

Supporting Information

Catalytic Asymmetric Conjugate Addition of Coumarins to Unsaturated Ketones

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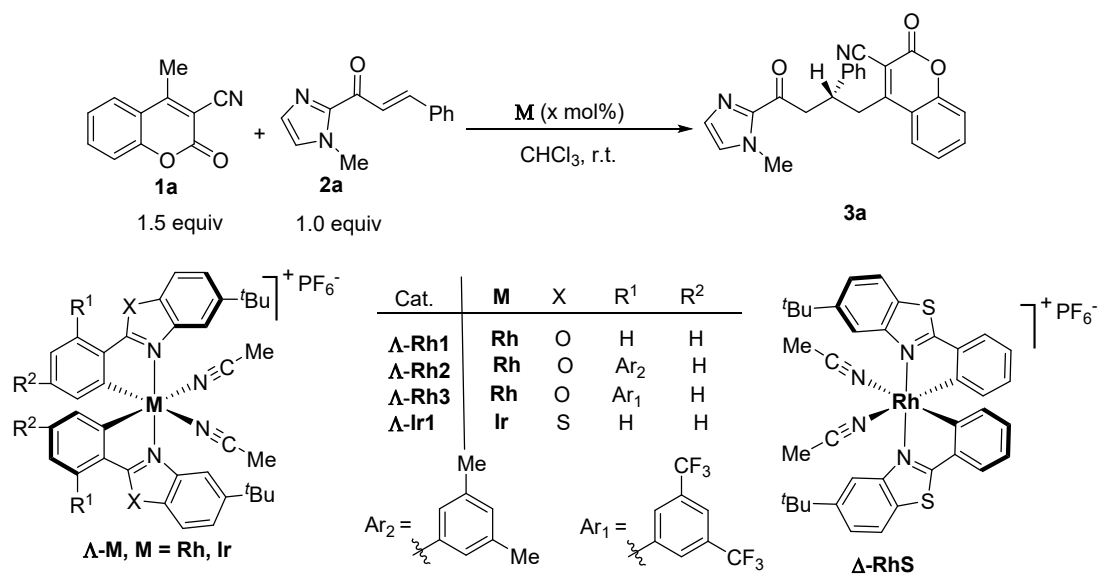
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I General Information

All reactions were performed in Schlenk tubes at room temperature using oven-dried glassware. Commercially obtained reagents were used without further purification, unless otherwise noted. THF was obtained from solvent distillation machine (Vigor VSPS-5) and stored under argon over 4 Å molecular sieves. Toluene was freshly distilled before use over sodium and benzophenone. Dichloromethane (DCM) was distilled over CaH₂. Methanol and Ethyl Alcohol were used without further purification. Reactions were monitored by TLC analysis and plates were visualized with short-wave UV light (254 nm). The ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were obtained in CDCl₃ using a Bruker-BioSpin AVANCE III HD NMR spectrometer at 400 MHz, 100 MHz and 376 MHz respectively. Chemical shifts are reported in parts per million (δ value) calibrated against the residual solvent peak. HPLC analyses of the compounds were done using chiralcel IA-IF columns and chiralcel IC, AD-H, AS-H, OJ-H and OD-H columns using hexane and isopropanol as eluent. High-resolution mass spectra were recorded on a Bruker Impact II UHR TOF LC/MS Mass Spectrometry.

II Optimization of Reaction Conditions

Table 1. Optimization of the Reaction Conditions^a



Entry	M (x mol %)	Solvent	Time (d) ^d	Yield (%) ^b	E _c (%) ^c
1	$\Delta\text{-Rh1}$ (2)	DCE	7 d	20	52
2	$\Delta\text{-Rh2}$ (2)	DCE	7 d	18	32
3	$\Delta\text{-Rh3}$ (2)	DCE	7 d	35	43
4	$\Delta\text{-Ir1}$ (2)	DCE	7 d	12	38
5	$\Delta\text{-RhS}$ (2)	DCE	7 d	70	72
6	$\Delta\text{-RhS}$ (0)	DCE	2 d	NR	/
7	$\Delta\text{-RhS}$ (2)	DCM	3 d	65	92
8	$\Delta\text{-RhS}$ (2)	MeOH	5 d	76	75
9	$\Delta\text{-RhS}$ (2)	THF	5 d	26	90
10	$\Delta\text{-RhS}$ (2)	MTBE	5 d	20	92
11	$\Delta\text{-RhS}$ (2)	Toluene	5 d	33	62
12	$\Delta\text{-RhS}$ (2)	CHCl ₃	3 d	86	98

13	Δ -RhS (1)	CHCl ₃	5 d	88	98
14 ^e	Δ -RhS (1)	CHCl ₃	7 d	85	98
15 ^f	Δ -RhS (1)	CHCl ₃	5 d	87	98

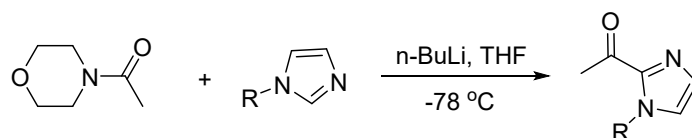
^aReaction conditions: **1a** (0.15 mmol), **2a** (0.10 mmol), Δ -Rh/ Δ -RhS/ Δ -Ir1 (1-2 mol %), solvent (0.5 mL) at room temperature under Ar atmosphere. ^bIsolated yields. ^cDetermined by chiral HPLC analysis on a chiral stationary phase. ^dd = days. ^e**1a:2a**= 1.0:1.0, **1a** (0.1 mmol), **2a** (0.1mmol). ^f**1a:2a**= 2:1, **1a** (0.2 mmol), **2a** (0.1 mmol).

III Experimental Section

Δ -Rh was prepared according to reported procedure.¹ α,β -unsaturated 2-acyl imidazoles were synthesized according to reported procedures.²⁻³ All methylcoumarins **1** were prepared according to the literature procedure.⁴

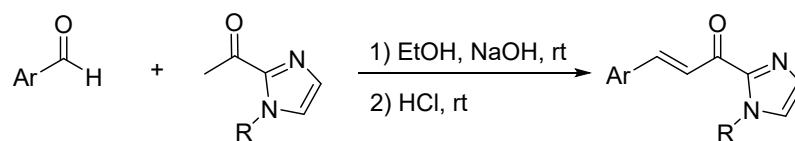
General procedures for the preparation of substrates:

General procedure A for synthesis of 2-acetyl imidazoles.²⁻³



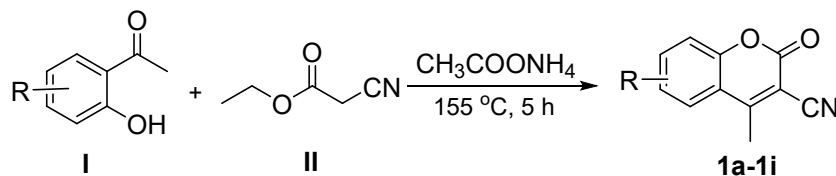
THF (60 mL) and 1-methylimidazole (4.4 mL, 55.2 mmol, 1.1 equiv) were added to a 250 mL Two-mouth round bottom flask and cooled to -78 °C. A solution of n-BuLi in hexanes (2.5 M, 34.1 mL, 85.3 mmol, 1.7 equiv) was added to the flask over 10 min. The solution was allowed to stir at -78 °C for 30 min. Then, the solution of 4-acetylmorpholine (6 mL, 50.1 mmol, 1.0 equiv) in THF(40 mL) was added to the flask over 10 min. After that, the mixture was stirred for 1 h at -78 °C. The solution was quenched with saturated NH₄Cl (20 mL) , then saturated NaHCO₃ (20 mL) were added. The mixture was transferred to a separatory funnel, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). Combined the organic phase and washed with saturated NaCl (60 mL) . Finally, the organic phase was dried over sodium sulfate, filtered and concentrated on a rotatory evaporator. The resulting residue was purified by column chromatography on silica gel (200-300 mesh, EtOAc/Petroleum ether v/v = 1:3) to afford the desired product.

General procedure B for synthesis of α,β -unsaturated 2-acyl imidazoles.²⁻³



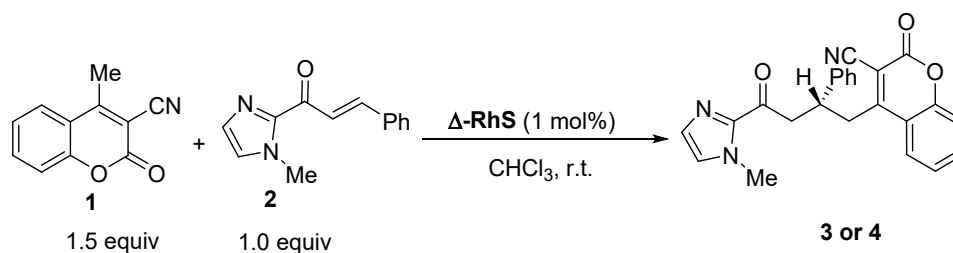
2-acetyl imidazoles (10.0 mmol, 1.0 equiv) and EtOH (20 mL) were added to a 50 mL round bottom flask followed by the desired aromatic aldehyde (10.5 mmol, 1.05 equiv) and NaOH (440 mg, 11 mmol, 1.1 equiv). The solution was stirred for 10-30 h, then dilute hydrochloric acid was added until the pH of solution was 7. The solution was transferred to a separatory funnel. H₂O (10 mL) were added and the mixture was extracted with EtOAc (3 x 50 mL). Combined the organic phase and washed with saturated NaCl (50 mL). Finally, the organic extracts were dried over sodium sulfate, filtered, and concentrated on a rotatory evaporator. The resulting residue was purified by flash column chromatography on silica gel (200-300 mesh, EtOAc/Petroleum v 77:100 ether v/v = 1:5-1:2) to afford the desired product.

General procedure C for synthesis of 3-cyano-4-methylcoumarins.⁴



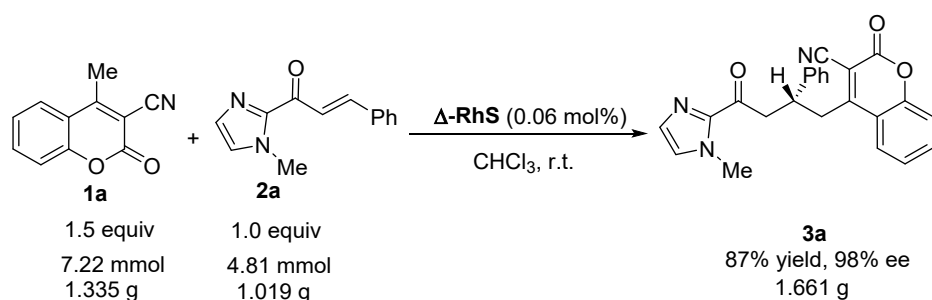
The mixture of **I** (10 mmol), **II** (15 mmol) and NH₄OAc (25 mmol) was heated to 155 °C for 5 hour. Then, the mixture was cooled to room temperature, an appropriate amount of ethanol was added, and stirred overnight. The reaction mixture was filtered and evaporated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc = 4:1) to give **1a-1i**.

General procedure for Catalytic Asymmetric Conjugate Addition of Coumarins to Unsaturated Ketones.



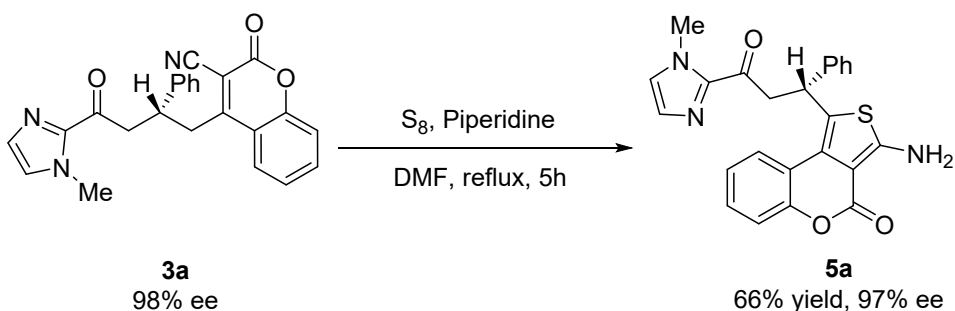
To an oven-dried 10 mL Schlenk tube equipped with a stir bar, Δ -RhS (1 mol%) was added along with 3-cyano-4-methylcoumarins **1** (1.5 equiv, 0.15 mmol) and α, β -unsaturated 2-acylimidazole **2** (1.0 equiv, 0.10 mmol) in CHCl_3 (1.0 mL). The reaction was stirring in an oil bath at room temperature until consumption of the β -unsaturated 2-acylimidazole **2** (monitored by TLC). The solution was directly purified by silica gel column chromatography to afford **3** or **4**.

General procedure for gram-scale experiments with lower catalyst loading.



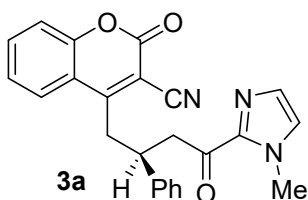
To an oven-dried 25 mL Schlenk tube equipped with a stir bar, Δ -RhS (0.06 mol%) was added along with α, β -unsaturated ketone **2a** (1.0 equiv, 4.81 mmol, 1.019 g) and 3-cyano-4-methylcoumarin **1a** (1.5 equiv, 7.22 mmol, 1.335 g) in CHCl_3 (10.0 mL). The reaction was stirring at room temperature until consumption of the **2a** (monitored by TLC). The solution was directly purified by silica gel column chromatography (EtOAc/DCM = 1:20) to afford **3a** (white solid, 1.661 g, 87% yield, 98% ee).

General Experimental Procedure for the Synthesis of Products **5a**.⁵

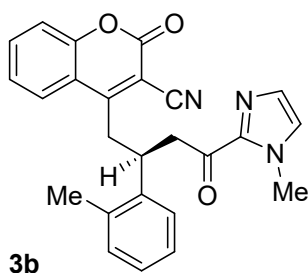


In an oven- and vacuum-dried seal tube, **3a** (39.8 mg, 0.1 mmol, 1 equiv), Sulfur (3.2 mg, 0.1 mmol, 1 equiv) and piperidine (3 μL , 0.3 mmol, 3 equiv) were taken in 150 μL of freshly distilled DMF. Next, the seal tube was purged with argon and was heated to reflux at 160 $^\circ\text{C}$ for 5 h. After cooling down to r.t., the reaction mixture was diluted with 2 mL water and 10 mL EtOAc. Subsequently the aqueous layer was extracted

with EtOAc(3 × 10 mL) and dried over Na₂SO₄. Then the solvent was removed under reduced pressure, and crude reaction mixture was purified through silica gel column chromatography (eluent: EtOAc/Petroleum ether = 1/2) to afford **5a** (white solid, 28.3 mg, 66% yield, 97% ee).

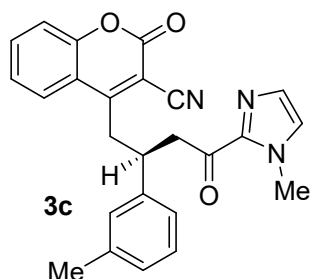


4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile (3a). White solid (35 mg, 88%). Mp: 185.5-186.8 °C. $[\alpha]_D^{25} = +256$ (c = 0.5 in CH₂Cl₂). HPLC: 98% ee (Chiralpak AD-H, hexane/ isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 18.49$ min (major), 34.34 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 7.36 (d, $J = 8$ Hz, 1H), 7.25-7.12 (m, 6H), 7.08 (s, 1H), 4.0 (s, 3H), 3.93-3.82 (m, 2H), 3.73-3.62 (m, 2H), 3.34-3.29 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.5, 164.1, 156.6, 153.4, 142.9, 142.7, 140.6, 134.9, 129.4, 128.8, 127.7, 127.7, 127.5, 126.9, 125.5, 117.7, 117.6, 113.3, 102.9, 44.9, 41.5, 43.2, 39.2, 36.2. HRMS (ESI) m/z : [M + H]⁺ calcd for C₂₄H₁₉N₃O₃H⁺, 398.1499; found, 398.1494.

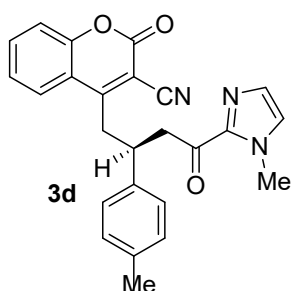


4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-(o-tolyl)butyl)-2-oxo-2H-chromene-3-carbonitrile (3b). White solid (35 mg, 85%). Mp: 145.5-156.8 °C. $[\alpha]_D^{25} = +339.4$ (c = 0.5 in CH₂Cl₂). HPLC: 97% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 14.91$ min (major), 25.48 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 81.0 (d, $J = 8$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.44-7.35 (m, 2H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.06 (s, 1H), 7.00-6.97 (m, 2H), 6.88-6.87 (m, 1H), 4.20-4.12 (m, 1H), 3.89 (s, 3H), 3.76-3.70 (m, 1H), 3.57-3.48 (m, 2H), 3.33-3.27 (m, 1H), 1.83 (s, 3H). ¹³C NMR (100 MHz,

CDCl_3 , 25 °C) δ /ppm: 190.5, 164.0, 156.6, 153.3, 142.7, 139.3, 135.3, 135.0, 130.4, 129.4, 127.4, 127.3, 127.2, 127.0, 126.7, 125.5, 117.8, 117.7, 113.4, 102.9, 45.7, 38.7, 36.2, 29.7, 19.5. **HRMS (ESI)** m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3\text{H}^+$, 412.1656; found, 412.1650.

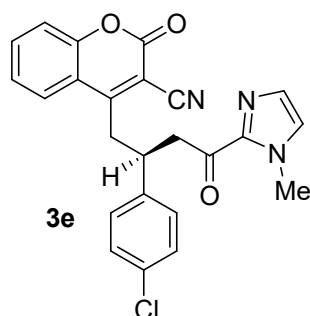


4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-(m-tolyl)butyl)-2-oxo-2H-chromene-3-carbonitrile (3c). White solid (39.9 mg, 97%). Mp: 140.5-146.8 °C. $[\alpha]_D^{25} = +368.0$ ($c = 0.5$ in CH_2Cl_2). HPLC: 96% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 15.55$ min (major), 26.95 min (minor). **^1H NMR (400 MHz, CDCl_3 , 25 °C)** δ /ppm: 81.0 (d, $J = 8$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.44-7.35 (m, 2H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.05 (s, 1H), 7.00-6.97 (m, 2H), 6.88-6.86 (m, 1H), 4.20-4.12 (m, 1H), 3.89 (s, 3H), 3.76-3.70 (m, 1H), 3.57-3.48 (m, 2H), 3.33-3.27 (m, 1H), 1.83 (s, 3H). **^{13}C NMR (100 MHz, CDCl_3 , 25 °C)** δ /ppm: 190.5, 164.0, 156.6, 153.3, 142.7, 139.3, 135.3, 135.0, 130.4, 129.4, 127.4, 127.3, 127.2, 127.0, 126.7, 125.5, 117.8, 117.7, 113.4, 102.9, 45.7, 38.7, 36.2, 19.5. **HRMS (ESI)** m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3\text{H}^+$, 412.1656; found, 416.1651.

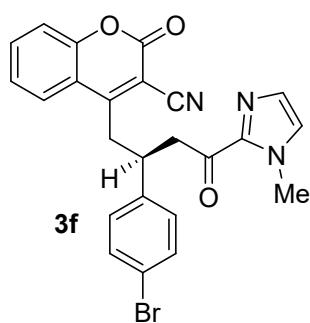


4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-(p-tolyl)butyl)-2-oxo-2H-chromene-3-carbonitrile (3d). White solid (40.7 mg, 99%). Mp: 160.5-166.8 °C. $[\alpha]_D^{25} = +328.6$ ($c = 0.5$ in CH_2Cl_2). HPLC: 96% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 19.54$ min (major), 49.64 min (minor). **^1H NMR**

(400 MHz, CDCl₃, 25 °C) δ /ppm: 81.3 (d, J = 10.0 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.07 (s, 1H), 6.98-6.90 (m, 5H), 3.91 (s, 3H), 3.82-3.70 (m, 2H), 3.59-3.50 (m, 2H), 3.23-3.18 (m, 1H), 2.18 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.6, 164.2, 156.7, 153.4, 142.8, 137.5, 137.2, 134.9, 129.5, 127.5, 127.4, 127.0, 125.5, 117.7, 117.6, 113.4, 102.9, 45.1, 41.2, 39.3, 36.2, 21.1. HRMS (ESI) m/z : [M + H]⁺ calcd for C₂₅H₂₁N₃O₃H⁺, 412.1656; found, 412.1650.

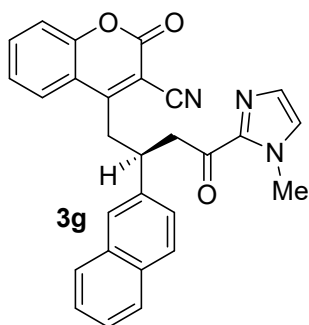


4-(2-(4-chlorophenyl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile (3e). White solid (39.7 mg, 92%). Mp: 165.5-171.8 °C. $[\alpha]_D^{25}$ = +251.6 (c = 0.5 in CH₂Cl₂). HPLC: 98% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, λ = 250 nm) t_R = 24.55 min (major), 51.96 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 81.8 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.24-7.19 (m, 3H), 7.12-7.09 (m, 3H), 4.01 (s, 3H), 3.87-3.81 (m, 2H), 3.73-3.61 (m, 2H), 3.35-3.30 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.0, 163.7, 156.5, 153.5, 142.6, 139.0, 135.0, 133.5, 129.4, 129.0, 127.5, 126.7, 125.6, 117.8, 117.4, 113.3, 103.1, 44.9, 41.0, 38.9, 36.2. HRMS (ESI) m/z : [M + H]⁺ calcd for C₂₄H₁₈ClN₃O₃ H⁺, 432.1110; found 432.1101 and 434.1066.

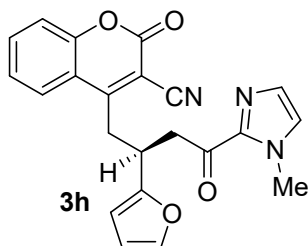


4-(2-(4-bromophenyl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile (3f). White solid (47.1 mg, 99%). Mp: 180.3-186.5 °C.

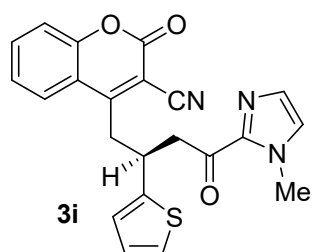
$[\alpha]_D^{25} = +397.2$ ($c = 0.5$ in CH_2Cl_2). HPLC: 97% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 30.91$ min (major), 65.56 min (minor). $^1\text{H NMR}$ (400 MHz, CDCl_3 , 25 °C) δ /ppm: 8.10 (d, $J = 4.4$ Hz, 1H), 7.65-7.61 (m, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 7.30-7.29 (m, 3H), 7.07-6.94 (m, 4H), 3.91 (s, 3H), 3.76-3.71 (m, 2H), 3.61-3.51 (m, 2H), 3.54-3.19 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , 25 °C) δ /ppm: 190.0, 163.7, 156.5, 153.4, 142.6, 139.7, 135.1, 131.9, 129.5, 129.4, 127.6, 126.8, 125.6, 117.8, 117.4, 113.3, 103.0, 44.8, 41.0, 38.8, 36.2. **HRMS (ESI) m/z :** $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{18}\text{BrN}_3\text{O}_3 \text{H}^+$, 476.0604; found 476.0596 and 478.0578.



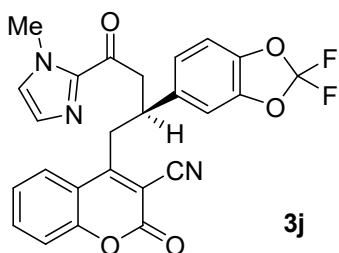
4-(4-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile (3g). White solid (38.9 mg, 87%). Mp: 185.2-195.4 °C. $[\alpha]_D^{25} = +350.0$ ($c = 0.5$ in CH_2Cl_2). HPLC: 98% ee (Chiralpak OD-H, hexane/isopropanol = 70:30, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 10.13$ min (major), 12.69 min (minor). $^1\text{H NMR}$ (400 MHz, CDCl_3 , 25 °C) δ /ppm: $^1\text{H NMR}$ (400 MHz, CDCl_3 , 25 °C) δ /ppm: 8.14 (d, $J = 4.4$ Hz, 1H), 7.69-7.61 (m, 1H), 7.58-7.54 (m, 1H), 7.45-7.34 (m, 1H), 7.24-7.20 (m, 1H), 7.16-7.14 (m, 1H), 7.06-7.03 (m, 1H), 6.95 (s, 3H), 4.80 (s, 1H), 4.00-3.93 (m, 2H), 3.86 (s, 3H), 3.69-3.65 (m, 2H), 3.38-3.27 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , 25 °C) δ /ppm: 190.5, 163.8, 156.4, 153.2, 142.7, 137.4, 134.9, 131.3, 129.5, 129.1, 128.0, 127.5, 126.6, 125.9, 125.8, 125.5, 125.5, 125.2, 121.8, 117.9, 117.5, 113.3, 102.8, 54.9, 45.6, 39.4, 36.2, 34.3. **HRMS (ESI) m/z :** $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_3 \text{H}^+$, 448.1656; found, 448.1649.



4-(2-(furan-2-yl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile (3h). White solid (31.0 mg, 80%). Mp: 175.2-183.5 °C. $[\alpha]_D^{25} = +173.4$ (c = 0.5 in CH₂Cl₂). HPLC: 99% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 43.8$ min (major), 72.77 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.02 (d, $J = 8.0$ Hz, 1H), 7.63-7.59 (m, 1H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.30-7.28 (m, 1H), 7.22-7.20 (m, 1H), 7.09-7.01 (m, 2H), 6.12-6.11 (m, 1H), 5.88 (d, $J = 3.2$ Hz, 1H), 3.94 (s, 3H), 3.86-3.82 (m, 1H), 3.78-3.60 (m, 2H), 3.48-3.44 (m, 1H), 3.32-3.27 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 189.9, 163.7, 156.7, 153.5, 153.4, 142.6, 142.1, 134.9, 129.5, 127.5, 126.6, 125.5, 117.6, 117.6, 112.8, 110.4, 107.0, 103.0, 42.9, 37.0, 36.2, 35.0. HRMS (ESI) m/z : [M + H]⁺ calcd for C₂₂H₁₇N₃O₄H⁺, 388.1292; found, 388.1287.

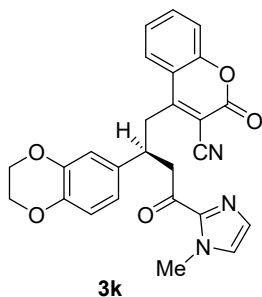


4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-(thiophen-2-yl)butyl)-2-oxo-2H-chromene-3-carbonitrile (3i). White solid (35.1 mg, 87%). Mp: 185.2-195.4 °C. $[\alpha]_D^{25} = +168.5$ (c = 0.5 in CH₂Cl₂). HPLC: 96% ee (Chiralpak OD-H, hexane/isopropanol = 90:10, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 35.19$ min (major), 40.09 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.06 (d, $J = 8.0$ Hz, 1H), 7.64-7.60 (m, 1H), 7.40-7.37 (m, 1H), 7.31-7.29 (m, 1H), 7.10-7.01 (m, 1H), 6.80-6.72 (m, 2H), 4.12-4.05 (m, 1H), 3.94 (s, 3H), 3.86-3.80 (m, 1H), 3.71-3.65 (m, 1H), 3.58-3.54 (m, 1H), 3.27-3.21 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 189.8, 163.5, 156.6, 153.4, 143.6, 142.6, 134.9, 129.6, 127.6, 127.1, 126.7, 125.6, 117.7, 117.5, 113.1, 103.2, 45.9, 39.9, 36.6, 36.2. HRMS(ESI) m/z : [M + H]⁺ calcd for C₂₂H₁₇N₃O₃SH⁺, 404.1063; found, 404.1057.



3j

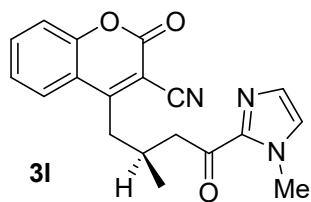
4-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile(3j). White solid (30.1 mg, 63%). Mp: 95.5-105.5 °C. $[\alpha]_D^{25} = +313.2$ (c = 0.5 in CH₂Cl₂). HPLC: 98% ee (Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 16.99$ min (major), 29.97 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.08 (d, $J = 8.4$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.31-7.29 (m, 1H), 7.08-7.00 (m, 1H), 6.85-6.78 (m, 3H), 3.91 (s, 3H), 3.81-3.68 (m, 2H), 3.62-3.51 (m, 2H), 3.26-3.20 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 189.8, 163.5, 156.5, 153.5, 143.9, 143.0, 142.6, 136.9, 135.2, 134.1, 131.6 (t, $J_{C-F} = 253.9$ Hz), 129.6, 129.0, 127.6, 126.6, 125.6, 123.0, 117.9, 117.4, 113.4, 109.6, 109.0, 103.1, 45.0, 41.4, 39.0, 36.2, 29.7. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C) δ /ppm: -49.86. HRMS (ESI) m/z : $[M + H]^+$ calcd for C₂₅H₁₇F₂N₃O₅ H⁺, 478.1210; found, 478.1201.



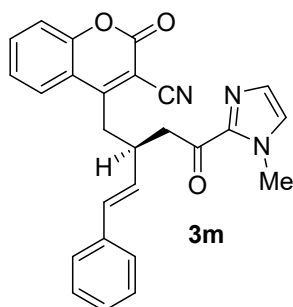
3k

5-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile(3k). White solid (38.2 mg, 84%). Mp: 198.2-202.5 °C. $[\alpha]_D^{25} = +118.7$ (c = 0.5 in CH₂Cl₂). HPLC: 96% ee (Chiralpak OJ-H, hexane/isopropanol = 70:30, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 57.91$ min (major), 47.09 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.19 (d, $J = 8.0$ Hz, 1H), 7.72-7.68 (m, 1H), 7.50-7.46 (m, 1H), 7.39-7.37 (m, 1H), 7.17-7.08 (m, 1H), 6.74-6.59 (m, 2H), 4.21 (s, 4H), 4.02 (s, 3H), 3.87-3.71 (m, 2H), 3.66-3.56 (m, 2H), 3.31-3.25 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.5, 164.1, 156.8, 153.4, 143.5, 142.9, 142.7, 134.8, 133.8, 129.4, 127.4, 126.9, 125.4, 120.5, 117.7, 117.6, 117.5, 116.5, 113.3, 103.0, 64.3, 45.2, 40.9, 39.3, 36.2. HRMS (ESI)

m/z : $[M + H]^+$ calcd for $C_{26}H_{21}N_3O_3H^+$, 456.1554; found, 456.1548.

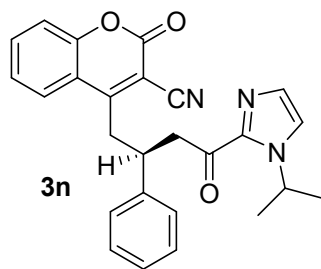


4-(2-methyl-4-(1-methyl-1H-imidazol-2-yl)-4-oxobutyl)-2-oxo-2H-chromene-3-carbonitrile (3l). White solid (25.1 mg, 75%). Mp: 143.4-149.8 °C. $[\alpha]_D^{25} = +186.2$ ($c = 0.5$ in CH_2Cl_2). HPLC: 98% ee (Chiralpak AD-H, hexane/isopropanol = 70:30, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 19.18$ min (major), 44.32 min (minor). 1H NMR (400 MHz, $CDCl_3$, 25 °C) δ /ppm: 8.21 (d, $J = 8.0$ Hz, 1H), 7.72-7.69 (m, 1H), 7.49-7.38 (m, 2H), 7.15-7.09 (m, 1H), 4.04 (s, 3H), 3.45-3.38 (m, 2H), 3.30-3.24 (m, 1H), 2.96-2.90 (m, 1H) 2.75-2.70 (m, 1H), 1.1 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ /ppm: 190.5, 164.1, 156.8, 153.4, 143.5, 142.9, 142.7, 134.8, 133.8, 129.4, 127.4, 126.9, 125.4, 120.5, 117.7, 117.6, 117.5, 116.5, 113.3, 103.0, 64.3, 45.2, 40.9, 39.3, 36.2. HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{19}H_{17}N_3O_3H^+$, 336.1343; found, 336.1337.

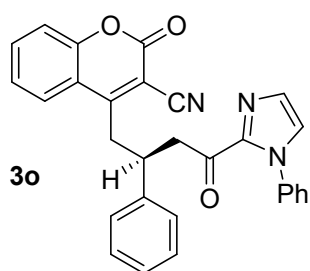


(E)-4-(2-(2-(1-methyl-1H-imidazol-2-yl)-2-oxoethyl)-4-phenylbut-3-en-1-yl)-2-oxo-2H-chromene-3-carbonitrile(3m). White solid (25.4 mg, 67%). Mp: 161.0-168.0 °C. $[\alpha]_D^{25} = +450.7$ ($c = 0.5$ in CH_2Cl_2). HPLC: 90% ee (Chiralpak AD-H, hexane/ isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 42.71$ min (major), 57.24 min (minor). 1H NMR (400 MHz, $CDCl_3$, 25 °C) δ /ppm: 1H NMR (400 MHz, $CDCl_3$, 25 °C) δ /ppm: 8.24 (d, $J = 8.0$ Hz, 1H), 7.71 (t, $J = 8.8$ Hz, 1H), 7.53-7.49 (m, 1H), 7.39-7.37 (m, 1H), 7.29-7.19 (m, 6H), 7.09 (s, 4H), 6.26-6.20 (m, 2H), 4.04 (s, 3H), 3.65-3.49 (m, 3H), 3.41 (s, 1H), 3.21-3.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ /ppm: 190.5, 164.3, 156.7, 153.6, 142.8, 136.2, 135.0, 132.3, 129.4, 129.3, 127.7, 127.5, 126.8, 126.4, 125.6, 117.8, 117.7, 113.8, 103.1, 44.6, 40.5, 37.4, 36.2. HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{26}H_{21}N_3O_3H^+$, 424.1656; found,

424.1650.

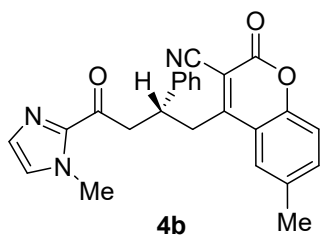


4-(4-(1-isopropyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(3n). White solid (42.1 mg, 99%). Mp: 155.0-160.0 °C. $[\alpha]_D^{25} = +283.7$ ($c = 0.5$ in CH_2Cl_2). HPLC: 96% ee (Chiralpak OD-H, hexane/isopropanol = 80:20, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 8.77$ min (major), 11.05 min (minor). $^1\text{H NMR}$ (400 MHz, CDCl_3 , 25 °C) δ/ppm : 8.20 (d, $J = 8.0$ Hz, 1H), 7.70 (t, $J = 4.0$ Hz, 1H), 7.49 (t, $J = 4.0$ Hz, 1H), 7.37-7.35 (m, 1H), 7.30-7.29 (m, 1H), 7.25-7.12 (m, 6H), 5.56-5.46 (m, 1H), 3.96-3.84 (m, 2H), 3.73-3.62 (m, 2H), 3.36-3.30 (m, 1H), 1.43 (q, $J = 6.8$ Hz, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , 25 °C) δ/ppm : 190.6, 164.1, 156.6, 153.4, 142.0, 140.6, 134.8, 129.9, 128.8, 127.7, 127.6, 126.9, 125.5, 117.7, 117.6, 113.3, 103.0, 49.3, 45.5, 41.7, 39.2, 23.6. **HRMS (ESI)** m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_3\text{H}^+$, 426.1812; found, 426.1805.

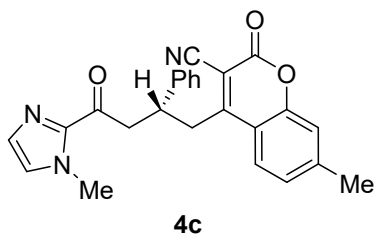


2-oxo-4-(4-oxo-2-phenylbutyl)-2H-chromene-3-carbonitrile(3o). White solid (45.5 mg, 99%). Mp: 111.0-118.0 °C. $[\alpha]_D^{25} = +303.6$ ($c = 0.5$ in CH_2Cl_2). HPLC: 90% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 26.57$ min (major), 45.36 min (minor). $^1\text{H NMR}$ (400 MHz, CDCl_3 , 25 °C) δ/ppm : 7.92 (d, $J = 8.0$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.37-7.35 (m, 3H), 7.31-7.20 (m, 3H), 7.10-7.02 (m, 8H), 3.80-3.64 (m, 3H), 3.51-3.47 (m, 1H), 3.26-3.20 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , 25 °C) δ/ppm : 189.0, 164.0, 156.6, 153.4, 142.7, 140.6, 138.1, 129.9, 129.1, 128.9, 128.8, 127.7, 127.7, 127.5, 126.8, 125.8, 125.5, 117.7, 117.5, 113.4, 103.0, 45.1, 41.5, 39.2. **HRMS (ESI)**

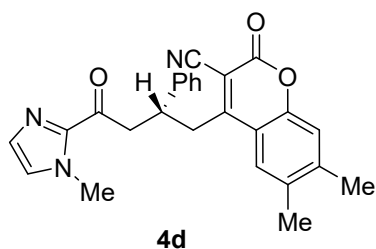
m/z : $[M + H]^+$ calcd for $C_{29}H_{21}N_3O_3H^+$, 460.1656; found, 460.1649.



