Organocatalytic cascade reaction for asymmetric synthesis of novel chroman-fused spirooxindoles that potently inhibit cancer cell proliferation

Rui Zhou,†[a] Qinjie Wu,†[a] MingruiGuo,†[a] Wei Huang,[b] XianghongHe,[b] Lei Yang,[b] Fu Peng,[c]

Gu He*[a] and Bo Han*[b]

[a] *State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China. E-mail: hegu@scu.edu.cn*

[b] *State Key Laboratory Breeding Base of Systematic Research, Development and Utilization of Chinese Medicine Resources,School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China. E-mail: hanbo@cdutcm.edu.cn*

[c] *School of Chinese Medicine, University of Hong Kong, Hong Kong, China*

†These authors contributed equally to this work.

Supporting Information

Table of Contents

1. Experimental details

1.1 General methods for synthesis

NMR data was obtained for ^{1}H at 400 MHz, and for ^{13}C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2. In each case, enantiomeric ratio was determined by HPLC analysis on chiral column in comparison with authentic racemates, using a Daicel Chiralpak AD-H Column (250 x 4.6 mm) or Daicel Chiralpak OD-H Column (250 x 4.6 mm). UV detection was monitored at 254 nm. Optical rotation data were examined in $CHCl_3$ solution at 20 ℃. Column chromatography was performed on silica gel (300-400 mesh) eluting with ethyl acetate and petroleum ether.TLC was performed on glass-backed silica plates. UV light and I_2 were used to visualize products. Melting points were determined on a Mel-Temp apparatus and are uncorrected. All chemicals were used without purification as commercially available unless otherwise noted.

1.2 Cell culture and cellular proliferation assay

TheA549,HepG2, MCF-7, HCT116 and U87 human cancer cells were purchased from American Type Culture Collection (ATCC,Manassas, VA, U.S.A.). The cells were cultured in DMEM or RPMI-1640 medium (GIBCO, NY, U.S.A.) supplemented with 10 % fetal bovine serum (GE Healthcare, Hyclone Laboratories, Logan, Utah, U.S.A.), 100 μg/ml streptomycin, 100 IU/ml penicillin, and0.03 % L-glutamine and maintained at 37 ℃ with 5 % CO_2 in a humidified atmosphere.

Human cancer cells were dispensed in 96-well flat bottom microtiter plates at a density of $5\times10^{4}$to 1×10^{5}cells/mL. After 24 h incubation, they were treated with different concentrations of 5a-5n, 6a, 7a-7f and 8a for the indicated time periods. Cell viability was measured by the 3-(4,5-dimetrylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

1.3 Molecular docking of 7e to MDM2

The initialthree dimensional geometric coordinates of the X-ray crystal structure of MDM2 (PDB code: 4LWU) was downloaded from the Protein Data Bank (PDB)(http://www.pdb.org/pdb/home/home.do). In addition, we used Accelrys Discovery Studioversion 3.5 (Accelrys Inc., USA) with CHARMm force-field parameters to dock

pre-generatedconformations of 7e into its targets for testing the binding conformation of the complex.We performed flexible-ligand docking to a rigid receptor with grid-based scoring, in which 7e was allowed to be flexible and structurally rearranged in response to MDM2.

1.4 Imaging the p53-MDM2 interaction in cytoplasm by fluorescent probe

Human breast adenocarcinoma MCF-7 cells were plate on confocal dish and allowed to adhere for12-24 h. After the medium was removed, the cells werecarefully washed with culture medium without fetalbovine serum and then incubated at room temperature inthe presence of the p53-MDM2fluorescent probe for 25 min. The fluorescence imaging was performed by using Zeiss AxioObserver A1 fluorescence microscope and Zeiss LSM780confocal fluorescence microscope.

1.5 Cell cycle and apoptosis assay by Flow Cytometry (FCM) and fluorescent microscopy

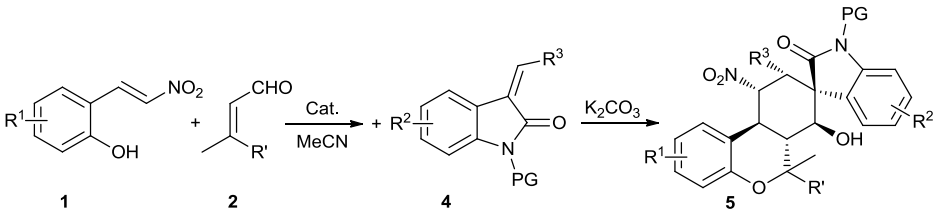
After incubation with 7e for 24 h, the cells were stained with PI at 37 ℃ for 30 min, and then the morphology was observed by a fluorescencemicroscopy (Olympus, Tokyo, Japan).Annexin V/PI dual staining assay was employed to determine the involvement ofapoptosis in 7e-induced cell death, using Annexin-V-FLUOS Staining Kit (Roche) as themanufacturer's instructions. In the caspase-dependent assay, pan-caspase inhibitor Z-VAD-FMK (5 μM) was added to MCF-7 cells 2 h before 7e treatment.

1.6 Western blot analysis

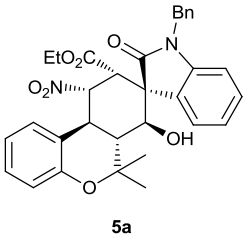
Antibodies against caspase-3, MDM2, β-actin andHRP-conjugated secondary antibodies were purchased from Santa Cruz Biotechnology (SantaCruz, CA, U.S.A.). Antibodies against p21 and p53 were purchased from Cell Signaling Technology (CST, Beverly, MA, U.S.A.).The MCF-7 cells were harvested, washed twice with cold PBS and then lysed incell lysis buffer, supplemented with the proteinase inhibitors 100 ug/mL at 4 ℃ for 1 h. After12,000 g centrifugation at 4 ℃ for 10 min, the protein concentration was determined by aBCA Protein Assay Kit (CWBIO, Beijing, China). Equal amounts of total proteins wereseparated by 12% SDS-PAGE, and transferred onto Immobilon-P Transfer Membrane(Millipore Corporation, Billerica, MA, USA). The membranes were blocked with 5 % skimmedmilk at room temperature for 1 h, incubated with indicated primary antibodies at 4 ℃overnight and horseradish peroxidase (HRP)-conjugated secondary antibody at roomtemperature for 2 h, then visualized by using ECL reagents.

2. General procedure for the asymmetric synthesis of chroman-fused spirooxindoles

2.1 Procedure for the asymmetric synthesis of 5

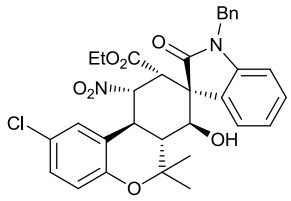


To a solution of 2-nitrovinyl phenol**1** (0.5 mmol) andβ,β-disubstitutedenal**2** (0.5 mmol) in 2 mL of acetonitrile was added 10 mol% of catalyst and AcOH subsequently. The reaction was stirred at 0 ^{o}C for 3-4 hours, After which olefinicoxindole**4** (0.4 mmol) was added followed by the addition of 0.2 mmol of K_2CO_3 in 0.4 mL of water. The reaction was kept in 0 ^{o}C for another 3 hours. Then water was added and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by silica-gel chromatographyto give chroman-fused spirooxindole**5**.



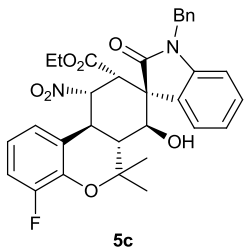
5a

Compound **5a** was obtained as white solidin 64% yield for two steps after flash chromatography. The dr value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 7.9 min, t_{minor} = 11.0 min. m.p. 214.2-215.8^{o}C, $[\alpha]_D^{20}$ = +151.5 (C=0.068, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.22 (m, 7H), 7.21 - 7.15 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.97 - 6.89 (m, 3H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.36(dd, *J* = 11.6, 5.6 Hz, 1H), 5.24 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.16 (m, 2H), 3.96 (t, *J* = 12.0 Hz, 1H), 3.56 (d, *J* = 5.6 Hz, 1H), 2.59 (dd, *J* = 12.2, 10.8 Hz, 1H), 1.68 (s, 3H), 1.42 (s, 3H), 1.39 (d, *J* = 4.8 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.24, 168.68, 153.76, 143.74, 135.06, 129.96, 129.21, 128.92, 128.03, 127.83, 127.15, 127.09, 123.79, 123.31, 121.99, 121.75, 118.43, 109.86, 82.50, 80.94, 69.83, 62.25, 54.54, 50.19, 47.42, 43.94, 33.62, 31.25, 23.40, 13.89. HRMS (ESI-TOF) calcd for $C_{32}H_{32}N_2NaO_7^+$ $[M+Na]^+$579.2102, found 579.2101.



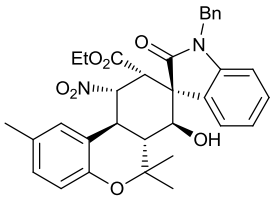
5b

Compound **5b** was obtained as white solid in 60% yield for two steps after flash chromatography. The dr value was calculated to be 88:12 by ^{1}H NMR analysis of the crude reaction mixture andthe enantiomeric excess was determined to be 99% by HPLC on Chiralpak OD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 16.3 min, t_{minor} = 10.0 min. m.p. 215.6-218.9 ^{o}C, $[\alpha]_D^{20}$ = +113.3 (C=0.060, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.22 (m, 7H), 7.15 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.92 - 6.82 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.31 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.23 (dd, *J* = 10.4, 4.4 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.23 - 4.10 (m, 2H), 3.93 (t, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 5.6 Hz, 1H), 2.60 - 2.51 (m, 1H), 1.67 (s, 3H), 1.46 - 1.36 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.16, 168.62, 152.41, 143.72, 134.98, 131.10, 130.06, 128.94, 128.05, 127.87, 127.17, 126.84, 126.78, 123.71, 123.36, 122.33, 119.68, 109.94, 82.03, 81.54, 69.64, 62.33, 54.42, 50.01, 47.18, 43.97, 33.67, 31.13, 23.33, 13.87. HRMS (ESI-TOF) calcd for $C_{32}H_{31}ClN_2NaO_7^+$ $[M+Na]^+$613.1712, found 613.1713.



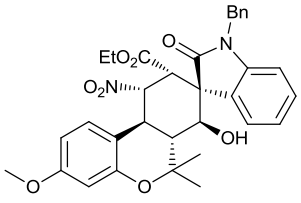
5c

Compound **5c** was obtained as white solid in 62% yield for two steps after flash chromatography. The dr value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254 nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 7.8 min, t_{minor} = 12.1 min. m.p. 191.3-193.0 ^{o}C, $[\alpha]_D^{20}$ = +100.9 (C = 0.114, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.22 (m, 7H), 7.10 - 6.98 (m, 3H), 6.91 - 6.83 (m, 1H), 6.73 (dd, *J* = 16.5, 7.8 Hz, 2H), 6.35 (dd, *J* = 11.7, 5.6 Hz, 1H), 5.25 (dd, *J* = 10.6, 4.7 Hz, 1H), 5.04 (d, *J* = 15.7 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 4.16 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.98 (t, *J* = 11.9 Hz, 1H), 3.56 (d, *J* = 5.6 Hz, 1H), 2.61 (dd, *J* = 12.0, 10.8 Hz, 1H), 1.73 (s, 3H), 1.49 - 1.42 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.21, 168.64, 152.83 (J_{CF} = 220 Hz), 143.73, 141.49, 141.43 (J_{CF} = 12 Hz), 135.00, 132.23, 130.07, 128.88 (J_{CF} = 15 Hz), 127.88, 127.03 (J_{CF} = 24 Hz), 123.77, 123.39, 121.60, 121.53, 117.24, 114.99 (J_{CF} = 18 Hz), 109.95, 82.33, 69.66, 62.34, 54.46, 50.10, 47.36, 43.97, 33.80, 31.35, 23.25, 13.89. HRMS (ESI-TOF) calcd for $C_{32}H_{31}FN_2NaO_7^+$ $[M+Na]^+$ 597.2008, found 597.2005.



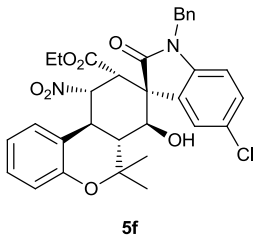
5d

Compound **5d** was obtained as white solid in 52% yield for two steps after flash chromatography. The dr value was calculated to be 92:8 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak OD-H column at 254nm (Hexane/isopropanol = 95/5, 1 mL/min), t_{major} =26.8 min, t_{minor} = 16.2 min. m.p. 121.2-123.1^{o}C, $[\alpha]_D^{20}$ = +109.5 (C = 0.116, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.21 (m, 7H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.77 - 6.68 (m, 2H), 6.35 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.24 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.23 - 4.09 (m, 2H), 3.92 (t, *J* = 12.0 Hz, 1H), 3.56 (d, *J* = 5.6 Hz, 1H), 2.59 - 2.47 (m, 1H), 2.26 (s, 3H), 1.66 (s, 3H), 1.45 - 1.32 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.28, 168.67, 151.42, 143.74, 135.09, 131.12 , 129.96, 129.46, 128.94, 128.42, 127.84, 127.16, 127.14, 123.80, 123.32, 122.45, 118.22, 109.85, 82.40, 80.77, 69.87, 62.24, 54.56, 50.20, 47.69, 43.94, 33.60, 31.10, 23.43, 21.11, 13.89. HRMS (ESI-TOF) calcdfor $C_{33}H_{34}N_2NaO_7^+$[M+Na]$^+$593.2258, found 593.2263.



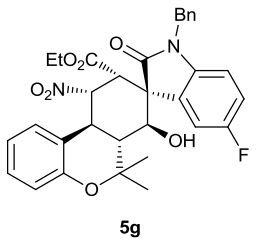
5e

Compound **5e** was obtained as white solid in 50% yield for two steps after flash chromatography. The dr value was calculated to be 92:8 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 13.7 min, t_{minor} = 15.8 min. m.p.112.7-115.3 ^{o}C, $[\alpha]_D^{20}$ = +94.1 (C = 0.136, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.17 (m, 7H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.54 - 6.42 (m, 2H), 6.29 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.20 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.15 (qd, *J* = 7.2, 3.6 Hz, 2H), 3.93 (t, *J* = 12.0 Hz, 1H), 3.76 (s, 3H), 3.52 (d, *J* = 5.6 Hz, 1H), 2.67 - 2.55 (m, 1H), 1.65 (s, 3H), 1.49 - 1.38 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.26, 168.73, 159.73, 154.75, 143.75, 135.09, 129.95, 128.93, 127.83, 127.17, 127.11, 123.83, 123.30, 122.70, 120.59, 109.85, 107.21, 104.17, 82.95, 80.95, 69.81, 62.23, 55.35, 54.58, 50.23, 47.26, 43.94, 33.14, 31.33, 23.23, 13.89. HRMS (ESI-TOF) calcd for $C_{33}H_{34}N_2NaO_8^+$[M+Na]$^+$ 609.2207, found 609.2211.



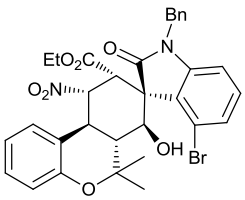
5f

Compound **5f** was obtained as white solid in 62% yield for two steps after flash chromatography. The dr value was calculated to be 88:12 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 98/2, 1 mL/min), t_{major} = 40.1 min, t_{minor} = 45.2 min. m.p. 257.8-258.2 ^{o}C, $[\alpha]_D^{20}$ = +98.1 (C = 0.054, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.38 - 7.13 (m, 8H), 6.98 - 6.87 (m, 3H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.30 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.22 (dd, *J* = 10.4, 4.8 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 15.6 Hz, 1H), 4.31 - 4.07 (m, 2H), 3.95 (t, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 5.6 Hz, 1H), 2.70 - 2.46 (m, 1H), 1.68 (s, 3H), 1.49 - 1.37 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.82, 168.62, 153.72, 142.23, 134.59, 129.84, 129.03, 128.98, 128.94, 128.78, 128.14, 128.01, 127.10, 124.47, 121.99, 121.79, 118.48, 110.80, 82.39, 80.80, 69.84, 62.54, 54.79, 50.01, 47.51, 44.06, 33.60, 31.29, 23.44, 13.95. HRMS (ESI-TOF) calcd for $C_{32}H_{31}ClN_2NaO_7^+$[M+Na]$^+$613.1712, found 613.1711.



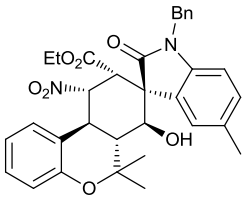
5g

Compound **5g** was obtained as white solid in 65% yield for two steps after flash chromatography. The dr value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and The enantiomeric excess was determined to be 97% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 95/5, 1 mL/min), t_{major} = 14.5 min, t_{minor} = 15.8 min. m.p. 251.6-252.4 ^{o}C, $[\alpha]_D^{20}$ = +129.2 (C = 0.072, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.23 (m, 5H), 7.22 - 7.16 (m, 1H), 7.07 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.99 - 6.89 (m, 4H), 6.65 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.33 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.23 (dd, *J* = 10.8, 5.2 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.92 (t, *J* = 12.0 Hz, 1H), 3.55 (d, *J* = 5.6 Hz, 1H), 2.58 (dd, *J* = 12.0, 10.8 Hz, 1H), 1.67 (s, 3H), 1.46 - 1.36 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.09, 171.46, 160.24, 157.85, 154.56, 137.63, 130.99, 130.92, 127.64, 122.30, 121.89, 118.73, 115.95, 115.71, 110.60, 110.53, 81.44, 61.08, 56.26, 55.39, 49.04, 31.31, 29.71, 23.08, 14.25. HRMS (ESI-TOF) calcd for $C_{32}H_{31}FN_2NaO_7^+$[M+Na]$^+$ 597.2008, found 597.2021.



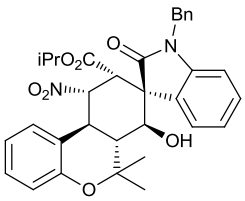
5h

Compound **5h** was obtained as white solid in 58% yield for two steps after flash chromatography. The dr value was calculated to be 85:15 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 29.8 min, t_{minor} = 16.4 min. m.p. 118.5-122.3 ^{o}C, $[\alpha]_D^{20}$ = -96.0 (C = 0.076, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.19 (m, 7H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.00 (dd, *J* = 9.6, 8.0 Hz, 1H), 5.15 - 5.04 (m, 2H), 4.77 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.51 (dd, *J* = 13.6, 7.6 Hz, 1H), 3.88 (m, 2H), 3.15 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.25 (d, *J*= 11.2 Hz, 1H), 1.63 (s, 3H), 1.30 (s, 3H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.06, 169.15, 154.07, 145.24, 134.75, 130.75, 128.96, 128.91, 128.68, 127.97, 127.90, 127.41, 127.16, 120.90, 120.23, 118.79, 118.20, 108.84, 86.84, 76.97, 69.91, 61.92, 57.40, 46.56, 44.45, 43.57, 31.50, 26.90, 21.98, 13.49. HRMS (ESI-TOF) calcd for $C_{32}H_{31}BrN_2NaO_7^+$[M+Na]$^+$ 657.1207, found 657.1205.



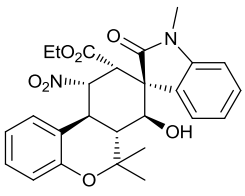
5i

Compound **5i** was obtained as white solid in 60% yield for two steps after flash chromatography. The dr value was calculated to be 92:8 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 6.6 min, t_{minor} = 7.4 min. m.p. 159.3-162.1 ^{o}C, $[\alpha]_D^{20}$ = +93.5 (C = 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.20 (m, 7H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.77 - 6.69 (m, 2H), 6.35 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.24 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.21 - 4.10 (m, 2H), 3.92 (t, *J* = 12.0 Hz, 1H), 3.56 (d, *J* = 5.6 Hz, 1H), 2.65 - 2.46 (m, 1H), 2.26 (s, 3H), 1.66 (s, 3H), 1.44 - 1.33 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.28, 168.67, 151.42, 143.74, 135.09, 131.12, 129.96, 129.46, 128.94, 128.42, 127.84, 127.16, 127.14, 123.80, 123.32, 122.45, 118.22, 109.85, 82.40, 80.77, 69.87, 62.24, 54.56, 50.20, 47.69, 43.94, 33.60, 31.10, 23.43, 21.11, 13.89. HRMS (ESI-TOF) calcd for $C_{33}H_{34}N_2NaO_7^+$[M+Na]$^+$ 593.2258, found 593.2260.



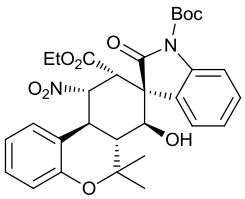
5j

Compound **5j** was obtained as white solid in 66% yield for two steps after flash chromatography. The dr value was calculated to be 93:7 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 92/8, 1 mL/min), t_{major} = 7.6 min, t_{minor} = 16.0 min. m.p. 224.0-226.2 ^{o}C, $[\alpha]_D^{20}$ = +123.5 (C = 0.098, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.24 (m, 7H), 7.24 - 7.18 (m, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.00 - 6.91 (m, 3H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.36 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.28 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.16 - 5.02 (m, 2H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.99 (t, *J* = 12.0 Hz, 1H), 3.53 (d, *J* = 5.6 Hz, 1H), 2.61 (dd, *J* = 12.0, 10.8 Hz, 1H), 1.70 (s, 3H), 1.45 (s, 3H), 1.41 (d, *J* = 4.8 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.30, 168.22, 153.77, 143.74, 135.11, 129.98, 129.31, 128.94, 128.02, 127.84, 127.19, 127.07, 123.94, 123.19, 122.01, 121.75, 118.42, 109.84, 82.43, 80.99, 70.40, 69.82, 54.57, 50.09, 47.40, 43.95, 33.59, 31.27, 23.44, 21.74, 21.37. HRMS (ESI-TOF) calcd for $C_{33}H_{34}N_2NaO_7^+$[M+Na]$^+$ 593.2258, found 593.2261.



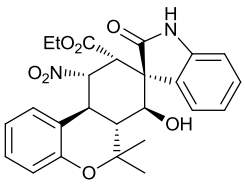
5k

Compound **5k** was obtained as white solid in 58% yield for two steps after flash chromatography. The dr value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 95/5, 1 mL/min), t_{major} = 17.8 min, t_{minor} = 21.4 min.m.p. 178.2-181.4 ^{o}C, $[\alpha]_D^{20}$ = +107.3 (C = 0.082, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.6 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.21 - 7.15 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 16.0, 8.0 Hz, 4H), 6.27 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.20 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.93 (t, *J* = 12.0 Hz, 1H), 3.50 (d, *J* = 5.6 Hz, 1H), 3.20 (s, 3H), 2.52 (dd, *J* = 12.0, 10.8 Hz, 1H), 1.65 (s, 3H), 1.39 - 1.33 (m, 4H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.01, 168.69, 153.74, 144.60, 130.11, 129.16, 128.04, 127.00, 123.73, 123.33, 122.01, 121.77, 118.41, 108.85, 82.44, 80.91, 69.56, 62.21, 54.50, 50.11, 47.43, 33.57, 31.25, 26.44, 23.35, 13.90. HRMS (ESI-TOF) calcd for $C_{26}H_{28}N_2NaO_7^+$[M+Na]$^+$ 503.1789, found 503.1790.



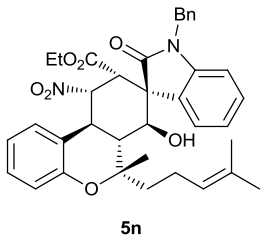
5l

Compound **5l** was obtained as white solid in 68% yield for two steps after flash chromatography. The dr value was calculated to be 92:8 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 95/5, 1 mL/min), t_{major} = 7.5 min, t_{minor} = 42.8 min.m.p. 178.2-181.4 ^{o}C, $[\alpha]_D^{20}$ = +111.8 (C = 0.068, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.45 - 7.38 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 13.2, 6.8 Hz, 2H), 6.98 - 6.84 (m, 3H), 6.14 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.15 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.96 (t, *J* = 12.0 Hz, 1H), 3.61 (d, *J* = 5.6 Hz, 1H), 2.51 (dd, *J* = 12.0, 10.8 Hz, 1H), 1.66 (s, 3H), 1.64 (s, 9H), 1.44 (d, *J* = 5.2 Hz, 1H), 1.40 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.44, 168.34, 153.72, 148.60, 140.84, 130.29, 128.83, 128.13, 125.96, 125.11, 123.44, 122.11, 121.67, 118.41, 115.59, 85.45, 82.54, 80.87, 70.14, 62.37, 54.82, 50.35, 47.31, 33.47, 31.25, 28.08, 23.36, 13.84. HRMS (ESI-TOF) calcd for $C_{30}H_{34}N_2NaO_9^+$[M+Na]$^+$ 589.2157, found 589.2151.



5m

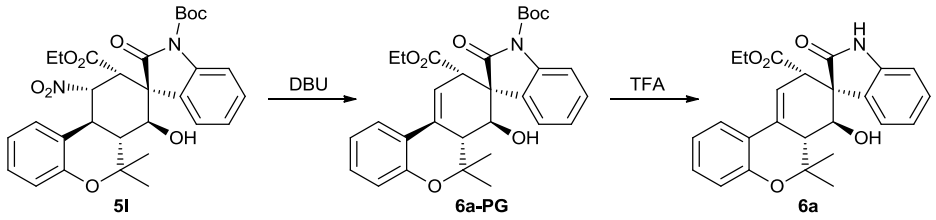
Compound **5m** was obtained by deprotection of compound **5l** with 25% CF_3COOH in DCM as white solid in 94% yield. The enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 93/7, 1 mL/min), t_{major} = 35.1 min, t_{minor} = 32.4 min. m.p. 208.5 - 210.2 ^{o}C, $[\alpha]_D^{20}$ = +188.5 (C = 0.076, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.31 - 7.23 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.97 - 6.86 (m, 3H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.18 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.19 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.20 - 4.10 (m, 2H), 3.93 (t, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 5.6 Hz, 1H), 2.55 - 2.41 (m, 1H), 1.76 (s, 1H), 1.65 (s, 3H), 1.37 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 176.89, 168.55, 153.73, 141.52, 130.04, 128.83, 128.08, 127.60, 124.09, 123.29, 122.00, 121.67, 118.43, 110.32, 82.47, 80.79, 69.63, 62.24, 54.87, 49.98, 47.36, 33.55, 31.27, 23.27, 13.85.HRMS (ESI-TOF) calcd for $C_{25}H_{26}N_2NaO_7^+$ [M+Na]$^+$ 489.1632, found 489.1636.



5n

Compound **5n** was obtained as white solid in 48% yield for two steps after flash chromatography. The dr value was calculated to be 88:12 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak OD-H column at 254nm (Hexane/isopropanol = 95/5, 1 mL/min), t_{major} = 26.0 min, t_{minor} = 11.7 min. m.p. 83.5-85.3 ^{o}C, $[\alpha]_D^{20}$ = +123.9 (C = 0.046, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.15 (m, 8H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.97 - 6.88 (m, 3H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.36 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.27 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.10 - 5.00 (m, 2H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.15 (m, 2H), 3.97 (t, *J* = 12.0 Hz, 1H), 3.56 (d, *J* = 5.6 Hz, 1H), 2.75 - 2.60 (m, 1H), 2.33 - 2.19 (m, 1H), 2.11 - 1.99 (m, 1H), 1.92 - 1.78 (m, 1H), 1.66 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.40 (d, *J* = 4.8 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 175.19, 168.72, 154.25, 143.75, 135.09, 131.45, 129.96, 129.00, 128.93, 128.09, 127.82, 127.17, 127.10, 124.42, 123.76, 123.29, 122.01, 121.60, 118.15, 109.87, 82.88, 82.54, 69.78, 62.26, 54.54, 50.17, 46.11, 43.93, 43.36, 33.40, 25.69, 22.11, 21.37, 17.57, 13.90.HRMS (ESI-TOF) calcd for $C_{37}H_{40}N_2NaO_7^+$ $[M+Na]^+$ 647.2728, found 647.2733.

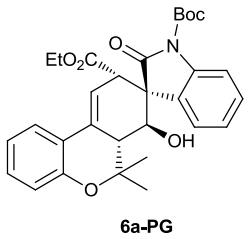
2.2 Procedure for the synthesis of compound 6a



5l 6a-PG 6a

To a solution of compound **5l** (113.2 mg, 0.2 mmol) in 1 mL of DMF was added 15.2 mg of DBU (0.1 mmol) and heated at 60 ^{o}C for 4 hours. The reaction mixture was cooled to room temperature before the addition of water, then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by silica-gel chromatography to afford the elimination product **6a-PG** (41.5 mg, 40% yield). **6a-PG** (31mg, 0.06 mmol) was subsequently dissolved in a mixture of 25% TFA in DCM (2 mL) and stirred for 30 min. The solvent was then distilled under reduced pressure. The residue was added to saturated $NaHCO_3$ and extracted with DCM. The organic layer was washed with saturated $NaHCO_3$ and saline then dried over anhydrous Na_2SO_4. The solvent was distilled under reduced pressure to afforded compound **6a** (23.9 mg, 38%

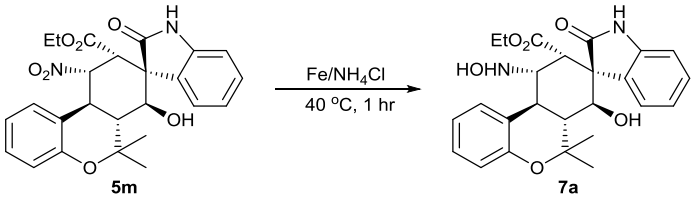
two-step yield) as white solid. The enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254 nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 15.8 min, t_{minor} = 9.4 min. m.p. 142.5-144.3 °C, $[\alpha]_D^{20}$ = -76.2 (C = 0.042, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (brs, 1H), 7.89 (s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.30 - 7.23 (m, 1H), 7.21 - 7.10 (m, 2H), 7.06 - 6.90 (m, 3H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 4.04 - 3.92 (m, 2H), 3.91 - 3.80 (m, 1H), 2.82 (d, *J* = 12.0 Hz, 1H), 2.01 (s, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.86, 165.64, 153.39, 146.71, 141.82, 130.06, 128.96, 128.30, 127.82, 126.51, 124.76, 122.30, 121.65, 120.13, 117.85, 110.27, 67.54, 60.72, 57.49, 43.21, 30.95, 29.03, 27.36, 22.60, 13.64.HRMS (ESI-TOF) calcd for $C_{25}H_{25}NNaO_5^+$[M+Na]$^+$ 442.1625, found 442.1627.



6a-PG

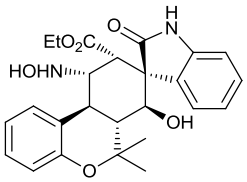
Compound **6a-PG** was obtained as white solid, m.p. 186.5-187.8 °C, $[\alpha]_D^{20}$ = -50.9 (C = 0.112, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.42 - 7.34 (m, 1H), 7.21 - 7.10 (m, 3H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.98 (s, 1H), 3.88 (qd, *J* = 7.2, 2.8 Hz, 2H), 2.78 (d, *J* = 12.0 Hz, 1H), 1.89 (d, *J* = 1.6 Hz, 1H), 1.63 (s, 9H), 1.45 (s, 3H), 1.35 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.63, 165.34, 153.37, 149.35, 147.15, 140.58, 129.23, 128.33, 128.23, 127.92, 126.48, 124.38, 124.25, 121.43, 120.18, 117.91, 115.41, 84.46, 67.56, 60.87, 57.09, 43.21, 30.97, 28.97, 28.11, 27.29, 22.62, 13.54. HRMS (ESI-TOF) calcd for $C_{30}H_{33}NNaO_7^+$[M+Na]$^+$ 542.2149, found 542.2152.

2.3 Procedure for the synthesis of compound 7



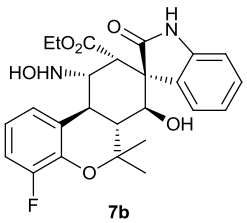
To a suspension of compound **5m** (46.6 mg, 0.1 mmol) and Fe powder (28mg, 0.5 mmol) in 3 mL of ethanol was added NH_4Cl (13.5 mg, 0.25 mmol) in 1 mL of water. The reaction mixture was heated at 40 °C for 1 hour, then filtrated. The filtrate was diluted with ethyl acetate and washed with saturated $NaHCO_3$, then saline. The organic layer was dried over anhydrous $NaSO_4$ and concentrated. The residue was purified by silica-gel chromatography to afford compound **7a** (29.8

mg, 66% yield). Compound **7b** - **7f** was synthesized following the same procedure using related substrate.



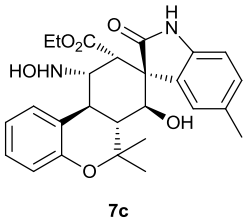
7a

7a was obtained as white solid in 66% yield. The enantiomeric excess was determined to be 99% by HPLC on Chiralpak OD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 16.5 min, t_{minor} = 13.4 min. m.p. 68.5-72.3 ^{o}C, $[\alpha]_D^{20}$ = +13.3 (C = 0.060, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 - 8.52 (m, 1H), 7.31 - 7.26 (m, 1H), 7.22 - 7.08 (m, 3H), 7.03 - 6.91 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.69 - 6.57 (m, 1H), 5.64 (brs, 1H), 5.03 (d, *J* = 5.6 Hz, 1H), 4.85 (s, 1H), 4.46 (d, *J* = 4.8 Hz, 1H), 4.31 - 4.06 (m, 2H), 3.52 - 3.39 (m, 1H), 2.86 (t, *J* = 11.6 Hz, 1H), 2.40 (t, *J* = 11.2 Hz, 1H), 2.32 - 2.09 (m, 1H), 1.58 (s, 3H), 1.31 - 1.18 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 178.23, 171.64, 154.57, 141.76, 131.21, 129.34, 129.25, 127.55, 123.54, 122.67, 122.30, 121.90, 118.71, 110.09, 81.61, 70.13, 60.89, 56.22, 54.79, 49.16, 48.47, 32.63, 31.34, 23.10, 14.26. HRMS (ESI-TOF) calcd for $C_{25}H_{28}N_2NaO_6^+$ $[M+Na]^+$ 475.1840, found 475.1843.



7b

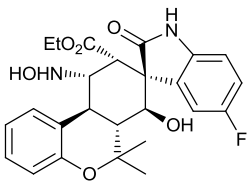
7b was obtained as white solid in 67% yield, m.p.138.1-148.5 ^{o}C, $[\alpha]_D^{20}$ = +17.7 (C = 0.062, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.23 - 7.11 (m, 2H), 7.10 - 6.87 (m, 4H), 6.71 (d, *J* = 7.2 Hz, 1H), 5.57 (brs, 1H), 5.14 - 4.94 (m, 1H), 4.76 (s, 1H), 4.56 - 4.40 (m, 1H), 4.31 - 4.06 (m, 2H), 3.47 (d, *J* = 4.8 Hz, 1H), 2.89 (t, *J* = 11.2 Hz, 1H), 2.44 (t, *J* = 11.2 Hz, 1H), 2.25 (brs, 1H), 1.65 (s, 3H), 1.33 (s, 3H), 1.28 - 1.14 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 178.10, 171.56, 154.36, 142.04, 141.93, 141.69, 129.41, 129.13, 123.64, 122.80, 121.72, 121.65, 117.60, 114.70, 114.51, 110.04, 82.95, 70.01, 60.96, 56.20, 54.70, 49.09, 48.41, 32.88, 31.37, 22.92, 14.25. HRMS (ESI-TOF) calcd for $C_{25}H_{27}FN_2NaO_6^+$ $[M+Na]^+$ 493.1745, found 493.1748.



7c

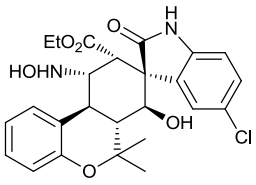
7c was obtained as white solid in 62% yield, m.p. 148.3-155.2 ^{o}C, $[\alpha]_D^{20}$ = +18.4 (C = 0.114, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.25 (m, 1H), 7.32 - 7.27 (m, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.09 - 6.93 (m, 3H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.68 - 6.54 (m, 1H), 5.62 (brs, 1H), 5.14 - 4.92 (m, 1H), 4.79 (s, 1H), 4.63 - 4.38 (m, 1H), 4.35 - 4.01 (m, 2H), 3.46 (d, *J* = 5.2 Hz, 1H), 2.87 (t, *J* = 11.2 Hz, 1H), 2.42 (t, *J* = 11.2 Hz, 1H), 2.24 (s, 3H), 2.02 (brs, 1H), 1.61 (s, 3H), 1.29 - 1.21 (m, 6H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 178.26, 171.46, 154.47, 140.20, 131.03, 129.68, 127.95, 127.70, 123.97, 122.07, 121.88, 120.36, 118.86, 111.02, 81.46, 69.97, 61.14, 56.12, 55.26, 49.01, 48.54, 32.48, 31.42, 26.92, 23.07, 14.29. HRMS (ESI-TOF) calcd for $C_{26}H_{30}N_2NaO_6^+$ $[M+Na]^+$ 489.1996, found 489.2001.



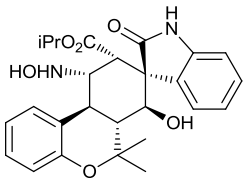
7d

7d was obtained as white solid in 50% yield, m.p. 133.2-144.5 °C, $[\alpha]_D^{20}$ = +16.6 (C = 0.048, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 - 8.43 (m, 1H), 7.32 - 7.28 (m, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.04 - 6.93 (m, 2H), 6.92 - 6.82 (m, 2H), 6.67 - 6.57 (m, 1H), 5.66 (brs, 1H), 5.13 - 4.91 (m, 1H), 4.73 (s, 1H), 4.47 (dd, *J* = 10.8, 6.1 Hz, 1H), 4.28 - 4.10 (m, 2H), 3.48 (d, *J* = 5.9 Hz, 1H), 2.85 (t, *J* = 11.6 Hz, 1H), 2.41 (t, *J* = 11.2 Hz, 1H), 2.13 (brs, 1H), 1.59 (s, 3H), 1.30 - 1.24 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.09, 171.46, 159.05 (J_{CF} = 239 Hz), 154.56, 137.63, 130.99, 130.92, 127.64, 122.30, 121.89, 118.73, 115.83 (J_{CF} = 24 Hz), 110.57 (J_{CF} = 7 Hz), 81.44, 61.08, 56.26, 55.39, 49.04, 31.31, 29.71, 23.08, 14.25. HRMS (ESI-TOF) calcd for $C_{25}H_{27}FN_2NaO_6^+$ $[M+Na]^+$ 493.1745, found 493.1740.



7e

7e was obtained as white solid in 67% yield, m.p. 147.2-152.3 °C, $[\alpha]_D^{20}$ = +13.6 (C=0.102, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.23 - 7.11 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 5.59 (brs, 1H), 5.11 - 4.91 (m, 1H), 4.80 (s, 1H), 4.37 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.32 - 4.03 (m, 2H), 3.43 (d, *J* = 5.6 Hz, 1H), 2.83 (t, *J* = 11.6 Hz, 1H), 2.75 - 2.50 (m, 1H), 2.33 (t, *J* = 11.2 Hz, 1H), 1.60 (s, 3H), 1.28 - 1.11 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.10, 171.74, 154.60, 139.19, 132.20, 129.57, 129.27, 127.50, 124.37, 122.86, 122.36, 121.85, 118.66, 109.72, 81.63, 70.17, 60.79, 56.29, 54.75, 49.20, 48.46, 32.62, 31.29, 23.15, 14.28. HRMS (ESI-TOF) calcd for $C_{25}H_{27}ClN_2NaO_6^+$ $[M+Na]^+$ 509.1450, found 509.1454.

