Supporting Information for:

Synthesis of Novel Symmetrical and Unsymmetrical Pyrazines

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General Experimental Section:

^{1}H NMR and ^{13}C NMR spectra were obtained as solutions in the deuterated solvents specified at 400 MHz and 100 MHz respectively. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methane carbons as 'd', from methylene and quaternary carbons as 'u'. The infrared (IR) spectra were determined as films or nujol mulls. R_f values indicated refer to thin layer chromatography (TLC) on 2.5 x 10 cm, 250 μm silica gel plates. Column chromatography was carried out as indicated on either silica gel or basic alumina. The solvent mixtures reported are volume/volume mixtures. All glassware was oven dried. All reactions were stirred magnetically, under dry N_2, unless otherwise noted.

Experimental Procedures:

Amino diols **3a**: In a 25 mL round bottom flask, *S*-(-)-2-amino-3-phenyl-1-propanol (**2a**) (1.1 g, 13 mmol) was combined with cyclohexene oxide (**1a**) (1.47 g, 15 mmol). The flask was sealed and the reaction was allowed to proceed for 2 weeks, at which point the mixture was subjected to bulb-to-bulb distillation (pot = 100 °C, 2 mmHg) to remove unreacted amino alcohol and epoxide, followed by column chromatography of the residue (acetone/ CH_2Cl_2/NH_4OH) over basic alumina to give the diastereomeric amino diols **3a** (1.1 g, 34% yield) as a viscous, pale yellow oil. TLC: R_f = 0.59 (5:44:1 MeOH/ CH_2Cl_2/NH_4OH). IR (film) 3352, 2930, 2861, and 1454 cm^{-1}; ^1H NMR (CD_3OD) δ 0.78-1.01 (m, 1H), 1.15 (m, 3H), 1.55 (m, 2H), 1.80 (m, 2H), 2.24-2.36 (m, 1H), 2.57-2.74 (m, 1H), 2.832 (m, 1H), 3.11 (m, 1H), 3.22-3.43 (m, 1H), and 7.13 (m, 5H); ^{13}C NMR (CD_3OD) δ d 40.40, 58.82, 59.48, 74.67, 75.17, 127.20, 127.32, 129.43, 129.45, 129.59, 130.38, 130.46; u 25.59, 25.76,31.61, 31.82, 35.07, 35.11, 37.81, 39.69; HRMS calcd for $C_{15}H_{23}NNaO_2$: 272.163, obsd: 272.163 [M+Na].

Amino diols **3c**: Trans-anethole oxide (**1b**) (2.7 g, 16.4 mmol) was combined neat with *R*-2-amino-1-butanol (**2b**) (1.5 g, 16.4 mmol). After a week of stirring under nitrogen at room temperature, the reaction mixture was diluted with 20 mL of methanol and evaporated onto 6 g of basic alumina. An alumina column was then run with a 0-40% acetone/ CH_2Cl_2/NH_4OH gradient. The eluted fractions still had traces of amino alcohol, therefore the residue after evaporation was then subjected to bulb-to-bulb distillation (2 mm Hg, Pot = 115 °C, pot residue) to give the amino diols **3c** (1.5 g , 36% yield). TLC: R_f = 0.41, (5:44:1 MeOH/CH_2Cl_2/NH_4OH); IR (film): 3386, 2965, 1512, and 1248 cm^{-1}; ^1H NMR (CD_3OD) δ 0.82 (t, J = 7.4 Hz, 1H), 0.88 (t, J = 7.6 Hz, 1H), 1.01

(t, J = 6 Hz, 3H), 1.25-1.45 (m, 1H), 1.45-1.65 (m, 1H), 1.89 (m, 1H), 2.39 (m, 1H), 3.30-3.60 (m, 2H), 3.65-3.75 (m, 2H), 4.00 (m, 1H), 6.90 (m, 2H), 7.25 (m, 2H); ^{13}C NMR (CD_3OD) δ d 8.88, 9.59, 18.12, 18.62, 54.24, 56.61, 57.27, 63.70, 64.61, 69.84, 113.03, 129.41, 129.61; u 22.13, 24.66, 25.11, 67.47, 130.99, 131.96, 158.94; HRMS calcd for $C_{14}H_{23}NNaO_3$: 276.158, obsd: 276.158 [M+Na].

Amino diols **3d**: Trans-anethole oxide (**1b**) (2.7 g, 16.4 mmol) and *S*-(-)-2-amino-3-phenyl-1-propanol (**2a**) (2.5g, 16.4 mmol) were combined with 5 mL MeOH and the solution was stirred for two weeks at room temperature under nitrogen. The reaction mixture was then taken directly to bulb-to-bulb distillation (2 mm Hg, pot = 100 °C, bottom fraction) and the residue was passed through a short alumina column (acetone/ CH_2Cl_2/NH_4OH) to give the amino diols **3d** (1.37 g, 30% yield).

TLC: R_f = 0.54, (5:44:1 MeOH/CH_2Cl_2/NH_4OH); IR (film): 3385, 2931, 1512, and 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9-1.0 (m, 4H), 1.2 (s, 1H), 2.4-3.0 (m, 3H), 3.0-4.0 (m, 4H), 6.7-7.4 (m, 11H). ^{13}C NMR ($CDCl_3$) δ d 19.12, 29.19, 30.88, 55.21, 56.77, 57.54, 64.21,64.74, 70.12, 70.21, 113.64, 113.84, 126.27, 126.42, 126.57, 128.42, 128.50, 128.57, 128.60, 128.81, 128.94, 129.19, 129.24, 129.33, 129.41; u 30.51, 37.69, 38.86, 39.55, 53.43, 53.81, 62.04, 63.89, 64.21, 131.19, 131.48, 158.78, 159.01; HRMS calcd for $C_{19}H_{26}N_1O_3$: 316.191, obsd: 316.192 [M+H].

Amino diol **3e**: Following the procedure of Taguchi,[8] cyclohexene oxide (**1a**) (10 g, 0.10 mol) and 6.0 ml conc. NH_4OH (29% aq.) were combined. The flask was sealed and the reaction was allowed to stir for 5 days. The white slurry was then vacuum filtered with 3 x 25 mL rinses of Et_2O and evaporated to give amino diols **3e** (3.1 g, 29% purified yield).

TLC: R_f = 0.28 (5:44:1 MeOH/CH_2Cl_2/NH_4OH). MP: 150-151 °C (Lit = 153 °C); IR

(film) 3336, 2929, 2855, 1449 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90-1.05 (m, 1H), 1.15-1.35 (m, 3H), 1.65-1.80 (m, 2H), 1.95-2.10 (m, 2H), 2.30-2.40 (m, 1H), 3.15-3.25 (m, 1H). ^{13}C NMR ($CDCl_3$) δ d 59.28, 74.11; u 24.49, 24.92, 31.20, 33.88; HRMS calcd for $C_{12}H_{23}NNaO_2$: 236.163, obsd: 236.163 [M+Na].

Pyrazine **4a**: Oxalyl chloride (2.13 g, 14.0 mmol) diluted to 10 mL with CH_2Cl_2 was added to a 100 mL round bottom flask in a –40 °C bath. DMSO (1.31 g, 16.9 mmol diluted to 10 mL with CH_2Cl_2) over the course of one minute with gas evolution. Amino diols **3a** (250 mg, 0.92 mmol in 10 mL CH_2Cl_2) were then added. The reaction was allowed to proceed with the temperature being kept between –20 °C and –40 °C. After 2h, triethylamine (5 mL, 35.8 mmol) was then added with accompanying exotherm to give a turbid yellow solution. The mixture was allowed to warm to 0 °C over the course of 30 min, and the mixture was then partitioned between water and CH_2Cl_2. The combined organic extract was dried over Na_2SO_4. TLC indicated the absence of amino diols **3a**. The CH_2Cl_2 solution was decanted into a 250 mL round bottom flask, to which was added 20 mL of absolute EtOH and $NH_2OH \cdot HCl$ (88 mg, 1.27 mmol). The round bottom flask was fitted with a distillation apparatus and the mixture was heated until the bulk of the CH_2Cl_2 had distilled out. The mixture was then kept at reflux for two hours with an air condenser. The brown solution was then concentrated onto flash silica gel and chromatographed on flash silica gel with a MTBE/PE gradient to give 88 mg of crude pyrazine **4a**. This was then further purified via TLC mesh chromatography (1:1 MTBE/PE) to give 48 mg of pyrazine **4a** as a pale yellow oil, 23% yield overall from **3a.**

Pyrazine **4c**: Oxalyl chloride (2.13 g, 14.0 mmol) diluted to 10 mL with CH_2Cl_2 was added to a 100 mL round bottom flask in a –40 °C bath. DMSO (1.31 g, 16.9 mmol

diluted to 10 mL with CH_2Cl_2) over the course of one minute with gas evolution. Amino diols **3c** (250 mg, 0.99 mmol) in 10 mL CH_2Cl_2 were then added. The reaction was allowed to proceed with the temperature being kept between –20 °C and –40 °C. After 2h, triethylamine (5mL, 35.8 mmol) was then added with accompanying exotherm to give a turbid yellow solution. The mixture was allowed to warm to 0 °C over the course of 30 min, and the mixture was then partitioned between water and CH_2Cl_2. The combined organic extract was dried over Na_2SO_4. TLC indicated the absence of amino diols **3c**. The CH_2Cl_2 solution was decanted into a 250 mL round bottom flask, to which was added 20 mL of absolute EtOH and $NH_2OH \cdot HCl$ (88 mg, 1.27 mmol). The round bottom flask was fitted with a distillation apparatus and the mixture was heated until the bulk of the CH_2Cl_2 had distilled out. The mixture was then kept at reflux for two hours with an air condenser. The brown solution was then concentrated onto flash silica gel and chromatographed on flash silica gel with a MTBE/PE gradient to give crude pyrazine **4c**. This was then further purified via TLC mesh chromatography (1:1 MTBE/PE) to give 25 mg of pyrazine **4c** as a, 20% yield overall from **3c**. TLC: R_f = 0.50, (MTBE); IR (film): 2970, 1610, 1514, 1382, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 13.2 Hz, 3H), 2.59 (s, 3H), 2.82 (q, J = 7.6, 13.2 Hz, 2H), 3.85 (s, 3H), 6.98 (d, J = 9.6 Hz, 2H), 7.51 (d, J = 9.6 Hz, 2H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ d 13.77, 22.84, 55.38, 113.82, 130.41, 140.51; u 28.36, 131.44, 148.23, 152.39, 155.18, 159.91; HRMS calcd for $C_{14}H_{17}N_2O$: 229.134, obsd: 229.133 [M+H].

