Supplementary Information

Bio-catalytic asymmetric Mannich reaction of ketimines using wheat germ lipase

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1. Materials

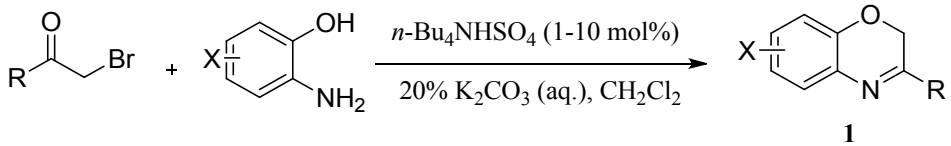
Lipase from wheat germ, Type I [lyophilized powder, 75% protein(Biuret), L-3001-5G, Lot # SLBG5523V, 7 units/mg protein, One unit will hydrolyze 1.0 microequivalent of fatty acid from a triglyceride in 1 h at pH 7.4 at 37 °C], Phosphatase acid from wheat germ, Type I (P3627-1G, 021M7014V, 0.5 units /mg solid, One unit will hydrolyze 1.0 micromole of *p*-nitrophenyl phosphate in 1 min at pH 4.8 at 37 °C), Lipase from porcine pancreas, Type II (L3126-25G, Batch # 020M1589, 300 units/mg solid, one unit will hydrolyze 1.0 microequivalent of fatty acid from triacetin in 1 h at pH 7.4 at 37 °C), Proteinase from *Aspergillus melleus*, Type XXIII (P4032-25G, Lot # 080M1456V, 4 units/mg solid, One unit will hydrolyze casein to produce color equivalent to 1.0 μmole (181 μg) of tyrosine per minute at pH 7.5 at 37°C), and Papain from *Carica pagaya* (76220-25G, Lot # BCBD3116V, 3 units/mg solid, One unit corresponds to the amount of enzyme which hydrolyzes 1 mol Nbenzoyl-L-arginine ethyl ester (BAEE, Fluka No. 12880) per minute at pH 6.2 at 25 °C) were purchased from Sigma-Aldrich, Shanghai, China. Nuclease p1 from *Penicillium citrinum* (EC 3.1.30.1, 5 U/mg, One unit of enzyme activity was defined as the amount of enzyme that produced an increase in the optical density of 1.0 in 1 min at 260 nm.) was purchased from Guangxi Nanning Pangbo Biological Engineering Co. Ltd. (Nanning, China). Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification.

2. General methods

Reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF 254 silica gel plates (Qingdao Haiyang chemical industry Co Ltd, Qingdao, China) using UV light and vanillic aldehyde as visualizing agents. Flash column chromatography was performed using 200-300 mesh silica gel at increased pressure. ^{1}H NMR spectra and ^{13}C NMR spectra were respectively recorded on 600 MHz and 150 MHz NMR spectrometers. Chemical shifts (δ) were expressed in ppm with TMS as the internal standard, and coupling constants (*J*) were reported in Hz. The enantiomeric excesses (ee) of Mannich products were determined by chiral HPLC analysis performed using Chiralpak AD-H, Chiralpak IC and Chiralcel OD-H (Daicel Chiral Technologies CO., LTD.; Shanghai, China). Absolute configurations of the products were determined by comparing with the known chiral HPLC analysis. All the Mannich products are known compounds.

3. Synthesis of 3-substituted-2*H*-1,4-benzoxazines.

3-Substituted-2*H*-1,4-benzoxazines were synthesized following the procedure described in the literature.[1]



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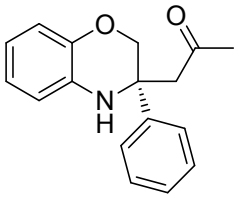
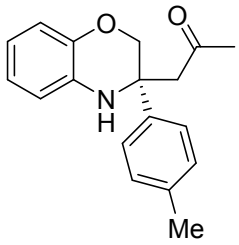
To a round bottom bottle were added the appropriate 2-aminophenol (3 mmol), CH_2Cl_2 (20 mL), 20% aqueous K_2CO_3 solution (20 mL) and *n*-Bu_4NHSO_4 (1-10 mol%). Substituted 2-bromoacetophenone was dissolved in 5 mL CH_2Cl_2 and added dropwisely to the reaction mixture. Then the reaction mixture was stirred at room temperature and monitored by TLC. After the consumption of the starting materials, organic layer was washed by water (30 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography using petroleum ether and EtOAc as eluent to obtain the corresponding benzoxazines (**1**).

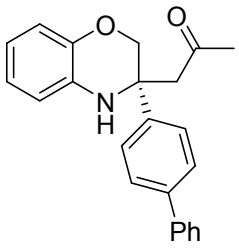
4. Characterization of Mannich products.



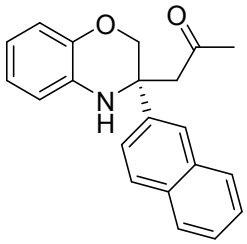
(S)-1-(3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3a)[2]: R_f = 0.21 (PE/EtOAc, 10:1); 49% yield, 87% ee; $[\alpha]^{20}_D$ = + 167.1 (*c* 0.96, $CHCl_3$); Colourless semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.25 (dd, *J* = 13.0, 5.6 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 5.27 (br, 1H), 3.97 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.35 (d, *J* = 17.8 Hz, 1H), 3.10 (d, *J* = 17.8 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.6 , 142.7, 141.4 , 132.8, 128.7, 127.5, 125.6, 122.2, 118.6, 116.5, 116.1, 73.9, 55.2, 47.2, 31.7; HPLC (Chiralcel AD-H column, hexane/iPrOH = 98/2, 0.8 mL/min, 254 nm): t_1 = 21.7 min (*S*), t_2 = 23.9 min (*R*).



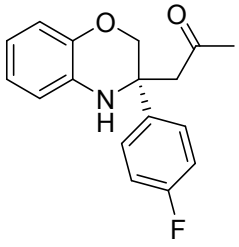
(S)-1-(3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3b)[2]: R_f = 0.28 (PE/EtOAc, 5:1); 54% yield, 83% ee; $[\alpha]^{20}_D$ = + 182.8 (*c* 0.91, $CHCl_3$); Colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.75 - 6.72 (m, 1H), 6.66 (td, *J* = 8.0, 1.3 Hz, 1H), 5.24 (br, 1H), 3.96 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.33 (d, *J* = 17.7 Hz, 1H), 3.09 (d, *J* = 17.7 Hz, 1H), 2.31 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.6, 142.7, 138.4, 137.1, 132.9, 129.4, 125.5, 122.1, 118.5, 116.5, 116.0, 73.9, 55.0, 47.2, 31.7, 20.92; HPLC (Chiralcel OD-H column, hexane/iPrOH 90/10, 0.8 mL/min, 254 nm): t_1= 9.9 min (*R*), t_2 = 11.4 min (*S*).



(S)-1-(3-([1,1'-biphenyl]-4-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3c)[2]: R_f = 0.25 (PE/EtOAc, 5:1); 31% yield, 95% ee; $[\alpha]^{20}_D$ = + 190.2 (*c* 0.74, $CHCl_3$); White solid; m.p. 121.8-122.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.8, 6.0 Hz, 4H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.85 (t, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.76 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.68 (t, *J* = 8.1 Hz, 1H), 5.31 (br, 1H), 4.01 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.38 (d, *J* = 17.8 Hz, 1H), 3.13 (d, *J* = 17.9 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.6, 142.7, 140.5, 140.5, 140.3, 132.8, 128.80, 127.5, 127.4, 127.1, 126.1, 122.2, 118.7, 116.6, 116.1, 73.9, 55.1, 47.3, 31.7; HPLC (Chiralcel AD-H column, hexane/iPrOH = 90/10, 0.8 mL/min, 254 nm): t_1 = 17.6 min (*S*), t_2 = 21.2 min (*R*).

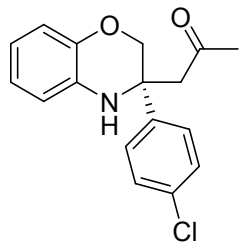


(S)-1-(3-(naphthalen-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3d)[2]: R_f = 0.20 (PE/EtOAc, 5:1); 20% yield, 85% ee; $[\alpha]^{20}_D$ = + 153.4 (*c* 0.26, $CHCl_3$); White solid; m.p. 129.1-130.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 1.3 Hz, 1H), 7.84 -7.79 (m, 3H), 7.54 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.48 -7.43 (m, 2H), 6.87 (td, *J* = 7.8, 1.3 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.4 Hz, 2H), 6.69 (td, *J* = 7.9, 1.5 Hz, 1H), 5.41 (br, 1H), 4.06 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.47 (d, *J* = 17.8 Hz, 1H), 3.18 (d, *J* = 17.8 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.6, 142.7, 138.8, 133.4, 132.8, 132.6, 128.6, 128.2, 127.5, 126.3, 126.2, 125.2, 123.3, 122.2, 118.7, 116.6, 116.2, 73.8, 55.4, 47.2, 31.7; HPLC (Chiralcel AD-H column, hexane/iPrOH 90/10, 0.8 mL/min, 254 nm): t_1 = 16.2 min (*S*), t_2 = 18.0 min (*R*).

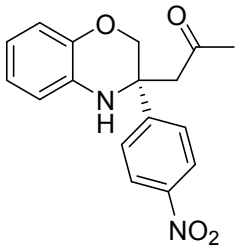


(S)-1-(3-(4-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3e)[2]: R_f = 0.20 (PE/EtOAc, 5:1); 21% yield, 87% ee; $[\alpha]^{20}_D$ = + 157.1 (*c* 0.73, $CHCl_3$); White solid; m.p.

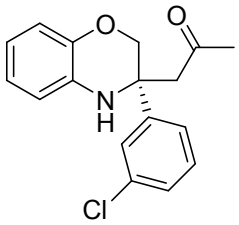
107.2-108.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 - 7.37 (m, 2H), 7.02 (t, *J* = 8.4 Hz, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 5.25 (br, 1H), 3.94 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.30 (d, *J* = 17.9 Hz, 1H), 3.09 (d, *J* = 17.9 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.5,162.0 (d, $^1J_{C\text{-}F}$ = 245.1 Hz), 142.6, 137.3 (d, $^4J_{C\text{-}F}$ = 2.6 Hz), 132.6, 127.5 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 122.3, 118.8, 116.6, 116.1, 115.6(d, $^2J_{C\text{-}F}$ = 21.3 Hz), 73.8, 54.9, 47.2, 31.7; HPLC (Chiralcel OD-H column, hexane/iPrOH 90/10, 0.8 mL/min, 254 nm): t_1 = 12.6 min (*R*), t_2 = 14.7 min (*S*).



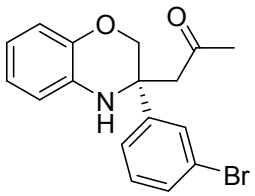
(S)-1-(3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3f)[2]: R_f = 0.16 (PE/EtOAc, 5:1); 17% yield, 86% ee; $[\alpha]^{20}_D$ = + 140.1 (*c* 0.56, $CHCl_3$); Colourless semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.83 (dd, *J* = 10.8, 4.3 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.73 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.70 - 6.66 (m, 1H), 5.25 (br, 1H), 3.93 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.30 (d, *J* = 18.0 Hz, 1H), 3.10 (d, *J* = 18.0 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.3, 142.6, 140.2, 133.4, 132.5, 128.9, 127.2, 122.3, 118.9, 116.6, 116.1, 73.6, 55.0, 47.2, 31.6; HPLC (Chiralcel IC column,hexane/iPrOH 95/5, 0.8 mL/min, 254 nm): t_1 = 10.3 min (*R*), t_2 = 11.5 min (*S*).



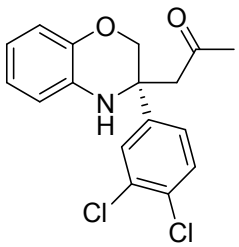
(S)-1-(3-(4-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3g)[2]: R_f = 0.10 (PE/EtOAc, 5:1); 21% yield, 89% ee; $[\alpha]^{20}_D$ = + 156.7 (*c* 0.39, $CHCl_3$); Yellow solid; m.p. 126.1-126.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 8.19 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 6.87 (dd, *J* = 11.0, 4.1 Hz, 1H), 6.80-6.76 (m, 2H), 6.72- 6.69 (m, 1H), 5.30 (br, 1H), 4.00 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.40 (d, *J* = 18.3 Hz, 1H), 3.20 (d, *J* = 18.4 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.9, 149.3, 147.2, 142.6, 132.0, 126.9, 123.9, 122.5 , 119.2, 116.7, 116.1, 73.2, 55.5, 47.8, 31.3; HPLC (Chiralcel AD-H column, hexane/iPrOH = 75/25, 0.8 mL/min, 254 nm): t_1 = 13.4 min (*R*), t_2 = 19.0 min (*S*).



(S)-1-(3-(3-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3h)[2]: R_f = 0.25 (PE/EtOAc, 5:1); 18% yield, 85% ee; $[\alpha]^{20}_D$ = + 163.8 (*c* 0.53, $CHCl_3$); Colourless semisolid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.24 - 7.15 (m, 3H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 5.16 (br, 1H), 3.86 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.06 (d, *J* = 18.1 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (150MHz, $CDCl_3$): δ = 207.3, 143.8, 142.6, 134.9, 132.4, 130.0, 127.7, 126.2, 123.8, 122.3, 118.9, 116.6, 116.1, 73.6, 55.0, 47.1, 31.6; HPLC (Chiralcel AD-H column, hexane/iPrOH = 90/10, 0.8 mL/min, 254 nm): t_1 =10.2 min (*S*), t_2 = 12.0 min (*R*).

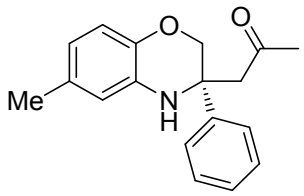


(S)-1-(3-(3-bromophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3i)[2]: R_f = 0.23 (PE/EtOAc, 5:1); 20% yield, 82% ee; $[\alpha]^{20}_D$ = + 163.3 (*c* 0.73, $CHCl_3$); Colourless semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.29 (dd, *J* = 25.2, 7.8 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 5.15 (br, 1H), 3.85 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz, 2H), 3.23 (d, *J* = 18.1 Hz, 1H), 3.05 (d, *J* = 18.1 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.3, 144.0, 142.6, 132.4, 130.6, 130.3, 129.1, 124.3, 123.1, 122.3, 118.9, 116.6, 116.2, 73.7, 55.0, 47.1, 31.6; HPLC (Chiralcel AD-H column, hexane/iPrOH 90/10, 0.8 mL/min, 254 nm): t_1 =10.3min (*S*), t_2 = 12.1 min (*R*).

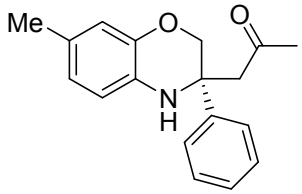


(S)-1-(3-(3,4-dichlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3J)[2]: R_f = 0.20 (PE/EtOAc, 5:1); 21% yield, 86% ee; $[\alpha]^{20}_D$ = + 162.6 (*c* 0.35, $CHCl_3$); White solid; m.p. 132.4-134.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 2.1 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.25 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.85 (td, *J* = 7.9, 1.1 Hz, 1H), 6.81 - 6.78 (m, 1H), 6.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.71 - 6.67 (m, 1H), 5.22 (br, 1H), 3.92 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.8 Hz,

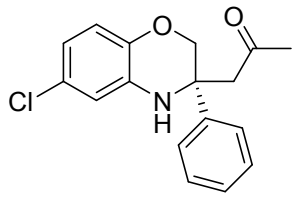
2H), 3.29 (d, J = 18.2 Hz, 1H), 3.13 (d, J = 18.3 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.1, 142.6, 142.2, 133.0, 132.2, 131.7, 130.6, 128.1, 125.2, 122.4, 119.1, 116.7, 116.2, 73.4, 54.8, 47.2, 31.5; HPLC (Chiralcel AD-H column, hexane/iPrOH = 90/10, 0.8 mL/min, 254 nm): t_1 = 11.5 min (*S*), t_2 = 12.5 min (*R*).



(S)-1-(6-methyl-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3k)[2]: R_f = 0.30 (PE/EtOAc, 5:1); 37% yield, 87% ee; $[\alpha]^{20}_D$ = + 183.1 (*c* 0.49, $CHCl_3$); Colourless semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.27 - 7.24 (m, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 0.9 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 5.20 (br, 1H), 3.94 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.7 Hz, 2H), 3.35 (d, J = 17.7 Hz, 1H), 3.11 (d, J = 17.7 Hz, 1H), 2.24 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.6, 141.5, 140.5, 132.4, 131.6, 128.7, 127.4, 125.6, 119.2, 116.6, 116.2, 74.0, 55.3, 47.1, 31.7, 20.8; HPLC (Chiralcel AD-H column, hexane/iPrOH = 90/10, 0.8 mL/min, 254 nm): t_1 = 10.2 min (*R*), t_2 = 11.0 min (*S*).

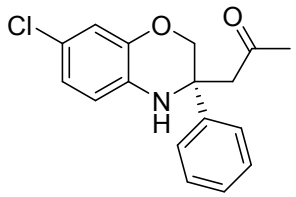


(S)-1-(7-methyl-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3l)[2]: R_f = 0.30 (PE/EtOAc, 5:1); 27% yield, 83% ee; $[\alpha]^{20}_D$ = + 142.7 (*c* 0.50, $CHCl_3$); Colourless semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.25 (dd, J = 12.3, 4.9 Hz, 1H), 6.64 (d, J = 18.1 Hz, 3H), 5.15 (br, 1H), 3.96 (AB quartet, $\Delta\delta AB$ = 0.036, J_{AB} = 10.7 Hz, 2H), 3.33 (d, J = 17.7 Hz, 1H), 3.09 (d, J = 17.7 Hz, 1H), 2.22 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.7, 142.5, 141.5, 130.2, 128.7, 128.4, 127.4, 125.7, 122.7, 117.0, 116.1, 74.0, 55.2, 47.0, 31.7, 20.6; HPLC (Chiralcel AD-H column, hexane/iPrOH = 90/10, 0.8 mL/min, 254 nm): t_1 = 11.6 min (*S*), t_2 =12.8 min *(R*).

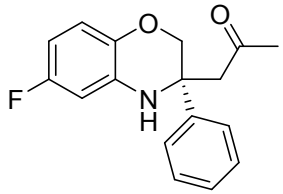


(S)-1-(6-chloro-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3m)[2]: R_f = 0.28 (PE/EtOAc, 5:1); 17% yield, 89% ee; $[\alpha]^{20}_D$ = + 182.6 (*c* 0.77, $CHCl_3$); Light Yellow semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.26 (dd, J =

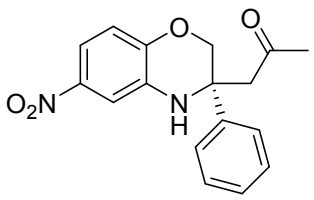
13.2, 5.9 Hz, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 2.3 Hz, 1H), 5.40 (br, 1H), 3.95 (AB quartet, $\Delta\delta AB$ = 0.036, J_{AB} = 10.7 Hz, 2H), 3.35 (d, J = 17.7 Hz, 1H), 3.04 (d, J = 17.7 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.4, 141.3, 140.9, 133.9, 128.8, 127.6, 126.8, 125.5, 118.2, 117.4, 115.4, 73.8, 55.2, 47.2, 31.7; HPLC (Chiralcel AD-H column, hexane/iPrOH = 90/10, 0.8 mL/min, 254 nm): t_1 = 12.2 min (*R*), t_2 = 13.0 min (*S*).



(S)-1-(7-chloro-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3n)[2]: R_f = 0.28 (PE/EtOAc, 5:1); 15% yield, 86% ee; $[\alpha]^{20}_D$ = + 171.3 (*c* 0.36, $CHCl_3$); Brown red semisolid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41 (d, J = 7.8 Hz, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.26 (dd, J = 12.5, 5.2 Hz, 1H), 6.82 - 6.77 (m, 2H), 6.65 (d, J = 8.0 Hz, 1H), 5.32 (br, 1H), 3.97 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.7 Hz, 2H), 3.34 (d, J = 17.7 Hz, 1H), 3.03 (d, J = 17.7 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.5, 143.1, 141.0, 131.6, 128.8, 127.6, 125.6, 122.8, 122.0, 116.7, 116.5, 73.8, 55.2, 47.1, 31.7; HPLC (Chiralcel AD-H column, hexane/iPrOH = 97/3, 0.8 mL/min, 254 nm): t_1 = 18.6 min (*S*), t_2 = 20.1 min (*R*).



(S)-1-(6-fluoro-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3o)[2]: R_f = 0.33 (PE/EtOAc, 5:1); 19% yield, 84% ee; $[\alpha]^{20}_D$ = + 156.8 (*c* 0.76, $CHCl_3$); Yellow semisolid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 -7.39 (m, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.26 (dd, J = 13.1, 5.8 Hz, 1H), 6.69 (dd, J = 8.8, 5.3 Hz, 1H), 6.46 (dd, J = 9.8, 2.9 Hz, 1H), 6.33 (td, J = 8.5, 2.9 Hz, 1H), 5.41 (br, 1H), 3.94 (AB quartet, $\Delta\delta_{AB}$ = 0.036, J_{AB} = 10.7 Hz, 2H), 3.36 (d, J = 17.7 Hz, 1H), 3.06 (d, J = 17.7 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.5, 158.3 (d, $^1J_{C\text{-}F}$ = 236.0 Hz), 141.0, 138.6, 133.70 (d, $^3J_{C\text{-}F}$ = 11.0 Hz), 128.8, 127.6, 125.6, 116.9(d, $^3J_{C\text{-}F}$ = 9.7 Hz), 104.4(d, $^2J_{C\text{-}F}$ = 23.2 Hz), 102.3(d,$^2J_{C\text{-}F}$ = 26.6 Hz), 73.8, 55.3, 47.3, 31.7; HPLC (Chiralcel IC column,hexane/iPrOH = 98/2, 0.8 mL/min, 220 nm): t_1 = 13.0 min (*S*), t_2 = 14.5 min (*R*).