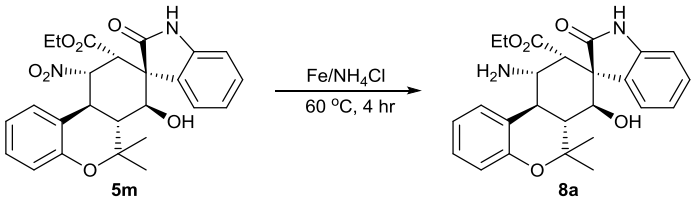


7f

7f was obtained as white solid in 66% yield, m.p. 136.5-142.8 °C, $[\alpha]_D^{20}$ = +33.3 (C = 0.024, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.41 - 7.10 (m, 5H), 7.08 - 6.95 (m, 2H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 5.66 (brs, 1H), 5.26 - 4.98 (m, 2H), 4.64 (s, 1H), 4.57 - 4.39 (m, 1H),

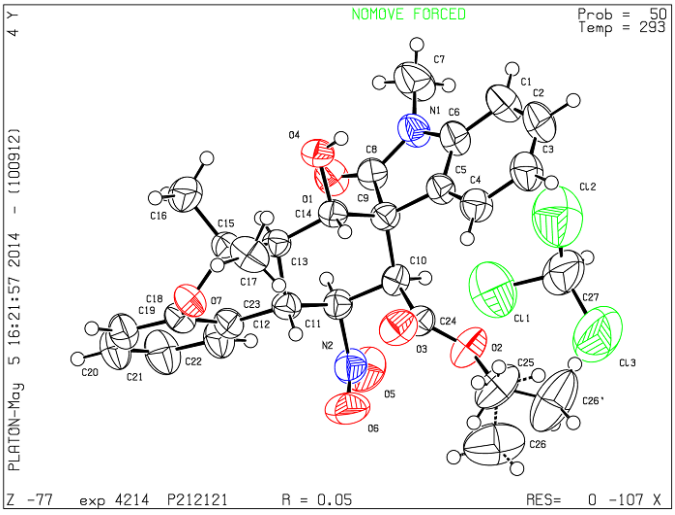
3.45 (d, *J* = 5.2 Hz, 1H), 2.87 (t, *J* = 11.6 Hz, 1H), 2.45 (t, *J* = 11.2 Hz, 1H), 1.95 (s, 1H), 1.60 (s, 3H), 1.33 - 1.24 (m, 6H), 1.15 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 178.02, 171.06, 154.61, 141.75, 131.16, 129.31, 129.24, 127.52, 123.97, 122.64, 122.39, 121.84, 118.64, 109.93, 81.58, 68.67, 56.35, 54.80, 49.13, 48.26, 32.70, 31.29, 23.13, 21.96, 21.88, 14.15. HRMS (ESI-TOF) calcd for $C_{26}H_{30}N_2NaO_6^+$ $[M+Na]^+$ 489.1996, found 489.1993.

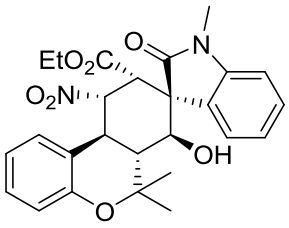
2.4 **Procedure for the synthesis of compound 8a**



To a suspension of compound **5m** (46.6 mg, 0.1 mmol) and Fe powder (56 mg, 1 mmol) in 3 mL of ethanol was added NH_4Cl (27 mg, 0.5 mmol) in 1 mL of water. The reaction mixture was heated at 60 °C for 4 hours, then filtrated. The filtrate was diluted with ethyl acetate and washed with saturated $NaHCO_3$, then saline. The organic layer was dried over anhydrous $NaSO_4$ and concentrated. The residue was purified by silica-gel chromatography to afford compound **8a** (27 mg, 62% yield) as white solid. The enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column at 254nm (Hexane/isopropanol = 90/10, 1 mL/min), t_{major} = 39.5 min, t_{minor} = 20.6 min. mp. 156.3- 159.5 °C, $[\alpha]_D^{20}$ = +107.5 (C = 0.036, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.23 - 7.14 (m, 3H), 7.03 - 6.95 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.39 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.25 - 4.03 (m, 2H), 3.17 - 2.93 (m, 2H), 2.40 (t, *J* = 11.2 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.24, 171.80, 154.75, 141.67, 131.89, 129.31, 129.22, 127.15, 124.59, 123.71, 122.65, 121.39, 118.36, 109.97, 81.37, 70.56, 60.73, 55.43, 53.35, 48.48, 45.59, 31.28, 29.70, 23.13, 14.18. HRMS (ESI-TOF) calcd for $C_{25}H_{29}N_2O_5^+$ $[M+Na]^+$ 437.2071, found 437.2074.

3. Crystal data of compound 5k



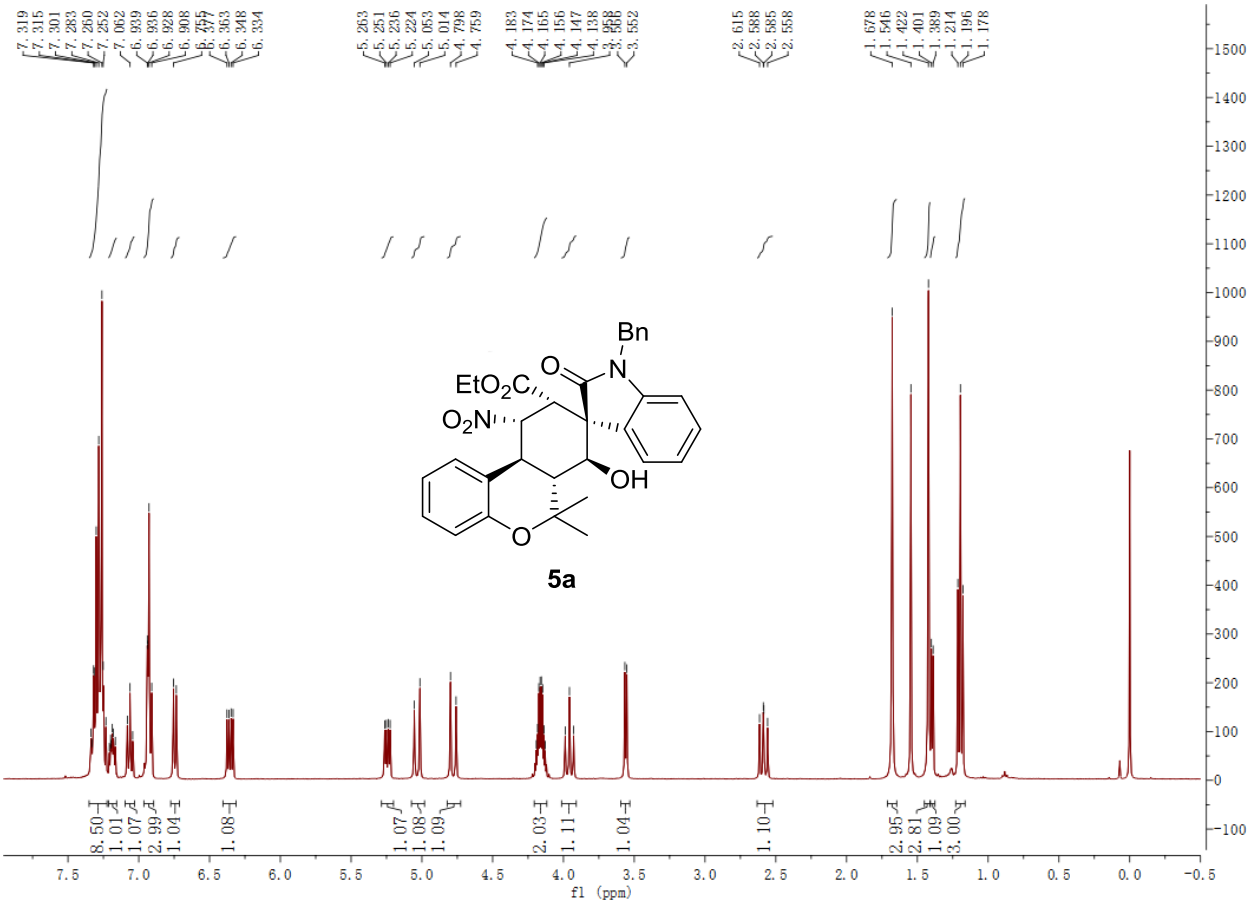


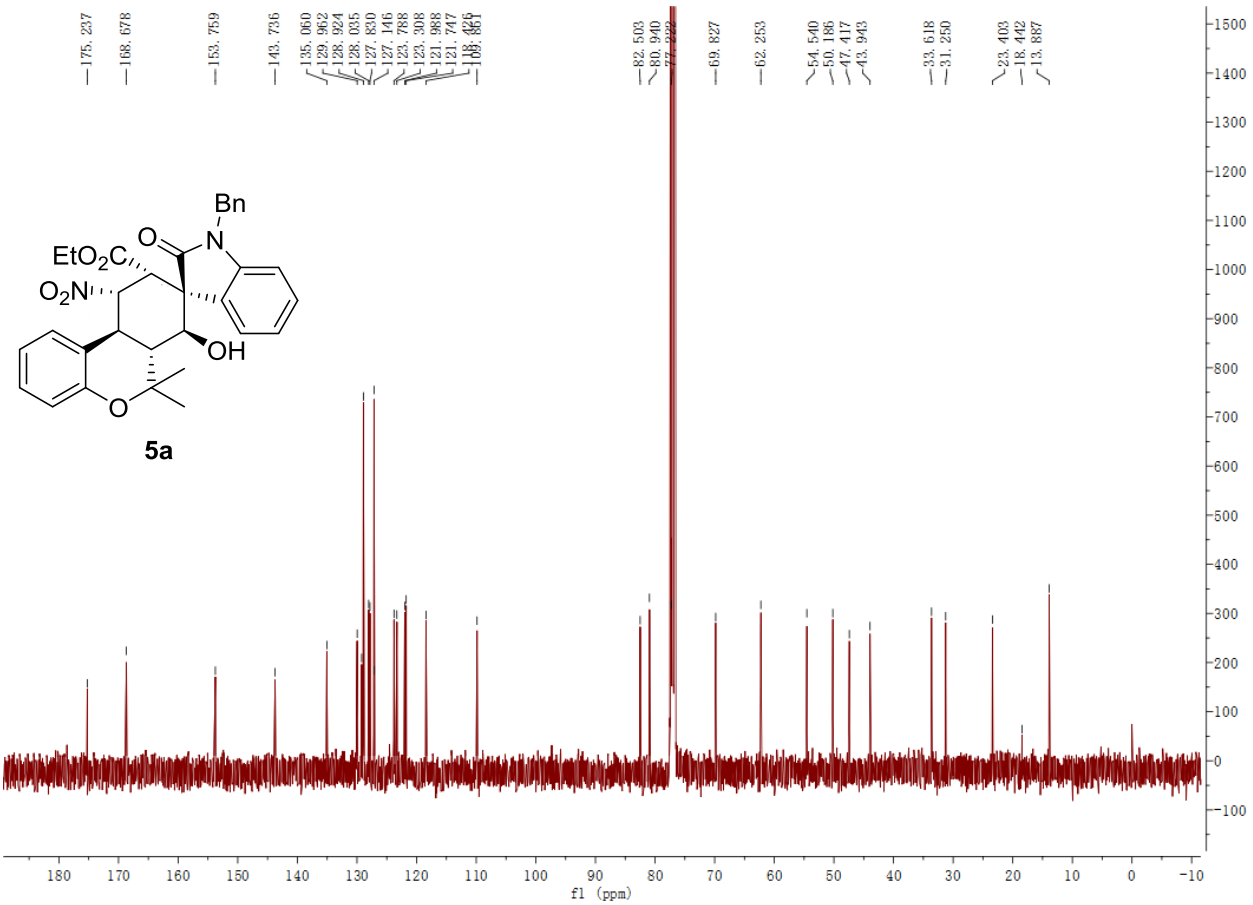
5k

Bond precision: C-C = 0.0051 A Wavelength=1.54184

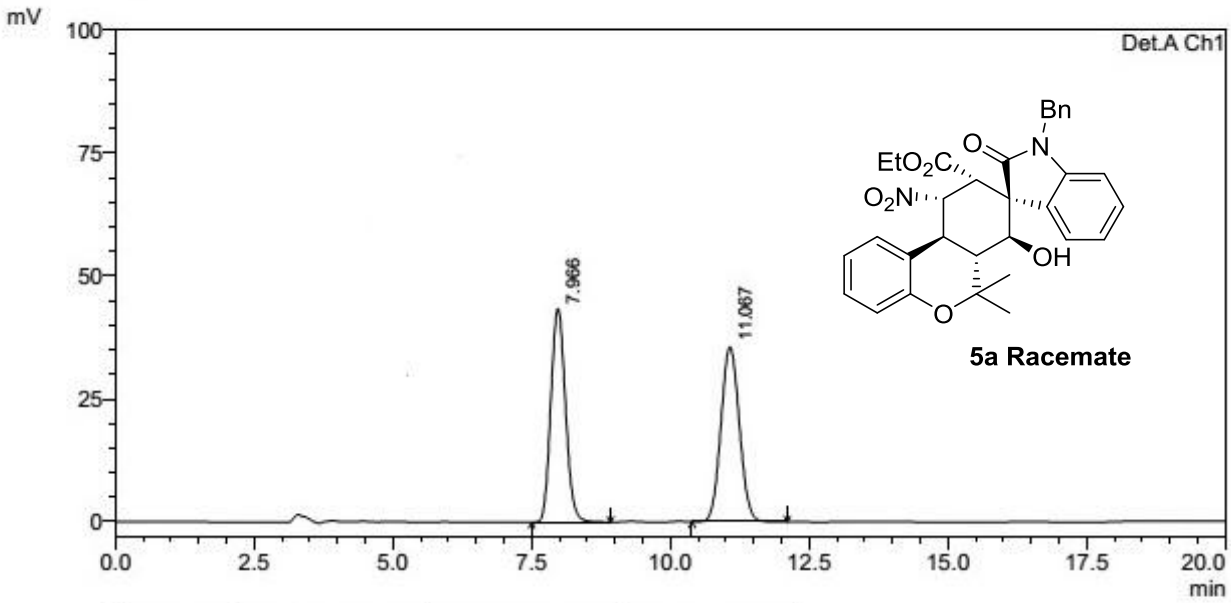
Empirical formula	$C_{27}H_{29}Cl_3N_2O_7$
Formula weight	599.87
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	11.0927(7)
b/Å	15.2908(9)
c/Å	17.2201(10)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	2920.8(3)
Z	4
ρ_{calc}mg/mm^3	1.364
m/mm^{-1}	3.237
F(000)	1248.0
Crystal size/mm^3	0.23 × 0.22 × 0.17
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection	7.74 to 134.48 °
Index ranges	-13 ≤ h ≤ 10, -18 ≤ k ≤ 18, -20 ≤ l ≤ 20
Reflections collected	19017
Independent reflections	5243 [R_{int} = 0.0462, R_{sigma} = 0.0428]
Data/restraints/parameters	5243/1297/367
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0532, wR_2 = 0.1389
Final R indexes [all data]	R_1 = 0.0751, wR_2 = 0.1619
Largest diff. peak/hole / e Å^{-3}	0.30/-0.35
Flack parameter	-0.01(3)

4. NMR spectra and HPLC chromatograms



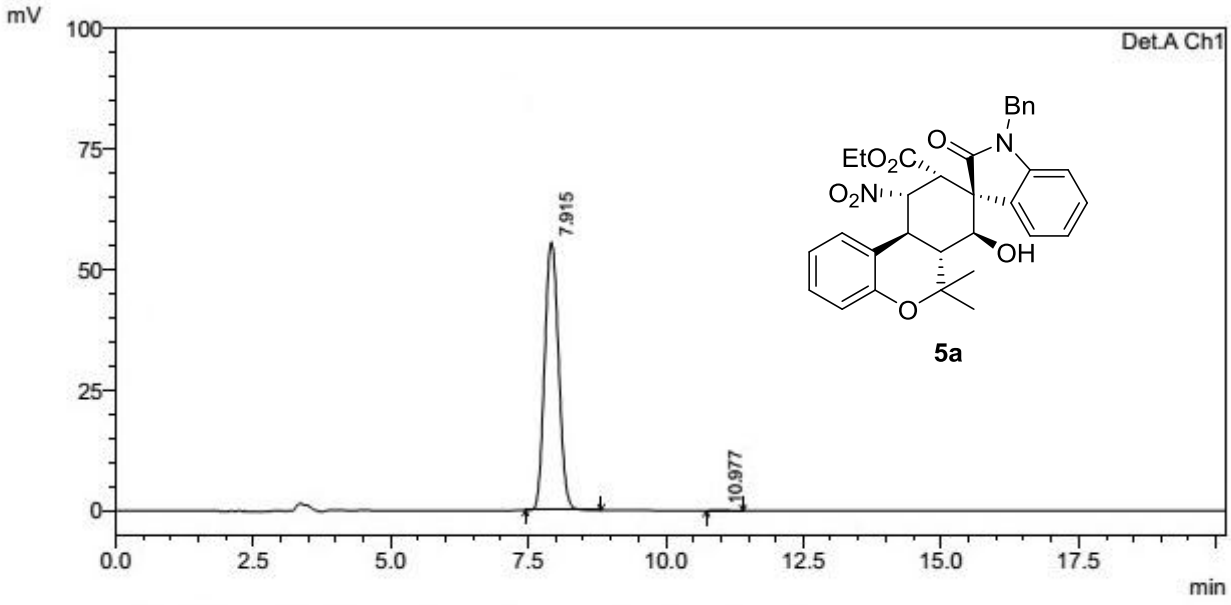


<Chromatogram>



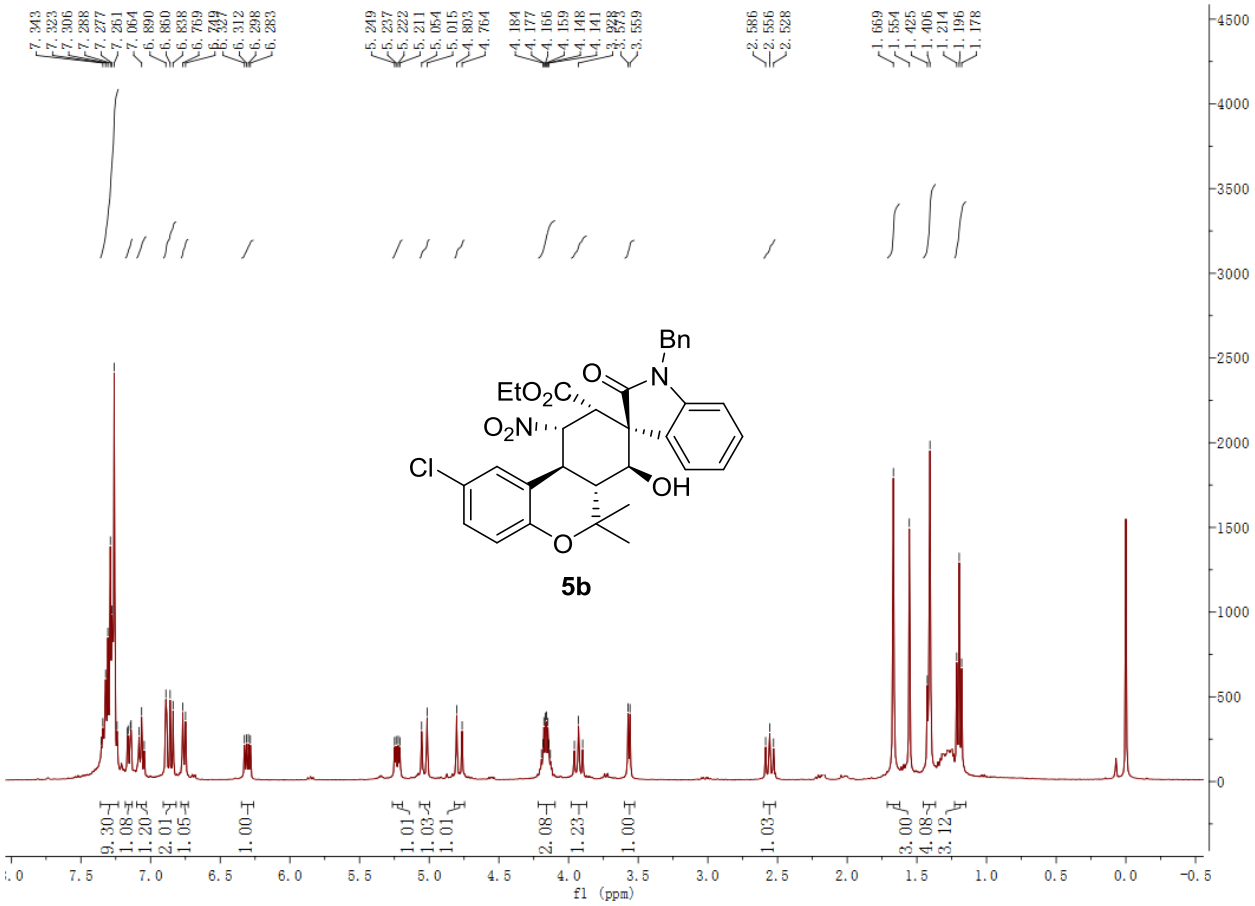
5a Racemate

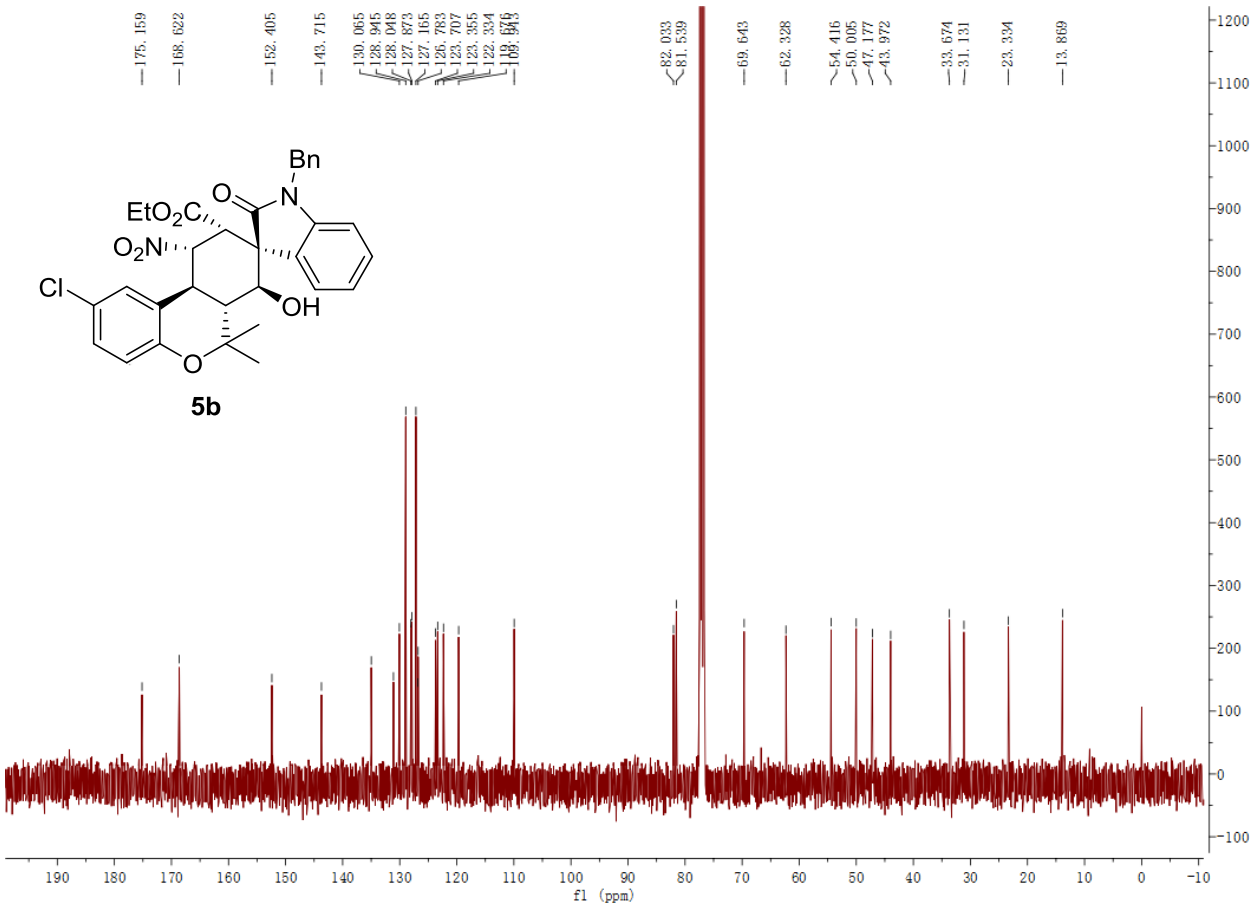
Peak#	Ret. Time	Area	Area %
1	7.966	799799	49.061
2	11.067	830427	50.939
Total		1630226	100.000



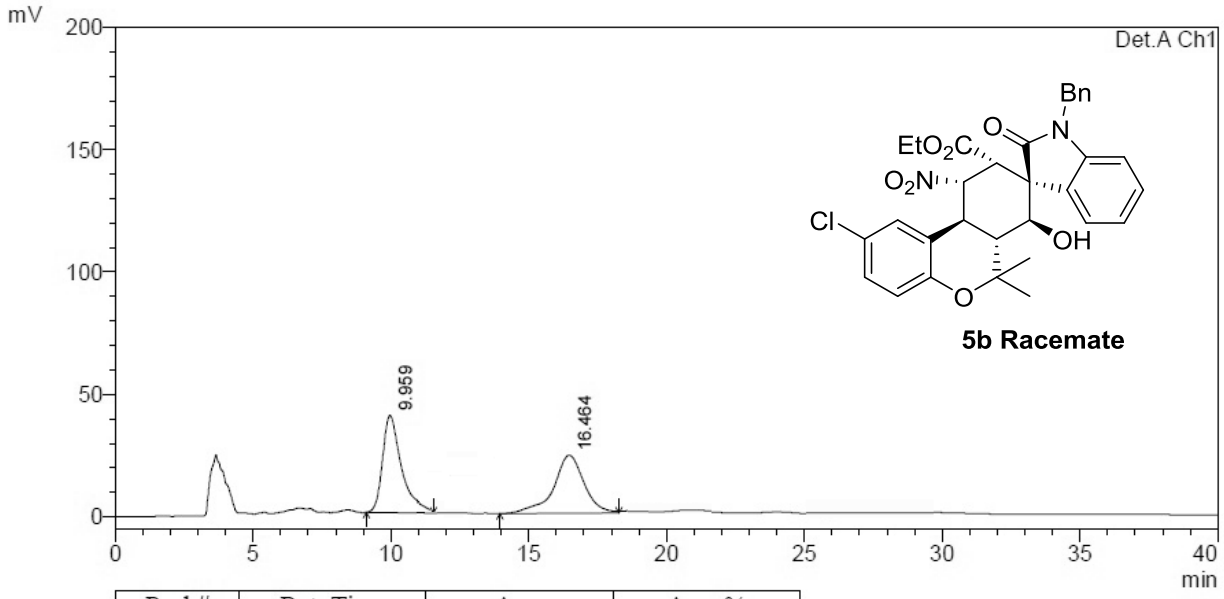
5a

Peak#	Ret. Time	Area	Area %
1	7.915	979930	99.873
2	10.977	1251	0.127
Total		981180	100.000


Bn
O
N
EtO2C
O2N
Cl
OH
O
5b
f1 (ppm)

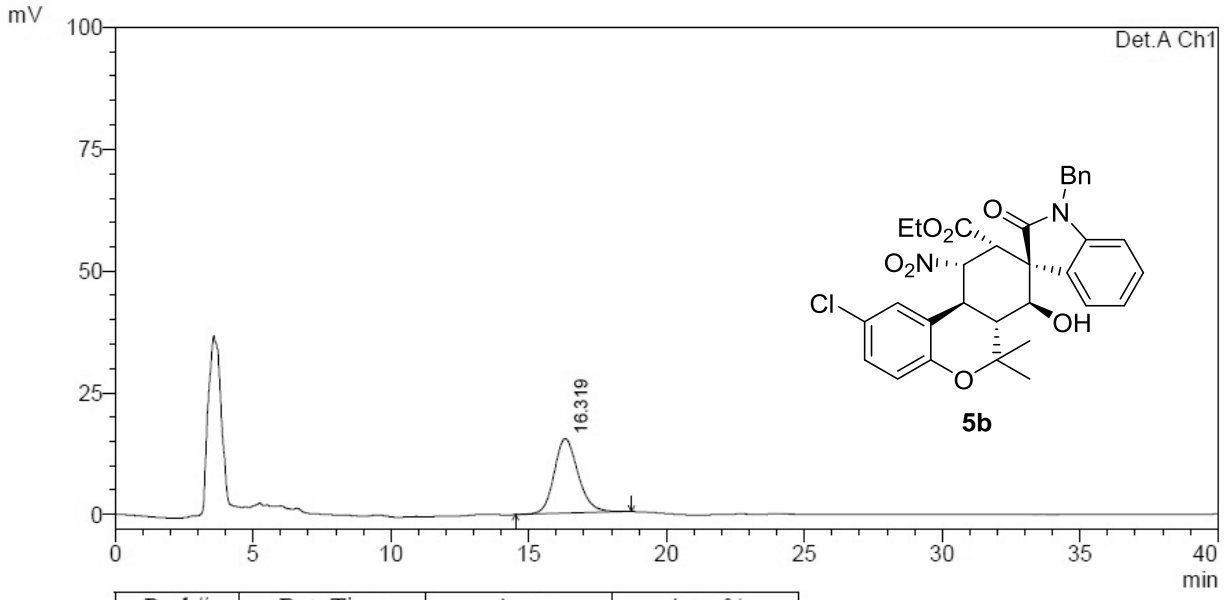

Bn
O
N
EtO2C
O2N
Cl
OH
O
5b
f1 (ppm)

<Chromatogram>



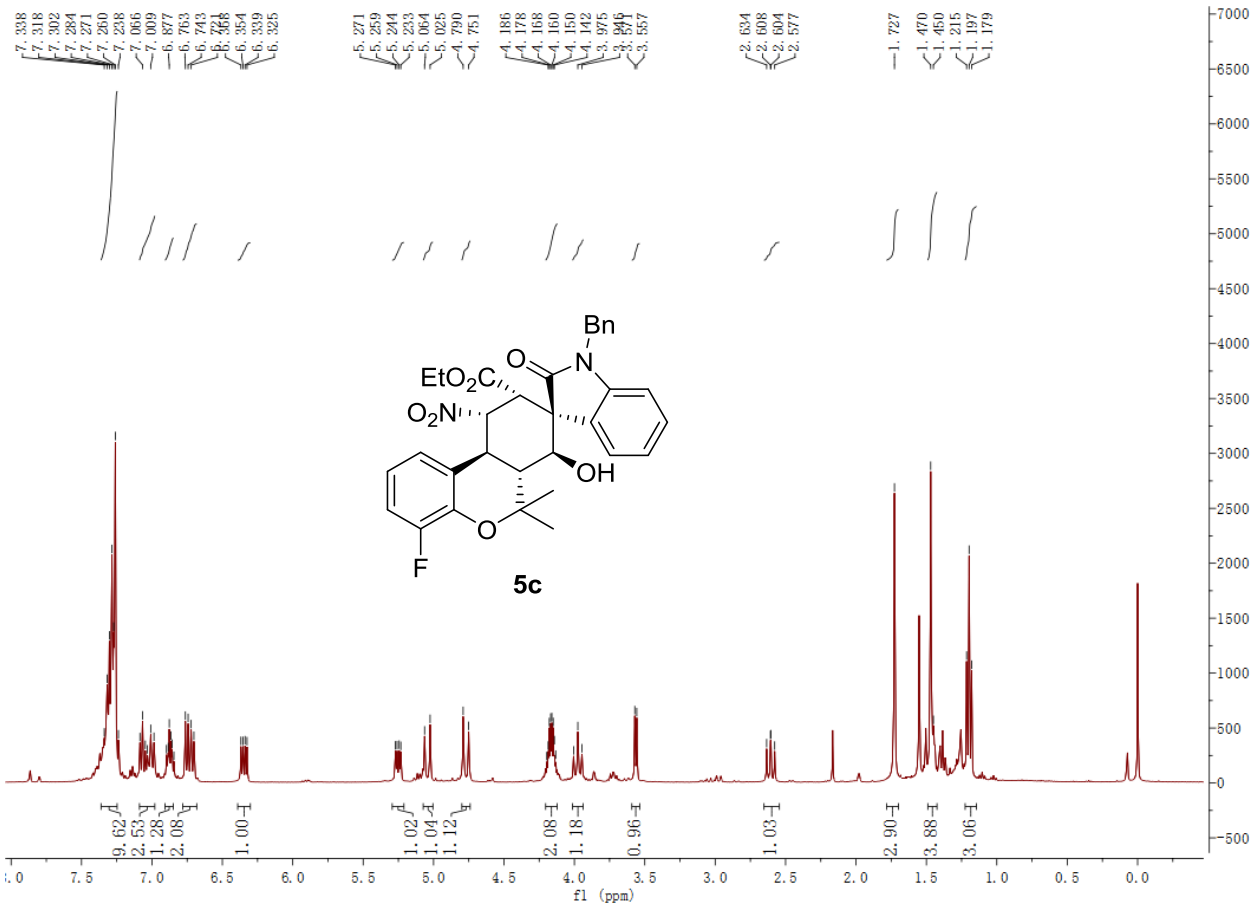
5b Racemate

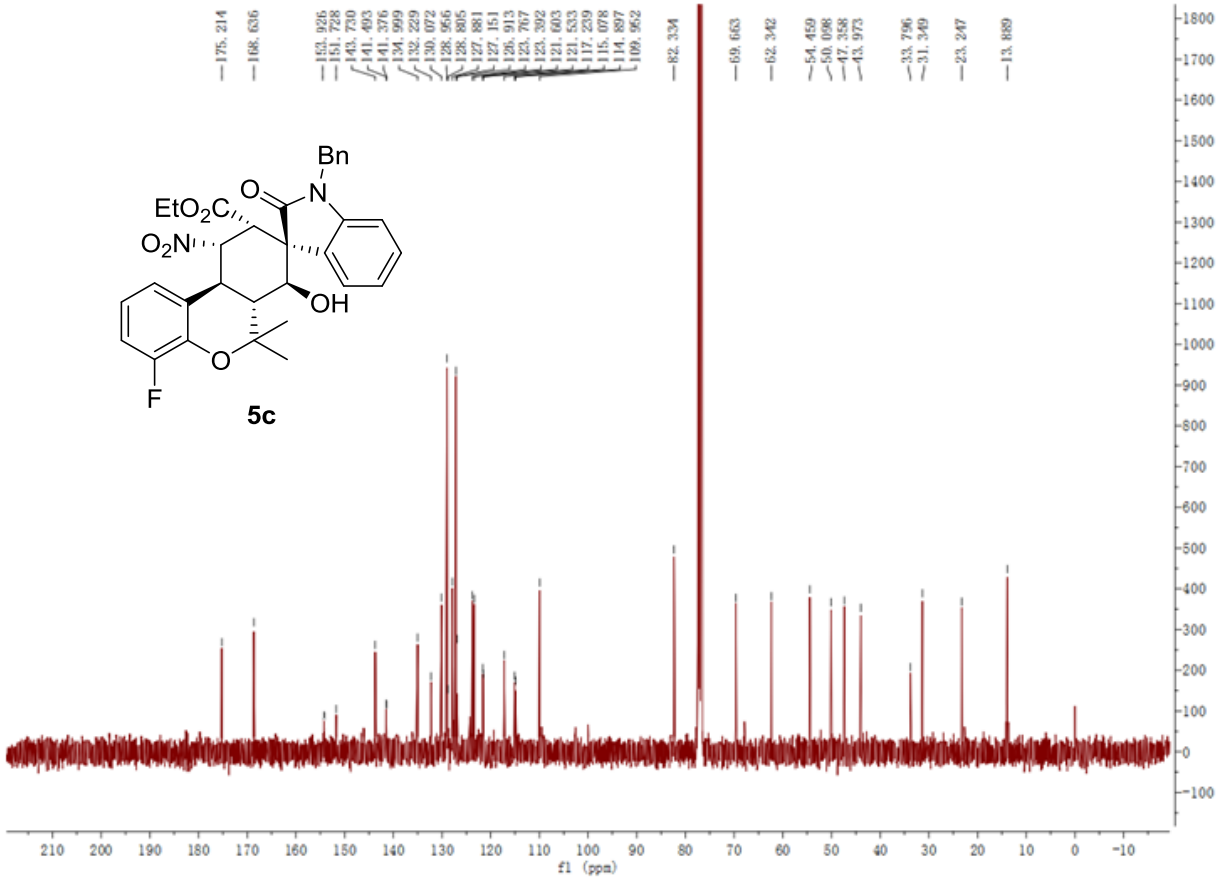
Peak#	Ret. Time	Area	Area %
1	9.959	1849463	50.317
2	16.464	1826151	49.683
Total		3675614	100.000



