Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Catalytic Asymmetric Conjugate Addition of Indolizines to Unsaturated Ketones Catalyzed by Chiral-at-metal Complexes

Cheng Huang[a], Zhifei Zhao[a], Shiwu Li[a],* Jixing Zhao[b], Leifang Wu[b], Chengzhi Gu[a]*

[a]Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan , School of Chemitry and Chemical Engineering, Shihezi University, Xinjiang Uygur Autonomous Region 832000, People's Republic of China. [b]Analysis and Testing Cent er of Shihezi University, Xinjiang Uygur Autonomous Region, 832000, China.

E-mail: lishiwu@shzu.edu.cn; gcz_tea@shzu.edu.cn

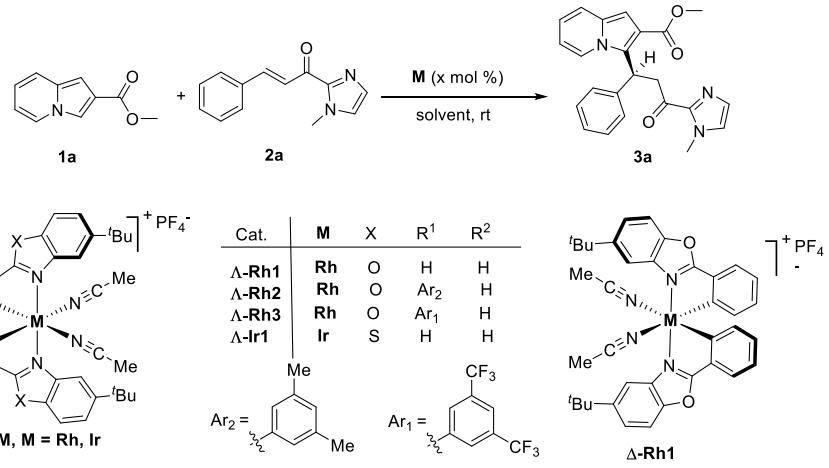
Table of Contents

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. Dry 1,2-dichloroethane (DCE) and THF were obtained from solvent distillation machine (Vigor VSPS-5) and stored under argon over 4 Å type molecular sieves. Toluene were distilled freshly before use over sodium and benzophenone. Dichloromethane (DCM) was distilled from CaH_2. Methanol was used without further purification. Reactions were checked by TLC analysis and plates were visualized with short-wave UV light (254 nm). The ^{1}H, ^{13}C NMR and ^{19}F spectra were obtained in $CDCl_3$ 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. Signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). HPLC analyses of the compounds were done using chiralcel IA-IF columns and chiralcel 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. Crystal structure data were collected on a SuperNova, Dual, Cu at zero, Atlas diffractometer.

II Optimization of Reaction Conditions

Table 1. Optimization of the Reaction Conditions[a]



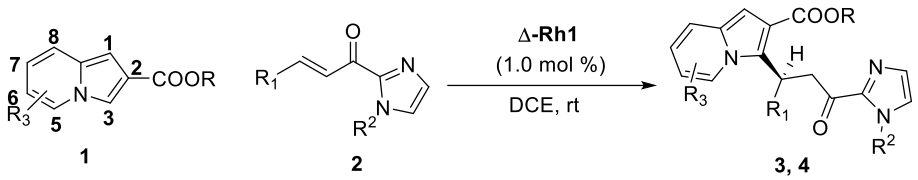
entry	**M** (x mol %)	solvent	time (h)	Yield (%)[b]	Ee(%)[c]
1	**Λ-Rh1** (2)	DCE	9	92	96(R)
2	**Λ-Rh2** (2)	DCE	9	92	97(R)
3	**Λ-Rh3** (2)	DCE	9	94	97(R)
4	**Λ-Ir1** (2)	DCE	9	85	92(R)
5	**Δ-Rh1** (2)	DCE	9	95	98(S)
6	**Δ-Rh1** (0)	DCE	9	NR	/
7	**Δ-Rh1** (2)	DCM	9	92	97(S)
8	**Δ-Rh1** (2)	THF	9	90	97(S)
9	**Δ-Rh1** (2)	Toluene	9	87	97(S)
10	**Δ-Rh1** (2)	$CHCl_3$	9	93	96(S)
11	**Δ-Rh1** (2)	CH_3OH	9	89	96(S)
12	**Δ-Rh1** (1)	DCE	7	96	98(S)
13[d]	**Δ-Rh1** (1)	DCE	9	94	98(S)

[a]Reaction conditions: **1a** (0.22 mmol), **2a** (0.20 mmol), **Λ/Δ-Rh** or **Λ-Ir1** (1-2 mol %), solvent (0.5 mL) at rt under argon atmosphere. [b]Isolated yields. [c] Determined by chiral HPLC analysis. [d] 0 ^{o}C.

III Experimental Section

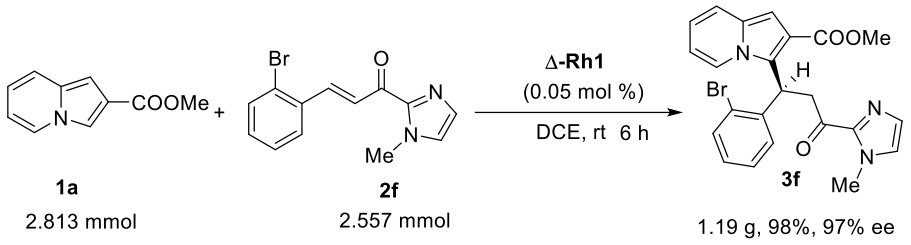
Λ/Δ-Rh or **Λ-Ir1** was prepared according to reported procedure.[1] *α,β*-unsaturated 2-acyl imidazoles and indolizines were synthesized according to reported procedures.[2-5]

General procedure for Catalytic Asymmetric Conjugate Addition of Indolizines to Unsaturated Ketones Catalyzed by Chiral-at-metal Complexes.



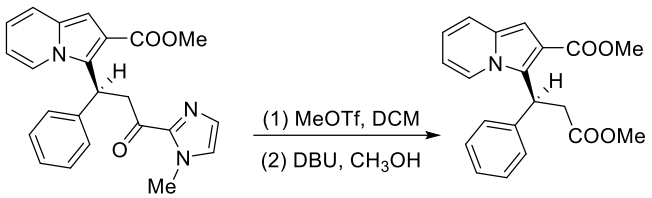
To an oven-dried 10 mL Schlenk tube equipped with a stir bar, **Δ-Rh1** (1 mol%) was added along with *α,β*-unsaturated 2-acyl imidazole **2** (1 equiv, 0.2 mmol) and indolizine (0.22 mmol) in DCE (0.5 mL). The reaction was stirring at at room temperature until consumption of the 2-acyl imidazole (monitored by TLC). The solution was directly purified by silica gel column chromatography (EtOAc/Petroleum ether = 1:3-1:2) to afford **3** or **4**.

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



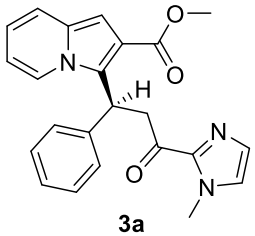
To an oven-dried 25 mL Schlenk tube equipped with a stir bar, **Δ-Rh1** (1 mol%) (0.05 mol%) was added along with *α,β*-unsaturated 2-acyl imidazole **2f** (1.0 equiv, 2.56 mmol, 742 mg) and indolizine (1.1 equiv, 2.81 mmol, 492 mg) in DCE (3.0 mL). The reaction was stirring at room temperature until consumption of the 2-acyl imidazole (monitored by TLC). The solution was directly purified by silica gel column chromatography (EtOAc/Petroleum ether = 1:2) to afford **3f** (white solid, 1.19 g, 98% yield, 97% ee).

General procedure for synthetic transformation of the Michael product 3l.



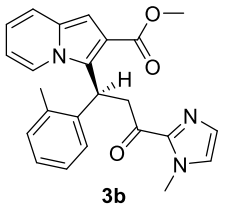
3a 98% ee **5** 70%, 93% ee

3a(50 mg, 0.13 mmol, 1.0 equiv) was added to a screw-cap tube followed by CH_2Cl_2 (2 mL). The solution was stirred at 0 ^oC and MeOTf (10.0 equiv) was added dropwise. The solution was stirred at room temperature overnight. A solution of MeOH (1.2 mL) and DBU (1.2 mL) was prepared and added slowly to the reaction tube. The mixture stirred at room temperature for an additional 12 h. The mixture was diluted with EtOAc (15 mL) and transferred to a separatory funnel. Brine (30 mL), and H_2O (30 ml) were added and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue **5** was purified by flash column chromatography 10% EtOAc/hexane. (Brown oil, 30 mg, 70% yield, 93% ee).



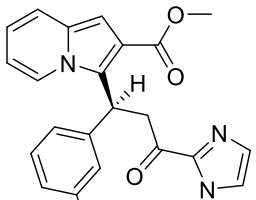
3a

Brown oil, 74 mg, 96% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 14.31 min, tr (minor) = 19.69 min); $[\alpha]_D^{25}$ = -181.80 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.64 (m, 1H), 7.30 (d, *J* = 8.0 Hz; 1H), 7.25 (d, *J* = 4.0 Hz; 4H), 7.19-7.15 (m, 1H), 7.97 (s, 1H), 6.97 (s, 1H), 6.83 (s, 1H), 6.62-6.58 (m, 1H), 6.41-6.33 (m, 2H), 4.48-4.42 (dd, J_1 = 16.0 Hz; J_2 = 8.0 Hz; 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.76-3.71 (dd, J_1 = 16.0 Hz; J_2 = 8.0 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 166.1, 142.8, 140.0, 131.9, 129.0, 128.6, 128.6, 127.1, 127.0, 126.4, 123.5, 120.4, 117.6, 117.2, 111.8, 101.0, 51.4, 39.9, 36.0, 35.5. HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{22}N_3O_3$ $[M+H]^+$: 388.1655, found: 388.1656.



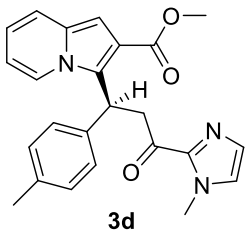
3b

Brown oil, 75 mg, 94% yield, 95% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 8.75 min, tr (minor) = 15.20 min); $[\alpha]_D^{25}$ = -342.80 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76-7.74 (m, 1H), 7.52 (d, *J* = 7.6 Hz; 1H), 7.28 (d, *J* = 9.2 Hz; 1H), 7.20-7.17 (m, 1H), 7.14-7.05 (m, 3H), 6.99 (s, 1H), 6.82 (s, 1H), 6.58-6.45 (m, 1H), 6.32-6.27 (m, 2H), 4.56-4.98 (dd, J_1 = 16.4 Hz; J_2 = 8.8 Hz; 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.64-3.58 (dd, J_1 = 16.4 Hz; J_2 = 6.4 Hz; 1H), 2.0 (s,3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.0, 166.0, 143.0, 137.8, 131.6, 131.3, 129.0, 128.0, 127.0, 126.7, 125.8, 123.2, 120.4, 117.3, 116.7, 111.8, 101.2, 51.4, 40.2, 36.0, 34.5, 19.6. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1814.



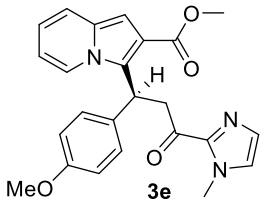
3c

Brown oil, 77 mg, 96% yield, 99% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 11.56 min, tr (minor) = 14.49 min); $[\alpha]_D^{25}$ = -120.88 (c = 0.5, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.19-7.11 (m, 1H), 7.08-7.04 (m, 3H), 6.97 (t, *J* = 8.8 Hz, 2H), 6.82 (s, 1H), 6.63-6.59 (m, 1H), 6.38-6.33 (m, 2H), 4.44-4.38 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.76-3.70(dd, J_1 = 23.6 Hz; J_2 = 7.6 Hz; 1H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 166.2, 142.8, 139.9, 138.2, 131.9, 128.9, 128.6, 128.5, 127.9, 127.2, 126.9, 124.0, 123.6, 120.4, 117.5, 117.2, 111.8, 101.0, 51.4, 39.8, 36.0, 35.0, 21.6. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1812.



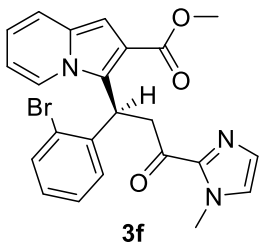
3d

Brown oil, 75 mg, 94% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 15.54 min, tr (minor) = 18.48 min); $[\alpha]_D^{25}$ = -255.56 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 1H), 7.30 (d, *J* = 9.2 Hz; 1H), 7.14 (d, *J* = 8.0 Hz; 2H), 7.07-7.04 (m, 3H), 6.96 (s, 1H), 6.82 (s, 1H), 6.61-6.58 (m, 1H), 6.37-6.32 (m, 2H), 4.46-4.40 (dd, *J1* = 16.4 Hz; *J2* = 8.0 Hz; 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74-3.69 (dd, *J1* = 16.4 Hz; *J2* = 7.2 Hz; 1H), 2.27 (s,3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 166.1, 142.8, 136.9, 135.9, 131.9, 129.3, 128.9, 128.7, 126.9, 123.6, 120.4, 117.5, 117.1, 111.8, 101.0, 51.4, 39.9, 36.0, 34.8, 21.0. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1810.



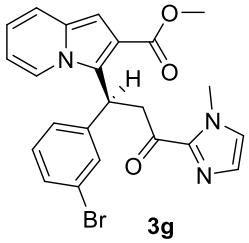
3e

Brown oil, 79 mg, 95% yield, 97% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 21.92 min, tr (minor) = 27.89 min); $[\alpha]_D^{25}$ = -45.32 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 1H), 7.30 (d, *J* = 9.2 Hz; 1H), 7.18-7.15 (m, 2H), 7.08 (s, 1H), 6.98 (s, 1H), 6.82-6.77 (m, 3H), 6.63-6.59 (m, 1H), 6.38-6.29 (m, 2H), 4.45-4.39 (dd, J_1 = 16.4 Hz; J_2 = 8.0 Hz; 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75 (s, 3H), 3.73-3.68 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 166.1, 158.0, 142.8, 132.0, 131.9, 129.0, 128.9, 128.1, 127.0, 123.6, 120.4, 117.5, 117.0, 114.0, 111.8, 101.0, 55.2, 51.4, 40.0, 36.0, 34.4. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_4$ $[M+H]^+$: 418.1761, found: 418.1759.



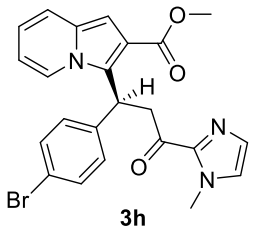
3f

Brown solid, 87 mg, 94% yield, 96% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 12.59 min, tr (minor) = 16.65 min); $[\alpha]_D^{25}$ = -44.08 (c = 0.5, CH_2Cl_2); mp = 160.8-162.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95-7.93 (d, *J* = 6.8 Hz; 1H), 7.56-7.49 (m, 2H), 7.33 (d, *J* = 9.2 Hz; 1H), 7.24-7.20 (m, 1H), 7.11 (s, 1H), 7.07-7.03 (m, 1H), 6.97 (s, 1H), 6.85 (s, 1H), 6.66-6.62 (m, 1H), 6.51-6.47 (m, 1H), 5.86 (t, *J* = 7.2 Hz; 1H), 4.35-4.29 (dd, J_1 = 17.6 Hz; J_2 = 8.4 Hz; 1H), 4.16-4.10 (dd, J_1 = 17.6 Hz; J_2 =6.8 Hz; 1H), 3.86 (s, 3H), 3.79(s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 165.9, 142.8, 139.5, 133.2, 131.5, 130.1, 129.1, 128.3, 127.3, 126.9, 126.8, 124.6, 123.0, 120.3, 118.0, 117.4, 112.1, 102.0, 51.6, 41.5, 37.2, 36.0. HRMS (ESI, *m/z*) calcd for $C_{23}H_{21}N_3O_3Br$ $[M+H]^+$: 466.0761, 468.0739, found: 466.0761, 468.0740.



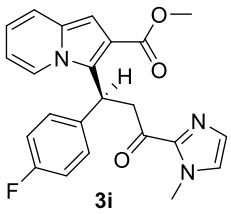
3g

Brown oil, 86 mg, 93% yield, 95% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 12.49 min, tr (minor) = 17.85 min); $[\alpha]_D^{25}$ = -85.72 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.64 (m, 1H), 7.42 (s, 1H), 7.34-7.30 (m, 2H), 7.19-7.09 (m, 3H), 6.99 (s, 1H), 6.84 (s, 1H), 6.66-6.62 (m, 1H), 6.44-6.40 (m, 1H),6.34 (t, *J* = 7.2 Hz; 1H), 4.42-4.36 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80-3.74 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.6, 166.0, 142.7, 132.0, 130.2, 130.1, 129.7, 129.1, 127.6, 127.1, 125.8, 123.2, 122.9, 120.5, 117.6, 117.3, 112.2, 101.2, 51.5, 39.8, 36.0, 34.8. HRMS (ESI, *m/z*) calcd for $C_{23}H_{21}N_3O_3Br$ $[M+H]^+$: 466.0761, 468.0735, found: 466.0759, 468.0737.



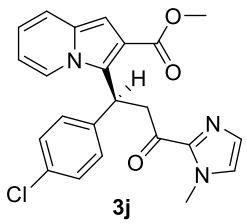
3h

Brown oil, 86 mg, 92% yield, 95% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 15.48 min, tr (minor) = 20.00 min); $[\alpha]_D^{25}$ = -8.92 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64-7.62 (m, 1H), 7.38-7.31 (m, 3H), 7.14-7.09 (m, 3H), 6.99 (s, 1H), 6.83 (s, 1H), 6.66-6.61 (m, 1H), 6.42-6.39 (m, 1H), 6.31 (t, *J* = 7.2 Hz; 1H), 4.46-4.40 (dd, J_1 =16.8 Hz; J_2 = 8.0 Hz; 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75-3.69 (dd, J_1 = 16.4 Hz; J_2 = 6.8 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.7, 166.0, 142.7, 139.3, 132.0, 131.7, 129.1, 128.9, 127.9, 127.1, 123.2, 120.5, 120.3, 117.7, 117.2, 112.1, 101.2, 51.5, 39.8, 36.0, 34.6. HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}N_3O_3Br$ $[M+H]^+$: 466.0761, 468.0739, found: 466.0762, 468.0740.



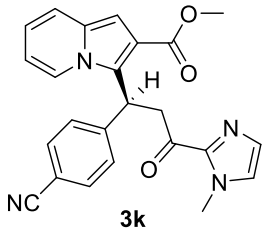
3i

Brown oil, 78 mg, 96% yield, 97% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 14.36 min, tr (minor) = 23.95 min); $[\alpha]_D^{25}$ = -182.00 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.2 Hz; 1H), 7.53-7.49 (m, 1H), 7.31 (d, *J* = 9.2 Hz; 1H), 7.18-7.12 (m, 1H), 7.10 (s, 1H), 7.05 (td, J_1 = 7.6 Hz; J_2 = 1.2 Hz; 1H), 6.96-6.91 (m, 2H), 6.84 (s, 1H), 6.65-6.61 (m, 1H), 6.51-6.47 (m, 1H), 6.16 (t, *J* = 7.2 Hz; 1H), 4.43-4.37 (dd, J_1 = 17.6 Hz; J_2 = 7.6 Hz; 1H), 3.86 (s, 3H), 3.84 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -116.71 ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}N_3O_3F$ $[M+H]^+$: 406.1561, found: 406.1561.



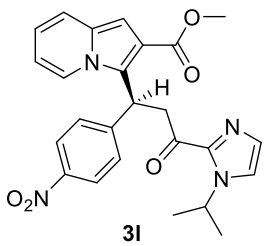
3j

Brown oil, 79 mg, 94% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 14.55 min, tr (minor) = 18.93 min); $[\alpha]_D^{25}$ = -156.60 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64-7.62 (m, 1H), 7.33-7.31 (m, 1H), 7.23-7.17 (m, 4H), 7.08 (s, 1H), 6.99 (s, 1H), 6.84 (s, 1H), 6.65-6.61 (m, 1H), 6.42-6.38 (m, 1H), 6.33 (t, *J* = 7.2 Hz; 1H), 4.46-4.40 (dd, J_1 = 16.4 Hz; J_2 = 8.0 Hz; 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.76-3.70 (dd, J_1 = 16.4 Hz; J_2 = 6.8 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.7, 166.0, 142.7, 138.7, 132.2, 132.0, 129.1, 128.7, 128.5, 128.0, 127.2, 123.2, 120.5, 117.7, 117.2, 112.1, 101.2, 51.5, 39.9, 36.0, 34.5. HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}N_3O_3Cl$ $[M+H]^+$: 422.1266, 423.1263, 424.1231, found: 422.1266, 423.1264, 424.1231.



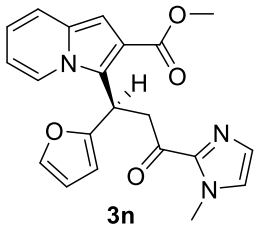
3k

Brown oil, 77 mg, 93% yield, 96% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 26.60 min, tr (minor) = 35.69 min); $[\alpha]_D^{25}$ = -13.40 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.2 Hz; 1H), 7.55-7.53 (m, 2H), 7.38-7.33 (m, 3H), 7.10 (s, 1H), 7.02 (s, 1H), 6.86 (s, 1H), 6.68-6.64 (m, 1H), 6.46-6.42 (m, 1H), 6.39 (t, *J* = 6.8 Hz; 1H), 4.51-4.45 (dd, J_1 = 16.8 Hz; J_2 = 8.0 Hz; 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.81-3.75 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.4, 165.9, 146.1, 142.5, 132.4, 132.1, 129.3, 128.0, 127.4, 127.3, 122.8, 120.6, 118.8, 117.9, 117.3, 112.4, 110.3, 101.4, 51.5, 39.8, 36.0, 35.1. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{21}N_4O_3$ $[M+H]^+$: 413.1608, found: 413.1610.



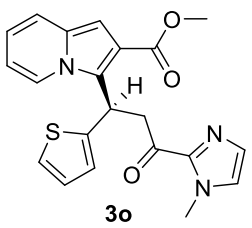
3l

Yellow oil, 88 mg, 96% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 27.93 min, tr (minor) = 20.86 min); $[\alpha]_D^{25}$ = -43.60(c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.8 Hz; 2H), 7.64 (d, *J* = 7.2 Hz; 1H), 7.44-7.42 (m, 2H), 7.35 (d, *J* = 9.2 Hz; 1H), 7.25 (s, 1H), 6.86 (s, 1H), 6.68-6.64 (m, 1H), 6.46-6.43 (m, 2H), 5.41-5.35 (m, 1H), 4.56-4.50 (dd, J_1 = 16.4 Hz; J_2 = 8.0 Hz; 1H), 3.85-3.80 (m, 4H), 1.37-1.34 (dd, J_1 = 6.8 Hz; J_2 = 4.0 Hz; 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.4, 165.8, 148.4, 146.5, 141.8, 132.1, 129.7, 128.1, 127.1, 123.8, 122.8, 121.6, 120.7, 117.9, 117.3, 112.5, 101.5, 51.5, 49.2, 40.5, 35.3, 23.6, 23.4. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{24}N_4O_5$ $[M+H]^+$: 461.1819, found: 461.1817.



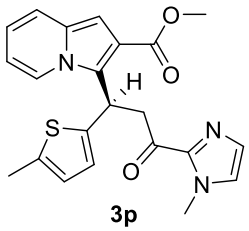
3n

Yellow solid, 72 mg, 95% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 11.82 min, tr (minor) = 15.27 min); $[\alpha]_D^{25}$ = -130.04 (c = 0.5, CH_2Cl_2); mp = 128.4-130.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 1H), 7.32 (d, *J* = 9.2 Hz; 1H), 7.09 (s, 1H), 6.99 (s, 1H), 6.83 (s, 1H), 6.66-6.61 (dd, J_1 = 8.8 Hz; *J2* = 6.4 Hz; 1H), 6.46-6.41 (m, 2H), 6.28-6.27(m, 2H), 6.13-6.12 (m, 1H), 4.44-4.38 (dd, J_1 = 16.8 Hz; J_2 = 8.0 Hz; 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.67-3,61 (dd, J_1 = 16.8 Hz; J_2 = 6.4 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.2, 165.9, 153.7, 142.7, 141.6, 132.1, 129.0, 127.1, 126.2, 123.6, 120.4, 117.6, 116.8, 112.0, 110.4, 106.3, 101.2, 51.4, 39.4, 36.1, 30.6. HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{20}N_3O_4$ $[M+H]^+$: 378.1448, found: 378.1447.



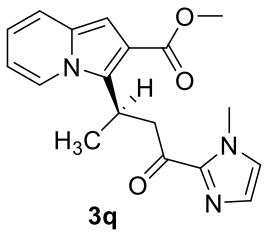
3o

Brown oil, 74 mg, 94% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 15.34 min, tr (minor) = 18.32 min); $[\alpha]_D^{25}$ = -64.80 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.2 Hz; 1H), 7.33 (d, *J* = 9.2 Hz; 1H), 7.13-7.12 (m, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 6.90-6.83 (m, 3H), 6.66-6.62 (m, 1H), 6.65 (t, *J* = 14.4 Hz; 1H), 6.44-6.41 (m, 1H), 4.46-4.40 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.89 (s, 3H),3.86 (s, 3H) , 3.84-3.78 (dd, J_1 = 16.4 Hz; J_2 = 7.2Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.2, 165.9, 144.9, 142.7, 132.2, 129.0, 127.5, 127.1, 126.8, 124.3, 124.0, 123.8, 120.4, 117.7, 116.9, 112.0, 101.1, 51.5, 41.5, 36.0, 32.1. HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{20}N_3O_3$ $[M+H]^+$: 394.1220, found: 394.1218.



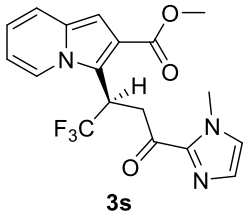
3p

Black oil, 85 mg, 96% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 14.04 min, tr (minor) = 17.53 min); $[\alpha]_D^{25}$ = -173.72 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83-7.81 (m; 1H), 7.32 (d, *J* = 9.2 Hz; 1H), 7.07 (s, 1H), 6.97 (s, 1H), 6.82 (s, 1H), 6.66-6.62 (m, 2H), 6.53-6.42 (m, 3H), 4.42-4.36 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.77-3.71 (dd, J_1 = 16.4 Hz; J_2 = 6.8 Hz; 1H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.3, 165.9, 142.8, 142.2, 138.7, 132.1, 129.0, 127.6, 127.1, 124.7, 123.9, 123.6, 120.4, 117.7, 116.8, 111.9, 101.1, 51.5, 41.1, 36.0, 32.1, 15.3. HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{22}N_3O_3S$ $[M+H]^+$: 408.1376, found: 408.1375.



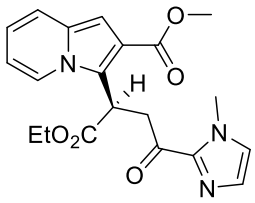
3q

Black oil, 62 mg, 96% yield, 99% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 11.04 min, tr (minor) = 19.72 min); $[\alpha]_D^{25}$ = +3.64 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81-8.09 (m, 1H), 7.33-7.30 (m, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 6.80 (s, 1H), 6.65-6.61 (m, 1H), 6.56-6.53 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79 (d, *J* = 7.2 Hz; 2H), 1.71 (s, 1H), 1.52 (d, *J* = 7.2 Hz; 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 143.0, 131.6, 131.3, 129.0, 126.7, 123.4, 120.5, 116.9, 115.9, 111.8, 101.7, 51.4, 43.4, 36.0, 25.9, 17.9. HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{20}N_3O_3$ $[M+H]^+$: 326.1499, found: 326.1499.



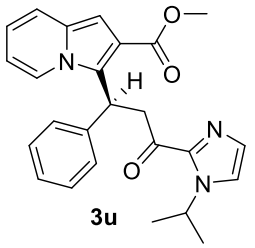
3s

Black oil, 86 mg, 97% yield, >99% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 6.95 min, tr (minor) = 7.49 min); $[\alpha]_D^{25}$ = -141.28 (c = 0.5, CH_2Cl_2); mp = 153.6-154.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.2 Hz; 1H), 7.39 (s, 5H), 7.14-7.08 (m, 3H), 6.87 (s, 1H), 6.76-6.62 (m, 2H), 6.33-6.27 (m, 1H), 4.26-4.20 (dd, J_1 = 17.2 Hz; J_2 = 6.8 Hz; 1H), 3.84 (s, 3H), 3.77-3.71 (dd, J_1 = 17.2 Hz; J_2 = 6.4 Hz; 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -67.05 ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 185.0, 165.4, 142.0, 137.8, 133.1, 129.7, 129.0, 128.8, 127.6, 125.7, 124.5, 120.6, 119.4, 118.3, 112.9, 102.1, 51.6, 35.6, 35.4, 35.0. HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{19}N_3O_3F_3$ $[M+H]^+$: 443.1370, found: 442.1370.



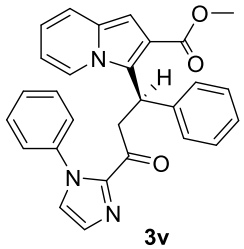
3t

Black oil, 70 mg, 92% yield, 95% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 11.27 min, tr (minor) = 10.41 min); $[\alpha]_D^{25}$ = -38.48 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.88 (m, 1H), 7.35 (d, *J* = 9.2 Hz; 1H), 7.12 (s, 1H), 6.83 (s, 1H), 6.70-6.66 (m, 1H), 6.57-6.54 (m, 1H), 5.76-5.72 (dd, J_1 = 16.0 Hz; J_2 = 2.0 Hz; 1H), 5.45-5.38 (m, 1H), 3.86 (s, 3H), 3.69-3.63 (dd, J_1 = 16.4 Hz; J_2 = 6.8 Hz; 1H), 1.38-1.34 (m, 6H), 1.24 (t, *J* = 7.2 Hz; 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.5, 166.3, 165.7, 147.1, 141.8, 129.6, 125.8, 123.5, 121.8, 121.3, 120.6, 117.7, 117.0, 112.2, 101.5, 60.4, 51.4, 49.1, 40.7, 33.4, 23.6, 14.2. HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{22}N_3O_5$ $[M+H]^+$: 384.1481, found: 384.1483.



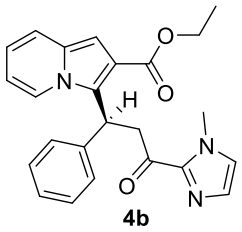
3u

Black oil, 79 mg, 95% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 10.18 min, tr (minor) = 13.09 min); $[\alpha]_D^{25}$ = -181.20 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 9.6 Hz; 1H), 7.33-7.25 (m, 7H), 7.17 (t, *J* = 7.2 Hz; 1H), 6.80 (s, 1H), 6.64-6.60 (m, 1H), 6.44-6.40 (m, 2H), 5.24-5.21 (m, 1H), 4.65-4.60 (dd, J_1 = 16.0 Hz; J_2 = 6.8 Hz; 1H), 4.05-3.99 (dd, J_1 = 15.6 Hz; J_2 = 8.4 Hz; 1H), 3.85 (s, 3H), 1.39-1.35 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.4, 166.1, 139.3, 132.1, 128.7, 127.5, 127.1, 126.6, 123.9, 121.1, 120.2, 118.0, 117.2, 112.2, 100.9, 51.5, 50.3, 41.5, 35.3, 23.4, 23.3. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{26}N_3O_3$ $[M+H]^+$: 416.1969, found: 416.1969.



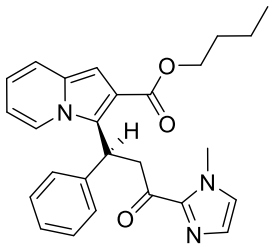
3v

Black oil, 85 mg, 95% yield, 96% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 14.86 min, tr (minor) = 18.49 min); $[\alpha]_D^{25}$ = -127.32 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.67 (m, 1H), 7.36-7.34 (m; 3H), 7.31-7.29 (m, 1H), 7.24 (d, *J* = 4.4 Hz; 4H), 7.18 (s, 1H), 7.17-7.14 (m, 1H), 7.09 (s, 1H), 7.08-7.06 (m, 2H), 6.84 (s, 1H), 6.62-6.58 (m, 1H), 6.37-6.33 (m, 1H), 6.27 (t, *J* = 7.6 Hz; 1H), 4.41-4.35 (dd, J_1 = 15.6 Hz; J_2 = 7.6 Hz; 1H), 3.87-3.81 (dd, J_1 = 15.6 Hz; J_2 = 7.6 Hz; 1H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.7, 166.0, 142.7, 140.2, 138.1, 131.9, 129.5, 128.9, 128.6, 128.2, 127.1, 127.1, 126.4, 125.8, 123.5, 120.3, 117.6, 117.4, 111.9, 101.2, 51.4, 40.2, 35.6. HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{24}N_3O_3$ $[M+H]^+$: 450.1812, found: 450.1812.



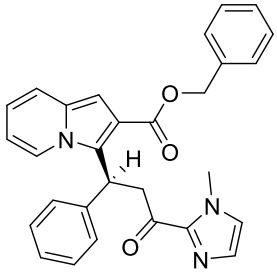
4b

Brown oil, 76 mg, 95% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 14.15 min, tr (minor) = 20.66 min); $[\alpha]_D^{25}$ = -143.84 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.63 (m, 1H), 7.30 (d, *J*= 9.2 Hz; 1H), 7.25 (s, 4H), 7.19-7.16 (m, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 6.62-6.58 (m, 1H), 6.42-6.33 (m, 2H), 4.48-4.42 (dd, J_1 = 16.4 Hz; J_2 = 8.0 Hz; 1H), 4.36-4.31 (m, 2H), 3.89 (s, 3H), 3.78-3.72 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H), 1.36 (t, *J* = 7.2 Hz; 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.0, 165.7, 142.8, 140.1, 131.9, 128.9, 128.6, 128.4, 127.0, 126.4, 126.4, 123.5, 120.3, 117.6, 117.5, 111.8, 101.1, 60.2, 39.9, 36.0, 35.0, 14.4. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1813.



4c

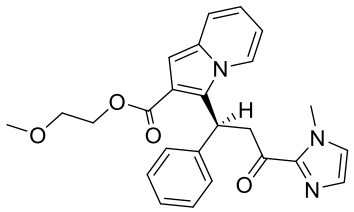
Brown oil, 82 mg, 95% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 12.64 min, tr (minor) = 16.62 min); $[\alpha]_D^{25}$ = -153.88 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.63 (m, 1H), 7.30 (d, *J* = 9.2 Hz; 1H), 7.25 (d, *J* = 4.4 Hz; 4H), 7.20-7.15 (m, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 6.62-6.58 (m, 1H), 6.43-6.33 (m, 2H), 4.48-4.42 (dd, J_1 = 16.4 Hz; J_2 = 8.0 Hz; 1H), 4.32-4.25 (m, 2H), 3.89 (s, 3H), 3.78-3.72 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H), 1.77-1.69 (m, 2H), 1.48-1.43 (m, 2H), 0.96 (t, *J* = 7.2 Hz; 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.0, 165.8, 142.8, 140.1, 131.8, 128.9, 128.6, 128.4, 127.1, 126.9, 126.4, 123.5, 120.3, 117.6, 117.5, 111.8, 101.0, 64.1, 39.8, 36.0, 35.0, 30.8, 19.3, 13.8. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{28}N_3O_3$ $[M+H]^+$: 430.2125, found: 430.2126.



4d

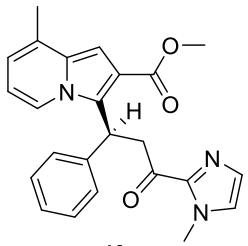
Brown oil, 89 mg, 96% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 20.80 min, tr (minor) = 38.99 min); $[\alpha]_D^{25}$ = -171.44 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.64 (m, 1H), 7.46-7.44 (m, 2H), 7.37-7.30 (m, 4H), 7.24 (d, *J* = 4.8 Hz; 4H), 7.18-7.15 (m, 1H), 7.06 (s, 1H), 6.94 (s, 1H), 6.87 (s, 1H), 6.62-6.57 (m, 1H), 6.42 (t, *J* = 7.6 Hz; 1H), 6.37-6.33 (m, 1H), 5.39-5.30 (q, *J* = 9.6 Hz; 2H), 4.46-4.40 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.83 (s, 3H), 3.81-3.75 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.0, 165.4, 142.8, 140.0, 136.6, 131.9, 129.0, 128.8, 128.6, 128.5, 128.1, 127.9, 127.1, 127.0, 126.4, 123.5, 120.4, 117.6, 117.1,

111.9, 101.2, 65.8, 39.8, 36.0, 35.0. HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{26}N_3O_3$ $[M+H]^+$: 464.1969, found: 464.1968.



4e

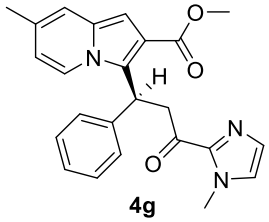
Brown oil, 81 mg, 94% yield, 96% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 19.01 min, tr (minor) = 24.71 min); $[\alpha]_D^{25}$ = -156.08 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 1H), 7.30 (d, *J* = 9.2 Hz; 1H), 7.26-7.24 (m, 4H), 7.19-7.15 (m, 1H), 7.08 (s, 1H), 6.97 (s, 1H), 6.87 (s, 1H), 6.62-6.58 (dd, J_1 = 9.2 Hz; J_2 = 6.4 Hz; 1H), 6.42-6.34 (m, 2H), 4.48-4.40 (m, 3H), 3.89 (s, 3H), 3.79-3.71 (m, 3H), 3.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.0, 165.5, 142.8, 140.1, 131.8, 128.9, 128.7, 128.6, 127.1, 127.0, 126.4, 123.5, 120.4, 117.5, 117.1, 111.9, 101.2, 70.6, 63.3, 59.0, 39.9, 36.0, 35.0. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{26}N_3O_4$ $[M+H]^+$: 432.1918, found: 432.1917.



4f

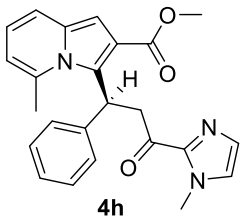
Brown solid, 77 mg, 96% yield, 97% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 11.55 min, tr (minor) = 13.73 min); $[\alpha]_D^{25}$ = -214.32 (c = 0.5, CH_2Cl_2); mp = 124.1-125.3 ºC.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.2 Hz; 1H), 7.24 (d, *J* = 4.4 Hz; 4H), 7.19-7.14 (m, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 6.43-6.37 (m, 2H), 6.31 (t, *J* = 6.8 Hz; 1H), 4.50-4.44 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75-3.69 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 166.2, 142.8, 140.2, 132.9, 129.4, 129.1, 129.0, 128.6, 127.1, 127.0, 126.3, 121.5, 116.8, 116.7, 112.1, 99.6, 51.4, 40.0, 36.0, 35.1, 18.0. HRMS (ESI, *m*/*z*)

calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1812.



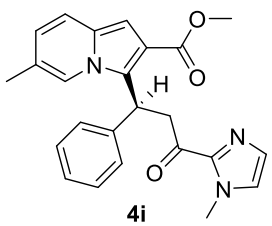
4g

Brown oil, 75mg, 93% yield, 95% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 16.48 min, tr (minor) = 29.70 min); $[\alpha]_D^{25}$ = -46.12 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.6 Hz; 1H), 7.25-7.24 (m, 4H), 7.19-7.14 (m, 1H), 7.08 (s, 1H), 7.05 (s, 1H), 6.98 (s, 1H), 6.67 (s, 1H), 6.36 (t, *J* = 7.6 Hz; 1H), 6.21-6.18 (m, 1H), 4.47-4.41 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.74-3.68 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.1, 166.2, 142.8, 140.3, 132.3, 129.0, 128.6, 127.9, 127.6, 127.1, 127.0, 126.3, 123.0, 118.2, 117.1, 114.7, 99.2, 51.4, 40.0, 36.0, 35.1, 20.8. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1812.



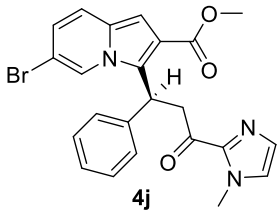
4h

Light yellow solid, 78 mg, 97% yield, 99% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 10.14 min, tr (minor) = 13.74 min); $[\alpha]_D^{25}$ = -195.64 (c = 0.5, CH_2Cl_2); mp = 152.6-153.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.40-7.38 (m, 2H), 7.26-7.19 (dd, J_1 = 17.2 Hz; J_2 = 10.0 Hz; 3H), 7.12-7.09 (m, 2H), 6.94 (s, 1H), 6.56-6.53 (dd, J_1 = 9.2 Hz; J_2 = 6.4 Hz; 1H), 6.34-6.33 (m, 1H), 5.87 (t, *J* = 7.6 Hz; 1H), 4.42-4.36 (dd, J_1 = 16.8 Hz; J_2 = 8.0 Hz; 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.43 (s, 3H), 1.42 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 191.3, 165.8, 144.2, 143.2, 132.8, 131.4, 128.9, 128.1, 127.6, 126.7, 125.7, 117.8, 117.7, 117.3, 117.2, 113.6, 111.4, 51.2, 43.6, 36.0, 35.7, 26.9, 18.5. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1812.



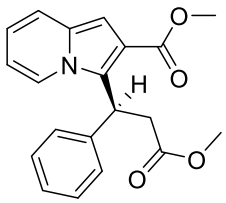
4i

Brown oil, 77 mg, 96% yield, 98% ee (HPLC: chiralpak AD-H column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 31.49 min, tr (minor) = 33.87 min); $[\alpha]_D^{25}$ = -63.72 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.25-7.21 (m, 5H), 7.19-7.15 (m, 1H), 7.10 (s, 1H), 6.98 (s, 1H), 6.79 (s, 1H), 6.48-6.46 (m, 1H), 6.34 (t, *J* = 7.2 Hz; 1H), 4.50-4.43 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.77-3.71 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.2, 166.2, 142.8, 140.3, 130.8, 129.0, 128.6, 128.2, 127.1, 127.0, 126.3, 121.1, 121.0, 120.7, 119.8, 116.7, 101.0, 51.4, 40.1, 36.0, 35.0, 18.9. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$: 402.1812, found: 402.1812.



4j

Brown oil, 79 mg, 85% yield, 96% ee (HPLC: chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 10.67 min, tr (minor) = 9.53 min); $[\alpha]_D^{25}$ = -79.68 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 1H), 7.29-7.20 (m, 6H), 7.11 (s, 1H), 7.00 (s, 1H), 6.87 (s, 1H), 6.69-6.66 (m, 1H), 6.27 (t, *J* = 7.2 Hz; 1H), 4.44-4.38 (dd, J_1 = 16.4 Hz; J_2 = 7.6 Hz; 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.81-3.75 (dd, J_1 = 16.4 Hz; J_2 = 7.2 Hz; 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.0, 165.6, 142.7, 139.5, 130.1, 129.2, 129.1, 128.8, 127.1, 126.7, 123.3, 121.2, 121.0, 117.8, 107.2, 102.7, 51.6, 40.0, 36.0, 35.2. HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}N_3O_3Br$ $[M+H]^+$: 466.0761, 468.0740, found: 466.0763, 468.0741.



5a

Brown oil, 30 mg, 70% yield, 93% ee (HPLC: chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 11.57 min, tr (minor) = 15.33 min); $[\alpha]_D^{25}$ = -58.40 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 1H), 7.33 (d, *J* = 9.2 Hz; 1H), 7.10 (s, 1H), 7.00 (s, 1H), 7.00 (s, 1H), 6.83 (s, 1H), 6.66-6.62 (m, 1H), 6.47-6.40 (m, 2H), 6.29-6.28 (m, 1H), 6.13-6.12 (m, 1H), 4.44-4.38 (dd, J_1 = 16.8 Hz; J_2 = 8.0 Hz; 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.66-3.61 (dd, J_1 = 16.8 Hz; J_2 = 6.4 Hz; 1H), 1.25 (s,1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.2, 186.0, 153.7, 141.6, 129.1, 127.0, 123.7, 120.4, 117.6, 112.0, 110.4, 106.3, 101.2, 51.5, 39.4, 36.1, 30.6. HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$: 338.1314, found: 338.1315.