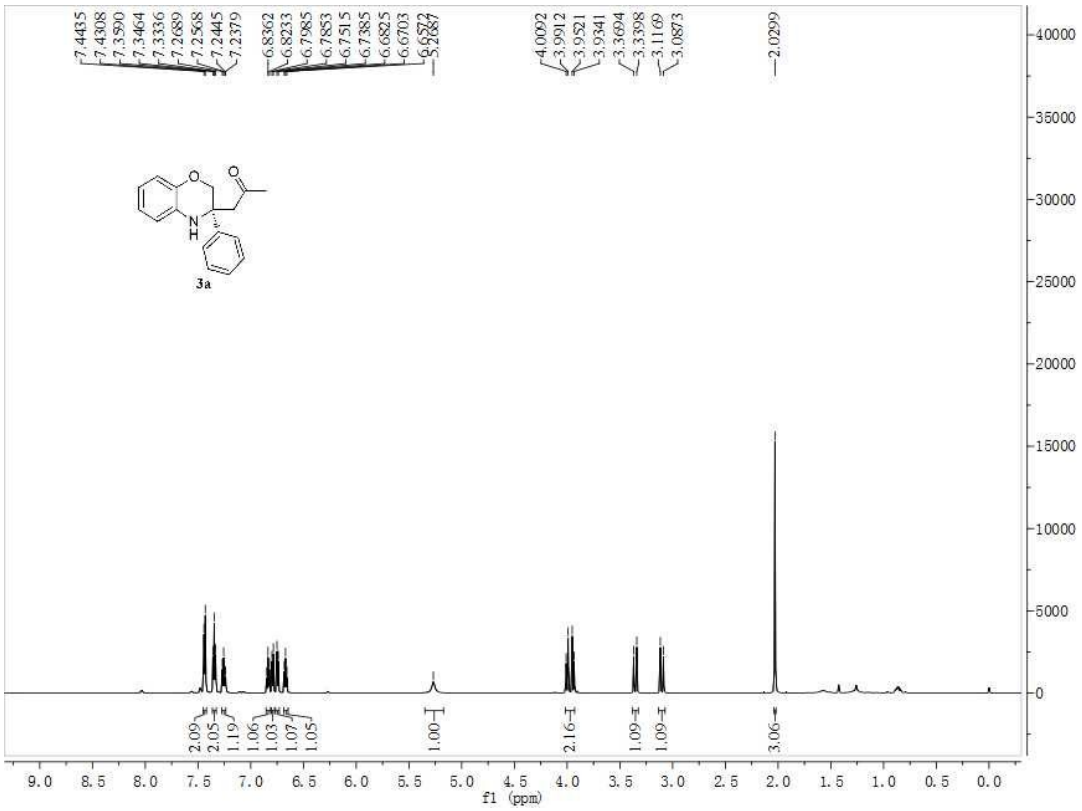


(S)-1-(6-nitro-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)propan-2-one (3p)[2]: R_f =

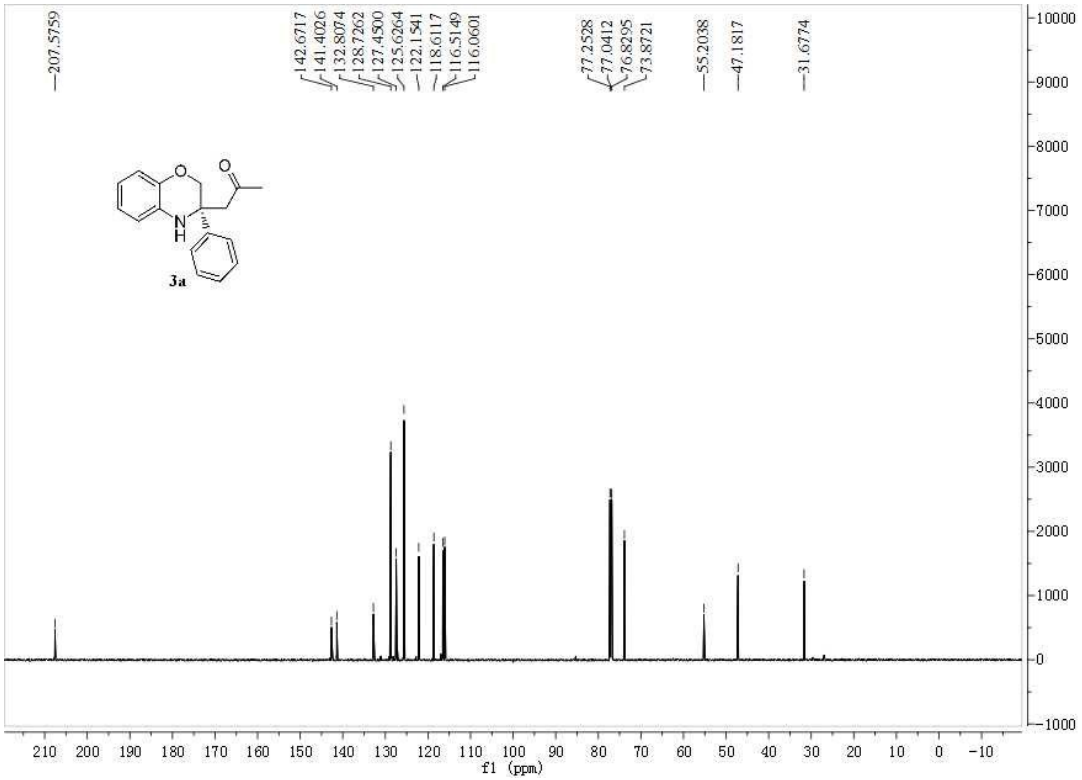
0.18 (PE/EtOAc, 3:1); 16% yield, 73% ee; $[\alpha]^{20}_{D}$ = + 106.3 (*c* 0.36, $CHCl_3$); Yellow solid; m.p. 136.7-138.1 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.39 (dd, *J* = 15.5, 7.3 Hz, 4H), 7.30 (d, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.72 (br, 1H), 4.09 (s, 2H), 3.39 (d, *J* = 17.6 Hz, 1H), 2.99 (d, *J* = 17.6 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.1, 148.0, 142.8, 140.2, 133.1, 129.0, 127.9, 125.5, 116.4, 114.8, 110.8, 73.9, 55.1, 47.3, 31.7; HPLC (Chiralcel AD-H column, hexane/iPrOH = 75/25, 0.8 mL/min, 254 nm): t_1 =13.4 min (*R*), t_2 = 16.1 min (*S*).

5. ^{1}H NMR, ^{13}C NMR and HPLC spectra for Mannich products

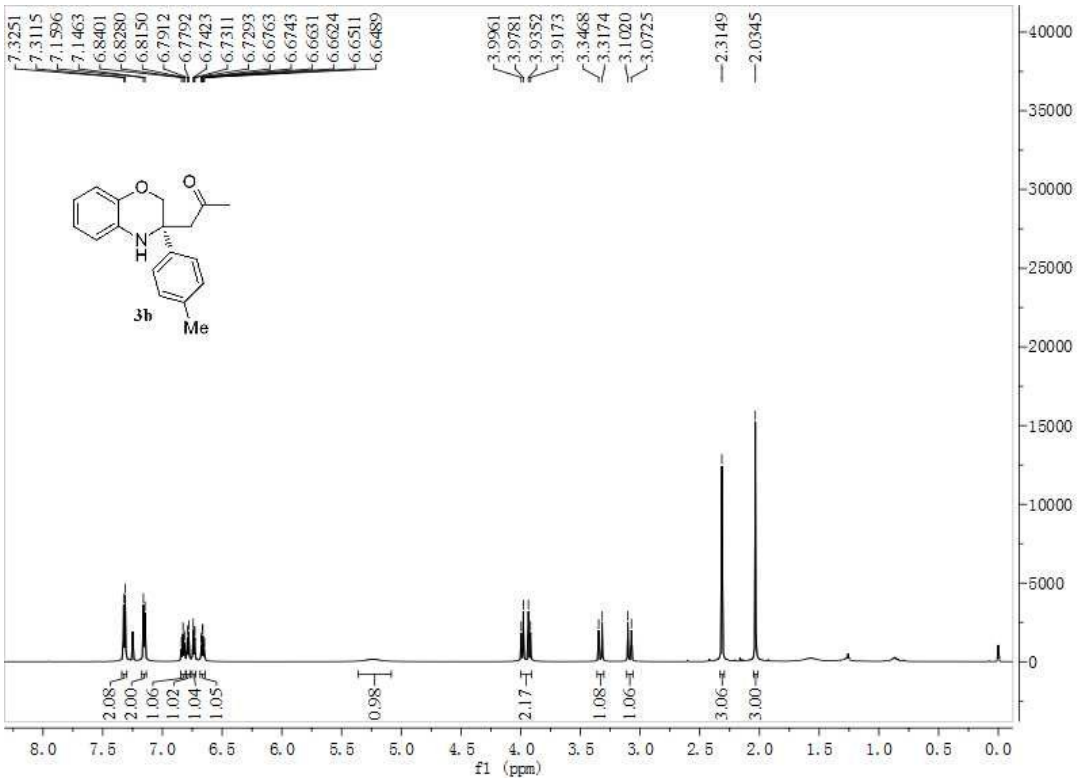
^{1}H NMR Spectrum ($CDCl_3$) of **3a**



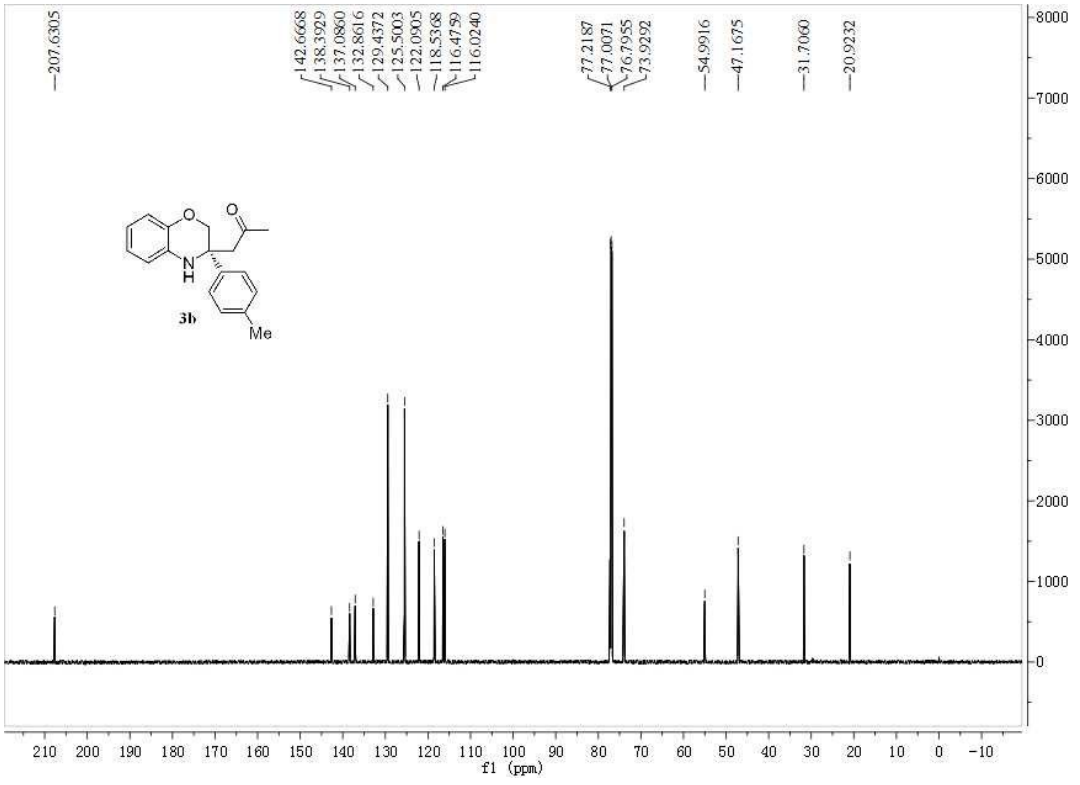
^{13}C NMR Spectrum ($CDCl_3$) of **3a**



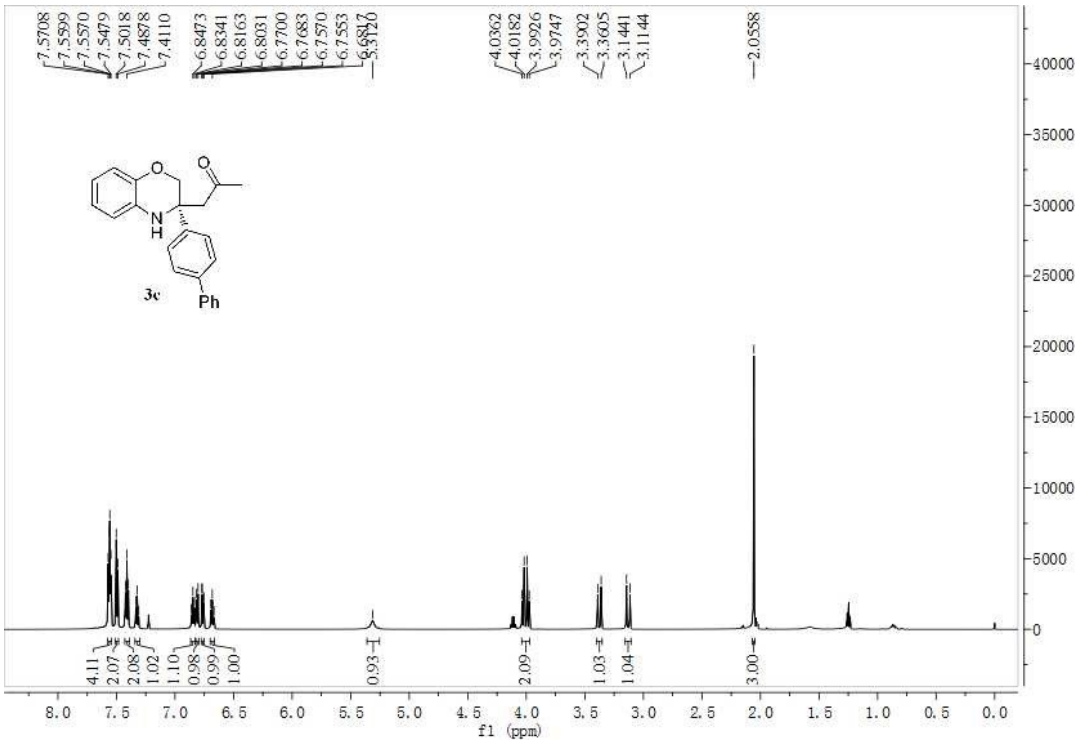
^{1}H NMR Spectrum ($CDCl_3$) of **3b**



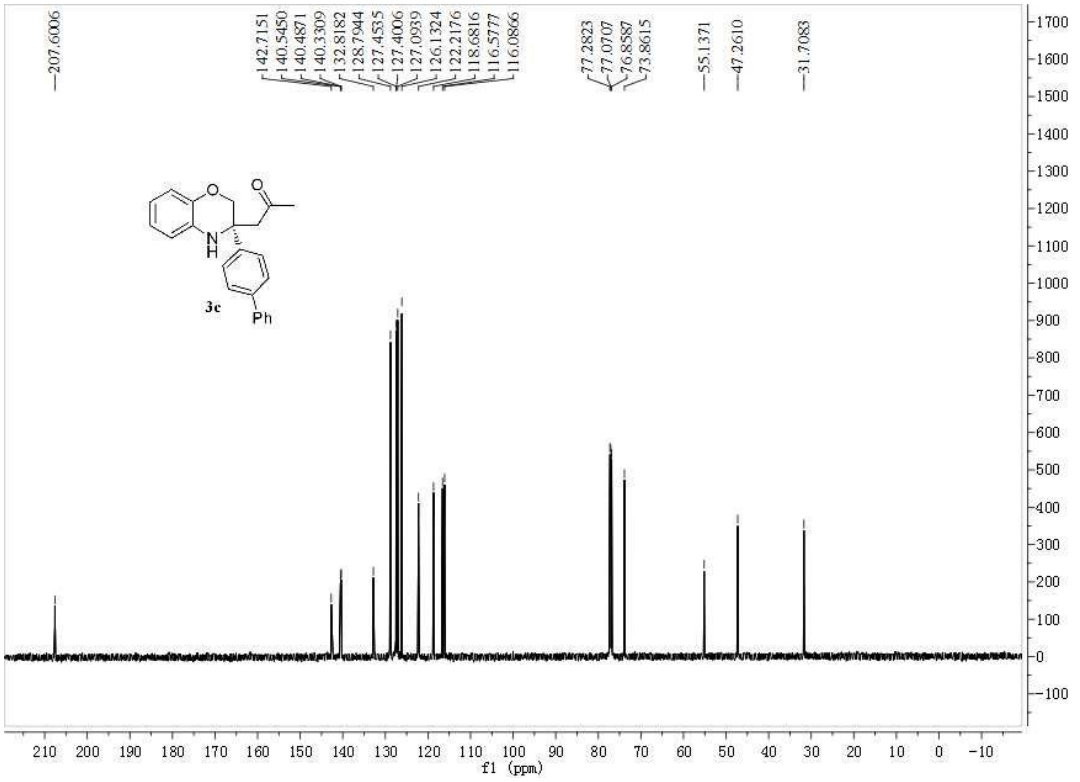
^{13}C NMR Spectrum ($CDCl_3$) of **3b**



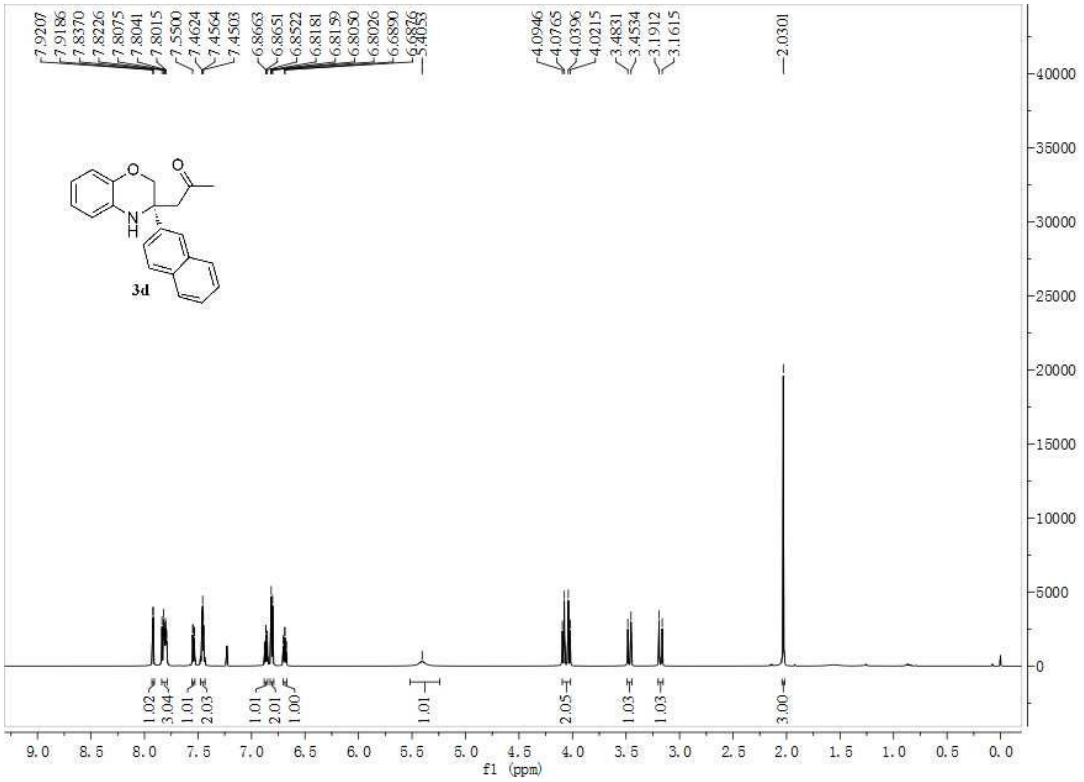
^{1}H NMR Spectrum ($CDCl_3$) of **3c**



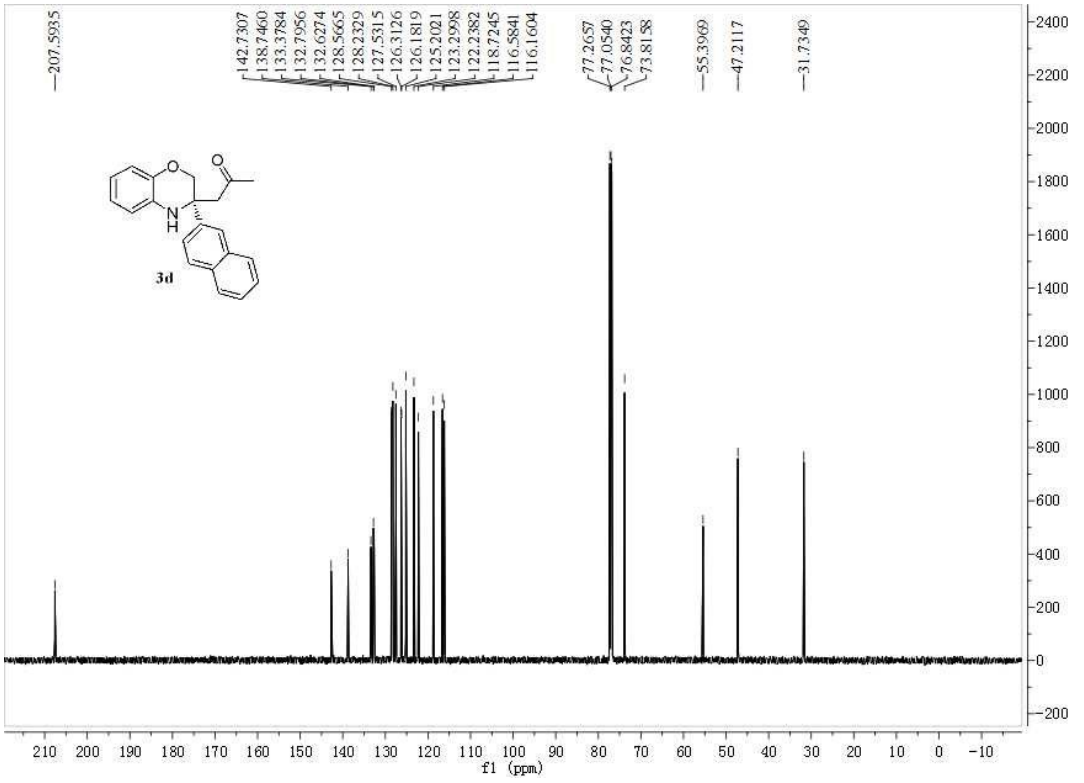
^{13}C NMR Spectrum ($CDCl_3$) of **3c**