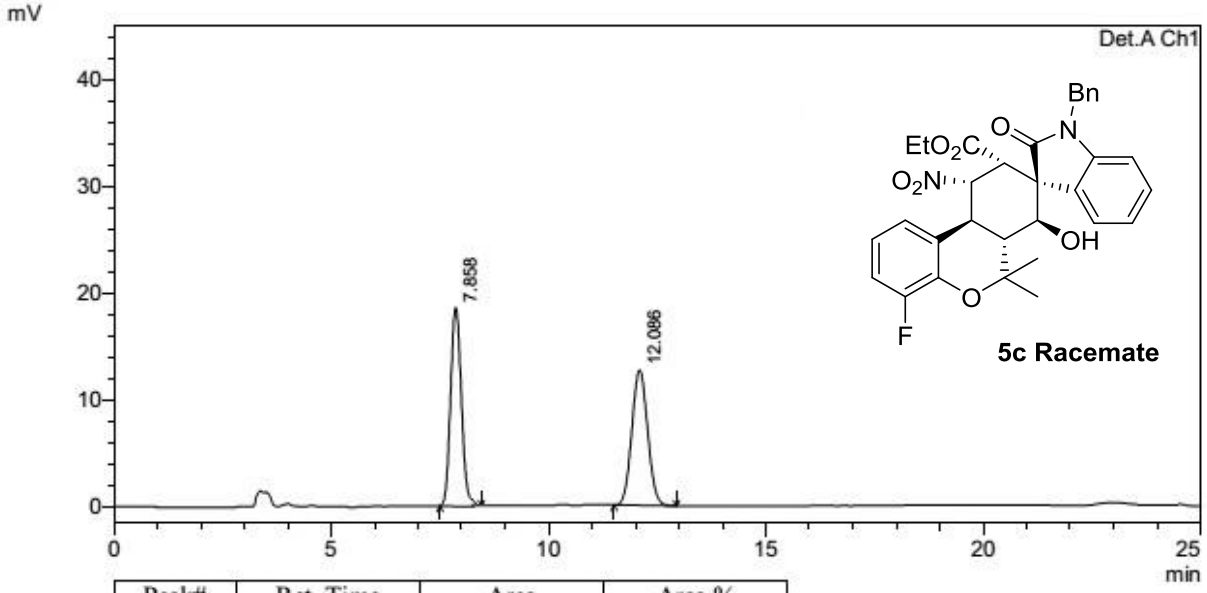
5b

Peak#	Ret. Time	Area	Area %
1	16.319	933022	100.000
Total		933022	100.000

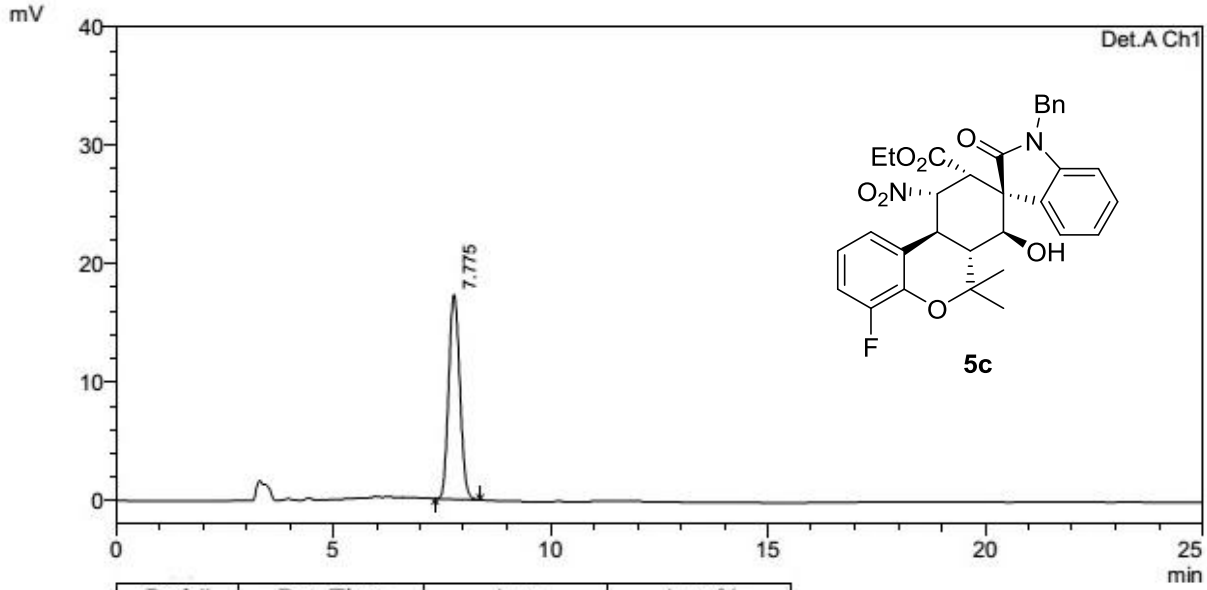

Bn
EtO2C
O
N
O2N
OH
O
F
5c
f1 (ppm)


Bn
EtO2C
O
N
O2N
OH
O
F
5c
f1 (ppm)

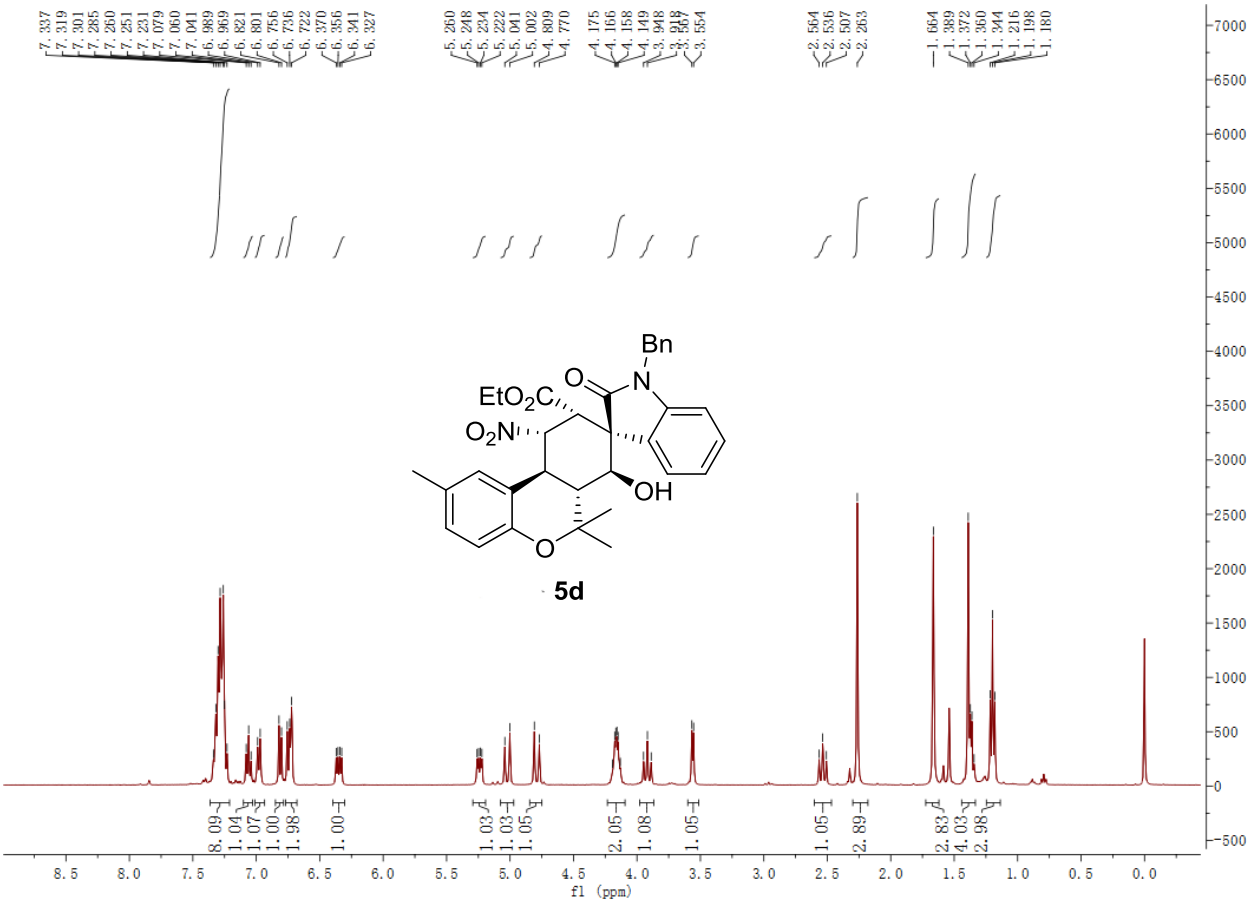
<Chromatogram>

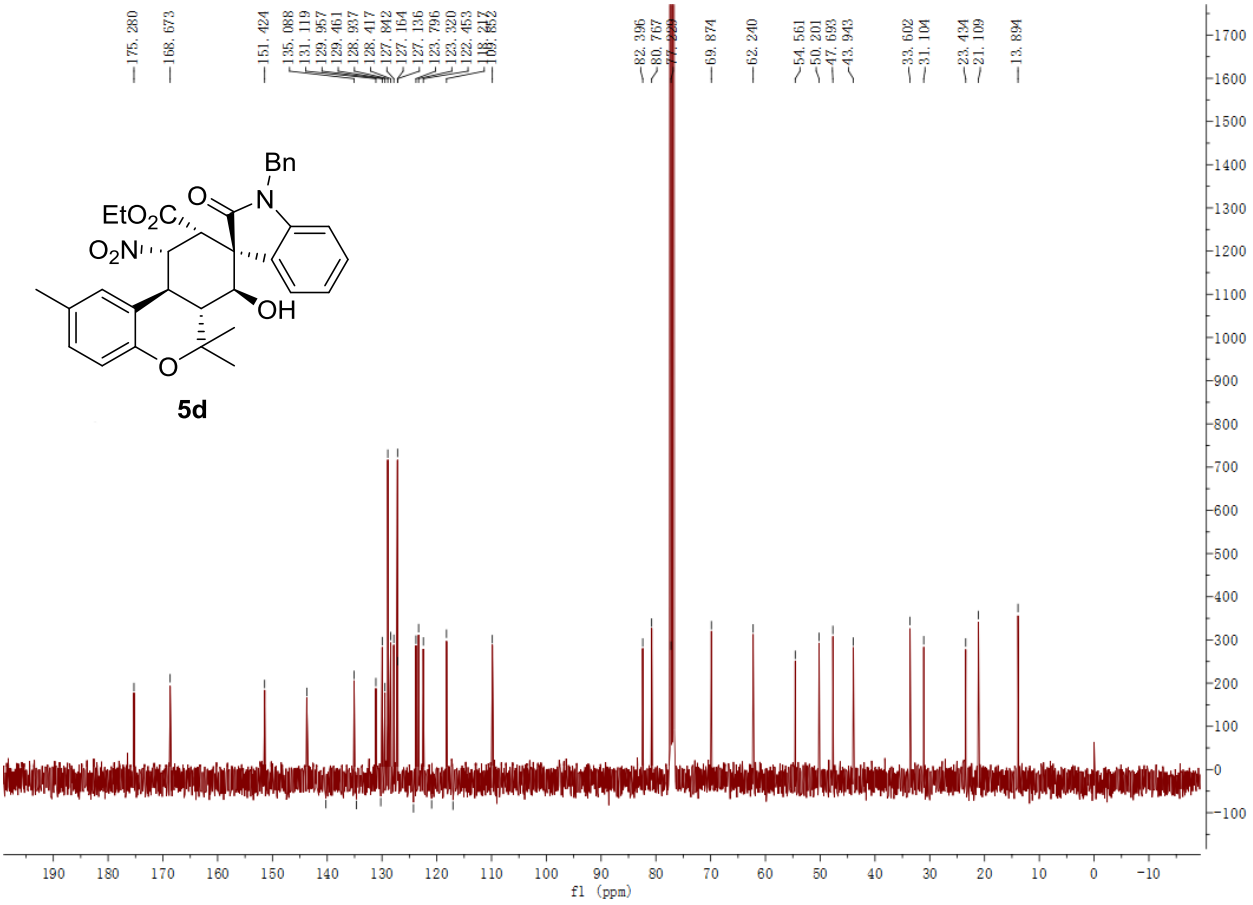


Peak#	Ret. Time	Area	Area %
1	7.858	320354	49.952
2	12.086	320970	50.048
Total		641324	100.000

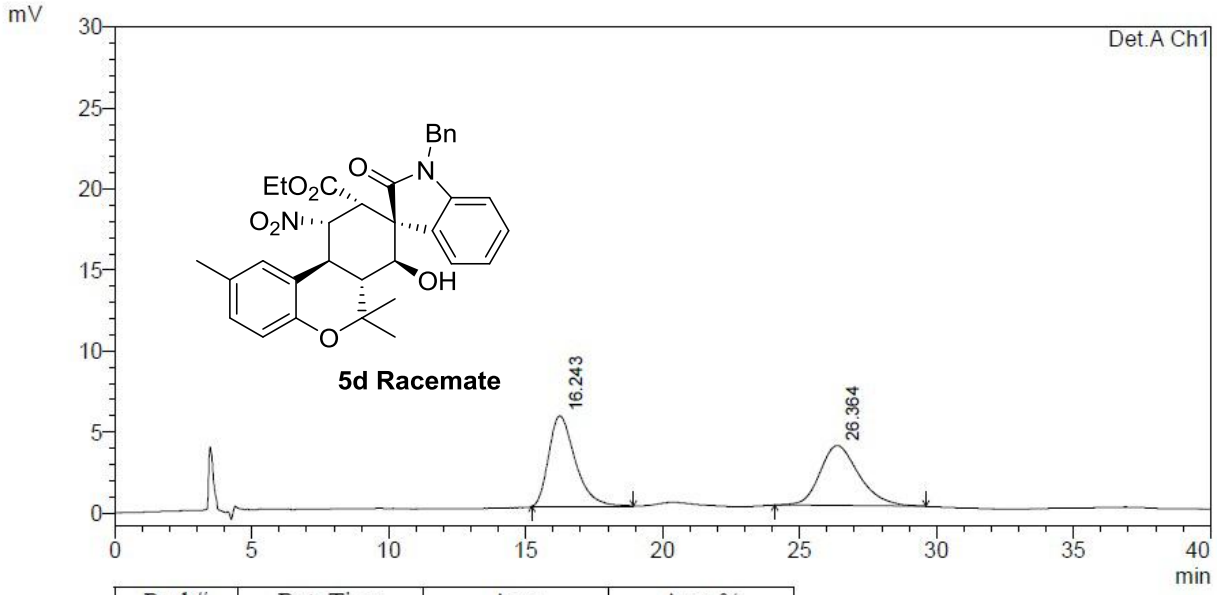


Peak#	Ret. Time	Area	Area %
1	7.775	309346	100.000
Total		309346	100.000

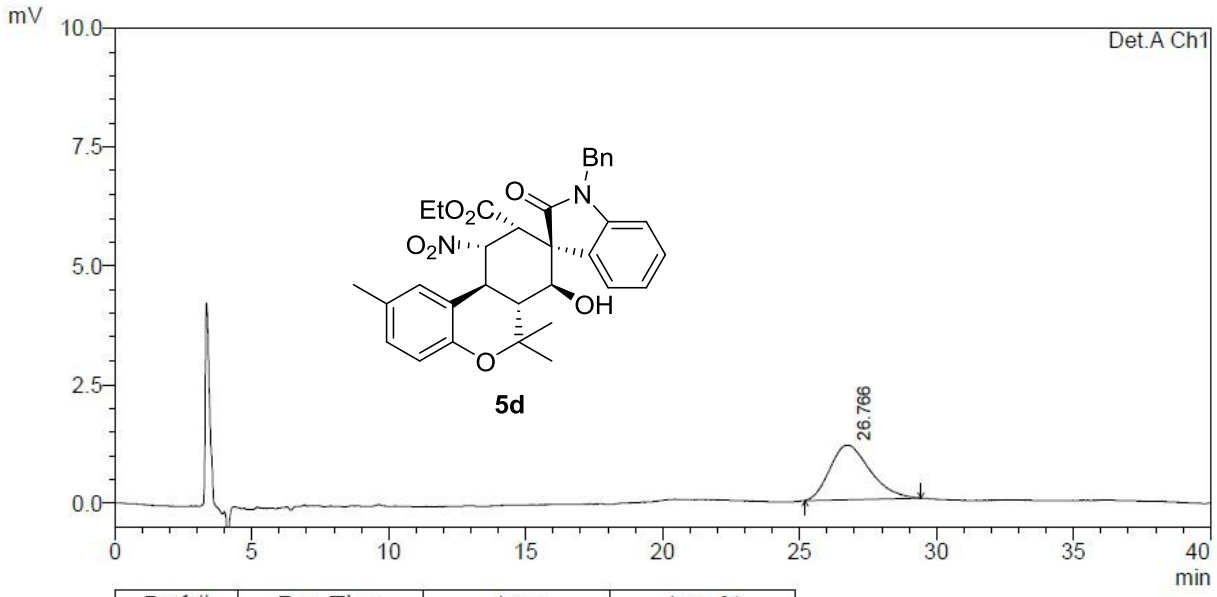

Bn
EtO2C
O2N
OH
5d
f1 (ppm)


Bn
EtO2C
O2N
OH
5d
f1 (ppm)

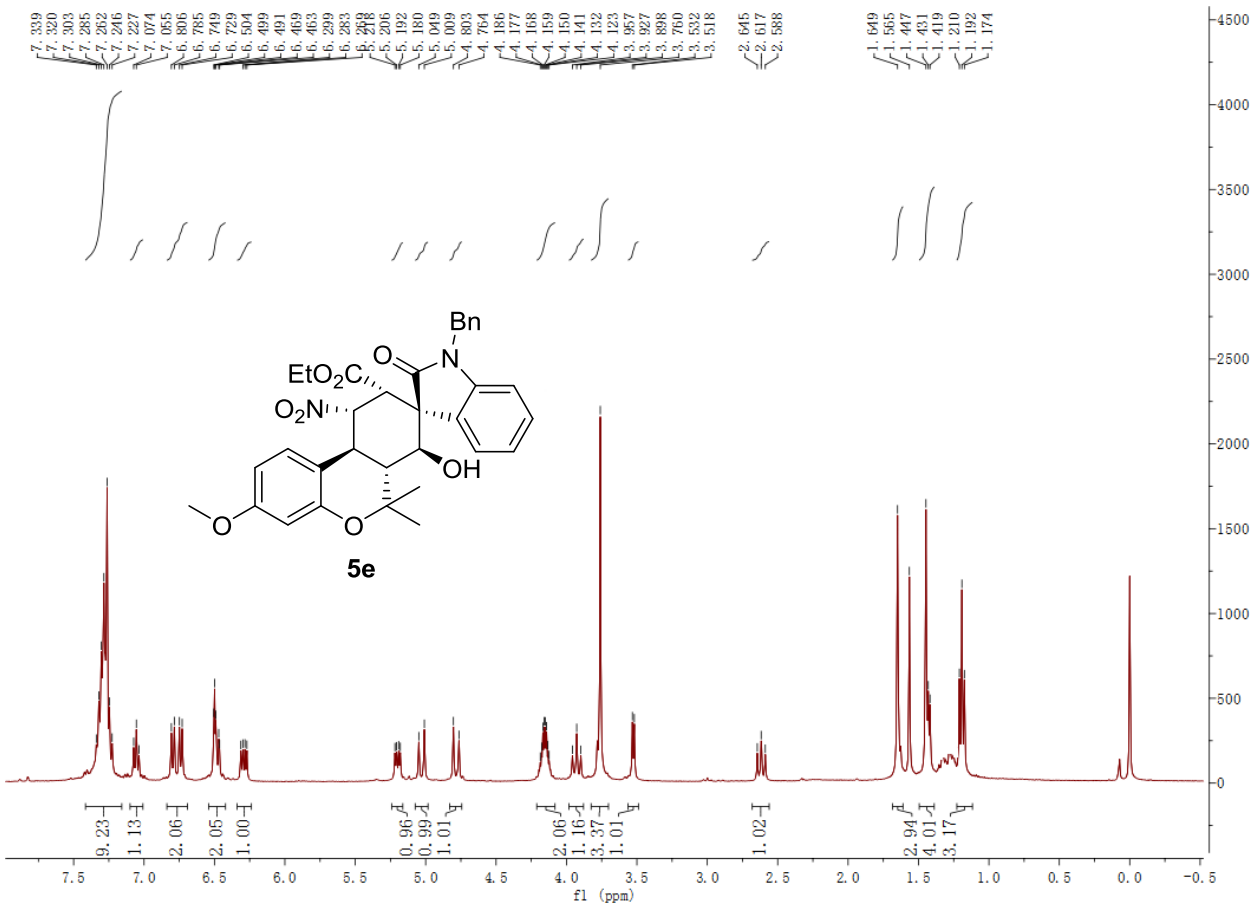
<Chromatogram>

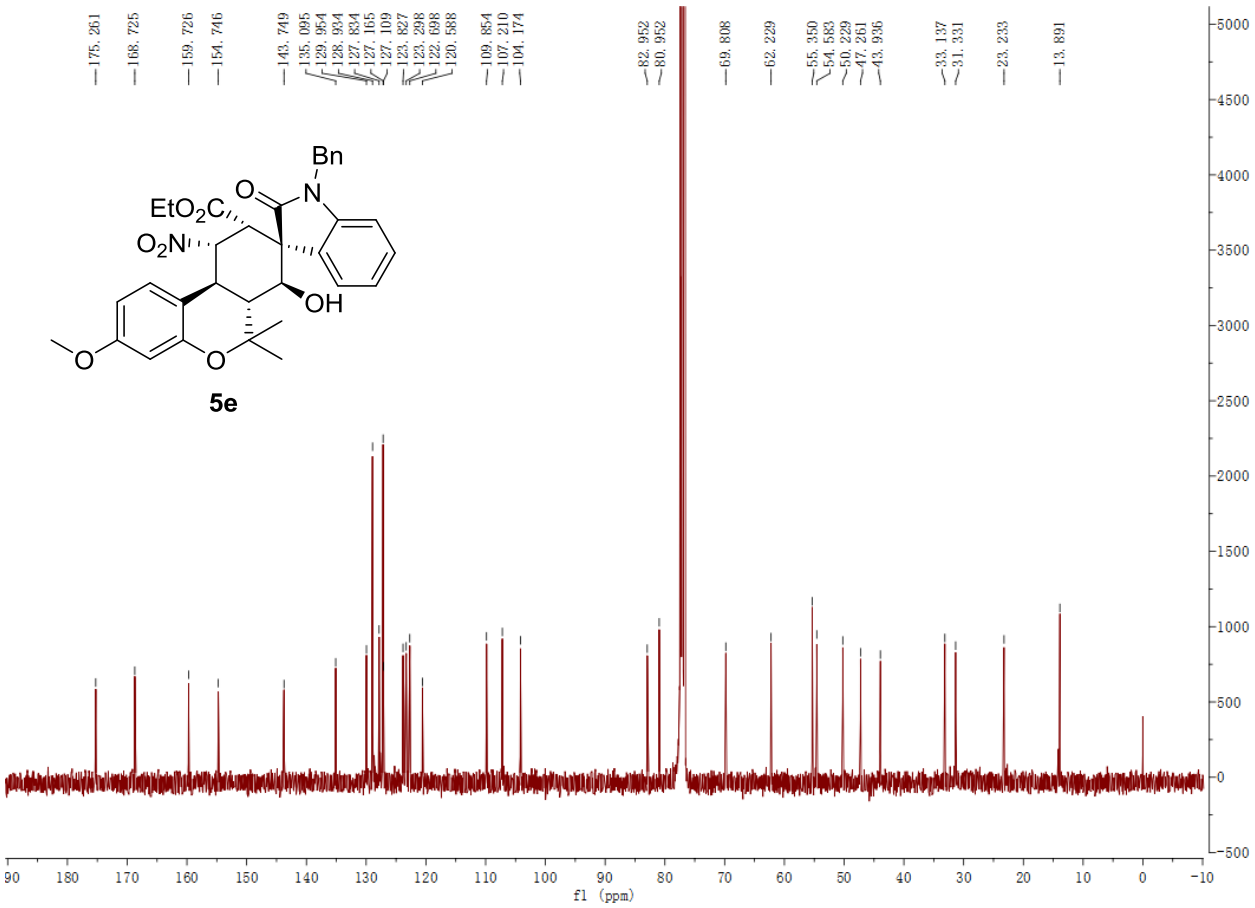


Peak#	Ret. Time	Area	Area %
1	16.243	374697	50.304
2	26.364	370169	49.696
Total		744866	100.000

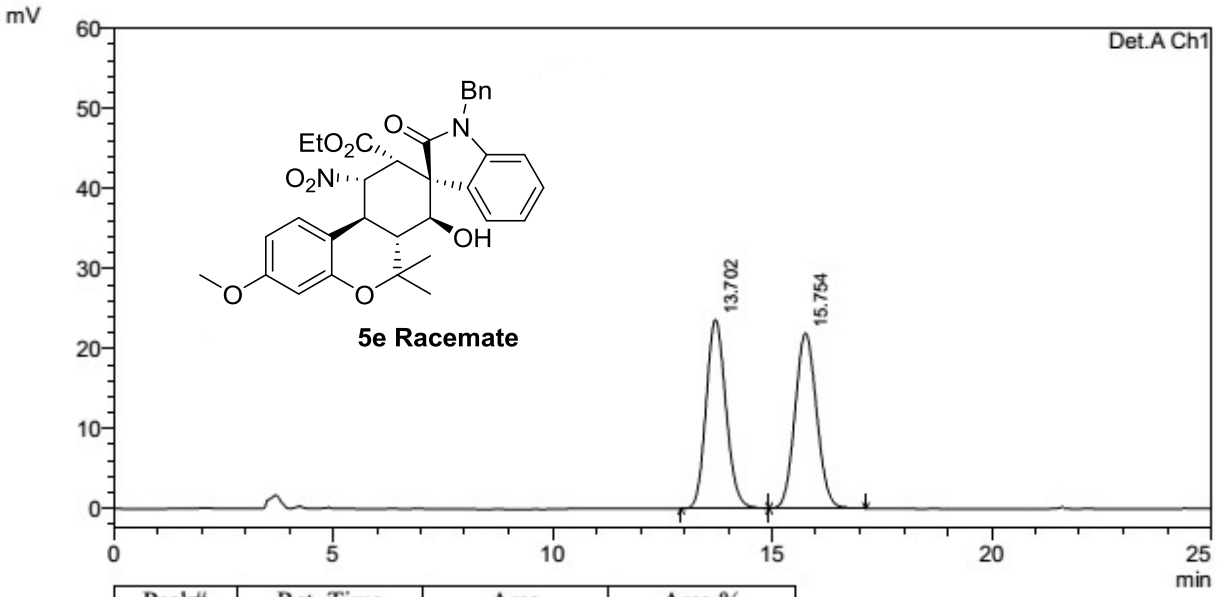


Peak#	Ret. Time	Area	Area %
1	26.766	116857	100.000
Total		116857	100.000


Bn
N
O
EtO2C
O2N
OH
O
O
5e
f1 (ppm)

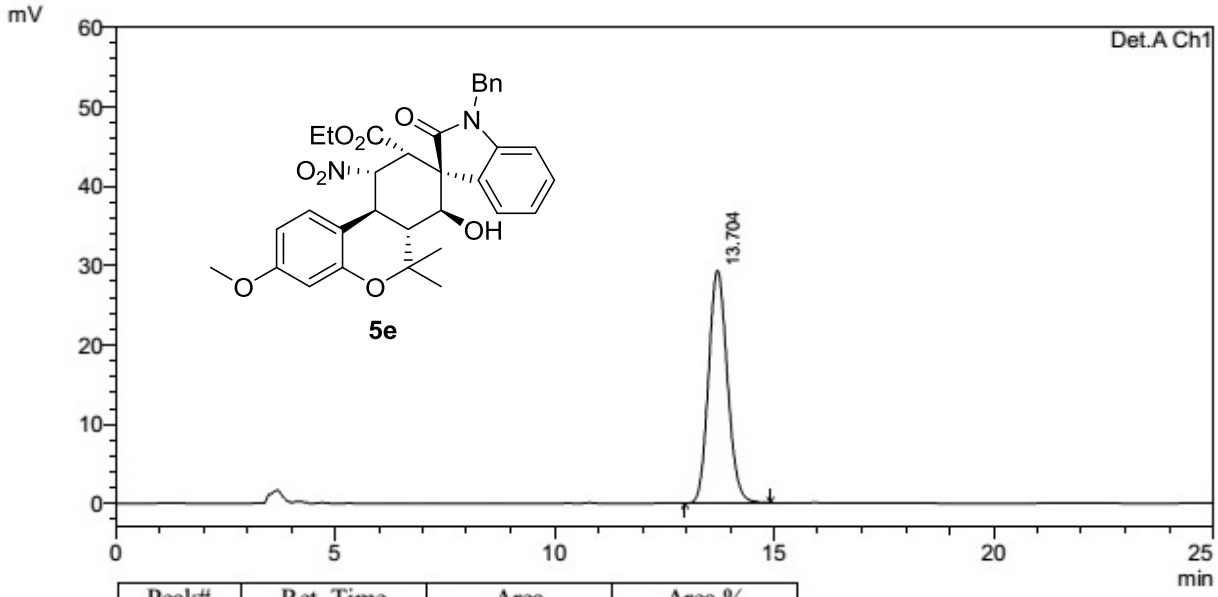

Bn
N
O
EtO2C
O2N
OH
O
O
5e
f1 (ppm)

<Chromatogram>



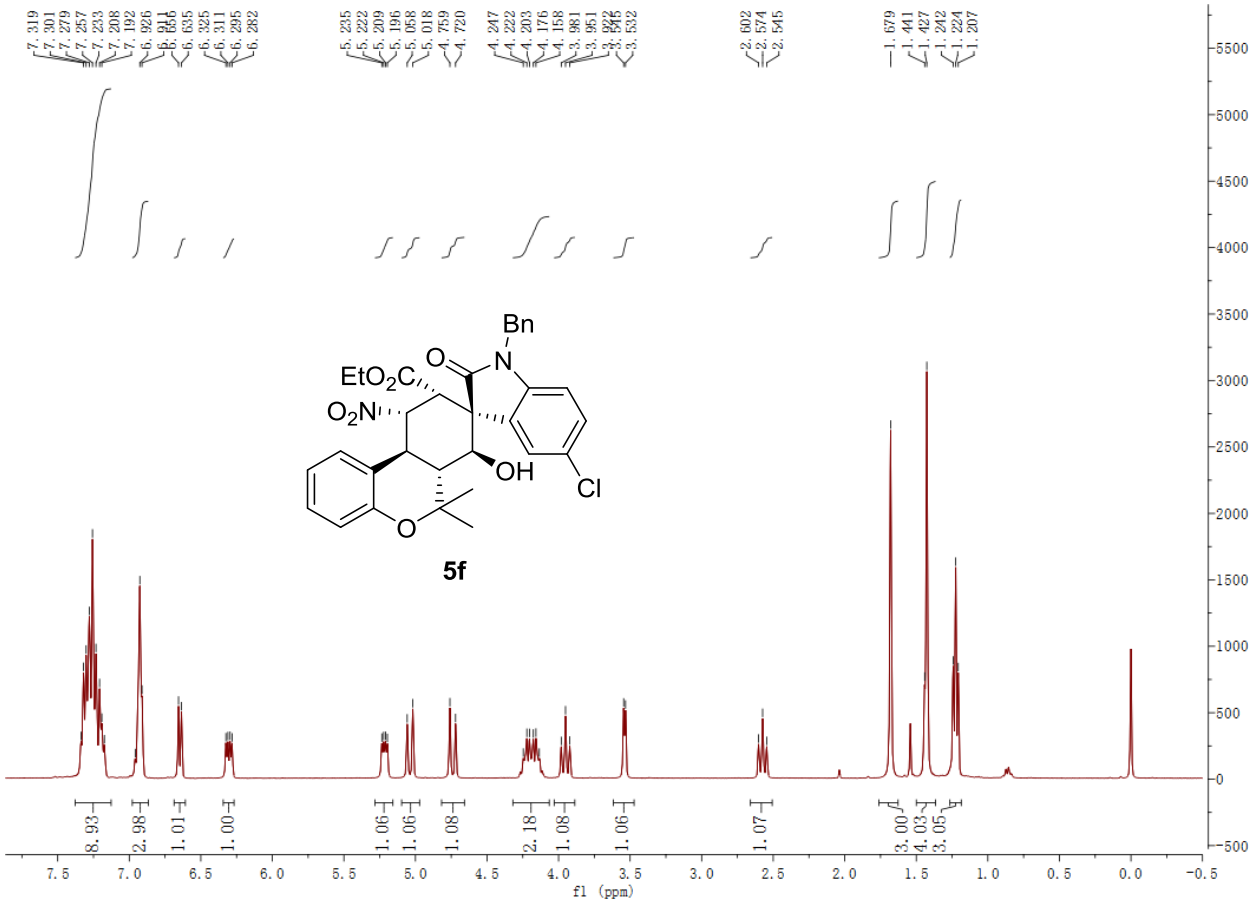
5e Racemate

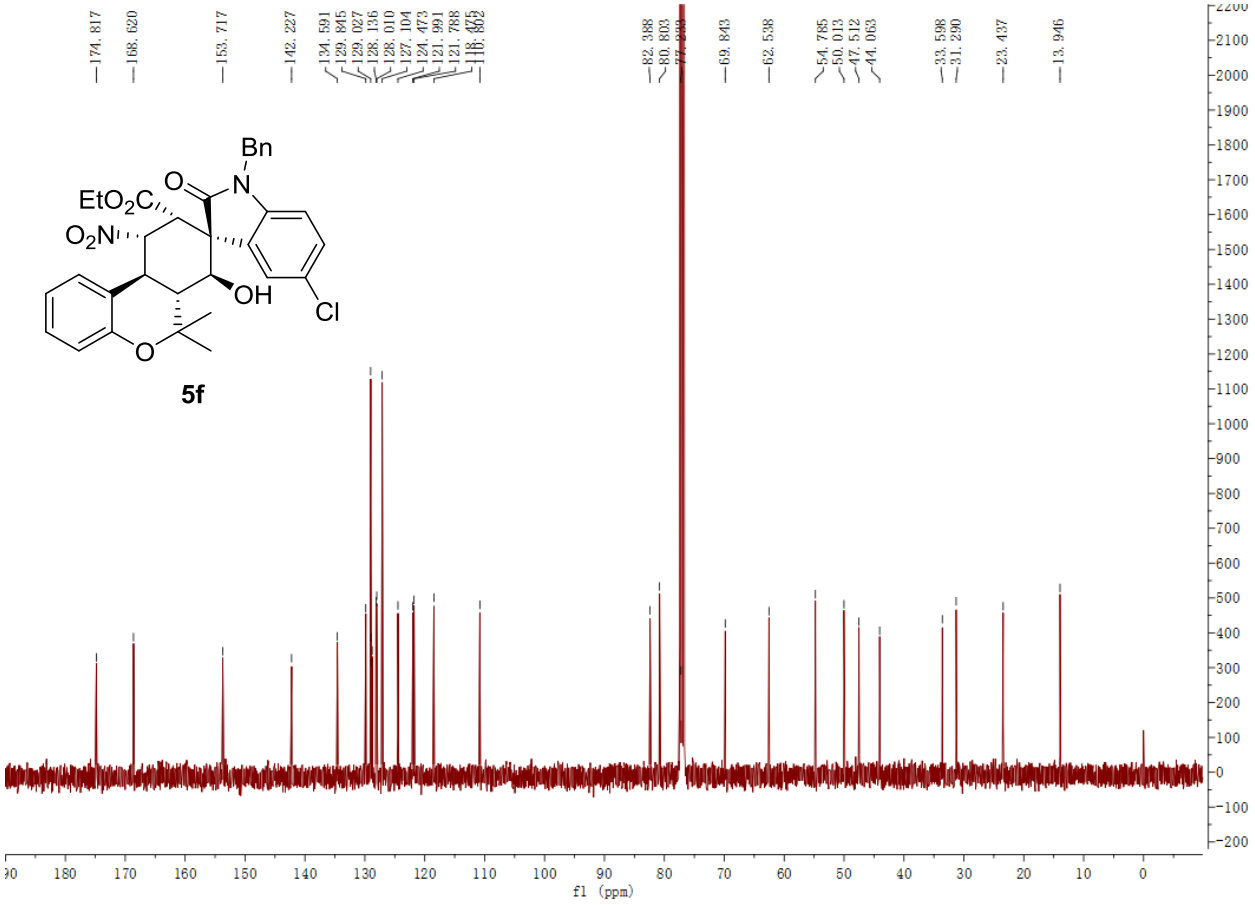
Peak#	Ret. Time	Area	Area %
1	13.702	741247	49.706
2	15.754	750003	50.294
Total		1491250	100.000



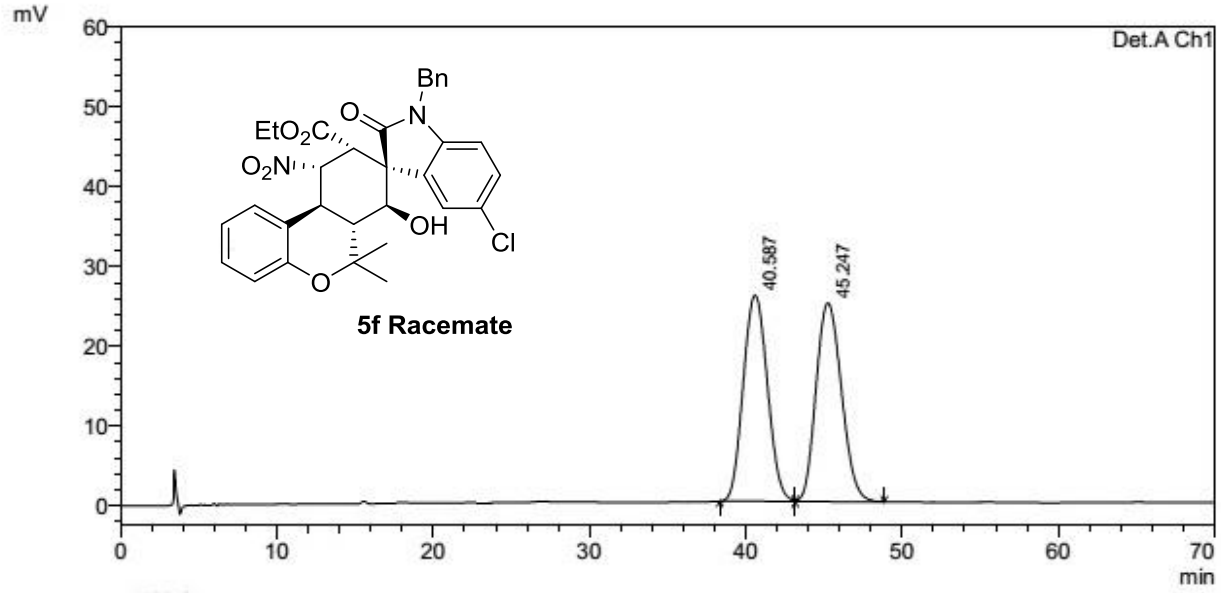
5e

Peak#	Ret. Time	Area	Area %
1	13.704	872217	100.000
Total		872217	100.000


Bn
EtO2C
O
N
O2N
OH
Cl
O
5f
f1 (ppm)

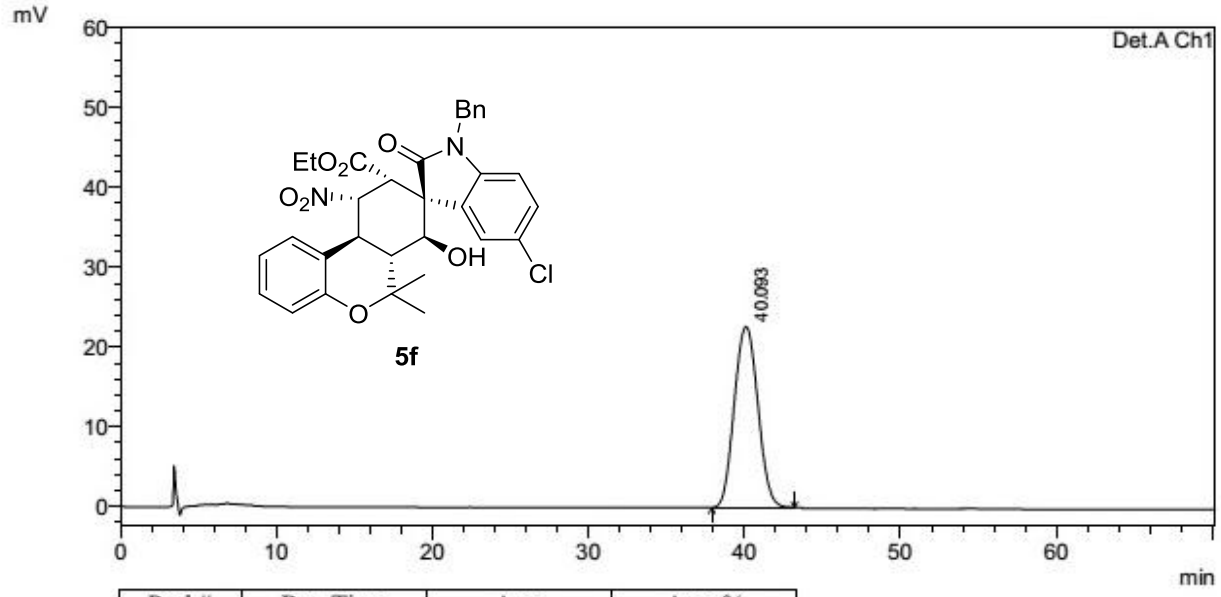

Bn
EtO2C
O
N
O2N
OH
Cl
O
5f
f1 (ppm)

