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## Alkaloids and Anthraquinones from Malaysian Flora

Nor Hadiani Ismail, Asmah Alias and Che Puteh Osman  
Universiti Teknologi MARA,  
Malaysia

### 1. Introduction

The flora of Malaysia is one of the richest flora in the world due to the constantly warm and uniformly humid climate. Malaysia is listed as 12<sup>th</sup> most diverse nation (Abd Aziz, 2003) in the world and mainly covered by tropical rainforests. Tropical rainforests cover only 12% of earth's land area; however they constitute about 50% to 90% of world species. At least 25% of all modern drugs originate from rainforests even though only less than 1% of world's tropical rainforest plant species have been evaluated for pharmacological properties (Kong, *et al.*, 2003). The huge diversity of Malaysian flora with about 12 000 species of flowering plants offers huge chemical diversities for numerous biological targets. Malaysian flora is a rich source of numerous class of natural compounds such as alkaloids, anthraquinones and phenolic compounds. Plants are usually investigated based on their ethnobotanical use. The phytochemical study of several well-known plants in folklore medicine such as *Eurycoma longifolia*, *Labisia pumila*, *Andrographis paniculata*, *Morinda citrifolia* and *Phyllanthus niruri* yielded many bioactive phytochemicals. This review describes our work on the alkaloids of *Fissistigma latifolium* and *Meiogyne virgata* from family Annonaceae and anthraquinones of *Renellia* and *Morinda* from Rubiaceae family.

### 2. The family Annonaceae as source of alkaloids

Annonaceae, known as *Mempisang* in Malaysia (Kamarudin, 1988) is a family of flowering plants consisting of trees, shrubs or woody lianas. This family is the largest family in the Magnoliales consisting of more than 130 genera with about 2300 to 2500 species. Plants of the family Annonaceae are well known as source of a variety of alkaloids (Cordell, 1981). Many alkaloids have important physiological effects on human and exhibit marked pharmacological activity which is useful as medicine. For examples, atropine is used widely as an antidote to cholinesterase inhibitors such as physostigmine. Morphine and codeine are narcotic analgesics and antitusive agent while caffeine, which occurs in coffee, tea and cocoa is a central nervous system stimulant. Caffeine is also used as cardiac and respiratory stimulant and besides as an antidote to barbiturate and morphine poisoning (Parker, 1997). The first report on phytochemical studies of alkaloids from Malaysian Annonaceae plants was on the leaves of *Desmos dasymachalus* which has led to the isolation of new 7-hydroxyaporphine, dasymachaline (Chan & Toh, 1985).

The phytochemical investigation of Malaysian Annonaceous plants for their alkaloidal content continue to flourish. Phytochemical survey of the flora of the Peninsula Malaysia and Sabah, with systematic screening for alkaloids resulted in reports on chemical constituents of several plants from Annonaceae illustrating great interest in this field (Teo, *et al.*, 1990). Lavault *et al.*, (1981) analysed the alkaloid content of three Annonaceae plants; *Disepalum pulchrum*, *Polyalthia macropoda* and *Polyalthia stenopetala* which led to the isolation of several isoquinoline compounds. Isolation of two new 7,7'-bisdehydroaporphine alkaloids; 7,7'-bisdehydro-*O*-methylisopiline and 7-dehydronornuciferine-7'-dehydro-*O*-methylisopiline from bark of *Polyalthia bullata* was reported by Connolly *et al.*, (1996). Kam (1999) reviewed the alkaloids derived from Malaysian flora in a book entitled chemical and biological approach of alkaloids.

In Malaysia, eight species of *Fissistigma* are known. They are *F. mobiforme*, *F. cylindrium*, *F. fulgens*, *F. kingii*, *F. lanuginosum*, *F. latifolium*, *F. munubriatum* and *F. kinabaluensis* (Nik Idris *et al.*, 1994). Not much has been reported on the phytochemical studies of *Fissistigma* species. The studies on the alkaloids from *Fissistigma fulgens* have led to the isolation of aporphine, oxoaporphine and protoberberine alkaloids. Liriodenine, anonaine, argentinine, discretamine and kikemanine were found from this species (Awang, *et al.*, 2000). The phytochemical work on alkaloidal composition of the Malaysian *Fissistigma munubriatum* by Saaid and Awang (2005) yielded two oxoaporphines, lanuginosine and liriodenine together with two tetrahydroprotoberberines, tetrahydropalmatine and discretine. We studied the alkaloids of *Fissistigma latifolium* and reported the isolation of nine alkaloids including a new aporphine compound (Alias *et al.*, 2010).

*Meiogyne cylindrocarpa*, *Meiogyne monosperma* and *Meiogyne virgata* are the only three *Meiogyne* species found in Malaysia. Only *Meiogyne virgata* was studied by Tadic *et al.* (1987). The sample collected from Mount Kinabalu, Sabah was reported to contain azafluorene alkaloid, kinabaline, together with liriodenine, cleistopholine and other aporphine alkaloids. Our work on *Meiogyne virgata* from Hulu Terengganu yielded nine alkaloids from aporphine, oxoaporphines and azaanthracene groups.

## 2.1 Alkaloids of *Fissistigma latifolium* and *Meiogyne virgata*

Since the last three decades, a large number of alkaloidal compounds have been isolated from some Annonaceae species. Tertiary and quaternary isoquinoline and quinoline alkaloids are pharmacologically important compounds commonly found in Annonaceae plants. Continuing our interest on this family of plants, we pursued phytochemical investigation on *Fissistigma latifolium* and *Meiogyne virgata*.

### 2.1.1 Alkaloids of *Fissistigma latifolium*

*Fissistigma latifolium* (Dunal) Merr. from the genus *Fissistigma* is a climbing shrub found in lowland forest of Malaysia, Sumatra, Borneo and Philippines (Verdout, 1976). The genus *Fissistigma* (Annonaceae) consists of about 80 species and is widely distributed in Asia and Australia (Sinclair, 1955). Several species of the genus *Fissistigma* have been used in Southeast Asia as traditional medicines (Perry, 1980). They have been used for muscular atrophy, hepatomegaly and hepatosplenomegaly (Kan, 1979). In Malaysia, the medicinal uses of *Fissistigma* species was briefly mentioned by Burkill as the treatment for childbirth, malaria, wounds, ulcer and rheumatism (Kamarudin, 1988).

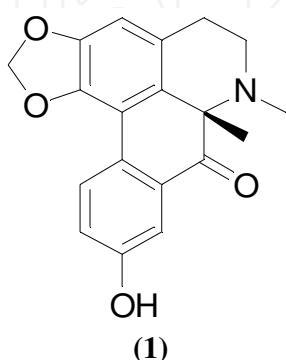


Fig. 1. *Fissistigma latifolium*

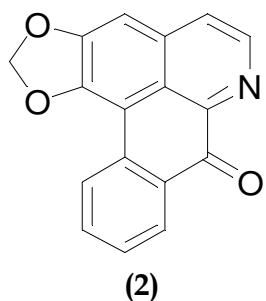
Previous studies on *F. fulgens* and *F. manubriatum* have resulted in the isolation of aporphine, oxoaporphine and protoberberine alkaloids. Similarly, the studies on alkaloids from *Fissistigma latifolium* led to the isolation of a new aporphine alkaloid, (-)-*N*-methylguattescidine **1** (Alias, *et al.*, 2010). This alkaloid, together with eight known alkaloids, namely liriodenine **2**, lanuginosine **3**, (-)-asimilobine **4**, dimethyltryptamine **5**, (-)-remerine **6**, (-)-anonaine **7**, columbamine **8** and lysicamine **9**, were obtained from the methanol extract of the bark of the plant. The new compound was characterized by analysis of spectroscopic methods such as NMR (Nuclear Magnetic Resonance), IR (Infrared) and GC-MS (Gas-Chromatography-Mass Spectrometry).

(-)-*N*-Methylguattescidine **1** exhibited a molecular formula of  $C_{19}H_{17}O_4N$  based on the HRESIMS spectrum (positive mode), which showed a pseudomolecular ion at  $m/z$  324.3581  $[M+H]^+$  (calcd. 324.3595). The UV spectrum showed an absorption band at 310 nm, suggesting the compound was an aporphine alkaloid with substitutions at position 1 and 2. The IR spectrum indicated the presence of C-H aromatic at 3056, C-O at 1266 and OH at 3409  $cm^{-1}$ , respectively. The absorption of methyl group appeared at 2945 and 2833. The  $^{13}C$ -NMR spectrum showed presence of 19 carbons. The signal at  $\delta$  198.0 ppm confirmed the presence of the carbonyl group, while the signal at  $\delta$  153.1 ppm is evidence for the oxygenated aromatic carbon. The DEPT spectrum revealed three methylene carbons at  $\delta$  26.9 ppm, 41.4 ppm and 96.9 ppm. Signal at  $\delta$  96.9 ppm is indicative of a methylenedioxy carbon. This is consistent with two doublets at  $\delta$  5.99 ppm ( $J = 1.2$  Hz) and  $\delta$  6.07 ppm ( $J = 1.2$  Hz) in the  $^1H$ -NMR spectrum for the protons of methylenedioxy group which is typically located at positions 1 and 2. The characteristic ABD aromatic signals of H-11, H-10 and H-8 of aporphine alkaloid were observed at  $\delta$  8.24 ppm ( $d$ ,  $J = 8.7$  Hz),  $\delta$  7.13 ppm ( $dd$ ,  $J = 8.7, 2.7$  Hz) and  $\delta$  7.39 ppm ( $d$ ,  $J = 2.7$  Hz), respectively. The  $^1H$ -NMR spectrum also exhibited an *N*-methyl signal at  $\delta$  2.34 ppm and another methyl group attached to C-6a gave a singlet at  $\delta$  1.52 ppm. The assignment of this methyl group at the 6a position is confirmed through its HMBC correlation with C-6a at  $\delta$  62.7 ppm, C-1b at  $\delta$  118.3 ppm and C-7 at  $\delta$  198.0 ppm. HMQC spectrum shows two cross peaks at  $\delta$  26.9 ppm (C-4) axis, represented the correlations of C-4 to H-4 ( $\delta$  2.55 ppm) and H-4' ( $\delta$  3.00 ppm). At  $\delta$  41.4 ppm (C-5) axis, two

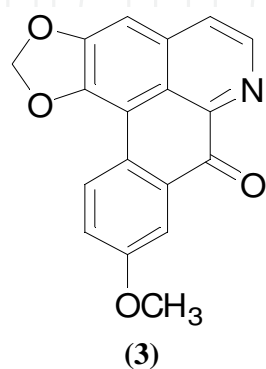
cross peaks showed the correlations between C-5 and H-5 ( $\delta$  2.99 ppm) and H-5' ( $\delta$  3.01 ppm). The quaternary carbon signals were assigned based on HMBC experiment. C-1a at  $\delta$  108.9 ppm, C-7a at  $\delta$  126.0 ppm and C-9 at  $\delta$  153.1 ppm were assigned based on their correlations with H-11 at  $\delta$  8.24 ppm, while C-1b at  $\delta$  118.3 ppm and C-2 at  $\delta$  143.2 ppm showed correlations with H-3 at  $\delta$  6.54 ppm. (-)-N-methylguattescidine, is a rare 6a-methylated-7-oxo-aporphine alkaloid, having only been previously reported by Reynald *et al.* in 1982. Presented below are structures and spectroscopic data of the isolated compounds.



