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Supplementary Materials for:

Conformational Study of Succinic and Glutaric β-Alanine Derivatives: Resistance of β-Alanine Amides to Form Intramolecular Hydrogen Bonds

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Experimental Section

THF was freshly distilled from sodium benzophenone under N_2. Hexanes were freshly distilled from calcium hydride under N_2. Routine ^1H NMR spectra (for characterization) were obtained on a Bruker AC-200 spectrometer. Commercially obtained starting materials were used without further purification. Column chromatography was carried out by using up to 5-psi air pressure with 230-400-mesh silica gel from VWR Scientific. Columns eluted with MeOH in EtOAc were slurry-packed after the slurry was stirred with hexanes. All glassware was dried in an oven at 120 °C.

Variable-Temperature NMR Procedure. Unless specifically noted otherwise all NMR experiments were performed using $CDCl_3$ as solvent. The samples for variable-temperature (VT) ^1H NMR experiments were dried in a desiccater (P_2O_5) under vacuum overnight. Deuterated chloroform was dried over activated 4-Å molecular sieves for two days. A 100-mM solution of the amide in $CDCl_3$ was prepared first and then two 1:9 dilutions with $CDCl_3$ were performed to give a final concentration of 1 mM. Even with these precautions, the resulting samples typically contained a small peak due to H_2O.

Variable-temperature NMR measurements were performed on a Bruker AC-300 spectrometer. The VT-NMR experiments all followed a general procedure. The sample tube was placed into the NMR probe using a heavy spinner. The air line responsible for spin was disconnected, and the delivery hose from the liquid nitrogen Dewar was connected to the NMR probe. The air line responsible for lifting the NMR tube and spinner out of the NMR probe was disconnected and the NMR probe was capped. The desired temperature was set on the variable-temperature unit (BVT 2000), and the self-tune procedure was initiated to calibrate the console. Following calibration, the temperature reading on the variable-temperature console was allowed to stabilize. The sample was equilibrated for approximately 10-15 minutes at the set temperature, and after the Z and Z^2 shims were adjusted, a 128-scan spectrum was obtained. Measurements were made in the temperature range of 213-323 K. In these experiments, the first measurement was made at the lowest temperature. Caution was taken to raise the temperature slowly especially when approaching 323 K to avoid the evaporation of the solvent. All chemical shifts were referenced to the signal for residual $CHCl_3$, which was assumed to be 7.240 ppm at all temperatures. The accuracy of the temperature display on the VT unit, which was measured from a thermocouple located inside the probe, was tested by

measuring the chemical shifts of methanol. Calibration of the temperature dependence of the separation (in hertz) between the OH resonance and the CH_3 resonance has been reported by Becker. The calibration results show a < 1 K deviation in the temperature range employed.

Variable-Temperature IR Procedure. Unless specifically noted otherwise all IR experiments were performed using $CDCl_3$ as solvent. Amides were dried as described for NMR samples. $CDCl_3$ solutions were prepared by dissolving several milligrams of amide in solvent that had been dried over molecular sieves and by performing serial dilutions to 1 mM as described for NMR samples. IR measurements were performed on a Perkin Elmer 1600 FT-IR instrument. A Specac variable-temperature cell P/N 21525 equipped with CaF_2 windows (path length = 1.0 mm) was used for variable-temperature experiments. Temperatures were maintained with dry ice-acetone slush bath and were monitored with a thermocouple attached directly to the cell. The cell temperature was allowed to stabilize for 20 min before measurements were obtained, and the cell temperature varied less than 1 °C during data acquisition. Spectra of 128 scans were obtained with 2-cm^{-1} resolution. Solvent subtraction was carried out by using background spectra obtained at approximately the same temperatures as the sample spectra.

Succinylglycyl N-Methylamide Methyl ester (1b). To a mixture of 30 mL of THF and 25 mL of triethylamine was added 4.19 g (30 mmol) of glycine ethyl ester hydrochloride and 3.10 g (30 mmol) of succinic anhydride. The resulting solution was stirred for 4 h and then concentrated to about 10 mL. The solution was acidified to pH = 2 with 20% hydrochloric acid and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 4.2 g (69%) of monosuccinyl glycine ethyl ester as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H, CH_3), 2.56 (t, J = 5.8 Hz, 2H, CH_2), 2.68 (t, J = 5.7 Hz, 2H, CH_2), 4.00 (d, J = 5.1 Hz, 2H, NCH_2), 4.18 (q, J = 7.1Hz, 2H, OCH_2), 6.55 (s, 1H, NH), 8.87 (broad, 1H, CO_2H). This material was carried on without further purification.

