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## Marine natural products targeting phospholipases A2

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► **To cite this version:**

Florence Folmer, Marcel Jaspars, Marc Schumacher, Mario Dicato, Marc Diederich. Marine natural products targeting phospholipases A2. *Biochemical Pharmacology*, 2010, 80 (12), pp.1793. 10.1016/j.bcp.2010.08.024 . hal-00637158

**HAL Id: hal-00637158**

**<https://hal.science/hal-00637158>**

Submitted on 31 Oct 2011

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## Accepted Manuscript

Title: Marine natural products targeting phospholipases A2

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PII: S0006-2952(10)00655-6  
DOI: doi:10.1016/j.bcp.2010.08.024  
Reference: BCP 10704

To appear in: *BCP*

Received date: 11-6-2010  
Revised date: 25-8-2010  
Accepted date: 27-8-2010

Please cite this article as: Folmer F, Jaspars M, Schumacher M, Dicato M, Diederich M, Marine natural products targeting phospholipases A2, *Biochemical Pharmacology* (2010), doi:10.1016/j.bcp.2010.08.024

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## Marine natural products targeting phospholipases A2

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## Abstract

Phospholipases A<sub>2</sub> (PLA<sub>2</sub>s) form a family of enzymes catalyzing the hydrolysis of membrane phospholipids into arachidonic acid, which is the major precursor of pro-inflammatory eicosanoids. As a result, PLA<sub>2</sub>s have been considered as potential targets in anti-inflammatory drug discovery.

Marine natural products are a rich source of bioactive compounds, including PLA<sub>2</sub> inhibitors. Here, we review the properties of marine PLA<sub>2</sub> inhibitors identified since the first discovery of PLA<sub>2</sub> inhibitory activity in the marine natural product manoalide in the mid 1980's.

**Keywords:** anti-inflammatory; arachidonic acid; eicosanoids; marine natural product; membrane phospholipids; PLA<sub>2</sub>

## Abbreviations

5-HPTETE, 5-hydroperoxyeicosatetraenoic acid; COX, cyclooxygenase; cPLA<sub>2</sub>, cytosolic PLA<sub>2</sub>; IP<sub>3</sub>, inositol 1,4,5-triphosphate; iPLA<sub>2</sub>, calcium independent PLA<sub>2</sub>; LOX, lipoxygenase; (Lp)PLA<sub>2</sub>, lipoprotein-associated PLA<sub>2</sub>; LT, leukotriene; NO, nitric oxide; PAF, platelet-activating factor; PG, prostaglandin; PLA<sub>2</sub>, phospholipase A<sub>2</sub>; PLC, phospholipase C; ROS, reactive oxygen species; sPLA<sub>2</sub>, secretory PLA<sub>2</sub>; TX, thromboxane

## 1. Introduction

1 Inflammation is the response of vascular tissues to harmful stimuli such as  
2 injury, pathogens, or irritants. While inflammation normally functions as a defense  
3 mechanism in higher animals, deregulated inflammation is implicated in a large  
4 number of diseases such as autoimmune diseases, allergies, asthma, rheumatoid  
5 arthritis, inflammatory bowel diseases, pelvic inflammatory diseases,  
6 glomerulonephritis, atherosclerosis, myocardial ischemia, and cancer [1-3]. The  
7 process of inflammation is controlled by a group of substances called chemical  
8 mediators [1]. Endogenous chemical mediators consist of vasoactive amines,  
9 cytokines, bradikinin, fibrin, complement components, eicosanoids, platelet activating  
10 factor (PAF), nitric oxide (NO), and neuropeptides [1]. Eicosanoids, in particular,  
11 play a critical role in virtually every step of inflammation. Eicosanoids, which  
12 comprise prostaglandins, prostacyclins, thromboxanes, and leukotrienes, are a family  
13 of oxygenated fatty acid metabolized by cyclooxygenases (COX) and lipoxygenases  
14 (LOX) from arachidonic acid [1]. Despite the extensive efforts invested in developing  
15 drugs that suppress the conversion of arachidonic acid into pro-inflammatory  
16 eicosanoids, the latter approach has been unsuccessful. Undesired side-effects  
17 resulting from the lack of specificity of COX and LOX are responsible for the failure  
18 of the concept [2]. As an alternative, the quest for inhibitors of phospholipases A<sub>2</sub>  
19 (PLA<sub>2</sub>s), the enzymes that catalyze the hydrolysis of membrane phospholipids into  
20 arachidonic acid, has opened up a new research avenue in anti-inflammatory drug  
21 discovery [2, 4-6]. As a matter of fact, PLA<sub>2</sub>s isolated from snake venom have been  
22 shown to induce all the inflammatory symptoms of snakebite such as acute pain,  
23 oedema, hypotension, hemorrhage, and neuromuscular junction blockage.  
24 Furthermore, rheumatoid arthritis, asthma, psoriasis, myocardial ischemia, and  
25 pancreatitis have all been shown to be associated with elevated levels of serum PLA<sub>2</sub>.  
26 Lysophospholipids produced by PLA<sub>2</sub>s have also been shown to induce gastric  
27 ulceration in rats, and to induce an inflammation similar to acute cholecystitis in the  
28 gall bladder mucosa [3]. Here, we review the properties of marine PLA<sub>2</sub> inhibitors  
29 identified since the first discovery of PLA<sub>2</sub> inhibitory activity in the marine natural  
30 product manoalide (**1**), by research groups lead by Edward Dennis [4] and by Robert  
31 Jacobs [5] at the universities of San Diego and Santa Barbara, respectively, in the mid  
32 1980's.

