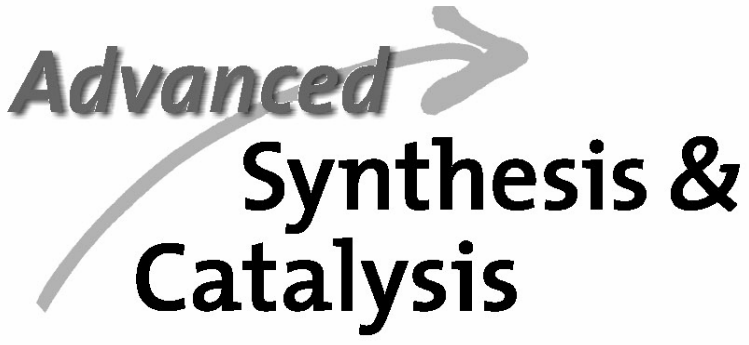

Supporting Information

Enantioselective Michael Addition of Dicyanoolefins to a, ß-Unsaturated Aldehydes in Aqueous Medium

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Supporting Information

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General Methods:

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate or ethanol solution of ninhydride.

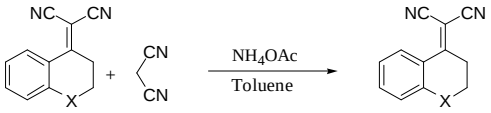
Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. Liquid samples were examined as film between NaCl salt plates.

Proton nuclear magnetic resonance spectra (1H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^1H NMR spectra are reported as d in units of parts per million (ppm) downfield from SiMe4 (d 0.0) and relative to the signal of chloroform-*d* (d 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as d in units of parts per million (ppm) downfield from SiMe4 (d 0.0) and relative to the signal of chloroform-*d* (d 77.03, triplet). The proportion of diastereomers was determined from the integration of ^1H NMR and ^{13}C NMR spectra.

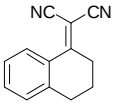
Mass spectral analyses were carried out on a VG 7035 micromass mass spectrophotometer at a source temperature of 200 ^oC and at an ion current of 70 eV. Mass spectral data were reported in units of mass to charge (m/z) and % intensity.

General procedures for the preparation of olefins:



Malononitrile (25 mmol) and the ketone (27.5 mmol) were dissolved in 30 mL of toluene containing ammonium acetate (500 mg) and glacial acetic acid (2 mL) in a 50 mL flask. By refluxing vigorously, the water formed in the reaction was removed by a Dean and Stark trap placed under the reflux condenser. After the completion of the reaction, the reaction mixture was diluted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was recrystallized from alcohol to give pure products.

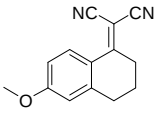
2-(2,3-Dihydronaphthalen-4(1H)-ylidene) malononitrile



^{1}H NMR (400 MHz, $CDCl_3$): *d* 8.20 (d, J = 10.5 Hz, 1H), 7.52-7.46 (m, 1H), 7.36-7.26 (m,2H), 3.02 (t, J = 8.7 Hz, 2H), 2.89 (t, J = 8.3 Hz, 2H), 2.02 (t, J = 8.6 Hz, 2H).

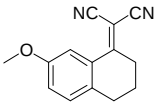
^{13}C NMR (100 MHz, $CDCl_3$): *d* 172.6, 142.0, 133.7, 130.0, 129.5, 127.9, 126.9, 114.0, 113.4, 79.8, 33.1, 29.7, 22.2.

2-(6-Methoxy-2,3-dihydronaphthalen-4(1H)-ylidene) malononitrile



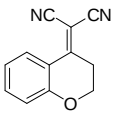
^{1}H NMR (400 MHz, $CDCl_3$): *d* 8.30 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.76 (s, 1H), 3.88 (s, 3H), 2.99 (t, J = 6.4 Hz, 2H), 2.85 (t, 6.2 Hz, 2H), 1.99-1.93 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): *d* 171.1, 163.5, 146.9, 130.4, 129.6, 126.3, 114.2, 113.0, 112.9, 55.4, 38.9, 30.2, 23.4.

2-(7-Methoxy-2,3-dihydronaphthalen-4(1H)-ylidene) malononitrile



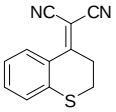
^{1}H NMR (400 MHz, $CDCl_3$): *d* 7.73 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.06 (dd, J = 8.5, 2.5 Hz, 1H), 3.84 (s, 3H), 3.00 (t, J = 6.5 Hz, 2H), 2.83 (t, J = 6.2 Hz, 2H), 1.99-1.96 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): *d* 172.6, 157.9, 134.5, 130.5, 130.4, 121.9, 114.2, 113.5, 110.9, 79.6, 55.7, 33.1, 28.9, 22.5.

2-(2,3-Dihydrochromen-4-ylidene) malononitrile



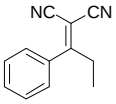
^{1}H NMR (400 MHz, $CDCl_3$): *d* 8.36 (dd, J = 8.2, 1.4 Hz, 1H), 7.53-7.48 (m, 1H), 7.07-7.03 (m, 1H), 6.98 (dd, J = 8.4, 0.9 Hz, 1H), 4.39 (t, J = 6.3 Hz, 2H), 3.15 (t, J = 6.3 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): *d* 163.4, 157.4, 136.8, 127.3, 121.7, 118.7, 117.2, 113.8, 113.2, 64.7, 30.9.

2-(2,3-Dihydrothiochromen-4-ylidene) malononitrile



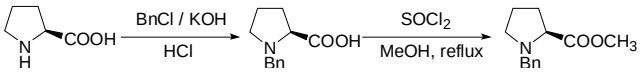
^{1}H NMR (400 MHz, $CDCl_3$): *d* 7.96 (d, J = 8.0 Hz, 1H), 7.42-7.40 (m, 1H), 7.38-7.27 (m, 1H), 7.22-7.18 (m, 1H), 3.31 (t, J = 6.5 Hz, 2H), 3.16 (t, J = 6.4 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): *d* 169.8, 138.9, 133.5, 129.4, 128.3, 128.0, 125.0, 113.4, 112.8, 81.9, 32.7, 25.7.

2-(1-Phenylpropylidene)malononitrile



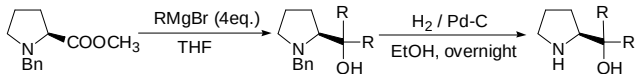
^{1}H NMR (400 MHz, $CDCl_3$): *d* 7.56-7.46 (m, 5H), 2.98 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): *d* 181.7, 134.6, 132.0, 129.2, 127.5, 112.8, 112.5, 84.3, 31.1, 12.8.

Preparation of dialkyl-(S)-pyrrolidin-2-yl-methanol



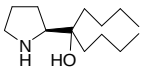
A solution of 17.3 g (0.15mol) of L-proline and 25.4 g (0.45 mol) of KOH in isopropanol (100 mL) was prepared with stirring at 40°C. As soon as the solution became transparent, slow addition of freshly distilled BnCl (18.9 mL, 0.16 mol) was commenced under stirring at the same temperature. The dropwise addition took 3 h to complete, and the stirring was continued for another 6 h at the same temperature. The reaction mixture was neutralized with concentrated aqueous HCl until pH 5–6, then was added to the reaction mixture $CHCl_3$ (40 ml) with stirring. The mixture was left overnight, then filtered and the precipitate was washed with CHCl3. The CHCl3 solutions were combined and evaporated, the residue was treated with acetone and the precipitate of crude BP filtered and additionally washed with acetone. The solid was dried over P_2O_5 to yield the unpurified benzylated acid (29.2g, unpurified yield), which was used further without any purification.

$SOCl_2$ (4 mL, 55 mmol) was added during 10 min at 0 oC to a mixture of N-benzyl-L-proline (12g , 50 mmol) in 40 mL MeOH and afterwards stirred at reflux for 1h. MeOH and excess of $SOCl_2$ were evaporated under reduced pressure; EA (150 mL) was added and washed with saturated sodium bicarbonate solution (50 mL×4). The organic phase was dried over anhydrous NaSO4 and evaporated under reduce pressure, remaining a brown oil. The product was used in the following step with further purification. Yield: 9.9 g (90 %). 1HNMR (400 MHz, CDCl3): d 7.38-7.23 (m, 5H), 3.83 (d, J = 29.7 Hz, 1H), 3.59 (s, 3H), 3.46 (d, J = 35 Hz, 1H), 3.26-3.23 (m, 1H), 3.08-3.04 (m, 1H), 2.42-2.36 (m, 1H), 2.18-2.08 (m, 1H), 2.00-1.86 (m, 2H), 1.81-1.74 (m, 1H).



The corresponding alkylmagnesium bromide (80 mmol) in THF was cooled at 0^oC and (S)-methyl 1-benzylpyrrolidine- 2-carboxylate (20 mmol in THF) was added dropwise over 20 min. Then the reaction mixture was stirred overnight at rt. The reaction was quenched with saturated NH_4Cl. The supernatant liquid was collected leaving behind a white precipitate which was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product obtained was used in the following step without further purification.

The crude dialkyl-(1-benzylpyrrolidin-2-yl)methanol (10 mmol) was disolved in 10 mL of ethanol and palladium, (10 wt. % on activated carbon, 20% mol % weight) was added. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The solution was filtered over celite in a Büchner funnel and the solvent evaporated under reduced pressure. The crude obtained was purified by column chromatography.

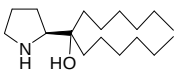


$[a]^{25}_{,D}$ = -31.4 (c = 2.5, DCM)

^{1}HNMR (400 MHz, $CDCl_3$) d: 3.49-3.36 (m, 1H), 3.08-2.92 (m, 1H), 2.90-2.76 (m, 2H), 1.75-1.58 (m, 4H), 1.40-1.30 (m, 3H), 1.35-1.06 (m, 8H), 0.79 (t, J = 6.5 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) d: 73.33, 64.32, 46.42, 37.36, 34.74, 25.82, 25.79, 25.57, 25.19, 23.36, 23.34, 14.03, 13.95.

MS: $C_{13}H_{27}NO$ 214.20 $[M+H]^+$.

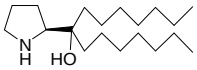


$[a]^{25}_{,D}$ = -15.4 (c 1.6, DCM).

