Asymmetric Addition of Chiral Boron-Ate Complexes to Cyclic Imminium Ions

Maziar Mohiti, Constantinos Rabalakos, Katie Feeney, Daniele Leonori, Varinder K. Aggarwal*

School of chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K.

v.aggarwal@bristol.ac.uk

Supporting Information

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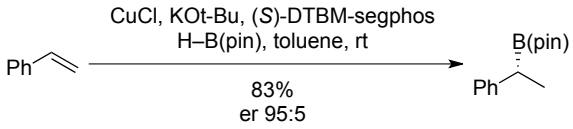
1. General Information

All required fine chemicals were used directly without purification unless mentioned. Compounds lacking experimental details were prepared according to the literature as cited and are in agreement with published spectra. All air- and water-sensitive reactions were carried out in flame-dried glassware under argon atmosphere using standard Schlenk manifold technique. ^{1}H NMR and ^{13}C NMR spectra were acquired at various field strengths as indicated, and were referenced to $CHCl_3$ (7.27 and 77.0 ppm for ^{1}H and ^{13}C respectively) or TMS (0.00 ppm for ^{1}H and ^{13}C). ^{1}H NMR coupling constants are reported in Hertz and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, qi = quintet, sx = sextet, m = multiplet, dd = doublet of doublet, etc.) and integration. ^{11}B NMR spectra were recorded with complete proton decoupling using BF_3•Et_2O (0.0 ppm) as an external standard. High-resolution mass spectra were recorded using Electronic Ionization (EI), Electron Spray Ionization (ESI) or Chemical Ionization (CI). For CI, methane or NH_4OAc/MeOH was used. All IR data was obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer 241MC polarimeter. Analytical TLC: aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualized by exposure to UV-light or by dipping the plates in 5% solution of $(NH_4)2Mo_7O_{24}$•$4H_2O$ in EtOH followed by heating. Flash column chromatography was performed using Merck Silica Gel 60 (40-63 μm) or on a Biotage SP1 system. All mixed solvent eluents are reported as v/v solutions. Melting points were determined with a Boetius hot stage apparatus and were not corrected. Chiral HPLC was performed using Diacel Chiralpak IA, IB and IC columns (4.6 × 250 mm × 5 μm) fitted with the respective guards (4 × 10 mm) and monitored by DAD (Diode Array Detector). Solvents were purified by standard methods and degassed by applying 3 freeze-pump-thaw cycles immediately before use. The molarity of organolithium solutions was determined by titration using salicylaldehyde phenylhydrazone as indicator.

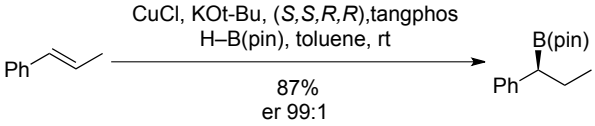
2. Preparation of boronic esters 3a–e

(*R*)-4,4,5,5-Tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane [(*R*)-3a]



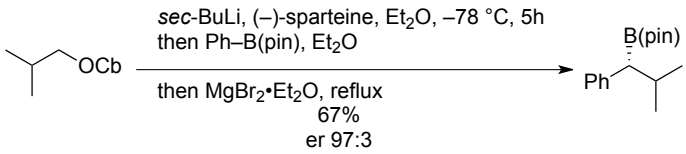
Prepared according to a literature procedure.[1]

(*R*)-4,4,5,5-Tetramethyl-2-(1-phenylpropyl)-1,3,2-dioxaborolane [(*S*)-3b]



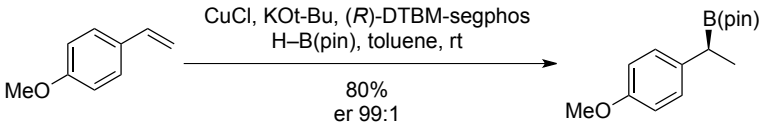
Prepared according to a literature procedure.[1]

(*R*)-4,4,5,5-Tetramethyl-2-(2-methyl-1-phenylpropyl)-1,3,2-dioxaborolane [(*R*)-3c]



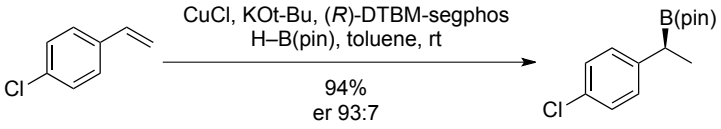
Prepared according to a literature procedure.[2]

(*R*)-2-(1-(4-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-3d]



Prepared according to a literature procedure.[1]

(*R*)-2-(1-(4-Chlorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-3e]



Prepared according to a literature procedure.[1]

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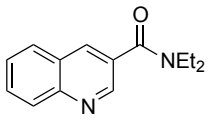
[1] (a) D. Noh, S. K. Yoon, J. Won, J. Y. Lee, J. Yun *Chem. Asian J.* **2011**, *6*, 1967. (b) D. Noh, H. Chea, J. Ju, J. Yun *Angew. Chem. Int. Ed.* **2009**, *48*, 6062.
[2] V. Bagutski, A. Ros, V. K. Aggarwal *Tetrahedron* **2009**, *65*, 9956.

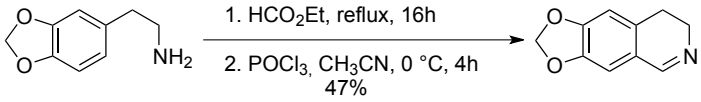
3. Preparation of heterocycles 6 and 20

N,*N*-Diethylquinoline-3-carboxamide (6)



A solution of 3-quinolinecarboxylic acid (5.0 g, 28.9 mmol, 1.0 equiv.) in thionyl chloride (50 mL) was heated under reflux for 1h. After evaporation of excess thionyl chloride, the residue was dissolved in dry CH_2Cl_2 (100 mL), cooled to 0 °C and Et_2NH (4.5 mL, 43.3 mmol, 1.5 equiv.) and Et_3N (6.0 mL, 43.3 mmol, 1.5 equiv.) were added. The reaction mixture was then heated under reflux overnight and then evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2:MeOH (9:1), gave **6** (4.8 g, 73%) as an oil; IR ν_{max}(neat)/cm^{-1} 3490, 2974, 1697, 1429, 1288, 1257, 1091, 788; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, 1H, *J* = 2.1 Hz), 8.26 (1H, d, *J* = 1.9 Hz), 8.19 (1H, d, *J* = 8.7 Hz), 7.88 (br d, 1H, *J* = 8.2 Hz), 7.81 (ddd, 1H, *J* = 8.5, 7.0, 1.5), 7.63 (ddd, 1H, *J* = 8.1, 7.0, 1.1 Hz), 3.62 (br s, 2H), 3.35 (br s, 2H), 1.30 (br s, 3H), 1.18 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 148.1, 134.1, 130.5, 129.4, 128.3, 127.5, 127.4, 43.6, 39.7, 14.4, 13.0; HRMS (ESI) calc'd. for $C_{14}H_{16}NaNO$ $[M+Na]^+$ 251.1160, found 251.1164.

7,8-Dihydro-[1,3]dioxolo[4,5-*g*]isoquinolines (20)



Prepared according to a literature procedure.[3]

[3] M. Del Pilar C. Soriano, N. Shankaraiah, L. Silva Santos *Tetrahedron Lett.* **2010**, *51*, 1770.

4. General Procedures

Addition to quinoline 6 – GP1

A Schlenk tube was charged with *n*-butyllithium (1.2 equiv., 1.55 M) and THF (0.5M) and it was cooled to –78 °C. A 0.5M solution of 3,5-bis-(trifluoromethyl)phenyl bromide (1.2 equiv.) in THF was added and the mixture was stirred at –78 °C for 30 min. A 0.5M solution of boronic ester (1.0 equiv.) in THF was added by dropwise. The mixture was stirred at –78 °C for 30 min and then it was warmed to r.t. and stirred for 30 min at which point ^{11}B NMR spectroscopy showed complete formation of the 'ate' complex [^{11}B NMR (96 MHz, no solvent) δ_B ~ 8 ppm]. The mixture was cooled to –78 °C and **6** (2.0 equiv.) and 2,2,2-trichlorethoxycarbonyl chloride (2.0 equiv.) were added. The mixture was allowed to warm to r.t. overnight and then it was diluted with H_2O and ether. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with *n*-hexane:EtOA (99:1 to 9:1), gave the desired product.

Addition to pyridines 7 and 8 – GP2

A Schlenk tube was charged with *n*-butyllithium (1.2 equiv., 1.55 M) and THF (0.5M) and it was cooled to –78 °C. A 0.5M solution of 3,5-bis-(trifluoromethyl)phenyl bromide (1.2 equiv.) in THF was added and the mixture was stirred at –78 °C for 30 min. The boronic ester (1.0 equiv.) was added neat. The mixture was stirred at –78 °C for 30 min and then it was warmed to r.t. and stirred for 30 min at which point ^{11}B NMR spectroscopy showed complete formation of the 'ate' complex [^{11}B NMR (96 MHz, no solvent) δ_B ~ 8 ppm]. The mixture was cooled to –40 °C and stirred for 15 min. **7** (or **8**) (2.0 equiv.) was added neat and the mixture was stirred at –40 °C for 10 min. 2,2,2-Trichlorethoxycarbonyl chloride (2.0 equiv.) was added neat, the mixture was stirred at –40 °C overnight and then it was diluted with H_2O and ether while at –40 °C. The mixture was warmed to r.t. and the organic layer was separated. The aqueous layer was extracted with Et_2O (x 3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with pentane:Et_2O (4:1 to 3:2), gave the desired product.

Addition to quinolines 5, 12, 13 and oxidation – GP3

A Schlenk tube was charged with *n*-butyllithium (1.2 equiv., 1.55 M) and THF (0.5M) and it was cooled to –78 °C. A 0.5M solution of 3,5-Bis-(trifluoromethyl)phenyl bromide (1.2 equiv.) in THF was added and the mixture was stirred at –78 °C for 30 min. A 0.5M solution

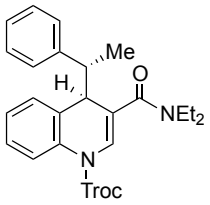
of boronic ester (1.0 equiv.) in THF was added by dropwise. The mixture was stirred at –78 °C for 30 min and then it was warmed to r.t. and stirred for 30 min at which point ^{11}B NMR spectroscopy showed complete formation of the 'ate' complex [^{11}B NMR (96 MHz, no solvent) δ_B ~ 8 ppm]. The mixture was cooled to –78 °C and **5** (or **12** or **13**) (2.0 equiv.) and 2,2,2-trichlorethoxycarbonyl chloride (2.0 equiv.) were added. The mixture was allowed to warm to r.t. overnight and it was then passed through a pad of silica and concentrated. The crude product was solubilised in THF–H_2O (1–1, 0.1M) and chloranil (1.2 equiv.) was added. The resulting mixture was stirred overnight and then filtered through celite. Purification by column chromatography on silica gel, eluting with *n*-hexane:EtOA (95:5) (to remove non-polar impurities) and CH_2Cl_2:MeOH (95:5 to 9:1), gave the desired product.

Addition to dihydroisoquinolines 17 and 20 – GP4

A Schlenk tube was charged with a 1.7M solution of the boronic ester (1.0 equiv.) 100 mg, 0.41 mmol) in THF, and the mixture was cooled to −78 °C. Phenyllithium (1.25 equiv., 1.8 M) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, and at room temperature for 30 min. A second Schlenk tube was charged with a 1.7M solution of **17** (or **20**) (2.0 equiv.) and 2,2,2-trichloro-1,1-dimethylethylchloroformate (2.1 equiv.) in THF, and the mixture was cooled to −78 °C. The boron 'ate'-complex solution was added dropwise to the iminium solution, and the reaction mixture was stirred at −78 °C overnight. A 2:1 solution of NaOH (2.5 M) and hydrogen peroxide (30% solution in H_2O) was added, and the mixture was stirred at room temperature for 1 h. H_2O and Et_2O were added and the layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel gave the pure products.

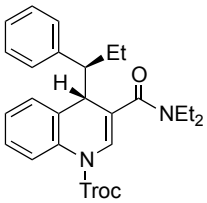
5. Characterization data

(*R*)-2,2,2-trichloroethyl 3-(diethylcarbamoyl)-4-((*R*)-1-phenylethyl)quinoline-1(4*H*)-carboxylate (9a)



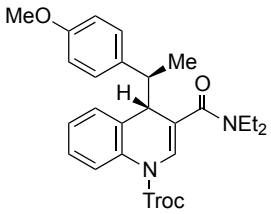
Using GP1: **9a** (72 mg, 68%); oil; dr 98:2; er 95:5; $[\alpha]_D$ –89 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2970, 1738, 1618, 1380, 1233; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* = 8.1 Hz), 7.24 (td, 1H, *J* = 7.7, 1.7 Hz), 7.16 (td, 1H, *J* = 7.3, 1.2 Hz), 7.12-7.04 (m, 5H), 6.87 (dd, 1H, *J* = 6.5, 3.3 Hz), 4.72 (br d, 1H, *J* = 10.1 Hz), 4.57 (br d, 1H, *J* = 10.1 Hz), 3.91 (d, 1H, *J* = 4.4 Hz), 3.50-3.30 (m, 5H), 1.31 (d, 3H, *J* = 7.2 Hz), 1.13 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 149.8, 142.1, 136.3, 129.6, 129.0, 128.5, 128.4, 127.6, 127.2, 126.8, 126.0, 125.2, 121.5, 120.8, 94.8, 75.6, 47.8, 44.6, 41.0, 25.4, 18.0, 13.7; HRMS (ESI) calc'd. for $C_{25}H_{27}{}^{35}Cl_3N_2NaO_3$ $[M+Na]^+$ 531.0985, found 531.0988.

(*S*)-2,2,2-trichloroethyl 3-(diethylcarbamoyl)-4-((*S*)-1-phenylpropyl)quinoline-1(4*H*)-carboxylate (9b)



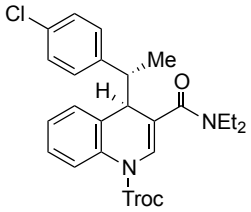
Using GP1: **9b** (78 mg, 69%); oil; dr >99:1; er 99:1; $[\alpha]_D$ +86 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2964, 2931, 1737, 1615, 1378, 1232, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 1H, *J* = 8.1 Hz), 7.24 (td, 1H, *J* = 7.6, 2.2 Hz), 7.19-7.04 (m, 5H), 6.98 (s, 1H), 6.77-6.74 (m, 2H), 4.66 (br s, 1H), 4.48 (br s, 1H), 3.90 (d, 1H, *J* = 3.8 Hz), 3.53-3.35 (m, 4H), 3.06 (dt, 1H, *J* = 9.5, 4.7 Hz), 1.88-1.72 (m, 2H), 1.17 (t, 6H, *J* = 7.1 Hz), 0.76 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 149.5, 140.2, 136.5, 129.4, 129.1, 128.8, 127.5, 127.2, 126.9, 125.9, 125.2, 125.1, 121.5, 120.8, 94.7, 75.6, 52.3, 46.7, 29.8, 25.8, 24.0, 13.7, 12.4; HRMS (ESI) calc'd. for $C_{26}H_{29}{}^{35}Cl_3N_2NaO_3$ $[M+Na]^+$ 545.1141, found 545.1136.

(*S*)-2,2,2-trichloroethyl 3-(diethylcarbamoyl)-4-((*S*)-1-(4-methoxyphenyl)ethyl)quinoline -1(4*H*)-carboxylate (9d)



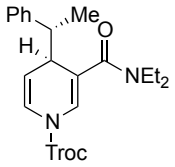
Using GP1: **8d** (74 mg, 64%); oil; dr >99:1; er 99:1; $[\alpha]_D$ +72 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2968, 2932, 1736, 1612, 1512, 1379, 1245, 1230, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1H, *J* = 8.0 Hz), 7.28-7.22 (m, 1H), 7.17 (td, 1H, *J* = 7.3, 1.3 Hz), 7.10 (dd, 1H, *J* = 7.5, 1.8 Hz), 7.03 (d, 1H, *J* = 0.6 Hz), 6.79 (d, 2H, *J* = 8.7 Hz), 6.64 (d, 2H, *J* = 8.7 Hz), 4.72 (br s, 1H), 4.61 (br s, 1H), 3.85 (d, 1H, *J* = 4.6 Hz), 3.72 (s, 3H), 3.50-3.29 (m, 5H), 1.27 (d, 3H, *J* = 7.2 Hz), 1.14 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.0, 149.8, 136.3, 134.0, 129.6, 129.2, 128.9, 127.3, 126.8, 125.2, 121.5, 120.7, 113.0, 94.8, 55.1, 47.9, 43.7, 41.6, 25.4, 18.0, 13.6; HRMS (ESI) calc'd. for $C_{26}H_{29}{}^{35}Cl_3N_2NaO_4$ $[M+Na]^+$ 561.1091, found 561.1112.

(*R*)-2,2,2-trichloroethyl 4-((*R*)-1-(4-chlorophenyl)ethyl)-3-(diethylcarbamoyl)quinoline-1(4*H*)-carboxylate (9e)



Using GP1: **9e** (102 mg, 87%); oil; dr 99:1; er 93:7; $[\alpha]_D$ +58 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2967, 2929, 1736, 1615, 1490, 1379, 1232, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* = 8.1 Hz), 7.30-7.12 (m, 3H), 7.05 (d, 1H, *J* = 8.5 Hz), 6.99 (s, 1H), 6.79 (d, 2H, *J* = 8.4 Hz), 4.75 (br s, 1H), 4.62 (br s, 1H), 3.76 (d, 1H, *J* = 3.9 Hz), 3.48-3.35 (m, 5H), 1.29 (d, 3H, *J* = 7.3 Hz), 1.14 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 149.6, 140.2, 136.4, 131.8, 129.9, 129.7, 127.9, 127.5, 127.2, 127.1, 125.3, 121.7, 120.2, 94.7, 75.7, 47.7, 43.5, 41.3, 29.8, 24.9, 18.1, 13.6; HRMS (ESI) calc'd. for $C_{25}H_{26}{}^{35}Cl_4N_2NaO_3$ $[M+Na]^+$ 565.0595, found 565.0611.

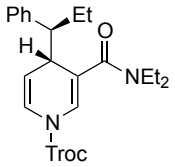
(*R*)-2,2,2-Trichloroethyl 3-(Diethylcarbamoyl)-4-((*R*)-1-phenylethyl)pyridine-1(4*H*)-carboxylate (10a)



Using GP2: **10a** (108 mg, 83%); oil; dr 94:6; er 98:2; $[\alpha]_D$ –16.3 (*c* 2.0, MeOH); IR ν_{max}(neat)/cm^{-1} 2971, 1732, 1687, 1616, 1265, 1102, 732; ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C) δ 7.25-7.12 (m, 5H), 6.88 (s, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 5.21 (dd, 1H, *J* = 8.0, 4.7 Hz), 4.94 (d, 1H, *J* = 12.4 Hz), 4.92 (d, 1H, *J* = 12.4 Hz), 3.66 (t, 1H, *J* = 5.0 Hz), 3.41-3.32 (m, 2H), 3.24-3.16 (m, 2H), 2.96-2.89 (m, 1H), 1.23 (d, 3H, *J* = 7.0 Hz), 1.09 (t, 6H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C) δ 168.0, 148.7, 142.7, 127.5, 127.2, 125.6, 122.8, 121.8, 116.8, 110.0, 94.6, 74.7, 43.9, 40.5, 40.0, 17.3, 12.6; *m/z* (ESI) 481 {M+Na$^+$ [$^{35}Cl_3$]}, 483 {M+Na$^+$ [$^{35}Cl_2{}^{37}Cl$]}, 485 {M+Na$^+$ [$^{35}Cl{}^{37}Cl_2$]}, 487 {M+Na$^+$ [$^{35}Cl{}^{37}Cl_3$]}; HRMS (ESI) calc'd. for $C_{21}H_{25}{}^{35}Cl_3N_2O_3Na$ [M+Na]$^+$ 481.0828, found 481.0822.

Chiral HPLC Chiralpak IC (250 x 4.6 mm) with Chiralpak IC Guard Cartridge (10 x 4 mm), 280 nm, hexane/2-propanol: 80/20, flow rate: 1 mL/min; t_R: major 27 min, minor 50 min.

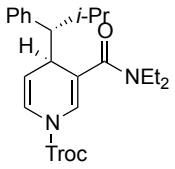
(*S*)-2,2,2-Trichloroethyl 3-(Diethylcarbamoyl)-4-((*S*)-1-phenylpropyl)pyridine-1(4*H*)-carboxylate (10b)



Using GP2: **10b** (115 mg, 87%), oil; dr 95:5; er 99:1; $[\alpha]_D{}^{31}$ +54.1 (*c* 0.6, MeOH); IR ν_{max}(neat)/cm^{-1} 2964 (C-H), 1732 (C=O), 1688 (C=C), 1615 (C=O), 1266 (NC=OO), 1128 (C-Cl), 702 (C-Cl); ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C) δ 7.25-7.13 (m, 5H), 6.81 (s, 1H), 6.75 (d, 1H, *J* = 8.2 Hz), 5.25 (dd, 1H, *J* = 8.2 , 7.7 Hz), 4.92 (d, 1H, *J* = 12.0 Hz), 4.90 (d, 1H, *J* = 12.0 Hz), 3.72 (t, 1H, *J* = 4.7 Hz, CH), 3.38-3.29 (m, 2H), 3.25-3.15 (m, 2H), 2.69-2.62 (m, 1H), 1.74-1.64 (m, 2H), 1.10 (t, 6H, *J* = 7.0 Hz), 0.73 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C) δ 167.9, 148.63, 140.9, 128.4, 127.1, 125.6, 122.7, 122.0, 116.8, 109.6, 94.6, 74.6, 51.5, 40.0, 39.1, 24.3, 12.6, 11.5; *m/z* (ESI) 495 {M+Na$^+$ [$^{35}Cl_3$]}, 497 {M+Na$^+$ [$^{35}Cl_2{}^{37}Cl$]}, 499 {M+Na$^+$ [$^{35}Cl{}^{37}Cl_2$]}, 501 {M+Na$^+$ [$^{35}Cl{}^{37}Cl_3$]}; HRMS (ESI) calc'd. for $C_{22}H_{27}{}^{35}Cl_3N_2O_3Na$ [M+Na]$^+$ 495.0984, found 495.0979.

Chiral HPLC Chiralpak IA column (250 x 4.6 mm) with Chiralpak IA Guard Cartridge (10 x 4 mm) , 280 nm, hexane/2-propanol: 90/10, flow rate: 0.7 mL/min; t_R: minor 18 min, major 42 min.

