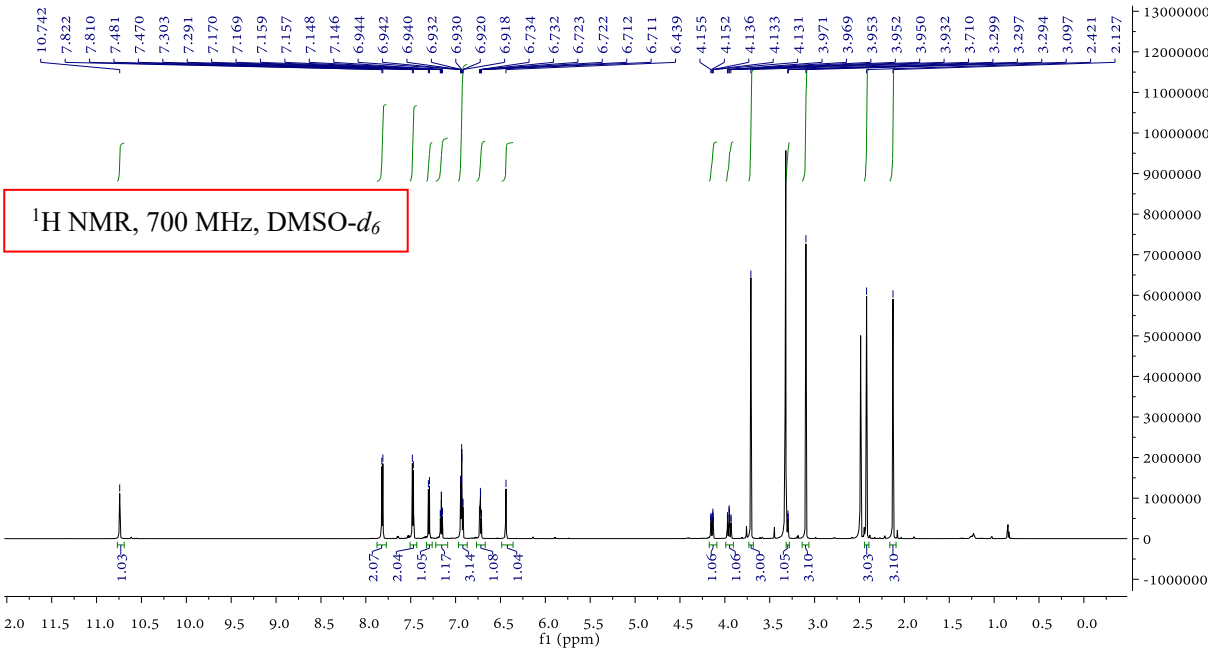
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.495	583920	31130269	96.079
2	26.785	12985	1270393	3.921
Total		596905	32400662	100.000

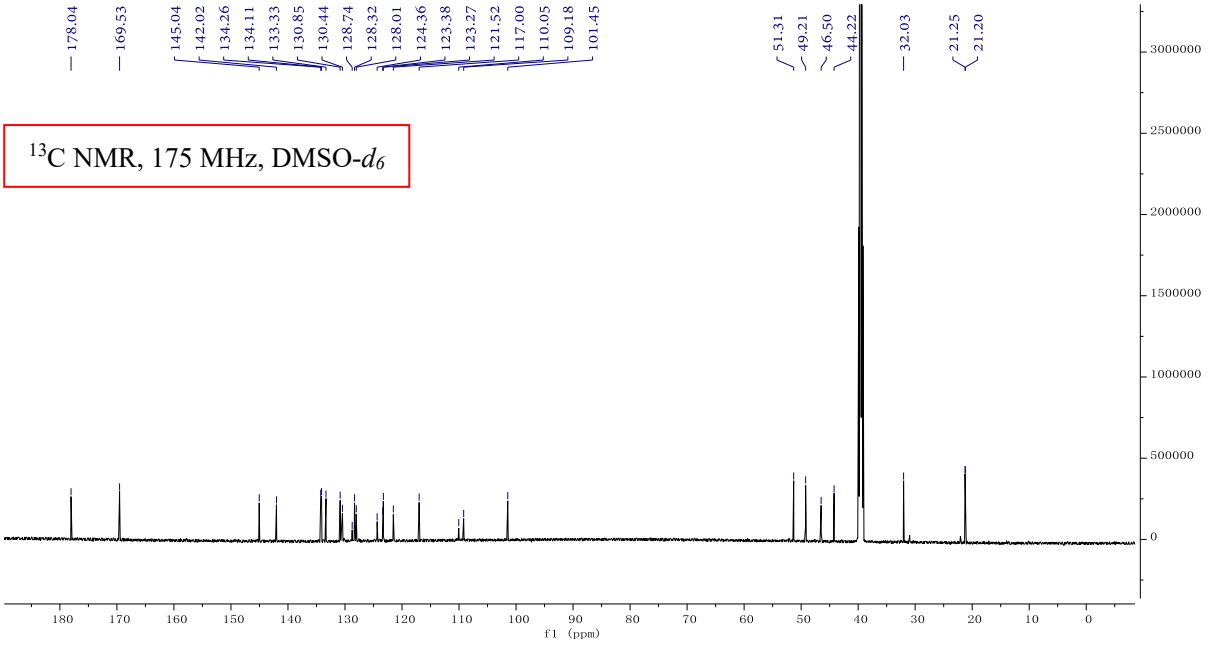


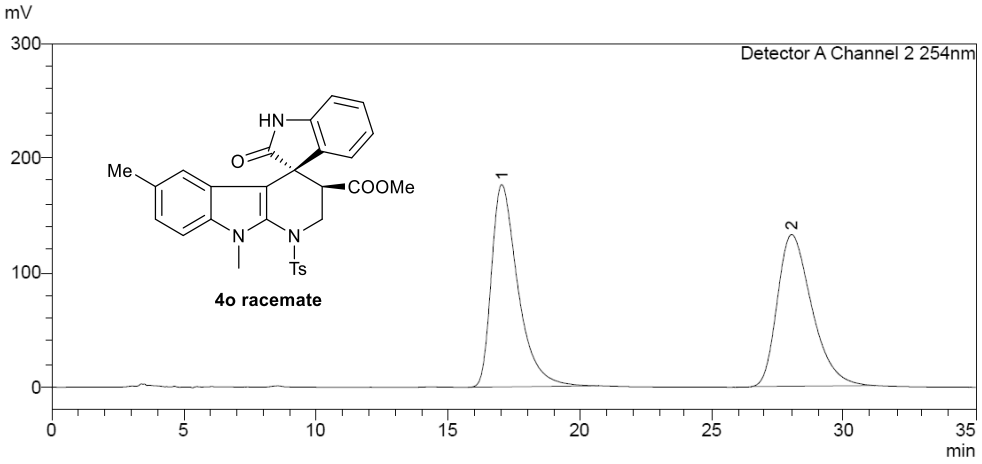
4o

^{1}H NMR, 700 MHz, DMSO-d_6



^{13}C NMR, 175 MHz, DMSO-d_6

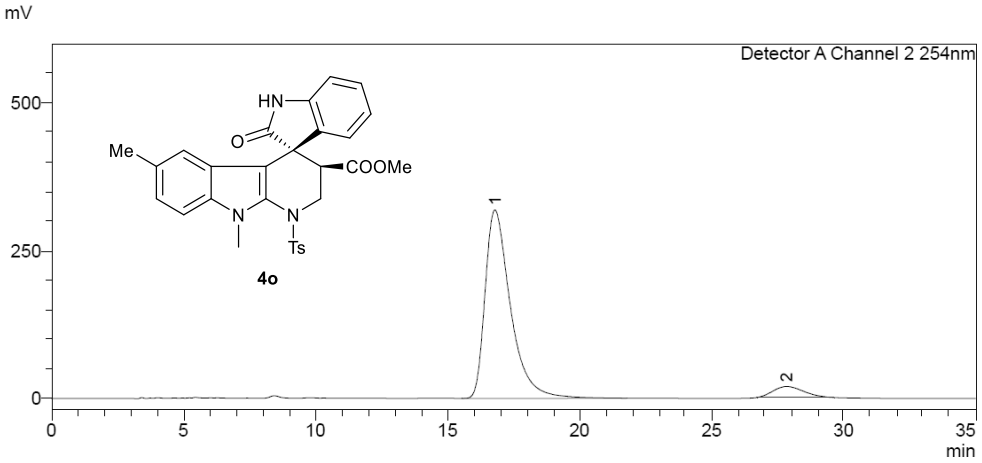




Peak Analysis Report

Detector A Channel 2 254nm

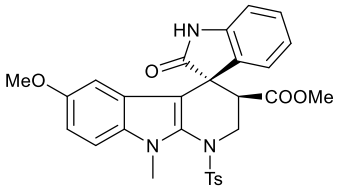
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	17.061	176492	12306311	50.567
2	28.037	132365	12030156	49.433
Total		308857	24336467	100.000



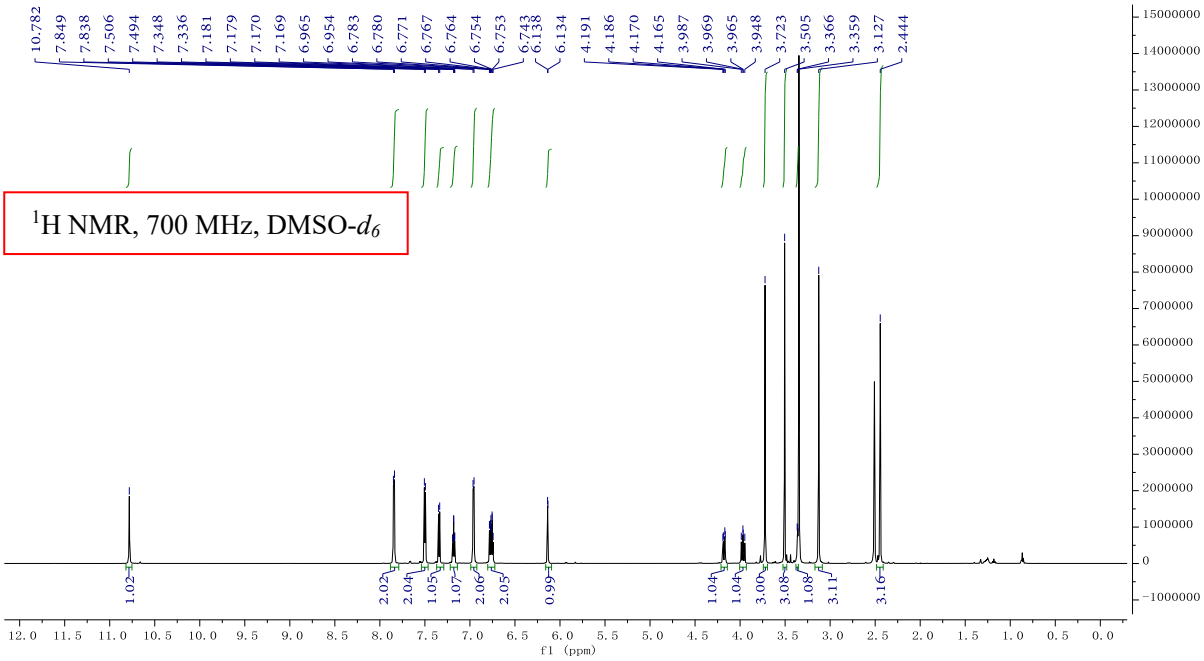
Peak Analysis Report

Detector A Channel 2 254nm

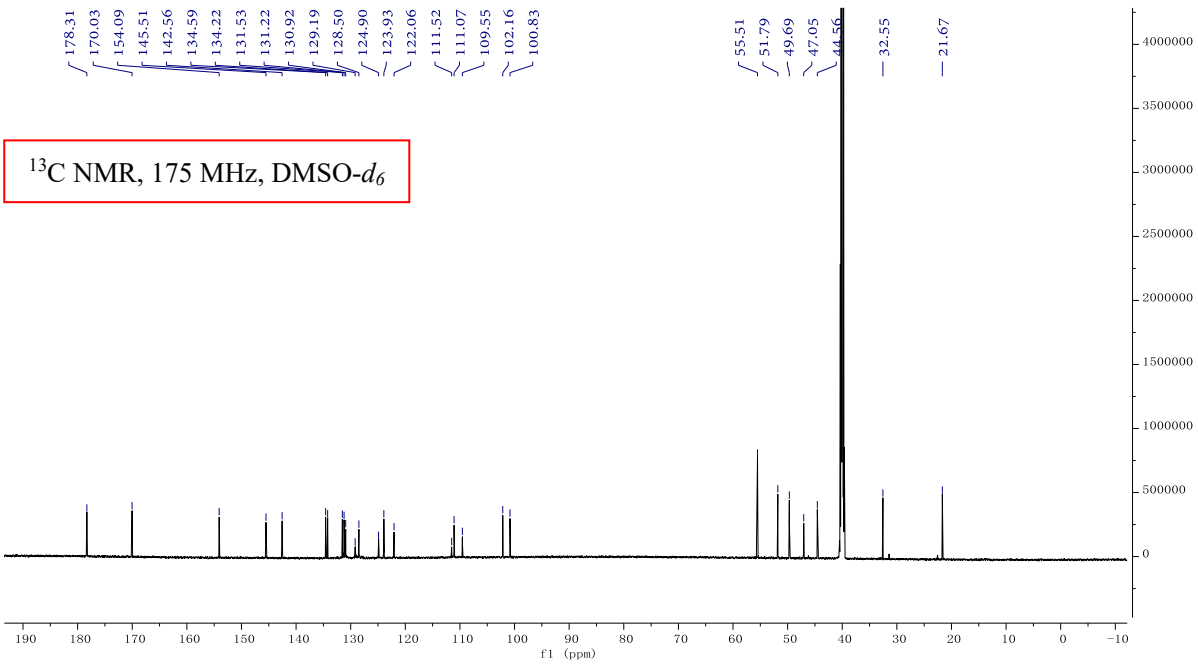
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.801	318488	21314102	93.448
2	27.841	18483	1494316	6.552
Total		336971	22808418	100.000