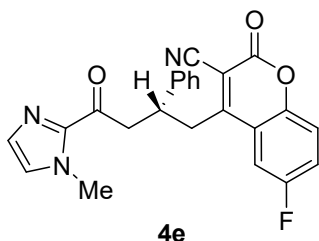
6-methyl-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4b). White solid (31.2 mg, 76%). Mp: 141.0-148.0 °C. $[\alpha]_D^{25} = +388.4$ ($c = 0.5$ in CH_2Cl_2). HPLC: 97% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 16.67$ min (major), 30.53 min (minor). 1H NMR (400 MHz, $CDCl_3$, 25 °C) δ /ppm: 7.80 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.19-7.10 (m, 6H), 7.07-7.05 (m, 1H), 6.98 (s, 1H), 3.92 (s, 3H), 3.86-3.73 (m, 2H), 3.64-3.59 (m, 1H), 3.52-3.48 (m, 1H), 3.26-3.20 (m, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ /ppm: 190.5, 164.0, 156.9, 151.6, 142.8, 140.8, 135.9, 135.2, 129.4, 128.8, 128.4, 127.7, 127.4, 126.8, 126.6, 117.3, 117.3, 113.4, 102.8, 44.9, 41.6, 39.2, 36.2, 21.0. HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{25}H_{21}N_3O_3H^+$, 412.1656; found, 412.1648.



6-methyl-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4c). White solid (32.1 mg, 78%). Mp: 155.0-158.0 °C. $[\alpha]_D^{25} = +138.7$ ($c = 0.5$ in CH_2Cl_2). HPLC: 98% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 16.94$ min (major), 29.58 min (minor). 1H NMR (400 MHz, $CDCl_3$, 25 °C) δ /ppm: 7.95 (d, $J = 8.0$ Hz, 1H), 7.20-7.11 (m, 6H), 7.08-7.05 (m, 2H), 6.98 (s, 1H), 3.91 (s, 3H), 3.81-3.72 (m, 2H), 3.63-3.49 (m, 2H), 3.25-3.19 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ /ppm: 190.5, 164.0, 157.0, 153.6, 142.7, 140.6, 129.4, 128.8, 127.6, 127.3, 126.8, 126.5, 117.8, 115.3, 113.5, 101.7, 44.9, 41.6, 39.1, 36.2, 22.0. HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{25}H_{21}N_3O_3H^+$, 412.1656; found, 412.1650.

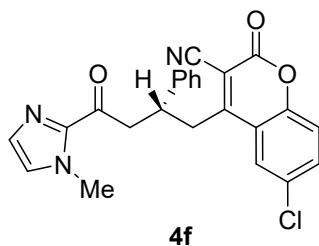


6,7-dimethyl-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile (4d). White solid (23.4 mg, 55%). Mp: 175.0-178.0 °C. $[\alpha]_D^{25} = +178.7$ (c = 0.5 in CH₂Cl₂). HPLC: 82% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 14.21$ min (major), 22.35 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 7.75 (s, 1H), 7.19-7.11 (m, 5H), 7.07-7.04 (m, 2H), 6.98 (s, 1H), 3.92 (s, 3H), 3.85-3.77 (m, 2H), 3.69-3.45 (m, 2H), 3.24-3.14 (m, 1H), 2.31 (s, 6H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.5, 164.0, 157.2, 151.9, 146.0, 142.8, 140.8, 134.5, 129.4, 128.7, 127.7, 127.6, 127.4, 126.8, 118.0, 115.3, 113.6, 101.4, 44.9, 41.6, 39.2, 36.2, 20.6, 19.5. **HRMS (ESI) m/z :** [M + H]⁺ calcd for C₂₆H₂₃N₃O₃H⁺H⁺, 426.1812; found, 426.1805.

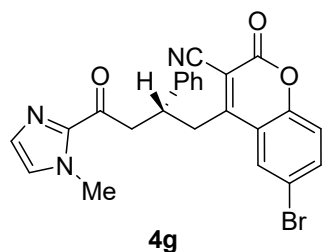


6-fluoro-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4e). White solid (34.0 mg, 82%). Mp: 158.0-167.0 °C. $[\alpha]_D^{25} = +196.8$ (c = 0.5 in CH₂Cl₂). HPLC: 94% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 21.53$ min (major), 41.02 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.14 (d, $J = 0.8$ Hz, 1H), 7.55-7.53 (m, 1H), 7.24-7.13 (m, 4H), 7.10 (s, 1H), 7.05-7.00 (m, 1H), 3.95 (s, 3H), 3.87-3.80 (m, 1H), 3.75-3.68 (m, 1H), 3.62-3.48 (m, 2H), 3.24-3.18 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.2, 163.1 (d, $J_{C-F} = 2.9$ Hz), 159.2 (d, $J_{C-F} = 244.7$ Hz), 156.2, 149.6 (d, $J_{C-F} = 1.9$ Hz), 142.7, 140.2, 129.5, 128.9, 127.9, 127.7, 127.5, 122.7 (d, $J_{C-F} = 24.6$ Hz), 119.3 (d, $J_{C-F} = 8.3$ Hz), 118.5 (d, $J_{C-F} = 8.9$ Hz), 112.9, 112.7, (d, $J_{C-F} = 25.4$ Hz), 104.0, 45.0, 41.4, 39.3, 36.2. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C) δ /ppm: -114.39. **HRMS (ESI) m/z :** [M + H]⁺ calcd for

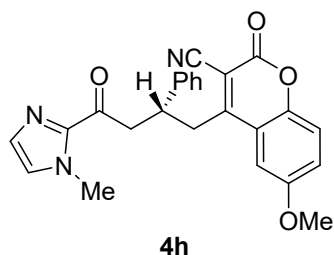
C₂₄H₁₈FN₃O₃H⁺, 416.1405; found, 416.1397.



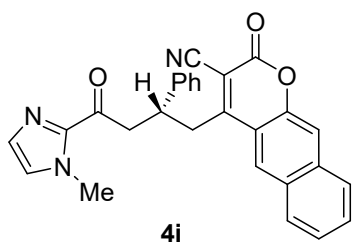
6-chloro-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4f). White solid (37.2 mg, 86%). Mp: 175.0-179.0 °C. $[\alpha]_D^{25} = +166.0$ (c = 0.5 in CH₂Cl₂). HPLC: 96% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 21.33$ min (major), 41.70 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.14 (d, $J = 0.8$ Hz, 1H), 7.55-7.53 (m, 1H), 7.24-7.13 (m, 4H), 7.10 (s, 1H), 7.05-7.00 (m, 3H), 3.95 (s, 3H), 3.87-3.80 (m, 1H), 3.75-3.68 (m, 1H), 3.62-3.48 (m, 2H), 3.24-3.18 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.5, 163.0, 156.0, 151.7, 142.7, 140.3, 134.7, 131.1, 129.5, 129.0, 127.9, 127.7, 127.5, 126.5, 119.0, 118.6, 112.8, 103.9, 44.9, 41.6, 39.2, 36.2. HRMS (ESI) m/z : [M + H]⁺ calcd for C₂₄H₁₈ClN₃O₃H⁺, 432.1110; found 432.1109 and 434.1063.



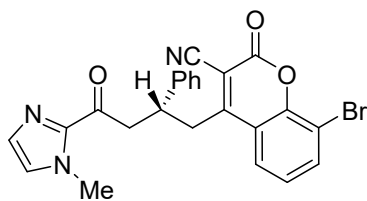
6-bromo-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4g). White solid (46.2 mg, 97%). Mp: 165.0-169.0 °C. $[\alpha]_D^{25} = +277.4$ (c = 0.5 in CH₂Cl₂). HPLC: 94% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 22.05$ min (major), 42.81 min (minor). ¹H NMR (400 MHz, CDCl₃, 25 °C) δ /ppm: 8.27 (d, $J = 1.6$ Hz, 1H), 7.68-7.65 (m, 1H), 7.20-7.10 (m, 5H), 7.05-7.00 (m, 3H), 3.95 (s, 3H), 3.86-3.80 (m, 1H), 3.72-3.67 (m, 1H), 3.61-3.56 (m, 2H), 3.22-3.16 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ /ppm: 190.5, 163.0, 155.9, 152.2, 142.7, 140.3, 137.5, 129.5, 129.5, 128.9, 127.9, 127.7, 127.5, 119.3, 119.0, 118.4, 112.8, 103.8, 44.9, 41.6, 39.2, 36.2. HRMS (ESI) m/z : [M + H]⁺ calcd for C₂₄H₁₈BrN₃O₃H⁺, 476.0604; found 476.0599 and 478.0576.



6-methoxy-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4h). White solid (26.0 mg, 61%). Mp: 173.0-178.0 °C. $[\alpha]_D^{25} = +154.8$ (c = 0.5 in CH₂Cl₂). HPLC: 99% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 18.97$ min (major), 31.19 min (minor). **¹H NMR (400 MHz, CDCl₃, 25 °C)** δ /ppm: 7.73 (m, 1H), 7.23-7.14 (m, 6H), 7.05-7.01 (m, 3H), 3.98 (s, 3H), 3.95-3.90 (m, 4H), 3.81-3.74 (m, 1H), 3.58-3.51 (m, 2H), 3.23-3.14 (m, 1H). **¹³C NMR (100 MHz, CDCl₃, 25 °C)** δ /ppm: 190.9, 163.6, 156.9, 148.0, 142.7, 140.4, 129.5, 128.9, 127.8, 127.8, 127.4, 123.6, 118.7, 117.9, 113.3, 108.2, 103.1, 56.3, 45.1, 41.2, 39.4, 36.2, 1.0. **HRMS (ESI) m/z :** [M + H]⁺ calcd for C₂₅H₂₁N₃O₄H⁺, 428.1605; found, 428.1600.

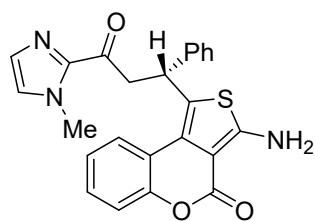


3-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-benzo[g]chromene-3-carbonitrile (4i). White solid (18.5 mg, 41%). Mp: 185.0-191.0 °C. $[\alpha]_D^{25} = -70.0$ (c = 0.5 in CH₂Cl₂). HPLC: 93% ee (Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 28.97$ min (major), 40.08 min (minor). **¹H NMR (400 MHz, CDCl₃, 25 °C)** δ /ppm: 8.63 (d, $J = 8.8$ Hz, 1H), 8.03 (d, $J = 8.8$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.71 (t, $J = 7.2$ Hz, 1H), 7.61-7.57 (m, 1H), 7.33-7.30 (m, 1H), 7.05-7.04 (m, 4H), 6.92-6.84 (m, 3H), 4.21-4.16 (m, 1H), 3.88-3.74 (m, 5H), 3.64-3.62 (m, 2H). **¹³C NMR (100 MHz, CDCl₃, 25 °C)** δ /ppm: 190.1, 176.2, 173.7, 169.7, 164.7, 156.6, 155.2, 143.9, 140.9, 137.3, 131.4, 130.1, 129.4, 129.4, 129.3, 127.4, 127.3, 127.2, 126.6, 125.3, 117.4, 112.9, 45.0, 43.3, 40.1, 36.1, 23.6. **HRMS (ESI) m/z :** [M + H]⁺ calcd for C₂₈H₂₁N₃O₃H⁺, 448.1656; found, 448.1650.



4j

(R)-8-bromo-4-(4-(1-methyl-1H-imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo-2H-chromene-3-carbonitrile(4j). White solid (39.54 mg, 83%). Mp: 168.0-170.3 °C. $[\alpha]_D^{25} = +256.6$ (c = 0.5 in CH₂Cl₂). HPLC: 99% ee (Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 38.59$ min (major), 17.99 min (minor). **¹H NMR (400 MHz, CDCl₃, 25 °C)** δ /ppm: 8.23-8.21 (m, 1H), 7.92-7.90 (m, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.24-7.20 (m, 3H), 7.16 (s, 1H), 7.12-7.08 (m, 3H), 4.0 (s, 3H), 3.95-3.88 (m, 1H), 3.84-3.77 (m, 1H), 3.67-3.60 (m, 2H), 3.33-3.72 (m, 1H). **¹³C NMR (100 MHz, CDCl₃, 25 °C)** δ /ppm: 190.5, 163.8, 155.5, 150.1, 142.7, 140.3, 130.3, 129.5, 128.9, 127.8, 127.7, 127.6, 126.3, 126.1, 118.9, 112.9, 112.3, 103.6, 44.9, 41.5, 39.2, 36.2. **HRMS (ESI) m/z : [M + H]⁺** calcd for C₂₄H₁₈BrN₃O₃H⁺, 476.0604; found, 476.0599. **HRMS (ESI) m/z : [M + H]⁺** calcd for C₂₄H₁₈BrN₃O₃H⁺, 476.0604; found 476.0596 and 478.0578.



5a

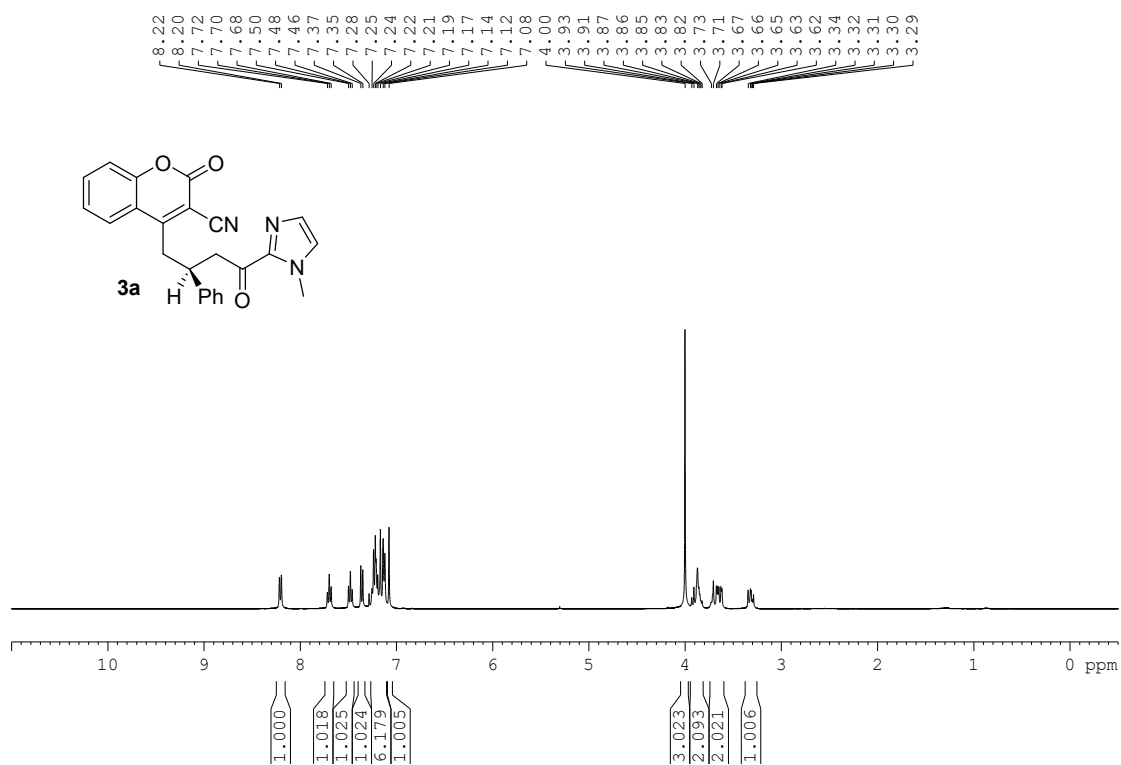
(R)-3-amino-1-(3-(1-methyl-1H-imidazol-2-yl)-3-oxo-1-phenylpropyl)-4H-thieno[3,4-c]chromen-4-one (5a). Yellow solid (28.3 mg, 66%). Mp: 176.3-178.2 °C. $[\alpha]_D^{25} = +270.9$ (c = 0.5 in CH₂Cl₂). HPLC: 97% ee (Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 1.0 mL/min, $\lambda = 250$ nm) $t_R = 23.24$ min (major), 32.50 min (minor). **¹H NMR (400 MHz, CDCl₃, 25 °C)** δ /ppm: 7.99-7.97 (m, 1H), 7.76 (s, 2H), 7.49 (s, 1H), 7.41-7.39 (m, 2H), 7.36-7.30 (m, 3H), 7.24-7.22 (m, 3H), 7.15 (d, $J = 0.8$ Hz, 1H), 5.52 (t, $J = 4.0$, 1H), 3.83-3.81 (m, 5H). **¹³C NMR (100 MHz, CDCl₃, 25 °C)** δ /ppm: 189.2, 164.0, 159.4, 151.6, 143.0, 142.6, 129.5, 129.2, 128.9, 127.9, 127.4, 125.5, 124.7, 124.5, 121.4, 118.9, 117.8, 127.2, 98.8, 46.3, 36.0. **HRMS (ESI) m/z : [M + H]⁺** calcd for C₂₄H₁₉N₃O₃SH⁺, 429.1248; found, 429.1253.

IV References

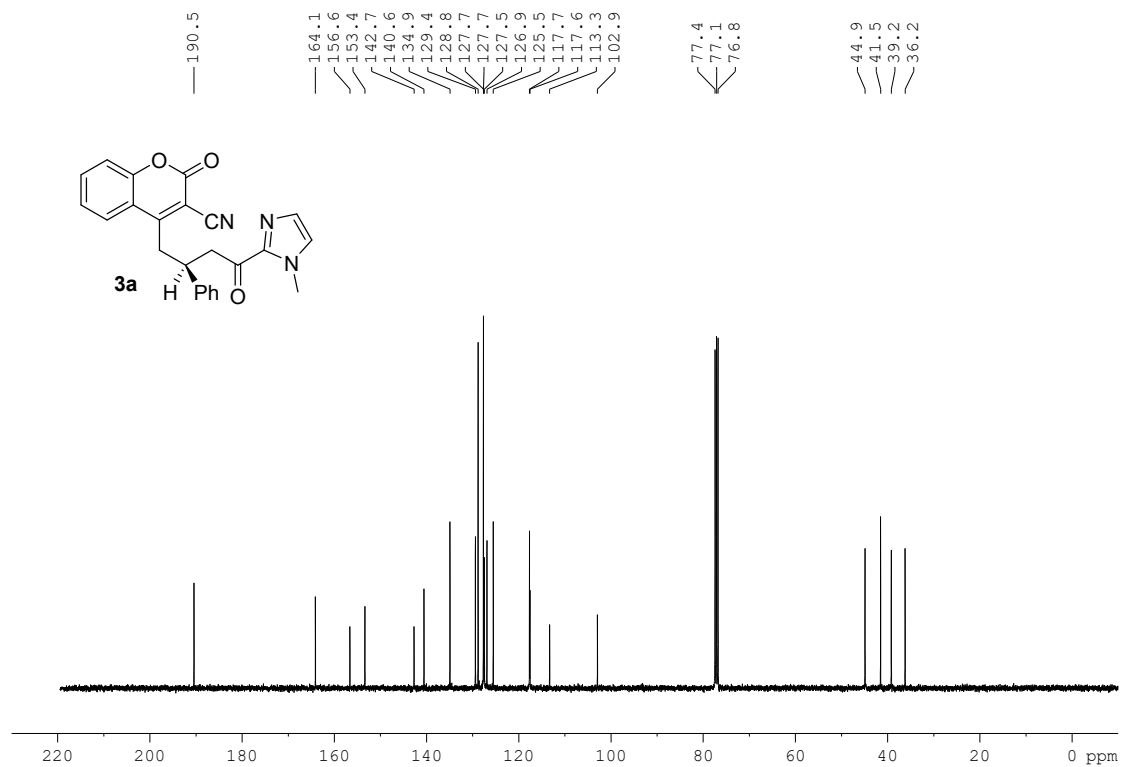
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V NMR Spectrum

