Supporting Information

Chiral Bifunctional Organocatalysts for Enantioselective Synthesis of 3-Substituted Isoindolinones

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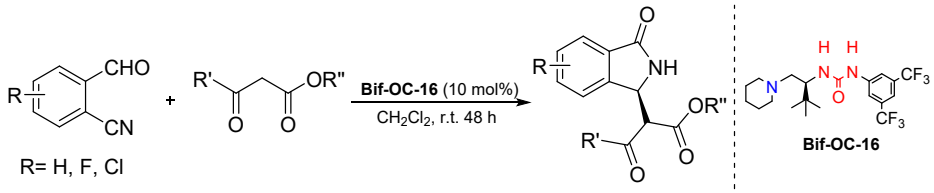
1. General Information and Starting Materials

^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ solution on a Bruker AV-400 spectrometer using TMS as an internal reference. Coupling constant (*J*) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High-resolution mass spectra were performed on a Bruker microTOF-Q II Mass Spectrometer with ES ionization (ESI). All commercially available reagents were used as received. Thin-layer chromatography on silica (with GF254) was used to monitor all reactions. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Chiral High Performance Liquid Chromatography (HPLC) analyses were performed using an Agilent 1200 Series apparatus and Chiralpak AD-H, OD-H and AS-H columns purchased from Daicel Chemical Industries. The configuration of the products has been assigned by comparison to the literature data or assigned by analogy. All solvents, inorganic reagents were from commercial sources and used without purification unless otherwise noted. The characterization data of chiral bifunctional organocatalysts **CPTC-1~16** and **Bif-OC-1~16** were found in our previous reports [1-3].

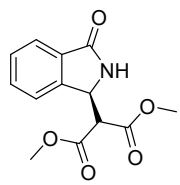
2. General Procedures



A mixture of 2-cyanobenzaldehyde (15 mg, 0.1 mmol), **Bif-OC-16** (10 mol%) and malonates or β-ketoesters (0.1 mmol) was dissolved in dichloromethane (2 mL) and stirred at room temperature. The reaction was monitored by TLC. After 2 days, the reaction mixture was directly purified by a flash column chromatography (2:1 ethyl acetate/*n*-hexane) to afford the desired product.

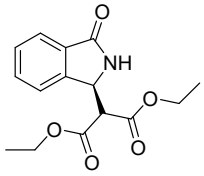
3. Characterization Data

Dimethyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (3aa)[4]



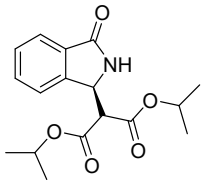
White solid, 93% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.88 (d, *J* = 7.4 Hz, 1H), 7.62-7.54 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.81 (s, 1H), 5.21 (d, *J* = 7 Hz, 1H), 4.00-3.85 (m, 3H), 3.76-3.66 (m, 3H), 3.64-3.62 (m, 1H). **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): 17.7 min (minor), 30.0 min (major), 57% *ee*.

Diethyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (3ab)[4]



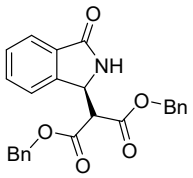
White solid, 88% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.89 (d, *J*=7Hz, 1H), 7.59-7.51 (m, 2H), 7.38 (d, *J* = 7.4 Hz, 1H), 6.80 (s, 1H), 5.19 (d, *J* = 7.2 Hz, 1H), 4.35-3.31 (m, 2H), 4.16-4.11 (m, 2H), 3.65 (d, *J* = 7.4 Hz, 1H), 1.36-1.32 (m, 3H), 1.15-1.12 (m, 3H). **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min): 37.0 min (minor), 46.2 min (major), 57% *ee*.

Diisopropyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (3ac)[4]



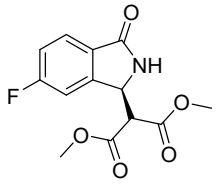
White solid, 73% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.88 (d, *J* = 7 Hz, 1H), 7.59-7.51 (m, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 6.80 (s, 1H), 5.25-5.16 (m, 2H), 4.99-4.94 (m, 1H), 3.62 (d, *J* = 7.2 Hz, 1H), 1.32 (d, *J* = 7.4 Hz, 6H), 1.15-1.10 (m, 6H). **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 79.8 min (minor), 82.0 min (major), 70% *ee*.

Dibenzyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (3ad)[4]



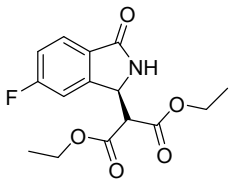
White solid, 89% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.82 (d, *J* = 7 Hz, 1H), 7.44-7.28 (m, 12H), 7.15-7.17 (m, 2H), 6.78 (s, 2H), 5.26 (s, 2H), 5.08 (s, 2H), 3.71 (d, *J* = 7.2 Hz, 1H). **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 46.8 min (minor), 49.0 min (major), 93% *ee*.

Dimethyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (3ba)[4]



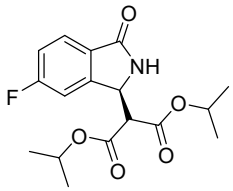
White solid, 94% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.55 (s, 1H), 7.32 (s, 1H), 6.87 (s, 1H), 5.18 (s, 1H), 3.88 (s, 3H), 3.72 (s, 3H), 3.63 (s, 1H). **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): 12.1 min (minor), 24.2 min (major), 66% *ee*.

Diethyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (3bb)



White solid, 85% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ (ppm) 7.61 (s, 1H), 7.47 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.38 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.23 (m, 1H), 5.16 (d, *J* = 7.0 Hz, 1H), 4.33-4.20 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.66 (d, *J* = 7.0 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm) 168.69 (d, *J* = 3.4 Hz), 167.30, 166.52, 164.54, 162.07, 139.17 (d, *J* = 2.8 Hz), 134.40 (d, *J* = 8.8 Hz), 124.78 (d, *J* = 8.6 Hz), 119.59 (d, *J* = 24.0 Hz), 110.88 (d, *J* = 24.0 Hz), 62.30 (d, *J* = 1.4 Hz), 55.99, 54.54, 14.01(d, *J* = 16.2 Hz); **^{19}F NMR** (376 MHz, Chloroform*d*) δ (ppm) -111.60. **HRMS** (ESI) *m/z* Calculated for [$C_{15}H_{16}FNO_5$+H] $(M+H)^+$: 310.1091, found: 310.1090. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min): 28.3 min (minor), 39.3 min (major), 63% *ee*.

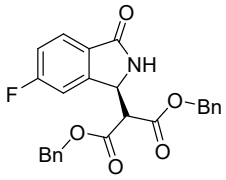
Diisopropyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (3bc)[4]



White solid, 79% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.53-7.28 (m, 2H), 6.92 (s, 1H), 5.20-5.14 (m, 2H), 4.98 (d, *J* = 7.4 Hz, 1H), 3.60 (s, 1H), 1.66 (s, 1H), 1.31-1.14 (m, 12H). **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 59.4 min (major),

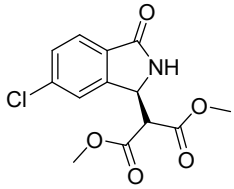
73.5 min (minor), 78% *ee*.

Dibenzyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (3bd)



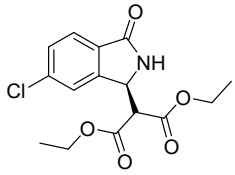
White solid, 86% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ (ppm) 7.46-7.30 (m, 9H), 7.22-7.15 (m, 2H), 7.14-7.05 (m, 2H), 7.01 (s, 1H), 5.25 (s, 2H), 5.17 (d, *J* = 7.4 Hz, 1H), 5.10 (d, *J* = 5.8 Hz, 2H), 3.72 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm) 168.56 (d, *J* = 3.6 Hz), 166.98, 166.30, 164.45, 161.97, 138.82 (d, *J* = 2.8 Hz), 134.54(d, *J* = 8.4 Hz), 134.24 (d, *J* = 8.4 Hz), 128.84, 128.75, 128.73, 128.68, 128.65, 128.37, 124.68 (d, *J* = 8.4 Hz), 119.51 (d, *J* = 24.0 Hz), 110.91 (d, *J* = 24.0 Hz), 68.02 (d, *J* = 10.0 Hz), 56.02, 54.50; **^{19}F NMR** (376 MHz, Chloroform-*d*) δ (ppm) -111.50. **HRMS (ESI)** *m/z* Calculated for [$C_{25}H_{20}FNO_5$+H] $(M+H)^+$: 434.1404, found: 434.1409. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 75:25, 1.0 mL/min): 34.1 min (minor), 40.2 min (major), 95% *ee*.

Dimethyl (*S*)-2-(6-chloro-3-oxoisoindolin-1-yl) malonate (3ca)



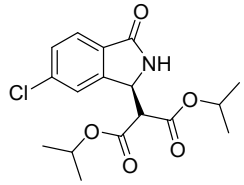
White solid, 91% yield. **^{1}H NMR** (**1H NMR** (400 MHz, Chloroform-*d*) δ (ppm) 7.83 (d, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.21 (s, 1H), 5.19 (d, *J* = 7.6 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.65 (d, *J* = 7.6 Hz, 1H); **13C NMR** (101 MHz, Chloroform-*d*) δ (ppm) 168.48, 167.52, 166.93, 141.77, 135.54, 133.90, 132.31, 124.36, 55.77, 54.65, 53.22; **HRMS (ESI)** *m/z* Calculated for [$C_{13}H_{12}ClNO_5$+H] $(M+H)^+$: 298.0482, found: 298.0484. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): 11.8 min (minor), 47.6 min (major), 60% *ee*.

Diethyl (*S*)-2-(6-chloro-3-oxoisoindolin-1-yl) malonate (3cb)



White solid, 85% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ (ppm) 7.81 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.23 (s, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 4.39-4.23 (m, 2H), 4.22-4.06 (m, 2H), 3.65 (d, *J* = 7.0 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm) 168.56, 167.20, 166.44, 141.97, 135.38, 134.02, 132.17, 124.45, 62.30, 55.88, 54.68, 14.00; **HRMS (ESI)** *m/z* Calculated for [$C_{15}H_{16}ClNO_5$+H] $(M+H)^+$: 326.0795, found: 326.0795. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 75:25, 1.0 mL/min): 26.8 min (minor), 56.8 min (major), 66% *ee*.

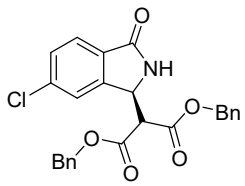
Diisopropyl (*S*)-2-(6-chloro-3-oxoisoindolin-1-yl) malonate (3cc)



White solid, 76% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.83 (d, *J* = 2.0 Hz, 1H), 7.54(dd, *J* = 8.0, 2.0 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 6.96 (s, 1H), 5.28-5.11 (m, 2H), 5.04-4.91 (m, 1H), 3.60 (d, *J* = 6.8 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 6H), 1.15 (t, *J* = 6.4 Hz, 6H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm) 168.77, 166.64, 165.87, 142.23, 134.98, 134.22, 131.87, 124.70, 123.80, 69.87, 55.83, 54.75, 21.32; **HRMS (ESI)** *m/z* Calculated for [$C_{17}H_{20}ClNO_5$+H] $(M+H)^+$: 354.1108, found: 354.1109. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5,

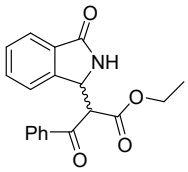
1.0 mL/min): 20.5 min (minor), 22.2 min (major), 81% *ee*.

Dibenzyl (*S*)-2-(6-chloro-3-oxoisoindolin-1-yl) malonate (3cd)



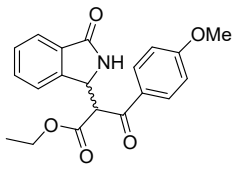
White solid, 84% yield. **^{1}H NMR** (400MHz, Chloroform-*d*) δ (ppm) 7.73 (s, 1H), 7.42-7.30 (m, 9H), 7.19-7.13 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 5.26 (s, 2H), 5.16 (d, *J* = 7.0 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 2H), 3.74 (d, *J* = 7.0 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm) 168.28, 166.94, 166.18, 141.54, 135.40, 134.51, 134.38, 133.76, 132.15, 128.75,128.86, 128.38, 124.32, 68.12, 55.85, 54.56. **HRMS (ESI)** *m/z* Calculated for [$C_{25}H_{20}ClNO_5$+H] $(M+H)^+$: 450.1108, found: 450.1107. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 75:25, 1.0 mL/min): 32.5 min (minor), 54.7 min (major), 72% *ee*.

Ethyl 3-oxo-2-((*S*)-3-oxoisoindolin-1-yl)-3-phenylpropanoate (6aa)



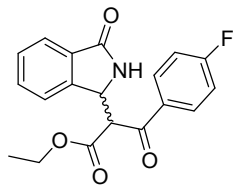
Light yellow oil, 77% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ (ppm): 8.02-7.97 (m, 1H), 7.90-7.85(m, 1H), 7.67-7.60 (m, 1H), 7.61-7.53 (m, 1H), 7.52-7.49 (m, 1H), 7.49-7.42 (m, 3H), 7.04 (s, 0.5H), 6.67 (s, 0.5H), 5.54-5.45 (m, 1H), 4.66-4.39 (m, 1H), 4.31-4.21 (m, 1H), 4.12-4.05 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 1.5H), 1.05 (t, *J* = 7.2 Hz, 1.5H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm): 193.83(193.04), 169.95(169.79), 166.99(166.95), 144.40(144.20), 135.98(135.41), 134.33(134.27), 132.04(131.98), 129.03(129.00), 128.95(128.94), 128.89(128.82), 124.25(124.09), 123.26(123.16), 62.27, 59.84, 57.98, 55.52(55.29), 13.90(13.77); **HRMS (ESI)** *m/z* Calculated for [$C_{19}H_{17}NO_4$+Na] $(M+Na)^+$: 346.1055, found: 346.1047. **HPLC** (Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min]: t_1(minor) = 36.0 min (12.0%), t_2(major) = 40.1 min, 49% *ee*; t_3(minor) = 45.2 min (12.6%), t_4(major) = 60.3 min (40.4%), 53% *ee*; *dr* = 47:53.

Ethyl 3-(4-methoxyphenyl)-3-oxo-2-((*S*)-3-oxoisoindolin-1-yl) propanoate (6ab)



Light yellow oil, 83% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ (ppm): 8.04-7.95 (m, 2H), 7.92-7.83 (m, 1H), 7.62-7.49 (m, 1H), 7.51-7.42 (m, 1H), 7.37-7.33 (m, 0.45H), 7.26-7.24 (m, 0.55H), 7.00-6.94 (m, 2H), 5.53 (d, *J* = 9.6 Hz, 0.45H), 5.46 (d, *J* = 7.8 Hz, 0.55H), 4.55 (d, *J* = 7.8 Hz, 0.55H), 4.34 (d, *J* = 9.6 Hz, 0.45H), 4.32-4.23 (m,1H), 4.14-4.06 (m, 1H), 3.90 (s, 1.4H), 3.89 (s, 1.6H), 1.24 (t, *J* = 7.2 Hz, 1.4H), 1.08 (t, *J* = 7.1 Hz, 1.6H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm): 191.95(191.10), 169.93(169.71), 167.28(167.19), 164.59(164.50), 144.64(144.29), 32.04(131.94), 131.62(131.49), 129.00(128.94), 128.82, 128.30, 124.26(124.04), 123.32(123.08), 114.17(114.07), 62.20, 59.64, 57.68, 55.60(55.37), 13.97(13.83); **HRMS (ESI)** *m/z* Calculated for [$C_{20}H_{19}NO_5$+Na] $(M+Na)^+$: 376.1161, found: 376.1152. **HPLC** (Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min]: t_1(minor) = 26.3 min (8.0%); t_2 (major) = 28.9 min (33.2%), 61%*ee*; t_3(minor) = 32.5 min (11.2%), t_4(major) = 55.0 min (47.6%), 61% *ee*; *dr* = 41:59.

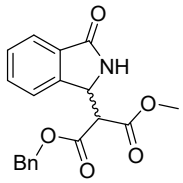
Ethyl 3-(4-fluorophenyl)-3-oxo-2-((*S*)-3-oxoisoindolin-1-yl) propanoate (6ac)



Light yellow oil, 70% yield. **^{1}H NMR** ((400 MHz, Chloroform-*d*) δ (ppm): 8.07-8.03 (m, 2H), 7.92-7.86 (m, 1H), 7.61-7.53 (m, 1H), 7.51-

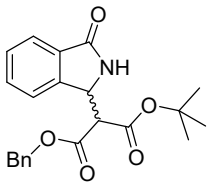
7.45 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 0.5H), 7.26 (d, *J* = 5.8 Hz, 0.5H), 7.23-7.18 (m, 1H), 7.18-7.12 (m, 1H), 6.88 (s, 0.55H), 6.48 (s, 0.45H), 5.52 (d, *J* = 9.4 Hz, 0.45H), 5.46 (d, *J* = 7.4 Hz, 0.55H), 4.57(d, *J* = 7.4 Hz, 0.55H), 4.36 (d, *J* = 9.4 Hz, 0.45H), 4.35-4.25 (m, 1H), 4.15-4.05 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 1.5H), 1.07 (t, *J* = 7.2 Hz, 1.5H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm): 192.22(191.41), 169.82(169.67), 166.84(166.81), 165.21(165.15), 144.31(144.07), 132.12, 132.05(132.03), 131.96(131.94), 131.85 (131.82), 131.72, 129.09(128.99), 124.35(124.19), 123.16(123.05), 116.29 and 116.06 (d, *J*C-F = 12.1 Hz), 62.42(62.39), 59.97, 55.40(55.18), 13.94(13.79); **^{19}F NMR** (376 MHz, Chloroform-*d*) δ (ppm): -111.60; **HRMS (ESI)** *m/z* Calculated for [$C_{19}H_{16}FNO_4$+Na] (M+Na)$^+$: 364.0961, found: 364.0955. **HPLC** (Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 75:25, 0.5 mL/min): t_1(minor) = 27.2 min (13.8%), t_2(major) = 28.9 min (31.3%), 40% *ee*; t_3(minor) = 41.3 min (17.2%), t_4(major) = 58.0 min (37.7%), 39% *ee*; *dr* = 45:55.

1-Benzyl 3-methyl 2-((*S*)-3-oxoisoindolin-1-yl) malonate (6ad)



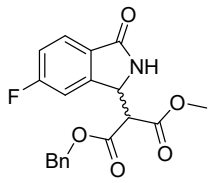
Light yellow oil, 77% yield. **^{1}H NMR** ((400 MHz, Chloroform-*d*) δ (ppm): 7.85 (t, *J* = 6.6 Hz, 1H), 7.57-7.50 (m, 1H), 7.49-7.42 (m, 1H), 7.40 (s, 2H), 7.37-7.32 (m, 2H),7.21-7.16 (m, 1H), 6.94 (d, *J* = 9.6 Hz, 1H), 5.32 (s, 3H), 5.22-5.18 (m, 1H), 5.11 (s, 1H), 3.83 (s, 1.5H), 3.68 (s, 1.5H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm): 169.83, 167.70(167.16), 167.00(166.39), 143.57(143.55), 134.68(134.60), 132.08, 132.01(131.92), 129.05(129.02), 128.80, 128.73(128.70), 128.61(128.57), 128.21, 124.19(124.12), 123.00(122.87), 67.97(67.84), 56.26(55.95), 54.81, 53.42, 53.04(52.99); **HRMS (ESI)** *m/z* Calculated for [$C_{19}H_{17}NO_5$+Na](M+Na)$^+$: 362.1004, found: 362.1000. **HPLC** (Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): t_1 = 23.6 min (13.9%), t_2 = 24.9 min (14.1%); t_3 = 26.9 min (35.8%), t_4 = 33.3 min (36.2%); *dr* = 28:72.

1-Benzyl 3-(tert-butyl) 2-((*S*)-3-oxoisoindolin-1-yl) malonate (6ae)



Light yellow oil, 64% yield. **^{1}H NMR** ((400 MHz, Chloroform-*d*) δ (ppm): 7.90-7.81 (m, 1H), 7.57-7.51(m, 1H), 7.50-7.49 (m, 1H), 7.49-7.43 (m, 1H), 7.42-7.35 (m, 3H),7.34-7.31 (m, 1H), 7.26-7.22 (m, 1H), 6.93 (s, 1H), 5.37-5.23 (m,1H), 5.20-5.15 (m, 1H), 5.17-5.03 (m, 1H), 3.67(d, *J* = 6.6 Hz, 0.53 H), 3.63 (d, *J* = 7.2 Hz, 0.47 H), 1.41 (s, 4.2H), 1.23 (s, 4.8H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm): 169.89, 167.69(166.92), 166.18(165.25), 143.94(143.85), 134.88(134.75), 132.18(132.09), 131.96(131.93), 128.91(128.87), 128.76(128.74), 128.69, 128.58(128.52), 124.06(123.99), 123.26(123.00), 83.50(83.41), 67.69(67.63), 56.93(56.78), 54.91(54.86), 27.75(27.52); **HRMS (ESI)** *m/z* Calculated for [$C_{22}H_{23}NO_5$+Na](M+Na)$^+$: 404.1474, found: 404.1466. **HPLC** (Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min): t_1(minor) = 39.3 min (6.7%), t_2(major) = 43.3 min (39.1%),71% *ee*; t_3(minor) = 45.5 min (6.3%), t_4(major) = 47.0 min (47.9%), 77% *ee*; *dr* = 46:54.

1-Benzyl 3-methyl 2-((*S*)-6-fluoro-3-oxoisoindolin-1-yl) malonate (6bd)



Light yellow oil, 79% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ (ppm): 7.53-7.41 (m, 1H), 7.40-7.37 (m, 3H), 7.37-7.30 (m, 2H), 7.27-7.19 (m, 1H), 7.23-7.15 (m, 1H), 7.13-7.09 (m, 1H), 5.28 (q, *J* = 12.0 Hz, 1H), 5.20-5.15 (m, 1H), 5.11 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.82 (s, 1.3H), 3.76 (d, *J* = 7.0 Hz, 0.42H), 3.71 (s, 1.7H), 3.63 (d, *J* = 8.0 Hz, 0.58H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ (ppm): 168.72(168.68), 167.62, 167.06, 166.86, 166.16, 164.49, 162.01, 138.99 (dd, *J*C-F = 4.0, 3.0 Hz), 134.63(134.53), 134.33 (dd, *J* = 6.2, 3.0 Hz), 28.76 (dd, *J* = 8.0, 5.0 Hz), 128.61, 128.32, 124.80 (dd, *J* = 11.0, 8.0 Hz), 119.53 (dd, *J* = 22.0, 1.0 Hz), 110.9 (dd, *J* = 18.0, 5.6 Hz), 68.03(67.89), 56.15(55.72), 54.56(54.52), 53.11(53.05); **^{19}F NMR** (376 MHz, Chloroform-*d*) δ (ppm): -111.50; **HRMS (ESI)** *m/z* Calculated for $[C_{19}H_{16}FNO_5+Na](M+Na)^+$: 380.0910, found: 380.0903. **HPLC** (Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): t_1= 15.4 min (11.7%), t_2 = 19.4 min (12.0%); t_3 = 21.4 min (37.6%), t_4 = 29.8 min (38.7%); *dr* = 49:51.

4. References

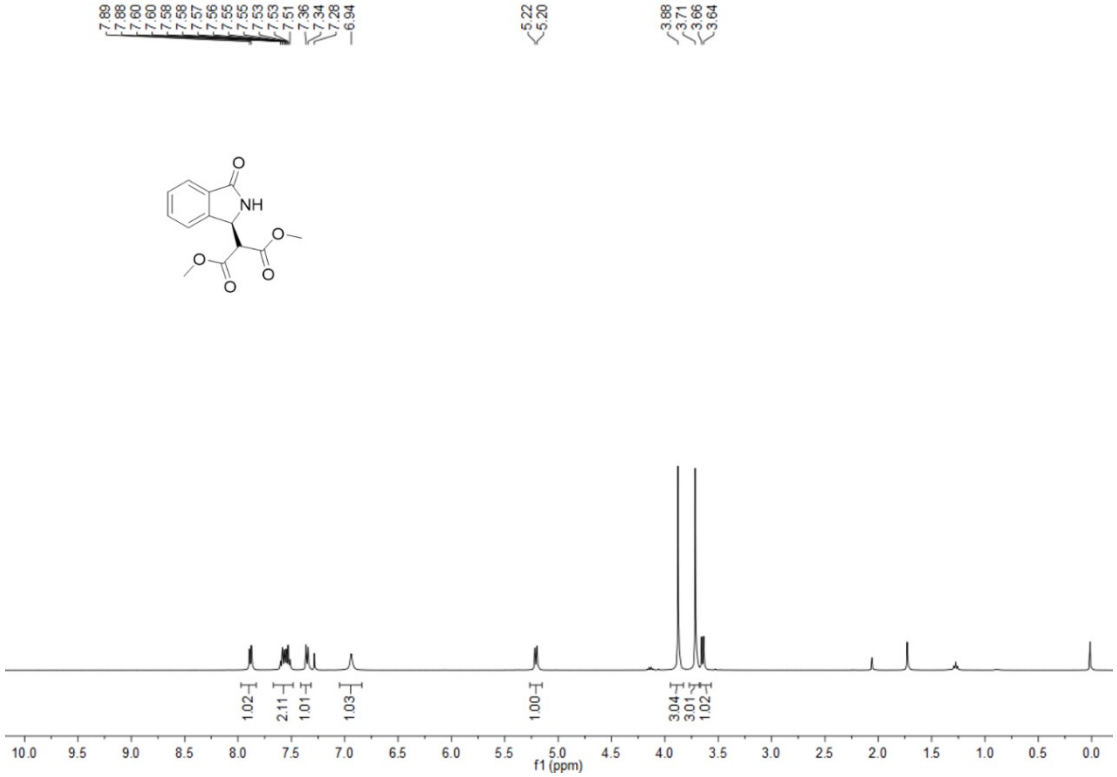
[1] Zhu, J. C.; Cui, D. X.; Li, Y. D.; He, J. X.; Chen, W. P.; Wang, P. A. *Org. Biomol. Chem.* **2018**, *16*, 3012-3017.

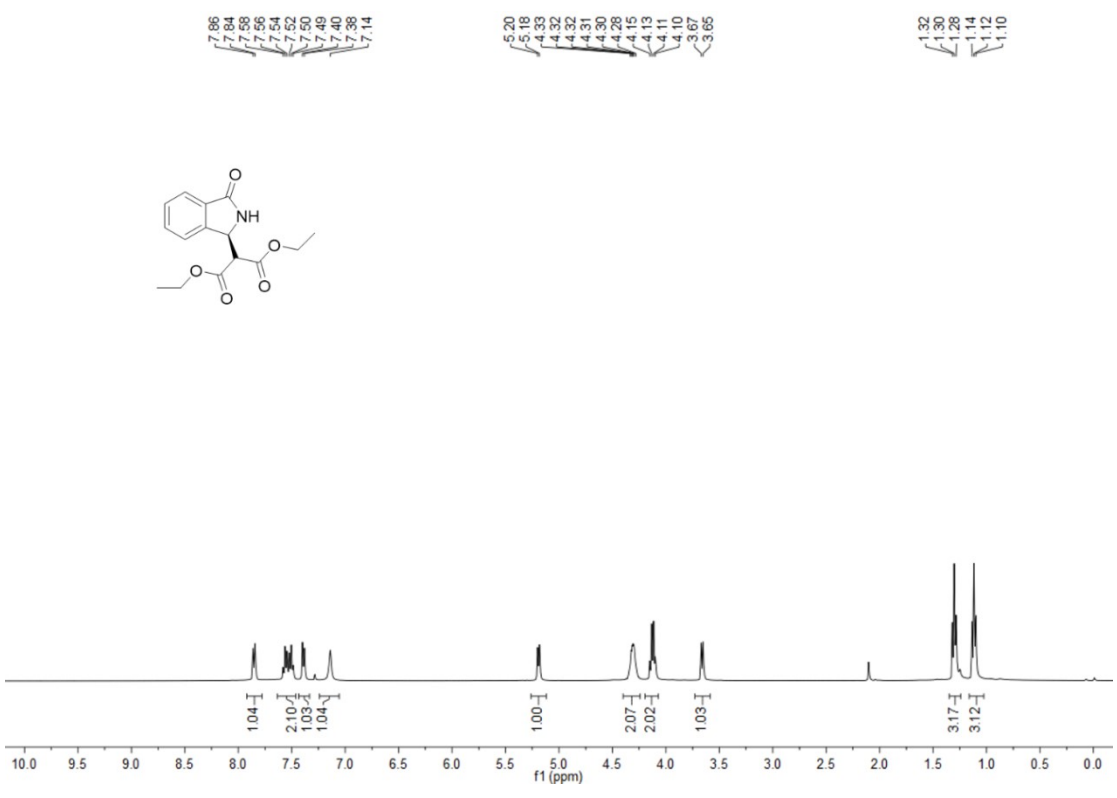
[2] Li, Y.D.; Cui, D. X.; Zhu, J. C.; Huang, P.; Tian, Z.; Jia, Y. Y.; Wang, P. A. *Green Chem.* **2019**, *21*, 5231-5237.

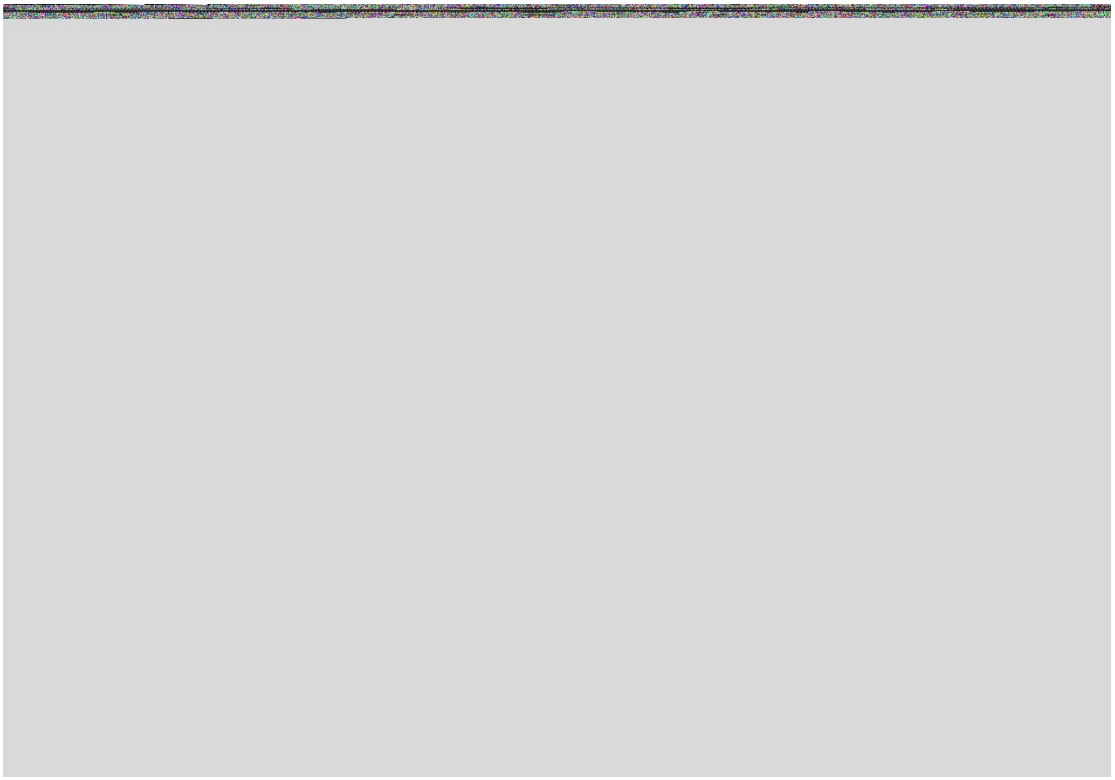
[3] Cui, D. X.; Li, Y. D.; Huang, P.; Tian, Z.; Jia, Y. Y.; Wang, P. A. *RSC Adv.*, **2020**, *10*, 12360-12364.

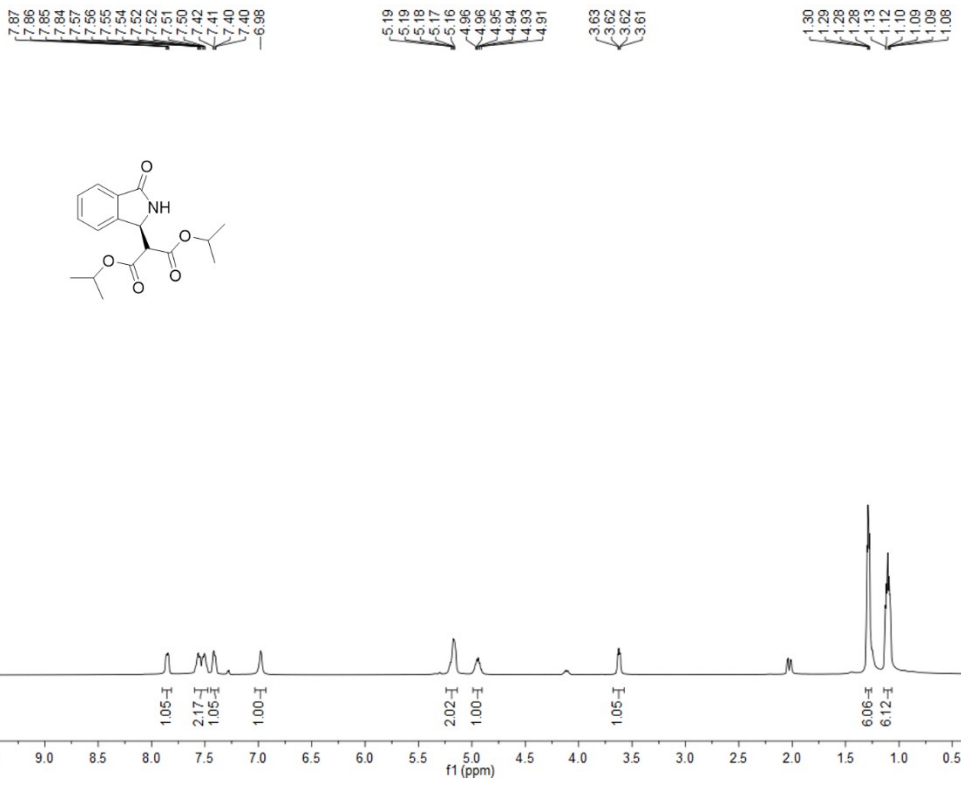
[4] Tiso, S.; Palombi, L.; Vignes, C.; Mola, A. D.; Massa, A. *RSC Adv.* **2013**, *3*, 19380-19387.

5. NMR Spectra





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2.02
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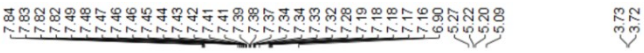
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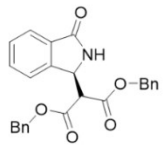
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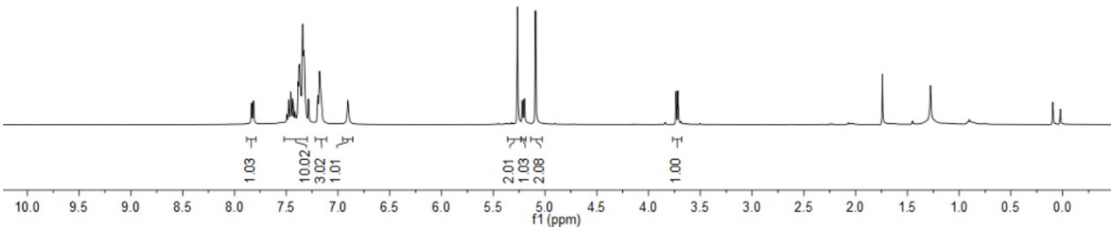
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3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


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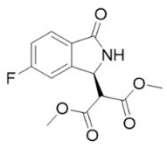
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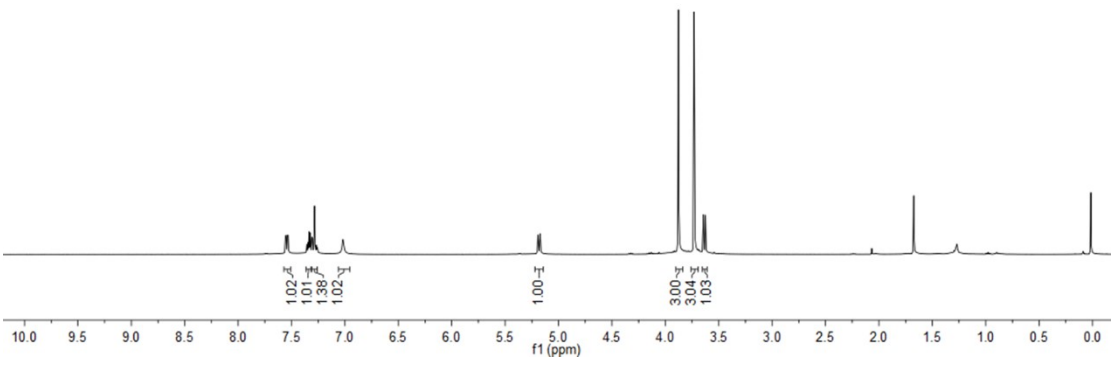
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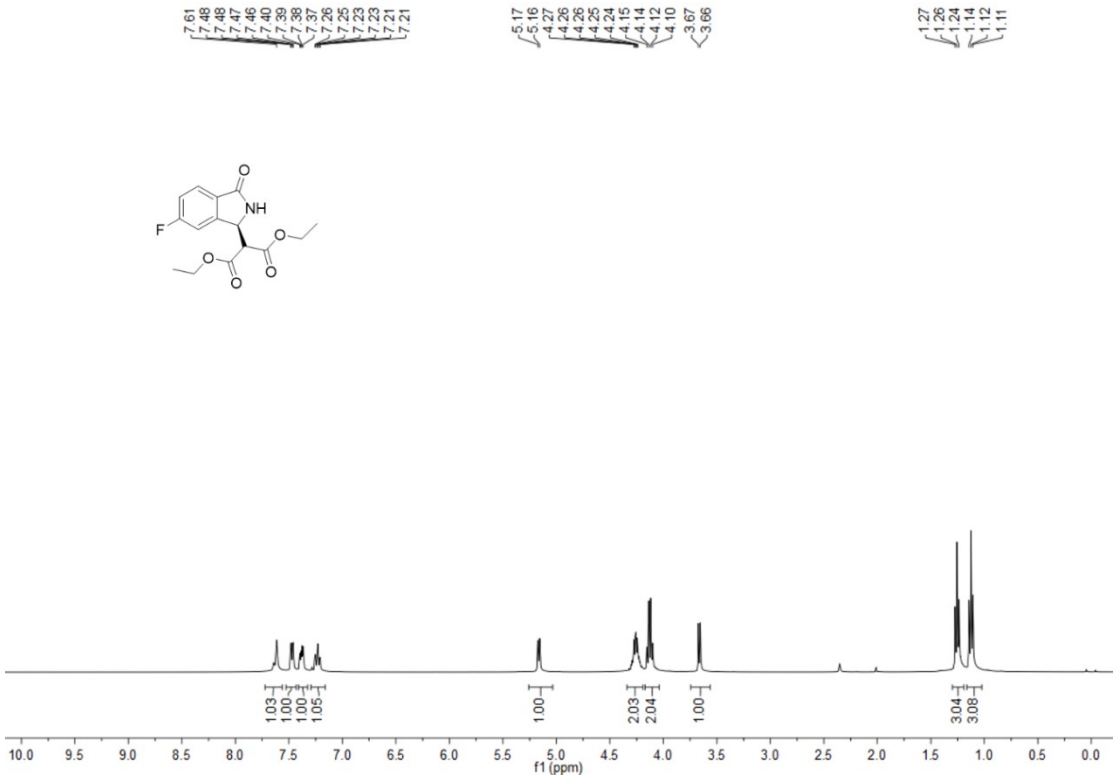
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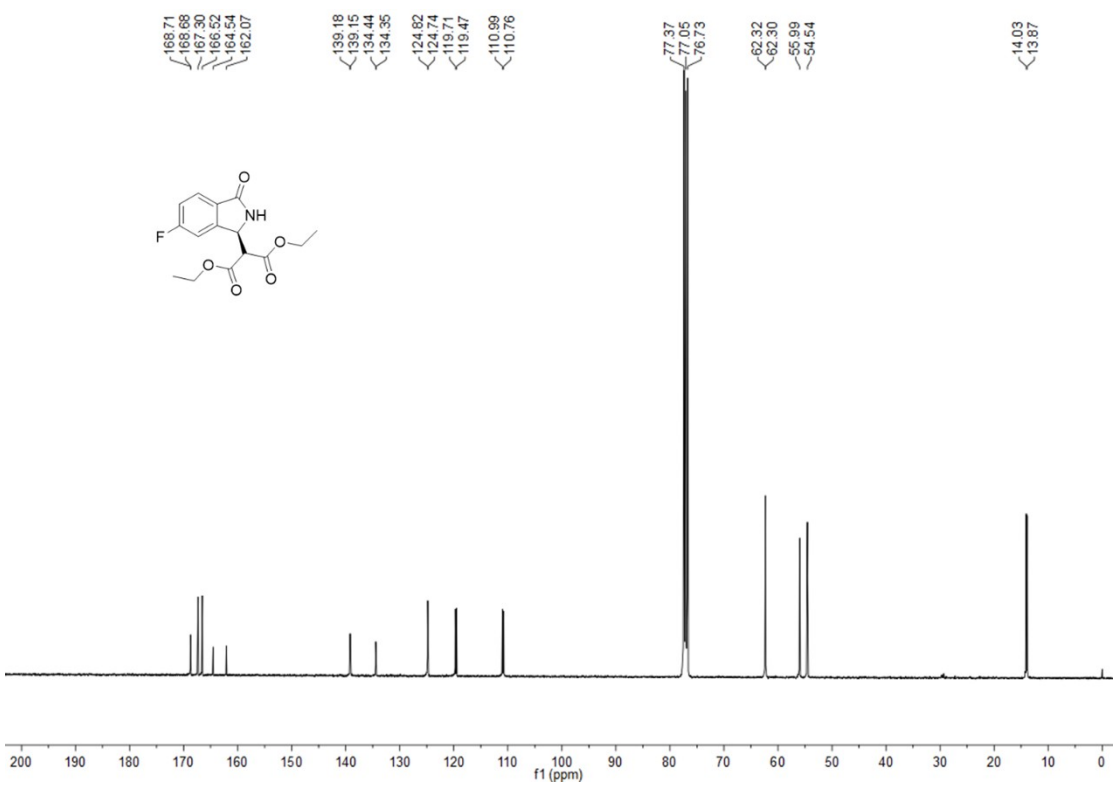
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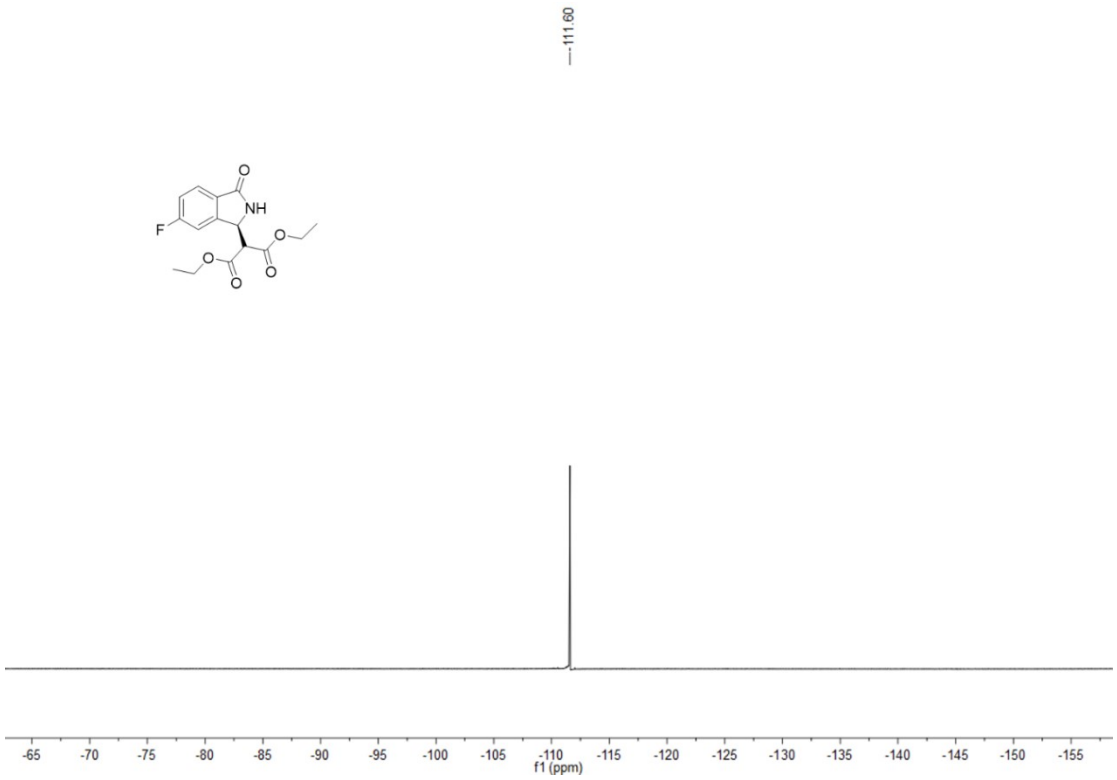
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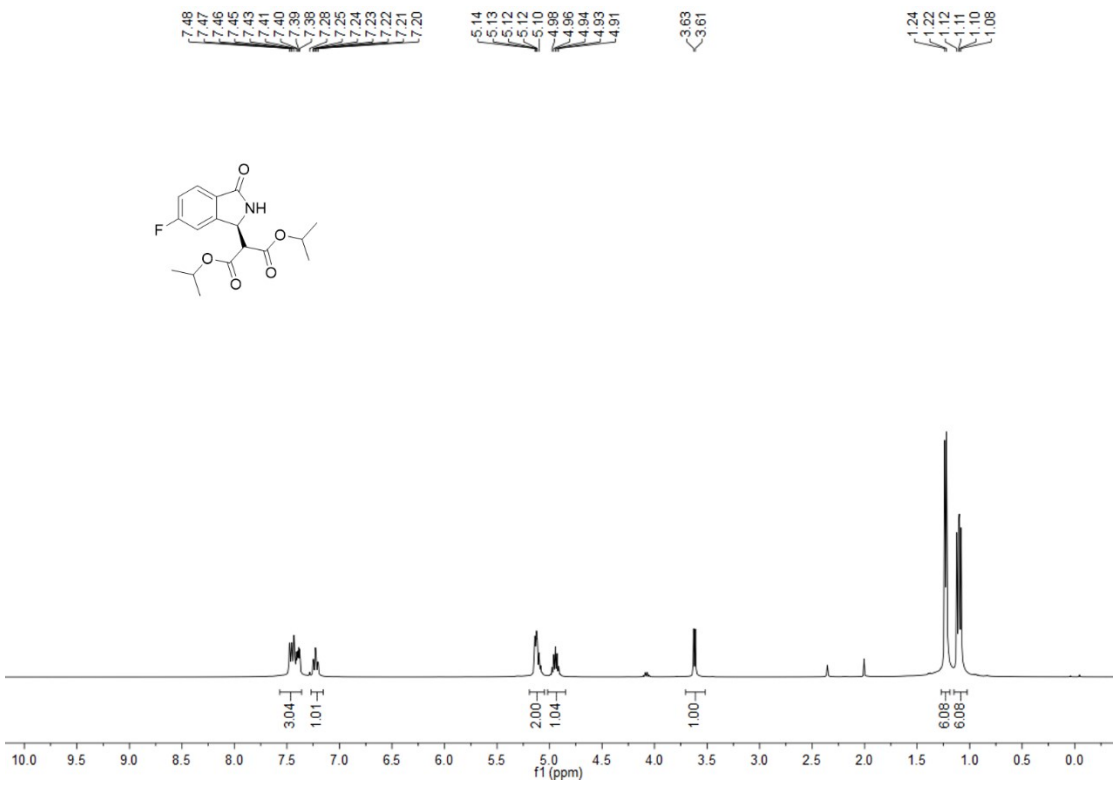
f1 (ppm)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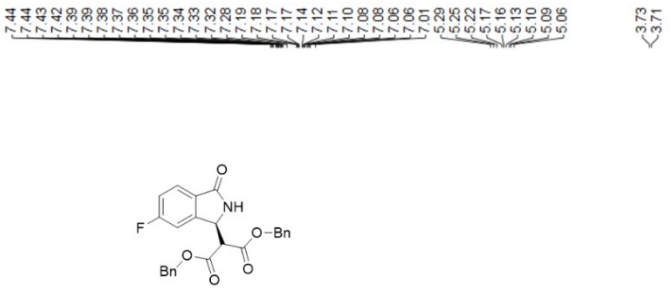
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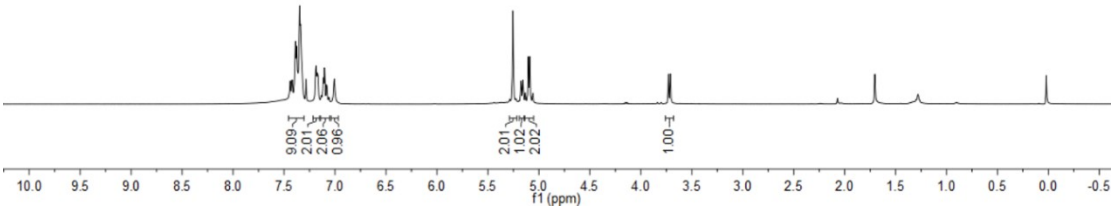
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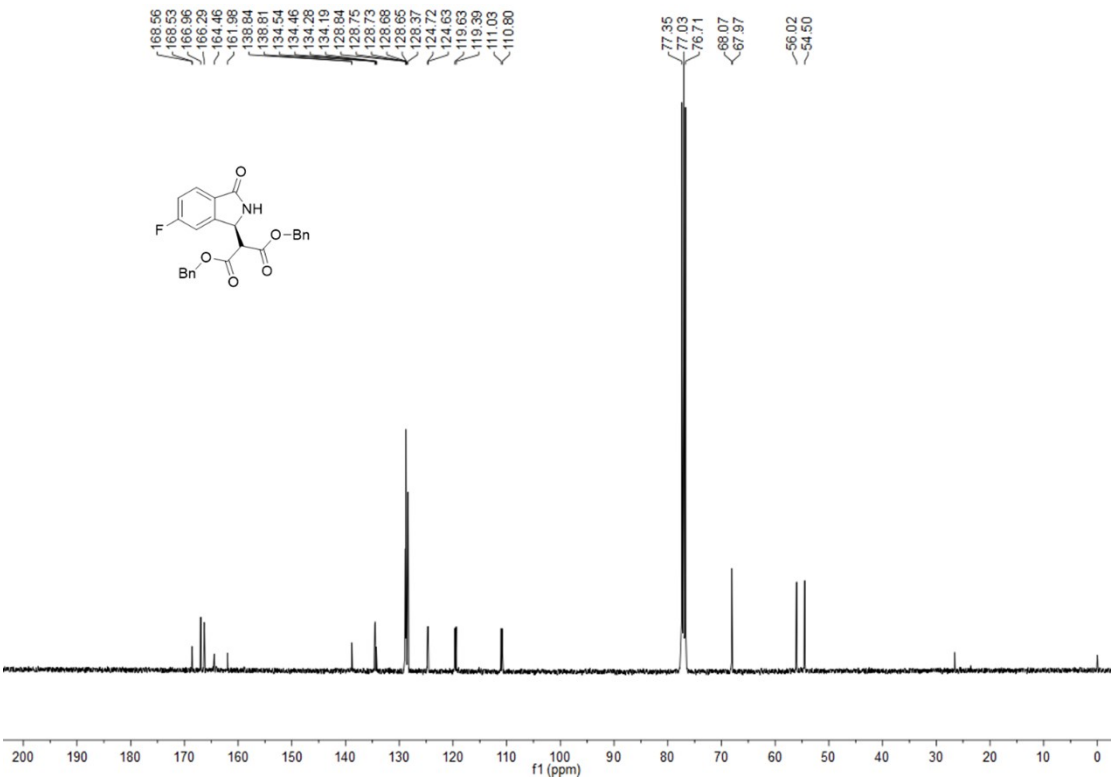
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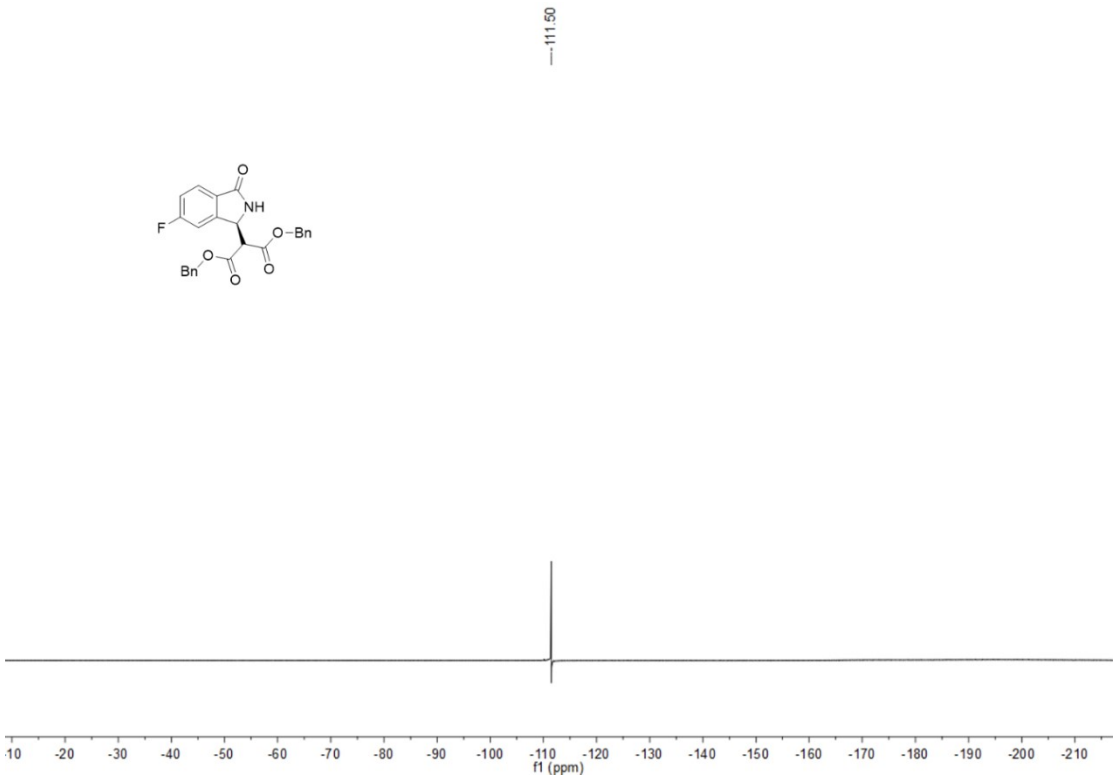
f1 (ppm)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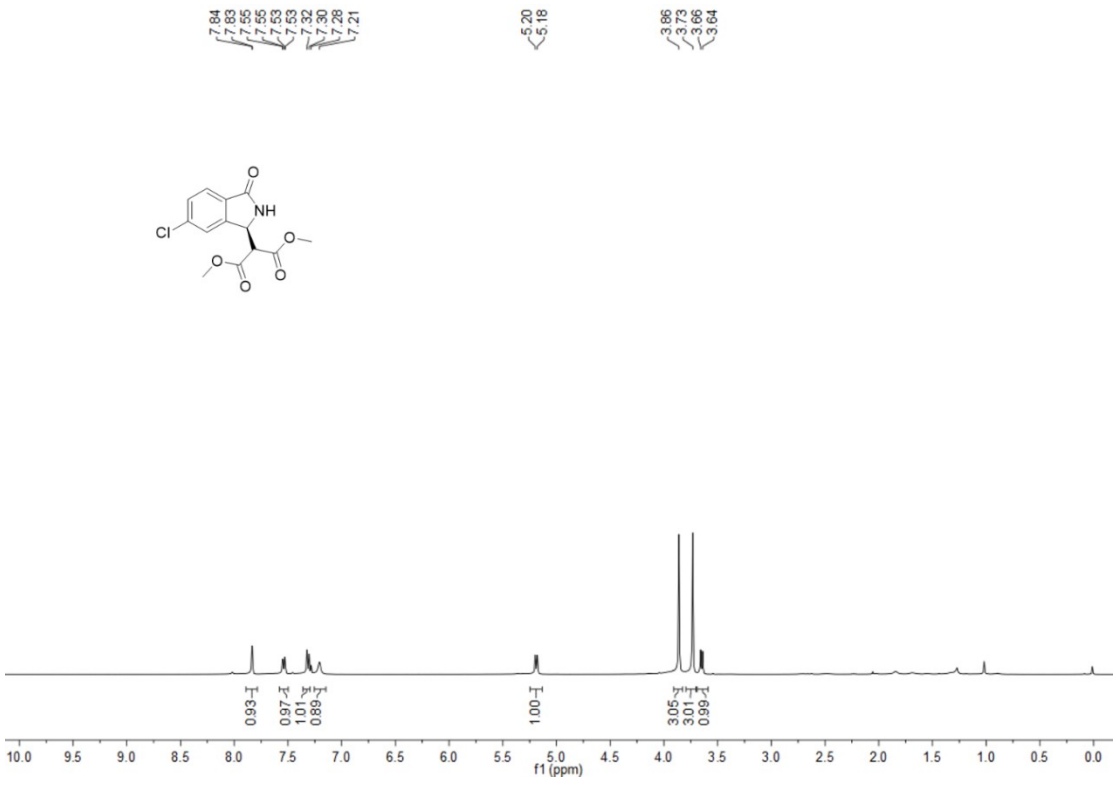
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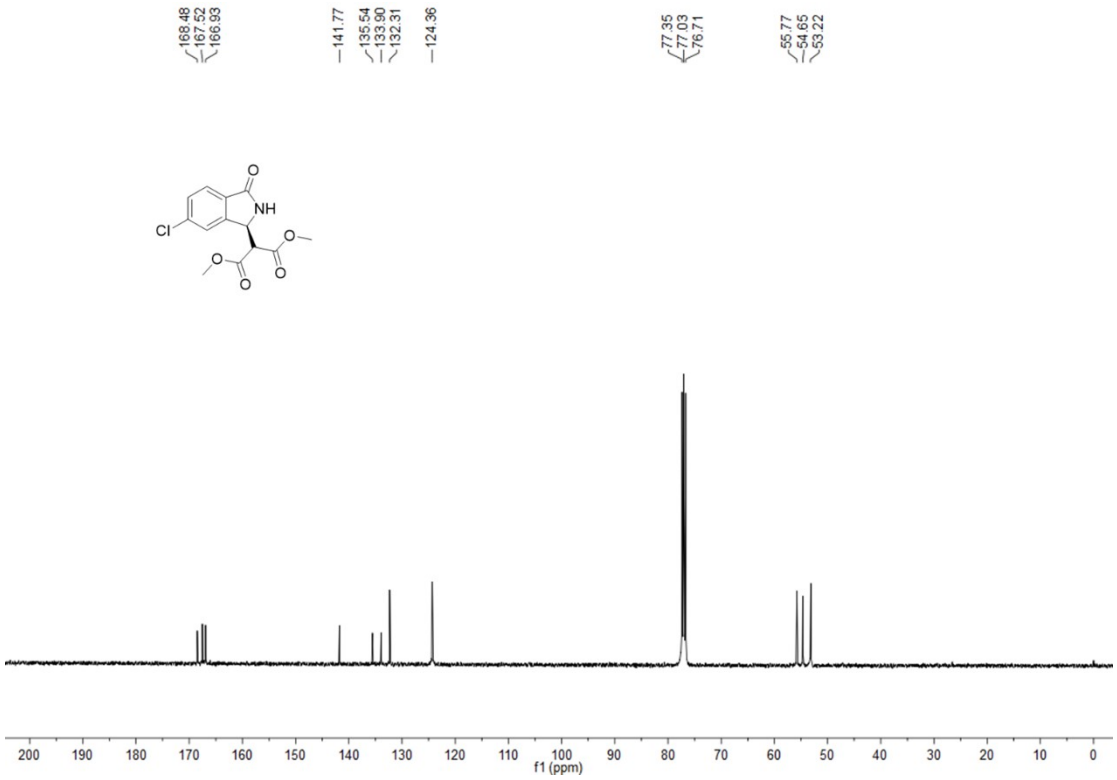
7.30
7.28
7.21
5.20
5.18
3.86
3.73
3.66
3.64
O
NH
Cl
O
O
O
O
0.93
0.97
1.01
0.89
1.00
3.05
3.01
0.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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167.52
166.93
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124.36
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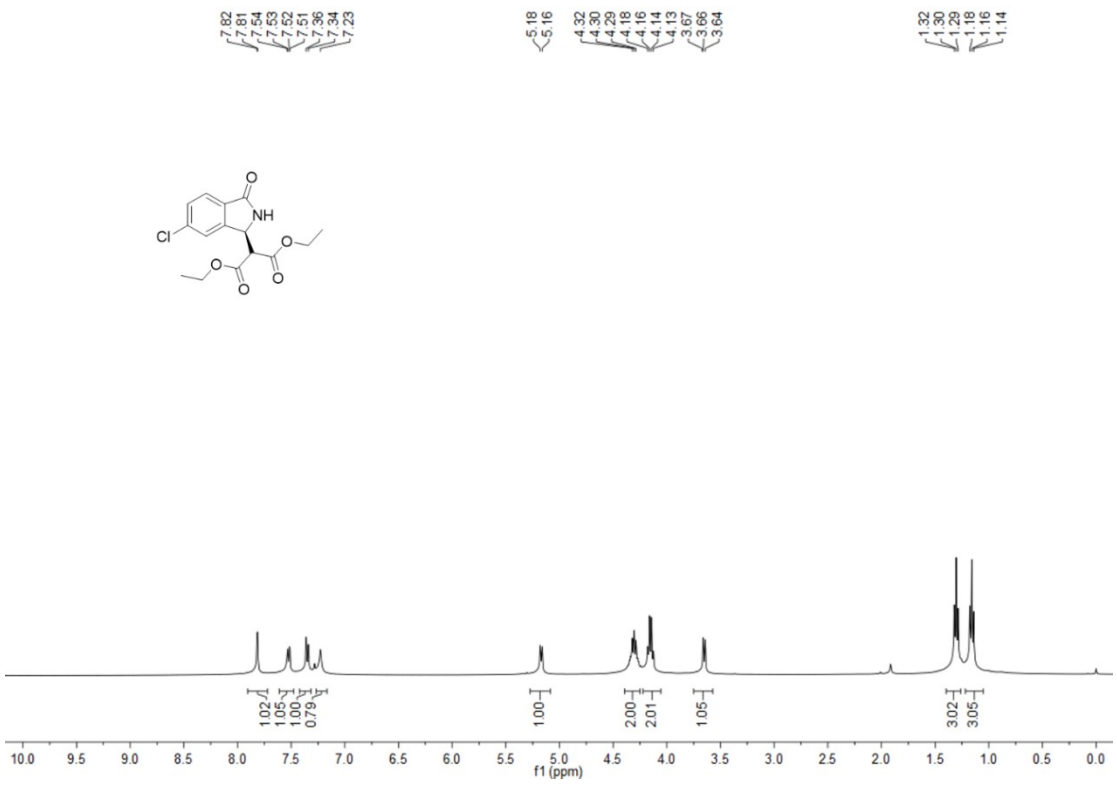
77.03
76.71
55.77
54.65
53.22
NH
Cl
f1 (ppm)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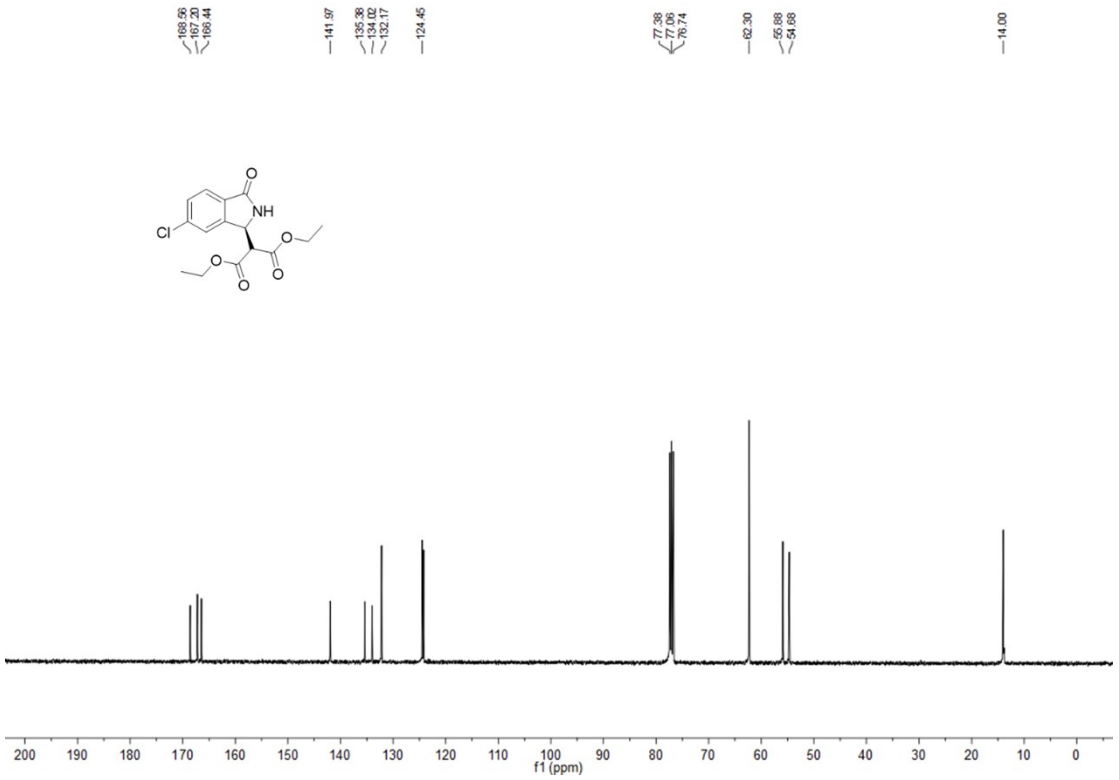
7.81
7.54
7.53
7.52
7.51
7.36
7.34
7.23
5.18
5.16
4.32
4.30
4.29
4.18
4.16
4.14
4.13
3.67
3.66
3.64
1.32
1.30
1.29
1.18
1.16
1.14
NH
Cl
1.02
1.05
1.00
0.79
1.00
2.00
2.01
1.05
3.02
3.05
f1 (ppm)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167.20
166.44
141.97
135.38
134.02
132.17
124.45
77.38
77.06
76.74
62.30
55.88
54.88
14.00
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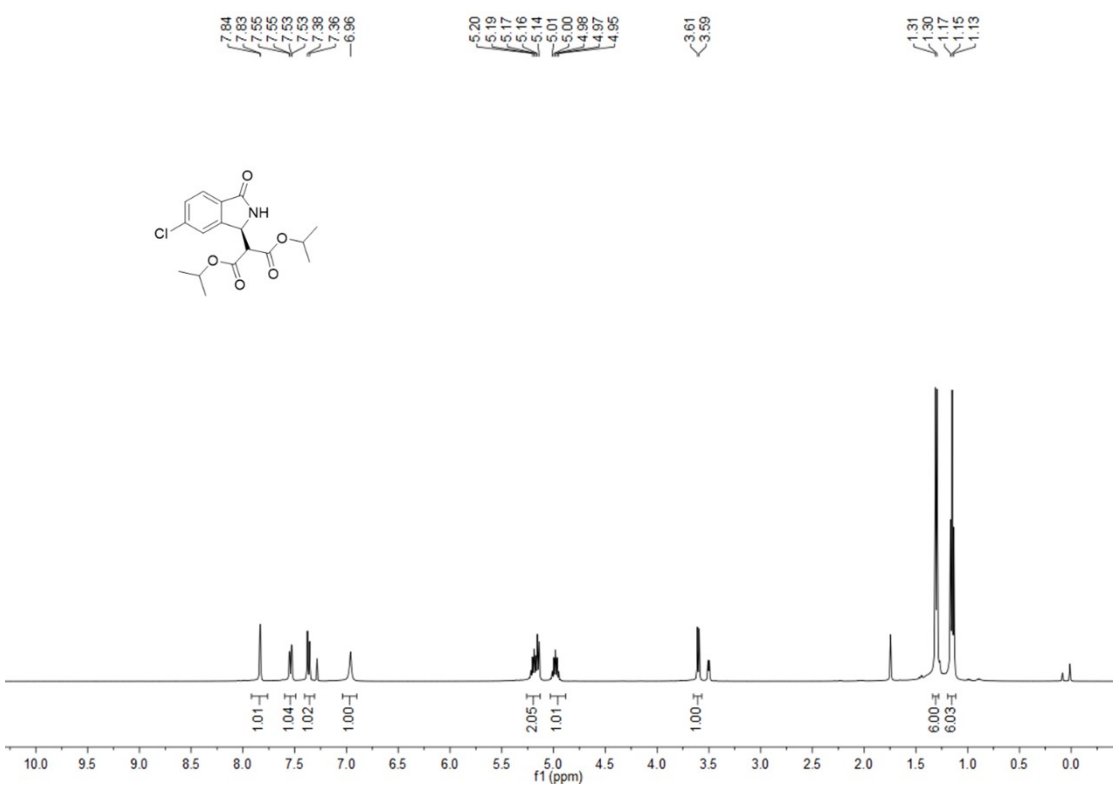
Cl
O
O
O
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.83
7.55
7.55
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7.53
7.38
7.36
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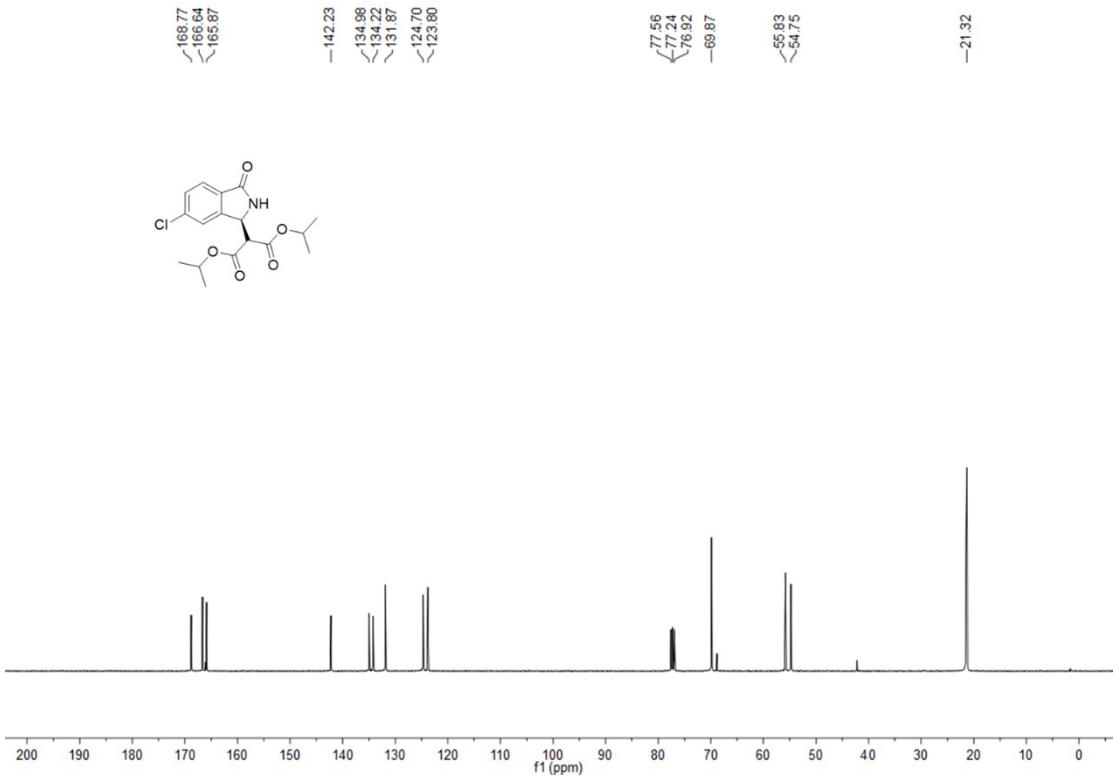
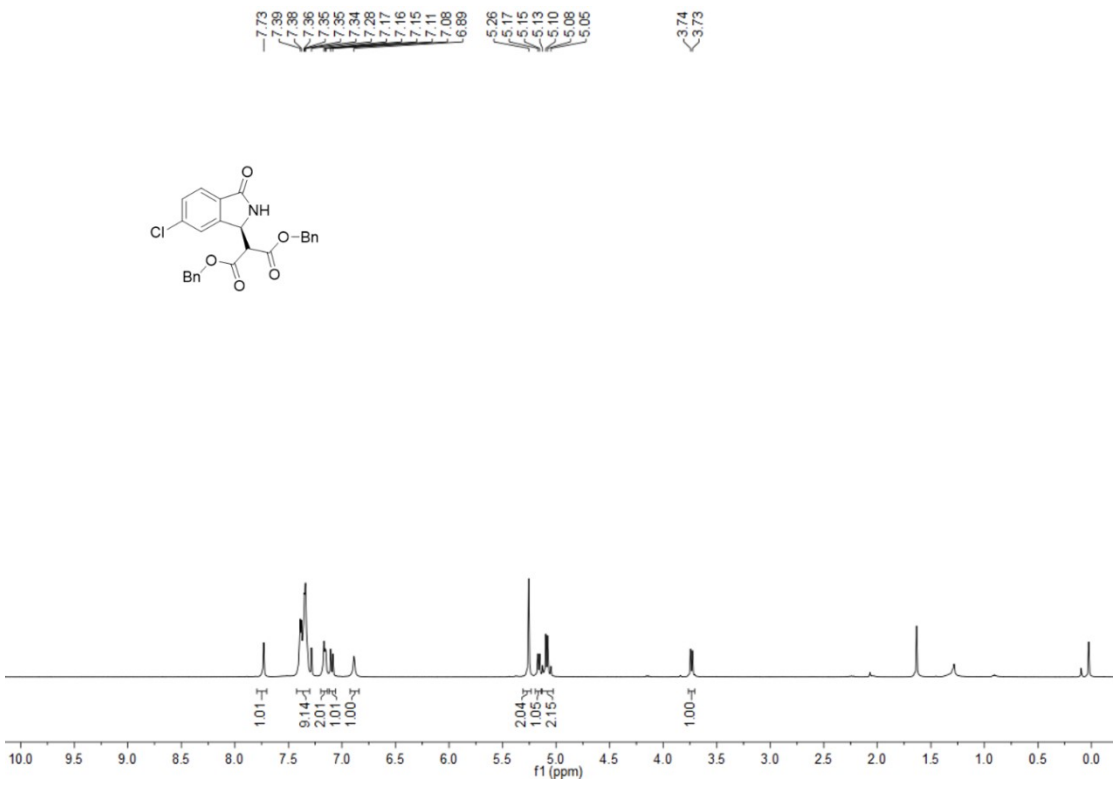
5.20
5.19
5.17
5.16
5.14
5.01
5.00
4.98
4.97
4.95
3.61
3.59
1.31
1.30
1.17
1.15
1.13
NH
Cl
O
O
O
O
O
O
1.01
1.04
1.02
1.00
2.05
1.01
1.00
6.00
6.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


168.77
166.64
165.87
142.23
134.98
134.22
131.87
124.70
123.60
77.56
77.24
76.92
69.87
55.83
54.75
21.32
NH
Cl
O
O
O
O
O
f1 (ppm)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7.39
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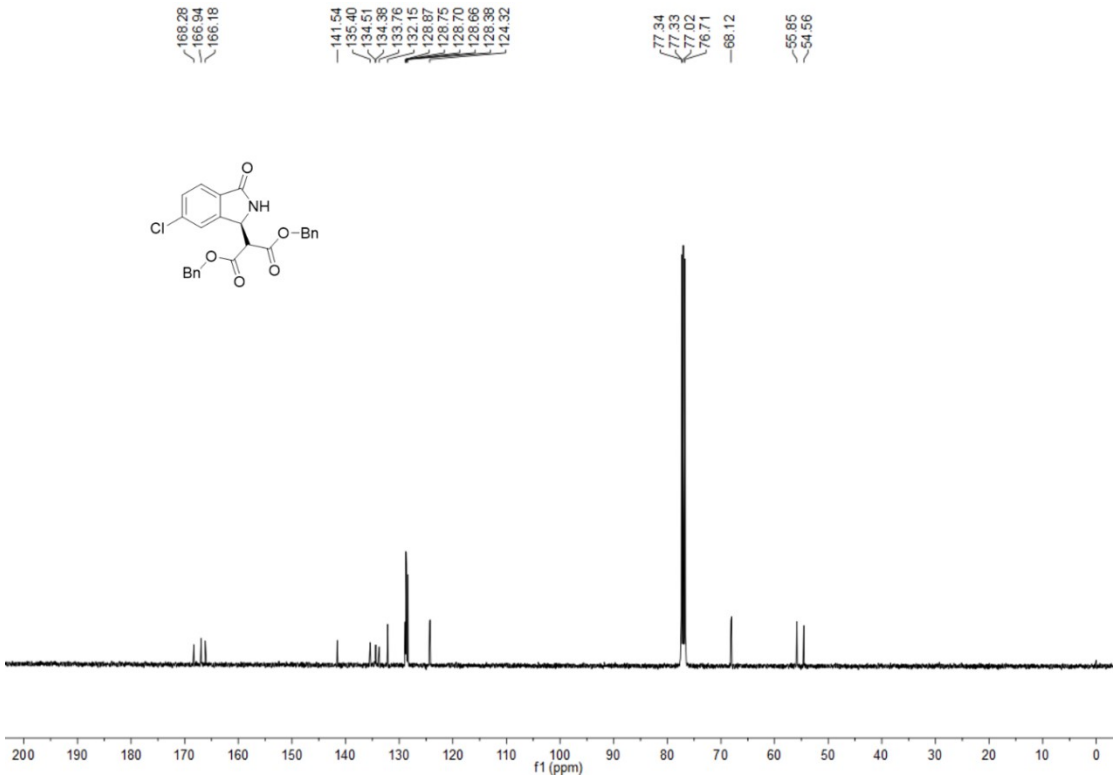
7.36
7.35
7.35
7.34
7.28
7.17
7.16
7.15
7.11
7.08
6.89
5.26
5.17
5.15
5.13
5.10
5.08
5.05
3.74
3.73
NH
Cl
O-Bn
Bn
O
O
O
1.01
9.14
2.01
1.01
1.00
2.04
1.05
2.15
1.00
f1 (ppm)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166.94
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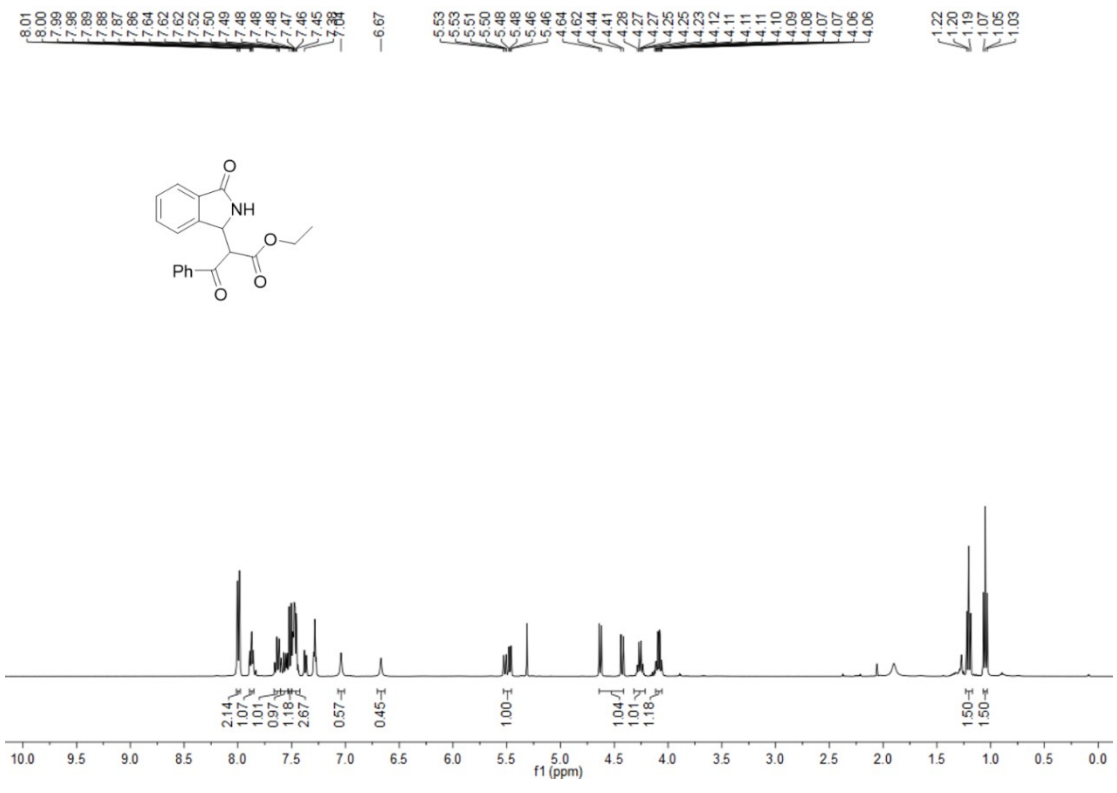
134.51
134.38
133.76
132.15
128.87
128.75
128.70
128.66
128.38
124.32
77.34
77.33
77.02
76.71
68.12
55.85
54.56
O
NH
Cl
O–Bn
Bn–O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.00
7.99
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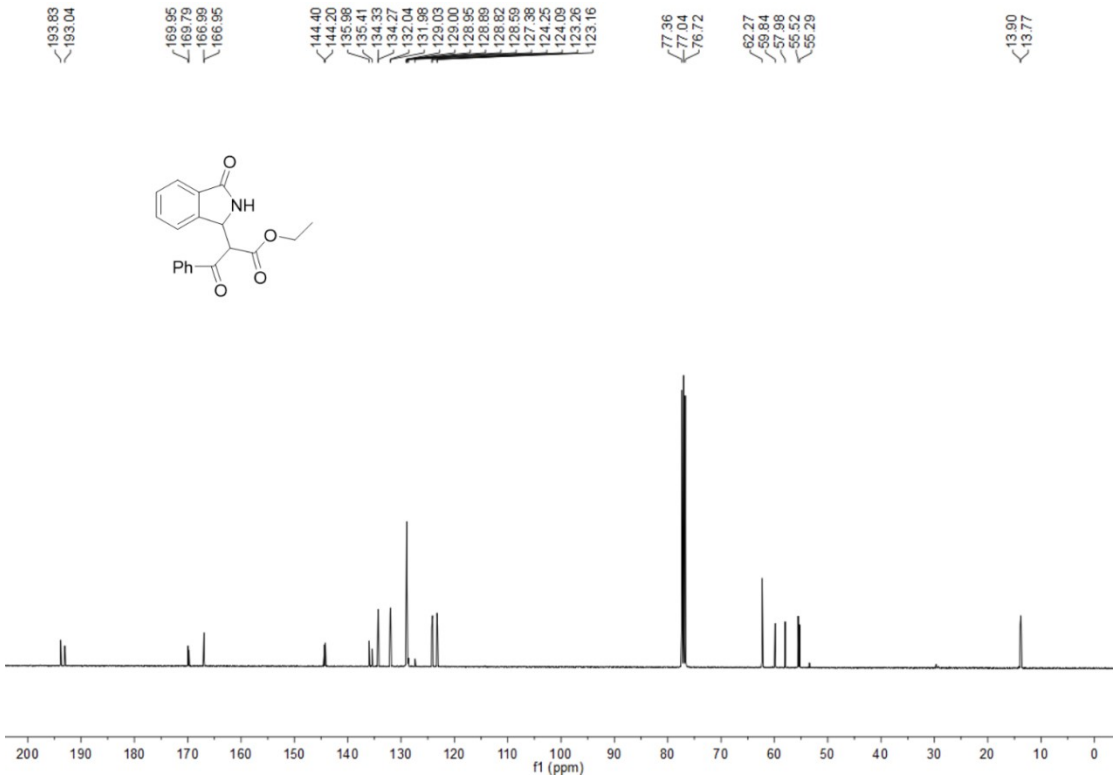
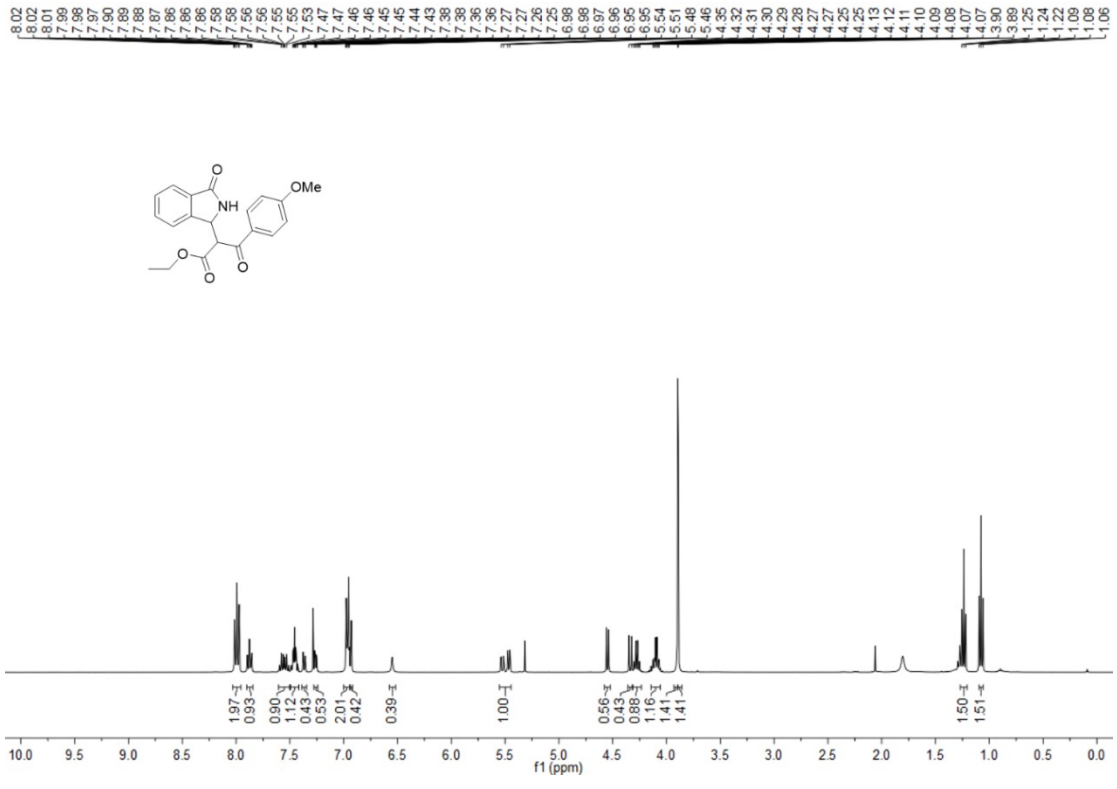
7.88
7.87
7.86
7.64
7.62
7.62
7.52
7.50
7.49
7.48
7.48
7.48
7.47
7.46
7.45
7.38
7.04
6.67
5.53
5.53
5.51
5.50
5.48
5.48
5.46
5.46
4.64
4.62
4.44
4.41
4.28
4.27
4.27
4.25
4.25
4.23
4.12
4.11
4.11
4.11
4.10
4.09
4.08
4.07
4.07
4.06
4.06
1.22
1.20
1.19
1.07
1.05
1.03
O
NH
O
Ph
O
O
2.14
1.07
1.01
0.97
1.18
2.67
0.57
0.45
1.00
1.04
1.01
1.18
1.50
1.50
10.0 9.5 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)


193.83
193.04
169.95
169.79
166.99
166.95
144.40
144.20
135.98
135.41
134.33
134.27
132.04
131.98
129.03
129.00
128.95
128.89
128.82
128.59
127.38
124.25
124.09
123.26
123.16
77.36
77.04
76.72
62.27
59.84
57.98
55.52
55.29
13.90
13.77
NH
Ph
O
f1 (ppm)


8.02
8.02
8.01
7.99
7.98
7.97
7.90
7.89
7.88
7.87
7.86
7.86
7.86
7.58
7.58
7.56
7.56
7.55
7.55
7.53
7.47
7.47
7.46
7.46
7.45
7.45
7.44
7.43
7.38
7.38
7.36
7.36
7.27
7.27
7.26
7.25
6.98
6.98
6.97
6.96
6.96
6.95
6.95
5.54
5.51
5.48
5.46
4.35
4.32
4.31
4.30
4.29
4.28
4.27
4.27
4.25
4.25
4.13
4.12
4.11
4.10
4.09
4.08
4.07
4.07
3.90
3.89
1.25
1.24
1.22
1.09
1.08
1.06
NH
OMe
O
1.97
0.93
0.90
1.12
0.43
0.53
2.01
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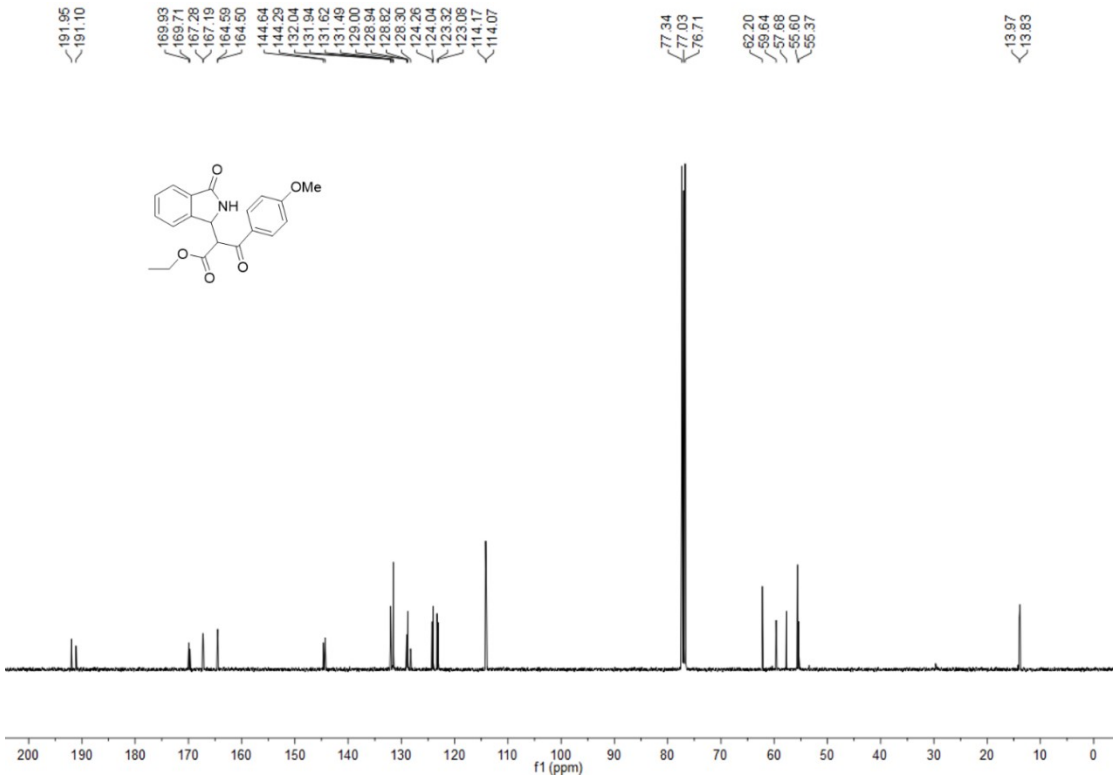
0.39
1.00
0.56
0.43
0.88
1.16
1.41
1.41
1.50
1.51
f1 (ppm)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191.10
169.93
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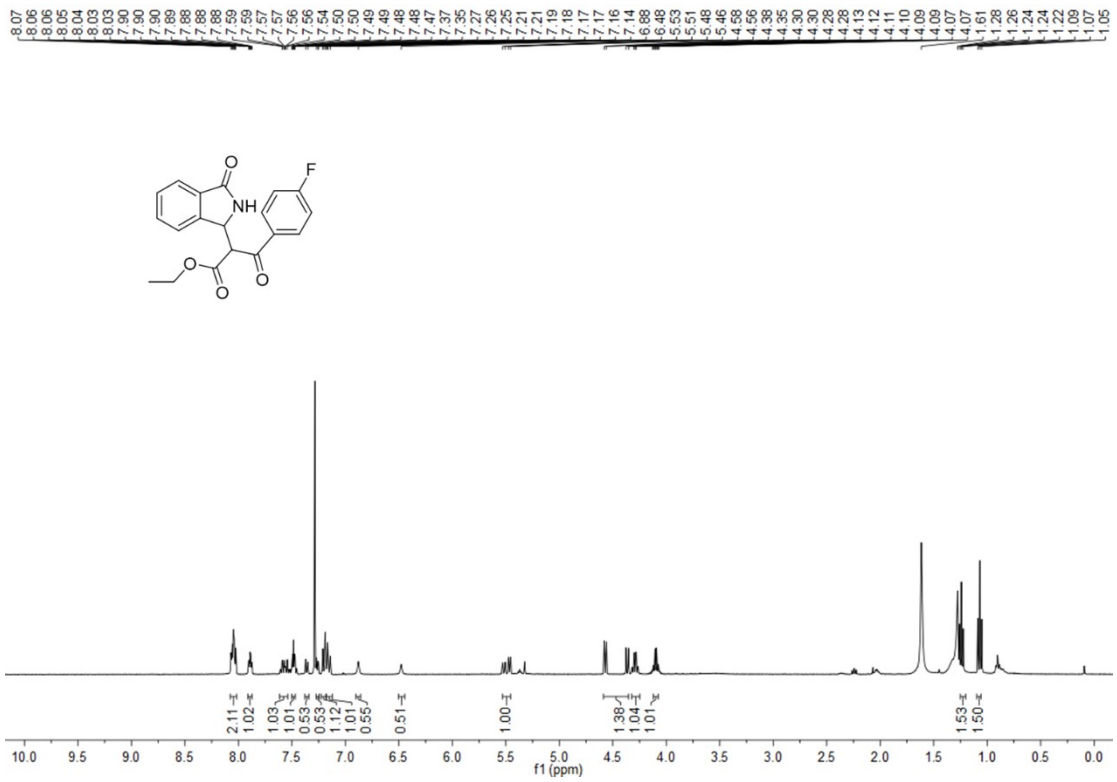
167.28
167.19
164.59
164.50
144.64
144.29
132.04
131.94
131.62
131.49
129.00
128.94
128.82
128.30
124.26
124.04
123.32
123.08
114.17
114.07
77.34
77.03
76.71
62.20
59.64
57.68
55.60
55.37
13.97
13.83
O
NH
OMe
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.06
8.06
8.05
8.04
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8.03
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7.90
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7.88
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7.26
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7.21
7.19
7.18
7.17
7.17
7.16
7.14
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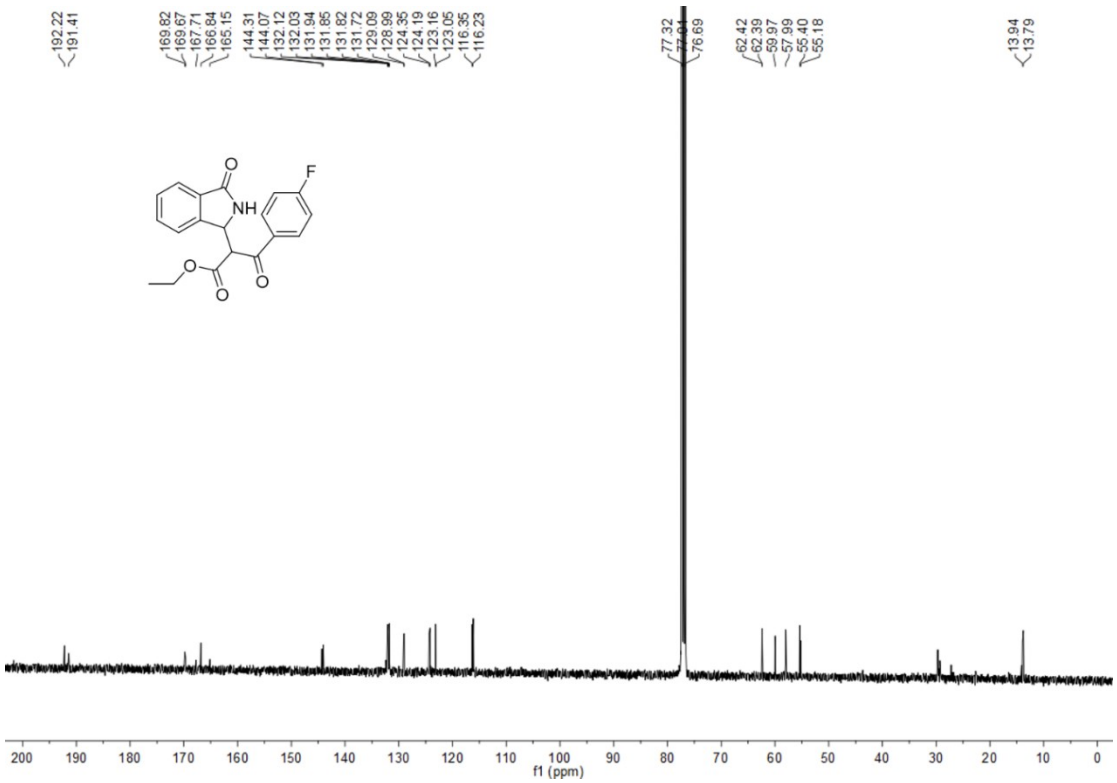
6.48
5.53
5.51
5.48
5.46
4.56
4.58
4.38
4.35
4.30
4.30
4.28
4.28
4.13
4.12
4.11
4.10
4.09
4.09
4.07
4.07
1.61
1.28
1.26
1.24
1.24
1.22
1.09
1.07
1.05
O
NH
F
O
O
O
2.11
1.02
1.03
1.01
0.53
0.53
1.12
1.01
0.55
0.51
1.00
1.38
1.04
1.01
1.53
1.50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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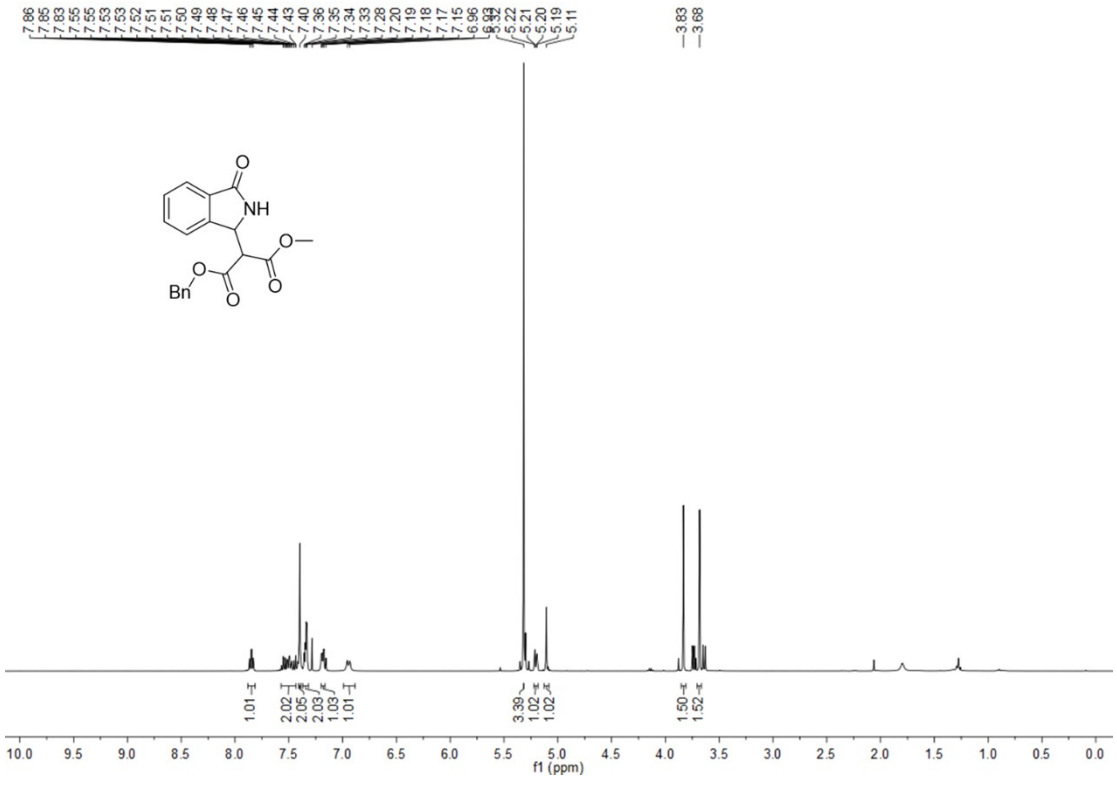
144.31
144.07
132.12
132.03
131.94
131.85
131.82
131.72
129.09
128.99
124.35
124.19
123.16
123.05
116.35
116.23
77.32
77.01
76.69
62.42
62.39
59.97
57.99
55.40
55.18
13.94
13.79
O
NH
F
O
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.47
7.46
7.45
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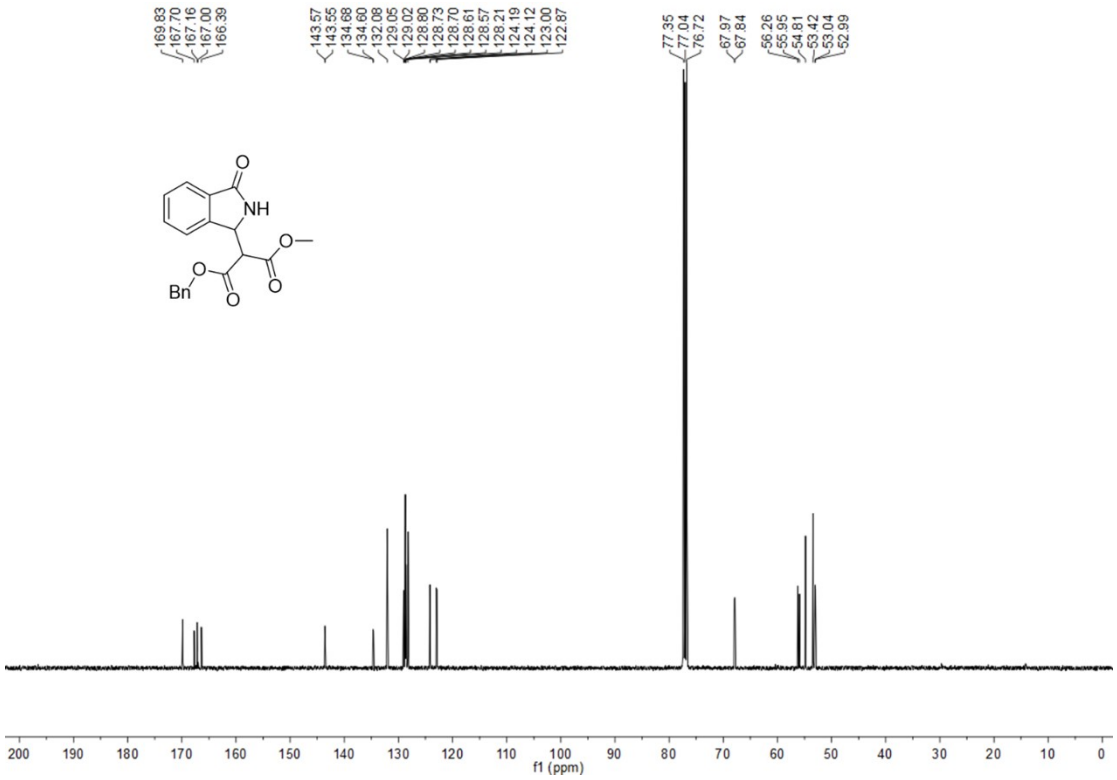
7.43
7.40
7.36
7.35
7.34
7.33
7.28
7.20
7.19
7.18
7.17
7.15
6.96
5.22
5.21
5.20
5.19
5.11
3.83
3.68
O
NH
O
O
Bn
O
O
1.01
2.02
2.05
2.03
1.03
1.01
3.39
1.02
1.02
1.50
1.52
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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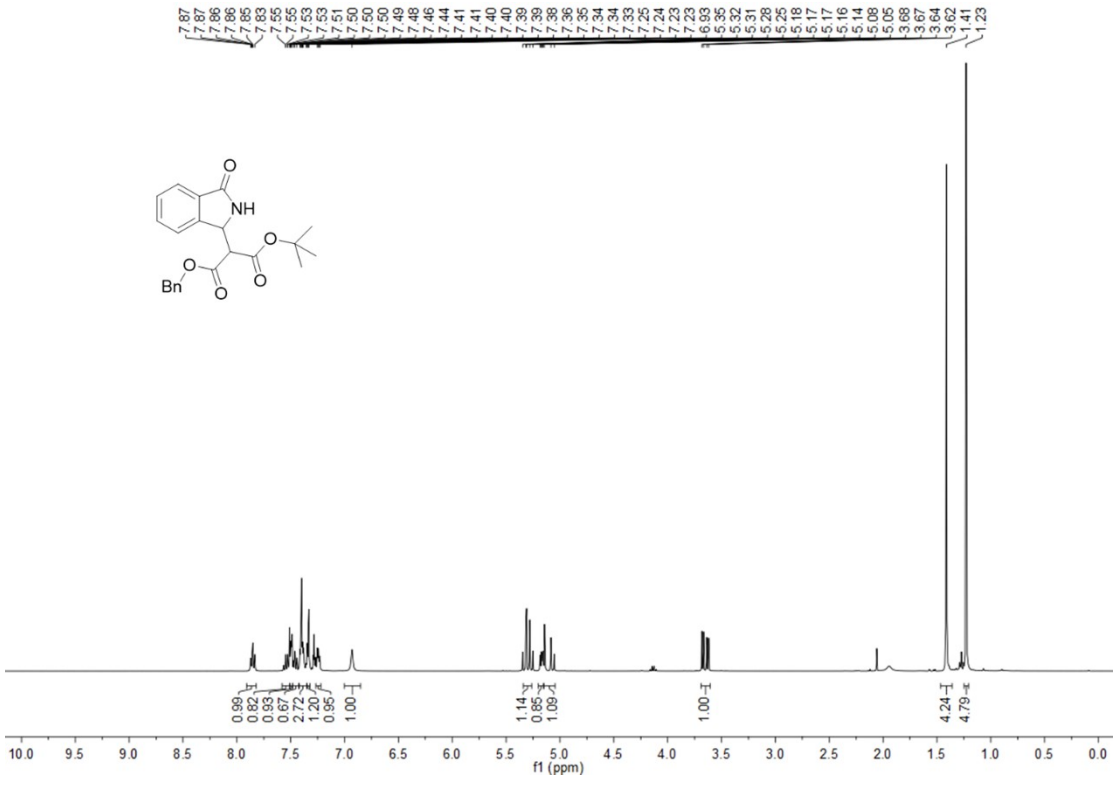
143.55
134.68
134.60
132.08
129.05
129.02
128.80
128.73
128.70
128.61
128.57
128.21
124.19
124.12
123.00
122.87
77.35
77.04
76.72
67.97
67.84
56.26
55.95
54.81
53.42
53.04
52.99
NH
O
O
O
O
O
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.87
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7.86
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7.55
7.53
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7.51
7.50
7.50
7.50
7.49
7.48
7.46
7.44
7.41
7.41
7.40
7.40
7.39
7.39
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7.36
7.35
7.34
7.34
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7.25
7.24
7.23
7.23
6.93
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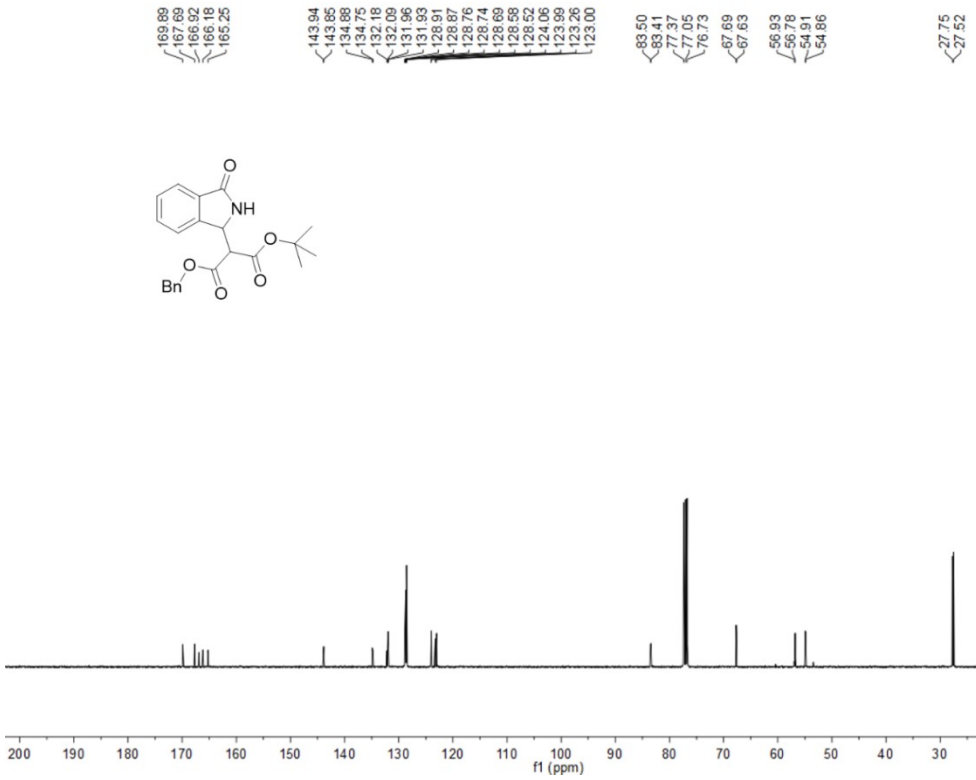
5.32
5.31
5.28
5.25
5.18
5.17
5.17
5.16
5.14
5.08
5.05
3.68
3.67
3.64
3.62
1.41
1.23
NH
O
O
O
O
O
Bn
0.99
0.62
0.93
0.67
2.72
1.20
0.95
1.00
1.14
0.85
1.09
1.00
4.24
4.79
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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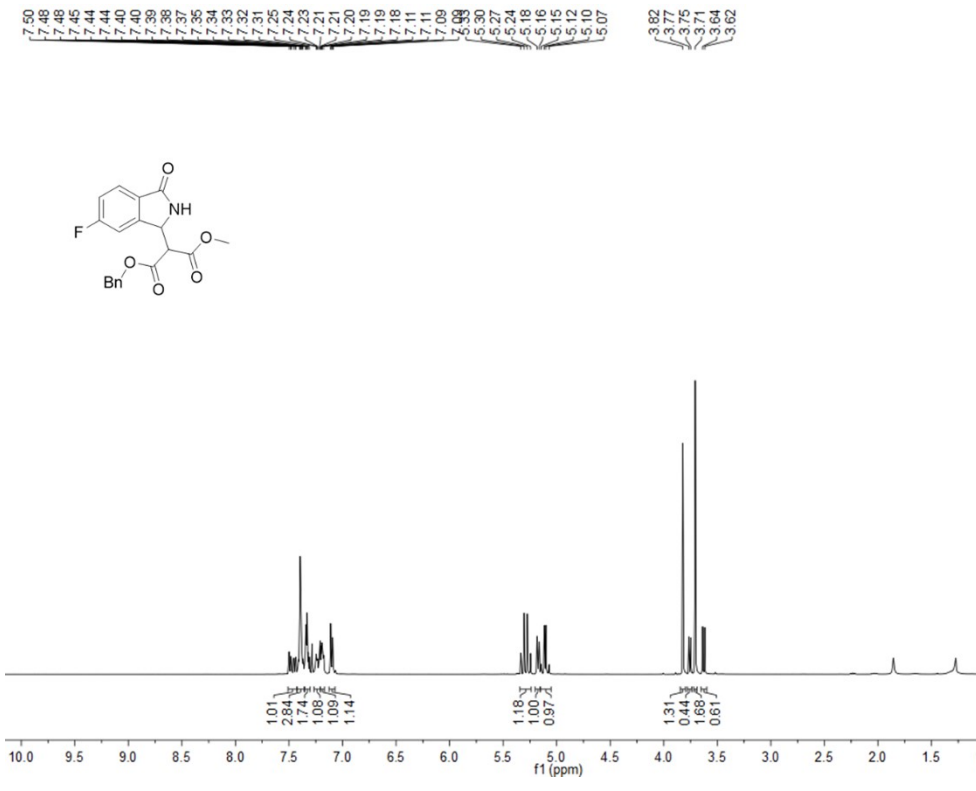
143.85
134.88
134.75
132.18
132.09
131.96
131.93
128.91
128.87
128.76
128.74
128.69
128.58
128.52
124.06
123.99
123.26
123.00
83.50
83.41
77.37
77.05
76.73
67.69
67.63
56.93
56.78
54.91
54.86
27.75
27.52
NH
O
Bn
f1 (ppm)


7.50
7.48
7.48
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7.40
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7.38
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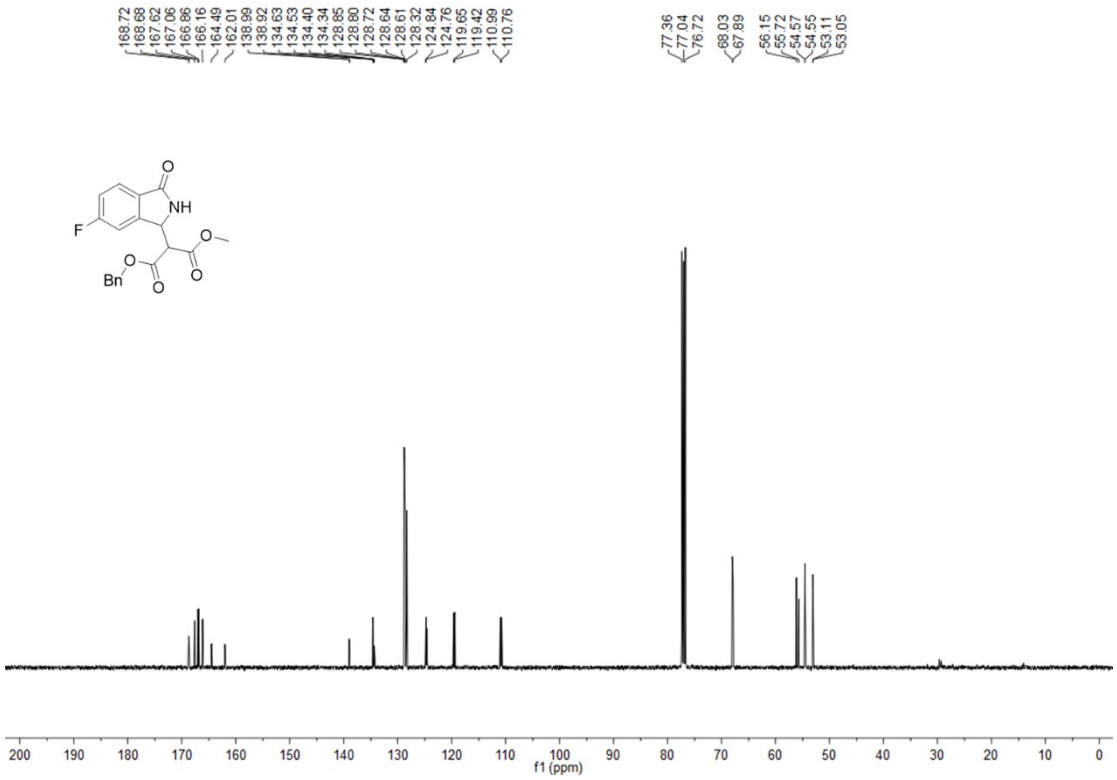
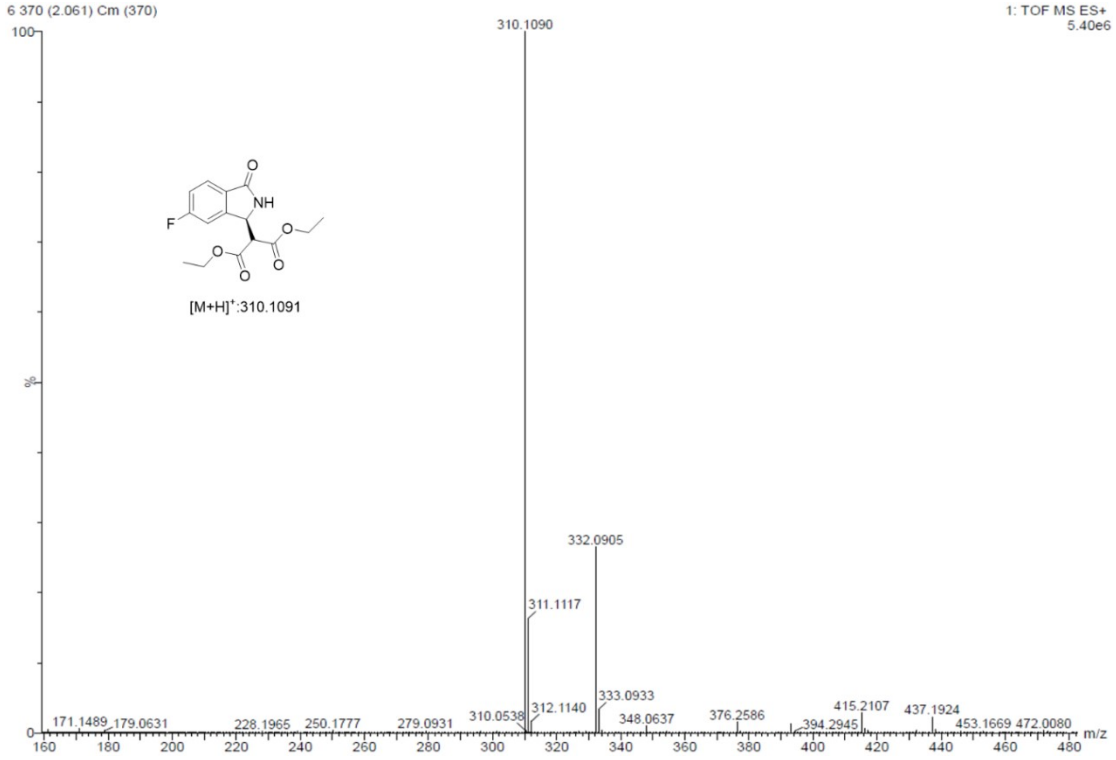
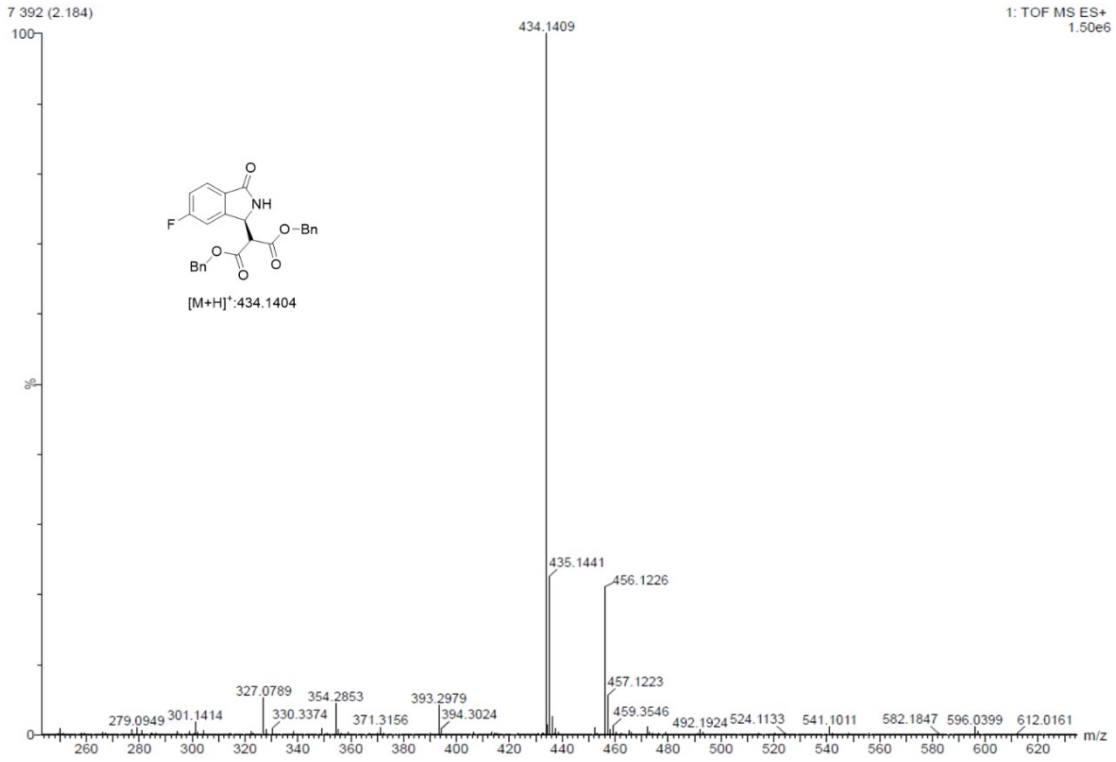
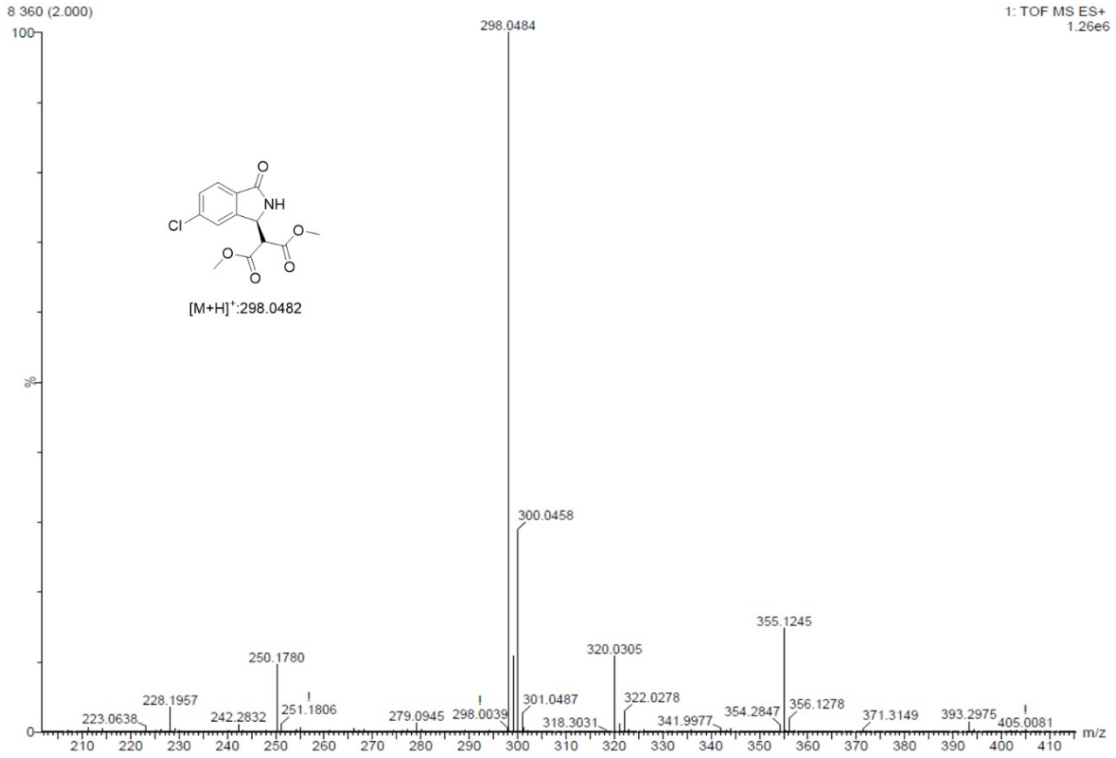
7.35
7.34
7.33
7.32
7.31
7.25
7.24
7.23
7.21
7.21
7.20
7.19
7.19
7.18
7.11
7.11
7.09
5.33
5.30
5.27
5.24
5.18
5.16
5.15
5.12
5.10
5.07
3.82
3.77
3.75
3.71
3.64
3.62
NH
F
O
Bn
1.01
2.84
1.74
1.08
1.09
1.14
1.18
1.00
0.97
1.31
0.44
1.68
0.61
f1 (ppm)

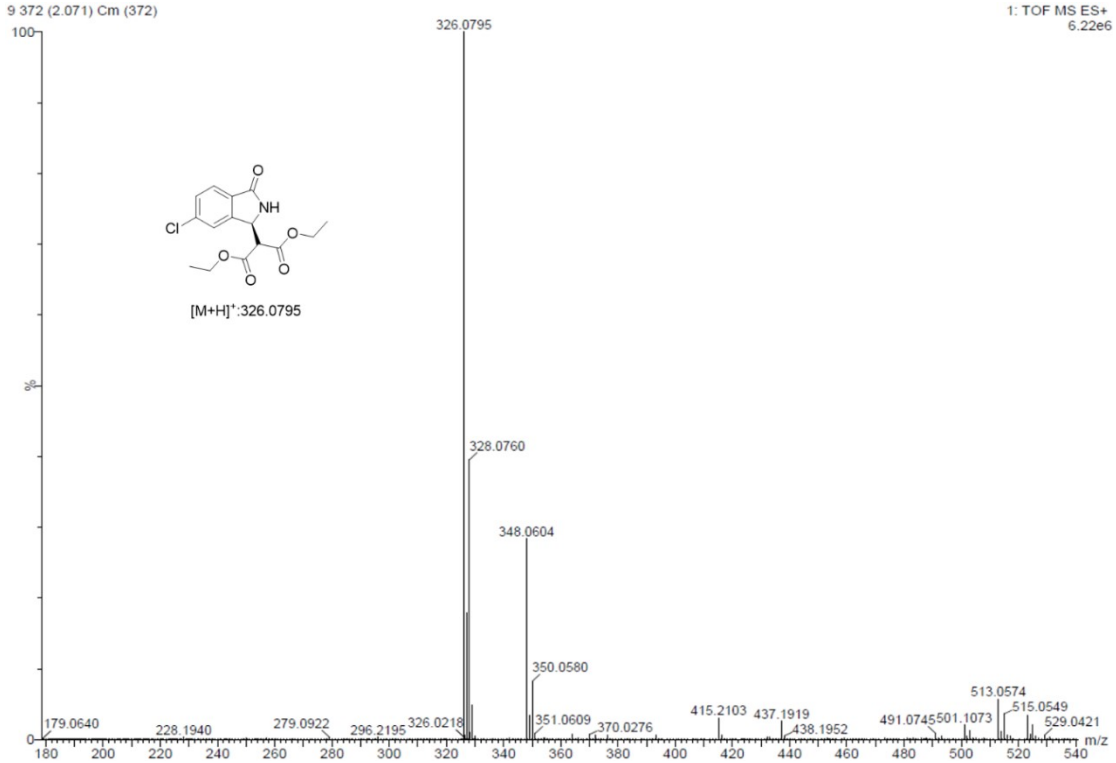

168.72
168.68
167.62
167.06
166.86
166.16
164.49
162.01
138.99
138.92
134.63
134.53
134.40
134.34
128.85
128.80
128.72
128.64
128.61
128.32
124.84
124.76
119.65
119.42
110.99
110.76
77.36
77.04
76.72
68.03
67.89
56.15
55.72
54.57
54.55
53.11
53.05
O
NH
F
O
O
Bn
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

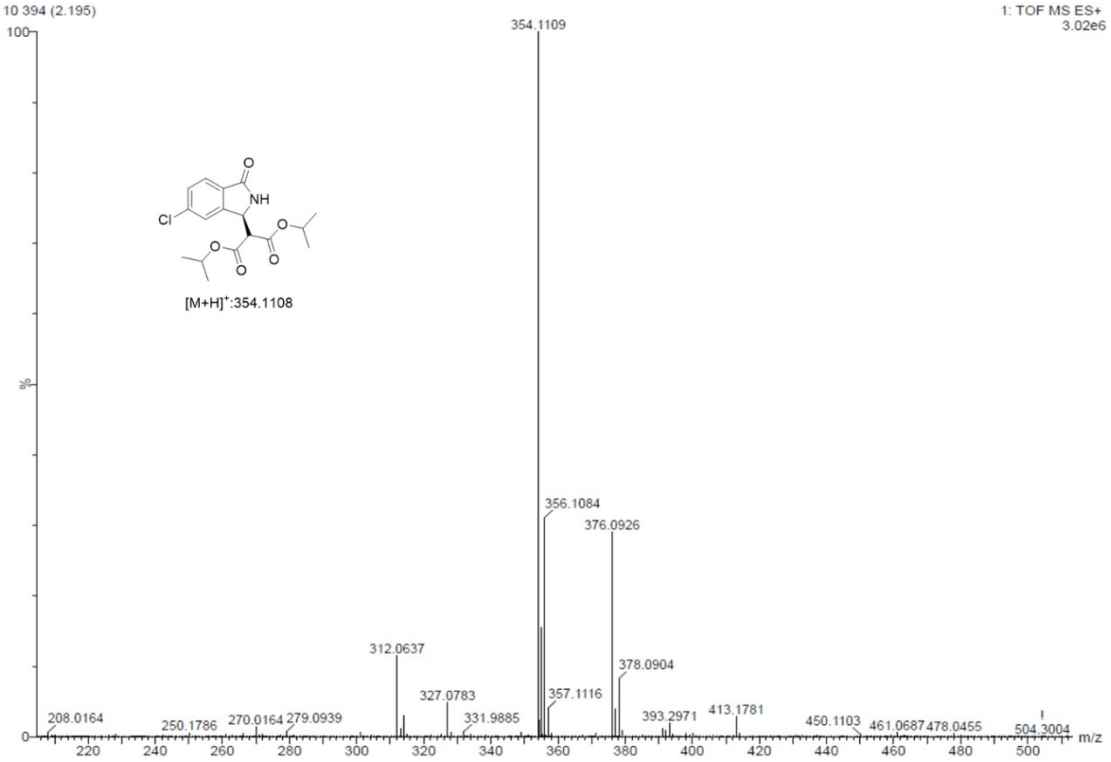
6. HRMS Charts

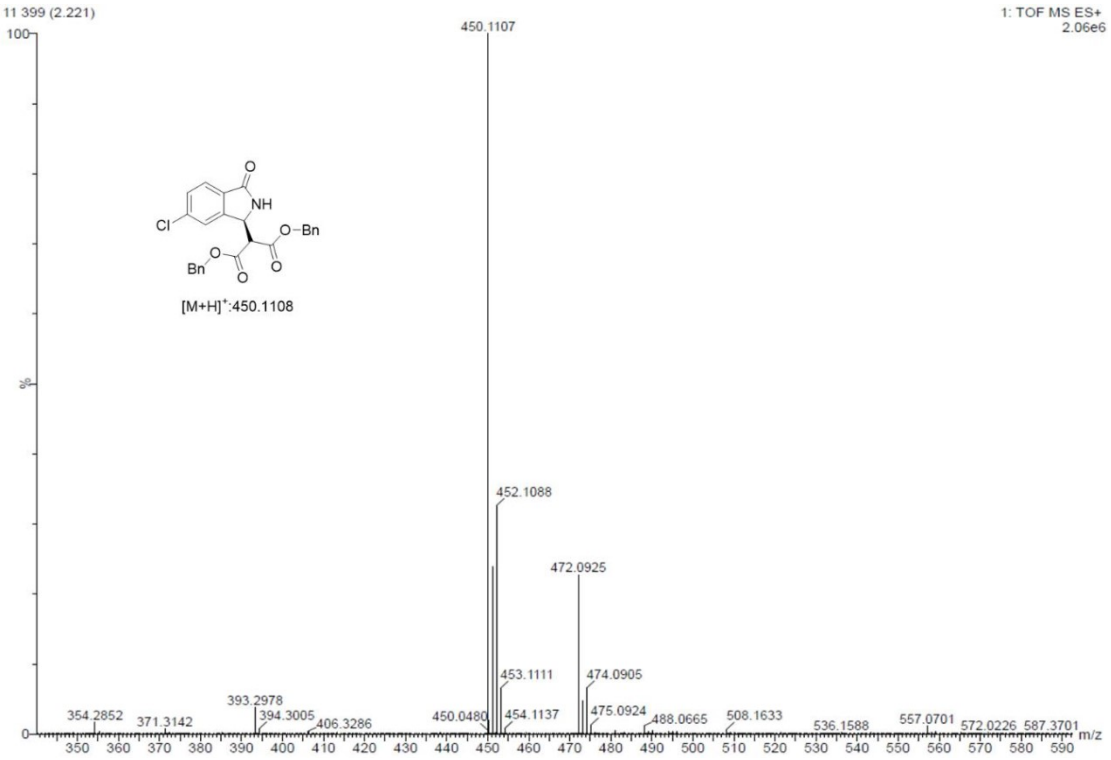


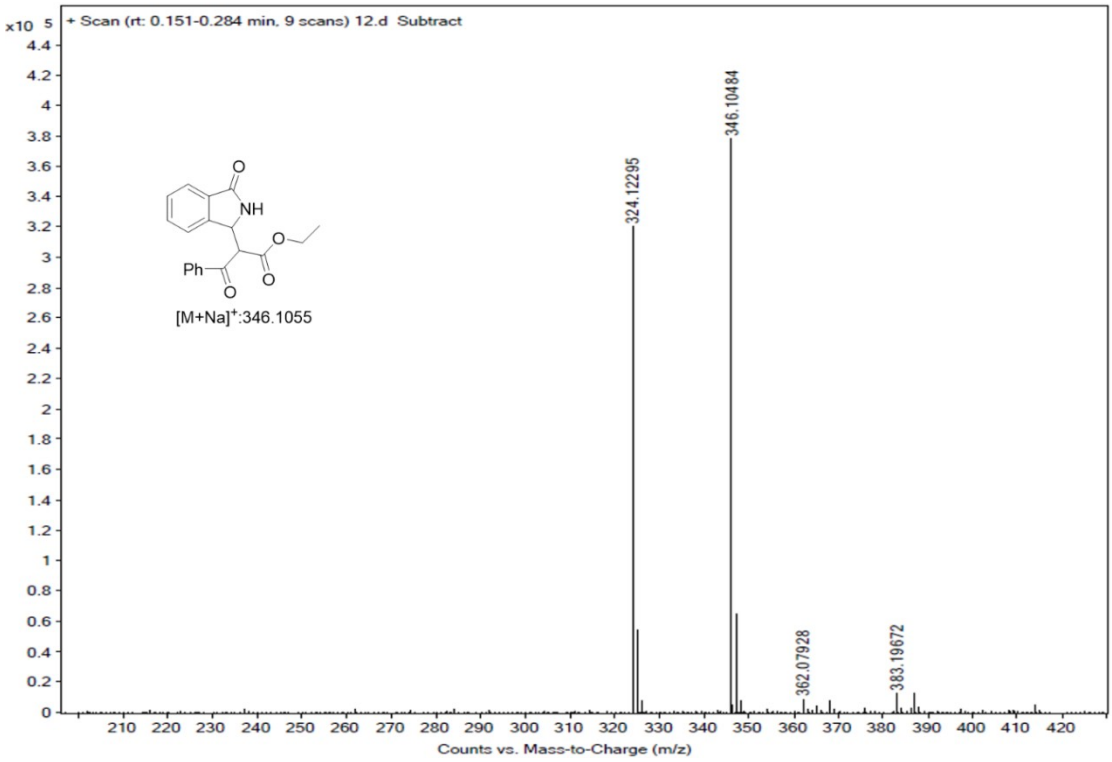


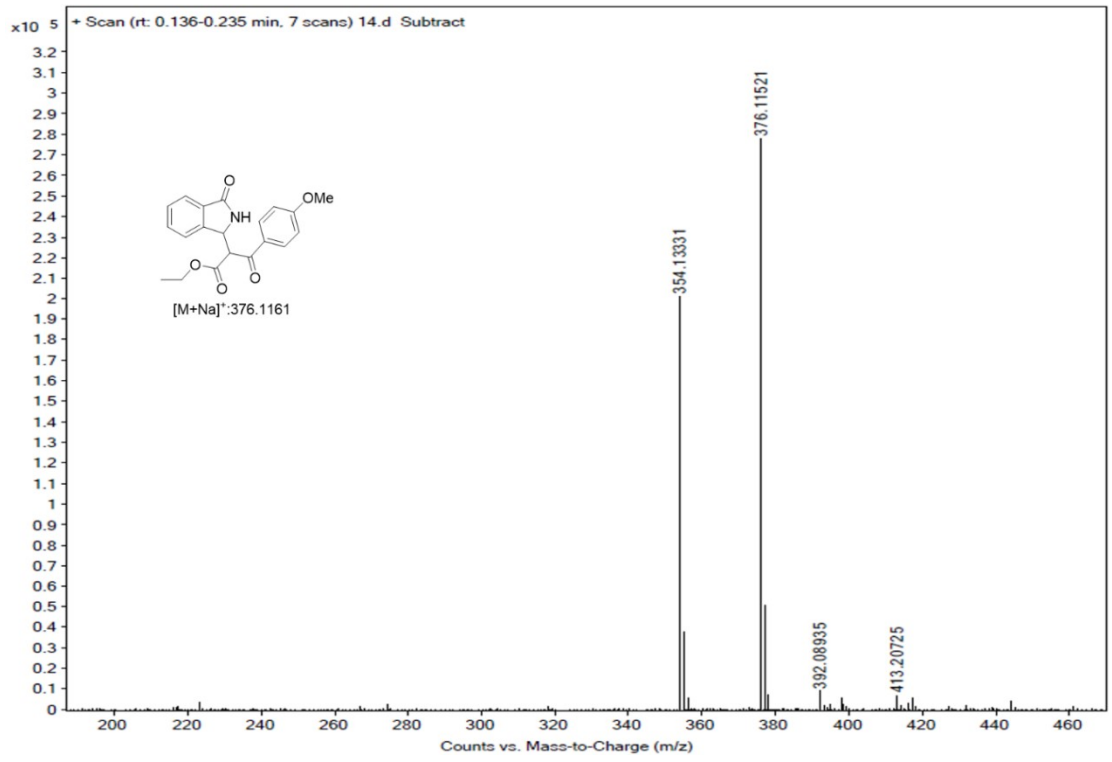

8 360 (2.000)
1: TOF MS ES+
1.26e6
298.0484
[M+H]+:298.0482
300.0458
355.1245
320.0305
250.1780
228.1957
301.0487
322.0278
223.0638
242.2832
251.1806
279.0945
298.0039
318.3031
341.9977
354.2847
356.1278
371.3149
393.2975
405.0081
m/z

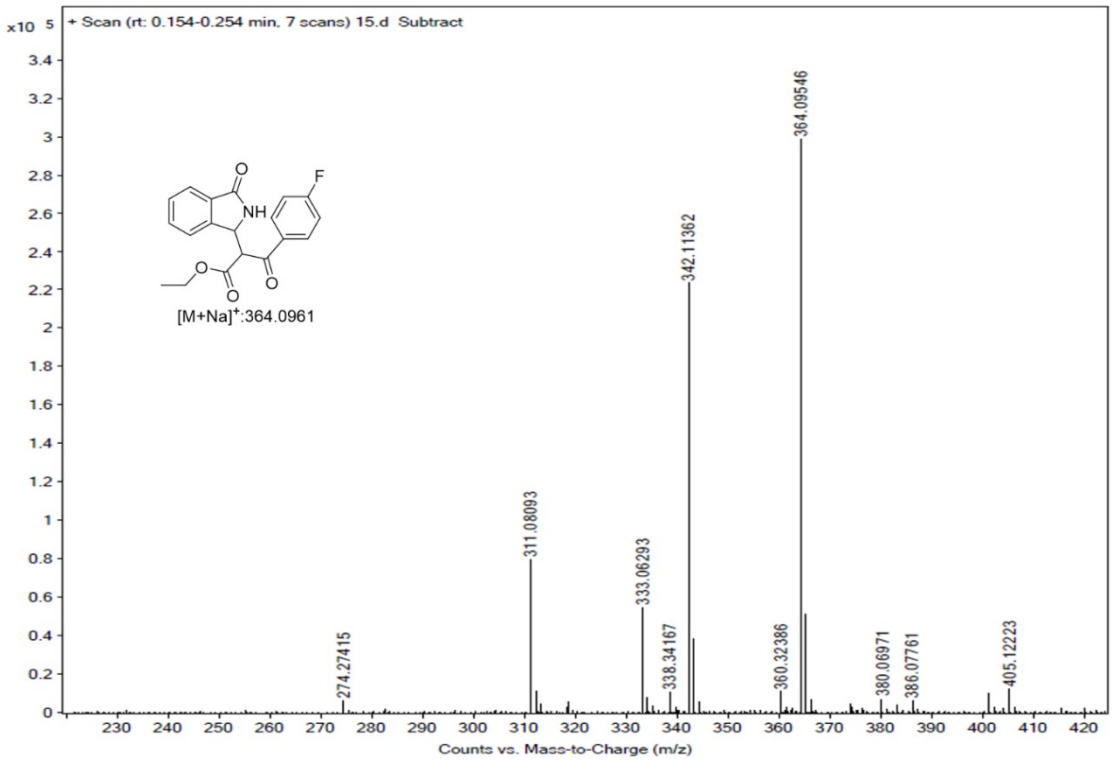

9 372 (2.071) Cm (372)
1: TOF MS ES+
6.22e6
326.0795
[M+H]+:326.0795
328.0760
348.0604
350.0580
513.0574
515.0549
529.0421
179.0640
228.1940
279.0922
296.2195
326.0218
351.0609
370.0276
415.2103
437.1919
438.1952
491.0745
501.1073
m/z

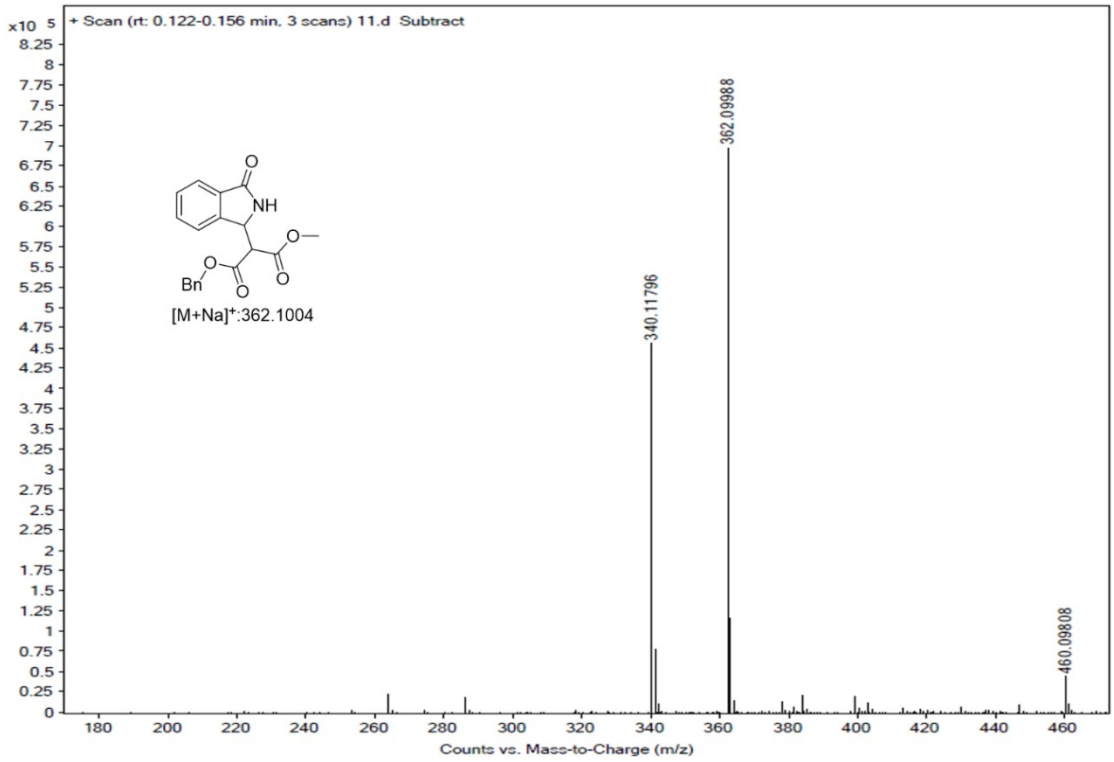

10 394 (2.195)
1: TOF MS ES+
3.02e6
354.1109
356.1084
376.0926
312.0637
378.0904
327.0783
357.1116
208.0164
250.1786
270.0164
279.0939
331.9885
393.2971
413.1781
450.1103
461.0687
478.0455
504.3004
[M+H]+:354.1108
m/z

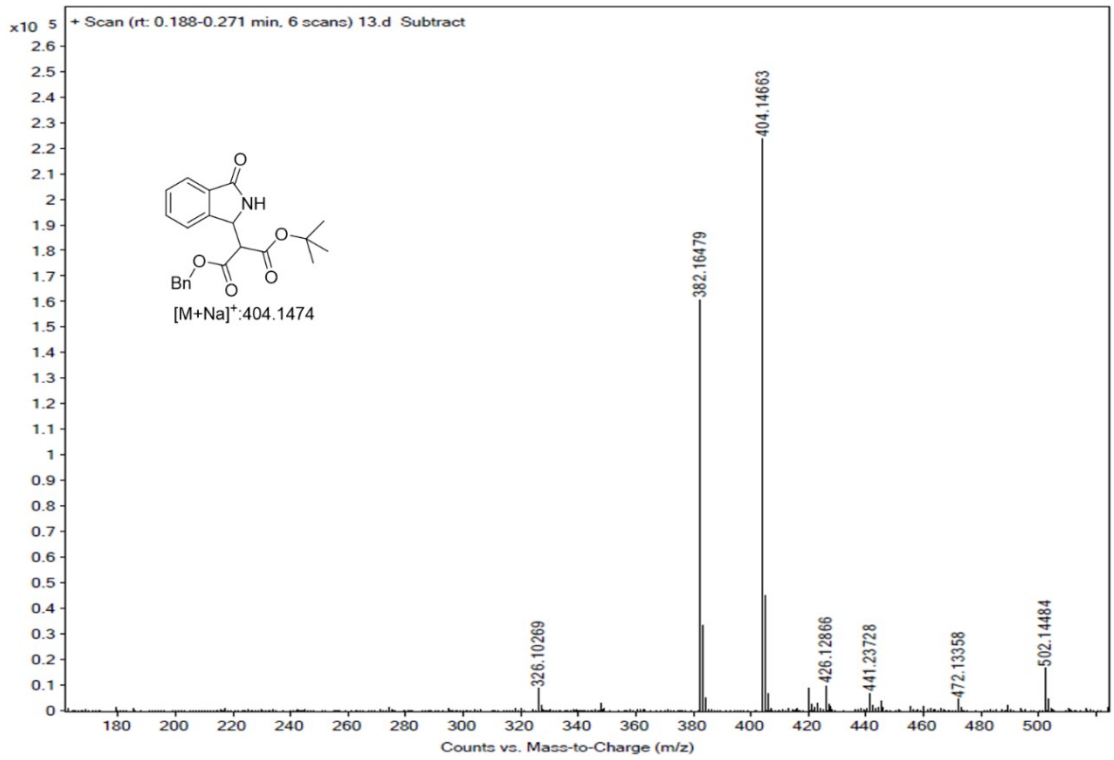

11 399 (2.221)
1: TOF MS ES+
2.06e6
450.1107
452.1088
472.0925
453.1111
474.0905
354.2852
371.3142
393.2978
394.3005
406.3286
450.0480
454.1137
475.0924
488.0665
508.1633
536.1588
557.0701
572.0226
587.3701
[M+H]+:450.1108
m/z

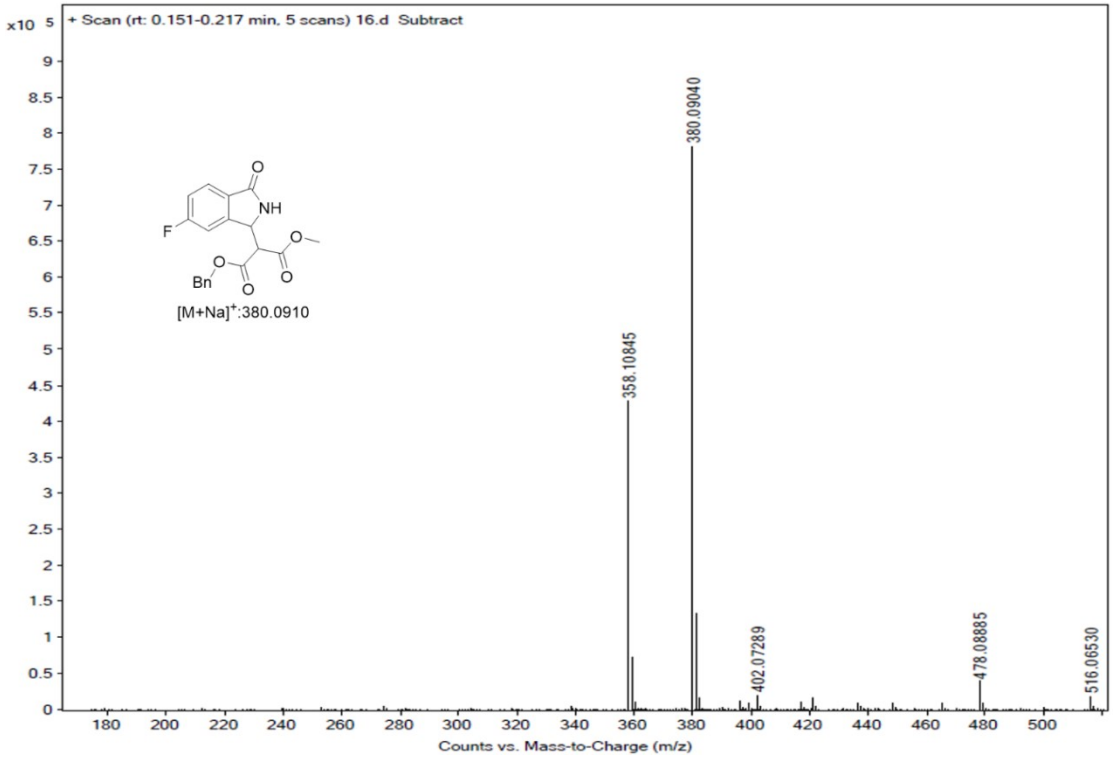

+ Scan (rt: 0.151-0.284 min, 9 scans) 12.d Subtract
x10 5
NH
O
Ph
O
O
O
[M+Na]+:346.1055
324.12295
346.10484
362.07928
383.19672
Counts vs. Mass-to-Charge (m/z)


+ Scan (rt: 0.136-0.235 min, 7 scans) 14.d Subtract
x10 5
NH
OMe
O
O
O
[M+Na]+:376.1161
354.13331
376.11521
392.08935
413.20725
Counts vs. Mass-to-Charge (m/z)


+ Scan (rt: 0.154-0.254 min, 7 scans) 15.d Subtract
x10 5
[M+Na]+:364.0961
364.09546
342.11362
311.08093
333.06293
274.27415
338.34167
360.32386
380.06971
386.07761
405.12223
Counts vs. Mass-to-Charge (m/z)


+ Scan (rt: 0.122-0.156 min, 3 scans) 11.d Subtract
x10 5
[M+Na]+:362.1004
362.09988
340.11796
460.09808
Counts vs. Mass-to-Charge (m/z)

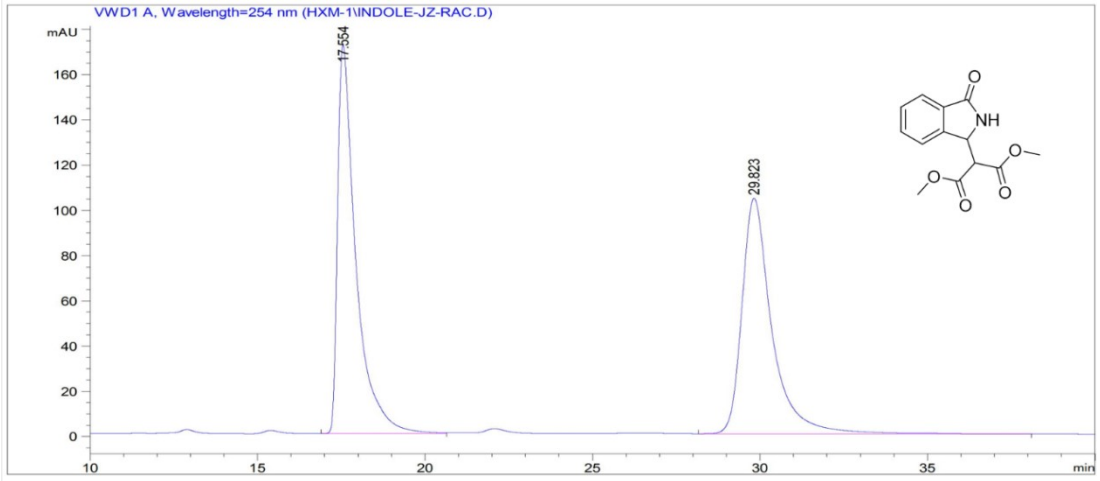

+ Scan (rt: 0.188-0.271 min, 6 scans) 13.d Subtract
x10 5
[M+Na]+:404.1474
404.14663
382.16479
326.10269
426.12866
441.23728
472.13358
502.14484
Counts vs. Mass-to-Charge (m/z)


+ Scan (rt: 0.151-0.217 min, 5 scans) 16.d Subtract
x10 5
[M+Na]+:380.0910
380.09040
358.10845
402.07289
478.08885
516.06530
Counts vs. Mass-to-Charge (m/z)

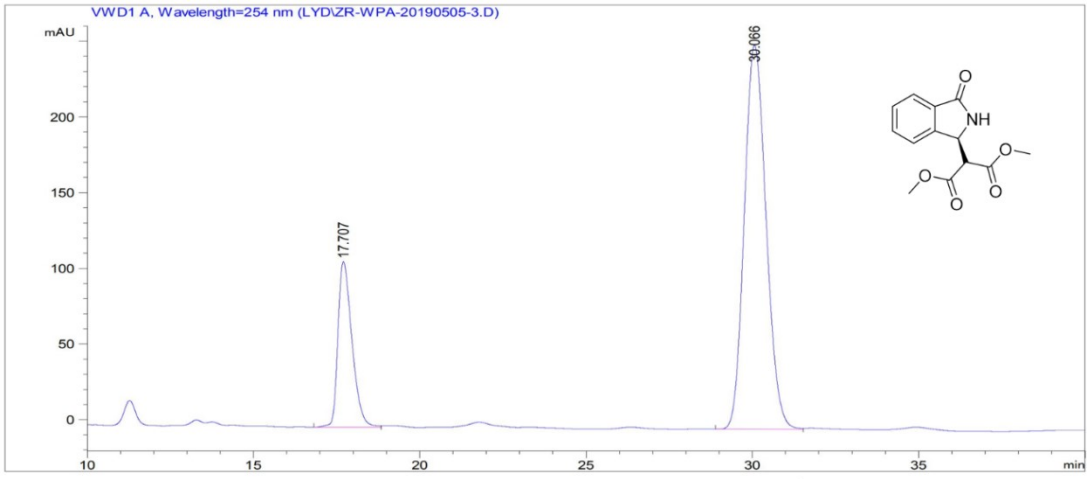
7. HPLC Analysis

Dimethyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (**3aa**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): 17.7 min (minor), 30.0 min (major), 57% *ee*



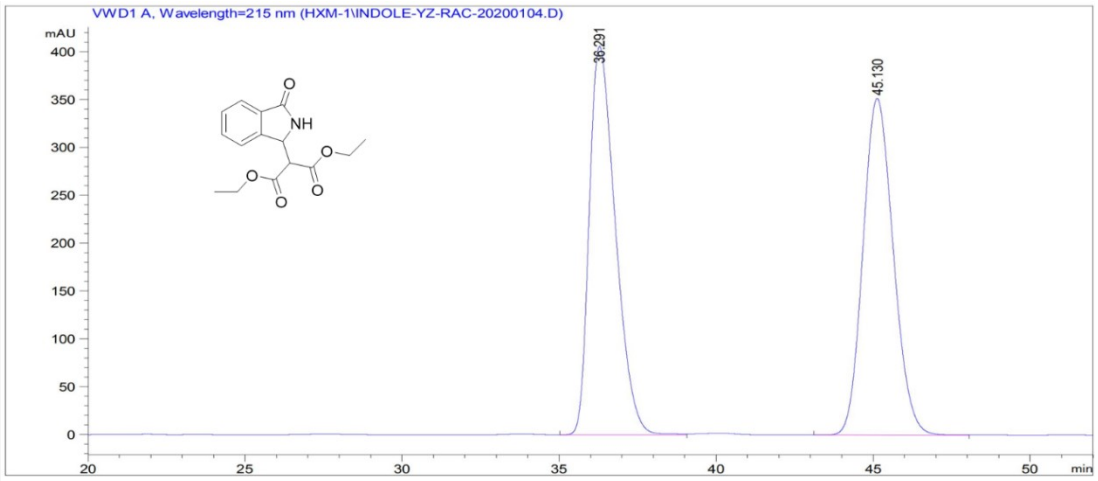
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	17.554	BV	0.5545	6508.12207	171.58238	50.1224
2	29.823	BB	0.9176	6476.34424	104.13645	49.8776



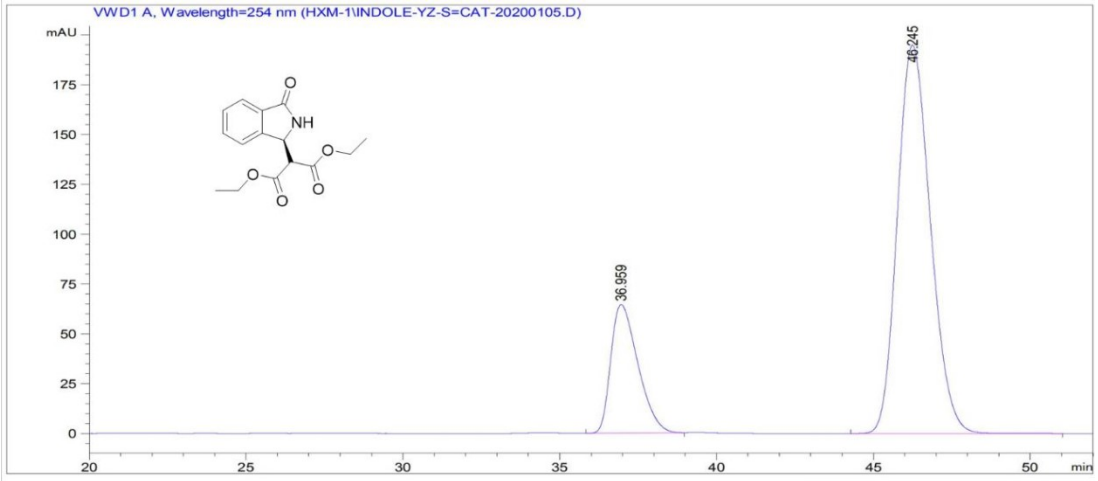
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	17.707	BV	0.4510	3218.89746	109.50158	21.7903
2	30.066	BV	0.7151	1.15533e4	253.80525	78.2097

Diethyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (**3ab**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min): 28.3 min (minor), 39.3 min (major), 63% *ee*



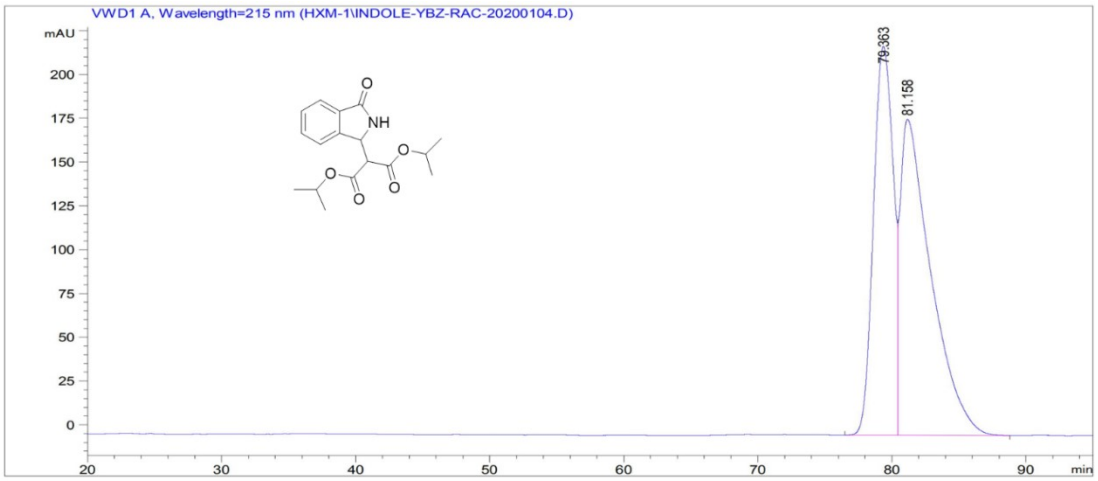
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	36.291	VV	0.8997	2.35167e4	406.05219	49.8811
2	45.130	BV	1.0578	2.36289e4	351.69232	50.1189



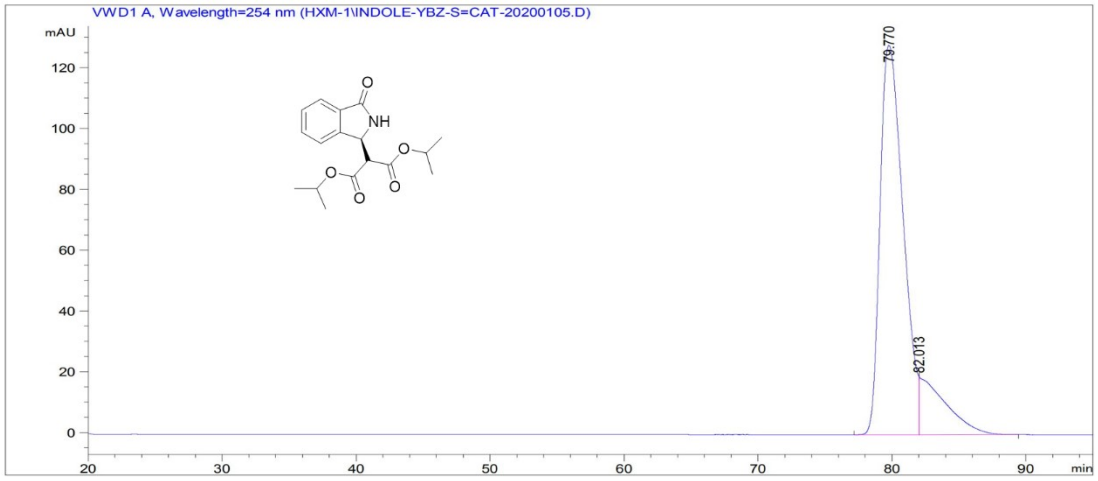
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	36.959	BB	0.9221	3877.42285	64.43004	21.3792
2	46.245	BB	1.1402	1.42590e4	194.74092	78.6208

Diisopropyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (**3ac**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 79.8 min (minor), 82.0 min (major), 70% *ee*



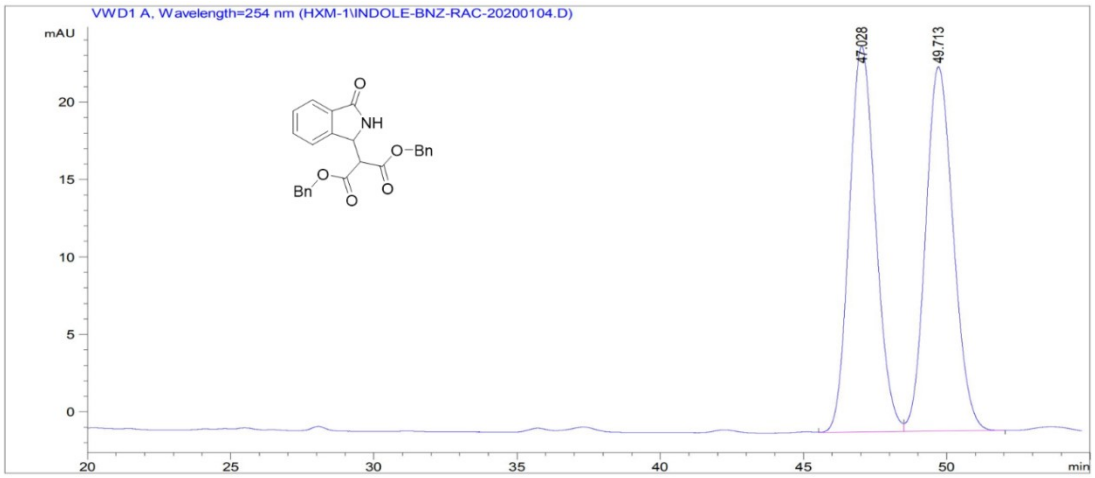
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	79.363	BV	1.6046	2.26110e4	221.94174	43.9155
2	81.158	VB	2.2014	2.88765e4	180.40706	56.0845



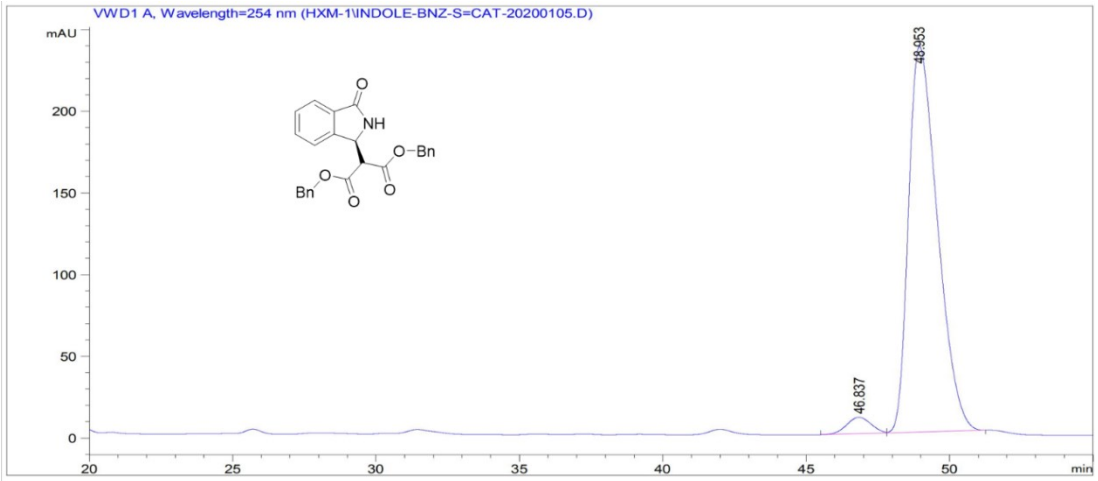
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	79.770	MF R	1.9892	1.52827e4	128.04893	85.1845
2	82.013	FM R	2.3071	2657.99292	19.20161	14.8155

Di-benzyl (*S*)-2-(3-oxoisoindolin-1-yl) malonate (**3ad**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 46.8 min (minor), 49.0 min (major), 93% *ee*



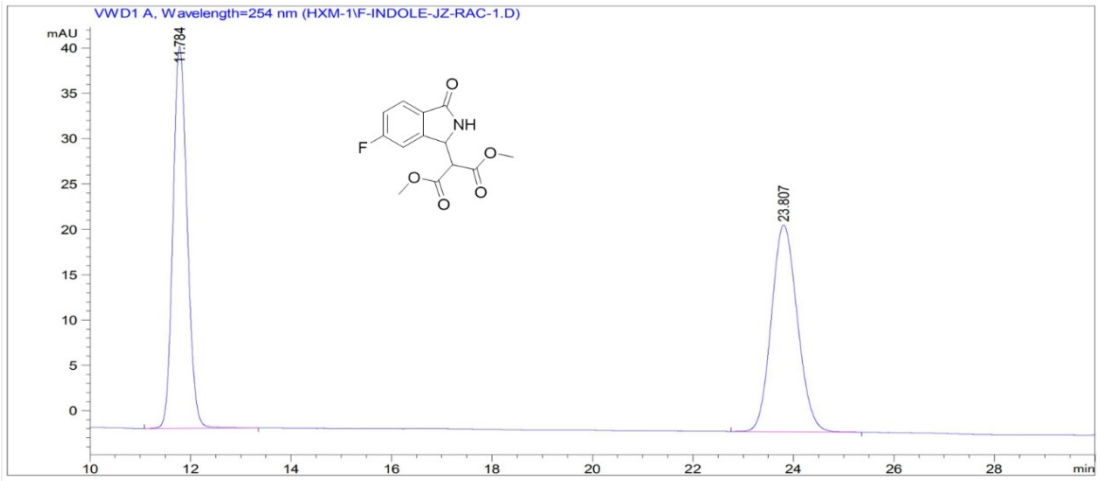
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	47.028	VV	0.9835	1592.64966	24.92492	50.2037
2	49.713	VB	1.0391	1579.72241	23.53344	49.7963



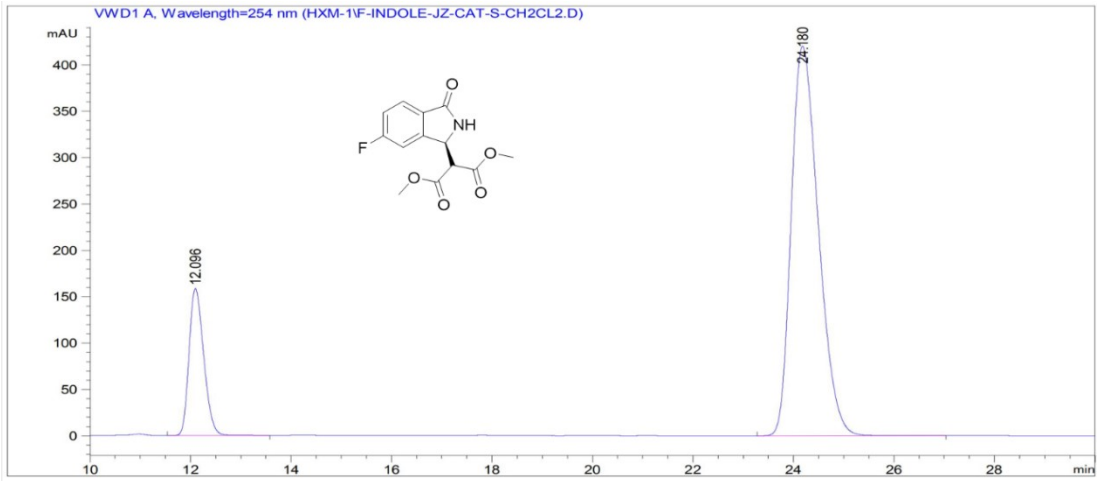
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	46.837	BV	0.9189	582.92603	9.98740	3.3970
2	48.953	VB	1.0893	1.65770e4	236.04410	96.6030

Dimethyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (**3ba**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): 12.1 min (minor), 24.2 min (major), 66% *ee*



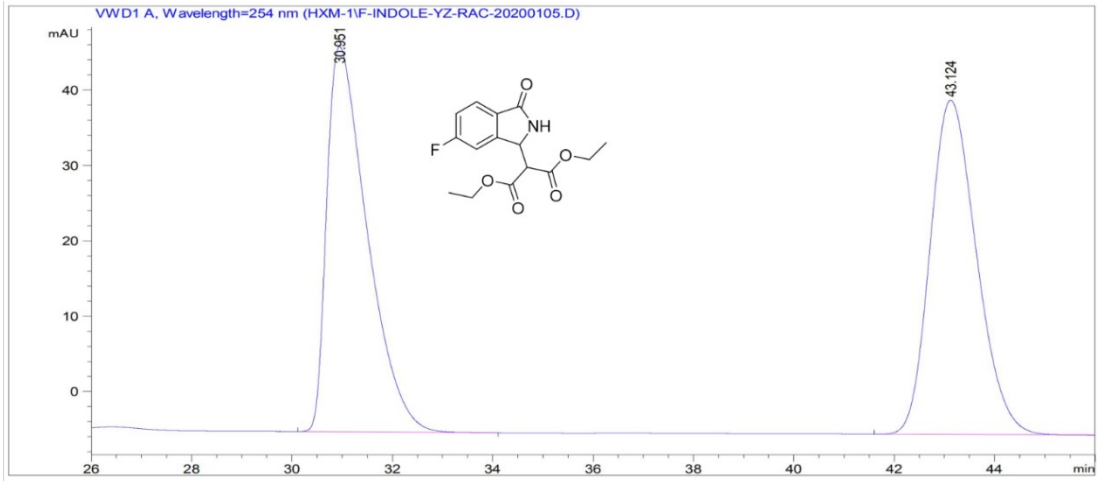
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	11.784	BB	0.3055	829.20459	42.15414	50.2776
2	23.807	BB	0.5594	820.04803	22.81327	49.7224



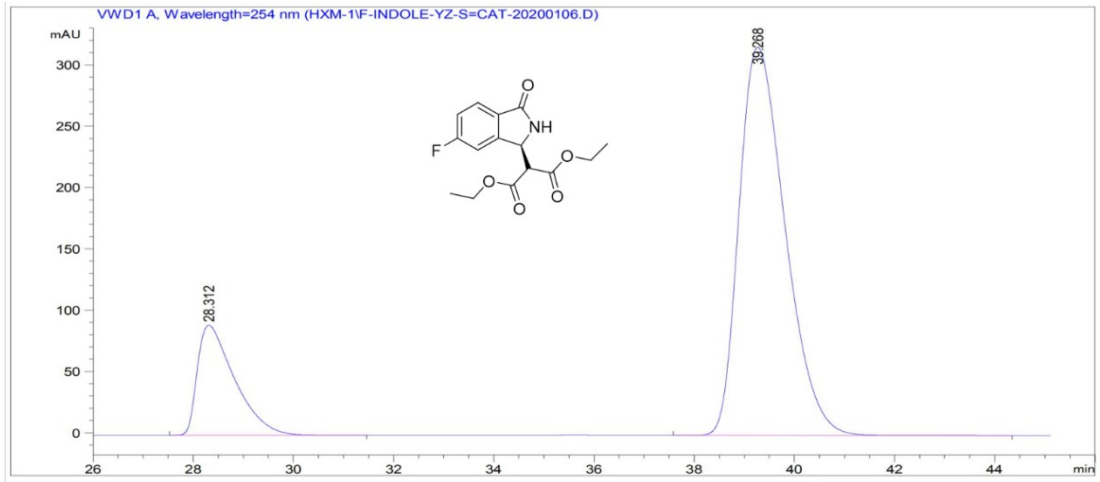
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	12.096	BV	0.3176	3228.52930	158.55678	17.0018
2	24.180	BB	0.5838	1.57608e4	419.98843	82.9982

Diethyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (**3bb**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min): 28.3 min (minor), 39.3 min (major), 63% *ee*



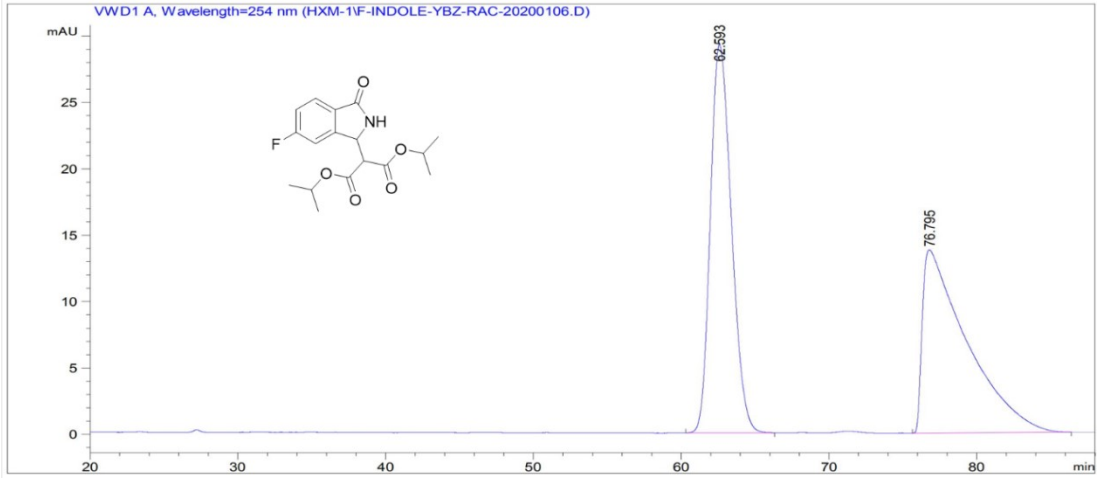
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	30.951	BB	0.8454	2853.06055	51.09736	50.0695
2	43.124	BB	0.9930	2845.14429	44.31693	49.9305



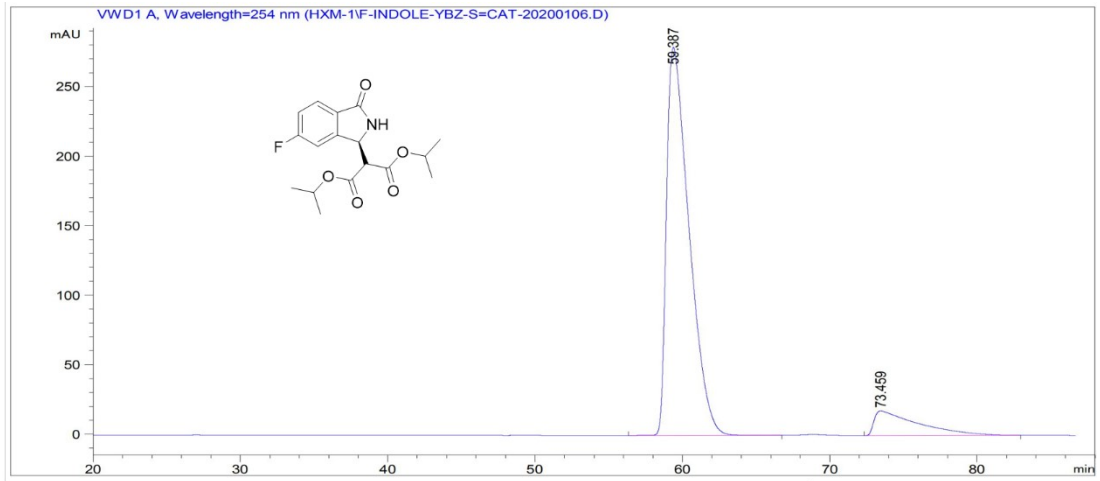
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	28.312	BB	0.7679	4602.26709	89.50819	18.5376
2	39.268	BB	0.9934	2.02244e4	316.54083	81.4624

Diisopropyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (**3bc**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 59.4 min (major), 73.5 min (minor), 78% *ee*.



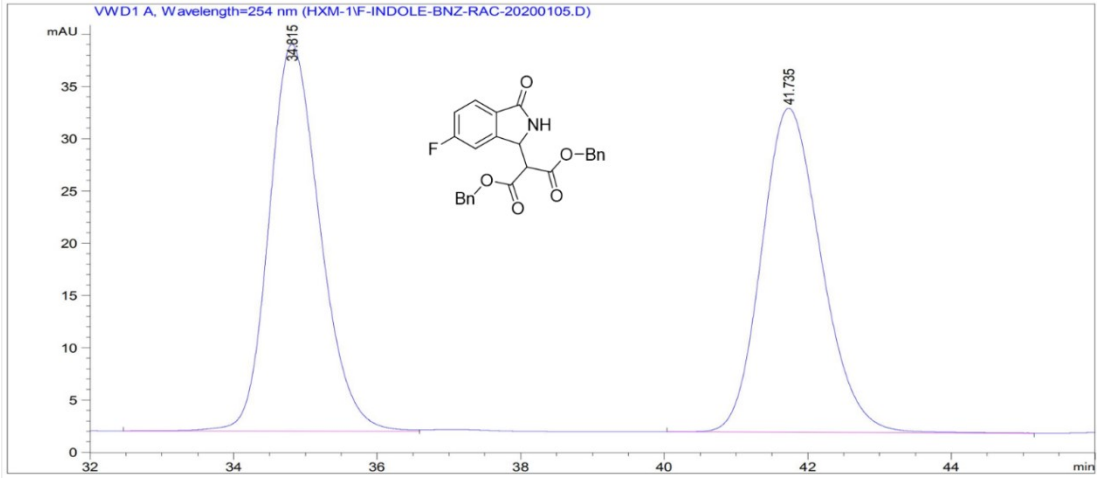
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	62.593	BB	1.5308	2890.97217	29.25859	50.1142
2	76.795	BB	2.6671	2877.79150	13.78743	49.8858



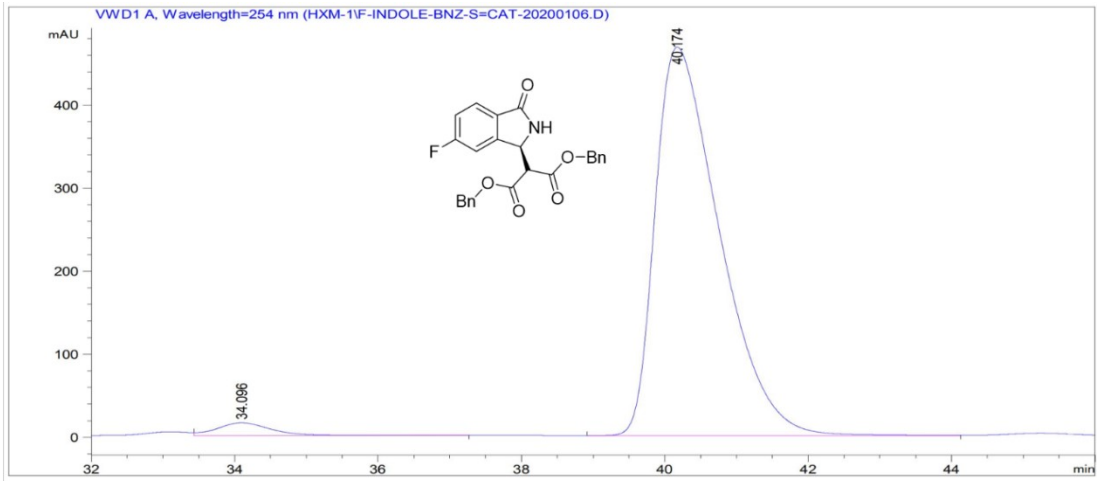
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	59.387	BB	1.5620	2.95773e4	279.17465	89.0951
2	73.459	BB	2.6366	3620.16064	17.54994	10.9049

Di-benzyl (*S*)-2-(6-fluoro-3-oxoisoindolin-1-yl) malonate (**3bd**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 75:25, 1.0 mL/min): 34.1 min (minor), 40.2 min (major), 95% *ee*.



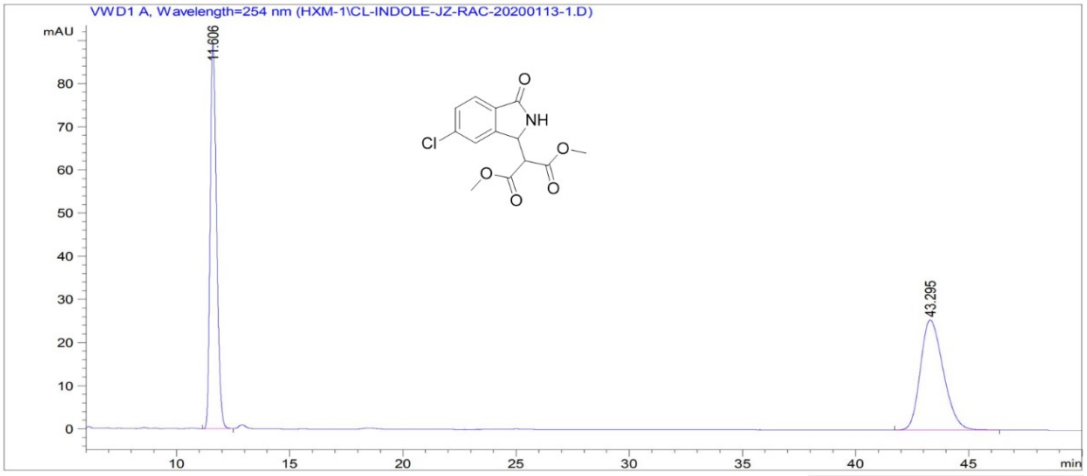
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	34.815	BV	0.7603	1821.93396	37.01261	50.3813
2	41.735	BB	0.9012	1794.35376	31.00246	49.6187



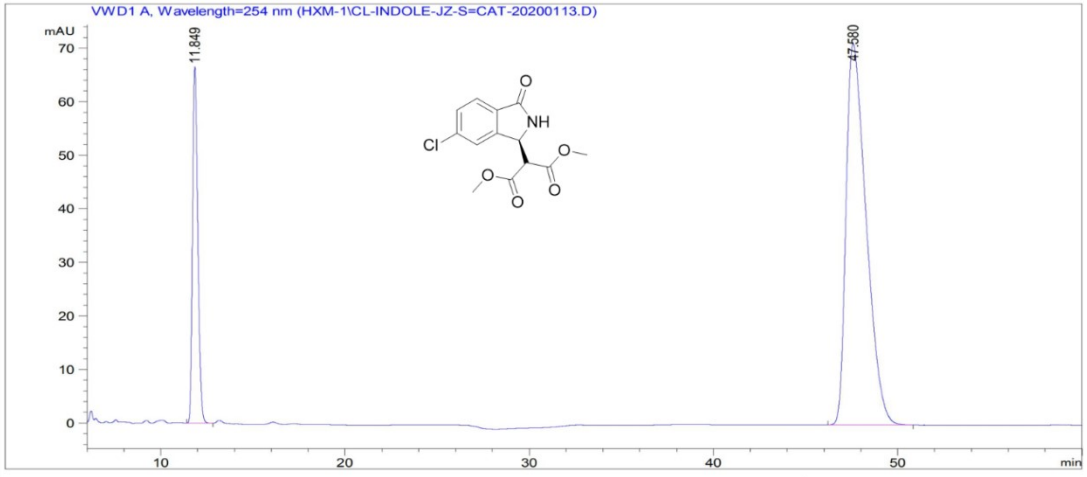
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	34.096	VB	0.7928	790.60199	15.15124	2.6426
2	40.174	BV	0.9488	2.91269e4	467.53766	97.3574

Dimethyl (*S*)-2-(6-chloro-3-oxoisoindolin-1-yl) malonate (**3ca**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): 11.8 min (minor), 47.6 min (major), 60% *ee*



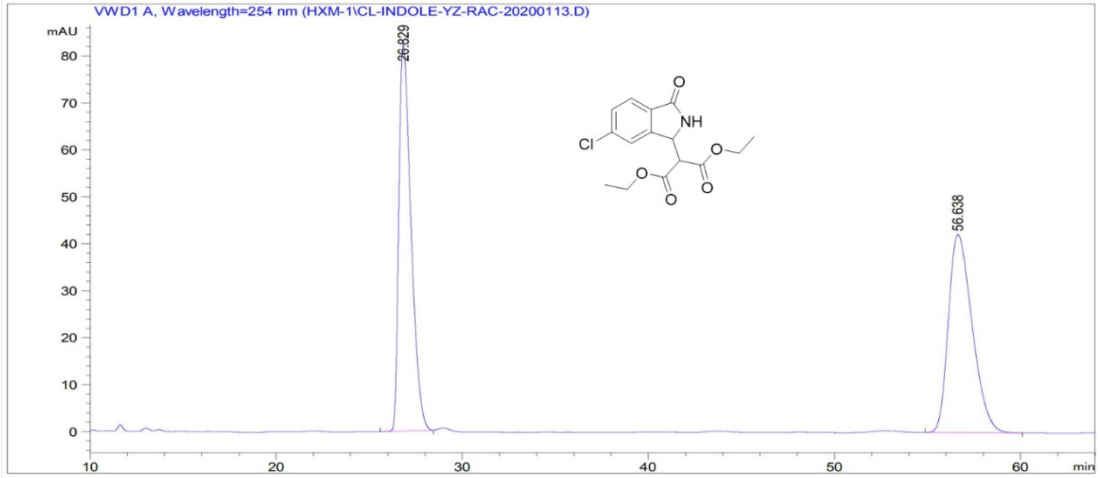
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	11.606	BB	0.3069	1755.30627	89.06296	49.6275
2	43.295	BB	1.0783	1781.65637	25.46485	50.3725



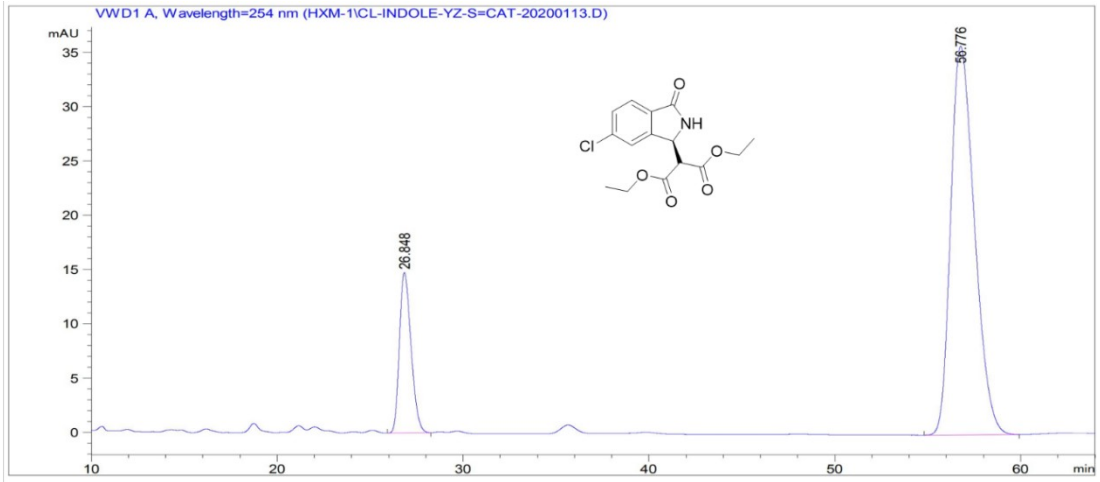
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	11.849	BB	0.3104	1331.29138	66.53971	19.8024
2	47.580	BB	1.1501	5391.59570	71.14611	80.1976

Diethyl (*S*)-2-(6-chloro-3-oxoisoindolin-1-yl) malonate (**3cb**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 75:25, 1.0 mL/min): 26.8 min (minor), 56.8 min (major), 66% *ee*



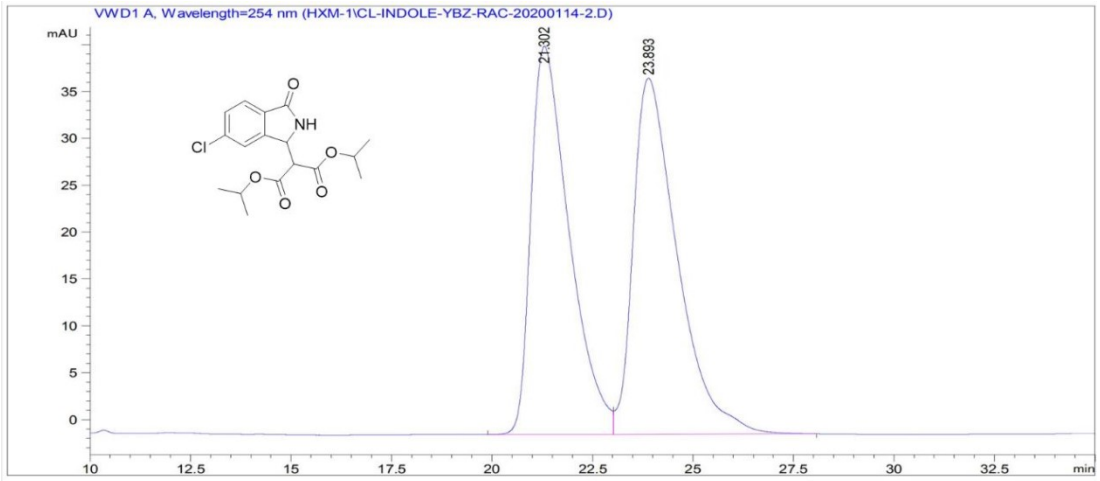
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.829	BB	0.6914	3738.09277	82.38175	49.9156
2	56.638	BB	1.3500	3750.73315	42.19815	50.0844



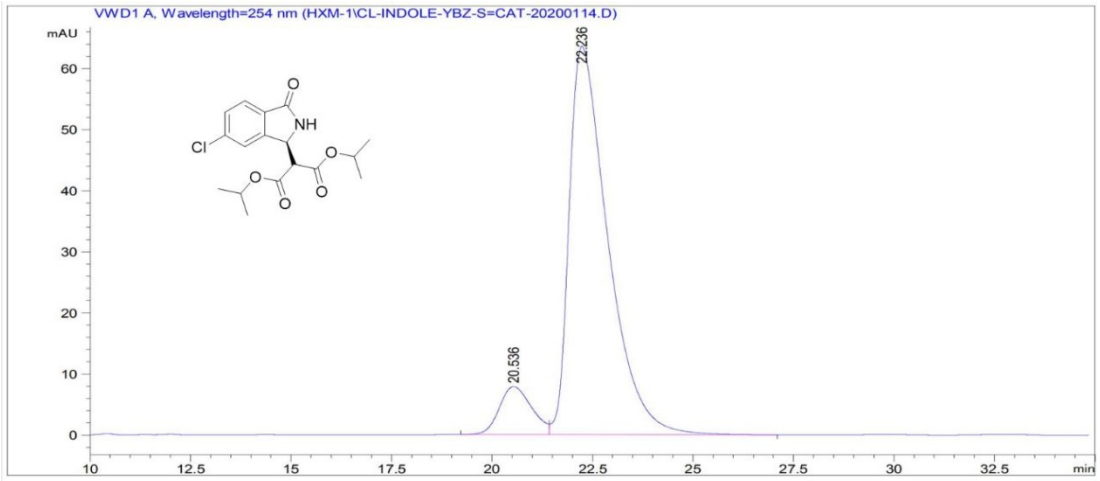
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.848	BB	0.6684	641.10065	14.76964	16.7820
2	56.776	BB	1.3567	3179.07617	35.77760	83.2180

Diisopropyl (*S*)- 2-(6-chloro-3-oxoisoindolin-1-yl) malonate (**3cc**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 95:5, 1.0 mL/min): 20.5 min (minor), 22.2 min (major), 81% *ee*



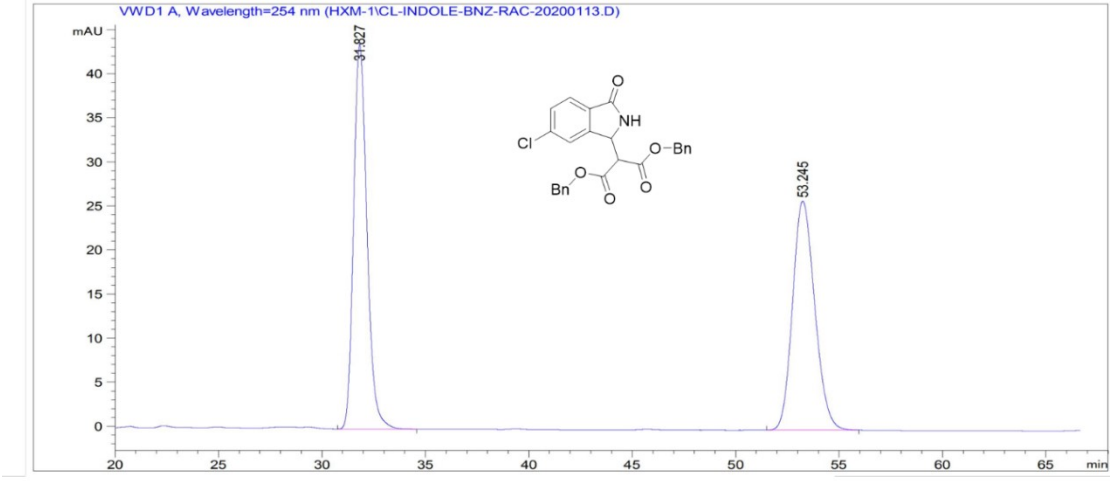
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	21.302	BV	0.9937	2742.38696	41.40533	48.6486
2	23.893	VB	1.1241	2894.74219	37.98659	51.3514



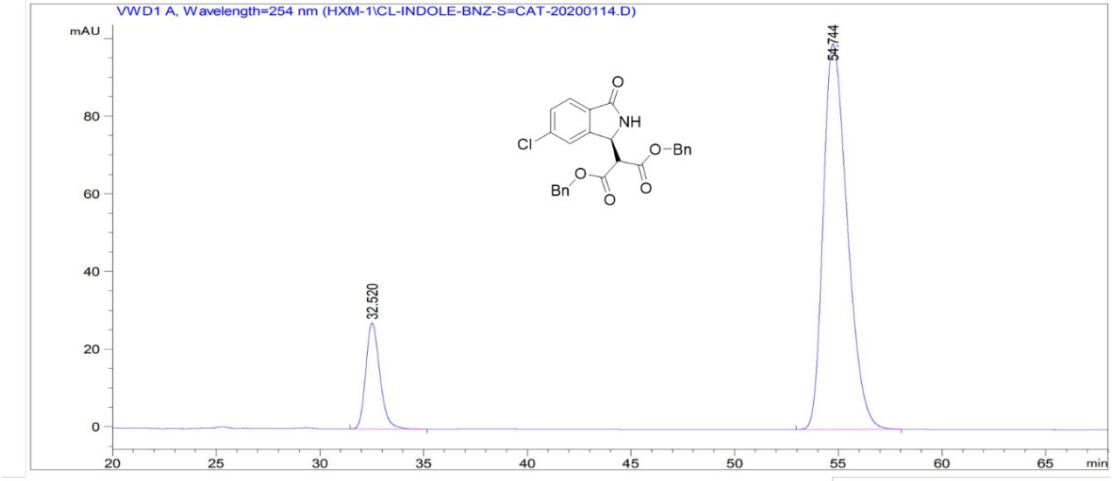
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	20.536	BV	0.8291	441.11002	7.86820	9.3842
2	22.236	VB	1.0125	4259.46289	63.59055	90.6158

Dibenzyl (*S*)- 2-(6-chloro-3-oxoisoindolin-1-yl) malonate (**3cd**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 75:25, 1.0 mL/min): 32.5 min (minor), 54.7 min (major), 72% *ee*



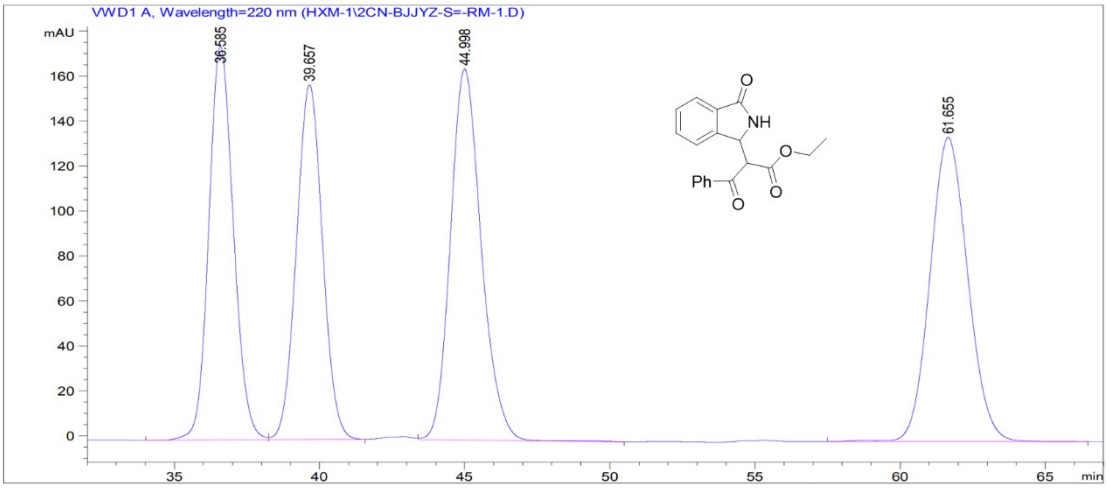
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	31.827	BB	0.6917	1964.55554	43.67816	50.3490
2	53.245	BB	1.1390	1937.32385	25.98054	49.6510



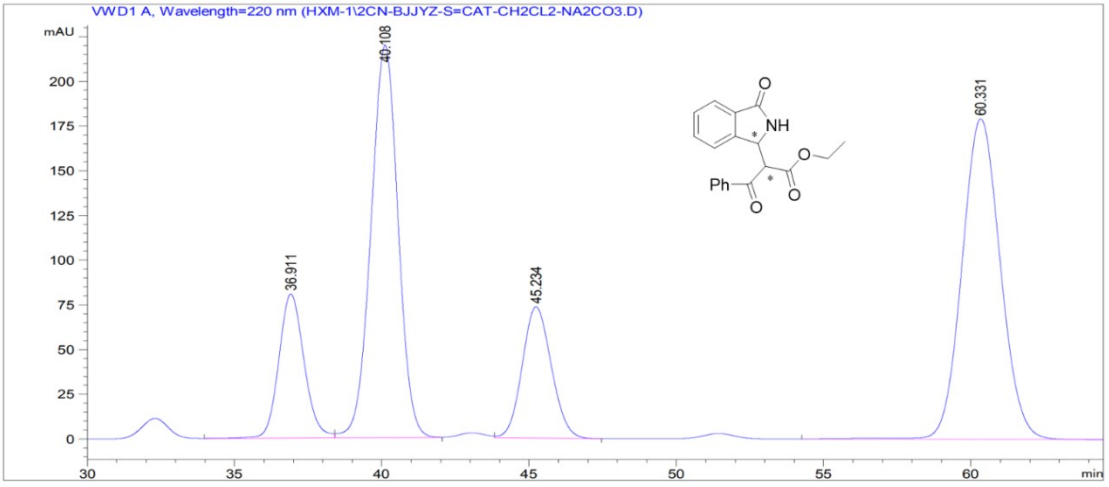
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	32.520	BB	0.7211	1287.39502	27.30312	13.8508
2	54.744	BB	1.2339	8007.30566	99.28381	86.1492

Ethyl 3-oxo-2-((S)-3-oxoisoindolin-1-yl)-3-phenylpropanoate (**6aa**)

Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min]: t_1(minor) = 36.0 min (12.0%), t_2(major) = 40.1 min, 49% *ee*; t_3(minor) = 45.2 min (12.6%), t_4(major) = 60.3 min (40.4%), 53% *ee*; *dr* = 47:53



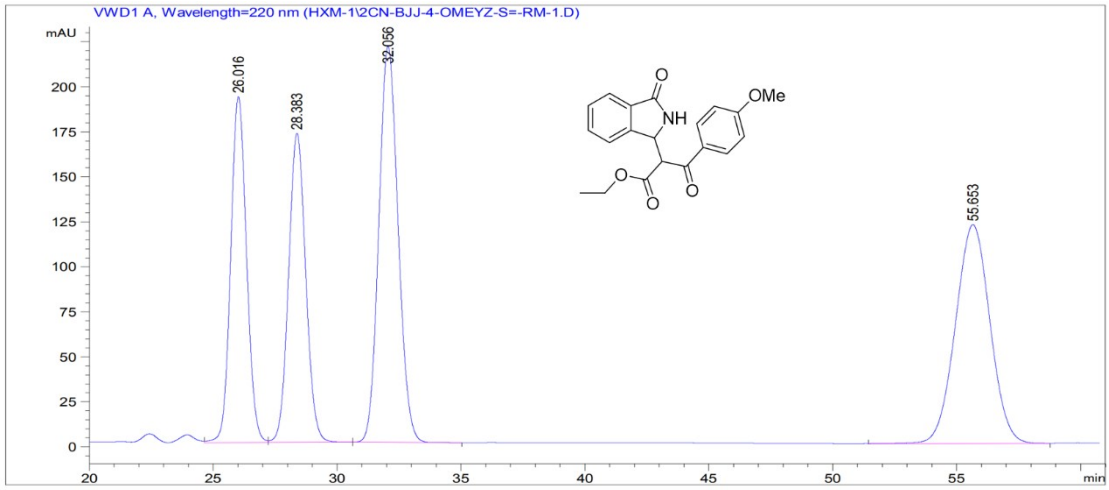
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	36.585	BV	0.9127	1.03418e4	175.19901	23.1662
2	39.657	VB	0.9768	9863.07715	157.89934	22.0938
3	44.998	VB	1.1345	1.22072e4	165.12257	27.3447
4	61.655	BB	1.4218	1.22298e4	135.39073	27.3953



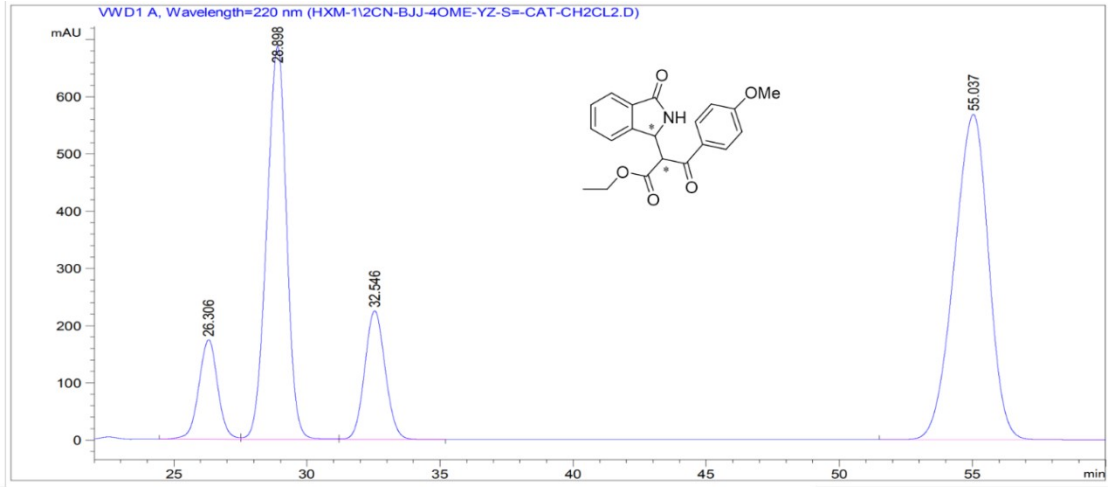
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	36.911	BV	0.9268	4796.36084	80.54327	11.9681
2	40.108	VB	1.0012	1.40185e4	219.45886	34.9797
3	45.234	VB	1.0828	5049.28516	73.37868	12.5992
4	60.331	BB	1.4079	1.62120e4	179.12041	40.4529

Ethyl 3-(4-methoxyphenyl)-3-oxo-2-((S)-3-oxoisoindolin-1-yl) propanoate (**6ab**)

Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min]: t_1(minor) = 26.3 min (8.0%); t_2 (major) = 28.9 min (33.2%), 61%*ee*; t_3(minor) = 32.5 min (11.2%), t_4(major) = 55.0 min (47.6%), 61% *ee*; *dr* = 41:59



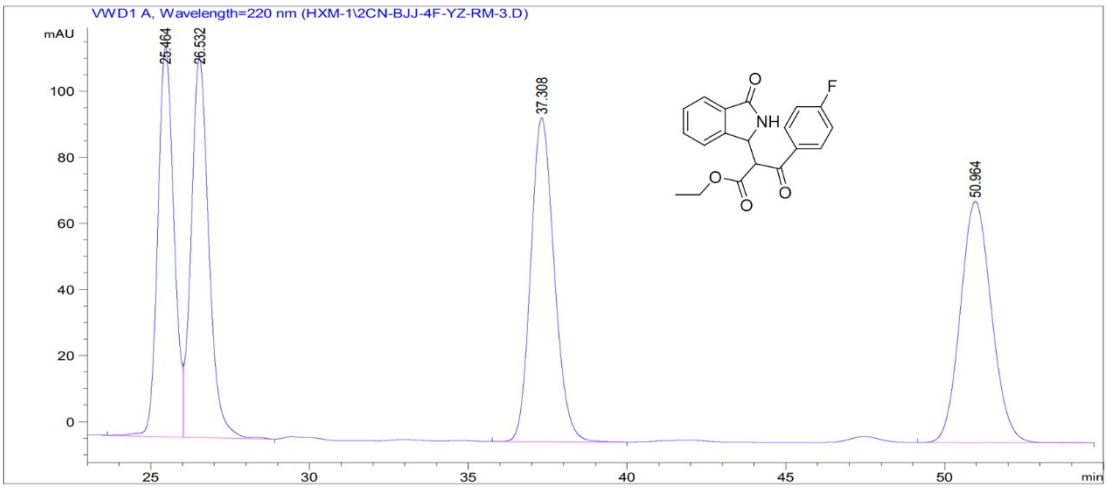
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.016	VV	0.6845	8506.73340	192.14240	21.0499
2	28.383	VB	0.7524	8241.40234	171.56032	20.3934
3	32.056	BB	0.8458	1.18691e4	219.86485	29.3700
4	55.653	BB	1.5153	1.17950e4	121.63839	29.3700



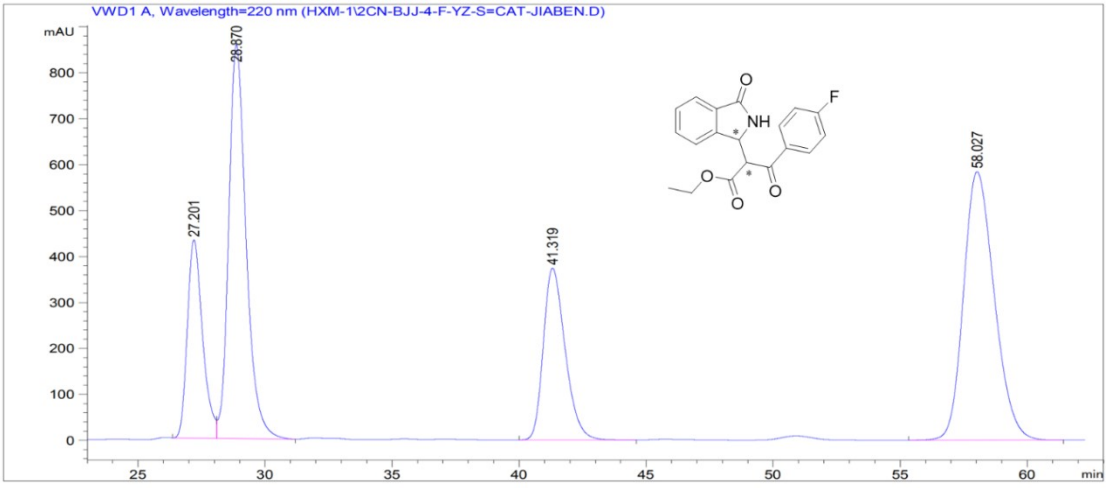
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.306	BV	0.7699	8617.64063	173.96677	8.0259
2	28.898	VV	0.8044	3.56216e4	687.57703	33.1754
3	32.546	VB	0.8332	1.20408e4	224.70558	11.2140
4	55.037	BB	1.3927	5.10933e4	568.39667	47.5847

Ethyl 3-(4-fluorophenyl)-3-oxo-2-((S)-3-oxoisoindolin-1-yl) propanoate (**6ac**)

Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 75:25, 0.5 mL/min): t_1(minor) = 27.2 min (13.8%), t_2(major) = 28.9 min (31.3%), 40% *ee*; t_3(minor) = 41.3 min (17.2%), t_4(major) = 58.0 min (37.7%), 39% *ee*; *dr* = 45:55



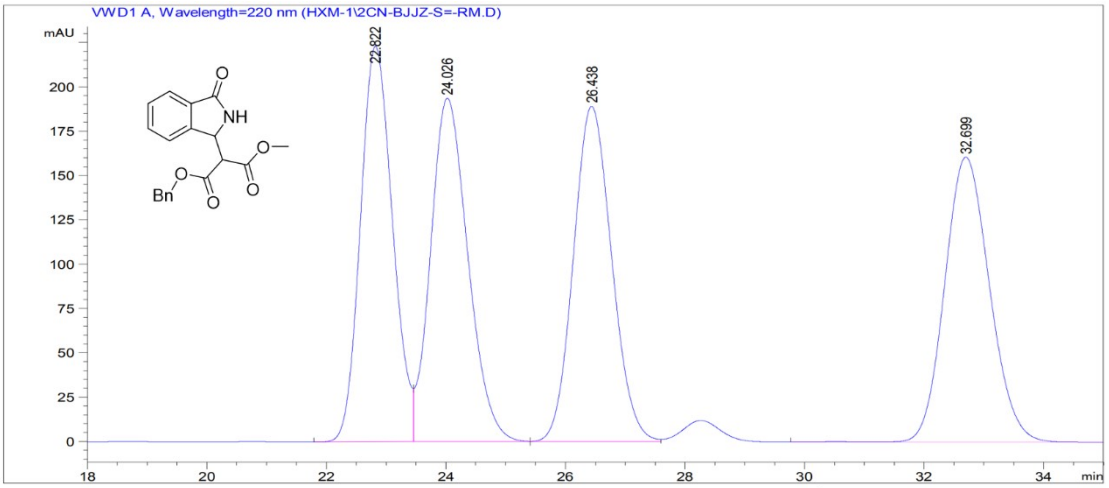
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	25.464	BV	0.5472	4151.88428	117.79941	22.2996
2	26.532	VV	0.5962	4449.88721	114.81395	23.9002
3	37.308	BB	0.7928	5042.98389	97.93446	27.0857
4	50.964	VBA	1.0671	4973.86035	72.98634	26.7144



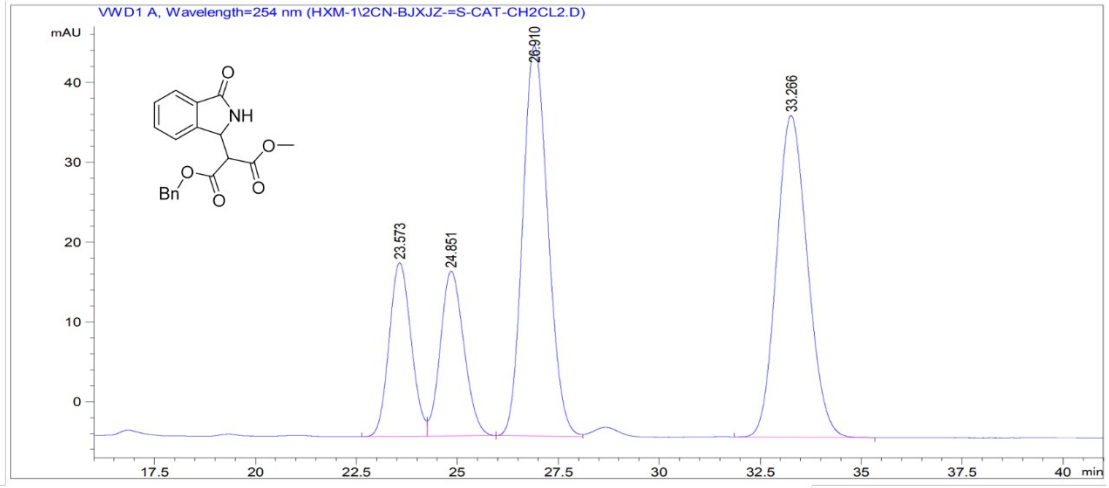
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	27.201	BV	0.6402	1.80410e4	431.14120	13.8366
2	28.870	VB	0.7322	4.08050e4	855.97162	31.2956
3	41.319	VV	0.9295	2.23636e4	374.05594	17.1519
4	58.027	BB	1.3102	4.91763e4	584.11578	37.7160

1-Benzyl 3-methyl 2-((S)-3-oxoisoindolin-1-yl) malonate (**6ad**)

Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): t_1 = 23.6 min (13.9%), t_2 = 24.9 min (14.1%); t_3 = 26.9 min (35.8%), t_4 = 33.3 min (36.2%); *dr* = 28:72



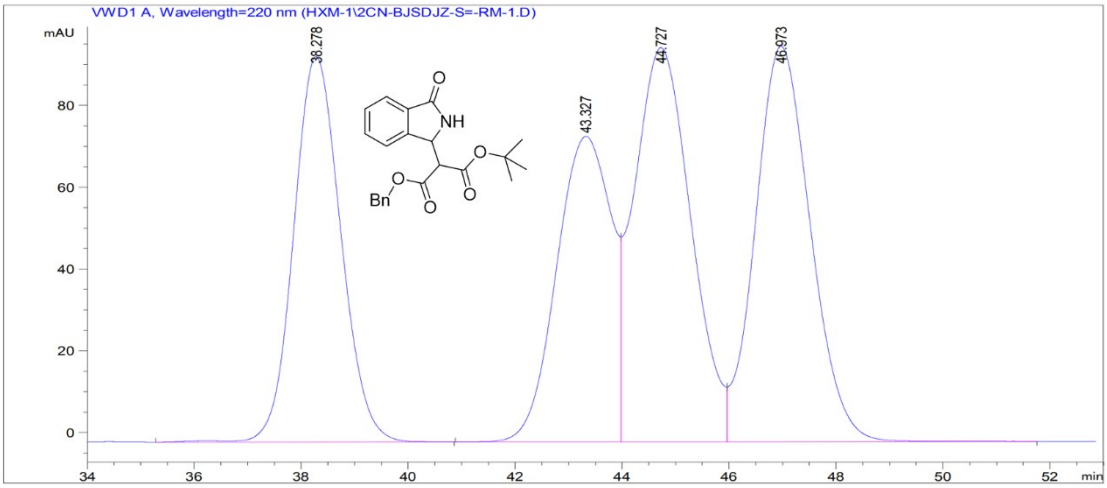
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	22.822	BV	0.5795	8323.89160	222.99487	24.8311
2	24.026	VB	0.6751	8412.85645	193.54848	25.0965
3	26.438	BV	0.6945	8399.61426	189.00778	25.0570
4	32.699	BBA	0.8169	8385.63379	160.66606	25.0153



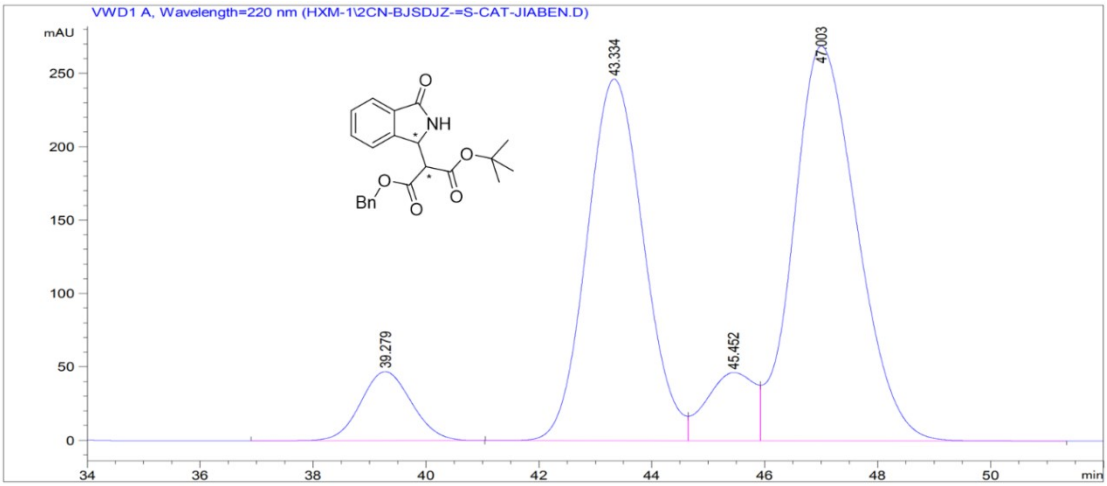
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	23.573	BV	0.5946	825.89142	21.77223	13.9220
2	24.851	VB	0.6330	837.46692	20.65695	14.1172
3	26.910	BV	0.6821	2121.26758	48.90053	35.7582
4	33.266	BB	0.8295	2147.63330	40.31196	36.2026

1-Benzyl 3-(tert-butyl) 2-((S)-3-oxoisoindolin-1-yl) malonate (**6ae**)

Chiralpak AD-H column, 220 nm, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min): t_1(minor) = 39.3 min (6.7%), t_2(major) = 43.3 min (39.1%),71% *ee*; t_3(minor) = 45.5 min (6.3%), t_4(major) = 47.0 min (47.9%), 77% *ee*; *dr* = 46:54



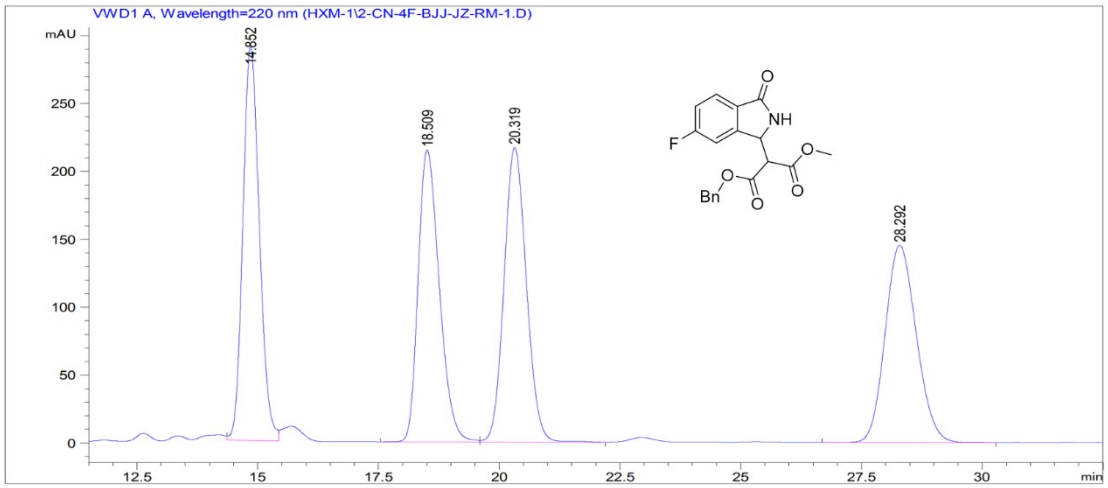
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	38.278	BB	0.9541	5770.10986	94.27213	22.9660
2	43.327	BV	1.1112	5324.36670	74.73509	21.1918
3	44.727	VV	1.1243	7105.10645	96.35870	28.2795
4	46.973	VB	1.1156	6925.01904	96.68777	27.5627



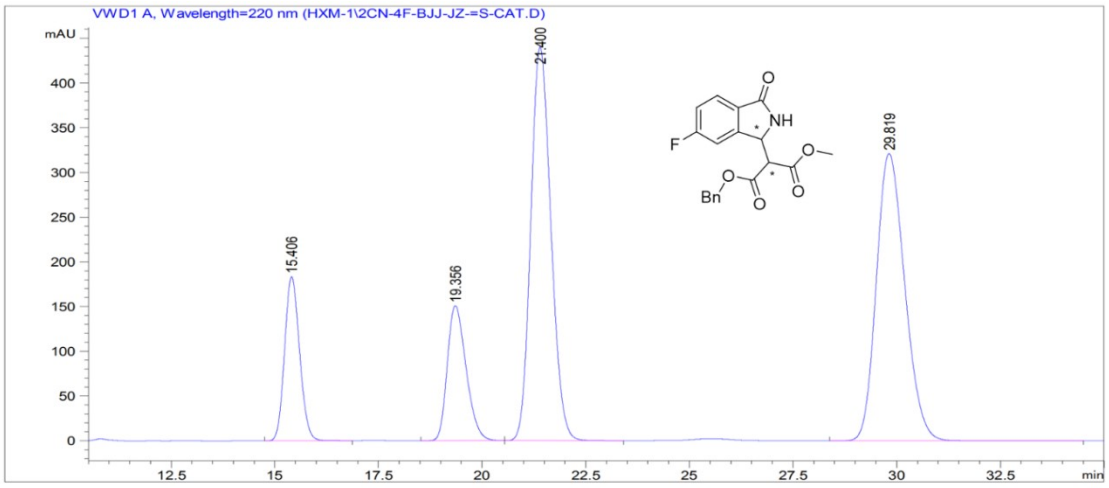
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	39.279	BB	0.9831	2947.69800	47.03569	6.7055
2	43.334	BV	1.0939	1.71924e4	246.42783	39.1098
3	45.452	VV	0.8999	2755.86743	46.47010	6.2691
4	47.003	VB	1.2255	2.10634e4	268.99695	47.9156

1-Benzyl 3-methyl 2-((S)-6-fluoro-3-oxoisoindolin-1-yl) malonate (**6bd**)

Chiralpak AD-H column, 254 nm, *n*-hexane: *i*-PrOH = 80:20, 1.0 mL/min): t_1= 15.4 min (11.7%), t_2 = 19.4 min (12.0%); t_3 = 21.4 min (37.6%), t_4 = 29.8 min (38.7%); *dr* = 49:51



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	14.852	VV	0.3745	6915.71777	289.74081	25.6561
2	18.509	BV	0.4716	6549.88721	214.90755	24.2989
3	20.319	VB	0.5030	6971.06445	216.85297	25.8614
4	28.929	BB	0.6999	6518.77100	145.17932	24.1835



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	15.406	BV	0.3941	4628.49805	183.58452	11.7191
2	19.356	BB	0.4872	4749.61963	150.88872	12.0257
3	21.400	BB	0.5252	1.48305e4	439.99326	37.5498
4	29.819	BB	0.7477	1.52869e4	320.95303	38.7054