Pyrazine **4d**: Oxalyl chloride (2.13 g, 14.0 mmol diluted to 10 mL with CH_2Cl_2) was added to a 100 mL round bottom flask in a –40 °C bath. DMSO (1.31 g, 16.9 mmol diluted to 10 mL with CH_2Cl_2) over the course of one minute with gas evolution. Amino

diols **3d** (315 mg, 1.0 mmol in 10 mL CH_2Cl_2) were then added. The reaction was allowed to proceed with the temperature being kept between –20 °C and –40 °C. After 2h, triethylamine (5 mL, 35.8 mmol) was then added with accompanying exotherm to give a turbid yellow solution. The mixture was allowed to warm to 0 °C over the course of 30 min, and the mixture was then partitioned between water and CH_2Cl_2. The combined organic extract was dried over Na_2SO_4. TLC indicated the absence of amino diols **3d**. The CH_2Cl_2 solution was decanted into a 250 mL round bottom flask, to which was added 20 mL of absolute EtOH and $NH_2OH \cdot HCl$ (88 mg, 1.27 mmol). The round bottom flask was fitted with a distillation apparatus and the mixture was heated until the bulk of the CH_2Cl_2 had distilled out. The mixture was then kept at reflux for two hours with an air condenser. The brown solution was then concentrated onto flash silica gel and chromatographed on flash silica gel with a MTBE/PE gradient to give crude pyrazine **4d**. This was then further purified via TLC mesh chromatography (1:1 MTBE/PE) to give 25 mg of pyrazine **4d** as a pale yellow oil, 15% yield overall from **3d.**

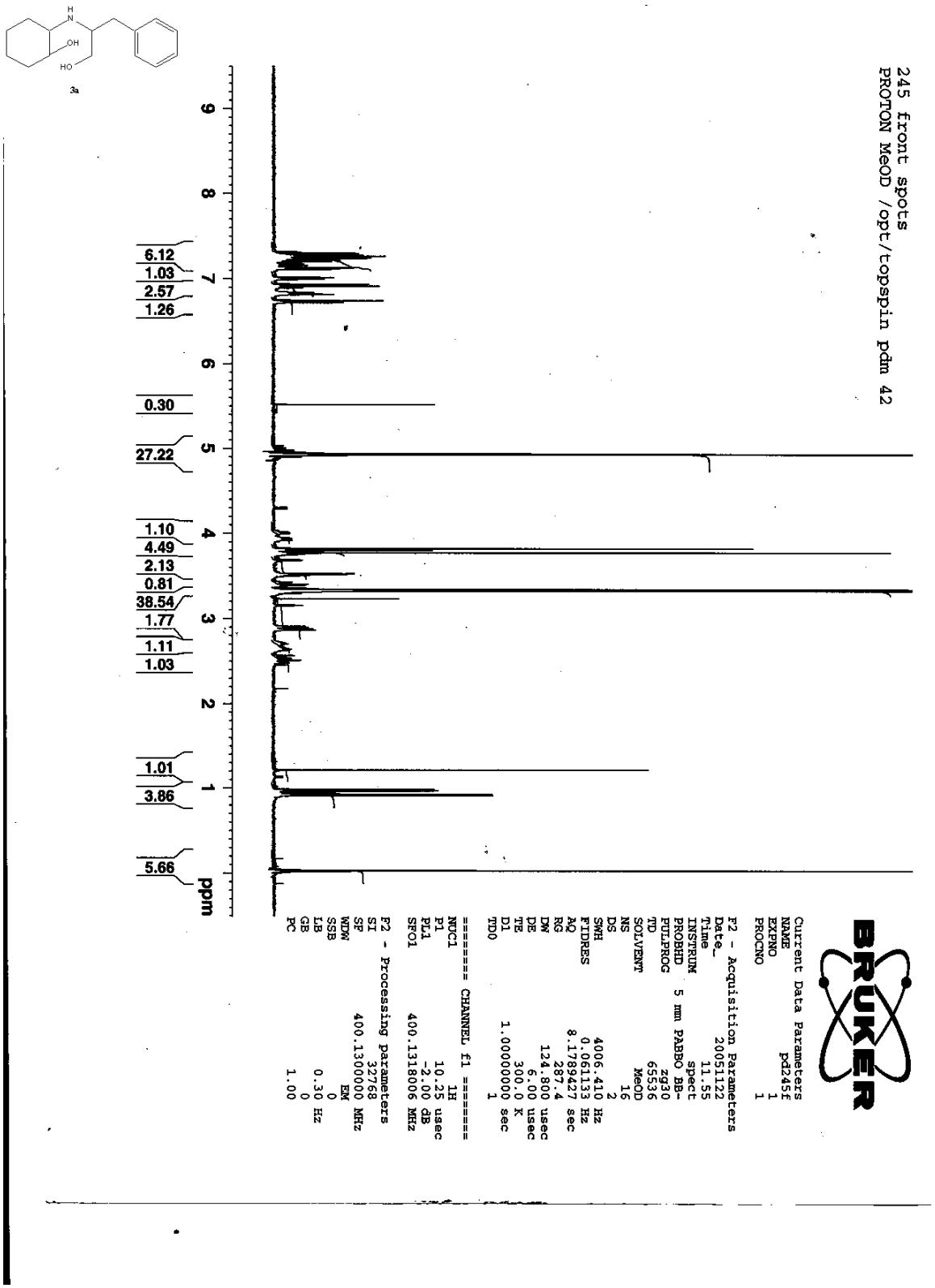
TLC: R_f =0.52, (MTBE); IR (film): 2920, 2360, 1514, and 1251 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3H), 1.49 (s, 2H), 2.42 (s, 3H), 3.04 (s, 1H), 3.69 (s, 3H), 4.01 (s, 2H), 6.83 (d, J = 6.4 Hz, 2H), 7.00-7.20 (m, 5H), 7.37 (d, J = 6.8 Hz, 2H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ d 22.70, 26.80, 55.20, 113.64, 126.40, 128.48, 128.84, 130.30, 141.07; u 41.51, 131.02, 138.53, 148.44, 152.54, 159.81; HRMS calcd for $C_{19}H_{18}N_2NaO$: 313.132, obsd: 313.133[M+Na].

Pyrazine **4e**:

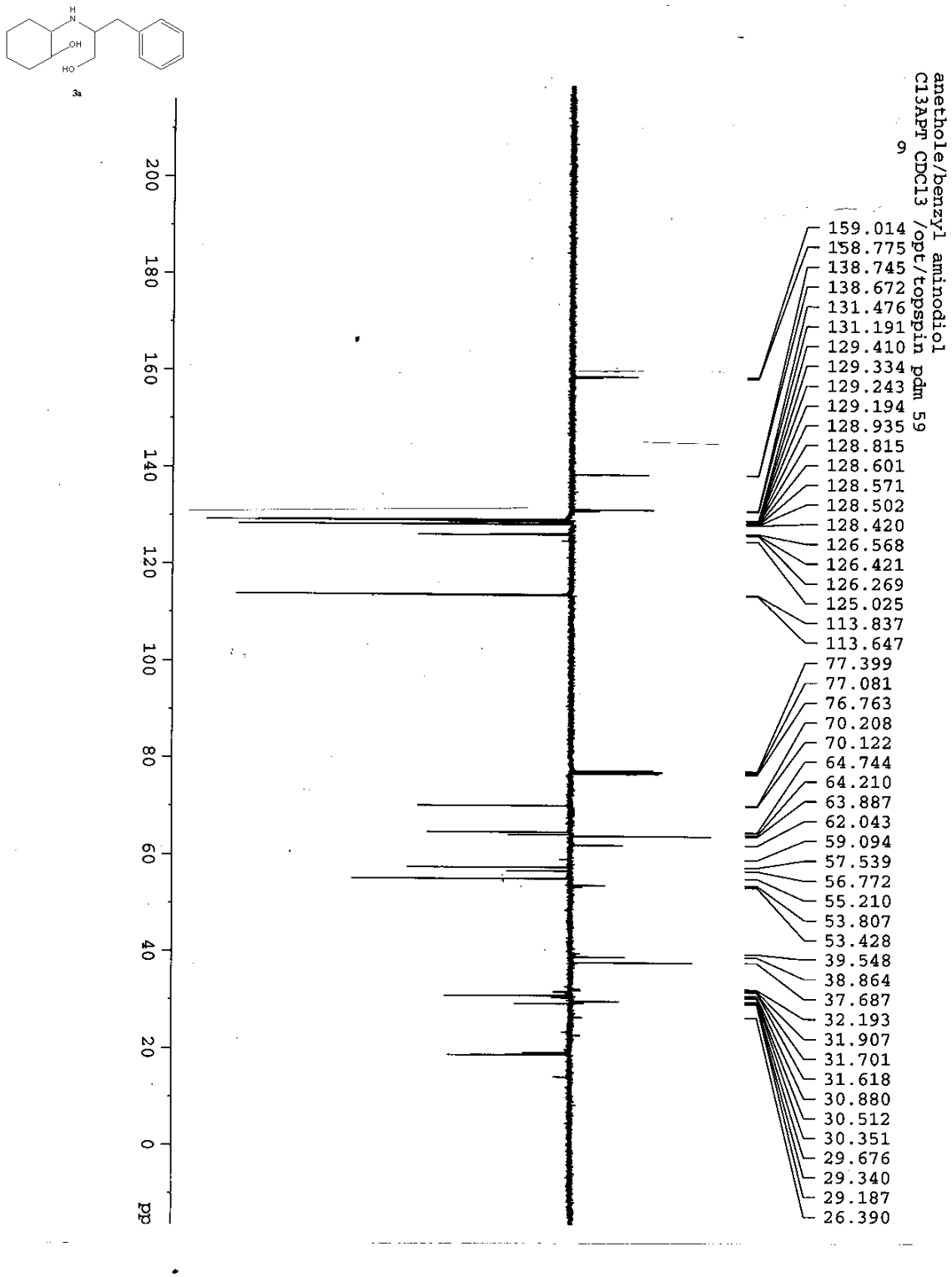
Amino diol **3e** (213 mg, 1.0 mmol) was suspended in 20 mL CH_2Cl_2, then DMSO was added dropwise until complete dissolution was observed (~5 drops). Meanwhile, 6.3 mL

of a 1.63 M oxalyl chloride/ CH_2Cl_2 solution was cooled to –78 °C. DMSO (1.2 mL diluted to 10 mL with CH_2Cl_2) was added dropwise over 5 min with stirring. The solution of amino diol **3e** was then added over 5 min, and the reaction was kept at -78 °C for an additional 2 h. Triethylamine (5 mL) was then added, and after 15 min the reaction was allowed to come to room temperature (~2 h). The mixture was then partitioned between water and CH_2Cl_2. The organic extract was dried over Na_2SO_4 then decanted into another flask, to which was added 20 mL abs EtOH and NH2OH · HCl (78 mg, 1.12 mmol). The mixture then had 95 mL solvent distilled out of it by fractional distillation and was refluxed at 90 °C (bath temp) for an additional 2 h. The mixture was then concentrated and the residue was chromatographed to give pyrazine **4e** as a white solid (80 mg, 43% yield from amino diol **7**). MP: 103-104 °C. Lit = 105-106 °C.[12] TLC: R_f = 0.62, (MTBE); ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 2H), 2.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ u 22.98, 32.02, 149.33; HRMS calcd for $C_{12}H_{16}N_2$: 188.131, obsd: 188.131 [M+].