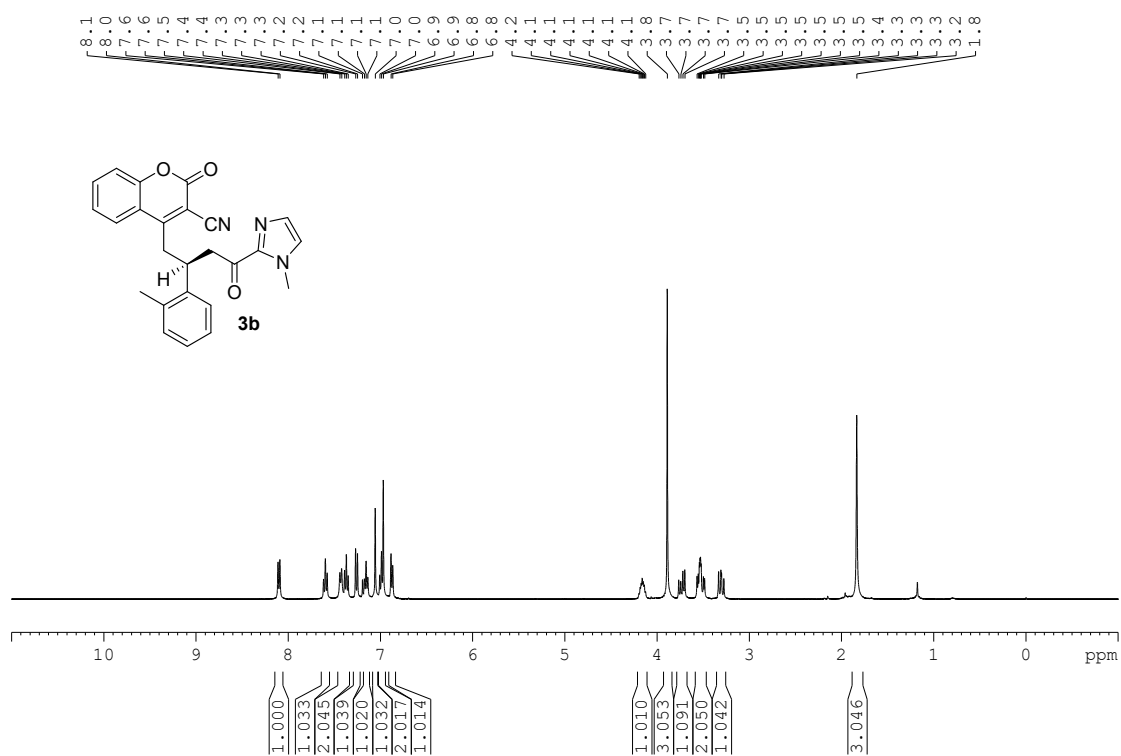
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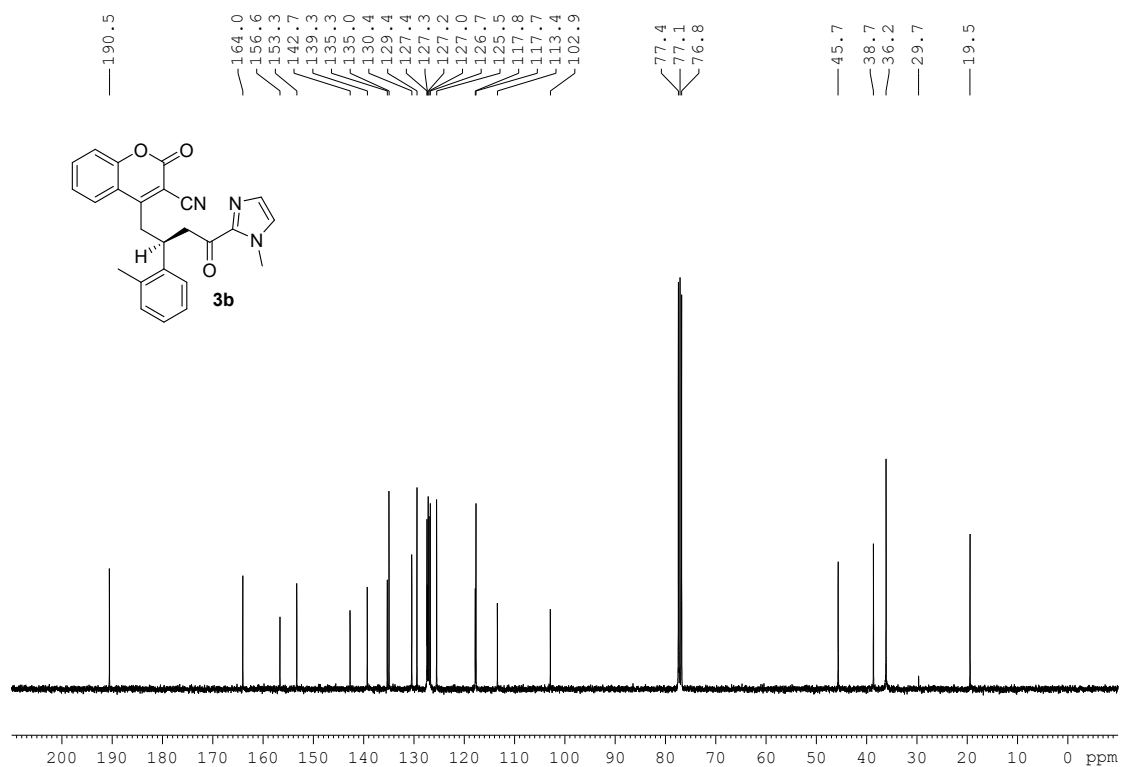
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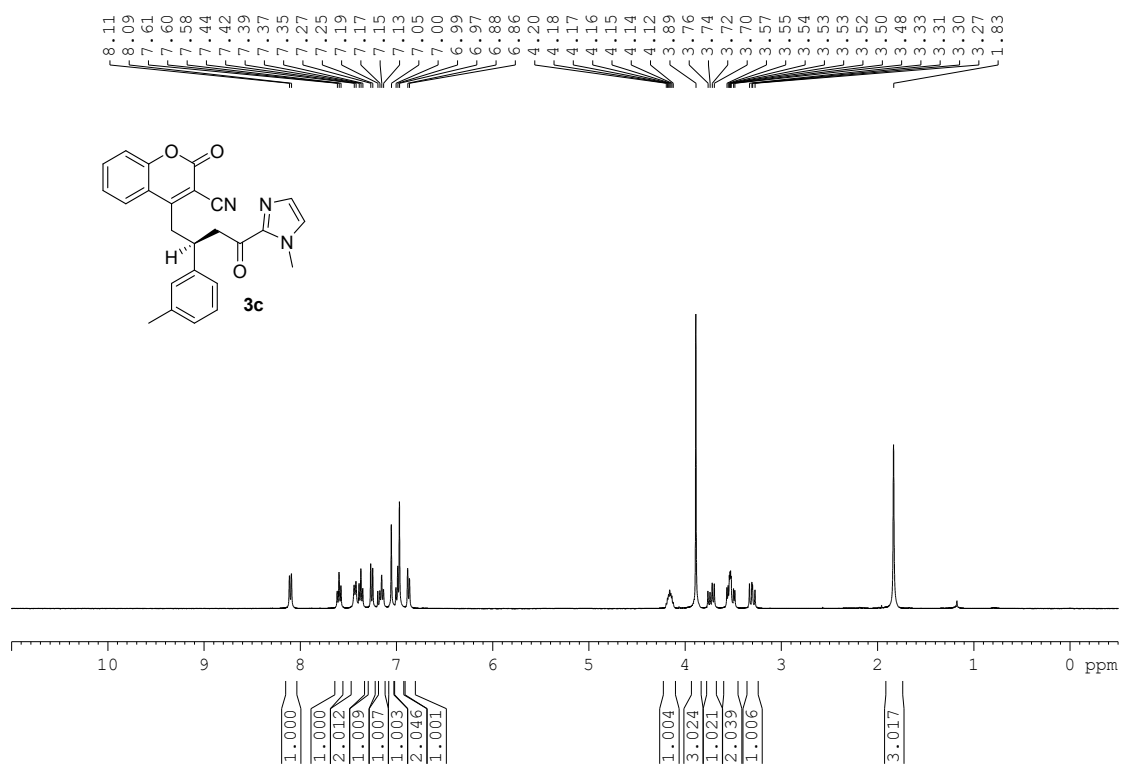
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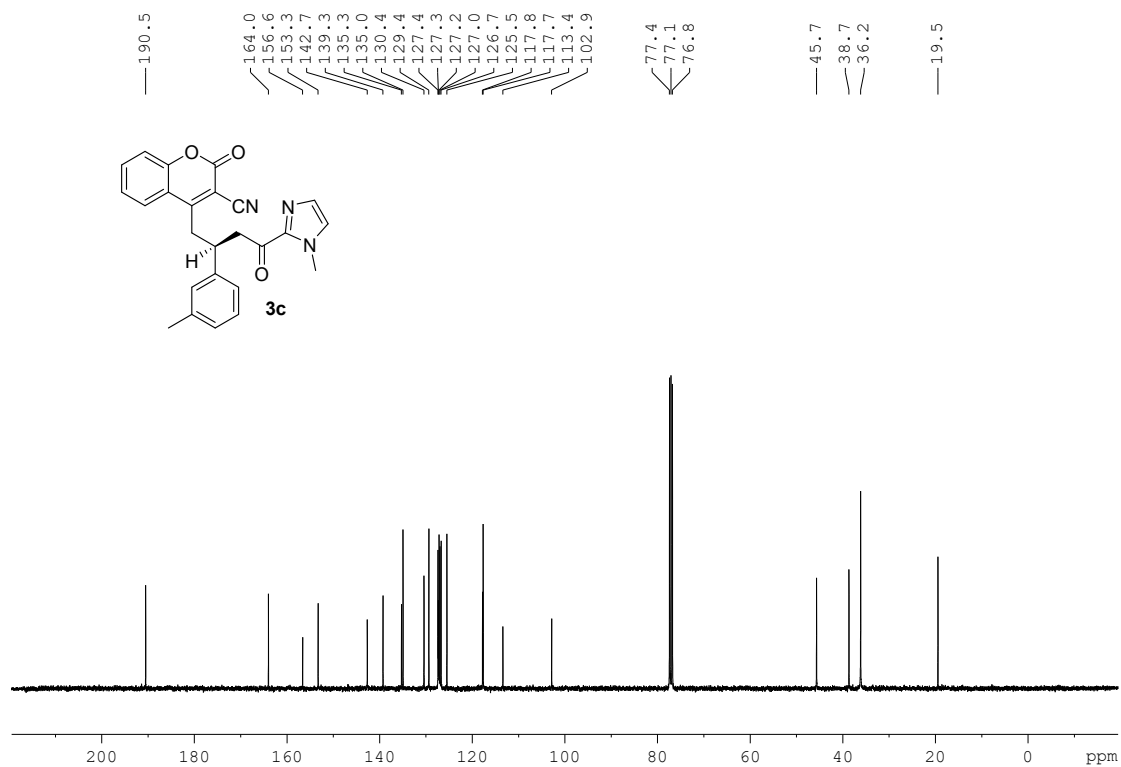
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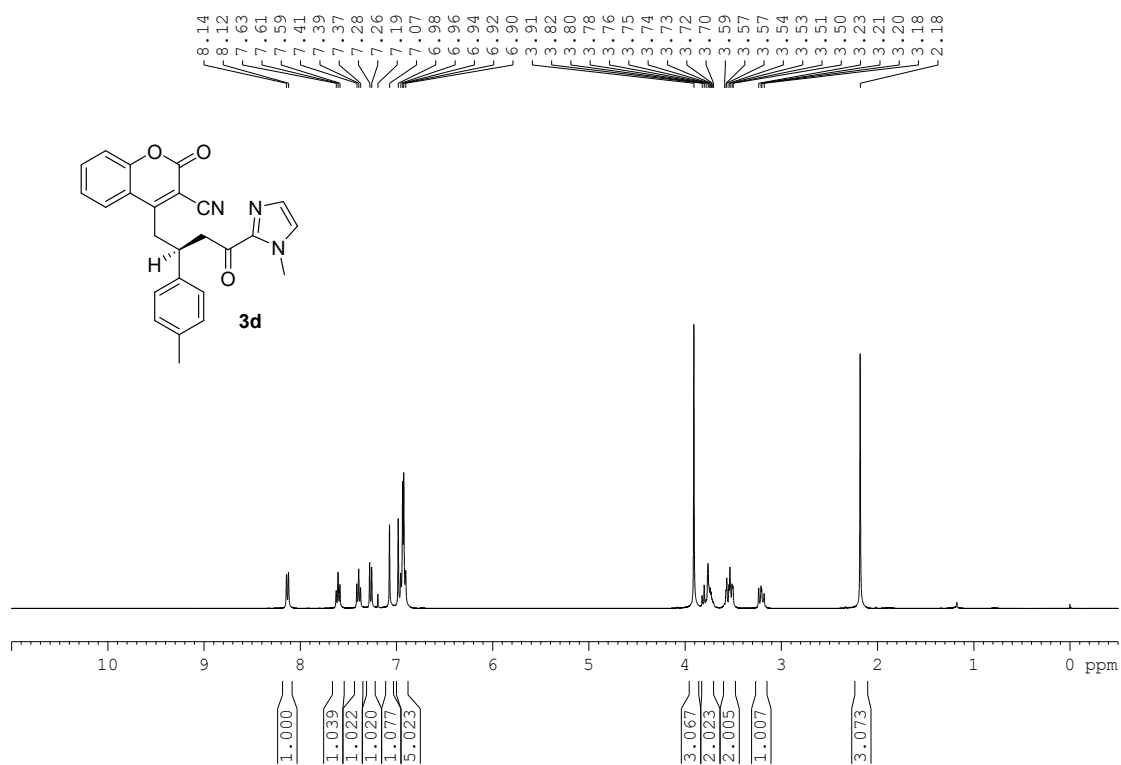
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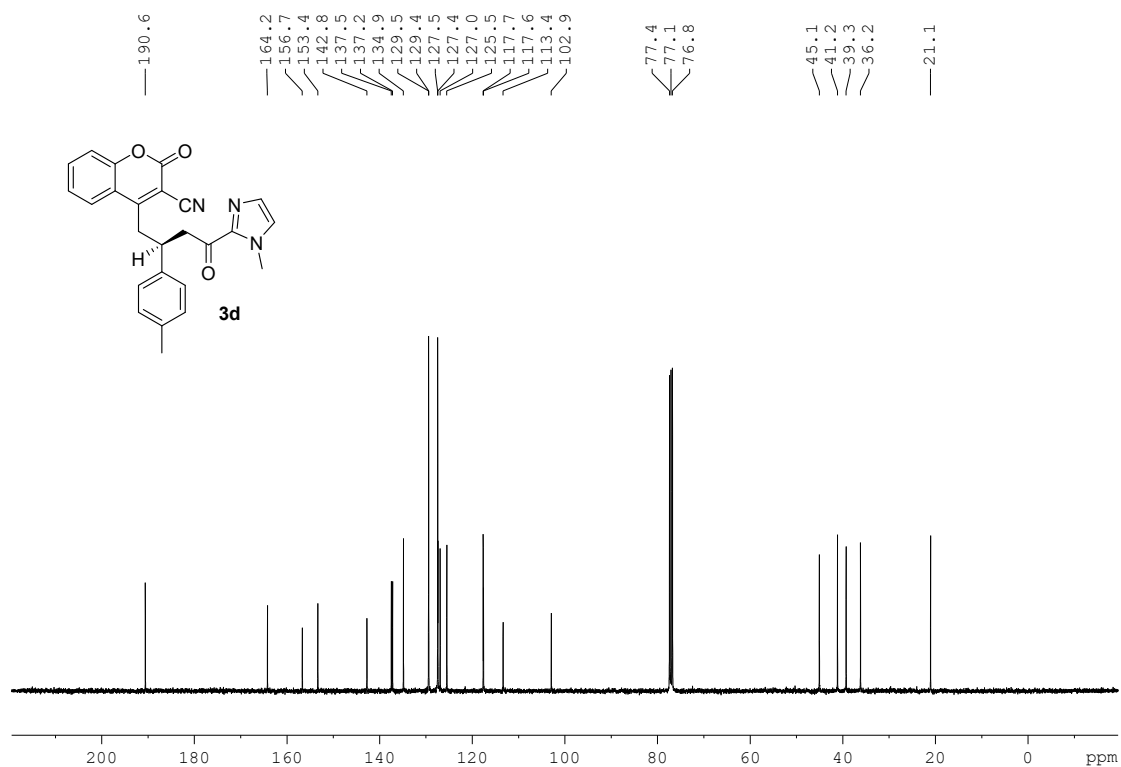
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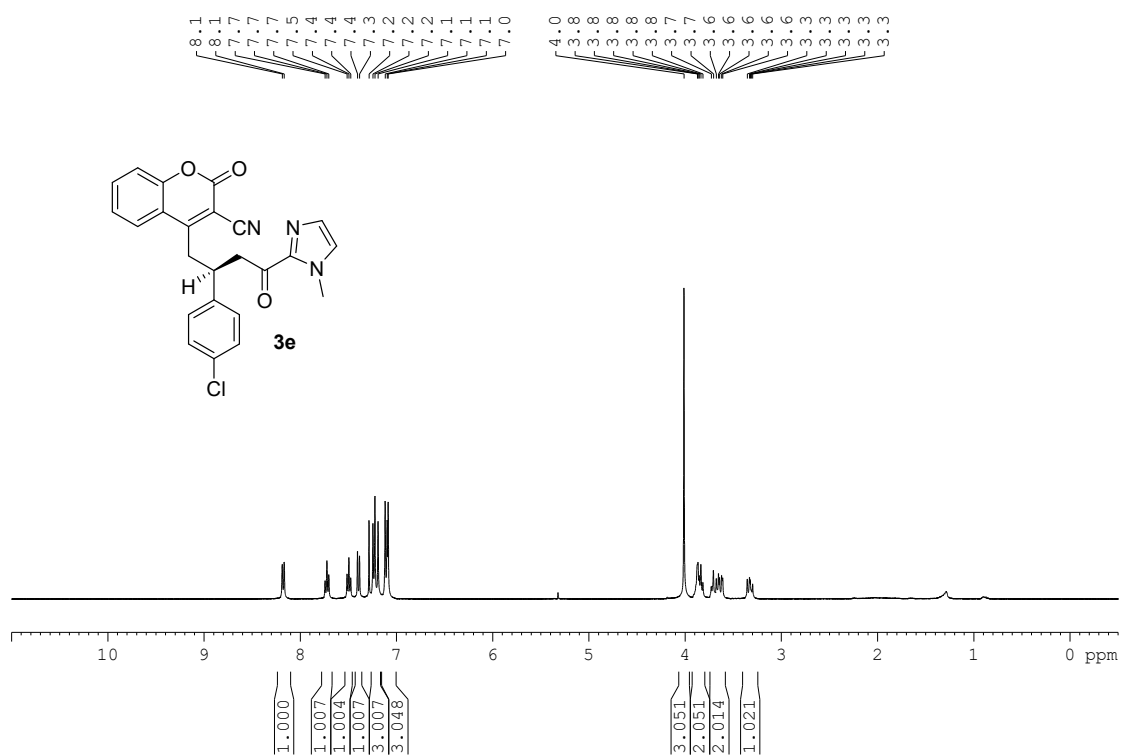
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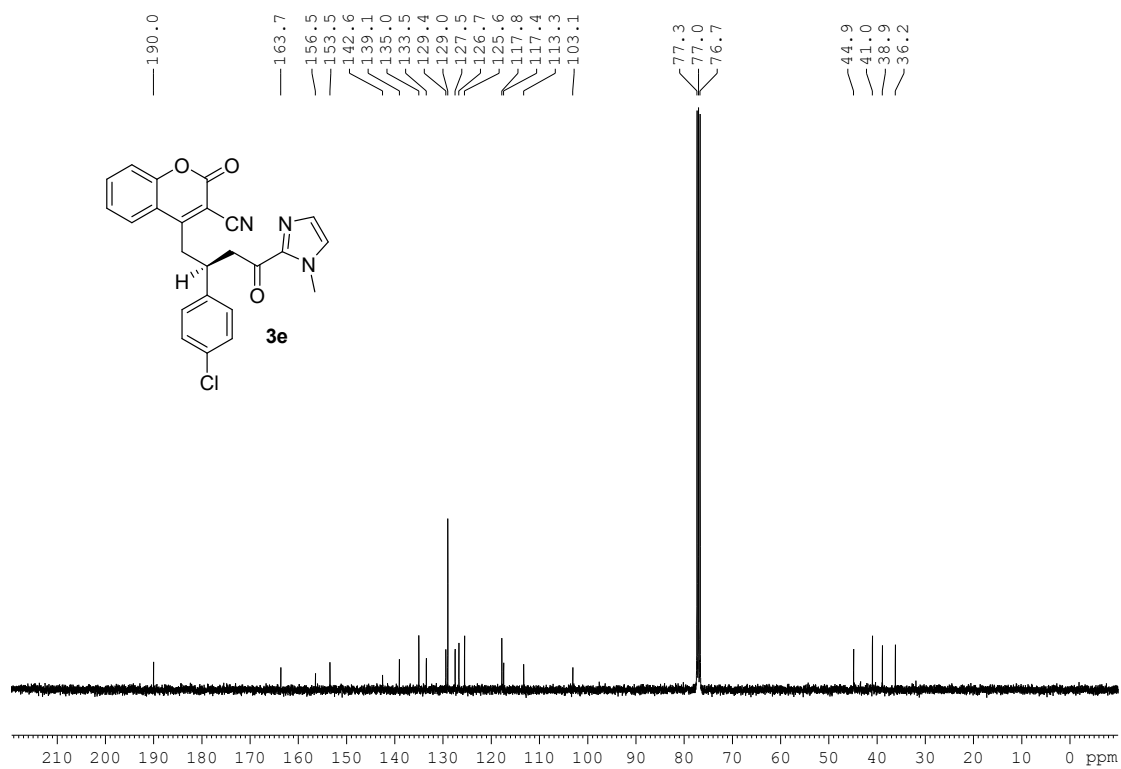
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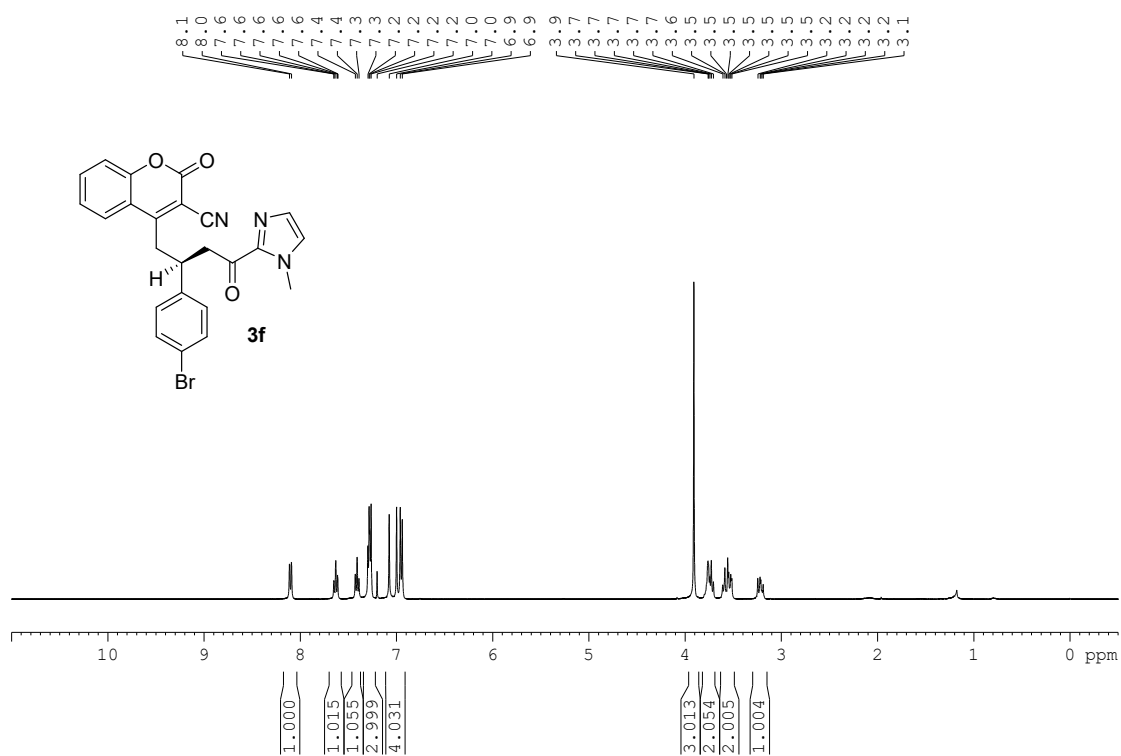
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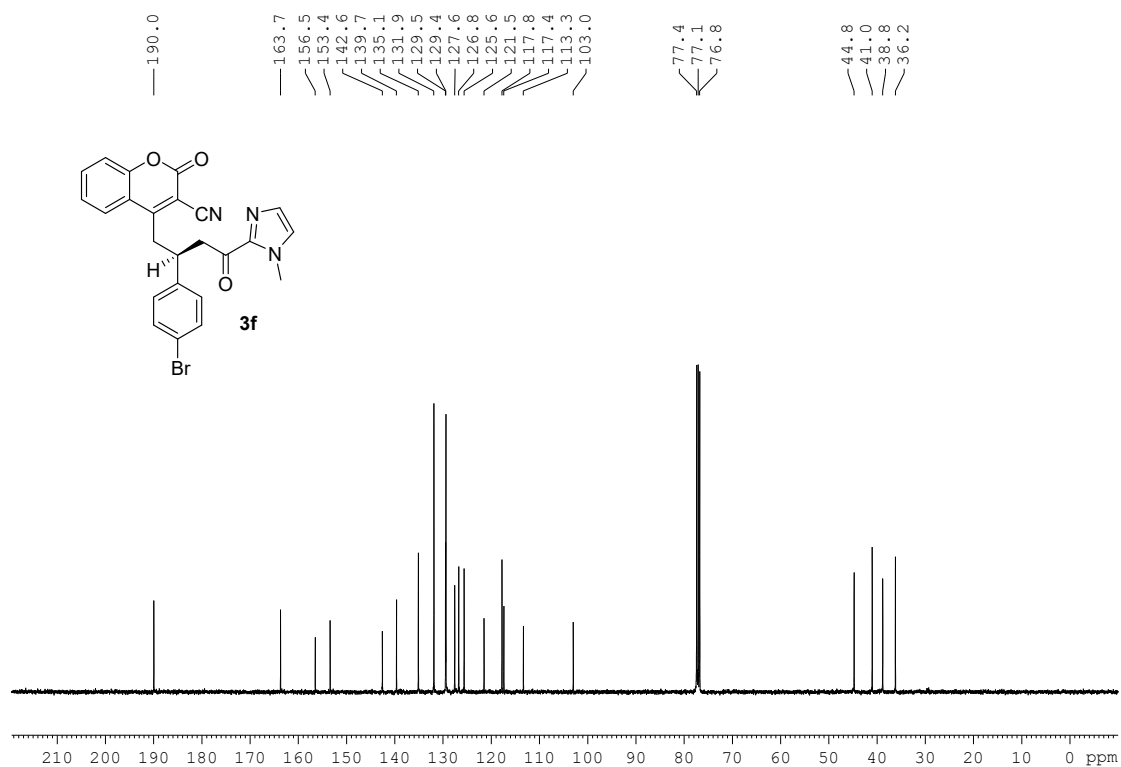
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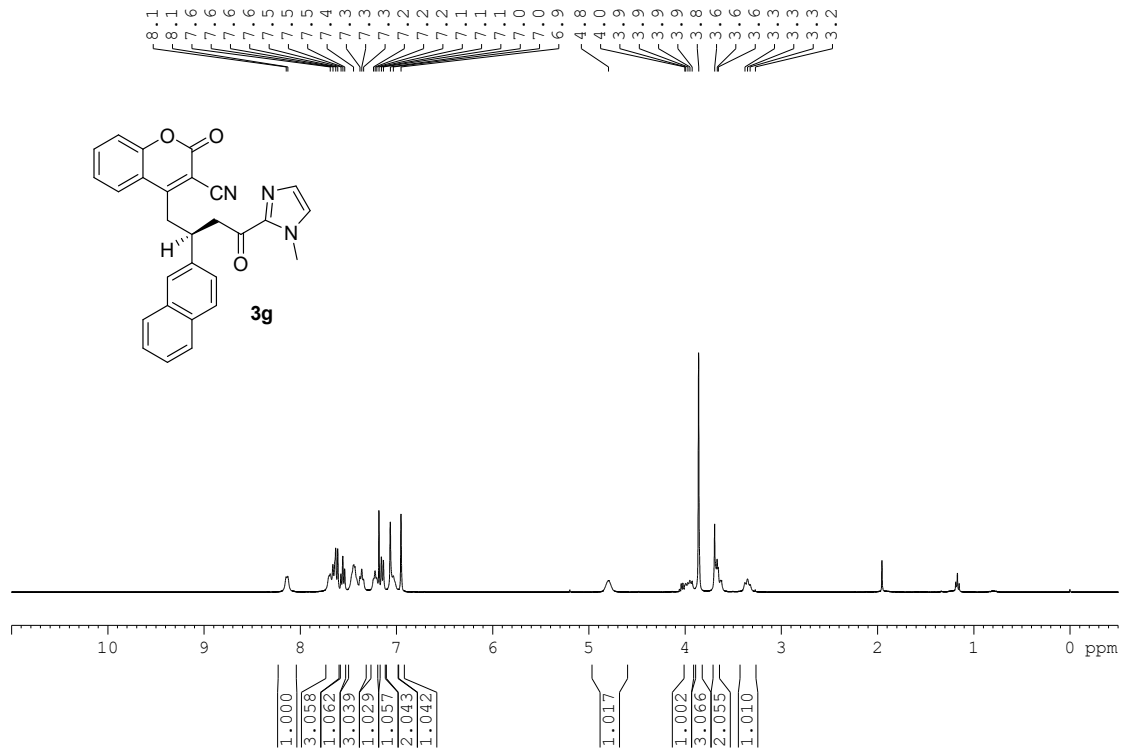
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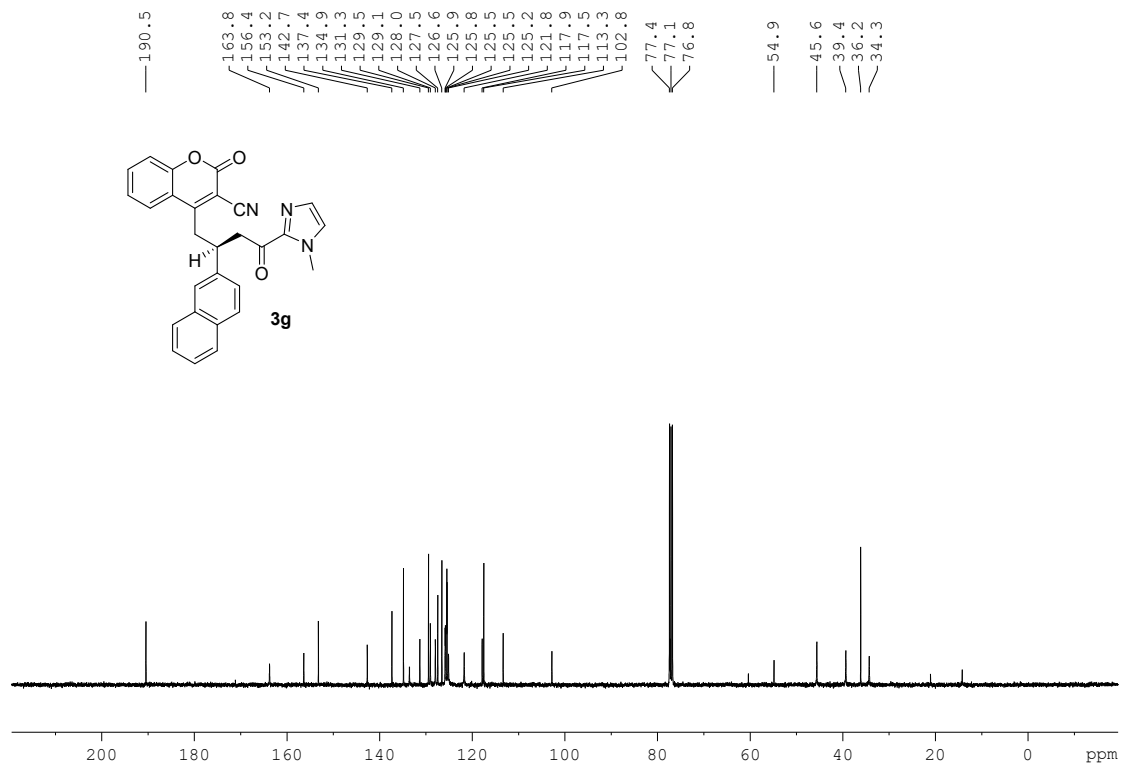
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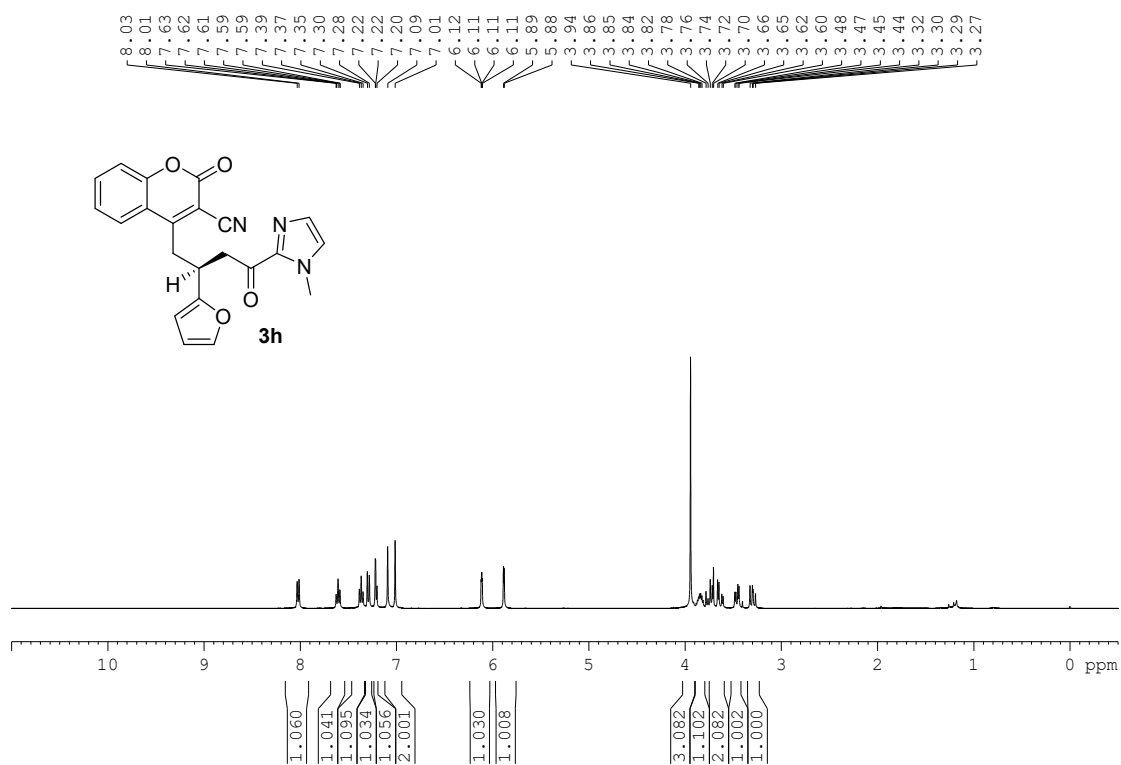
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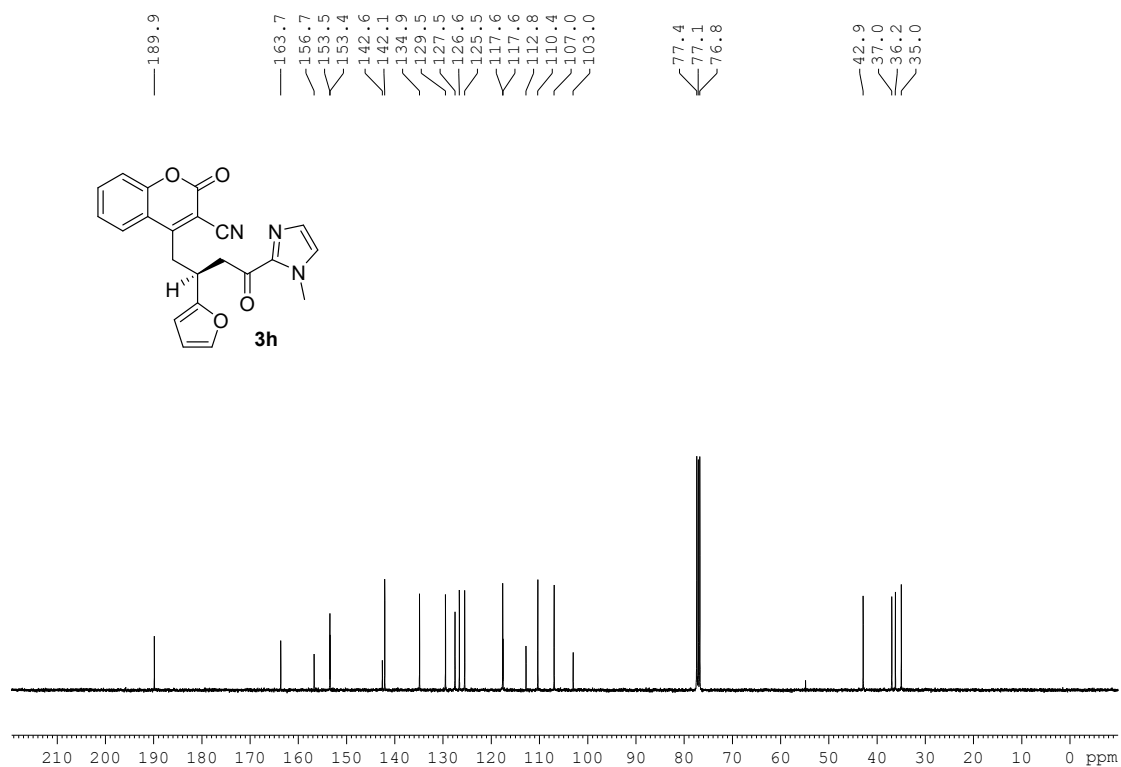
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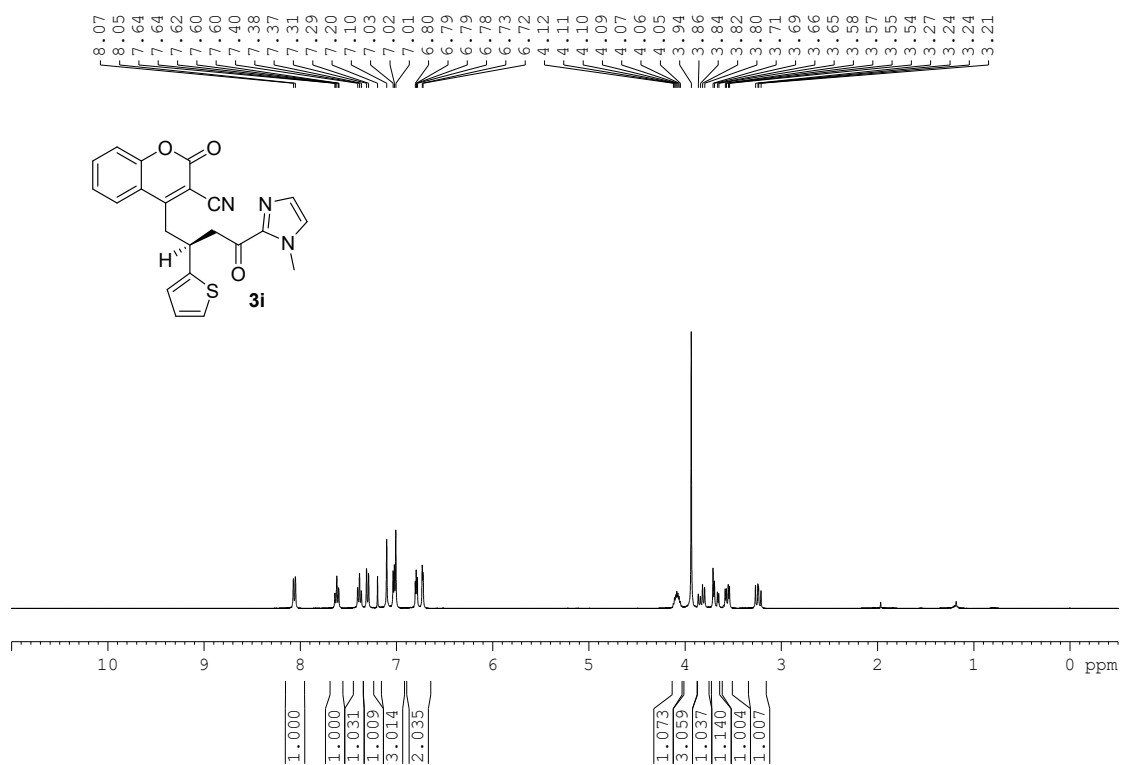
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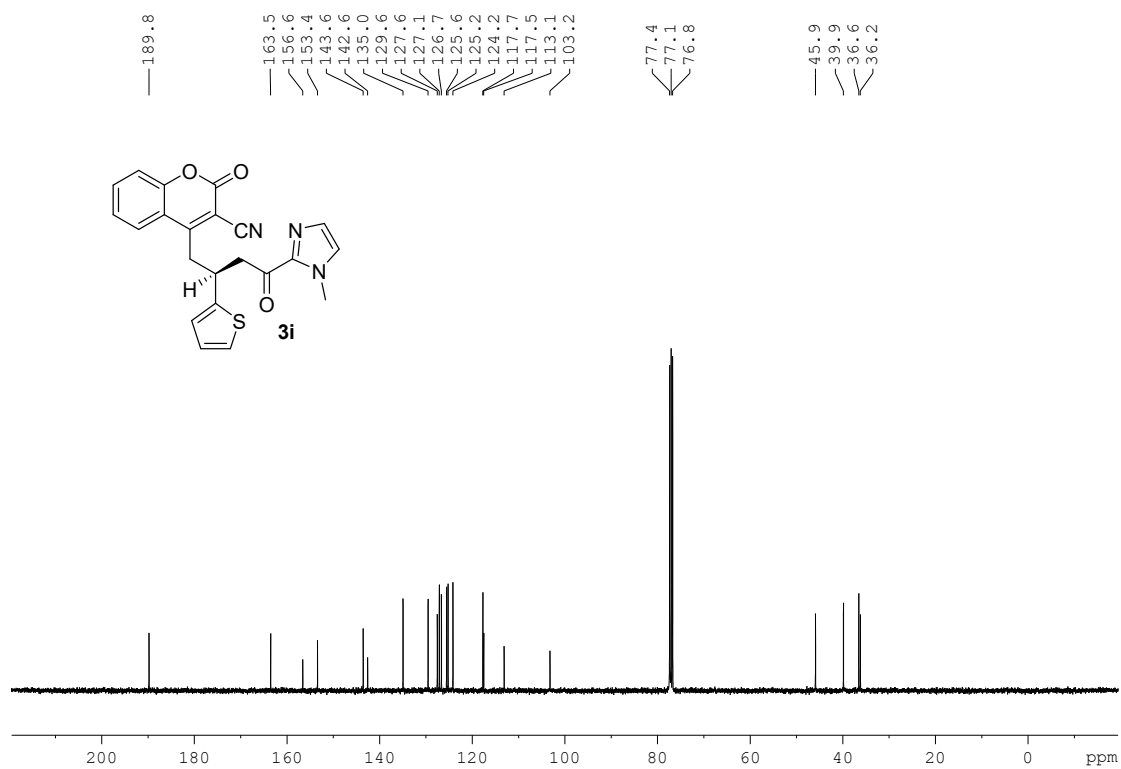
