Electronic Supplementary Material (ESI) for Chemical Science.

Asymmetric Synthesis of Chromanone Lactones *via* Vinylogous Conjugate Addition of Butenolide to 2-Ester Chromones

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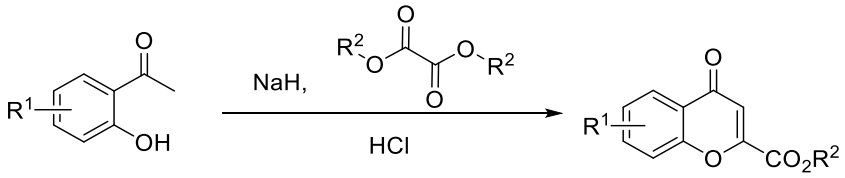
1. General remarks

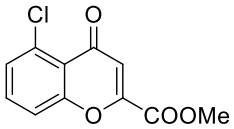
Enantiomeric excess (e.e.) were determined by UPC^2 analysis using the corresponding commercial chiral column as stated in the experimental procedures at 35 ºC. Data for ^{1}H NMR spectra were recorded on bruker ASCENDTM 400M (400 MHz) and ASCENDTM 600M (600 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl3, δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets), coupling constants (Hz), integration and assignment. ^{13}C{1H} NMR spectra were collected on ASCENDTM 400M (101 MHz) and ASCENDTM 600M (153 MHz) with complete proton decoupling. ^{19}F{1H} NMR spectra were collected on ASCENDTM 400M (376 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). HRMS was recorded on Thermo Q-Exactive Focus (FTMS+c ESI). The chiral UPC^2 methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured on a Rudolph Autopol V automatic polarimeter and are reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, in $CHCl_3$). IR spectra were recorded on Bruker TENSOR II IR spectrophotometer. All catalytic reactions were run in dried glassware. All the solvents were purified by usual methods before use. Silica gel for thin-layer chromatography (HG/T2354-92) made in Qingdao Haiyang Chemical Co., Ltd. Unless otherwise indicated, reagents obtained from commercial sources were used without further purification. The chiral *N,N'*-dioxide ligands were synthesized by the same procedure in the literature.[1]

2. Synthesis of chromones

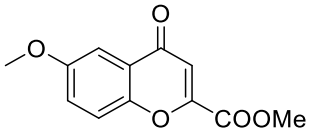
The chromones were prepared from the corresponding substituted *o*-hydroxyacetophenone according to reported methods.[2]



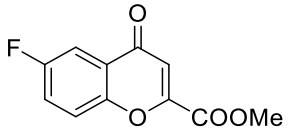
Procedure: A solution of the 2′-hydroxy acetophenone derivatives (10 mmol) and the oxalate (11 mmol, 1.1 equiv.) in dry THF (25 mL) were cooled to 0 °C. Into this mixture was added NaH (60 % in oil, 3.5 equiv.). The temperature was allowed to rise to room temperature and stirred overnight. The crude mixture was quenched with MeOH (2.5 mL) and acidified (pH 0 – 1) with concentrated HCl. The resultant heterogeneous mixture was stirred at room temperature for an additional 24 h. MeOH was removed by rotary evaporation and the residue was diluted with EtOAc. The two layers were separated and the aqueous layer was washed with EtOAc (25 mL × 3). The combined organic solution was dried using anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude material was then purified on silica gel column chromatography.



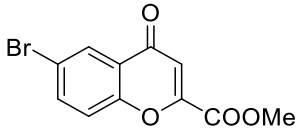
methyl 5-chloro-4-oxo-4H-chromene-2-carboxylate, white solid, 43% yield.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (t, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 4.01 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.6, 160.3, 157.1, 150.1, 133.4, 128.4, 121.1, 117.5, 115.8, 53.2.



methyl 6-methoxy-4-oxo-4H-chromene-2-carboxylate, white solid, 53% yield.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.45 (m, 2H), 7.34 (dd, *J* = 9.2, 3.1 Hz, 1H), 7.11 (s, 1H), 4.02 (s, 3H), 3.91 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.2, 161.1, 157.5, 151.6, 150.8, 125.1, 125.0, 120.2, 114.0, 104.6, 56.0, 53.5.



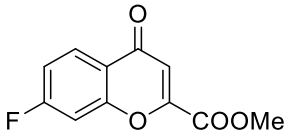
methyl 6-fluoro-4-oxo-4H-chromene-2-carboxylate, white solid, 62% yield.
^{1}H NMR (400 MHz, Chloroform-d) δ 7.83 (dd, J = 8.0, 3.1 Hz, 1H), 7.63 (dd, J = 9.1, 4.1 Hz, 1H), 7.47 (ddd, J = 9.1, 7.5, 3.1 Hz, 1H), 7.10 (s, 1H), 4.02 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 177.6, 161.2, 160.8, 152.2, 123.2, 123.0, 121.0, 121.0, 114.1, 110.8, 110.6, 53.6.
^{19}F NMR (376 MHz, Chloroform-d) δ -113.64.



methyl 6-bromo-4-oxo-4H-chromene-2-carboxylate, white solid 70% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.12 (s, 1H), 4.02 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.9, 160.7, 154.7, 152.1, 137.8, 128.4, 125.7, 120.7, 119.6, 114.9, 53.6.

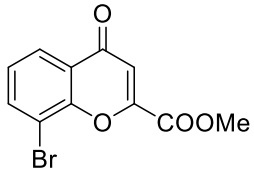


methyl 7-fluoro-4-oxo-4H-chromene-2-carboxylate, red solid, 63% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.30 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.19 (ddd, *J* = 8.9, 8.0, 2.4 Hz, 1H), 7.10 (s, 1H), 4.02 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 191.6, 177.2, 160.7, 152.2, 128.4, 115.2, 114.8, 105.6, 105.3, 53.6.

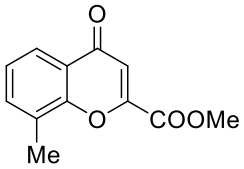
^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.63.



methyl 8-bromo-4-oxo-4H-chromene-2-carboxylate, white solid, 66% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 9.4 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.14 (s, 1H), 4.04 (s, 3H).

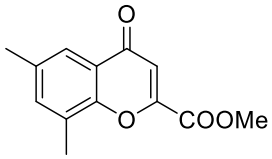
^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.71, 160.61, 152.63, 152.24, 138.25, 126.52, 125.72, 125.13, 114.90, 112.41, 53.72, 53.69.



methyl 8-methyl-4-oxo-4H-chromene-2-carboxylate, white solid, 65% yield

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.9 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 4.02 (s, 3H), 2.56 (s, 3H).

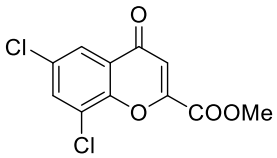
^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.8, 161.2, 154.5, 135.6, 128.4, 125.5, 124.4, 123.3, 114.6, 53.5, 15.6.



methyl 6,8-dimethyl-4-oxo-4H-chromene-2-carboxylate, white solid, 78% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.40 (s, 1H), 7.09 (s, 1H), 4.01 (s, 3H), 2.53 (s, 3H), 2.42 (s, 3H).

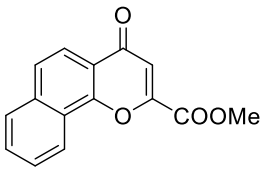
^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.8, 152.8, 152.5, 151.6, 137.0, 135. 5, 128.0, 124.1, 122.6, 114.5, 53.4, 20.9, 15.5.



methyl 6,8-dichloro-4-oxo-4H-chromene-2-carboxylate, white solid, 70% yield

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.79 (s, 1H), 7.15 (s, 1H), 4.04 (s, 3H).

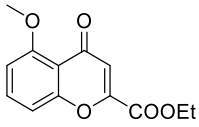
^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.5, 172.8, 160.4, 152.3, 134.9, 131.8, 126.1, 125.2, 123.9, 114.9, 53.9.



methyl 4-oxo-4H-benzo[h]chromene-2-carboxylate, white solid, 81% yield

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.74 (dq, *J* = 14.0, 6.9 Hz, 2H), 7.28 (s, 1H), 4.08 (s, 3H).

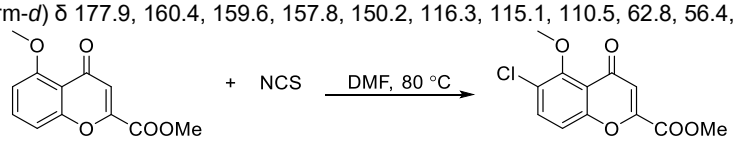
^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.1, 161.0, 153.6, 151.4, 136.2, 129.9, 128.1, 127.5, 126.2, 124.0, 121.0, 120.3, 116.2, 53.6.



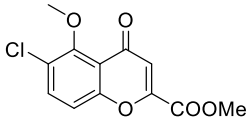
ethyl 5-methoxy-4-oxo-4H-chromene-2-carboxylate, white solid, 73% yield

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.62 (t, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.02 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.9, 160.4, 159.6, 157.8, 150.2, 116.3, 115.1, 110.5, 62.8, 56.4, 14.0.



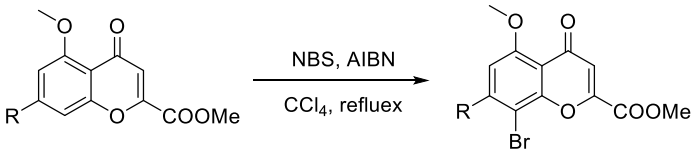
Procedure: A solution of the chromone (3.0 mmol) in DMF (15 mL) was heated at 70 °C, and NCS (5.5 mmol, 1.1 equiv.) were added. The reaction mixture was heated to 80 °C for 24 h. The reaction was cooled to rt, H_2O was added and extracted with EtOAc, wash with H_2O and brine, dried over Na_2SO_4, and filtered. Concentration in a vacuum afforded the crude product, and the residue was purified by silica gel column chromatography to give the product.



methyl 6-chloro-5-methoxy-4-oxo-4H-chromene-2-carboxylate, white solid, 60% yield

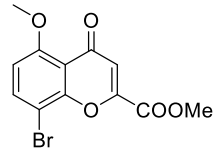
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 9.1 Hz, 1H), 7.36 (d, *J* = 9.1 Hz, 1H), 7.02 (s, 1H), 3.99 (d, *J* = 23.0 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.6, 160.7, 155.8, 155.0, 150.5, 135.2, 125.9, 120.2, 116.0, 115.4, 61.9, 53.6.



R= H or Me R= H or Me

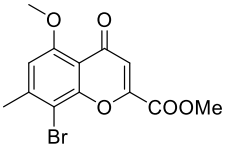
Procedure: A solution of chromone (5 mmol) in CCl_4 (15 mL) was heated at 80 °C, and then AIBN (0.5 mmol, 10 mol%) and NBS (5.5 mmol, 1.1 equiv.) were added. The reaction mixture was heated to 80 °C for 7 h. The reaction was cooled to rt, then H_2O was added and extracted with CH_2Cl_2, washed with 1 N HCl and brine, dried over Na_2SO_4, and filtered. Concentration in a vacuum afforded the crude product. The residue was purified by silica gel column chromatography to give the product.



methyl 8-bromo-5-methoxy-4-oxo-4H-chromene-2-carboxylate, white solid, 72% yield

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.9 Hz, 1H), 7.05 (s, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 4.00 (d, *J* = 17.7 Hz, 6H).

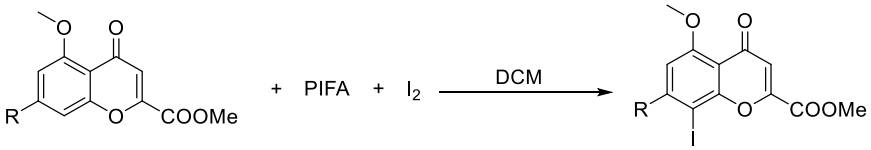
^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.7, 159. 2, 154.0, 150.3, 137.9, 116.7, 116.3, 108.0, 102.3, 56.7.



methyl 8-bromo-5-methoxy-7-methyl-4-oxo-4H-chromene-2-carboxylate, white solid 92% yield

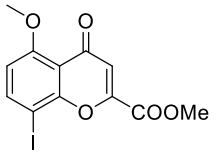
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (s, 1H), 6.78 (s, 1H), 3.99 (dd, *J* = 14.0, 1.3 Hz, 6H), 2.56 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.4, 160.8, 158.2, 154.1, 150.2, 146.3, 116.5, 109.3, 104.6, 56.6, 53.6, 24.3.

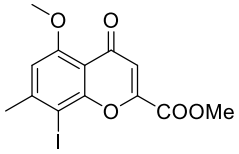


R= H or Me R= H or Me

Procedure: A solution of the chromone (3.0 mmol) in dry DCM at room temperature was treated with PIFA (1.2 equiv.) and I_2 (0.6 equiv.). The mixture was then stirred at room temperature for 24 h. The solution was then quenched using saturated aqueous sodium bisulfite (30 mL) and extracted using DCM (25 mL × 3). The combined organic solution was dried using anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude material was then purified on silica gel column chromatography.

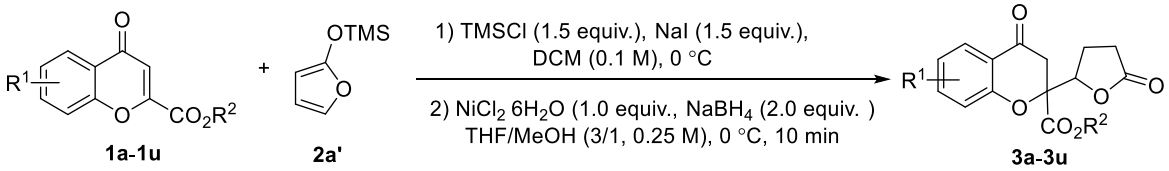


methyl 8-iodo-5-methoxy-4-oxo-4H-chromene-2-carboxylate, white solid, 84% yield
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 7.08 (s, 1H), 4.03 (s, 3H), 3.91 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.0, 160.3, 159.4, 156.3, 151.8, 150.9, 120.0, 116.0, 90.6, 80.7, 62.2, 53.7.



methyl 8-iodo-5-methoxy-7-methyl-4-oxo-4H-chromene-2-carboxylate, white solid, 81% yield
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.02 (s, 1H), 6.83 (s, 1H), 4.00 (d, *J* = 14.6 Hz, 6H), 2.61 (s, 3H).

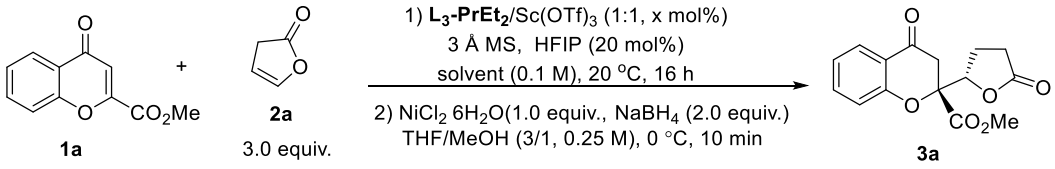
3. Preparation of the racemic products [3]



1a-1u **2a'** 2.0 equiv. **3a-3u**

Procedure: NaI (0.3 mmol, 1.5 equiv) and TMSCl (0.3 mmol, 1.5 equiv) were added to a solution of the corresponding chromone (0.2 mmol) in anhydrous DCM (2.0 mL), and the mixture was stirred for 10 min at room temperature. Then the reaction mixture was brought to the appropriate temperature, and 2-(trimethylsilyloxy)-furan (0.4 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred at this temperature until the reaction was complete, as indicated by thin-layer chromatography (TLC). The reaction mixture was quenched by H_2O and extracted with DCM. The combined organic layers were washed with saturated $Na_2S_2O_3$ and brine in turn, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.
The mixture was dissolved in THF/MeOH (3/1, 3.0 mL). At 0 °C, $NiCl_2$•$6H_2O$ (0.2 mmol) and $NaBH_4$ (0.4 mmol, 2.0 equiv) were added. The mixture was stirred for 10 min at 0 °C. Saturated NH_4Cl solution (0.5 mL) and water (2 mL) were added. The mixture was extracted by EtOAc (5 mL). The organic layer was concentrated under reduced pressure. The residual product was purified by gel column chromatography.

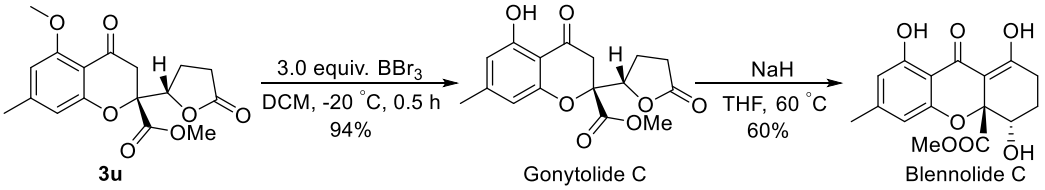
4. Preparation of enantiomeric enriched product



1a 3.0 equiv. **2a** **3a**

Procedure: An oven-dried test tube was charged with the catalyst **L_3-PrEt$_2$**/Sc(OTf)$_3$ (1:1, 1 mol %), **1a** (0.10 mmol), HFIP (0.02 mmol) and 3 Å MS (20 mg) in THF (1 mL) under N_2 atmosphere. The resulted solution was stirred at 20 °C for 0.5 h, then **2a** (0.3 mmol) was added into the above solution and stirred until the reaction was complete, as indicated by thin-layer chromatography (TLC).
The above mixture was dissolved in THF/MeOH (2/1, 3.0 mL). At 0 °C, $NiCl_2$•$6H_2O$ (0.10 mmol) and $NaBH_4$ (0.2 mmol) were added. The mixture was stirred for 10 min at 0 °C. Saturated NH_4Cl solution (0.5 mL) and water (2 mL) were added. The mixture was extracted by EtOAc (5 mL). The organic layer was concentrated under reduced pressure. The residual product was purified by silica gel column chromatography.

5. Further transformation of the products into the natural products.



Procedure: BBr_3 (0.6 mL of a 2.0 M solution in CH_2Cl_2, 1.2 mmol, 3 equiv) was added slowly to a solution of **3u** (133.6 mg, 0.4 mmol, 1.0 equiv, >19:1 dr and >99% ee) in CH_2Cl_2 (2.0 mL) at -20 °C. The resulting orange solution was stirred for 30 min at -20 °C before being quenched with saturated NH_4Cl aqueous solution (2.0 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. Column chromatography on silica gel (EA/ PE=2:1) provided pure Gonytolide C (120.6 mg, 94%) as a white solid.

Gonytolide C

$[\alpha]^{28}_D$ = 23.5 (*c* = 0.4 in $CHCl_3$), ref 4: $[\alpha]^{28}_D$ = 23.1 (*c* = 0.39 in $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.39 (s, 1H), 6.39 (d, *J* = 10.4 Hz, 2H), 4.86 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.74 (s, 3H), 3.19 – 2.85 (m, 2H), 2.81 – 2.53 (m, 2H), 2.43 (dq, *J* = 9.9, 7.8, 6.7 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.1, 175.6, 169.0, 161.7, 159.0, 151.6, 111.0, 108.5, 105.6, 84.0, 53.7, 39.4, 27.6, 22.7.

ESI-HRMS: calcd for $C_{15}H_{14}O_6Na^+$ ([M + Na]$^+$) = 343.0788, found 343.0783.

IR (neat):2923, 1785, 1644, 1570, 1454, 1366, 1263, 1200, 1131, 1074, 1055, 1033, 936, 837, 748 cm^{-1}.

Procedure: The Gonytolide C (32 mg, 0.1 mmol) and NaH (10 mg, 0.25 mmol, 2.5 equiv) were placed into a flask under a N_2 atmosphere. THF (3 mL) was added to the flask which was warmed up to 60 °C and stirred for 16 h. After cooling to room temperature, 2 M HCl was used to quench the reaction which was extracted twice with EtOAc (10 mL x 2). The organic phase was combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification by column chromatography (PE/EtOAc = 3: 1) afforded Blennolide C (19.3 mg, 60%) as a yellow powder.[5]

Blennolide C

$[a]_D^{25}$= +182.9 (c = 0.04, $CHCl_3$), ref 6: $[a]_D^{25}$= +181.7 (c = 0.06, $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.04 (s, 1H), 11.27 (s, 1H), 6.52 – 6.12 (m, 2H), 3.70 (s, 3H), 2.82 (dd, *J* = 19.2 7.0 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.38 (dd, *J* = 19.2, 7.0, Hz, 1H), 2.29 (s, 3H), 2.20 – 2.08 (m, 1H), 2.02 – 1.89 (m, 1H).

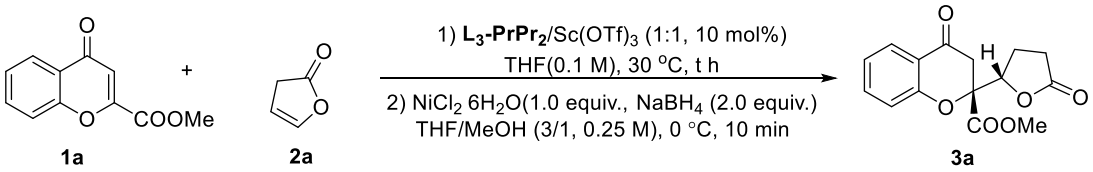
^{13}C NMR (101 MHz, Chloroform-*d*) δ 186.9, 179.1, 171.2, 161.9, 149.9, 111.7, 108.7, 104.9, 100.1, 83.8, 66.9, 53.4, 24.3, 23.1.

ESI-HRMS: calcd for $C_{15}H_{14}O_6Na^+$ ([M + Na]$^+$) = 343.0788, found 343.0785.

IR (neat): 2925, 1786, 1649, 1558, 1459, 1361, 1265, 1244, 1189, 1130, 1076, 1058, 1036, 902, 840, 731 cm^{-1}.

6. Optimization of the reaction conditions.

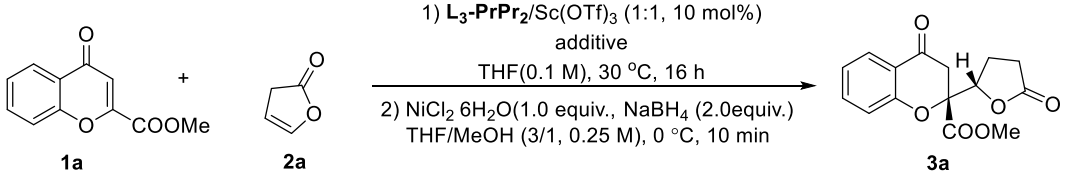
(a) Preliminary screening of the reaction time.



4 h: 19% yield, 94% ee, 4:1 dr
8 h: 35% yield, 90% ee, 3.6:1 dr
24 h: 42% yield, 74% ee, 2.3:1 dr

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), **L_3-PrPr$_2$**/Sc(OTf)$_3$ (1:1, 10 mol %) in THF (0.1 M) at 30 °C. Isolated yields. The ee values were determined by UPC^2, the dr values were determined by the ^{1}H NMR.

(b) Screening of the additives.

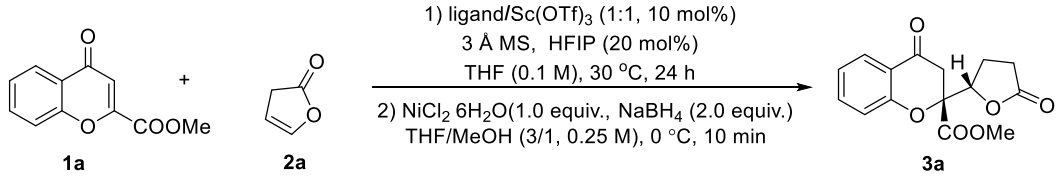


Entry	additive	Yield(%)	ee (%)	dr
1	3 Å MS (20 mg)	56	>99	>19:1
2	4 Å MS (20 mg)	43	>99	19:1
3	5 Å MS (20 mg)	78	99	16:1

4	Na_2SO_4 (20 mg)	41	99	16:1
5	HFIP (20 mol%)	46	96	7:1
6	3 Å MS (20 mg)+ HFIP (20 mol%)	82	>99	>19:1

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), **L_3-PrPr$_2$**/Sc(OTf)$_3$ (1:1, 10 mol %) in THF (0.1 M) and additive at 30 °C. Isolated yields. The ee values were determined by UPC[2], the dr values were determined by the ^{1}H NMR.

(c) Screening of the ligand.

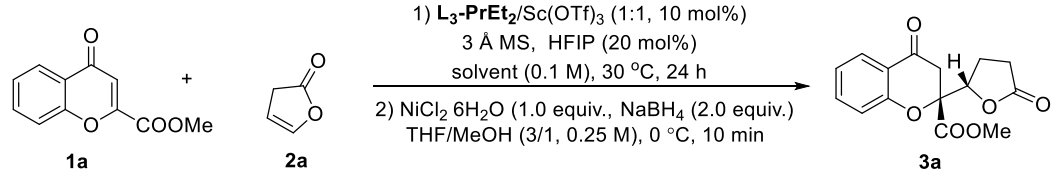


1a **2a** **3a**

Entry	Ligand	Yield(%)	ee (%)	dr
1	**L_3-PrPr$_2$**	82	>99	>19:1
2	**L_3-PiPr$_2$**	42	>99	1:1
3	**L_3-RaPr$_2$**	23	85	6:1
4	**L_3-PrMe$_2$**	70	78	9:1
5	**L_3-PrEt$_2$**	79	>99	12:1
6	**L_3-PrEt$_2$Me**	73	>99	>19:1

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), ligand/Sc(OTf)$_3$ (1:1, 10 mol %) in THF (0.1 M), 3 Å MS (20 mg), and HFIP (20 mol%) at 30 °C. Isolated yields. The ee values were determined by UPC[2], the dr values were determined by the ^{1}H NMR.

(d) Screening of the solvents.

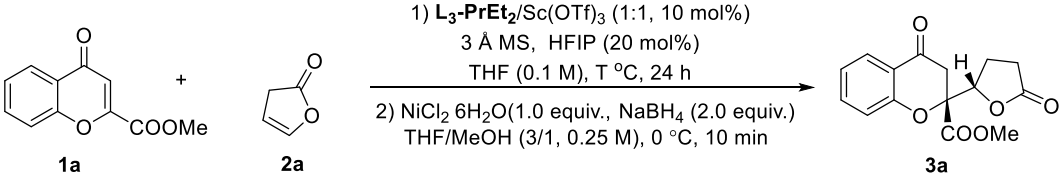


1a **2a** **3a**

Entry	solvent	Yield(%)	ee (%)	dr
1	THF	79	>99	12:1
2	CH_2Cl_2	56	>99	6:1
3	CH_3CN	73	99	19:1
4	PhMe	44	95	5:1
5	EA	74	>99	6:1
6	CH_2ClCH_2Cl	58	94	3.5:1

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), **L_3-PrEt$_2$**/Sc(OTf)$_3$ (1:1, 10 mol %) in solvent (0.1 M) and 3 Å MS (20 mg), and HFIP (20 mol%) at 30 °C. Isolated yields. The ee values were determined by UPC[2], the dr values were determined by the ^{1}H NMR.

(e) Screening of the temperature.

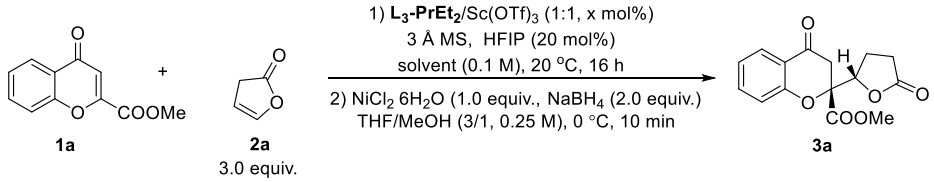


1a **2a** **3a**

Entry	Temperature (°C)	Yield(%)	ee (%)	dr
1	20	83	>99	19:1
2	30	79	>99	12:1
3	40	70	96	4:1
4	50	40	90	1.3:1

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), **L_3-PrEt$_2$**/Sc(OTf)$_3$ (1:1, 10 mol %) in THF (0.1 M), 3 Å MS (20 mg), and HFIP (20 mol%) at T °C. Isolated yields. The ee values were determined by UPC[2], the dr values were determined by the ^{1}H NMR.

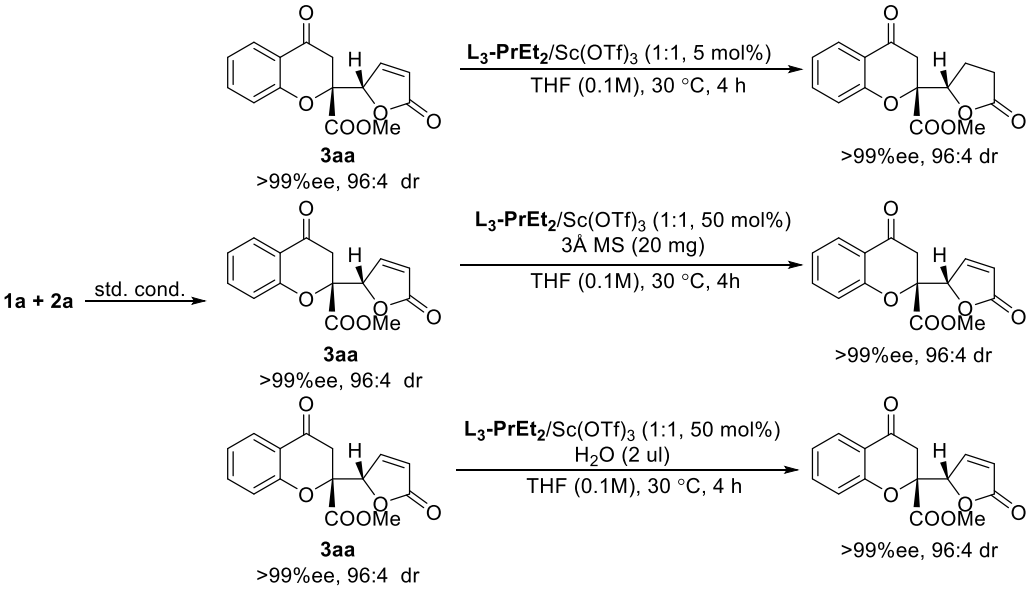
(f) Screening of the amount of catalyst.



Entry	x mol%	Yield(%)	ee (%)	dr
1	10	83	>99	19:1
2	5	83	>99	19:1
3	2	81	>99	19:1
4	1	82	>99	19:1
5	0.5	49	>99	19:1
6	0.1	33	>99	19:1
7	0.05	25	>99	19:1
8	0.01	-	>99	19:1

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (3 equiv.), **L3-PrEt2**/Sc(OTf)3 (1:1, x mol %) in THF (0.1 M) and 3 Å MS (20 mg), and HFIP (20 mol%) at 20 °C. Isolated yields. The ee values were determined by UPC[2], the dr values were determined by the ^{1}H NMR. [b]In THF (0.2 M) for 48 h.

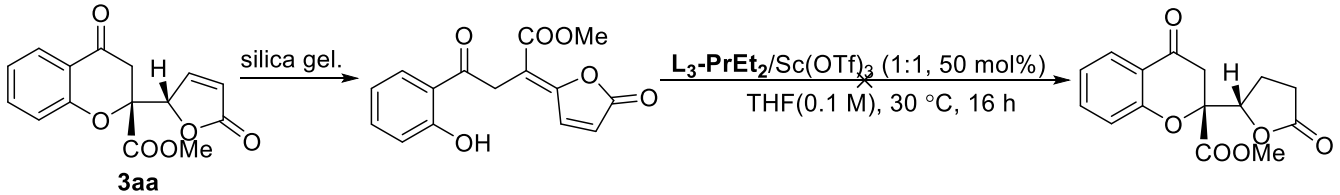
7. Control experiments.



Procedure: An oven-dried test tube was charged with the catalyst **L3-PrEt2**/Sc(OTf)3 (1:1, 1 mol %), **1a** (0.10 mmol), HFIP (0.02 mmol) and 3 Å MS (20 mg) THF (1 mL) under N_2 atmosphere. The resulted solution was stirred at 20 °C for 0.5 h, then **2a** (0.3 mmol) was added into the above solution and stirred until the reaction was complete, as indicated by thin-layer chromatography (TLC).

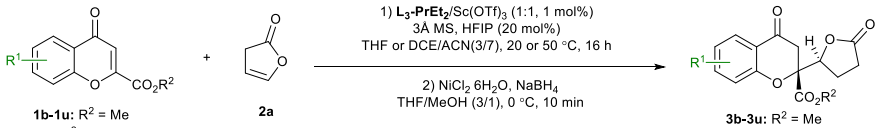
The mixture crude purified by a short silica gel column chromatography to remove the 3 Å MS and catalyst. the solvent removed in vacuo to get the crude 3aa, then the catalyst **L3-PrEt2**/Sc(OTf)3 (1:1, 5 mol %) ,additive and 1 ML THF was added, The resulted solution was stirred at 30 °C for 4 h.

The above mixture was dissolved in THF/MeOH (2/1, 3.0 mL). At 0 °C, $NiCl_2$•$6H_2O$ (0.10 mmol) and $NaBH_4$ (0.2 mmol) were added. The mixture was stirred for 10 min at 0 °C. Saturated NH_4Cl solution (0.5 mL) and water (2 mL) were added. The mixture was extracted by EtOAc (5 mL). The organic layer was concentrated under reduced pressure. The residual product was purified by silica gel column chromatography. The ee and dr value determinded by UPC[2].



The reo-oxo-Michael reaction product was detected and isolated during the column chromatography with silica gel. But this polysubstituted olefin cann't converted to **3aa** again under the **L3-PrEt2**/Sc(OTf)3 catalysis.

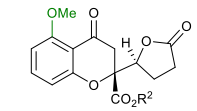
8. The list of substrates scope.



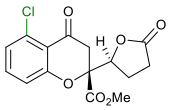
1b-1u: R^2 = Me
1b': R^2 = Et

2a

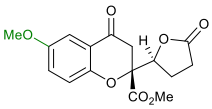
3b-3u: R^2 = Me
3b': R^2 = Et



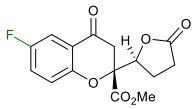
3b[b,c], 38% yield, >19:1 dr, >99% ee
3b'[b,c], 38% yield, >19:1 dr, >99% ee



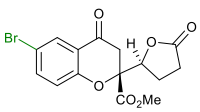
3c, 34% yield,
6:1 dr, 99%/75% ee



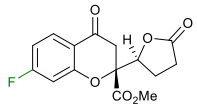
3d[b], 49% yield,
3:1 dr, 98%/94% ee



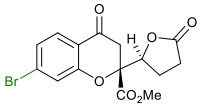
3e, 64% yield,
5:1 dr, 99%/79% ee



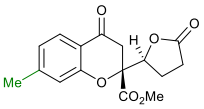
3f, 78% yield,
1.2:1 dr, >99%/89% ee



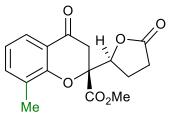
3g, 66% yield,
>19:1 dr, >99% ee



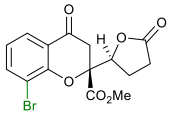
3h, 82% yield,
>19:1 dr, >99% ee



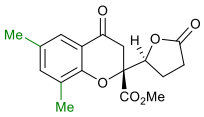
3i, 52% yield,
>19:1 dr, >99% ee



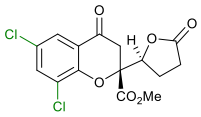
3j,64% yield,
19:1 dr, >99% ee



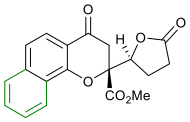
3k, 76% yield,
>19:1 dr, >99% ee



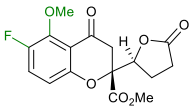
3l[b], 58% yield,
3:1 dr, >99%/95% ee



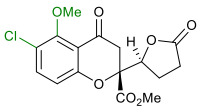
3m[b], 65% yield,
1:1 dr, 96%/80% ee



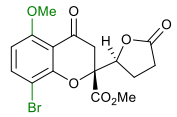
3n, 72% yield,
12:1 dr, >99%/84% ee



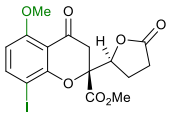
3o[b-d], 44% yield,
12:1 dr, >99%/95% ee



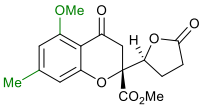
3p[b-d], 49% yield,
5:1 dr, 98%/94% ee



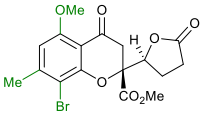
3q[b-d], 59% yield,
>19:1 dr, >99% ee



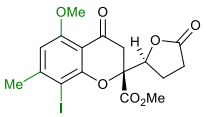
3r[b-d], 69% yield,
>19:1 dr, >99% ee



3s[b-d], 31% yield,
>19:1 dr, >99% ee



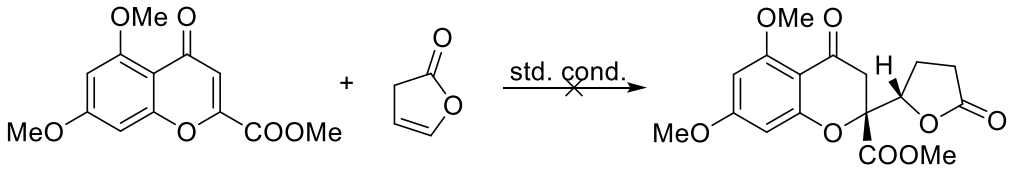
3t[b-d], 68% yield,
>19:1 dr, >99% ee



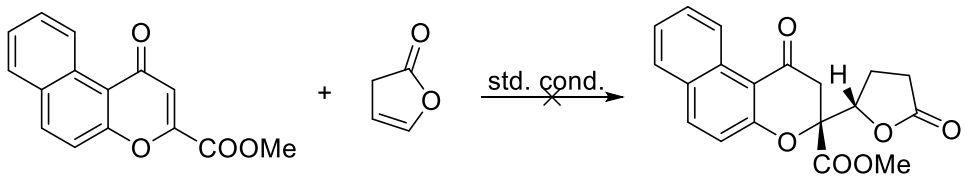
3u[b-d], 68% yield,
>19:1 dr, >99% ee

[a]Unless otherwise noted, the reactions were carried out with **1** (0.1 mmol), **2a** (0.3 mmol), **L_3-PrEt$_2$**/Sc(OTf)$_3$ (1:1, 1 mol %) in THF (0.1 M) at 20 °C for 16 hours. Then, $NiCl_2$ $6H_2O$ (1.0 equiv), $NaBH_4$ (2.0 equiv) in THF/MeOH (3/1, 0.25 M) at 0 °C for 10 min. Isolated yield of **3**. The ee values were determined by UPC[2], and the d.r. values were determined by the ^{1}H NMR. [b]**L_3-PrEt$_2$**/Sc(OTf)$_3$ (5 mol %). [c]At 50 °C. [d]DCE/MeCN (3:7, 0.1 M) as the solvent.

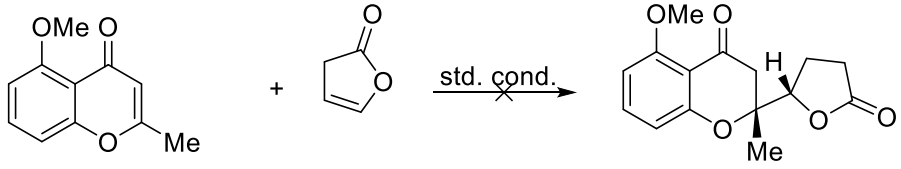
Scope limitation:



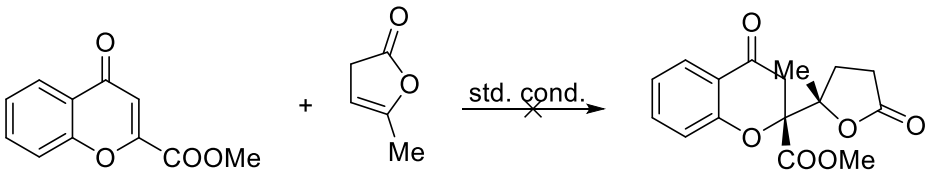
N.R.



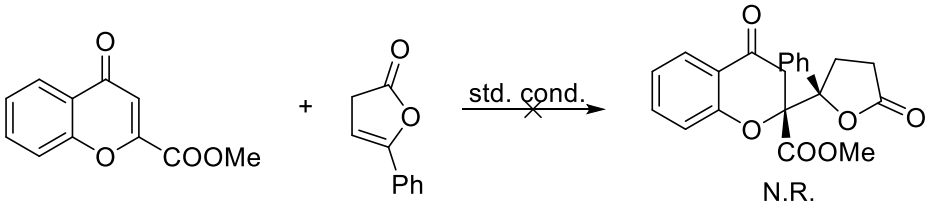
N.R.



N.R.

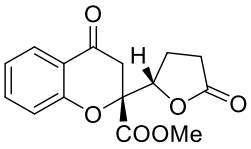


N.R.



N.R.

9. The analytical and spectral characterization data of the products



3a

3a: methyl (R)-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, white solid **3a** was isolated in 83% yield (23.9 mg) and >99% ee, 19:1 dr. $[\alpha]^{30}_{D}$ = 76.8 (*c* = 0.194 in $CHCl_3$). M.p.= 148.1-150.2 °C

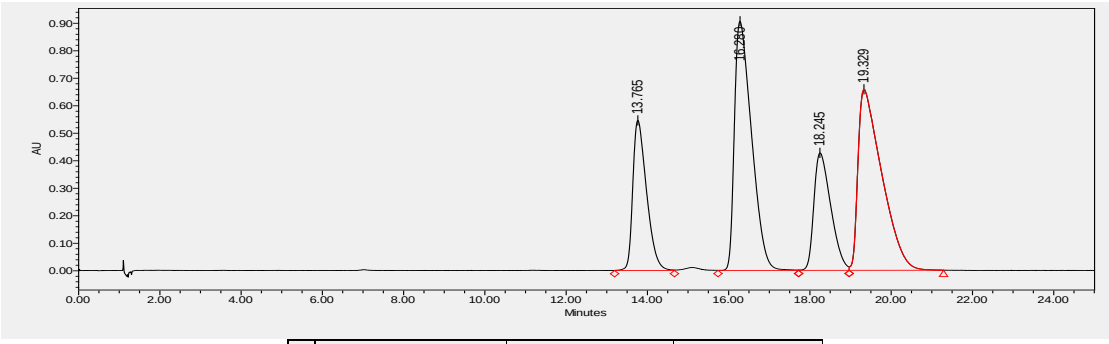
UPC² (chiral IC-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 16.1 min, t_2= 19.4 min; (minor isomer) t_1 = 18.1 min, t_2 = 13.6 min

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.85 (d, *J* = 9.5 Hz, 1H), 7.61 – 7.46 (m, 1H), 7.16 – 6.98 (m, 2H), 4.96 – 4.78 (m, 1H), 4.35 (t, *J* = 7.1 Hz, 1H), 3.70 (s, 3H), 3.17 – 2.87 (m, 2H), 2.80 – 2.66 (m, 1H), 2.67 – 2.55 (m, 1H), 2.50 (t, *J* = 8.2 Hz, 2H), 2.27 (p, *J* = 7.5 Hz, 1H).

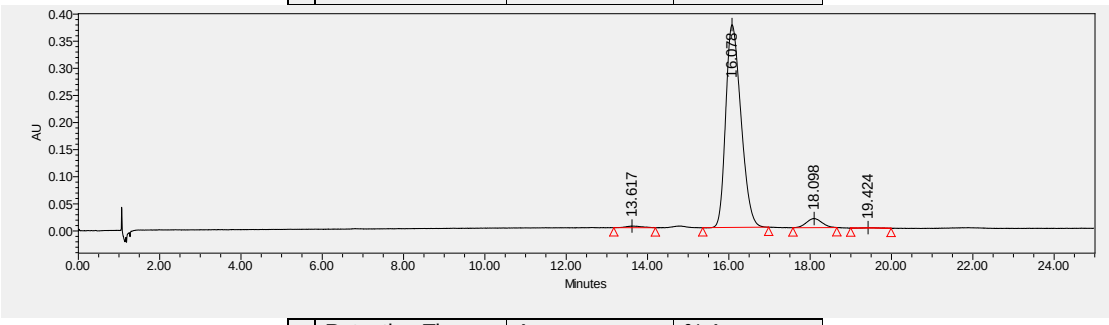
^{13}C NMR (100 MHz, $CDCl_3$). δ 188.0, 175.7, 169.1, 159.8, 136.9, 126.8, 122.4, 120.4, 118.2, 84.5, 81.2, 53.5, 40.2, 27.7, 22.1.

ESI-HRMS: calcd for $C_{15}H_{14}O_6Na^+$ ([M + Na]$^+$) = 329.0422, found 329.0416.

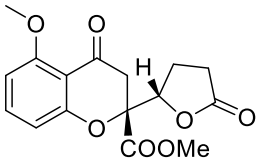
IR (neat): 2921, 1785, 1756, 1693, 1608, 1305, 1199, 1132, 1705, 1037, 943, 867, 769 cm^{-1}.



	Retention Time	Area	% Area
1	13.765	12842818	16.38
2	16.280	26541284	33.85
3	18.245	12327924	15.72
4	19.329	26699445	34.05



	Retention Time	Area	% Area
1	13.617	78360	0.76
2	16.078	9739434	94.73
3	18.098	445324	4.33
4	19.424	17978	0.17



3b

3b: methyl (R)-5-methoxy-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, white solid **3b** was isolated in 38% yield (12.1 mg) and >99% ee/75% ee, >19:1 dr. $[\alpha]^{29}_{D}$ = 73.4 (*c* = 0.158 in $CHCl_3$). M.p.= 194.2-196.1 °C

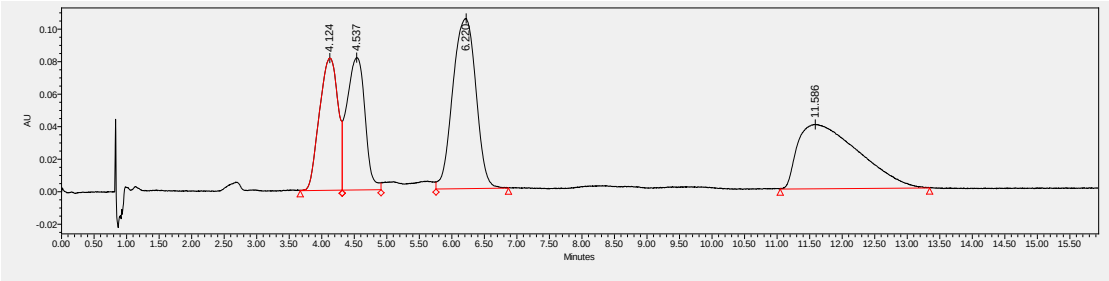
UPC² (chiral IA-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 6.2 min, t_2 = 11.2 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.45 (t, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 4.87 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.90 (s, 3H), 3.71 (s, 3H), 3.12 – 2.84 (m, 2H), 2.82 – 2.53 (m, 2H), 2.53 – 2.29 (m, 2H).

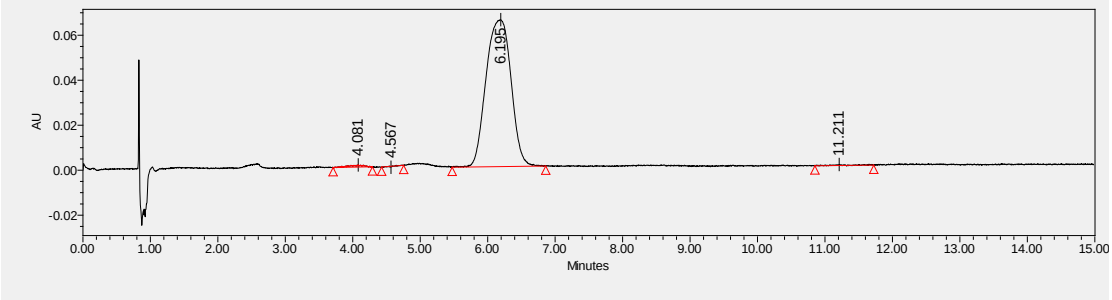
^{13}C NMR (100 MHz, $CDCl_3$). δ 186.4, 175.7, 169.0, 161.3, 160.5, 136.8, 110.9, 110.1, 104.8, 84.0, 56.3, 53.5, 41.4, 27.7, 22.0.

ESI-HRMS: calcd for $C_{16}H_{16}O_7Na^+$ ([M + Na]$^+$) = 343.0788, found 343.0783.

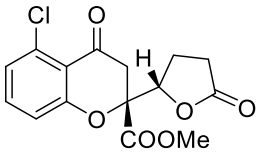
IR (neat): 2923, 1782, 1756, 1686, 1603, 1577, 1473, 1438, 1339, 1259, 1197, 1134, 1103, 1077, 1048, 790, 745 cm^{-1}.



	Retention Time	Area	% Area
1	4.124	1610793	19.25
2	4.537	1580308	18.89
3	6.220	2595397	31.02
4	11.586	2579389	30.83



	Retention Time	Area	% Area
1	4.081	13718	0.80
2	4.567	1695	0.10
3	6.195	1683658	98.64
4	11.211	7737	0.45



3c

3c: methyl (R)-5-chloro-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, white solid **3c** was isolated in 34% yield (11.2 mg) >99% ee/75% ee , 6:1 dr. $[\alpha]^{27}_{D}$ = 72.0 (*c* = 0.118 in $CHCl_3$). M.p.= 123.1-124.5 °C

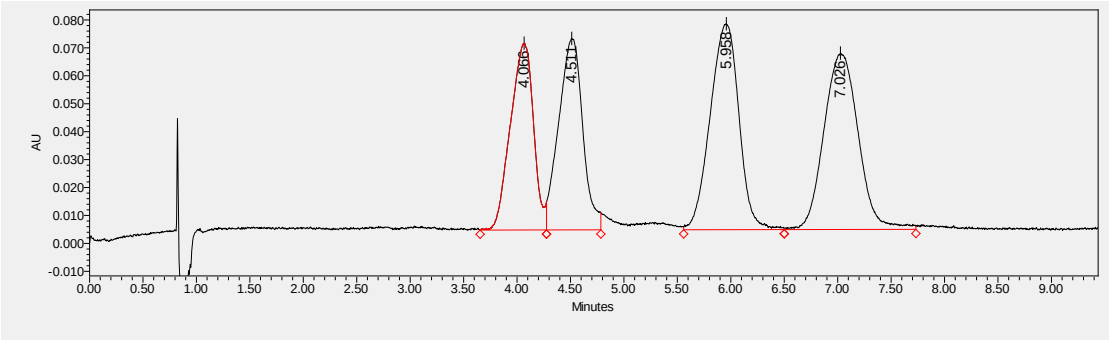
UPC² (chiral AS-3 column), CO_2/MeOH = 95/5, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 5.6 min, t_2 = 6.7 min; (minor isomer) t_1 = 3.8 min, t_2 = 4.3 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.41 (t, *J* = 8.1 Hz, 1H), 7.15 – 6.95 (m, 2H), 4.94 – 4.88 (m, 1H), 3.74 (d, *J* = 2.5 Hz, 3H), 3.19 – 2.92 (m, 2H), 2.79 – 2.52 (m, 2H), 2.44 (dtd, *J* = 10.0, 7.5, 7.0, 2.9 Hz, 2H).

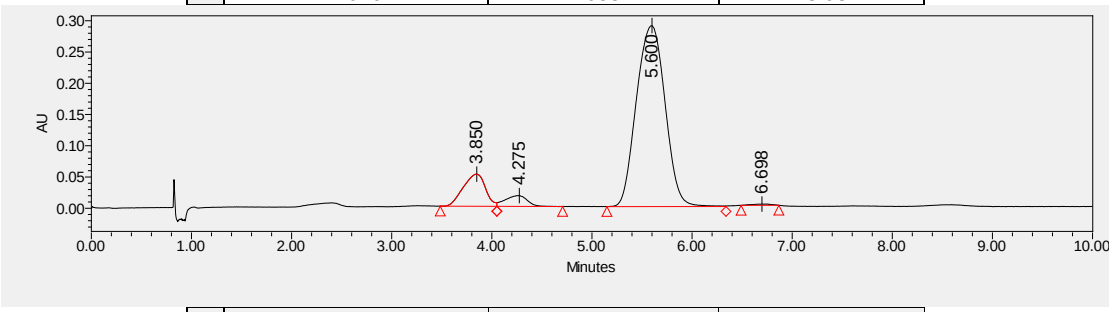
^{13}C NMR (100 MHz, $CDCl_3$). δ 185.9, 175.5, 168.6, 161.2, 135.5, 134.2, 125.6, 117.8, 117.1, 84.1, 80.9, 53.6, 42. 2, 27.7, 21.9.

ESI-HRMS: calcd for $C_{15}H_{13}ClO_6Na^+$ ([M + Na]$^+$) = 347.0293 and 349.0263, found 347.0287 and 349.0255.

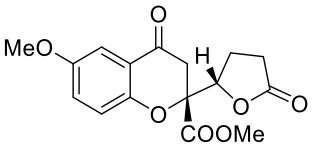
IR (neat): 2933, 1851, 1785, 1755, 1698, 1595, 1566, 1451, 1318, 1266, 1196, 1132, 1071, 1051, 949, 901, 767 cm^{-1}:



	Retention Time	Area	% Area
1	4.066	1005764	20.70
2	4.511	1066966	21.96
3	5.958	1378499	28.37
4	7.026	1408371	28.98



	Retention Time	Area	% Area
1	3.850	790430	11.52
2	4.275	266424	3.88
3	5.600	5778619	84.21
4	6.698	26899	0.39



3d

3d: methyl (R)-6-methoxy-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, white solid **3d** was isolated in 49% yield (15.6 mg) and 98% ee/94% ee, 3:1 dr. $[\alpha]^{26}_{D}$ = 51.2 (*c* = 0.186 in $CHCl_3$). M.p.= 134.3-135.9 °C

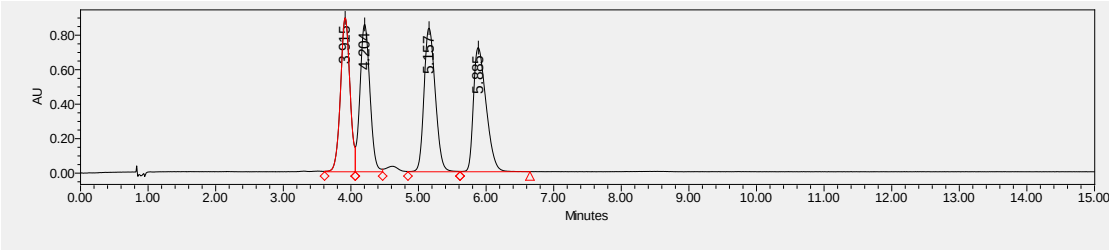
UPC² (chiral OD-3 column), CO_2/MeOH = 90/10, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 5.1 min, t_2 = 5.9 min; (minor isomer) t_1 = 4.2 min, t_2 = 3.9 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.18 – 7.10 (m, 1H), 7.07 – 6.96 (m, 1H), 4.94 – 4.85 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 2.4 Hz, 3H), 3.01 (m, 2H), 2.87 – 2.40 (m, 4H).

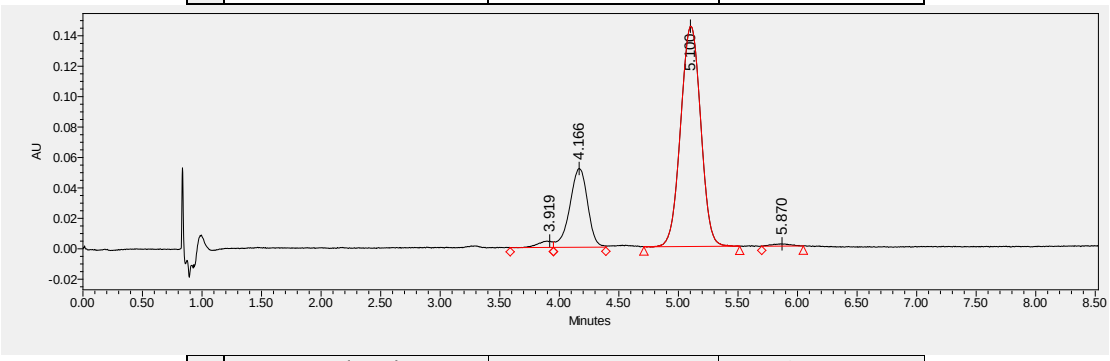
^{13}C NMR (100 MHz, $CDCl_3$). δ 188.1, 175.7, 169.3, 154.7, 154.4, 125.9, 120.2, 119.5, 107.2, 84.6, 81.2, 55.8, 53.5, 40.2, 27.9, 22.1.

ESI-HRMS: calcd for $C_{16}H_{16}O_7Na^+$ ([M + Na]$^+$) = 343.0788, found 343.0782.

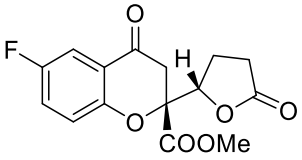
IR (neat): 2921, 1785, 1691, 1488, 1432, 1283, 1203, 1131, 1058, 1033, 943, 835, 765 cm^{-1}.



	Retention Time	Area	% Area
1	3.915	8640774	23.74
2	4.204	8728321	23.99
3	5.157	9634435	26.48
4	5.885	9386874	25.79



	Retention Time	Area	% Area
1	3.919	35823	1.57
2	4.166	539229	23.63
3	5.100	1690880	74.09
4	5.870	16114	0.71



3e

3e: methyl (R)-6-fluoro-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, white solid **3e** was isolated in 64% yield (19.6 mg) and 99% ee/79% ee, 5:1 dr. $[\alpha]^{25}_{D}$ = 58.3 (*c* = 0.312 in $CHCl_3$). M.p.= 138.1-140.3 °C

UPC² (chiral IC-3 column), CO_2/MeOH = 91/9, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 7.4 min, t_2 = 8.3 min; (minor isomer) t_1= 7.8 min, t_2 = 6.4 min.

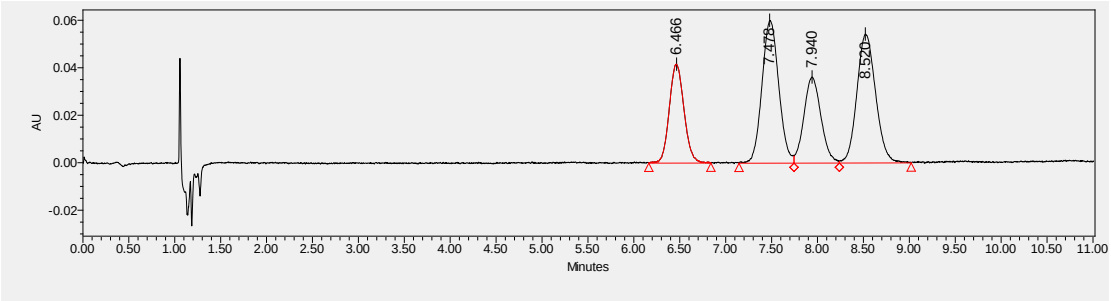
^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.49 (dt, *J* = 8.0, 2.9 Hz, 1H), 7.32 – 7.22 (m, 1H), 7.15 – 7.04 (m, 1H), 4.90 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.71 (d, *J* = 3.0 Hz, 3H), 3.24 – 2.86 (m, 2H), 2.86 – 2.55 (m, 2H), 2.54 – 2.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$). δ 187.2, 175.5, 168.8, 158.9 (d, *J* = 244.4 Hz), 155.9, 124.5 (d, *J* = 25.3 Hz), 120.9 (d, *J* = 6.1 Hz), 119.9 (d, *J* = 7.1 Hz), 112.07 (d, *J* = 24.2 Hz), 84.7, 81.0, 53.6, 40.0, 27.7, 22.0.

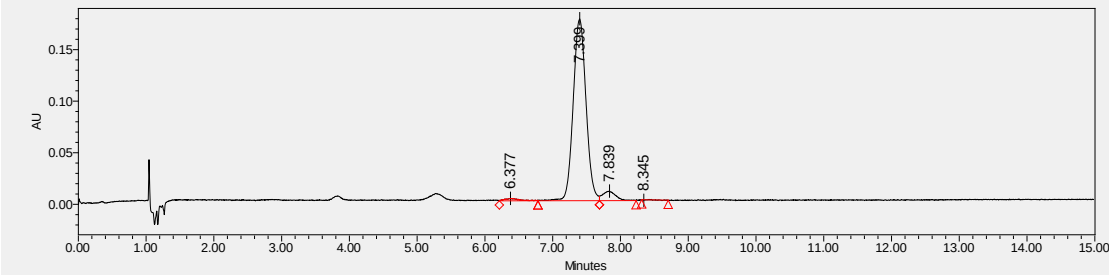
^{19}F NMR (376 MHz, $CDCl_3$) δ -119.81.

ESI-HRMS: calcd for $C_{15}H_{13}FO_6Na^+$ ([M + Na]$^+$) = 331.0588, found 331.0583.

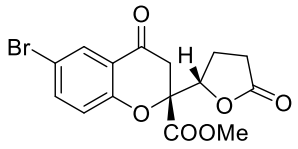
IR (neat): 2922, 1785, 1697, 1621, 1484, 1437, 1273, 1273, 1190, 1126, 1071, 1034, 943, 835 cm^{-1}.



	Retention Time	Area	% Area
1	6.466	464264	18.82
2	7.478	764441	30.99
3	7.940	467414	18.95
4	8.520	770269	31.23



	Retention Time	Area	% Area
1	6.377	31797	1.29
2	7.399	2310622	93.56
3	7.839	123428	5.00
4	8.345	3877	0.16



3f

3f: methyl (R)-6-bromo-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3f** was isolated in 78% yield (28.6 mg) and 94% ee/89% ee, 1.2:1 dr. $[\alpha]^{25}_{D}$ = 5.0 (*c* = 0.222 in $CHCl_3$).

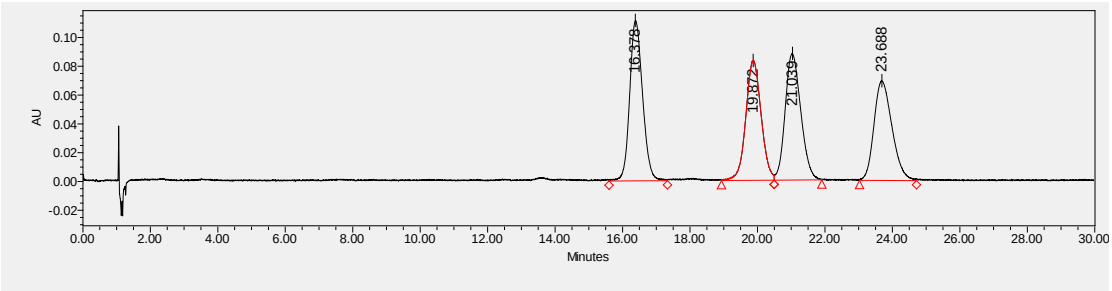
UPC² (chiral IC-3 column), CO_2/MeOH = 90/10, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 19.9 min, t_2 = 23.8 min; (minor isomer) t_1 = 21.0, t_2 = 16.4 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.95 (t, *J* = 2.8 Hz, 1H), 7.62 (ddd, *J* = 8.7, 6.1, 2.5 Hz, 1H), 7.00 (dd, *J* = 20.7, 8.8 Hz, 1H), 4.90 (dd, *J* = 7.6, 6.4Hz, 1H), 3.72 (d, *J* = 2.4 Hz, 3H), 3.50 – 2.87 (m, 2H), 2.86 – 2.65 (m, 1H), 2.65 – 2.31 (m, 3H).

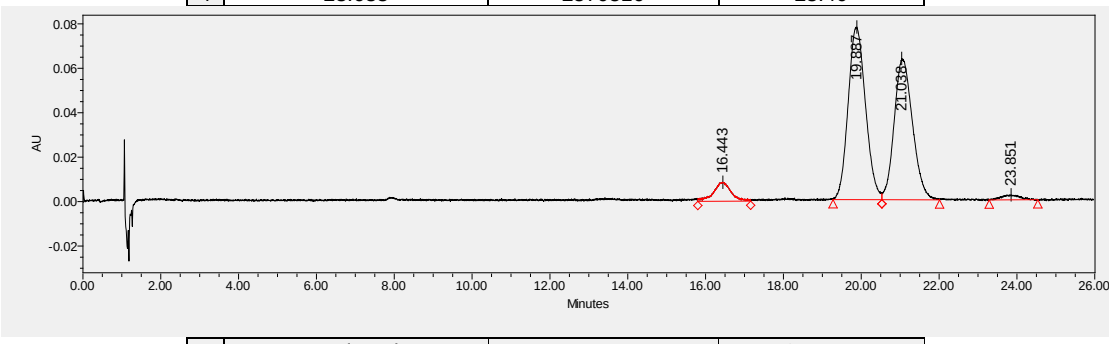
^{13}C NMR (100 MHz, $CDCl_3$). δ 187.7, 175.9, 168.8, 158.4, 139.2, 129.2, 121.5, 120.1, 115.2, 85.3, 79.7, 53.7, 41.1, 27.8, 22.0.

ESI-HRMS: calcd for $C_{15}H_{13}BrO_6Na^+$ ([M + Na]$^+$) = 390.9788 and 392.9767, found 390.9778 and 392.9754.

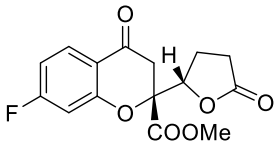
IR (neat): 2921, 2850, 1787, 1754, 1697, 1649, 1599, 1536, 1468, 1416, 1275, 1199, 1138, 1061, 833, 765 cm^{-1}.



	Retention Time	Area	% Area
1	16.378	2960998	26.96
2	19.872	2621630	23.87
3	21.039	2830060	25.77
4	23.688	2570516	23.40



	Retention Time	Area	% Area
1	16.443	264314	5.48
2	19.887	2407599	49.89
3	21.038	2081699	43.14
4	23.851	72110	1.49



3g

3g: methyl (R)-7-fluoro-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, white solid **3g** was isolated in 66% yield (20.2 mg) and >99% ee, >19:1 dr. $[\alpha]_D^{25}$ = 31.1 (*c* = 0.364 in $CHCl_3$). M.p.= 174.1-178.2 °C

UPC² (chiral AD-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 4.0 min, t_2 = 5.4 min; (minor isomer) t_1 = 2.6 min, t_2 = 4.5 min.

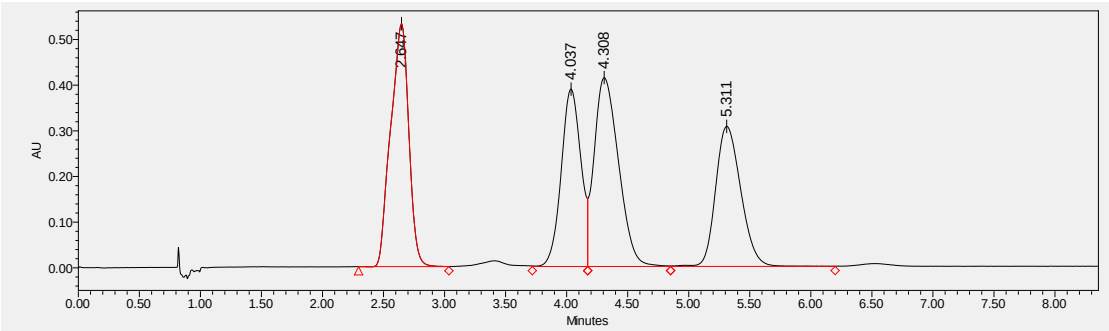
^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.99 – 7.74 (m, 1H), 6.94 – 6.74 (m, 2H), 4.91 (dd, *J* = 7.7, 6.2 Hz, 1H), 3.72 (s, 3H), 3.24 – 2.83 (m, 2H), 2.83 – 2.55 (m, 2H), 2.55 – 2.35 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$). δ 186.5, 175.9, 169.2 (d, *J* = 256.0 Hz), 168.7, 166.6, 161.4, 129.52 (d, *J* = 11.1 Hz), 117.3, 111.0 (d, *J* = 22.0 Hz), 105.34 (d, *J* = 25.1 Hz), 85.1, 80.9, 53.7, 39.9, 27.7, 22.0.

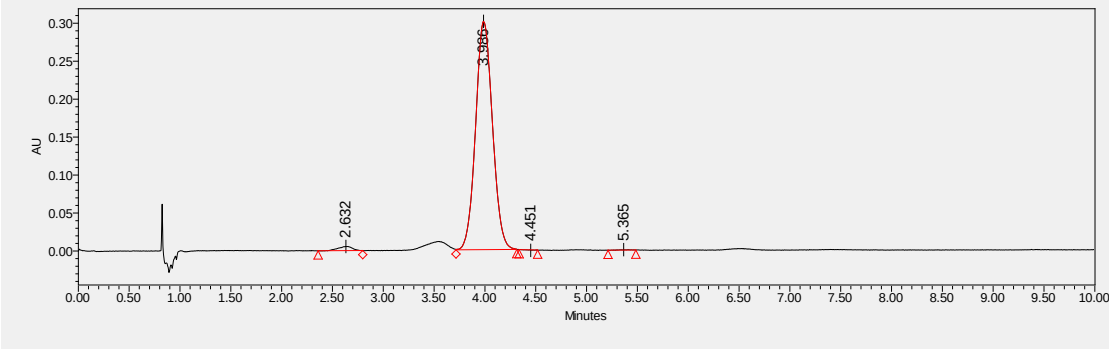
^{19}F NMR (376 MHz, $CDCl_3$) δ -98.42.

ESI-HRMS: calcd for $C_{15}H_{13}FO_6Na^+$ ([M + Na]$^+$) = 331.0588, found 331.0581.

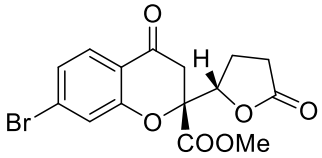
IR (neat): 2922, 1785, 1756, 1695, 1440, 1285, 1261, 1199, 978, 856, 817, 753 cm^{-1}.



	Retention Time	Area	% Area
1	2.647	5476006	27.39
2	4.037	4356584	21.79
3	4.308	5754047	28.78
4	5.311	4403389	22.03



	Retention Time	Area	% Area
1	2.632	53010	1.50
2	3.986	3463663	98.33
3	4.451	2430	0.07
4	5.365	3241	0.09



3h

3h: methyl (R)-7-bromo-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3h** was isolated in 82% yield (31.0 mg) and >99% ee, >19:1 dr. $[\alpha]^{25}_{D}$ = 31.1 (*c* = 0.588 in $CHCl_3$). M.p.= 178.1-164.3 °C

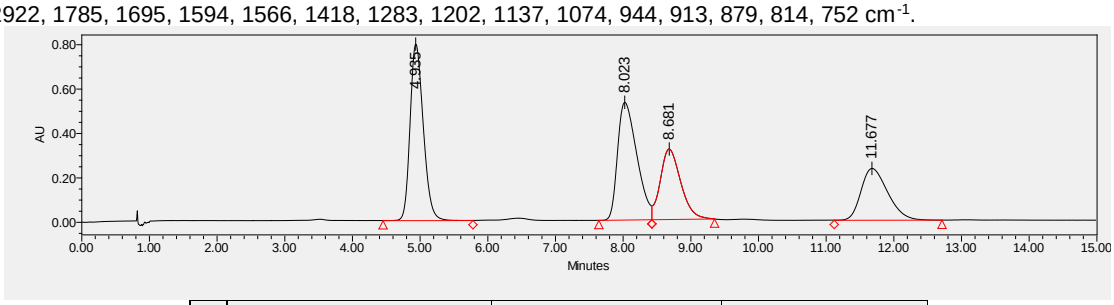
UPC² (chiral AD-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 8.5 min, t_2 = 11.4 min; (minor isomer) t_1 = 4.9 min, t_2 = 7.8 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.70 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.22 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.90 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.72 (s, 3H), 3.19 – 2.84 (m, 2H), 2.80 – 2.54 (m, 2H), 2.51 – 2.38 (m, 2H).

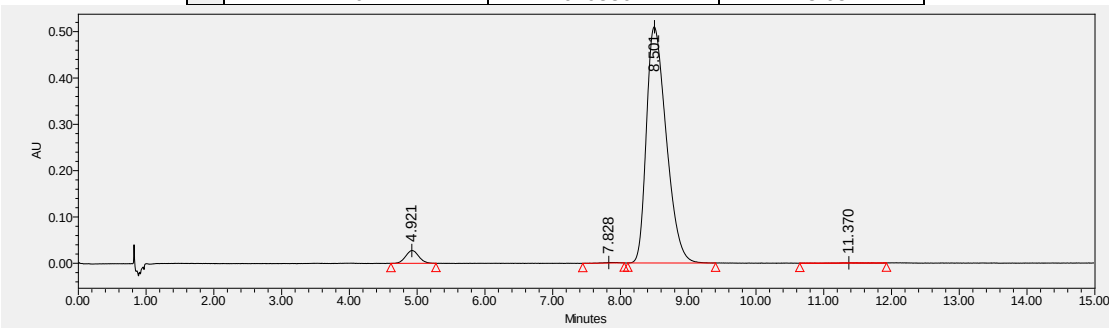
^{13}C NMR (100 MHz, $CDCl_3$). δ 187.0, 175.4, 168.6, 159.8, 131.3, 127.9, 126.0, 121.3, 119.2, 84.9, 80.8, 53.6, 40.0, 27.6, 21.9.

ESI-HRMS: calcd for $C_{15}H_{13}BrO_6Na^+$ ($[M + Na]^+$) = 390.9788 and 392.9767, found 390.9782 and 392.9760.

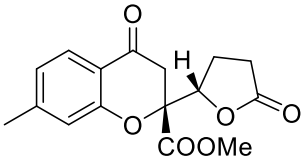
IR (neat): 2922, 1785, 1695, 1594, 1566, 1418, 1283, 1202, 1137, 1074, 944, 913, 879, 814, 752 cm^{-1}.



	Retention Time	Area	% Area
1	4.935	10785898	31.41
2	8.023	10479315	30.51
3	8.681	6674259	19.43
4	11.677	6403362	18.65



	Retention Time	Area	% Area
1	4.921	374078	3.48
2	7.828	18645	0.17
3	8.501	10345528	96.24
4	11.370	11899	0.11



3i

3i: methyl (R)-7-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3i** was isolated in 52% yield (15.7 mg) and >99% ee, >19:1 dr. $[\alpha]^{25}_{D}$ = 53.8 (*c* = 0.234 in $CHCl_3$). M.p.= 148.1-150.2 °C

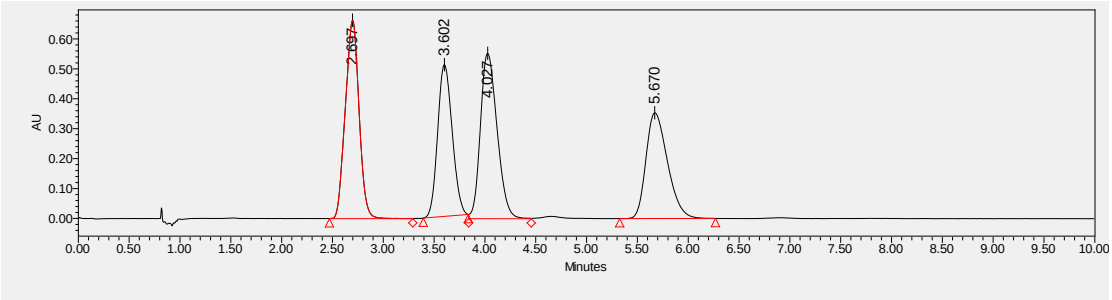
UPC² (chiral OX-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 3.6 min, t_2 = 5.7 min; (minor isomer) t_1 = 2.7 min, t_2 = 4.9 min .

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.00 – 6.79 (m, 2H), 4.89 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.71 (s, 3H), 3.15 – 2.81 (m, 2H), 2.84 – 2.41 (m, 4H), 2.39 (s, 3H).

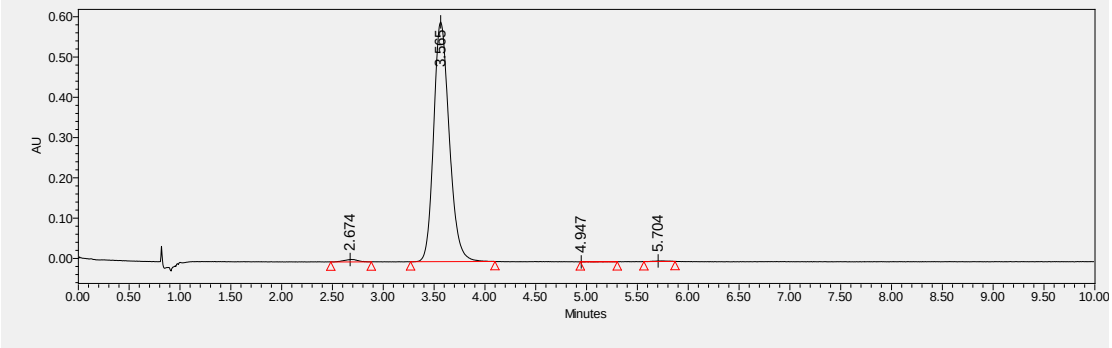
^{13}C NMR (100 MHz, $CDCl_3$). δ 187.5, 175.7, 169.1, 148.7, 126.7, 123.7, 118.1, 118.1, 84.5, 81.1, 40.1, 27.7, 22.0.

ESI-HRMS: calcd for $C_{16}H_{16}O_6Na^+$ ([M + Na]$^+$) = 327.0839, found 327.0833.

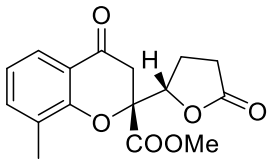
IR (neat): 2922, 1785, 1757, 1688, 1617, 1507, 1457, 1294, 1250, 1154, 1073, 817, 751 cm^{-1}.



	Retention Time	Area	% Area
1	2.697	6232475	27.35
2	3.602	5045821	22.14
3	4.027	6309581	27.69
4	5.670	5199256	22.82



	Retention Time	Area	% Area
1	2.674	57614	0.90
2	3.565	6344676	98.82
3	4.947	3428	0.05
4	5.704	14948	0.23



3j

3j: methyl (R)-8-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3j** was isolated in 64% yield (19.4 mg) and >99% ee, 19:1 dr. $[\alpha]_D^{25}$ = 76.2 (*c* = 0.328 in $CHCl_3$). M.p.= 148.1-150.2 °C

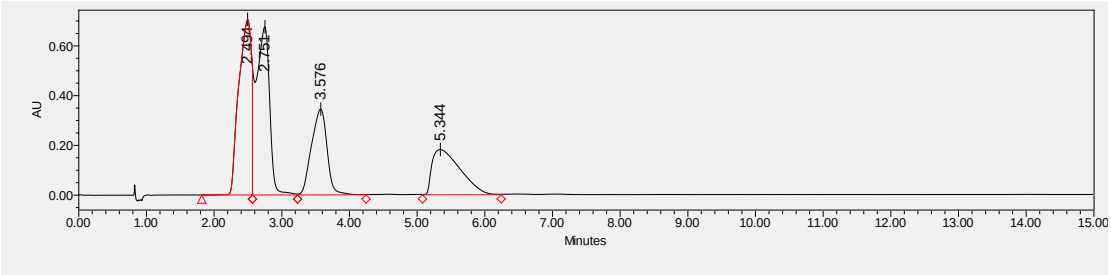
UPC² (chiral OX-3 column), CO_2/MeOH = 95/5, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 3.6, t_2 = 5.7 min; (minor isomer) t_1 = 2.8 min, t_2 = 2.5 min .

^{1}H NMR (400 MHz, Chloroform-*d*). 7.69 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.2, 1.9, 1.0 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 4.92 (dd, *J* = 8.2, 4.6 Hz, 1H), 3.69 (s, 3H), 3.20 – 2.87 (m, 2H), 2.51 (d, *J* = 8.2 Hz, 4H), 2.29 (s, 3H).

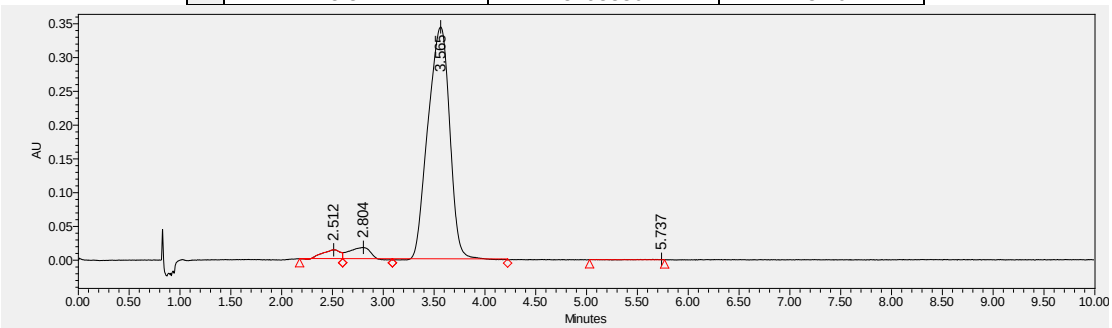
^{13}C NMR (100 MHz, $CDCl_3$). δ 188.3, 175.7, 169.1, 158.0, 137.7, 127.5, 124.4, 121.9, 120.1, 84.9, 81.2, 53.5, 40.3, 27.6, 22.0, 15.6.

ESI-HRMS: calcd for $C_{16}H_{16}O_6Na^+$ ([M + Na]$^+$) = 327.0839, found 327.0833.

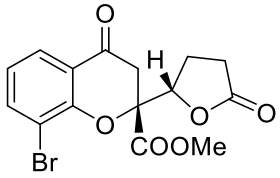
IR (neat): 2922, 1785, 1757, 1691, 1600, 1431, 1297, 1202, 1137, 1077, 1038, 944, 790, 745 cm^{-1}.



	Retention Time	Area	% Area
1	2.494	8982114	30.72
2	2.751	9470768	32.39
3	3.576	5496304	18.80
4	5.344	5293330	18.10



	Retention Time	Area	% Area
1	2.512	161340	2.93
2	2.804	245960	4.47
3	3.565	5087979	92.45
4	5.737	8341	0.15



3k

3k: methyl (R)-8-bromo-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3k** was isolated in 76% yield (28.0 mg) and >99% ee, >19:1 dr. $[\alpha]_D^{25}$ = 27.0 (*c* = 0.508 in $CHCl_3$). M.p.= 148.1-150.2 °C

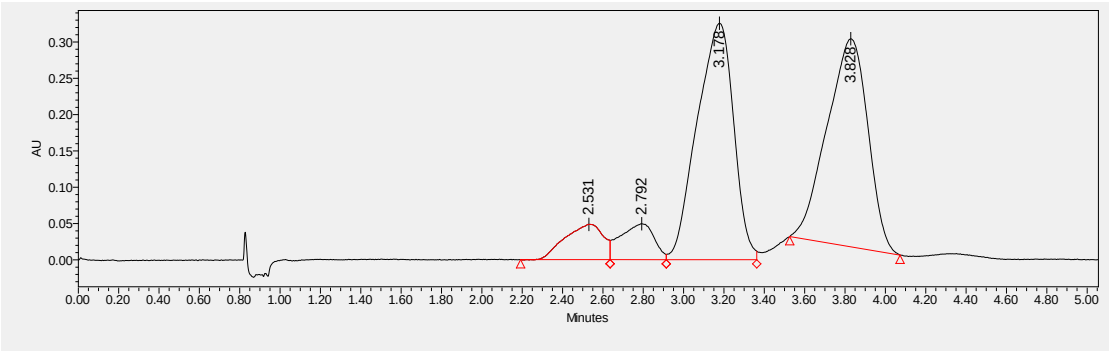
UPC² (chiral OX-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 3.8 min, t_2 = 3.1 min; (minor isomer) t_1 = 2.5 min, t_2 = 2.3 min .

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.80 (ddd, *J* = 7.8, 5.3, 1.6 Hz, 2H), 6.97 (t, *J* = 7.8 Hz, 1H), 4.95 (dd, *J* = 7.4, 4.6 Hz, 1H), 3.72 (s, 3H), 3.25 – 2.79 (m, 3H), 2.73 – 2.36 (m, 3H).

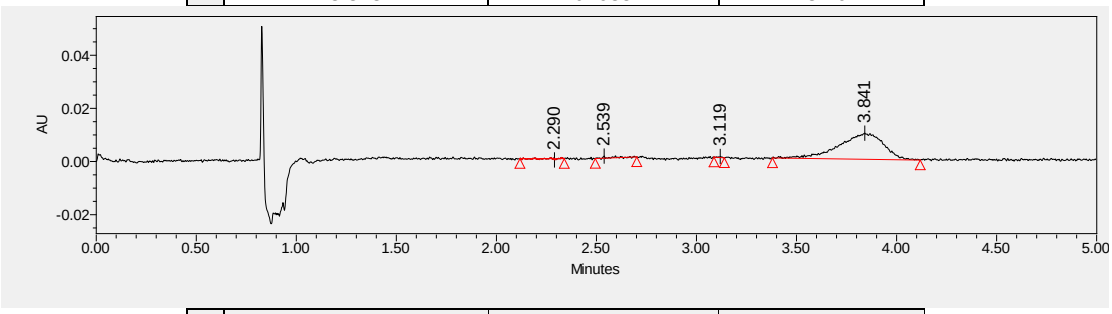
^{13}C NMR (100 MHz, $CDCl_3$). δ 187.3, 175.7, 168.4, 156.3, 139.9, 126.0, 123.0, 121.5, 111.9, 85.8, 80.9, 53.7, 40.2, 27.5, 22.2.

ESI-HRMS: calcd for $C_{15}H_{13}BrO_6Na^+$ ([M + Na]$^+$) = 390.9788 and 392.9767, found 390.9779 and 392.9758.

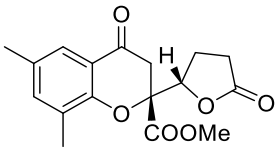
IR (neat): 2921, 1785, 1757, 1697, 1505, 1462, 1438, 1285, 1126, 1003, 867, 750 cm^{-1}.



	Retention Time	Area	% Area
1	2.531	641104	6.86
2	2.792	571724	6.12
3	3.178	4103627	43.92
4	3.828	4026857	43.10



	Retention Time	Area	% Area
1	2.290	2313	1.48
2	2.539	2356	1.51
3	3.119	408	0.26
4	3.841	150881	96.74



3l

3l methyl (R)-6,8-dimethyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3l** was isolated in 48% yield (18.3 mg) and >99% ee/95% ee, 3:1 dr. $[\alpha]^{25}_{D}$ = 34.3 (*c* = 0.254 in $CHCl_3$).

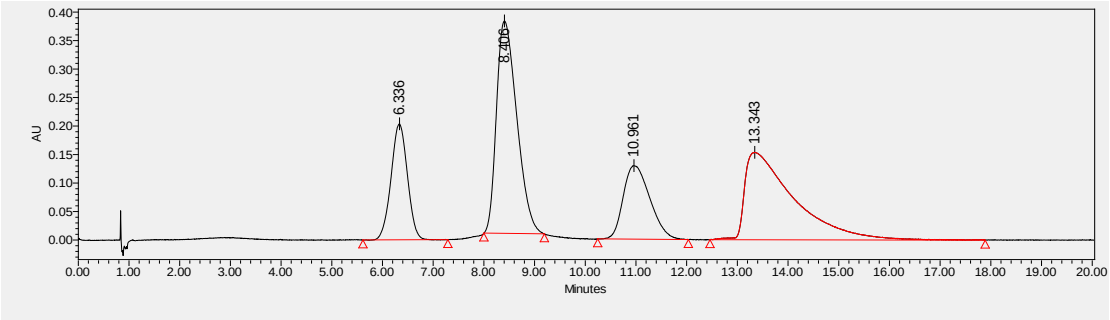
UPC² (chiral AD-3 column), CO_2/MeOH = 96/4, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 8.3 min, t_2 = 13.8 min; (minor isomer) t_1 = 6.2 min, t_2 = 11.1 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.48 (s, 1H), 7.23 (s, 1H), 4.91 (dd, *J* =5.6 ,2.8 Hz, 1H), 3.69 (d, *J* = 3.1 Hz, 3H), 3.23 – 2.86 (m, 2H), 2.86 – 2.67 (m, 1H), 2.77 – 2.41 (m, 4H), 2.27 (s, 3H), 2.25 (s, 3H).

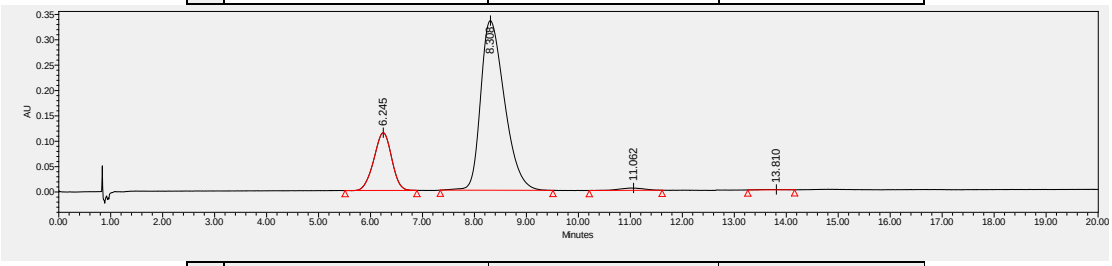
^{13}C NMR (100 MHz, $CDCl_3$). δ 163.9, 149.5, 148.1, 146.7, 126.5, 124.5, 79.8, 63.5, 27.6, 26.0, 21.0, 19.8, 19.0.

ESI-HRMS: calcd for $C_{17}H_{18}O_6Na^+$ ([M + Na]$^+$) = 341.0996, found 341.0992.

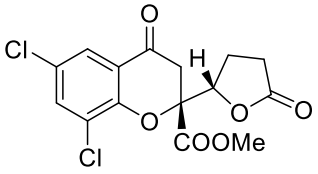
IR (neat): 2922, 1786, 1757, 1690, 1612, 1476, 1266, 1176, 1063, 1040 cm^{-1}.



	Retention Time	Area	% Area
1	6.336	4571768	15.24
2	8.406	10385845	34.62
3	10.961	4708689	15.70
4	13.343	10333882	34.45



	Retention Time	Area	% Area
1	6.245	2709713	20.07
2	8.308	10623626	78.67
3	11.062	151724	1.12
4	13.810	18274	0.14



3m

3m: methyl (R)-6,8-dichloro-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3m** was isolated in 65% yield (22.8 mg) and 96% ee/80% ee, 1.1:1 dr. $[\alpha]^{25}_{D}$ = –1.0 (*c* = 0.20 in $CHCl_3$).

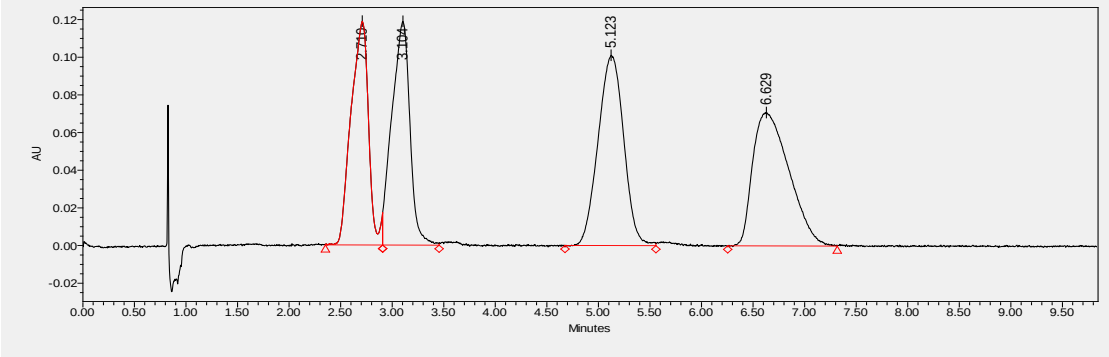
UPC² (chiral AS-3 column), CO_2/MeOH = 95/5, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 5.0 min, t_2 = 6.7 min; (minor isomer) t_1 = 2.7 min, t_2 = 3.1 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 8.49 (d, *J* = 5.0 Hz, 1H), 7.83 (s, 1H), 7.14 (d, *J* = 5.8 Hz, 1H), 4.95 (t, *J* = 4.4 Hz, 1H), 4.19 – 3.75 (d, *J* = 2.8 Hz, 3H), 3.51 – 2.93 (m, 3H), 2.66 – 2.38 (m, 3H).

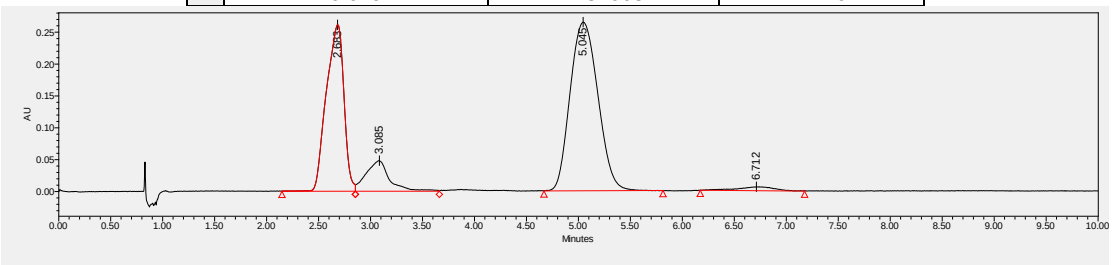
^{13}C NMR (100 MHz, $CDCl_3$). δ 186.2, 175.6, 168.4, 154.2, 136.3, 127.8, 124.8, 124.4, 121.9, 86.5, 90.4, 53.9, 40.1, 27.5, 22.2.

ESI-HRMS: calcd for $C_{15}H_{12}Cl_2O_6Na^+$ ([M + Na]$^+$) =380.9903 and 382.9874, found 380.9898 and 382.9868.

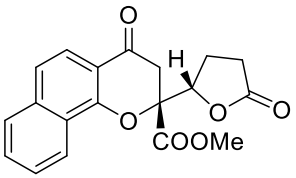
IR (neat): 2923, 1787, 1755, 1703, 1592, 1455, 1262, 1239, 1177, 1065, 1038, 879, 818, 758 cm^{-1}.



	Retention Time	Area	% Area
1	2.710	1397893	22.12
2	3.104	1442069	22.82
3	5.123	1741740	27.56
4	6.629	1737063	27.49



	Retention Time	Area	% Area
1	2.683	3065564	34.48
2	3.085	753282	8.47
3	5.045	4919926	55.33
4	6.712	153361	1.72



3n

3n: methyl (R)-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)-3,4-dihydro-2H-benzo[h]chromene-2-carboxylate

Following the typical procedure, colourless oil **3n** was isolated in 72% yield (24.4 mg) and >99% ee/84% ee, 12:1 dr. $[\alpha]^{25}_{D}$ = -35.5 (*c* =0.442 in $CHCl_3$). M.p.= 148.1-150.2 °C

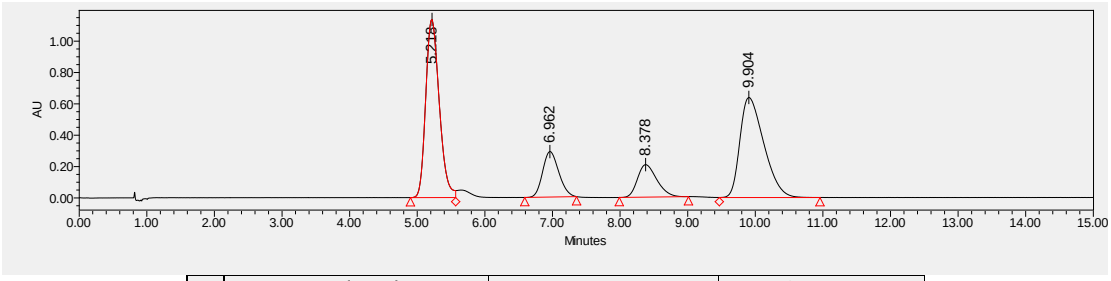
UPC² (chiral AD-3 column), CO_2/MeOH = 95/5, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 7.0 min, t_2 = 10.4 min; (minor isomer) t_1 = 5.3 min, t_2 = 8.4 min .

^{1}H NMR (400 MHz, Chloroform-*d*). δ 8.25 (d, *J* = 8.3 Hz, 1H), 7.81 (dd, *J* = 8.5, 2.8 Hz, 2H), 7.73 – 7.63 (m, 1H), 7.64 – 7.56 (m, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 5.03 (dd, *J* = 8.2, 5.1 Hz, 1H), 3.66 (s, 3H), 3.35 – 3.00 (m, 2H), 2.91 – 2.41 (m, 4H).

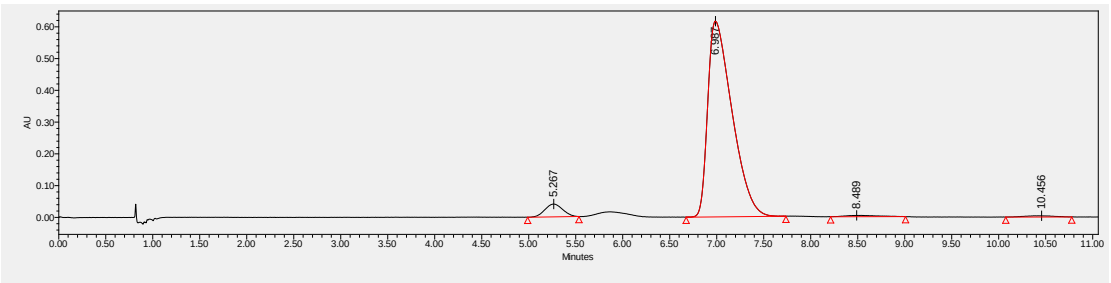
^{13}C NMR (101 MHz, Chloroform-*d*) δ 187.5, 175.8, 169.0, 158.0, 137.8, 130.2, 127.9, 127.0, 124.3, 123.4, 122.2, 121.0, 115.2, 85.5, 81.2, 53.6, 53.6, 39.7, 27.7, 22.1.

ESI-HRMS: calcd for $C_{19}H_{16}O_6Na^+$ ([M + Na]$^+$) = 363.0839, found 363.0834.

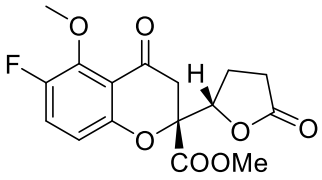
IR (neat): 2924, 1786, 1758, 1682, 1626, 1598, 1575, 1509, 1438, 1351, 1283, 1257, 1198, 1132, 1096, 1069, 1038, 943, 815, 751 cm^{-1}.



	Retention Time	Area	% Area
1	5.218	15797930	39.12
2	6.962	4808536	11.91
3	8.378	4120037	10.20
4	9.904	15658580	38.77



	Retention Time	Area	% Area
1	5.267	532038	4.51
2	6.987	11070665	93.91
3	8.489	104364	0.89
4	10.456	81396	0.69



3o

3o: methyl (R)-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3o** was isolated in 48% yield (14.7 mg) and 99% ee/95% ee, 12:1 dr. $[\alpha]^{25}_{D}$ = 52.6 (*c* = 0.268 in $CHCl_3$).

UPC² (chiral AD-3 column), CO_2/MeOH = 90/10, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 3.0 min, t_2 = 5.4 min; (minor isomer) t_1 = 2.4 min, t_2 = 3.4 min.

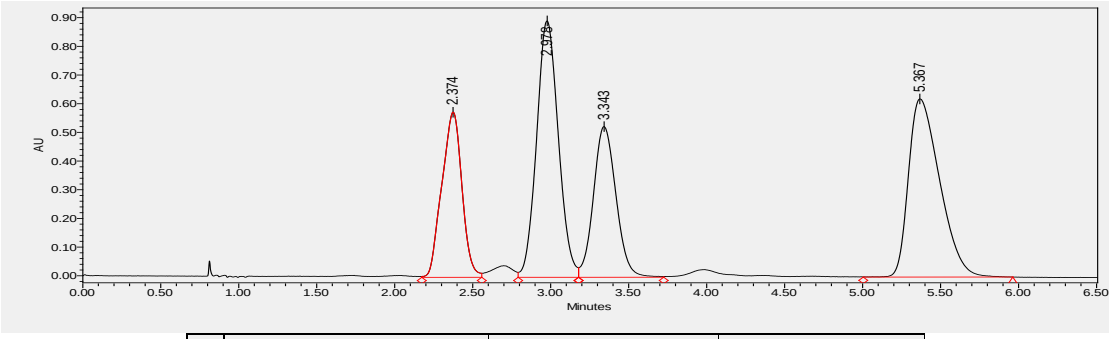
^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.36 – 7.21 (m, 2H), 6.79 (dd, *J* = 9.2, 3.7 Hz, 1H), 4.88 (dd, *J* = 7.8, 6.0 Hz, 1H), 3.98 (d, *J* = 2.1 Hz, 3H), 3.73 (s, 3H), 3.15 – 2.84 (m, 2H), 2.82 – 2.54 (m, 2H), 2.43 (tdd, *J* = 13.3, 11.0, 6.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$). δ 186.3, 175.6, 168.8, 156.3 (d *J* = 2.1 Hz), 151.7 (d *J* = 241.1 Hz), 147.3 (d *J* = 12.0 Hz), 124.1 (d *J* = 22.1 Hz), 115.2, 112.6, 84.2, 81.0, 62.0, 53.6, 41.3, 27.7, 22.0.

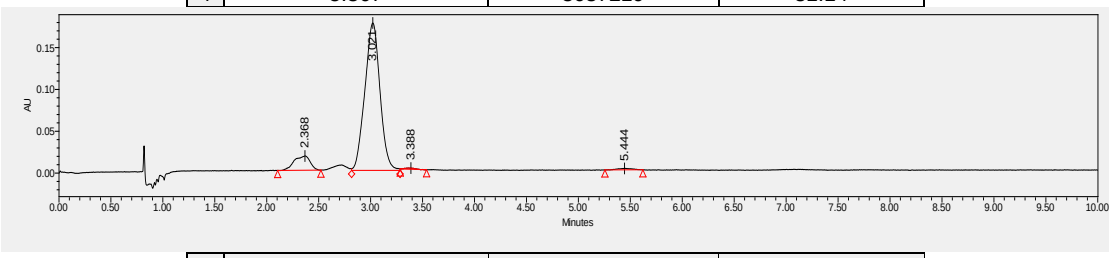
^{19}F NMR (376 MHz, $CDCl_3$) δ -137.57.

ESI-HRMS: calcd for $C_{16}H_{15}FO_6Na^+$ ([M + Na]$^+$) = 361.0694, found 361.0688.

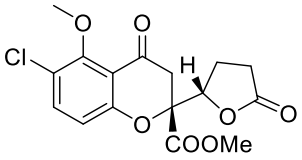
IR (neat): 2922, 1784, 1695, 1613, 1479, 1413, 1266, 1194, 1060, 1038, 941, 820 cm^{-1}.



	Retention Time	Area	% Area
1	2.374	5153119	18.58
2	2.978	8669811	31.26
3	3.343	5277378	19.03
4	5.367	8637219	31.14



	Retention Time	Area	% Area
1	2.368	183528	9.20
2	3.021	1784765	89.50
3	3.388	9350	0.47
4	5.444	16531	0.83



3p

3p: methyl (R)-6-bromo-5-methoxy-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3p** was isolated in 36% yield (12.7 mg) and 98% ee/94% ee, 5:1 dr. $[\alpha]^{25}_{D}$ = 20.6 (*c* = 0.248 in $CHCl_3$).

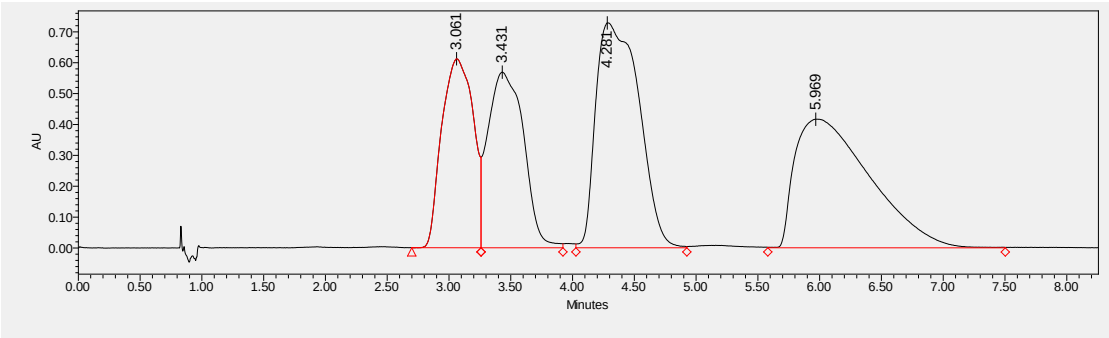
UPC² (chiral AS-3 column), CO_2/MeOH = 95/5, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 4.3 min, t_2 = 6.4 min; (minor isomer) t_1 = 3.0 min, t_2 = 3.4 min .

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 9.2 Hz, 1H), 6.85 (dd, *J* = 33.2, 9.0 Hz, 1H), 4.96 – 4.86 (m, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.12 – 2.89 (m, 2H), 2.85 – 2.55 (m, 2H), 2.51 – 2.38 (m, 2H).

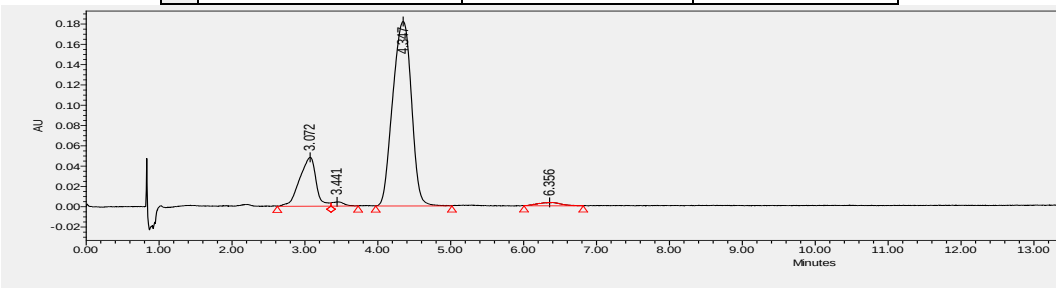
^{13}C NMR (151 MHz, Chloroform-*d*) δ 175.5, 168.6, 159.3, 155.9, 136.8, 122.6, 116.0, 114.7, 114.5, 84.3, 80.8, 53.7, 61.6, 41.1, 27.7, 22.0.

ESI-HRMS: calcd for $C_{16}H_{15}ClO_6Na^+$ ([M + Na]$^+$) = 377.0399 and 379.0369, found 377.0394 and 379.0363.

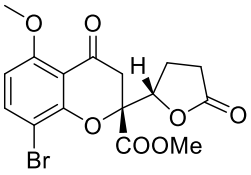
IR (neat): 2921, 2851, 1786, 1756, 1697, 1592, 1462, 1442, 1399, 1319, 1198, 1132, 1508, 1035, 818, 766 cm^{-1}.



	Retention Time	Area	% Area
1	3.061	10844636	18.81
2	3.431	11437420	19.83
3	4.281	17722649	30.73
4	5.969	17659168	30.62



	Retention Time	Area	% Area
1	3.072	750697	18.27
2	3.441	46964	1.14
3	4.347	3235834	78.75
4	6.356	75287	1.83



3q

3q: methyl (R)-8-bromo-5-methoxy-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3q** was isolated in 59% yield (23.3 mg) and >99% ee, >19:1 dr. $[\alpha]_D^{25}$ = 37.0 (*c* = 0.30 in $CHCl_3$). M.p.= 148.1-150.2 °C

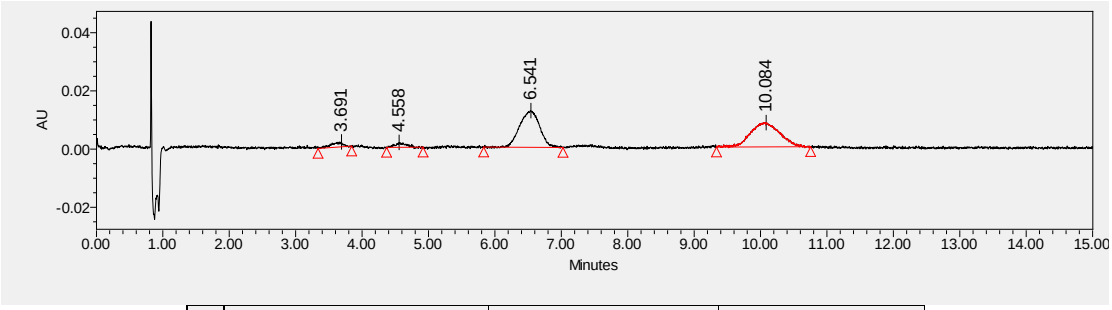
UPC² (chiral IC-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 6.5 min, t_2 = 3.8 min; (minor isomer) t_1 = 4.2 min, t_2 = 3.5 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.67 (d, *J* = 9.0 Hz, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 4.92 (dd, *J* = 7.2, 4.7 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H), 3.17 – 2.83 (m, 3H), 2.67 – 2.40 (m, 3H).

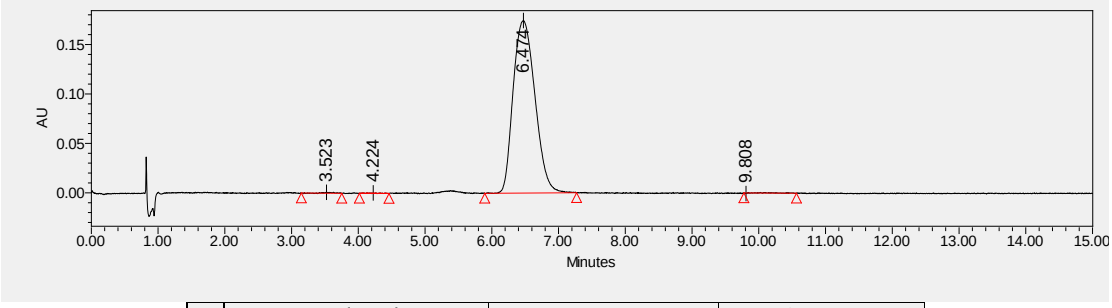
^{13}C NMR (101 MHz, Chloroform-*d*) δ 185.8, 168.3, 159.8, 157.3, 139.5, 111.8, 106.0, 102.2, 85.4, 80.8, 56.4, 53.6, 41.5, 27.6, 22.0.

ESI-HRMS: calcd for $C_{16}H_{15}BrO_6Na^+$ ([M + Na]$^+$) = 420.9893 and 422.9873, found 420.9889 and 422.9867.

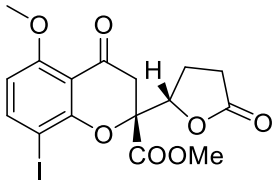
IR (neat): 2923, 1784, 1768, 1690, 1589, 1565, 1473, 1407, 1317, 1251, 1184, 1117, 1049, 836, 805, 753 cm^{-1}.



	Retention Time	Area	% Area
1	3.691	20661	3.69
2	4.558	19317	3.45
3	6.541	264164	47.16
4	10.084	255960	45.70



	Retention Time	Area	% Area
1	3.523	12100	0.30
2	4.224	5151	0.13
3	6.474	3961999	99.36
4	9.808	8178	0.21



3r

3r: methyl (R)-8-iodo-5-methoxy-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3r** was isolated in 69% yield (30.7 mg) and >99% ee, >19:1 dr. $[\alpha]_D^{25}$ = 34.3 (*c* = 0.51 in $CHCl_3$). M.p.= 148.1-150.2 °C

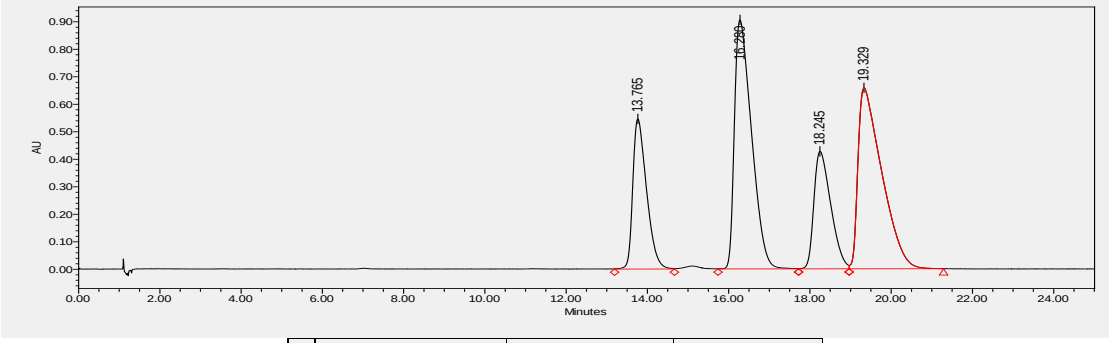
UPC² (chiral AS-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 16.1 min, t_2 = 19.4 min; (minor isomer) t_1 = 13.6 min, t_2 = 18.1 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.87 (d, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 8.9 Hz, 1H), 4.92 (dd, *J* = 8.0, 4.3 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H), 3.18 – 2.86 (m, 3H), 2.65 – 2.41 (m, 3H).

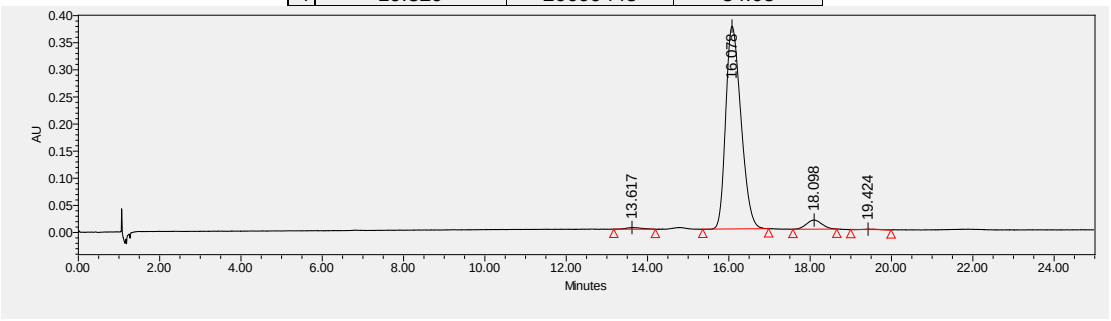
^{13}C NMR (101 MHz, Chloroform-*d*) δ 186.0, 175.8, 168.3, 160.8, 159.6, 145.5, 111.6, 107.3, 85.4, 80.8, 74.2, 56.4, 53.6, 41.4, 27.9, 21.9.

ESI-HRMS: calcd for $C_{16}H_{16}IO_6^+$ ([M + H]$^+$) = 446.9939, found 446.9925.

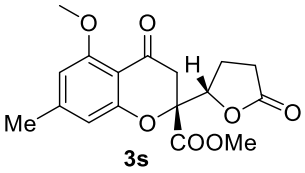
IR (neat): 2923, 2852, 1781, 1757, 1687, 1582, 1558, 1469, 1436, 1400, 1306, 1253, 1182, 1117, 1094, 1049, 803, 734 cm^{-1}.



	Retention Time	Area	% Area
1	13.765	12842818	16.38
2	16.280	26541284	33.85
3	18.245	12327924	15.72
4	19.329	26699445	34.05



	Retention Time	Area	% Area
1	13.617	78360	0.76
2	16.078	9739434	94.73
3	18.098	445324	4.33
4	19.424	17978	0.17



3s

3s: methyl (R)-5-methoxy-7-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3s** was isolated in 32% yield (10.7 mg) and >99% ee, >19:1 dr. $[\alpha]^{25}_{D}$ = 25.6 (*c* = 0.164 in $CHCl_3$). M.p.= 170.3-174.2 °C

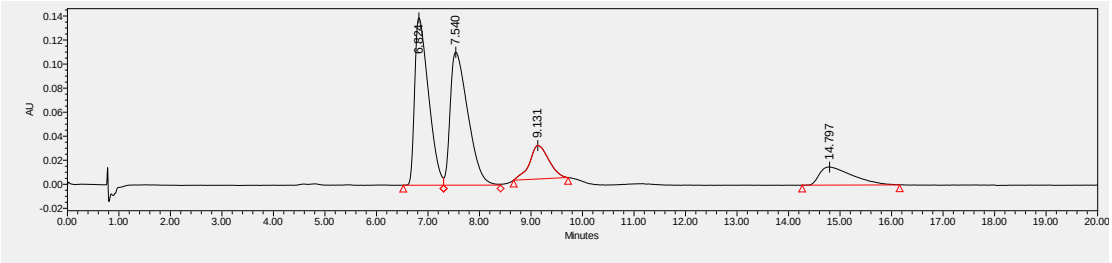
UPC² (chiral IA-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 9.2 min, t_2 = 14.3 min.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.54 (s, 1H), 6.37 (s, 1H), 4.86 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 3.09 – 2.81 (m, 2H), 2.66 (dddd, *J* = 84.2, 17.9, 10.2, 6.6 Hz, 2H), 2.51 – 2.37 (m, 2H), 2.35 (s, 3H).

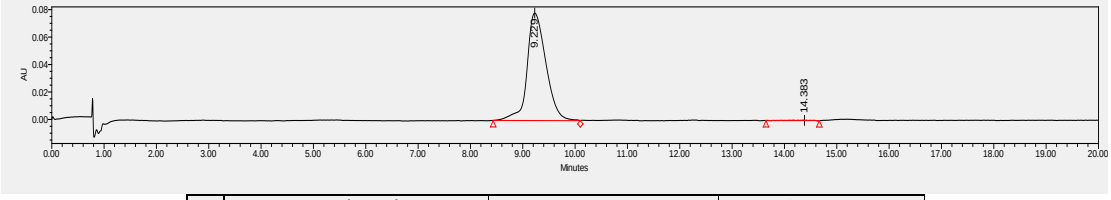
^{13}C NMR (100 MHz, $CDCl_3$). δ 186.1, 175.8, 169.0, 161.2, 160.4, 148.8, 110.6, 105.9, 83.9, 81.13, 56.2, 53.5, 41.3, 27.7, 22.6, 22.0.

ESI-HRMS: calcd for $C_{17}H_{18}O_7Na^+$ ([M + Na]$^+$) = 337.0945, found 337.0938.

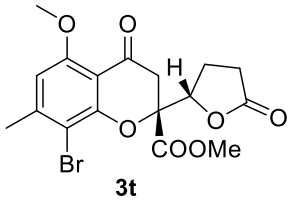
IR (neat): 2921, 1785, 1739, 1681, 1656, 1616, 1566, 1464, 1348, 1259, 1225, 1196, 1071, 1051, 833, 753 cm^{-1}.



	Retention Time	Area	% Area
1	6.824	2593406	39.06
2	7.540	2645287	39.84
3	9.131	728688	10.98
4	14.797	671574	10.12



	Retention Time	Area	% Area
1	9.229	1962482	99.76
2	14.383	4705	0.24



3t

3t: methyl (R)-8-bromo-5-methoxy-7-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3t** was isolated in 68% yield (27.8 mg) and >99% ee, >19:1 dr. $[\alpha]_D^{25}$ = 5.8 (*c* = 0.204 in $CHCl_3$). M.p.= 143.2-145.7 °C

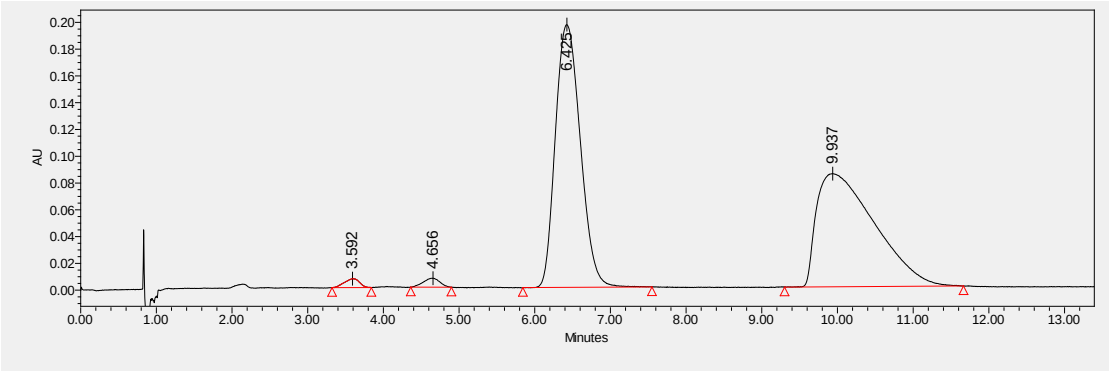
UPC² (chiral AS-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 6.3 min, t_2 = 9.3 min; (minor isomer) t_1 = 3.5 min, t_2 = 4.2 min .

^{1}H NMR (400 MHz, Chloroform-*d*). δ 6.51 (s, 1H), 4.91 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.16 – 2.85 (m, 3H), 2.65 – 2.38 (m, 6H).

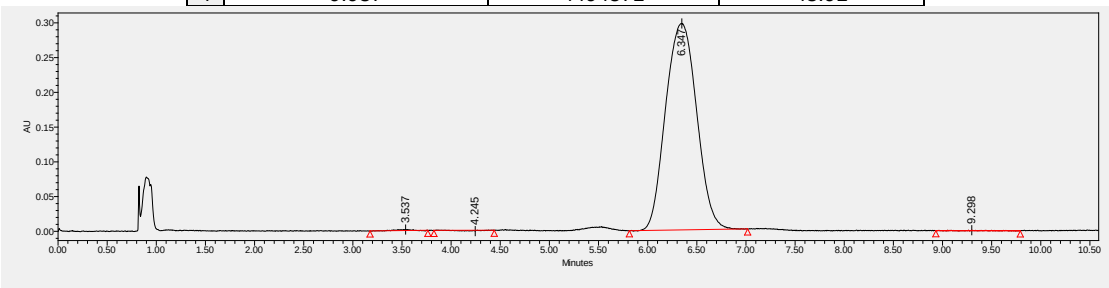
^{13}C NMR (100 MHz, $CDCl_3$). δ 185.7, 175.9, 168.4, 159.0, 157.3, 148.1, 109.8, 107.2, 104.9, 85.4, 81.2, 56.3, 53.6, 41.3, 27.6, 24.5, 22.1.

ESI-HRMS: calcd for $C_{17}H_{17}BrO_7Na^+$ ([M + Na]$^+$) = 435.0050 and 437.0029, found 435.0047 and 437.0020.

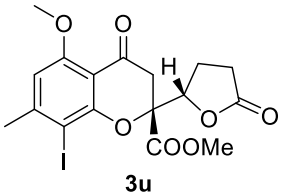
IR (neat): 2922, 1784, 1686, 1598, 1547, 1464, 1392, 1343, 1258, 1131, 1076, 1053, 821, 752 cm^{-1}.



	Retention Time	Area	% Area
1	3.592	91734	1.00
2	4.656	101088	1.10
3	6.425	4501214	48.99
4	9.937	4494571	48.91



	Retention Time	Area	% Area
1	3.537	17968	0.27
2	4.245	13764	0.21
3	6.347	6527303	99.33
4	9.298	12003	0.18



3u

3u: methyl (R)-8-iodo-5-methoxy-7-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3u** was isolated in 69% yield (31.4 mg) and 99% ee, >19:1 dr. $[\alpha]^{25}_{D}$ = –6.1 (*c* = 0.62 in $CHCl_3$). M.p.= 185.1-189.2 °C

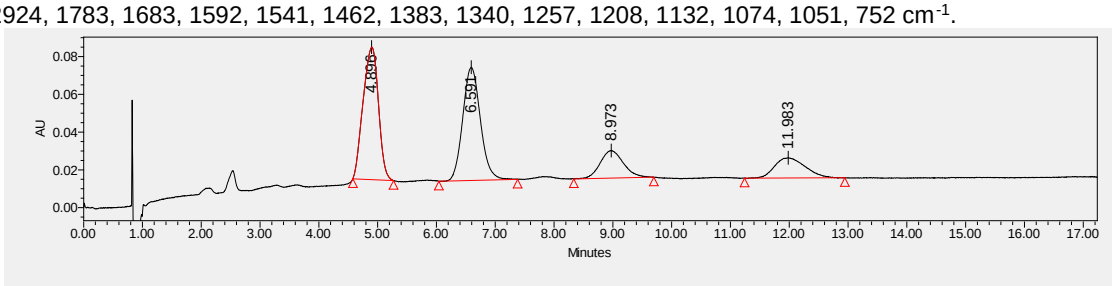
UPC² (chiral AD-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 8.4 min; t_2 = 11.1 min; (minor isomer) t_1 = 6.2 min, t_2 = 4.8 min.

^{1}H NMR (400 MHz, Chloroform-*d*). δ 6.58 (s, 1H), 4.91 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 3.19 – 2.80 (m, 3H), 2.69 – 2.41 (m, 6H).

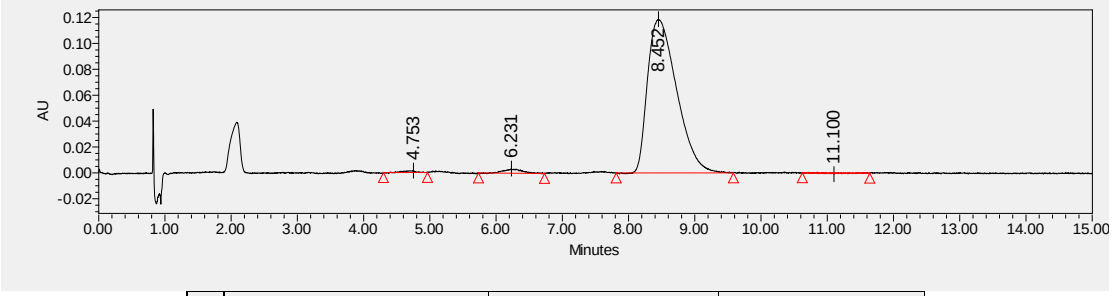
^{13}C NMR (100 MHz, $CDCl_3$). δ 185.8, 175.9, 168. 5, 160.2, 159.6, 151.8, 109.3, 107.1, 85.4, 81.5, 81.0, 56.3, 53.6, 41.2, 29.8, 28.0, 21.9.

ESI-HRMS: calcd for $C_{17}H_{17}IO_7Na^+$ ([M + Na]$^+$) = 482.9911 and 483.9945, found 482.9905 and 483.9939.

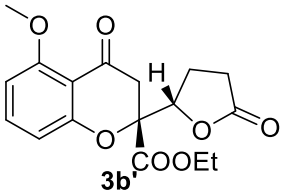
IR (neat):2924, 1783, 1683, 1592, 1541, 1462, 1383, 1340, 1257, 1208, 1132, 1074, 1051, 752 cm^{-1}.



	Retention Time	Area	% Area
1	3.592	91734	1.00
2	4.656	101088	1.10
3	6.425	4501214	48.99
4	9.937	4494571	48.91



	Retention Time	Area	% Area
1	4.753	19501	0.52
2	6.231	64263	1.73
3	8.452	3627230	97.38
4	11.100	13940	0.37



3b

3b': methyl (R)-8-iodo-5-methoxy-7-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate

Following the typical procedure, colourless oil **3b'** was isolated in 38% yield (12.5 mg) >99% ee, >19:1 dr. $[\alpha]^{25}_{D}$ = 89.6 (*c* = 0.23 in $CHCl_3$).

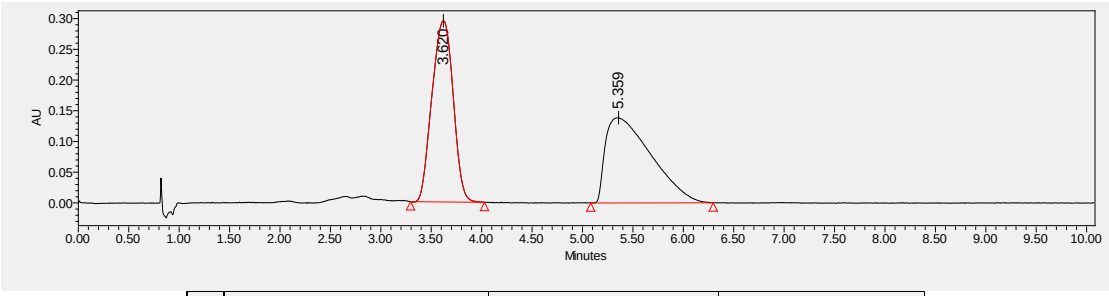
UPC² (chiral OX-3 column), CO_2/MeOH = 93/7, flow rate 1.5 mL/min, λ = 254 nm, retention time: (major isomer) t_1 = 3.5 min, t_2 = 5.3 min;

^{1}H NMR (400 MHz, Chloroform-*d*). δ 7.44 (t, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 4.88 (dd, *J* = 8.0, 5.7 Hz, 1H), 4.28 – 4.05 (m, 2H), 3.90 (s, 3H), 3.18 – 2.81 (m, 2H), 2.81 – 2.53 (m, 2H), 2.43 (dddd, *J* = 23.3, 18.1, 13.1, 6.8 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

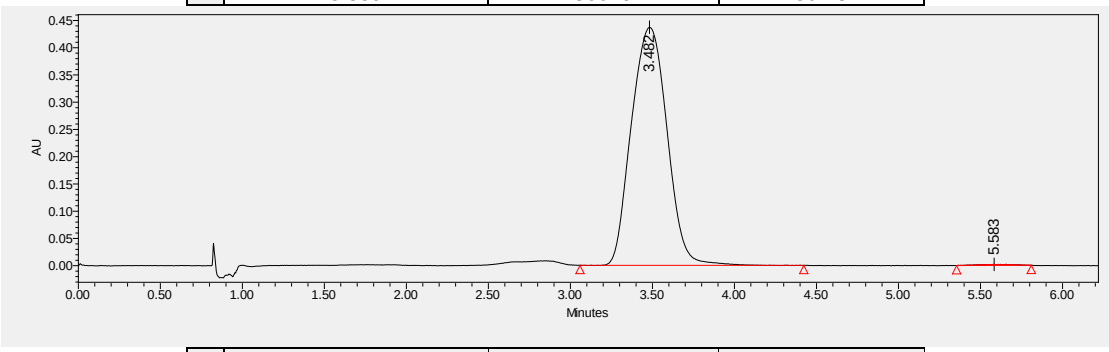
^{13}C NMR (100 MHz, $CDCl_3$). δ 186.5, 175.7, 168.3, 161.4, 160.5, 136.7, 110.1, 104.7, 83.9, 81.1, 62.7, 56.2, 41.5, 27.7, 13.9.

ESI-HRMS: calcd for $C_{17}H_{18}O_7Na^+$ ([M + Na]$^+$) = 367.0945, found 357.0938.

IR (neat): 2922, 1783, 1753, 1688, 1603, 1577, 1473, 1339, 1259, 1188, 1103, 1078, 1048, 791 cm^{-1}.



	Retention Time	Area	% Area
1	3.620	4318426	49.72
2	5.359	4366254	50.28



	Retention Time	Area	% Area
1	3.482	6613215	99.55
2	5.583	29675	0.45

10. References

[1]: (a) Y. H. Wen, X. Huang, J. L. Huang, Y. Xiong, B. Qin, X. M. Feng, *Synlett* **2005**, 2445; (b) Z. P. Yu, X. H. Liu, Z. H. Dong, M. S. Xie, X. M. Feng, *Angew. Chem. Int. Ed.* **2008**, *47*, 1308; *Angew. Chem*. **2008**, *120*, 1328; (c) X. Zhou, D. J. Shang, Q. Zhang, L. L. Lin, X. H. Liu, X. M. Feng, *Org. Lett.* **2009**, *11*, 1401 and references therein.

[2]: R. Ali, Y. Guan, A. N. Leveille, E. Vaughn, S. Parelkar, P. R. Thompson, A. E. Mattson. *Eur. J. Org. Chem*. **2019**, 6917–6929.

[3] : J. Liu, Z. C. Li, P. Tong, Z. X. Xie, Y. Zhang, Y. Li. *J. Org. Chem.* **2015**, *80*, 1632−1643

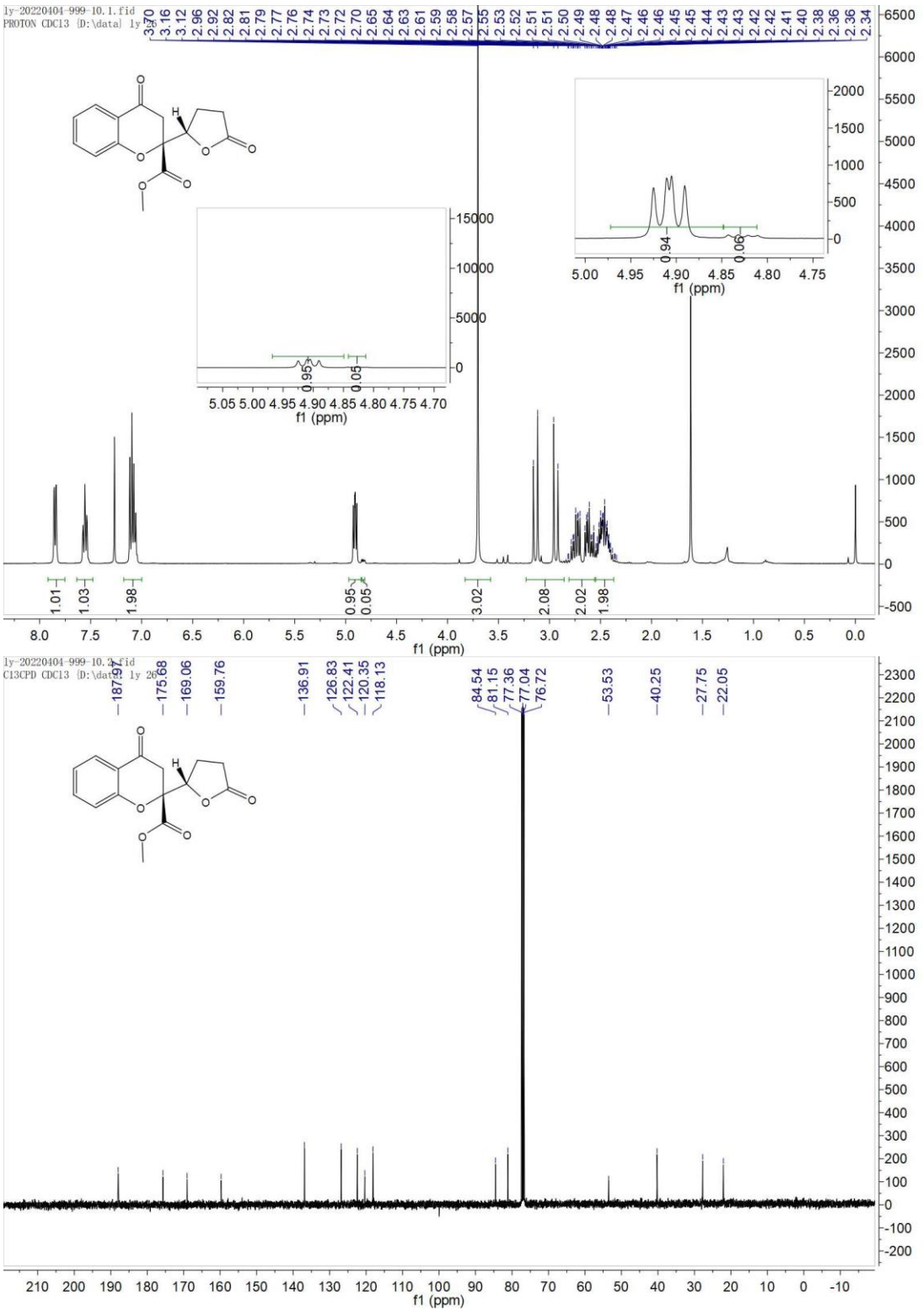
[4] : G. Sudhakar, S.Bayya, V. D. Kadama, J. Babu Nanubolu, *Org. Biomol. Chem*., **2014**, *12*, 5601–5610

[5]: Qin, T.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 1714−1717.

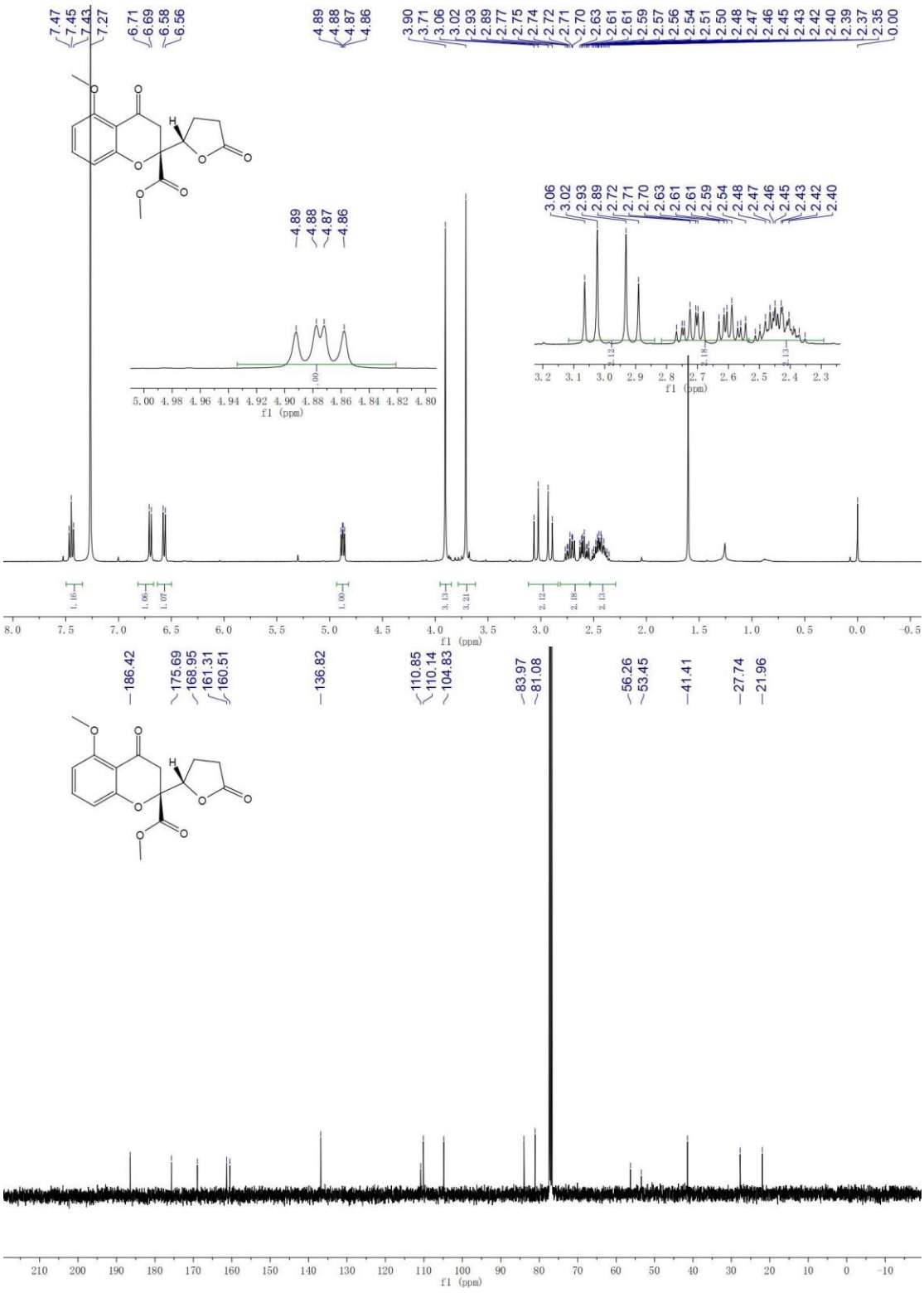
[6]: W. Zhang, K. Krohn, Zia-Ullah, U. Flçrke, G. Pescitelli, L. Di Bari, S. Antus, T. Kurtµn, J. Rheinheimer, S. Draeger, B. Schulz, *Chem. Eur. J.***2008**,14, 4913-4923.

11. Copies of NMR spectra for products.

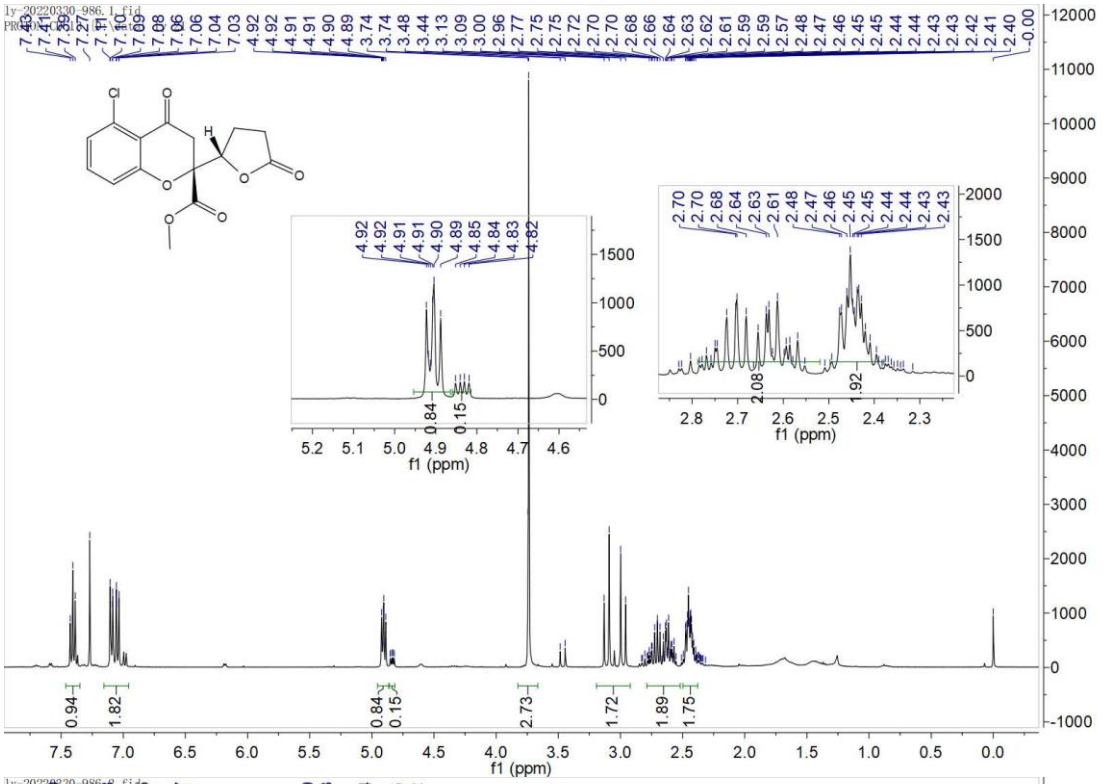
3a

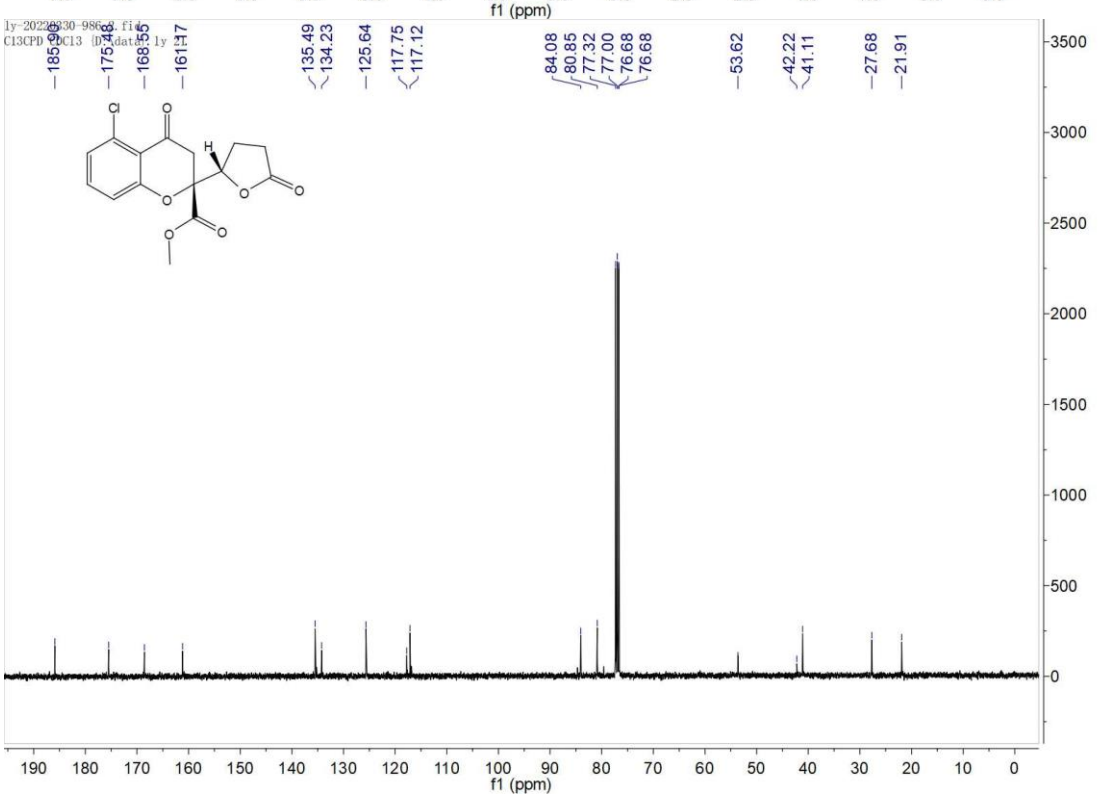


3b

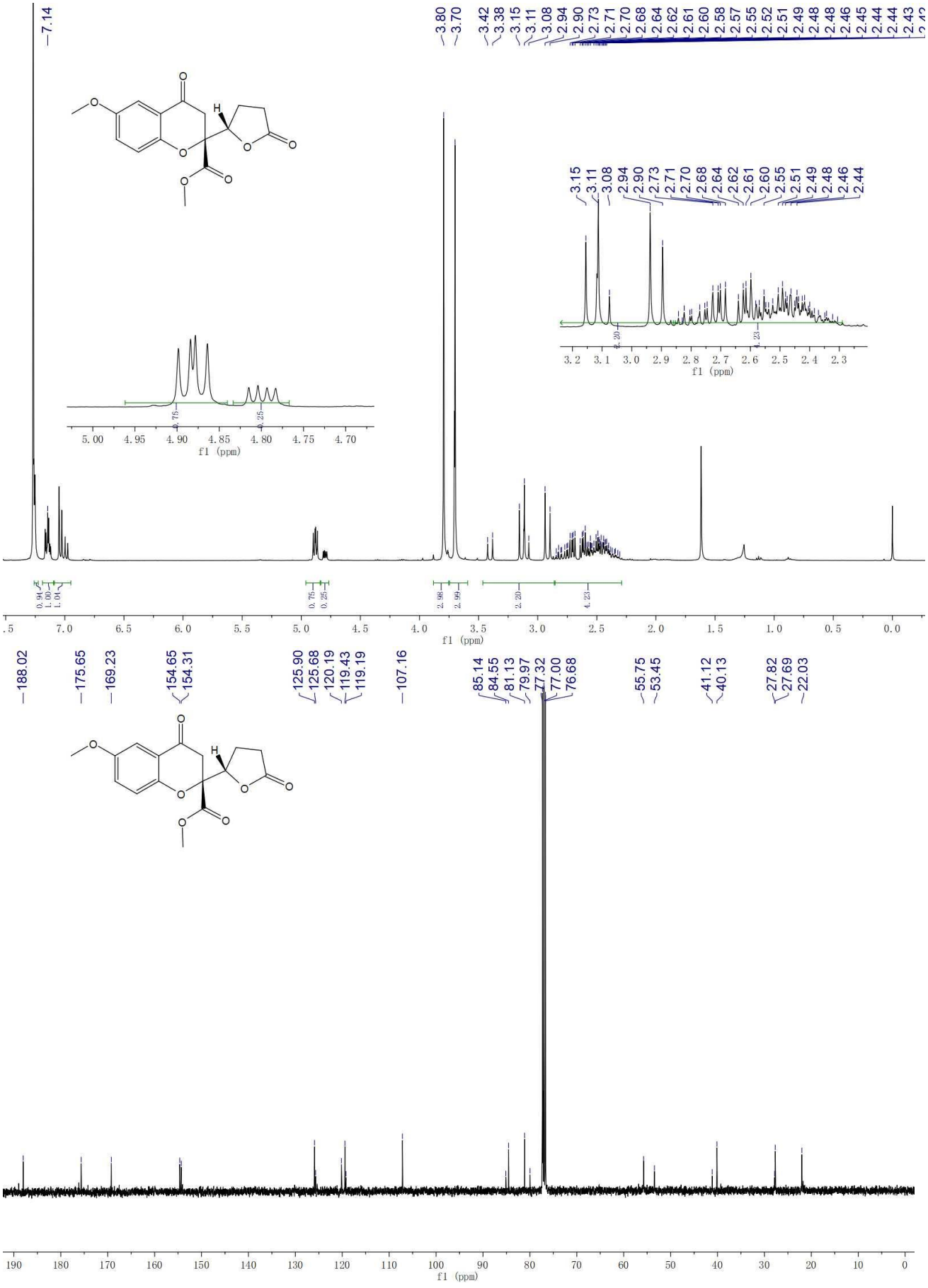

7.47
7.45
7.43
7.27
6.71
6.69
6.58
6.56
4.89
4.88
4.87
4.86
3.90
3.71
3.06
3.02
2.93
2.89
2.77
2.75
2.74
2.72
2.71
2.70
2.63
2.61
2.61
2.59
2.57
2.56
2.54
2.51
2.50
2.48
2.47
2.46
2.45
2.43
2.42
2.40
2.39
2.37
2.35
0.00
f1 (ppm)
186.42
175.69
168.95
161.31
160.51
136.82
110.85
110.14
104.83
83.97
81.08
56.26
53.45
41.41
27.74
21.96
f1 (ppm)

3c

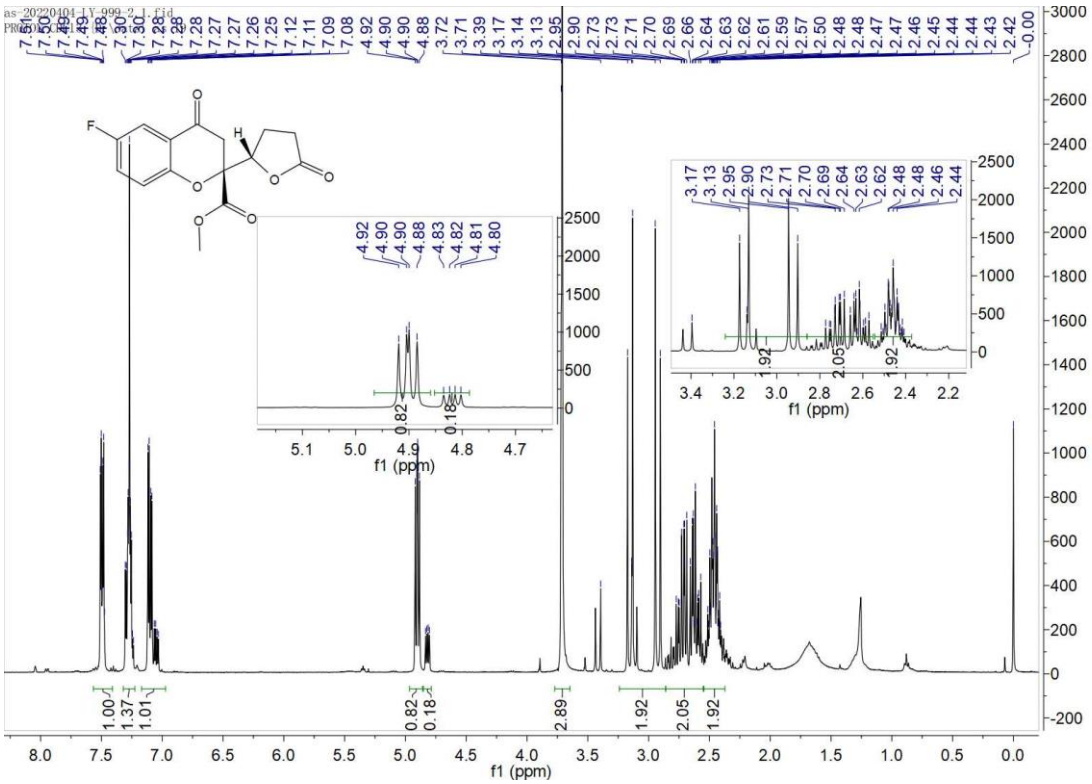


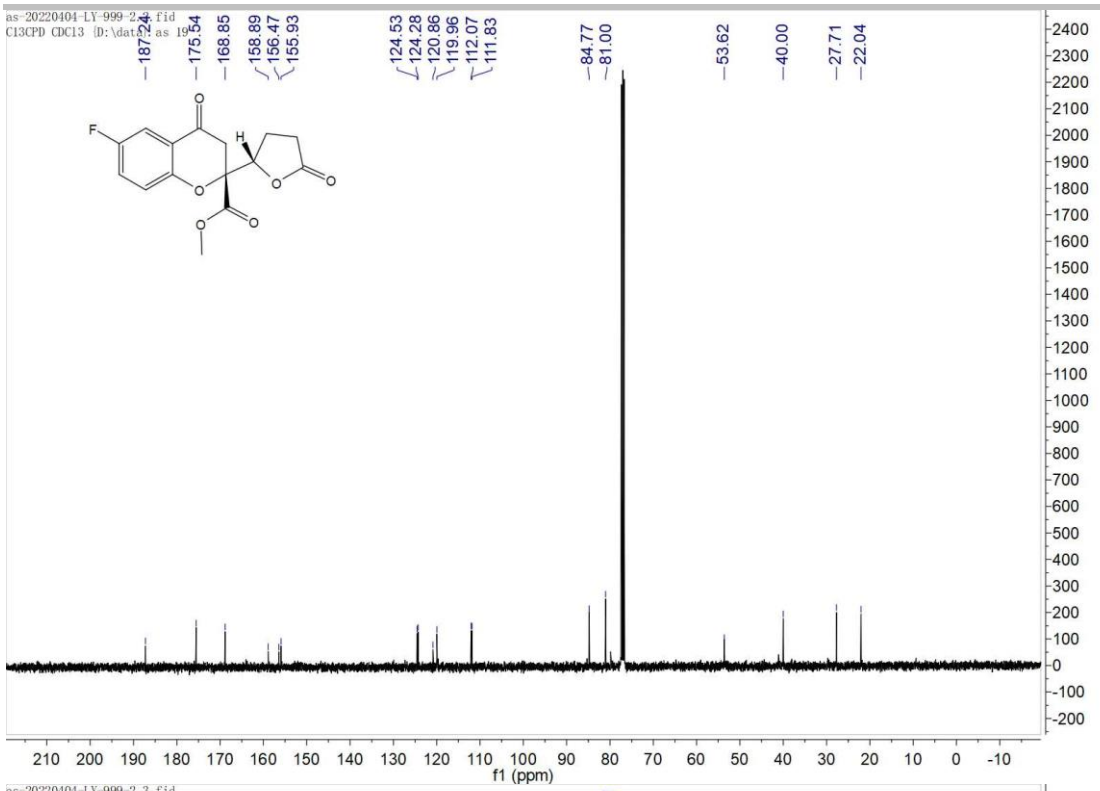


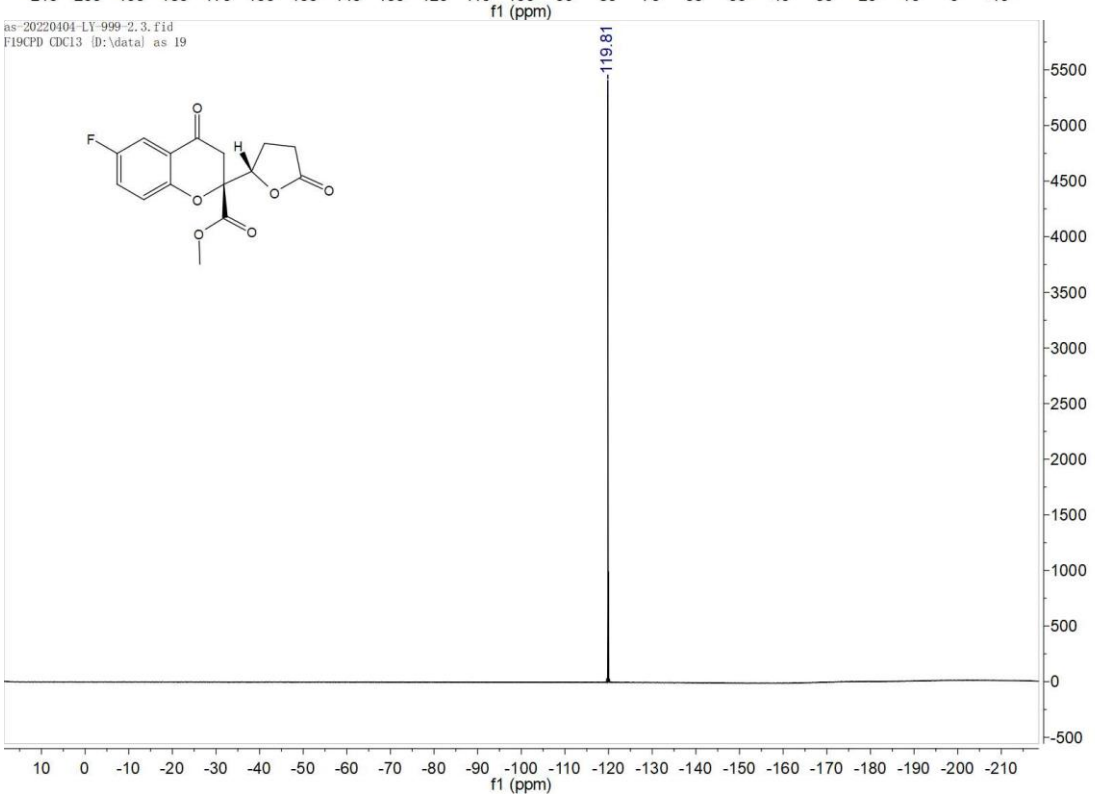
3d


7.14
3.80
3.70
3.42
3.38
3.15
3.11
3.08
2.94
2.90
2.73
2.71
2.70
2.68
2.64
2.62
2.61
2.60
2.58
2.57
2.55
2.52
2.51
2.49
2.48
2.48
2.46
2.45
2.44
2.44
2.43
f1 (ppm)
188.02
175.65
169.23
154.65
154.31
125.90
125.68
120.19
119.43
119.19
107.16
85.14
84.55
81.13
79.97
77.32
77.00
76.68
55.75
53.45
41.12
40.13
27.82
27.69
22.03
f1 (ppm)

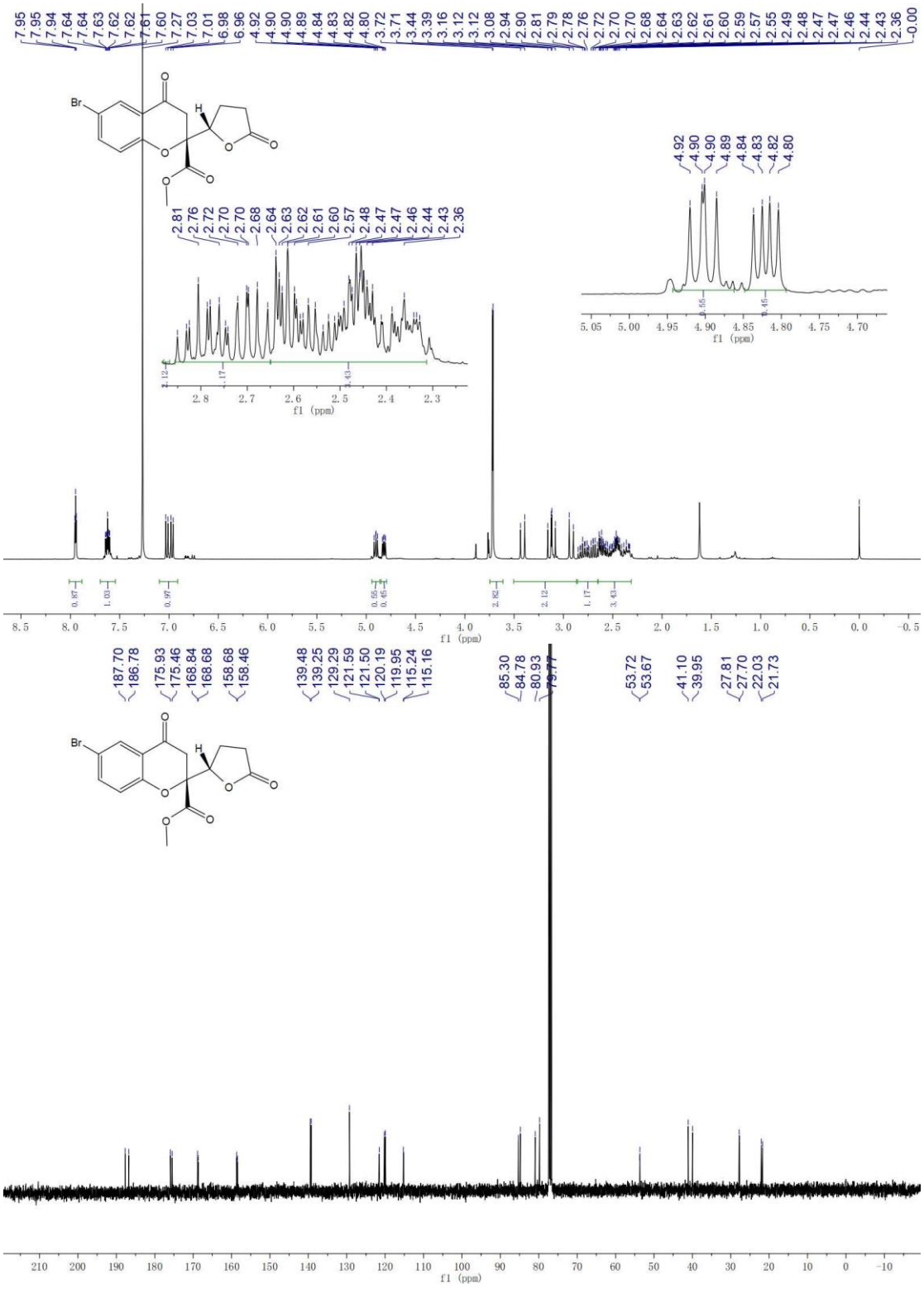
3e



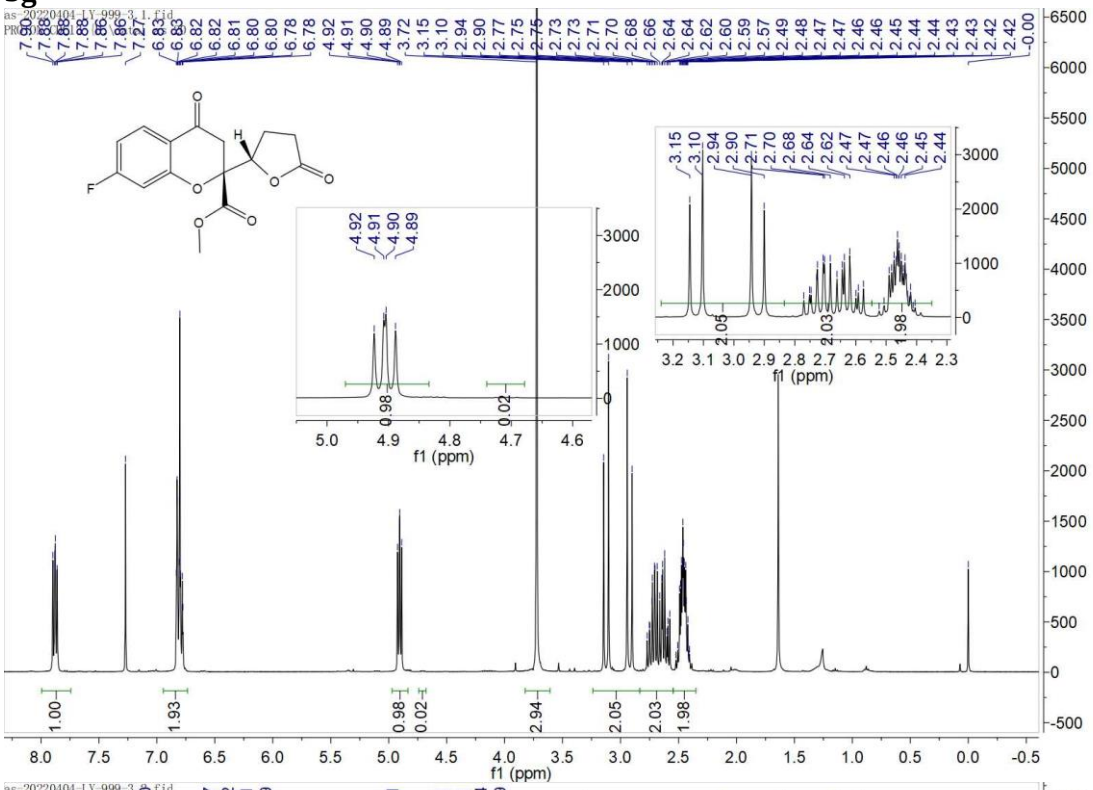

as-20220404-LY-999-2.3.fid
C13CPD CDC13 {D:\data} as 19
187.24
175.54
168.85
158.89
156.47
155.93
124.53
124.28
120.86
119.96
112.07
111.83
84.77
81.00
53.62
40.00
27.71
22.04
F
H
O
f1 (ppm)

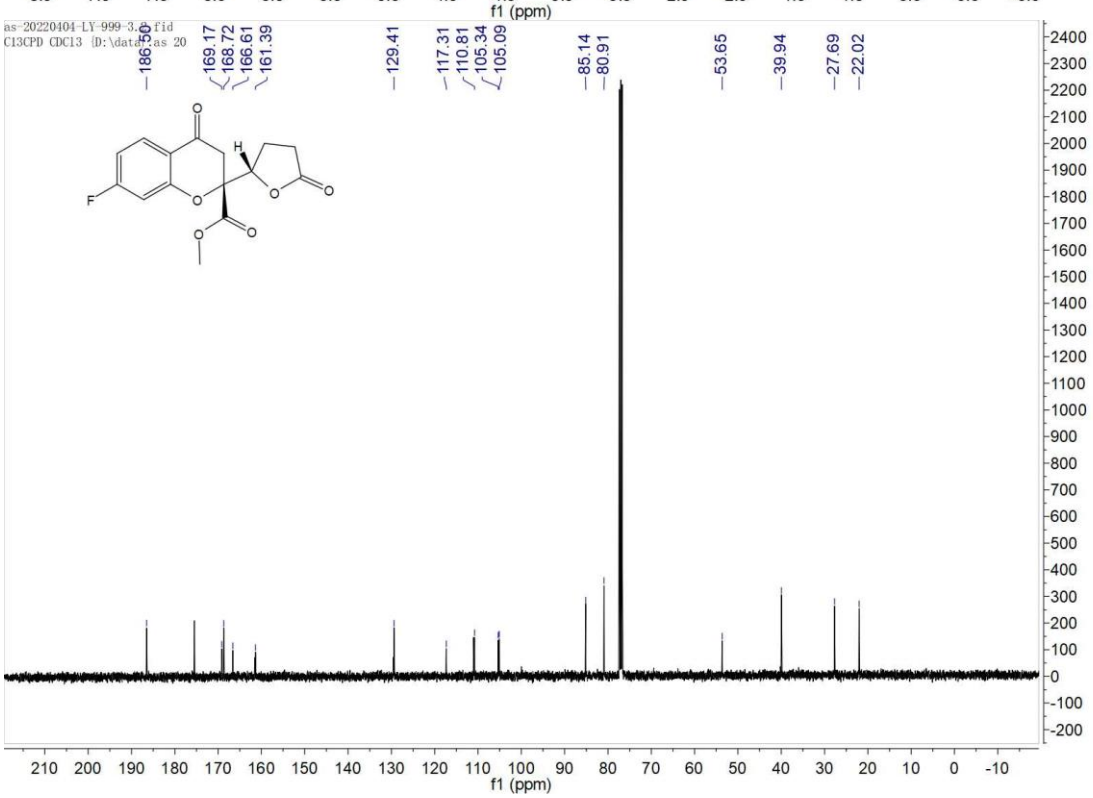

as-20220404-LY-999-2.3.fid
F19CPD CDC13 {D:\data} as 19
119.81
F
H
O
f1 (ppm)

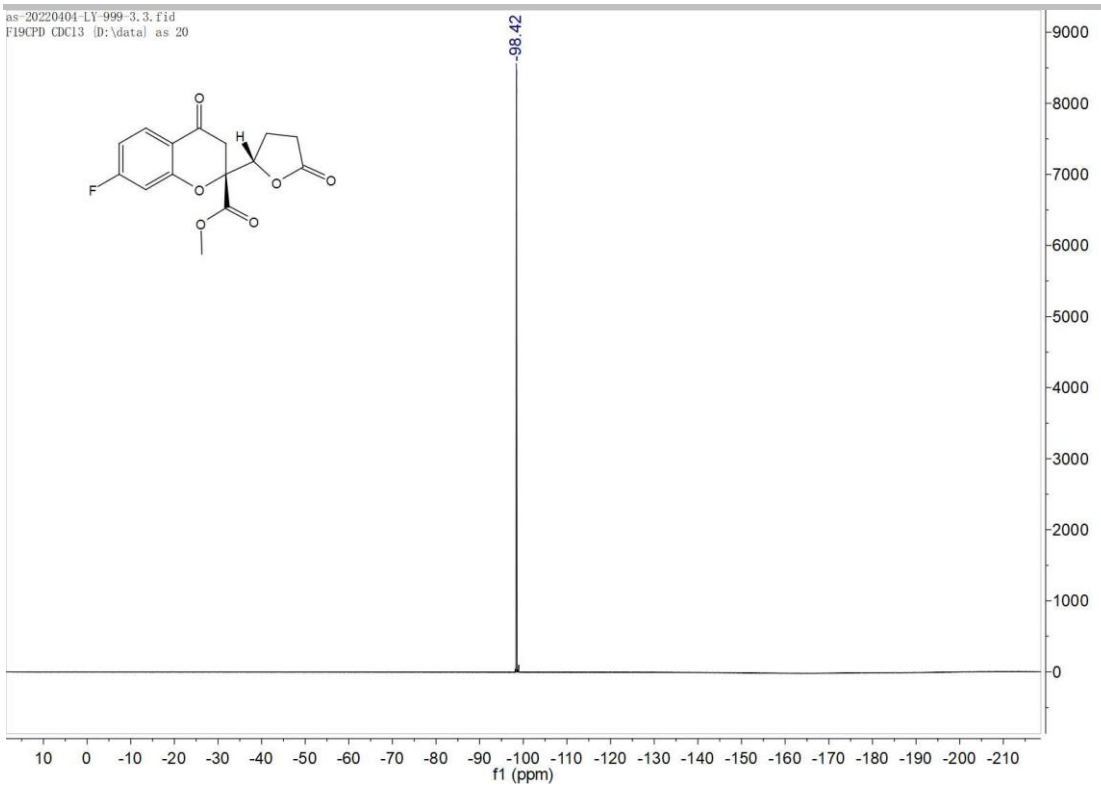
3f



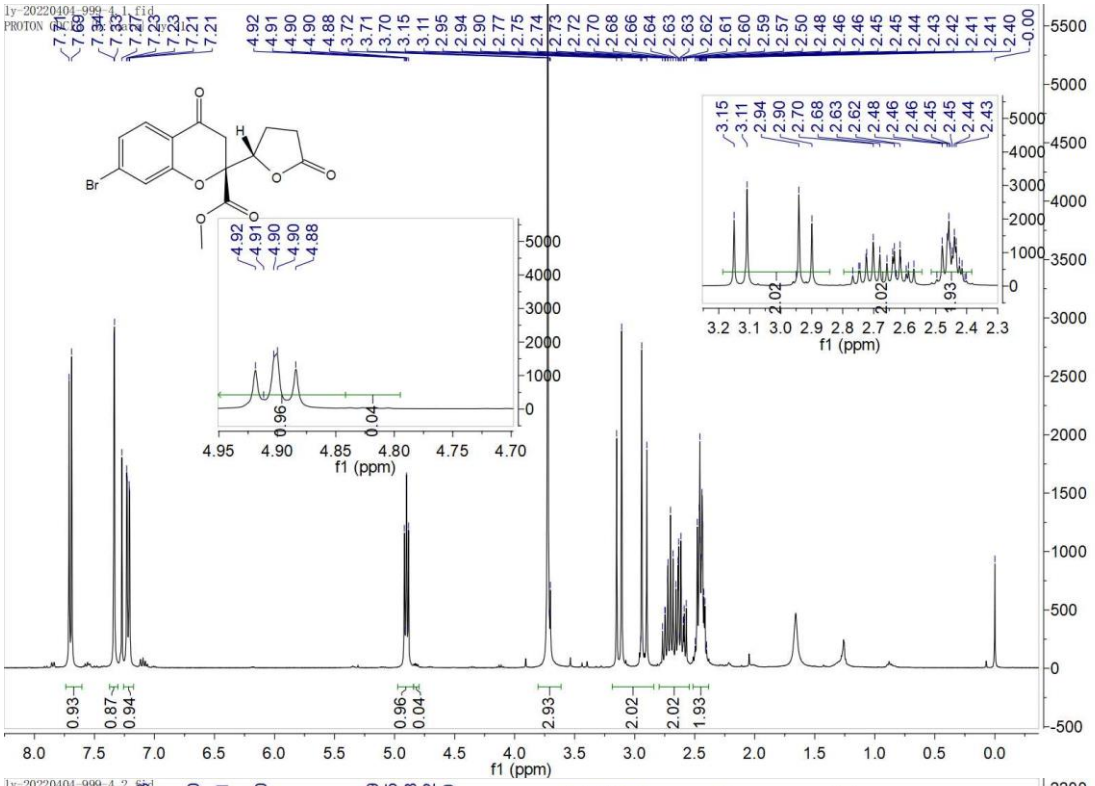
3g

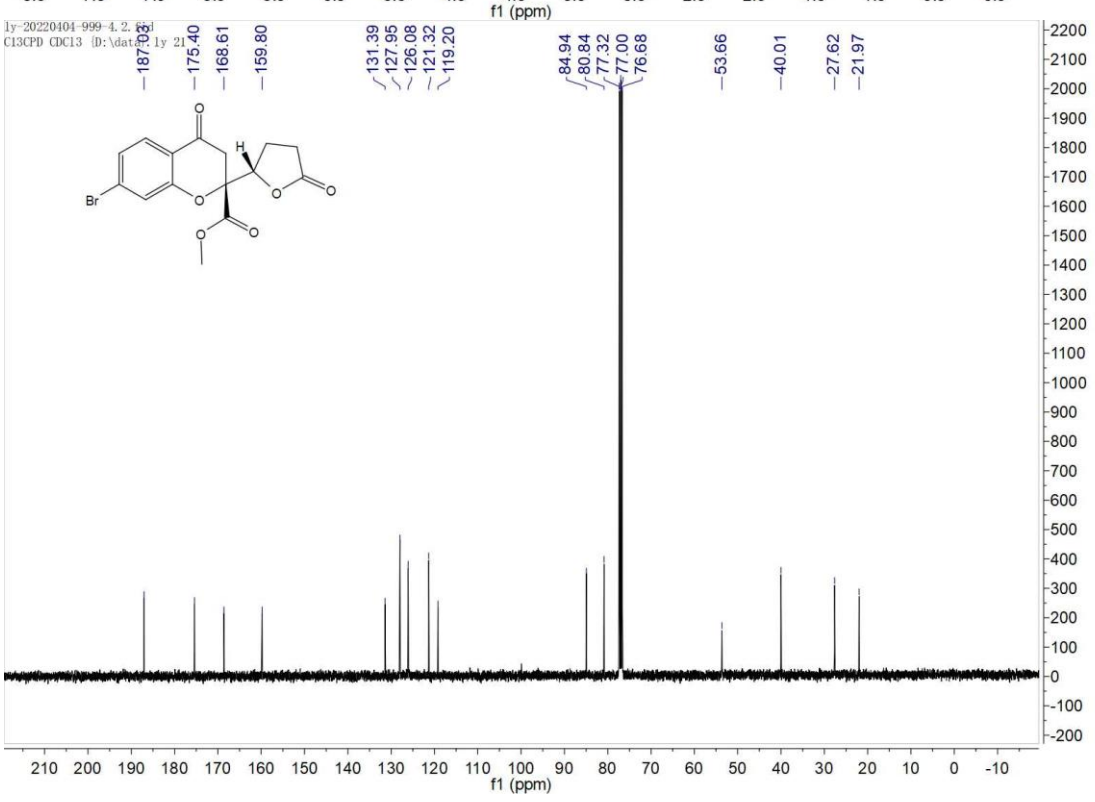




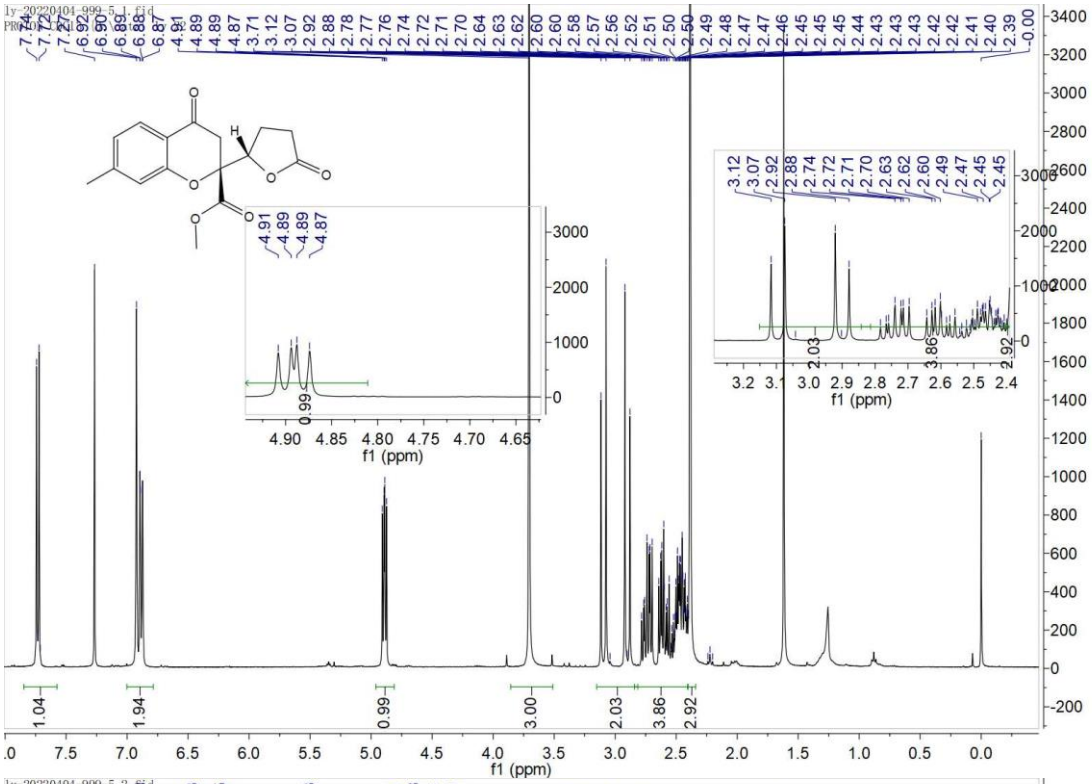

as-20220404-LY-999-3.3.fid
F19CPD CDCl3 (D:\data) as 20
-98.42
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

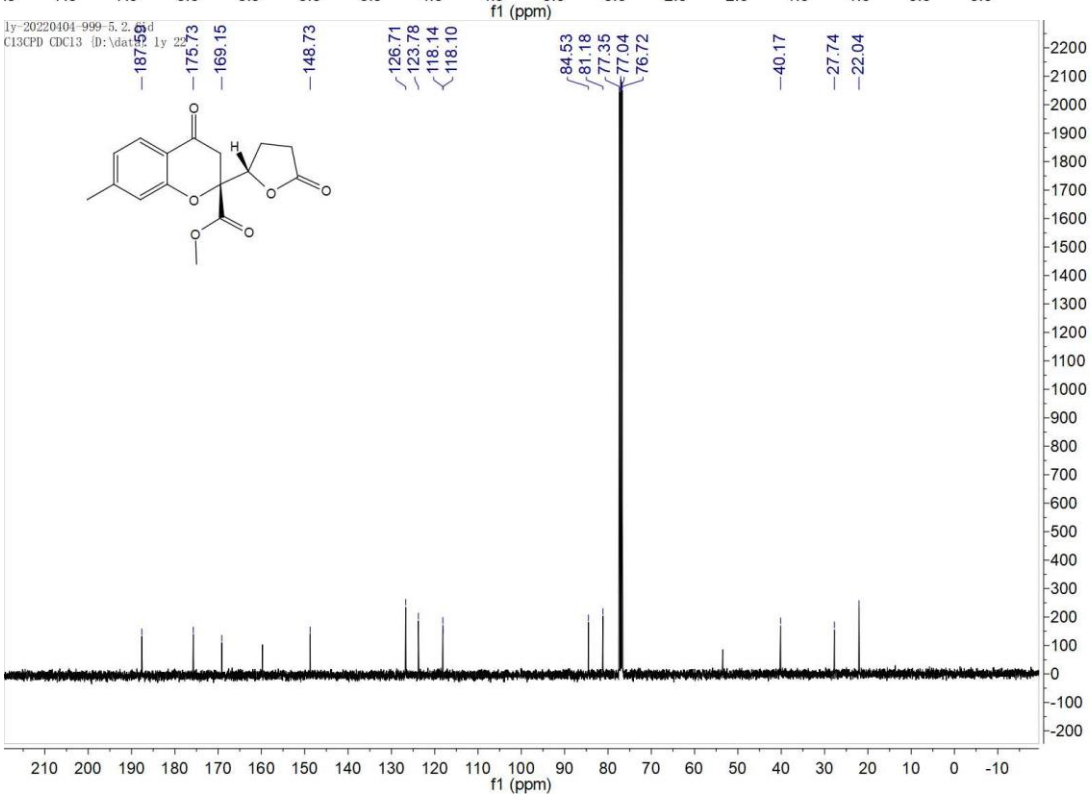
3h



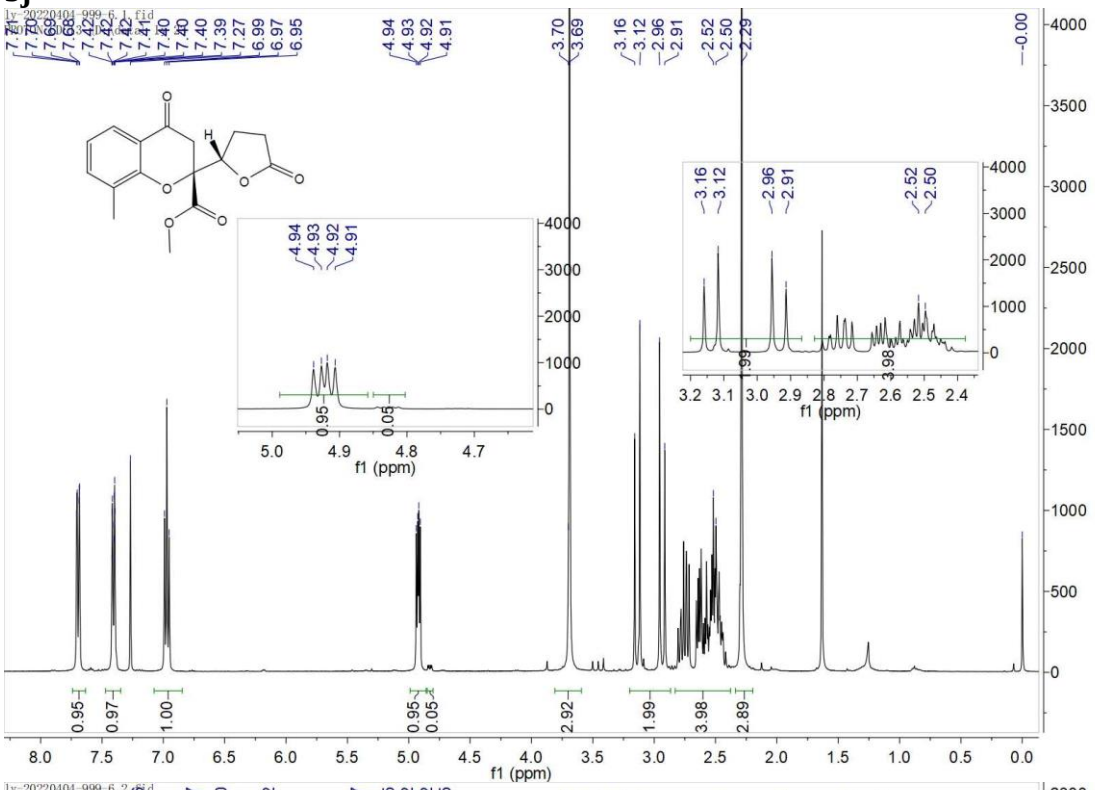


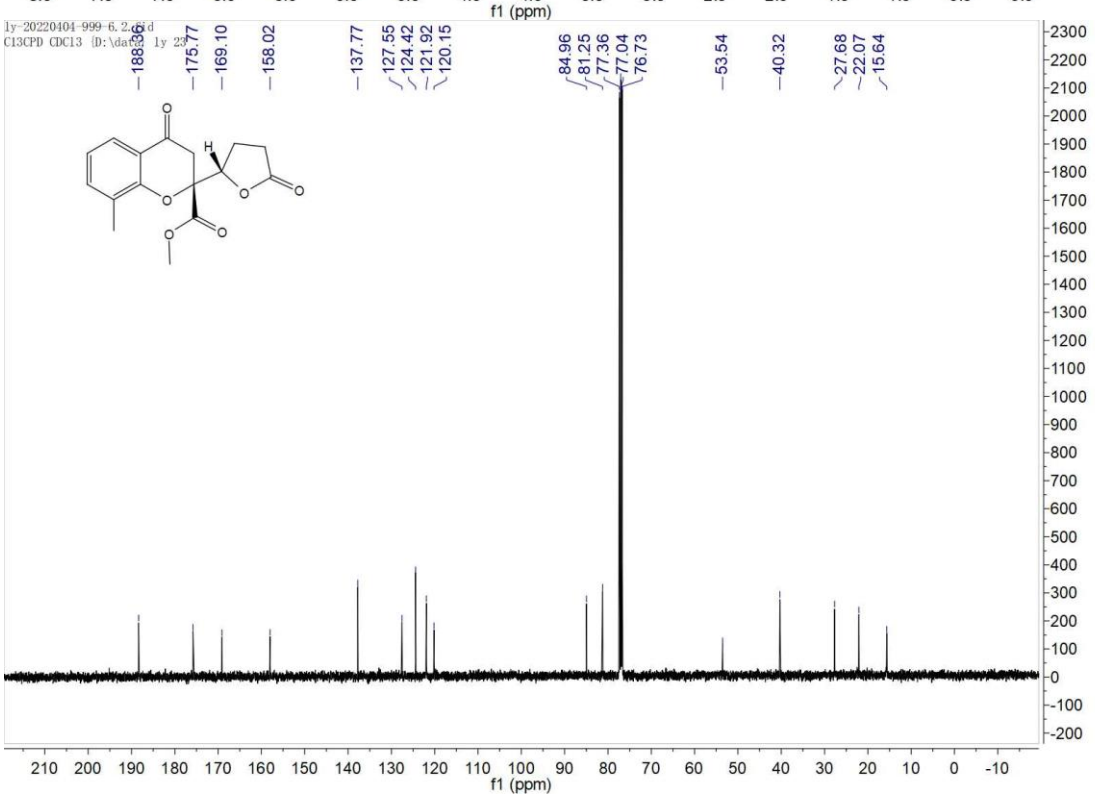
3i



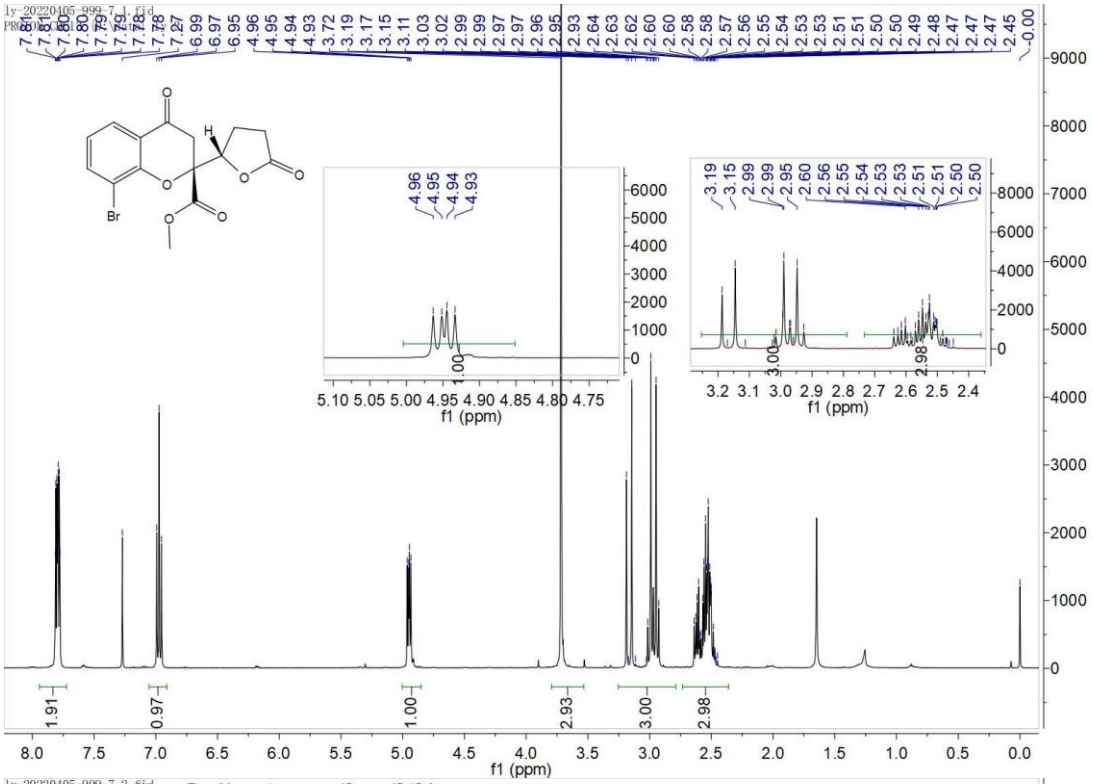


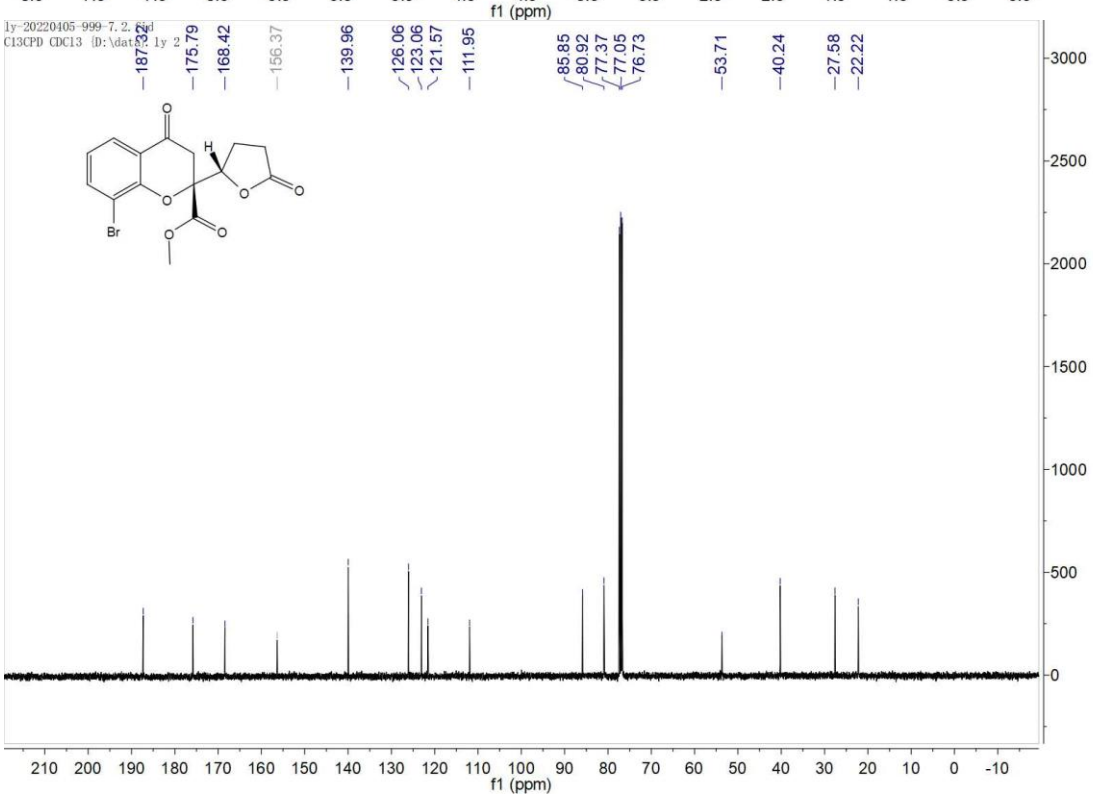
3j


7.71
7.70
7.69
7.68
7.42
7.42
7.41
7.40
7.40
7.40
7.39
7.27
6.99
6.97
6.95
4.94
4.93
4.92
4.91
3.70
3.69
3.16
3.12
2.96
2.91
2.52
2.50
2.29
0.00
0.95
0.97
1.00
0.95
0.05
2.92
1.99
3.98
2.89
f1 (ppm)

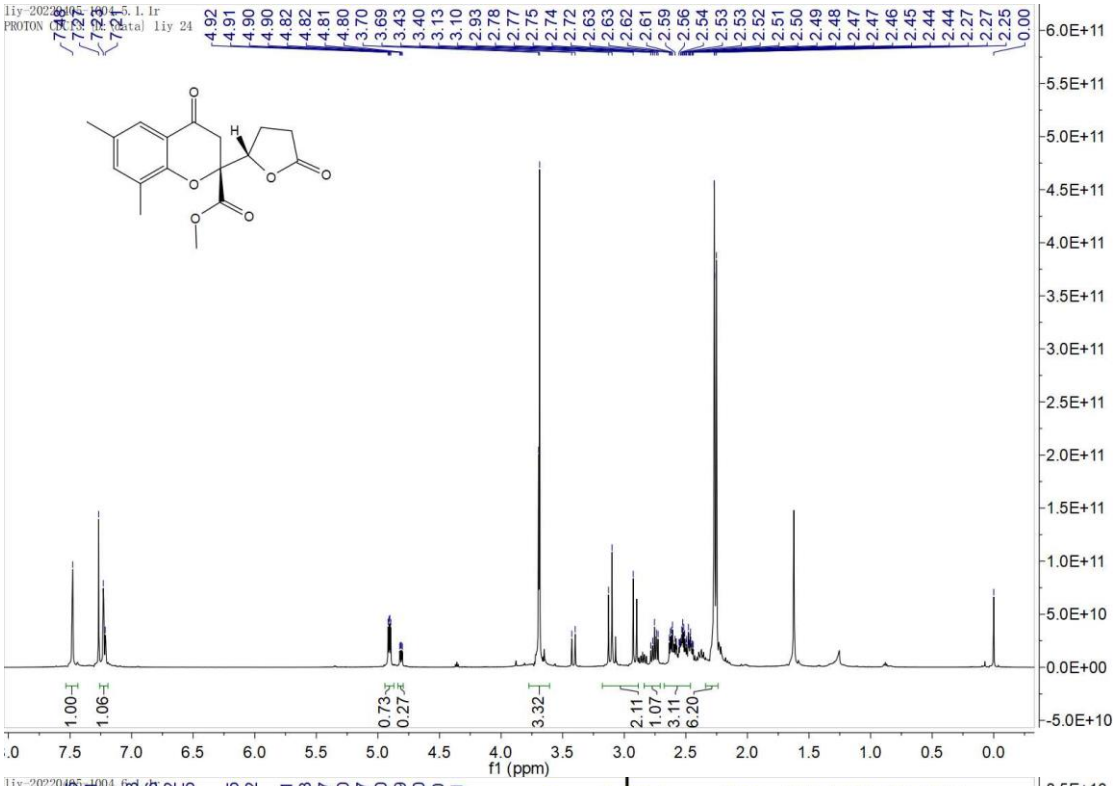

188.36
175.77
169.10
158.02
137.77
127.55
124.42
121.92
120.15
84.96
81.25
77.36
77.04
76.73
53.54
40.32
27.68
22.07
15.64
f1 (ppm)

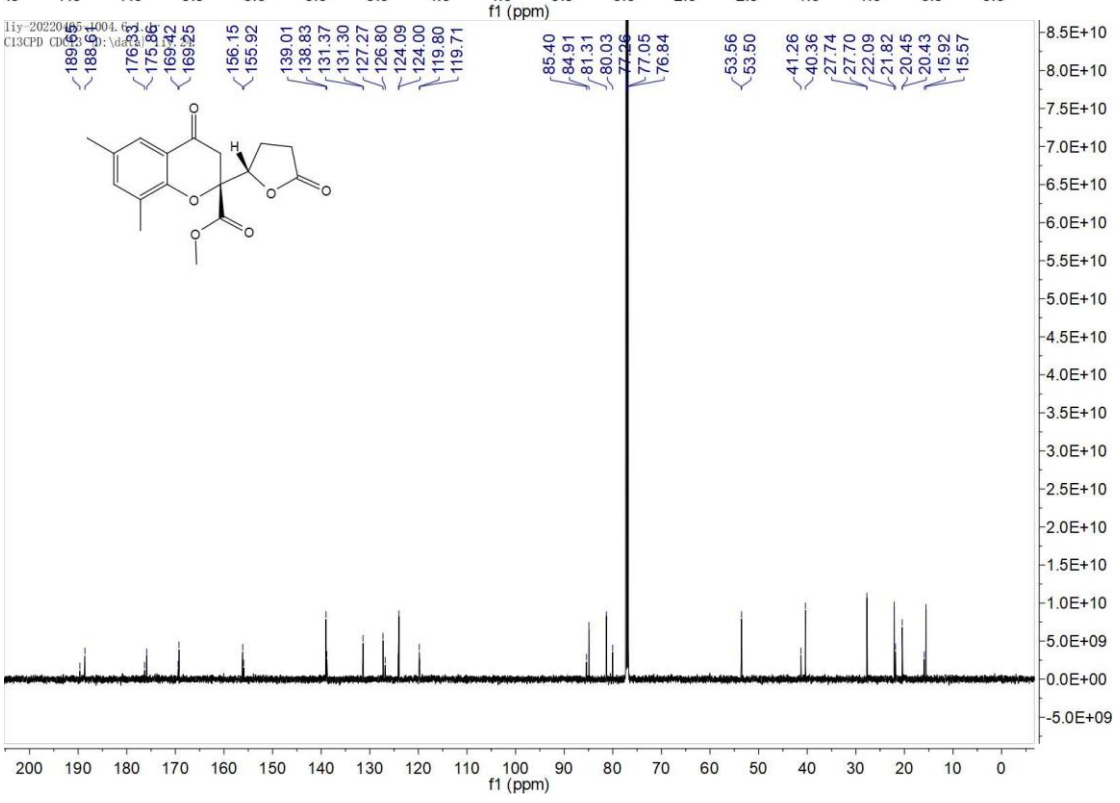
3k


f1 (ppm)
1.91
0.97
1.00
2.93
3.00
2.98

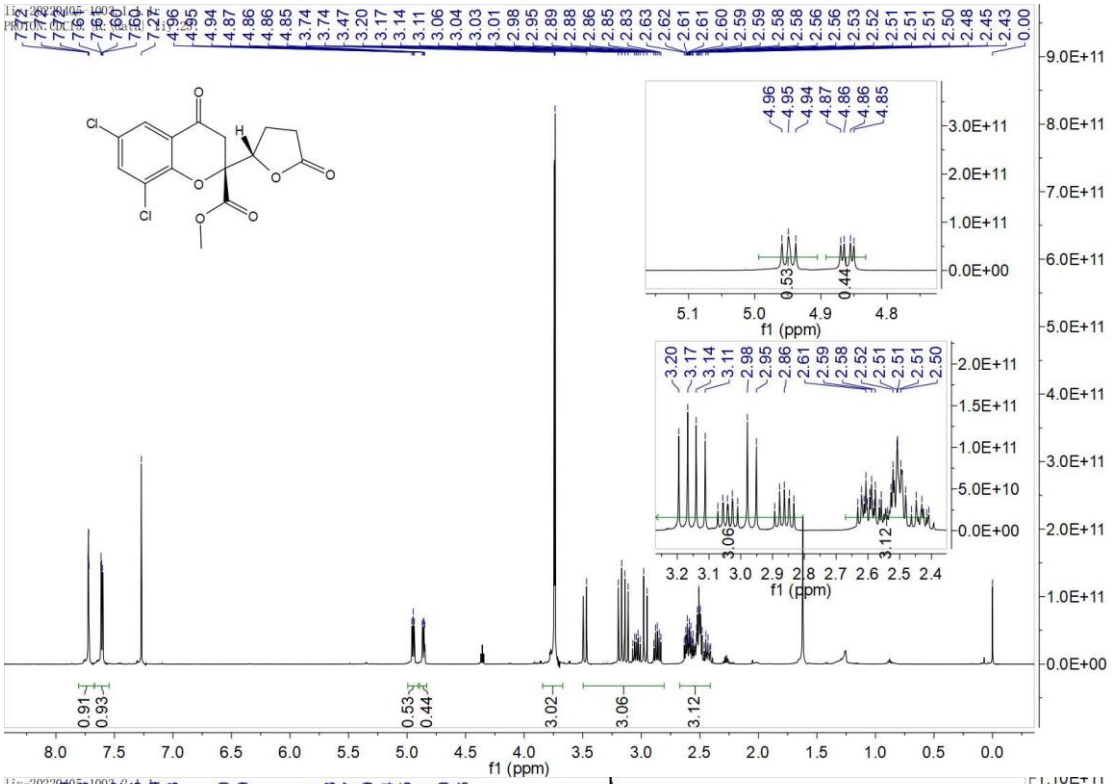

187.32
175.79
168.42
156.37
139.96
126.06
123.06
121.57
111.95
85.85
80.92
77.37
77.05
76.73
53.71
40.24
27.58
22.22
f1 (ppm)

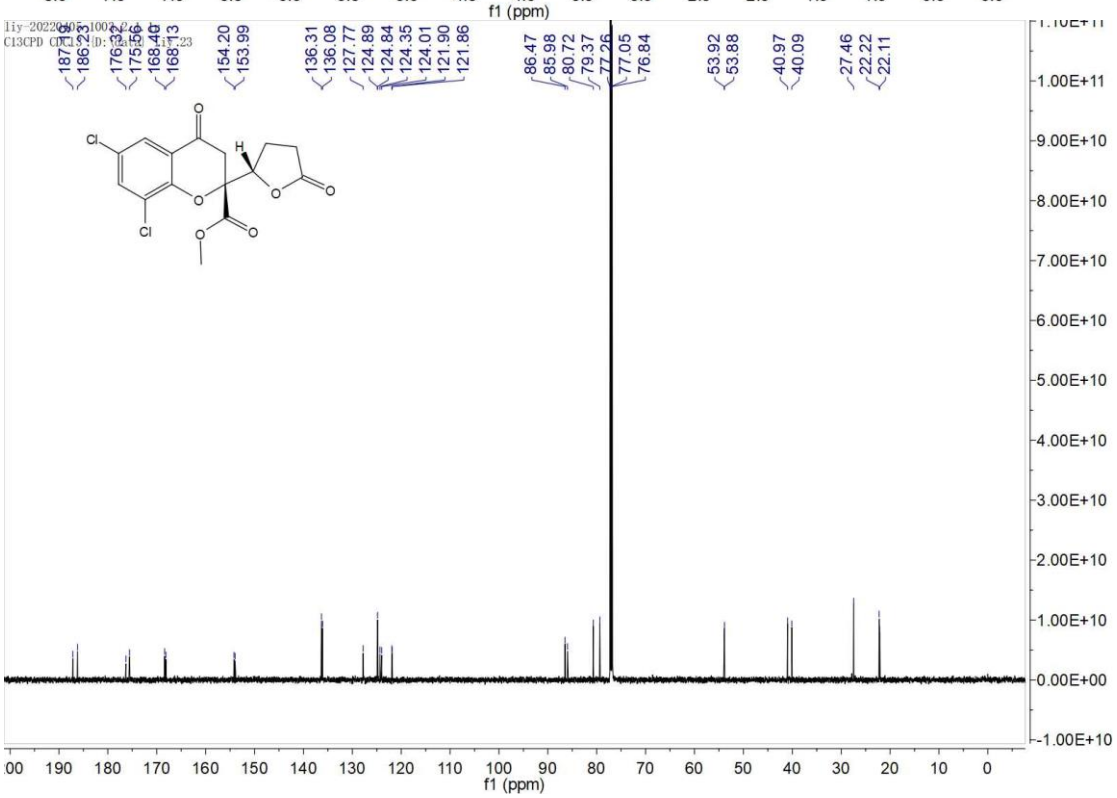
3l

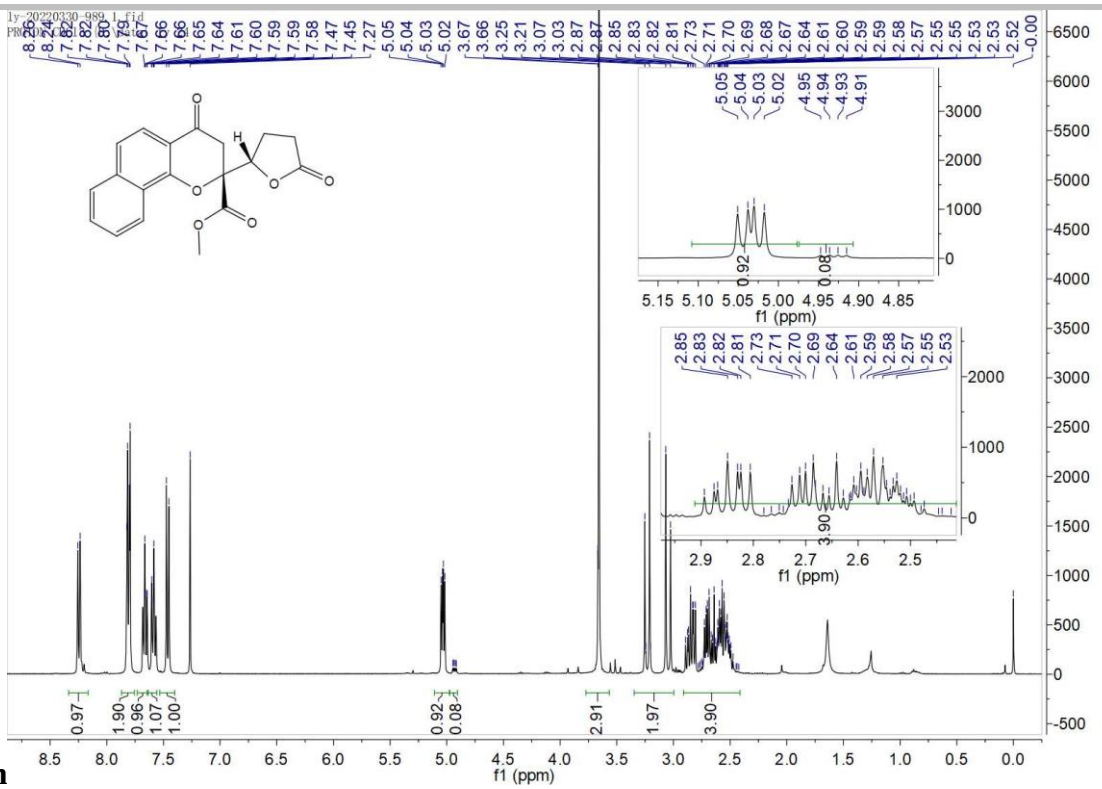




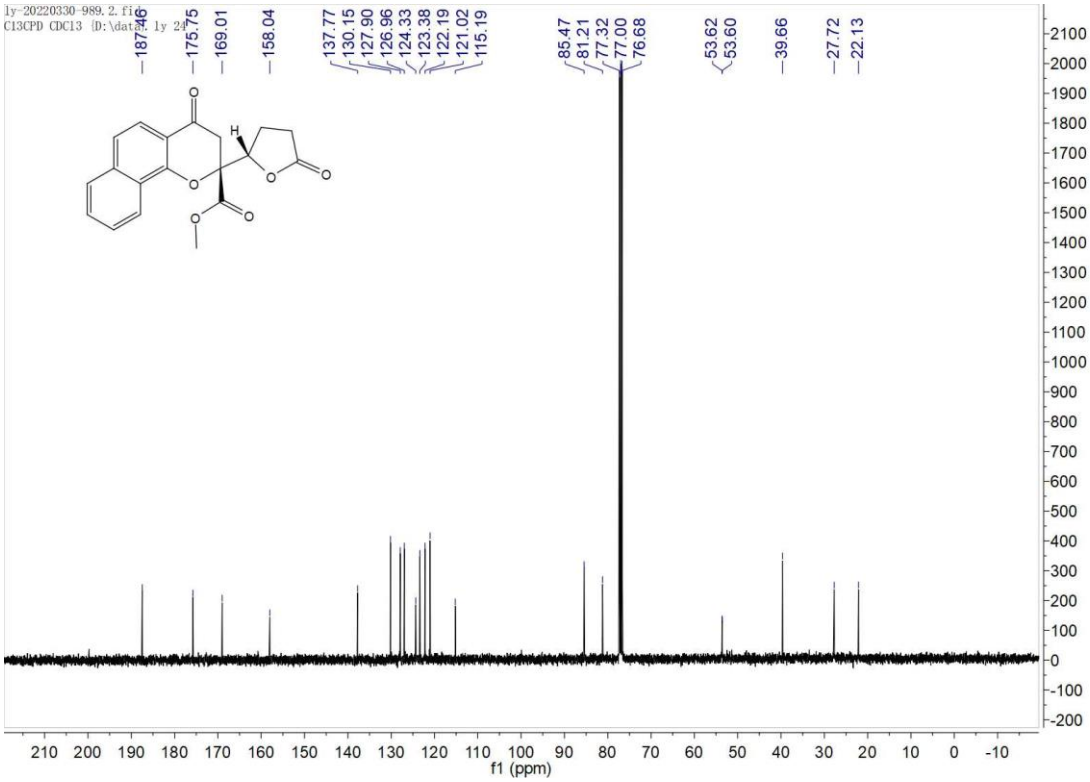
3m



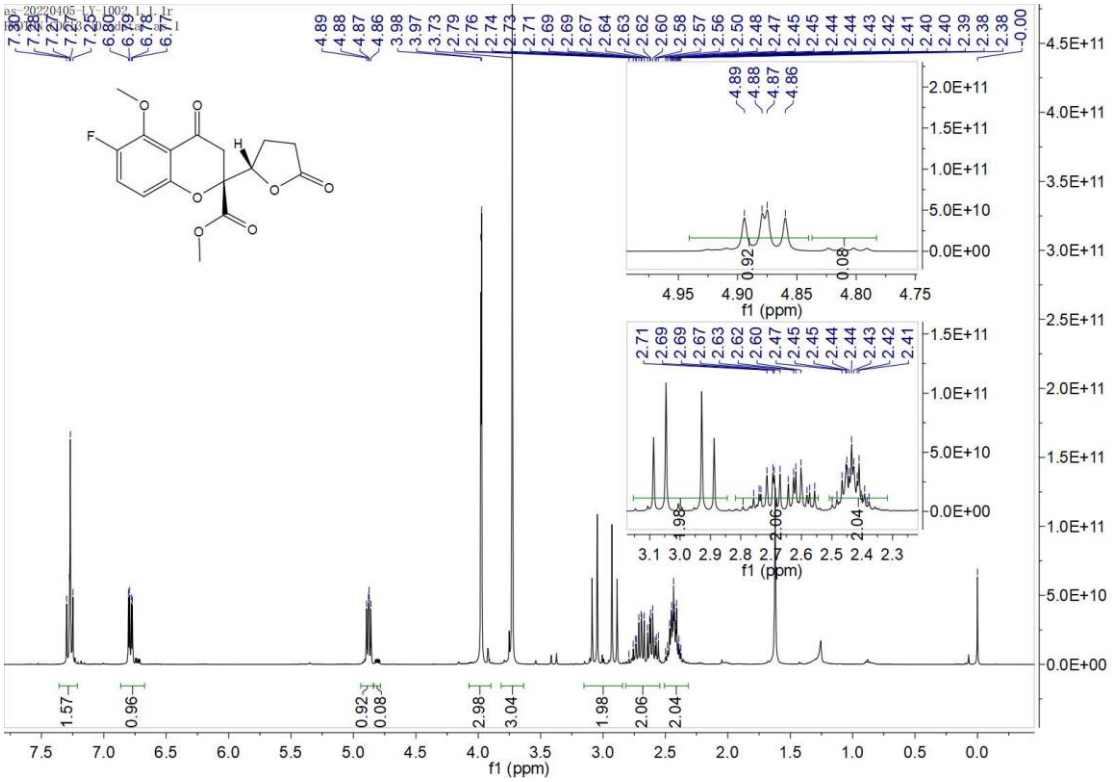


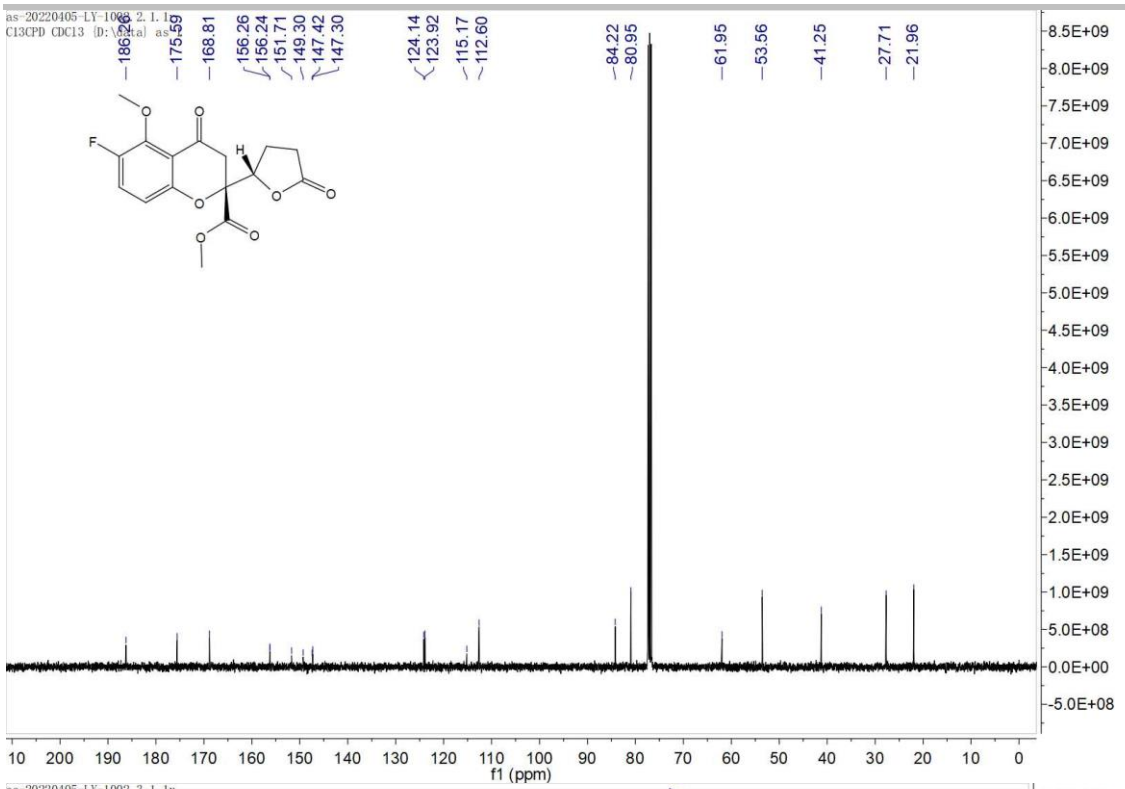


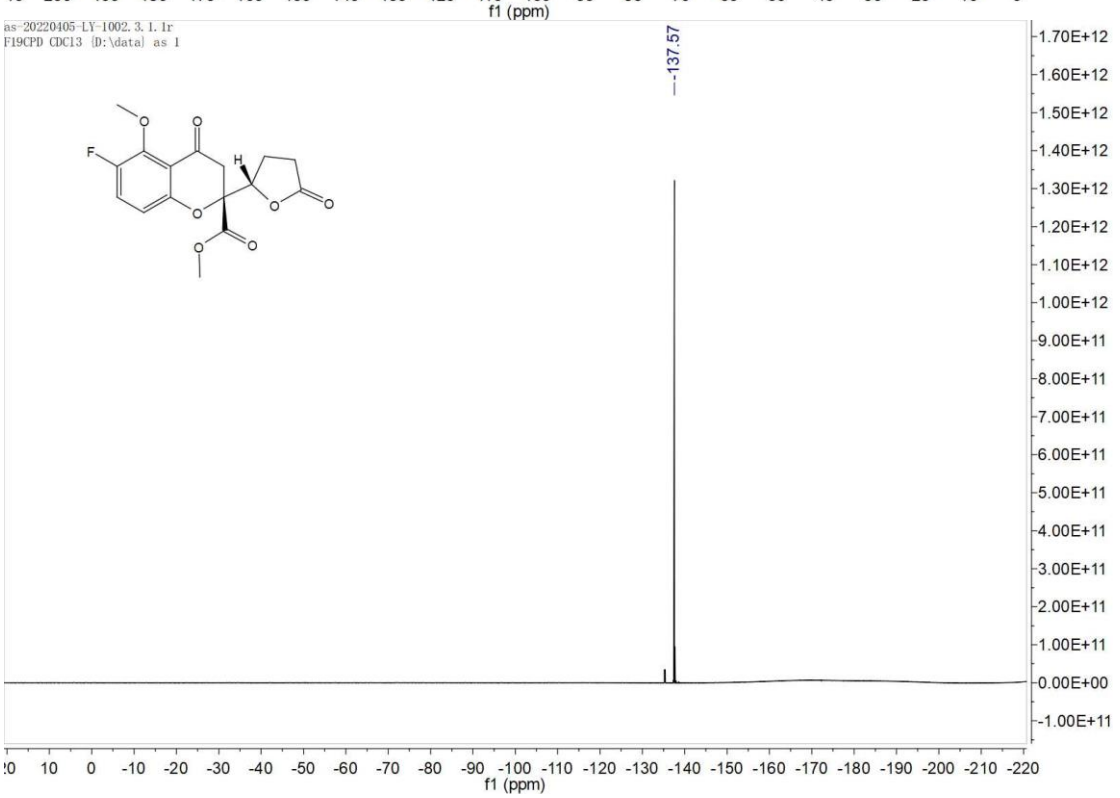
3n



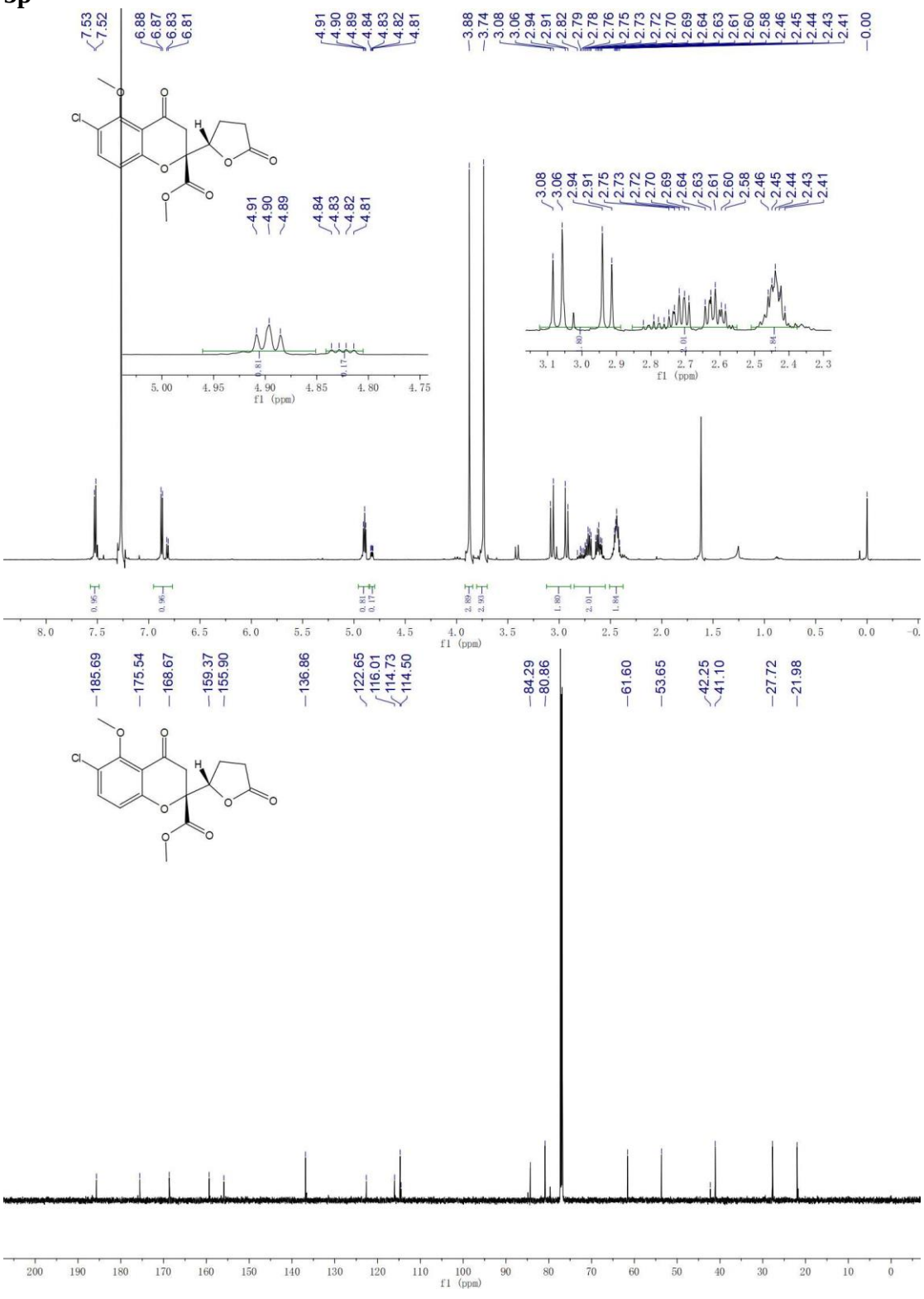
3o



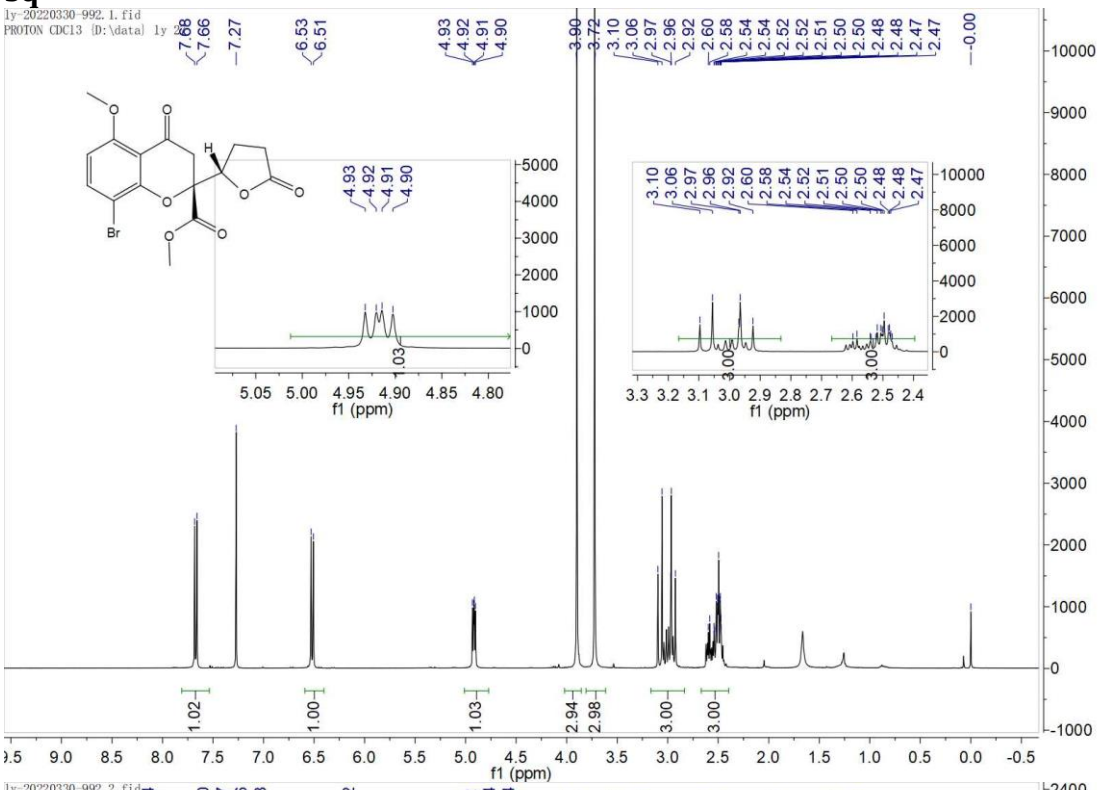

as-20220405-LY-1002. 2. 1. 1r
C13CPD CDC13 {D:\data} as 1
186.06
175.59
168.81
156.26
156.24
151.71
149.30
147.42
147.30
124.14
123.92
115.17
112.60
84.22
80.95
61.95
53.56
41.25
27.71
21.96
f1 (ppm)

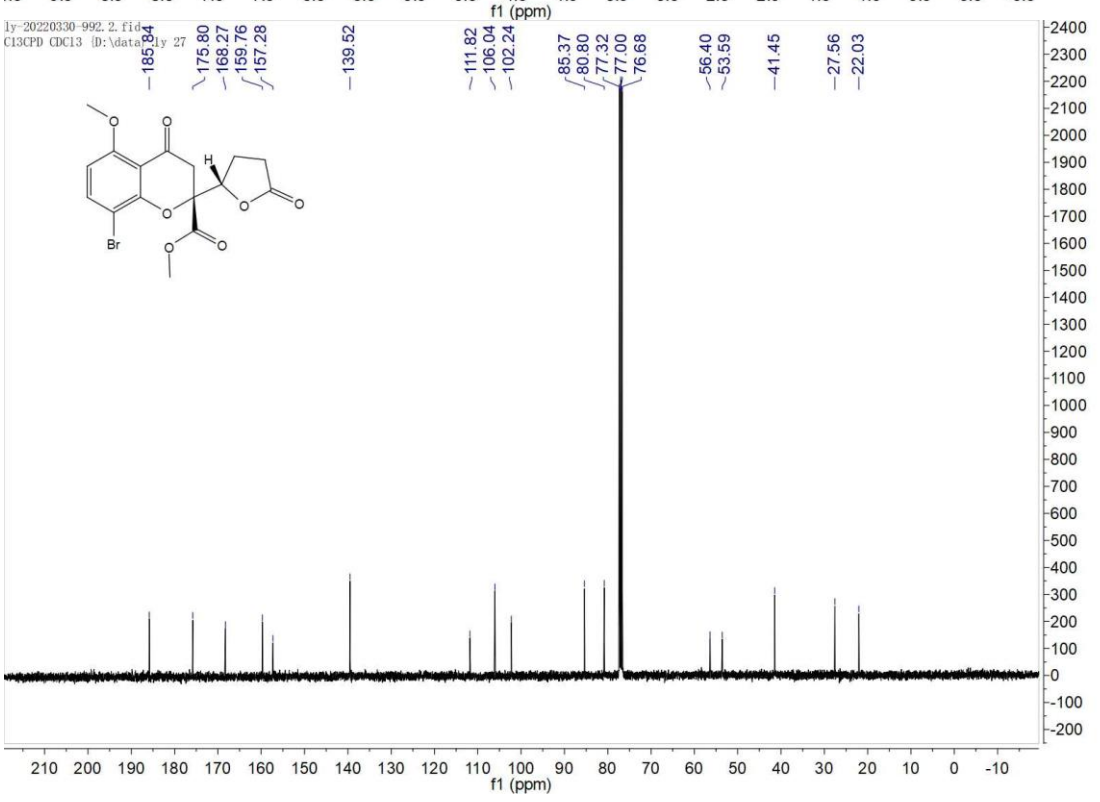

as-20220405-LY-1002. 3. 1. 1r
F19CPD CDC13 {D:\data} as 1
-137.57
f1 (ppm)

3p

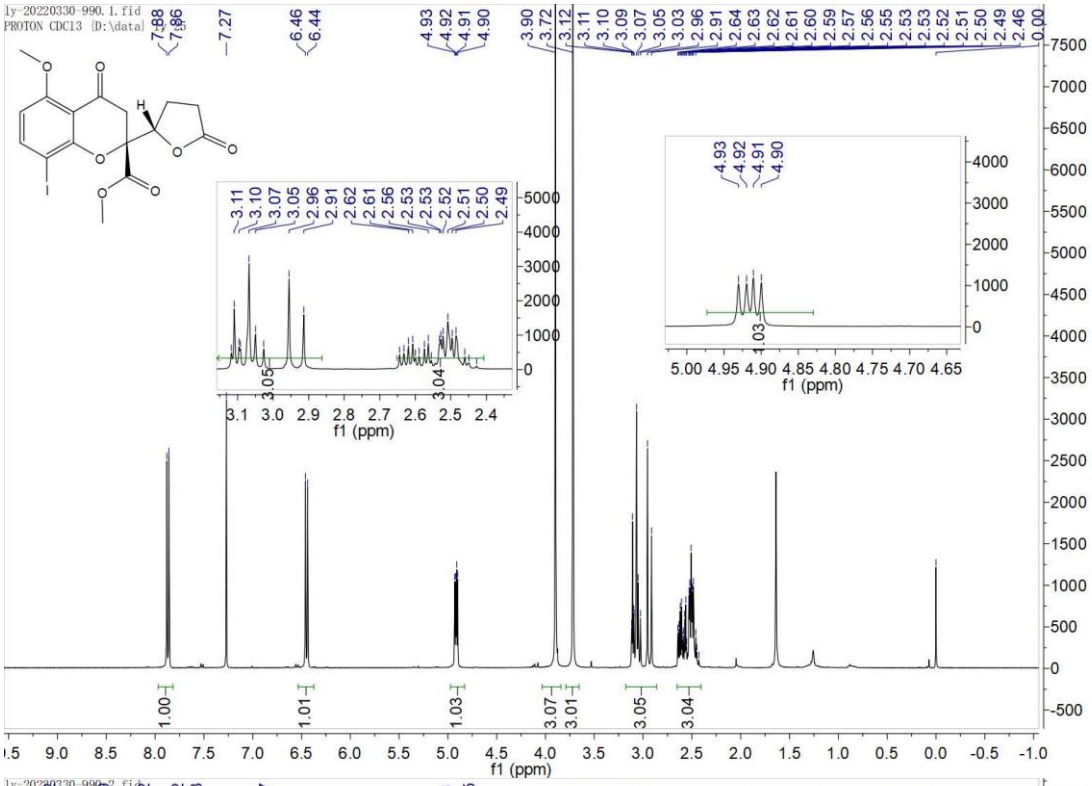


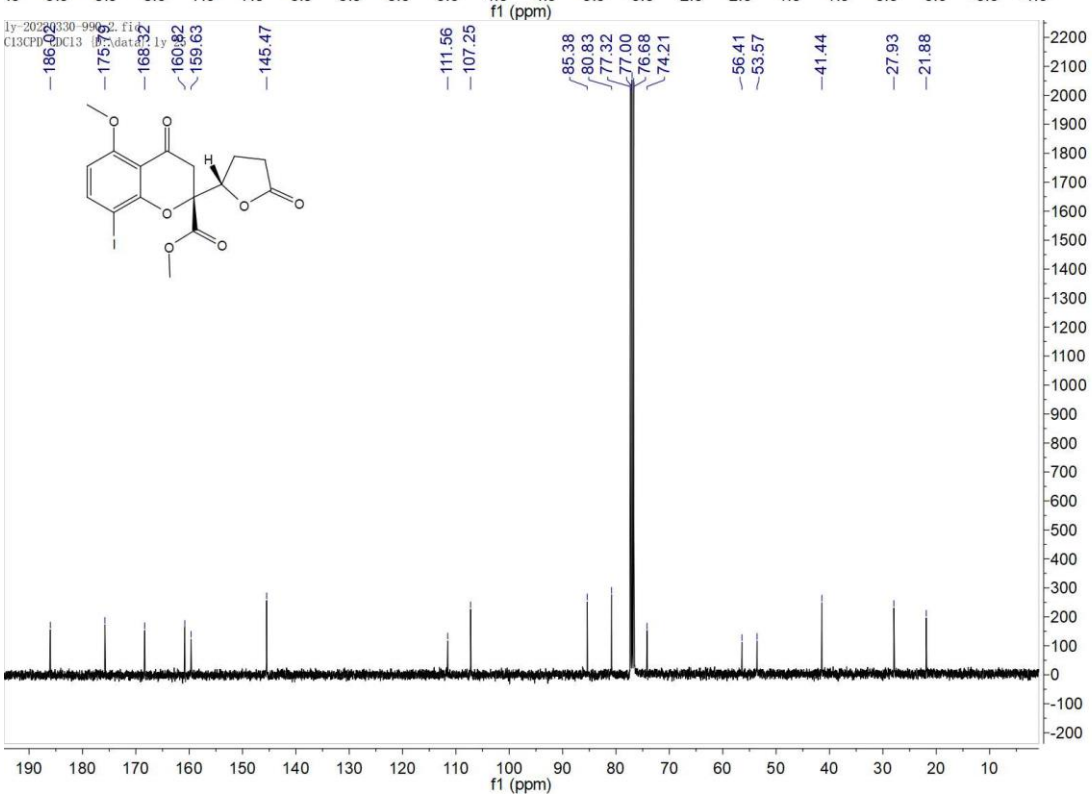
3q


PROTON CDCl3
7.68
7.66
7.27
6.53
6.51
4.93
4.92
4.91
4.90
3.90
3.72
3.10
3.06
2.97
2.96
2.92
2.60
2.58
2.54
2.54
2.52
2.52
2.51
2.50
2.50
2.48
2.48
2.47
2.47
-0.00
Br
1.02
1.00
1.03
2.94
2.98
3.00
3.00
f1 (ppm)

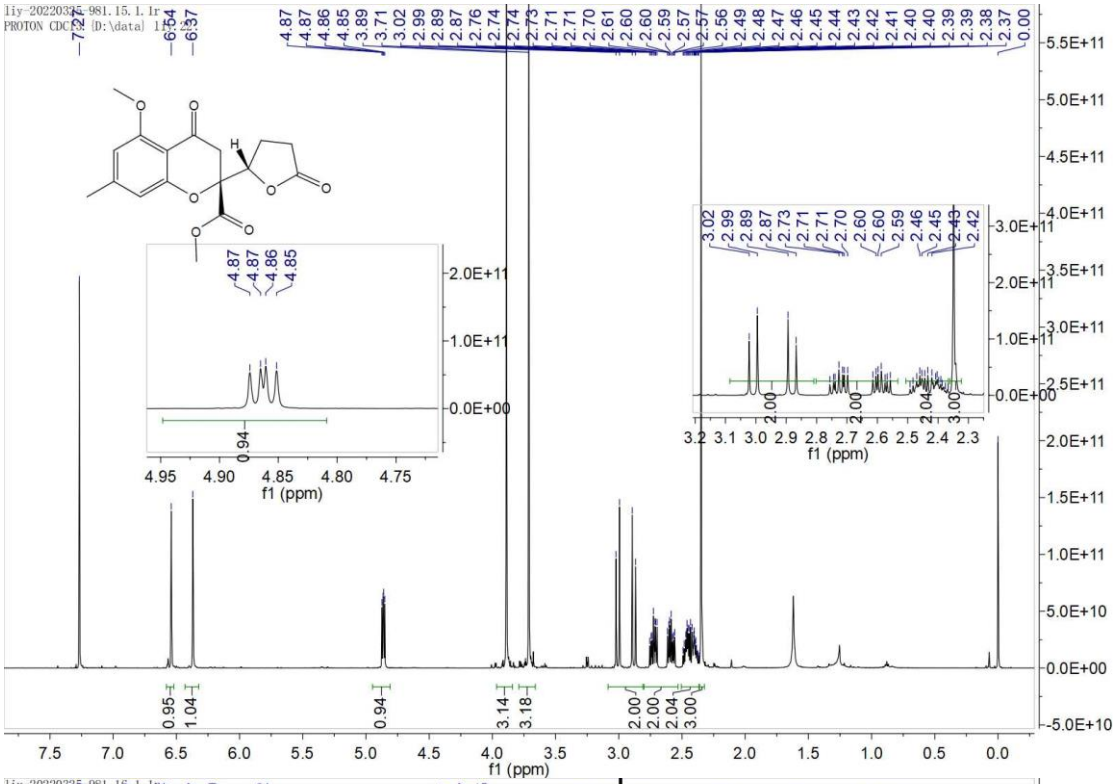

C13CPD CDCl3
185.94
175.80
168.27
159.76
157.28
139.52
111.82
106.04
102.24
85.37
80.80
77.32
77.00
76.68
56.40
53.59
41.45
27.56
22.03
Br
f1 (ppm)

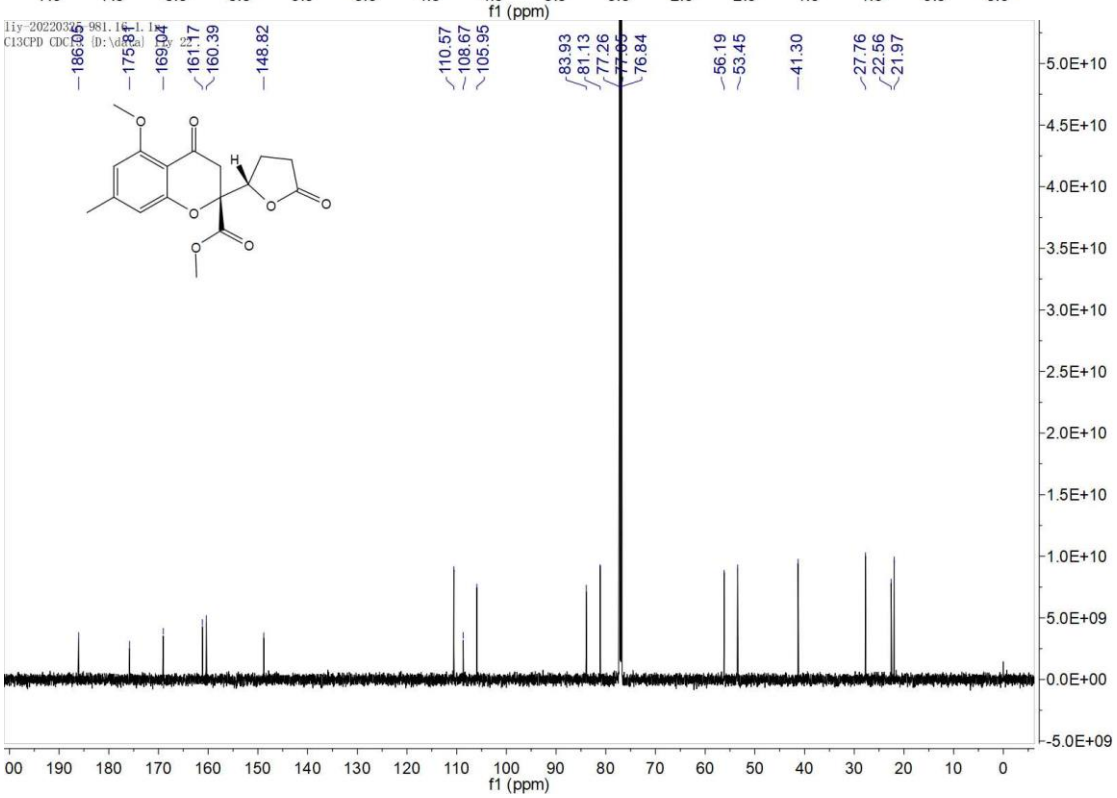
3r



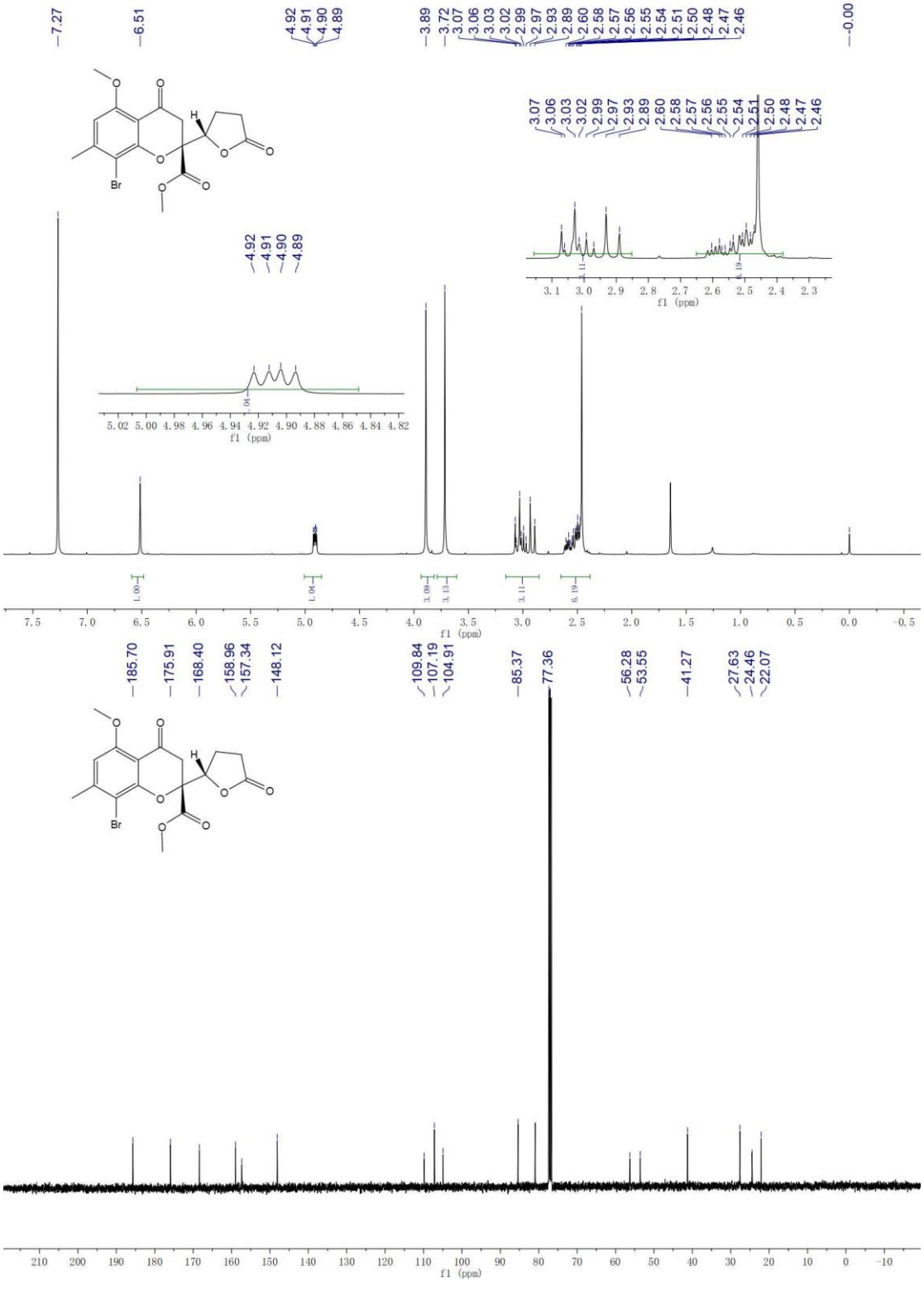


3s

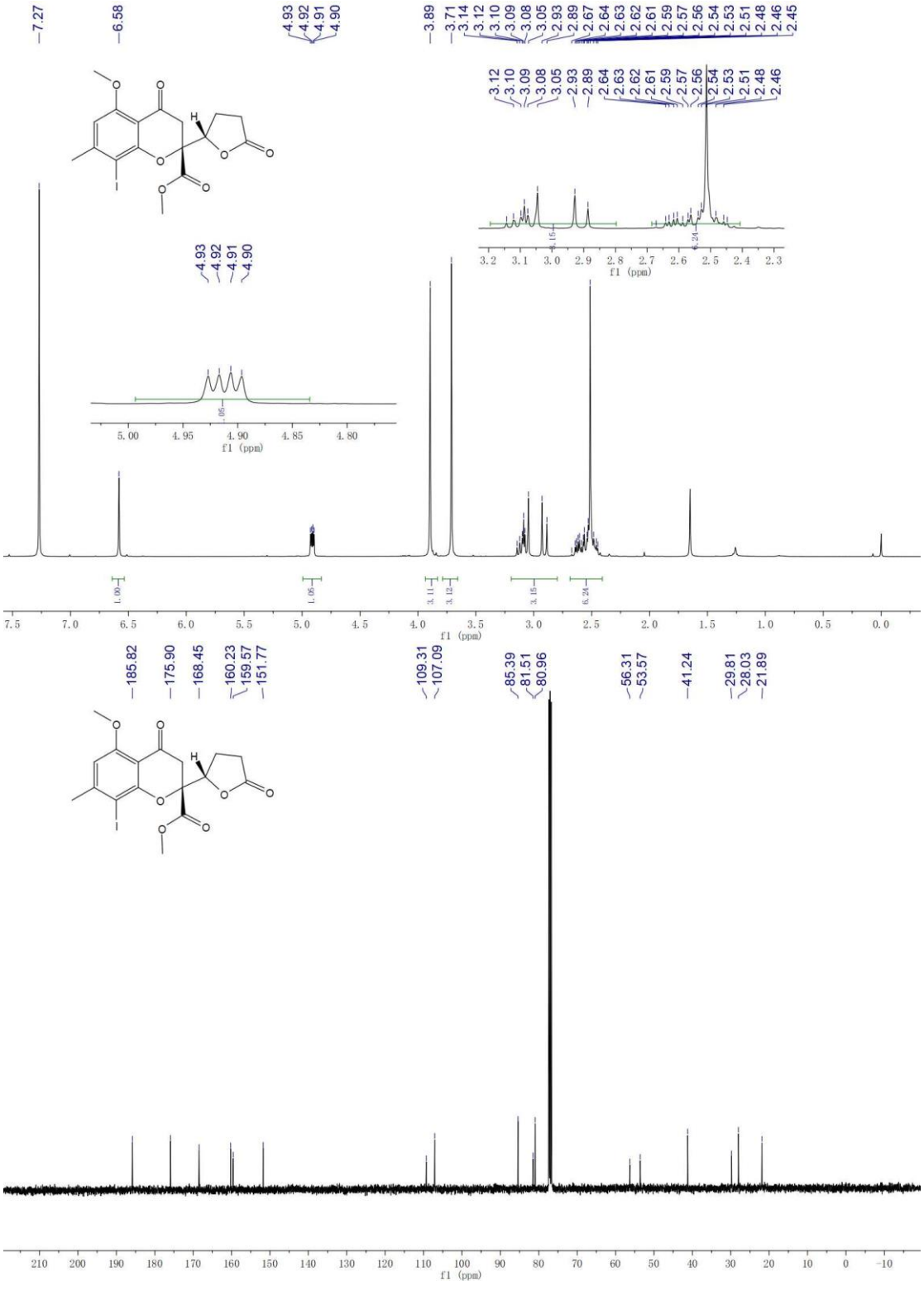




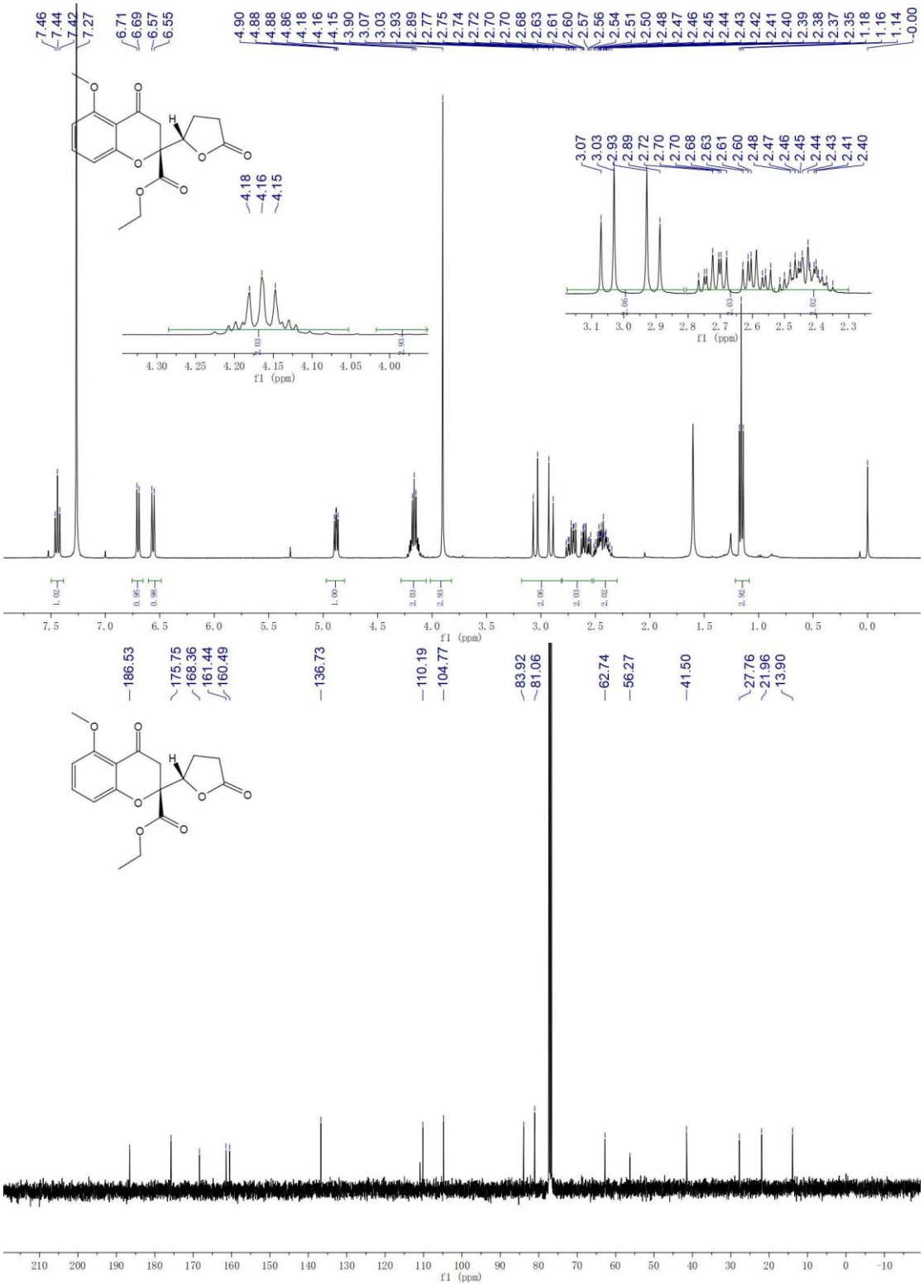
3t


7.27
6.51
4.92
4.91
4.90
4.89
3.89
3.72
3.07
3.06
3.03
3.02
2.99
2.97
2.93
2.89
2.60
2.58
2.57
2.56
2.55
2.54
2.51
2.50
2.48
2.47
2.46
0.00
Br
f1 (ppm)
185.70
175.91
168.40
158.96
157.34
148.12
109.84
107.19
104.91
85.37
77.36
56.28
53.55
41.27
27.63
24.46
22.07

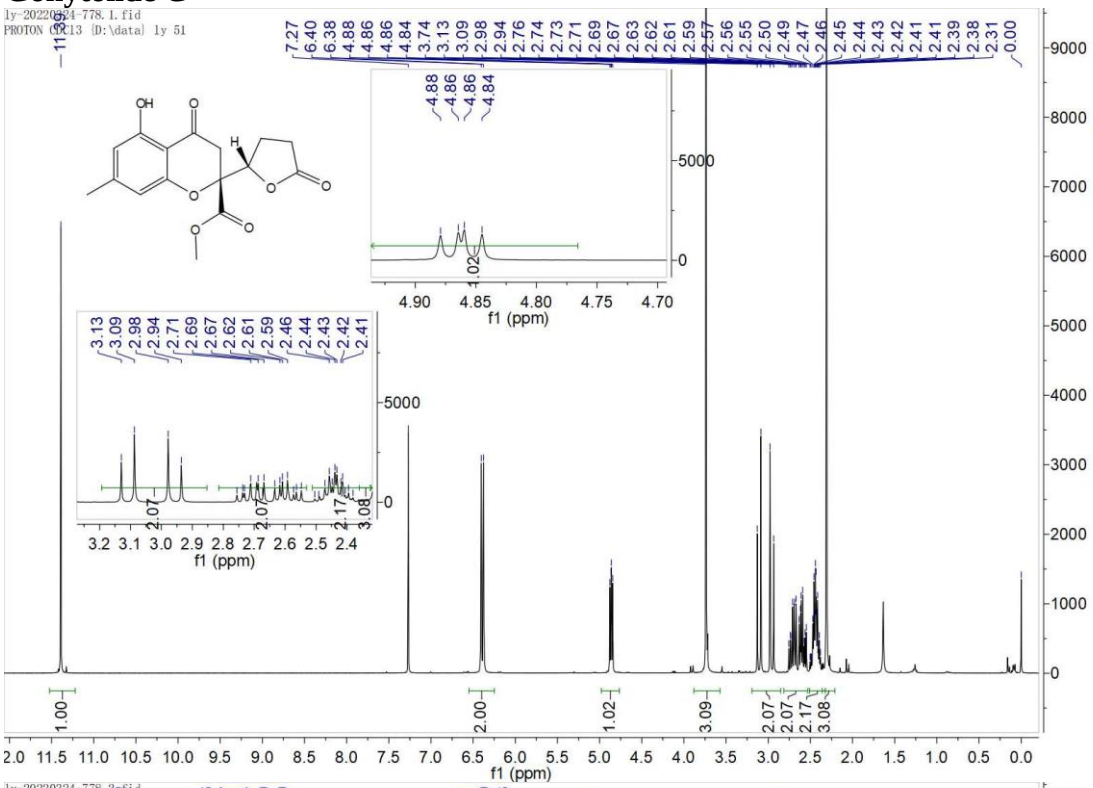
3u

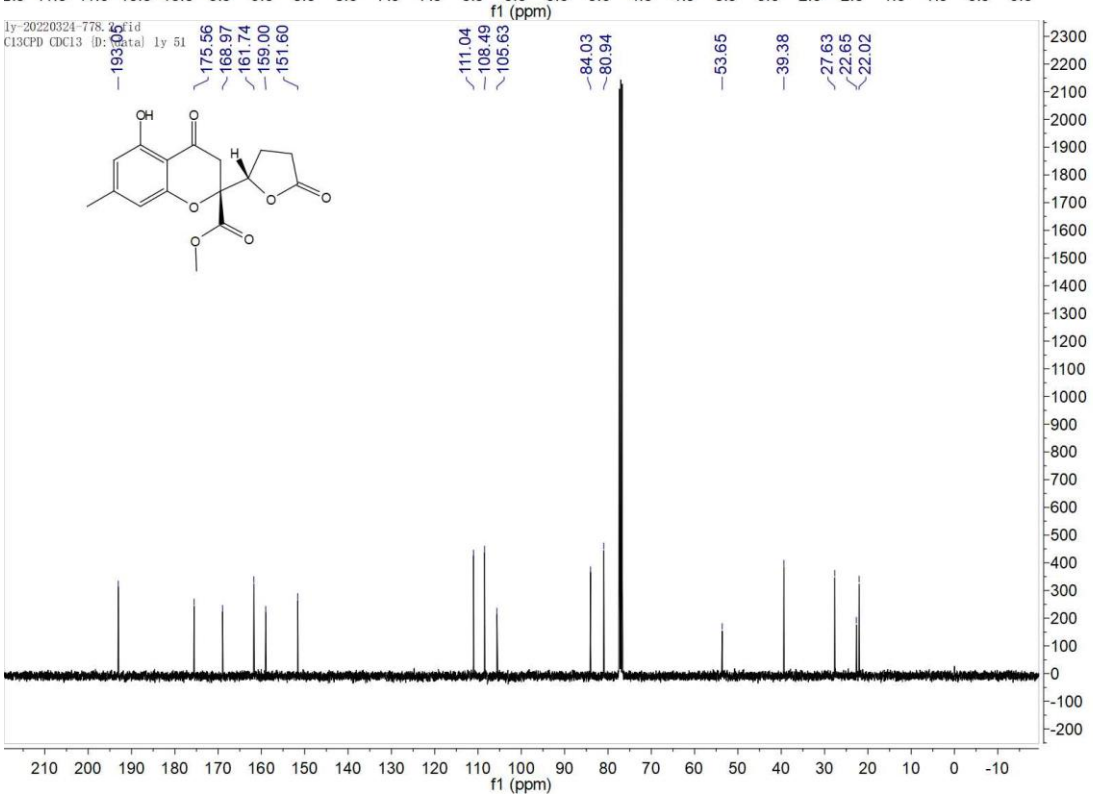

7.27
6.58
4.93
4.92
4.91
4.90
3.89
3.71
3.14
3.12
3.10
3.09
3.08
3.05
2.93
2.89
2.67
2.64
2.63
2.62
2.61
2.59
2.57
2.56
2.54
2.53
2.51
2.48
2.46
2.45
f1 (ppm)
185.82
175.90
168.45
160.23
159.57
151.77
109.31
107.09
85.39
81.51
80.96
56.31
53.57
41.24
29.81
28.03
21.89

3b‘

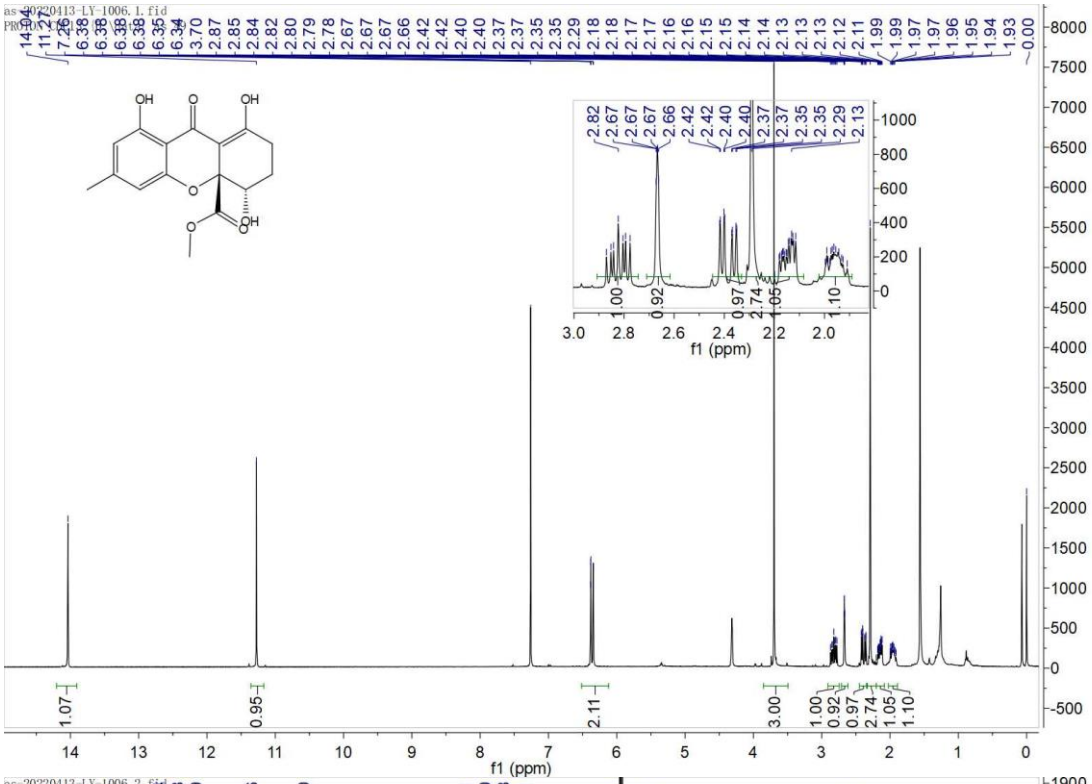


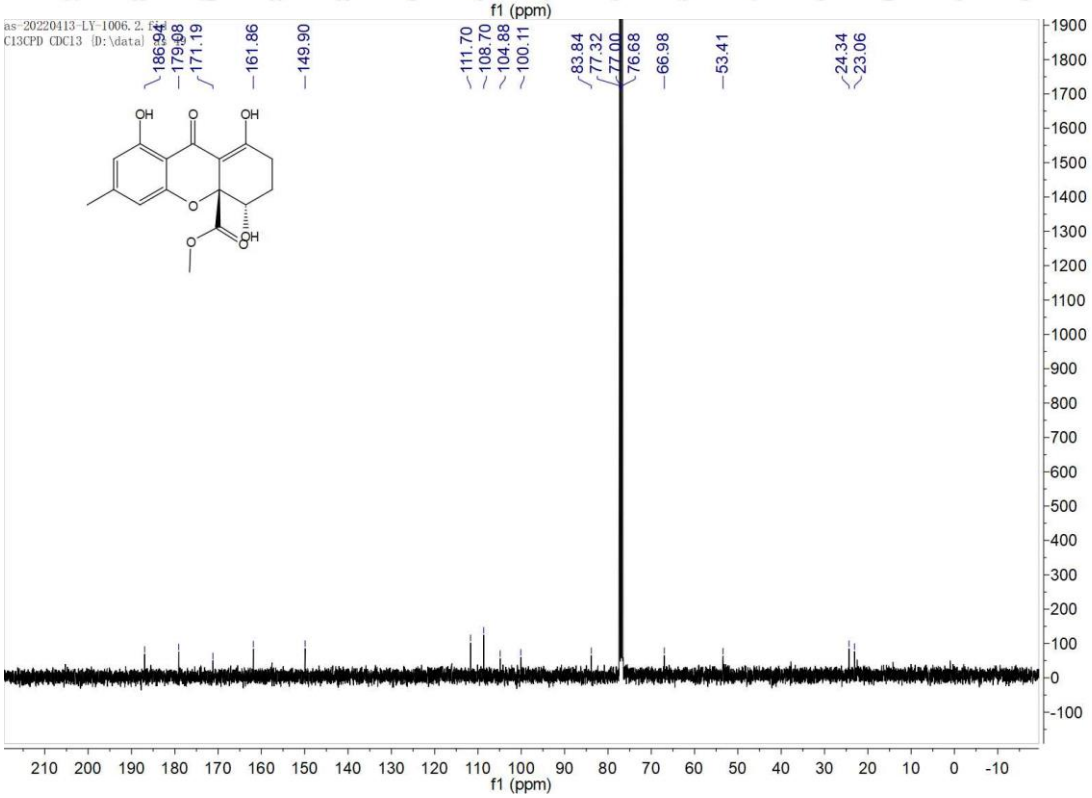
Gonytolide C

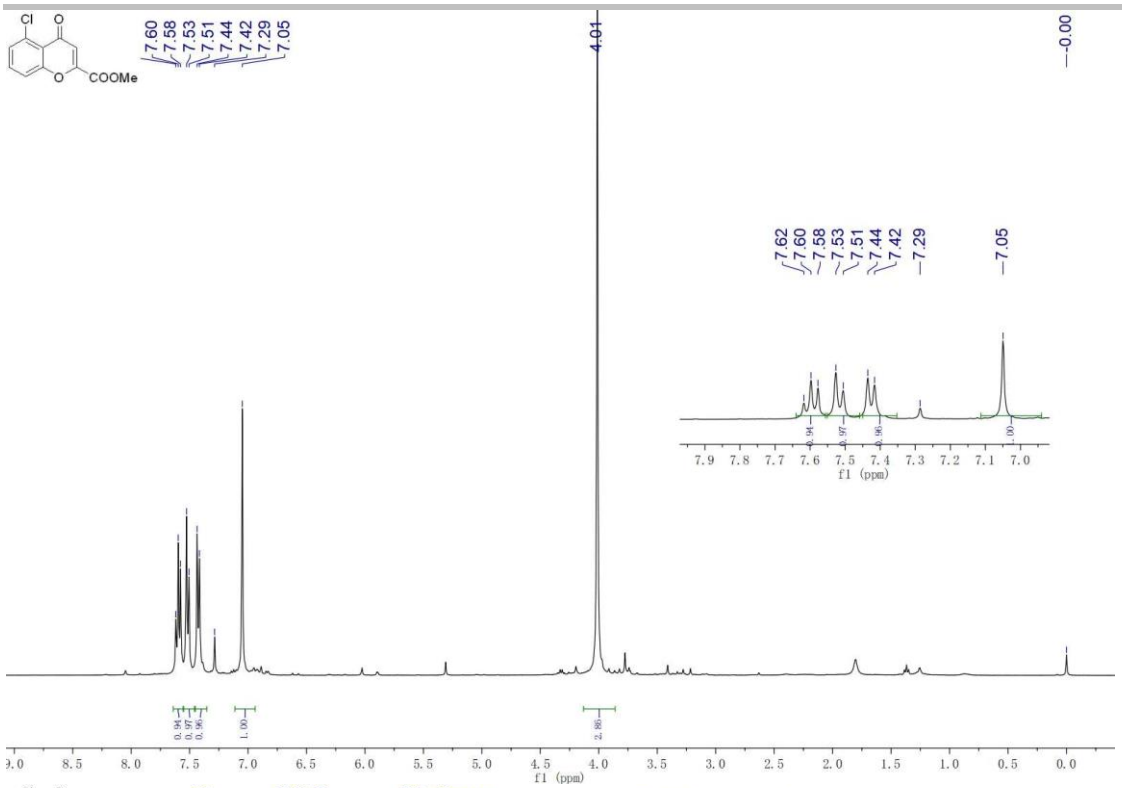


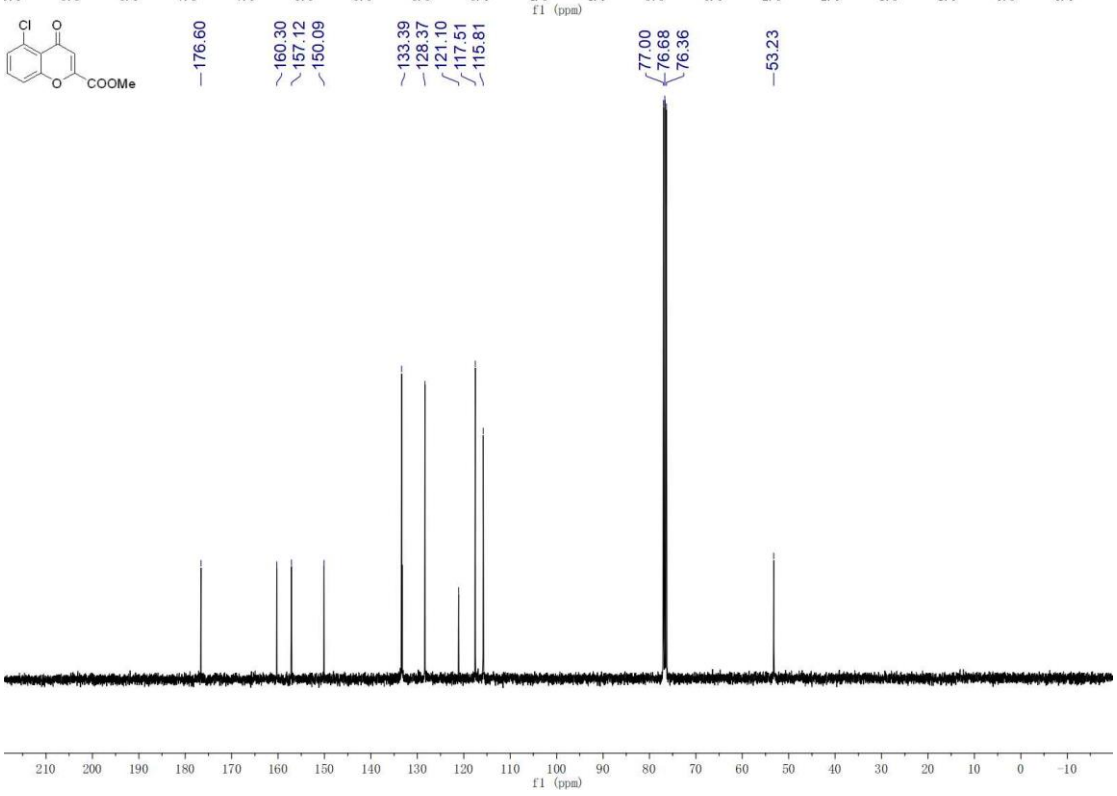


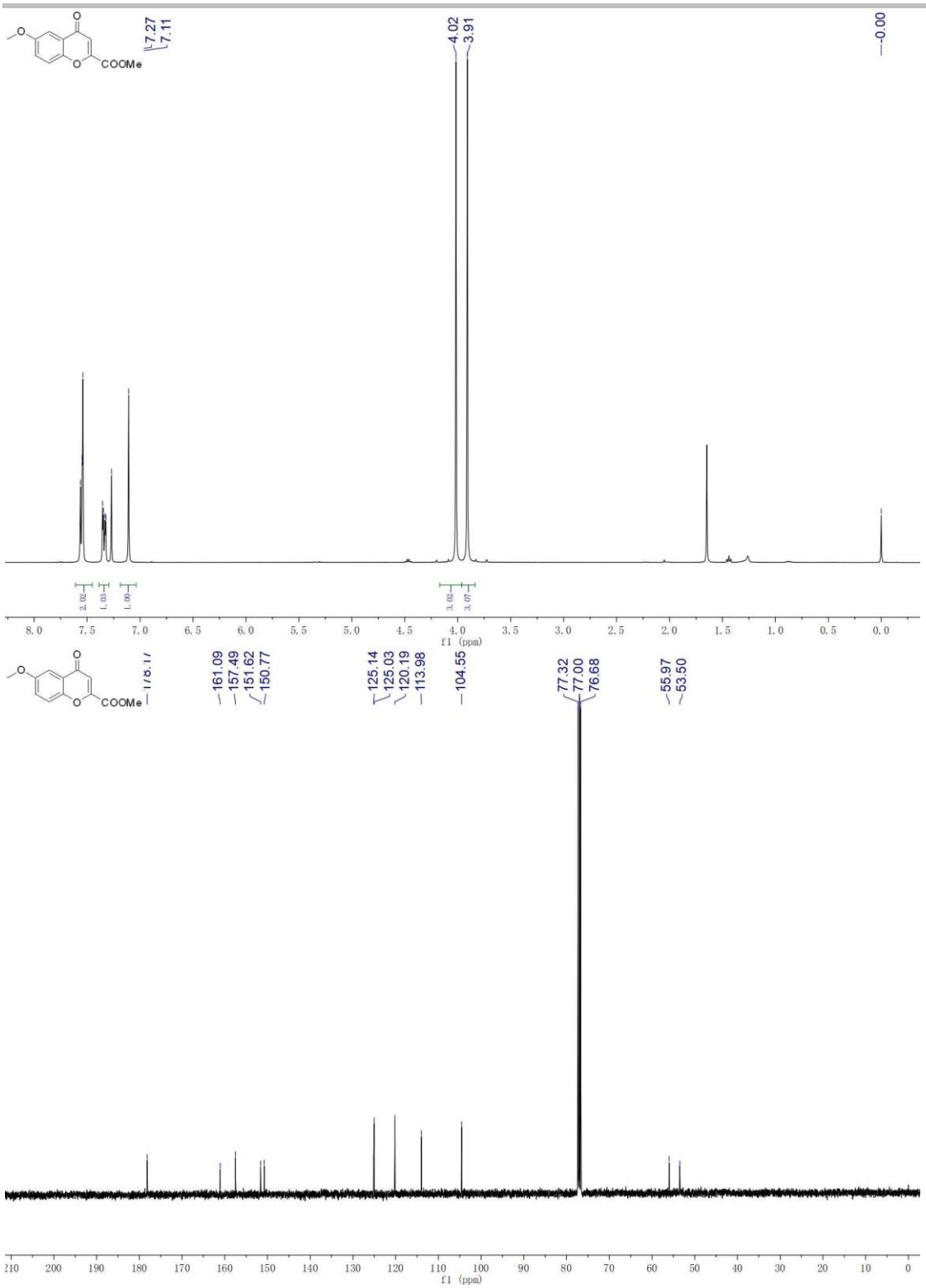
Blennolide C

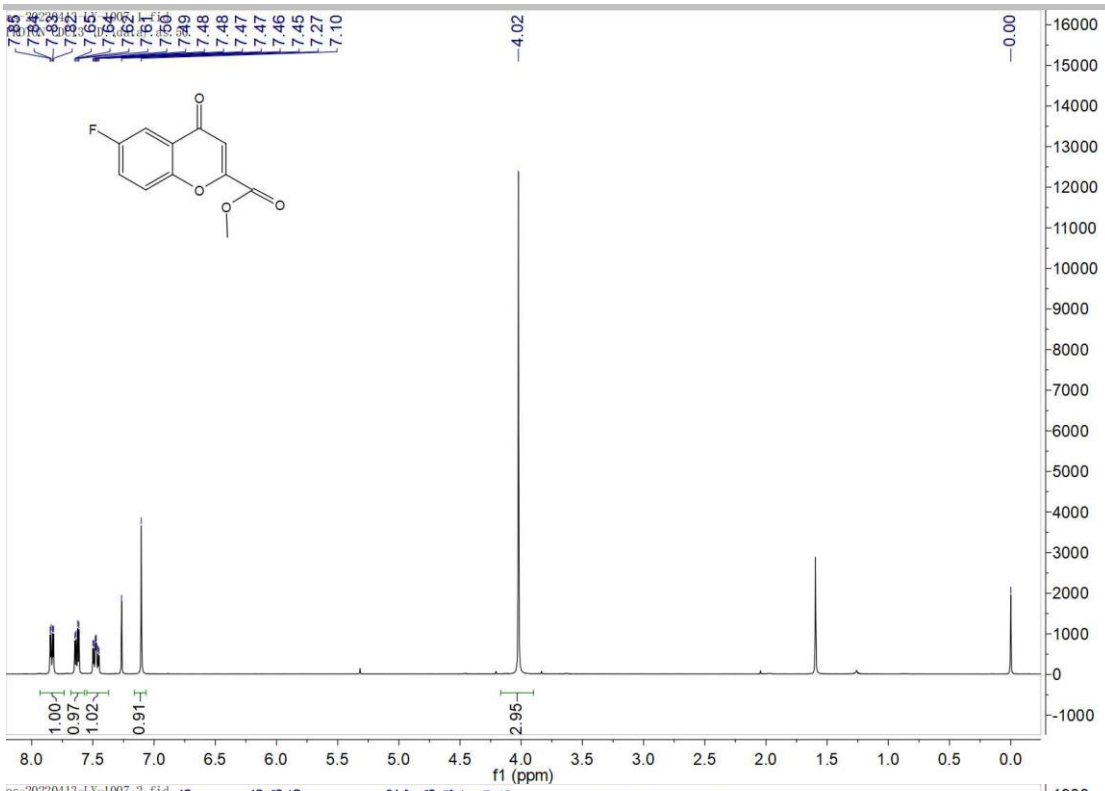


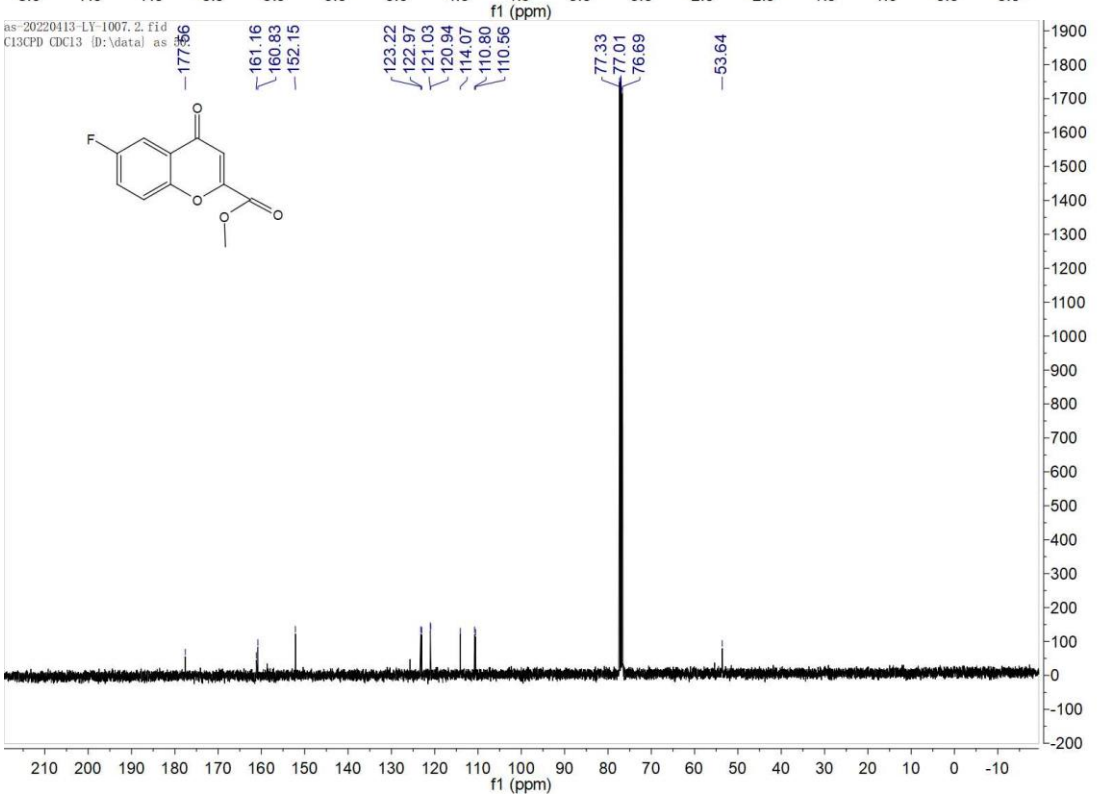


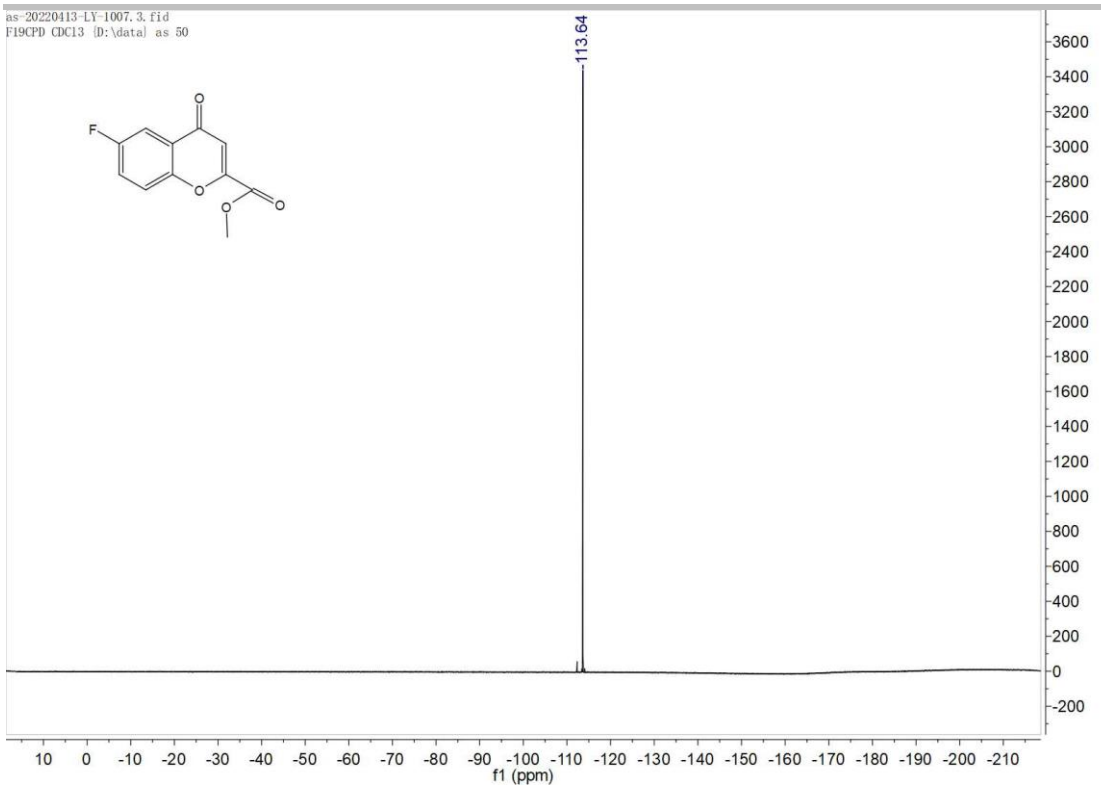

Cl
O
O
COOMe
7.60
7.58
7.53
7.51
7.44
7.42
7.29
7.05
4.01
0.00
7.62
7.60
7.58
7.53
7.51
7.44
7.42
7.29
7.05
f1 (ppm)

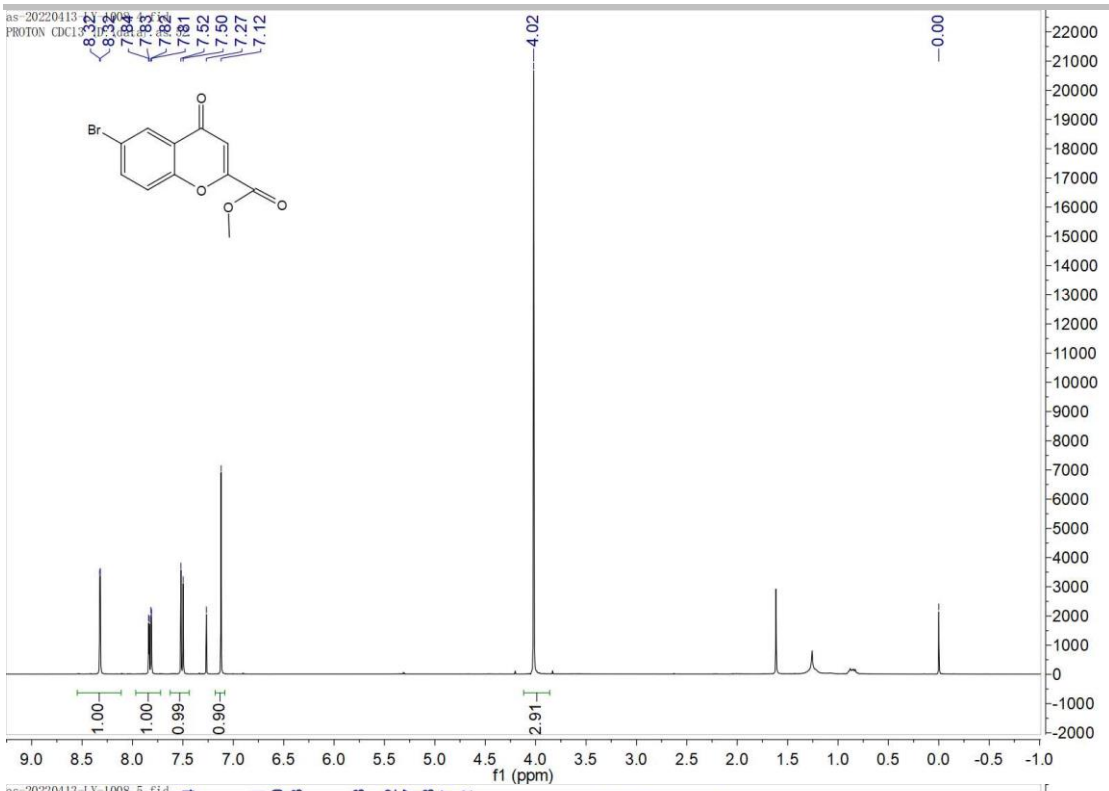

Cl
O
O
COOMe
176.60
160.30
157.12
150.09
133.39
128.37
121.10
117.51
115.81
77.00
76.68
76.36
53.23
f1 (ppm)

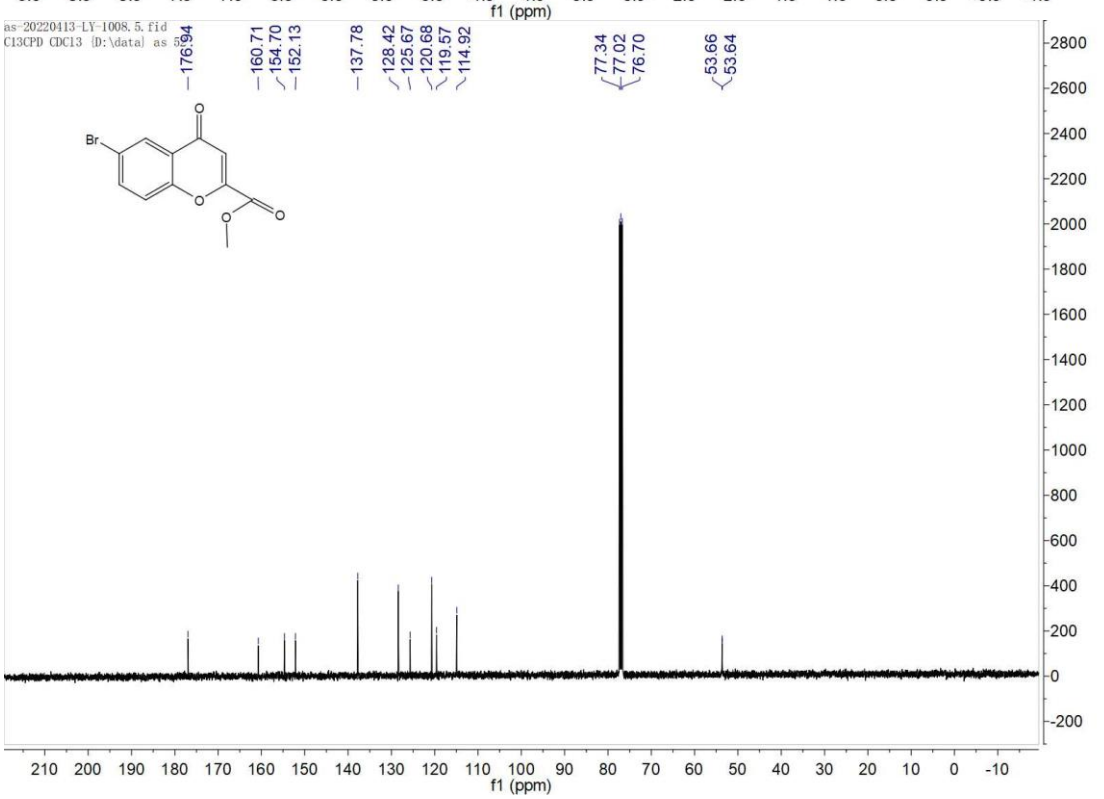

COOMe
7.27
7.11
4.02
3.91
0.00
2.02
1.03
1.00
3.02
3.07
f1 (ppm)
161.09
157.49
151.62
150.77
125.14
125.03
120.19
113.98
104.55
77.32
77.00
76.68
55.97
53.50
f1 (ppm)

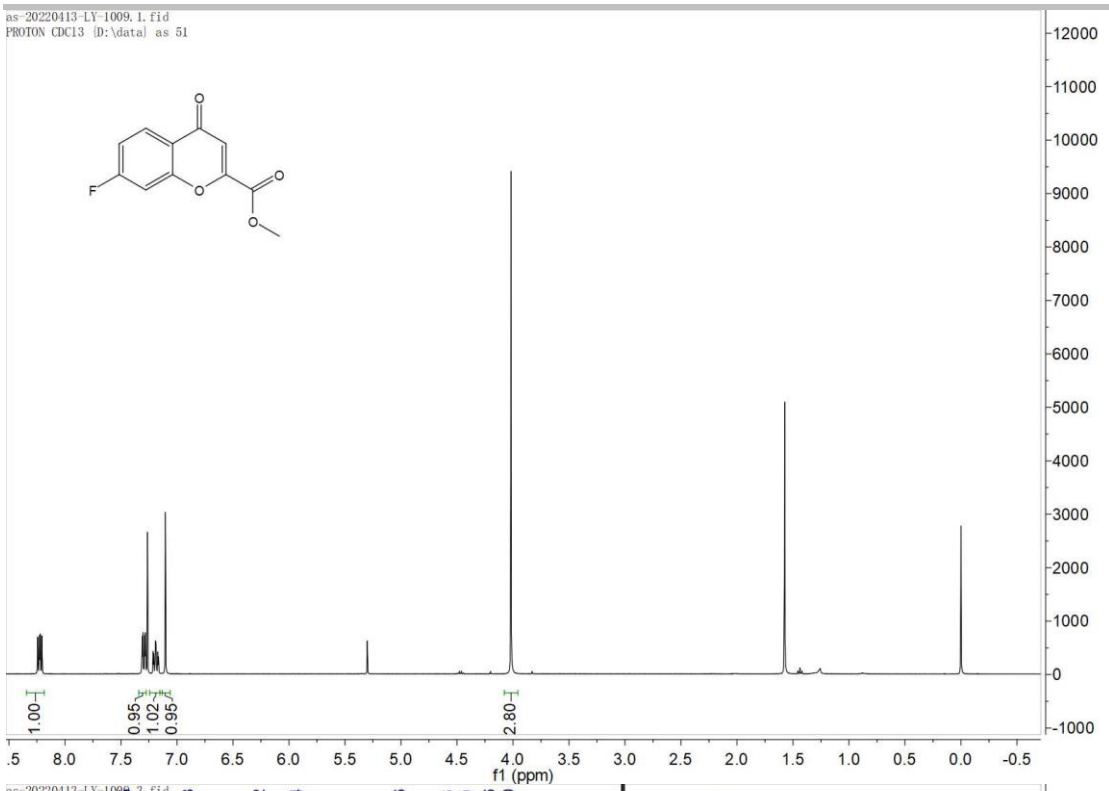

7.85
7.84
7.83
7.82
7.65
7.64
7.62
7.61
7.56
7.49
7.48
7.48
7.47
7.47
7.46
7.45
7.27
7.10
4.02
0.00
F
O
O
O
O
1.00
0.97
1.02
0.91
2.95
f1 (ppm)

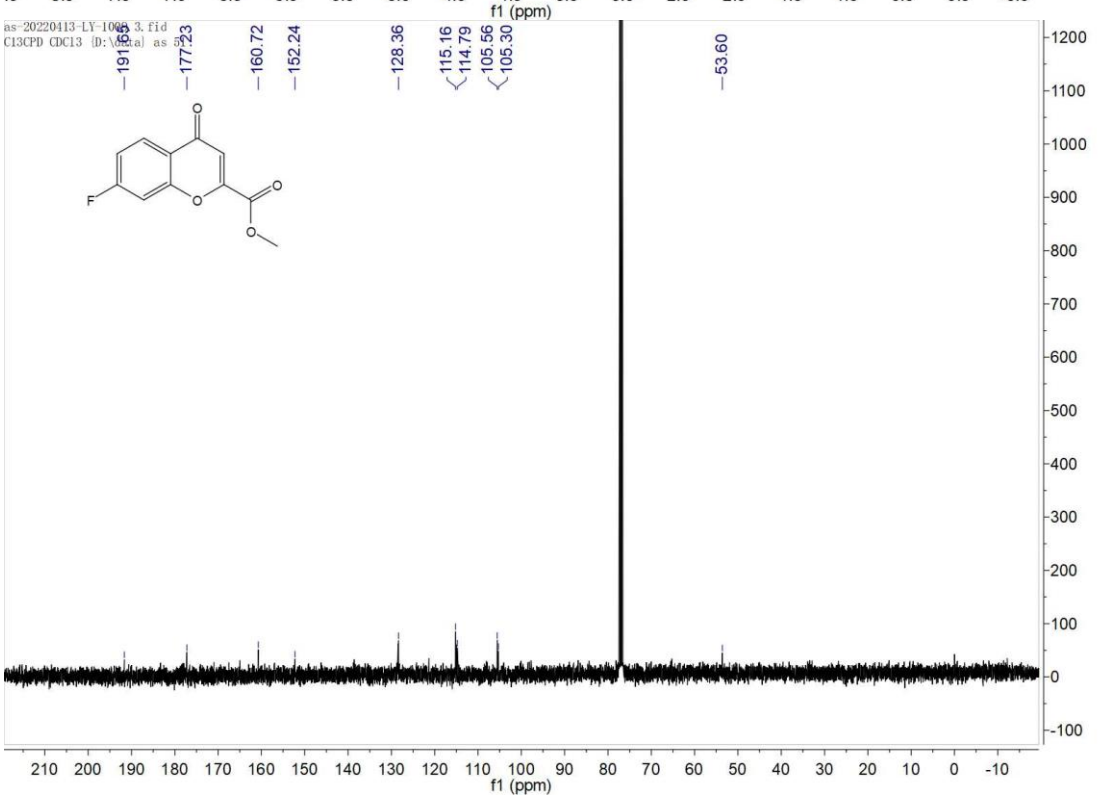

as-20220413-LY-1007.2.fid
C13CPD CDCl3 {D:\data} as
177.66
161.16
160.83
152.15
123.22
122.97
121.03
120.94
114.07
110.80
110.56
77.33
77.01
76.69
53.64
F
O
O
O
O
f1 (ppm)

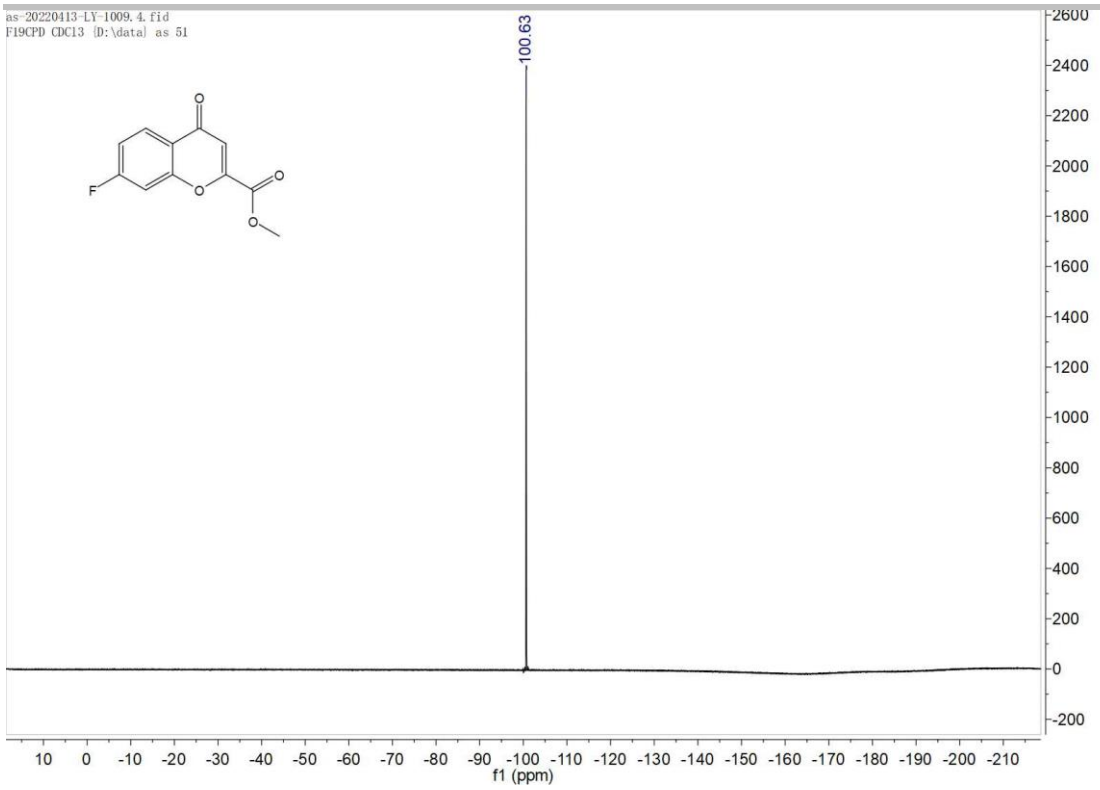

as-20220413-LY-1007.3.fid
F19CPD CDCl3 (D:\data) as 50
113.64
F
O
O
O
O
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

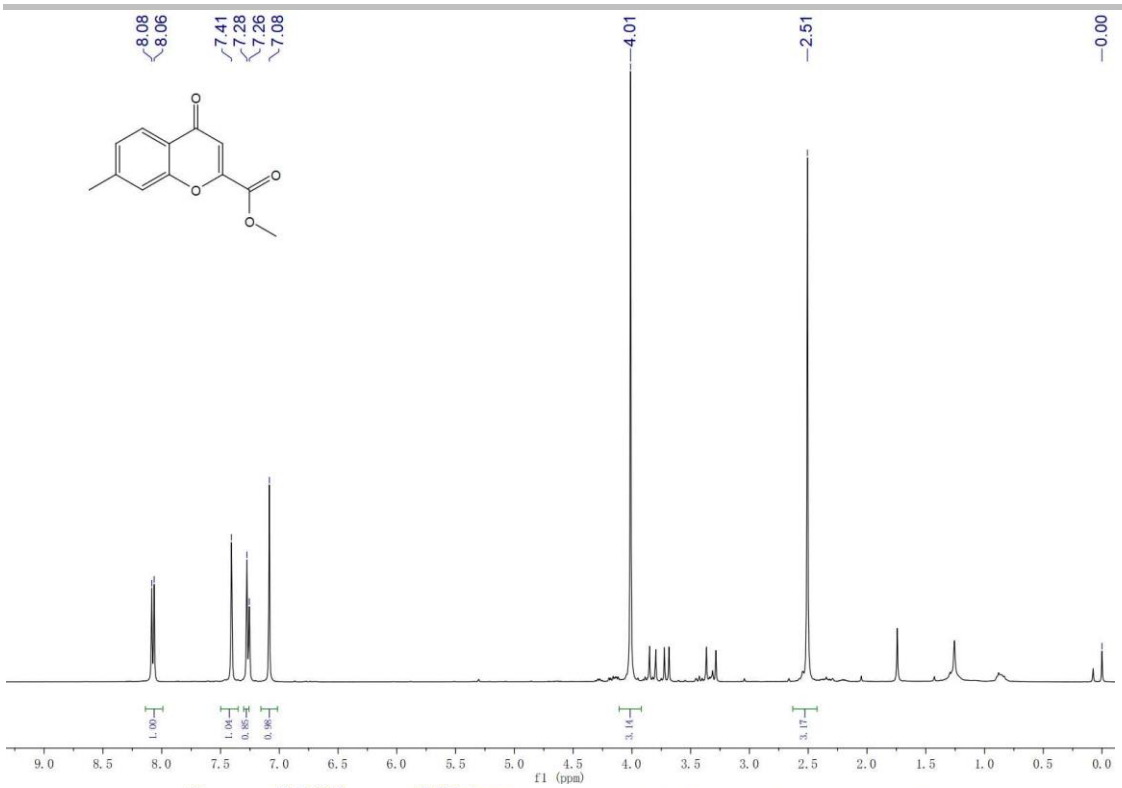

PROTON CDCl3
8.32
8.31
7.84
7.83
7.82
7.81
7.52
7.50
7.27
7.12
4.02
0.00
Br
O
O
O
O
1.00
1.00
0.99
0.90
2.91
f1 (ppm)

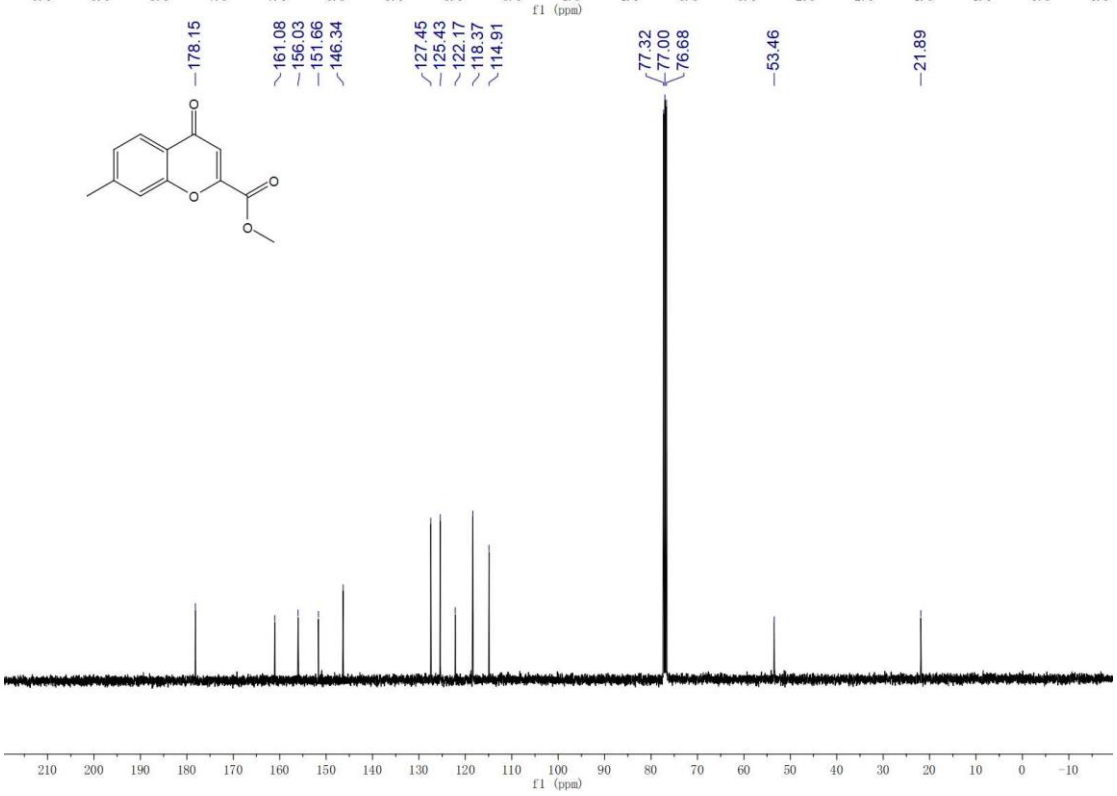

C13CPD CDCl3
176.94
160.71
154.70
152.13
137.78
128.42
125.67
120.68
119.57
114.92
77.34
77.02
76.70
53.66
53.64
Br
O
O
O
O
f1 (ppm)

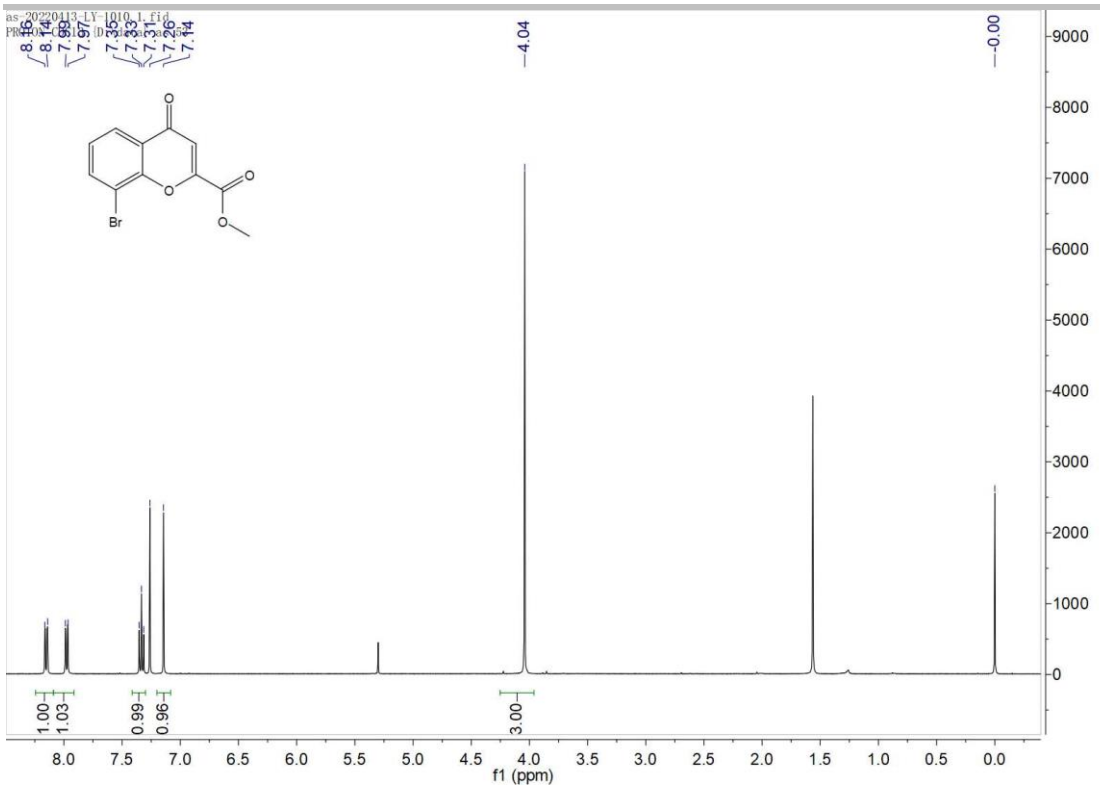

as-20220413-LY-1009.1.fid
PROTON CDCl3 {D:\data} as 51
1.00
0.95
1.02
0.95
2.80
f1 (ppm)

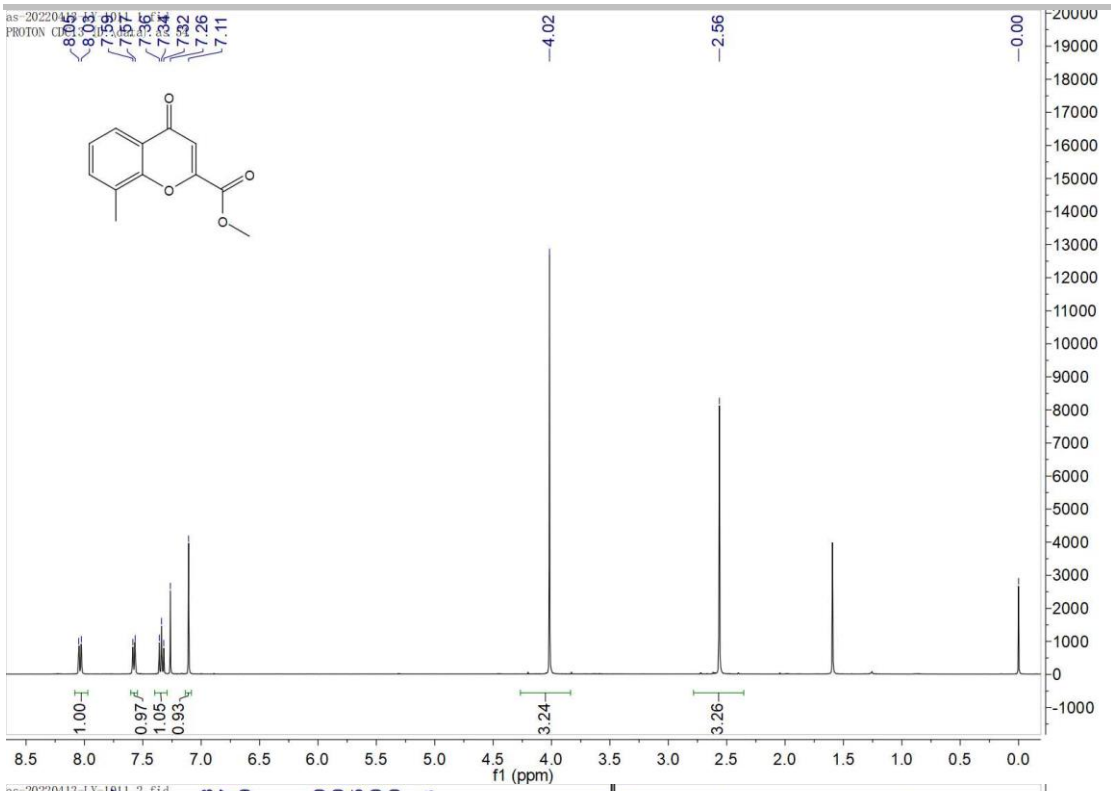

191.65
177.23
160.72
152.24
128.36
115.16
114.79
105.56
105.30
53.60
f1 (ppm)

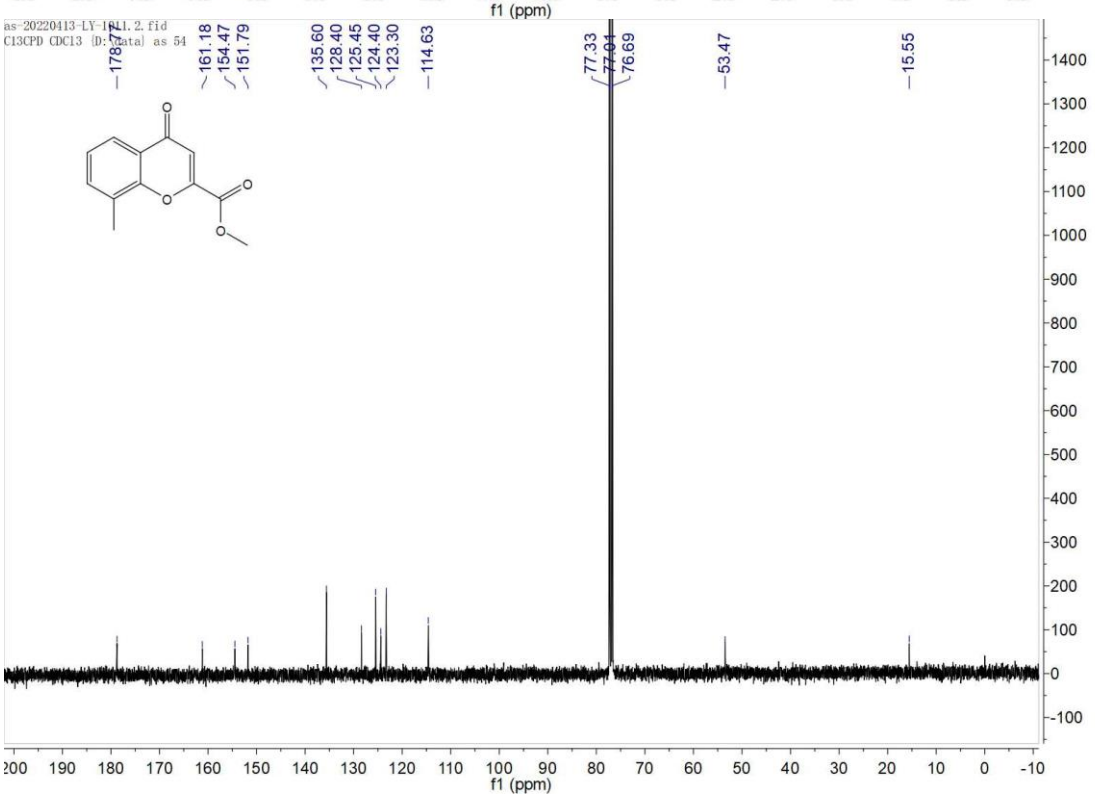

as-20220413-LY-1009.4.fid
F19CPD CDCl3 (D:\data) as 51
100.63
F
O
O
O
O
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

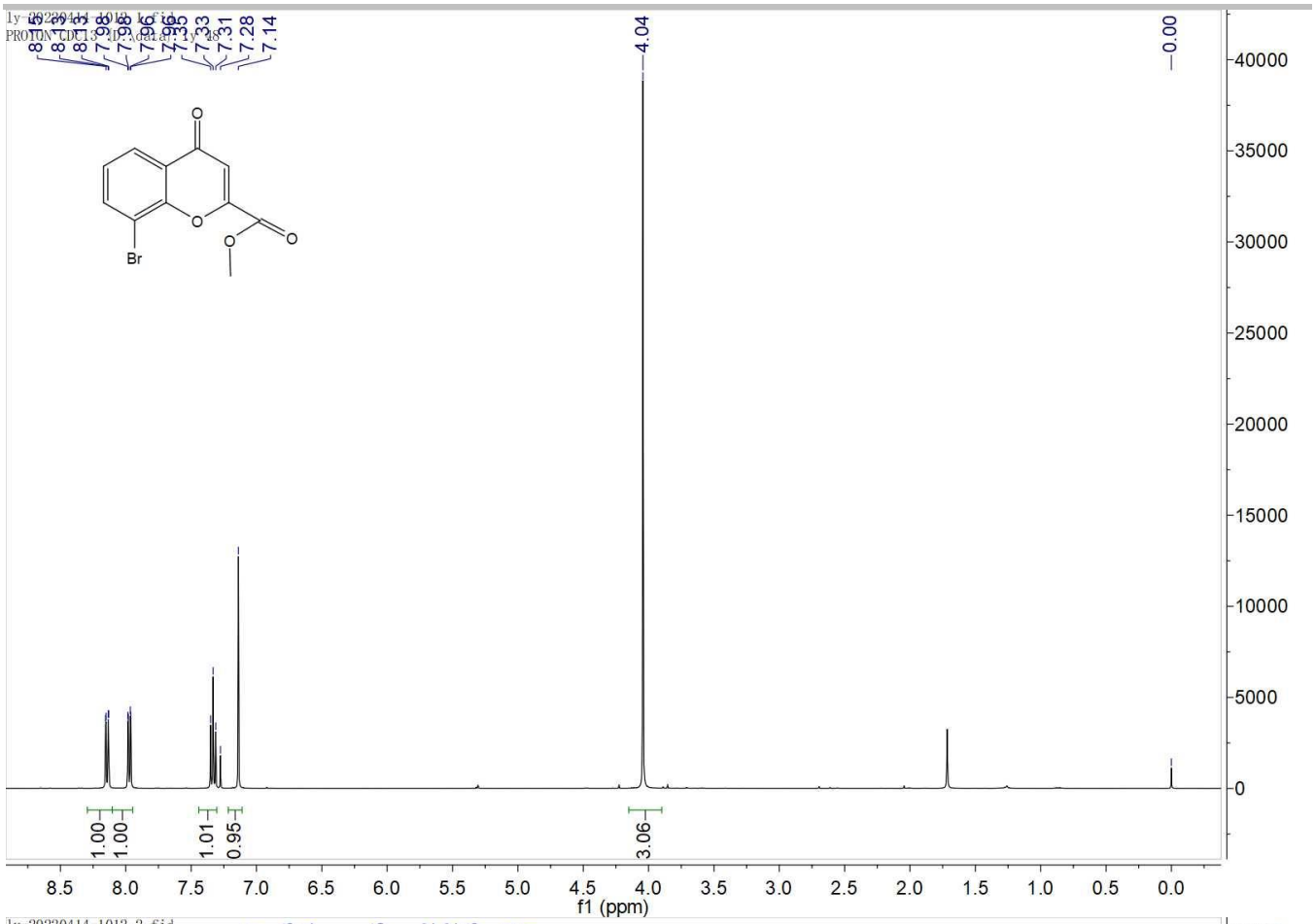

8.08
8.06
7.41
7.28
7.26
7.08
4.01
2.51
0.00
1.00
1.04
0.85
0.98
3.14
3.17
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

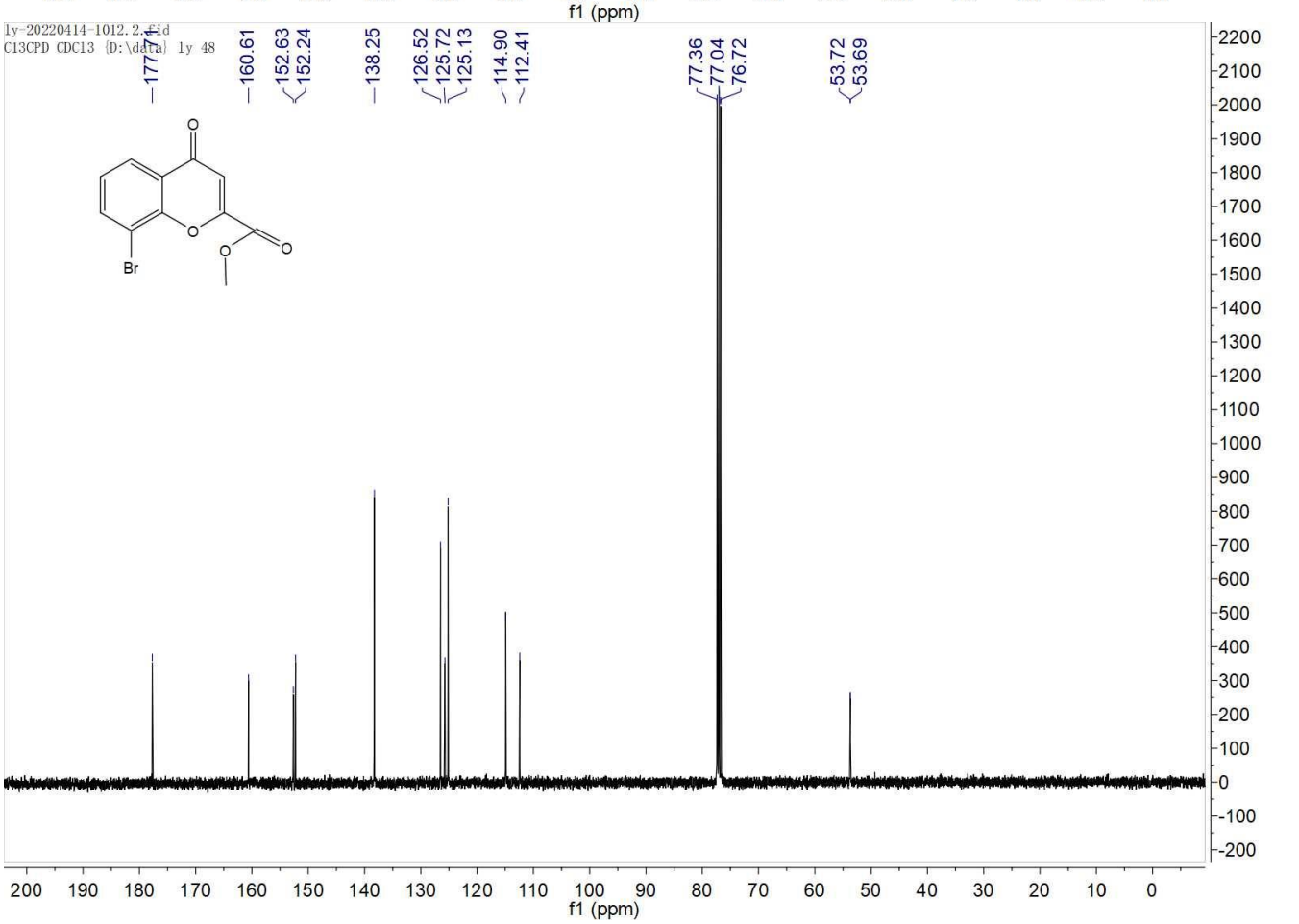

178.15
161.08
156.03
151.66
146.34
127.45
125.43
122.17
118.37
114.91
77.32
77.00
76.68
53.46
21.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

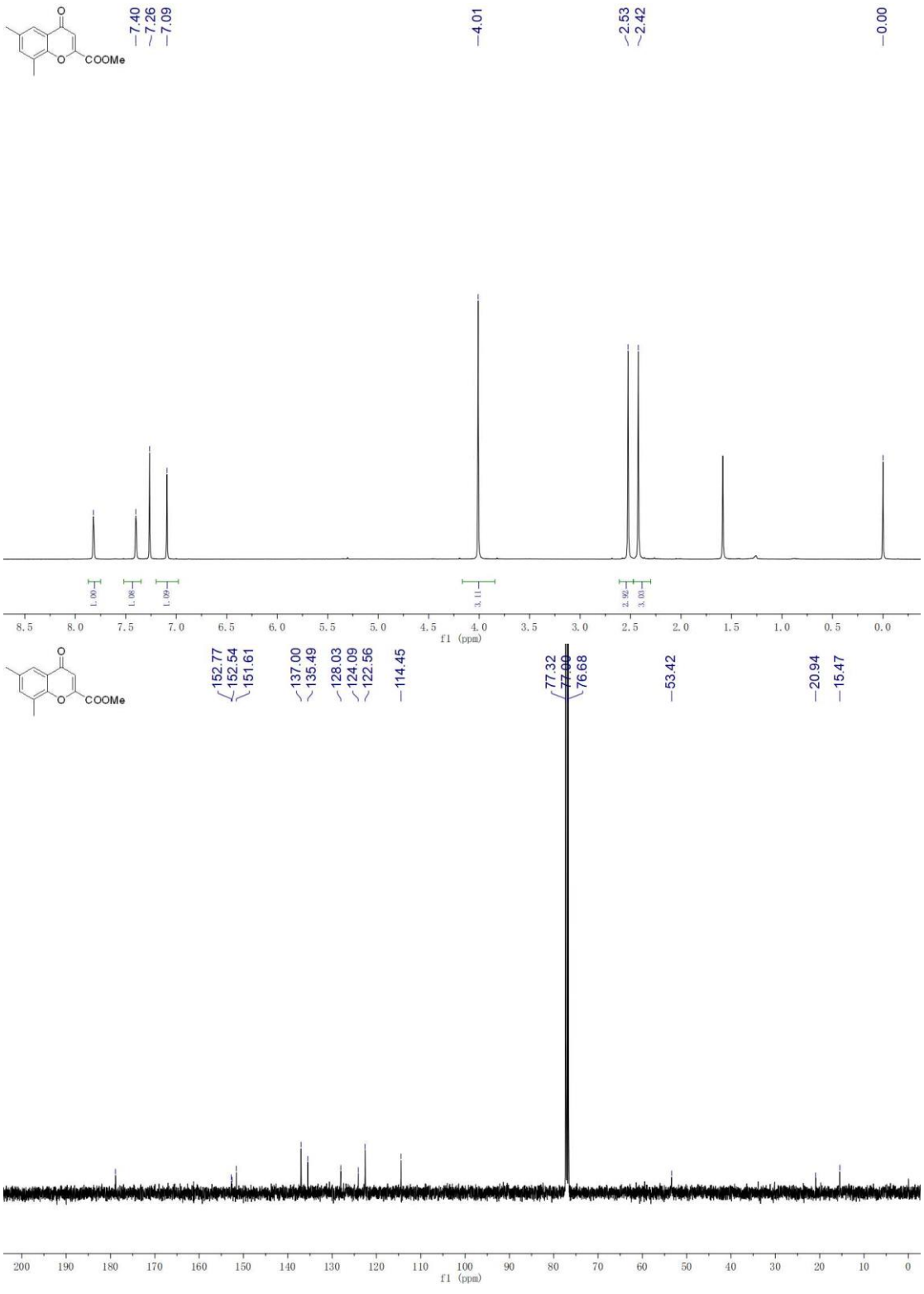

8.16
8.14
7.99
7.97
7.35
7.33
7.31
7.26
7.14
4.04
0.00
Br
O
O
O
O
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
1.03
0.99
0.96
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

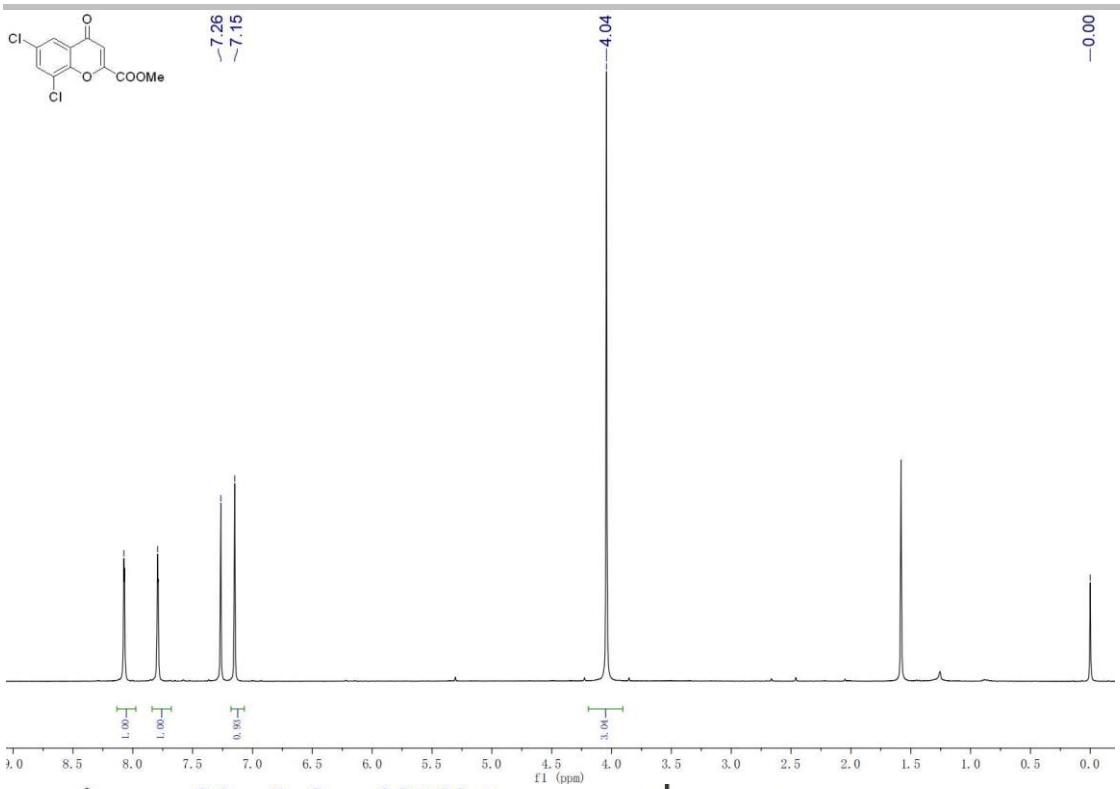

8.05
8.03
7.57
7.36
7.34
7.32
7.26
7.11
4.02
2.56
0.00
1.00
0.97
1.05
0.93
3.24
3.26
f1 (ppm)

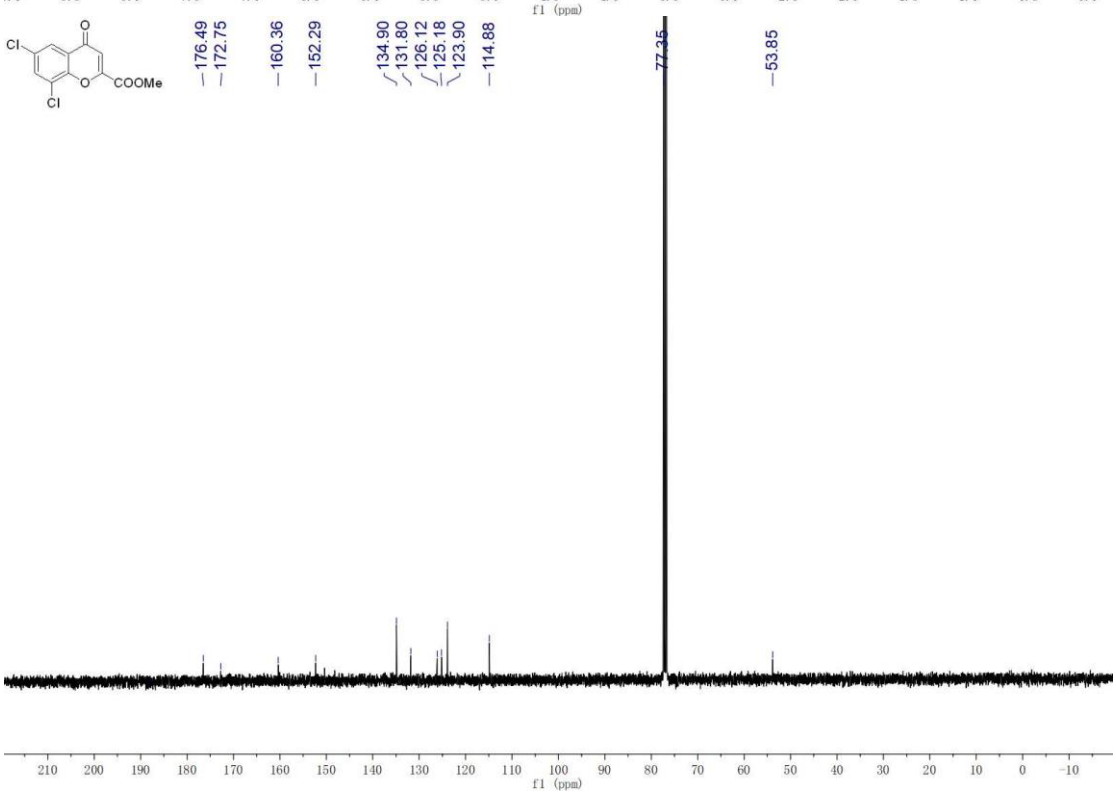

178.71
161.18
154.47
151.79
135.60
128.40
125.45
124.40
123.30
114.63
77.33
77.04
76.69
53.47
15.55
f1 (ppm)