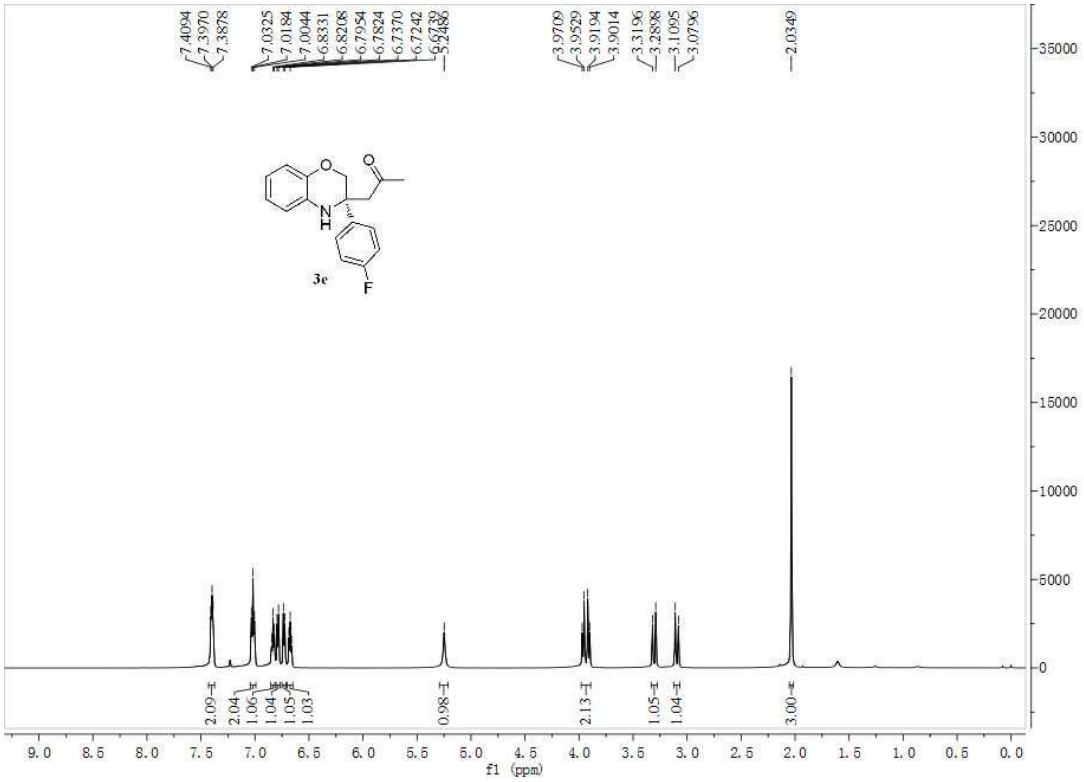
^{1}H NMR Spectrum ($CDCl_3$) of **3d**



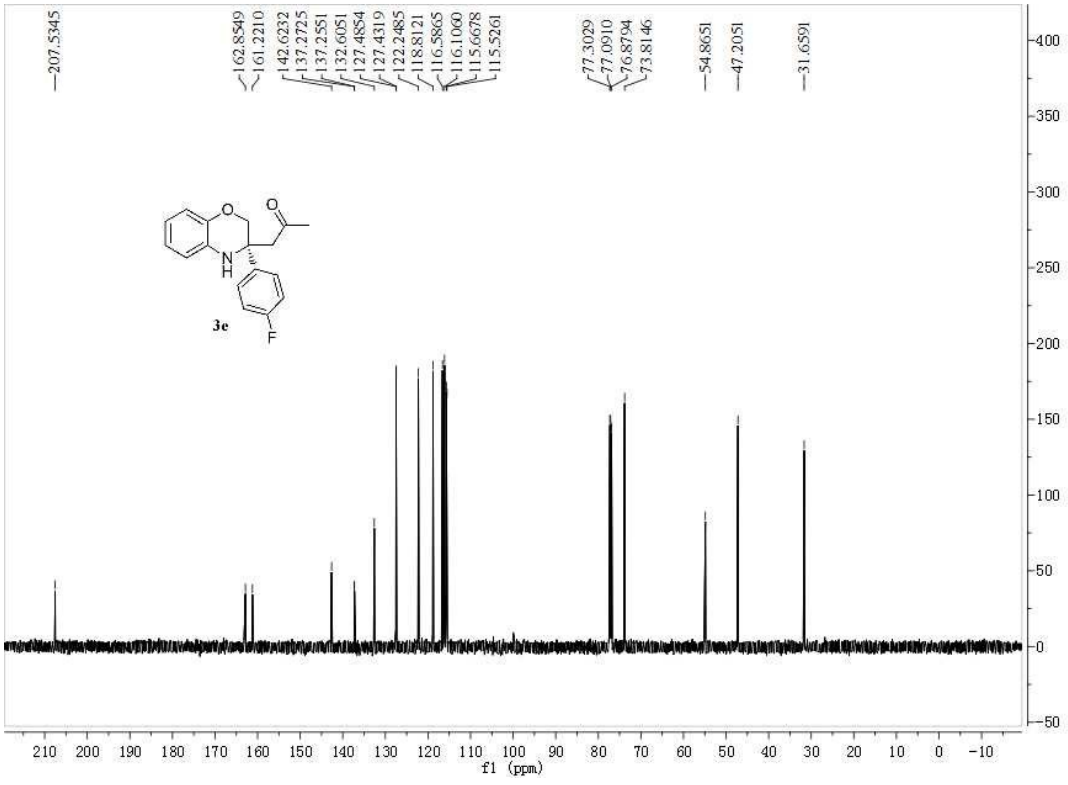
^{13}C NMR Spectrum ($CDCl_3$) of **3d**



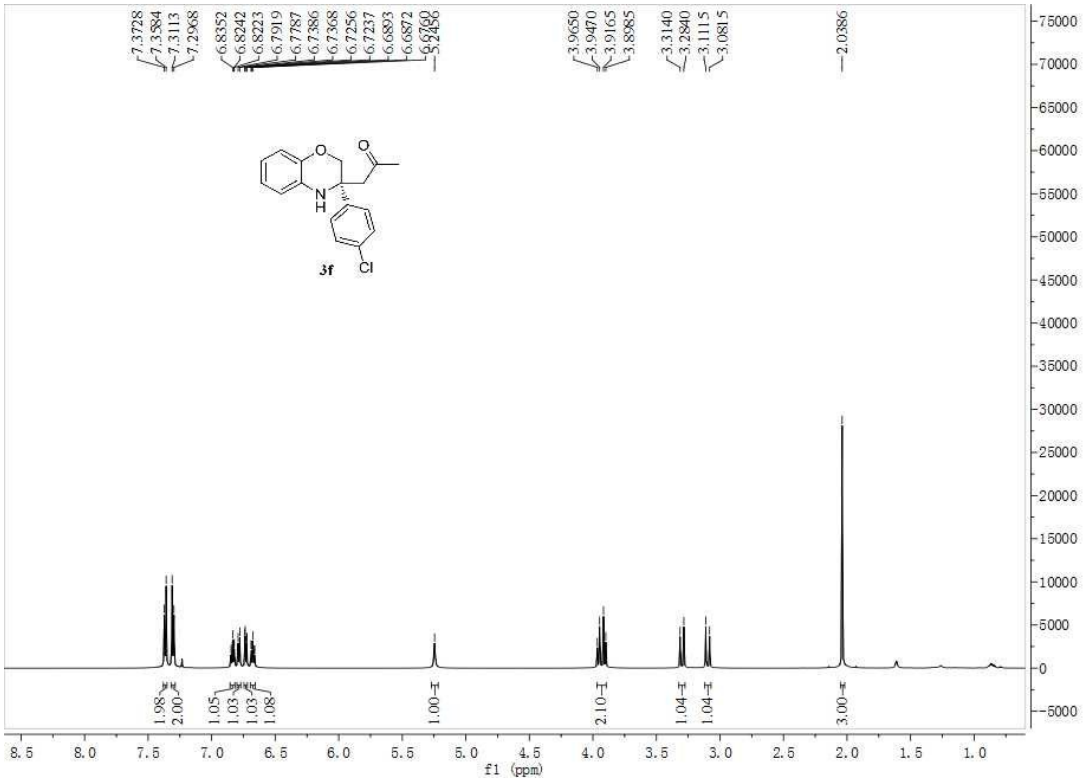
^{1}H NMR Spectrum ($CDCl_3$) of **3e**



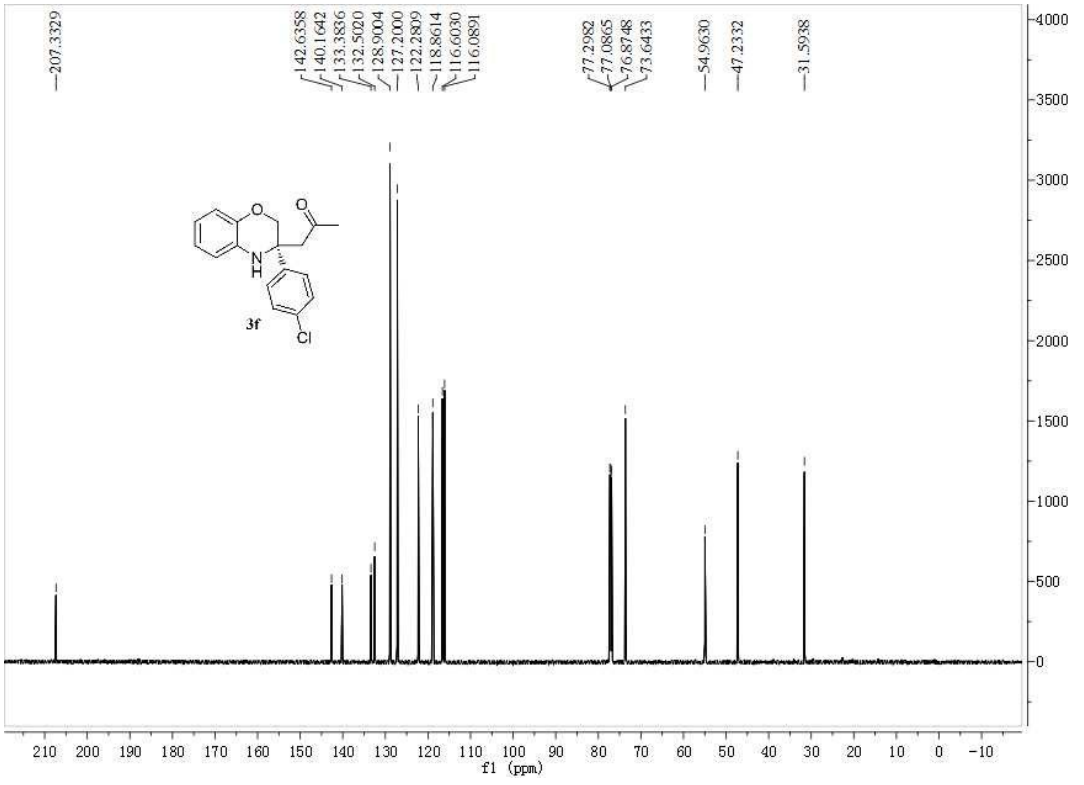
^{13}C NMR Spectrum ($CDCl_3$) of **3e**



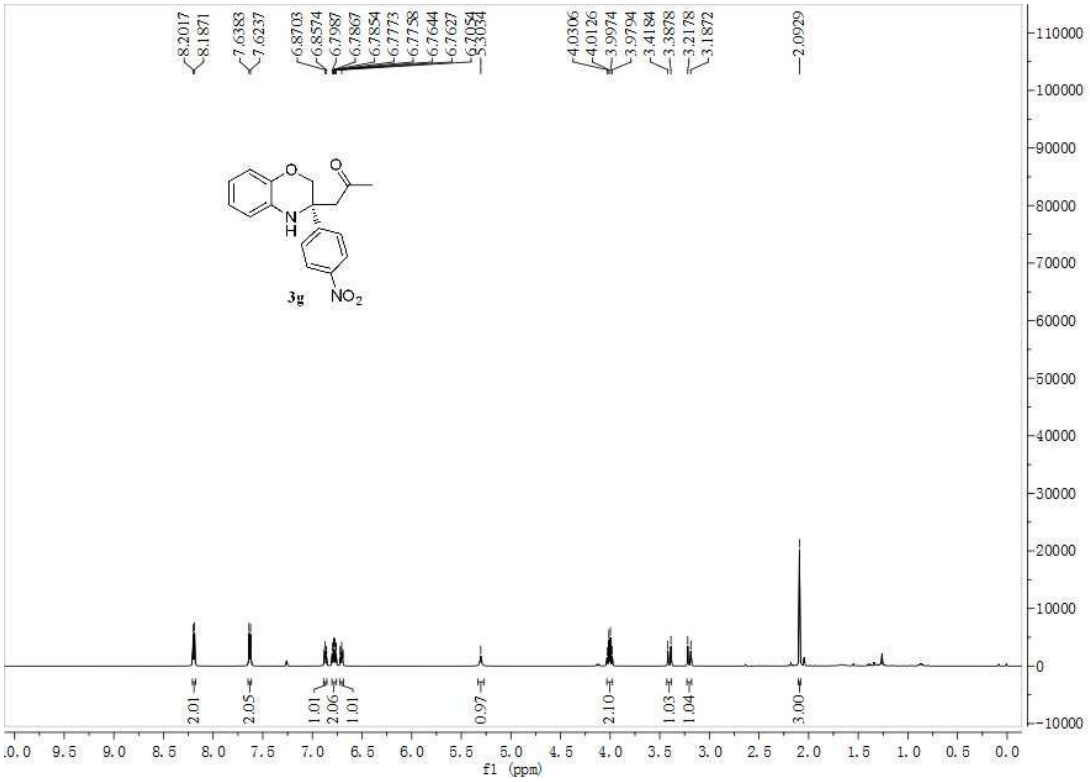
^{1}H NMR Spectrum ($CDCl_3$) of **3f**



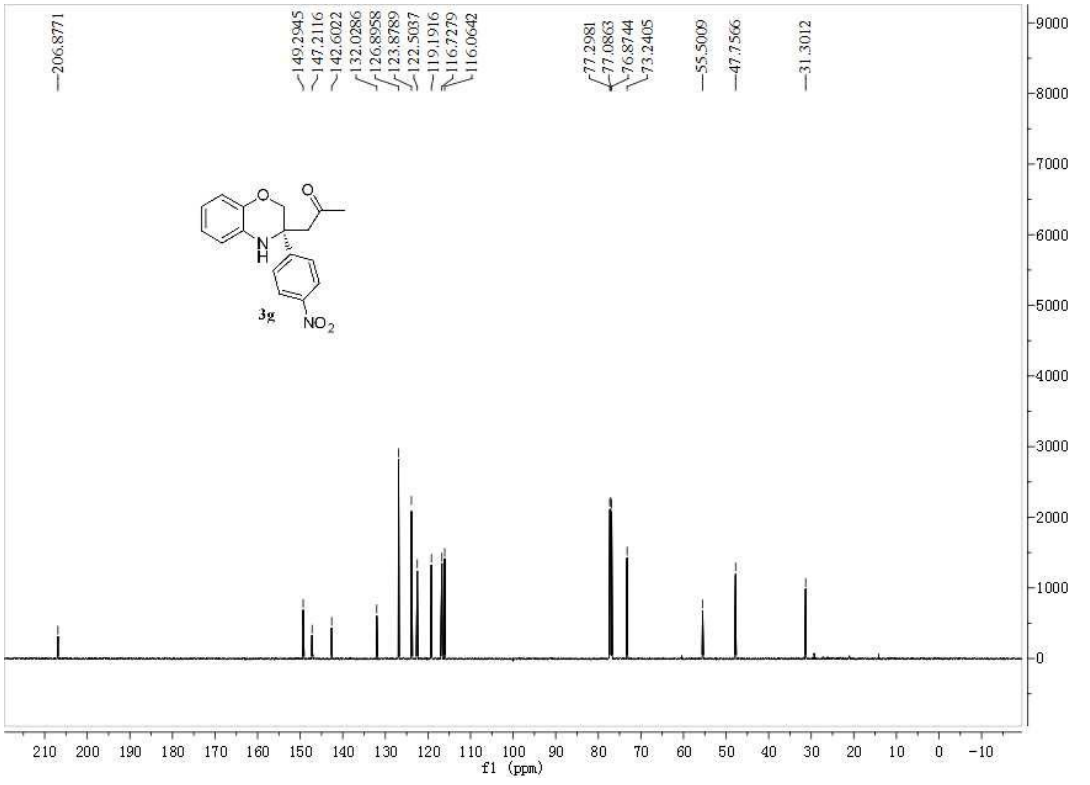
^{13}C NMR Spectrum ($CDCl_3$) of **3f**



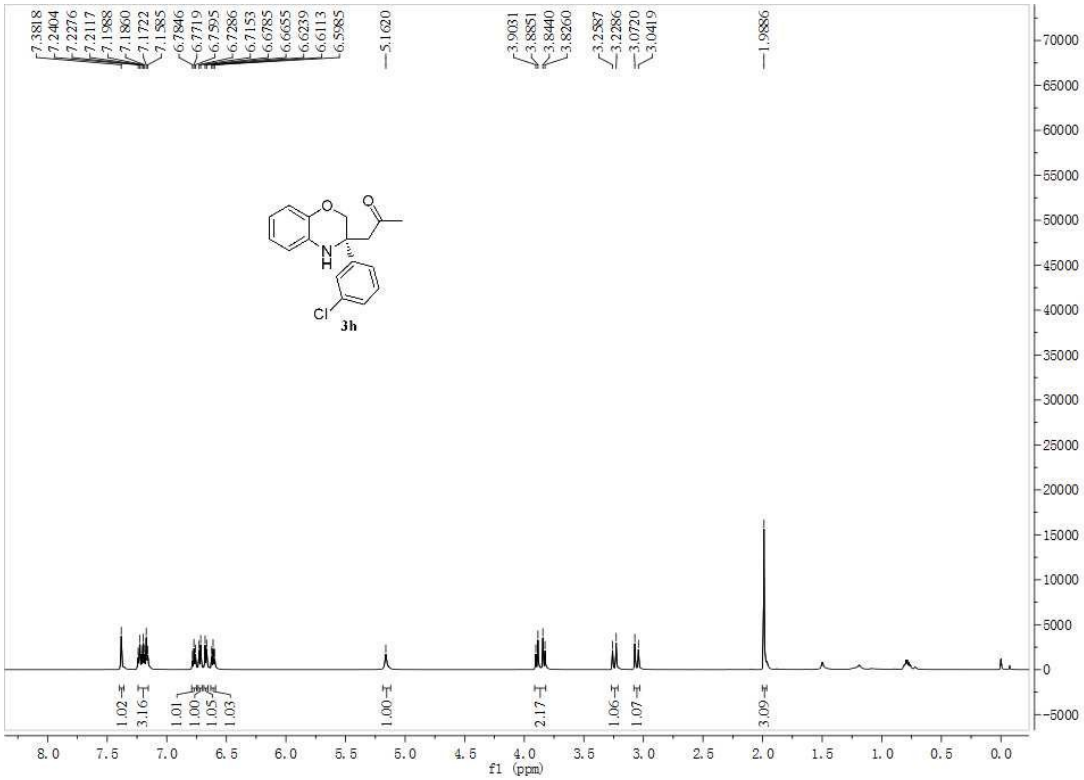
^{1}H NMR Spectrum ($CDCl_3$) of **3g**



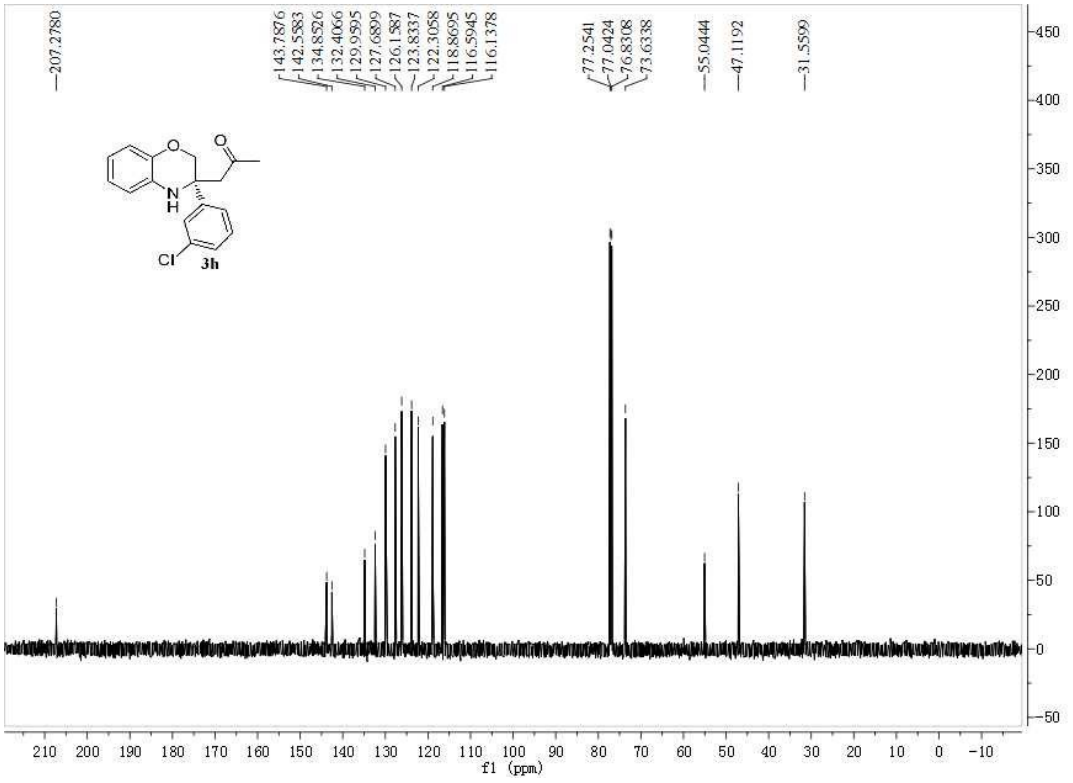
^{13}C NMR Spectrum ($CDCl_3$) of **3g**