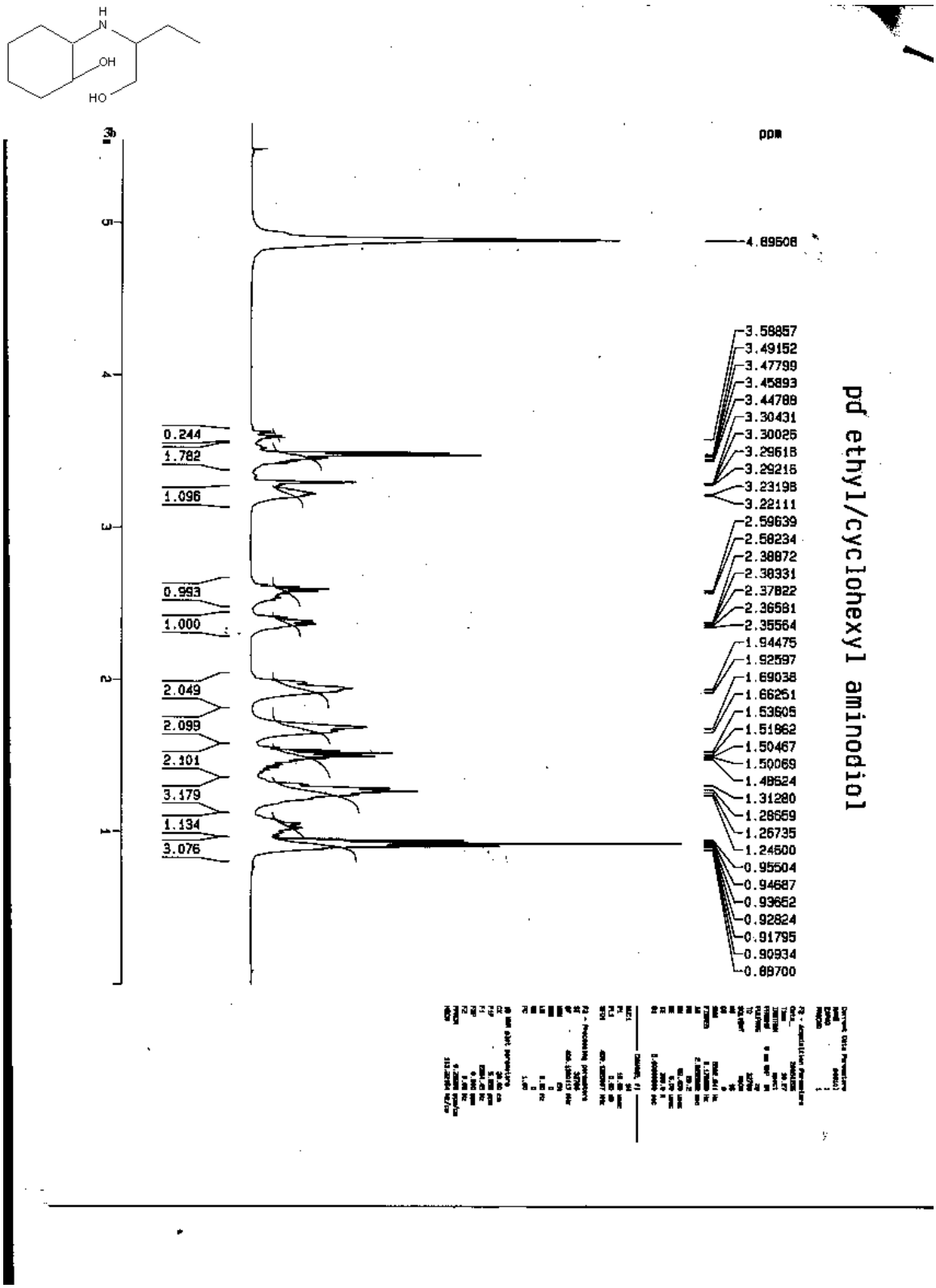
Amino Diols **3a**: ^{1}H Spectrum



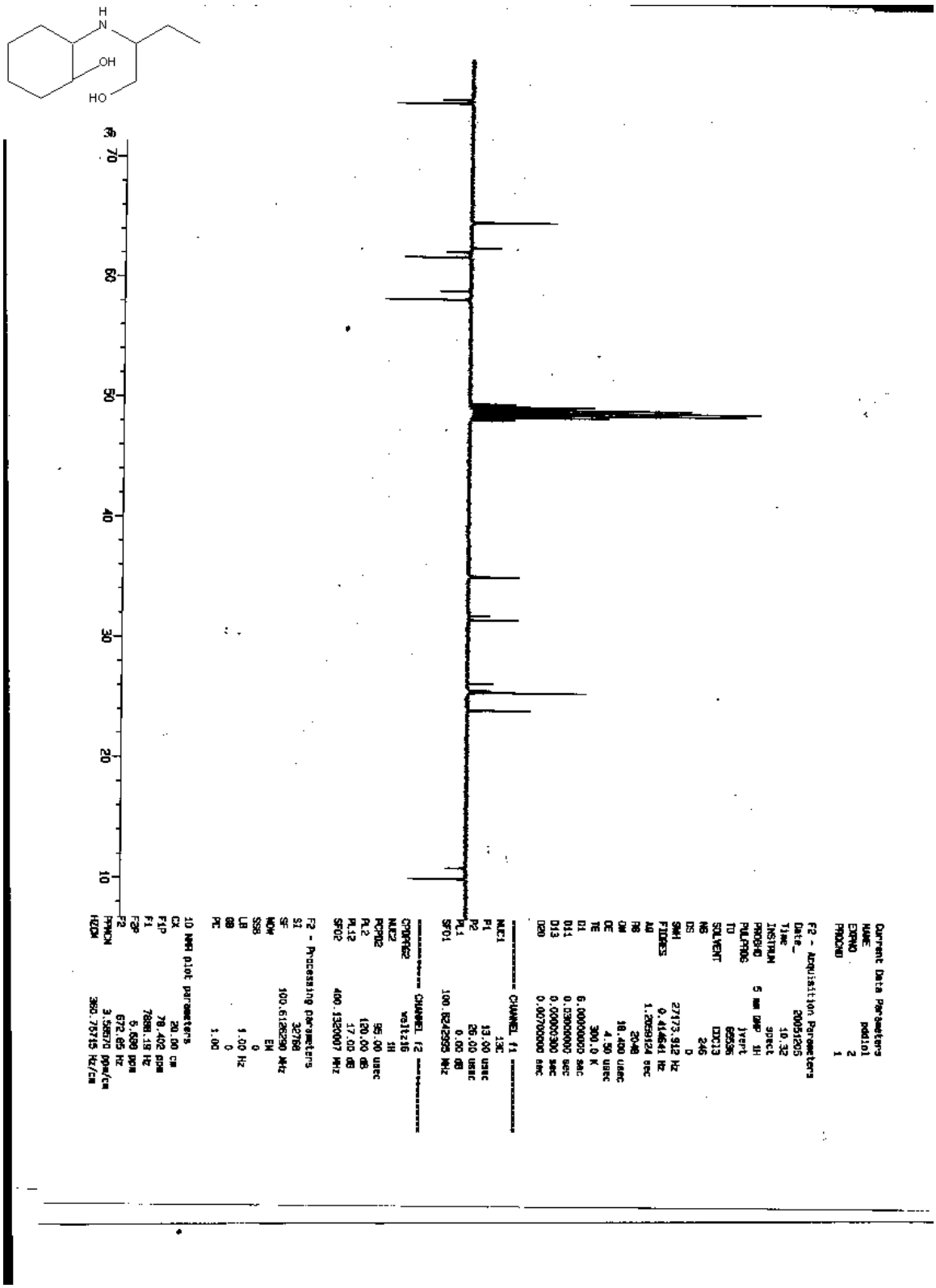
Amino Diols **3a**: ^{13}C Spectrum



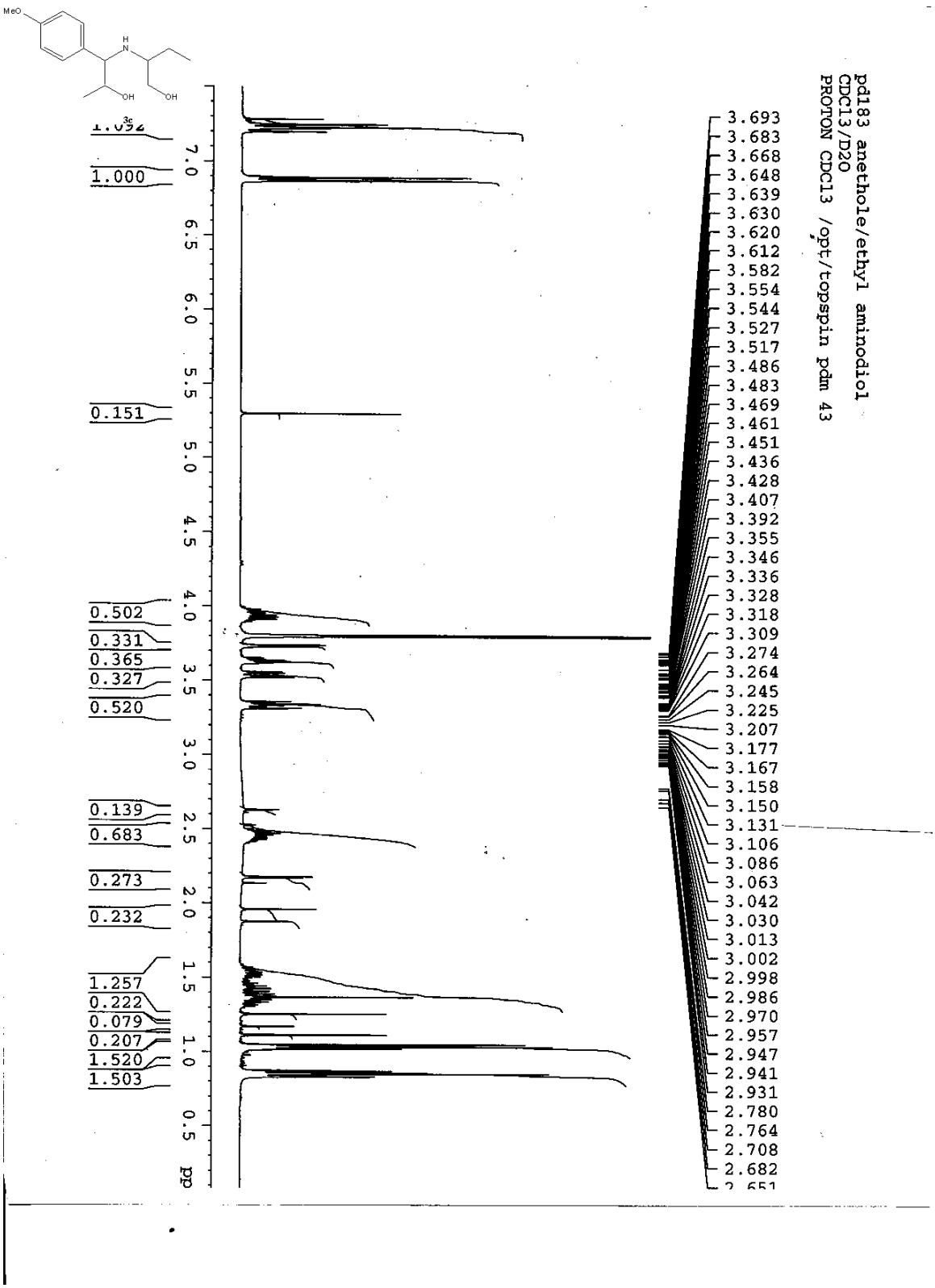
Amino Diols **3b**: ^{1}H Spectrum



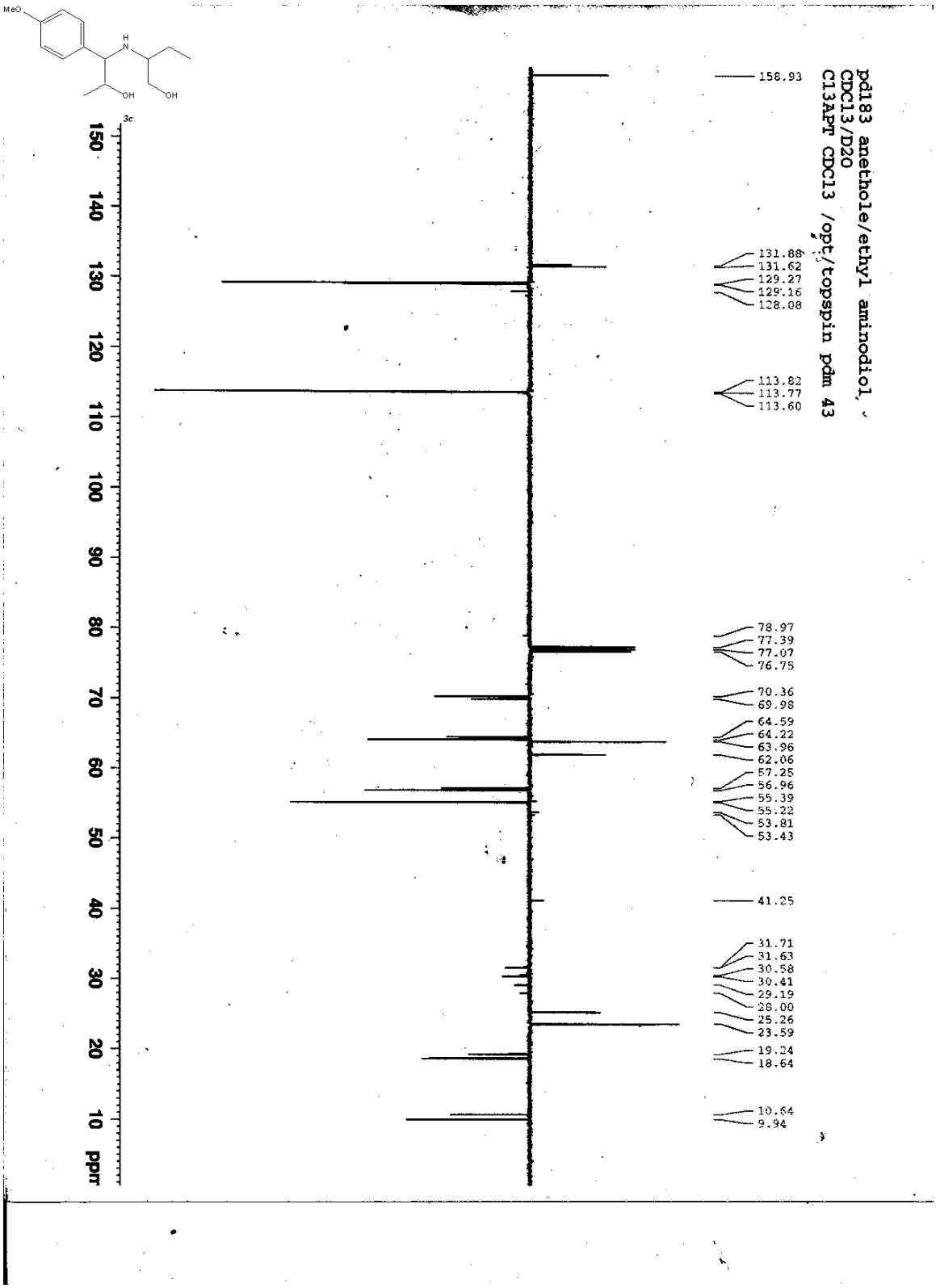
