Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A One-pot Asymmetric Organocatalytic Cascade Reaction for The Synthesis of Oxazine Derivatives

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Supporting Information

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A. General Information and Starting Materials.

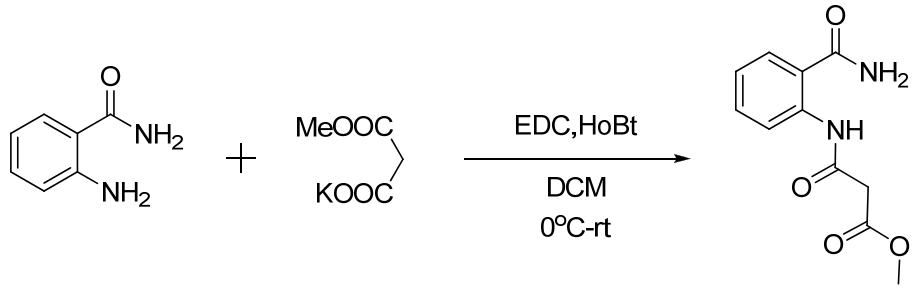
General Information.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra and carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Bruker AV-400 spectrometer (400 MHz and 100 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.28). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.41-76.77, $(CD_3)_2SO$: δ 45.25-44.00). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Mass spectra (EI) were measured on a Waters Micromass GCT spectrometer. High performance liquid chromatographys (HPLC) were performed on an Agilent 1200 or 1100 Series chromatographs using several types of Chiral columns (0.46cm x 25 cm) as noted.

Starting Materials.

All solvents and inorganic reagents were from commercial sources and used without purification unless otherwise noted.

B. General Procedure and Characterization Data for the Synthesis of The Nucleophilic Reagents.



General.

The nucleophilic reagent of methyl 3-(2-hydroxyphenylamino)-3-oxopropanoate was synthesised following the literature procedures. The starting materials of substituted 2-aminophenols and the dimethyl malonate were from commercial sources and used without further purification.

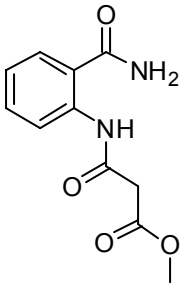
General procedure for the synthesis of the nucleophilic reagents of the amide.

The solvent of methyl malonate (70.1g, 0.5mol) in methanol (300mL) was cooled with an ice bath and stirred vigorously. A few minutes later, the solid KOH (29.8g, 0.5mol) was added into the solvent in one portion and the mixture was allowed to warm to room temperature and stirred overnight. After that the reaction mixture was filtered under reduced pressure and the filter cake was washed twice with ethyl ether. Then the filtrate was evaporised to about 200 mL and the residue was combined together and washed once with ethyl ether. All the solid product (62.6g, 0.4mol) was collected together and used in the next step without further purification[1].

To a 500mL round bottom bottle was added 2-aminobenzamide (2.8g, 20.7mmol), dimethylmalonate (3.9g, 24.8mmol), EDC·HCl (6.2g, 32.3mmol), and HOBt (5.0g, 37.3mmol). The mixture was disolved at 0 ^{o}C with 300mL of CH_2Cl_2 and then stirred overnight at room temperature. After the disappearance of 2-aminophenol (determined by TLC), the reaction mixture was first filtered to remove the solid residue and then washed successively with saturated $NaHCO_3$, 1M HCl and water. The solvent was removed in vaccum and the crude product was purefied by column chromatography to give the final product in 93% yield[2].

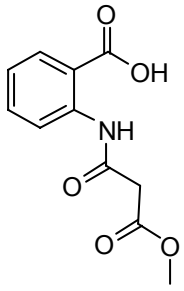
Characterization data for the nucleophilic reagents of the amide.

Methyl 3-(2-carbamoylphenylamino)-3-oxopropanoate 1a:



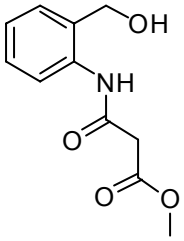
The title compound was prepared from 2-aminobenzamide according to the general procedure described above as a white solid in 93% yield. Mp 120-121 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.79 (br s, 1H), 8.42-8.40 (d, *J* = 8.4 Hz, 1H), 8.28 (br s, 1H), 7.82-7.80 (d, *J* = 7.2 Hz, 1H), 7.75 (br s, 1H), 7.52-7.48 (t, *J* = 14.8 Hz, 1H), 7.17-7.13 (t, *J* = 14.8 Hz, 1H), 3.68 (s, 3H), 3.57 (s, 2H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 171.0, 168.3, 164.4, 139.4, 132.5, 129.0, 123.4, 121.0, 52.5, 44.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{12}N_2O_4$) requires m/z 236.0797, found m/z 236.0799.

2-(3-Methoxy-3-oxopropanamido)benzoic acid 1b:



The title compound was prepared from hydrolyzation of **1a** with 2eq. of TsOH in CH_2Cl_2 (0.4M) as a white solid. Mp 112-114 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.39 (br s, 1H), 8.75 (br s, 1H), 8.72-8.70 (d, *J* = 8.4 Hz, 1H), 8.16-8.13 (dd, *J* = 7.6 Hz, 0.8 Hz, 1H), 7.64-7.60 (td, *J* = 15.6 Hz, 0.8 Hz, 1H), 7.19-7.16 (t, *J* = 15.2 Hz, 1H), 3.83 (s, 3H), 3.61 (s, 2H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 171.7, 168.2, 164.6, 140.9, 135.3, 131.7, 123.5, 121.0, 115.2, 52.7, 44.3. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{11}NO_5$) requires m/z 237.0637, found m/z 237.0633.

Methyl 3-(2-(hydroxymethyl)phenylamino)-3-oxopropanoate 1c:

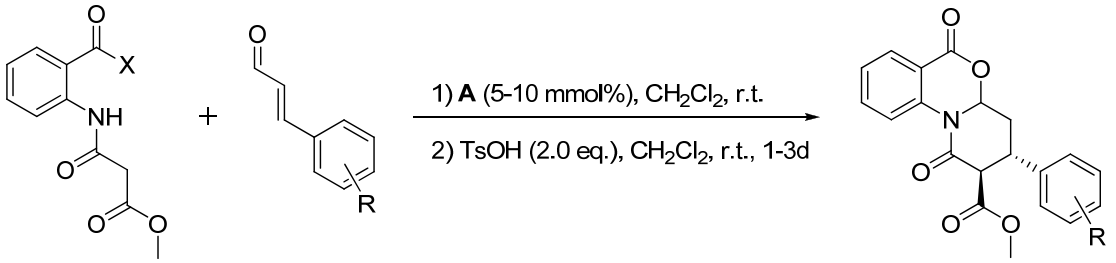


The title compound was prepared from (2-aminophenyl)methanol according to the general procedure described above as a white solid in 60% yield. Mp 75-76 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 9.61 (br s, 1H), 7.54-7.52 (d, *J* = 8.0 Hz, 1H), 7.48-7.47 (d, *J* = 7.2 Hz, 1H), 7.28-7.18 (m, 2H), 5.29 (br s, 1H), 4.55 (s, 2H), 3.69 (s, 3H), 3.55 (s, 2H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 168.8, 164.6, 135.7, 135.2, 127.8, 127.4, 125.6, 124.6, 60.3, 52.4, 43.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{13}NO_4$) requires m/z 223.0845, found m/z 223.0846.

C. General Procedure for The Asymmetric Cascade Reaction.

Part One:

General Procedure for The Asymmetric Cascade Reaction of **1a** (**1b**) and **2**

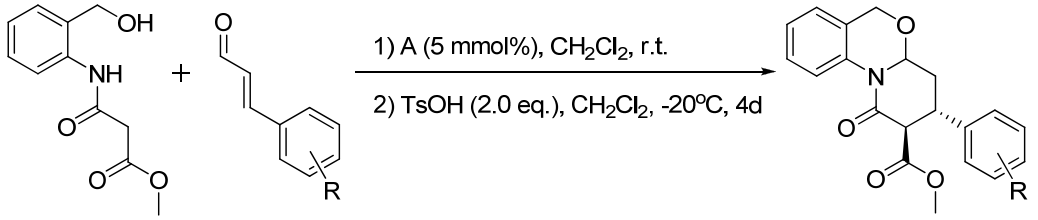


X = NH_2, **1a**; OH, **1b**. **2** **4**

To a solution of methyl 3-(2-hydroxyphenylamino)-3-oxopropanoate **1a** (**1b**) (0.4mmol) in CH_2Cl_2 (0.6mL) was added the solution of the catalyst **A** (0.02mmol) and cinnamyl aldehyde (0.6mmol) in CH_2Cl_2 (0.4mL) and the reaction mixture was stirred at room temperature for 1.5h (determined by TLC of the disapprarence of **1a** (**1b**)). Then TsOH•H_2O (0.8mmol) was added into the mixture in one portion and the solution was stirred for 1 day. At last the reaction mixture was separated by column chromotography with petrol ether:ethyl acetate = 9:1 to 4:1 as eluant to give the product of both diastereoisomers as a white solid with the yield of 53%.

Part Two:

General Procedure for The Asymmetric Cascade Reaction of **1c** and **2**

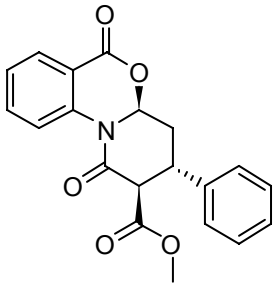


1c **2** **4**

To a solution of methyl 3-(2-(hydroxymethyl)phenylamino)-3-oxopropanoate **1c** (0.4mmol) in CH_2Cl_2 (0.6mL) was added the solution of the catalyst **A** (0.02mmol) and cinnamyl aldehyde (0.6mmol) in CH_2Cl_2 (0.4mL) and the reaction mixture was stirred at room temperature for 1.5h (determined by TLC of the disapprarence of **1c**). Then the reaction mixture was cooled down to -20 ^oC and stirred for about an hour. After that TsOH•H_2O (0.8mmol) was added into the mixture in one portion and the solution was stirred at -20 ^oC for 4 days. At last the reaction mixture was separated by column chromotography with petrol ether:ethyl acetate = 9:1 as eluant to give the product mixture of both diastereoisomers as a white solid with the yield of 86%.

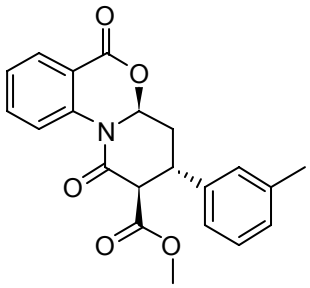
D. Characterization Data of The Products.

1) (2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4a



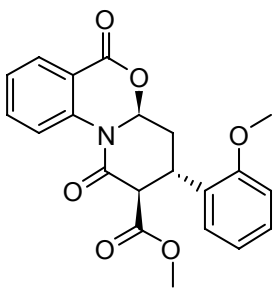
The product was obtained in 58% yield, white solid. Mp 72-74 °C; $[\alpha]^{22}_{D}$ = +46.3 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17-8.14 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.87-7.85 (d, *J* = 8.4 Hz, 1H), 7.71-7.67 (td, *J* = 15.6, 1.6 Hz, 1H), 7.46-7.37 (m, 3H), 7.34-7.28 (m, 3H), 5.75-5.74 (d, *J* = 2.4 Hz, 1H), 4.05-3.98 (td, *J* = 25.2, 2.8 Hz, 1H), 3.90-3.87 (d, *J* = 12.4 Hz, 1H), 3.61 (s, 3H), 2.63-2.58 (m, 1H), 2.53-2.45 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 165.7, 163.3, 140.7, 139.2, 134.4, 130.4, 129.2, 128.0, 127.0, 126.9, 124.4, 119.8, 84.6, 57.0, 52.5, 37.7, 34.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{17}NO_5$) requires m/z 351.1107, found m/z 351.1105. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 8.6 min (major), 14.8 min (minor), ee = 97%.

2) (2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-m-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4b



The product was obtained in 57% yield, white solid. Mp 97-101 °C; $[\alpha]^{22}_{D}$ = +70.6 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16-8.14 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.87-7.85 (d, *J* = 8.4 Hz, 1H), 7.71-7.66 (td, *J* = 15.6, 1.2 Hz, 1H), 7.45-7.41 (t, *J* = 15.2 Hz, 1H), 7.28-7.25 (t, *J* = 14.0 Hz, 1H), 7.13-7.00 (m, 3H), 5.74-5.73 (d, *J* = 2.4 Hz, 1H), 4.01-3.94 (td, *J* = 25.2, 3.2 Hz, 1H), 3.89-3.86 (d, *J* = 12.4 Hz, 1H), 3.61 (s, 3H), 2.60-2.56 (m, 1H), 2.51-2.44 (m, 1H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 165.8, 163.3, 140.7, 139.1, 138.8, 134.4, 130.4, 129.0, 128.7, 127.7, 127.0, 124.4, 123.8, 119.8, 84.7, 56.9, 52.5, 37.6, 34.1, 21.5. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_5$) requires m/z 365.1263, found m/z 365.1259. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 8.3 min (major), 14.4 min (minor), ee = 97%.

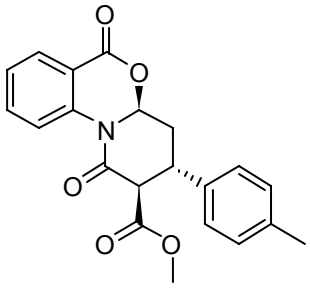
3) (2*R*,3*S*,4a*S*)-methyl 3-(2-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4c



The product was obtained in 63% yield, white solid. Mp 99-101 °C; $[\alpha]^{22}_{D}$ = +69.7 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17-8.15 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.89-7.87 (d, *J* = 8.0 Hz, 1H), 7.71-7.66 (td, *J* = 15.6, 1.6 Hz, 1H), 7.45-7.41 (t, *J* = 15.2 Hz, 1H), 7.31-7.28 (m, 1H), 7.22-7.19 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.98-6.93 (m, 1H), 5.71-5.70 (d, *J* = 2.8 Hz, 1H), 4.39-4.35 (d, *J* = 12.4 Hz, 1H),

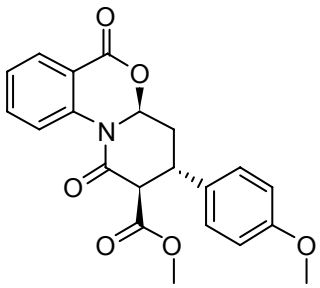
4.20-4.12 (td, *J* = 25.2, 3.2 Hz, 1H), 3.91 (s, 3H), 3.59 (s, 3H), 2.88-2.80 (m, 1H), 2.54-2.50 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 168.4, 166.4, 163.6, 157.7, 140.9, 134.3, 130.4, 129.4, 129.1, 126.8, 126.5, 124.3, 121.0, 119.8, 111.3, 85.1, 55.4, 54.4, 52.4, 35.6, 31.6. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_6$) requires m/z 381.1212, found m/z 381.1213. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 8.9 min (major), 30.9 min (minor), ee = 93%.

4) (2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-p-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4d



The product was obtained in 52% yield, white solid. Mp 174-175 °C; $[\alpha]^{22}_D$ = +149.4 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15-8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.86-7.84 (d, *J* = 8.4 Hz, 1H), 7.70-7.66 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44-7.41 (t, *J* = 15.2 Hz, 1H), 7.18 (s, 4H), 5.73-5.73 (d, *J* = 2.4 Hz, 1H), 4.00-3.93 (td, *J* = 25.2, 3.2 Hz, 1H), 3.87-3.84 (d, *J* = 12.4 Hz, 1H), 3.60 (s, 3H), 2.59-2.54 (m, 1H), 2.51-2.43 (m, 1H), 2.35 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 165.8, 163.3, 140.7, 137.7, 136.2, 134.4, 130.4, 129.8, 126.9, 126.7, 124.4, 119.8, 84.7, 57.1, 52.5, 37.3, 34.1, 21.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_5$) requires m/z 365.1263, found m/z 365.1260. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 8.9 min (major), 12.6 min (minor), ee = 95%.

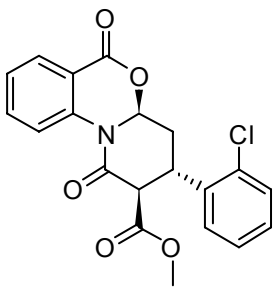
5) (2*R*,3*S*,4a*S*)-methyl 3-(4-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4e



The product was obtained in 48% yield, white solid. Mp 194-196 °C; $[\alpha]^{22}_D$ = +89.2 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15-8.13 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.85-7.83 (d, *J* = 8.0 Hz, 1H), 7.70-7.65 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44-7.40 (t, *J* = 15.2 Hz, 1H), 7.22-7.20 (m, 2H), 6.91-6.89 (m, 2H), 5.73-5.72 (d, *J* = 2.4 Hz, 1H), 3.98-3.91 (td, *J* = 25.2, 3.2 Hz, 1H), 3.83-3.80 (m, 4H), 3.60 (s, 3H), 2.58-2.53 (m, 1H), 2.49-2.41 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 165.8, 163.3, 159.1, 140.7, 134.4, 131.2, 130.4, 128.0, 126.9, 124.4, 119.8, 114.5, 84.7, 57.3, 52.3, 52.5, 36.9, 34.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_6$) requires m/z 381.1212, found m/z 381.1213. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 15.4 min (major), 25.1 min (minor), ee = 95%.

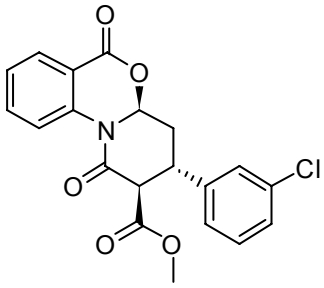
6) (2*R*,3*S*,4a*S*)-methyl 3-(2-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4f

The product was obtained in 69% yield, white solid. Mp 186-188 °C; $[\alpha]^{22}_D$ = +115.2 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13-8.11 (d, *J* = 7.6



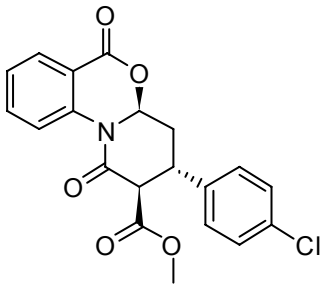
Hz, 1H), 7.85-7.83 (d, *J* = 8.0 Hz, 1H), 7.68-7.64 (t, *J* = 16.0 Hz, 1H), 7.46-7.39 (m, 2H), 7.32-7.23 (m, 3H), 5.72-5.71 (d, *J* = 2.8 Hz, 1H), 4.55-4.48 (td, *J* = 25.6, 2.4 Hz, 1H), 4.15-4.12 (d, *J* = 12.4 Hz, 1H), 3.60 (s, 3H), 2.62-2.59 (m, 1H), 2.48-2.38 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.6, 163.2, 140.6, 136.3, 134.4, 133.9, 130.6, 130.4, 129.1, 127.6, 127.0, 124.3, 119.8, 84.6, 55.0, 52.6, 34.7, 33.0, 26.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Cl$) requires m/z 385.0717, found m/z 385.0709. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL/min]: 5.6 min (minor), 6.6 min (major), ee = 97%.

7) (2*R*,3*S*,4a*S*)-methyl 3-(3-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4g



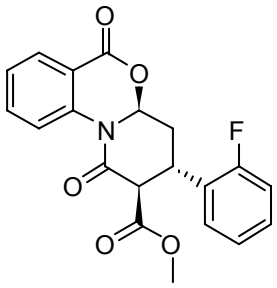
The product was obtained in 35% yield, white solid. Mp 190-192 °C; $[\alpha]^{22}_D$ = +81.2 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16-8.14 (d, *J* = 7.6 Hz, 1H), 7.86-7.84 (d, *J* = 8.4 Hz, 1H), 7.71-7.67 (t, *J* = 15.6 Hz, 1H), 7.46-7.42 (t, *J* = 15.2 Hz, 1H), 7.35-7.28 (m, 3H), 7.22-7.18 (m, 1H), 5.75-5.74 (d, *J* = 2.4 Hz, 1H), 4.03-3.96 (td, *J* = 25.6, 2.8 Hz, 1H), 3.86-3.83 (d, *J* = 12.4 Hz, 1H), 3.63 (s, 3H), 2.60-2.57 (m, 1H), 2.51-2.44 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.3, 163.1, 141.2, 140.6, 135.0, 134.5, 130.5, 128.3, 127.1, 127.1, 125.3, 124.4, 119.7, 84.4, 56.8, 52.7, 37.4, 33.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Cl$) requires m/z 385.0717, found m/z 385.0721. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 7.7 min (major), 8.9 min (minor), ee = 95%.

8) (2*R*,3*S*,4a*S*)-methyl 3-(4-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4h



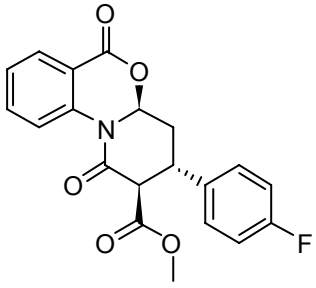
The product was obtained in 84% yield, white solid. Mp 188-190 °C; $[\alpha]^{22}_D$ = +89.5 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11-8.10 (d, *J* = 6.8 Hz, 1H), 7.82-7.80 (d, *J* = 8.0 Hz, 1H), 7.68-7.63 (td, *J* = 15.6, 1.2 Hz, 1H), 7.43-7.39 (t, *J* = 15.2 Hz, 1H), 7.35-7.33 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (d, *J* = 8.4 Hz, 2H), 5.73-5.73 (d, *J* = 2.0 Hz, 1H), 4.00-3.93 (td, *J* = 24.8, 3.2 Hz, 1H), 3.85-3.82 (d, *J* = 12.4 Hz, 1H), 3.59 (s, 3H), 2.55-2.42 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.8, 165.4, 163.2, 140.6, 137.7, 134.5, 133.8, 130.4, 129.4, 128.4, 127.0, 124.3, 119.7, 84.5, 56.9, 52.6, 37.2, 33.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Cl$) requires m/z 385.0717, found m/z 385.0719. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL/min]: 5.9 min (minor), 7.1 min (major), ee = 93%.

9) (2*R*,3*S*,4a*S*)-methyl 3-(2-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4i



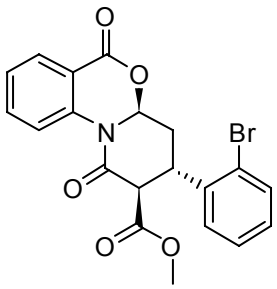
The product was obtained in 84% yield, white solid. Mp 180-182 °C; $[\alpha]^{22}_D$ = +70.9 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12-8.10 (d, *J* = 7.6 Hz, 1H), 7.84-7.82 (d, *J* = 8.4 Hz, 1H), 7.68-7.64 (td, *J* = 15.6, 1.2 Hz, 1H), 7.42-7.38 (t, *J* = 15.2 Hz, 1H), 7.32-7.26 (m, 2H), 7.15-7.06 (m, 2H), 5.73-5.72 (d, *J* = 2.4 Hz, 1H), 4.18-4.03 (m, 2H), 3.57 (s, 3H), 2.75-2.68 (td, *J* = 26.8, 4.0 Hz, 1H), 2.57-2.53 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 165.5, 163.3, 140.7, 134.4, 130.3, 129.8, 129.6, 127.0, 125.7, 124.8, 124.4, 119.8, 116.5, 116.3, 84.7, 55.1, 52.5, 34.2, 32.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5F$) requires m/z 369.1013, found m/z 369.1010. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 7.8 min (major), 14.9 min (minor), ee = 95%.

10) (2*R*,3*S*,4a*S*)-methyl 3-(4-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4j



The product was obtained in 76% yield, colorless oil. $[\alpha]^{22}_D$ = +72.5 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13-8.11 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.84-7.82 (d, *J* = 8.0 Hz, 1H), 7.69-7.64 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44-7.40 (t, *J* = 15.2 Hz, 1H), 7.29-7.25 (m, 2H), 7.09-7.04 (m, 2H), 5.74-5.73 (d, *J* = 2.4 Hz, 1H), 4.02-3.95 (td, *J* = 24.8, 3.2 Hz, 1H), 3.84-3.81 (d, *J* = 12.4 Hz, 1H), 3.59 (s, 3H), 2.57-2.53 (m, 1H), 2.51-2.43 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 165.5, 163.5, 163.2, 161.0, 140.6, 135.0, 134.4, 130.4, 128.6, 128.6, 127.0, 124.3, 119.7, 116.2, 116.0, 84.5, 57.1, 52.6, 37.0, 34.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5F$) requires m/z 369.1013, found m/z 369.1014. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 7.7 min (major), 9.7 min (minor), ee = 94%.

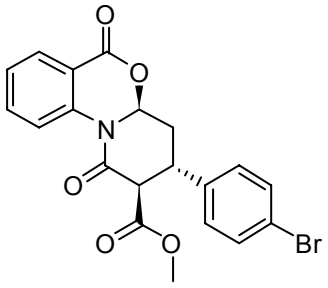
11) (2*R*,3*S*,4a*S*)-methyl 3-(2-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4k



The product was obtained in 85% yield, white solid. Mp 190-192 °C; $[\alpha]^{22}_D$ = +82.6 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12-8.10 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.84-7.82 (d, *J* = 8.0 Hz, 1H), 7.70-7.60 (m, 2H), 7.43-7.11 (m, 4H), 5.70-5.70 (d, *J* = 2.4 Hz, 1H), 4.56-4.49 (td, *J* = 25.2, 2.4 Hz, 1H), 4.12-4.09 (d, *J* = 12.8 Hz, 1H), 3.60 (s, 3H), 2.63-2.59 (m, 1H), 2.41-2.32 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.6, 163.2, 140.6, 138.0,

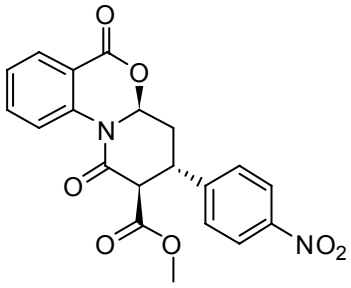
134.4, 134.0, 130.4, 129.3, 128.2, 127.2, 126.9, 124.4, 124.3, 119.8, 84.6, 55.2, 52.6, 36.9, 33.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Br$) requires m/z 429.0212, found m/z 429.0213. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL/min]: 5.6 min (minor), 6.8 min (major), ee = 94%.

12) (2*R*,3*S*,4a*S*)-methyl 3-(4-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4l



The product was obtained in 78% yield, white solid. Mp 120-122 °C; $[\alpha]^{22}_D$ = +95.7 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12-8.10 (d, *J* = 6.8 Hz, 1H), 7.83-7.81 (d, *J* = 8.0 Hz, 1H), 7.68-7.64 (td, *J* = 15.6, 1.2 Hz, 1H), 7.51-7.49 (t, *J* = 8.4 Hz, 2H), 7.43-7.39 (t, *J* = 15.2 Hz, 1H), 7.19-7.16 (d, *J* = 8.4 Hz, 2H), 5.73-5.72 (d, *J* = 2.4 Hz, 1H), 4.00-3.93 (td, *J* = 24.8, 3.2 Hz, 1H), 3.85-3.82 (d, *J* = 12.4 Hz, 1H), 3.59 (s, 3H), 2.55-2.52 (m, 1H), 2.50-2.42 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.8, 165.4, 163.2, 140.6, 138.2, 134.5, 132.3, 130.4, 128.7, 127.1, 124.3, 121.9, 119.7, 84.5, 56.8, 52.6, 37.2, 33.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Br$) requires m/z 429.0212, found m/z 429.0214. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 0.6 mL/min]: 13.4 min (major), 15.2 min (minor), ee>99%.

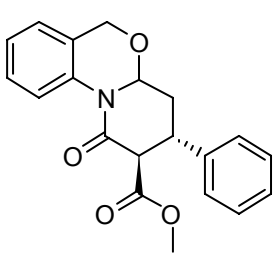
13) (2*R*,3*S*,4a*S*)-methyl 3-(4-nitrophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydro benzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4m



The product was obtained in 89% yield, yellow solid. Mp 84-86 °C; $[\alpha]^{22}_D$ = +59.3 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.23-8.21 (d, *J* = 8.4 Hz, 2H), 8.11-8.09 (d, *J* = 6.8 Hz, 1H), 7.82-7.80 (d, *J* = 8.0 Hz, 1H), 7.68-7.64 (td, *J* = 15.6, 1.2 Hz, 1H), 7.52-7.49 (d, *J* = 8.4 Hz, 2H), 7.44-7.40 (t, *J* = 15.0 Hz, 1H), 5.77 (m, 1H), 4.16-4.07 (m, 1H), 3.95-3.92 (d, *J* = 12.4 Hz, 1H), 3.58 (s, 3H), 2.58-2.56 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 167.5, 164.9, 163.0, 147.6, 146.5, 140.5, 134.6, 130.4, 128.2, 127.2, 124.4, 124.4, 119.7, 84.3, 56.4, 52.7, 37.6, 33.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}N_2O_7$) requires m/z 396.0958, found m/z 396.0961. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, nHex/DCM = 1/1, 1.0 mL/min]: 19.8 min (minor), 31.3 min (major), ee = 94%.

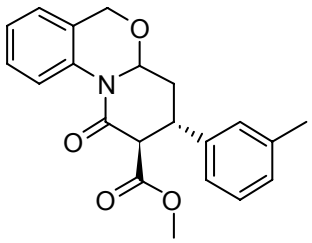
14) (2*R*,3*S*)-methyl 1-oxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*] [1,3]oxazine-2-carboxylate 4n

The product was obtained as a mixture of both diastereoisomers in 86% yield, colorless oil. $[\alpha]^{22}_D$ = +11.0 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16-7.80 (m, 1H), 7.36-7.34 (m, 2H), 7.32-7.24 (m, 4H), 7.21-7.15 (m, 1H),



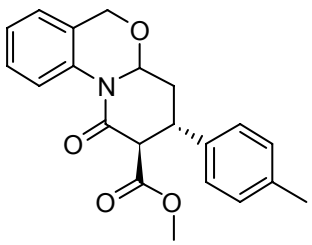
7.07-7.03 (m, 1H), 5.21-4.93 (m, 3H), 3.97-3.42 (m, 5H), 2.59-2.39 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 169.0, 166.0, 165.5, 140.5, 139.9, 137.1, 135.3, 129.0, 129.0, 127.7, 127.6, 127.2, 127.0, 126.9, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.7, 84.0, 82.8, 67.8, 67.2, 58.4, 57.5, 52.4, 52.2, 38.4, 37.6, 35.2, 35.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{19}NO_4$) requires m/z 337.1314, found m/z 337.1313. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 13.9 min (major), 18.3 min (minor), ee = 94%; 15.9 min (major), 51.4 min (minor), ee = 97%.

15) (2*R*,3*S*)-methyl 1-oxo-3-m-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4o



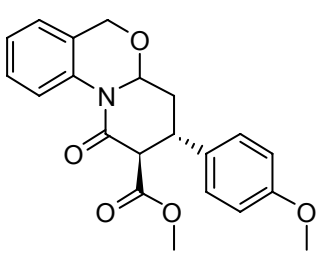
The product was obtained as a mixture of both diastereoisomers in 97% yield, colorless oil. $[\alpha]^{22}_D$ = -5.4 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16-7.81 (m, 1H), 7.28-7.04 (m, 7H), 5.21-4.93 (m, 3H), 3.94-3.42 (m, 5H), 2.58-2.10 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.0, 166.1, 165.5, 140.5, 139.9, 138.6, 138.5, 137.2, 135.3, 128.9, 128.8, 128.5, 128.3, 127.8, 127.7, 127.2, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.9, 123.8, 123.7, 84.0, 82.8, 67.8, 67.2, 58.4, 57.5, 52.4, 52.2, 38.2, 37.5, 35.3, 35.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{21}NO_4$) requires m/z 351.1471, found m/z 351.1468. [IC column, 254 nm, DCM, 1.0 mL/min]: 11.6 min (major), 25.0 min (minor), ee = 97%; 14.6 min (major), 48.3 min (minor), ee = 97%.

16) (2*R*,3*S*)-methyl 1-oxo-3-p-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4p



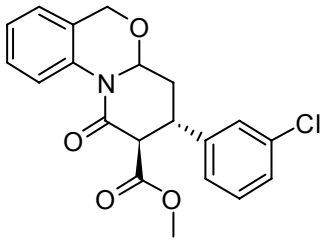
The product was obtained as a mixture of both diastereoisomers in 89% yield, white solid. Mp 124-126 °C; $[\alpha]^{22}_D$ = +9.1 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16-7.81 (m, 1H), 7.28-7.03 (m, 7H), 5.20-4.93 (m, 3H), 3.93-3.42 (m, 5H), 2.57-2.06 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.0, 166.1, 165.5, 137.5, 137.3, 137.2, 137.1, 137.0, 135.3, 129.7, 129.6, 127.2, 126.8, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.7, 84.0, 82.8, 67.8, 67.2, 58.5, 57.6, 52.4, 52.2, 37.9, 37.2, 35.4, 35.2, 21.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{21}NO_4$) requires m/z 351.1471, found m/z 351.1469. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 11.3 min (minor), 12.9 min (major), ee = 99%; 16.1 min (major), 31.6 min (minor), ee = 94%.

17) (2*R*,3*S*)-methyl 3-(4-methoxyphenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4q



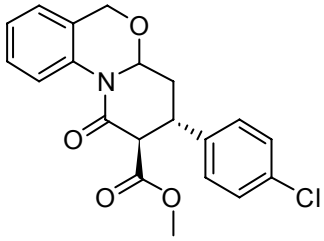
The product was obtained as a mixture of both diastereoisomers in 98% yield, yellow solid. Mp 75-77 °C; $[\alpha]^{22}_D$ = +11.4 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14-7.78 (m, 1H), 7.28-7.13 (m, 4H), 7.05-7.02 (m, 1H), 6.89-6.86 (m, 2H), 5.19-4.92 (m, 3H), 3.90-3.39 (m, 8H), 2.55-2.05 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.1, 166.0, 165.5, 159.0, 158.8, 137.2, 135.3, 132.6, 132.0, 128.0, 127.9, 127.2, 126.8, 126.4, 126.1, 125.6, 125.3, 125.2, 124.5, 124.4, 123.7, 114.3, 114.3, 84.0, 82.8, 67.8, 67.2, 58.7, 57.9, 55.2, 52.4, 52.2, 37.6, 36.8, 35.5, 35.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{21}NO_5$) requires m/z 367.1420, found m/z 367.1423. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 15.0 min (major), 24.2 min (minor), ee = 92%; 17.0 min (major), 39.9 min (minor), ee = 93%.

18) (2*R*,3*S*)-methyl 3-(3-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4r



The product was obtained as a mixture of both diastereoisomers in 76% yield, yellow solid. Mp 78-80 °C; $[\alpha]^{22}_D$ = +4.5 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13-7.78 (m, 1H), 7.43-7.04 (m, 7H), 5.30-4.94 (m, 3H), 3.95-3.44 (m, 5H), 2.59-2.06 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.7, 165.6, 165.0, 142.5, 142.0, 137.0, 135.1, 134.8, 134.7, 130.3, 130.3, 130.2, 128.0, 127.8, 127.3, 127.1, 126.9, 126.5, 126.1, 125.8, 125.3, 125.2, 125.1, 124.5, 124.4, 123.7, 83.8, 82.6, 67.8, 67.2, 58.1, 57.3, 52.6, 52.4, 38.0, 37.3, 35.0, 34.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4Cl$) requires m/z 371.0924, found m/z 371.0921. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, nHexane/DCM = 2/1, 1.0 mL/min]: 12.9 min (minor), 28.3 min (major), ee = 97%; 15.0 min (minor), 17.7 min (major), ee = 97%.

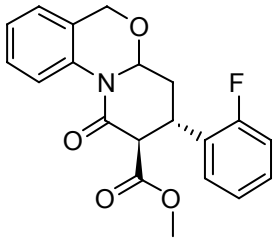
19) (2*R*,3*S*)-methyl 3-(4-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4s



The product was obtained as a mixture of both diastereoisomers in 99% yield, white solid. Mp 129-132 °C; $[\alpha]^{22}_D$ = +4.3 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12-7.77 (m, 1H), 7.33-7.30 (m, 2H), 7.26-7.14 (m, 4H), 7.06-7.02 (m, 1H), 5.20-4.92 (m, 3H), 3.93-3.41 (m, 5H), 2.55-2.06 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.8, 165.7, 165.1, 139.0, 138.5, 137.0, 135.2, 133.5, 133.3, 129.2, 129.1, 128.4, 128.4, 127.1, 126.8, 126.4, 126.1, 125.8, 125.3, 124.5, 124.4, 123.7, 83.8, 82.6, 67.8, 67.2, 58.2, 57.4, 52.5, 52.3, 37.8, 37.0, 35.1, 34.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4Cl$) requires m/z 371.0924, found m/z 371.0916. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, nHexane/DCM = 2/1, 1.0 mL/min]: 13.5 min (minor),

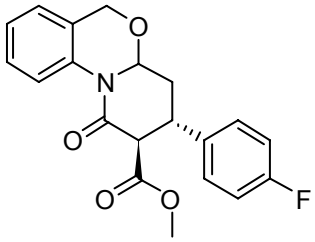
41.1 min (major), ee = 93%; 14.1 min (minor), 24.1 min (major), ee = 93%.

20) (2*R*,3*S*)-methyl 3-(2-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4t



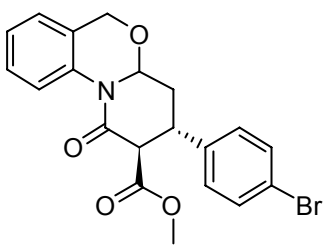
The product was obtained as a mixture of both diastereoisomers in 99% yield, yellow solid. Mp 106-111 °C; $[\alpha]^{22}_D$ = -3.4 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13-7.79 (m, 1H), 7.28-7.04 (m, 7H), 5.21-4.91 (m, 3H), 4.19-3.40 (m, 5H), 2.58-2.16 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.9, 165.8, 165.3, 137.1, 135.3, 129.3, 129.3, 129.2, 129.0, 129.0, 128.4, 128.3, 127.2, 127.1, 127.0, 126.8, 126.7, 126.6, 126.4, 126.1, 125.7, 125.3, 125.3, 124.7, 124.7, 124.6, 124.6, 124.5, 124.4, 123.7, 116.3, 116.1, 116.1, 116.0, 83.9, 82.8, 67.8, 67.2, 56.4, 55.6, 52.5, 52.3, 34.2, 33.5, 33.2, 32.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4F$) requires m/z 355.1220, found m/z 355.1219. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, nHexane/DCM = 1/1, 1.0 mL/min]: 6.3 min (minor), 9.5 min (major), ee = 95%; 7.3 min (minor), 8.0 min (major), ee = 94%.