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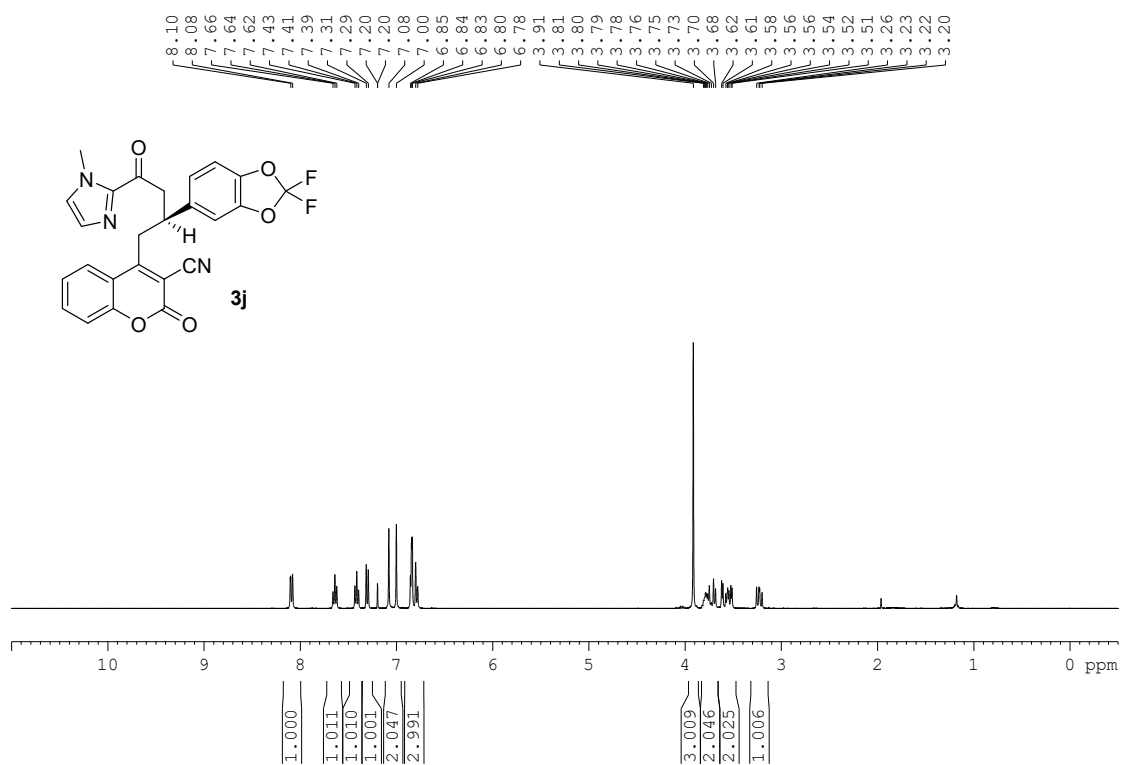
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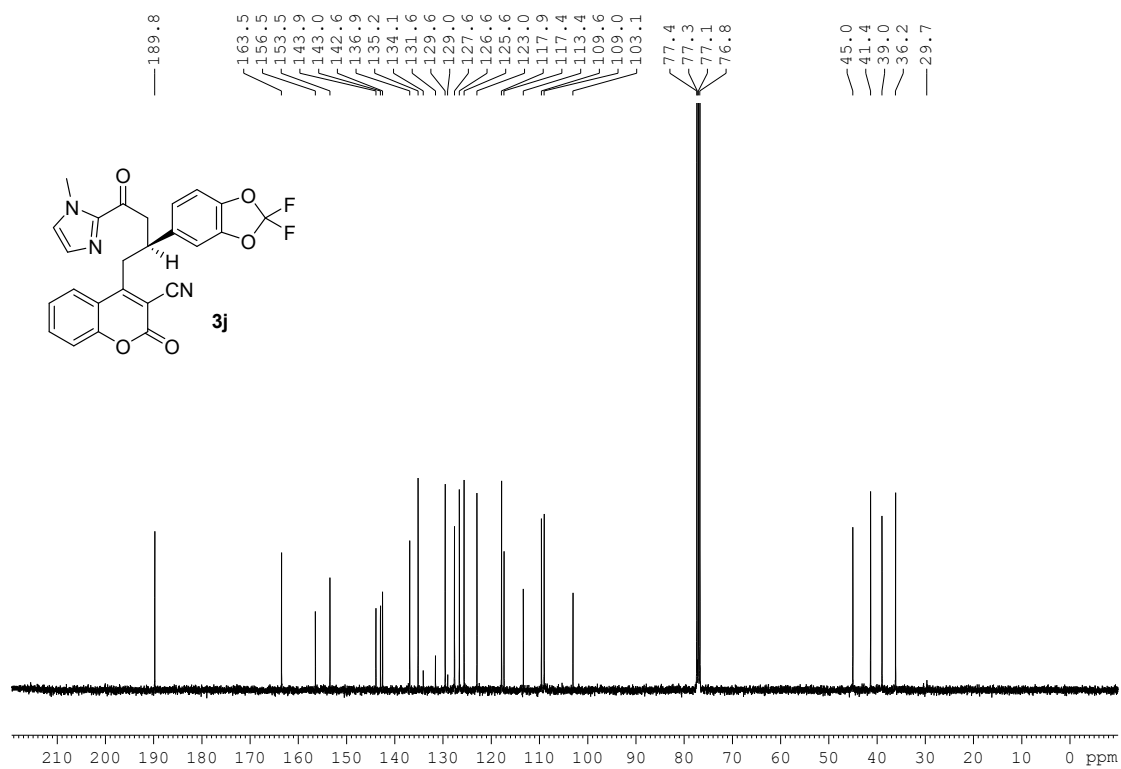
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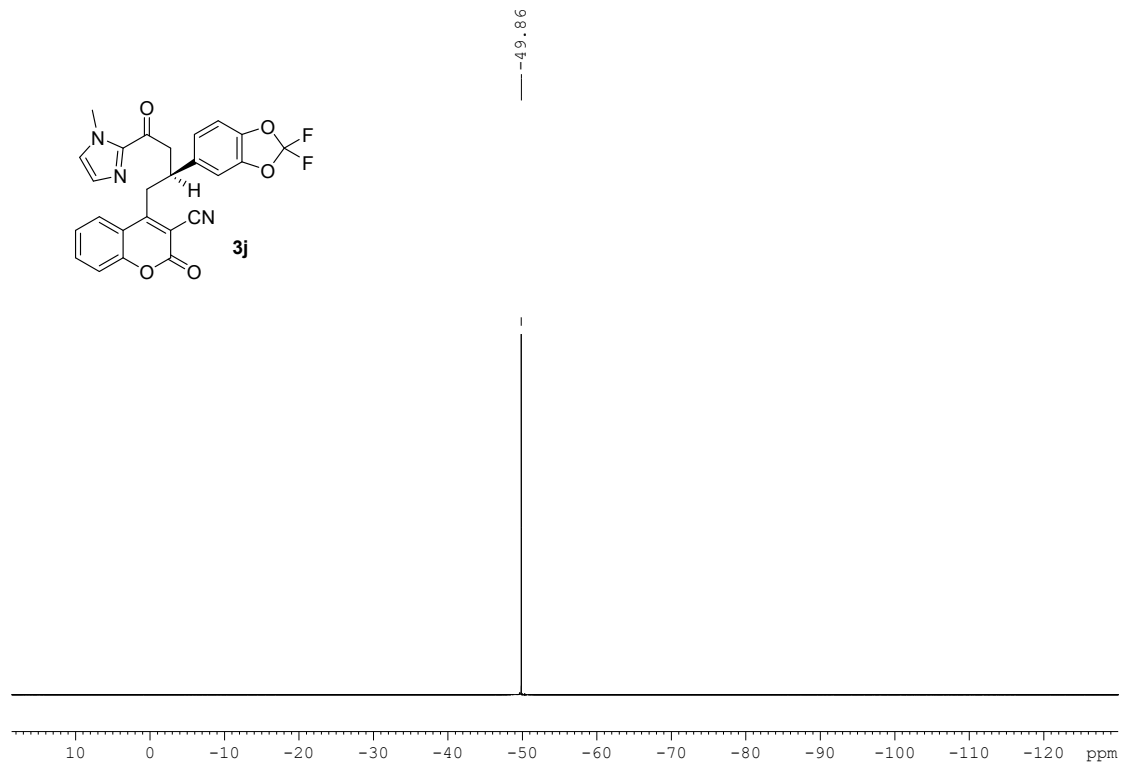
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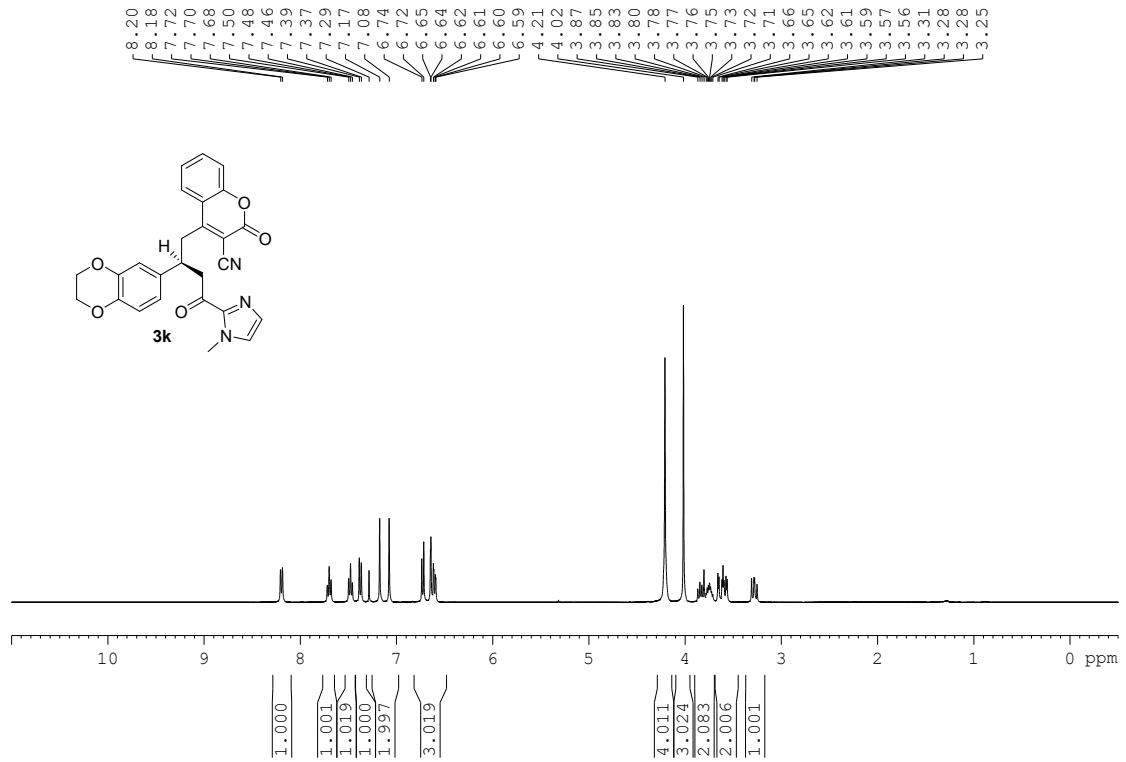
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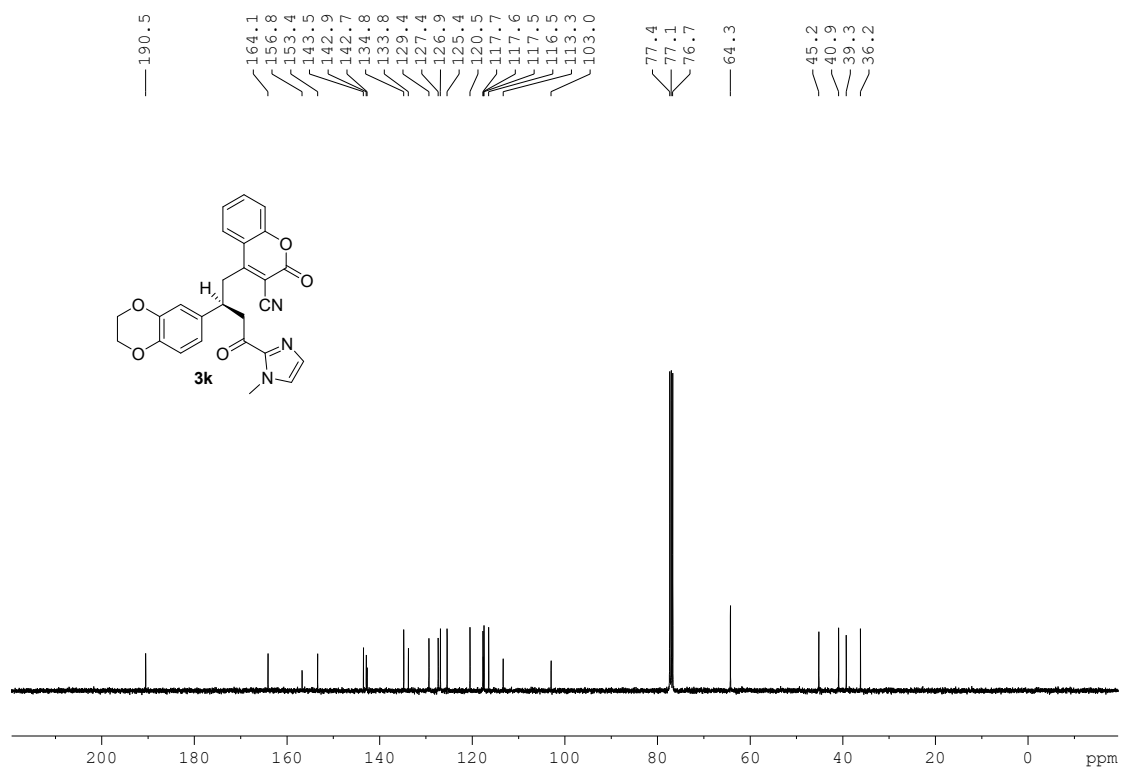
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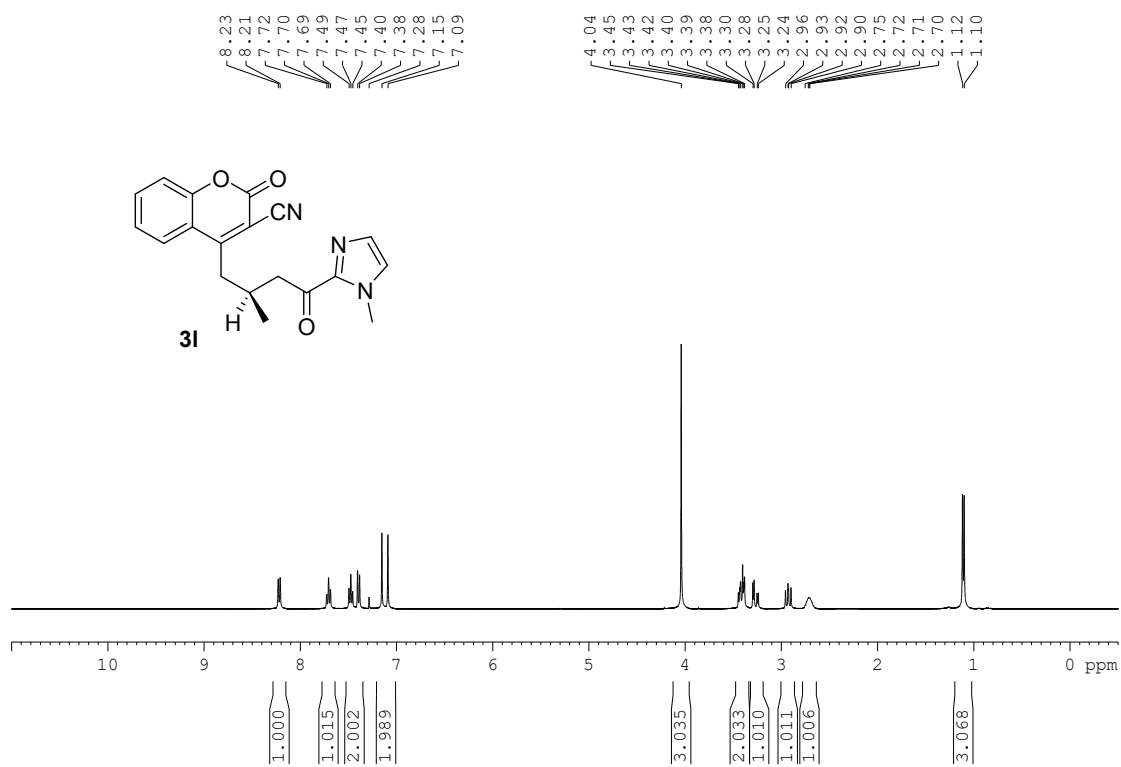
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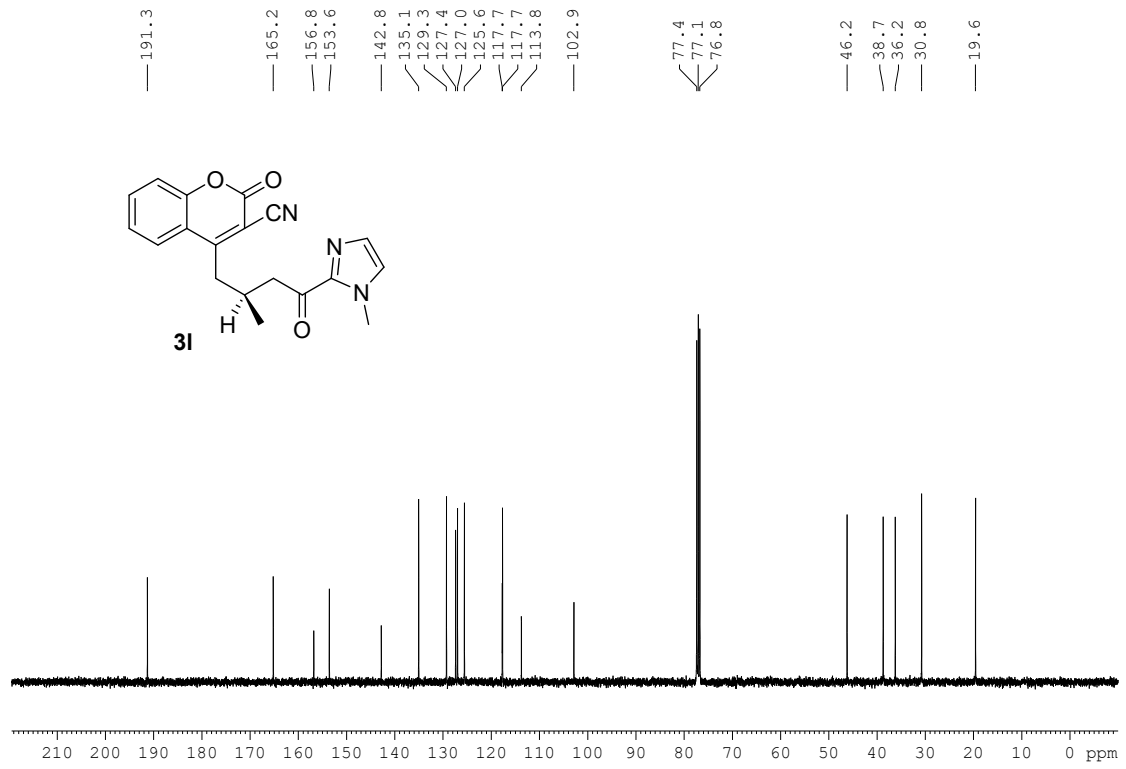
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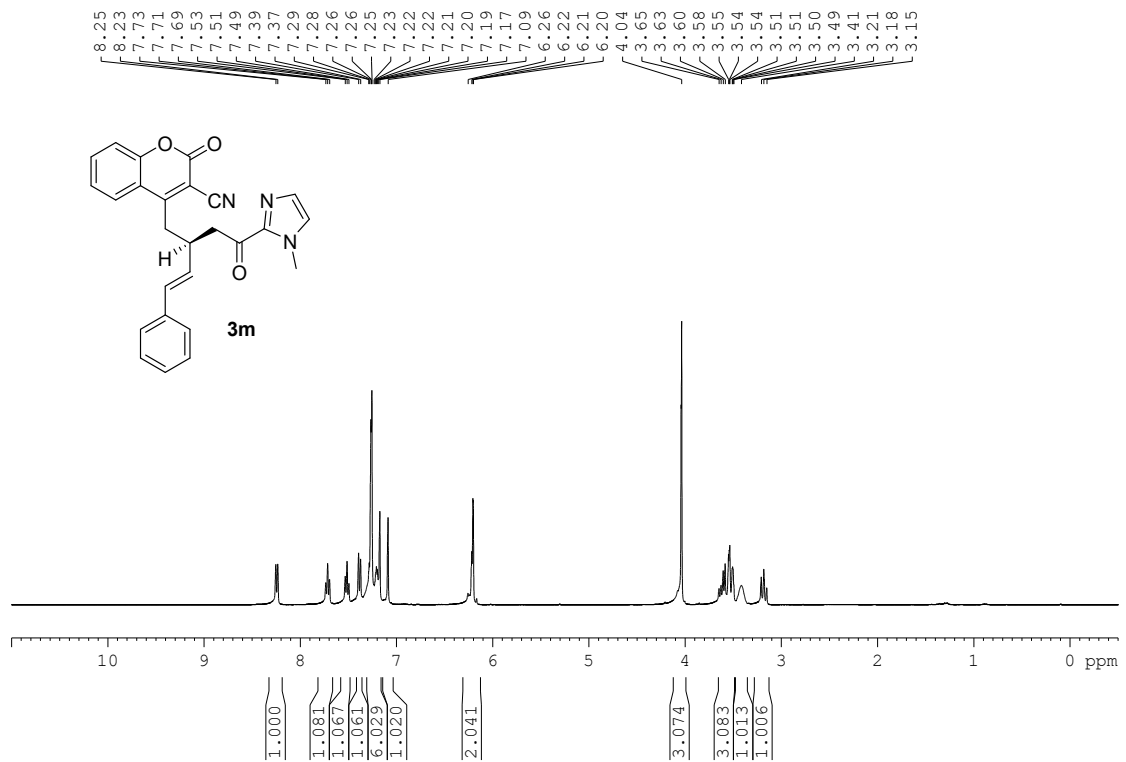
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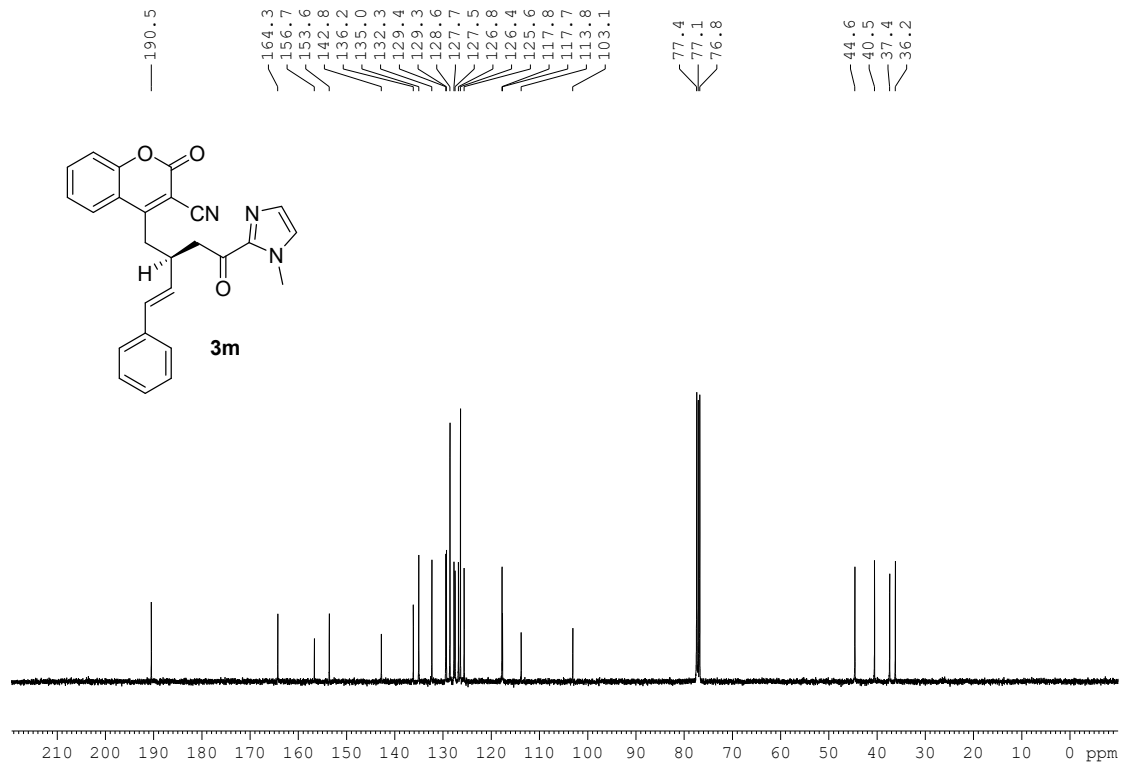
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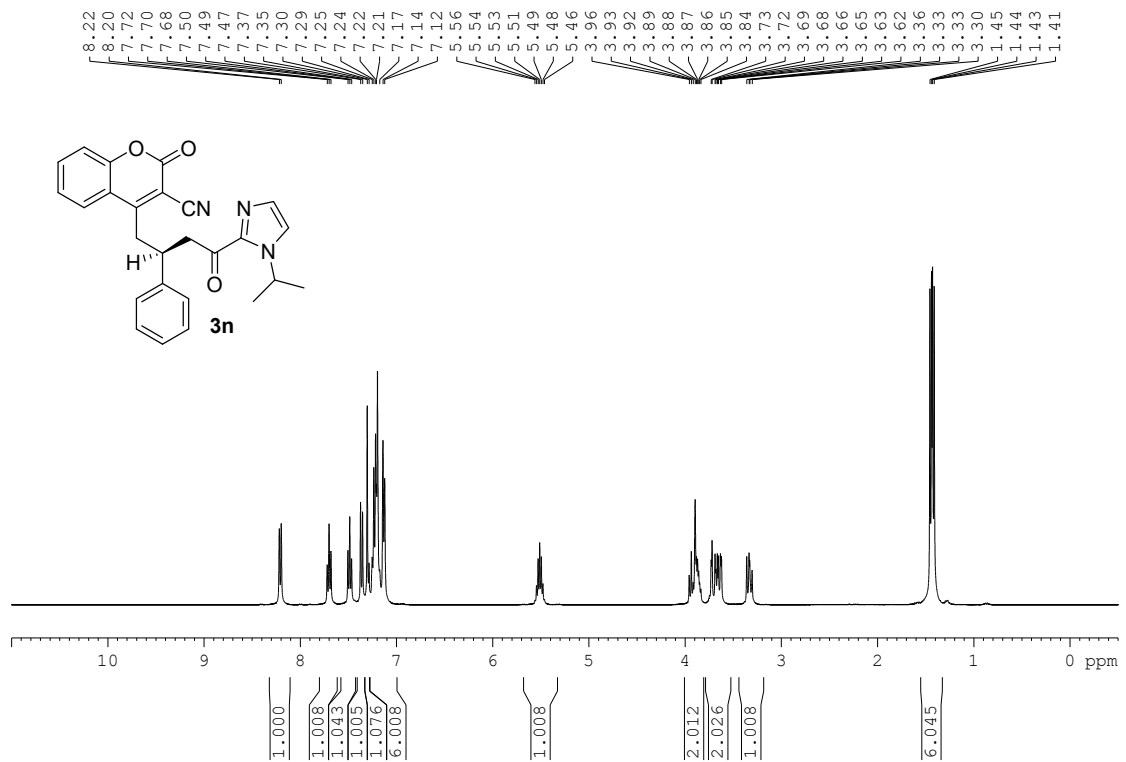
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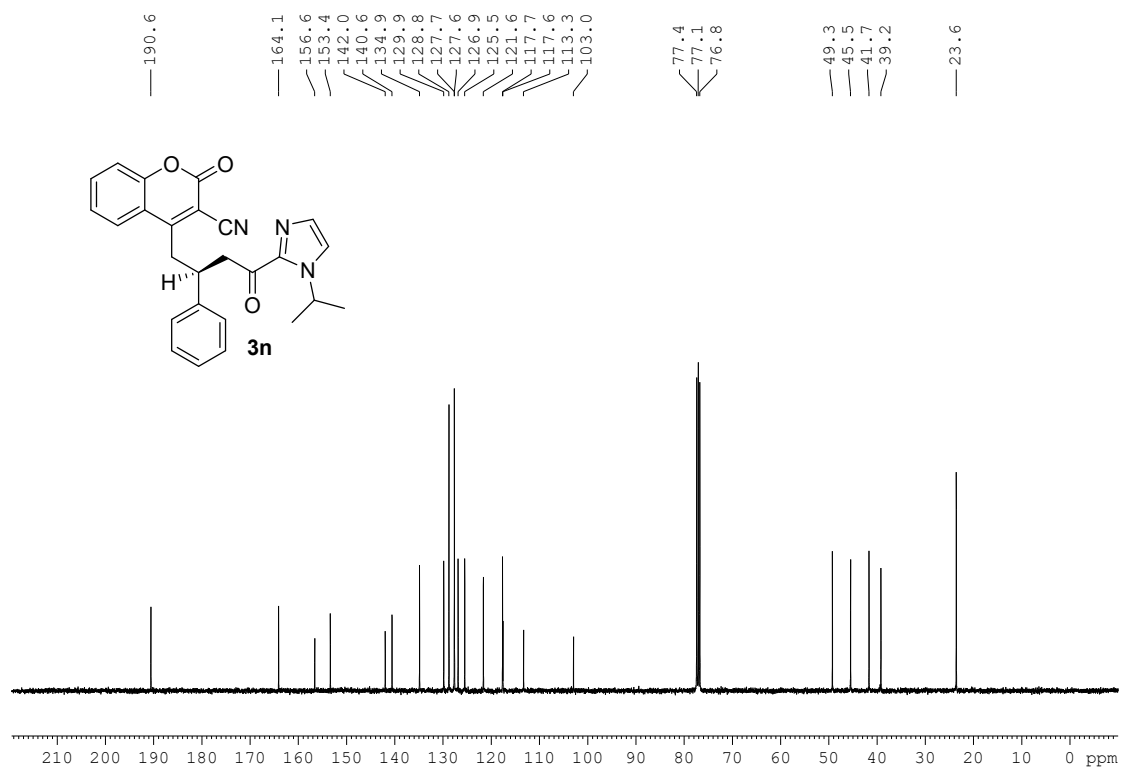
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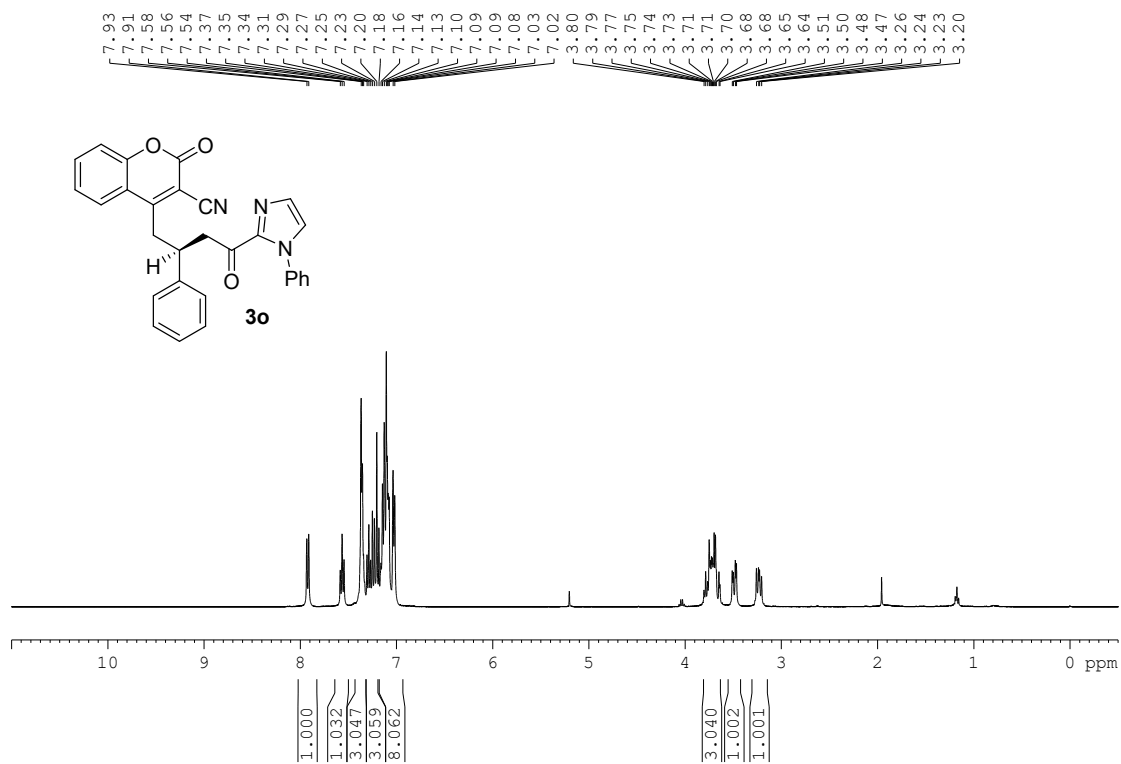
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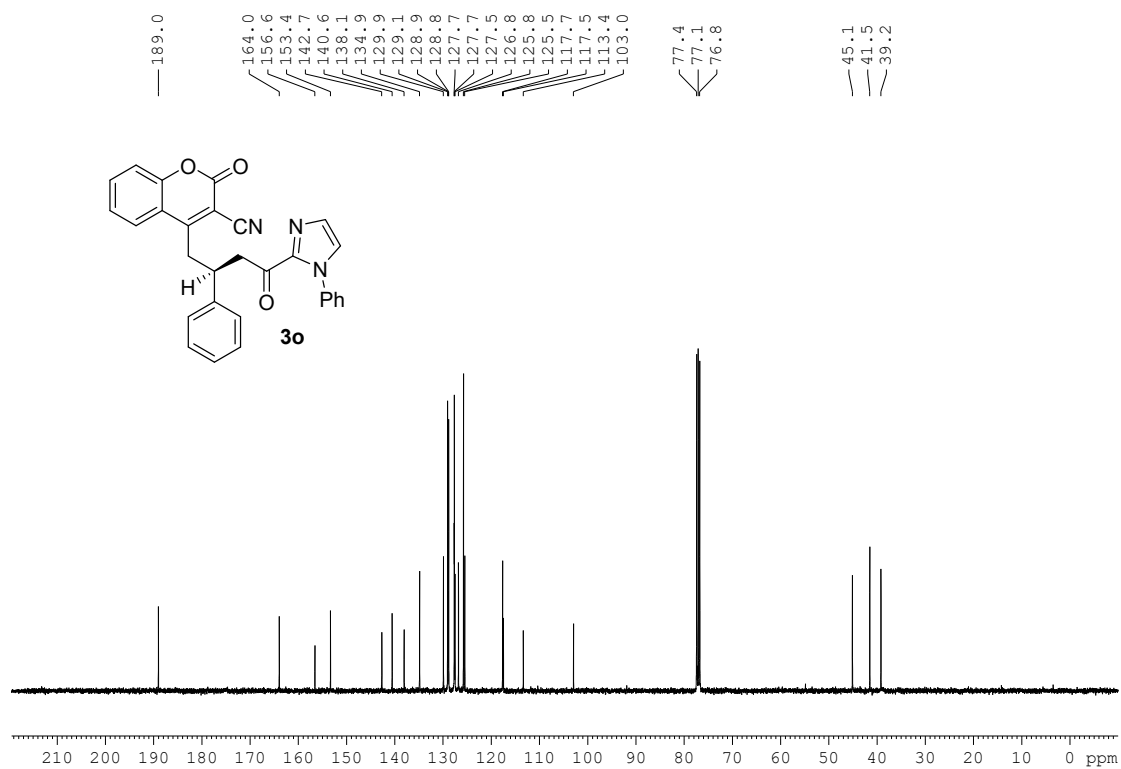
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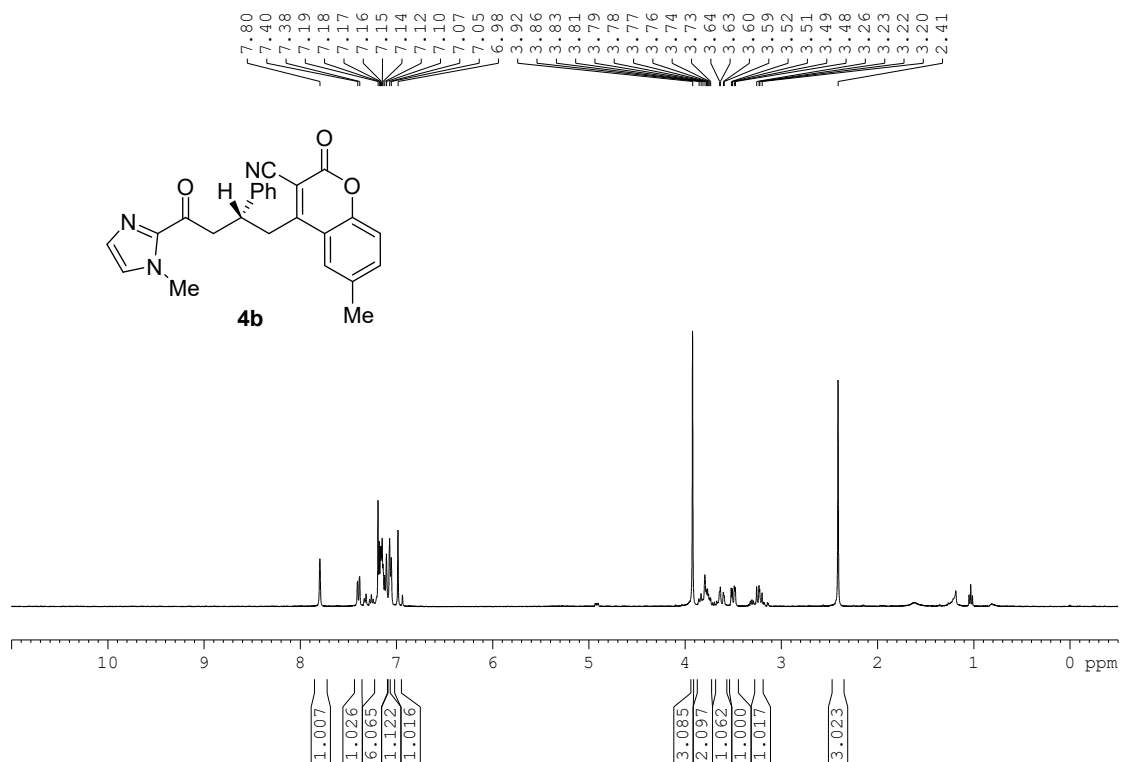
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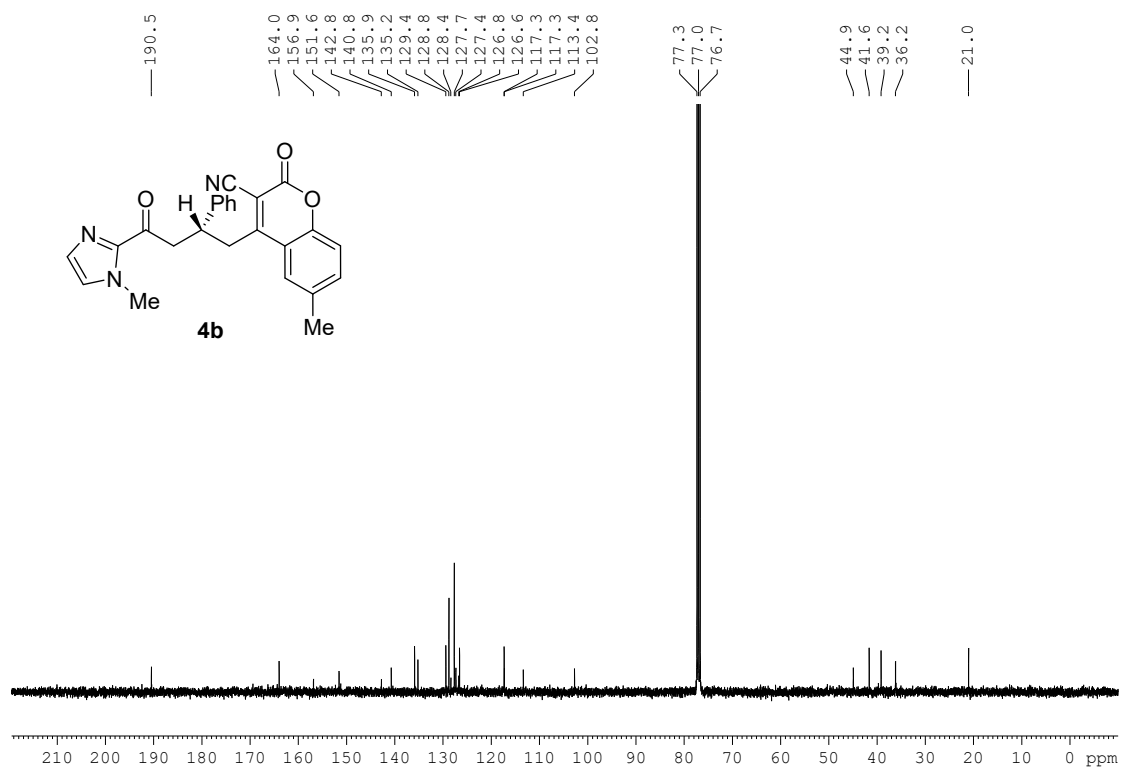
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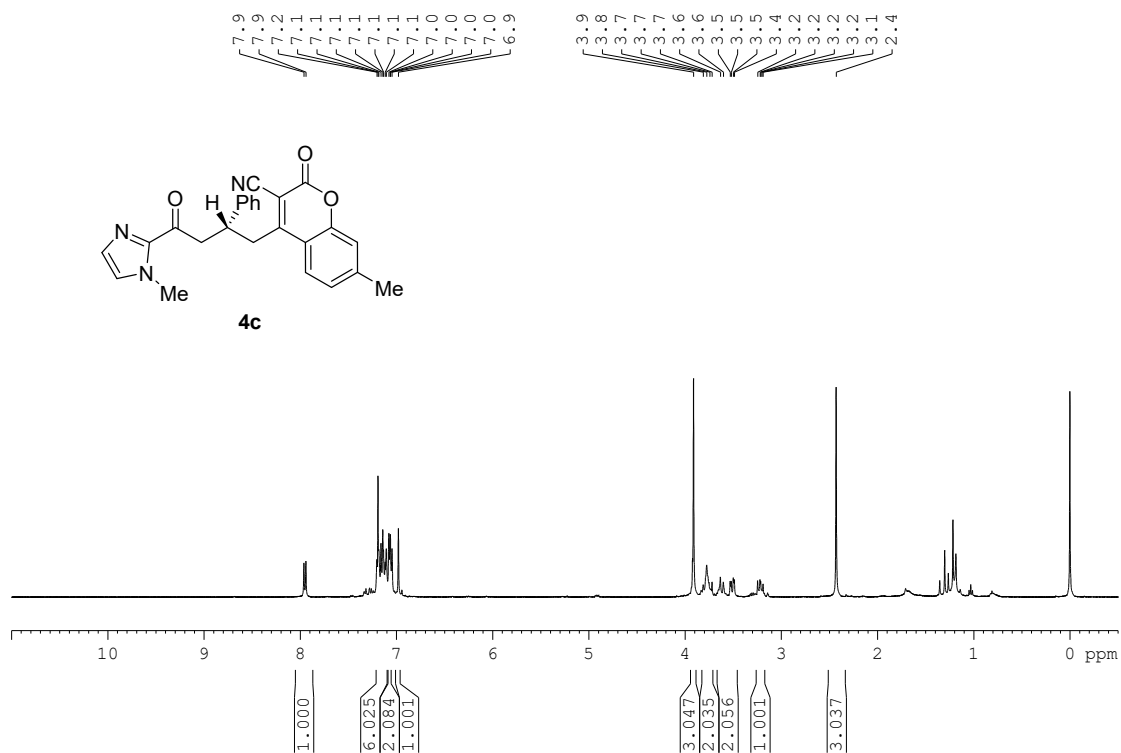
