Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Catalytic asymmetric dearomative [4+2] annulation of 2-nitrobenzofurans and 5*H*-thiazol-4-ones: stereoselective construction of dihydrobenzofuran-bridged polycyclic skeletons

Jian-Qiang Zhao,[a,§,*] Shun Zhou,[a,b,§] Zhen-Hua Wang,[a] Yong You,[a] Shuang Chen,[c] Xiong-Li Liu,[c] Ming-Qiang Zhou,[b] and Wei-Cheng Yuan[a,*]

[a]Institute for Advanced Study, Chengdu University, Chengdu 610106, China.
[b]National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, China.
[c]Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guizhou University, Guiyang, Guizhou 550025, China.

yuanwc@cioc.ac.cn
zhaojianqiang@cdu.edu.cn

Supporting Information

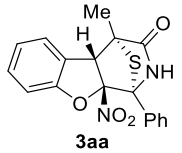
Table of Contents

1. General experimental information

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6. ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (DMSO-d_6 at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (DMSO-d_6 at 39.51 ppm). Melting points were recorded on a melting point apparatus.

2. General experimental procedures for asymmetric synthesis of compounds 3

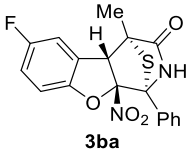
To a flame dried reaction tube were added 2-nitrobenzofurans **1** (0.2 mmol), 5*H*-thiazol-4-ones **2** (0.26 mmol, 1.3 equiv), **Cat. D** (20 mol%), and activated 5 Å molecular sieve (100 mg), followed by addition CH_2Cl_2 (2.0 mL). The reaction solution was stirred at room temperature for specified time under a nitrogen atmosphere. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8:1～12:1) to give the corresponding products **3**.



3aa

(1*R*,4*S*,4a*S*,9a*R*)-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro [2,3-*c*]pyridin-3(2*H*)-one (*3aa*)

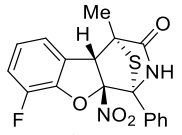
White solid, 83% yield, 58.8 mg, >20:1 dr, 94% ee; m.p. 163.1-164.0 °C, $[\alpha]_D^{25}$ = -182.6 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 15.79 min, t_{minor} = 10.01 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.62 – 7.54 (m, 2H), 7.48 (dd, *J* = 6.9, 2.9 Hz, 4H), 7.44 – 7.35 (m, 1H), 7.25 – 7.07 (m, 2H), 4.81 (s, 1H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 206.1, 176.2, 160.0, 130.4, 129.9, 129.2, 128.7, 127.1, 126.1, 125.8, 123.2, 123.0, 110.3, 81.6, 62.5, 59.5, 11.8. HRMS (ESI-TOF) Calcd. for $C_{18}H_{15}N_2O_4S$ $[M+H]^+$: 355.0747; found: 355.0747.



3ba

(1*R*,4*S*,4a*S*,9a*R*)-6-fluoro-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ba*)

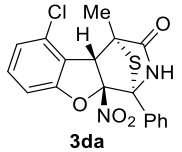
Pale yellow solid, 73% yield, 54.4 mg, >20:1 dr, 94% ee; m.p. 178.5-179.5 °C, $[\alpha]_D^{25}$ = -425.5 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 21.78 min, t_{minor} = 12.01 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.59 – 7.53 (m, 2H), 7.51 – 7.45 (m, 3H), 7.37 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.26 – 7.18 (m, 2H), 4.83 (s, 1H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.5, 159.6, 157.2, 156.7, 130.5, 129.1, 128.1 (d, *J* = 266.6 Hz, 1C), 127.6, 125.3 (d, *J* = 9.1 Hz, 1C), 117.3 (d, *J* = 25.2 Hz, 1C), 113.7 (d, *J* = 26.3 Hz, 1C), 111.6 (d, *J* = 9.0 Hz, 1C), 82.1, 62.8, 60.0, 12.3. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}FN_2NaO_4S$ $[M+Na]^+$: 395.0472; found: 395.0466.



3ca

(1*R*,4*S*,4a*S*,9a*R*)-8-fluoro-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3ca*)

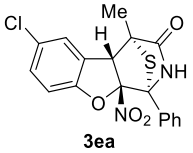
Pale yellow solid, 95% yield, 70.7 mg, >20:1 dr, 90% ee; m.p. 138.2-139.1 °C, $[\alpha]_D^{25}$ = -538.6 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 23.51 min, t_{minor} = 14.52 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.55 (dd, *J* = 6.8, 3.1 Hz, 2H), 7.52 – 7.46 (m, 3H), 7.39 – 7.27 (m, 2H), 7.18 – 7.11 (m, 1H), 4.92 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.4, 146.7 (d, *J* = 11.1 Hz, 1C) 146.5 (d, *J* = 247.4 Hz, 1C), 130.6, 129.2, 127.5, 127.4, 126.6, 124.5 (d, *J* = 5.0 Hz, 1C), 122.4, 122.3, 117.9 (d, *J* = 16.2 Hz, 1C), 82.2, 62.9, 60.4, 55.4, 12.3.HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}FN_2NaO_4S$ $[M+Na]^+$: 395.0472; found: 395.0465.



3da

(1*R*,4*S*,4a*S*,9a*R*)-5-chloro-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3da*)

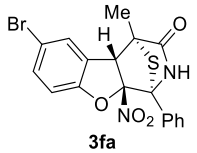
Pale yellow solid, 90% yield, 70.0 mg, >20:1 dr, 84% ee; m.p. 144.3-145.2 °C, $[\alpha]_D^{25}$ = -345.6 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 9.46 min, t_{minor} = 7.60 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.59 – 7.52 (m, 2H), 7.51 – 7.43 (m, 3H), 7.44 – 7.36 (m, 1H), 7.27 – 7.14 (m, 2H), 4.84 (s, 1H), 1.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.2, 161.4, 132.7, 130.8, 130.6, 129.2, 129.1, 127.6, 125.7, 124.5, 122.4, 110.1, 81.9, 64.8, 60.1, 14.8. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}ClN_2NaO_4S$ $[M+Na]^+$: 411.0177; found: 411.0159.



3ea

(1*R*,4*S*,4a*S*,9a*R*)-6-chloro-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3ea*)

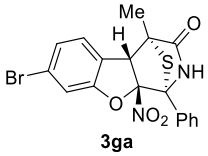
White solid, 75% yield, 58.3 mg, >20:1 dr, 93% ee; m.p. 155.3-156.2 °C, $[\alpha]_D^{25}$ = -419.1 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 11.11 min, t_{minor} = 7.89 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.61 – 7.54 (m, 3H), 7.53 – 7.47 (m, 3H), 7.45 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 4.85 (s, 1H), 1.62 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.4, 159.3, 130.7, 130.5, 129.3, 129.2, 127.5, 127.3, 126.5, 126.4, 126.0, 112.3, 82.1, 62.8, 59.8, 12.3. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}ClN_2NaO_4S$ $[M+Na]^+$: 411.0177; found: 411.0161.



3fa

(1*R*,4*S*,4a*S*,9a*R*)-6-bromo-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3fa*)

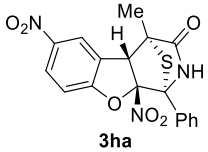
White solid, 86% yield, 74.5 mg, >20:1 dr, 91% ee; m.p. 149.3-150.3 °C, $[\alpha]_D^{25}$ = -444.4 (c 1.0, CH_2Cl_2); The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 10.66 min, t_{minor} = 8.61 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.68 (d, J = 2.1 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.53 – 7.45 (m, 3H), 7.18 (d, J = 8.6 Hz, 1H), 4.86 (s, 1H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.4, 159.8, 133.5, 130.5, 129.3, 129.2, 129.1, 127.6, 126.5, 126.4, 114.9, 112.8, 82.1, 62.8, 59.8, 12.3. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}{}^{79}BrN_2NaO_4S$ $[M+Na]^+$: 454.9672; found: 454.9653; For $C_{18}H_{13}{}^{81}BrN_2NaO_4S$ $[M+Na]^+$: 456.9651; found: 454.9630.



3ga

(1*R*,4*S*,4a*S*,9a*R*)-7-bromo-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3ga*)

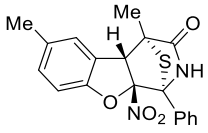
White solid, 86% yield, 74.5 mg, >20:1 dr, 92% ee; m.p. 161.8-162.8 °C, $[\alpha]_D^{25}$ = -597.1 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 28.17 min, t_{minor} = 15.67 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 7.60 – 7.54 (m, 2H), 7.53 – 7.47 (m, 4H), 7.43 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.0, 1.8 Hz, 1H), 4.81 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.4, 161.2, 130.5, 129.3, 129.1, 128.0, 127.6, 126.5, 126.4, 123.5, 123.0, 114.1, 82.1, 62.8, 59.5, 12.2. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}{}^{79}BrN_2NaO_4S$ $[M+Na]^+$: 454.9672; found: 454.9662; For $C_{18}H_{13}{}^{81}BrN_2NaO_4S$ $[M+Na]^+$: 456.9651; found: 454.9642.



3ha

(1*R*,4*S*,4a*S*,9a*R*)-4-methyl-6,9a-dinitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3ha*)

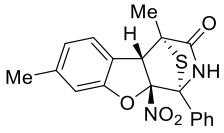
Yellow solid, 72% yield, 57.6 mg, >20:1 dr, 88% ee; m.p. 222.8-223.5 °C, $[\alpha]_D^{25}$ = -47.9 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 9.73 min, t_{minor} = 10.65 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.39 – 8.28 (m, 2H), 7.56 – 7.52 (m, 2H), 7.51 – 7.47 (m, 3H), 7.44 (d, J = 8.7 Hz, 1H), 4.95 (s, 1H), 1.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.2, 164.8, 143.8, 130.7, 129.7, 129.2, 129.0, 128.4, 127.7, 127.5, 126.7, 125.9, 122.6, 111.4, 82.3, 62.9, 59.2, 12.1. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}N_3NaO_6S$ $[M+Na]^+$: 422.0417; found: 422.0403.



3ia

(1*R*,4*S*,4a*S*,9a*R*)-4,6-dimethyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro [2,3-c]pyridin-3(2*H*)-one (*3ia*)

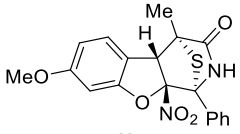
White solid, 64% yield, 47.2 mg, >20:1 dr, 89% ee; m.p. 193.1-193.8 °C, $[\alpha]_D^{25}$ = -350.3 (c 1.0, CH_2Cl_2); The ee was determined by HPLC (Chiralpak IC, ^{i}PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 15.27 min, t_{minor} = 9.51 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.58 (dd, *J* = 6.8, 2.9 Hz, 2H), 7.52 – 7.46 (m, 3H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 4.76 (s, 1H), 2.32 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.7, 158.6, 132.6, 131.1, 130.4, 129.7, 129.1, 127.6, 126.8, 126.5, 123.6, 110.3, 82.0, 62.9, 60.0, 20.9, 12.4. HRMS (ESI-TOF) Calcd. for $C_{19}H_{16}N_2NaO_4S$ $[M+Na]^+$: 391.0723; found: 391.0706.



3ja

(1*R*,4*S*,4a*S*,9a*R*)-4,7-dimethyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro [2,3-*c*]pyridin-3(2*H*)-one (*3ja*)

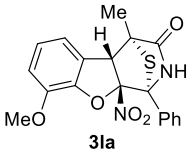
White solid, 66% yield, 48.7 mg, >20:1 dr, 89% ee; m.p. 140.2-140.9 °C, $[\alpha]_D^{25}$ = -284.3 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 10.12 min, t_{minor} = 7.33 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.58 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.53 – 7.45 (m, 3H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.01 (s, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 4.74 (s, 1H), 2.34 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.7, 160.8, 141.0, 130.4, 129.7, 129.1, 127.5, 126.5, 126.1, 124.1, 120.7, 111.2, 82.0, 63.0, 59.8, 21.6, 12.3. HRMS (ESI-TOF) Calcd. for $C_{19}H_{16}N_2NaO_4S$ $[M+Na]^+$: 391.0723; found: 391.0710.



3ka

(1*R*,4*S*,4a*S*,9a*R*)-7-methoxy-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ka*)

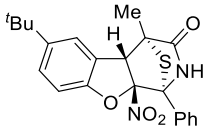
White solid, 62% yield, 47.6 mg, >20:1 dr, 89% ee; m.p. 188.7 - 189.5 °C, $[\alpha]^{25}$ = -219.5 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 12.69 min, t_{minor} = 9.04 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.57 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.52 – 7.46 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.70 (s, 1H), 3.78 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.7, 162.0, 161.8, 130.4, 129.6, 129.1, 127.5, 127.0, 126.7, 115.2, 109.7, 97.0, 81.9, 63.1, 59.6, 56.2, 12.2. HRMS (ESI-TOF) Calcd. for $C_{19}H_{16}N_2NaO_5S$ $[M+Na]^+$: 407.0672; found: 407.0656.



3la

(1*R*,4*S*,4a*S*,9a*R*)-8-methoxy-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3la*)

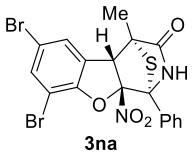
White solid, 73% yield, 56.1 mg, >20:1 dr, 98% ee; m.p. 186.2-187.0 °C, $[\alpha]_D^{25}$ = -391.8 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 12.43 min, t_{minor} = 19.72 min); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.57 – 7.49 (m, 2H), 7.48 – 7.43 (m, 3H), 7.08 – 7.03 (m, 2H), 7.00 (dd, *J* = 6.1, 2.5 Hz, 1H), 4.78 (s, 1H), 3.80 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.7, 148.8, 144.5, 130.5, 129.7, 129.2, 127.6, 126.6, 124.8, 124.3, 118.0, 114.3, 82.1, 63.0, 60.6, 56.5, 12.5. HRMS (ESI-TOF) Calcd. for $C_{19}H_{16}N_2NaO_5S$ $[M+Na]^+$: 407.0672; found: 407.0661.



3ma

(1*R*,4*S*,4a*S*,9a*R*)-6-(tert-butyl)-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2H)-one (*3ma*)

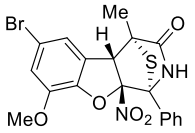
White solid, 54% yield, 44.3 mg, >20:1 dr, 89% ee; m.p. 177.4-178.3 °C, $[\alpha]_D^{25}$ = -214.1 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 11.02 min, t_{minor} = 8.88 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.62 – 7.55 (m, 2H), 7.49 (dd, *J* = 4.3, 2.3 Hz, 4H), 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 4.76 (s, 1H), 1.61 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.7, 158.5, 146.1, 130.4, 129.9, 129.7, 129.1, 127.6, 127.5, 126.6, 123.4, 123.3, 109.9, 81.9, 62.9, 60.1, 34.8, 31.8, 12.4. HRMS (ESI-TOF) Calcd. for $C_{22}H_{22}N_2NaO_5S$ $[M+Na]^+$: 433.1192; found: 433.1181.



3na

(1*R*,4*S*,4a*S*,9a*R*)-6,8-dibromo-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3na*)

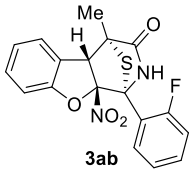
Yellow solid, 94% yield, 96.0 mg, >20:1 dr, 93% ee; m.p. 160.9-161.8 °C, $[\alpha]_D^{25}$ = -160.4 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 14.17 min, t_{minor} = 23.12 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.72 – 7.65 (m, 1H), 7.58 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.54 – 7.45 (m, 3H), 4.97 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.6, 156.8, 134.8, 130.1, 128.7, 128.0, 127.1, 127.0, 124.9, 114.8, 103.1, 81.5, 62.5, 60.2, 11.8. HRMS (ESI-TOF) Calcd. for $C_{18}H_{12}{}^{79}Br_2N_2NaO_4S$ $[M+Na]^+$: 532.8777; found: 532.8777; For $C_{18}H_{12}{}^{79}Br^{81}BrN_2NaO_4S$ $[M+Na]^+$: 534.8756; found: 534.8757; for $C_{18}H_{12}{}^{81}Br_2N_2NaO_4S$ $[M+Na]^+$: 536.8736; found: 536.8741.



3oa

(1*R*,4*S*,4a*S*,9a*R*)-6-bromo-8-methoxy-4-methyl-9a-nitro-1-phenyl-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3oa*)

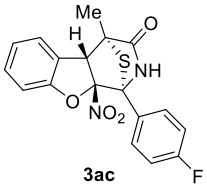
Pale yellow solid, 85% yield, 78.8 mg, >20:1 dr, 91% ee; m.p. 156.9-157.7 °C, $[\alpha]_D^{25}$ = -285.5 (c 1.0, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 32.45 min, t_{minor} = 39.30 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.55 – 7.50 (m, 2H), 7.50 – 7.45 (m, 3H), 7.32 – 7.21 (m, 2H), 4.83 (s, 1H), 3.85 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.6, 148.7, 144.4, 130.4, 130.0, 129.6, 129.1, 129.0, 127.6, 126.5, 124.8, 124.2, 118.0, 114.3, 82.0, 62.9, 60.5, 56.4, 12.4. HRMS (ESI-TOF) Calcd. for $C_{19}H_{15}{}^{79}BrN_2NaO_5S$ $[M+Na]^+$: 484.9777; found: 484.9764; For $C_{19}H_{15}{}^{81}BrN_2NaO_5S$ $[M+Na]^+$: 486.9757; found: 486.9739.



3ab

(1*R*,4*S*,4a*S*,9a*R*)-1-(2-fluorophenyl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ab*)

White solid, 41% yield, 30.6 mg, >20:1 dr, 89% ee; m.p. 160.7-161.5 °C, $[\alpha]^{25}$ = -171.5 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 23.50 min, t_{minor} = 14.23 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.56 (dd, J = 14.6, 7.4 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.17 – 7.10 (m, 2H), 4.80 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.2, 160.6 (d, J = 250.7 Hz, 1C), 160.5, 133.2 (d, J = 9.1 Hz, 1C), 130.8, 130.4 (d, J = 3.0 Hz, 1C), 126.5, 125.7, 125.2 (d, J = 4.5 Hz, 1C), 123.7, 123.4, 117.2 (d, J = 22.6 Hz, 1C), 116.5 (d, J = 10.6 Hz. 1C), 110.7, 79.8 (d, J = 3.0 Hz, 1C), 62.4, 59.9, 12.2. HRMS (ESI-TOF) Calcd. for $C_{18}H_{14}FN_2O_4S$ $[M+H]^+$: 373.0653; found: 373.0652.

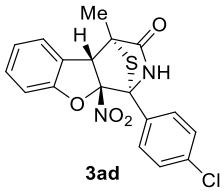


3ac

(1*R*,4*S*,4a*S*,9a*R*)-1-(4-fluorophenyl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ac*)

white solid, 47% yield, 35.0 mg, >20:1 dr, 93% ee; m.p. 173.4-174.1 °C, $[\alpha]_D^{25}$ = -64.2 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 11.64 min, t_{minor} = 16.50 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.53 – 7.44 (m, 3H), 7.43 – 7.35 (m, 1H), 7.20 – 7.11 (m, 2H), 7.06 – 7.01 (m, 2H), 4.79 (s, 1H), 1.58 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.6, 163.3 (d, J = 249.2 Hz, 1C), 160.4, 130.8, 130.0 (d, J = 9.1 Hz, 2C), 126.6, 126.2, 126.0 (d, J = 3.0 Hz, 1C), 123.6, 123.5,

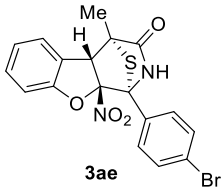
116.2 (d, *J* = 22.6 Hz, 2C), 110.7, 81.3, 63.1, 59.8, 12.3. HRMS (ESI-TOF) Calcd. for $C_{18}H_{14}FN_2O_4S$ $[M+H]^+$: 373.0653; found: 373.0662.



3ad

(1*R*,4*S*,4a*S*,9a*R*)-1-(4-chlorophenyl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ad*)

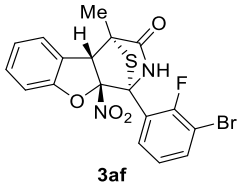
White solid, 58% yield, 45.2 mg, >20:1 dr, 98% ee; m.p. 186.0-186.7 °C, $[\alpha]_D^{25}$ = -389.3 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 13.93 min, t_{minor} = 8.09 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.66 – 7.56 (m, 4H), 7.53 – 7.46 (m, 1H), 7.45 – 7.37 (m, 1H), 7.22 – 7.12 (m, 2H), 4.85 (s, 1H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.6, 160.5, 135.3, 130.9, 129.5, 129.2, 128.7, 126.6, 126.2, 123.6, 123.5, 110.8, 81.2, 63.1, 59.8, 12.3. HRMS (ESI-TOF) Calcd. for $C_{18}H_{14}ClN_2O_4S$ $[M+H]^+$: 389.0357; found: 389.0364.



3ae

(1*R*,4*S*,4a*S*,9a*R*)-1-(4-bromophenyl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ae*)

White solid, 58% yield, 50.3 mg, >20:1 dr, 96% ee; m.p. 175.7-176.6 °C, $[\alpha]_D^{25}$ = -37.8 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 11.44 min, t_{minor} = 9.76 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.79 – 7.67 (m, 2H), 7.58 – 7.45 (m, 3H), 7.44 – 7.35 (m, 1H), 7.22 – 7.08 (m, 2H), 4.84 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.4, 160.2, 131.9, 130.6, 129.4, 128.8, 126.3, 125.9, 123.8, 123.3, 123.2, 110.5, 81.0, 62.9, 59.5, 12.0. HRMS (ESI-TOF) Calcd. for $C_{18}H_{14}{}^{79}BrN_2O_4S$ $[M+H]^+$: 432.9858; found: 432.9852; For $C_{18}H_{14}{}^{81}BrN_2O_4S$ $[M+H]^+$: 434.9833; found: 434.9843.

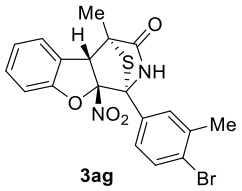


3af

(1*R*,4*S*,4a*S*,9a*R*)-1-(3-bromo-2-fluorophenyl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one1 (*3af*)

White solid, 57% yield, 49.4 mg, >20:1 dr, 90% ee; m.p. 224.0-224.8 °C, $[\alpha]_D^{25}$ = -112.3 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 32.08 min, t_{minor} = 17.18 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.99 – 7.82 (m, 1H), 7.62 – 7.54 (m, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.34 – 7.26 (m, 1H), 7.19 – 7.10 (m, 2H), 4.82 (s, 1H), 1.60 (s, 3H). ^{13}C NMR (101 MHz,

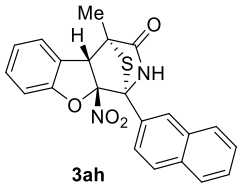
DMSO-d_6) δ 176.1, 160.5, 156.7 (d, J = 253.5 Hz, 1C), 136.3, 130.9, 129.9, 126.6, 126.4 (d, J = 4.0 Hz, 1C), 125.7, 123.6 (d, J = 8.1 Hz, 1C), 118.5 (d, J = 13.1 Hz, 1C), 110.8, 110.3 (d, J = 22.2 Hz, 1C), 79.4, 79.4, 62.7, 59.9, 12.2. HRMS (ESI-TOF) Calcd. for $C_{18}H_{13}{}^{79}BrFN_2O_4S$ $[M+H]^+$: 450.9783; found: 450.9758; For $C_{18}H_{13}{}^{81}BrFN_2O_4S$ $[M+H]^+$: 452.9739; found: 452.9712.



3ag

(1*R*,4*S*,4a*S*,9a*R*)-1-(4-bromo-3-methylphenyl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ag*)

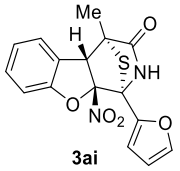
Pale yellow solid, 42% yield, 37.6 mg, >20:1 dr, 97% ee. m.p. 202.4-203.3 °C, $[\alpha]_D^{25}$ = -54.2(c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 14.76 min, t_{minor} = 9.13 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.20 – 7.08 (m, 2H), 4.81 (s, 1H), 2.37 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.5, 160.4, 138.2, 132.9, 130.8, 130.0, 129.3, 126.9, 126.5, 126.4, 126.2, 123.6, 123.5, 110.8, 81.2, 63.1, 59.8, 23.1, 12.3. HRMS (ESI-TOF) Calcd. for $C_{19}H_{15}{}^{79}BrN_2NaO_4S$ $[M+Na]^+$: 468.9828; found: 468.9813; For $C_{19}H_{15}{}^{81}BrN_2NaO_4S$ $[M+Na]^+$: 470.9809; found: 470.9807.



3ah

(1*R*,4*S*,4a*S*,9a*R*)-4-methyl-1-(naphthalen-2-yl)-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3ah*)

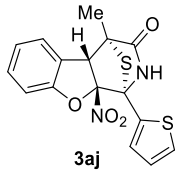
White solid, 52% yield, 42.0 mg, >20:1 dr, 81% ee; m.p. 121.3-122.3 °C, $[\alpha]_D^{25}$ = -71.2 (c 0.5, CH_2Cl_2); The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 36.56 min, t_{minor} = 20.45 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.21 – 8.16 (m, 1H), 8.08 – 7.95 (m, 3H), 7.69 – 7.60 (m, 3H), 7.51 (d, J = 7.4 Hz, 1H), 7.46 – 7.36 (m, 1H), 7.28 – 7.12 (m, 2H), 4.88 (s, 1H), 1.63 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.6, 160.5, 133.6, 132.6, 130.8, 128.8, 128.7, 128.1, 128.0, 127.5, 127.3, 127.1, 126.6, 126.5, 124.7, 123.7, 123.5, 110.8, 82.1, 63.1, 60.0, 12.3. HRMS (ESI-TOF) Calcd. for $C_{22}H_{17}N_2O_4S$ $[M+H]^+$: 405.0904; found: 405.0906.



3ai

(1*R*,4*S*,4a*S*,9a*R*)-1-(furan-2-yl)-4-methyl-9a-nitro-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro [2,3-*c*]pyridin-3(2*H*)-one (*3ai*)

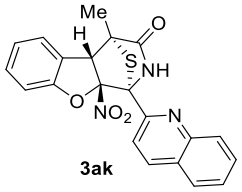
Yellow solid, 83% yield, 57.2 mg, >20:1 dr, 81% ee; m.p. 134.3-135.1 °C, $[\alpha]_D^{25}$ = -86.6 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 24.80 min, t_{minor} = 14.80 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.94 – 7.80 (m, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.24 – 7.09 (m, 2H), 6.85 (d, *J* = 3.5 Hz, 1H), 6.60 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.81 (s, 1H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.3, 160.2, 145.2, 142.3, 130.4, 126.1, 125.1, 123.1, 123.0, 111.4, 111.2, 110.4, 75.9, 63.1, 58.9, 11.9. HRMS (ESI-TOF) Calcd. for $C_{16}H_{12}N_2O_5S$ $[M+Na]^+$: 367.0359; found: 367.0360.



3aj

(1*S*,4*S*,4a*S*,9a*R*)-4-methyl-9a-nitro-1-(thiophen-2-yl)-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3aj*)

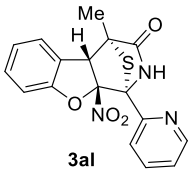
Yellow solid, 60% yield, 43.3 mg, >20:1 dr, 75% ee; m.p. 155.2-156.0 °C, $[\alpha]_D^{25}$ = -1.6 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 22.54 min, t_{minor} = 10.56 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.75 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.44 – 7.37 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.09 (m, 2H), 4.85 (s, 1H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.6, 160.0, 130.9, 130.4, 129.2, 128.1, 127.1, 126.1, 124.9, 123.3, 123.1, 110.3, 78.6, 63.7, 59.3, 11.8. HRMS (ESI-TOF) Calcd. for $C_{16}H_{13}N_2O_4S_2$ $[M+H]^+$: 361.0311; found: 361.0314.



3ak

(1*R*,4*S*,4a*S*,9a*R*)-4-methyl-9a-nitro-1-(quinolin-2-yl)-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-c]pyridin-3(2*H*)-one (*3ak*)

Pale yellow solid, 64% yield, 51.8 mg, >20:1 dr, 80% ee; m.p. 221.9-222.7 °C, $[\alpha]_D^{25}$ = -60.3 (c 0.5, CH_2Cl_2). The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 19.62 min, t_{minor} = 16.90 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.62 – 8.55 (m, 1H), 8.13 – 8.02 (m, 2H), 7.92 – 7.83 (m, 1H), 7.78 – 7.66 (m, 2H), 7.55-7.48 (m, 1H), 7.44 – 7.35 (m, 1H), 7.20 – 7.12 (m, 2H), 4.86 (s, 1H), 1.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.0, 160.6, 149.0, 146.8, 138.3, 131.2, 130.8, 129.5, 128.5, 128.4, 128.3, 126.6, 125.8, 123.7, 123.4, 119.9, 110.9, 83.4, 63.5, 60.0, 12.5. HRMS (ESI-TOF) Calcd. for $C_{21}H_{16}N_2O_4S_2$ $[M+H]^+$: 406.0856; found: 406.0864.



3al

(1*R*,4*S*,4a*S*,9a*R*)-4-methyl-9a-nitro-1-(pyridin-2-yl)-1,4,4a,9a-tetrahydro-1,4-epithiobenzofuro[2,3-*c*]pyridin-3(2*H*)-one (*3al*)

White solid, 70% yield, 49.8 mg, >20:1 dr, 82% ee; m.p. 182.6-183.5 °C, $[\alpha]_D^{25}$ = -113.2 (c 0.5, CH_2Cl_2); The ee was determined by HPLC (Chiralpak IC, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 35.00 min, t_{minor} = 28.40 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.69 – 8.61 (m, 1H), 8.05 – 7.93 (m, 1H), 7.56 (dd, *J* = 8.2, 4.2 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.31 (m, 1H), 7.13 (dd, *J* = 8.0, 5.7 Hz, 2H), 4.77 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.2, 160.6, 149.6, 148.5, 137.9, 130.7, 126.5, 125.7, 125.6, 123.8, 123.3, 123.0, 110.8, 83.5, 62.9, 60.1, 12.4. HRMS (ESI-TOF) Calcd. for $C_{17}H_{14}N_3O_4S$ $[M+H]^+$: 356.0700; found: 356.0694.

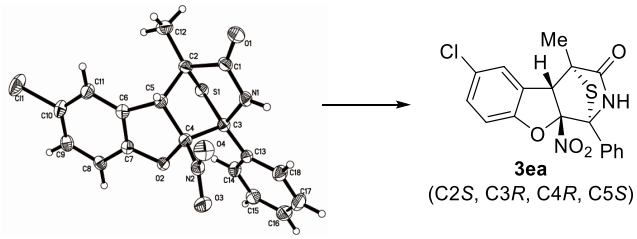
3. Scale-up experiment

To a flame dried reaction tube were added 2-nitrobenzofurans **1a** (1.0 mmol), 5*H*-thiazol-4-ones **2a** (1.3 mmol, 1.3 equiv), **Cat. D** (20 mol%), and activated 5 Å molecular sieve (500 g), followed by addition CH_2Cl_2 (10.0 mL). The reaction solution was stirred at room temperature for 48 h under a nitrogen atmosphere. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the corresponding products **3a** (0.317 g, 89% yield, >20:1 dr, and >96% ee).

To a flame dried reaction tube were added 2-nitrobenzofurans **1f** (3.0 mmol), 5*H*-thiazol-4-ones **2a** (3.9 mmol, 1.3 equiv), **Cat. D** (20 mol%), and activated 5 Å molecular sieve (1.5 g), followed by addition CH_2Cl_2 (30.0 mL). The reaction solution was stirred at room temperature for 48 h under a nitrogen atmosphere. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the corresponding products **3a** (1.01 g, 78% yield, >20:1 dr, and 93% ee).

4. X-Ray crystal data for compounds 3ea

Single crystals of compound **3ea** was prepared from the mixture solvent of EtOH and CH_2Cl_2. A suitable crystal was selected for structure determination on a Xcalibur, Eos, Gemini diffractometer. The crystal was kept at 293(2) K during data collection. Using Olex2, the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXLrefinement package using Least Squares minimisation.



ORTEP of **3ea** (at 50% level)

Crystal data and structure refinement for **3ea** (CCDC-2095172)

Identification code	**3ea**
Empirical formula	$C_{20}H_{19}ClN_2O_5S_2$
Formula weight	466.94
Temperature/K	293(2)
Crystal system	monoclinic
Space group	C2
a/Å	26.7417(6)

b/Å	6.38250(16)
c/Å	12.8324(3)
α/°	90
β/°	103.440(2)
γ/°	90
Volume/Å^3	2130.24(9)
Z	4
ρ_{calc}g/cm^3	1.456
μ/mm^{-1}	3.728
F(000)	968.0
Crystal size/mm^3	0.17 × 0.12 × 0.09
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.796 to 134.108
Index ranges	-28 ≤ h ≤ 31, -7 ≤ k ≤ 7, -15 ≤ l ≤ 15
Reflections collected	7977
Independent reflections	3813 [R_{int} = 0.0320, R_{sigma} = 0.0422]
Data/restraints/parameters	3813/1/278
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0425, wR_2 = 0.1083
Final R indexes [all data]	R_1 = 0.0462, wR_2 = 0.1133
Largest diff. peak/hole / e Å^{-3}	0.23/-0.46
Flack parameter	0.001(14)

5. General experimental procedures for in vitro cytotoxicity assay

Two human cancer cell lines, human leukemia cells K562 and human lung cancer cells A549 were purchased from Chinese Academy of Sciences, Kunming Cell Bank and Chinese Academy of Sciences, Shanghai Cell Bank respectively. All the cells werecultured in RPMI-1640 medium (GIBICO, USA), supplemented with 10% fetal bovine serum (Hyclone, USA) and Penicillin-Streptomycin (respectively 100 U/mL) in 5% CO_2 at 37 °C. The cytotoxicity assay was performed according to the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) method in 96-well microplates. Briefly, 5000 cells were seeded into each well of 96-well cell culture plates and allowed to grow for 24 h before the drug is added. Unless K562 tumor cell line was exposed to compounds at the concentrations of 1, 2, 4, 8 and 20 μmol·L^{-1}, each A549 tumor cell line was exposed to the test compounds at the concentrations of 5, 10, 20, 40 and 80 μmol·L^{-1} in triplicates for 48 h, comparable to cisplatin (Aladdin, China). Then the MTT reagent was added to reaction with the cancer cells for 4 hours. At least, measure the OD value at 490 wavelengths. The average 50% inhibitory concentration (IC_{50}) of all the compounds is calculated by IBM SPSS Statistics (version 19). Each concentration was analyzed in triplicate at least, and the whole experiment was repeated three times.

Table 1. Cell Inhibitory Assay of target products in K562 and A549.