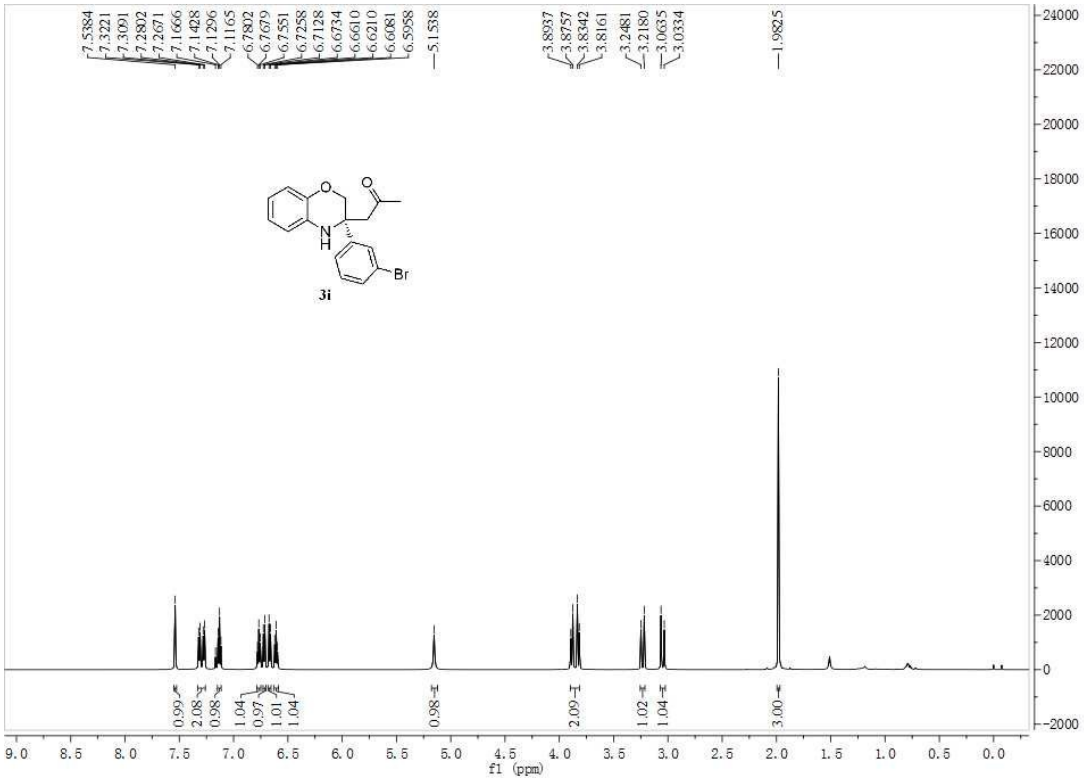
^{1}H NMR Spectrum ($CDCl_3$) of **3h**



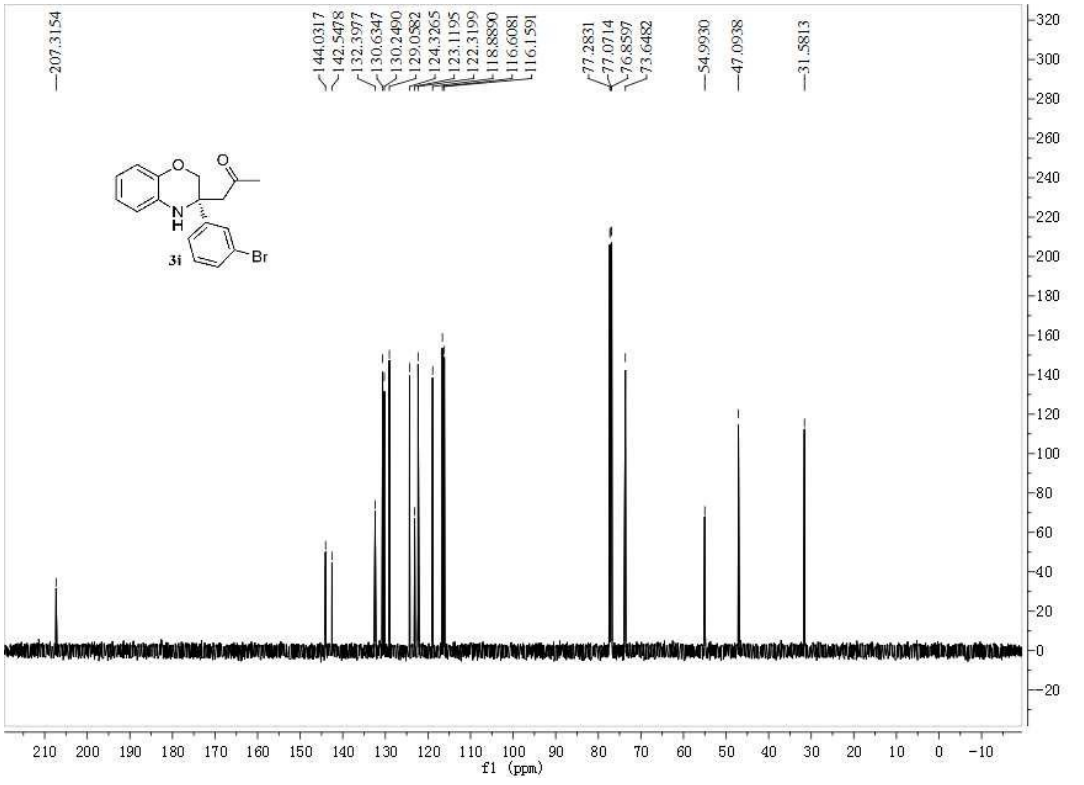
^{13}C NMR Spectrum ($CDCl_3$) of **3h**



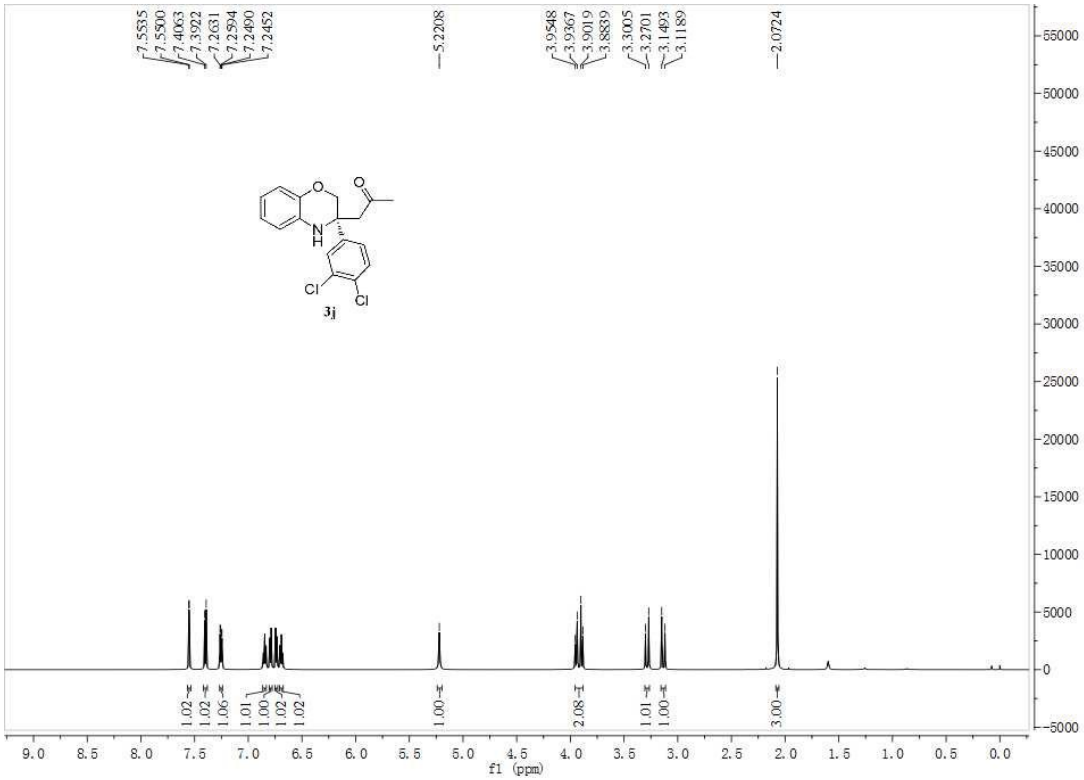
^{1}H NMR Spectrum ($CDCl_3$) of **3i**



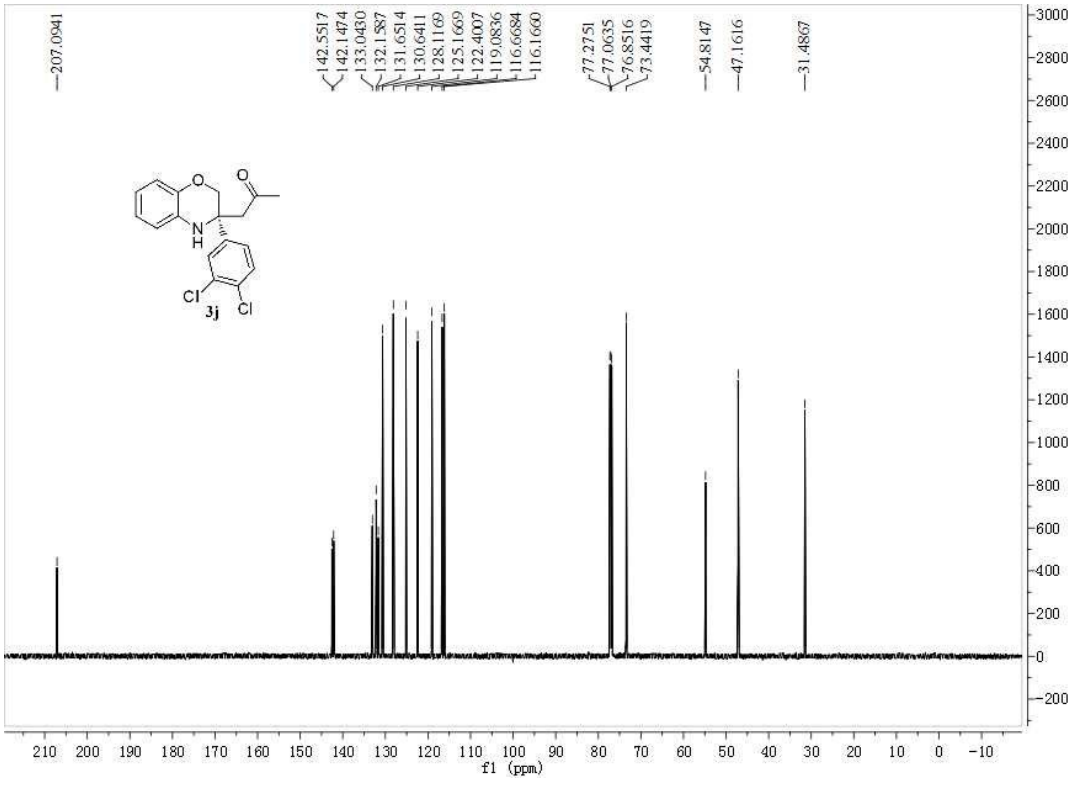
^{13}C NMR Spectrum ($CDCl_3$) of **3i**



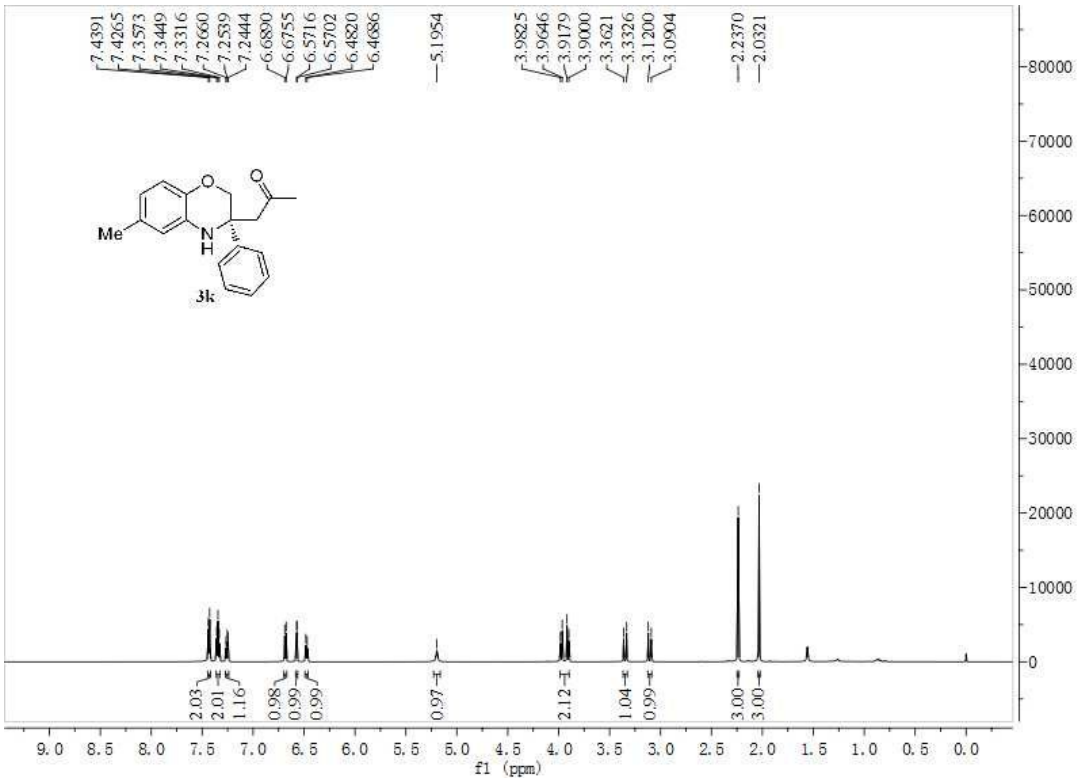
^{1}H NMR Spectrum ($CDCl_3$) of **3j**



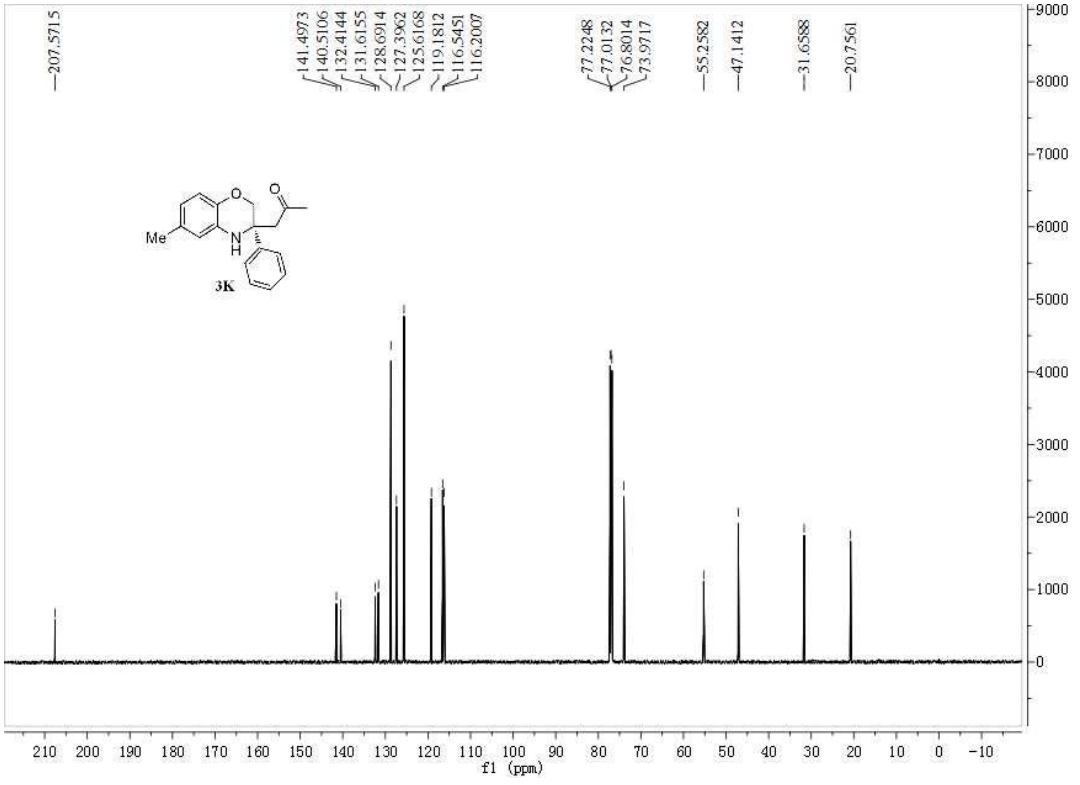
^{13}C NMR Spectrum ($CDCl_3$) of **3j**



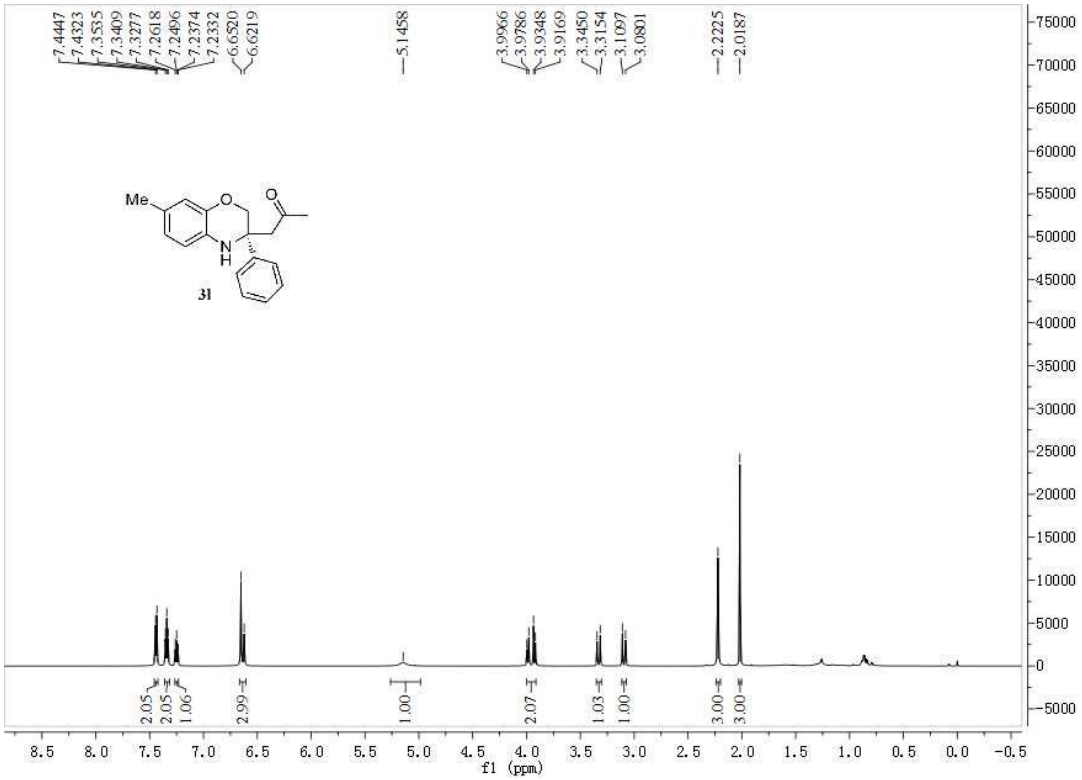
^{1}H NMR Spectrum ($CDCl_3$) of **3k**



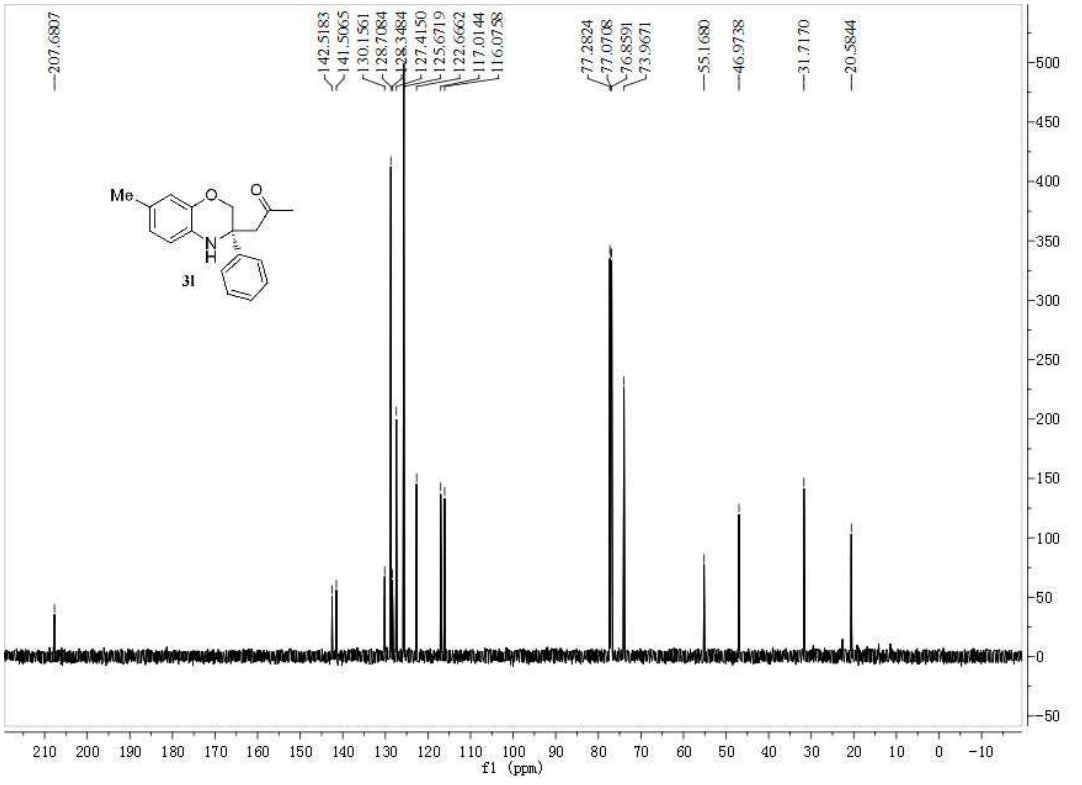
^{13}C NMR Spectrum ($CDCl_3$) of **3k**



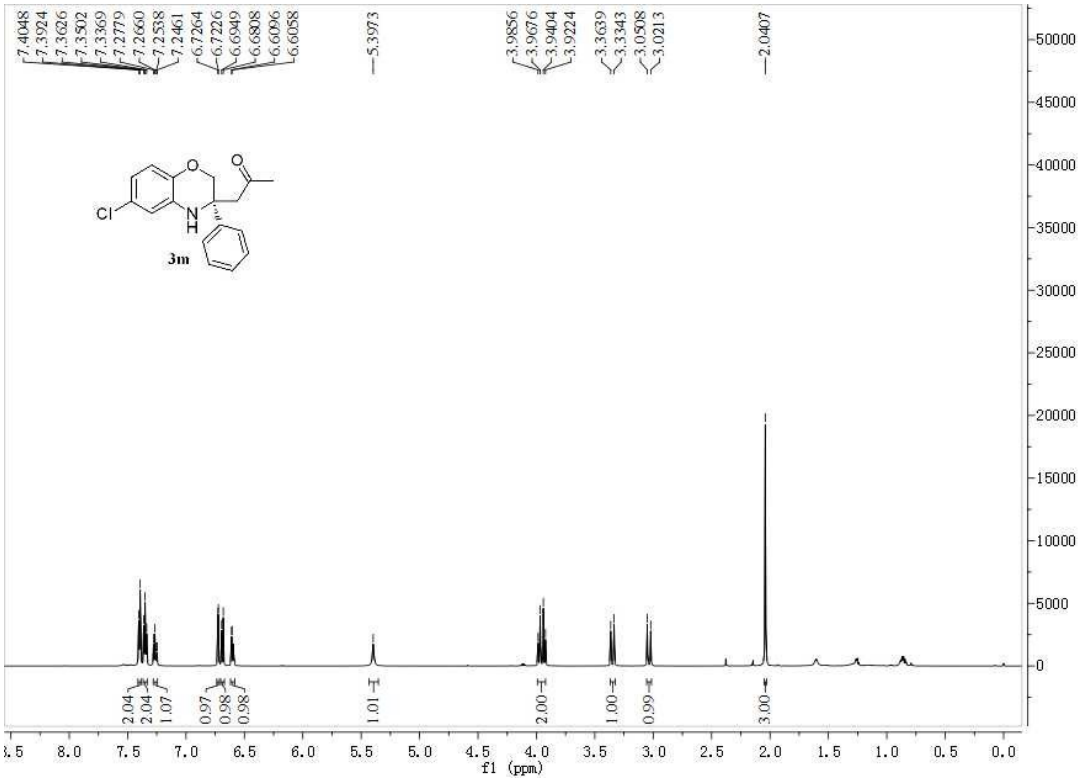
^{1}H NMR Spectrum ($CDCl_3$) of **3l**



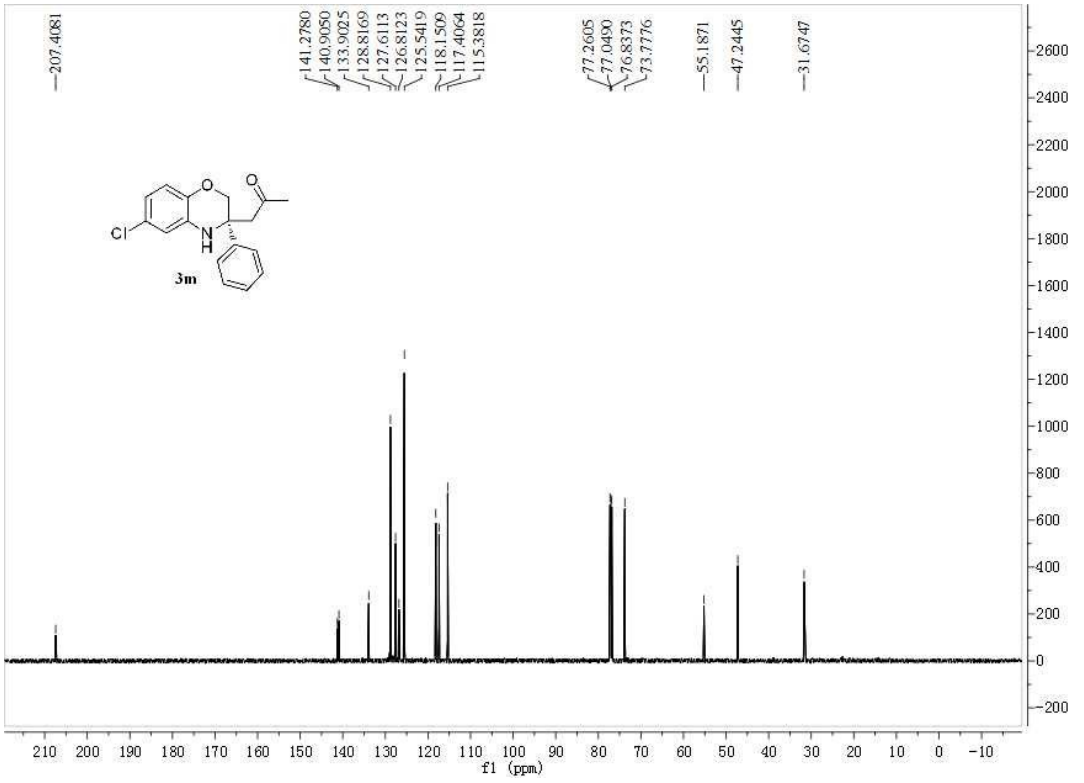
^{13}C NMR Spectrum ($CDCl_3$) of **3l**