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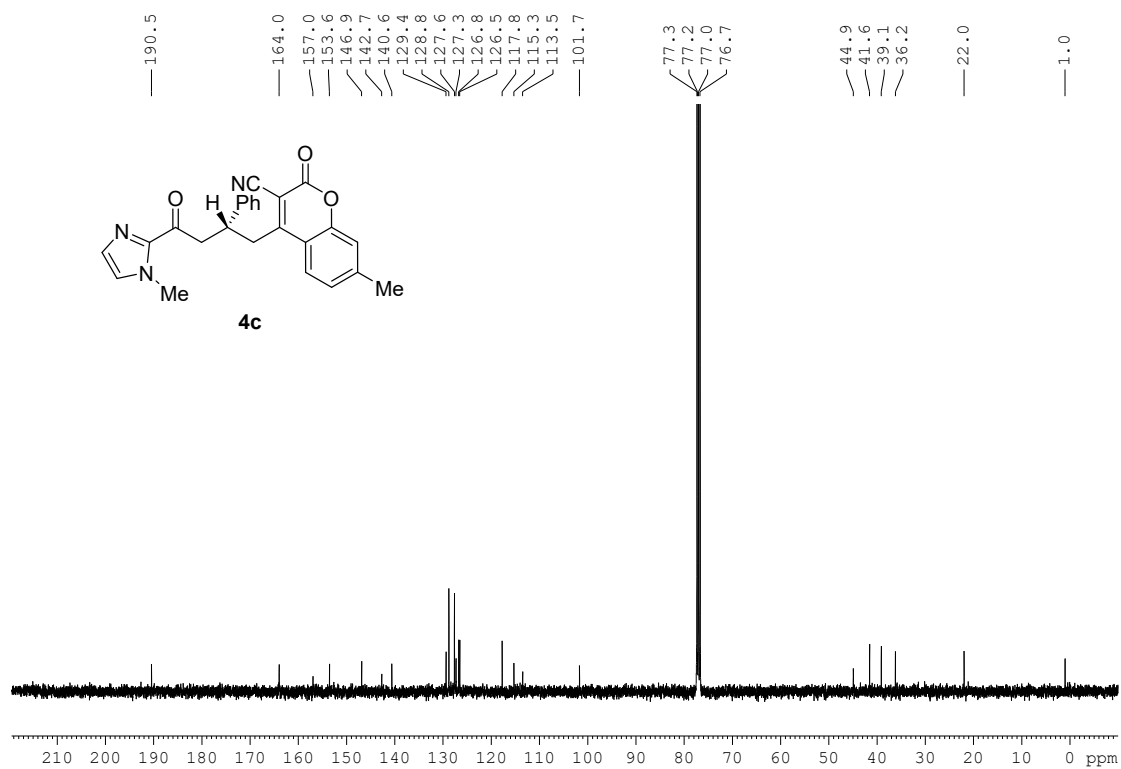
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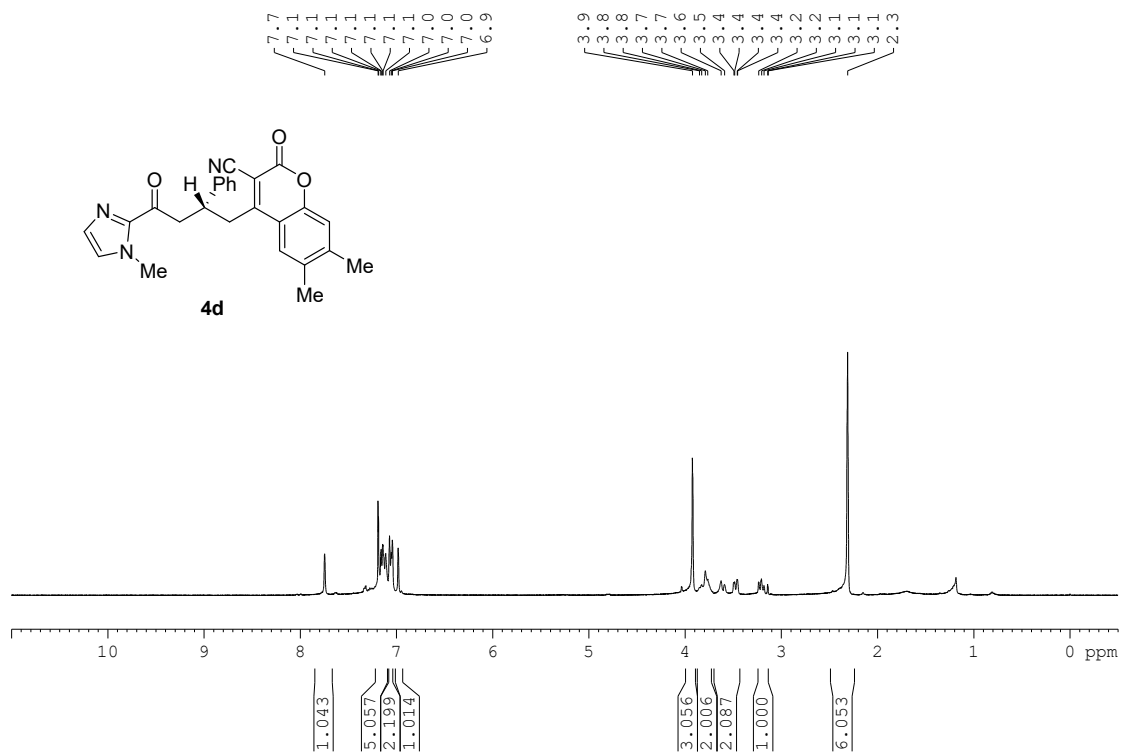
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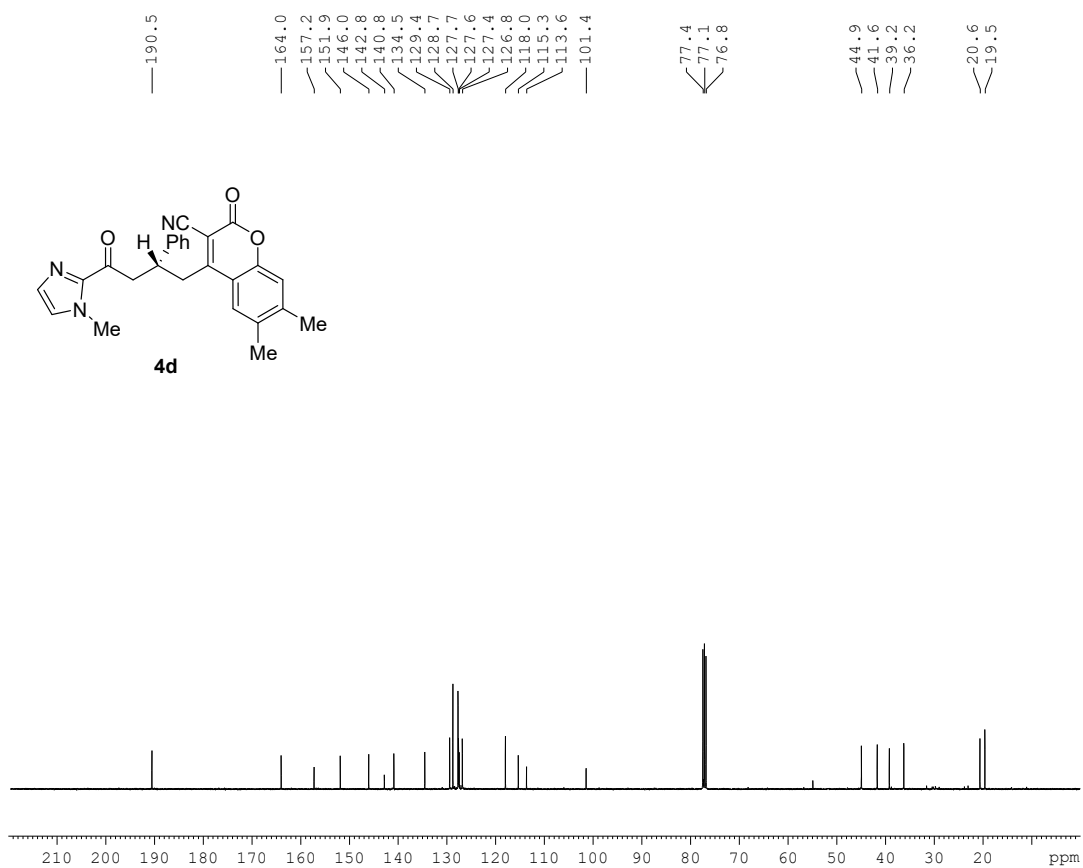
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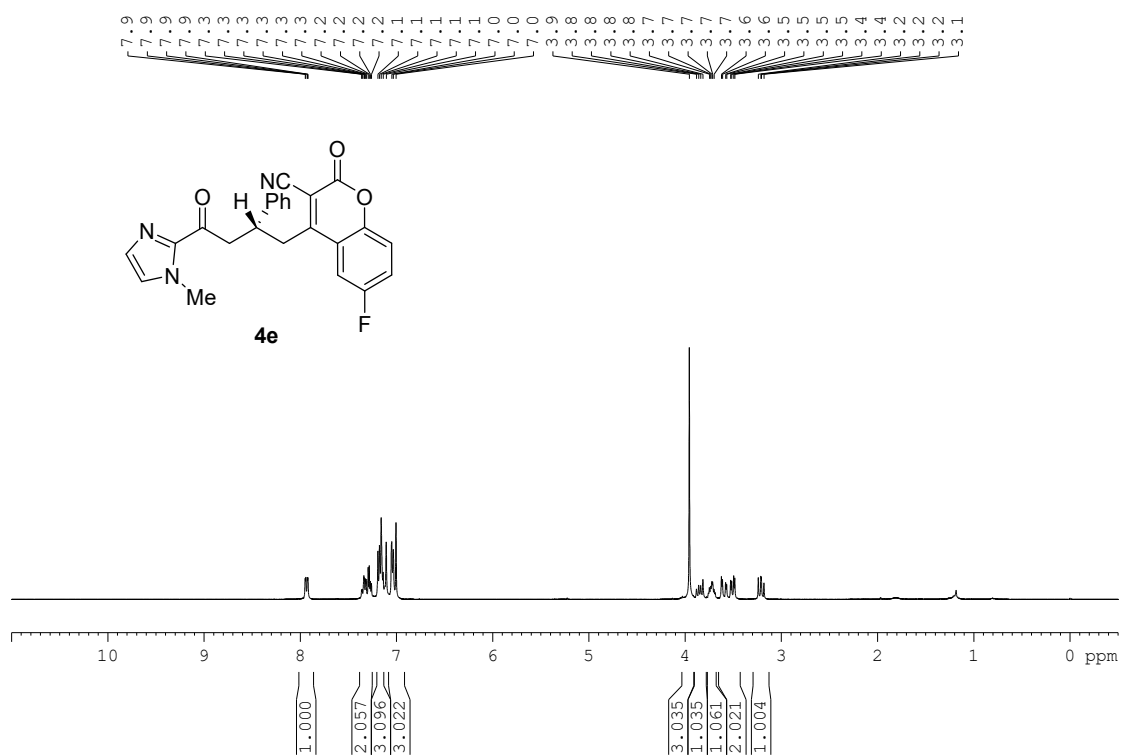
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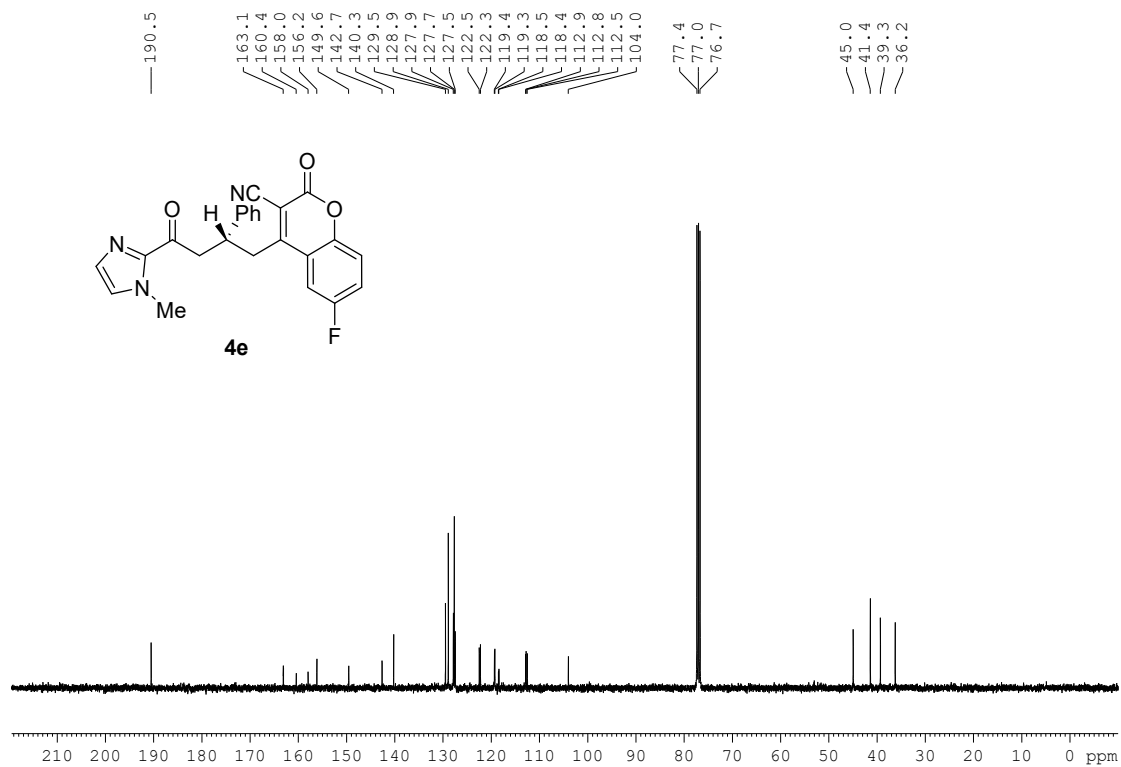
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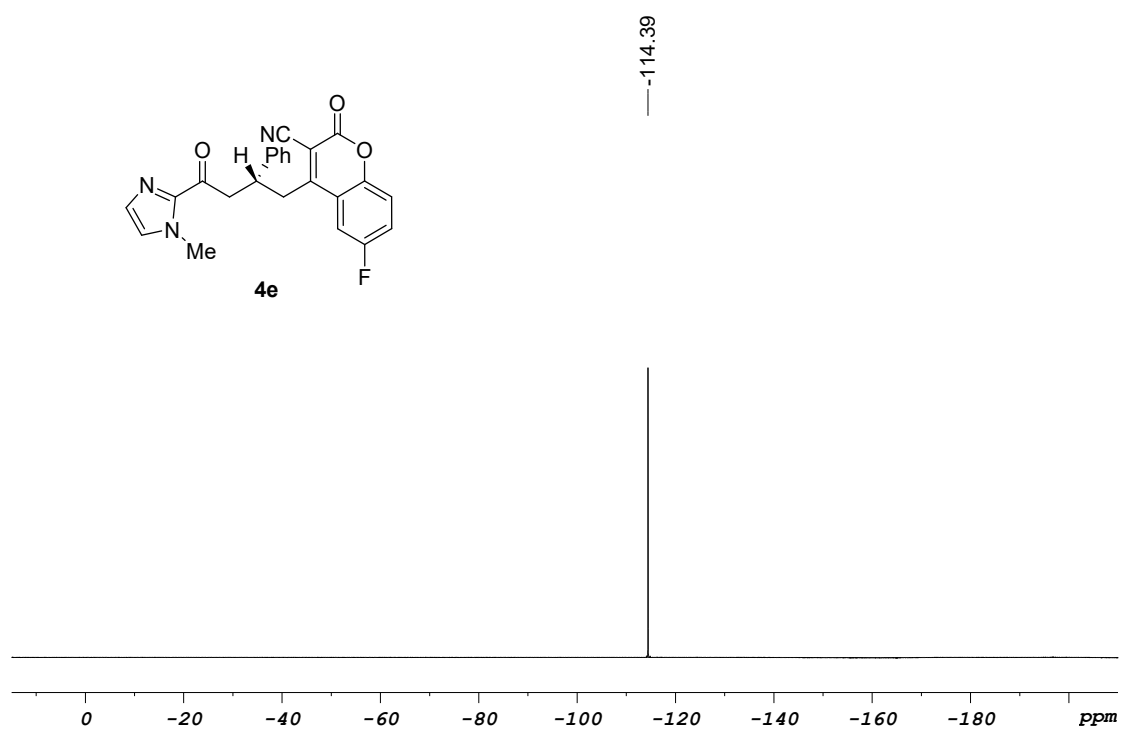
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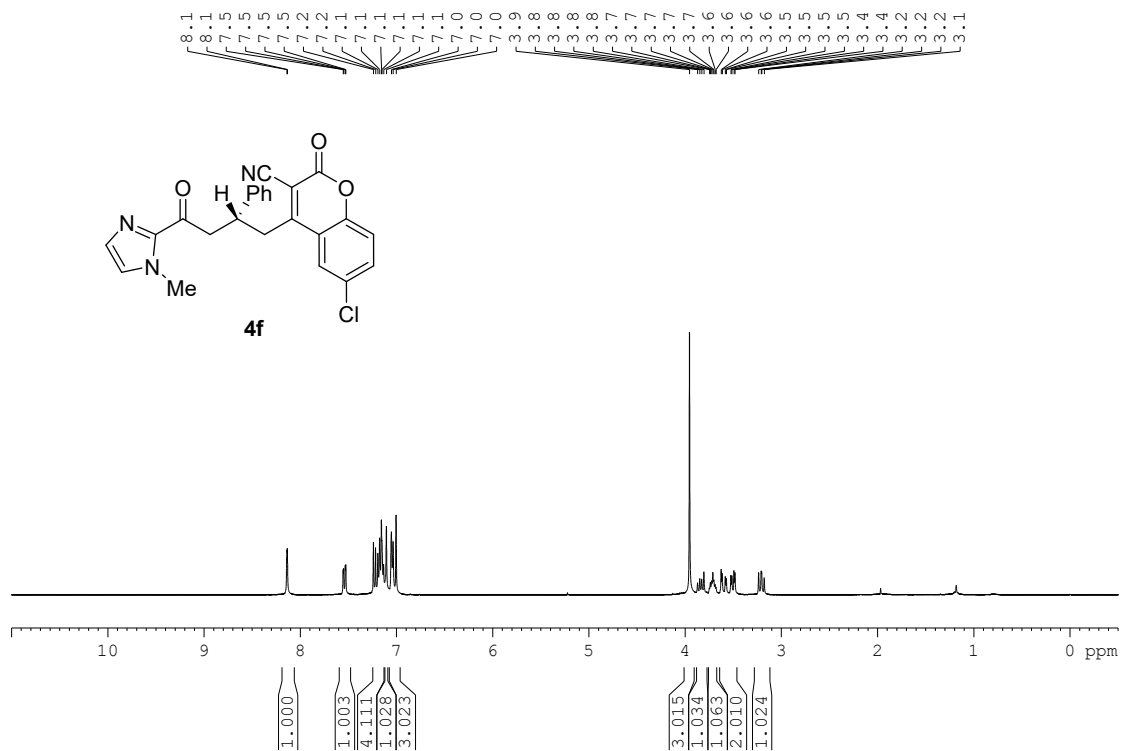
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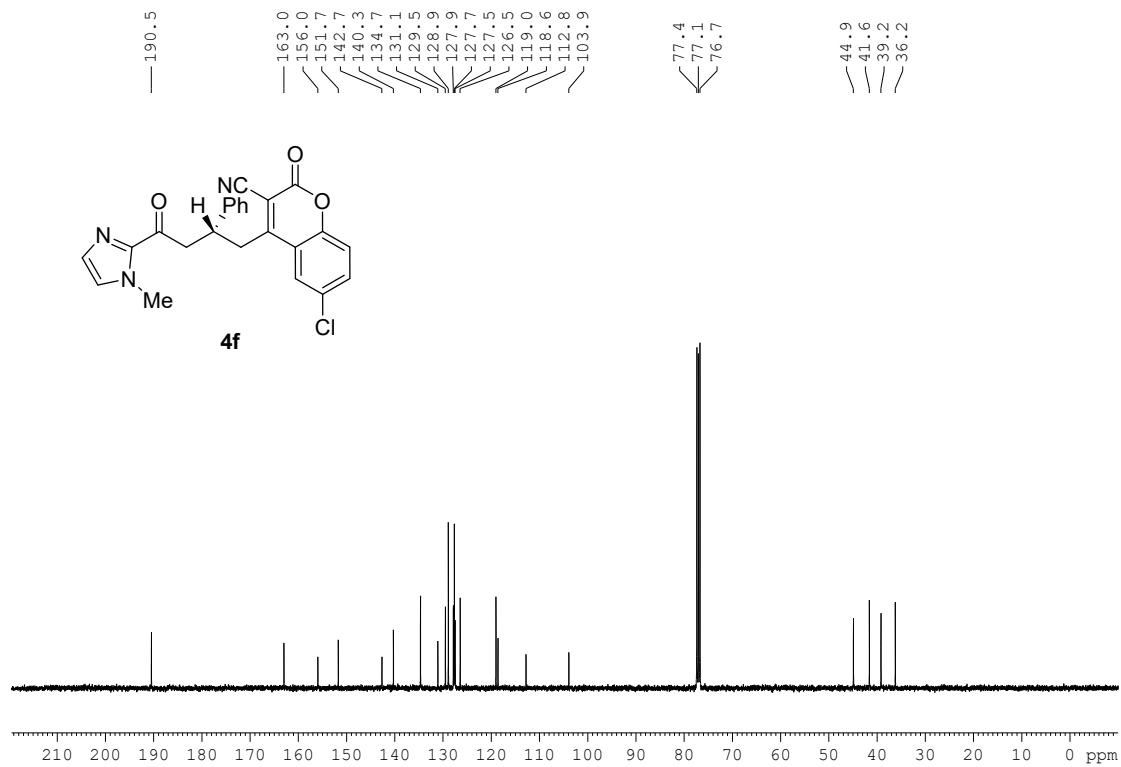
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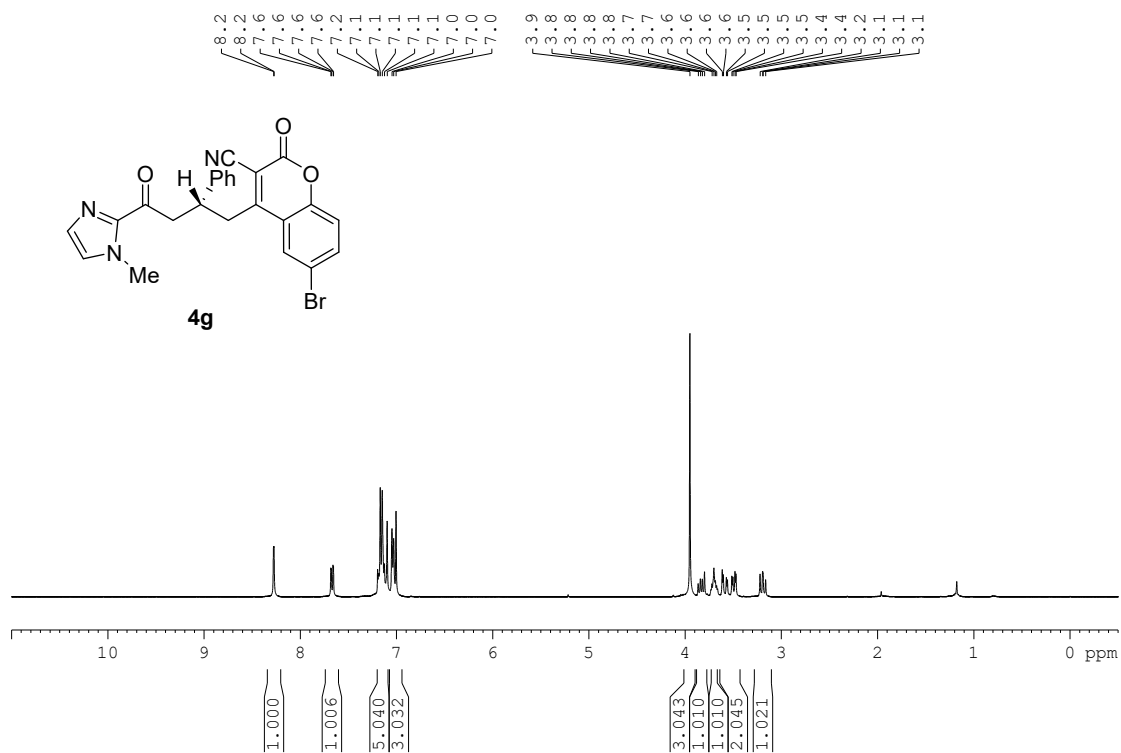
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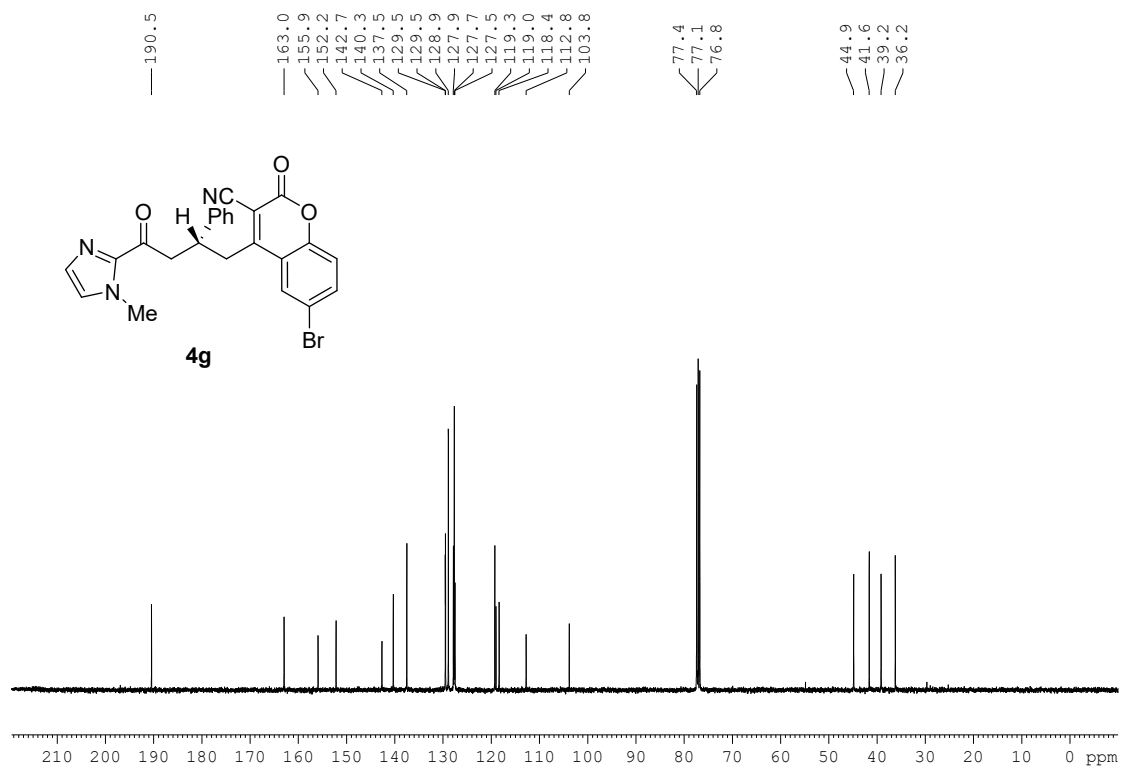
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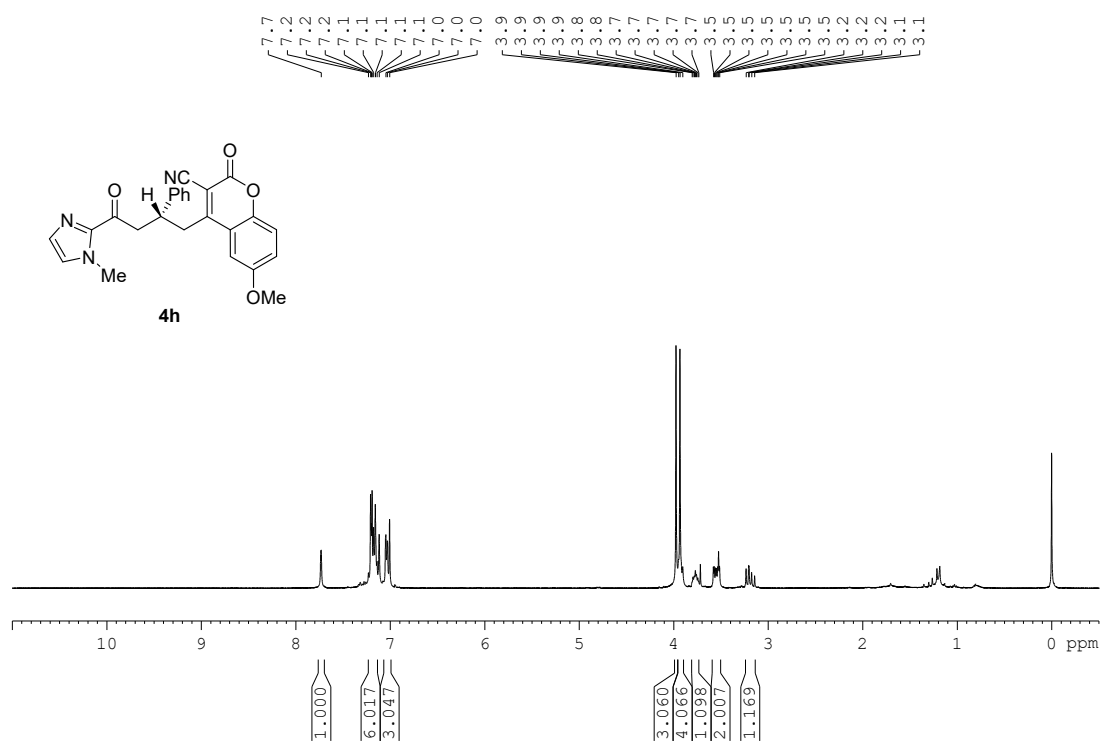
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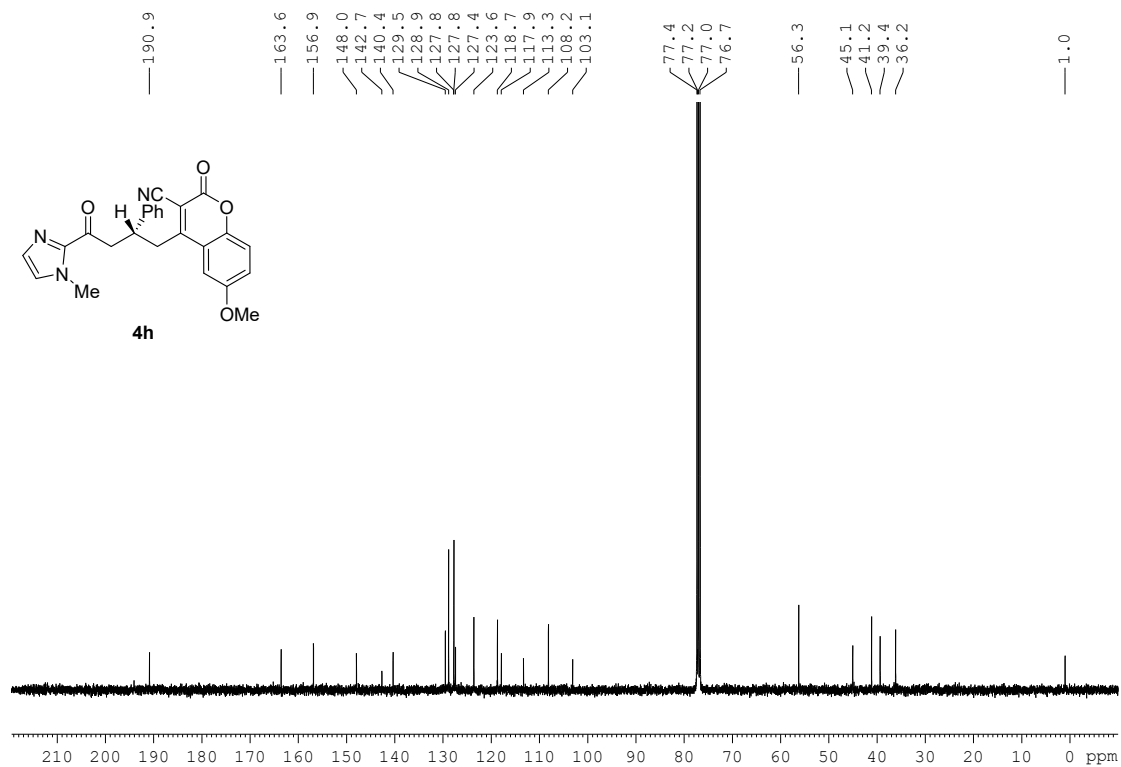
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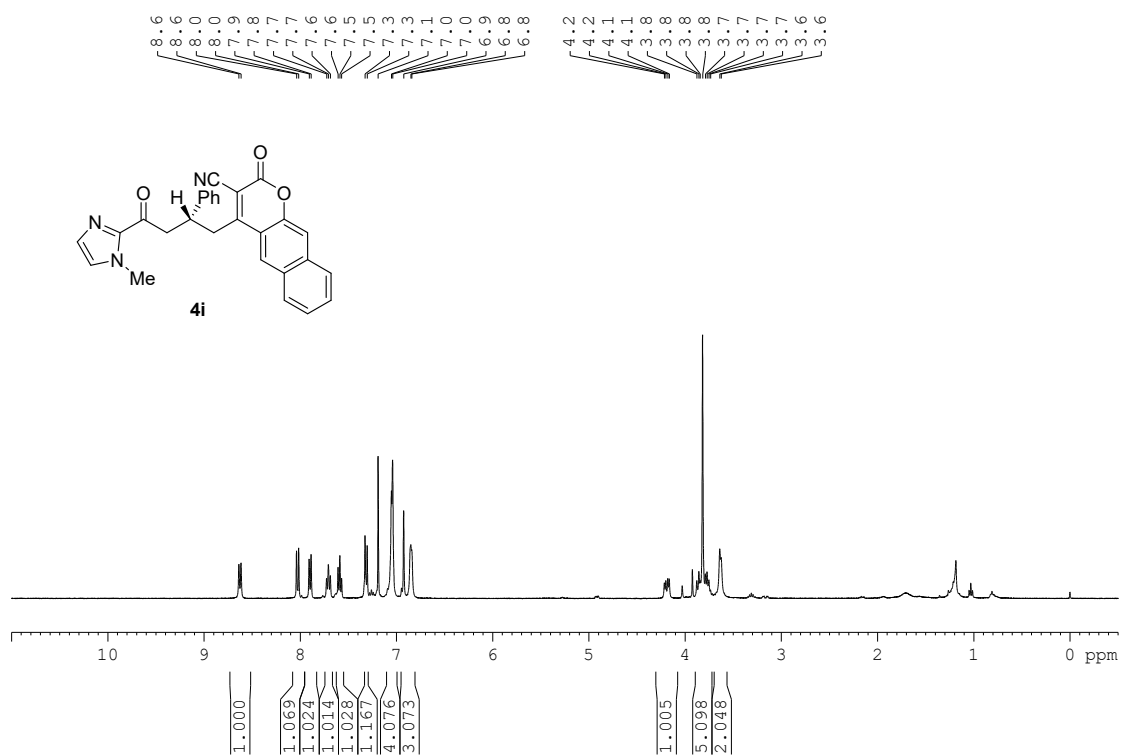
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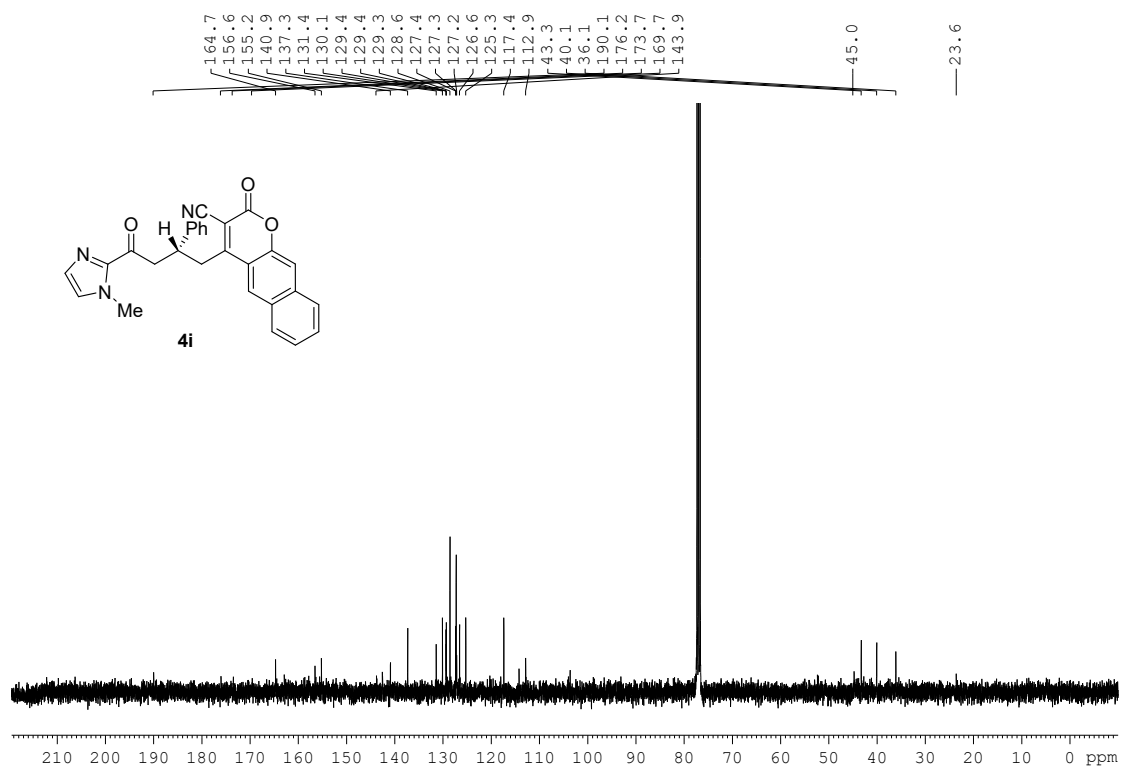
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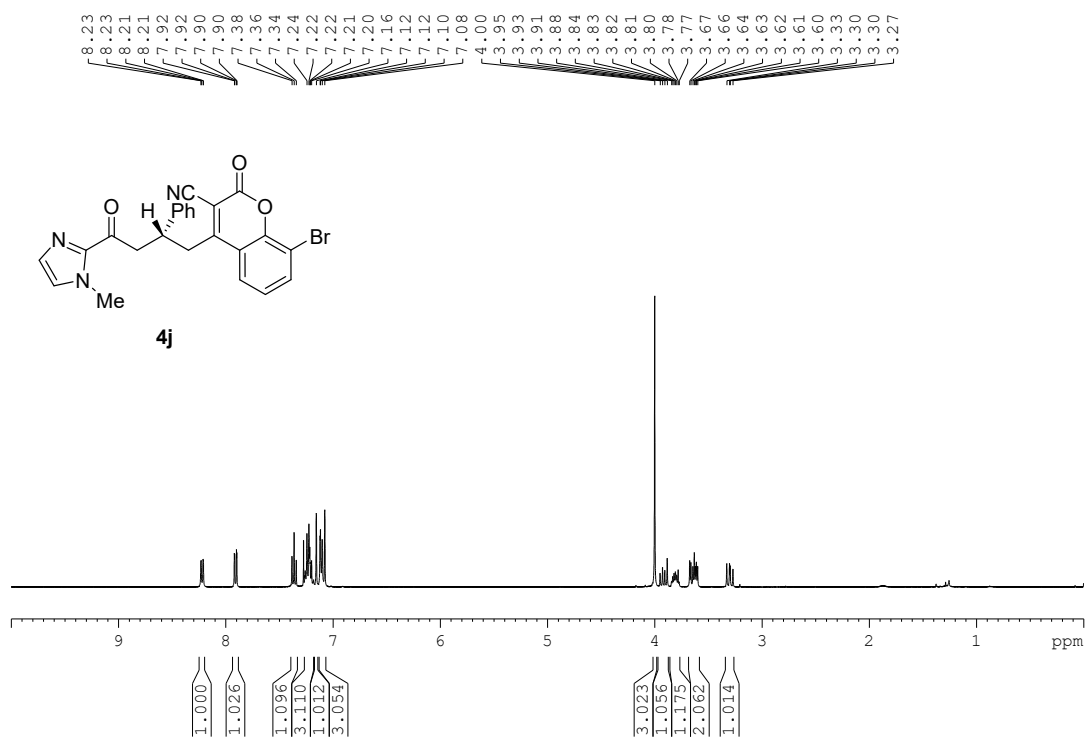
¹H NMR 4i



