Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Asymmetric Synthesis of Substituted NH-Piperidines from Chiral Amines

Lekh Nath Gautam,[a] Yijin Su,[a] Novruz G. Akhmedov,[a] Jeffrey L. Petersen,[a] and Xiaodong Shi*[a]

[a]C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506, United States

Email: xiaodong.shi@mail.wvu.edu

Supplementary Information

Table of Contents

General Information. All of the reactions dealing with air and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen using oven/flame-dried glassware and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents were obtained from the commercial provider and used without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 600 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. Flash column chromatography was performed on 230-430 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios. Optical rotations were measured on a commercial automatic polarimeter and reported as follows: $[\alpha]^{T}_{D}$ (c = mg/mL, solvent). HRMS were recorded on LTQ-FTUHRA spectrometer (ESI-MS). All the solvents were distilled freshly according to standard procedures. High-performance Liquid chromatography (HPLC) was performed using a Daicel Chiralcel OD-H column (250*4.6 mm) or Chiralpak AS-H (250*4.6 mm). Enantiomeric excess was determined by HPLC analysis, described below in detail.

General Procedure for the Preparation of Substituted *N*-protected Piperidine (3d-3j). To a solution of nitroalkene **1a** (149 mg, 1 mmol, 1 eq.) in dry THF (2 mL, 0.5 M), were added successively Chiral 4-methoxy-phenylethanamine (227 mg, 1.5 mmol, 1.5 eq.) and MVK (140 mg, 2.0 mmol, 2.0 eq.) under N_2 atmosphere. The mixture was stirred at room temperature for 36 hr and monitored by TLC. After removing the solvent, the residue was purified by flash silica gel chromatography (Hexane-EtOAc v/v 8:1), which gave a major diastereomeric **piperidine 3d** (266 mg, 0.72 mmol, yield: 72%) as white solid.

(2S,3S,4R)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitro-2-phenylpiperidin-4-ol (3d major) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 8/1) as white solid, 266 mg, yield 72%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19-7.40 (m, 7H), 6.76 (d, J = 8.2 Hz, 2H), 4.64 (d, J = 10.1 Hz, 1H), 4.27 (d, J = 10.1 Hz, 1H), 3.72 (s, 3H), 3.66 (q, J = 6.2 Hz, 1H), 2.96 (s, 1H), 2.77 (t, J =11.7 Hz, 1H), 2.30 (d, J = 13.6 Hz, 1H), 1.71 (d, J = 13.9 Hz, 1H), 1.51 (t, J = 13.2 Hz, 1H), 1.22 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.5, 137.2, 135.5, 129.2, 129.1, 129.0, 128.6, 113.5, 98.5, 69.5, 63.9, 55.4, 54.5, 38.7, 37.1, 27.5, 8.9. HRMS Calculated for $C_{21}H_{27}N_2O_4$ $[M+H]^{+}$: 371.19453, Found: 371.19475.

(2S,3S,4R)-2-(4-chlorophenyl)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitropiperidin-4-ol (3e major) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 8/1) as white solid,303 mg, yield 75%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43-7.33 (m, 4H), 7.22 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.64 (d, J = 10.1 Hz, 1H), 4.32 (d, J = 10.1 Hz, 1H), 3.78 (s, 3H), 3.66 (q, J = 6.9 Hz, 1H), 2.94 (s, 1H), 2.81 (td, J = 12.2, 2.5 Hz,

1H), 2.36 (td, *J* = 11.9, 4.2 Hz, 1H), 1.76 (td, *J* = 13.8, 2.5 Hz, 1H), 1.57 (d, *J* = 6.7 Hz, 1H), 1.22 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, CDCl3): δ 158.5, 136.7, 135.8, 135.1, 134.7, 129.5, 128.6, 127.5, 113.5, 98.3, 69.5, 63.2, 55.4, 54.7, 38.7, 37.1, 27.5, 8.9. HRMS Calculated for $C_{21}H_{26}ClN_2O_4$ $[M+H]^+$: 405.15029, Found: 405.15120.

(2S,3S,4R)-2-(4-fluorophenyl)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitropiperidin-4-ol (3f major) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 9/1) as white solid, 283 mg, yield 73%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46-7.38 (m, 2H), 7.25-7.23 (m, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.64 (d, *J* = 7.8 Hz, 1H), 4.33 (d, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.67 (d, *J* = 6.6 Hz, 3H), 2.97 (s, 1H), 2.81 (t, *J* = 11.1 Hz, 1H), 2.36 (d, *J* = 7.2 Hz, 1H), 1.76 (d, *J* = 15.4 Hz, 1H), 1.50 (m, 1H), 1.27 (s, 3H), 1.20 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.0, 158.3, 136.5, 135.6, 134.9, 134.5, 129.3, 129.2, 128.3, 113.3, 98.1, 69.2, 63.0, 55.2, 54.4, 38.4, 36.8, 27.2, 8.7. HRMS Calculated for $C_{21}H_{26}FN_2O_4$ $[M+H]^+$: 389.18319, Found: 389.18301.

(2S,3S,4R)-2-(4-methoxyphenyl)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitropiperidin-4-ol (3g major) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 8/1) as white solid, 220 mg, yield 55%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40-7.35 (m, 4H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.67 (d, *J*= 10.0 Hz, 1H), 4.28 (d, *J*= 10.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (d, *J* = 6.9 Hz, 1H), 3.02 (s, 1H), 2.80 (t, *J* =10.1 Hz, 1H), 2.35 (d, *J* = 15.4 Hz, 1H), 1.76 (d, *J* = 13.8 Hz, 1H), 1.56 (d, *J* = 11.3 Hz, 1H), 1.27 (s, 3H), 1.20 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.9, 158.4, 135.6, 128.9, 128.6, 114.6, 113.5, 98.6, 69.5, 63.3, 55.4, 38.8, 37.1, 27.5, 8.90. HRMS Calculated for $C_{22}H_{29}N_2O_5$ $[M+H]^+$: 401.20318, Found: 401.20322.

(2S,3S,4R)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitro-2-(p-tolyl)piperidin-4-ol (3h major) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 9/1) as white solid, 253 mg, yield 66%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.24 (m, 4H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 10.1 Hz, 1H), 4.31 (d, *J* = 10.0 Hz, 1H), 3.79 (s, 3H), 3.74 (q, *J* = 6.7 Hz, 3H), 3.05 (s, 1H), 2.82 (td, *J* =12.3, 2.3 Hz, 1H), 2.36 (d, *J* = 4.4 Hz, 1H), 2.32 (s, 3H), 1.76 (d, *J* = 13.8 Hz, 1H), 1.57 (td, *J* = 12.9, 3.8 Hz, 1H), 1.28 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.4, 138.7, 135.6, 134.0, 129.9, 128.6, 126.0, 113.5, 98.5, 69.5, 63.7, 55.4, 54.4, 38.7, 37.2, 27.5, 21.4, 8.9. HRMS Calculated for $C_{22}H_{29}N_2O_4$ $[M+H]^+$: 385.20826, Found: 385.20491.

(2R,3S,4R)-2-(furan-2-yl)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitropiperidin-4-ol (3i) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 9/1) as white solid, 263 mg, yield: 73%. ^{1}H NMR (150 MHz, $CDCl_3$): δ 7.34-7.33 (m, 3H), 7.05 (m, 1H), 6.91 (m, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.71 (d, *J* = 10.1 Hz, 1H), 4.34 (d, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.64 (s, 1H), 2.82 (t, *J* = 10.0 Hz, 1H), 2.35 (d, *J* = 14.2 Hz, 1H), 1.76 (d, *J* = 13.8 Hz, 1H), 1.59 (m, 1H), 1.27 (s, 3H), 1.21(d, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.2, 136.9, 135.3, 129.0, 129.1, 128.4, 125.9, 132.0, 98.3, 69.2, 63.7, 55.2, 54.3, 38.5, 36.9, 27.3, 8.6. HRMS Calculated for $C_{19}H_{25}N_2O_5$ $[M+H]^+$: 361.17188, Found: 361.17156.

(2R,3S,4R)-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-3-nitro-2-(thiophen-2-yl)piperidin-4-ol (3j major) was purified by flash silica gel chromatography (Hexane- EtOAc, v/v 9/1) as white solid, 271 mg, yield 72%. ^{1}H

NMR (600 MHz, $CDCl_3$): δ 7.33-7.31 (m, 4H), 7.04 (m, 1H), 6.90 (t, *J* = 4.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.70 (m, 2H), 3.78 (s, 3H), 2.97 (m, 1H), 2.83 (td, *J* =12.4, 2.5 Hz, 1H), 2.32 (d, *J* = 10.5 Hz, 1H), 1.75 (d, *J* = 13.76 Hz, 1H), 1.56 (m, 1H), 1.27 (s, 3H), 1.25 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.4, 137.2, 135.5, 129.2, 129.1, 129.0, 128.6, 113.5, 98.5, 69.5, 63.9, 55.4, 54.5, 38.7, 37.1, 27.5, 8.9. HRMS Calculated for $C_{19}H_{25}N_2O_4S$ $[M+H]^+$: 377.1535, Found: 377.1534.

General Procedure for the Preparation of *NH*-piperidine (4a-4g). TFA was added dropwise to a stirred solution of the substrate **3d** (266 mg, 0.72 mmol) in minimum amount of DCM and stirred at room temperature 12-18hr (TFA:DCM = 1:1). After concentration in rotary evaporator, the residue was partitioned between saturated aqueous sodium bicarbonate solution (8ml) and Dichloromethane (8ml). The separated aqueous phase was extracted with Dichloromethane (3×8ml), and the combined organic extracts dried over sodium or magnesium sulfate for 2hr then filtered through the cotton plug. Finally, the dilute solution was concentrated in vacuo and the residue was purified by column chromatography using solvent system (Dichloromethane: Methanol from 200:1 to 50:1) to afford piperidine **4a**. Using the same mentioned procedure other *NH*-piperidines were prepared from **3d-3j**.

(2S,3S,4R)-4-methyl-3-nitro-2-phenylpiperidin-4-ol (-4a) and (2R,3R,4S)-4-methyl-3-nitro-2-phenylpiperidin-4-ol (+4a) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, **-4a**, 149 mg, yield 88%; **+4a**, 151 mg, yield 89%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 4.56 (d, *J* = 10.3 Hz, 1H), 4.45 (d, *J* = 10.3 Hz, 1H), 3.29 (td, *J* = 12.3, 2.9 Hz, 1H), 2.92 (ddd, *J* = 12.1, 4.8, 2.2 Hz, 1H), 1.89 (dt, *J* = 13.8, 2.5 Hz, 1H), 1.71 (td, *J* = 12.6, 4.8 Hz, 1H), 1.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.2, 129.1, 129.0, 127.7, 96.9, 69.9, 60.4, 41.5, 38.1, 27.7. HRMS Calculated for $C_{12}H_{17}N_2O_3$ $[M+H]^+$: 237.11945, Found: 237.11933. Enantiomeric excess of the piperidine was determined by HPLC analysis with a Chiralcel OD-H column (90:10 hexane: isopropanol, 0.9 mL/min, 220 nm); Racemic mixture t_{R1} = 13.8 min, t_{R2} = 17.8 min; Enantiopure isomer: **-4a**: >95% ee, t_R = 19.2 min; **+4a**: >95% ee, t_R = 14.1 min; and optical rotation $[\alpha]_D^{20}$ -25.6 and + 25.6 (c = 0.1, CH_2Cl_2).

(2S,3S,4R)-2-(4-chlorophenyl)-4-methyl-3-nitropiperidin-4-ol (-4b) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, 186 mg, yield 92%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32-7.24 (m, 4H), 4.47 (d, *J* = 10.2 Hz, 1H), 4.43 (d, *J* = 10.2 Hz, 1H), 3.28 (td, *J* = 12.5, 2.7 Hz, 1H), 2.90 (dd, *J* = 11.7, 4.7 Hz, 1H), 1.86 (dt, *J* = 13.7, 2.7 Hz, 1H), 1.68 (td, *J* = 12.5, 5.1 Hz, 1H), 1.31 (s, 3H) ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.7, 134.6, 129.0, 128.9, 96.7, 69.7, 59.6, 41.3, 37.8, 27.4 HRMS Calculated for $C_{12}H_{16}ClN_2O_3$ $[M+H]^+$: 272.07417, Found: 272.07327. Enantiomeric excess of the piperidine was determined by HPLC analysis with a Chiralcel OD-H column (90:10 hexane: isopropanol, 0.9 mL/min, 220 nm); Racemic mixture: t_{R1} = 16.5 min, t_{R2} = 19.1 min; Enantiopure isomer: >95% ee, t_R = 16.4 min and $[\alpha]_D^{20}$ -34.4 (c = 0.1, CH_2Cl_2).

(2S,3S,4R)-2-(4-fluorophenyl)-4-methyl-3-nitropiperidin-4-ol (-4c) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, 167 mg, yield 90%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (t, *J*

= 6.7 Hz, 2H), 6.99 (d, *J* = 6.7 Hz, 2H), 4.48 (d, *J* = 10.2 Hz, 1H), 4.43 (d, *J* = 10.2 Hz, 1H), 3.28 (td, *J* = 12.1, *J* = 2.7 Hz, 1H), 2.90 (dq, *J* = 11.7, 2.0 Hz, 1H), 1.87 (dt, *J* = 13.7, 2.4 Hz, 1H), 1.69 (td, *J* = 13.7, 4.7 Hz, 1H), 1.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.3, 161.9, 134.3, 129.5, 129.4, 116.1, 115.9, 97.2, 70.0, 59.8, 41.6, 38.1, 27.7 HRMS Calculated for $C_{12}H_{16}FN_2O_3$ $[M+H]^+$: 255.1103, Found: 255.1133. Enantiomeric excess of the piperidine was determined by HPLC analysis with a Chiralcel OD-H column (90:10 hexane: isopropanol, 0.9 mL/min, 220 nm); Racemic mixture: t_{R1} = 16.6 min, t_{R2} = 21.4 min; Enantiopure isomer: >95% ee, t_R = 16.2 min and $[\alpha]_D^{20}$ -39.5 (c = 0.1, CH_2Cl_2).

(2S,3S,4R)-4-methyl-3-nitro-2-(p-tolyl)piperidin-4-ol (-4d) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, 127 mg, yield 77%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 4.52 (d, *J* = 10.2 Hz, 1H), 4.41 (d, *J* = 10.2 Hz, 1H), 3.28 (td, *J* = 12.5, 2.7 Hz, 1H), 2.91 (dd, *J* = 11.7, 2.3 Hz, 1H), 2.30 (s, 3H), 1.88 (d, *J* = 11.7 Hz, 1H), 1.66 (td, *J* = 13.3, 4.7 Hz, 1H), 1.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.6, 135.0, 129.4, 127.3, 96.8, 69.7, 60.0, 41.3, 37.9, 27.4, 21.1; HRMS Calculated for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.13510, Found: 251.13521. Enantiomeric excess of the piperidine was determined by HPLC analysis with a Chiralcel OD-H column (90:10 hexane: isopropanol, 0.9 mL/min, 220 nm); Racemic mixture: t_{R1} = 15.9 min, t_{R2} = 18.4 min; Enantiopure isomer: >95% ee, t_R = 16.4 min and $[\alpha]_D^{20}$ -29.3 (c = 0.1, CH_2Cl_2).

(2S,3S,4R)-2-(4-methoxyphenyl)-4-methyl-3-nitropiperidin-4-ol (-4e) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, 109 mg, yield 75%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.51 (d, *J* = 10.2 Hz, 1H), 4.39 (d, *J* = 10.2 Hz, 1H), 3.76 (s, 3H), 2.82 (td, *J* = 12.1, 2.7 Hz, 1H), 2.90 (dd, *J* = 11.7, 2.0 Hz, 1H), 1.86 (dt, *J* = 13.7 Hz, 1H), 1.68 (m, 1H), 1.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.8, 130.1, 128.6, 114.1, 96.9, 69.7, 59.7, 55.2, 41.4, 37.8, 27.4 HRMS Calculated for $C_{13}H_{18}N_2O_4$ $[M+H]^+$: 267.13001, Found: 267.13054. Enantiomeric excess of the piperidine was determined by HPLC analysis with a Chiralcel OD-H column (95:5 hexane: isopropanol, 0.5 mL/min, 220 nm); Racemic mixture: t_{R1} = 27.1 min, t_{R2} = 34.4 min; Enantiopure isomer: >95% ee, t_R = 35.5 min and $[\alpha]_D^{20}$ -42.7 (c = 0.1, CH_2Cl_2).

(2R,3S,4R)-2-(furan-2-yl)-4-methyl-3-nitropiperidin-4-ol (-4f) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, 108 mg, yield 65%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (m, 1H), 6.27 (m, 2H), 4.67 (d, *J* = 10.2 Hz, 1H), 4.62 (d, *J* = 10.2 Hz, 1H), 3.33 (s, 1H), 3.26 (td, *J* = 12.5, 2.7 Hz, 1H), 2.93 (dd, *J* = 12.5, 2.0 Hz, 1H), 1.88 (d, *J* = 14.1 Hz, 1H), 1.33 (s, 3H). ^{13}C NMR (150 MHz, CDCl3): δ 143.2, 110.5, 108.6, 94.6, 69.8, 53.8, 41.1, 38.5, 29.9, 27.7 HRMS Calculated for $C_{10}H_{15}N_2O_4$ $[M+H]^+$: 227.09871, Found: 227.09751. Enantiomeric excess of the piperidine was determined by HPLC analysis with a Chiralcel OD-H column (90:10 hexane: isopropanol, 1 mL/min, 220 nm); Racemic mixture: t_{R1} = 19.1 min, t_{R2} = 25.1 min; Enantiopure isomer: >95% ee, t_R = 18.4 min and $[\alpha]_D^{20}$ +57.2 (c = 0.1, CH_2Cl_2).

(2R,3S,4R)-4-methyl-3-nitro-2-(thiophen-2-yl)piperidin-4-ol (-4g) was purified by flash silica gel chromatography (CH_2Cl_2-MeOH, v/v 100/1) as solid, 148 mg, yield: 85%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 4.7 Hz, 1H), 6.94 (d, *J* = 3.5 Hz, 2H), 6.90 (t, *J* = 5.1 Hz, 1H), 4.81 (d, *J* = 10.2 Hz, 1H), 4.47 (d, *J* = 10.2 Hz, 1H), 3.28 (td, *J* = 12.1, 2.2 Hz, 1H), 2.90 (dq, *J* = 11.7, 2.3 Hz, 1H), 1.87 (dt, *J* = 13.7, 2.7 Hz, 1H), 1.69 (td, *J* = 12.5, 5.1 Hz, 1H), 1.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.9, 126.9, 126.2, 125.9, 98.1, 70.0, 56.1, 36.4, 28.4, 26.9; HRMS Calculated for $C_{10}H_{15}N_2O_3S[M+H]^+$: 243.07587, Found: 243.07551. Enantiomeric excess of the

piperidine was determined by HPLC analysis with a Chiralcel OD-H column (90:10 hexane: isopropanol, 1 mL/min, 220 nm); Racemic mixture: t_{R1} = 20.1 min, t_{R2} = 26.7 min; Enantiopure isomer: >95% ee, t_R = 26.3 min and $[\alpha]_D^{20}$ +51.8 (c = 0.1, CH_2Cl_2).

General Procedure for the Preparation of Thiourea-Based-Piperidine (5 and 6). To a solution of 3d (major) (800 mg, 2.16 mmol, 1eq) were added 1N HCl in MeOH (25 mL, >10 eq.) and Zn powder (2.20 g, 34.6 mmol, 15 eq.). The mixture was then stirred at room temperature and monitored by TLC. After the complete consumption of 3d, MeOH was completely evaporated followed by treatment with saturated aqueous $NaHCO_3$ until pH > 10, and CH_2Cl_2. Organic layer was extracted with CH_2Cl_2 (30 mL x 5). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was dissolved in minimum CH_2Cl_2 and purified by flash silica gel chromatography (CH_2Cl_2-MeOH v/v 100:1), which gave almost quantitative amount of **5** (700 mg, 2.0 mmol, yield 95%).

To a solution of amine **5** (700 mg, 2.0mmol) in 20 ml dichloromethane was added 3,5 di-trifluoromethyl-phenyl isothiocyanate (557 mg, 2.0 mmol, 1.0 eq.) and stirred for overnight. After, TLC showed the disappearance of **5**, the solution was evaporated and the residue was chromatographed in solvent system (EtoAc: Hexane, v/v 5:1 to 1:1) to afford white solid **6** (1.078 g, 1.78 mmol, yield: 86%).

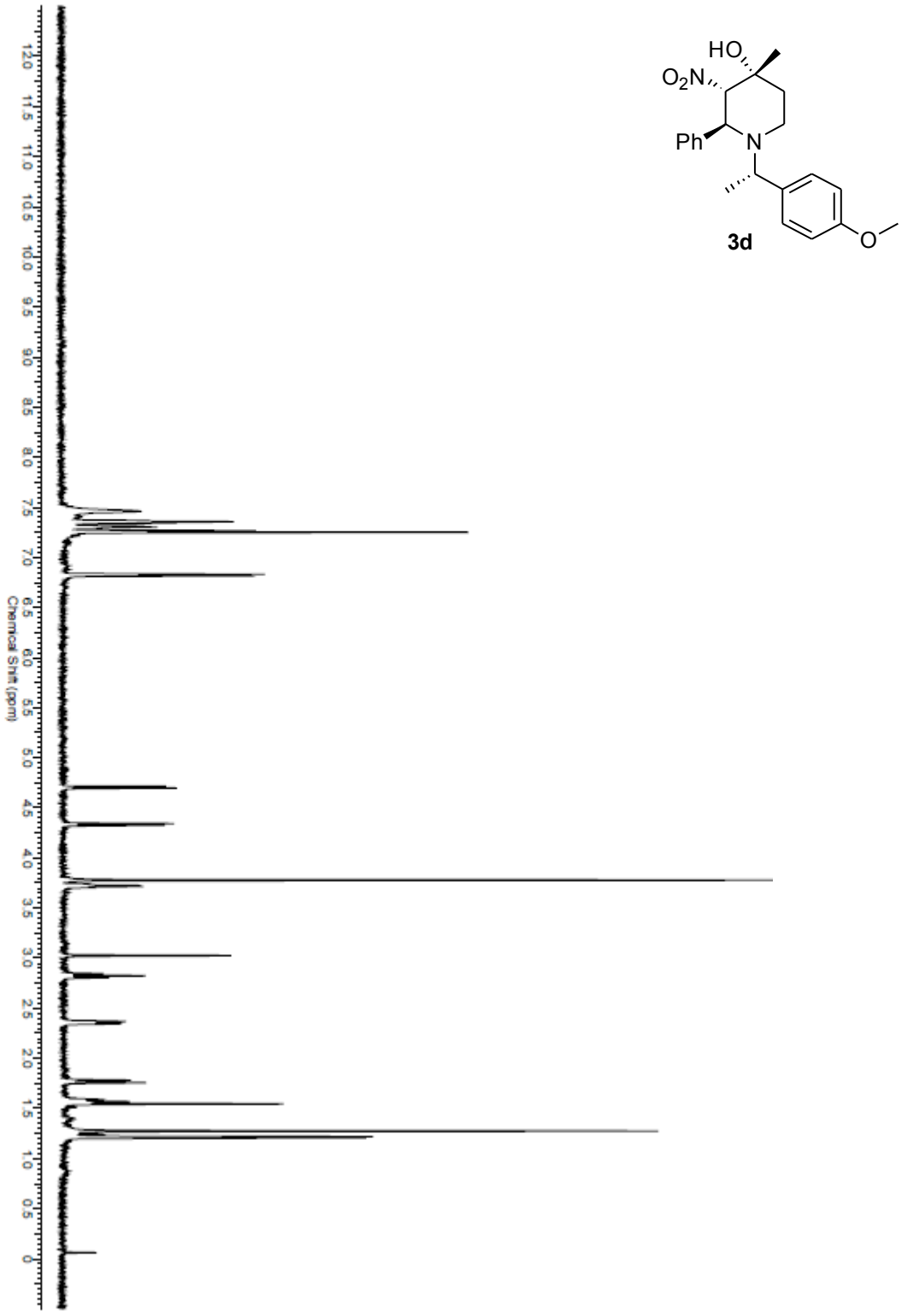
1-(3,5-bis(trifluoromethyl)phenyl)-3-((2S,3S,4R)-4-hydroxy-1-((S)-1-(4-methoxyphenyl)ethyl)-4-methyl-2-phenylpiperidin-3-yl)thiourea (6) was purified by flash silica gel chromatography (Hexane/EtOAc, v/v 5/1 to 1/1) as solid, 1.078g, yield 86 %. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (s, 2H), 7.73 (t, *J* = 10.0 Hz, 1H), 7.65 (s, 1H), 7.49 (m, 2H) 7.31 (d, *J* = 8.8 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.93 (s, 1H), 4.73 (s, 2H), 4.65 (t, *J* = 10.0 Hz, 1H), 3.73 (s, 3H), 3.70 (m, 1H), 3.60 (q, *J* = 6.85 Hz, 1H), 2.66 (m, 2H), 2.19 (m, 1H), 1.62 (m, 1H), 1.14 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (150 MHz, CDCl3): δ 185.7, 162.8, 147.2, 145.2, 140.8, 135.7, 135.3, 135.0, 134.7, 133.4, 132.1, 129.7, 127.0, 126.3, 120.8, 118.4, 74.9, 70.3, 68.1, 60.1, 58.9, 43.4, 43.0, 32.9, 13.3. HRMS Calculated for $C_{30}H_{32}F_6N_3O_2S$ $[M+H]^+$: 612.20747, Found: 612.20711.

