Supporting information for 'Diastereoselective Synthesis of Piperazines by Manganese-Mediated Reductive Cyclization'.

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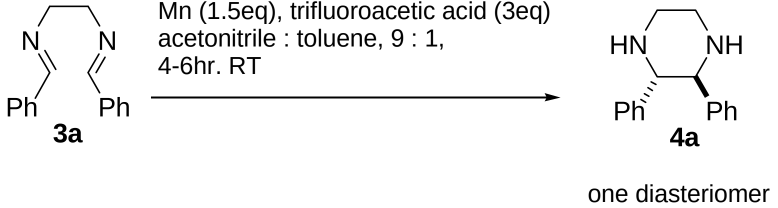
General methods:

All reactions were run under a nitrogen atmosphere. Acetonitrile and toluene were purified through a solvent column.[1] All amines and carbonyl compounds were obtained from Sigma-Aldrich and used without further purification. All melting points are uncorrected and were recorded on an Electrothermal Melting Point apparatus. IR spectra were recorded using a Mattson Satellite FTIR instrument. NMR spectra were recorded using either a Varian Unity – 300 spectrometer, or a Varian XL – 300 spectrometer. HRMS were recorded using a Finnigan MAT 95 spectrometer.

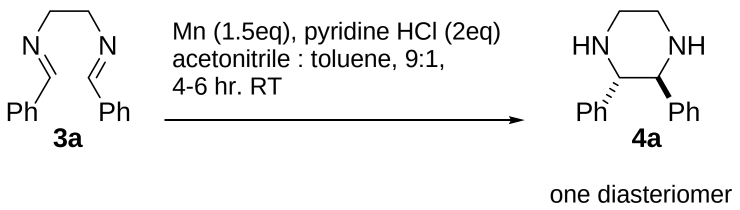
Synthesis of vicinal diamines:

Starting Materials. All imines were prepared from the respective commercially sold aldehydes and amines by known methods.[2] Pyridine hydrochloride from Aldrich contains a large amount of water. It was dried by azeotroping with toluene several times and concentrating *in vacuo*. Alternatively, pyridine hydrochloride can be precipitated out of an ether pyridine solution with addition of dry HCl gas. This was the method used for preparation of other amine salts. When needed the amine salts were dried by refluxing in benzene with a Dean Stark trap, then concentrating and storing under nitrogen. A 1M solution of each salt in acetonitrile was prepared and stored under nitrogen for ease of use. Acetic and trifluoroacetic acids were freshly distilled prior to use and stored with there respective anhydride (~5% by volume) under nitrogen, to avoid significant water accumulation.

General method for reductive coupling of imines.



Method A: To a flame dried flask was added Mn(0) (325 mesh) (70 mg, 1.3 mmol) followed by acetonitrile (16 mL). The imine **3a** (205 mg, 0.9 mmol) was added to the heterogeneous mixture as a solution in toluene (2 mL). Finally; trifluoroacetic acid was added to this stirring solution (200 µL, 2.6 mmol) [Note: the acid must be added last or the reaction will fail], and the heterogeneous mixture was stirred vigorously under nitrogen with two stir bar magnets (one larger than the other, to effectively suspend the manganese), at room temperature for 6 hrs. The acetonitrile and toluene were removed *in vacuo* and the residue was washed with sodium carbonate (10% w/v, ca. 10 mL) and chloroform (ca. 50 mL). The aqueous layer was further extracted with chloroform (2 X 50 mL). The organics were combined, dried with anhydrous sodium sulfate, and concentrated *in vacuo* to give an amorphous solid **4a** (193 mg, **95%**).



Method B (same for all amine salts): To a flame dried flask was added Mn(0) (325 mesh) (55mg, 0.8 mmol) followed by acetonitrile (9 mL). The imine **3a** (118 mg, 0.5 mmol) was added to the heterogeneous mixture as a solution in toluene (1 mL). Pyridine hydrochloride was added (1 mL of 1M solution in acetonitrile, 1 mmol), and the heterogeneous mixture was stirred vigorously under nitrogen with two stir bar magnets to effectively suspend the manganese, at room temperature for 6 hrs. The acetonitrile and toluene were removed *in vacuo* and the residue was washed with sodium carbonate (10% w/v, ca. 5 mL) and chloroform (ca. 30 mL). The aqueous layer was further extracted with chloroform (2 X 30 mL). The organics were combined, dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (ca. 5 mL) and the hydrochloride salt was precipitated from solution by adding hydrochloric acid in diethyl ether until strongly acidic. The solute was decanted or filtered through a glass fiber (Whatman 934-AH grade) filter depending on the nature of the precipitate. The precipitate was free based with a solution of sodium carbonate (5% w/v) and sodium chloride (until saturated)(ca. 10 mL), and extracted with chloroform (3 X 30 mL). The solution was dried with anhydrous sodium sulfate, concentrated and dried *in vacuo* yielding an off white amorphous solid **4a** (110 mg., **93%**).

Larger scale procedure for 4b: An overhead stirrer was used to effectively suspend the heterogeneous reaction mixture (stirring rate: 250 revolutions/min). The imine **3b** (10 g, 34.2 mmole) was submitted to the procedure in method-A with the exception of using 2 equivalents of manganese and 4 equivalents of TFA. The reaction yielded a white amorphous powder **4b** (9.6 g., **96%**)

Acetylation of diamine. The *racemic* diamine mixture **4a** (0.1 mmol) in dichloromethane (ca. 10 mL) was stirred overnight with excess trifluoroacetic anhydride (TFAA). The solution was concentrated in vacuo to remove solvent and excess TFAA.

Confirmation of formation of *trans* diastereomer. The trifluoroacetamide of the piperazine **4a** was dissolved in isopropanol ~10 mg./ mL. HPLC analysis was performed using a chiral OD column from Diacel Chemical Industries Ltd. with an isochratic method of 95:5, hexanes:isopropanol. Retention times for the enantiomers of the trifluoroacetamide of the piperazine **4a** are 15.2 minutes and 20.6 minutes.

Cyclic Voltammetry experiments. Evaluated by single sweep cyclic voltammetry (CV) at room temperature with acetonitrile solutions ca. 10^{-3} M in substrate. Scan rates were 20 mV/s. A Ag/Ag+ non-aqueous reference electrode was used, a platinum wire was the counter electrode, and a platinum bead was the working electrode. The supporting electrolyte was tetraethyl ammonium perchlorate. Potentials were referred to the ferrocene/ ferrocenium couple.[3] CV spectra are included (pg. 16 and 17).

Imines **3a,3d-g,3j-l** were prepared and purified by known methods, and have ^{1}H NMR identical to the reported values.[2,4]

(3b) Yield: 89%, white crystalline solid; mp: 110.2-111.1°C; IR (KBr) 2910, 2904, 2844, 1639, 1496, 1462, 1373, 1276, 1016, 822; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.6 (s, 2H), 7.7 (s, 2H), 7.1 (dd, J^1=8Hz, J^2=2Hz, 2H), 7.0 (d, *J*=8Hz, 2H), 4.0 (s, 4H), 2.4 (s, 6H), 2.3 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 136.8, 134.8, 134.0, 134.6, 131.0, 127.7, 62.2, 20.9, 18.7; HRMS (CI, isobutane) *m/z* calc'd. for ($C_{20}H_{24}N_2$ + H^+)=239.1939, found: 293.2034.

(3c) Yield: 89%, white crystalline solid; mp: 82.2-82.8°C; IR (KBr) 3024, 2921, 2919, 2843, 1637, 1631, 1456, 1369, 1280, 1244, 1024, 829; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.5 (s, 2H), 7.7 (d, *J*=8Hz, 2H), 7.0 (d, *J*=8Hz, 2H), 6.39 (s, 2H), 4.0 (s, 4H), 2.4 (s, 6H), 2.3 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 140.5, 137.7, 132.3, 131.7, 131.1, 127.5, 62.3, 21.4, 19.2; HRMS (CI, isobutane) *m/z* calc'd. for ($C_{20}H_{24}N_2$ + H^+)=239.1939, found: 293.2026.