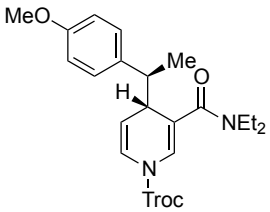
(*R*)-2,2,2-Trichloroethyl 3-(Diethylcarbamoyl)-4-((*R*)-2-methyl-1-phenylpropyl) pyridine-1(4*H*)-carboxylate (10c)



Using GP2: **10c** (104 mg, 76%), oil; dr 9:1; er 97:3; $[\alpha]_D$ –25.6 (*c* 0.6, MeOH); IR ν_{max}(neat)/cm^{-1} 2968, 1732, 1689, 1611, 1266, 1130, 732; ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C): δ 7.23-7.10 (m, 5H), 6.78 (d, 1H, *J* = 8.3 Hz), 6.72 (s, 1H), 5.39 (dd, 1H, *J* = 8.3, 4.7 Hz), 4.90 (d, 1H, *J* = 12.0 Hz), 4.88 (d, 1H, *J* = 12.0 Hz), 3.98 (t, 1H, *J* = 4.7 Hz), 3.29-3.20 (m, 2H), 3.20-3.11 (m, 2H), 2.42 (dd, 1H, *J* = 10.0, 4.7 Hz), 2.11-2.02 (m, 1H), 1.10 (t, 6H, *J* = 7.0 Hz), 1.03 (d, 3H, *J* = 6.6 Hz), 0.61 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C) δ 167.5, 148.5, 140.6, 129.0, 126.9, 125.6, 122.8, 122.5, 116.8, 109.1, 94.6, 74.6, 56.1, 39.8, 36.2, 27.8, 20.9, 20.4, 12.6; *m/z* (ESI) 487 {M+H$^+$ [$^{35}Cl_3$]}, 489 {M+H$^+$ [$^{35}Cl_2{}^{37}Cl$]}, 491 {M+H$^+$ [$^{35}Cl{}^{37}Cl_2$]}, 493 {M+H$^+$ [$^{35}Cl{}^{37}Cl_3$]}; HRMS (ESI) calc'd. for $C_{23}H_{30}{}^{35}Cl_3N_2O_3$ [M+H]$^+$ 487.1322, found 487.1316.

Chiral HPLC Chiralpak IC (250 x 4.6 mm) coulmn with Chiralpak IC Guard Cartridge (10 x 4 mm), 280 nm, hexane/2-propanol: 85/15, flow rate: 0.7 mL/min; t_R: major 31 min, minor 67 min.

(*S*)-2,2,2-trichloroethyl 3-(diethylcarbamoyl)-4-((*S*)-1-(4-methoxyphenyl)ethyl)pyridine-1(4*H*)-carboxylate (10d)

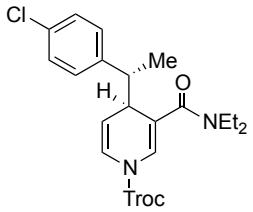


Using GP2: **10d** (110 mg, 80%), oil; dr 97:3; er 99:1; $[\alpha]_D$ +29.3 (*c* 0.7, MeOH); IR ν_{max}(neat)/cm^{-1} 2965, 1731, 1687, 1611, 1512, 1266, 1247, 1036, 1173, 1128, 713; ^{1}H NMR (500 MHz; DMSO-d_6, 90 °C): δ 7.11 (d, 2H, *J* = 8.3 Hz), 6.87 (s, 1H), 6.79 (d, 2H, *J* = 8.3 Hz), 6.76 (d, 1H, *J* = 8.3 Hz), 5.21 (dd, 1H, *J* = 8.3, 4.7 Hz), 4.94 (d, 1H, *J* = 12.0 Hz), 4.92

(d, 1H, J = 12.0 Hz), 3.71 (s, 3H), 3.61 (t, 1H, J = 4.7 Hz), 3.42-3.33 (m, 2H), 3.25-3.16 (m, 2H), 2.91-2.84 (m, 1H), 1.21 (d, 3H, J = 7.0 Hz), 1.09 (t, 6H, J = 7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C): δ 168.0, 157.4, 148.6, 134.6, 128.5, 122.7, 121.8, 116.9, 112.9, 110.1, 94.6, 74.6, 54.6, 43.0, 40.6, 40.0, 17.4, 12.6; *m/z* (ESI) 511 {M+Na$^+$ [$^{35}Cl_3$]}, 513 {M+Na$^+$ [$^{35}Cl_2{}^{37}Cl$]}, 515 {M+Na$^+$ [$^{35}Cl{}^{37}Cl_2$]}, 517 {M+Na$^+$ [$^{37}Cl_3$}; HRMS (ESI) calc'd. for $C_{22}H_{27}{}^{35}Cl_3N_2O_4Na$ [M+Na]$^+$ 511.0934, found 511.0928.

Chiral HPLC Chiralpak IA (250 x 4.6 mm) with Chiralpak IA Guard Cartridge (10 x 4 mm), 250 nm, hexane/2-propanol: 85/15, flow rate: 0.7 mL/min; t_R: minor 25 min, major 37 min.

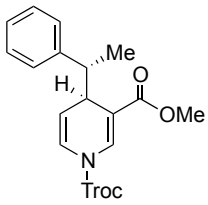
(*S*)-2,2,2-Trichloroethyl 4-((*S*)-1-(4-Chlorophenyl)ethyl)-3-(diethylcarbamoyl)pyridine-1(4*H*)-carboxylate (10e)



Using GP2: **10e** (130 mg, 94%), oil; dr 97:3; er 93:7; $[\alpha]_D$ 14.6 (*c* 0.3, MeOH); IR ν_{max}(neat)/cm^{-1} 2970, 1732, 1686, 1614, 1265, 1013, 729; ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C) δ 7.24 (d, 2H, J = 8.6 Hz), 7.22 (d, 2H, J = 8.6 Hz), 6.87 (s, 1H), 6.77 (d, 1H, J = 8.2 Hz), 5.23 (dd, 1H, J = 8.2, 4.7 Hz), 4.93 (d, 1H, J = 12.0 Hz), 4.92 (d, 1H, J = 12.0 Hz), 3.62 (t, 1H, J = 4.7 Hz), 3.41-3.32 (m, 2H), 3.26-3.16 (m, 2H), 3.00-2.93 (m, 1H), 1.23 (d, 3H, J = 7.0 Hz), 1.08 (t, 6H, J = 7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C) δ 167.9, 148.6, 141.3, 130.4, 129.5, 127.0, 123.0, 122.2, 116.5, 109.4, 94.6, 74.6, 42.9, 40.6, 40.1, 16.7, 12.6; *m/z* (ESI) 515 {M+Na$^+$ [$^{35}Cl_3$]}, 517 {M+Na$^+$ [$^{35}Cl_2{}^{37}Cl$]}, 519 {M+Na$^+$ [$^{35}Cl{}^{37}Cl_2$]}, 521 {M+Na$^+$ [$^{37}Cl_3$}; HRMS (ESI) calc'd. for $C_{21}H_{24}{}^{35}Cl_4N_2NaO_4$ [M+Na]$^+$ 515.0438, found 515.0433.

Chiral SFC Chiralpak IC, 125 bar, 40 °C, 4 mL/min, 10% co-solvent (MeOH), t_R: major 6.6 min, minor 10.6 min.

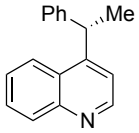
(*R*)-3-Methyl 1-(2,2,2-Trichloroethyl)-4-((*R*)-1-phenylethyl)pyridine-1,3(4*H*)-dicarboxylate (11a)



Using GP2: **11a** (97 mg, 83%), oil; dr 89:11; er 95:5; $[\alpha]_D$ –133.0 (*c* 1, MeOH); IR ν_{max}(neat)/cm^{-1} 2971, 2901, 1742, 1704, 1402, 1057, 1066, 700; ^{1}H NMR (500 MHz; DMSO-d_6, 70 °C) δ 7.60 (s, 1H), 7.21-7.02 (m, 5H), 6.72 (d, 1H, *J* = 8 Hz), 5.37 (dd, 1H, *J* = 8.0, 5.0 Hz), 4.90 (1H, d, J = 12.4 Hz), 4.95 (d, 2H, *J* = 12.4 Hz), 3.70 (s, 3H), 3.57 (t, 1H, *J* = 5.0 Hz), 3.09-3.01 (m, 1H), 1.27 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 70 °C) δ 166.1, 148.9, 141.9, 131.8, 127.8, 127.0, 125.8, 122.4, 111.8, 109.8, 94.5, 74.7, 51.2, 43.4, 38.4, 16.5.

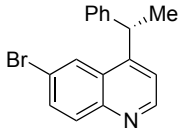
Chiral HPLC Chiralpak IA (250 x 4.6 mm) with Chiralpak IA Guard Cartridge (10 x 4 mm), 280 nm, hexane/2-propanol: 95/5, flow rate: 0.5 mL/min, 0°C; t_R: major 31 min, minor 61 min.

(*S*)-4-(1-Phenylethyl)quinoline (14)



Using GP1: **14** (25 mg, 50%); oil; er 95:5; $[\alpha]_D$ –20 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2969, 1457, 1378, 1128, 950; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (br s, 1H), 8.14 (br d, 1H, *J* = 5.5 Hz), 8.07 (br d, 1H, *J* = 4.4 Hz), 7.65 (t, 1H, *J* = 5.9 Hz), 7.46 (t, 1H, *J* = 7.6 Hz), 7.34-7.16 (m, 6H), 4.89 (q, 1H, *J* = 7.1 Hz), 1.75 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 144.9, 129.0, 128.8, 126.6, 124.0, 40.3, 22.0; HRMS (ESI) calc'd. for $C_{17}H_{16}N$ $[M+H]^+$ 234.1283, found 234.1228.

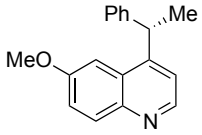
(*S*)-6-bromo-4-(1-phenylethyl)quinoline (15)



Using GP1: **15** (65 mg, 33%); oil; er 95:5; $[\alpha]_D$ –135 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2917, 2849, 1588, 1490, 844, 824, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, 1H, *J* = 4.5

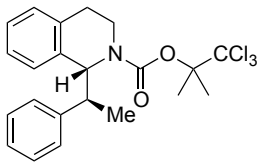
Hz), 8.19 (d, 1H, *J* = 2.1 Hz), 7.96 (d, 1H, *J* = 8.9 Hz), 7.70 (dd, 1H, *J* = 8.9, 2.1 Hz), 7.32-7.19 (m, 7H), 4.80 (q, 1H, *J* = 7.1 Hz), 1.73 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 150.7, 147.1, 144.2, 132.5, 132.1, 128.9, 127.6, 126.9, 126.3, 120.0, 40.2, 21.9; HRMS (ESI) calc'd. for $C_{17}H_{15}BrN$ $[M+H]^+$ 312.0310, found 312.0279.

(*S*)-6-Methoxy-4-(1-phenylethyl)quinoline (16)



Using GP1: **16** (70 mg, 42%); oil; er 94:6; $[\alpha]_D$ –81 (*c* 1.0, CH_2Cl_2); IR ν_{max}(neat)/cm^{-1} 2968, 1620, 1506, 1226, 1028, 854, 828, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, 1H, J = 4.5 Hz), 7.99 (d, 1H, J = 9.2 Hz), 7.32-7.17 (m, 8H), 4.75 (q, 1H, J = 7.1 Hz), 3.76 (s, 3H), 1.75 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 147.9, 131.7, 128.8, 127.6, 126.6, 121.3, 119.4, 102.4, 55.4, 40.9, 21.9; HRMS (ESI) calc'd. for $C_{18}H_{18}NO$ $[M+H]^+$ 264.1388, found 264.1302.

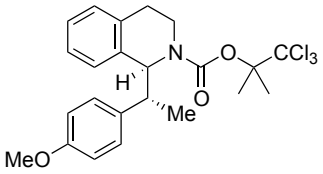
(*R*)-1,1,1-trichloro-2-methylpropan-2-yl 1-((*S*)-1-phenylethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (19a)



Using GP4: **19a** (132 mg, 70%), amorphous solid; dr 93:7; er 94:6; m.p. 86-88 °C; $[\alpha]_D$ −21.8 (*c* 0.9, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3027, 1699, 1367, 1158; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers and diastereomers) δ 7.31-7.16 (m, 4H), 7.14-6.95 (m, 4H), 6.86 (m, 1H), 5.27-5.16 (t, 1H, *J* 9.3 Hz), 3.95 (dt, 0.5H, *J* 13.0, 6.5 Hz), 3.83 (ddd, 0.5H, *J* 13.3, 7.7, 6.0 Hz), 3.61 (dt, 0.5H, *J* 12.7, 6.3 Hz), 3.45 (ddd, 0.5H, *J* 13.3, 7.8, 5.8 Hz), 3.19 (dq, 0.5H, *J* 9.0, 7.1 Hz), 3.13 (dq, 0.5H, *J* 9.0, 7.1 Hz), 2.79 (m, 1H), 2.47 (m, 1H), 2.07 (s, 1.5H), 2.01 (s, 1.5H), 1.93 (s, 1.5H), 1.92 (s, 1.5H), 1.40 (d, 3H, *J* 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers and diastereomers) δ 153.8, 153.3, 143.7, 143.4, 135.7, 135.4, 134.4, 134.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 126.9, 126.7, 125.2, 124.9, 61.2, 60.9, 45.9, 45.8, 40.6, 38.9, 27.9, 27.3, 22.0, 21.8, 21.6, 18.7, 18.6 ; HRMS (EI$^+$) calc'd for $C_{22}H_{24}O_2N^{35}Cl_3$ $[M+H]^+$ 440.0951, found 440.0955.

Chiral Supercritical Fluid Chromatography ((S,S)-Whelk-01, 5/100 Kromasil, 25 cm × 4.6 mm I.D.), 125 bar CO_2, 40 °C, 4 mL/min, 50% co-solvent (IPA)); t_R: 5.02 min (major diastereomer, minor enantiomer), 5.91 min (major diastereomer, major enantiomer), 7.35 min (minor diastereomer, both enantiomers). Chiral Supercritical Fluid Chromatography ChiralPak IA, 125 bar CO_2, 40 °C, 4 mL/min, 50% co-solvent (IPA)); t_R: 4.89 min (major diastereomer, both enantiomers), 6.64 min (minor diastereomer, major enantiomer), 6.84 min (minor diastereomer, minor enantiomer).

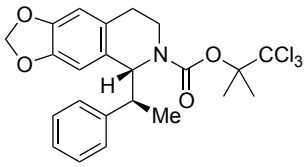
(*S*)-1,1,1-Trichloro-2-methylpropan-2-yl-(*R*)-1-(4-methoxyphenyl)ethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (19b)



Using GP4: **19b** (113 mg, 66%), oil; dr 87:13; er major 96:4; m.p. 86–88 °C; $[\alpha]_D$ +19.5 (*c* 0.8, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 2921, 1705, 1369, 1160; ^{1}H NMR (300 MHz, $CDCl_3$, rotamers and diastereomers) δ 7.25–7.02 (m, 3H), 6.94–6.73 (m, 5H), 6.41–6.34 (m, 0.5H), 6.28–6.24 (dd, 0.5H, *J* 7.7, 1.4 Hz), 5.17 (d, 0.5H, *J* 8.7 Hz), 5.14 (d, 0.5H, *J* 8.7 Hz), 3.92 (dt, 0.5H, *J* 13.0, 6.2 Hz), 3.79 (m, 0.5H), 3.80 (s, 1.5H), 3.79 (s, 1.5H), 3.59 (ddd, 0.5H, *J* 12.8, 6.7, 5.8 Hz), 3.53–3.38 (m, 0.5H), 3.12 (m, 1H), 2.86 (m, 1H), 2.45 (dt, 0.5H, *J* 13.0, 6.2 Hz), 2.44 (dt, 0.5H, *J* 13.0, 6.2 Hz), 2.06 (s, 1.5H), 2.01 (s, 1.5H), 1.92 (s, 1.5H), 1.91 (s, 1.5H), 1.36 (d, 3H, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers and diastereomers) δ 158.5, 158.4, 153.9, 153.4, 135.8, 135.8, 135.5, 135.5, 134.5, 134.3, 129.6, 129.5, 129.1, 128.5, 128.4, 128.1, 127.0, 126.9, 125.3, 125.1, 113.7, 113.7, 107.2, 107.0, 89.0, 88.5, 61.5, 61.1, 55.3, 45.0, 45.0, 40.7, 39.1, 28.0, 27.5, 22.1, 21.9, 21.8, 21.7, 19.0, 18.9; HRMS (EI^+) calcd for $C_{23}H_{26}{}^{35}Cl_3NO_3$ requires 470.1057 $[M+H]^+$, found 470.1063.

Chiral Supercritical Fluid Chromatography ((S,S)-Whelk-01, 5/100 Kromasil, 25 cm × 4.6 mm I.D.), 125 bar CO_2, 40 °C, 4 mL/min, 50% co-solvent (IPA)); t_R: 8.02 min (major diastereomer, major enantiomer), 9.32 min (major diastereomer, minor enantiomer), 12.43 min (minor diastereomer, major enantiomer).

(*R*)-1,1,1-Trichloro-2-methylpropan-2-yl 5-((*S*)-1-Phenylethyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-carboxylate (21a)

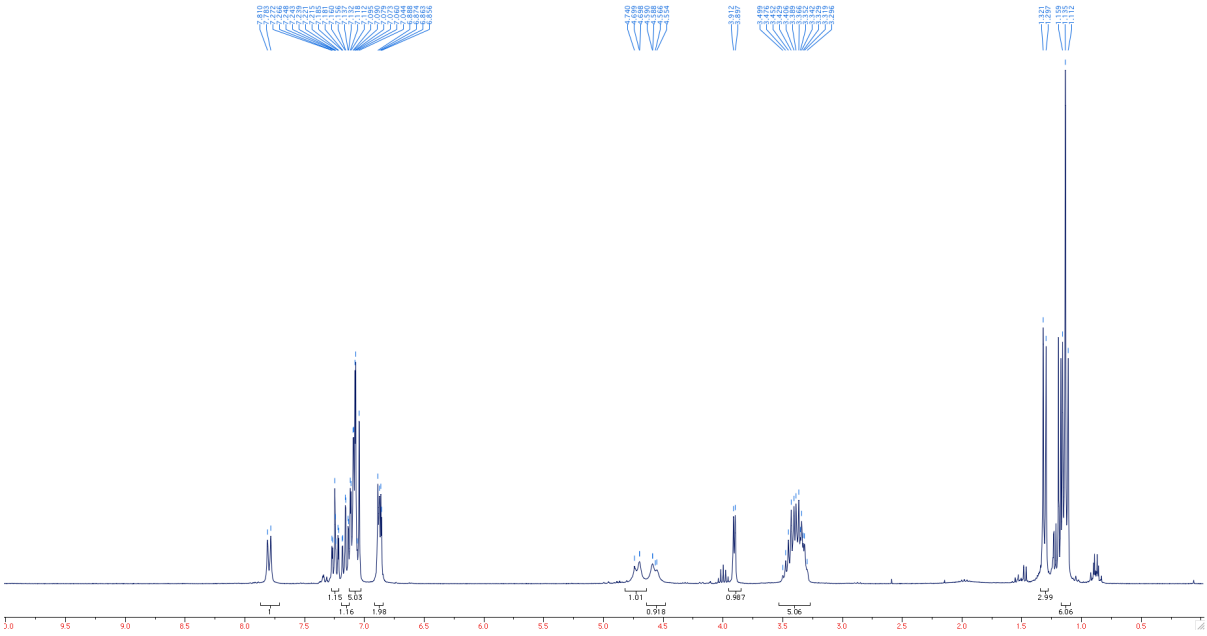


Using GP4: **21a** (93 mg, 80%), oil; dr 97:3; er major 93:7; $[\alpha]_D$ –19.6 (*c* 0.9, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 2920, 1702, 1485, 1162; ^1H NMR (300 MHz, $CDCl_3$, rotamers and diastereomers) δ 7.25-7.21 (m, 3H), 7.03 (ddd, 2H, *J* = 7.3, 5.6, 2.0 Hz), 6.52 (s, 1H), 5.85 (d, 0.5H, *J* = 4.8 Hz), 5.85 (d, 0.5H, *J* = 4.8 Hz), 5.80 (d, 0.5H, *J* = 4.8 Hz), 5.80 (d, 0.5H, *J* = 4.8 Hz), 5.11 (d, 0.5H, *J* = 9.1 Hz), 5.09 (d, 0.5H, *J* = 9.1 Hz), 3.90 (dt, 0.5H, *J* = 13.0, 6.5 Hz), 3.78 (ddd, 0.5H, *J* = 13.1, 7.6, 6.0 Hz), 3.54 (dt, 0.5H, *J* = 12.8, 6.5 Hz), 3.38 (d, 0.5H, *J* = 6.6 Hz), 3.39 (m, 0.5H), 3.14 (ddd, 1H, *J* = 12.7, 8.4, 6.5 Hz), 2.68 (m, 1H), 2.34 (m, 1H), 2.05 (s, 1.5H), 2.00 (s, 1.5H), 1.93 (s, 1.5H), 1.91 (s, 1.5H), 1.37 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers and diastereomers) δ 153.8, 153.3, 146.4, 146.3, 145.0, 144.8, 143.7, 143.4, 129.6, 128.9, 128.6, 128.5, 128.3, 128.3, 127.9, 127.7, 127.5, 126.9, 126.8, 115.3, 108.6, 108.4, 108.3, 108.1, 100.7, 89.1, 88.7, 61.3, 60.9, 46.0, 45.9, 40.5, 38.9, 27.9, 27.3, 22.0, 21.8, 21.6, 21.6, 18.8, 18.7; HRMS (EI^+) calcd for $C_{23}H_{24}{}^{35}Cl_3NO_4$ requires 484.0849 $[M+H]^+$, found 484.0844.