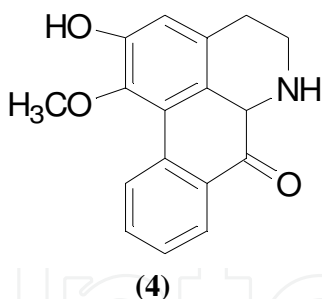
(-)-N-Methylguattescidine (**1**), yellow amorphous solid;  $[\alpha]^{30}_D$  :  $-20^\circ$  ( $c = 0.1 \text{ mg mL}^{-1}$ ,  $\text{CHCl}_3$ ); MS  $m/z$ : 324.1242,  $\text{C}_{19}\text{H}_{17}\text{O}_4\text{N}$ ; UV  $\lambda_{\text{max}}$  nm EtOH: 235, 310; IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3409, 1710, 1266;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm : 8.24 (1H, d,  $J = 8.7$  Hz, H-11), 7.39 (1H, d,  $J = 2.7$  Hz, H-8), 7.13 (1H, dd,  $J_o = 8.7$  Hz;  $J_m = 2.7$  Hz, H-10), 6.54 (1H, s, H-3), 6.07 (1H, d,  $J = 1.2$  Hz, H-2), 5.99 (1H, d,  $J = 1.2$  Hz, H-1), 3.52 (1H, m, H-11a), 3.01 (1H, m, H-5), 3.00 (1H, m, H-4), 2.99 (1H, m, H-5'), 2.55 (1H, m, H-4');  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ ppm : 153.1 (C-9), 143.2 (C-2), 138.8 (C-1), 126.0 (C-7a), 125.3 (C-3a), 123.1 (C-11a), 122.7 (C-11), 122.2 (C-10), 118.3 (C-1b), 110.3 (C-8), 108.9 (C-1a), 103.9 (C-3), 96.9 (O-CH<sub>2</sub>-O), 62.7 (C-6a), 41.4 (C-5), 34.1 (N-CH<sub>3</sub>), 26.9 (C-4), 25.0 (CH<sub>3</sub>).



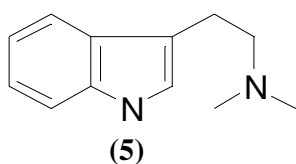
Liriodenine (**2**), yellow needles; MS  $m/z$  : 275,  $\text{C}_{17}\text{H}_9\text{O}_3\text{N}$ ; UV  $\lambda_{\text{max}}$  nm EtOH : 215, 246, 268, 395, 412; IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  : 3054, 1726, 1421, 1265;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm : 8.9 (1H, d,  $J = 5.1$  Hz, H-5), 8.66 (1H, dd,  $J_o = 7.2$  Hz;  $J_m = 1.2$  Hz, H-11), 8.59 (1H, dd,  $J_o = 7.8$  Hz;  $J_m = 1.2$  Hz, H-8), 7.79 (1H, d,  $J = 5.1$  Hz, H-4), 7.76 (1H, td,  $J_o = 7.8$  Hz; 7.2 Hz;  $J_m = 1.5$  Hz, H-10), 7.59 (1H, td,  $J_o = 7.8$  Hz; 7.2;  $J_m = 1.2$  Hz, H-9), 7.16 (1H, s, H-3), 6.40 (2H, s, O-CH<sub>2</sub>-O);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ ppm : 151.7 (C-2), 147.9 (C-1), 146 (C-6a), 145.4 (C-3a), 144.9 (C-5), 135.7 (C-1a), 133.9 (C-10), 132.9 (C-7a), 131.3 (C-11a), 128.8 (C-8), 128.6 (C-9), 127.4 (C-11), 124.2 (C-4), 108.2 (C-1b), 103.3 (C-3), 102.4 (O-CH<sub>2</sub>-O), 182.4 (C-7).



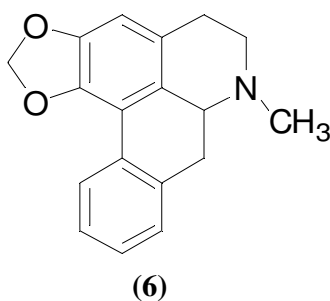
Lanuginosine (**3**), yellow needles; MS  $m/z$  : 305,  $\text{C}_{18}\text{H}_{11}\text{O}_4\text{N}$ ; UV  $\lambda_{\text{max}}$  nm EtOH : 246, 271, 315, 258, 283, 334; IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  : 3055, 2987, 2306, 1712, 1635, 1363, 1265, 1046, 896;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  ppm : 8.85 (1H, d,  $J = 5.4$  Hz, H-5), 8.58 (1H, d,  $J_o = 9.0$  Hz, H-11), 8.04 (1H, d,  $J = 3$  Hz, H-8), 7.79 (1H, d,  $J = 5.4$  Hz, H-4), 7.32 (1H, dd,  $J_o = 9.0$  Hz;  $J_m = 3$  Hz, H-10), 7.17 (1H, s, H-3), 6.47 (2H, s, O - CH<sub>2</sub> - O);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75MHz)  $\delta$  ppm : 158.0 (C-9), 151.0 (C-2), 146.0 (C-1), 144.9 (C-5), 144.0 (C-6a), 136.0 (C-3a), 133.0 (C-7a), 131.9 (C-1b), 129.1 (C-11), 126.2 (C-11a), 124.3 (C-4), 122.6 (C-10), 110.2 (C-8), 109.0 (C-1a), 102.3 (C-3), 55.8 (OCH<sub>3</sub>), 102.5 (O - CH<sub>2</sub> - O), 182.0 (C-7).



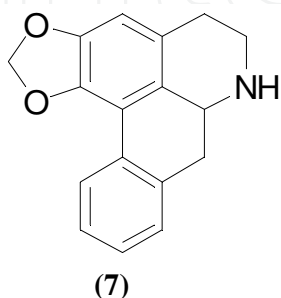
Asimilobine (4), brownish amorphous; MS  $m/z$  : 267,  $C_{17}H_{17}O_2N$ ; UV  $\lambda_{max}$  nm EtOH : 274, 308; IR  $\nu_{max}$   $cm^{-1}$  : 3390, 1675, 1600, 1225;  $^1H$  NMR ( $CDCl_3$ , 300MHz)  $\delta$  ppm : 8.30 (1H, d,  $J = 7.8$  Hz, H-11), 7.36 - 7.25 (3H, m, H-8, H-9, H-10), 6.73 (1H, s, H-3), 3.92 (1H, m, H-6a), 3.50 (1H, m, H-5'), 3.08 (1H, d, H-4'), 3.04 (1H, d, H-5), 2.99 (1H, m, H7), 2.85 (1H, m, H7), 2.74 (1H, d, H-4), 3.61 (3H, s,  $OCH_3$ ), 2.00 (1H, s, N-H);  $^{13}C$  NMR ( $CDCl_3$ , 75MHz)  $\delta$  ppm : 148.6 (C-2), 143.0 (C-1), 135.6 (C-7a), 131.7 (C-11a), 129.4 (C-16), 128.1 (C-3a), 127.7 (C-8), 127.4 (C-10), 127.3 (C-9), 127.2 (C-11), 125.5 (C-1a), 114.6 (C-3), 53.4 (C-6a), 42.8 (C-5), 36.7 (C-7), 28.2 (C-4), 60.4 ( $OCH_3$ ).



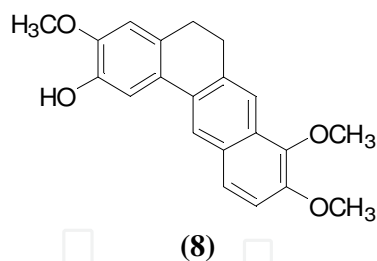
Dimethyltryptamine (5), reddish amorphous; MS  $m/z$  : 188,  $C_{12}H_{16}N_2$ ; UV  $\lambda_{max}$  nm EtOH : 240, 252; IR  $\nu_{max}$   $cm^{-1}$  : 3945, 3055, 2305, 1634, 1422, 1265, 1046, 896;  $^1H$  NMR ( $CDCl_3$ , 300MHz)  $\delta$  ppm : 7.60 (1H, d,  $J_o = 5.7$  Hz, H-7), 7.38 (1H, d,  $J_o = 7.1$  Hz, H-4), 7.20 (1H, td,  $J_o = 6.9$ Hz;  $J_m$ 0.9 Hz, H-5), 7.12 (1H, td,  $J_o = 6.9$  Hz;  $J_m = 0.9$  Hz, H-6), 3.03 (2H, m, H-8), 2.80 (2H, m, H-9), 8.28 (1H, brs, N-H), 2.49 (6H, s, 2( $CH_3$ ));  $^{13}C$ NMR ( $CDCl_3$ , 75MHz)  $\delta$  ppm : 136.0 (C-7), 127.0 (C-3a), 122.0 (C-6), 121.7 (C-2), 119.2 (C-5), 118.7 (C-4), 59.4 (C-9), 44 (C-3), 22.9 (C-8), 44.9 (2 $CH_3$ ).