Amino Diols **3b**: ^{13}C Spectrum



Amino Diols **3c**: ^{1}H Spectrum



Amino Diols **3c**: ^{13}C Spectrum



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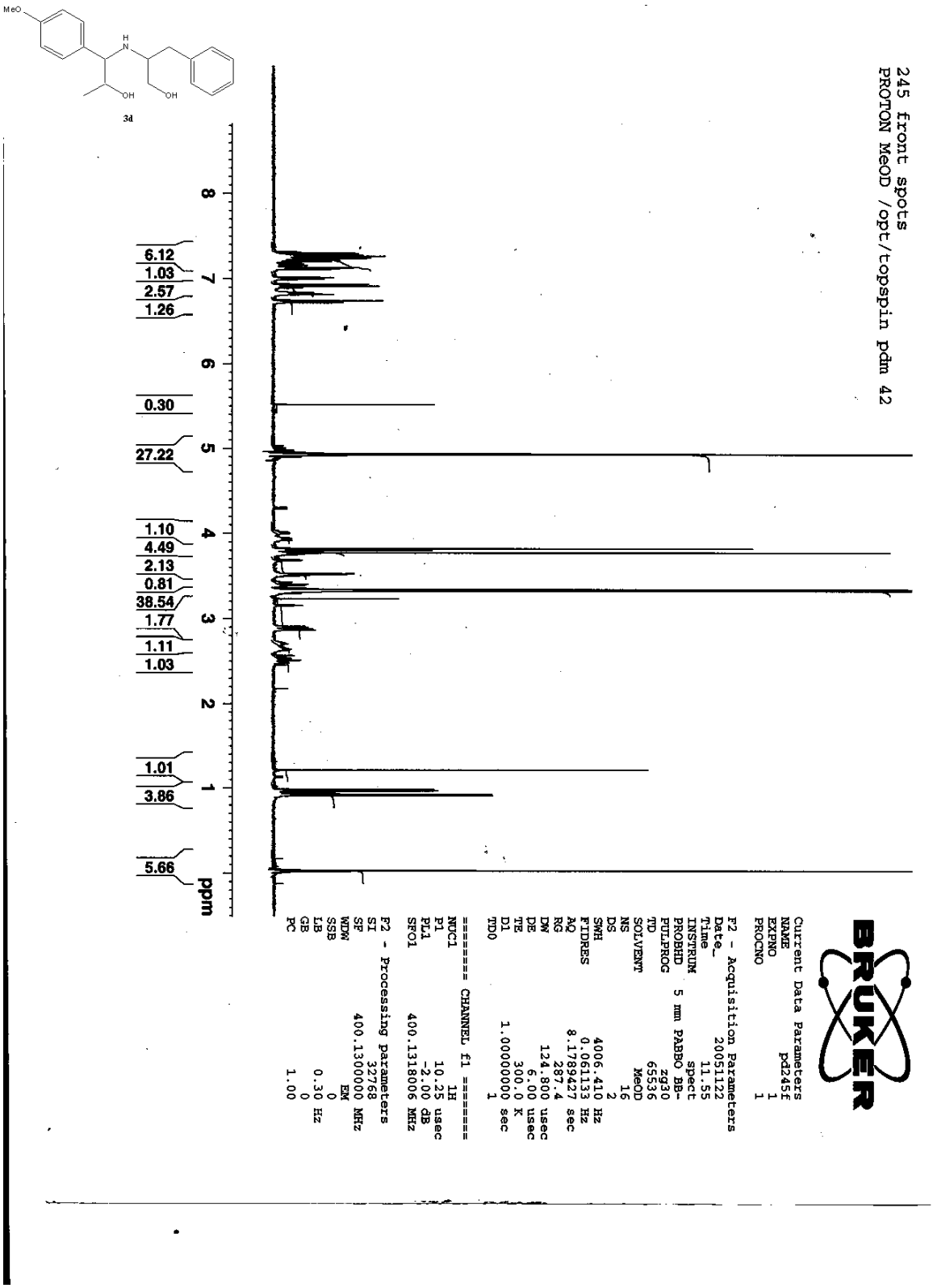
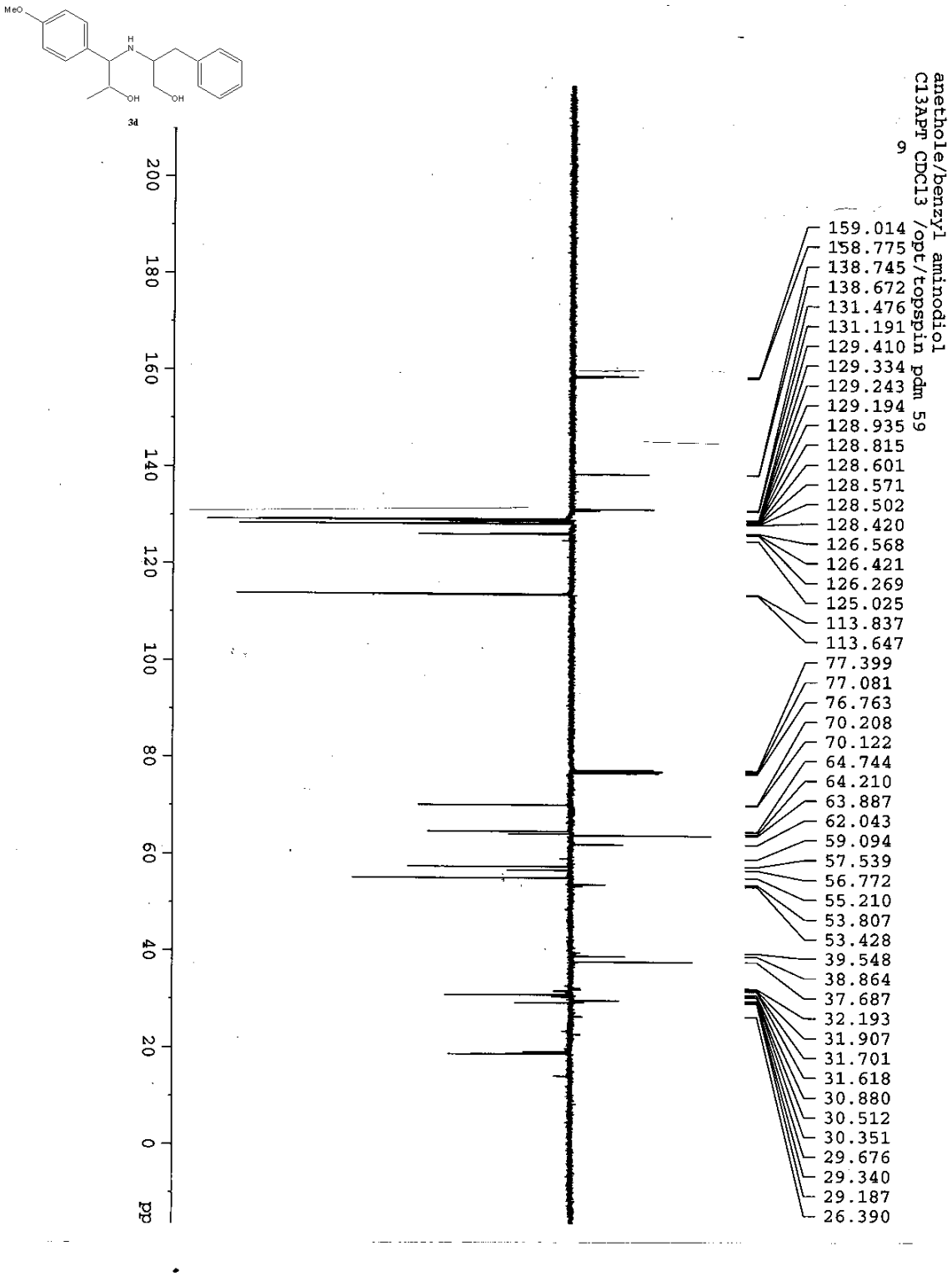
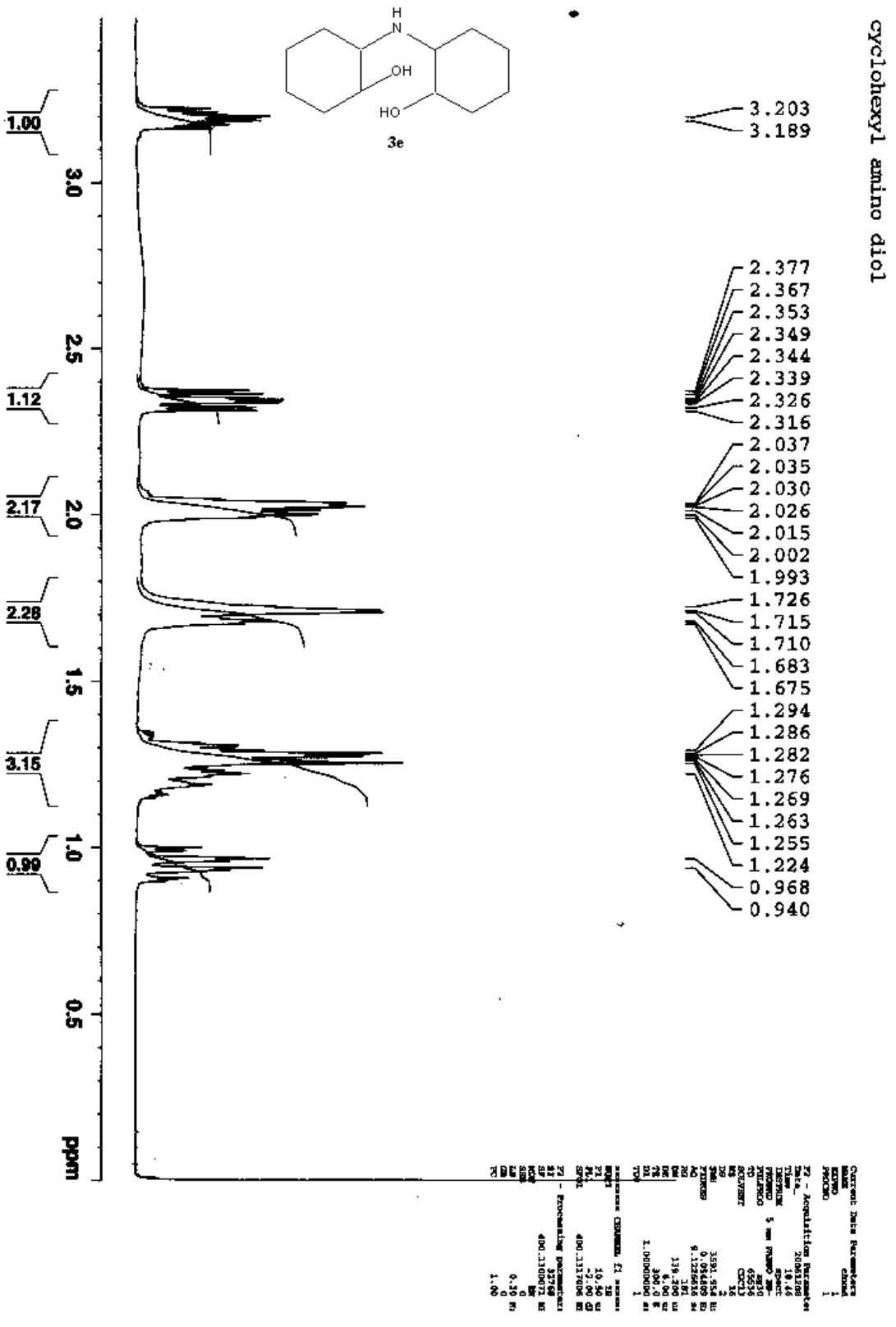