21) (2*R*,3*S*)-methyl 3-(4-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4u



The product was obtained as a mixture of both diastereoisomers in 63% yield, yellow solid. Mp 144-149 °C; $[\alpha]^{22}_D$ = +16.2 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13-7.78 (m, 1H), 7.28-7.02 (m, 7H), 5.30-4.94 (m, 3H), 3.95-3.45 (m, 5H), 2.58-2.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 168.9, 165.8, 165.2, 163.3, 160.8, 137.1, 136.3, 136.2, 128.6, 128.5, 127.1, 126.8, 126.4, 125.8, 125.3, 124.5, 124.4, 123.7, 116.0, 115.9, 115.8, 115.7, 83.8, 82.7, 67.8, 67.2, 58.5, 57.7, 52.5, 52.3, 37.7, 36.9, 35.3, 35.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4F$) requires m/z 355.1220, found m/z 355.1215. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, nHexane/DCM = 3/1, 1.0 mL/min]: 23.1 min (minor), 78.5 min (major), ee = 99%; 25.8 min (minor), 50.2 min (major), ee = 94%.

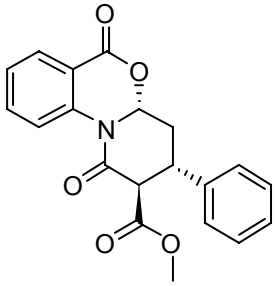
22) (2*R*,3*S*)-methyl 3-(4-bromophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4v



The product was obtained in 86% yield, white solid. Mp 146-148 °C; $[\alpha]^{22}_D$ = +15.9 ° (c = 1.00 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12-7.77 (m, 1H), 7.48-7.46 (m, 2H), 7.27-7.23 (m, 1H), 7.20-7.11 (m, 3H), 7.06-7.02 (m, 1H), 5.20-4.92 (m, 3H), 3.92-3.42 (m, 5H), 2.55-2.06 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.8, 165.6, 165.1, 139.5, 139.0, 137.0, 135.2,

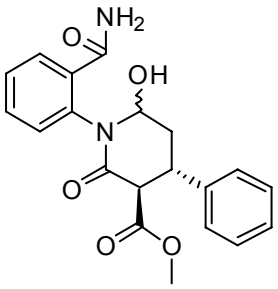
132.1, 132.1, 128.8, 128.7, 127.1, 126.8, 126.4, 126.1, 125.8, 125.3, 124.5, 124.4, 123.7, 121.6, 121.4, 83.8, 82.6, 67.8, 67.2, 58.1, 57.3, 52.5, 52.4, 37.8, 37.1, 35.0, 34.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4Br$) requires m/z 415.0419, found m/z 415.0416. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, nHexane/DCM = 3/1, 1.0 mL/min]: 27.4 min (minor), 102.3 min (major), ee = 99%; 30.4 min (minor), 54.5 min (major), ee = 96%.

23) (2*R*,3*S*,4a*R*)-methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4a1



White solid. Mp 181-183 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15-8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.07-8.05 (d, *J* = 8.4 Hz, 1H), 7.70-7.67 (td, *J* = 15.6, 1.2 Hz, 1H), 7.42-7.38 (m, 3H), 7.35-7.32 (m, 1H), 7.27-7.26 (m, 2H), 5.89-5.85 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.82-3.79 (d, *J* = 12.0 Hz, 1H), 3.65 (s, 3H), 3.59-3.52 (td, *J* = 26.0, 2.8 Hz, 1H), 2.79-2.73 (m, 1H), 2.53-2.44 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.0, 165.3, 162.2, 139.8, 138.8, 134.8, 130.3, 129.2, 128.1, 126.9, 126.5, 123.0, 118.5, 84.4, 57.8, 52.7, 38.1, 34.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{17}NO_5$) requires m/z 351.1107, found m/z 351.1106. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL/min]: 12.6 min (major), 18.1 min (minor), ee = 98%.

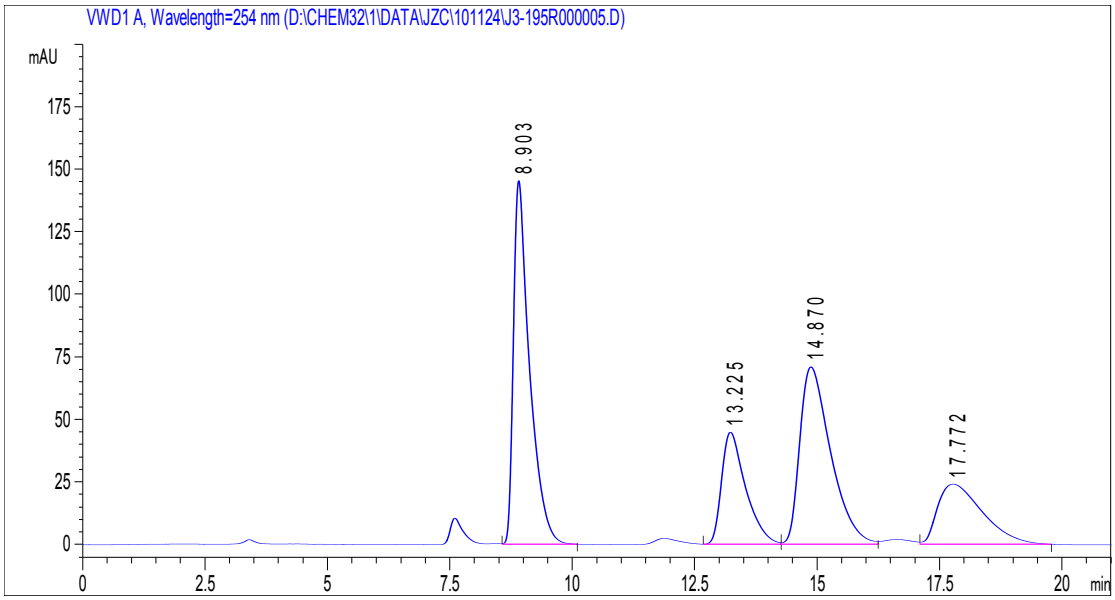
24) (3*R*,4*S*,6*S*)-methyl 1-(2-carbamoylphenyl)-6-hydroxy-2-oxo-4-phenyl piperidine-3-carboxylate 4a2



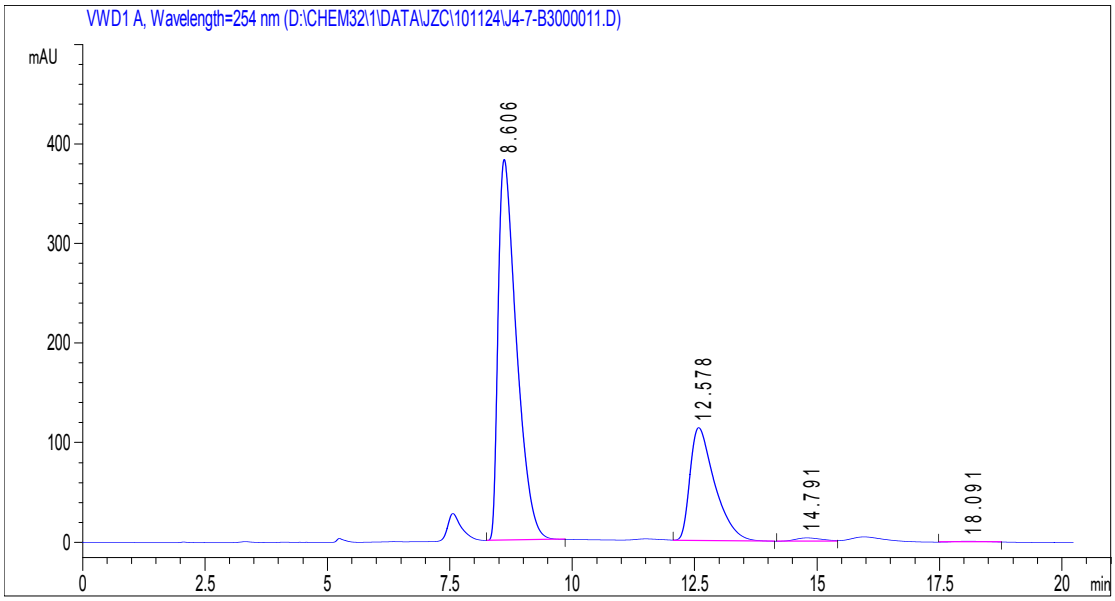
The intermediate product was isolated as a mixture of two diastereomers by colomn chromatography after full conversion of **1a** using ethyl acetate and then 1,4-dioxane as the elute. White solid. Mp 198-199 °C; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.15-6.89 (m, 9H), 6.46-5.18 (m, 1H), 3.95-3.81 (m, 1H), 3.57-3.24 (m, 4H), 2.58-2.37 (m, 1H), 2.03-1.37 (m, 1H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 174.9, 174.4, 174.0, 173.9, 170.9, 170.6, 146.9, 144.2, 143.7, 140.8, 139.7, 136.9, 136.0, 135.4, 134.2, 134.0, 133.6, 133.2, 132.9, 132.8, 132.5, 132.4, 132.3, 132.1, 87.0, 86.0, 62.5, 61.8, 56.9, 42.9, 42.2, 41.8, 41.7, 35.7. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{20}N_2O_5$) requires m/z 368.1372, found m/z 368.1378.

E. HPLC Analysis of The Products.

(2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4a (together with the minor diastereomer 4a1)

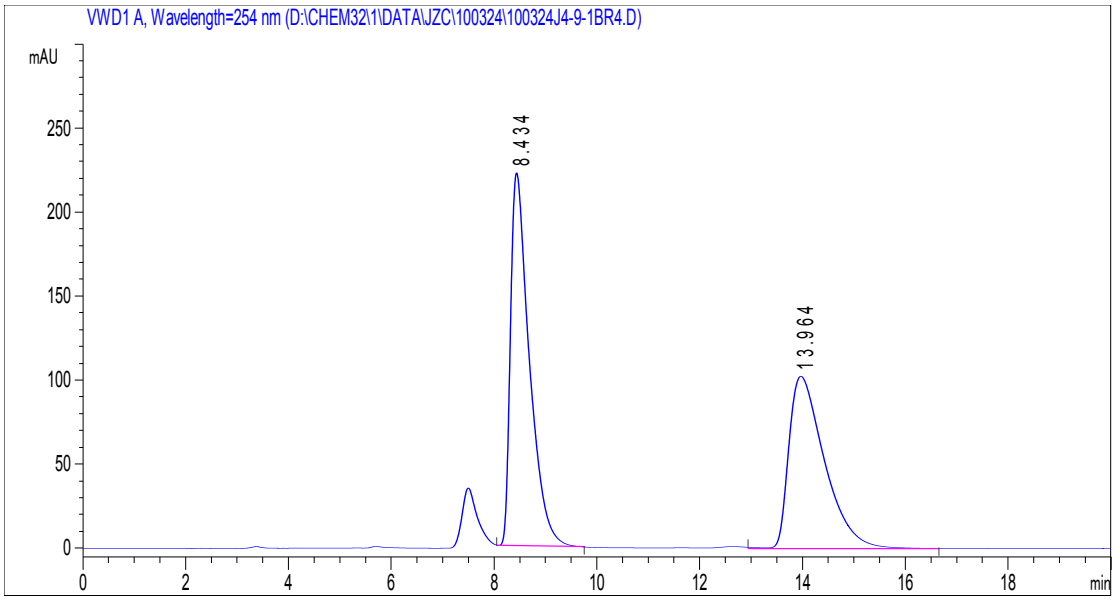


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.903	3333.7	145.4	0.3302	0.452	34.950
2	13.225	1538.9	44.9	0.5059	0.543	16.134
3	14.87	3120.9	71	0.6702	0.53	32.718
4	17.772	1545.1	24.1	0.9725	0.493	16.199

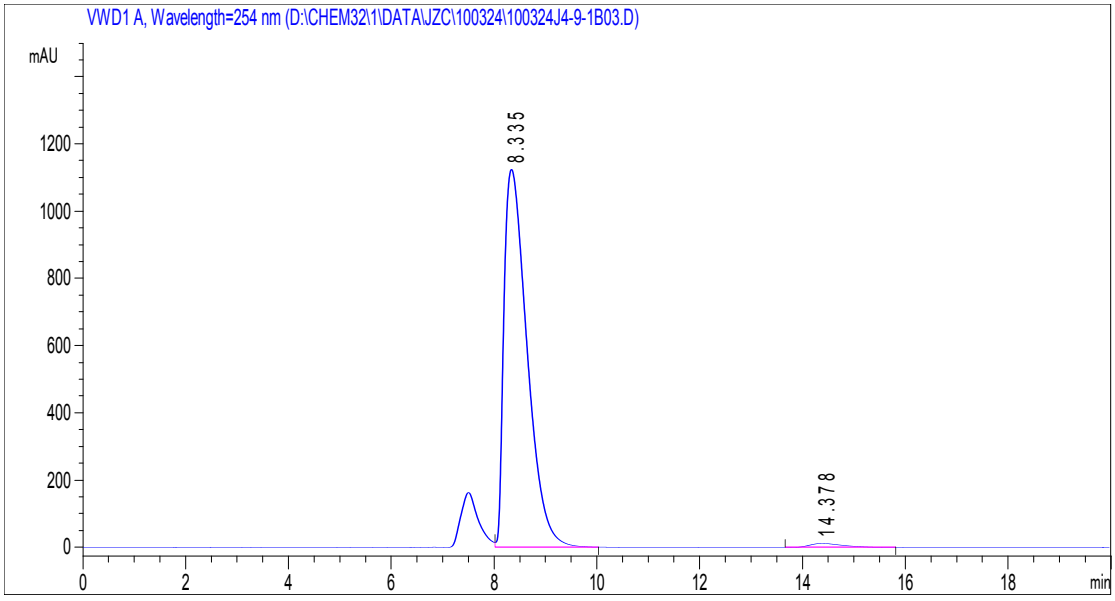


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.606	9982.2	382.7	0.3946	0.455	70.615
2	12.578	3977.2	113.4	0.5211	0.507	28.135
3	14.791	138.8	3.5	0.5937	0.671	0.982
4	18.091	38	9.1E-1	0.6917	0.89	0.269

(2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-m-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4b

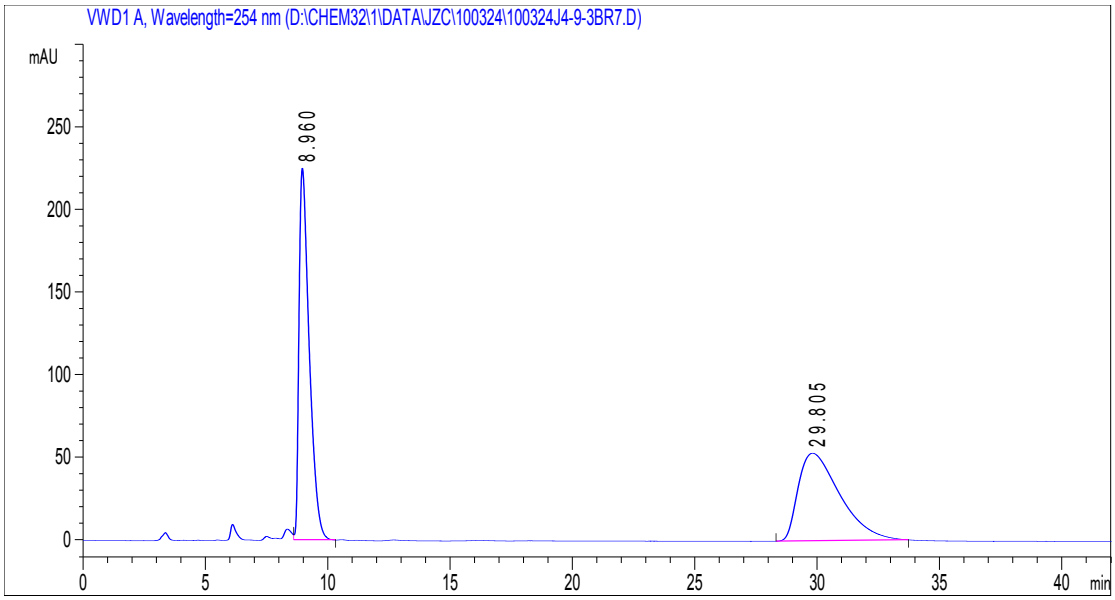


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.434	5666.8	222	0.4254	0.462	53.371
2	13.964	4951	102.6	0.8043	0.492	46.629

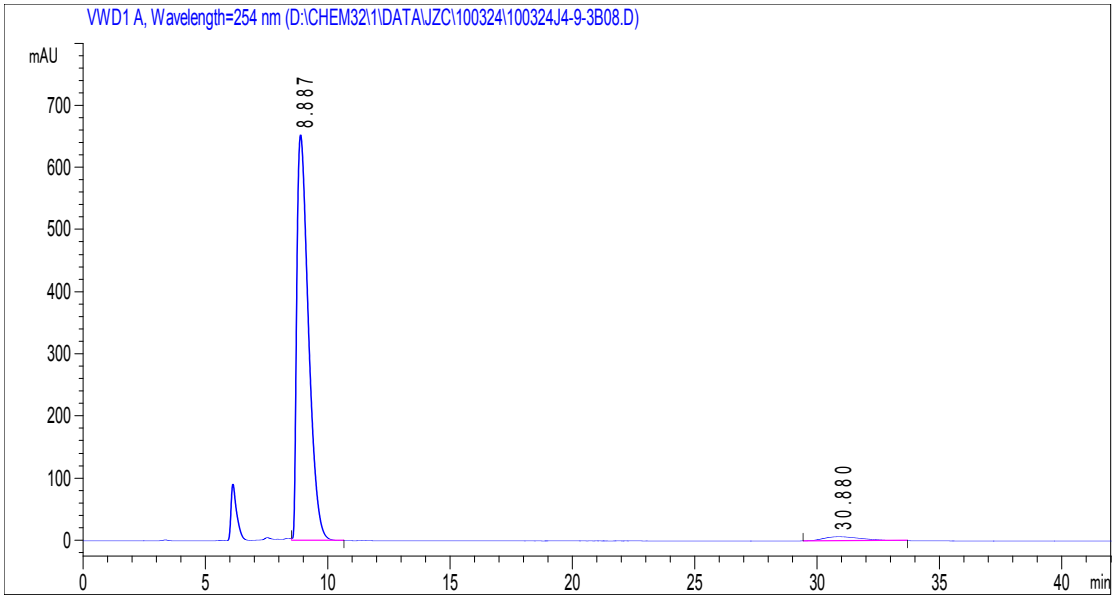


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.335	35090.3	1124.4	0.4864	0.445	98.434
2	14.378	558.2	12.1	0.6908	0.553	1.566

(2*R*,3*S*,4a*S*)-methyl 3-(2-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4c

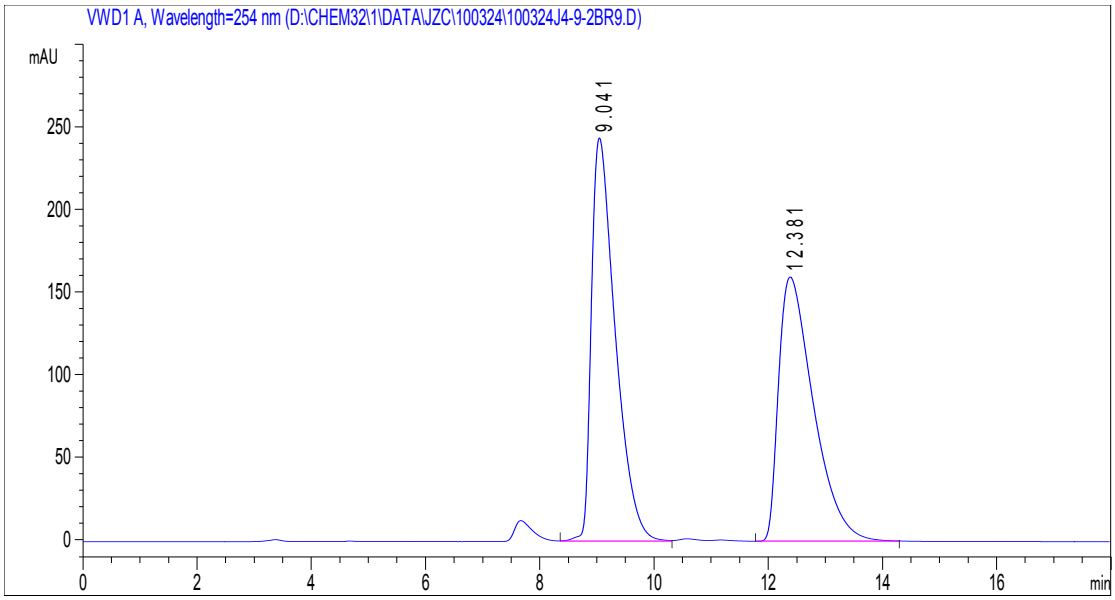


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.96	6579	225	0.4401	0.452	51.125
2	29.805	6289.6	53	1.6888	0.495	48.875

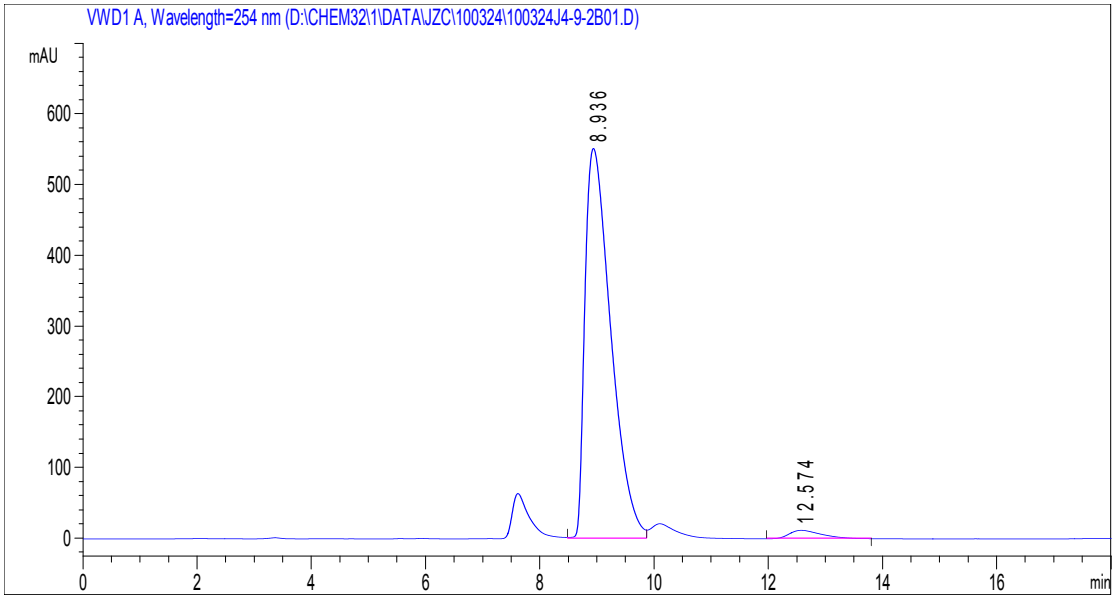


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.887	21615.8	653.3	0.5156	0.443	96.699
2	30.88	738	6.7	1.3046	0.617	3.301

(2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-p-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4d

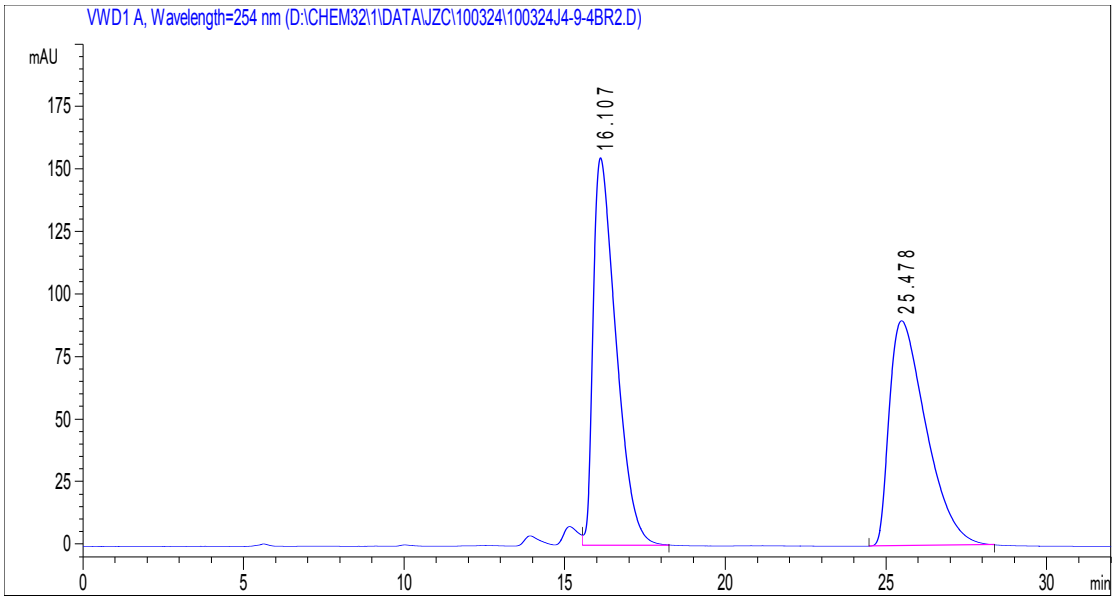


Number	Time	Area	Height	Width	Symmetry	Area %
1	9.041	7112.8	244	0.4391	0.469	51.267
2	12.381	6761.2	159.8	0.6465	0.461	48.733

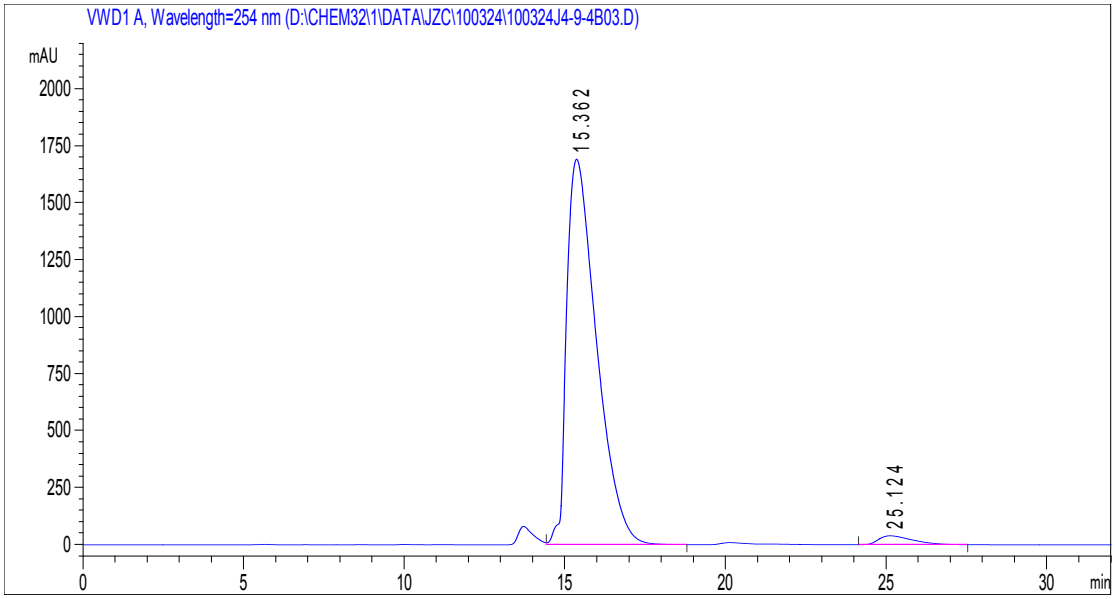


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.936	17383	552.1	0.4867	0.451	97.340
2	12.574	475	11.9	0.588	0.541	2.660

(2*R*,3*S*,4a*S*)-methyl 3-(4-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4e

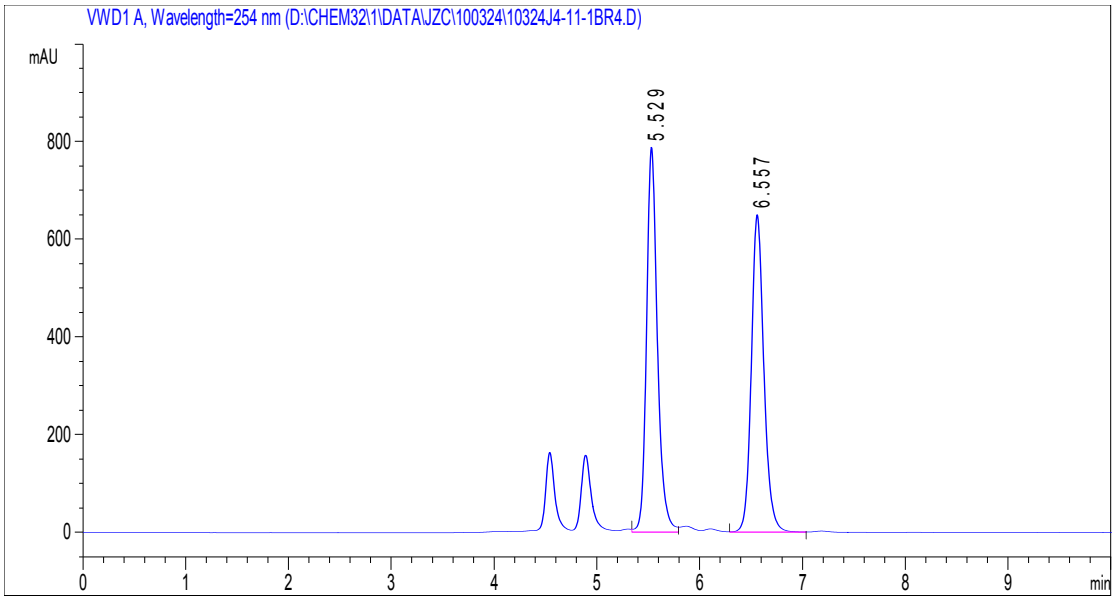


Number	Time	Area	Height	Width	Symmetry	Area %
1	16.107	7688.1	155.1	0.7501	0.443	51.806
2	25.478	7152.1	90	1.1992	0.466	48.194

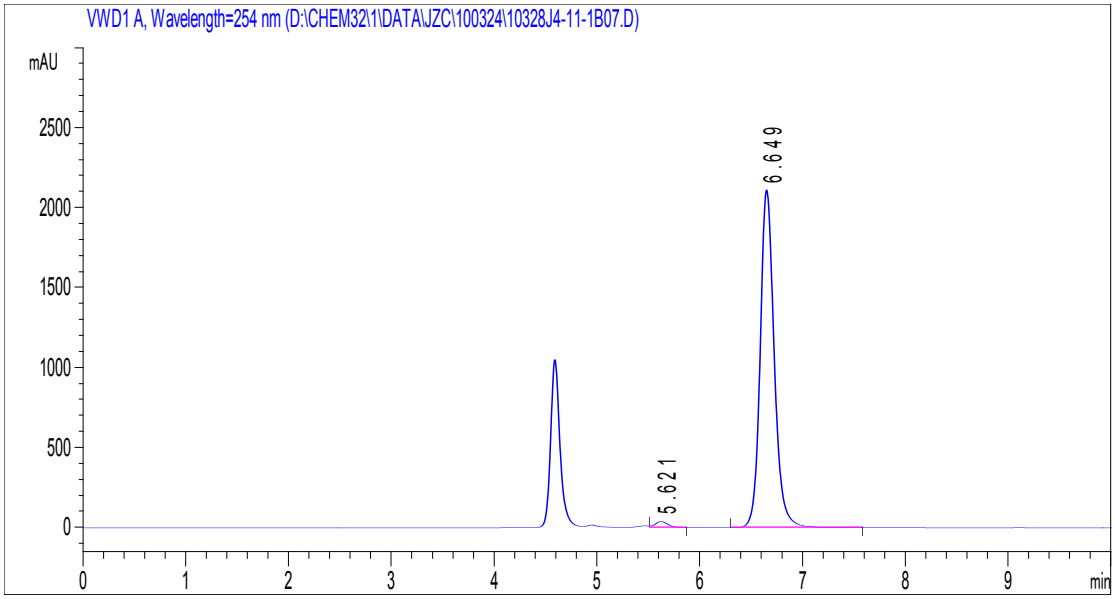


Number	Time	Area	Height	Width	Symmetry	Area %
1	15.362	109367.4	1692.1	0.9957	0.467	97.442
2	25.124	2871.1	39.1	1.101	0.482	2.558

(2*R*,3*S*,4a*S*)-methyl 3-(2-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4f

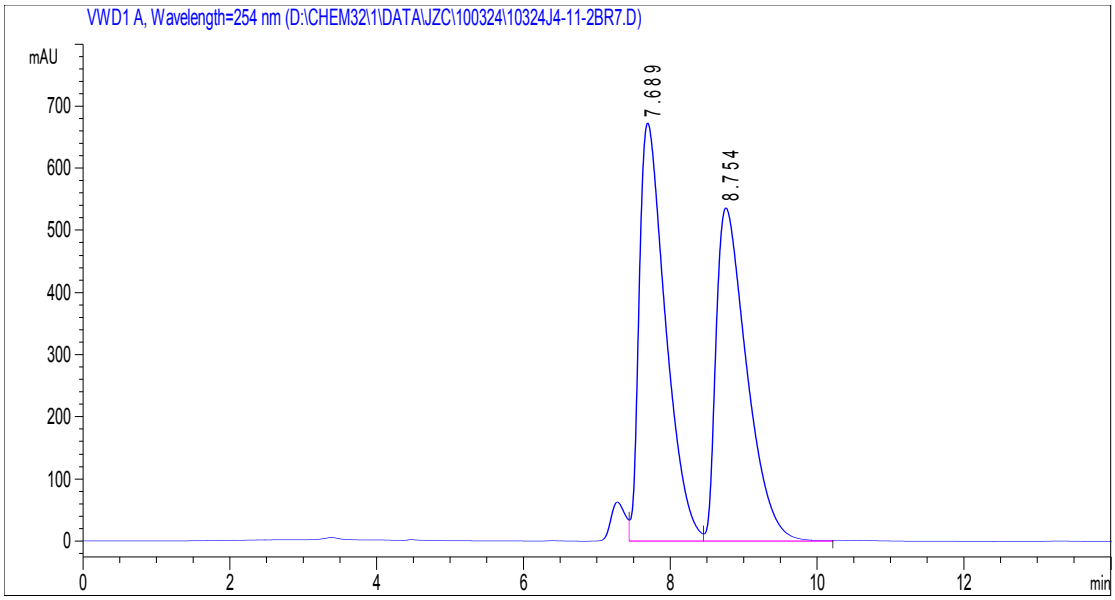


Number	Time	Area	Height	Width	Symmetry	Area %
1	5.529	5821.8	789.6	0.1108	0.78	51.122
2	6.557	5566.2	650.9	0.1303	0.828	48.878

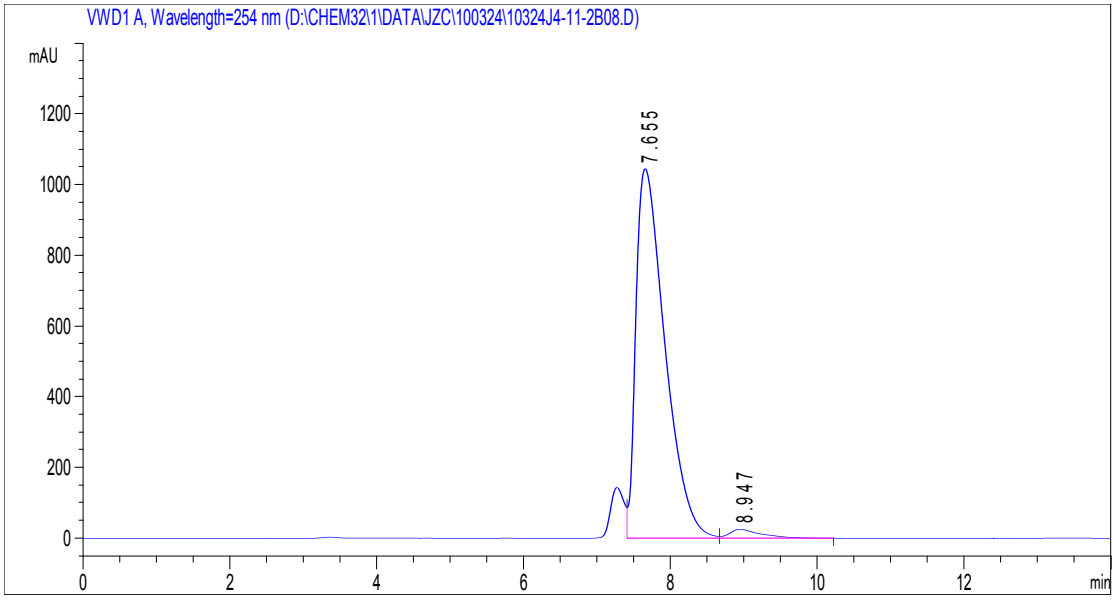


Number	Time	Area	Height	Width	Symmetry	Area %
1	5.621	366.7	40.1	0.1359	0.767	1.788
2	6.649	20149.6	2113.1	0.1462	0.793	98.212

(2*R*,3*S*,4a*S*)-methyl 3-(3-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4g

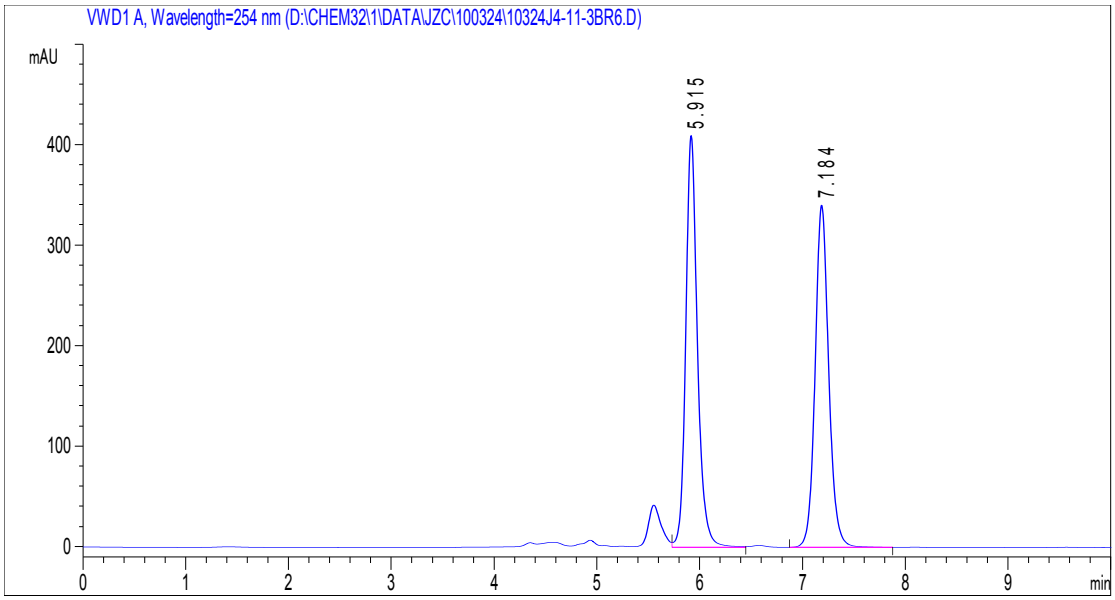


Number	Time	Area	Height	Width	Symmetry	Area %
1	7.689	16766.6	673	0.378	0.44	51.819
2	8.754	15589.3	536.5	0.4424	0.438	48.181