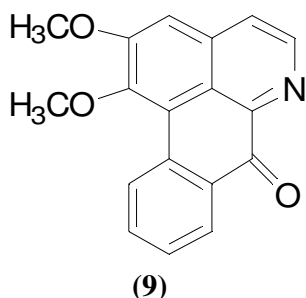
Remerine (6), yellow amorphous; MS  $m/z$  : 279,  $C_{18}H_{17}O_2N$ ; UV  $\lambda_{max}$  nm EtOH : 234, 264; IR  $\nu_{max}$   $cm^{-1}$  : 1401, 1361, 1053, 942;  $^1H$  NMR ( $CDCl_3$ , 300MHz)  $\delta$  ppm : 8.09 (1H, d,  $J_o = 7.5$  Hz, H-11), 7.34 - 7.24 (3H, m, H-8, H-9, H-10), 6.59 (1H, s, H-3), 4.000 (1H, m, H-6a), 3.4 (1H, m, H-5'), 3.10 (1H, m, H-4'), 3.00 (1H, m, H-5), 2.90 (1H, m, H-7'), 2.80 (2H, m, H-7, H-4), 6.11 (1H, d,  $J_m = 1.2$  Hz, CH-O), 5.96 (1H, d,  $J_o = 1.2$  Hz, CH-O), 2.62 (3H, s,  $CH_3$ );  $^{13}C$  NMR ( $CDCl_3$ , 75MHz)  $\delta$ ppm : 146.7 (C-2), 142.8 (C-1), 136.3 (C-7a), 128.1 (C-8), 128.0 (C-1b), 127.6 (C-9), 127.0 (C-10), 127.0 (C-11), 125.4 (C-3a), 126.5 (C-1a), 126.0 (C-11a), 125.4 (C-3a), 62.4 (C-6a), 53.3 (C-6a), 43 (C-5), 36.9 (C-7), 28 (C-4), 100.7 (O -  $CH_2$  - O), 39.0 ( $CH_3$ ).



Anonaine (7), yellow amorphous; MS  $m/z$  : 265,  $C_{17}H_{13}O_2N$ ; UV  $\lambda_{max}$  nm EtOH : 234, 272, 315; IR  $\nu_{max}$   $cm^{-1}$  : 1040, 945;  $^1H$  NMR ( $CDCl_3$ , 300MHz)  $\delta$  ppm : 8.09 (1H, d,  $J_o = 7.5$  Hz, H=11), 7.36 - 7.19 (3H, m, H-8, H-9, H-10), 6.6 (1H, s, H-3), 4.04 (1H, dd, H-6a), 3.48 (1H, m, H-5'), 3.1 (1H, m, H-4'), 3.07 (1H, m, H-5), 3.02 (1H, m, H-7'), 6.12 (1H, d,  $J_m = 1.5$ , CH - O), 5.97 (1H, d,  $J_m = 1.5$ , CH - O);  $^{13}C$  NMR ( $CDCl_3$ , 75MHz)  $\delta$  ppm : 147.0 (C-2), 143.0 (C-1), 135.4 (C-7a), 131.4 (C-11a), 129.0 (C-1b), 128.0 (C-3a), 127.8 (C-8), 127.7 (C-9), 127.0 (C-10), 126.1 (C-11), 116.3 (C-1a), 53.6 (C-6a), 43.6 (C-5), 37.4 (C-7), 29.6 (C-4), 100.6 (O -  $CH_2$  - O).



Columbamine (**8**), red amorphous solid; MS  $m/z$  : 338,  $C_{20}H_{20}O_4N$ ; UV  $\lambda_{max}$  nm EtOH : 206, 225, 265, 345; IR  $\nu_{max}$   $cm^{-1}$  : 3390, 1600;  $^1H$  NMR ( $CDCl_3$ , 300MHz)  $\delta$  ppm : 9.00 (1H, s, H-8), 8.08 (1H, s, H-13), 7.65 (1H, d,  $J_o = 9.0$  Hz, H-11), 7.61 (1H, d,  $J_o = 8.7$  Hz, H-12), 7.27 (1H, s, H-1), 6.79 (1H, s, H-4), 4.68 (2H, t,  $J_o = 6.6$  Hz; 6.3 Hz, H-6), 3.18 (2H, t,  $J_o = 6.0$  Hz, H-5), 4.02 (3H, OCH<sub>3</sub>), 3.99 (3H, OCH<sub>3</sub>), 3.92 (3H, OCH<sub>3</sub>). ;  $^{13}C$  NMR ( $CDCl_3$ , 75MHz)  $\delta$  ppm : 163.0 (C-10), 151.0 (C-3), 150.0 (C-4a), 149.0 (C-2), 142.0 (C-9), 140.0 (C-8), 139.0 (C-11), 132.0 (C-14), 129.0 (C-12a), 126.0 (C-1a), 123.3 (C-12), 120.0 (C-13), 119.0 (C-8a), 111.0 (C-4), 108.0 (C-1), 56.0 (C-6), 27.0 (C-5), 60.0 (OCH<sub>3</sub>), 58.0 (OCH<sub>3</sub>), 57.0 (OCH<sub>3</sub>).



Lysicamine (**9**), yellow amorphous; MS  $m/z$  : 291,  $C_{18}H_{13}O_3N$ ; UV  $\lambda_{max}$  nm EtOH : 214, 250, 255, 261, 319; IR  $\nu_{max}$   $cm^{-1}$  : 1675, 1600, 1225;  $^1H$  NMR ( $CDCl_3$ , 300MHz)  $\delta$  ppm : 9.10 (1H, d,  $J_o = 5.1$  Hz, H-11), 8.70 (1H, d,  $J_o = 6.9$  Hz, H-5), 8.48 (1H, dd,  $J_o = 7.5$  Hz;  $J_m = 1.5$  Hz, H-8), 7.76 (1H, td,  $J_o = 7.2$  Hz;  $J_m = 1.5$  Hz, H-10), 7.7 (1H, d,  $J_o = 6.9$  Hz, H-4), 7.55 (1H, td,  $J_o = 7.2$  Hz;  $J_m = 1.2$  Hz, H-9), 7.24 (1H, s, H-3), 4.05 (3H, s, OCH<sub>3</sub>), 3.97 (3H, s, OCH<sub>3</sub>);  $^{13}C$  NMR ( $CDCl_3$ , 75MHz)  $\delta$  ppm : 156.7 (C-6a), 152.0 (C-2), 145.2 (C-1), 139.0 (C-5), 135.3 (C-3a), 134.7 (C-11a), 132.0 (C-7a), 130.9 (C-10), 125.7 (C-9), 122.0 (C-1b), 119.6 (C-1a), 108.7 (C-3), 65.1 (OCH<sub>3</sub>), 56.8 (OCH<sub>3</sub>), 182.5 (C=O).

Table 1.

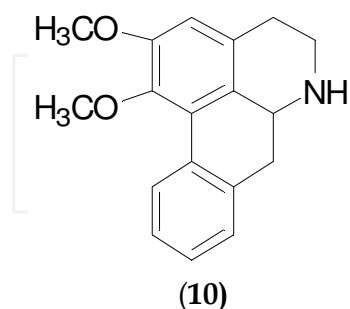
### 2.1.1 Alkaloids of *Meiogyne virgata*

*Meiogyne virgata* is a rainforest tree grows in Peninsular Malaysia, Borneo, Java and Sumatra. The genus *Meiogyne* (Annonaceae) consists of about 24 species and widely distributed in Indo-china, Thailand, Peninsular Malaysia, Sumatra, Java, Borneo and the Philippines. There is no formal report on the traditional uses of *Meiogyne virgata* in Malaysia. However, being an alkaloid rich species, it could be useful medicinally.

We have conducted phytochemical work on *Meiogyne virgata*. Six of the aporphine alkaloids in *Fissistigma latifolium* were also found in *Meiogyne virgata* collected from the Peninsular Malaysia. Isolation and purification of alkaloids from the bark of *Meiogyne virgata* afforded nine alkaloids; four oxoaporphines, liriodenine **2**, lanuginosine **3**, asimilobine **4** and lysicamine **9**; four aporphines, anonaine **7**, remerine **6**, norruciferine **10** and norushinsunine **11**; and one azaanthracene alkaloid, cleistopholine **12**.

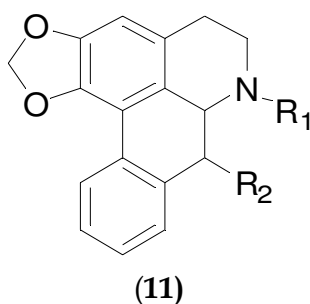
Most of the compounds are yellowish or colorless hygroscopic liquid at room temperature while impure samples will appear brownish. They have low solubility in water but dissolve well in methanol, chloroform, acetone, dichloromethane and other common organic solvent. They are also soluble in dilute acid as the protonated derivative. The melting point of these type of compounds in range 100-300 °C.

