The Constituents of the Leaves of *Clinacanthus nutans* Lindau Part II

Santi Sakdarat[a*], Ketthai Panyakom[a], Aussavashai Shuyprom[b], Nuttaporn Samart[a], Thaweephol Dechatiwongse Na Ayudhya[b], Peter G. Waterman[c] and Gloria Karagianis[c]

[a] School of Chemistry, Institute of Science, Suranaree University of Technology, Nakhon Ratchasima, Thailand.

[b] Medicinal Plant Research Institute, Department of Medical Science, Ministry of Public Health, Nonthaburi, Thailand.

[c] Centre for Phytochemistry, Southern Cross University, Lismore, P.O. Box 151 NSW 2480, Australia.

Abstract

The leaves of *Clinacanthus nutans* Lindau have long been traditionally used in Thailand as an anti-inflammatory drug for the treatment of insect bites, herpes infection and allergic responses. A crude chloroform extract was separated by column chromatography and further purified by preparative thin-layer chromatography to give eight pure compounds. Structure elucidation of the isolated compounds was carried out on the basis of spectral analyses, including DEPT, COSY, NOESY, HMQC and HMBC. Eight of these were known compounds with structures related to chlorophyll a and chlorophyll b namely 13^2-hydroxy-(13^2-S)-chlorophyll b, 13^2-hydroxy-(13^2-R)-chlorophyll b, 13^2-hydroxy-(13^2-S)-phaeophytin b, 13^2-hydroxy-(13^2-R)-phaeophytin b, 13^2-hydroxy-(13^2-S)-phaeophytin a, 13^2-hydroxy-(13^2-R)-phaeophytin a, purpurin 18 phytyl ester and phaeophorbide a, which was not previously reported in this species.

Keyword: Clinacanthus nutans Lindau, chlorophyll a and chlorophyll b related compounds, 13^2-hydroxy-(13^2-S)-chlorophyll b, 13^2-hydroxy-(13^2-R)-chlorophyll b, 13^2-hydroxy-(13^2-S)-phaeophytin b, 13^2-hydroxy-(13^2-R)-phaeophytin b, 13^2-hydroxy-(13^2-S)-phaeophytin a, 13^2-hydroxy-(13^2-R)-phaeophytin a, purpurin 18 phytyl ester, phaeophorbide a.

* Corresponding author. Tel.: +6644-224302; Fax: +6644-224185.

E-mail address: santi@sut.ac.th

1. Introduction

Clinacanthus nutans (Burm. f.) Lindau (Thai name: Phaya Yo or Phaya Plong Thong) is a small shrub, native to tropical Asia, and is often cultivated. *C. nutans* has long been used in Thailand as a traditional medicine for the treatment of skin rashes, insect and snake-bite, including herpes simplex virus (HSV), and varicella-zoster virus (VZV) lesions. Extracts from the leaves were reported to possess analgesic and anti-inflammatory activities[1], antiviral activities against varicella-zoster virus[2] and herpes simplex virus type-2[3]. Clinical trials in patients with genital herpes patients are also reported[4,5]. However, negative results have also been reported[6]. Nonetheless clinical trials have reported the successful use of a *C. nutans* preparation (cream or lotion) for the relief of minor skin inflammation and insect bites, including treatment of genital herpes and varicella-zoster lesions in patients[7]. *C. nutans* has been chemically investigated previously stigmasterol[8], lupeol, β-sitosterol[9], belutin[10], six known C-glycosyl flavones, vitexin, isovitexin, shaftoside, isomollupentin-7-O- β-glucopyranoside, orientin, isoorientin[11], five sulfur-containing glycosides[12], two glycoglycerolipids[13], a mixture of nine cerebroside and a monoacylmonogalactosylglycerol[14], have been isolated. This present communication deals with the isolation of compounds from the chloroform extract and structure elucidation of the eight isolated compounds as chlorophyll a and chlorophyll b related compounds by spectroscopic methods.

2. Meterial and Methods

2.1 General

The UV spectra were obtained with a Hewlett Packard 8452A diode array UV-VIS spectrophotometer, whereas the IR spectra were measured with a Perkin-Elmer FT-IR 2000 spectrophotometer (by a KBr disk method). Mass spectra were measured on a Micromass LCZ spectrometer. The ^{1}H and ^{13}C NMR, DEPT, COSY, NOESY, HMQC, and HMBC spectra were recorded with a Bruker DRX 500 spectrometer in pyridine-d_5 solution and chemical shifts are expressed in δ (ppm) with reference to the solvent signals. Silica gel 60 (70-230 mesh) and silica gel 60 PF 254 were used for column chromatography and preparative thin-layer chromatography, respectively.

Solvents of technical grade were used for chromatographic purposes. Anisaldehyde-sulfuric acid spraying reagent (modification b) was prepared according to the method of Stahl (1965).

2.2 Plant material

Fresh aerial parts of C. *nutans* (Burm. f.) Lindau (Family Acanthaceae) were collected during October to December 1998, from Bangkok, Chanthaburi and Nakhon Pathom Provinces of Thailand. The specimens were authenticated by the Botanical Section, Medicinal Plant Research Institute, Department of Medical Sciences, where a voucher specimens (Bansiddhi 432) is deposited. The leaves were separated from the stems, washed thoroughly and dried in an oven at 50 °C. The dried sample was ground to powder.

2.3 Extraction and isolation

The dried powdered leaves (4.9 kg) were sequentially extracted with hexane and chloroform, respectively. The chloroform extract was concentrated *in vacuo* to give a residue (90.5 g) which was chromatographed on a silica gel 60 column. The column was eluted successively with hexane-ethyl acetate (1:1), ethyl acetate, chloroform-ethanol (1:1), and ethanol. Four major fractions (I, 32.92 g; II, 6.50 g; III, 30.51 g and IV, 4.90 g) were obtained by monitoring with TLC (toluene-petroleum ether 35-60°C-methanol-methyl ethyl ketone 30:60:5:5) A portion of **Fraction I** (1.0017 g) was further separated by preparative thin-layer chromatography (hexane-ethyl acetate 7:3) to afford five fractions (A, 0.0450 g; B, 0.0406 g; C, 0.0791 g; D, 0.0697 g and E, 0.1469 g). Fraction A (0.0450 g) was purified by preparative thin-layer chromatography using the same developing solvent to give crude **compound 1** (0.0105 g) and **compound 2** (0.0098 g), which were recrystallized from methanol (0.0052 g) and (0.0048 g), respectively. Fraction B (0.0406 g) was further purified by preparative thin-layer chromatography using the same developing solvent to give crude **compound 3** (0.0105 g), which was recrystallized from methanol (0.0047 g). Fraction C (0.0791 g) was further purified by preparative thin-layer chromatography using the same developing solvent to give crude **compound 4** (0.0136 g), Fraction D (0.0791 g) was further purified by preparative thin-layer chromatography using the same developing solvent to give crude **compound 5** (0.0117 g) and **compound 6**

(0.0113 g), which was recrystallized from methanol (0.0061 g) and (0.0057 g), respectively. **Fraction III** (30.51 g) was chromatographed on a silica gel 60 column (855 g), eluting successively with chloroform, followed by chloroform-ethanol gradient. Monitoring by TLC using the same solvent system as mentioned above, five fractions (A', 1.39 g; B', 0.80 g; C', 0.49 g; D', 6.13 g and E', 2.55 g) were obtained. Fraction A' (1.39 g) was purified by preparative thin-layer chromatography using chloroform-methanol (9:1) as the developing solvent to give crude **compound 7** (0.3503 g). The crude compound was further purified by preparative thin-layer chromatography using hexane-ethyl acetate (7:3) as the solvent system to provide pure **compound 7** (0.0285 g). Purification of fraction B' (0.80 g) by the preparative thin-layer chromatography, developing with chloroform-methanol (9:1) and recrystallization from chloroform-ethanol yielded **compound 8** (0.0136 g). The structures of compounds isolated from the chloroform extract of *C. nutans* leaves were elucidated on the basis of spectral analysis, including DEPT, COSY, NOESY, HMQC and HMBC. The known compounds **1-8** were identified as chlorophyll a and chlorophyll b derivatives.

2.4 13^2-hydroxy-(13^2-S)-chlorophyll b (1)

A bright green powder; UV ($CHCl_3$) λ_{max} nm 410, 506, 535, 612 and 668; FI-IR (KBr) ν_{max} cm^{-1} : 3430, 3028, 1730, 1638, 1310; TOF MS ES m/z 923.6 $(M+1)^+$; $C_{55}H_{70}N_4O_7Mg$ requires 922.5; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.5 13^2-hydroxy-(13^2-R)-chlorophyll b (2)

A bright green powder; UV ($CHCl_3$) λ_{max} nm 410, 507, 536, 612 and 666; FI-IR (KBr) ν_{max} cm^{-1} : 3030, 1728, 1630 and 1306; TOF MS ES m/z 923.6 $(M+1)^+$; $C_{55}H_{70}N_4O_7Mg$ requires 922.5; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.6 13^2-hydroxy-(13^2-S)-phaeophytin b (3)

A green powder; UV ($CHCl_3$) λ_{max} nm 412, 433, 526, 603 and 656; FI-IR (KBr) ν_{max} cm^{-1} : 3429, 3032, 1743, 1720, 1630 and 1310; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.7 13^2-hydroxy-(13^2-R)-phaeophytin b (4)

A dark green powder; UV ($CHCl_3$) λ_{max} nm 412, 438, 520, 600 and 670; FI-IR (KBr) ν_{max} cm^{-1} : 3429, 2925, 2852, 1740, 1721, 1637 and 1300; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.8 13^2-hydroxy-(13^2-S)-phaeophytin a (5)

A bright green color; UV ($CHCl_3$) λ_{max} nm 408, 506, 536, 613 and 670 ; FI-IR (KBr) ν_{max} cm^{-1} : 3430, 2924, 1741, 1620 and 1460; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.9 13^2-hydroxy-(13^2-R)-phaeophytin a (6)

A bright green color; UV ($CHCl_3$) λ_{max} nm 412, 507, 537, 612 and 668; FI-IR (KBr) ν_{max} cm^{-1} : 3429, 2995, 1740, 1617 and 1455; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.10 purpurin 18 phytyl ester (7)

A grayish green powder; UV ($CHCl_3$) λ_{max} nm 408, 480, 508, 546, 642 and 698; FI-IR (KBr) ν_{max} cm^{-1} : 3430, 2925, 2856, 1734, 1705 and 1620; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

2.11 phaeophorbide a (8)

A dark green powder; UV ($CHCl_3$) λ_{max} nm 413, 507, 538, 612 and 670; FI-IR (KBr) ν_{max} cm^{-1} : 3429, 2925, 1740, 1700, 1615, 1260 and 1150; ^1H NMR see Table 1, ^{13}C NMR see Table 2.

3. Results and discussion

Compound 1 was obtained as a bright green powder. The TOF MS ES mass spectrum of **1** showed a molecular ion peak at m/z 923.6 $(M+1)^+$; $C_{55}H_{70}N_4O_7Mg$ requires 922.5. The ^1H-NMR and ^{13}C-NMR data of **1** were found to be closely similar to those of compound **3** and **4**. It was therefore proved to have a chlorin ring system like compounds **3** and **4**, except for the lack of two NH protons for chlorin (dihydroporphine) ring. Furthermore, the ^1H-NMR and ^{13}C-NMR spectroscopic

properties established the presence of three downfield methine protons (δ 11.01 for H-5, δ 10.16 for H-10, δ 8.92 for H-20), methyls attached to C-2, C-12, and C-18, an ethyl at C-8 and an aldehyde at C-7^1 (Tables 1 and 2). The ^{13}C-NMR spectrum of compound **1** displayed four carbonyl carbon signals at δ 194.9, 188.0, 174.0 and 173.5. The absolute configuration at C-13^2 of compound **1** was further confirmed by the observed correlations of H-18^1 to H-13^4 and H-17 to H-13^4 in the NOESY spectrum of compound **1** (Fig. 2). By direct comparison of the ^{1}H-NMR and ^{13}C-NMR data of compound **1** (Table 1 and 2) with those of the known compound 13^2-hydroxy-(13^2-S)-chlorophyll b[15] they were closely equivalent indicated that compound **1** is 13^2-hydroxy-(13^2-S)-chlorophyll b(Fig. 1).

Compound 2 was obtained as a bright green powder. The TOF MS ES mass spectrum, The ^{1}H-NMR and ^{13}C-NMR data of **2** were found to be closely similar to those of compound **1.** By direct comparison of the ^{1}H-NMR and ^{13}C-NMR data of compound **2** (Table 1 and 2) with those of the known compound 13^2-hydroxy-(13^2-R)-chlorophyll b[15] they were closely equivalent indicated that compound **2** is 13^2-hydroxy-(13^2-R)-chlorophyll b(Fig. 1).

Compound 3 was obtained as a green powder. The IR spectrum present of amine, hydroxyl, and ester functional groups. The absolute configuration at C-13^2 of compound **3** was further confirmed by the observed correlations of H-17^1 to H-13^4 and H-17^2 to H-13^4 in the NOESY spectrum of compound **3** (Fig. 2). These features indicated the structure of **3** was similar to the known compound phaeophytin a[16], expect for the presence of an aldehyde group at C-7^1. Thus compound **3** was identified as 13^2-hydroxy-(13^2-S)-phaeophytin b (Fig. 1).

Compound 4 was obtained as a dark green amorphous solid. The IR, ^{1}H-NMR and ^{13}C-NMR data of **4** were found to be closely similar to those of compound **3.** By direct comparison of the ^{1}H-NMR and ^{13}C-NMR data of compound **4** (Table 1 and 2) with those of the known compound 13^2-hydroxy-(13^2-S)-phaeophytin b they were closely equivalent indicated that compound **4** is 13^2-hydroxy-(13^2-R)-phaeophytin b (Fig. 1).

Compound 5 was obtained as a green powder. The IR spectrum present of amine, hydroxyl, and ester functional groups. The absolute configuration at C-13^2 of compound **5** was further confirmed by the observed correlations of H-17^1 to H-13^4 and H-17^2 to H-13^4 in the NOESY spectrum of compound **5** (Fig. 2). These features

indicated the structure of **5** was similar to the known compound phaeophytin a[16]. Thus compound **5** was identified as 13^2-hydroxy-(13^2-S)-phaeophytin a (Fig. 1).

Compound 6 was obtained as a green powder. The IR, ^{1}H-NMR and ^{13}C-NMR data of **6** were found to be closely similar to those of compound **5.** By direct comparison of the ^{1}H-NMR and ^{13}C-NMR data of compound **6** (Table 1 and 2) with those of the known compound 13^2-hydroxy-(13^2-R)-phaeophytin a they were closely equivalent indicated that compound **6** is 13^2-hydroxy-(13^2-R)-phaeophytin a (Fig. 1).

Compound 7 was isolated as a grayish green solid. The ^{1}H-NMR and ^{13}C-NMR spectra of compound **7** (Tables 1 and 2) closely matched with those of compound **7** and purpurin 18[17]. The ^{1}H-NMR data comparison showed similarity to purpurin 18 with an extra phytyl ester proton side chain. Thus compound **7** was identified as purpurin 18 phytyl ester (Fig. 1).

Compound 8 was isolated as dark green powder. The ^{1}H-NMR and ^{13}C-NMR spectra of compound **8** (Tables 1 and 2) showed similar to that of the known compound phaeophorbide a methyl ester[18]. The ^{1}H-NMR spectrum of compound **8** however, lacked the methyl ester signal at δ 3.57 (Table 1). The HMBC spectrum of compound **8** (Fig. 3) showed the interaction *via* multiple bonds between C and H giving the support to the assignments. Thus compound **8** was identified as phaeophorbide a (Fig. 1).

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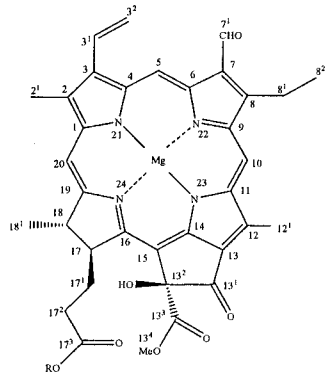

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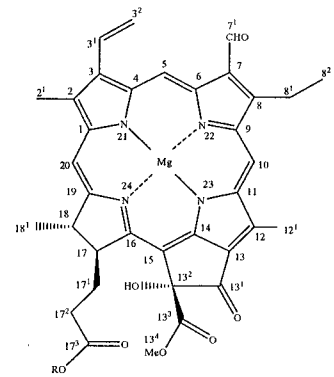

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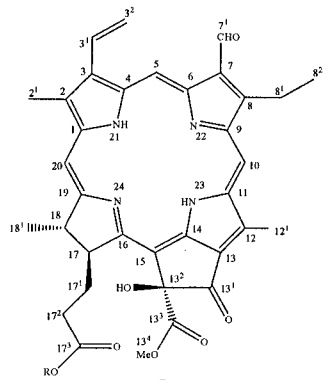

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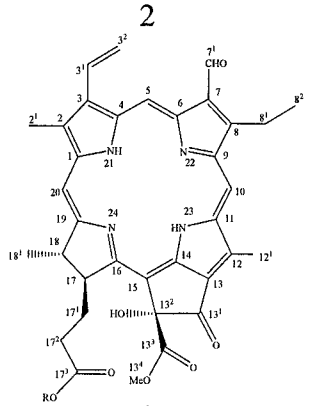

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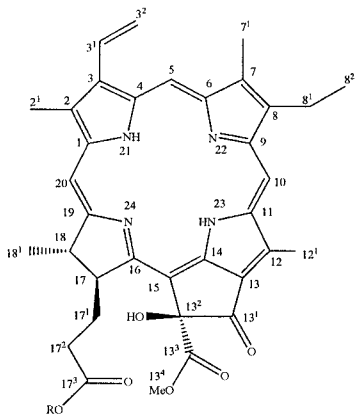

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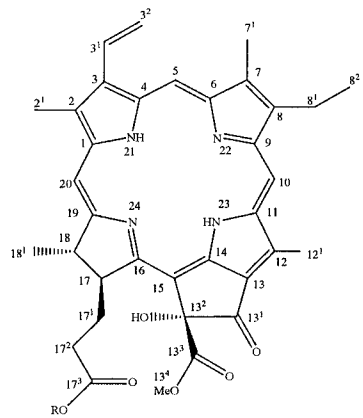

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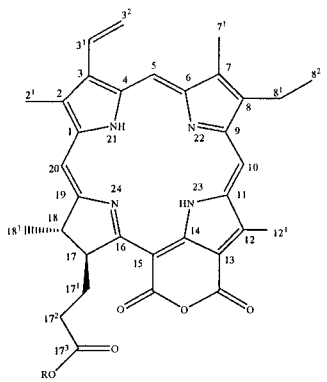

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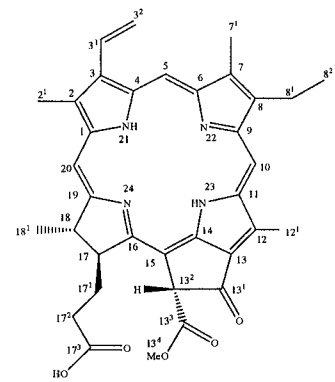

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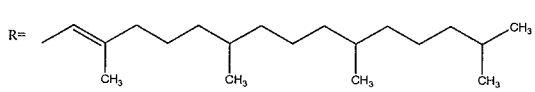


Fig. 1. Structure of compounds **1-8**

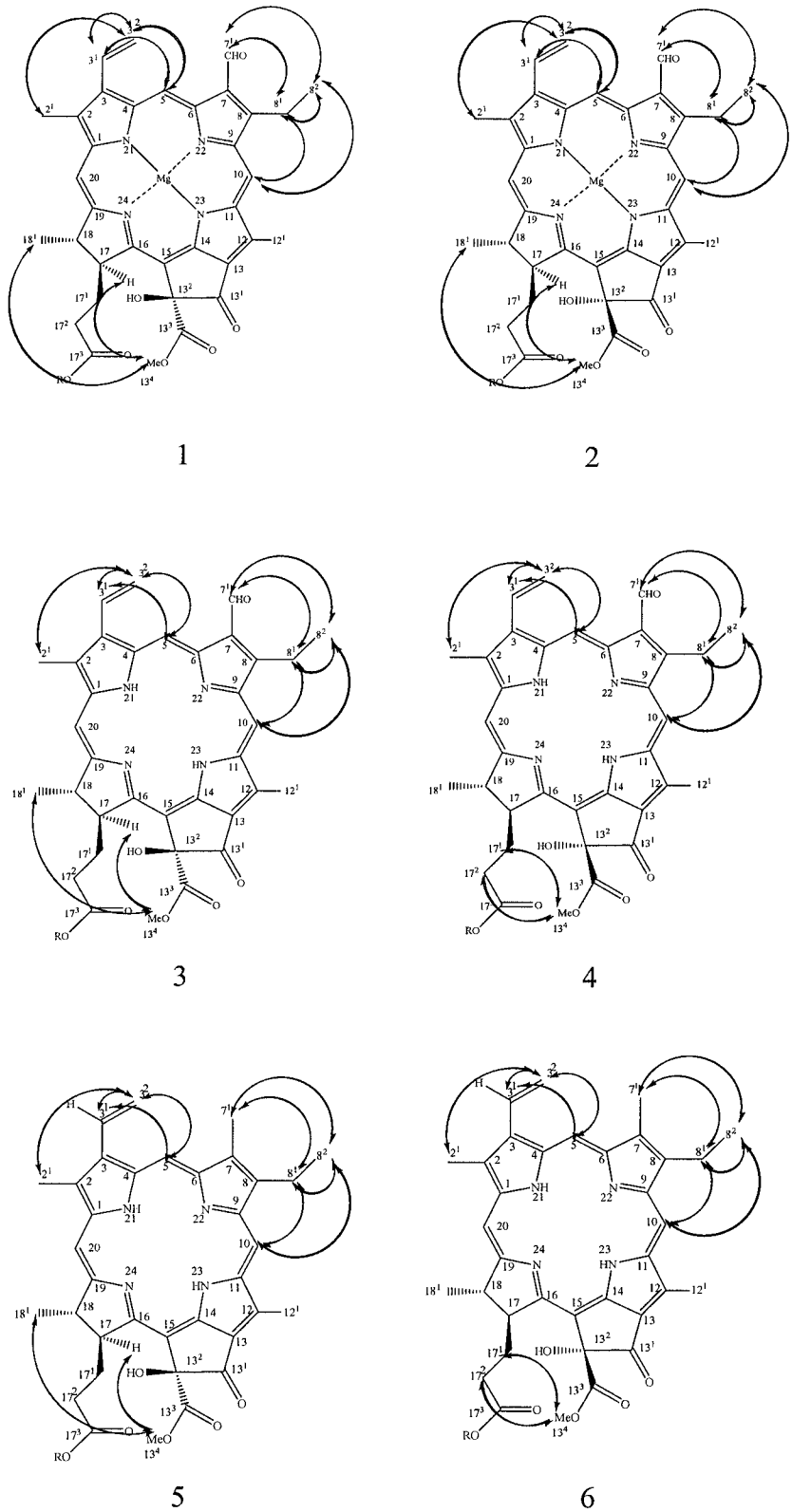
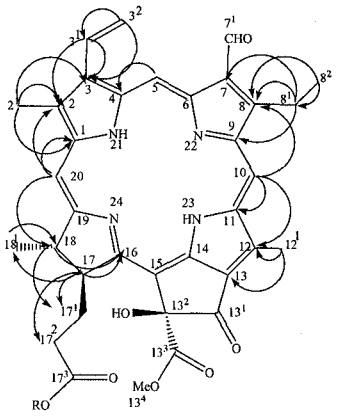


Fig. 2. The NOESY correlations of compounds **1**, **2**, **3**, **4**, **5** and **6**



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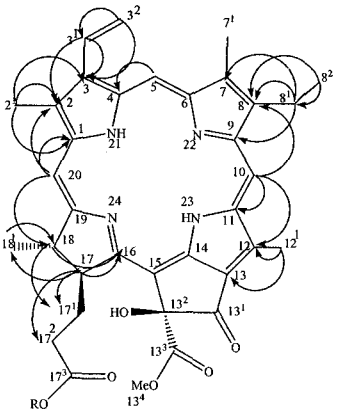

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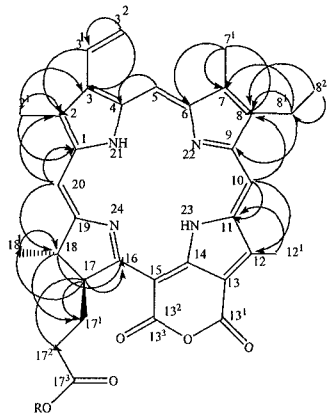

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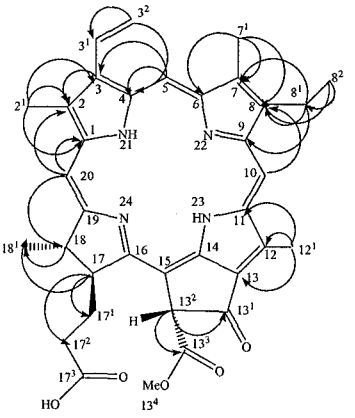

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Fig. 3. The HMBC correlations of compounds **3**, **5**, **7** and **8**

1. 13^2-hydroxy-(13^2-S)-chlorophyll b
2. 13^2-hydroxy-(13^2-R)-chlorophyll b
3. 13^2-hydroxy-(13^2-S)-phaeophytin b
4. 13^2-hydroxy-(13^2-R)-phaeophytin b
5. 13^2-hydroxy-(13^2-S)-phaeophytin a
6. 13^2-hydroxy-(13^2-R)-phaeophytin a
7. purpurin 18 phytyl ester
8. phaeophorbide a

Table 1. ^{1}H-NMR chemical shifts of the compounds **1-8**

Proton		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
2^1	*s*	3.27	3.27	3.45	3.35	3.61	3.40	3.32	3.38
3^1	*dd, J* = 11.65,10.9	8.26	8.26	8.18	8.19	7.85	8.10	8.10	8.22
3^2 (E)	*dd, J* = 17.8, 2.5	6.49	6.49	6.54	6.54	6.41	6.37	6.41	6.40
3^2 (Z)	*dd, J* = 12.6, 2.5	6.06	6.06	6.21	6.21	6.25	6.18	6.20	6.21
5	*s*	10.91	10.91	11.01	11.00	9.91	9.70	9.66	9.73
7^1	*s*	11.57	11.57	11.48	11.50	3.29	3.19	3.17	3.26
8^1	*q, J* = 7.65	4.18	4.18	4.19	4.22	3.76	3.66	3.71	3.75
8^2	*t, J* = 7.55	1.75	1.75	1.81	1.83	1.73	1.68	1.69	1.71
10	*s*	10.06	10.06	10.16	10.16	9.76	9.88	9.89	9.90
12^1	*s*	3.68	3.68	3.72	3.70	3.87	3.73	3.84	3.69
13^2-H	*s*								6.90
13^2-OH	*s*	6.48	6.46	6.52	6.20	5.53	5.35		
13^4-OMe	*s*	3.74	3.74	3.85	3.85	3.69	3.71		3.93
17	*m*	5.14	5.54	5.23	5.41	5.24	5.77	5.46	4.59
18	*dq, J* = 7.3	4.49	4.50	4.67	4.60	4.41	4.60	4.67	4.66
18^1	*d, J* = 6.95	1.56	1.56	1.74	1.71	1.61	1.74	1.74	1.86
20	*s*	8.55	8.57	8.92	8.89	8.74	8.93	8.84	8.86
21-NH	*(br,s)*			-1.33	-1.32	-0.89	-1.48	0.11	-1.30
23-NH	*(br,s)*			0.66	0.68	0.78	0.67	0.38	0.89

Table 2. ^{13}C-NMR chemical shifts of the compounds **1-8**

Carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	148.7	148.6	144.0	150.0	142.6	142.6	144.8	142.7
2	149.5	149.5	133.5	135.5	132.8	132.8	133.0	133.0
2^1	12.8	12.8	12.4	12.1	12.4	12.5	12.3	12.5
3	140.9	140.8	137.5	135.5	136.8	136.7	137.9	137.8
3^1	130.9	130.9	129.5	124.3	129.9	129.8	129.3	129.9
3^2	120.8	120.7	123.0	121.5	123.4	123.3	123.0	123.0
4	137.3	137.1	137.4	136.0	136.3	136.8	138.0	137.3
5	104.5	104.2	102.6	104.9	98.7	98.6	104.0	90.3
6	156.6	156.4	160.2	152.0	155.9	156.1	157.2	156.4
7	132.2	131.9	138.8	134.3	137.4	137.4	137.5	137.3
7^1	188.8	188.7	188.0	191.7	11.5	11.5	11.4	11.6
8	143.3	143.5	148.2	149.7	146.2	146.0	147.0	146.1
8^1	19.9	19.8	19.6	18.7	19.1	19.3	20.0	20.0
8^2	19.9	19.6	19.6	18.7	18.0	18.0	20.0	20.0
9	156.4	156.2	151.8	150.2	152.0	151.9	151.4	152.0
10	110.5	109.9	108.2	114.6	105.2	105.1	108.9	105.5
11	139.4	139.3	138.1	135.9	137.9	138.6	132.5	138.8
12	131.4	131.0	138.8	135.7	129.7	129.9	140.8	129.7
12^1	12.8	12.9	12.5	12.3	12.5	12.4	12.7	12.3
13	149.0	149.1	128.8	135.8	128.3	128.1	112.7	130.1
13^1	195.4	195.3	194.9	196.5	194.6	194.7	160.1	190.3
13^2	92.2	92.4	91.3	92.1	91.1	91.2	165.0	65.9
13^3	175.0	174.4	174.0	172.8	174.2	173.5		170.8
13^4	53.3	53.4	53.6	54.9	53.1	53.1		53.1
14	163.2	163.8	151.1	150.4	150.7	150.7	140.0	150.5
15	110.7	109.2	111.0	106.0	111.7	111.2	94.0	106.9
16	160.1	160.4	166.8	162.5	163.5	163.5	178.3	163.0
17	50.8	50.4	51.5	51.8	51.7	51.3	56.0	52.5
17^1	31.1	31.0	32.4	31.1	31.1	32.4	32.4	31.2
17^2	31.6	31.0	32.7	31.6	32.3	32.7	33.6	32.9
17^3	173.5	173.3	173.5	173.6	173.9	173.9	173.6	177.8
18	50.6	50.3	51.1	50.3	51.1	51.1	49.8	50.9
18^1	23.3	23.3	23.3	22.7	23.1	23.1	24.4	23.6
19	170.4	171.7	175.6	178.7	173.5	173.0	177.7	173.8
20	94.1	94.2	95.1	95.1	94.9	91.8	96.2	94.6