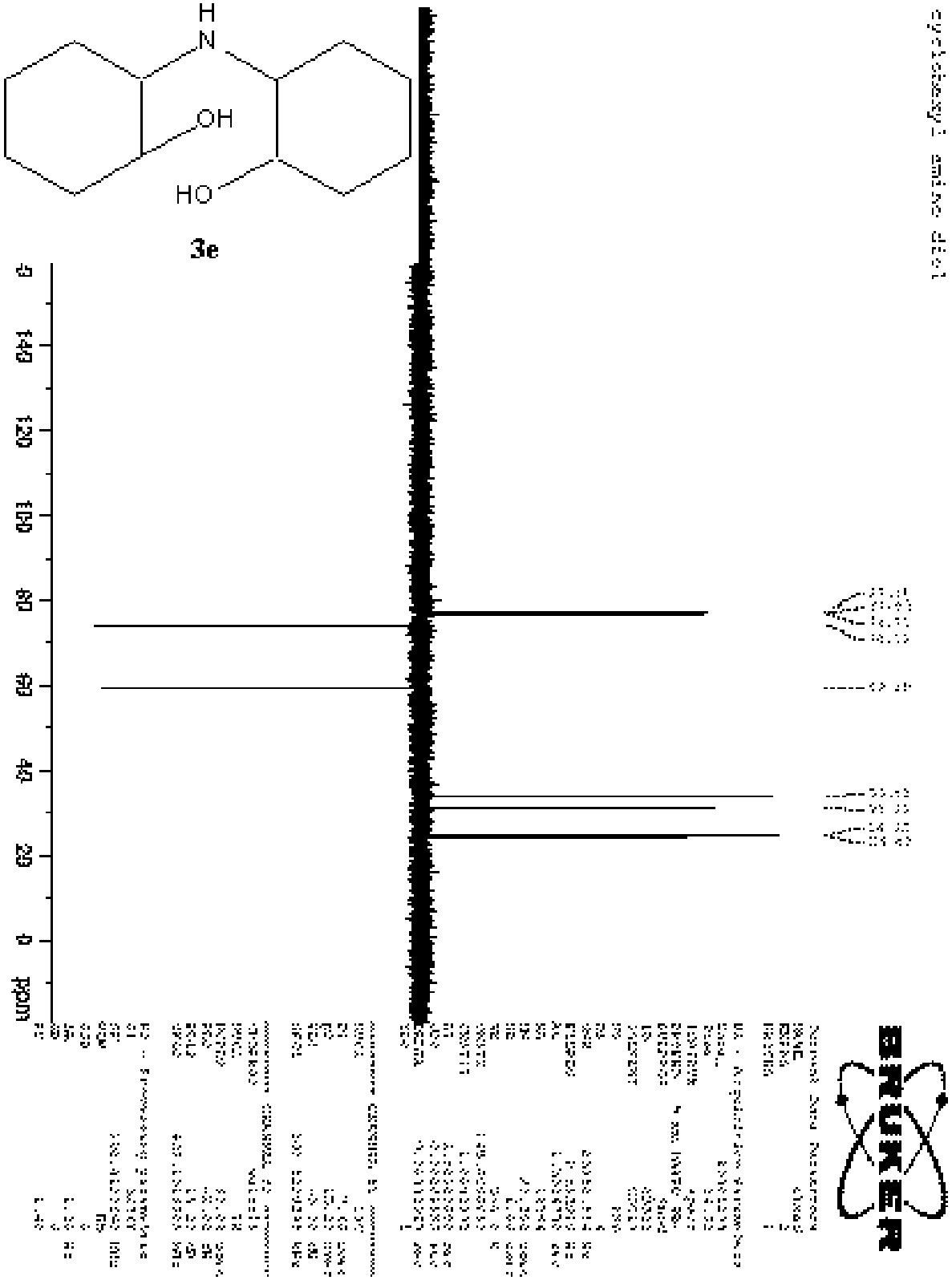
Amino Diols **3d**: ^{13}C Spectrum



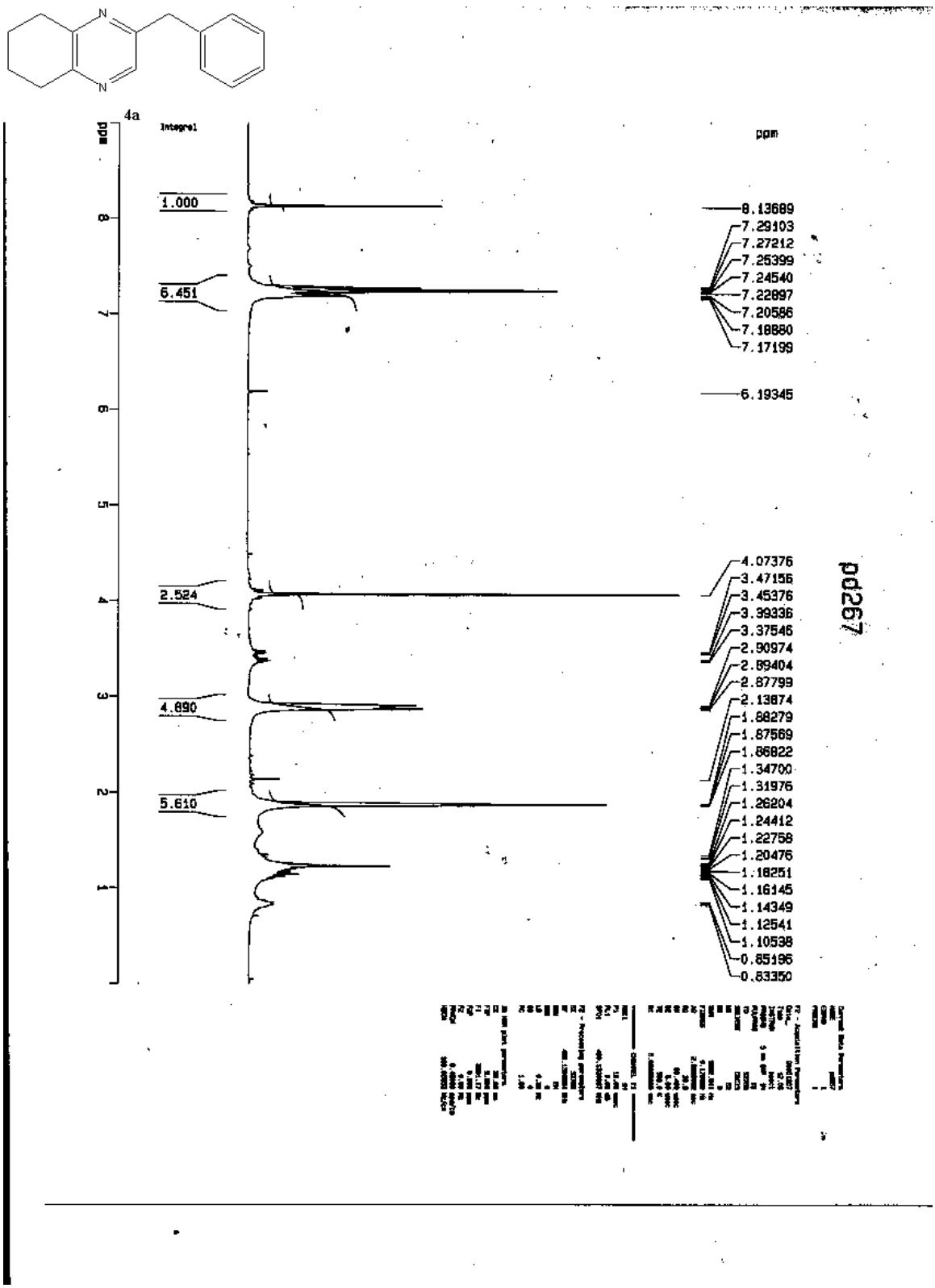
Amino Diol **3e**: ^{1}H Spectrum



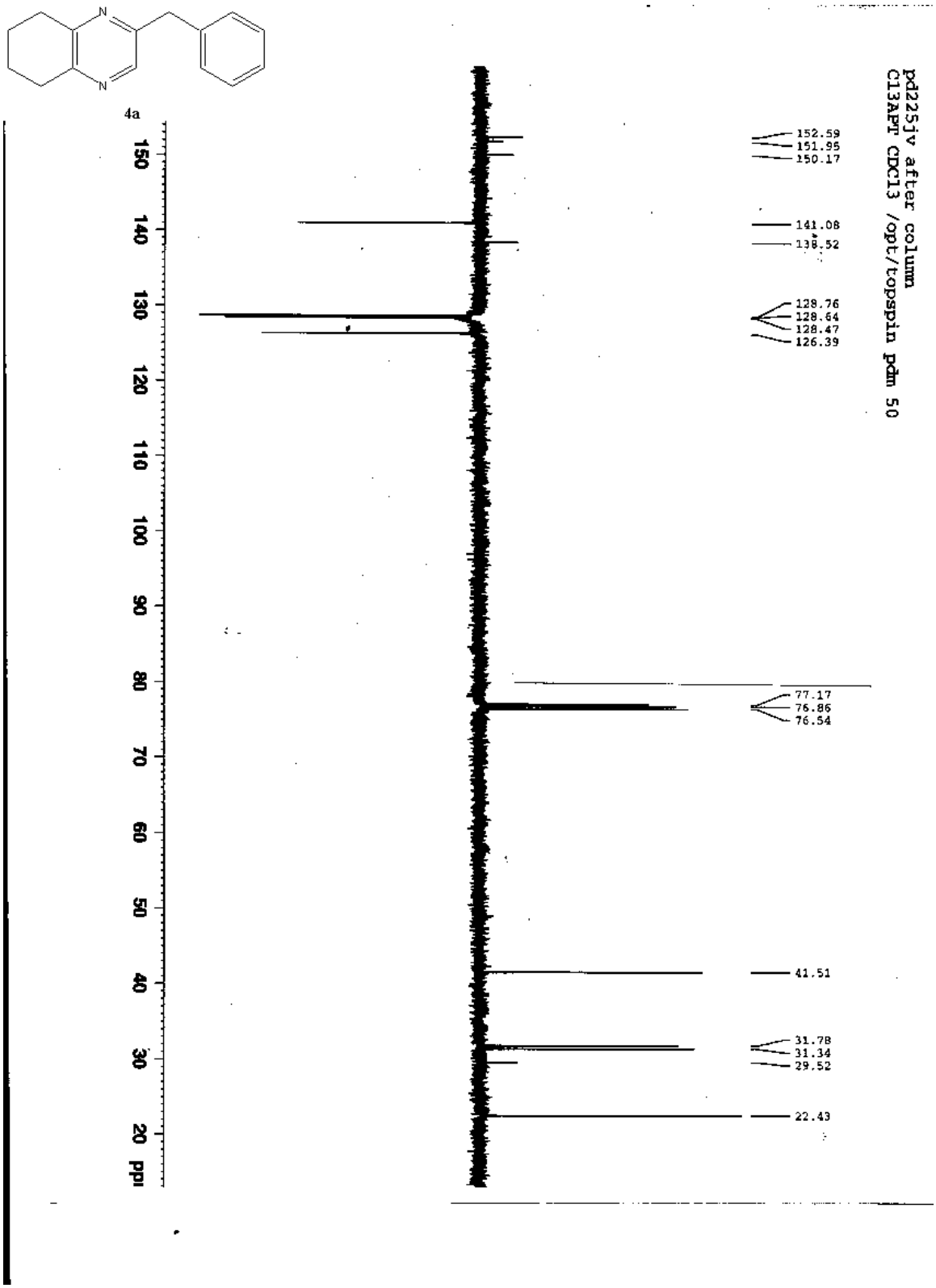
Amino Diol **3e**: ^{13}C Spectrum