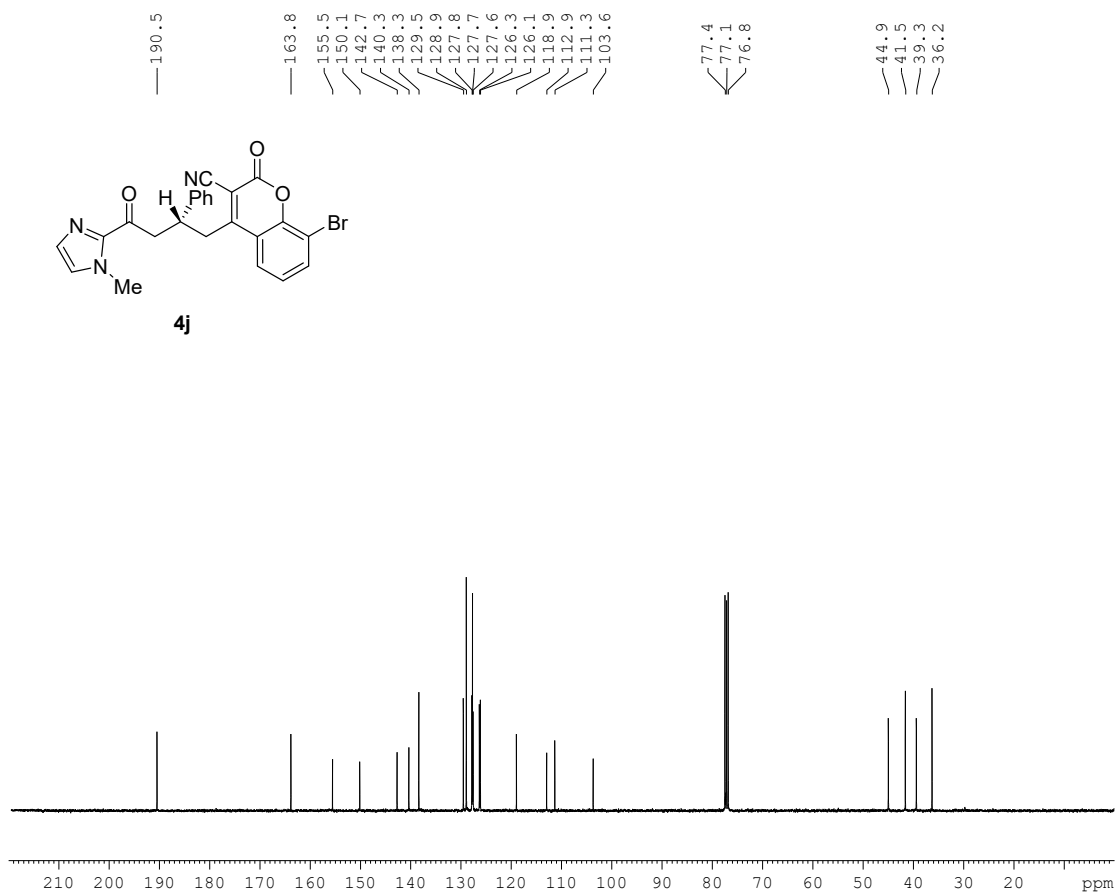
¹³C NMR 4i



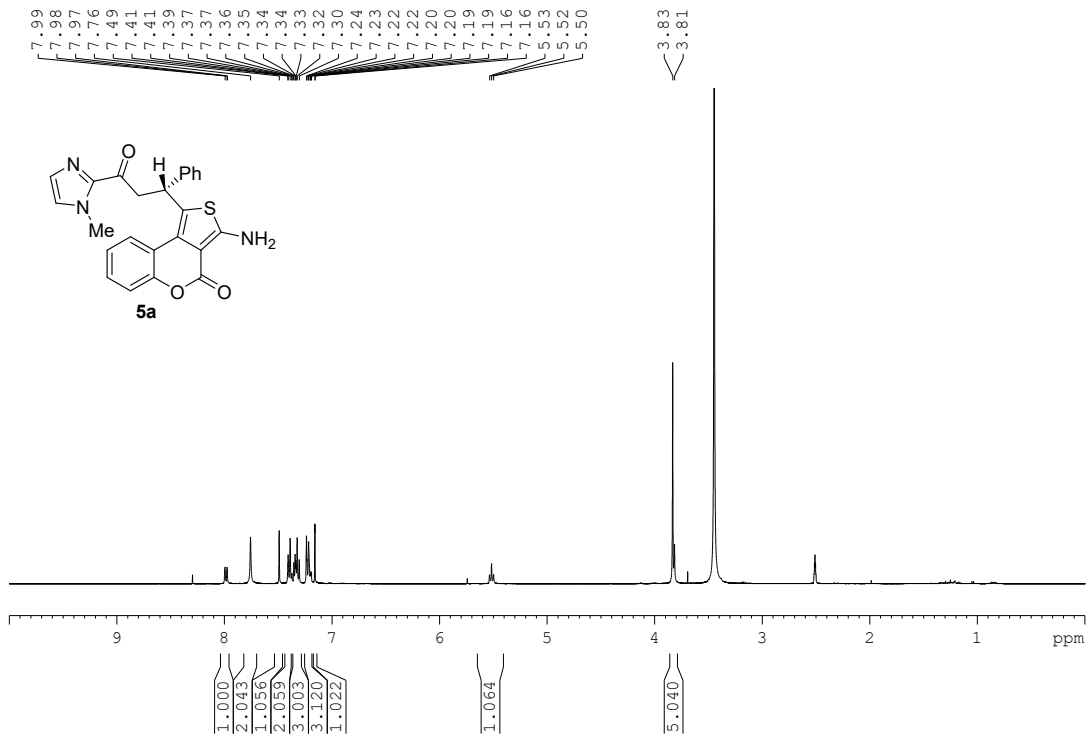
¹H NMR 4j



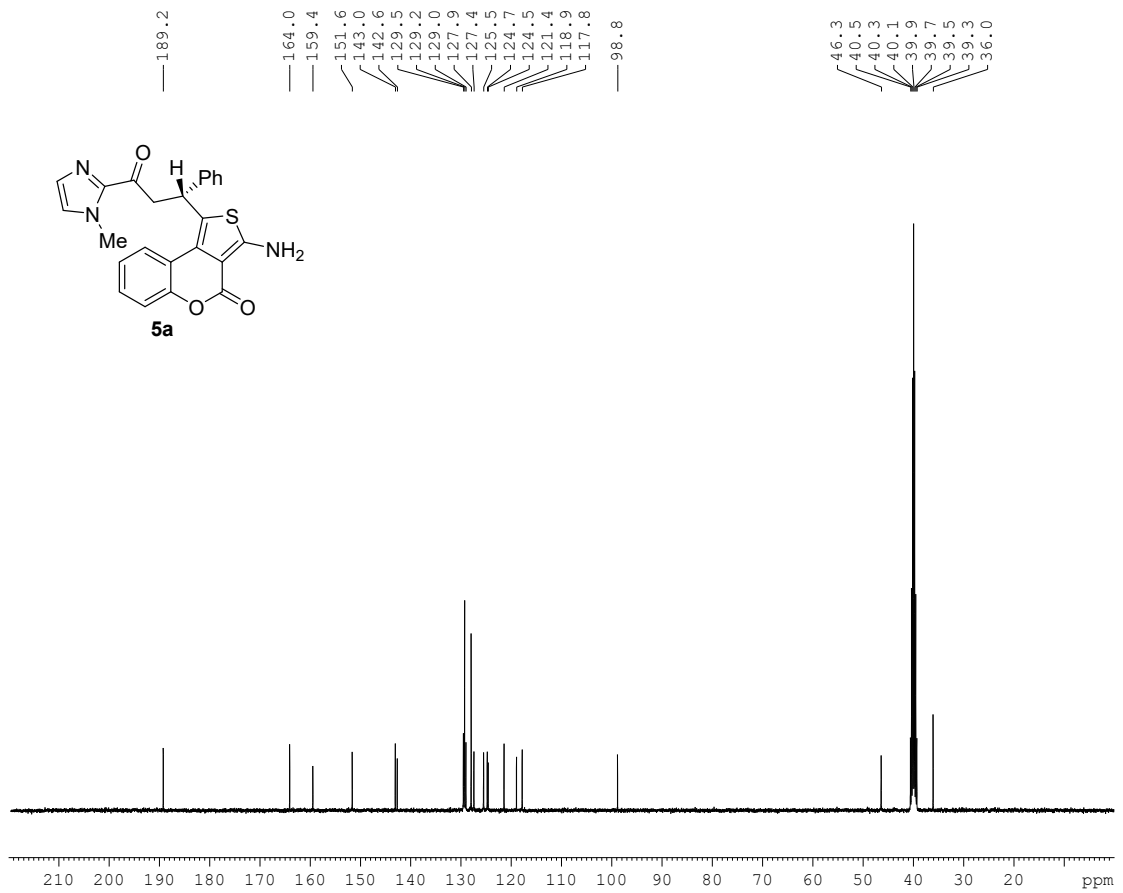
¹³C NMR 4j



¹H NMR 5a

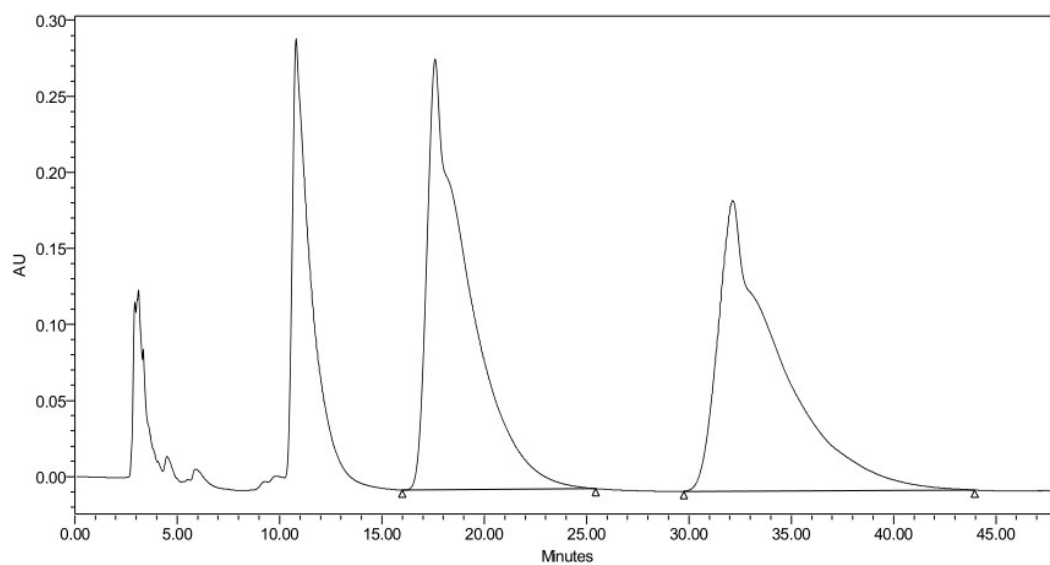


¹³C NMR 5a



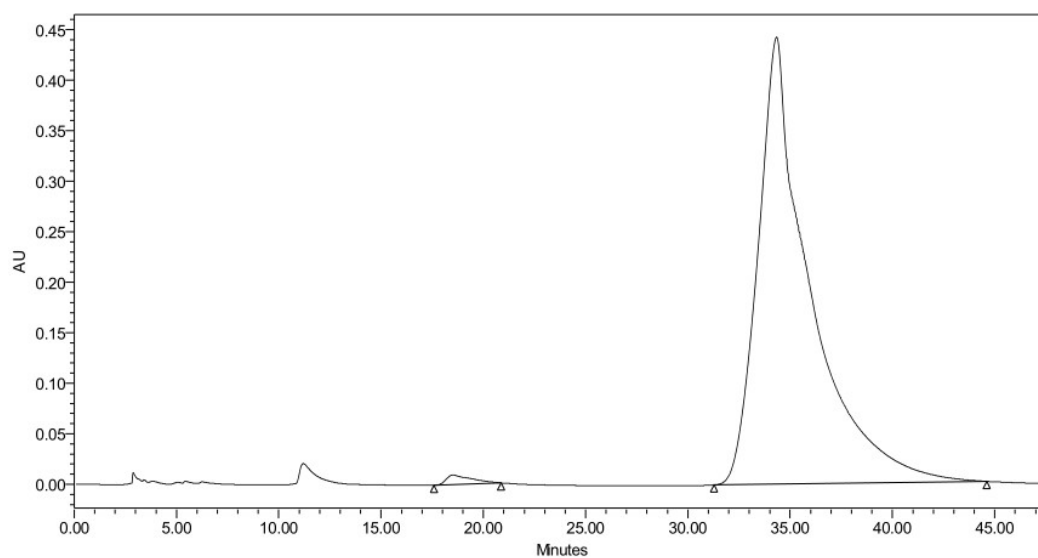
VI Chiral HPLC analysis trace

racemic-3a



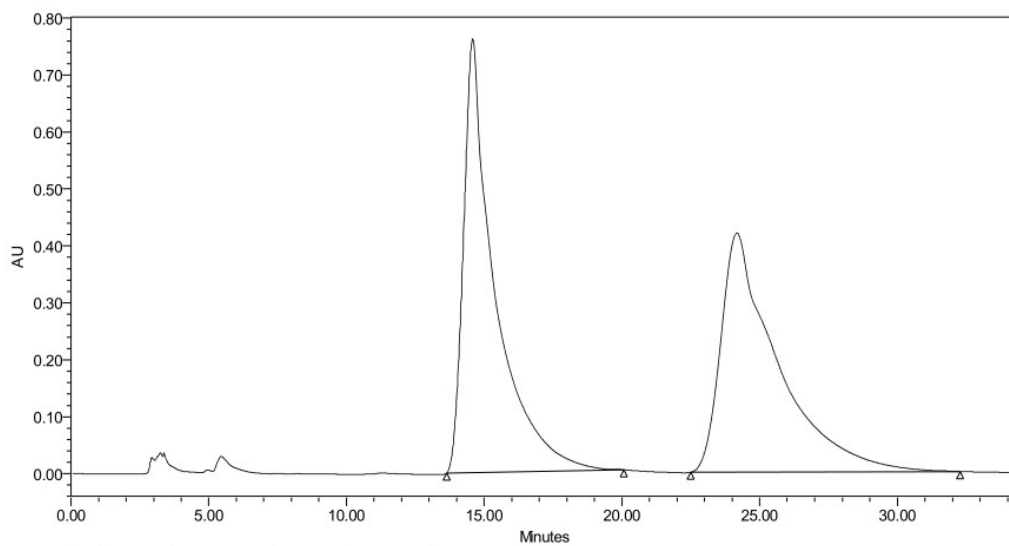
	RT	Area	% Area	Height
1	17.60	38792754	49.97	282987
2	32.13	38837646	50.03	190954

chiral-3a



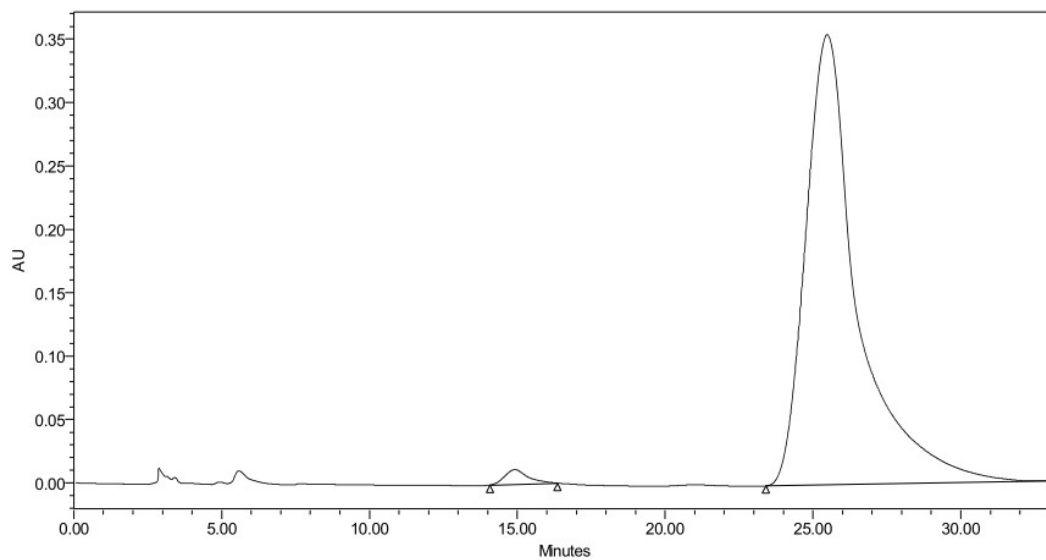
	RT	Area	% Area	Height
1	18.49	808463	1.03	9560
2	34.34	77344054	98.97	442524

racemic-3b



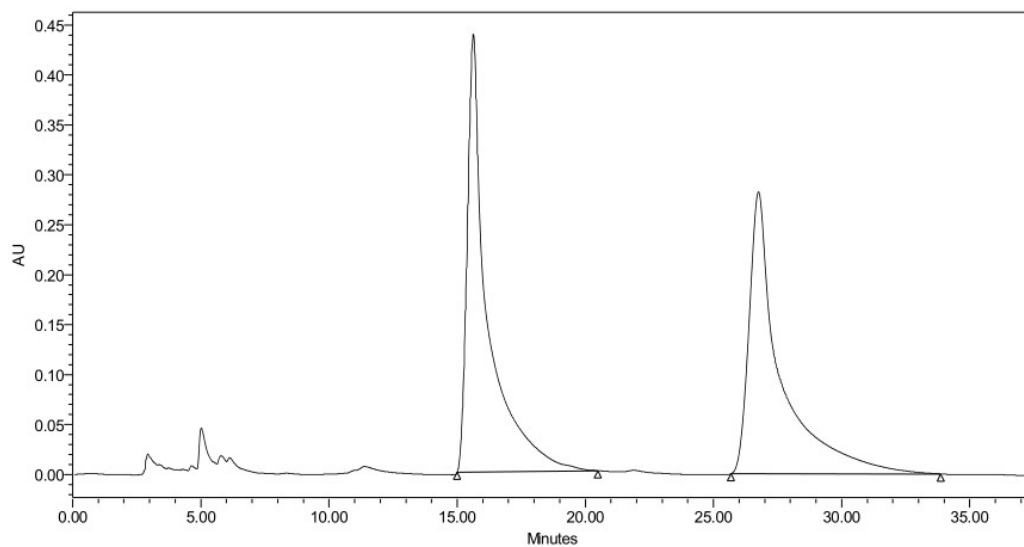
	RT	Area	% Area	Height
1	14.58	59891537	50.09	760997
2	24.18	59681671	49.91	419713

chiral-3b



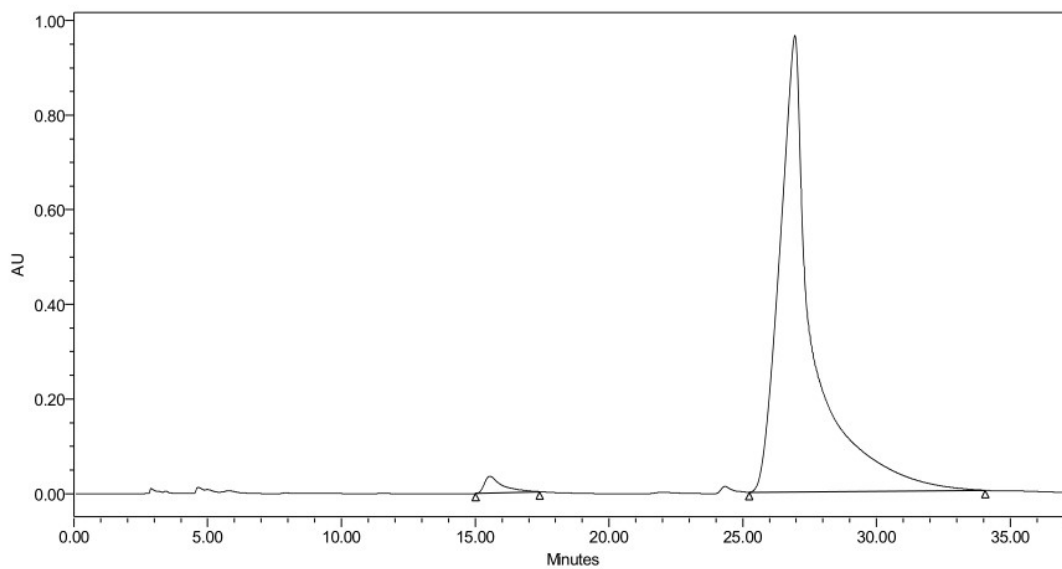
	RT	Area	% Area	Height
1	14.91	631811	1.44	11622
2	25.48	43318220	98.56	354975

racemic-3c



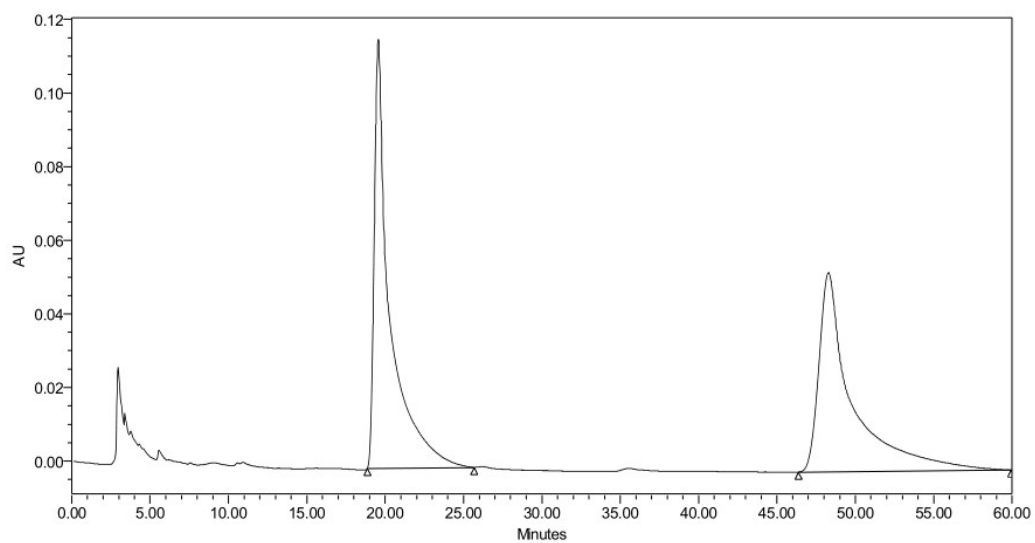
	RT	Area	% Area	Height
1	15.63	24071820	50.10	438179
2	26.76	23975007	49.90	282385

chiral-3c



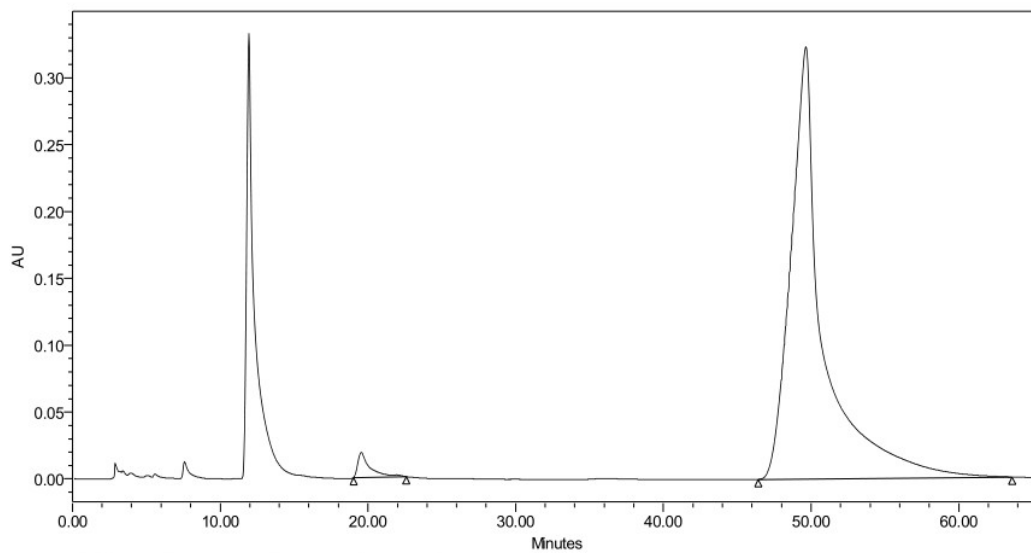
	RT	Area	% Area	Height
1	15.55	1700448	1.99	35621
2	26.95	83835456	98.01	964568

racemic-3d



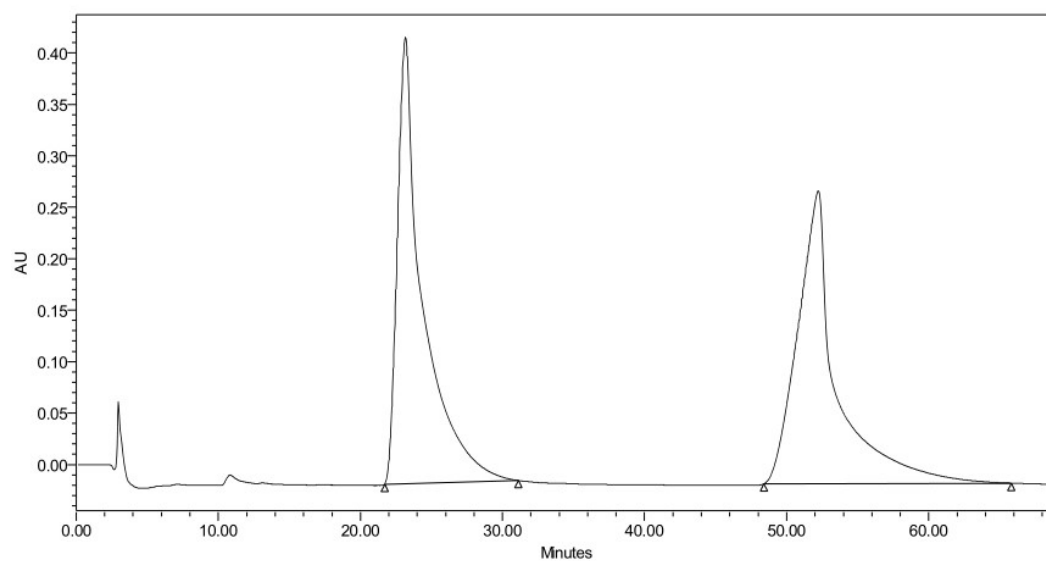
	RT	Area	% Area	Height
1	19.56	7988223	50.13	116475
2	48.29	7945908	49.87	54117

chiral-3d



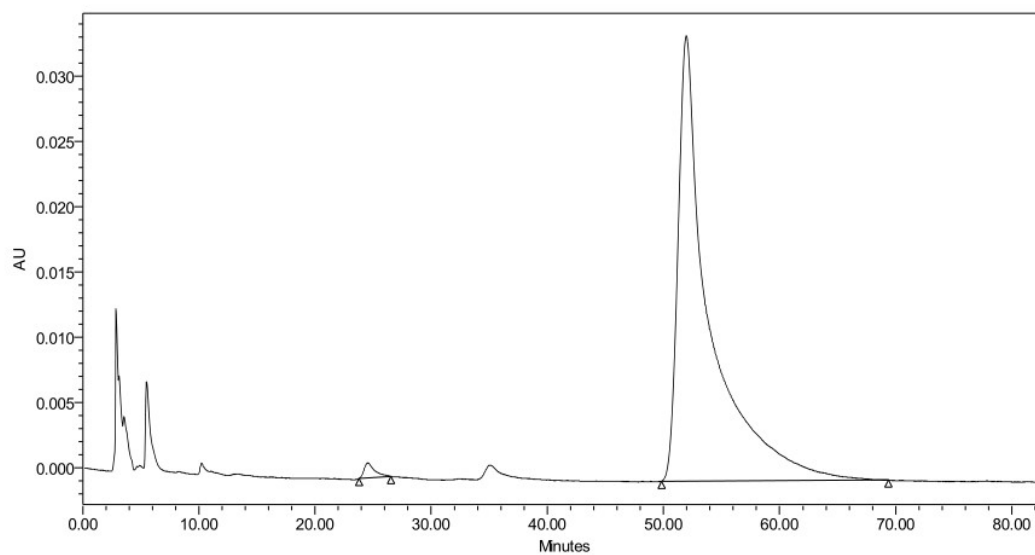
	RT	Area	% Area	Height
1	19.54	1073418	2.14	18644
2	49.64	49095586	97.86	323303

racemic-3e



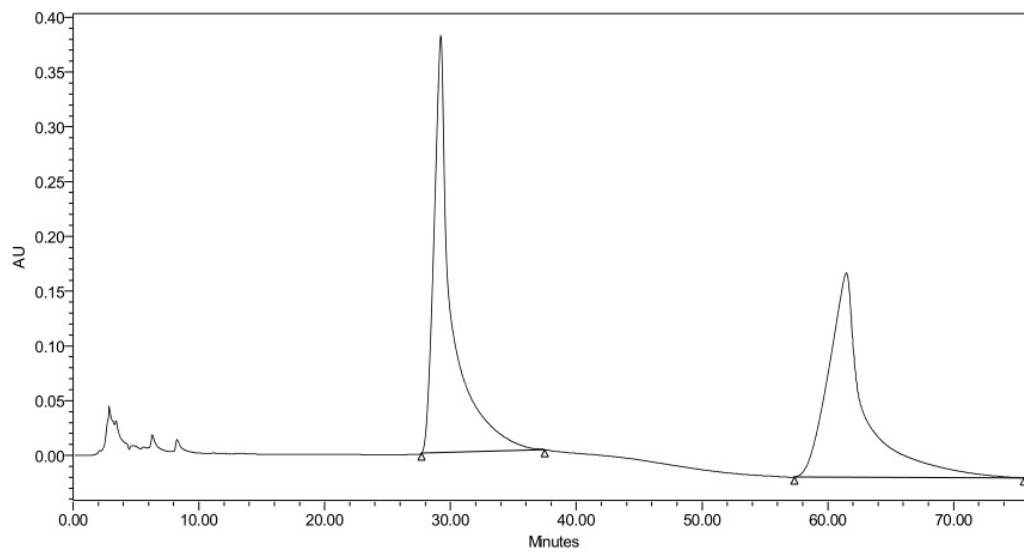
	RT	Area	% Area	Height
1	23.16	53786158	50.02	433397
2	52.22	53740921	49.98	284500

chiral-3e



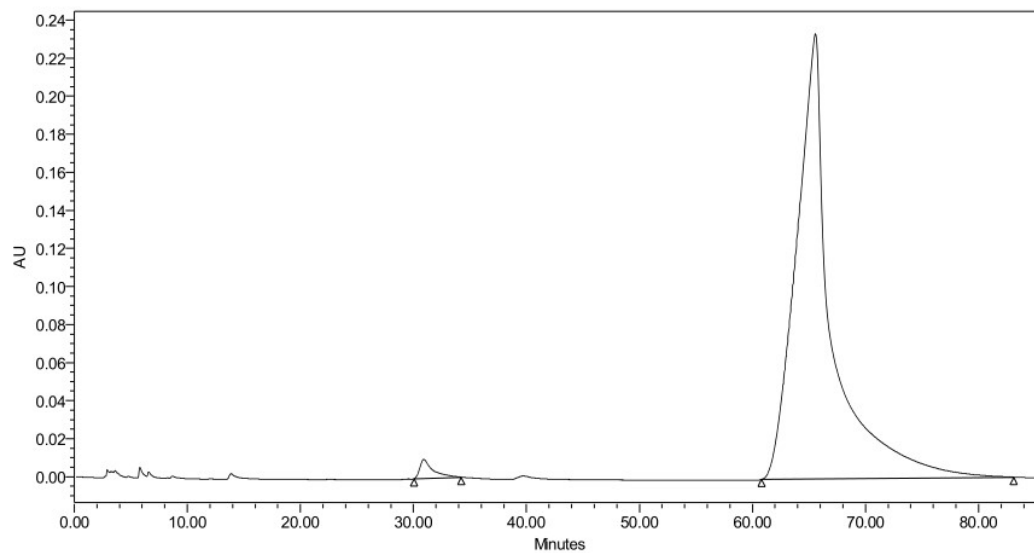
	RT	Area	% Area	Height
1	24.55	73072	1.13	1148
2	51.96	6399626	98.87	34119

racemic-3f



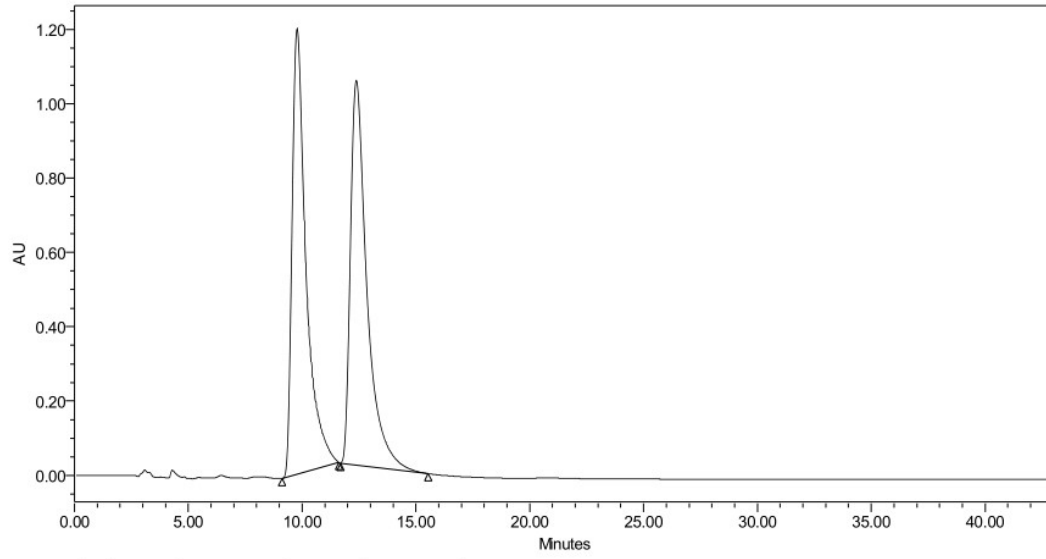
	RT	Area	% Area	Height
1	29.23	37293827	50.10	380567
2	61.47	37151031	49.90	186543

chiral-3f



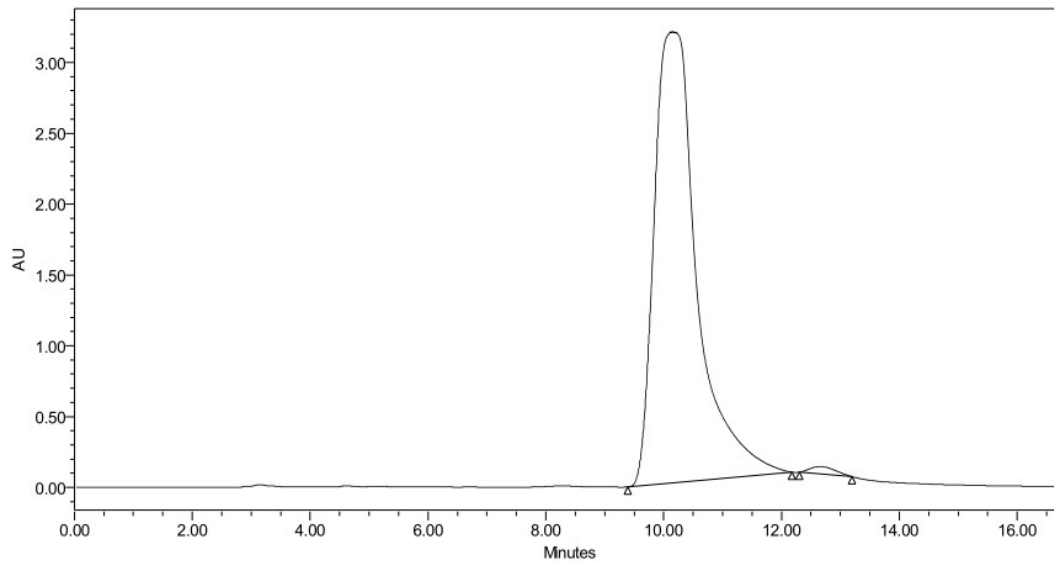
	RT	Area	% Area	Height
1	30.91	810288	1.56	9964
2	65.56	51185245	98.44	233954