IV References

(1) Wang, C.; Chen, L.-A.; Huo, H.; Shen, X.; Harms, K.; Gong, L.; Meggers, E. *Chem. Sci.* **2015**, *6*, 1094-1100.

(2) Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc*. **2014**, *136*, 2990-2993.

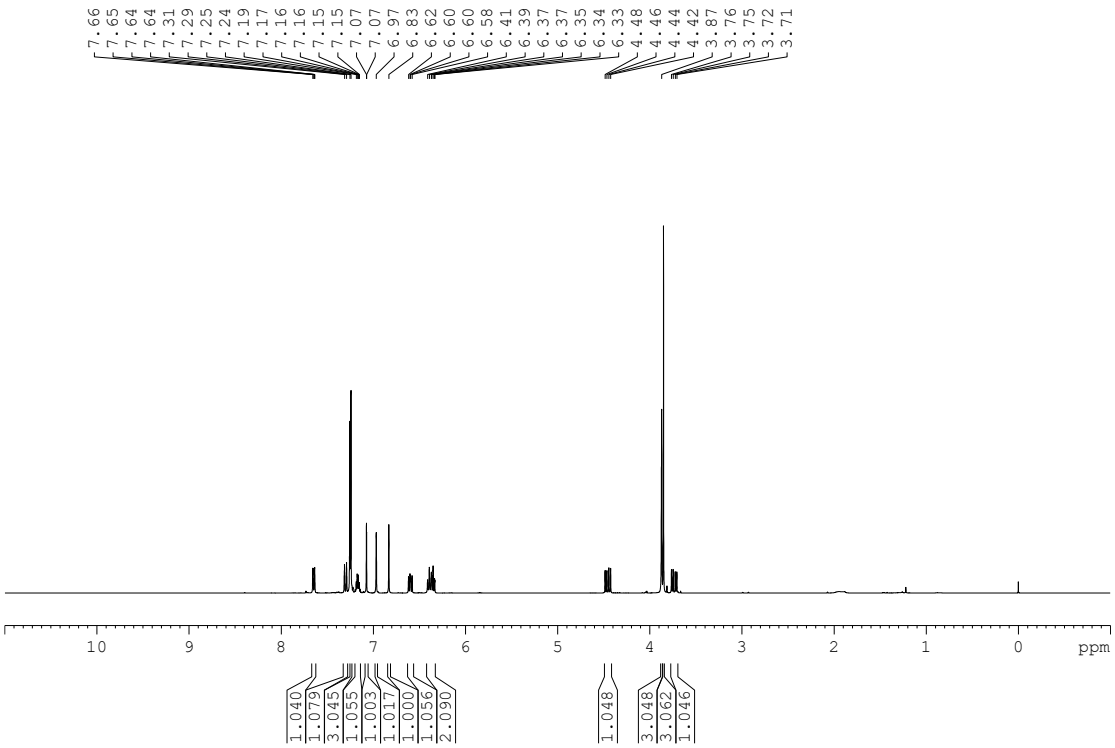
(3) Benedetti, E.; Duchemin, N.; Bethge, L.; Vonhoff, S.; Klussmann, S.; Vasseur, J.-J.; Cossy, J.; Smietana, M.; Arseniyadis, S. *Chem. Commun.* **2015**, *51*, 647-650.

(4) Drissi-Amraoui, S.; Morin, M. S. T.; Crévisy, C.; Baslé, O.; Figueiredo, R. M.; Mauduit, M.; Campagne, J.-M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11830 -11834.

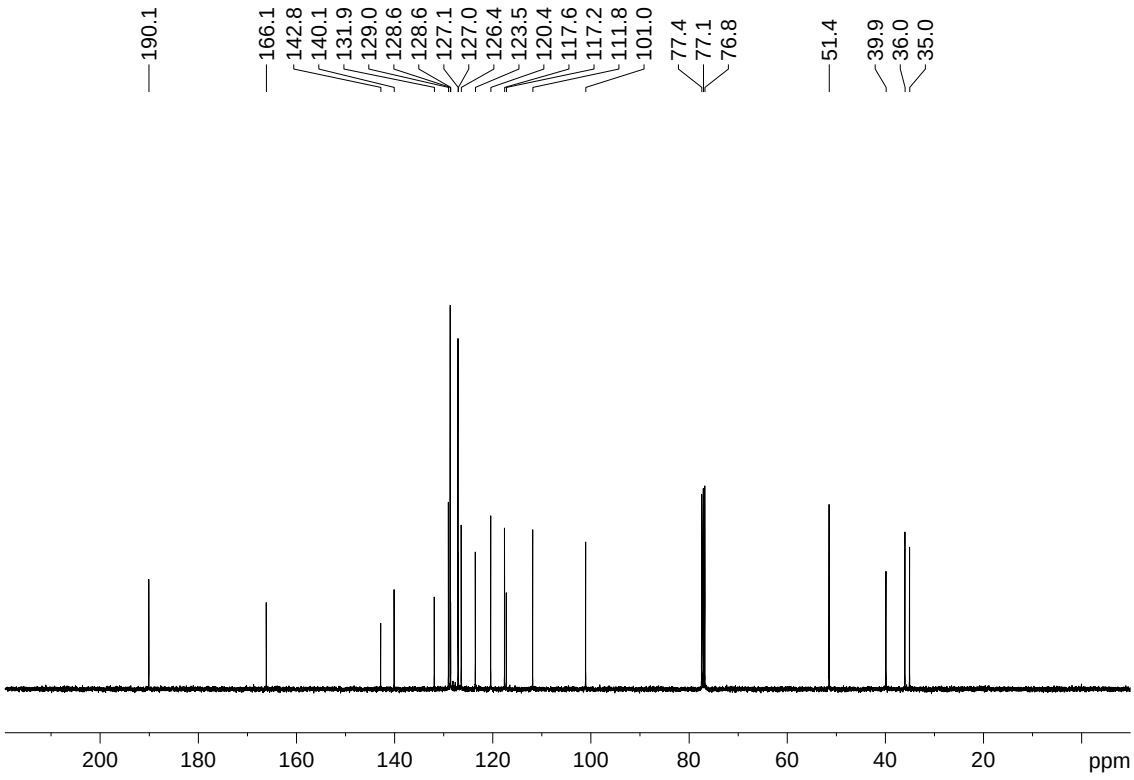
(5) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc*. **2008**, *130*, 10848-10849.