Pyrazine **4a** ^{1}H Spectrum:



Pyrazine **4a** ^{13}C Spectrum:



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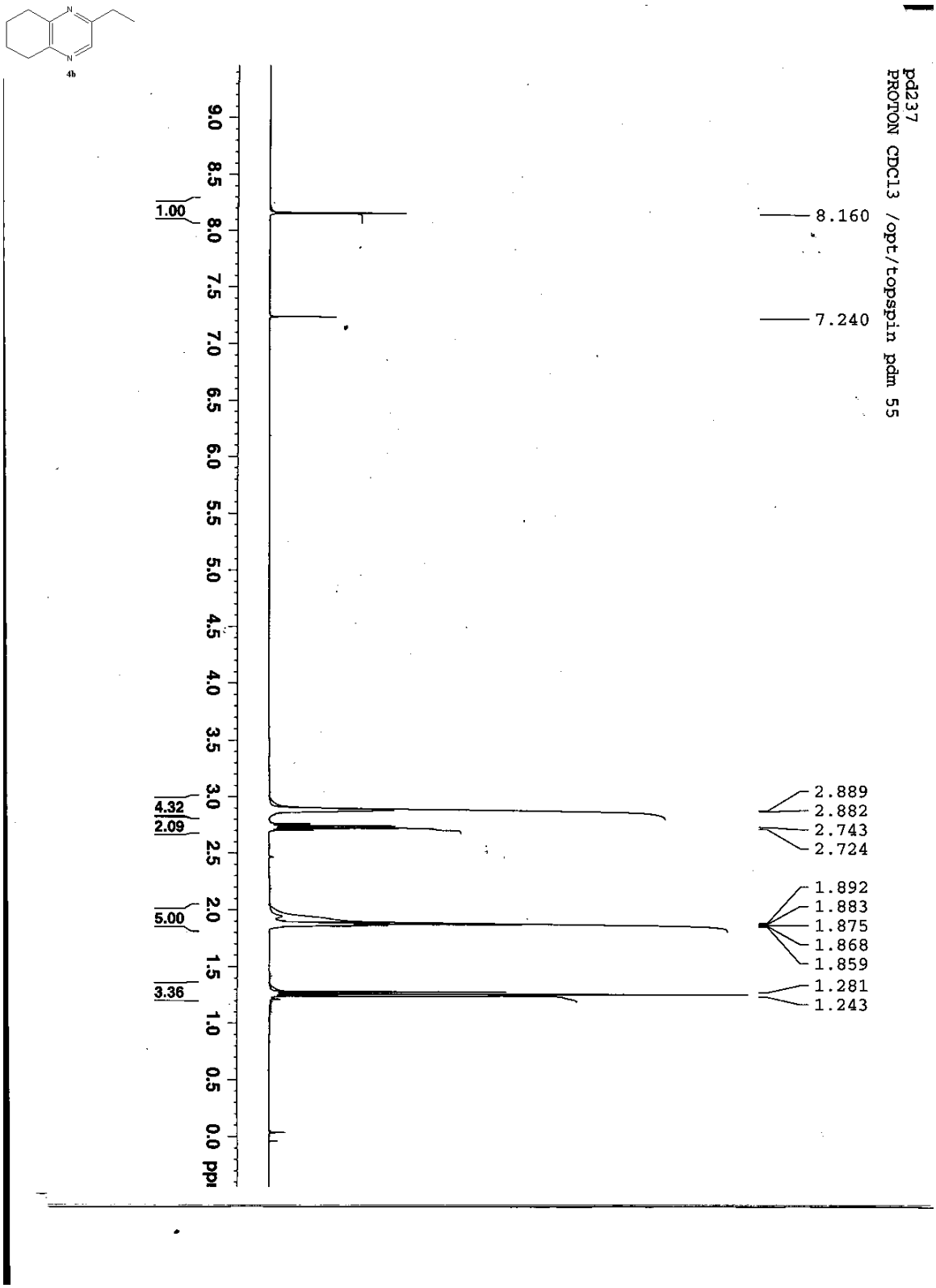
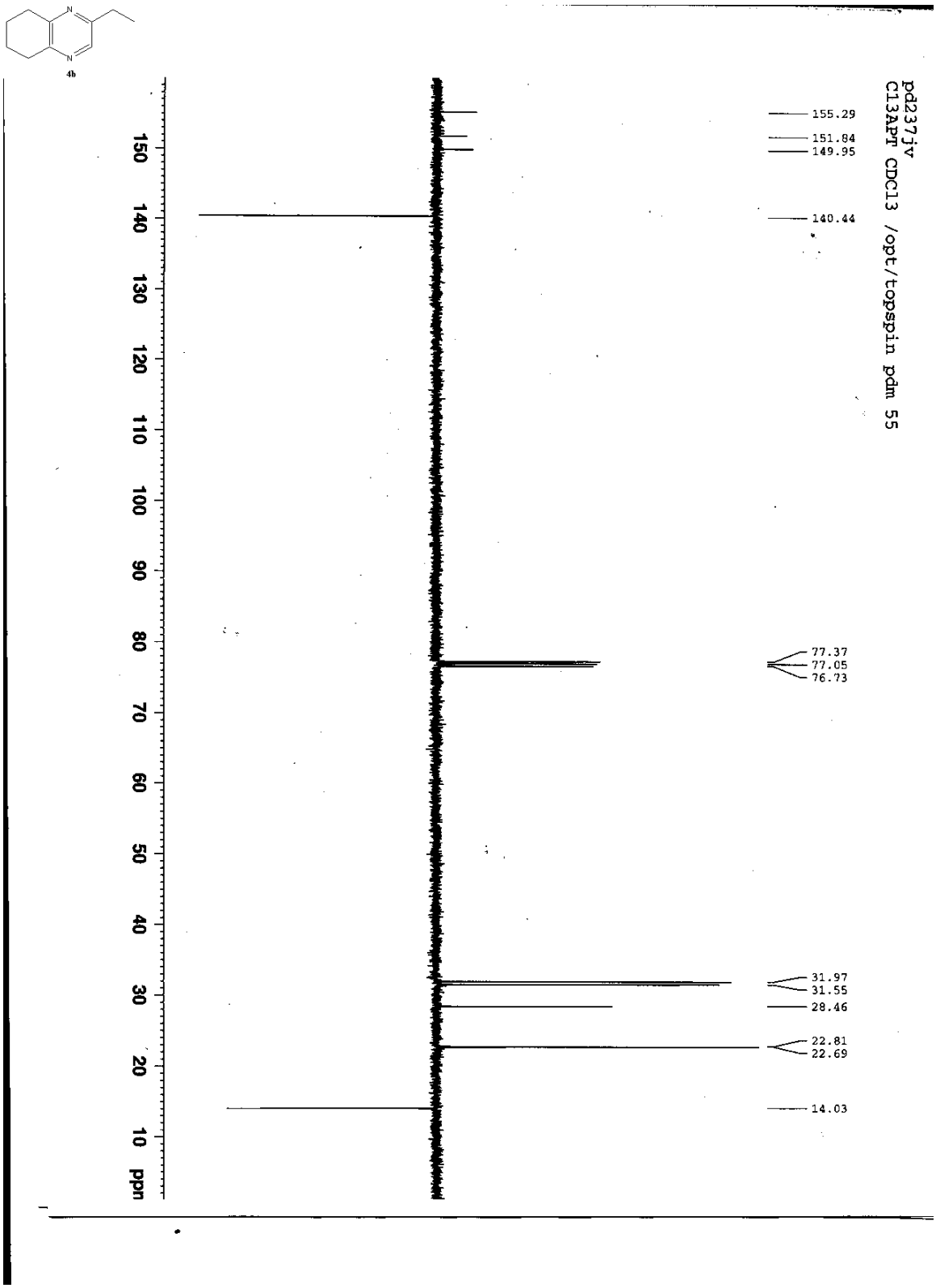