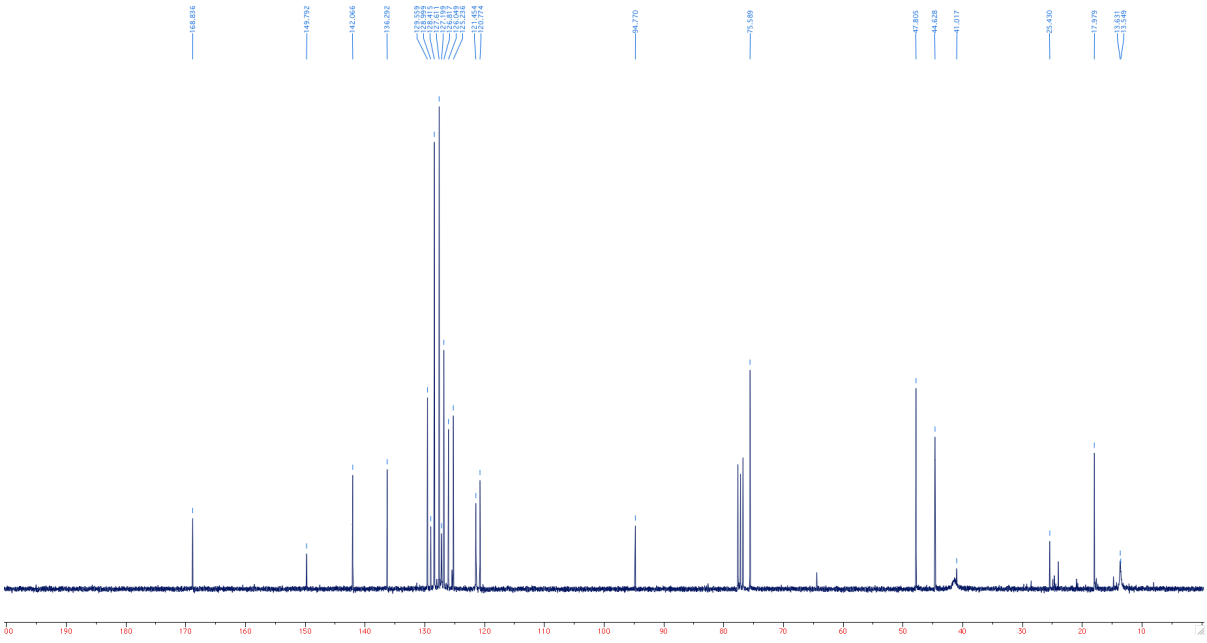
6. ^{1}H, and ^{13}C Spectra

9a

^{1}H NMR

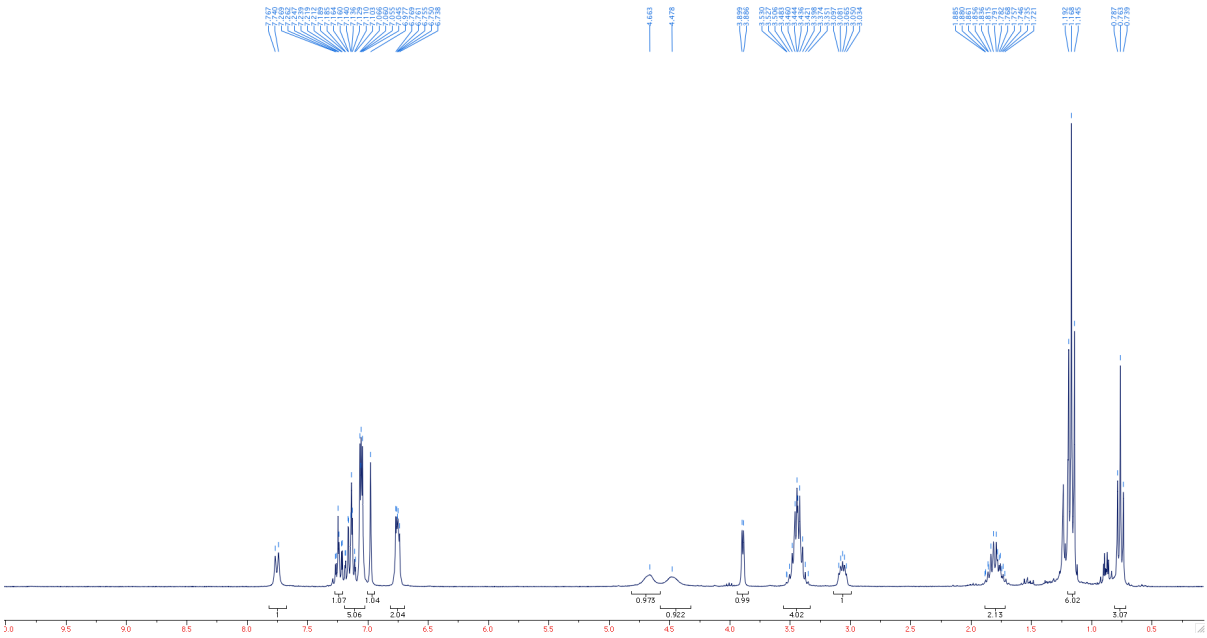


^{13}C NMR

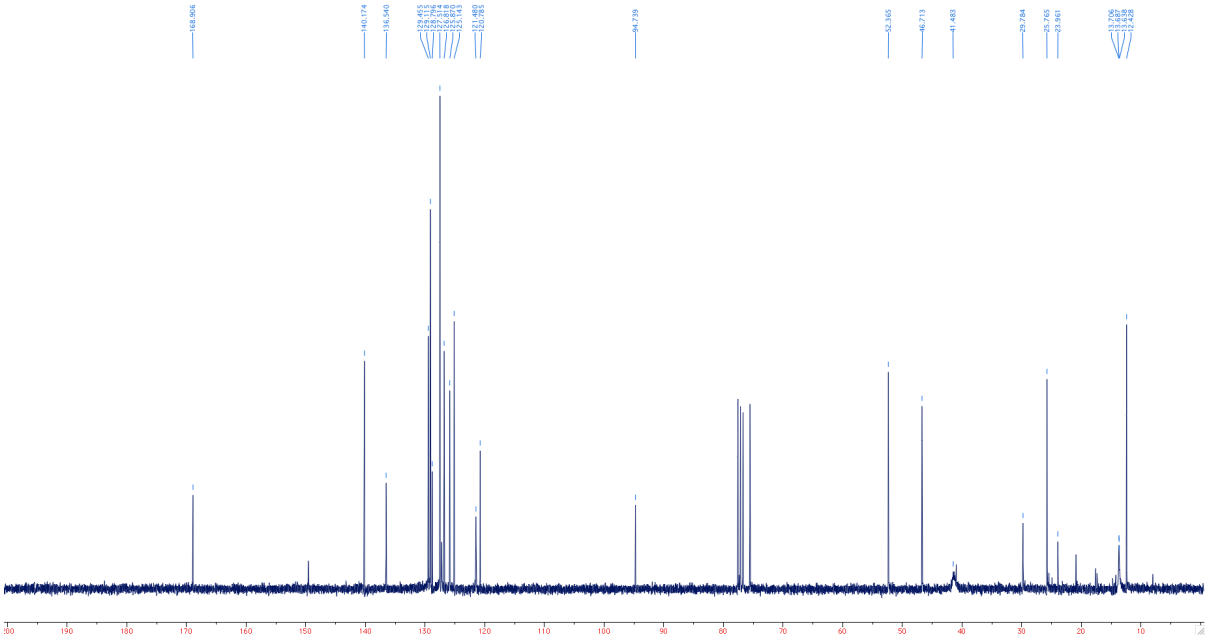


9b

^{1}H NMR

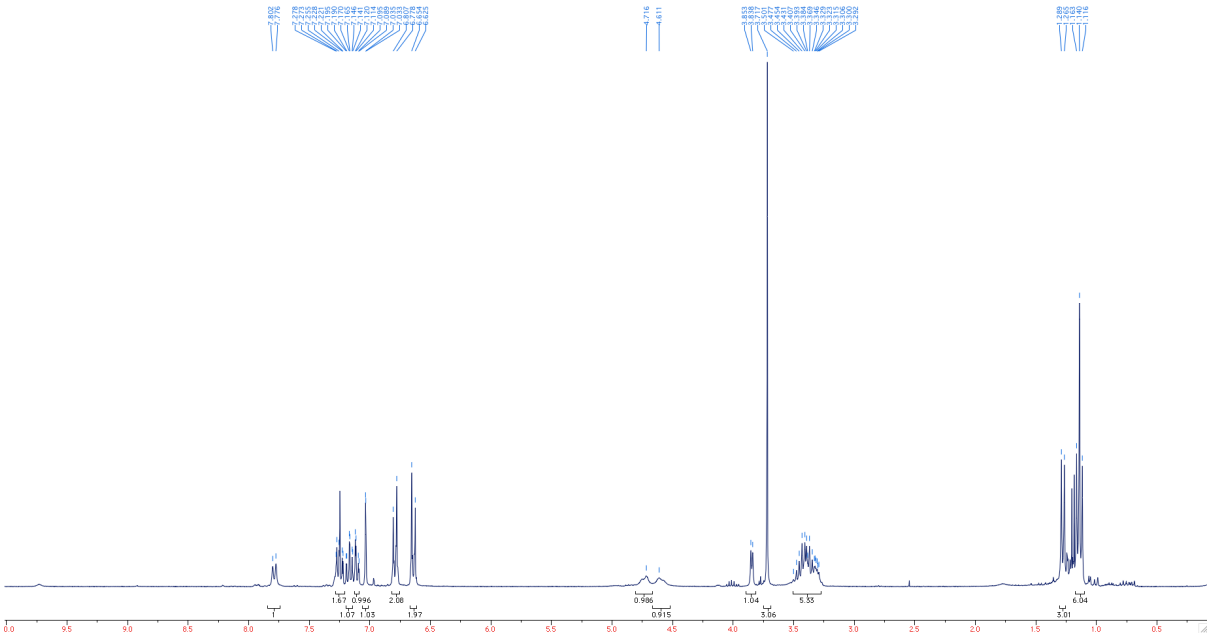


^{13}C NMR

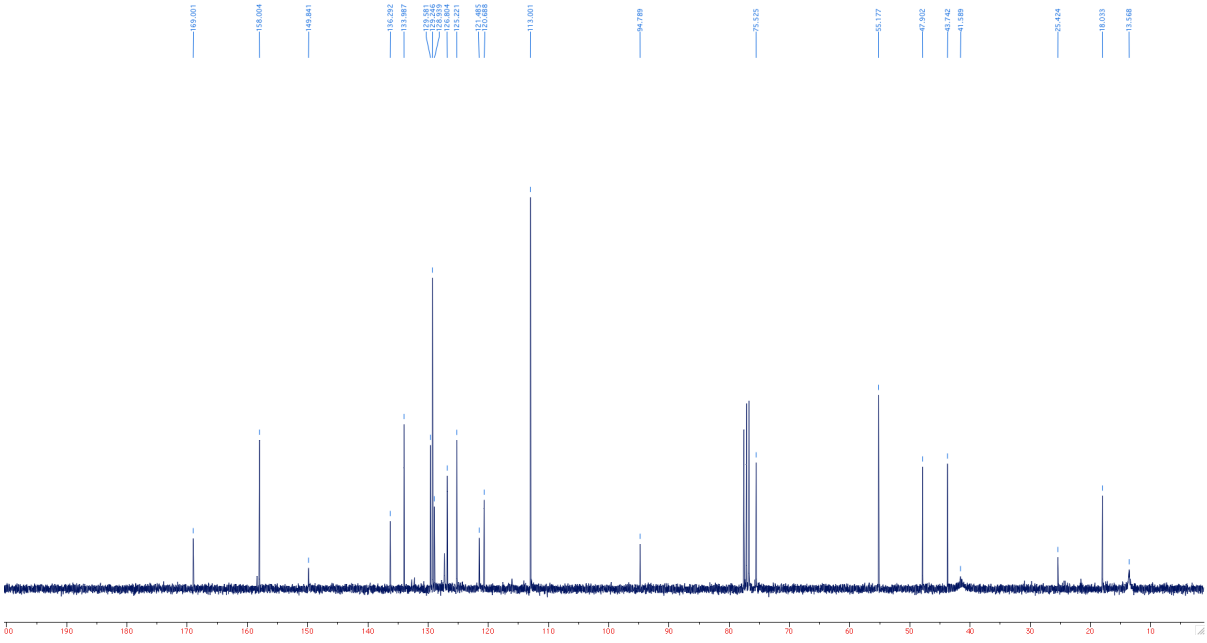


9d

^{1}H NMR

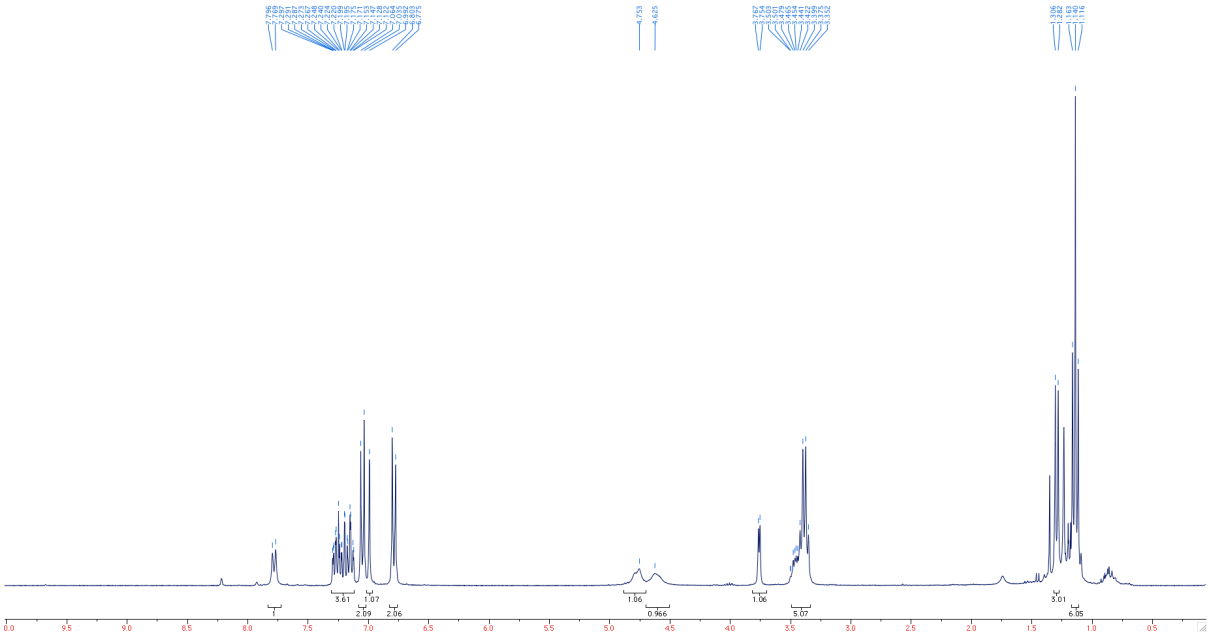


^{13}C NMR

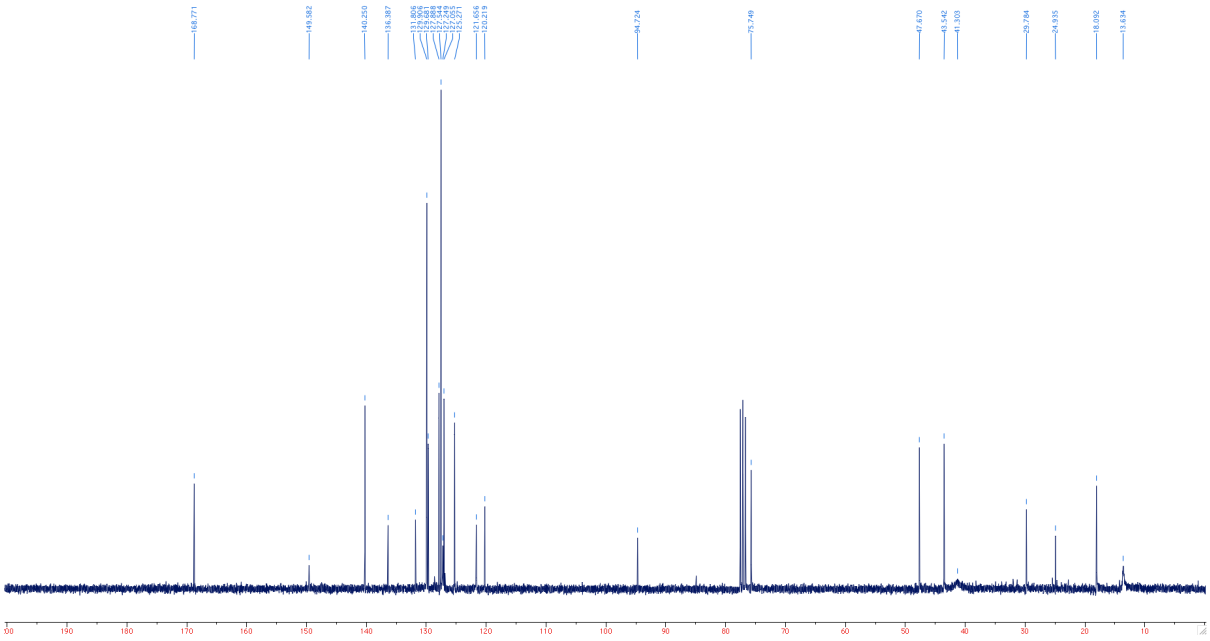


9e

^{1}H NMR

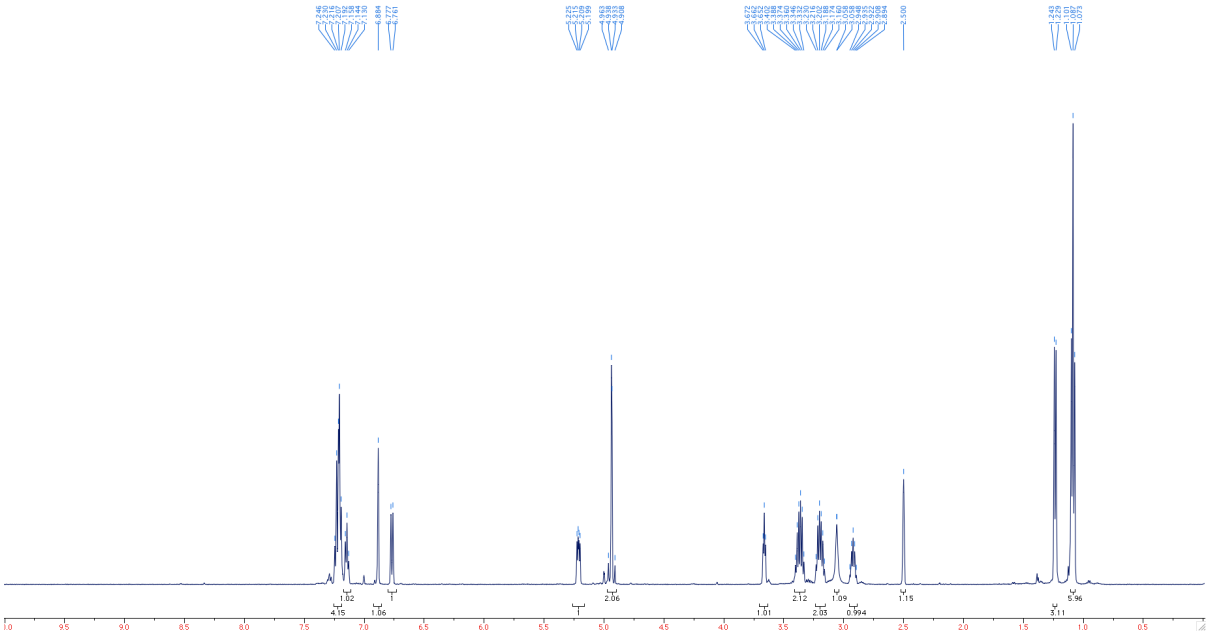


^{13}C NMR

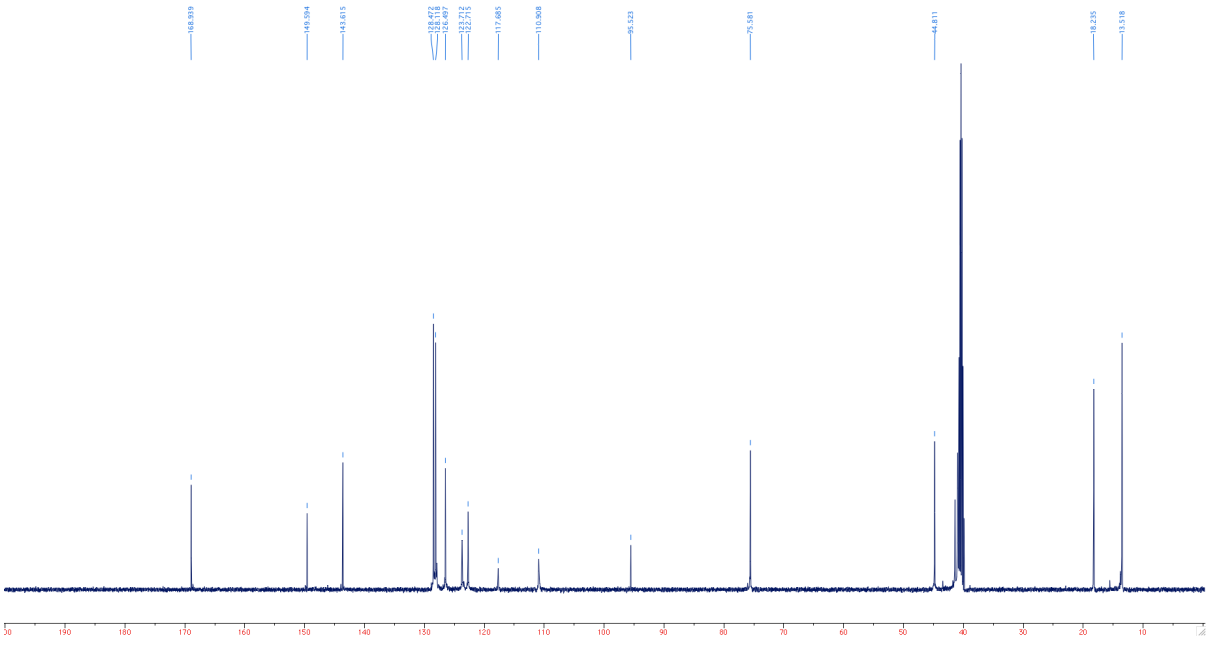


10a

^{1}H NMR

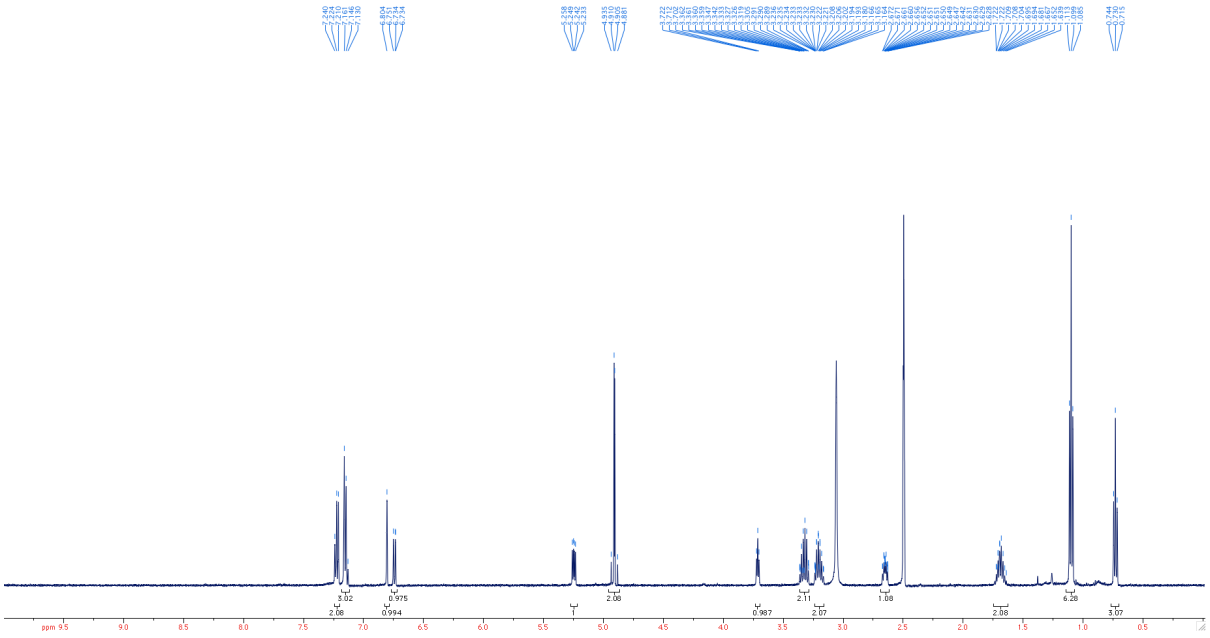


^{13}C NMR

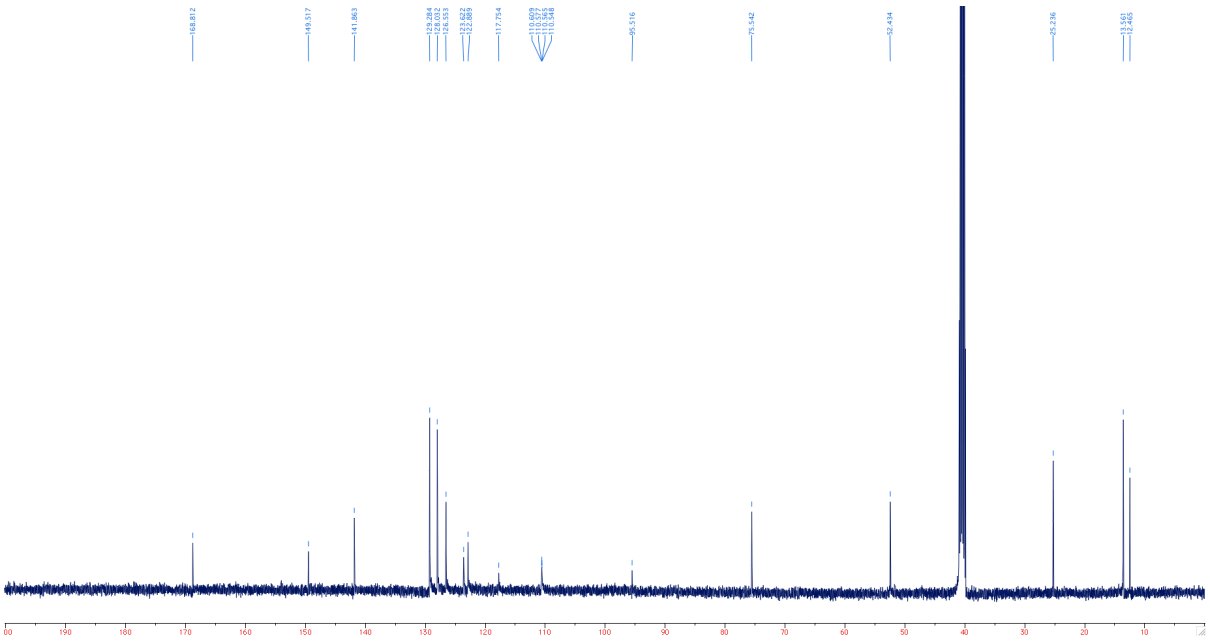


10b

^{1}H NMR

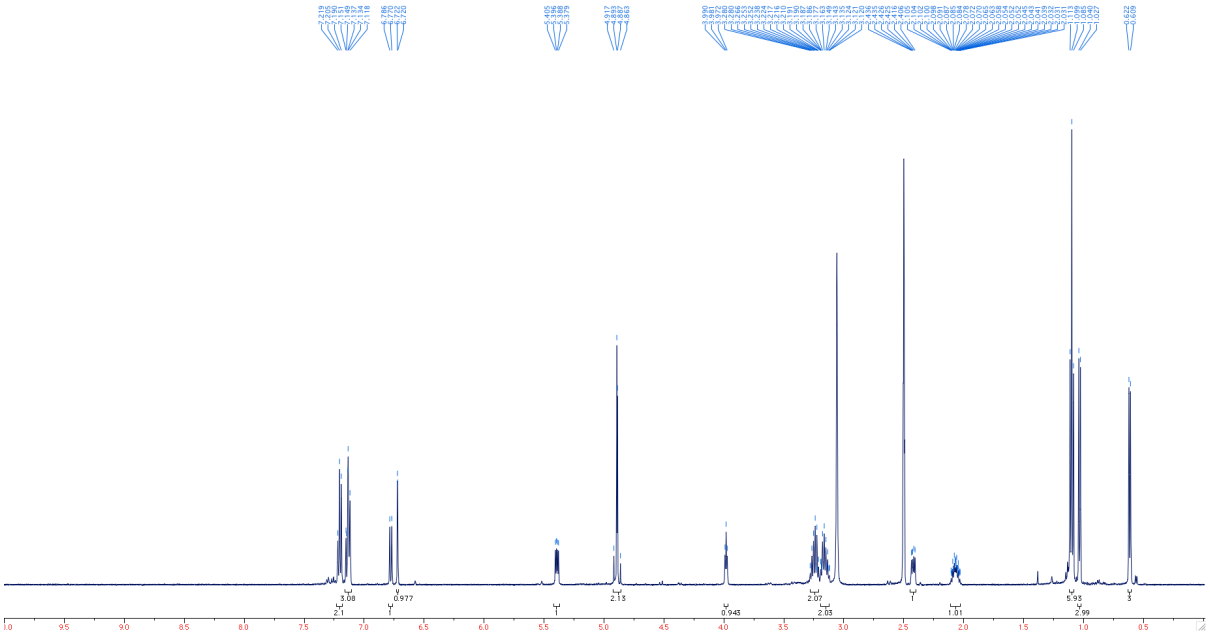


^{13}C NMR