Amines 4**a,4d-e,4j** were prepared by the methods mentioned above, and had ^{1}H NMR showing >95% purity without further purification. Amines **4k** and **l** required chromatography through Brockman III alumina with a gradient mobile phase: 20% hexanes/ethyl acetate to ethyl acetate to dichloromethane to 10% methanol/dichloromethane. The ^{1}H NMR spectra (included in this supporting information pg 4-15) were identical to the reported values.[5]

(4a) Yield; method A: 95%, method B: 93%.

(4b) Yield; method A: 96%, method B: 96%;white solid; mp: 132.2–132.9°C; IR (KBr) 3535-3310 (broad), 3022-2790 (broad), 1637, 1502, 1460, 810; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5 (s, 2H), 6.8 (d, *J*=8Hz, 2H), 6.7 (d, *J*=8Hz, 2H) 4.1 (s, 2H), 3.2 (s, 4H), 2.3 (s, 6H), 1.8 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 134.9, 133.0, 129.9, 128.8, 127.8, 62.6, 47.6, 21.2, 19.0; HRMS (CI, isobutane) *m/z* calc'd. for ($C_{20}H_{26}N_2$ + H^+) = 295.2130, found: 295.2170.

(4c) Yield; method A: 99%, method B: 96%; off-white solid; mp: 68–70^{o}C; IR (KBr) 3434-3169 (broad), 3045-2748 (broad), 1614, 1500, 1452, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5 (d, *J*=8Hz, 2H), 6.9 (d, *J*=8Hz, 2H), 6.7 (s, 2H), 4.1 (s, 2H), 3.1 (s, 4H), 2.2 (s, 6H),1.8 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 136.2, 130.2, 128, 127.1, 126, 62.3, 47.2, 21.2, 19.5; HRMS (CI, isobutane) *m/z* calc'd. for ($C_{20}H_{26}N_2$ + H^+)= 295.2130, found: 295.2171.

(4d) Yield; method A: 90%, method B: 89%.

(4e) Yield; method A: 99%, method B: 76%.

(4f) Yield; method A (0.01M to limit oligomerization): 85%, method B: 93%; off-white solid; mp: 105.7–106^{o}C; IR (KBr) 3340-3140 (broad), 2937, 2840, 1651, 1504, 1153, 1012, 739; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (d, *J* = 1.9 Hz, 2H), 6.2 (dd, J_1 = 3.2 Hz J_2 = 1.9 Hz, 2H), 6.0 (d, *J* = 3.2 Hz, 2H), 4.0 (s, 2H), 3.1 (t, *J* = 8 Hz, 2H), 3.0 (t, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 141.8, 110.14, 106.9, 58.8, 46.7; HRMS (CI, isobutane) *m/z* calc'd for ($C_{12}H_{14}N_2O_2$ + H^+). 219.1055, found 219.1132.

(4g) Yield; method A: 97%, method B: 80%; off-white solid; mp: 175-176^{o}C; IR (KBr) 3593-3313 (broad), 3055, 2939, 2833, 1639, 1126, 819, 748; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.6-7.7 (m, 6H), 7.5 (m, 2H), 7.3-7.4 (m, 4H), 7.1-7.2 (m, 2H), 4.1 (s, 2H), 3.3 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 133.3, 133.1, 128.2, 127.7, 127.2, 126.6, 126.0, 125.9, 67.7, 46.8; HRMS (CI, isobutane) *m/z* calc'd. for ($C_{24}H_{22}N_2$ + H^+) 339.1817, found 339.1860.

(4j) Yield; method A: 99%.

(4k) Yield; method B: 30%,

(4l) Yield; method A (0.01M to limit oligomerization): 73%.

NOTES AND REFERENCES.

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[1] The solvent columns are composed of activated alumina (A-2). Pnagborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R.K.; Timmers, F. J. Organometallics 1996, 15, 1518-1520

[2] Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.

[3] *Electrochemical Reactions In Nonaqueous Systems,* Mann, C. K.; Barnes, K. K. Ed. Marcel Dekker, Inc., New York, 1970, pg. 1-29.

[4] Mukhopadhyay, M.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *J. Org. Chem.* **1995,** *60*, 2670-2676; Karupaijan, K.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron*, **2000,** *56*, 8555-8560;

[5] Hirao, T.; Ogawa, A.; Hatano, B. *J. Org. chem.* **1998,** *63*, 9421-9424; Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. chem..* **1991,** *56*, 3063-3067.

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disubstituted methyl benzyl aldimine

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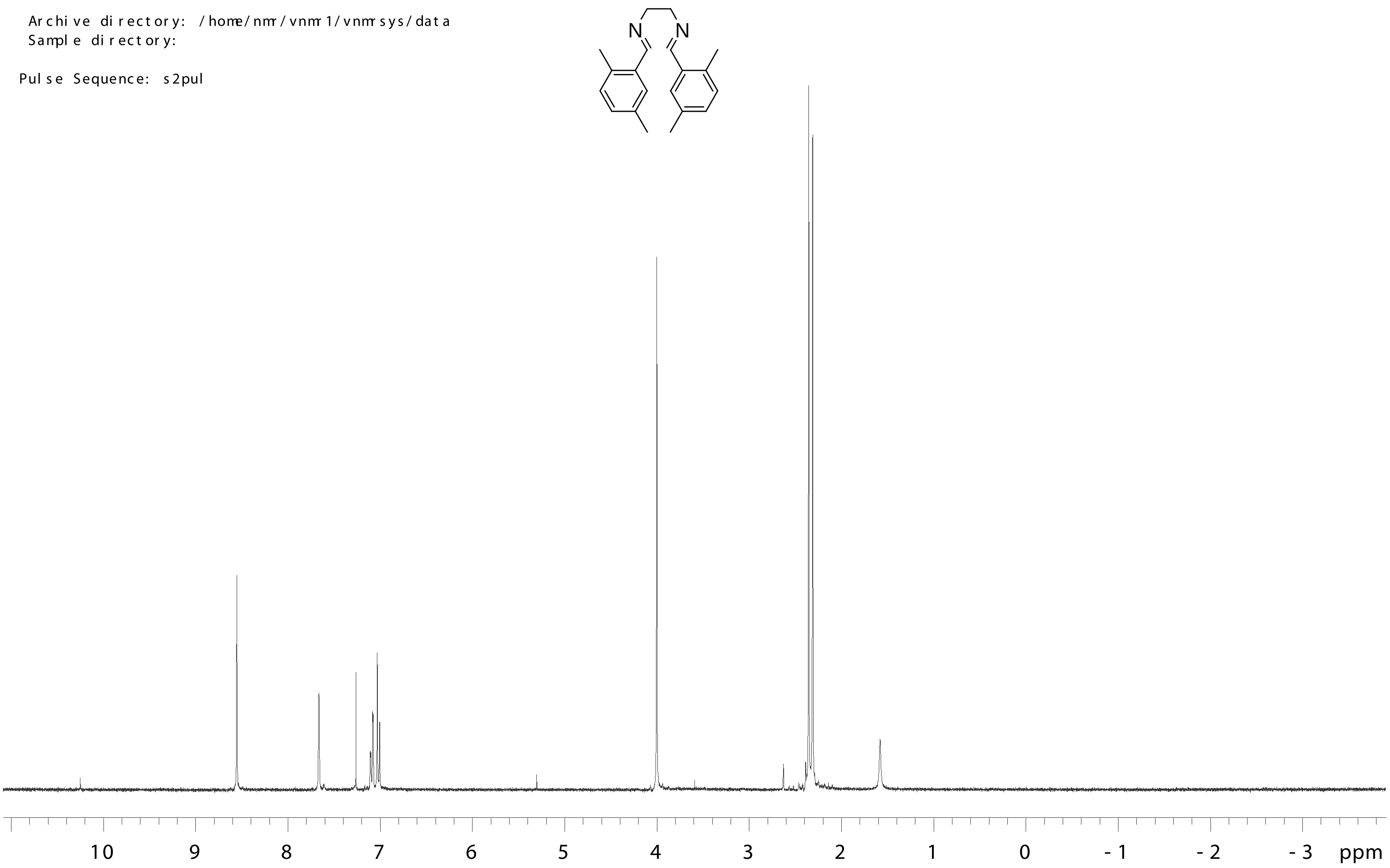