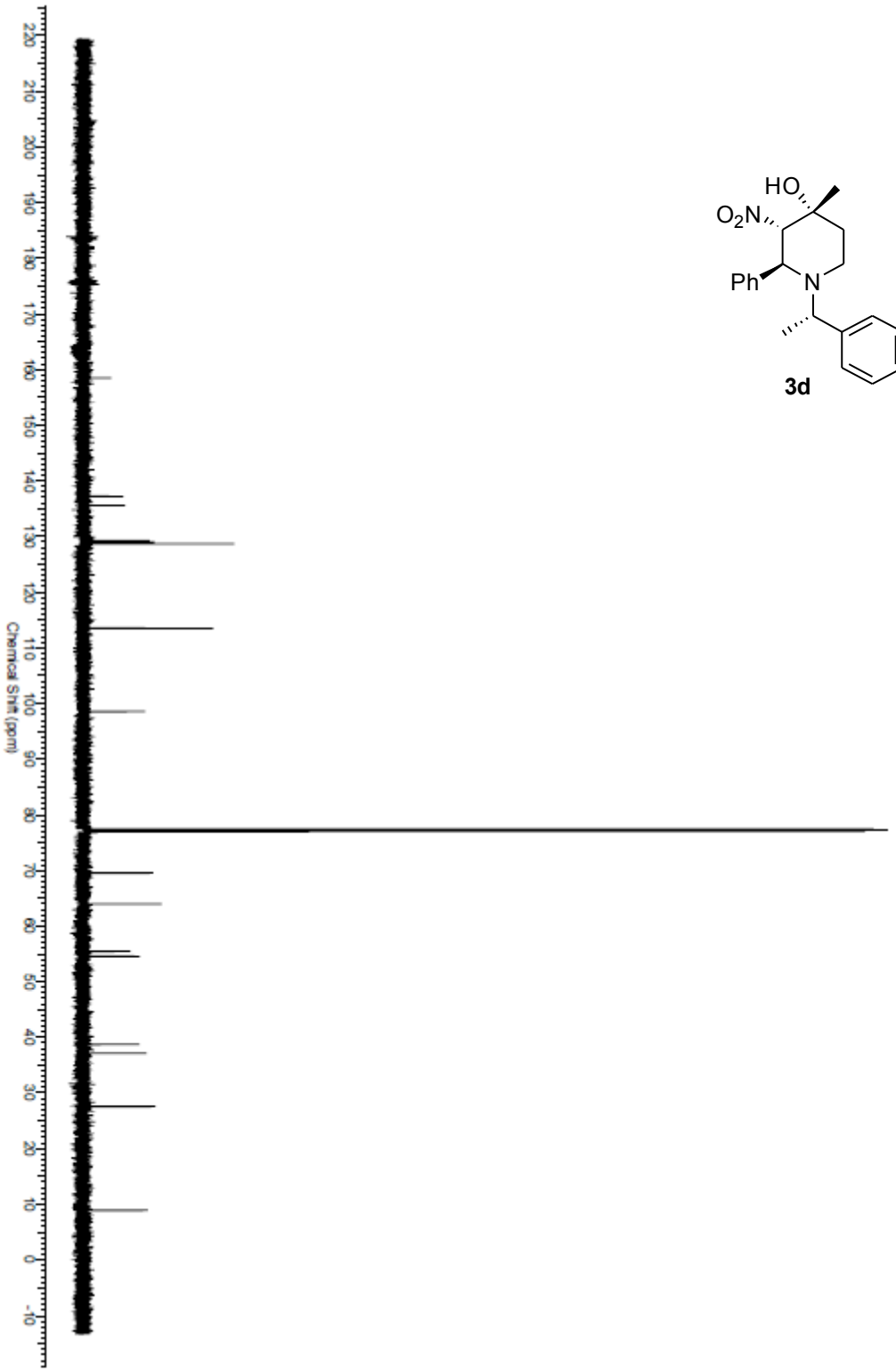
Asymmetric Michael addition of Nitromethane to Chalcone with Chiral Organocatalysis.[1] To a solution of chalcone (1 mmol, 1.0 equiv) and nitromethane (915 mg/0.80 ml, 15 mmol, 15.0 equiv) was added thiourea-catalyst **6** (122 mg, 0.2 mmol, 20 mol%). The reaction mixture was stirred in capped vial for 6 h at 50 °C. Then the volatiles were removed by concentration and the residue purified by silica gel flash column chromatography (ethyl acetate-petroleum ether 1:15 V/V) to afford the product as white solid (253 mg, 80% yield). Enantiomeric excess was determined by HPLC on Chiralpak AS-H column (n-hexane-isopropanol 90:10 V/V, flow rate 1.0 mL/min, 220 nm), major enantiomer t_R = 10.3 min, minor enantiomer t_R = 13.6 min, 88 % ee (R) $[\alpha]_D^{25}$ = +

[1] For the preparation of racemic product, see: N. Ono, A. Kamimura, H. Miyake, L. Hamamoto, and A. Kaji, , *J. Org. Chem.* **1985**, *50*, 3692.

26.7 8 (c = 0.1, CH_2Cl_2, 88 % ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.91–7.89 (m, 2H), 7.57–7.54 (m, 1 H), 7.46–7.42 (m, 2H), 7.32–7.27 (m, 5H), 4.81 (dd, *J* = 12.5, 6.6 Hz,1H), 4.68 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.22 (ps quint, *J* = 7.1 Hz, 1H), 3.50-3.37 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 139.1, 136.3, 133.5, 129.3, 129.1, 129.0, 128.7, 127.4, 79.5, 41.5, 39.2.

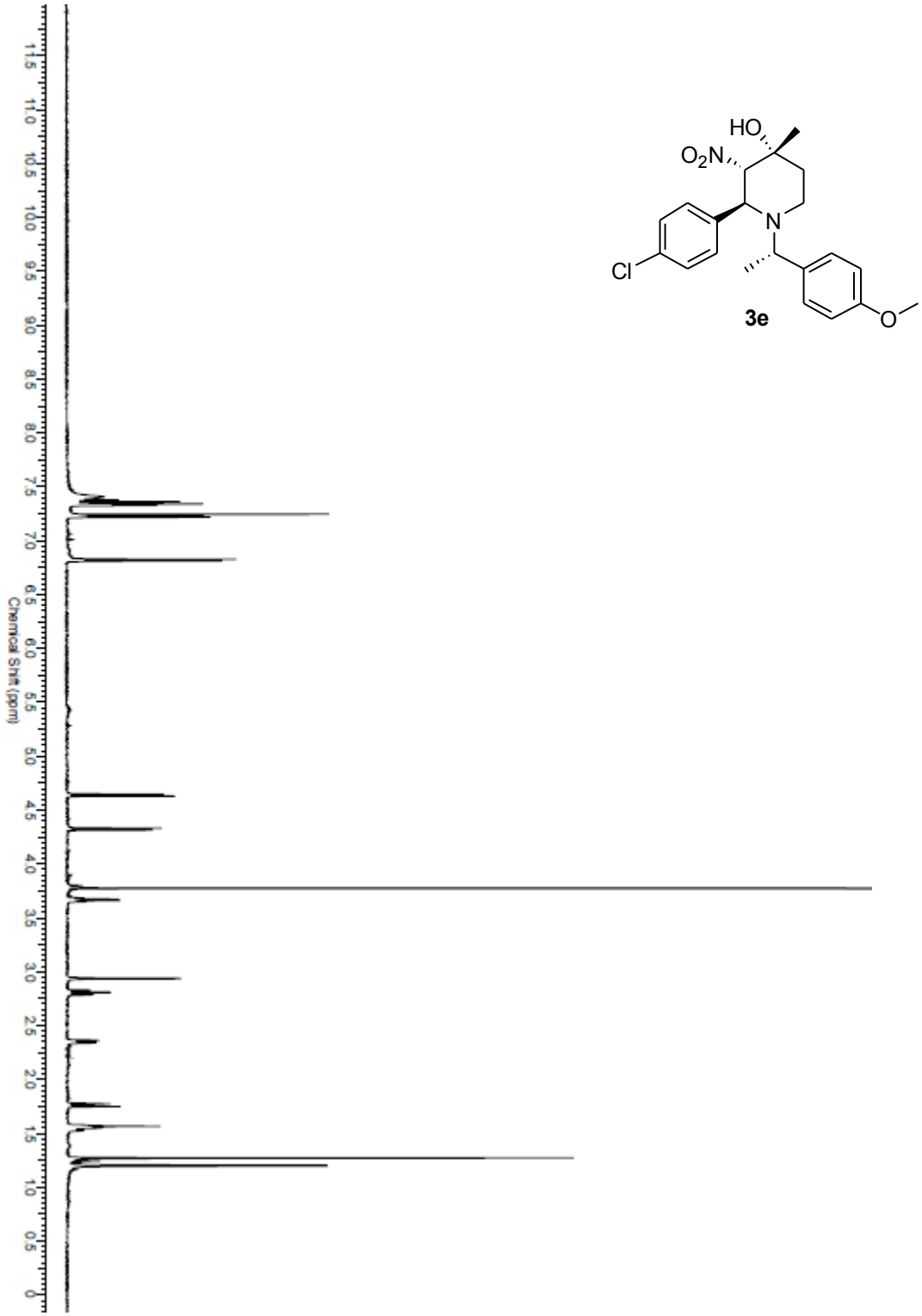
III. ^{1}H NMR and ^{13}C NMR Spectra

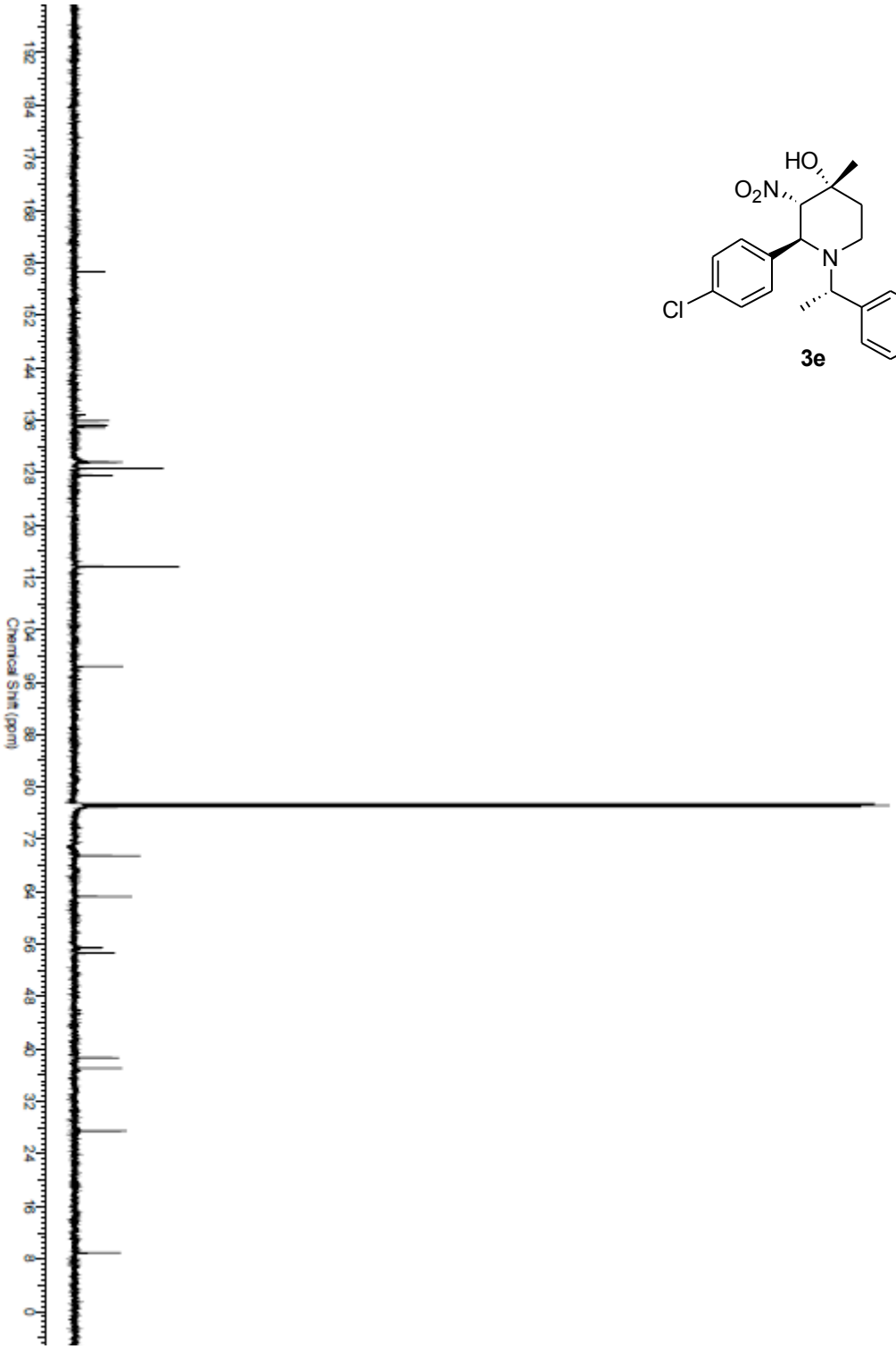

HO
O2N
Ph
N
O
3d
Chemical Shift (ppm)


Chemical Shift (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

HO
O2N
Ph
N
O

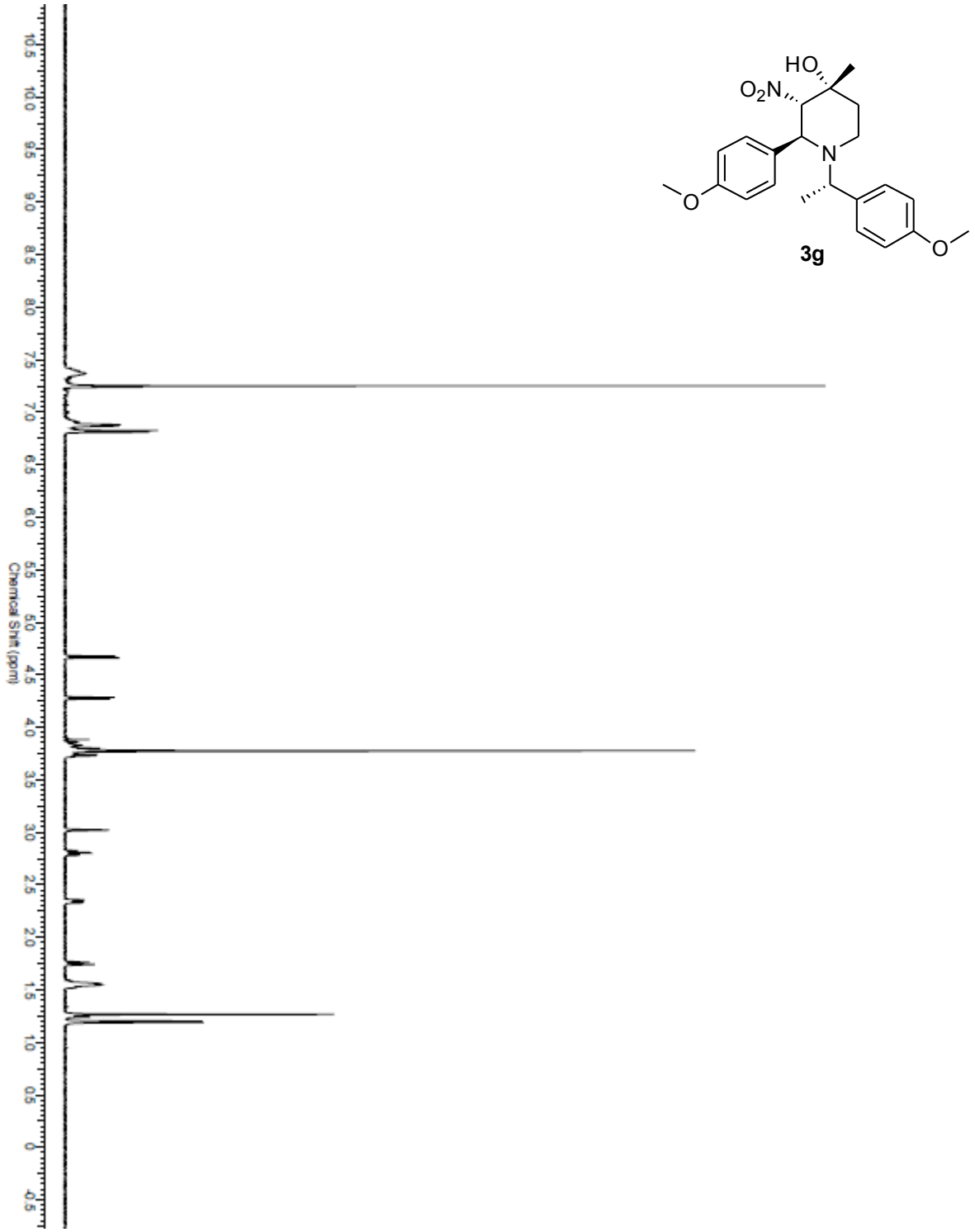
3d

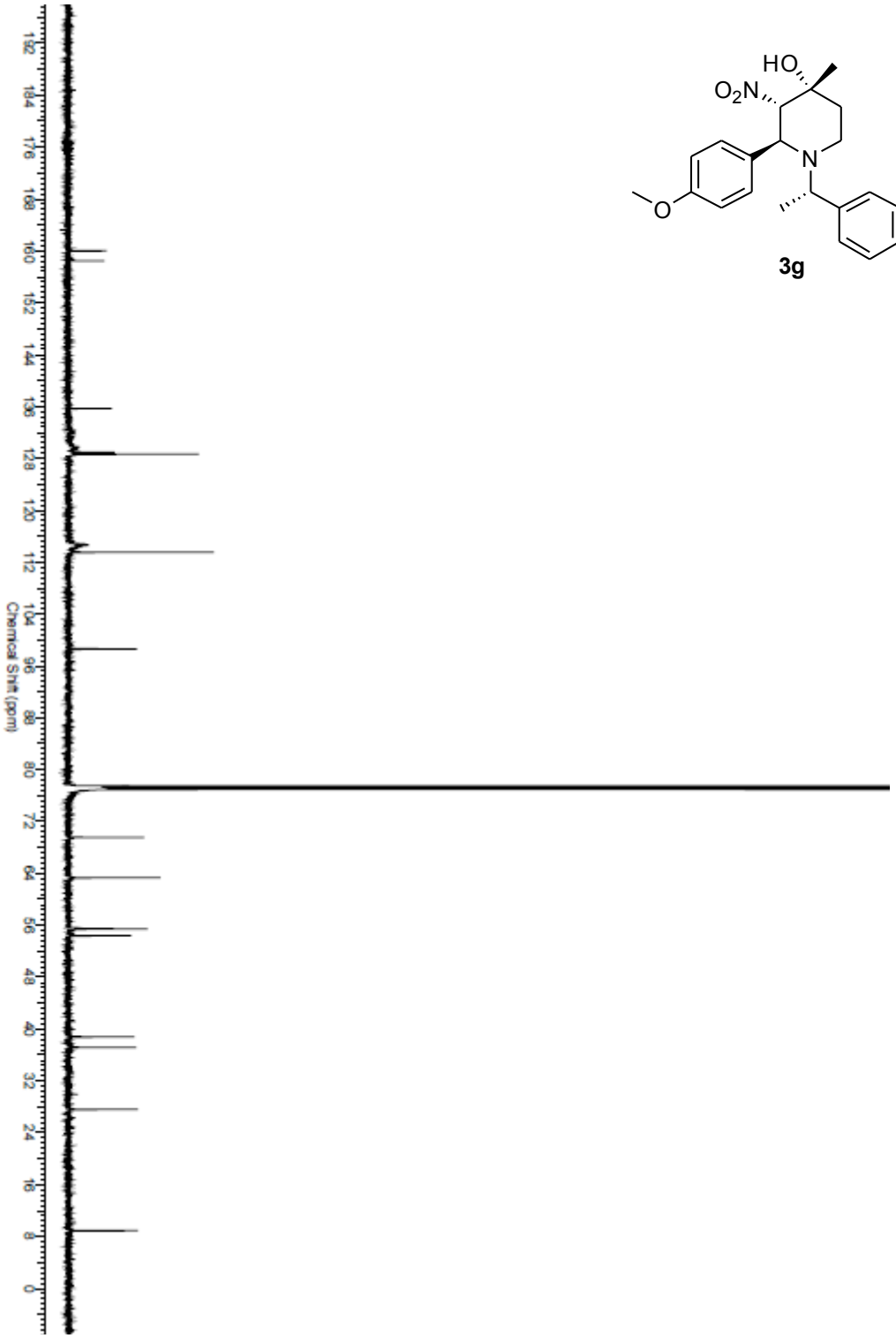

HO
O2N
N
Cl
O
3e
Chemical Shift (ppm)

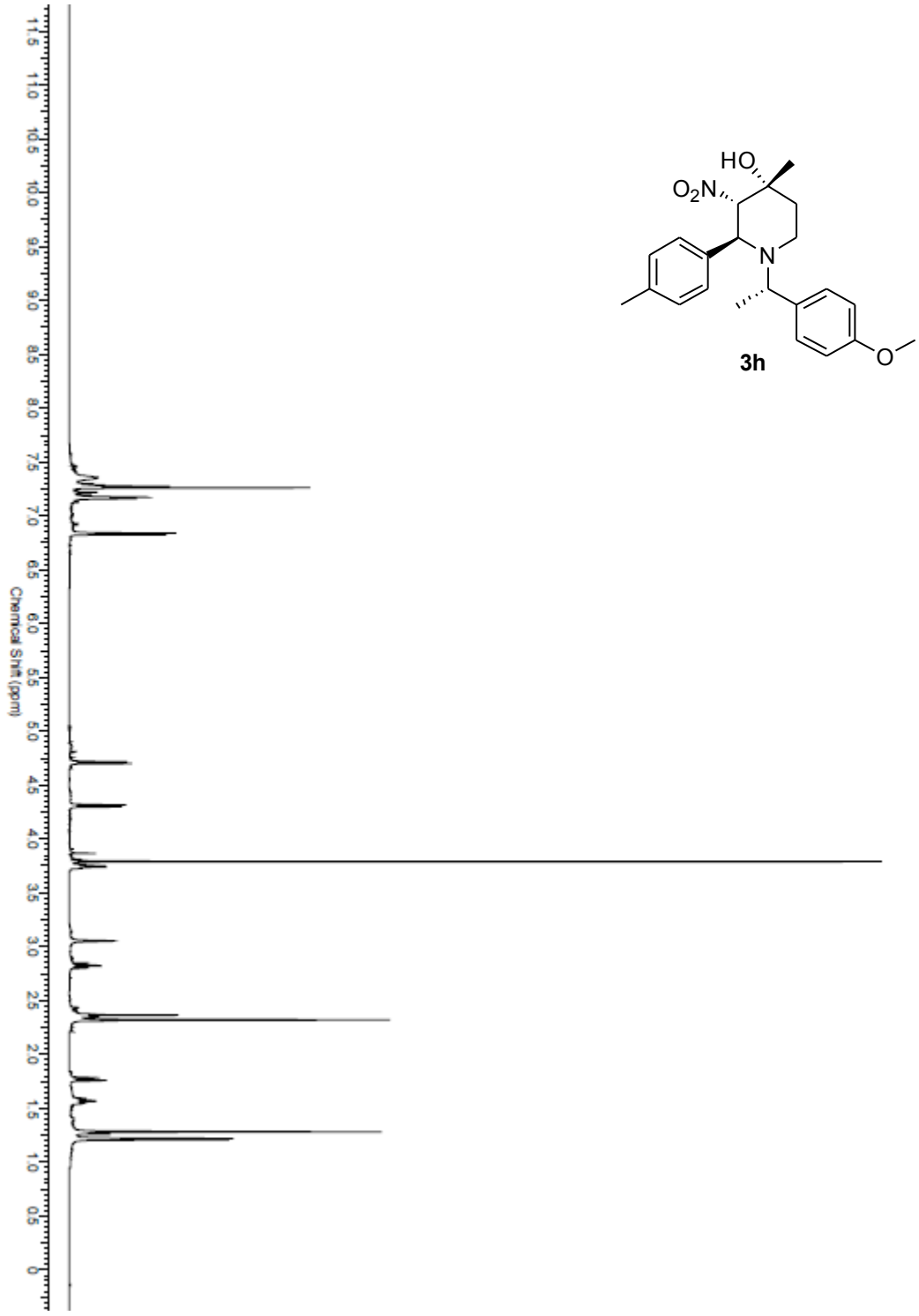

Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

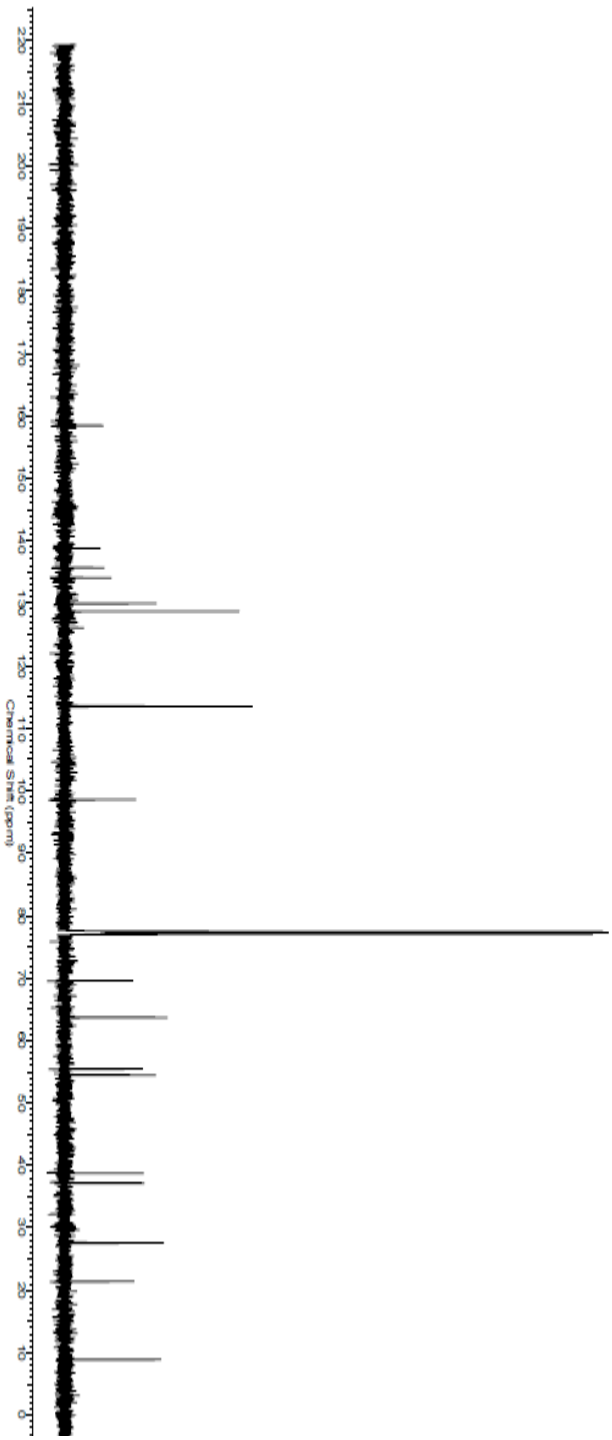
HO
O2N
N
Cl
O

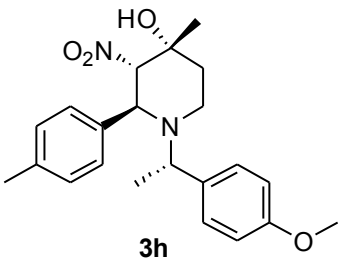
3e


HO
O2N
N
O
O
3g
Chemical Shift (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5