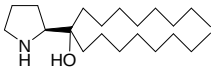
^{1}HNMR (400 MHz, $CDCl_3$) d: 3.14-3.08 (m, 1H), 2.99-2.91 (m, 2H,), 1.80-1.53 (m, 4H), 1.49-1.18 (m, 20H), 0.89 (t, J = 6.8 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) d: 73.48, 64.28, 46.49, 37.80, 35.05, 31.85, 31.76, 30.06, 30.04, 25.93, 25.25, 23.63,

23.39, 22.65, 22.62, 14.05.
MS: $C_{17}H_{35}NO$ 270.25 $[M+H]^+$.



[a] $^{25}_{D}$ = -13.8 (c = 2.3, DCM)
^{1}HNMR (400 MHz, $CDCl_3$) d: 3.15-3.12 (m, 1H), 3.04-2.93 (m, 2H), 1.82-1.70 (m, 3H), 1.57-1.43 (m, 3H), 1.40-1.06 (m, 22H), 0.88 (t, J = 6.7 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$) d: 73.52, 64.39, 46.46, 37.78, 35.07, 31.90, 31.86, 29.71, 29.66, 29.34, 29.24, 29.11, 25.90, 25.29, 23.70, 23.44, 22.69, 14.11.
MS: $C_{19}H_{39}NO$ 298.26 $[M+1]^+$.

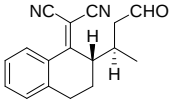


[a] $^{25}_{D}$ = -10.4 (c = 2.2, DCM)
^{1}HNMR (400 MHz, $CDCl_3$) d: 3.29-3.23 (m, 1H), 3.08-2.98 (m, 2H), 1.90-1.74 (m, 3H), 1.58-1.44 (m, 3H), 1.38-1.12 (m, 26H), 0.86 (t, J = 6.7 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$) d: 73.55, 65.08, 46.18, 37.48, 35.15, 31.92, 31.88, 30.33, 30.30, 29.70, 29.63, 29.36, 29.28, 25.45, 25.32, 23.63, 23.39, 22.69, 22.67, 14.12.
MS: $C_{21}H_{43}NO$ 326.35 $[M+H]^+$.

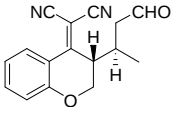
[a] $^{25}_{D}$ = -6.4 (c = 1.8, DCM)
^{1}HNMR (400 MHz, $CDCl_3$) d: 3.18-3.04 (m, 1H), 2.96-2.86 (m, 2H), 1.72-1.61 (m, 3H), 1.40-1.22 (m, 37H), 0.87 (t, J = 7.2 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$) d: 73.50, 64.04, 46.61, 37.95, 35.02, 32.86, 31.96, 30.47, 30.44, 29.73, 29.69, 29.61, 29.48, 29.39, 26.13, 25.80, 25.26, 23.73, 23.47, 22.71, 14.09.
MS: $C_{25}H_{51}NO$ 382.33 $[M+H]^+$.

Direct Vinylogous Michael Addition Reaction:

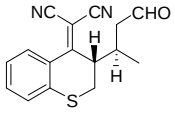
Typical Procedure (Table 2, entry 1): A mixture of **6a** (19.4 mmg, 0.1 mmol), **7a** (32 μL, 0.4 mmol), cat. (0.02 mmol) and PNBA (3.4 mmg, 0.02 mmol) in brine (0.5 mL) was stirred for 36 h at 0^{o}C. Then the reaction was quenched by adding 0.5 mL 1M HCl. The mixture was extracted with EtOAc, dried with anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel to give the desired product **8aa** in 82% yield with 90% ee, determined by HPLC (Chiralpak AS, 0% 2-propanol/hexane, 1 mL/min): tminor = 18.756 min, tmajor = 26.674 min.



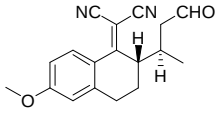
8aa [a] $^{22}_{,D}$ = -368 (c 1.02, DCM), 90%ee;
R_f = 0.32 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.64 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.28-7.26 (m, 1H), 3.04-3.02 (m, 1H), 3.00-2.96 (m, 1H), 2.91-2.84 (m, 1H), 2.45-2.41 (m, 2H), 2.38-2.19 (m, 2H), 2.12-2.04 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.4, 177.4, 140.2, 133.8, 129.5, 129.2, 128.3, 127.0, 113.5, 113.3, 81.1, 48.7, 47.1, 28.8, 24.9, 24.5, 17.3;
IR (KBr): 2226, 1762 cm^{-1};
MS: $C_{17}H_{16}N_2O$ 264.12 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 18.756 min, *t*major = 26.674 min.



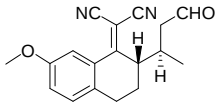
8ba [a] $^{22}_{,D}$ = -475 (c 0.98, DCM), 92%ee;
R_f = 0.24 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.63 (s, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 7.6 Hz,), 6.96 (d, J = 8.2 Hz, 1H), 4.68 (dd, J = 1.4, 11.2 Hz, 1H), 4.26 (dd, J = 2.1, 12.6 Hz, 1H), 2.85 (d, J = 10.1 Hz, 1H), 2.53-2.33 (m, 3H), 1.19 (d, J = 6.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 199.9, 167.9, 156.2, 136.9, 127.9, 121.9, 118.2, 115.7, 113.2, 78.5, 66.3, 48.0, 44.5, 27.8, 17.9;
IR (KBr): 2225, 1720 cm^{-1};
MS: $C_{16}H_{14}N_2O_2$ 266.09 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 16.176 min, *t*major = 21.493 min.



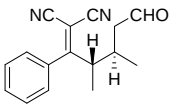
8ca [a] $^{22}_{,D}$ = -514 (c 0.89, DCM), 91%ee;
R_f = 0.16 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.58 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.23-7.15 (m, 2H), 3.48-3.43 (m, 1H), 3.27-3.22 (m, 2H), 2.47-2.23 (m, 3H), 1.15 (d, J = 6.3 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 199.8, 173.4, 138.2, 133.8, 130.3, 127.2, 125.6, 124.9, 113.0, 112.6, 82.6, 48.1, 43.9, 28.5, 27.9, 17.5;
IR (KBr): 2229, 1721 cm^{-1};
MS: $C_{16}H_{14}N_2OS$ 282.09 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 21.464 min, *t*major = 39.825 min.



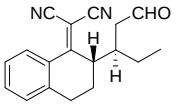
8da[a] $^{22}_{,D}$ = -171 (c 0.85, DCM), 88%ee;
R_f = 0.18 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.62 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.74 (s, 1H), 3.86 (s, 3H), 3.06-2.82 (m, 3H), 2.45-2.38 (m, 2H), 2.36-2.21 (m, 2H), 2.09-1.99 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.6, 176.4, 163.9, 142.8, 130.6, 121.9, 114.4, 114.2, 113.9, 113.1, 77.8, 55.6, 48.6, 47.0, 28.6, 25.1, 24.5, 17.5;
IR (KBr): 2224, 1725 cm^{-1};
MS: $C_{18}H_{18}N_2O_2$ 294.14 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 20.088 min, *t*major = 24.691 min.



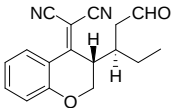
8ea [a] $^{22}_{,D}$ = -48 (c = 0.32, DCM), 87%ee;
R_f = 0.17 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.64 (s, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.08-7.05 (m, 1H), 3.84 (s, 3H), 3.11-3.06 (m, 1H), 2.98-2.89 (m, 1H), 2.83-2.77 (m, 1H), 2.45-2.35 (m, 1H), 2.31-2.19 (m, 2H), 2.10-2.01 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.5, 177.5, 157.9, 132.3, 130.6, 129.6, 121.7, 113.6, 113.3, 111.6, 80.7, 55.7, 48.7, 47.1, 28.8, 24.9, 24.1, 17.4;
IR (KBr): 2221, 1724 cm^{-1};
MS: $C_{18}H_{18}N_2O_2$ 294.4 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 12.136 min, *t*major = 22.946 min.



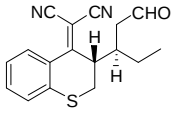
8fa [a] $^{24}_{,D}$ = -19 (c = 0.26, DCM), 75%ee;
R_f = 0.29 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d*9.75 (s, 1H), 7.53-7.48 (m, 3H), 7.30-7.28 (m, 2H), 3.16-3.09 (m, 1H), 2.63-2.58 (m, 1H), 2.39-2.21 (m, 2H), 1.22 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.6, 183.9, 134.1, 131.0, 129.1, 127.1, 111.9, 88.4, 48.0, 47.3, 31.2, 19.3, 17.3;
IR (KBr): 2228, 1726 cm^{-1};
MS: $C_{16}H_{16}N_2O$ 252.14 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min) after converted to the alcohol, *t*minor = 10.742 min, *t*major = 13.389 min.



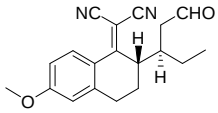
8ab [a]$^{23}_{,D}$=-269 (c 0.58, DCM), 84%ee;
R_f = 0.39 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.61 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.1 Hz, 1H), 7.35-7.26 (m, 2H), 3.27-3.23 (m, 1H), 2.98-2.88(m, 2H), 2.56-2.49 (m, 1H), 2.22-2.16 (m, 2H), 2.11-2.04 (m, 1H), 1.61-1.54 (m, 1H), 1.49-1.42 (m, 1H), 1.36-1.28 (m, 1H), 0.89 (t, J = 7.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.6, 177.5, 140.2, 133.7, 129.4, 129.3, 128.5, 126.9, 113.5, 113.3, 80.9, 45.2, 44.7, 34.0, 25.1, 24.6, 23.1, 9.6;
IR (KBr): 2219, 1743 cm^{-1};
MS: $C_{18}H_{18}N_2O$ 301.11 $[M+Na]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 14.866 min, *t*major = 18.309 min.



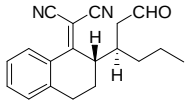
8bb [a] $^{24}_{,D}$ = - 291 (c = 2.4, DCM), 88%ee;
R_f = 0.45 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.58 (s, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 8.2 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 4.64 (dd, J = 1.7, 12.6 Hz, 1H), 4.24 (dd, J = 2.2, 12.6 Hz, 1H), 2.98 (d, J = 8.3 Hz, 1H), 2.60-2.53 (m, 1H), 2.38-2.23 (m, 2H), 1.75-1.68 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 199.9, 168.1, 156.2, 136.9, 127.9, 121.8, 118.1, 115.8, 113.2, 113.1, 78.5, 66.3, 44.6, 42.1, 32.6, 23.5, 9.46;
IR (KBr): 2226, 1719 cm^{-1};
MS: $C_{17}H_{16}N_2O_2$ 280.12 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 14.009 min, *t*major = 19.113 min.



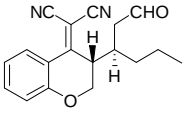
8cb [a] $^{24}_{,D}$= -492 (c = 1.3, DCM), 90%ee;
R_f = 0.27 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.54 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.23-7.16 (m, 2H), 3.40 (dd, J = 1.8, 12.5 Hz, 1H), 3.21 (dd, J = 2.3, 12.6 Hz, 1H), 2.48-2.36 (m, 2H), 2.23-2.18 (m, 1H), 1.73-1.54 (m, 3H), 0.96 (t, J = 7.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 199.9, 173.3, 138.2, 133.8, 130.4, 127.1, 125.8, 124.9, 113.0, 112.6, 82.7, 44.5, 41.4, 32.7, 28.5, 23.1, 9.4;
IR (KBr): 2223, 1725 cm^{-1};
MS: $C_{17}H_{16}N_2OS$ 296.12 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 19.394 min, *t*major = 31.557 min.



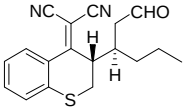
8db [a] $^{24}_{,D}$ = -198 (c = 2.1, DCM), 84%ee;
R_f = 0.22 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.60 (s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 6.84(dd, J = 2.6, 8.9 Hz, 1H), 6.74 (s, 1H), 3.86 (s, 3H), 3.21-3.16 (m, 1H), 2.98-2.94 (m, 1H), 2.88-2.82 (m, 1H), 2.55-2.49 (m, 1H), 2.28-2.18 (m, 3H), 2.06-2.01 (m, 1H), 1.61-1.55 (m, 1H), 1.50-1.42 (m, 1H), 0.89 (t, J = 7.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.7, 176.5, 163.9, 142.7, 130.7, 122.1, 114.3, 114.2, 113.9, 113.0, 77.9, 55.6, 45.2, 44.5, 33.7, 25.3, 24.5, 23.1, 9.4;
IR (KBr): 2225, 1726 cm^{-1};
MS: $C_{19}H_{20}N_2O_2$ 308.13 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 19.145 min, *t*major = 21.763 min.



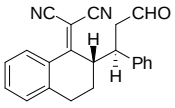
8ac [a]$^{23}_{,D}$=-269 (c 0.58, DCM), 85%ee;
R_f = 0.59 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.61 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 3.28-3.23 (m, 1H), 3.01-2.94 (m, 1H), 2.89-2.82 (m, 1H), 2.53-2.45 (m, 1H), 2.30-2.23 (m, 2H), 2.19-2.13 (m, 1H), 2.11-2.04 (m, 1H), 1.46-1.28 (m, 4H), 1.27-1.19 (m, 1H), 0.89 (t, J = 7.0 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.6, 177.5, 140.2, 133.7, 129.5, 129.4, 128.4, 126.9, 113.5, 113.3, 81.0, 46.0, 45.3, 33.2, 32.9, 25.2, 24.5, 18.8, 14.3;
IR (KBr): 2225, 1730 cm^{-1};
MS: $C_{19}H_{20}N_2O$ 292.10 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 12.974 min, *t*major = 15.776 min.



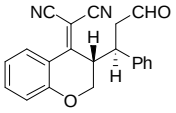
8bc [a]$^{23}_{D}$=-529 (c 0.63, DCM), 87%ee;
R_f = 0.35 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.57 (s, 1H), 8.08 (d, J = 7.1 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.64 (dd, J = 1.4, 12.3 Hz, 1H), 4.24 (dd, J = 2.2, 12.6 Hz, 1H), 2.98 (d, J = 9.9 Hz, 1H), 2.57-2.49 (m, 1H), 2.39-2.32 (m, 2H), 1.65-1.42 (m, 2H), 1.40-1.24 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.0, 168.2, 156.2, 136.9, 127.9, 121.8, 118.1, 115.8, 113.2, 78.6, 66.4, 45.3, 42.7, 33.4, 31.8, 18.8, 14.2;
IR (KBr): 2228, 1744 cm^{-1};
MS: $C_{18}H_{18}N_2O_2$ 294.14 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 12.723 min, *t*major = 16.203 min.



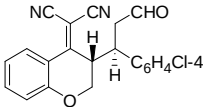
8cc [a]$^{23}_{D}$=-278 (c 2.8, DCM), 84%ee;
R_f = 0.28 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.54 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.24-7.16 (m, 2H), 3.45-3.42 (m, 2H), 3.24-3.20 (m, 1H), 2.45-2.42 (m, 2H), 2.27-2.19 (m, 1H), 1.38-1.14 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 200.7, 174.1, 137.8, 133.6, 130.2, 127.2, 126.1, 125.1, 113.1, 112.5, 82.9, 44.5, 42.7, 34.2, 32.7, 28.8, 19.6, 13.9;
IR (KBr): 2221, 1724 cm^{-1};
MS: $C_{18}H_{18}N_2OS$ 310.12 $[M]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 17.132 min, *t*major = 24.571 min.



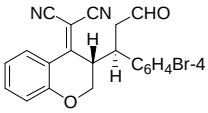
8ad [a]$^{23}_{D}$=-176 (c 1.8, DCM), 85%ee;
R_f = 0.31 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.40 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.39-7.25 (m, 7H), 3.59-3.54 (m, 1H), 3.20-3.13 (m, 1H), 3.08-2.92 (m, 2H), 2.87-2.81 (m, 1H), 2.56-2.51 (m, 1H), 1.98-1.88 (m, 1H), 1.79-1.74 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 199.6, 176.5, 140.0, 139.9, 134.2, 129.9, 129.2, 128.7, 128.4, 127.8, 127.1, 113.5, 113.4, 80.8, 48.1, 47.3, 43.5, 40.4, 25.3, 24.3;
IR (KBr): 2213, 1748 cm^{-1};
MS: $C_{22}H_{18}N_2O$ 327.13 $[M+H]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*major = 20.732 min, *t*minor = 30.280 min.



8bd [a] $^{22}_{,D}$ = -218 (c 1.08, DCM), 87%ee;
R_f = 0.26 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.44 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.41-7.37 (m, 2H), 7.33-7.29 (m, 3H), 7.10 (t, J = 7.7 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.12-4.02 (m, 2H), 3.45-3.38 (m, 1H), 3.28-3.18 (m, 1H), 3.12-3.05 (m, 1H), 2.65-2.59 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 199.2, 167.1, 156.3, 139.2, 137.3, 129.4, 128.1, 128.0, 122.0, 118.4, 115.3, 113.2, 78.7, 66.5, 46.8, 45.2, 39.5;
IR (KBr): 2224, 1719 cm^{-1};
MS: $C_{21}H_{16}N_2O_2$ 327.15 $[M-H]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 19.582 min, *t*major = 22.589 min.



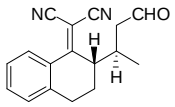
8be [a]$^{24}_{,D}$=-153 (c 0.67, DCM), 88% ee.
R_f = 0.38 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d*9.44 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.56 (t, J = 8.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.10 (t, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.13-4.01 (m, 2H), 3.45-3.35 (m, 1H), 3.19-3.02 (m, 2H), 2.68-2.63 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): *d*198.6, 166.7, 156.2, 137.8, 137.4, 132.5, 129.9, 127.9, 122.2, 118.4, 116.2, 115.2, 113.4, 113.0, 78.8, 66.4, 46.7, 44.9, 38.6;
IR (KBr): 2216, 1720 cm^{-1};
MS: $C_{21}H_{15}ClN_2O_2$ 363.11 $[M+H]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 20.517 min, *t*major = 23.797 min.

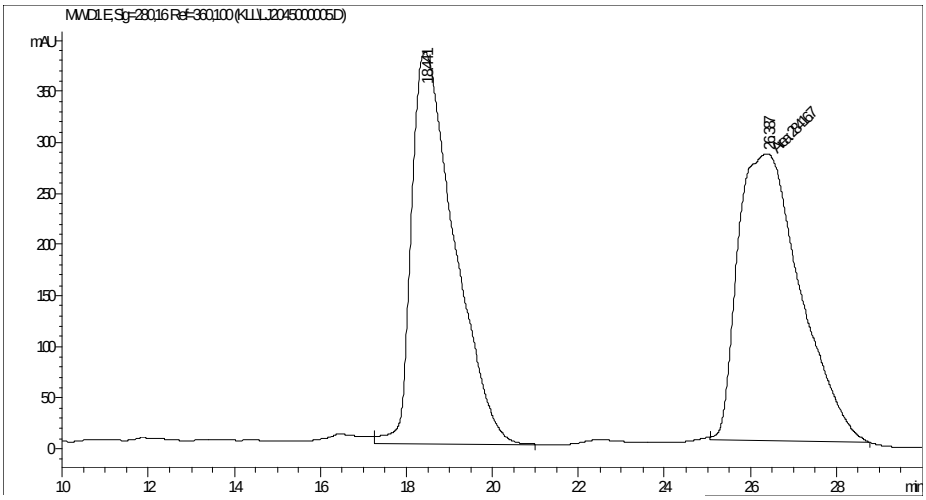


8bf [a]$^{24}_{,D}$=-174 (c 0.45, DCM), 85% ee;
R_f = 0.33 (Hex:EA = 4 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): *d* 9.46 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.11 (t, J = 8.3 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.12-4.01 (m, 2H), 3.44-3.37 (m, 1H), 3.19-3.04 (m, 2H), 2.66-2.61 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): *d* 198.6, 166.7, 156.2, 138.4, 137.4, 132.5, 129.9, 127.9, 122.2, 118.4, 116.2, 115.2, 113.4, 113.1, 78.8, 66.4, 46.7, 44.9, 38.8;
IR (KBr): 2209, 1719cm^{-1};
MS: $C_{21}H_{15}BrN_2O_2$ 429.03 $[M+Na]^+$.
The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t*minor = 22.685 min, *t*major = 25.682 min.