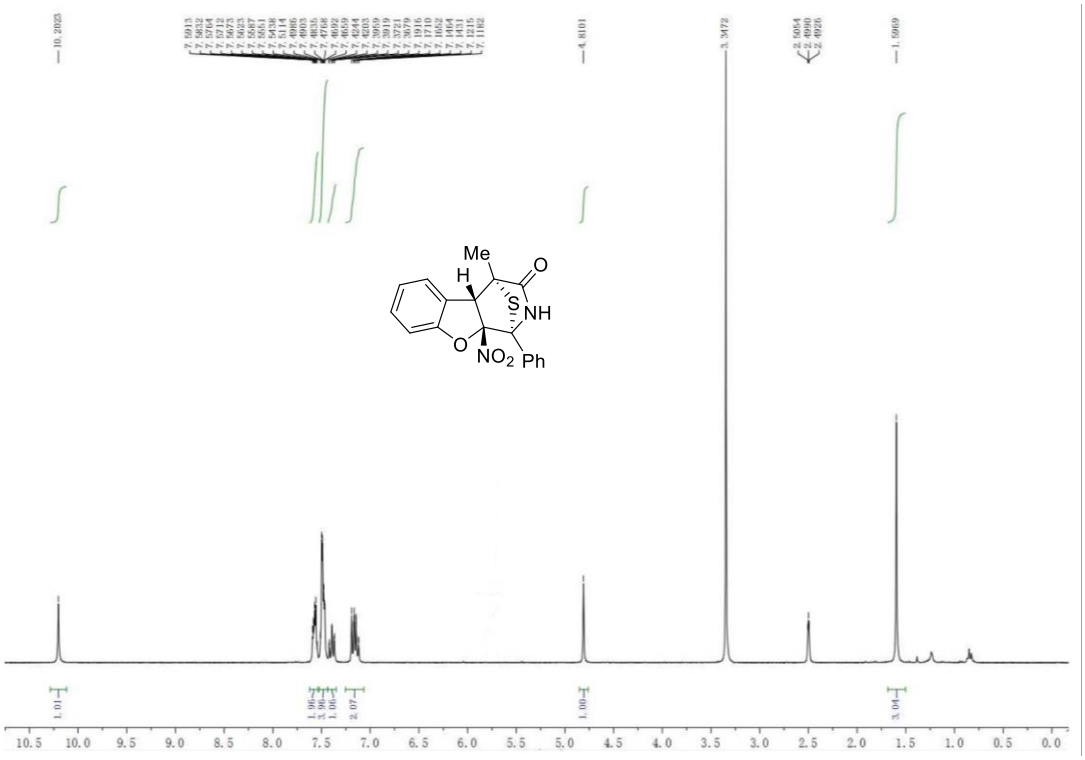
compound	IC_{50} (uM)^a	compound	IC_{50} (uM)^a

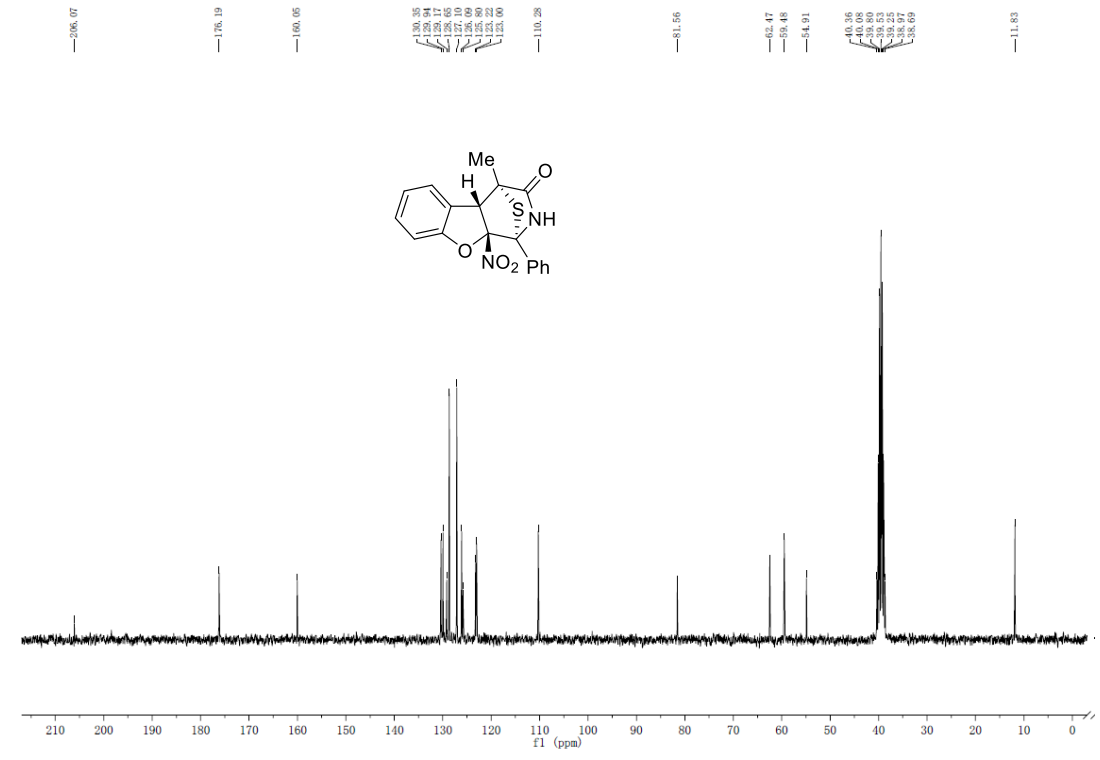
	A549	K562		A549	K562
3aa	28.15	12.4	**3ba**	32.58	13.02
3ca	57.72	18.97	**3da**	34.29	10.27
3ea	45.33	21.42	**3fa**	67.59	30.87
3ga	30.84	7.09	**3ha**	67.32	22.27
3ja	33.26	14.54	**3ka**	4.83	2.60
3la	31.84	20.33	**3ma**	33.00	29.62
3oa	15.61	3.10	**3ab**	57.00	52.19
3ac	58.23	74.61	**3ad**	39.95	50.23
3ae	45.51	54.74	**3af**	39.50	46.39
3ai	44.60	30.21	**3aj**	61.08	45.05
3ak	20.46	59.39	**3al**	23.88	32.32
cisplatin[b]	23.96	20.33			

[a]IC_{50} is the concentration of a compound that affords a 50% reduction in cell growth (after 48 h of incubation), expressed as the mean of triplicate experiments. [b]Commercially available broad-spectrum anticancer drug cisplatin as a positive control.

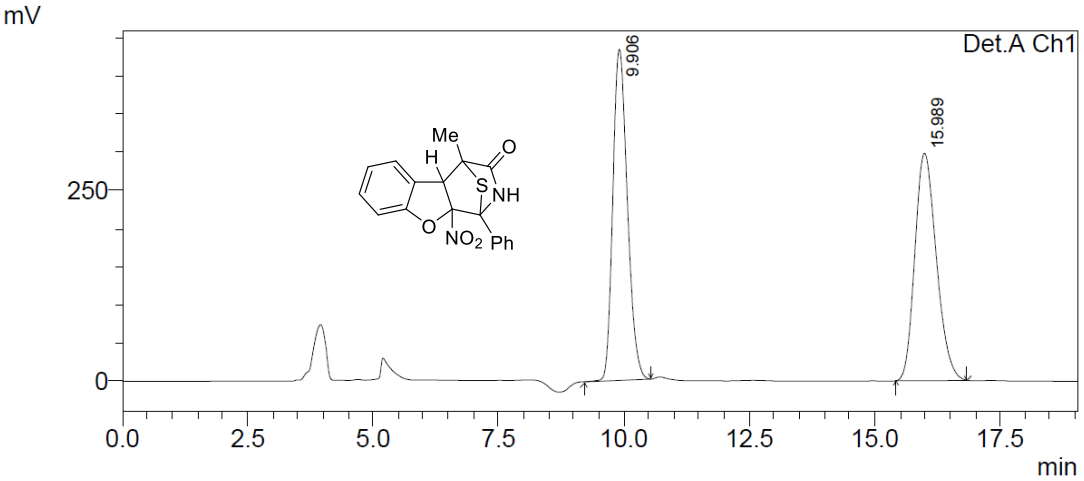
6. ^{1}H, ^{13}C NMR, and HPLC spectra for compounds 3

^{1}H, ^{13}C NMR of compound **3aa**





HPLC of compound **3aa**

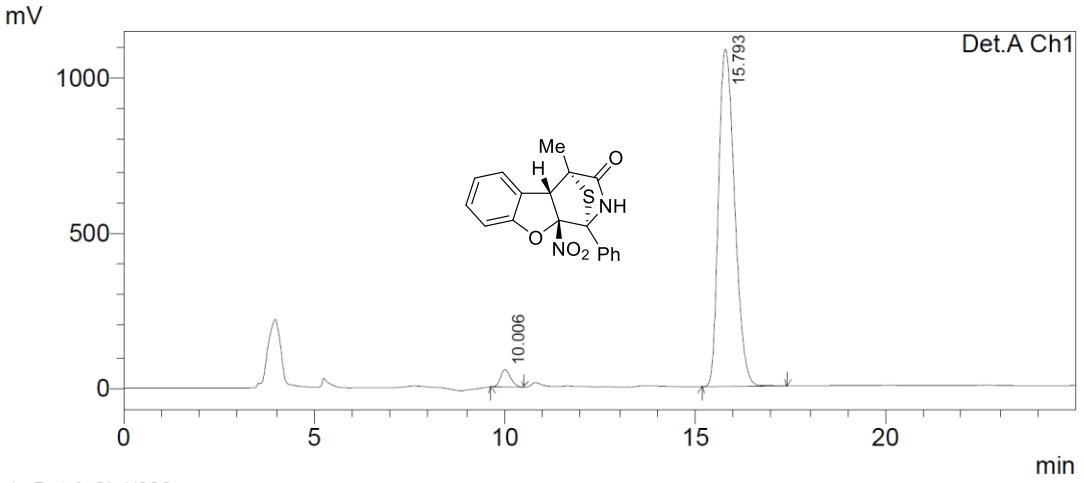


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.906	8746512	433106	49.640
2	15.989	8873271	297338	50.360
Total		17619783		100.000



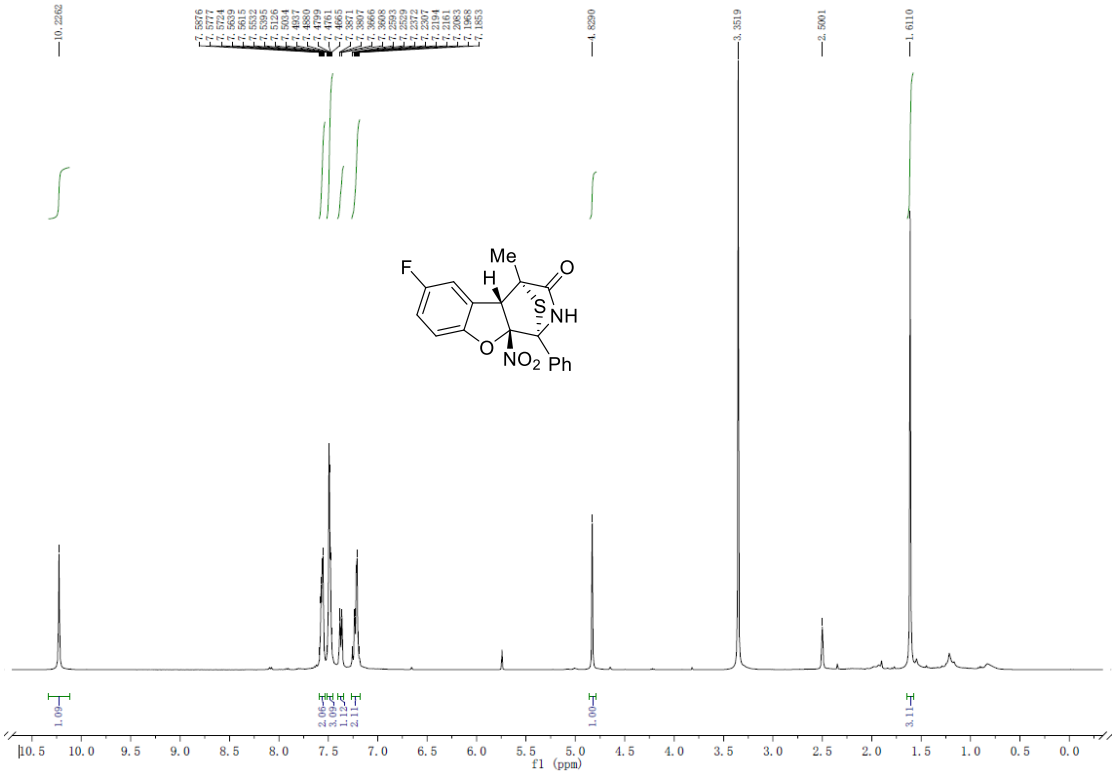
1 Det.A Ch1/220nm

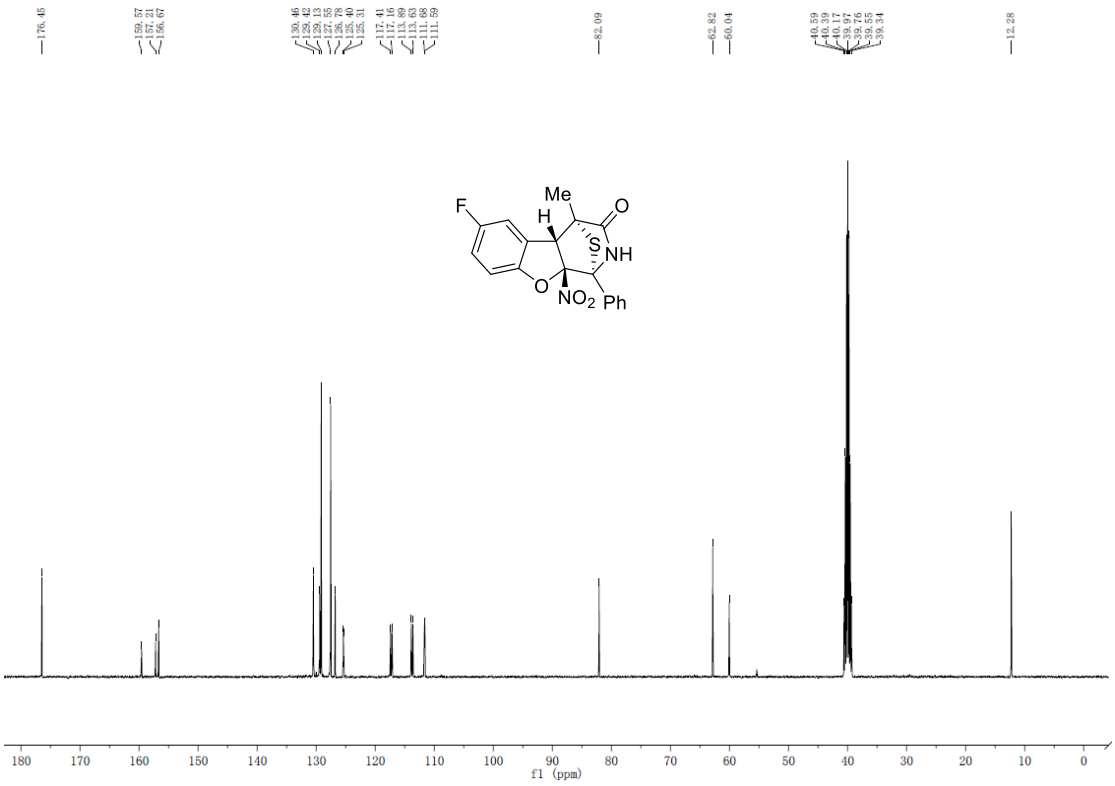
PeakTable

Detector A Ch1 220nm

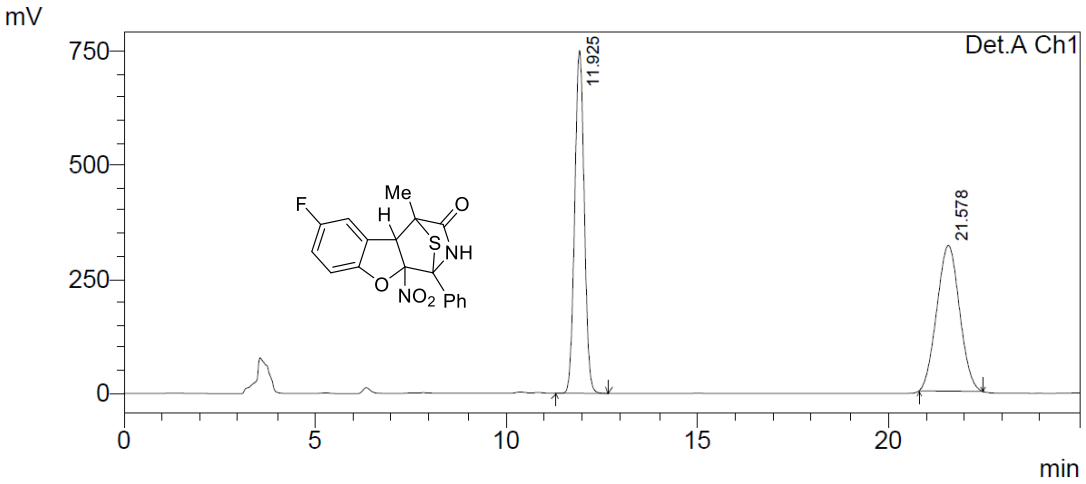
Peak#	Ret. Time	Area	Height	Area %
1	10.006	1025293	55973	3.098
2	15.793	32068345	1088783	96.902
Total		33093639		100.000

^{1}H, ^{13}C NMR of compound **3ba**





HPLC of compound **3ba**

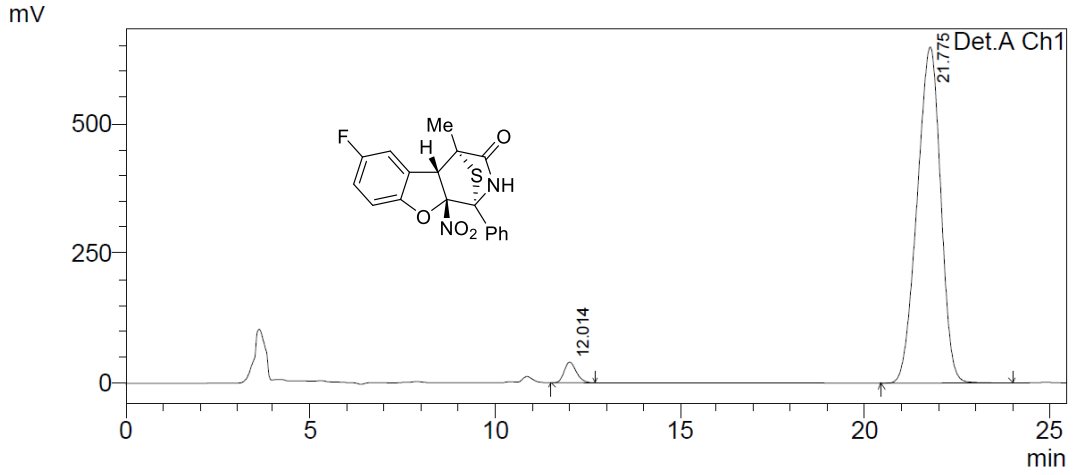


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	11.925	13010510	750662	49.631
2	21.578	13203885	319046	50.369
Total		26214395		100.000



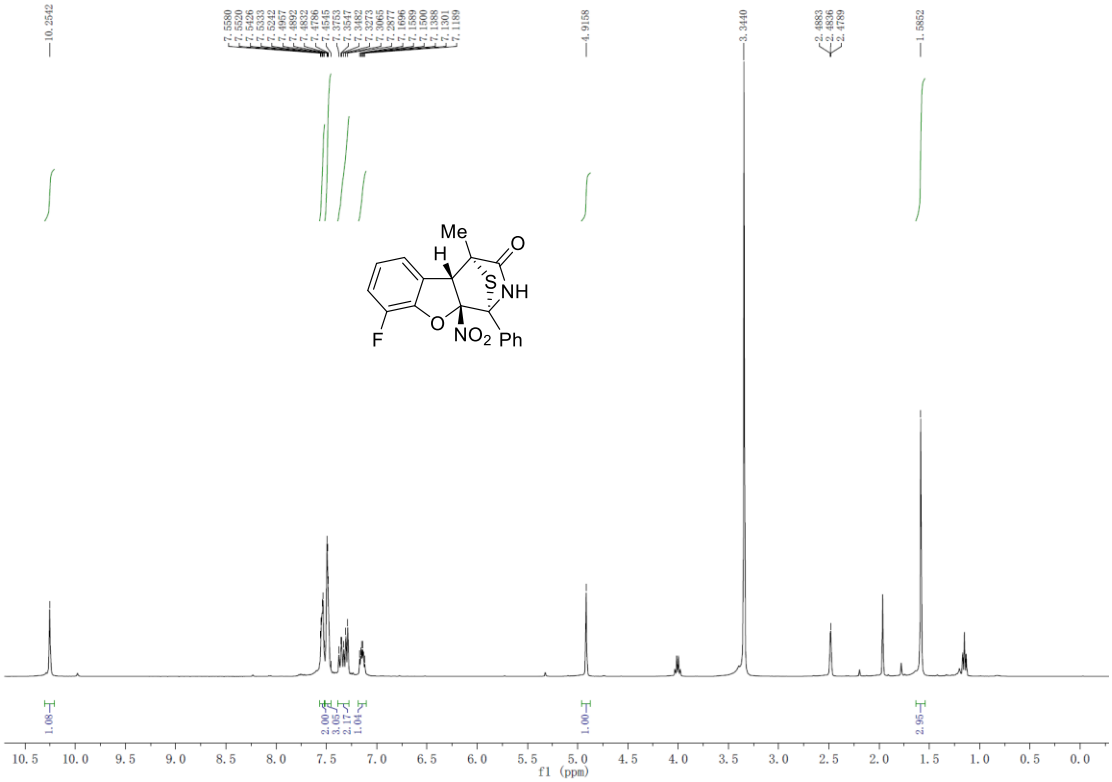
1 Det.A Ch1/220nm

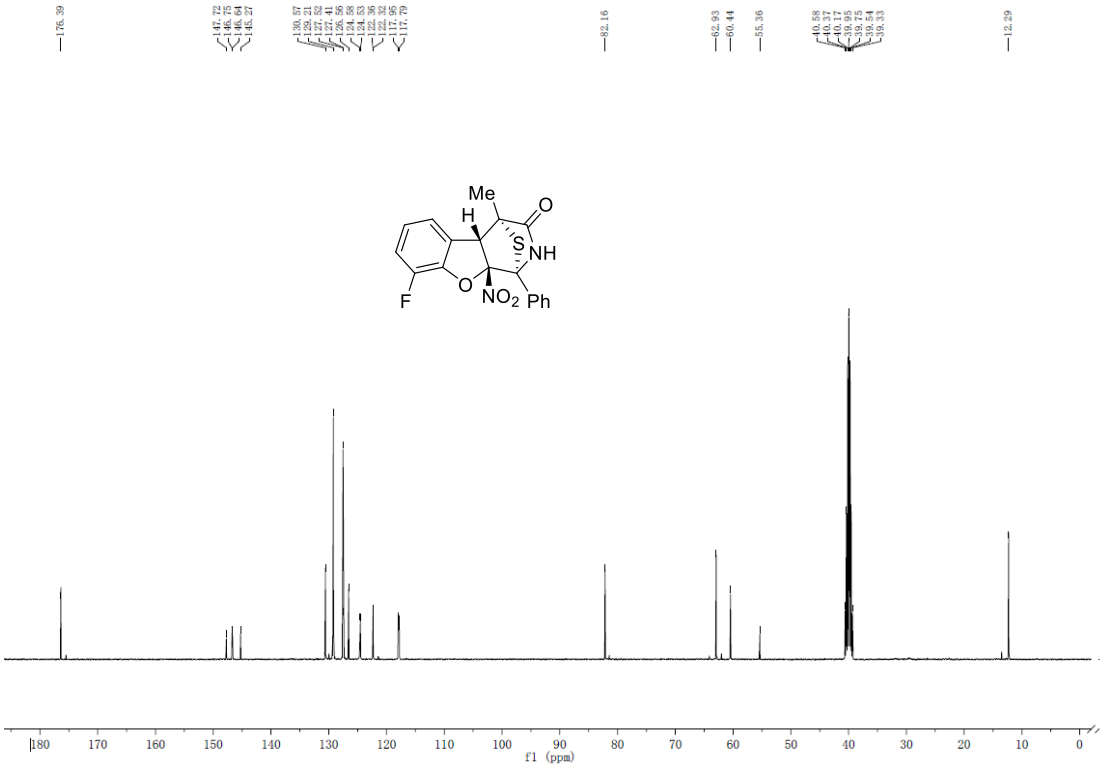
PeakTable

Detector A Ch1 220nm

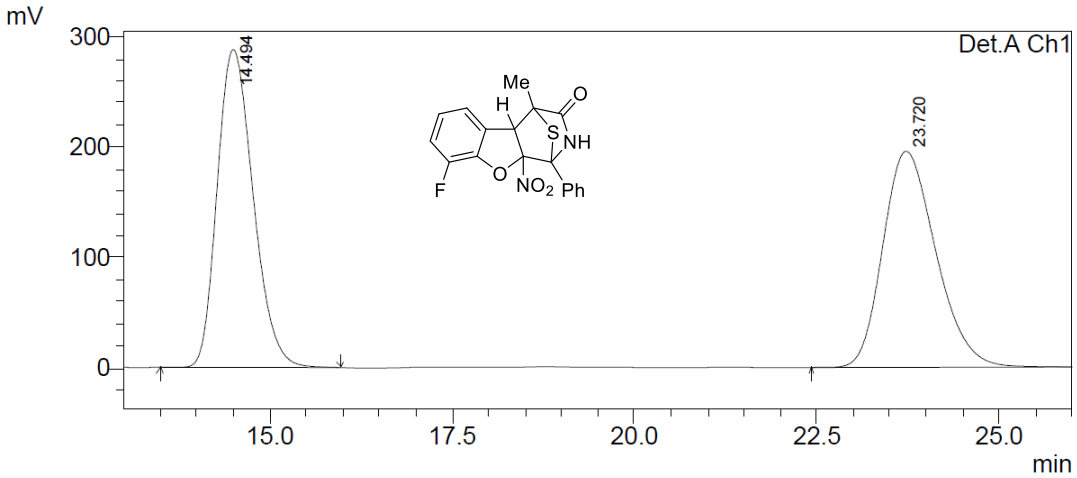
Peak#	Ret. Time	Area	Height	Area %
1	12.014	904259	39667	3.063
2	21.775	28621222	646290	96.937
Total		29525481		100.000

^{1}H, ^{13}C NMR of compound **3ca**





HPLC of compound **3ca**

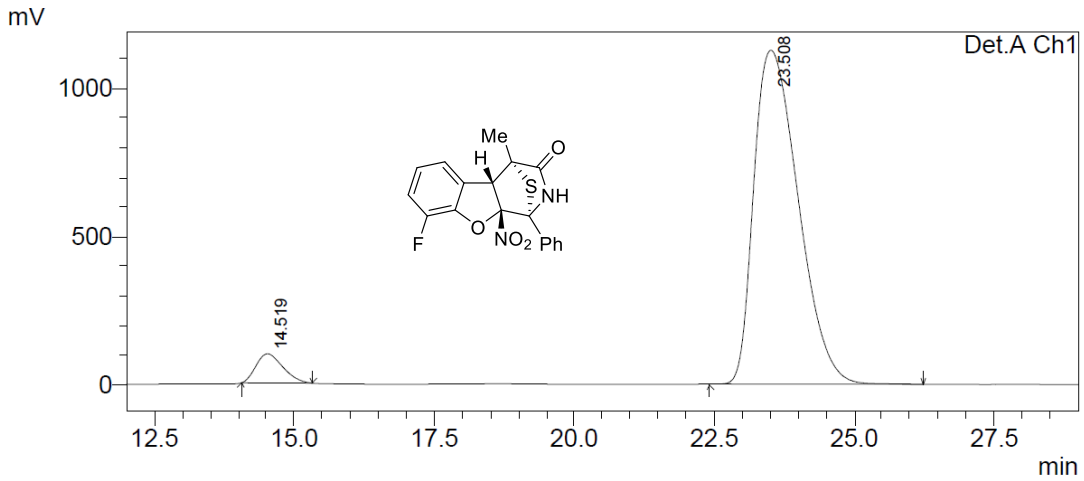


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	14.494	9902093	288120	50.012
2	23.720	9897222	195793	49.988
Total		19799315		100.000



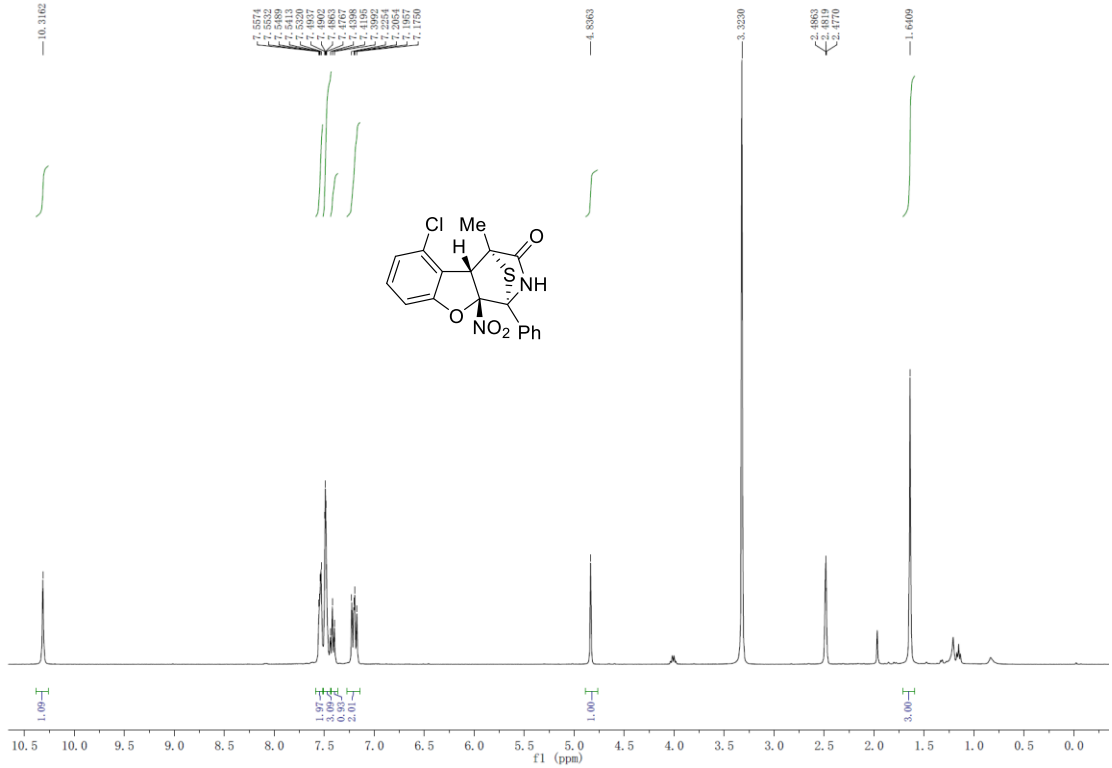
1 Det.A Ch1/220nm

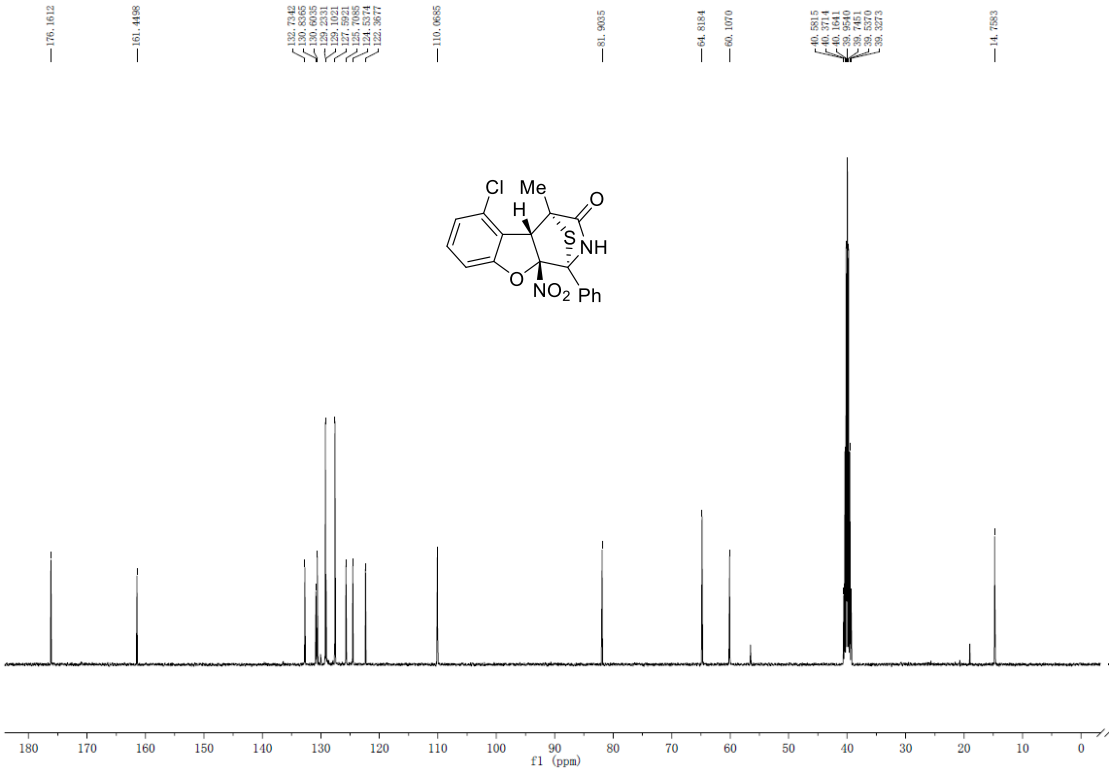
PeakTable

Detector A Ch1 220nm

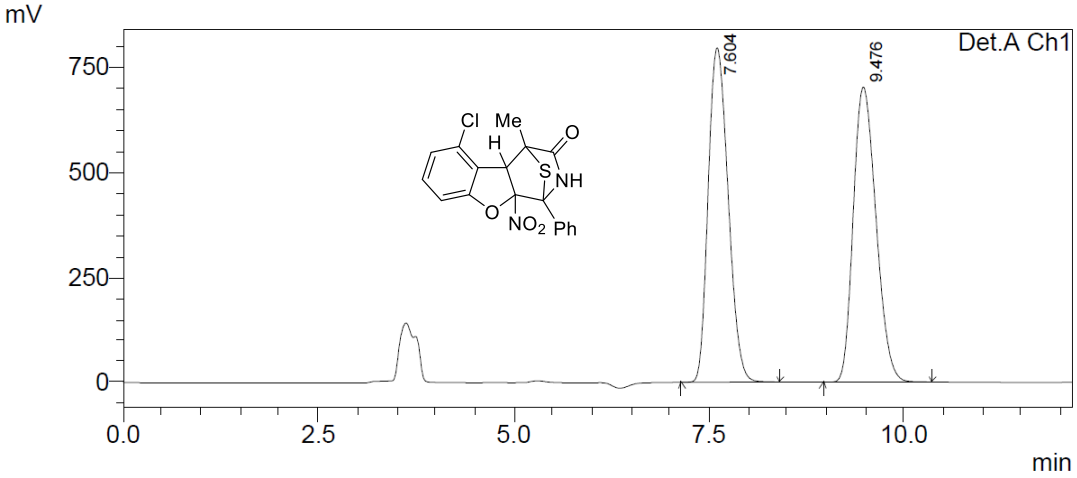
Peak#	Ret. Time	Area	Height	Area %
1	14.519	3298316	98486	5.032
2	23.508	62253856	1126090	94.968
Total		65552173		100.000

