SUPPORTING INFORMATION

for

"Recoverable Resin-Supported Pyridylamide Ligand for Microwave-Accelerated Molybdenum-Catalyzed Asymmetric Allylic Alkylations: Enantioselective Synthesis of Baclofen"

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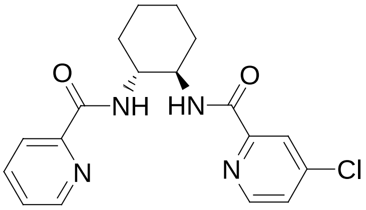
(12 pages)

General Methods. THF was distilled over Na/benzophenone and CH_2Cl_2 over CaH_2. The microwave heating was performed with a Smith Creator™ single mode cavity from Personal Chemistry AB, Uppsala, Sweden equiped with magnetic stirrer and automatic temperature control. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 500 or 400 MHz instrument. Chemical shifts are reported in ppm relative to the solvent as internal standard.



1b

(1*R*,2*R*)-1-[(4-Chloropyridine)-2-carboxamido]-2-(pyridine-2-carboxamido)cyclohexane (1b). A solution of picolinic acid (250 mg, 2.03 mmol) and *N*,*N*'-carbonyldiimidazole (329 mg, 2.03 mmol) in THF (5 mL) was stirred for 90 min at 50 °C under nitrogen. The mixture was diluted with THF (35 mL) and added dropwise to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (232 mg, 2.03 mmol) in THF (40 mL). The reaction mixture was stirred for an additional 1 h and the solvent was removed by rotatory evaporation. The resulting solid monoamide was dissolved in CH_2Cl_2 (10 mL) and added to a suspension of 4-chloropicolinic acid[1] mixed salt (519 mg, 2.03 mmol), *N*,*N*'-carbonyl-diimidazole (329 mg, 2.03 mmol) and K_2CO_3 (281 mg, 2.03 mmol), which had been stirred in THF (5 mL) in a separate flask for 1 h at 50 °C under nitrogen. The yellow suspension was stirred for 1 h at room temperature and then an aqueous solution of saturated K_2CO_3 (20 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The crude product was

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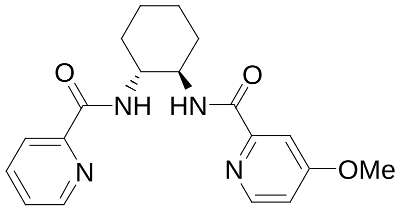
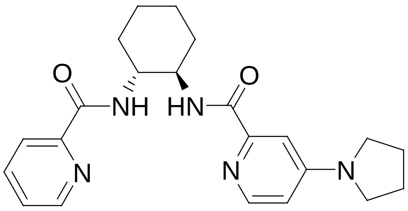
[1] Belda, O.; Moberg, C. *Synthesis* **2002**, 1601.

purified by column chromatography on silica gel (eluent: hexane/EtOAc 1/3). Yield: 335 mg (46%) of **1b** as a solid: mp 60-64 °C; $[\alpha]^{20}_{D}$ –45.3 (*c* 0.31, $CHCl_3$); ^1H NMR: δ 8.52 (1H, d, *J* = 4.5 Hz), 8.41 (1H, d, *J* = 5.3 Hz), 8.18 (2H, d, *J* = 7.3 Hz), 8.1-8.0 (2H, m), 7.74 (1H, ddd, *J* = 7.3, 1.51 Hz), 7,36-7,24 (2H, m), 4.04 (2H, br), 2.18 (2H, br), 1.83 (2H, br), 1.45 (4H, br); ^{13}C NMR: δ 165.0, 163.8, 151.7, 150.7, 149.5, 145.9, 137.5, 126.5, 126.4, 123.1, 122.5, 54.1, 53.5, 33.0, 32.9, 25.2, 25.1. MS (EI) (m/z) 360, 358 (M^+), 236, 202.