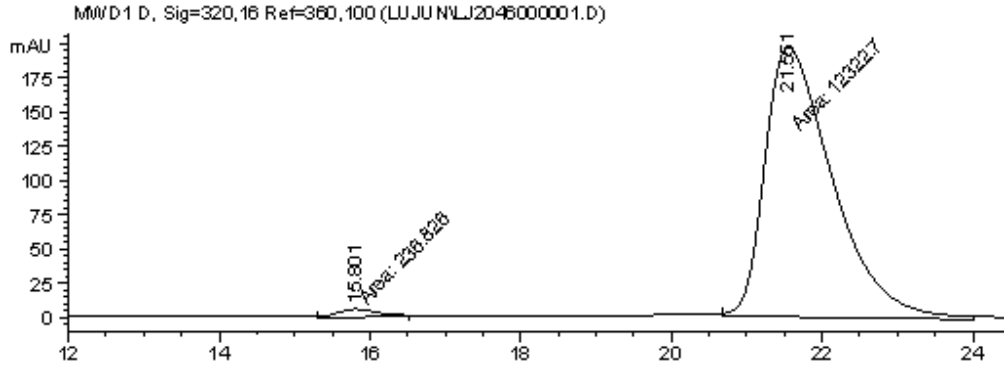
HPLC spectra of products:

8aa

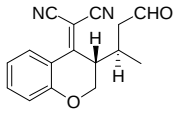




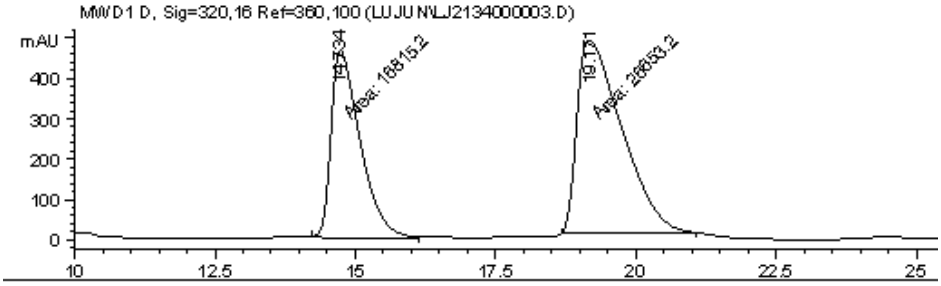
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.441	VB	1.0312	2.65250e4	383.35468	47.5160
2	26.387	MM	1.7159	2.92984e4	284.57108	52.4840
Totals :				5.58234e4	667.92575	



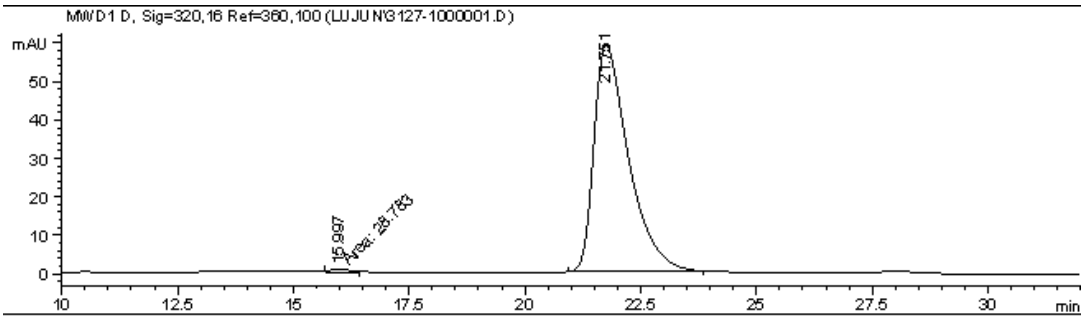
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.801	MM	0.6492	236.82565	6.08029	1.8856
2	21.551	MM	1.0425	1.23227e4	197.00284	98.1144
Totals :				1.25595e4	203.08313	



8ba

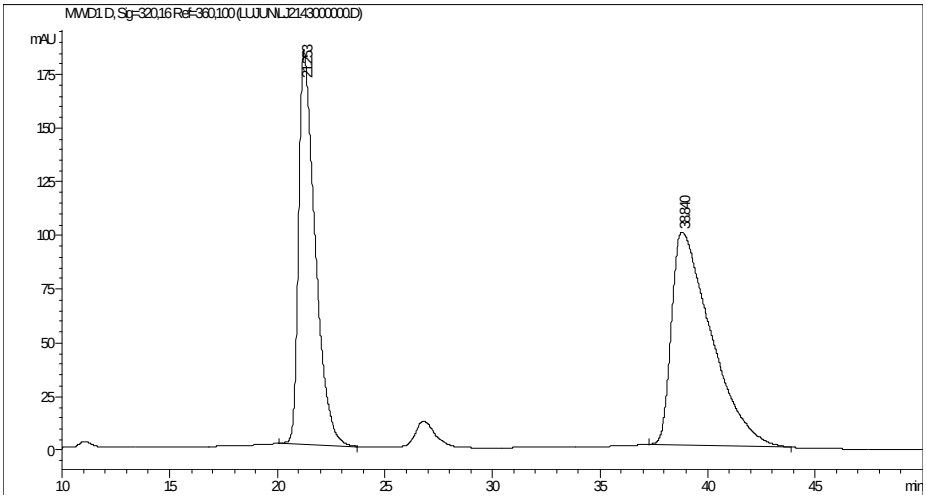


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.734	MM	0.6034	1.68152e4	464.48425	38.6837
2	19.171	MM	0.9279	2.66532e4	478.71790	61.3163
Totals :				4.34683e4	943.20215	



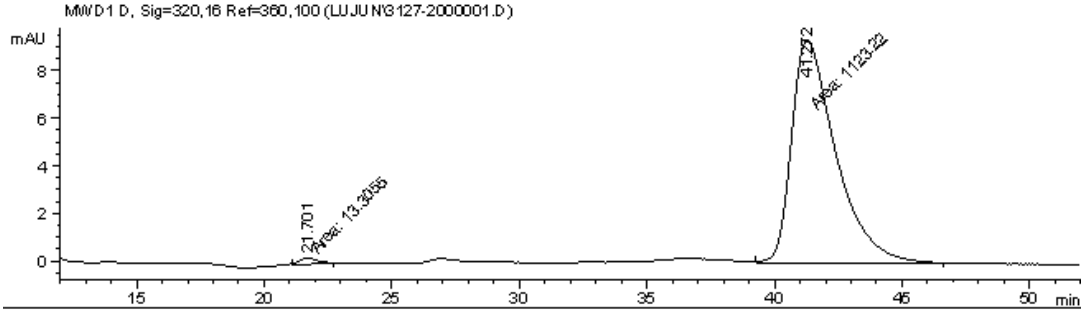
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.997	MM	0.5243	28.78300	9.14992e-1	0.9249
2	21.751	BB	0.7792	3083.30664	59.05229	99.0751
Totals :				3112.08964	59.96728	

8ca



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.253	BB	0.8013	9826.14746	183.93390	43.5414
2	38.840	BB	1.7987	1.2741 2e4	99.31683	56.4586

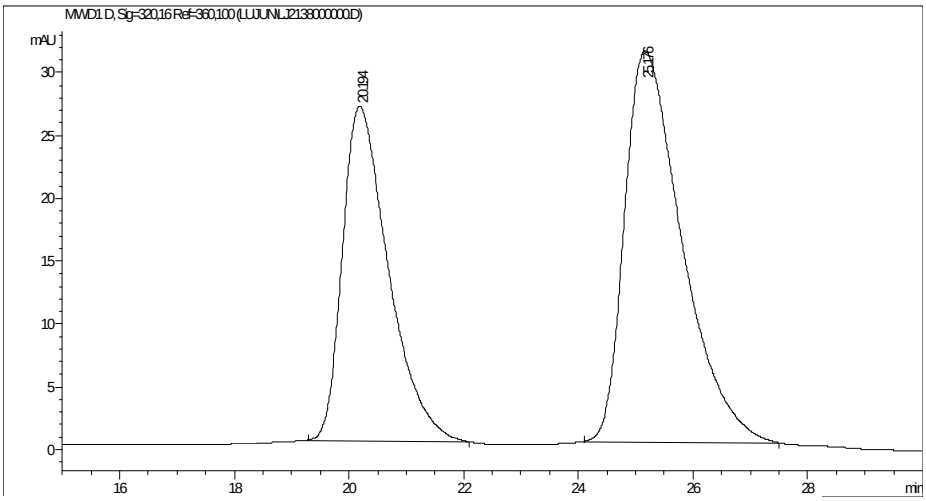
Totals : 2.25673e4 283.25073



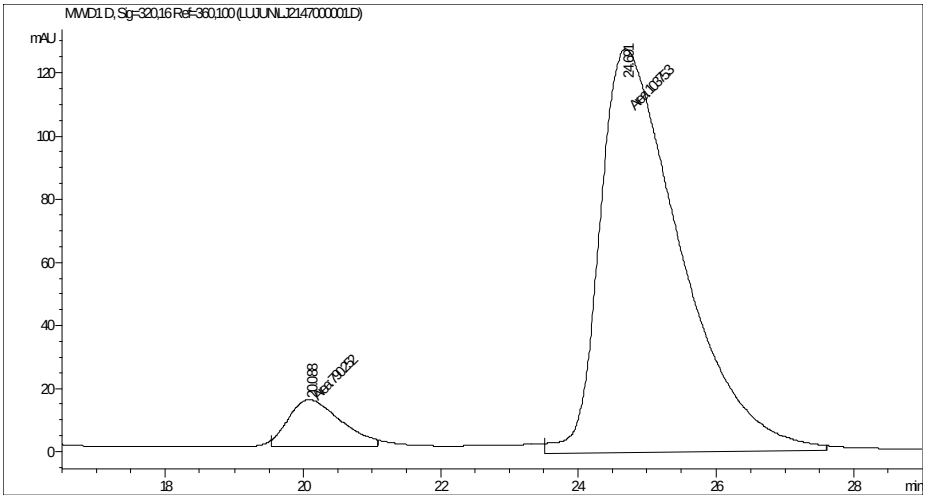
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.701	MM	0.8366	13.30549	2.65072e-1	1.1707
2	41.272	MM	1.9940	1123.22412	9.38844	98.8293