^{1}H, ^{13}C NMR of compound **3da**





HPLC of compound **3da**

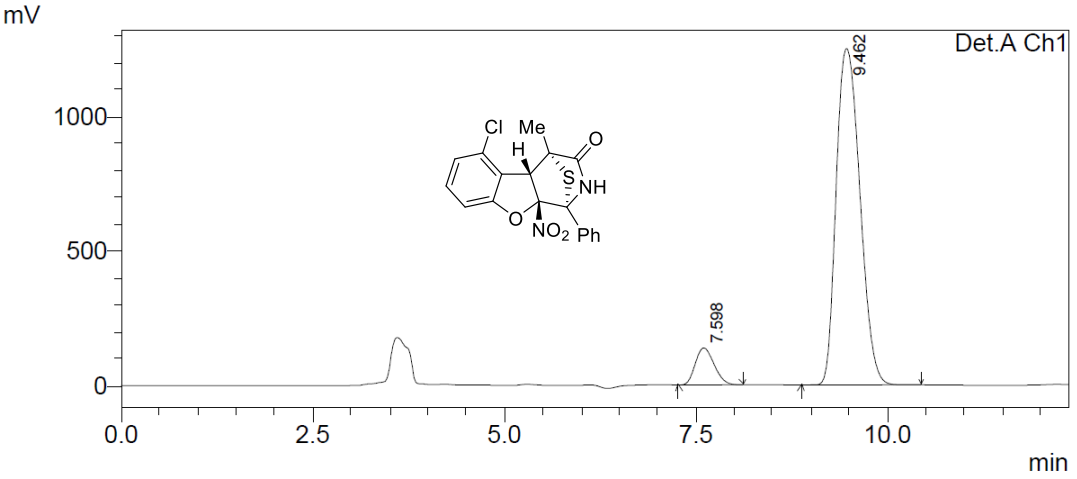


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	7.604	14141982	794418	49.914
2	9.476	14190453	700566	50.086
Total		28332435		100.000



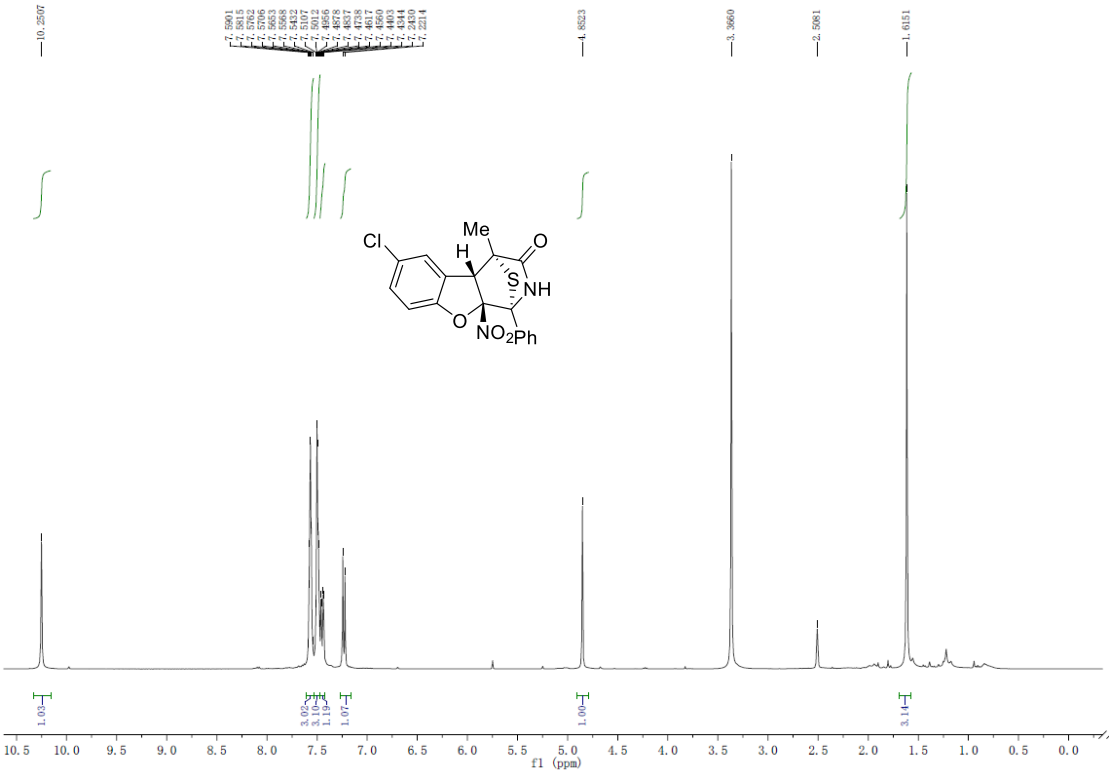
1 Det.A Ch1/220nm

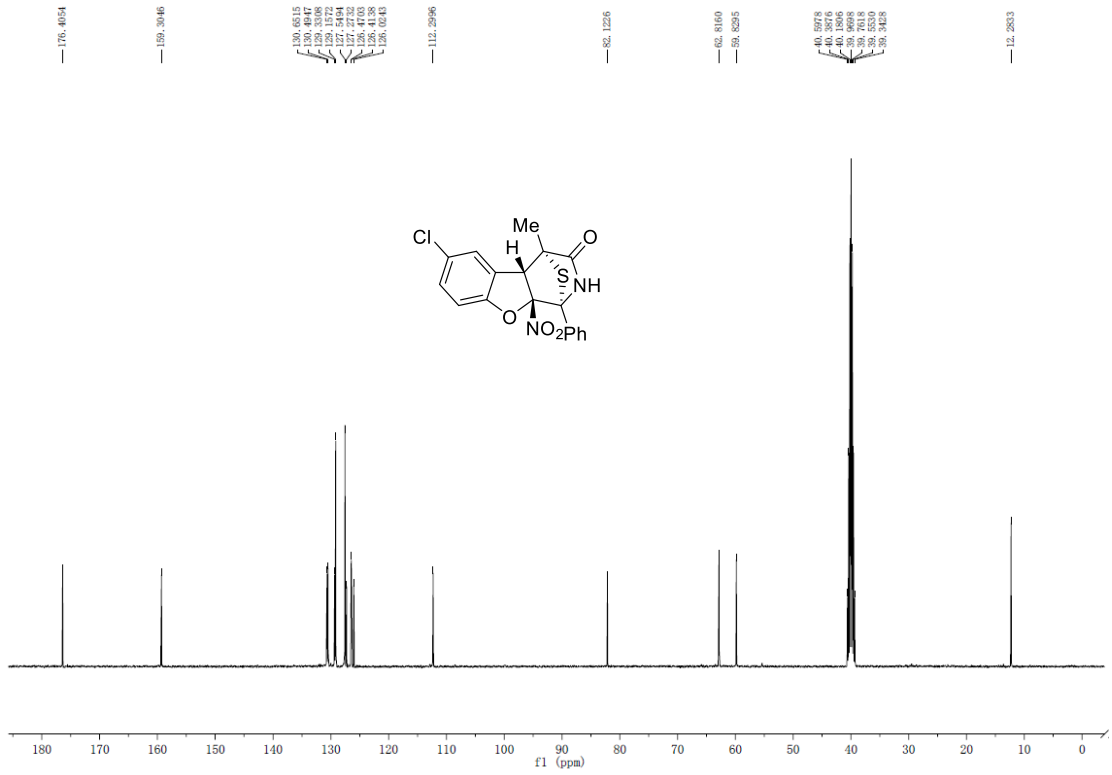
PeakTable

Detector A Ch1 220nm

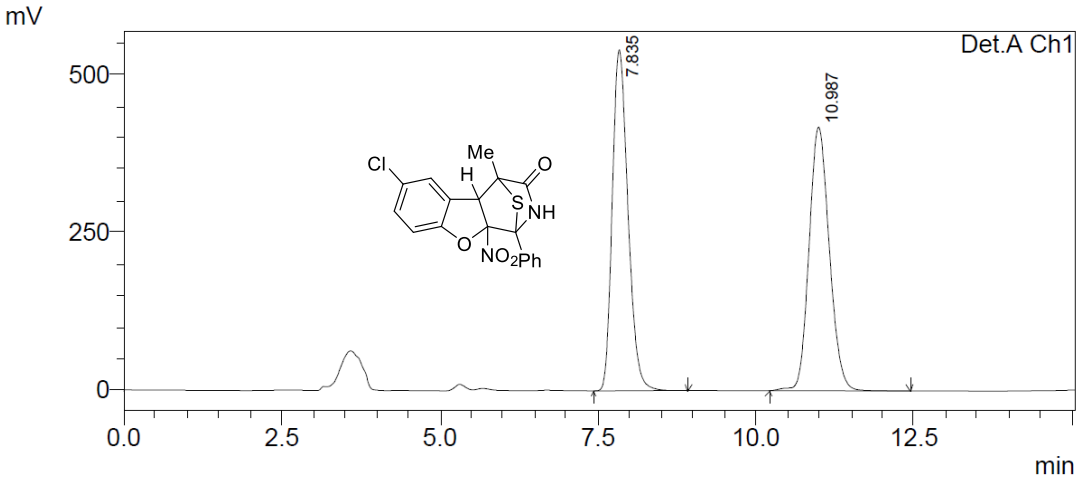
Peak#	Ret. Time	Area	Height	Area %
1	7.598	2354077	137726	8.031
2	9.462	26957742	1250875	91.969
Total		29311819		100.000

^{1}H, ^{13}C NMR of compound **3ea**





HPLC of compound **3ea**

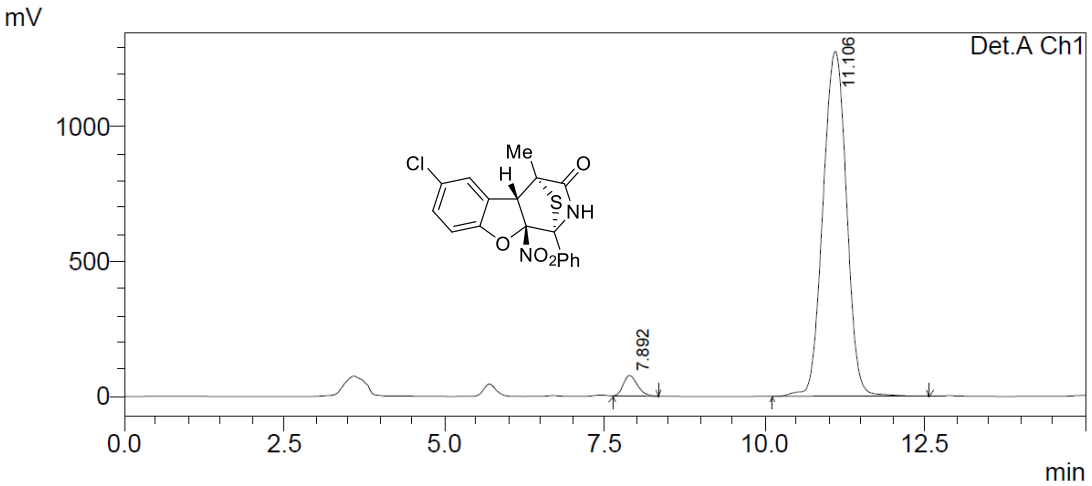


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	7.835	9343910	541010	50.026
2	10.987	9334129	418361	49.974
Total		18678039		100.000



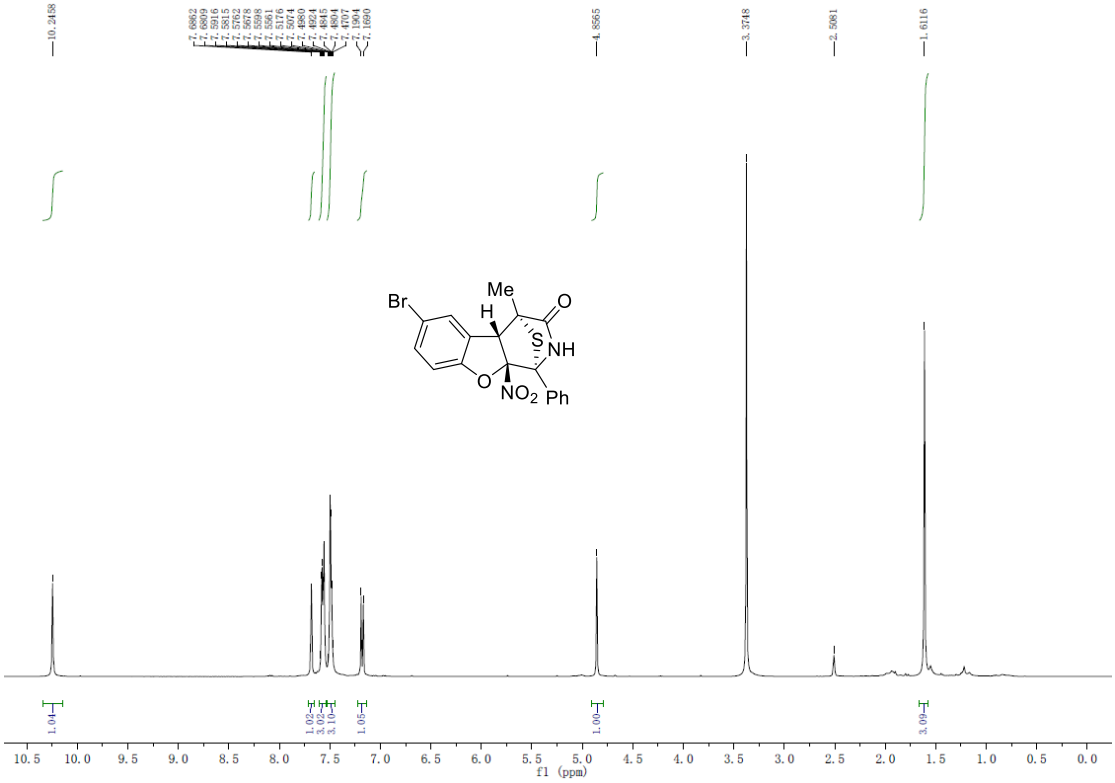
1 Det.A Ch1/220nm

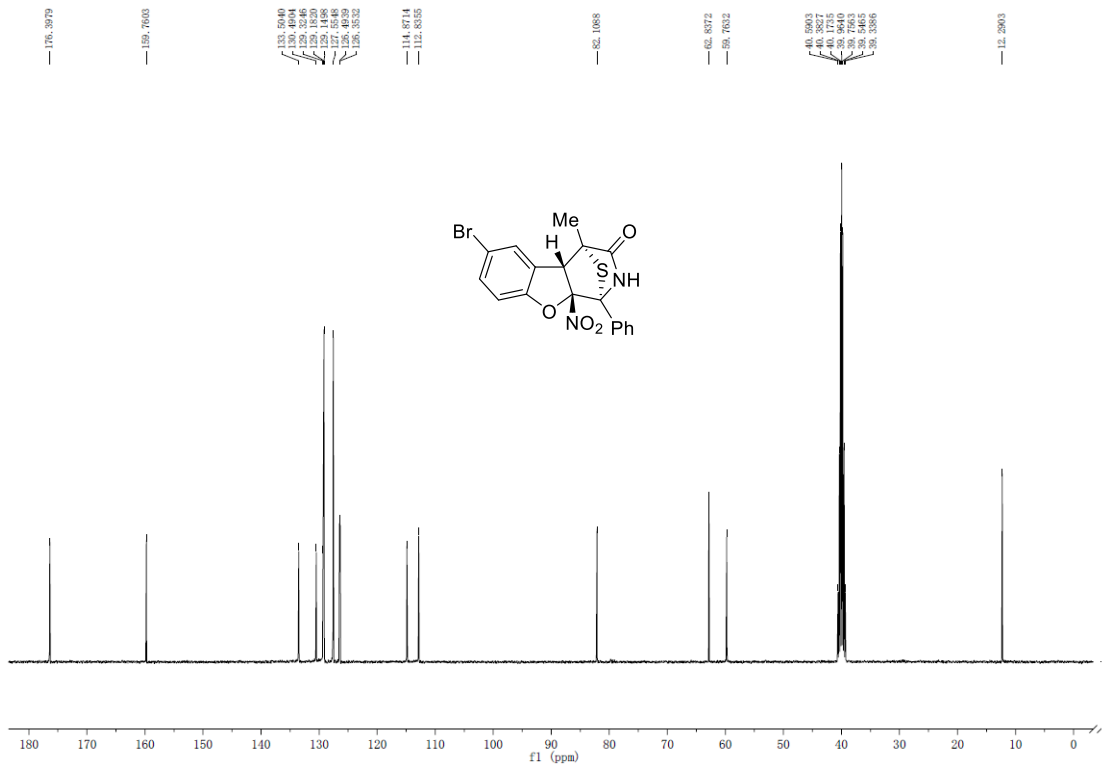
PeakTable

Detector A Ch1 220nm

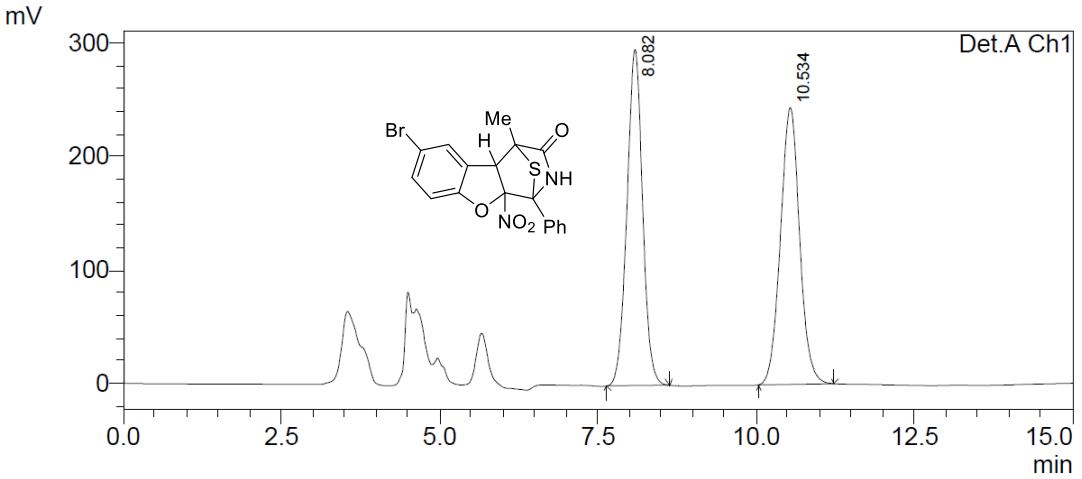
Peak#	Ret. Time	Area	Height	Area %
1	7.892	1160770	76013	3.413
2	11.106	32847844	1280990	96.587
Total		34008614		100.000

^{1}H, ^{13}C NMR of compound **3fa**





HPLC of compound **3fa**

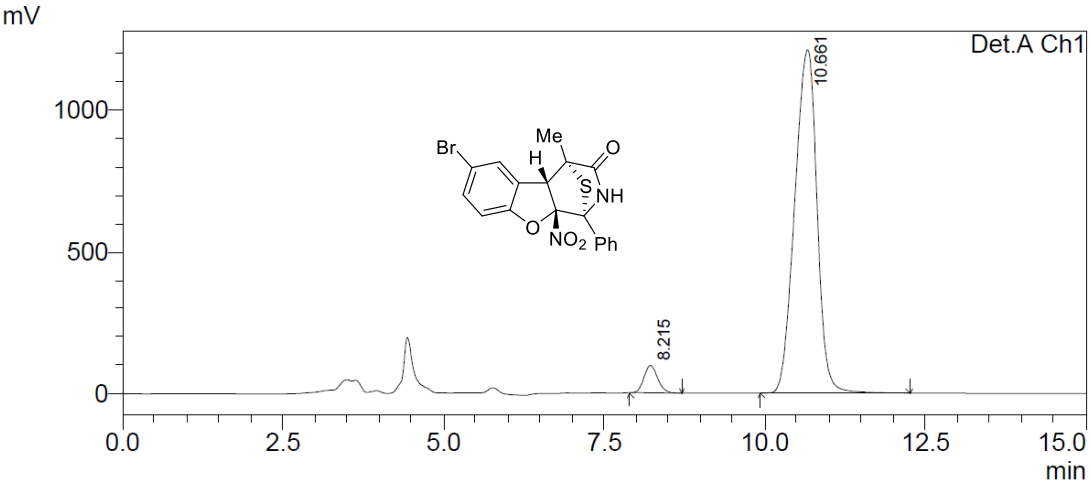


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.082	5095754	295938	49.774
2	10.534	5141990	243511	50.226
Total		10237744		100.000



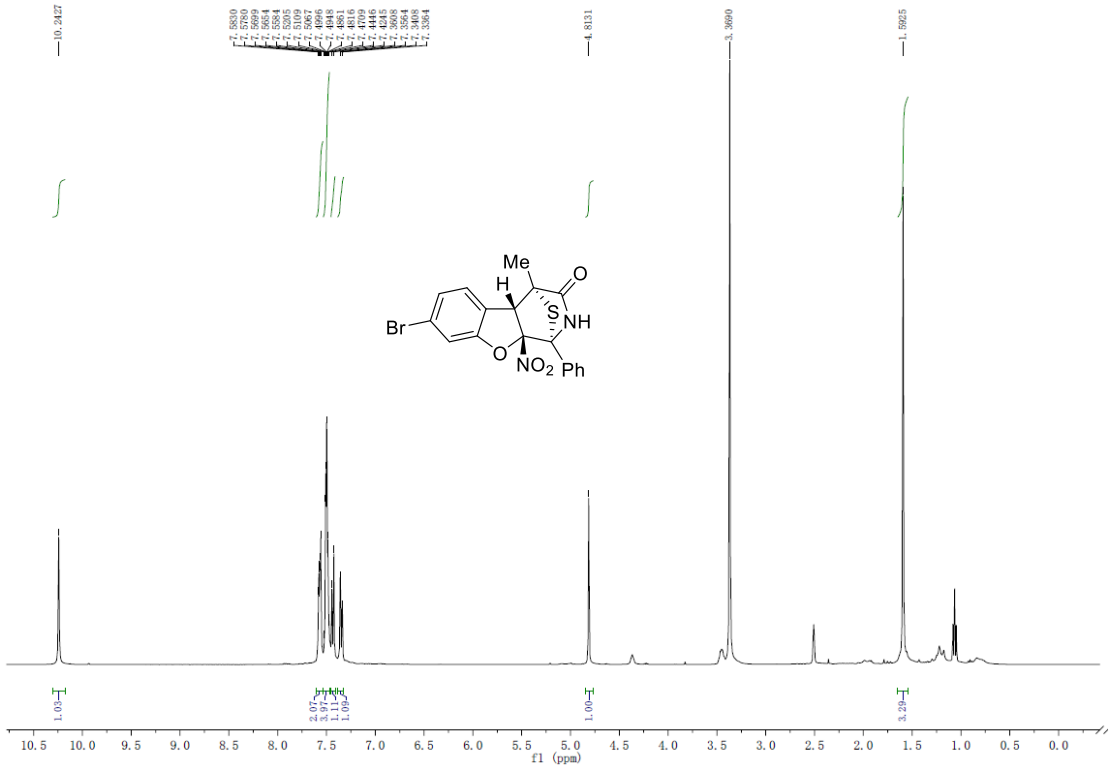
1 Det.A Ch1/220nm

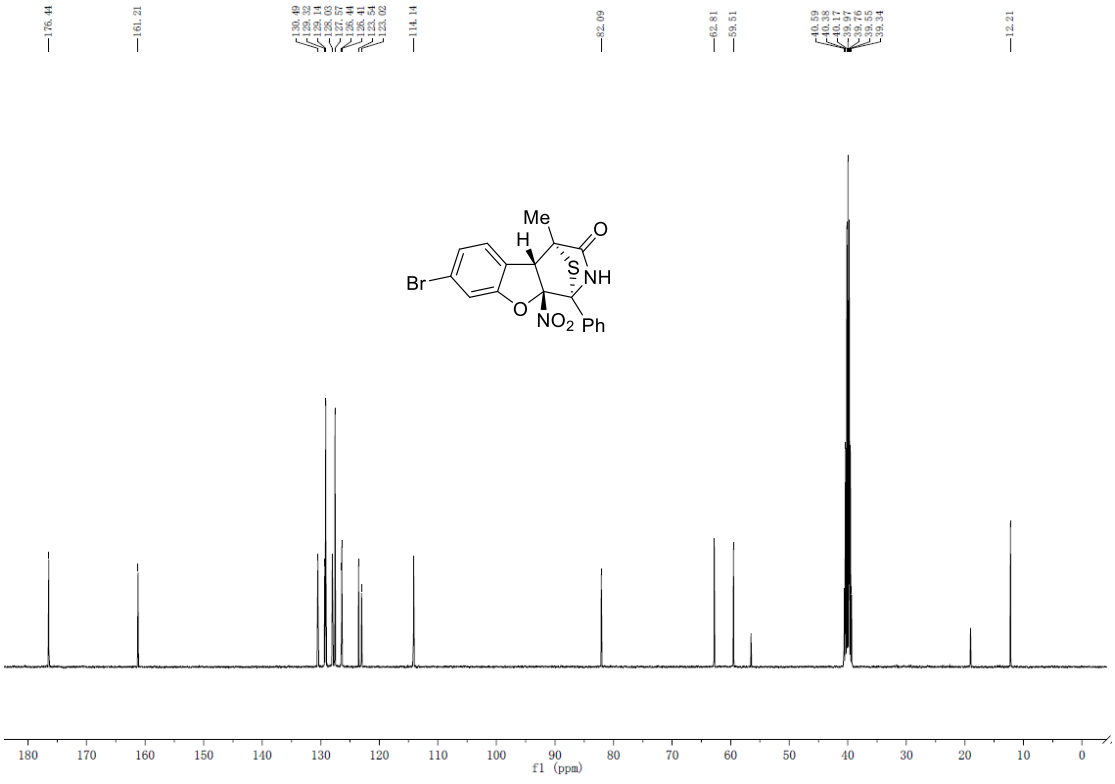
PeakTable

Detector A Ch1 220nm

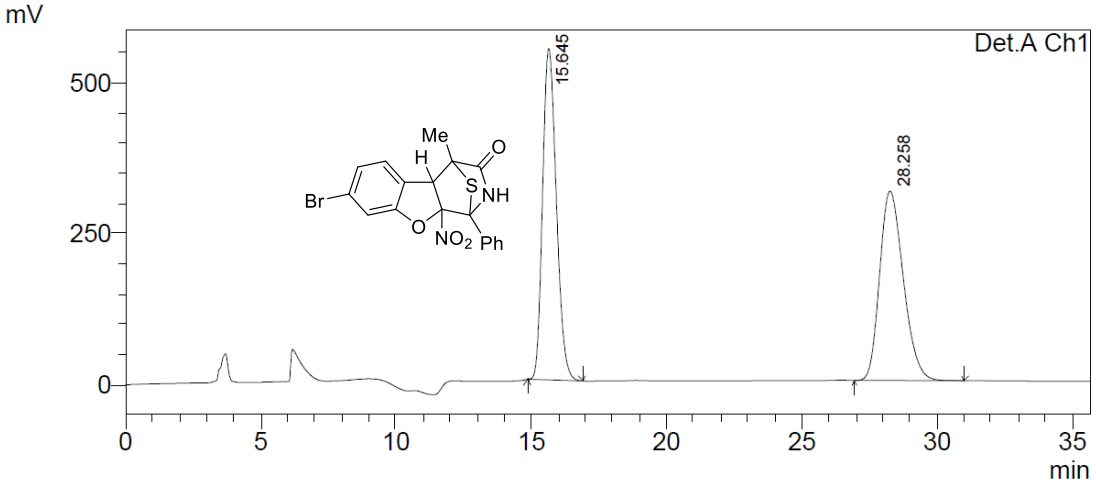
Peak#	Ret. Time	Area	Height	Area %
1	8.215	1423202	96310	4.649
2	10.661	29191194	1211374	95.351
Total		30614397		100.000

^{1}H, ^{13}C NMR of compound **3ga**





HPLC of compound **3ga**

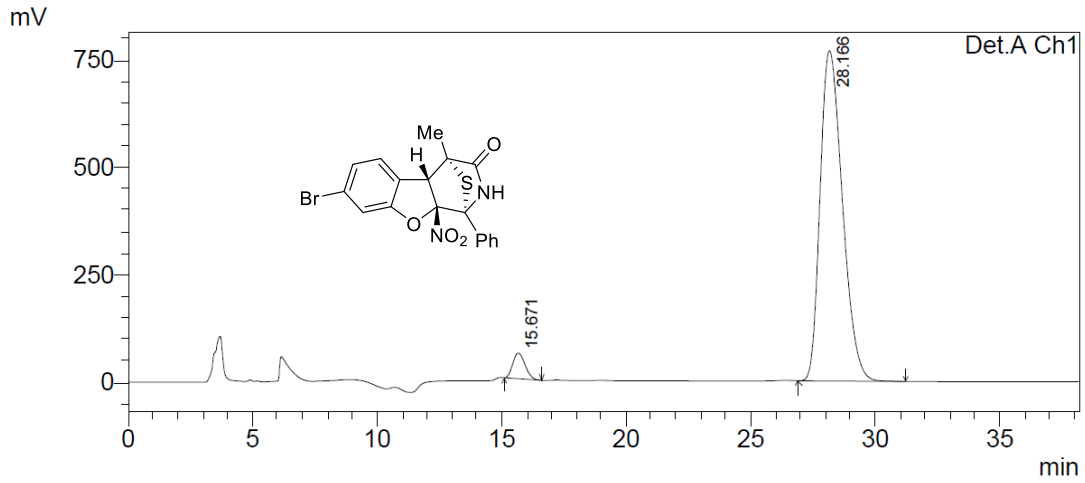


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	15.645	19420022	549281	50.453
2	28.258	19070917	314008	49.547
Total		38490939		100.000



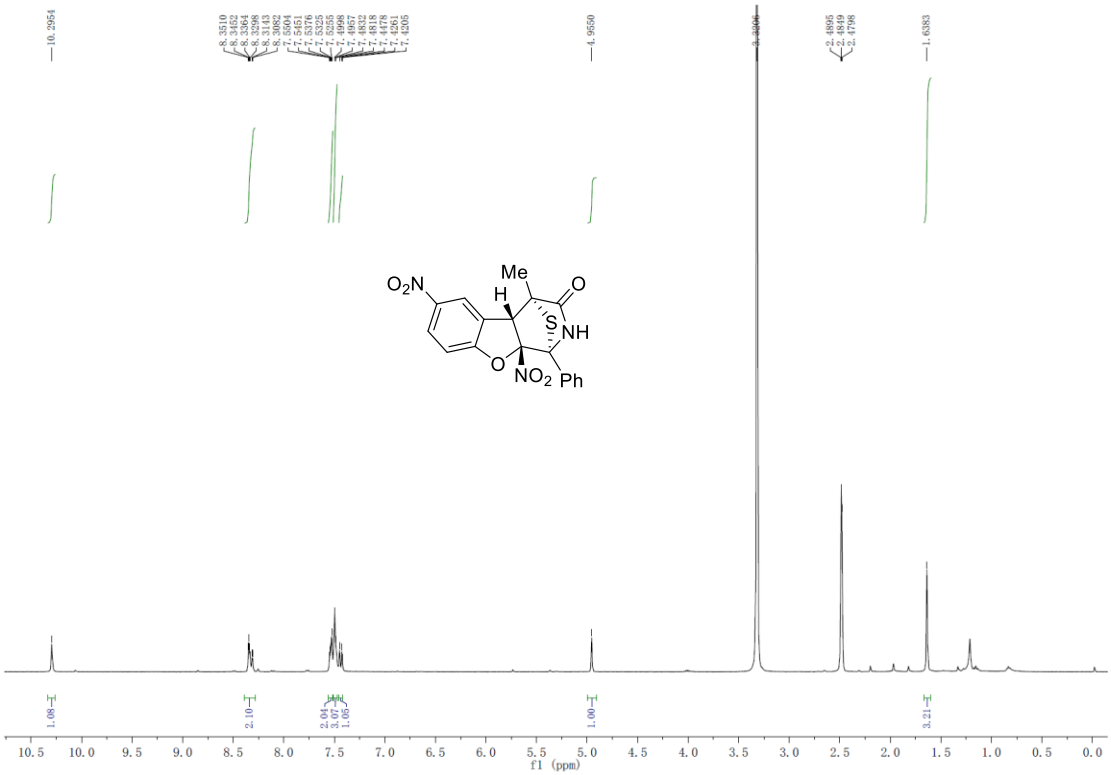
1 Det.A Ch1/220nm

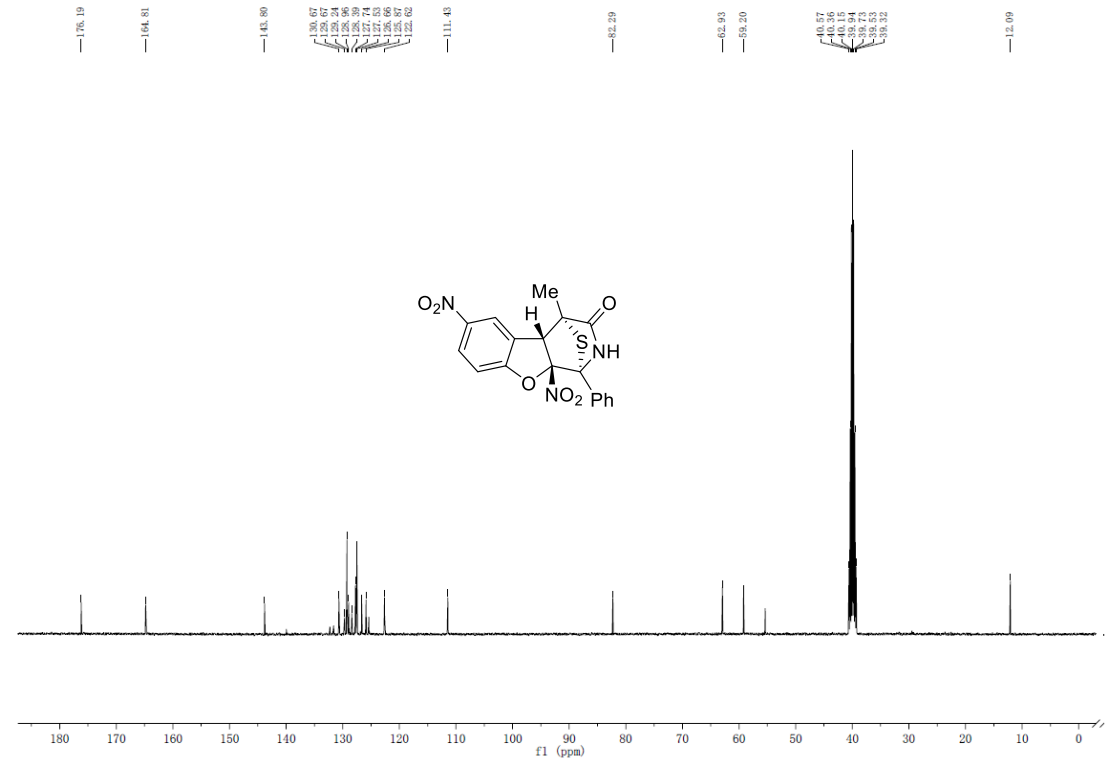
PeakTable

Detector A Ch1 220nm

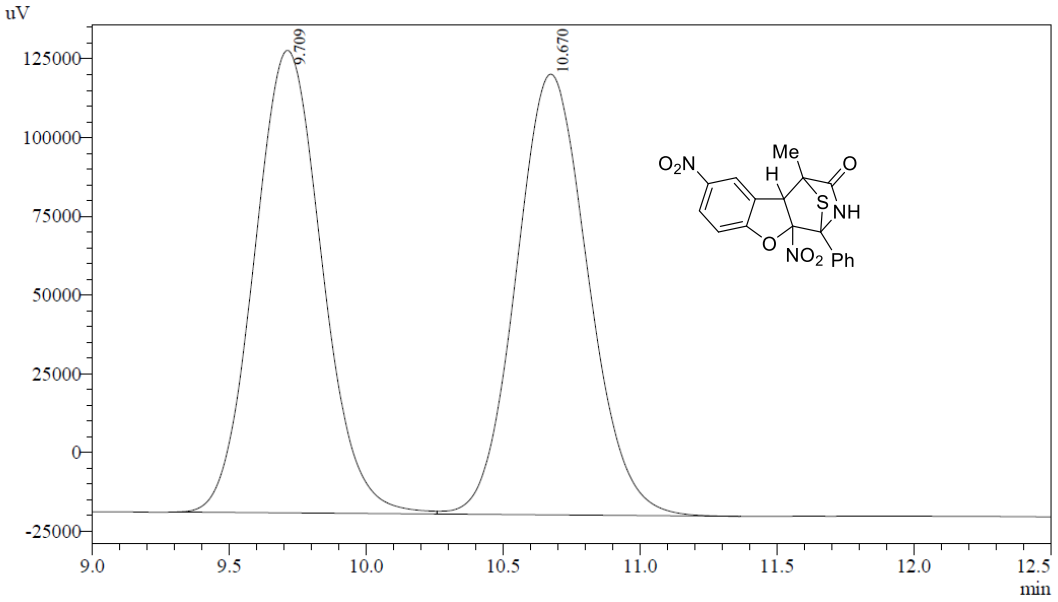
Peak#	Ret. Time	Area	Height	Area %
1	15.671	2047054	59786	4.104
2	28.166	47837845	767764	95.896
Total		49884899		100.000

