

Reaction chemistry of metallotexaphyrins: the synthesis and characterization of the first *meso*-oxotexaphlorin

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Supplementary Information

Experimental

General

All reagents were used as supplied commercially unless otherwise noted. Motexafin gadolinium (**1**) was prepared according to the literature procedure.¹ UV-vis spectra were measured on a Hewlett-Packard 8452A Diode Array spectrophotometer. ¹H and ¹³C NMR spectra, COSY, and HMQC were performed by NuMega Resonance Labs, San Diego, on a Varian XL-400 instrument using a deuterated solvent as specified. FAB and FAB high resolution mass spectra were performed by University of California at Berkeley, Mass Spectrometry Facility.

Preparation of (acetato-*O*)[9,10-diethyl-5,14-bis(3-hydroxypropyl)-20,21-bis[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl-7H-3,6:8,11-diimino-13,16-nitrilo-1,18-benzodiazacycloicosin-7-onato(2-)-*N*¹, *N*¹⁸, *N*²³, *N*²⁴, *N*²⁵]gadolinium (3**)**

In a 250 mL round-bottom flask, were placed MGd **1** (230.0 mg, 0.20 mmol), anhydrous CH₂Cl₂ (100 mL), and a magnetic stir bar. With stirring, NaOMe (43.2 mg, 0.80 mmol) was added to the mixture in one portion. The reaction mixture was stirred at room

temperature under air for 12 hours, and then concentrated to dryness by rotary evaporation. The residue was subjected to column chromatography on a silica gel column (eluent: MeOH/CH₂Cl₂ = 7/100 (v/v)) to yield **3** as a deep green solid (73 mg, 33%).

FAB MS (m/z): 1045 [M-OAc⁻], 985, 913, 897, 659, 443.

ESI MS (m/z): 1105.4 [M+H⁺].

HRMS: Calcd for C₄₈H₆₅¹⁵⁸GdN₅O₁₁ [M-OAc⁻]: 1045.3933; found: 1045.3962.

FT-IR: 3400, 1650, 1575, 1525 cm⁻¹.

UV-vis (CH₃OH): 330, 432, 630, 672 nm.

Anal. Calcd for C₅₀H₆₈GdN₅O₁₃: C, 54.38; H, 6.21; N, 6.34; found: C, 53.99; H, 5.89; N, 6.08.

Preparation of bis(acetato-*O*)[9,10-diethyl-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanolato-*N*¹, *N*¹⁸, *N*²³, *N*²⁴, *N*²⁵]lutetium (4**)**

Compound **4** was prepared from *o*-phenylenediamine and 5,5'-[(3,4-diethyl-1*H*-pyrrole-2,5-diyl)bis(methylene)]bis[4-(3-hydroxypropyl)-3-methyl-1*H*-pyrrole-2-carboxaldehyde according to the literature procedure.¹

¹H NMR (400MHz, CD₃OD): 11.55(s, 2H), 9.61(dd, J = 5.1, 2.6 Hz, 2H), 9.59(s, 2H), 8.32(dd, J = 5.1, 2.6 Hz, 2H), 3.62(t, J = 5.2 Hz, 4H), 3.57(t, J = 5.2 Hz, 4H), 3.50(q, J = 6.0 Hz, 4H), 3.05(s, 6H), 2.13(quint, J = 5.2 Hz, 4H), 1.55(t, J = 6.0 Hz, 6H), 0.55(brs, 6H) ppm.

¹³C NMR (400 MHz, CD₃OD) 179.33, 158.00, 151.44, 147.75, 146.88, 145.57, 144.22, 141.81, 135.64, 129.73, 119.76, 118.84, 60.74, 34.42, 22.10, 21.79, 19.25, 17.86, 10.47ppm.

¹ J. L. Sessler, T. D. Mody, G. W. Hemmi and V. Lynch, *Inorg. Chem.* 1993, **32**, 3175.

ESI MS (m/z): 782 [M-OAc⁻].

HRMS: Calcd for C₃₄H₃₈LuN₅O₂⁺ [M-2OAc]⁺: 723.2433; found: 723.2460.

FT-IR: 3400, 1580, 1525 cm⁻¹.

UV-vis (CH₃OH): 333, 436, 762 nm.

Anal. calcd for C₃₈H₄₄LuN₅O₆: C, 54.22; H, 5.27; N, 8.32; found: C, 53.93; H, 5.26; N, 8.03.

Preparation of (acetato-*O*)[9,10-diethyl-5,14-bis(3-hydroxypropyl)-4,15-dimethyl-7H-3,6:8,11-diimino-13,16-nitrilo-1,18-benzodiazacycloeicosin-7-onato(2-)-N¹, N¹⁸, N²³, N²⁴, N²⁵]lutetium (5**)**

In a 250 mL round-bottom flask, were placed **4** (168 mg, 0.20 mmol), anhydrous CH₂Cl₂ (100 mL), and a magnetic stir bar. With stirring, NaOMe (43.2 mg, 0.80 mmol) was added to the mixture in one portion. The reaction mixture was stirred at room temperature under air for 12 hours, and then concentrated to dryness by rotary evaporation. The residue was subjected to column chromatography on silica gel column (eluent: MeOH/CH₂Cl₂ = 5/100 (v/v)) to yield **5** as a deep green solid (54 mg, 34%).

¹H NMR (400MHz, CD₃OD): 9.91(s, 1H), 9.85(s, 1H), 8.45(d, J = 6.6Hz, 1H), 8.41(d, J = 6.6Hz, 1H), 8.18(s, 1H), 7.59(t, J = 6.6 Hz, 1H), 7.53(t, J = 6.6 Hz, 1H), 3.62-3.55(m, 4H), 3.11(t, J = 5.7 Hz, 2H), 3.08-2.95(m, 6H), 2.55(s, 3H), 2.53(s, 3H), 1.92-1.84(m, 4H), 1.52(brs, 3H), 1.29(t, J = 6.0 Hz, 3H), 1.25(t, J = 5.9 Hz, 3H) ppm.

¹³C NMR (400 MHz, CD₃OD) 183.60, 182.81, 161.40, 152.99, 150.49, 149.03, 144.85, 144.33, 143.79, 142.99, 142.56, 142.08, 141.27, 136.44, 133.06, 131.89, 129.49, 127.78, 127.23, 118.48, 118.11, 62.82, 62.18, 35.87, 34.17, 23.57, 23.41, 22.06, 21.60, 19.46, 18.37, 16.10, 9.63, 9.89 ppm.

FAB MS (m/z): 738 [M-OAc⁻], 676, 648, 573, 487.

HRMS: calcd for C₃₄H₃₇LuN₅O₃ [M-OAc⁻]: 738.2303; found: 738.2301.

FT-IR: 3400, 1650, 1576, 1525 cm⁻¹.

UV-vis (CH₃OH): 326, 424, 654 nm.

Anal. calcd for C₃₆H₄₀LuN₅O₅: C, 54.20; H, 5.05; N, 8.78; found: C, 54.36; H, 5.20; N, 8.68.

Studies of reaction conditions for ring-oxygenation of metallotexaphyrins

The experimental procedures are similar to that for the preparation of **3** and **5**, except for using the specified solvent and base as listed in Table 1. The reaction yields are given in Table 1.

Reaction of MGd (1**) with sodium t-butoxide under anaerobic conditions**

In a 50 mL Schlenk tube, were placed MGd (**1**, 46.0 mg, 0.04 mmol), anhydrous CH₂Cl₂ (20 mL), and a magnetic stir bar. The mixture was de-aerated by the freeze-thaw method. Under a stream of N₂ bleed, NaO^tBu (0.16 mmol) was added to the mixture. The system was de-aerated again by freeze-thaw method, and protected under a N₂ atmosphere. The reaction mixture was then stirred at room temperature for 12 hours, and sampled for HPLC analysis.

Observation: No oxotexaphlorin product was detected by HPLC.

Ring-oxygenation reaction of MGd (1) under strictly anhydrous conditions

In a 50 mL Schlenk tube, were placed MGd (**1**, 46.0 mg, 0.04 mmol), anhydrous CH₂Cl₂ (20 mL, freshly distilled from P₂O₅), and a magnetic stir bar. With a stream of 16% O₂/N₂ gas mixture (dried by passing through a CaSO₄ column), NaO^tBu (0.16 mmol) was added. The reaction mixture was then stirred at room temperature under a 16% O₂/N₂ atmosphere for 12 hours, and sampled for HPLC analysis.

Observation: Based on HPLC, the yield of oxotexaphlorin was comparable to that obtained in the reaction under air.

Preparation of silyl-protected MGd (6)

In a 100 mL three-neck round-bottom flask, were placed MGd (**1**, 1.148 g, 1.00 mmol), imidazole (81.7 mg, 1.20 mmol), t-butyldimethylsilyl chloride (166 mg, 1.10 mmol), and a magnetic stir bar. The materials were dried at room temperature by applying vacuum for 1 hour. Then anhydrous DMF (50 mL) was added into the flask, and the mixture was stirred under N₂ at room temperature for 24 hours. The reaction mixture was then poured into a 500 mL separation funnel, diluted with 300 mL CH₂Cl₂, and washed with a 50 mM NH₄OAc buffer solution (100 mL × 3). The organic layer was separated and dried with anhydrous Na₂SO₄. After removing the solvents by rotary evaporation, the crude product was purified by silica gel column chromatography (eluent: MeOH/HOAc/CH₂Cl₂ = 5/0.5/100) to give **6** (1.046 g, 76%).

ESI MS (m/z): 1317.6 [M-OAc⁻].

HRMS: calcd for C₆₀H₉₄GdN₅O₁₀Si₂⁺ [M-2OAc]⁺: 1258.5779; found: 1258.5744.

Reaction of silyl-protected MGd with sodium t-butoxide under air

In a 50 mL round-bottom flask were placed silyl-protected MGd (**6**, 55.1 mg, 0.04 mmol), anhydrous CH₂Cl₂ (20 mL), and a magnetic stir bar. To the mixture, was added NaO^tBu

(0.16 mmol). The reaction mixture was then stirred at room temperature under air for 12 hours, and sampled for HPLC analysis.

Observation: No oxotexaphlorin product was detected by HPLC.

Preparation of bis(acetato-*O*)[9,10-diethyl-4,15-dimethyl-20,21-dimethoxy-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-diethylato-*N*¹, *N*¹⁸, *N*²³, *N*²⁴, *N*²⁵]gadolinium (7)

This material was prepared from 1,2-dimethoxy-4,5-dinitrobenzene and 5,5'-[(3,4-diethyl-1*H*-pyrrole-2,5-diyl)bis(methylene)]bis[4-ethyl-3-methyl-1*H*-pyrrole-2-carboxaldehyde according to the literature procedure.¹

ESI MS (m/z): 765.2 [M-OAc⁻].

HRMS: calcd for C₃₄H₃₈GdN₅O₂⁺ [M-2OAc]⁺: 706.2266; found: 706.2282.

Reaction of 7 with sodium t-butoxide under air

In a 50 mL round-bottom flask were placed all-alkyl Gd-Tex derivative (**7**, 33.0 mg, 0.04 mmol), anhydrous CH₂Cl₂ (20 mL), and a magnetic stir bar. To the mixture, was added NaO^tBu (0.16 mmol). The reaction mixture was stirred at room temperature under air for 12 hours, and sampled for HPLC analysis.

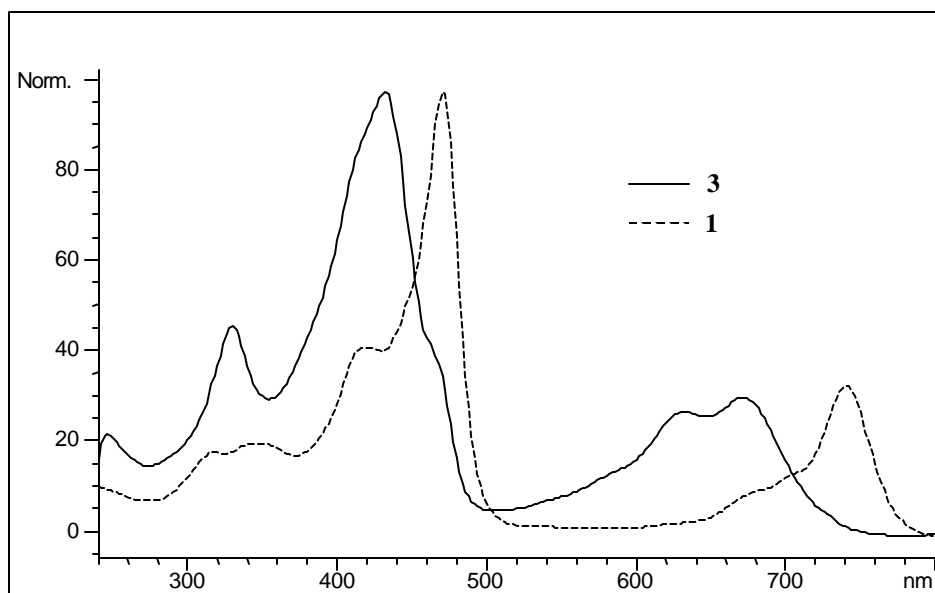
Observation: No oxotexaphlorin product was detected by HPLC.

Reaction of MGd (1) with hydrogen peroxide

In a 50 mL round bottom flask were placed MGd (**1**, 230 mg, 0.04 mmol), CH₂Cl₂ (20 mL), 30% H₂O₂ (23 mg, 0.20 mmol), and a magnetic stir bar. The reaction mixture was stirred under a N₂ atmosphere for 4 hours, and analyzed by HPLC.

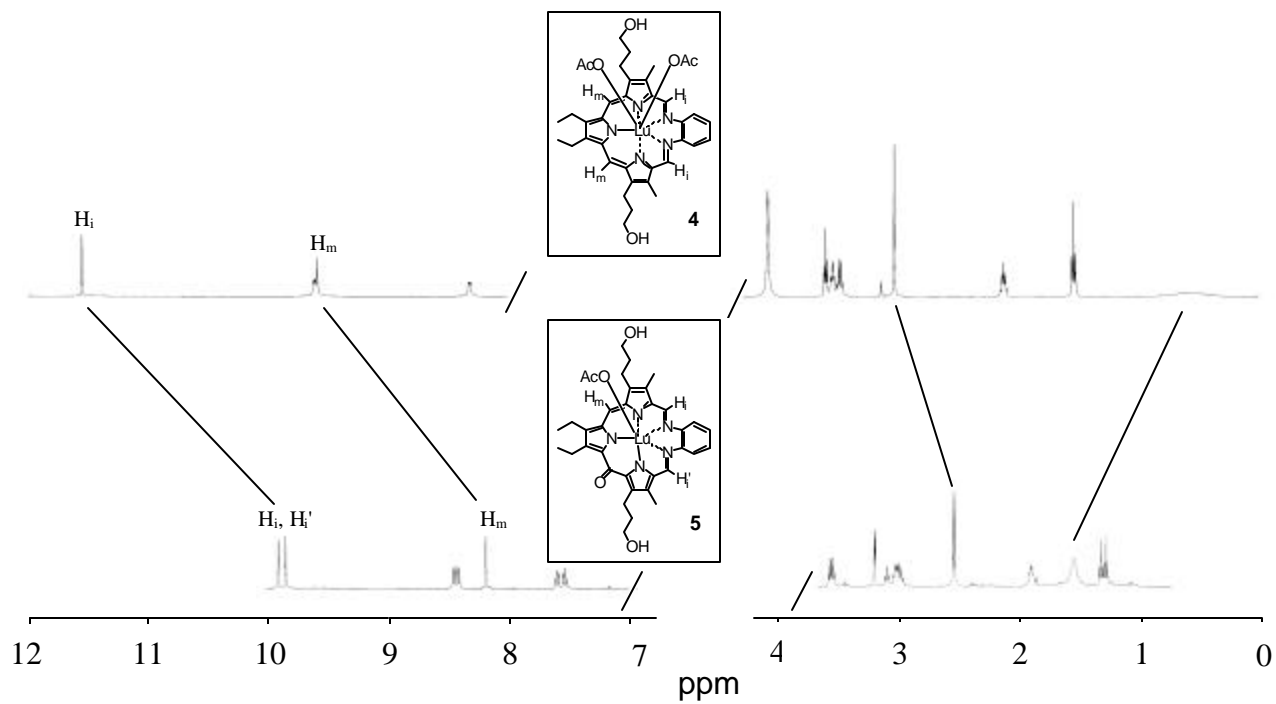
Observation: Multiple demetalated species were formed based on their UV-vis spectra and LC/MS; no oxotexaphlorin product was detected by HPLC.

UV-vis spectra of 1 and 3



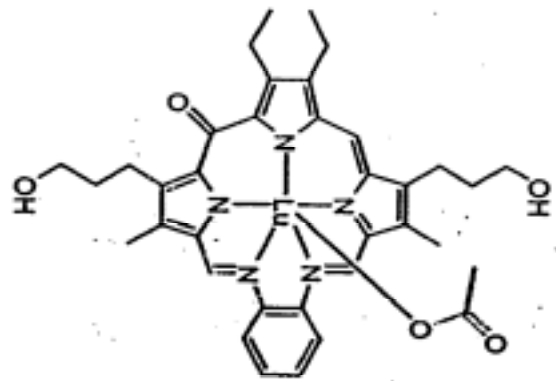
(spectra normalized by the strongest absorption peak)

^1H NMR spectra comparison of 4 and 5

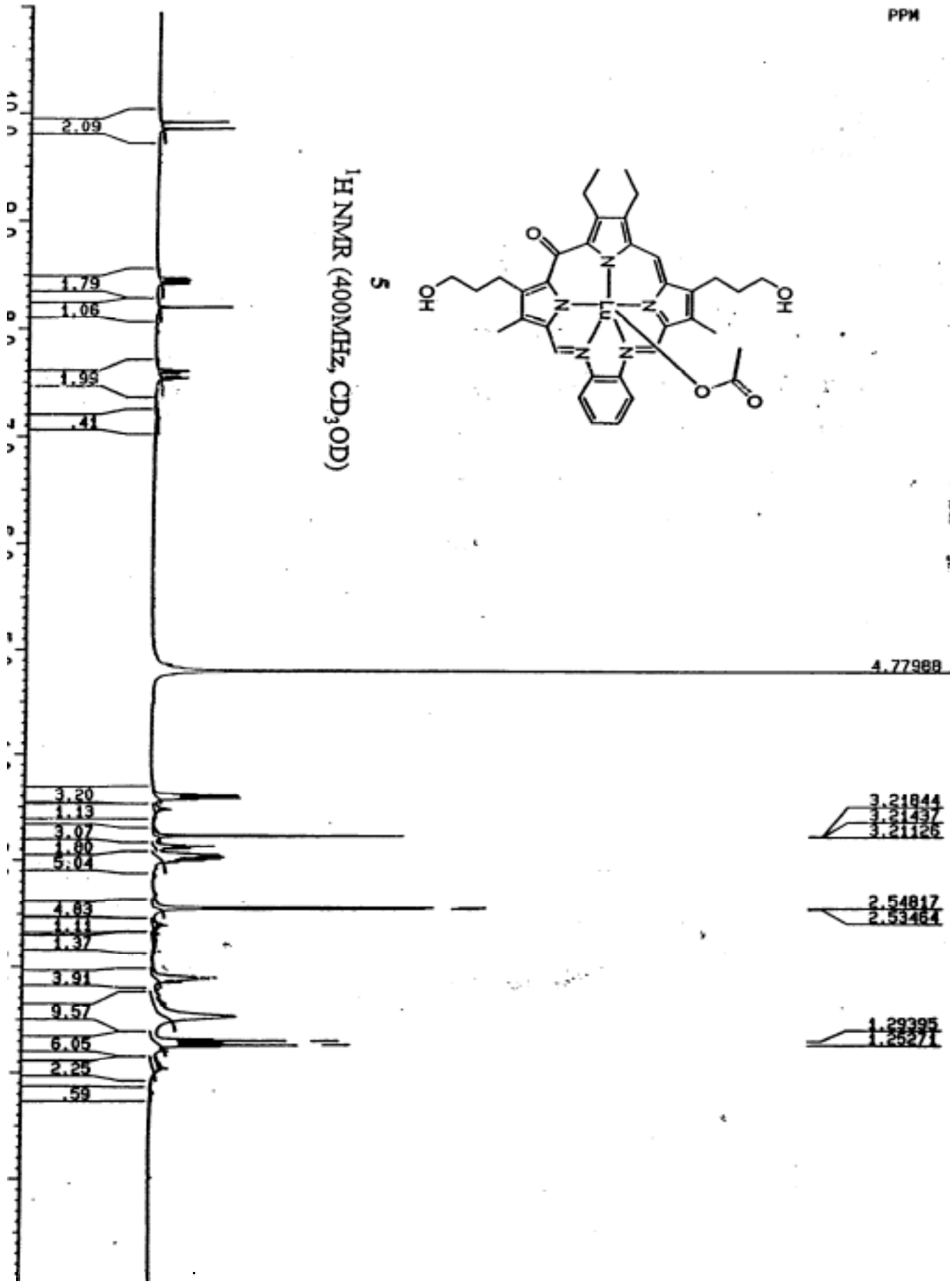


PPM

PHCY009H.347, ZM379-49, CD3OD, H-1, NUNEGA 11-8-00



5
¹H NMR (400MHz, CD₃OD)



PHCY009C.347, ZM379-49, CD3OD, C-13, NUMEGA 11-10-00

PPM

183.599
182.805

161.395
153.385
151.433
150.433
149.033
147.808
144.333
143.789
142.561
142.079
141.271
138.436
137.055
131.890
129.485
127.784
127.228

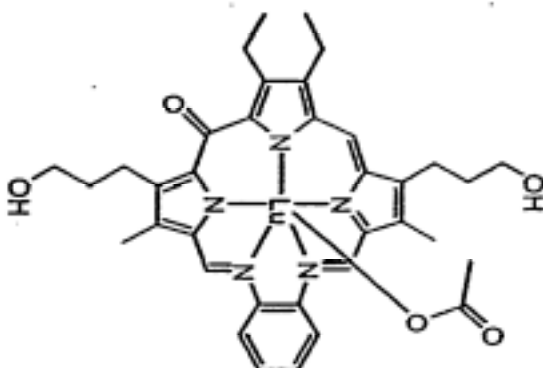
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118.112

62.819
62.176

49.653
49.484
49.316
49.147
48.973
48.802
48.634

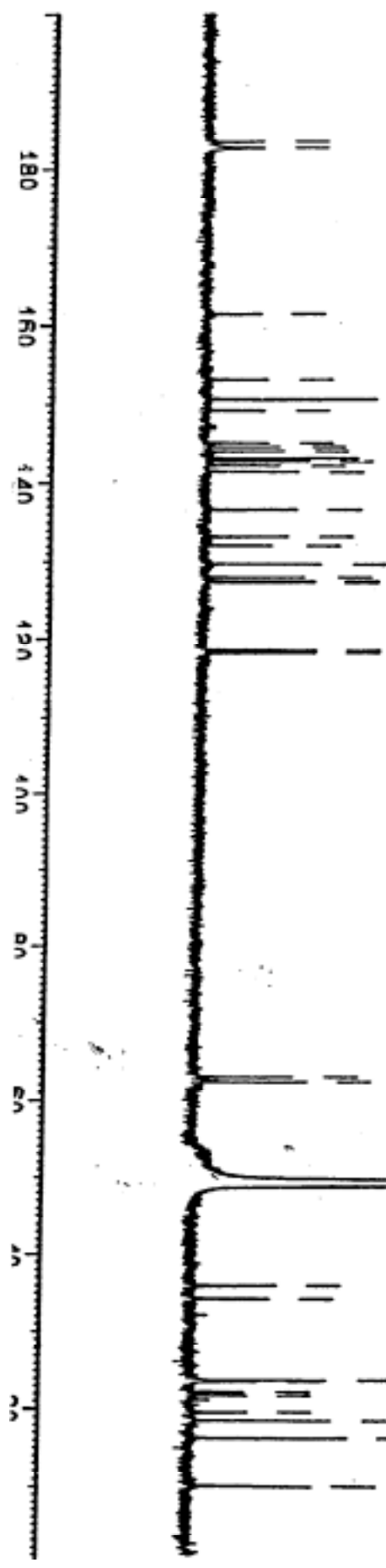
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19.455
18.374
16.103
9.963
9.885

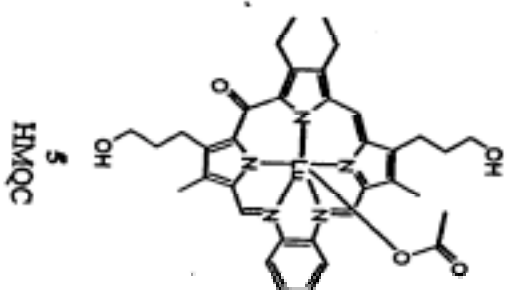
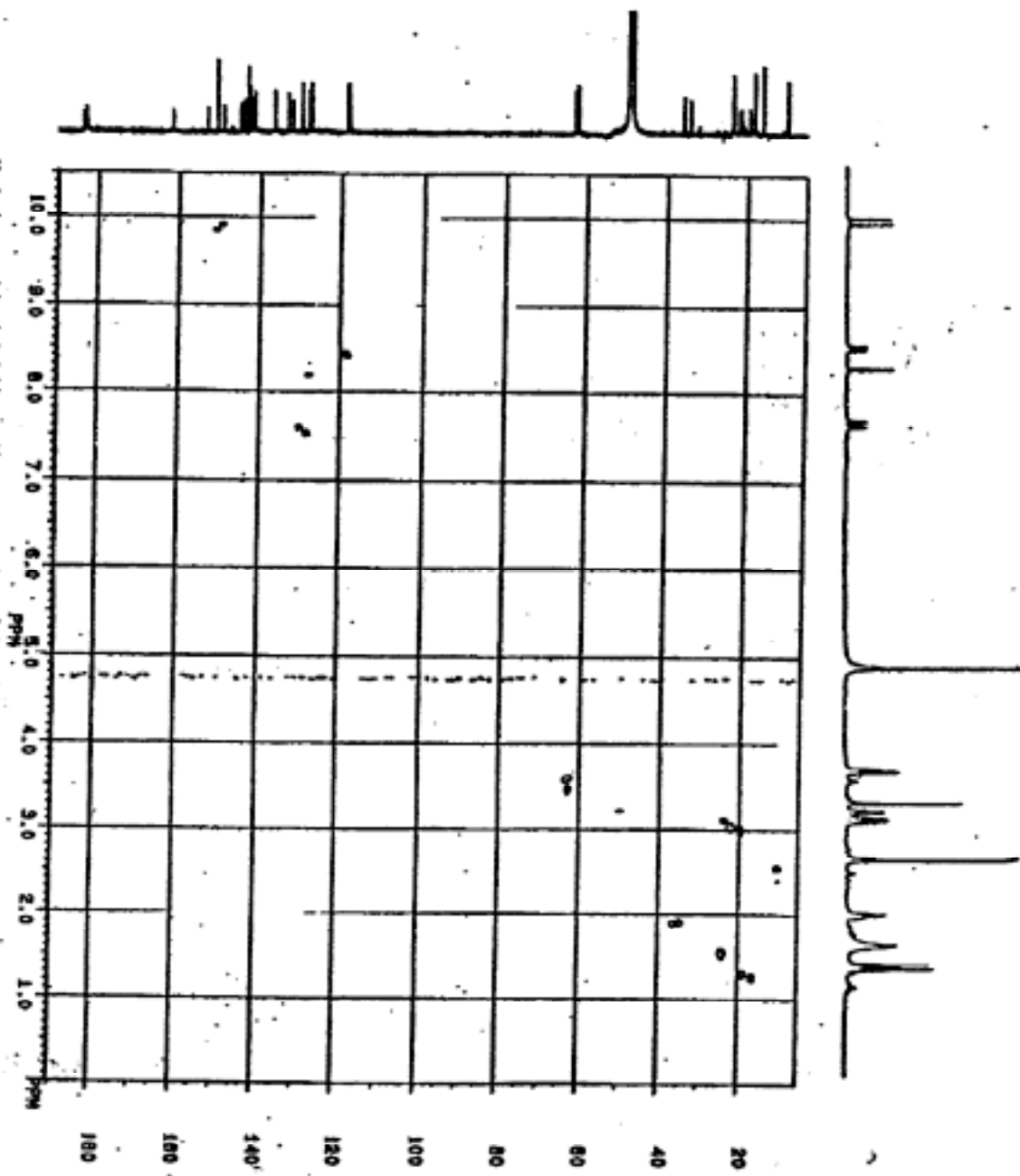


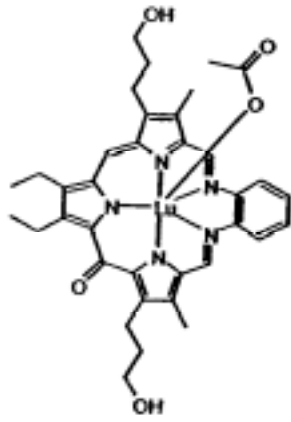
5

¹³C NMR (400MHz, CD₃OD)



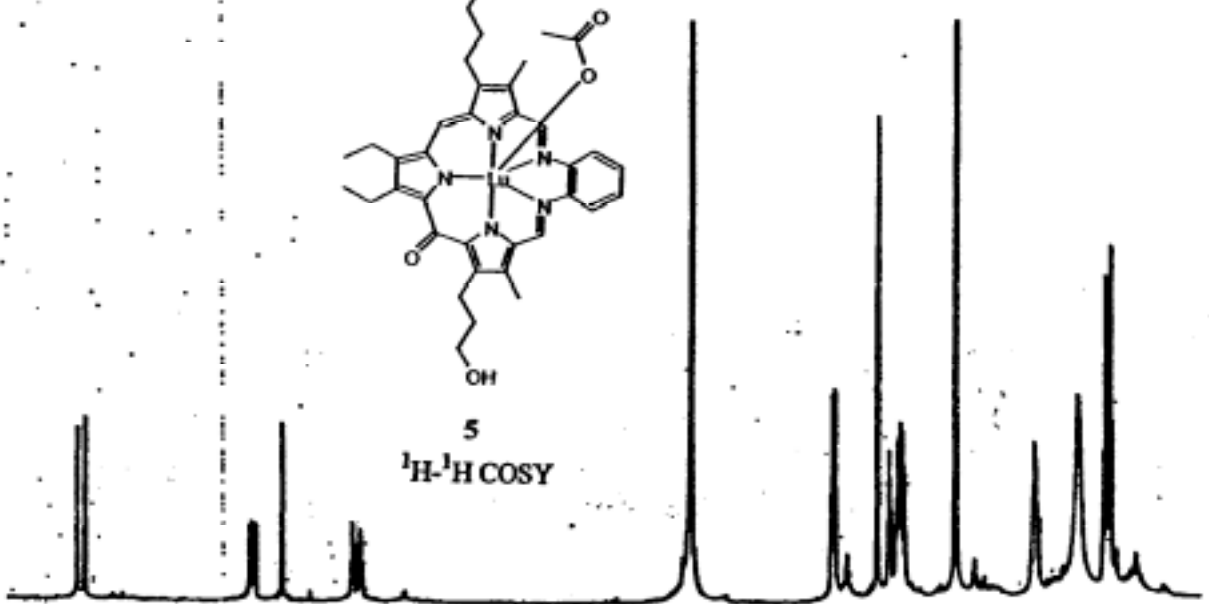
PMGYS470.SEG, ZN979-48, CD300, H-1, RUNREQ, 11-10-00