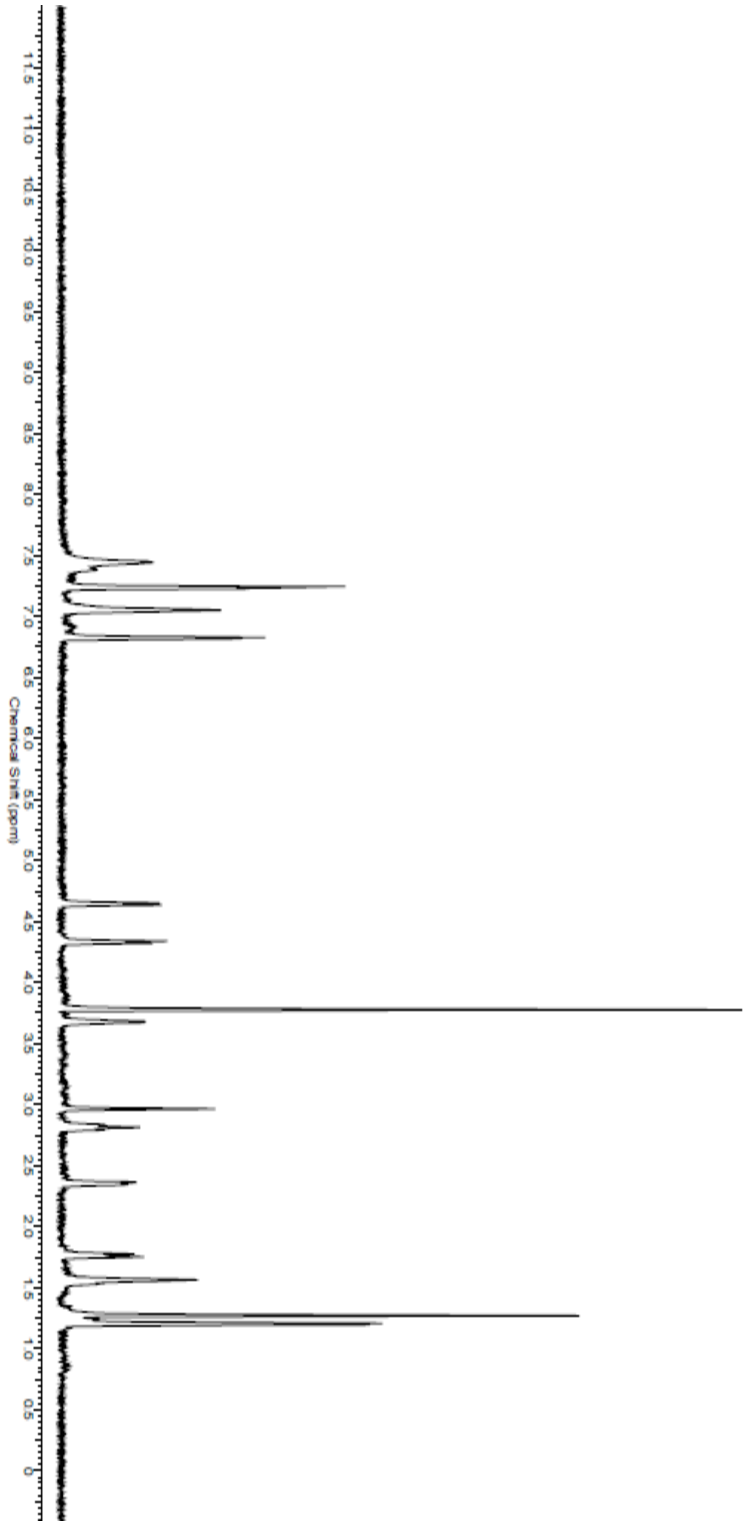

HO
O2N
N
O
O
3g
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

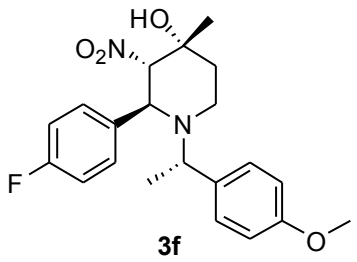

HO
O2N
N
O
3h
Chemical Shift (ppm)



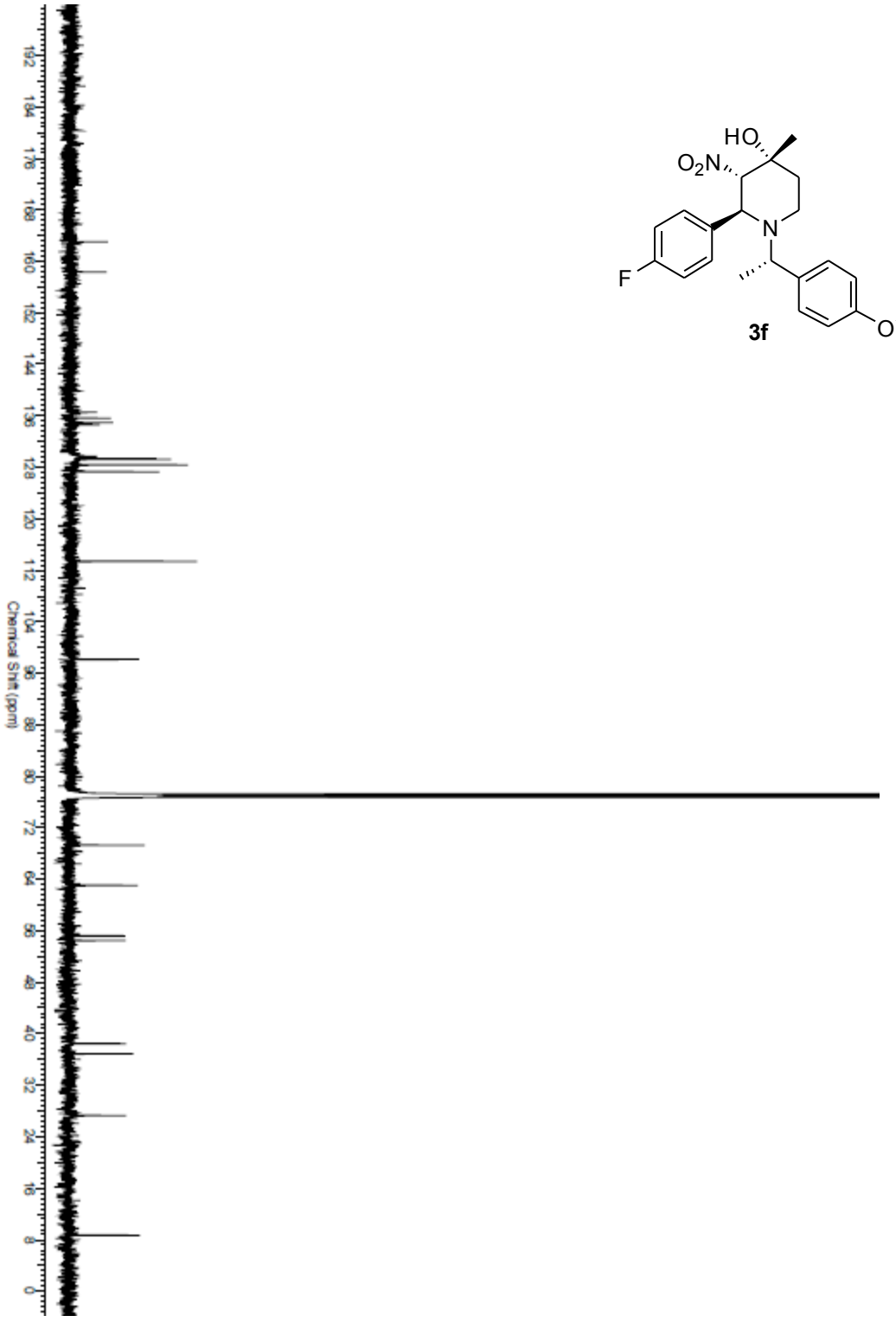


3h



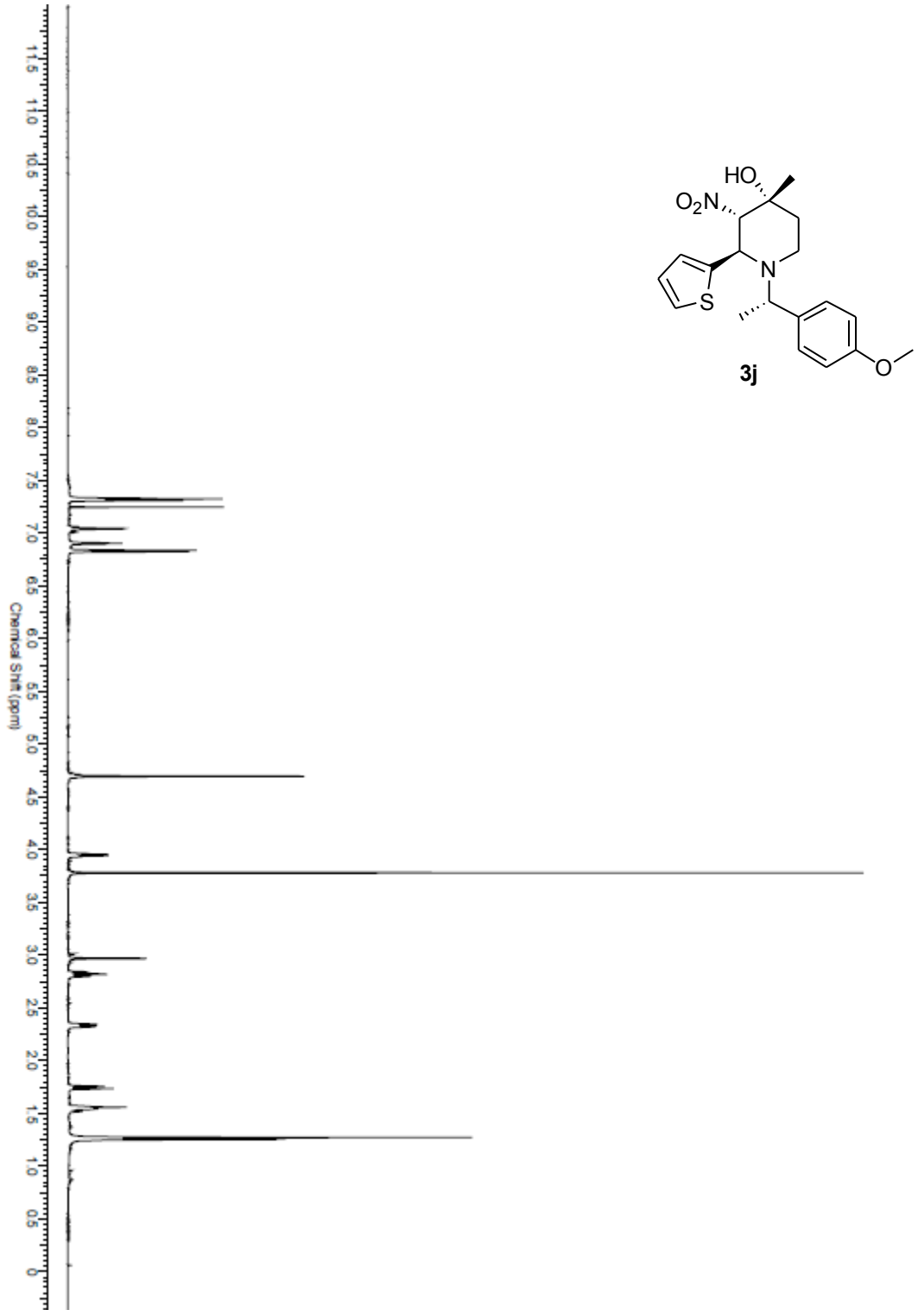


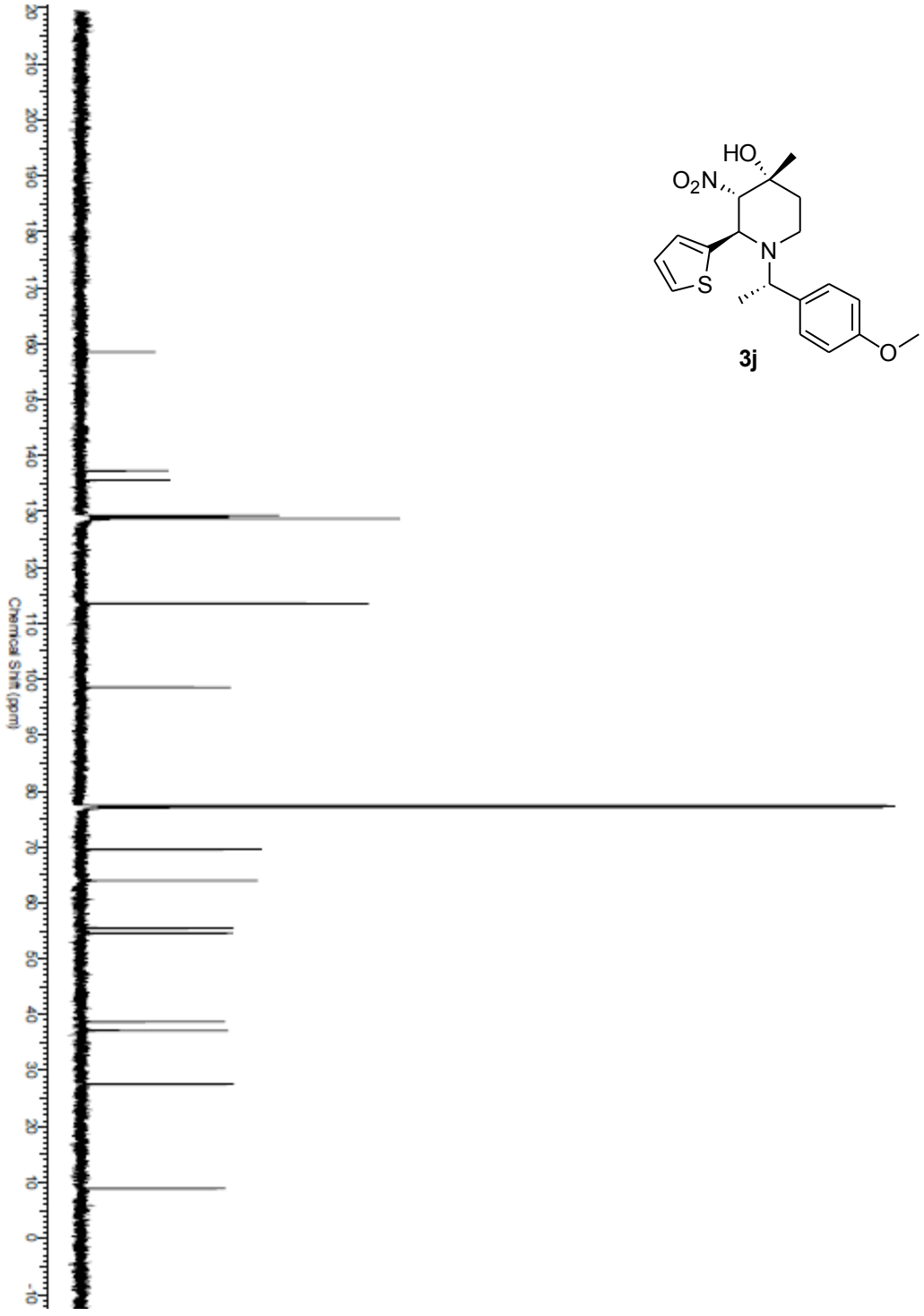
3f


Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

HO
O2N
N
F
O

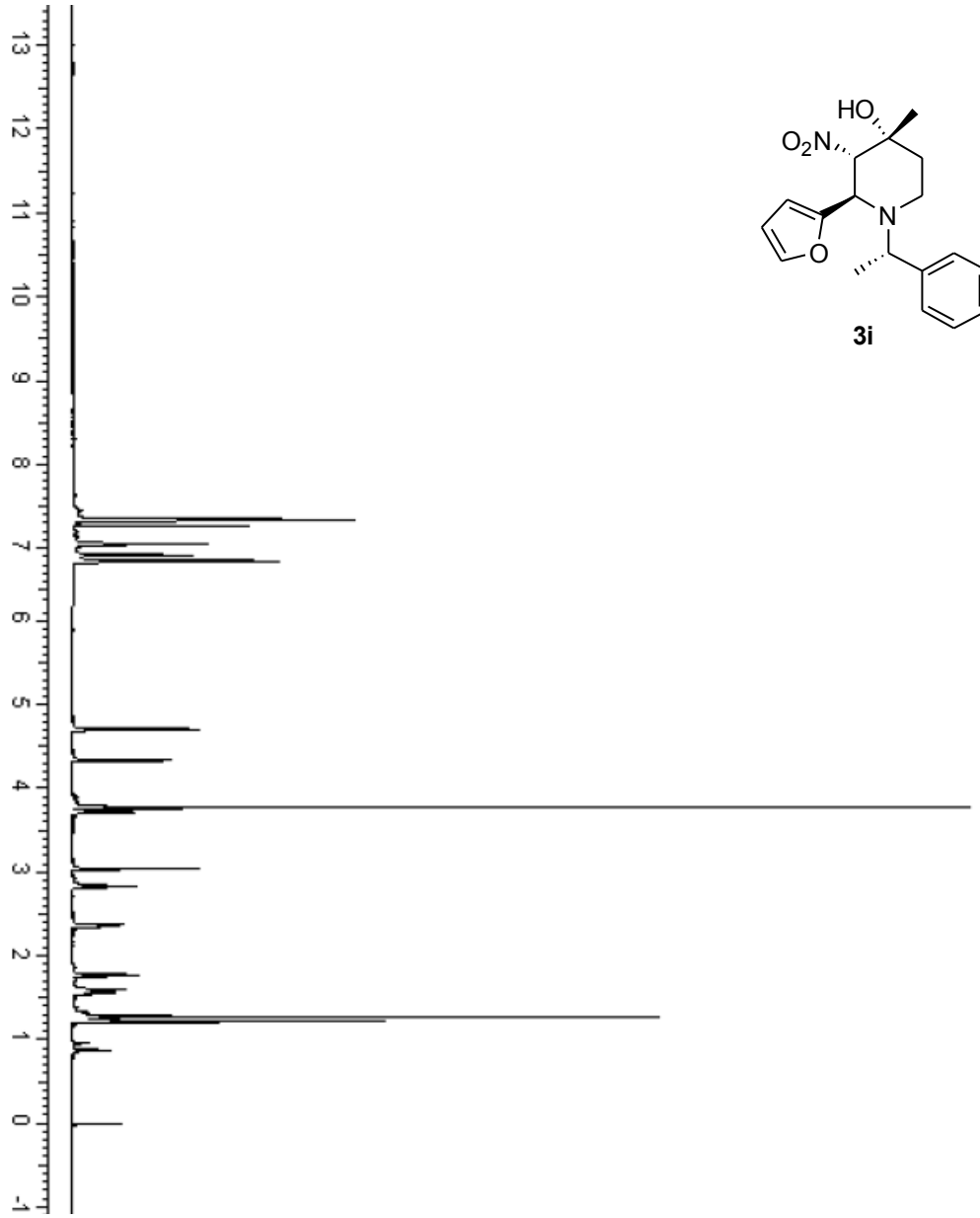
3f


HO
O_2N
N
S
O
3j
Chemical Shift (ppm)