A pressure-resistant glass tube was loaded with a solution of 2.03 g (10 mmol) of the ester in 10 mL of THF and was cooled to -78°C. Anhydrous methyl amine was added into the solution through a long stainless-steel needle and a Tygon tubing from a lecture bottle until the volume of the solution increased about 2 mL. The pressure tube was sealed and warmed up to room temperature slowly. The mixture was stirred for one week. After being cooled to -78°C, the seal was opened and the excess methylamine and the solvent were removed under reduced pressure to give 2.12 g (97%) of the corresponding N-methyl amide (as its ammonium salt) as a white solid: ^{1}H NMR (DMSO) δ 2.22 (t, J = 4.0 Hz, 2H, CH_2), 2.23 (t, J = 3.9 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.53 (d, J = 4.6 Hz, 3H, CH_3),3.56 (d J = 5.9 Hz, 2H, CH_2), 4.78 (broad, 3H, $MeNH_3^+$), 8.16 (q, J = 4.1 Hz, 1H, NH), 8.26 (t, J = 5.8 Hz, 1H, NH). This material was carried on without further purification.

To a solution of 2.12 g (9.7 mmol) of the ammonium carboxylate in 10 mL of methanol was added 2.58 g (13.4 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was cooled to 0 °C and

then added ethereal diazomethane. The completion of the reaction was monitored by TLC (20% MeOH/EtOAc). The mixture was concentrated and purified by column chromatography and eluted with 20% MeOH in EtOAc to give 1.14 g (58%) of the corresponding diamide ester (**1b**) as a white solid (m.p. 115-125 °C): ^{1}H NMR ($CDCl_3$) δ 2.48 (t, J = 6.7 Hz, 2H, CH_2), 2.71 (t, J = 6.6 Hz, 2H, CH_2), 2.79 (d, J = 4.8 Hz, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 3.91 (d, J = 5.7 Hz, 2H, NCH_2), 6.55 (broad at r.t., triplet at 213 K, 1H, NH), 6.62 (broad at r.t., quartet at 213 K, 1H, NH).

Diamide esters **2b, 3b**, and **4b** are prepared using similar procedures starting from glutaric anhydride and glycine, succinic anhydride and β-alanine, and glutaric anhydride and β-alanine, respectively.

N,N-Dimethylamino Succinyl β-Alanyl N-Methylamide (3a). A pressure-resistant glass tube was loaded with 0.90 g (4.2 mmol) of the diamide ester (**3b**) and cooled to -78°C. Anhydrous dimethyl amine was added through a long stainless-steel needle and a Tygon tubing from a lecture bottle until the volume of the solution increased about 5 mL. The tube was sealed and warmed up to room temperature slowly. The mixture was stirred for one week. After being cooled to -78°C, the seal was opened and the excess dimethylamine and the solvent were removed under reduced pressure to give 1.00 g (100%) of the desired triamide **3a** as a white solid (m.p. 100-115 °C) : ^{1}H NMR ($CDCl_3$) δ 2.36 (t, J = 6.7 Hz, 2H, CH_2),2.43 (t, J = 5.9 Hz, 2H, CH_2), 2.63 (t, J = 6.1 Hz, 2H, CH_2), 2.76 (d, J = 4.7 Hz, 3H, CH_3), 2.90 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.47 (dt, J = 6.4 Hz, 5.3 Hz, 2H, NCH_2), 6.50 (broad at r.t., triplet at 213 K, 1H, NH), 6.62 (broad at r.t., quartet at 213 K, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 26.2, 28.7, 31.2, 35.4, 36.0, 36.1, 37.0, 171.9, 172.3, 172.9; IR (1 mM in $CDCl_3$) 3457 (NH), 3351 (broad, NH), 1662 (C=O), 1639 (C=O) cm^{-1}.