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dimethyl substituted benzyl aldimine

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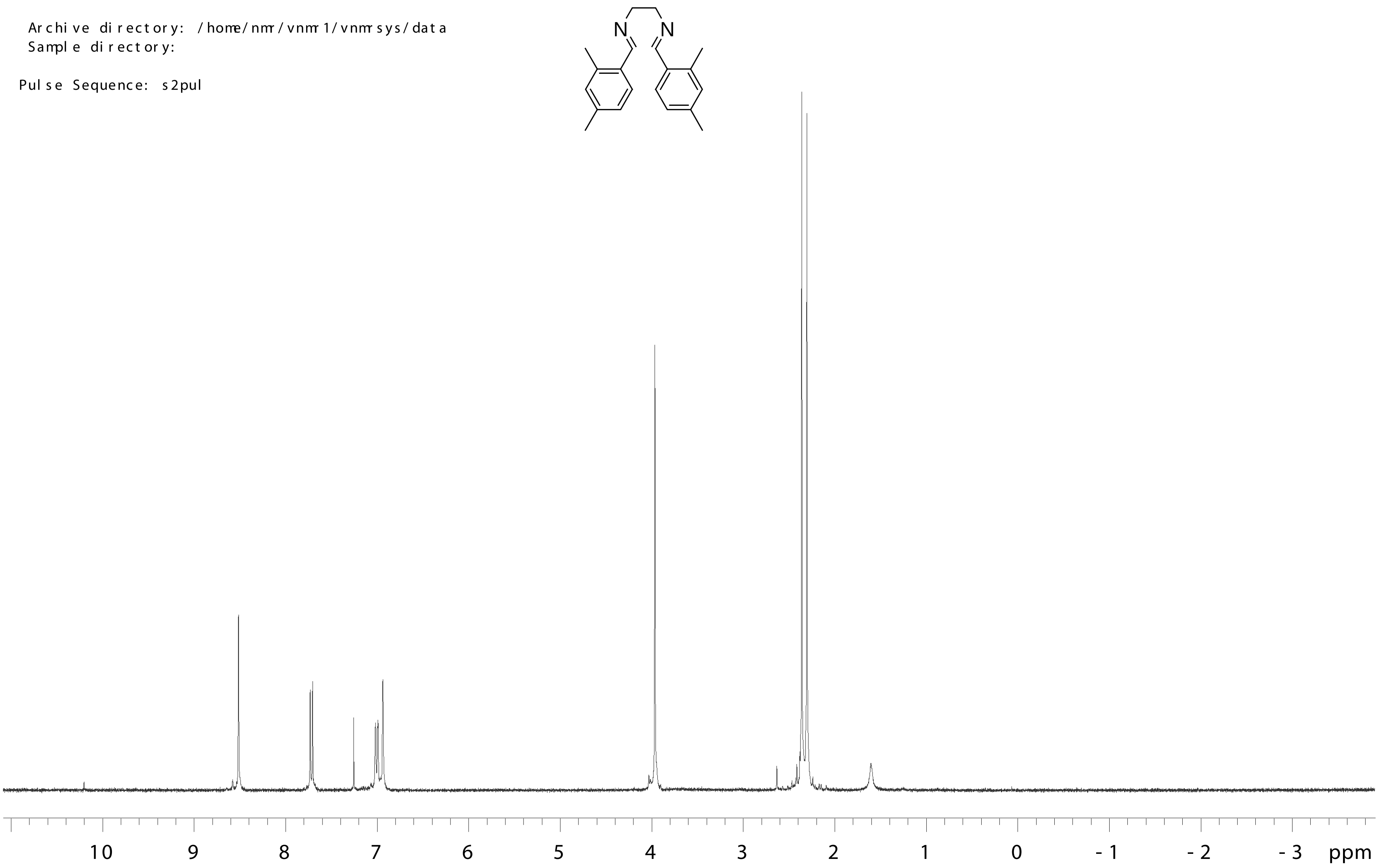

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di pheynyl pi per azi ne

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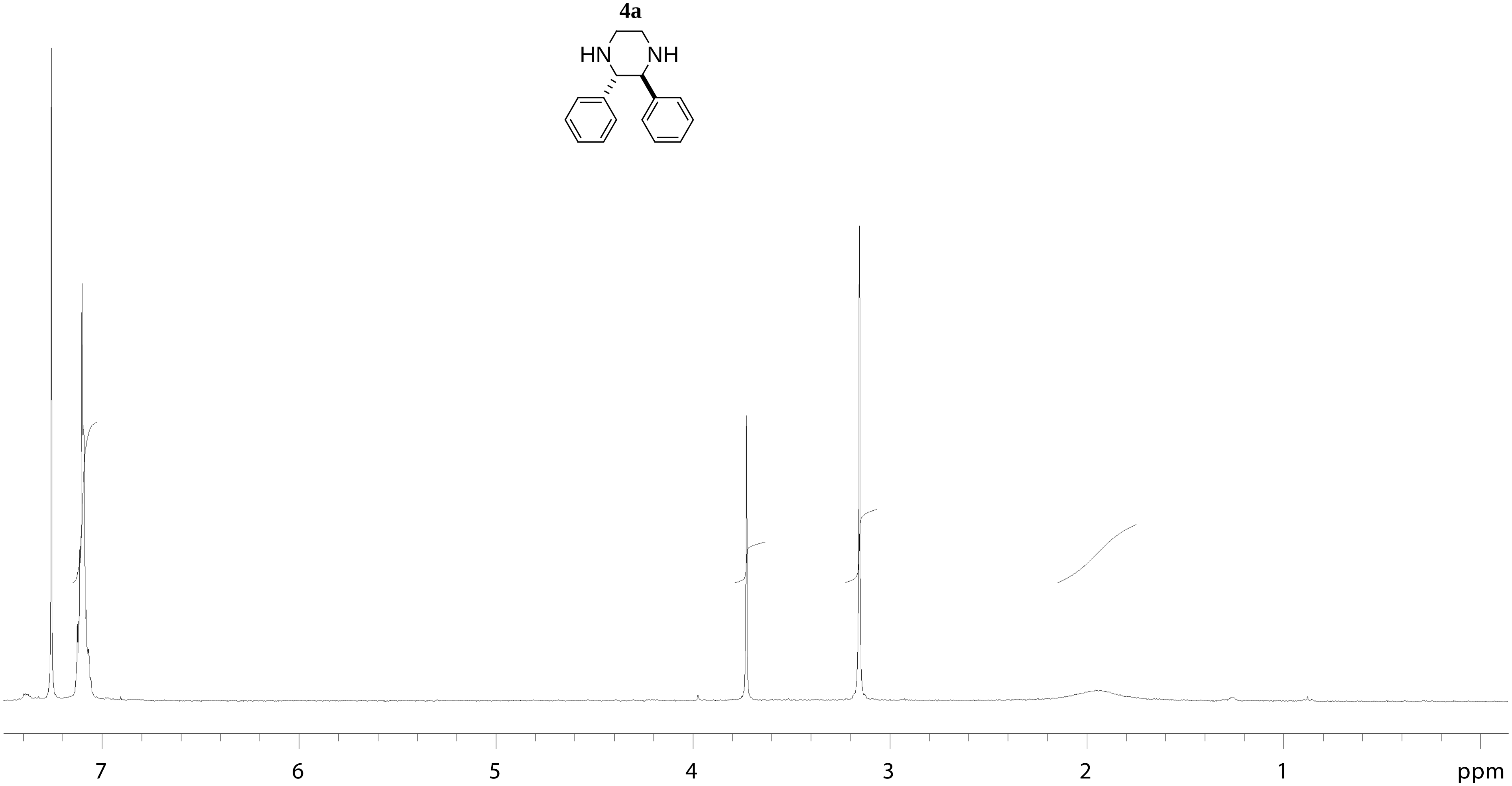