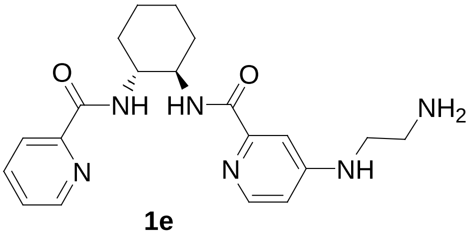
1c

(1*R*,2*R*)-1-[(4-Methoxypyridine)-2-carboxamido]-2-(pyridine-2-carboxamido)cyclohexane (1c). A mixture of solid MeONa (75 mg, 1.39 mmol) and **1b** (50 mg, 0.14 mmol) in MeOH (2 mL) was heated in the microwave cavity for 15 min at 140 °C. Water (4 mL) was added to the mixture and the product was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 1/3) to give 47 mg (95%) of **1c** as a solid: mp 121-122 °C; $[\alpha]^{20}_{D}$ +49.6 (*c* 0.50, $CHCl_3$); ^1H NMR δ 8.50 (1H, d, *J* = 4.5 Hz), 8.28 (1H, d, *J* = 5.8 Hz), 8.22 (2H, br), 8.05 (1H, d, *J* = 7.8 Hz), 7.72 (1H, dd, *J* = 7.8, 1.8 Hz), 7.59 (1H, d, *J* = 2.8 Hz), 7.32 (1H, ddd, *J* = 4.8, 2.8 Hz), 6.81 (1H, dd, *J* = 8.3, 2.8 Hz), 4.03 (2H, br), 3.82 (3H, s), 2.19 (2H, br), 1.89 (2H, br), 1.44 (4H, br); ^{13}C NMR δ 165.68, 163.5, 163.4, 150.8, 148.8, 148.3, 147.1, 136.0, 124.9, 121.1, 111.6, 106.3, 54.4, 52.3, 52.2, 31.6, 23.8, 23.7. Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.53; H, 6.37; N, 15.66.



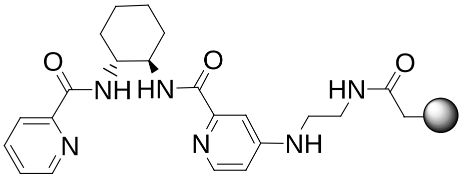
1d

(1*R*,2*R*)-1-[(4-*N*-Pyrrolidylpyridine)-2-carboxamido]-2-(pyridine-2-carboxamido)cyclohexane (1d). A solution of **1b** (50 mg, 0.14 mmol) in pyrrolidine (2 mL) was heated in the microwave cavity for 10 min at 160 °C. The unreacted pyrrolidine was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic solution was washed with 20% aqueous solution of K_2CO_3 (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed by evaporation. The crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 1/3) to give 51 mg (93%) of **1d** as a solid: mp 101-104 °C; $[\alpha]^{20}_{D}$ –9.23 (*c* 0.65, $CHCl_3$); ^{1}H NMR δ 8.46 (1H, ddd, *J* = 0.8, 1.5, 4.8 Hz), 8.20 (2H, d, *J* = 7.6 Hz), 8.05-7.98 (2H, m), 7.67 (1H, ddd, *J* = 7.6, 1.8 Hz), 7.26 (1H, ddd, *J* = 7.6, 4.8, 1.3 Hz), 7.15 (1H, d, *J* = 2.5 Hz), 6.29 (1H, dd, *J* = 5.8, 2.5 Hz), 3.96 (2H, br), 3.24 (4H, br), 2.18 (1H, br), 2.11 (1H, br), 1.93 (4H, br), 1.75 (2H, br), 1.39 (4H, br); ^{13}C NMR δ 148.5, 148.4, 146.7, 142.1, 138.9, 135.5, 124.4, 120.6, 106.9, 106.9, 104.1, 51.2, 45.7, 31.2, 31.1, 29.5, 23.9, 23.5, 23.3.