<Chromatogram>



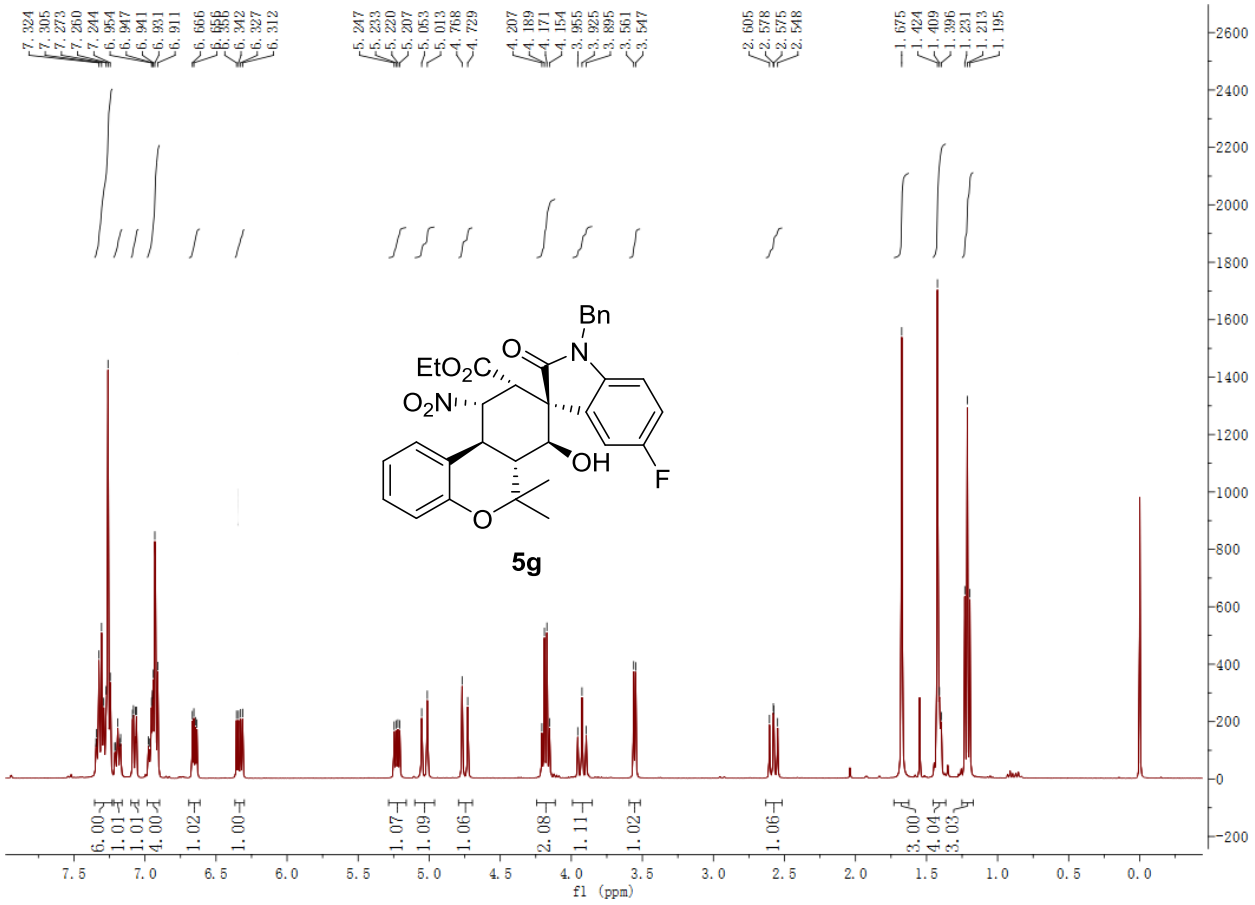
5f Racemate

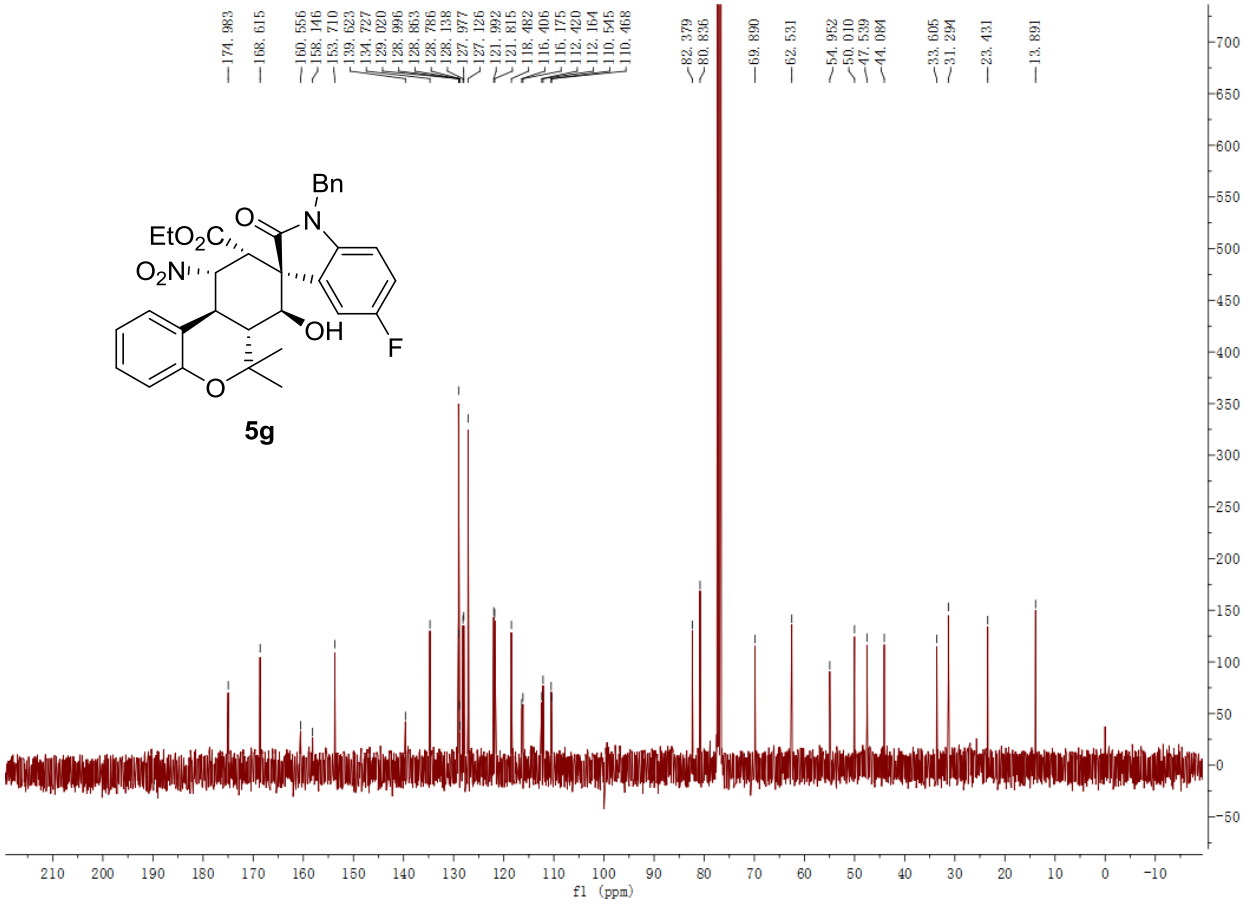
Peak#	Ret. Time	Area	Area %
1	40.587	2780971	49.640
2	45.247	2821278	50.360
Total		5602248	100.000



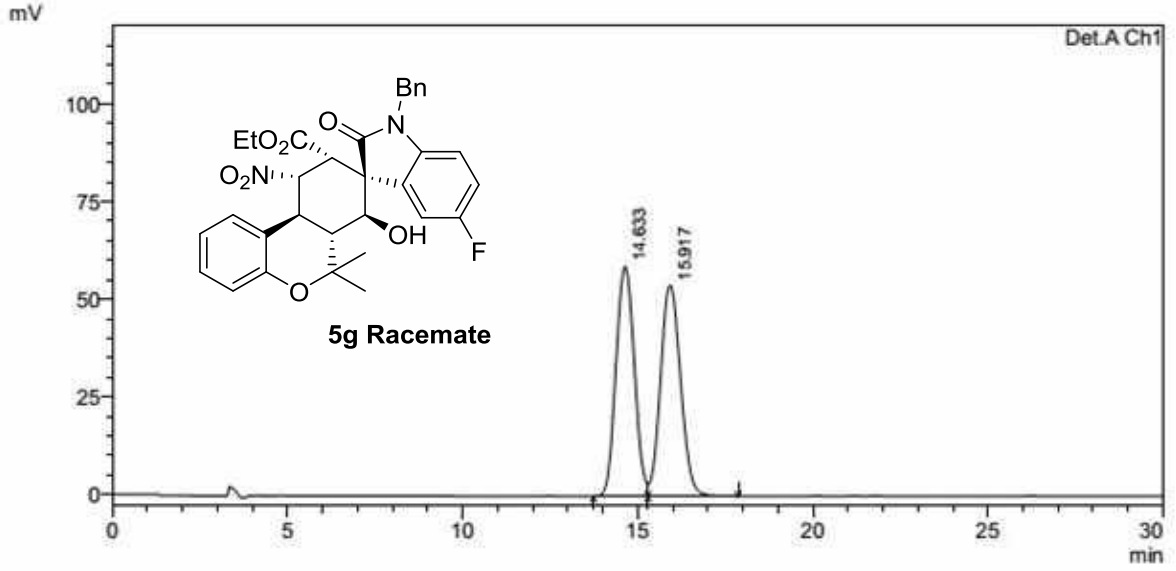
5f

Peak#	Ret. Time	Area	Area %
1	40.093	2403572	100.000
Total		2403572	100.000

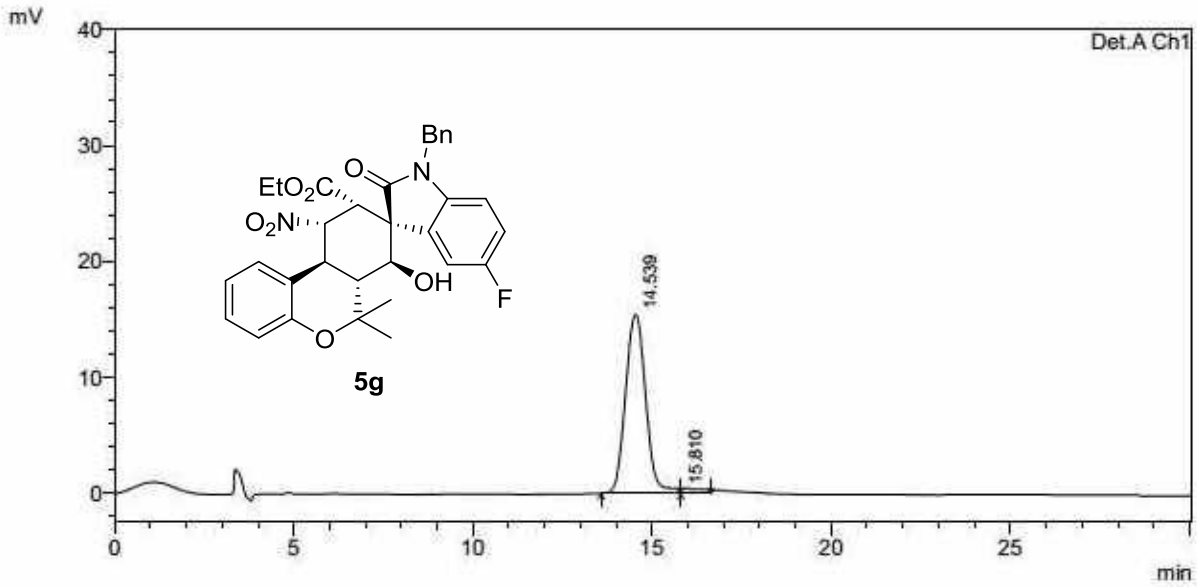

Bn
N
O
EtO2C
O2N
OH
F
O
5g
f1 (ppm)


Bn
N
O
EtO2C
O2N
OH
F
O
5g
f1 (ppm)

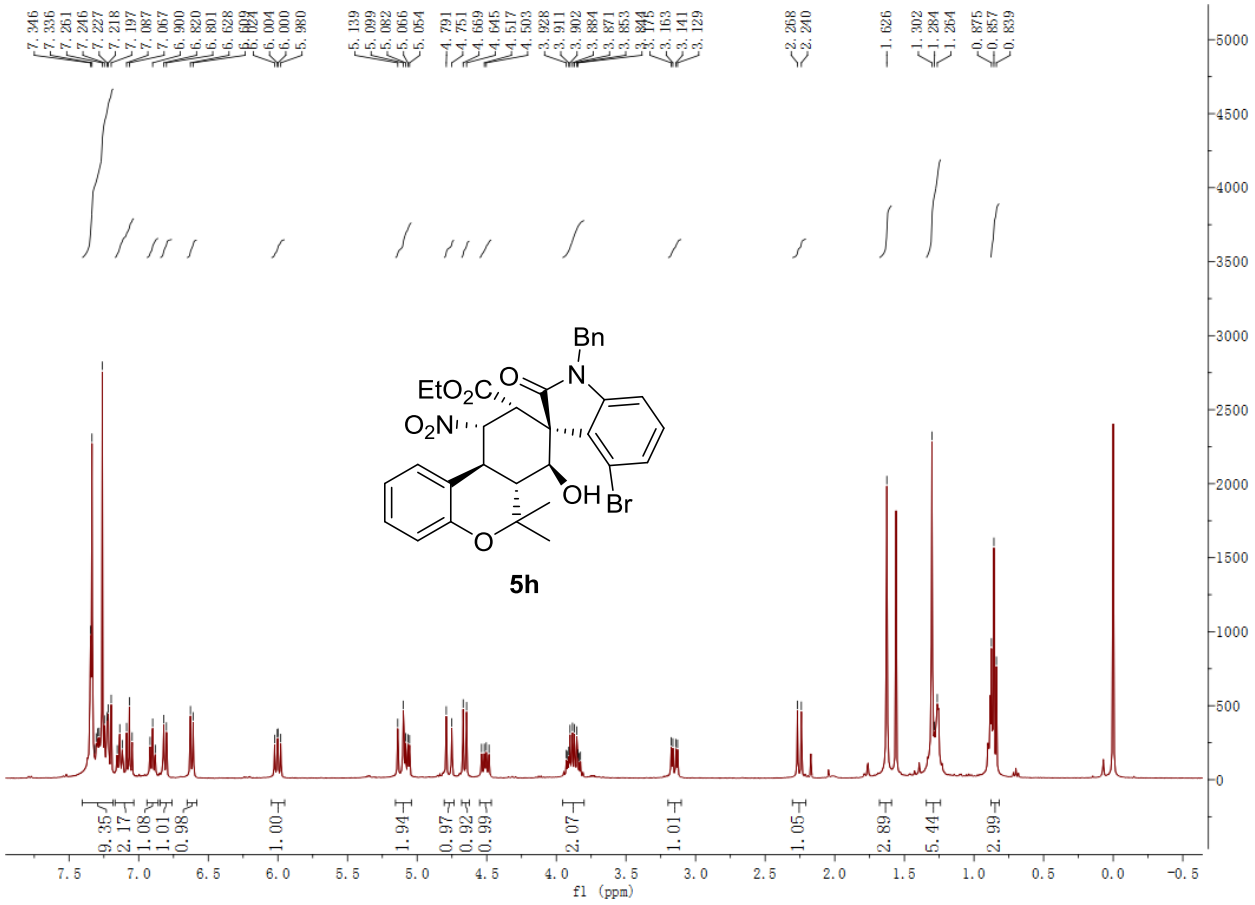
<Chromatogram>

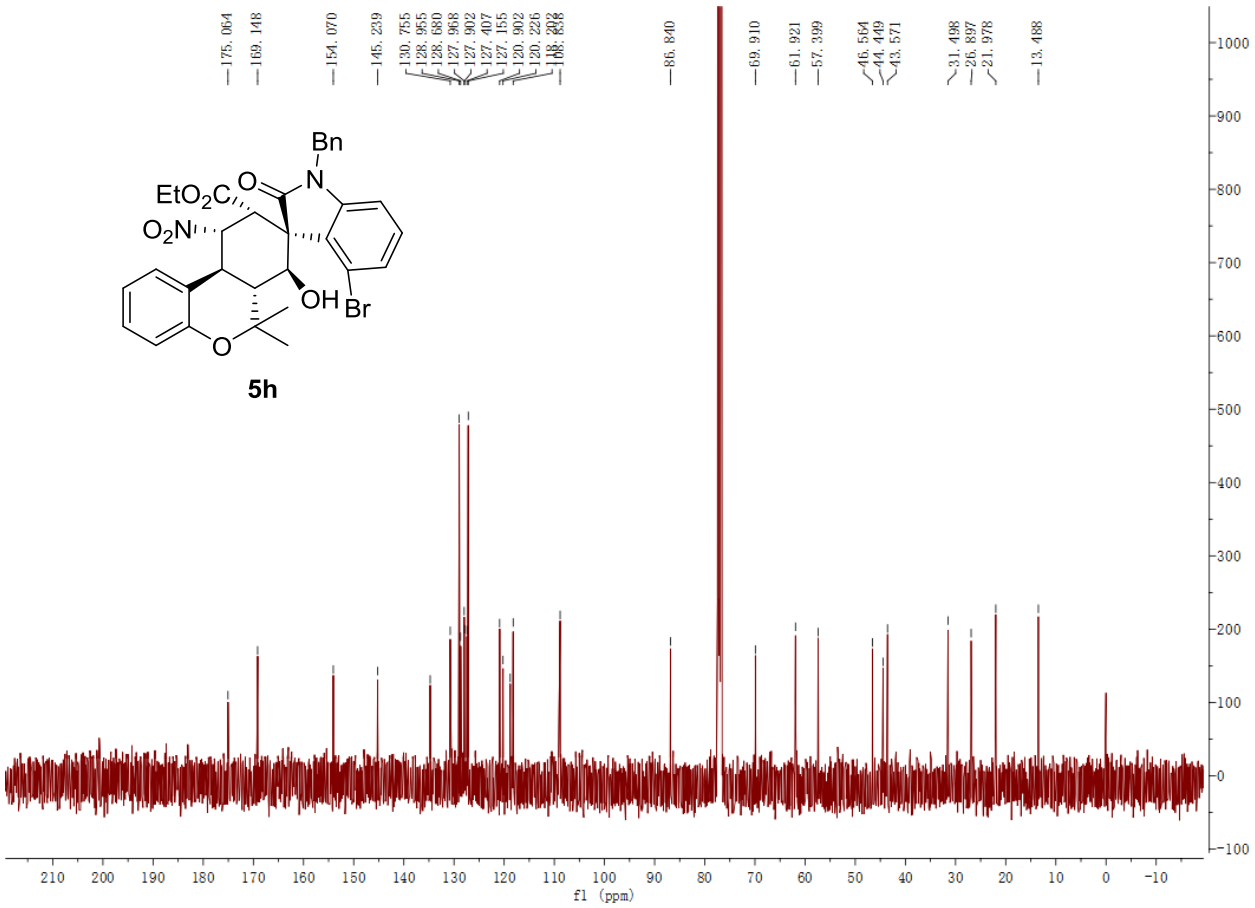


Peak#	Ret. Time	Area	Area %
1	14.633	2136057	49.814
2	15.917	2152013	50.186
Total		4288070	100.000

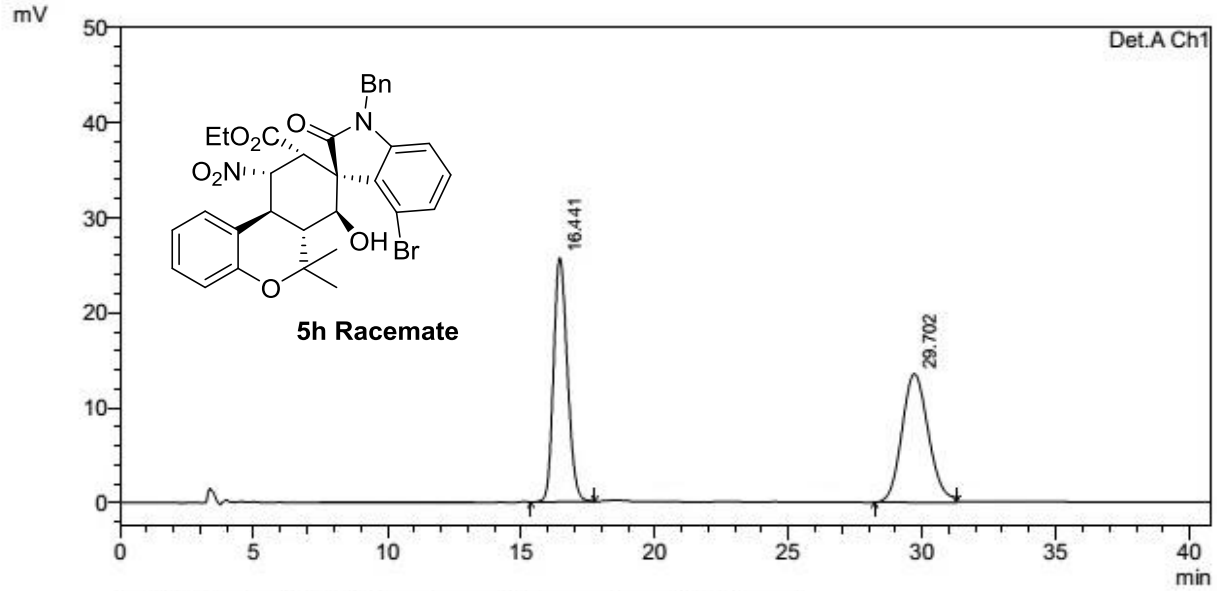


Peak#	Ret. Time	Area	Area %
1	14.539	605143	98.663
2	15.810	8203	1.337
Total		613346	100.000

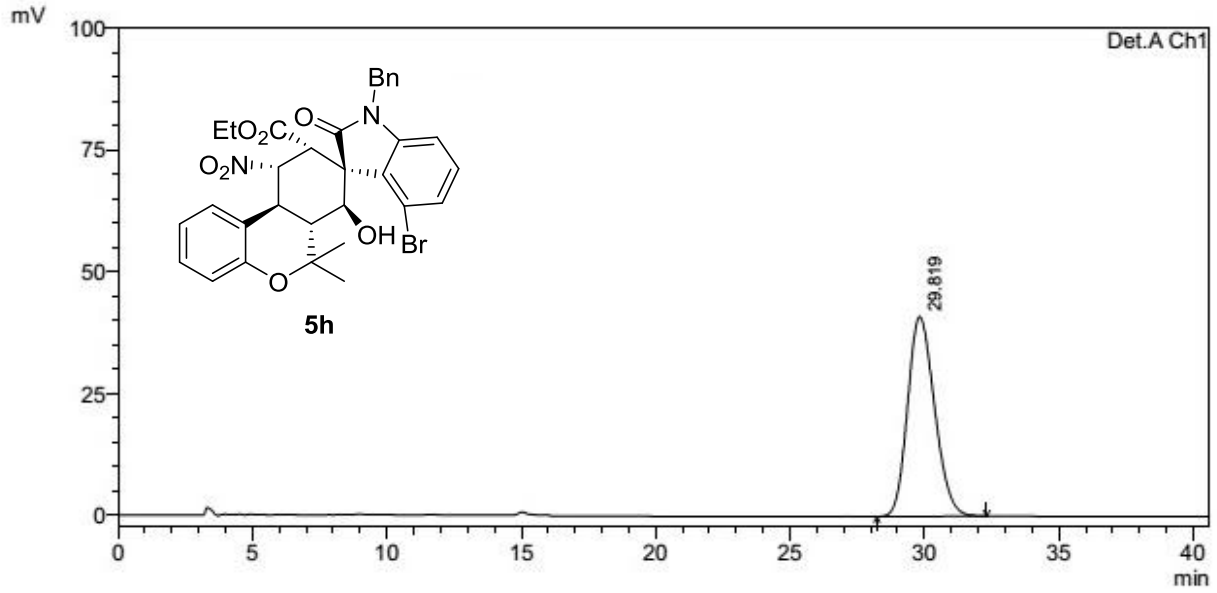

Bn
N
EtO2C
O
O2N
OH
Br
O
5h
f1 (ppm)


Bn
N
EtO2C
O
O2N
OH
Br
O
5h
f1 (ppm)

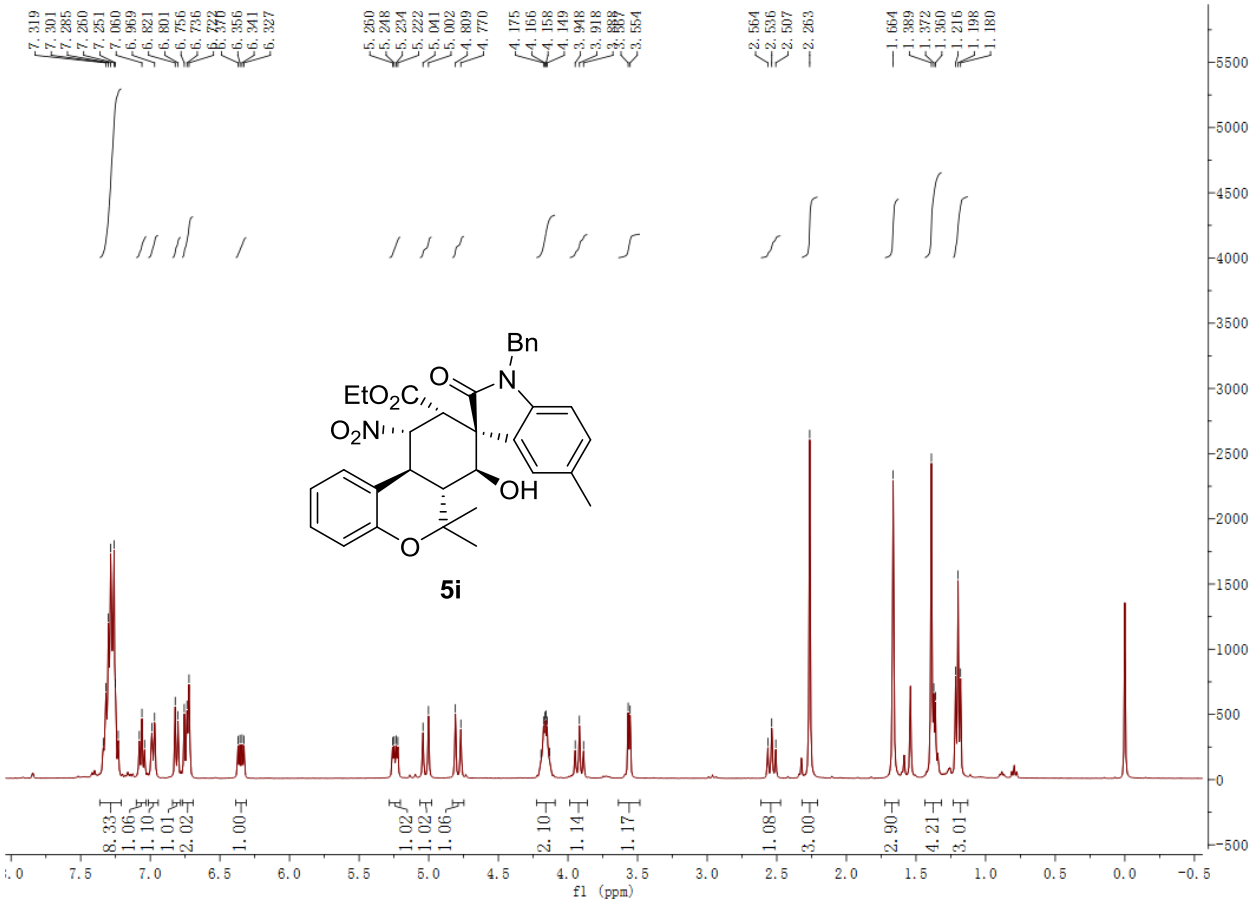
<Chromatogram>

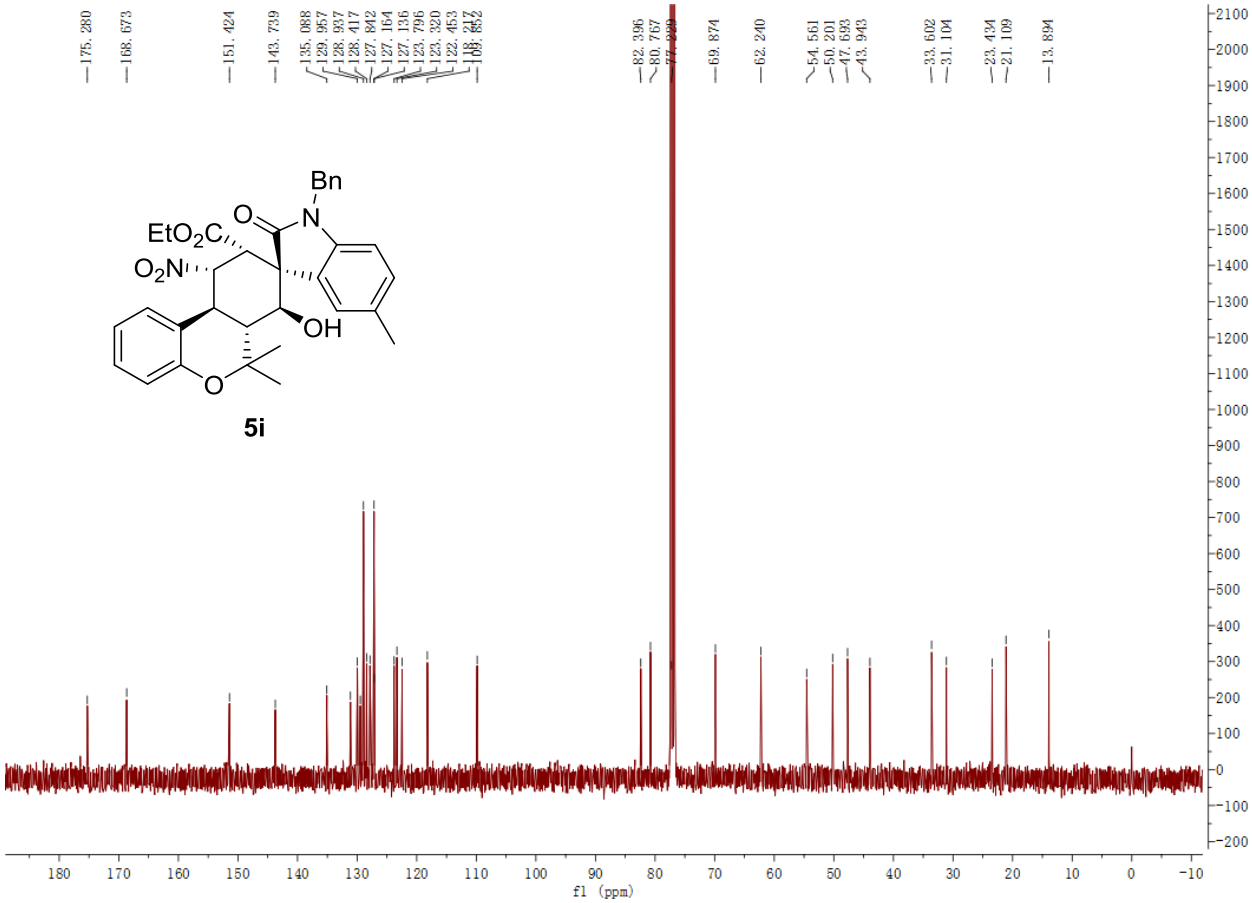


Peak#	Ret. Time	Area	Area %
1	16.441	920927	49.587
2	29.702	936256	50.413
Total		1857183	100.000

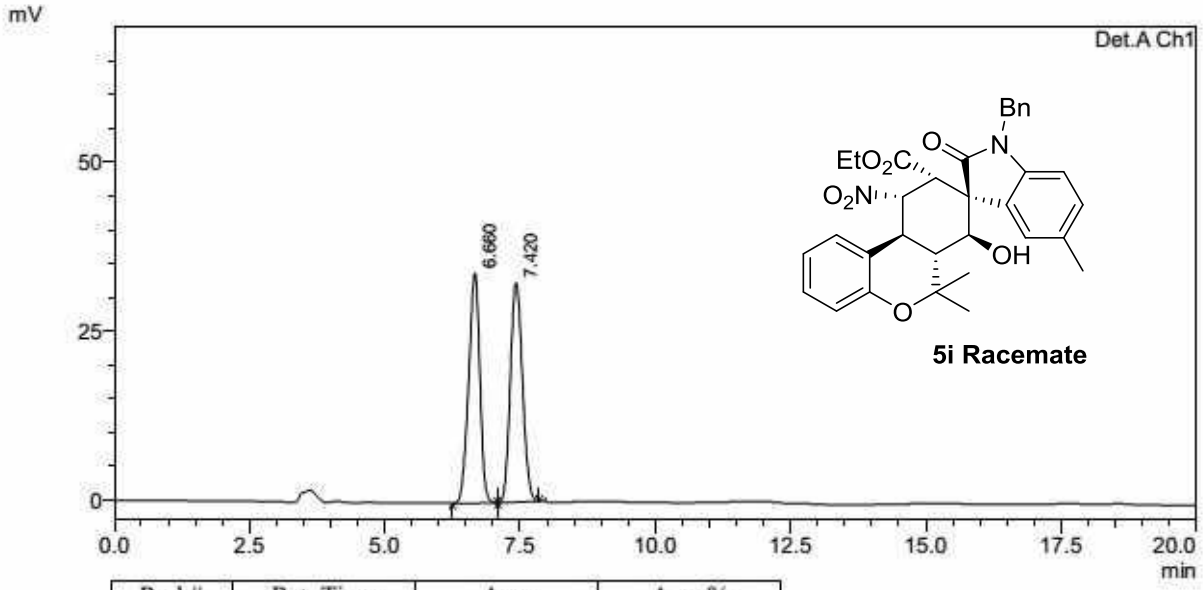


Peak#	Ret. Time	Area	Area %
1	29.819	2871392	100.000
Total		2871392	100.000


Bn
EtO2C
O2N
OH
5i
f1 (ppm)

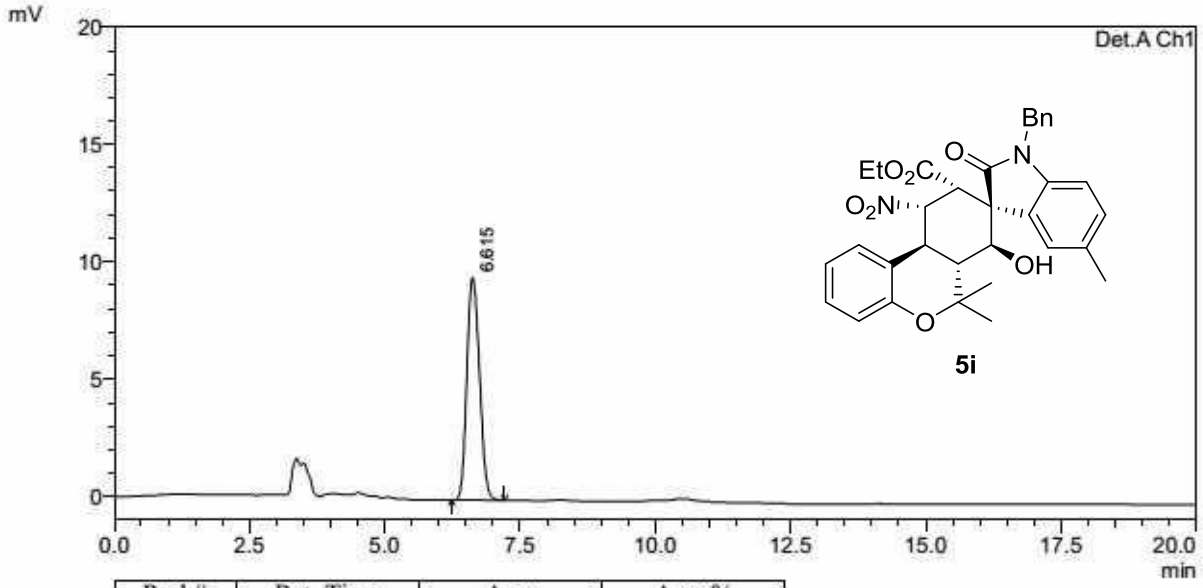

Bn
EtO2C
O2N
OH
5i
f1 (ppm)