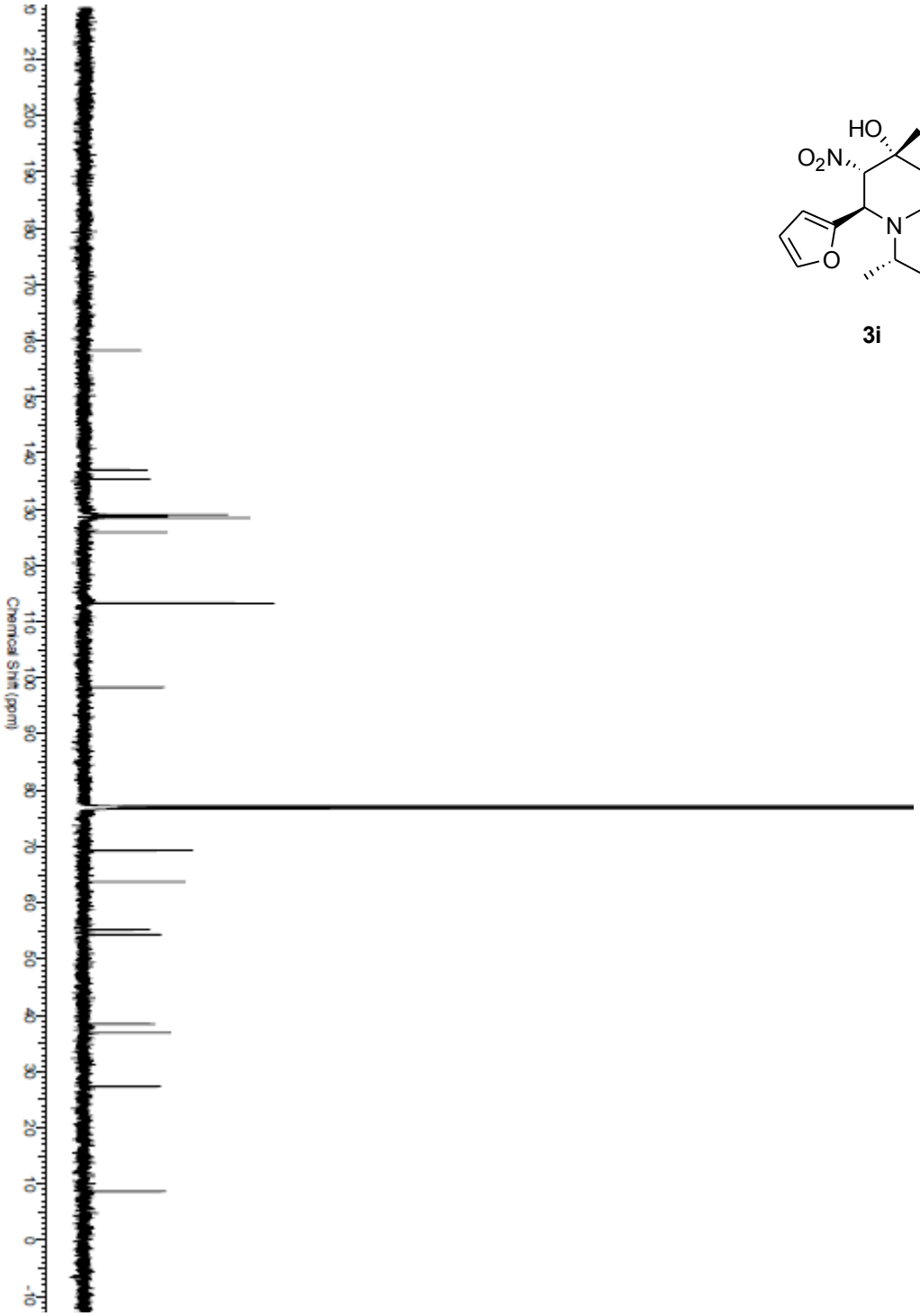

Chemical Shift (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

HO
O2N
N
S
O

3j

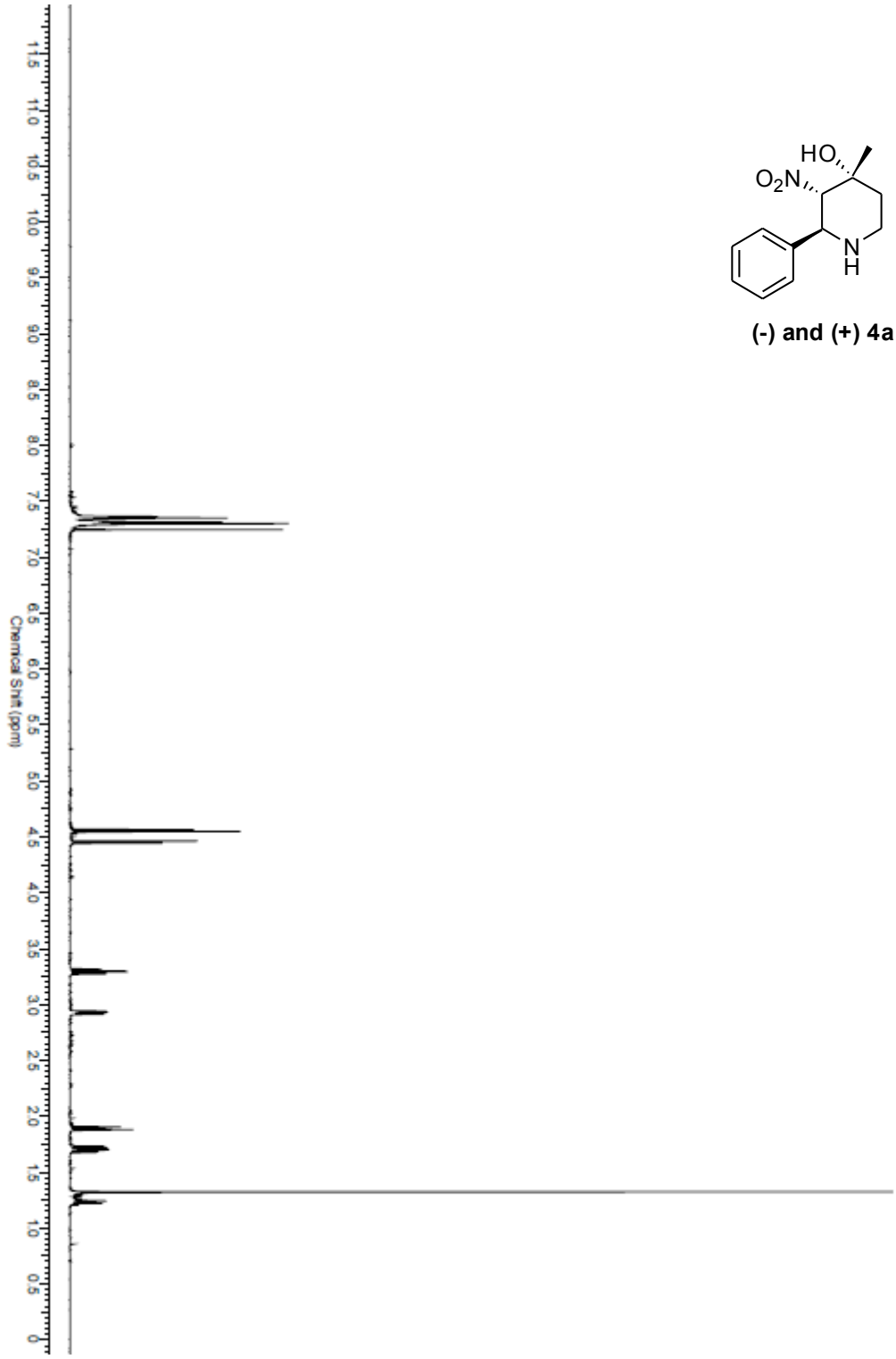


3i


Chemical Shift (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

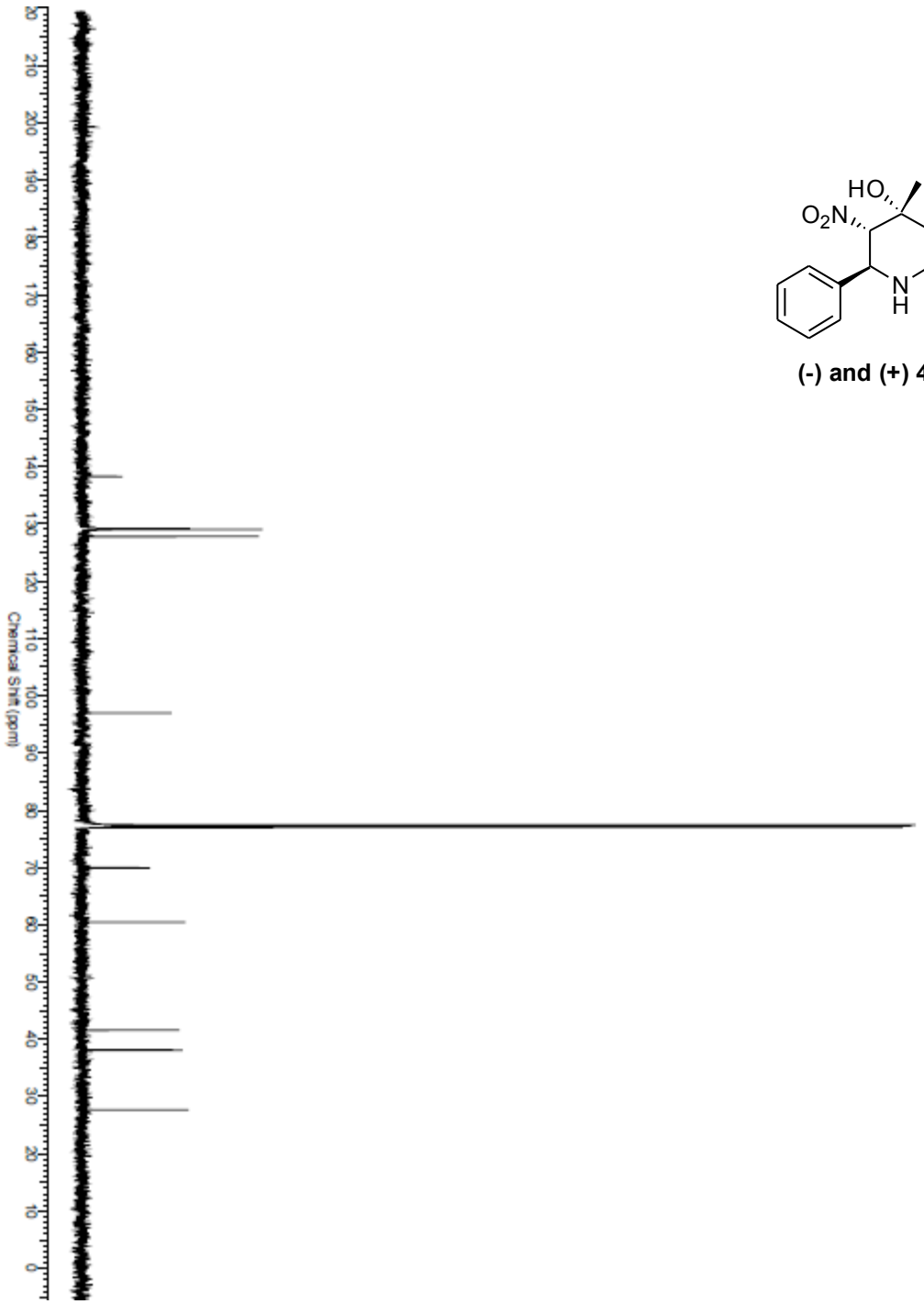
HO
O2N
N
O
O

3i


Chemical Shift (ppm)
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

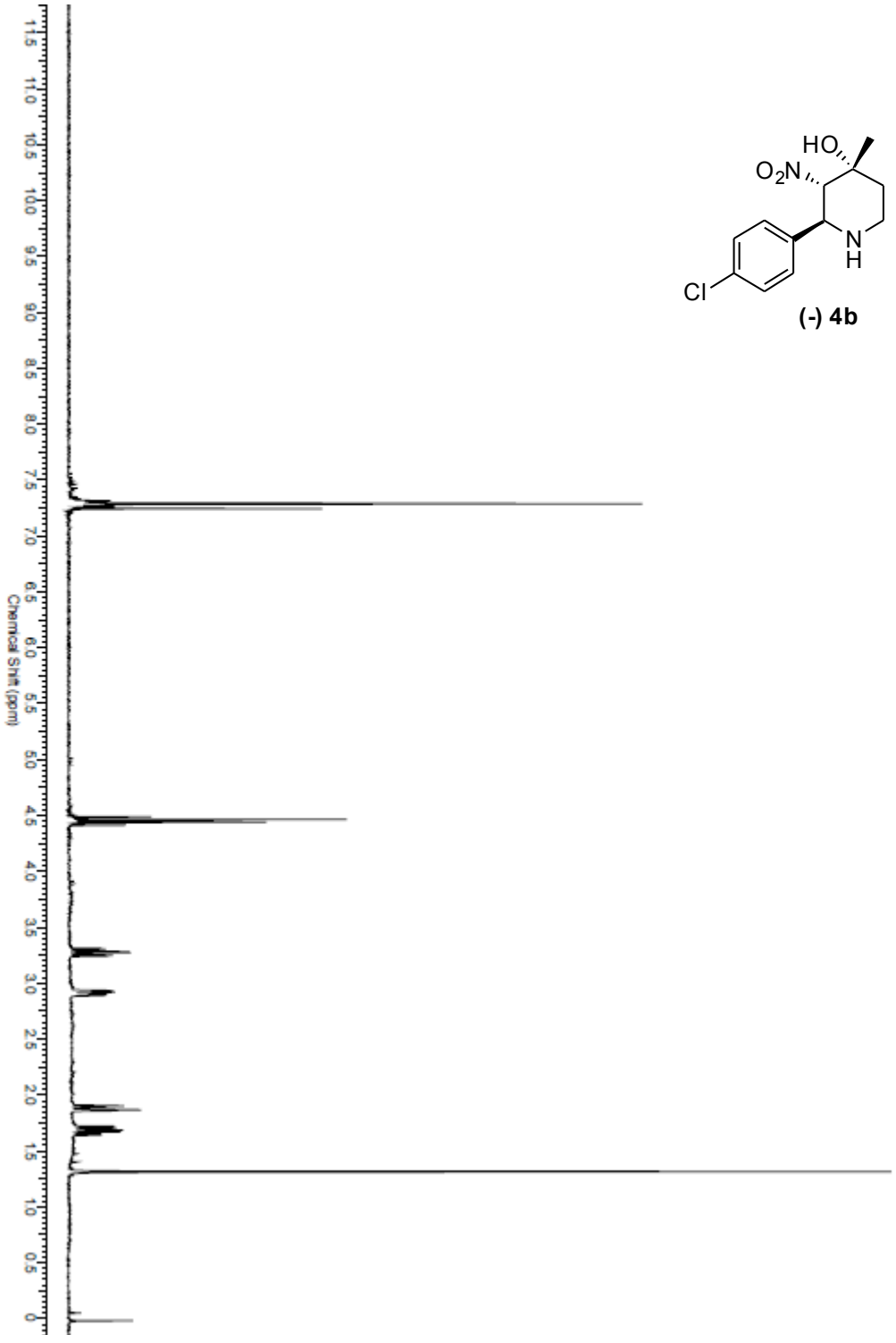
HO
O2N
N
H

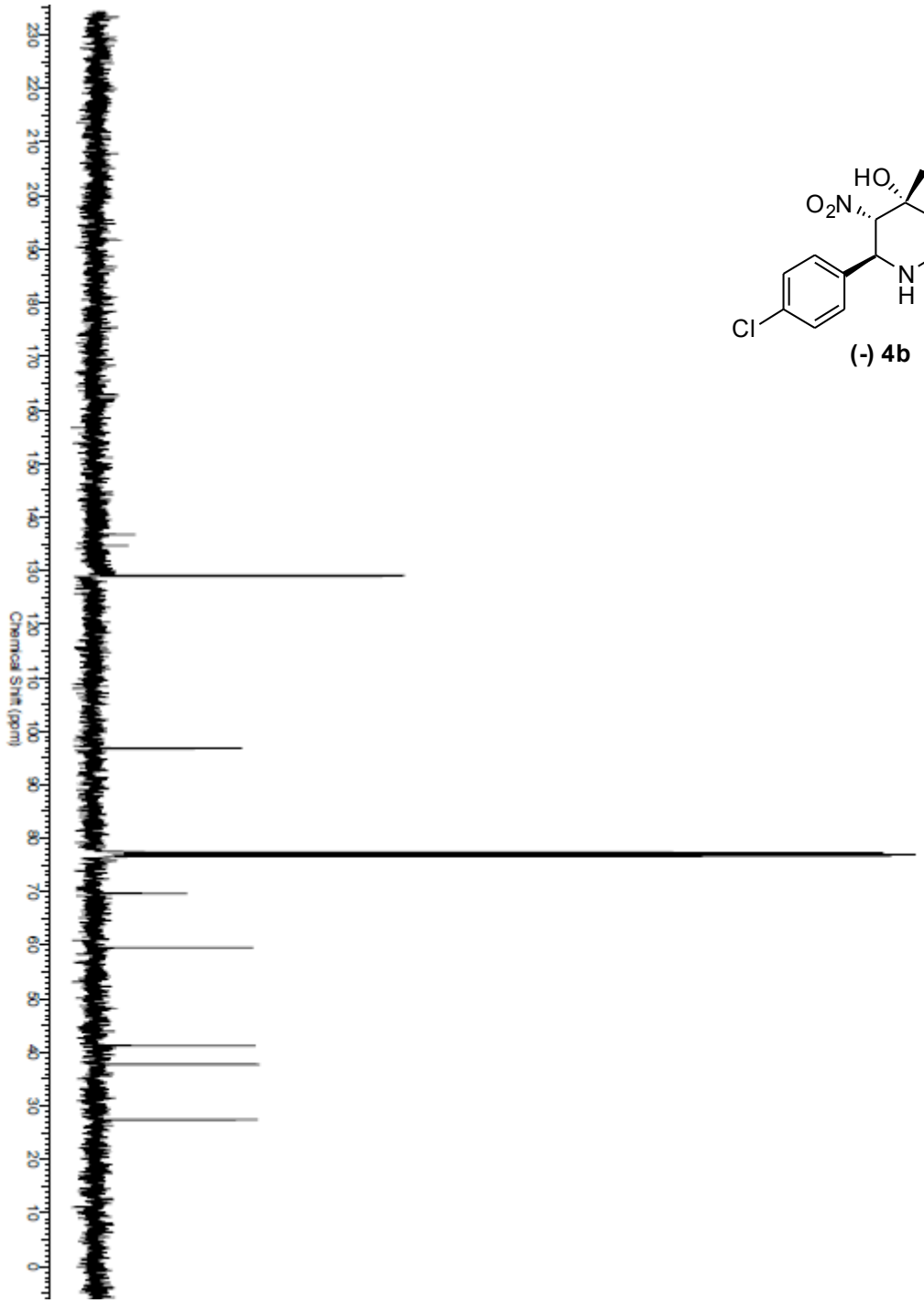
(-) and (+) 4a


Chemical Shift (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

HO
O2N
N
H

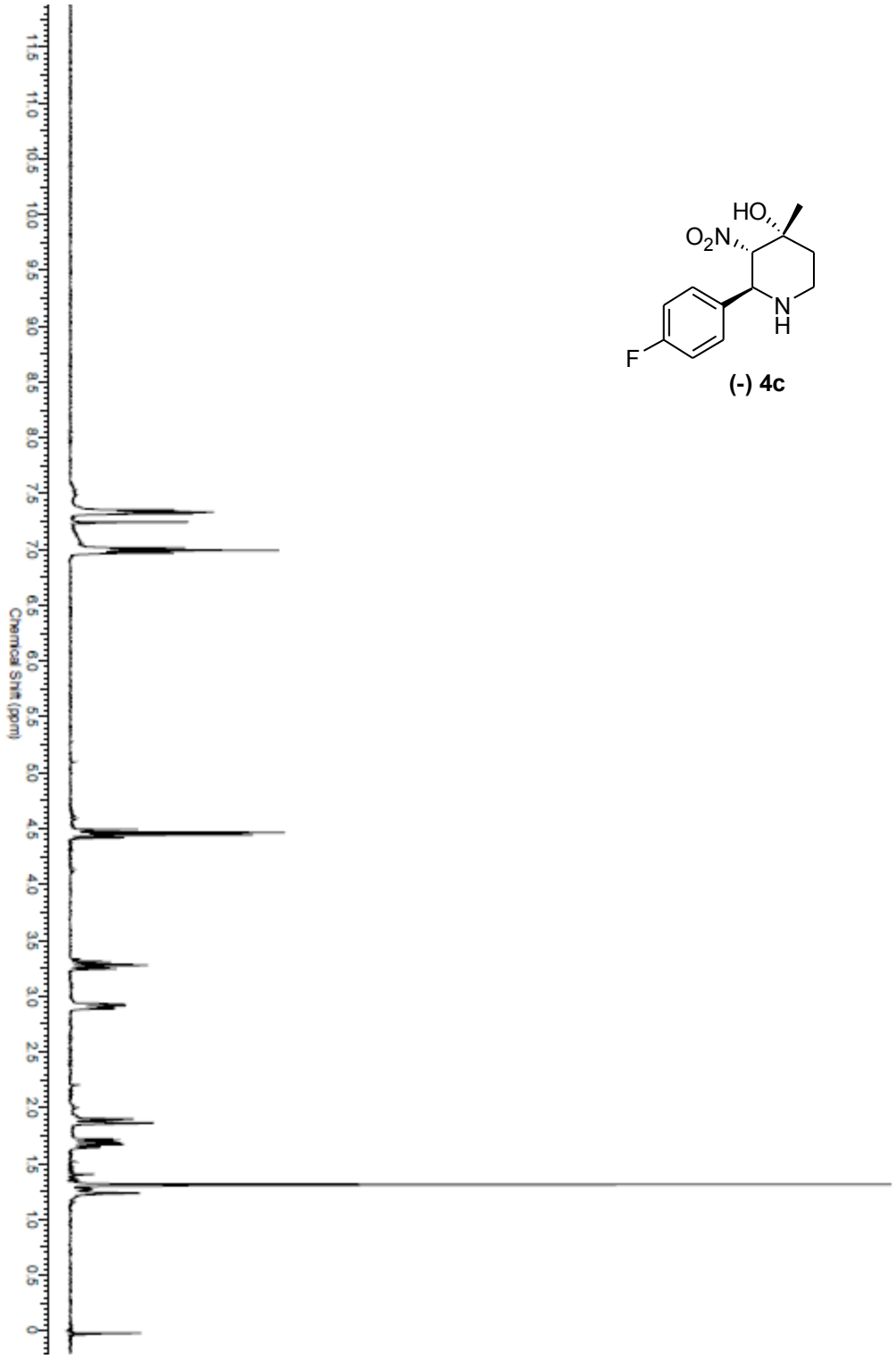
(-) and (+) 4a


HO
O2N
N
H
Cl
(-) 4b
Chemical Shift (ppm)