V NMR Spectrum

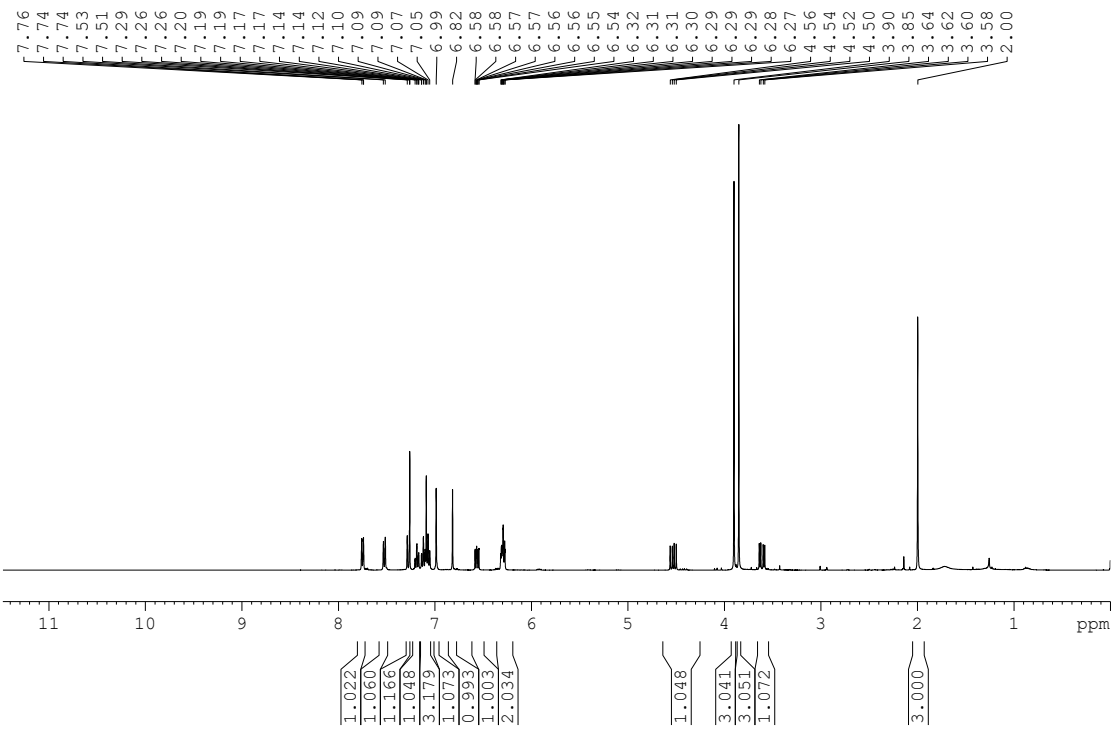
^{1}H NMR-3a



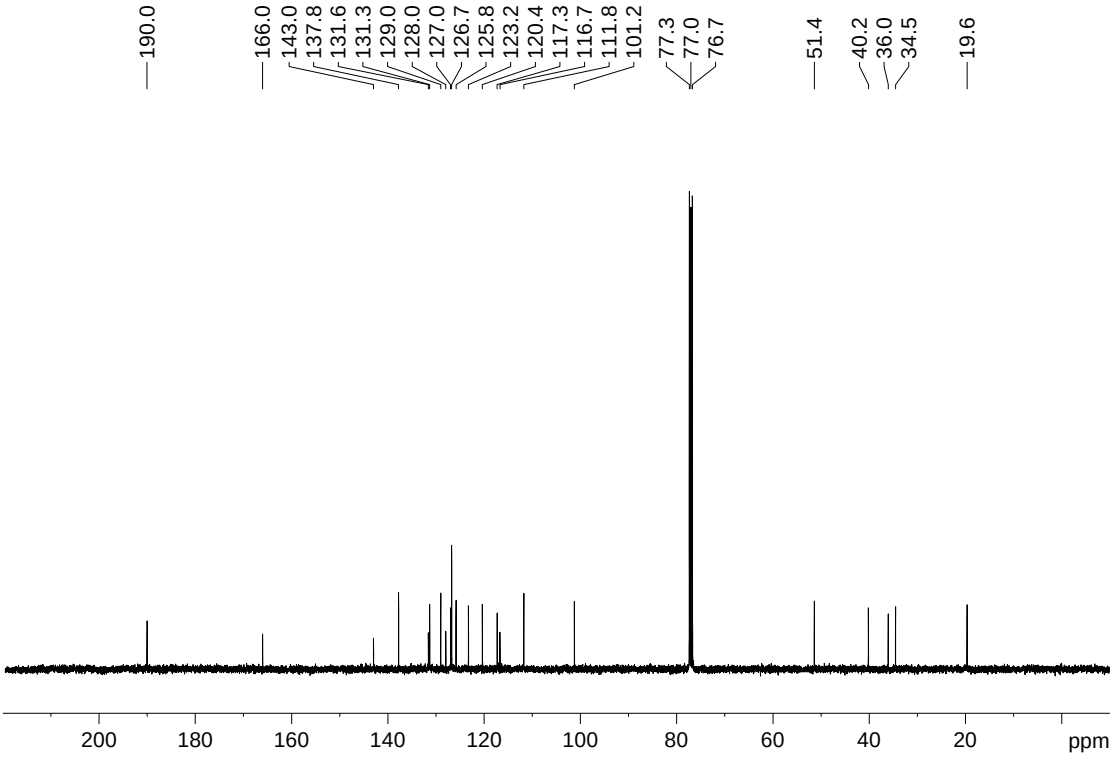
^{13}C NMR-3a



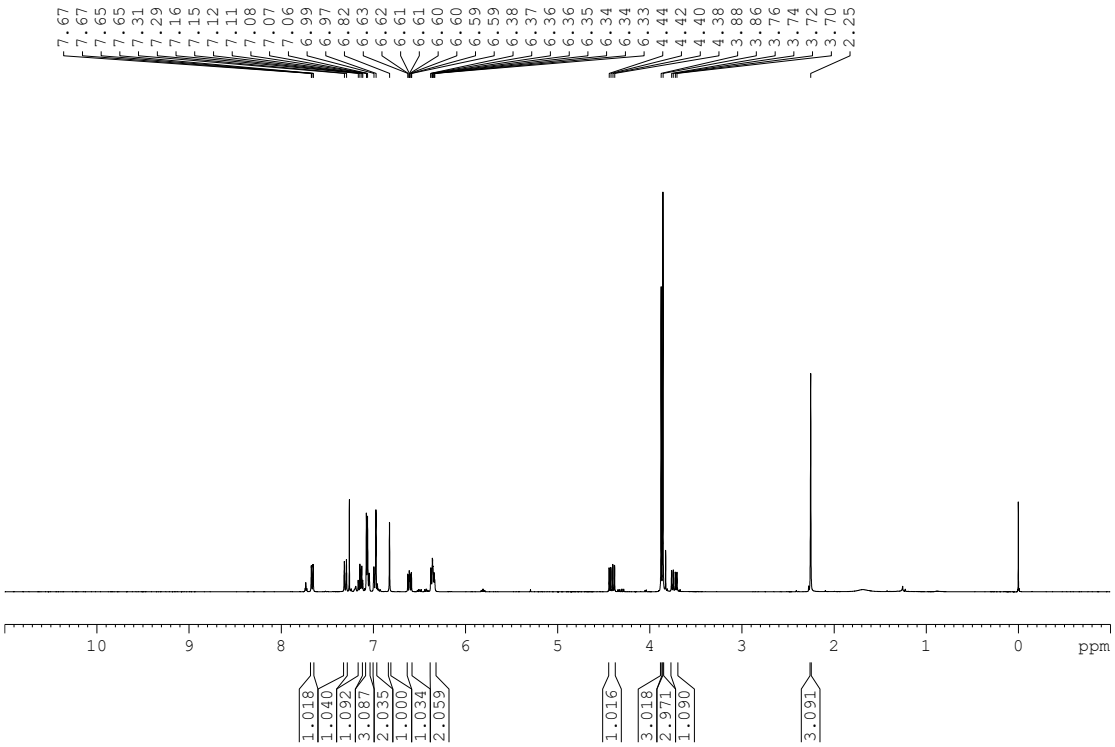
^{1}H NMR-3b



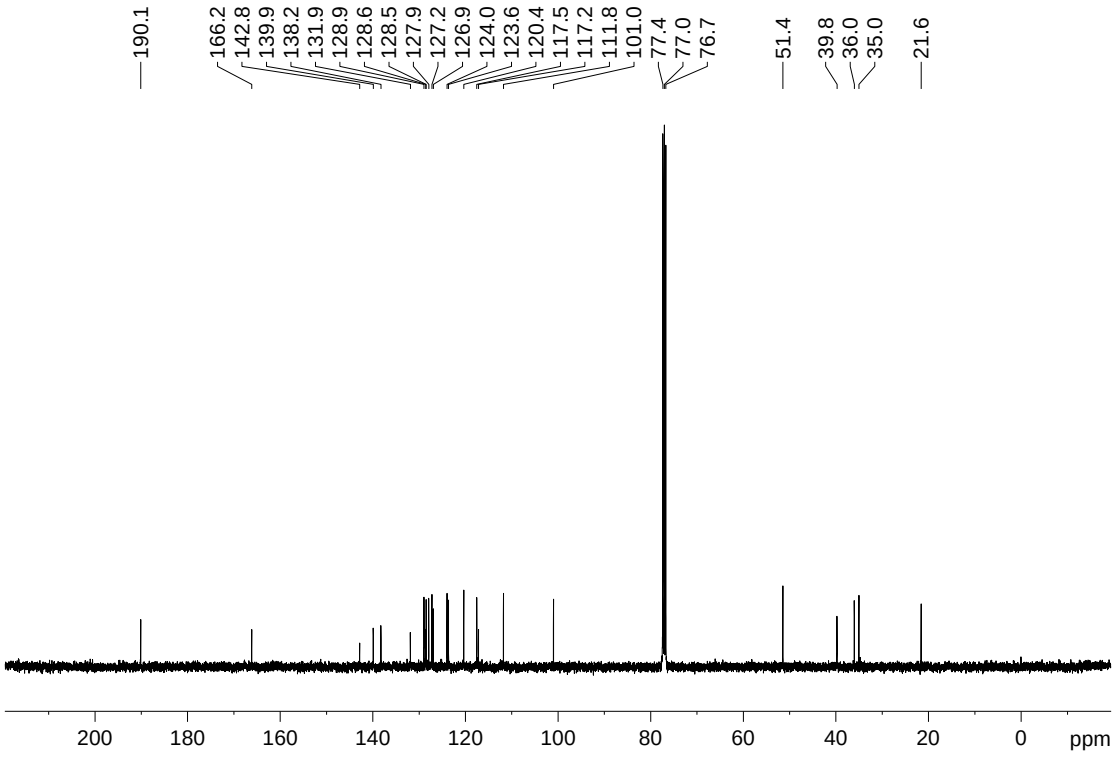
^{13}C NMR-3b



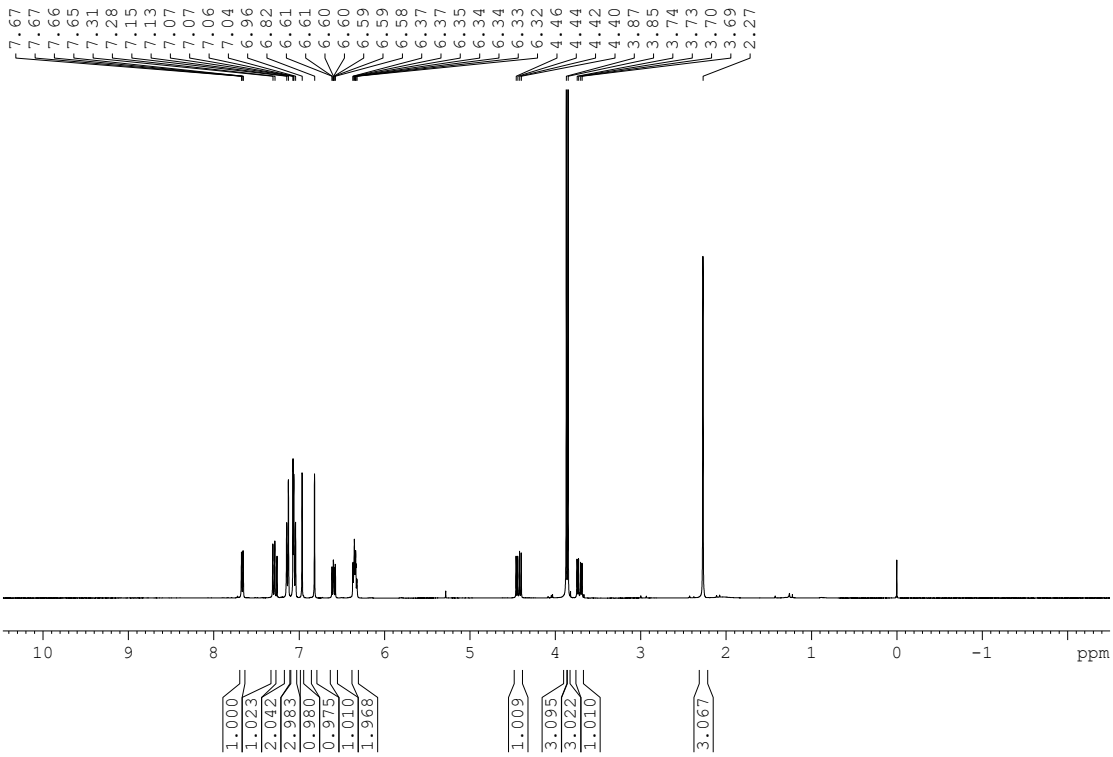
^{1}H NMR-3c



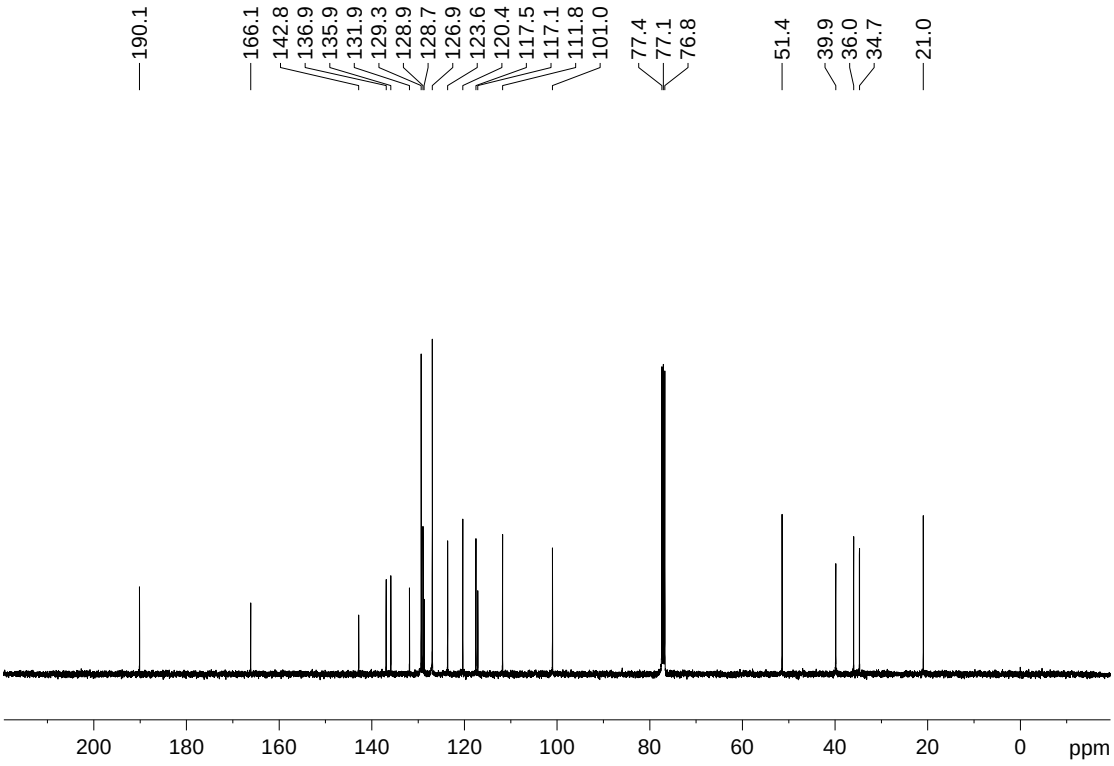
^{13}C NMR-3c



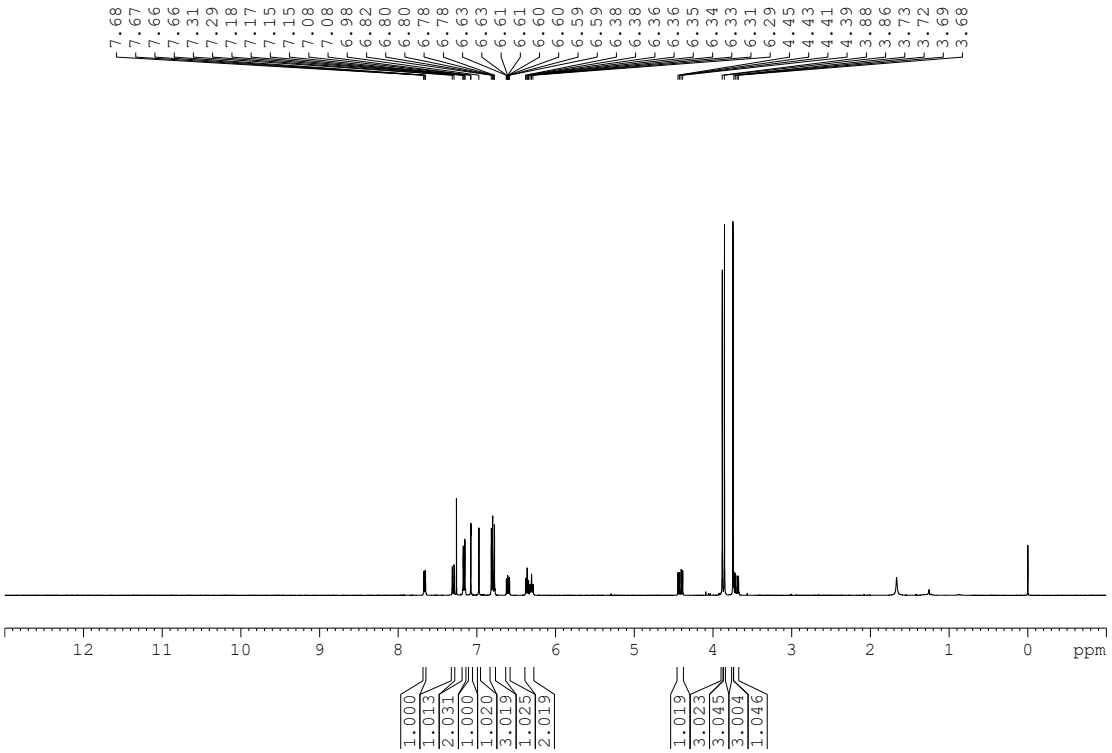
^{1}H NMR-3d



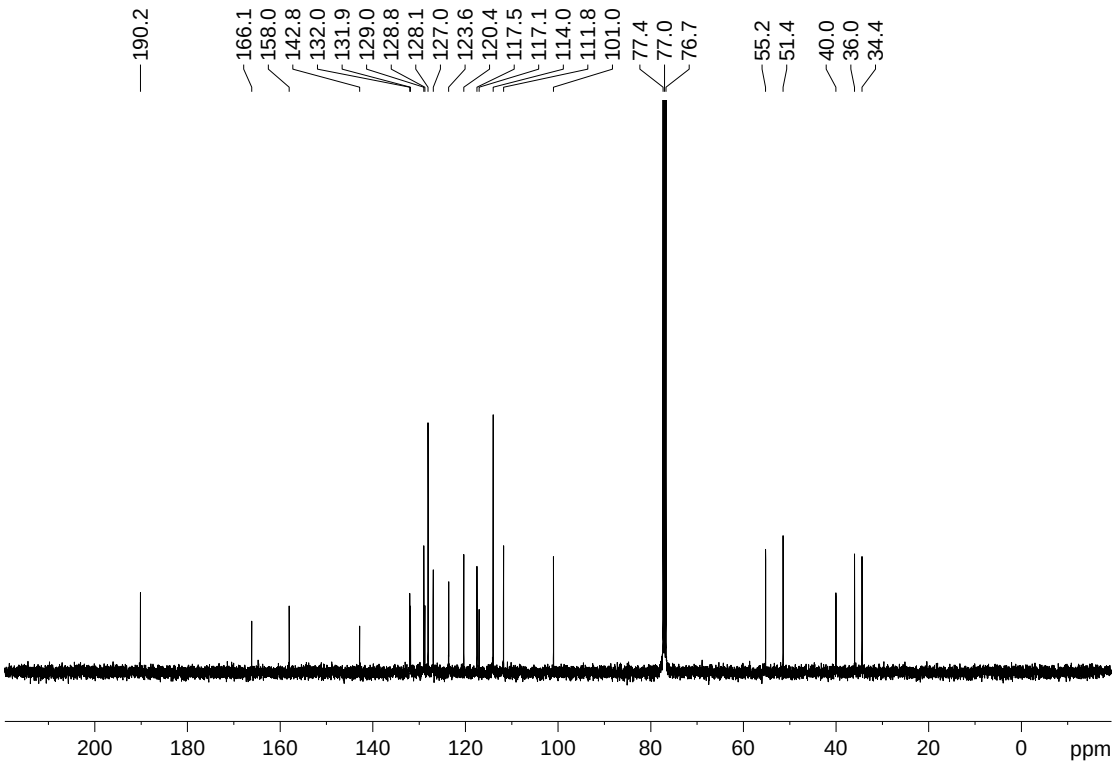
^{13}C NMR-3d



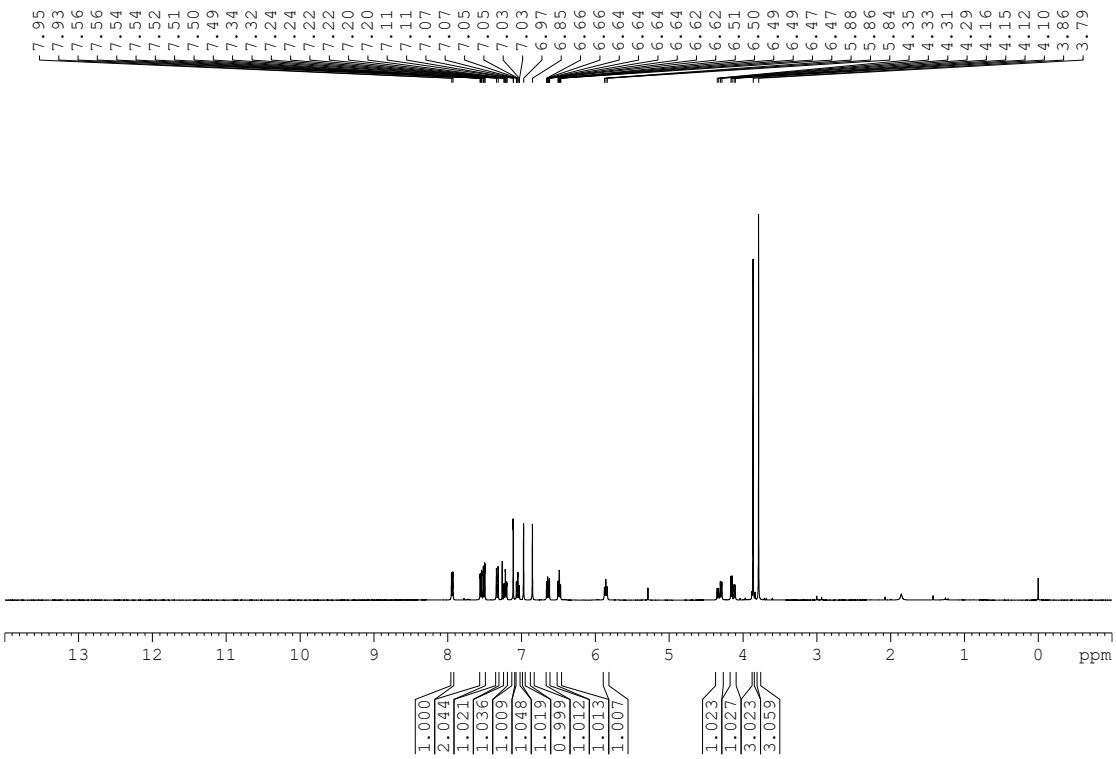
^{1}H NMR-3e



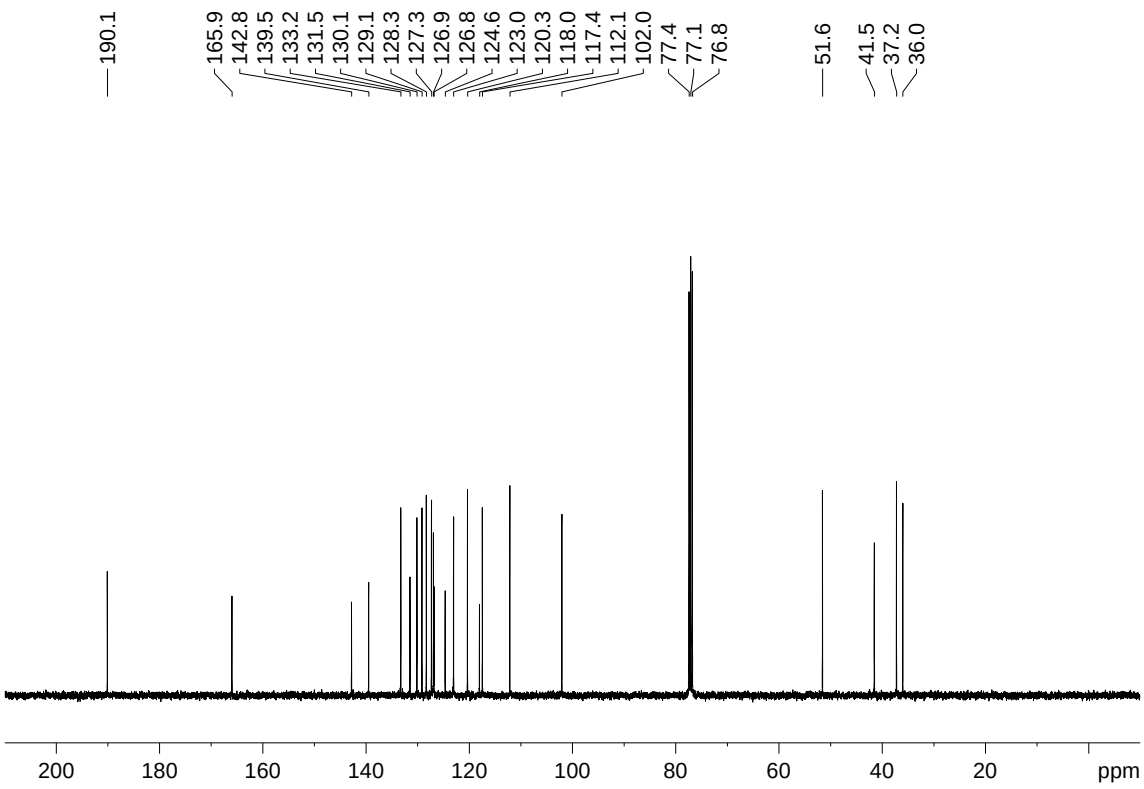
^{13}C NMR-3e



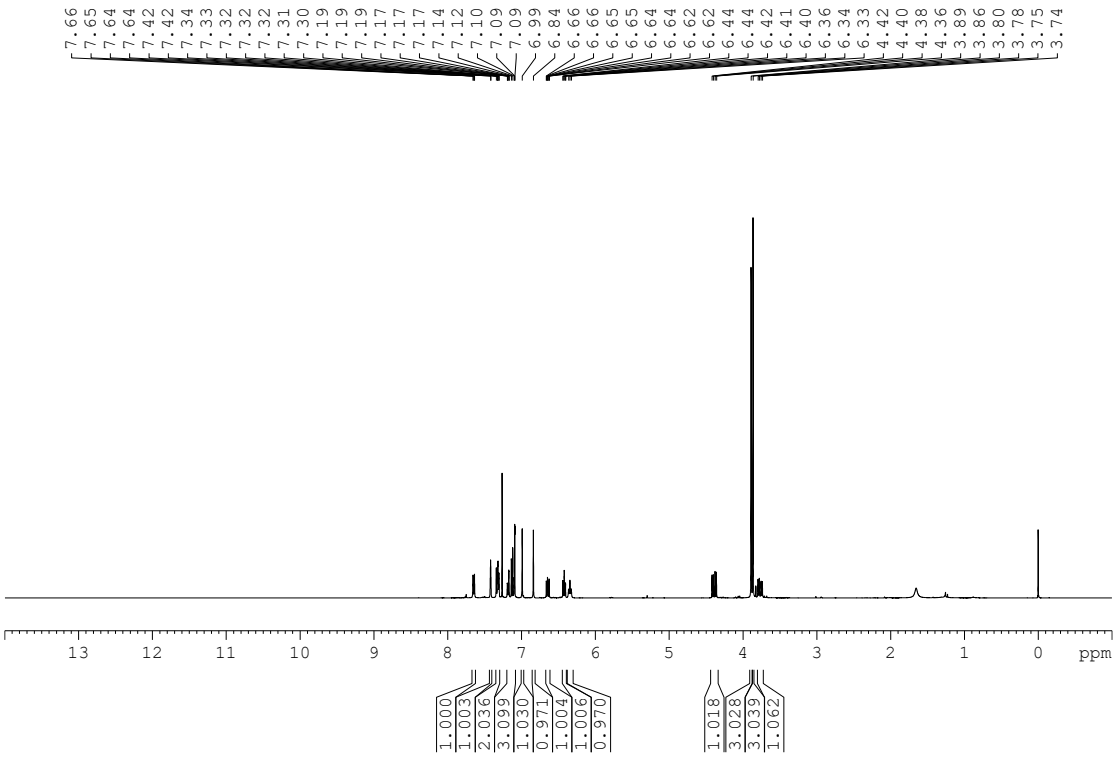
^{1}H NMR-3f



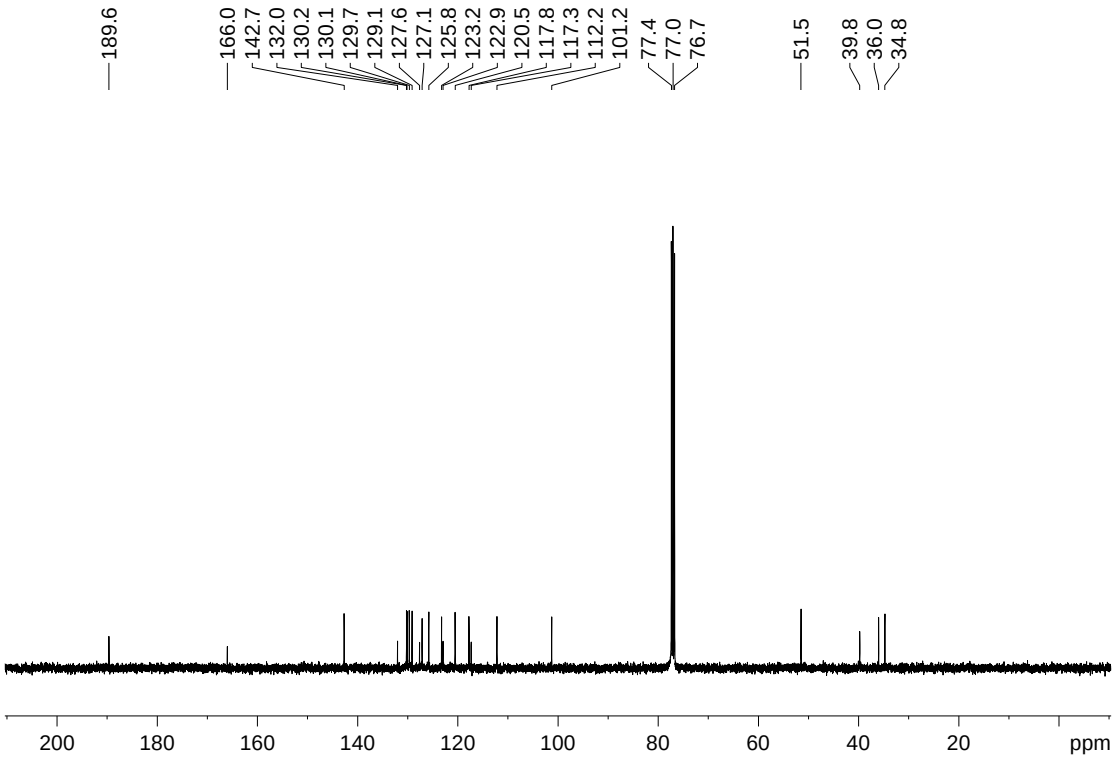
^{13}C NMR-3f



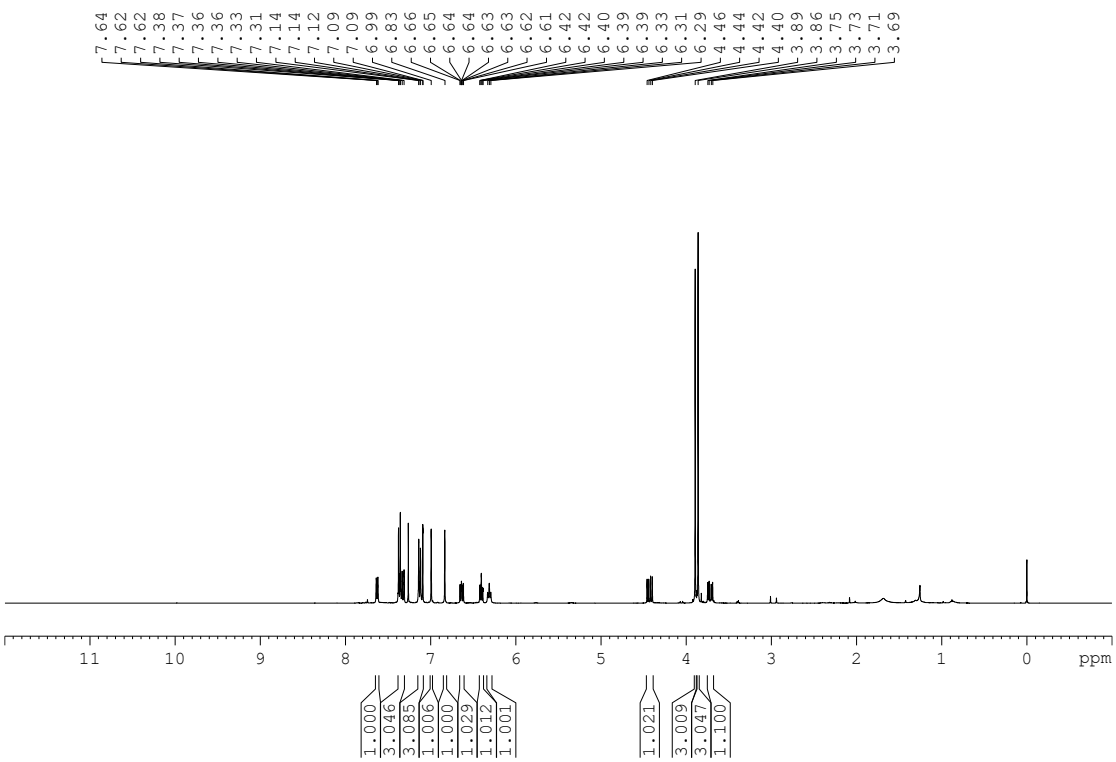
^{1}H NMR-3g



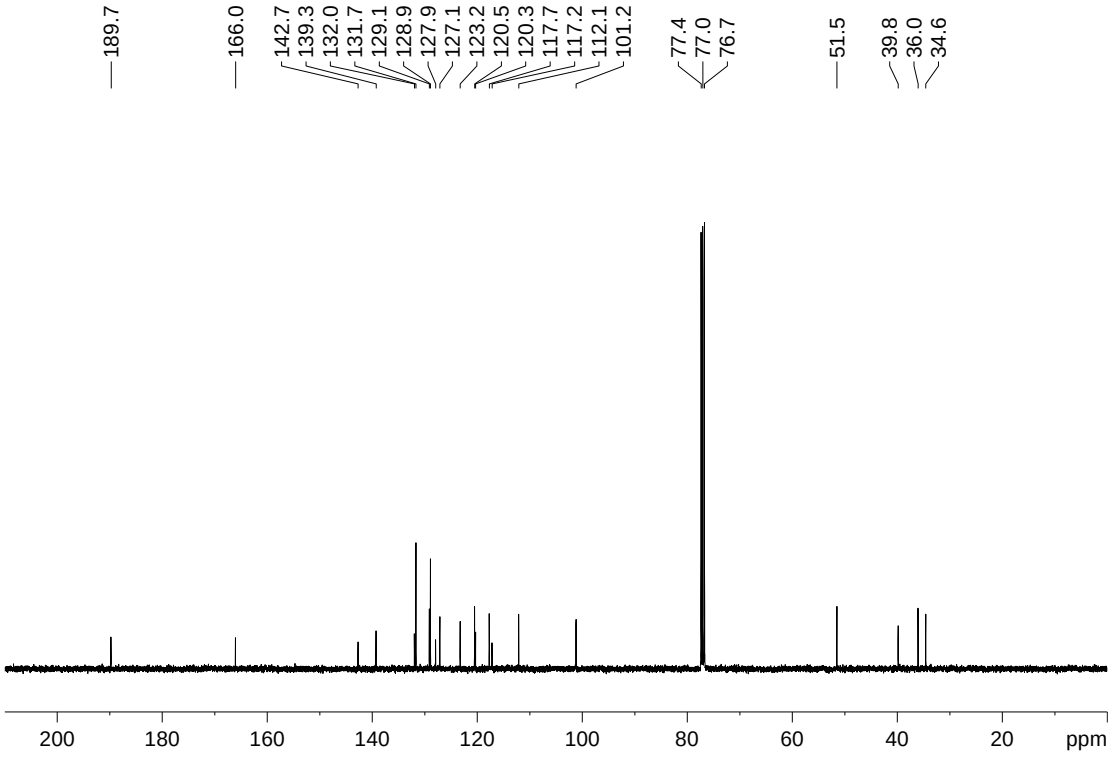
^{13}C NMR-3g



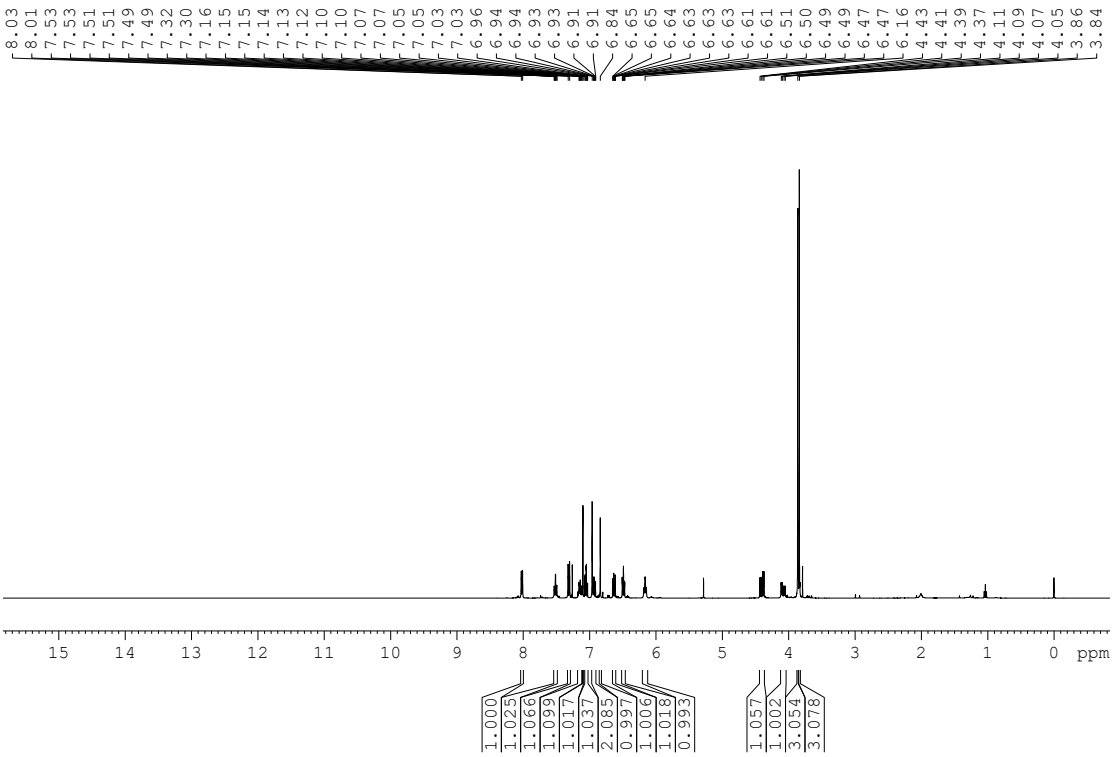
^{1}H NMR-3h



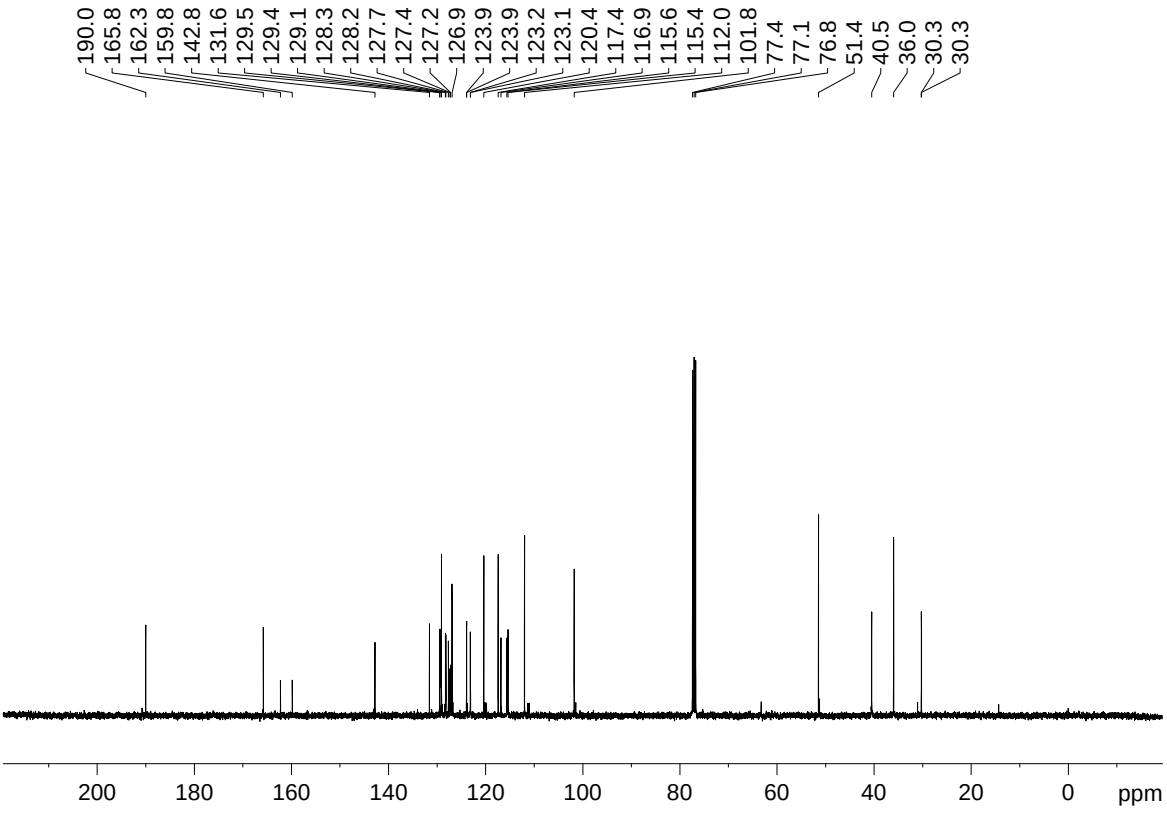
^{13}C NMR-3h



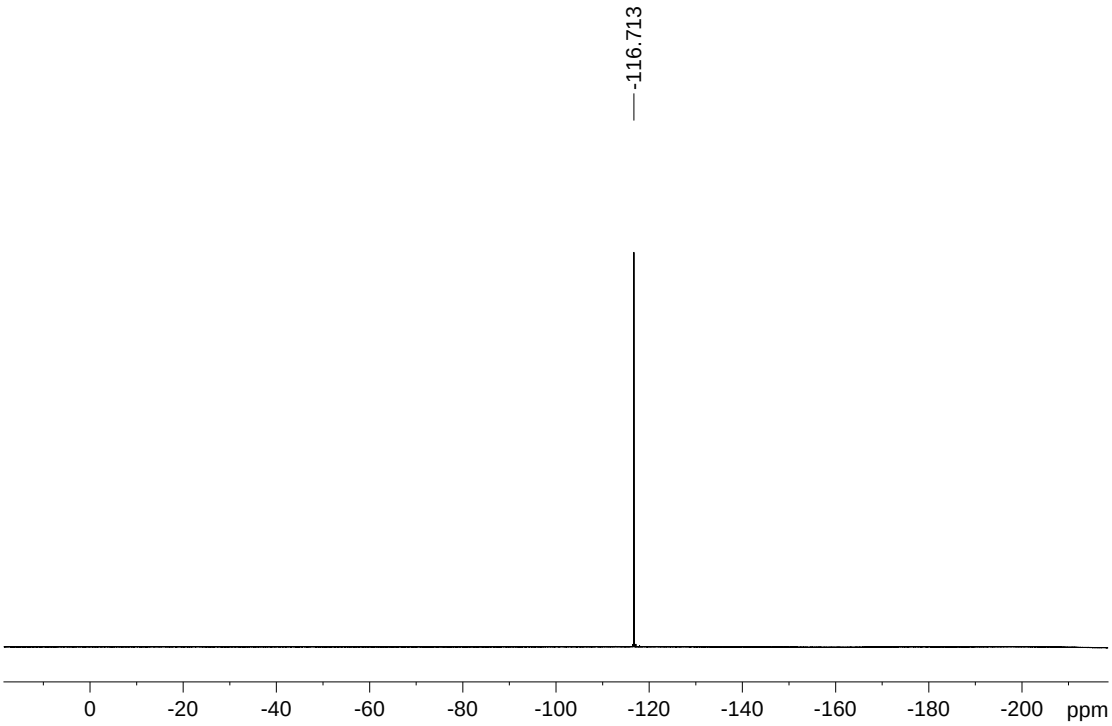
^{1}H NMR-3i



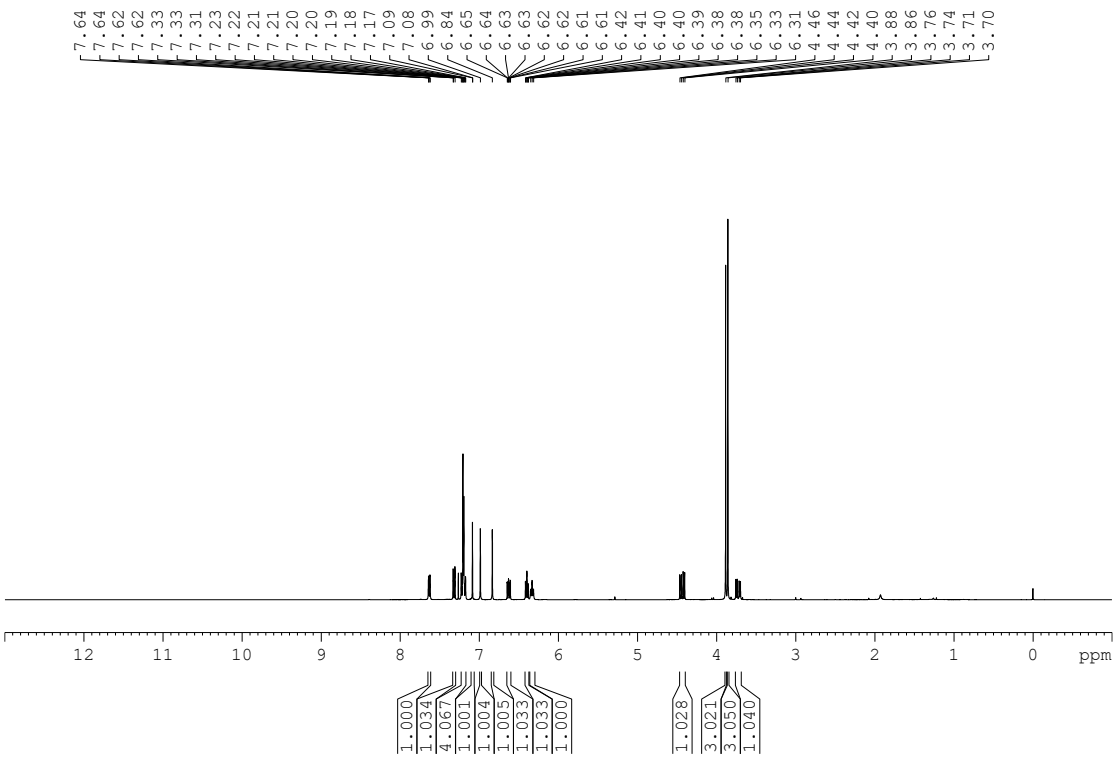
^{13}C NMR-3i



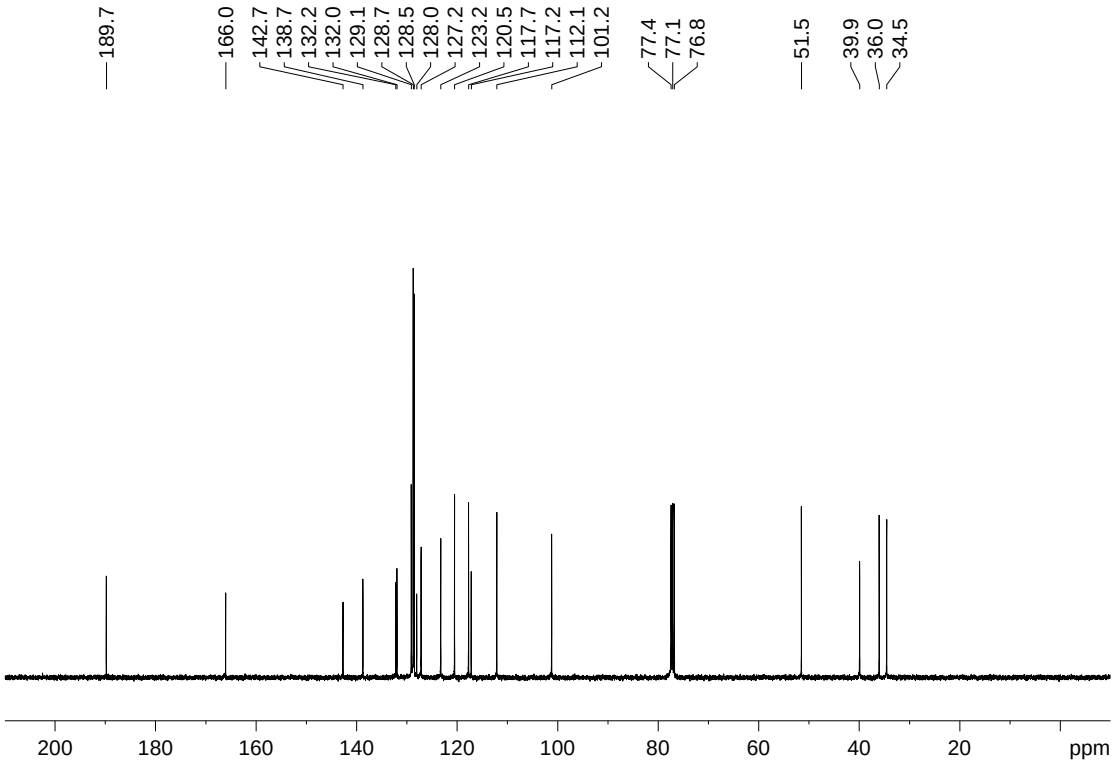
^{19}FNMR-3i



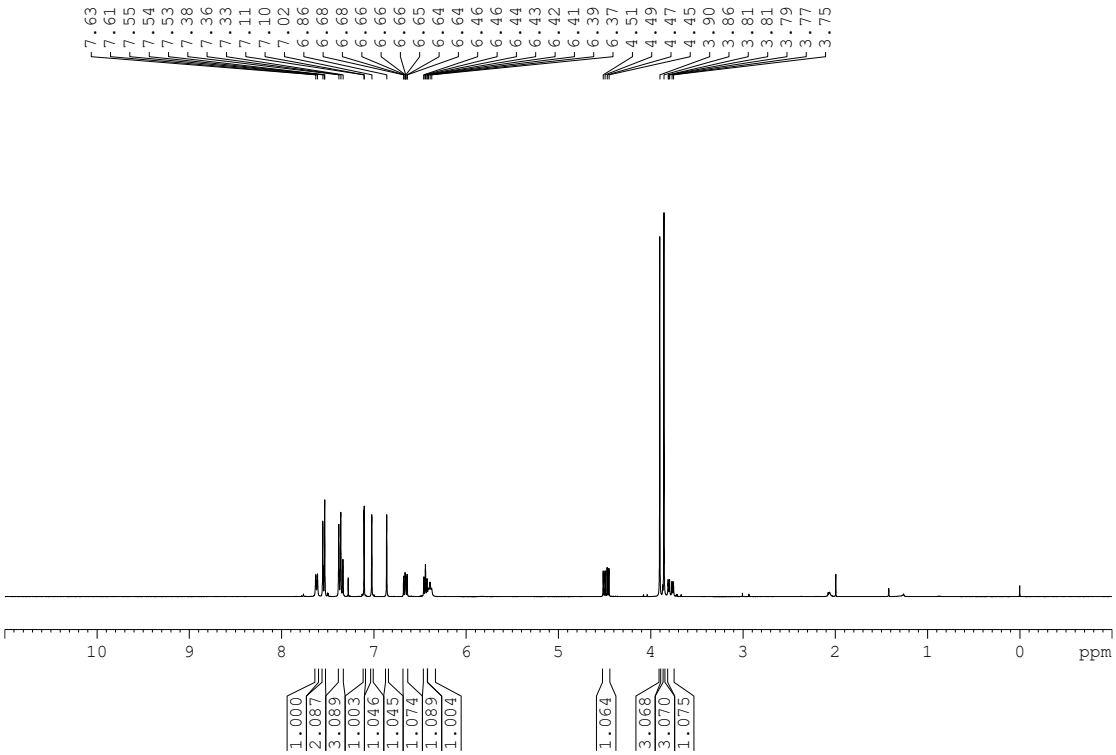
^{1}H NMR-3j



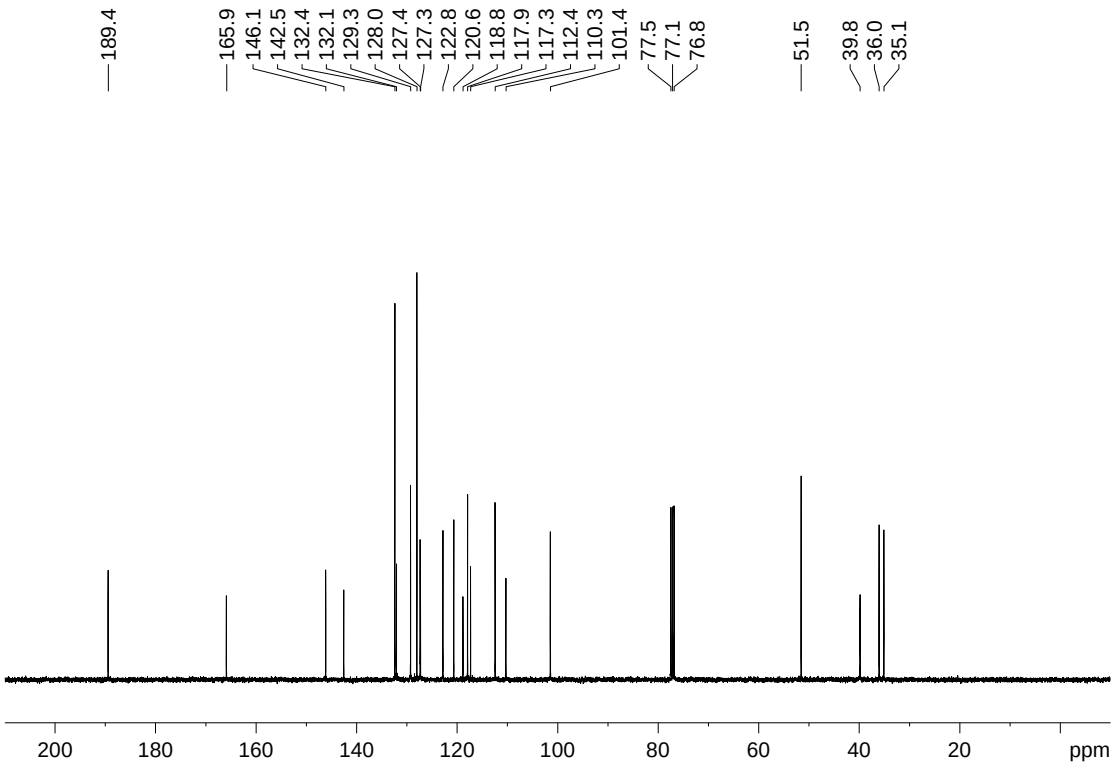
^{13}C NMR-3j



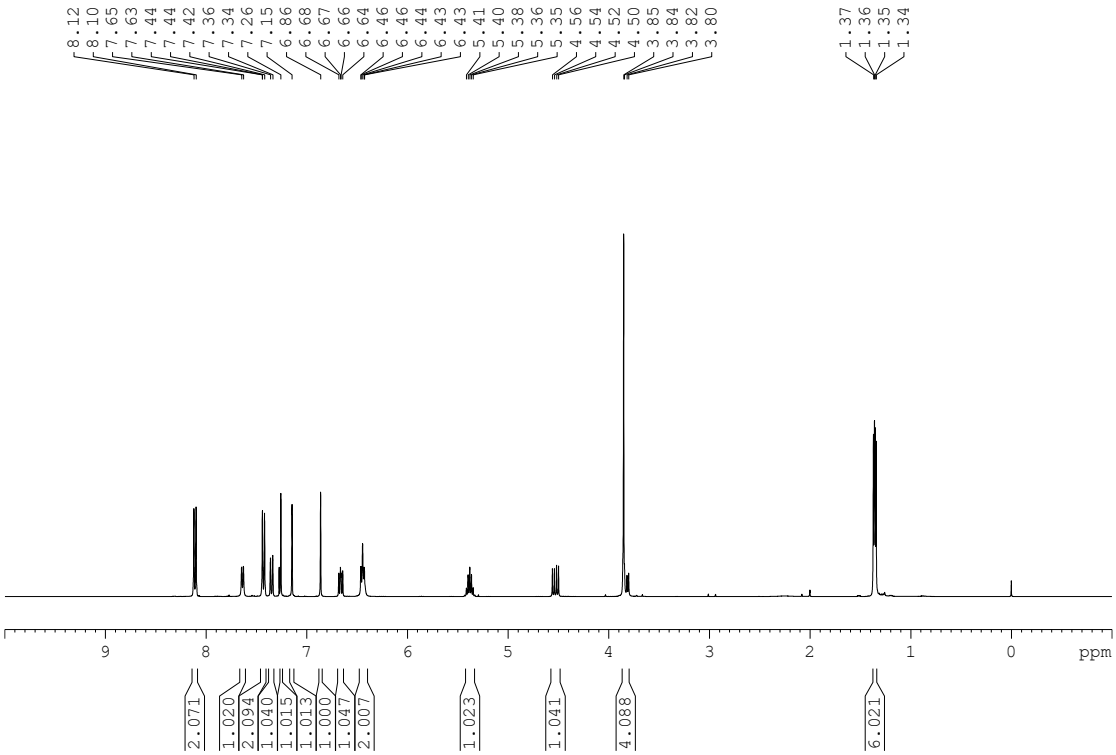