Most of oxoaporphine and aporphine alkaloids showed IR spectra typified by the 7-oxo group with absorption band in the 1635-1660  $\text{cm}^{-1}$  region. The UV spectra data for these type of compounds are quite characteristic for the skeletal type. There is indication that they may also be diagnostic for a particular oxygenation pattern. For example, 1, 2-methylenedioxy

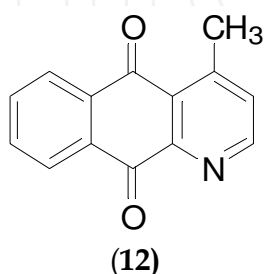


Nornuciferine (**10**), Colourless crystalline solid; MS  $m/z$  : 281 ( $M^+$ ); UV  $\lambda_{\text{max}}$  nm EtOH : 234, 272, 315; IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  : 1040, 945

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm : 8.39 (1H, *d*,  $J=7.8$  Hz, H-11), 7.33-7.20 (3H, *m*, H-8, H-9, H-10), 6.65 (1H, *s*, H-3), 3.98 (1H, *dd*,  $J=13.4; 5.2$  Hz, H-6a), 3.41 (1H, *dd*,  $J=12.3; 6.3$  Hz, H-5'), 3.90 (3H, *s*, OMe-2), 3.68 (3H, *s*, OMe-1), 3.08 (1H, *dd*,  $J=13.2$  Hz, H-4), 3.04 (1H, *td*,  $J=12.3; 5.1$  Hz, H-5), 2.85 (1H, *dd*,  $J=13.4; 5.2$  Hz, H-7'), 2.68 (1H, *dd*,  $J=13.2; 6.0$  Hz, H-4'), 2.64 (1H, *t*,  $J=13.4$  Hz, H-7);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  ppm : 152.3 (C-2), 145.2 (C-1), 135.0 (C-7a), 132.1 (C-1b), 132.1 (C-11a), 131.2 (C-3a), 128.4 (C-8), 127.8 (C-10), 127.4 (C-9), 127.1 (C-11), 126.6 (C-1a), 111.8 (C-3), 60.3 (OMe-1), 55.9 (OMe-2), 53.6 (C-6a), 43.0 (C-5), 37.2 (C-7), 29.7 (C-4).



Norushinsunine (**11**), Colourless crystalline solid; MS  $m/z$  : 281; UV  $\lambda_{\text{max}}$  nm EtOH : 217, 247, 252, 259, 273, 319; IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  : 3488, 3355, 1574, 1215;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  ppm : 8.16 (1H, *dd*,  $J=7.2; 1.2$  Hz, H=11), 7.45 (1H, *td*,  $J=8.7; 1.2$  Hz, H-10), 7.40 (1H, *dd*,  $J=8.1; 0.9$  Hz, H-8), 7.34 (1H, *td*,  $J=7.2; 1.2$  Hz, H-9), 6.59 (1H, *s*, H-3), 6.11 (1H, *d*,  $J=1.5$  Hz, O -  $\text{CH}_2$  - O), 5.95 (1H, *d*,  $J=1.2$  Hz, O -  $\text{CH}_2$  - O), 4.61 (1H, *d*,  $J=3.0$  Hz, H-7), 4.06 (1H, *d*,  $J=3.3$  Hz, CH - O), 3.37 (1H, *ddd*,  $J=5.0; 3.9; 1.2$  Hz, H-4'), 2.68 (1H, *dd*,  $J=16.2; 3.9$  Hz, H-4);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75MHz)  $\delta$  ppm : 147.1 (C-1), 142.6 (C-2), 135.6 (C-1a), 130.3 (C-7a), 129.4 (C-9), 129.1 (C-3a), 123.6 (C-1b), 115.6 (C-11a), 108.4 (O -  $\text{CH}_2$  - O), 71.0 (C-7), 57.2 (C-6a), 43.1 (C-5), 29.2 (C-4).



Cleistopholine (**12**), yellow glassy solid; MS  $m/z$  : 281 ( $M^+$ ); UV  $\lambda_{\text{max}}$  nm EtOH : 234, 272, 315; IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  : 1040, 945;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm : 8.95 (1H, *d*,  $J=4.8$  Hz, H-2), 8.31 (1H, *dd*,  $J=8.5; 2.2$  Hz, H-5), 8.21 (1H, *dd*,  $J=8.5; 2.2$  Hz, H-8), 7.79 (1H, *m*, H-6), 7.79 (1H, *m*, H-7), 2.89 (1H, *s*, CH<sub>3</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  ppm : 184.7 (C-9), 181.9 (C-10), 153.4 (C-2), 151.6 (C-4), 150.1 (C-9a), 134.6 (C-7), 134.2 (C-6), 132.6 (C-10a), 131.2 (C-3), 129.1 (C-4a), 127.4 (C-5), 127.2 (C-8), 22.8 (CH<sub>3</sub>).

Table 2.



derivative in compound **2** gives increase to a bathochromic shift in the 235-250 nm bands on comparison with the corresponding compound **9**. The addition of acid will give a substantial bathochromic shift of the longest-wavelength band. In oxoaporphine and aporphine, position 1 and 2 are constantly oxygenated. It is frequent to find further oxygen substituent at C-9, C-10 and C-11 and occasionally at C-8. Other than that, H-4 and H-5 will give a characteristic AB system with doublet of doublet at about 7.6 ppm and 8.7 ppm with a coupling constant about 5.4 Hz. The small *J* value is due to the adjacent of electronegative nitrogen atom. The methylenedioxy group gives singlet peak at about 6.0 ppm due to the inductive effect caused by existence of the neighboring C-7 carbonyl. The C-11 proton usually the most deshielded and the C-3 protons always appeared at a higher field than the aromatic hydrogen (Cordell, 1981). Presented below are structures and spectroscopic data of the isolated compounds.

### 3. The family of Rubiaceae as source of anthraquinones

Rubiaceae is among the largest flowering plants family comprising of 450 genera and 13,000 species. In Malaysia, 70 genera and 555 species of Rubiaceae plants were reported (Wong, 1989). Most Rubiaceae plants are shrubs or small trees and infrequently herbs (Hutchinson, 1973). Rubiaceae plants are distributed worldwide but they are mainly tropical. They are easily recognized at family level by decussate, entire leaves, presence of stipules, actinomorphic flowers and inferior ovary.

Rubiaceae plants are known to accumulate substantial amount of anthraquinones particularly in the roots (Han, *et al.*, 2001). Anthraquinones containing plants are used traditionally for various ailments and health complaints such as diarrhea, loss of appetite, fever, wounds and cancer. The plant extracts are used in form of poultice, lotion and decoction from various plant parts. *Morinda*, *Hedyotis*, *Prismatomeris* and *Rennellia* are among anthraquinone containing-genera that are widely used in Malaysian traditional medicine (Ismail, *et al.*, 1997; Jasril, *et al.*, 2003; Ahmad, *et al.*, 2005; Lajis, *et al.*, 2006; Osman, *et al.*, 2010).

*Morinda* comprises of approximately 80 species, distributed worldwide in tropical areas. It is considered to be highly nutritious plant and is used as traditional medicine. In Malaysia *M. citrifolia* and *M. elliptica* are widely used. The roots of *M. elliptica* are used to treat jaundice and gastric complaints and the leaves are used to treat flatulence and fever. *Prismatomeris* and *Hedyotis* species on the other hand are recorded in various traditional medicine systems such as Traditional Chinese Medicine. Several well-known *Prismatomeris* species used in folk medicine in Malaysia are *P. glabra* and *P. malayana*. *P. glabra* is claimed to be aphrodisiac and widely used in the east coast of Malaysia. *P. malayana* contained the anthraquinones, rubiadin and rubiadin-1-methyl ether (Lee, 1969). *Hedyotis* plants are generally consumed as tonic or febrifuge for treatment of diarrhea and dysentery (Lajis, *et al.*, 2006). Several species of *Hedyotis* native to Malaysia are *H. capitellata*, *H. herbaceae*, *H. dichotoma*, *H. diffusa* and *H. verticillata*. Besides anthraquinones, *Hedyotis* also contain  $\beta$ -carboline alkaloids, flavonoids and triterpenes. *Rennellia* is another small genus of Rubiaceae family. Consists of shrubs and small trees, the plants may be found in lowland tropical rainforest of Peninsular Malaysia and Sumatra. *R. elliptica*, is used for general health improvements and dubbed as Malaysian Ginseng most likely due to the appearance of its yellow roots.

Anthraquinones of the Malaysian Rubiaceae are generally of the *Rubia* type. Rings A and B of the anthraquinone skeleton are biosynthetically derived from chorismic acid and  $\alpha$ -ketoglutarate *via* *o*-succinylbenzoic acid, whereas ring C is formed from isopentenyl diphosphate *via* the terpenoid pathway (Han, *et al.*, 2001). Chorismate is first converted to isochorismate, and then to *o*-succinylbenzoic acid (OSB) in the presence of  $\alpha$ -ketoglutarate and thiamine diphosphate. OSB is activated at the aliphatic carboxyl group to produce an OSB-CoA ester. It is the ring closure of OSB-CoA which results in the formation of 1,4-dihydroxy-2-naphthoic acid (DHNA) leading to ring A and B. The prenylation of DHNA at C-3, leads to naphthoquinol or naphthoquinone. The ring C formation is a consequence of the cyclization *via* C-C bond between the aromatic ring of the naphthoquinone and an isoprene unit, isopentenyl diphosphate (IPP) or 3,3-dimethylallyl diphosphate (DMAPP).