Pyrazine **4b** ^{13}C Spectrum:



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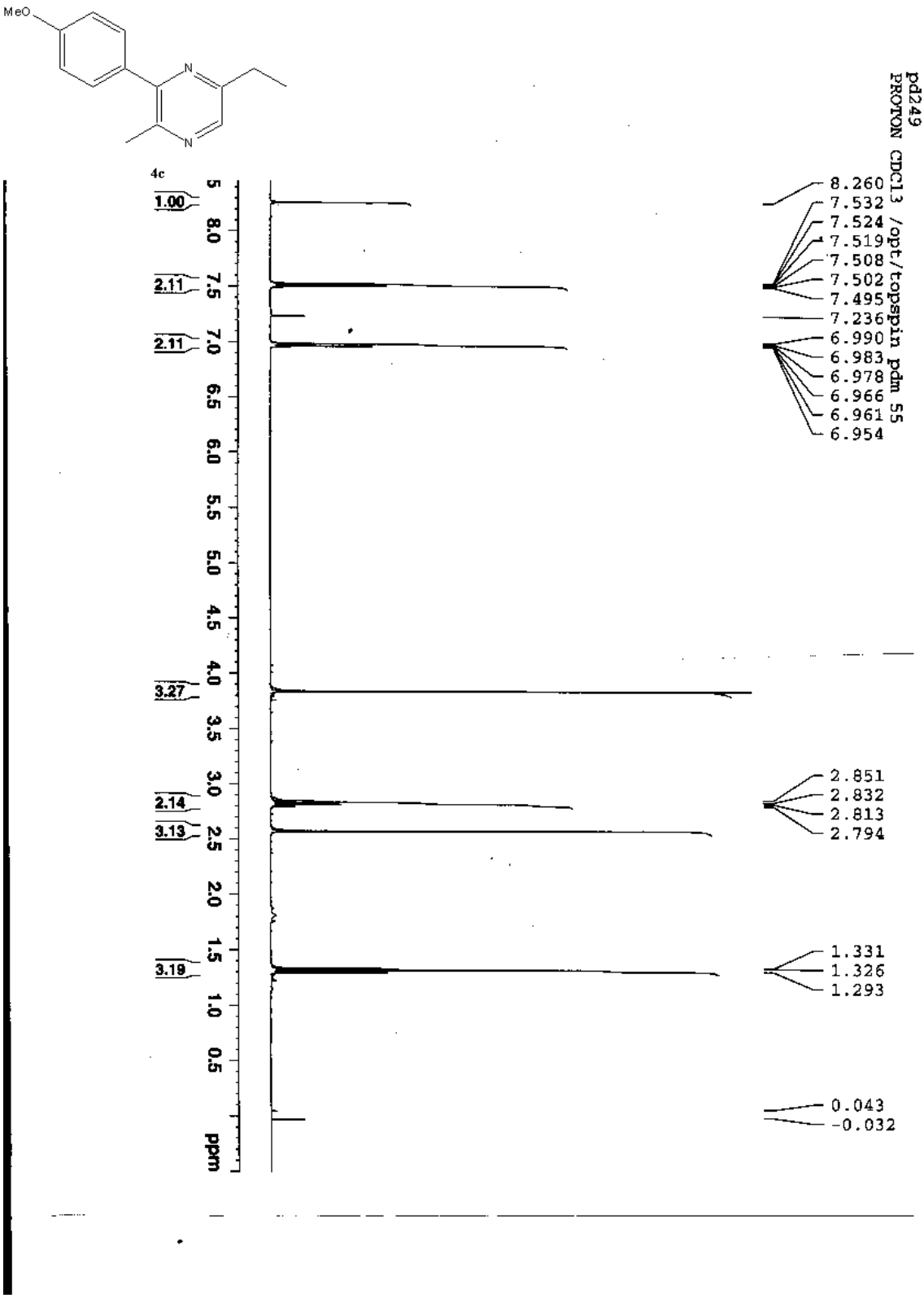
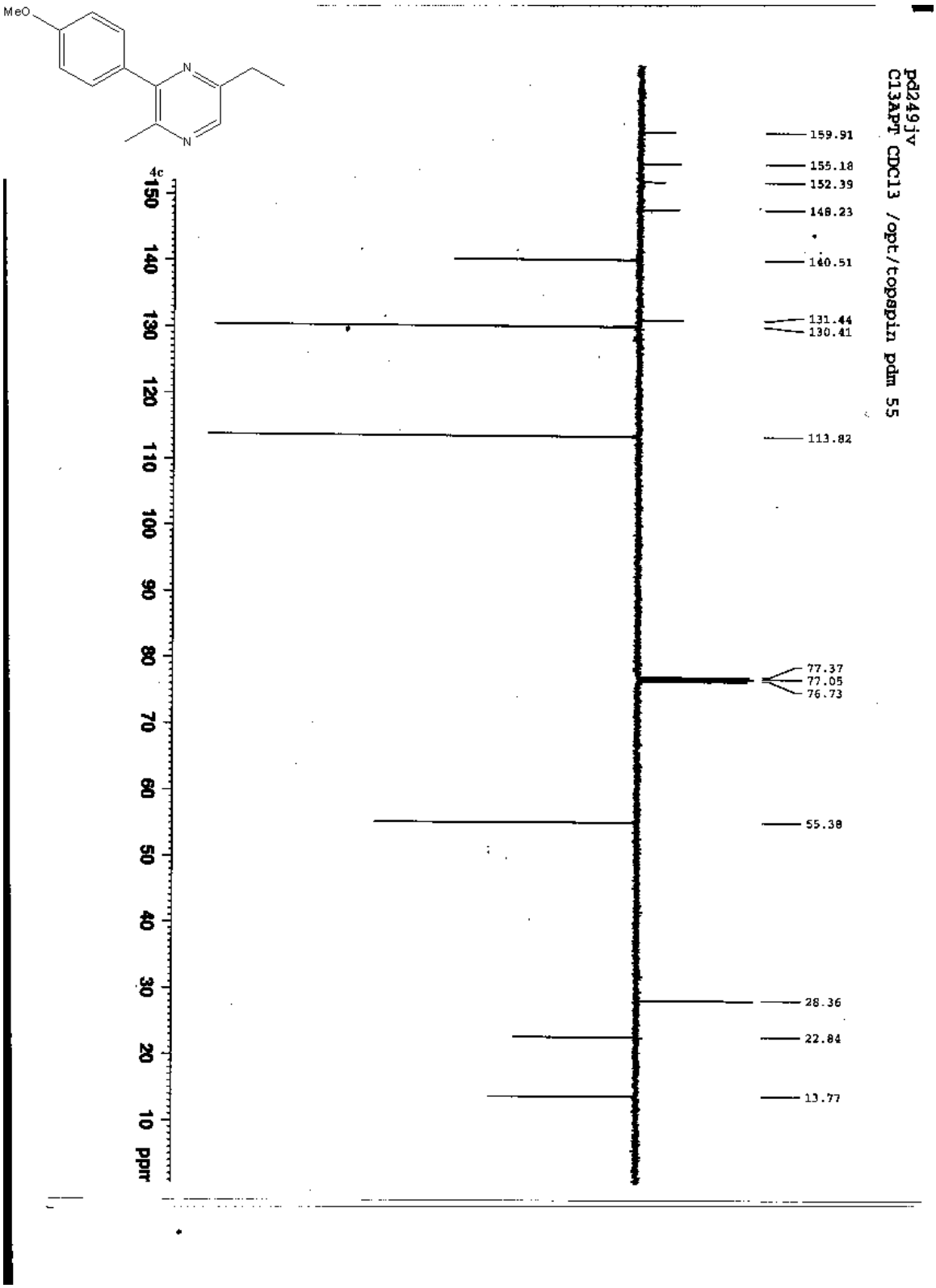
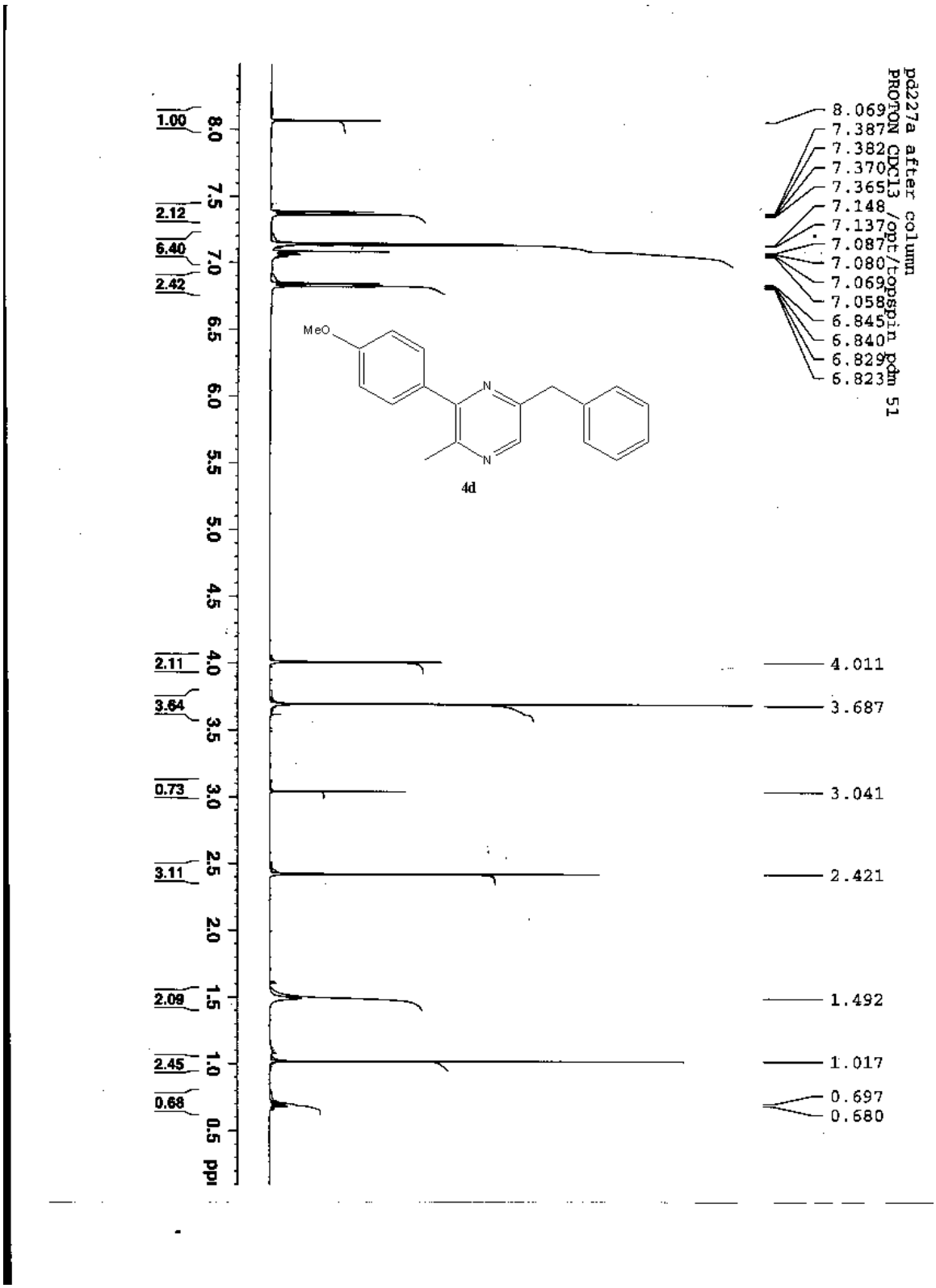