<Chromatogram>



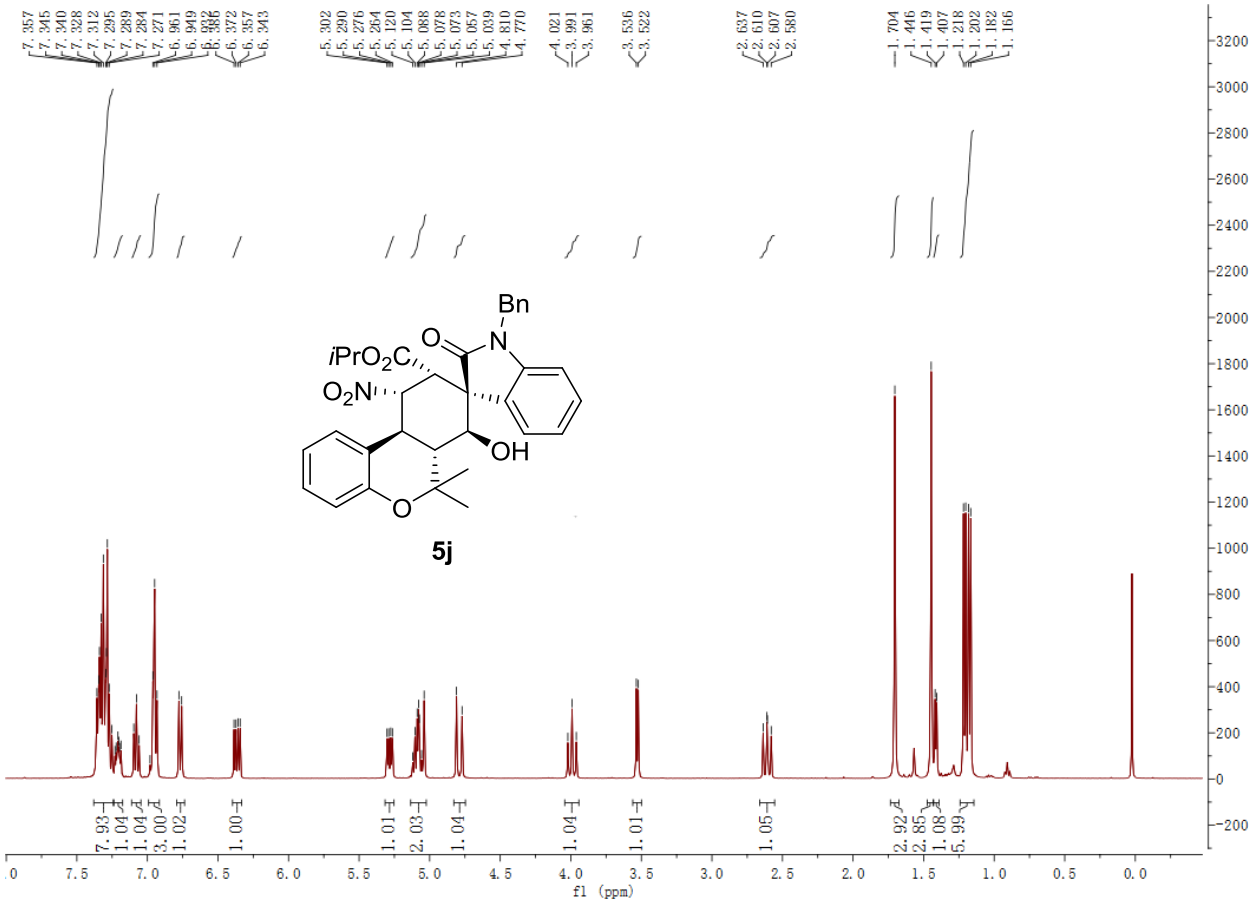
5i Racemate

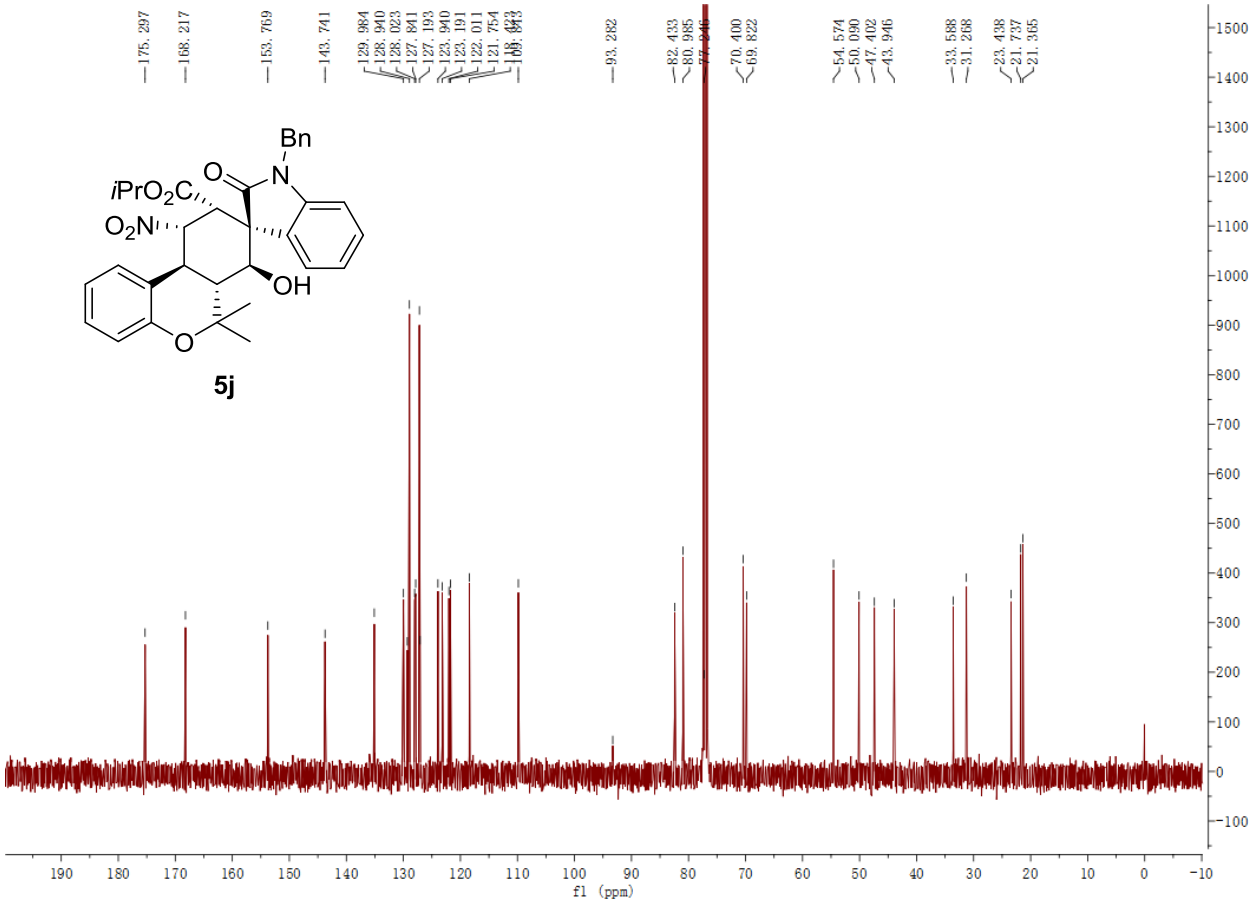
Peak#	Ret. Time	Area	Area %
1	6.660	492545	49.297
2	7.420	506596	50.703
Total		999142	100.000



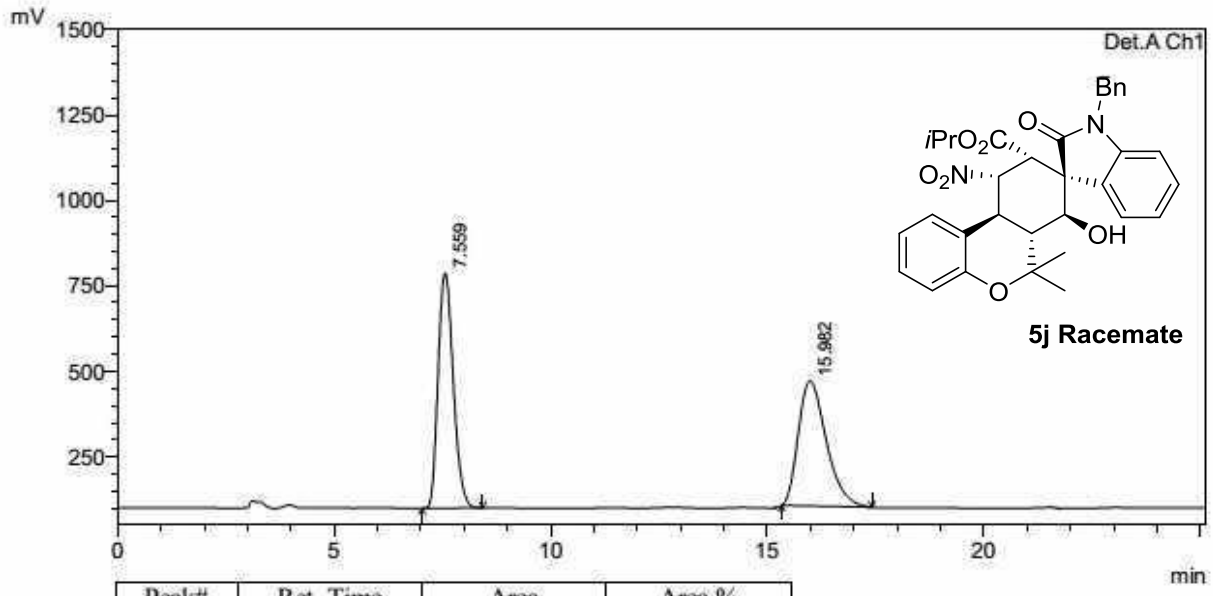
5i

Peak#	Ret. Time	Area	Area %
1	6.615	154827	100.000
Total		154827	100.000


Bn
N
O
iPrO2C
O2N
OH
O
5j
f1 (ppm)

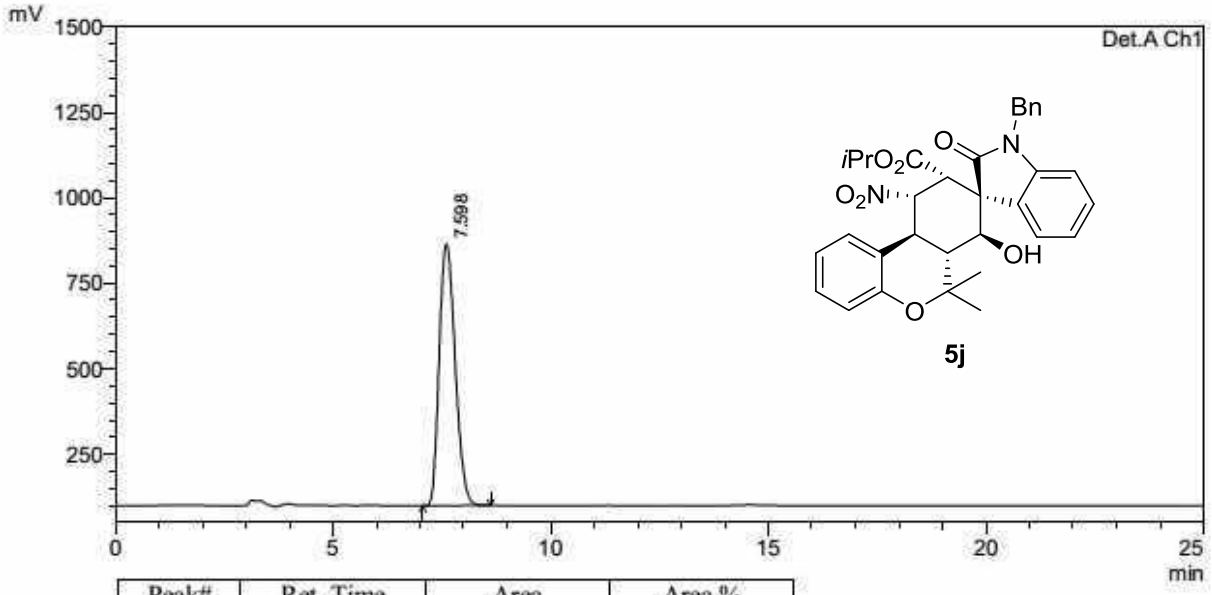

Bn
N
O
iPrO2C
O2N
OH
O
5j
f1 (ppm)

<Chromatogram>



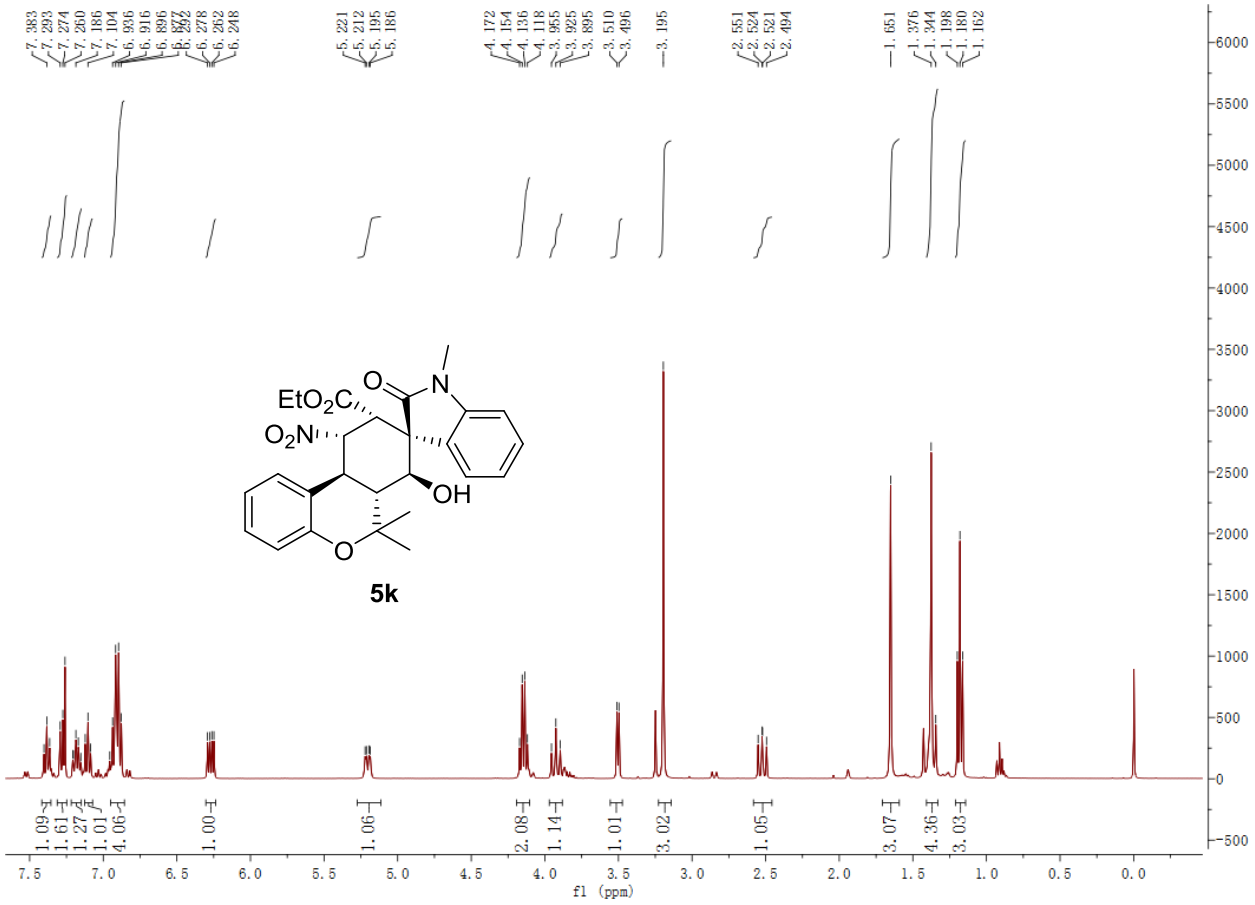
5j Racemate

Peak#	Ret. Time	Area	Area %
1	7.559	16678708	50.303
2	15.982	16477504	49.697
Total		33156212	100.000

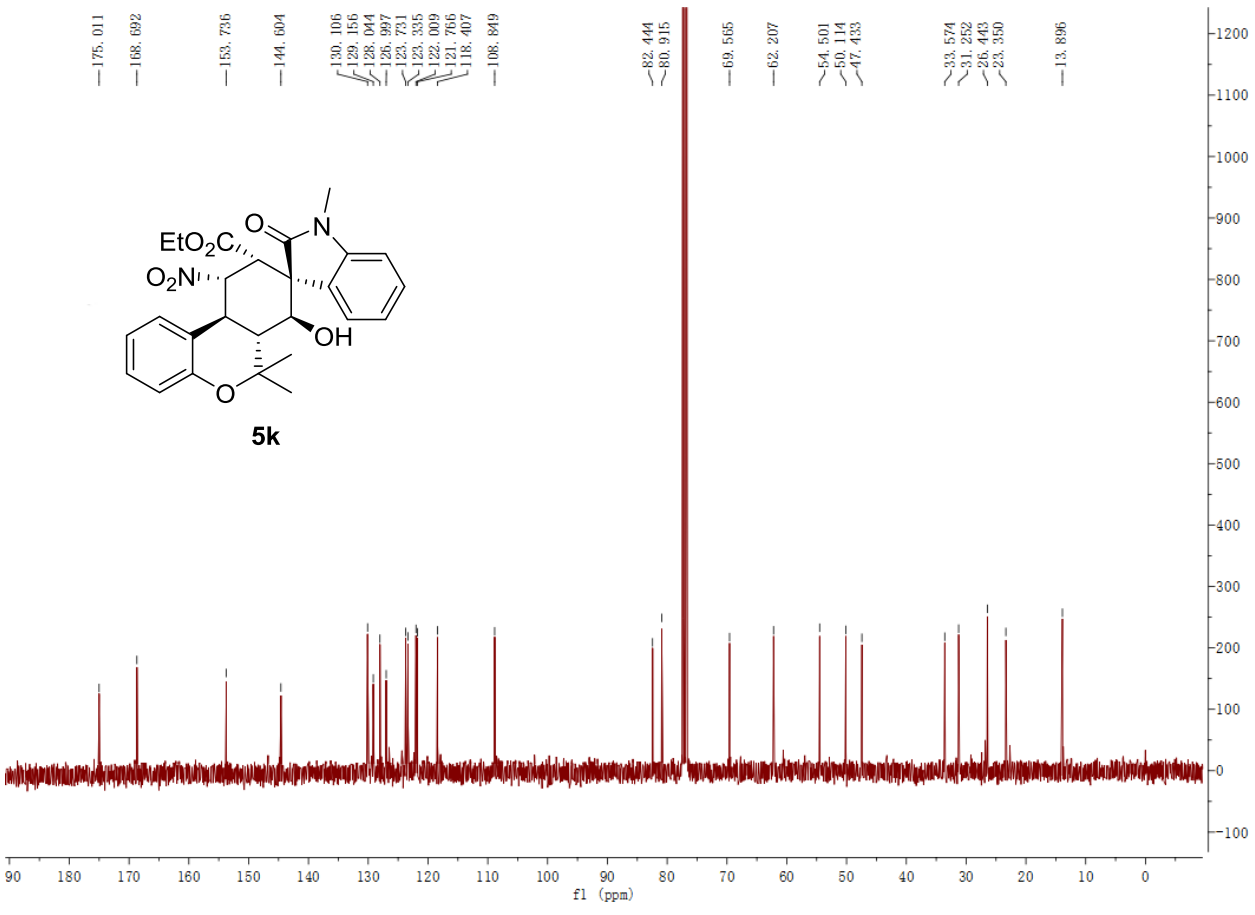


5j

Peak#	Ret. Time	Area	Area %
1	7.598	19508285	100.000
Total		19508285	100.000

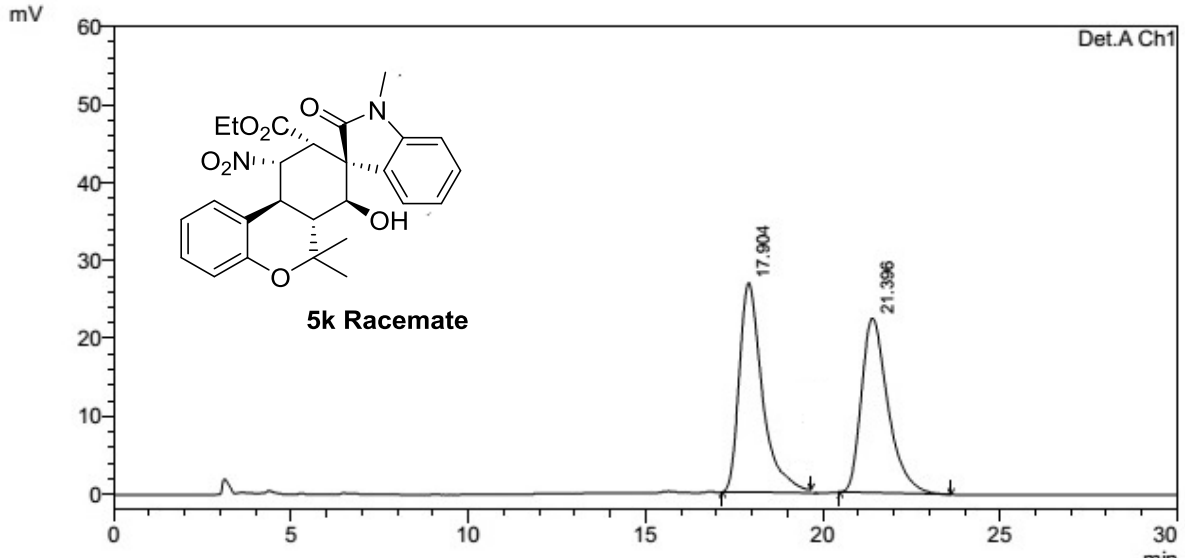

7.383
7.293
7.274
7.260
7.186
7.104
6.936
6.916
6.896
6.278
6.262
6.248
5.221
5.212
5.195
5.186
4.172
4.154
4.136
4.118
3.965
3.925
3.895
3.510
3.496
3.195
2.551
2.524
2.521
2.494
1.651
1.376
1.344
1.198
1.180
1.162
EtO2C
O2N
O
N
OH
O
1.09
1.61
1.27
1.01
4.06
1.00
1.06
2.08
1.14
1.01
3.02
1.05
3.07
4.36
3.03
f1 (ppm)

5k


175.011
168.692
153.736
144.604
130.106
129.156
128.044
126.997
123.731
123.335
122.009
121.766
118.407
108.849
82.444
80.915
69.565
62.207
54.501
50.114
47.433
33.574
31.252
26.443
23.350
13.896
EtO2C
O2N
O
N
OH
O
f1 (ppm)

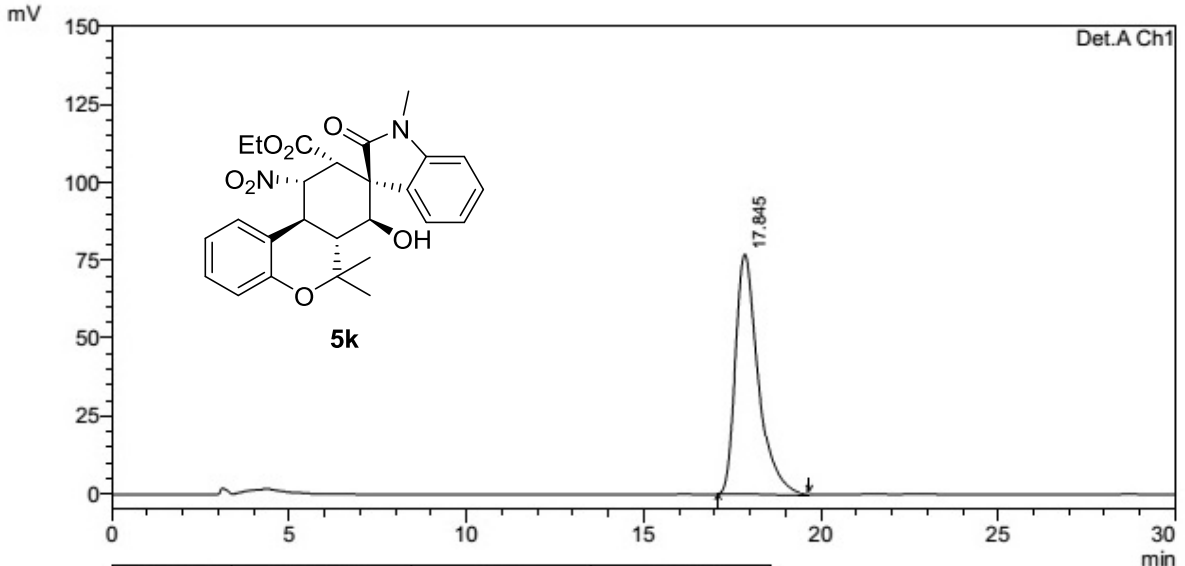
5k

<Chromatogram>



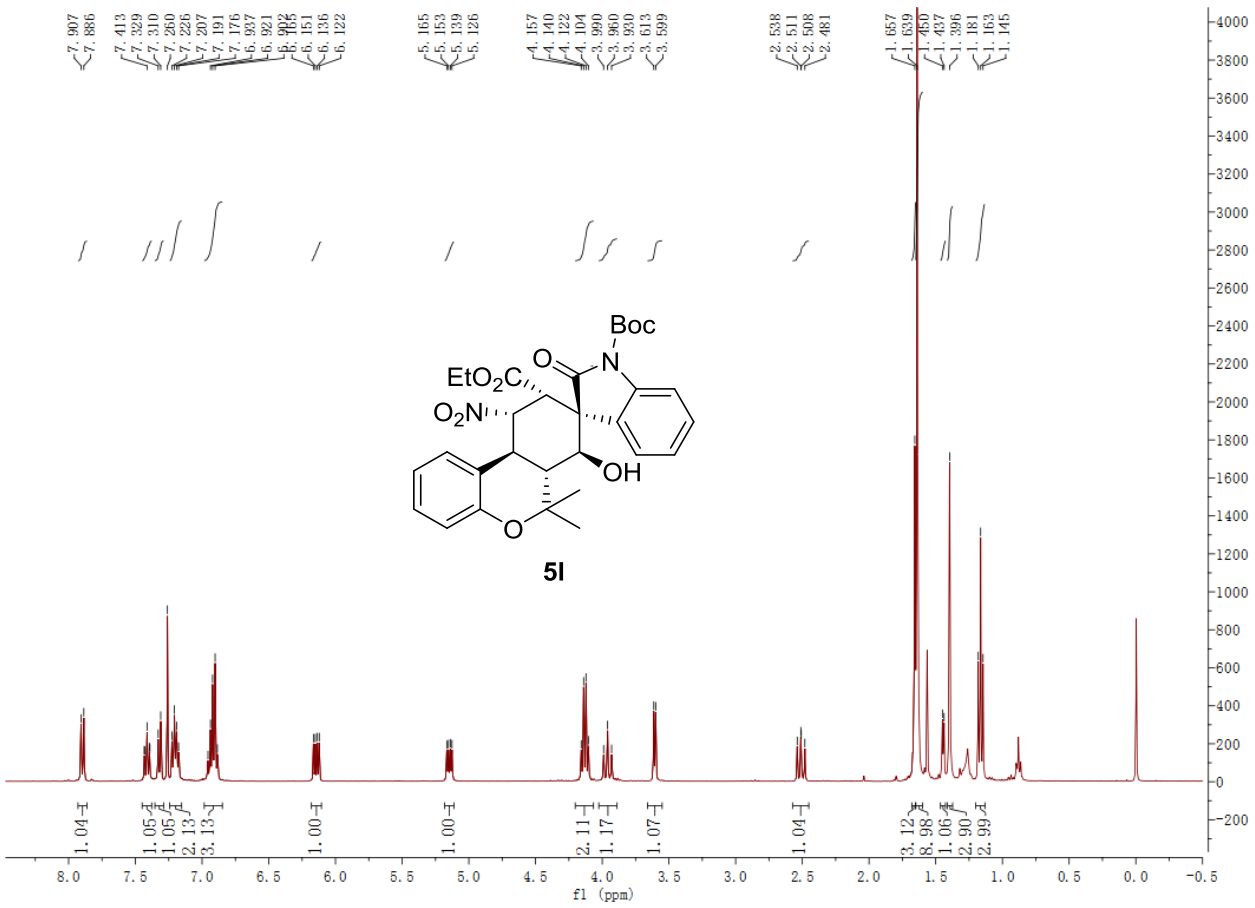
5k Racemate

Peak#	Ret. Time	Area	Area %
1	17.904	1181400	50.337
2	21.396	1165563	49.663
Total		2346963	100.000

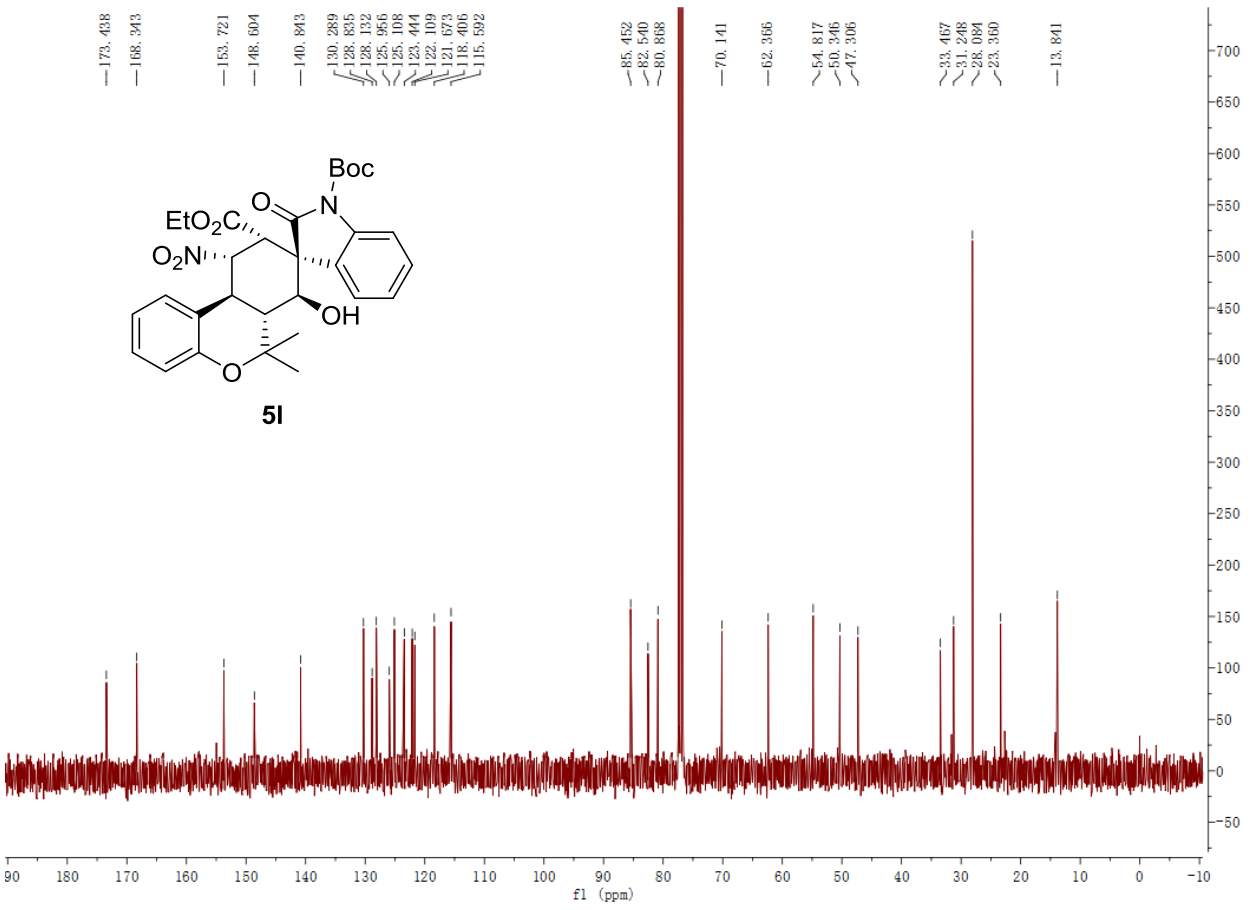


5k

Peak#	Ret. Time	Area	Area %
1	17.845	3532315	100.000
Total		3532315	100.000

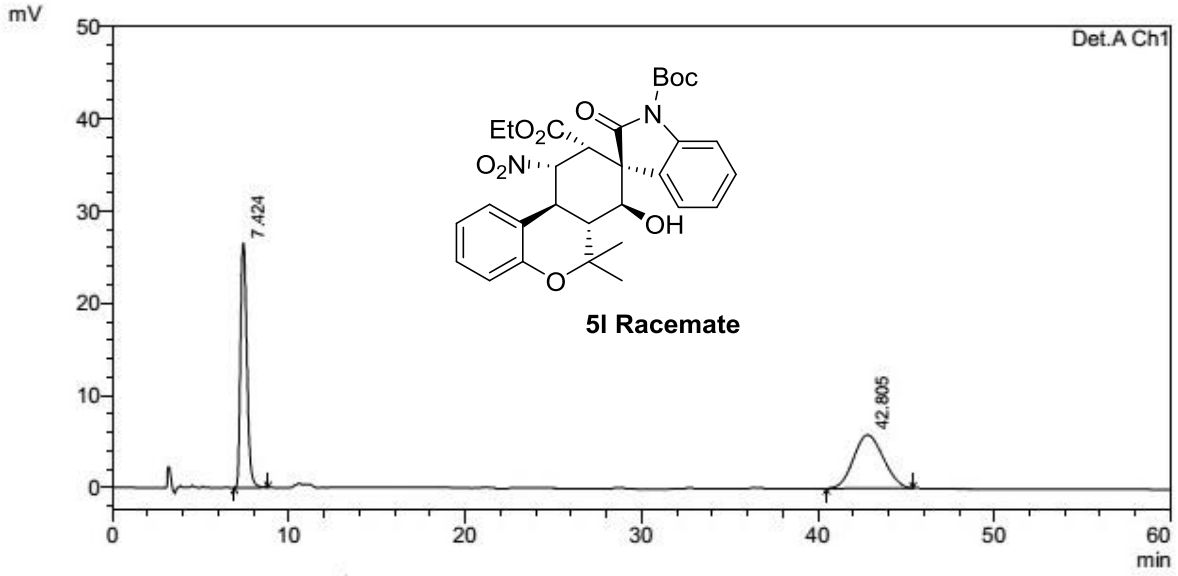


5l



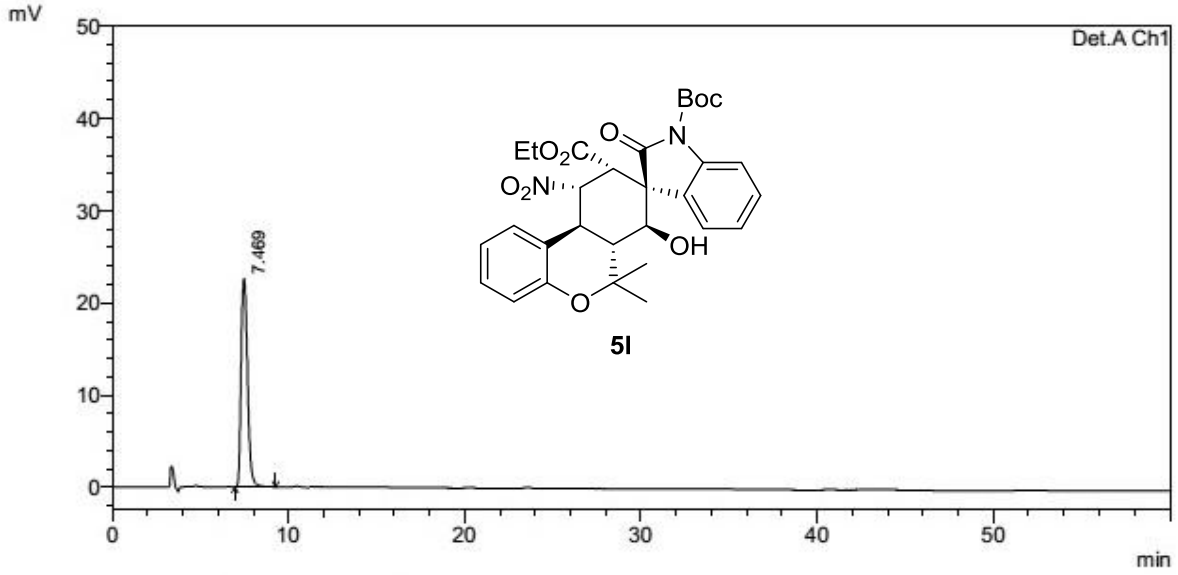
5l

<Chromatogram>



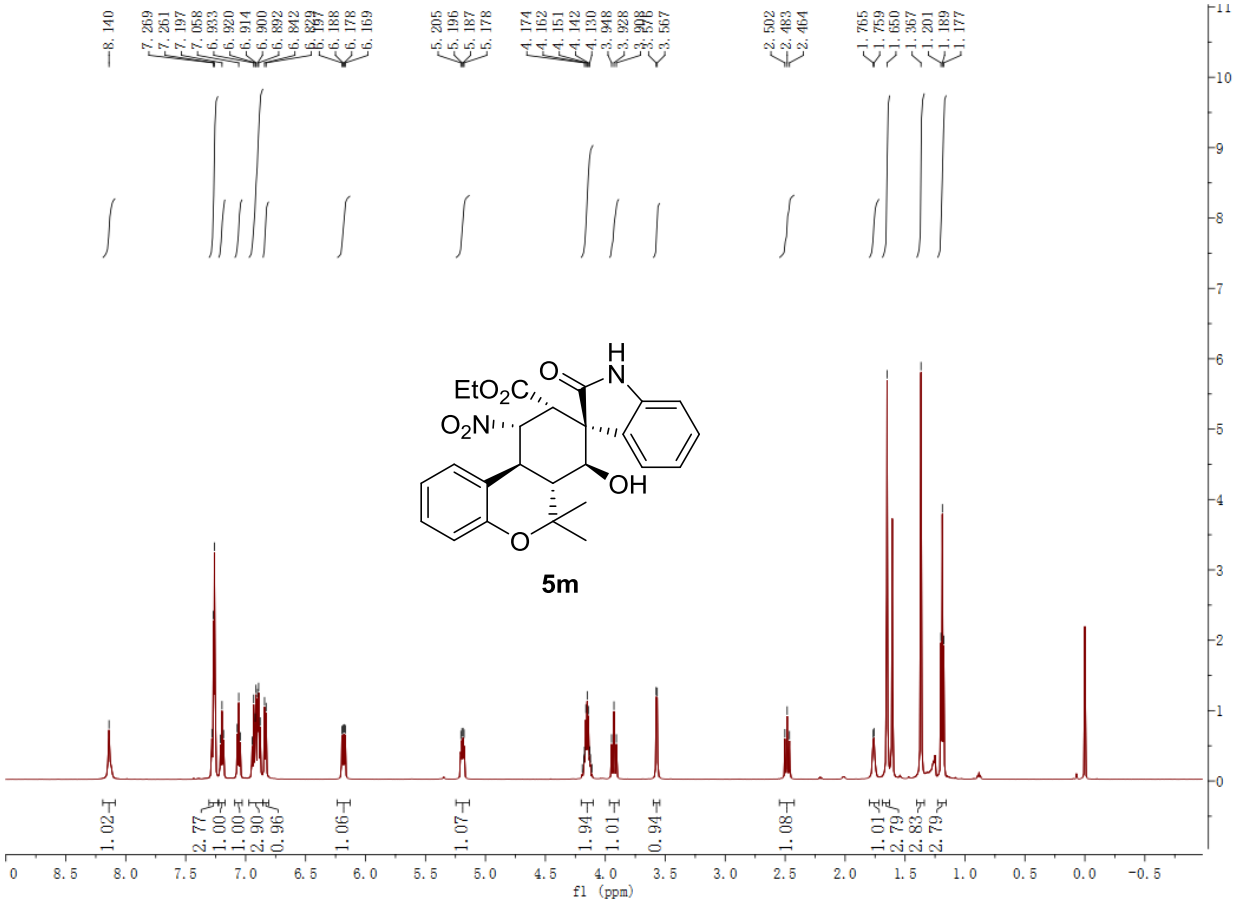
5l Racemate

Peak#	Ret. Time	Area	Area %
1	7.424	674231	49.627
2	42.805	684354	50.373
Total		1358586	100.000