Totals : 1136.52962 9.65352

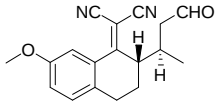
8da



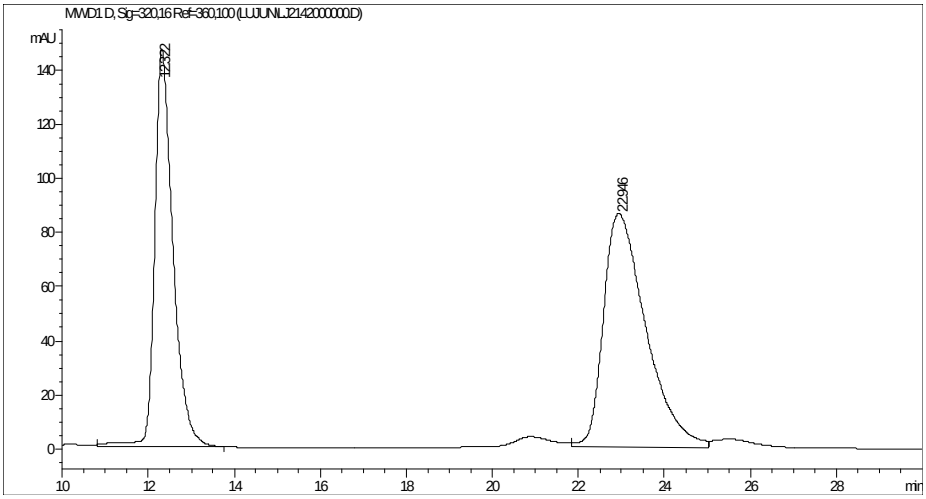
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.194	BB	0.8240	1495.50134	26.67845	40.7103
2	25.176	BB	1.0082	2178.02393	31.13301	59.2897
Totals :				3673.52527	57.81146	



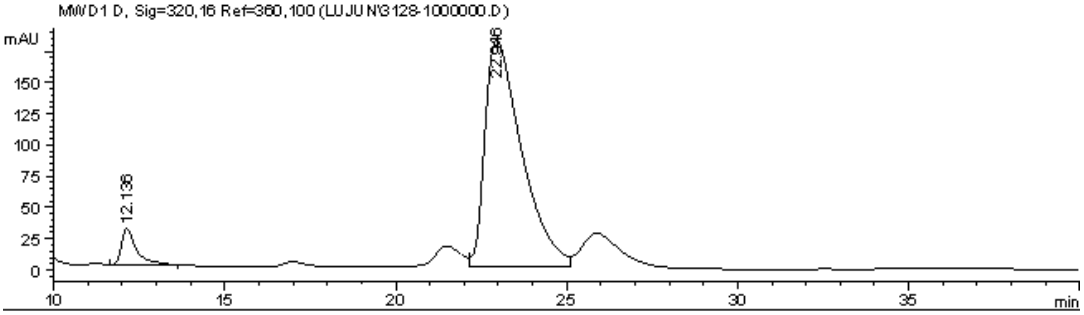
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.088	MM	0.8115	670.05554	13.76126	6.1565
2	24.691	MM	1.3409	1.02137e4	126.95211	93.8435
Totals :				1.08837e4	140.71337	



8ea

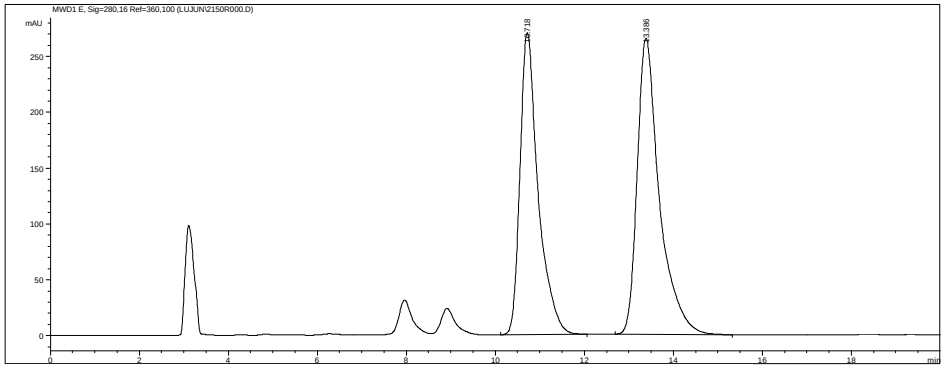


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.322	BB	0.4412	4350.37939	147.04796	42.3114
2	22.946	VB	1.0330	5931.44287	86.60807	57.6886
Totals :				1.02818e4	233.65603	

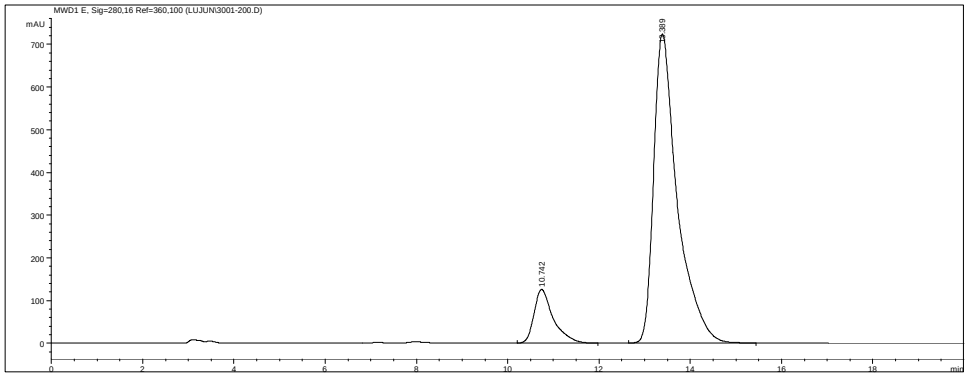


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.136	VB	0.4647	938.41187	29.37506	6.4351
2	22.946	VV	1.1204	1.36443e4	182.04903	93.5649
Totals :				1.45827e4	211.42409	

8fa

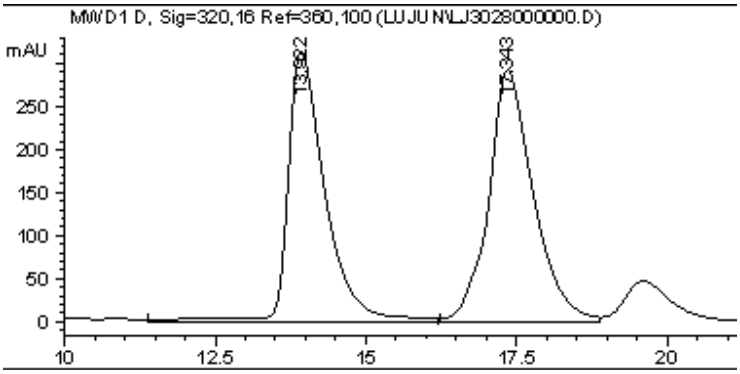


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.719	PB	0.4228	6710.71387	233.87077	45.4675
2	13.386	BB	0.5177	8048.66016	229.19559	54.5325
Totals :				1.47594e4	463.06636	

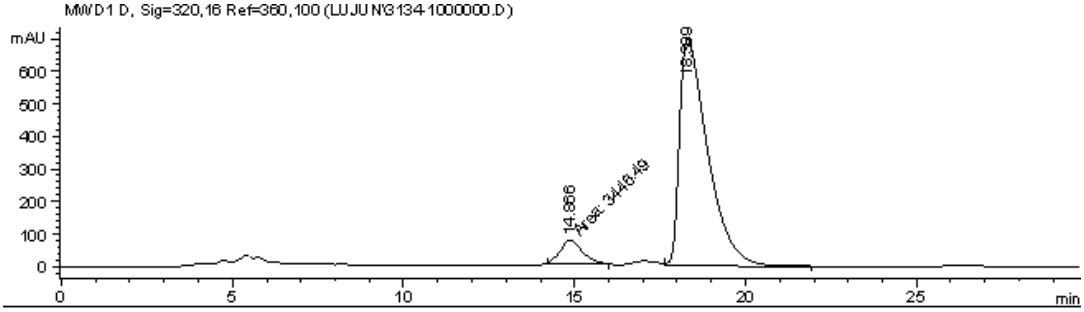


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.742	PB	0.4299	3653.79932	125.39944	12.2827
2	13.389	BB	0.5308	2.60936e4	723.51379	87.7173
Totals :				2.97474e4	848.91323	

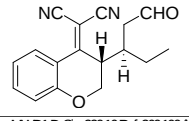
8ab



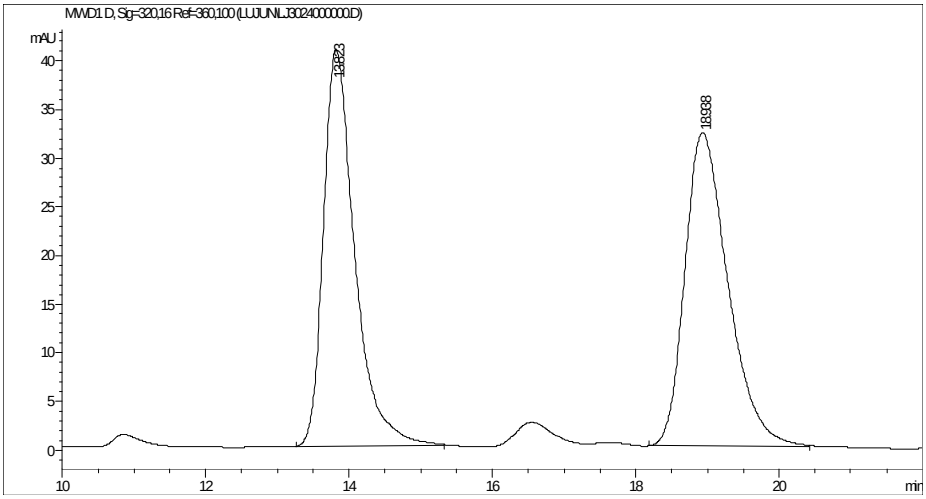
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.922	VB	0.6329	1.34304e4	314.09564	47.1998
2	17.343	BV	0.7601	1.50240e4	292.09741	52.8002
Totals :				2.84545e4	606.19305	



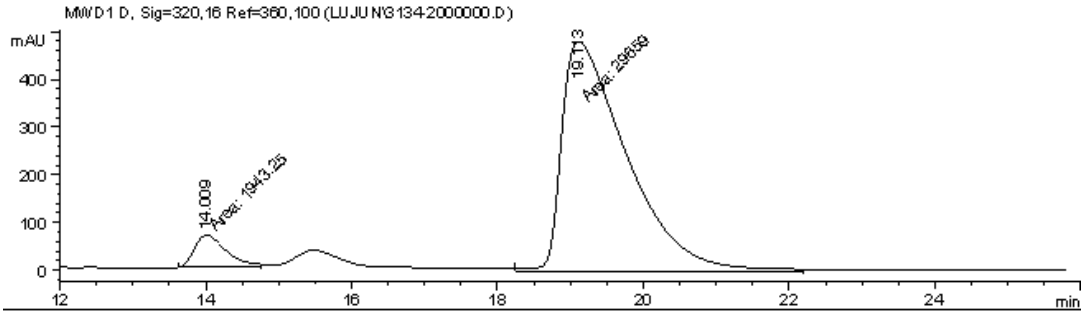
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.866	MM	0.7690	3446.48950	74.69913	7.9300
2	18.309	VB	0.8607	4.00152e4	698.09027	92.0700
Totals :				4.34617e4	772.78940	