4a

gj m004058
bis 2,5 dimethyl phenyl piperazine
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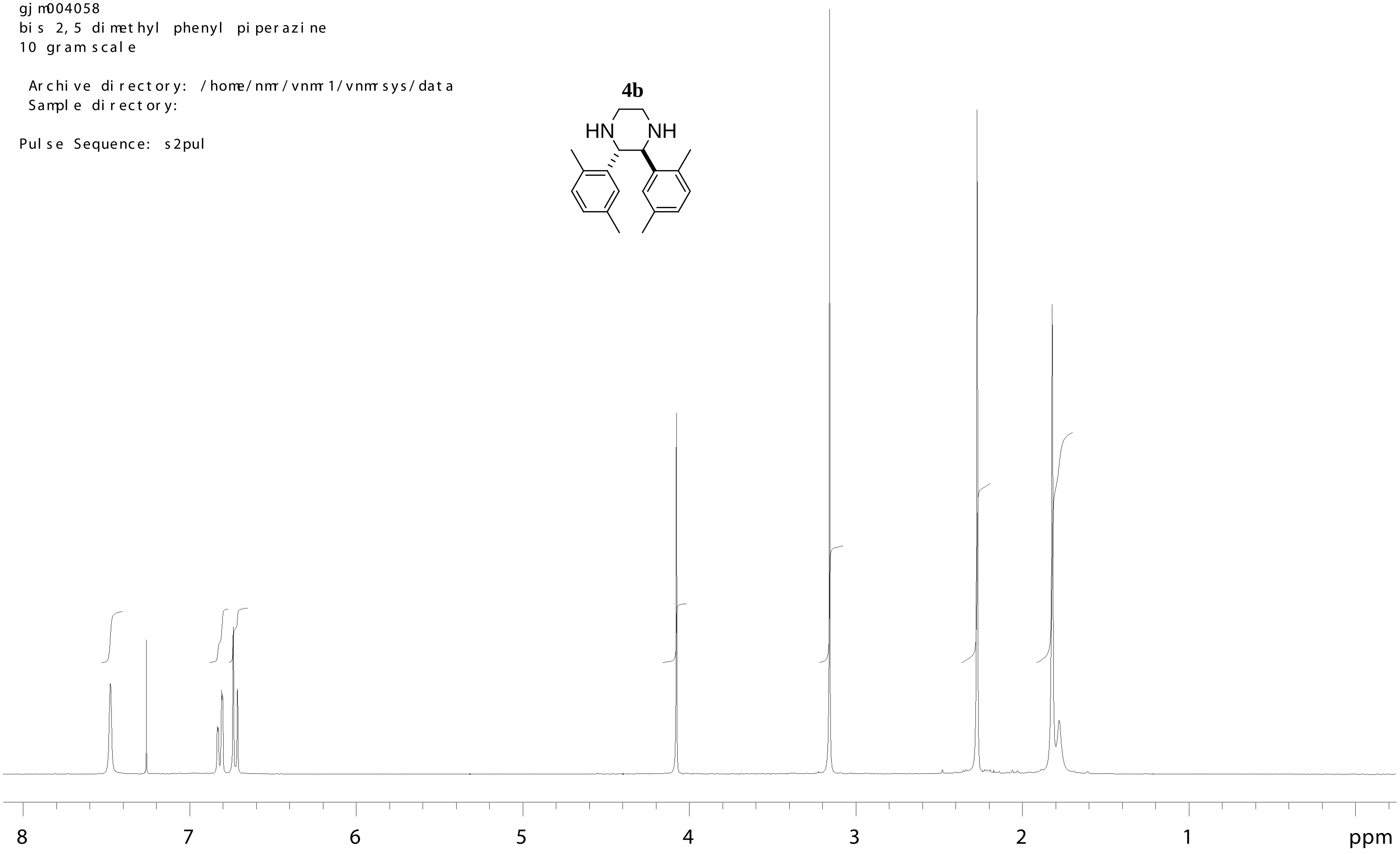

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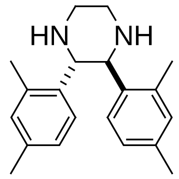
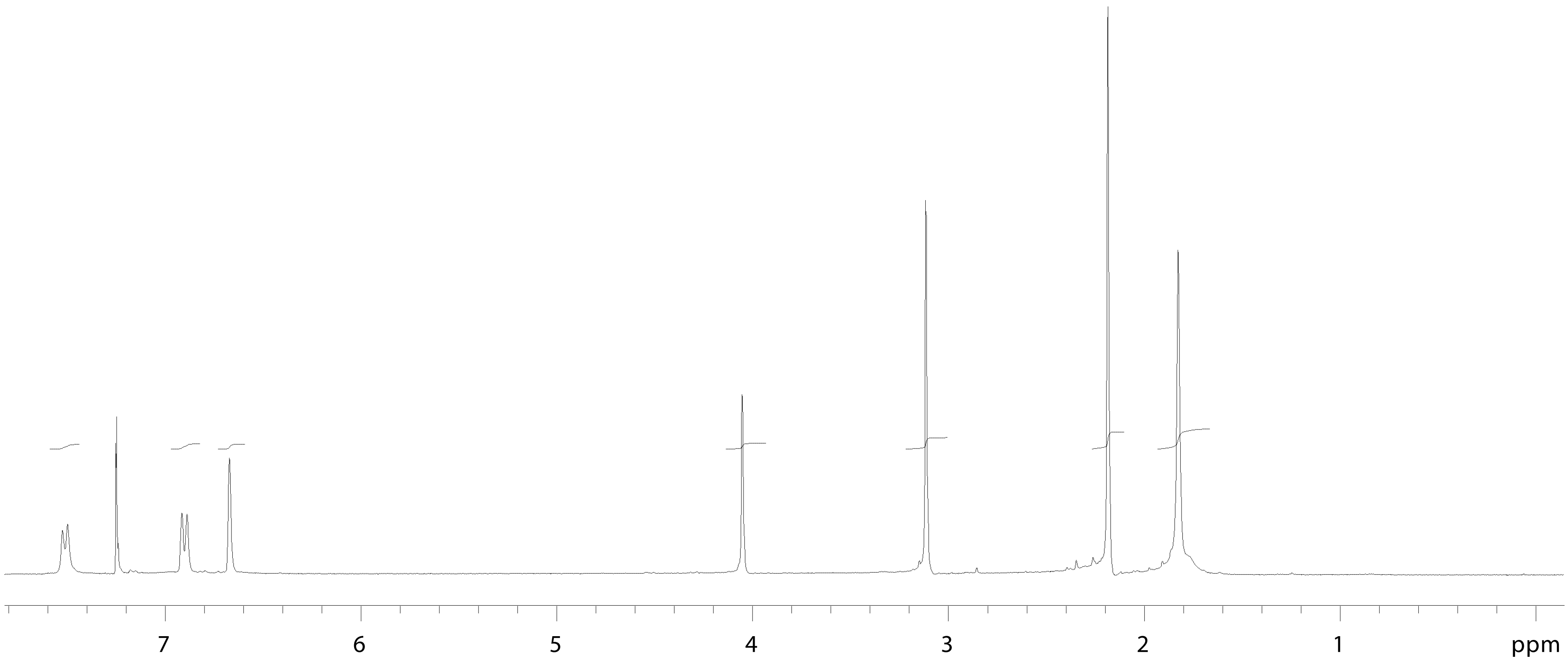
4c