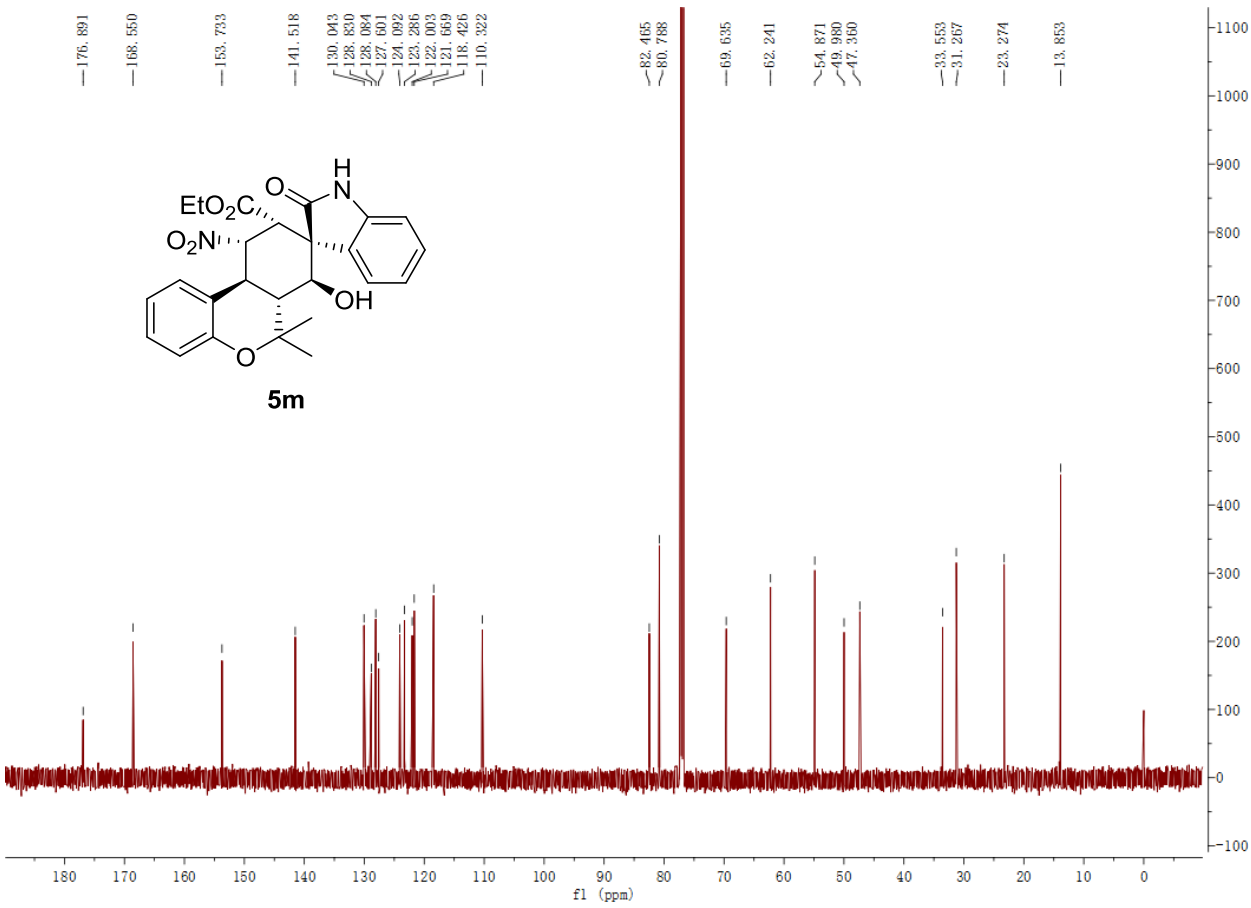


5l

Peak#	Ret. Time	Area	Area %
1	7.469	579987	100.000
Total		579987	100.000

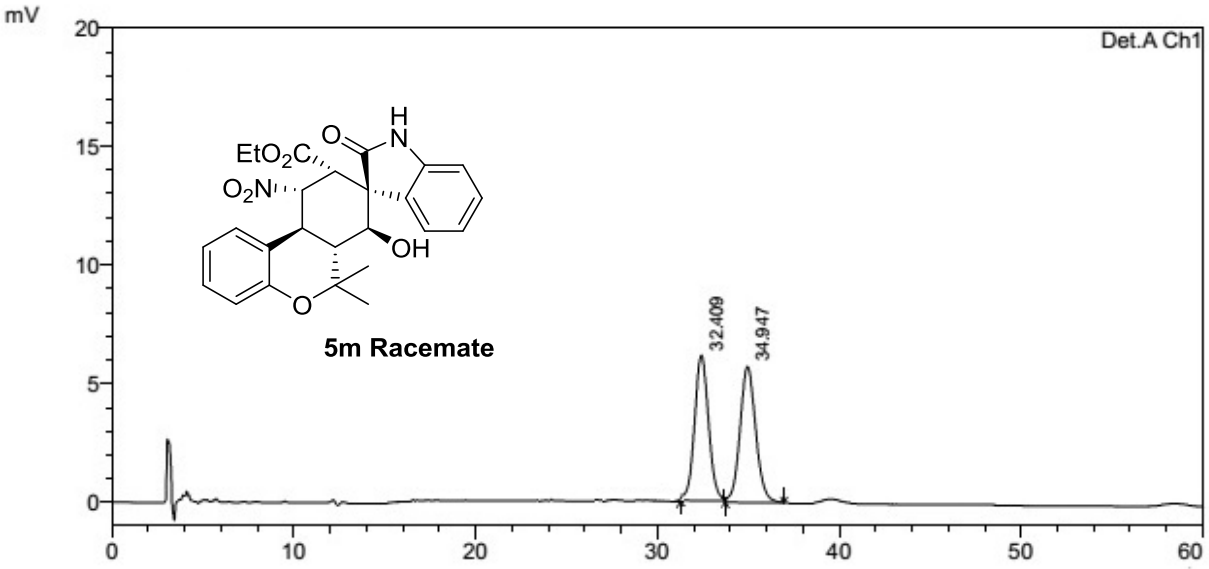

8.140
7.269
7.261
7.197
7.058
6.933
6.920
6.914
6.900
6.892
6.842
6.188
6.178
6.169
5.205
5.196
5.187
5.178
4.174
4.162
4.151
4.142
4.130
3.948
3.928
3.567
2.502
2.483
2.464
1.765
1.759
1.650
1.367
1.201
1.189
1.177
EtO2C
O2N
O
H
N
OH
O
1.02
2.77
1.00
1.00
2.90
0.96
1.06
1.07
1.94
1.01
0.94
1.08
1.01
2.79
2.83
2.79
f1 (ppm)

5m

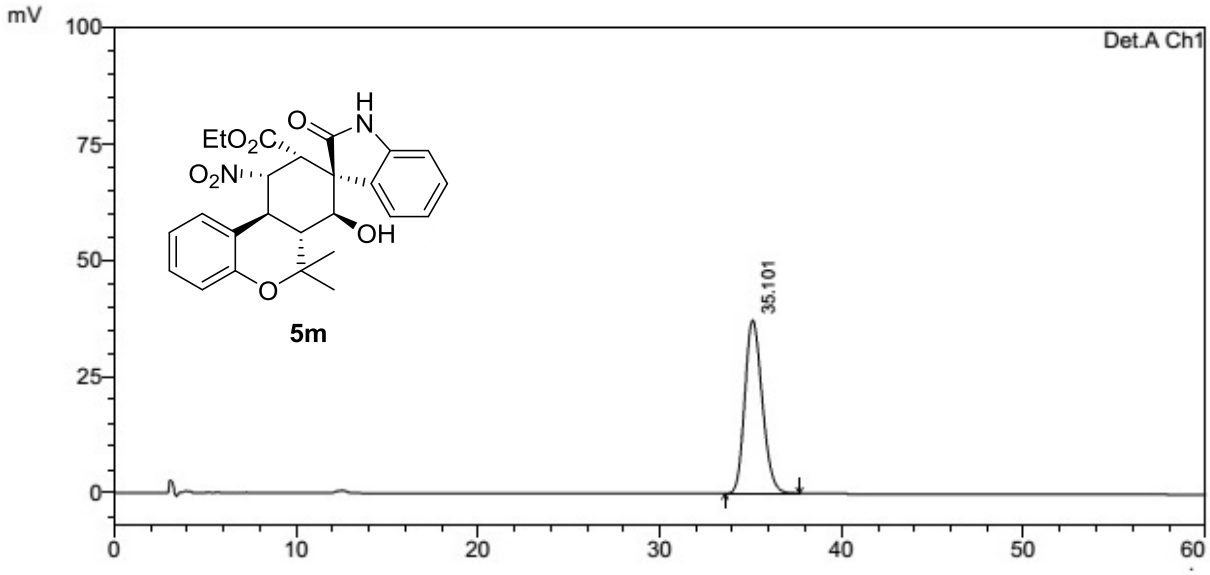

176.891
168.550
153.733
141.518
130.043
128.830
128.084
127.601
124.092
123.286
122.003
121.669
118.426
110.322
82.465
80.788
69.635
62.241
54.871
49.980
47.360
33.553
31.267
23.274
13.853
EtO2C
O2N
O
H
N
OH
O
f1 (ppm)

5m

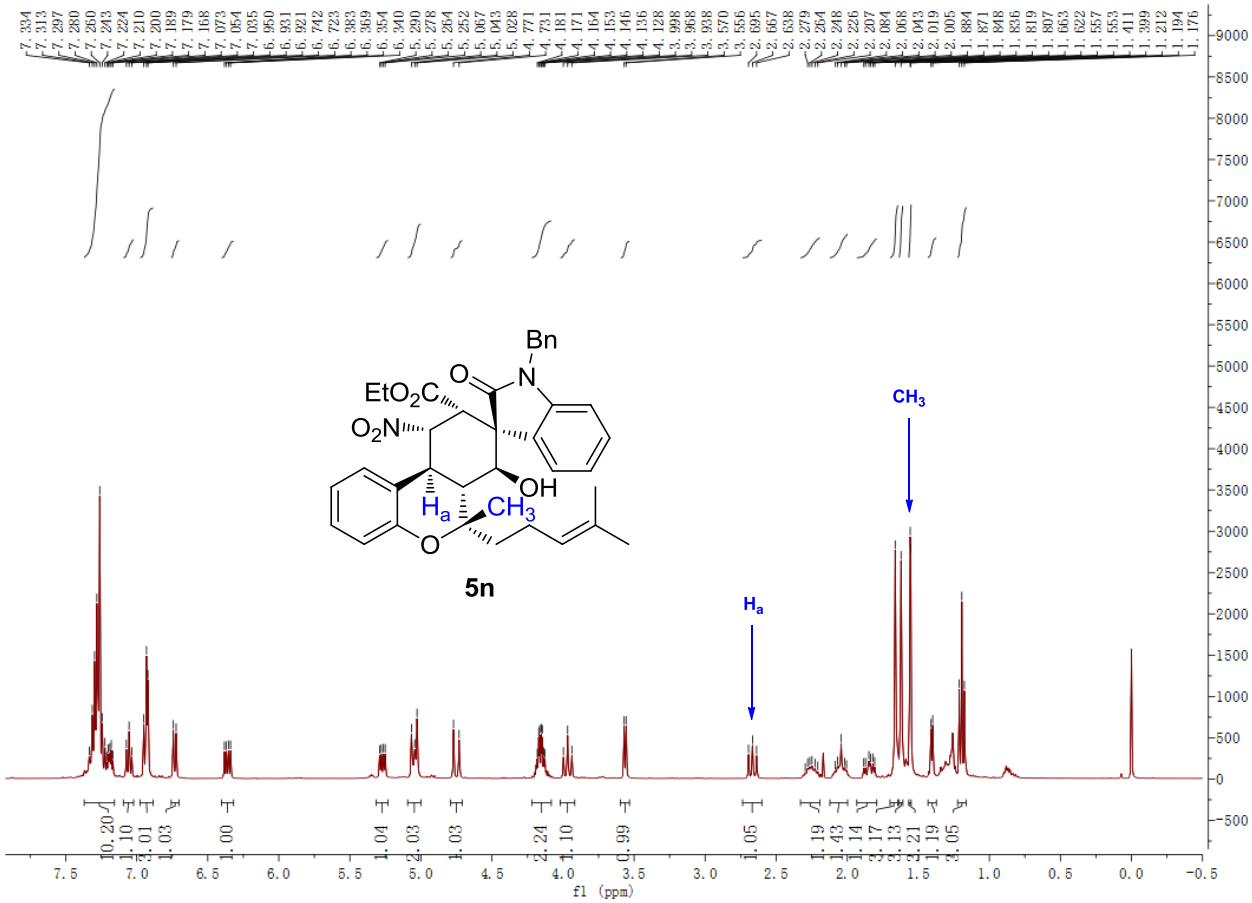
<Chromatogram>

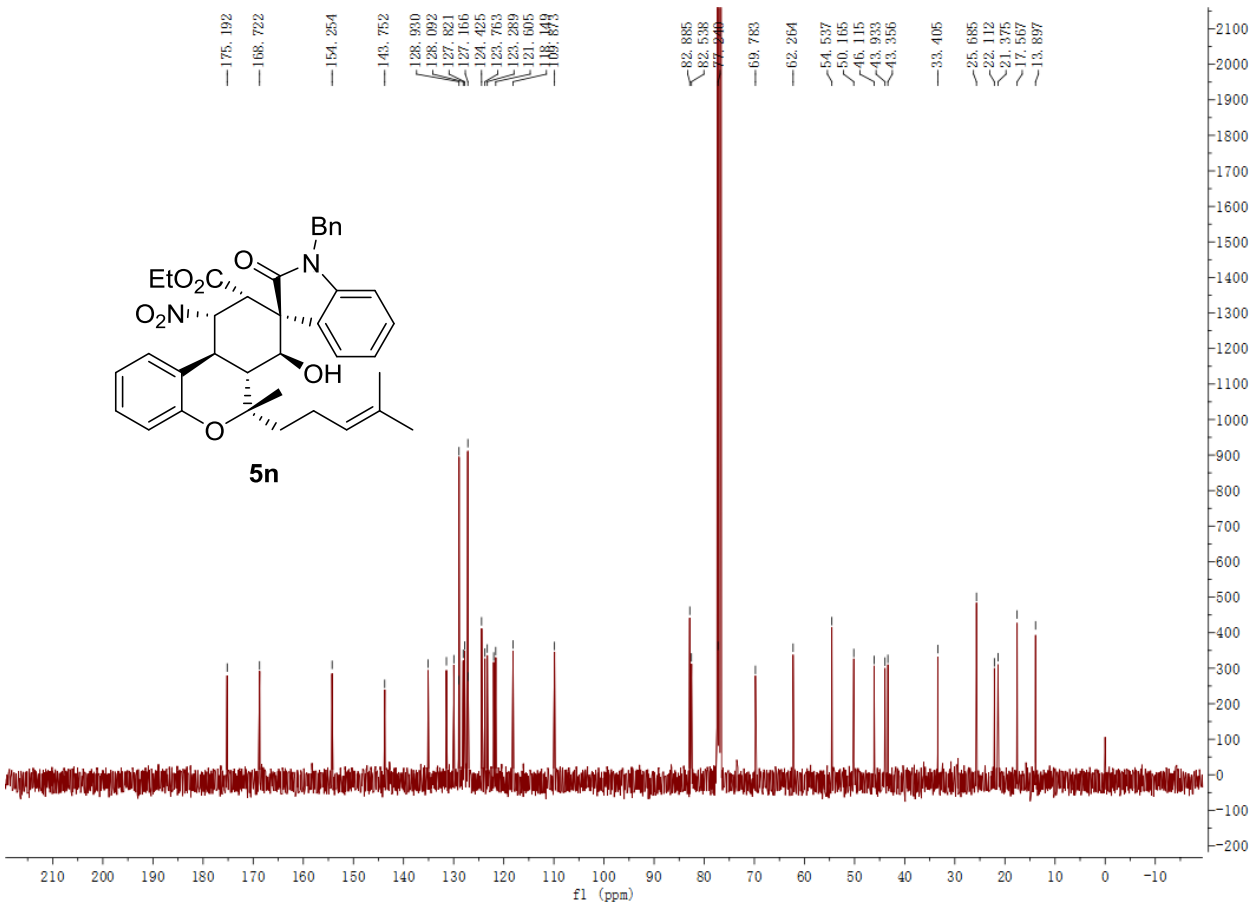


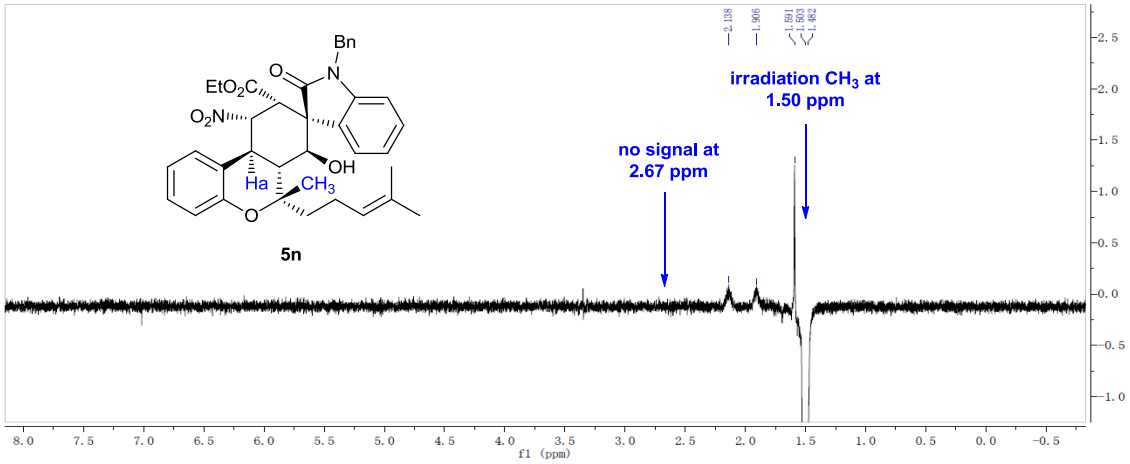
Peak#	Ret. Time	Area	Area %
1	32.409	341541	49.650
2	34.947	346352	50.350
Total		687893	100.000



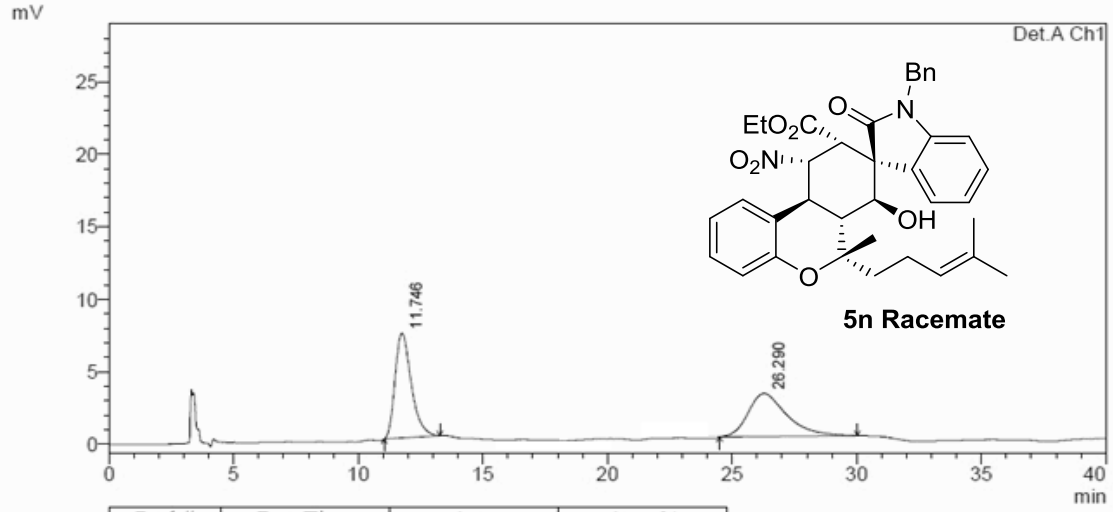
Peak#	Ret. Time	Area	Area %
1	35.101	2486580	100.000
Total		2486580	100.000


Bn
EtO2C
O
N
O2N
OH
Ha
CH3
CH3
Ha
5n
f1 (ppm)

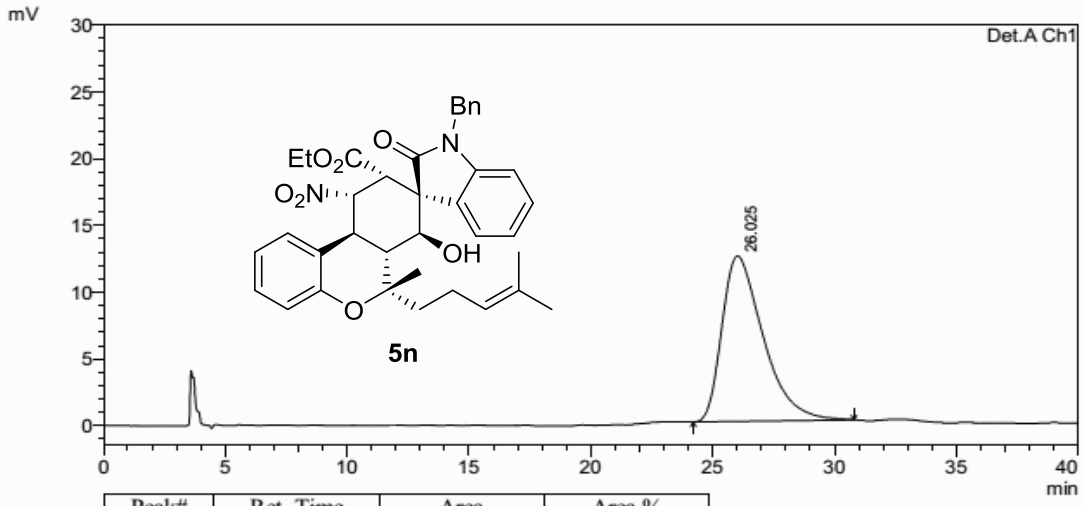

Bn
EtO2C
O
N
O2N
OH
5n
f1 (ppm)



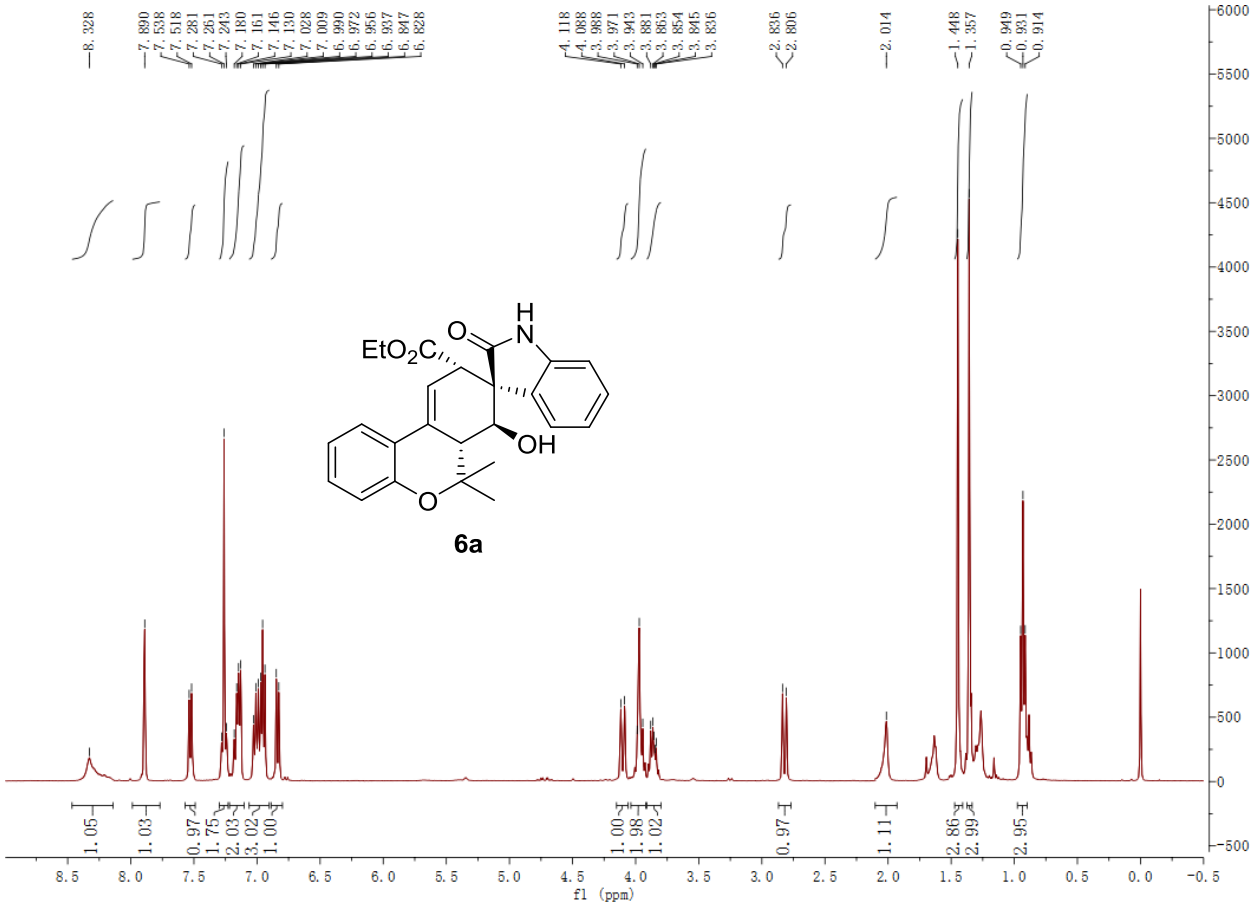
<Chromatogram>



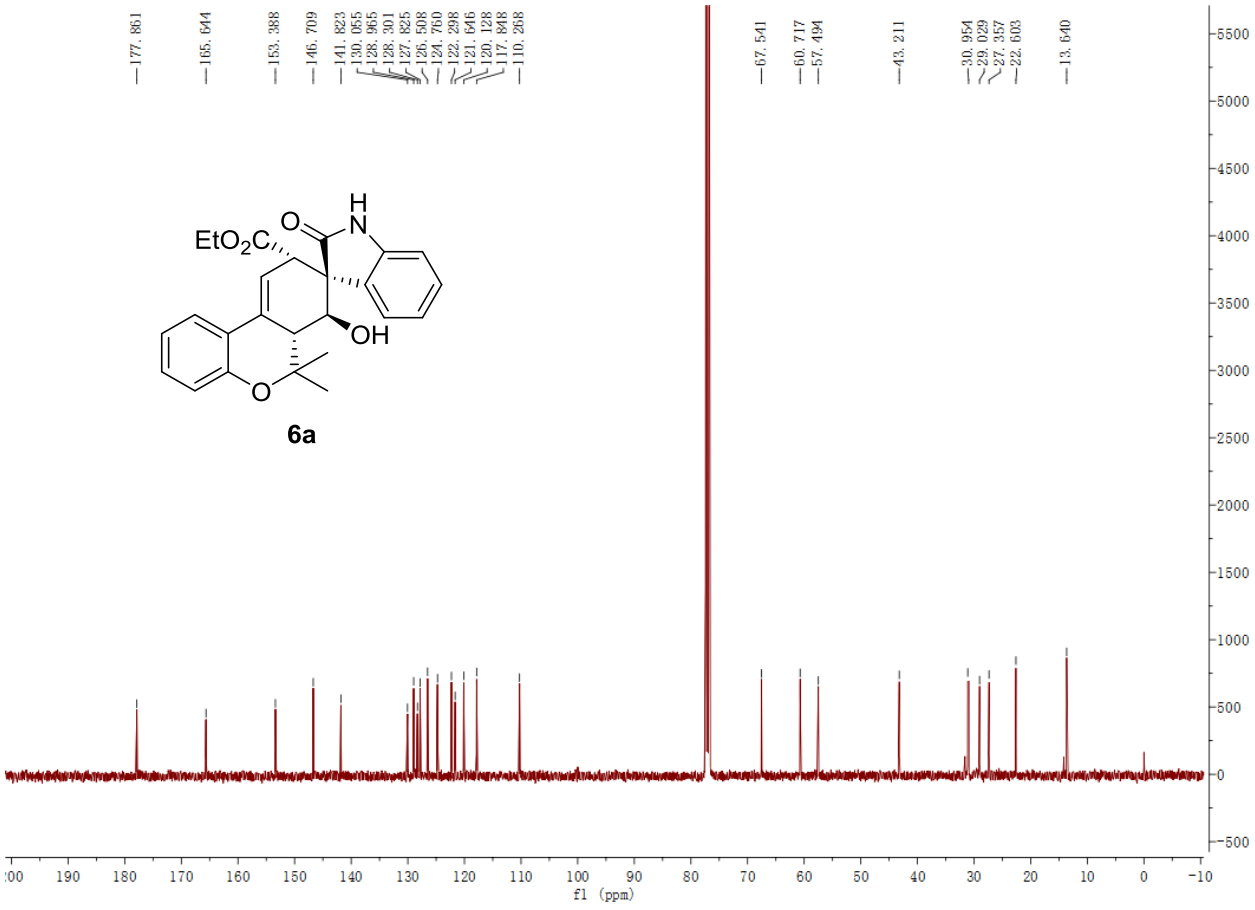
Peak#	Ret. Time	Area	Area %
1	11.746	328382	50.486
2	26.290	322060	49.514
Total		650442	100.000



Peak#	Ret. Time	Area	Area %
1	26.025	1464293	100.000
Total		1464293	100.000

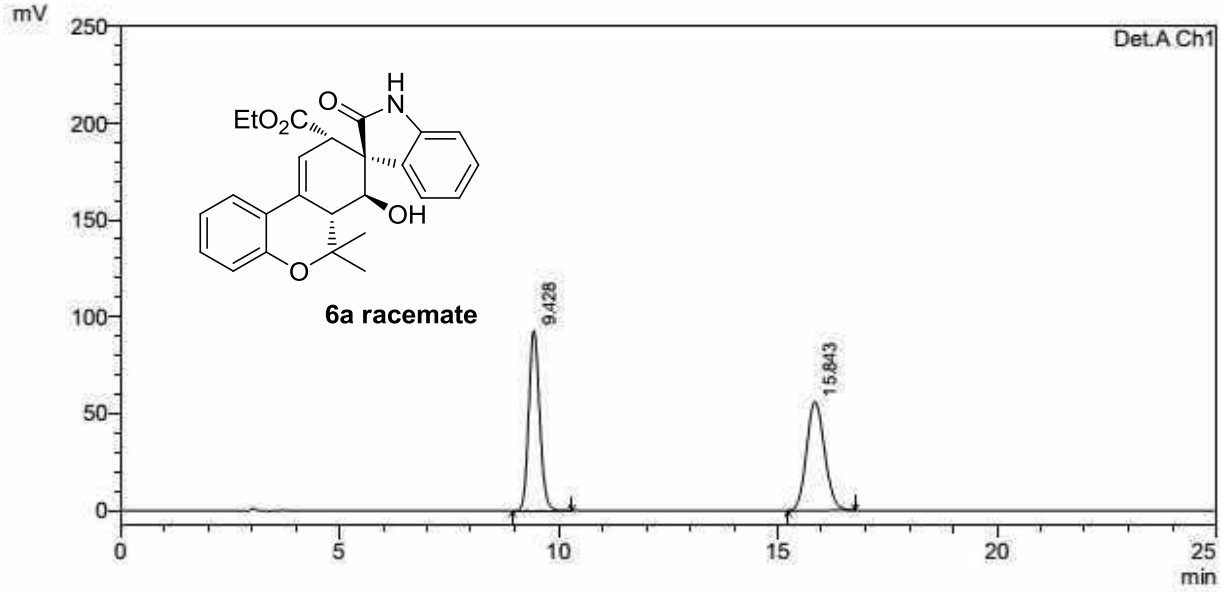

8.328
7.890
7.538
7.518
7.281
7.261
7.243
7.180
7.161
7.146
7.130
7.028
7.009
6.990
6.972
6.956
6.937
6.847
6.828
4.118
4.088
3.988
3.971
3.943
3.881
3.863
3.854
3.845
3.836
2.836
2.806
2.014
1.448
1.357
0.949
0.931
0.914
EtO2C
O
H
N
OH
O
1.05
1.03
0.97
1.75
2.03
3.02
1.00
1.00
1.98
1.02
0.97
1.11
2.86
2.99
2.95
f1 (ppm)

6a


177.861
165.644
153.388
146.709
141.823
130.055
128.965
128.301
127.825
126.508
124.760
122.298
121.646
120.128
117.848
110.268
67.541
60.717
57.494
43.211
30.954
29.029
27.357
22.603
13.640
EtO2C
O
H
N
OH
O
f1 (ppm)

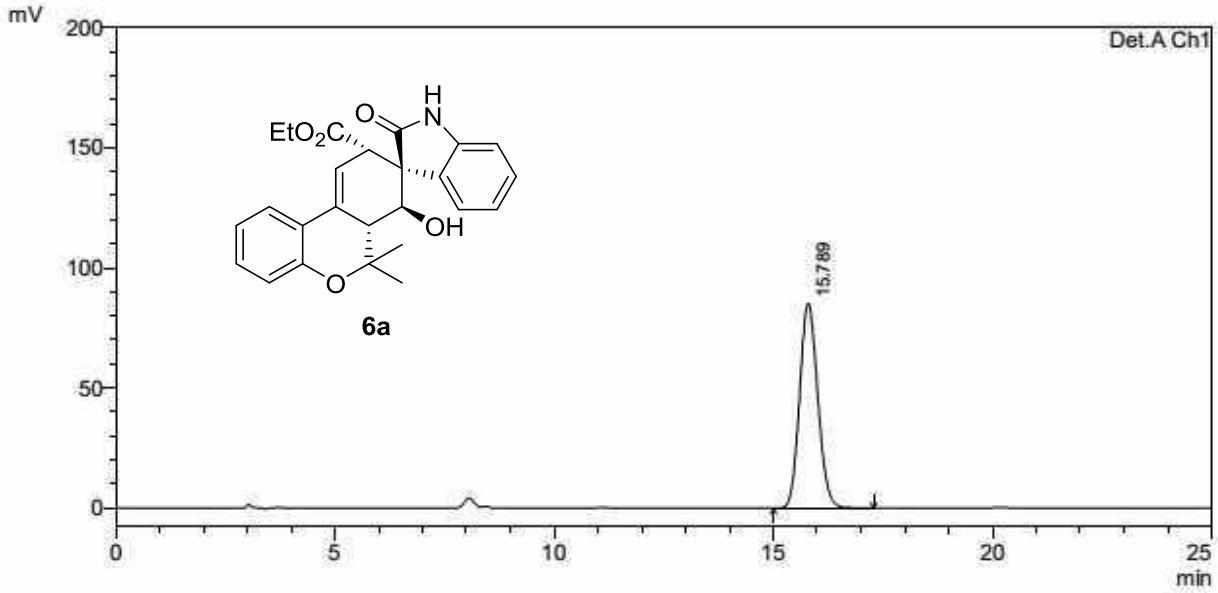
6a

<Chromatogram>



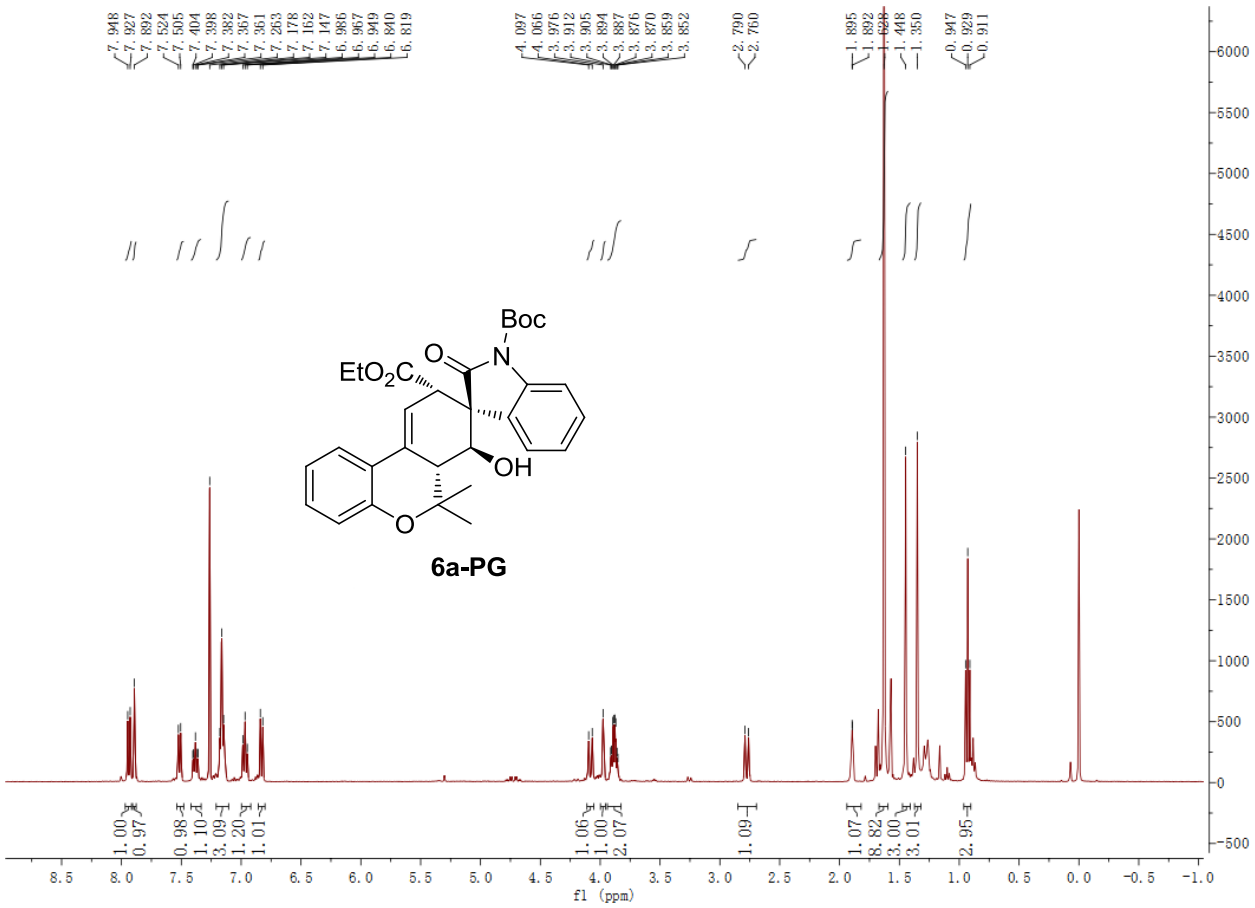
6a racemate

Peak#	Ret. Time	Area	Area %
1	9.428	1607431	49.949
2	15.843	1610697	50.051
Total		3218128	100.000