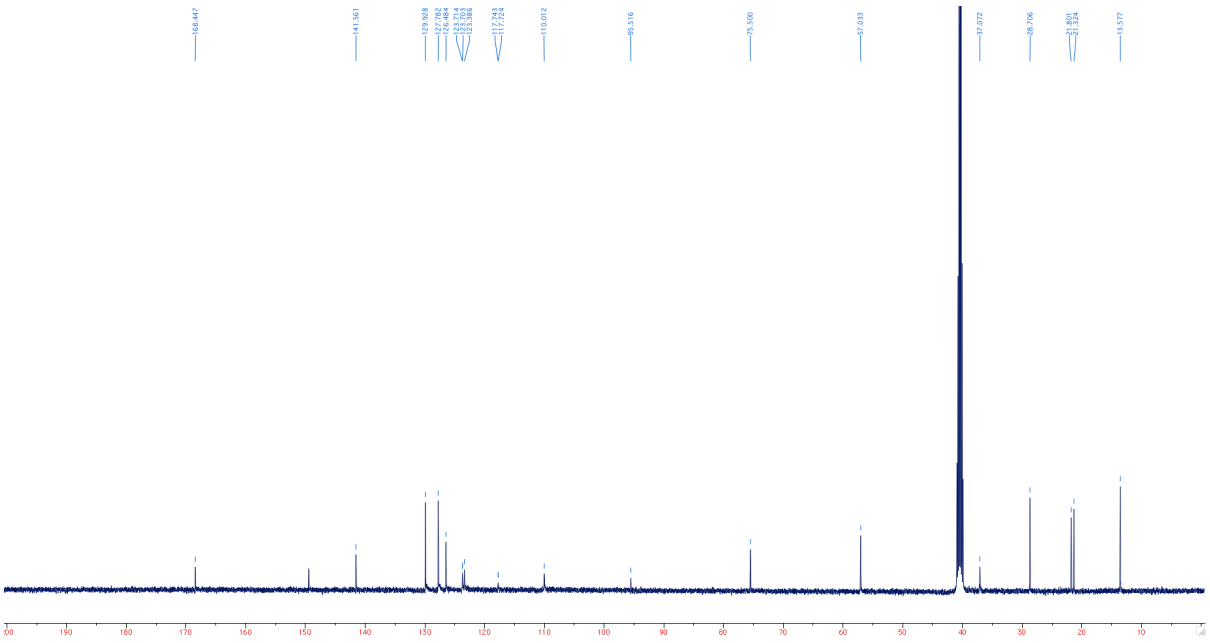


10c

^{1}H NMR

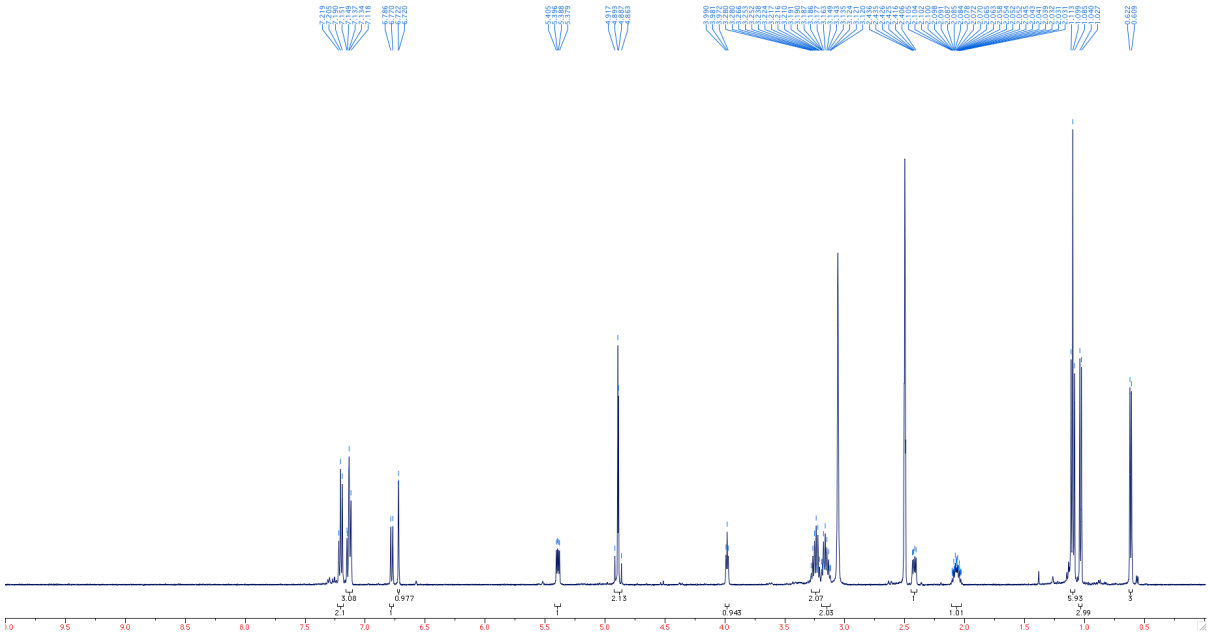


^{13}C NMR

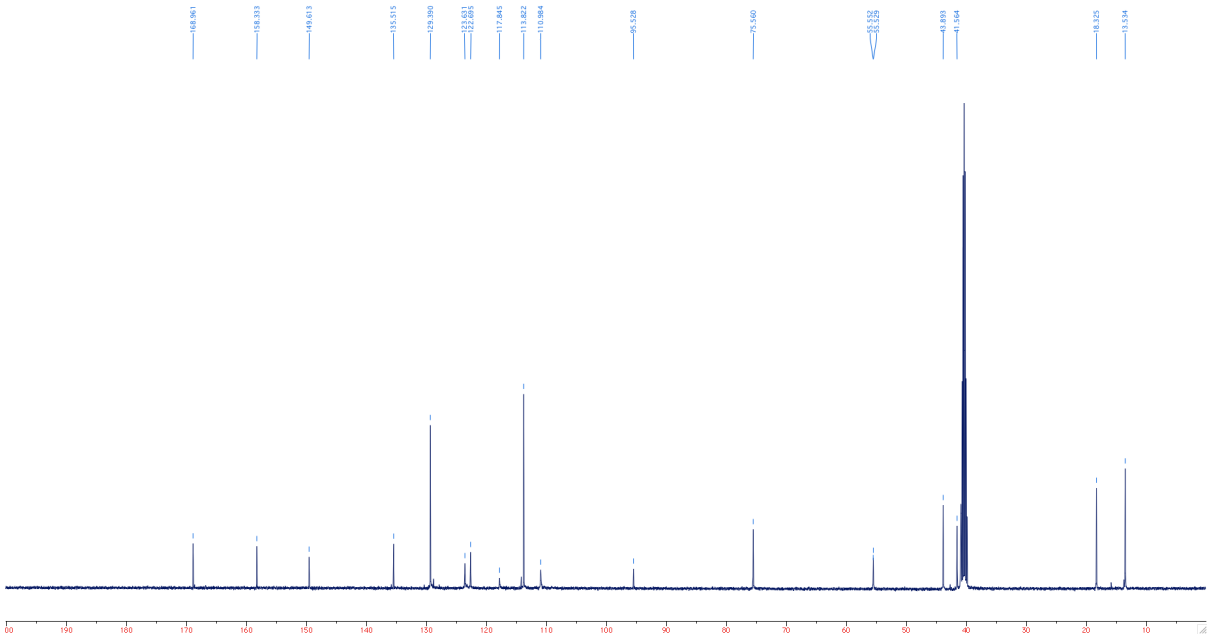


10d

^{1}H NMR

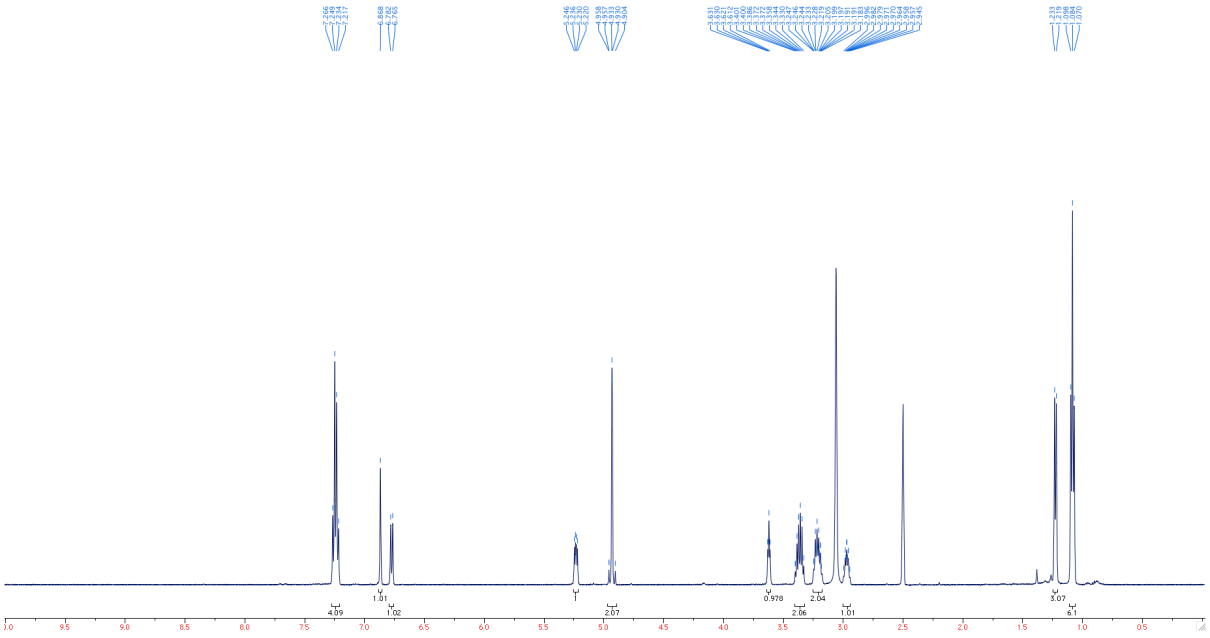


^{13}C NMR

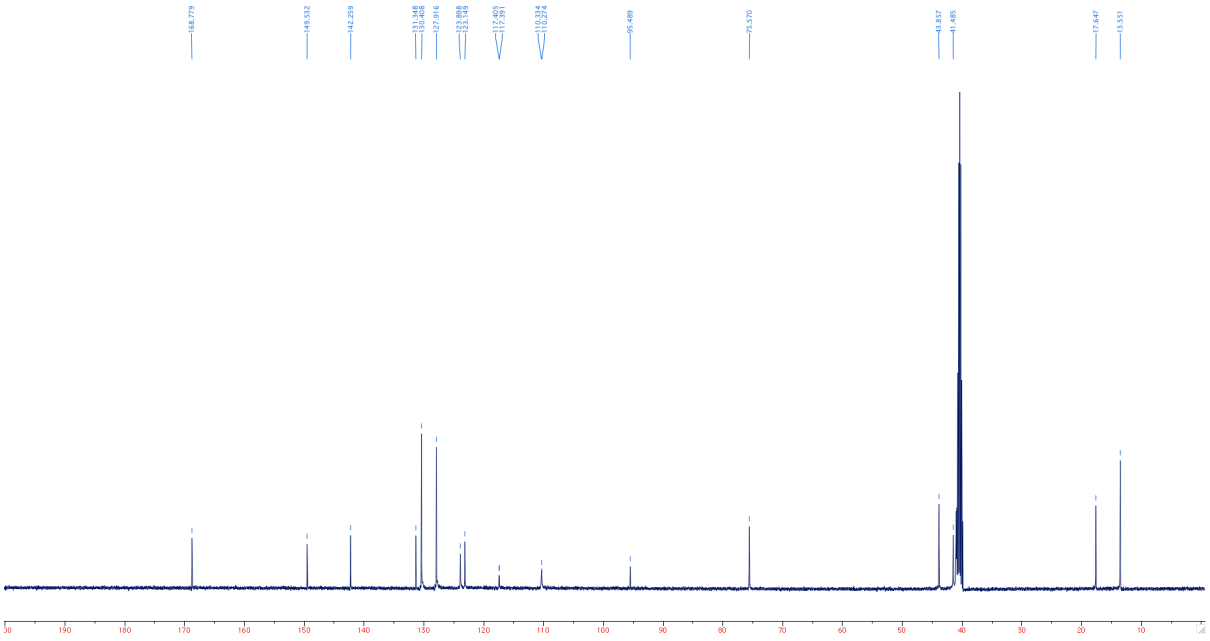


10e

^{1}H NMR

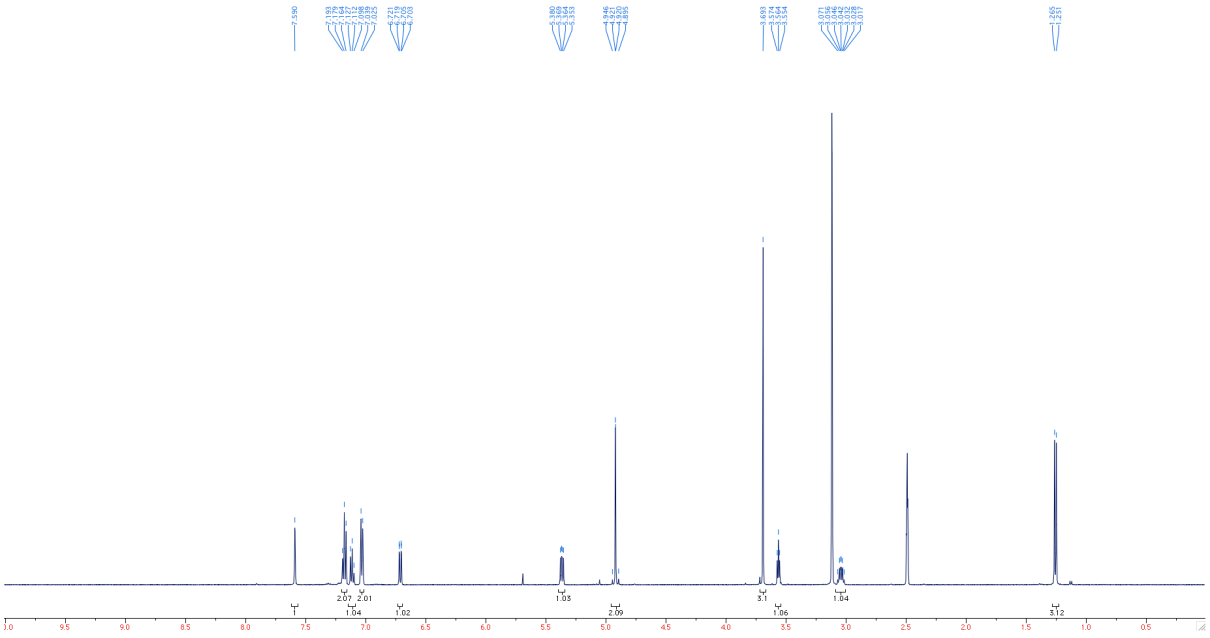


^{13}C NMR

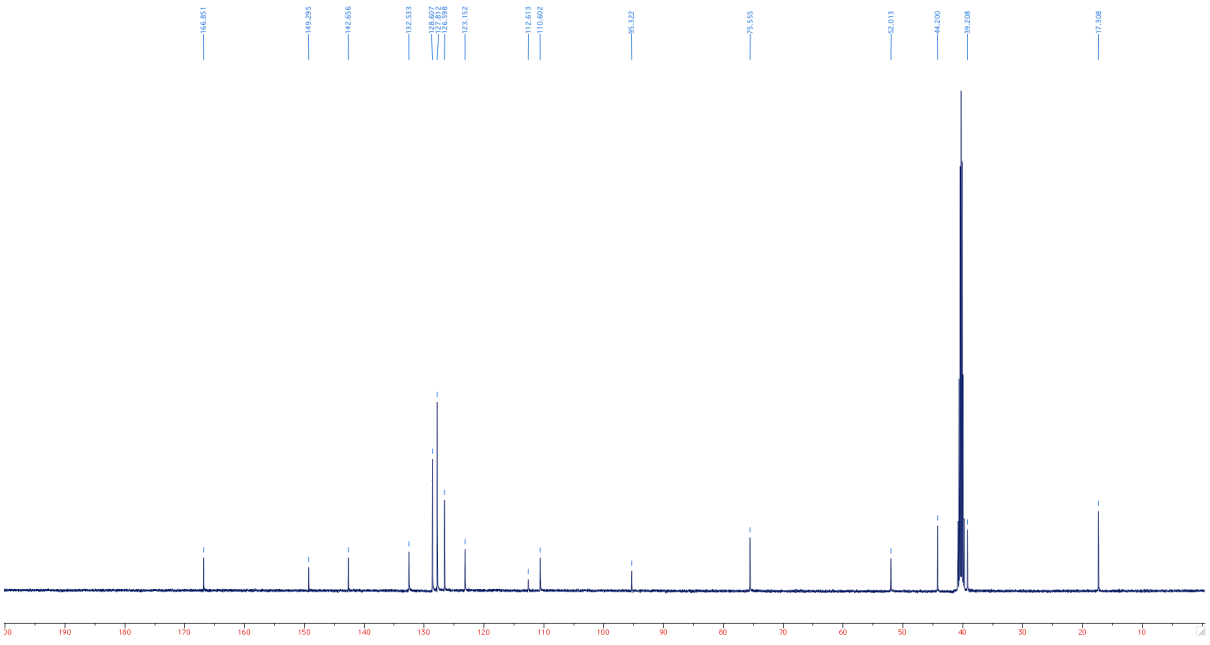


11a

^{1}H NMR

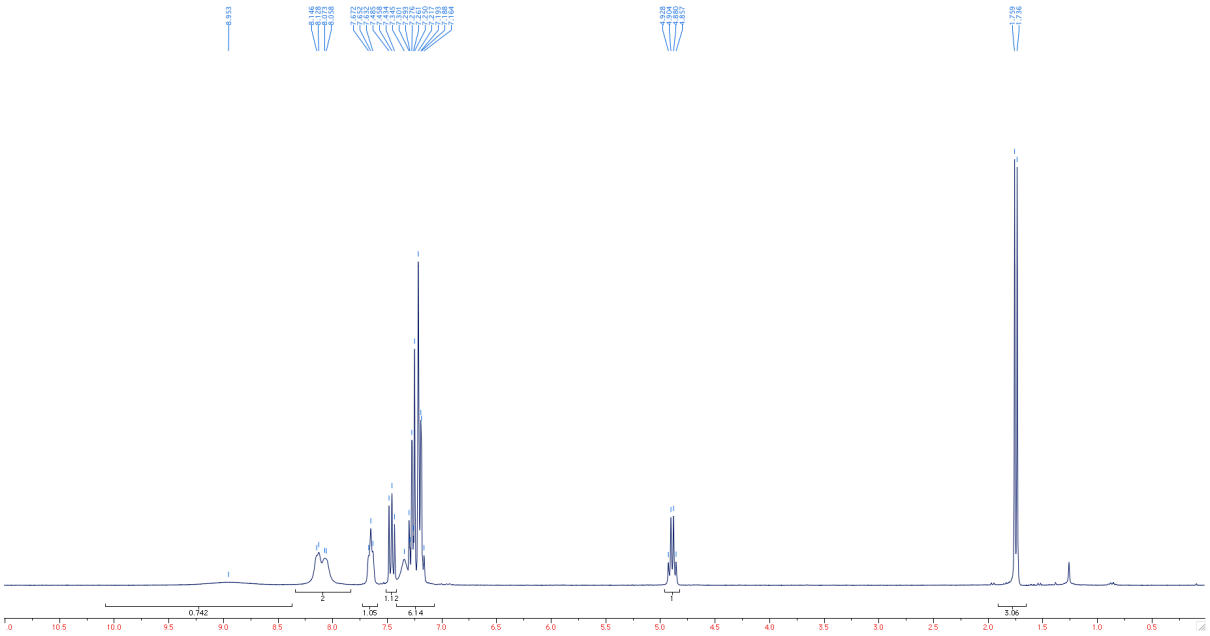


^{13}C NMR

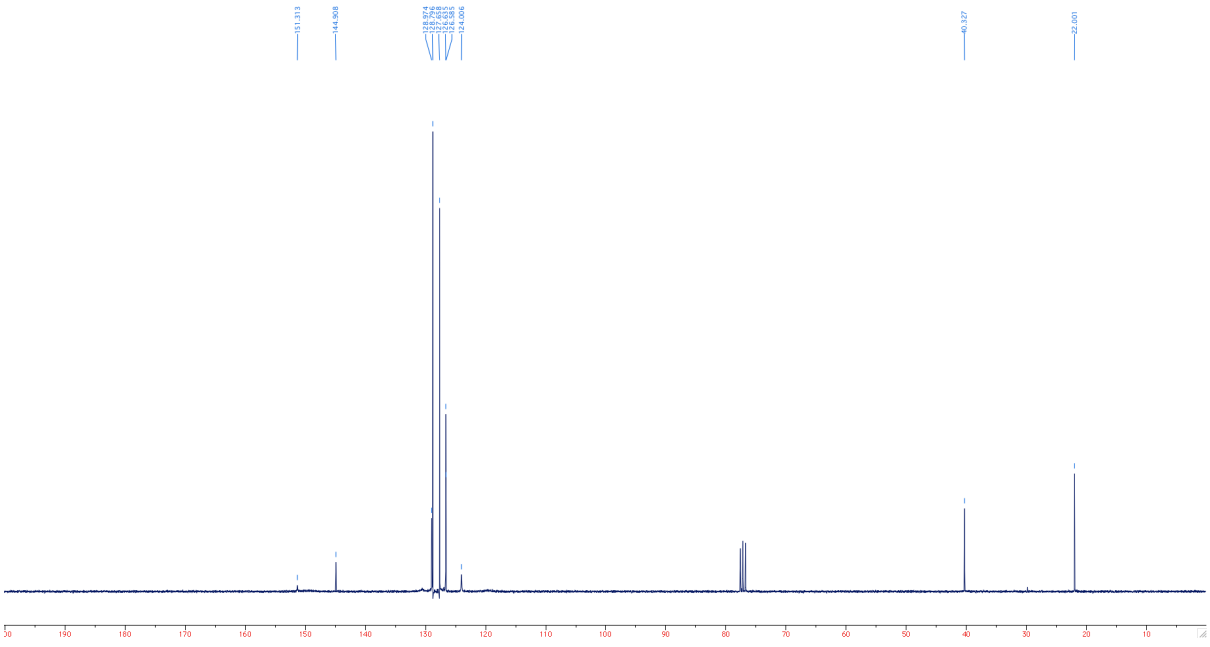


14

^{1}H NMR

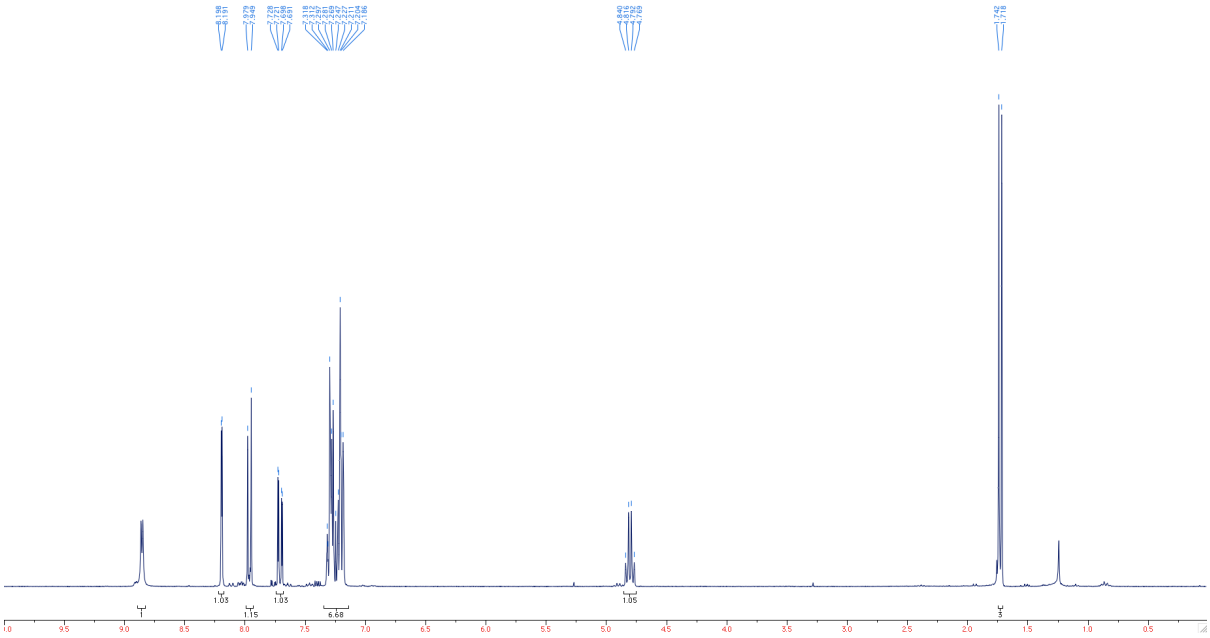


^{13}C NMR

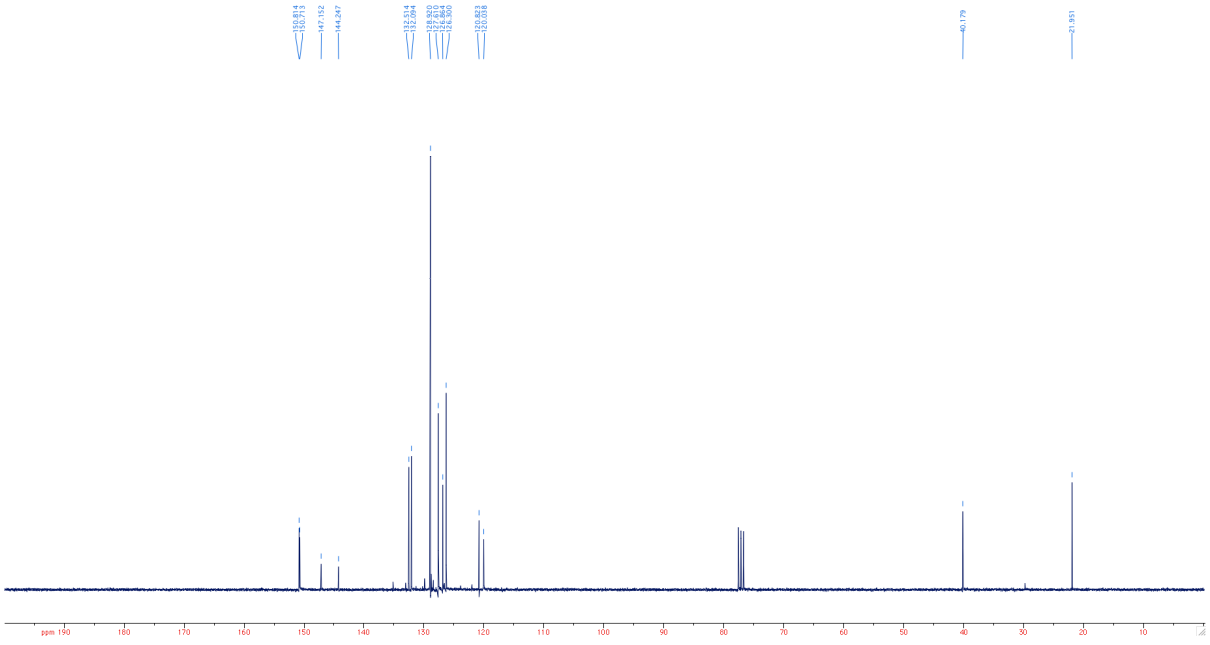


15

^{1}H NMR

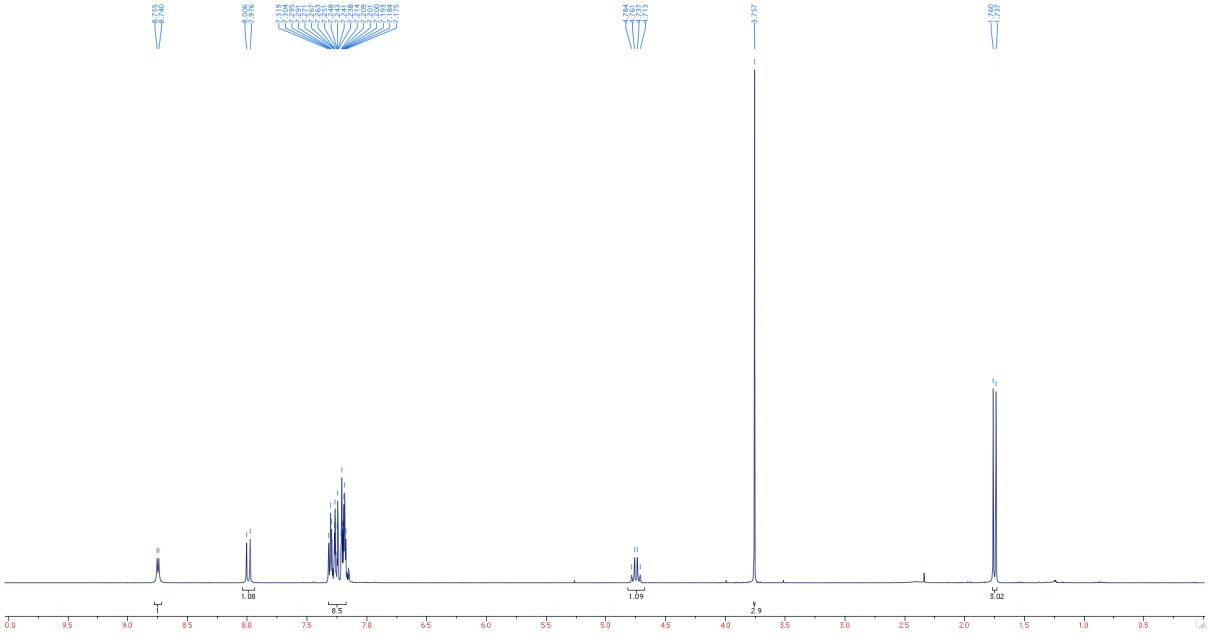


^{13}C NMR