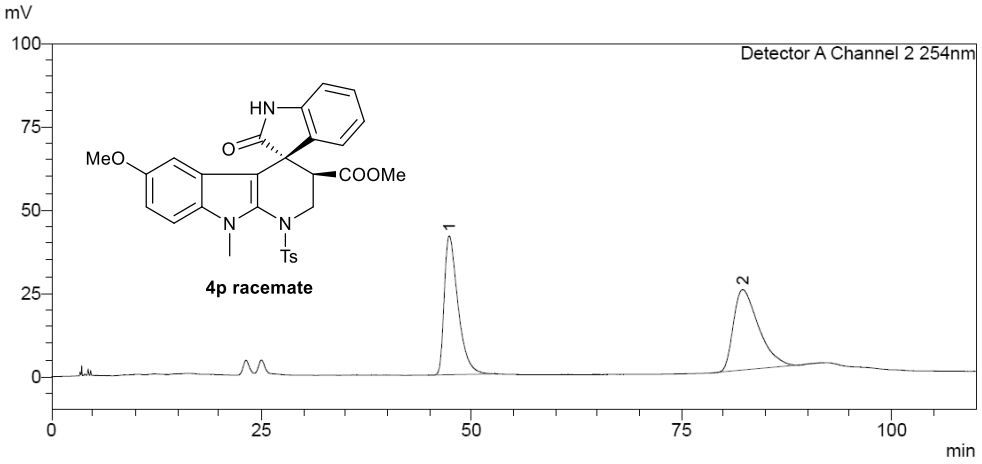
4p



^{1}H NMR, 700 MHz, DMSO-d_6



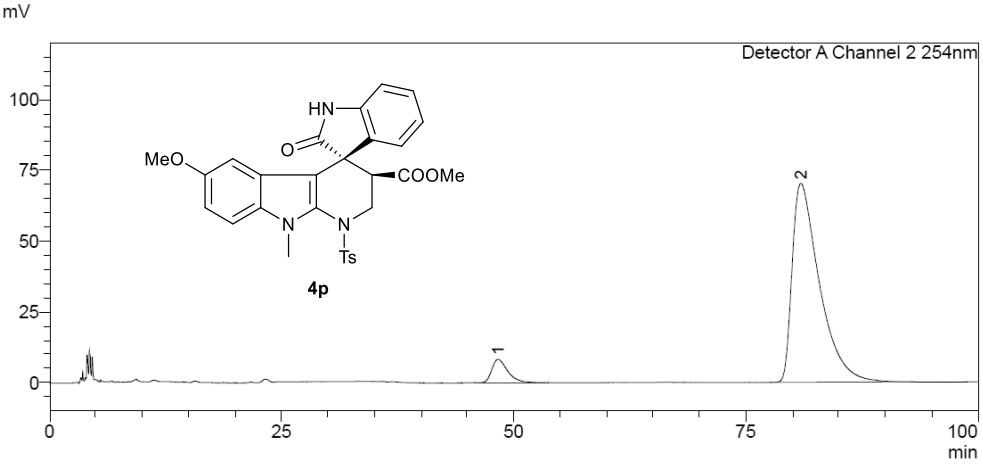
^{13}C NMR, 175 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

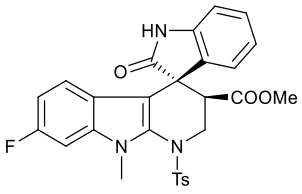
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	47.371	41678	4738376	48.493
2	82.286	24143	5032874	51.507
Total		65821	9771250	100.000



Peak Analysis Report

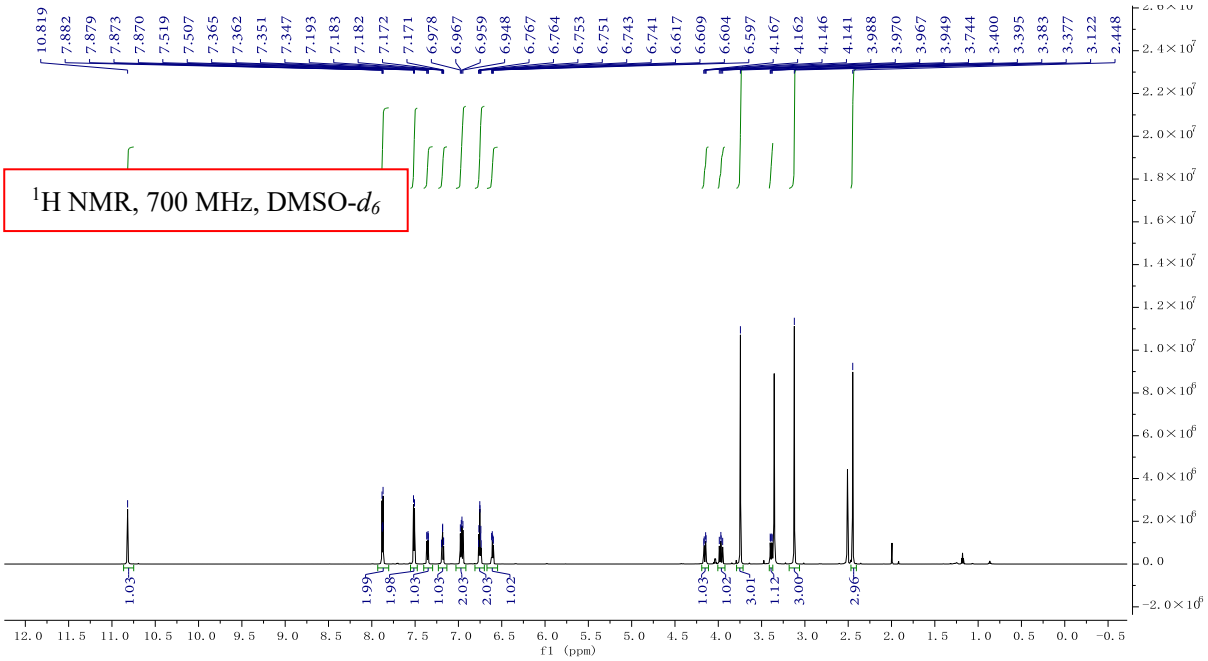
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	48.319	8297	996136	6.489
2	80.952	70119	14355178	93.511
Total		78416	15351313	100.000