gjm004024
4methoxy phenyl piperazine

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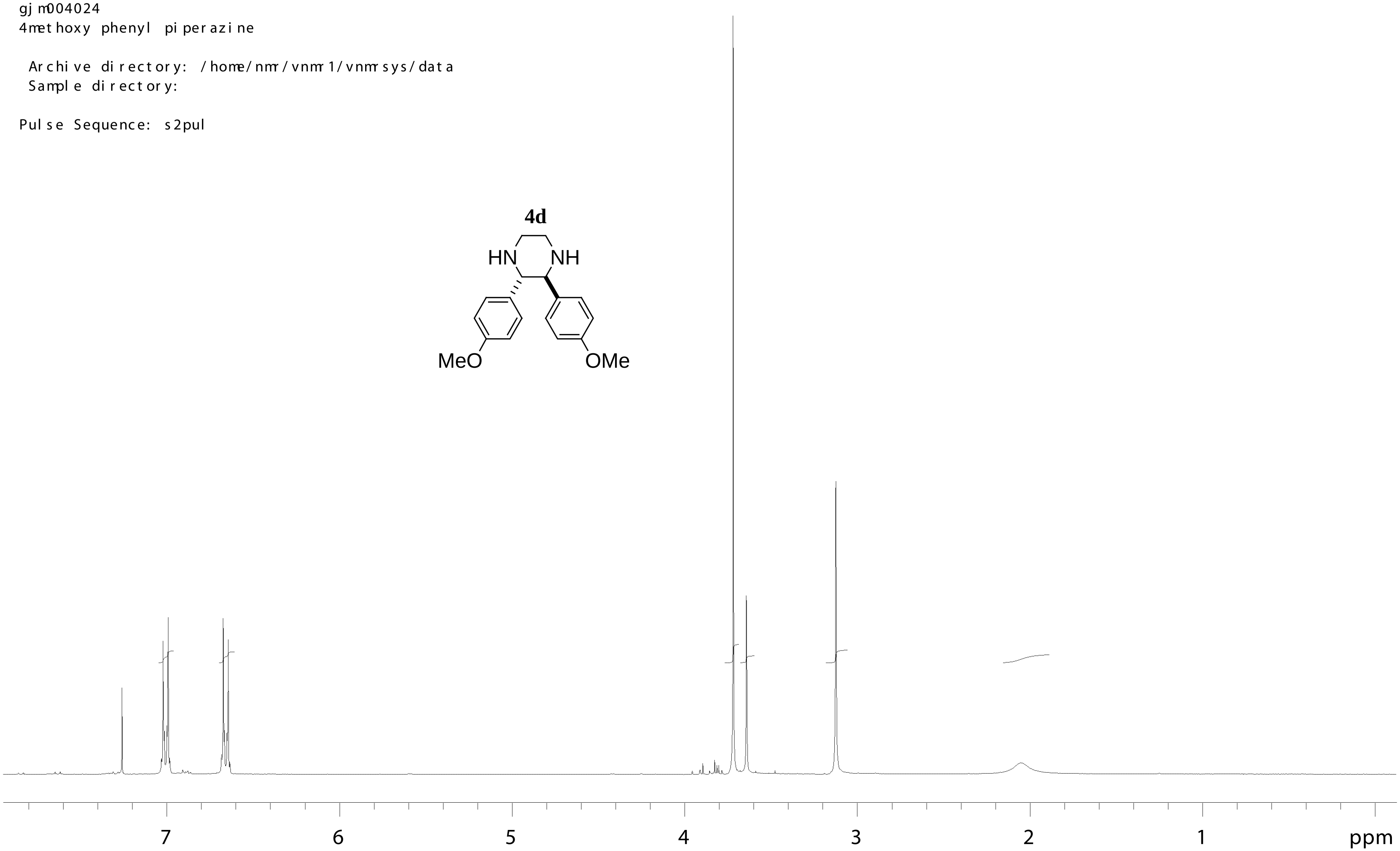

4d

gjm004041
4,chloro phenyl piperazine

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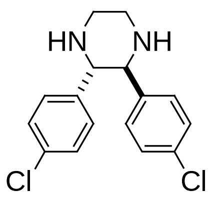
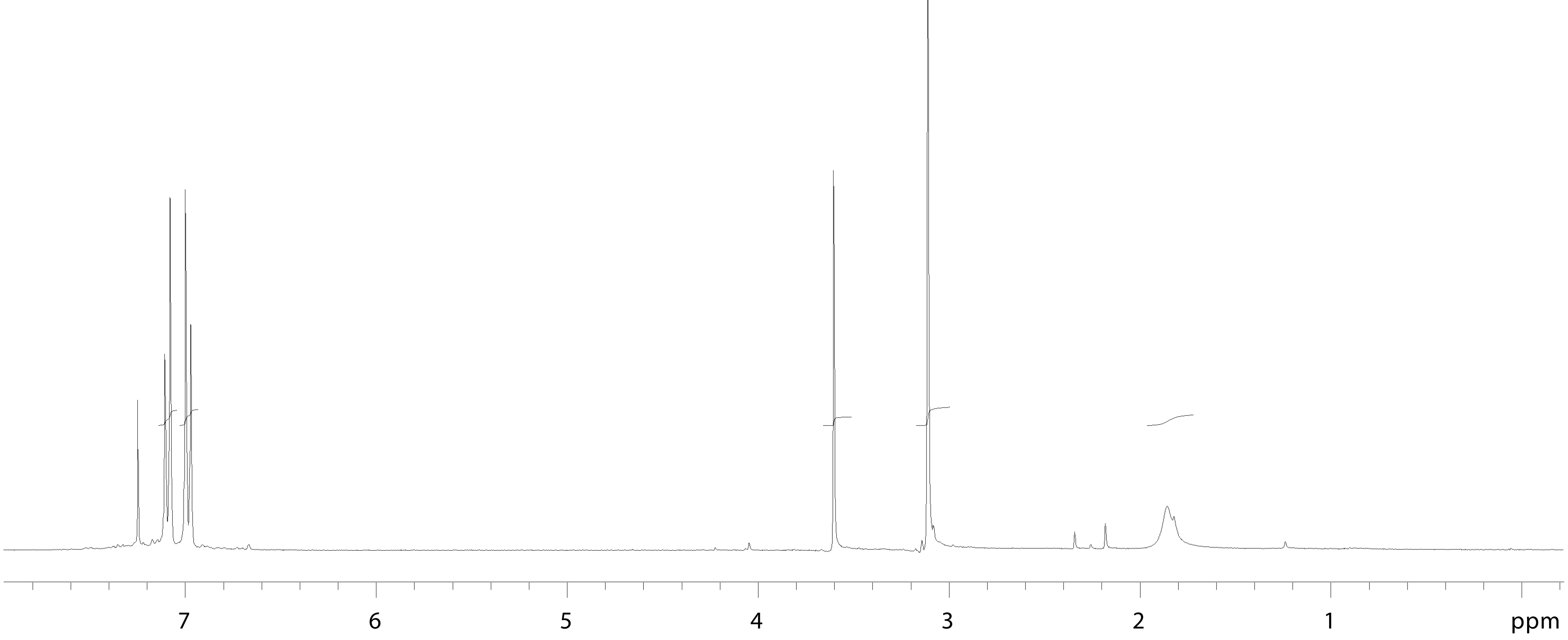
4e