^{1}H NMR-3k



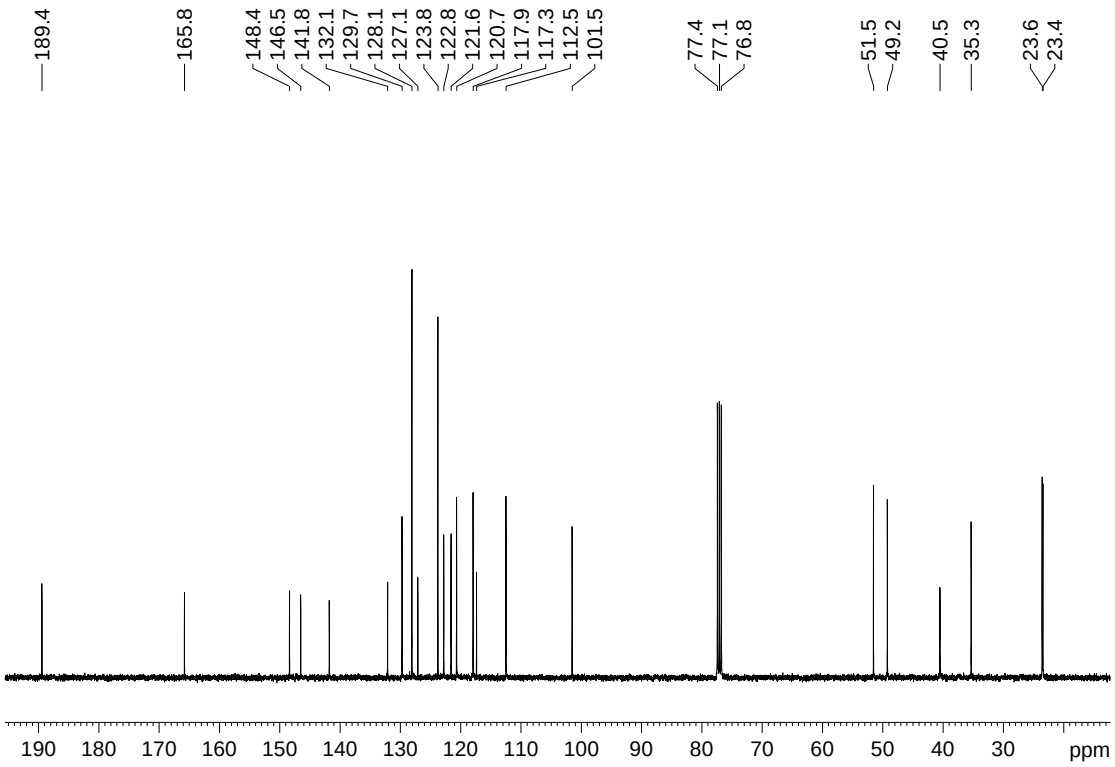
^{13}C NMR-3k



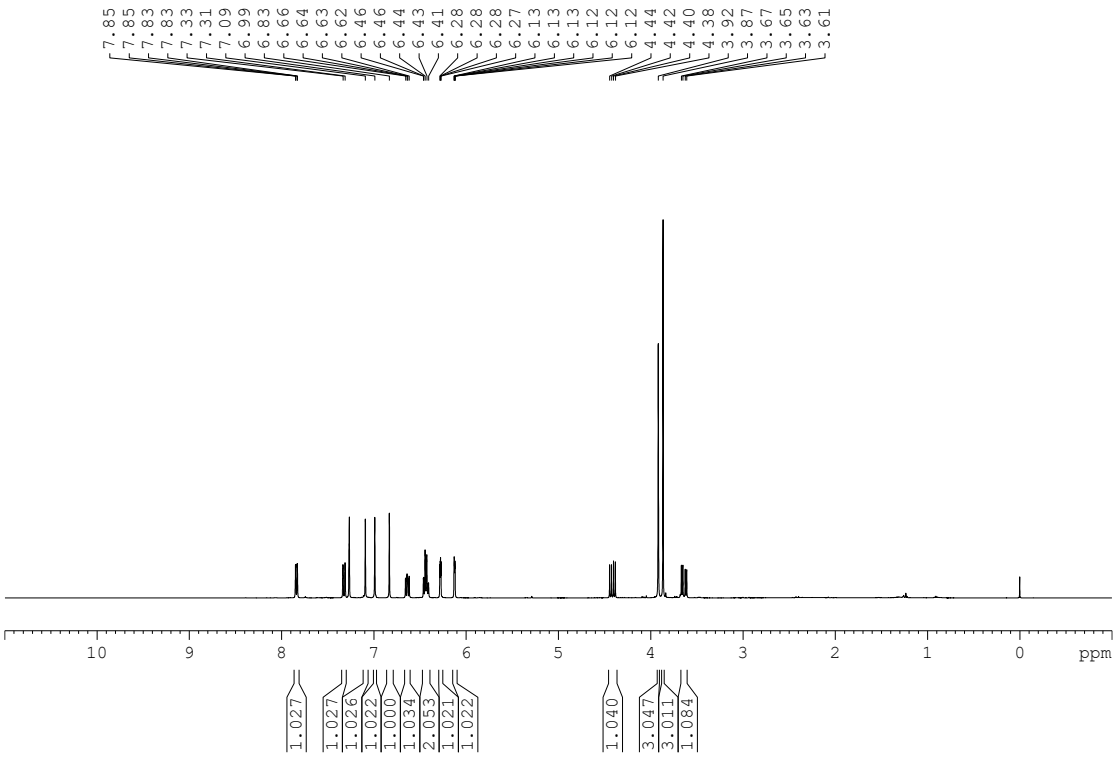
^{1}HNMR-3l



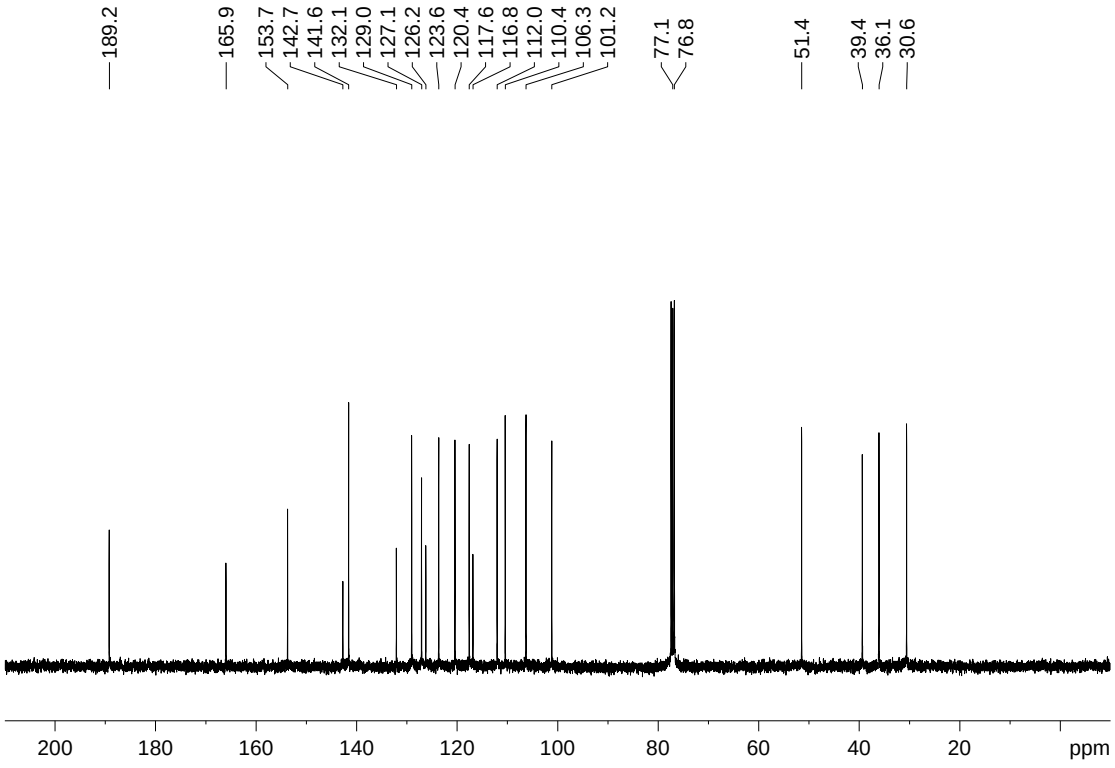
^{13}C NMR-3l



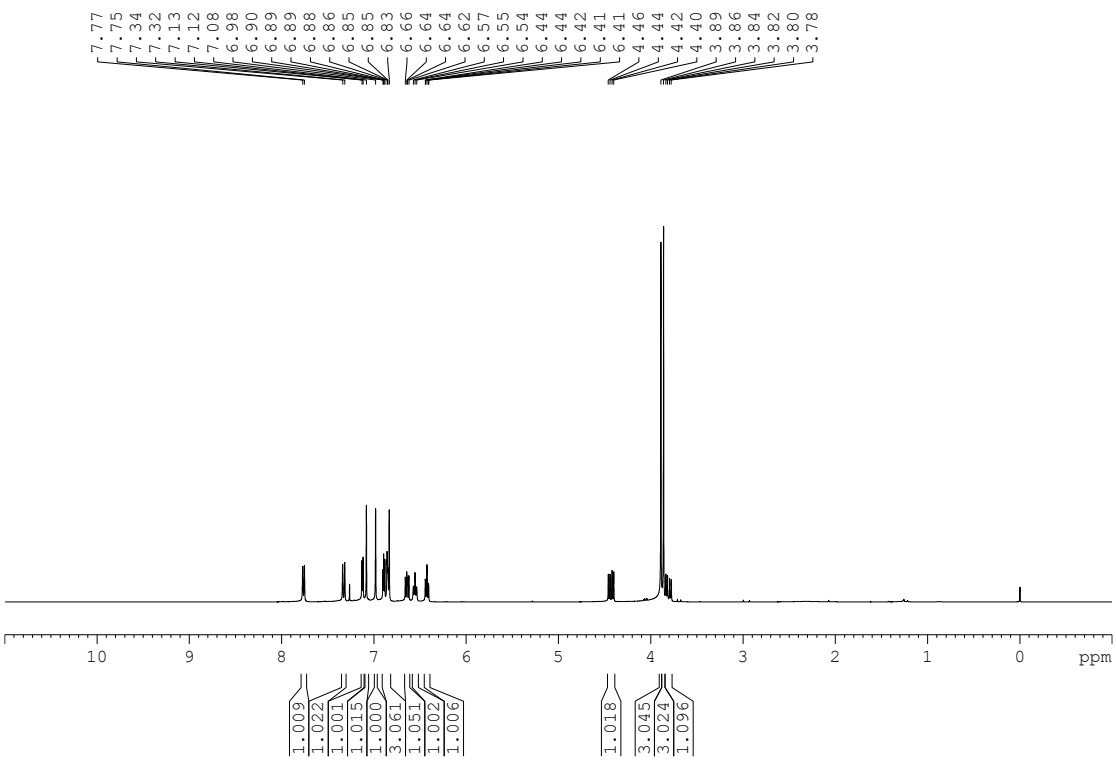
^{1}H NMR-3n



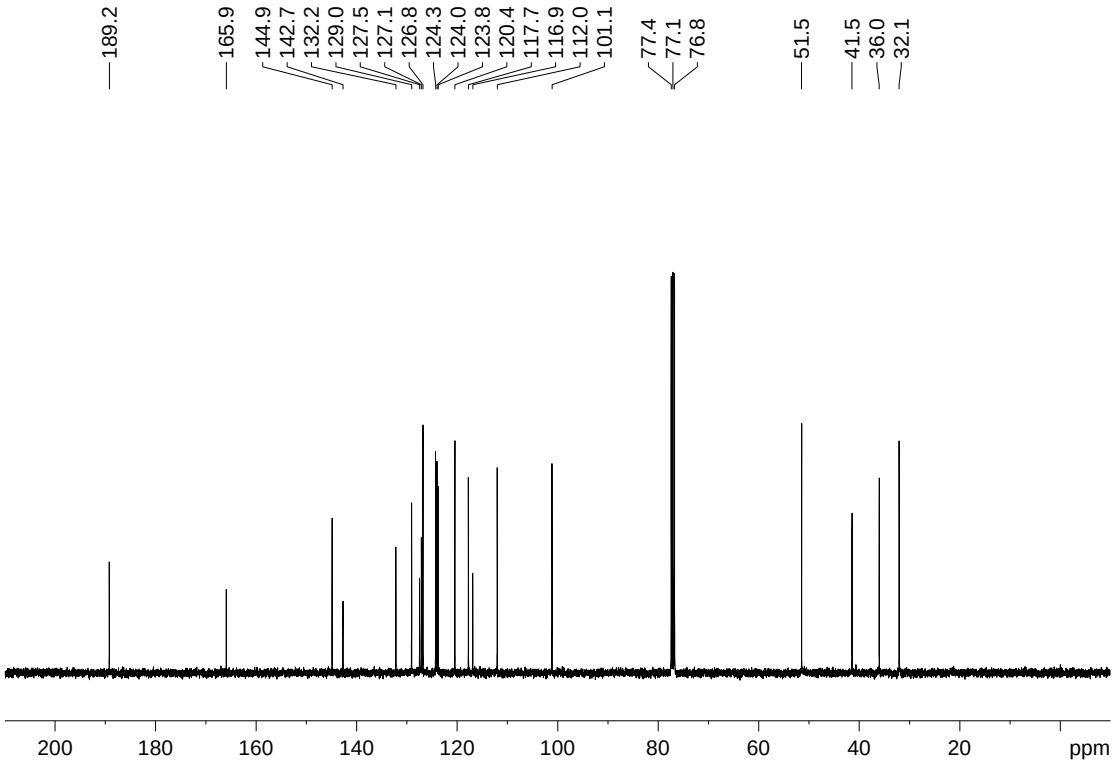
^{13}C NMR-3n



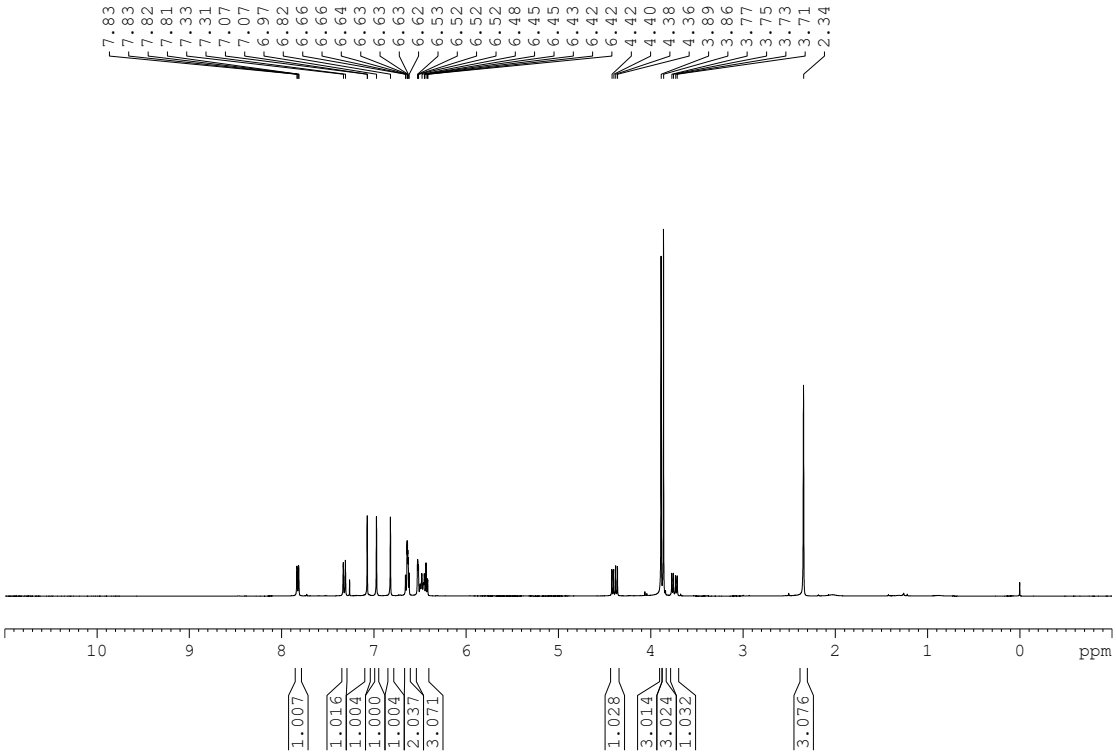
^{13}C NMR-3o



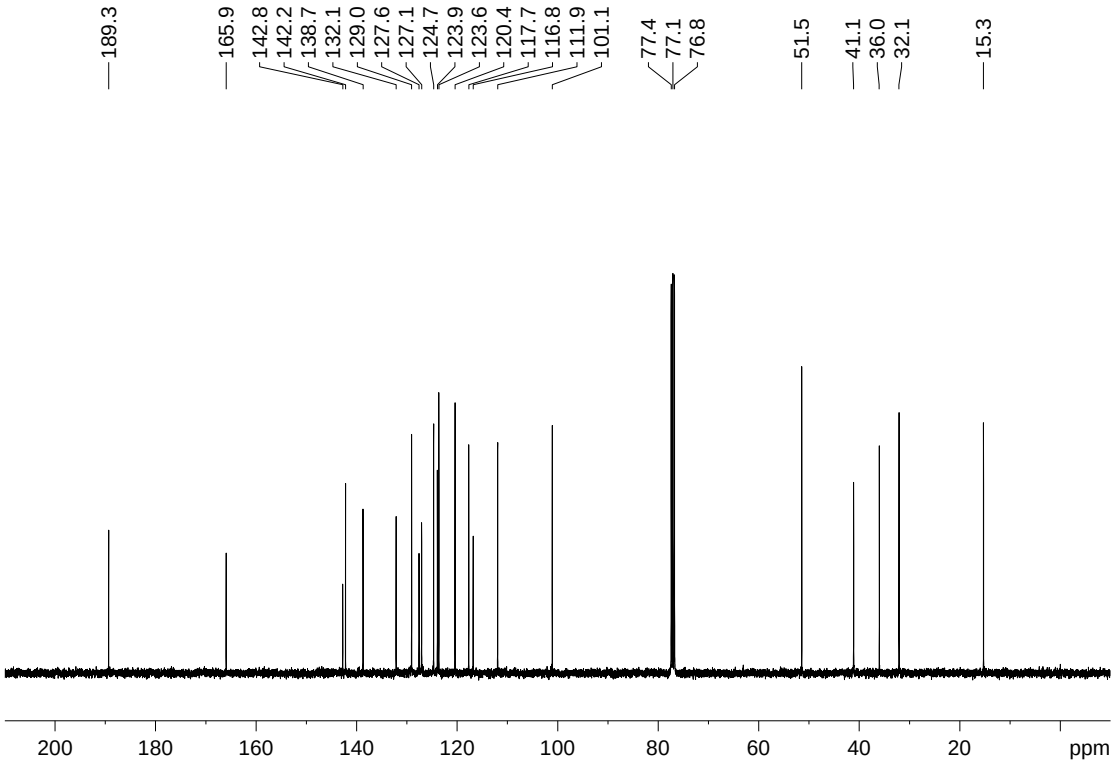
^{13}C NMR-3o



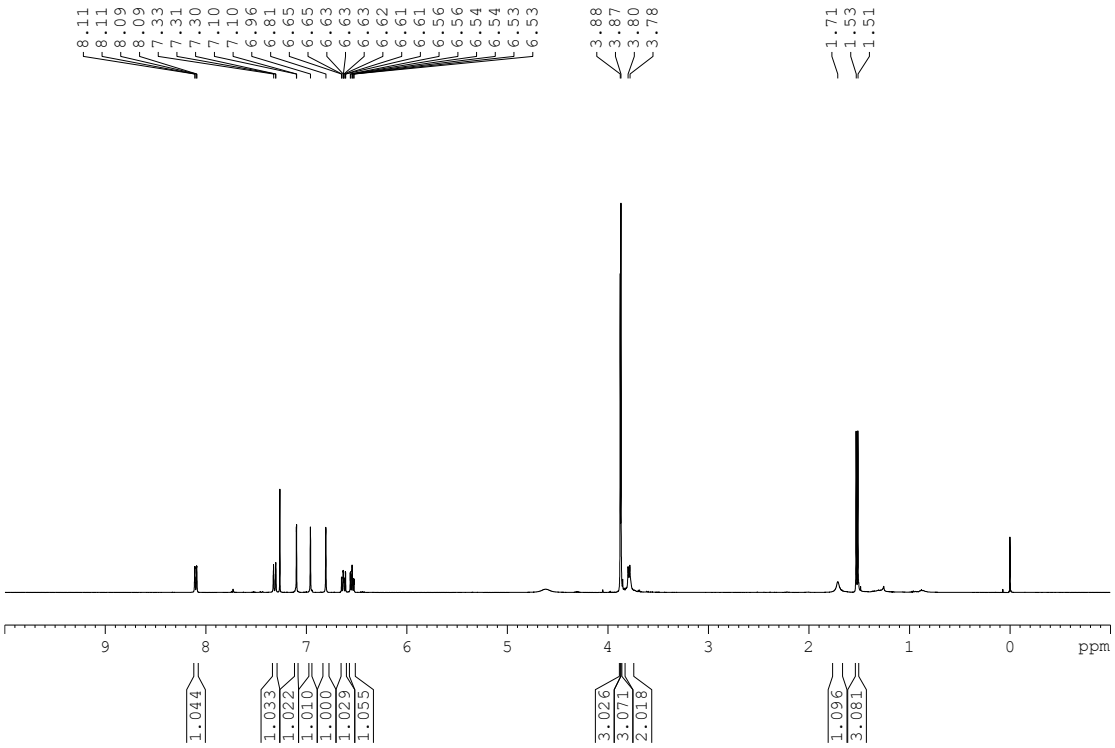
^{1}H NMR-3p



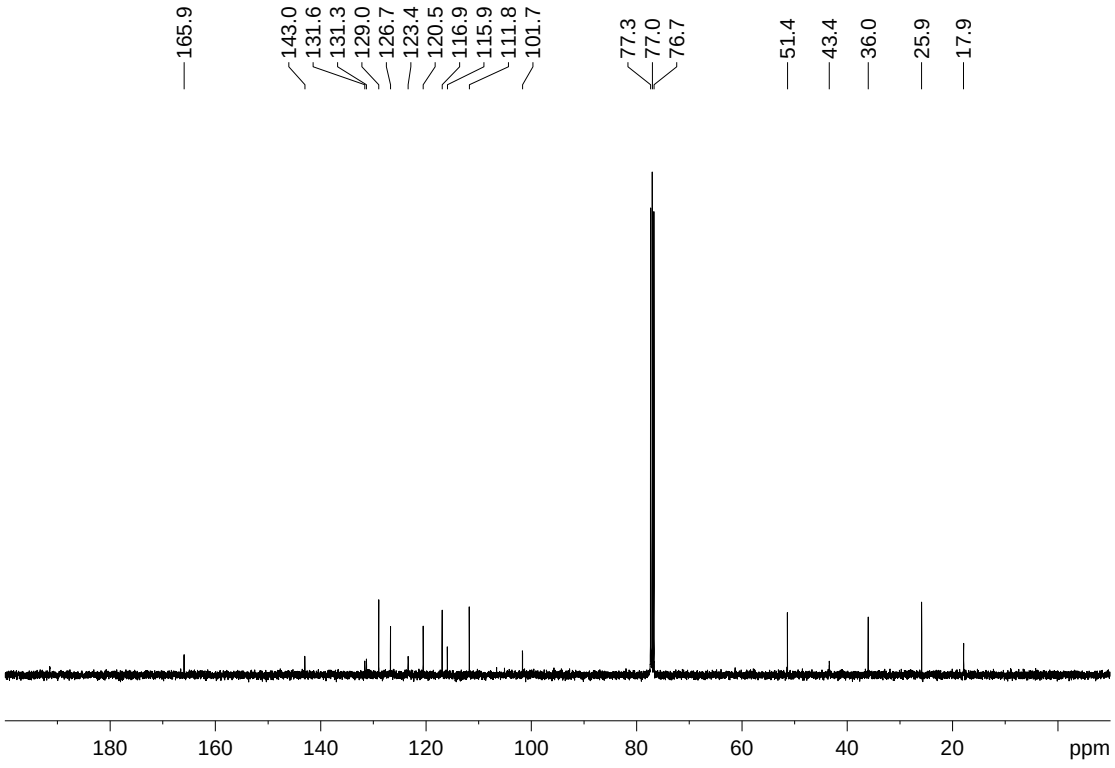
^{13}C NMR-3p



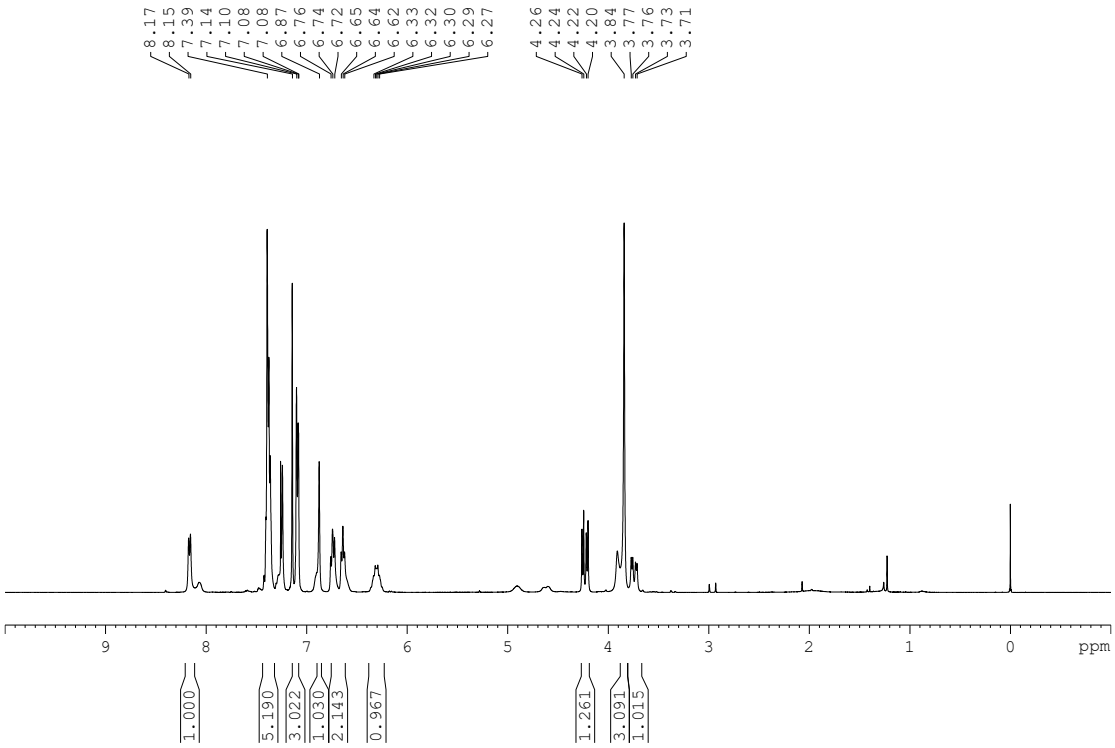
^{1}H NMR-3q



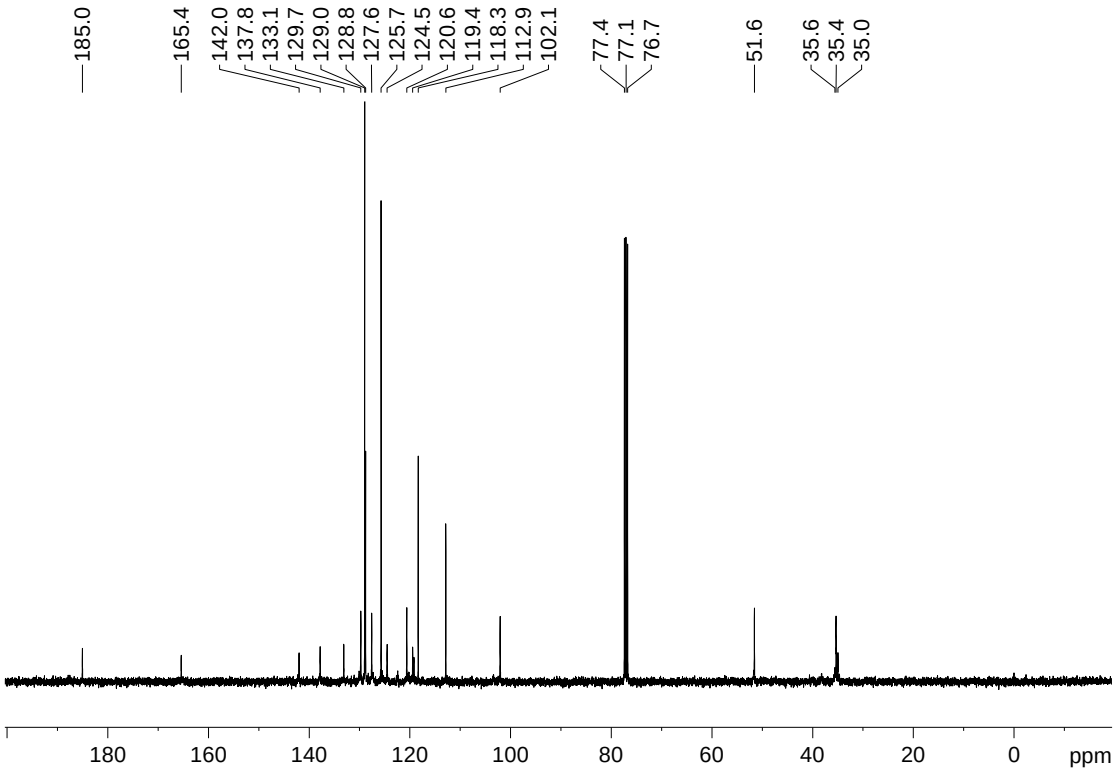
^{13}C NMR-3q



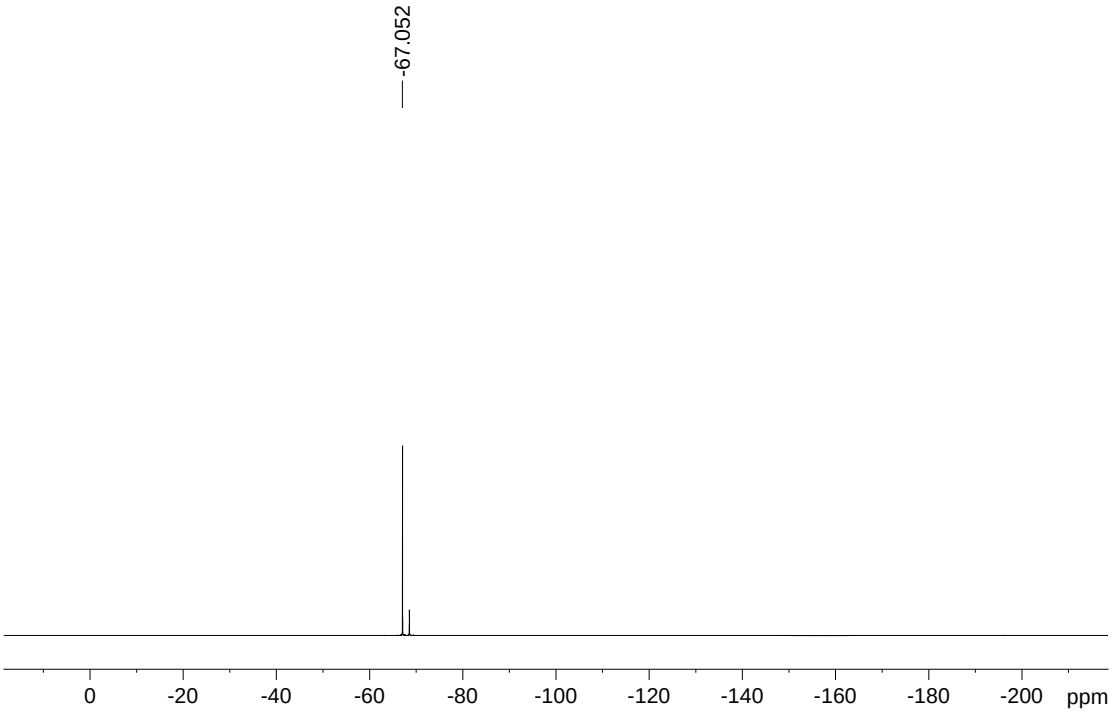
^{1}H NMR-3s



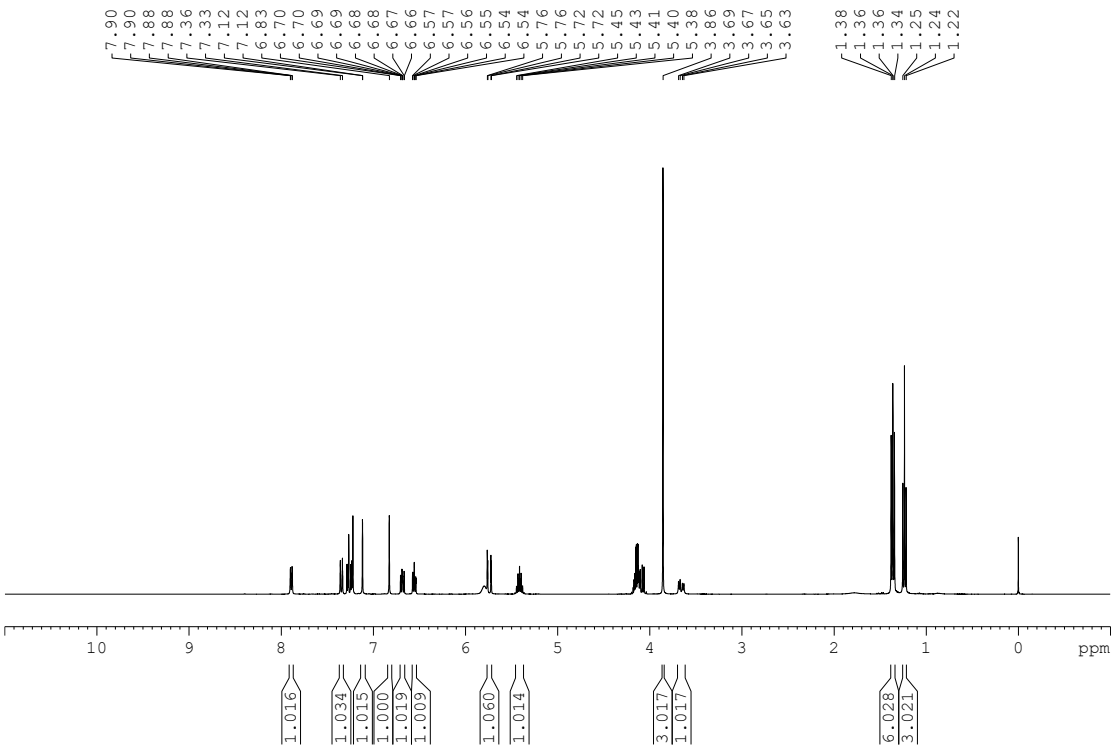
^{13}C NMR-3s



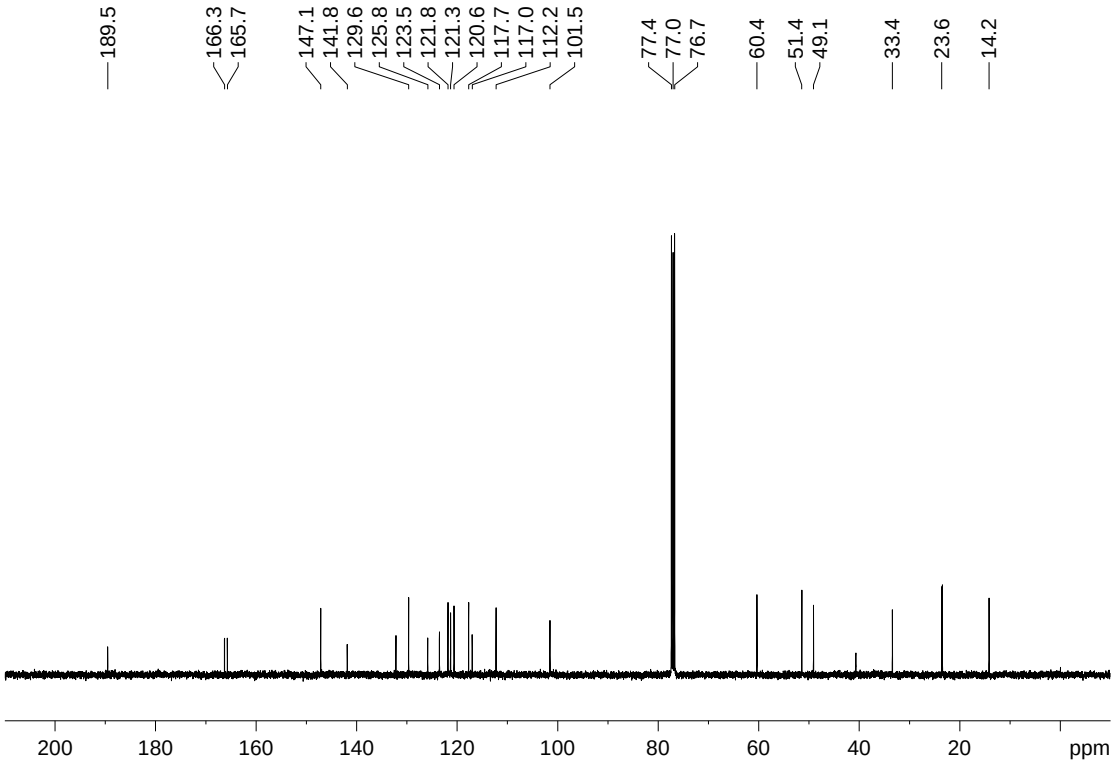
^{19}F NMR-3s



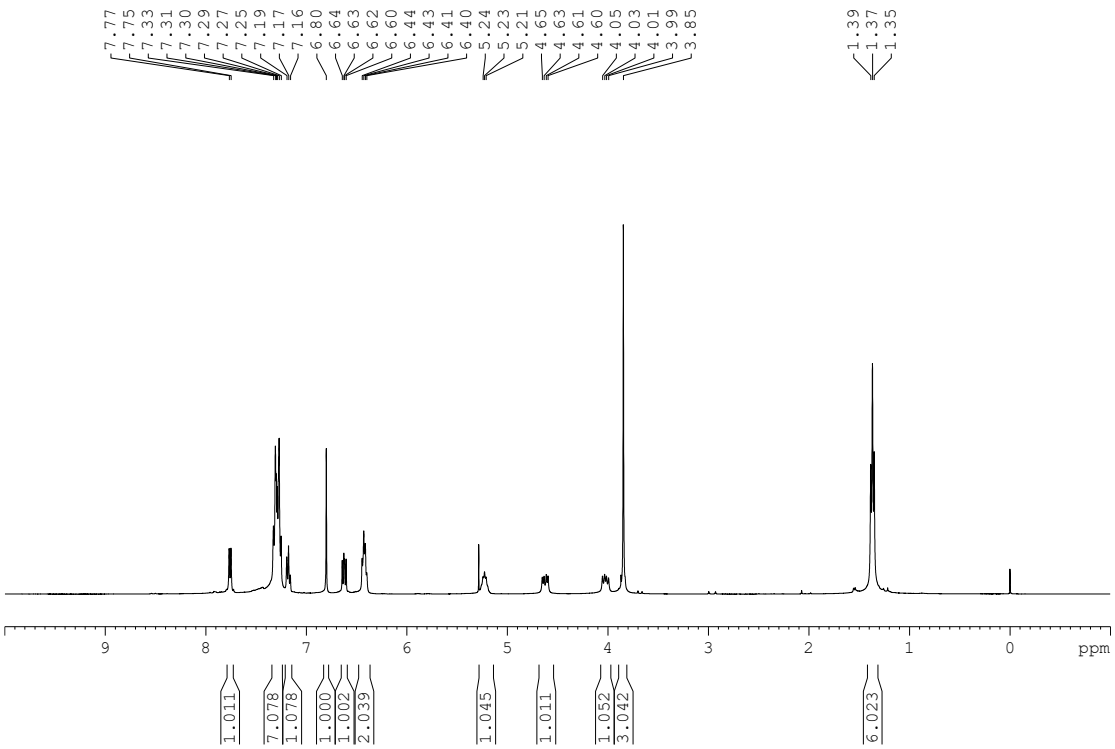
^{1}H NMR-3t



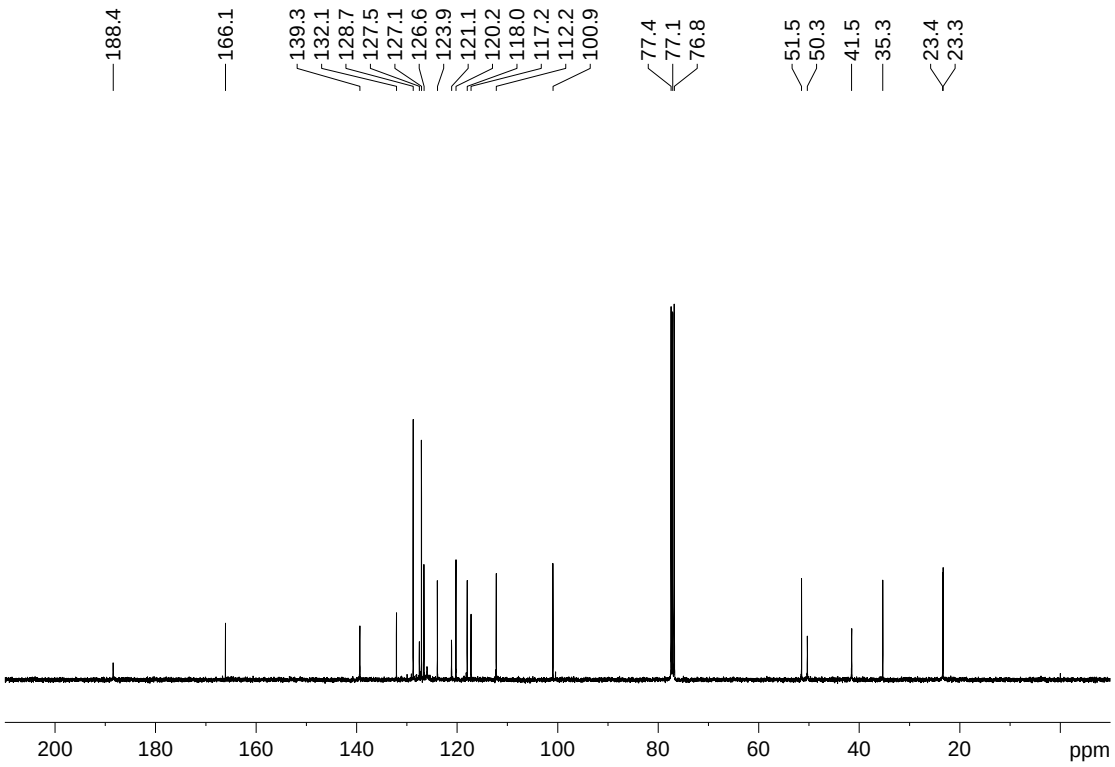
^{13}C NMR-3t



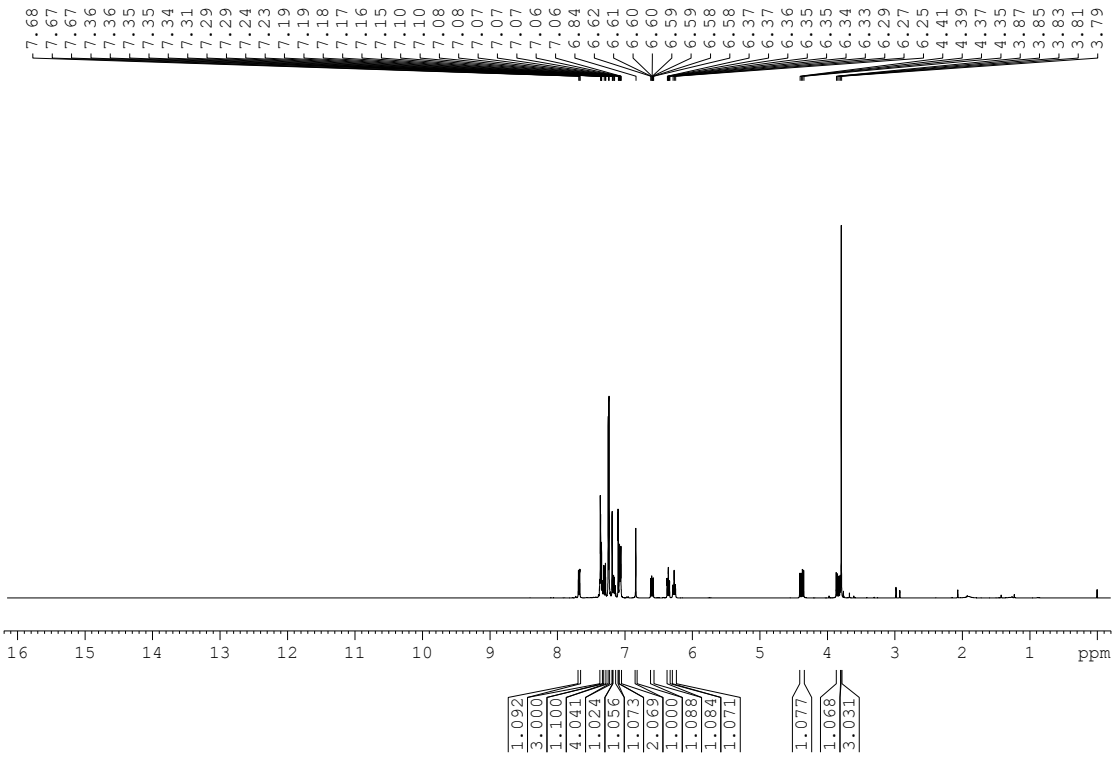
^{1}H NMR-3u



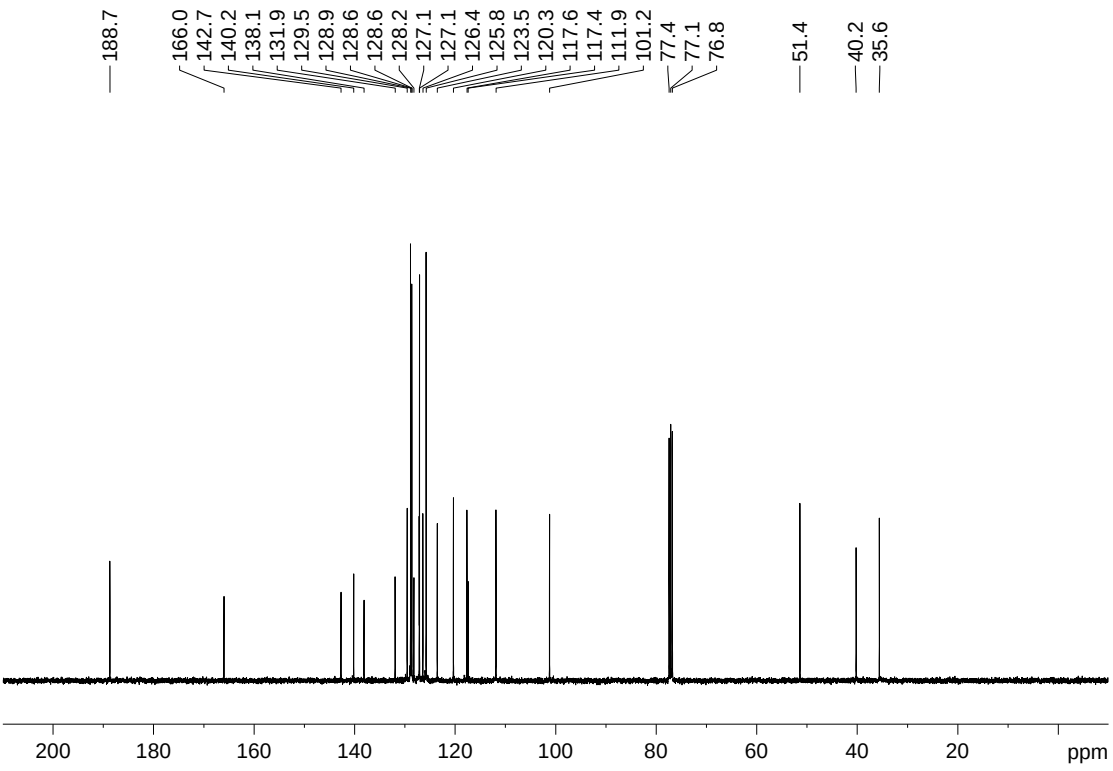
^{13}C NMR-3u



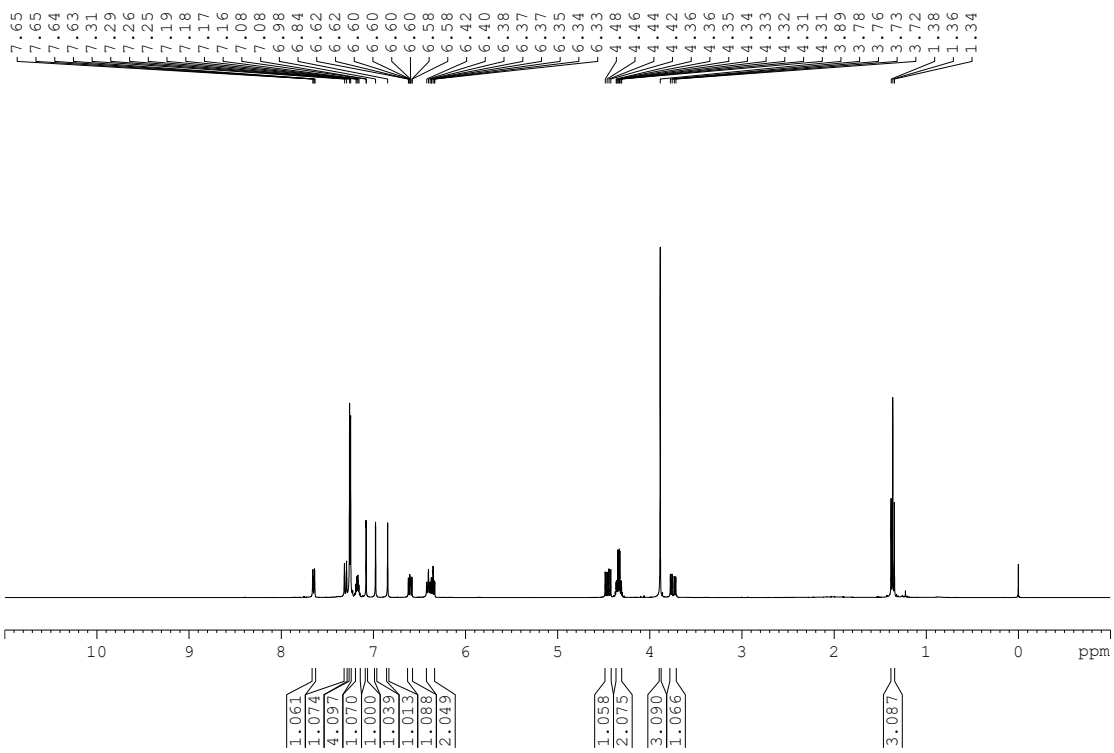
^{1}H NMR-3v



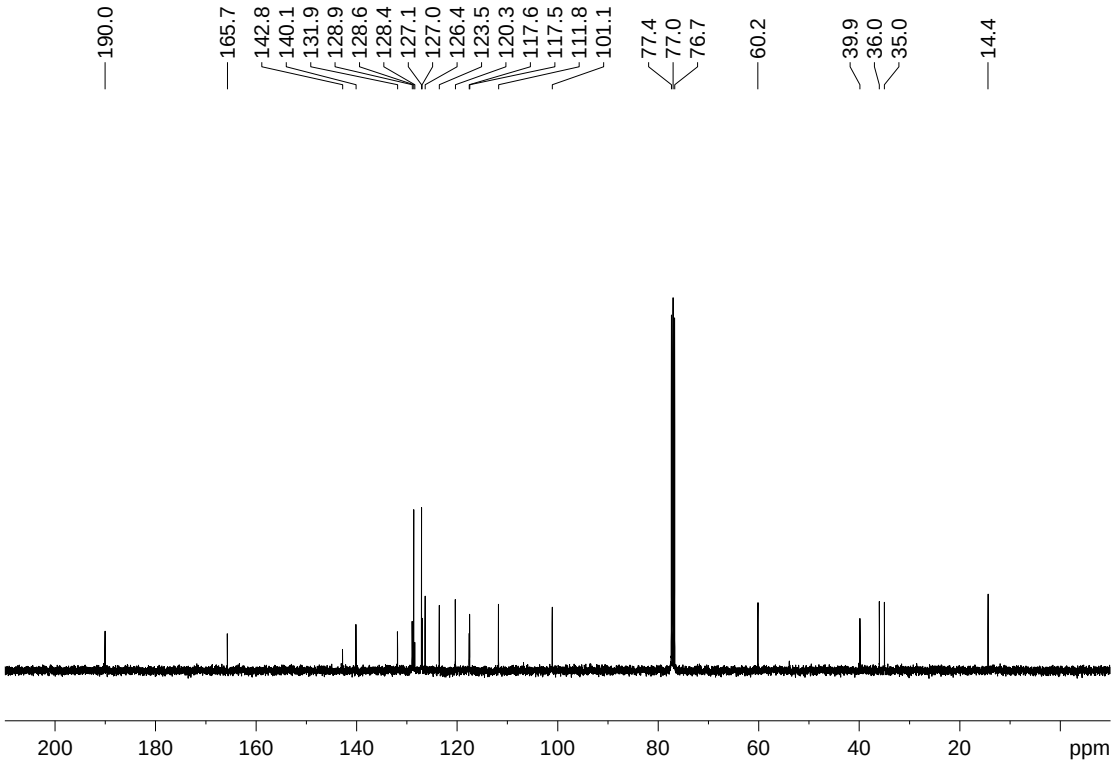
^{13}C NMR-3v



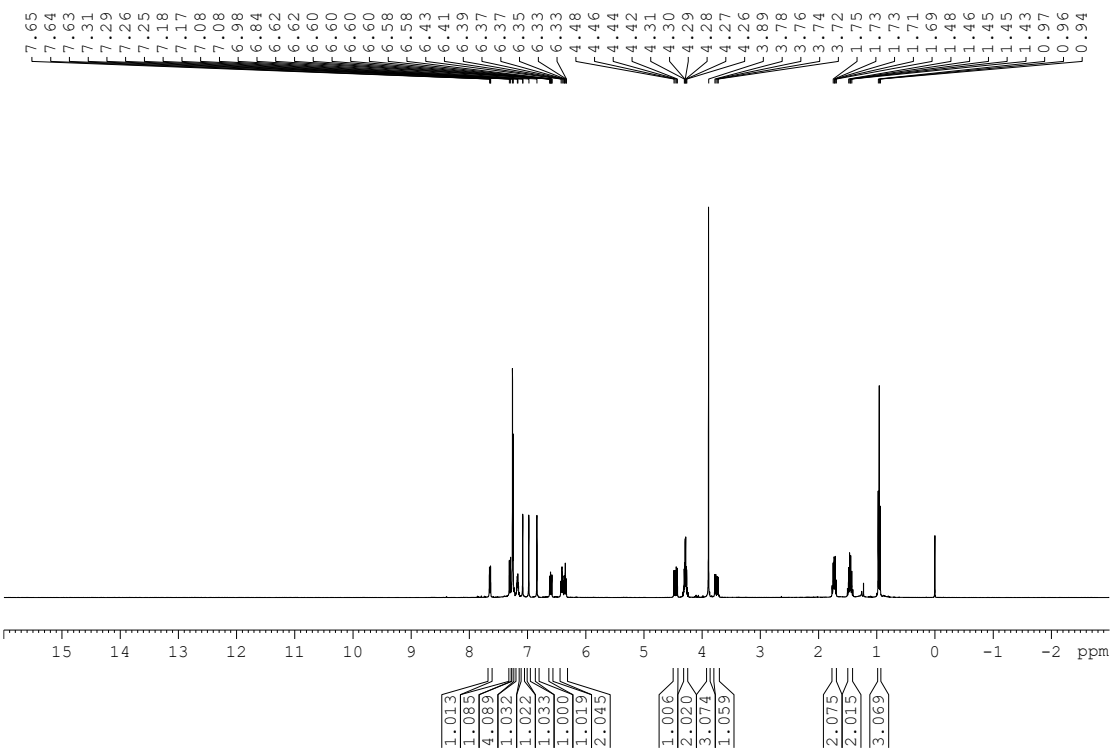
^{1}H NMR-4b