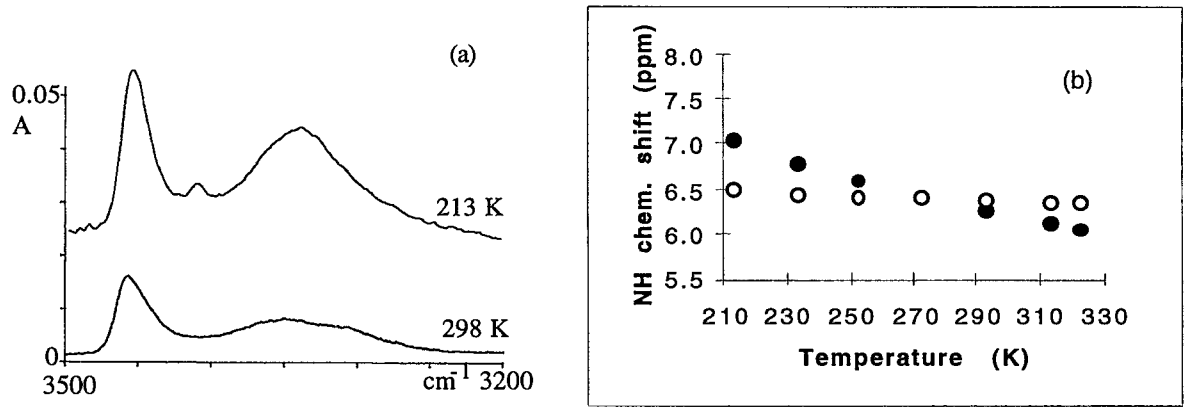
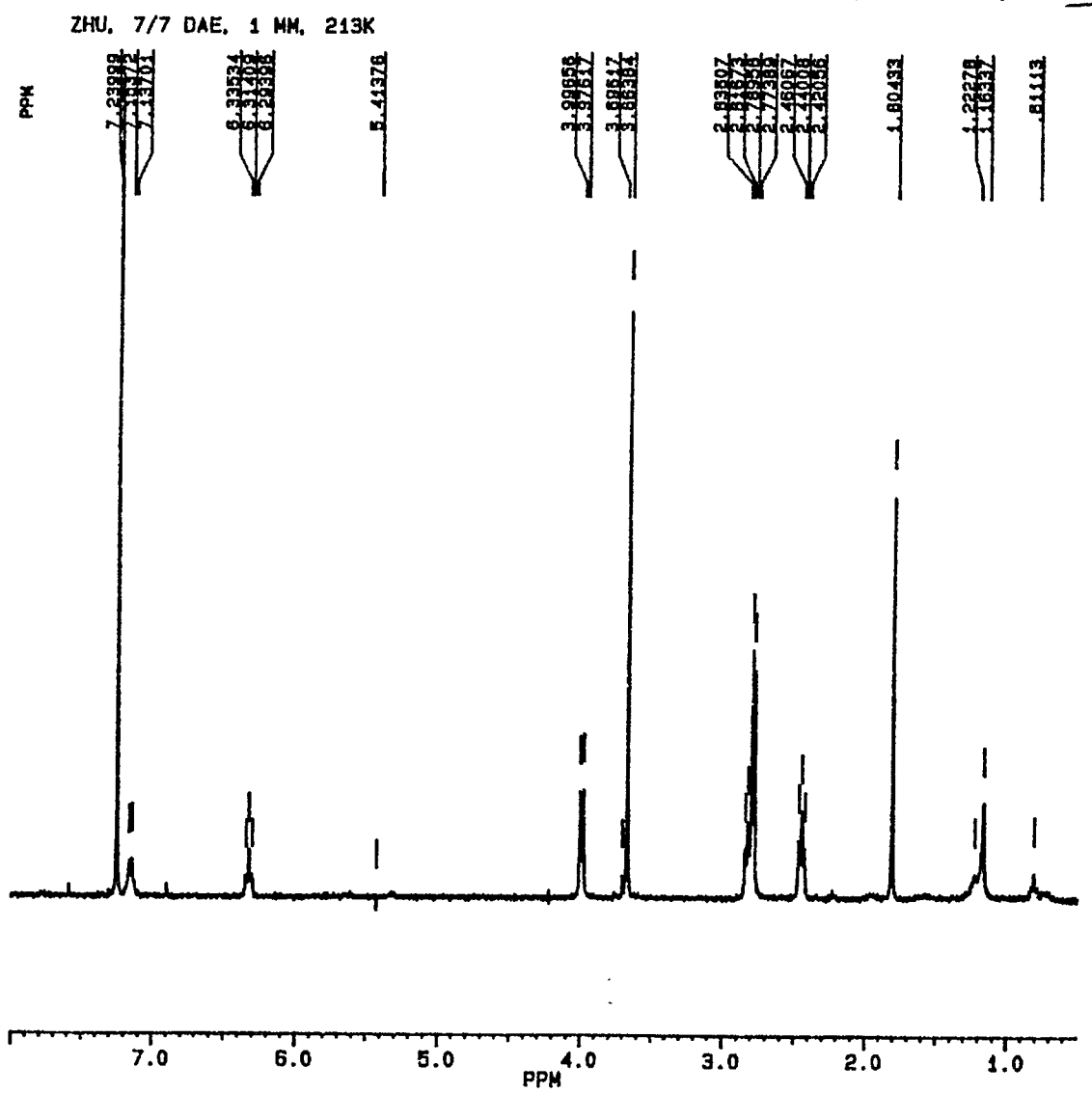