^{1}H, ^{13}C NMR of compound **3ha**





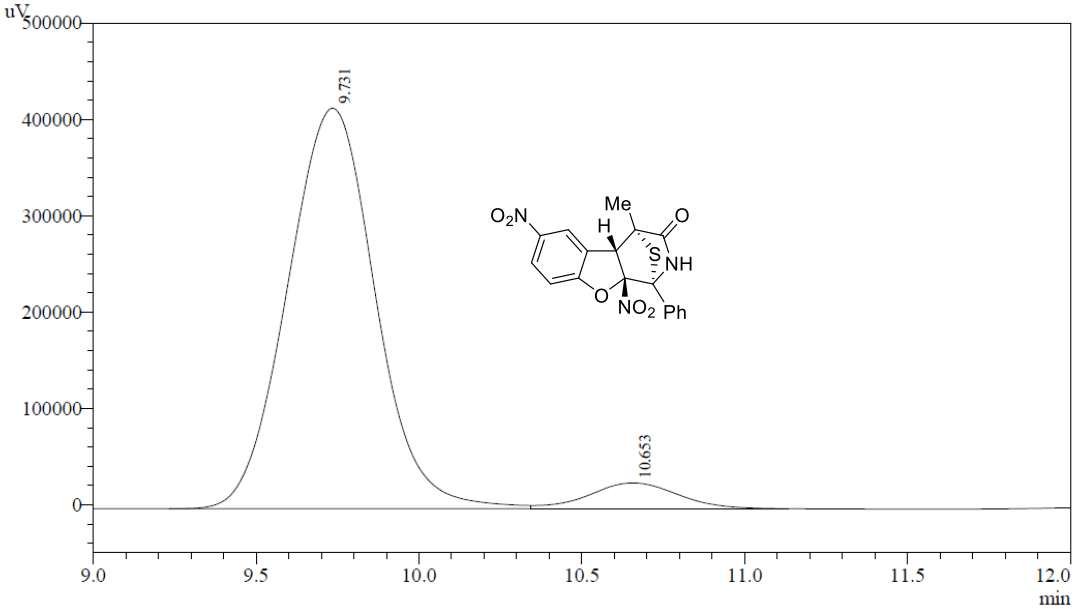
HPLC of compound **3ha**



1 Det.A Ch1 / 220nm

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.709	2527321	146831	49.720	51.190
2	10.670	2555777	140006	50.280	48.810
Total		5083098	286838	100.000	100.000

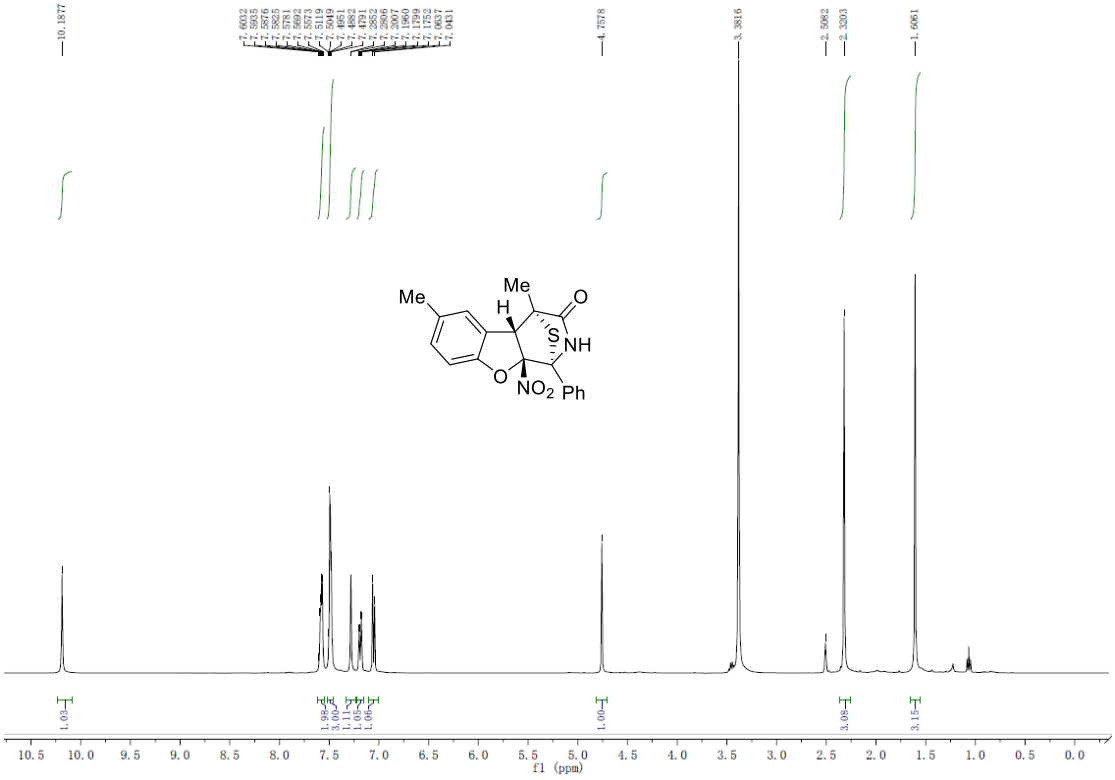


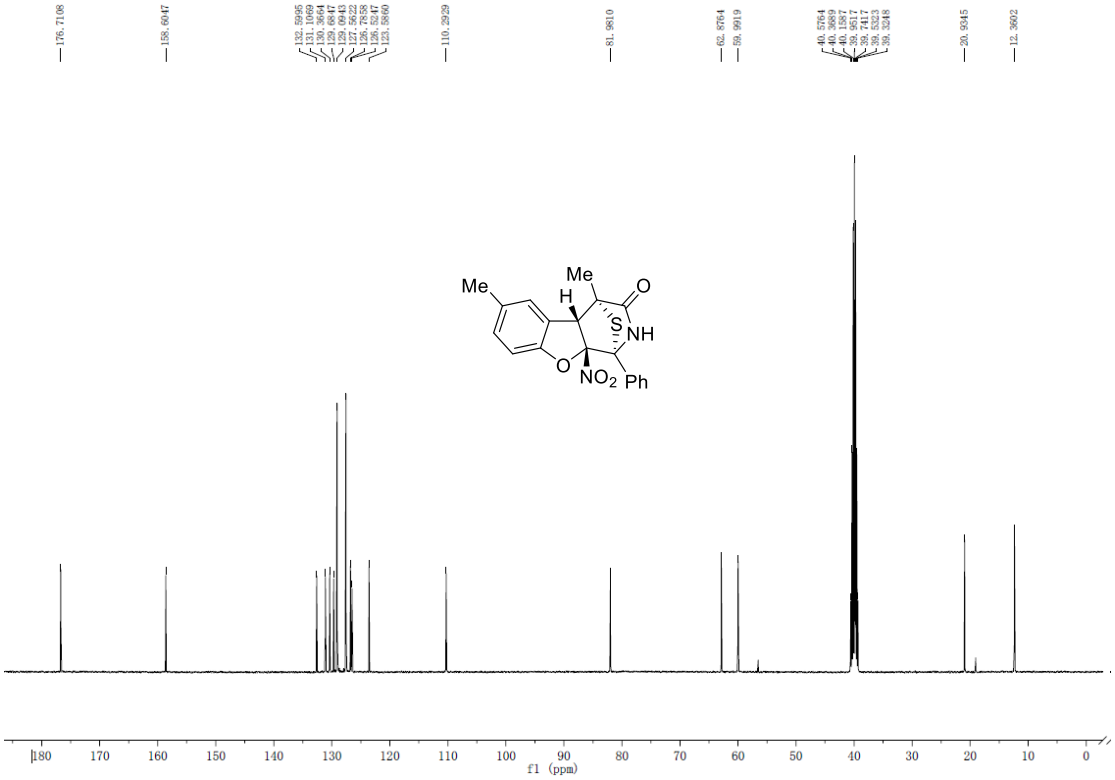
1 Det.A Ch1 / 220nm

Detector A Ch1 220nm

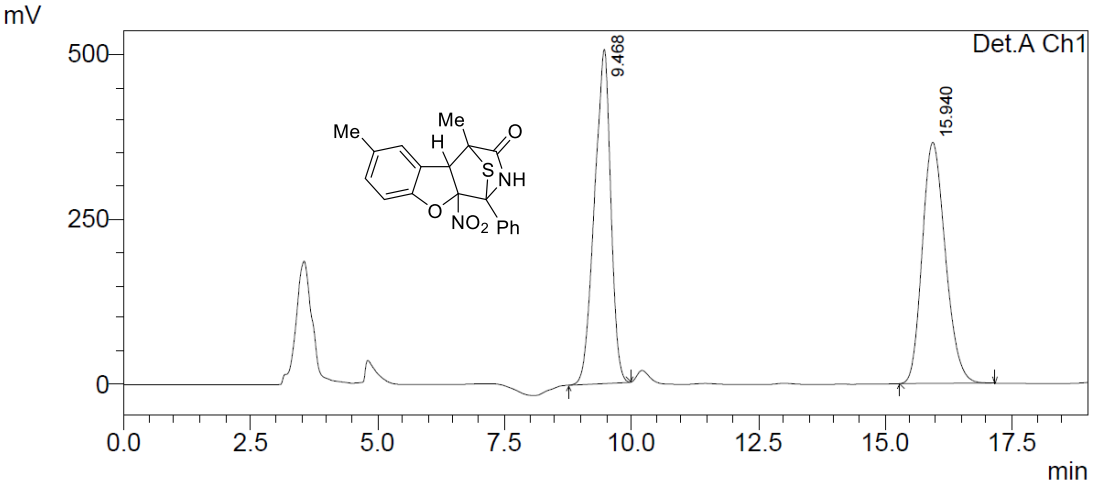
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.731	7783316	415656	93.860	93.926
2	10.653	509143	26879	6.140	6.074
Total		8292459	442535	100.000	100.000

^{1}H, ^{13}C NMR of compound **3ia**





HPLC of compound **3ia**

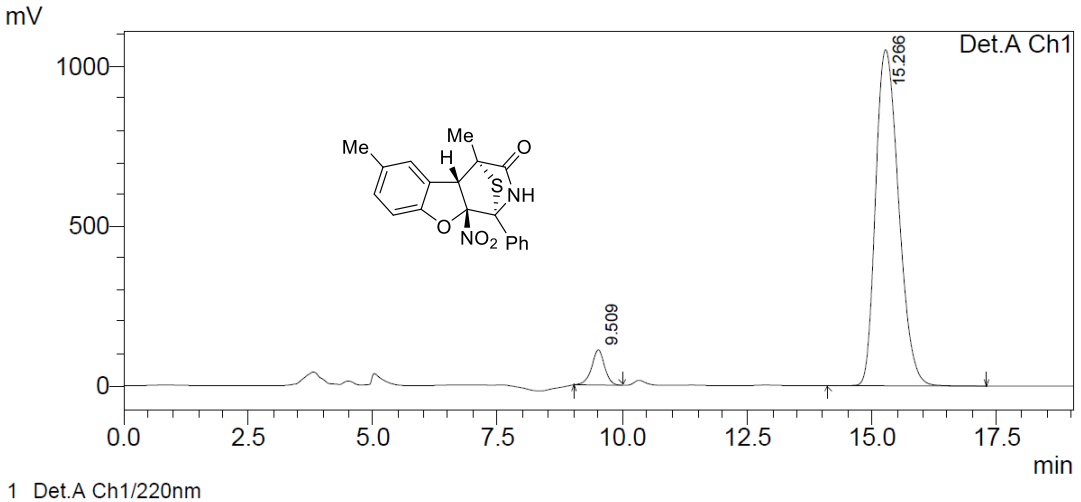


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.468	11313175	505500	49.427
2	15.940	11575644	364415	50.573
Total		22888819		100.000



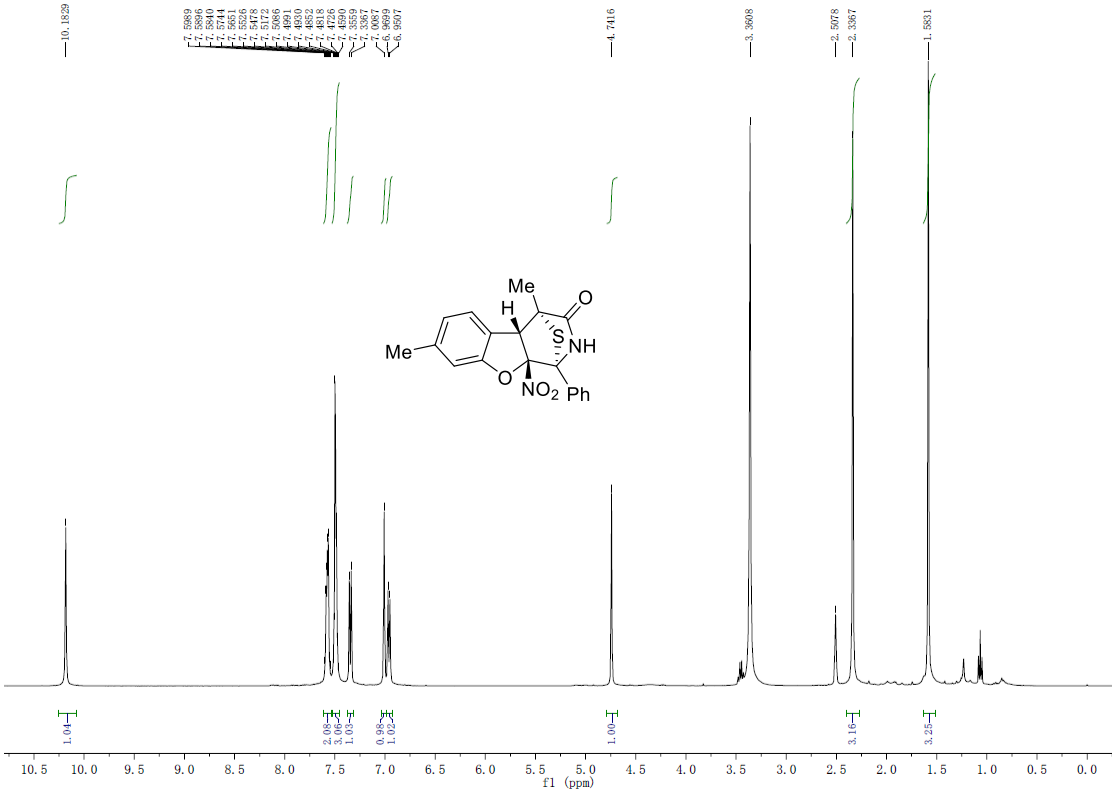
1 Det.A Ch1/220nm

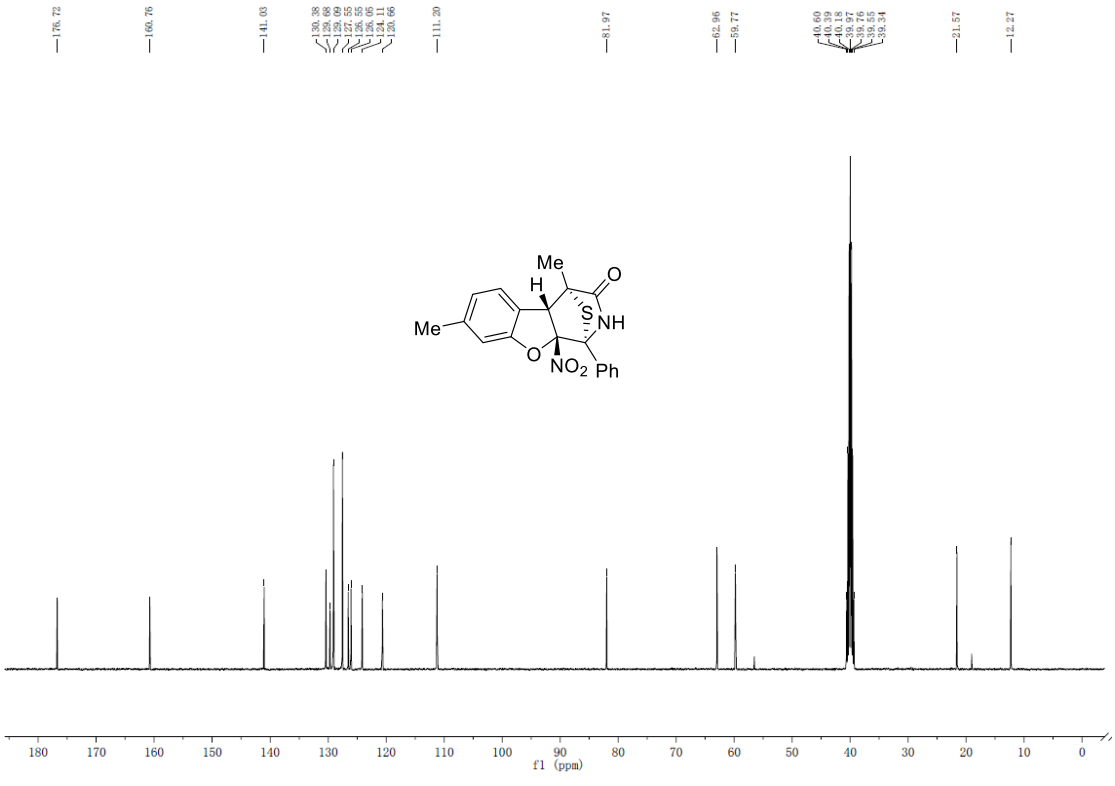
PeakTable

Detector A Ch1 220nm

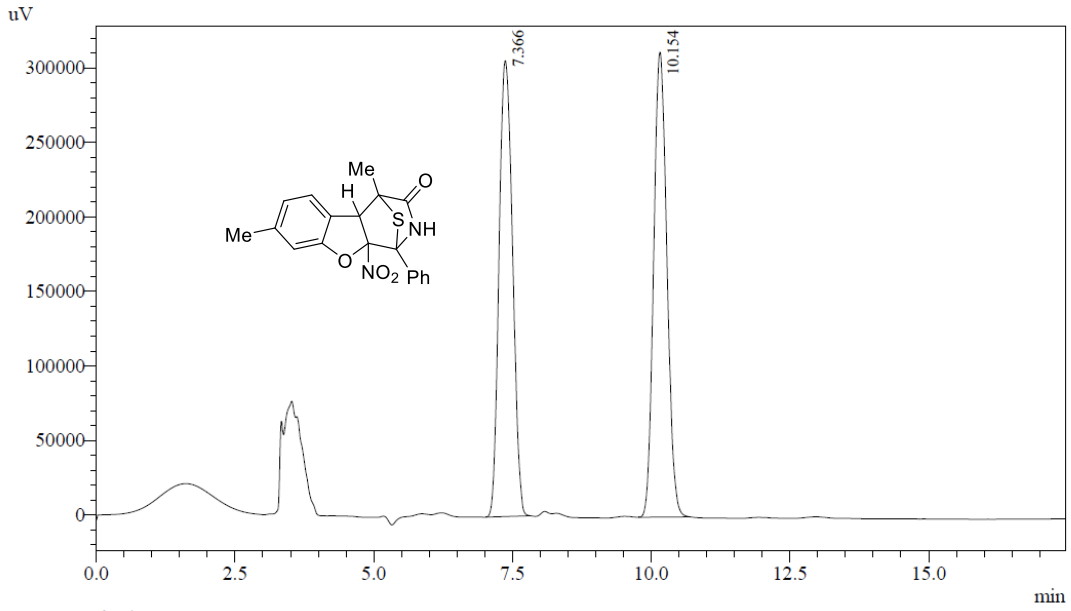
Peak#	Ret. Time	Area	Height	Area %
1	9.509	1992468	110351	5.569
2	15.266	33786476	1053149	94.431
Total		35778944		100.000

^{1}H, ^{13}C NMR of compound **3ja**





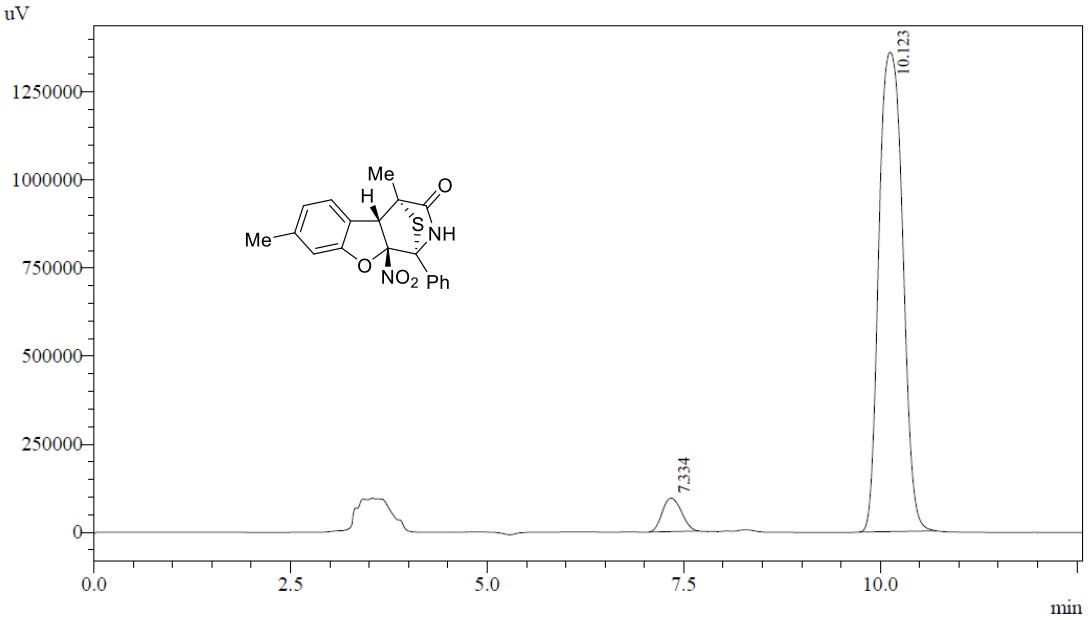
HPLC of compound **3ja**



1 Det.A Ch1 / 220nm

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.366	5180674	305862	49.979	49.499
2	10.154	5185075	312053	50.021	50.501
Total		10365749	617915	100.000	100.000

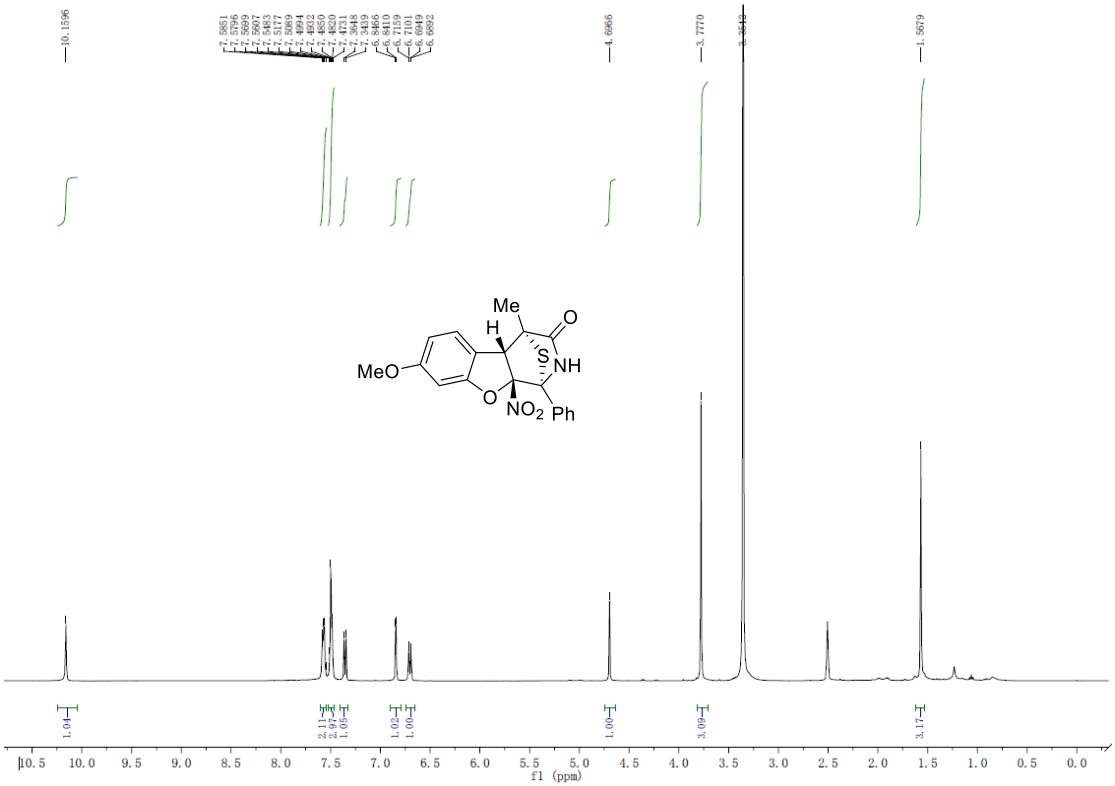


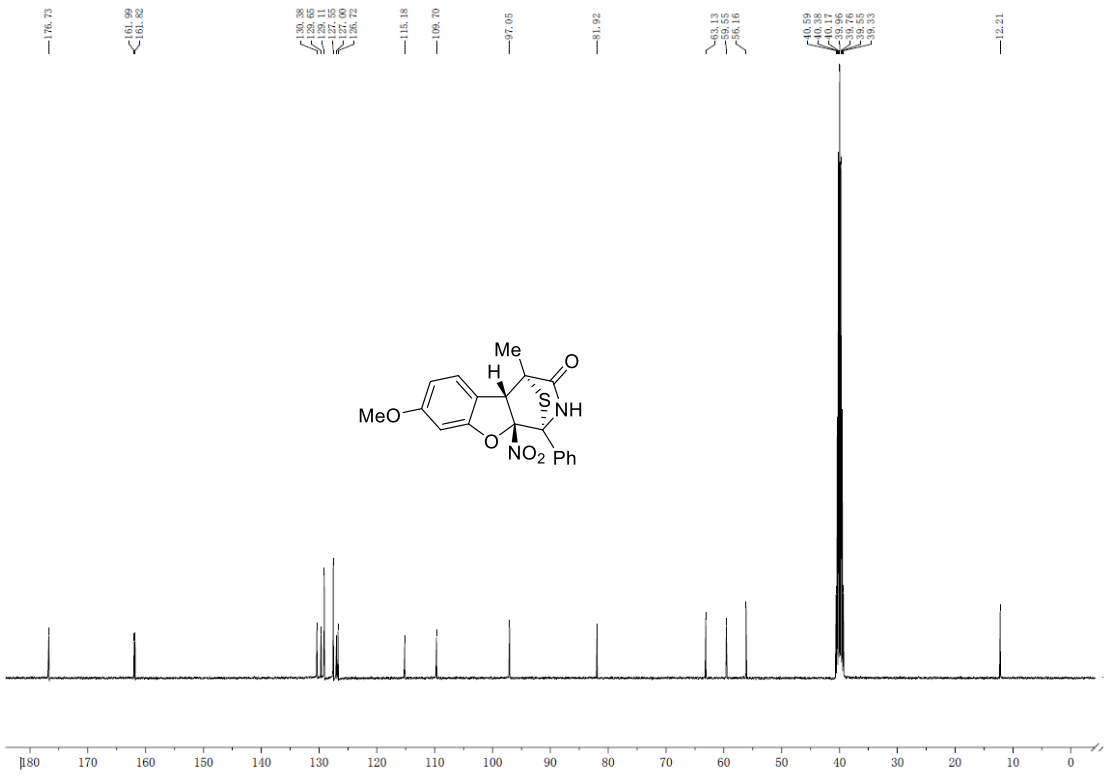
1 Det.A Ch1 / 220nm

Detector A Ch1 220nm

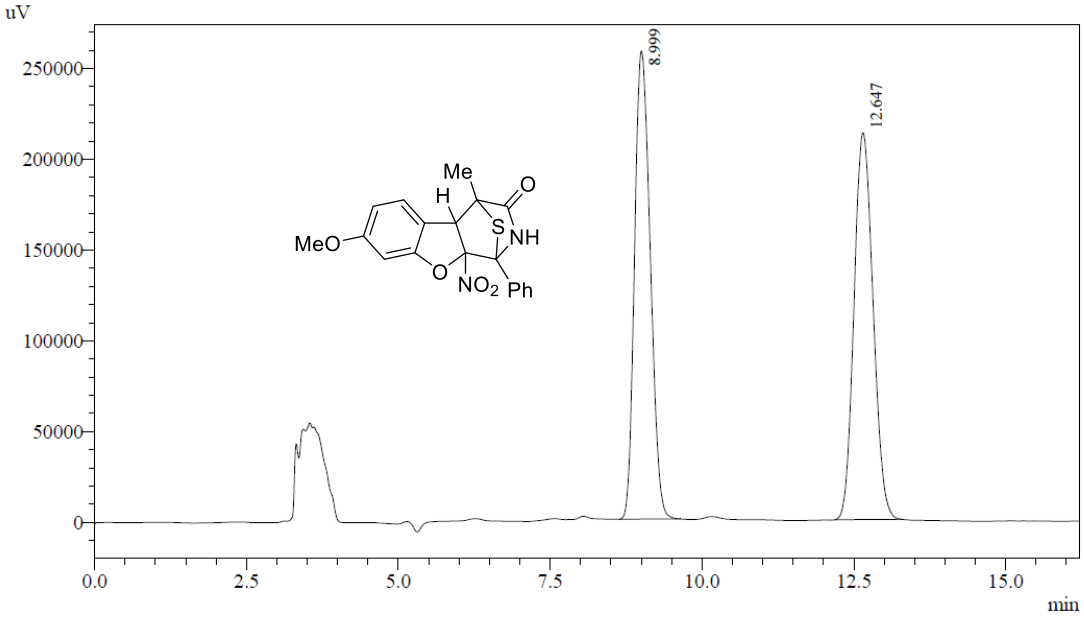
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.334	1610690	94998	5.320	6.524
2	10.123	28667322	1361040	94.680	93.476
Total		30278012	1456038	100.000	100.000

^{1}H, ^{13}C NMR of compound **3ka**





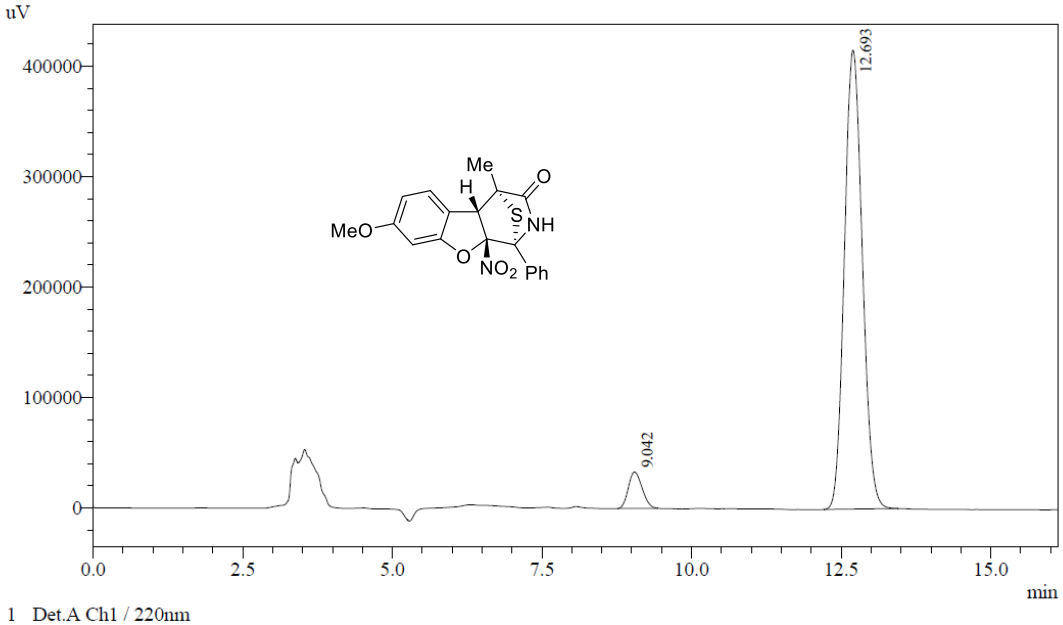
HPLC of compound **3ka**



1 Det.A Ch1 / 220nm

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.999	4643193	257880	49.944	54.754
2	12.647	4653547	213104	50.056	45.246
Total		9296741	470984	100.000	100.000