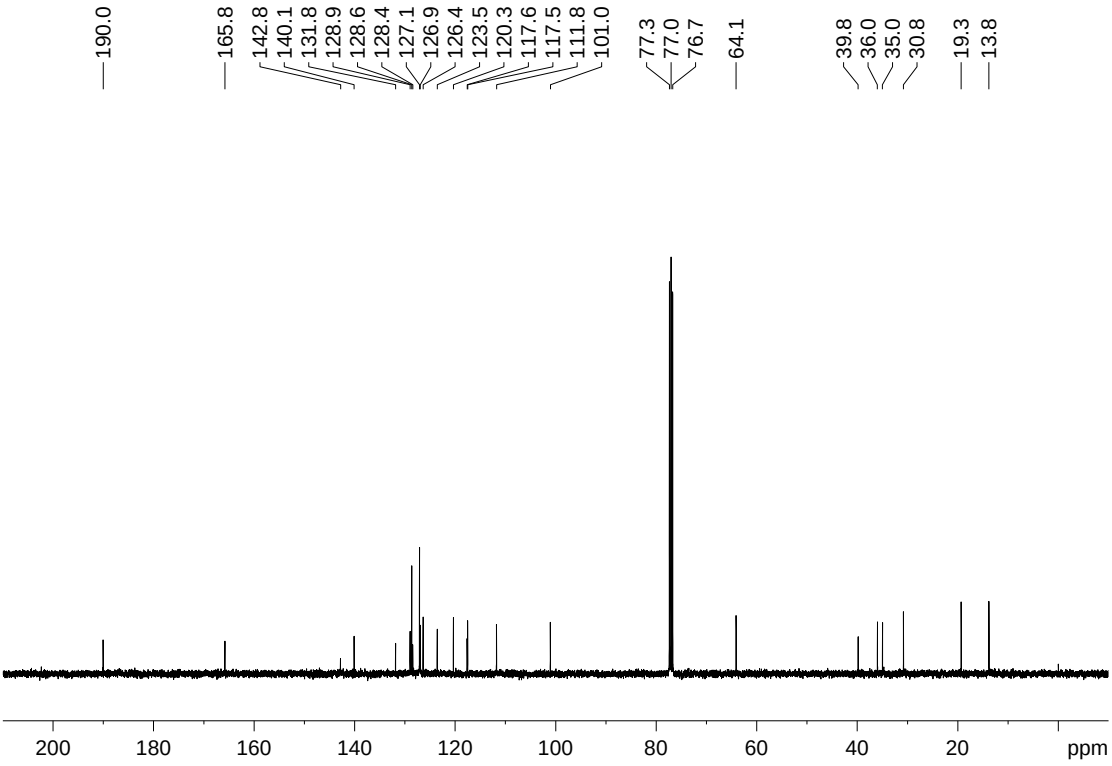
^{13}C NMR-4b



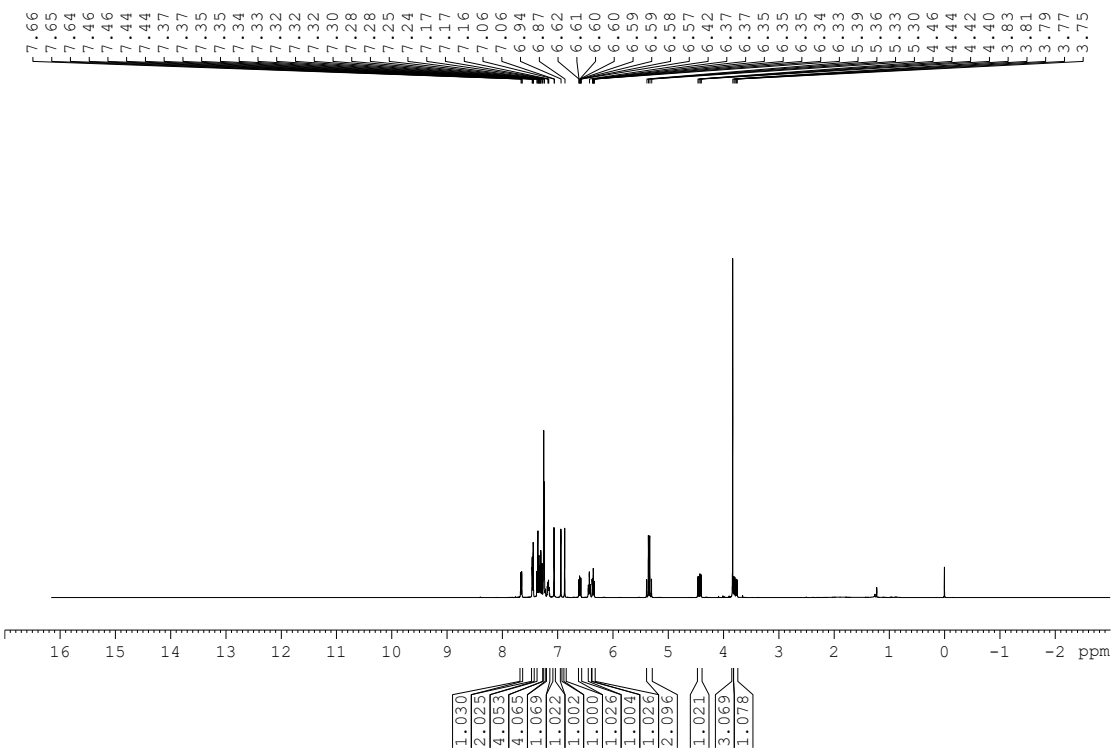
^{1}H NMR-4c



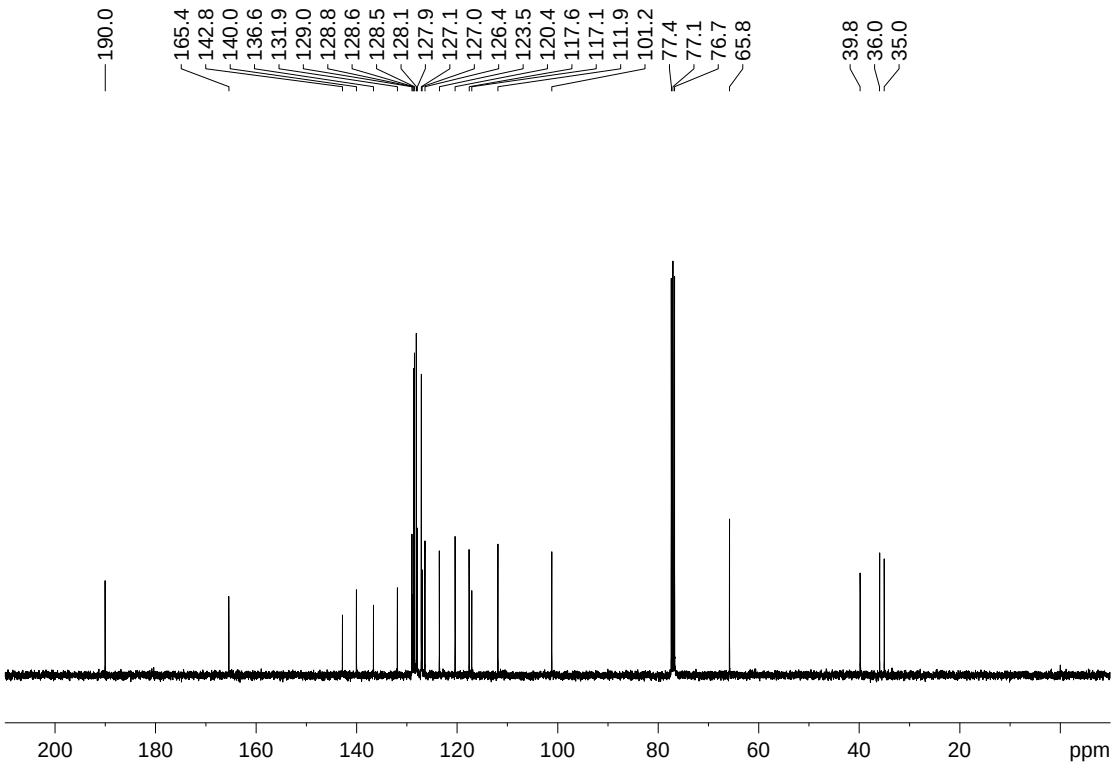
^{13}C NMR-4c



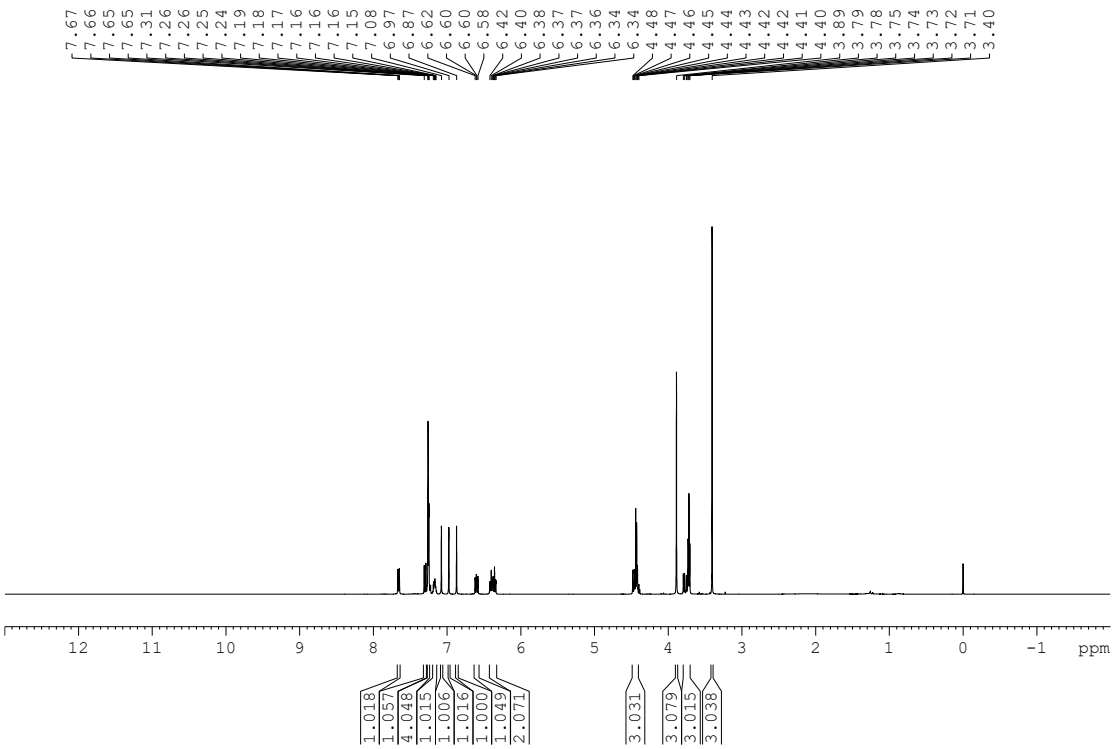
^{1}H NMR-4d



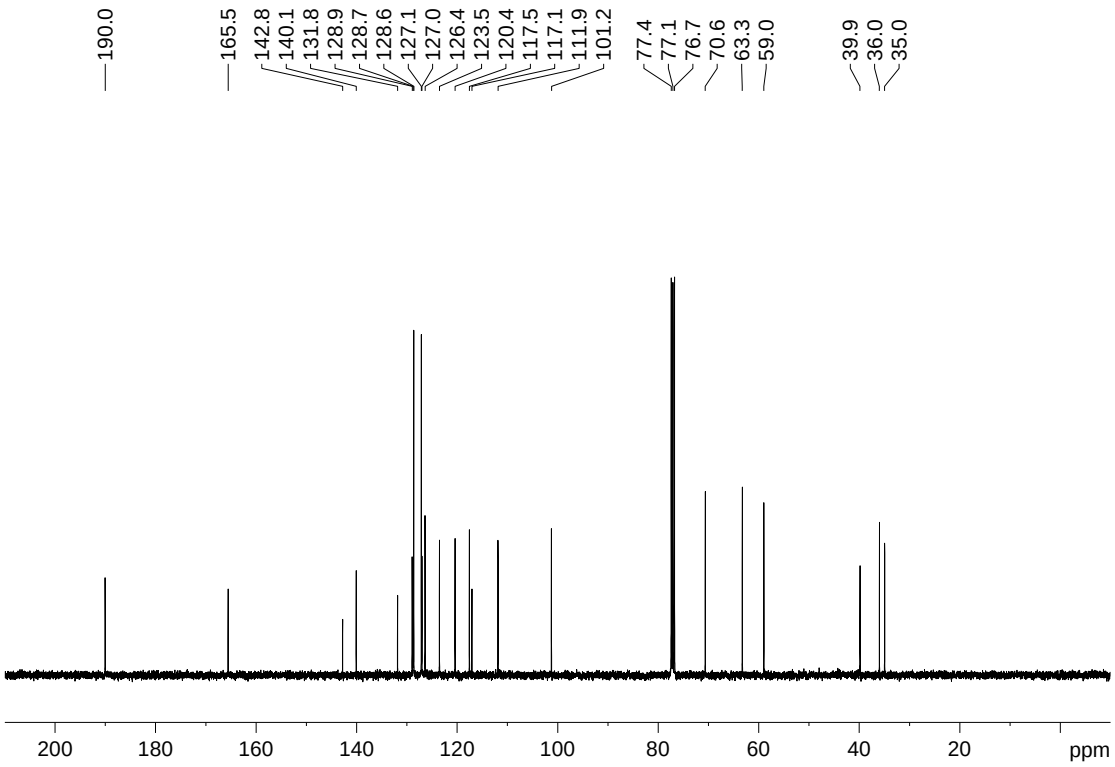
^{13}C NMR-4d



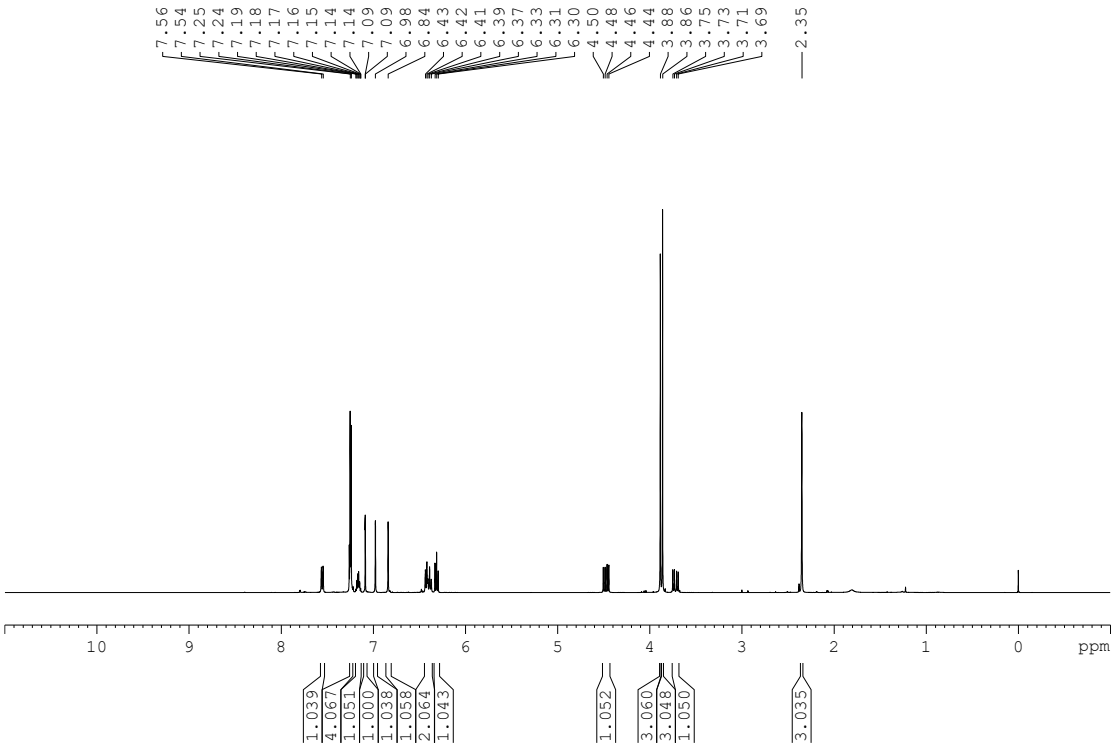
^{1}H NMR-4e



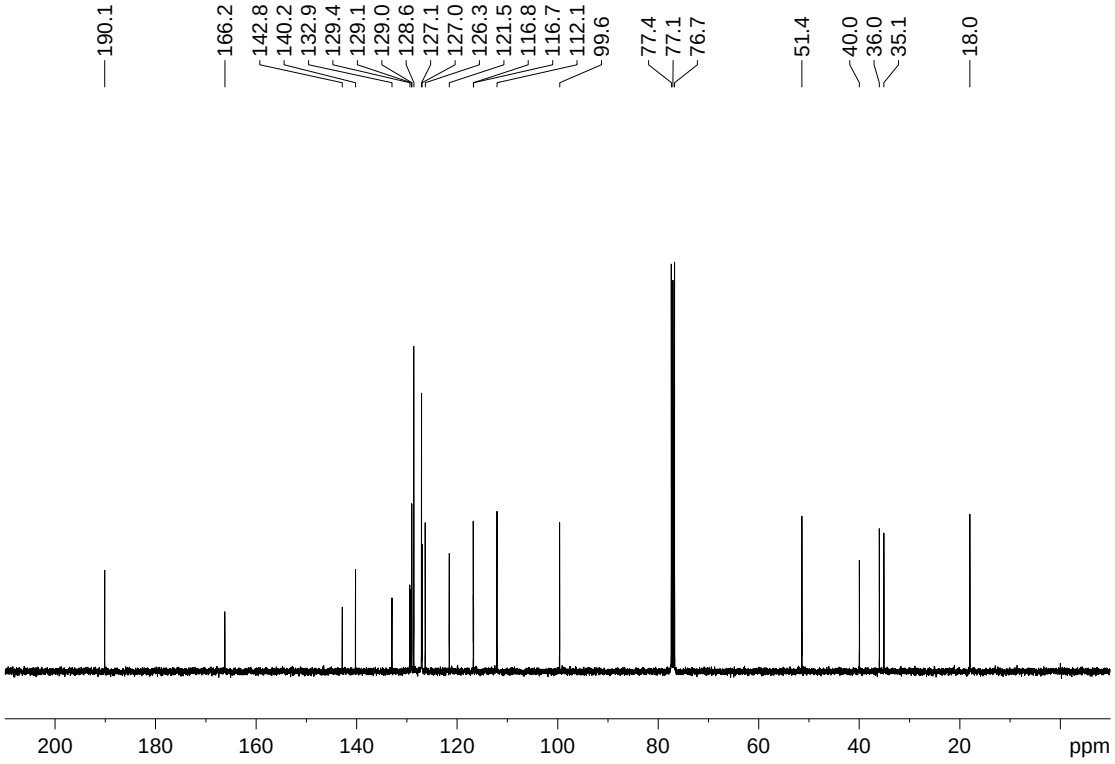
^{13}C NMR-4e



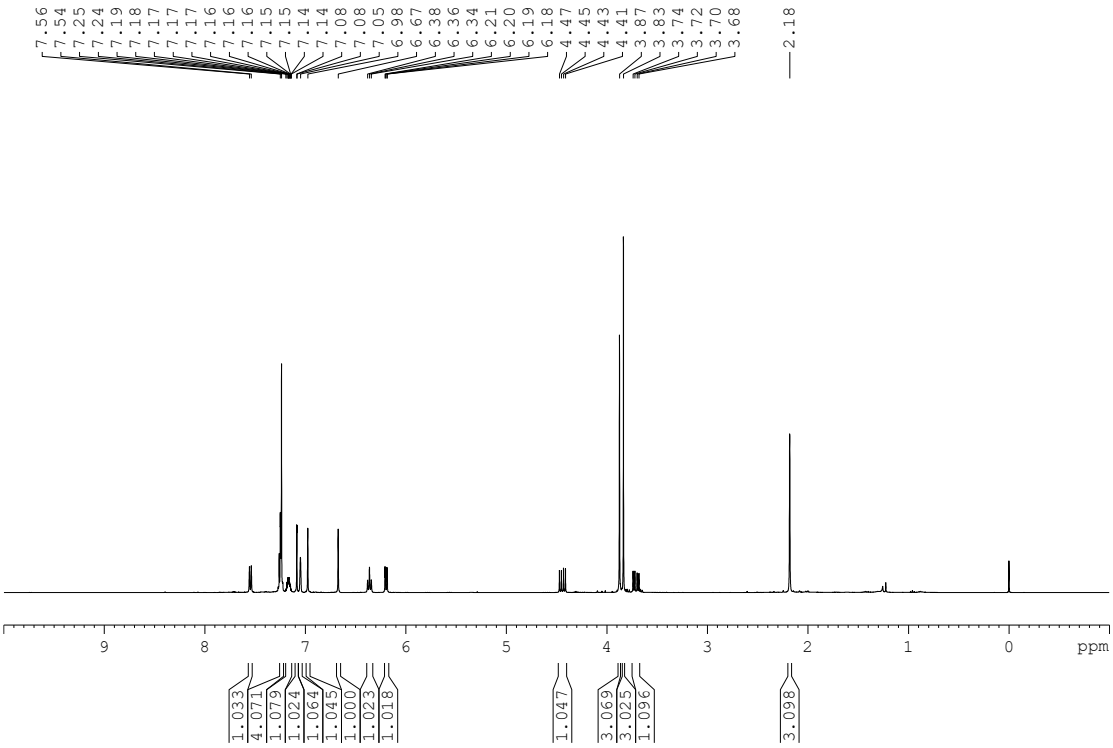
^{1}H NMR-4f



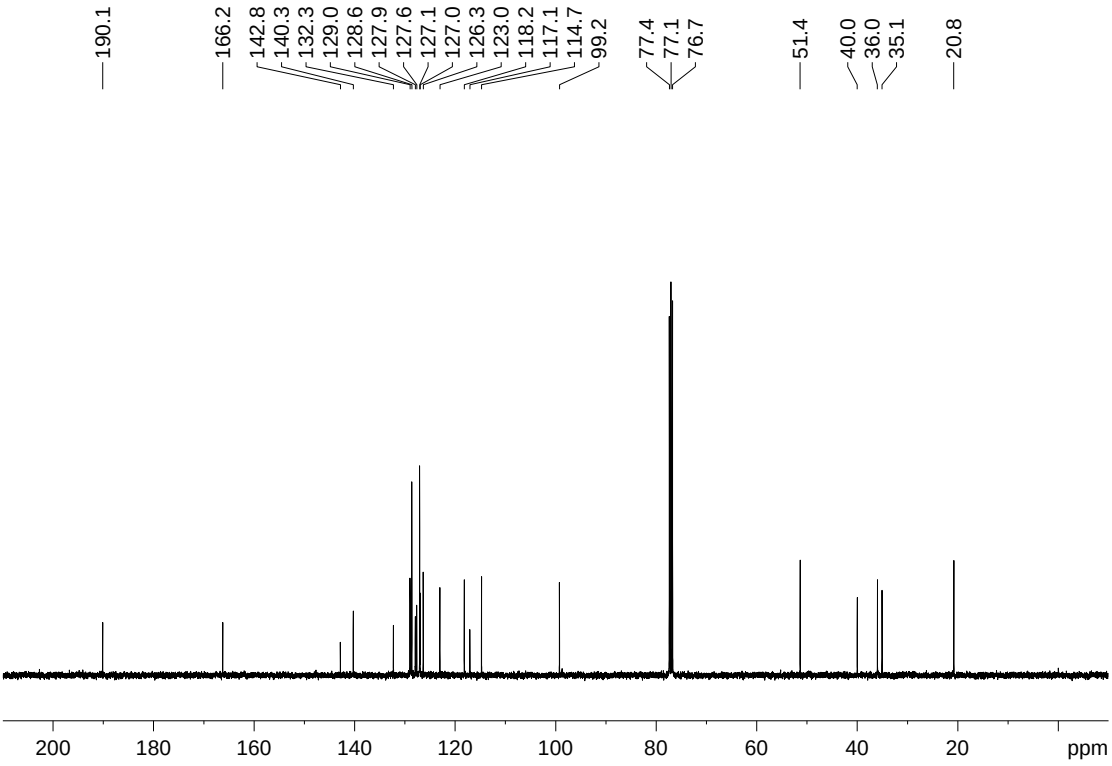
^{13}C NMR-4f



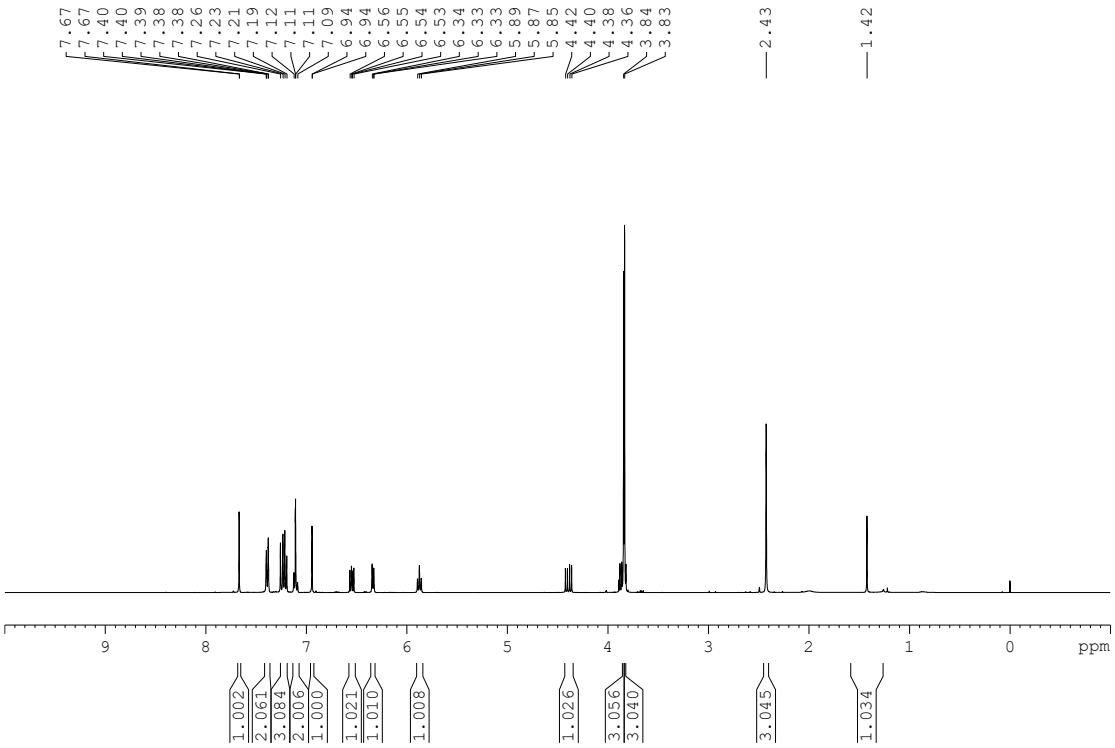
^{1}H NMR-4g



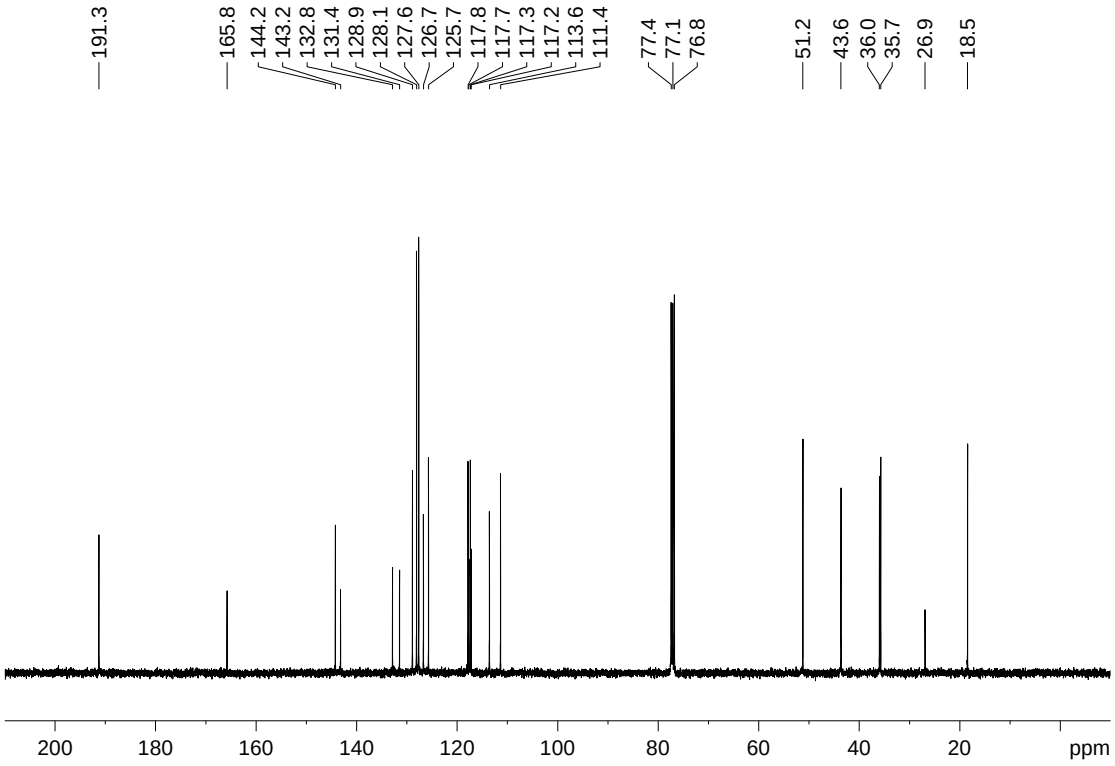
^{13}C NMR-4g



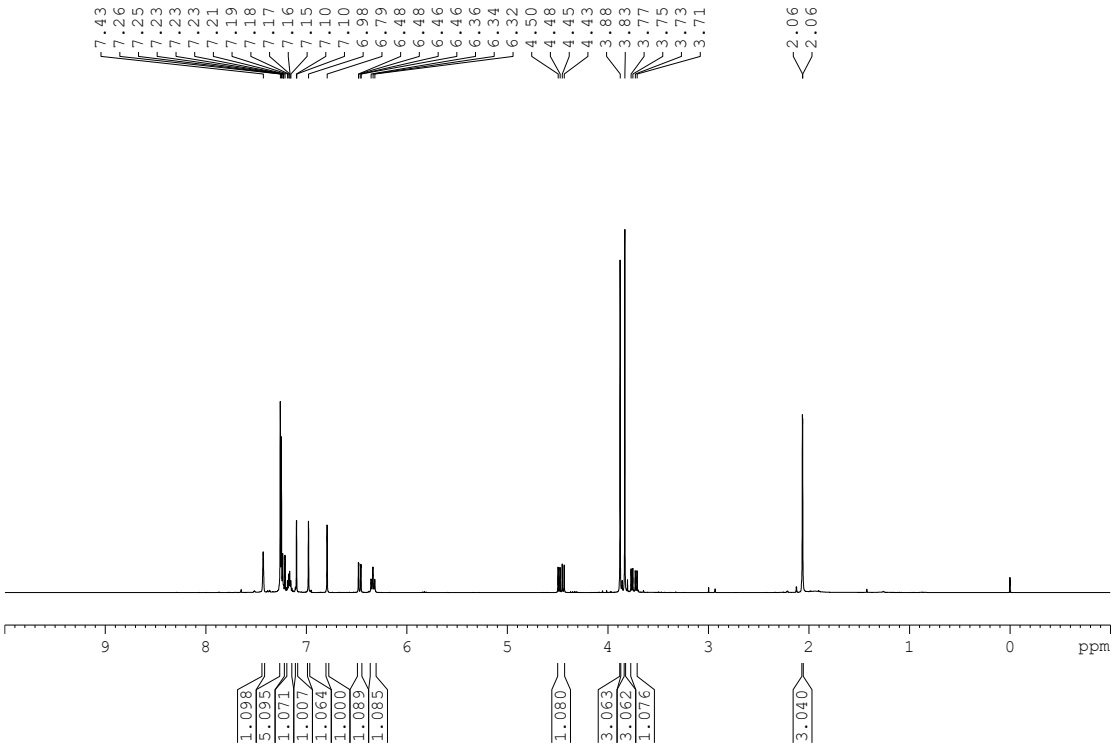
^{1}H NMR-4h



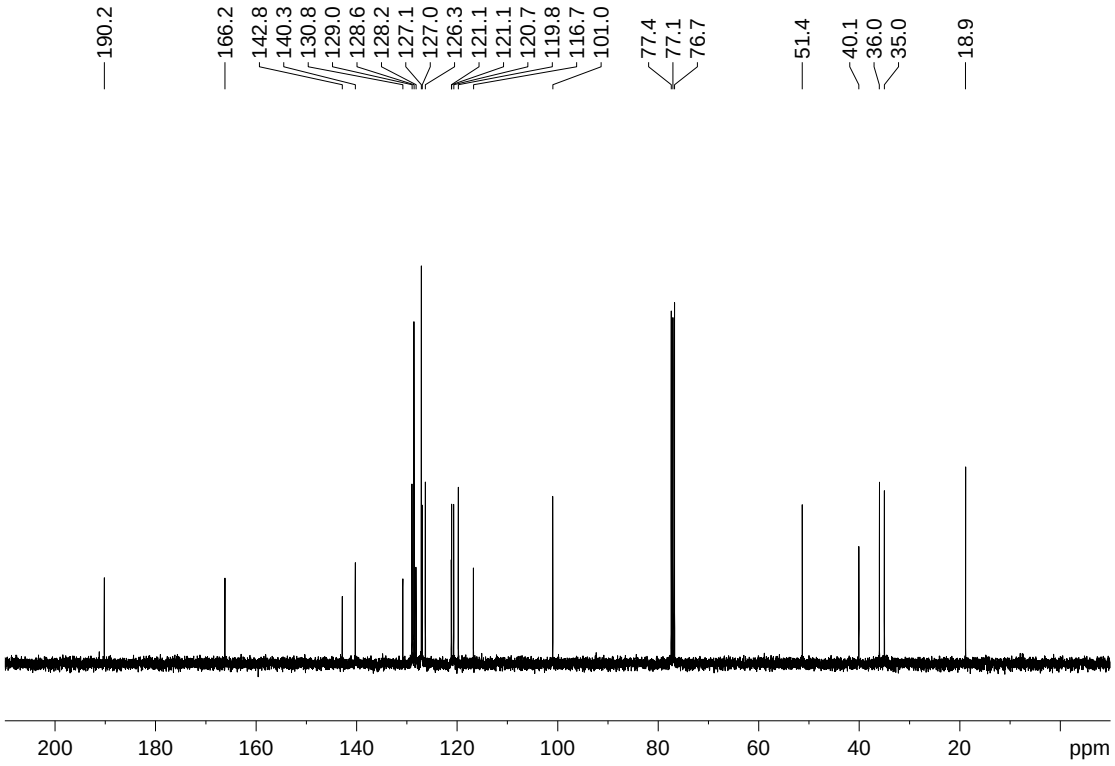
^{13}C NMR-4h



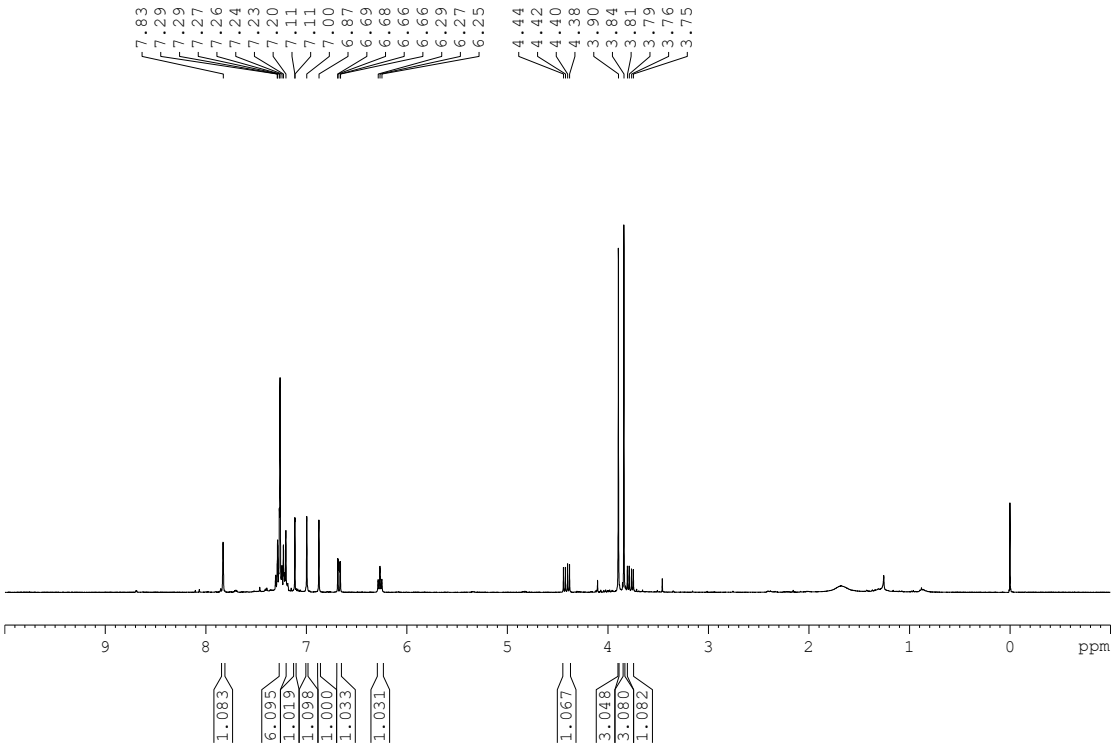
^{1}H NMR-4i



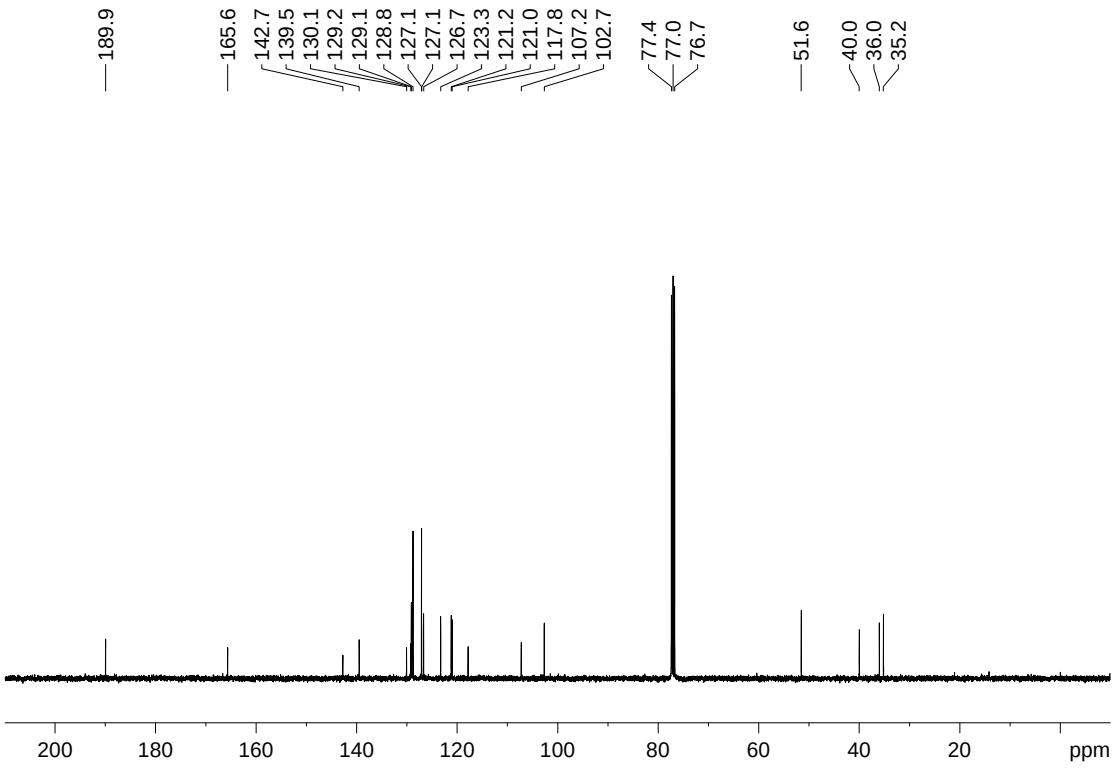
^{13}C NMR-4i



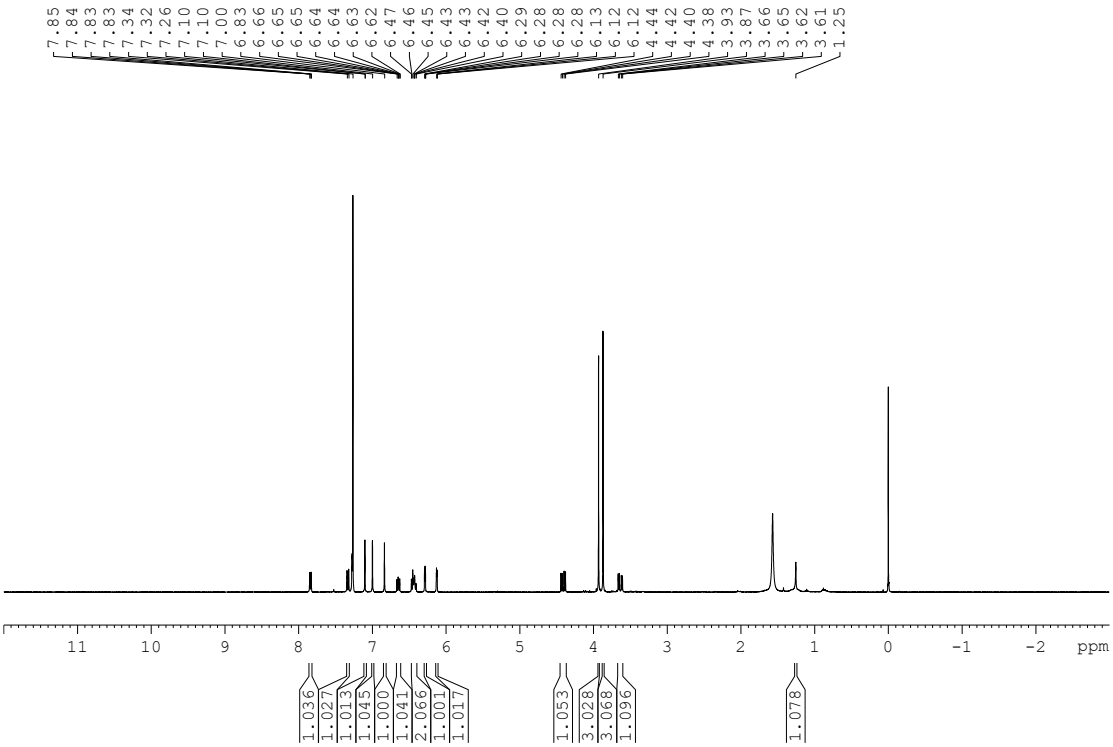
^{1}H NMR-4j



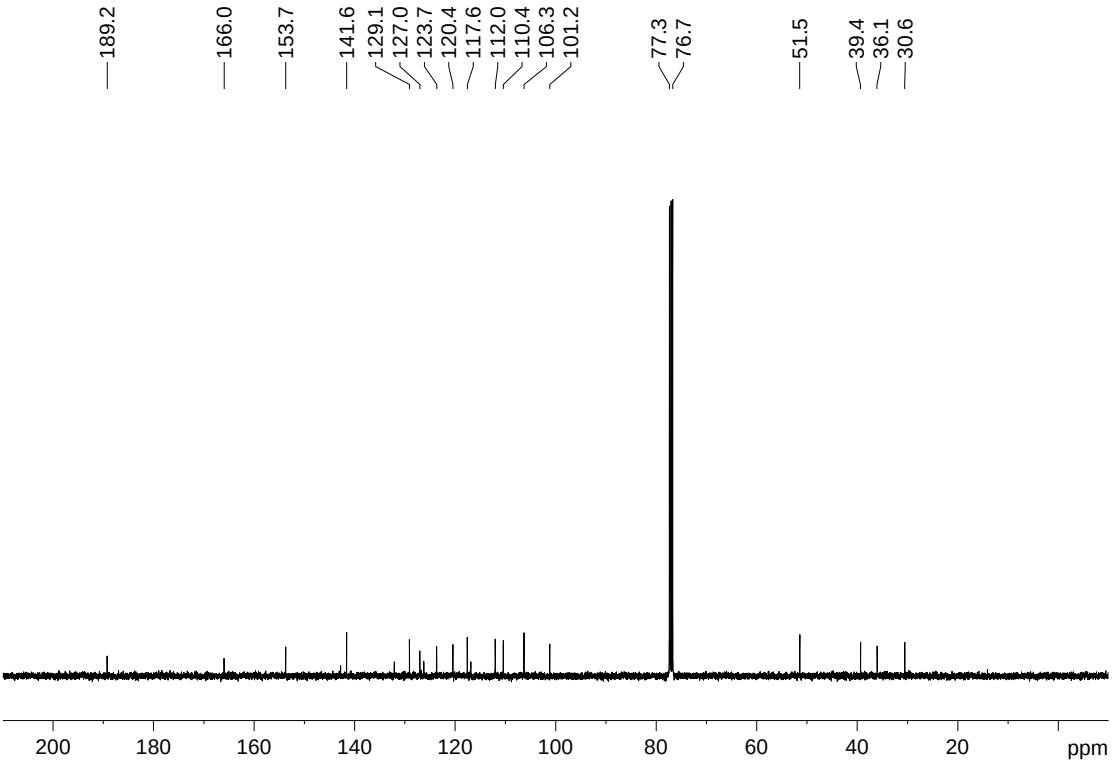
^{13}C NMR-4j



^{1}H NMR-5a

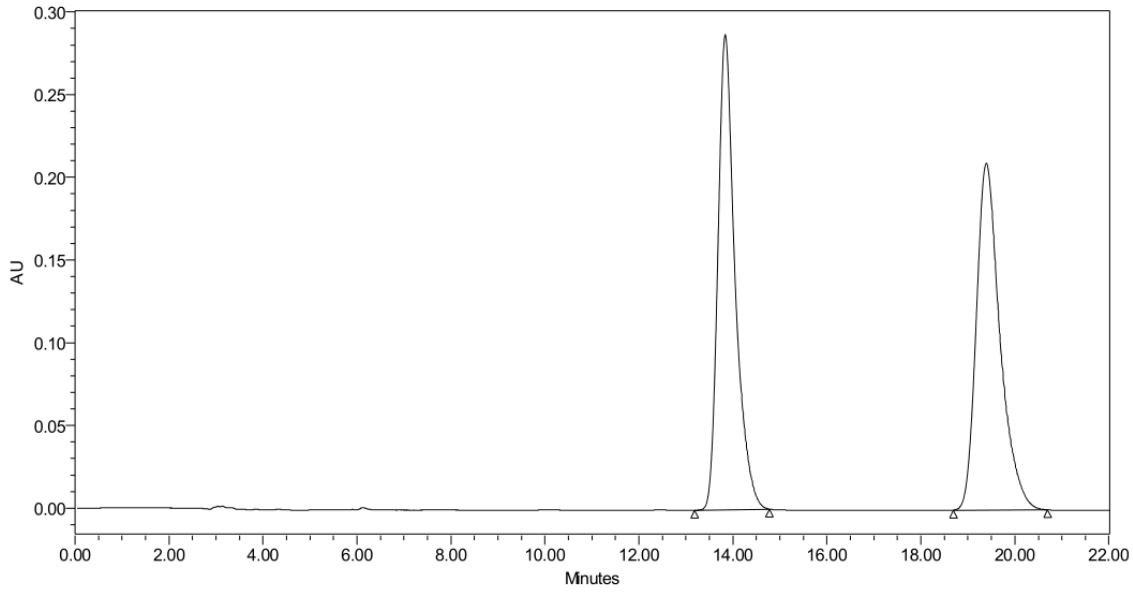


^{13}C NMR-5a



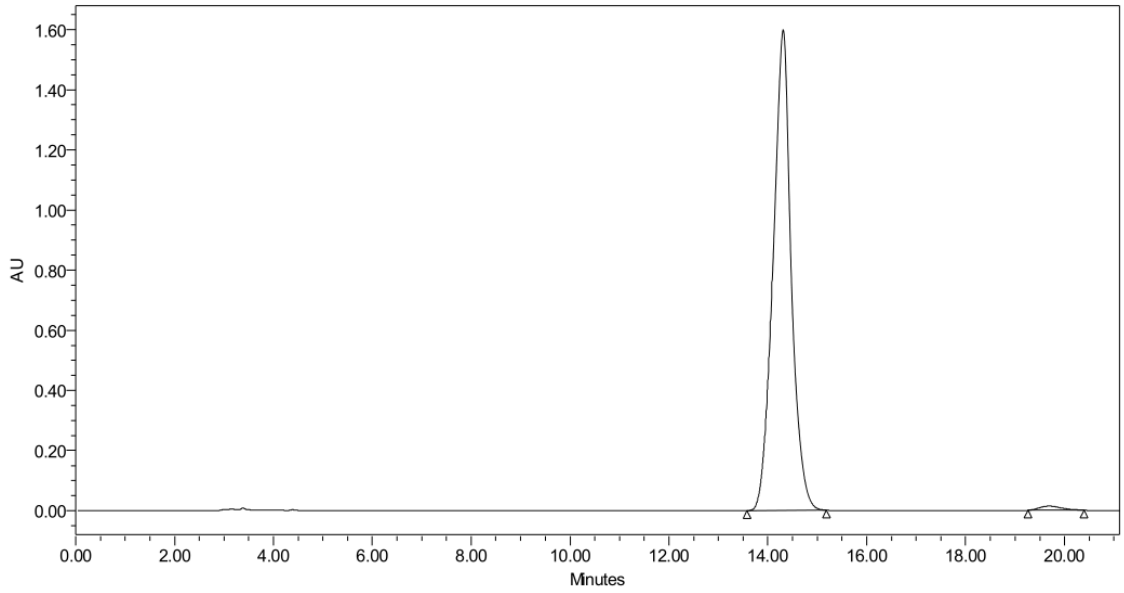
VI Chiral HPLC analysis trace

racemic-3a



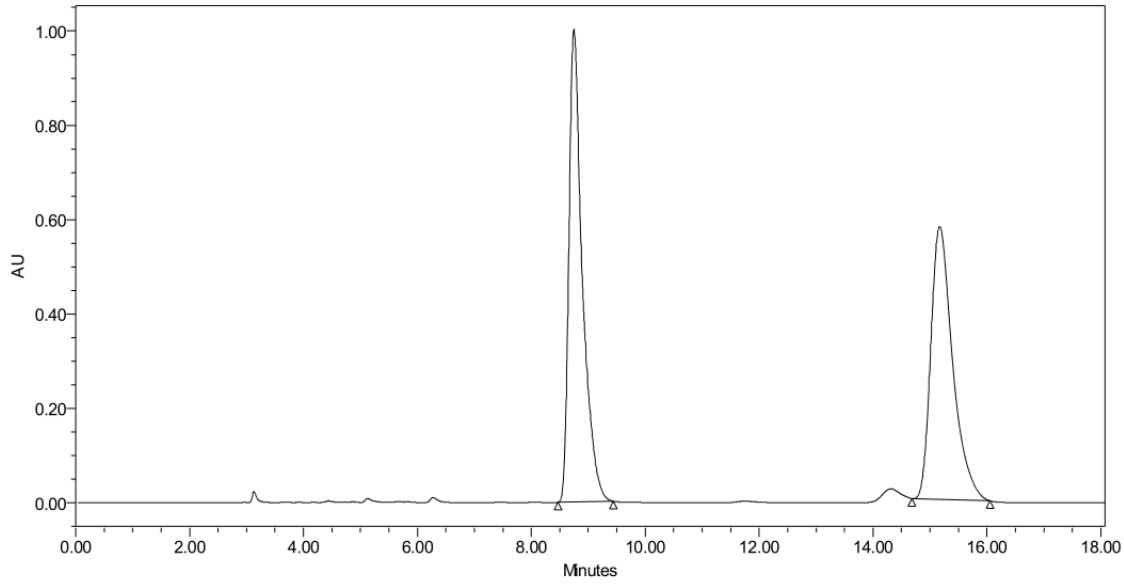
	RT	Area	% Area	Height
1	13.84	7335822	49.97	287203
2	19.39	7345719	50.03	209678