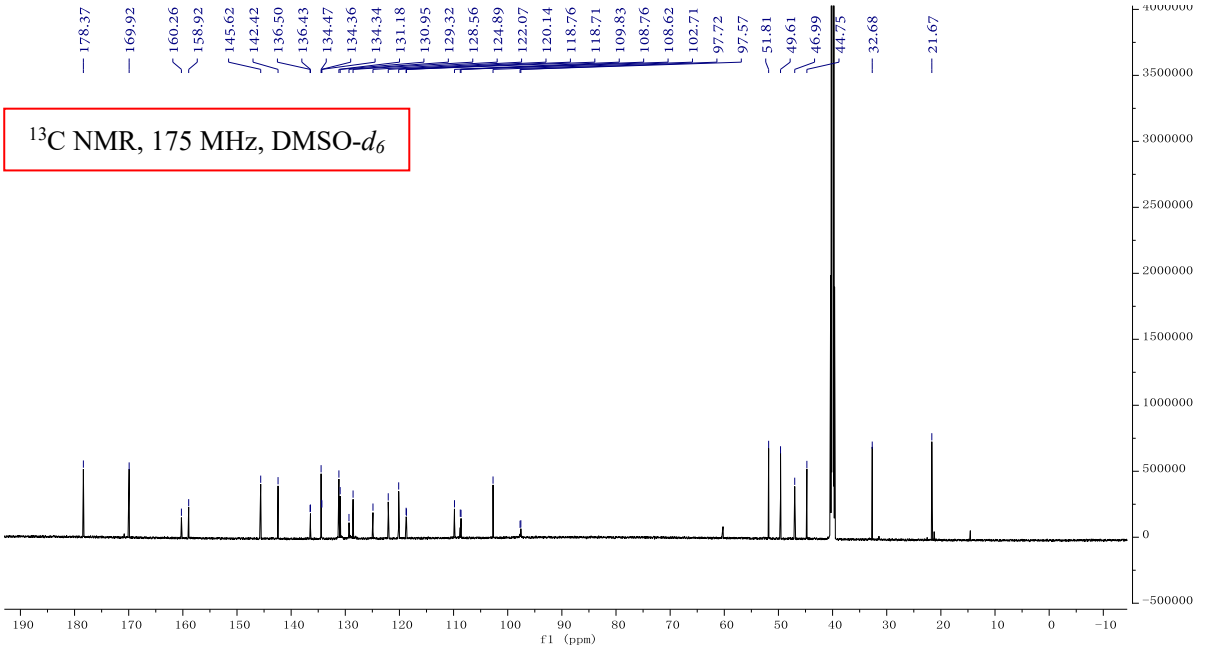


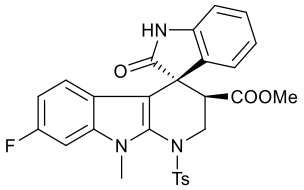
4q

^{1}H NMR, 700 MHz, DMSO-d_6

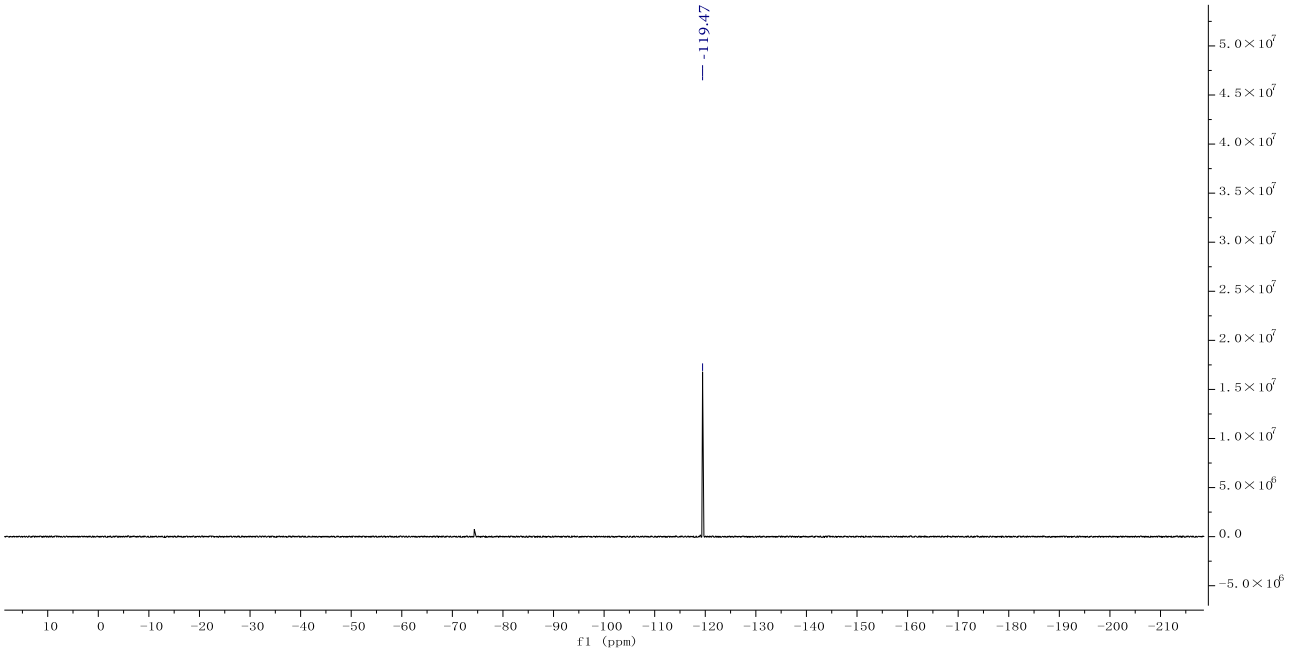


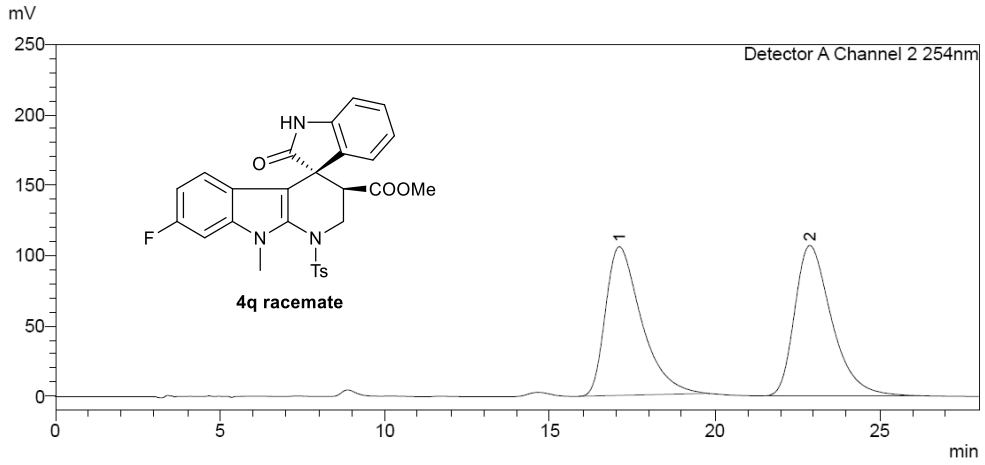
^{13}C NMR, 175 MHz, DMSO-d_6




HN
O
COOMe
F
N
N
Ts

4q

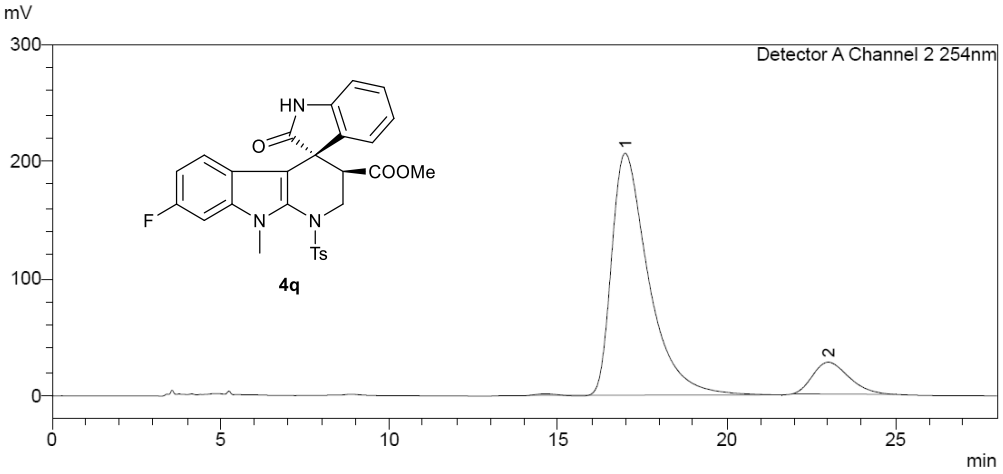

-119.47
5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
-5.0×10^6
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



Peak Analysis Report

Detector A Channel 2 254nm

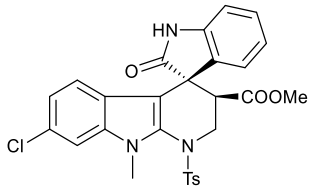
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	17.108	105470	8010230	49.111
2	22.883	106551	8300070	50.889
Total		212021	16310300	100.000



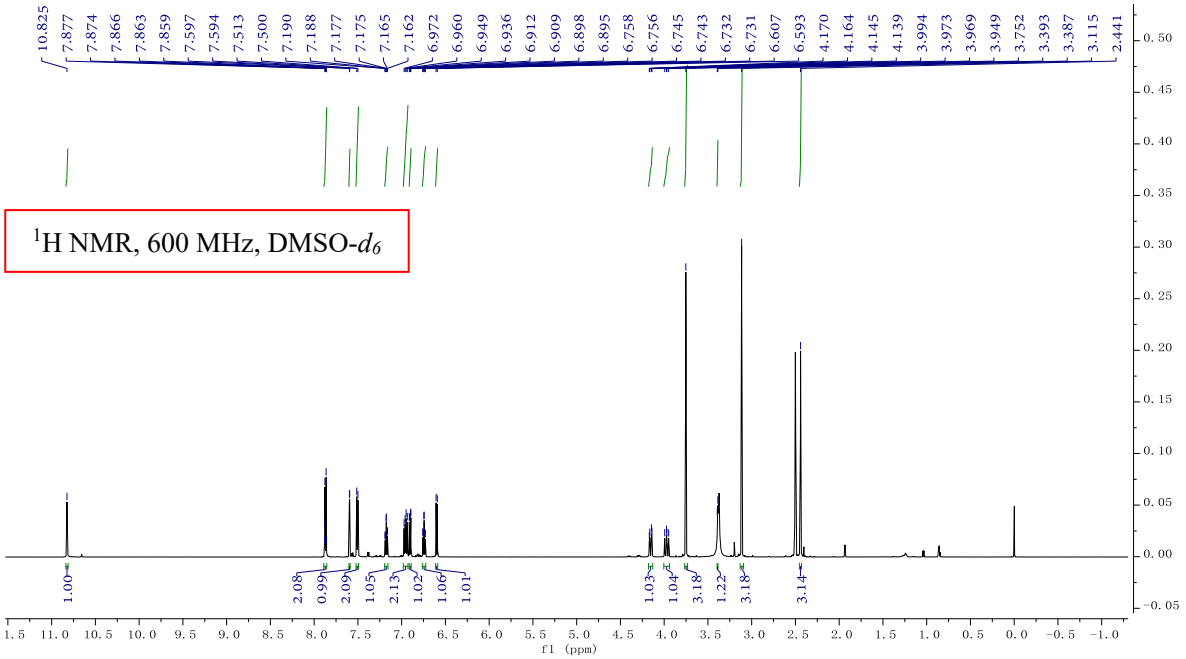
Peak Analysis Report

Detector A Channel 2 254nm

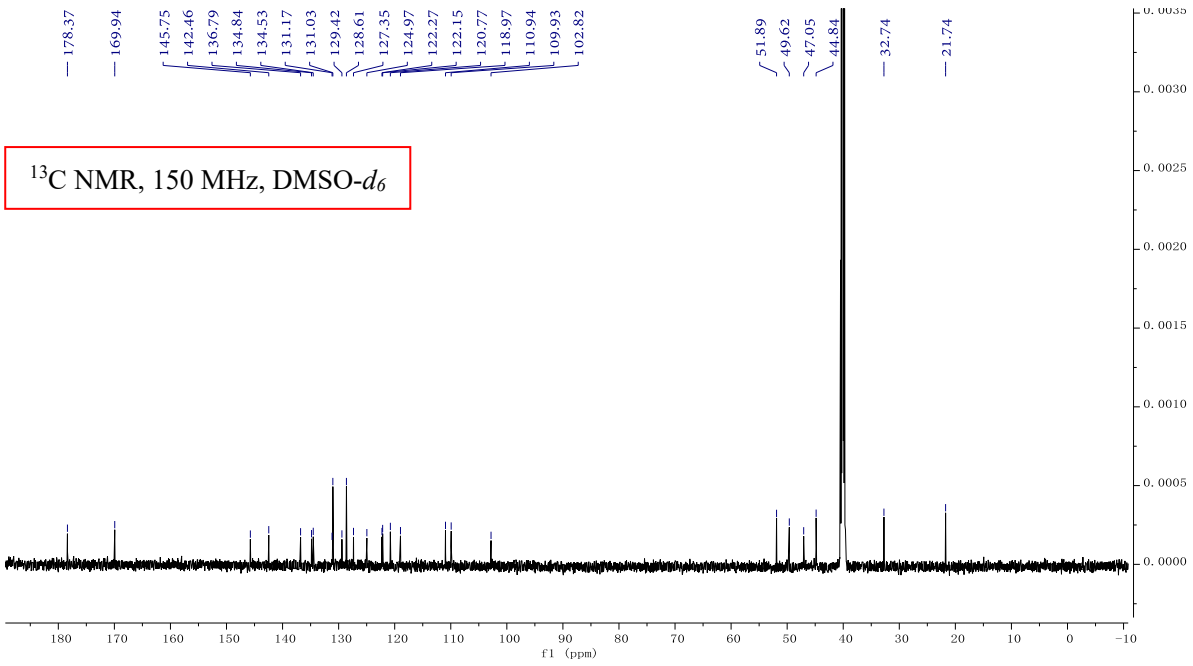
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.992	206438	15718275	88.568
2	23.014	27149	2028926	11.432
Total		233587	17747202	100.000



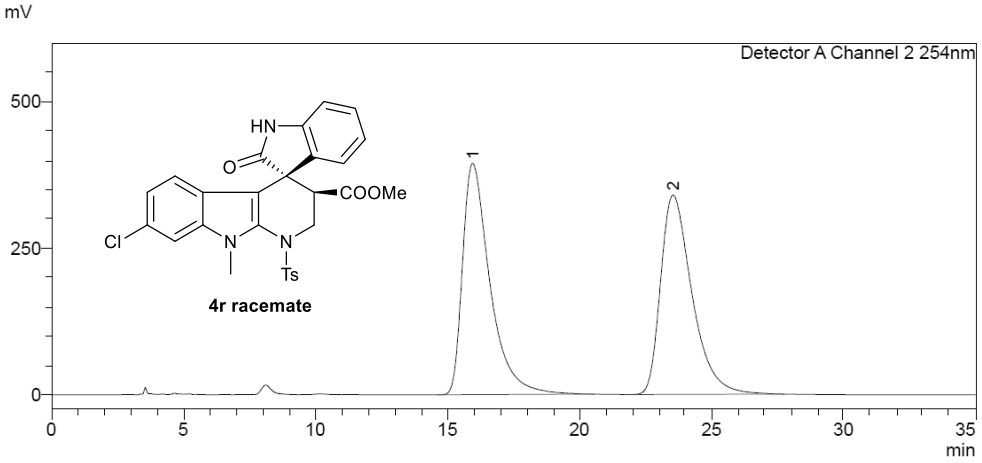
4r



^{1}H NMR, 600 MHz, DMSO-*d*$_6$



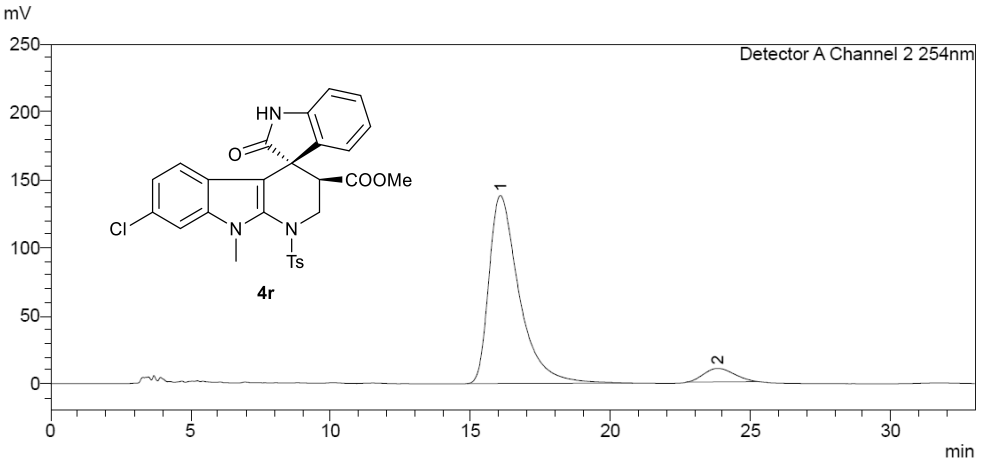
^{13}C NMR, 150 MHz, DMSO-*d*$_6$



Peak Analysis Report

Detector A Channel 2 254nm

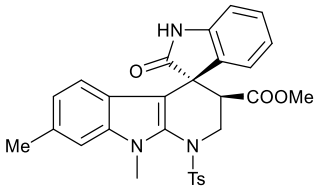
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	15.964	394108	28482322	50.379
2	23.551	339609	28054314	49.621
Total		733717	56536635	100.000