8bb

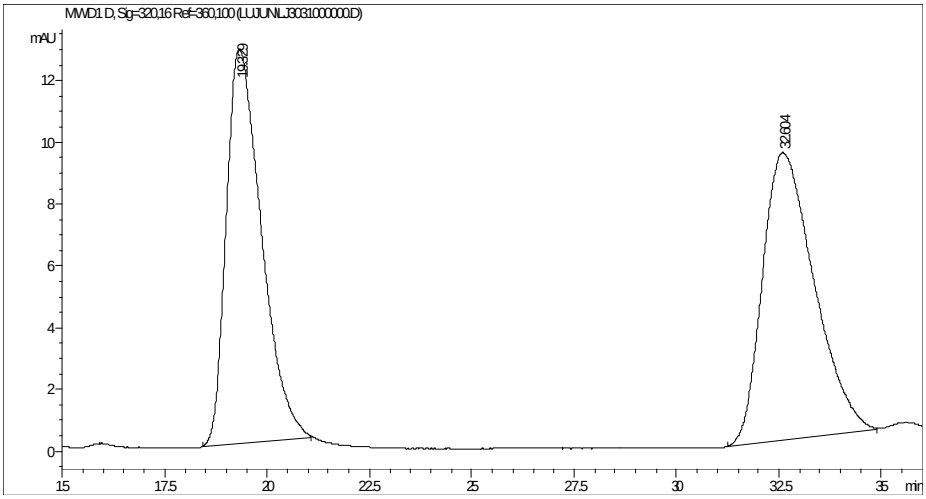


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.823	BB	0.4566	1240.91223	40.82467	47.9402
2	18.938	BB	0.6301	1347.54651	32.20778	52.0598
Totals :				2588.45874	73.03245	

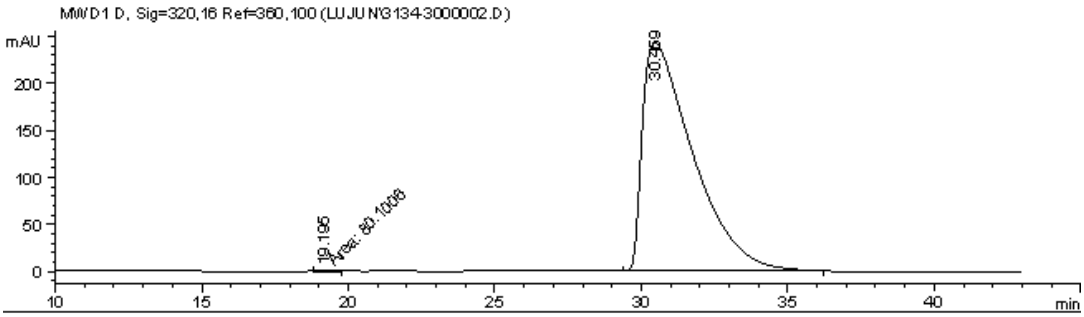


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.009	MM	0.4889	1943.24585	66.24547	6.1491
2	19.113	MM	1.0283	2.96590e4	480.73212	93.8509
Totals :				3.16022e4	546.97758	

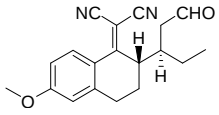
8cb



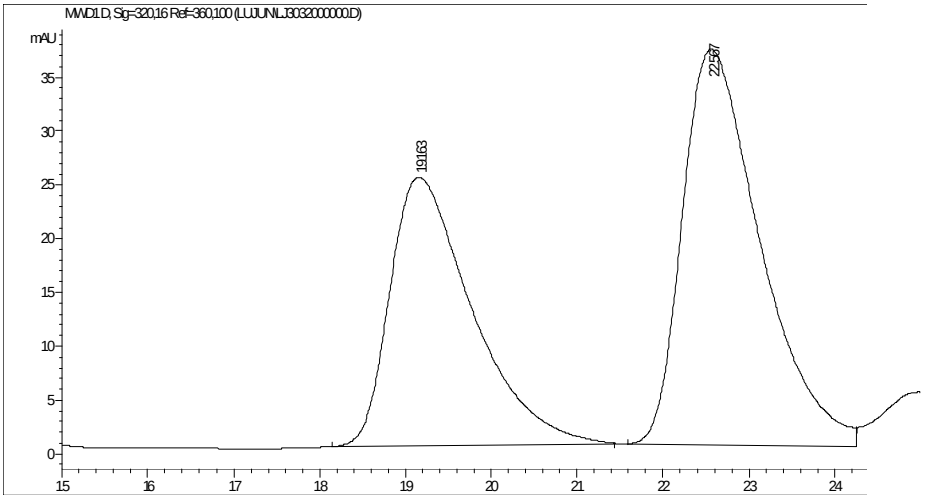
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.329	BB	0.8583	764.93243	12.77971	48.4356
2	32.604	BB	1.1621	814.34363	9.29515	51.5644
Totals :				1579.27606	22.07486	



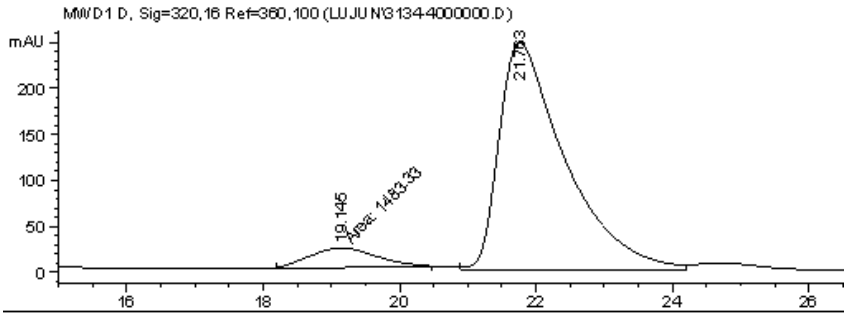
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.195	MM	0.5543	80.10063	1.73169	0.2750
2	30.459	BB	1.7438	2.90488e4	242.46143	99.7250
Totals :				2.91289e4	244.19312	



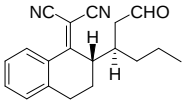
8db



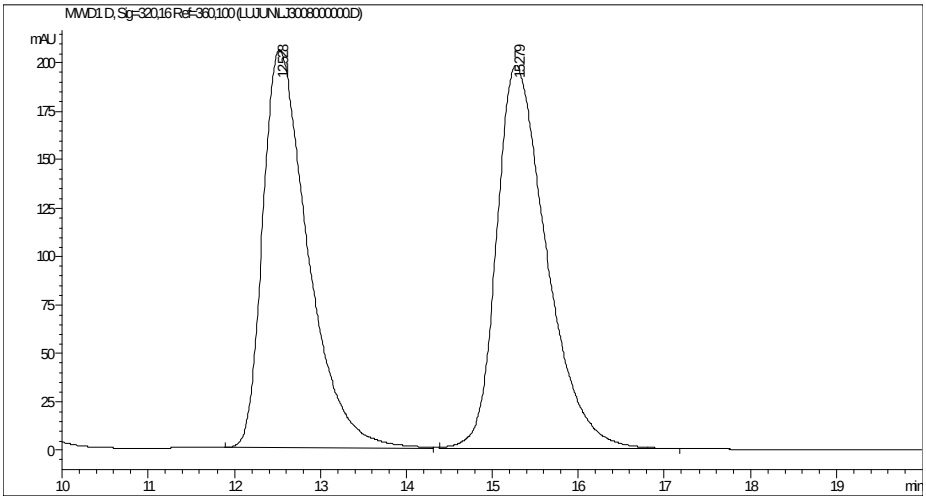
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.163	BB	0.9689	1662.22009	24.96114	41.7639
2	22.567	BB	0.9372	2317.82446	36.78011	58.2361
Totals :				3980.04456	61.74125	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.145	MM	1.1530	1483.32727	21.44216	8.1697
2	21.763	VB	0.9524	1.66731e4	247.35474	91.8303
Totals :				1.81564e4	268.79690	

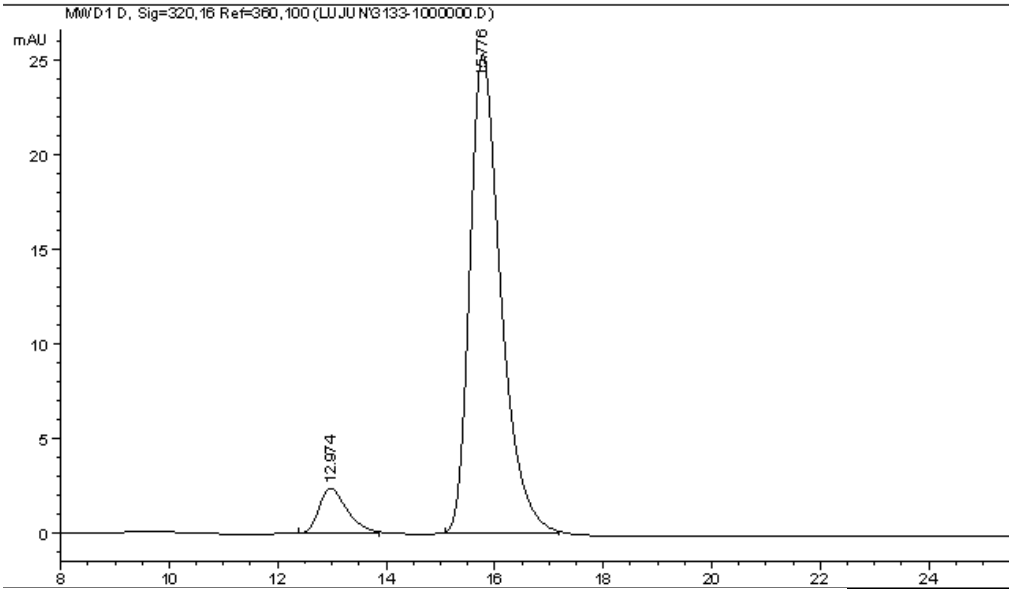


8ac



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.528	BB	0.5499	7456.85986	205.21529	48.3640
2	15.279	BB	0.6124	7961.35449	197.46574	51.6360