racemic-3g



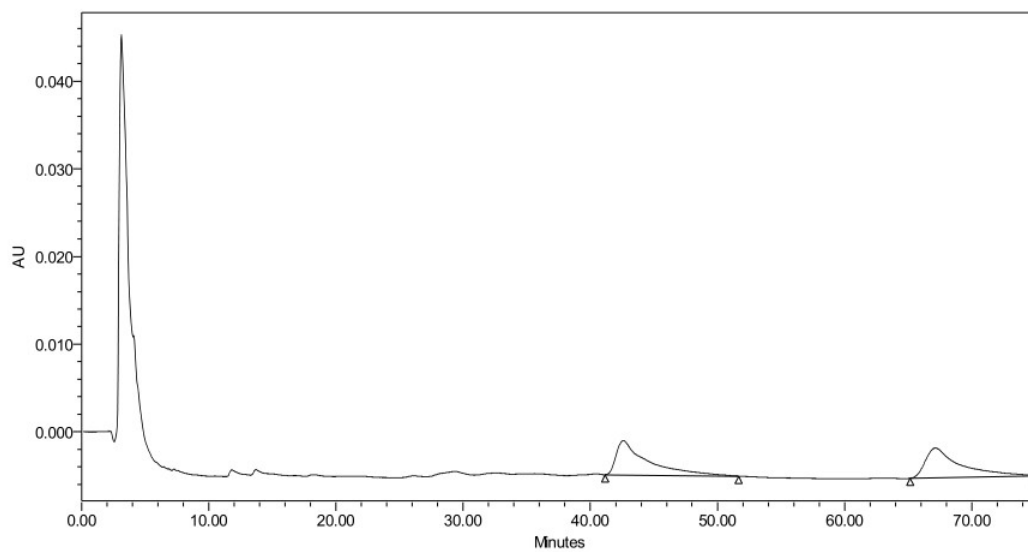
	RT	Area	% Area	Height
1	9.78	51272316	49.46	1200061
2	12.38	52381793	50.54	1035688

chiral-3g



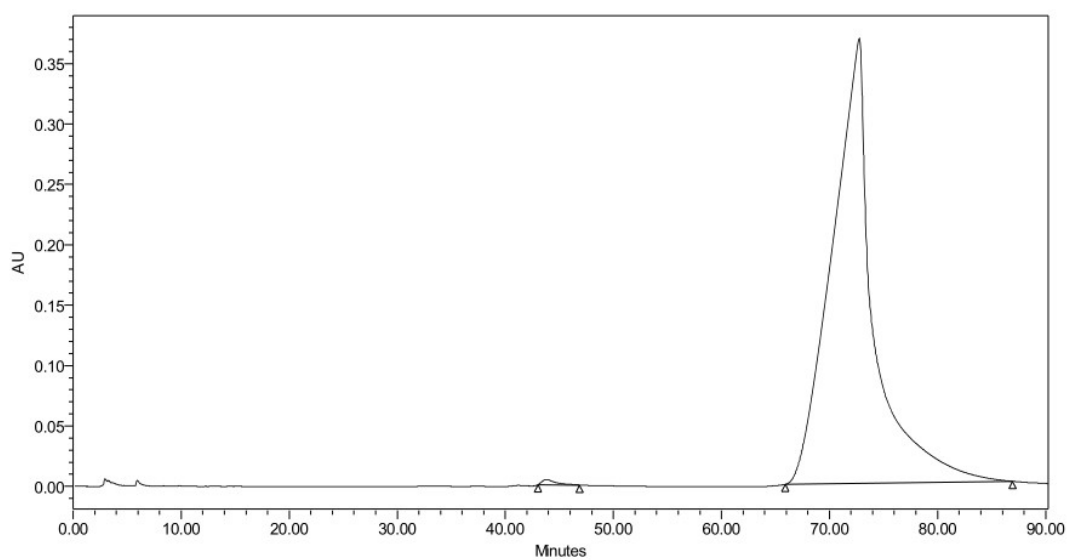
	RT	Area	% Area	Height
1	10.13	161465666	99.03	3185577
2	12.69	1576647	0.97	52764

racemic-3h



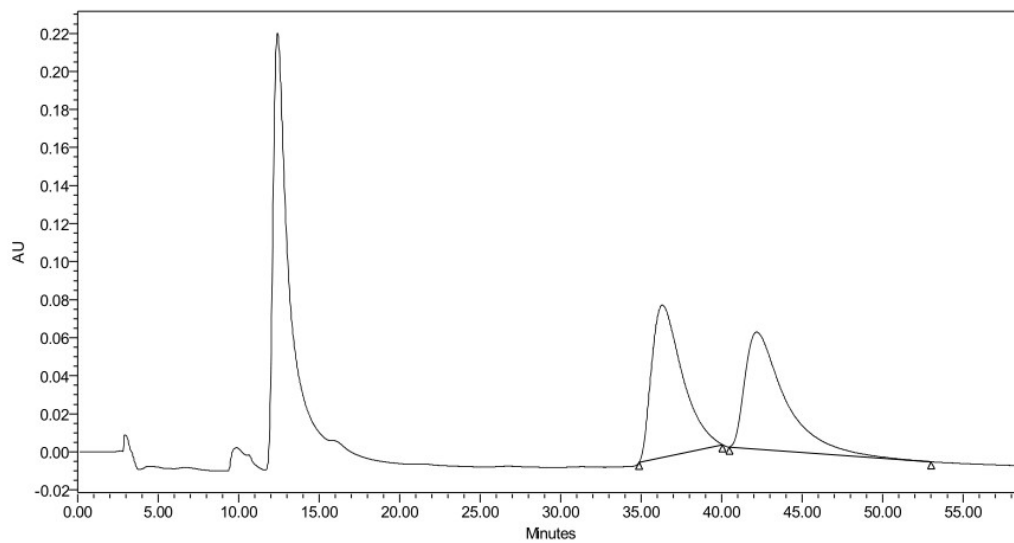
	RT	Area	% Area	Height
1	42.60	669547	50.78	3905
2	67.10	648865	49.22	3401

chiral-3h



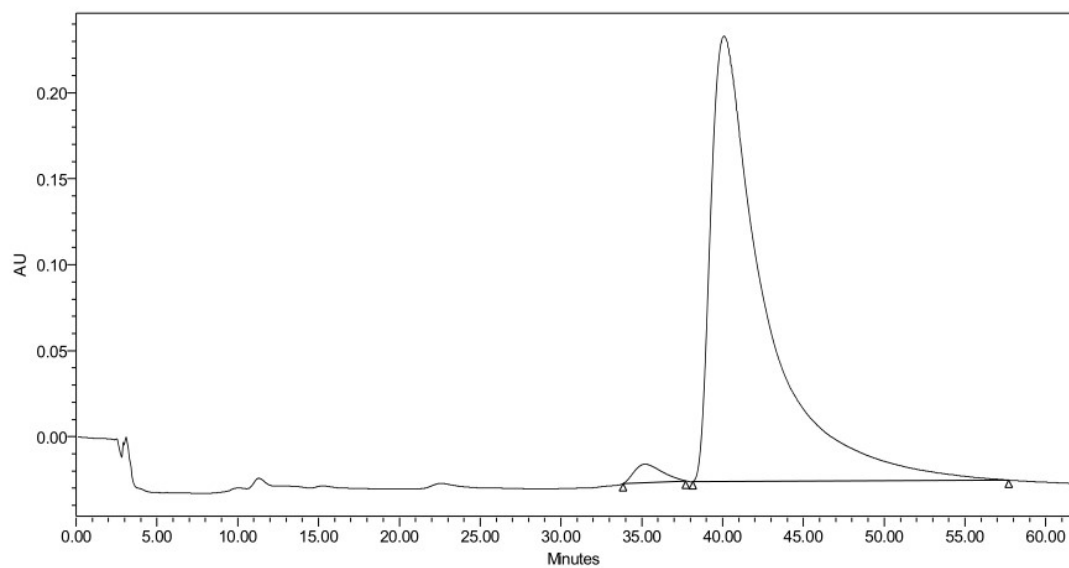
	RT	Area	% Area	Height
1	43.80	369865	0.37	4246
2	72.77	99079474	99.63	368592

racemic-3i



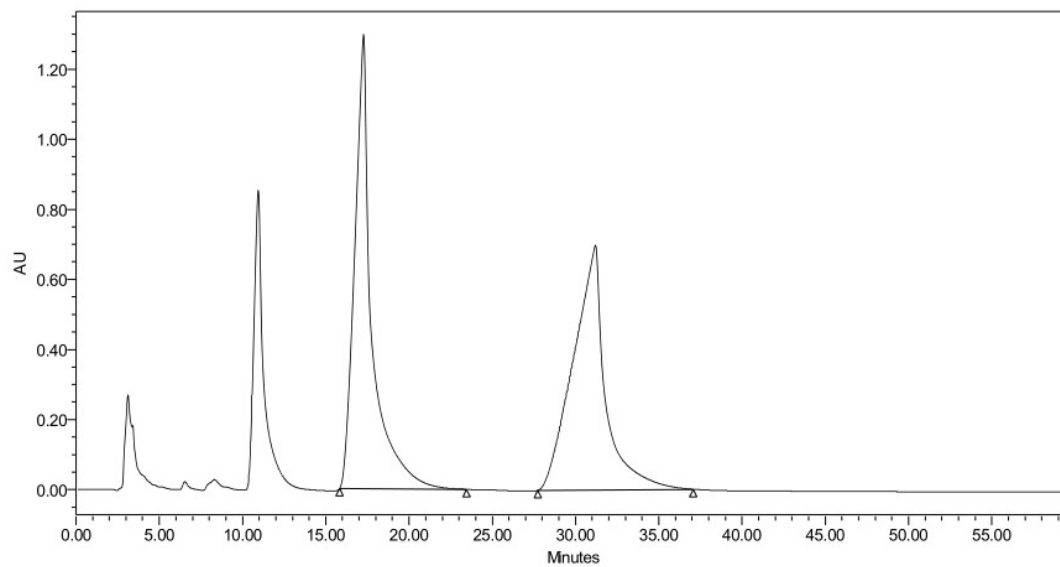
	RT	Area	% Area	Height
1	36.30	10653240	50.13	80221
2	42.17	10597094	49.87	61441

chiral-3i



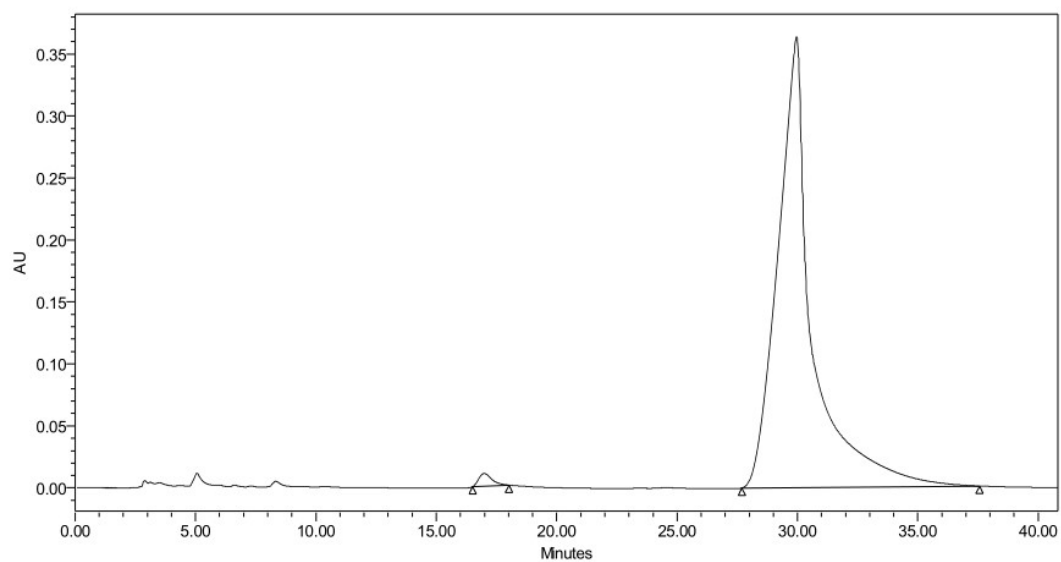
	RT	Area	% Area	Height
1	35.19	1275354	2.09	10673
2	40.09	59787686	97.91	258851

racemic-3j



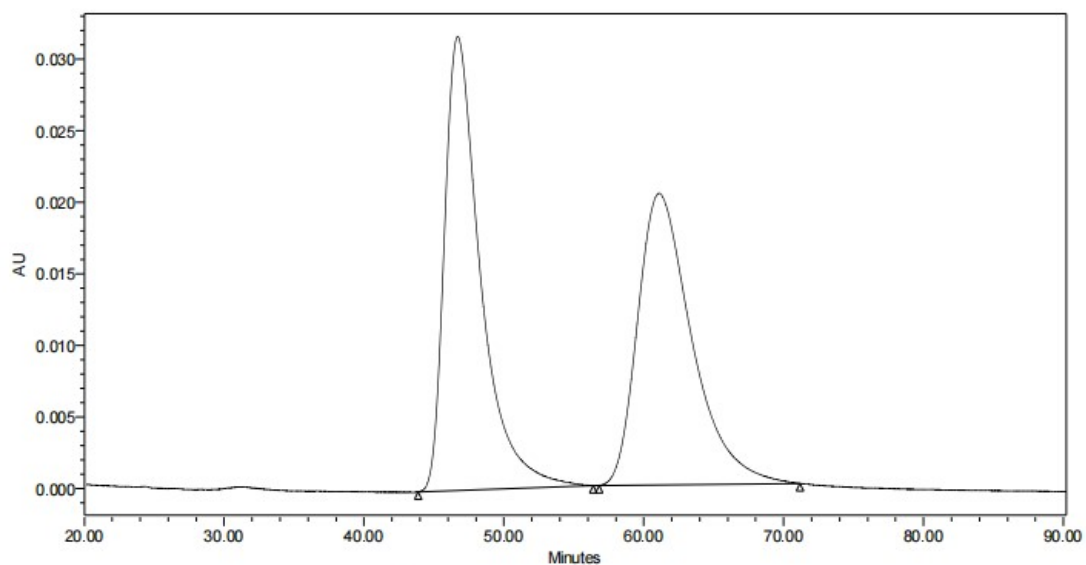
	RT	Area	% Area	Height
1	17.27	93114697	49.85	1296543
2	31.19	93659365	50.15	698957

chiral-3j



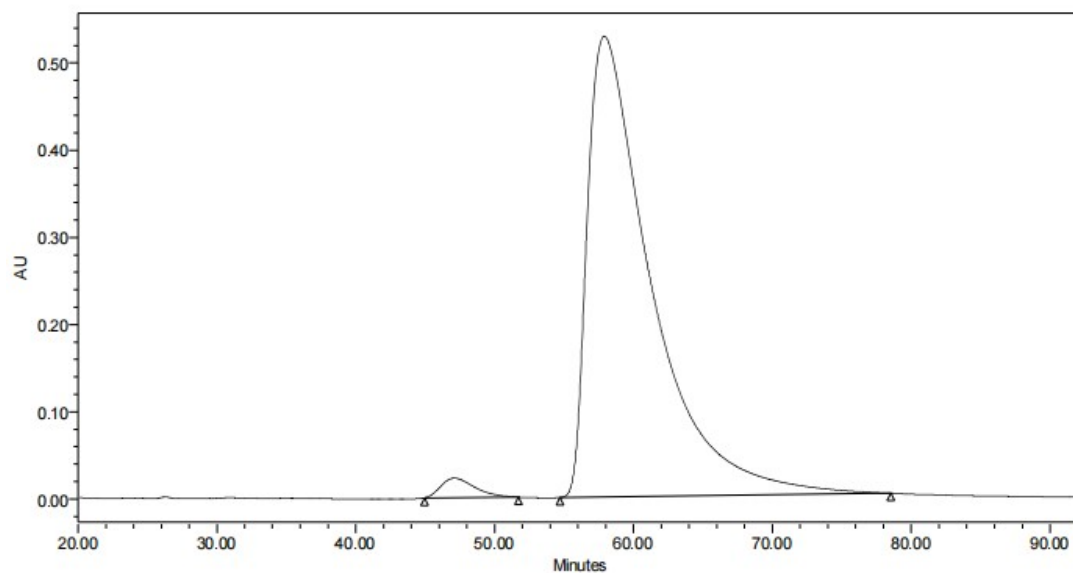
	RT	Area	% Area	Height
1	16.99	393860	1.08	10229
2	29.97	35944416	98.92	363606

racemic-3k



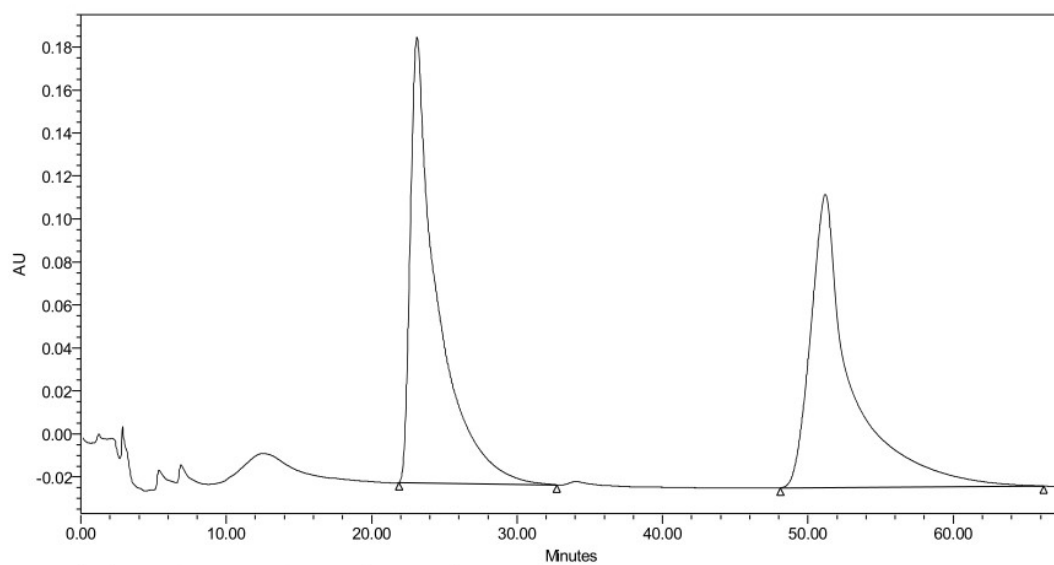
	RT	Area	% Area	Height
1	46.69	5672452	50.98	31707
2	61.10	5453900	49.02	20360

chiral-3k



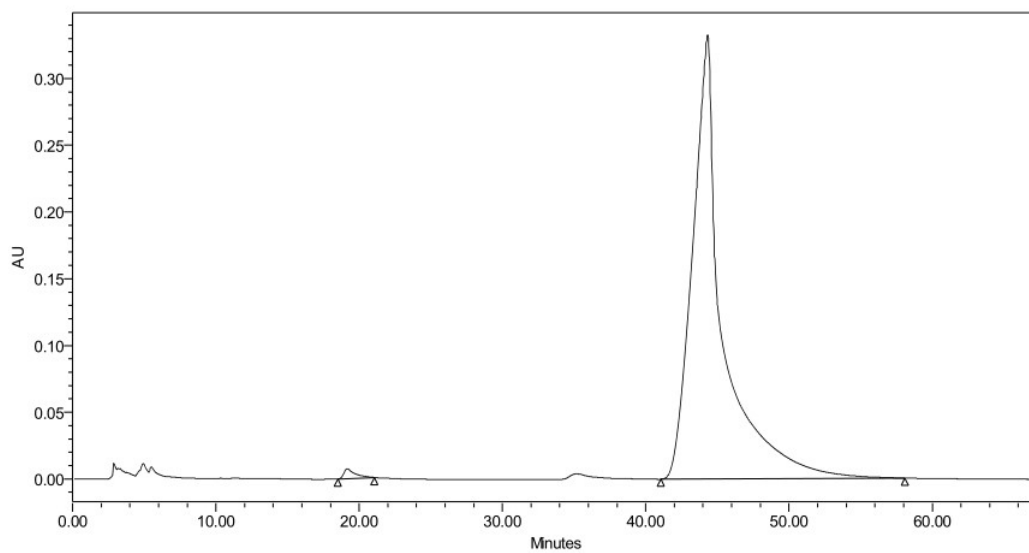
	RT	Area	% Area	Height
1	47.09	3796293	2.20	22364
2	57.91	169063944	97.80	528339

racemic-3l



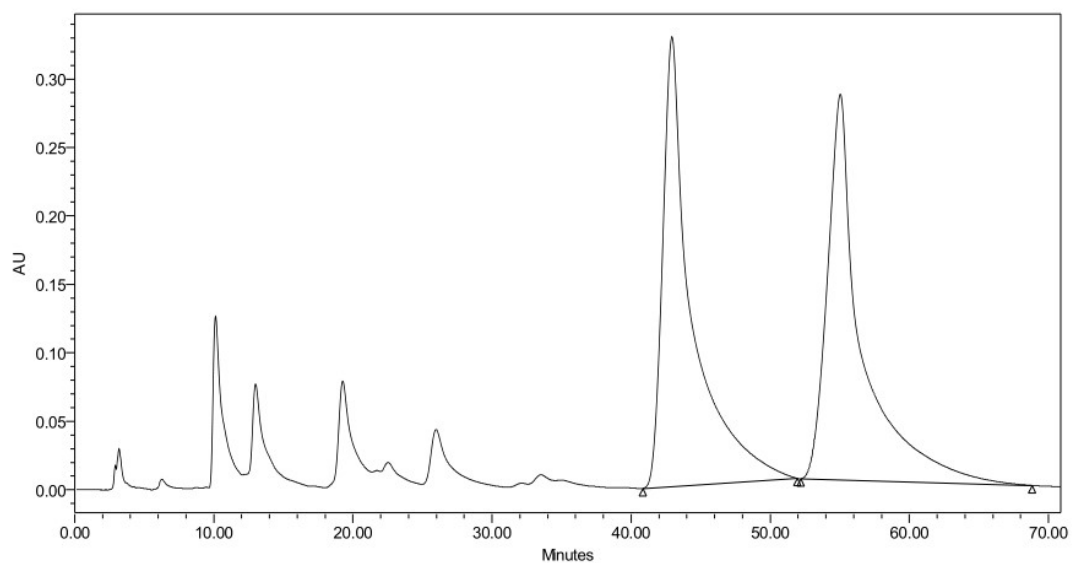
	RT	Area	% Area	Height
1	23.11	26374984	50.00	207102
2	51.19	26379485	50.00	136382

chiral-3l



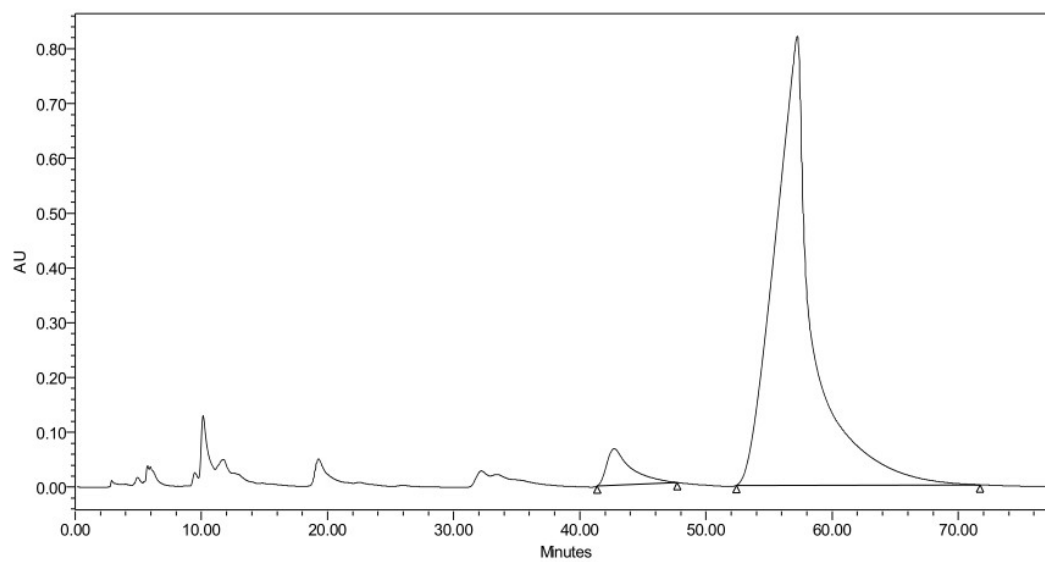
	RT	Area	% Area	Height
1	19.18	413027	0.84	7498
2	44.32	48472129	99.16	332622

racemic-3m



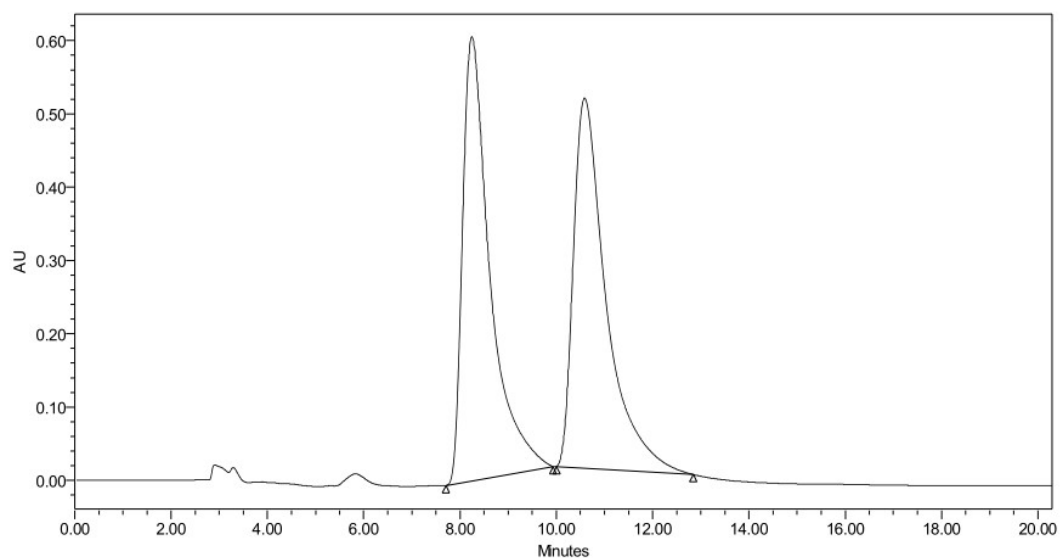
	RT	Area	% Area	Height
1	42.93	48244367	50.05	328450
2	55.03	48147778	49.95	281660

chiral-3m



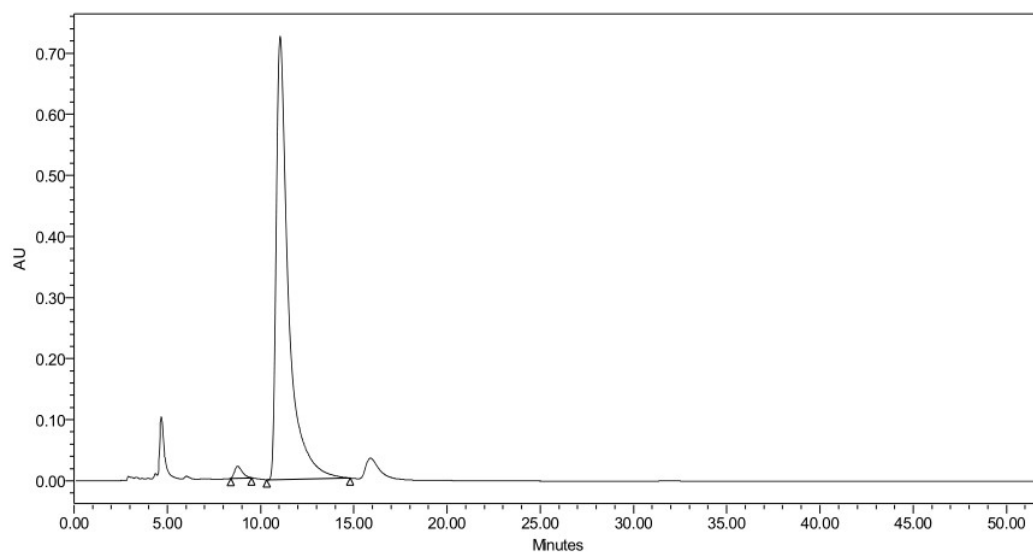
	RT	Area	% Area	Height
1	42.71	8961139	4.95	66750
2	57.24	172090558	95.05	819254

racemic-3n



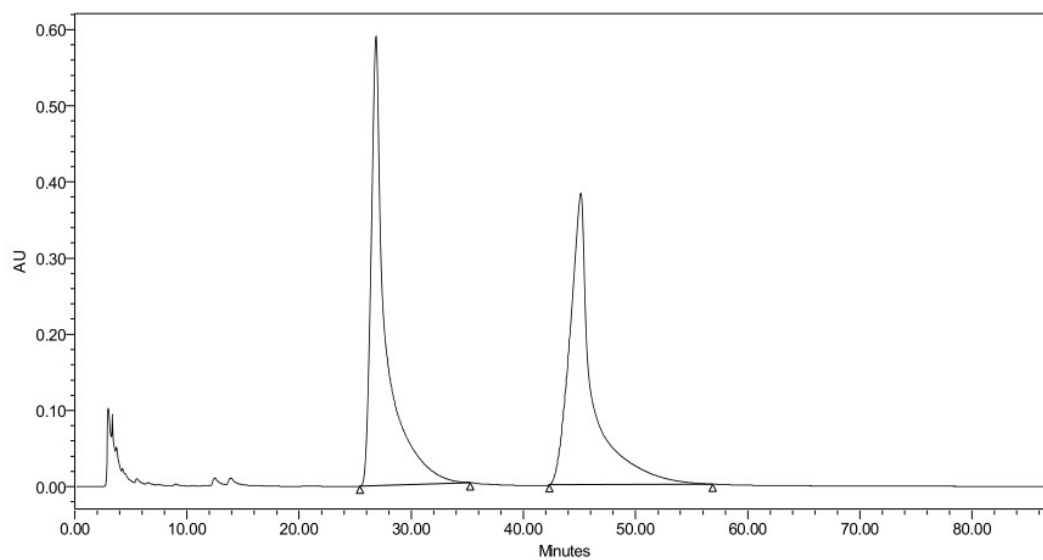
	RT	Area	% Area	Height
1	8.25	23830678	49.94	605751
2	10.59	23890581	50.06	504813

chiral-3n



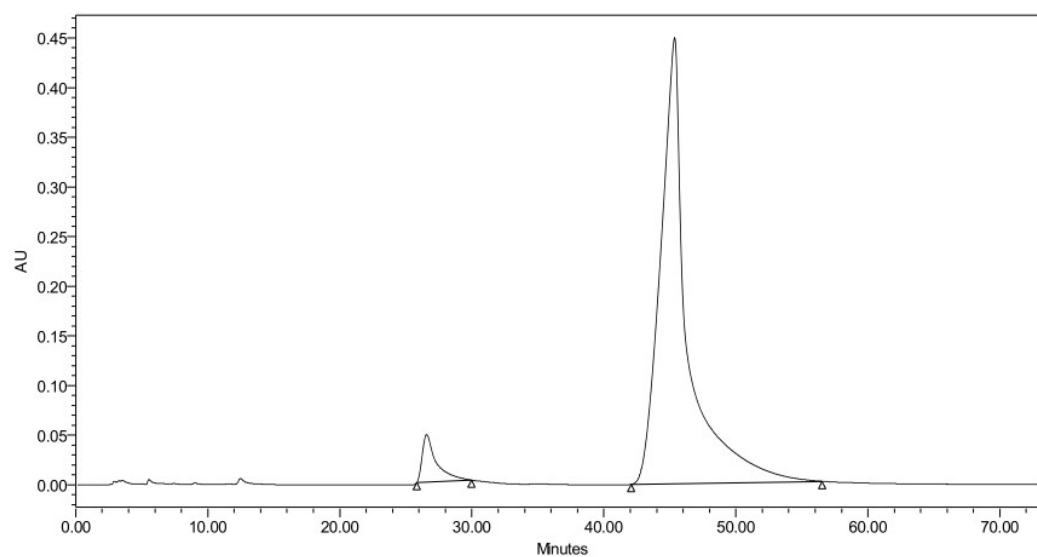
	RT	Area	% Area	Height
1	8.77	549507	1.63	19286
2	11.05	33214965	98.37	725477

racemic-3o



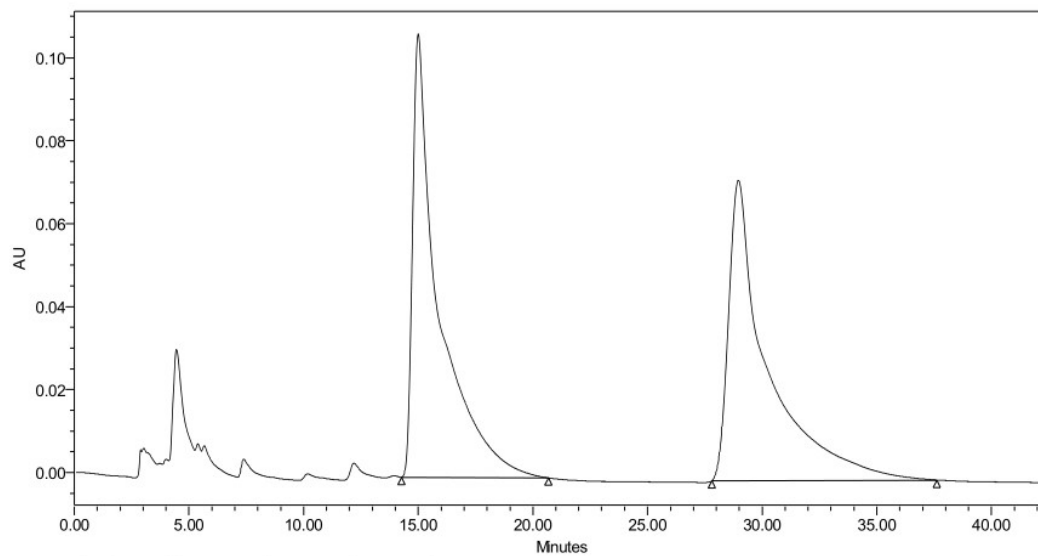
	RT	Area	% Area	Height
1	26.86	53229257	49.96	590122
2	45.10	53308742	50.04	382759

chiral-3o



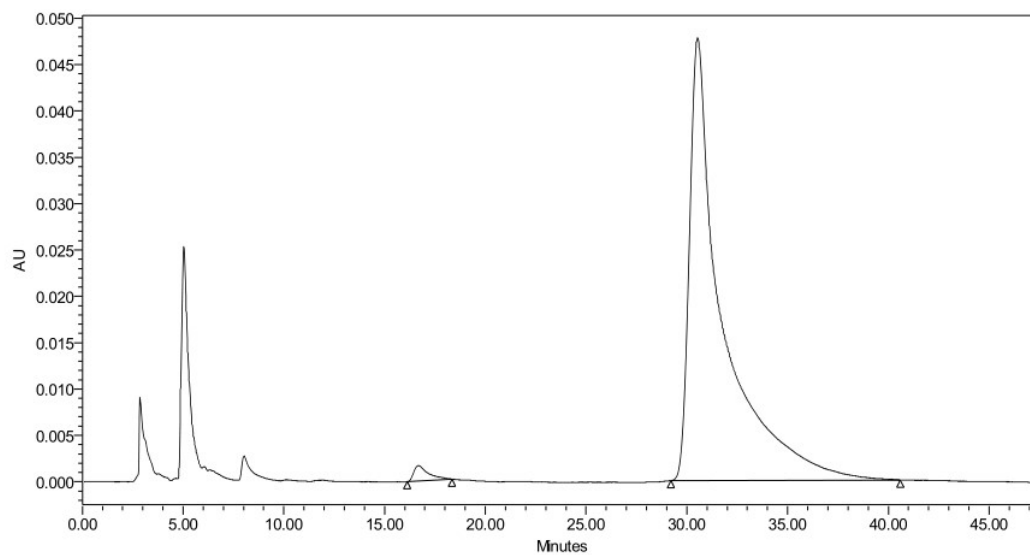
	RT	Area	% Area	Height
1	26.57	3556334	5.23	47717
2	45.36	64464966	94.77	449147

racemic-4b



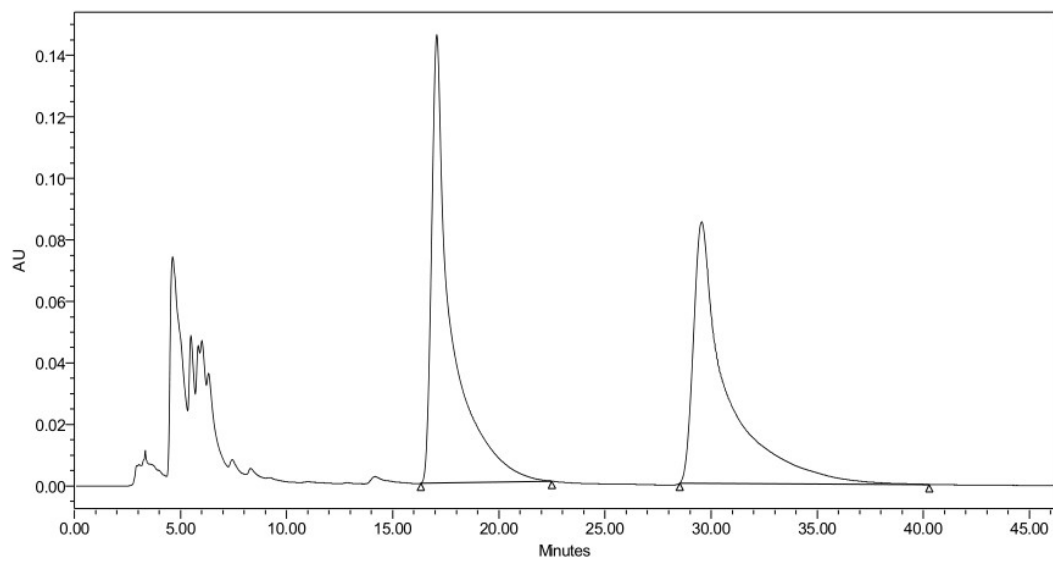
	RT	Area	% Area	Height
1	14.99	8488614	49.97	106896
2	28.96	8498589	50.03	72403

chiral-4b



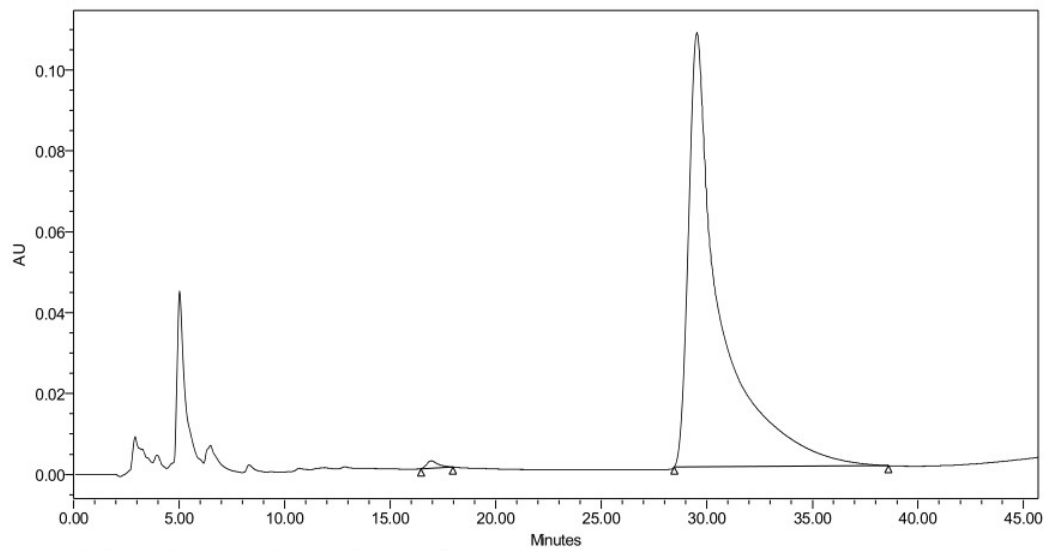
	RT	Area	% Area	Height
1	16.67	84168	1.53	1682
2	30.53	5415418	98.47	47757

racemic-4c



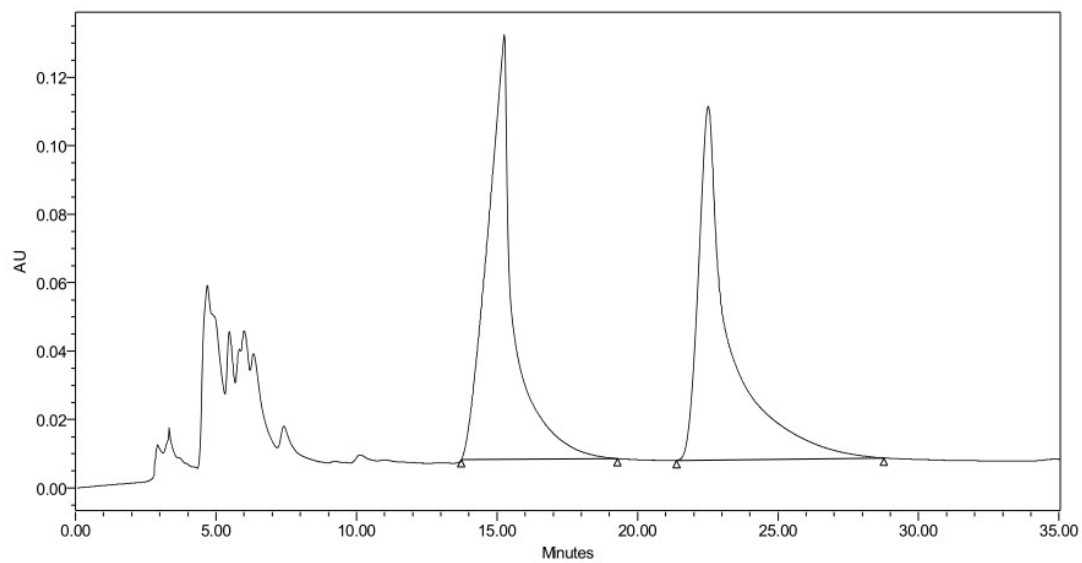
	RT	Area	% Area	Height
1	17.07	9287910	50.20	145672
2	29.56	9212575	49.80	85091

chiral-4c



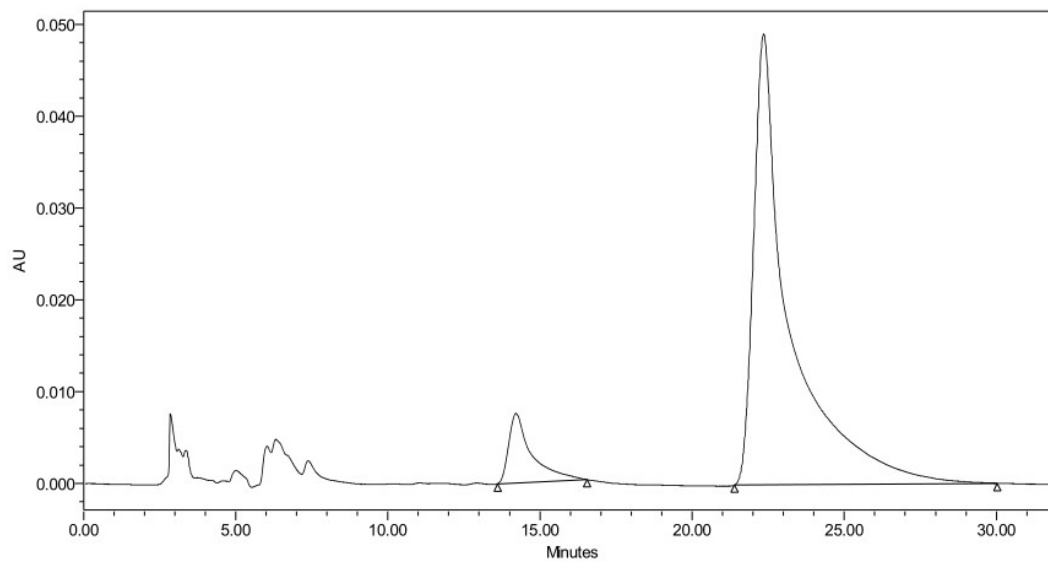
	RT	Area	% Area	Height
1	16.94	69533	0.62	1828
2	29.53	11157913	99.38	107355

racemic-4d



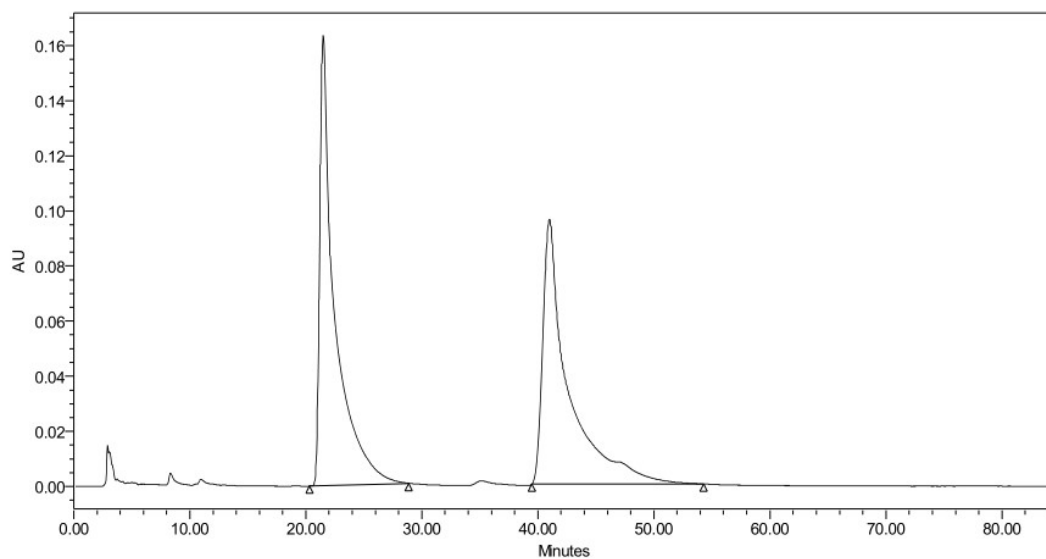
	RT	Area	% Area	Height
1	15.26	8046920	50.54	123998
2	22.52	7876469	49.46	103300

chiral-4d



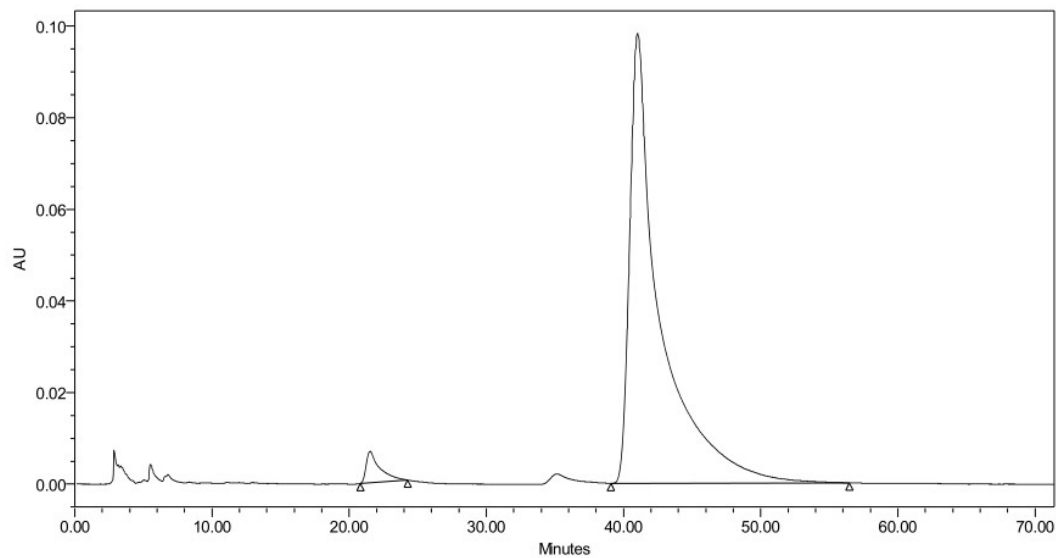
	RT	Area	% Area	Height
1	14.21	398223	8.90	7580
2	22.35	4074841	91.10	49122

racemic-4e



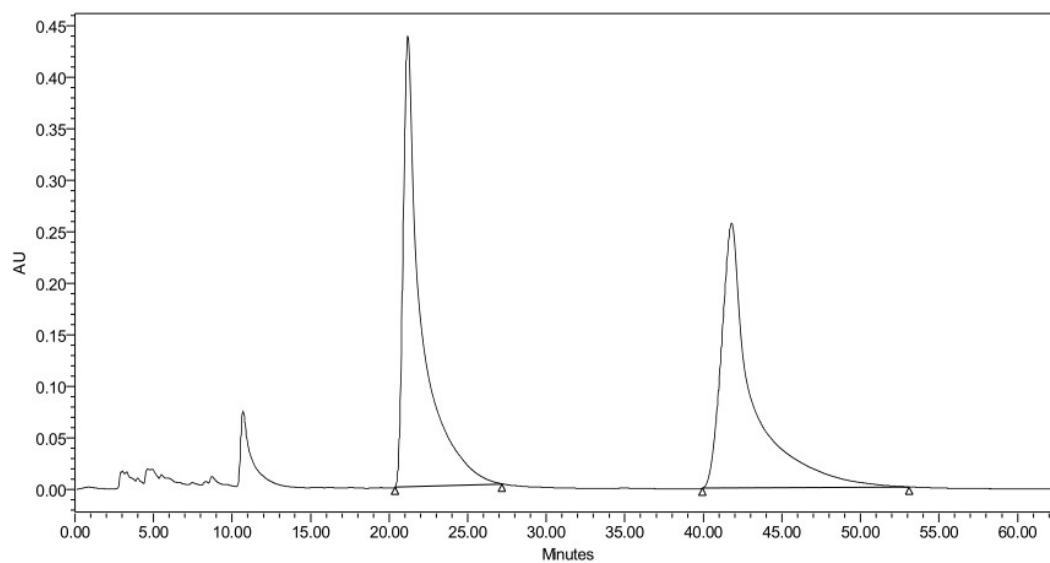
	RT	Area	% Area	Height
1	21.48	14622932	50.10	163353
2	40.99	14564252	49.90	96040

chiral-4e



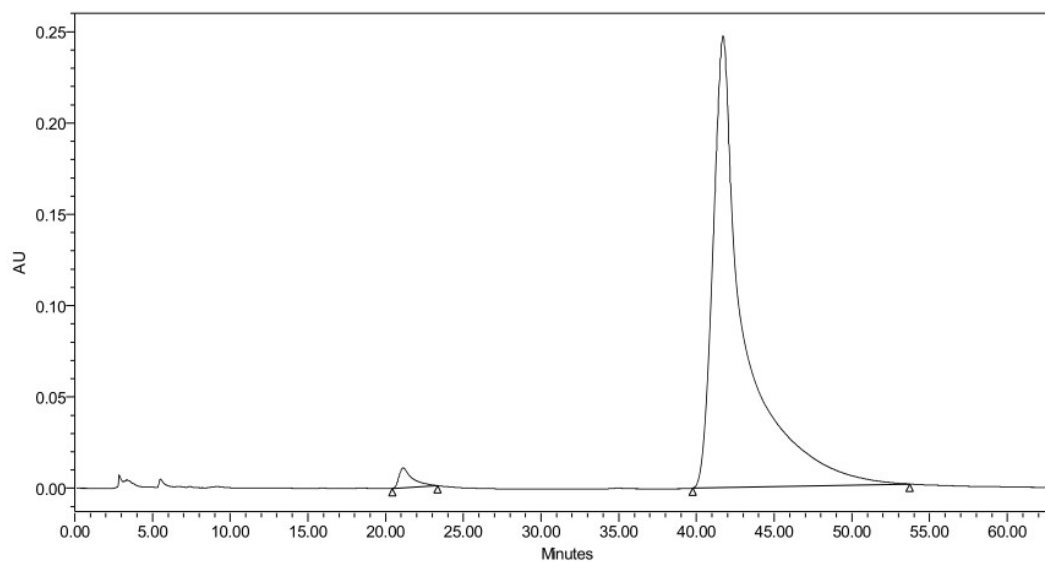
	RT	Area	% Area	Height
1	21.53	477062	3.09	6884
2	41.02	14974299	96.91	98180

racemic-4f



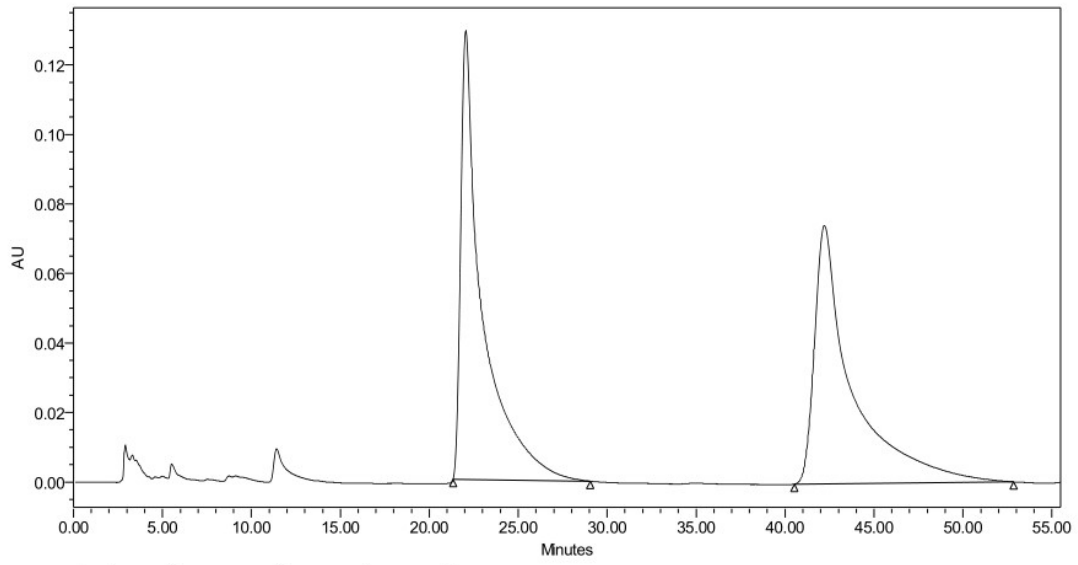
	RT	Area	% Area	Height
1	21.18	34770563	49.97	437073
2	41.79	34812029	50.03	256910

chiral-4f



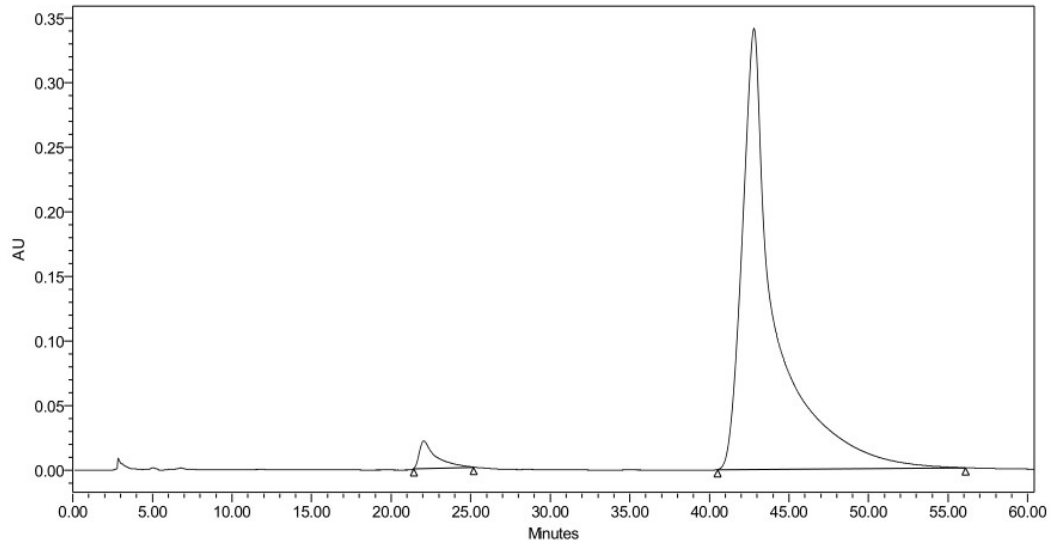
	RT	Area	% Area	Height
1	21.13	663631	1.89	10958
2	41.70	34425872	98.11	247186

racemic-4g



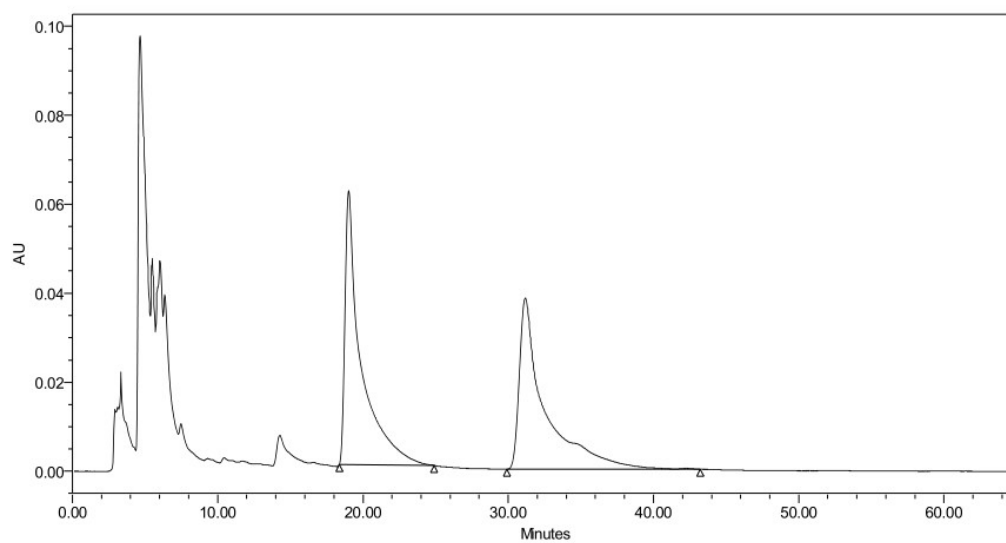
	RT	Area	% Area	Height
1	22.06	10861425	49.98	129212
2	42.20	10869827	50.02	74372

chiral-4g



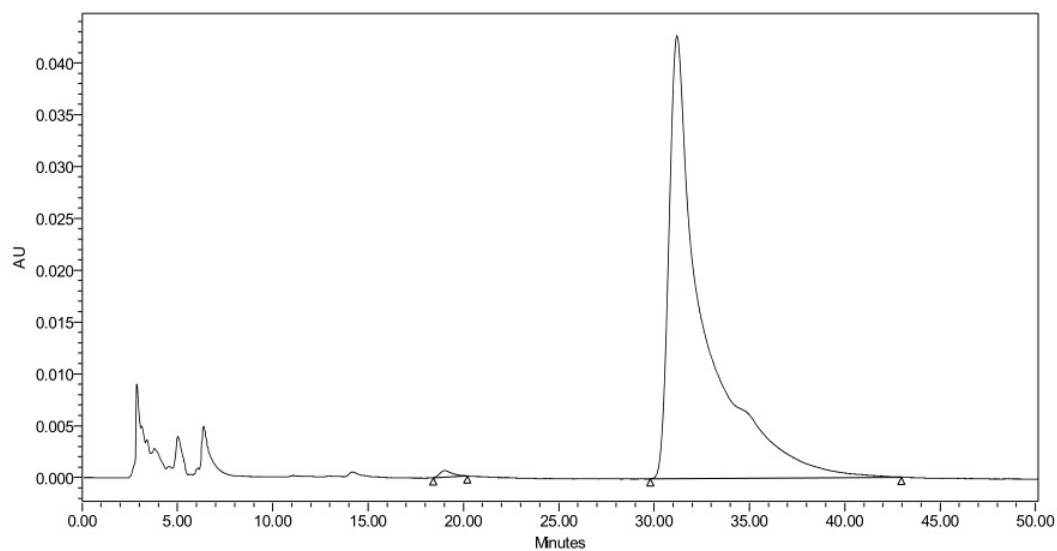
	RT	Area	% Area	Height
1	22.05	1552742	3.05	21301
2	42.81	49308616	96.95	341514

racemic-4h



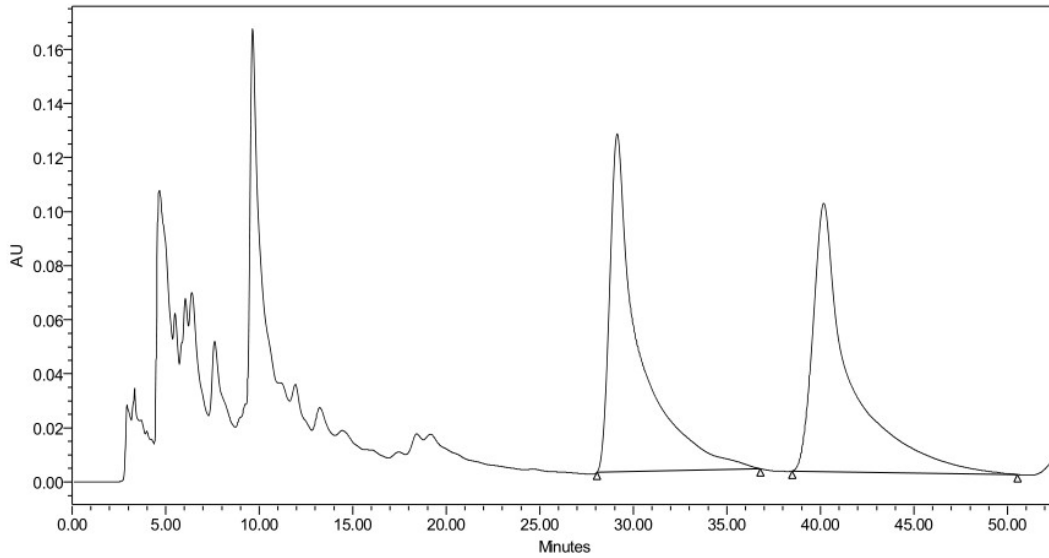
	RT	Area	% Area	Height
1	19.02	4716822	50.24	61595
2	31.18	4671893	49.76	38519

chiral-4h



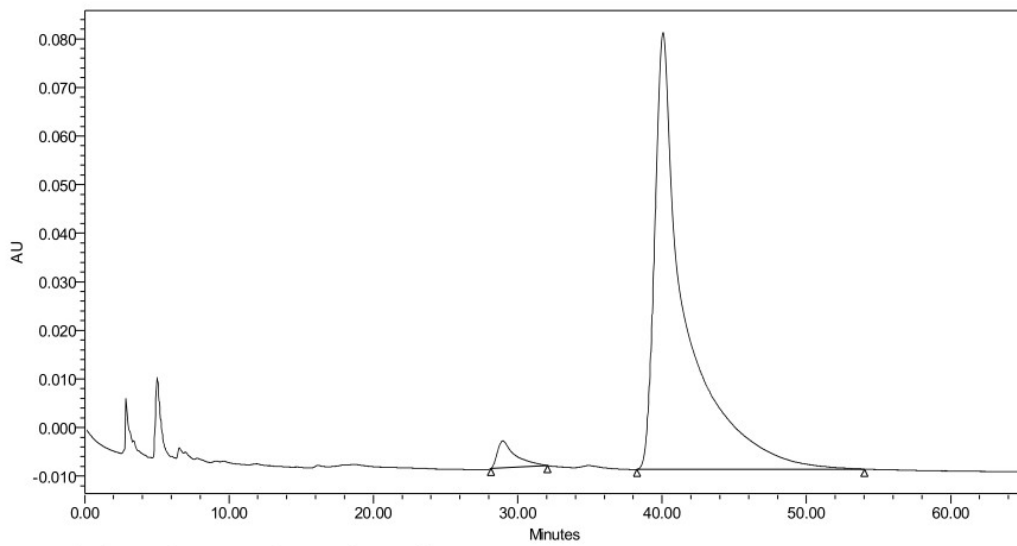
	RT	Area	% Area	Height
1	18.97	29075	0.54	631
2	31.19	5351134	99.46	42734

racemic-4i



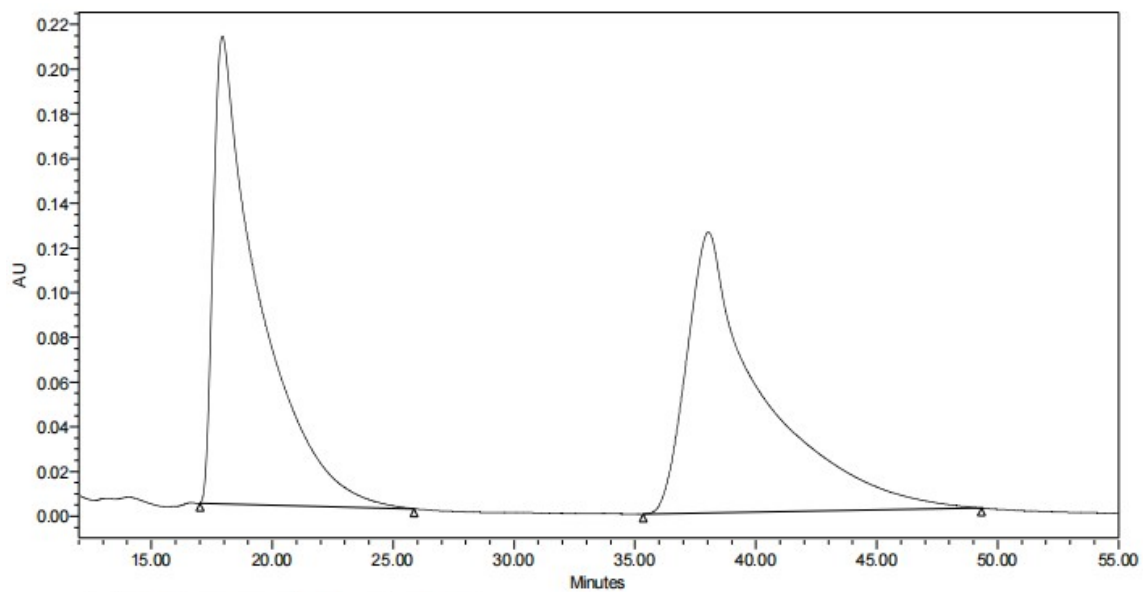
	RT	Area	% Area	Height
1	29.14	13557413	49.93	125006
2	40.17	13594524	50.07	99221

chiral-4i



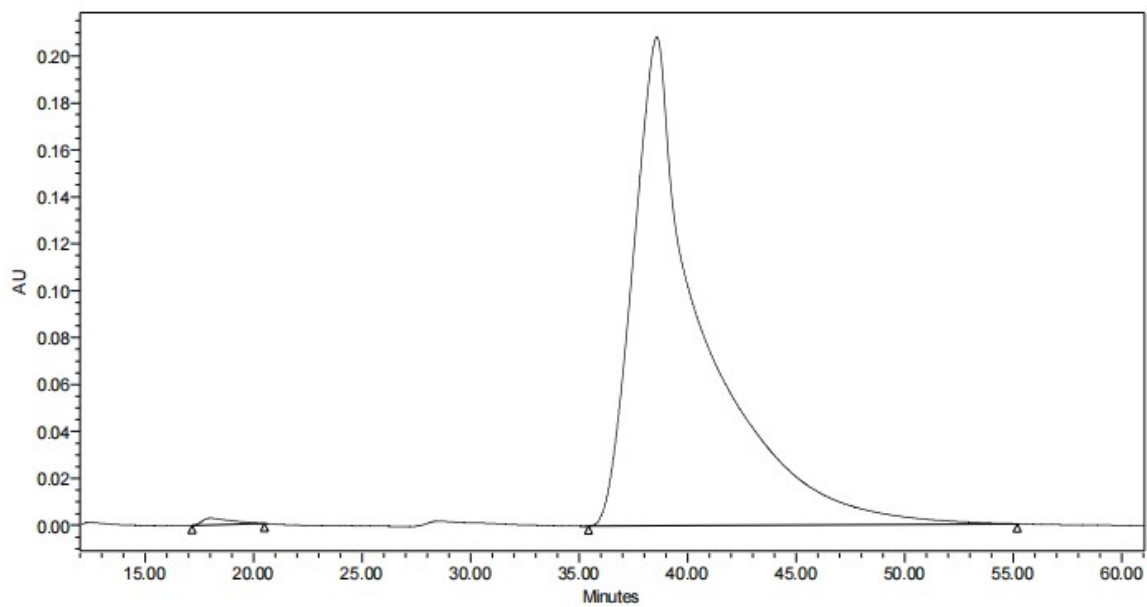
	RT	Area	% Area	Height
1	28.97	477034	3.49	5561
2	40.08	13187577	96.51	89924

racemic-4j



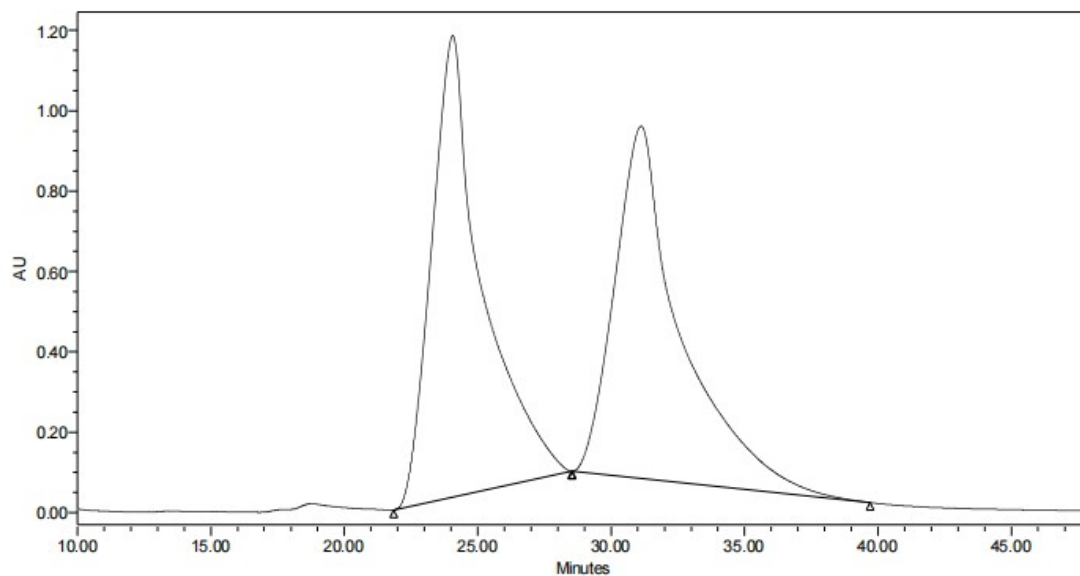
	RT	Area	% Area	Height
1	17.94	27331423	50.04	209132
2	38.04	27292685	49.96	125581

chiral-4j



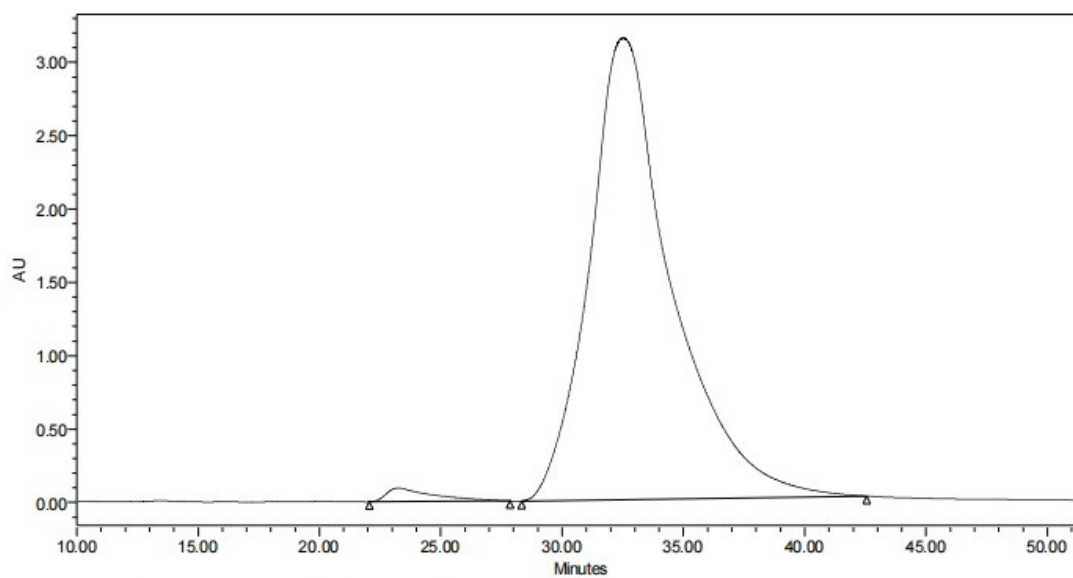
	RT	Area	% Area	Height
1	17.99	270127	0.57	2898
2	38.59	46826897	99.43	208261

racemic-5a



	RT	Area	% Area	Height
1	24.06	152162412	50.23	1148078
2	31.13	150791344	49.77	877652

chiral-5a



	RT	Area	% Area	Height
1	23.24	12522523	1.66	93452
2	32.50	741764328	98.34	3150069

VIII. Single Crystal X-Ray Diffraction of 4g

Table 1. Crystal data and structure refinement for 4g.

CCDC 2245007

Identification code	4g
Empirical formula	C ₂₄ H ₁₈ BrN ₃ O ₃
Formula weight	476.32
Temperature/K	220.00(10)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	10.11185(14)
b/Å	13.81714(17)
c/Å	15.0875(2)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2107.98(5)
Z	4
ρ _{calc} /cm ³	1.501
μ/mm ⁻¹	2.922
F(000)	968.0
Crystal size/mm ³	0.15 × 0.13 × 0.1
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	8.678 to 147.5
Index ranges	-12 ≤ h ≤ 12, -17 ≤ k ≤ 15, -13 ≤ l ≤ 18
Reflections collected	11365
Independent reflections	4198 [R _{int} = 0.0294, R _{sigma} = 0.0304]
Data/restraints/parameters	4198/0/281
Goodness-of-fit on F ²	1.037
Final R indexes [I >= 2σ (I)]	R ₁ = 0.0281, wR ₂ = 0.0694
Final R indexes [all data]	R ₁ = 0.0304, wR ₂ = 0.0707
Largest diff. peak/hole / e Å ⁻³	0.16/-0.58
Flack/Hooft parameter	-0.019(7)/-0.005(7)