Peak Analysis Report

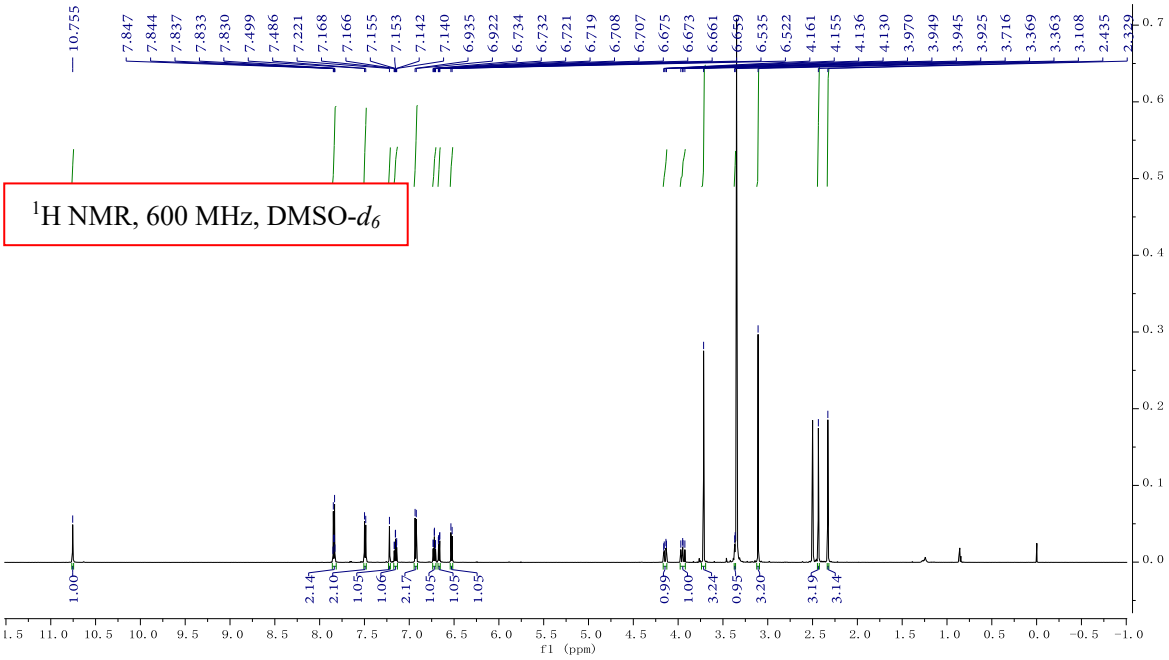
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	16.074	138368	10346464	93.167
2	23.829	10021	758774	6.833
Total		148389	11105237	100.000

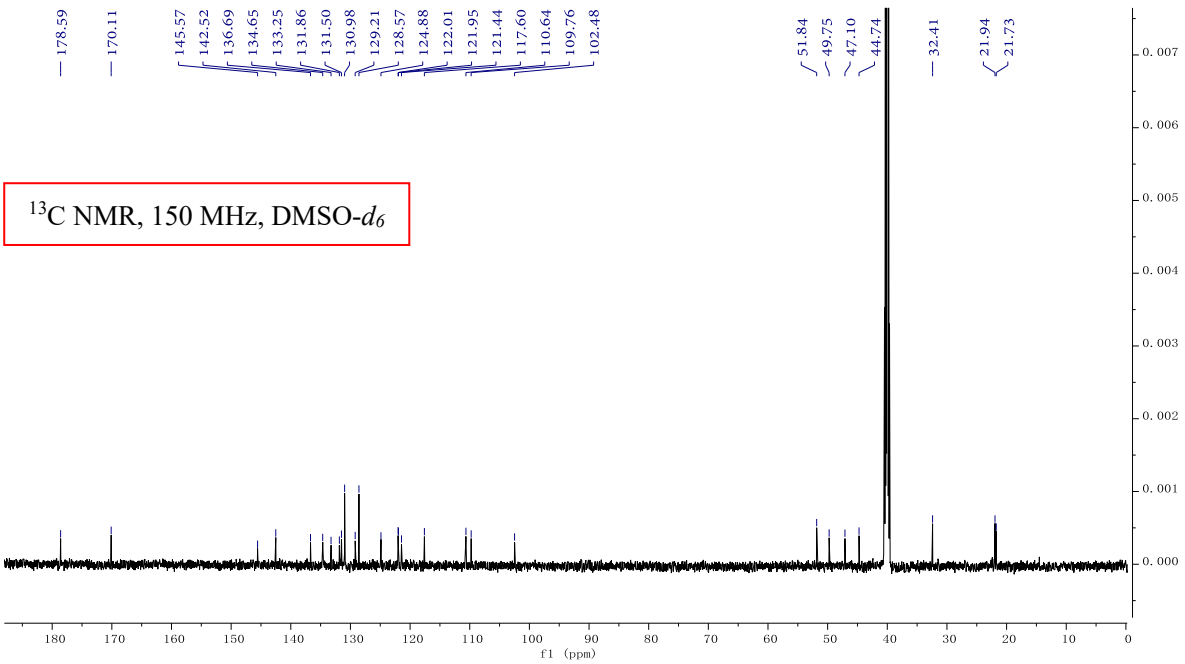


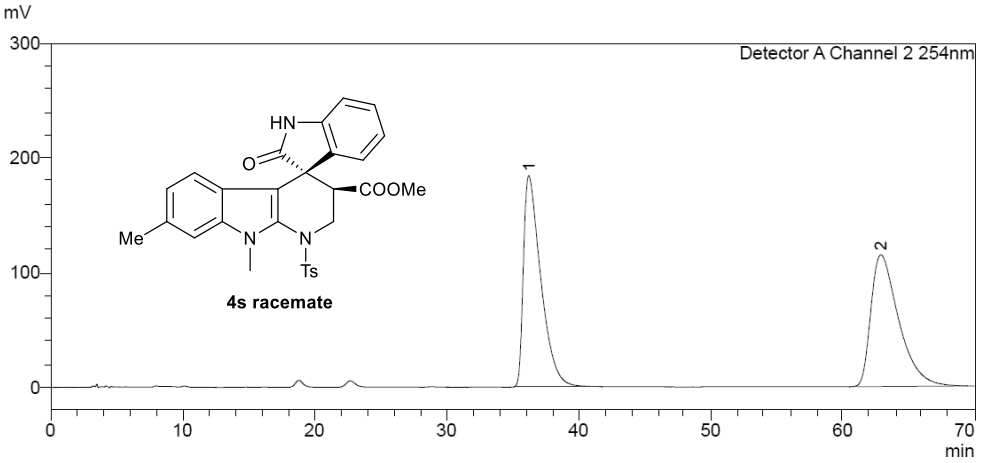
4s

^{1}H NMR, 600 MHz, DMSO-d_6



^{13}C NMR, 150 MHz, DMSO-d_6

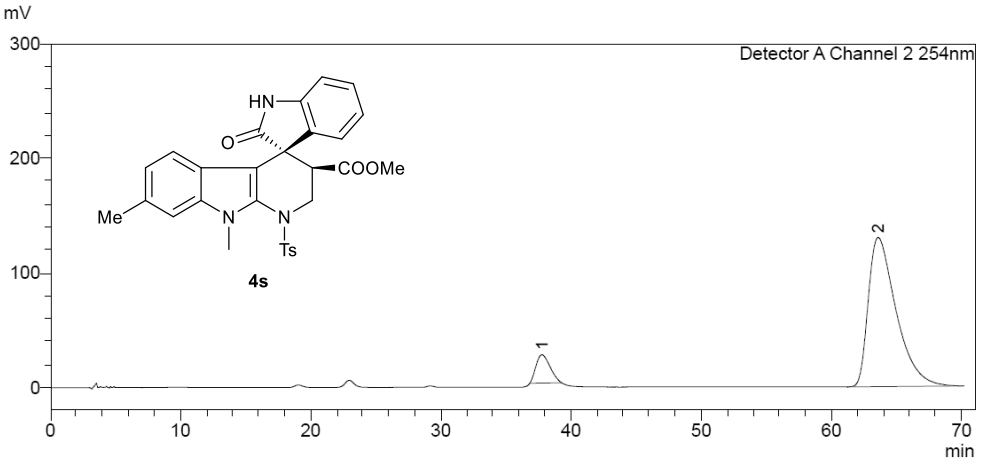




Peak Analysis Report

Detector A Channel 2 254nm

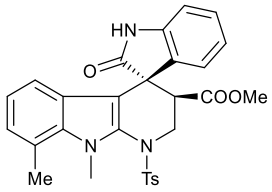
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	36.244	183979	16841872	50.068
2	62.901	114766	16796139	49.932
Total		298745	33638011	100.000



Peak Analysis Report

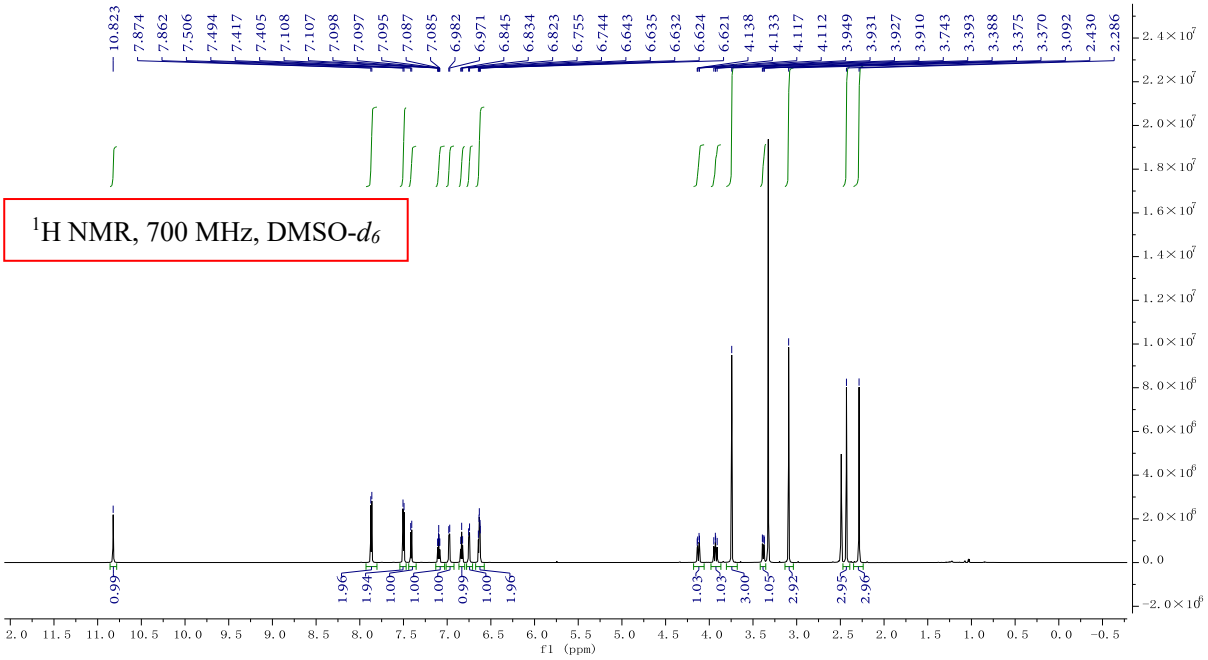
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	37.767	24733	1857936	8.750
2	63.595	130143	19375919	91.250
Total		154877	21233855	100.000

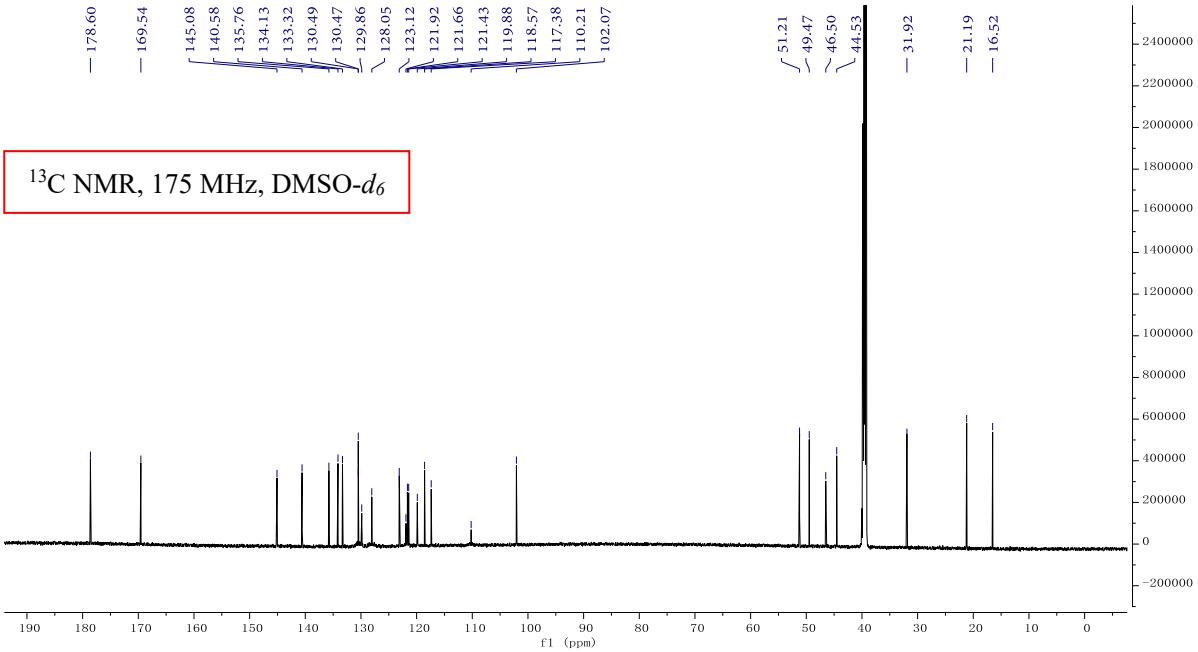


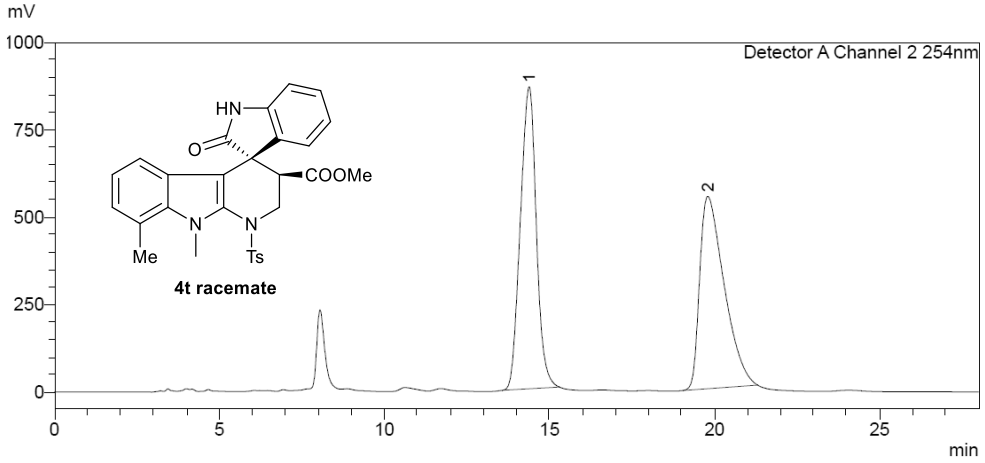
4t

^{1}H NMR, 700 MHz, DMSO-*d*$_6$



^{13}C NMR, 175 MHz, DMSO-*d*$_6$

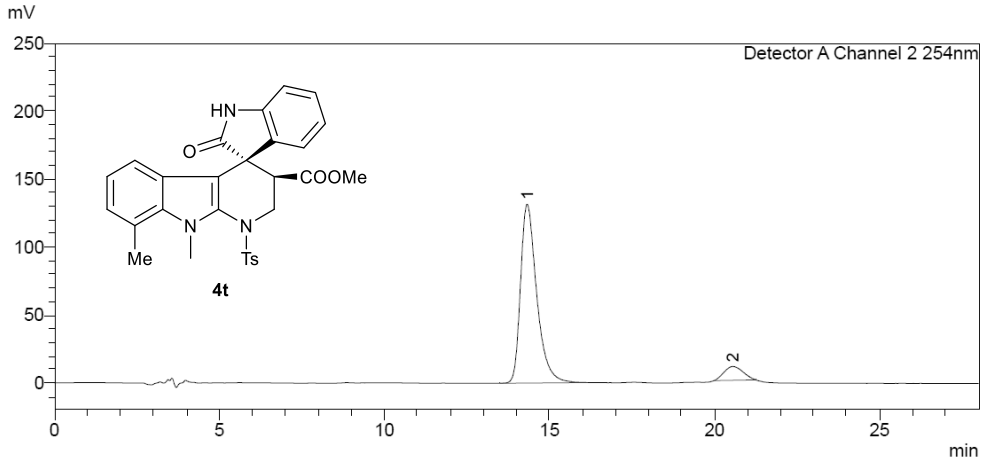




Peak Analysis Report

Detector A Channel 2 254nm

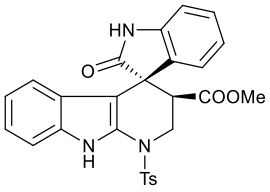
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	14.387	863517	29033832	50.625
2	19.800	549804	28316740	49.375
Total		1413322	57350572	100.000



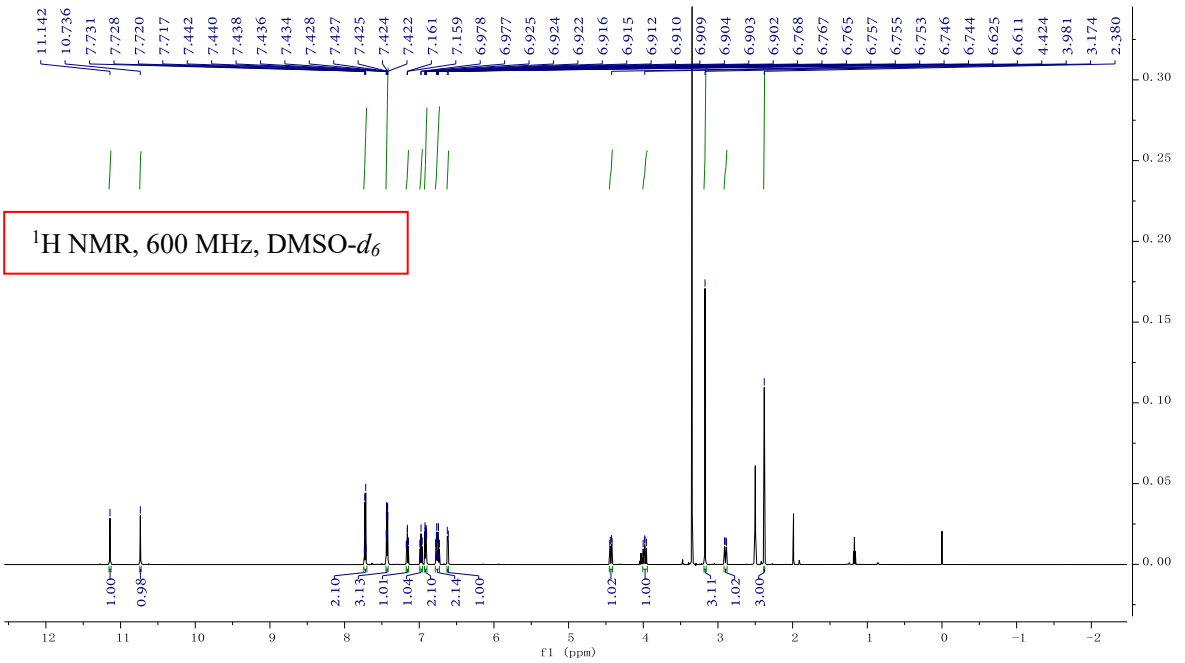
Peak Analysis Report

Detector A Channel 2 254nm

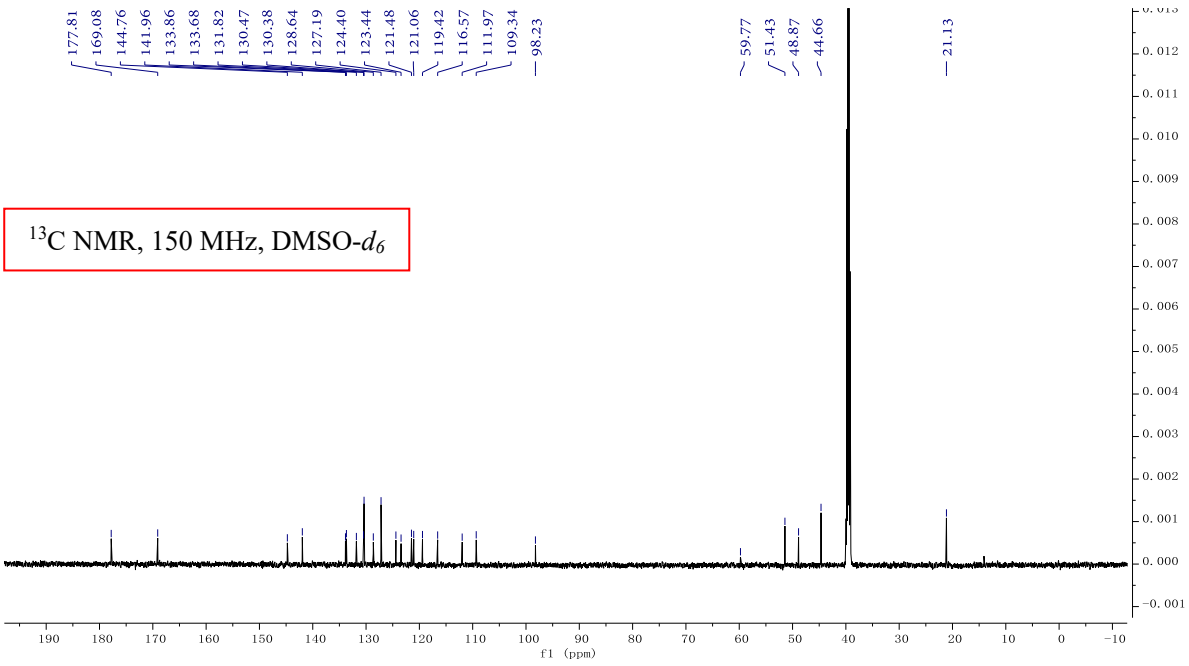
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	14.326	131619	4485010	91.626
2	20.559	10168	409893	8.374
Total		141787	4894903	100.000



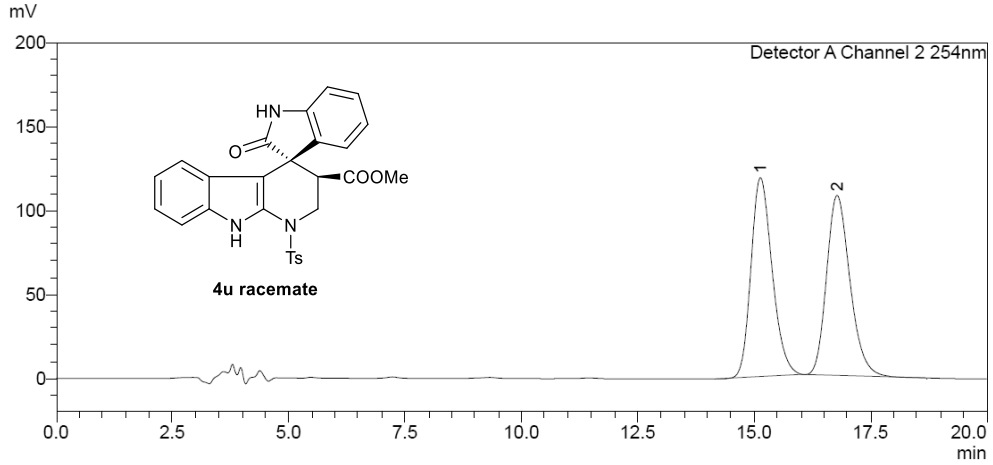
4u



^{1}H NMR, 600 MHz, DMSO-d_6



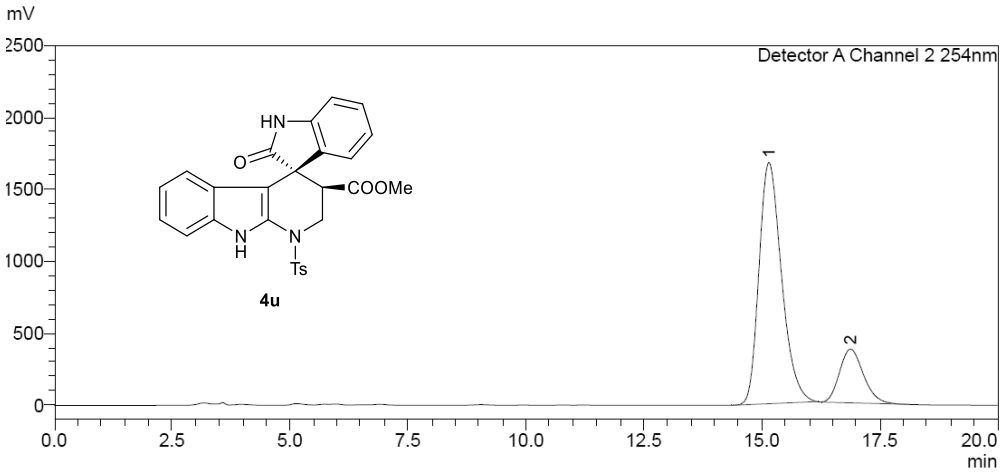
^{13}C NMR, 150 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

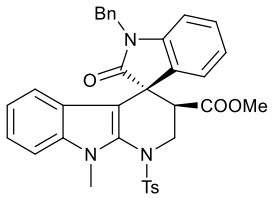
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	15.139	118363	3738633	49.955
2	16.787	107046	3745397	50.045
Total		225409	7484030	100.000



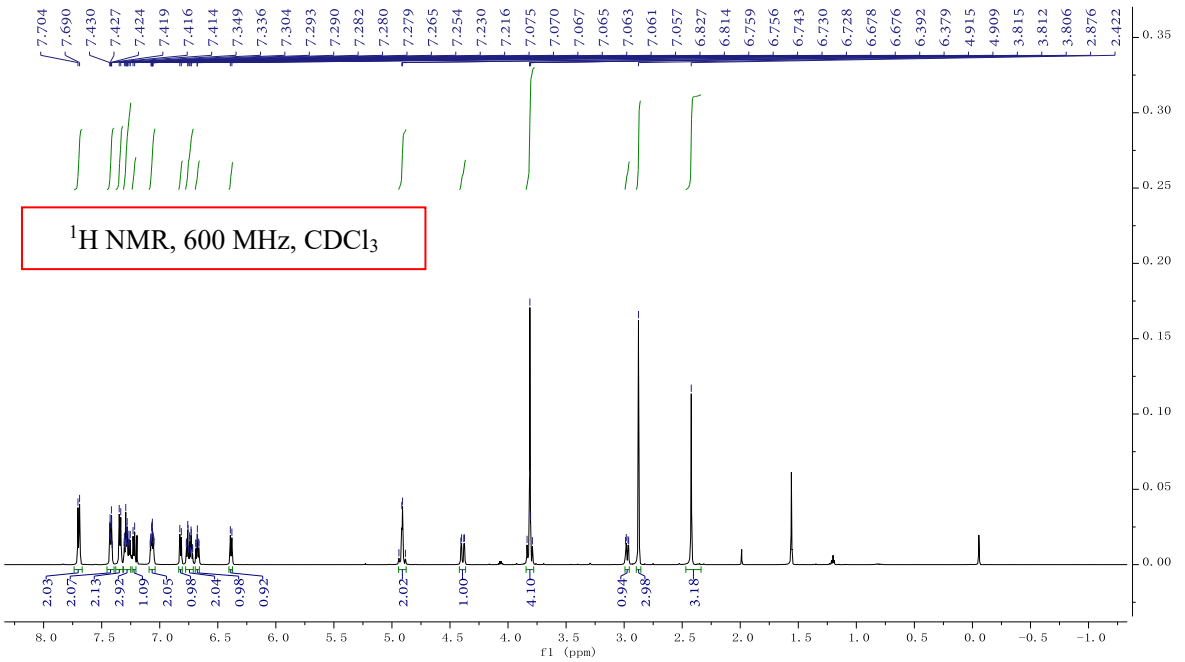
Peak Analysis Report

Detector A Channel 2 254nm

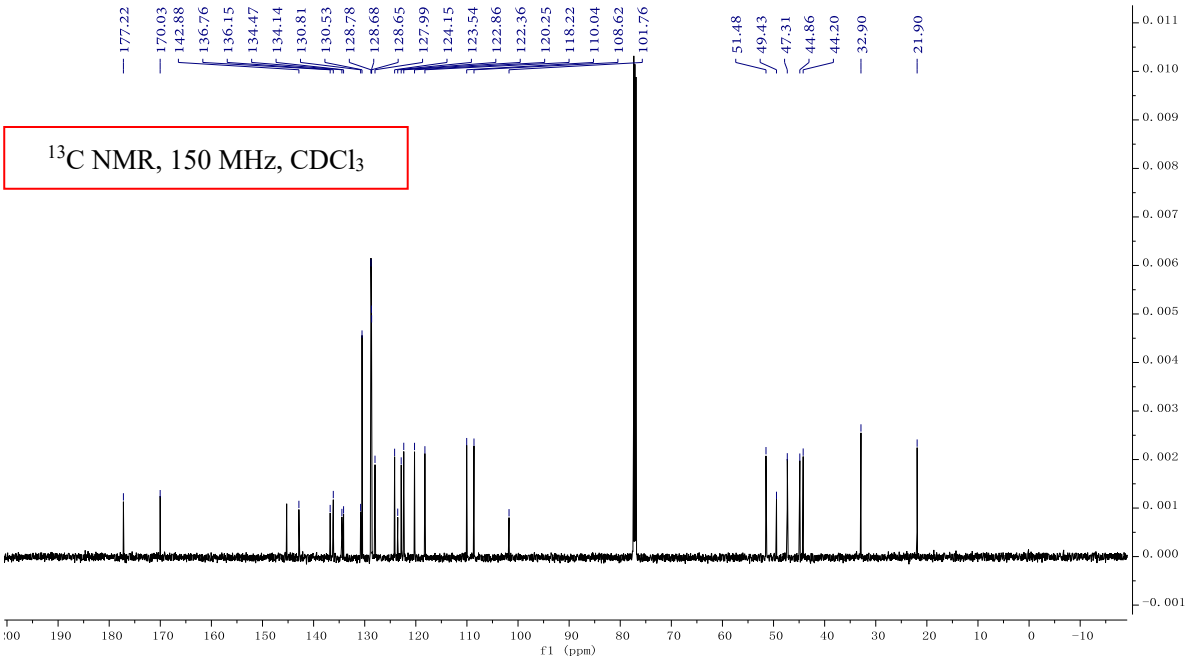
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	15.155	1671988	55738794	80.935
2	16.884	372581	13129928	19.065
Total		2044569	68868721	100.000



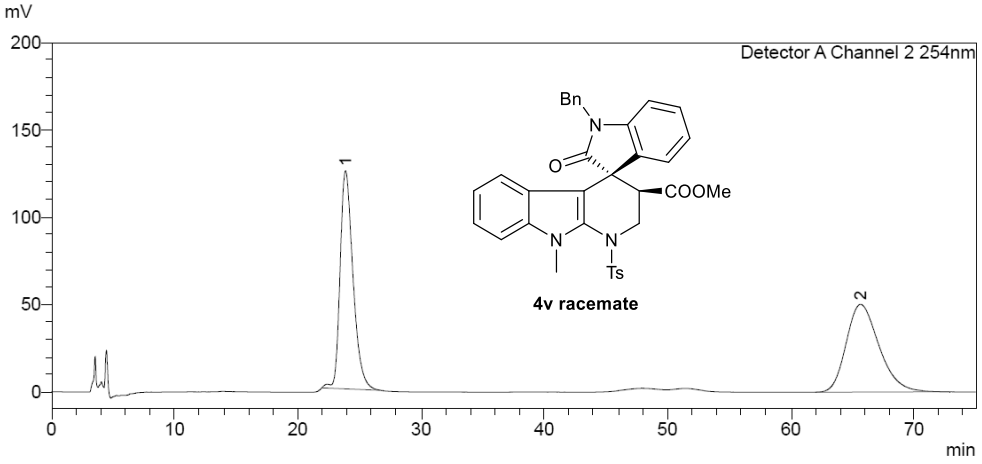
4v



^{1}H NMR, 600 MHz, $CDCl_3$



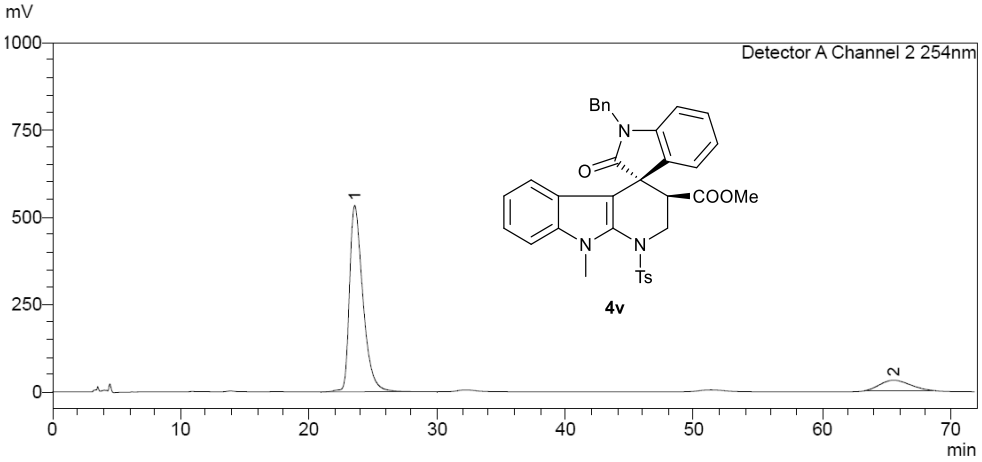
^{13}C NMR, 150 MHz, $CDCl_3$



Peak Analysis Report

Detector A Channel 2 254nm

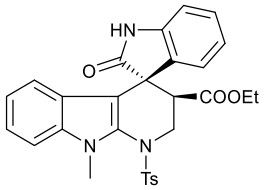
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	23.881	124901	9118471	49.444
2	65.666	50231	9323619	50.556
Total		175132	18442090	100.000



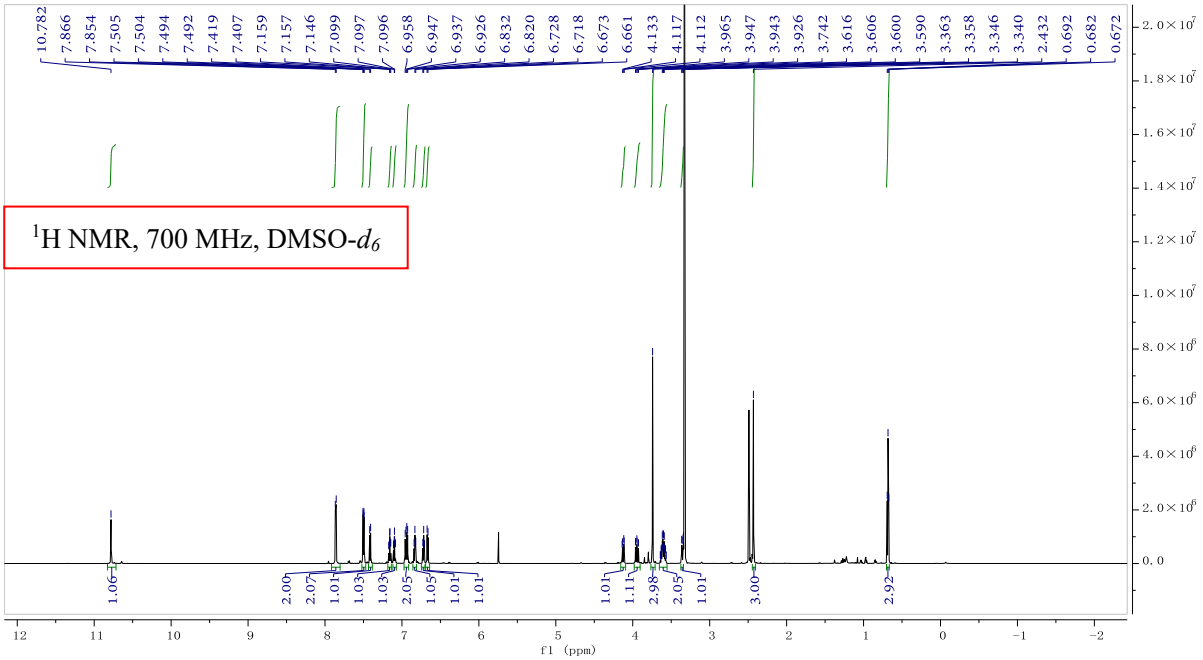
Peak Analysis Report

Detector A Channel 2 254nm

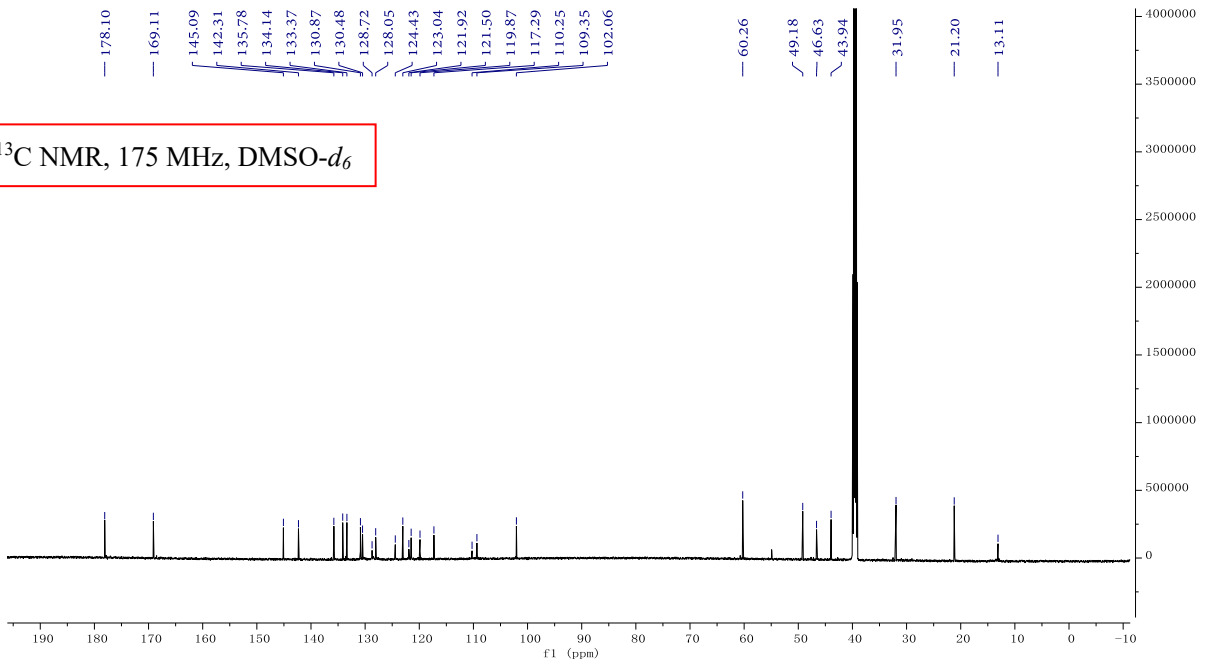
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	23.574	532845	38762150	93.941
2	65.542	20862	2500078	6.059
Total		553708	41262228	100.000



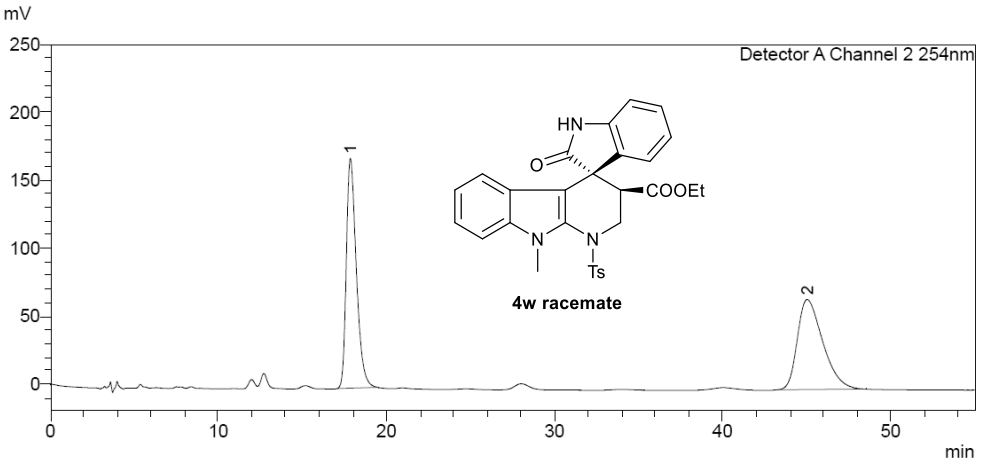
4w



^{1}H NMR, 700 MHz, DMSO-d_6



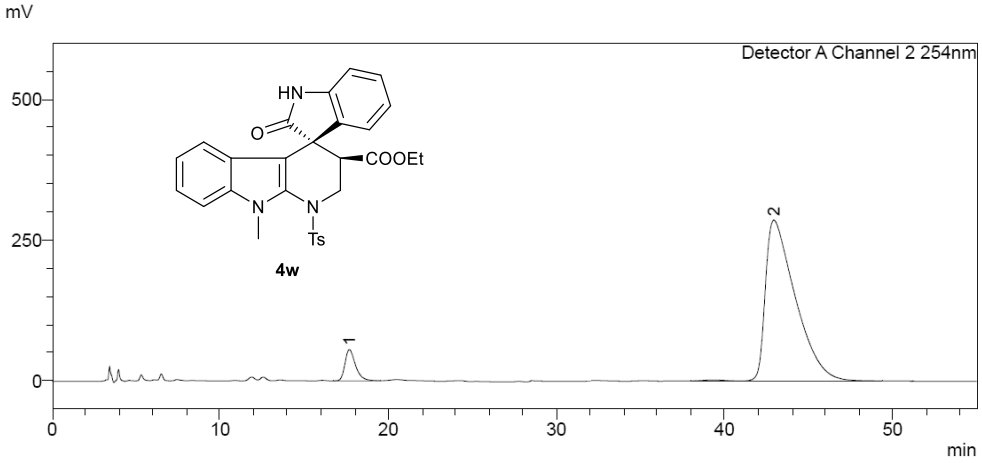
^{13}C NMR, 175 MHz, DMSO-d_6



Peak Analysis Report

Detector A Channel 2 254nm

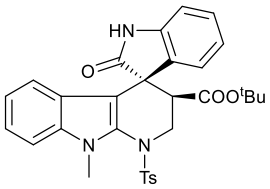
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	17.860	169162	6993421	50.062
2	45.046	66321	6976202	49.938
Total		235483	13969622	100.000



Peak Analysis Report

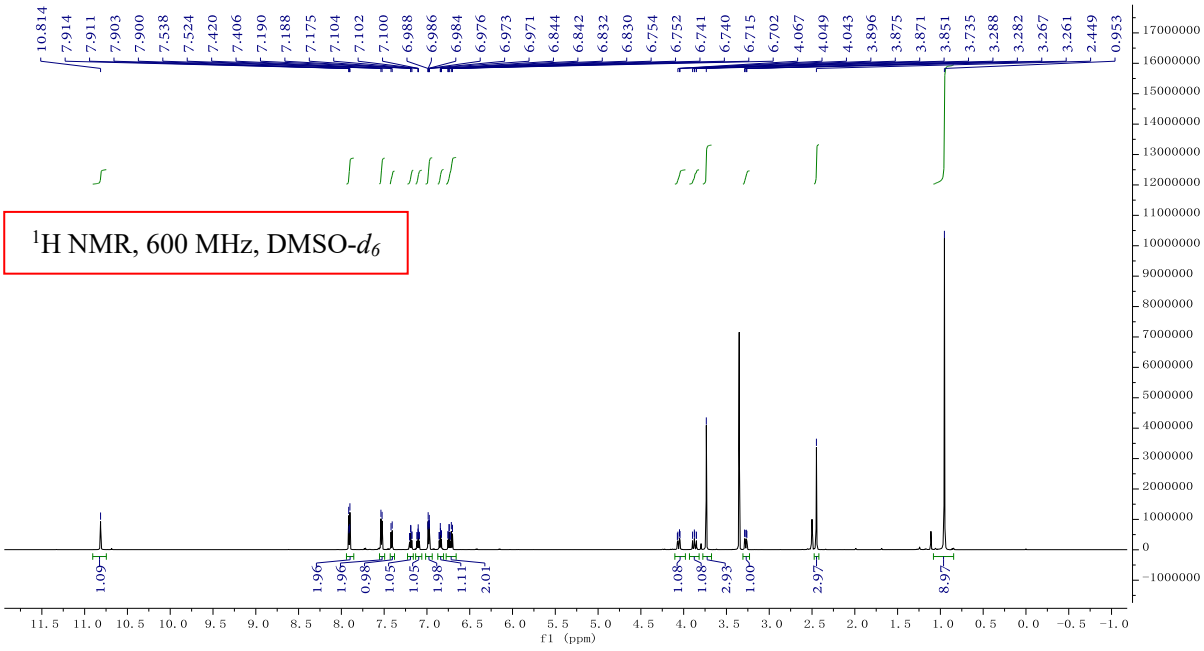
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	17.688	55506	2426366	6.424
2	42.943	285088	35341049	93.576
Total		340593	37767415	100.000

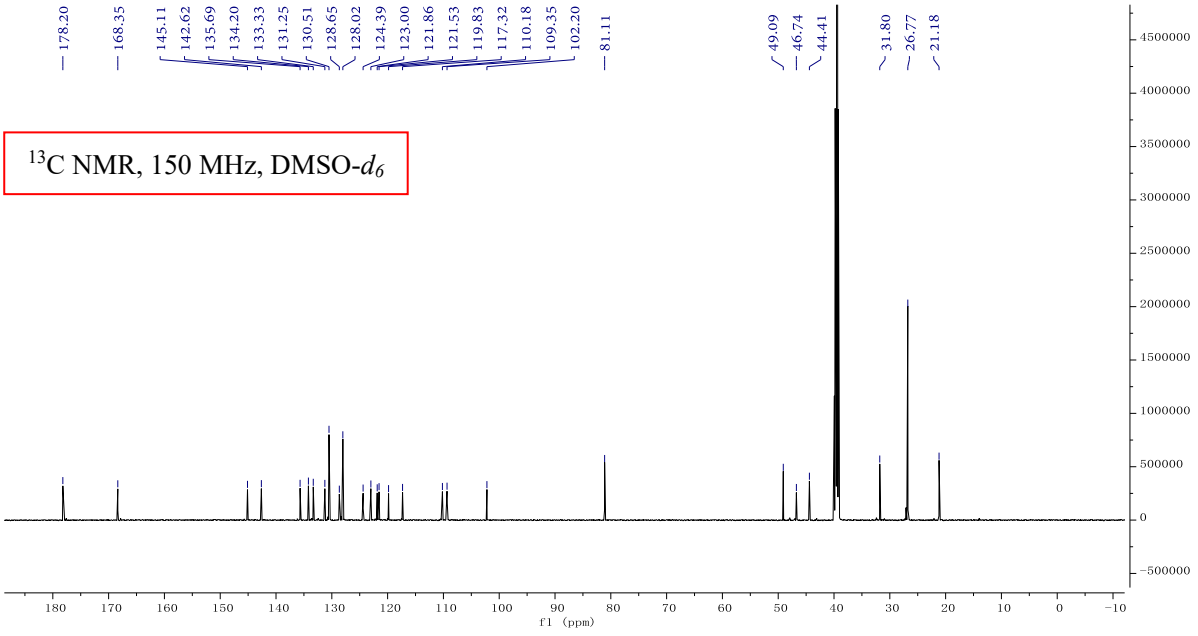


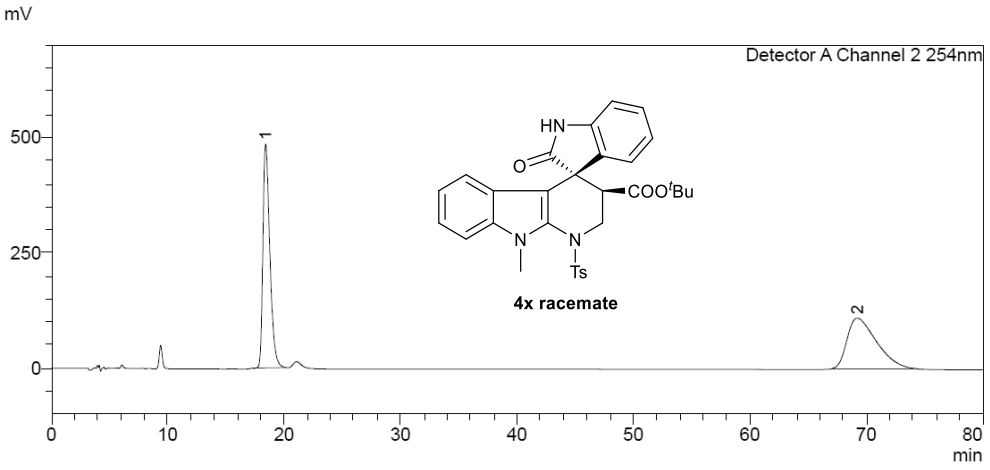
4x

^{1}H NMR, 600 MHz, DMSO-d_6



^{13}C NMR, 150 MHz, DMSO-d_6

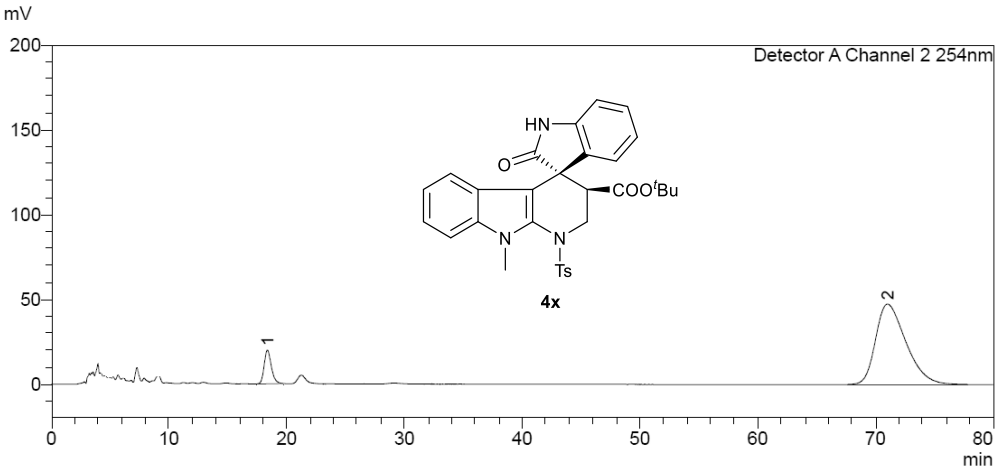




Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	18.419	484769	20006638	50.809
2	69.242	109741	19369261	49.191
Total		594510	39375899	100.000



Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	18.366	19820	836220	8.977
2	71.053	47364	8479333	91.023
Total		67183	9315553	100.000

5. Experimental procedures and results of bioassays

Cytotoxicity assay

The cytotoxic effects of synthesized compounds toward colorectal cancer cell lines were determined by the CCK-8 cell proliferation kit. In brief, SW620, SW480 and HCT116 cells were plated in 96-well microplates at a density of $5*10^3$ cells/well and incubated in a humidified atmosphere with 5% CO_2 at 37ºC for24h. Test compounds were determined in three independently repeated wells, and 0.1% DMSO was used as the control. After 48h of incubation, 10 μL of the CCK-8 solution was added to each well, followed by incubation for another two hours. Subsequently, the absorbance (OD) of each well was measured at 450nm on a Microplate reader. The inhibition ratios or IC_{50} values were determined. All experiments were repeated three times independently

Apoptosis assay

HCT116 cells ($1*10^5$ cells per well) were cultured in the six-well plates and exposed to the test compounds at the indicated concentration for 24 hours. The cells were harvested after trypsin digestion and washed twice by cold PBS. After centrifugation for 5 minutes at 2000g, the supernatant was removed and the cells were resuspended in 400 μL binding buffer, combined with 10 μL AnnexinV-FITC staining buffer and 10 μL of PI, and then incubated at room temperature for 15min in dark. The flow cytometry instrument was used to analyze the stained cells.