chiral-3a



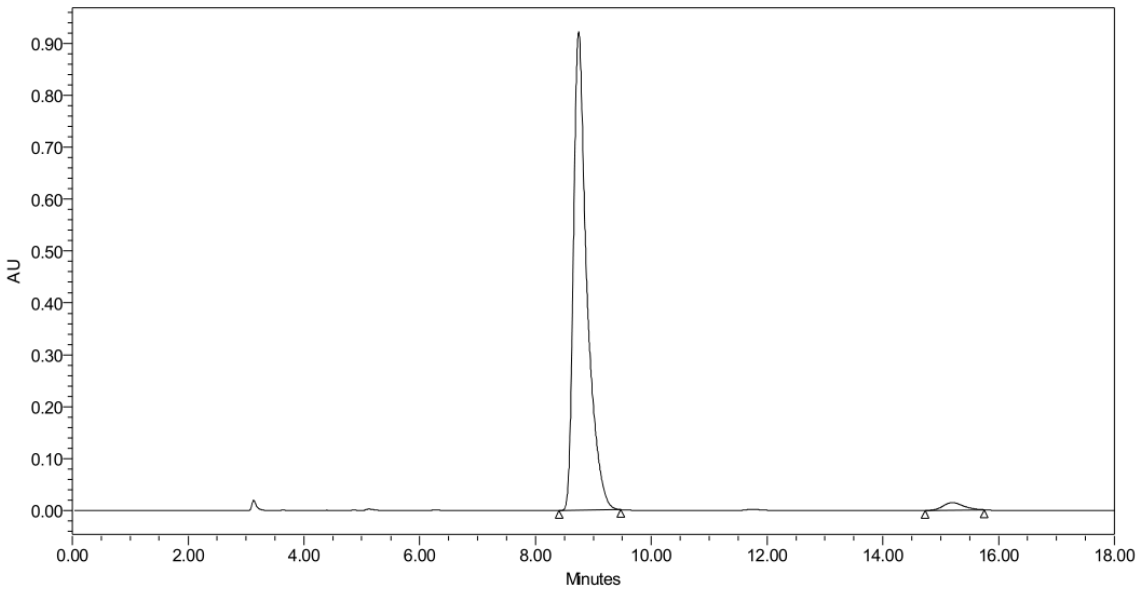
	RT	Area	% Area	Height
1	14.31	40842764	98.92	1598616
2	19.69	444718	1.08	14272

racemic-3b



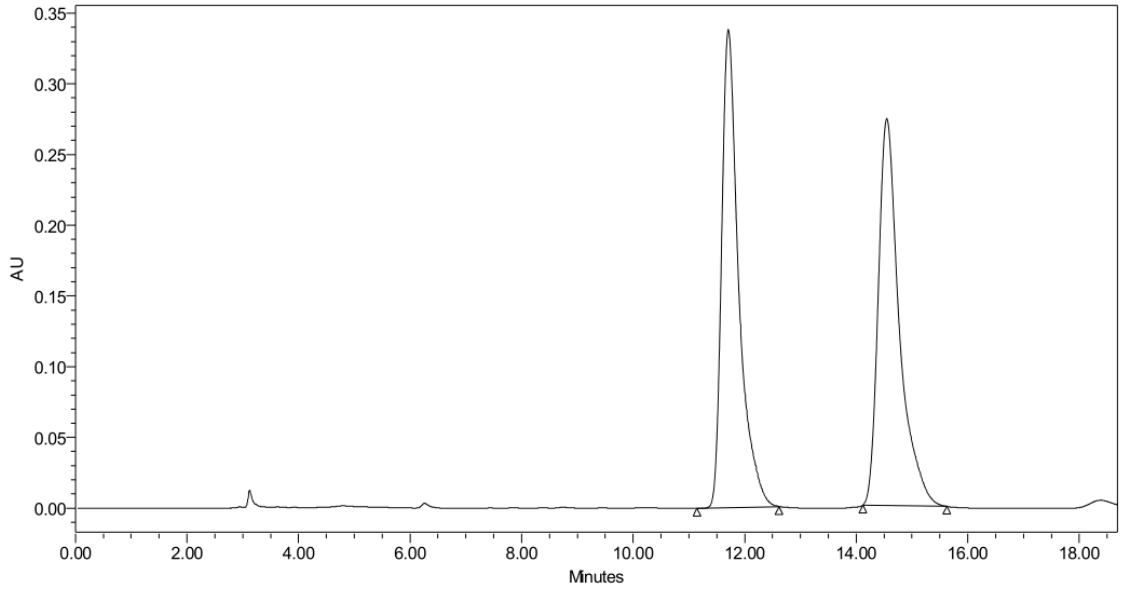
	RT	Area	% Area	Height
1	8.75	16401316	51.50	1001589
2	15.17	15444267	48.50	578378

chiral-3b



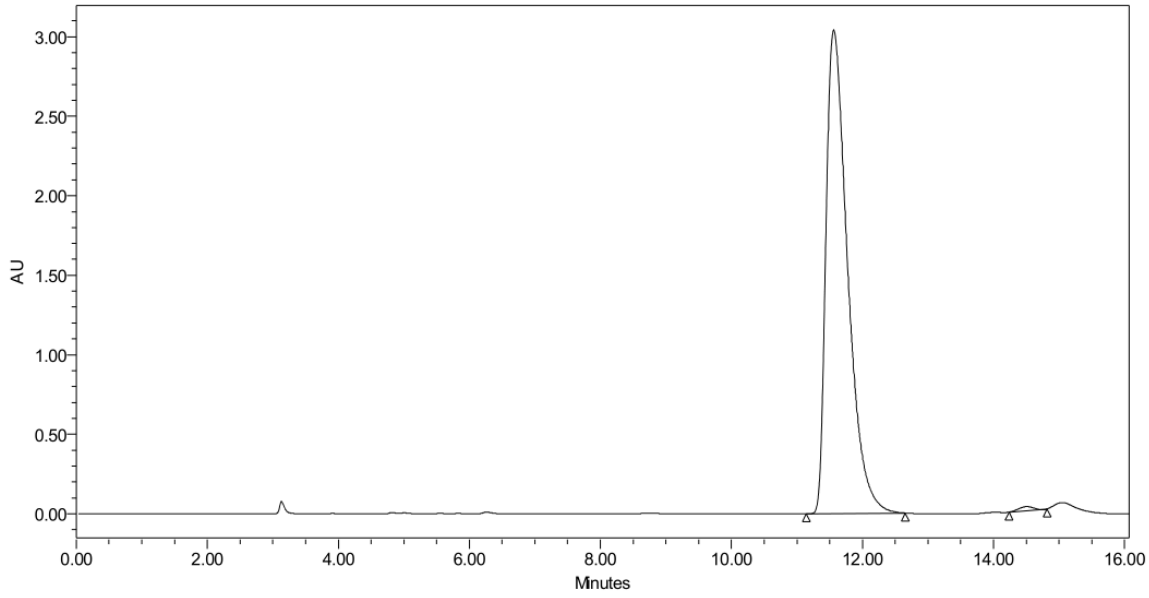
	RT	Area	% Area	Height
1	8.75	14839321	97.63	921761
2	15.20	359540	2.37	14660

racemic-3c



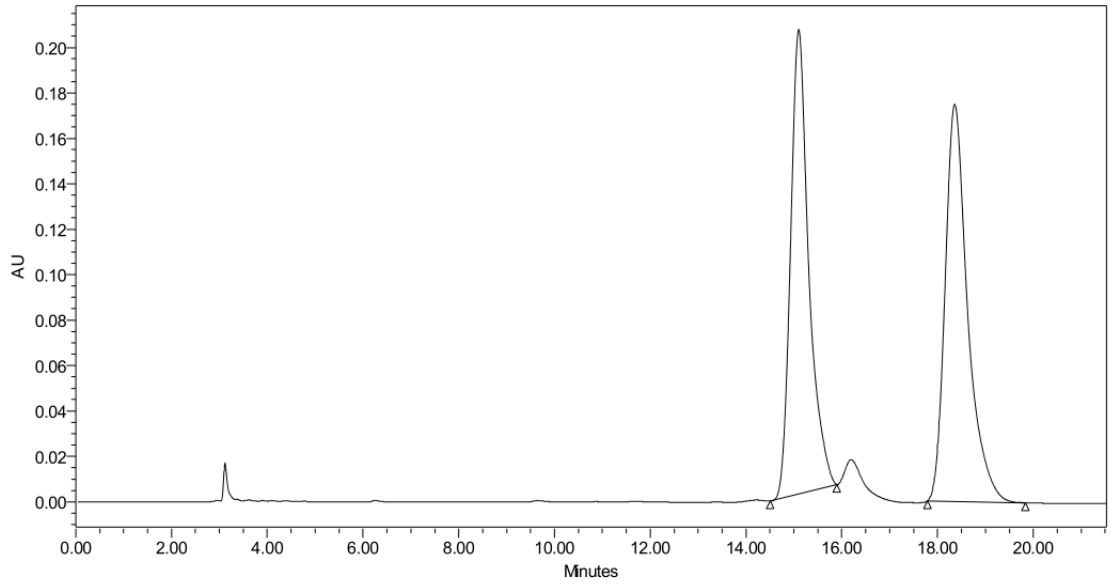
	RT	Area	% Area	Height
1	11.71	7218924	50.04	338040
2	14.55	7208585	49.96	273673

chiral-3c



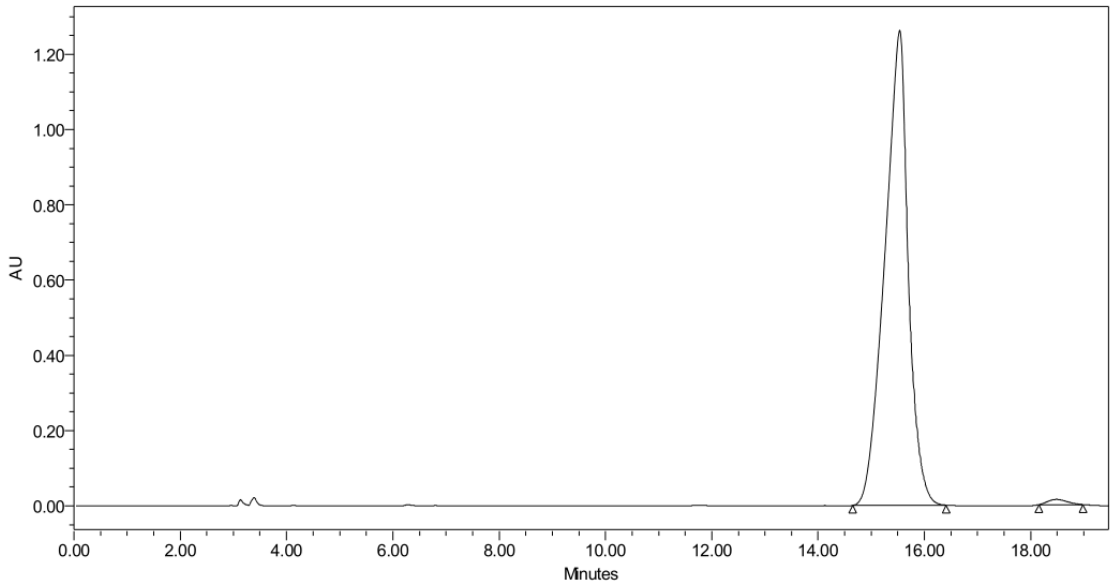
	RT	Area	% Area	Height
1	11.56	69541403	99.42	3042124
2	14.49	402661	0.58	25427

racemic-3d



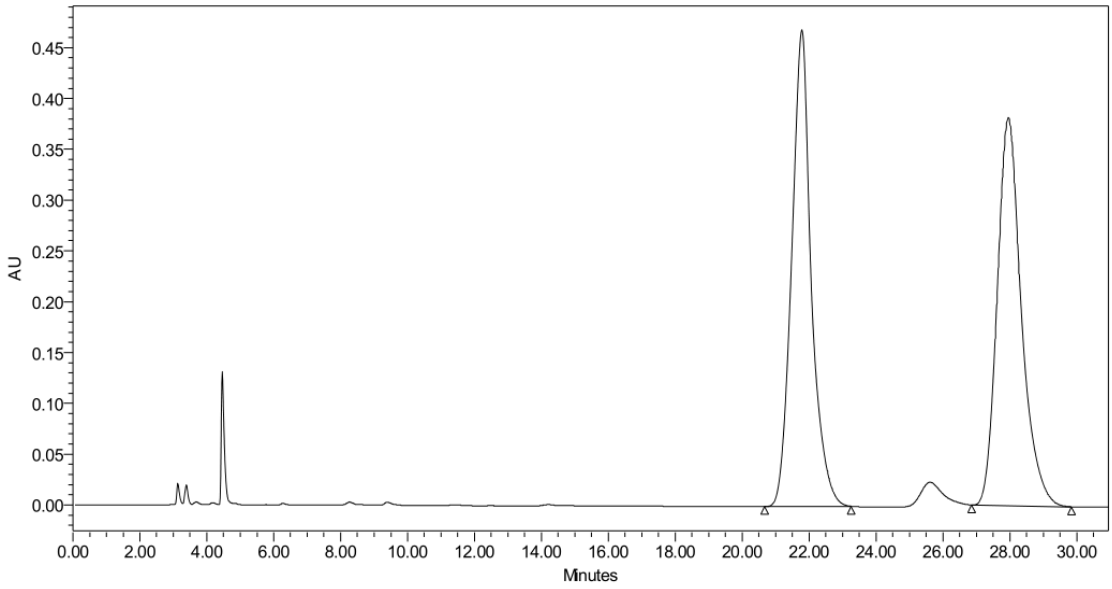
	RT	Area	% Area	Height
1	15.10	5429090	48.62	204431
2	18.36	5737984	51.38	174812

chiral-3d



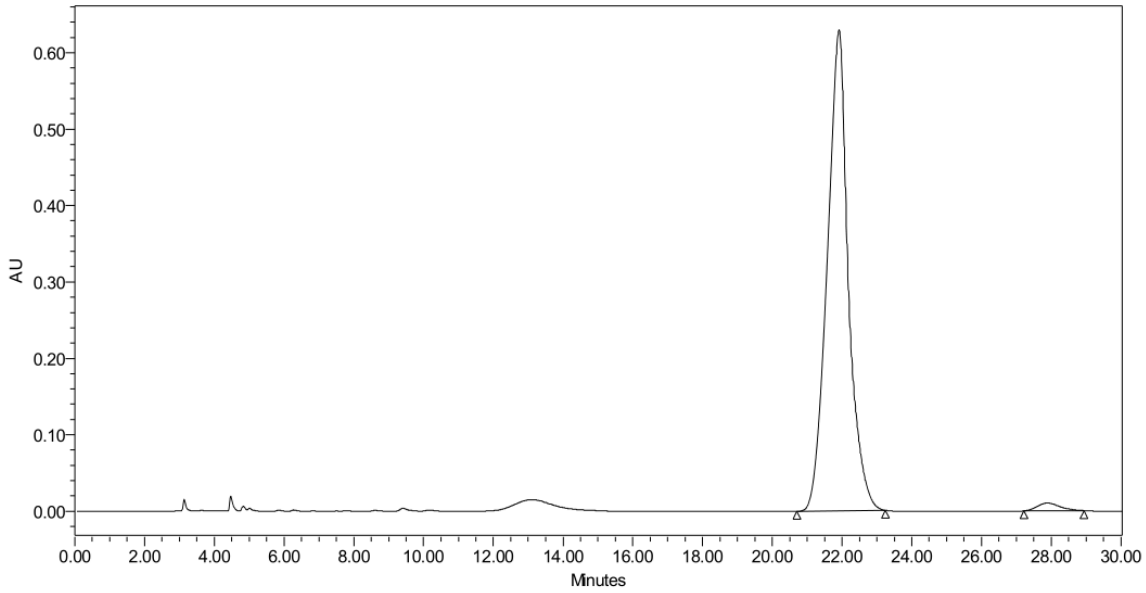
	RT	Area	% Area	Height
1	15.54	38751220	99.09	1261898
2	18.48	354070	0.91	13956

racemic-3e



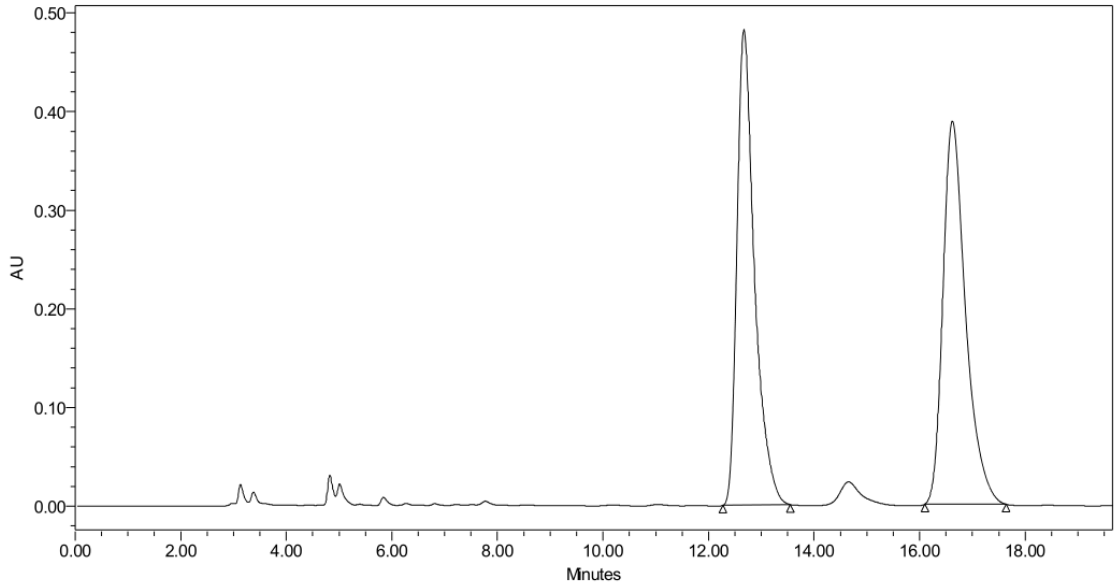
	RT	Area	% Area	Height
1	21.78	19163365	50.16	469007
2	27.95	19041975	49.84	381871

chiral-3e



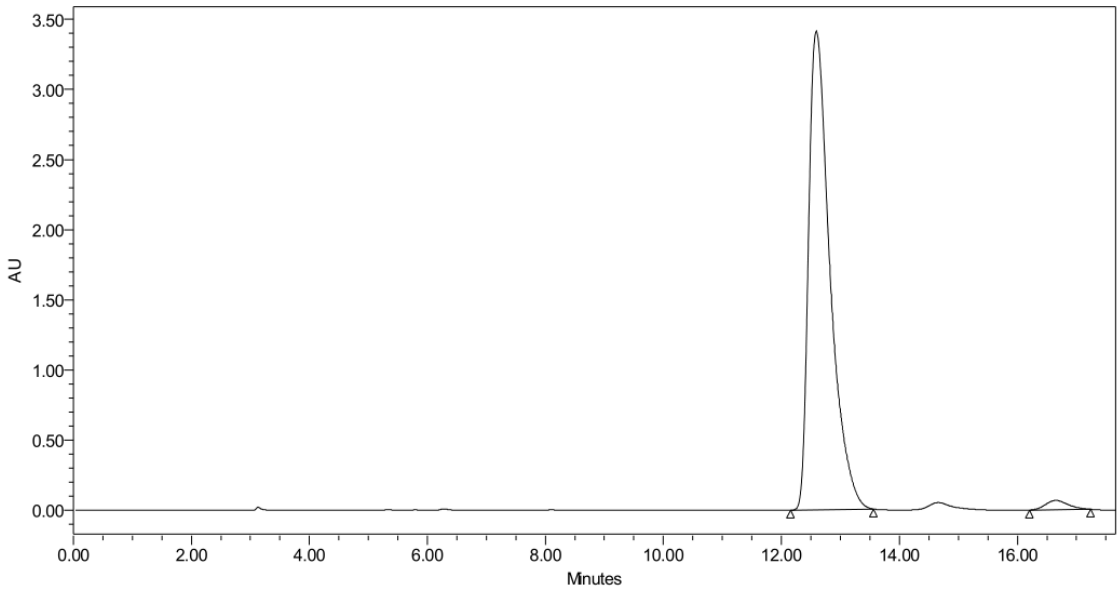
	RT	Area	% Area	Height
1	21.92	26254711	98.27	629195
2	27.89	463279	1.73	10225

racemic-3f



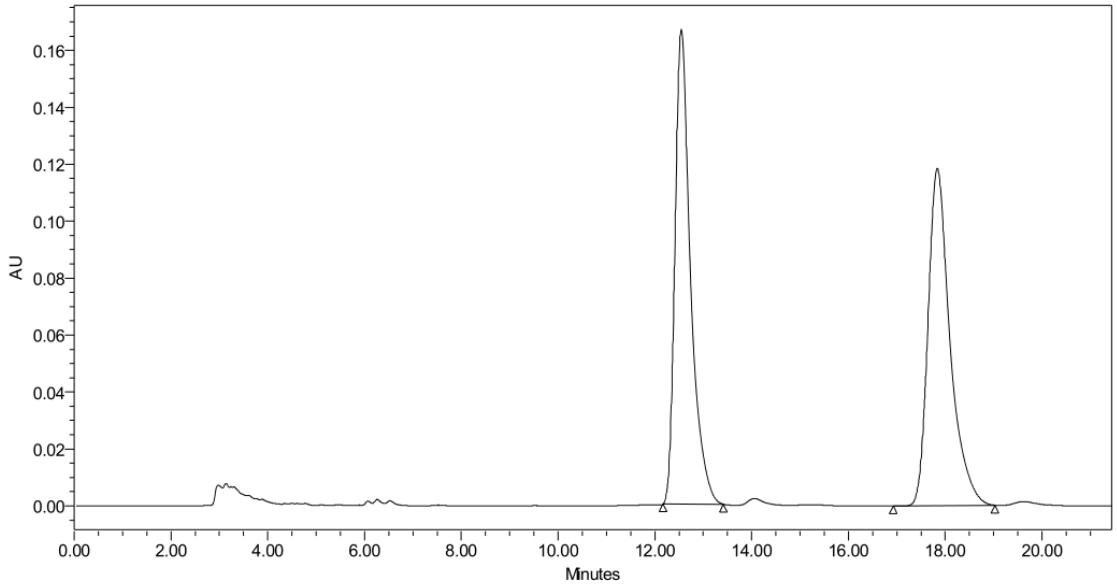
	RT	Area	% Area	Height
1	12.67	11073000	48.77	481948
2	16.62	11630677	51.23	388339

chiral-3f



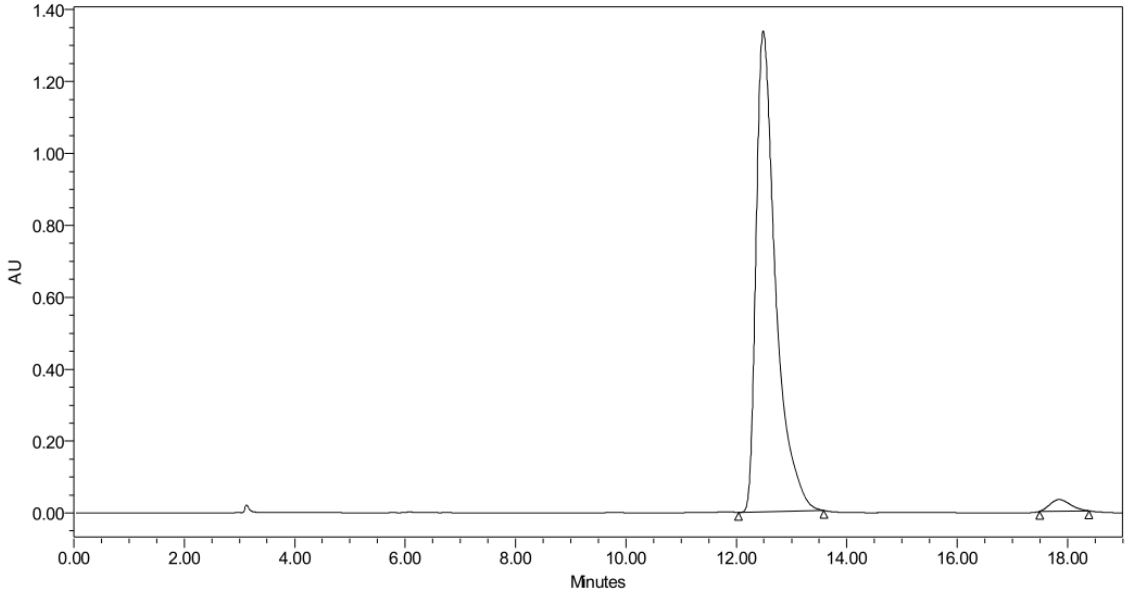
	RT	Area	% Area	Height
1	12.59	86256194	97.99	3413918
2	16.65	1772765	2.01	66609

racemic-3g



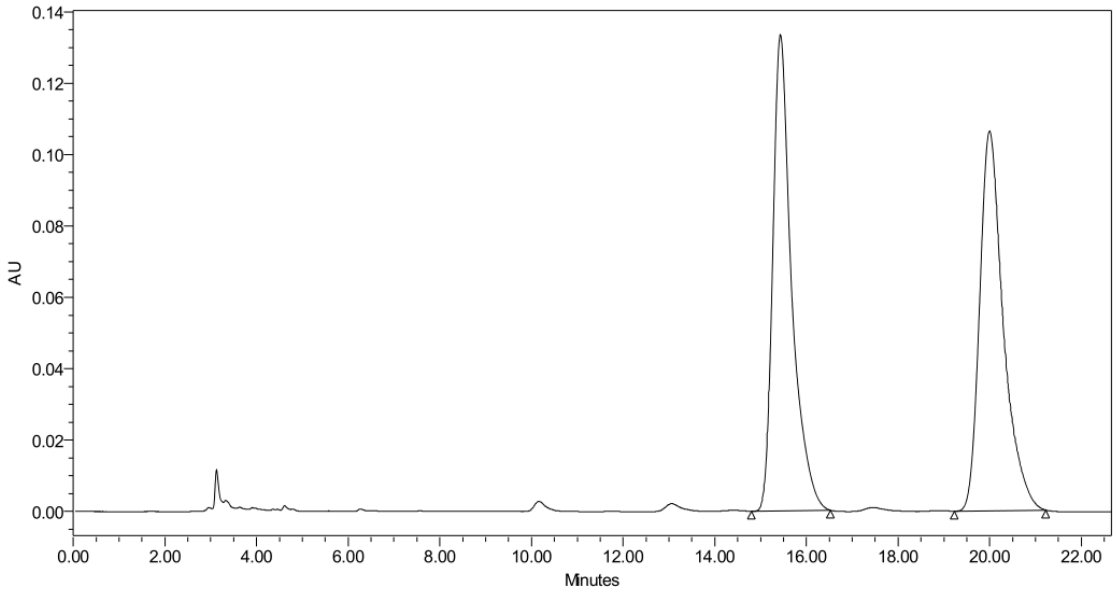
	RT	Area	% Area	Height
1	12.54	3713359	49.85	166752
2	17.83	3735920	50.15	118495

chiral-3g



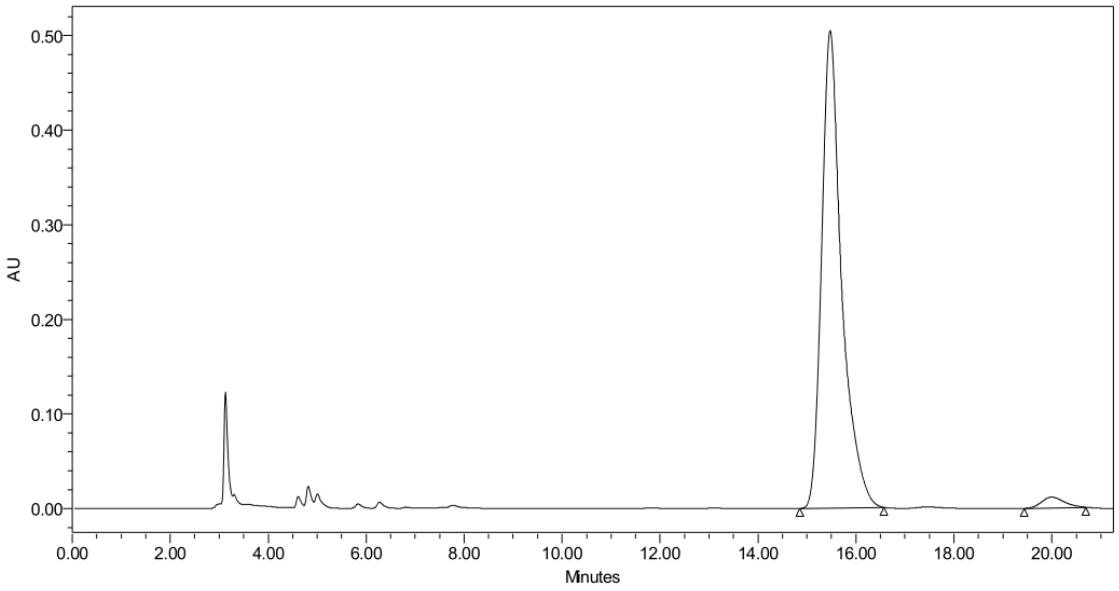
	RT	Area	% Area	Height
1	12.49	32614277	97.53	1337153
2	17.85	827131	2.47	32125

racemic-3h



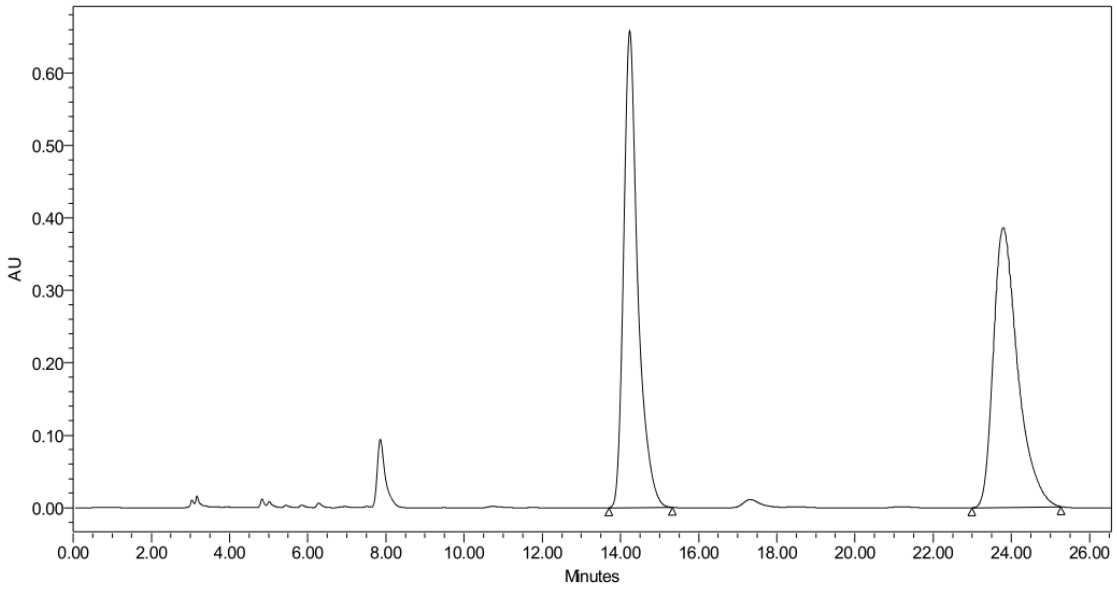
	RT	Area	% Area	Height
1	15.43	3831370	50.06	133525
2	20.00	3822276	49.94	106433

chiral-3h



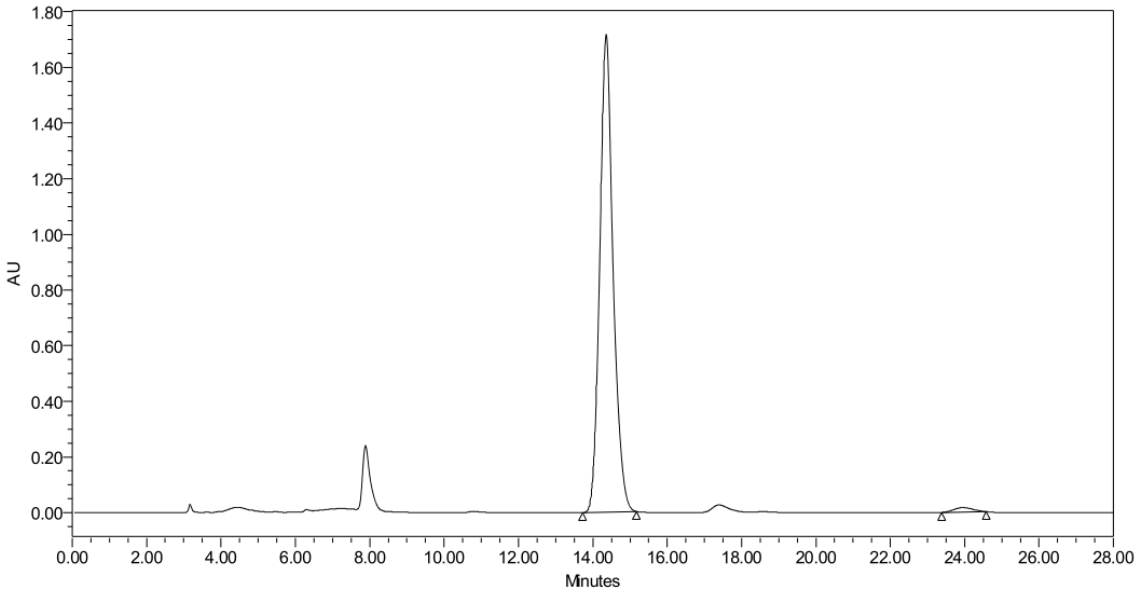
	RT	Area	% Area	Height
1	15.48	14329885	97.52	504776
2	20.00	364264	2.48	11400

racemic-3i



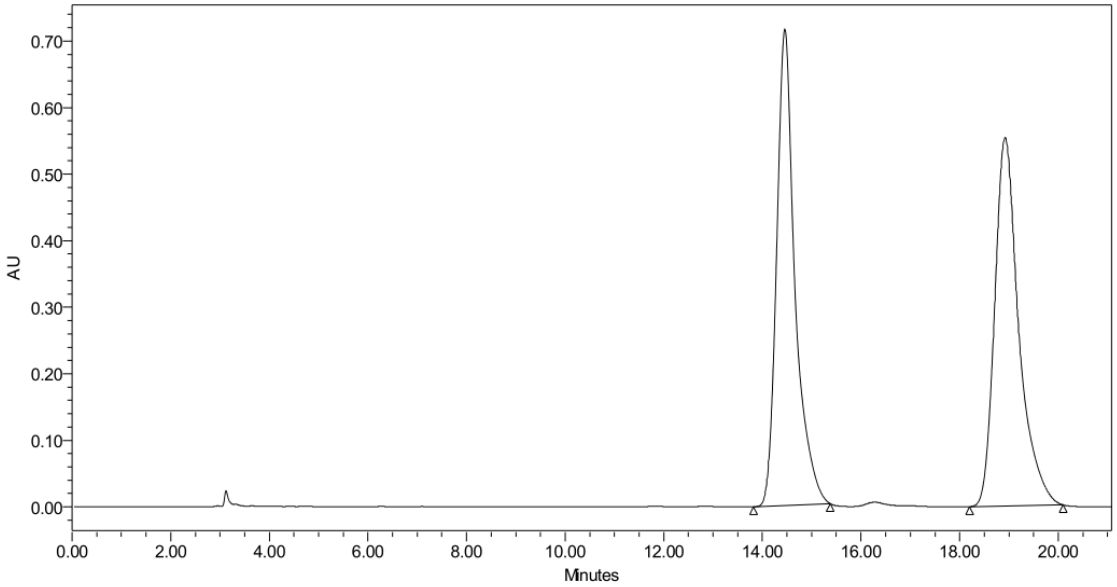
	RT	Area	% Area	Height
1	14.24	16722608	50.16	658540
2	23.79	16618996	49.84	386066

chiral-3i



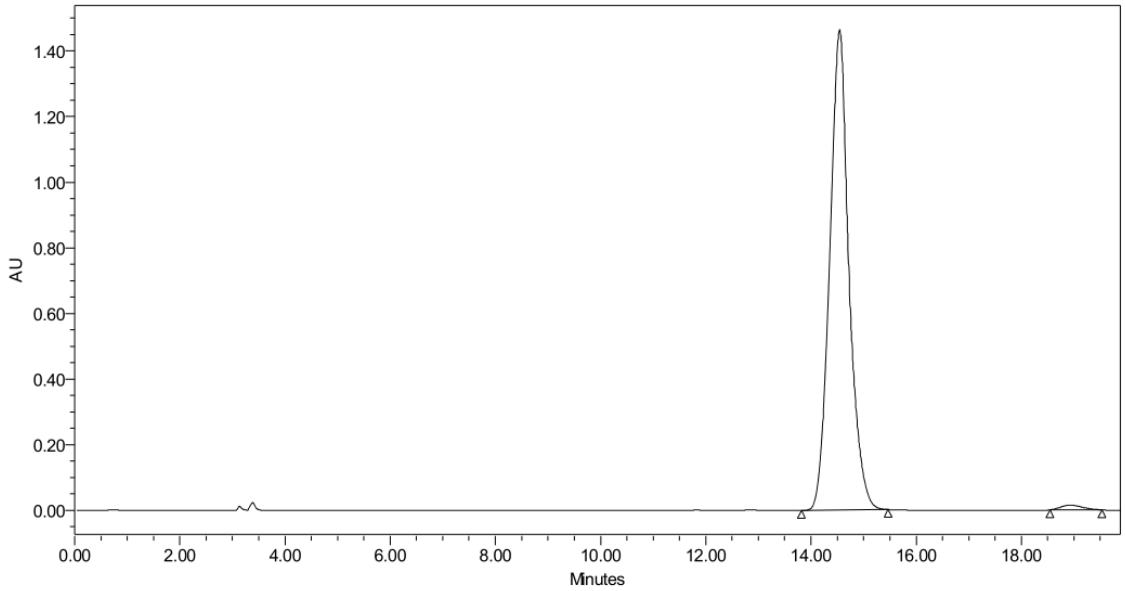
	RT	Area	% Area	Height
1	14.36	42967629	98.66	1716319
2	23.95	582688	1.34	16380

racemic-3j



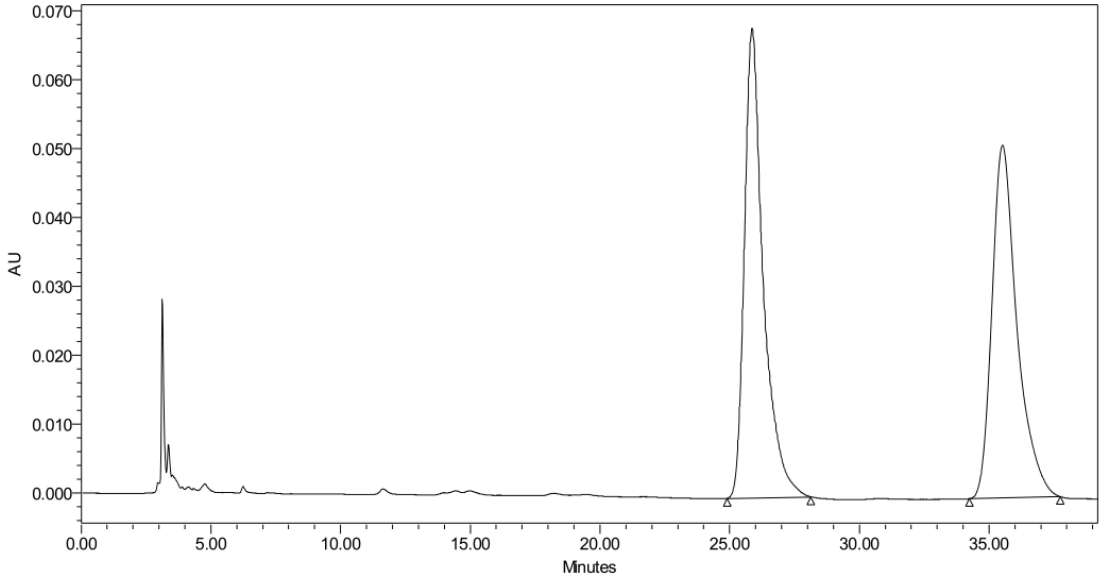
	RT	Area	% Area	Height
1	14.45	18592650	49.87	716157
2	18.92	18690088	50.13	553780

chiral-3j



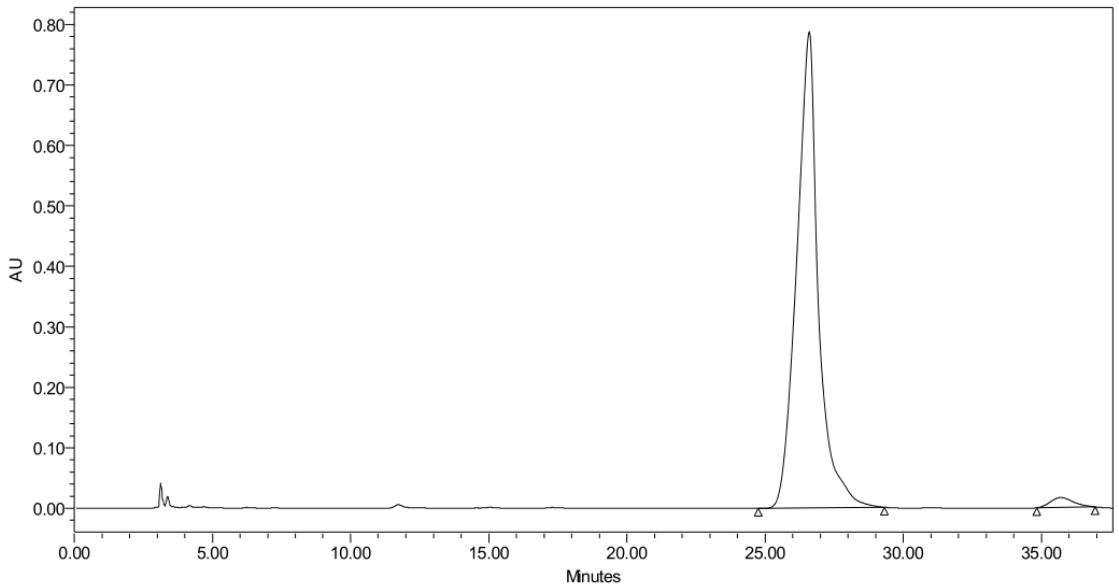
	RT	Area	% Area	Height
1	14.55	36947920	98.88	1463587
2	18.93	420323	1.12	14798

racemic-3k



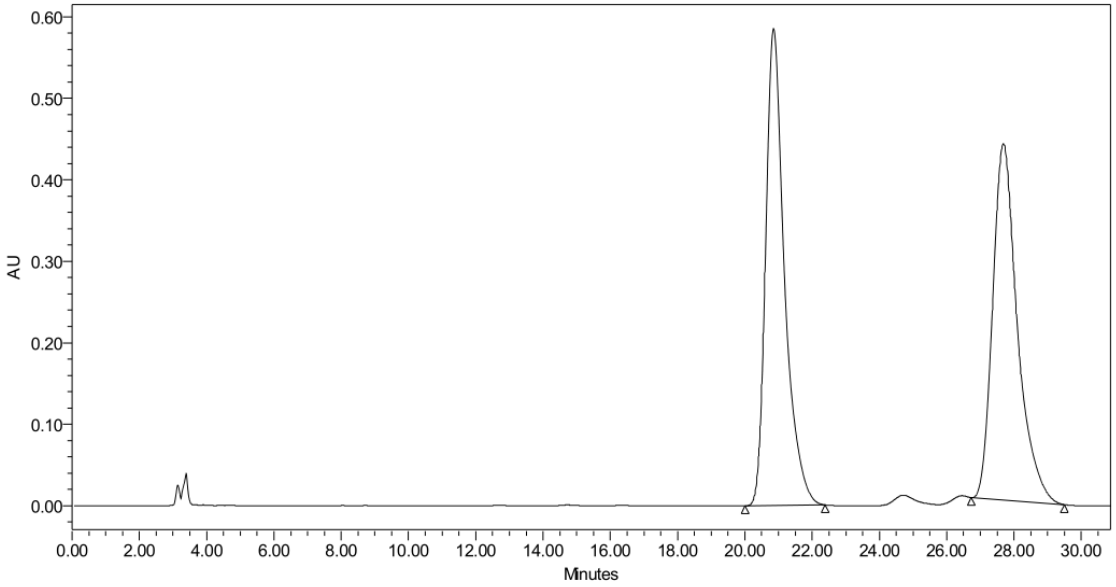
	RT	Area	% Area	Height
1	25.86	3473473	50.38	68140
2	35.53	3421559	49.62	51211

chiral-3k



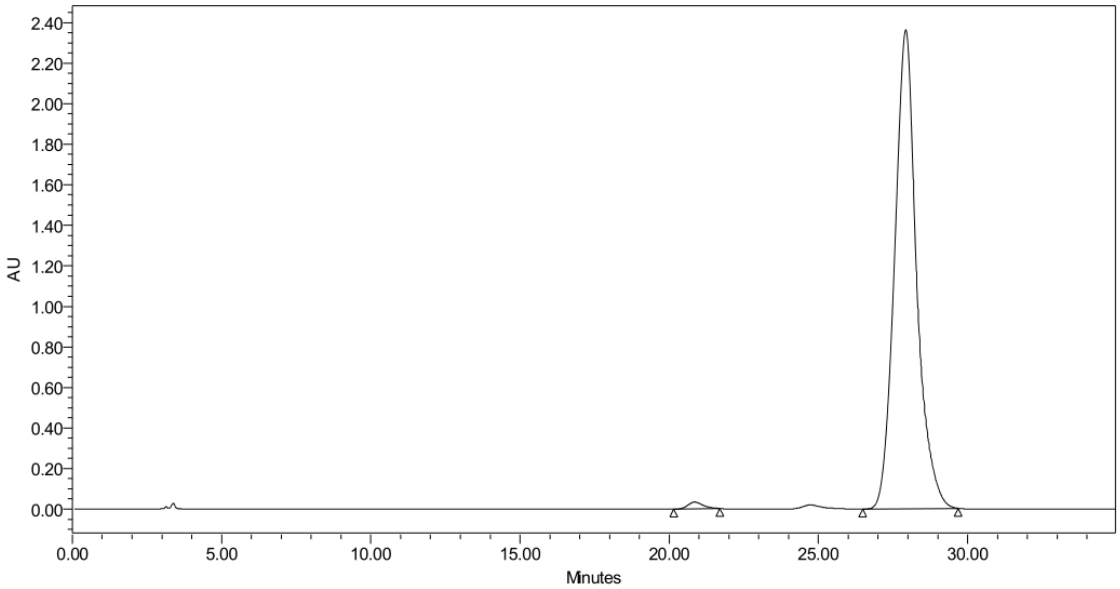
	RT	Area	% Area	Height
1	26.60	43362900	97.86	787732
2	35.69	946097	2.14	16385

racemic-3l



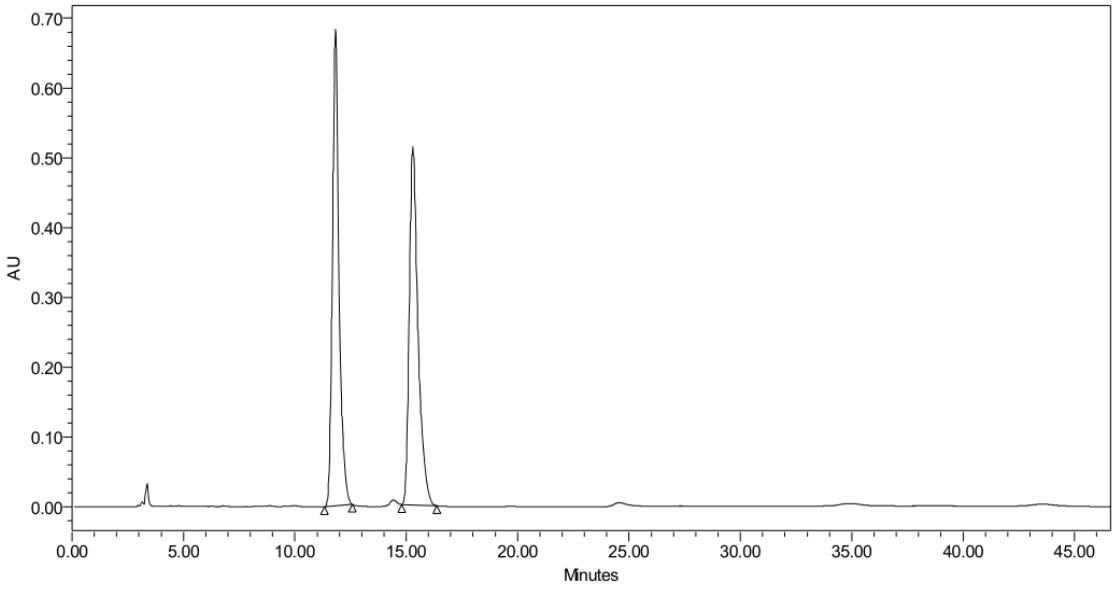
	RT	Area	% Area	Height
1	20.85	22818332	50.71	585474
2	27.68	22182390	49.29	437620

chiral-3l



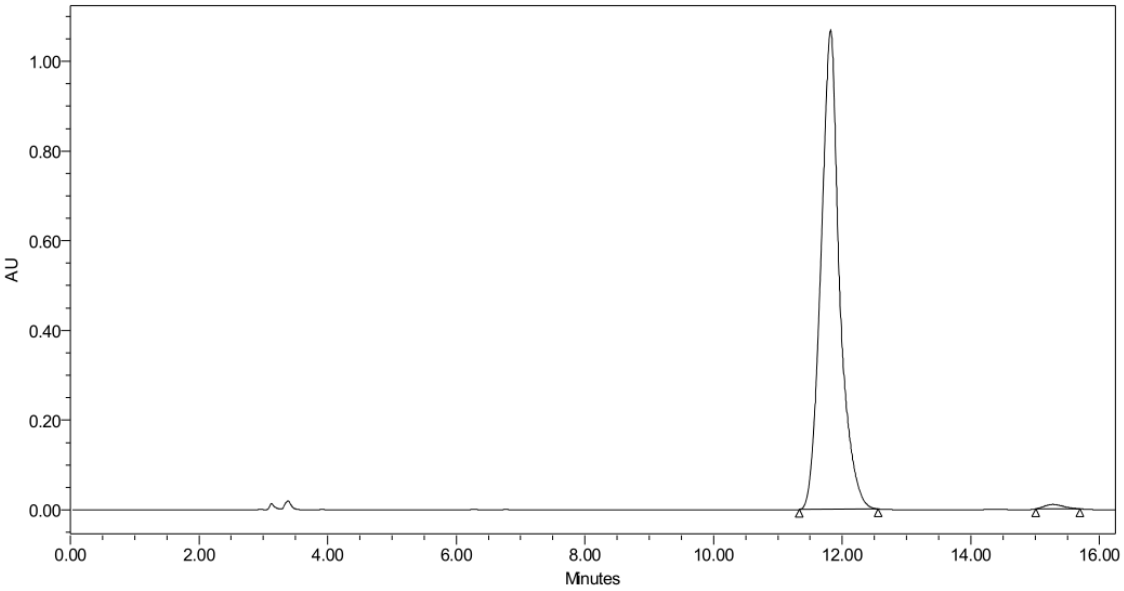
	RT	Area	% Area	Height
1	20.86	1181127	0.97	33393
2	27.93	120796511	99.03	2362150

racemic-3n



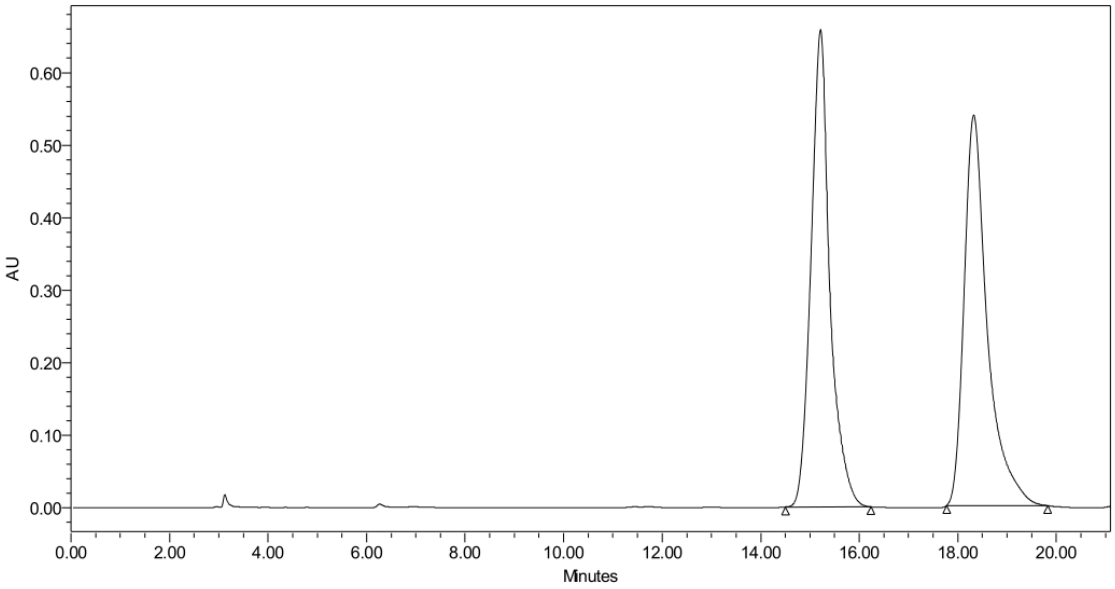
	RT	Area	% Area	Height
1	11.82	13870173	50.04	682060
2	15.30	13846506	49.96	513378

chiral-3n



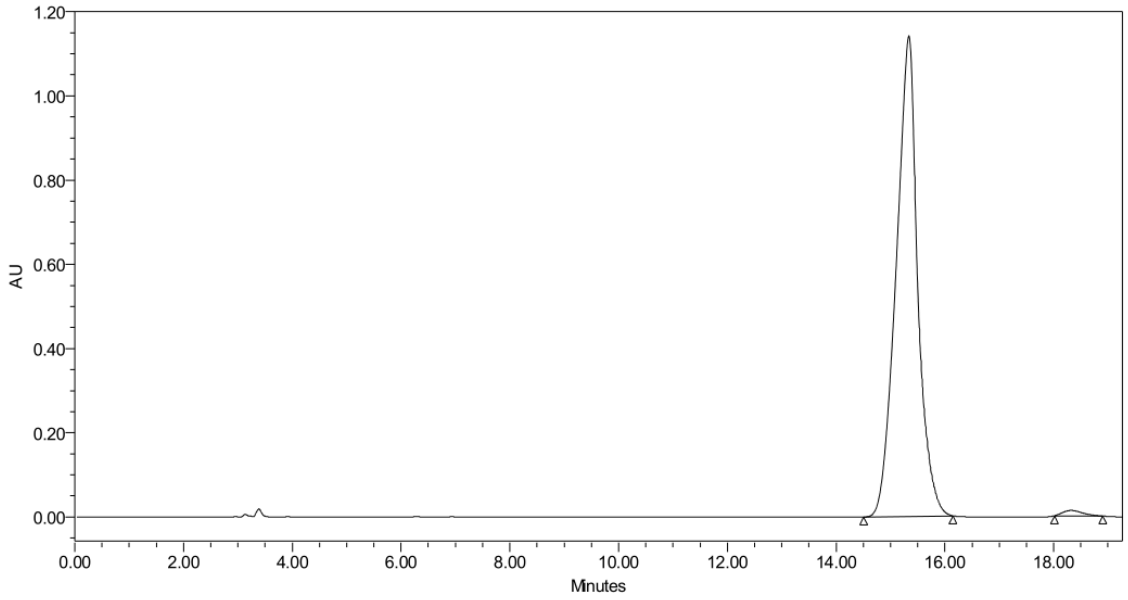
	RT	Area	% Area	Height
1	11.82	21425881	99.04	1069066
2	15.27	207714	0.96	10027

racemic-3o



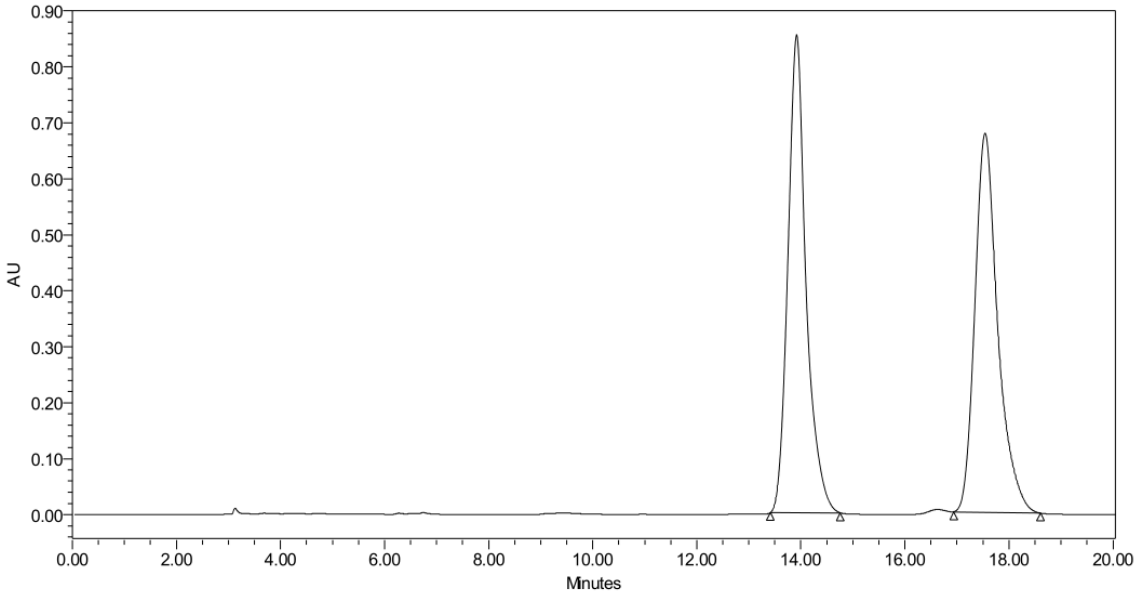
	RT	Area	% Area	Height
1	15.22	17518572	49.67	658106
2	18.32	17747963	50.33	538659

chiral-3o



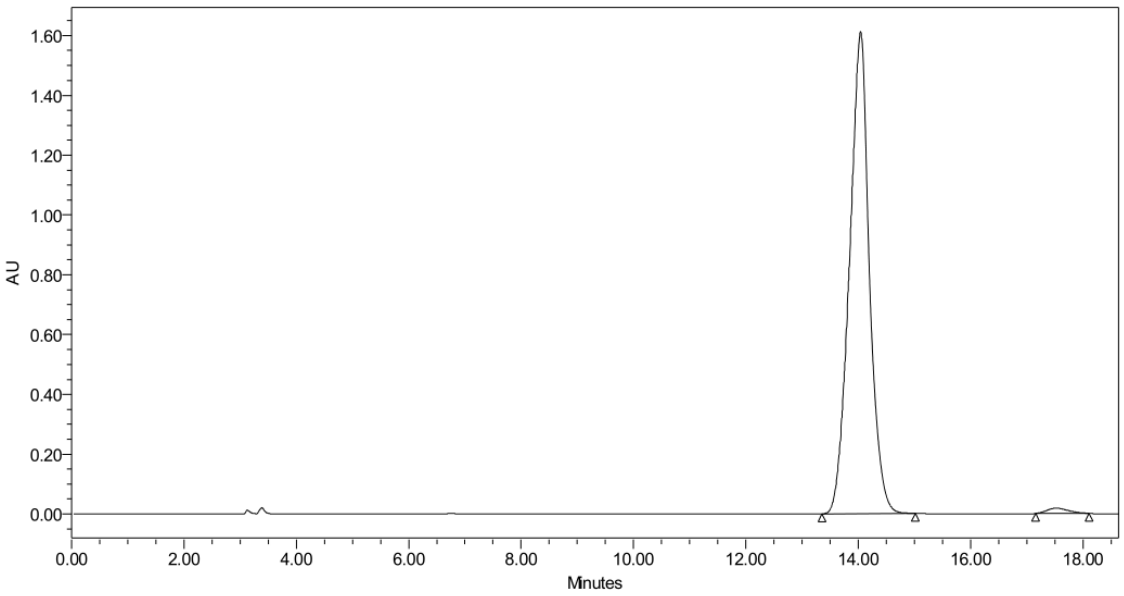
	RT	Area	% Area	Height
1	15.34	31414773	98.96	1141505
2	18.32	331158	1.04	12954

racemic-3p



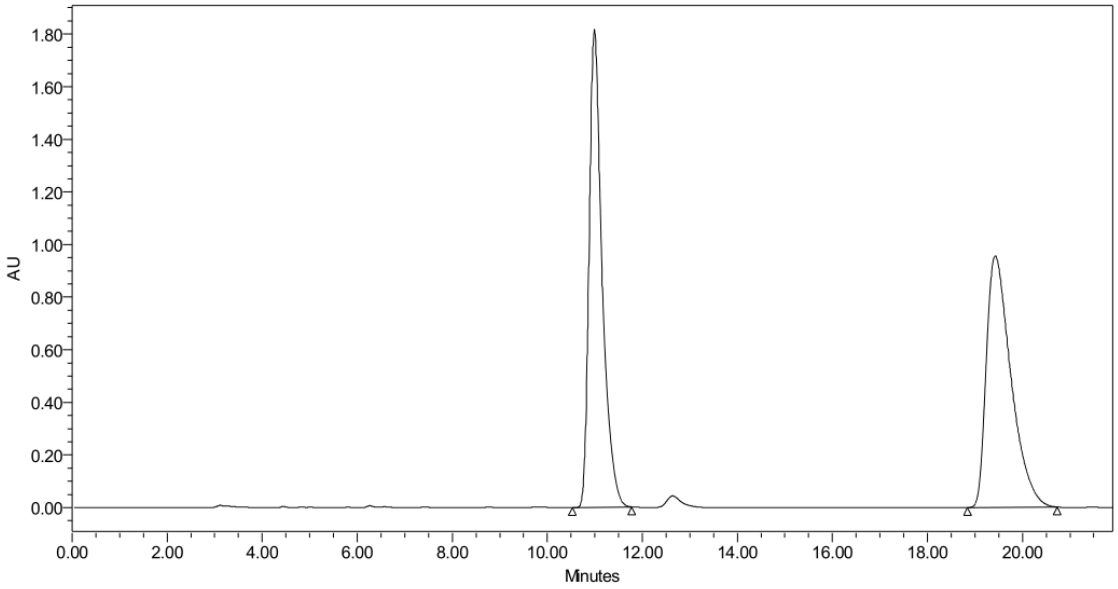
	RT	Area	% Area	Height
1	13.92	20811096	50.05	854007
2	17.54	20771151	49.95	677486

chiral-3p



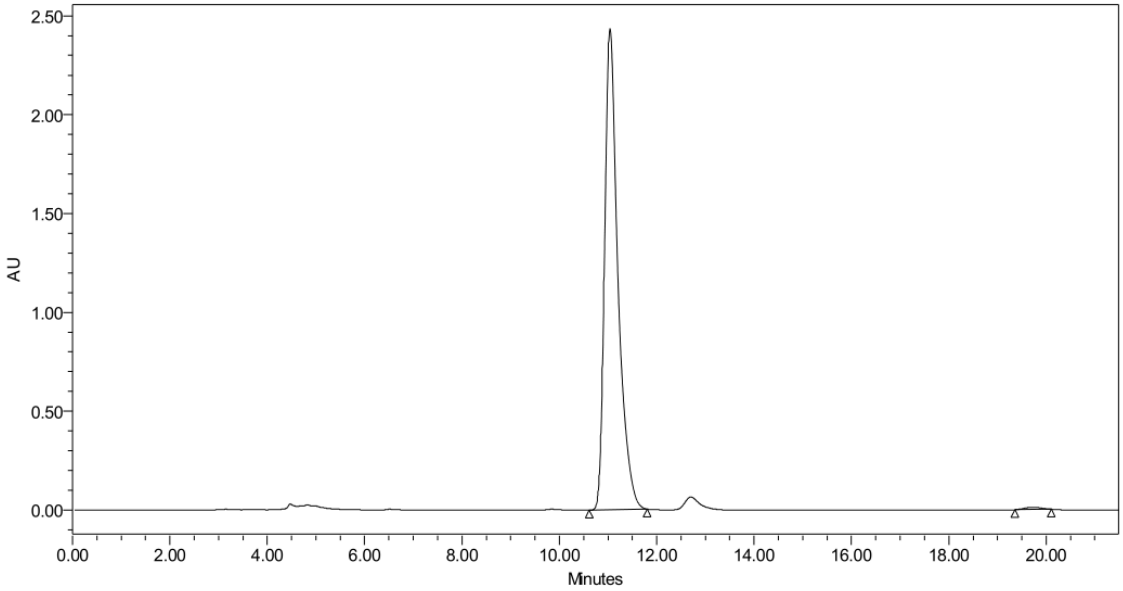
	RT	Area	% Area	Height
1	14.04	39473970	98.82	1612065
2	17.53	469375	1.18	17574

racemic-3q



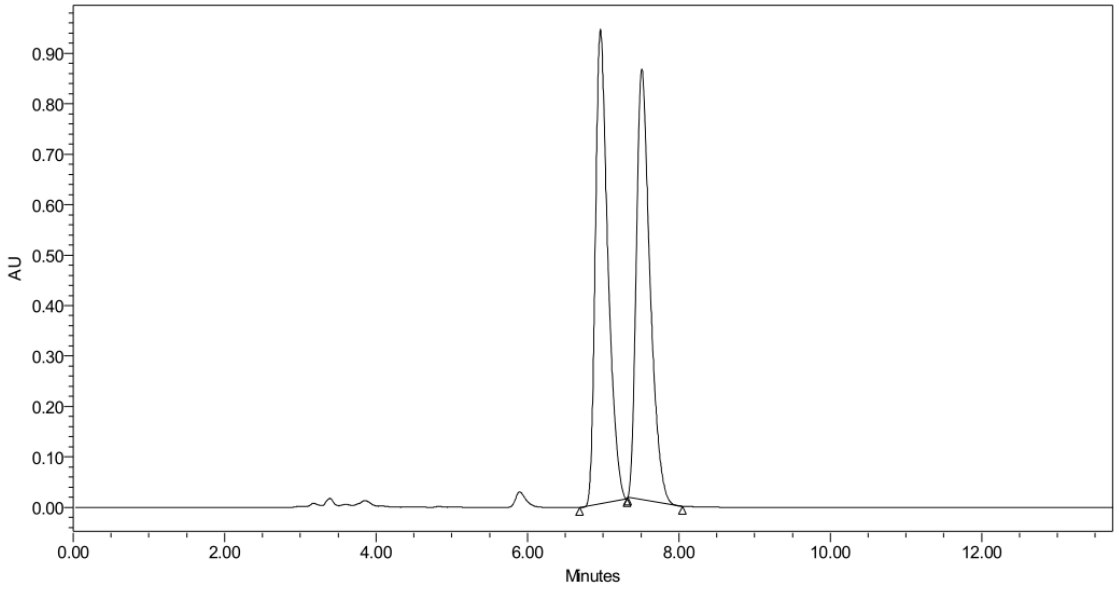
	RT	Area	% Area	Height
1	10.99	34254221	49.92	1816545
2	19.43	34366335	50.08	956741

chiral-3q



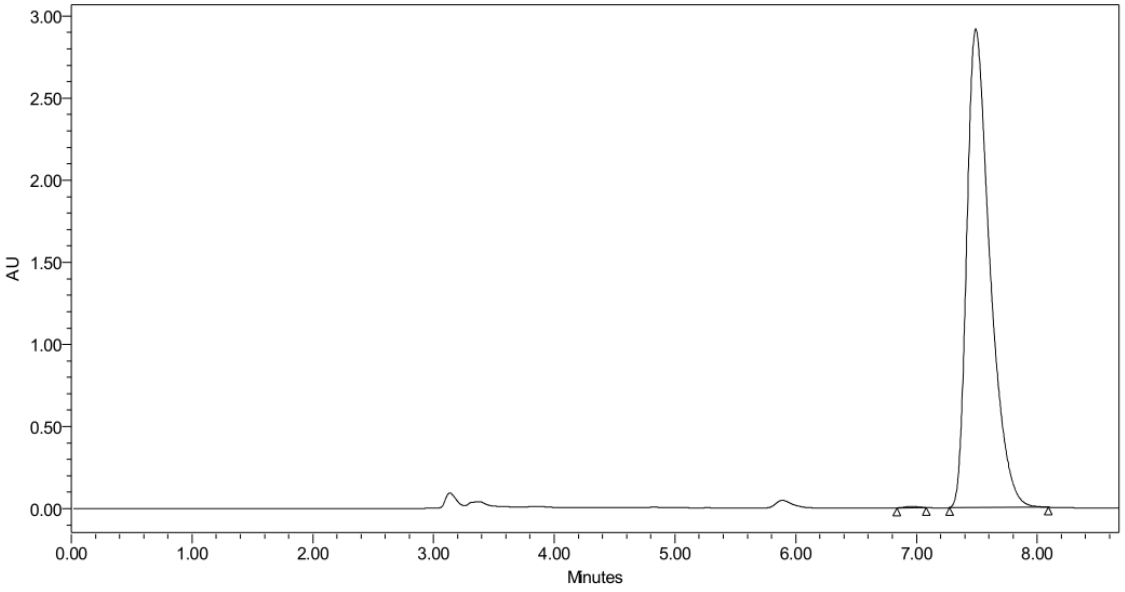
	RT	Area	% Area	Height
1	11.04	46375962	99.41	2433237
2	19.72	273848	0.59	11370

racemic-3s



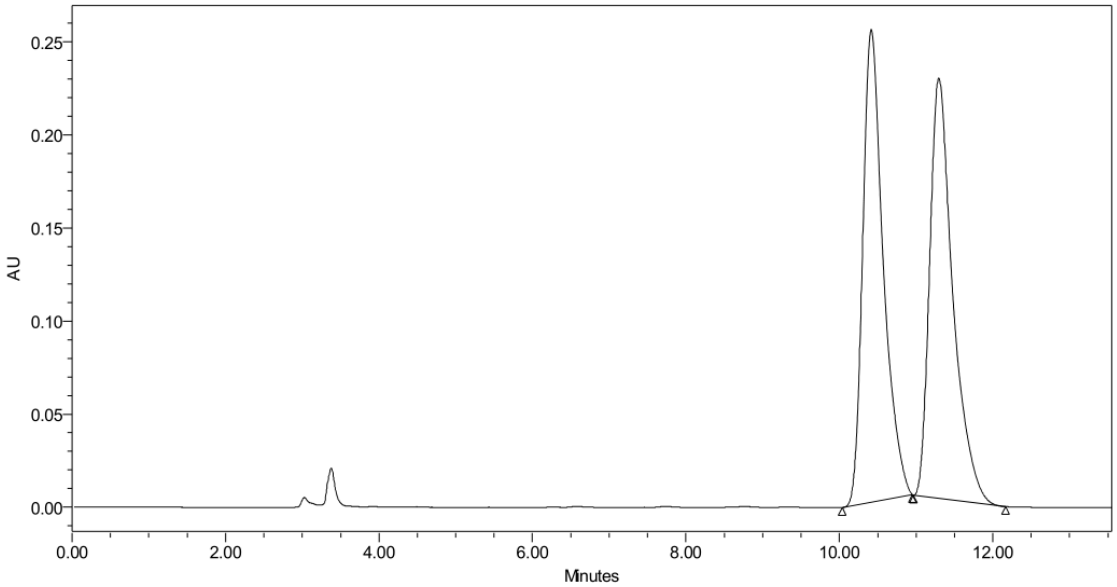
	RT	Area	% Area	Height
1	6.96	10802058	50.11	939673
2	7.51	10756601	49.89	854084

chiral-3s



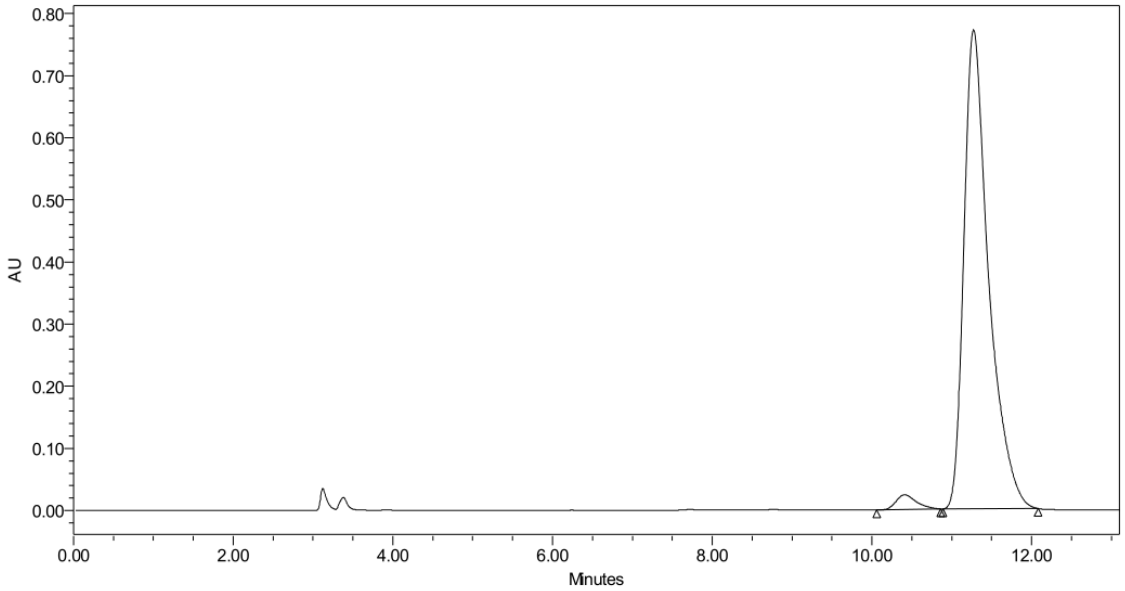
	RT	Area	% Area	Height
1	6.95	64097	0.16	8058
2	7.49	38797029	99.84	2914653

racemic-3t



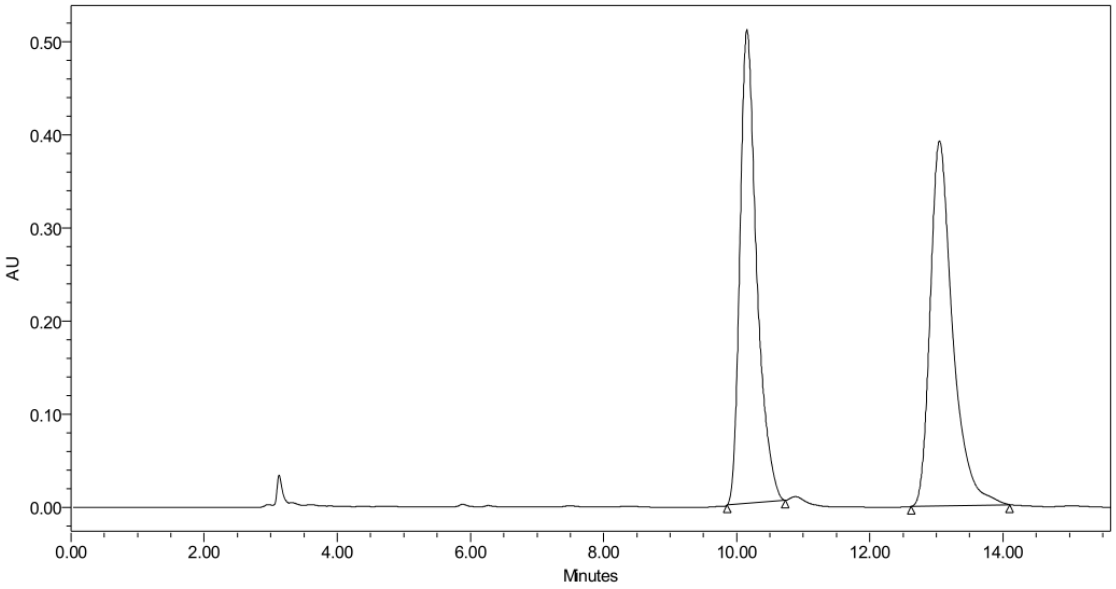
	RT	Area	% Area	Height
1	10.41	4735958	50.01	253789
2	11.29	4735005	49.99	225738

chiral-3t



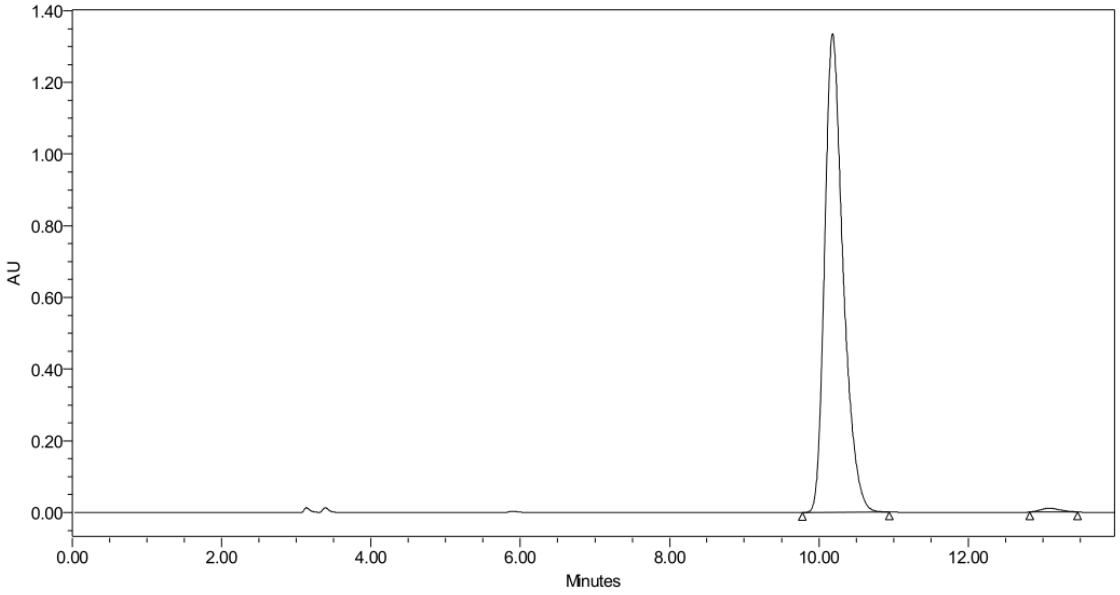
	RT	Area	% Area	Height
1	10.41	428512	2.50	23964
2	11.27	16704097	97.50	771377

racemic-3u



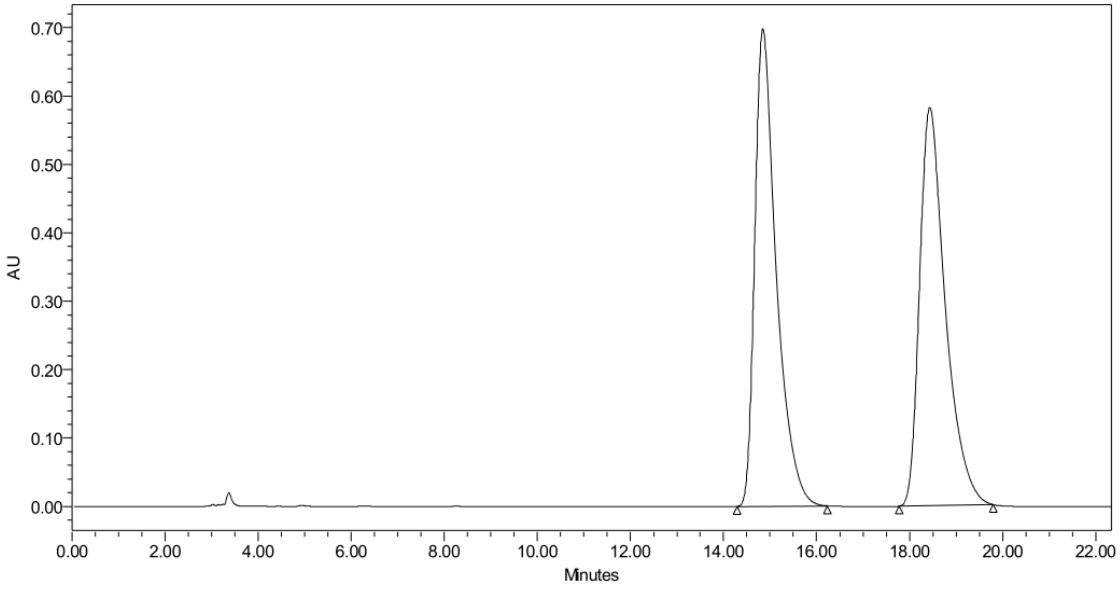
	RT	Area	% Area	Height
1	10.15	8862297	49.08	508850
2	13.05	9195418	50.92	392148

chiral-3u



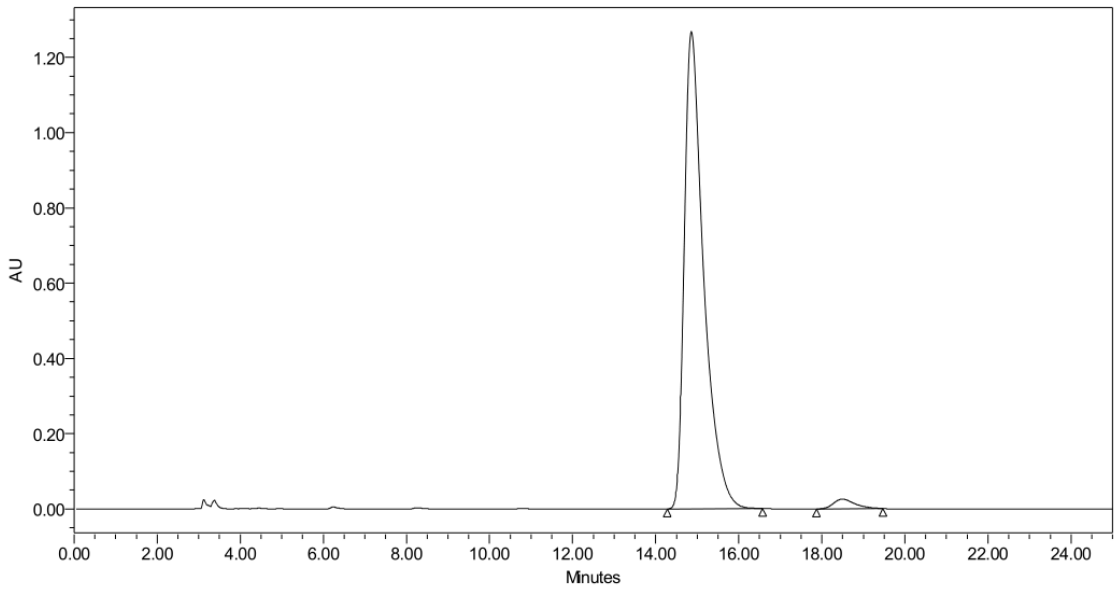
	RT	Area	% Area	Height
1	10.18	22852433	99.14	1334866
2	13.09	197079	0.86	10440

racemic-3v



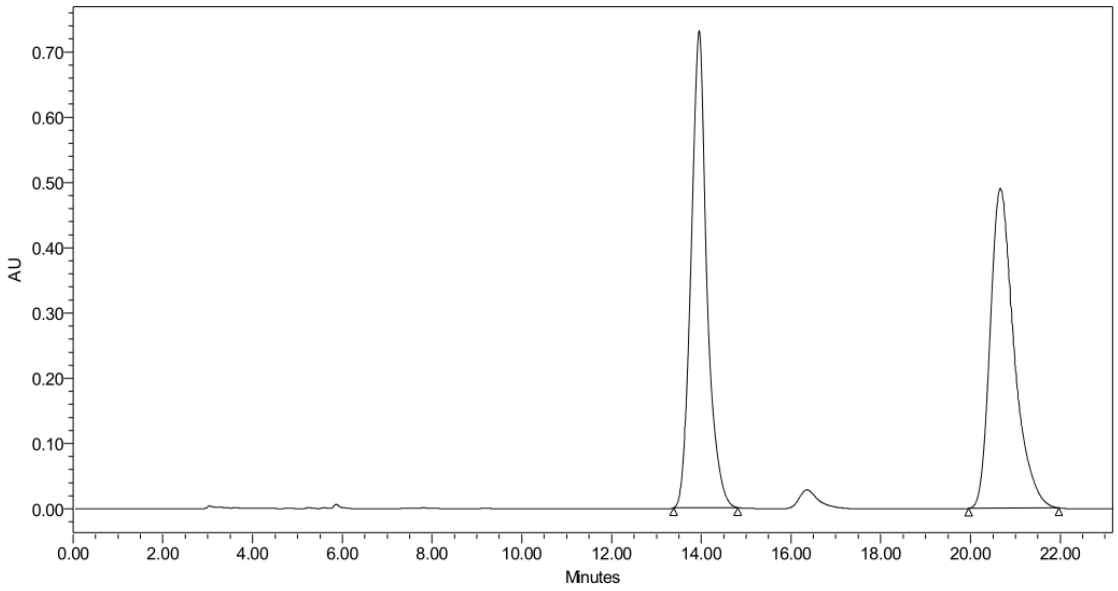
	RT	Area	% Area	Height
1	14.84	22352027	50.11	698099
2	18.43	22256596	49.89	582299

chiral-3v



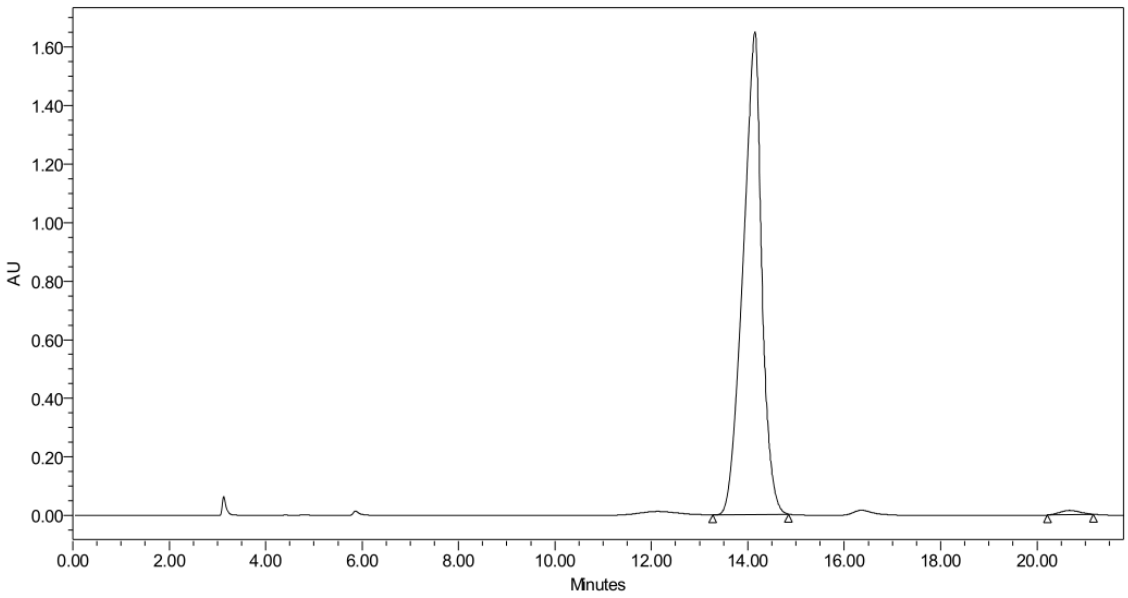
	RT	Area	% Area	Height
1	14.86	41373042	97.79	1268157
2	18.49	936134	2.21	25793

racemic-4b



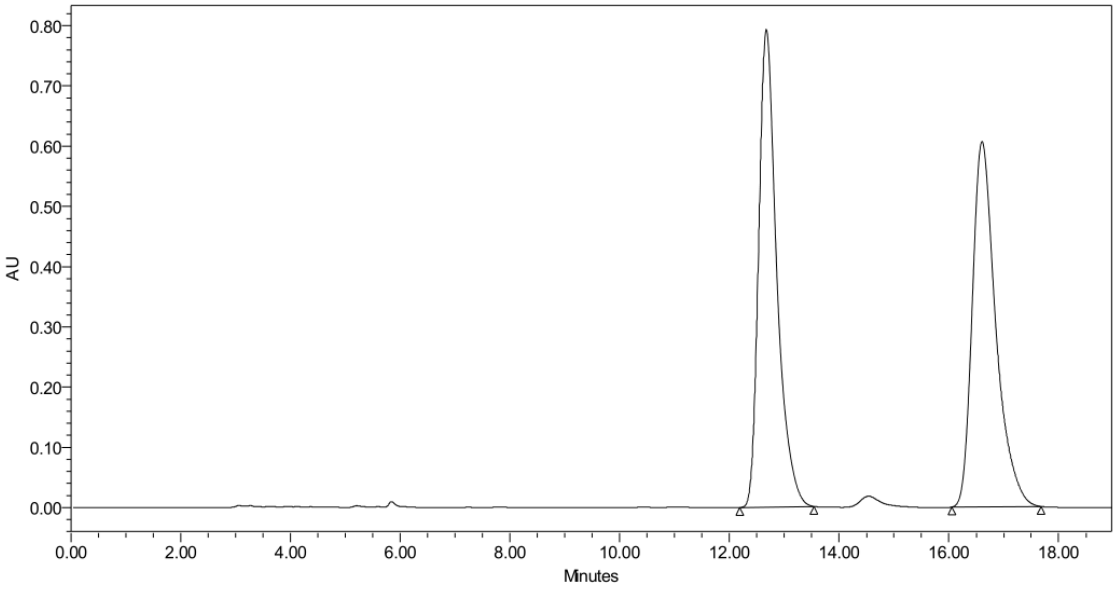
	RT	Area	% Area	Height
1	13.95	17969605	49.92	731069
2	20.67	18030116	50.08	490133

chiral-4b



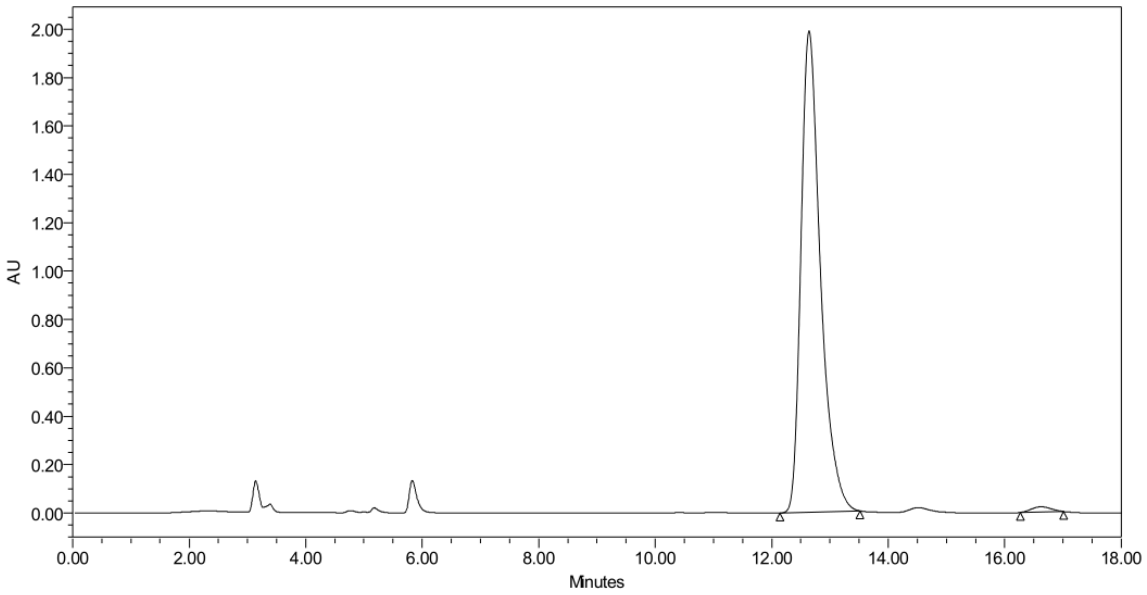
	RT	Area	% Area	Height
1	14.15	44129478	99.05	1647957
2	20.66	422833	0.95	14679

racemic-4c



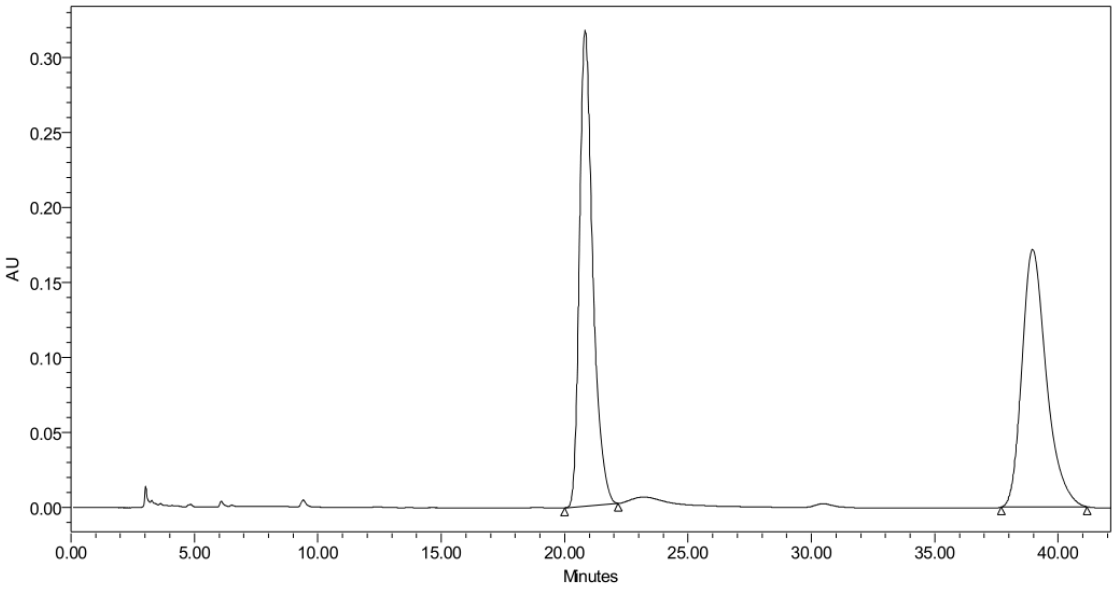
	RT	Area	% Area	Height
1	12.67	18103592	50.02	792849
2	16.61	18089511	49.98	606391

chiral-4c



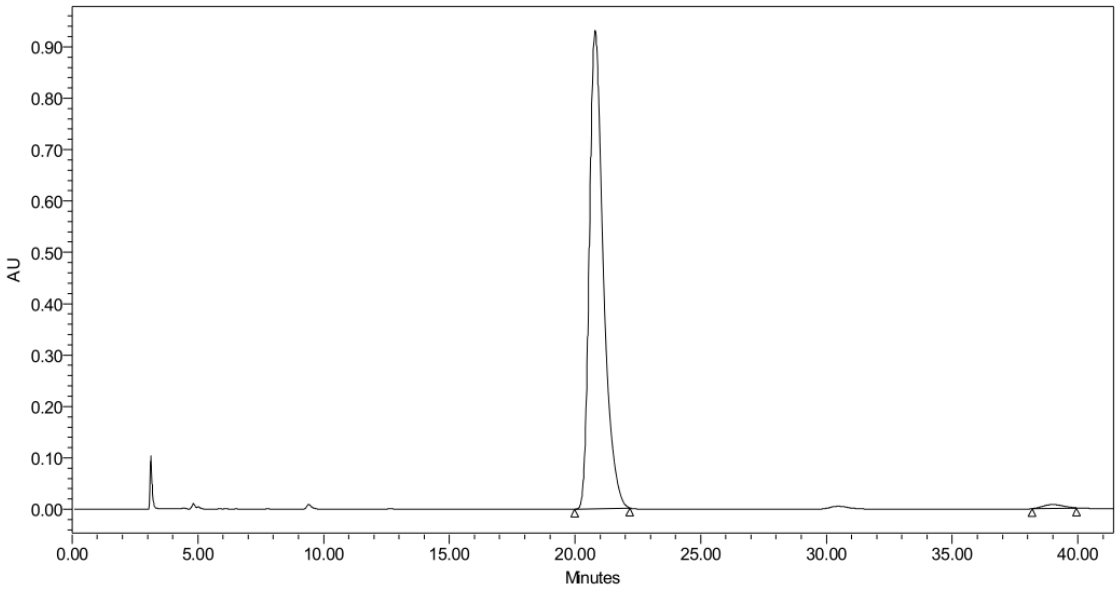
	RT	Area	% Area	Height
1	12.64	46557619	98.91	1988398
2	16.62	511166	1.09	22116

racemic-4d



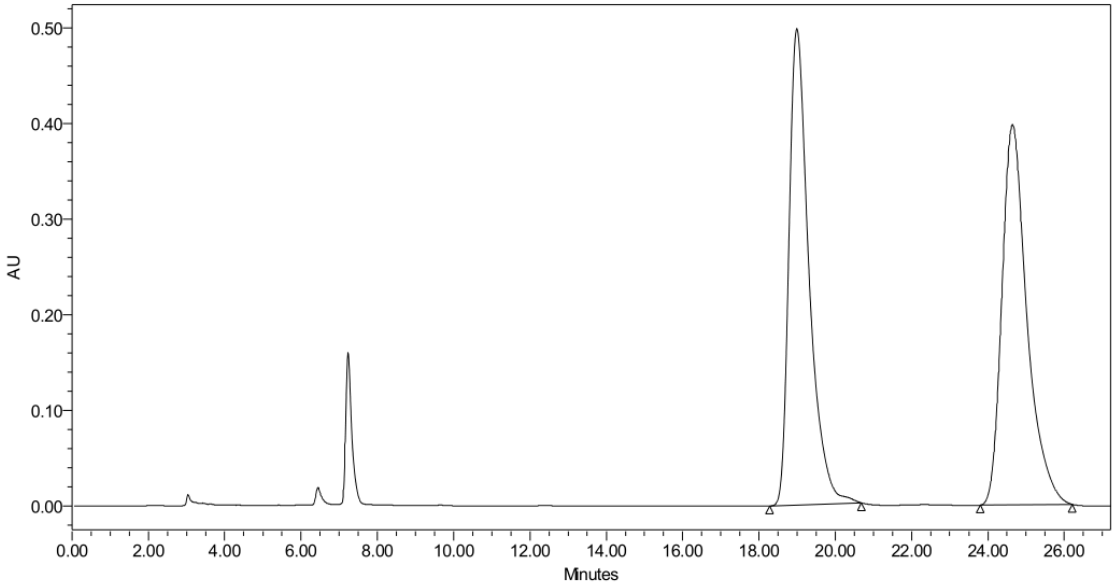
	RT	Area	% Area	Height
1	20.83	11822028	49.91	317042
2	38.96	11863058	50.09	171709

chiral-4d



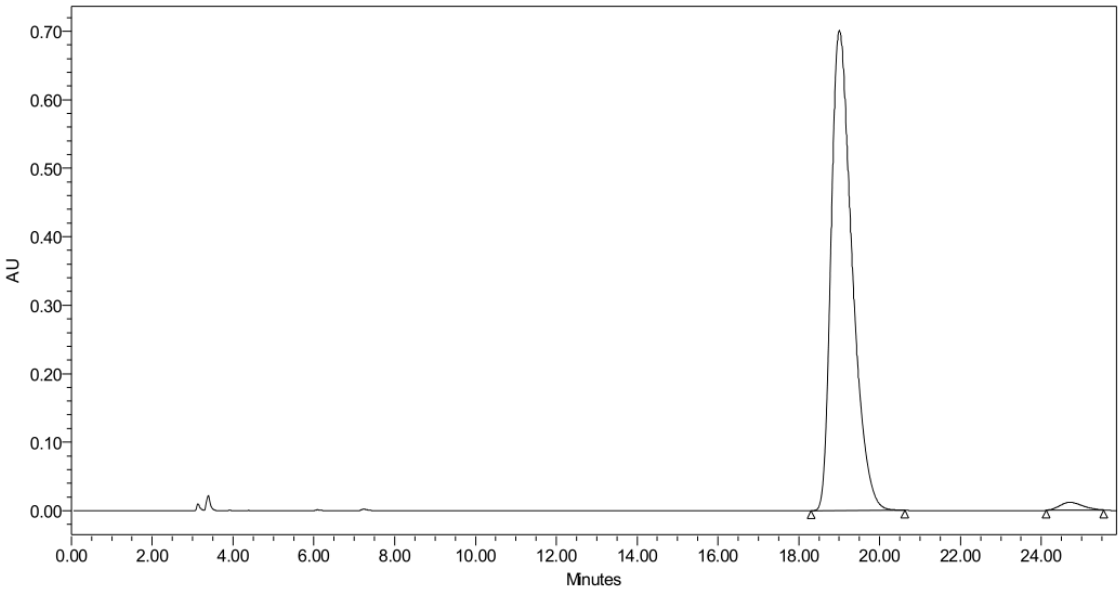
	RT	Area	% Area	Height
1	20.80	35676939	98.87	930623
2	38.99	406053	1.13	7433

racemic-4e



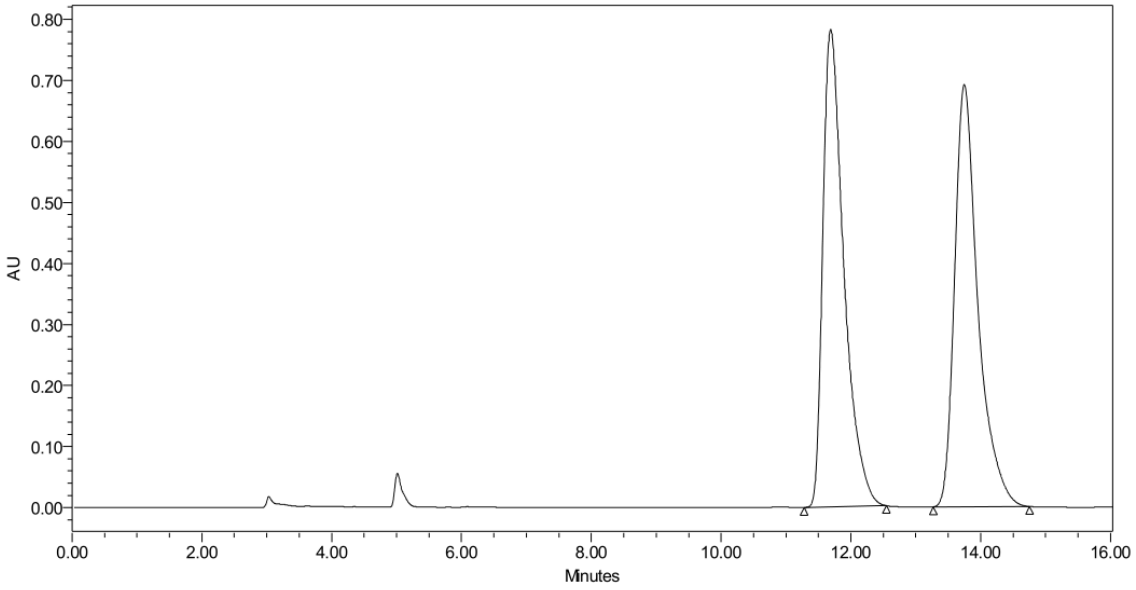
	RT	Area	% Area	Height
1	18.99	18238936	50.24	498128
2	24.64	18062252	49.76	397653

chiral-4e



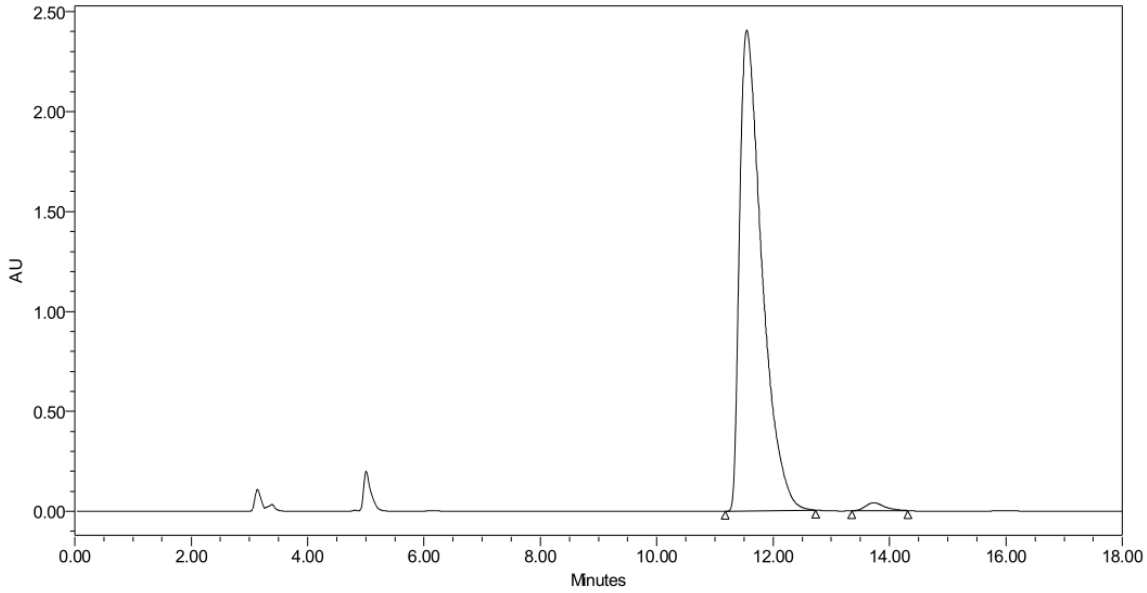
	RT	Area	% Area	Height
1	19.01	25086150	98.22	700975
2	24.71	454463	1.78	11513

racemic-4f



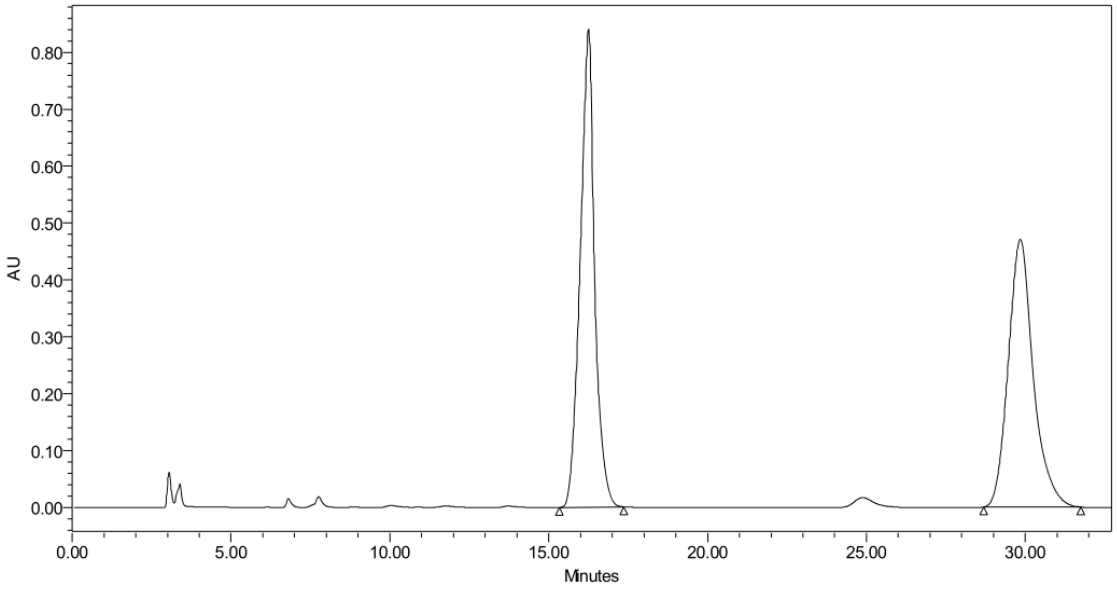
	RT	Area	% Area	Height
1	11.69	17555681	50.24	782229
2	13.75	17385021	49.76	691945

chiral-4f



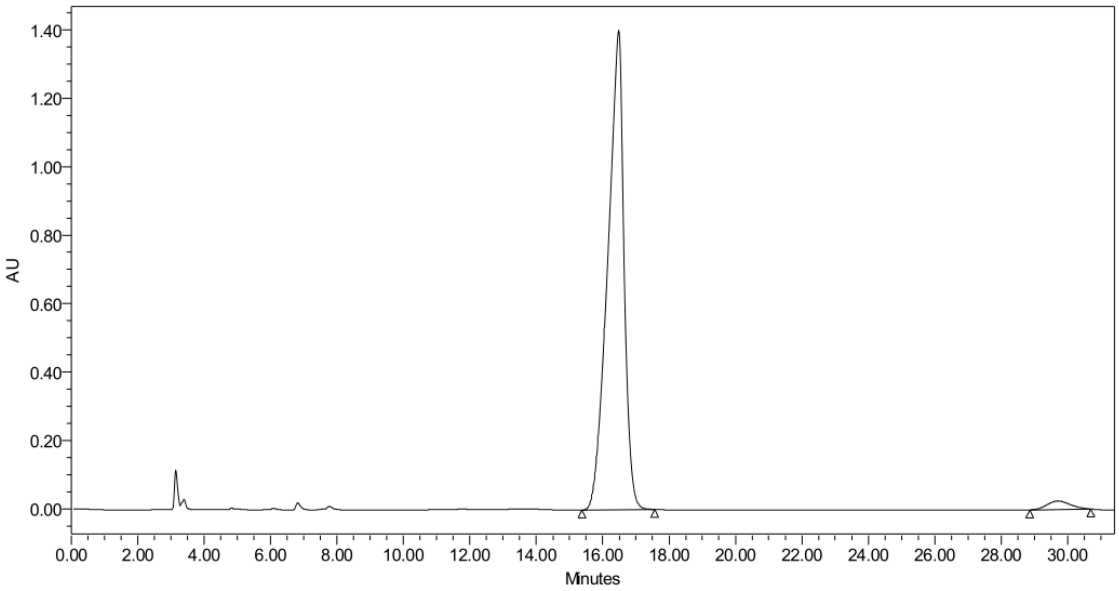
	RT	Area	% Area	Height
1	11.55	63976799	98.58	2406044
2	13.73	921302	1.42	39921

racemic-4g



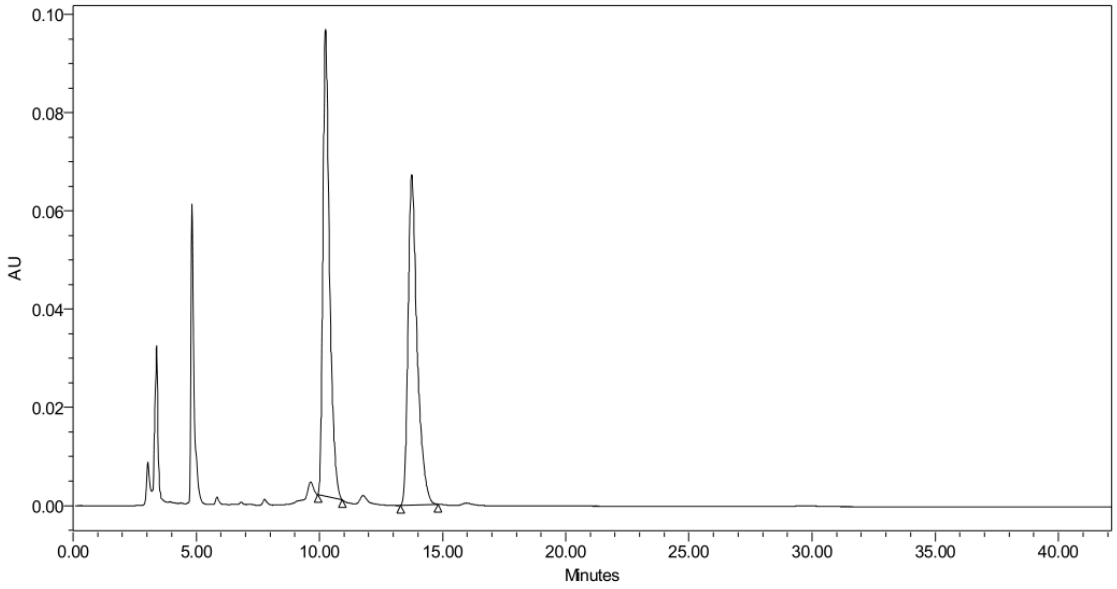
	RT	Area	% Area	Height
1	16.26	26376574	50.70	839433
2	29.84	25645485	49.30	470603

chiral-4g



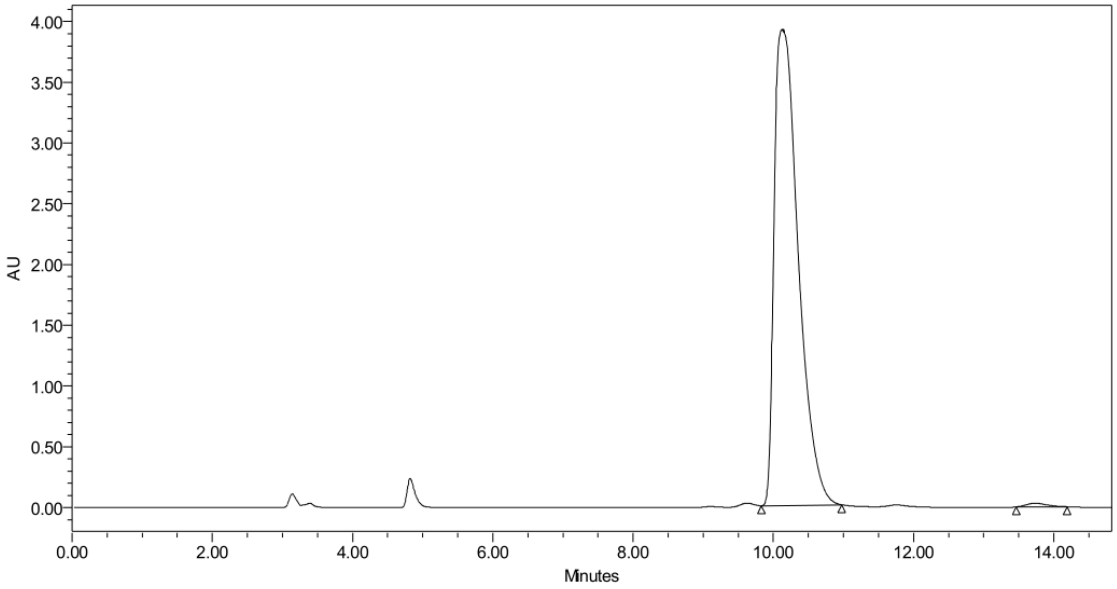
	RT	Area	% Area	Height
1	16.48	47751466	97.50	1400892
2	29.70	1225150	2.50	25223

racemic-4h



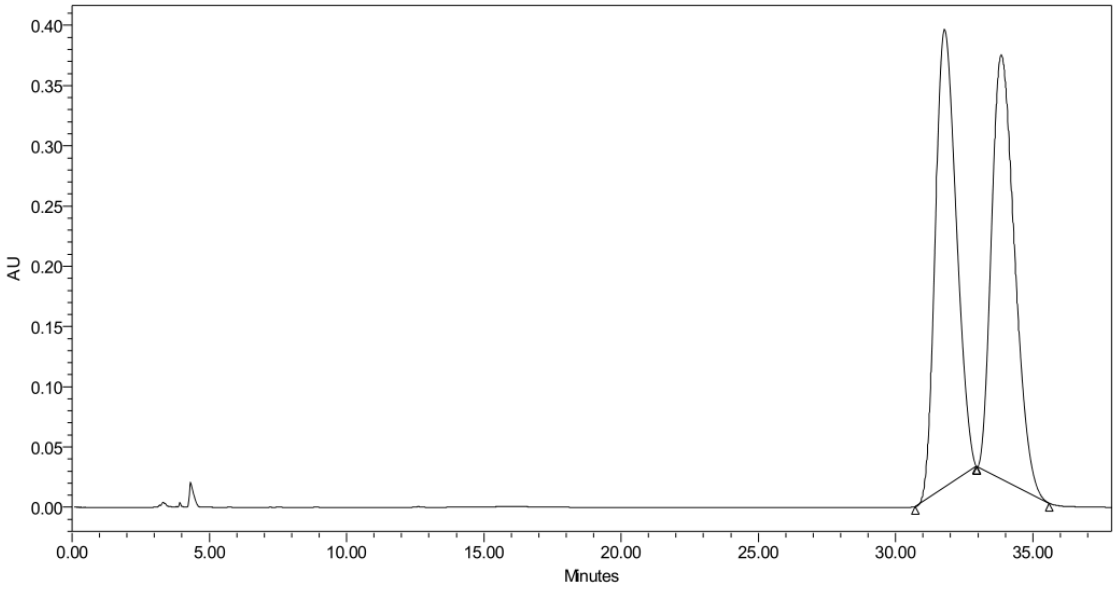
	RT	Area	% Area	Height
1	10.25	1749191	50.70	94972
2	13.75	1700559	49.30	67254

chiral-4h



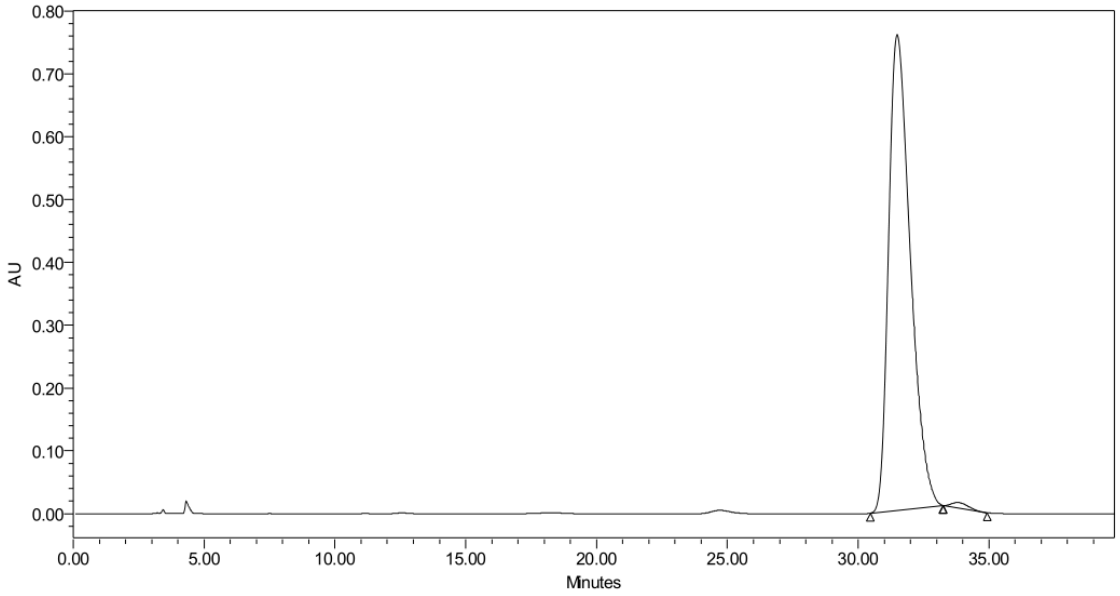
	RT	Area	% Area	Height
1	10.14	94053402	99.35	3919385
2	13.74	617193	0.65	29771

racemic-4i



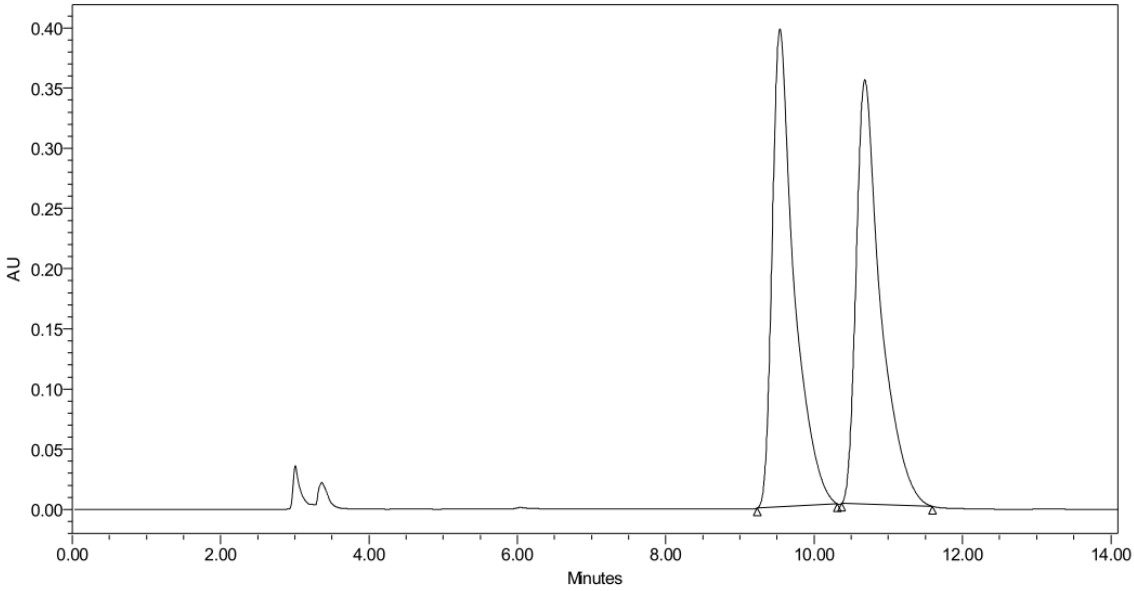
	RT	Area	% Area	Height
1	31.77	20323869	49.90	380044
2	33.86	20402452	50.10	352100

chiral-4i



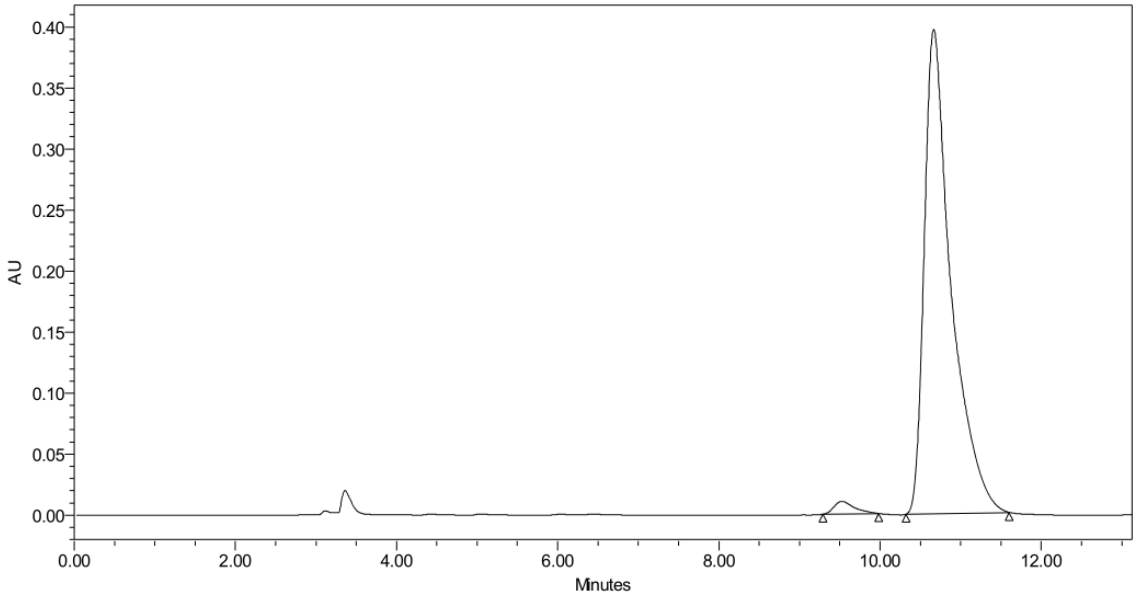
	RT	Area	% Area	Height
1	31.49	43842030	99.13	757133
2	33.87	385931	0.87	8847

racemic-4j



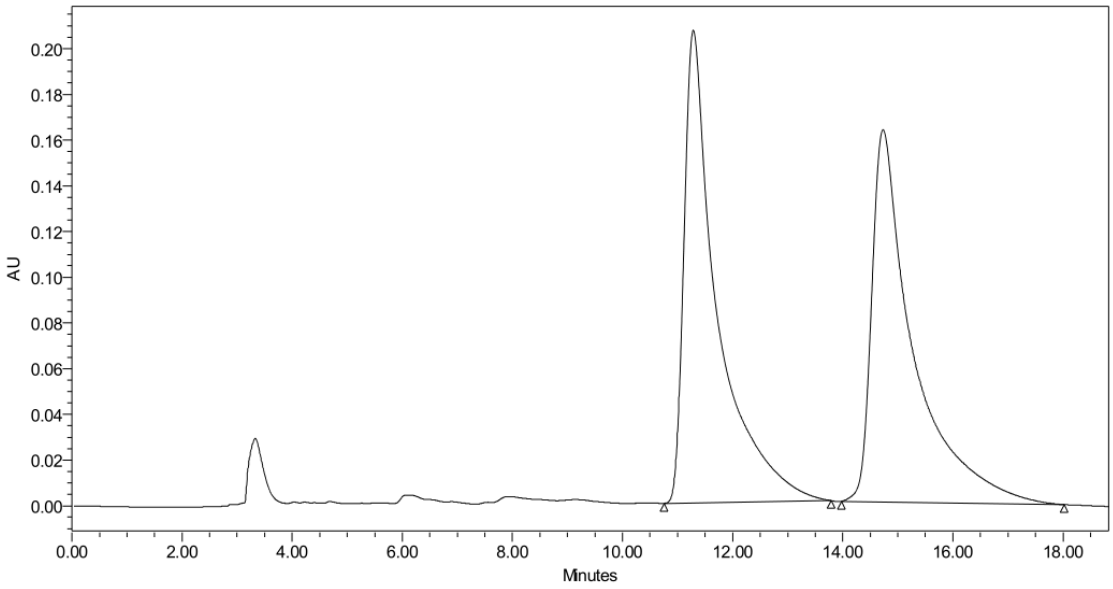
	RT	Area	% Area	Height
1	9.54	8161259	50.21	397093
2	10.68	8093966	49.79	352569

chiral-4j



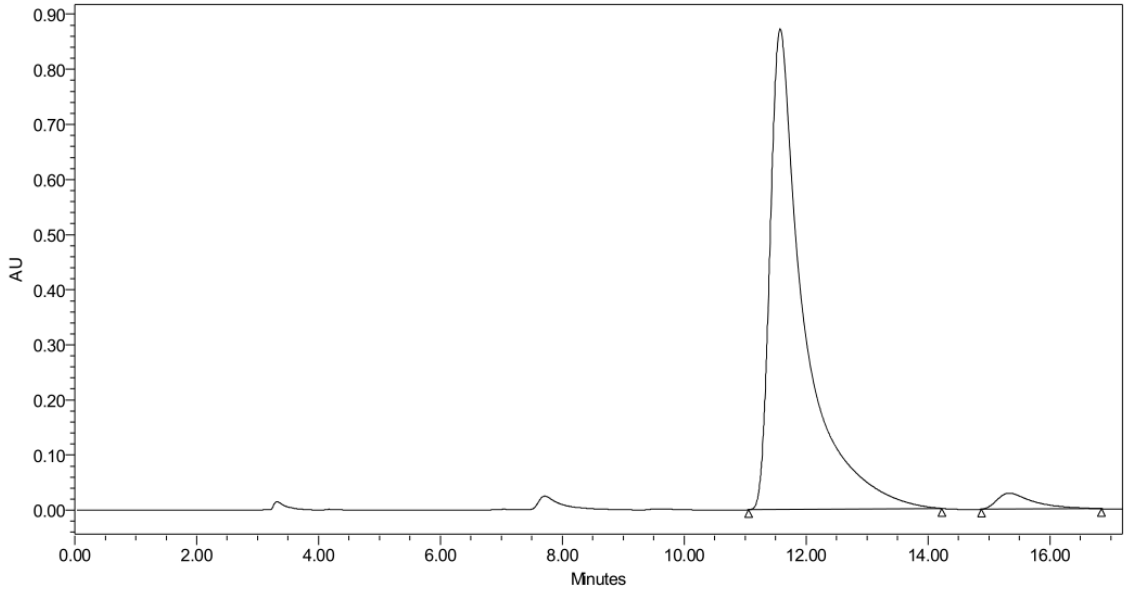
	RT	Area	% Area	Height
1	9.53	182942	1.95	10428
2	10.67	9196665	98.05	396802

racemic-5a



	RT	Area	% Area	Height
1	11.28	8665558	50.47	206762
2	14.73	8505659	49.53	162826

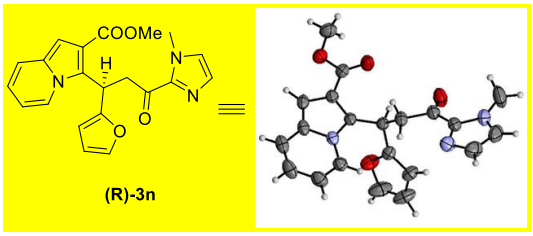
chiral-5a



	RT	Area	% Area	Height
1	11.57	33587855	96.51	872593
2	15.33	1214439	3.49	29028

VII. Single Crystal X-Ray Diffraction of 3n

Table 1. Crystal data and structure refinement for 3n.



CCDC 2117336

Table 1. Crystal data and structure refinement for **3n.**

Identification code	**3n**	
Empirical formula	$C_{21}H_{19}N_3O_4$	
Formula weight	377.39	
Temperature	173.0 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12$	
Unit cell dimensions	a = 7.3671(3) Å	α= 90°.
	b = 14.9482(6) Å	β= 90°.
	c = 17.1529(7) Å	γ = 90°.
Volume	1888.96(13) $Å^3$	
Z	4	
Density (calculated)	1.327 Mg/m^3	
Absorption coefficient	0.770 mm^{-1}	
F(000)	792	
Crystal size	0.21 x 0.19 x 0.13 mm^3	
Theta range for data collection	2.576 to 68.268°.	
Index ranges	-8<=h<=8, -18<=k<=18, -20<=l<=20	
Reflections collected	48412	
Independent reflections	3462 [R(int) = 0.0597]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.6630	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3462 / 0 / 255	

Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0328, wR2 = 0.0804
R indices (all data)	R1 = 0.0357, wR2 = 0.0831
Absolute structure parameter	-0.05(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.136 and -0.135 e.$Å^{-3}$