gjm004047
furan substrate
more dilute

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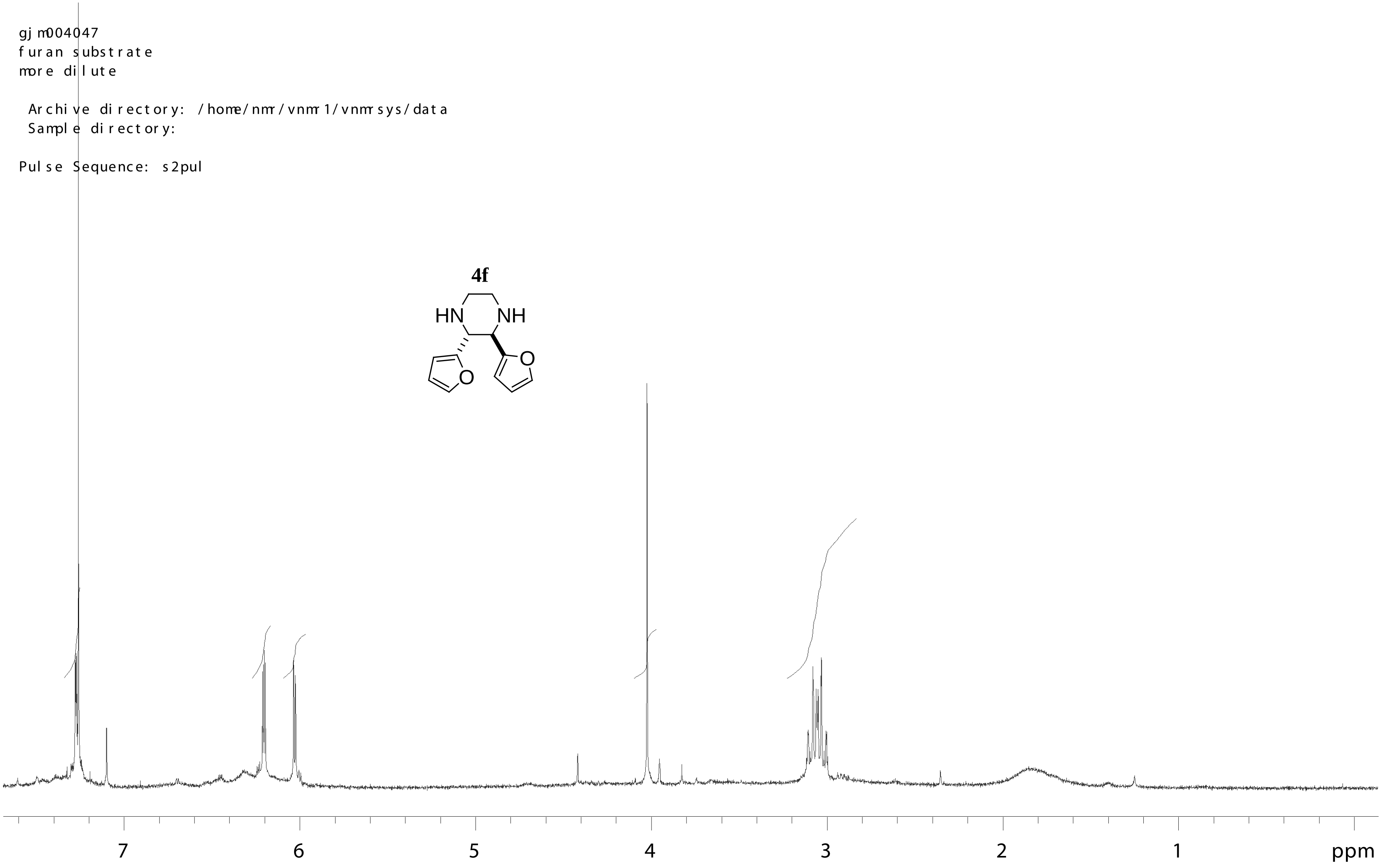

4f

gjm004023
2-naphthalene piperazine

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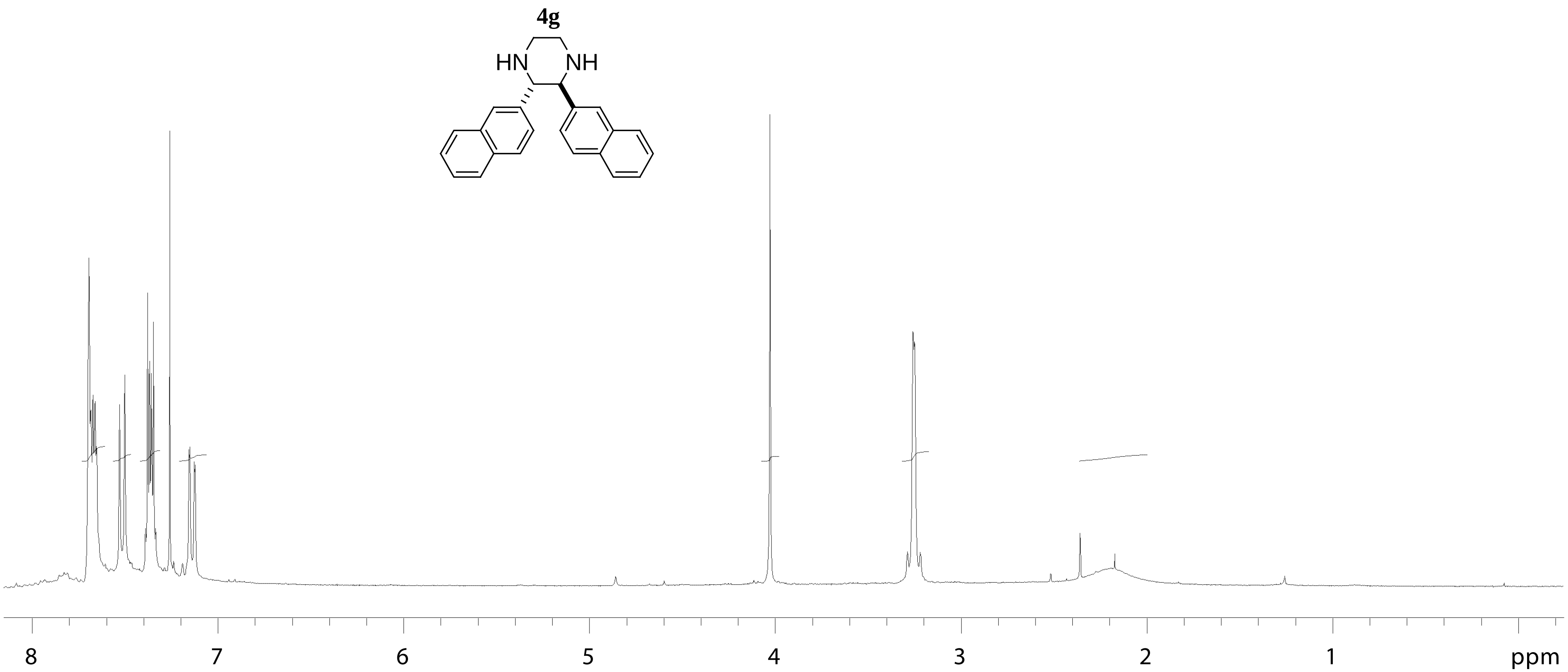