Figure 5. (a) NH stretch region of the IR spectra at 213 K and 298 K for N,N-dimethylamino succinyl β-alanyl N-methylamide, **3a**. The sharp band at 3451-3457 cm^{-1} is assigned to the free NH stretch and the broad band at 3337-3351 cm^{-1} to the intramolecularly hydrogen-bonded NH. (b) Amide proton NMR chemical shifts as a function of temperature for triamide **3a.** Internal NH (o, $\Delta\delta NH/\Delta T$ = -1.2 ppb/K). Terminal NH (•, $\Delta\delta NH/\Delta T$ = -8.7 ppb/K).

^{1}H NMR 16b



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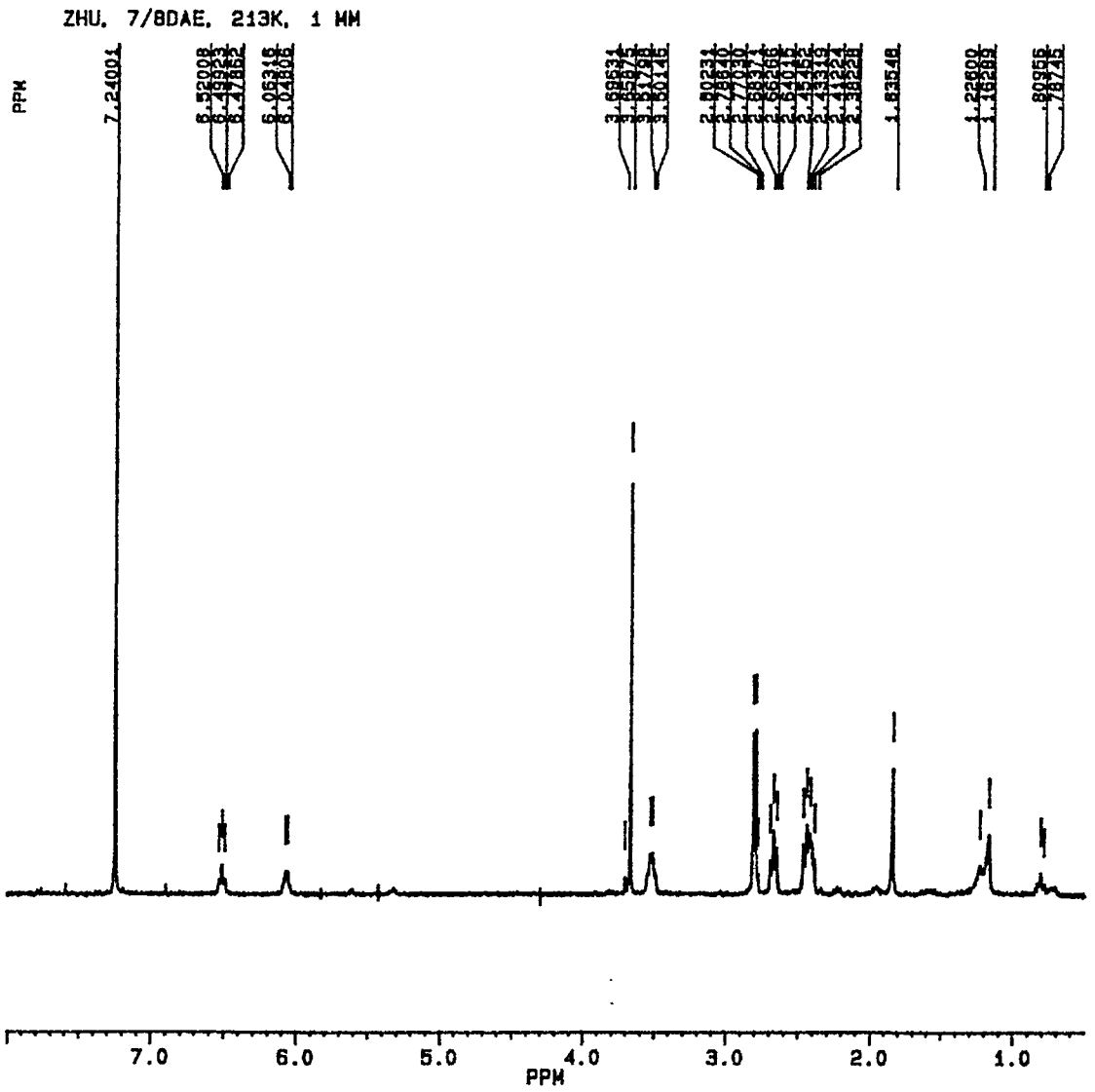
^{1}H NMR 26