1e

(1*R*,2*R*)-1-{[*N*-(1,2-Diaminoethyl)pyridine]-2-caboxamido}-2-(pyridine-2-carboxamido)cyclohexane (1e). A solution of ligand **1b** (100 mg, 0.28 mmol) in 1,2-diaminoethane (2 mL) was heated in the microwave cavity for 20 min at 180 °C. Saturated K_2CO_3 (10 mL) was added to the mixture and the product was extracted with CH_2Cl_2 (5 × 3 mL). The solvent was removed by evaporation and the product was dried under vacuum to give 80 mg (75%) of the pure product: $[\alpha]^{20}_D$ –21.8 (*c* 0.46, $CHCl_3$); ^1H NMR δ 8.49 (1H, d, *J* = 4.8 Hz), 8.26 (1H, d, *J* = 8.1 Hz), 8.19 (1H, d, *J* = 8.1 Hz), 8.05 (1H, d, *J* = 7.81 Hz), 7.96 (1H, d, *J* = 5.8 Hz), 7.72 (1H, ddd, *J* = 7.6, 1.5 Hz), 7.31 (1H, ddd, *J* = 7.8, 4.8, 1.5 Hz), 7.26 (1H, d, *J* = 2.3 Hz), 6.43 (1H, d, *J* = 5.8, 2.3 Hz), 5.00 (1H, t, *J* = 5.3 Hz), 4.00 (2H, br), 3.11 (2H, dt, *J* = 6.0, 5.3 Hz), 2.84 (2H, t, *J* = 6.0), 2.15 (1H, br), 2.09 (1H, br), 1.73 (2H, br), 1.62 (2H, br), 1.36 (4H, br); ^{13}C NMR δ 167.4, 166.5, 156.5, 152.3, 152.0, 150.6, 150.2, 139.0, 127.9, 124.2, 111.1, 108.2, 55.6, 54.8, 46.9, 42.7, 34.7, 26.9, 26.8.



1f

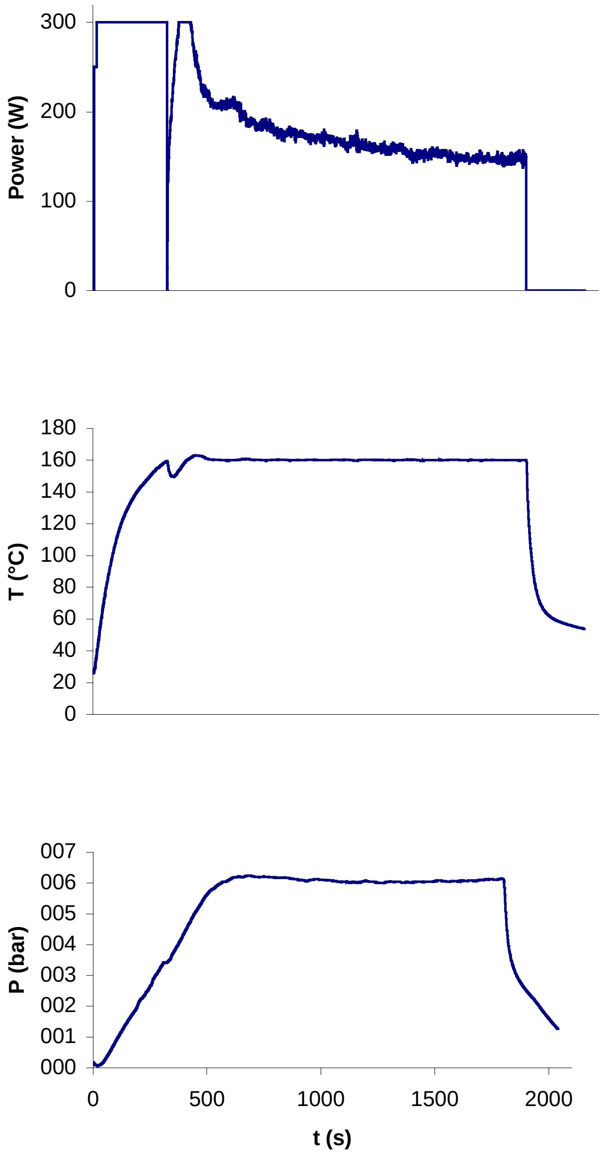
Polymer-bound ligand (1f). DCC (23 mg, 0.11 mmol) was added to a suspension of TentaGel HL-COOH (0.37 mmol/g, 225 mg, 0.083 mmol), ligand **1e** (38 mg, 0.099 mmol) and DMAP (2.0 mg, 0.010 mmol) in dry CH_2Cl_2 (1.5 mL). The reaction mixture was stirred for 24 h at room temperature. The polymer was filtered off and washed with MeOH (2 mL), EtOH (2 mL), THF/ H_2O 1/1 (2 mL), H_2O (2 mL) acetone (2 mL) CH_2Cl_2 (2 mL) and MeOH (2 mL) and then dried under vacuum overnight, resulting in 245 mg of a polymer containing 2.72 % N, corresponding to 0.28 mmol ligand/g of polymer (84%): ^{13}C NMR δ 173.9, 173.0, 165.8, 164.9, 154.9, 150.0, 148.6, 139.6, 137.7, 126.6, 122.6, 53.9, 53.0, 43.0, 40.7, 39.6, 38.6, 33.0, 31.9, 31.8, 30.9, 25.1.