Of the anthraquinone from Malaysian Rubiaceae are substituted only on ring C while the remaining are substituted on both ring A and ring C. Anthraquinones from genus *Morinda* are typically substituted at C-1, C-2, and C-5, C-6 or C-7, C-8 and C-1, C-2 and C-3

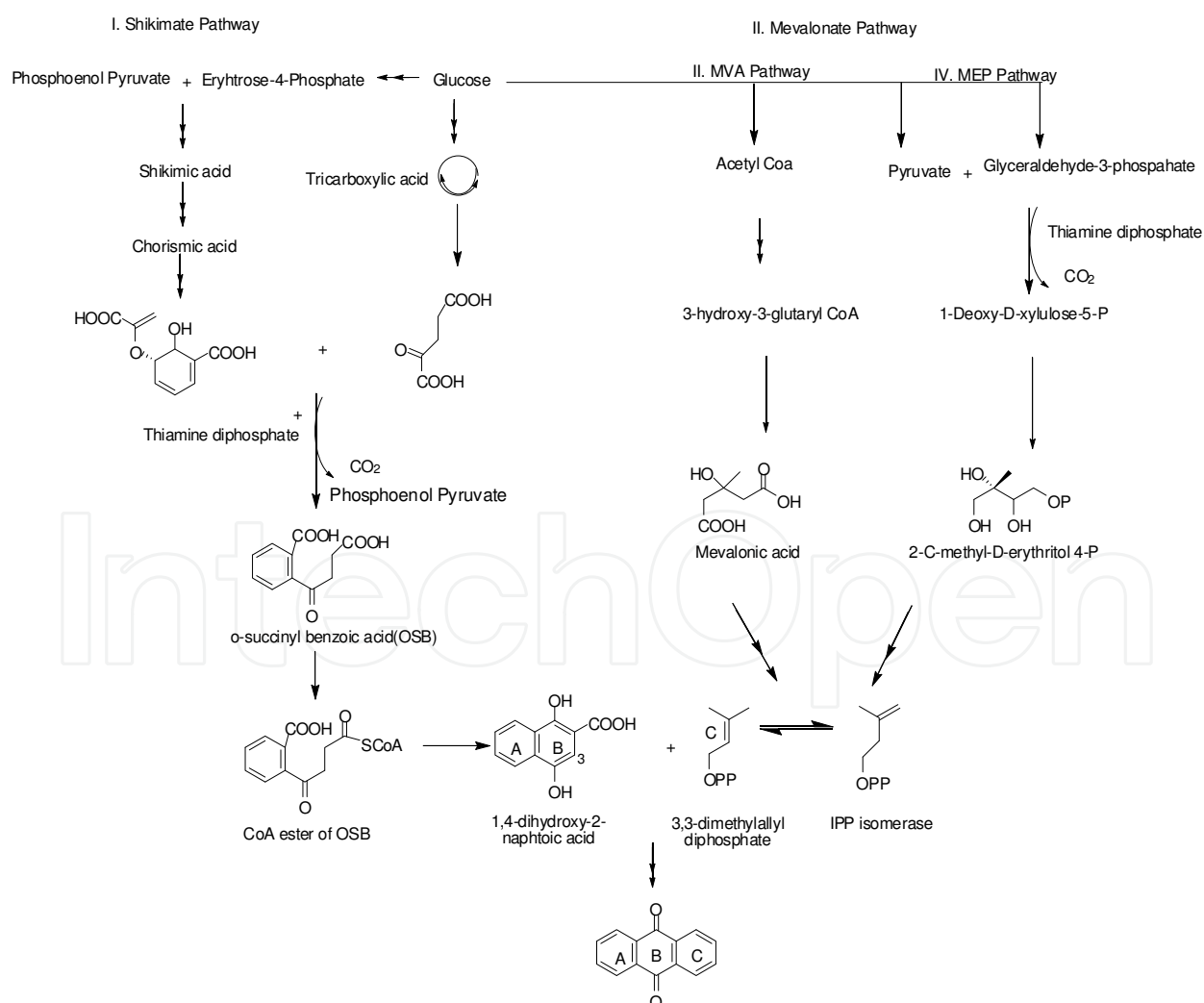


Fig. 2. Biosynthetic Pathway of Anthraquinones

meanwhile anthraquinones from *Hedyotis* are differed by rare substitution at C-1, C-2 and C-4. Anthraquinones from *Hedyotis* displayed wide structural variation. *H. capitellata* contains furanoanthraquinones (Ahmad, *et al.*, 2005) and *H. dichotoma* was reported to contain both 9,10- and 1,4-anthraquinone (Hamzah & Lajis, 1998). Genus *Rennellia* is closely related to *Morinda* and anthraquinones reported from *R. elliptica* are similar to those from genus *Morinda* (Osman *et al.*, 2010). One particular difference is the occurrence of anthraquinone with methyl substitution at C-6 which is characteristic to this plant.

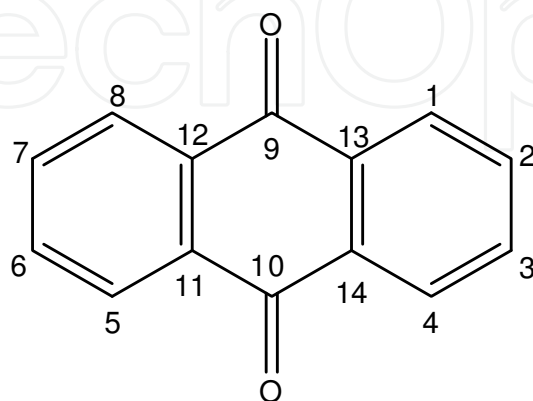


Fig. 3. Basic Skeleton of Anthraquinones

There are several characteristic spectroscopic data that distinguished anthraquinones from other types of compounds. In mass spectra, the major fragmentations are due to two consecutive loss of carbonyls,  $[M-CO]^+$  and  $[M-2CO]^+$ . In the IR spectra, the unchelated carbonyl only viewed as one sharp stretching band at  $1670\text{ cm}^{-1}$  due to symmetrical character of 9,10-anthraquinone (Derksen, *et al.*, 2002). Anthraquinones substituted with hydroxyl at *peri* position displayed two carbonyl absorption bands at about  $1670\text{ cm}^{-1}$  and  $1630\text{ cm}^{-1}$ . Anthraquinones give several characteristic UV absorptions at 265-280 nm and 285-290 nm due to electron transfers bonds of benzoid chromophore and at 430-437 nm due local excitation of quinoid carbonyls. The location hydroxyl substituent can be distinguished by observing the absorption maxima in UV spectra. Addition of dilute sodium hydroxide solution caused bathchromic shift of absorption maxima. The shift is useful in distinguishing substitution pattern of polyhydroxyanthraquinones. Proton NMR spectra of 9,10-anthraquinones shows typical  $A_2B_2$  substitution pattern of *ortho*-substituted aromatic ring. An unsubstituted anthraquinone ring can be easily distinguished by the presence of at least two sets of multiplets at ca.  $\delta_H$  8.10 and ca.  $\delta_H$  7.20 in the aromatic region. Anthraquinones substituted at both rings A and C will give several doublets in the aromatic region. The two carbonyl groups in the molecule can be easily distinguished if hydroxyl substituents present in *para* position. Hydroxyl groups adjacent to carbonyl can be seen as sharp singlets much downfield at  $\delta_H$  12-14 due to strong intramolecular hydrogen bonding to the adjacent carbonyl. The presence of hydroxyl adjacent to carbonyl cause significant shift of carbonyl carbon resonance to downfield region at 186-189 ppm.

### 3.1 Anthraquinones of *Rennellia elliptica* Korth.

*R. elliptica* Korth. was also previously known as *R. elongata* (King & Gamble) Ridl. It is a shrub of about 2 m tall. This shrub can be found in lowland to hill forest to c. 500m above sea level. *R. elliptica* Korth. is widely distributed from Southern Myanmar to West Malaysia.

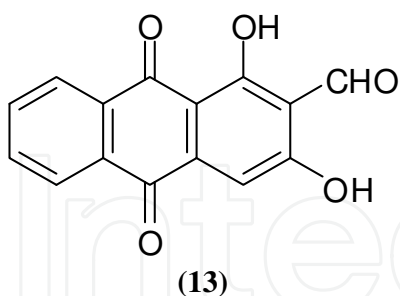
*R. elliptica* is used for general health improvements and dubbed as Malaysian Ginseng may be due to the appearance of its yellow roots. Its medicinal uses were documented as treatment of body aches, after-birth tonic and aphrodisiac (Mat Salleh & Latiff, 2002). The root extract of *R. elliptica* was reported to be antimalarial (Osman, *et al.*, 2010) and antioxidant (Ahmad, *et al.*, 2010). Further study is warranted to investigate the antimalarial potential of roots of *R. elliptica*.



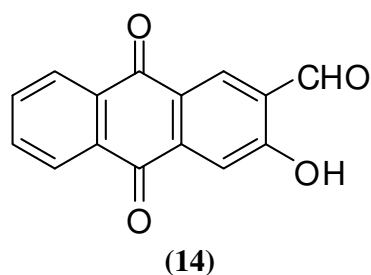
Fig. 4. *Rennellia elliptica* Korth

Phytochemical studies of the roots of *R. elliptica* Korth. resulted a new anthraquinone 1,2-dimethoxy-6-methyl-9,10-anthraquinone **18**, along with ten known ones. The known anthraquinones were nordamnacanthal **13**, 2-formyl-3-hydroxy-9,10-anthraquinone **14**, damnacanthal **15**, 1-hydroxy-2-methoxy-6-methyl-9,10-anthraquinone **16**, lucidin- $\omega$ -methyl ether **17**, 3-hydroxy-2-methoxy-6-methyl-9,10-anthraquinone **19**, rubiadin **20**, 3-hydroxy-2-methyl-9,10-anthraquinone **21**, rubiadin-1-methyl ether **22** and 3-hydroxy-2-hydroxymethyl-9,10-anthraquinone **23**.