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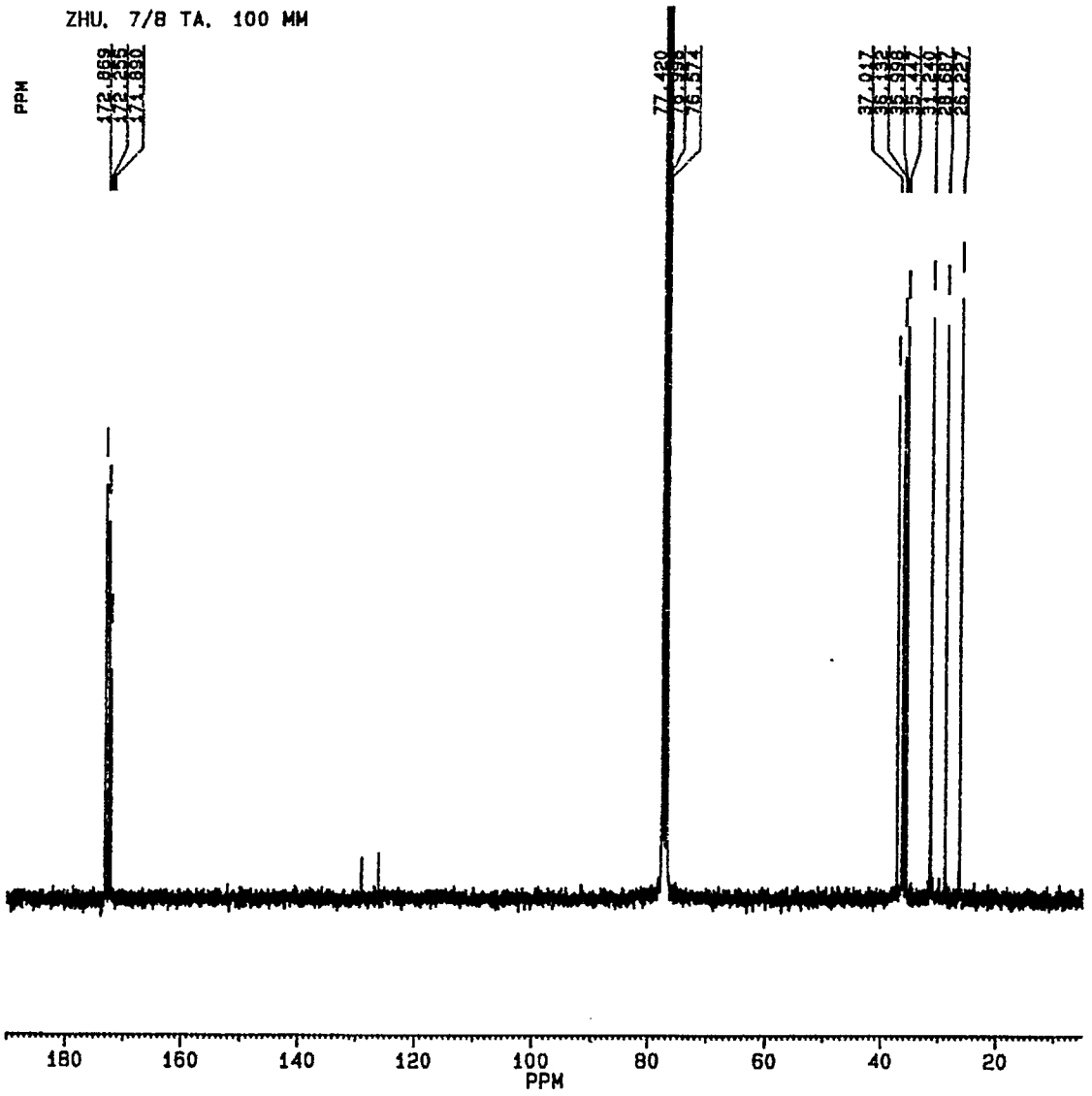
^{13}C NMR 3a