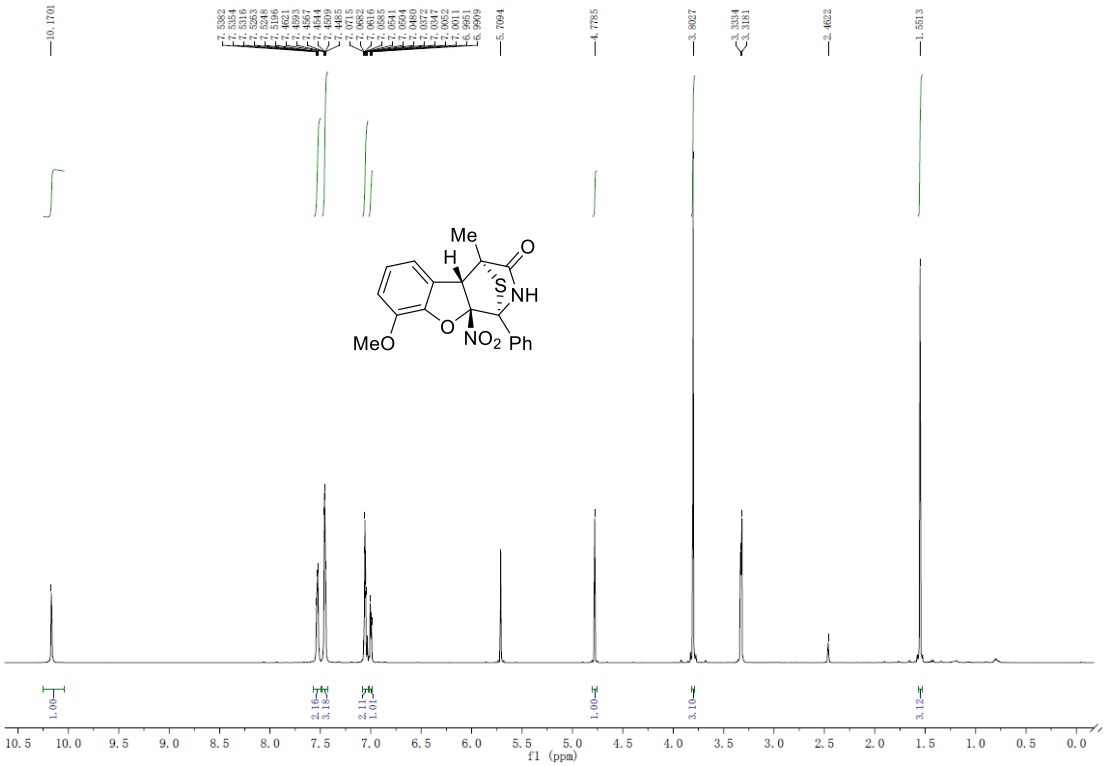


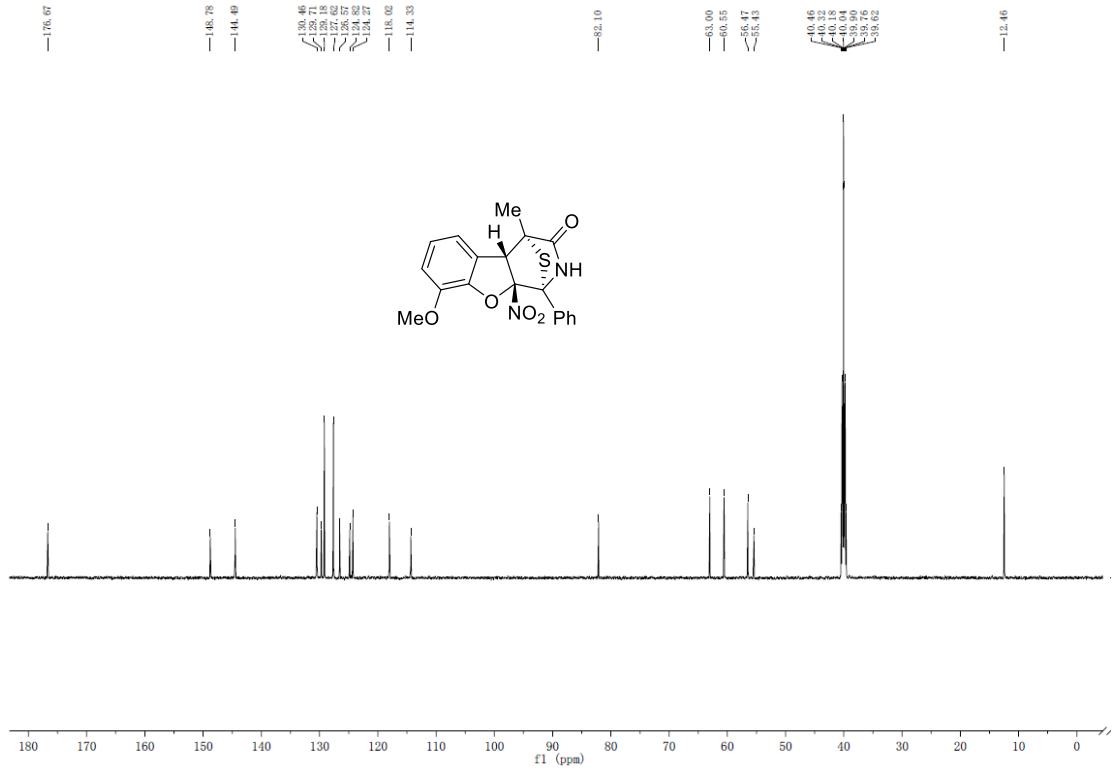
1 Det.A Ch1 / 220nm

Detector A Ch1 220nm

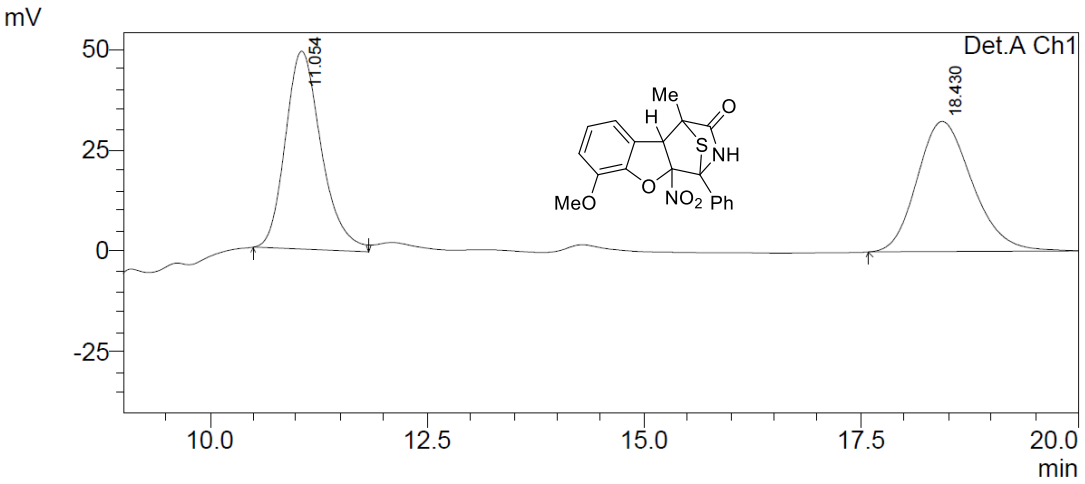
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.042	529166	33042	5.757	7.362
2	12.693	8663183	415762	94.243	92.638
Total		9192349	448804	100.000	100.000

^{1}H, ^{13}C NMR of compound **3la**





HPLC of compound **3la**

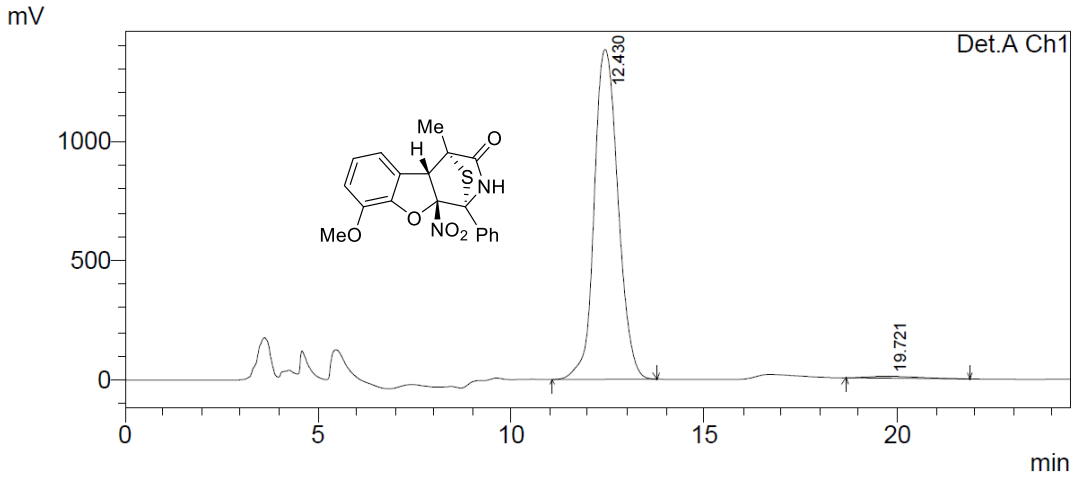


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	11.054	1416281	48993	49.870
2	18.430	1423678	32189	50.130
Total		2839959		100.000



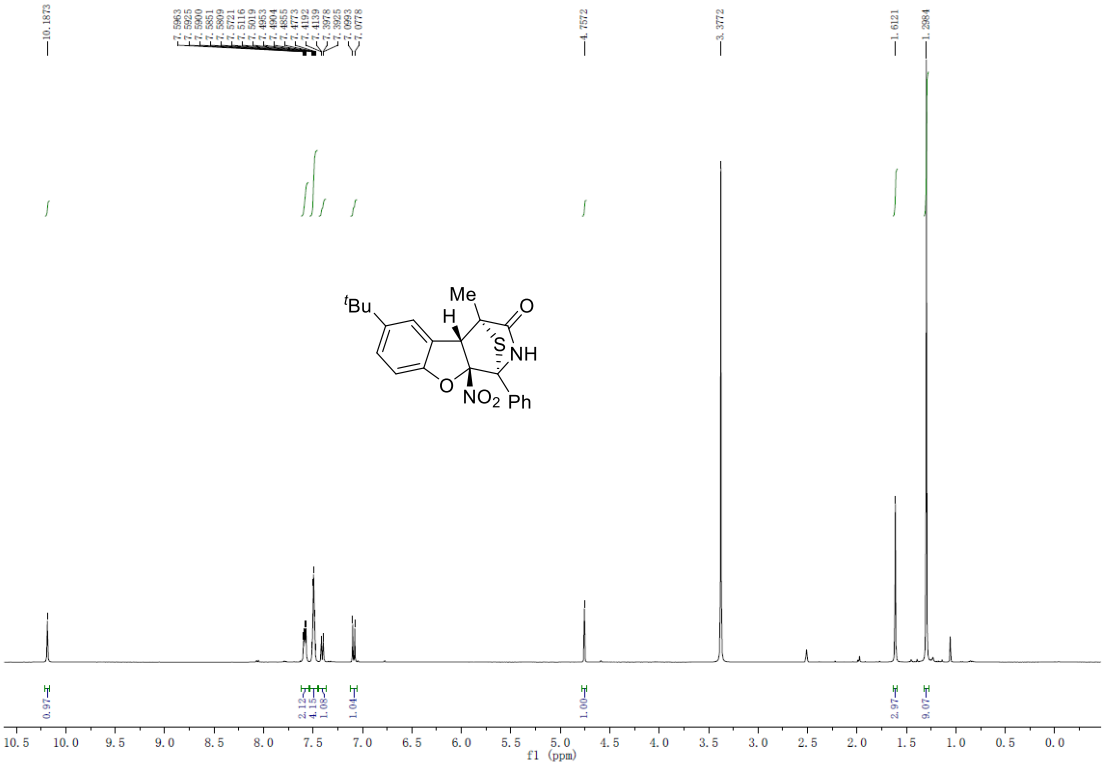
1 Det.A Ch1/220nm

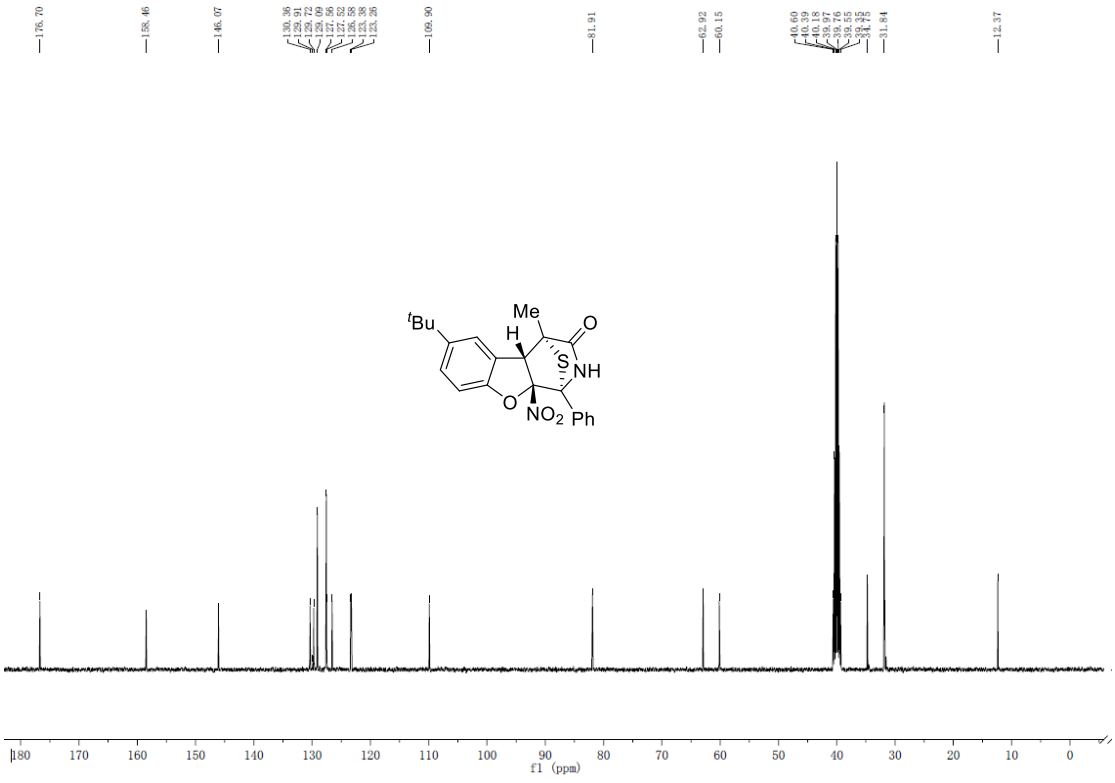
PeakTable

Detector A Ch1 220nm

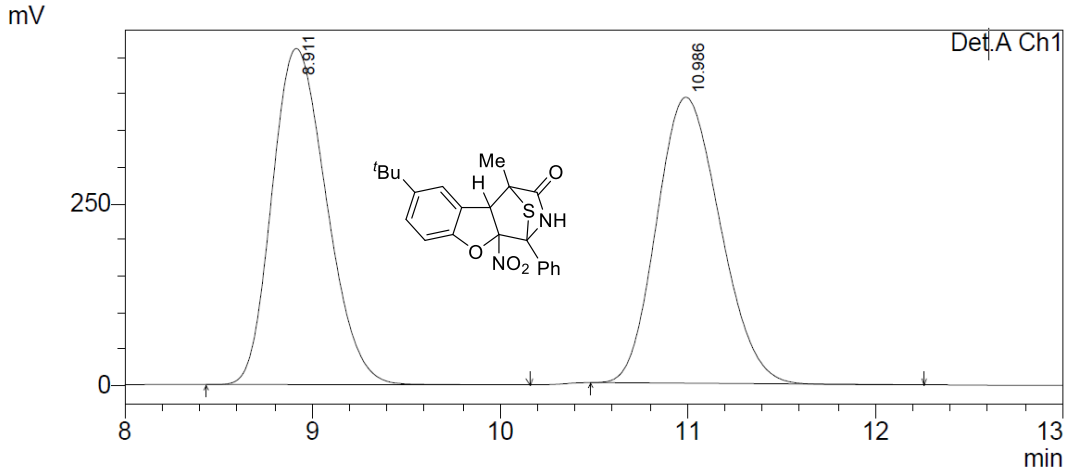
Peak#	Ret. Time	Area	Height	Area %
1	12.430	59223134	1378349	98.734
2	19.721	759396	8403	1.266
Total		59982530		100.000

^{1}H, ^{13}C NMR of compound **3ma**





HPLC of compound **3ma**

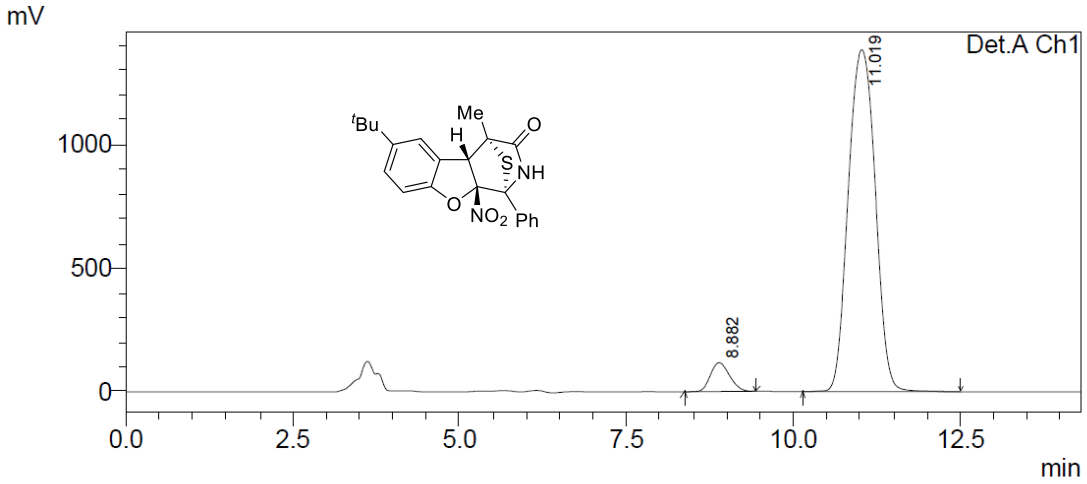


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.911	9322069	462098	50.216
2	10.986	9241897	393033	49.784
Total		18563966		100.000



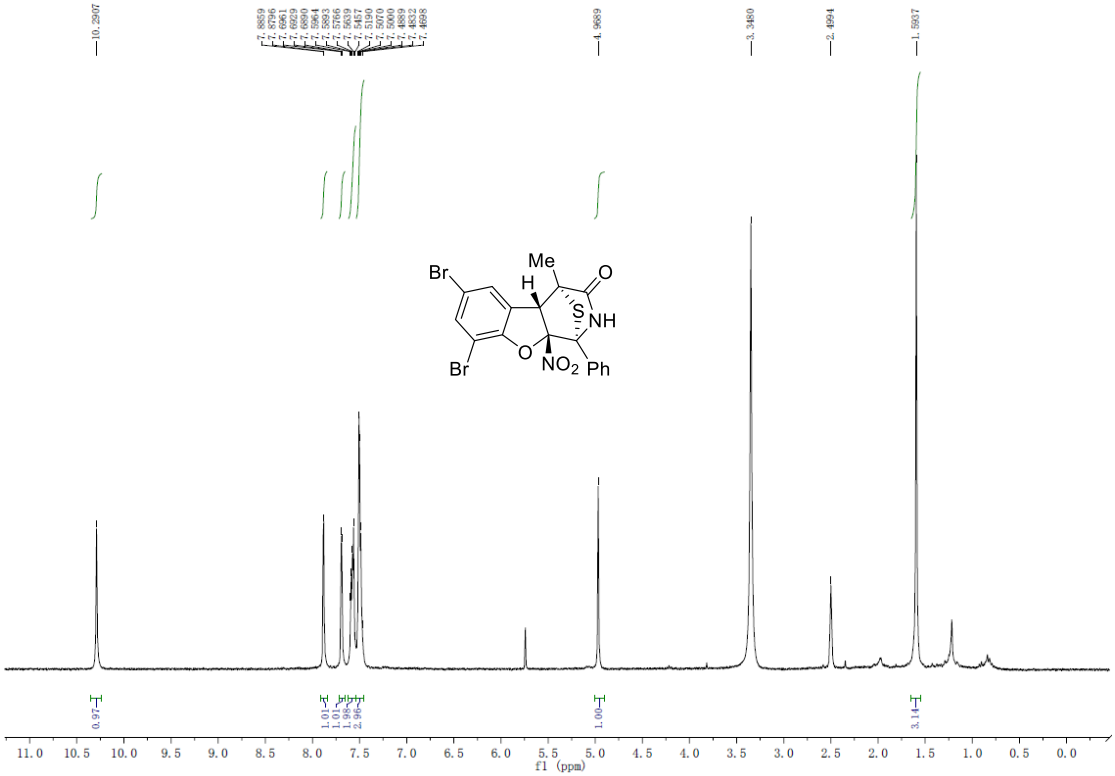
1 Det.A Ch1/220nm

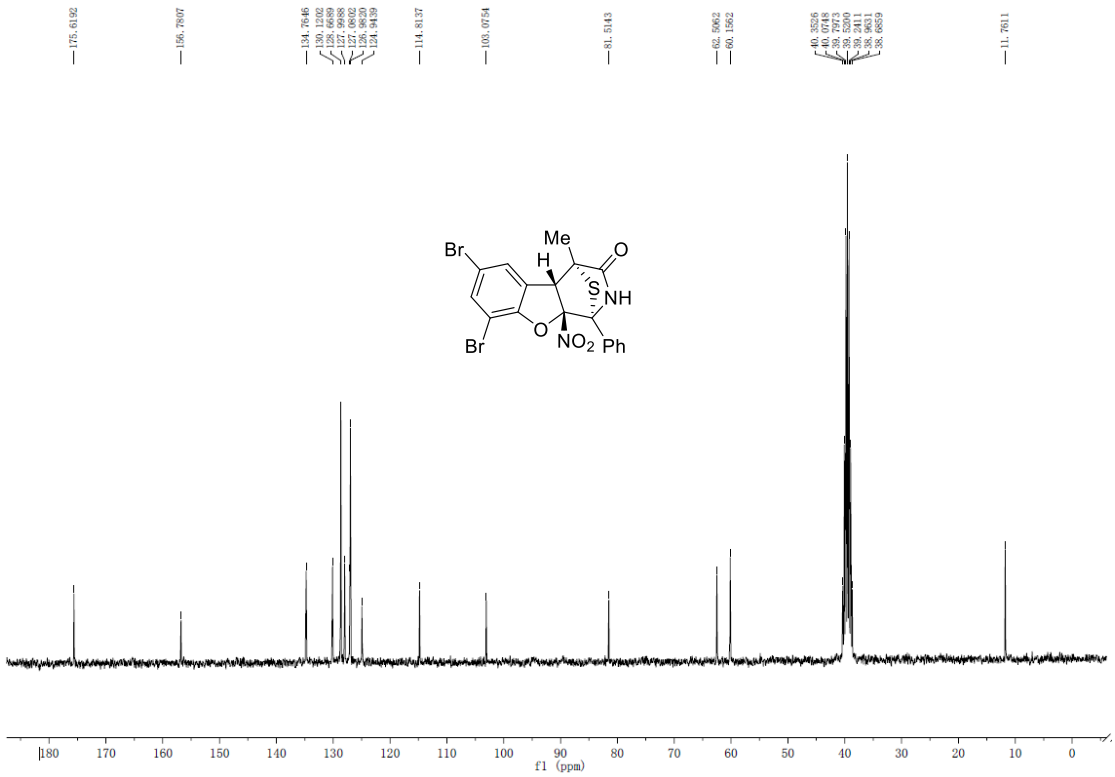
PeakTable

Detector A Ch1 220nm

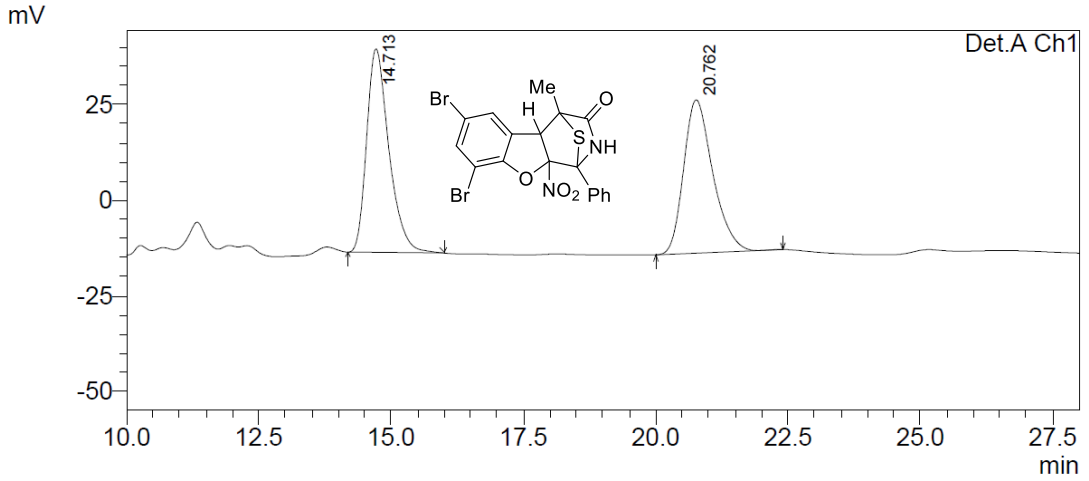
Peak#	Ret. Time	Area	Height	Area %
1	8.882	2326947	116822	5.640
2	11.019	38932882	1383017	94.360
Total		41259828		100.000

^{1}H, ^{13}C NMR of compound **3na**





HPLC of compound **3na**

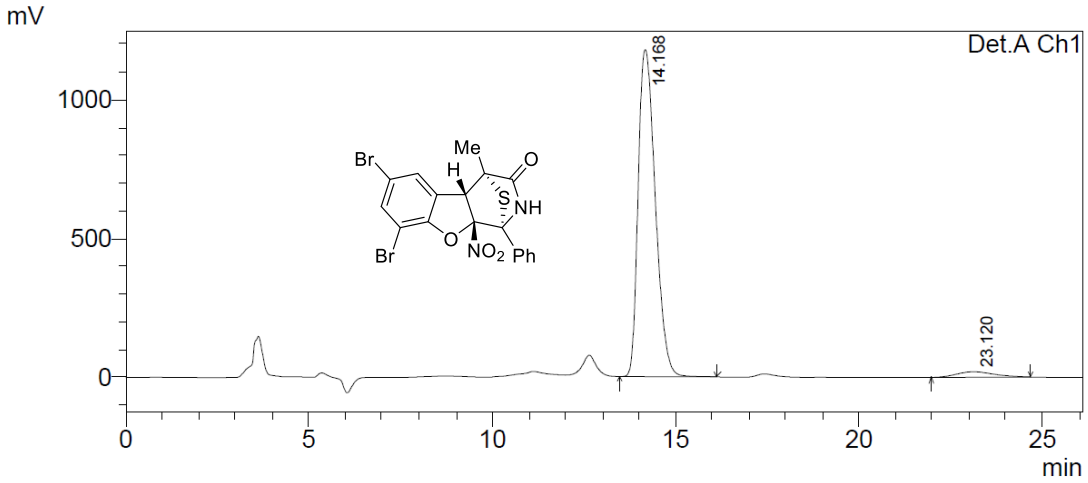


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	14.713	1561177	53247	50.396
2	20.762	1536619	40105	49.604
Total		3097796		100.000



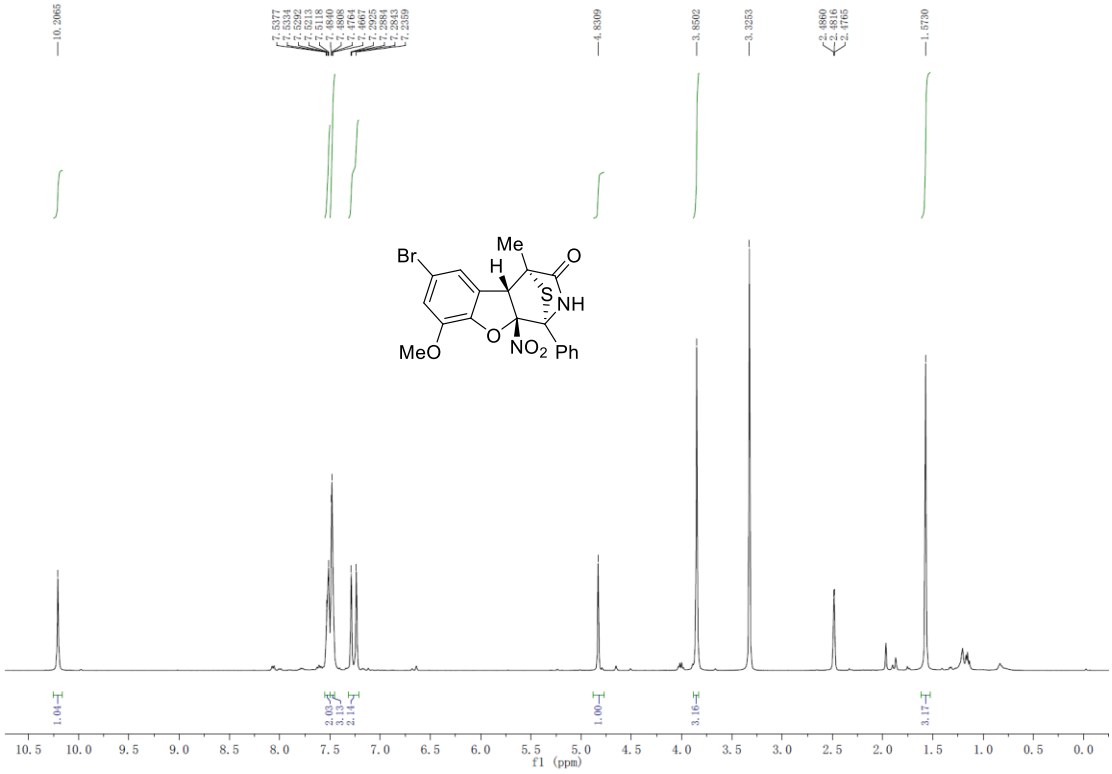
1 Det.A Ch1/220nm

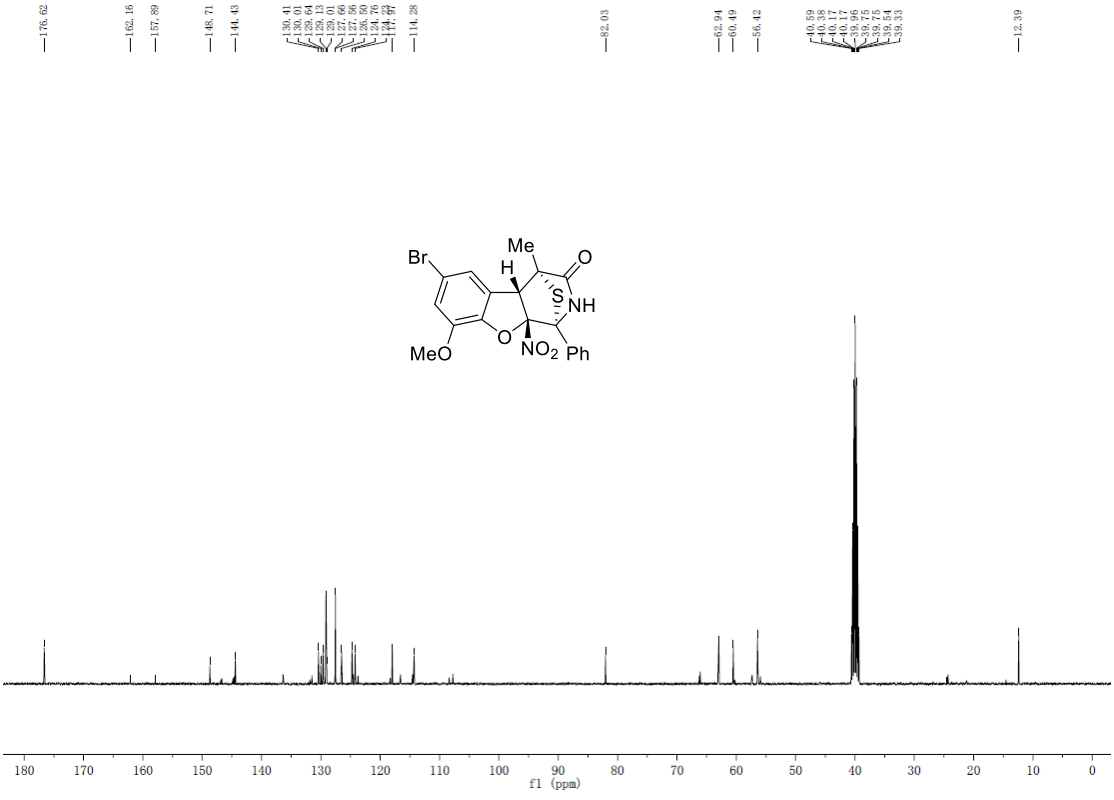
PeakTable

Detector A Ch1 220nm

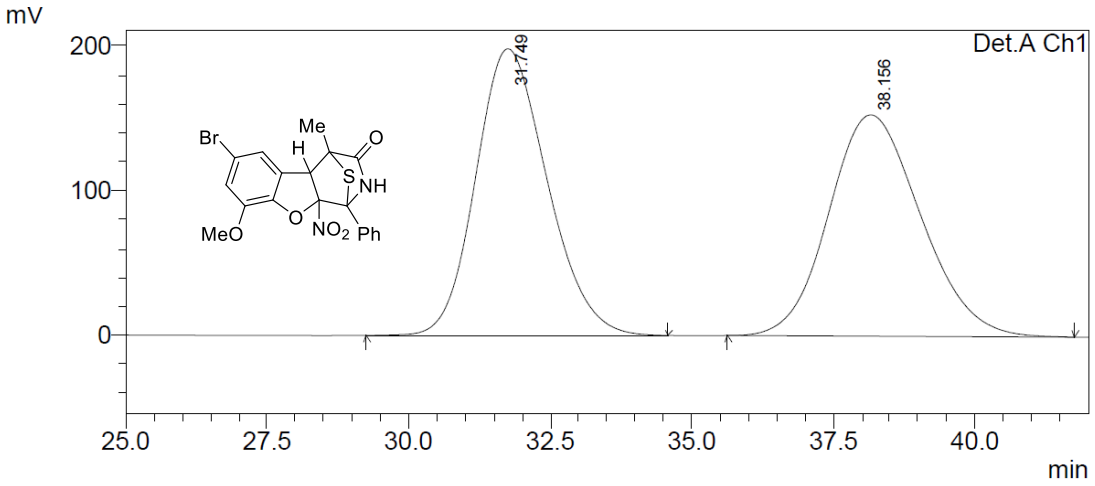
Peak#	Ret. Time	Area	Height	Area %
1	14.168	38255273	1175999	96.495
2	23.120	1389593	19583	3.505
Total		39644866		100.000