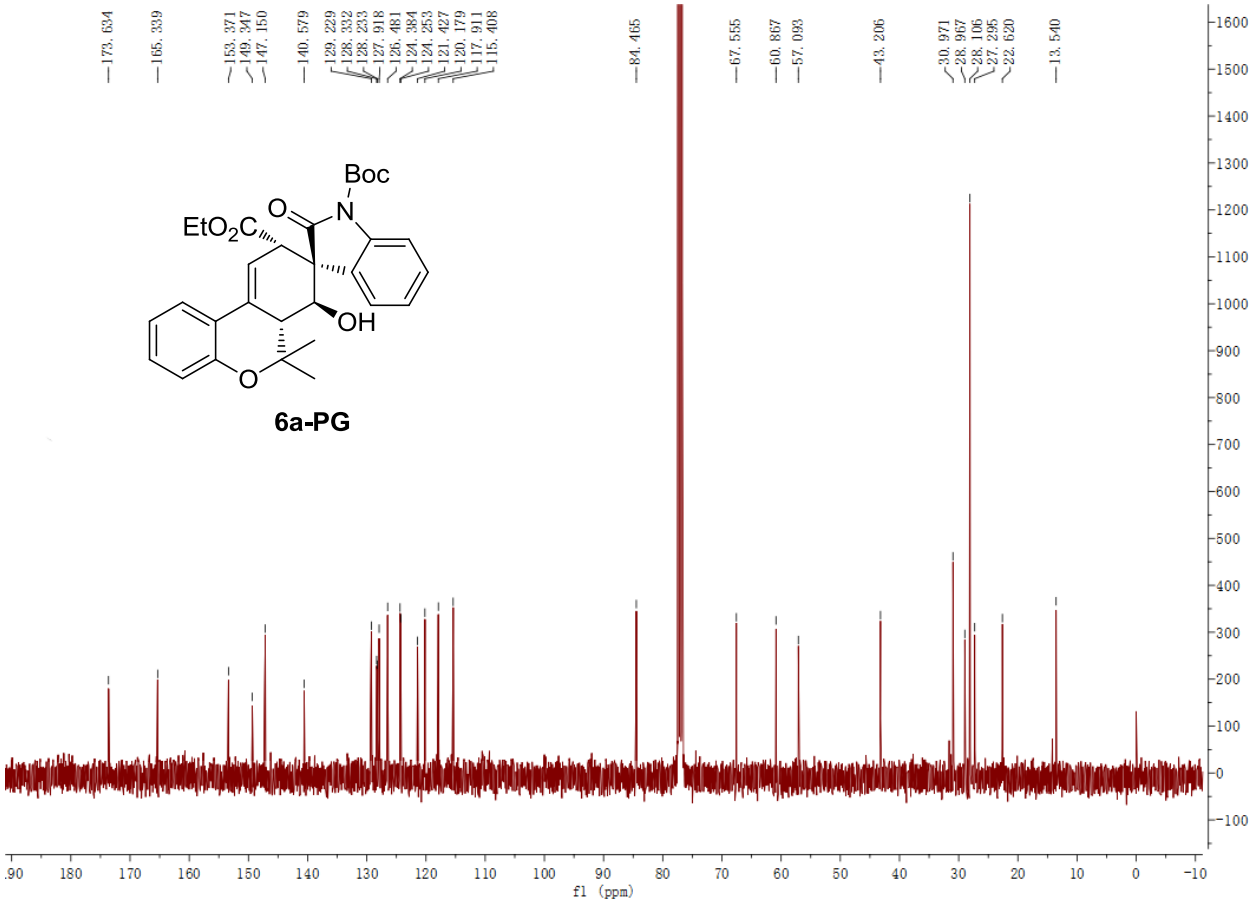


6a

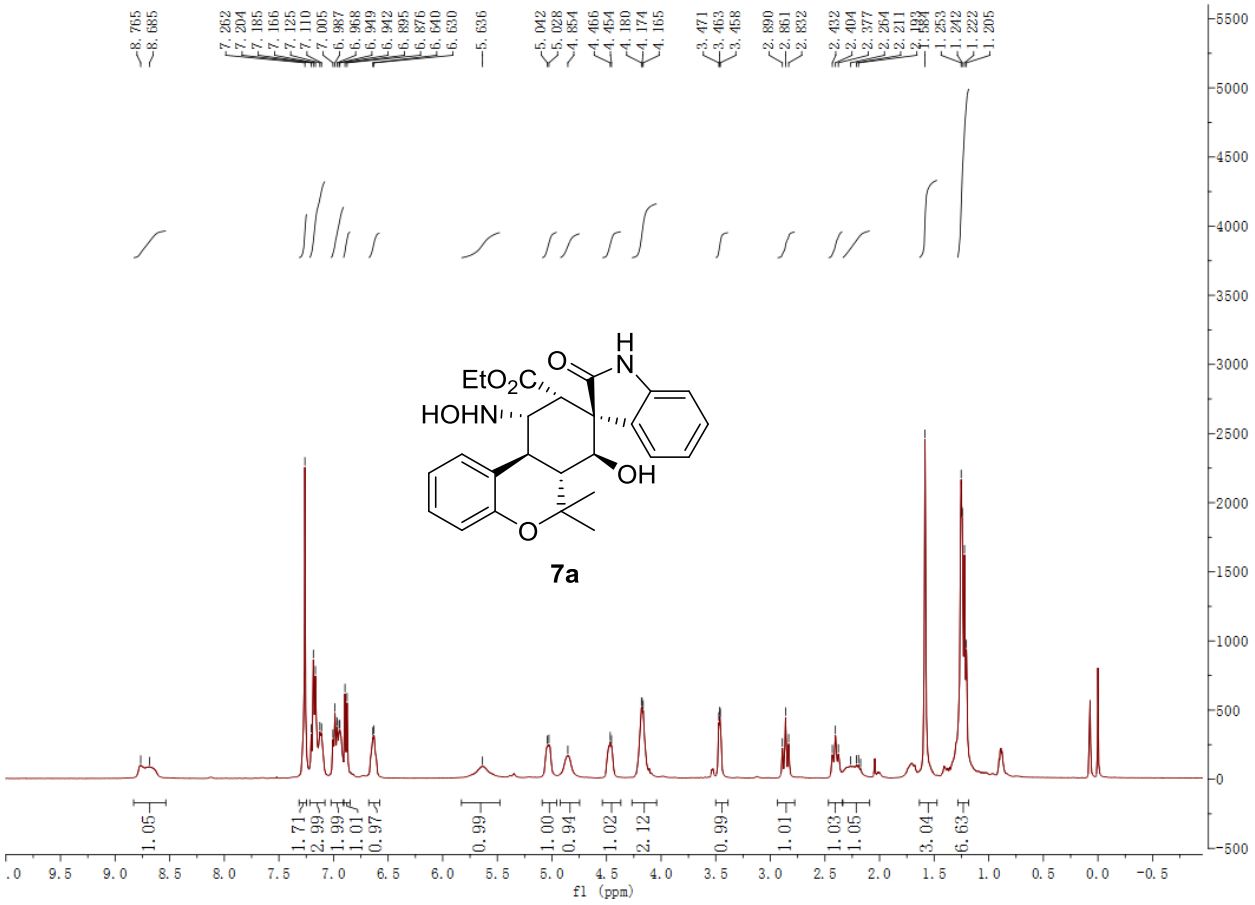
Peak#	Ret. Time	Area	Area %
1	15.789	2468489	100.000
Total		2468489	100.000

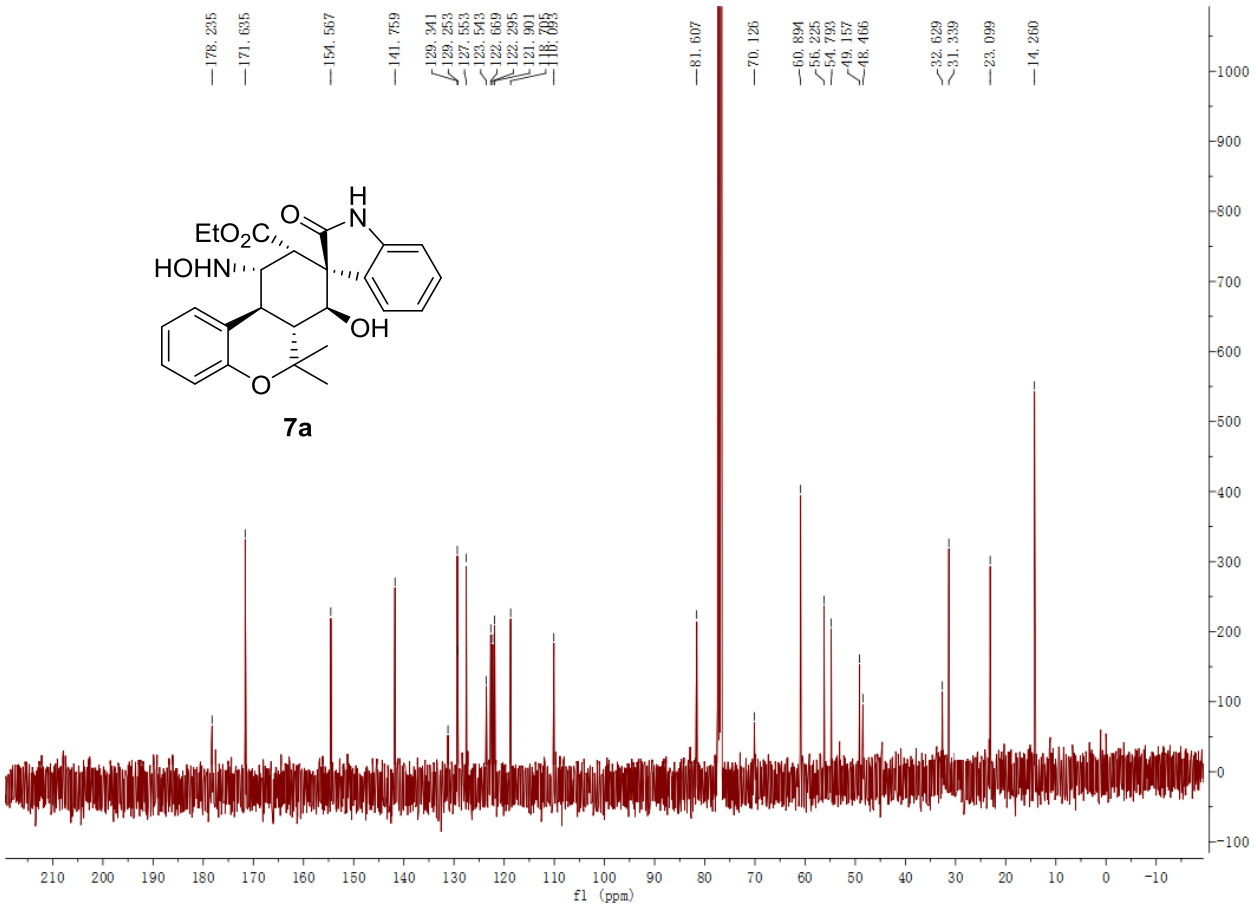


6a-PG

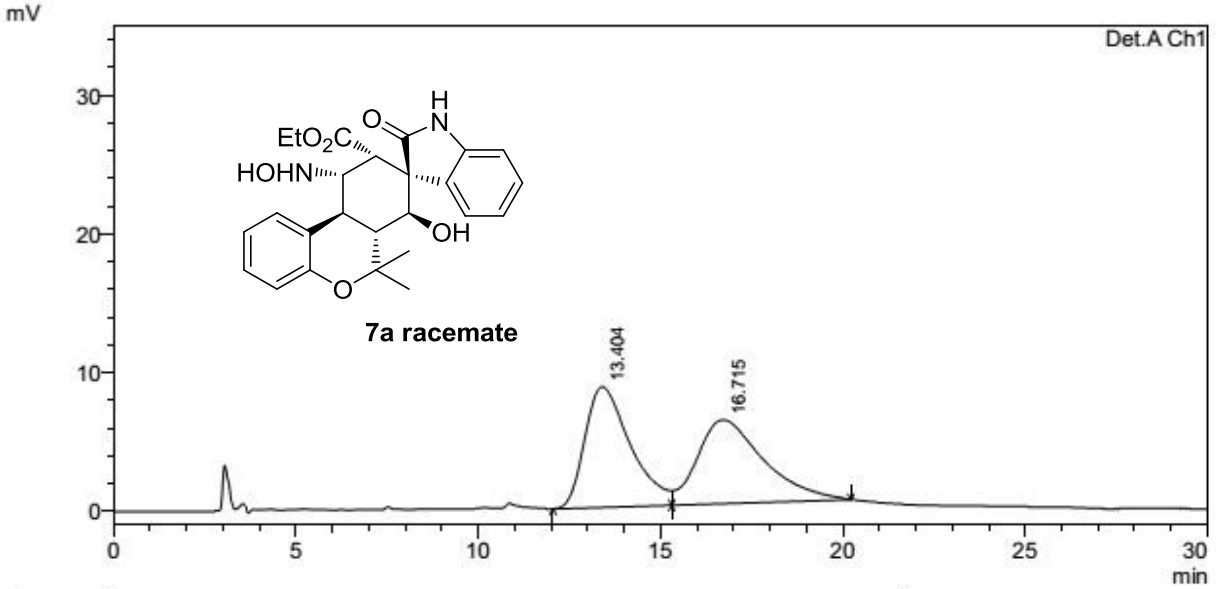


6a-PG


8.765
8.685
7.252
7.204
7.185
7.166
7.125
7.110
7.005
6.987
6.968
6.949
6.942
6.895
6.876
6.640
6.630
5.636
5.042
5.028
4.854
4.466
4.454
4.180
4.174
4.165
3.471
3.463
3.458
2.890
2.861
2.832
2.432
2.404
2.377
2.264
2.211
1.253
1.242
1.222
1.205
EtO2C
HOHN
O
H
N
OH
O
7a
1.05
1.71
2.99
1.99
1.01
0.97
0.99
1.00
0.94
1.02
2.12
0.99
1.01
1.03
1.05
3.04
6.63
f1 (ppm)

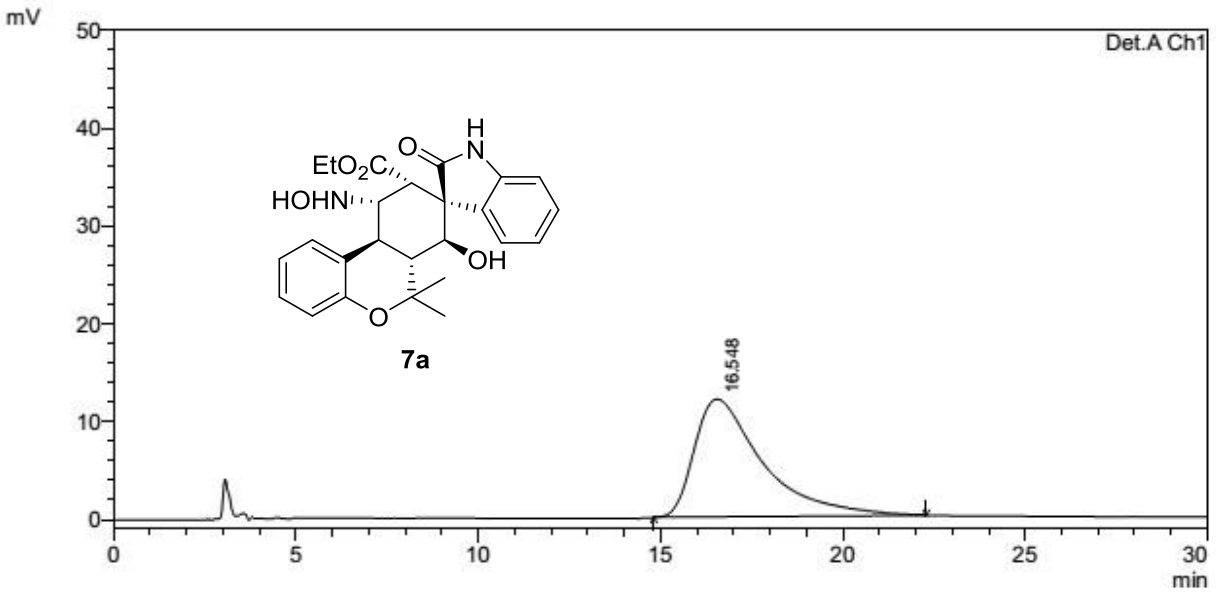

178.235
171.635
154.567
141.759
129.341
129.253
127.553
123.543
122.669
122.295
121.901
81.607
70.126
60.894
56.225
54.793
49.157
48.466
32.629
31.339
23.099
14.260
EtO2C
HOHN
O
H
N
OH
O
7a
f1 (ppm)

<Chromatogram>



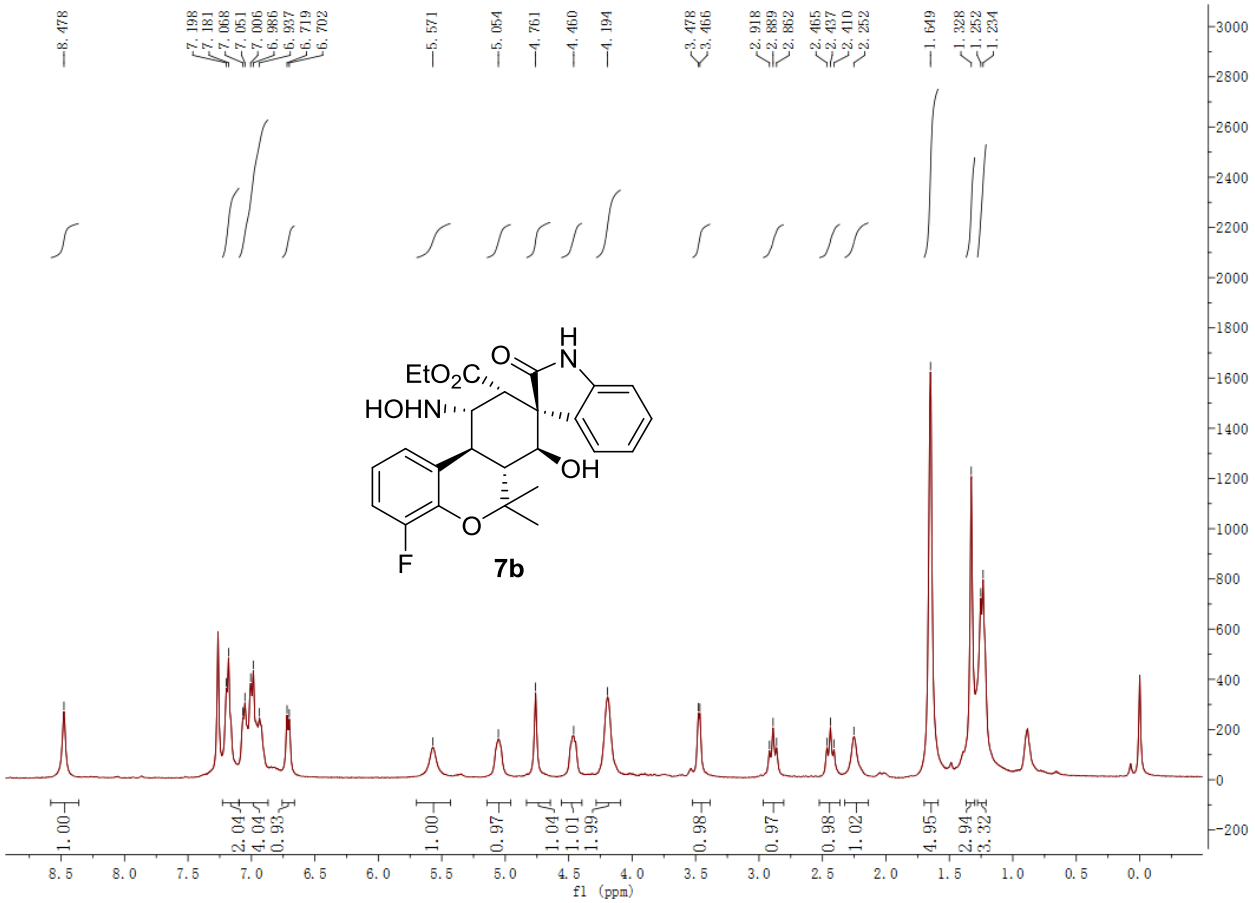
7a racemate

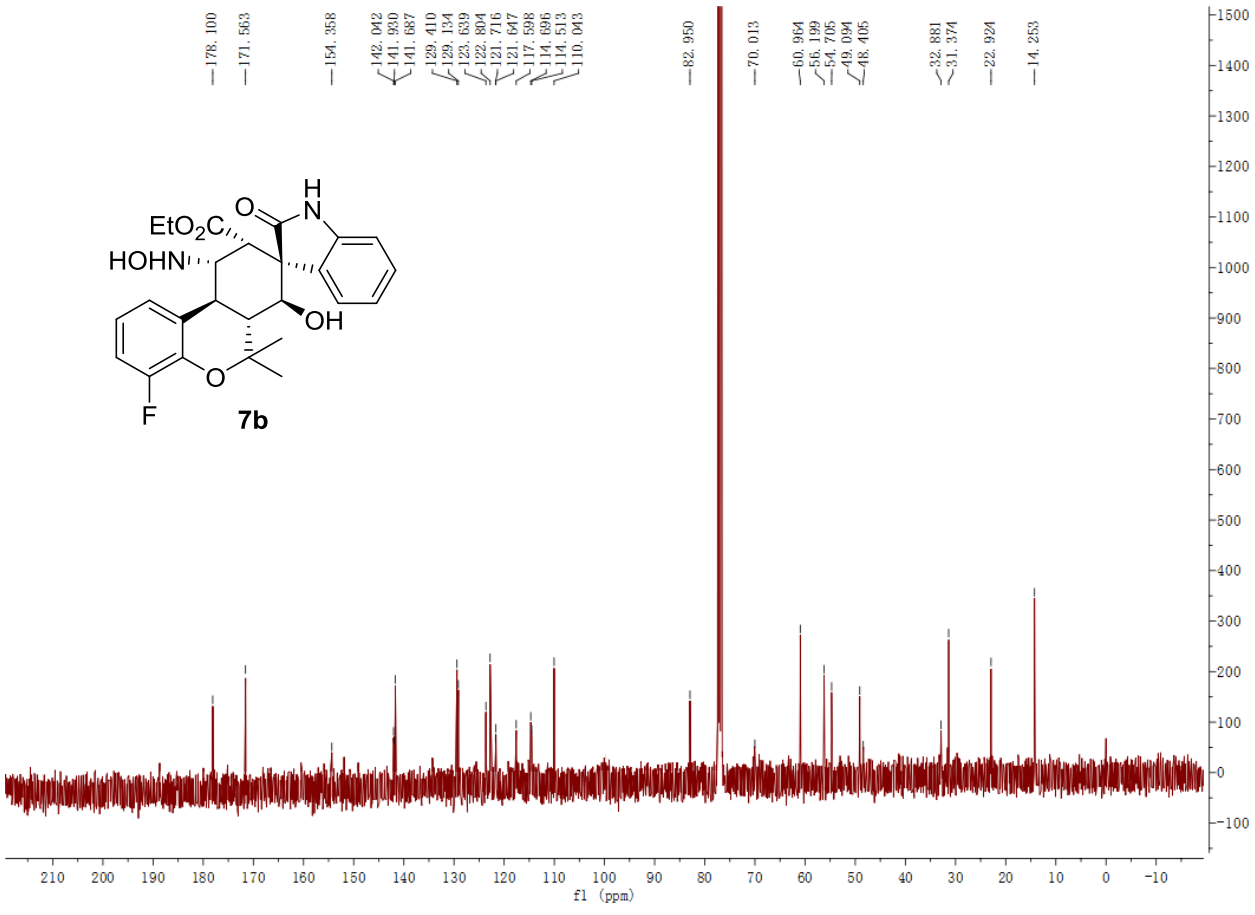
Peak#	Ret. Time	Area	Area %
1	13.404	752485	49.690
2	16.715	761876	50.310
Total		1514362	100.000

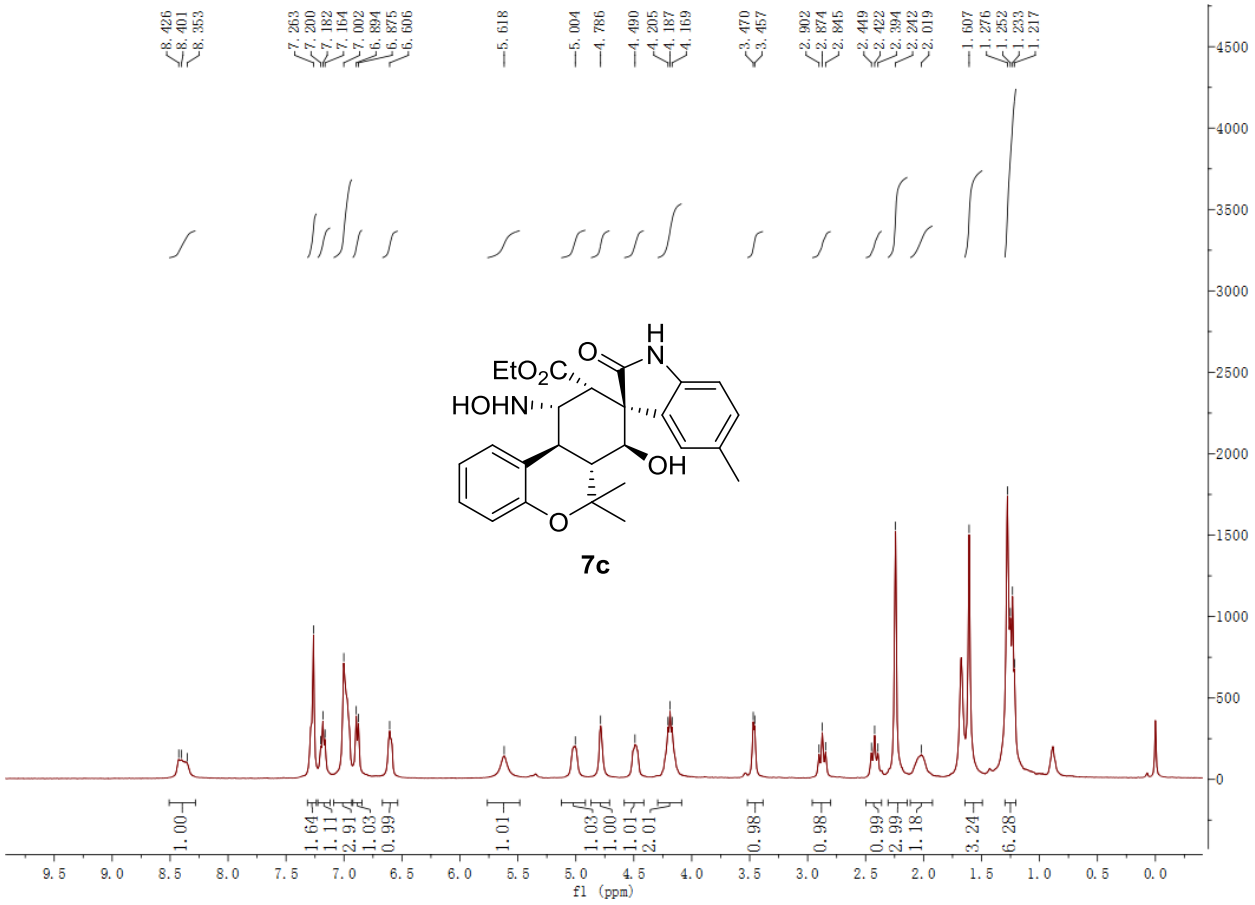


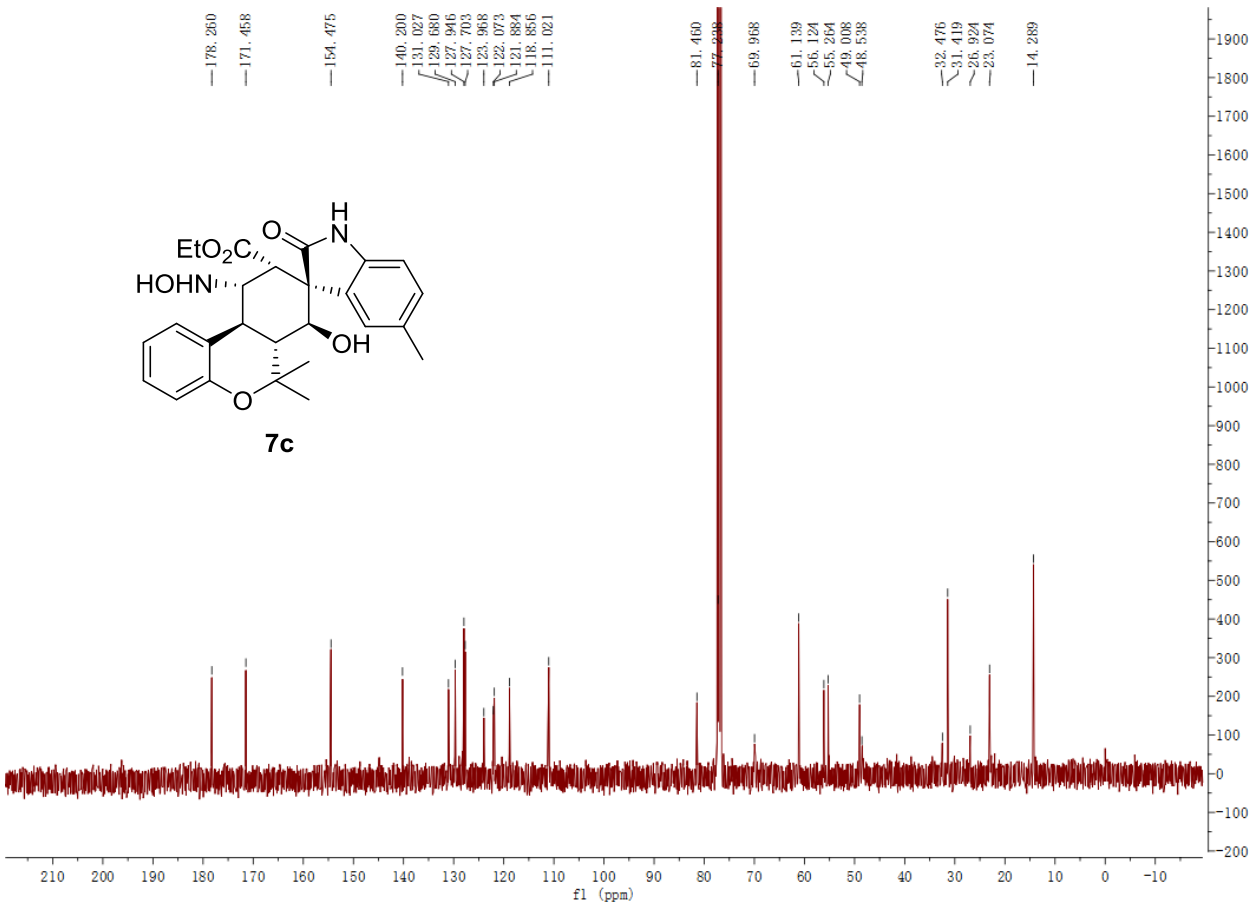
7a

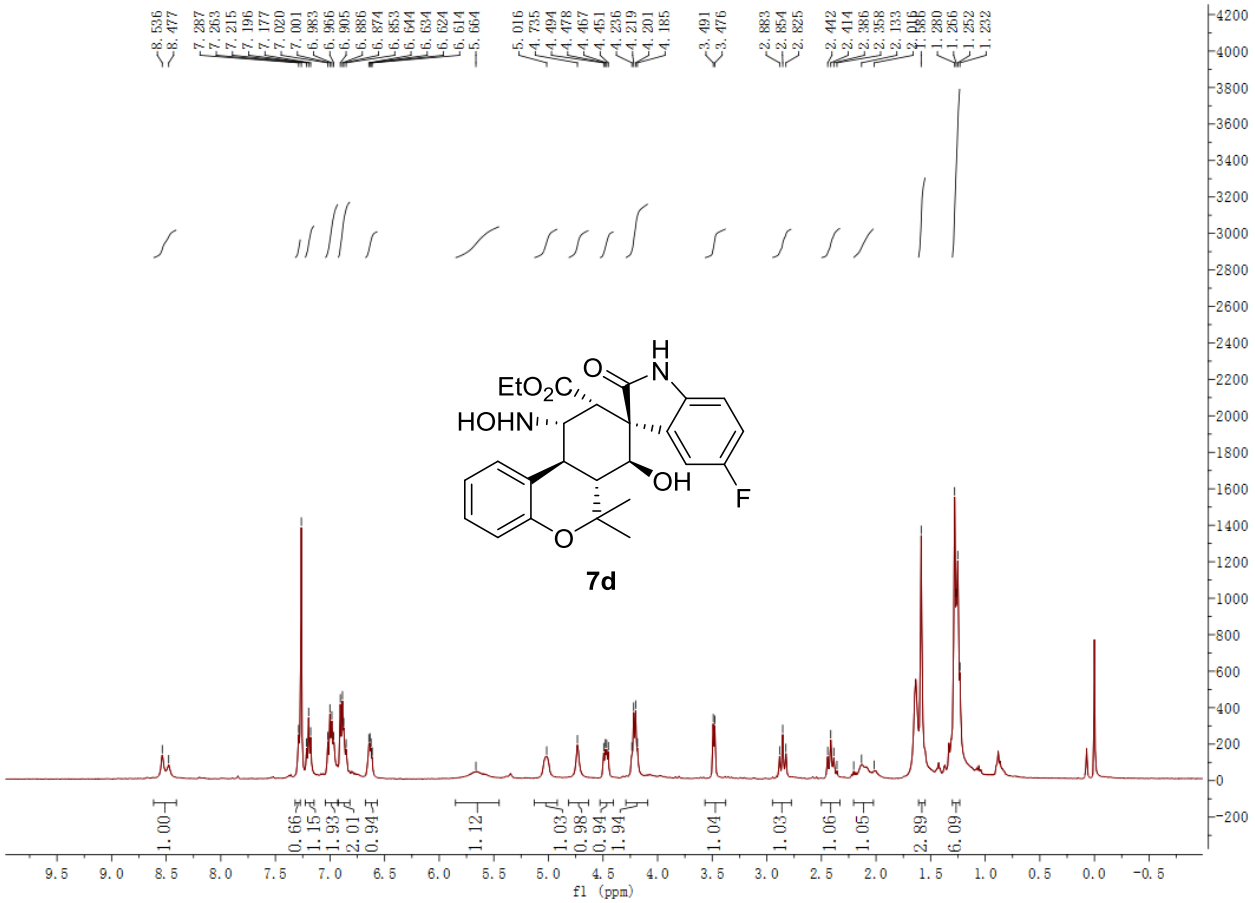
Peak#	Ret. Time	Area	Area %
1	16.548	1567770	100.000
Total		1567770	100.000


8.478
7.198
7.181
7.068
7.051
7.006
6.986
6.937
6.719
6.702
5.571
5.054
4.761
4.460
4.194
3.478
3.466
2.918
2.889
2.862
2.465
2.437
2.410
2.252
1.649
1.328
1.252
1.234
EtO2C
HOHN
O
H
N
OH
O
F
7b
1.00
2.04
4.04
0.93
1.00
0.97
1.04
1.01
1.99
0.98
0.97
0.98
1.02
4.95
2.94
3.32
f1 (ppm)

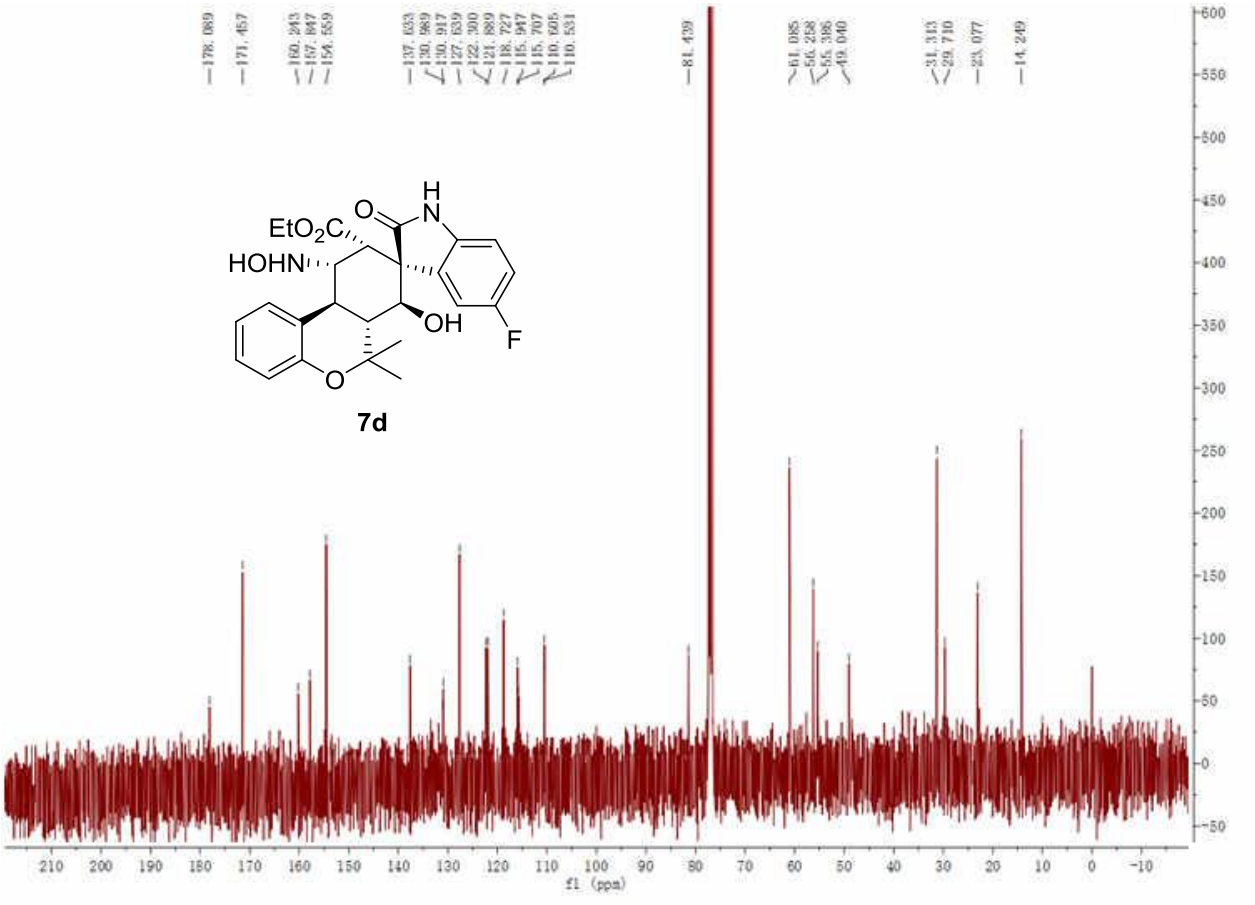

178.100
171.563
154.358
142.042
141.930
141.687
129.410
129.134
123.639
122.804
121.716
121.647
117.598
114.696
114.513
110.043
82.950
70.013
60.964
56.199
54.705
49.094
48.405
32.881
31.374
22.924
14.253
EtO2C
HOHN
O
H
N
OH
O
F
7b
f1 (ppm)


8.426
8.401
8.353
7.263
7.200
7.182
7.164
7.002
6.894
6.875
6.606
5.618
5.004
4.786
4.490
4.205
4.187
4.169
3.470
3.457
2.902
2.874
2.845
2.449
2.422
2.394
2.242
2.019
1.607
1.276
1.252
1.233
1.217
EtO2C
HOHN
O
H
N
OH
O
7c
1.00
1.64
1.11
2.91
1.03
0.99
1.01
1.03
1.00
1.01
2.01
0.98
0.98
0.99
2.99
1.18
3.24
6.28
f1 (ppm)