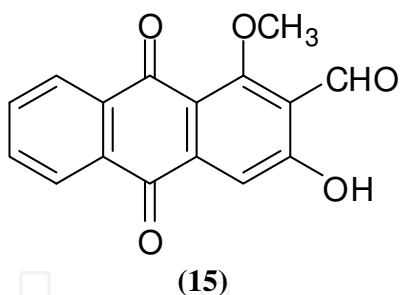
Anthraquinone **18**, 1,2-dimethoxy-6-methyl-9,10-anthraquinone, isolated for the first time as bright yellow amorphous solid. The HREIMS of **18** displayed a  $[M + H]^+$  peak at 283.0968 [calc 283.3067] suggesting a molecular formula of  $C_{17}H_{14}O_4$ . The absorption maxima in the UV spectrum were observed at 373, 341 and 257 nm, indicative of an anthraquinone moiety. The IR spectrum did not show presence of chelated carbonyl and hydroxyl groups. The  $sp^2$  C-H stretch for the aromatic ring was observed at 3,081  $cm^{-1}$ . With the exception of the sharp singlet in the downfield region for the hydrogen-bonded hydroxyl group, the  $^1H$  NMR spectrum resembles that of compound **16**, suggesting a similar substitution pattern. Splitting pattern of the five aromatic proton signals suggested substitutions on both rings. Two overlapping doublets centered at  $\delta_H$  8.17 are due to H-8 ( $d$ ,  $J = 7.8$  Hz) and H-4 ( $d$ ,  $J = 8.7$  Hz), the *peri*-hydrogens. A doublet at  $\delta_H$  7.28 ( $J = 8.7$  Hz) is due to H-3, meanwhile H-7 gave another doublet of doublet at  $\delta_H$  7.58 ( $J_o = 7.8$  Hz,  $J_m = 1.7$  Hz). These assignments were confirmed by their respective correlations in the COSY spectrum. H-5 resonated as a singlet at 8.06 ppm. In addition, two sharp singlets at  $\delta_H$  2.53 (3H,  $s$ ) and 4.02 (6H,  $s$ ) due to a methyl and two methoxy groups, respectively, were also observed. The location of the methoxy groups were established at C-1 and C-2 of ring C based on its NOE correlation with H-3. Thus, the only possible location for the methyl substituent is at C-6. This assignment was confirmed through NOE correlations of the methyl group with H-5 and H-7. The placement of methyl group at C-6 was further confirmed by HMBC experiment



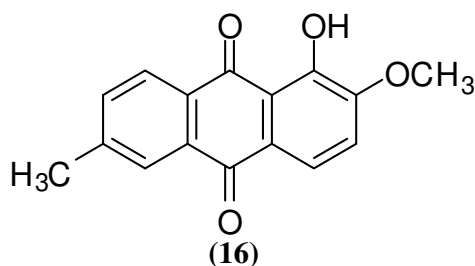
Nordamnacanthal. (13) Orange crystals. Mps 216-219 ° [lit. 220 ° C (Me<sub>2</sub>CO) Chang (1984)]. UVλ<sub>max</sub> EtOH nm: 421, 295, 259. UVλ<sub>max</sub> EtOH/ -OH nm: 512, 357, 283. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3460, 1646, 1627, 1382. MS m/z 268 [M<sup>+</sup>], 240, 212, 184, 138. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz): 14.05 (1H, s, 1-OH), 12.70 (1H, s, 3-OH), 10.52 (1H, s, 2-CHO), 8.30 (2H, m, H-5, H-8), 7.88 (2H, m, H-6, H-7), 7.36 (1H, s, H-4). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): 193.9 (2-CHO), 186.8 (C=O, C-9), 181.4 (C=O, C-10), 169.2 (C-OH, C-1), 168.1 (C-OH, C-3), 139.1 (C-2), 134.8 (C-7), 134.7 (C-6), 133.3 (C-14), 133.2 (C-13), 127.8 (C-8), 127.0 (H-5), 112.1 (C-14), 109.4 (C-4), 109.1 (C-13)



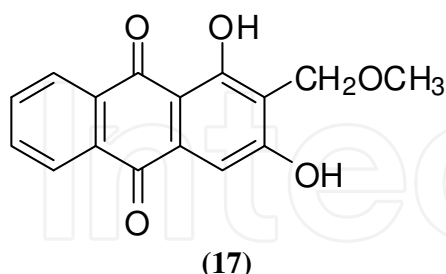
3-Formyl-2-hydroxy-9,10-anthraquinone (14). Bright orange needle crystals. Mps 212-214 ° C [259-260 ° C, Rath et al. (1995)]. UVλ<sub>max</sub> EtOH nm: 380, 277, 246. UVλ<sub>max</sub> EtOH/ -OH nm: 466, 392, 310, 254. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3467, 1655, 1657, 1564. MS m/z 252 [M<sup>+</sup>], 229, 206, 167, 139. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz): 11.45 (1H, s, 3-OH), 10.17 (1H, s, 2-CHO), 8.68 (1H, s, H-4), 8.35 (2H, m, H-5, H-8), 7.88 (2H, m, H-6, H-7), 7.86 (1H, s, H-1). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): 196.8 (2-CHO), 181.0 (C=O, C-9, C-10), 165.3 (C-OH, C-3), 139.1, 134.8 (C-4), 134.8, 133.3, 127.6, 127.5, 127.3, 126.1, 124.5, 123.4, 116.5 (C-1)



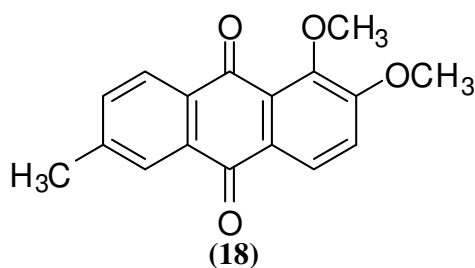
Damnacanthal (15). Yellow crystals. Mps 208-211 ° C [ lit. 218-218.5 ° C (Me<sub>2</sub>CO) Chang (1984)]. UVλ<sub>max</sub> EtOH nm: 381, 284, 250, 213. UVλ<sub>max</sub> EtOH/ -OH nm: 460, 379, 315, 262, 250. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3437, 1644, 1561. MS m/z: 282 [M<sup>+</sup>], 254, 225, 196. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz): 12.29 (1H, s, 3-OH), 10.49 (1H, s, 2-CHO), 8.25 (2H, m, H-5, H-8), 7.84 (2H, m, H-6, H-7), 7.68 (1H, s, H-4), 4.14 (3H, s, 1-OCH<sub>3</sub>)



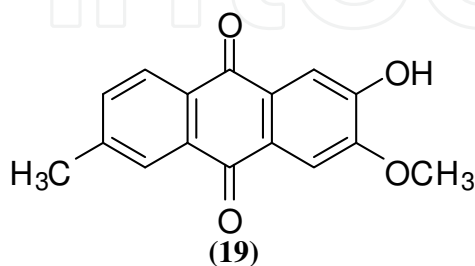
1-Hydroxy-2-methoxy-6-methyl-9,10-anthraquinone (16). Red needle crystals. Mps 220-221 ° C. UVλ<sub>max</sub> EtOH nm: 421, 278, 262, 231. UVλ<sub>max</sub> EtOH/ -OH nm: 505, 314, 258. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3467, 1653, 1637. MS m/z: 268 [M<sup>+</sup>], 239, 197, 169, 139, 115. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz): 13.20 (1H, s, 1-OH), 8.23 (1H, d, J=8.1, H-8), 8.12 (1H, s, H-5), 7.89 (1H, d, J=8.4, H-4), 7.61 (1H, d, J=8.1, H-7), 7.19 (1H, d, J=8.4, H-3), 4.04 (3H, s, 2-OCH<sub>3</sub>), 2.56 (3H, s, 6-CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): 189.1 (C=O, C-9), 181.8 (C=O, C-10), 154.0 (C-OH, C-1), 152.7 (C-OCH<sub>3</sub>, C2), 146.2 (C-6), 134.6 (C-7), 134.0 (C-11), 131.10 (C-12), 127.8 (C-5), 127.1 (C-8), 125.5 (C-14), 121.0 (C-4), 116.1 (C-13), 115.6 (C-3), 56.4 (2-OCH<sub>3</sub>), 22.0 (6-CH<sub>3</sub>)



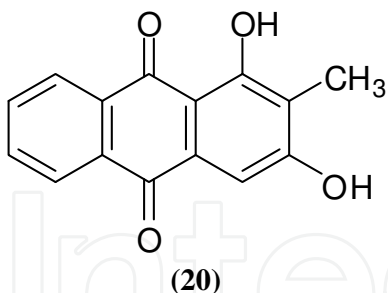
Lucidin- $\omega$ -methyl ether (**17**). Yellow crystals. Mps 175-179°C [lit 170°C, Dictionary of Natural Products (1995); 163-166°C, Leistner (1975)]. UV $\lambda_{\max}$  EtOH nm: 412, 280, 24. UV $\lambda_{\max}$  EtOH/ -OH nm: 491, 314, 242 IR  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 3428, 2927, 1668, 162. MS  $m/z$ : 284 [ $M^+$ ], 263, 241, 213, 185.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz): 13.29 (1H, s, 1-OH), 9.39 (1H, s br, 3-OH), 8.27 (2H, m, H-5, H-8), 7.80 (2H, m, H-6, H-7), 7.32 (1H, s, H-4), 4.90 (2H, s, 2- $\text{CH}_2\text{OCH}_3$ ), 3.59 (3H, s, 2- $\text{CH}_2\text{OCH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz): 186.9 (C=O, C-9), 182.2 (C=O, C-10), 164.1 (C-1), 161.7 (C-3), 134.1 (C-11), 134.1 (C-12), 133.6 (C-6), 133.5 (C-7), 126.8 (C-2), 114.4 (C-4), 109.7 (C-8), 109.7 (C-13), 109.6 (C-5), 109.6 (C-14), 68.9 (2- $\text{CH}_2\text{OCH}_3$ ), 59.3 (2- $\text{CH}_2\text{OCH}_3$ )



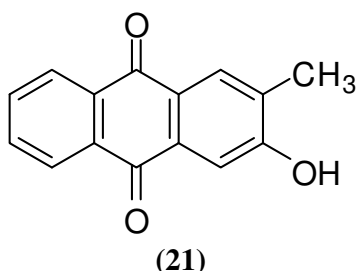
1,2-Dimethoxy-6-methyl-9,10-anthraquinone (**18**). Bright yellow crystals. Mps 193-196°C. UV $\lambda_{\max}$  EtOH nm: 373, 341, 257, 222. UV $\lambda_{\max}$  EtOH/ -OH nm: 373, 342, 257, 222. IR  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 1666, 1601, 1327, 1267. MS  $m/z$ : 282 [ $M^+$ ], 253, 221, 194, 165, 139.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz): 8.17 (2H, dd,  $J=8.7, 7.8$ , H-4, H-8), 8.06 (1H, s, H-5), 7.58 (1H, d,  $J=7.8$ , H-7), 7.28 (1H, d,  $J=8.7$ , H-3), 4.02 (6H, s, 1- $\text{OCH}_3$ , 2- $\text{OCH}_3$ ), 2.53 (3H, s, 6- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz): 182.7 (C=O, C-9), 182.7 (C=O, C-10), 159.1 (C-1), 149.6 (C-2), 144.6 (C-6), 134.8 (C-7), 132.9 (C-11), 132.9 (C-12), 127.5 (C-14), 127.4 (C-13), 127.1 (C-8), 126.9 (C-5), 125.2 (C-4), 115.9 (C-3), 61.3 (1- $\text{OCH}_3$ ), 56.3 (2- $\text{OCH}_3$ ), 21.8 (6- $\text{CH}_3$ )



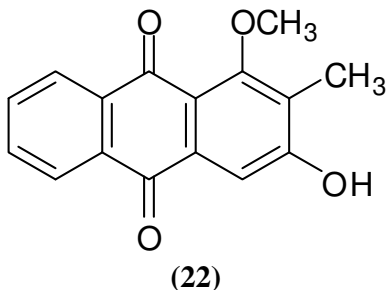
2-Hydroxy-3-methoxy-6-methyl-9,10-anthraquinone (**19**). Light yellow amorphous solid. Mp 210-215°C. UV $\lambda_{\max}$  EtOH nm: 393, 286, 244. UV $\lambda_{\max}$  EtOH/ -OH nm: 509, 316, 250. IR  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 3203, 2927, 2869, 1666, 1265. MS  $m/z$ : 268 ( $M^+$ ), 239, 207, 169.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz): 8.18 (1H, d,  $J=8.1$ , H-8), 8.08 (1H, s, H-5), 7.79 (1H, s, H-1), 7.76 (1H, s, H-4), 7.57 (1H, d,  $J=8.1$ , H-7), 6.23 (1H, s br, 2-OH), 4.11 (3H, s, 3- $\text{OCH}_3$ ), 2.54 (3H, s, 6- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz): 182.4 (C=O), 162.8 (C-OH, C-2), 151.4 (C- $\text{OCH}_3$ , C-3), 144.9, 134.5, 133.6, 127.4, 127.2, 112.6, 108.3, 56.6 (3- $\text{OCH}_3$ ), 21.9 (6- $\text{CH}_3$ )



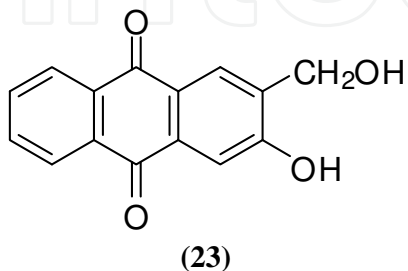
Rubiadin (**20**). Yellow crystals. Mps 250-258 °C [lit. 280-283 °C, Leistner (1975)]. UVλ<sub>max</sub> EtOH nm: 413, 279. UVλ<sub>max</sub> EtOH/ -OH nm: 496, 314, 241 IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3436, 1653, 1626. MS m/z: 254 [M<sup>+</sup>], 226, 197, 152, 115. <sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300MHz): 13.20 (1H, s, 1-OH), 8.31 (1H, m, H-8), 8.23 (1H, m, H-5), 7.92 (2H, m, H-6, H-7), 7.38 (1H, s, H), 2.20 (3H, s, 2-CH<sub>3</sub>). <sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75.5 MHz): 186.9 (C=O, C9), 181.8 (C=O, C-10), 163.2 (C-OH, C-1), 162.4 (C-OH, C-3), 134.3, 134.2, 133.5, 133.5, 132.4, 126.8, 126.5, 117.9, 107.17, 7.3



3-Hydroxy-2-methyl-9,10-anthraquinone (**21**). Yellow crystals. Mps 138- 142 °C. UVλ<sub>max</sub> EtOH nm: 379, 329, 274, 245, 239. UVλ<sub>max</sub> EtOH/ -OH nm: 496, 314, 246 . IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3436, 1663, 651. MS m/z 238 [M<sup>+</sup>], 238, 210, 181, 152, 105. <sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300MHz): 8.23 (2H, m, H-5, H-8), 8.05 (1H, s, H-1), 7.89 (2H, m, H-6, H-7), 7.67 (1H, s, H-4), 2.39 (3H, s, 2-CH<sub>3</sub>). <sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75.5 MHz): 182.6 (C=O, C-10), 181.5 (C=O, C-9), 161.0 (C-OH, C-3), 134.1 (C-2), 133.8 (C-14), 133.7 (C-7), 133.6 (C-6), 132.2 (C-13), 130.1 (C-1), 126.6 (C-5), 126.5 (C-8), 111.4 (C-4), 15.6 (2-CH<sub>3</sub>)



Rubiadin-1-methyl ether (**22**). Light yellow crystal. Mps 302-304 °C [282-284, Briggs (1976); 300 °C, Roberts (1977)]. UVλ<sub>max</sub> EtOH nm: 354, 332, 279. UVλ<sub>max</sub> EtOH/ -OH nm: 440, 314, 246. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3437, 2913, 2847, 1668, 1651. MS m/z : 268, 239, 207, 181. <sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300MHz): 9.50 (1H, s, br, 3-OH), 8.20 (2H, m, H-5, H-8), 7.87 (2H, m, H-6, H-7), 7.63 (1H, s, H-4), 3.90 (3H, s, 1-OCH<sub>3</sub>), 2.27 (3H, s, 2-CH<sub>3</sub>). <sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75.5 MHz): 182.7 (C=O), 180.4 (C=O), 161.2 (C-OH), 140.6, 134.4, 134.2, 133.0, 132.6, 126.8, 126.0, 60.4 (OCH<sub>3</sub>), 8.4 (CH<sub>3</sub>)



3-Hydroxy-2-hydroxymethyl-9,10-anthraquinone (**23**). Light yellow solid . UVλ<sub>max</sub> EtOH nm: 374, 274, 238. UVλ<sub>max</sub> EtOH/ -OH nm: 481, 311, 246 IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3468, 1628. <sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300MHz): 8.38 (1H, s, H-4), 8.24 (2H, m, H-5, H-8), 7.89 (2H, m, H-6, H-7), 7.63 (1H, s, H-1), 4.803 (2H, s, 2-CH<sub>2</sub>OH). <sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75.5 MHz): 182.9 (C=O, C-9), 181.7 (C=O, C-10), 160.1 (C-OH, C-3), 136.1 (C-2), 134.2 (C-14), 134.1 (C-11), 133.8 (C-6), 133.7 (C-7), 133.6 (C-12), 126.7 (C-4), 126.6 (C-5), 125.9 (C-13), 125.6 (C-8), 111.5 (C-1), 59.0 (2-CH<sub>2</sub>OH)

Table 3.

which showed a  $^3J$  correlation with H-7. The methine carbons (C-3, C-4, C-5, C-7 and C-8) were assigned through HMQC correlations while the quaternary carbons (C-1, C-2, C-6, C-11, C-12, C-13 and C-14) were assigned based on careful analysis of HMBC spectrum. Both carbonyl carbons in this compound resonated very closely to each other with only 0.01 ppm difference at  $\delta_C$  182.70 and 182.71, which further confirmed the unchelated nature of the carbonyls. Presented below are structures and spectroscopic data of the isolated compounds.

### 3.2 Anthraquinones of *Morinda elliptica*

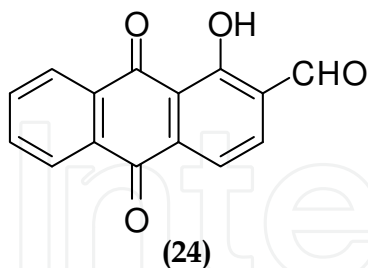
*Morinda elliptica* or locally known as 'mengkudu kecil' is a shrub or small tree and it is very common in wild state of Malay Peninsula and northwards Burma (Burkill, 1966). It can be seen growing wild in newly developed areas, bushes and lowland secondary forest throughout the peninsula. *M. elliptica* is very common and always available and mostly used by the Malays for medicinal purposes. Traditionally, different parts of the plant are used in various ways for a number of health problems and ailments. The leaves may be added to rice for loss of appetite and taken for headache, cholera, diarrhea and wounds. Sometimes a lotion is made and used for hemorrhoid and applied upon body after childbirth (Burkill, 1966). The extracts and anthraquinones isolated from *M. elliptica* were reported to possess wide spectrum of biological activities such as antioxidant (Ismail, *et al.*, 2002; Jasril, *et al.*, 2003), antimicrobial, anti-HIV and anticancer (Ali, *et al.*, 2000).