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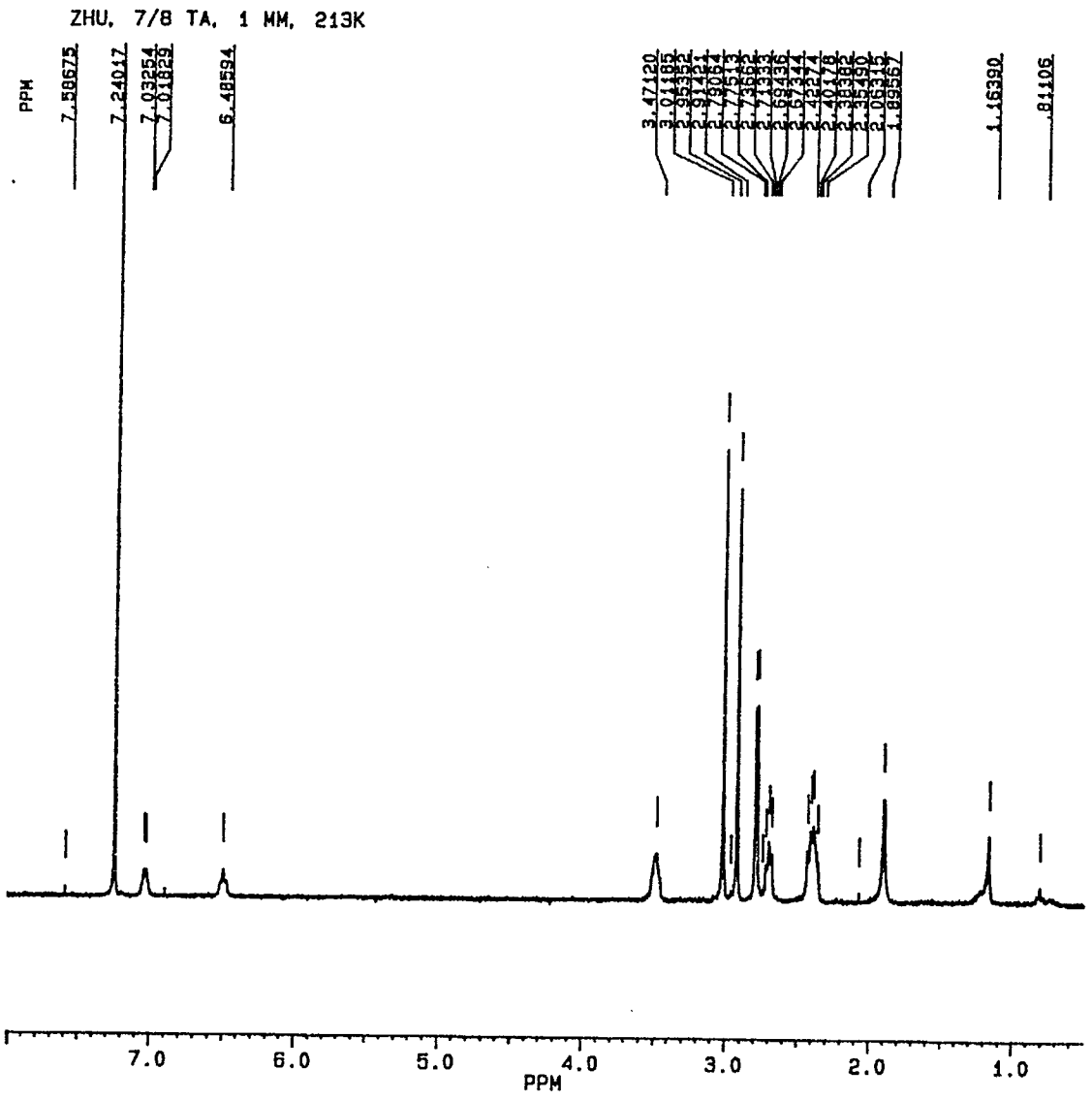
^1H NMR 3a