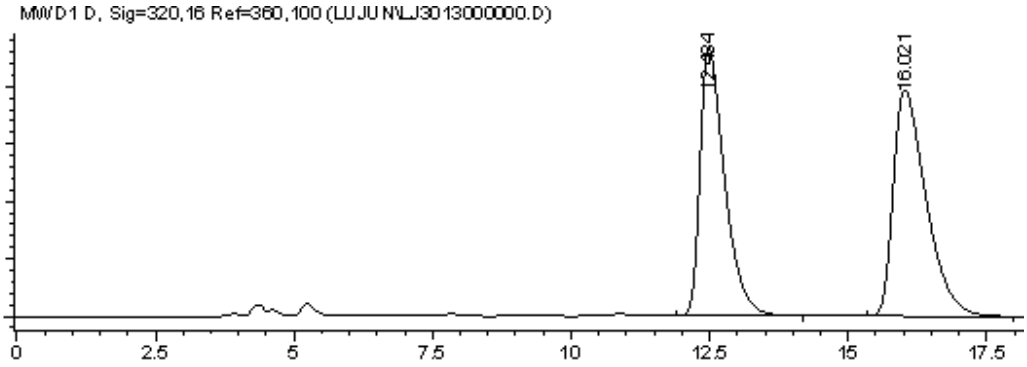
Totals : 1.54182e4 402.68103



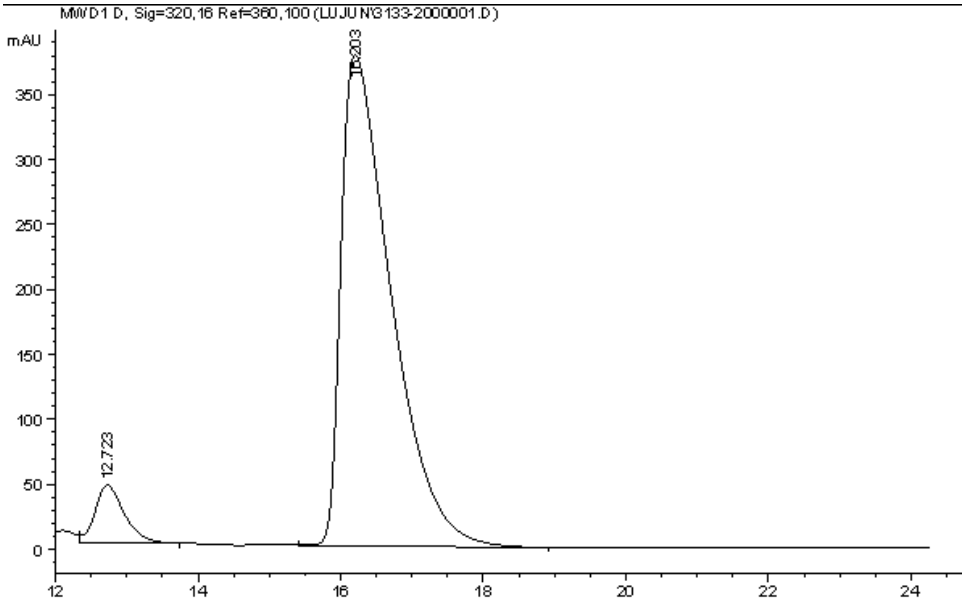
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.974	BB	0.5095	84.51665	2.37332	7.7437
2	15.776	BB	0.5996	1006.90967	25.33673	92.2563

Totals : 1091.42632 27.71005

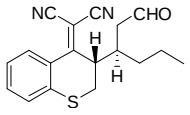
8bc



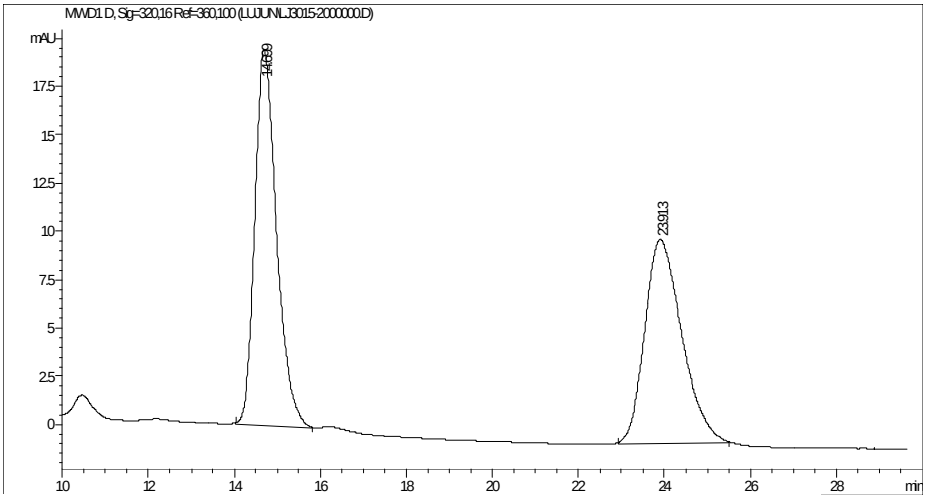
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.484	VB	0.4640	7220.45557	234.02757	47.1133
2	16.021	BB	0.6242	8105.28711	196.91902	52.8867
Totals :				1.53257e4	430.94659	



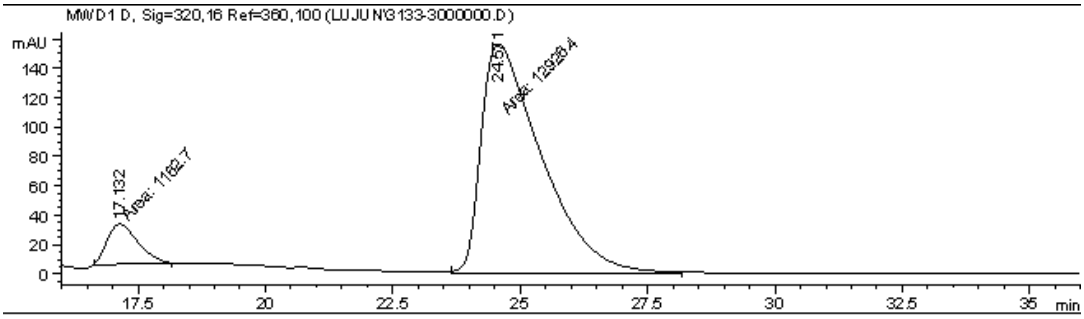
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.723	VB	0.4309	1287.24353	44.84673	6.5084
2	16.203	VB	0.7339	1.84908e4	378.53036	93.4916
Totals :				1.97781e4	423.37709	



8cc

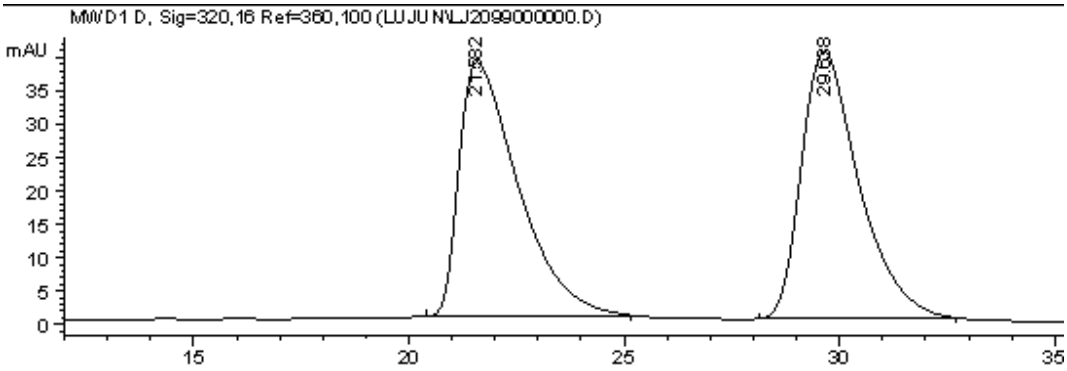


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.699	BB	0.5319	684.04742	19.47105	51.9720
2	23.913	BB	0.8702	632.13739	10.56251	48.0280
Totals :				1316.18481	30.03356	

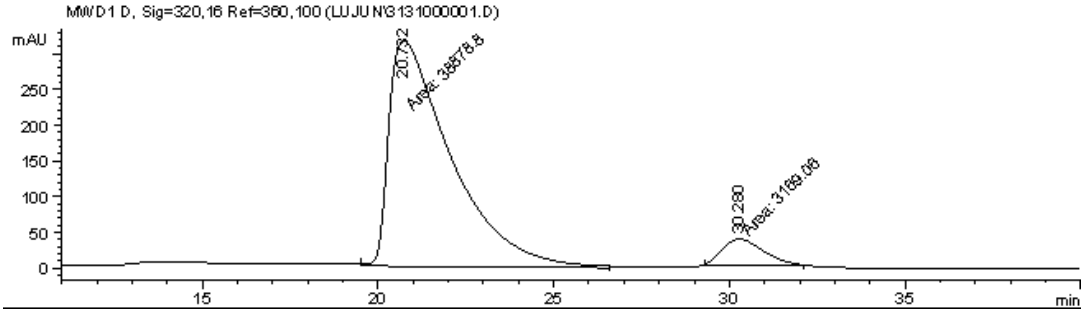


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.132	MM	0.7113	1162.69885	27.24472	8.2525
2	24.571	MM	1.3777	1.29264e4	156.37955	91.7475
Totals :				1.40891e4	183.62427	

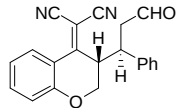
8ad



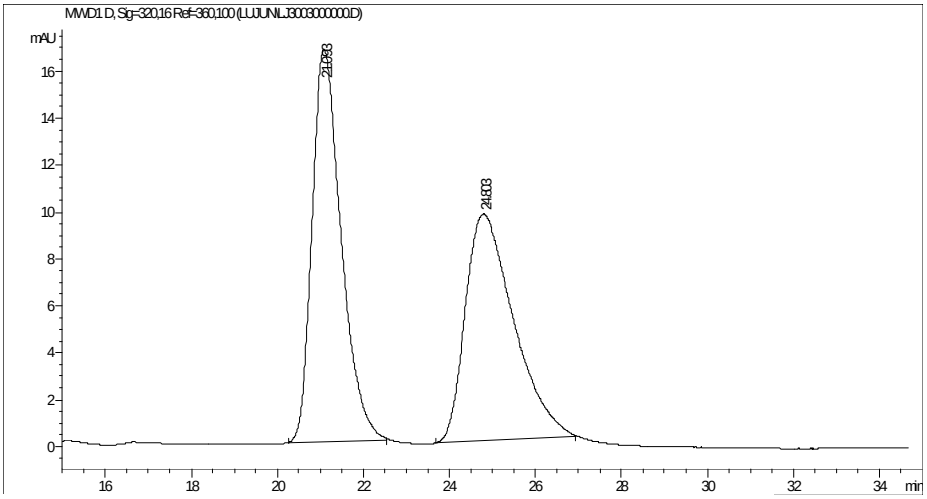
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.582	BB	1.4104	3643.73877	38.07954	49.3409
2	29.638	BB	1.3651	3741.08325	40.07685	50.6591
Totals :				7384.82202	78.15639	



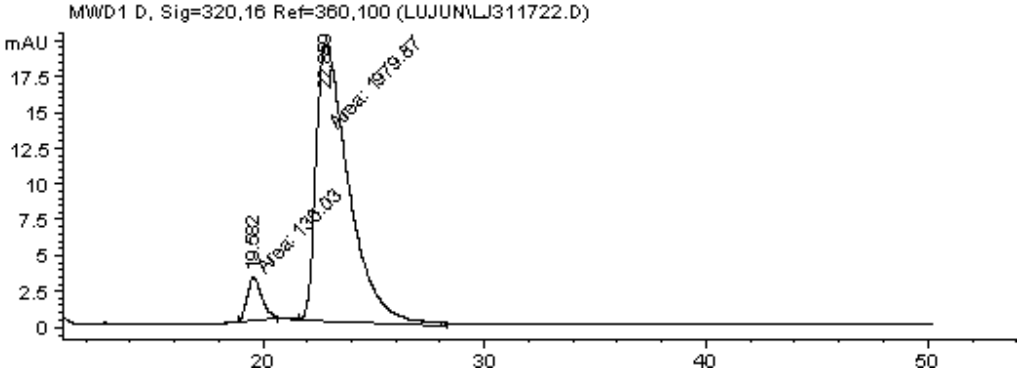
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.732	MM	2.0511	3.88788e4	315.92508	92.4632
2	30.280	MM	1.4028	3169.06030	37.65275	7.5368
Totals :				4.20478e4	353.57783	



8bd

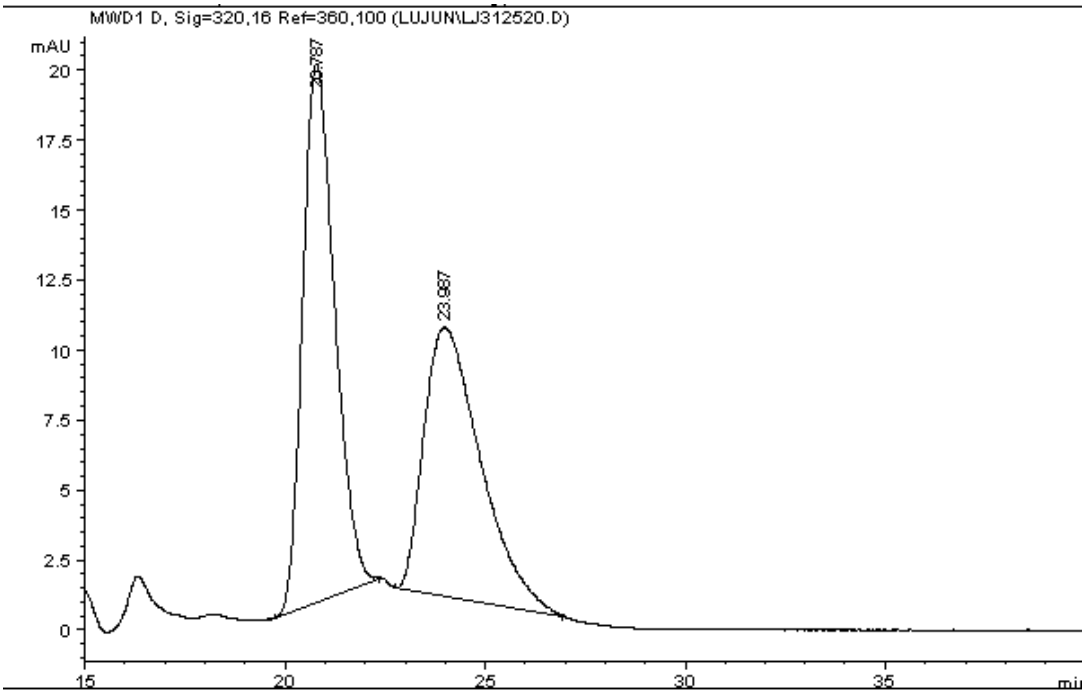


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.093	BB	0.7073	787.62866	16.72939	50.9622
2	24.803	BB	1.0954	757.88525	9.67999	49.0378
Totals :				1545.51392	26.40938	

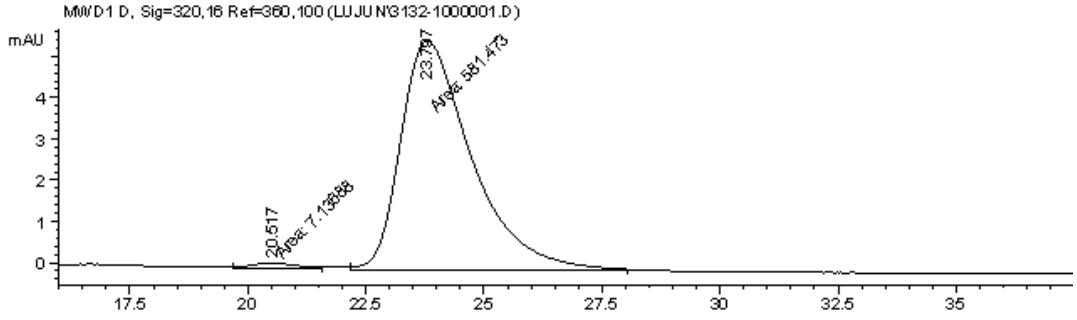


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.582	MM	0.7677	136.02953	2.95317	6.4289
2	22.859	MM	1.7166	1979.86804	19.22271	93.5711
Totals :				2115.89757	22.17588	

8be

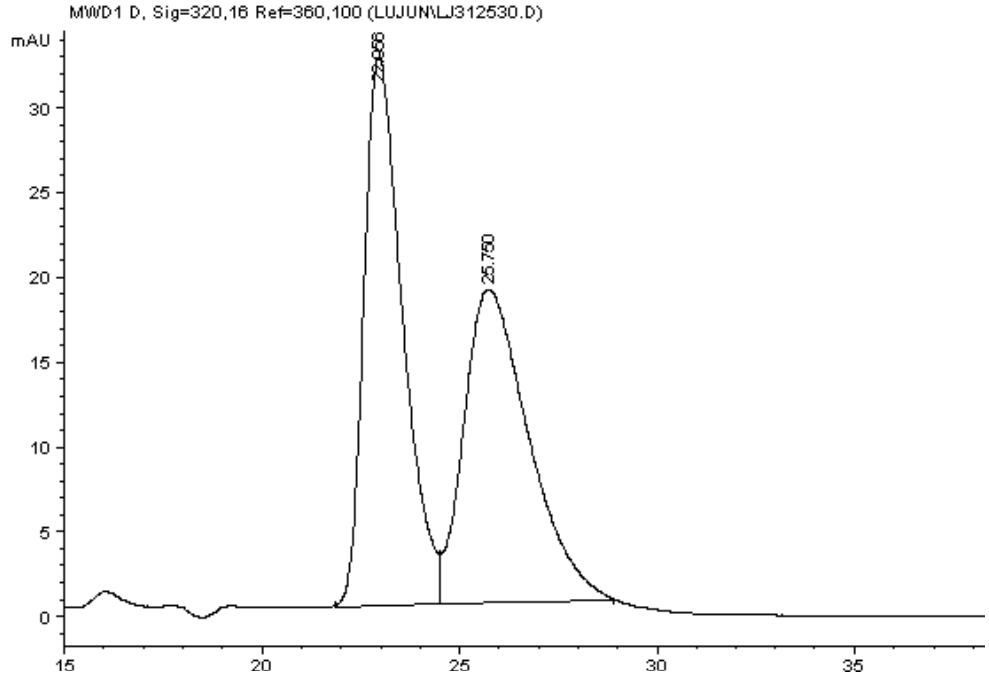


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.787	PB	0.8056	1067.68127	19.23425	52.9542
2	23.987	PB	1.1760	948.55377	9.60594	47.0458
Totals :				2016.23505	28.84019	

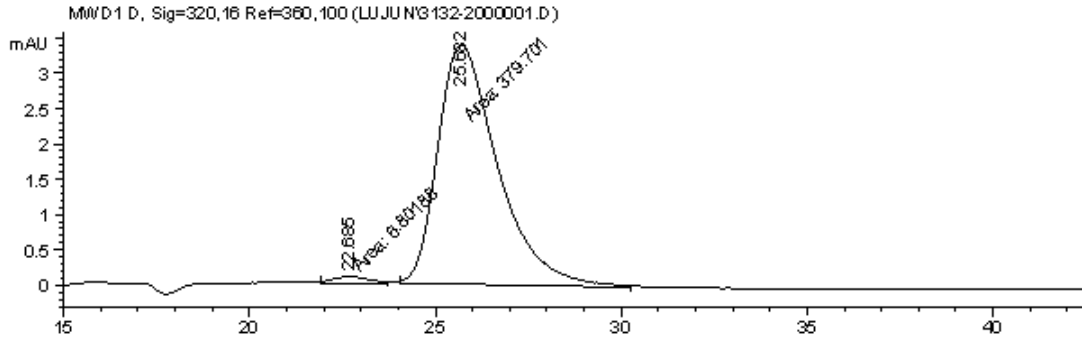


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.517	MM	0.9703	7.13688	1.22593e-1	1.2125
2	23.797	MM	1.7444	581.47253	5.55560	98.7875
Totals :				588.60941	5.67819	

8bf



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.956	BV	0.9959	2203.47070	32.30103	50.9943
2	25.750	VB	1.3865	2117.54053	18.48512	49.0057
Totals :				4321.01123	50.78614	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.685	MM	1.1010	6.80188	1.02965e-1	1.7599
2	25.682	MM	1.8665	379.70093	3.39057	98.2401
Totals :				386.50281	3.49353	