^{1}H, ^{13}C NMR of compound **3oa**





HPLC of compound **3oa**

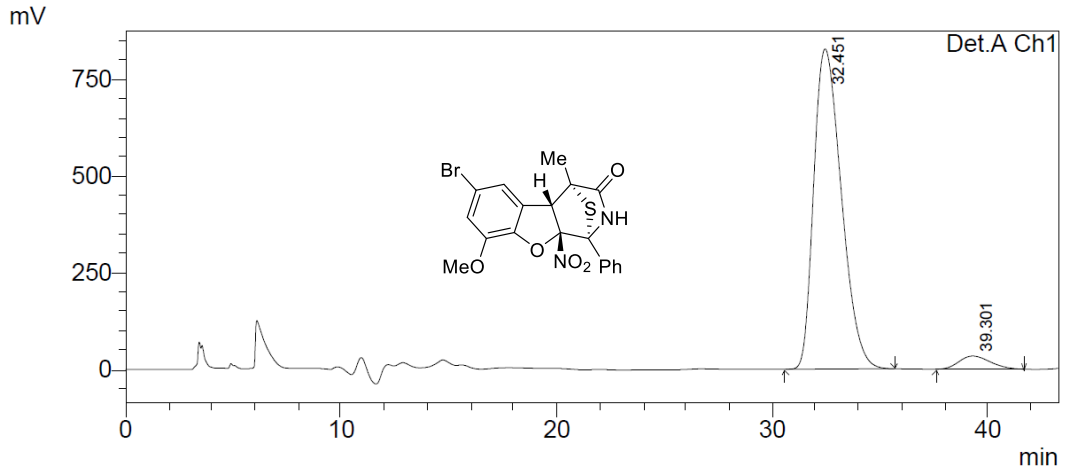


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	31.749	17403710	198119	50.149
2	38.156	17299961	152986	49.851
Total		34703671		100.000



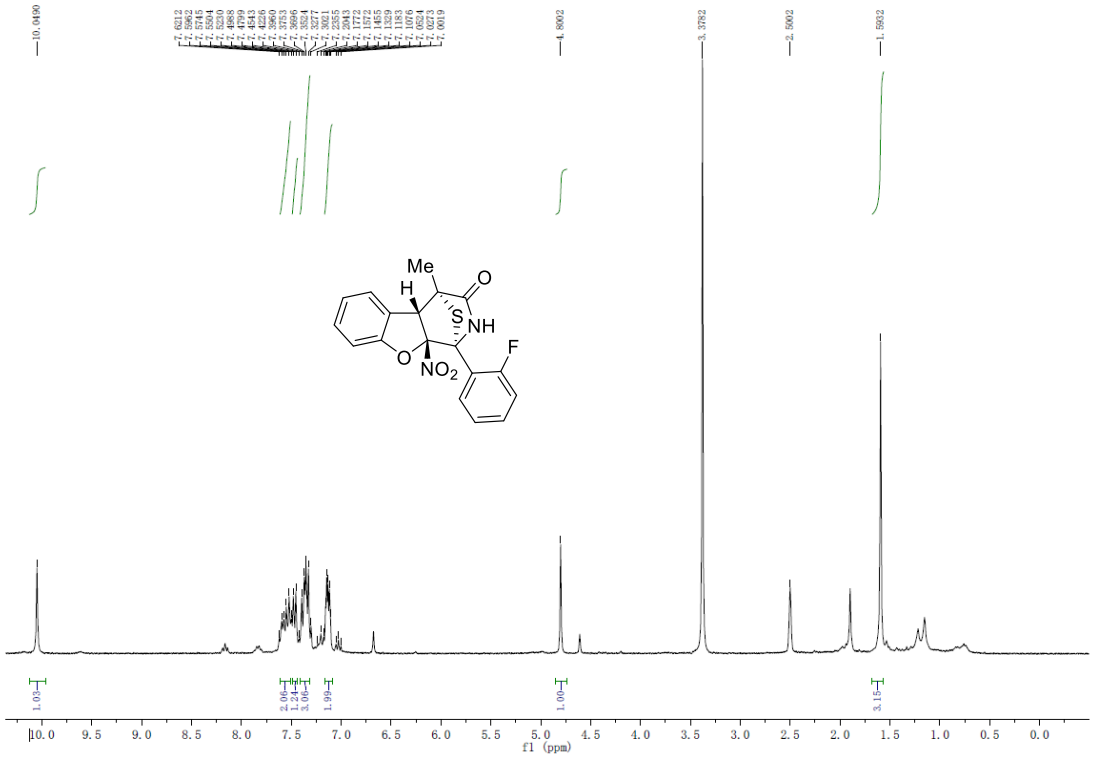
1 Det.A Ch1/220nm

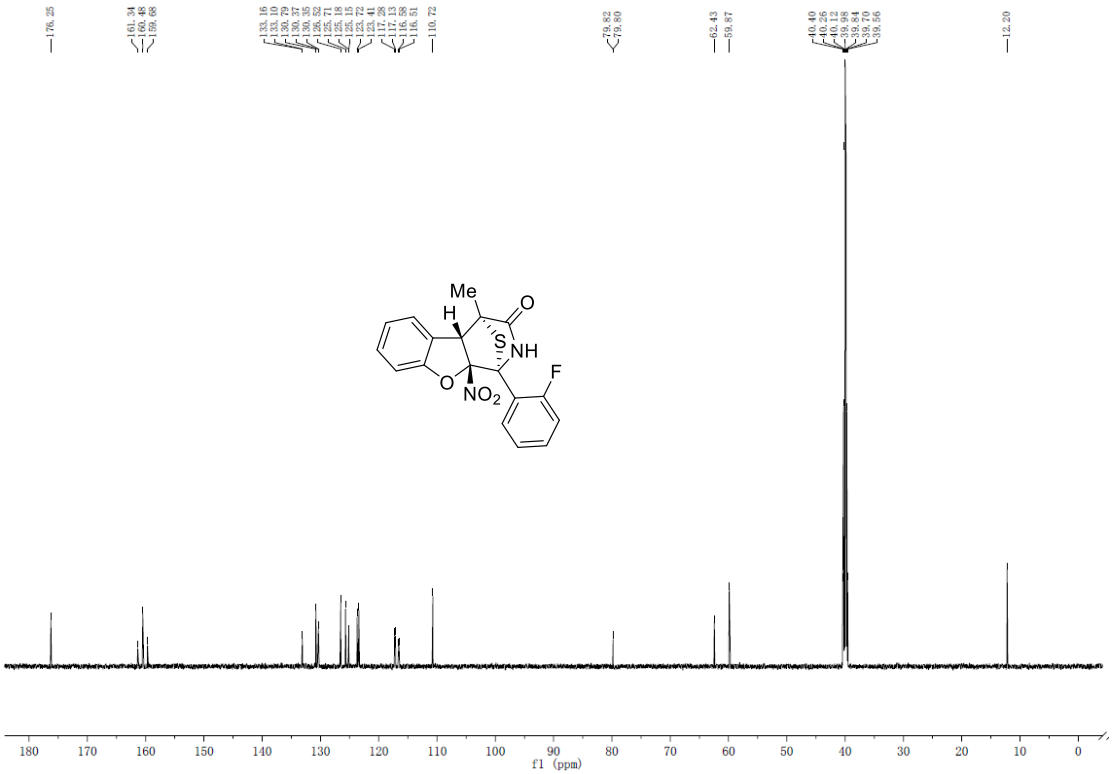
PeakTable

Detector A Ch1 220nm

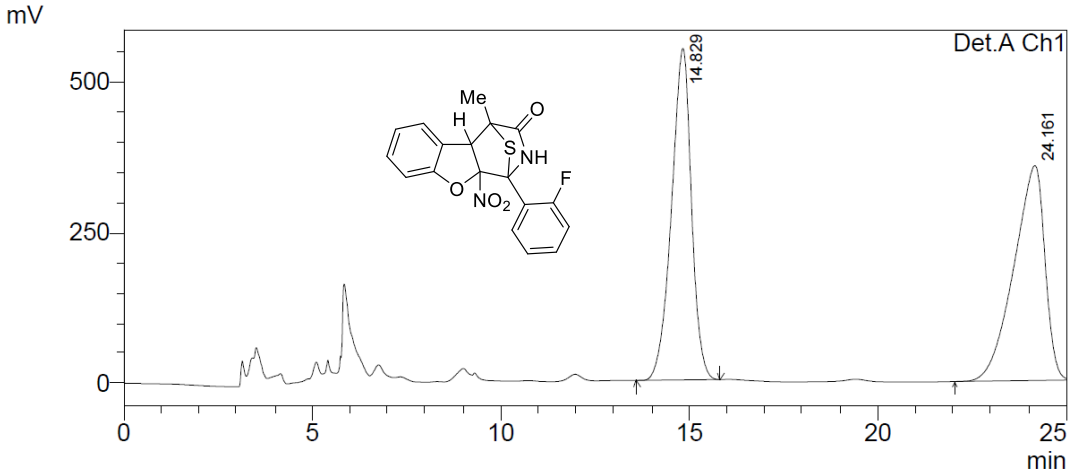
Peak#	Ret. Time	Area	Height	Area %
1	32.451	73691537	827009	95.525
2	39.301	3451910	34085	4.475
Total		77143447		100.000

^{1}H, ^{13}C NMR of compound **3ab**





HPLC of compound **3ab**

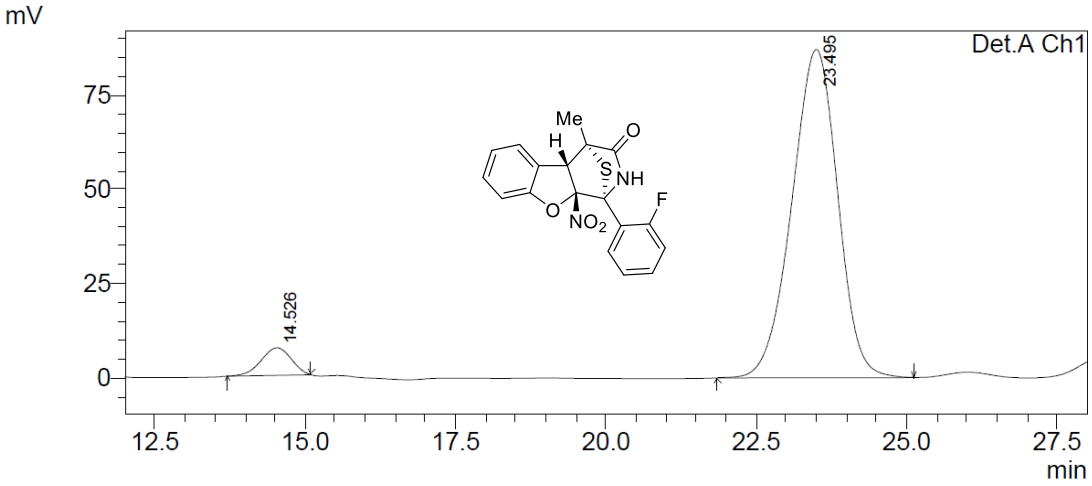


1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	14.829	20224244	549728	49.708
2	24.161	20461943	356693	50.292
Total		40686187		100.000



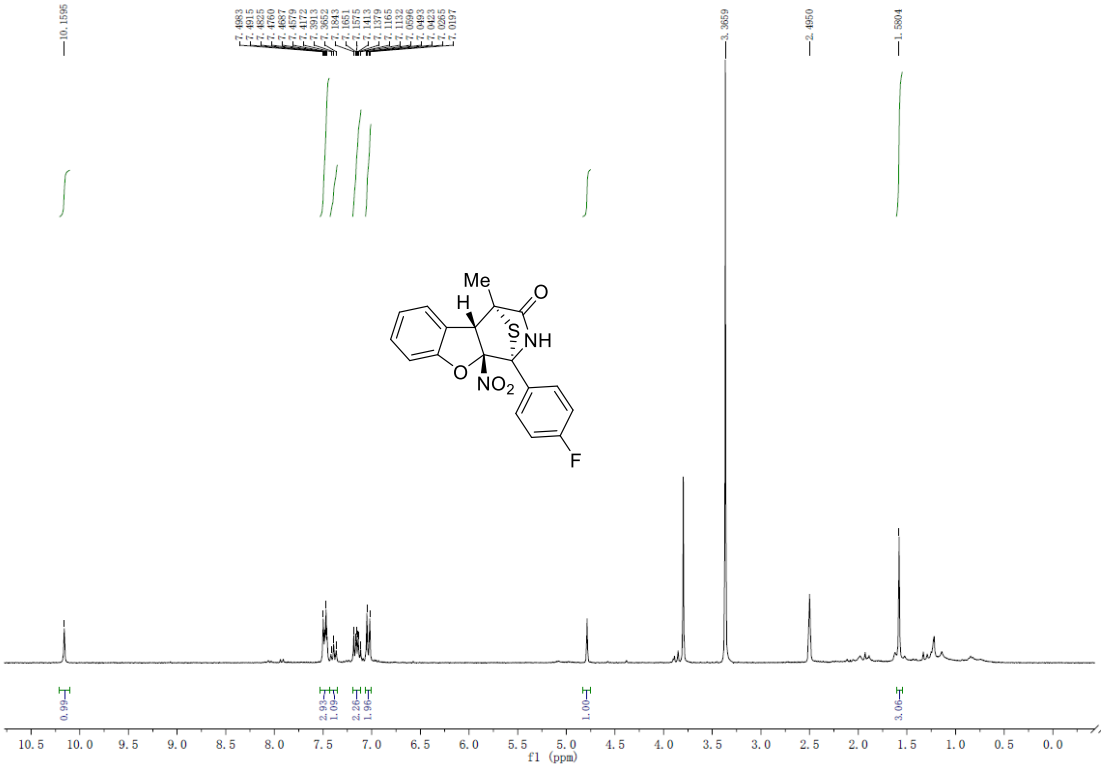
1 Det.A Ch1/254nm

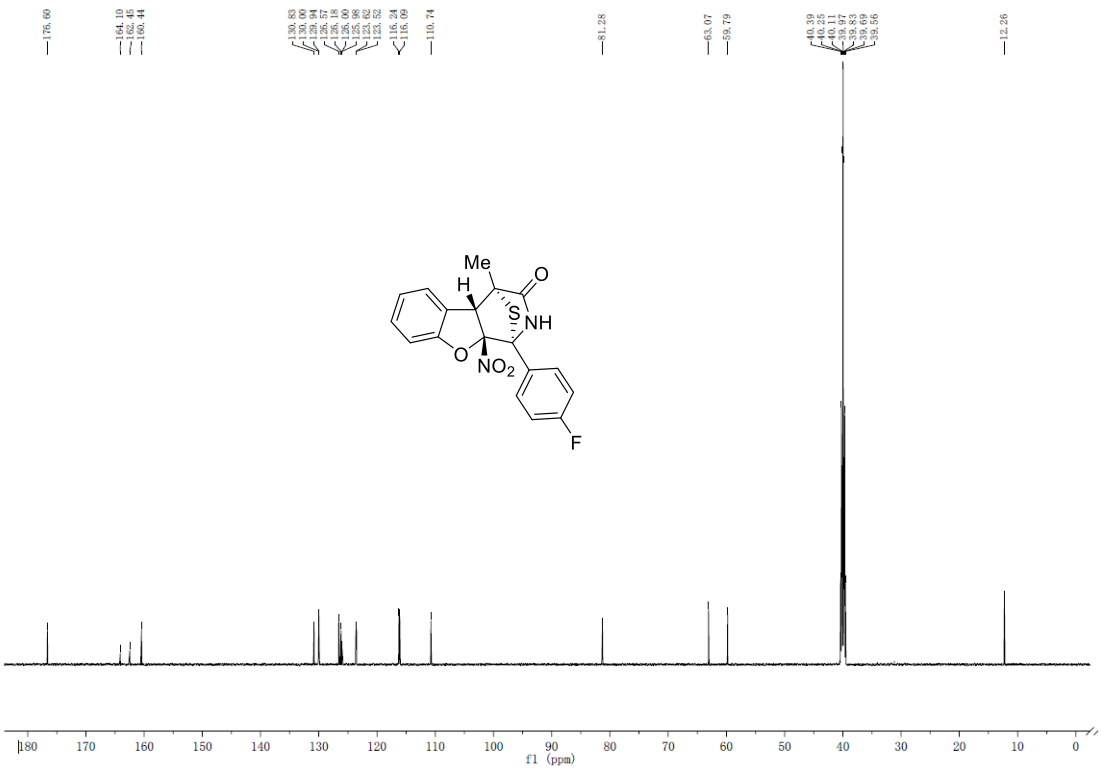
PeakTable

Detector A Ch1 254nm

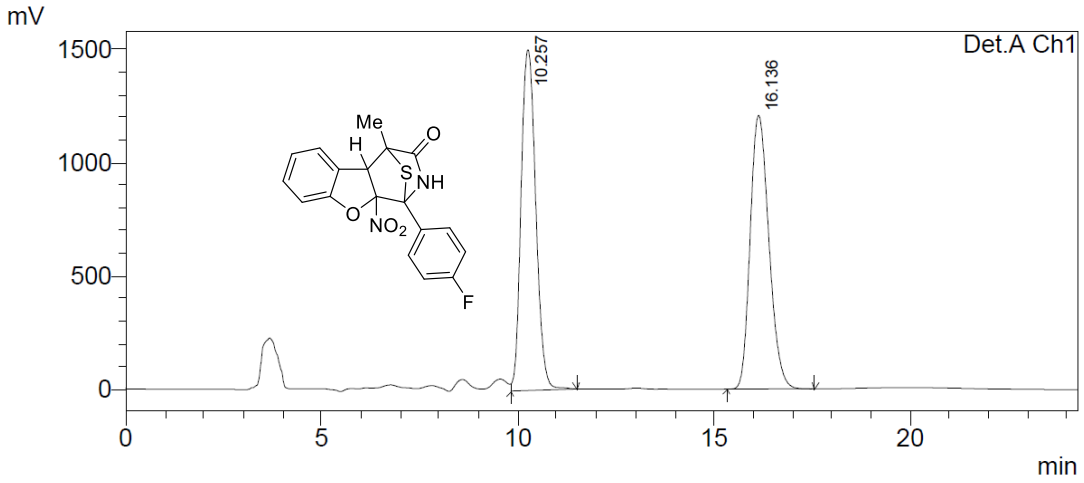
Peak#	Ret. Time	Area	Height	Area %
1	14.526	257370	7337	5.284
2	23.495	4613783	87056	94.716
Total		4871152		100.000

^{1}H, ^{13}C NMR of compound **3ac**





HPLC of compound **3ac**

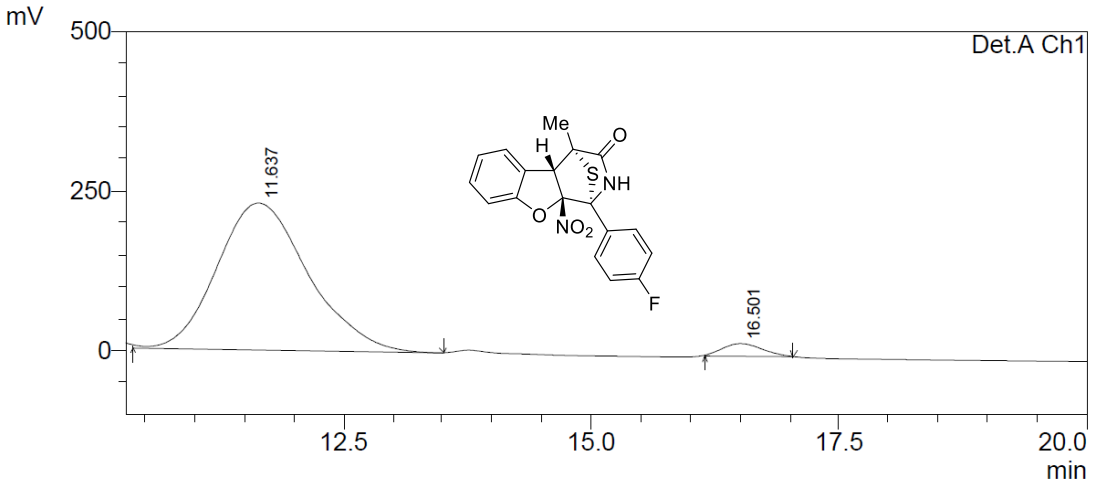


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.257	39219369	1504184	49.446
2	16.136	40098282	1208044	50.554
Total		79317652		100.000



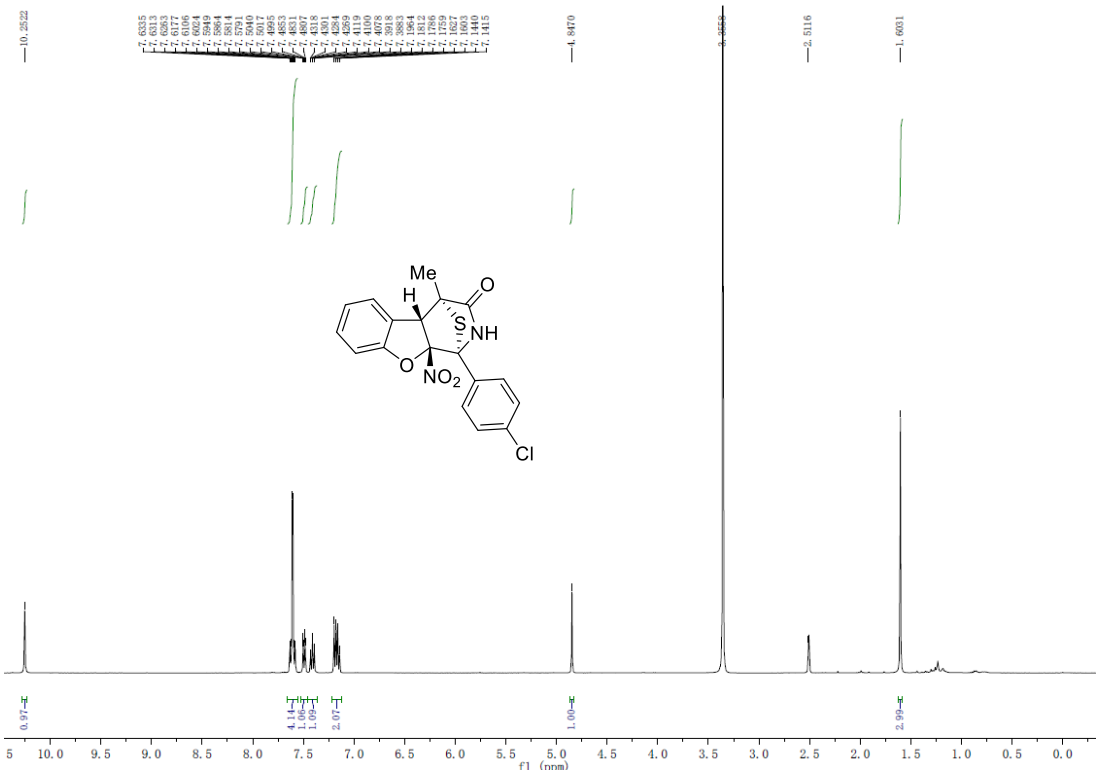
1 Det.A Ch1/220nm

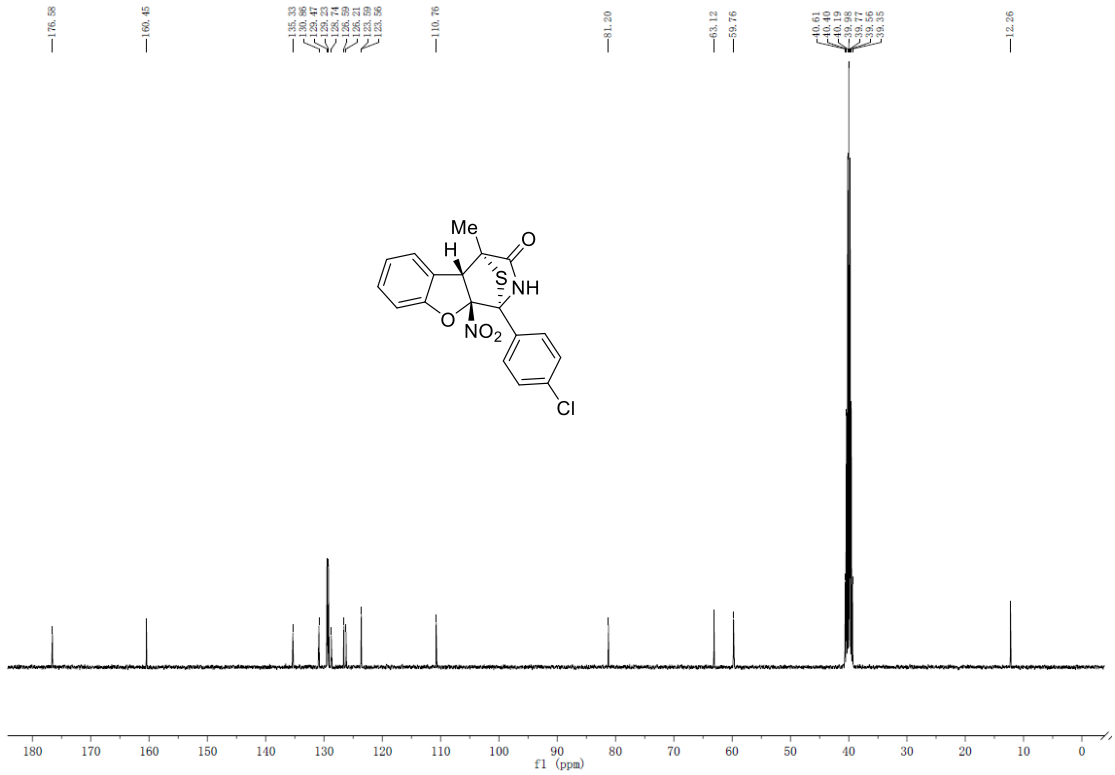
PeakTable

Detector A Ch1 220nm

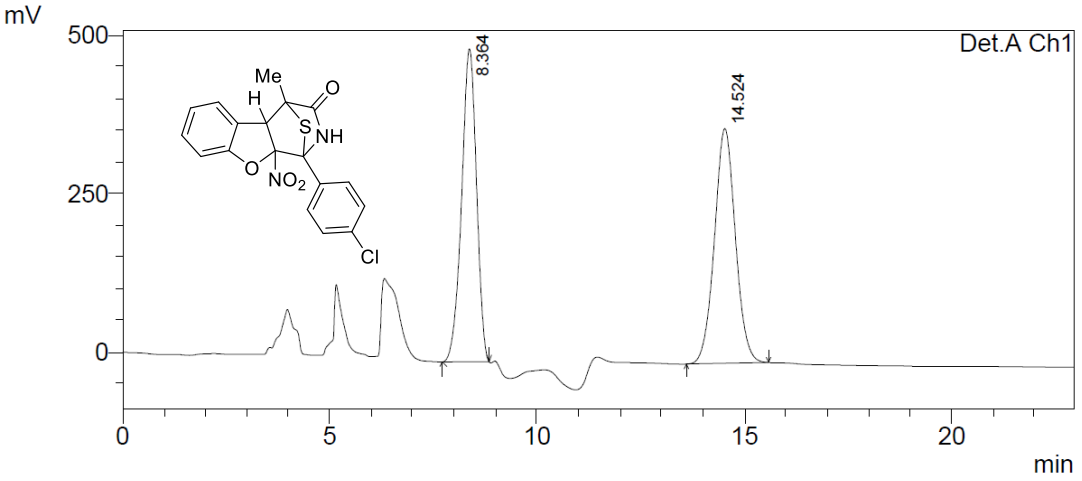
Peak#	Ret. Time	Area	Height	Area %
1	11.637	14736811	230007	96.405
2	16.501	549513	19658	3.595
Total		15286323		100.000

^{1}H, ^{13}C NMR of compound **3ad**





HPLC of compound **3ad**

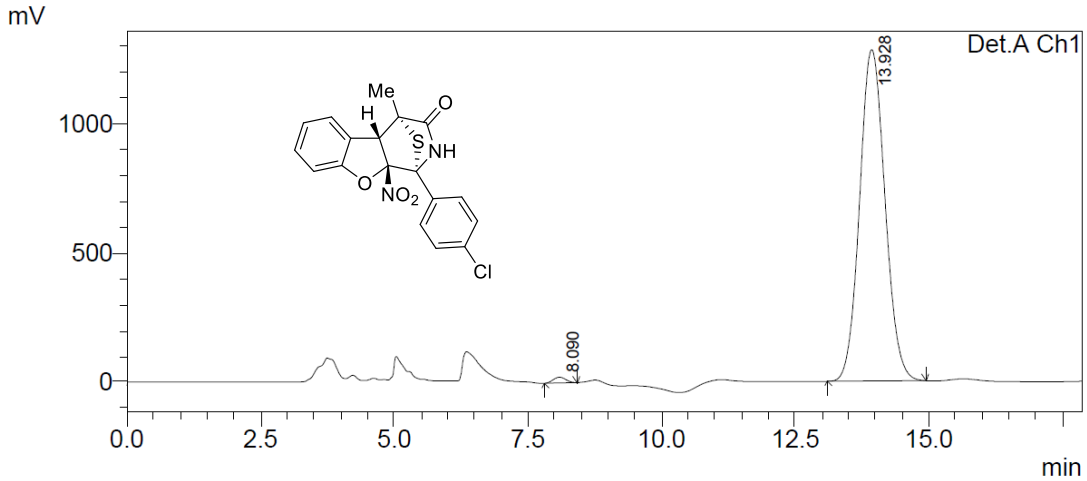


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.364	12324406	493928	48.628
2	14.524	13019776	370267	51.372
Total		25344182		100.000



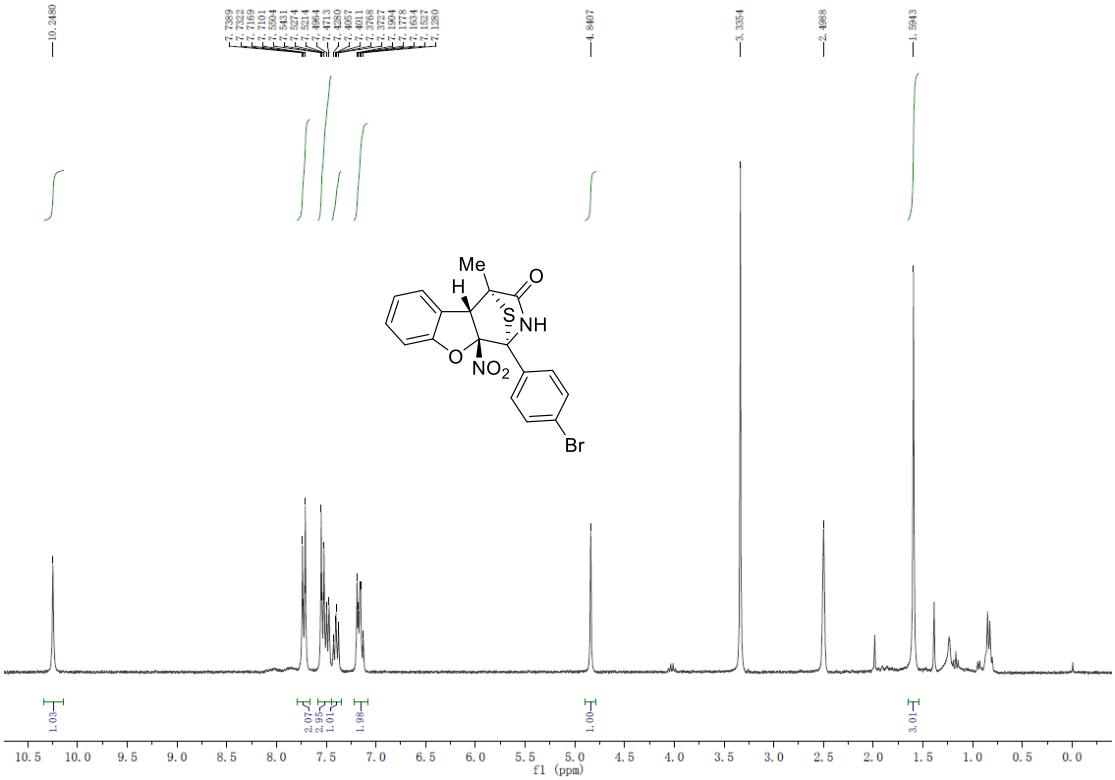
1 Det.A Ch1/220nm

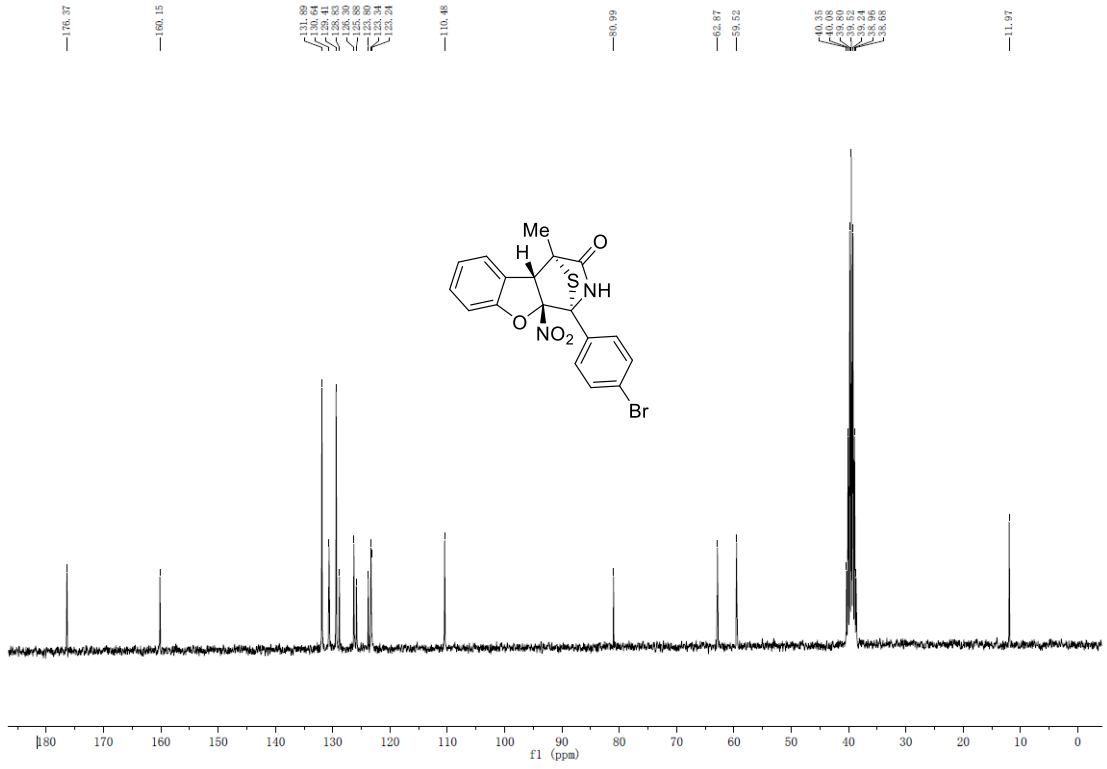
PeakTable

Detector A Ch1 220nm

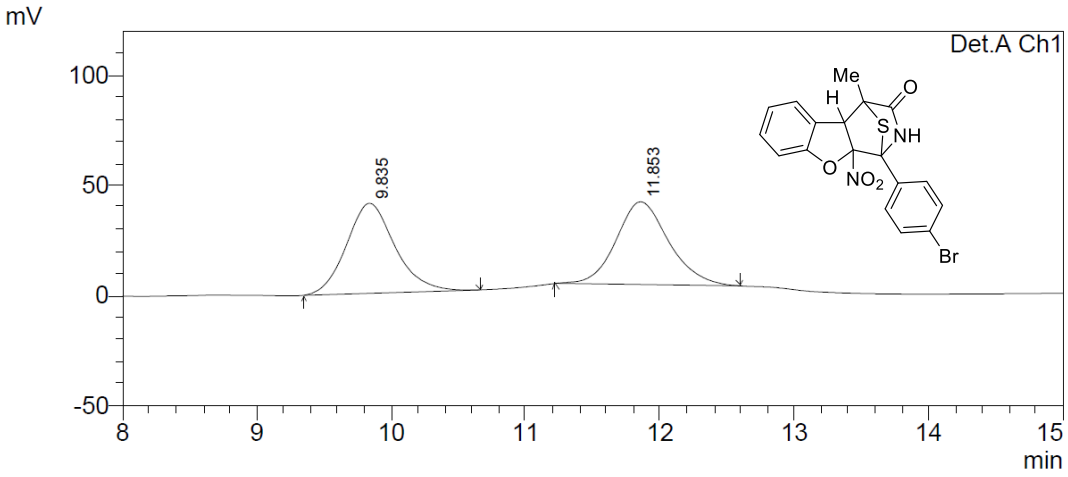
Peak#	Ret. Time	Area	Height	Area %
1	8.090	363138	22328	0.848
2	13.928	42474636	1286107	99.152
Total		42837774		100.000