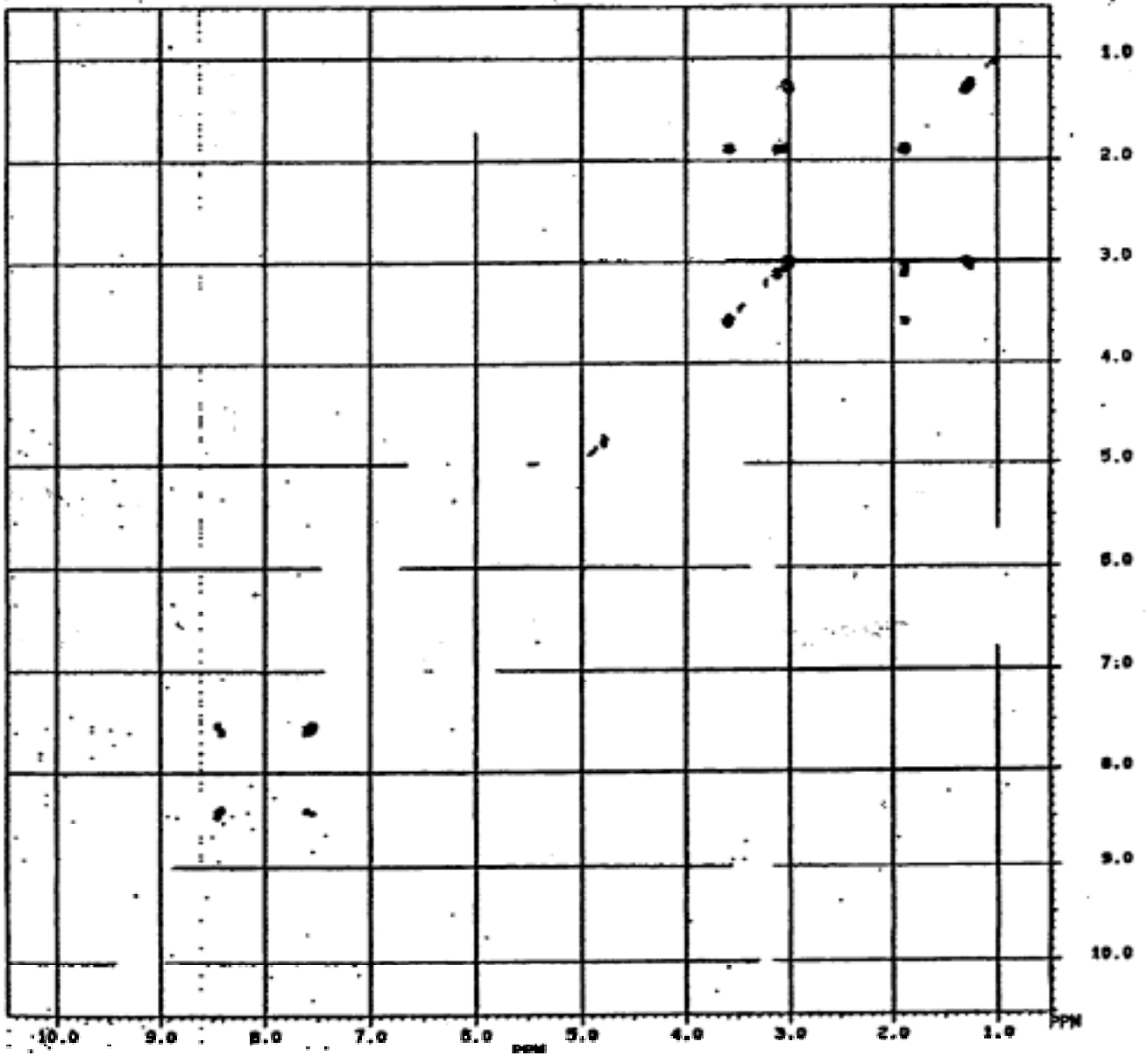


5

¹H-¹H COSY



PHCY347C, SEA, ZM379-48, CD300, DOP-COSY, NUMEGA 11-11-00



PHCY010H.045, ZH379-128, CDCL3/CD300, H-1, NUMEGA 12-1-00

11.5927

9.5867

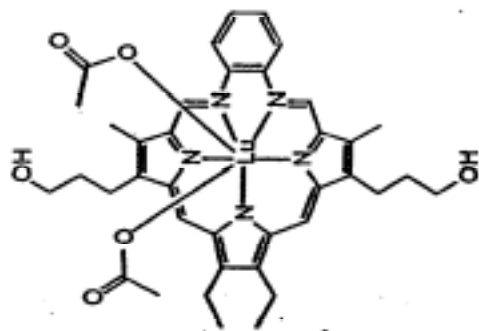
4.1088

3.6234

3.5119

3.0481

1.5632
1.5470
1.5319



4

¹H NMR (400MHz, CD₃OD)

1.09

2.00

1.01

7.00

5.45

2.13

1.92

2.22

3.07

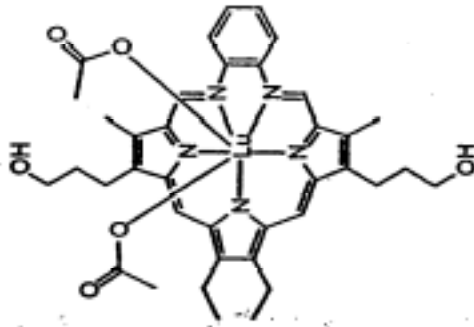
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3.12

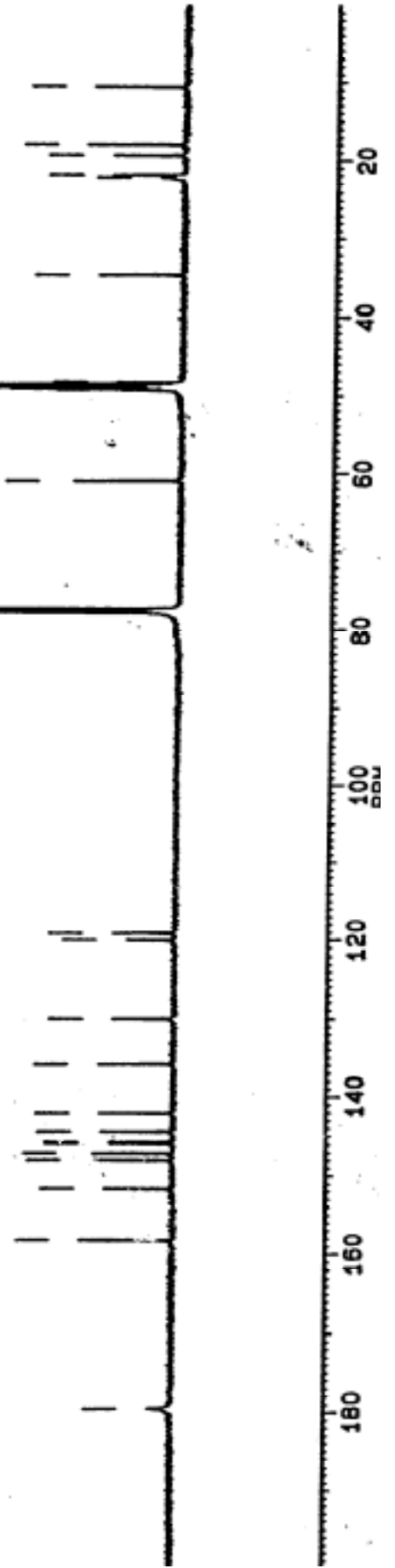
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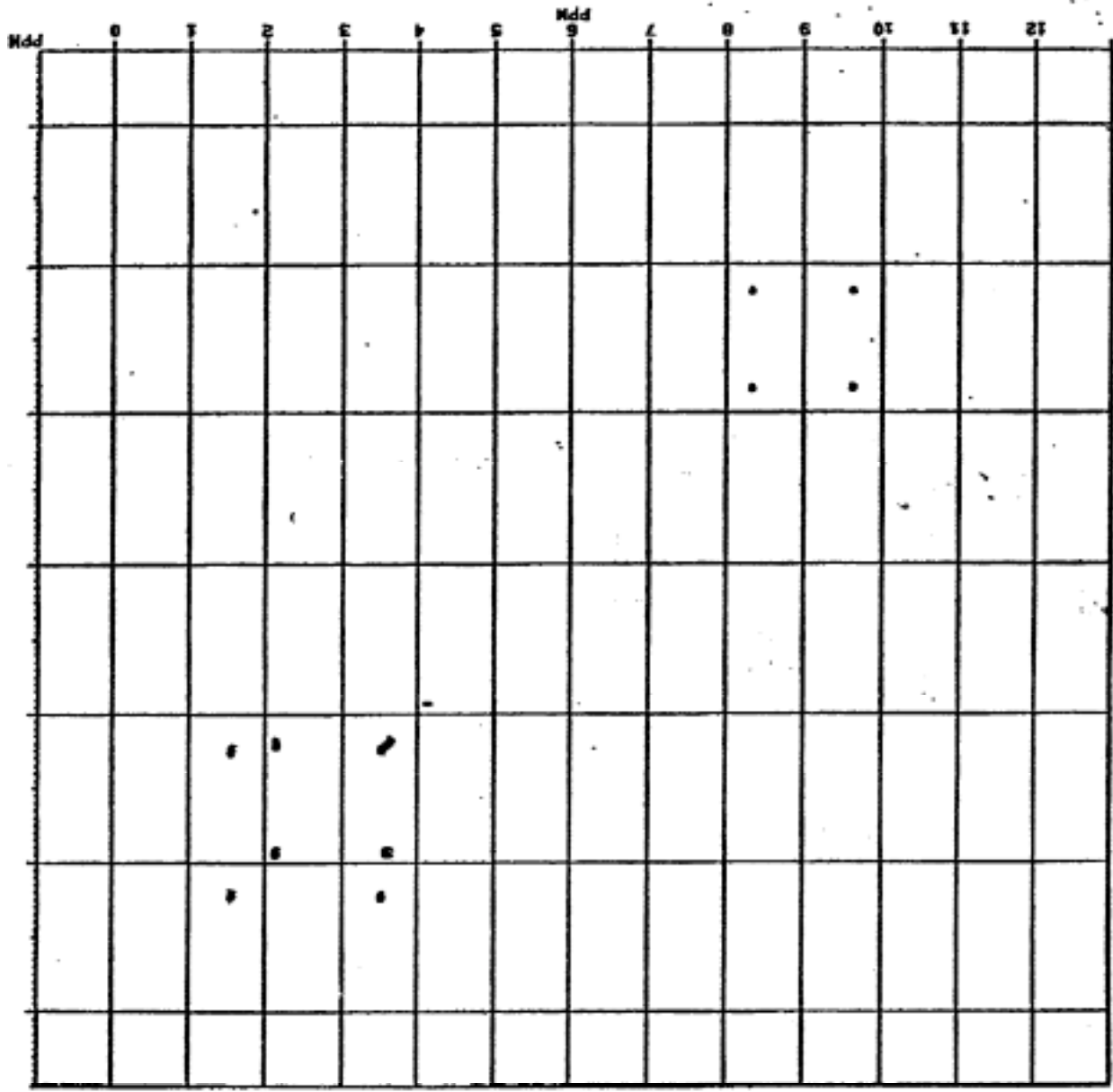
PPM

PHCY010C.045, ZN379-128, CDCL3/CD30D, C-13, NUMEGA 12-1-00



¹³C NMR (400MHz, CD₃OD)





PHC045C.SEM, 28379-128, CDCl3/CD300, DQF-COSY, MMR5A

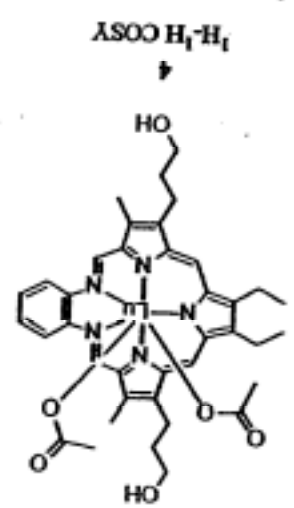


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