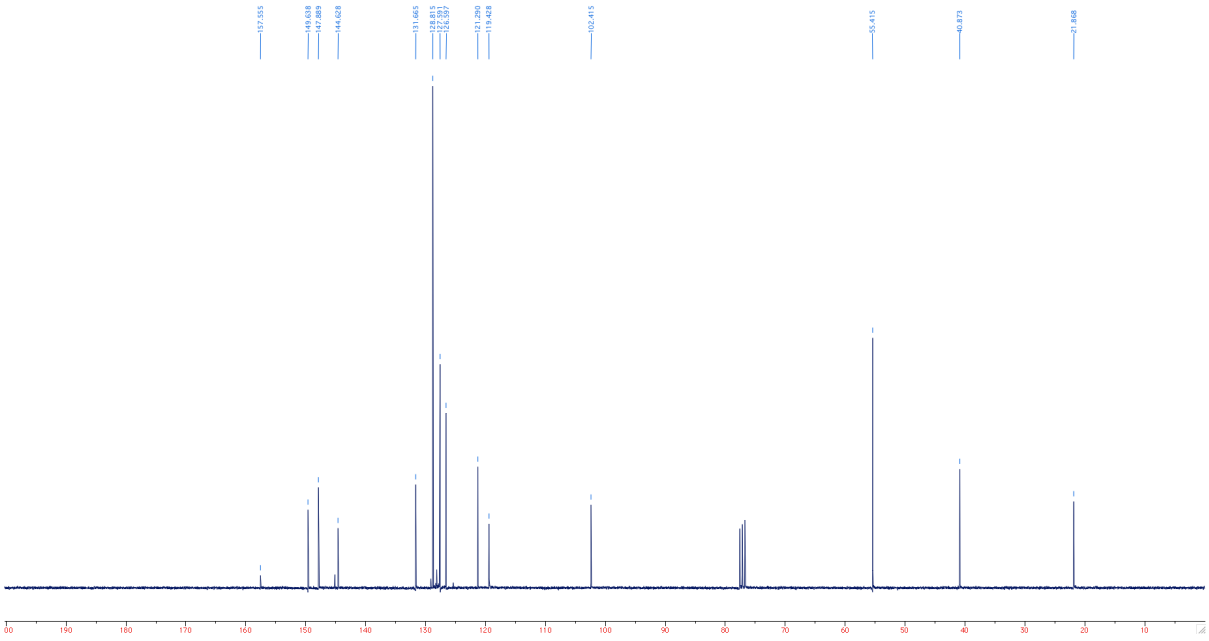


16

^{1}H NMR

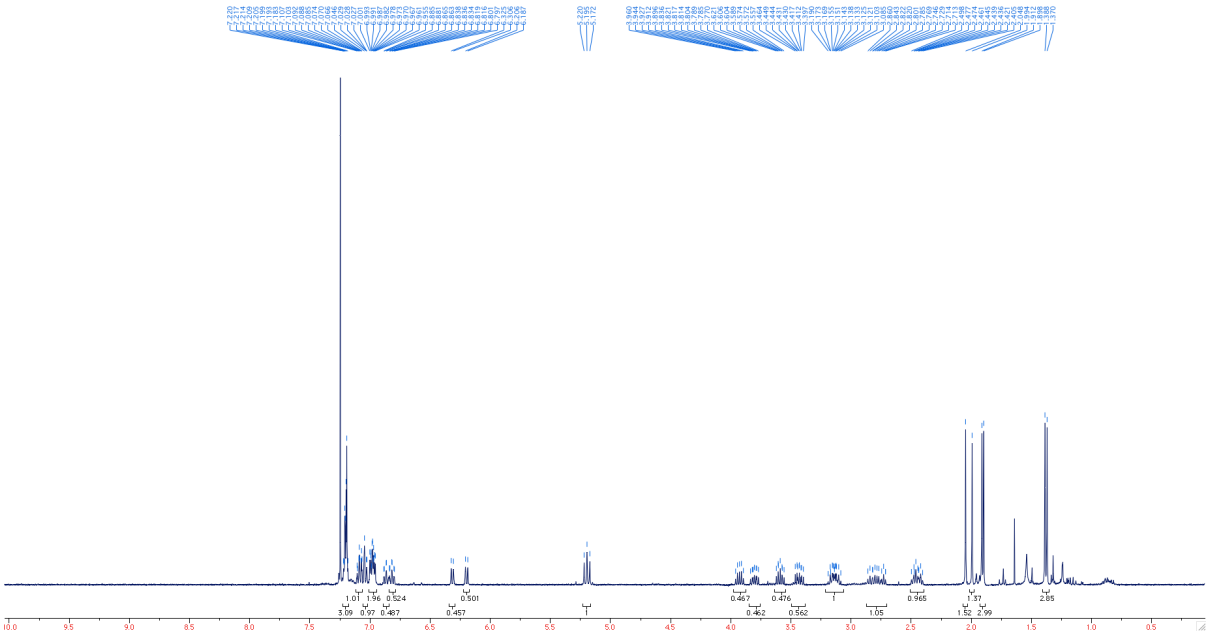


^{13}C NMR

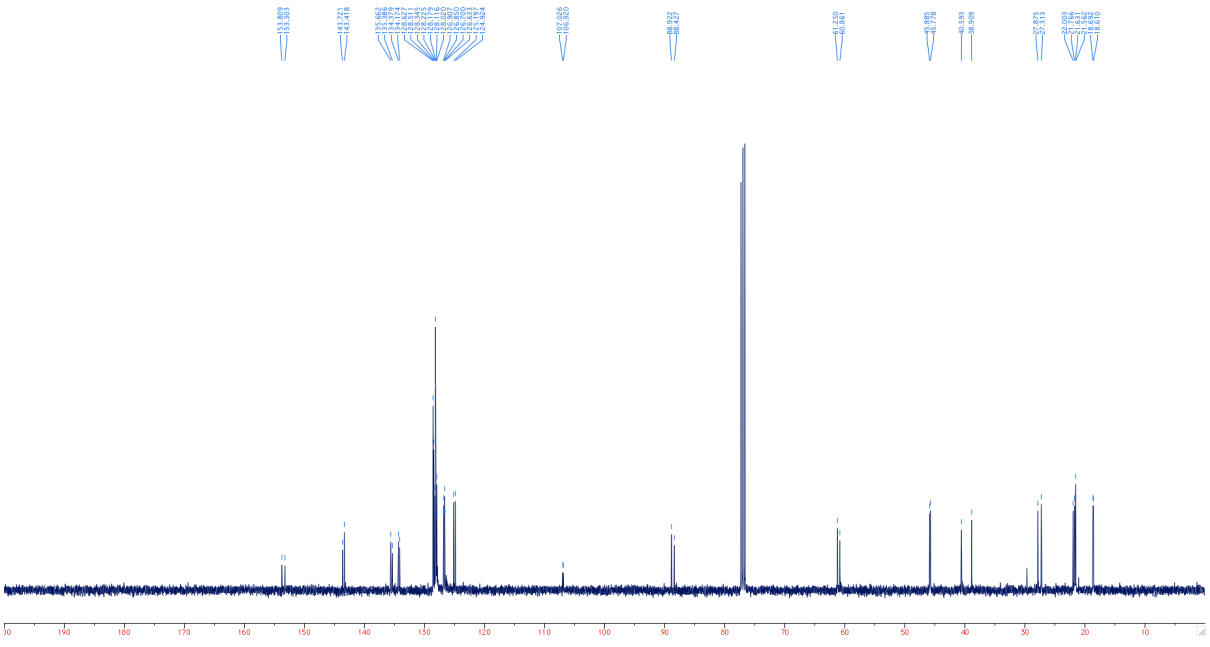


19a

^{1}H NMR

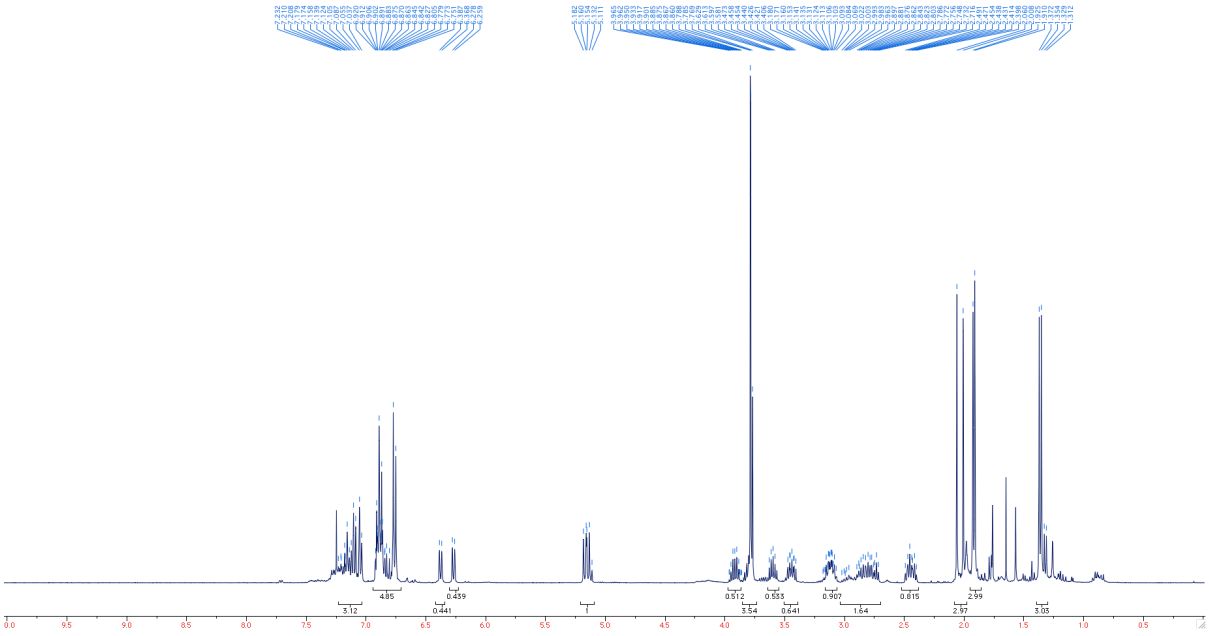


^{13}C NMR

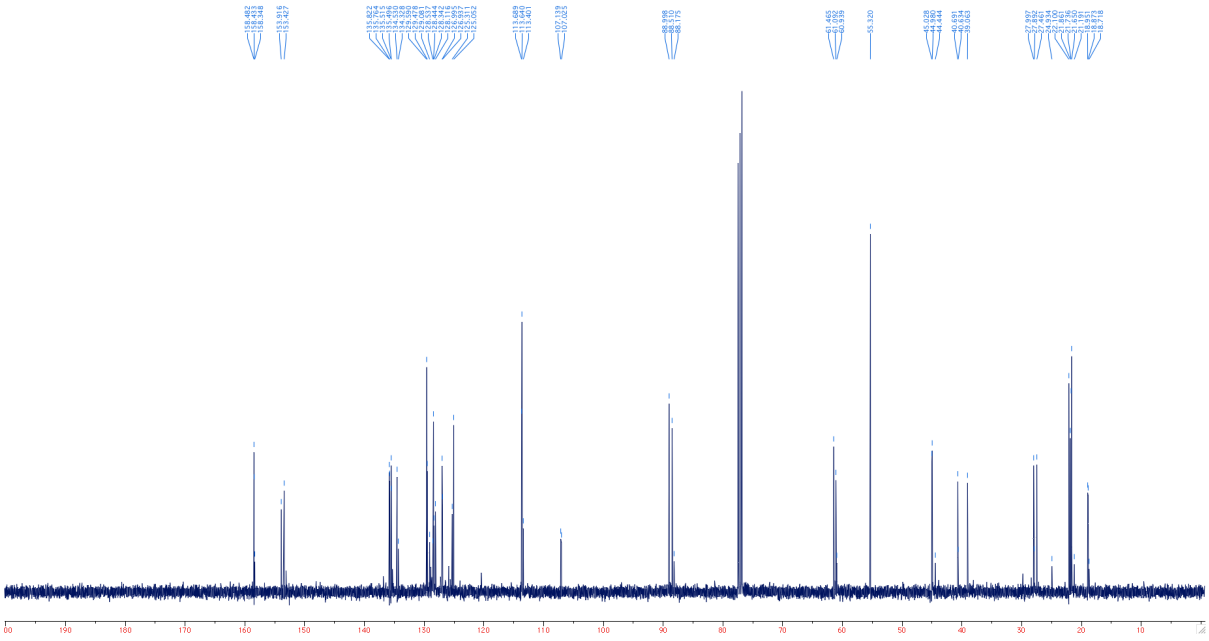


19b

^{1}H NMR

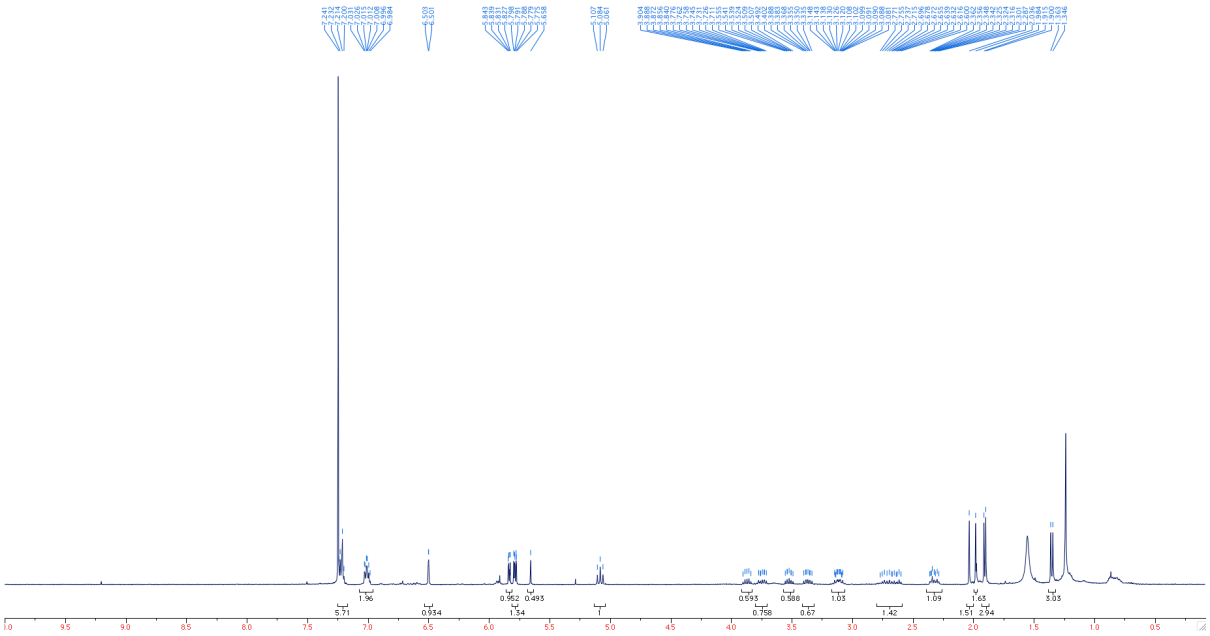


^{13}C NMR

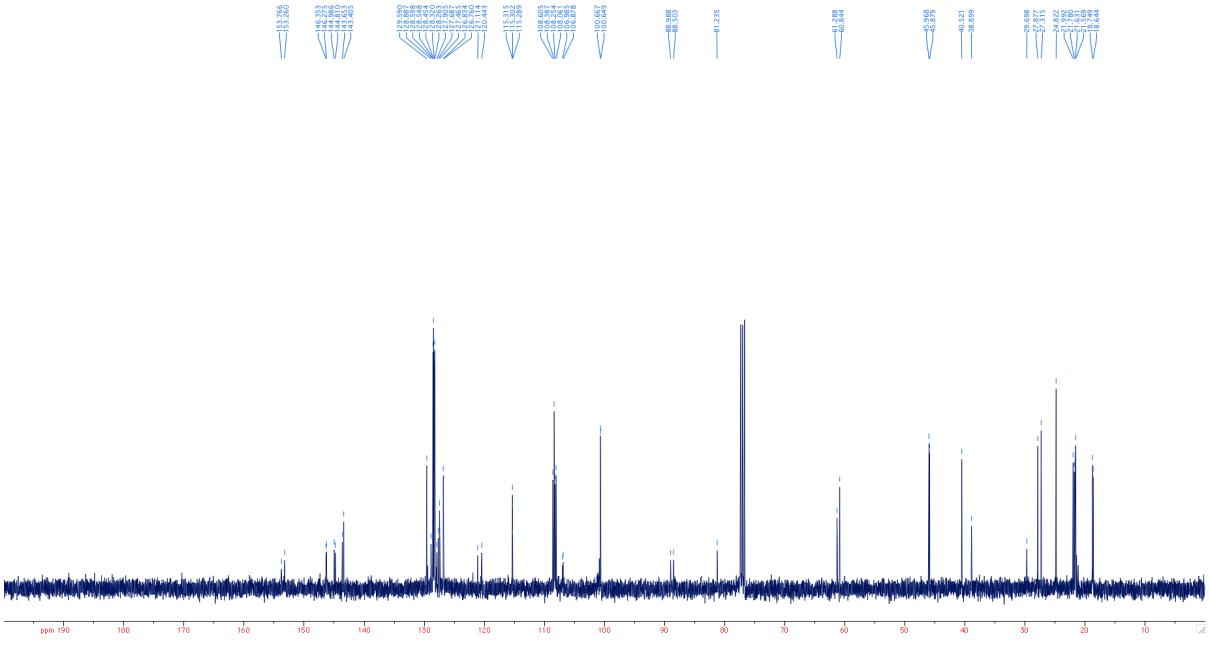


21a

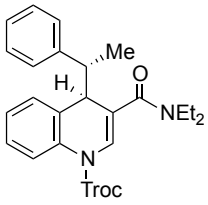
^{1}H NMR



^{13}C NMR

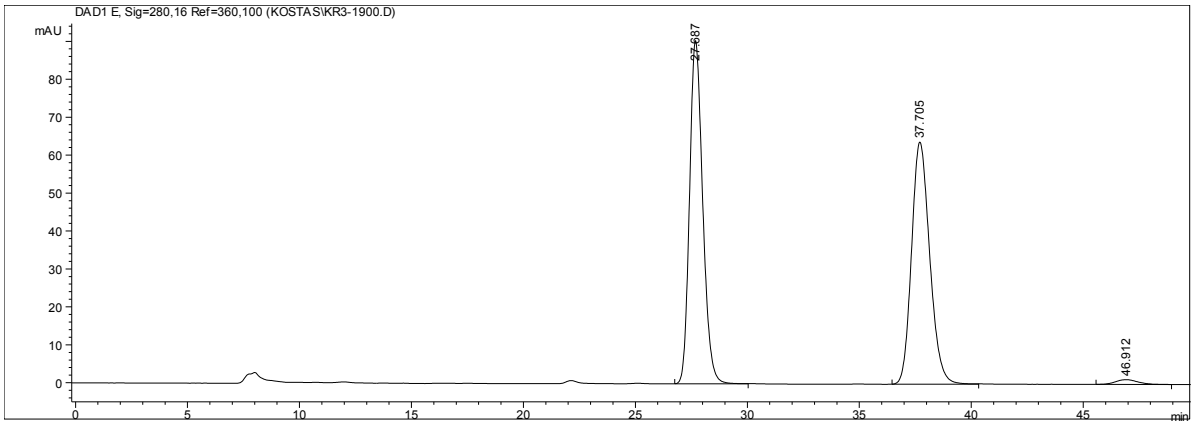


7. Chiral HPLC and SFC traces

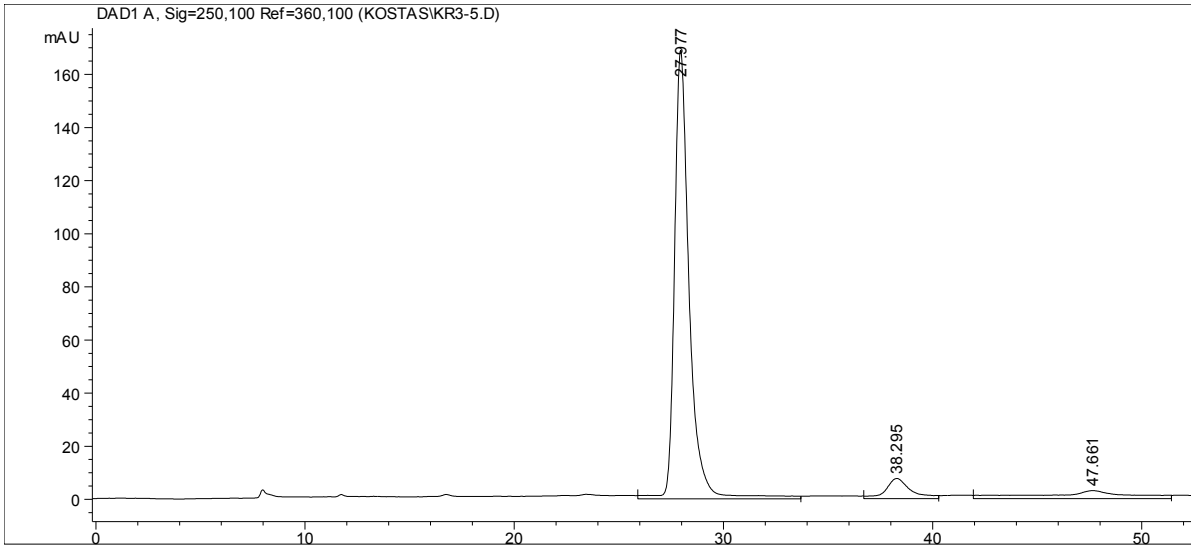


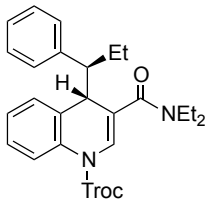
8a

Racemic



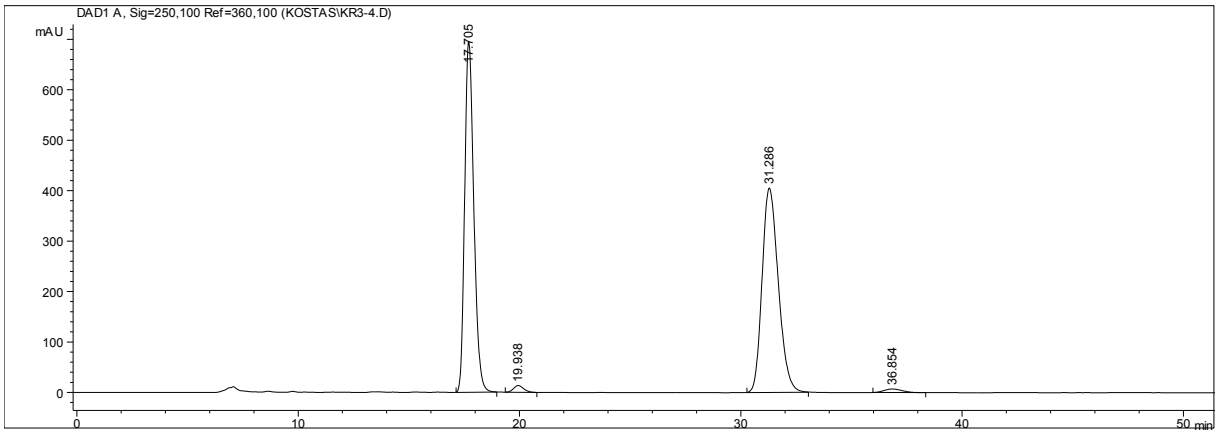
Enantioenriched



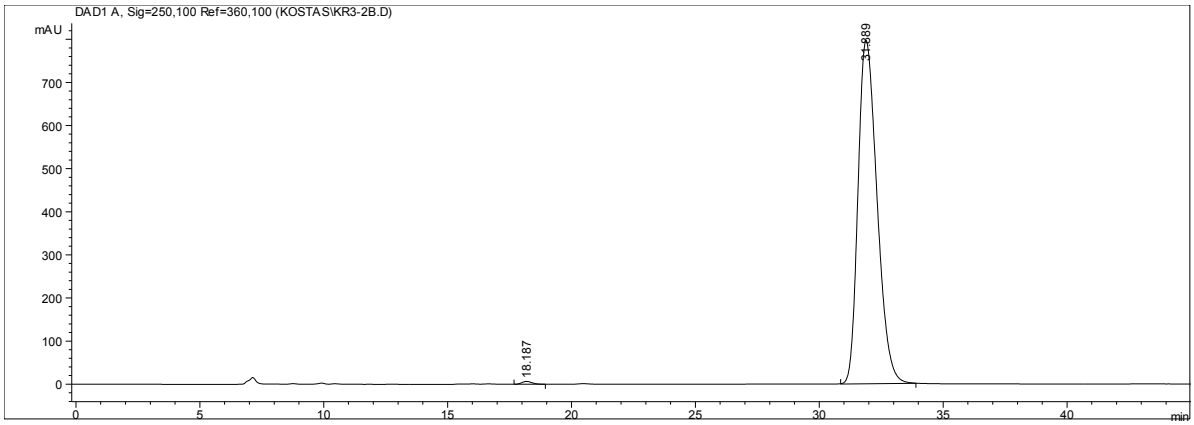