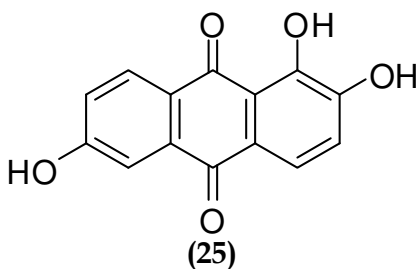
Fig. 5. *Morinda elliptica*

Five anthraquinones in roots of *M. elliptica* which are nordamnacanthal **13**, damnacanthal **15**, lucidin- $\omega$ -methyl ether **17**, rubiadin **20** and rubiadin-1-methyl ether **22** are the same constituents found in *R. elliptica*. The others are 1-hydroxy-2-methylantraquinone **23**, soranjidiol **25**, morindone **26**, morindone-5-methyl ether **27** and alizarin-1-methyl ether **28**. In addition, 2-formyl-1-hydroxyanthraquinone **24** was reported as a new naturally occurring anthraquinone from roots of *M. elliptica*. HR-MS of **24** showed molecular ion peak at 252.0414 consistent with molecular formula of  $C_{15}H_{14}O_4$ . A bathchromic shift (407 to 531 nm) upon adding NaOH suggested the presence of OH at C-1 of the anthraquinone skeleton. The presence of hydroxyl group was evident from the broad stretching band observed at  $3448\text{ cm}^{-1}$ . Two sharp stretching vibrations due to chelated and unchelated carbonyls were observed at  $1638$  and  $1676\text{ cm}^{-1}$ , respectively. In the proton NMR, the signal for chelated hydroxyl group is at  $\delta_H$  13.26. The splitting pattern of  $^1H$  NMR suggest substitution pattern

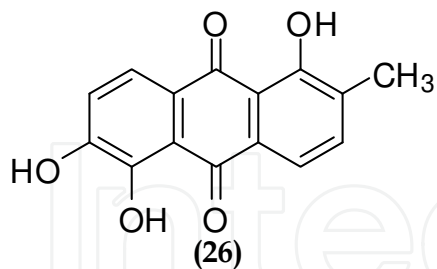




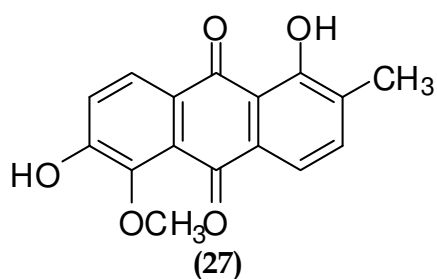
2-Formyl-1-hydroxy-9,10-anthraquinone (**24**). Mps 183-185° C [lit. 259-260° C, Rath et al. (1995)]. UVλ<sub>max</sub> EtOH nm: 229, 278, 331, 407. UVλ<sub>max</sub> EtOH/ -OH nm: 229, 280, 308, 531. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3448 (OH), 1696 (aldehyde), 1676 (C=O unchelated), 1638 (C=O chelated), 1592 (C=C aromatic). MS m/z 252 (M<sup>+</sup>), 2224, 196, 168. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500MHz): 13.26 (1H, s, 1-OH), 10.63 (1H, s, CHO), 8.35 (1H, m, H-8), 8.32 (1H, m, H-5), 8.23 (1H, d, J= 8.0 Hz, H-3), 7.89 (1H, d, J= 8.0 Hz, H-4), 7.88 (2H, m, H-6, H-7). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): 164.5 (C-1), 128.4 (C-2), 135.4 (C-3), 118.7 (C-4), 127.7 (C-5), 134.7 (C-6), 135.3 (C-7), 127.2 (C-8), 188.9 (C-9), 181.8 (C-10), 117.4 (C-11), 137.2 (C-12), 134.8 (C-13), 133.3 (C-14) and 188.0 (C-15)



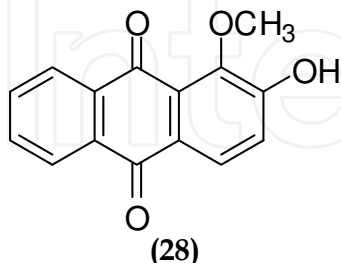
Soranjidiol. Yellow-orange needles (**25**) Mps 276-273° C [lit. 271-272° C, Adesogan (1973)]. UVλ<sub>max</sub> EtOH nm: 265, 409. UVλ<sub>max</sub> EtOH/ -OH nm: 308, 489. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3401 (OH), 1667 (C=O unchelated), 1635 (C=O chelated), 1593 (C=C aromatic). MS m/z 254 (M<sup>+</sup>), 226, 197, 115. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): 13.10 (1H, s, 1-OH), 11.21 (1H, s, 6-OH), 7.63 (1H, d, J= 7.57 Hz, H-3), 7.57 (1H, d, J=7.57 Hz, H-4), 7.25 (1H, dd, J<sub>7,8</sub> = 8.55 Hz, J<sub>7,5</sub> = 2.69 Hz, H-7), 7.45 (1H, d, J= 2.69 Hz, H-5), 2.27 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 125 MHz): 187.6 (C=O), 181.8 (C=O), 163.8 (C-OH), 160.0 (C-OH), 136.9, 135.6, 134.2, 131.1, 129.8, 124.5, 121.4, 118.6, 114.7, 112.5, 15.8 (CH<sub>3</sub>)



Morindone (**26**). Orange needles. Mps 240-241° C (CHCl<sub>3</sub>) [lit. 248-249.5° C, Leistner (1975)]. UVλ<sub>max</sub> EtOH nm: 260, 299, 448. UVλ<sub>max</sub> EtOH/ -OH nm: 260, 302, 338, 558. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3462 (OH), 1628 (C=O chelated). MS m/z 270 (M<sup>+</sup>), 242, 135. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500MHz): 13.21 (1H, s, 1-OH), 12.95 (1H, s, 5-OH), 7.85 (1H, d, J=8.2 Hz, H-8), 7.75 (1H, d, J= 7.7 Hz, H-4), 7.52 (1H, d, J=7.6Hz, H-3), 7.26 (1H, d, J=8.2 Hz, H-7), 6.32 (1H, s, 6-OH), 2.39 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): 186.6 (C=O), 179.9 (C=O), 170.4 (C-OH), 169.8 (C-OH), 161.4 (C-OH), 151.3, 149.4, 136.6, 130.9, 121.3, 119.8, 118.9, 115.3, 16.3 (CH<sub>3</sub>)



Morindone-5-methyl ether (**27**). Orange crystals. Mp 232° C [lit. 223° C, Chang & Lee (1984)]. UVλ<sub>max</sub> EtOH nm: 410, 497. UVλ<sub>max</sub> EtOH/ -OH nm: 314, 388, 498. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3389 (OH), 2926, 1672 (C=O unchelated), 1630 (C=O chelated), 1581 (C=C aromatic). MS m/z 284 (M<sup>+</sup>), 266, 238, 197. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500MHz): 13.02 (1H, s, 1-OH), 8.14 (1H, d, J=8.55 Hz, H-8), 7.70 (1H, d, J= 8.06 Hz, H-4), 7.51 (1H, d, J=7.81 Hz, H-3), 7.35 (1H, d, J=8.54 Hz, H-7), 6.73



(1H, s, 6-OH), 4.03 (3H, s, OCH<sub>3</sub>), 2.37 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): 187.8 (C=O), 182.0 (C=O), 160.6 (C-OH), 155.9, 146.8, 136.9, 134.5, 132.3, 127.1, 125.9, 125.5, 112.0, 118.9, 114.7, 62.3 (OCH<sub>3</sub>), 16.1 (CH<sub>3</sub>)

Alizarin-1-methyl ether. Yellow-orange crystals (28). Mp 164 [lit 178-179°C, Chang & Lee (1984)]. UVλ<sub>max</sub> EtOH nm: 313, 378, 485. UVλ<sub>max</sub> EtOH/ -OH nm: 315, 333, 493. IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3443 (OH), 2926, 1671 (C=O unchelated), 1589 (C=C) aromatic. MS m/z 254 (M<sup>+</sup>), 236, 208, 183. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500MHz): 8.28 (2H, m, H-5, H-8), 8.15 (1H, d, J = 8.55 Hz, H-4), 7.78 (2H, m, H-7, H-6), 7.37 (1H, d, J = 8.54 Hz, H-3), 6.70 (1H, s, 2-OH), 4.04 (3H, s, OCH<sub>3</sub>). <sup>13</sup>C NMR (DMSO-d<sub>6</sub> 125 MHz): 182.7 (C=O), 182.1 (C=O), 155.5, 146.6, 131.4, 133.9, 132.9, 127.5, 127.1, 126.8, 125.8, 125.6, 120.2, 62.3 (OCH<sub>3</sub>)

on ring C only. H-3 and H-4 appeared as doublets at δ<sub>H</sub> 8.23 and 7.89 respectively. A formyl group (δ<sub>H</sub> 10.63) is attached to C-2. HMBC correlations of C-10 with H-3 and H-5 confirmed the assignment of the protons at their respective positions and supported by their respective COSY correlations. <sup>13</sup>C NMR showed fifteen carbons peaks as expected. One of the chelated carbonyl carbon was further downfield at δ<sub>C</sub> 188.9 (C-9), confirming the chelated nature of this carbonyl. The assignment of carbons were accomplished using FGHMQC and FGHMBC experiment. Presented below are structures and spectroscopic data of the isolated compounds.

#### 4. Conclusion

The phytochemical study on *Fissistigma latifolium* and *Meiogyne virgata* (Annonaceae) yielded twelve alkaloids; (-)-*N*-methylguattescidine **1**, liriodenine **2**, lanuginosine **3**, (-)-asimilobine **4**, dimethyltryptamine **5**, (-)-remerine **6**, (-)-anonaine **7**, columbamine **8**, lysicamine **9**, norruciferine **10**, norushinsunine **11** and cleistopholine **12**. Tryptamine alkaloids have never been reported from *Fissistigma* species, whereas (-)-*N*-methylguattescidine **1** represents a rare finding of a naturally occurring 6a-methylated-7-oxo-aporphine alkaloid. Alkaloids **3**, **6**, **9** and **10** have never been reported from *Meiogyne* species.

*Rennellia* and *Morinda* are often confused with each other due to their similar traditional usage. Both plants are traditionally used for fever, postpartum and body ache treatment. Our phytochemical study on roots extract of *R. elliptica* showed significant similarities of major anthraquinones with those found in *Morinda* species. The major constituents of *R. elliptica*, nordamnacanthal, damnacanthal, rubiadian, rubiadin methyl ether and lucidin-ω-methyl ether are also present in *M. elliptica* and *M. citrifolia*.

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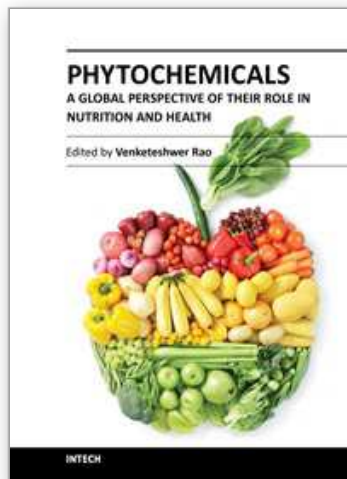
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