General procedure for microwave-accelerated allylic alkylations. Two different stock solutions were prepared: *Solution-N*, containing the nucleophile, sodium dimethyl malonate in THF, was prepared by adding dimethyl malonate (880 µL, 7.7

mmol) to a suspension of 60% NaH (27 mg, 0.68 mmol) in THF (10 mL). *Solution-S*, containing the corresponding allylic substrate, was prepared by dissolving the allylic carbonate (7.1 mmol) in THF (10 mL). The appropriate ligand (0.034 mmol) and $Mo(CO)_6$ (6.9 mg, 0.026 mmol) were transferred to a SmithProcess Vial™. *Solution-N* (1 mL, 0.77 mmol of the nucleophile), *Solution-S* (1 mL, 0.71 mmol of the substrate) and BSA (208 μL) were added in this order and the sample was heated in the microwave cavity to the appropriate temperature for the indicated time. Directly after reaction, the reaction mixture (dark coloured) was diluted with diethyl ether to a total volume of 10 mL (a precipitate appeared). The yellow-orange solution was filtrated and analysed by GC-MS. Purification of the crude product was achieved by liquid chromatography on silica gel (eluent: EtOAc in hexanes).

General procedure for microwave-accelerated allylic alkylations using polymer-supported ligand 1f. Two different stock solutions were prepared: *Solution-N*, containing the nucleophile, sodium dimethyl malonate in THF, was prepared by adding dimethyl malonate (880 μL, 7.7 mmol) to a suspension of 60% NaH (27 mg, 0.68 mmol) in THF (5 mL). *Solution-S*, containing the corresponding allylic substrate, was prepared by dissolving the allylic carbonate (7.1 mmol) in THF (5 mL). Polymer-supported ligand **1f** (160 mg, 0.045 mmol) and $Mo(CO)_6$ (6.9 mg, 0.026 mmol) were transferred to a SmithProcess Vial™. *Solution-N* (0.5 mL, 0.77 mmol of the nucleophile), *Solution-S* (0.5 mL, 0.71 mmol of the substrate) and BSA (208 μL) were added in this order and the sample was heated in the microwave cavity to the appropriate temperature for the indicated time. Directly after reaction, the reaction mixture was diluted with diethyl ether to a total volume of 10 mL. The solution was filtered and the polymer was washed with more ether. Evaporation of the solvent afforded the crude product that was purified by column chromatography on silica gel (eluent: EtOAc in hexanes). The filtered ligand was washed with 5 mL each of the following solvents: water, CH_2Cl_2, DMF, MeOH, acetone and CH_2Cl_2. The polymer was then dried under vacuum for at least 5 hours before being reused as ligand in the catalytic reaction.

Typical power, temperature and pressure vs. time profile for microwave-accelerated allylic alkylations using polymer-supported ligand 1f.[2]



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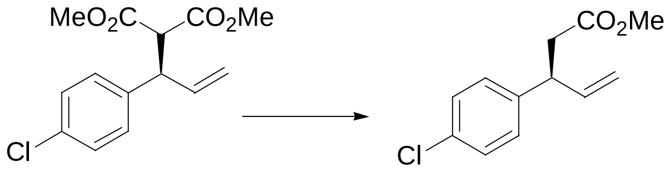
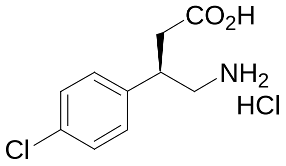
[2] For a comparison between conventional heating and microwave heating in this reaction see: Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596.



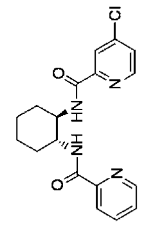
6 **7**

(*S*)-Methyl-3-(4-chlorophenyl)-4-pentenoate (7). A solution of **6** (240 mg, 0.85 mmol) and NaCl (100 mg, 1.71 mmol) in DMSO/H_2O (20/1) (1 mL) was heated at 200 °C for 20 min in the microwave cavity. To the reaction mixture H_2O (3 mL) was added and the resulting mixture was extracted with ether (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated to give the crude product that was purified by column chromatography on silica gel (eluent: hexanes/EtOAc 20/1) to afford 180 mg (94 %) of **7** as a colorless oil: $[\alpha]^{20}_{D}$ –11.5 (*c* 1.44, $CHCl_3$); ^1H NMR δ 7.26 (2H, d, *J* = 8.6 Hz), 7.13 (2H, d, *J* = 8.6), 5.93 (1H, ddd, *J* = 17.1, 10.7, 6.8 Hz), 5.00-5.12 (2H, m), 3.84 (1H, ddd, *J* = 7.8, 6.8 Hz), 3.61 (3H, s), 2.75 (1H, dd, *J* = 15.4, 7.8), 2.66 (1H, dd, *J* = 15.4, 7.8); ^{13}C NMR δ 172.4, 141.3, 140.2, 132.9, 129.4, 129.1, 115.6, 52.1, 45.3, 40.3. Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83. Found: C, 63.97; H, 5.69.



8

(*R*)-Baclofen (8). A solution of **7** (80 mg, 0.36 mmol) in CH_2Cl_2/MeOH (1/1, 1 mL) was treated with ozone at –78 °C for 10 min. The ozonide was reduced to the aldehyde by addition of MeS_2 (400 μL) at –78 °C and stirring while slowly warming to room temperature for 2 h. The solvent was evaporated and the resulting oil was dissolved in MeOH and NH_4OAc (277 mg, 3.6 mmol) and $NaBH_3CN$ (22.6, 0.36 mmol) were added. The reaction mixture was stirred at rt for 18 h. Then, 2N NaOH (2 mL) was added and the mixture was stirred for 2 h. The reaction mixture was concentrated to dryness and the residue was taken in water (0.5 mL) and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The resulting solid was taken in 6 N HCl and heated at 100 °C for a period of 12 h. Evaporation of the solvent afforded a white solid that was triturated in ^{i}PrOH to give **8** (20 mg, 22 %) which spectroscopical data was in accordance with that of an authentical sample: $[\alpha]^{20}_D$ –1.5 (*c* 0.89, H_2O).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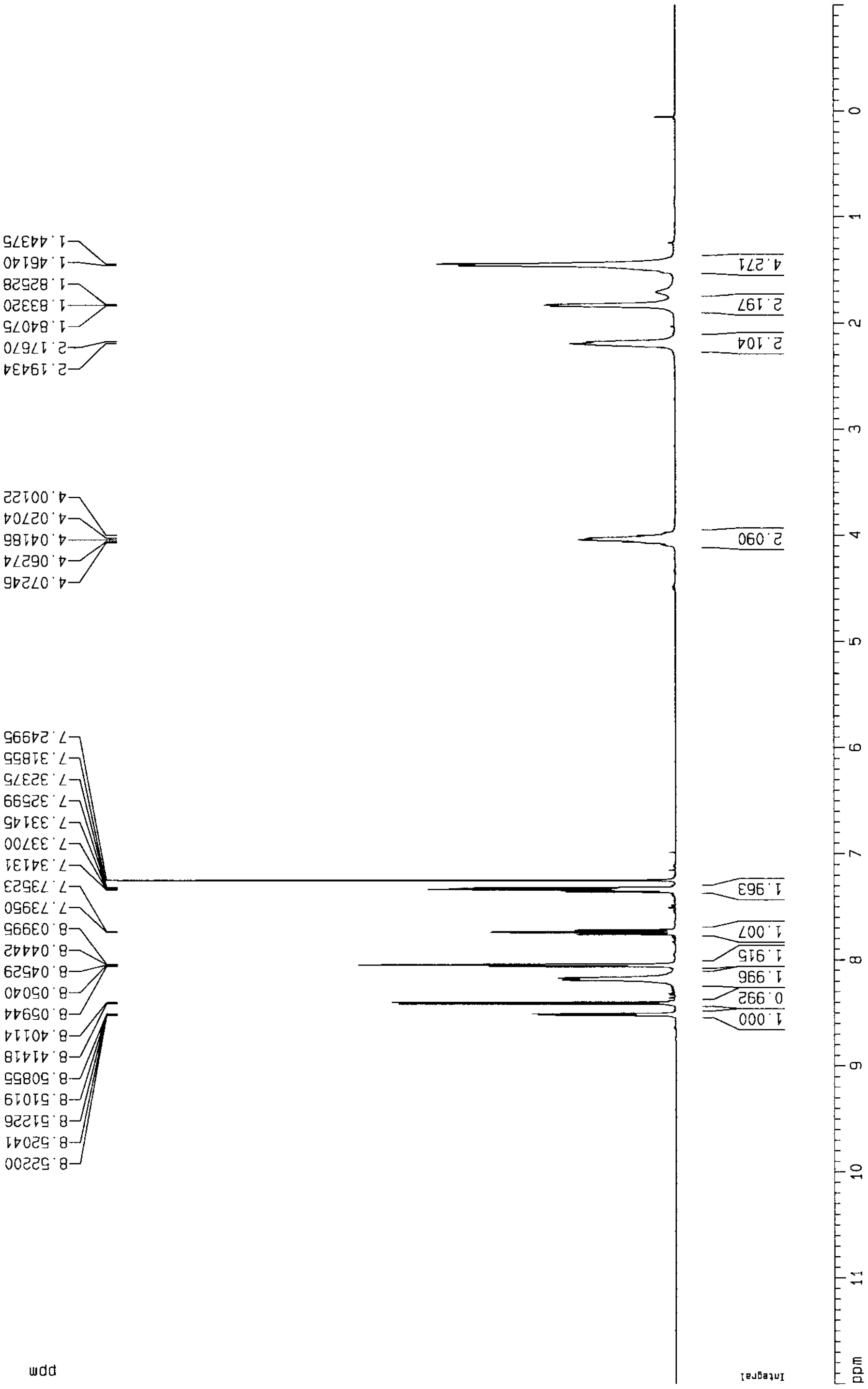
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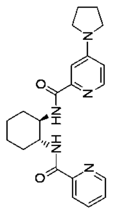
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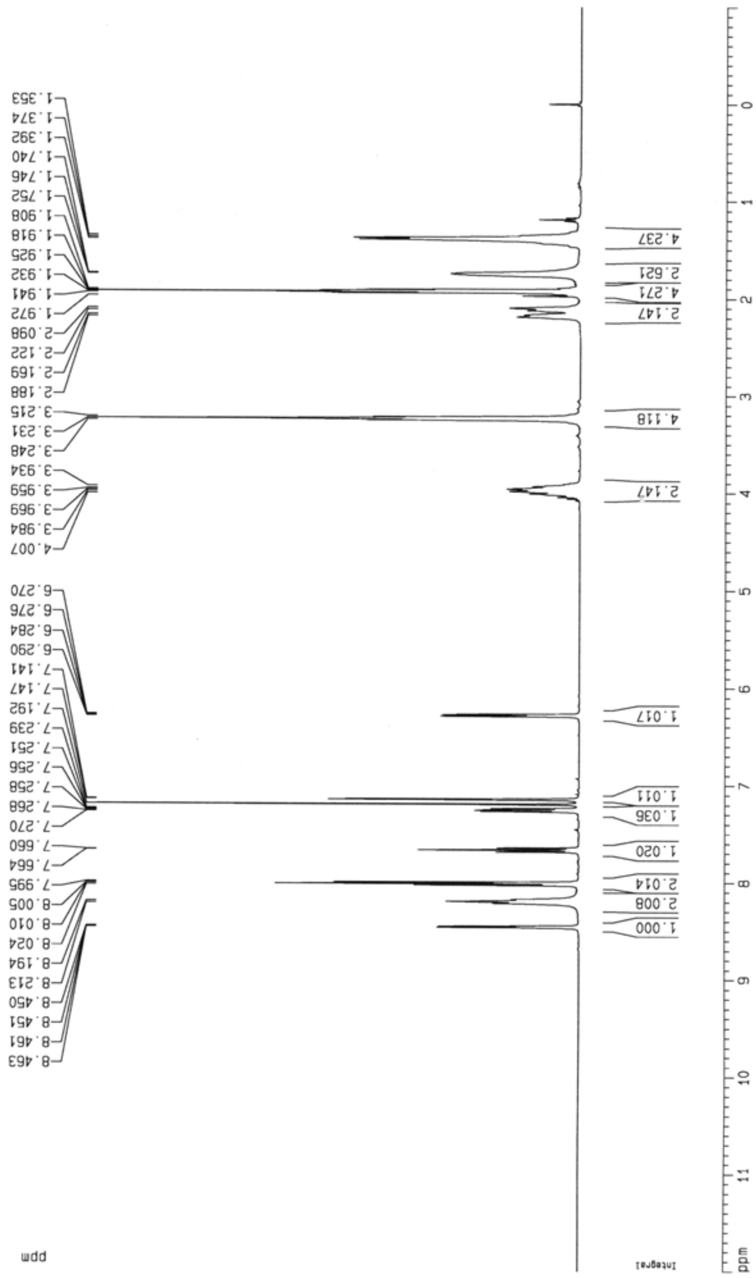
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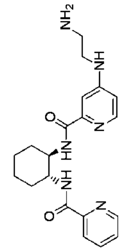
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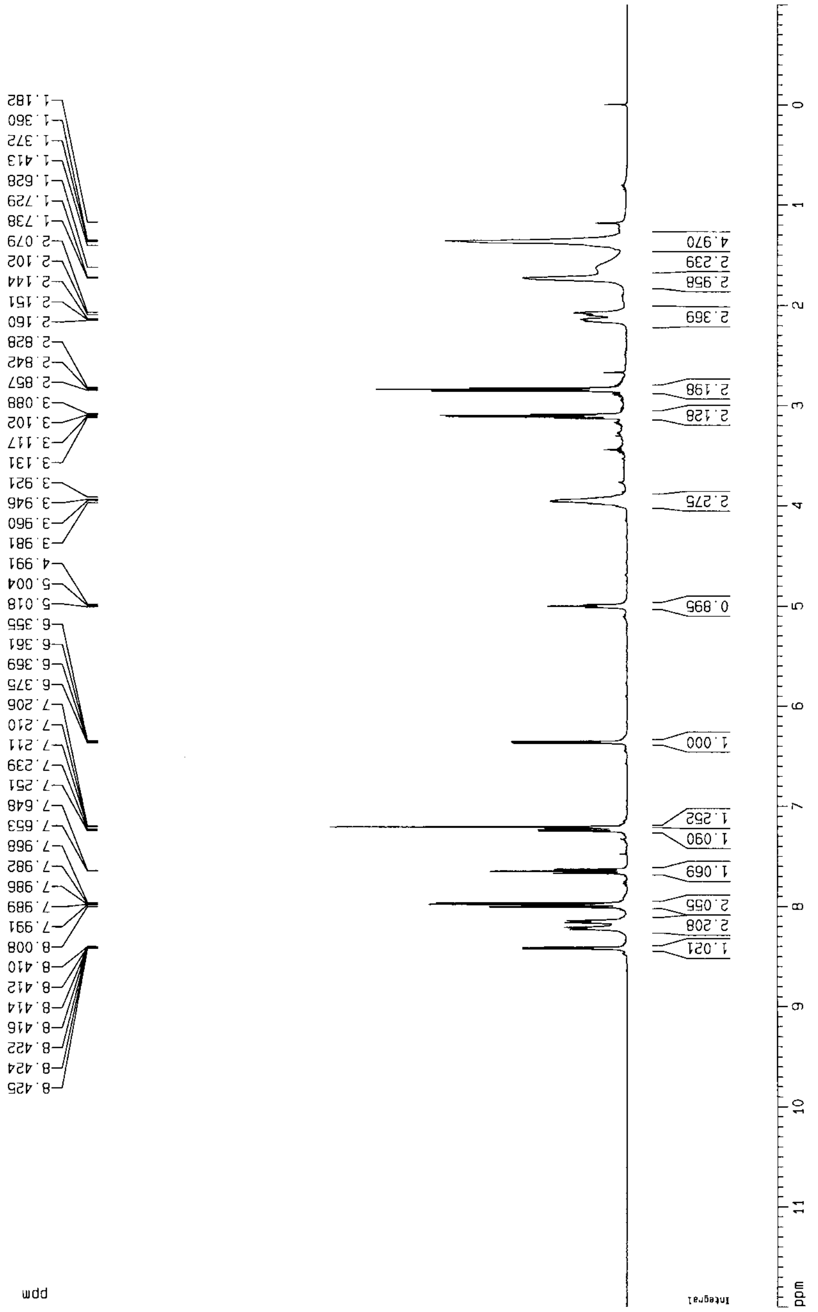
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