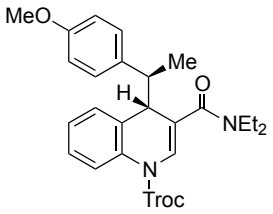
8b

Racemic



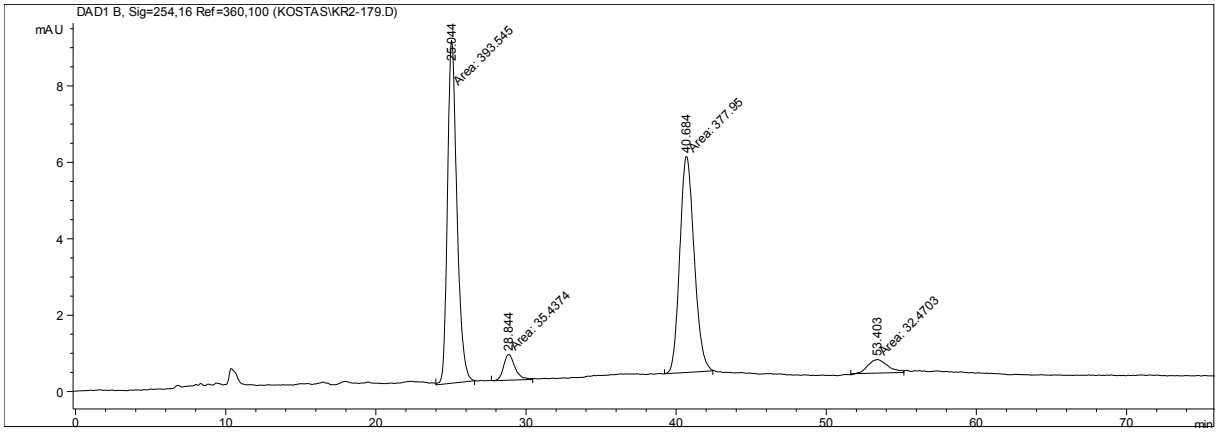
Enantioenriched



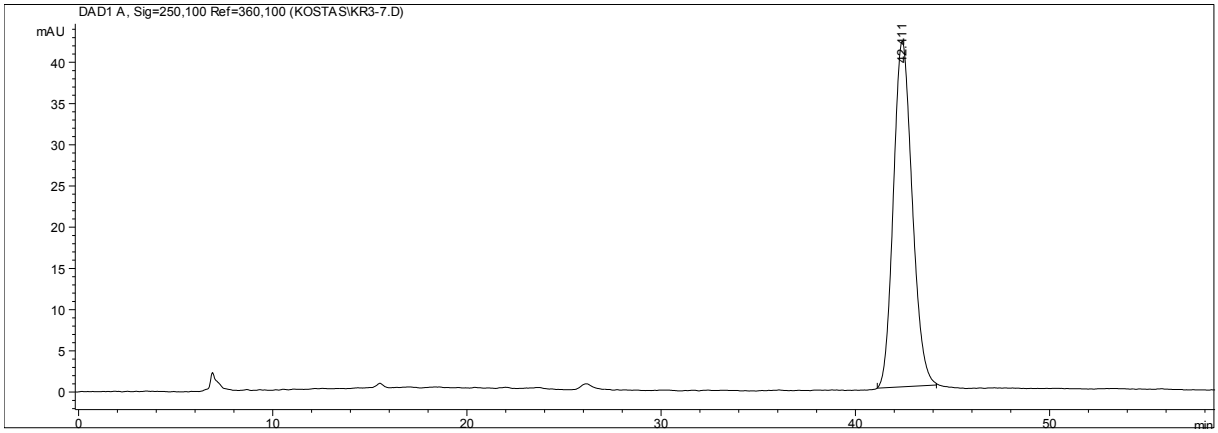


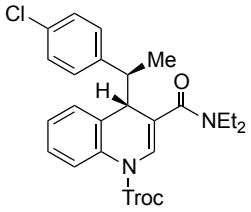
8d

Racemic



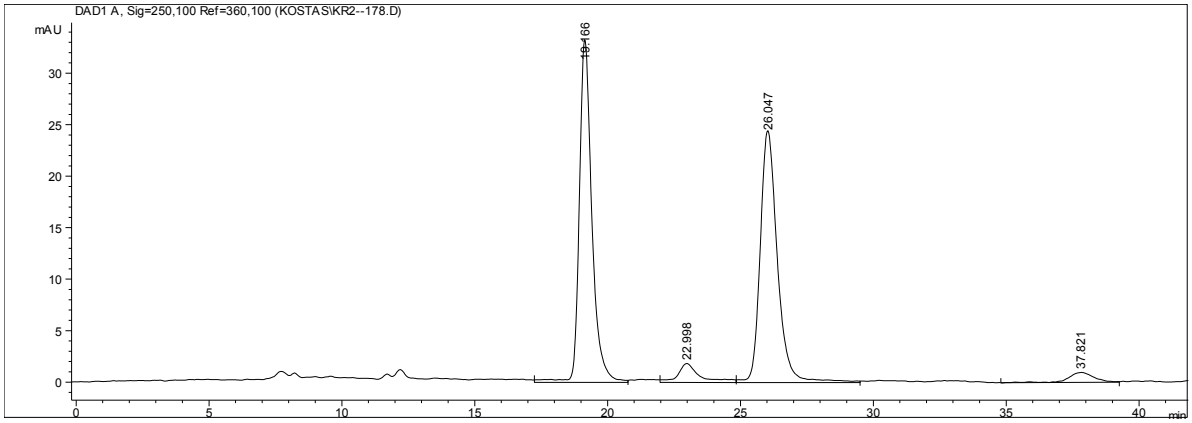
Enantioenriched



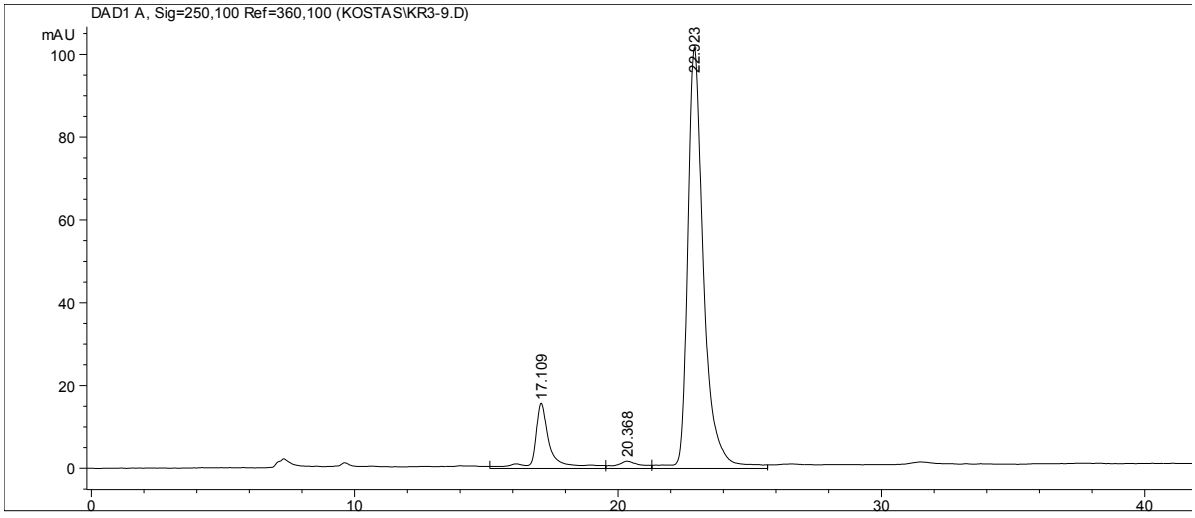


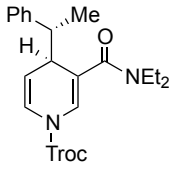
8e

Racemic



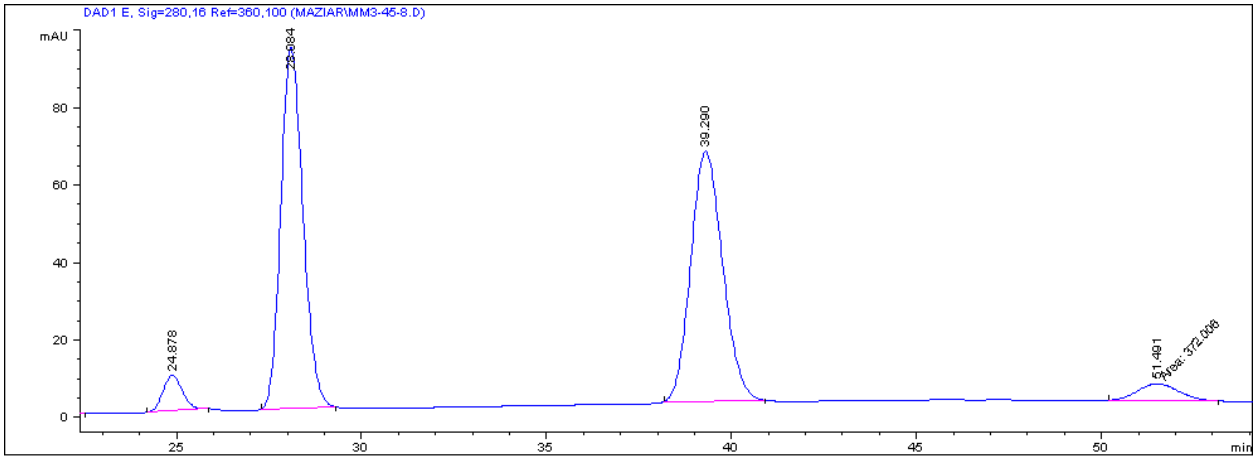
Enantioenriched



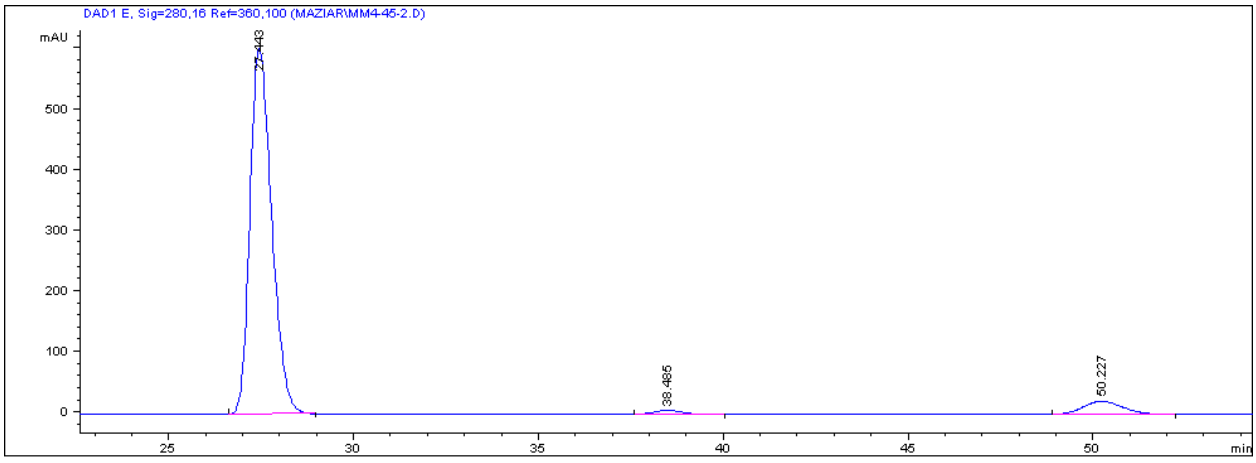


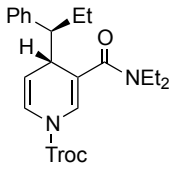
10a

Racemic



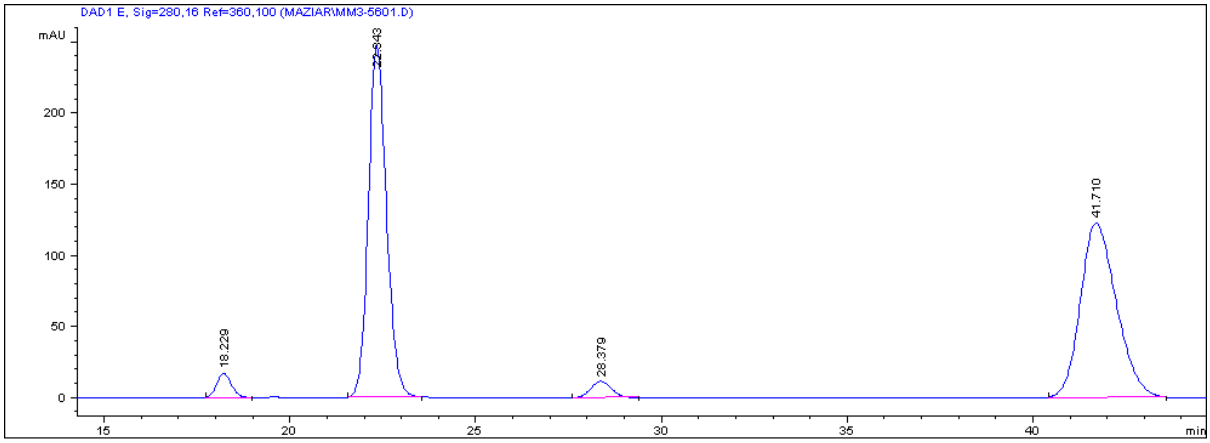
Enantioenriched



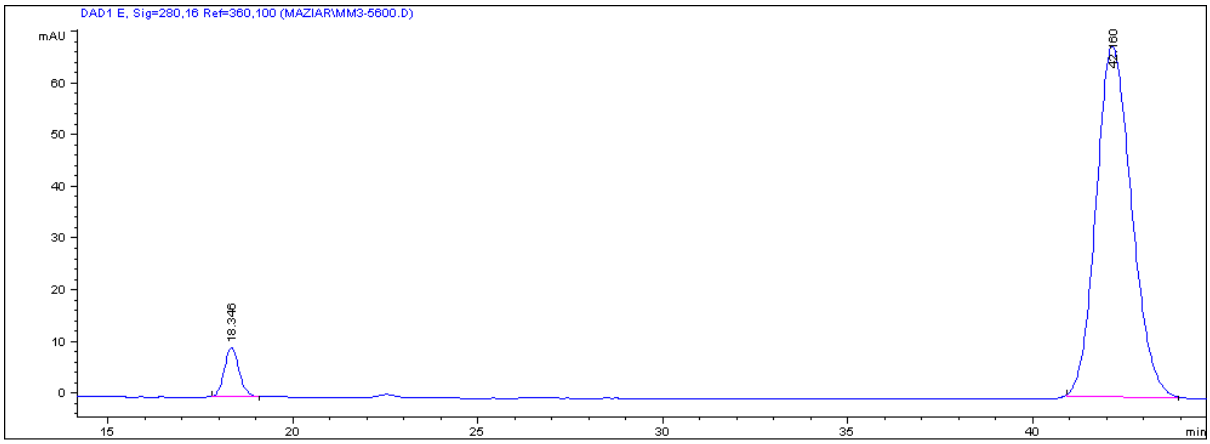


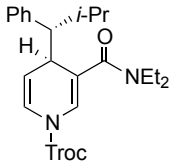
10b

Racemic



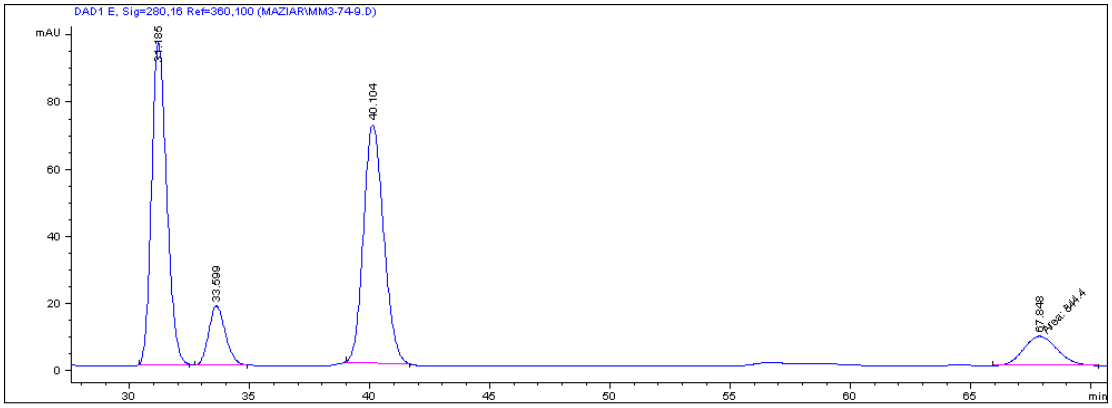
Enantioenriched



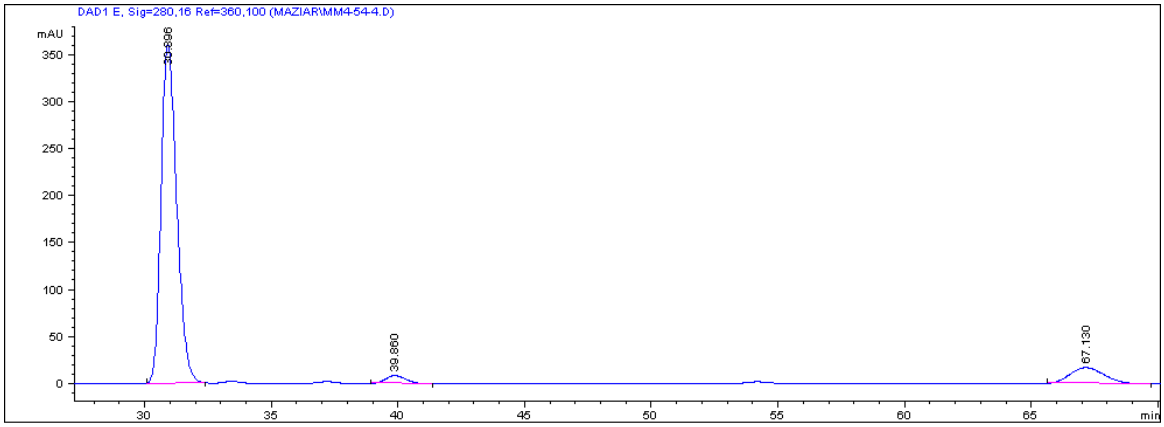


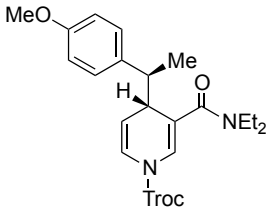
10c

Racemic



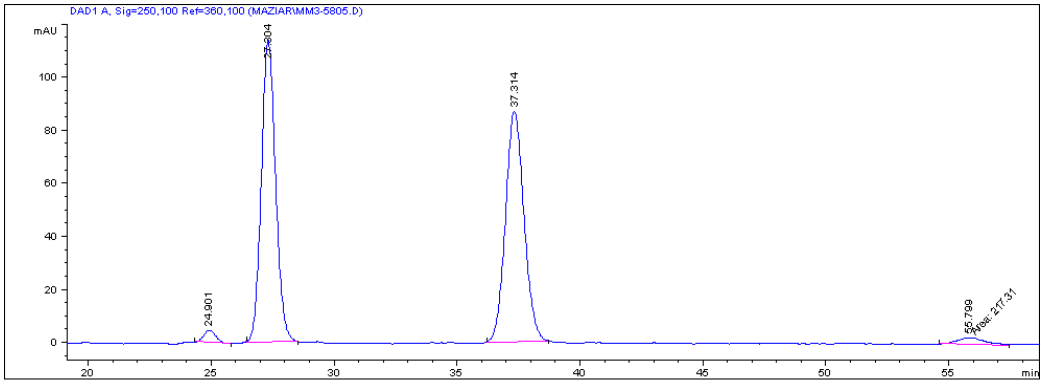
Enantioenriched



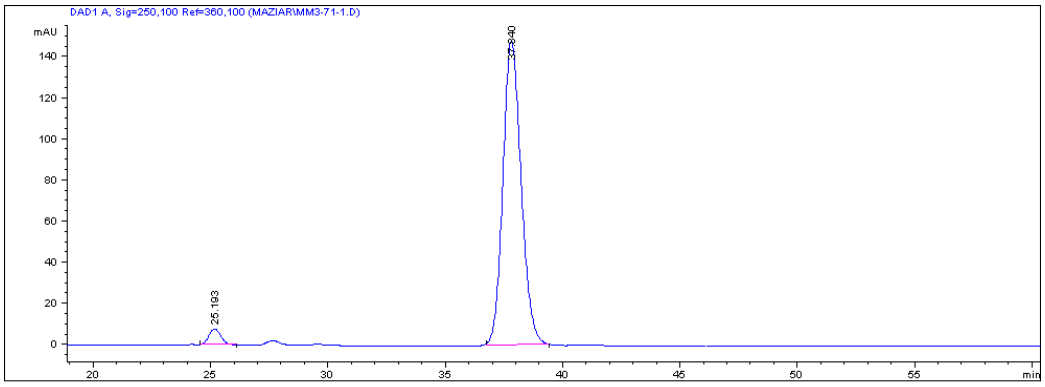


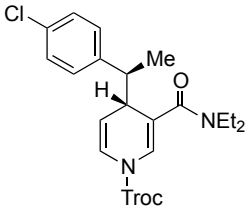
11d

Racemic



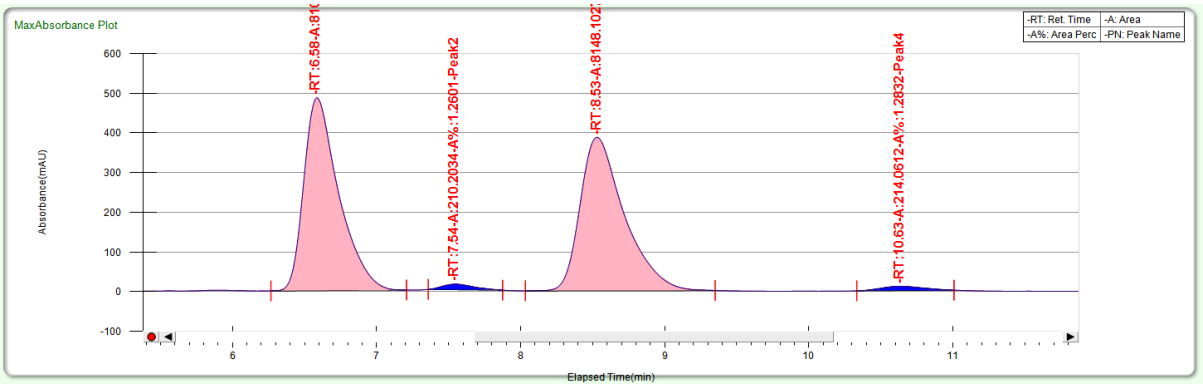
Enantioenriched



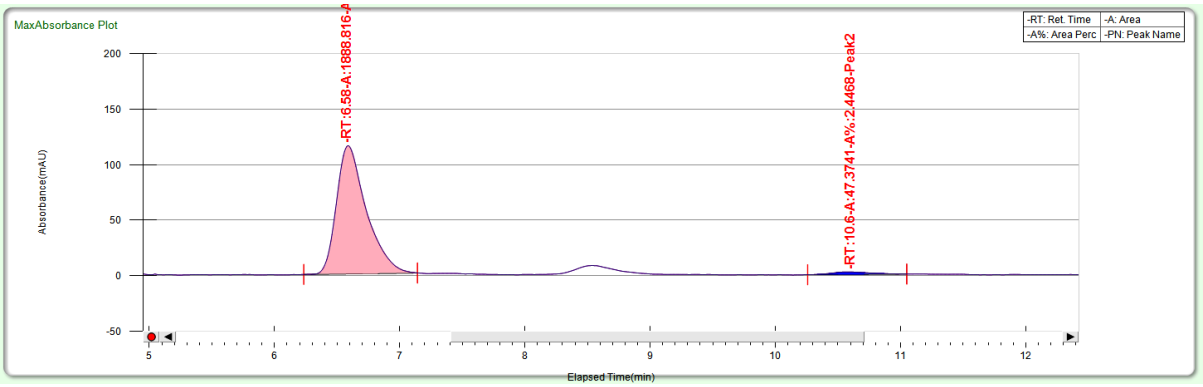


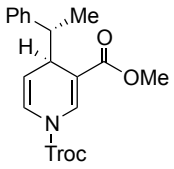
11e

Racemic



Enantioenriched





11a

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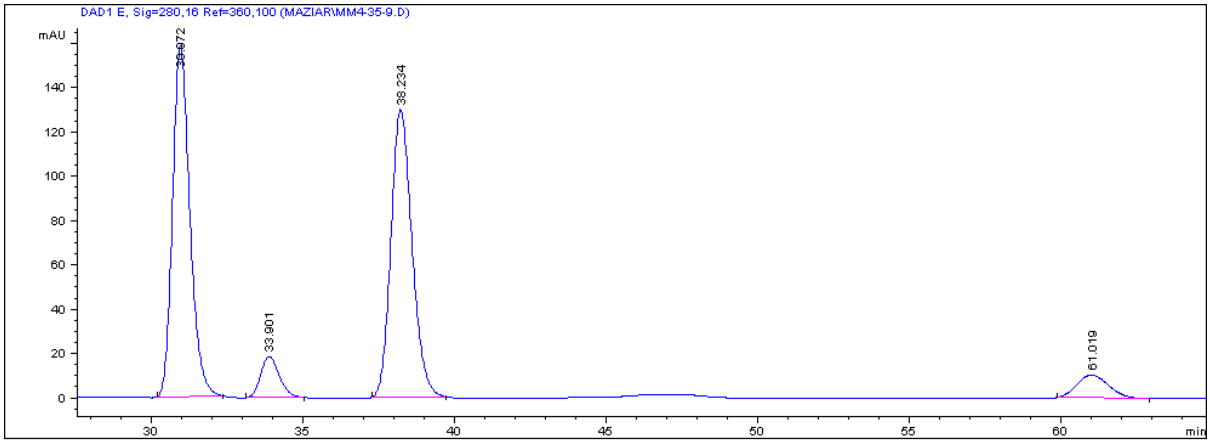

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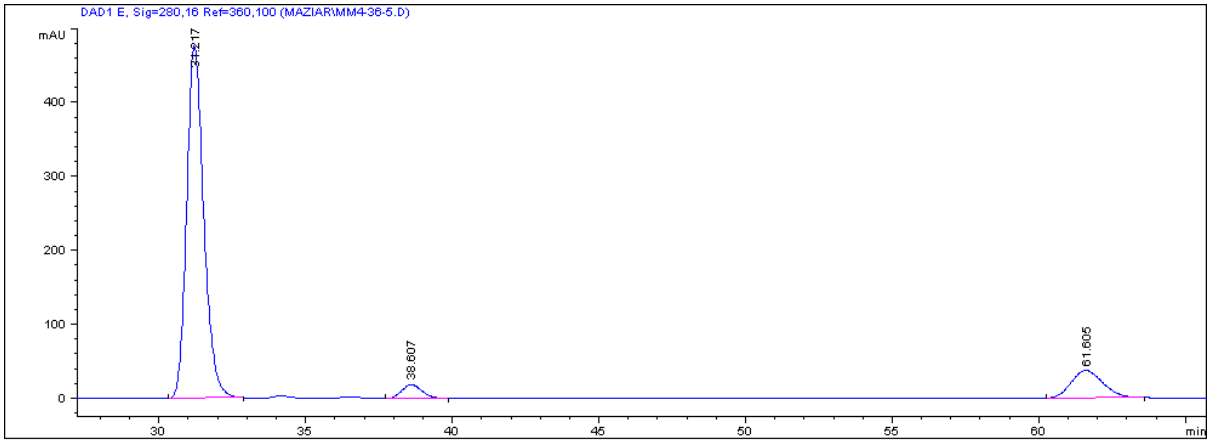