^{1}H, ^{13}C NMR of compound **3ae**





HPLC of compound **3ae**

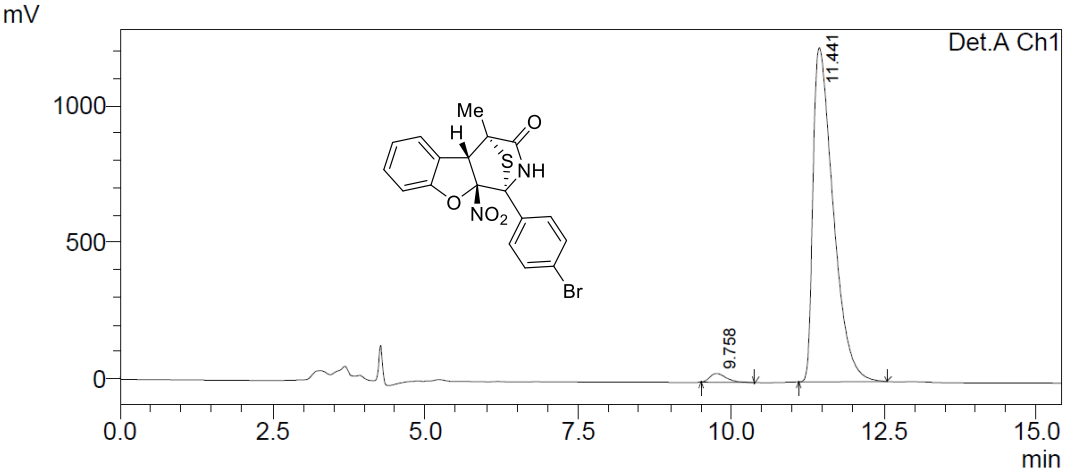


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.835	1023749	40819	50.008
2	11.853	1023417	37535	49.992
Total		2047165		100.000



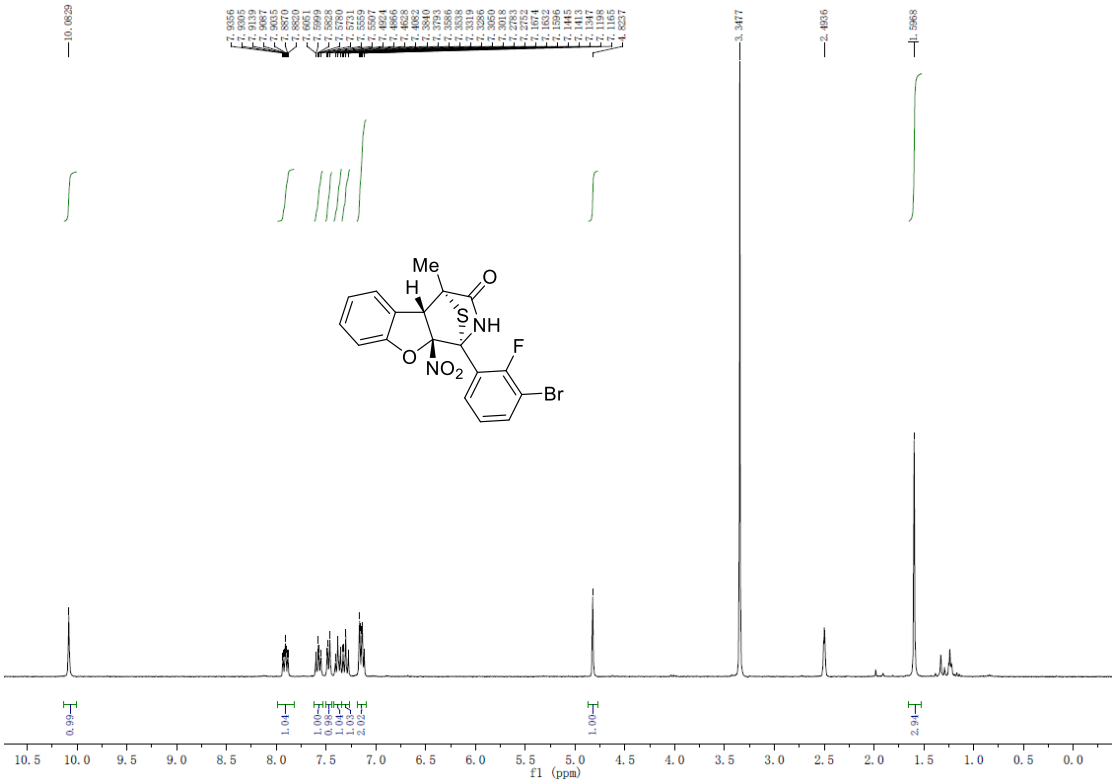
1 Det.A Ch1/220nm

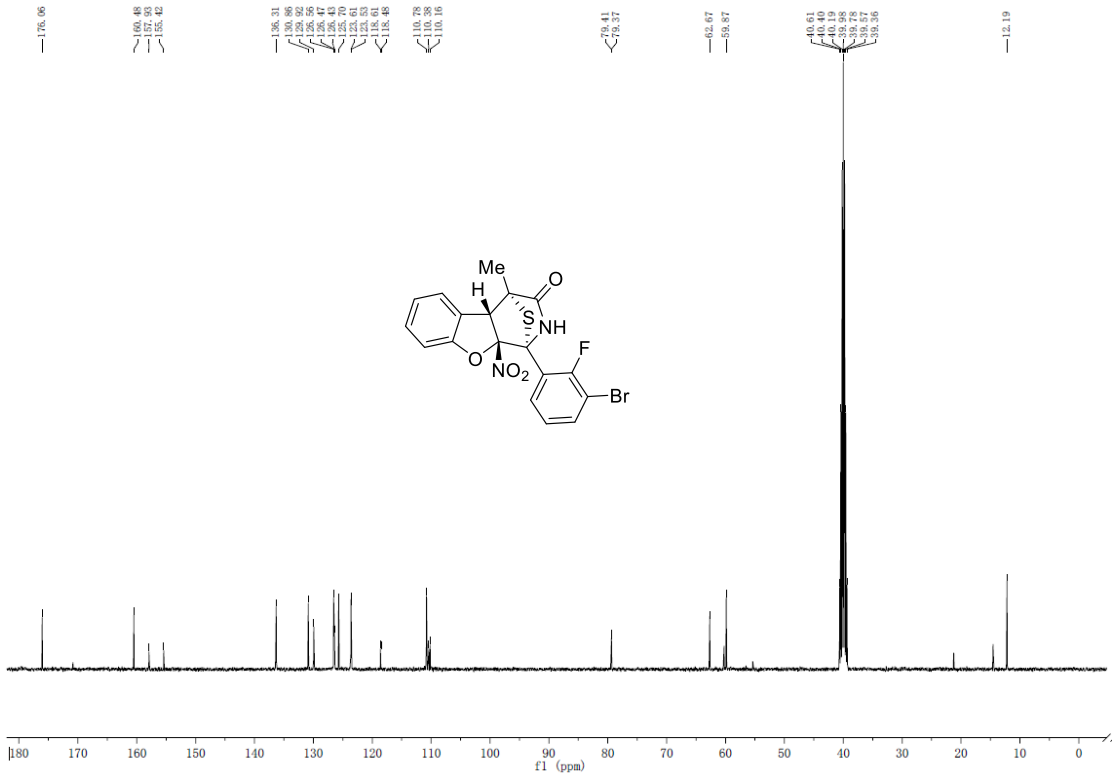
PeakTable

Detector A Ch1 220nm

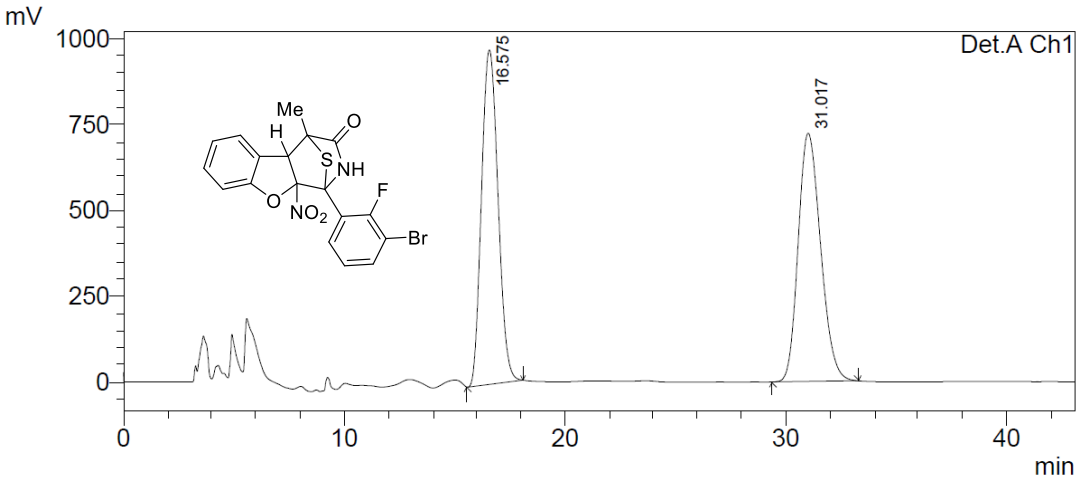
Peak#	Ret. Time	Area	Height	Area %
1	9.758	598887	32120	2.086
2	11.441	28108410	1221375	97.914
Total		28707297		100.000

^{1}H, ^{13}C NMR of compound **3af**





HPLC of compound **3af**

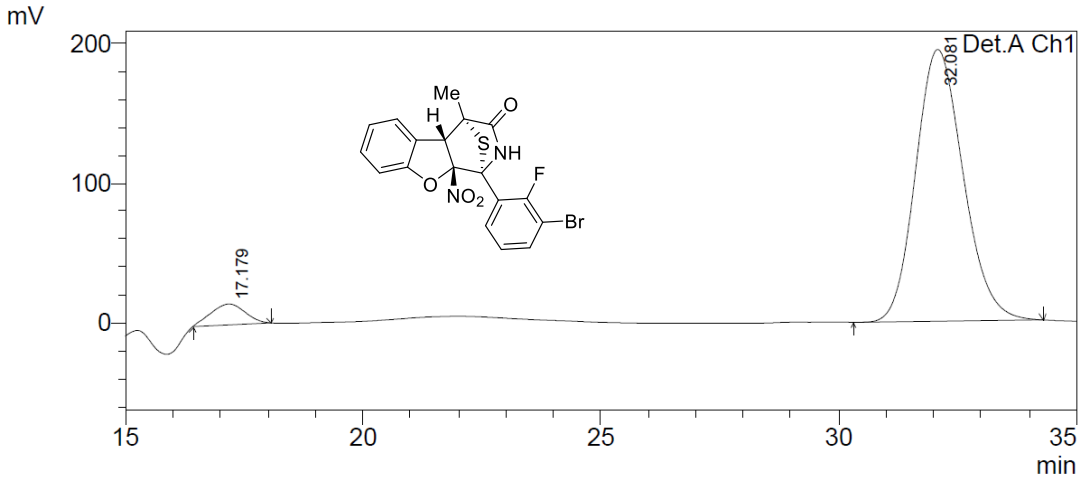


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	16.575	50628160	974487	49.798
2	31.017	51038156	723237	50.202
Total		101666316		100.000



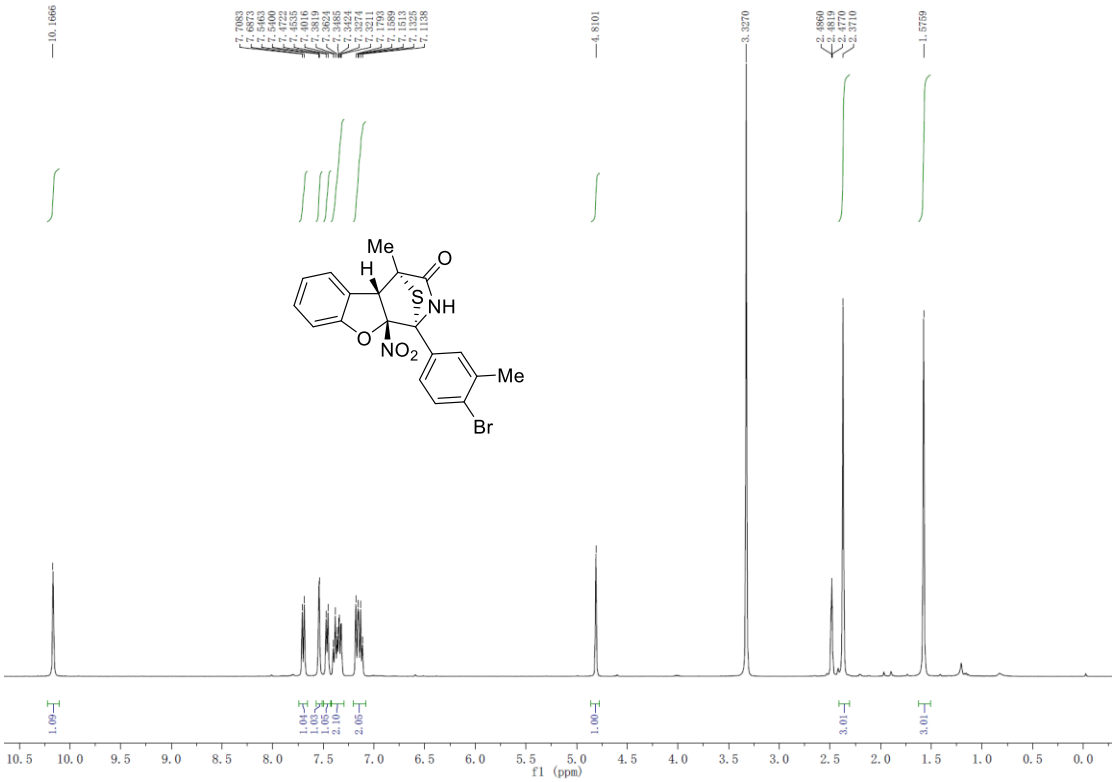
1 Det.A Ch1/220nm

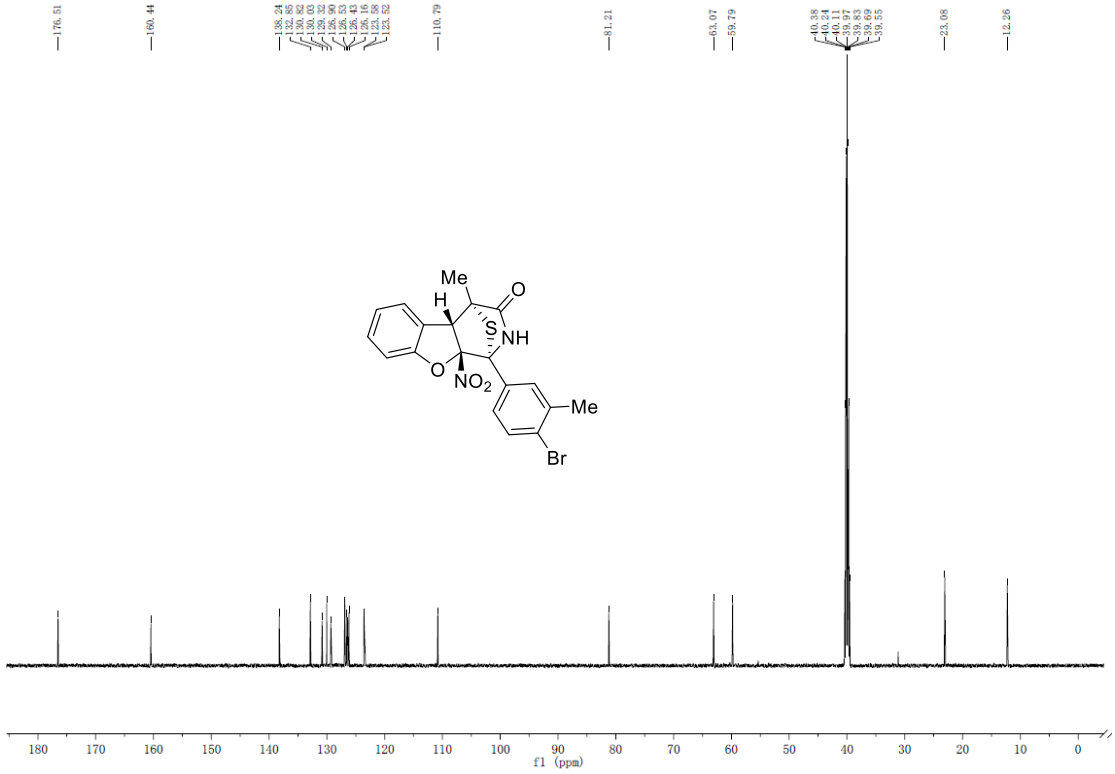
PeakTable

Detector A Ch1 220nm

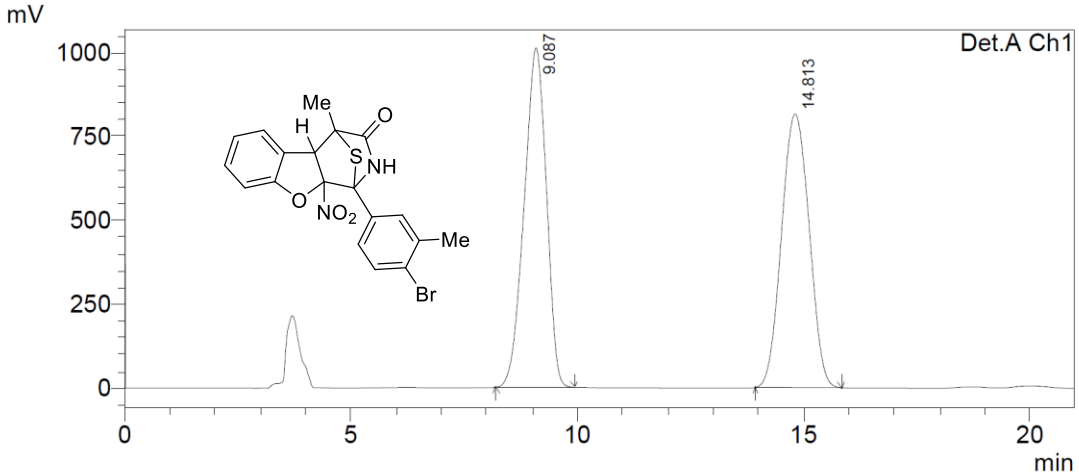
Peak#	Ret. Time	Area	Height	Area %
1	17.179	745090	14887	5.218
2	32.081	13533873	194676	94.782
Total		14278963		100.000

^{1}H, ^{13}C NMR of compound **3ag**





HPLC of compound **3ag**

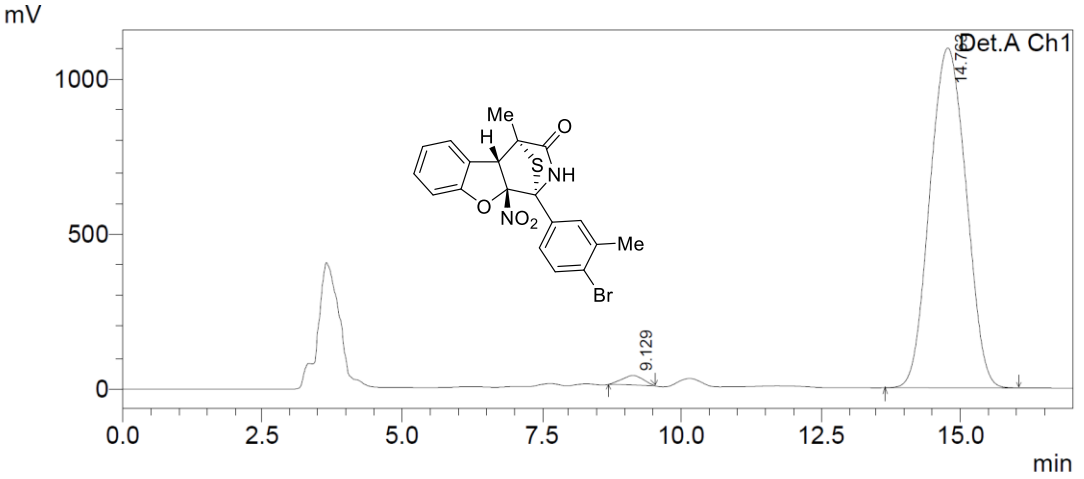


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.087	34518577	1011405	49.949
2	14.813	34589729	815256	50.051
Total		69108306		100.000



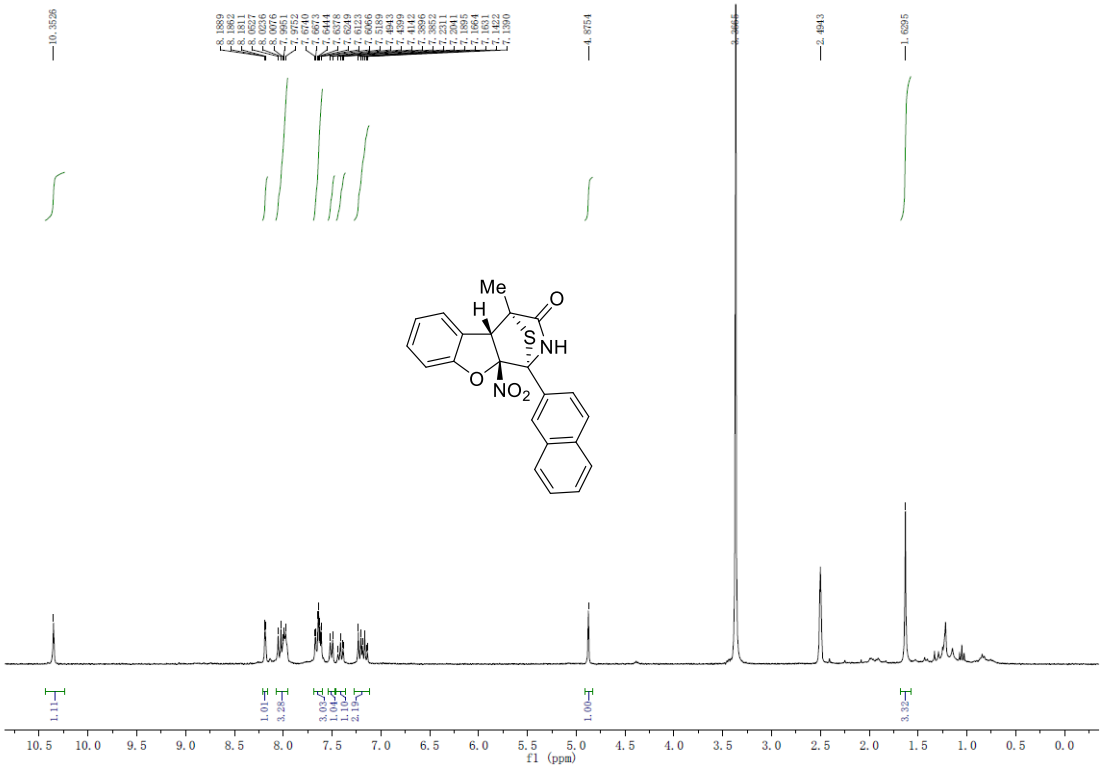
1 Det.A Ch1/220nm

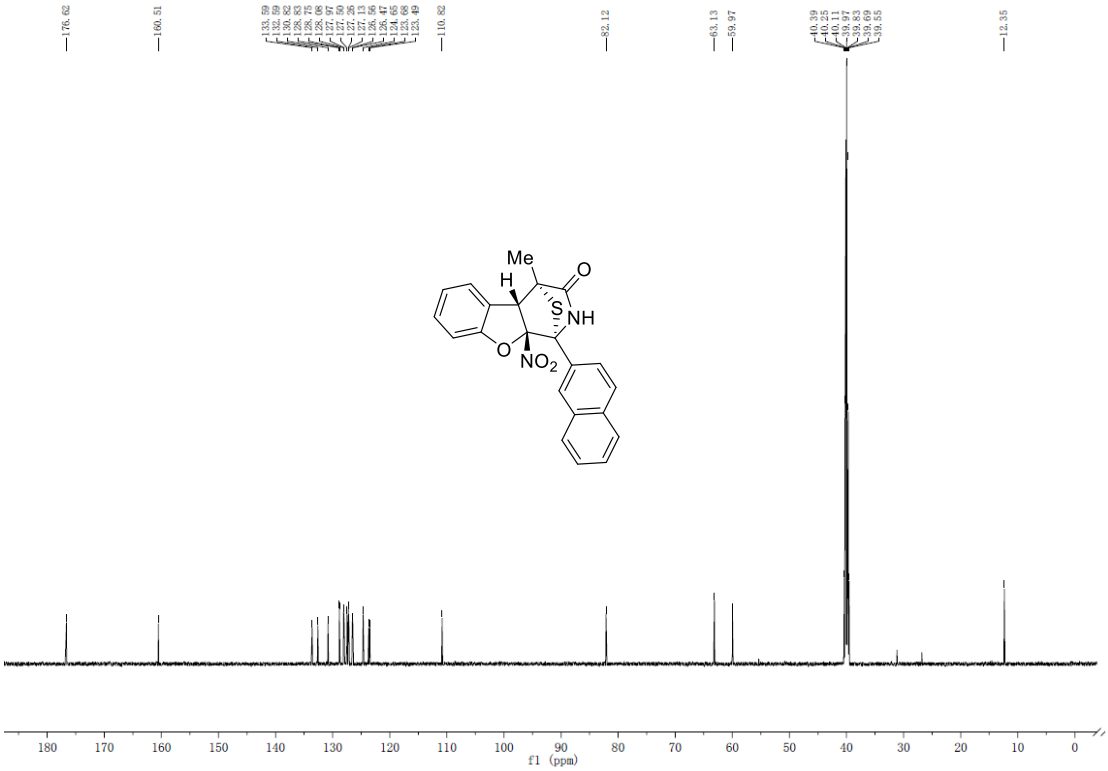
PeakTable

Detector A Ch1 220nm

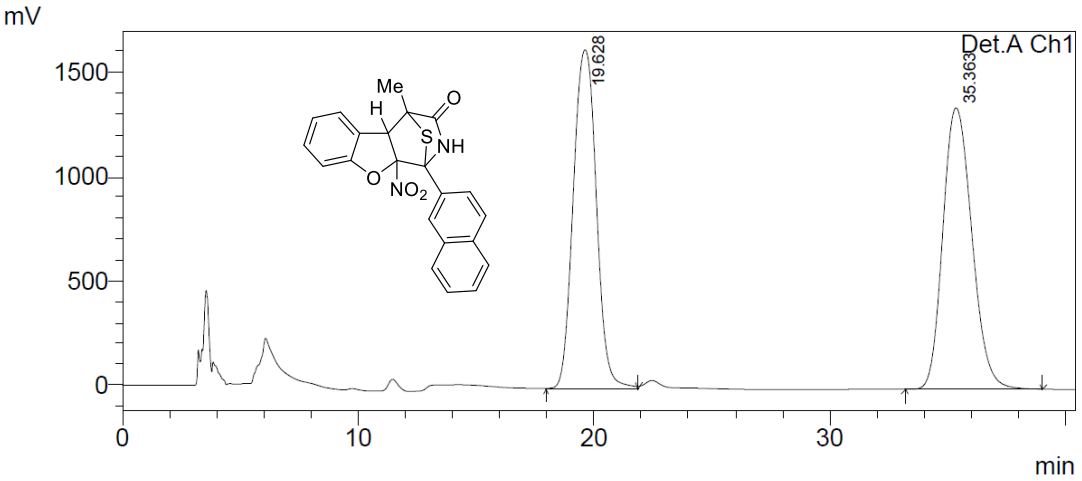
Peak#	Ret. Time	Area	Height	Area %
1	9.129	822680	31088	1.631
2	14.763	49627395	1098111	98.369
Total		50450075		100.000

^{1}H, ^{13}C NMR of compound **3ah**





HPLC of compound **3ah**

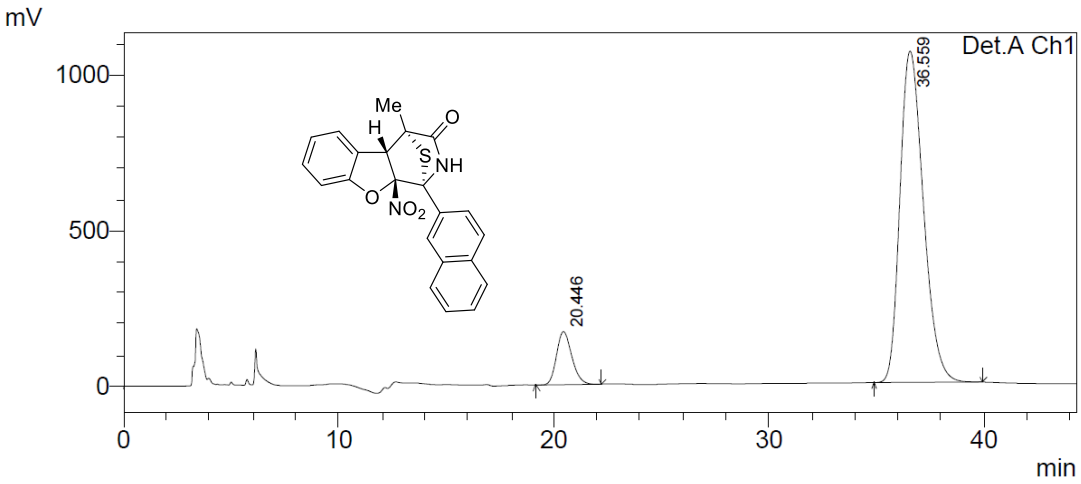


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	19.628	110425732	1623035	48.877
2	35.363	115497798	1347961	51.123
Total		225923530		100.000