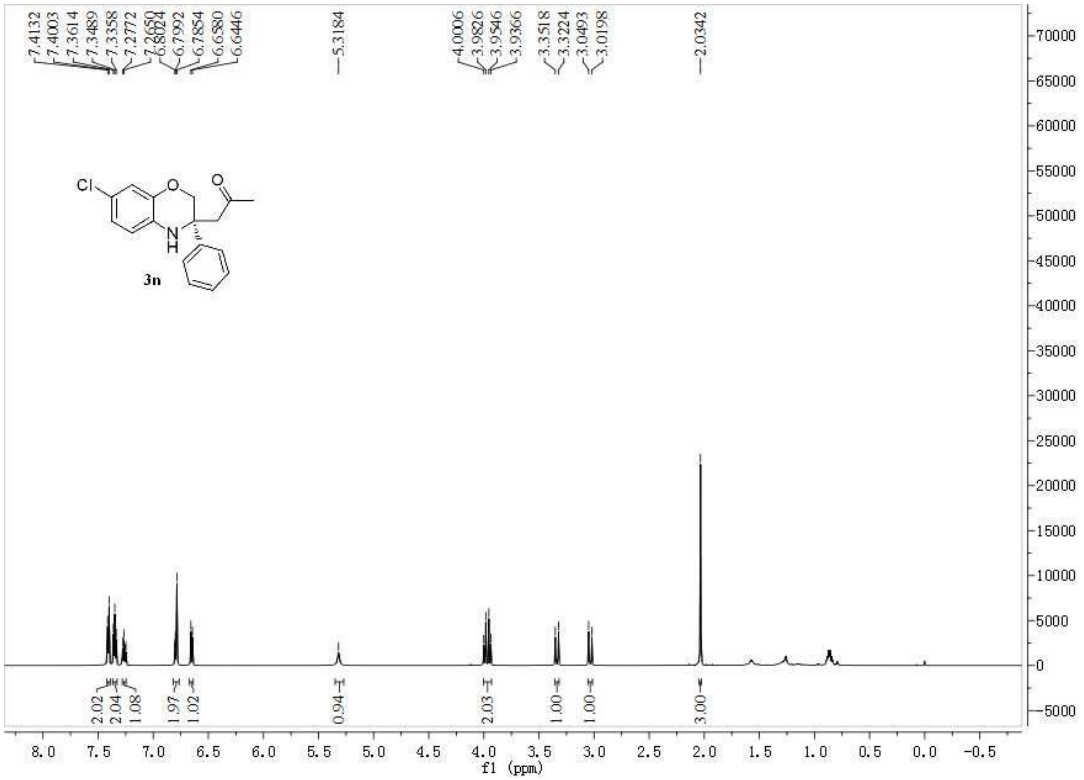
^{1}H NMR Spectrum ($CDCl_3$) of **3m**



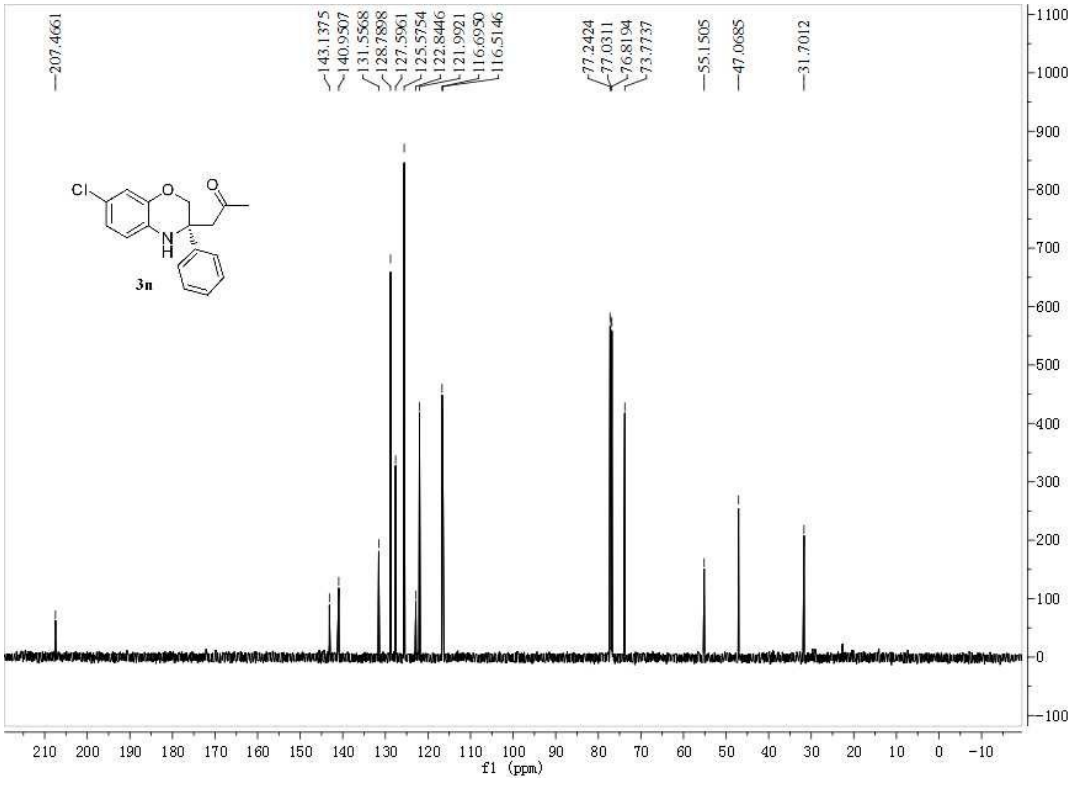
^{13}C NMR Spectrum ($CDCl_3$) of **3m**



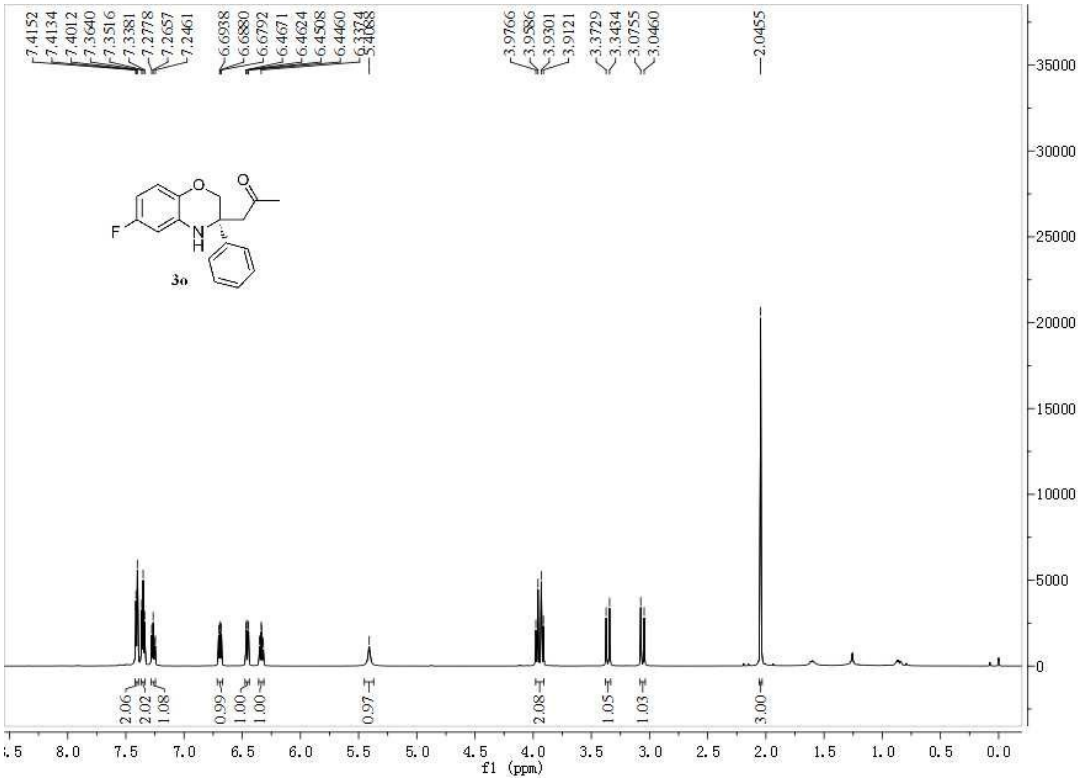
^{1}H NMR Spectrum ($CDCl_3$) of **3n**



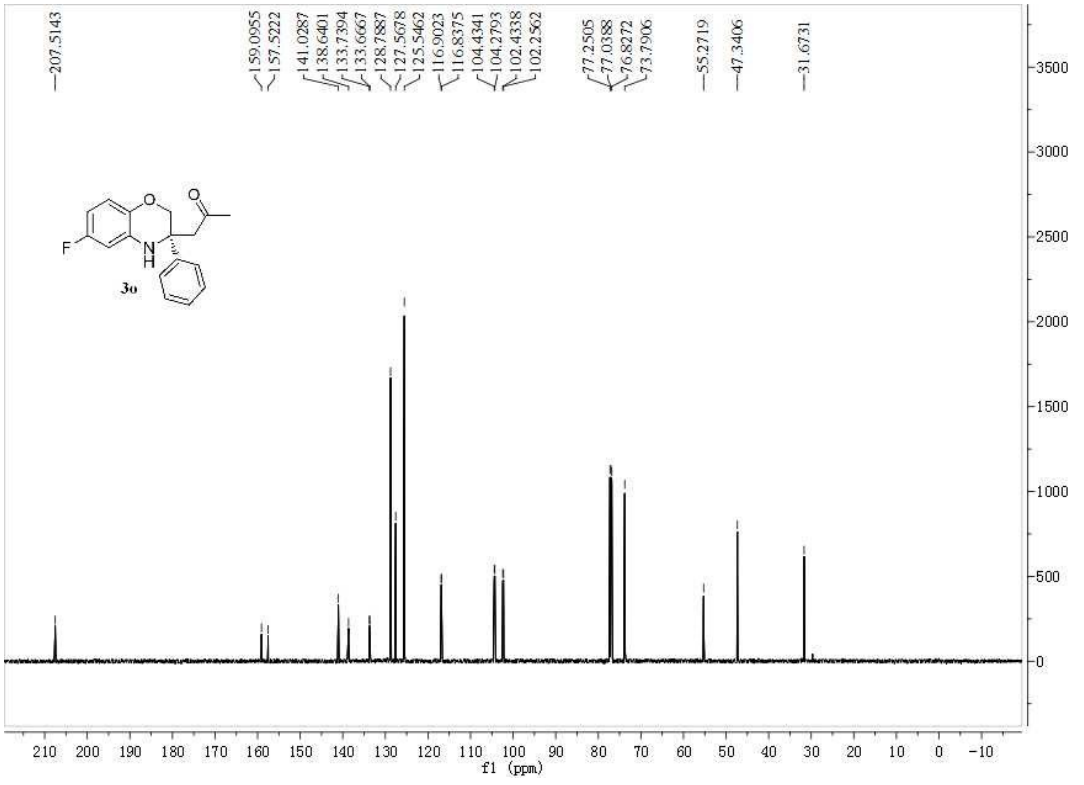
^{13}C NMR Spectrum ($CDCl_3$) of **3n**



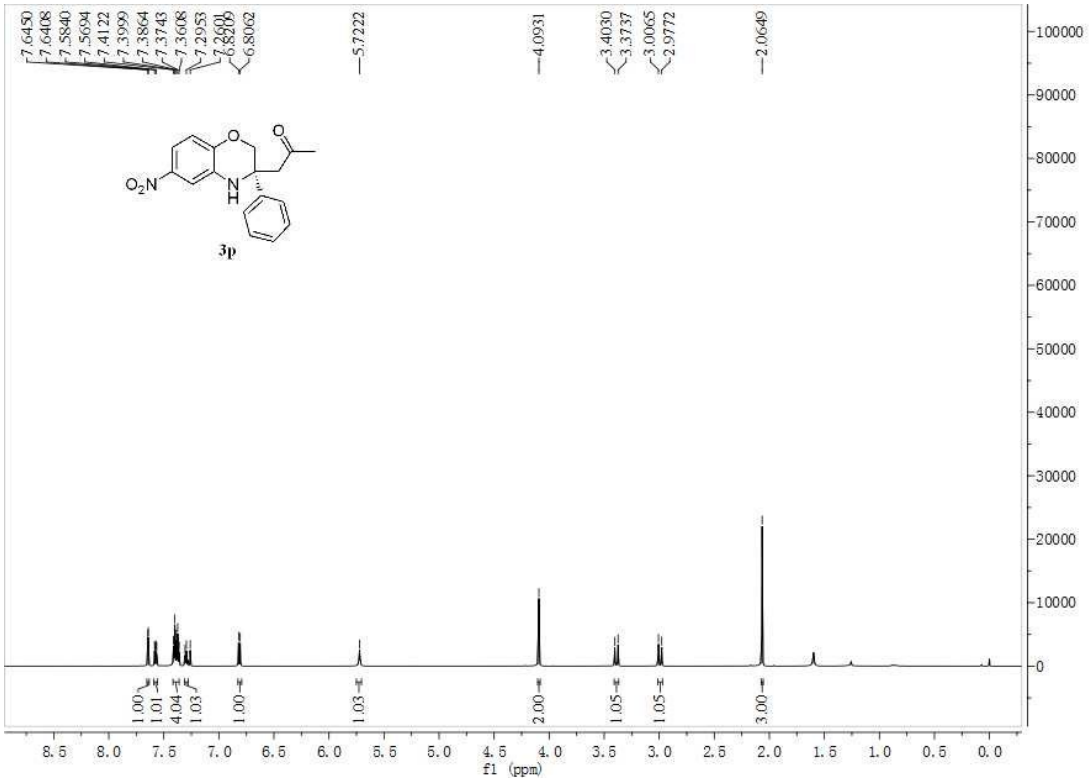
^{1}H NMR Spectrum ($CDCl_3$) of **3o**



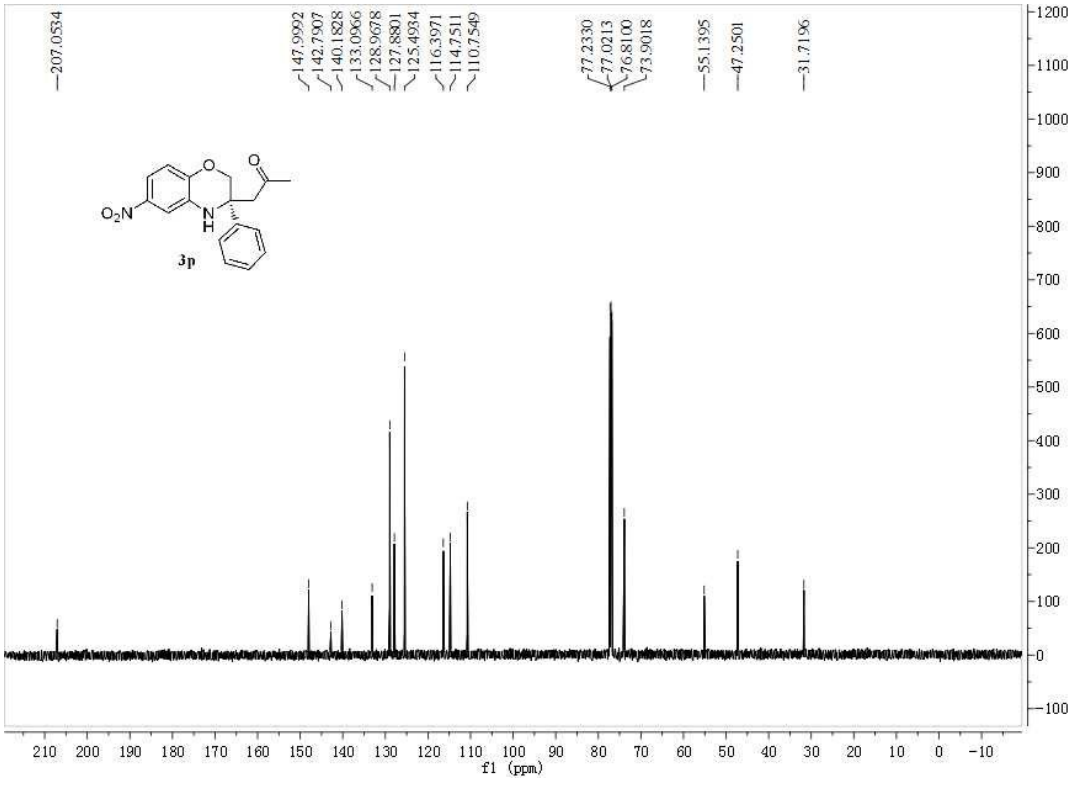
^{13}C NMR Spectrum ($CDCl_3$) of **3o**



^{1}H NMR Spectrum ($CDCl_3$) of **3p**

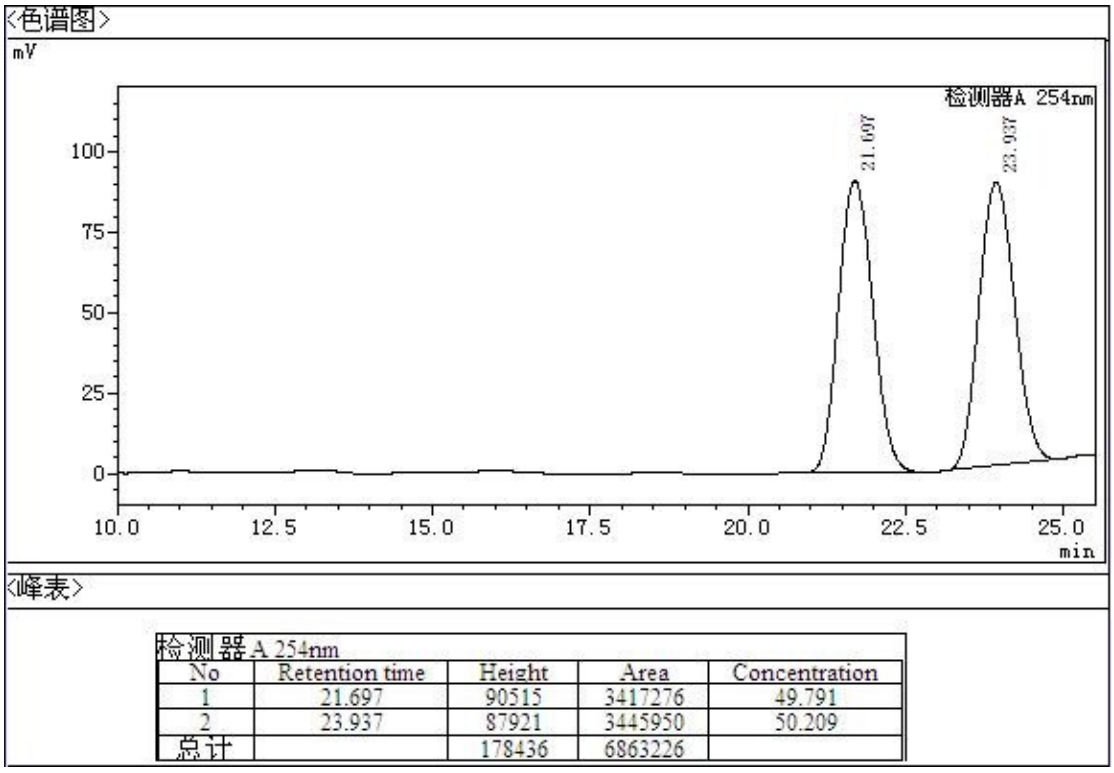


^{13}C NMR Spectrum ($CDCl_3$) of **3p**



HPLC chromatograms

3a (Racemic)