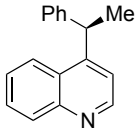

14

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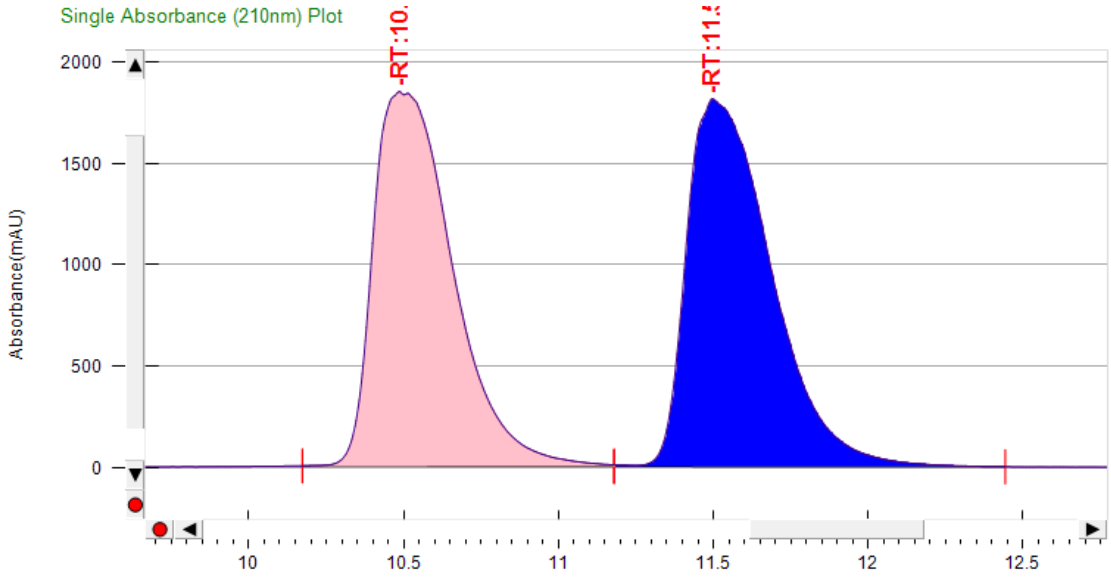

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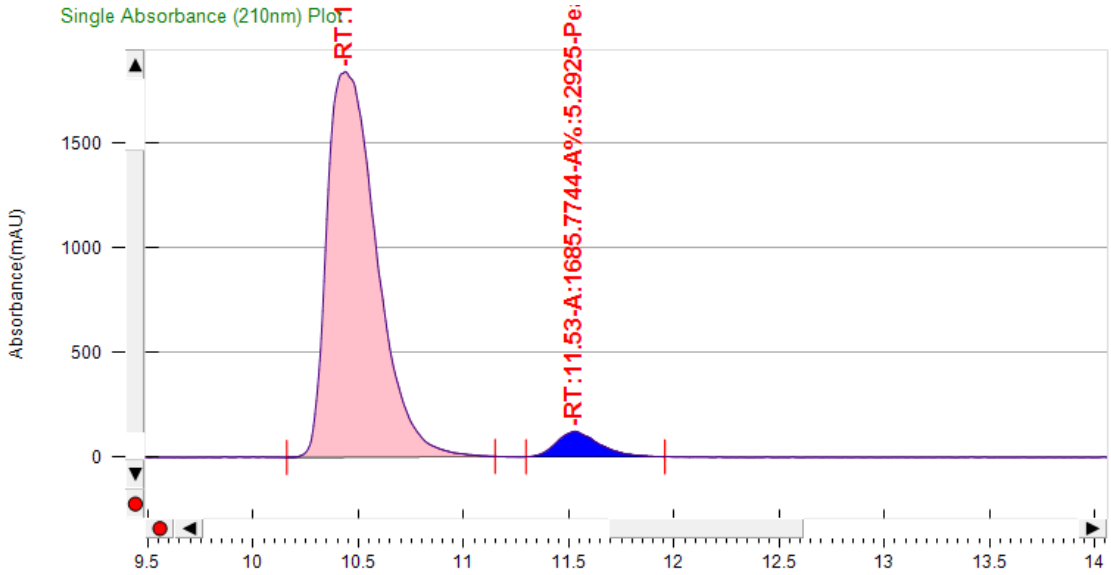

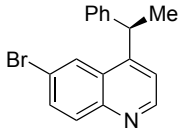

15

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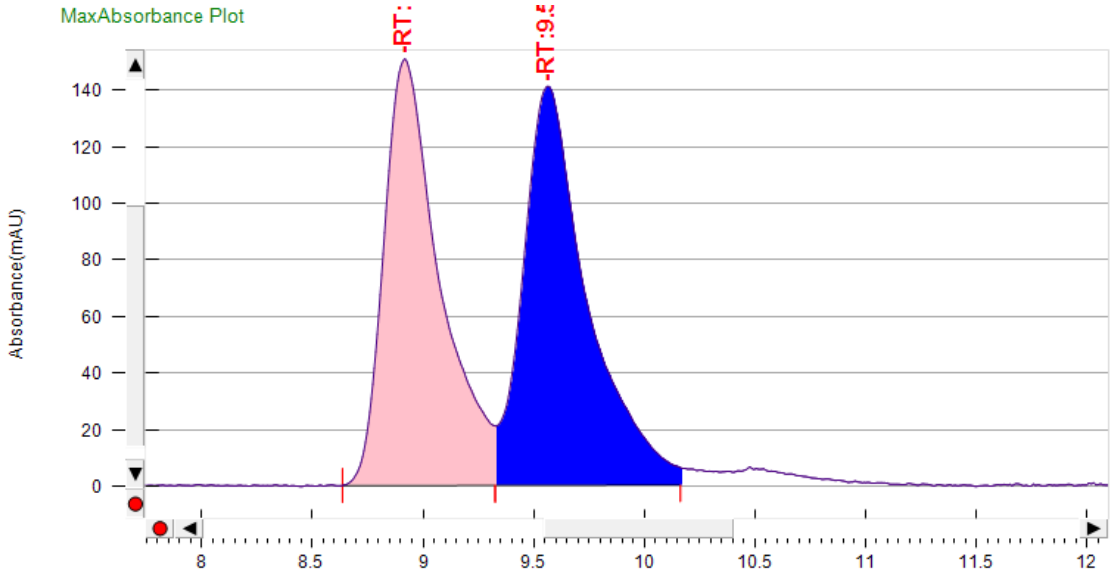

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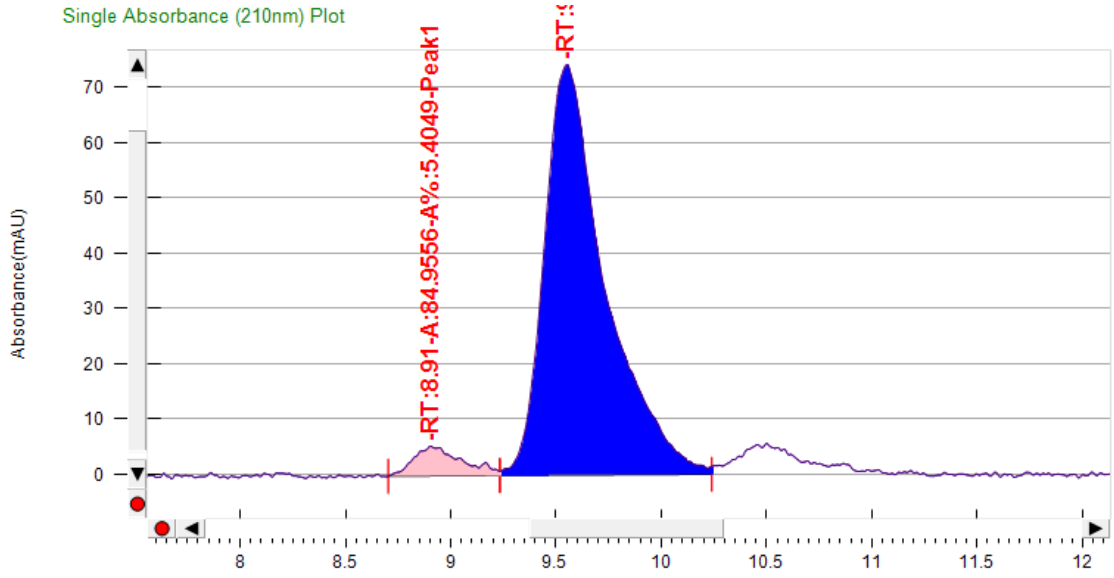

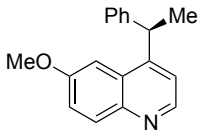

16

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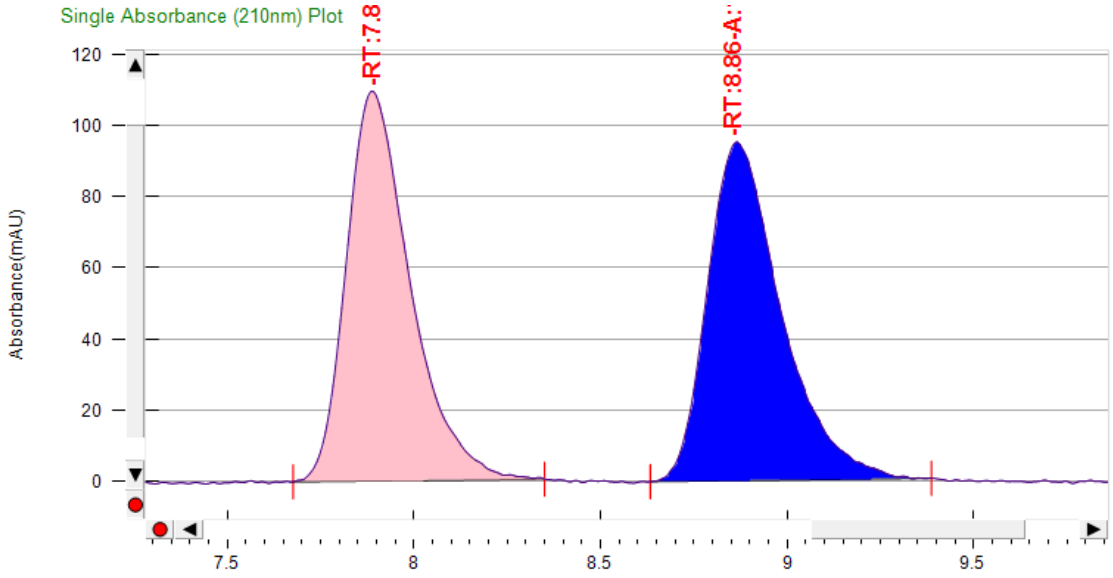

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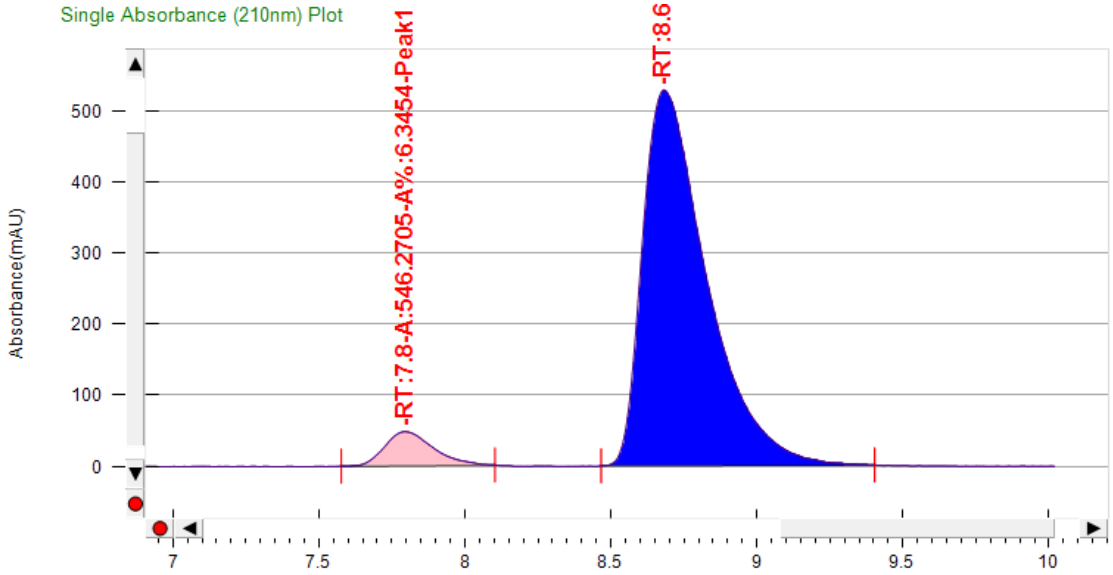

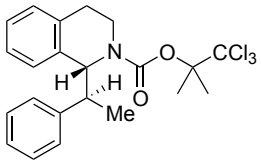

19a

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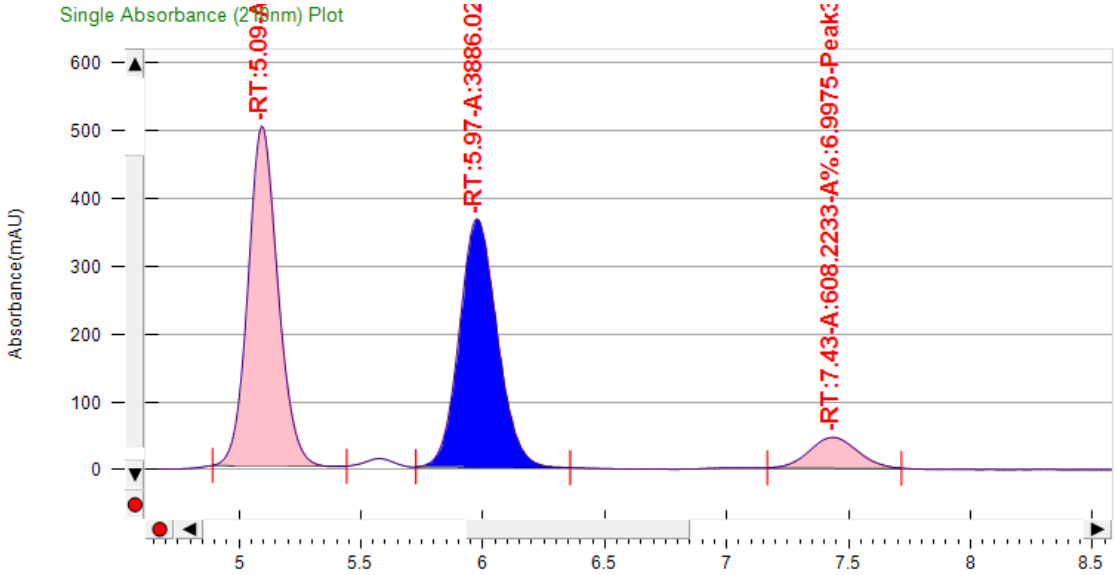

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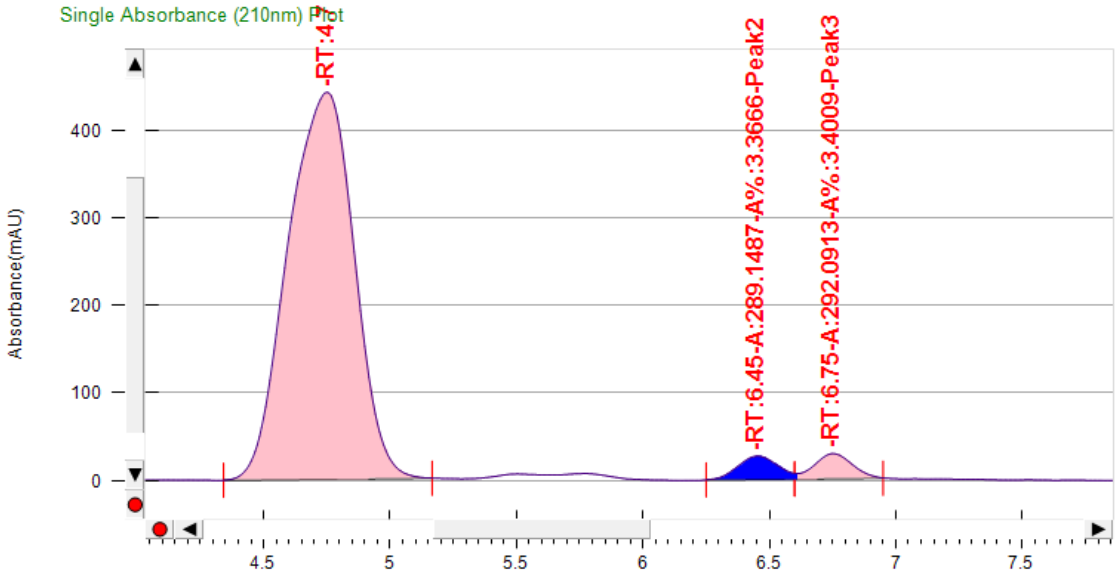

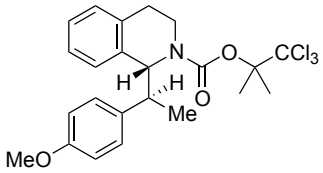

19b

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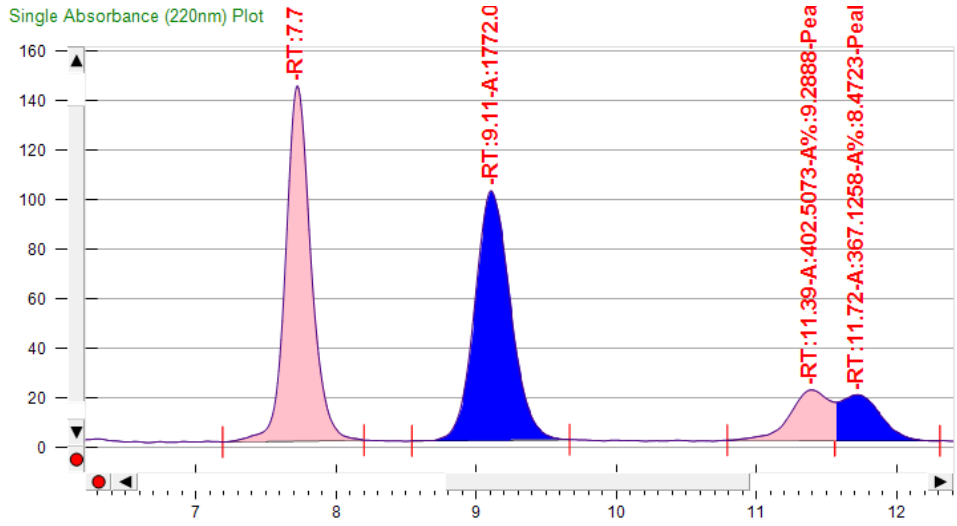

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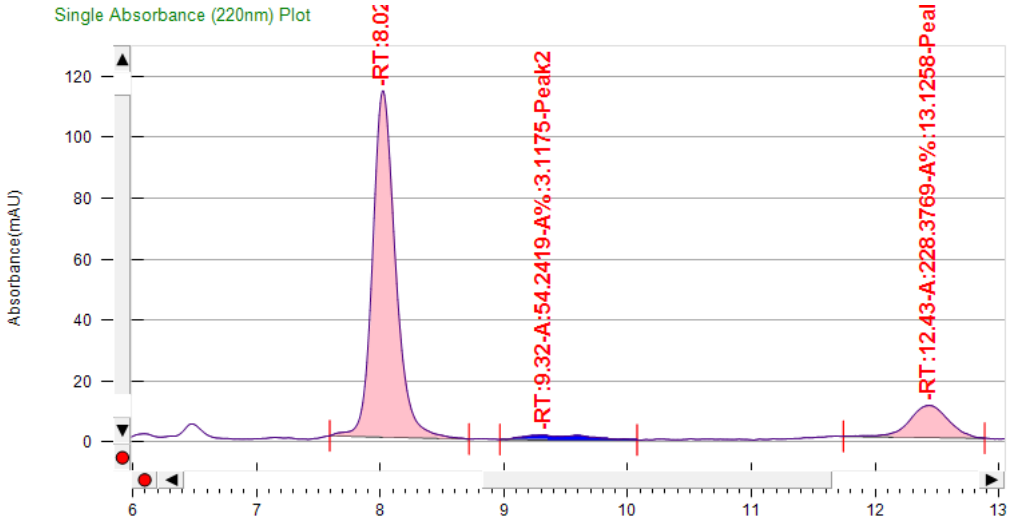

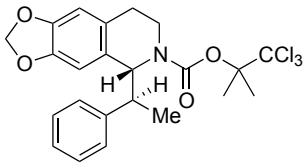

21a

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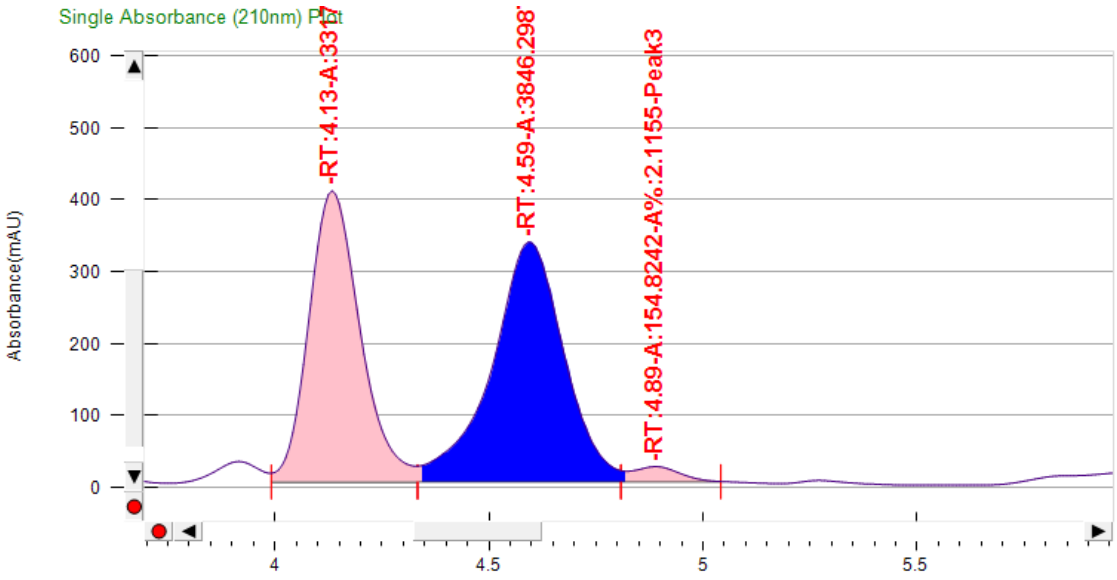

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