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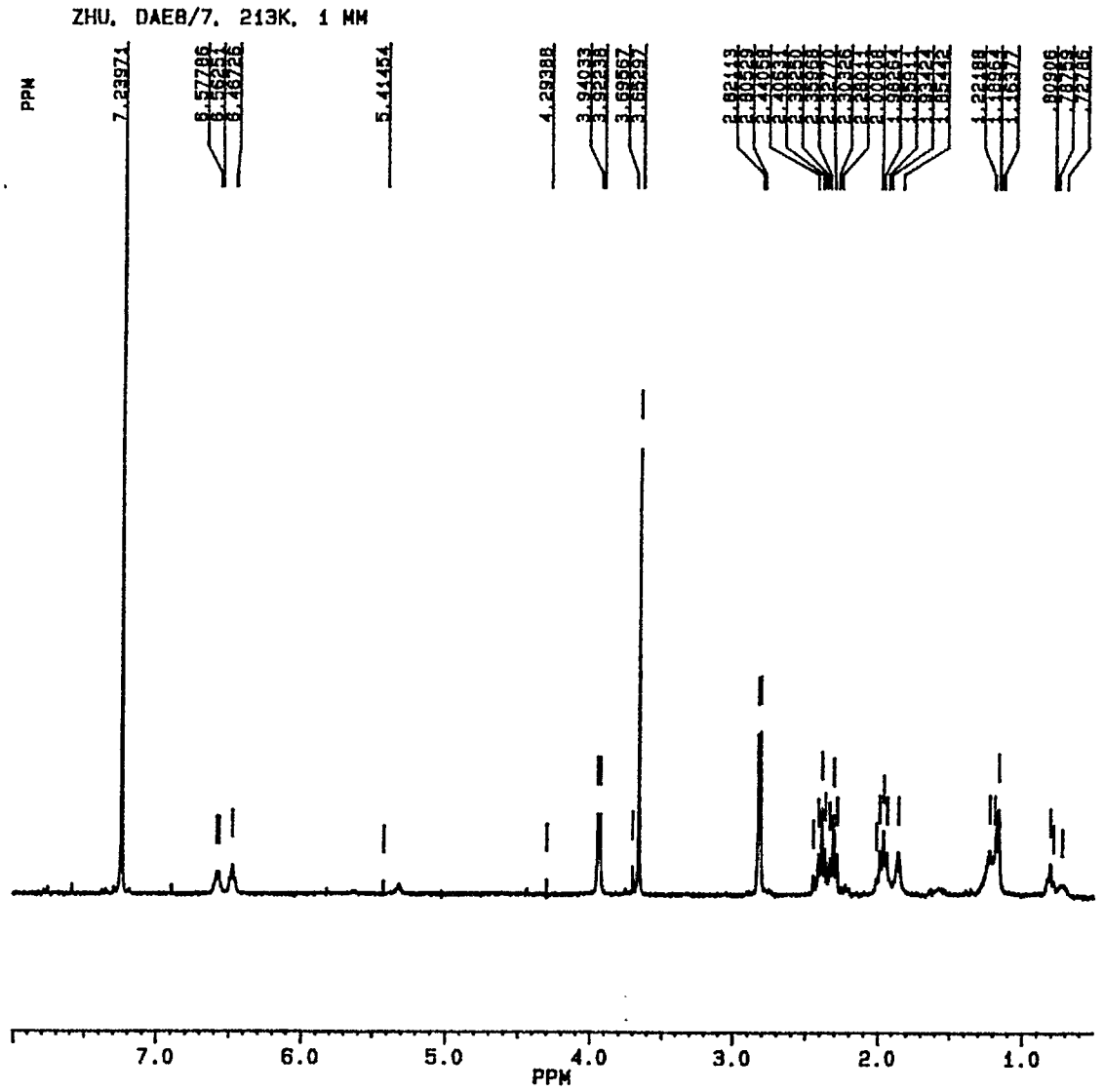