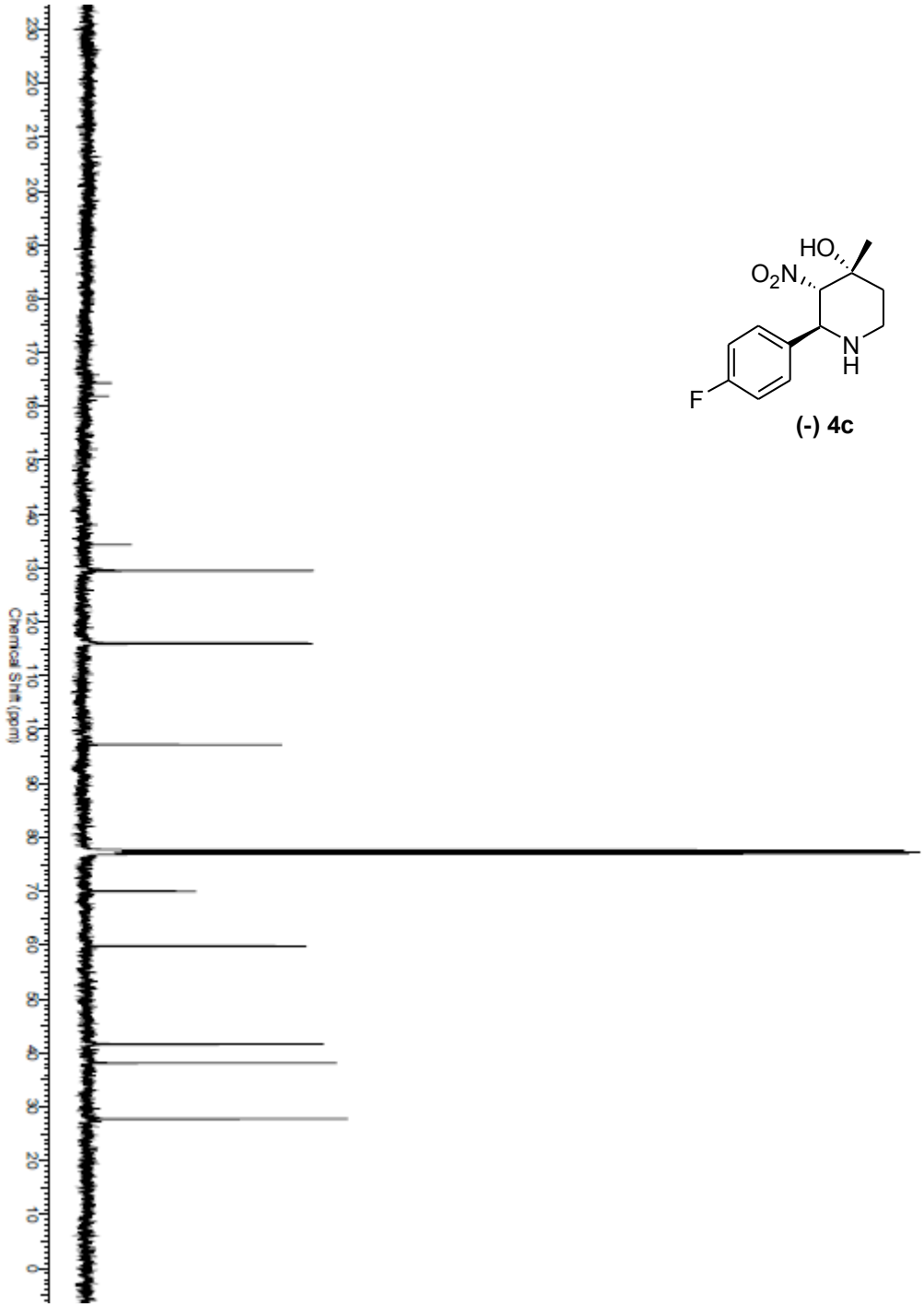

Chemical Shift (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

HO
O2N
N
H
Cl

(-) 4b

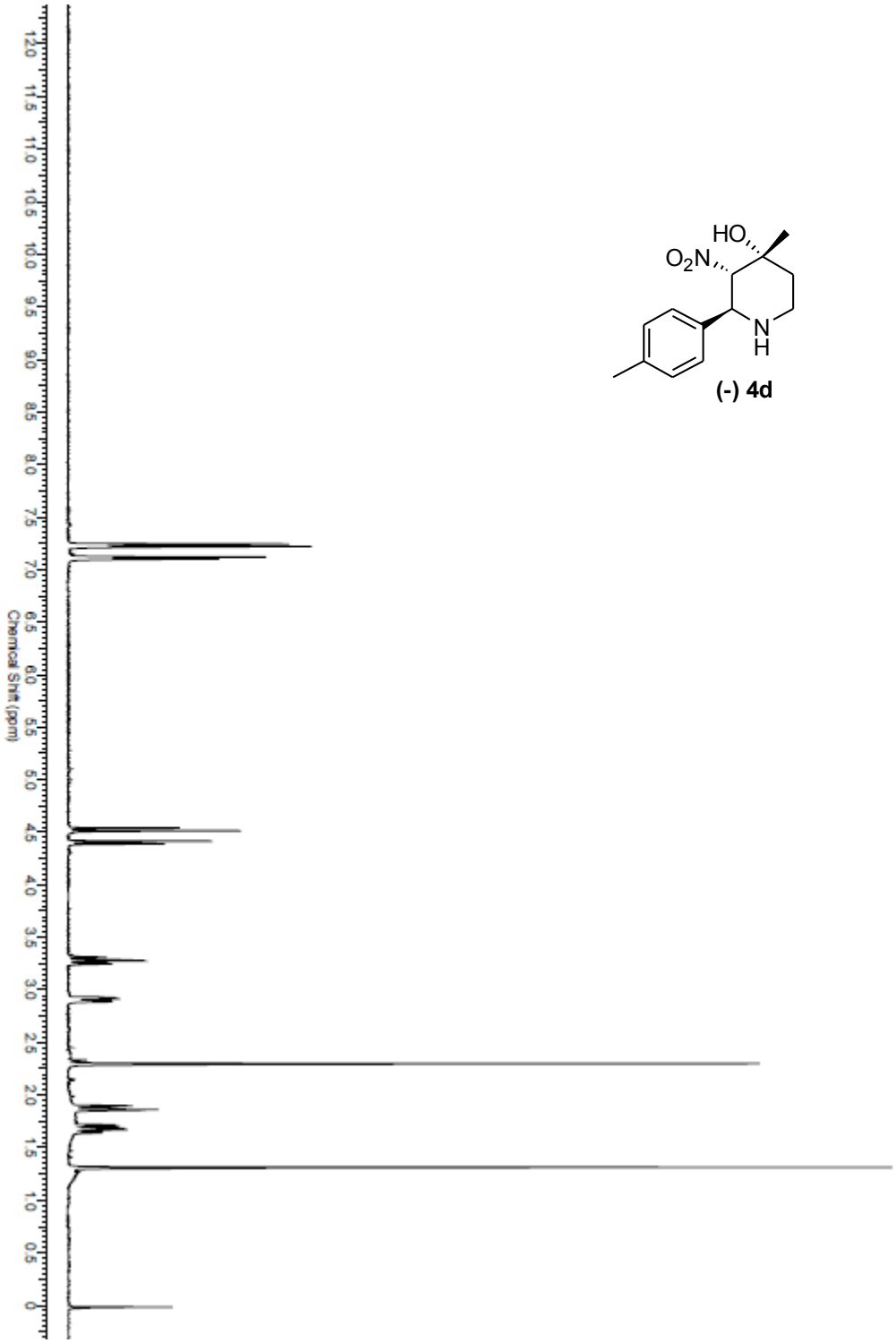


(-) 4c

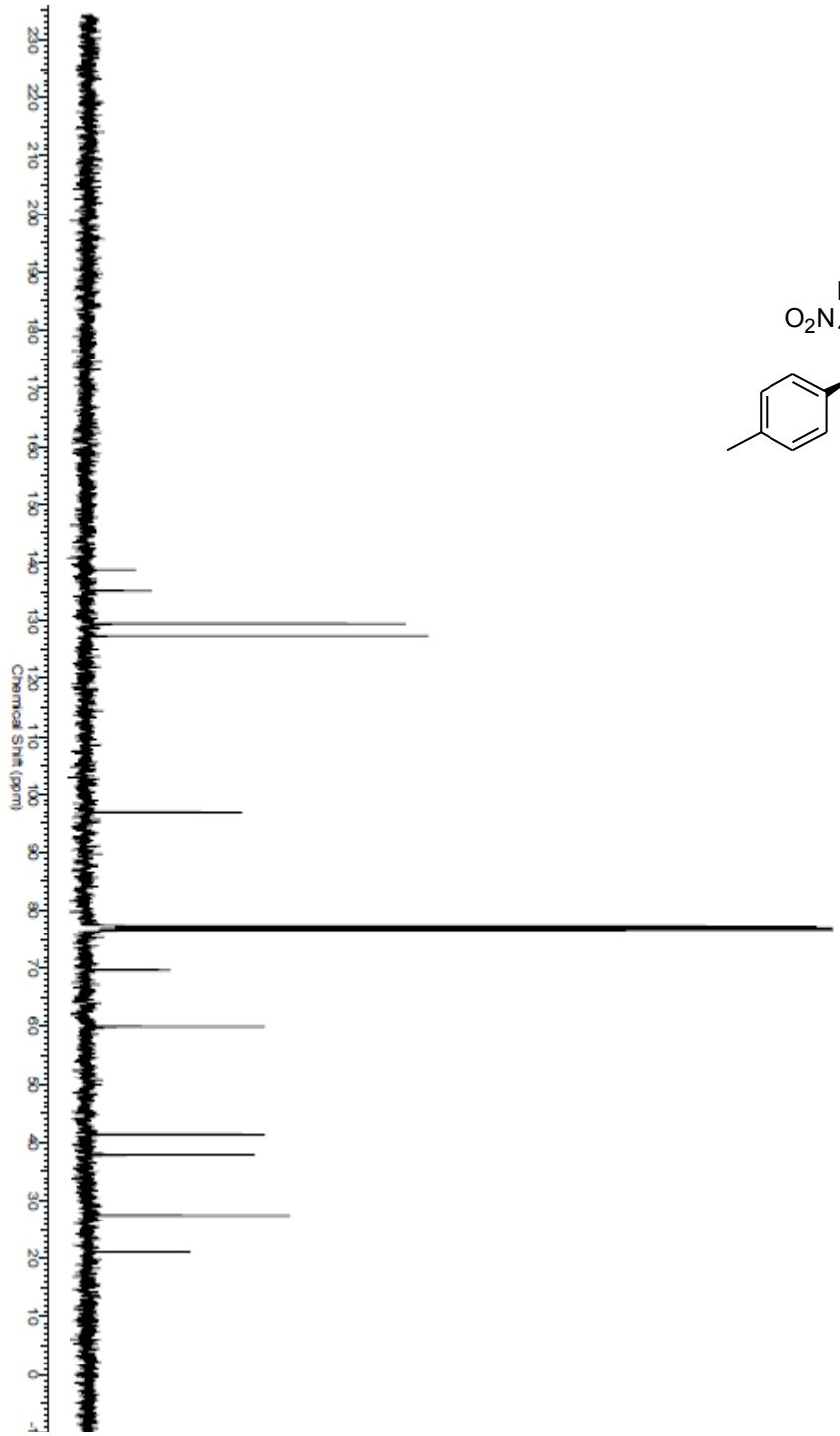

Chemical Shift (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

HO
O2N
N
H
F

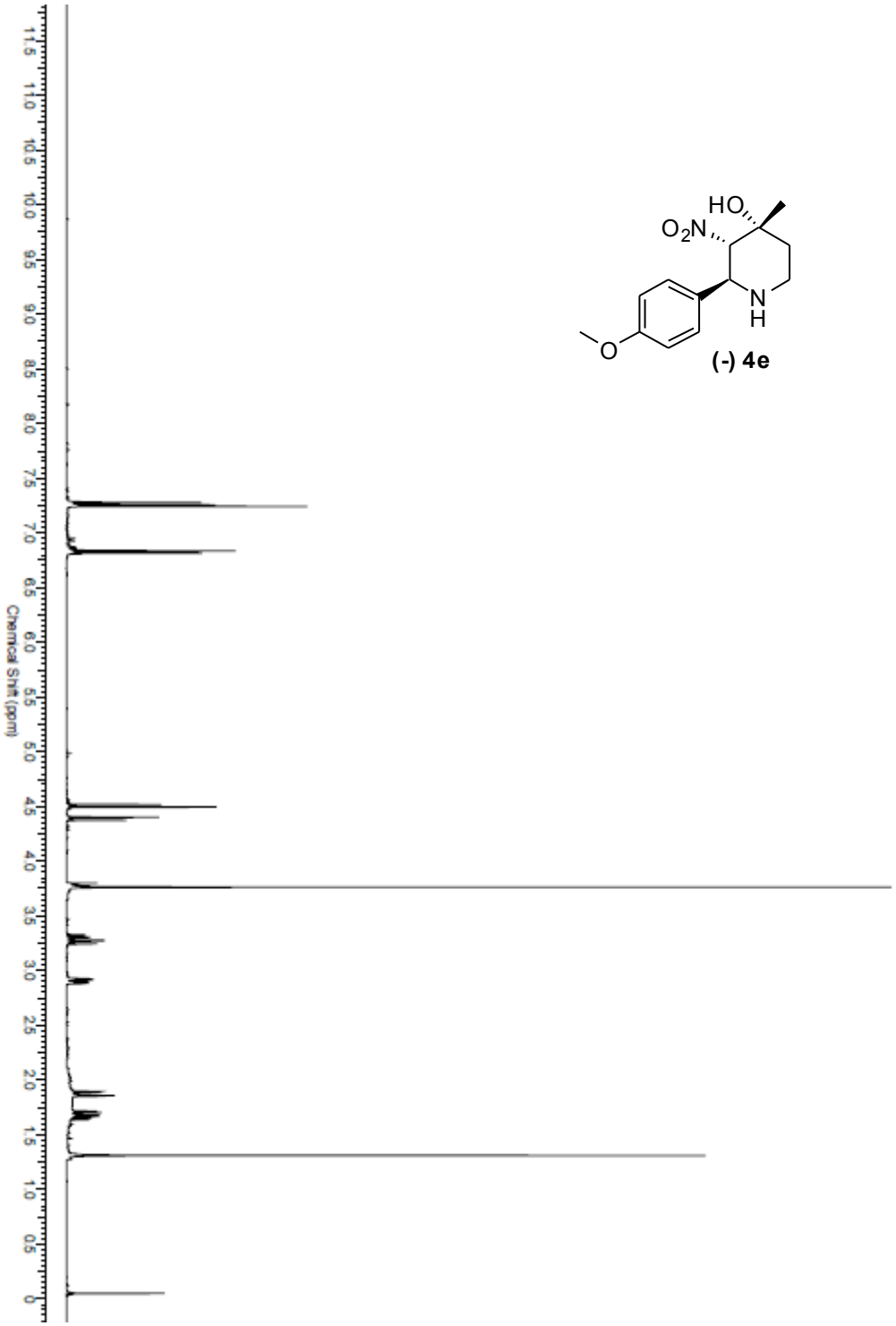
(-) 4c



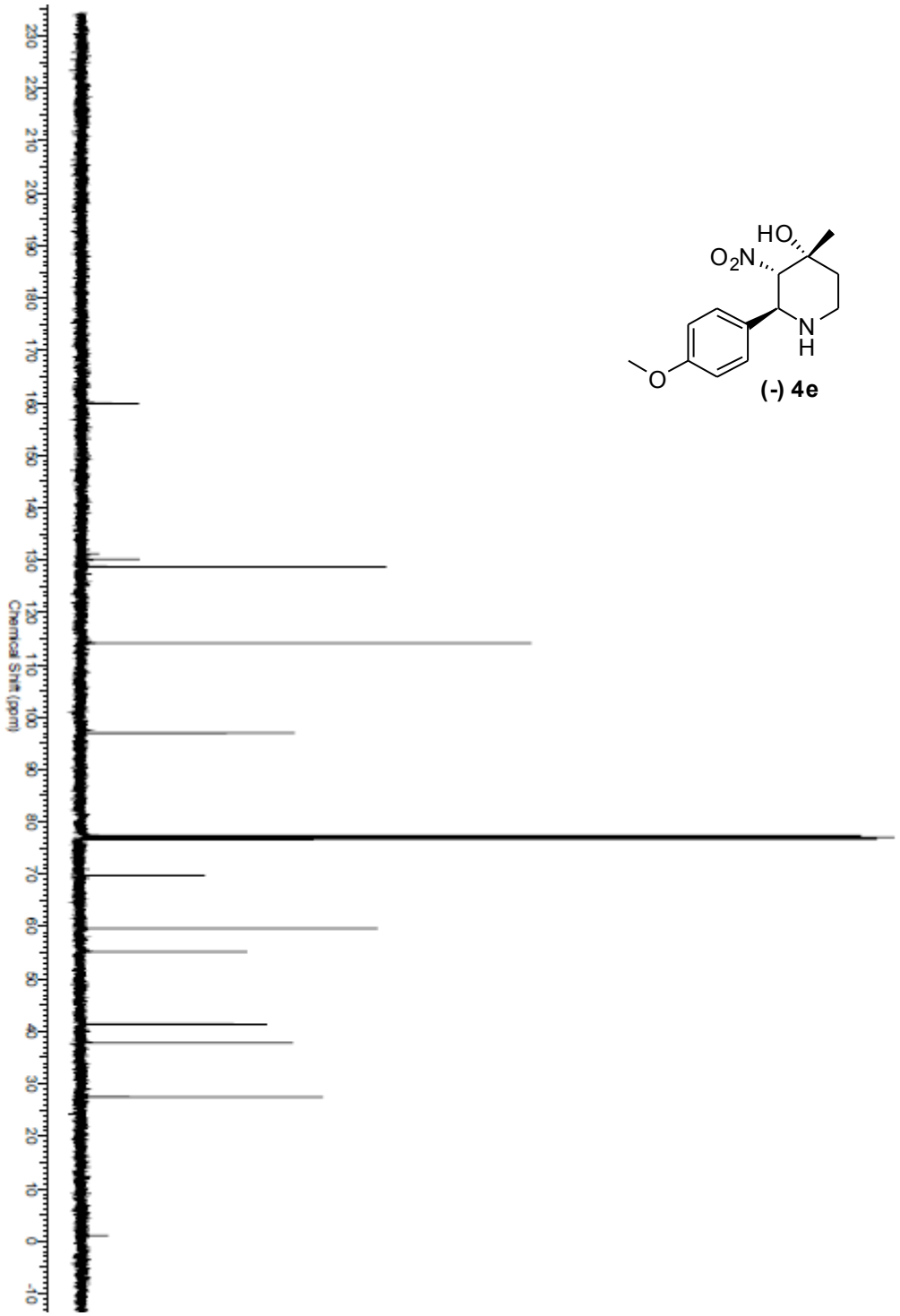
(-) 4d



(-) 4d

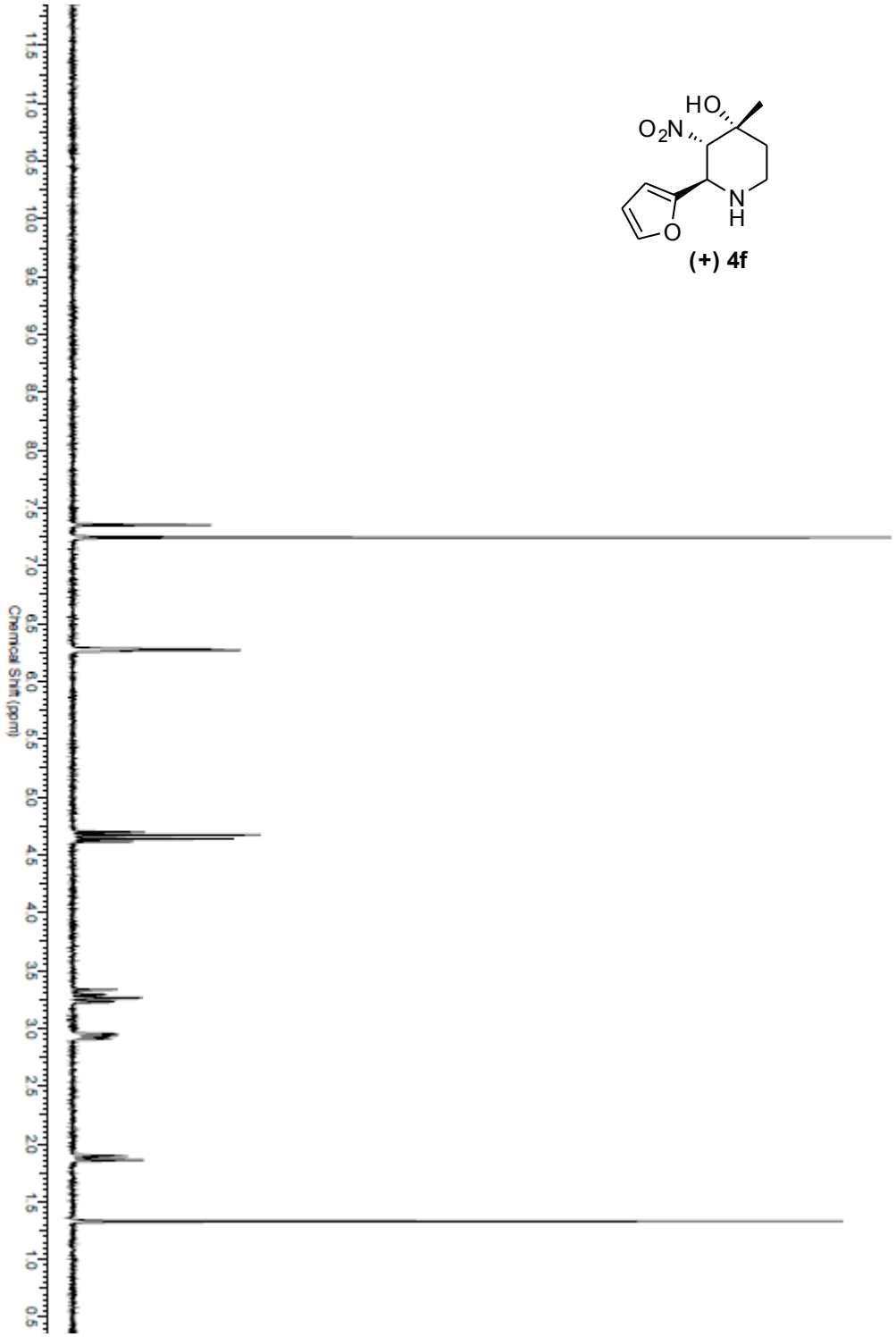


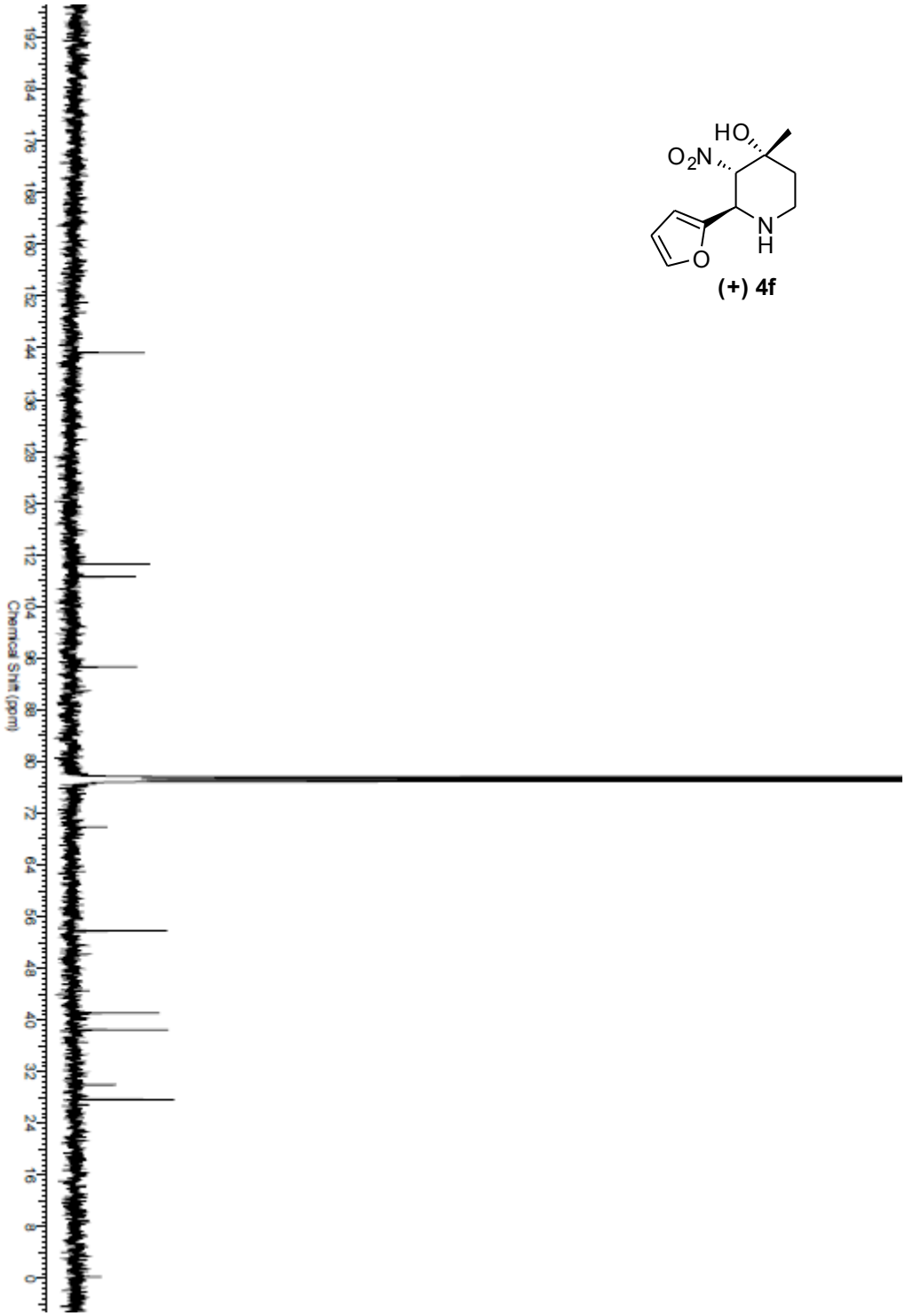
(-) 4e

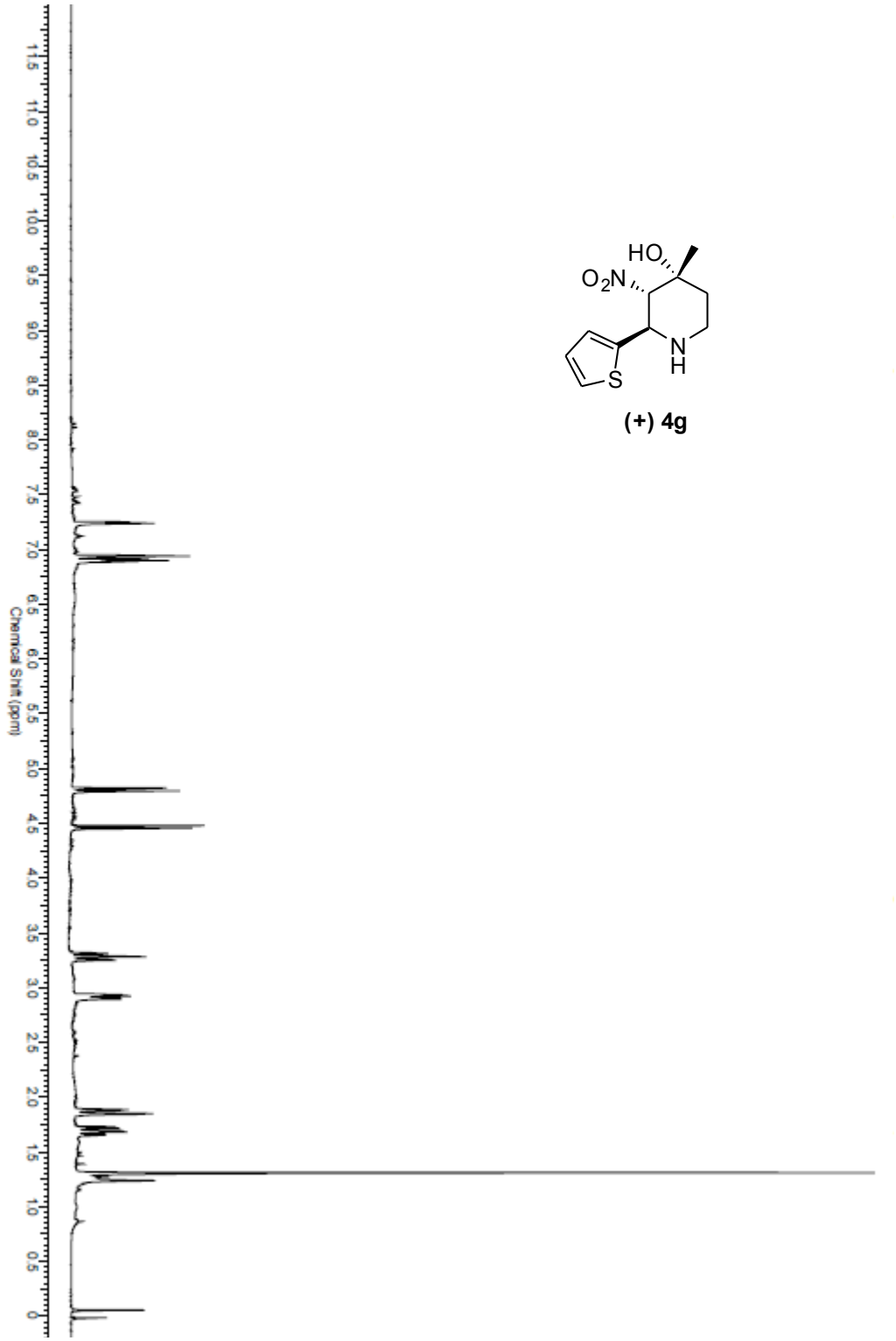

Chemical Shift (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

HO
O2N
N
H
O

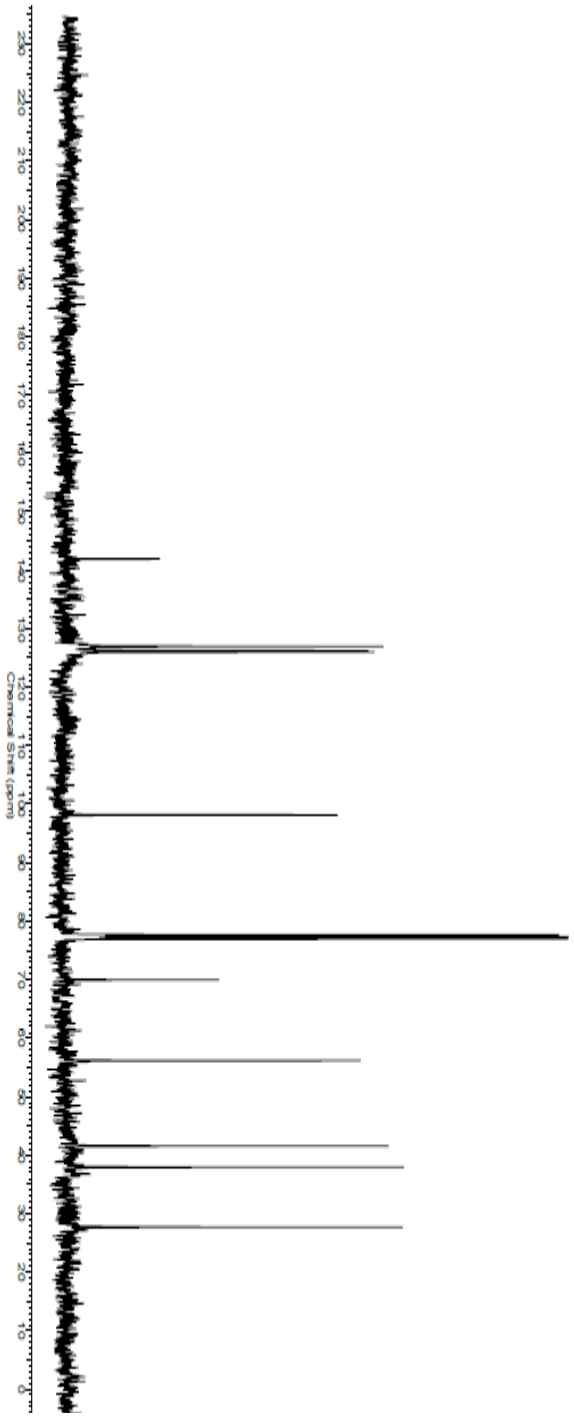
(-) 4e

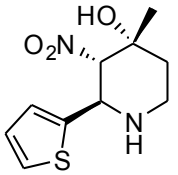

HO
O2N
N
H
O
(+) 4f
Chemical Shift (ppm)


HO
O2N
N
H
O
(+) 4f
Chemical Shift (ppm)

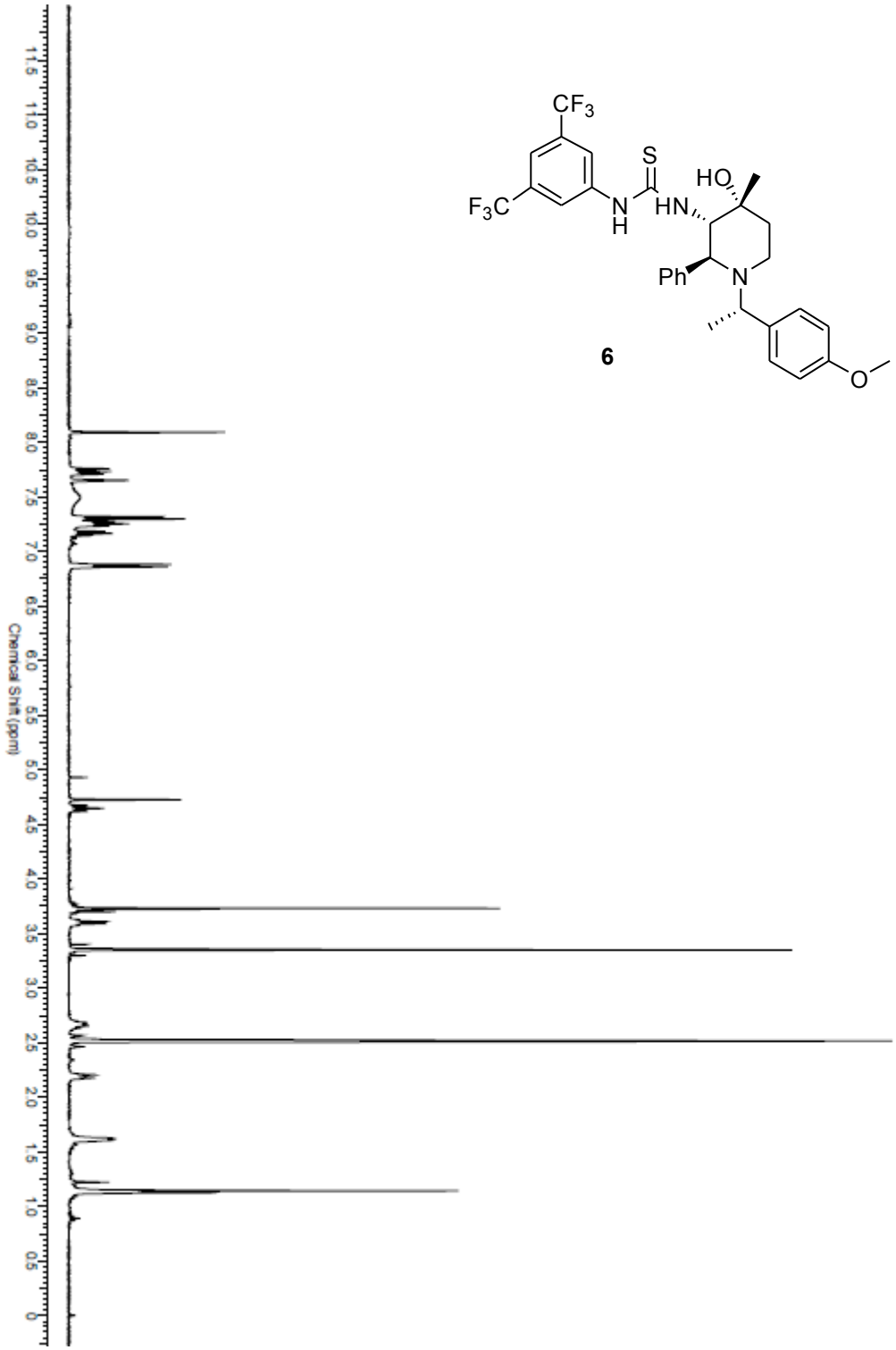


(+) 4g

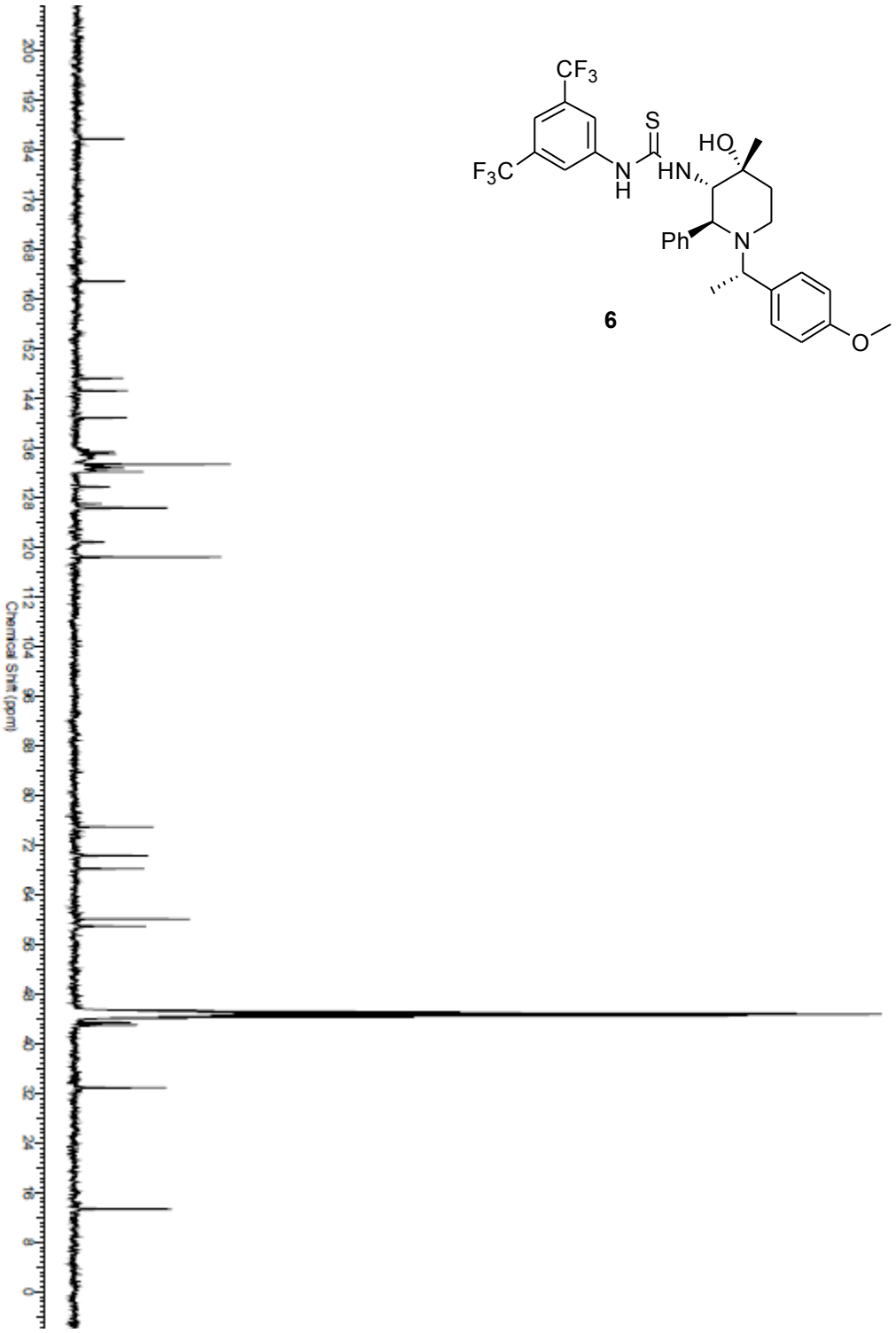




(+) 4g

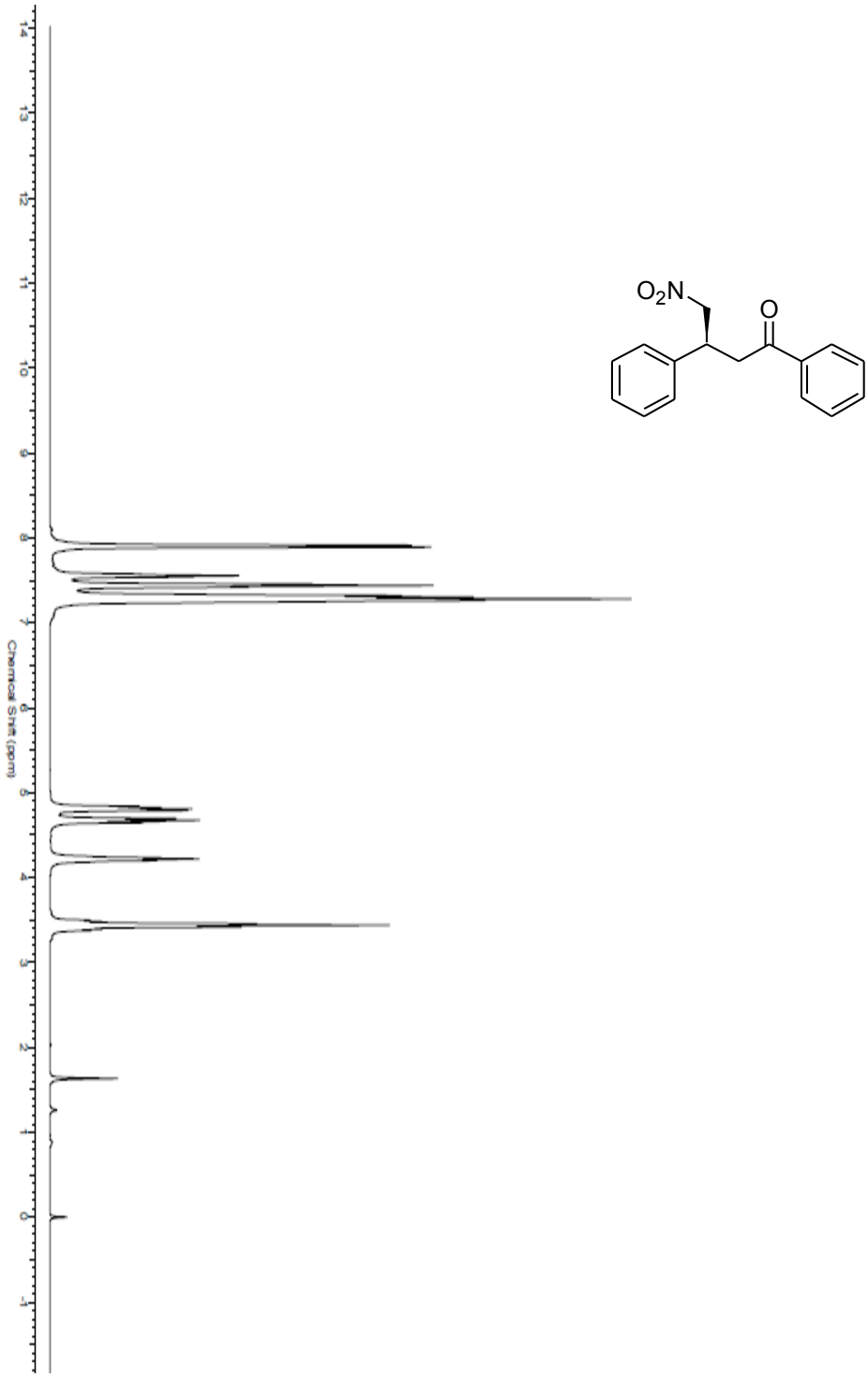


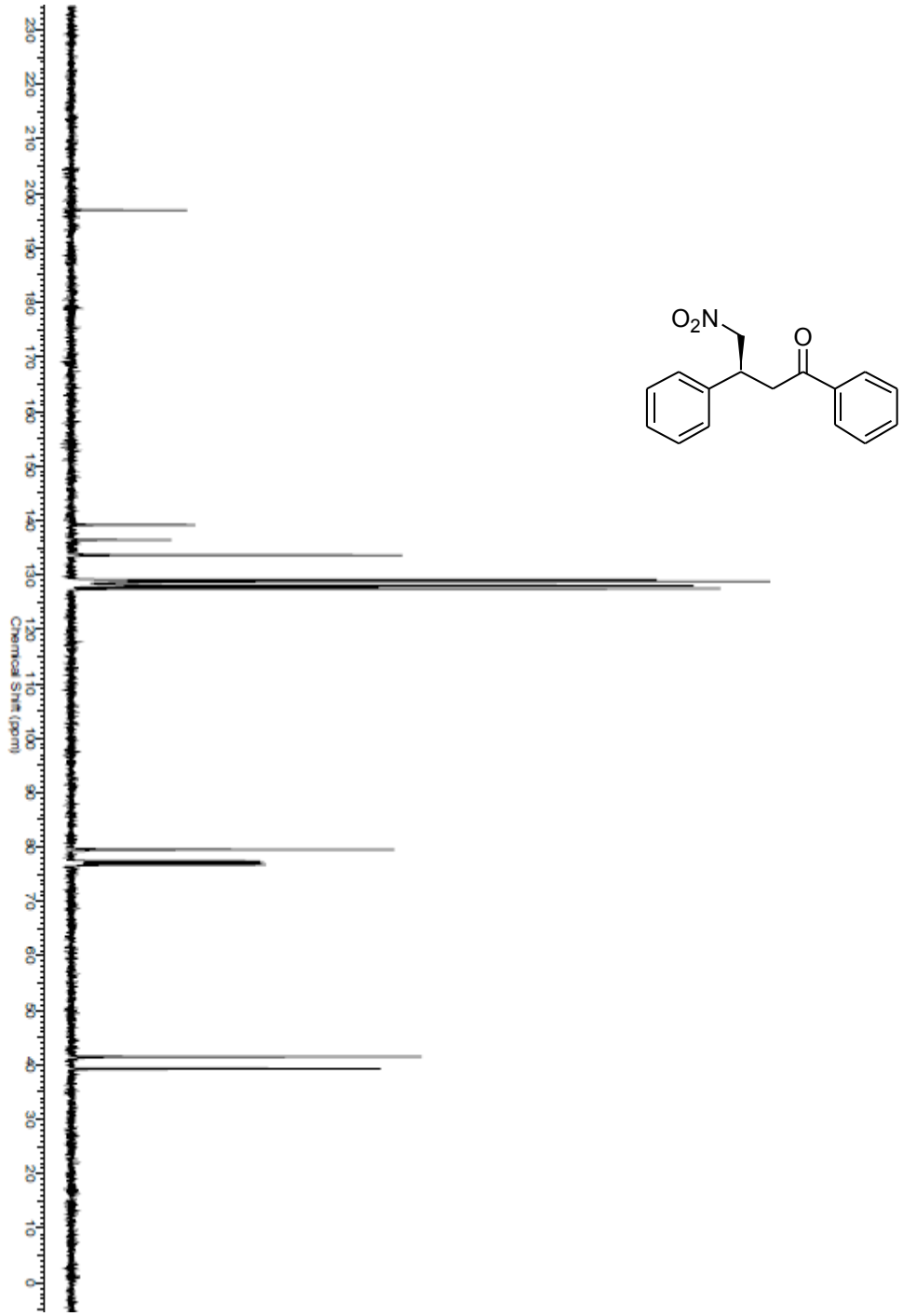
6


Chemical Shift (ppm)
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

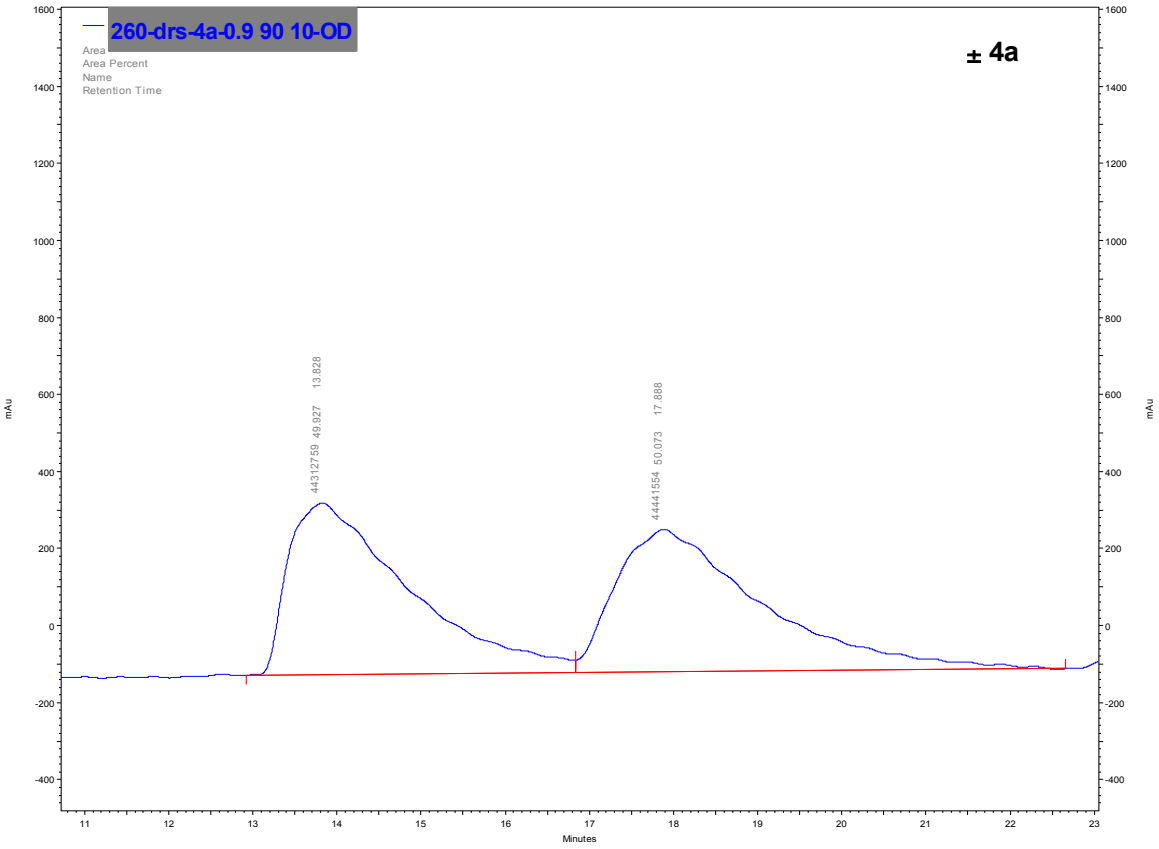
CF3
F3C
S
N
H
HN
HO
Ph
N
O

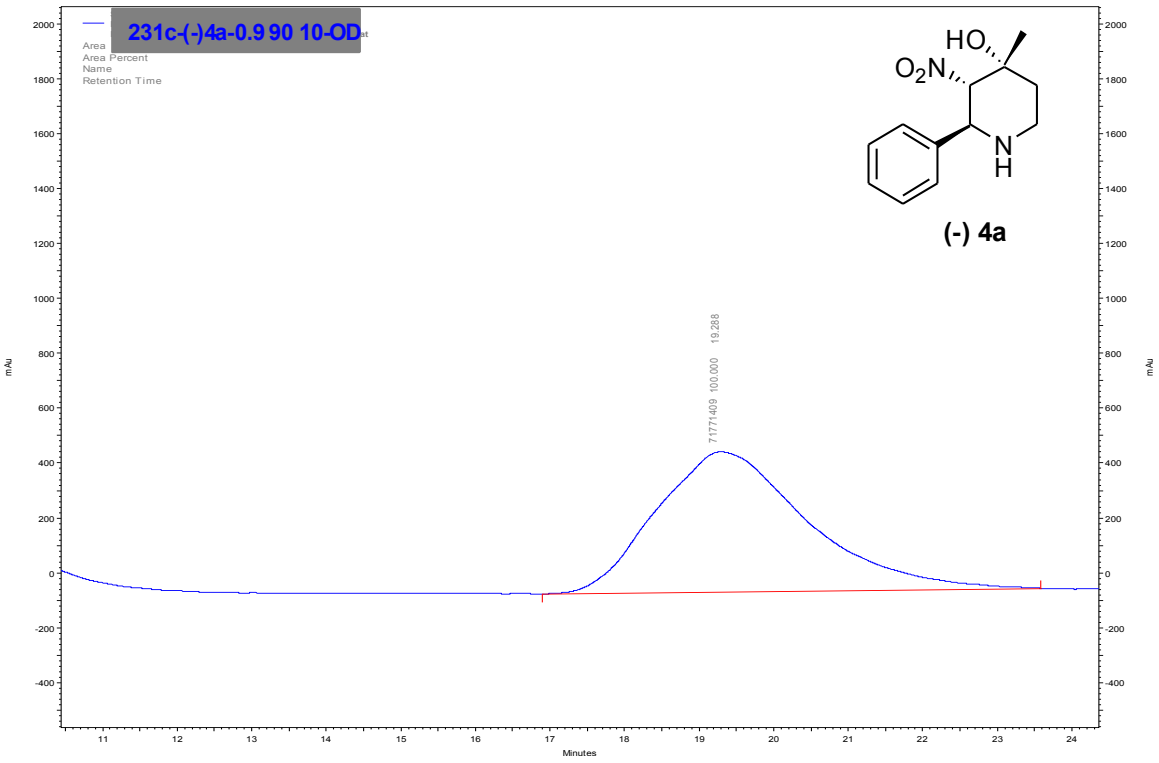
6

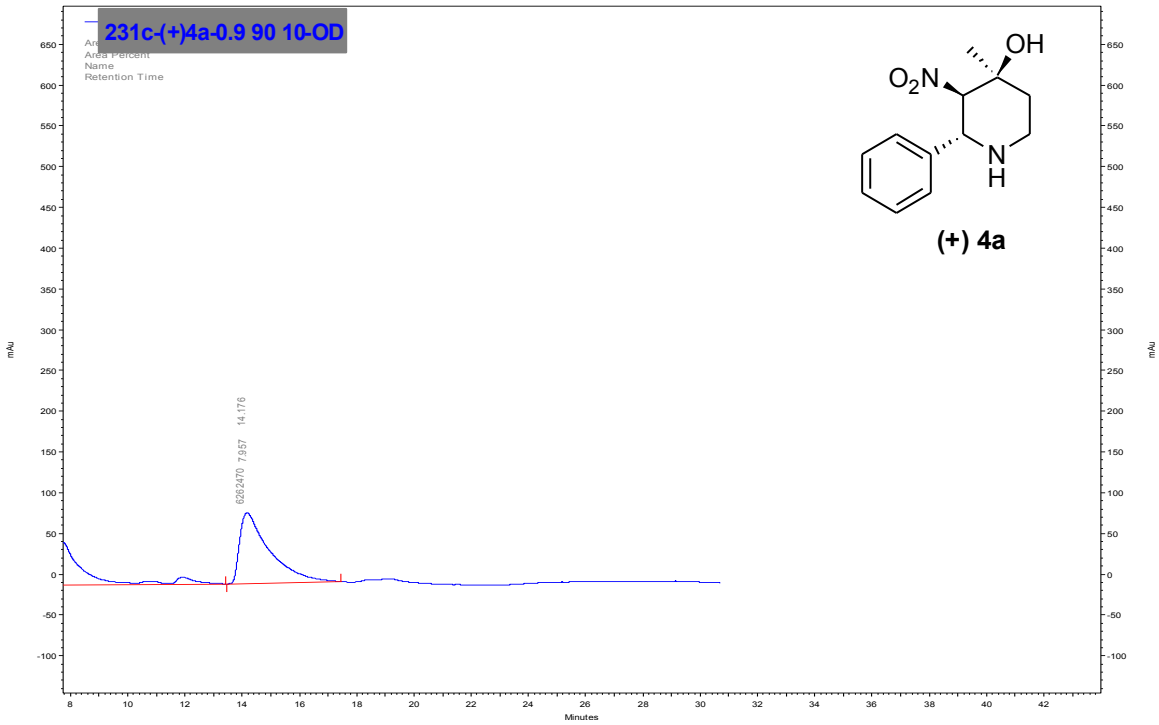

O2N
O
Chemical Shift (ppm)

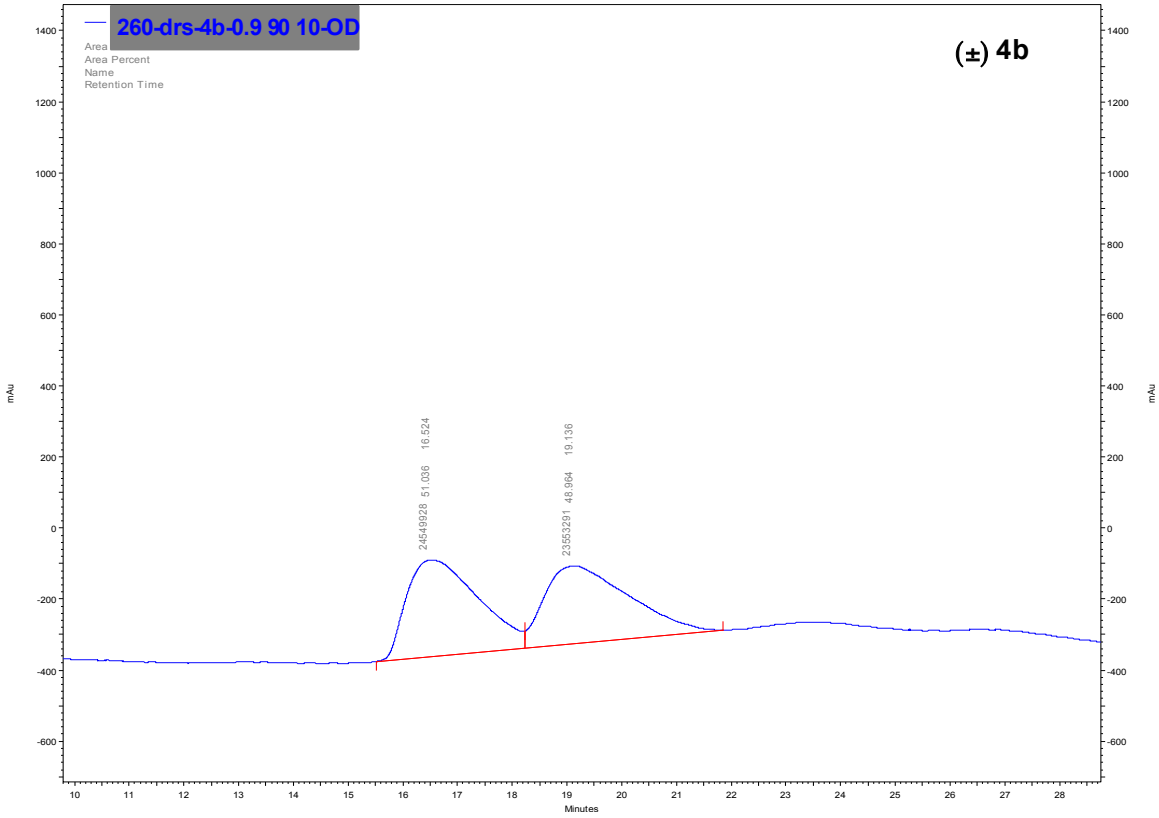

O2N
O
Chemical Shift (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

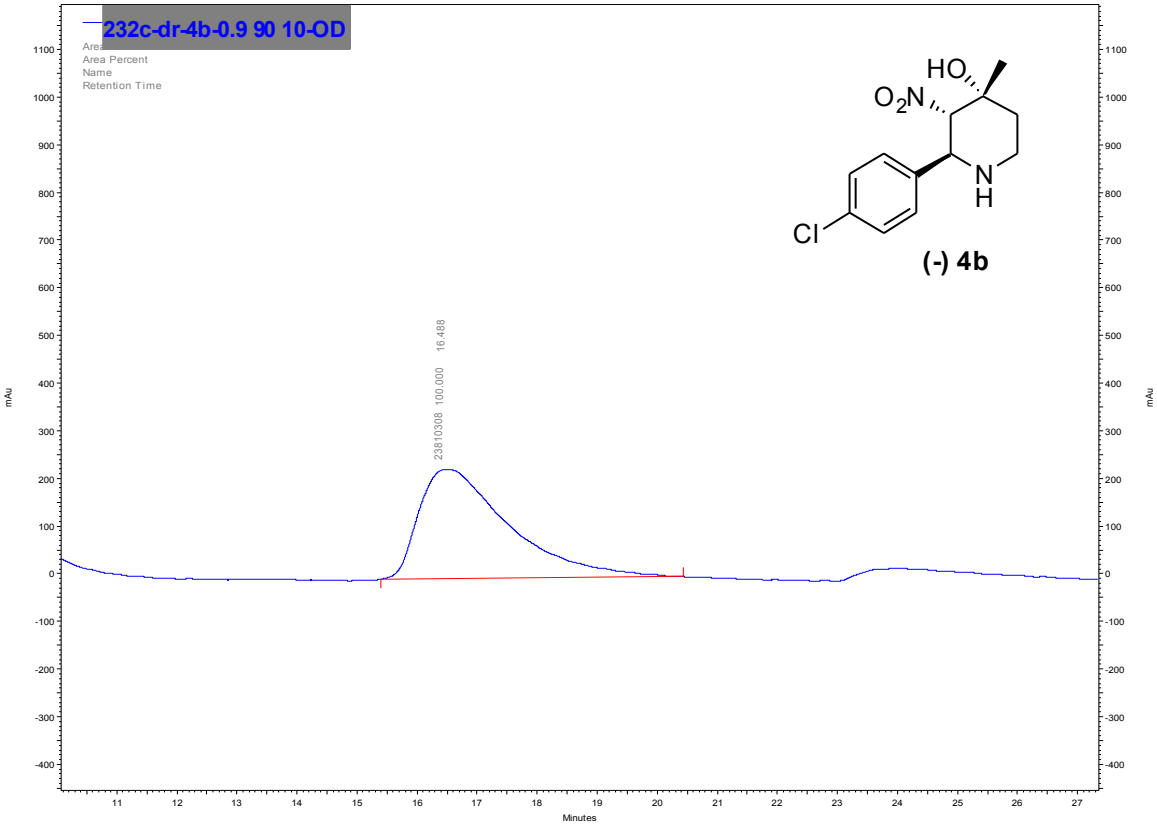
IV HPLC profiles: Racemates and Enantiopure product

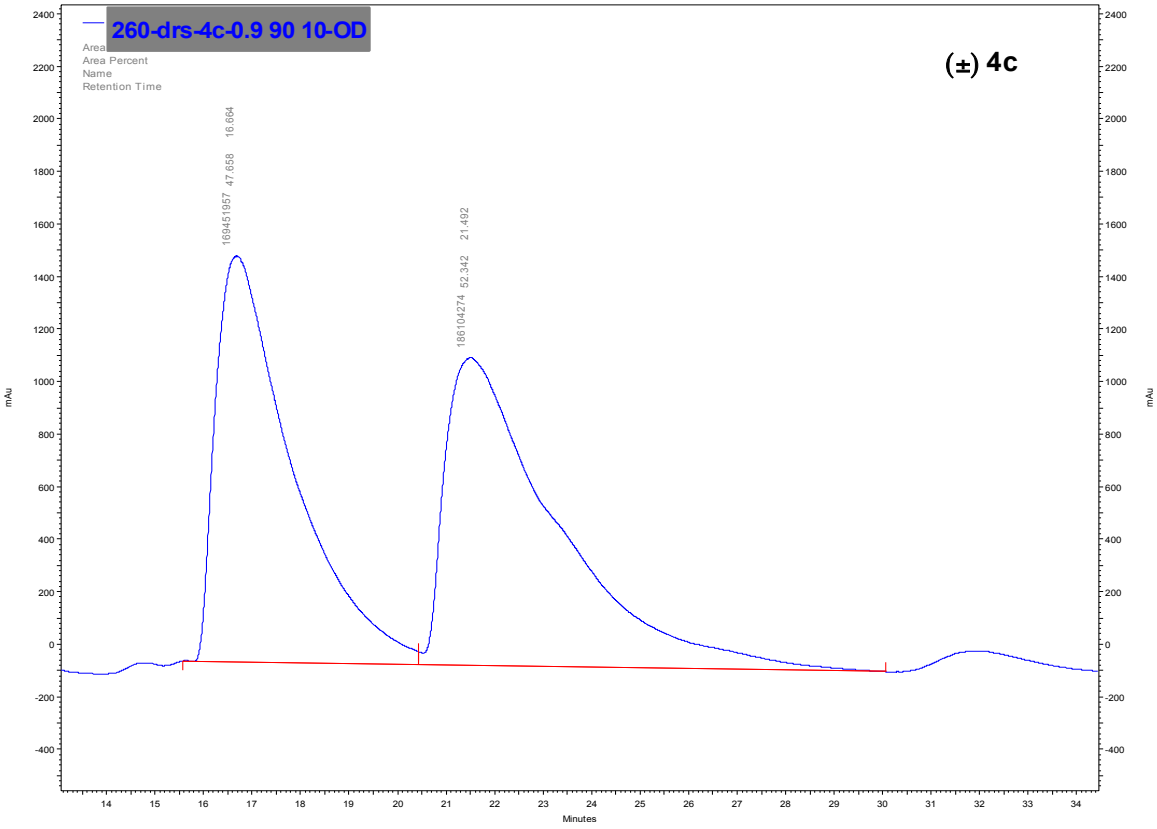


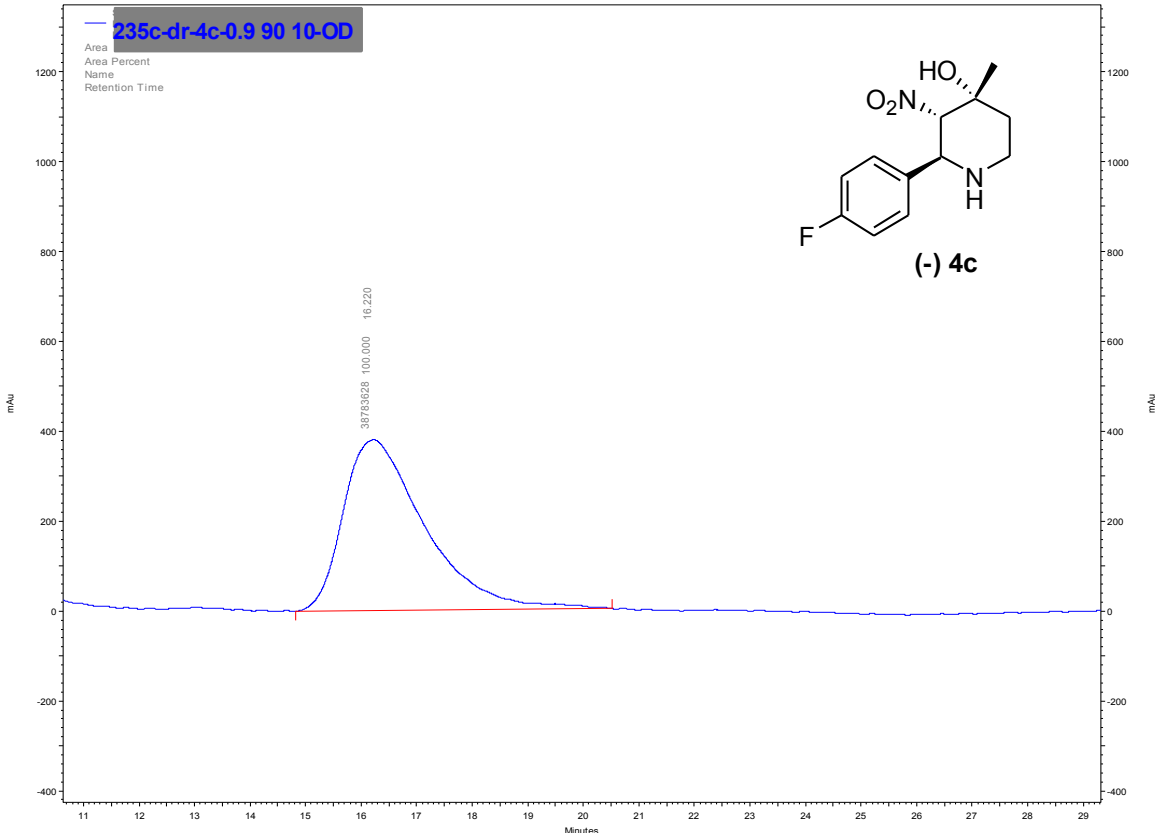


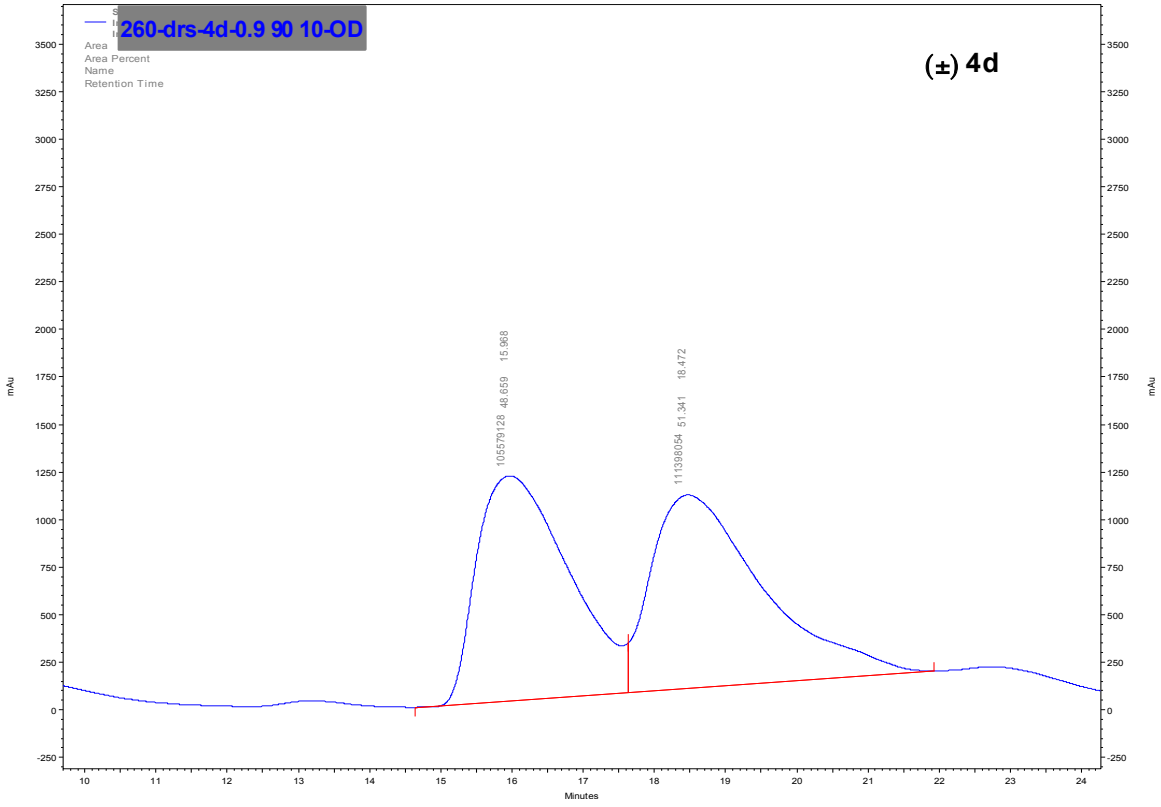

231c-(+)4a-0.9 90 10-OD
Area Percent
Name
Retention Time
626470 7.957
14.176
mAu
Minutes
OH
O_2N
N
H
(+) 4a

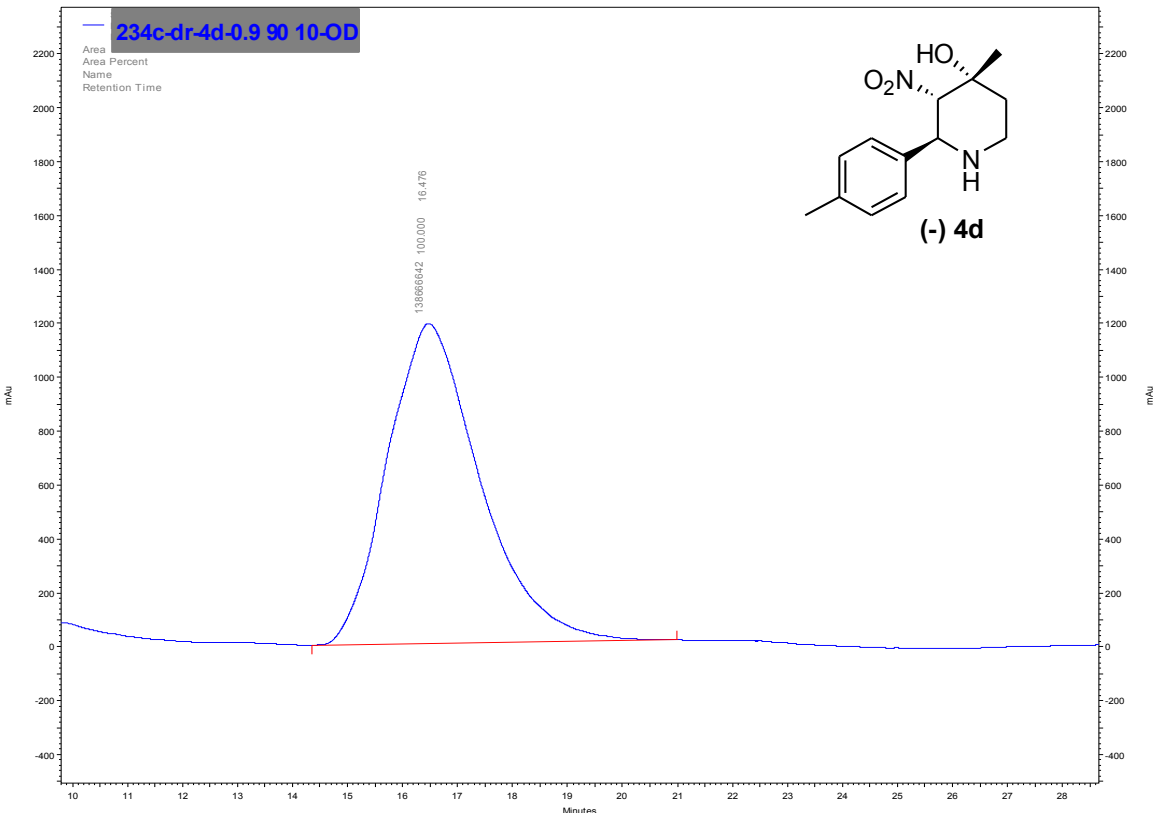

260-drs-4b-0.9 90 10-OD
Area Percent
Name
Retention Time
24549928 51.036
16.524
23553291 48.964
19.136
mAu
Minutes
(±) 4b

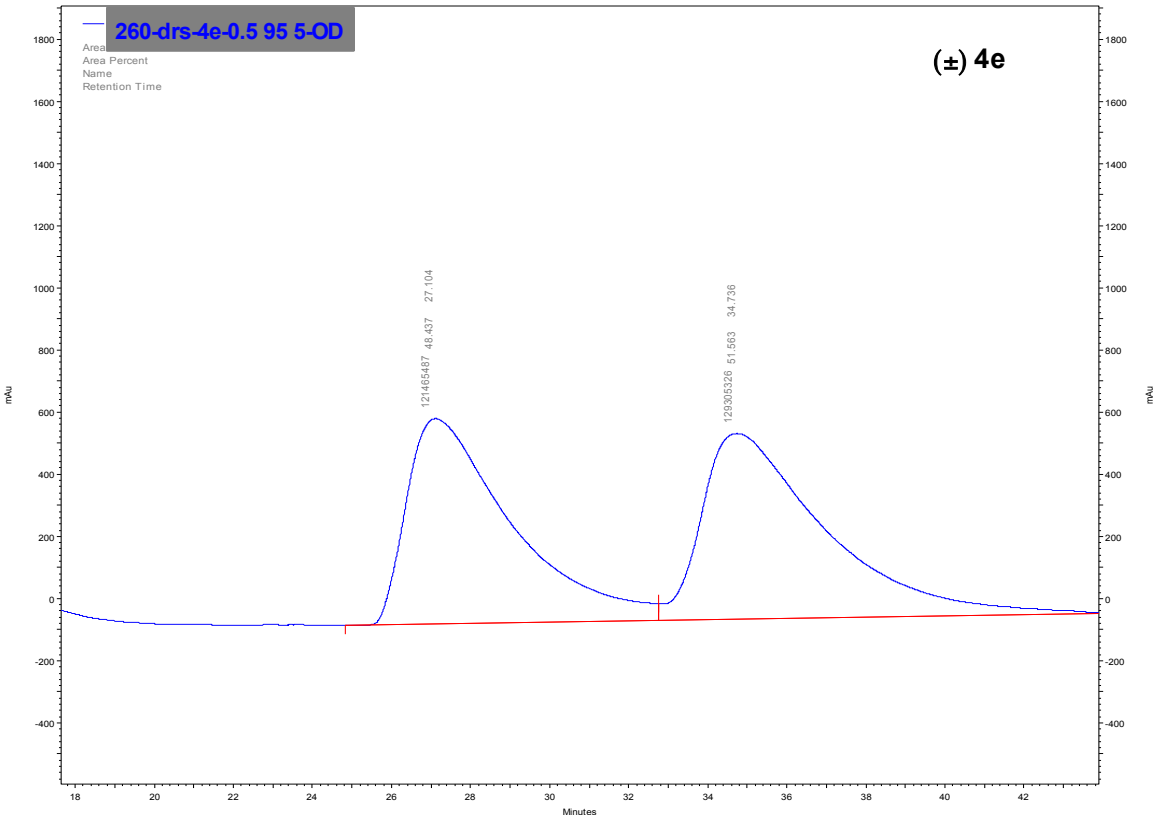

232c-dr-4b-0.9 90 10-OD
Area
Area Percent
Name
Retention Time
HO
O2N
N
H
Cl
(-) 4b
16.488
100.000
23810308
mAu
Minutes

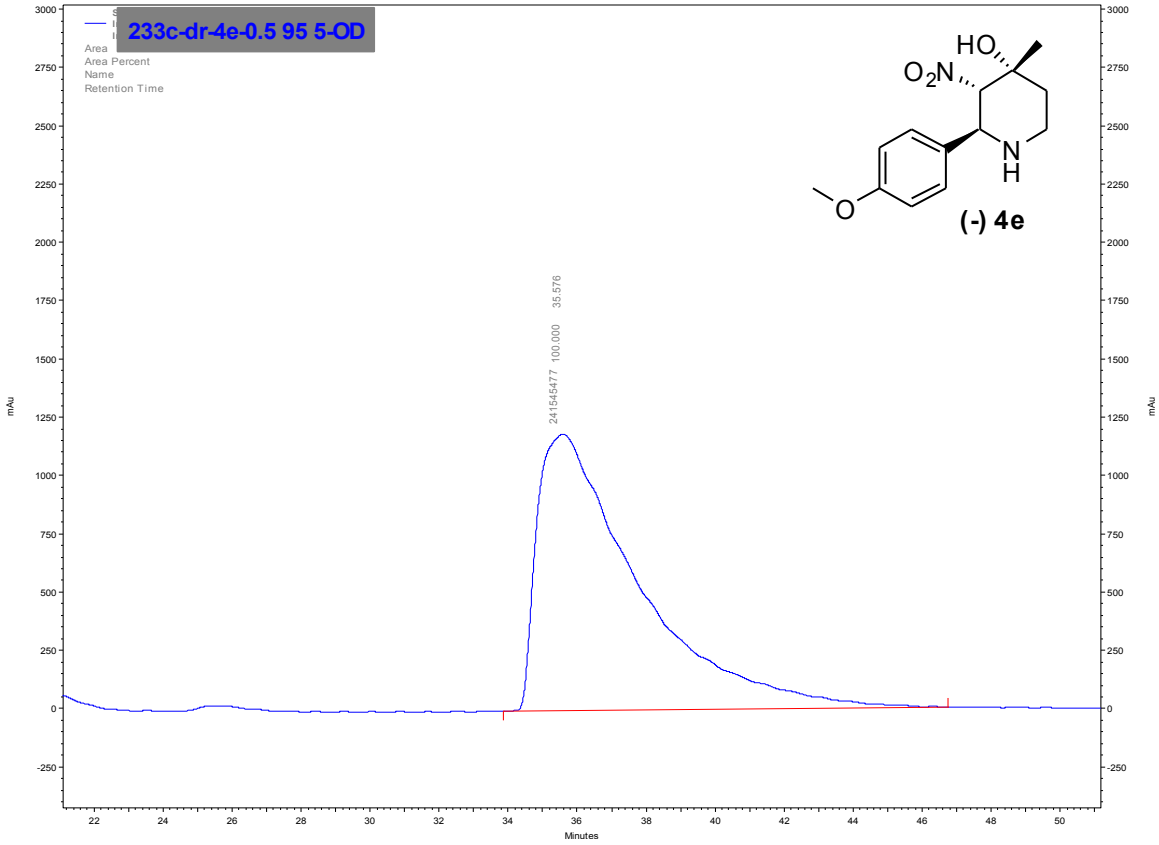

260-drs-4c-0.9 90 10-OD
Area
Area Percent
Name
Retention Time
(±) 4c
16.664
47.658
16945957
21.492
52.342
186104274
mAu
Minutes

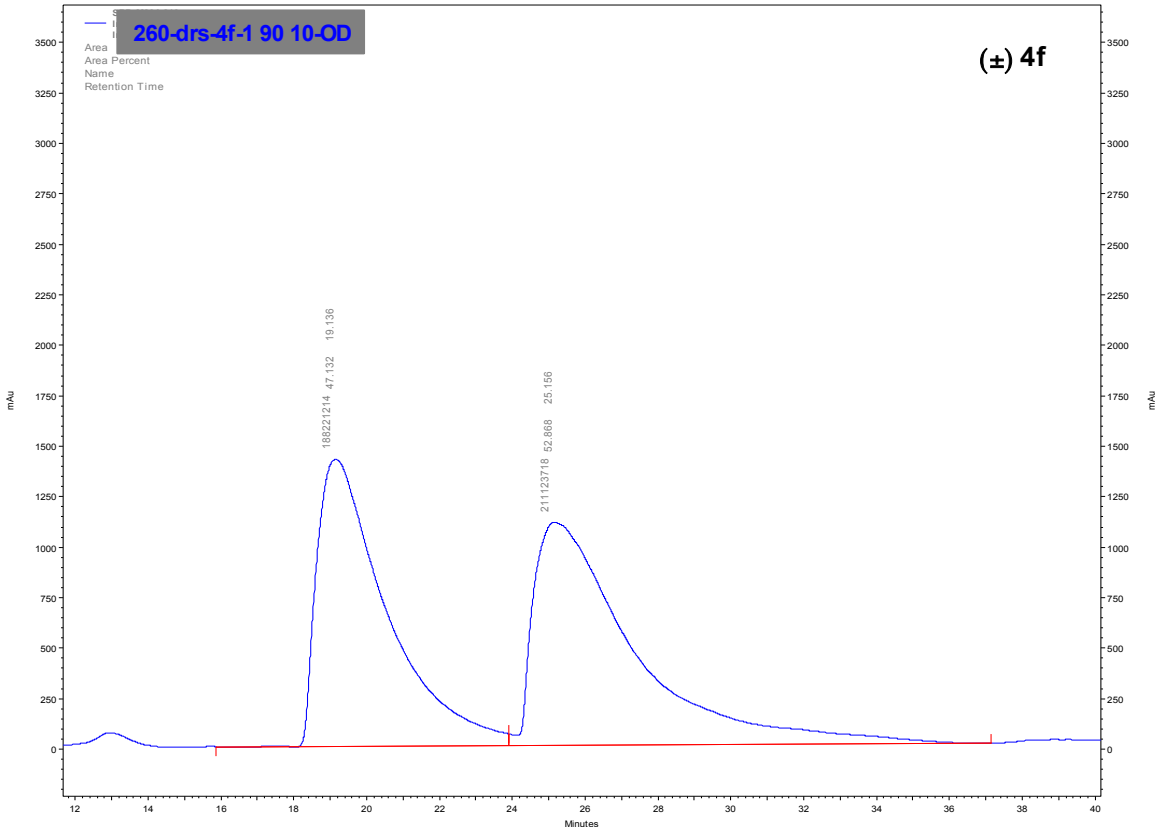

235c-dr-4c-0.9 90 10-OD
Area
Area Percent
Name
Retention Time
HO
O2N
N
H
F
(-) 4c
16.220
38783628
100.000
mAu
Minutes

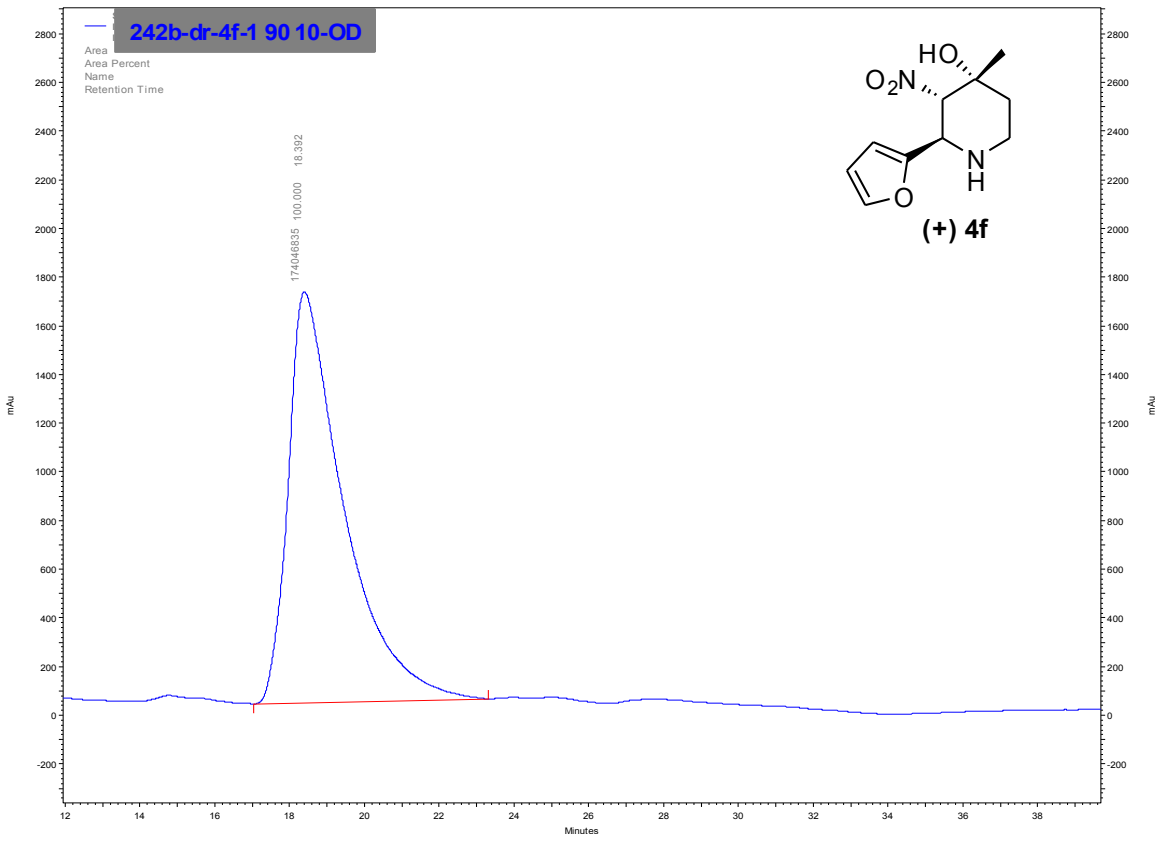

260-drs-4d-0.9 90 10-OD
Area
Area Percent
Name
Retention Time
(±) 4d
15.968
48.659
105579128
18.472
51.341
111398054
mAu
Minutes

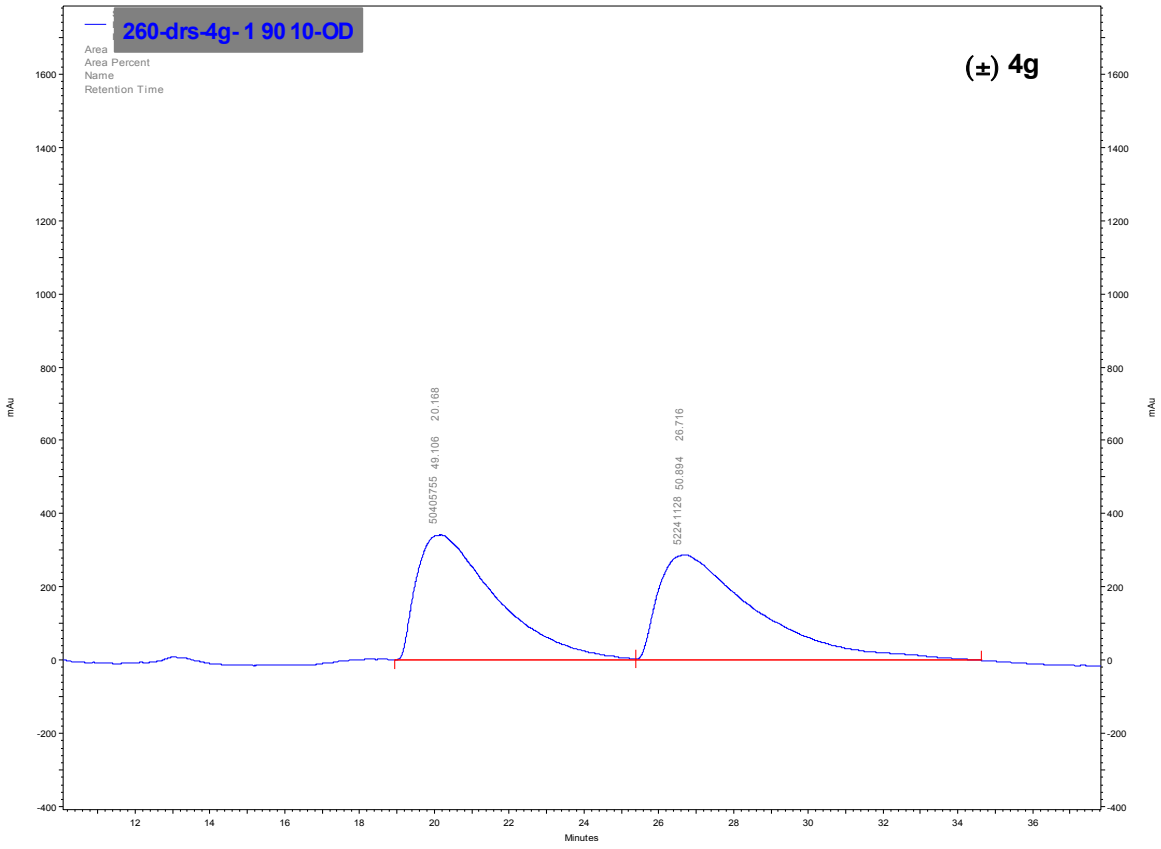

234c-dr-4d-0.9 90 10-OD
Area
Area Percent
Name
Retention Time
16.476
100.000
1386666442
HO
O2N
N
H
(-) 4d
mAu
Minutes

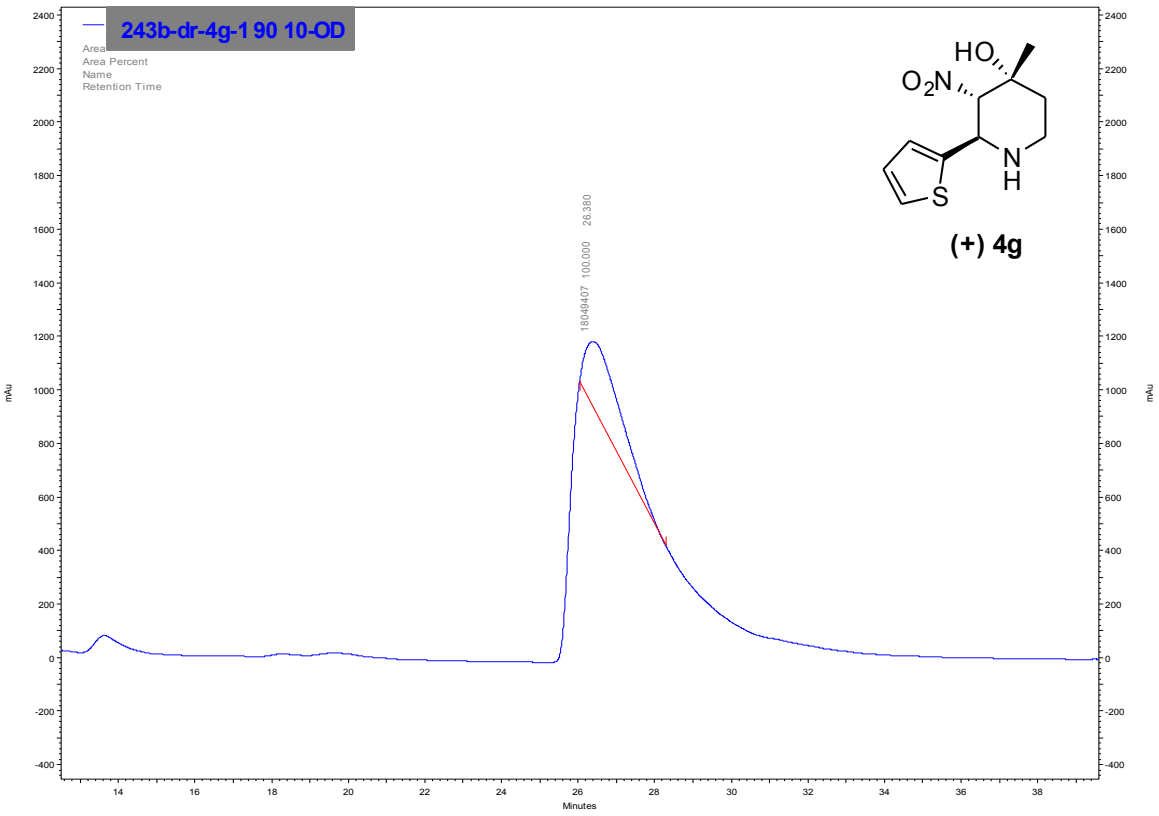

260-drs-4e-0.5 95 5-OD
Area
Area Percent
Name
Retention Time
(±) 4e
27.104
48.437
1214654487
34.736
51.563
1293053326
mAu
Minutes


233c-dr-4e-0.5 95 5-OD
Area
Area Percent
Name
Retention Time
HO
O2N
N
H
O
(-) 4e
35.576
100.000
241545477
mAu
Minutes

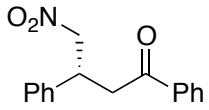

260-drs-4f-1 90 10-OD
Area
Area Percent
Name
Retention Time
(±) 4f
19.136
47.132
18822121 4
25.156
52.868
21112371 8
mAu
Minutes

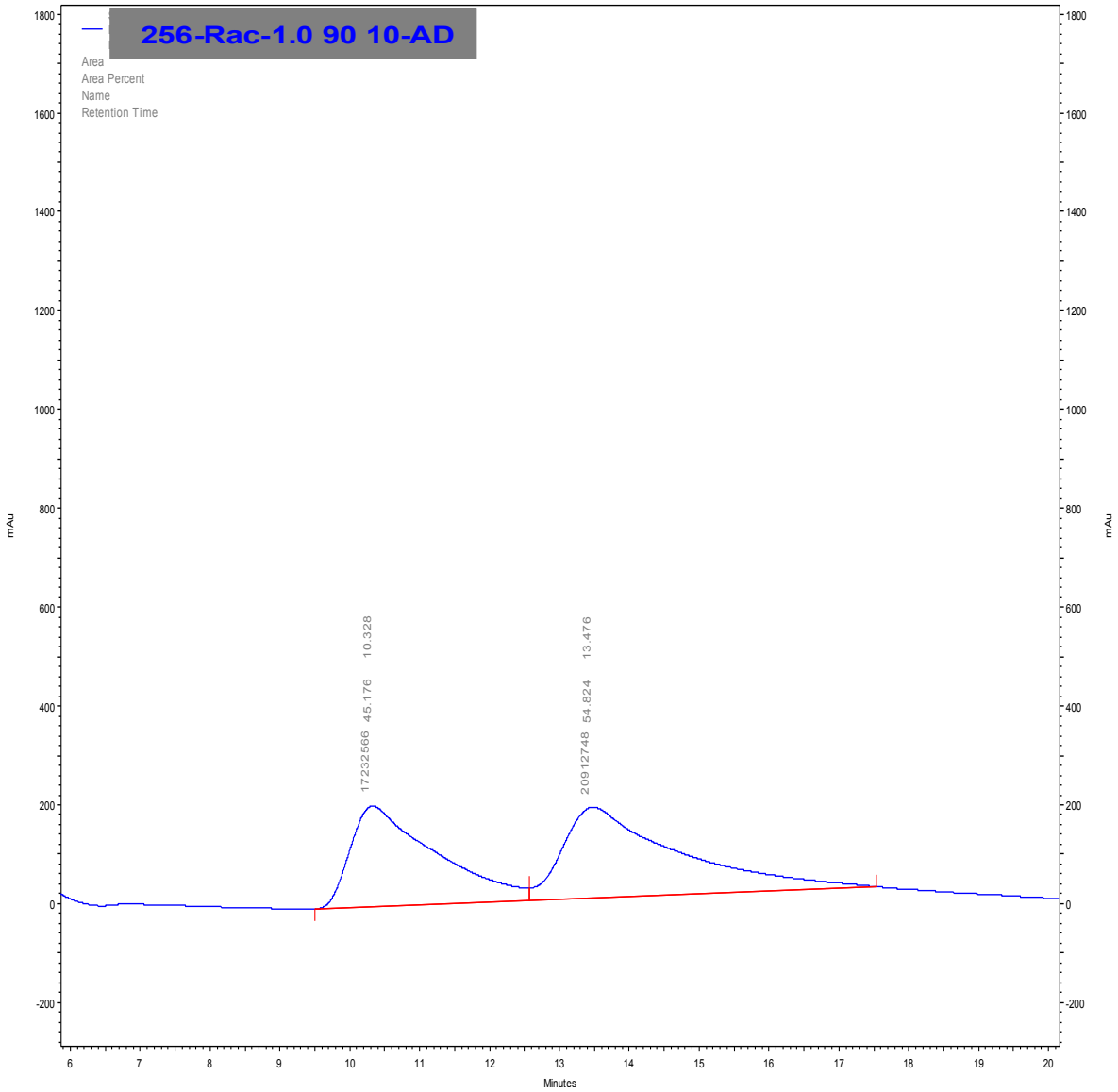

242b-dr-4f-1 90 10-OD
Area
Area Percent
Name
Retention Time
174046835 100.000 18.392
HO
O2N
N
H
O
(+) 4f
mAu
Minutes

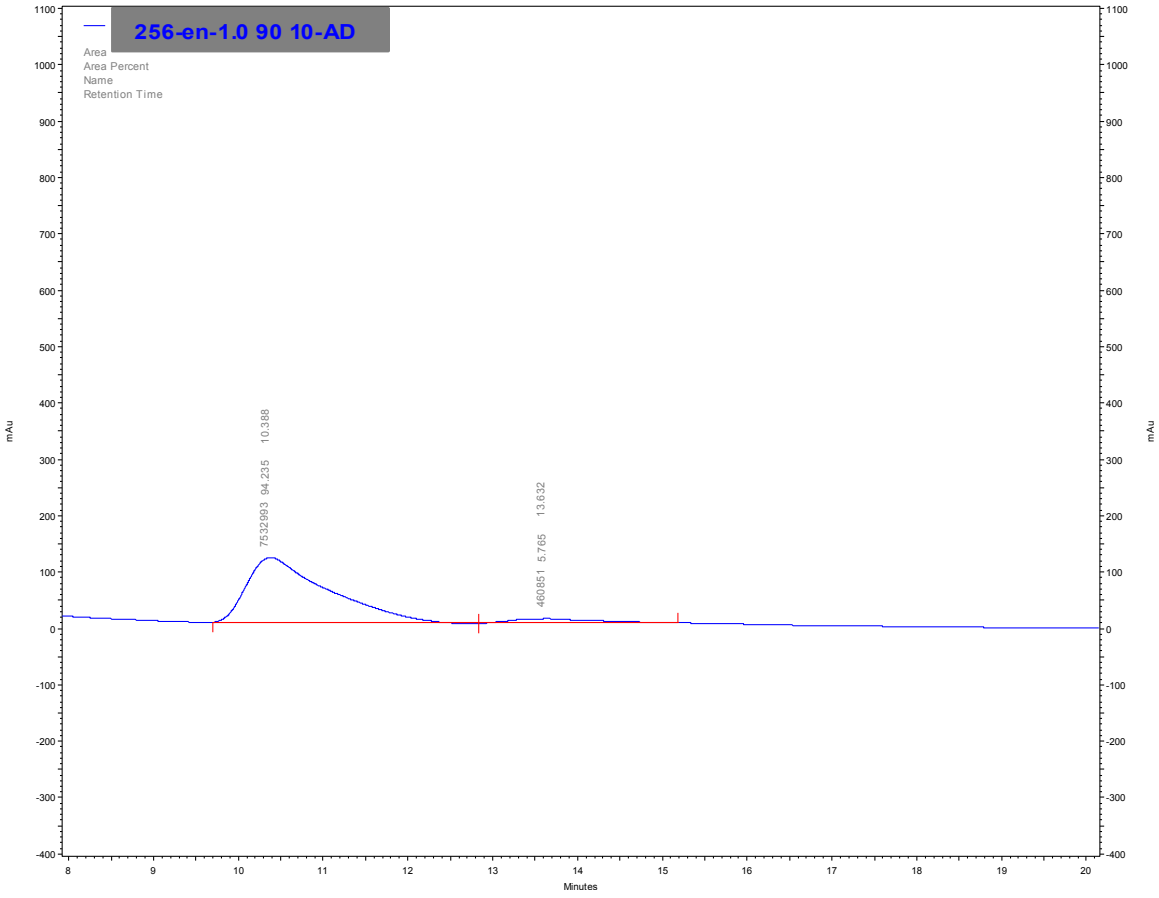

260-drs-4g-1 90 10-OD
Area
Area Percent
Name
Retention Time
(±) 4g
50405755 49.106 20.168
52241128 50.894 26.716
mAu
Minutes


243b-dr-4g-1 90 10-OD
Area
Area Percent
Name
Retention Time
18049407 100.000 26.380
mAu
Minutes
HO
O2N
N
H
S
(+) 4g

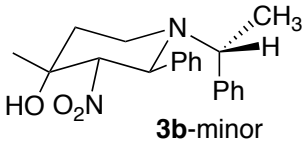
HPLC of Asymmetric product





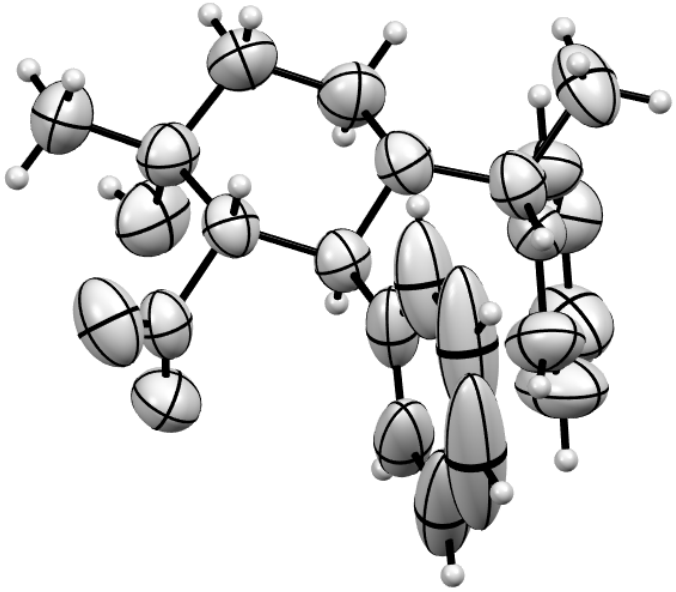

256-en-1.0 90 10-AD
Area
Area Percent
Name
Retention Time
mAu
Minutes
10.388
7532993
94.235
13.632
460851
5.765

III. OTEP crystal structure of **3b** minor



3b-minor

≡



END