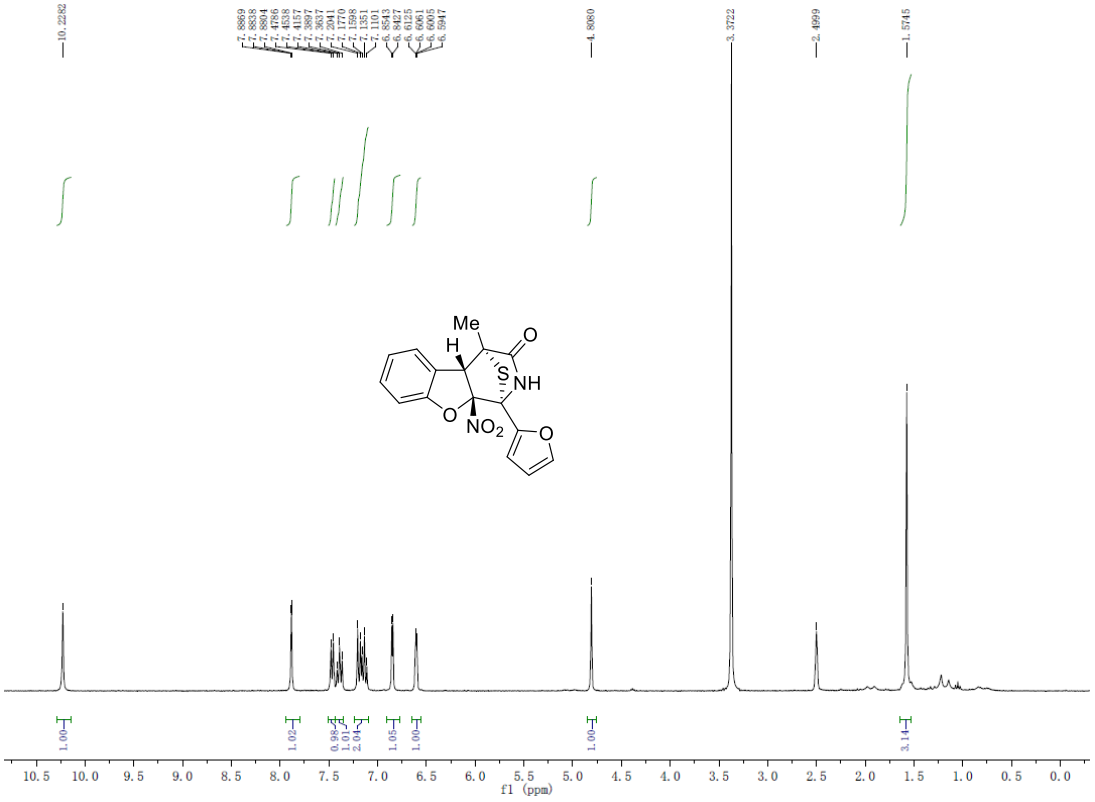
1 Det.A Ch1/220nm

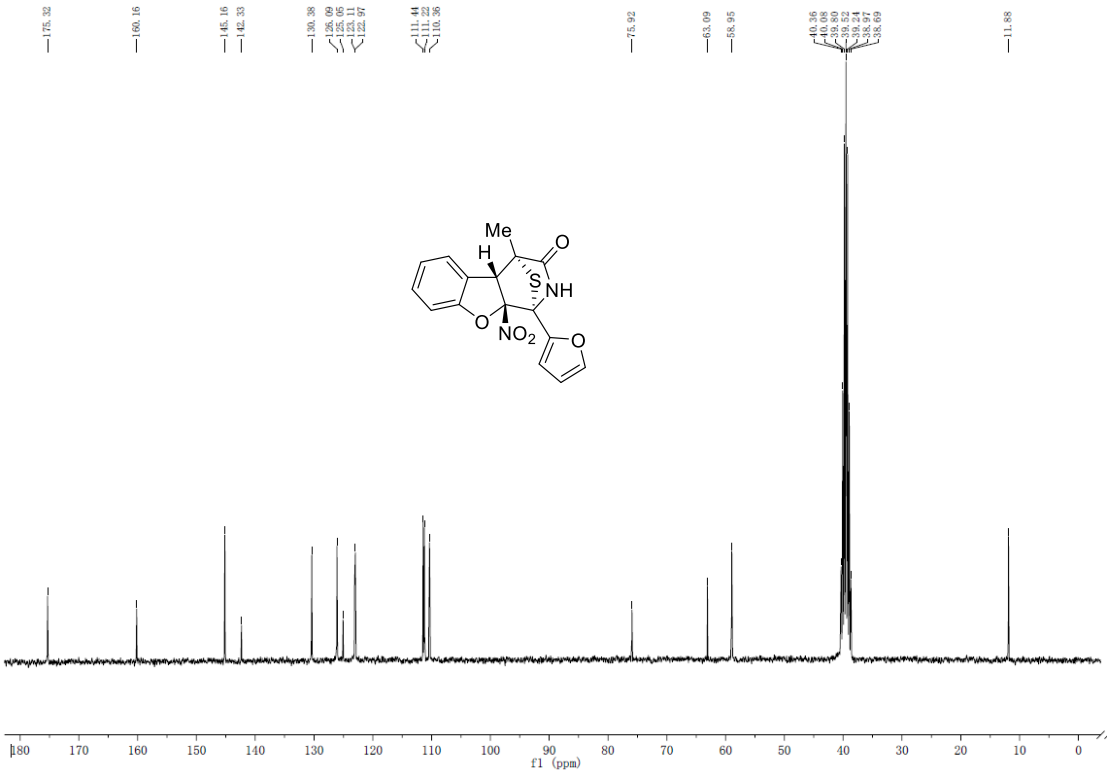
PeakTable

Detector A Ch1 220nm

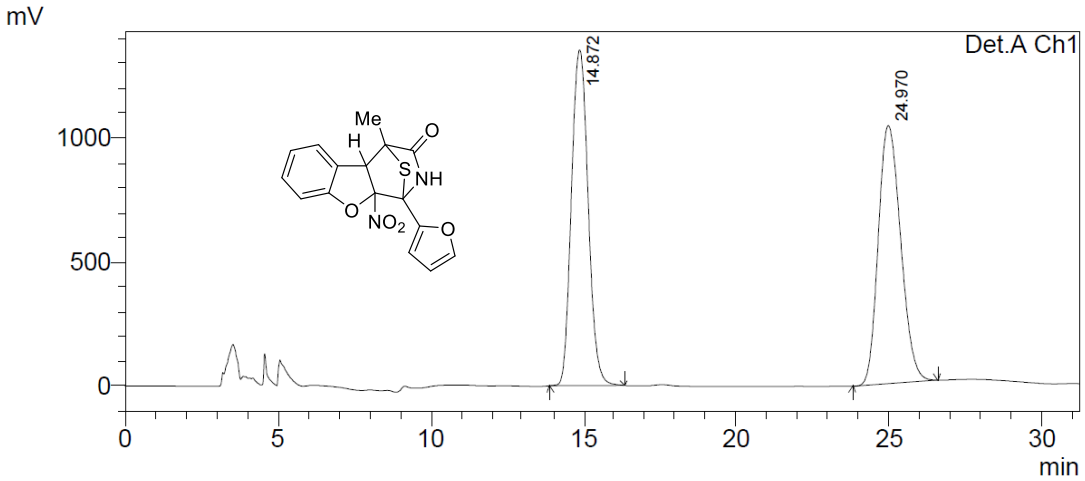
Peak#	Ret. Time	Area	Height	Area %
1	20.446	8381733	170325	9.418
2	36.559	80612750	1063935	90.582
Total		88994483		100.000

^{1}H, ^{13}C NMR of compound **3ai**





HPLC of compound **3ai**

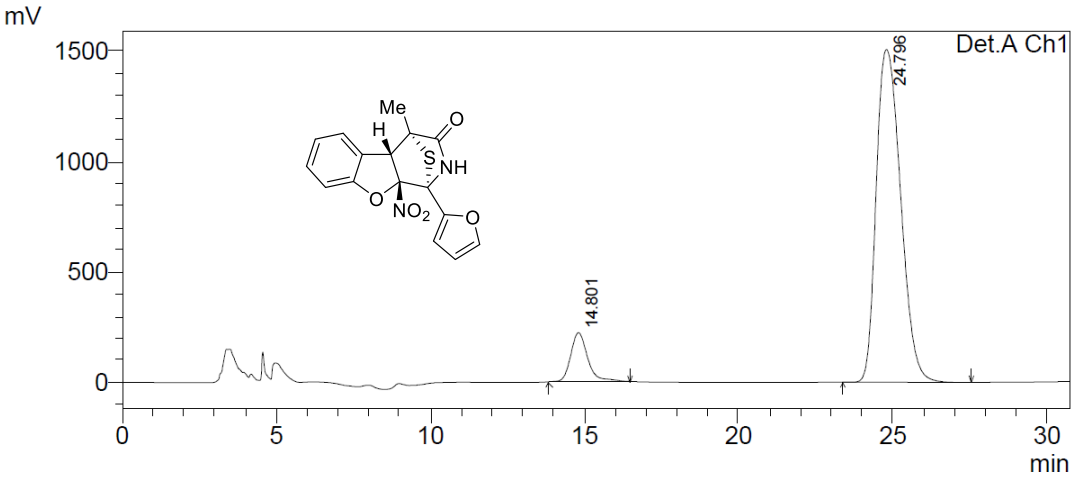


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	14.872	51477173	1353387	49.212
2	24.970	53126465	1041020	50.788
Total		104603638		100.000



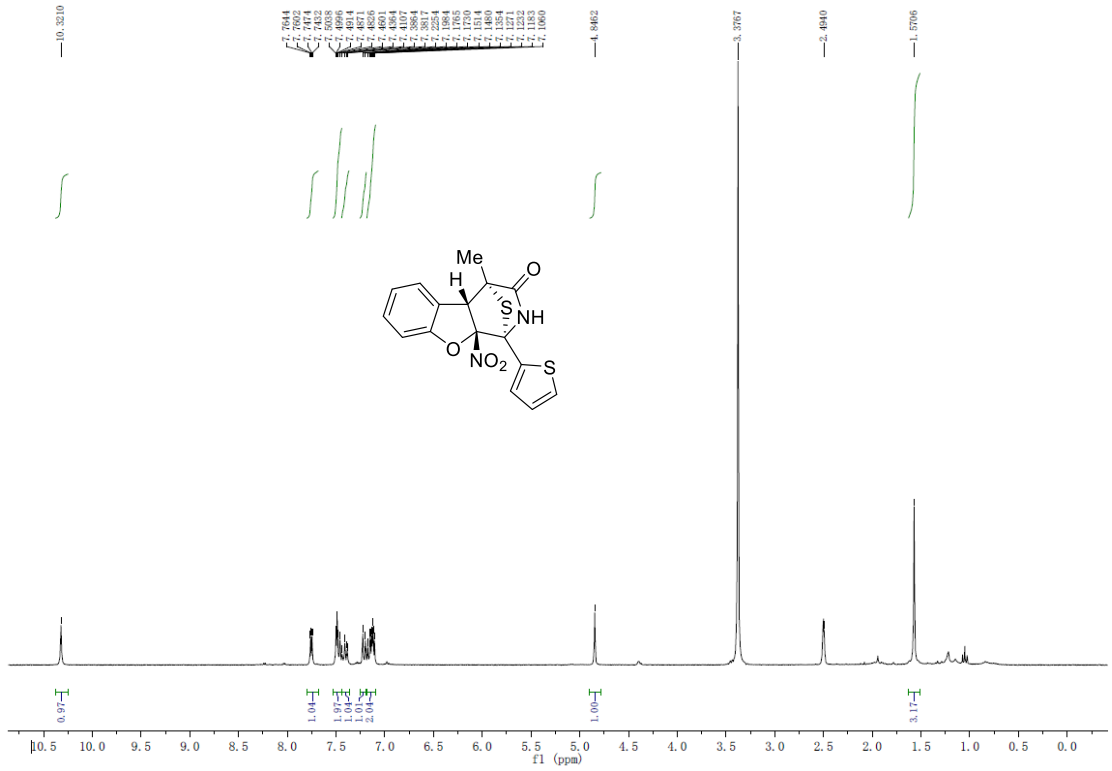
1 Det.A Ch1/220nm

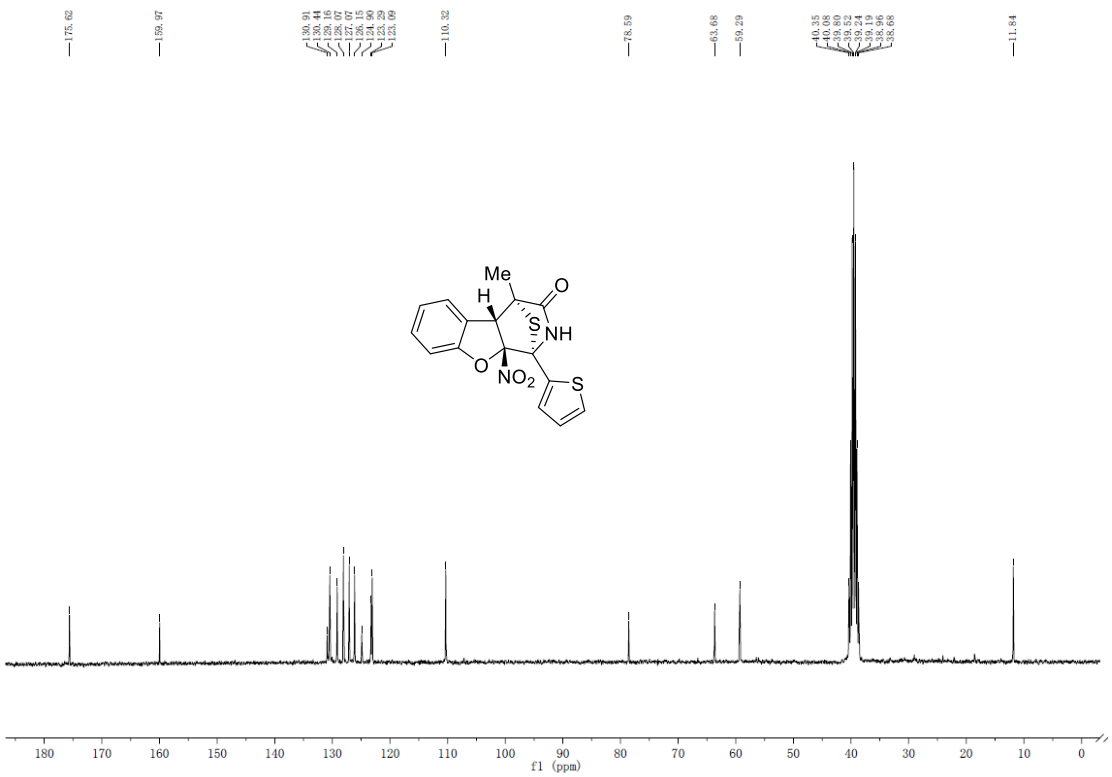
PeakTable

Detector A Ch1 220nm

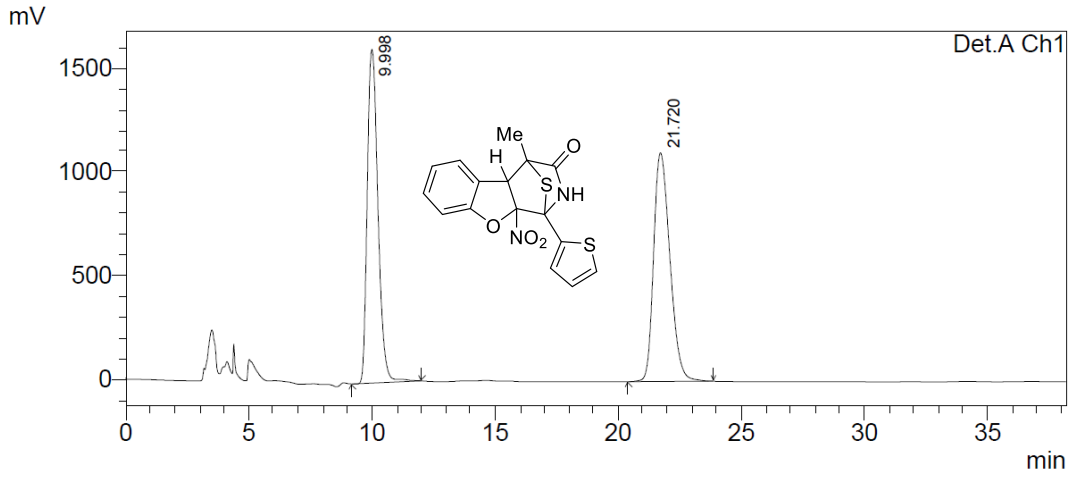
Peak#	Ret. Time	Area	Height	Area %
1	14.801	8492728	221891	9.265
2	24.796	83169493	1507561	90.735
Total		91662221		100.000

^{1}H, ^{13}C NMR of compound **3aj**





HPLC of compound **3aj**

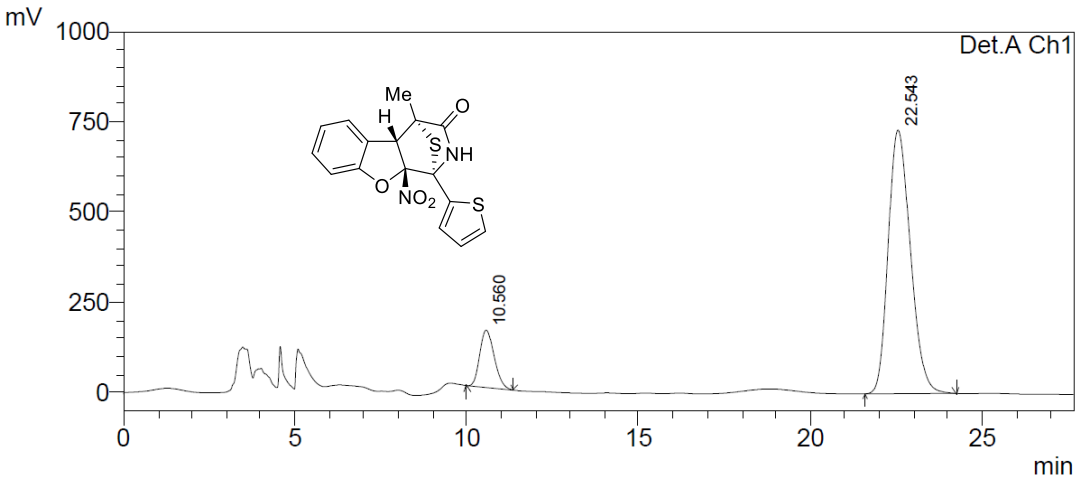


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.998	48776592	1610640	48.996
2	21.720	50775385	1103711	51.004
Total		99551977		100.000



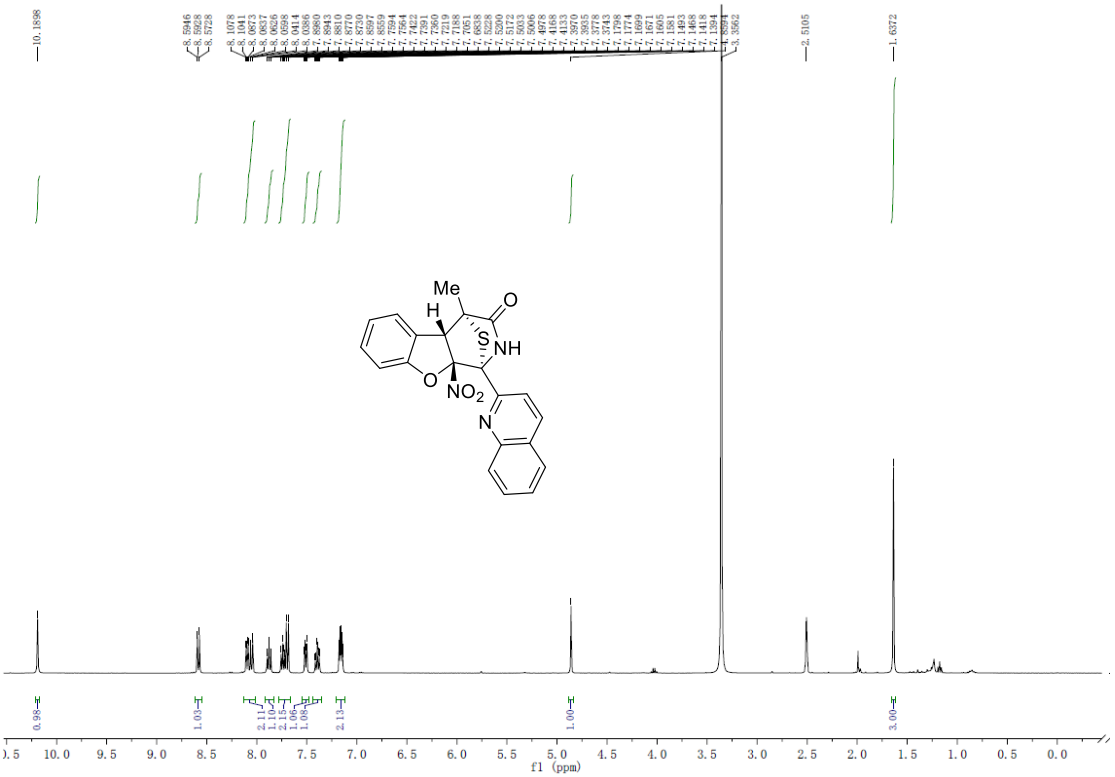
1 Det.A Ch1/220nm

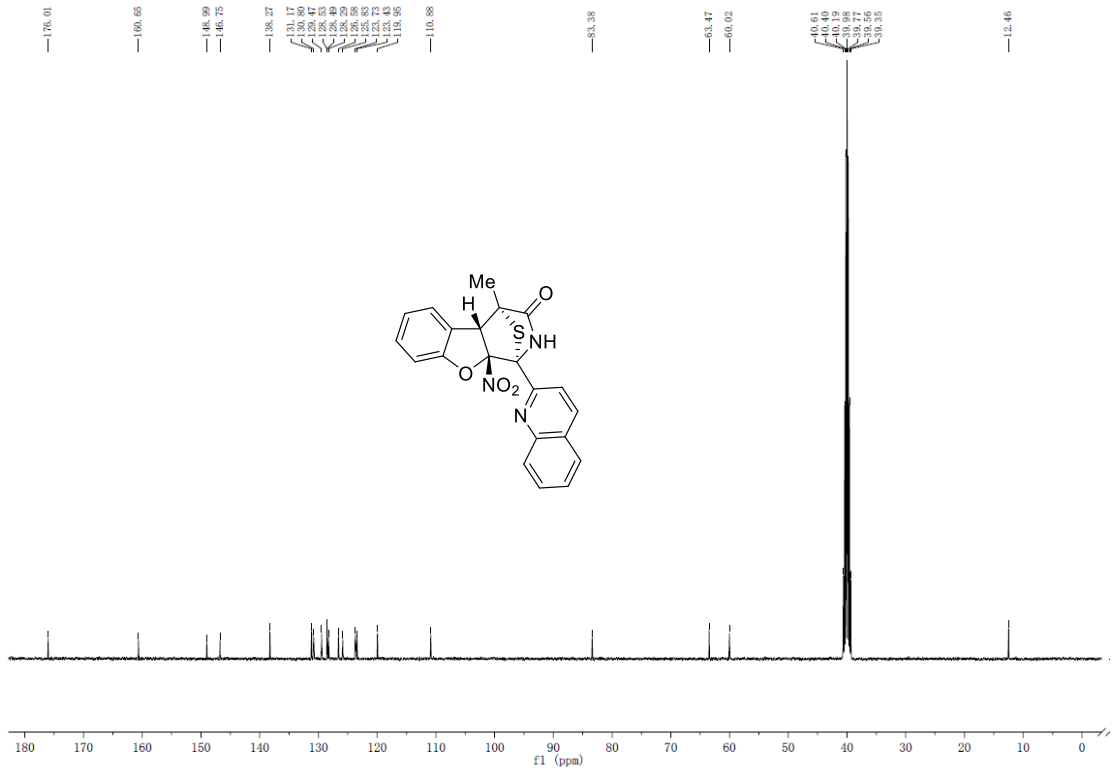
PeakTable

Detector A Ch1 220nm

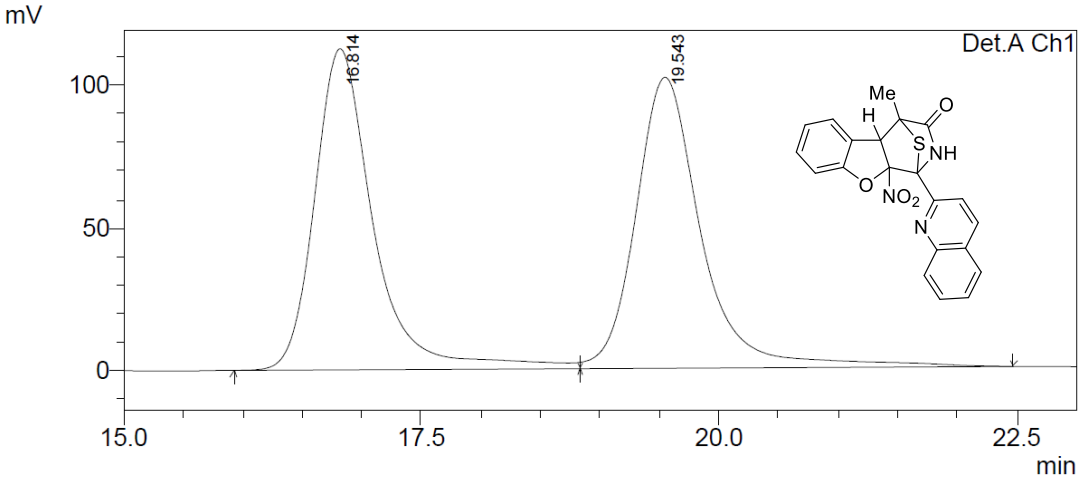
Peak#	Ret. Time	Area	Height	Area %
1	10.560	4671593	158796	12.444
2	22.543	32870574	730194	87.556
Total		37542168		100.000

^{1}H, ^{13}C NMR of compound **3ak**





HPLC of compound **3ak**

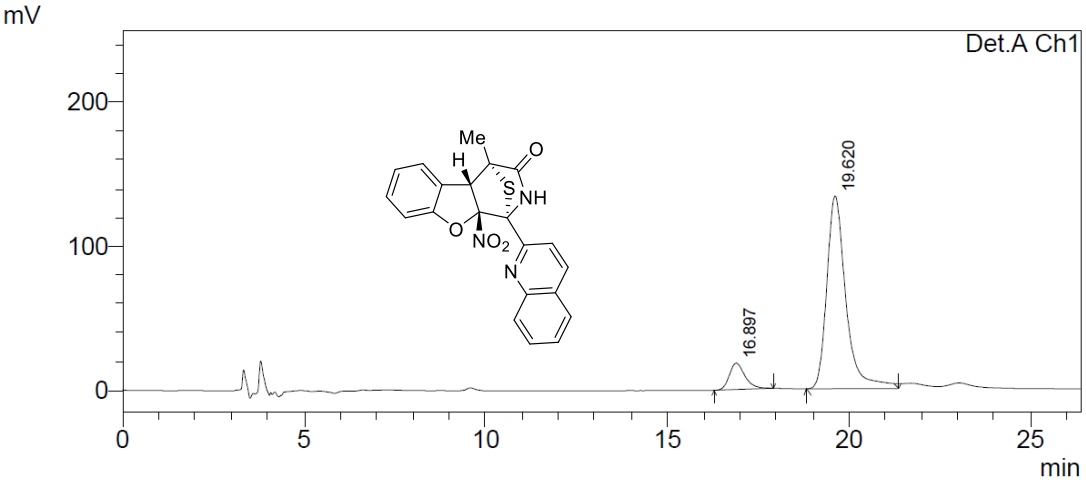


1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	16.814	3873402	112487	49.680
2	19.543	3923259	101872	50.320
Total		7796661		100.000



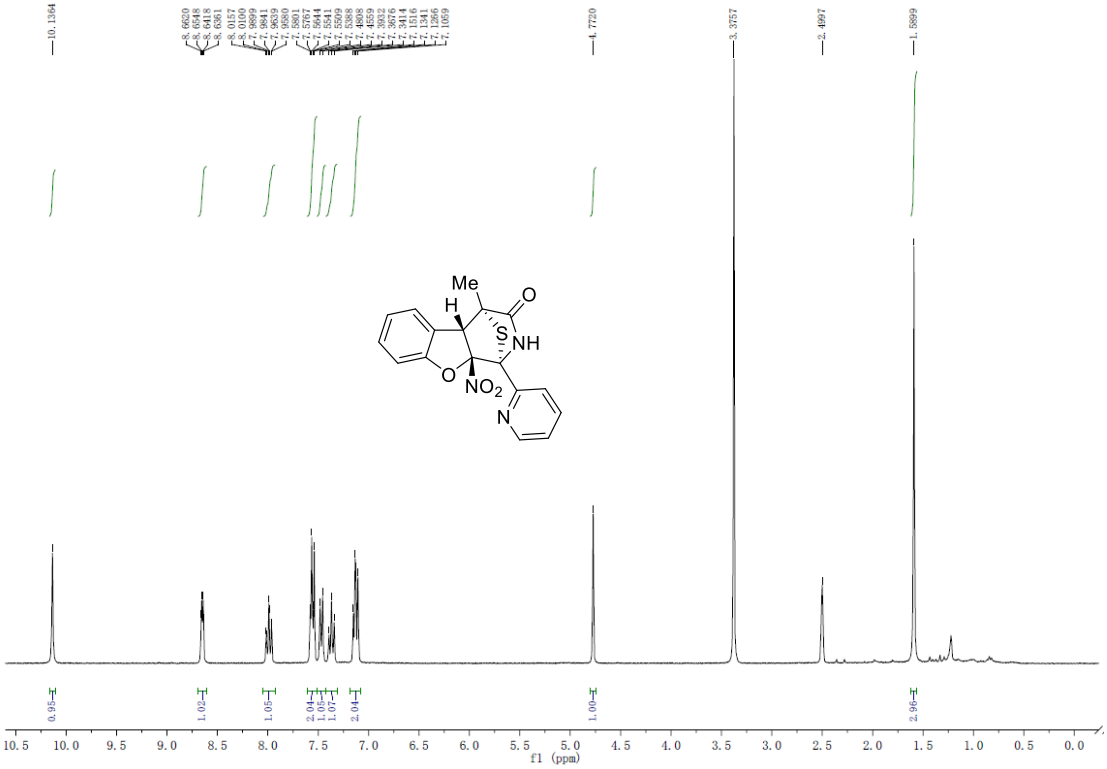
1 Det.A Ch1/254nm

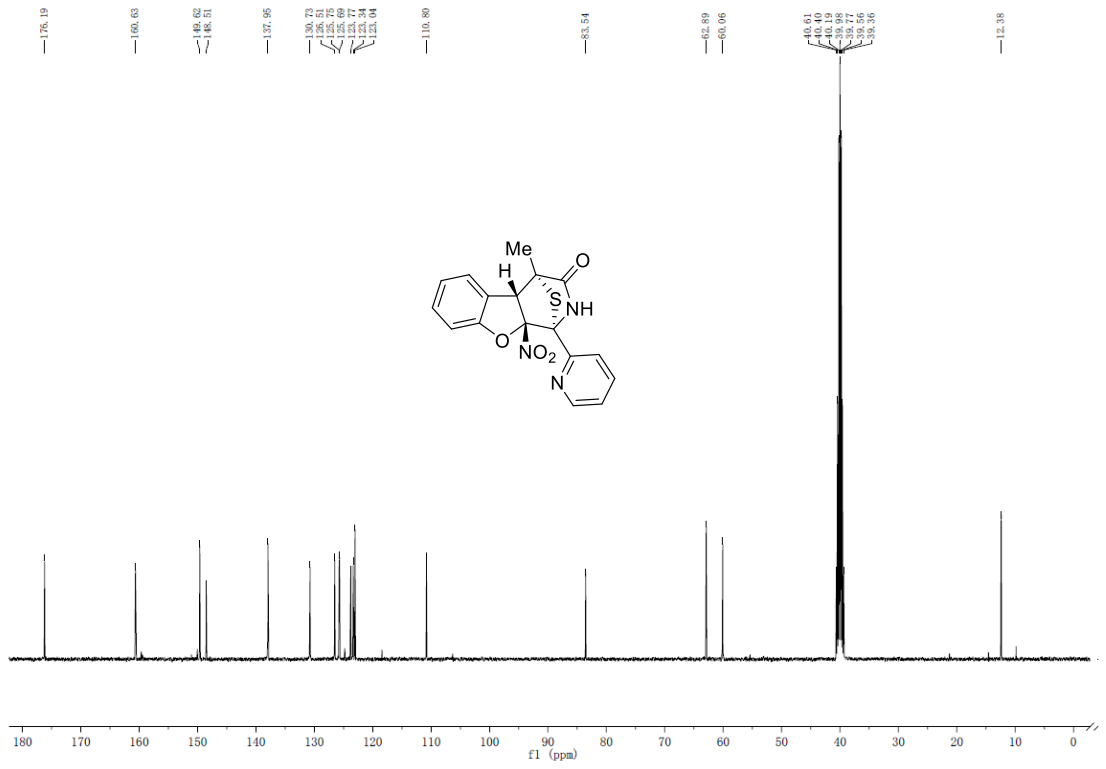
PeakTable

Detector A Ch1 254nm

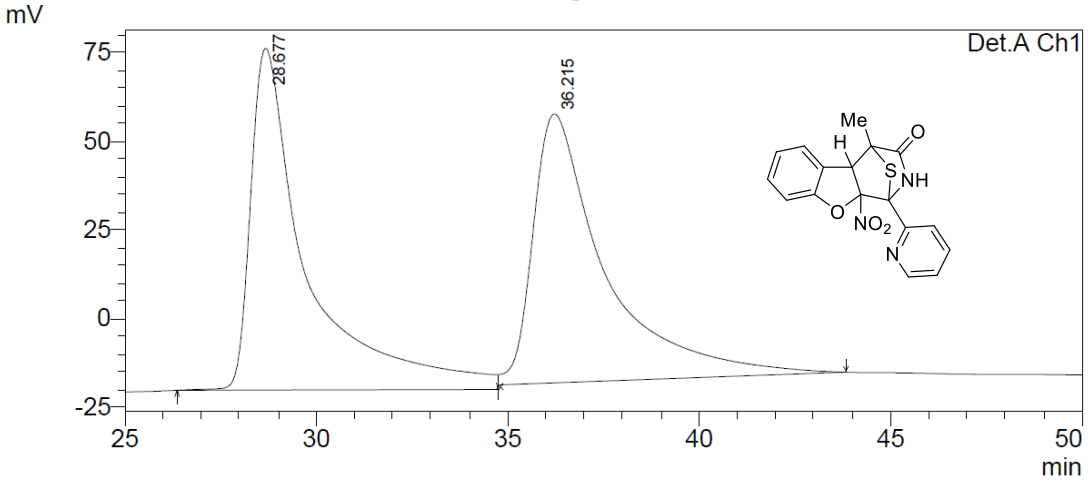
Peak#	Ret. Time	Area	Height	Area %
1	16.897	548730	18366	10.040
2	19.620	4916898	133693	89.960
Total		5465629		100.000

^{1}H, ^{13}C NMR of compound **3al**





HPLC of compound **3al**

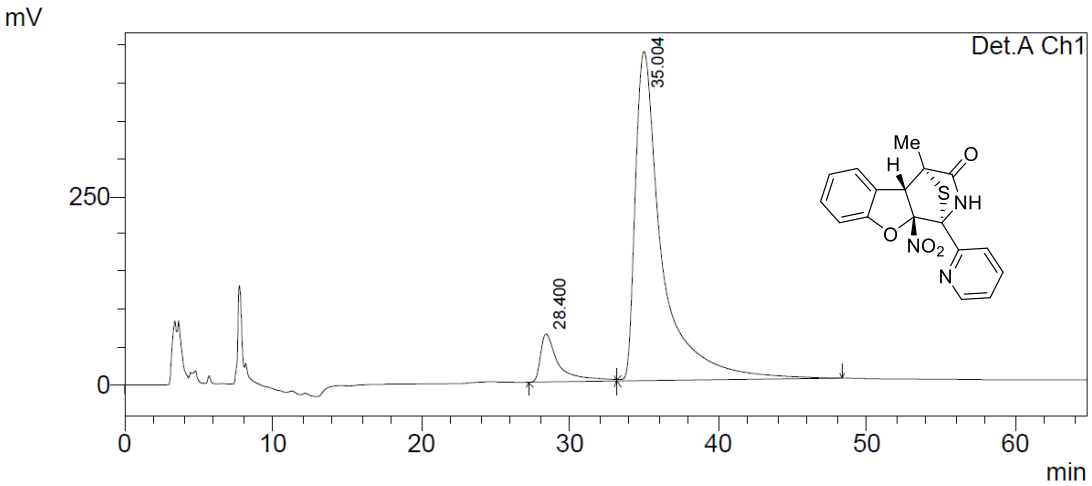


1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	28.677	9882747	96318	49.785
2	36.215	9967958	75823	50.215
Total		19850705		100.000



1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	28.400	5476164	63621	9.092
2	35.004	54757652	436443	90.908
Total		60233816		100.000