gjm004038
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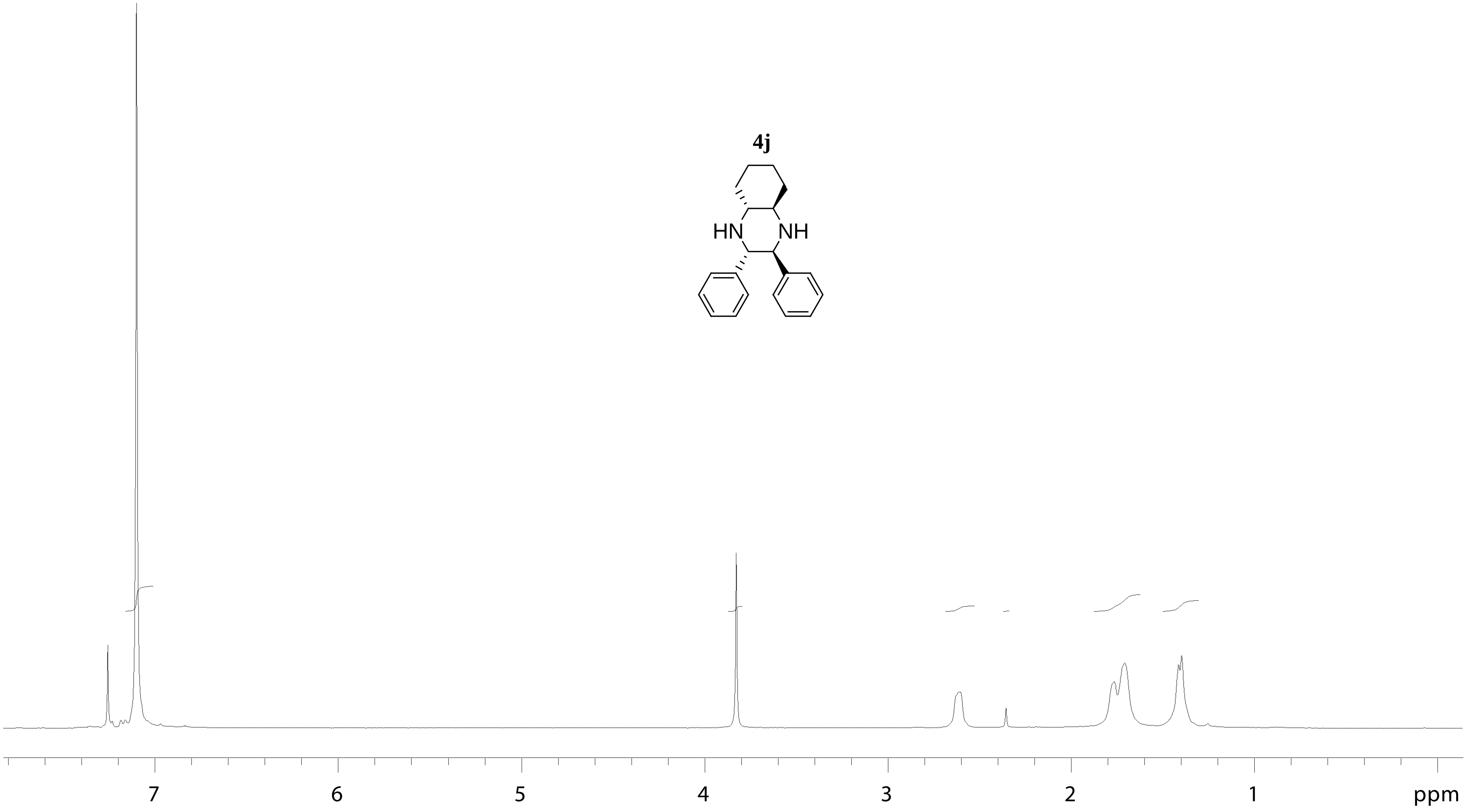
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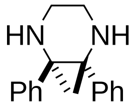
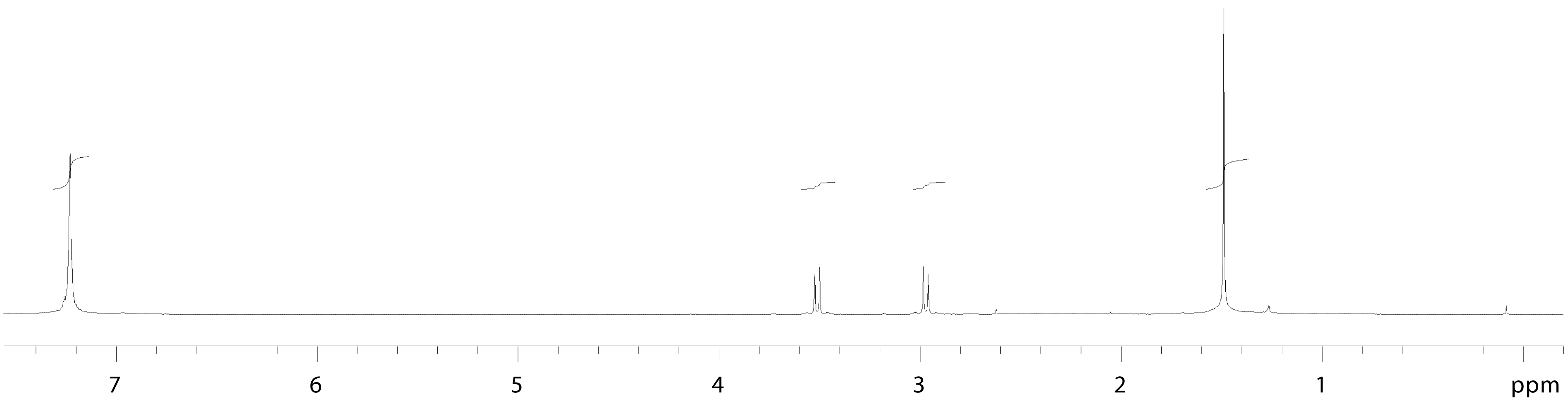
4k





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crystalized
7mem ring substrate

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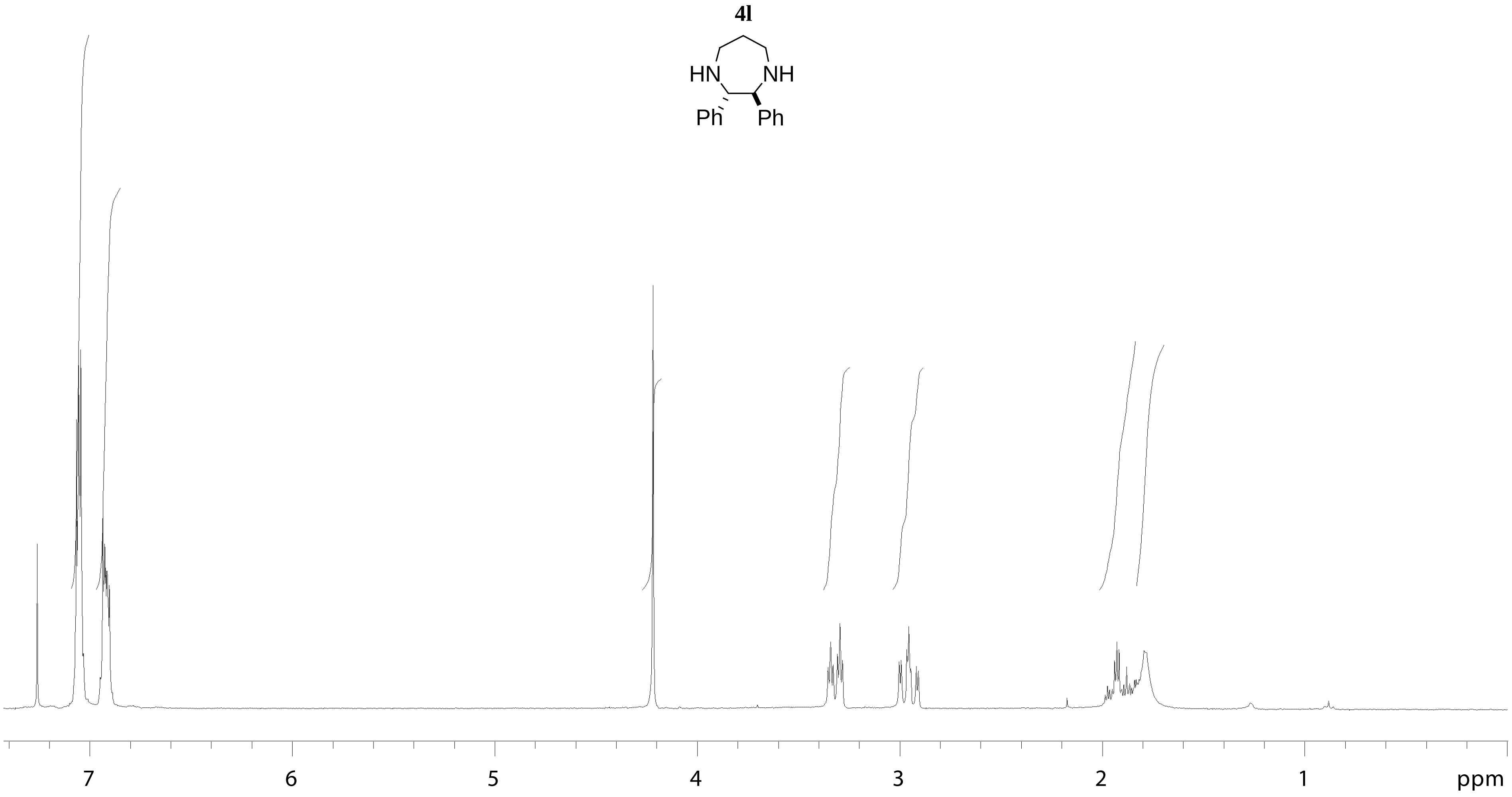