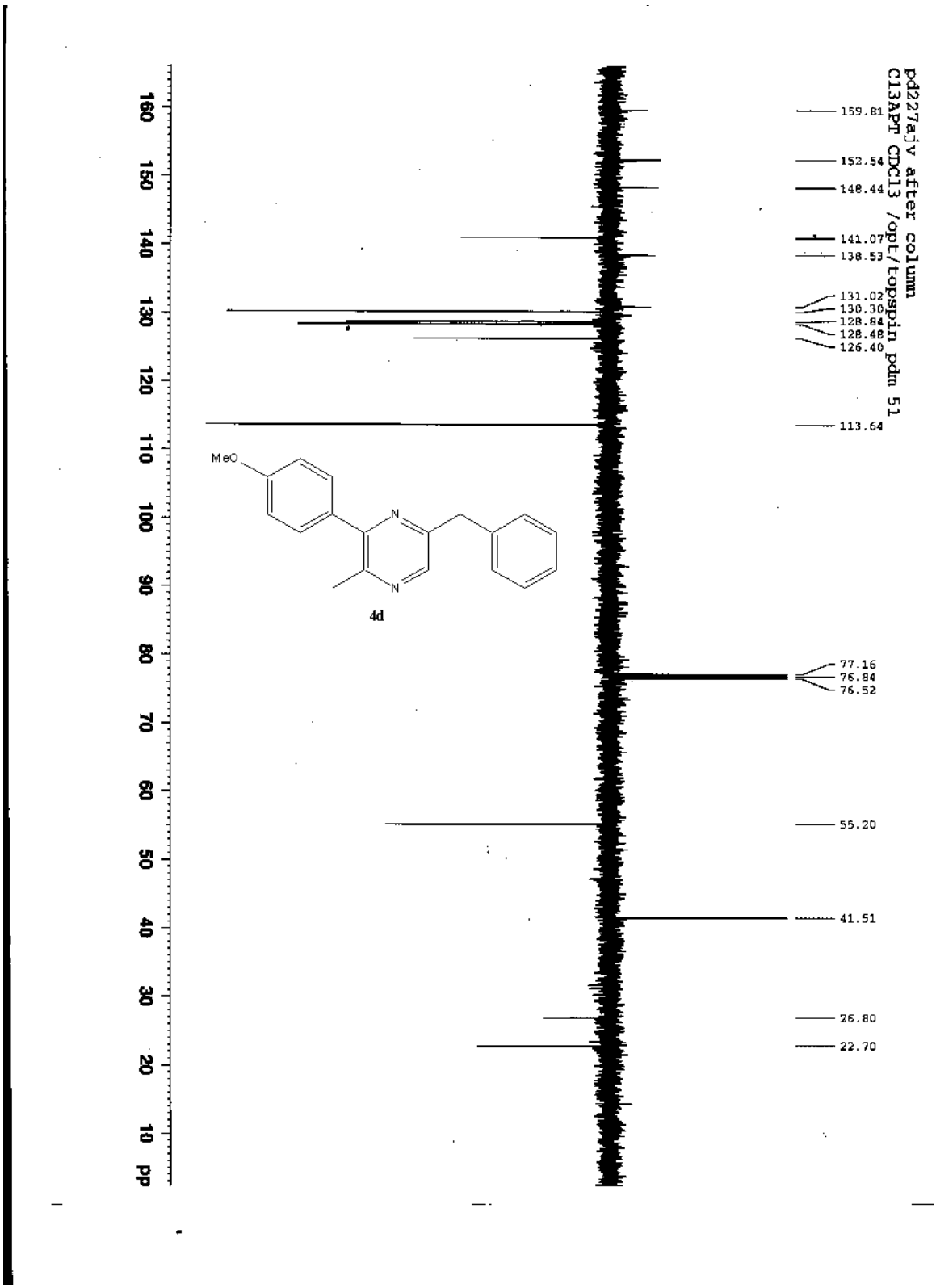
Pyrazine **4c** ^{13}C Spectrum:



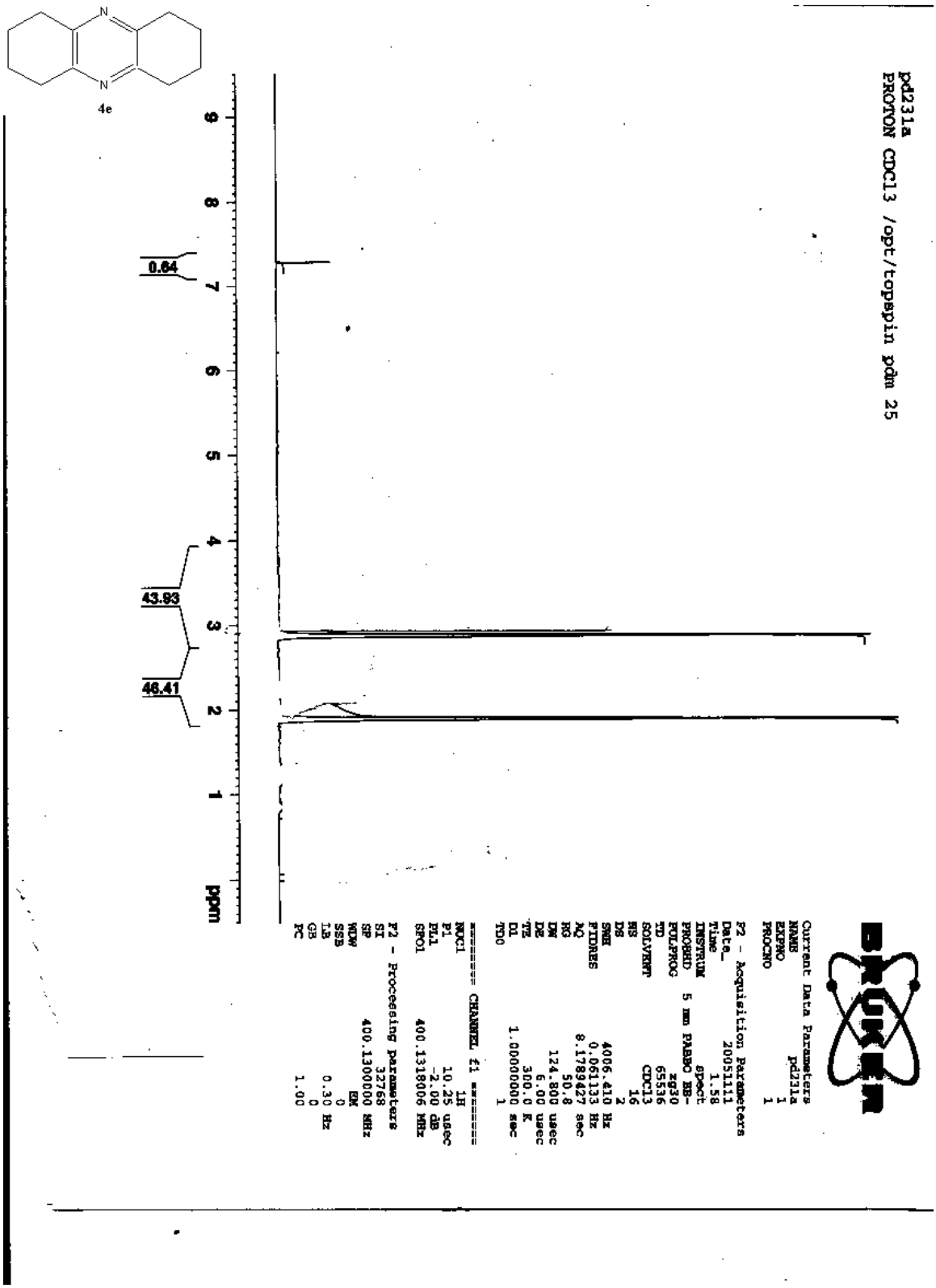
Pyrazine **4d** ^{1}H Spectrum:



Pyrazine **4d** ^{13}C Spectrum:



Pyrazine **4e** ^{1}H Spectrum:



Pyrazine **4e** ^{13}C Spectrum: