Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Organocatalytic Conjugate Addition Promoted by a Multi-Hydrogen-Bond Cooperation: Access to Chiral 2-Amino-3-nitrile-chromenes

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A: General Information and Starting Materials

General Information. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker ACF300 spectrometer (500 MHz and 125 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.16). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T mass spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

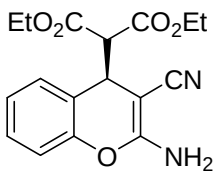
Starting Materials. All solvents and inorganic reagents were from commercial sources and used without purification unless otherwise noted. Chromene derivatives were prepared following the literature procedures.[1]

B: General Procedure for Michael Reactions

To a solution of Et_2O (0.5 mL) were added chromene derivatives **1** (0.10 mmol), malonate **2** (0.30 mmol) and catalyst **VI** (0.01 mmol). The reaction mixture was stirred at room temperature for the time given and then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel, eluting with hexane/EtOAc (10:1 to 5:1), to afford the desired product.

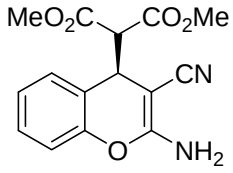
C: Characterization Data of Michael Reaction Products

(R)-diethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3da)



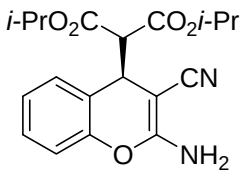
Yellow oil. $[\alpha]_D^{25}$ = - 1.5 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.29-7.28 (m, 1H), 7.25-7.21 (m, 1H), 7.11-7.10 (m, 1H), 7.00-6.97 (m, 1H), 4.73-4.72 (br, 2H), 4.39 (d, *J* = 9.0 MHz, 1H), 4.20-4.15 (m, 2H), 4.12-4.08 (m, 2H), 3.63 (d, *J* = 9.0 MHz, 1H), 1.26-1.14 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.1, 167.0, 162.3, 150.0, 128.7, 128.4, 124.9, 120.8, 119.4, 116.3, 61.7, 61.6, 58.9, 55.9, 35.5, 13.8, 13.7. MS (ESI) m/z [M+Na$^+$]: 352.91. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{17}H_{18}N_2O_5Na$) requires m/z 353.1121, found m/z 353.1108. The enantiomeric excess was determined to be 85% by HPLC. [ID column, 254 nm, n-hexane:IPA = 9:1, 1.0 mL/min]: 38.8 min (major), 43.2 min (minor).

(R)-dimethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3db)

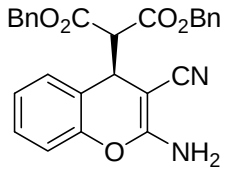


Yellow oil. $[\alpha]_D^{25}$ = + 4.1 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.24-7.23 (m, 2H), 7.13-7.10 (m, 1H), 7.01-6.99 (m, 1H), 4.78-4.77 (br, 2H), 4.39-4.37 (m, 1H), 3.73 (s, 3H), 3.66-3.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.4, 162.4, 150.0, 128.8, 128.2, 125.0, 120.7, 119.3, 116.4, 58.6, 55.7, 52.6, 52.5, 35.8. MS (ESI) m/z [M+Na$^+$]: 324.92. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{15}H_{14}N_2O_5Na$) requires m/z 325.0801, found m/z 325.0795. The enantiomeric excess was determined to be 77% by HPLC. [OJ-H column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 18.9 min (minor), 24.5 min (major).

(R)-diisopropyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3dc)



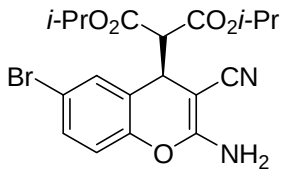
Yellow oil. $[\alpha]_D^{25}$ = + 11.8 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.33-7.32 (m, 1H), 7.25-7.22 (m, 1H), 7.11-7.09 (m, 1H), 6.97-6.96 (m, 1H), 5.06-5.04 (m, 1H), 4.94-4.92 (m, 1H), 4.73-4.72 (br, 2H), 4.38 (d, *J* = 5.0 MHz, 1H), 3.59 (d, *J* = 5.0 MHz, 1H), 1.22-1.20 (m, 6H), 1.13-1.11 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.5, 161.9, 150.0, 128.6, 128.5, 124.8, 120.7, 116.2, 69.3, 69.2, 59.2, 56.4, 35.1, 21.5, 21.4, 21.3, 21.2. MS (ESI) m/z [M+Na$^+$]: 381.01. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{22}N_2O_5Na$) requires m/z 381.1437, found m/z 381.1421. The enantiomeric excess was determined to be 94% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 11.3 min (major), 14.3 min (minor).



(R)-dibenzyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3de)

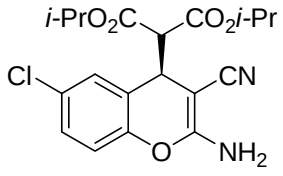
Yellow oil. $[\alpha]_D^{25}$ = - 3.2 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.31-7.26 (m, 6H), 7.23-7.15 (m, 6H), 7.03-7.00 (m, 1H), 6.93-6.91 (m, 1H), 5.18-5.06 (m, 4H), 4.66-4.65 (br, 2H), 4.28 (d, *J* = 5.5 MHz, 1H), 3.60 (d, *J* = 5.0 MHz, 1H).^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.8, 166.7, 162.3, 149.9, 135.1, 135.0, 128.9, 128.8, 128.5, 128.4, 128.3, 125.0, 124.5, 120.4, 119.4, 116.4, 67.5, 67.4, 58.8, 55.7, 35.7. MS (ESI) m/z [M+Na$^+$]: 476.91. HRMS (ESI): exact mass calculatd for [M+Na$^+$] ($C_{27}H_{22}N_2O_5Na$) requires m/z 477.1422, found m/z 477.1421. The enantiomeric excess was determined to be 55% by HPLC. [IC column, 254 nm, n-hexane:IPA = 9:1, 1.0 mL/min]: 47.6 min (minor), 54.0 min (major).

(R)-diisopropyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3ec)



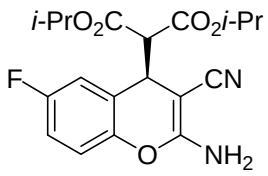
Yellow oil. $[\alpha]_D^{25}$ = + 4.6 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.46-7.45 (m, 1H), 7.36-7.32 (m, 1H), 6.86 (d, *J* = 14.5 MHz, 1H), 5.12-5.03 (m, 1H), 4.98-4.90 (m, 1H), 4.79-4.78 (br, 2H), 4.33 (d, *J* = 8.5 MHz, 1H), 3.59 (d, *J* = 8.5 MHz, 1H), 1.25-1.21 (m, 6H), 1.15-1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.7, 166.4, 161.7, 149.2, 131.6, 131.3, 122.8, 119.0, 117.9, 117.2, 69.7, 69.4, 59.0, 56.2, 35.0, 21.6, 21.5, 21.4, 21.3. MS (ESI) m/z [M+Na$^+$]: 460.89. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{21}BrN_2O_5Na$) requires m/z 459.0536, found m/z 459.0526. The enantiomeric excess was determined to be 95% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 9.1 min (major), 10.3 min (minor).

(R)-diisopropyl 2-(2-amino-6-chloro-3-cyano-4H-chromen-4-yl)malonate (3fc)



Yellow oil. $[\alpha]_D^{25}$ = + 2.5 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.31-7.30 (m, 1H), 7.20-7.17 (m, 1H), 6.91 (d, *J* = 14.5 MHz, 1H), 5.11-5.03 (m, 1H), 4.97-4.89 (m, 1H), 4.85-4.84 (br, 2H), 4.32 (d, *J* = 8.5 MHz, 1H), 3.58 (d, *J* = 8.5 MHz, 1H), 1.24-1.22 (m, 6H), 1.15-1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.7, 166.4, 161.8, 148.6, 129.7, 128.6, 128.3, 122.3, 117.5, 69.7, 69.4, 58.9, 55.9, 35.0, 21.5, 21.4, 21.3, 21.2. MS (ESI) m/z [M+Na$^+$]: 414.97. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{21}ClN_2O_5Na$) requires m/z 415.1030, found m/z 415.1031. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 8.7 min (major), 10.0 min (minor).

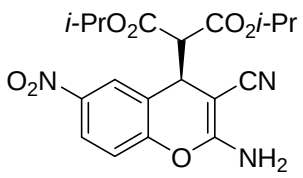
(R)-diisopropyl 2-(2-amino-3-cyano-6-fluoro-4H-chromen-4-yl)malonate (3gc)



Yellow oil. $[\alpha]_D^{23}$ = + 21.4 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.08 (d, *J* = 8.5 MHz, 1H), 6.93 (d, *J* = 5.5 MHz, 2H), 5.09-5.04 (m, 1H), 4.95-4.90 (m, 1H), 4.81-4.80 (br, 2H), 4.34 (d, *J* = 4.5 MHz, 1H), 3.58 (d, *J* = 4.5 MHz, 1H), 1.24-1.22 (m, 6H), 1.13-1.11 (m, 6H). ^{13}C NMR ($CDCl_3$, 125

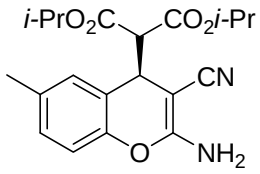
MHz): δ (ppm) 166.8, 166.5, 162.0, 160.0, 158.1, 146.2, 122.4, 122.3, 119.3, 117.6, 117.5, 115.3 (q, *J* = 45.0 MHz, 1H), 69.7, 69.4, 59.0, 55.8, 35.3, 21.6, 21.5, 21.4, 21.3. MS (ESI) m/z [M+Na$^+$]: 398.98. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{21}FN_2O_5Na$) requires m/z 399.1333, found m/z 399.1327. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 8.7 min (major), 9.7 min (minor).

(R)-diisopropyl 2-(2-amino-3-cyano-6-nitro-4H-chromen-4-yl)malonate (3hc)



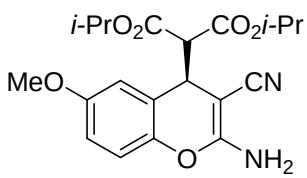
Yellow oil. $[\alpha]_D^{25}$ = - 4.6 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.27-8.26 (m, 1H), 8.16-8.13 (m, 1H), 7.12 (d, *J* = 15.0 MHz, 1H), 5.12-5.08 (m, 1H), 4.97-4.92 (m, 3H), 4.45 (d, *J* = 7.5 MHz, 1H), 3.68 (d, *J* = 7.5 MHz, 1H), 1.28-1.22 (m, 6H), 1.17-1.13 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.6, 166.3, 161.0, 154.3, 144.4, 124.7, 124.4, 121.9, 118.4, 117.2, 70.2, 69.7, 58.6, 56.2, 35.0, 21.6, 21.5, 21.4, 21.3. MS (ESI) m/z [M+Na$^+$]: 426.01. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{21}N_3O_7Na$) requires m/z 426.1275, found m/z 426.1272. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 13.4 min (minor), 15.7 min (major).

(R)-diisopropyl 2-(2-amino-3-cyano-6-methyl-4H-chromen-4-yl)malonate (3ic)



Yellow oil. $[\alpha]_D^{25}$ = + 3.8 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.09-7.08 (m, 1H), 7.02-7.01 (m, 1H), 6.85 (d, *J* = 9.0 MHz, 1H), 5.08-5.03 (m, 1H), 4.97-4.92 (m, 1H), 4.87-4.86 (br, 2H), 4.33 (d, *J* = 5.0 MHz, 1H), 3.58 (d, *J* = 5.0 MHz, 1H), 2.28 (s, 3H), 1.23-1.22 (m, 6H), 1.15-1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.7, 162.2, 148.0, 134.4, 129.2, 128.7, 120.4, 119.6, 115.9, 69.4, 69.2, 59.3, 56.4, 35.3, 21.6, 21.5, 21.4, 20.7. MS (ESI) m/z [M+Na$^+$]: 395.00. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{20}H_{24}N_2O_5Na$) requires m/z 395.1581, found m/z 395.1577. The enantiomeric excess was determined to be 91% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 11.1 min (major), 15.8 min (minor).

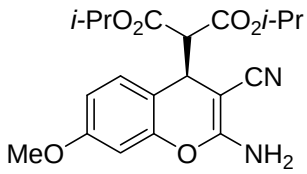
(R)-diisopropyl 2-(2-amino-3-cyano-6-methoxy-4H-chromen-4-yl)malonate (3jc)



Yellow oil. $[\alpha]_D^{25}$ = + 0.6 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.03-7.00 (m, 1H), 6.87 (d, *J* = 7.5 MHz, 1H), 6.81 (d, *J* = 7.5 MHz, 1H), 5.05-5.03 (m, 1H), 4.95-4.91 (m, 3H), 4.36 (d, *J* = 5.0 MHz, 1H), 3.84 (s, 3H), 3.55 (d, *J* = 5.0 MHz, 1H), 1.22-1.20 (m, 6H), 1.15-1.10 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.8, 166.6, 162.2, 147.3, 139.6, 124.5, 122.0, 119.9, 119.5, 110.9, 69.3, 69.2, 59.4, 55.9, 35.3, 21.5, 21.4, 21.3. MS (ESI) m/z [M+Na$^+$]: 410.93. HRMS (ESI): exact mass calculated for [M+Na$^+$]

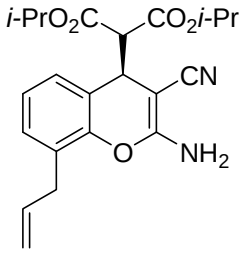
($C_{20}H_{24}N_2O_6Na$) requires m/z 411.1537, found m/z 411.1527. The enantiomeric excess was determined to be 91% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 16.1 min (major), 20.2 min (minor).

(R)-diisopropyl 2-(2-amino-3-cyano-7-methoxy-4H-chromen-4-yl)malonate (3kc)



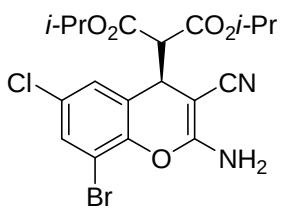
Yellow oil. $[\alpha]_D^{25}$ = + 1.6 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.24-7.22 (m, 1H), 6.67-6.63 (m, 1H), 6.50 (d, *J* = 4.0 MHz, 1H), 5.07-5.03 (m, 1H), 4.95-4.91 (m, 1H), 4.71-4.70 (br, 2H), 4.32 (d, *J* = 8.0 MHz, 1H), 3.77 (s, 3H), 3.57 (d, *J* = 8.0 MHz, 1H), 1.23-1.21 (m, 6H), 1.15-1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.1, 166.7, 161.9, 159.8, 150.7, 129.3, 119.5, 112.6, 111.0, 101.6, 69.3, 69.1, 59.2, 56.9, 55.9, 55.4, 34.6, 21.6, 21.5, 21.4. MS (ESI) m/z [M+Na$^+$]: 410.94. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{20}H_{24}N_2O_6Na$) requires m/z 411.1529, found m/z 411.1527. The enantiomeric excess was determined to be 84% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 14.2 min (major), 19.5 min (minor).

(R)-diisopropyl 2-(8-allyl-2-amino-3-cyano-4H-chromen-4-yl)malonate (3lc)



Yellow oil. $[\alpha]_D^{25}$ = + 6.2 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.19-7.17 (m, 1H), 7.09-7.08 (m, 1H), 7.05-7.03 (m, 1H), 5.94-5.89 (m, 1H), 5.08-5.00 (m, 3H), 4.94-4.91 (m, 1H), 4.75-4.74 (br, 2H), 4.37 (d, *J* = 5.5 MHz, 1H), 3.55-3.51 (m, 1H), 3.45-3.35 (m, 2H), 1.23-1.21 (m, 6H), 1.15-1.10 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.7, 162.2, 148.1, 135.8, 129.4, 127.3, 127.2, 126.8, 124.6, 121.0, 119.5, 117.1, 116.2, 69.4, 69.3, 59.5, 56.7, 35.5, 33.8, 33.1, 21.6, 21.4. MS (ESI) m/z [M+Na$^+$]: 421.00. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{22}H_{26}N_2O_5Na$) requires m/z 421.1740, found m/z 421.1734. The enantiomeric excess was determined to be 89% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 8.6 min (major), 10.9 min (minor).

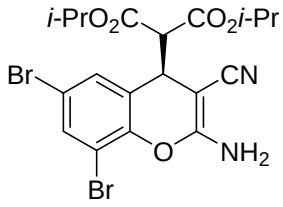
(R)-diisopropyl
2-(2-amino-8-bromo-6-chloro-3-cyano-4H-chromen-4-yl)malonate (3mc)



Yellow oil. $[\alpha]_D^{25}$ = + 6.2 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.47 (d, *J* = 4.0 MHz, 1H), 7.30 (d, *J* = 4.0 MHz, 1H), 5.12-5.04 (m, 1H), 4.99-4.92 (m, 3H), 4.34 (d, *J* = 8.5 MHz, 1H), 3.58 (d, *J* = 8.5 MHz, 1H), 1.26-1.23 (m, 6H), 1.16-1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.6, 166.2, 161.6, 145.9, 131.9, 130.0, 127.7, 123.8, 118.5, 110.8, 69.9, 69.6, 59.0, 56.5, 35.6, 21.6, 21.5, 21.4, 21.3. MS (ESI) m/z [M+Na$^+$]: 492.85. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{20}BrClN_2O_5Na$) requires m/z 493.0137, found m/z 493.0136. The enantiomeric excess was determined

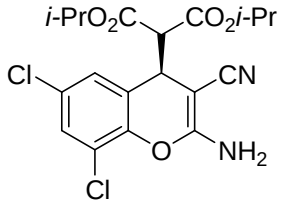
to be 84% by HPLC. [ID column, 254 nm, n-hexane:IPA = 85:15, 1.0 mL/min]: 9.5 min (major), 11.9 min (minor).

(R)-diisopropyl 2-(2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl)malonate (3nc)



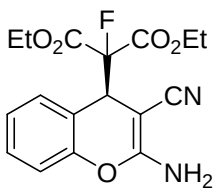
Yellow oil. $[\alpha]_D^{25}$ = + 5.8 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.61 (d, *J* = 4.0 MHz, 1H), 7.44 (d, *J* = 4.0 MHz, 1H), 5.10-5.06 (m, 1H), 4.97-4.93 (m, 3H), 4.34 (d, *J* = 8.5 MHz, 1H), 3.58 (d, *J* = 8.5 MHz, 1H), 1.26-1.23 (m, 6H), 1.16-1.13 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.6, 166.2, 161.6, 146.4, 134.7, 130.6, 124.3, 118.5, 117.2, 111.1, 70.0, 69.6, 59.1, 56.6, 35.5, 21.6, 21.5, 21.4, 21.3. MS (ESI) m/z [M+Na$^+$]: 533.66. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{20}Br_2N_2O_5Na$) requires m/z 536.9629, found m/z 536.9631. The enantiomeric excess was determined to be 84% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 7.7 min (major), 9.6 min (minor).

(R)-diisopropyl 2-(2-amino-6,8-dichloro-3-cyano-4H-chromen-4-yl)malonate (3oc)



Yellow oil. $[\alpha]_D^{25}$ = + 1.6 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.32-7.31 (m, 1H), 7.27-7.26 (m, 1H), 5.10-5.08 (m, 1H), 4.97-4.94 (m, 1H), 4.84-4.83 (br, 2H), 4.36 (d, *J* = 5.0 MHz, 1H), 3.59 (d, *J* = 5.0 MHz, 1H), 1.26-1.21 (m, 6H), 1.16-1.14 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.5, 166.1, 161.4, 144.8, 129.6, 129.0, 126.9, 123.8, 122.3, 118.4, 69.9, 69.5, 58.9, 56.4, 35.4, 21.5, 21.4, 21.3, 21.2. MS (ESI) m/z [M+Na$^+$]: 448.93. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{19}H_{20}Cl_2N_2O_5Na$) requires m/z 449.0649, found m/z 449.0641. The enantiomeric excess was determined to be 82%, 81% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 7.2 min (major), 8.9 min (minor).

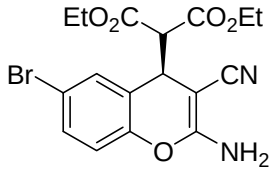
(R)-diethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)-2-fluoromalonate (3df)



Yellow oil. $[\alpha]_D^{25}$ = + 10.8 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.33-7.30 (m, 1H), 7.24-7.21 (m, 1H), 7.15-7.10 (m, 1H), 7.06-7.03 (m, 1H), 4.93-4.92 (br, 2H), 4.63 (d, *J* = 20.5 MHz, 1H), 4.42-4.35 (m, 2H), 4.27-4.19 (m, 2H), 1.36 (t, *J* = 12.0 MHz, 3H), 1.23 (t, *J* = 12.0 MHz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 164.1, 151.2, 129.4, 128.4, 125.0, 118.9, 117.6, 116.7, 97.5, 95.8, 63.2, 62.9, 60.4, 51.8, 41.6, 41.4, 21.0, 14.2, 13.8. MS (ESI) m/z [M+Na$^+$]: 370.89. HRMS (ESI): exact mass calculated for [M+Na$^+$] ($C_{17}H_{17}FN_2O_5Na$) requires m/z 371.1021, found m/z 371.1014. The enantiomeric excess was determined to be 86%, 95% by HPLC. [IC column, 254 nm, n-hexane:IPA = 9:1, 1.0 mL/min]: 44.2 min

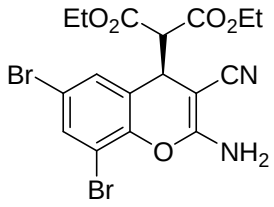
(minor), 48.9 min (major).

(R)-diethyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3ea)



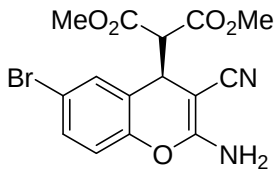
Yellow oil. $[\alpha]_D^{25}$ = + 7.0 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.42-7.41 (m, 1H), 7.37-7.33 (m, 1H), 6.87 (d, *J* = 14.0 MHz, 1H), 4.83-4.82 (br, 2H), 4.33 (d, *J* = 9.0 MHz, 1H), 4.24-4.10 (m, 4H), 3.62 (d, *J* = 9.0 MHz, 1H), 1.25 (t, *J* = 12.0 MHz, 3H), 1.18 (t, *J* = 12.0 MHz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.8, 161.9, 149.1, 131.6, 131.1, 122.8, 118.9, 117.9, 117.2, 61.8, 61.7, 58.6, 55.7, 35.2, 13.8, 13.7. MS (ESI) m/z [M+Na^+]: 430.83. HRMS (ESI): exact mass calculated for [M+Na^+] ($C_{17}H_{17}BrN_2O_5Na$) requires m/z 431.0220, found m/z 431.0213. The enantiomeric excess was determined to be 86% by HPLC. [IC column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 12.3 min (major), 14.1 min (minor).

(R)-diethyl 2-(2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl)malonate (3na)



Yellow oil. $[\alpha]_D^{25}$ = + 7.8 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.61 (d, *J* = 3.5 MHz, 1H), 7.37 (d, *J* = 3.5 MHz, 1H), 5.05-5.04 (br, 2H), 4.30 (d, *J* = 9.0 MHz, 1H), 4.25-4.08 (m, 4H), 3.60 (d, *J* = 9.0 MHz, 1H), 1.26 (t, *J* = 12.0 MHz, 3H), 1.18 (t, *J* = 12.0 MHz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.7, 166.6, 161.8, 146.4, 134.7, 130.4, 124.2, 117.2, 111.1, 62.0, 61.8, 58.6, 55.9, 35.7, 13.8, 13.7. MS (ESI) m/z [M-H]$^-$: 485.96. HRMS (ESI): exact mass calculated for [M+Na^+] ($C_{17}H_{16}Br_2N_2O_5Na$) requires m/z 508.9333, found m/z 508.9318. The enantiomeric excess was determined to be 95% by HPLC. [ID column, 254 nm, n-hexane:IPA = 4:1, 1.0 mL/min]: 9.5 min (major), 10.9 min (minor).

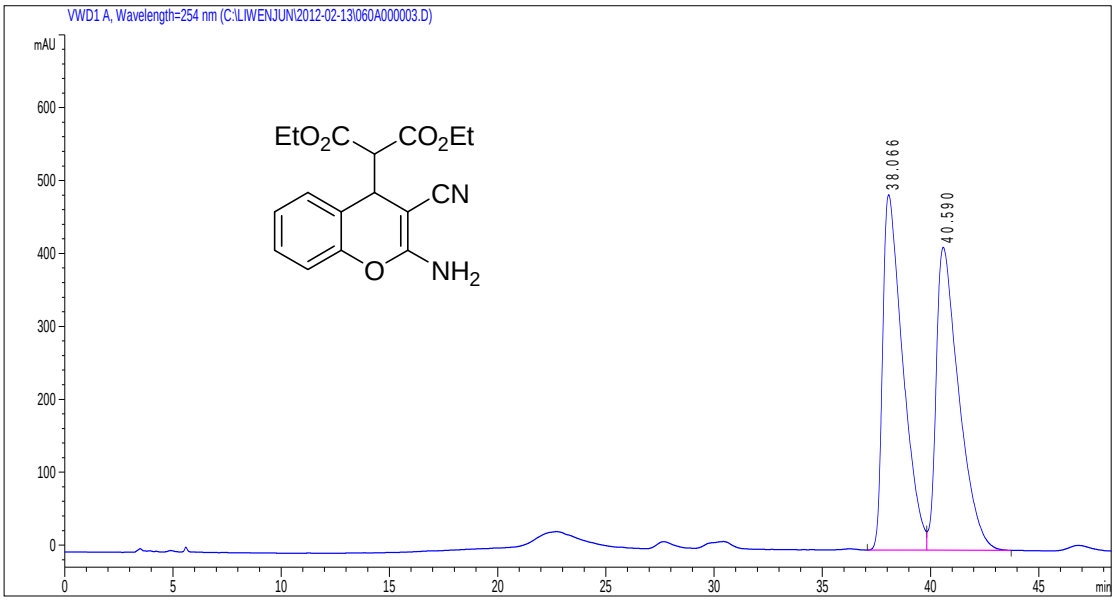
(R)-dimethyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3eb)



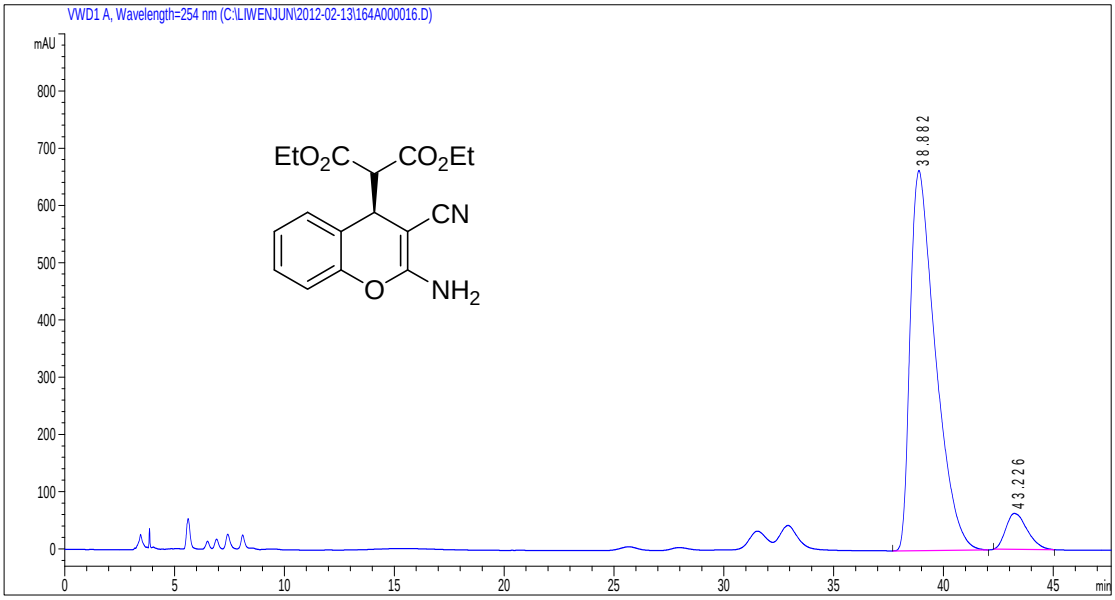
Yellow oil. $[\alpha]_D^{25}$ = + 9.0 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.36-7.34 (m, 2H), 6.90-6.87 (m, 1H), 4.91-4.90 (br, 2H), 4.31 (d, *J* = 10.0 MHz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.63 (d, *J* = 10.0 MHz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.2, 167.1, 162.1, 149.1, 131.7, 130.9, 122.7, 118.0, 117.3, 58.2, 55.1, 52.7, 52.6, 35.5. MS (ESI) m/z [M+Na^+]: 404.73. HRMS (ESI): exact mass calculated for [M+Na^+] ($C_{15}H_{13}BrN_2O_5Na$) requires m/z 402.9894, found m/z 402.9900. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, n-hexane:IPA = 9:1, 1.0 mL/min]: 32.2 min (major), 33.4 min (minor).

D: HPLC Analysis of Michael Reaction Products

(R)-diethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3da)

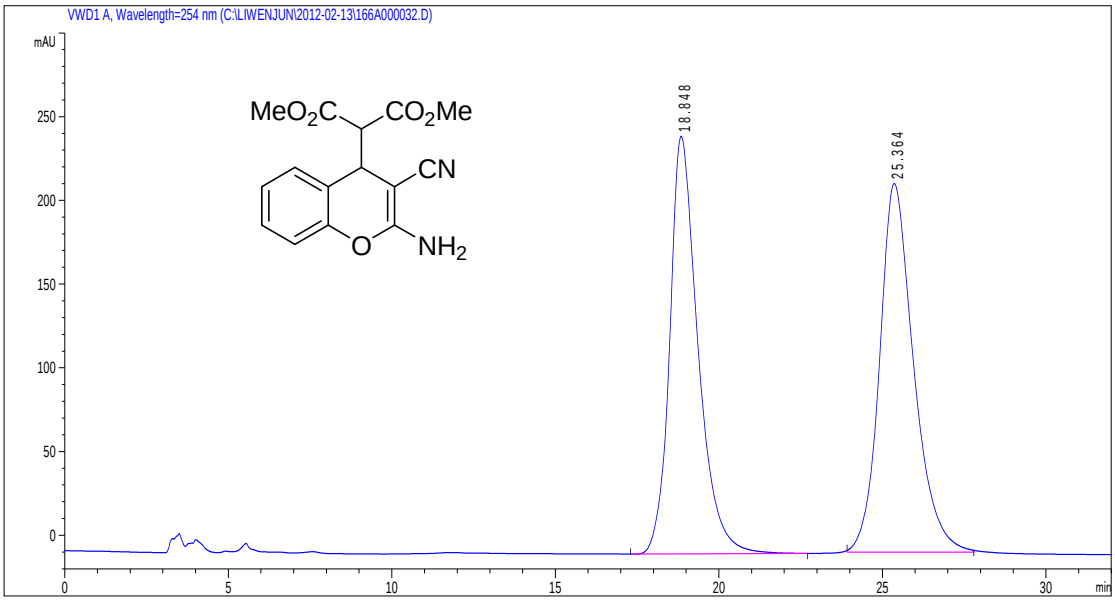


#	Time	Area	Height	Width	Area%	Symmetry
1	38.066	31633.7	487.5	0.9786	51.039	0.395
2	40.59	30346	415.4	1.0432	48.961	0.429

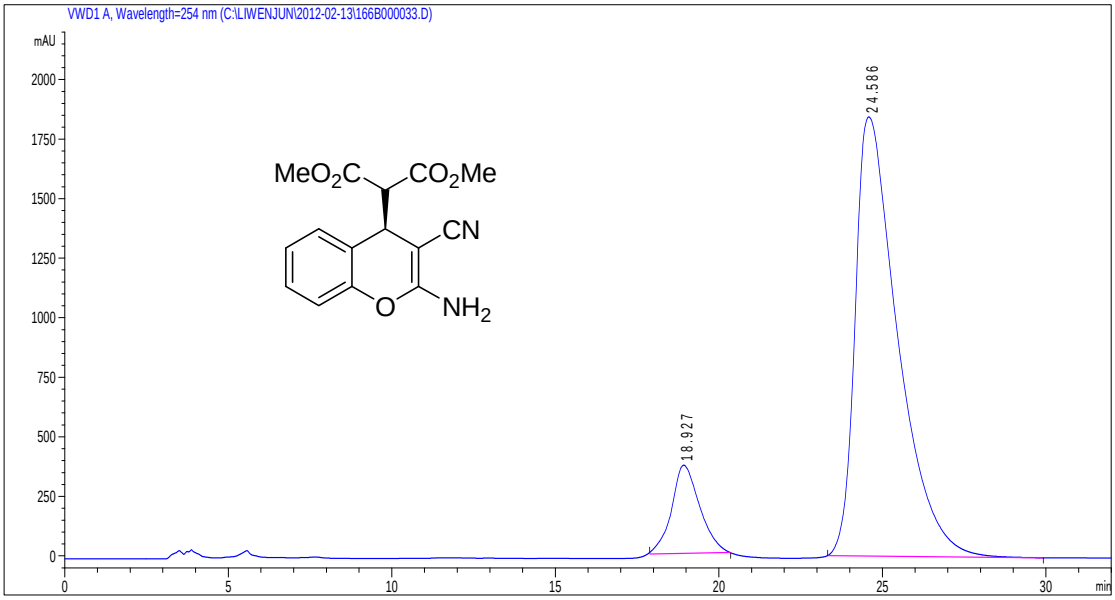


#	Time	Area	Height	Width	Area%	Symmetry
1	38.882	52924.5	664.1	1.2039	92.584	0.487
2	43.226	4239.5	62.5	1.131	7.416	0.65

(R)-dimethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3db)

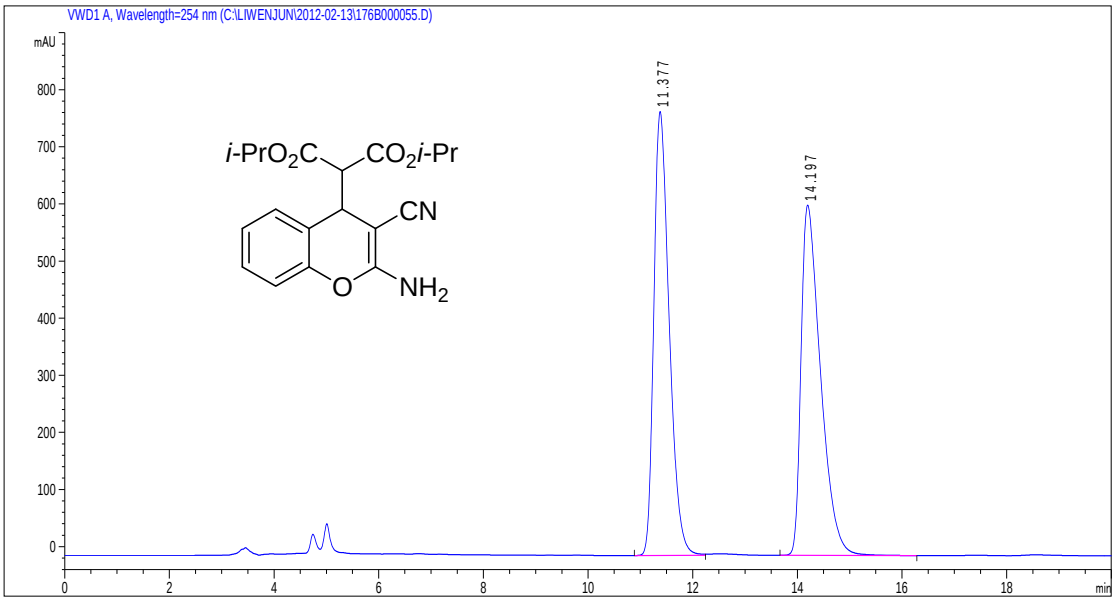


#	Time	Area	Height	Width	Area%	Symmetry
1	18.848	14939.8	249.3	0.89	48.425	0.649
2	25.364	15911.5	220.2	1.2042	51.575	0.738

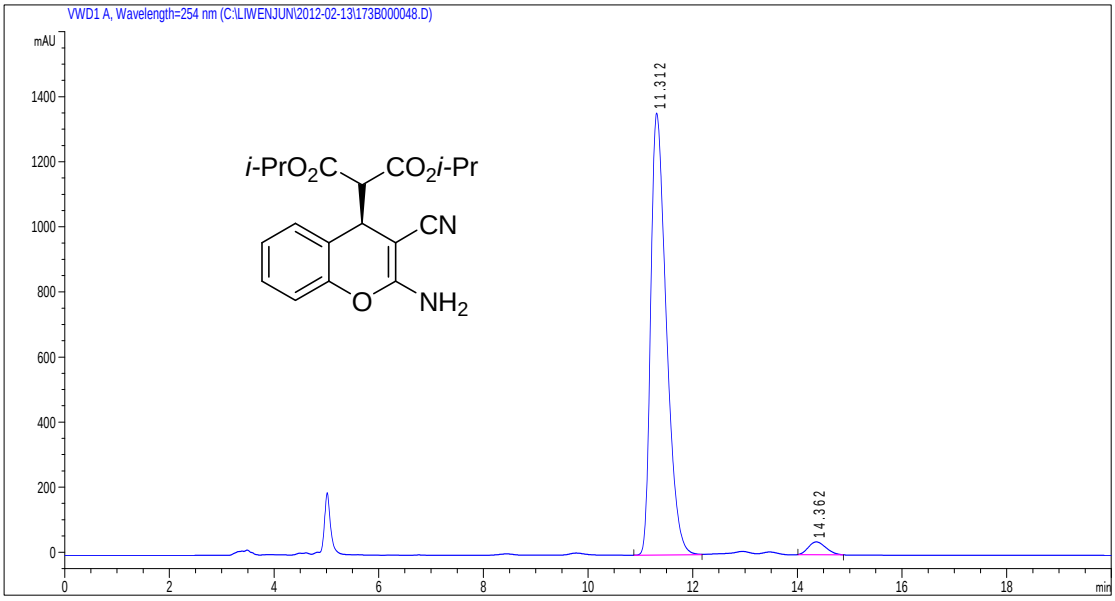


#	Time	Area	Height	Width	Area%	Symmetry
1	18.927	22150.4	370.5	0.9963	11.772	0.76
2	24.586	166017.6	1843.3	1.2723	88.228	0.436

(R)-diisopropyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3dc)

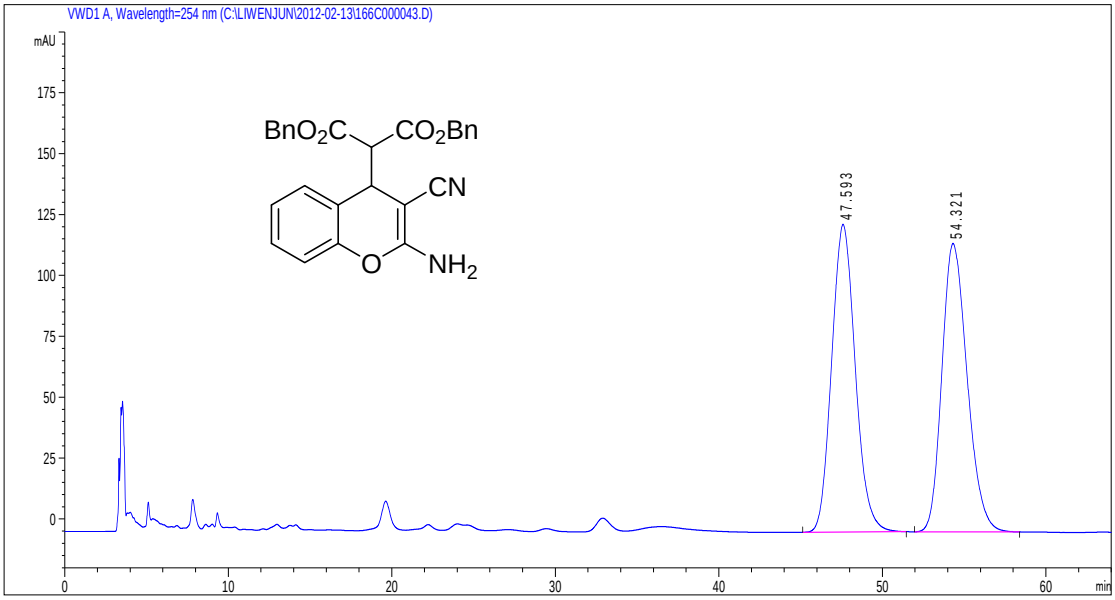


#	Time	Area	Height	Width	Area%	Symmetry
1	11.377	15824.4	777.2	0.3134	49.992	0.643
2	14.197	15829.3	612.9	0.3903	50.008	0.477

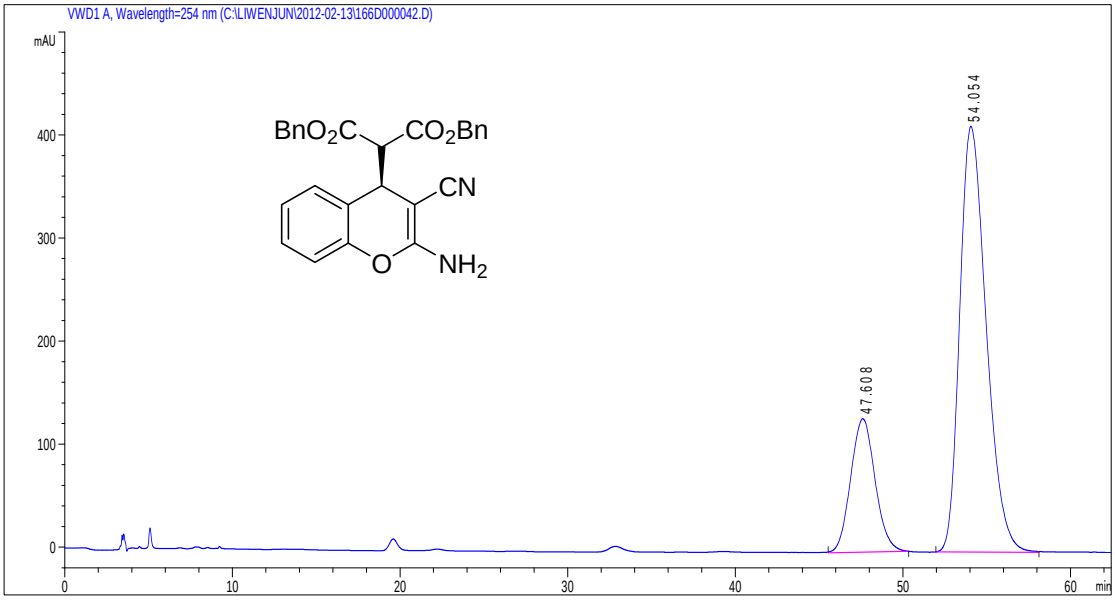


#	Time	Area	Height	Width	Area%	Symmetry
1	11.312	28070.6	1357.9	0.3112	96.820	0
2	14.362	922.1	39.6	0.3883	3.180	0.798

(R)-dibenzyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3de)

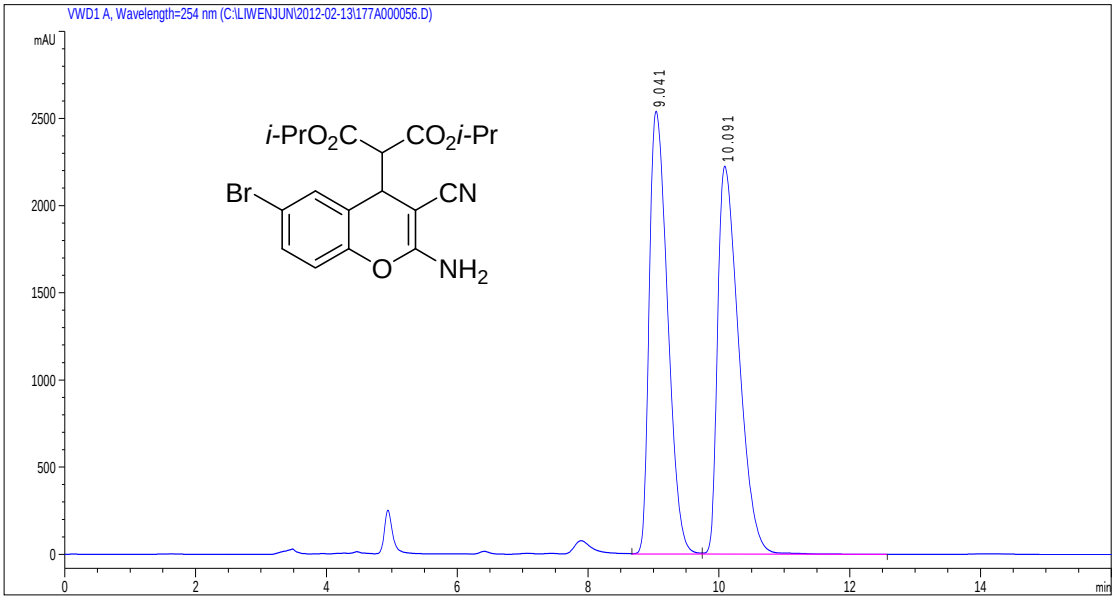


#	Time	Area	Height	Width	Area%	Symmetry
1	47.593	12667.3	126.4	1.566	49.923	0.877
2	54.321	12706.6	118.4	1.6425	50.077	0.751

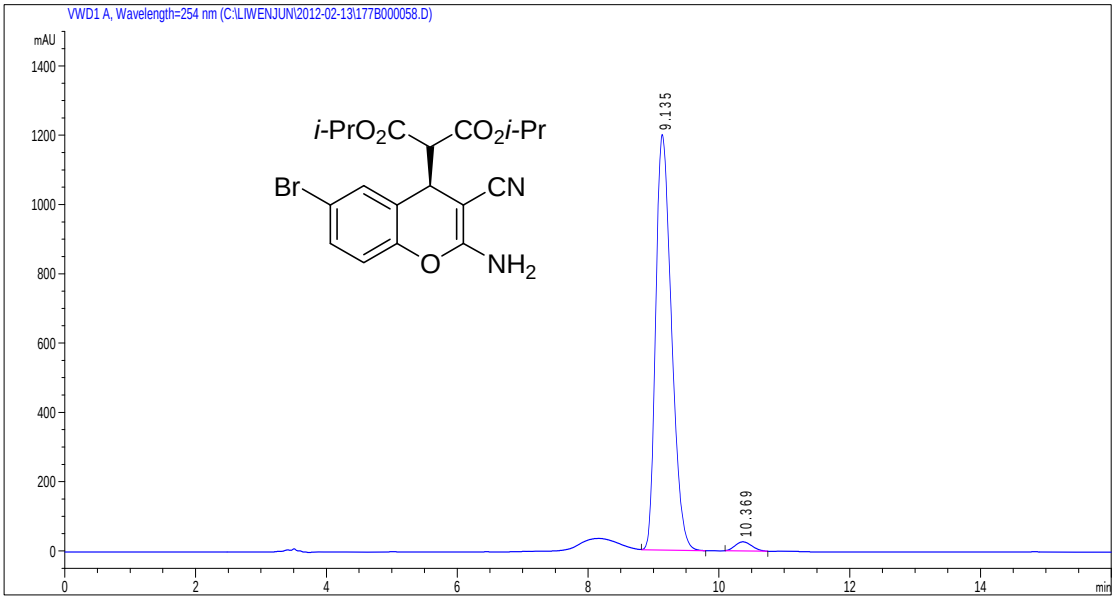


#	Time	Area	Height	Width	Area%	Symmetry
1	47.608	13104.7	129.5	1.6835	22.461	0
2	54.054	45238.5	413.1	1.7205	77.539	0

(R)-diisopropyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3ec)

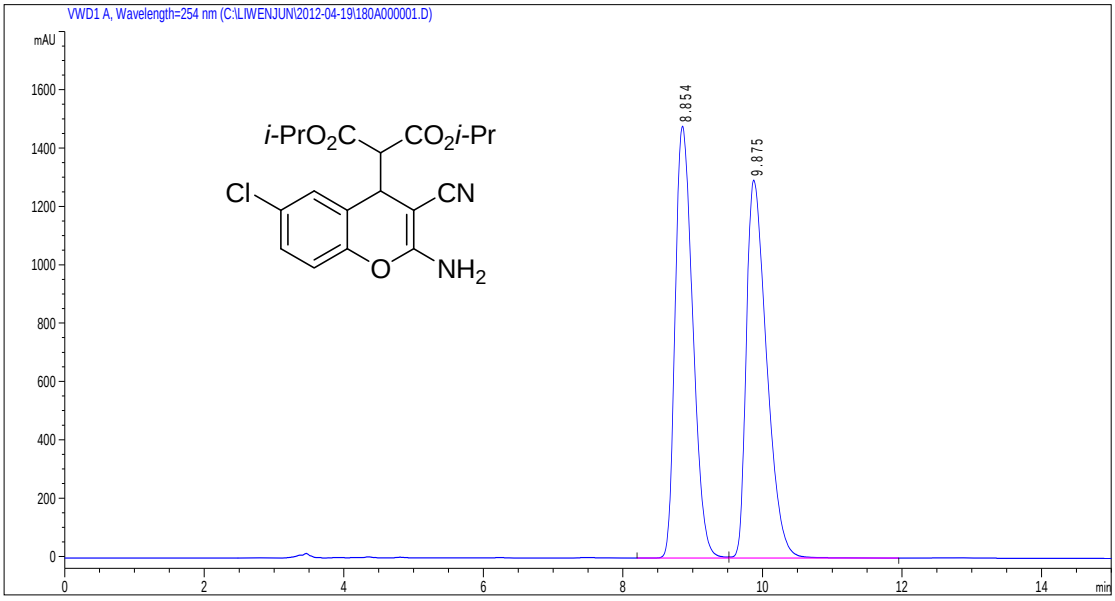


#	Time	Area	Height	Width	Area%	Symmetry
1	9.041	49637	2539.5	0.3097	49.722	0.565
2	10.091	50191.4	2225.5	0.3491	50.278	0.477

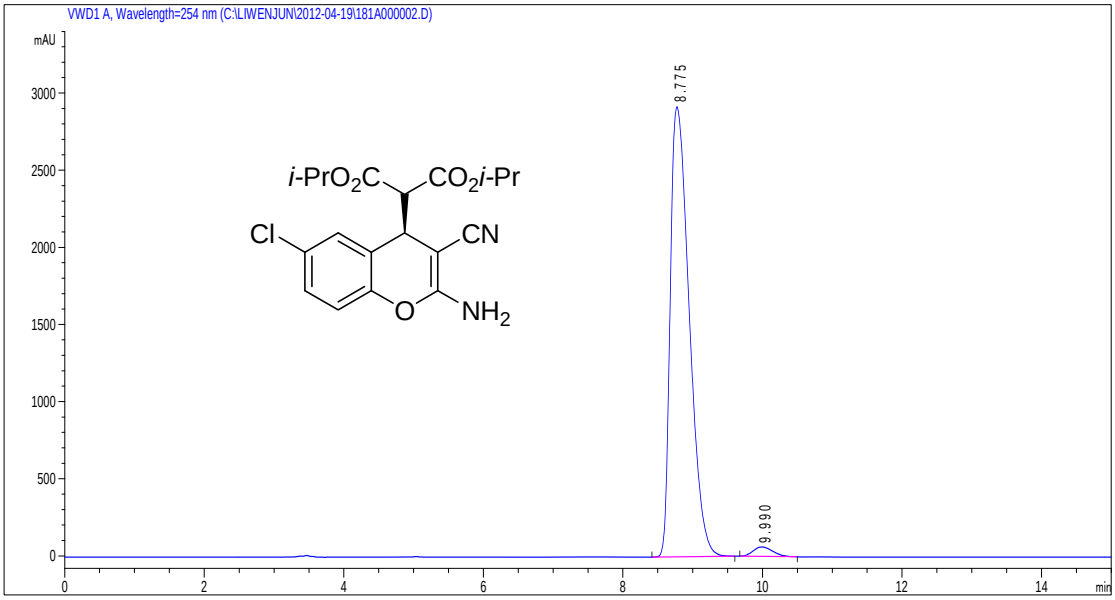


#	Time	Area	Height	Width	Area%	Symmetry
1	9.135	20088.2	1199.8	0.2166	97.737	0
2	10.369	465.1	26.4	0.2936	2.263	0.847

(R)-diisopropyl 2-(2-amino-6-chloro-3-cyano-4H-chromen-4-yl)malonate (3fc)

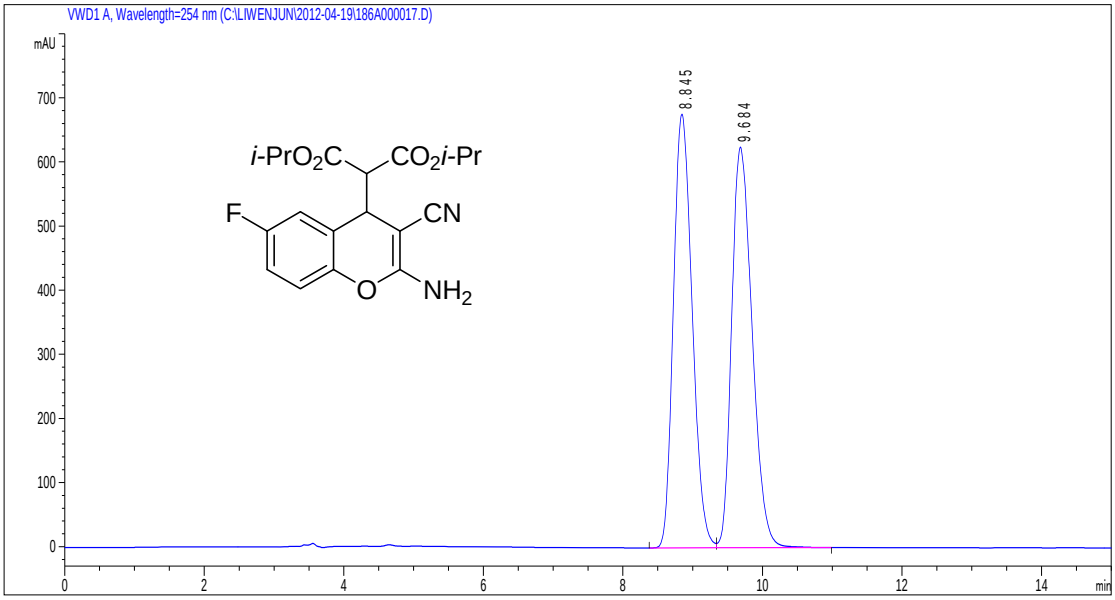


#	Time	Area	Height	Width	Area%	Symmetry
1	8.854	26047.7	1480.5	0.2767	49.854	0.672
2	9.875	26200.5	1295.7	0.3117	50.146	0.543

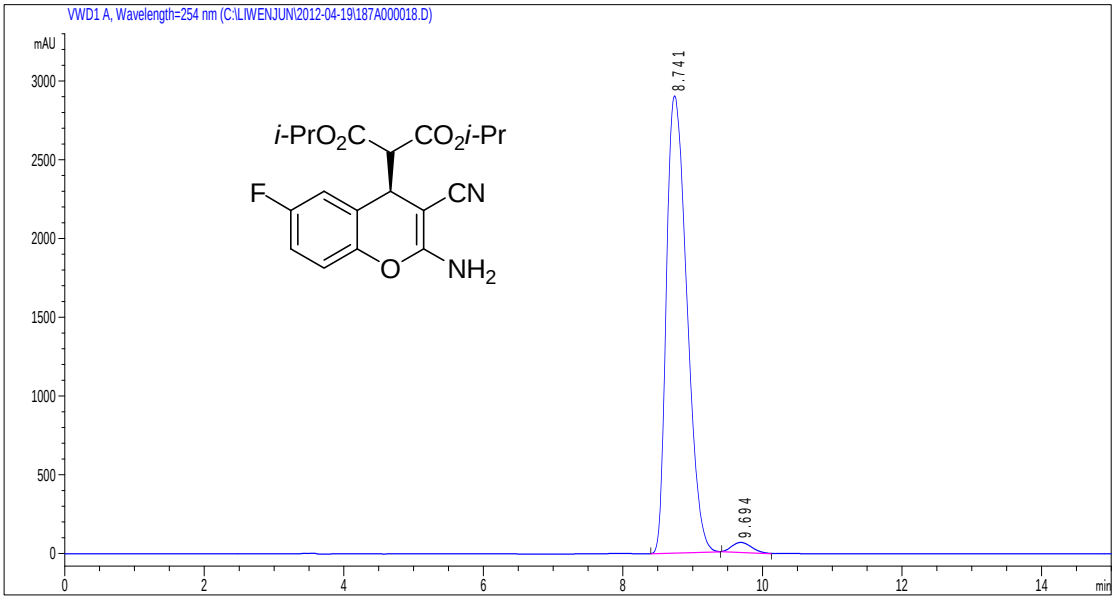


#	Time	Area	Height	Width	Area%	Symmetry
1	8.775	54980	2918.1	0.314	97.866	0.533
2	9.99	1199	61.8	0.3232	2.134	0.783

(R)-diisopropyl 2-(2-amino-3-cyano-6-fluoro-4H-chromen-4-yl)malonate (3gc)

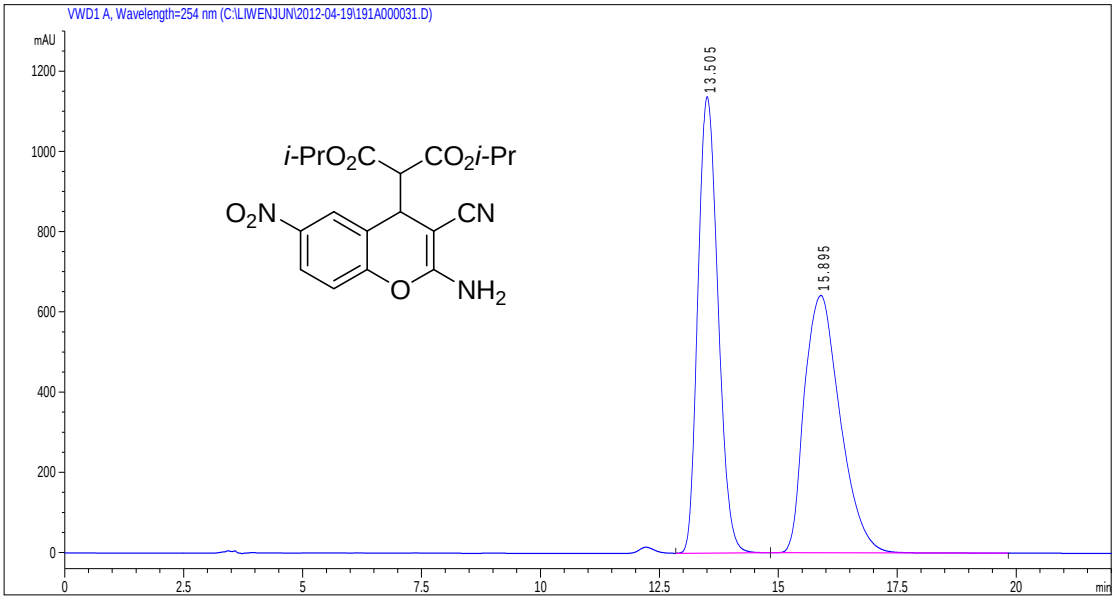


#	Time	Area	Height	Width	Area%	Symmetry
1	8.845	12619.1	676.1	0.2936	49.790	0.78
2	9.684	12725.6	624.3	0.3194	50.210	0.702

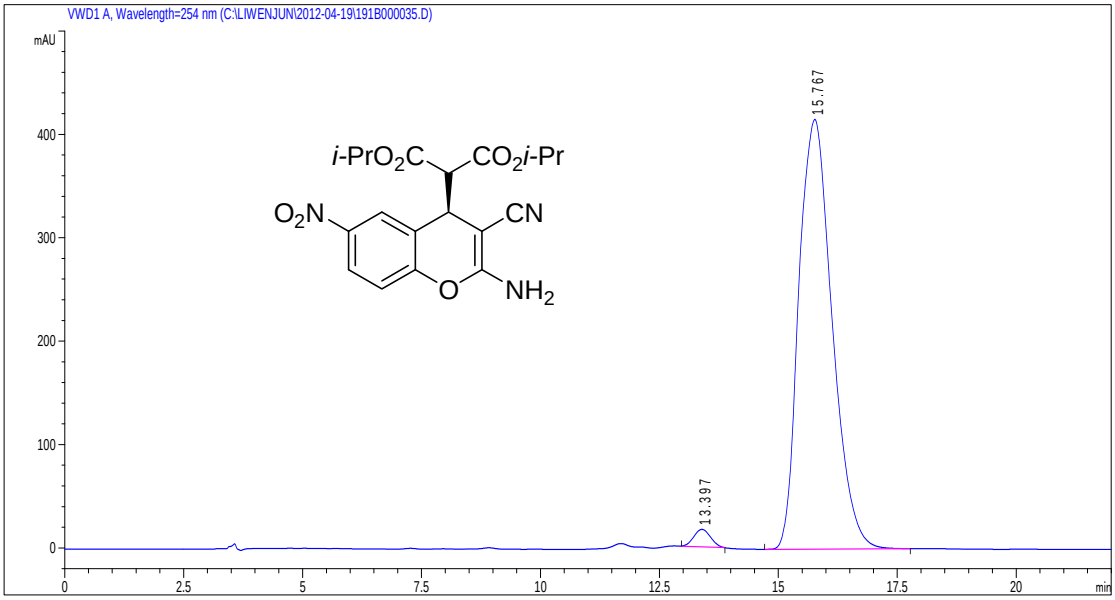


#	Time	Area	Height	Width	Area%	Symmetry
1	8.741	59118.6	2901.8	0.2926	97.907	0
2	9.694	1263.7	63.7	0.3305	2.093	0.763

(R)-diisopropyl 2-(2-amino-3-cyano-6-nitro-4H-chromen-4-yl)malonate (3hc)

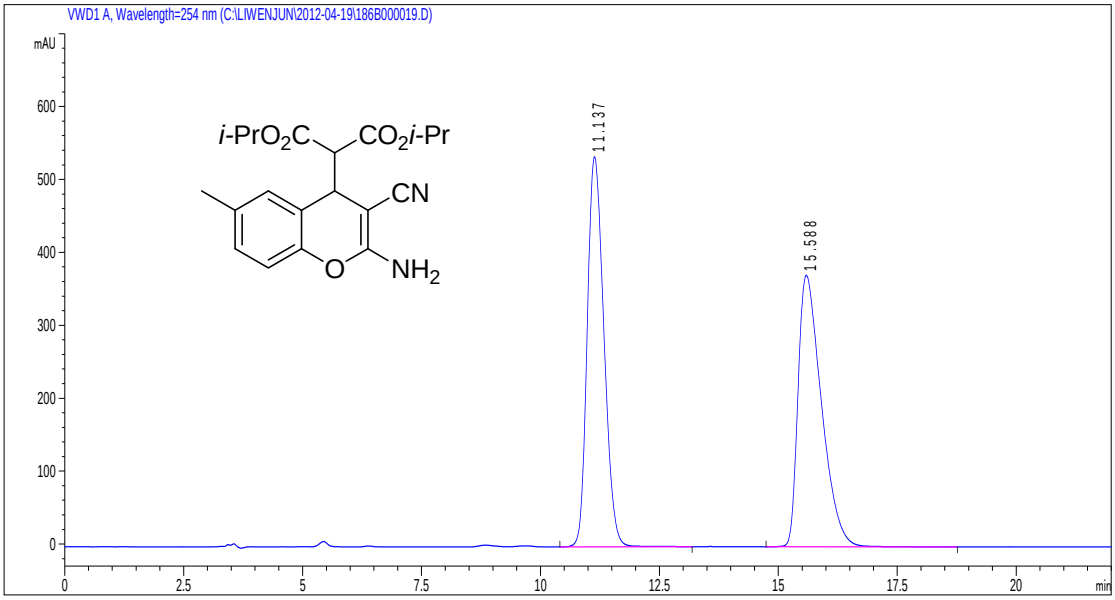


#	Time	Area	Height	Width	Area%	Symmetry
1	13.505	33423.7	1137.5	0.4652	49.986	0.807
2	15.895	33442.6	641.6	0.8136	50.014	0.787

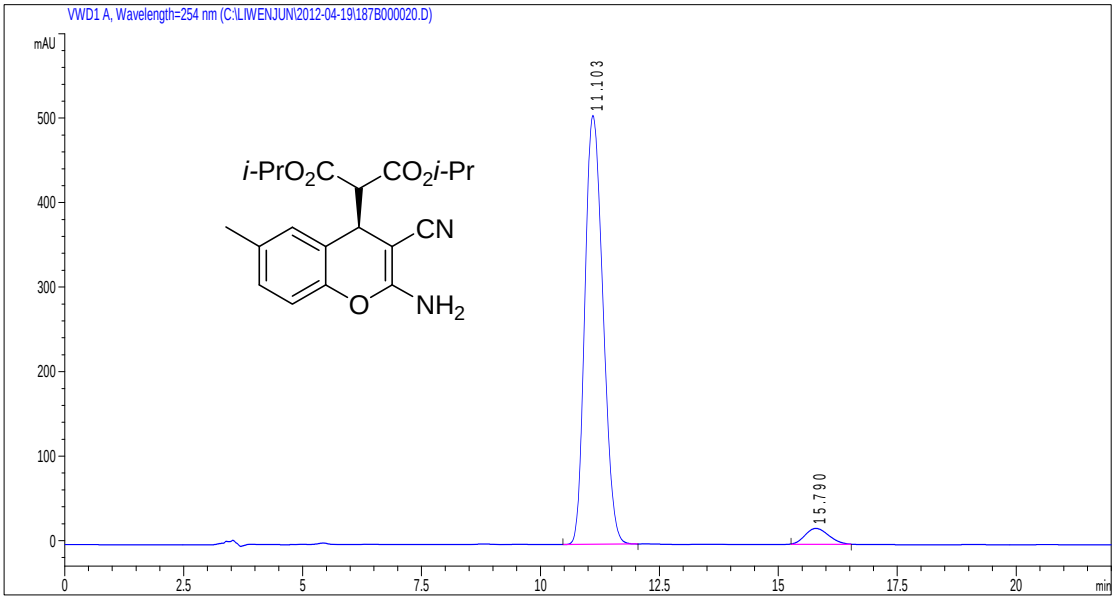


#	Time	Area	Height	Width	Area%	Symmetry
1	13.397	415.3	16.9	0.4087	2.017	0.926
2	15.767	20176.6	415.6	0.7662	97.983	0.846

(R)-diisopropyl 2-(2-amino-3-cyano-6-methyl-4H-chromen-4-yl)malonate (3ic)

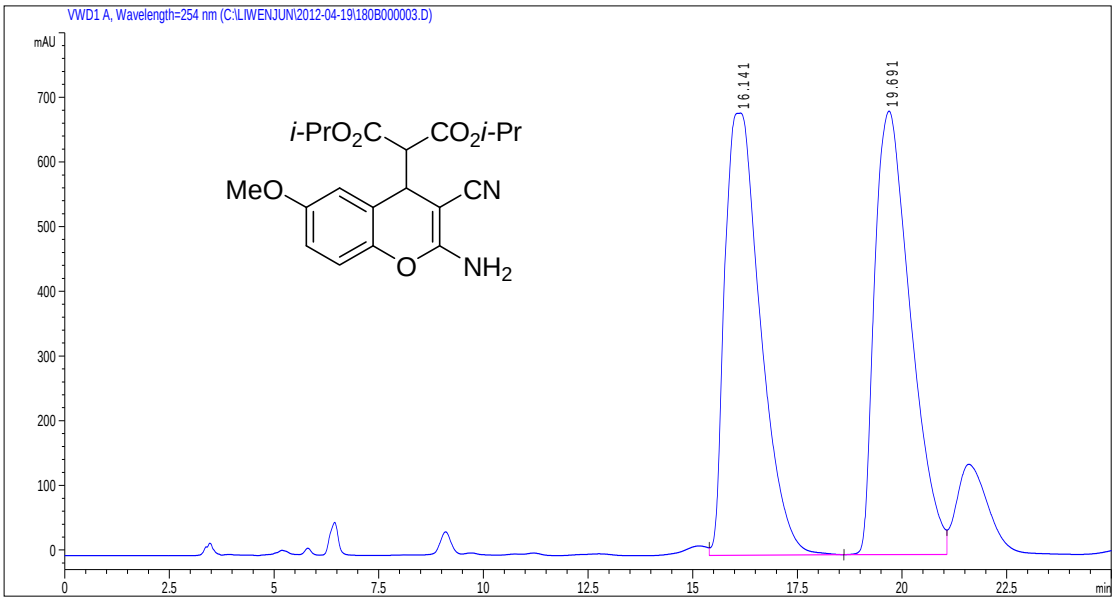


#	Time	Area	Height	Width	Area%	Symmetry
1	11.137	13014	534.8	0.3816	50.568	0.739
2	15.588	12721.4	372.3	0.5211	49.432	0.508

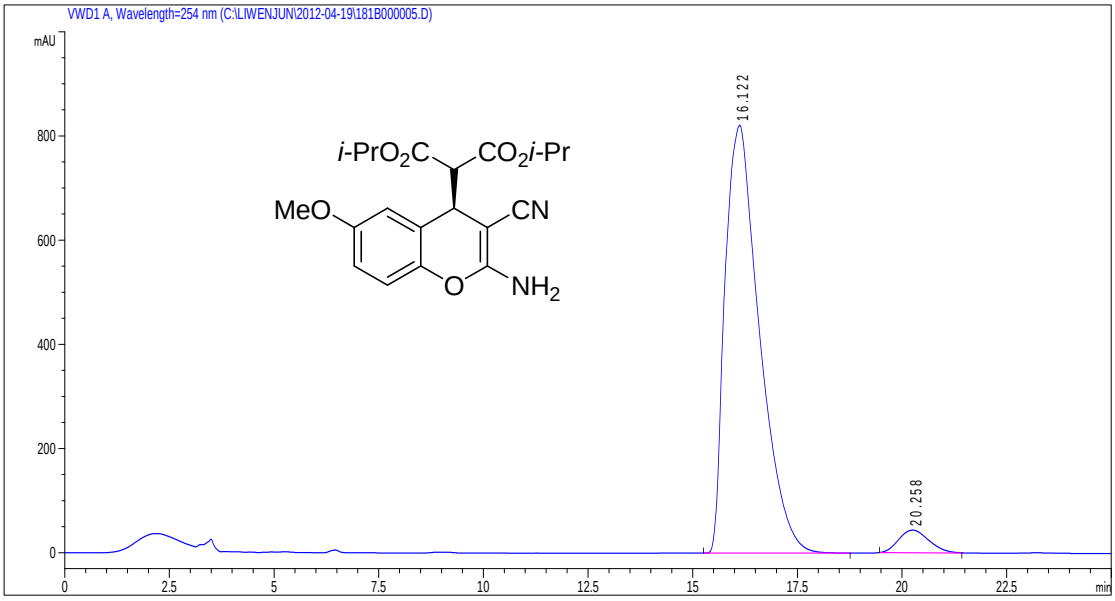


#	Time	Area	Height	Width	Area%	Symmetry
1	11.103	13407	507.5	0.4219	95.390	0.767
2	15.79	648	18.8	0.5758	4.610	0.809

(R)-diisopropyl 2-(2-amino-3-cyano-6-methoxy-4H-chromen-4-yl)malonate (3jc)

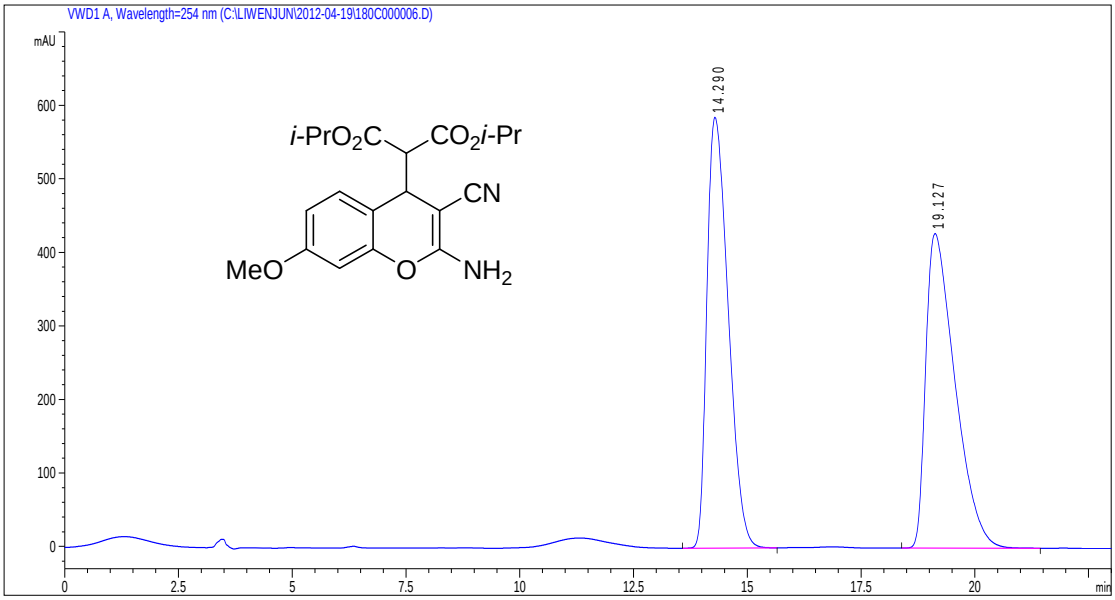


#	Time	Area	Height	Width	Area%	Symmetry
1	16.141	40532.9	683.4	0.7823	49.754	0.74
2	19.691	40934.1	685.7	0.9195	50.246	0.615

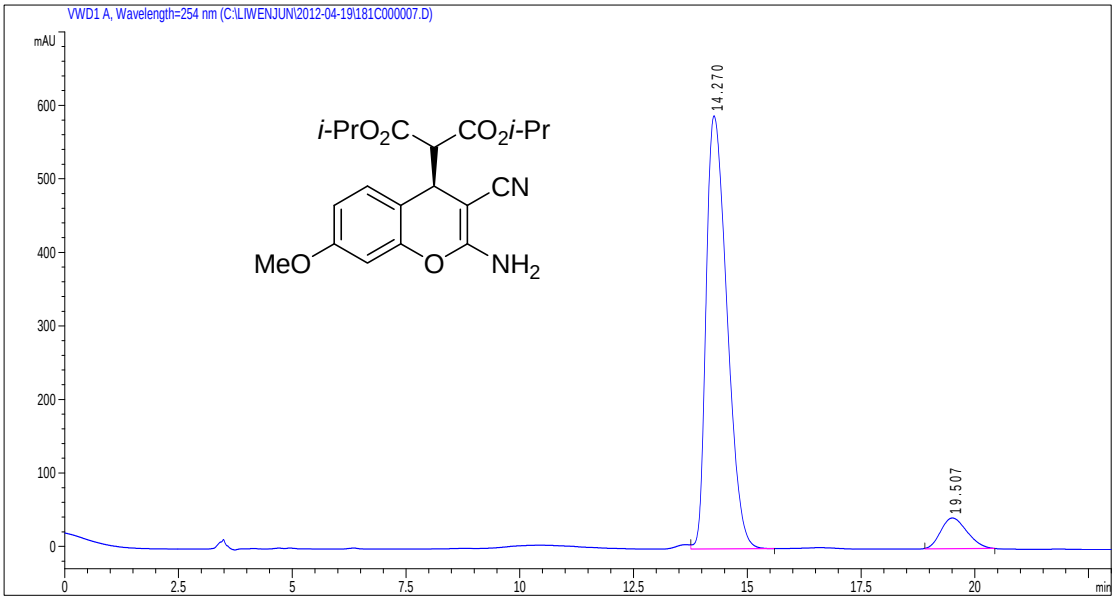


#	Time	Area	Height	Width	Area%	Symmetry
1	16.122	46803.2	820.9	0.8663	95.523	0.669
2	20.258	2193.5	43.6	0.8385	4.477	0.826

(R)-diisopropyl 2-(2-amino-3-cyano-7-methoxy-4H-chromen-4-yl)malonate (3kc)

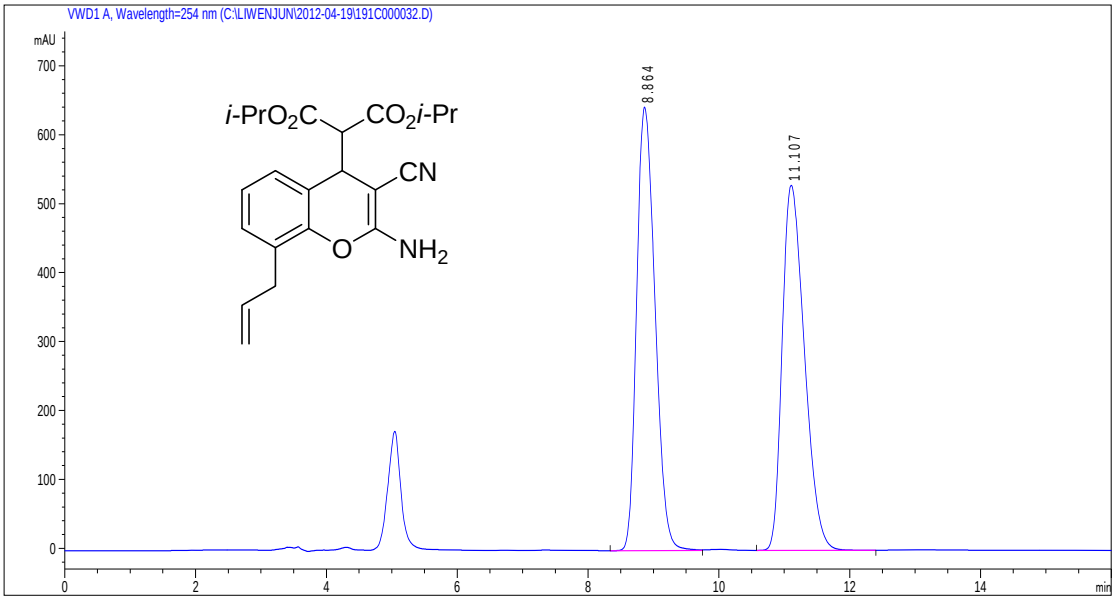


#	Time	Area	Height	Width	Area%	Symmetry
1	14.29	19017.9	585.6	0.5144	49.959	0.577
2	19.127	19049.2	427.7	0.6858	50.041	0.437

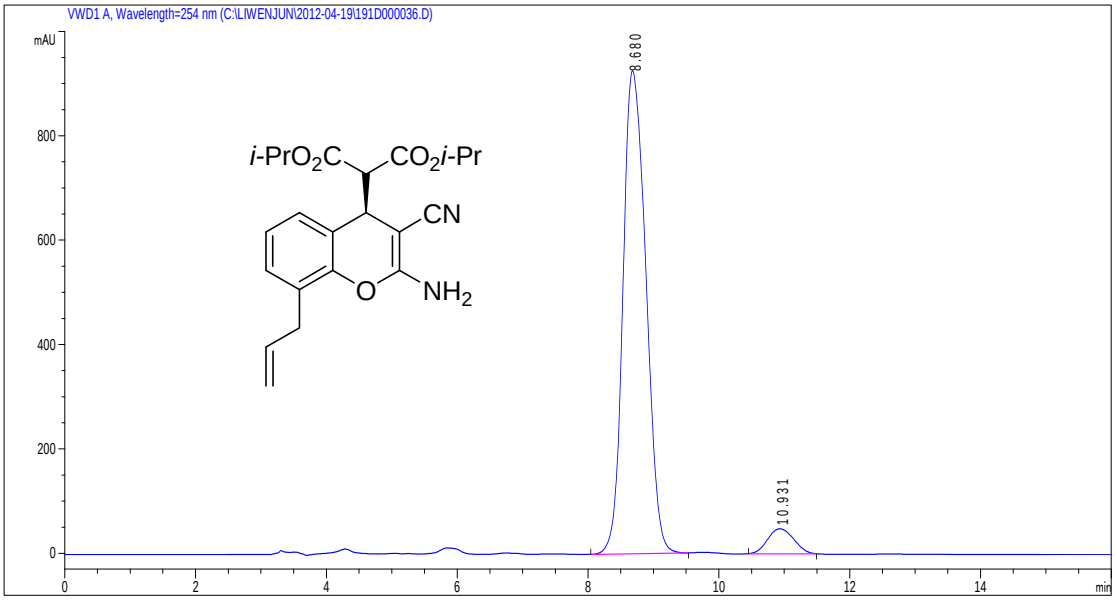


#	Time	Area	Height	Width	Area%	Symmetry
1	14.27	18728.8	588.9	0.5066	91.825	0.582
2	19.507	1667.4	41.7	0.6623	8.175	0

(R)-diisopropyl 2-(8-allyl-2-amino-3-cyano-4H-chromen-4-yl)malonate (3lc)

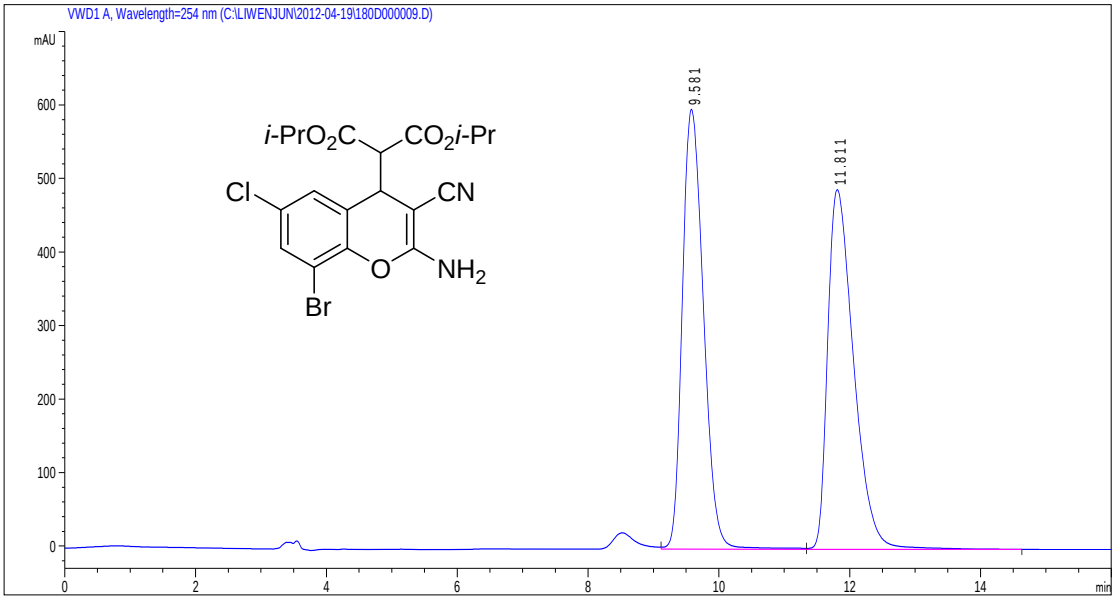


#	Time	Area	Height	Width	Area%	Symmetry
1	8.864	12564.3	643.4	0.3109	50.137	0.714
2	11.107	12495.6	529.7	0.3685	49.863	0.646

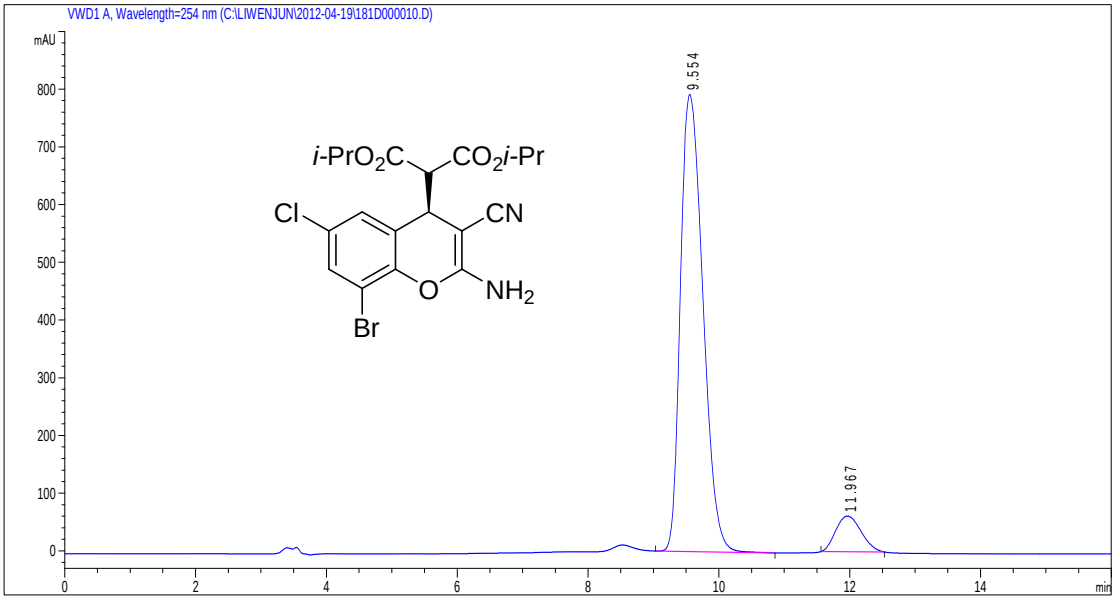


#	Time	Area	Height	Width	Area%	Symmetry
1	8.68	22473.1	925.6	0.357	94.406	0
2	10.931	1331.7	47.8	0.4617	5.594	0

(R)-diisopropyl
2-(2-amino-8-bromo-6-chloro-3-cyano-4H-chromen-4-yl)malonate (3mc)

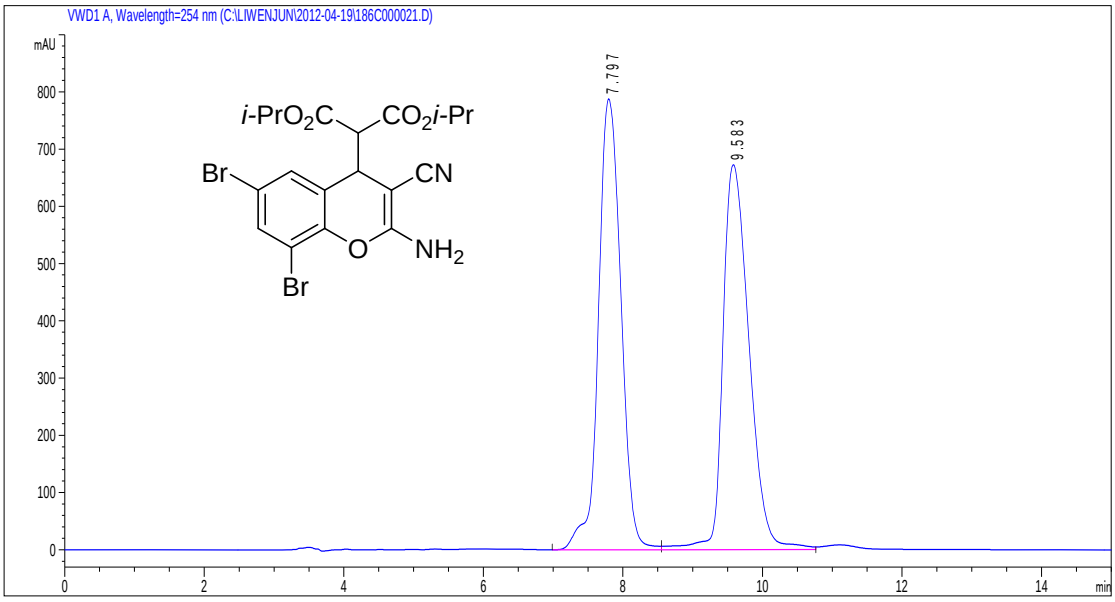


#	Time	Area	Height	Width	Area%	Symmetry
1	9.581	13450.4	598.1	0.3557	49.962	0.711
2	11.811	13471.1	489	0.4249	50.038	0.545

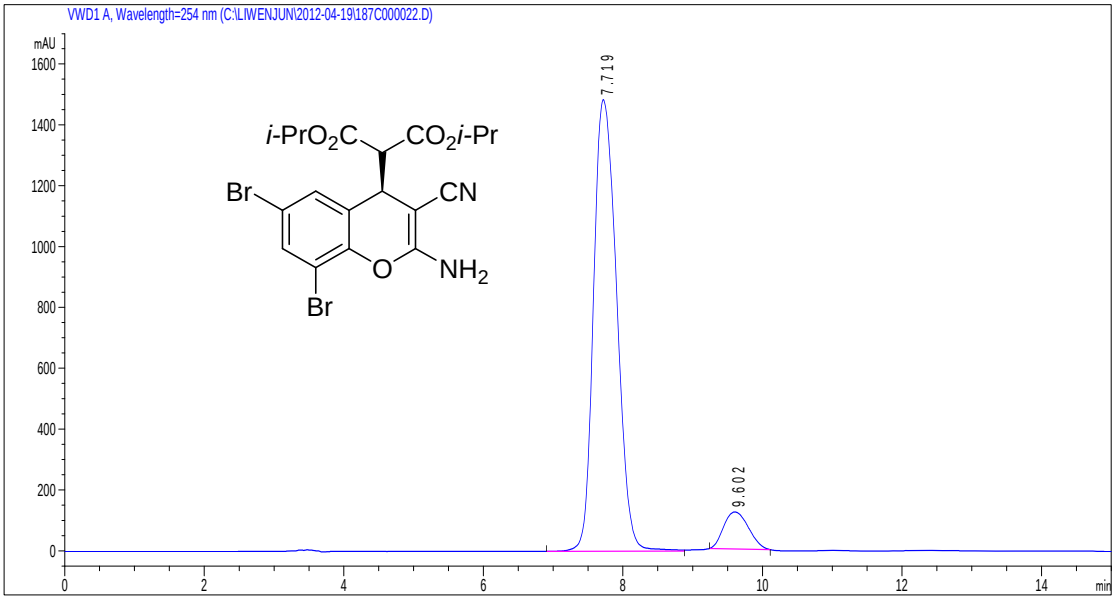


#	Time	Area	Height	Width	Area%	Symmetry
1	9.554	18883.6	792.2	0.3468	91.878	0
2	11.967	1669.3	61.8	0.4486	8.122	0

(R)-diisopropyl 2-(2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl)malonate (3nc)

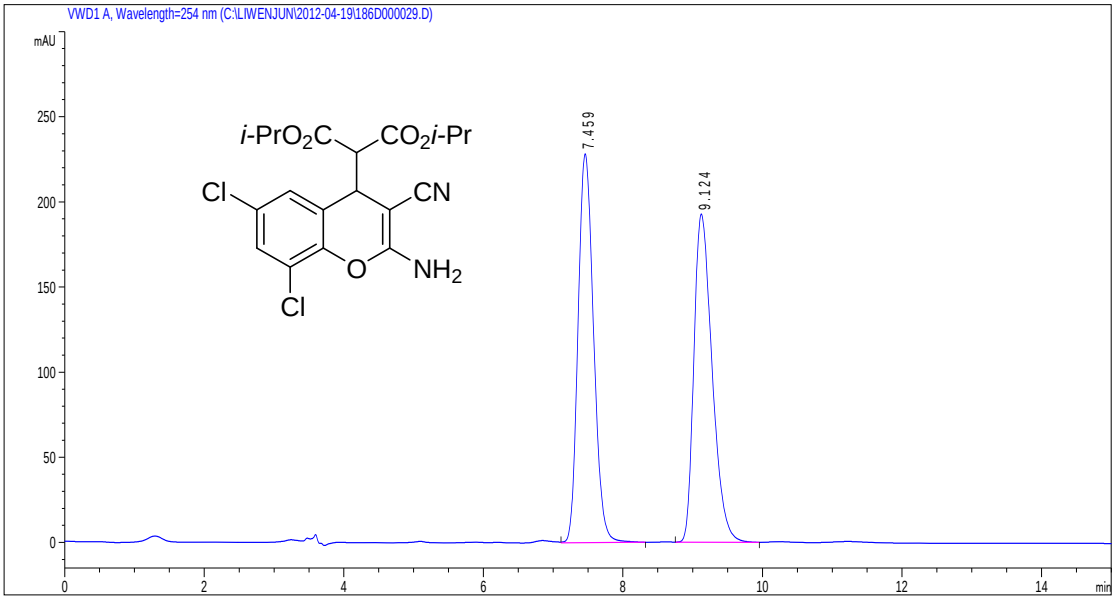


#	Time	Area	Height	Width	Area%	Symmetry
1	7.797	17710.5	788.1	0.3555	50.187	0.838
2	9.583	17578.5	672.6	0.4099	49.813	0.641

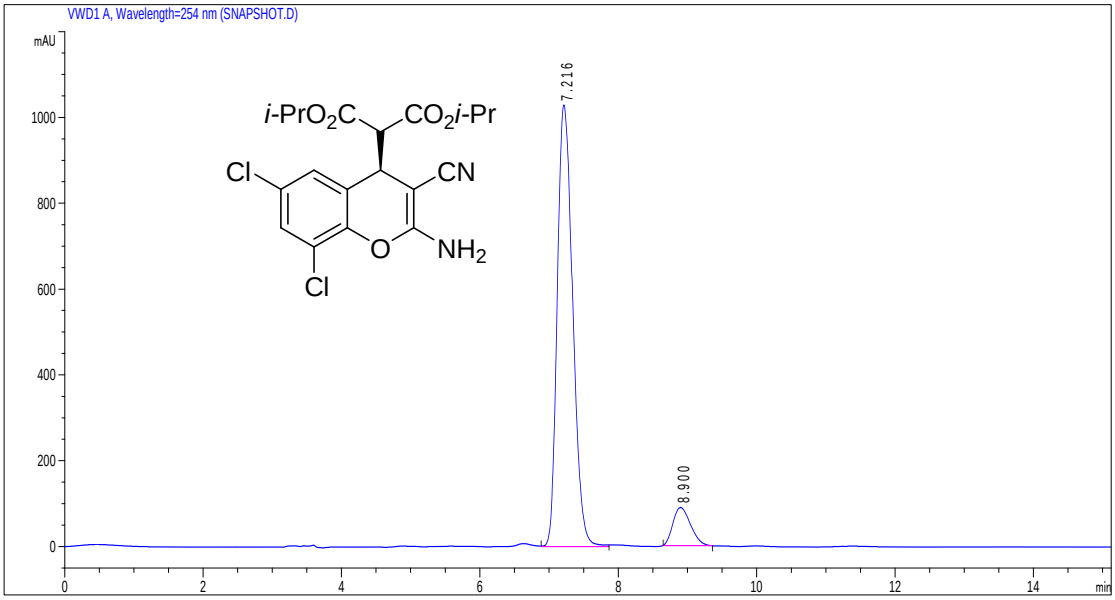


#	Time	Area	Height	Width	Area%	Symmetry
1	7.719	34132.3	1484.8	0.3688	91.854	0.703
2	9.602	3027.1	121.9	0.4139	8.146	0.79

(R)-diisopropyl 2-(2-amino-6,8-dichloro-3-cyano-4H-chromen-4-yl)malonate (3oc)

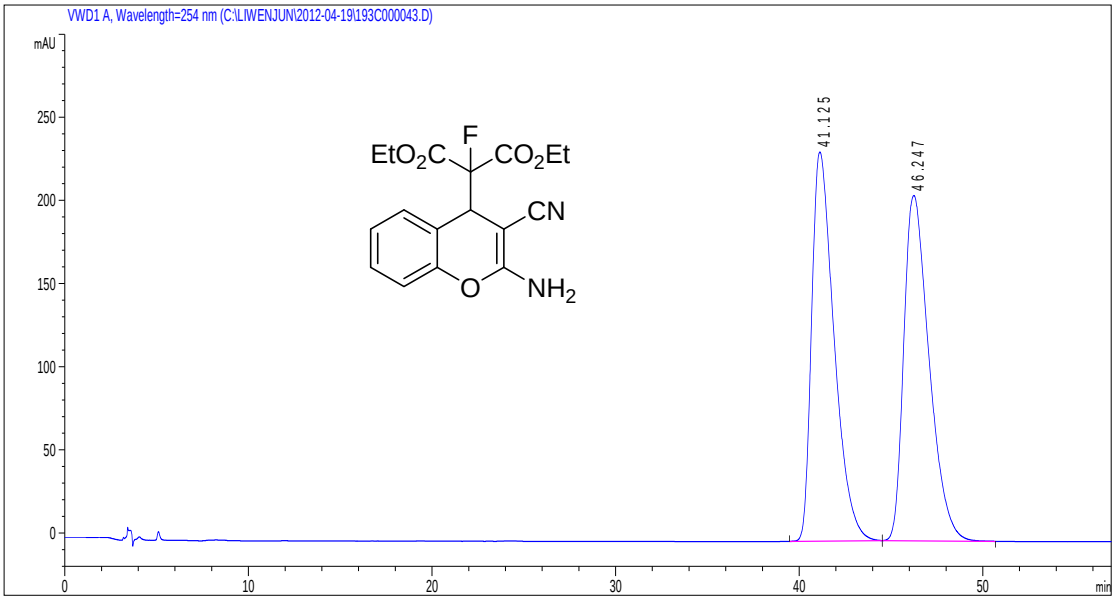


#	Time	Area	Height	Width	Area%	Symmetry
1	7.459	3528.8	228.4	0.2415	50.255	0.8
2	9.124	3493.1	192.7	0.2814	49.745	0.648

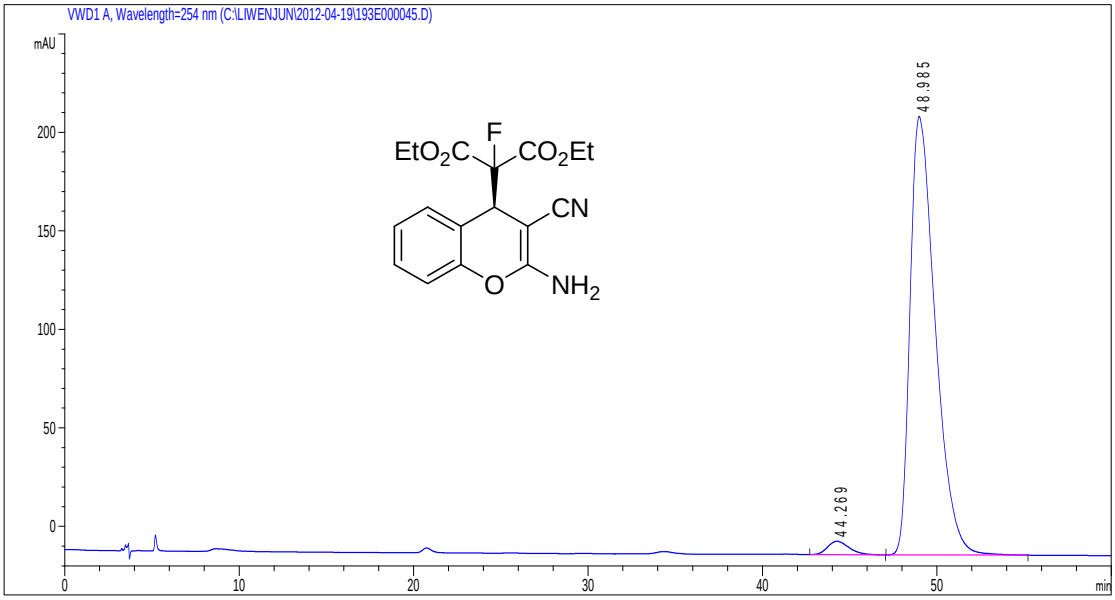


#	Time	Area	Height	Width	Area%	Symmetry
1	7.216	15985.8	1029.5	0.2453	91.036	0.725
2	8.9	1574.1	89.1	0.2945	8.964	0.742

(R)-diethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)-2-fluoromalonate (3df)

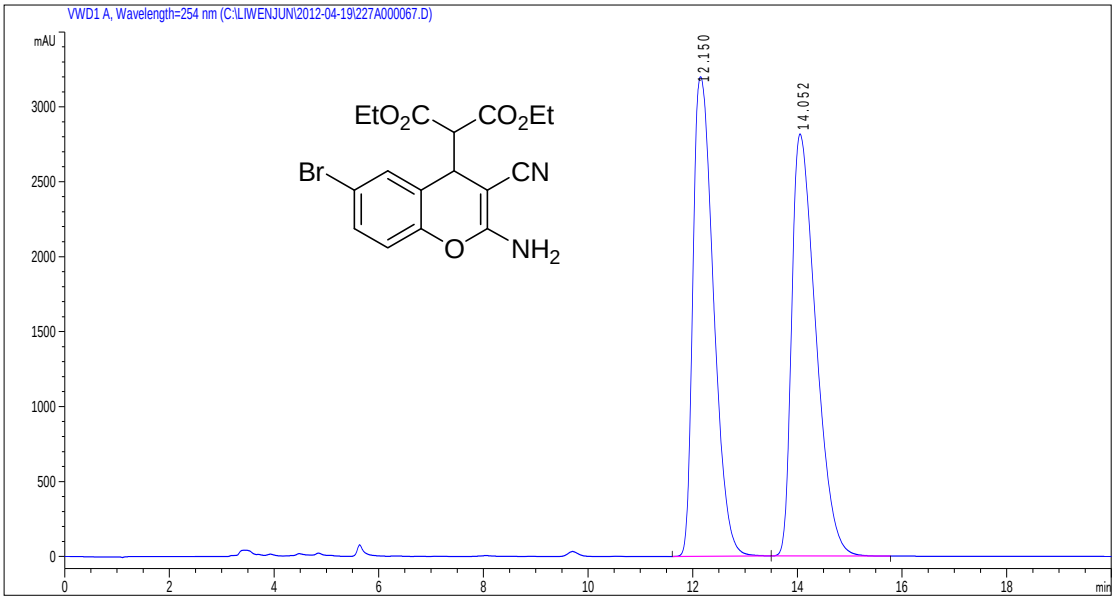


#	Time	Area	Height	Width	Area%	Symmetry
1	41.125	19844	234.1	1.2909	49.963	0.541
2	46.247	19873.1	207.7	1.4415	50.037	0.62

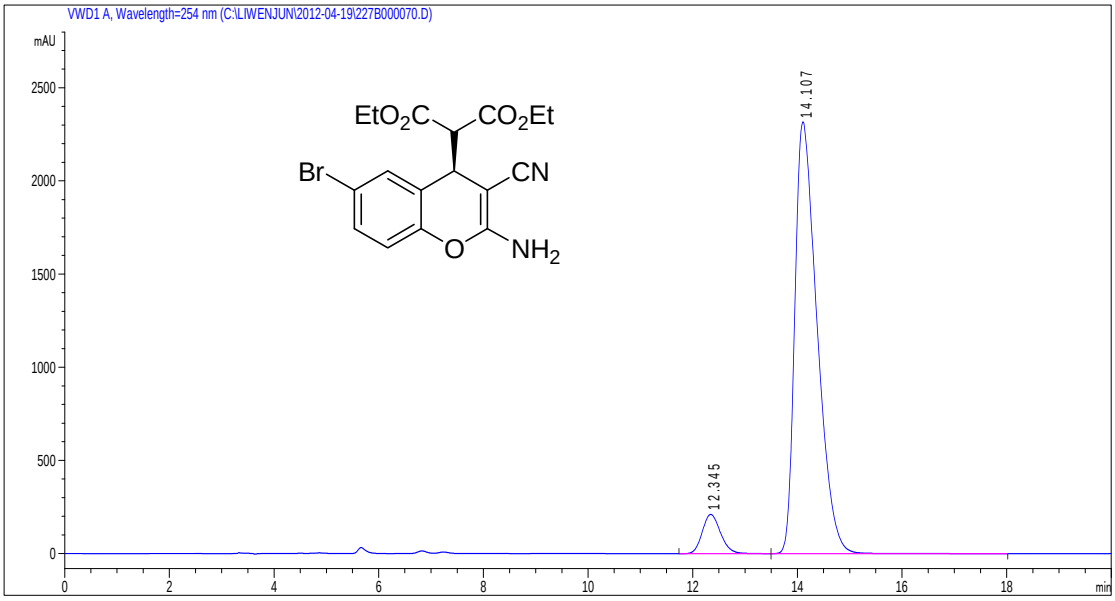


#	Time	Area	Height	Width	Area%	Symmetry
1	44.269	584.1	6.8	1.1687	2.544	0.729
2	48.985	22372.5	222.5	1.4967	97.456	0.536

(R)-diethyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3ea)

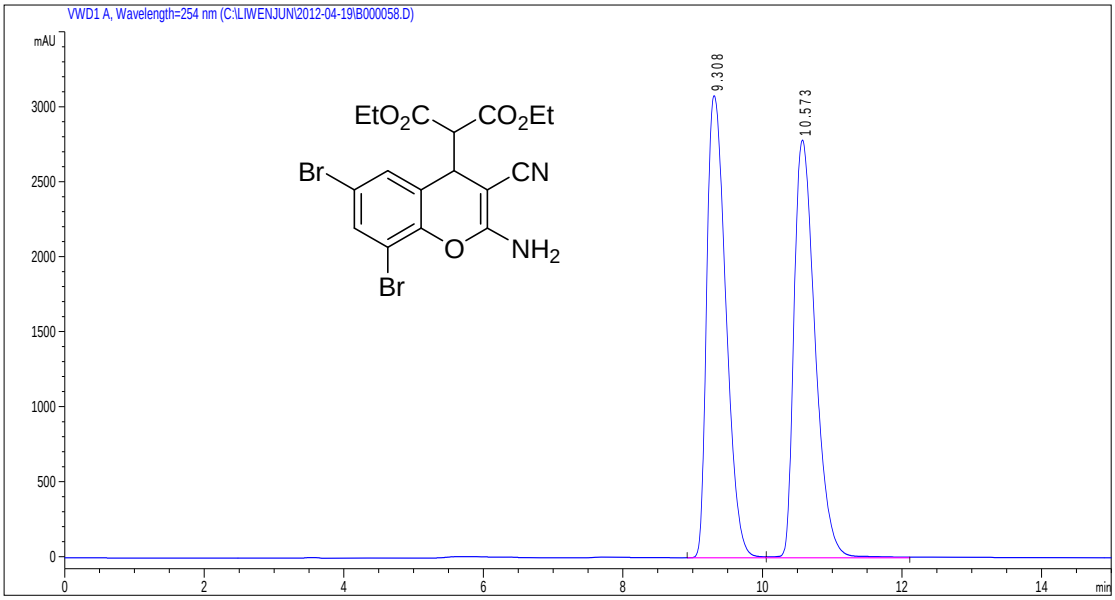


#	Time	Area	Height	Width	Area%	Symmetry
1	12.15	87514.8	3200.9	0.4254	49.330	0.548
2	14.052	89892.8	2815.6	0.4935	50.670	0.496

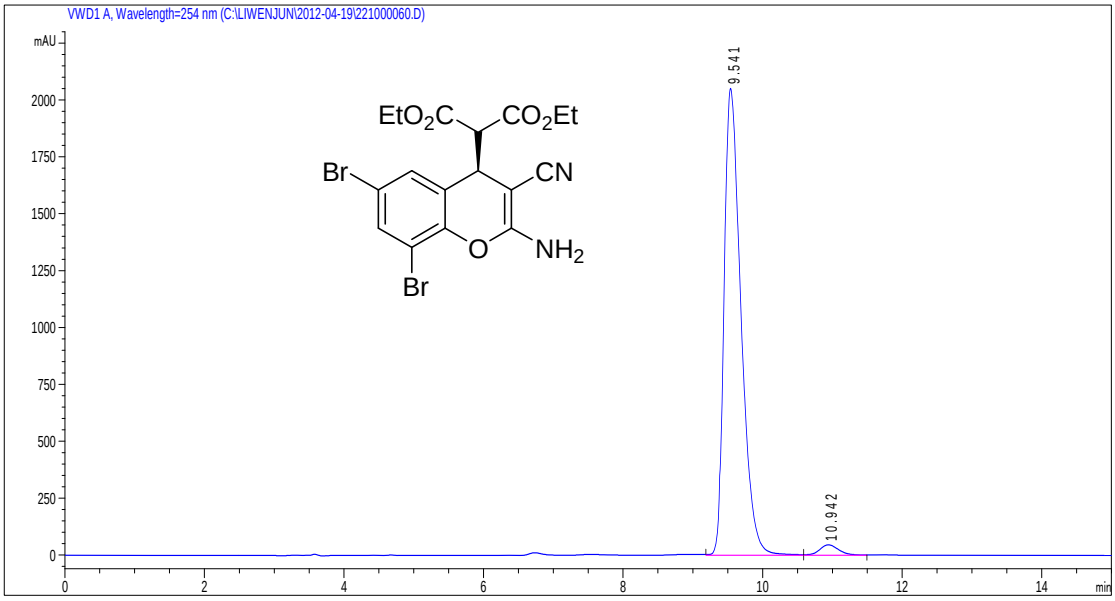


#	Time	Area	Height	Width	Area%	Symmetry
1	12.345	5112.2	210.4	0.3767	6.978	0.824
2	14.107	68146.3	2317.5	0.4495	93.022	0.54

(R)-diethyl 2-(2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl)malonate (3na)

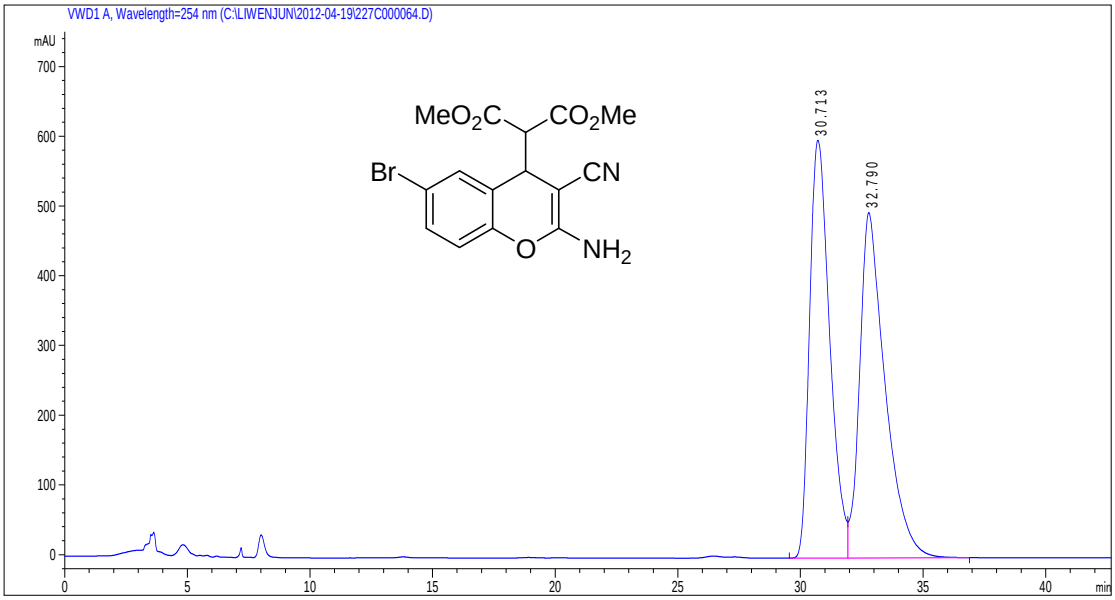


#	Time	Area	Height	Width	Area%	Symmetry
1	9.308	58697.7	3081	0.2981	50.091	0.59
2	10.573	58483.9	2785.1	0.3266	49.909	0.61

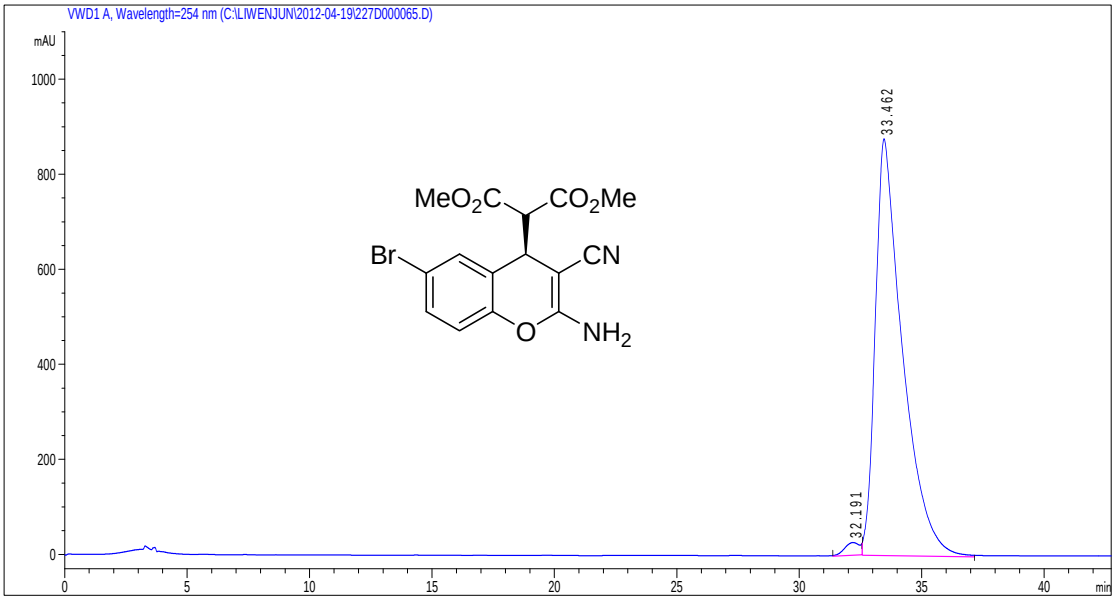


#	Time	Area	Height	Width	Area%	Symmetry
1	9.541	34484.5	2052.2	0.2587	97.481	0.586
2	10.942	891.2	46.2	0.2933	2.519	0.807

(R)-dimethyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3eb)



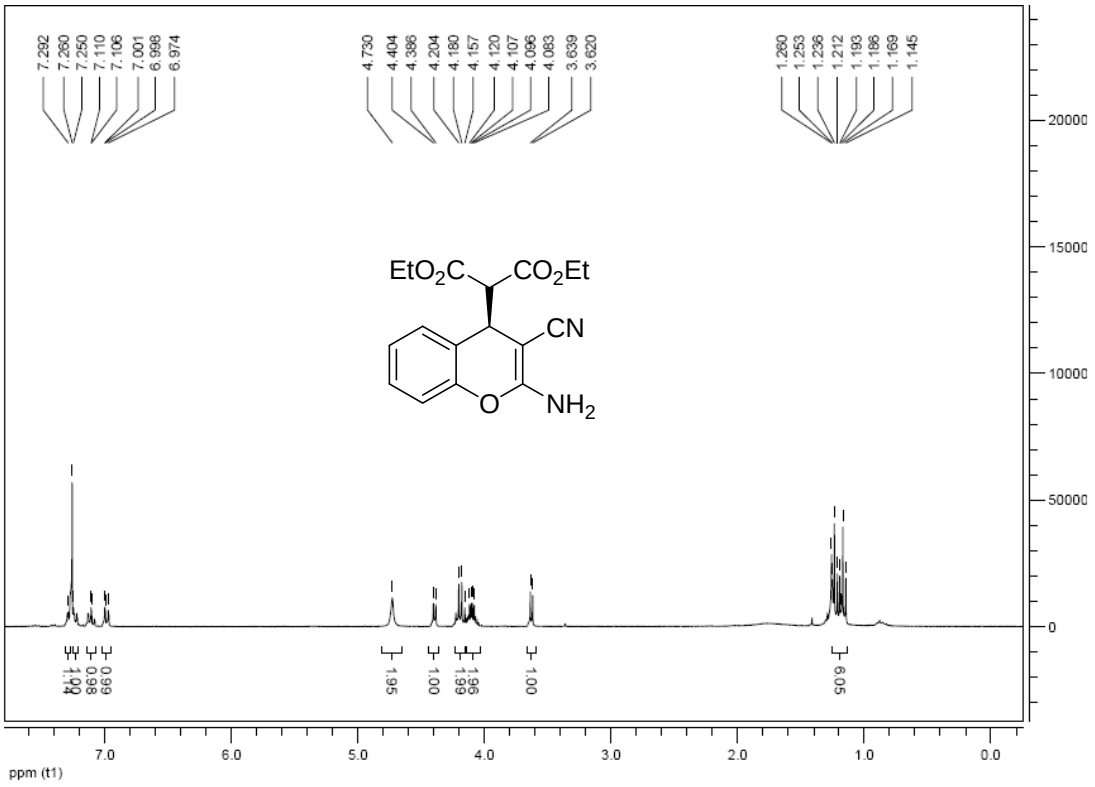
#	Time	Area	Height	Width	Area%	Symmetry
1	30.713	34182.9	599.1	0.8552	48.886	0.665
2	32.79	35740.7	495.2	1.0462	51.114	0.537

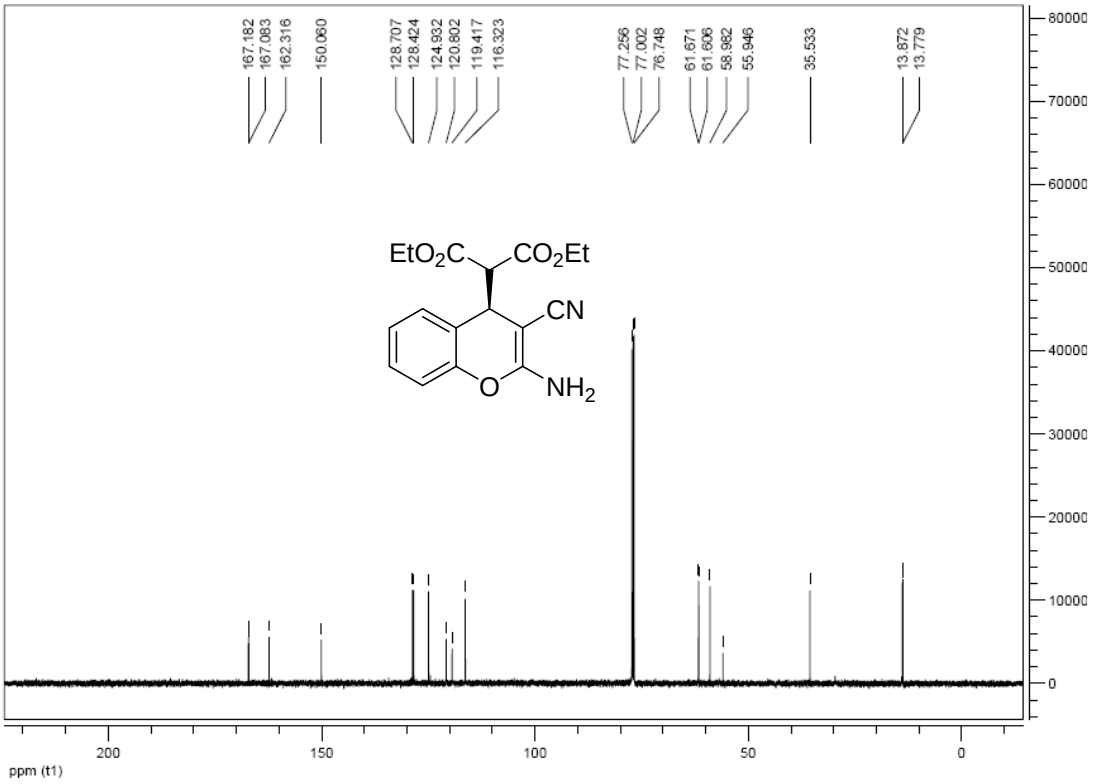


#	Time	Area	Height	Width	Area%	Symmetry
1	32.191	1157.1	26.7	0.7222	1.679	1.201
2	33.462	67775.9	876.9	1.2077	98.321	0

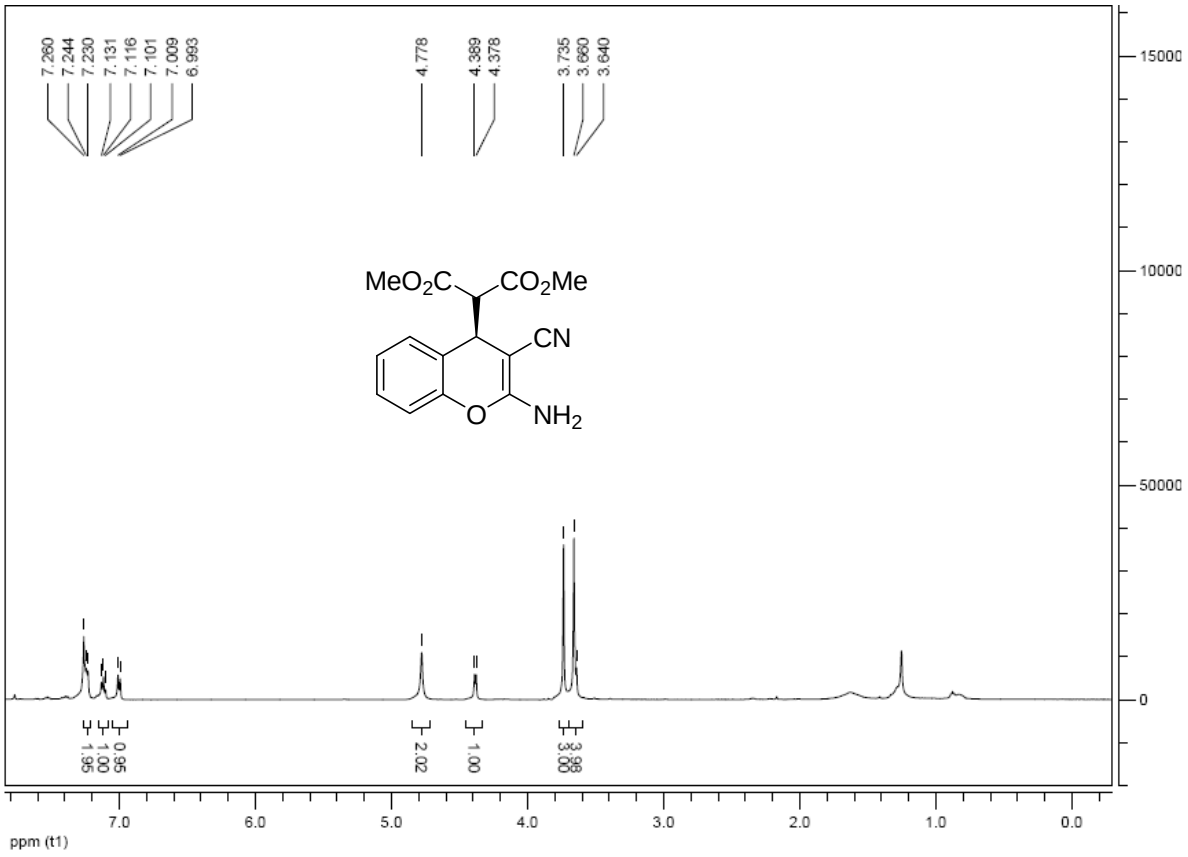
E: NMR Analysis of Michael Reaction Products

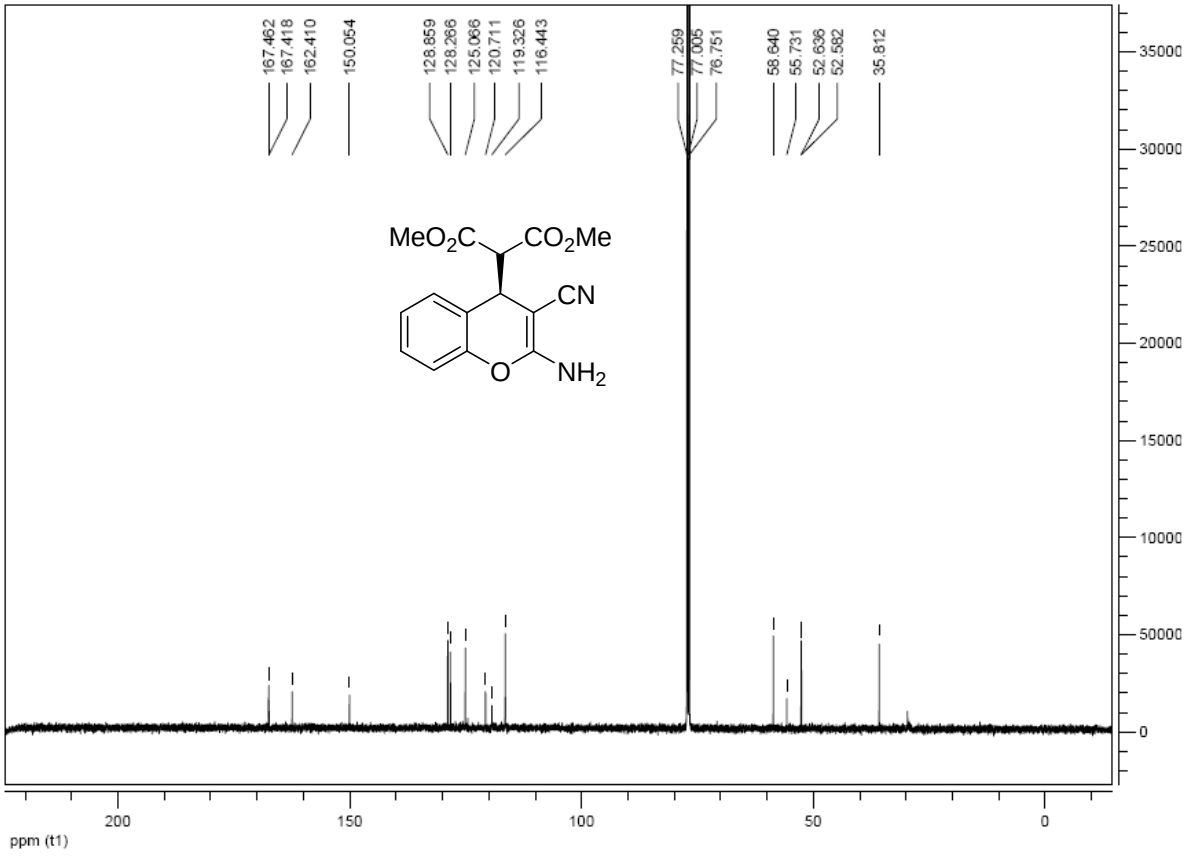
(R)-diethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3da)



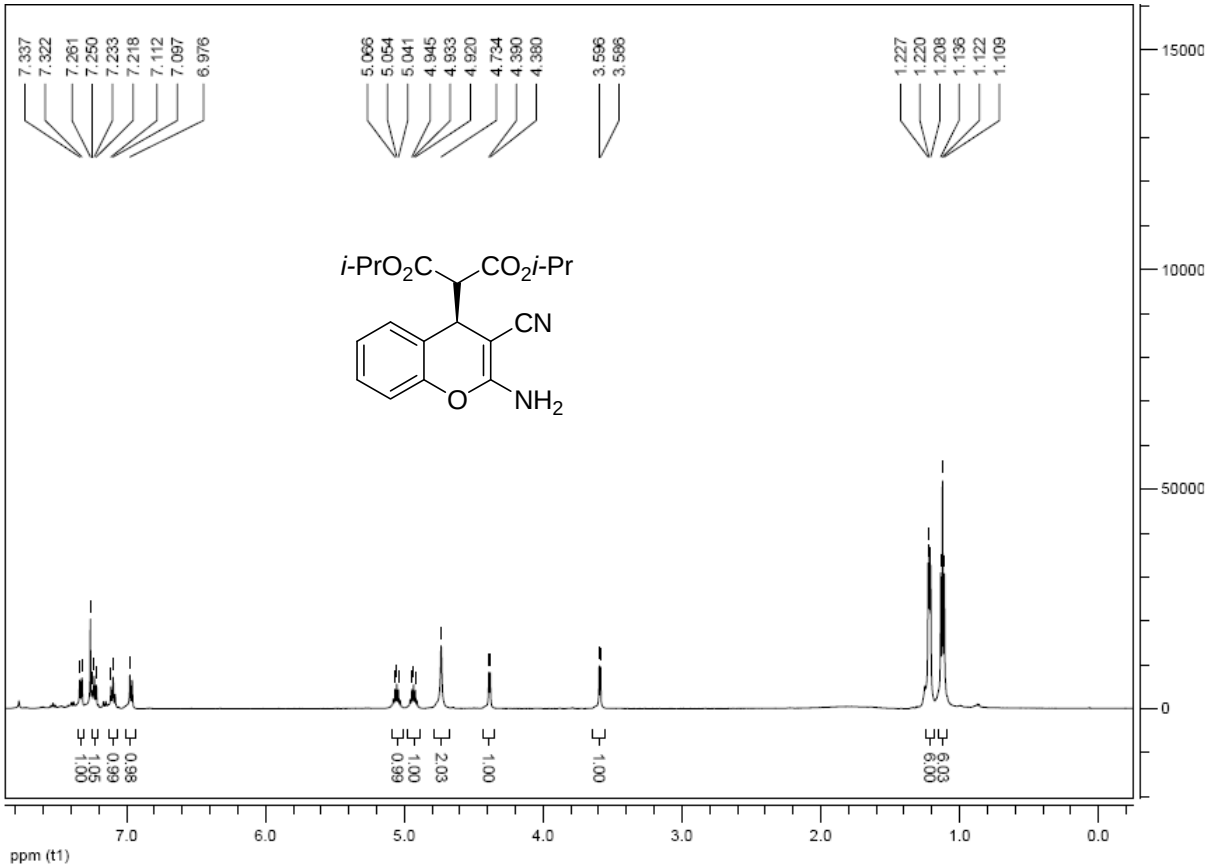


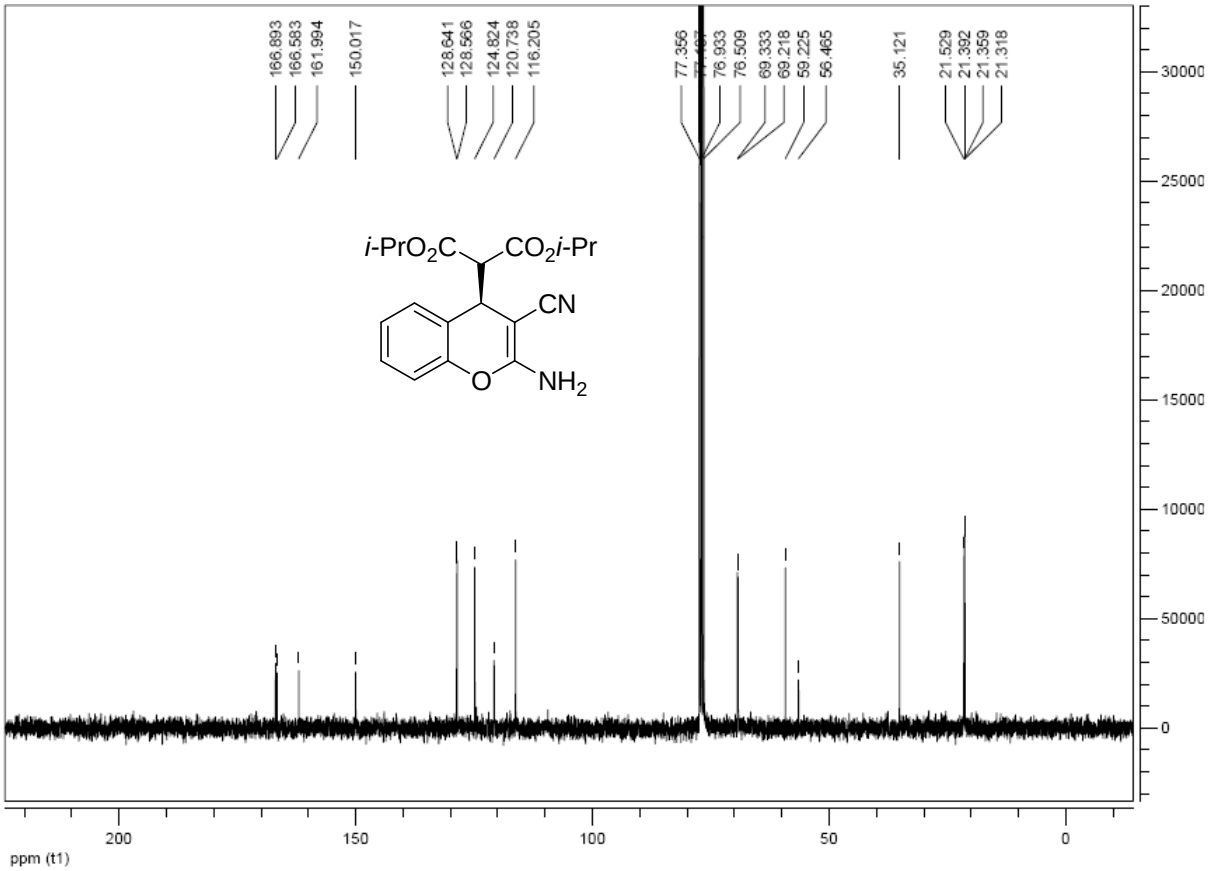
(R)-dimethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3db)



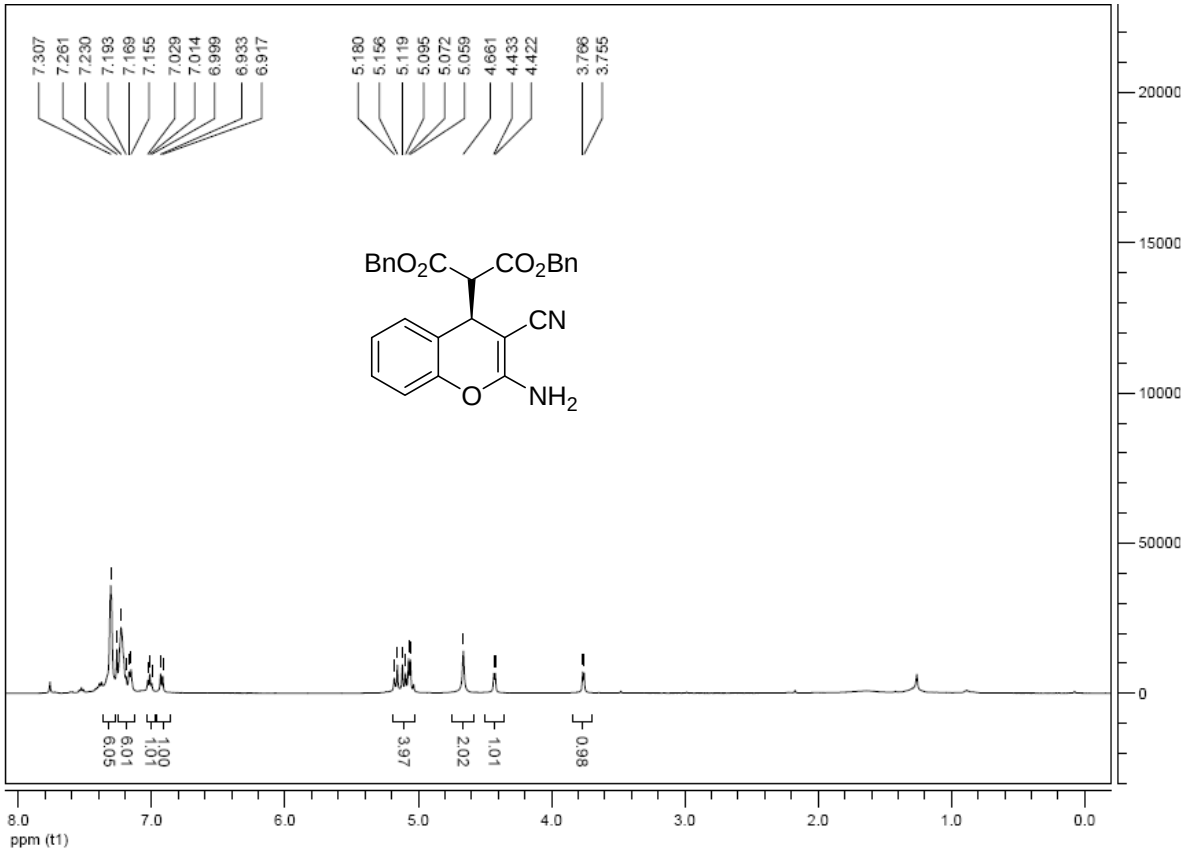


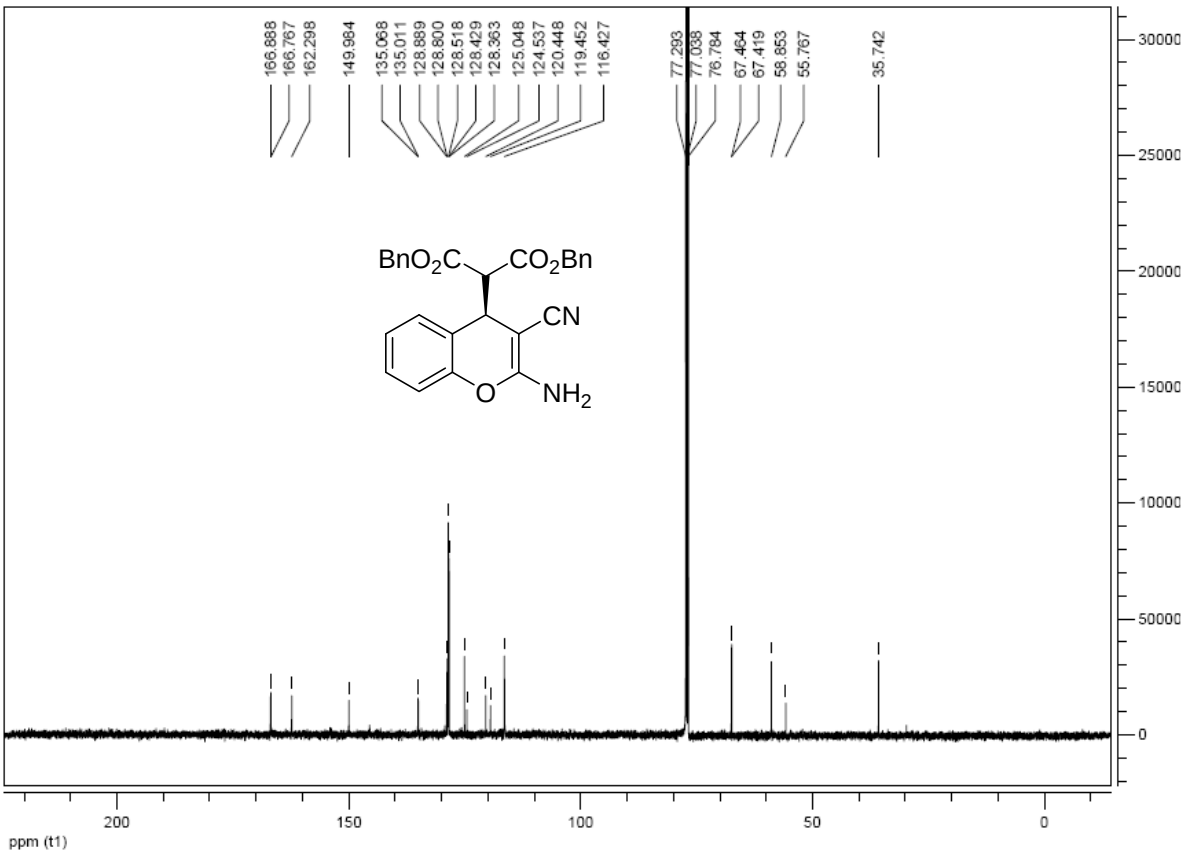
(R)-diisopropyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3dc)



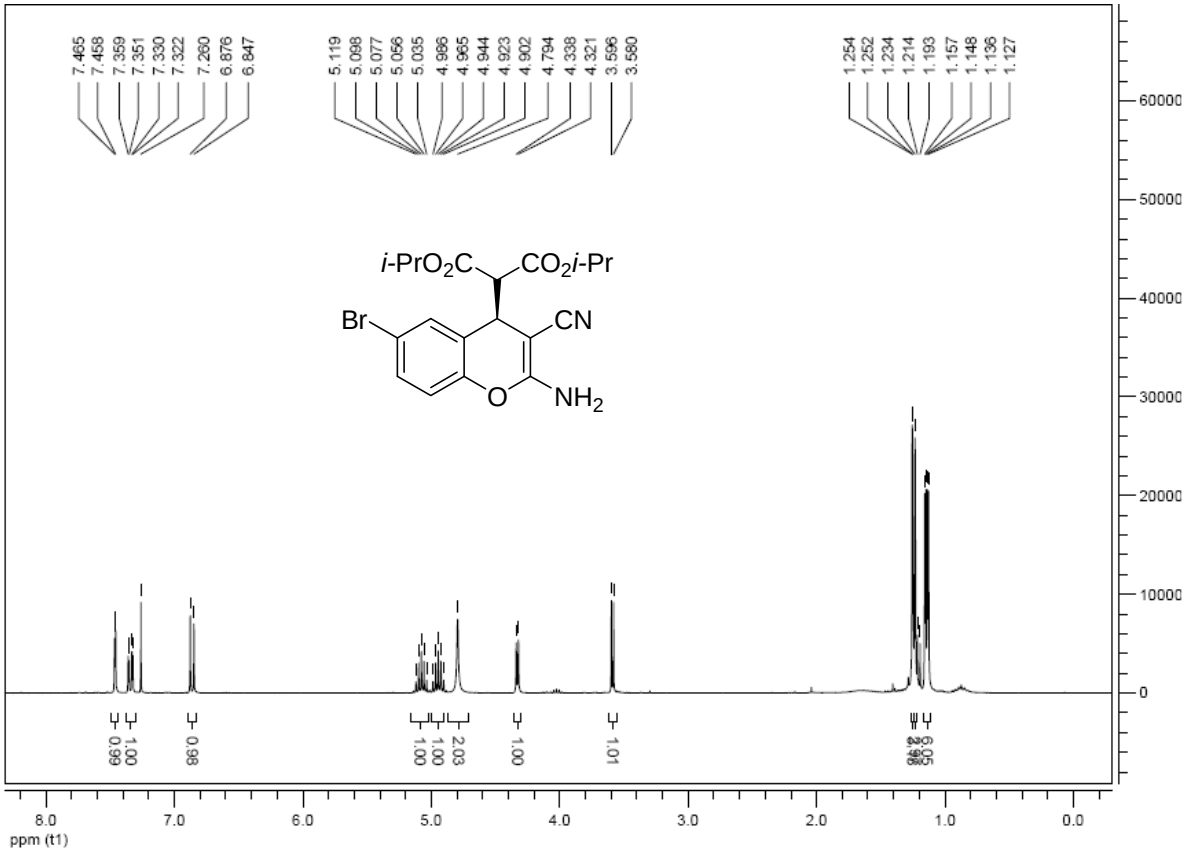


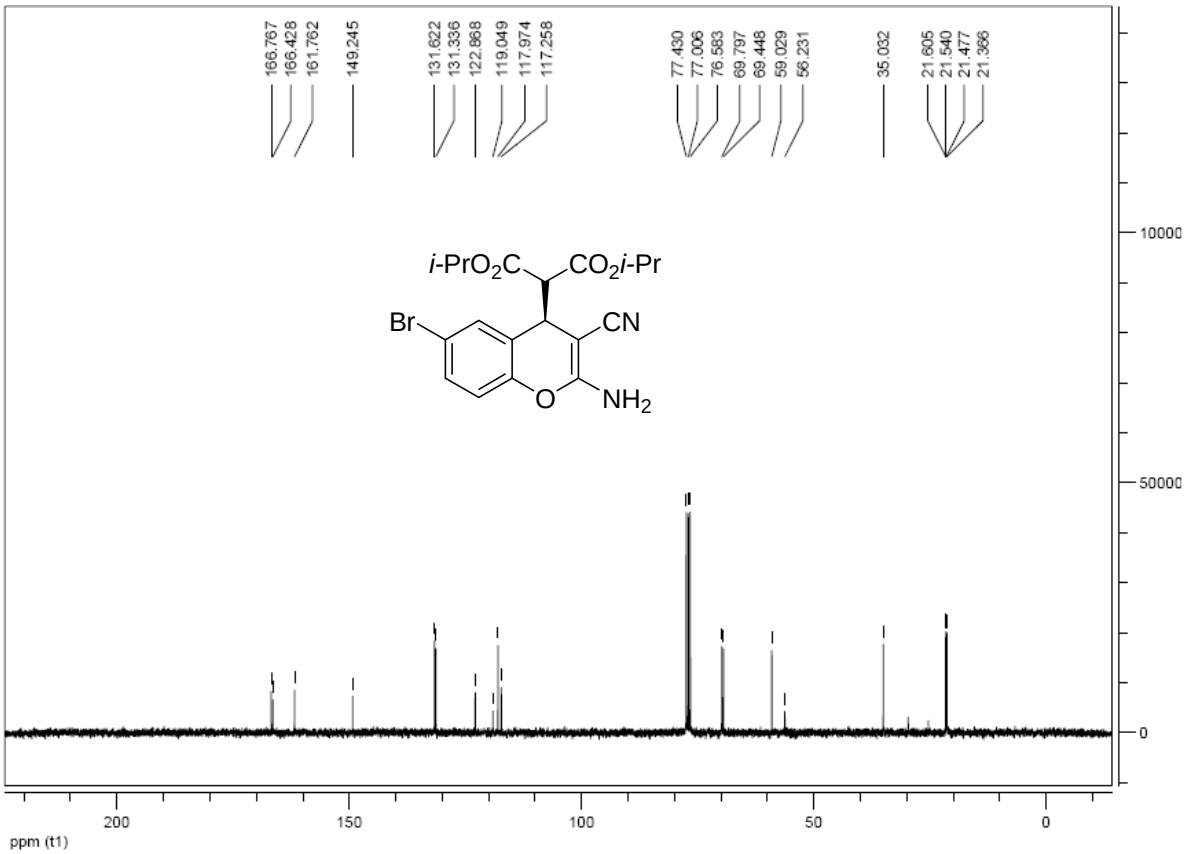
(R)-dibenzyl 2-(2-amino-3-cyano-4H-chromen-4-yl)malonate (3de)



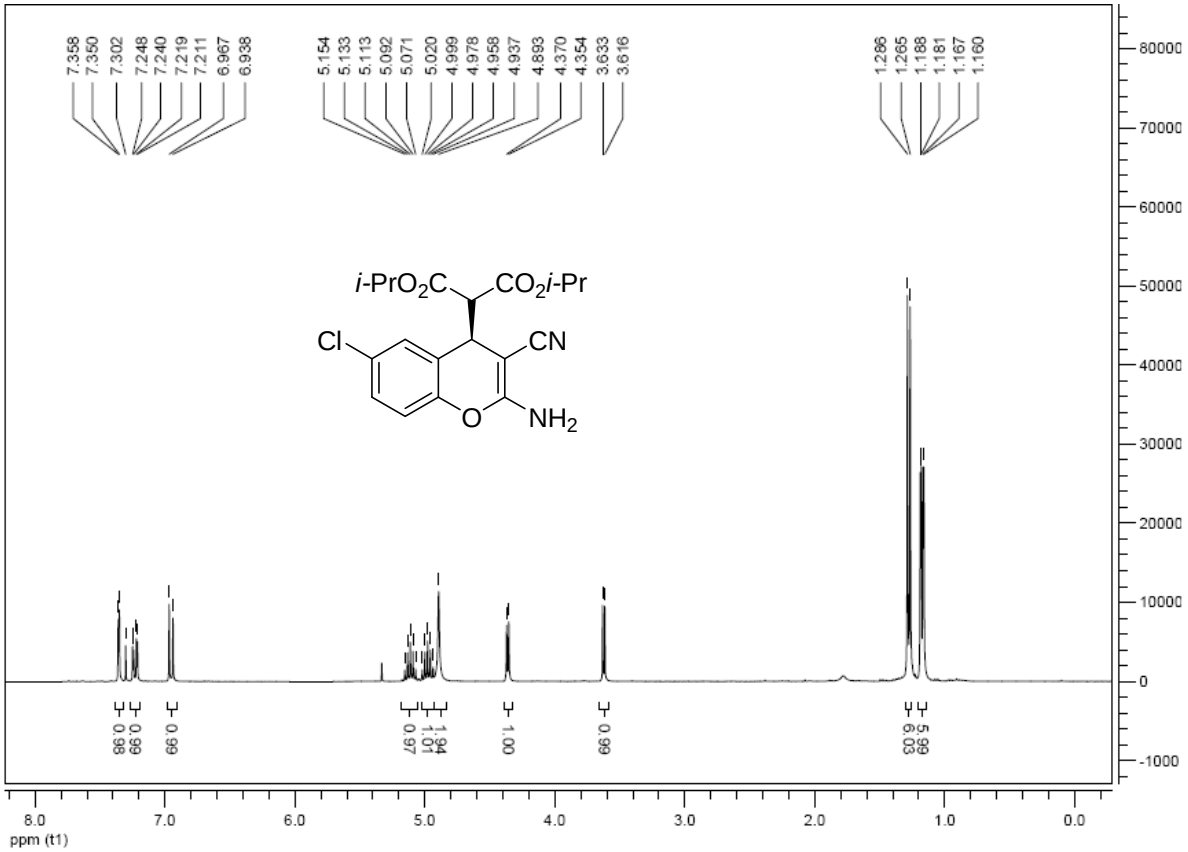


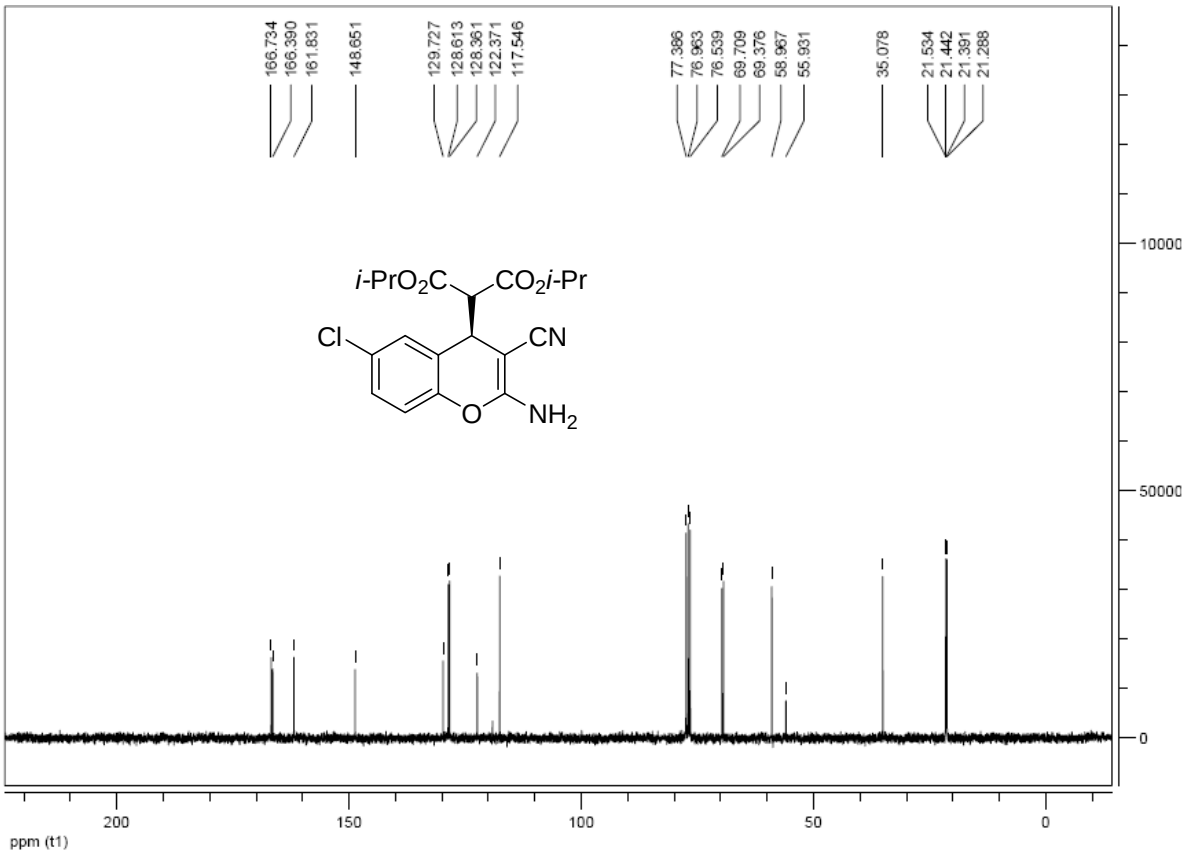
(R)-diisopropyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3ec)



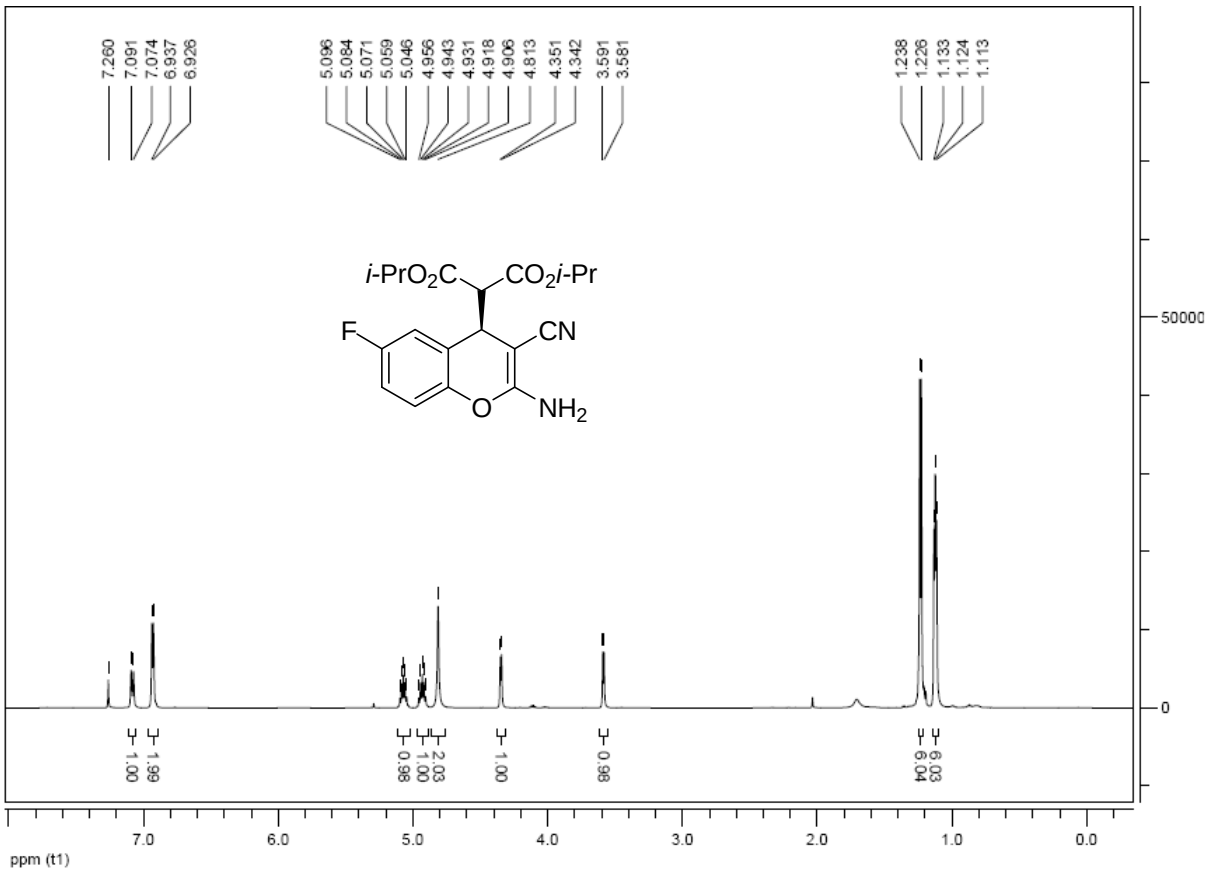


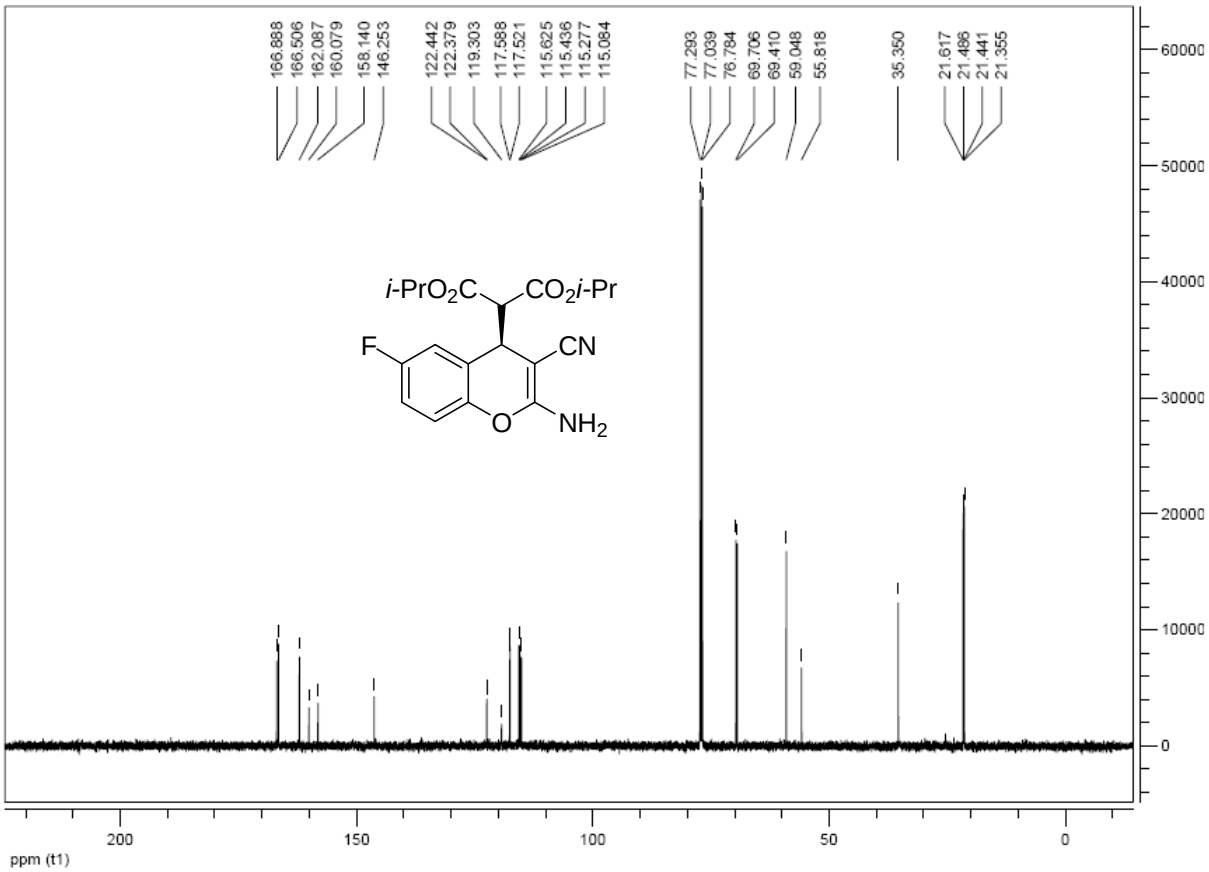
(R)-diisopropyl 2-(2-amino-6-chloro-3-cyano-4H-chromen-4-yl)malonate (3fc)



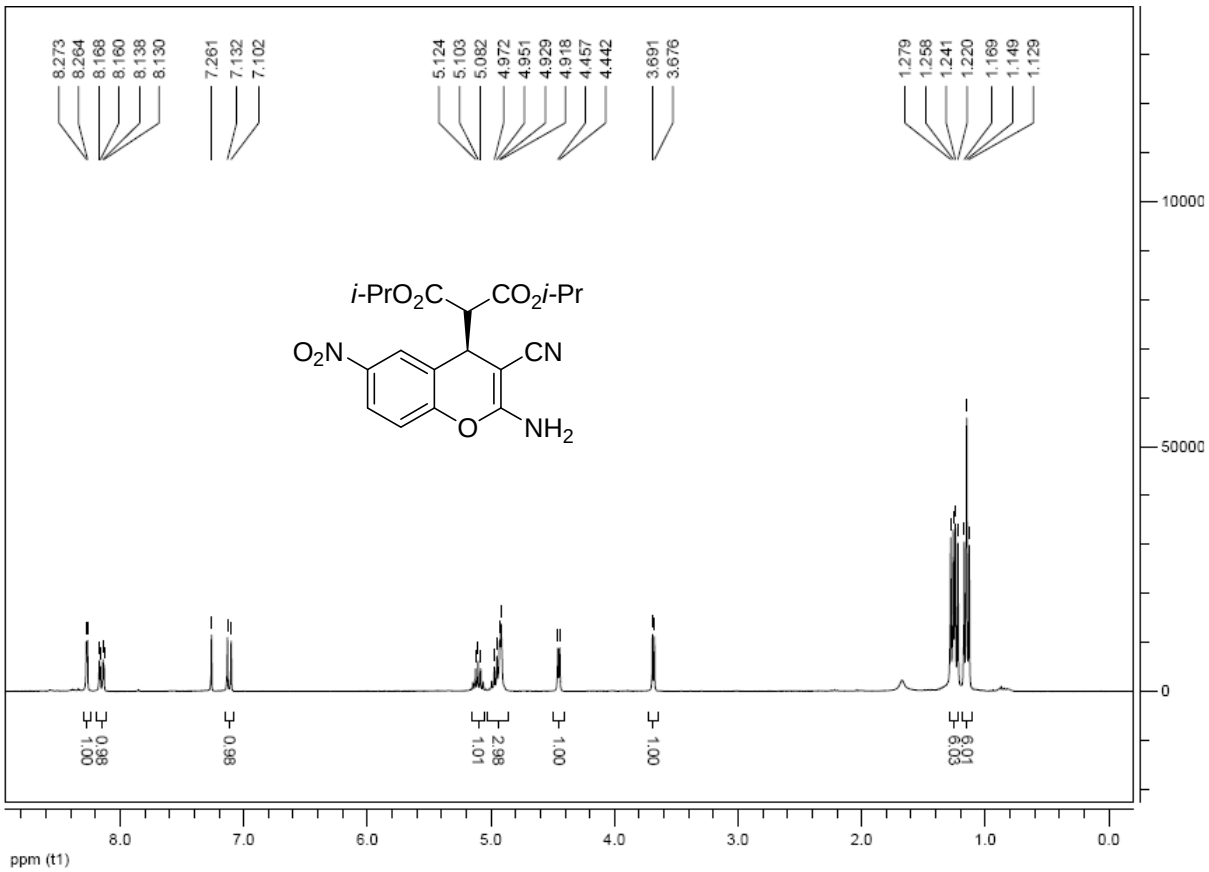


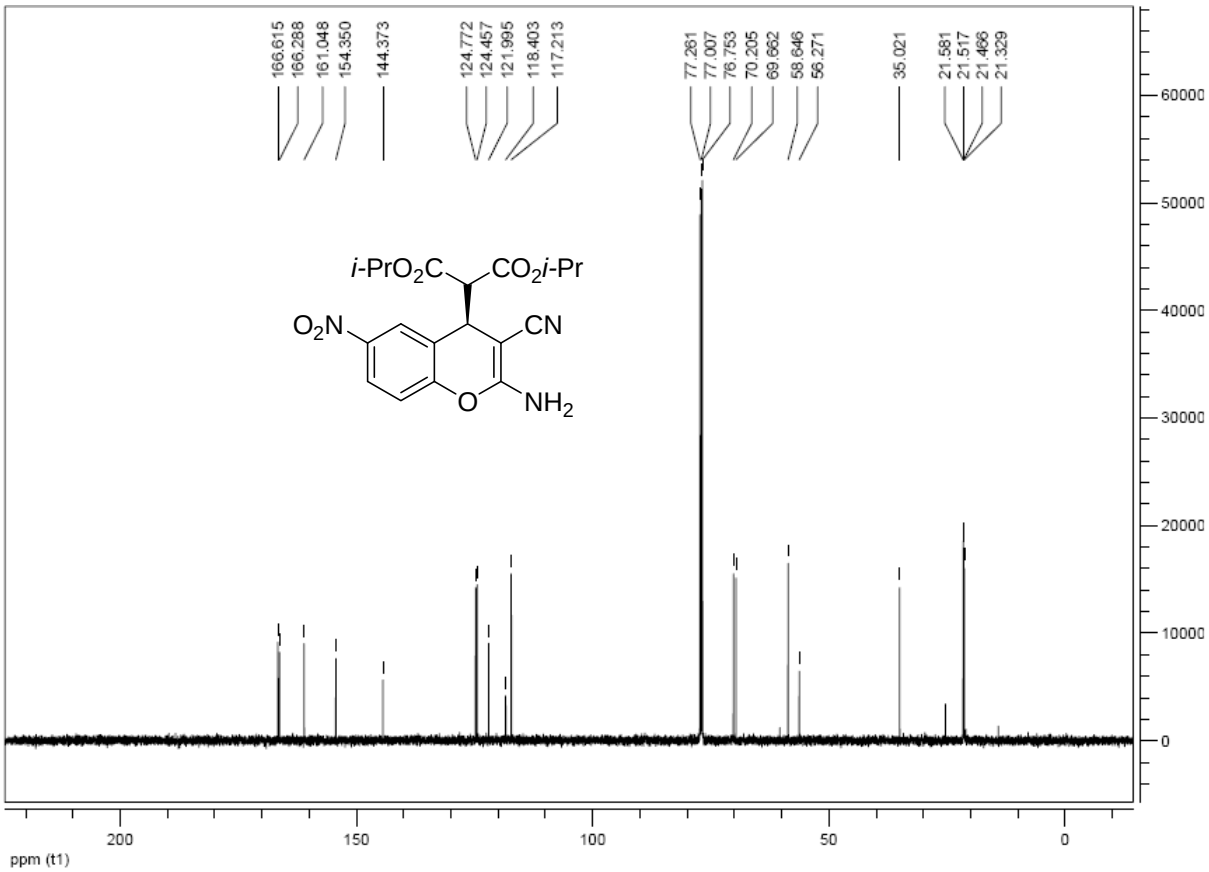
(R)-diisopropyl 2-(2-amino-3-cyano-6-fluoro-4H-chromen-4-yl)malonate (3gc)



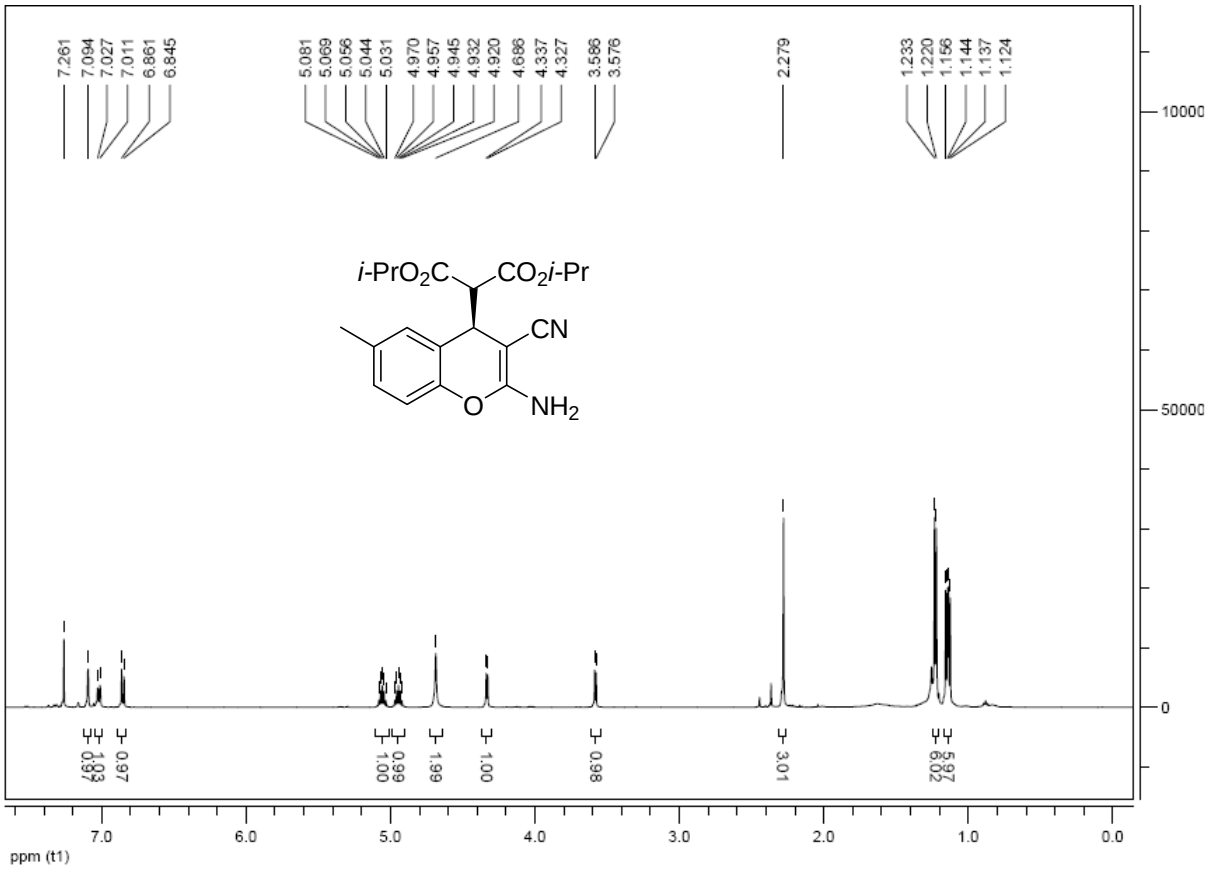


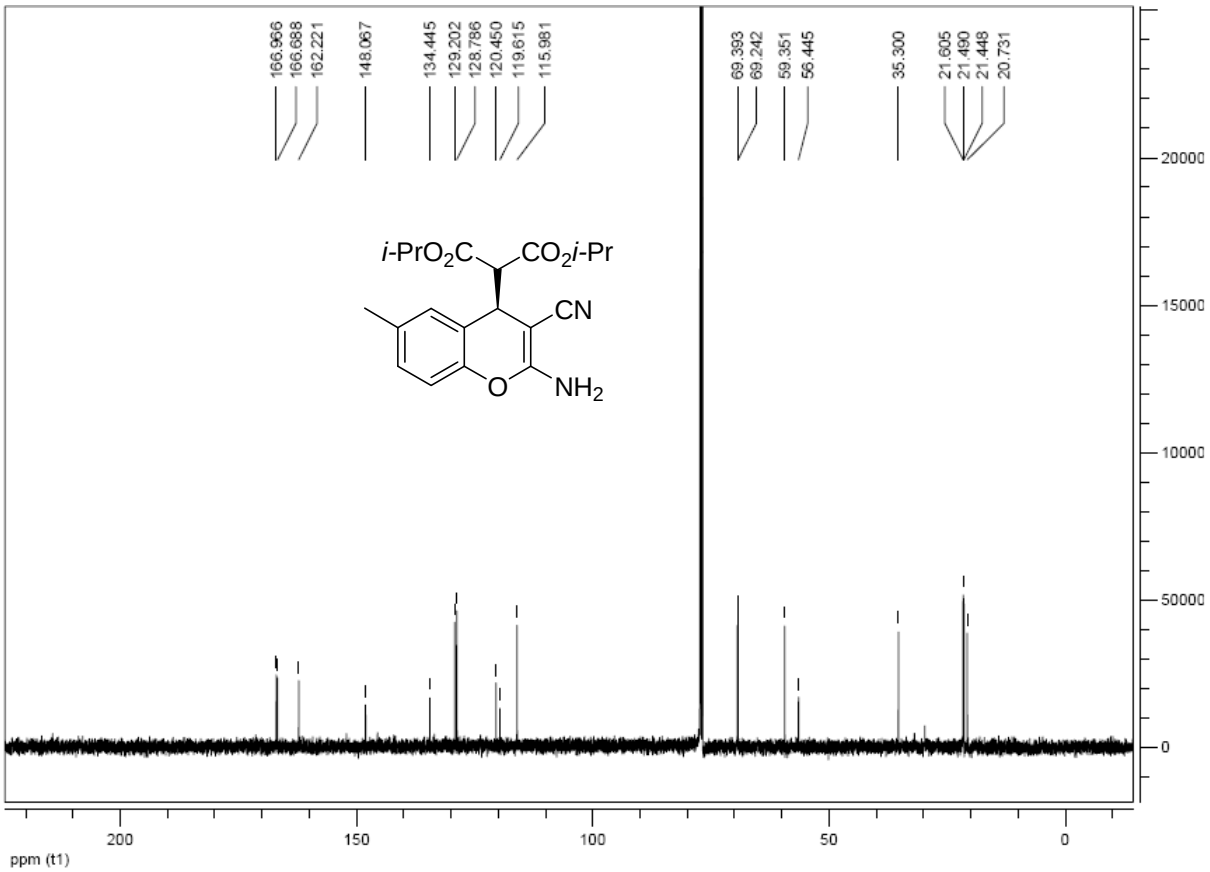
(R)-diisopropyl 2-(2-amino-3-cyano-6-nitro-4H-chromen-4-yl)malonate (3hc)



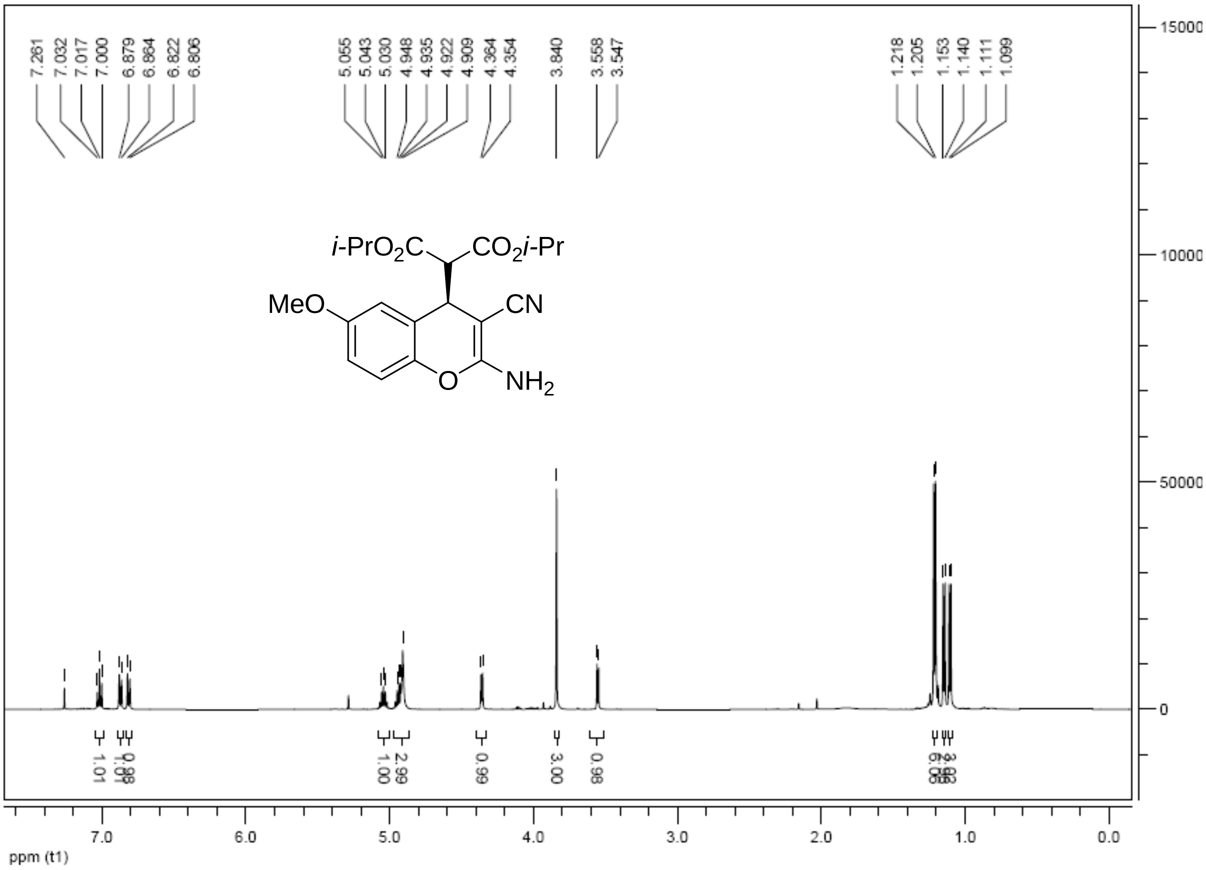


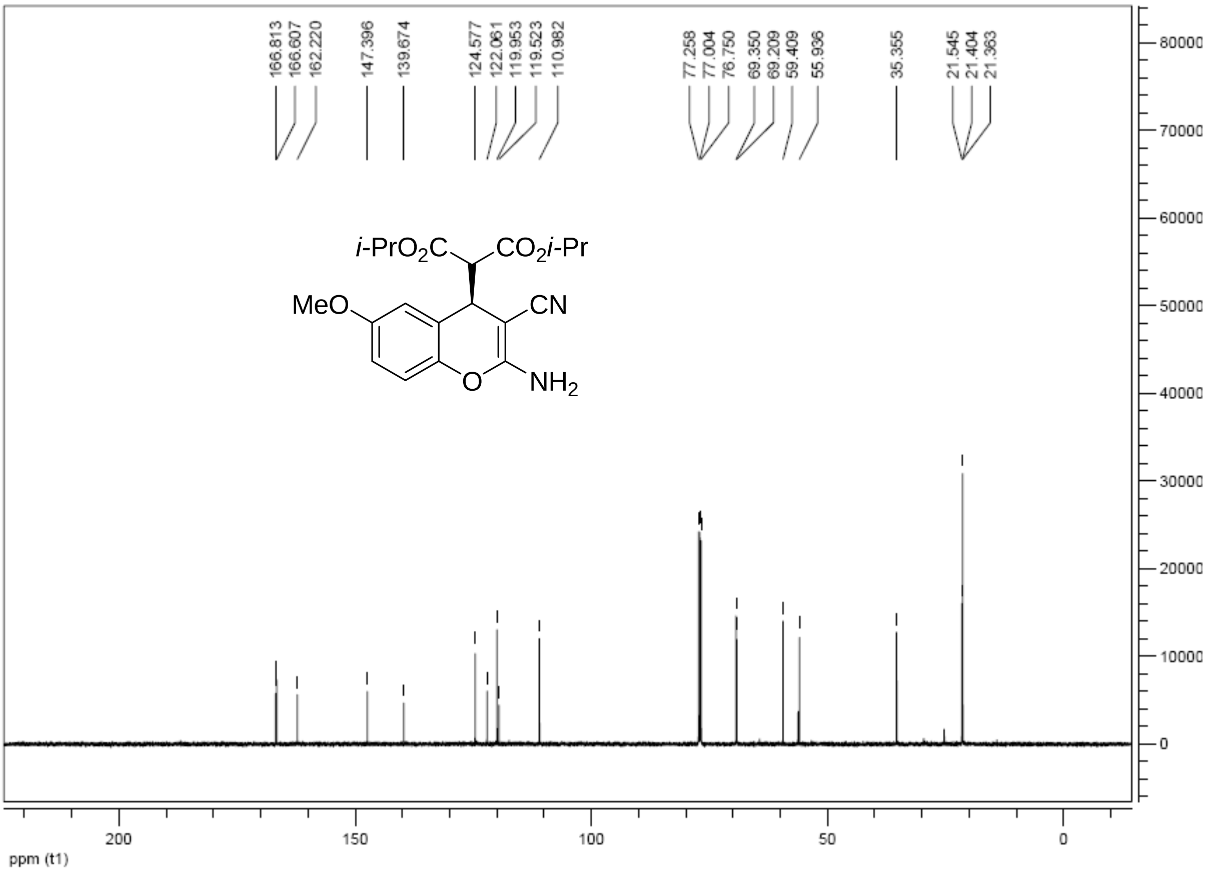
(R)-diisopropyl 2-(2-amino-3-cyano-6-methyl-4H-chromen-4-yl)malonate (3ic)



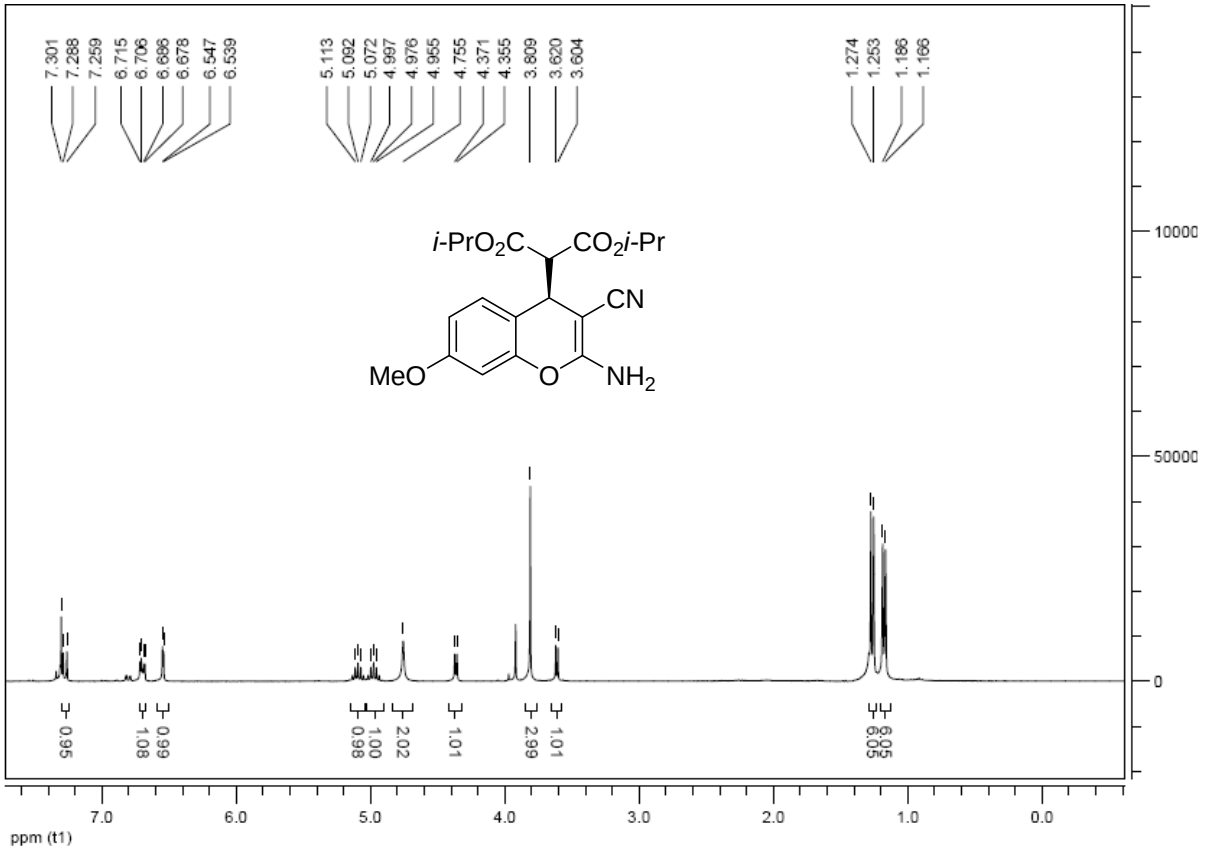


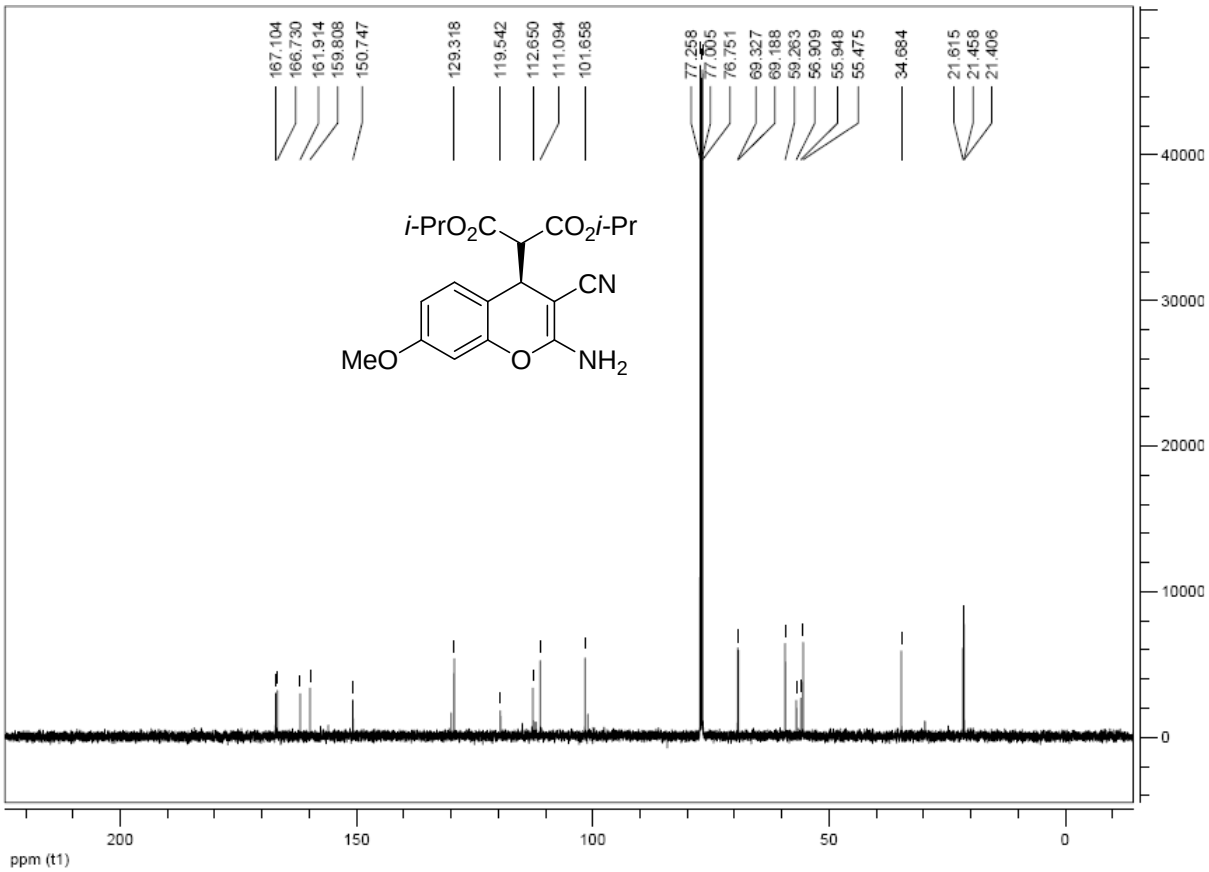
(R)-diisopropyl 2-(2-amino-3-cyano-6-methoxy-4H-chromen-4-yl)malonate (3jc)



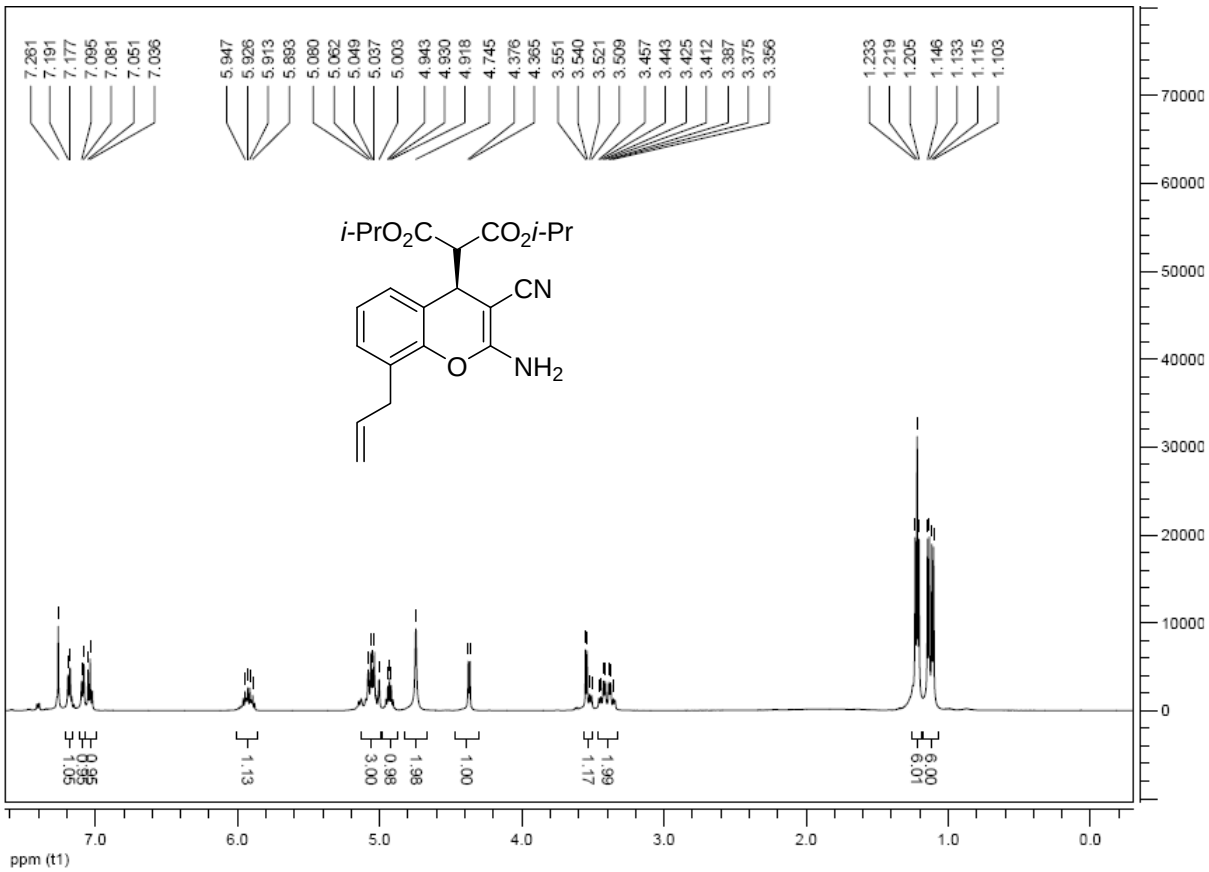


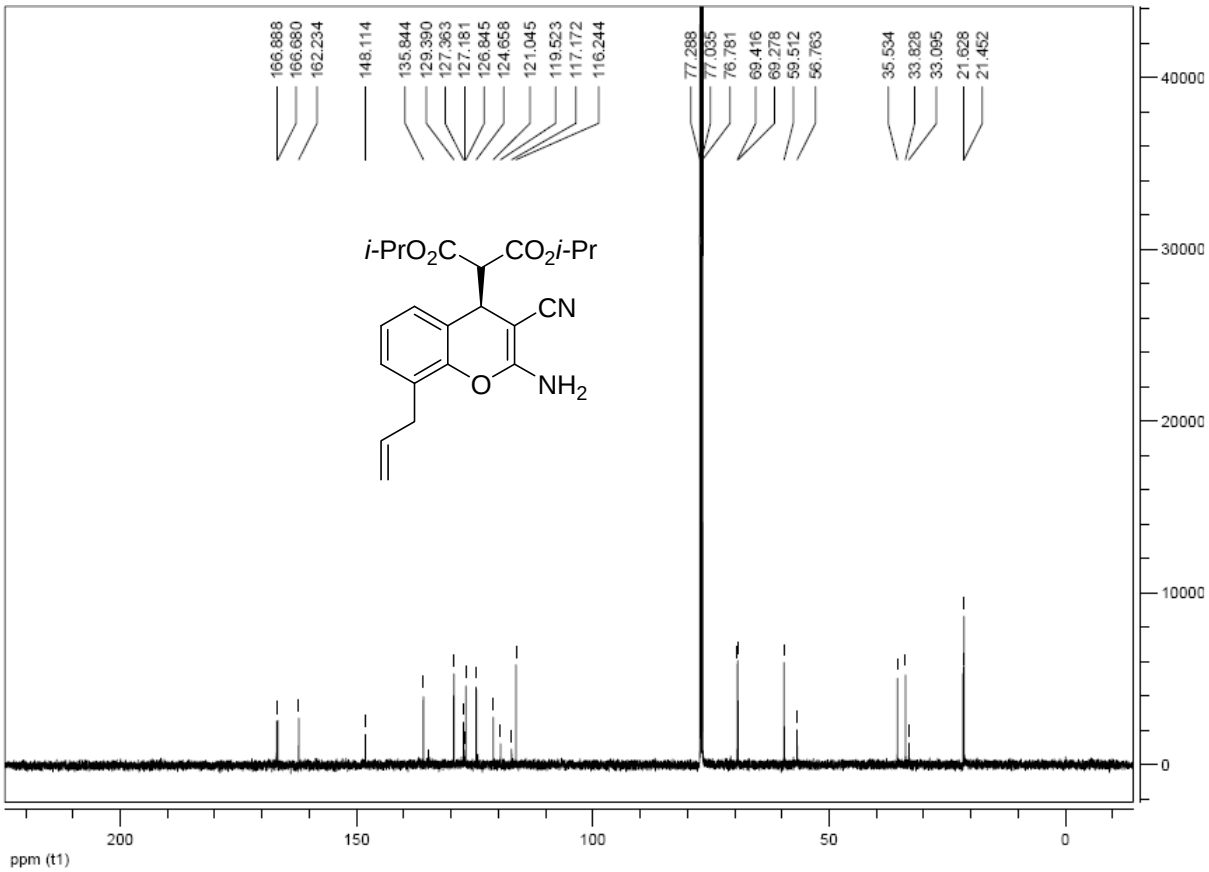
(R)-diisopropyl 2-(2-amino-3-cyano-7-methoxy-4H-chromen-4-yl)malonate (3kc)



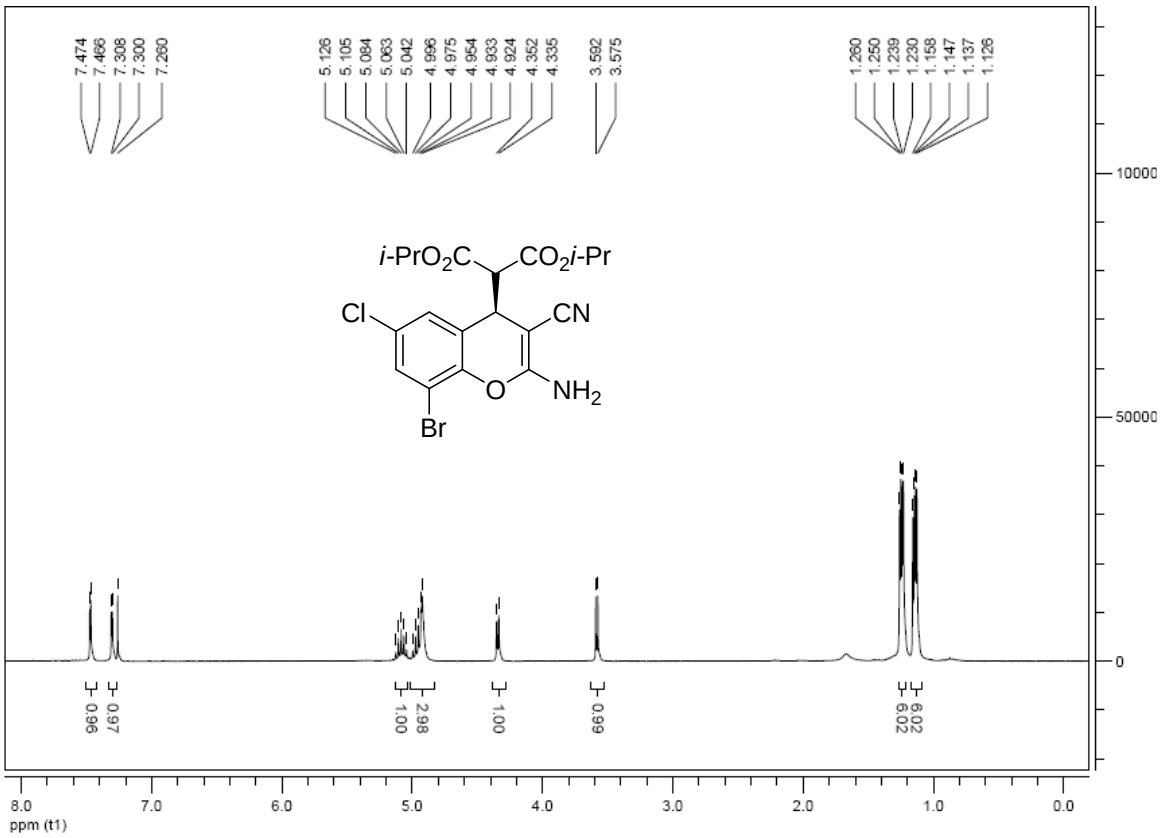


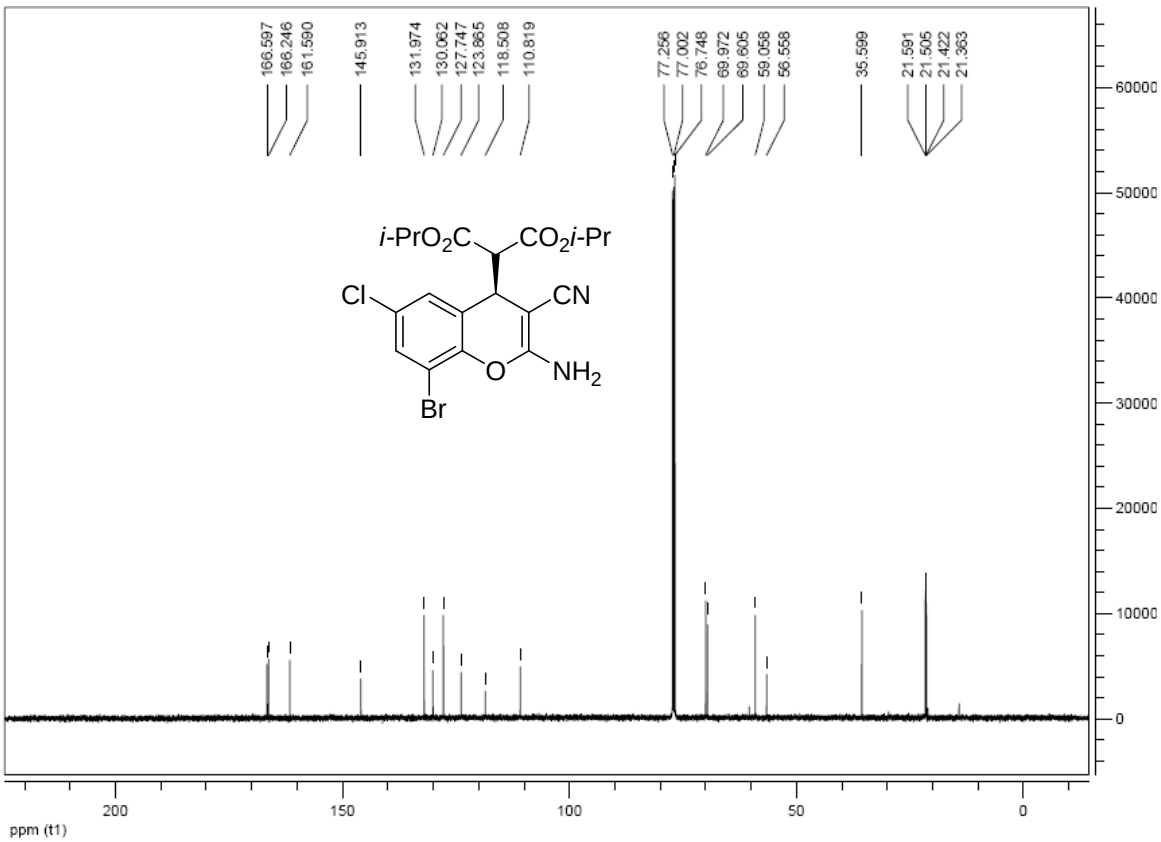
(R)-diisopropyl 2-(8-allyl-2-amino-3-cyano-4H-chromen-4-yl)malonate (3lc)



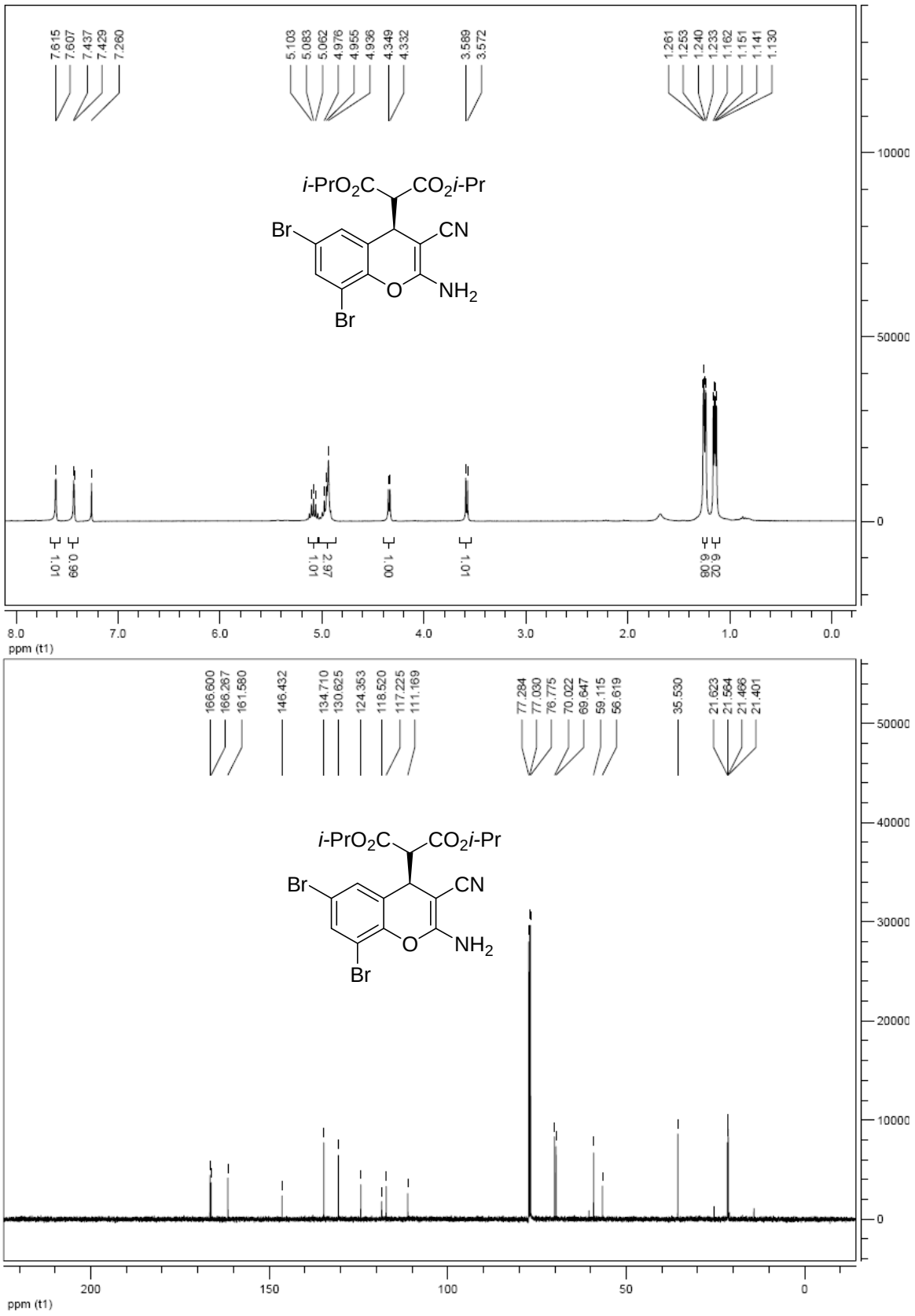


(R)-diisopropyl
2-(2-amino-8-bromo-6-chloro-3-cyano-4H-chromen-4-yl)malonate (3mc)

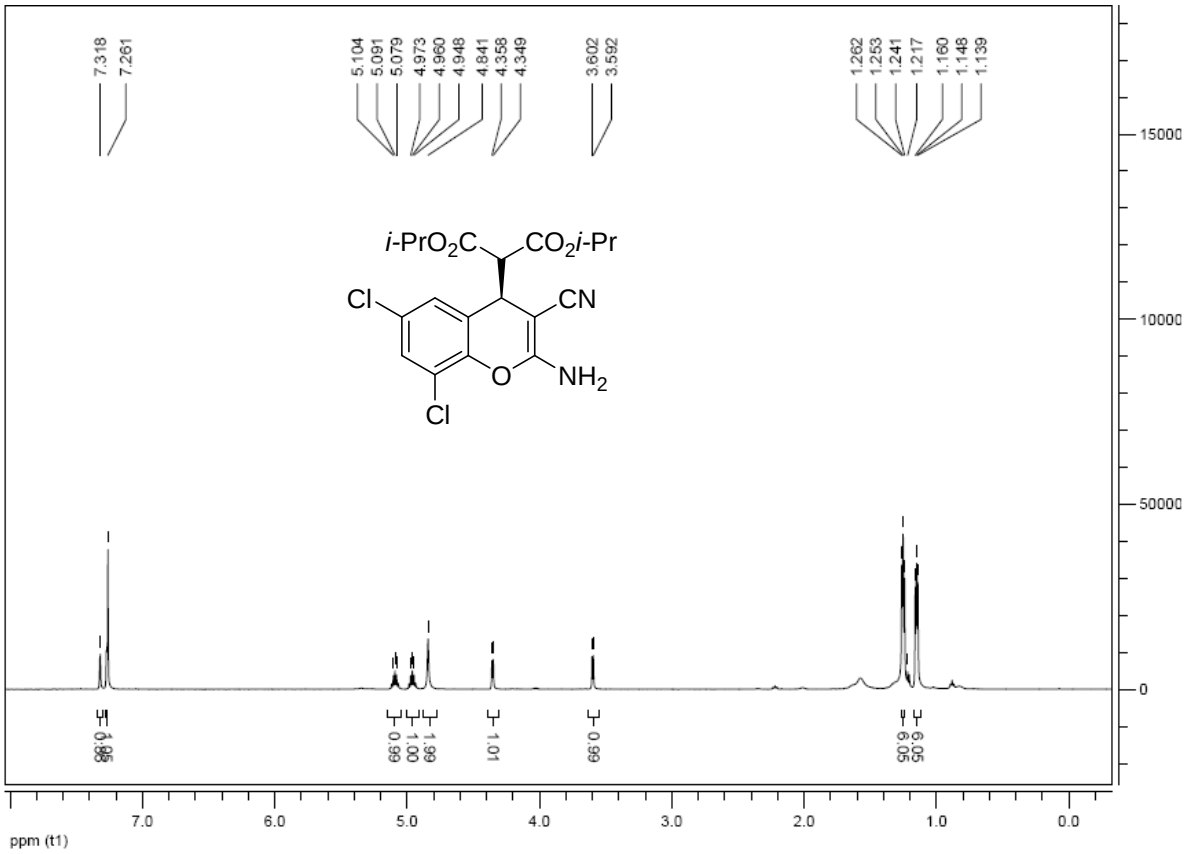


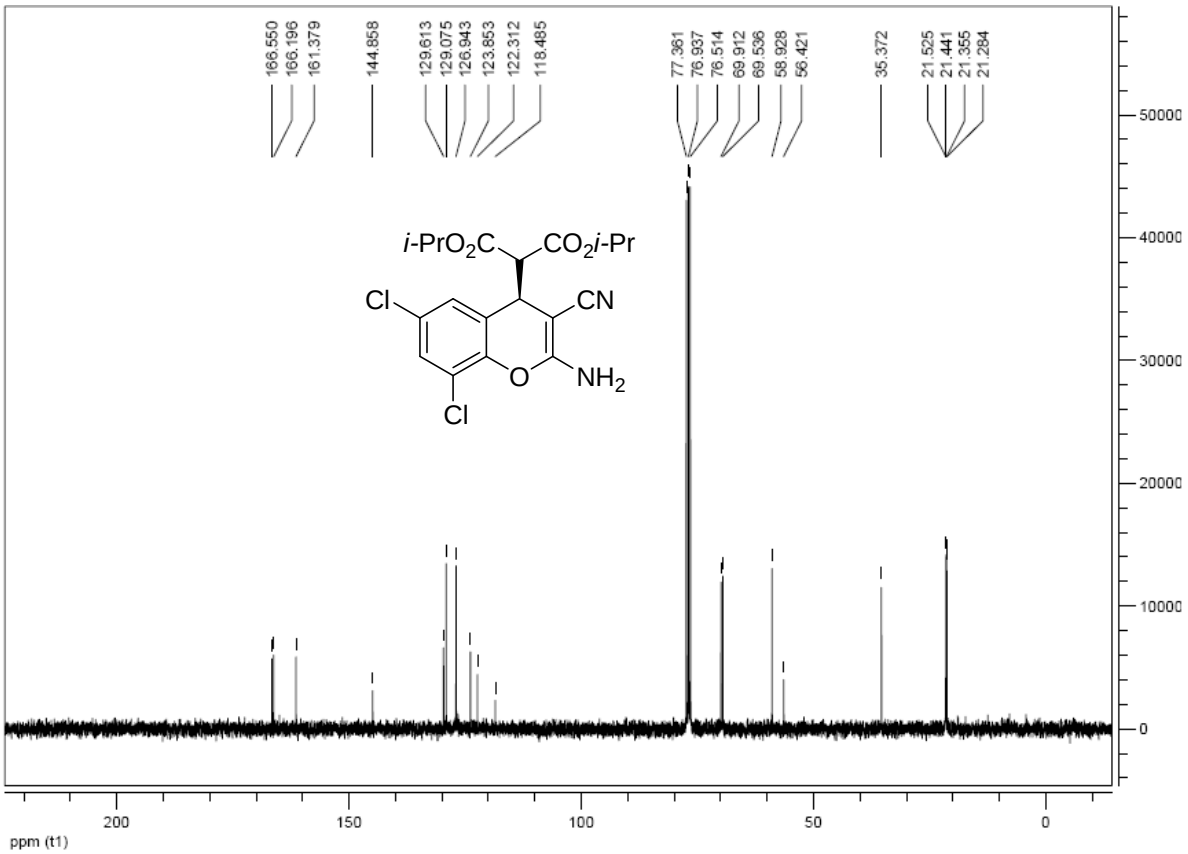


(R)-diisopropyl 2-(2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl)malonate (3nc)

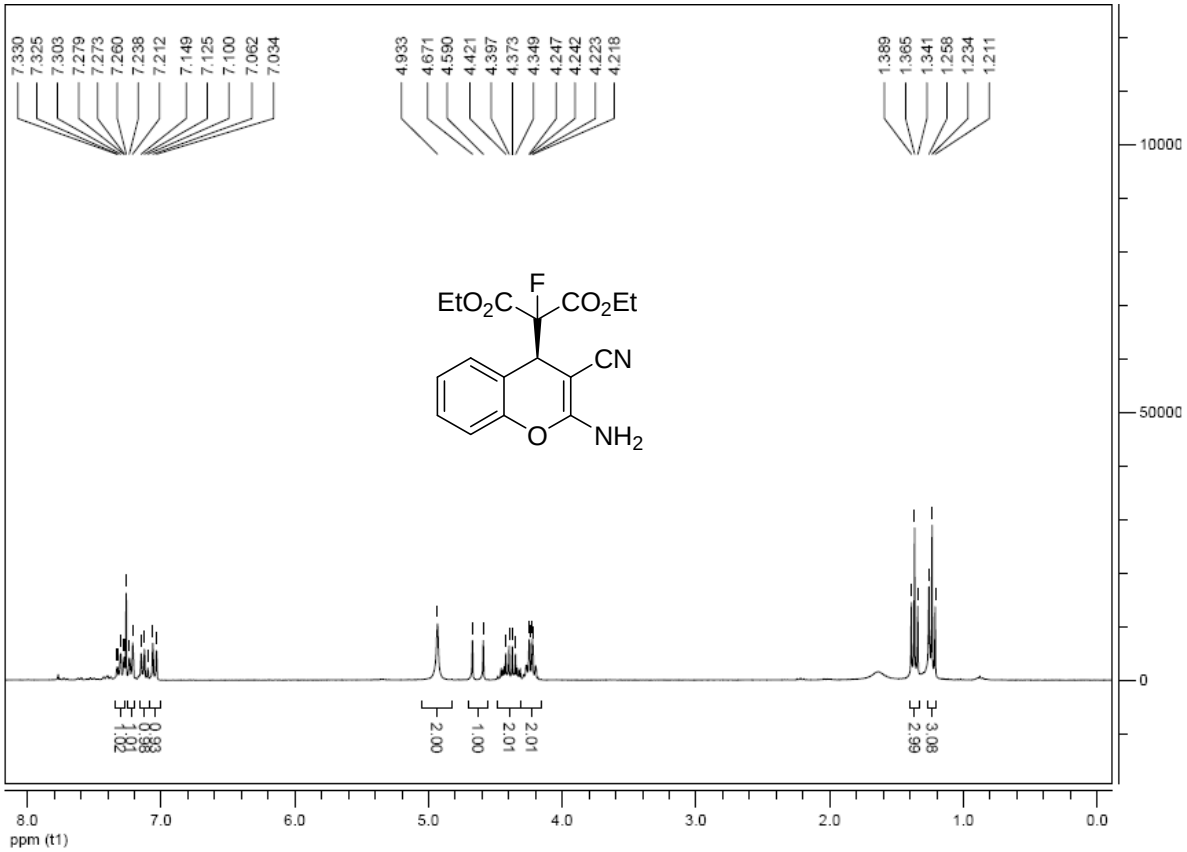


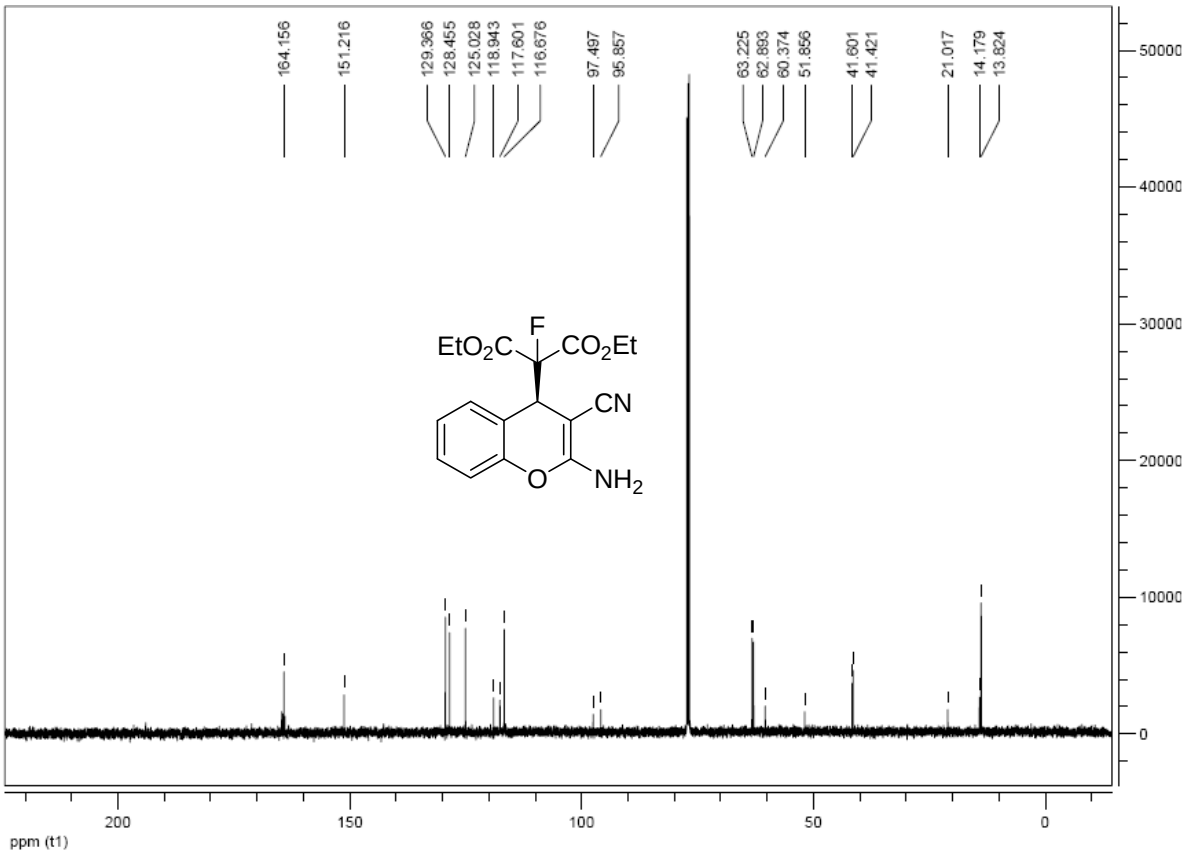
(R)-diisopropyl 2-(2-amino-6,8-dichloro-3-cyano-4H-chromen-4-yl)malonate (3oc)



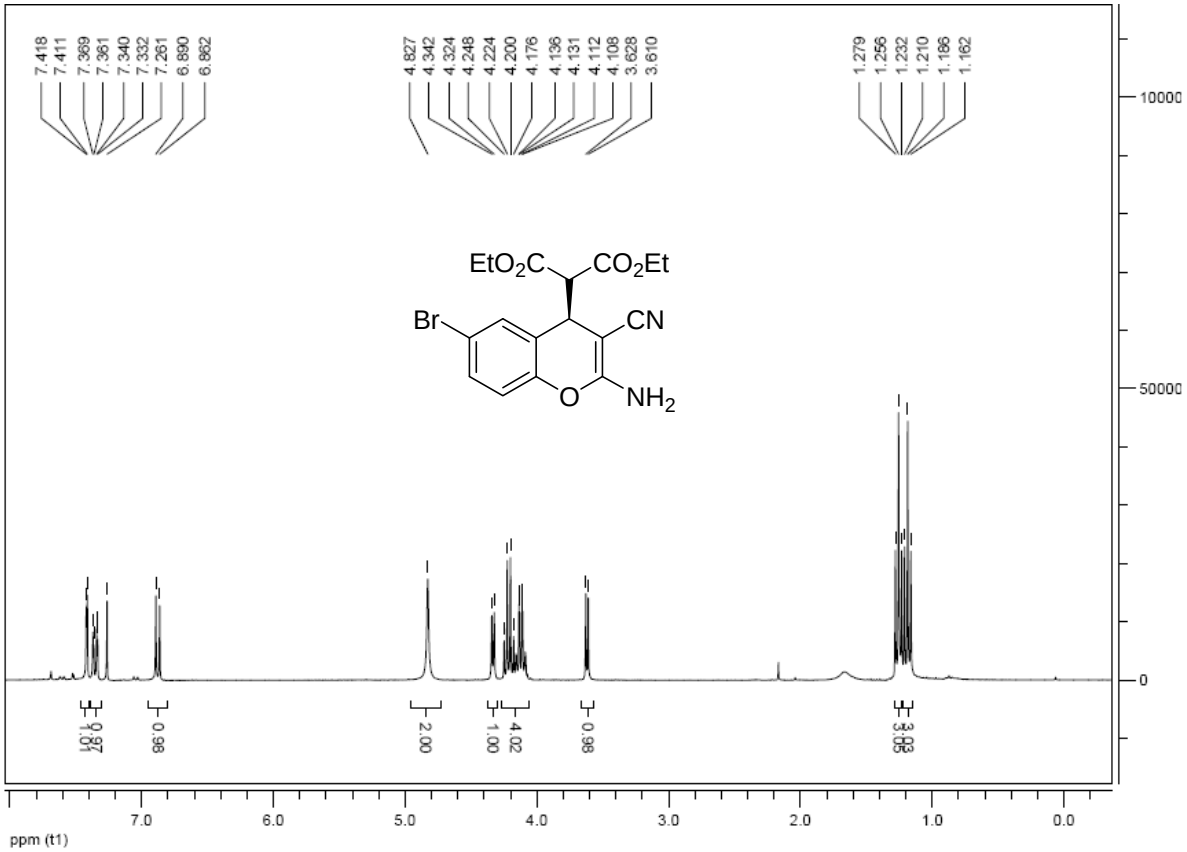


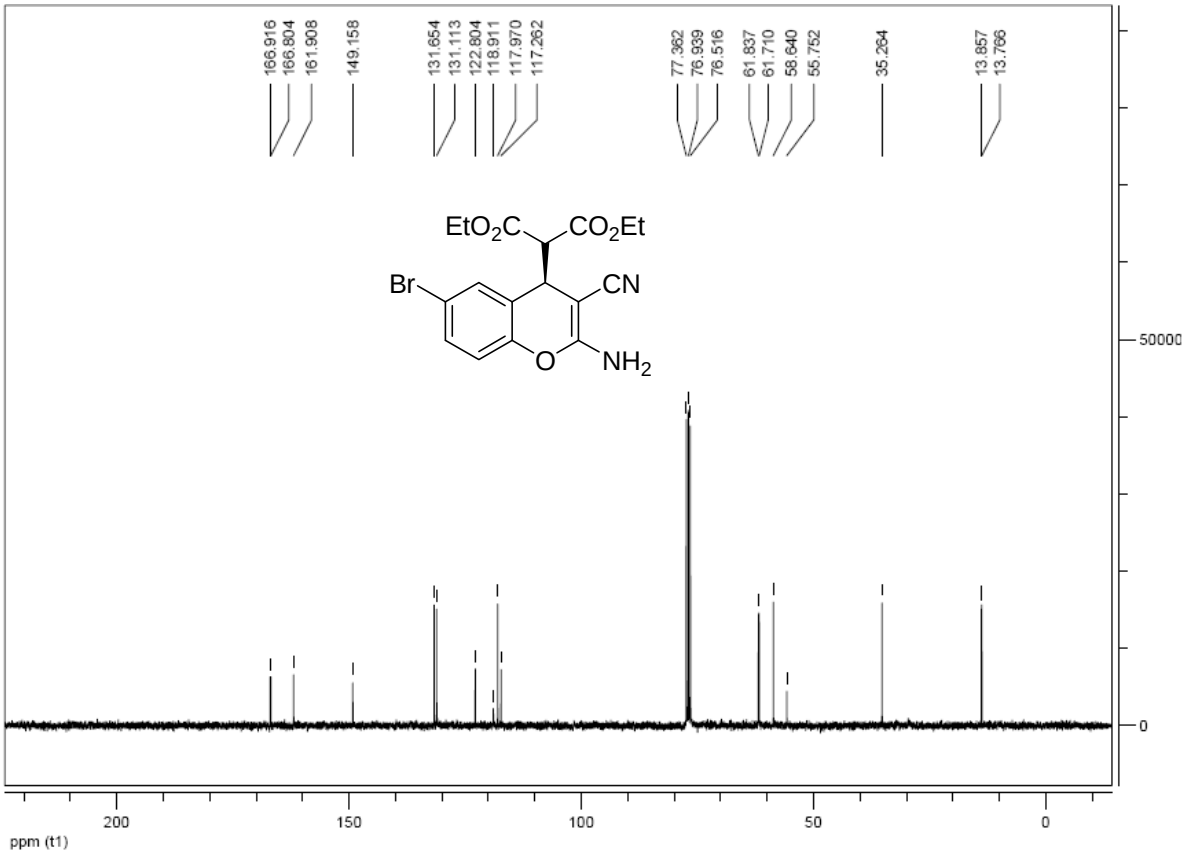
(R)-diethyl 2-(2-amino-3-cyano-4H-chromen-4-yl)-2-fluoromalonate (3df)



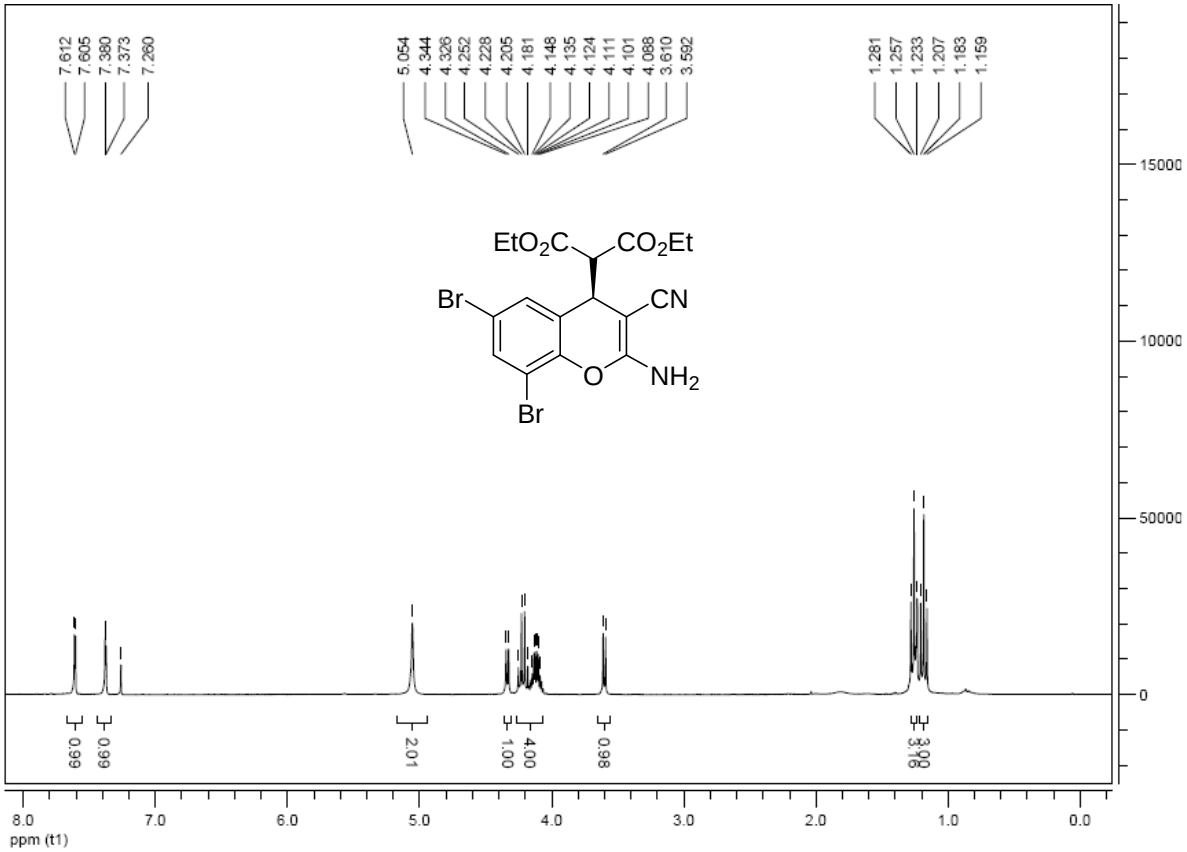


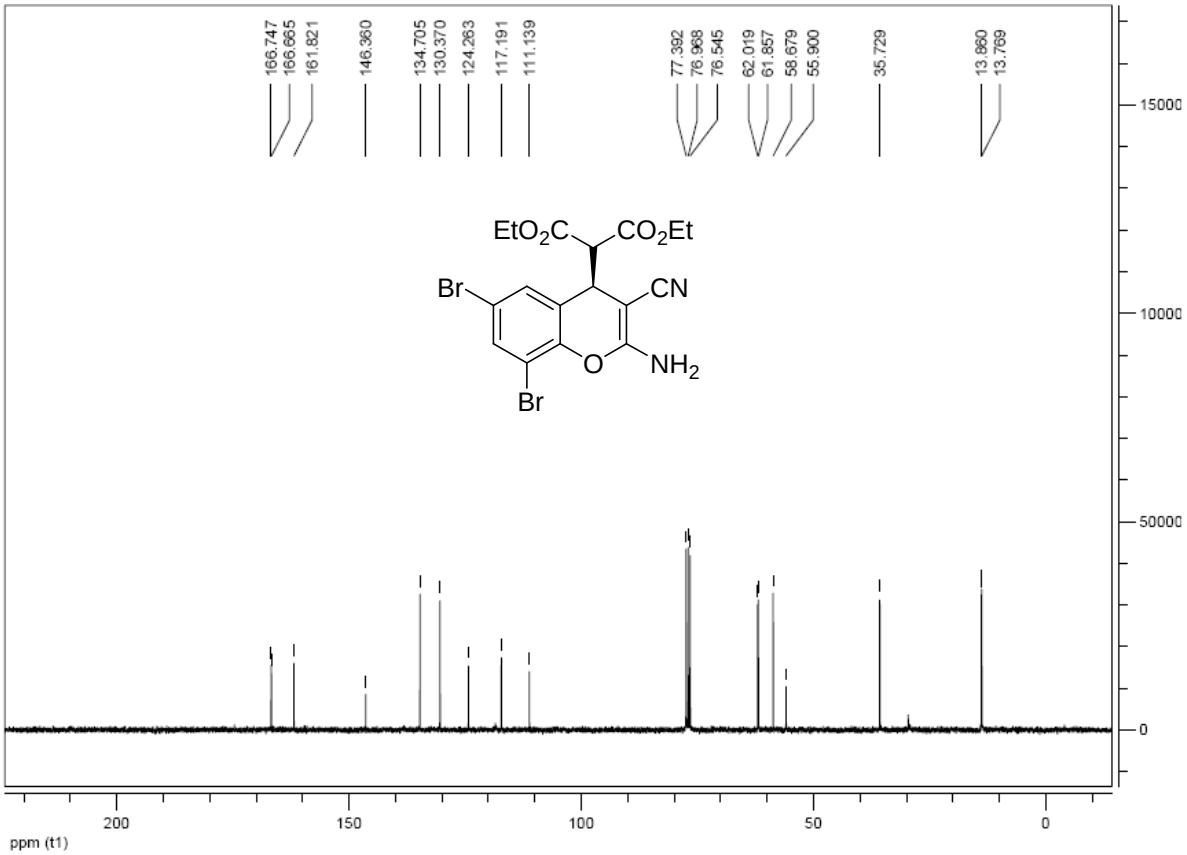
(R)-diethyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3ea)



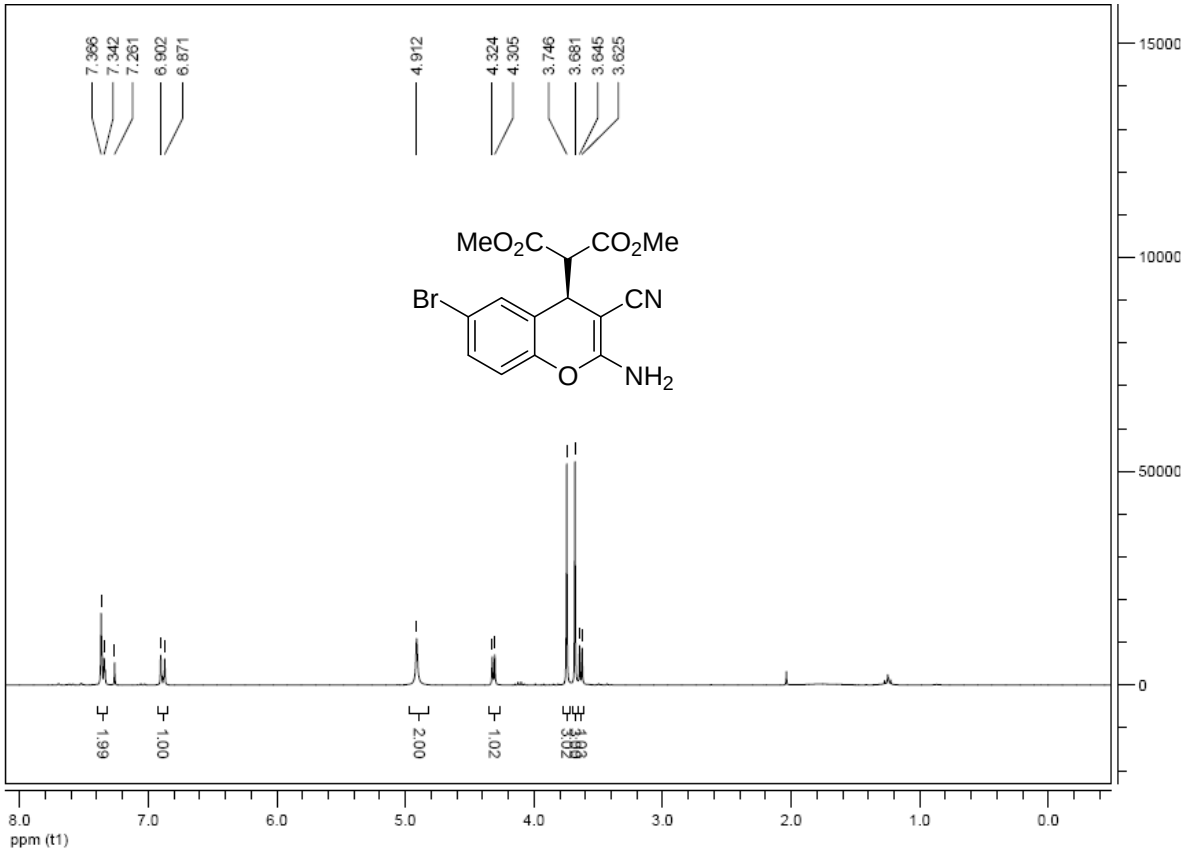


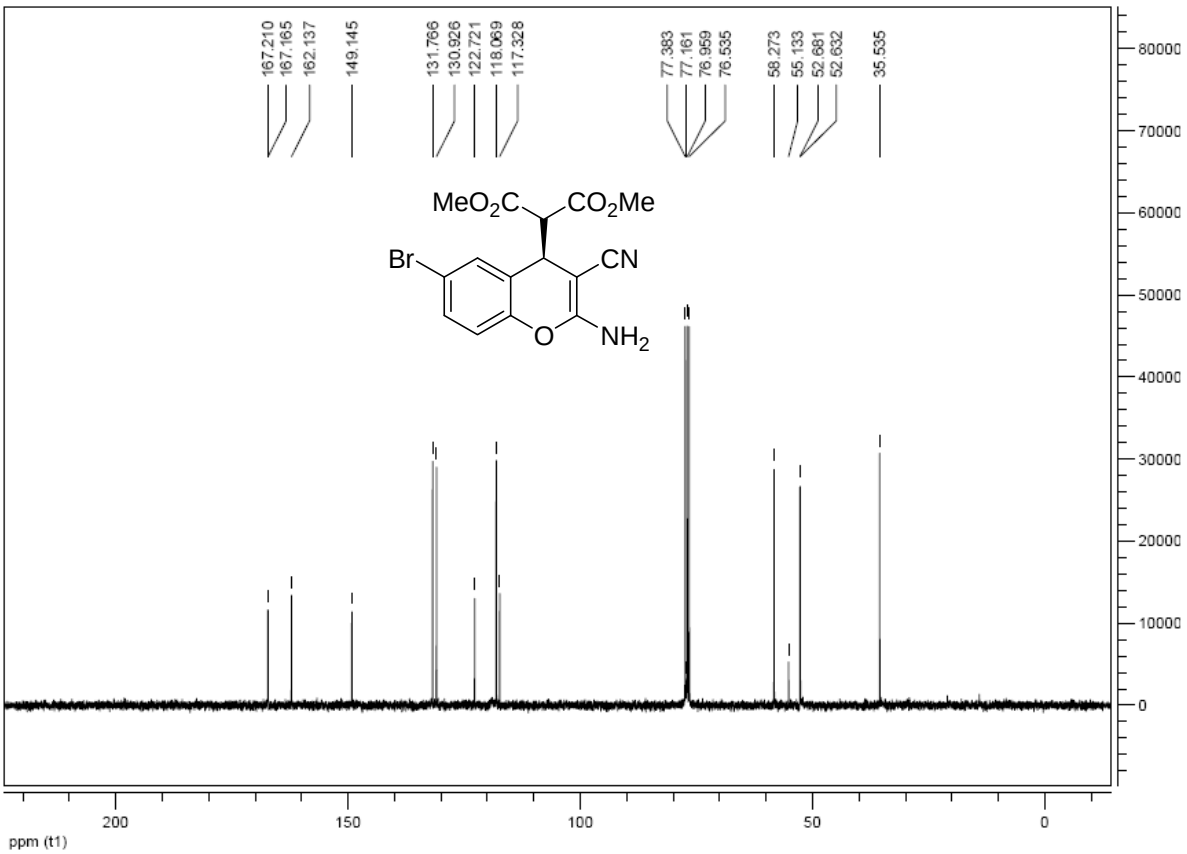
(R)-diethyl 2-(2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl)malonate (3na)





(R)-dimethyl 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)malonate (3eb)





F: References

1. (a) Sakurai, A.; Motomura, Y.; Midorikawa, H. *J. Org. Chem.* 1972, **37**, 1523-1526; (b) M. Costa, F. Areias, L. Abrunhosa, A. Venâncio, F. Proenca, *J. Org. Chem.* 2008, **73**, 1954-1962.