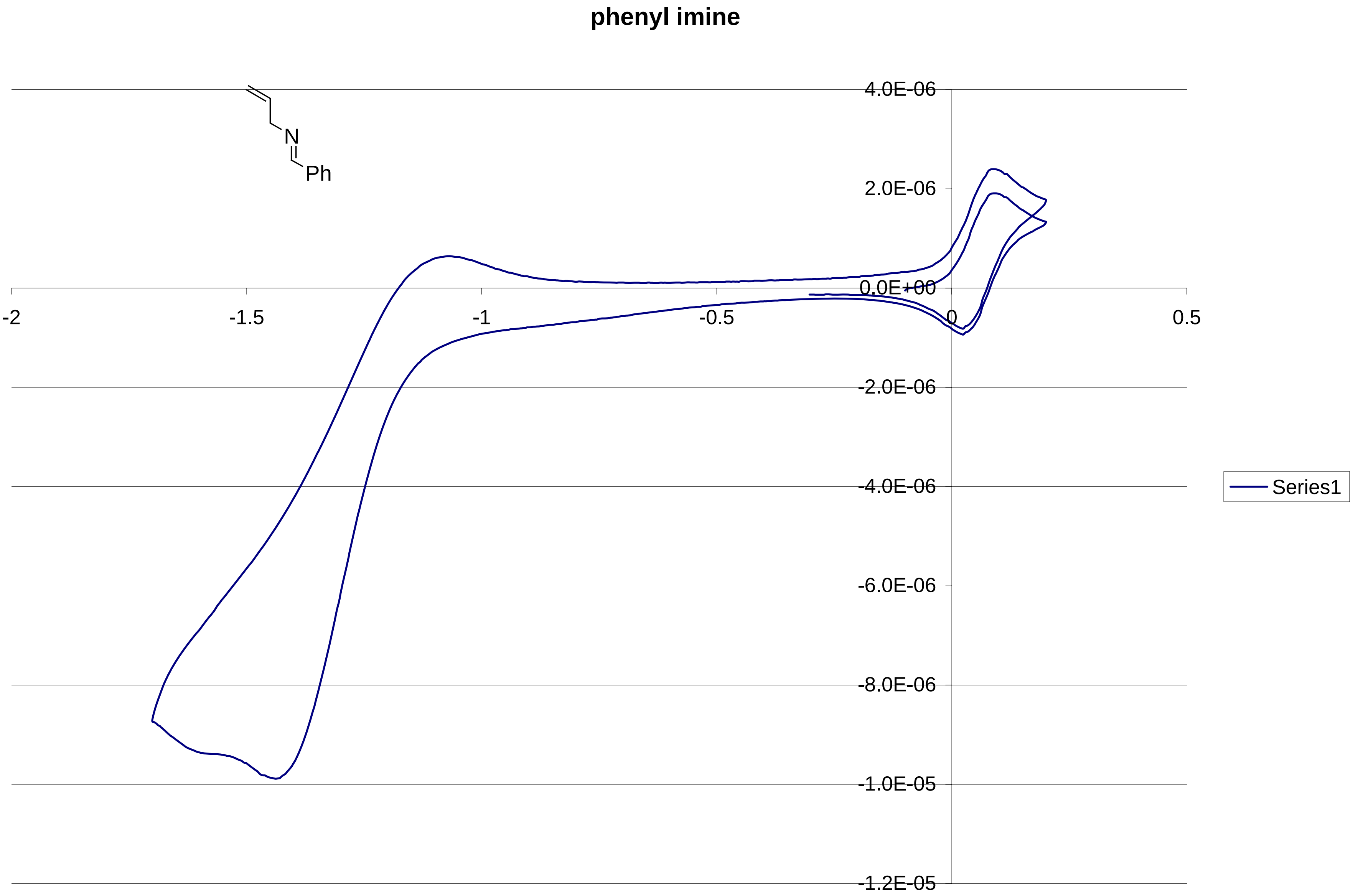
phenyl imine
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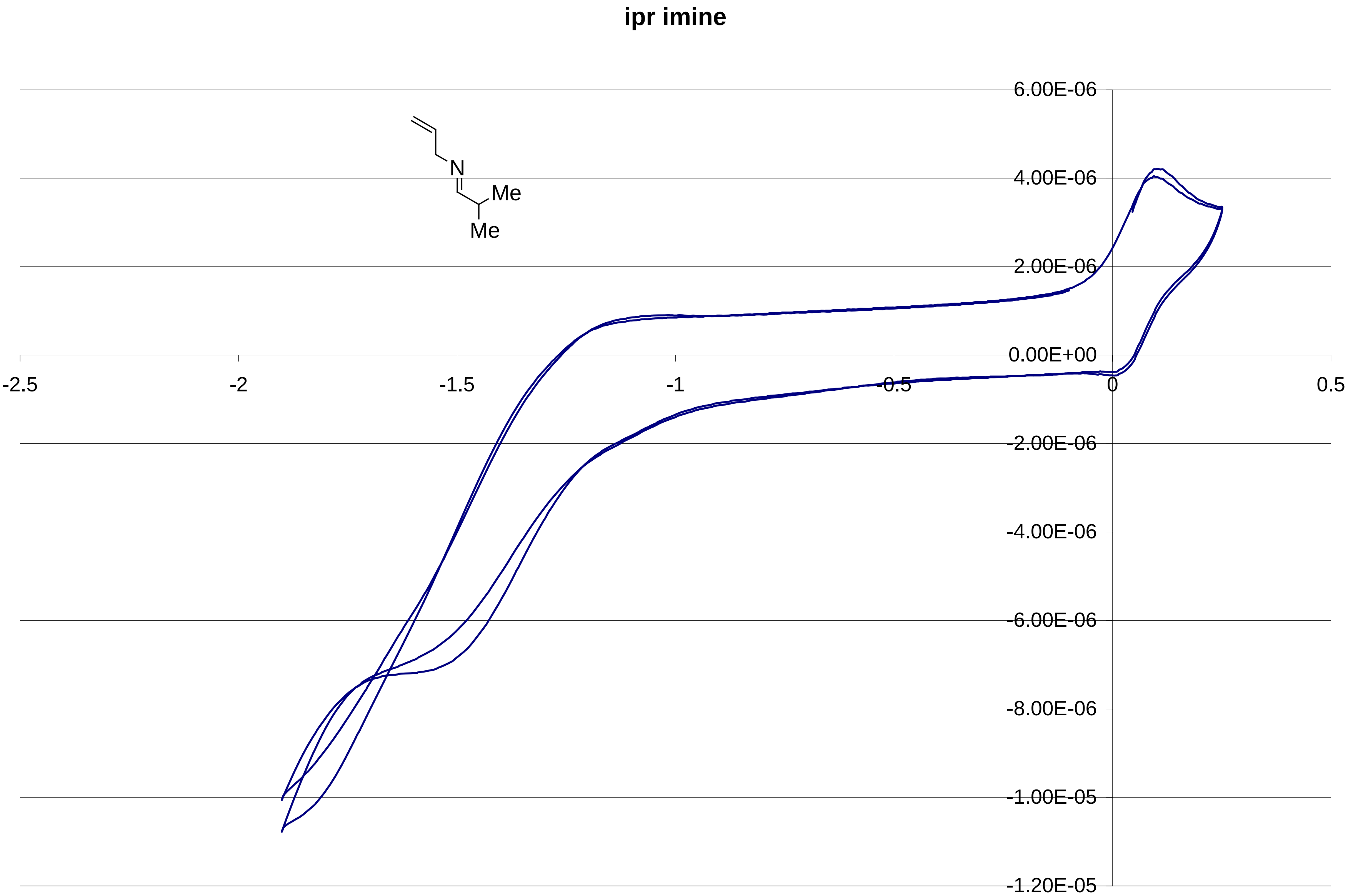
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