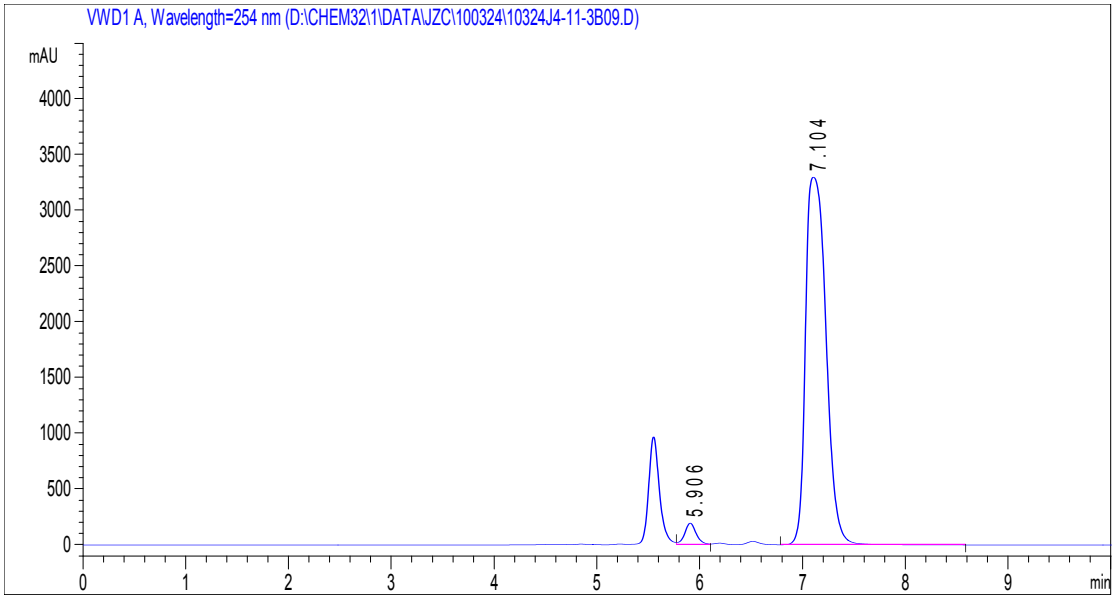


Number	Time	Area	Height	Width	Symmetry	Area %
1	7.655	28665.6	1045.2	0.4204	0.431	97.433
2	8.947	755.3	25.4	0.4239	0.46	2.567

(2*R*,3*S*,4a*S*)-methyl 3-(4-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4h

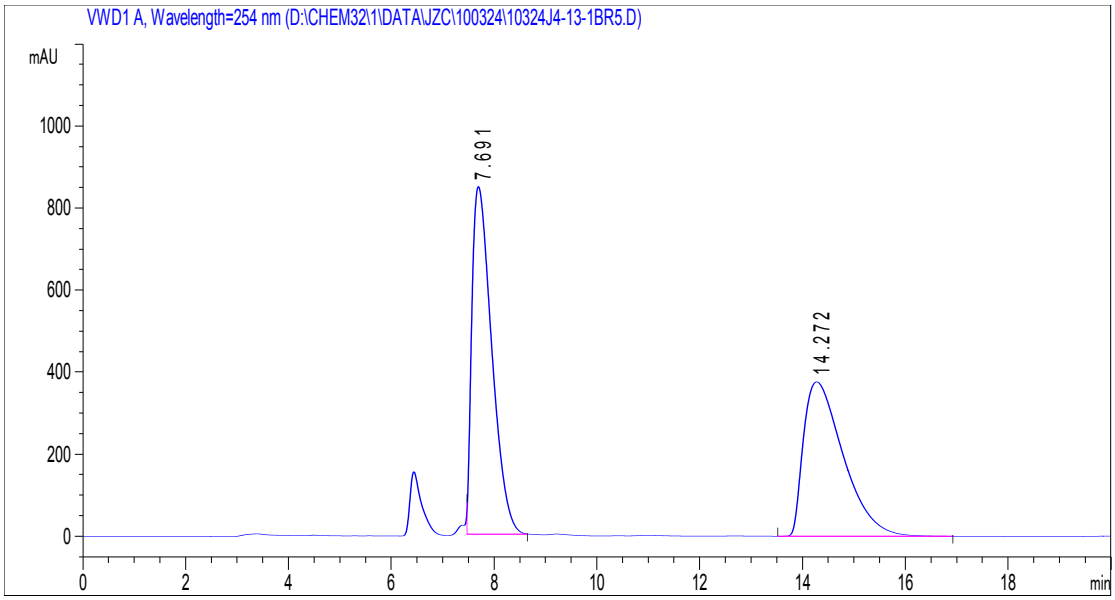


Number	Time	Area	Height	Width	Symmetry	Area %
1	5.915	3239.2	409.9	0.1184	0.791	50.786
2	7.184	3139	340.7	0.141	0.868	49.214

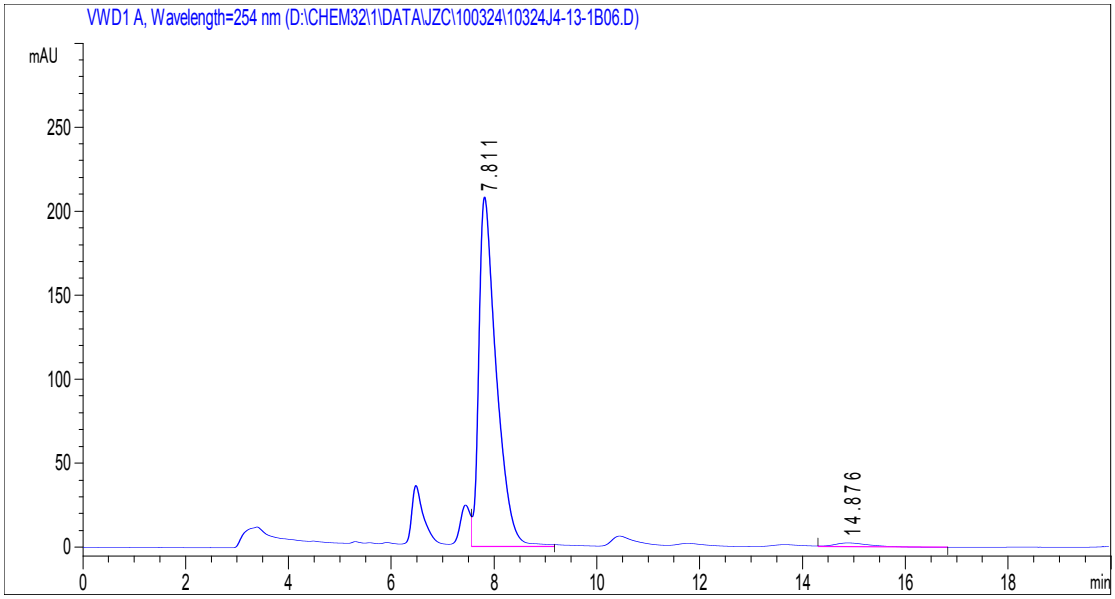


Number	Time	Area	Height	Width	Symmetry	Area %
1	5.906	1577.1	196.4	0.1199	0.867	3.336
2	7.104	45692.2	3300.5	0.2212	0.596	96.664

(2*R*,3*S*,4a*S*)-methyl 3-(2-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4i

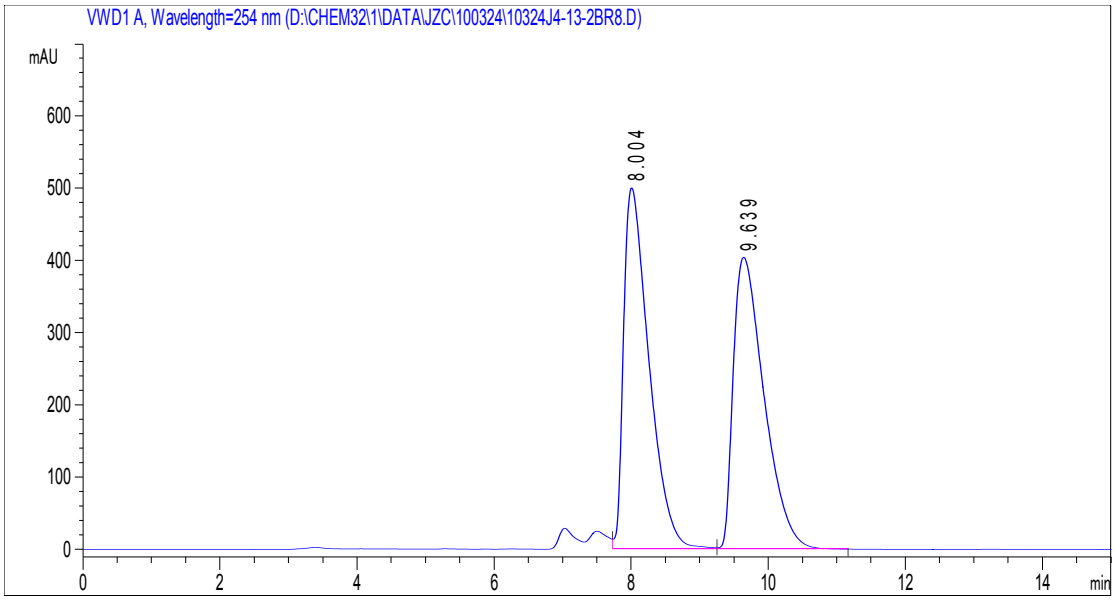


Number	Time	Area	Height	Width	Symmetry	Area %
1	7.691	22735.8	847.7	0.447	0.469	52.558
2	14.272	20523.1	377.8	0.9054	0.477	47.442

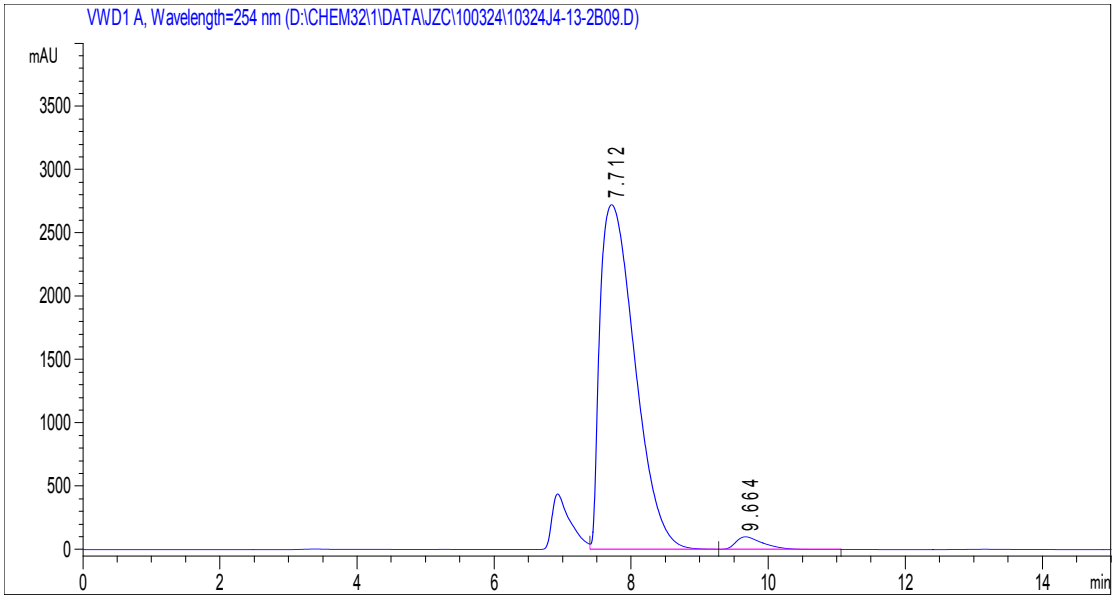


Number	Time	Area	Height	Width	Symmetry	Area %
1	7.811	4908.8	208	0.3933	0.469	97.624
2	14.876	119.5	2.4	0.6636	0.623	2.376

(2*R*,3*S*,4a*S*)-methyl 3-(4-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4j

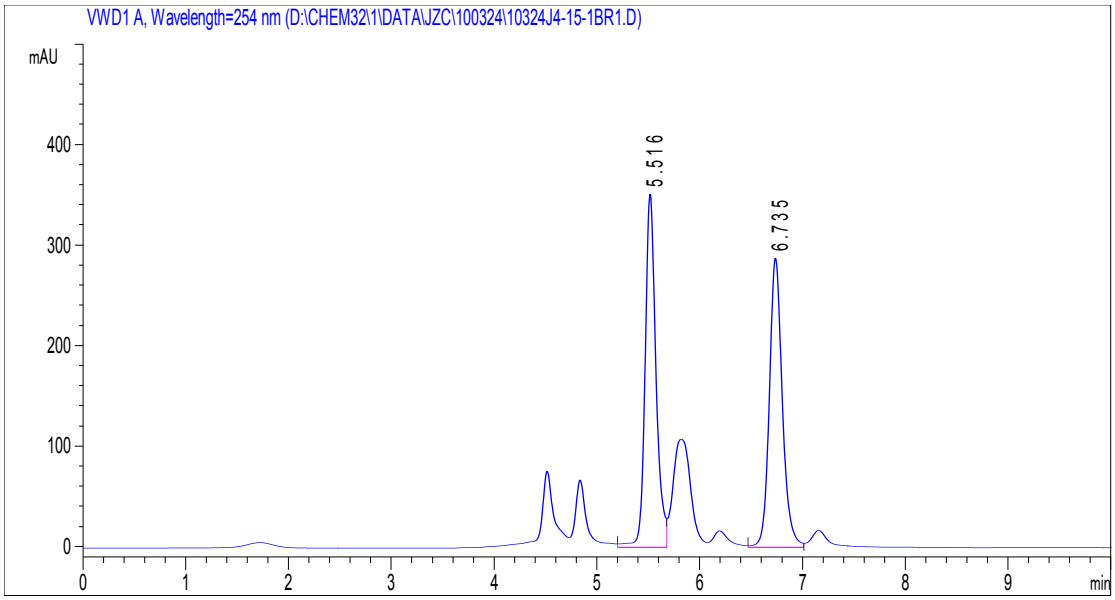


Number	Time	Area	Height	Width	Symmetry	Area %
1	8.004	12911.1	500.6	0.3897	0.428	50.553
2	9.639	12628.7	404.4	0.4779	0.472	49.447

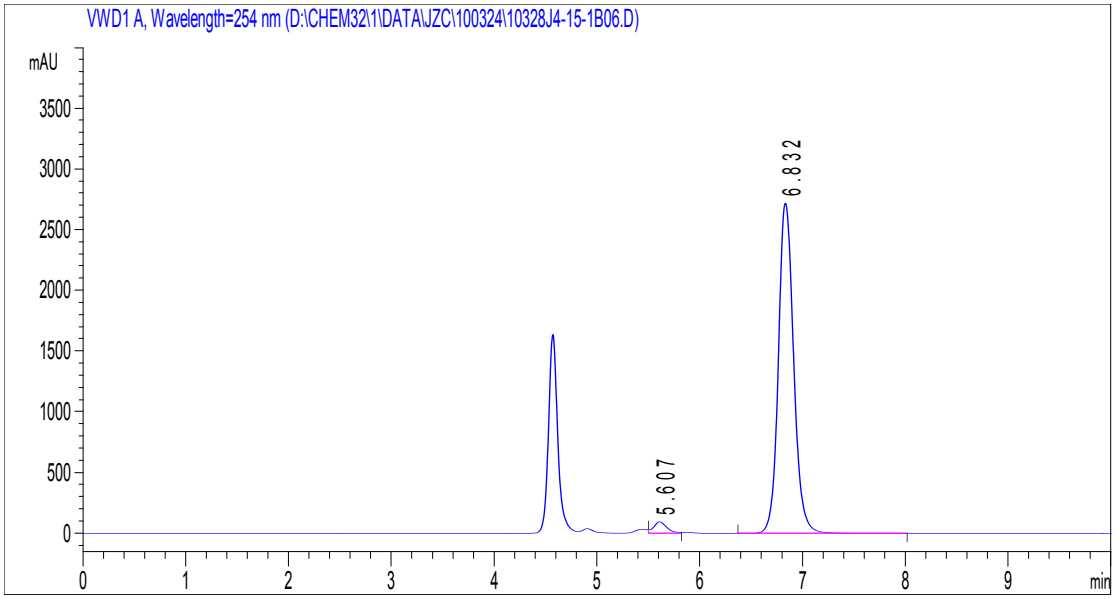


Number	Time	Area	Height	Width	Symmetry	Area %
1	7.712	96506.5	2724.2	0.5633	0.466	97.156
2	9.664	2825.5	100.9	0.4127	0.512	2.844

(2*R*,3*S*,4a*S*)-methyl 3-(2-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4k

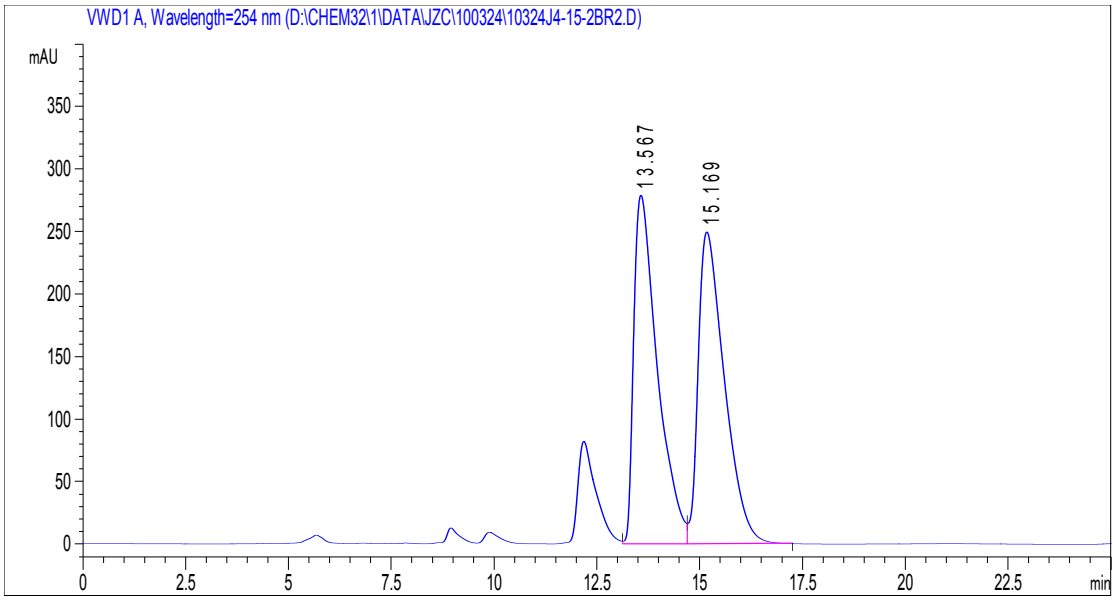


Number	Time	Area	Height	Width	Symmetry	Area %
1	5.516	2596.5	352.3	0.1107	0.832	50.674
2	6.735	2527.4	288	0.133	0.839	49.326

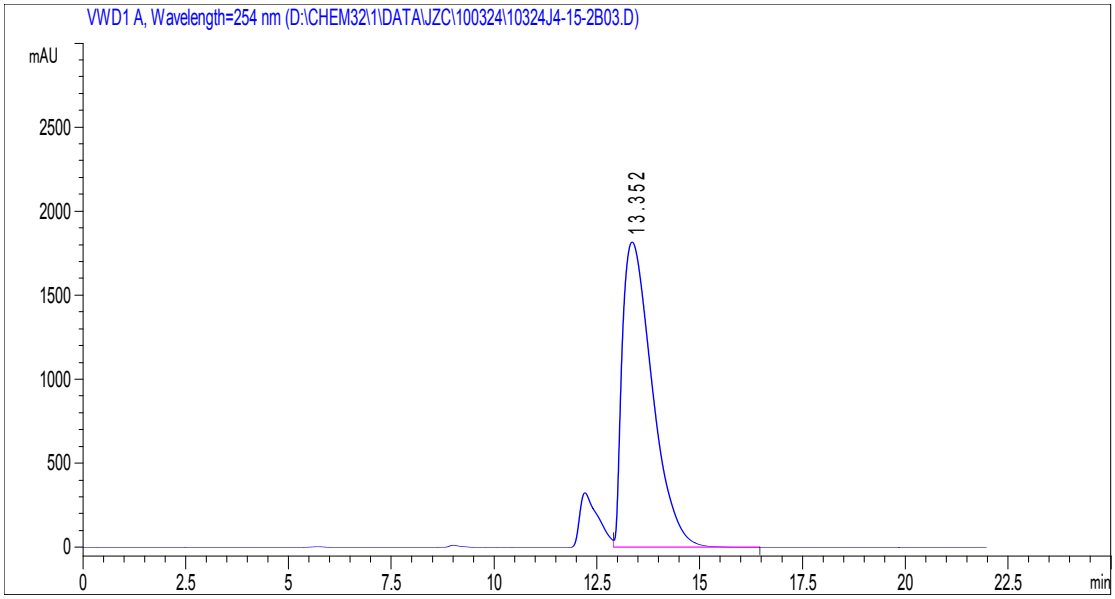


Number	Time	Area	Height	Width	Symmetry	Area %
1	5.607	880.1	96.6	0.1325	0.741	3.028
2	6.832	28190.4	2722.2	0.1587	0.813	96.972

(2*R*,3*S*,4a*S*)-methyl 3-(4-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4l

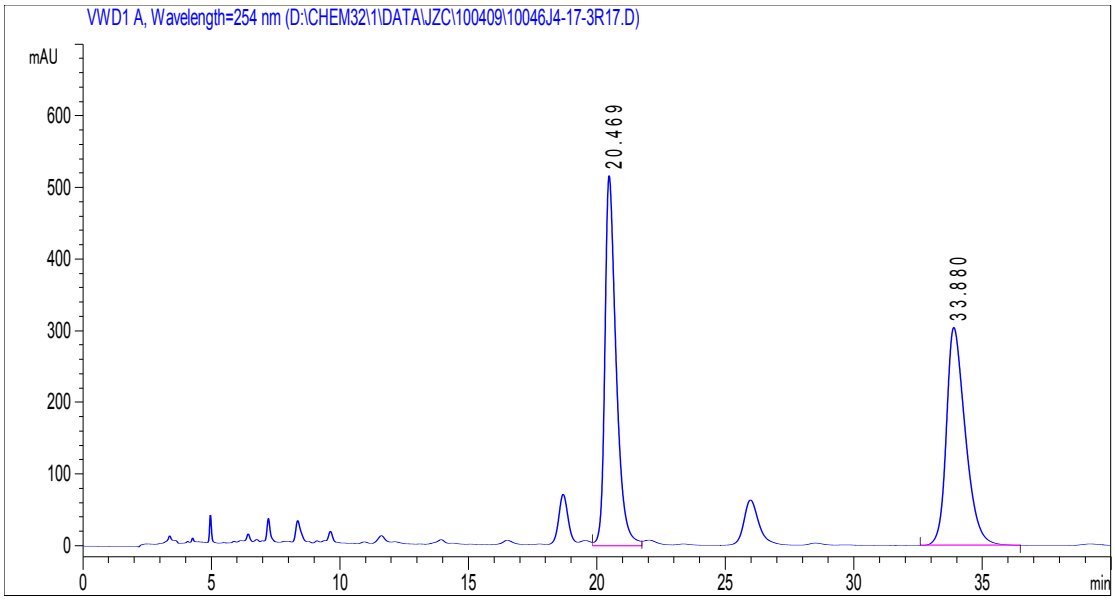


Number	Time	Area	Height	Width	Symmetry	Area %
1	13.567	11148.7	278.9	0.596	0.403	50.187
2	15.169	11065.6	249.5	0.6646	0.457	49.813

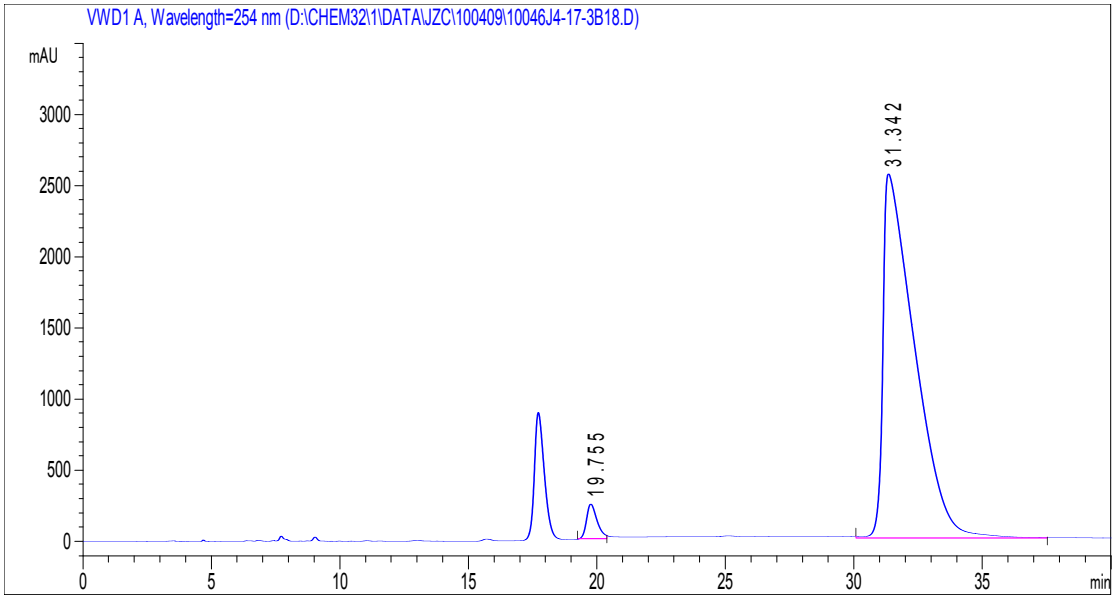


Number	Time	Area	Height	Width	Symmetry	Area %
1	13.352	92349.6	1818	0.8008	0.454	100.000

(2*R*,3*S*,4a*S*)-methyl 3-(4-nitrophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4m

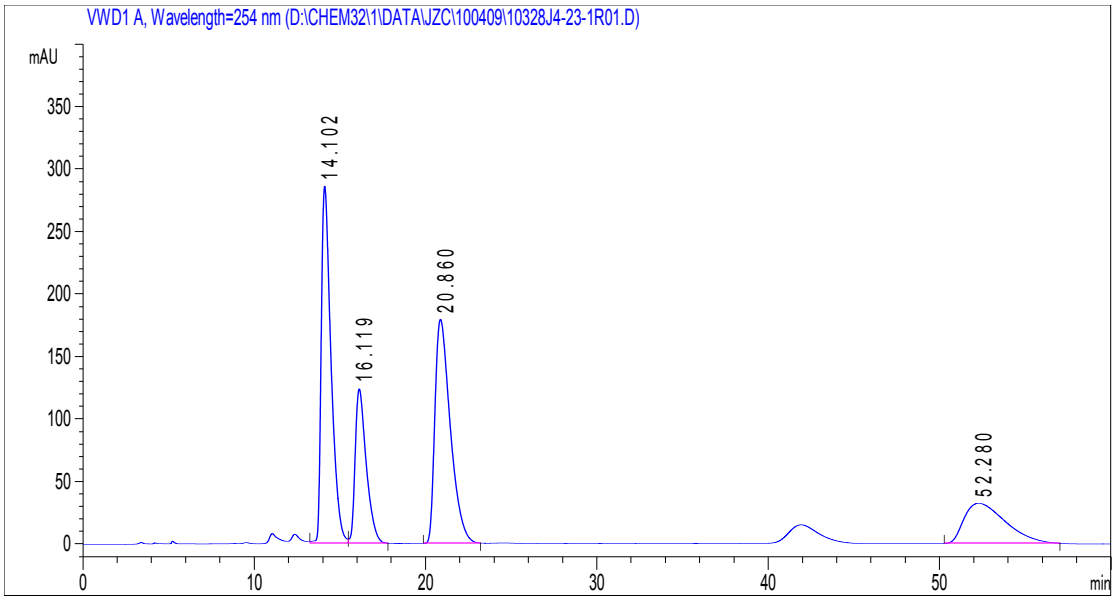


Number	Time	Area	Height	Width	Symmetry	Area %
1	20.469	15806.9	517	0.4557	0.576	50.276
2	33.88	15633.6	304.4	0.7738	0.617	49.724

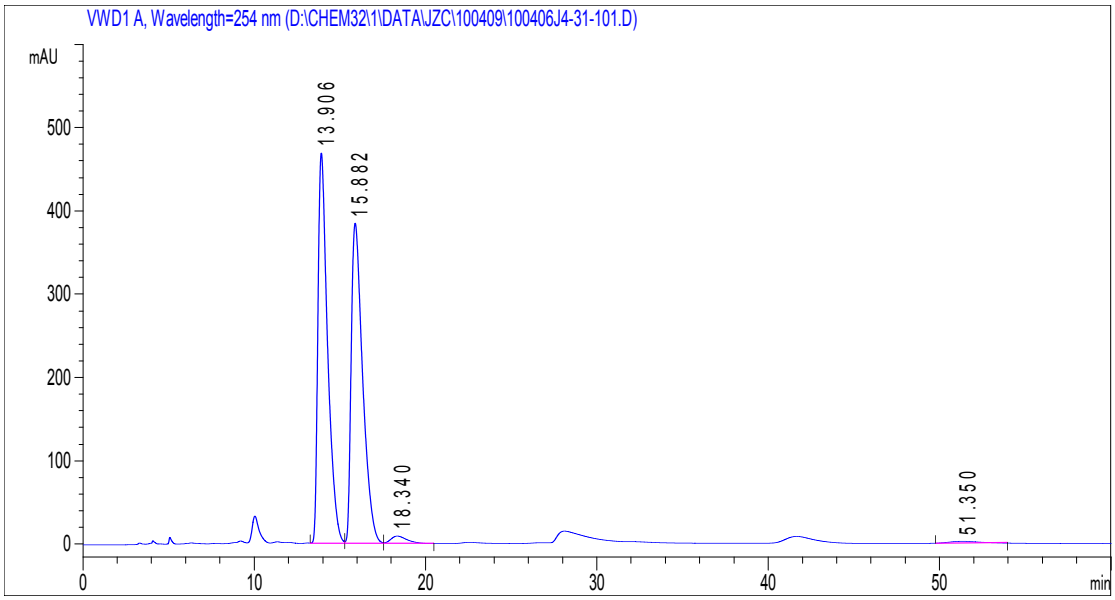


Number	Time	Area	Height	Width	Symmetry	Area %
1	19.755	7144.9	246.4	0.4833	0.646	3.137
2	31.342	220588.1	2562.7	1.4346	0.215	96.863

(2*R*,3*S*)-methyl 1-oxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3] oxazine-2-carboxylate 4n

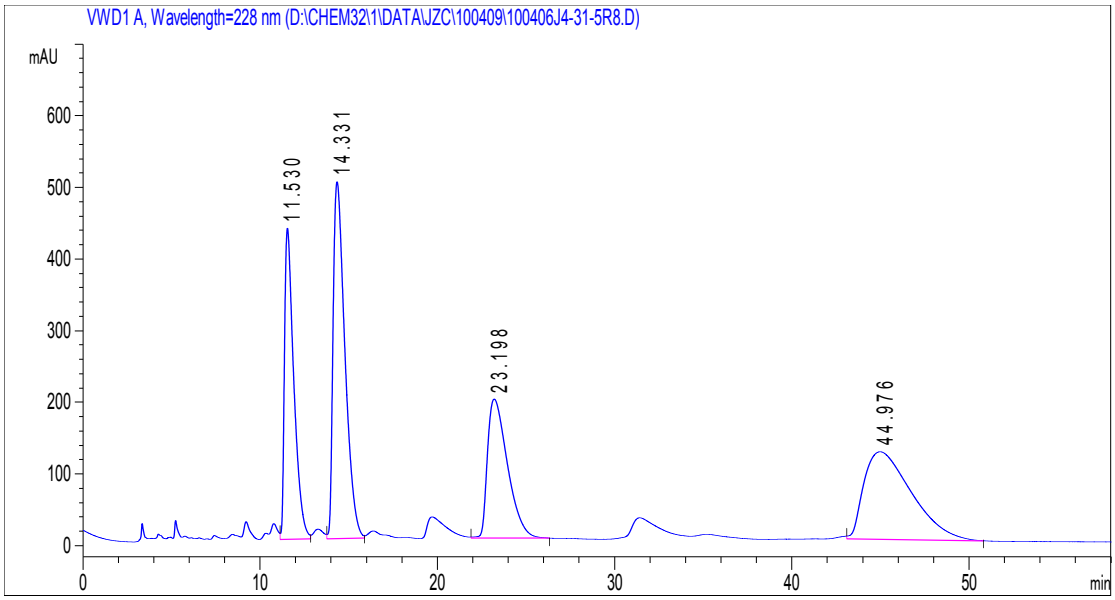


Number	Time	Area	Height	Width	Symmetry	Area %
1	14.102	11396.8	286	0.6003	0.504	33.950
2	16.119	5581.2	123.7	0.6795	0.548	16.626
3	20.86	11172.5	179.3	0.9498	0.523	33.282
4	52.28	5419	32.2	2.0216	0.545	16.143

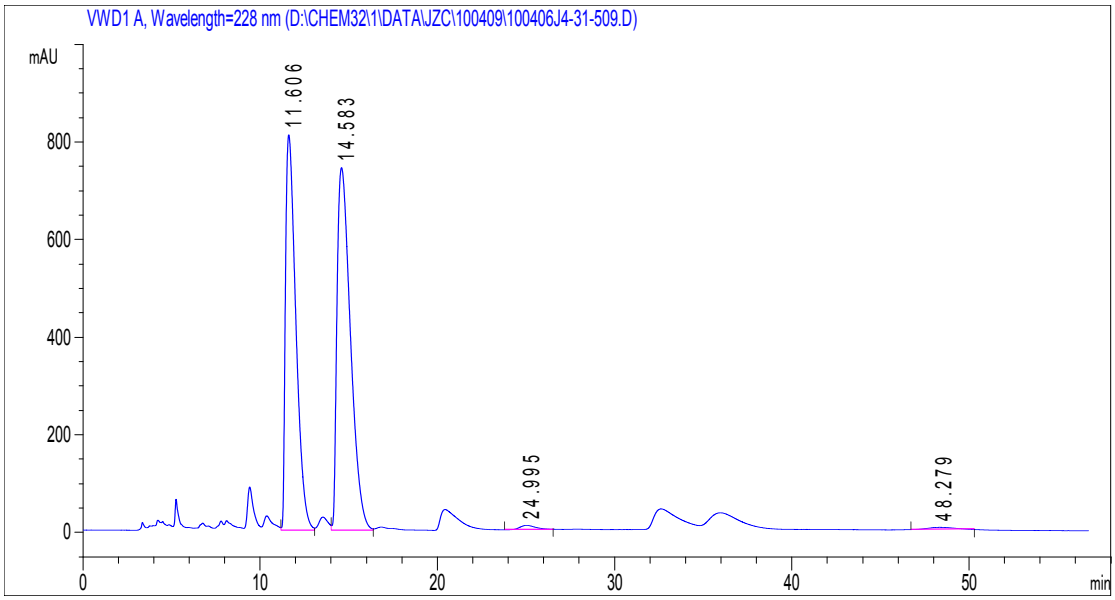


Number	Time	Area	Height	Width	Symmetry	Area %
1	13.906	18442.9	469.1	0.5868	0.5	49.499
2	15.882	17920.7	384.7	0.708	0.493	48.098
3	18.34	614.9	9.2	0.9537	0.624	1.650
4	51.35	280.4	2.2	1.4669	0.746	0.753

(2*R*,3*S*)-methyl 1-oxo-3-m-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3] oxazine-2-carboxylate 4o

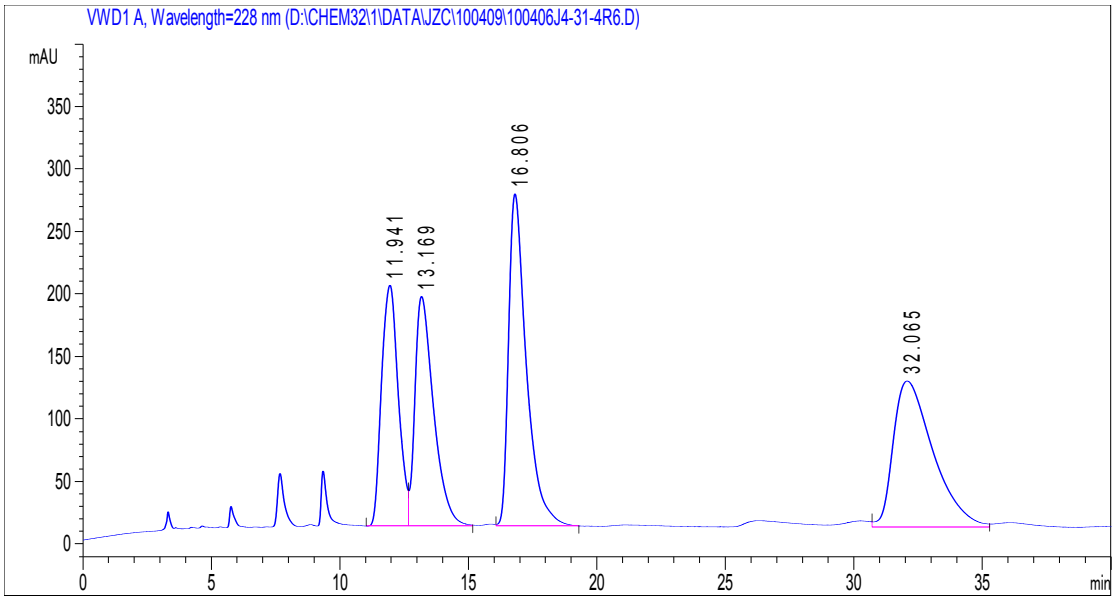


Number	Time	Area	Height	Width	Symmetry	Area %
1	11.53	15973.7	434.4	0.5426	0.427	20.584
2	14.331	23150.9	498.2	0.7081	0.47	29.832
3	23.198	15374.9	194.7	1.1337	0.485	19.812
4	44.976	23103.6	122.9	2.2075	0.506	29.772

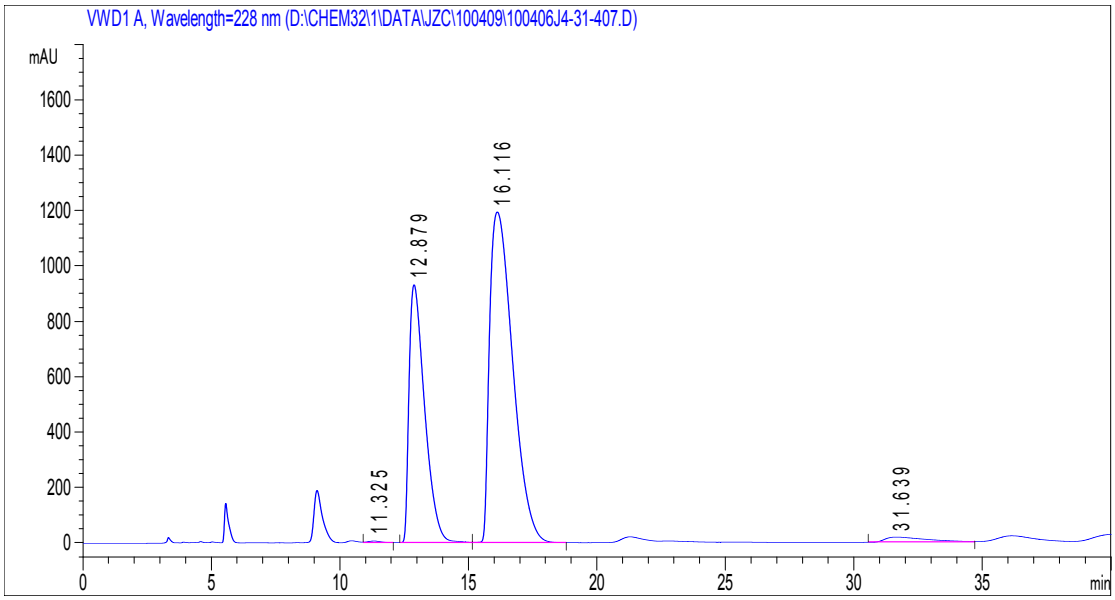


Number	Time	Area	Height	Width	Symmetry	Area %
1	11.606	33032.9	810.3	0.6372	0.43	45.085
2	14.583	39187.2	742.9	0.8294	0.47	53.484
3	24.995	558.3	8.7	0.7703	0.611	0.762
4	48.279	489.9	4.7	1.7437	0.762	0.669

(2*R*,3*S*)-methyl 1-oxo-3-p-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3] oxazine-2-carboxylate 4p

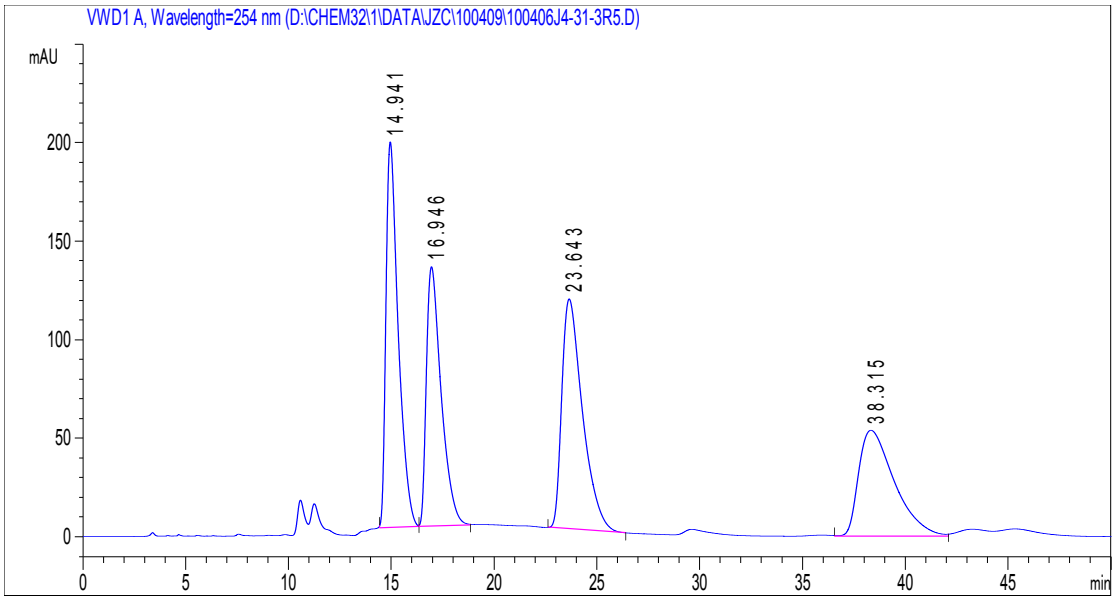


Number	Time	Area	Height	Width	Symmetry	Area %
1	11.941	8739.5	192.9	0.7194	0.933	20.111
2	13.169	9288.2	183.9	0.7494	0.511	21.373
3	16.806	12804.4	265.9	0.7162	0.516	29.465
4	32.065	12624.7	117	1.4015	0.499	29.051

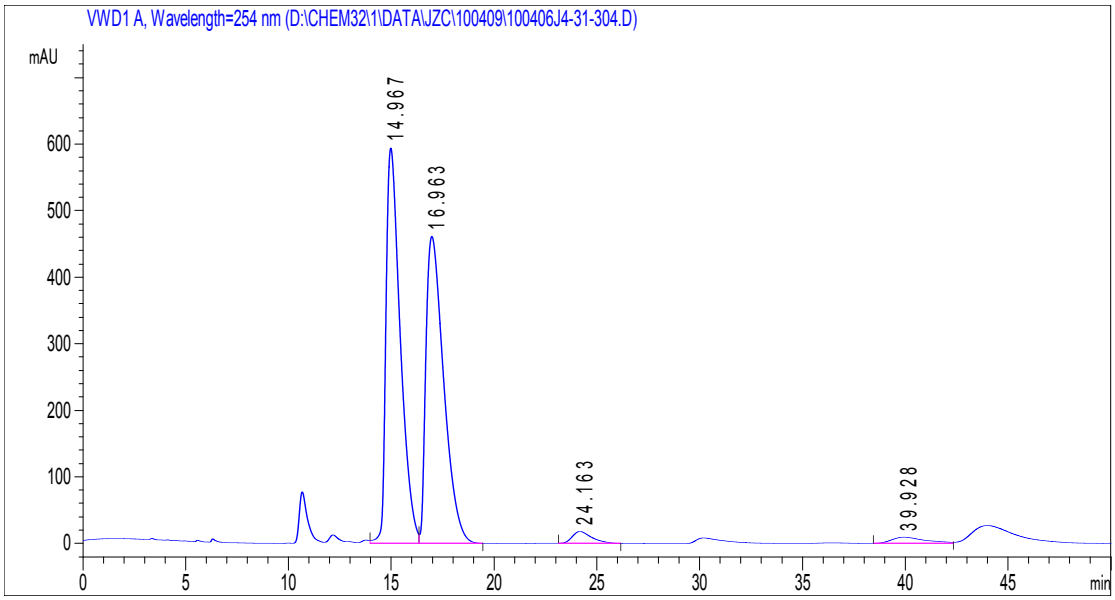


Number	Time	Area	Height	Width	Symmetry	Area %
1	11.325	288.1	7.1	0.5039	0.789	0.247
2	12.879	39440.3	932.3	0.6537	0.433	33.796
3	16.116	74617.7	1194.7	0.9864	0.462	63.939
4	31.639	2354.4	19.3	1.4356	0.324	2.017

(2*R*,3*S*)-methyl 3-(4-methoxyphenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4q

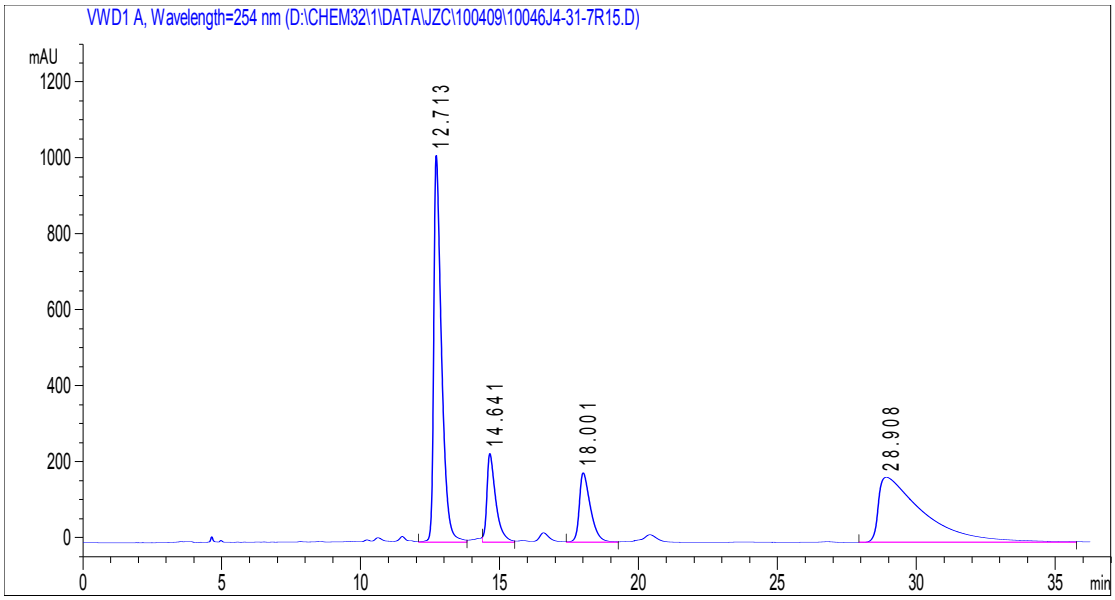


Number	Time	Area	Height	Width	Symmetry	Area %
1	14.941	8144	195.9	0.693	0	27.605
2	16.946	6603.1	131.8	0.835	0.507	22.382
3	23.643	8169.2	116.7	1.0436	0.514	27.690
4	38.315	6585.6	54	2.0323	0.504	22.323

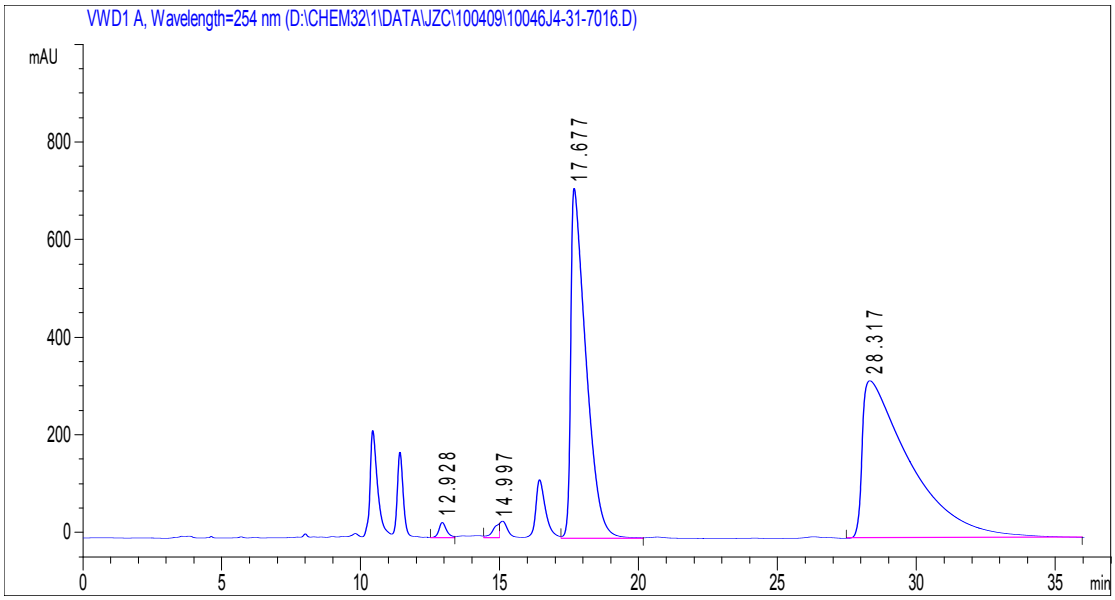


Number	Time	Area	Height	Width	Symmetry	Area %
1	14.967	28777.4	594.1	0.7354	0.476	48.983
2	16.963	27766.1	461.4	0.938	0.464	47.262
3	24.163	1167.2	17.7	0.9645	0.596	1.987
4	39.928	1038.9	9.2	1.3728	0.574	1.768

(2*R*,3*S*)-methyl 3-(3-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4r

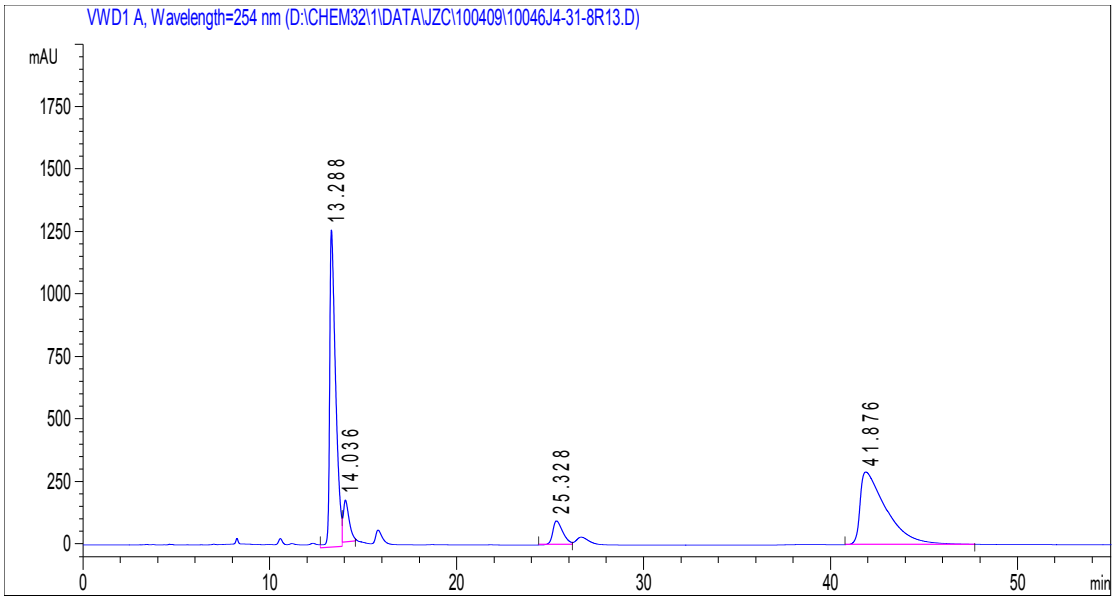


Number	Time	Area	Height	Width	Symmetry	Area %
1	12.713	19946	1019.6	0.2894	0.451	39.921
2	14.641	5201.4	233.7	0.371	0.491	10.410
3	18.001	5150	183.5	0.4177	0.515	10.308
4	28.908	19665.8	172.4	1.9008	0.2	39.361

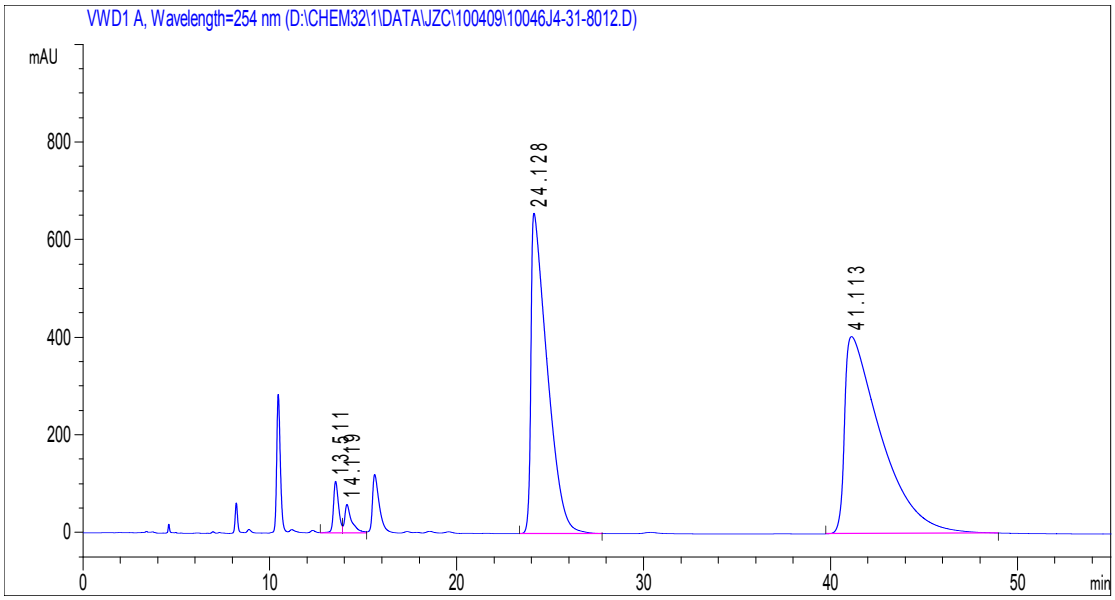


Number	Time	Area	Height	Width	Symmetry	Area %
1	12.928	677.3	32.6	0.3047	0.753	1.008
2	14.997	518.6	30.6	0.2825	0	0.772
3	17.677	27333.6	717.4	0.561	0.275	40.669
4	28.317	38681.1	322.7	1.624	0.167	57.552

(2*R*,3*S*)-methyl 3-(4-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4s

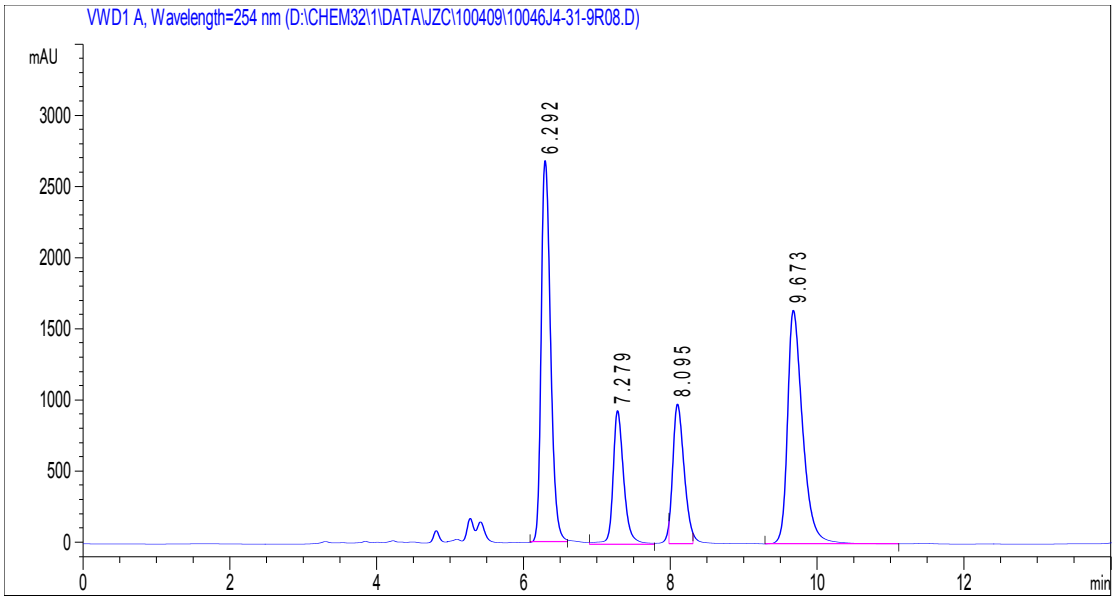


Number	Time	Area	Height	Width	Symmetry	Area %
1	13.288	28210.9	1269.8	0.3703	0.418	44.142
2	14.036	3661.1	169.9	0.3591	0.532	5.729
3	25.328	3702.6	96.7	0.5751	0.56	5.794
4	41.876	28334.5	291.3	1.3969	0.256	44.336

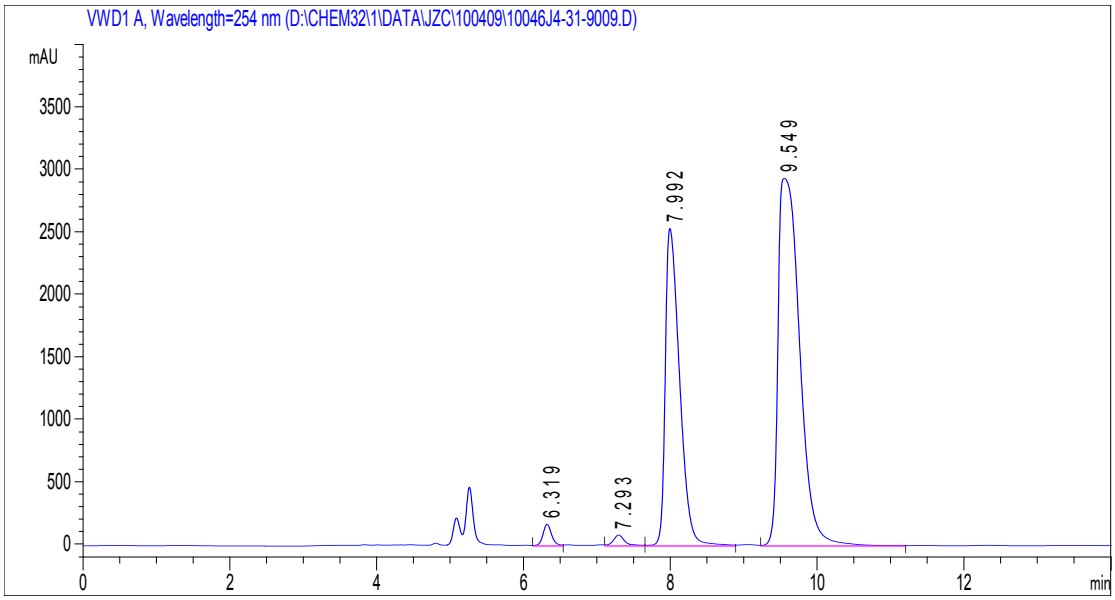


Number	Time	Area	Height	Width	Symmetry	Area %
1	13.511	2119.3	106.9	0.2953	0.74	2.157
2	14.119	1595.5	59.4	0.3775	0.413	1.624
3	24.128	39647.1	656.6	0.885	0.221	40.347
4	41.113	54902.9	404.1	1.9462	0.211	55.872

(2*R*,3*S*)-methyl 3-(2-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4t

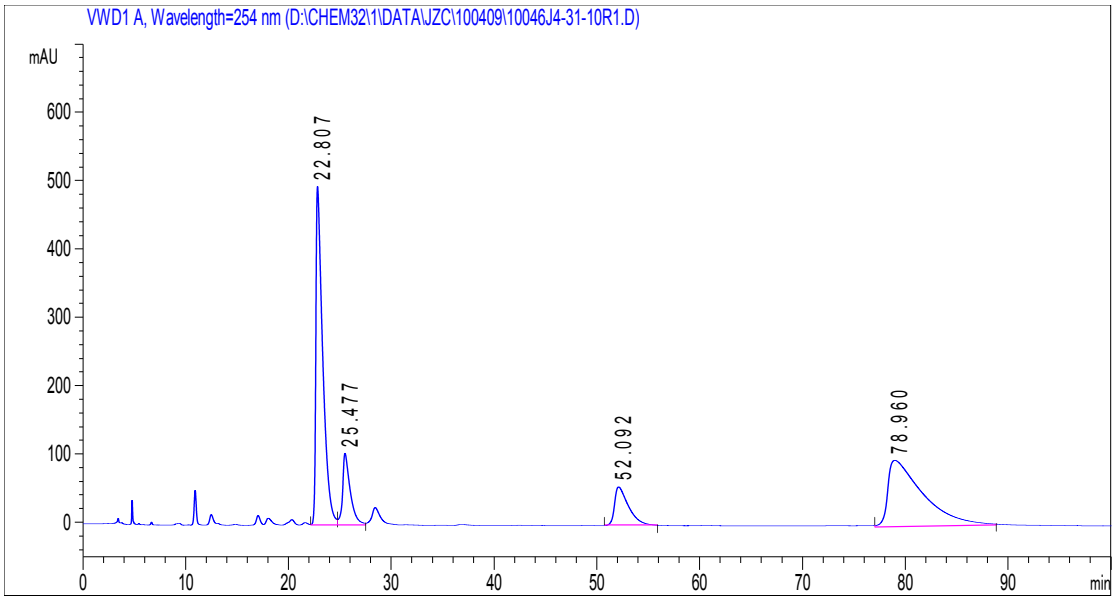


Number	Time	Area	Height	Width	Symmetry	Area %
1	6.292	23722.5	2680.9	0.1475	0.7	35.217
2	7.279	9633.6	941.4	0.1706	0.72	14.301
3	8.095	10321.4	982.9	0.175	0.681	15.323
4	9.673	23683.4	1643.4	0.2176	0.58	35.159

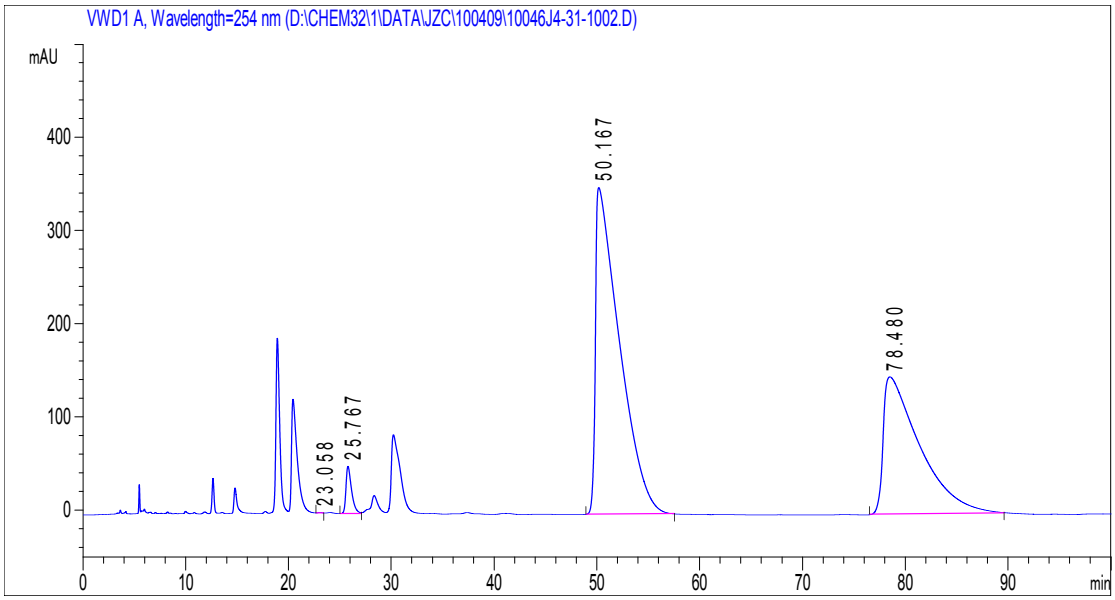


Number	Time	Area	Height	Width	Symmetry	Area %
1	6.319	1481.1	174	0.1284	0.847	1.522
2	7.293	1005	88.1	0.168	0.77	1.033
3	7.992	34521.9	2540.8	0.2095	0.452	35.475
4	9.549	60304.2	2942.1	0.3192	0.385	61.970

(2*R*,3*S*)-methyl 3-(4-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4u

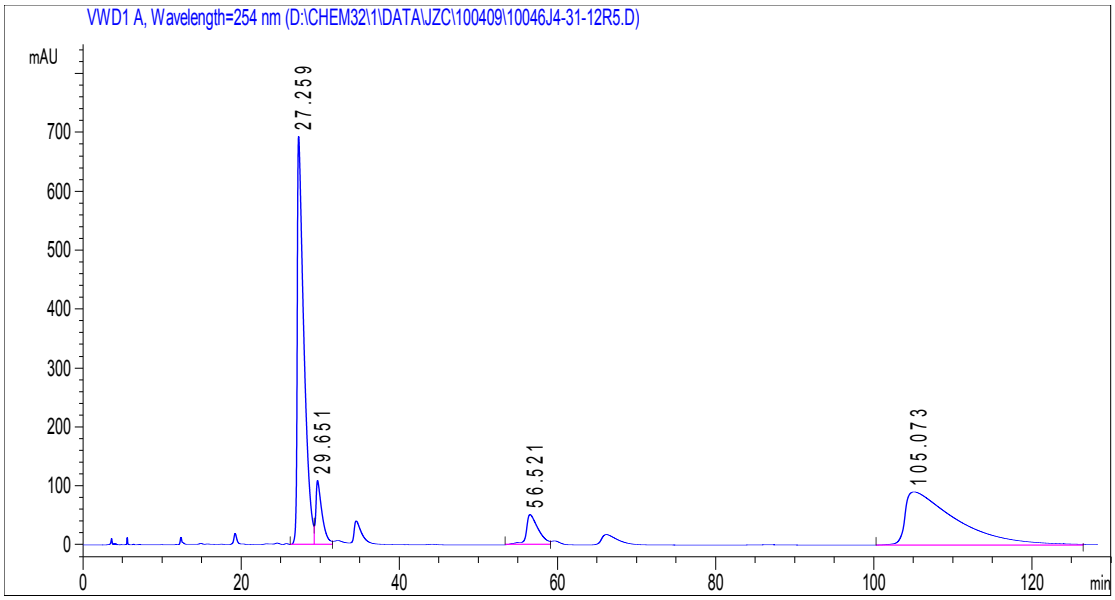


Number	Time	Area	Height	Width	Symmetry	Area %
1	22.807	23099.3	495.5	0.6706	0.298	40.457
2	25.477	5454.5	105.2	0.7346	0.448	9.553
3	52.092	5362.7	56.8	1.3364	0.39	9.392
4	78.96	23179.8	97.3	3.9707	0.243	40.598

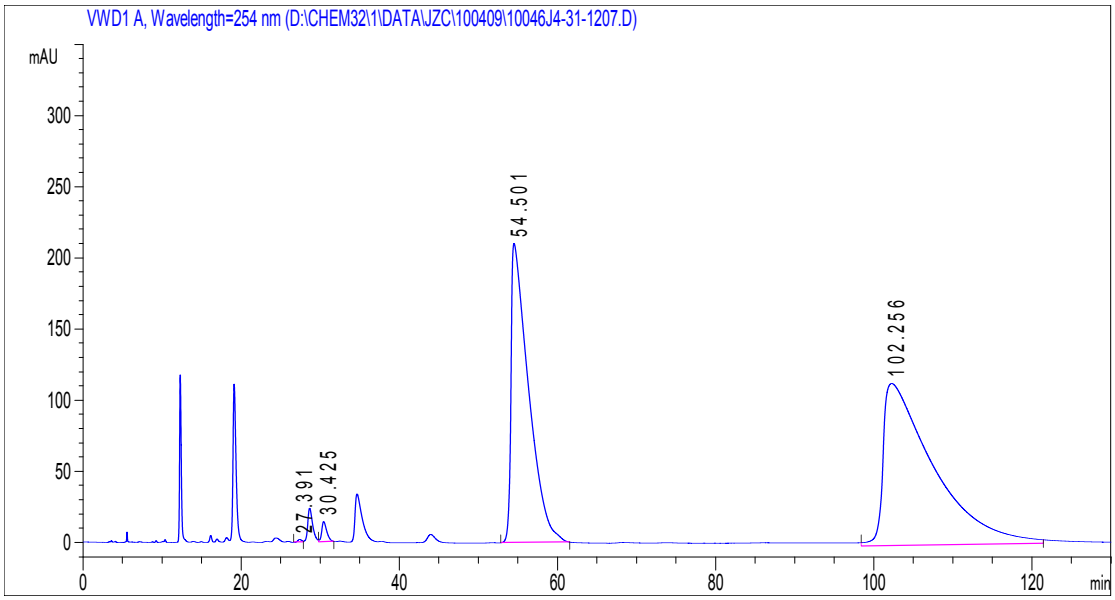


Number	Time	Area	Height	Width	Symmetry	Area %
1	23.058	15.7	6.5E-1	0.4049	1.011	0.016
2	25.767	1934.3	50.9	0.5631	0.517	2.026
3	50.167	56998.6	350.9	2.1865	0.151	59.708
4	78.48	36513.5	147.8	3.3416	0.205	38.249

(2*R*,3*S*)-methyl 3-(4-bromophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4v



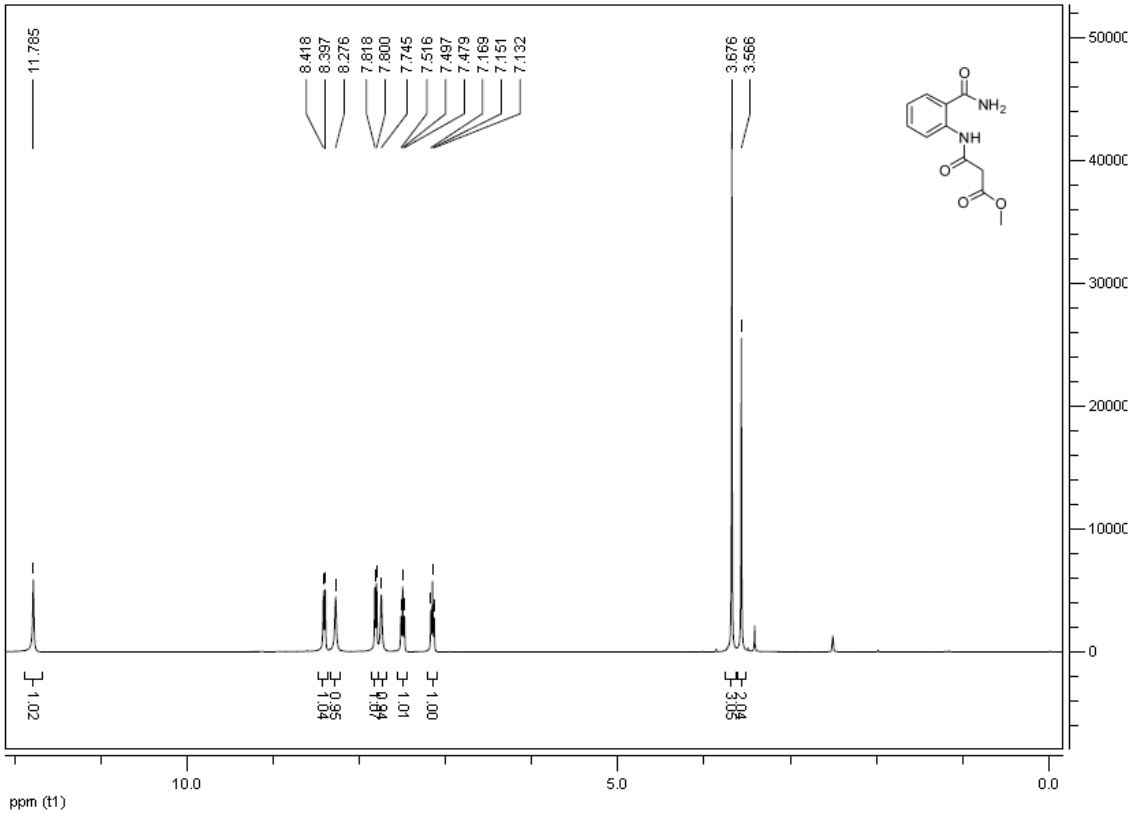
Number	Time	Area	Height	Width	Symmetry	Area %
1	27.259	40391.1	692.8	0.8258	0.252	43.621
2	29.651	5994.2	108.3	0.7929	0.369	6.474
3	56.521	5579.2	51.4	1.5055	0.491	6.025
4	105.073	40630.7	90.3	7.5006	0.204	43.880

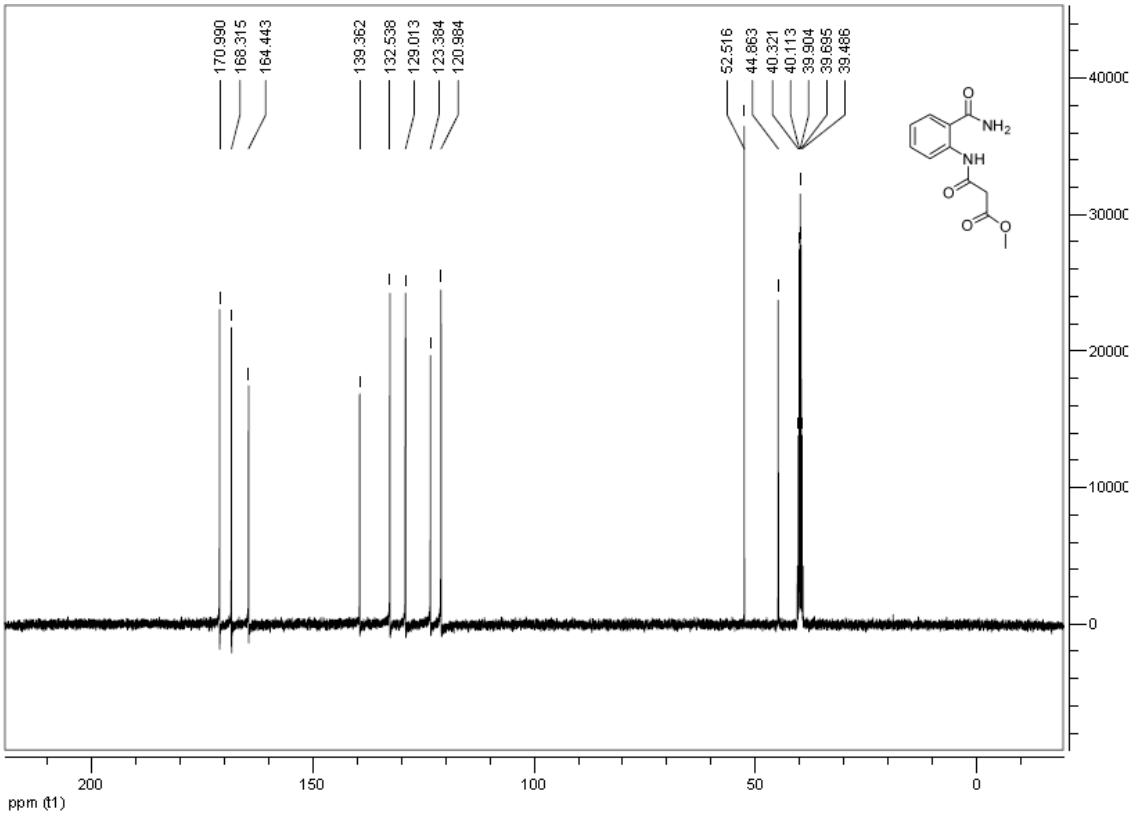


Number	Time	Area	Height	Width	Symmetry	Area %
1	27.391	75.2	2.1	0.5332	0.852	0.090
2	30.425	642.6	14.3	0.6618	0.597	0.768
3	54.501	32356.8	210.2	2.084	0.198	38.679
4	102.256	50579.1	114	7.3978	0.202	60.462

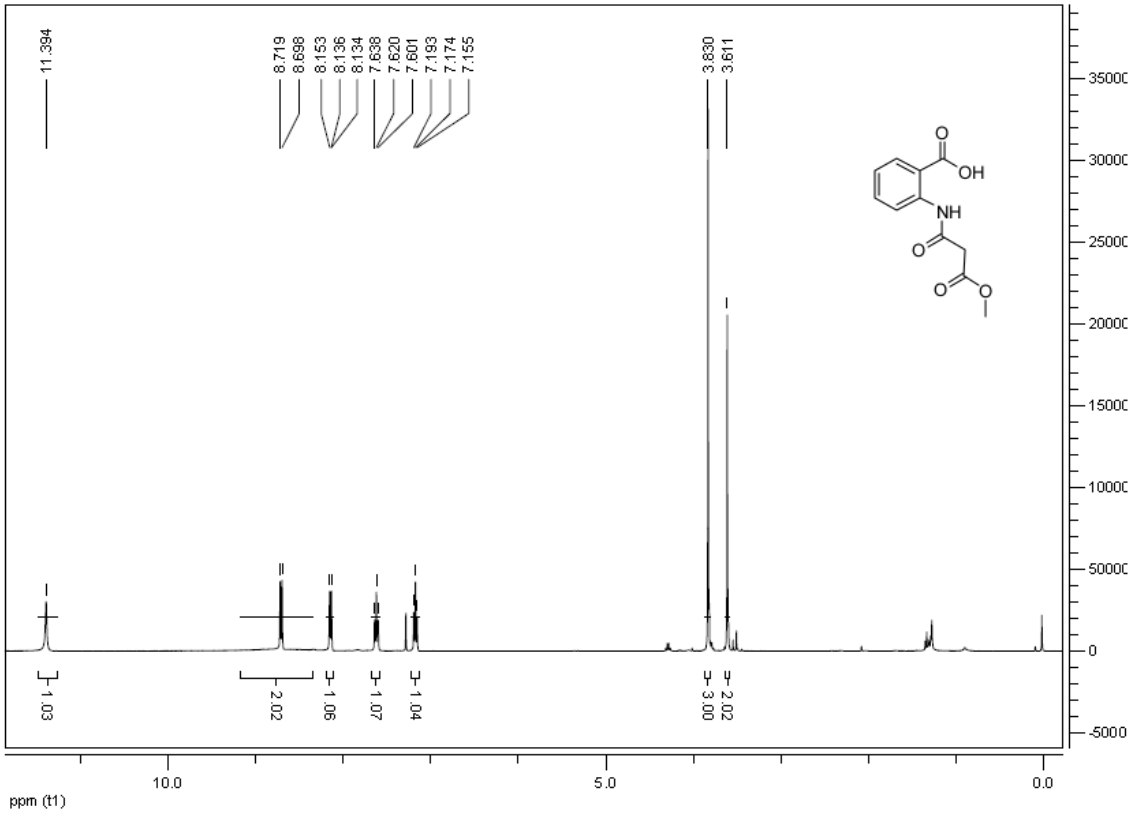
F. NMR Analysis of The Starting Materials and The Products.

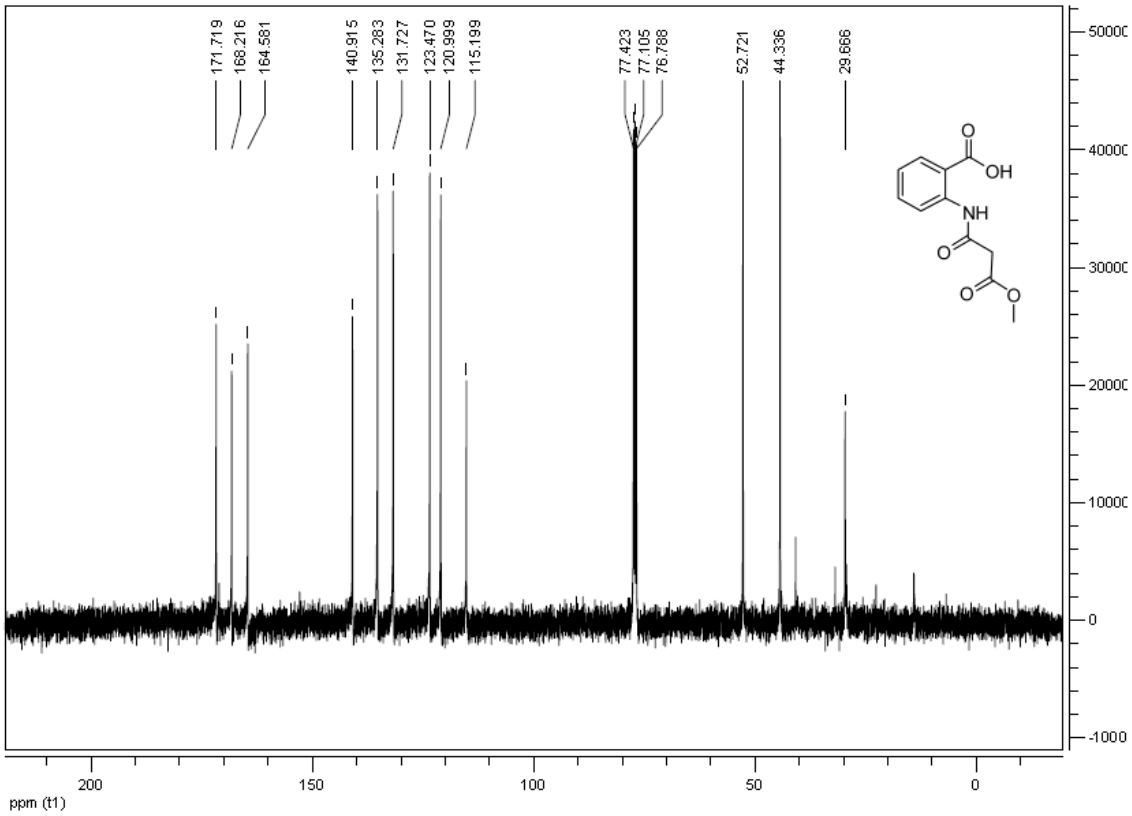
Methyl 3-(2-carbamoylphenylamino)-3-oxopropanoate 1a



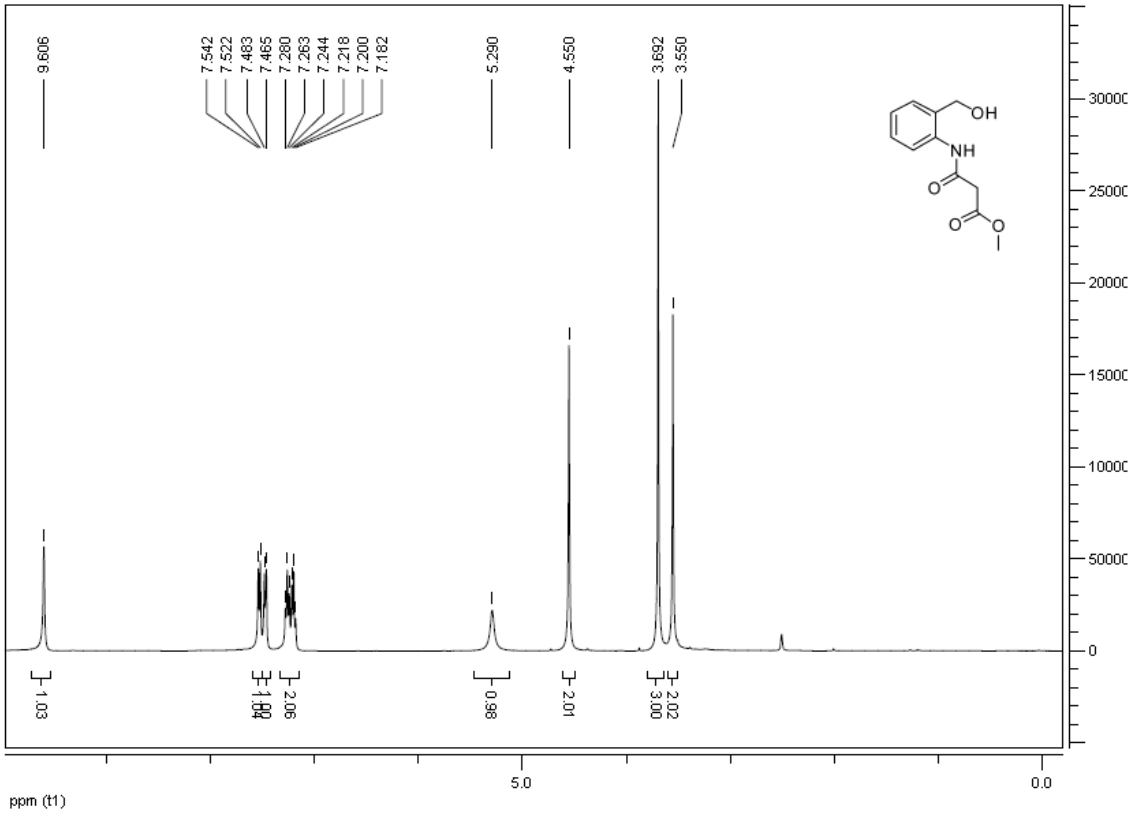


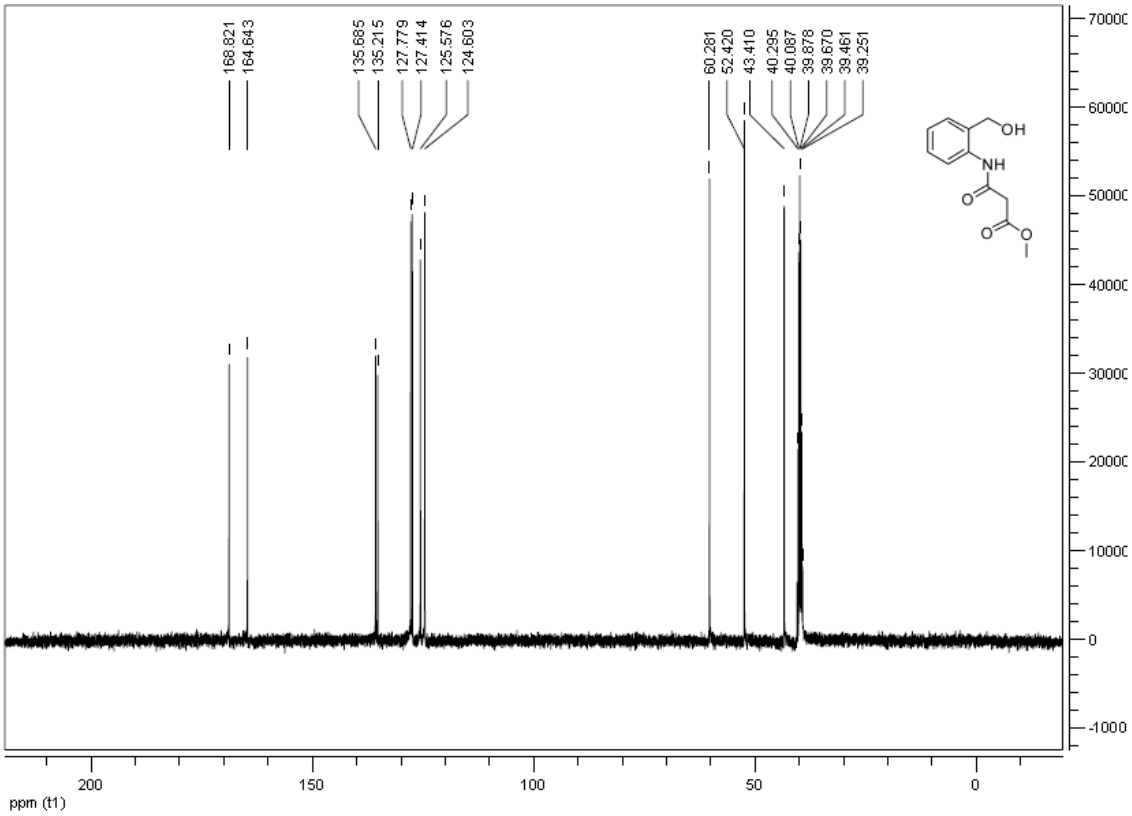
2-(3-Methoxy-3-oxopropanamido)benzoic acid 1b



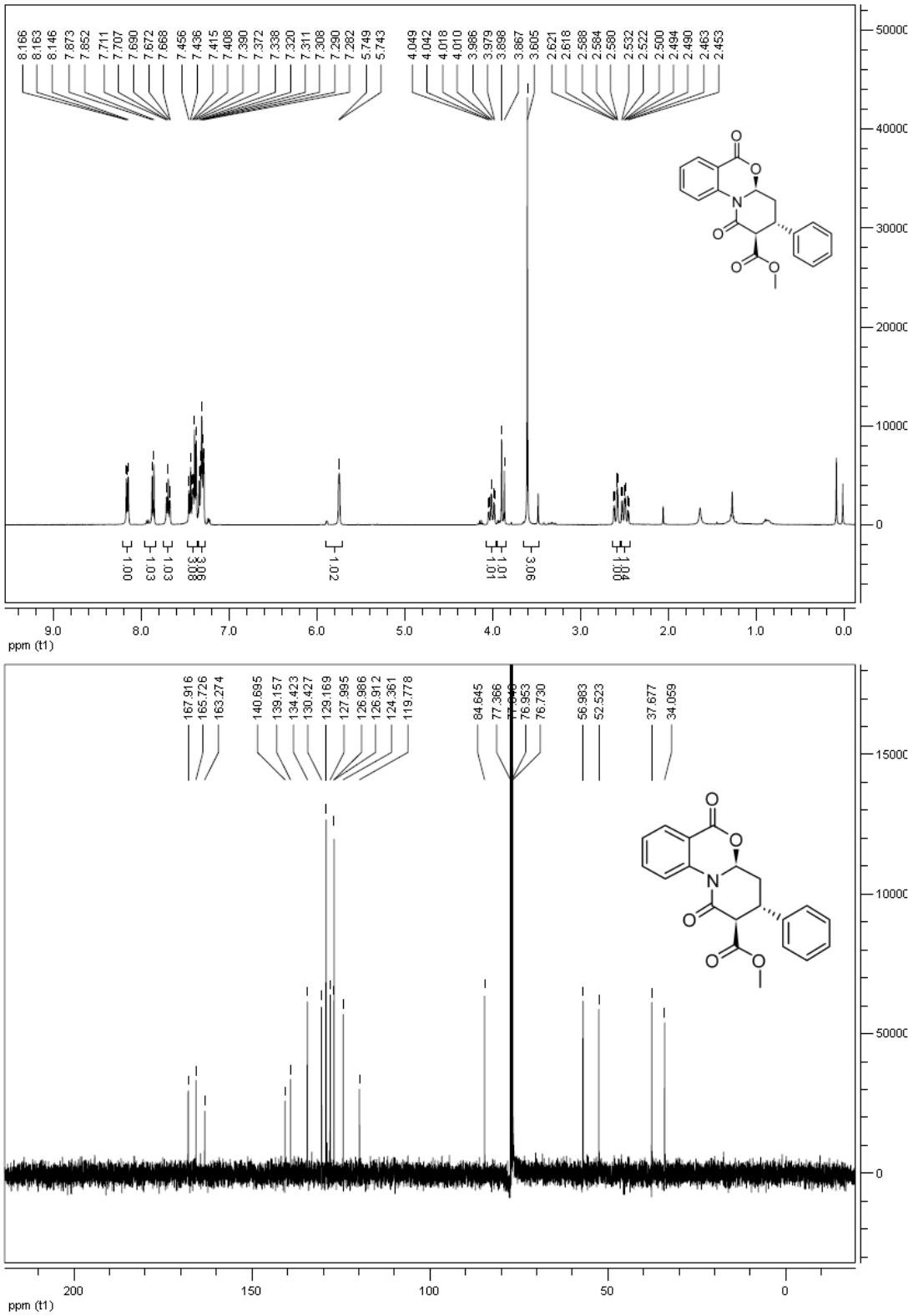


Methyl 3-(2-carbamoylphenylamino)-3-oxopropanoate 1c

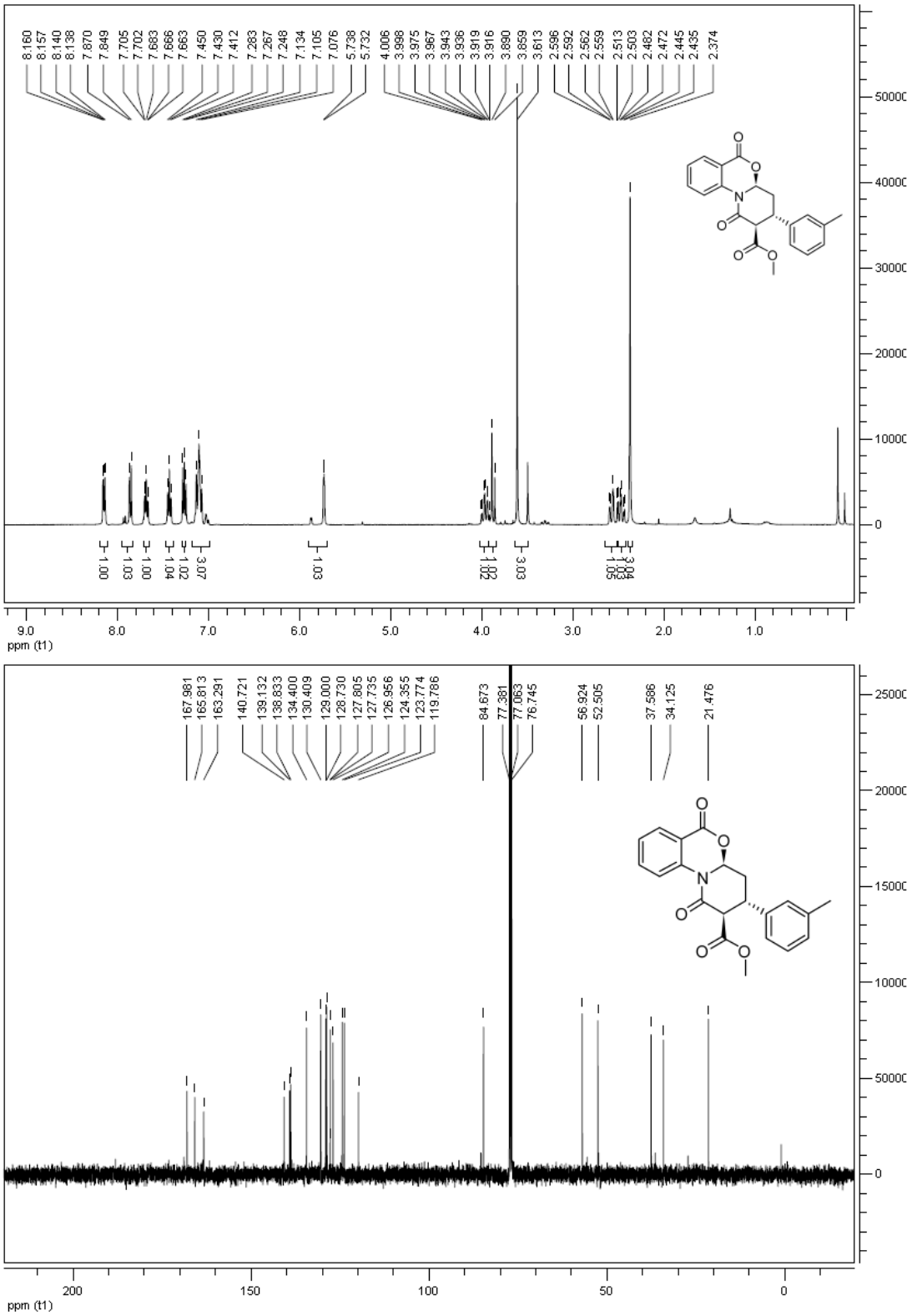




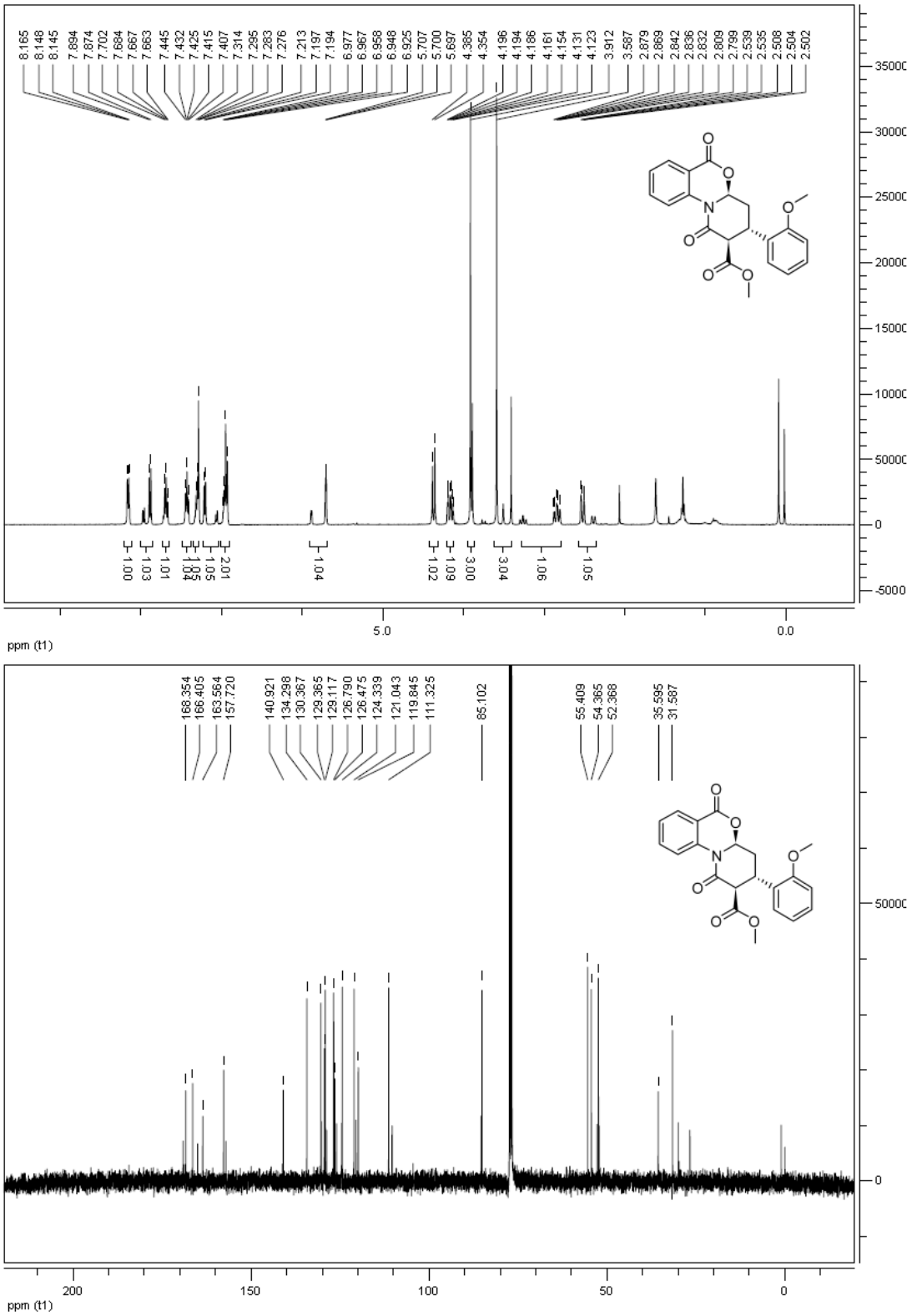
(2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4a



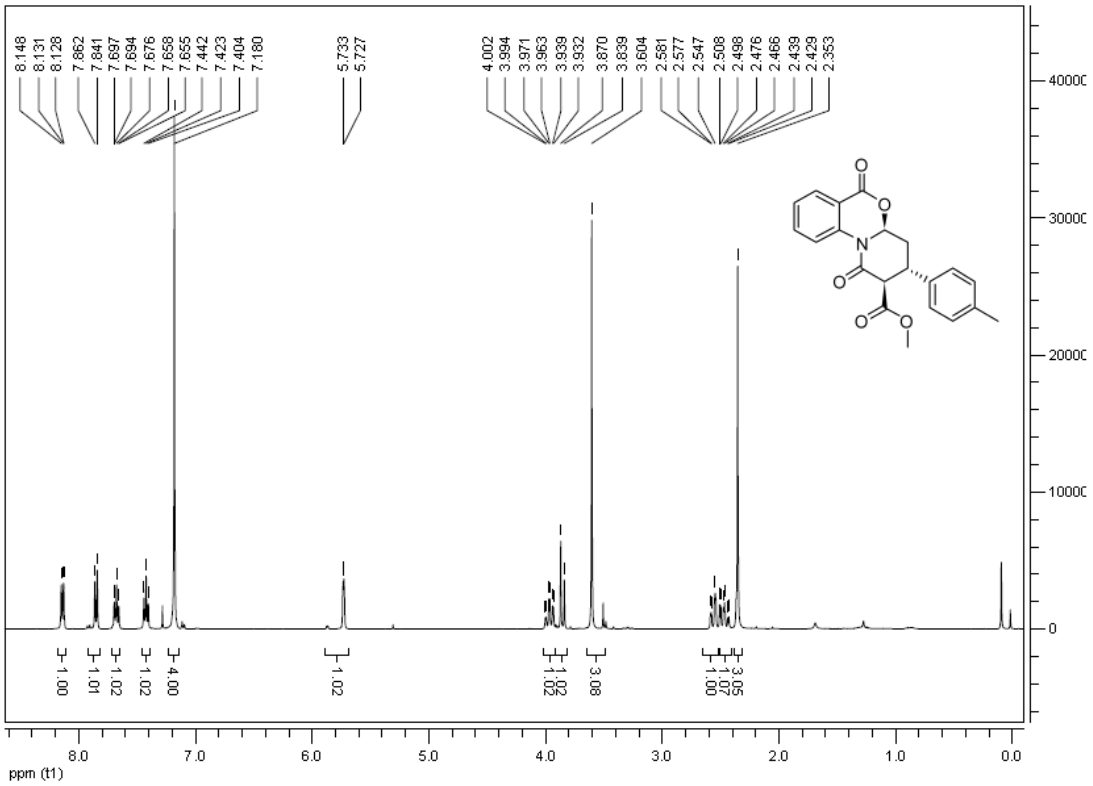
(2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-m-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4b

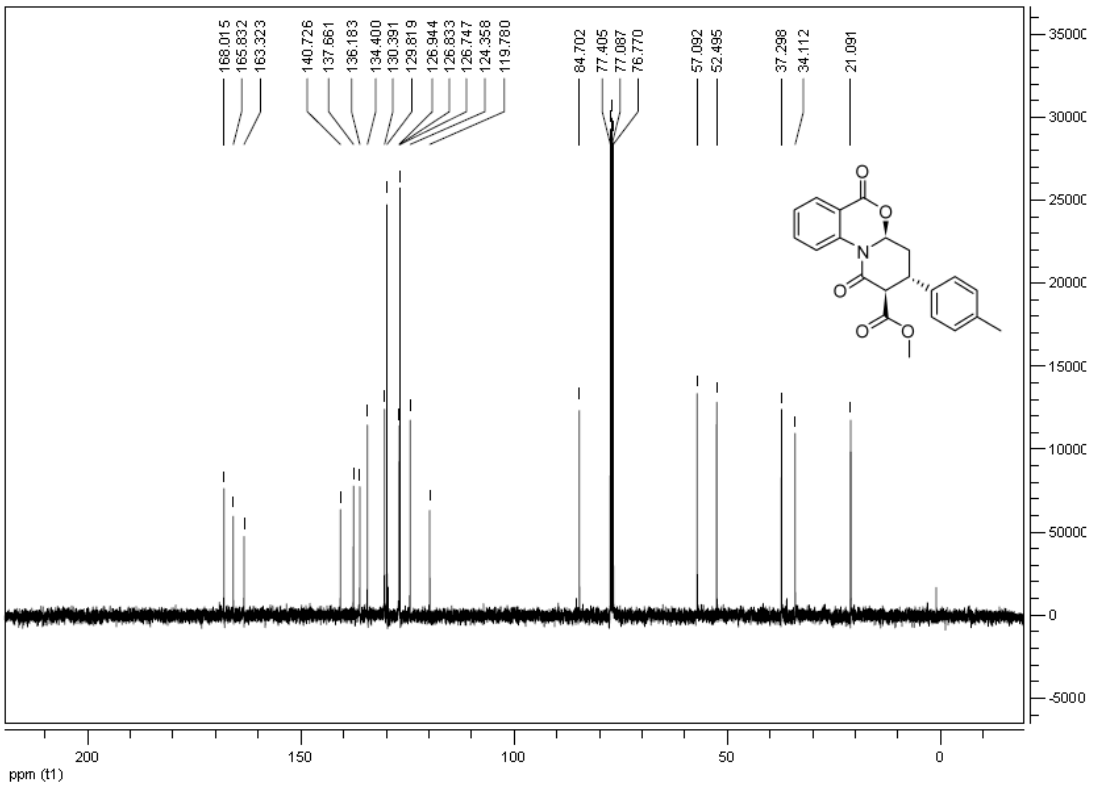


(2*R*,3*S*,4a*S*)-methyl 3-(2-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4c

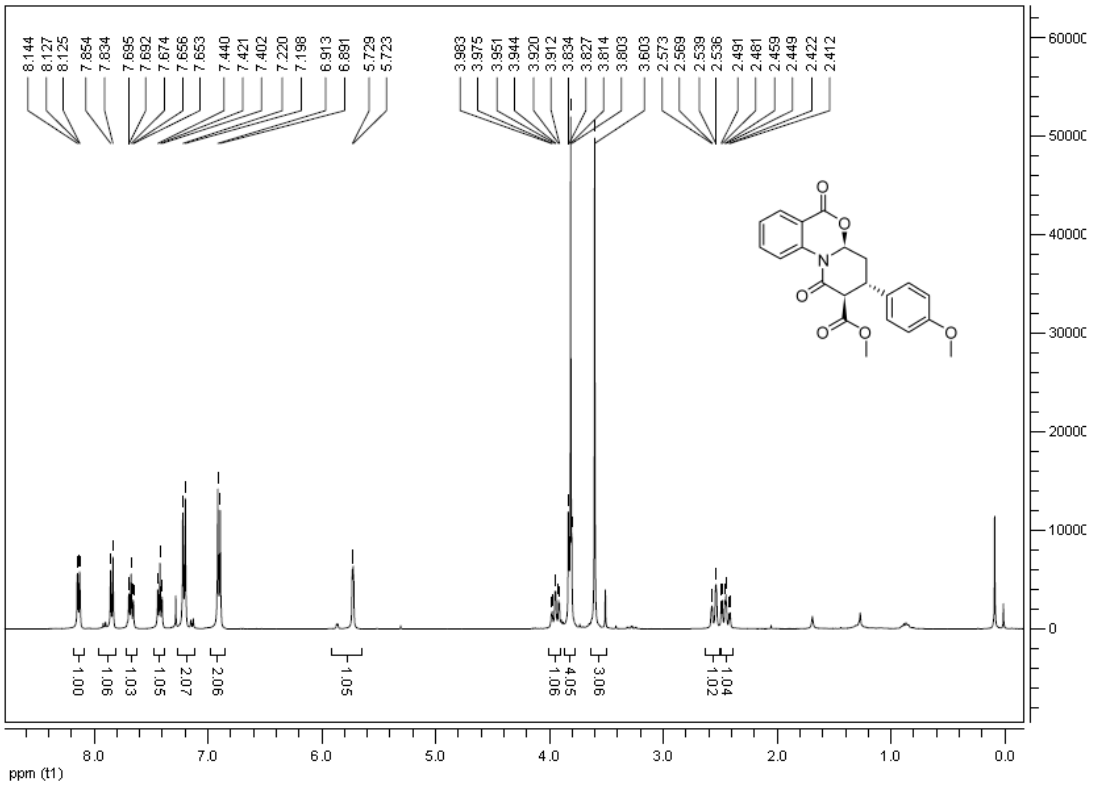


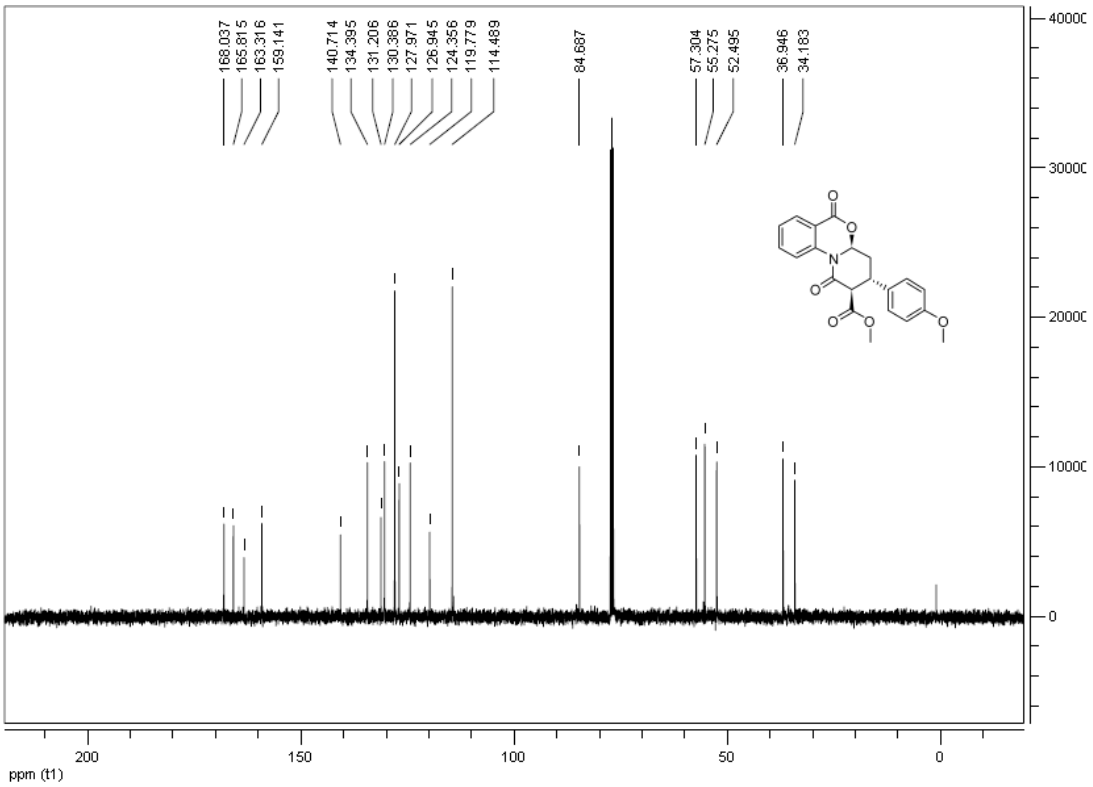
(2*R*,3*S*,4a*S*)-methyl 1,6-dioxo-3-p-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4d



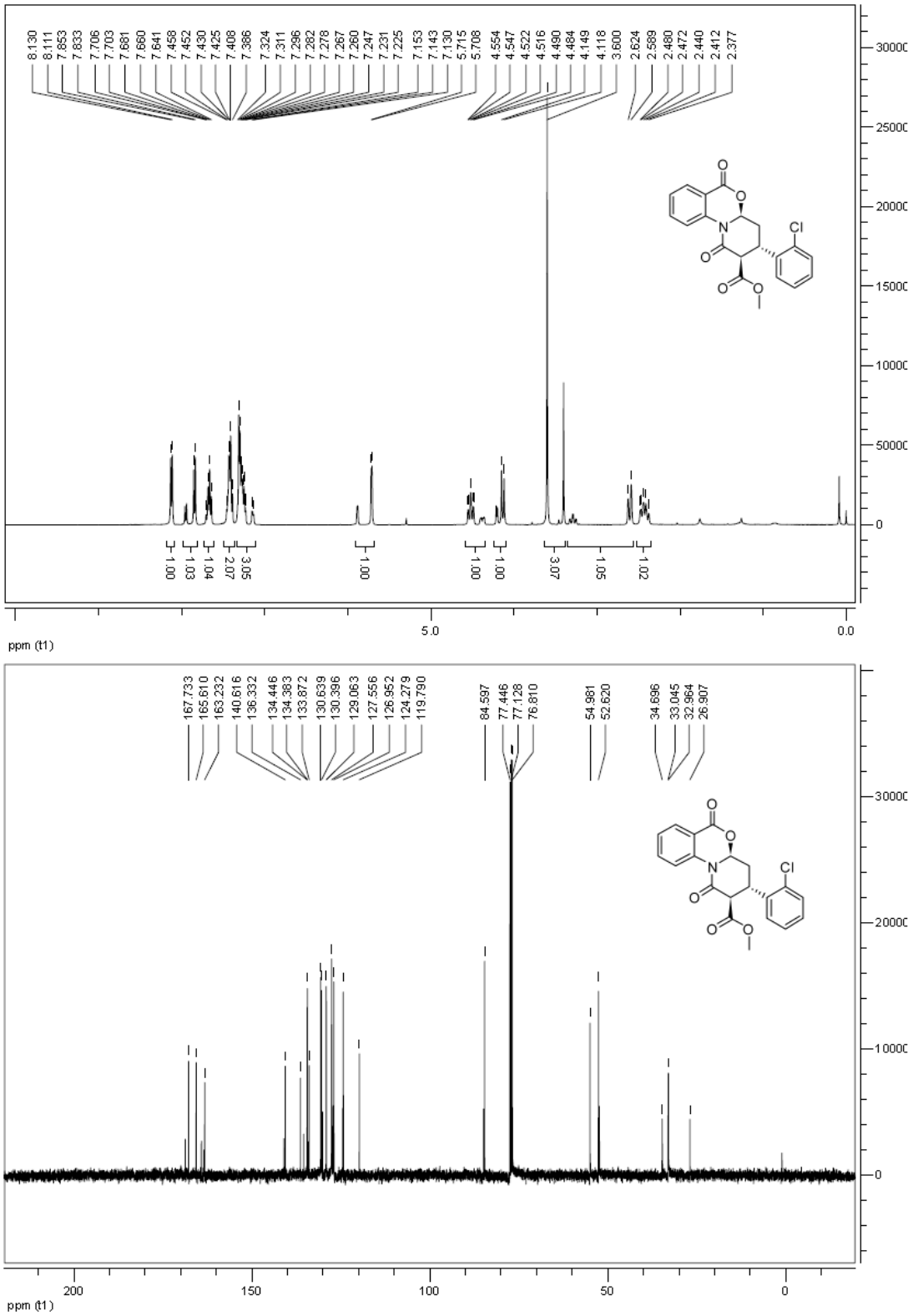


(2*R*,3*S*,4a*S*)-methyl 3-(4-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4e

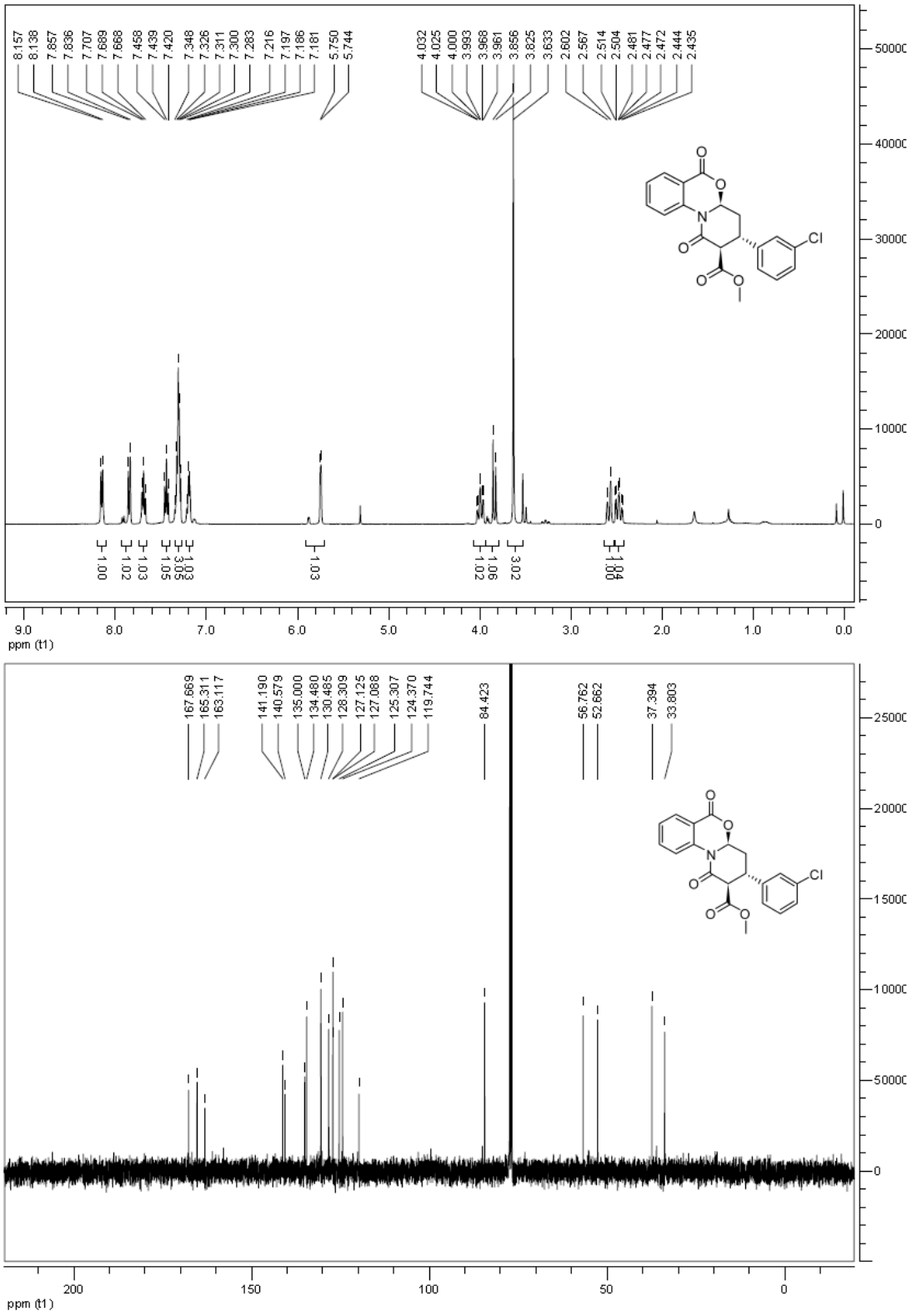




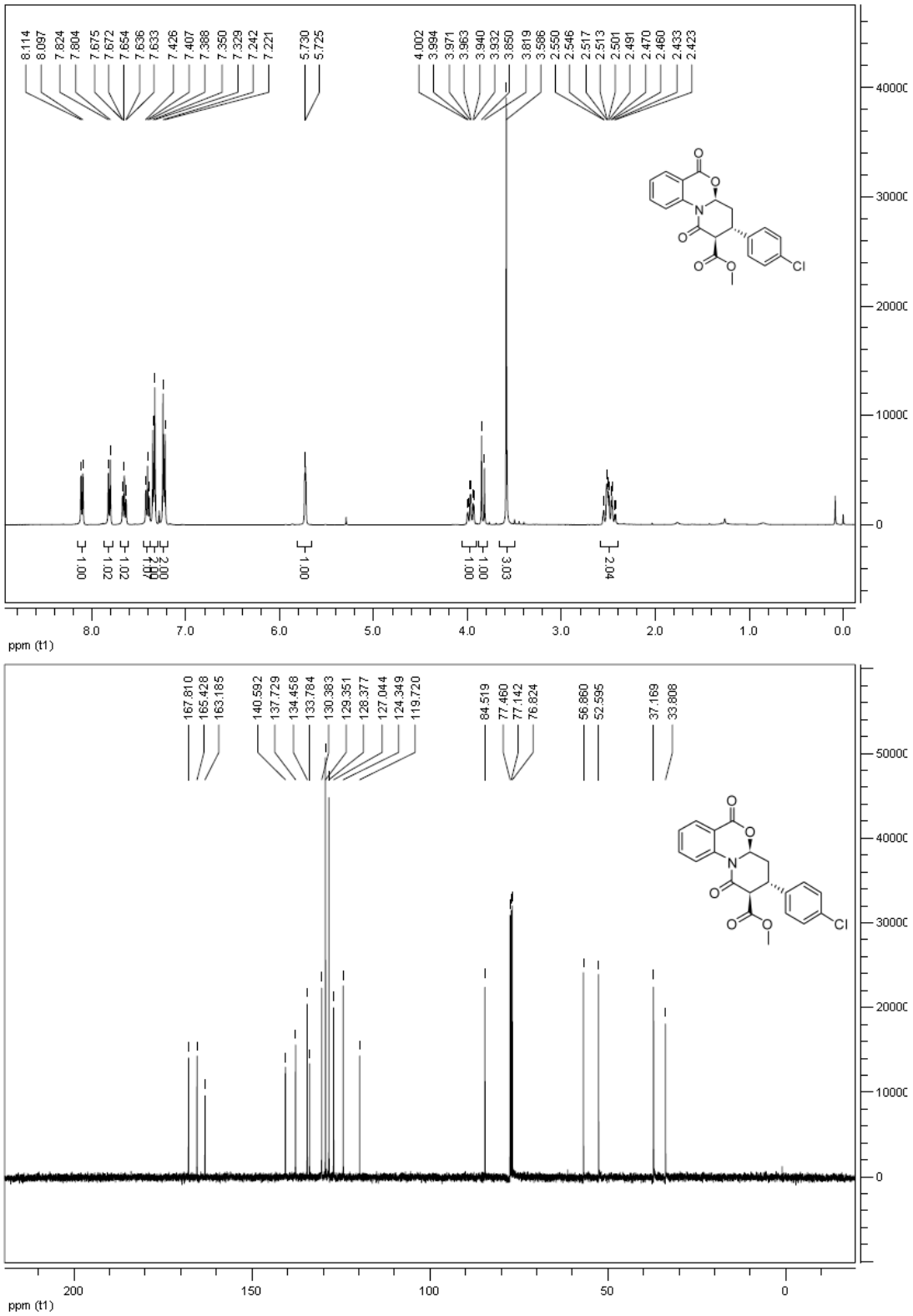
(2*R*,3*S*,4a*S*)-methyl 3-(2-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4f



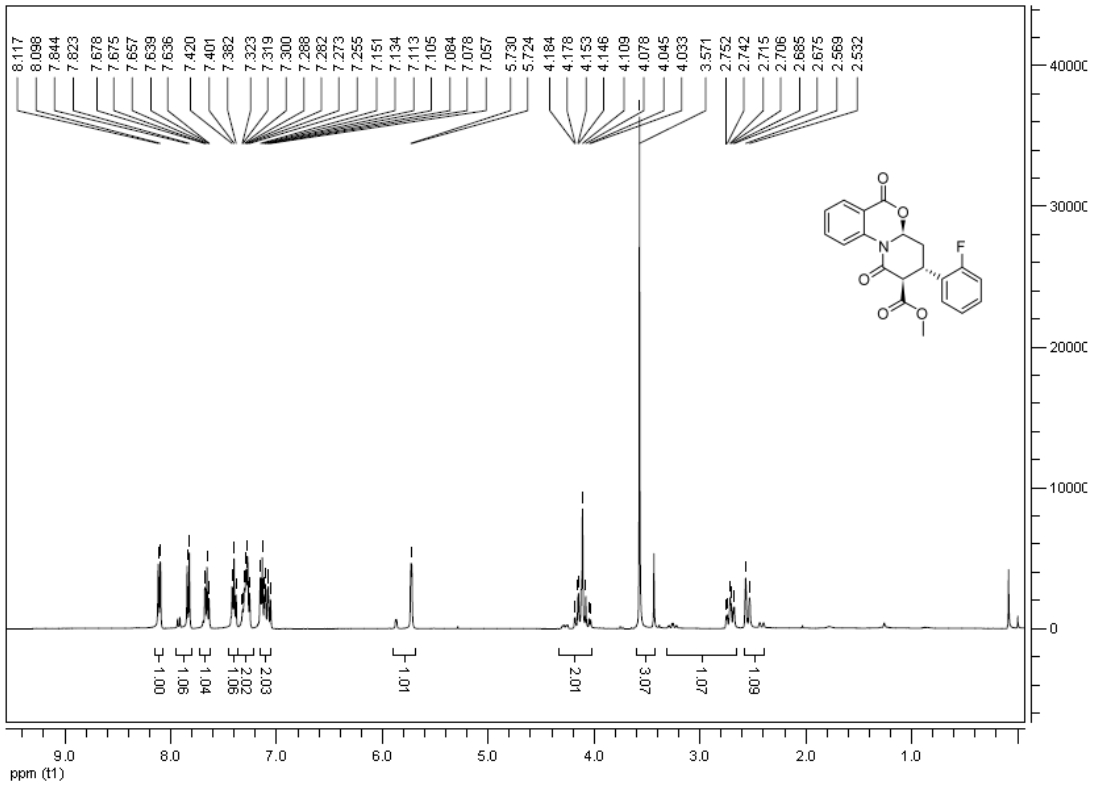
(2*R*,3*S*,4a*S*)-methyl 3-(3-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4g

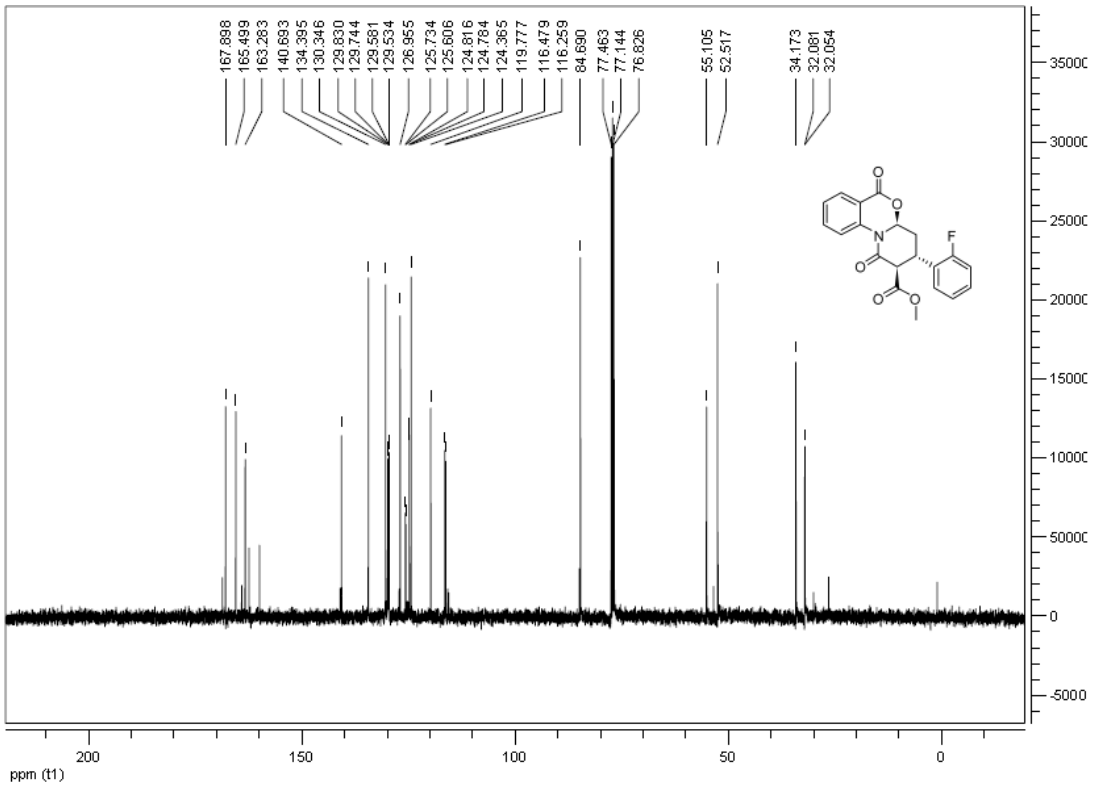


(2*R*,3*S*,4a*S*)-methyl 3-(4-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4h

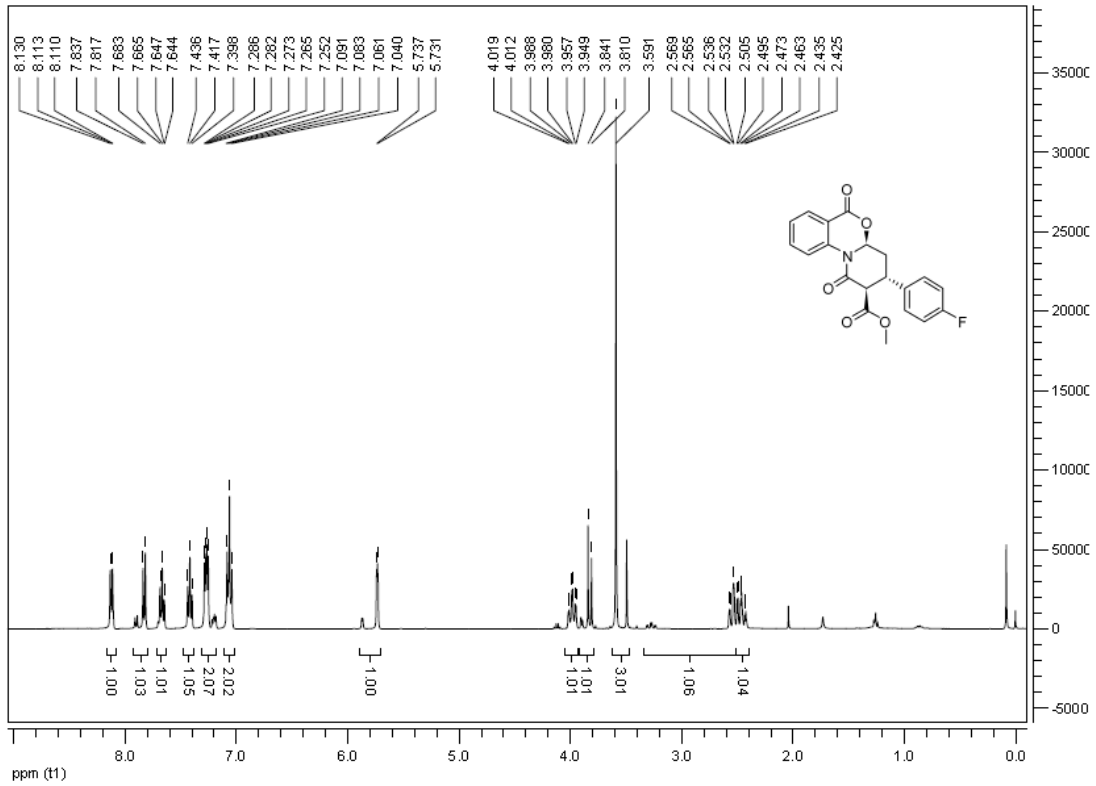


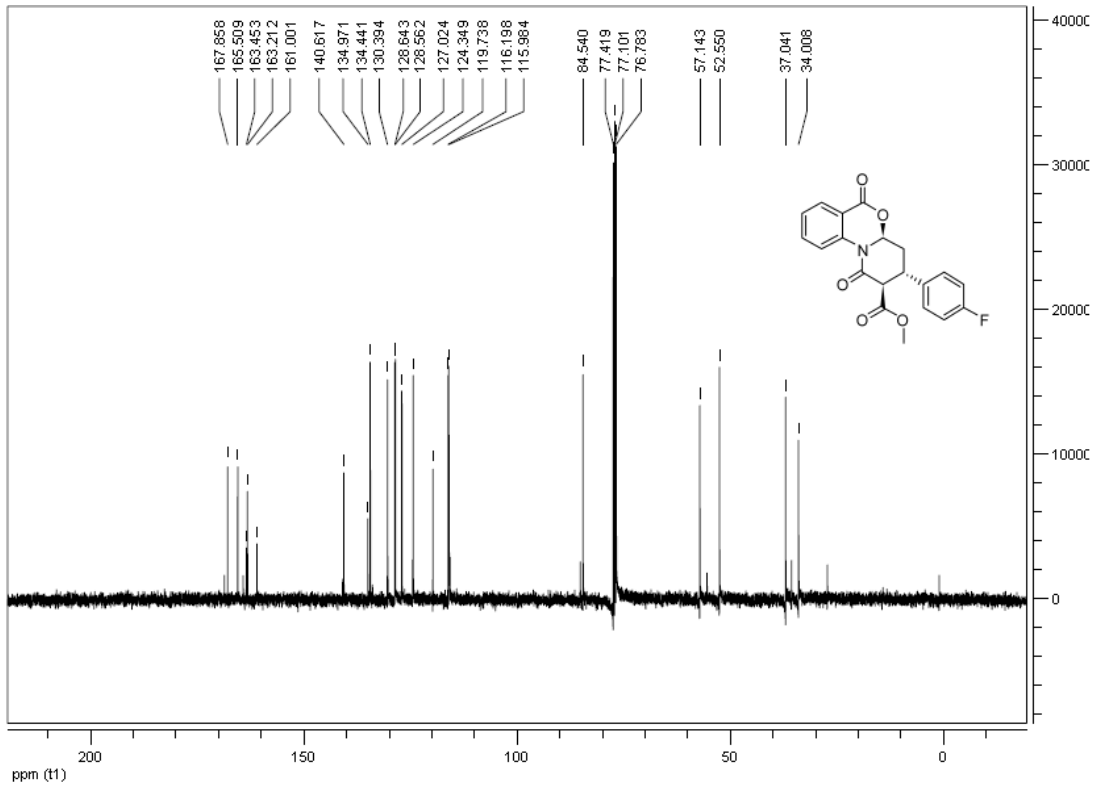
(2*R*,3*S*,4a*S*)-methyl 3-(2-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4i



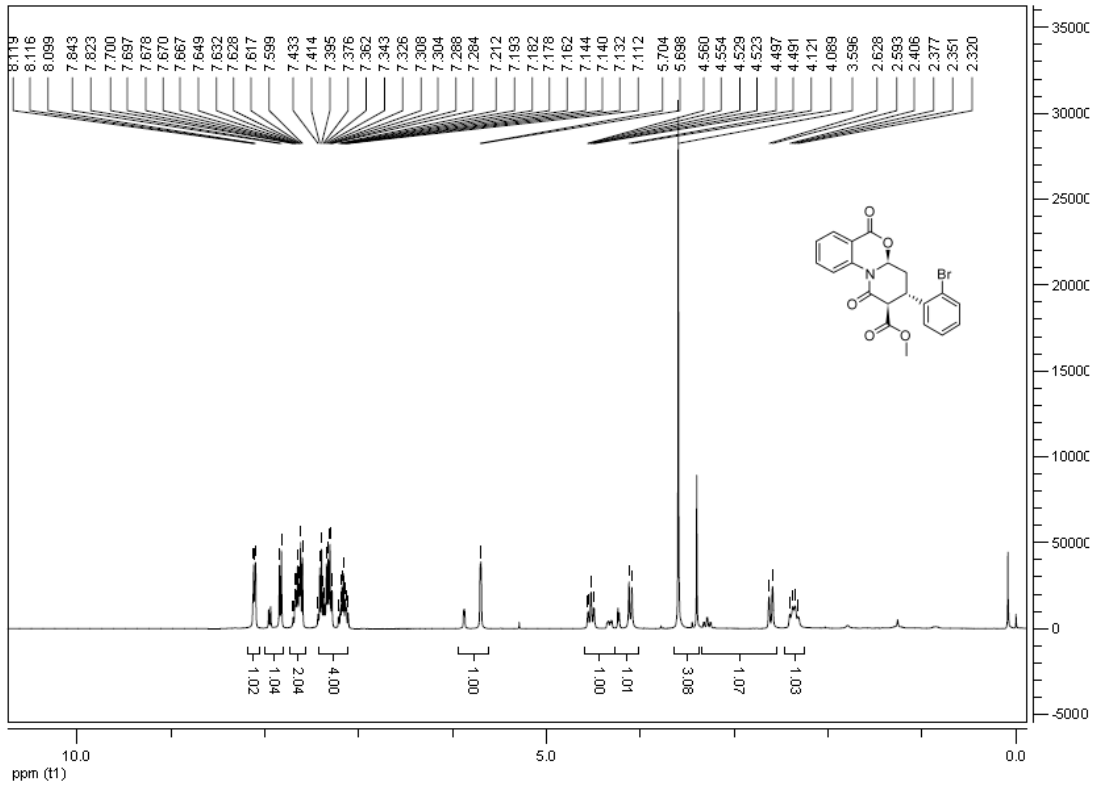


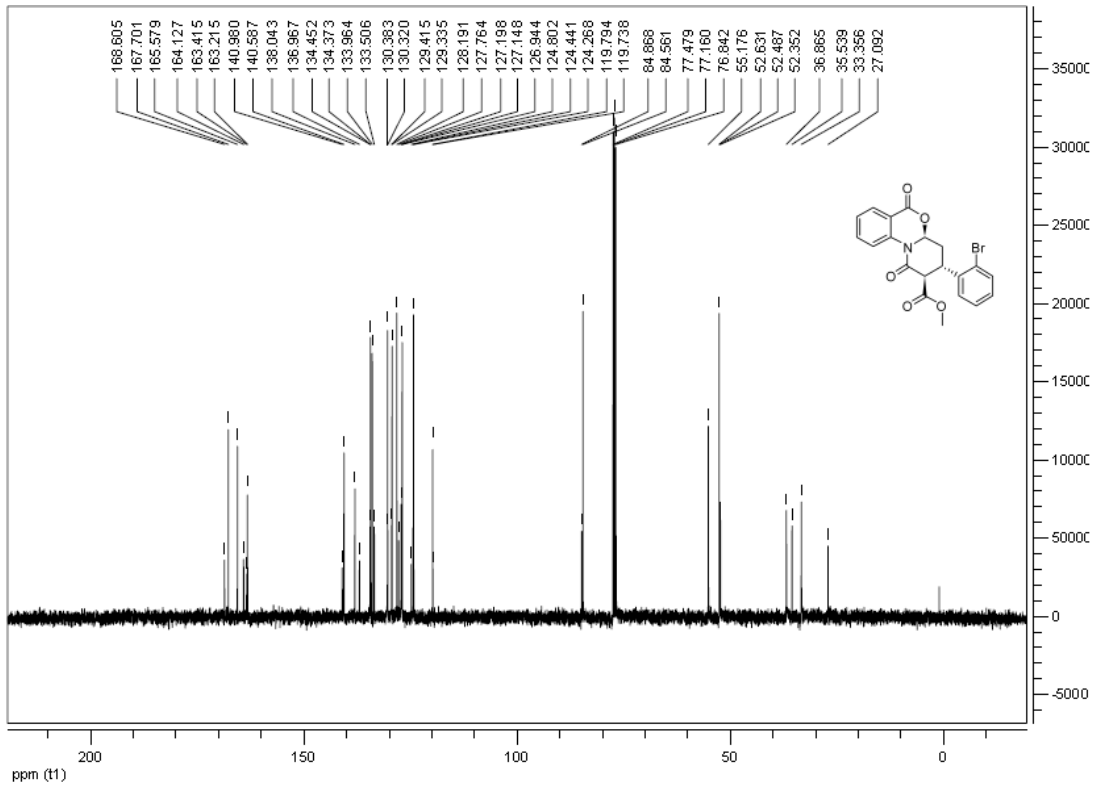
(2*R*,3*S*,4a*S*)-methyl 3-(4-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4j



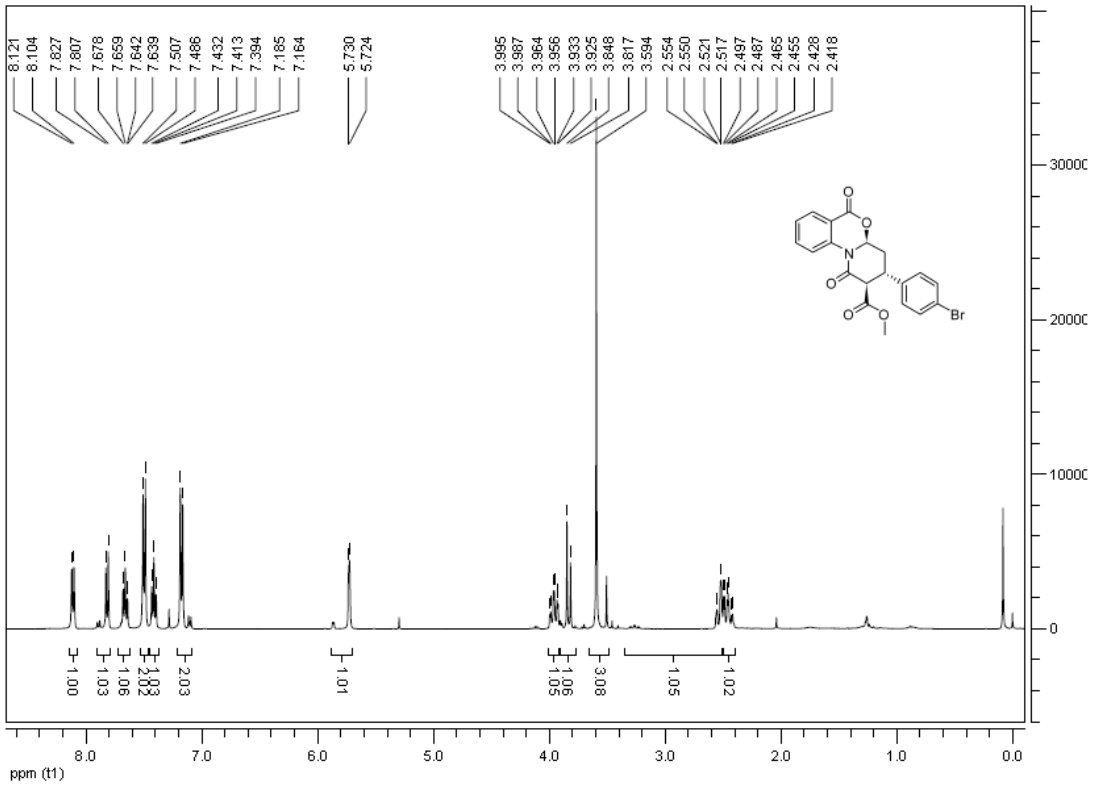


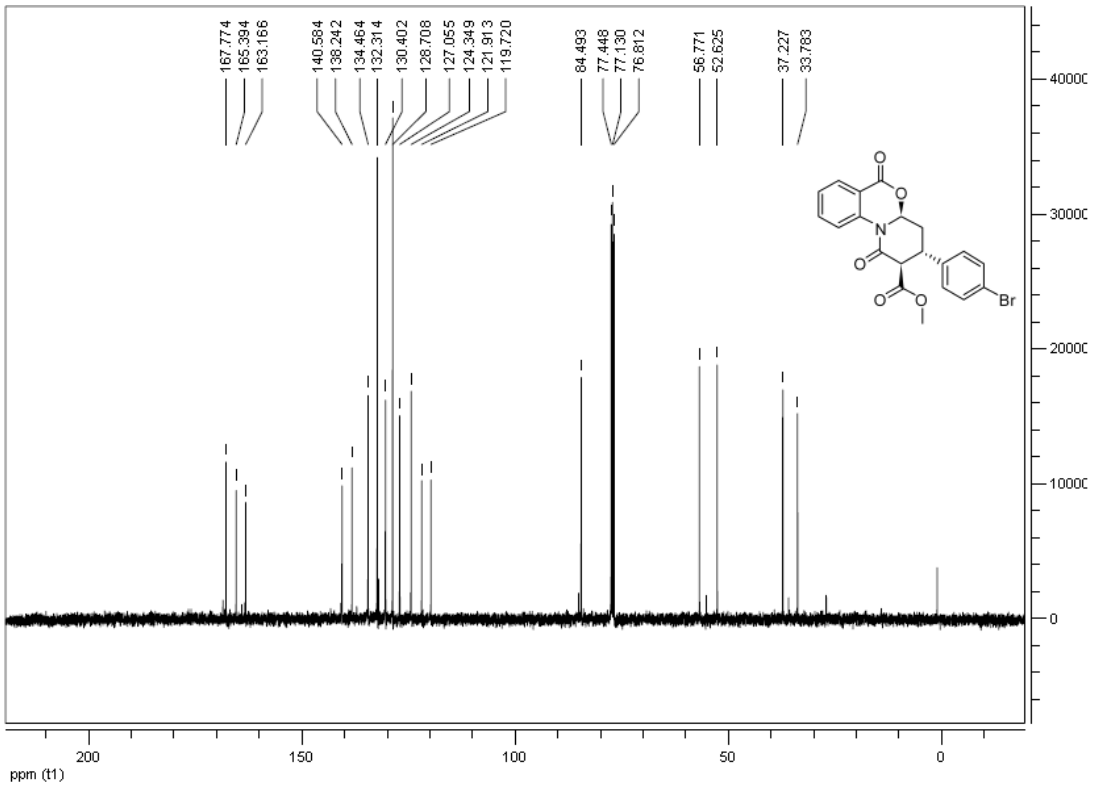
(2*R*,3*S*,4a*S*)-methyl 3-(2-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4k



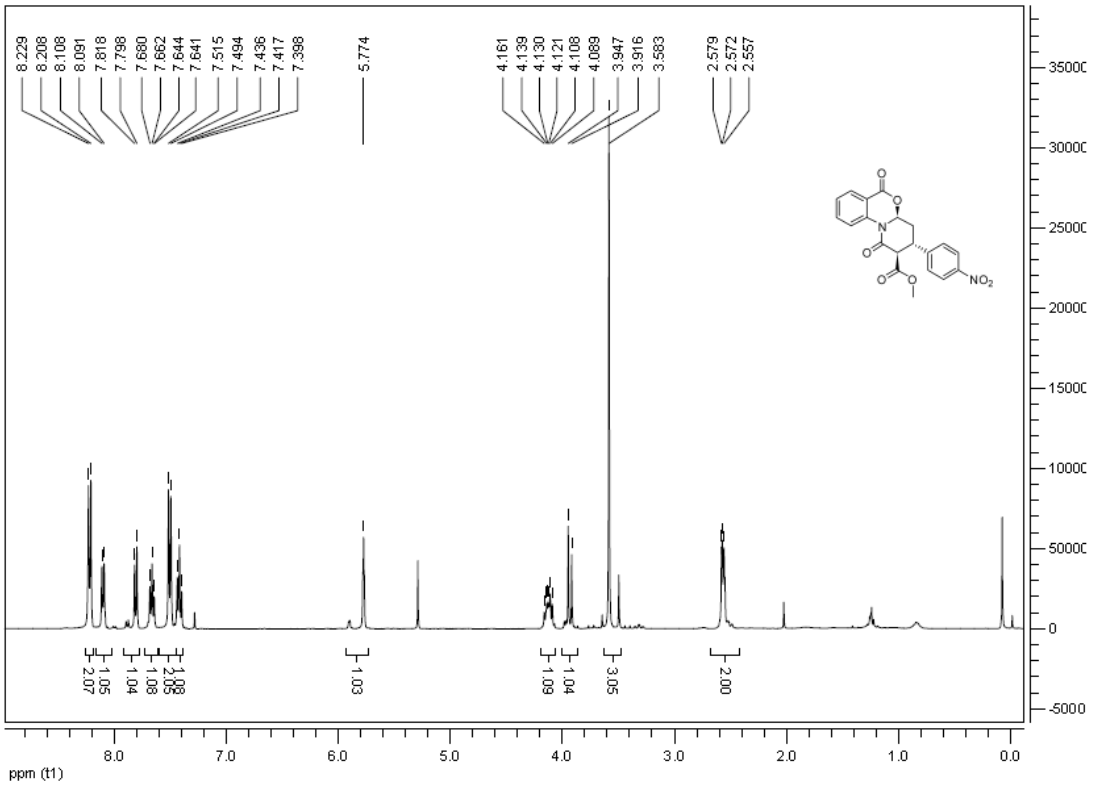


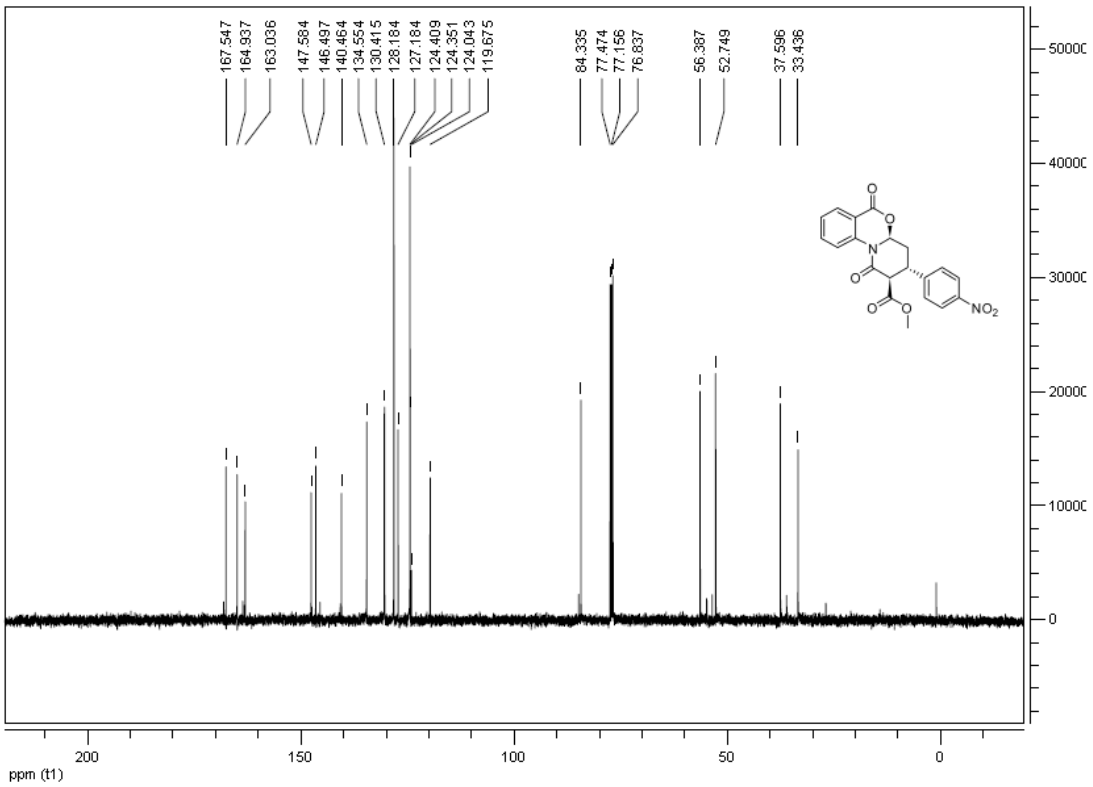
(2*R*,3*S*,4a*S*)-methyl 3-(4-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4l



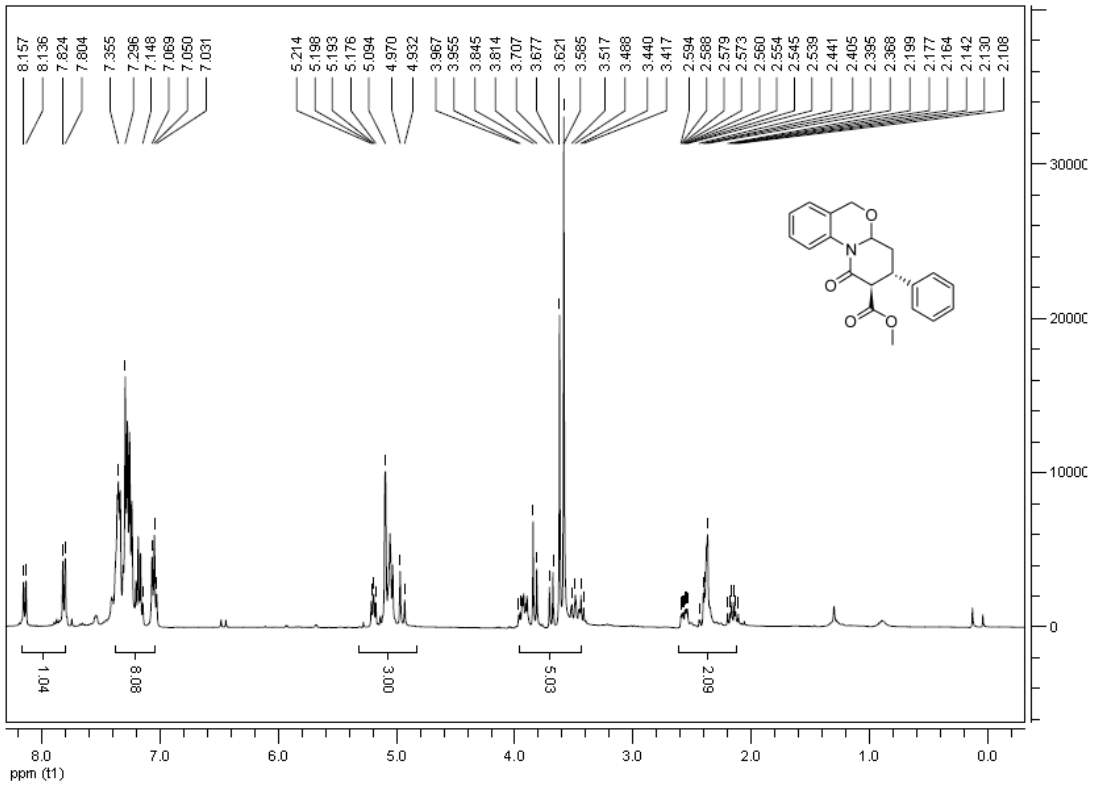


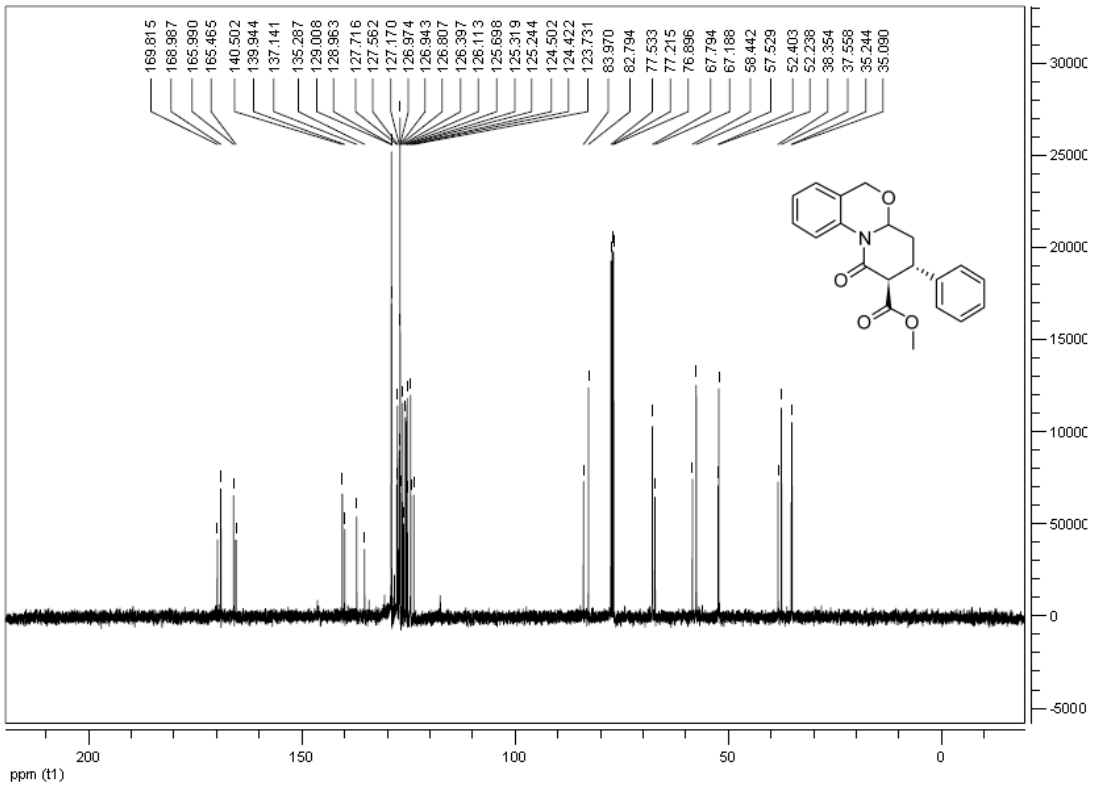
(2*R*,3*S*,4a*S*)-methyl 3-(4-nitrophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4m



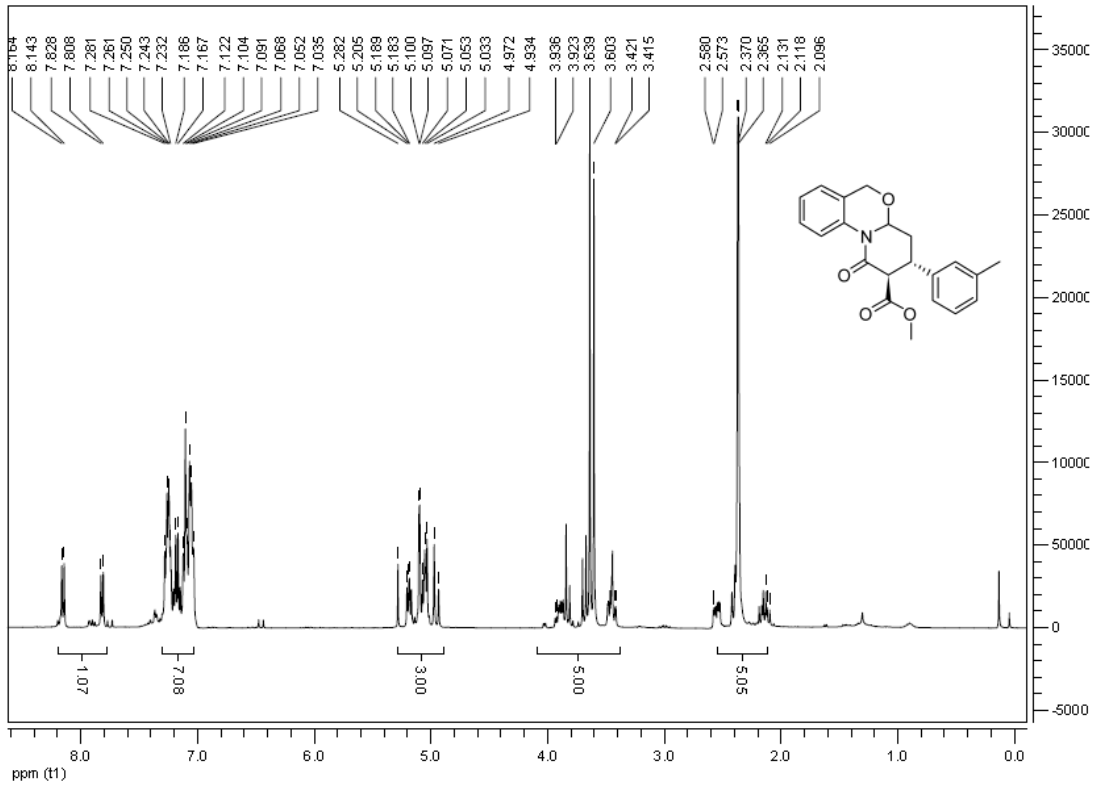


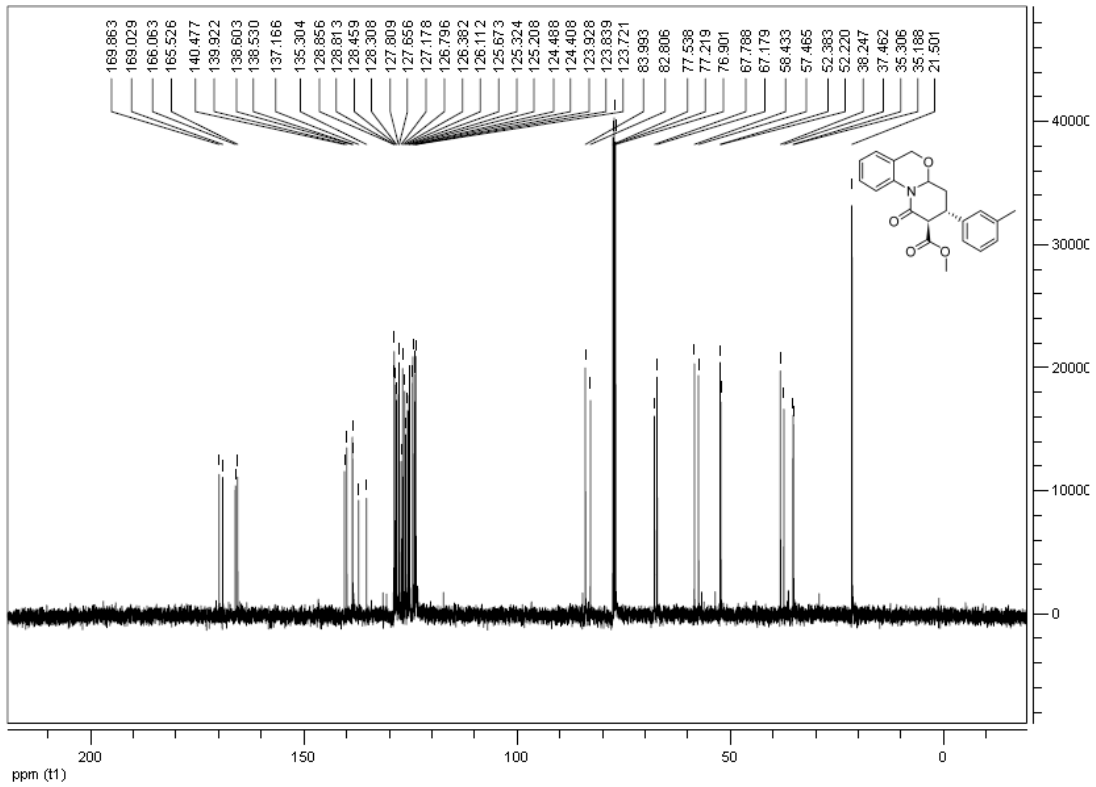
(2*R*,3*S*)-methyl 1-oxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3] oxazine-2-carboxylate 4n



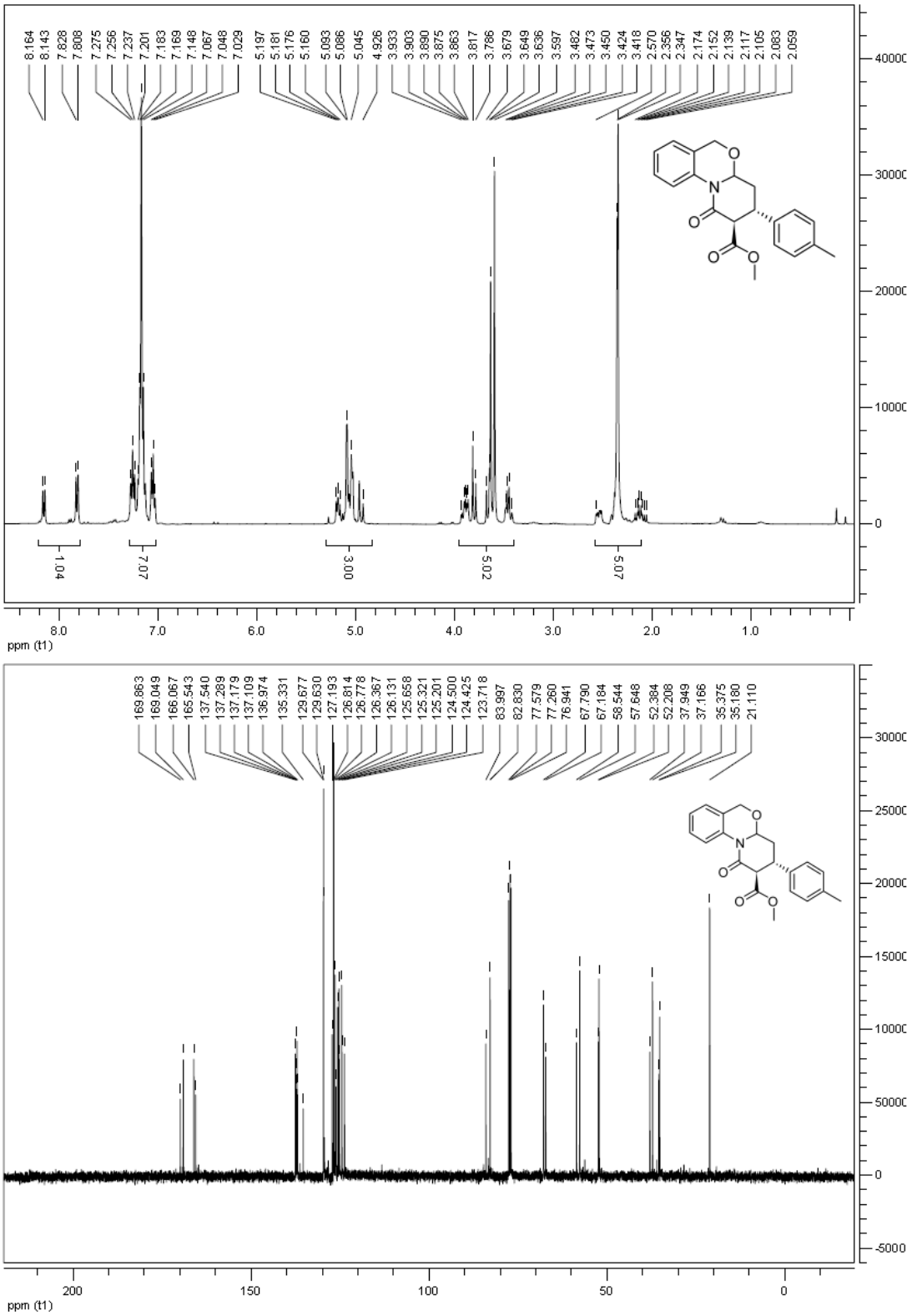


(2*R*,3*S*)-methyl 1-oxo-3-m-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3] oxazine-2-carboxylate 4o

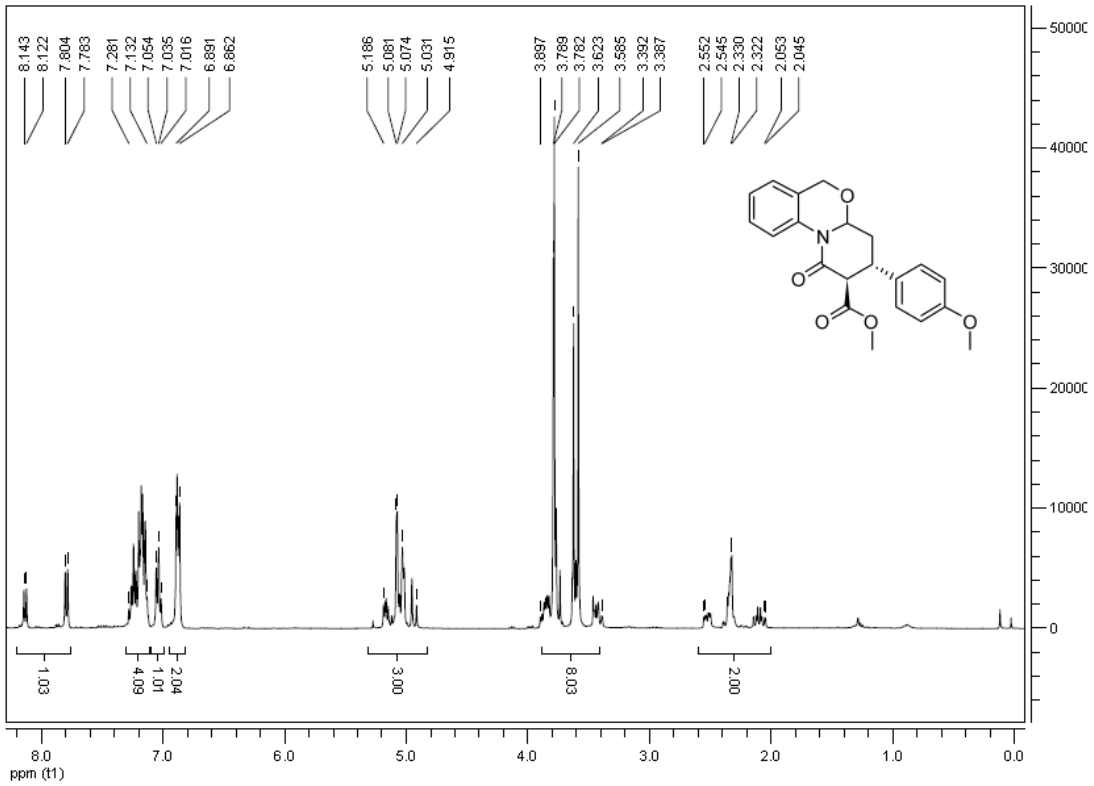


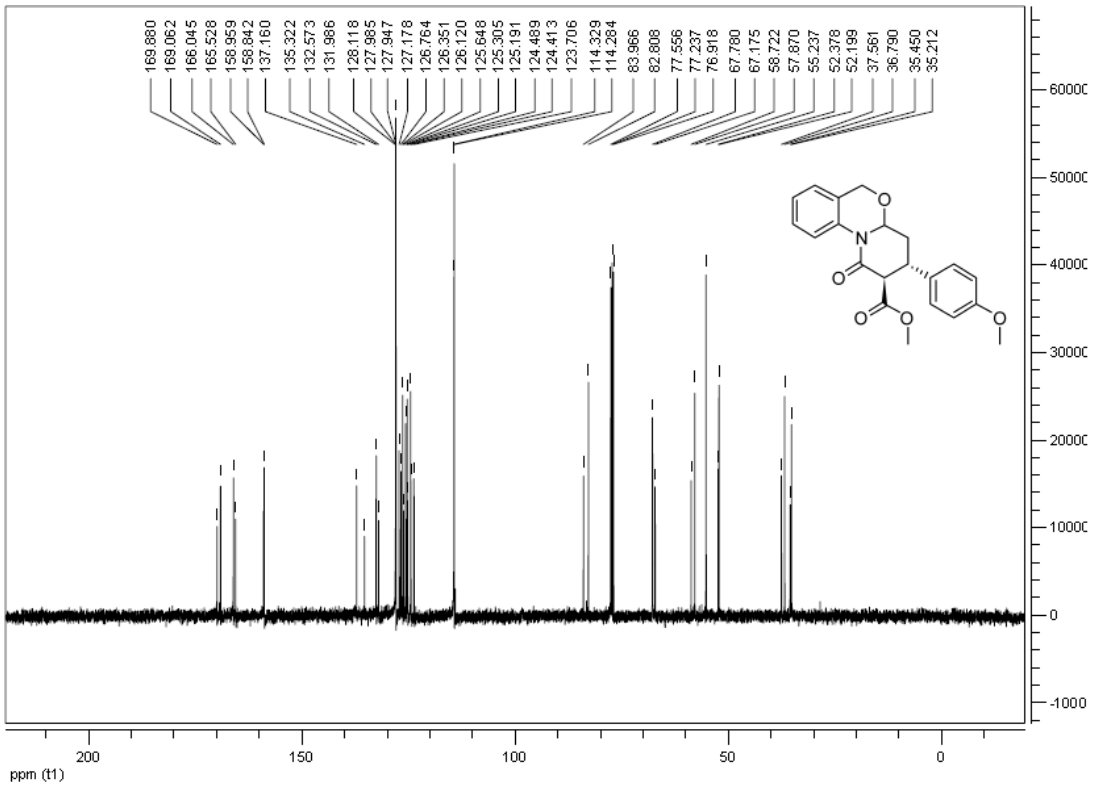


(2*R*,3*S*)-methyl 1-oxo-3-p-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3] oxazine-2-carboxylate 4p

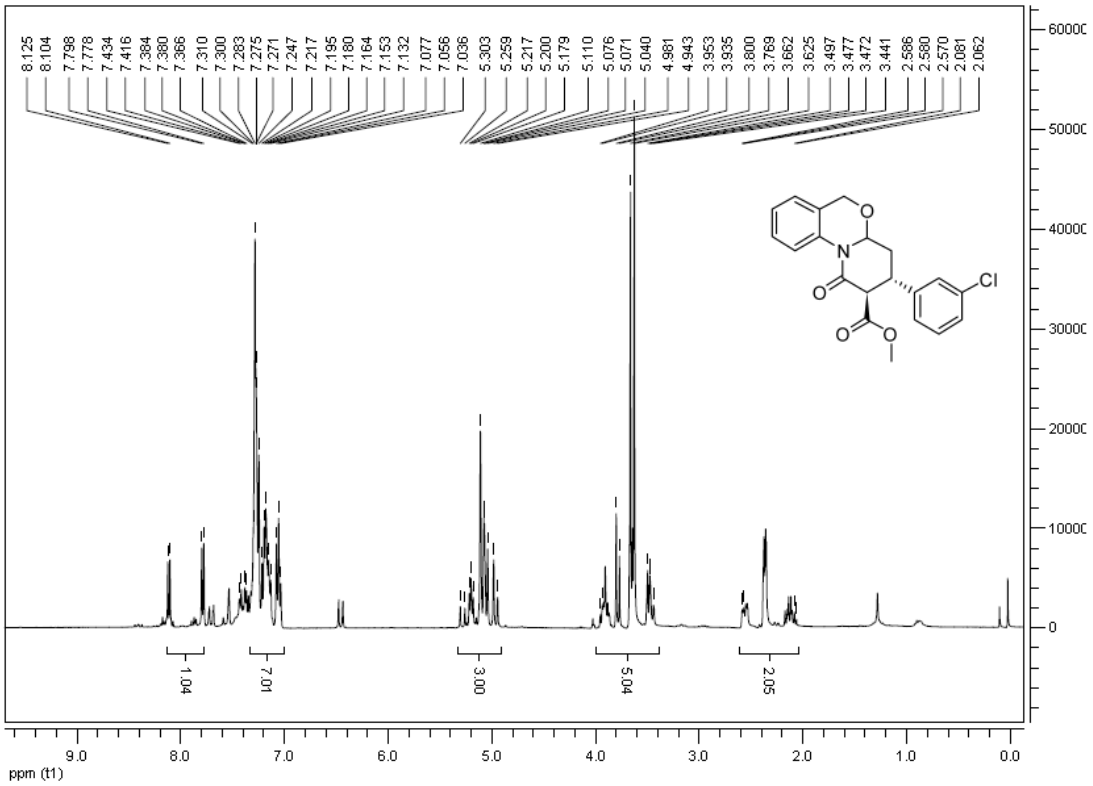


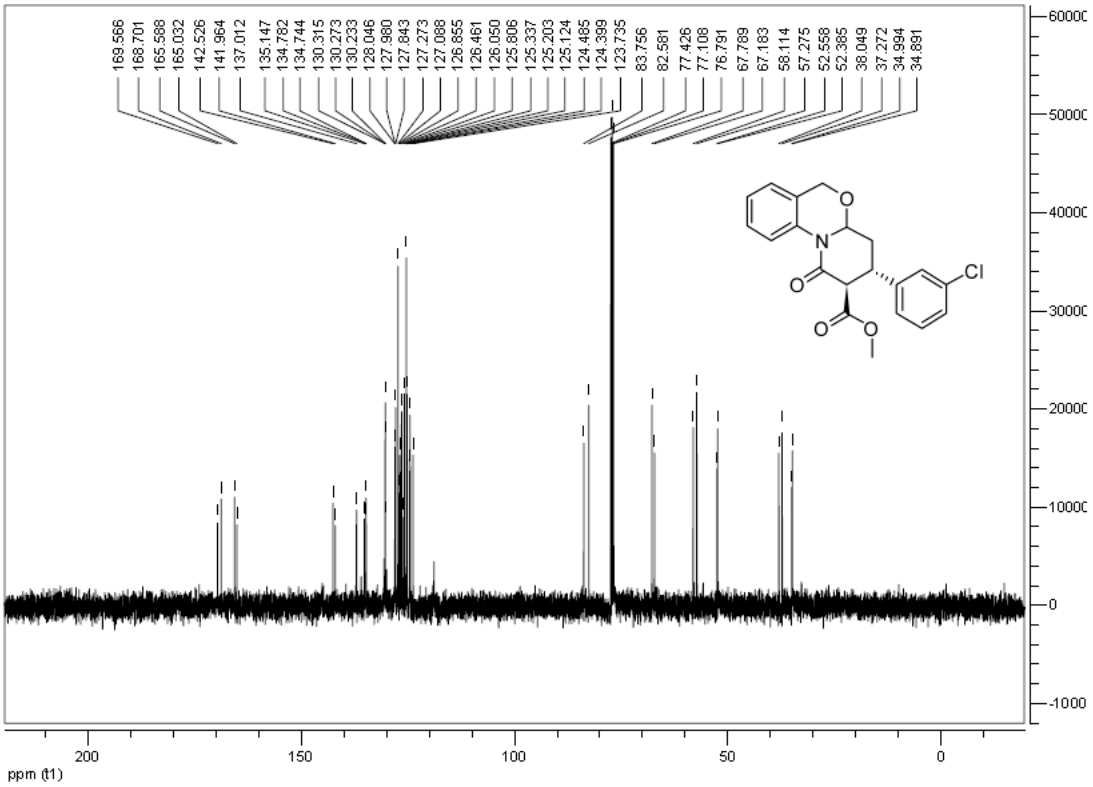
(2*R*,3*S*)-methyl 3-(4-methoxyphenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*] pyrido[2,1-*b*][1,3]oxazine-2-carboxylate 4q



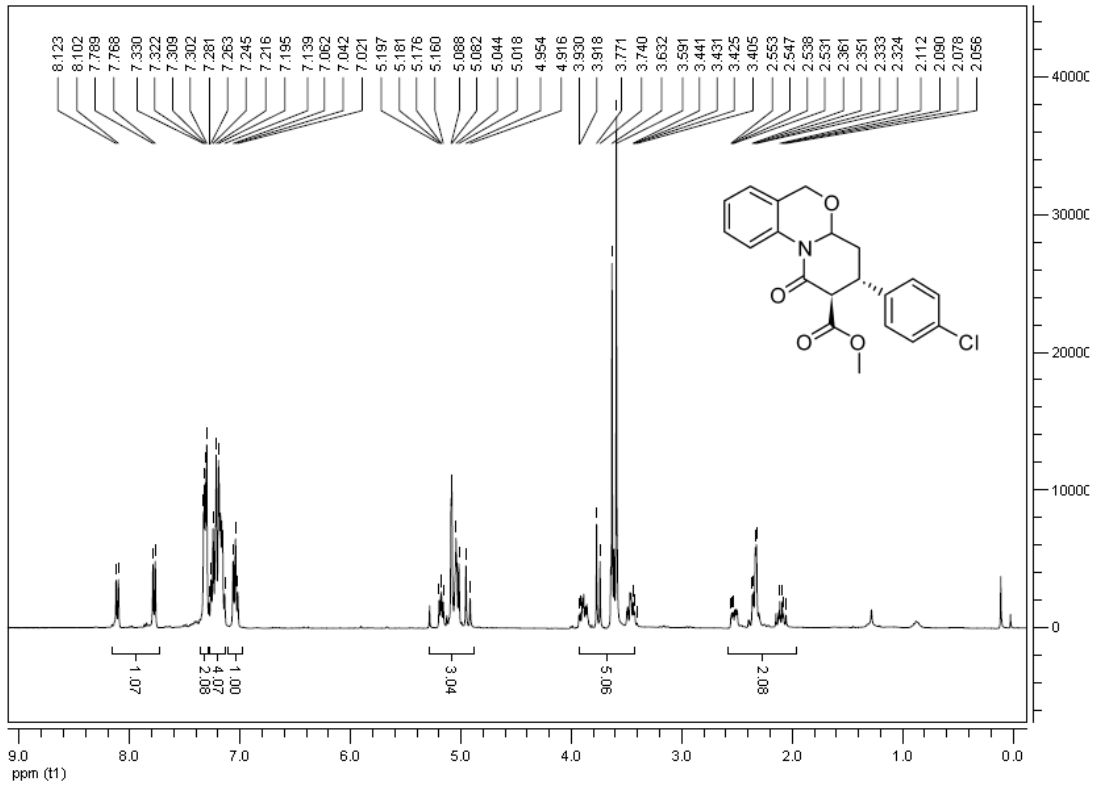


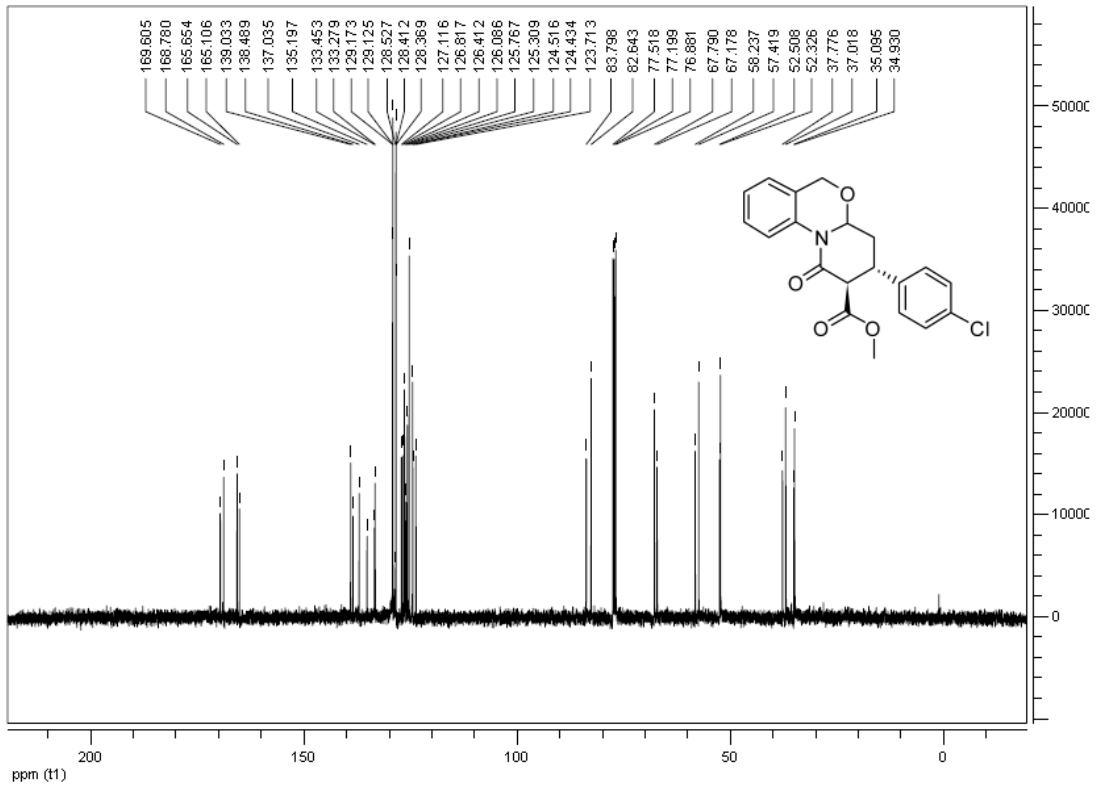
(2*R*,3*S*)-methyl 3-(3-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4r



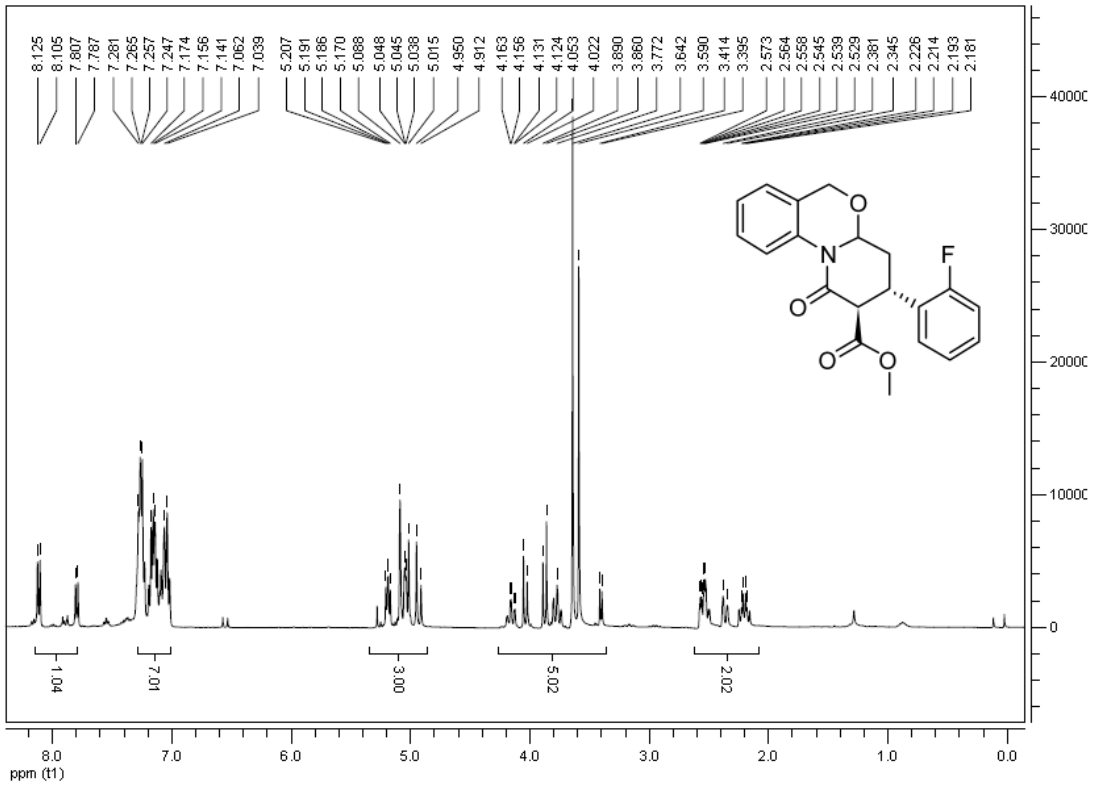


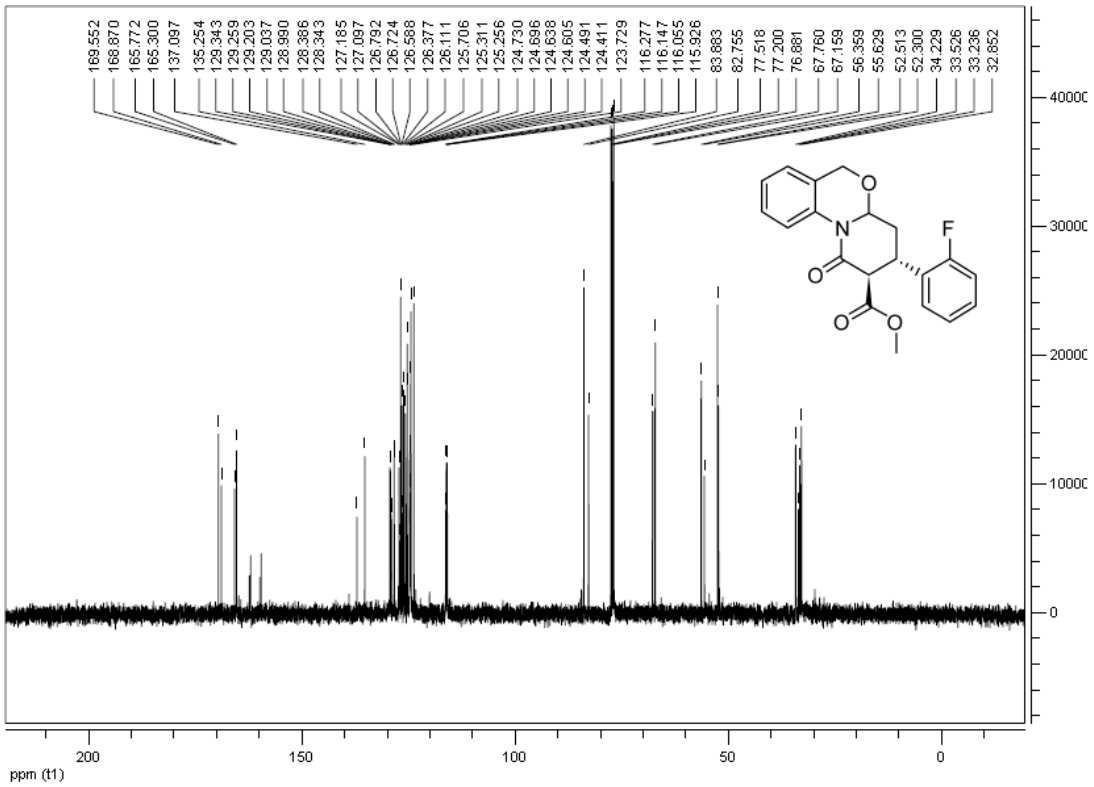
(2*R*,3*S*)-methyl 3-(4-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4s



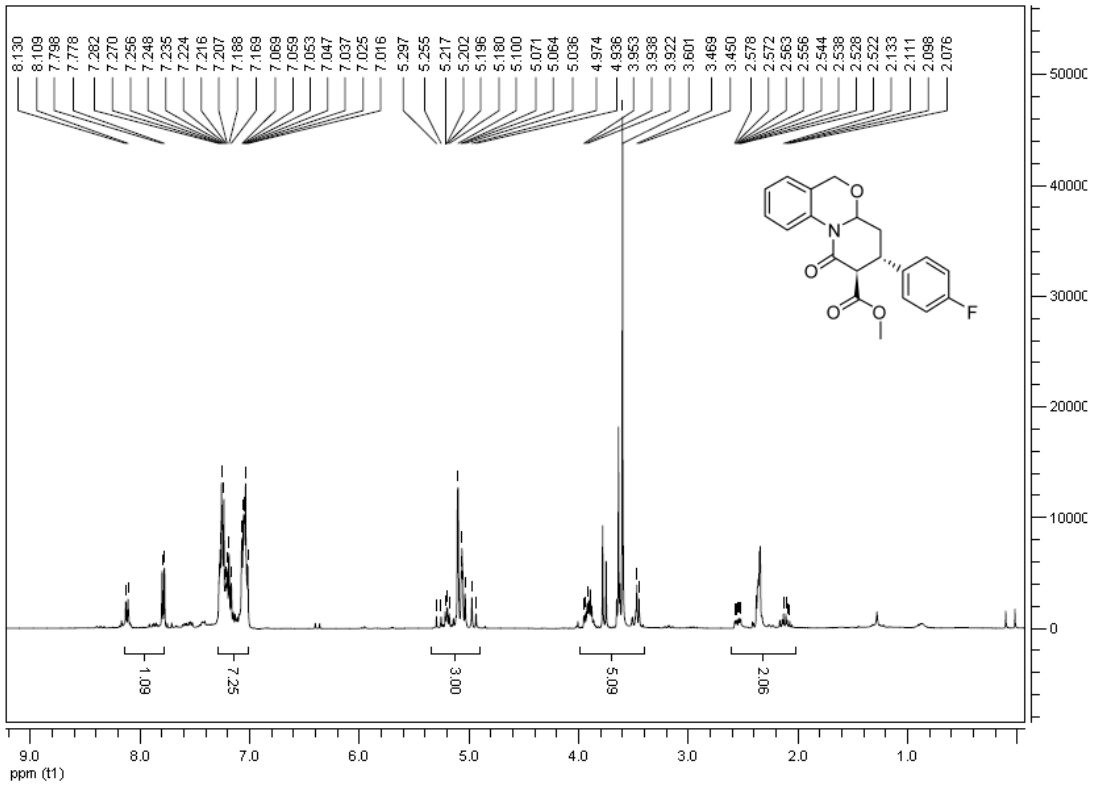


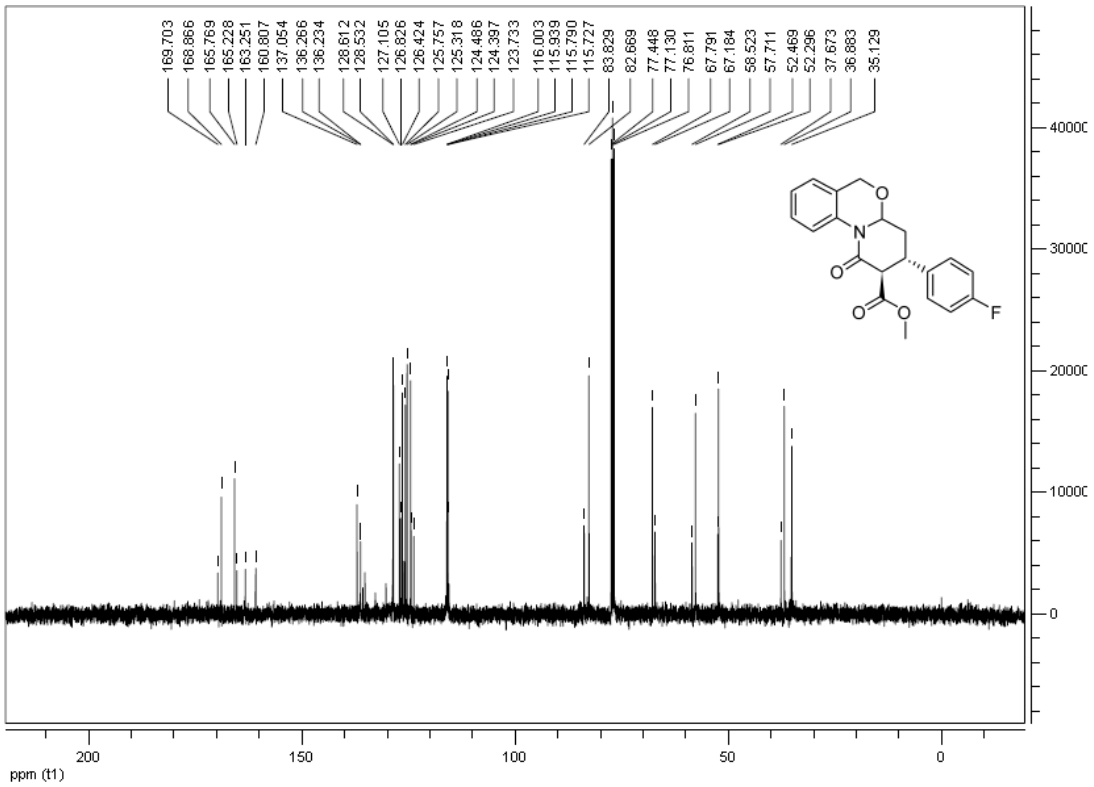
(2*R*,3*S*)-methyl 3-(2-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4t



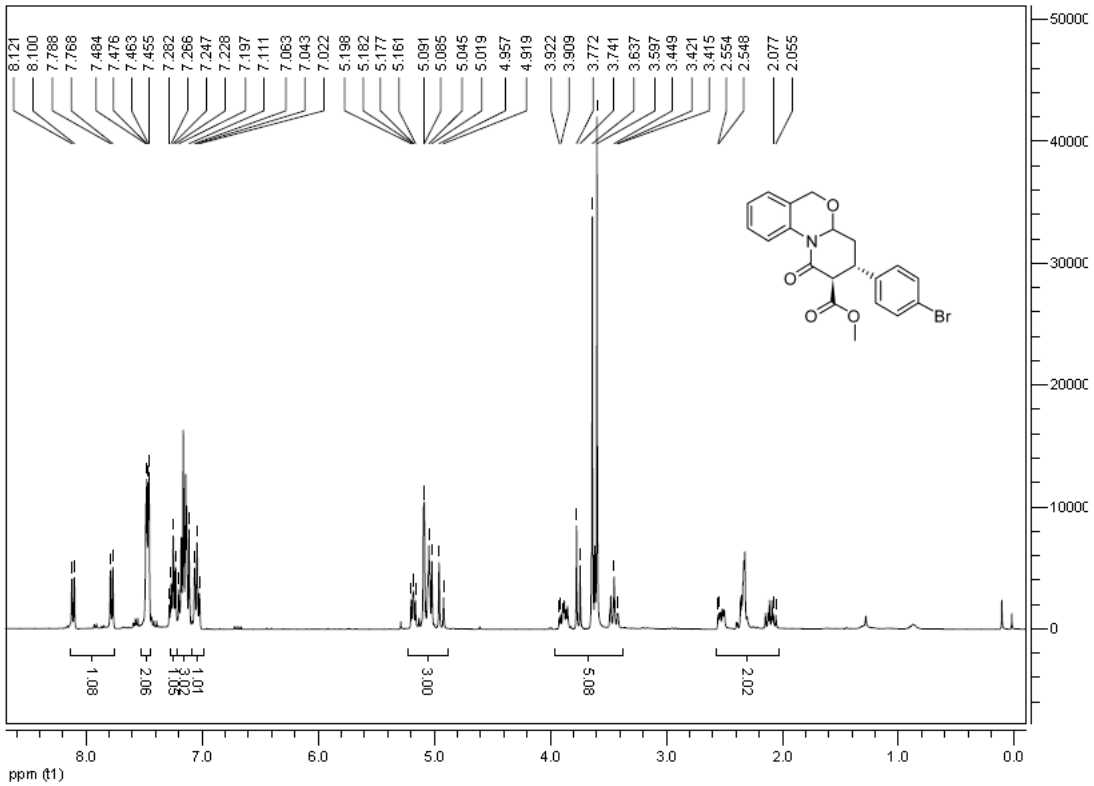


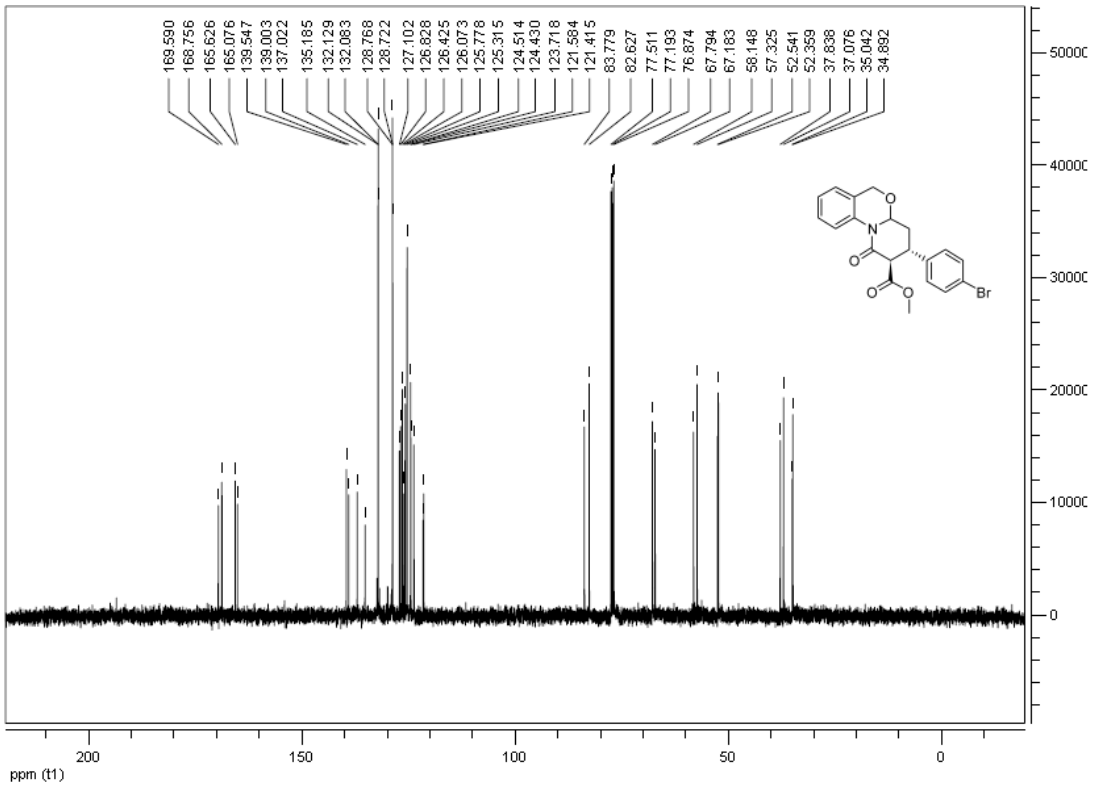
(2*R*,3*S*)-methyl 3-(4-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4u



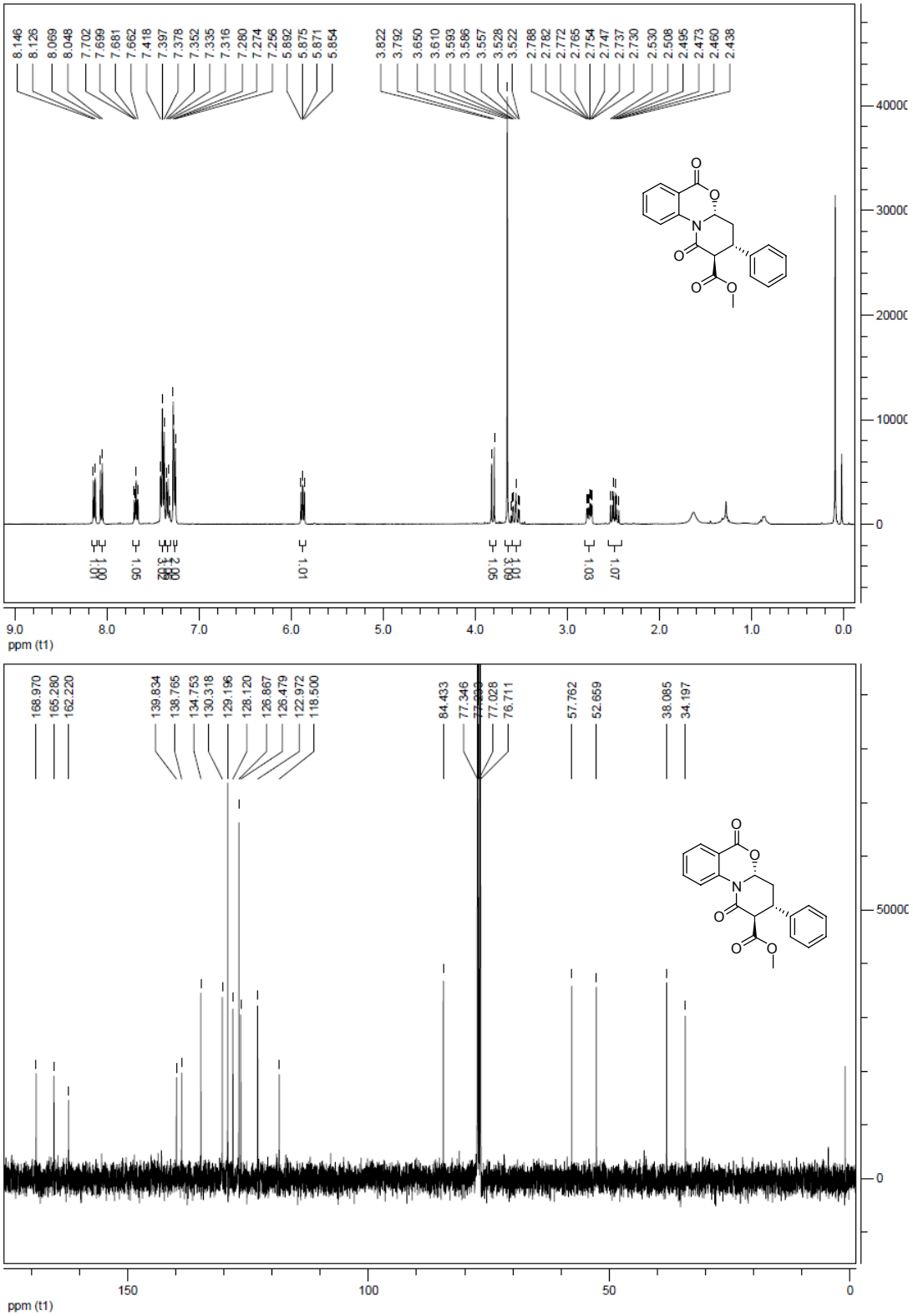


(2*R*,3*S*)-methyl 3-(4-bromophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4v

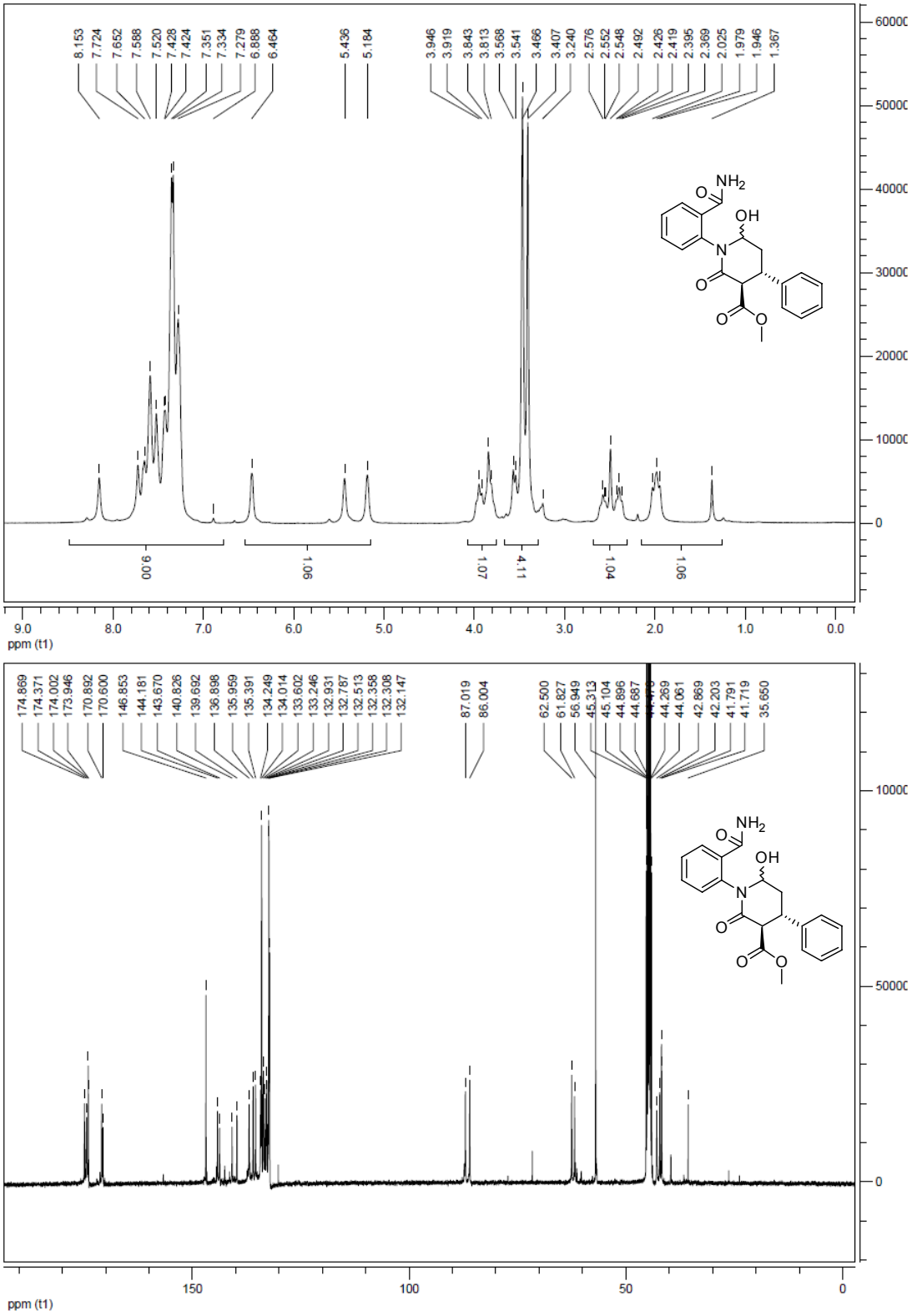




(2*R*,3*S*,4a*R*)-methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido [2,1-*b*][1,3]oxazine-2-carboxylate 4a1

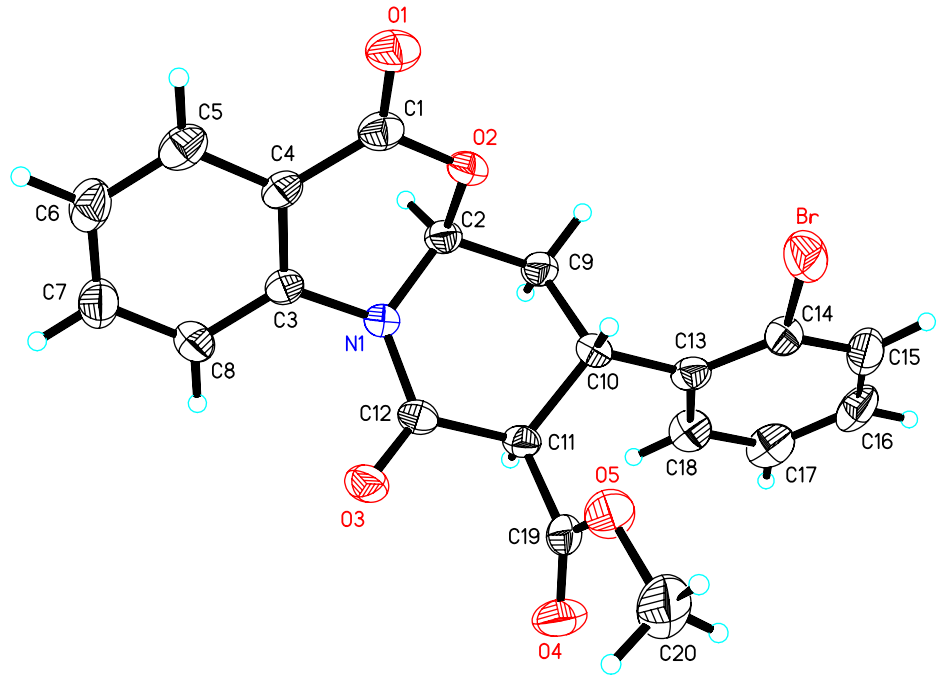


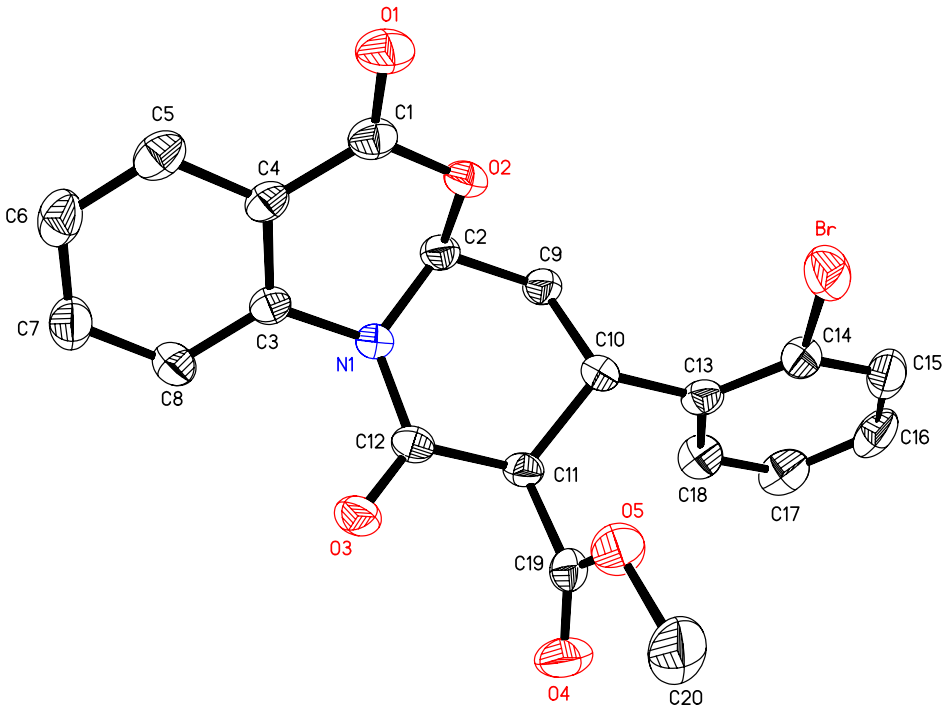
(3*R*,4*S*,6*S*)-methyl 1-(2-carbamoylphenyl)-6-hydroxy-2-oxo-4-phenylpiperidine -3-carboxylate 4a2

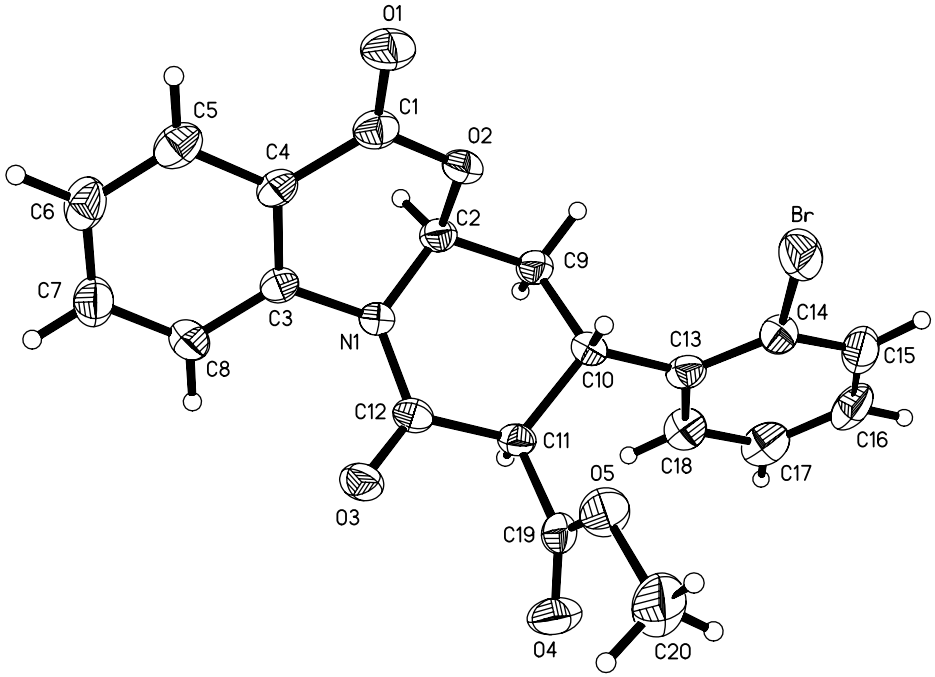


G. Determination of Absolute Configuration.

X-ray crystal structure of 4k






O1
C1
O2
C2
C3
C4
C5
C6
C7
C8
N1
C9
C10
C11
C12
O3
O4
O5
C19
C20
C13
C14
C15
C16
C17
C18
Br

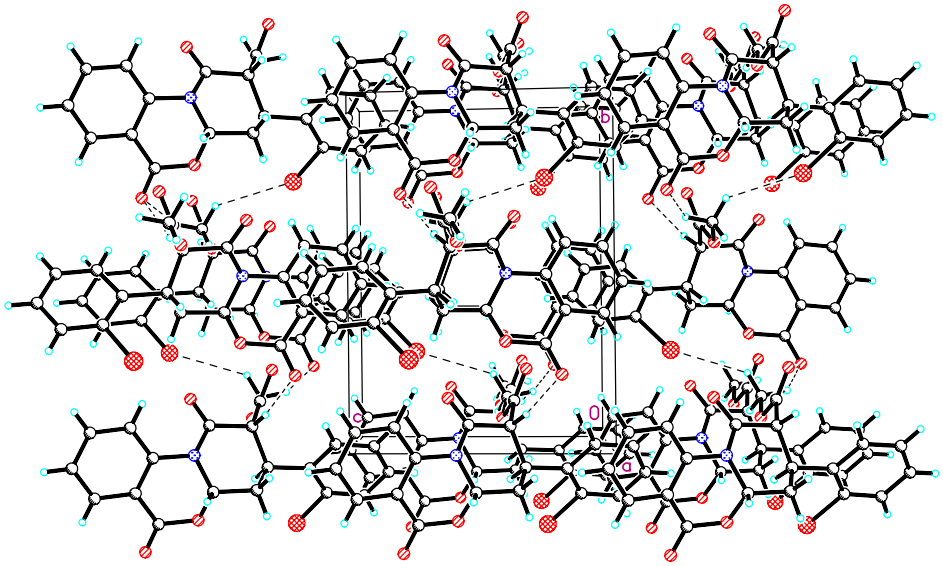


Table 1. Crystal data and structure refinement for cd201276.

Identification code	cd201276
Empirical formula	C20 H16 Br N O5
Formula weight	430.25
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 8.2259(12) A alpha = 90 deg. b = 12.3386(17) A beta = 97.552(2) deg. c = 9.1136(13) A gamma = 90 deg.
Volume	917.0(2) A^3
Z, Calculated density	2, 1.558 Mg/m^3
Absorption coefficient	2.273 mm^-1
F(000)	436
Crystal size	0.355 x 0.256 x 0.208 mm
Theta range for data collection	2.25 to 27.00 deg.
Limiting indices	-10<=h<=10, -14<=k<=15, -11<=l<=7
Reflections collected / unique	5418 / 3774 [R(int) = 0.0347]
Completeness to theta = 27.00	99.4 %
Absorption correction	Empirical
Max. and min. transmission	1.0000 and 0.6354
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	3774 / 1 / 246
Goodness-of-fit on F^2	0.896
Final R indices [I>2sigma(I)]	R1 = 0.0468, wR2 = 0.1032
R indices (all data)	R1 = 0.0661, wR2 = 0.1086
Absolute structure parameter	0.085(13)
Extinction coefficient	0.014(2)
Largest diff. peak and hole	0.479 and -0.428 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for cd201276.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br	4909(1)	2714(1)	7567(1)	78(1)
O(1)	579(4)	2191(3)	2001(4)	61(1)
O(2)	614(4)	3100(2)	4080(3)	47(1)
O(3)	1417(4)	6481(2)	3724(3)	53(1)
O(4)	3496(5)	7240(3)	6754(4)	83(1)
O(5)	4626(4)	5795(3)	5827(4)	72(1)
N(1)	-50(4)	4959(2)	4032(3)	39(1)
C(1)	182(5)	3011(3)	2582(5)	48(1)
C(2)	-241(5)	3942(3)	4776(4)	41(1)
C(3)	-748(5)	4917(3)	2517(4)	42(1)
C(4)	-673(5)	3927(3)	1817(4)	42(1)
C(5)	-1352(5)	3824(4)	337(5)	56(1)
C(6)	-2096(6)	4698(5)	-398(5)	63(1)
C(7)	-2158(6)	5684(5)	321(5)	63(1)
C(8)	-1489(6)	5790(4)	1763(5)	54(1)
C(9)	443(5)	3958(3)	6394(4)	45(1)
C(10)	2103(5)	4506(3)	6675(4)	39(1)
C(11)	1867(5)	5680(3)	6096(4)	40(1)
C(12)	1095(5)	5742(3)	4500(4)	40(1)
C(13)	2809(5)	4438(3)	8285(4)	45(1)
C(14)	3944(5)	3668(4)	8852(5)	52(1)
C(15)	4466(6)	3564(5)	10334(6)	68(1)
C(16)	3939(7)	4273(5)	11325(5)	69(2)
C(17)	2843(7)	5064(5)	10807(5)	66(1)
C(18)	2285(6)	5151(4)	9325(5)	56(1)
C(19)	3399(6)	6339(4)	6272(5)	53(1)
C(20)	6204(7)	6345(6)	6032(7)	107(2)

Table 3. Bond lengths [A] and angles [deg] for cd201276.

Br-C(14)	1.906(5)
O(1)-C(1)	1.206(5)
O(2)-C(1)	1.370(5)
O(2)-C(2)	1.447(5)
O(3)-C(12)	1.204(5)
O(4)-C(19)	1.194(6)
O(5)-C(19)	1.320(6)
O(5)-C(20)	1.455(6)
N(1)-C(12)	1.377(5)
N(1)-C(3)	1.425(5)
N(1)-C(2)	1.444(5)
C(1)-C(4)	1.459(6)
C(2)-C(9)	1.507(6)
C(2)-H(2)	0.9800
C(3)-C(8)	1.376(6)
C(3)-C(4)	1.384(5)
C(4)-C(5)	1.397(6)
C(5)-C(6)	1.372(7)
C(5)-H(5)	0.9300
C(6)-C(7)	1.385(7)
C(6)-H(6)	0.9300
C(7)-C(8)	1.363(6)
C(7)-H(7)	0.9300
C(8)-H(8)	0.9300
C(9)-C(10)	1.516(5)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-C(13)	1.508(5)
C(10)-C(11)	1.545(5)
C(10)-H(10)	0.9800
C(11)-C(19)	1.491(6)
C(11)-C(12)	1.510(6)
C(11)-H(11)	0.9800
C(13)-C(14)	1.383(6)
C(13)-C(18)	1.402(6)
C(14)-C(15)	1.368(6)
C(15)-C(16)	1.369(7)
C(15)-H(15)	0.9300
C(16)-C(17)	1.369(7)
C(16)-H(16)	0.9300

C(17)-C(18)	1.372(7)
C(17)-H(17)	0.9300
C(18)-H(18)	0.9300
C(20)-H(20A)	0.9600
C(20)-H(20B)	0.9600
C(20)-H(20C)	0.9600

C(1)-O(2)-C(2)	114.6(3)
C(19)-O(5)-C(20)	115.4(5)
C(12)-N(1)-C(3)	119.8(3)
C(12)-N(1)-C(2)	125.2(3)
C(3)-N(1)-C(2)	111.6(3)
O(1)-C(1)-O(2)	117.0(4)
O(1)-C(1)-C(4)	125.5(4)
O(2)-C(1)-C(4)	117.4(3)
N(1)-C(2)-O(2)	109.2(3)
N(1)-C(2)-C(9)	113.5(3)
O(2)-C(2)-C(9)	107.3(3)
N(1)-C(2)-H(2)	108.9
O(2)-C(2)-H(2)	108.9
C(9)-C(2)-H(2)	108.9
C(8)-C(3)-C(4)	120.3(4)
C(8)-C(3)-N(1)	123.5(4)
C(4)-C(3)-N(1)	116.2(4)
C(3)-C(4)-C(5)	119.3(4)
C(3)-C(4)-C(1)	120.8(3)
C(5)-C(4)-C(1)	119.8(4)
C(6)-C(5)-C(4)	119.8(4)
C(6)-C(5)-H(5)	120.1
C(4)-C(5)-H(5)	120.1
C(5)-C(6)-C(7)	120.1(4)
C(5)-C(6)-H(6)	120.0
C(7)-C(6)-H(6)	120.0
C(8)-C(7)-C(6)	120.4(5)
C(8)-C(7)-H(7)	119.8
C(6)-C(7)-H(7)	119.8
C(7)-C(8)-C(3)	120.2(5)
C(7)-C(8)-H(8)	119.9
C(3)-C(8)-H(8)	119.9
C(2)-C(9)-C(10)	112.5(3)
C(2)-C(9)-H(9A)	109.1
C(10)-C(9)-H(9A)	109.1
C(2)-C(9)-H(9B)	109.1
C(10)-C(9)-H(9B)	109.1

H(9A)-C(9)-H(9B)	107.8
C(13)-C(10)-C(9)	111.3(3)
C(13)-C(10)-C(11)	113.6(3)
C(9)-C(10)-C(11)	106.9(3)
C(13)-C(10)-H(10)	108.3
C(9)-C(10)-H(10)	108.3
C(11)-C(10)-H(10)	108.3
C(19)-C(11)-C(12)	108.6(3)
C(19)-C(11)-C(10)	114.1(4)
C(12)-C(11)-C(10)	113.2(3)
C(19)-C(11)-H(11)	106.8
C(12)-C(11)-H(11)	106.8
C(10)-C(11)-H(11)	106.8
O(3)-C(12)-N(1)	122.9(4)
O(3)-C(12)-C(11)	120.4(4)
N(1)-C(12)-C(11)	116.5(3)
C(14)-C(13)-C(18)	115.5(4)
C(14)-C(13)-C(10)	123.8(4)
C(18)-C(13)-C(10)	120.6(4)
C(15)-C(14)-C(13)	122.8(5)
C(15)-C(14)-Br	116.5(4)
C(13)-C(14)-Br	120.7(3)
C(14)-C(15)-C(16)	120.4(5)
C(14)-C(15)-H(15)	119.8
C(16)-C(15)-H(15)	119.8
C(15)-C(16)-C(17)	118.7(5)
C(15)-C(16)-H(16)	120.7
C(17)-C(16)-H(16)	120.7
C(16)-C(17)-C(18)	121.0(5)
C(16)-C(17)-H(17)	119.5
C(18)-C(17)-H(17)	119.5
C(17)-C(18)-C(13)	121.5(5)
C(17)-C(18)-H(18)	119.2
C(13)-C(18)-H(18)	119.2
O(4)-C(19)-O(5)	124.8(5)
O(4)-C(19)-C(11)	124.2(5)
O(5)-C(19)-C(11)	111.0(4)
O(5)-C(20)-H(20A)	109.5
O(5)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(5)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for cd201276. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br	77(1)	65(1)	86(1)	-11(1)	-12(1)	26(1)
O(1)	64(2)	49(2)	72(2)	-17(2)	16(2)	3(2)
O(2)	58(2)	31(1)	50(2)	-2(1)	4(1)	2(1)
O(3)	70(2)	42(2)	45(2)	6(1)	9(2)	-11(1)
O(4)	106(3)	59(2)	80(2)	-8(2)	-6(2)	-33(2)
O(5)	49(2)	77(2)	90(3)	18(2)	8(2)	-15(2)
N(1)	43(2)	33(2)	40(2)	0(1)	2(2)	-3(1)
C(1)	42(3)	46(3)	57(3)	-6(2)	10(2)	-5(2)
C(2)	37(2)	36(2)	49(2)	-2(2)	4(2)	-3(2)
C(3)	36(2)	41(2)	47(2)	1(2)	3(2)	-7(2)
C(4)	36(2)	47(2)	44(2)	-5(2)	5(2)	-9(2)
C(5)	50(3)	68(3)	50(3)	-9(2)	11(2)	-13(2)
C(6)	65(3)	84(4)	38(2)	8(3)	6(2)	-13(3)
C(7)	60(3)	73(3)	52(3)	13(3)	-2(2)	-6(3)
C(8)	57(3)	43(2)	60(3)	7(2)	2(2)	4(2)
C(9)	51(3)	40(2)	41(2)	2(2)	2(2)	-8(2)
C(10)	43(2)	32(2)	42(2)	2(2)	7(2)	1(2)
C(11)	47(2)	31(2)	41(2)	-4(2)	7(2)	-2(2)
C(12)	44(2)	32(2)	45(2)	-3(2)	13(2)	3(2)
C(13)	47(2)	43(2)	45(2)	-1(2)	8(2)	-12(2)
C(14)	49(3)	51(3)	54(3)	4(2)	-1(2)	-4(2)
C(15)	53(3)	79(3)	66(3)	21(3)	-10(3)	-11(3)
C(16)	62(3)	101(5)	42(3)	9(3)	-6(3)	-32(3)
C(17)	68(3)	87(4)	47(3)	-1(3)	20(3)	-24(3)
C(18)	59(3)	65(3)	46(3)	0(2)	14(2)	-5(2)
C(19)	61(3)	54(3)	41(2)	10(2)	-10(2)	-9(2)
C(20)	55(4)	138(6)	124(5)	57(5)	0(4)	-31(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for cd201276.

	x	y	z	U(eq)
H(2)	-1410	3760	4682	49
H(5)	-1299	3164	-149	67
H(6)	-2560	4630	-1381	75
H(7)	-2659	6276	-183	75
H(8)	-1534	6454	2239	65
H(9A)	543	3219	6758	54
H(9B)	-319	4335	6942	54
H(10)	2851	4133	6091	47
H(11)	1107	6034	6687	48
H(15)	5182	3007	10669	81
H(16)	4318	4220	12329	83
H(17)	2471	5549	11470	79
H(18)	1541	5696	9003	67
H(20A)	6120	7014	5491	160
H(20B)	7015	5891	5674	160
H(20C)	6517	6491	7065	160

Table 6. Torsion angles [deg] for cd201276.

C(2)-O(2)-C(1)-O(1)	-164.5(3)
C(2)-O(2)-C(1)-C(4)	17.4(5)
C(12)-N(1)-C(2)-O(2)	-97.2(4)
C(3)-N(1)-C(2)-O(2)	61.8(4)
C(12)-N(1)-C(2)-C(9)	22.4(5)
C(3)-N(1)-C(2)-C(9)	-178.6(3)
C(1)-O(2)-C(2)-N(1)	-53.9(4)
C(1)-O(2)-C(2)-C(9)	-177.3(3)
C(12)-N(1)-C(3)-C(8)	-53.7(5)
C(2)-N(1)-C(3)-C(8)	146.0(4)
C(12)-N(1)-C(3)-C(4)	127.3(4)
C(2)-N(1)-C(3)-C(4)	-33.0(5)
C(8)-C(3)-C(4)-C(5)	0.2(6)
N(1)-C(3)-C(4)-C(5)	179.2(4)
C(8)-C(3)-C(4)-C(1)	176.9(4)
N(1)-C(3)-C(4)-C(1)	-4.1(6)
O(1)-C(1)-C(4)-C(3)	-165.3(4)
O(2)-C(1)-C(4)-C(3)	12.6(6)
O(1)-C(1)-C(4)-C(5)	11.3(6)
O(2)-C(1)-C(4)-C(5)	-170.7(4)
C(3)-C(4)-C(5)-C(6)	-0.6(6)
C(1)-C(4)-C(5)-C(6)	-177.4(4)
C(4)-C(5)-C(6)-C(7)	0.7(7)
C(5)-C(6)-C(7)-C(8)	-0.3(7)
C(6)-C(7)-C(8)-C(3)	-0.1(7)
C(4)-C(3)-C(8)-C(7)	0.2(7)
N(1)-C(3)-C(8)-C(7)	-178.7(4)
N(1)-C(2)-C(9)-C(10)	-43.7(5)
O(2)-C(2)-C(9)-C(10)	77.0(4)
C(2)-C(9)-C(10)-C(13)	-175.9(3)
C(2)-C(9)-C(10)-C(11)	59.5(4)
C(13)-C(10)-C(11)-C(19)	57.5(5)
C(9)-C(10)-C(11)-C(19)	-179.4(3)
C(13)-C(10)-C(11)-C(12)	-177.7(3)
C(9)-C(10)-C(11)-C(12)	-54.5(4)
C(3)-N(1)-C(12)-O(3)	8.6(6)
C(2)-N(1)-C(12)-O(3)	166.1(4)
C(3)-N(1)-C(12)-C(11)	-175.6(3)
C(2)-N(1)-C(12)-C(11)	-18.2(5)
C(19)-C(11)-C(12)-O(3)	-21.8(5)

C(10)-C(11)-C(12)-O(3)	-149.6(4)
C(19)-C(11)-C(12)-N(1)	162.3(4)
C(10)-C(11)-C(12)-N(1)	34.5(5)
C(9)-C(10)-C(13)-C(14)	97.7(5)
C(11)-C(10)-C(13)-C(14)	-141.6(4)
C(9)-C(10)-C(13)-C(18)	-79.9(4)
C(11)-C(10)-C(13)-C(18)	40.8(5)
C(18)-C(13)-C(14)-C(15)	3.3(6)
C(10)-C(13)-C(14)-C(15)	-174.4(4)
C(18)-C(13)-C(14)-Br	-175.0(3)
C(10)-C(13)-C(14)-Br	7.4(6)
C(13)-C(14)-C(15)-C(16)	-3.7(7)
Br-C(14)-C(15)-C(16)	174.6(4)
C(14)-C(15)-C(16)-C(17)	2.1(7)
C(15)-C(16)-C(17)-C(18)	-0.3(7)
C(16)-C(17)-C(18)-C(13)	0.1(7)
C(14)-C(13)-C(18)-C(17)	-1.5(6)
C(10)-C(13)-C(18)-C(17)	176.3(4)
C(20)-O(5)-C(19)-O(4)	3.3(7)
C(20)-O(5)-C(19)-C(11)	-176.7(4)
C(12)-C(11)-C(19)-O(4)	99.3(5)
C(10)-C(11)-C(19)-O(4)	-133.4(5)
C(12)-C(11)-C(19)-O(5)	-80.7(4)
C(10)-C(11)-C(19)-O(5)	46.6(5)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for cd201276 [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

H. References

[1] C. R. Hutchinson, M. Nakane, H. Gollman, and P. L. Knutson, *Org*. *Syn*. *Coll*. 1990, **7**, 323.

[2] J. Yu, G. Lian, and D. Zhang, *Syn*. *Commun*. 2007, **37**, 37.