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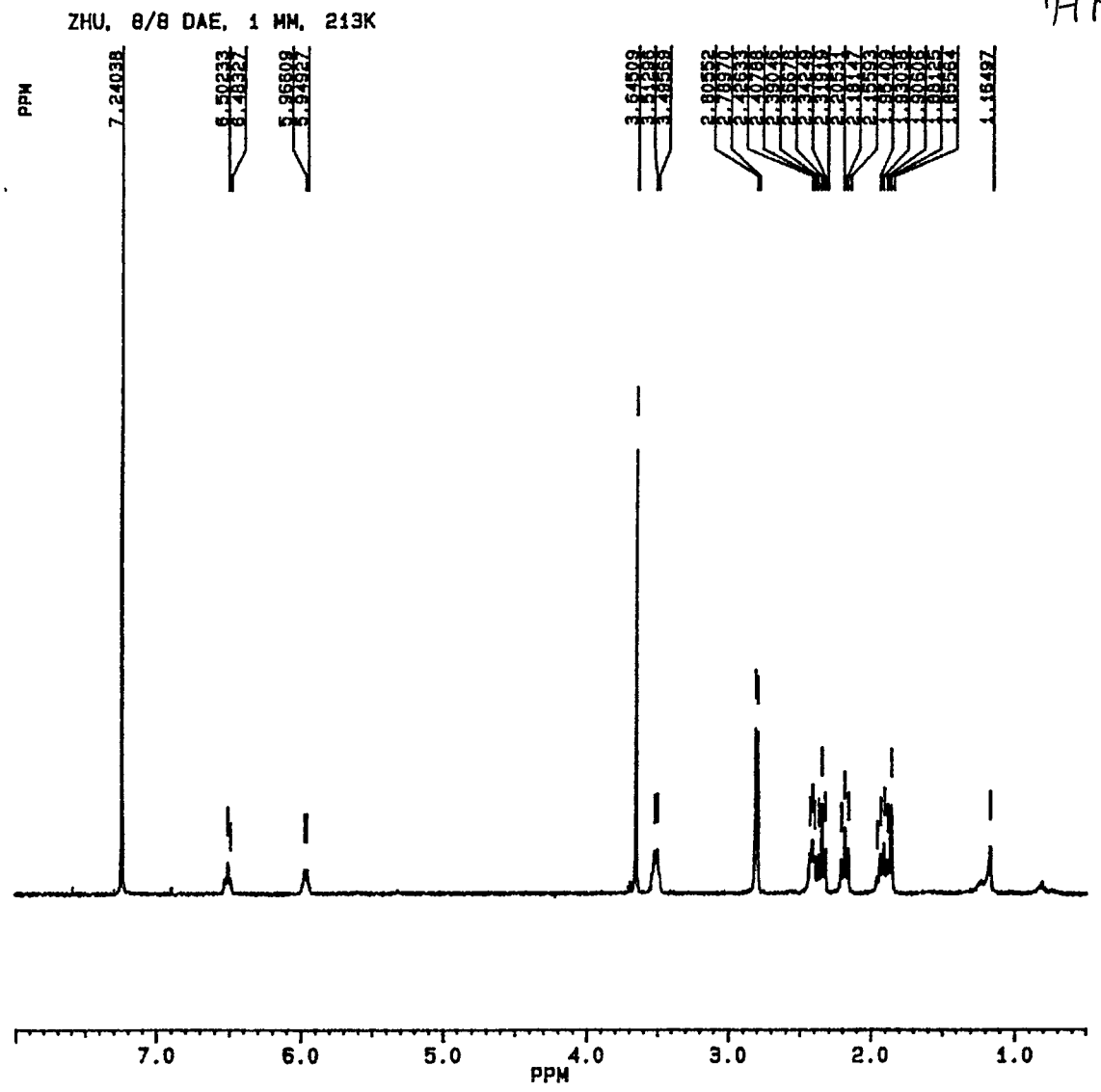
^{1}HMR 4b



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