Autophagy assay

HCT116 cells were cultured in a six well plate and when the cell fusion rate reached 60-70%, adenovirus containing LC3-EGFP-mCherry plasmid was added for infection. After incubating with adenovirus for four hours, replaced the cells with fresh medium supplemented with 10%(v/v) FBS and cultured for another 48h to ensure the high efficiency of transfection. After transfection, the cells were incubated with 0.2 μmol/L compound 4h for 12h, and the fluorescent spots in the treated cells were then imaged by confocal laser scanning microscope. For the TEM (Transmission electronic microscopy) analysis, HCT116 cells ($1*10^5$ cells per well) were seeded in six-well plates and treated with or without compound 4h for 12h. Then cells were harvested and fixed 2 hours at room temperature in 2.5% glutaraldehyde in 0.1 mol/L PBS, and then post-fixed in 1% buffered osmiumtetroxide for 2h. Subsequently, specimens were examined under a transmission electronic microscope.

Western blotting

HCT116 cells were exposed to various concentration of compound 4h and collected after 24 hours. The cells were washed twice with ice cold PBS and scraped off by the cell scraper, incubated with lysis buffer on ice for 20 minutes. Then the lysates were centrifuged at 12,000g at 4ºC for 15min. The BCA protein assay reagents were employed to determine the protein concentration in the supernatant. Equal amounts of protein were resolved using SDS-PAGE and transferred to PVDF membrane. The PVDF membranes were blocked with 5% BSA （Dilute with TBST buffer） at room temperature. Then the PVDF membranes were gently rinsed with TBST buffer and incubated with specific primary antibodies against LC3, SQSTM1, caspase-3, Bax, Bcl-2, Cytochrome C, and GAPDH with gentle rotation overnight. Finally, the membranes were incubated with secondary antibodies for one hour at room temperature and then visualized using an ECL (Enhanced chemiluminescence) kit.

Table S1. Mean inhibitory ratio @1.0 μmol/L.[a]

Compd.	HCT116	SW620	SW480	Compd.	HCT116	SW620	SW480
4a	34.82	43.71	44.58	**4m**	39.56	41.82	30.52
4b	44.1	42.8	37.68	**4n**	32.21	40.18	20.72
4c	57.82	59.79	54.36	**4o**	39.72	42.8	38.2
4d	52.83	60.3	55.71	**4p**	38.82	30.19	39.24
4e	38.98	45.07	48.41	**4q**	33.04	34.41	26.38
4f	44.62	37.89	44.53	**4r**	37.84	31.47	34.23
4g	59.96	59.78	54.6	**4s**	29.04	30.17	38.65
4h	75.7	72.51	71.47	**4t**	20.9	33.19	37.96
***ent*-4h**	65.64	63.67	60.37	**4u**	29.77	34.42	37.54
4i	71.45	69.56	70.22	**4v**	8.16	11.59	16.71
4j	42.93	44.17	45.39	**4w**	12.21	13.41	13.65
4k	41.87	37.73	40.59	**4x**	9.6	11.24	13.68
4l	31.98	31.86	28.04				

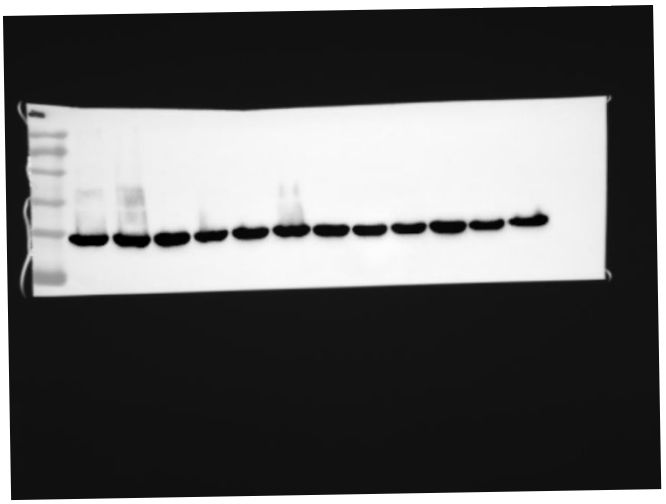
[a] Each compound was tested in triplicate; the data are presented as the mean values.

Table S2. In vitro antiproliferative activities of compound 4h in combination with autophagy inhibitors.[a]

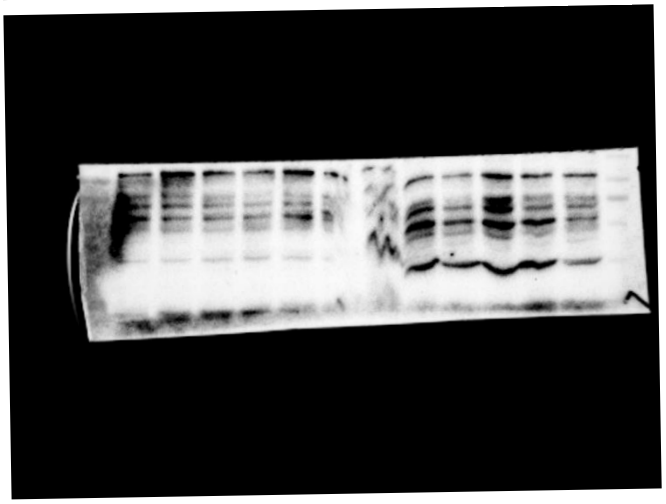
Compd.	HCT116 cell IC_{50} (μmol/L)
4h	0.857 ± 0.43
4h + **3-MA**	0.104 ± 0.056
4h + **HCQ**	0.101 ± 0.034
4h + **Wortmannin**	0.026 ± 0.007

[a] Each compound was tested in triplicate; the data are presented as the mean values.

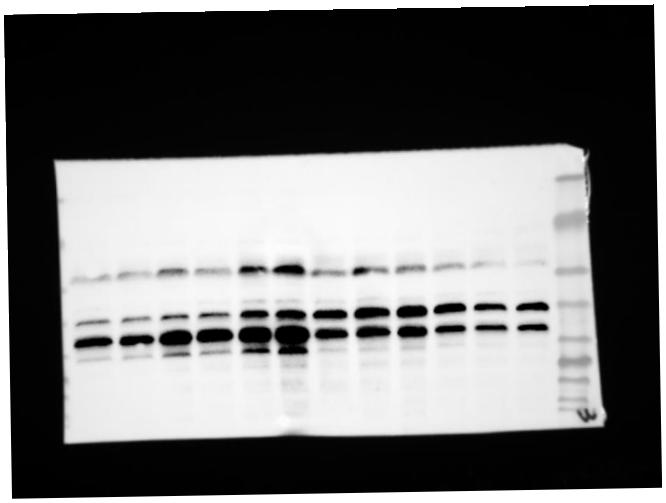
Raw images of Western blot



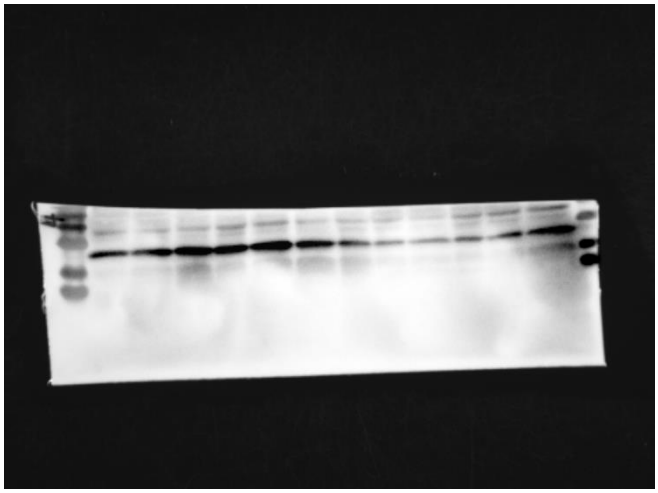
GAPDH



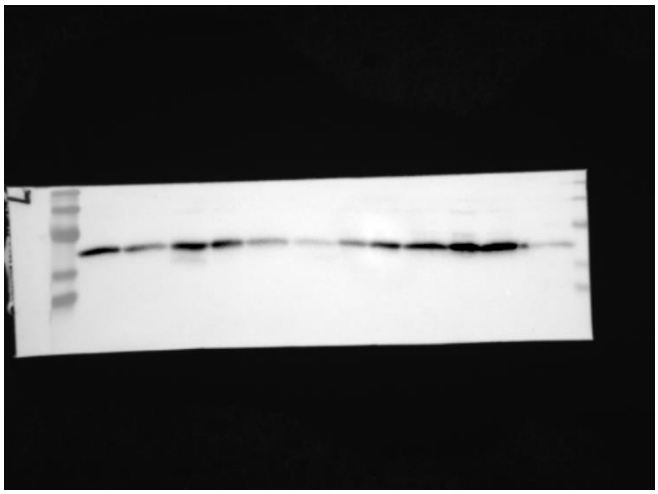
clev_caspase-3



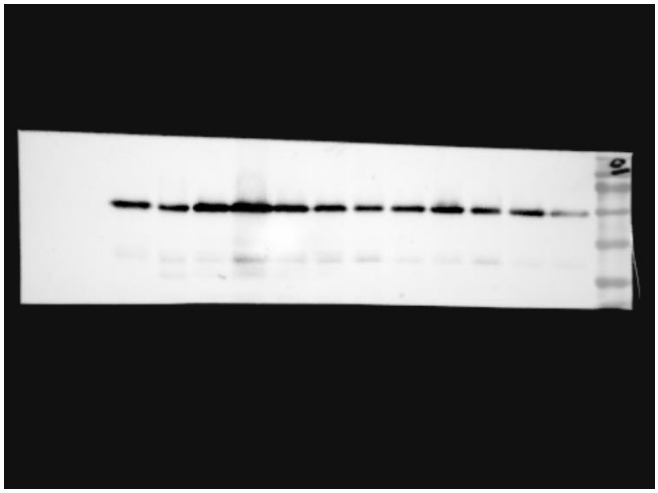
LC3



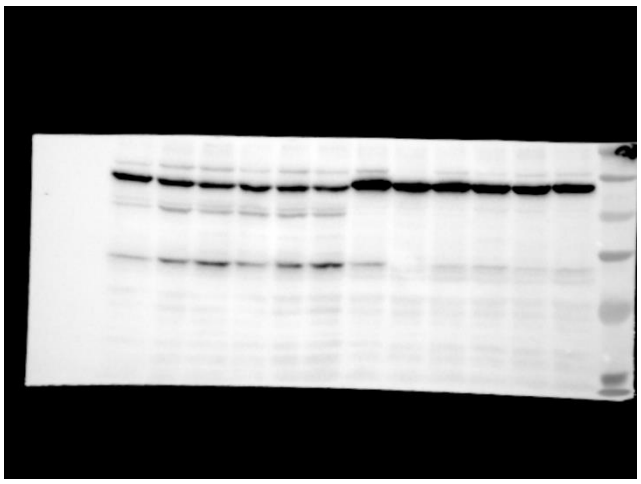
total_caspase-3



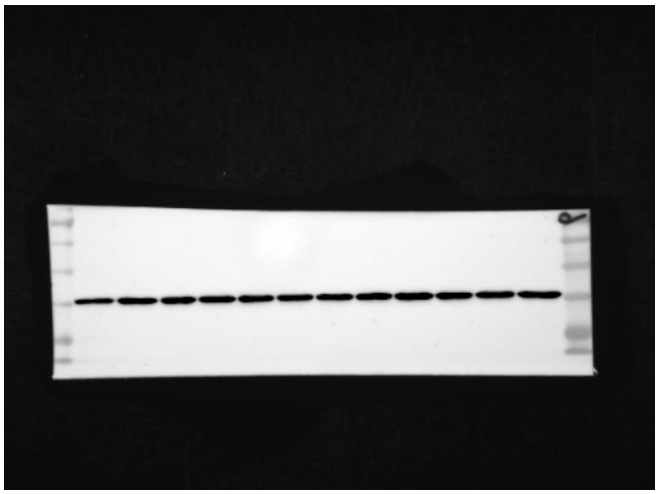
Cyto. C



SQSTM1



Bcl-2



GAPDH