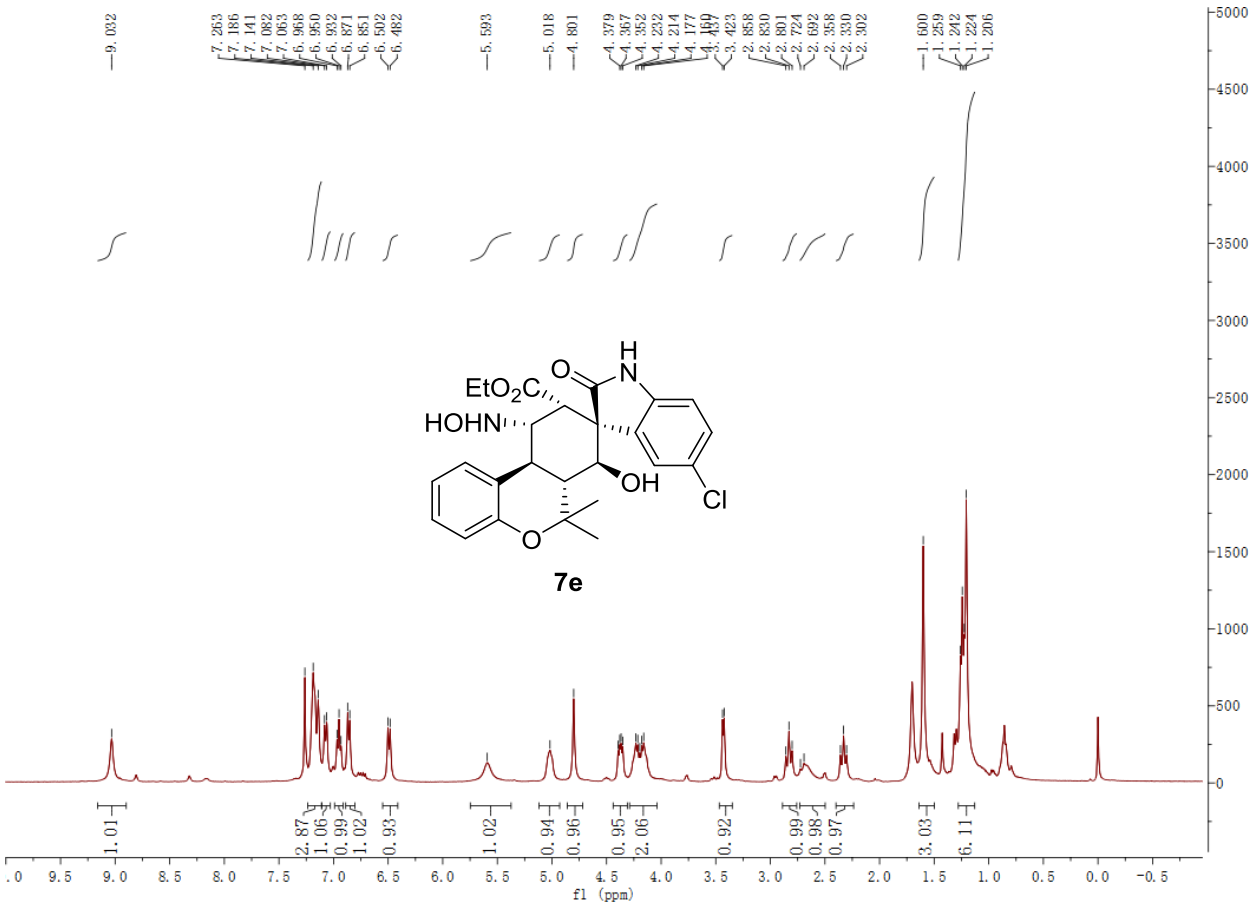

178.260
171.458
154.475
140.200
131.027
129.680
127.946
127.703
123.968
122.073
121.884
118.856
111.021
81.460
77.238
69.968
61.139
56.124
55.264
49.008
48.538
32.476
31.419
26.924
23.074
14.289
EtO2C
HOHN
O
H
N
OH
O
7c
f1 (ppm)

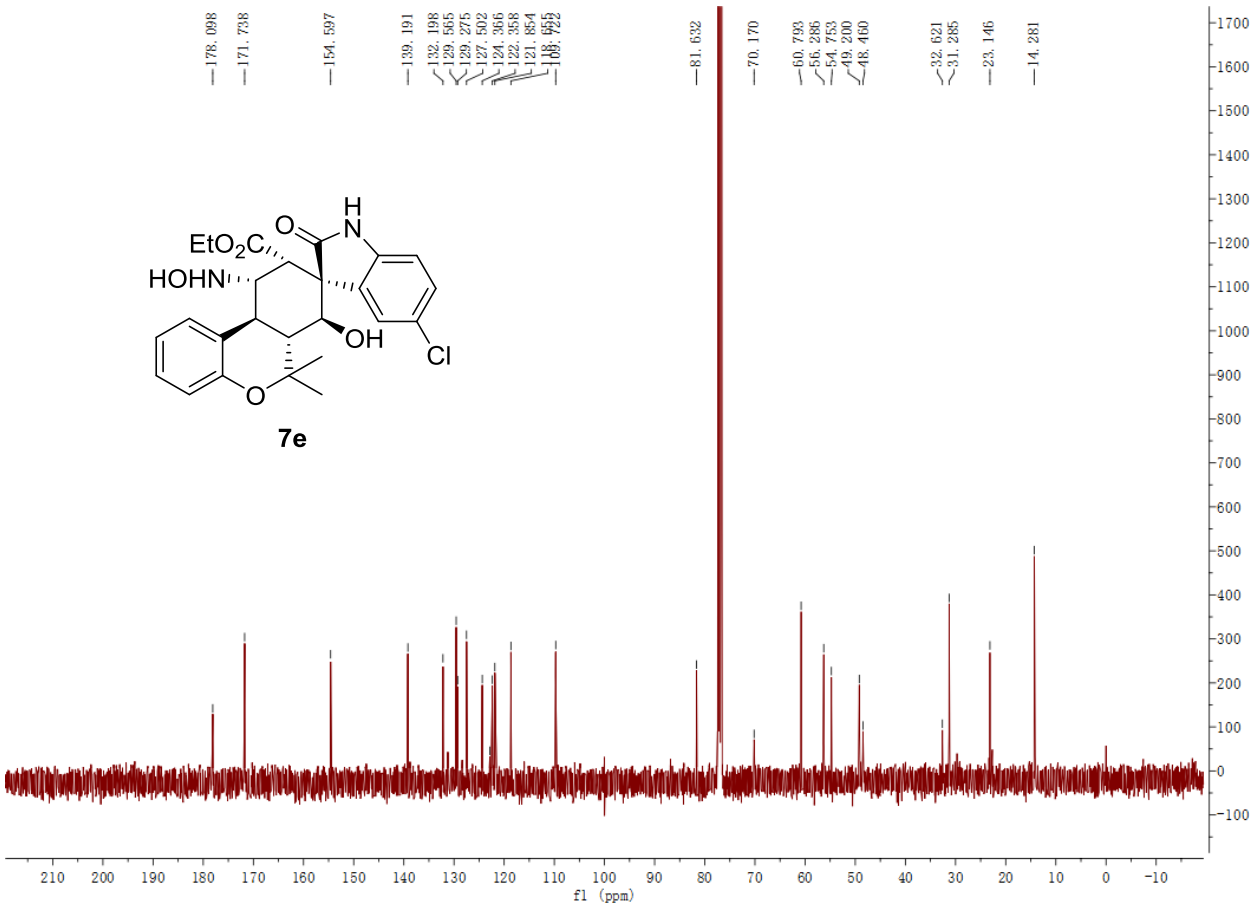


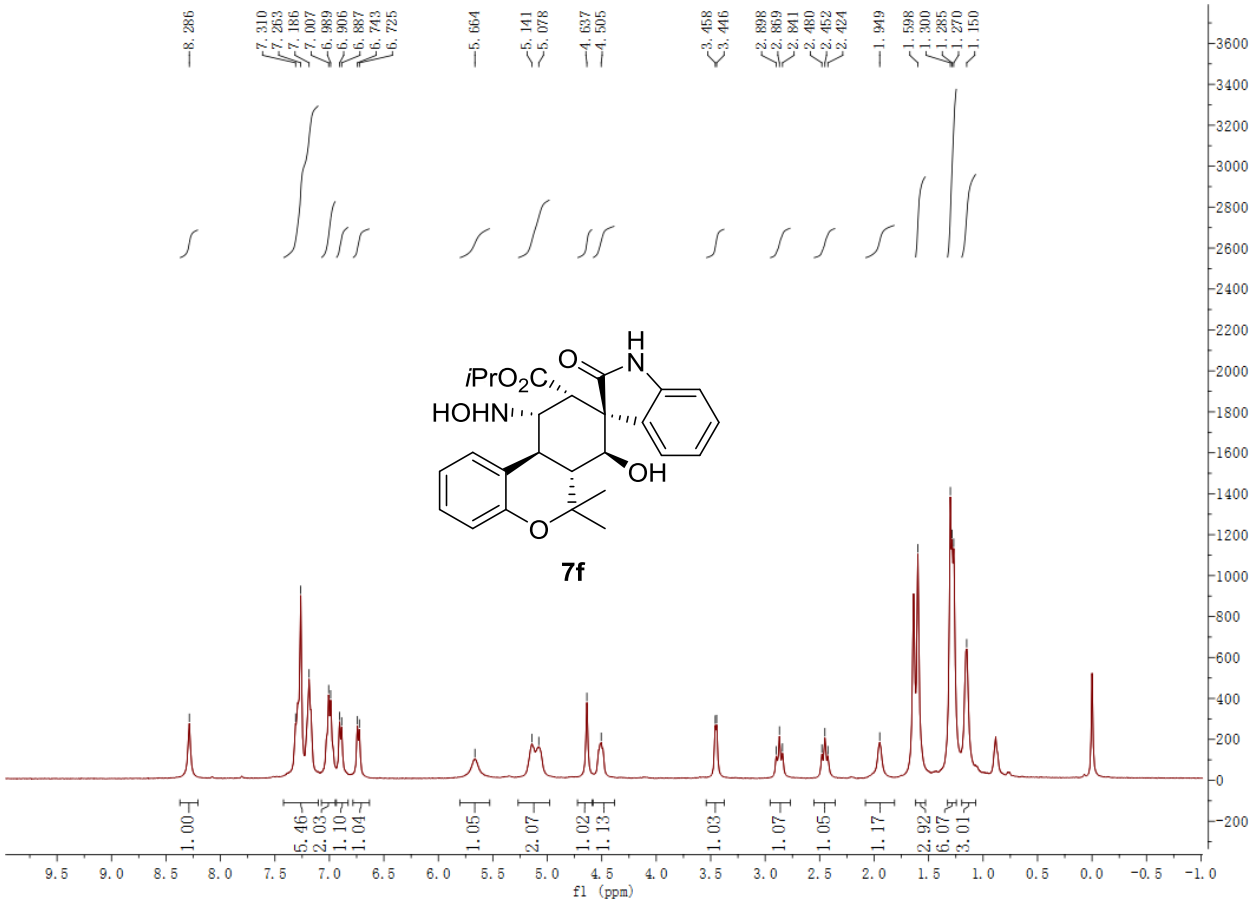
7d



7d

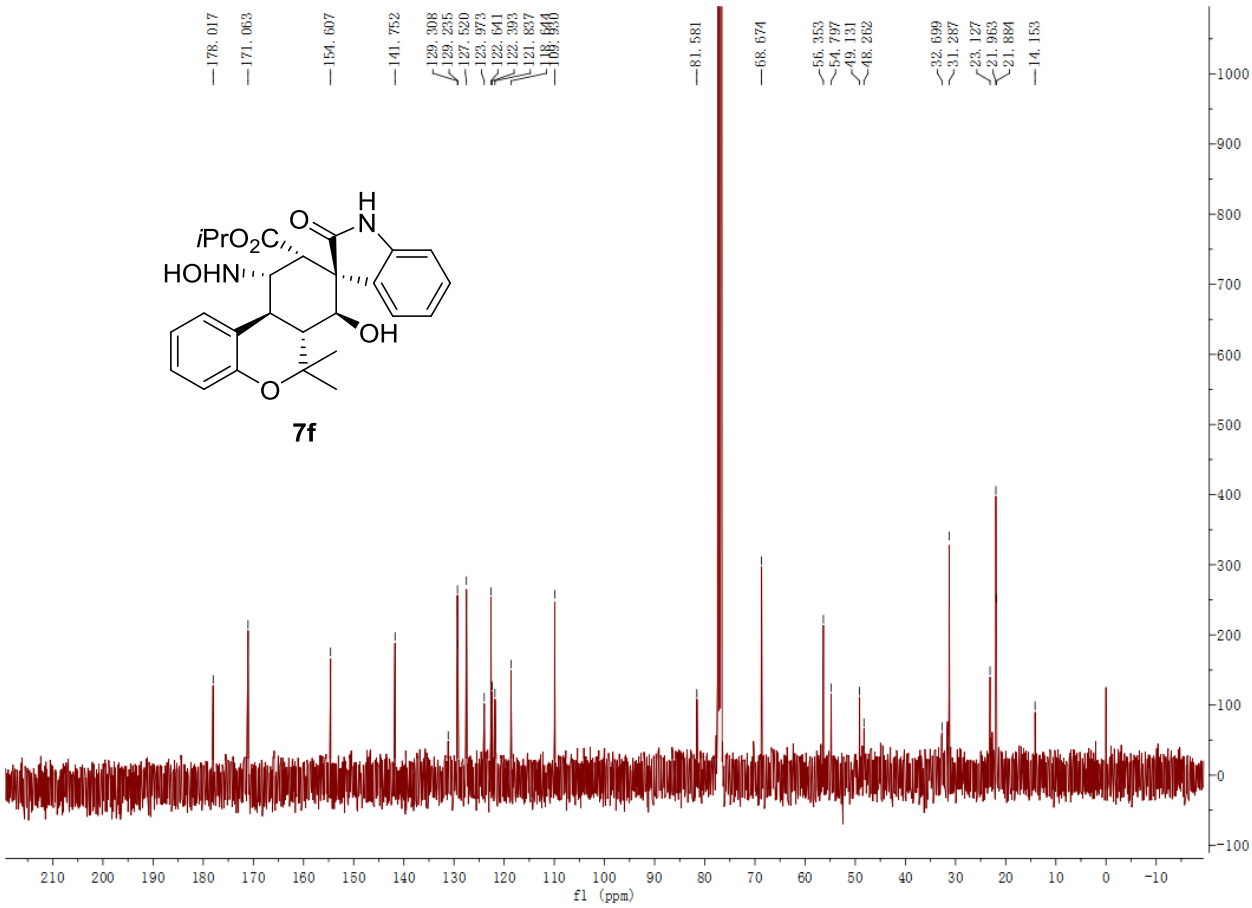

9.032
7.263
7.186
7.141
7.082
7.063
6.968
6.950
6.932
6.871
6.851
6.502
6.482
5.593
5.018
4.801
4.379
4.367
4.352
4.232
4.214
4.177
3.423
2.858
2.830
2.801
2.724
2.692
2.358
2.330
2.302
1.600
1.259
1.242
1.224
1.206
EtO2C
HOHN
O
H
N
OH
Cl
O
7e
1.01
2.87
1.06
0.99
1.02
0.93
1.02
0.94
0.96
0.95
2.06
0.92
0.99
0.98
0.97
3.03
6.11
f1 (ppm)


178.098
171.738
154.597
139.191
132.198
129.565
129.275
127.502
124.366
122.358
121.854
81.632
70.170
60.793
56.286
54.753
49.200
48.460
32.621
31.285
23.146
14.281
EtO2C
HOHN
O
H
N
OH
Cl
O
7e
f1 (ppm)


8.286
7.310
7.263
7.186
7.007
6.989
6.906
6.887
6.743
6.725
5.664
5.141
5.078
4.637
4.505
3.458
3.446
2.898
2.869
2.841
2.480
2.452
2.424
1.949
1.598
1.300
1.285
1.270
1.150
1.00
5.46
2.03
1.10
1.04
1.05
2.07
1.02
1.13
1.03
1.07
1.05
1.17
2.92
6.07
3.01
f1 (ppm)

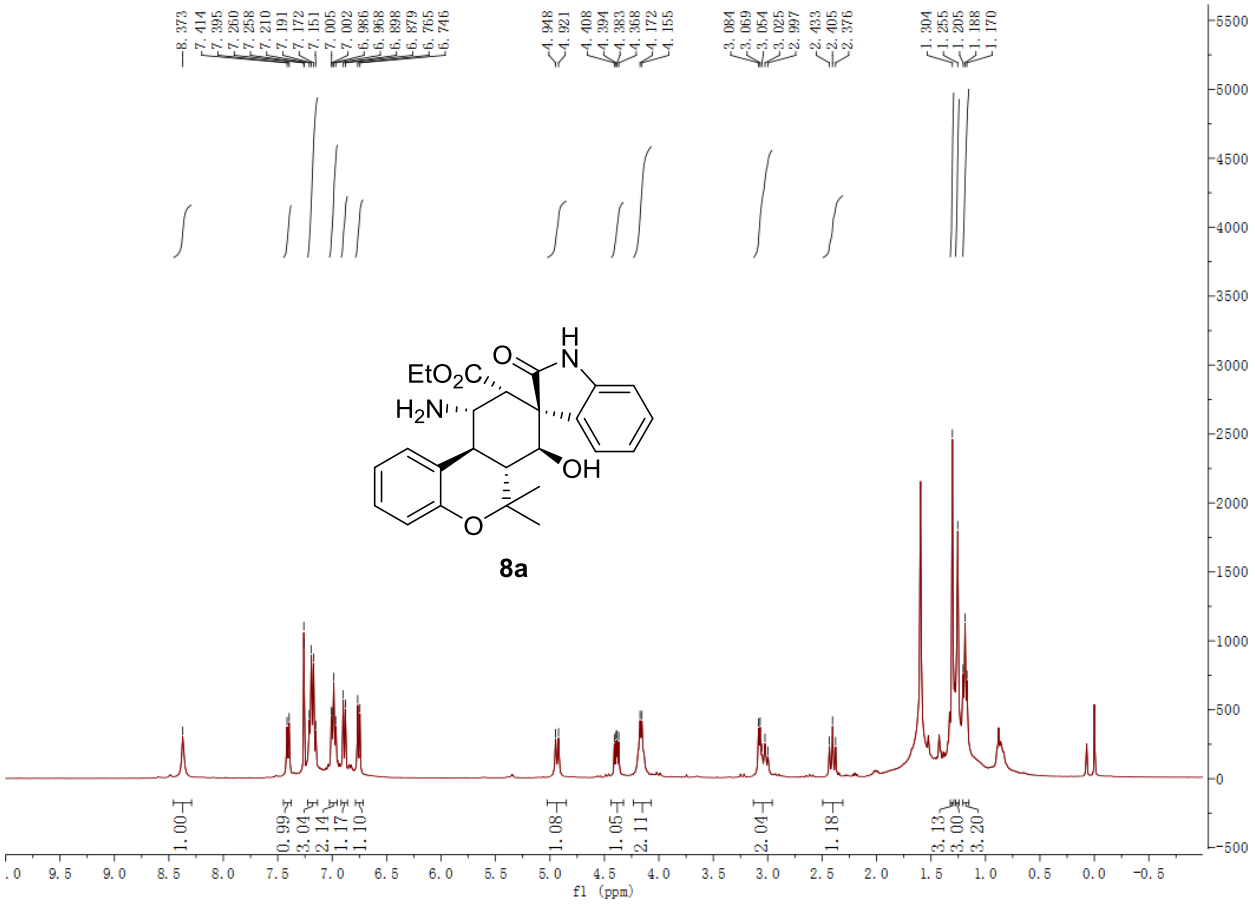
iPrO2C
HOHN
O
H
N
OH
O

7f

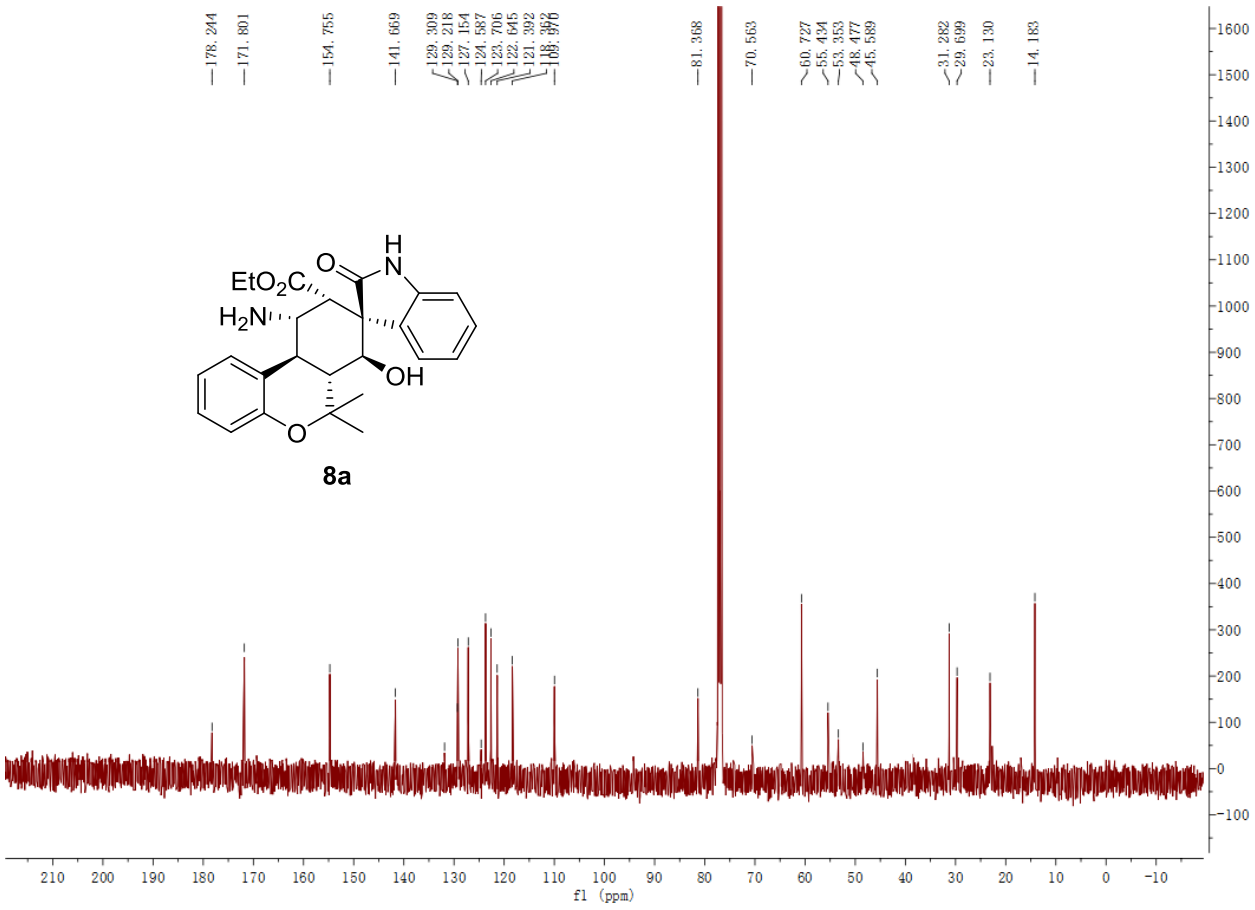

178.017
171.063
154.607
141.752
129.308
129.235
127.520
123.973
122.641
122.393
121.837
81.581
68.674
56.353
54.797
49.131
48.262
32.699
31.287
23.127
21.963
21.894
14.153
f1 (ppm)

iPrO2C
HOHN
O
H
N
OH
O

7f

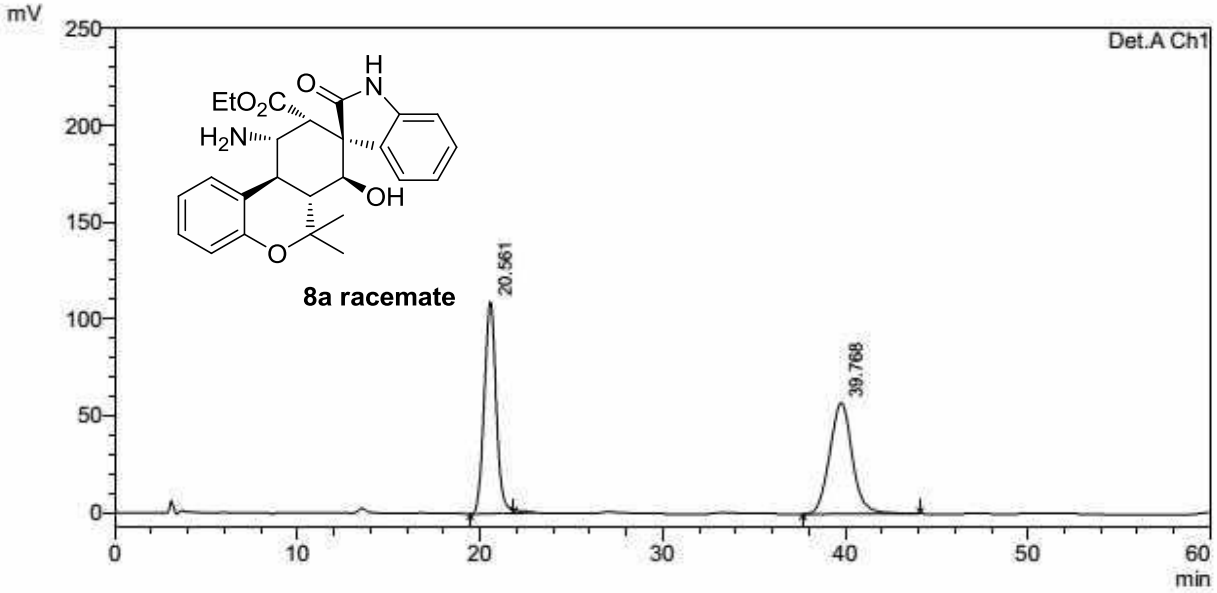

8.373
7.414
7.395
7.260
7.258
7.210
7.191
7.172
7.151
7.005
7.002
6.986
6.968
6.898
6.879
6.765
6.746
4.948
4.921
4.408
4.394
4.383
4.368
4.172
4.155
3.084
3.069
3.064
3.025
2.997
2.433
2.405
2.376
1.304
1.255
1.205
1.188
1.170
EtO2C
H2N
O
H
N
OH
O
1.00
0.99
3.04
2.14
1.17
1.10
1.08
1.05
2.11
2.04
1.18
3.13
3.00
3.20
f1 (ppm)

8a

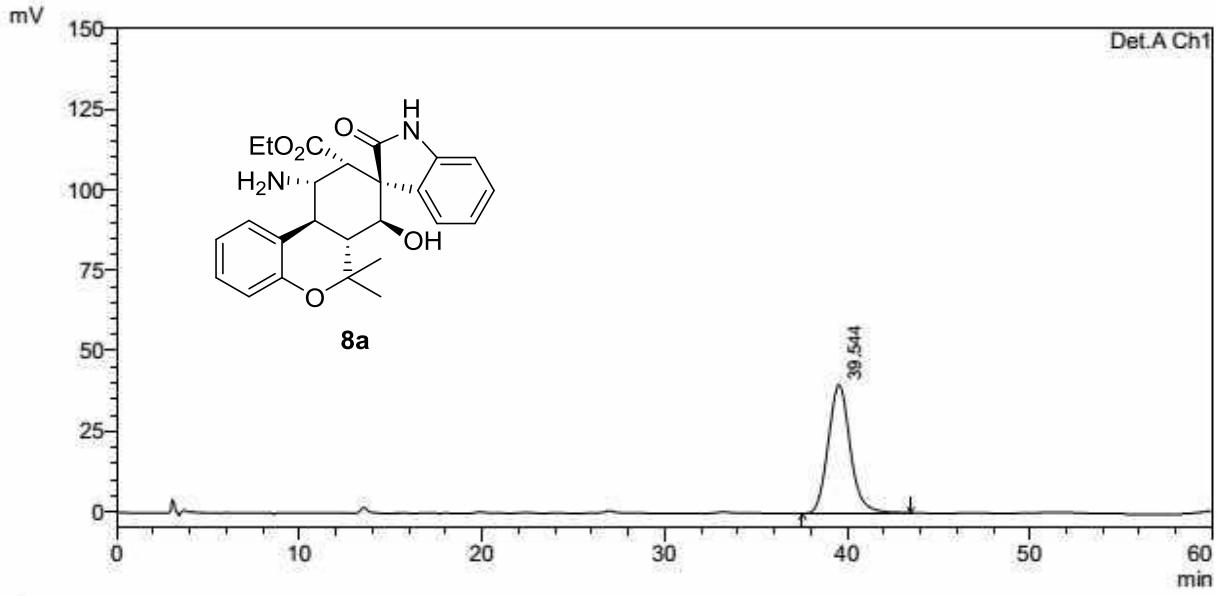

178.244
171.801
154.755
141.669
129.309
129.218
127.154
124.587
123.706
122.645
121.392
81.368
70.563
60.727
55.434
53.353
48.477
45.589
31.282
29.699
23.130
14.183
EtO2C
H2N
O
H
N
OH
O
f1 (ppm)

8a

<Chromatogram>



Peak#	Ret. Time	Area	Area %
1	20.561	4949773	49.999
2	39.768	4949658	50.001
Total		9899431	100.000



Peak#	Ret. Time	Area	Area %
1	39.544	3358345	100.000
Total		3358345	100.000

5. SupplementaryTable S1-2

Table S1. Sensitivity of Different Cancer Cell Linesto Compounds **5a**-**5n**, **6a**, **7a**-**7f** and **8a** [a].

	MCF-7	A549	HepG2	HCT116	U87
5a	71.4	84.6	71.7	83.3	86.4
5b	82.0	87.1	82.6	87.6	72.7
5c	76.4	73.2	85.1	70.1	85.6
5d	70.6	75.7	71.2	74.4	70.1
5e	75.0	86.6	73.7	76.9	72.4
5f	82.0	80.4	75.5	79.9	76.6
5g	79.2	76.1	89.0	75.4	90.3
5h	78.6	91.6	78.0	91.1	88.0
5i	72.2	87.5	91.6	88.6	75.1
5j	90.0	85.0	89.5	86.3	90.6
5k	46.5	66.7	56.4	57.2	63.7
5l	68.2	75.5	65.2	72.9	63.6
5m	32.3	29.3	33.5	21.7	60.2
5n	59.1	66.1	68.4	65.3	63.7
6a	40.3	56.0	65.5	73.2	75.9
7a	30.1	36.9	55.7	32.8	24.1
7b	46.7	67.1	64.7	54.6	87.2
7c	23.6	14.8	52.6	37.5	40.3
7d	12.3	18.6	24.5	27.0	36.5
7e	15.7	15.4	21.3	23.9	40.4
7f	29.9	67.9	66.1	68.6	65.3
8a	45.7	51.0	58.9	61.4	66.9

[a] The cellular viable percentage (%) at 50 μM were obtained by the MTT assay.

.

Table S2. The cellular proliferation IC_{50} of different cancer cell linesto Compounds **5k**, **5m**, **6a**, **7a-7f** and **8a** [a].

	MCF-7	A549	HepG2	HCT116	U87
5k	49.8±9.6	>50	>50	>50	>50
5m	27.6±6.5	38.0±7.3	46.9±8.0	33.2±9.4	>50
6a	41.9±8.2	>50	>50	>50	>50
7a	21.8±6.4	44.2±12.1	>50	37.1±10.7	42.3±8.6
7b	47.6±7.1	>50	>50	>50	>50
7c	9.4±3.5	17.3±7.2	>50	43.8±10.1	36.6±7.6
7d	2.5±1.1	4.8±1.8	16.2±5.0	25.4±6.9	41.9±13.8
7e	1.7±0.5	5.9±3.2	18.4±5.1	13.0±3.5	37.5±8.4
7f	35.3±8.8	>50	40.8±13.6	>50	>50
8a	47.5±11.3	>50	>50	>50	>50

[a] The cellular proliferation IC_{50} were obtained by the MTT assay and were expressedas the mean ± SD of three independent experiments.

6. Supplementary Figure S1-4

Figure S1. Fluorescence microscopic imaging of MCF-7cells. A1: bright-field image of blank cells;A2: fluorescence microscopic image of blank cells;B1: bright-field image of cell treated with 10μM probe; B2: fluorescence microscopic image of cells stained by 10μM probe; C1: bright-field image of cell treated with 0.1μM **7e** and 10μM probe; C2: fluorescence microscopic image of celltreated with 0.1μM **7e** and 10μM probe; D1: bright-field image of cell treated with 0.25μM **7e** and 10μM probe; D2: fluorescence microscopic image of celltreated with 0.25μM **7e** and 10μM probe; E1: bright-field image of cell treated with 1μM **7e** and 10μM probe; E2: fluorescence microscopic image of celltreated with 1μM **7e** and 10μM probe; F1: bright-field image of cell treated with 5μM **7e** and 10μM probe; F2: fluorescence microscopic image of celltreated with 5μM **7e** and 10μM probe;G1: bright-field image of cell treated with 25μM **7e** and 10μM probe; G2: fluorescence microscopic image of celltreated with 25μM **7e** and 10μM probe;H1: bright-field image of cell treated with 50μM **7e** and 10μM probe; H2: fluorescence microscopic image of celltreated with 50μM **7e** and 10μM probe;.

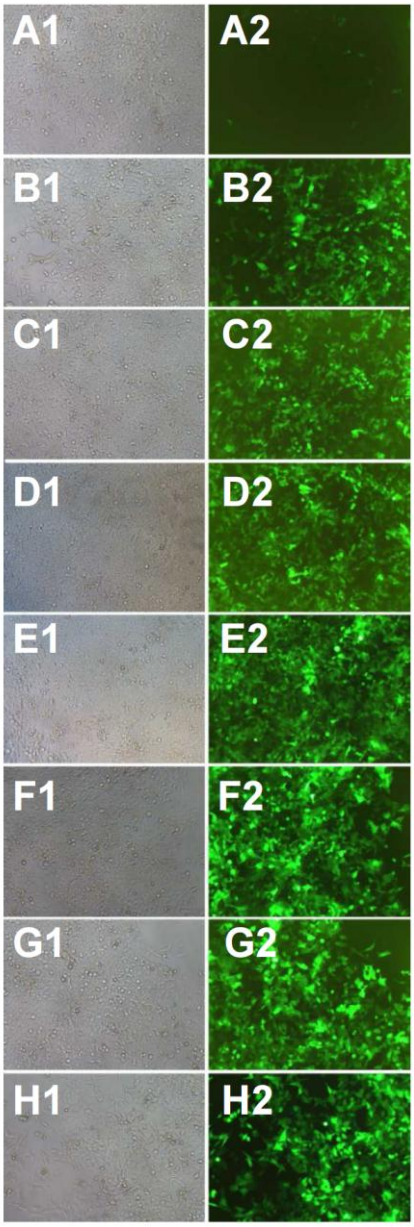


Figure S2. Cell cycle analysis of blank cells (A), Nutlin-3 5μM treated cells(B), Nutlin-3 10μM treated cells(C),**7e** 5μM treated cells(D), **7e** 10μM treated cells(E).

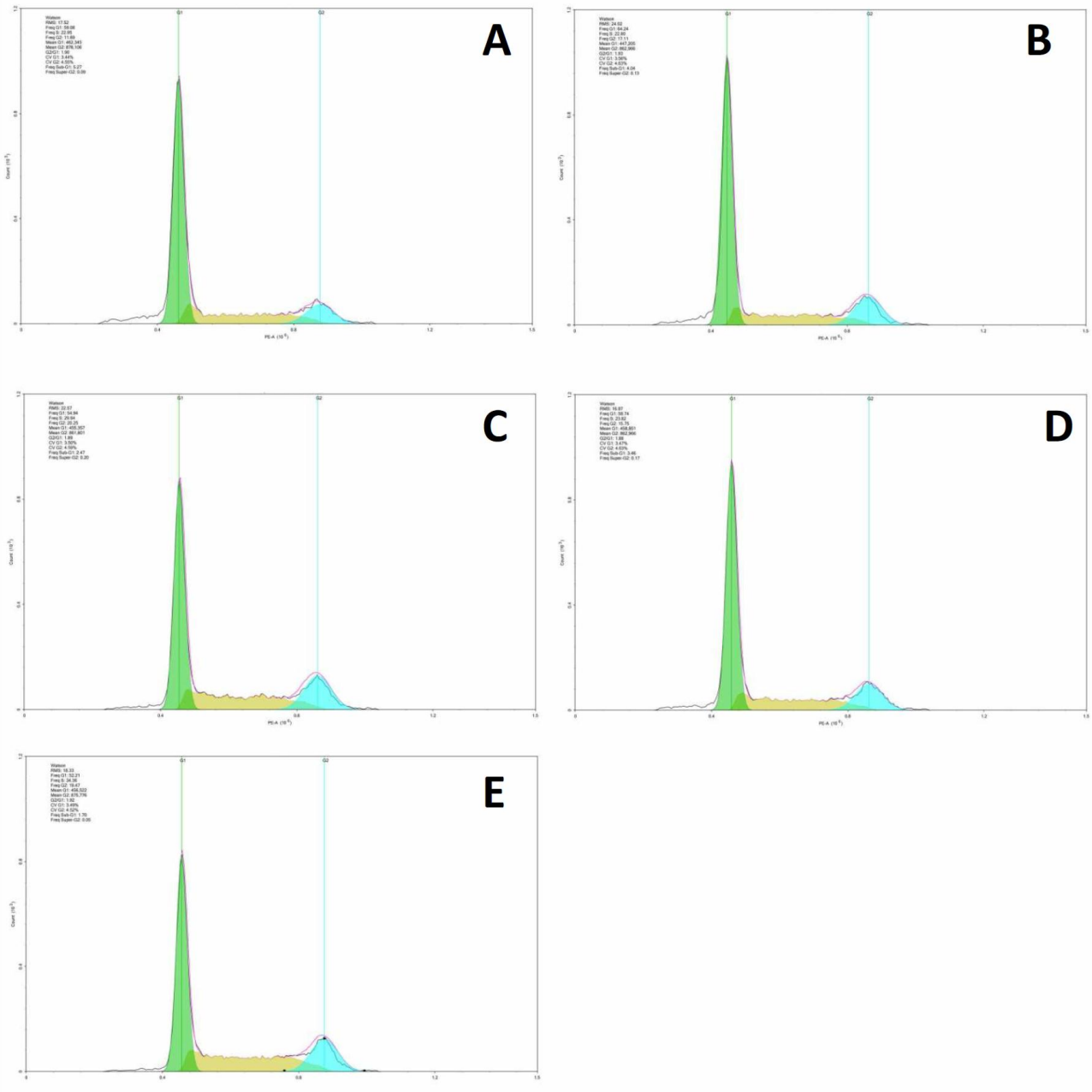


Figure S3. The MCF-7 cells were treated with Nutlin-3 (5μM) or **7e** (5μM) for 24 h thenstained with PI and observed by fluorescence microscope (×200 magnification), the blue arrow suggested mitotic cells, the yellow arrow suggested apoptotic cells.

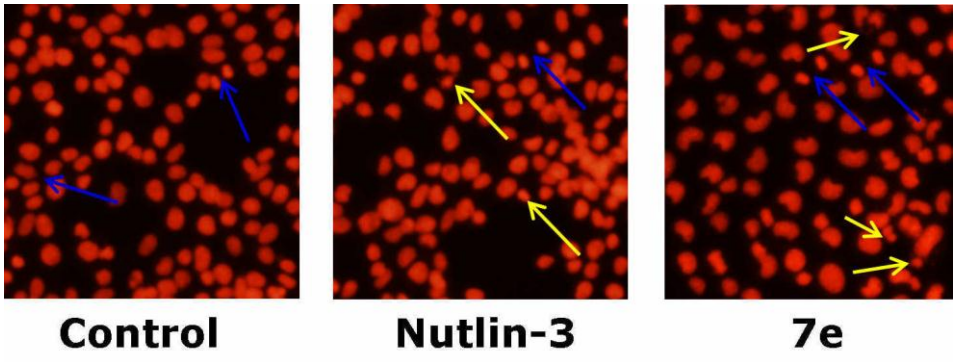


Figure S4. The MCF-7 cells weretreated with **7e** (5μM) for 24 h without or with co-incubation of pan-caspase inhibitorZ-VAD-FMK (5 μM), then revealed by Annexin-V/PI double staining using flow cytometryanalysis.