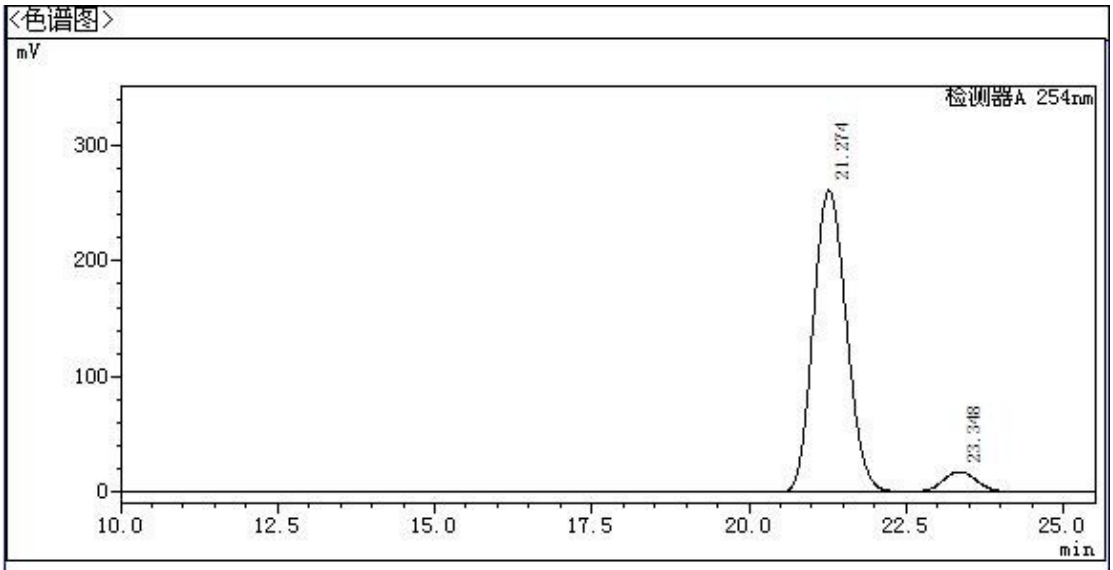


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	21.697	90515	3417276	49.791
2	23.937	87921	3445950	50.209
总计		178436	6863226	

3a (Chiral)

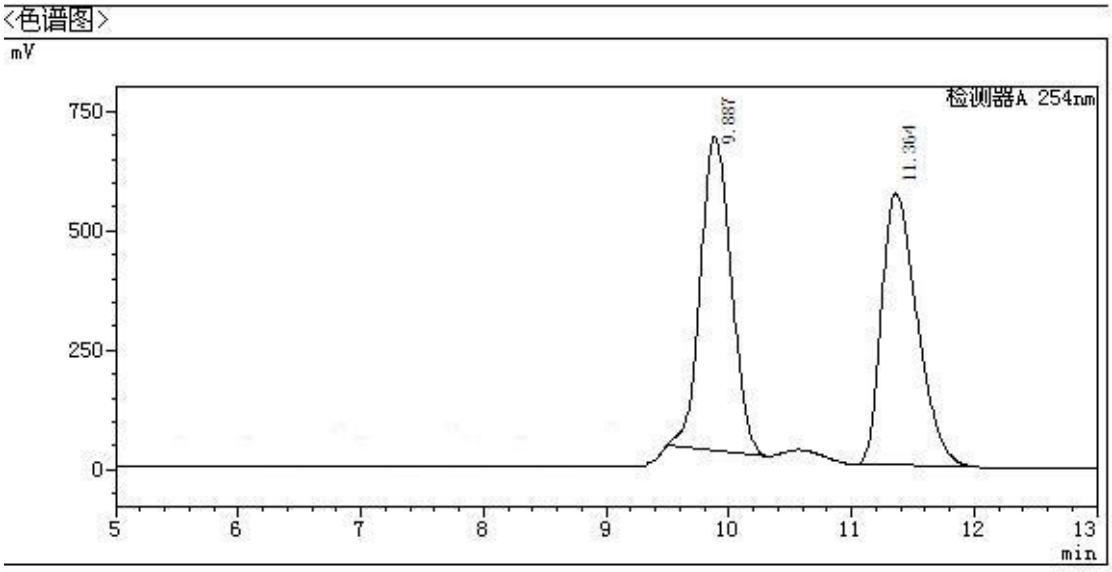


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	21.274	260399	9525248	93.688
2	23.348	17338	641783	6.312
总计		277738	10167031	

3b (Racemic)

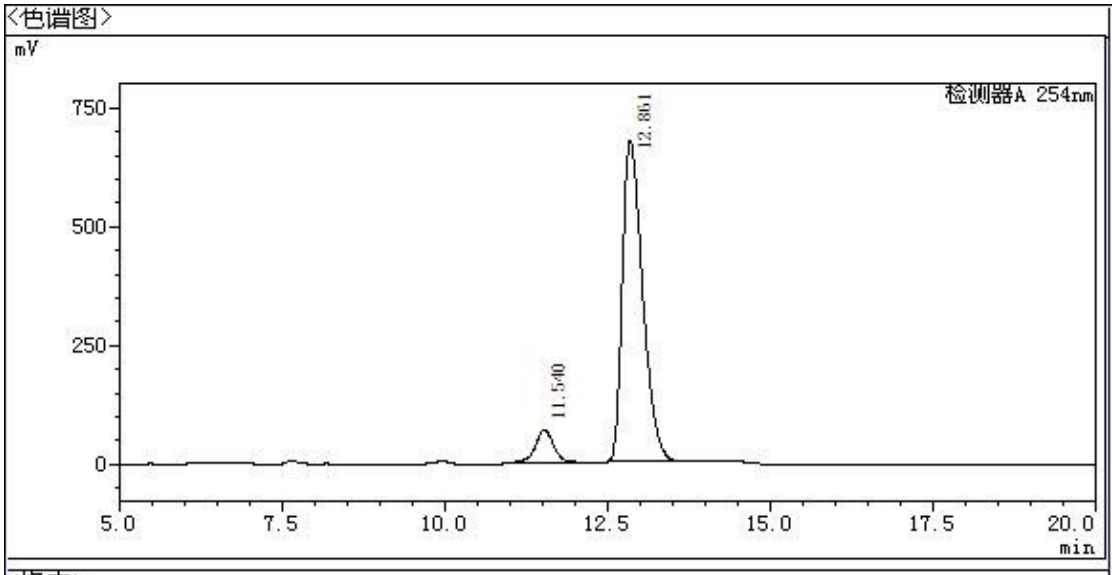


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	9.887	657862	11438909	50.008
2	11.364	567228	11435333	49.992
总计		1225090	22874243	

3b (Chiral)



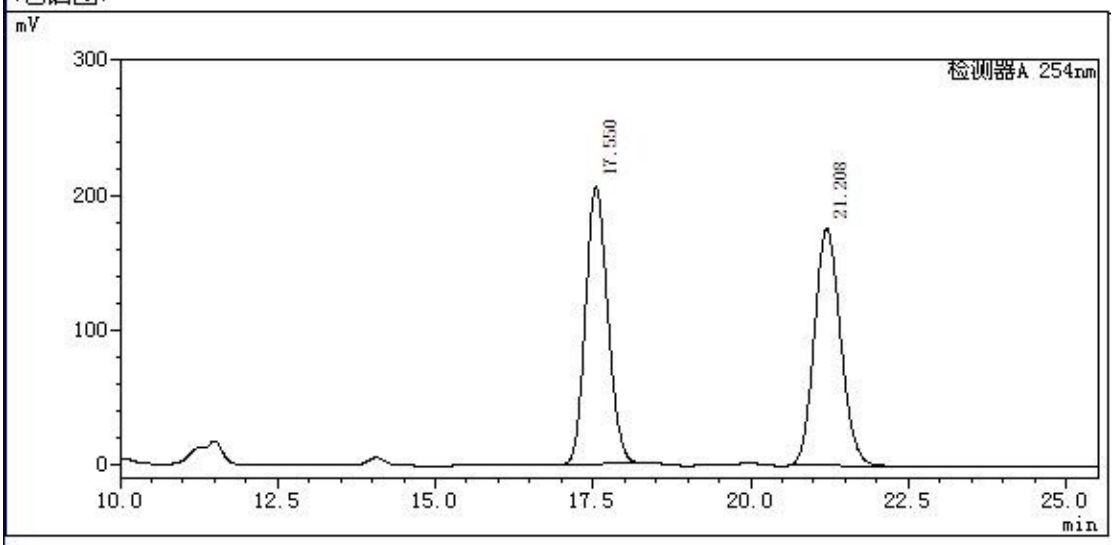
〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	11.540	70272	1389782	8.703
2	12.861	675856	14580027	91.297
总计		746128	15969809	

3c (Racemic)

<色谱图>



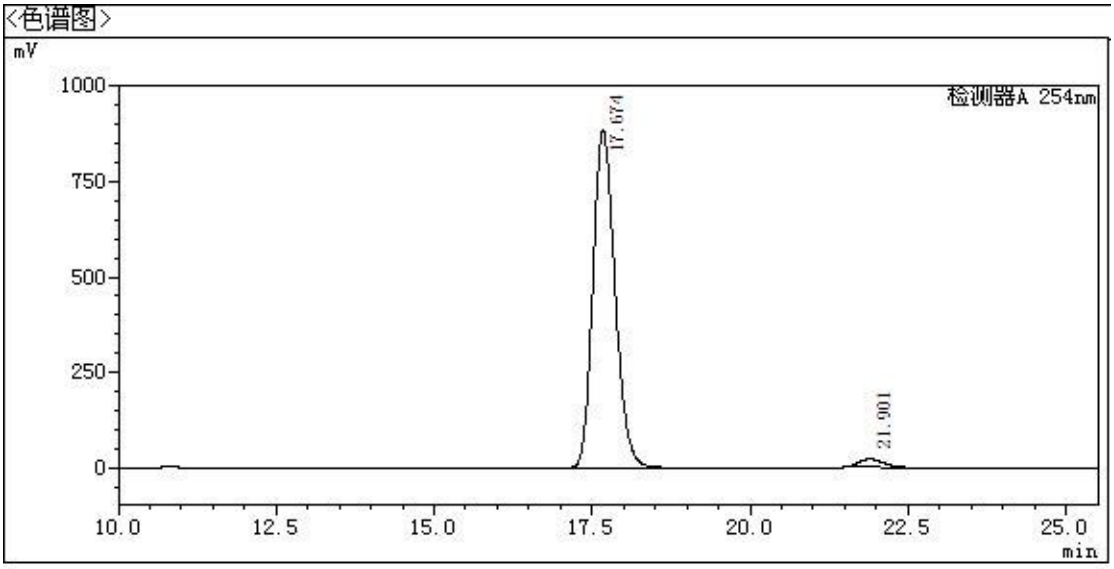
<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	17.550	205461	5026731	49.804
2	21.208	175138	5066200	50.196
总计		380600	10092931	

3c (Chiral)

<色谱图>

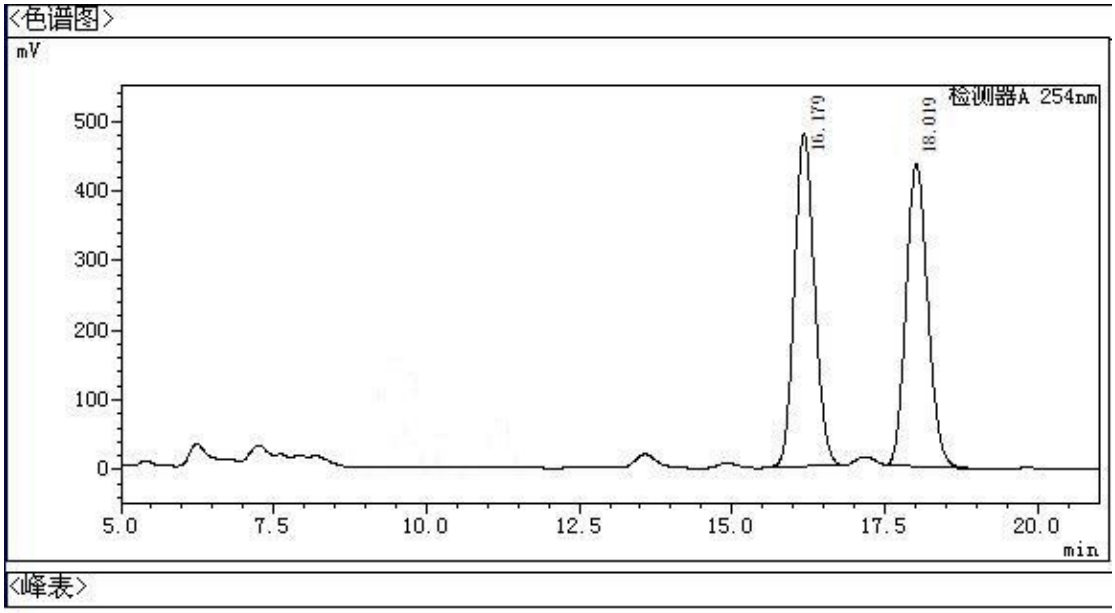


<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	17.674	884811	21455126	97.370
2	21.901	21440	579525	2.630
总计		906251	22034651	

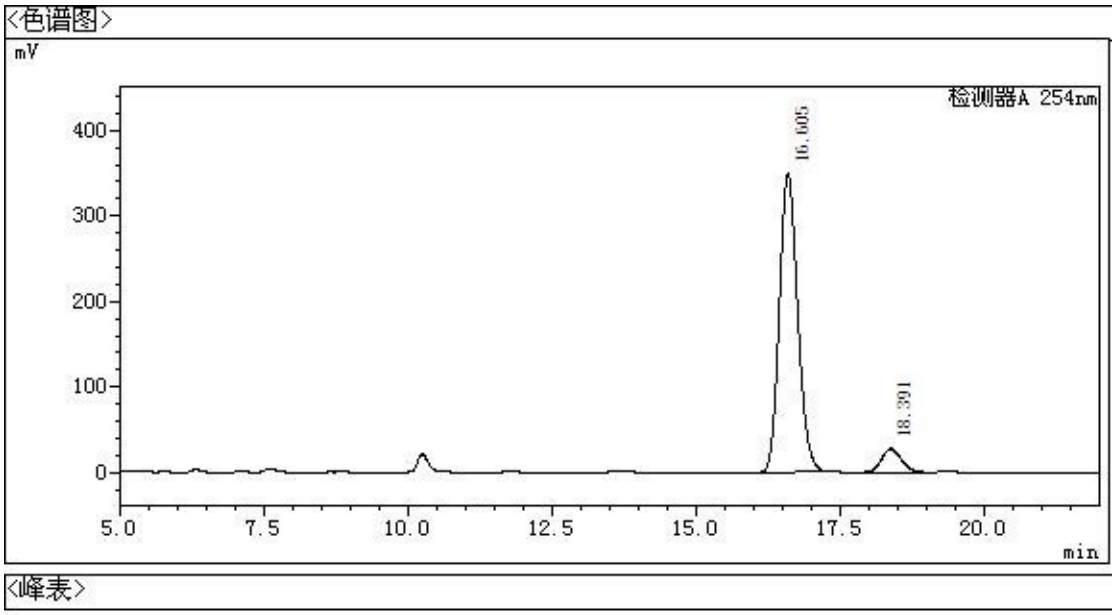
3d (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	16.179	477231	10894328	50.545
2	18.019	434080	10659262	49.455
总计		911311	21553590	

3d (Chiral)

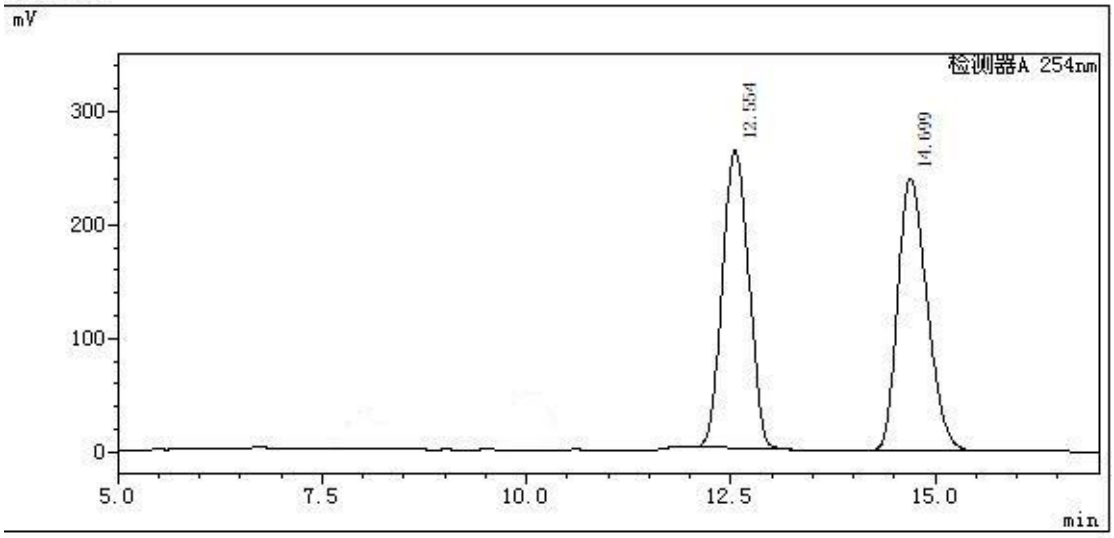


检测器A 254nm

No	Retention time	Height	Area	Concentration
1	16.605	348735	7714389	92.298
2	18.391	27240	643707	7.702
总计		375975	8358096	

3e (Racemic)

<色谱图>

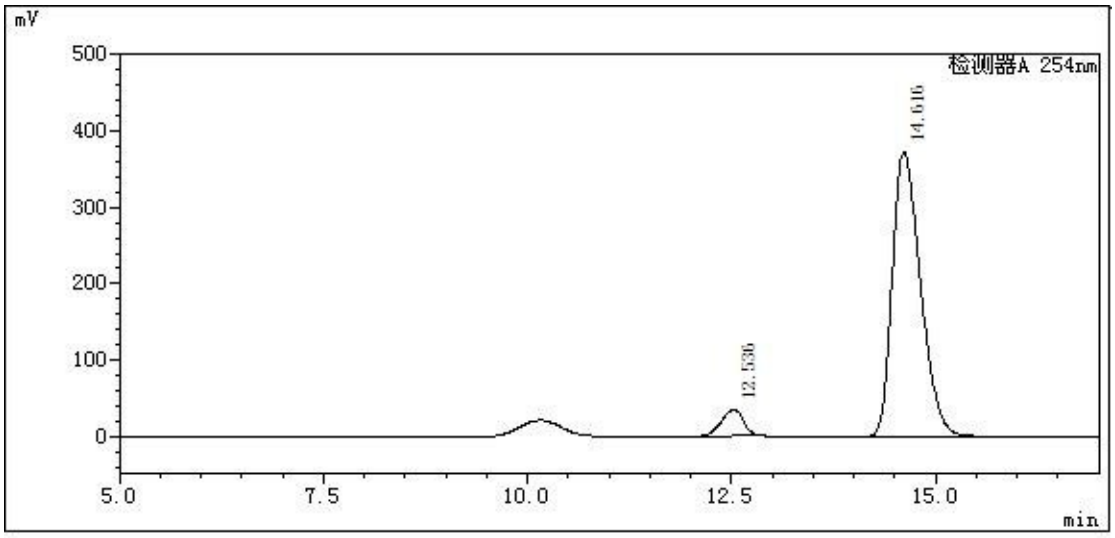


<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	12.554	262569	5929513	49.575
2	14.699	240665	6031260	50.425
总计		503234	11960773	

3e (Chiral)

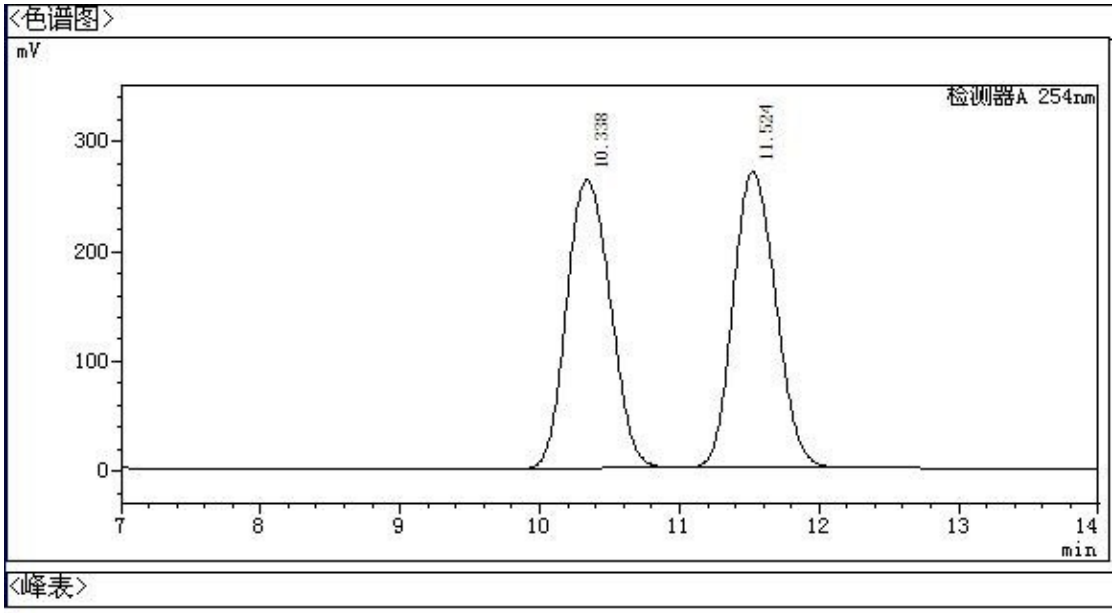


<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	12.536	34356	651691	6.790
2	14.616	372672	8945423	93.210
总计		407028	9597114	

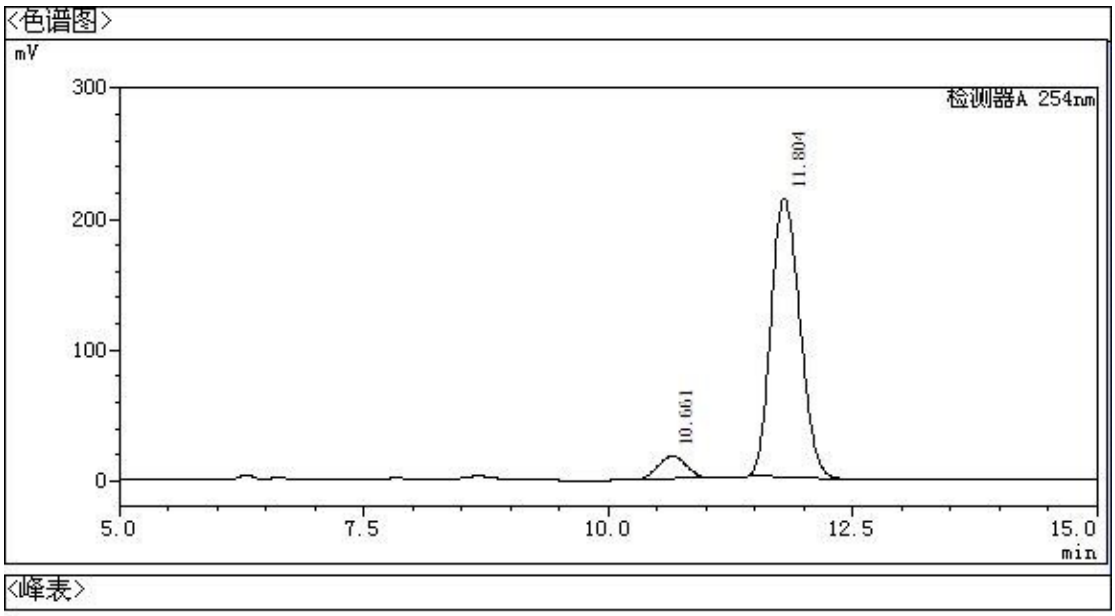
3f (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.338	261794	5703682	50.022
2	11.524	268500	5698762	49.978
总计		530293	11402443	

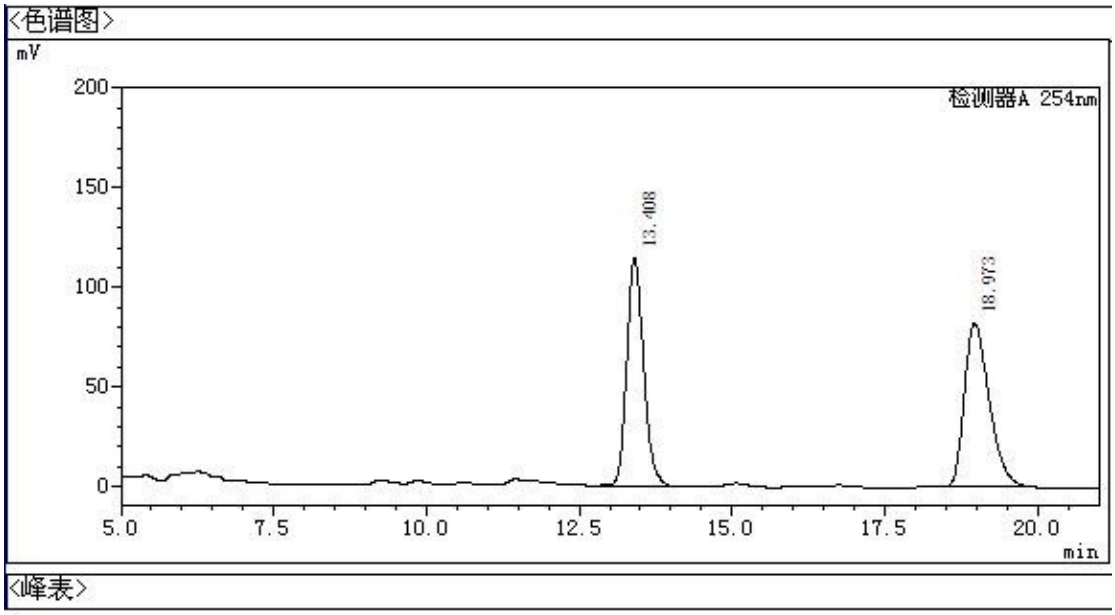
3f(Chiral)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.661	17061	338849	7.190
2	11.804	212934	4373675	92.810
总计		229994	4712523	

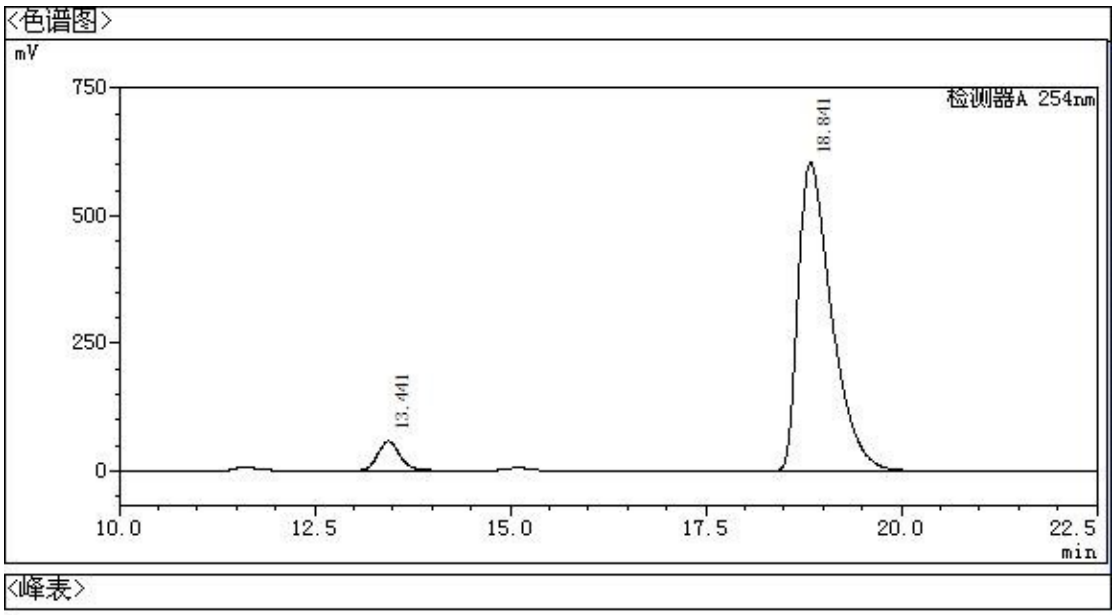
3g (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	13.408	114868	2210281	49.069
2	18.973	81697	2294149	50.931
总计		196565	4504431	

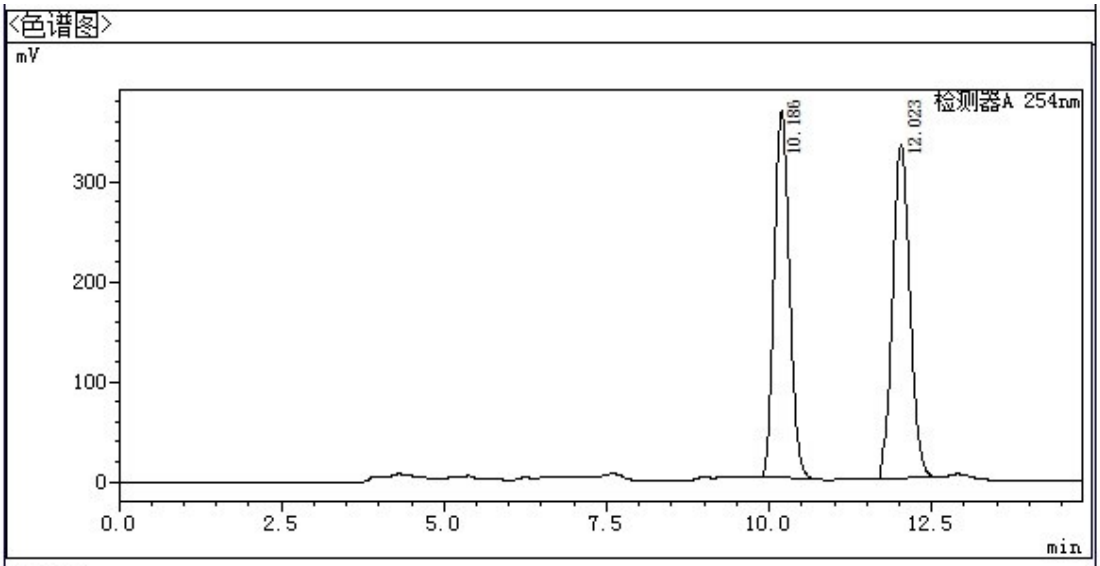
3g (Chiral)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	13.441	57011	1100935	5.780
2	18.841	604036	17944897	94.220
总计		661047	19045832	

3h (Racemic)

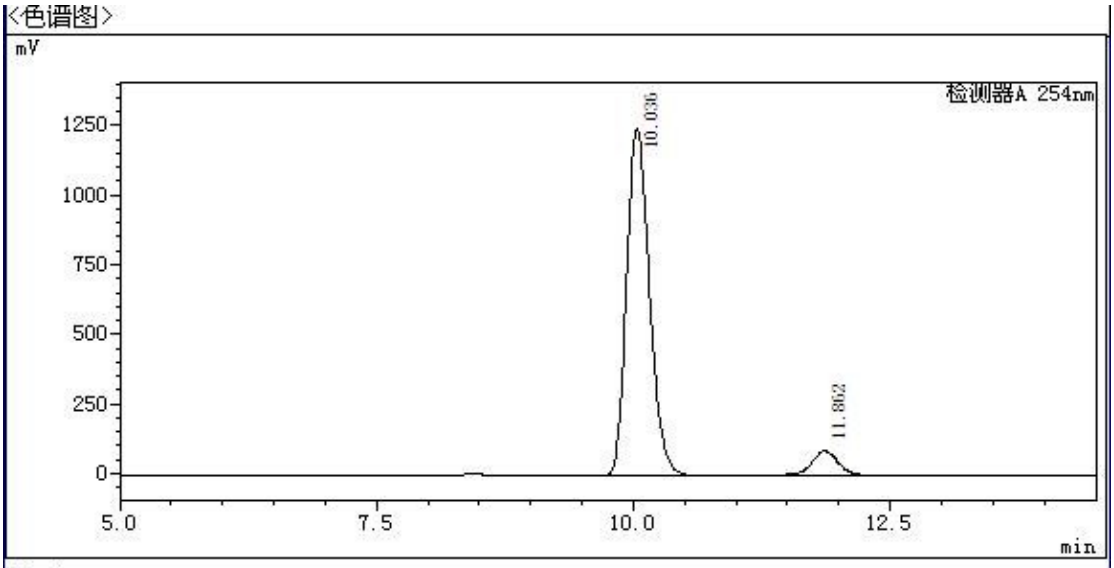


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.186	366837	6062785	49.409
2	12.023	333731	6207731	50.591
总计		700568	12270516	

3h (Chiral)

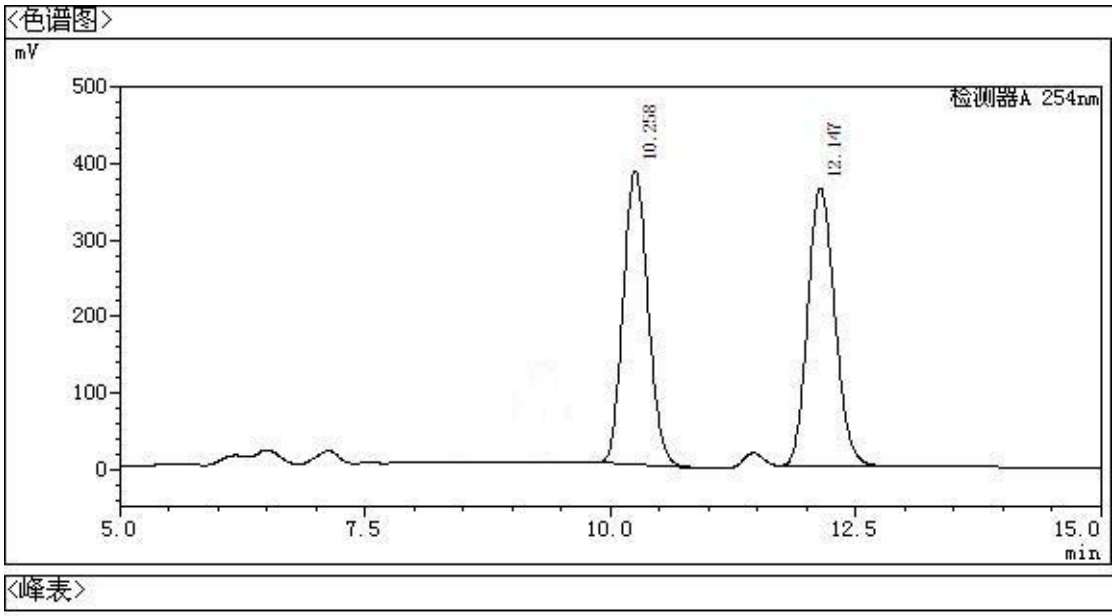


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.036	1246398	19351866	92.307
2	11.862	89028	1612916	7.693
总计		1335427	20964782	

3i (Racemic)

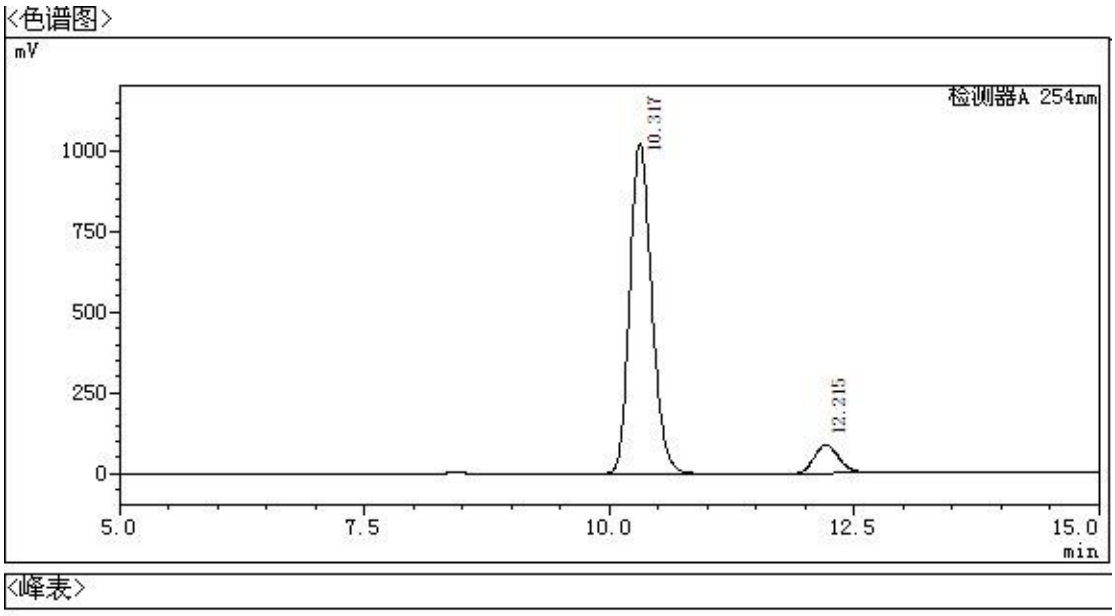


<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.258	384934	6764712	49.152
2	12.147	364006	6998058	50.848
总计		748940	13762770	

3i (Chiral)

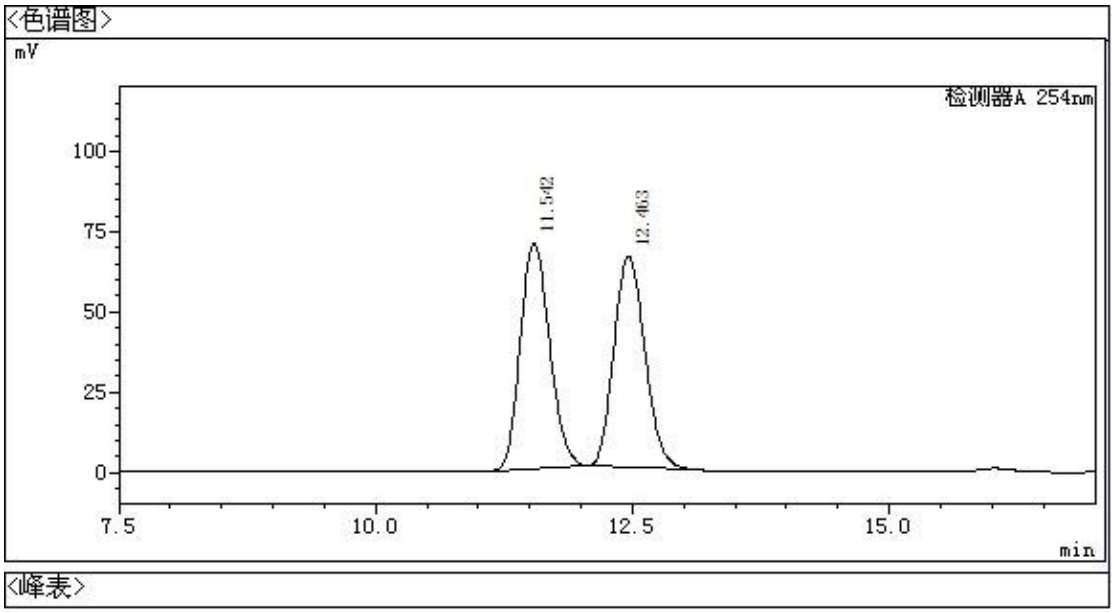


<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.317	1025128	16012266	91.100
2	12.215	88700	1564249	8.900
总计		1113828	17576515	

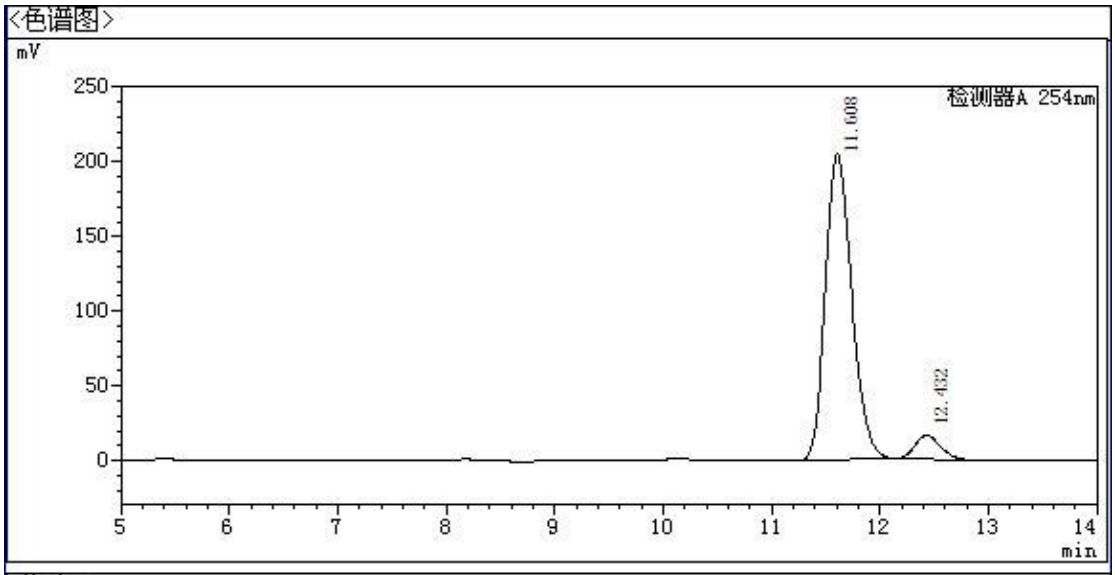
3j (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	11.542	70250	1391073	50.202
2	12.463	65759	1379879	49.798
总计		136009	2770952	

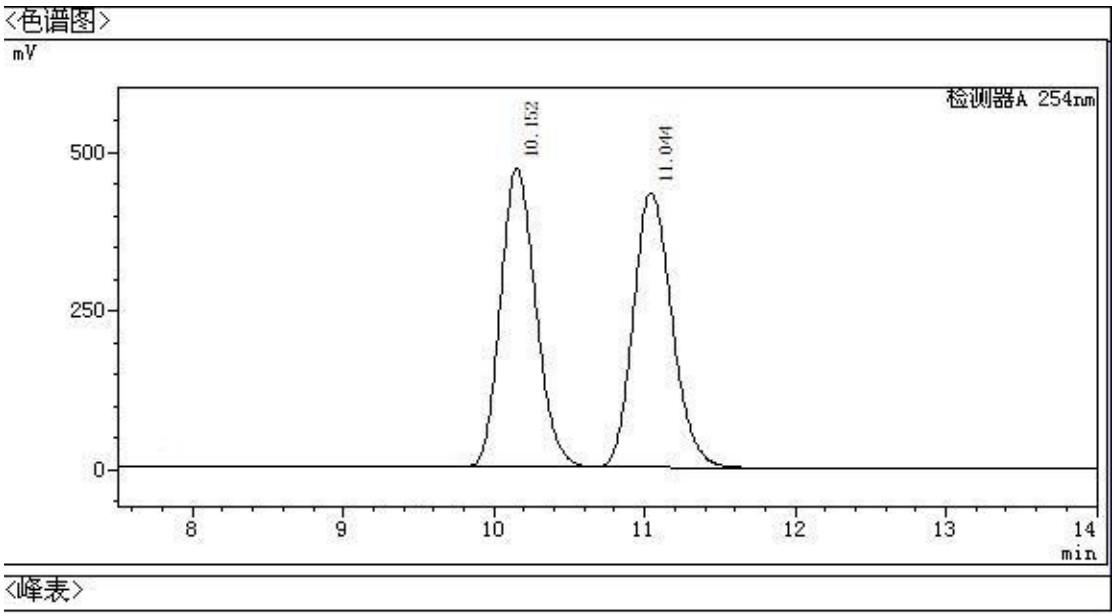
3j (Chiral)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	11.608	205358	3459967	93.117
2	12.432	15623	255752	6.883
总计		220981	3715719	

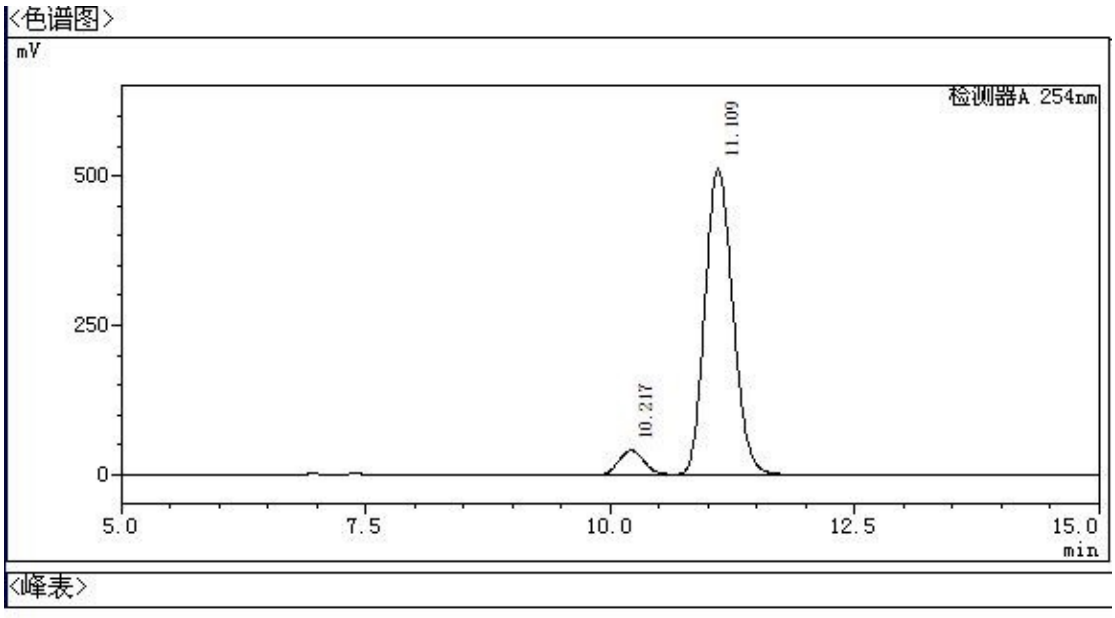
3k (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.152	469142	7598380	49.749
2	11.044	431996	7675170	50.251
总计		901138	15273551	

3k (Chiral)

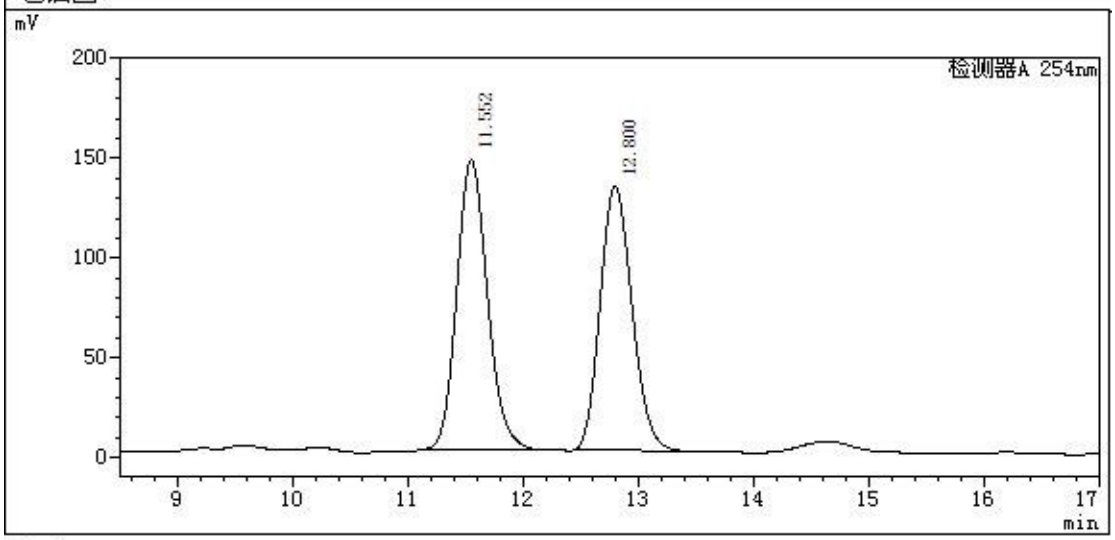


检测器A 254nm

No	Retention time	Height	Area	Concentration
1	10.217	40182	711219	6.580
2	11.109	511100	10097154	93.420
总计		551282	10808373	

3l (Racemic)

<色谱图>



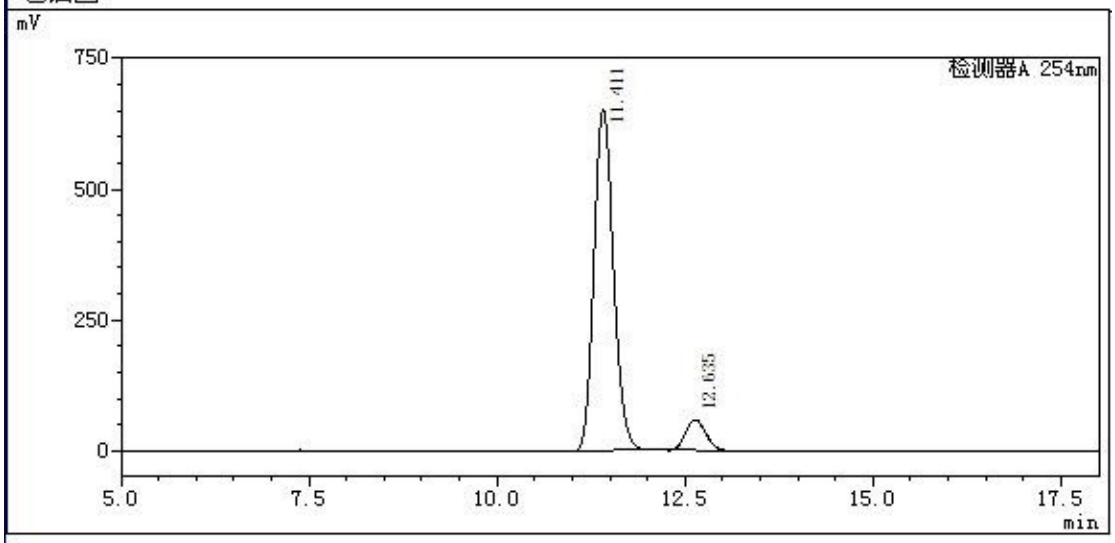
<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	11.552	145501	2690263	51.233
2	12.800	132660	2560776	48.767
总计		278160	5251040	

3l (Chiral)

<色谱图>

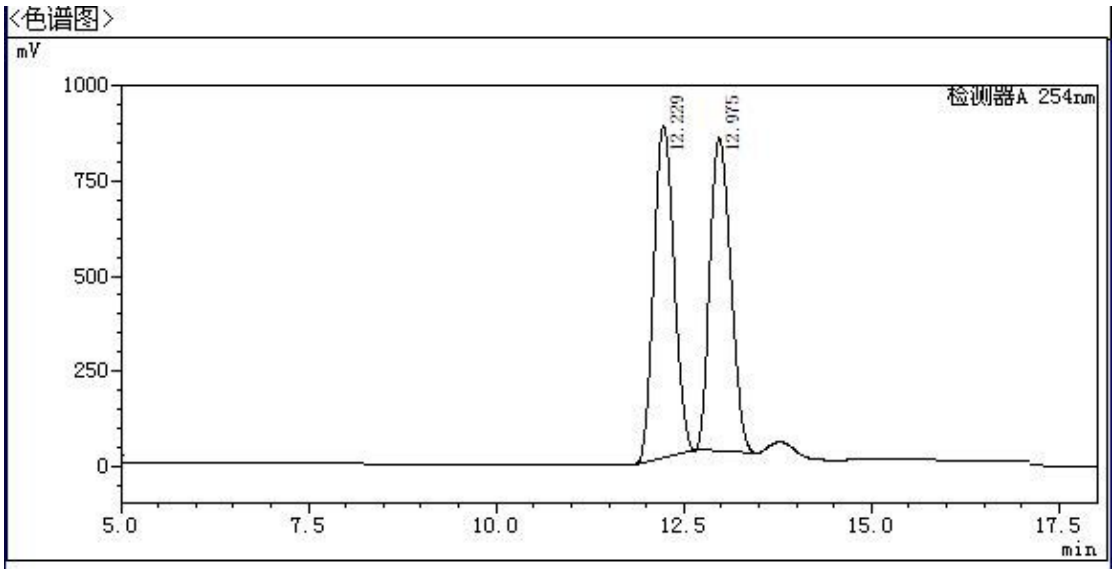


<峰表>

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	11.411	651427	11728554	91.657
2	12.635	58589	1067571	8.343
总计		710016	12796125	

3m (Racemic)

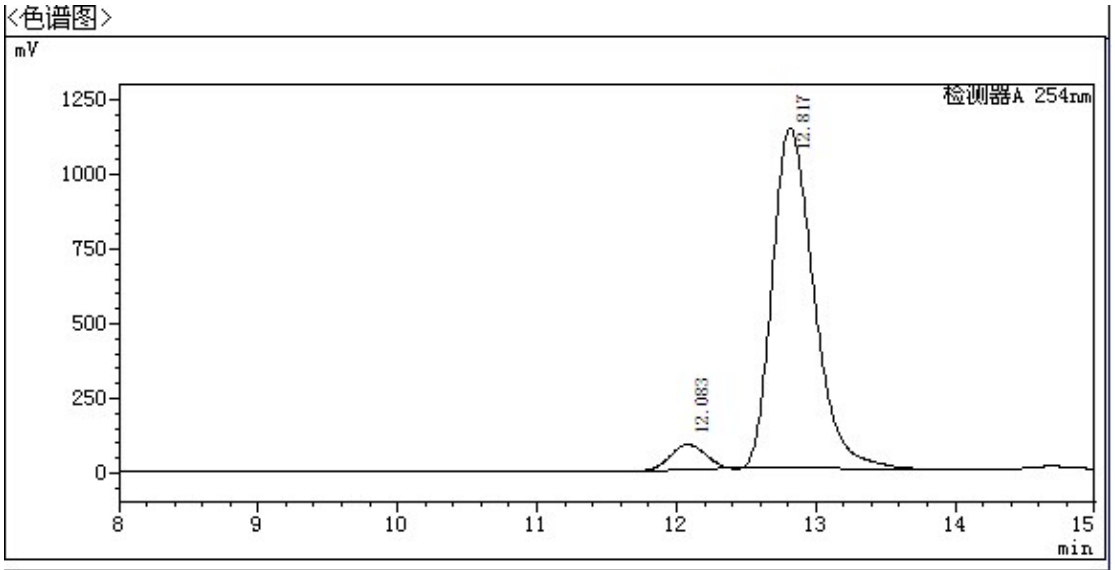


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	12.229	873850	16287952	50.727
2	12.975	823330	15820773	49.273
总计		1697179	32108724	

3m (Chiral)

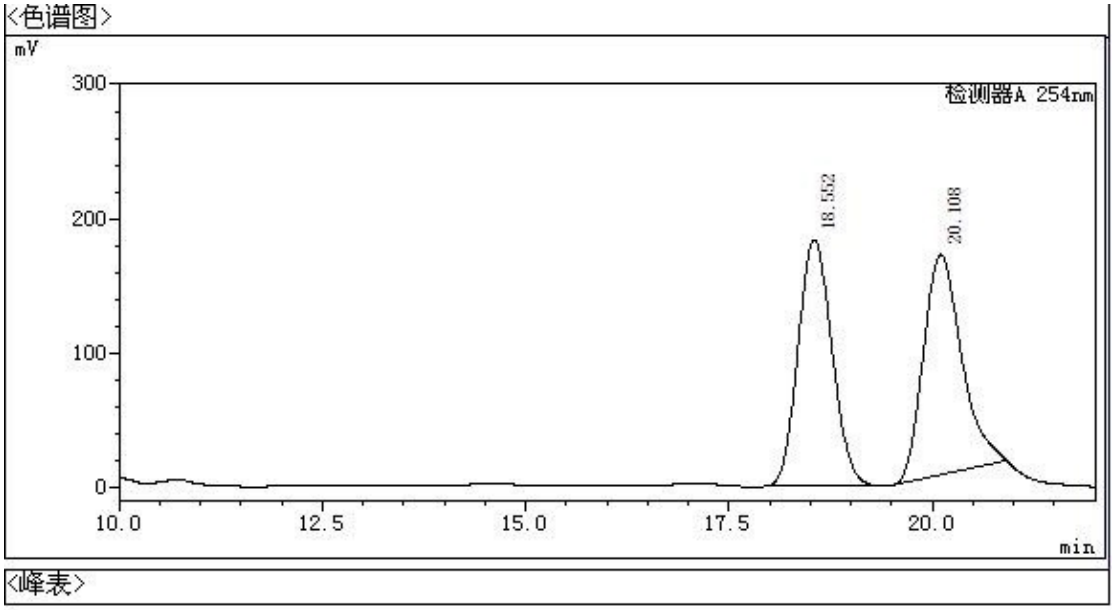


〈峰表〉

检测器A 254nm

No	Retention time	Height	Area	Concentration
1	12.083	82822	1416433	5.666
2	12.817	1139444	23582833	94.334
总计		1222266	24999266	

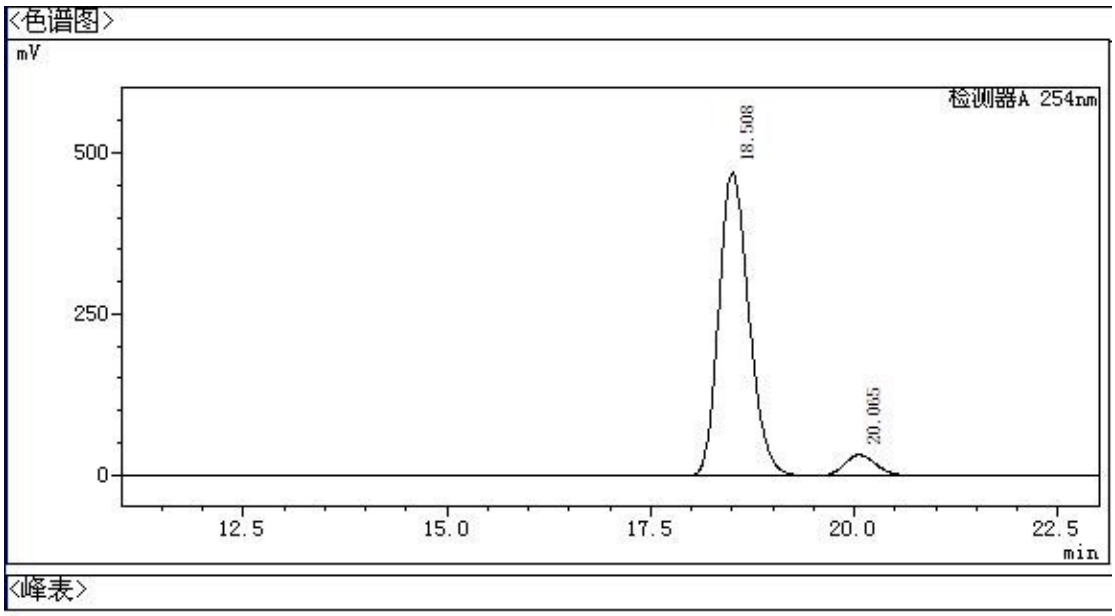
3n (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	18.552	182917	5299209	49.636
2	20.108	163662	5376977	50.364
总计		346579	10676186	

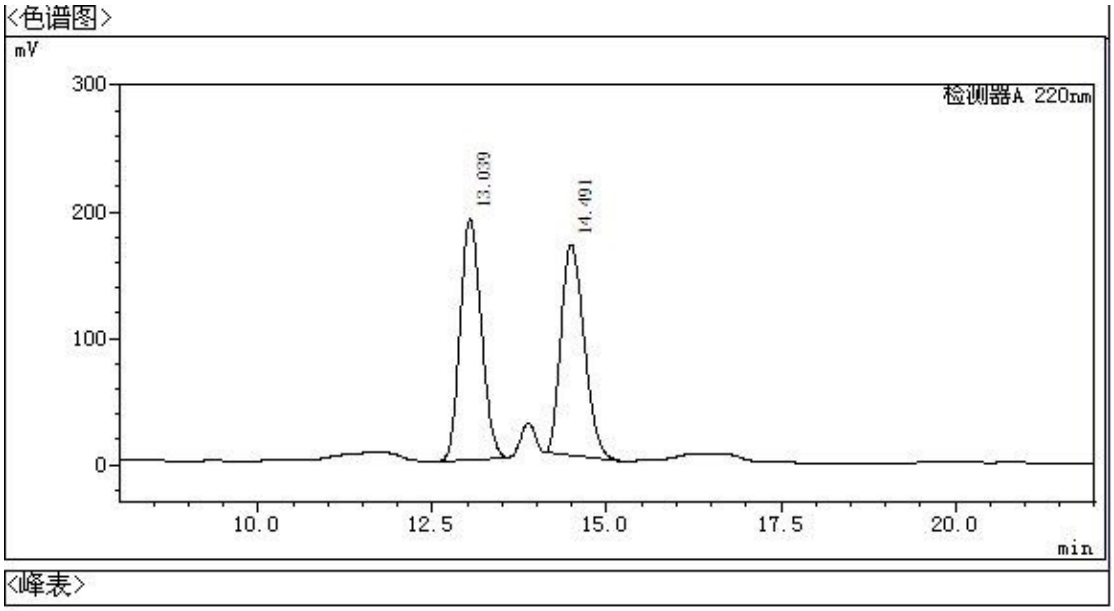
3n (Chiral)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	18.508	469942	12052484	93.698
2	20.065	31229	810622	6.302
总计		501171	12863105	

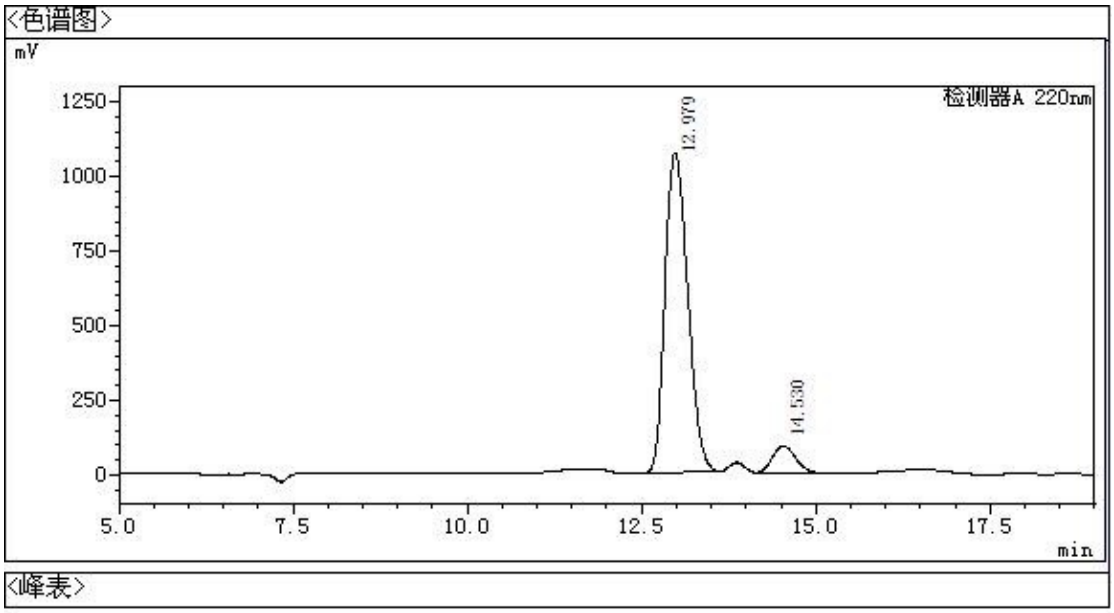
3o (Racemic)



检测器A 220nm

No	Retention time	Height	Area	Concentration
1	13.039	189978	4007821	50.844
2	14.491	166699	3874727	49.156
总计		356677	7882548	

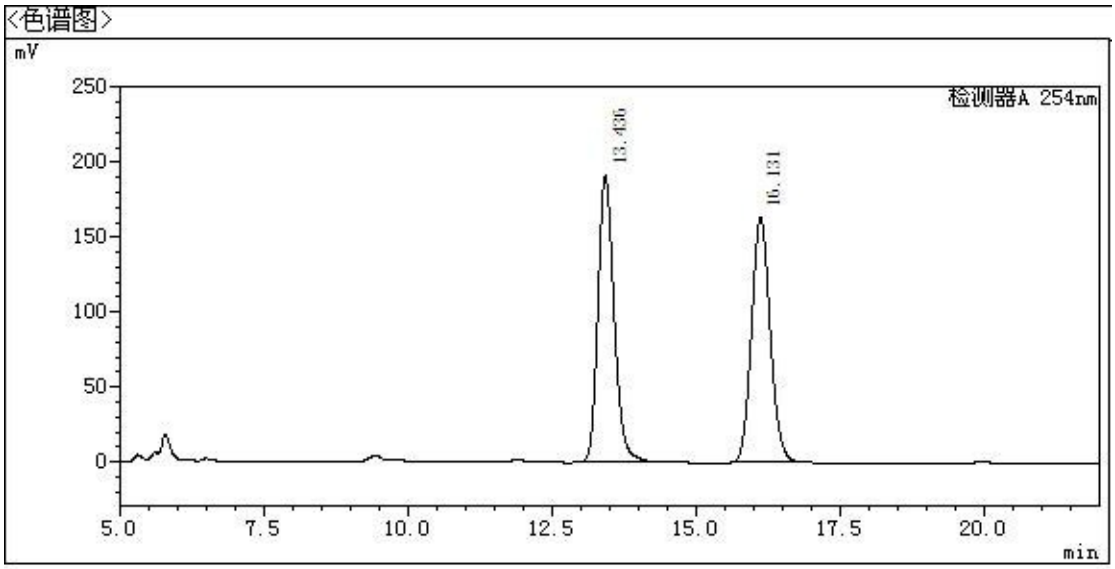
3o (Chiral)



检测器A 220nm

No	Retention time	Height	Area	Concentration
1	12.979	1070271	24346450	92.107
2	14.530	89790	2086404	7.893
总计		1160062	26432854	

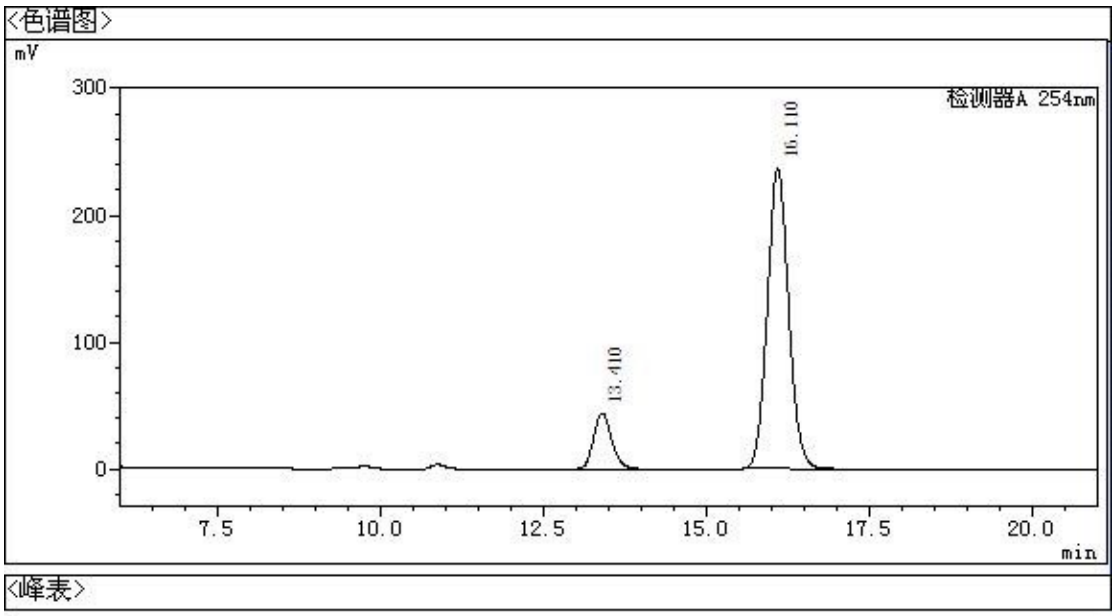
3p (Racemic)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	13.436	191305	3729663	50.299
2	16.131	163172	3685266	49.701
总计		354477	7414929	

3p (Chiral)



检测器A 254nm

No	Retention time	Height	Area	Concentration
1	13.410	43971	839312	13.484
2	16.110	236924	5385281	86.516
总计		280895	6224592	

6. References

[1] a) K. Gao, C. B. Yu, D. S. Wang, Y. G. Zhou, *Adv. Synth. Catal*. **2012**, *354*, 483-488; b) Z. P. Chen, M. W. Chen, R. N. Guo, Y. G. Zhou, *Org. Lett*. **2014**, *16*, 1406-1409; c) C. J. Ding, Y. Wang, W. W. Zhang, L. Liu, Y. J. Liang, D. W. Dong, *Chem. Res. Chinese Universitie*s. **2009**, *25*, 174-177.

[2] Y. Q. Wang, Y. Zhang, K. Pan, J. X. You, J. Zhao, *Adv. Synth. Catal*. **2013**, *355*, 3381-3386.