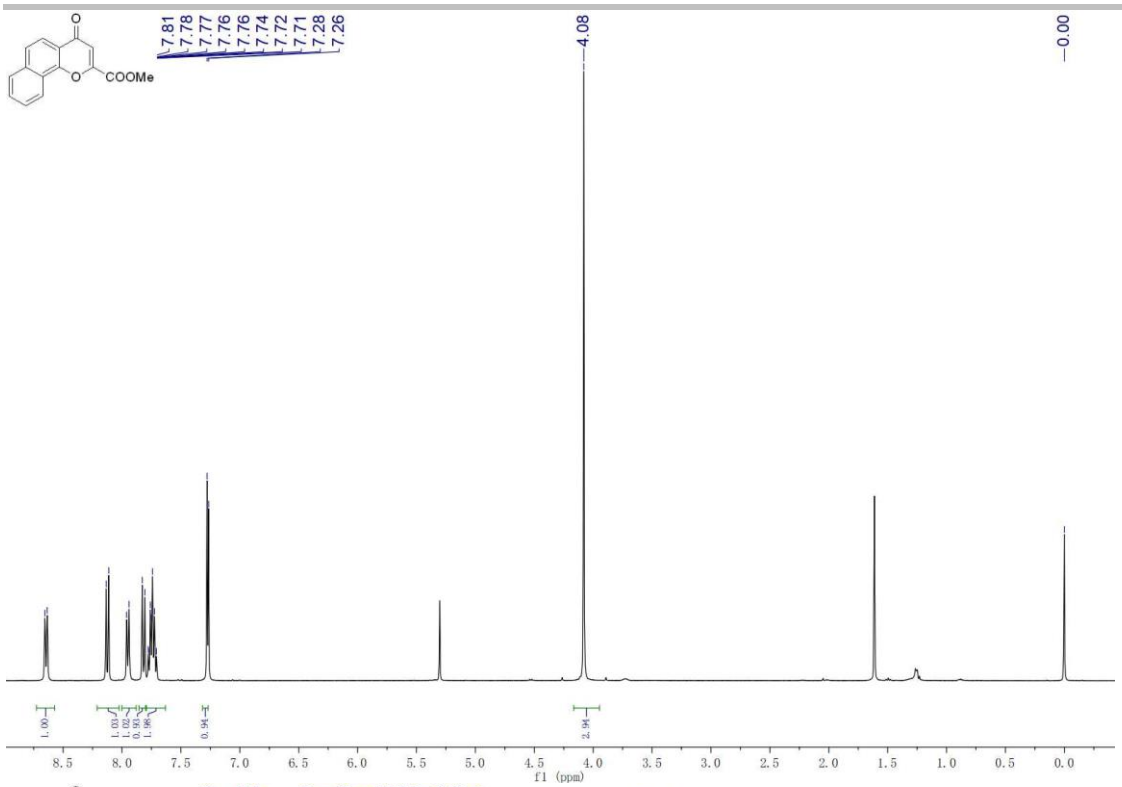

PROTON CDCl3
8.18
8.13
7.98
7.96
7.35
7.33
7.31
7.28
7.14
4.04
0.00
Br
1.00
1.00
1.01
0.95
3.06
f1 (ppm)

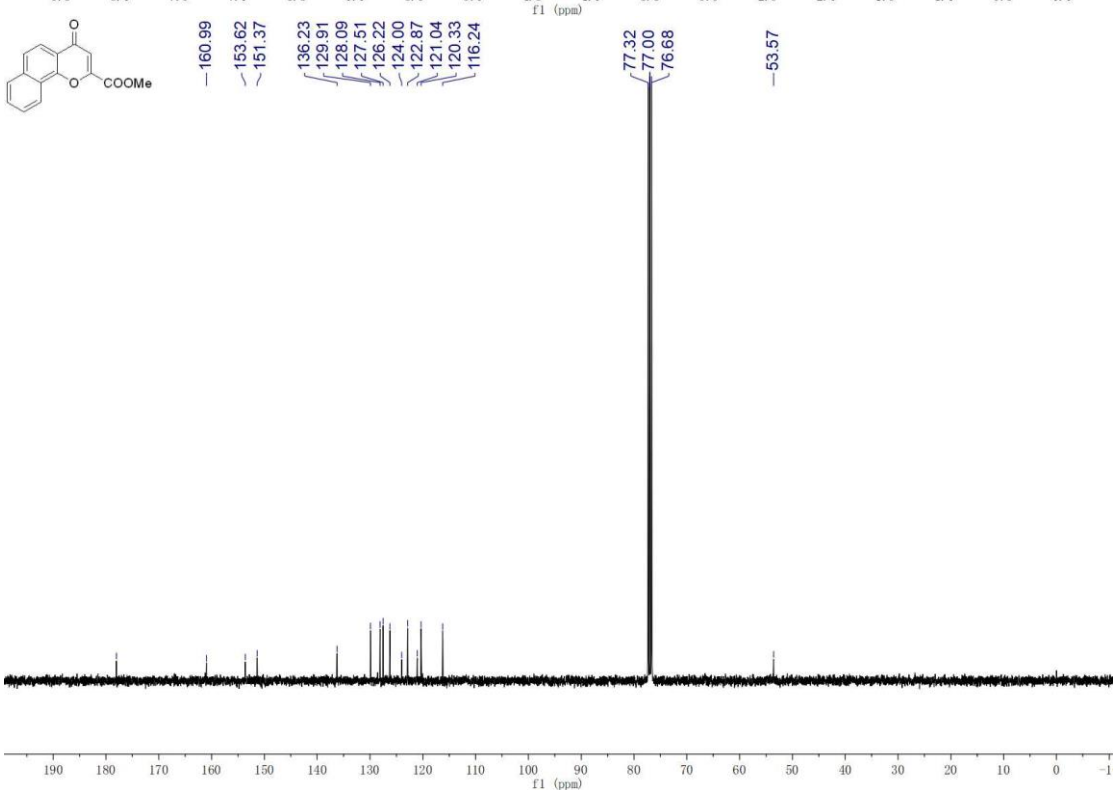

C13CPD CDCl3
177.11
160.61
152.63
152.24
138.25
126.52
125.72
125.13
114.90
112.41
77.36
77.04
76.72
53.72
53.69
Br
f1 (ppm)

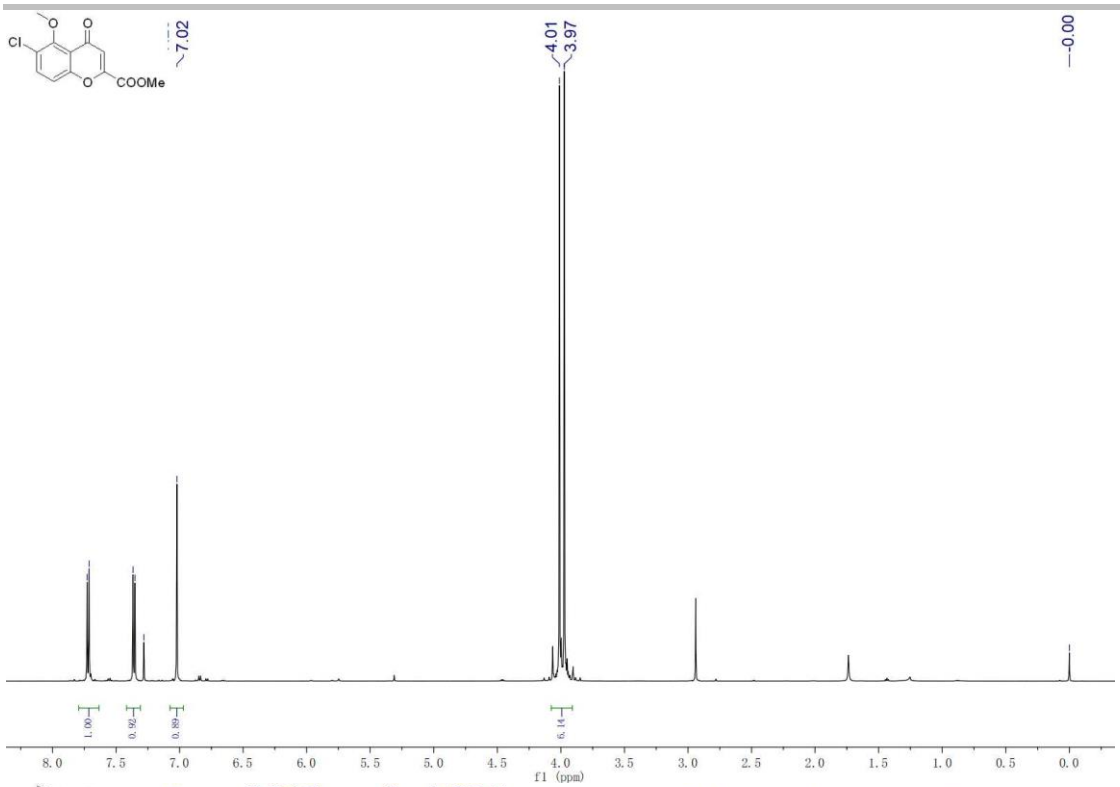

COOMe
7.40
7.26
7.09
4.01
2.53
2.42
0.00
1.00
1.08
1.09
3.11
2.92
3.03
f1 (ppm)
COOMe
152.77
152.54
151.61
137.00
135.49
128.03
124.09
122.56
114.45
77.32
77.00
76.68
53.42
20.94
15.47
f1 (ppm)

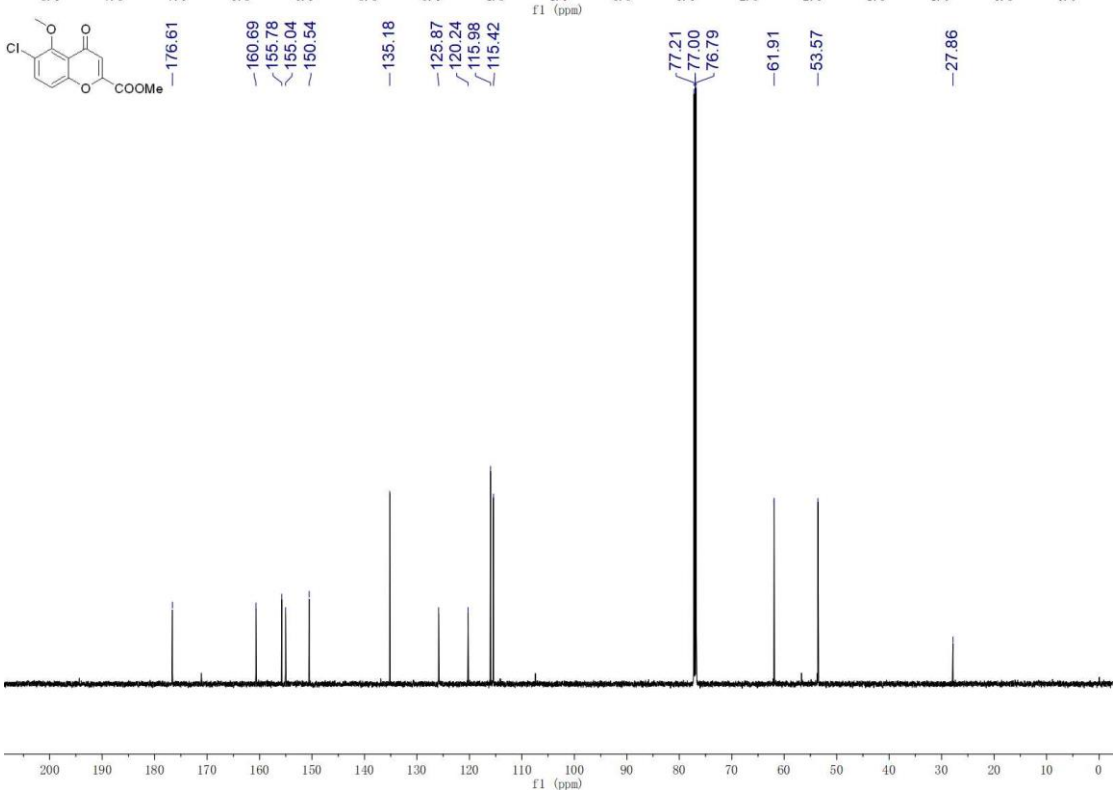

Cl
O
COOMe
Cl
7.26
7.15
4.04
0.00
1.00
1.00
0.98
3.04
f1 (ppm)

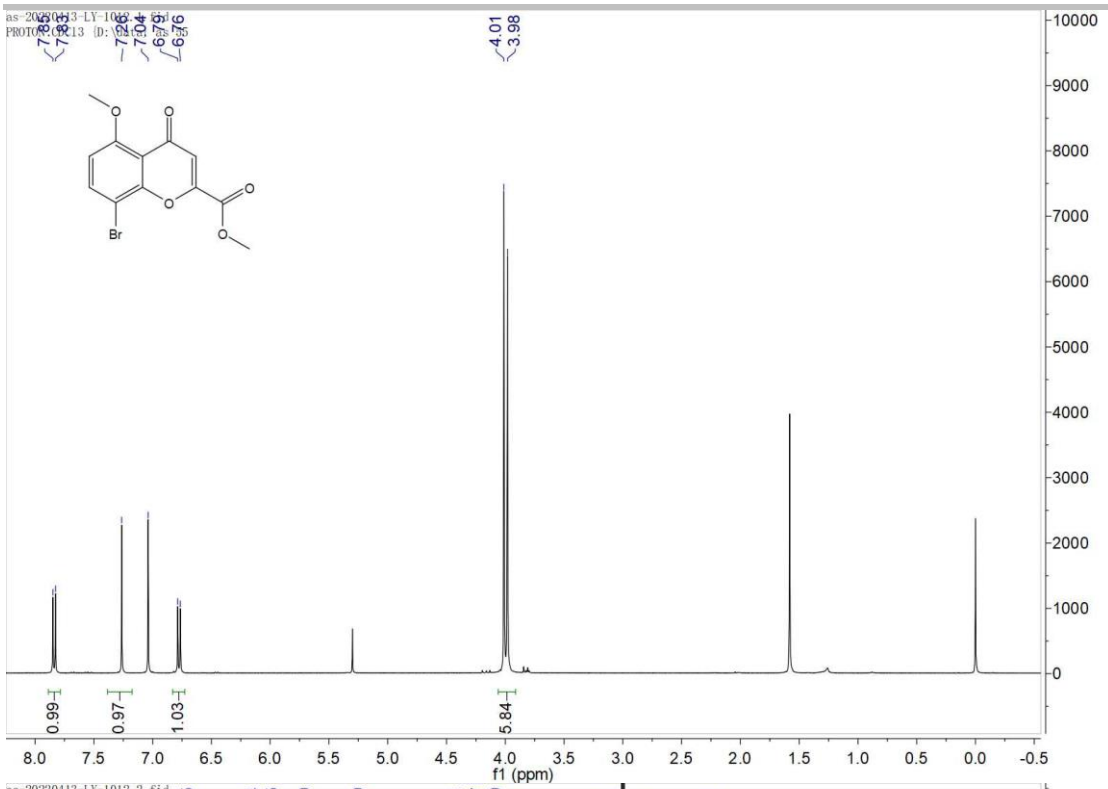

Cl
O
COOMe
Cl
176.49
172.75
160.36
152.29
134.90
131.80
126.12
125.18
123.90
114.88
77.35
53.85
f1 (ppm)

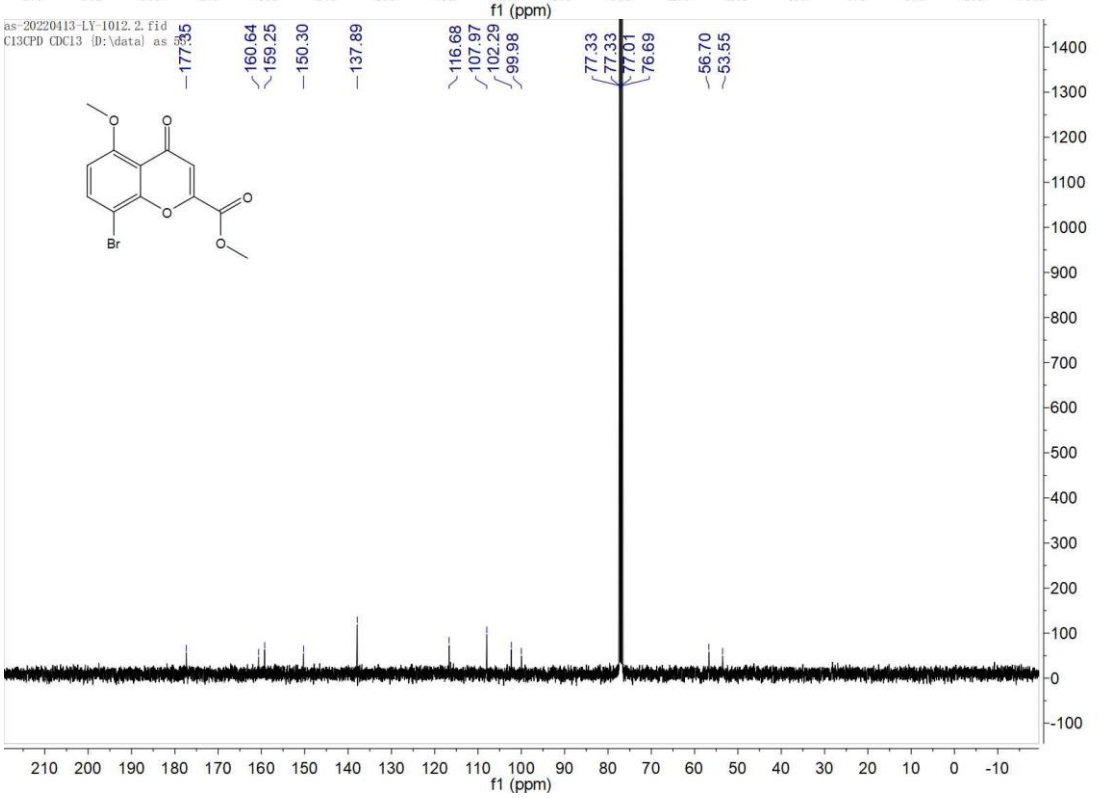

COOMe
7.81
7.78
7.77
7.76
7.76
7.74
7.72
7.71
7.28
7.26
4.08
0.00
1.00
1.03
1.02
0.93
1.96
0.94
2.94
f1 (ppm)

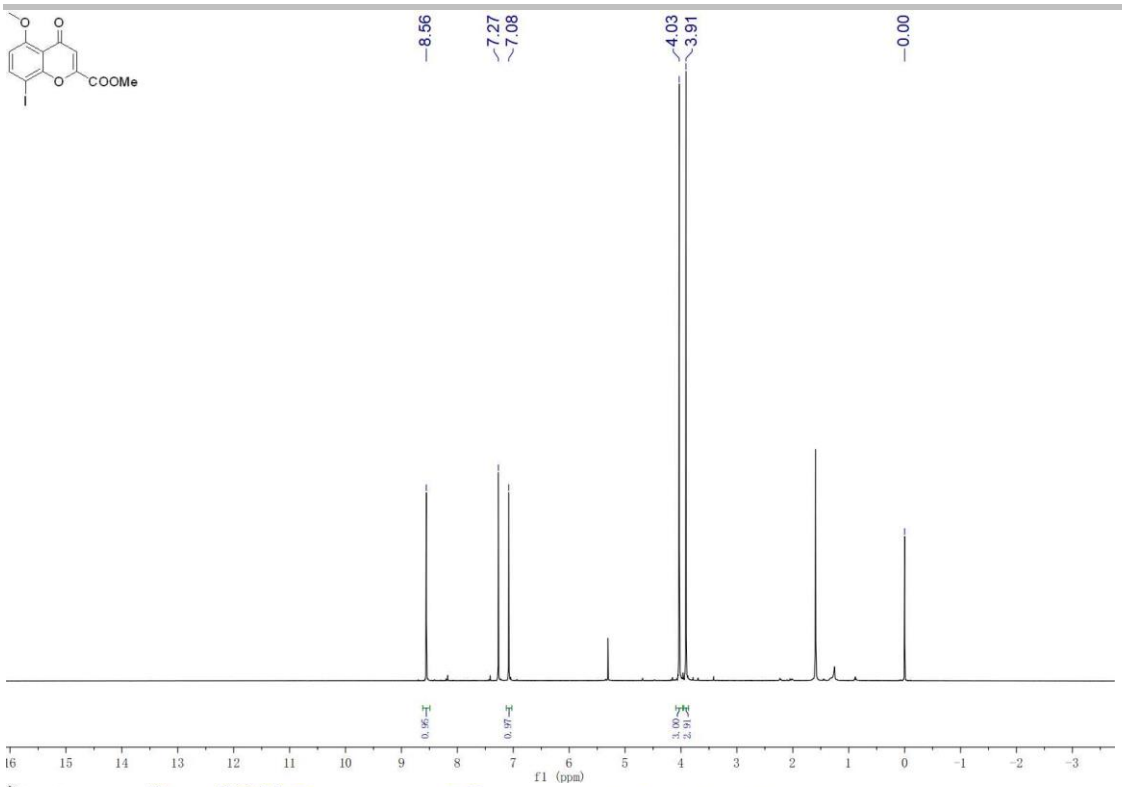

COOMe
160.99
153.62
151.37
136.23
129.91
128.09
127.51
126.22
124.00
122.87
121.04
120.33
116.24
77.32
77.00
76.68
53.57
f1 (ppm)

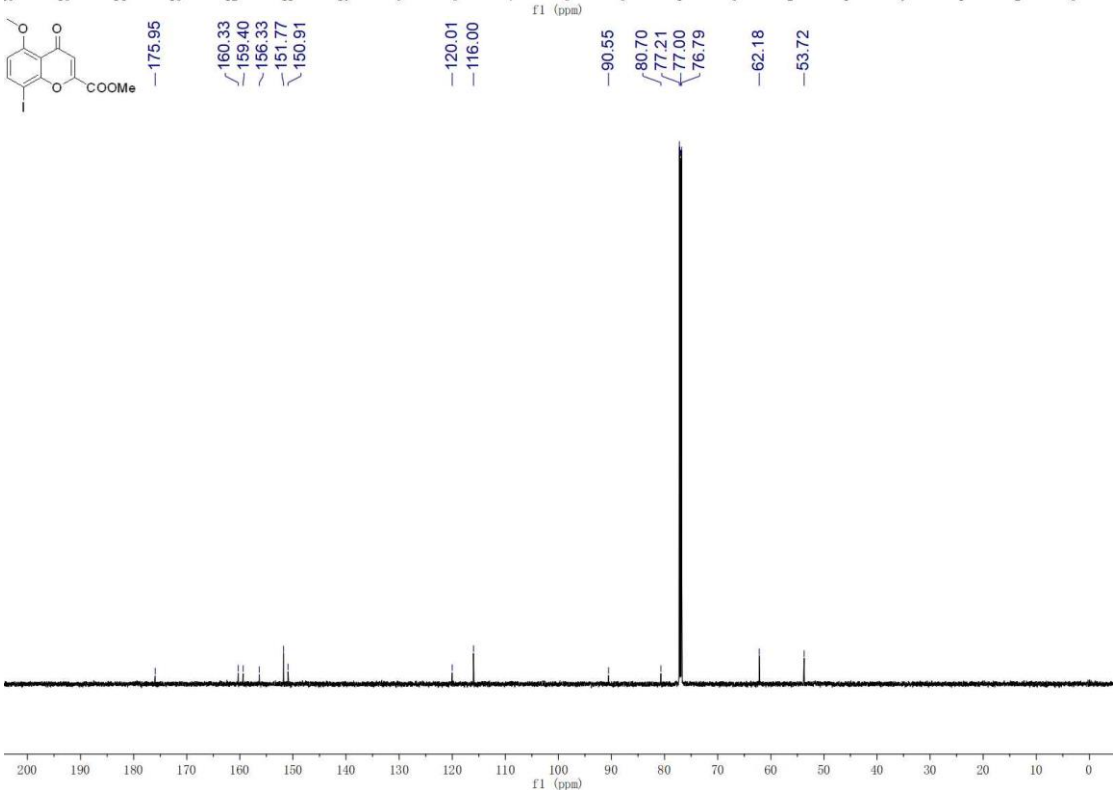

Cl
O
O
COOMe
7.02
4.01
3.97
0.00
1.00
0.92
0.89
6.14
f1 (ppm)

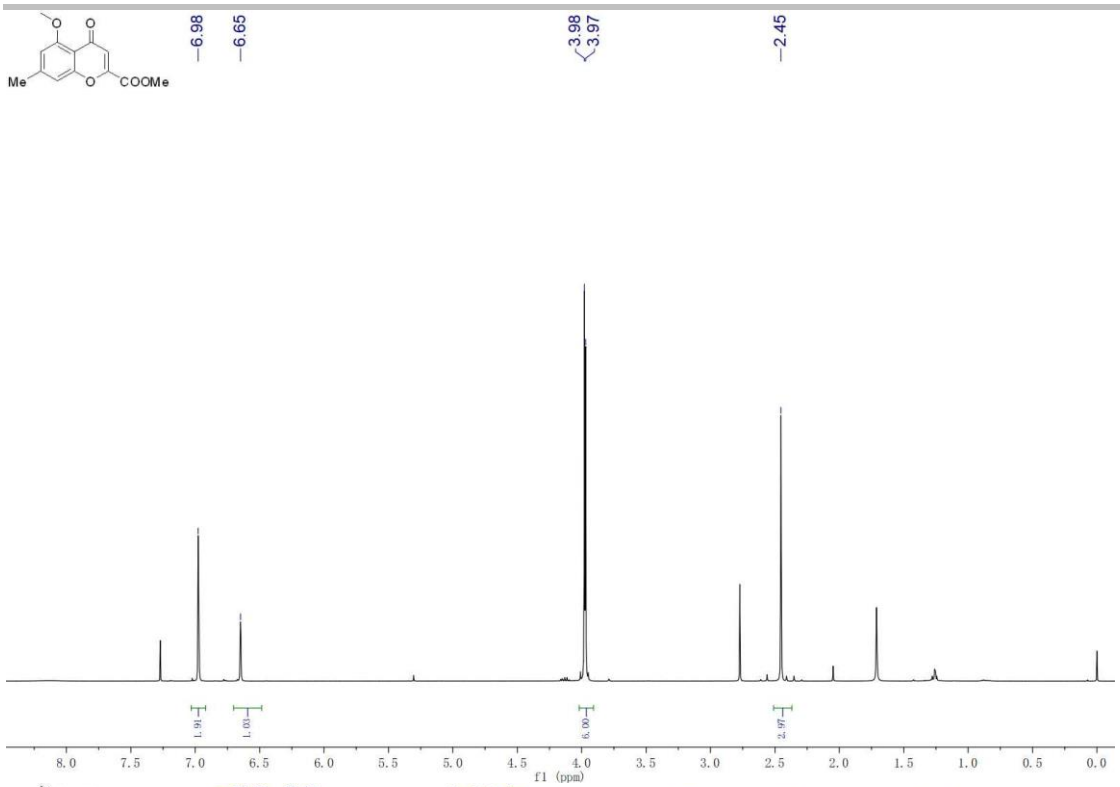

Cl
O
O
COOMe
176.61
160.69
155.78
155.04
150.54
135.18
125.87
120.24
115.98
115.42
77.21
77.00
76.79
61.91
53.57
27.86
f1 (ppm)

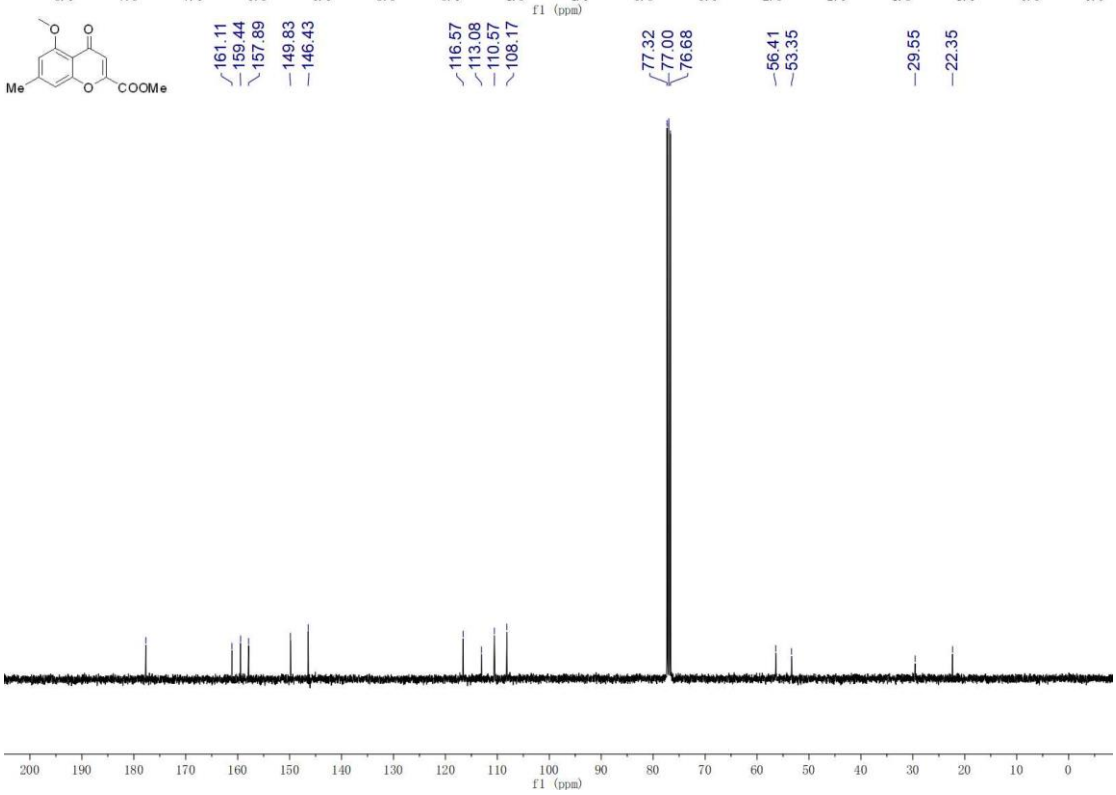

4.01
3.98
0.99
0.97
1.03
5.84
f1 (ppm)

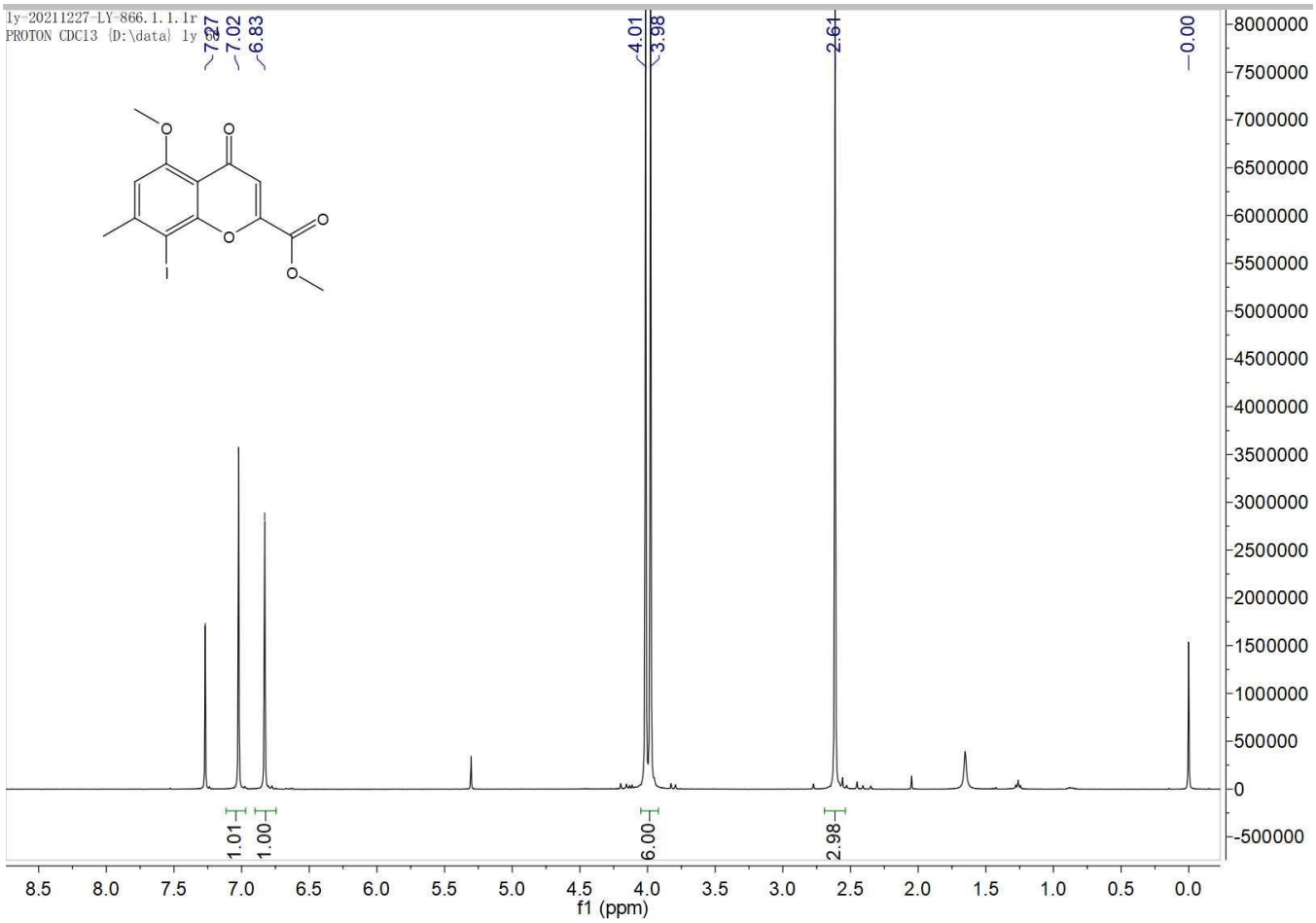

177.35
160.64
159.25
150.30
137.89
116.68
107.97
102.29
99.98
77.33
77.33
77.01
76.69
56.70
53.55
f1 (ppm)

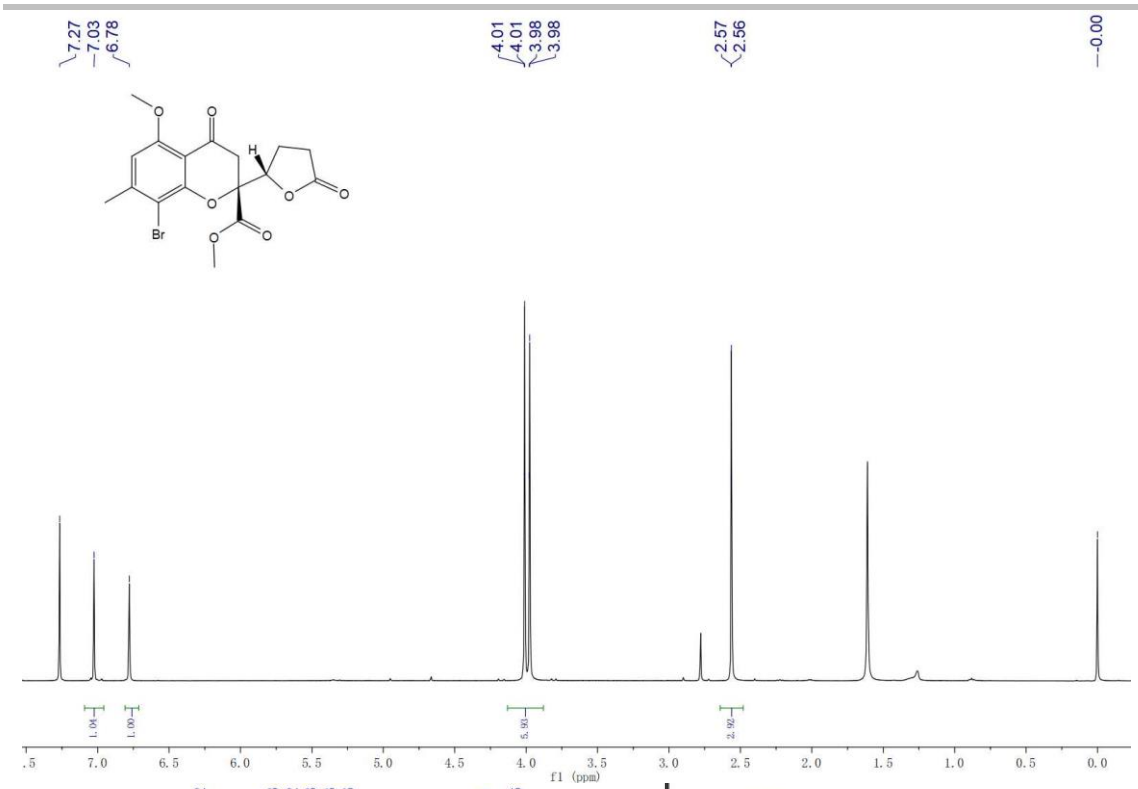

COOMe
8.56
7.27
7.08
4.03
3.91
0.00
f1 (ppm)

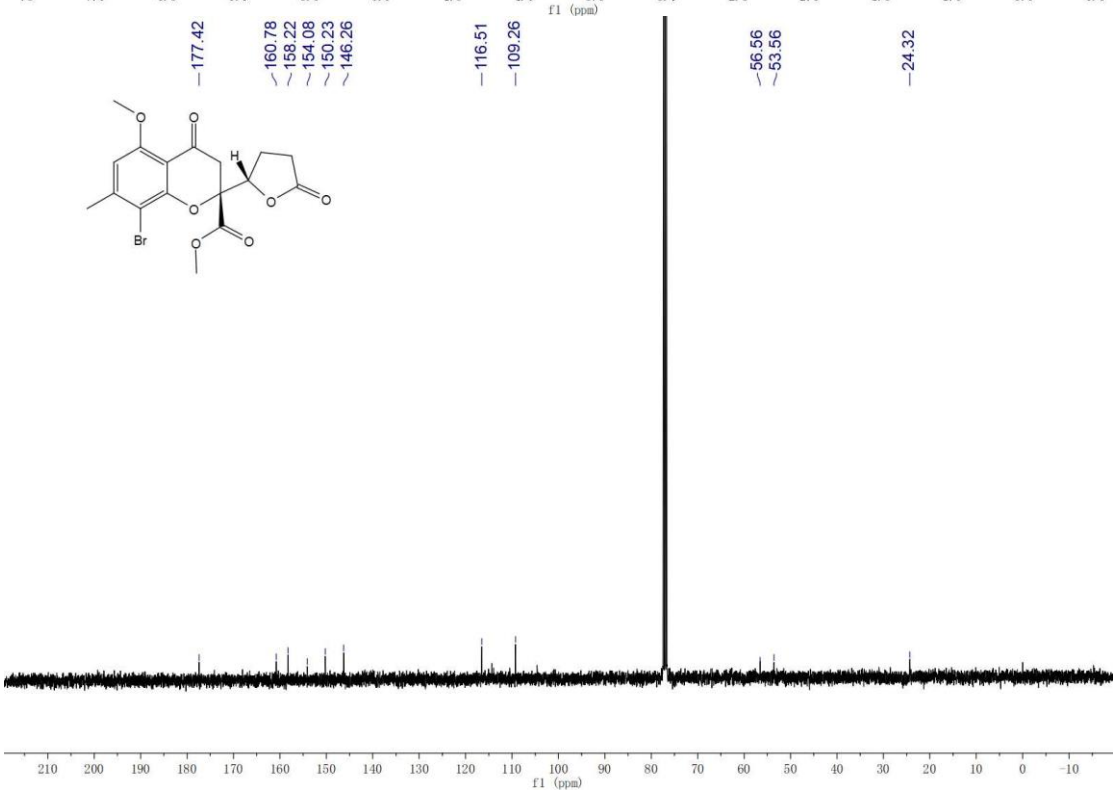

COOMe
175.95
160.33
159.40
156.33
151.77
150.91
120.01
116.00
90.55
80.70
77.21
77.00
76.79
62.18
53.72
f1 (ppm)

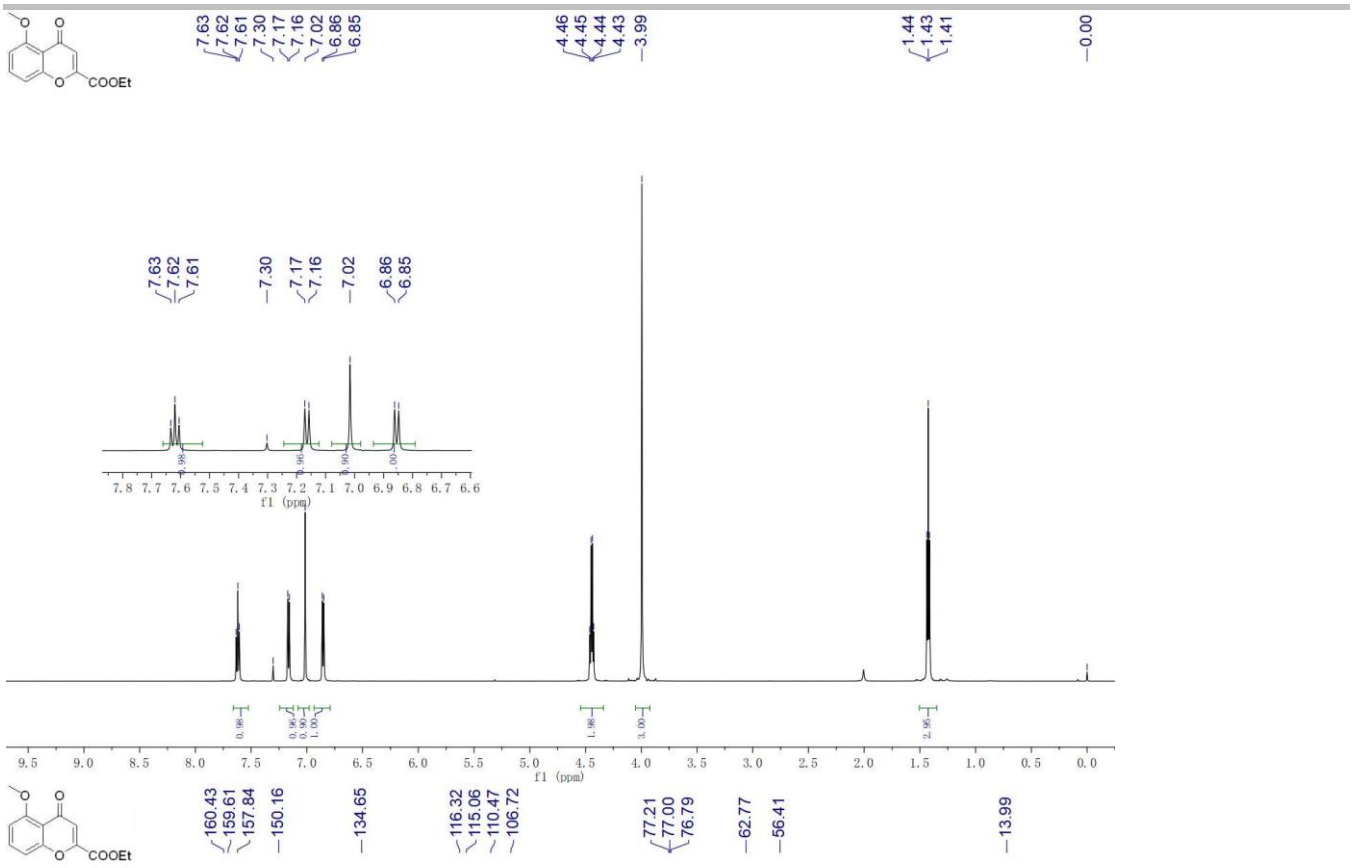

Me
COOMe
6.98
6.65
3.98
3.97
2.45
1.91
1.03
6.00
2.97
f1 (ppm)

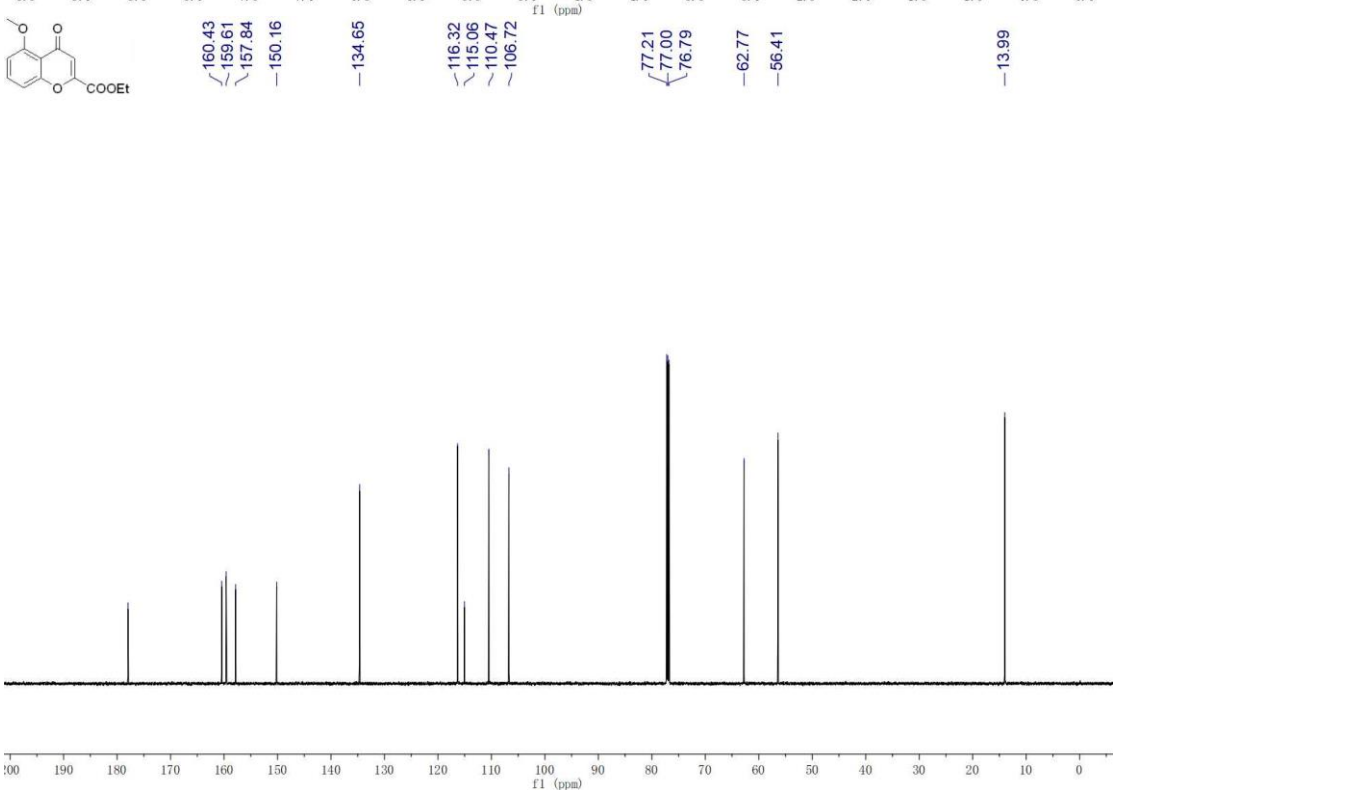

Me
COOMe
161.11
159.44
157.89
149.83
146.43
116.57
113.08
110.57
108.17
77.32
77.00
76.68
56.41
53.35
29.55
22.35
f1 (ppm)


ly-20211227-LY-866.1.1.1r
PROTON CDC13 {D:\data} ly
7.27
7.02
6.83
4.01
3.98
2.61
0.00
1.01
1.00
6.00
2.98
f1 (ppm)


7.27
7.03
6.78
4.01
4.01
3.98
3.98
2.57
2.56
0.00
Br
f1 (ppm)


177.42
160.78
158.22
154.08
150.23
146.26
116.51
109.26
56.56
53.56
24.32
Br
f1 (ppm)


7.63
7.62
7.61
7.30
7.17
7.16
7.02
6.86
6.85
4.46
4.45
4.44
4.43
3.99
1.44
1.43
1.41
0.00
COOEt
f1 (ppm)


160.43
159.61
157.84
150.16
134.65
116.32
115.06
110.47
106.72
77.21
77.00
76.79
62.77
56.41
13.99
COOEt
f1 (ppm)