## 2. The PLA<sub>2</sub>-mediated inflammation signaling cascade

PLA<sub>2</sub>s are lipolytic enzymes found in almost all types of cells. They specifically hydrolyze the 2-acyl ester bond of 1,2-diacyl-*sn*-3-glycerophospholipids such as arachidonic acid. Fifteen different PLA<sub>2</sub>s have been characterized to date. They are grouped into four families: secreted PLA<sub>2</sub>s (sPLA<sub>2</sub>s), cytosolic PLA<sub>2</sub>s (cPLA<sub>2</sub>s), lipoprotein associated PLA<sub>2</sub>s ((Lp)PLA<sub>2</sub>), and calcium-independent PLA<sub>2</sub>s (iPLA<sub>2</sub>s) [2, 5, 6]. The calcium-dependent sPLA<sub>2</sub>s are commonly found in snake, scorpion, and bee venom. They are of low molecular weight (13-15 kDa) and characteristically contain a histidine residue in their catalytic site [2, 6]. The mode of action of sPLA<sub>2</sub>s involves a nucleophilic attack onto the phospholipid's *sn*-2 bond. While the role of sPLA<sub>2</sub>s in inflammation remains poorly understood, it has been suggested that sPLA<sub>2</sub>s induce an increase in cPLA<sub>2</sub>-dependent eicosanoid release, and that they synergize with other pro-inflammatory mediators [2, 6]. cPLA<sub>2</sub>s are 85 kDa enzymes containing a serine and an aspartic acid residue in the active site. Noteworthy, cPLA<sub>2</sub>s are the only PLA<sub>2</sub>s with specificity for arachidonic acid at the phospholipase *sn*-2 position. cPLA<sub>2</sub>s are calcium-dependent enzymes activated by extra-cellular stimulations from pathogens, tissue injury, or physical or chemical stresses. The cytosolic concentrations of calcium required for PLA<sub>2</sub> activation result from the cleavage of phospholipids into inositol 1,4,5-triphosphate (IP<sub>3</sub>) by phospholipase C (PLC), followed by the binding of IP<sub>3</sub> to calcium channels in the endoplasmic reticulum [7]. Because of their central role in mediating the generation of eicosanoids and of PAFs, and hence in mediating inflammation, cPLA<sub>2</sub>s have been recognized as very attractive targets in drug discovery, despite some rare side-effects including the formation of intestinal ulcers, and several pharmaceutical companies, such as Pfizer have started to develop promising cPLA<sub>2</sub>-specific drug candidates [7-9]. Unlike cPLA<sub>2</sub>s, (Lp)PLA<sub>2</sub>s, or platelet aggregation factor acetylhydrolases (PAF-AHs), have anti-inflammatory properties, as they are able to degrade the pro-inflammatory signaling molecules PAFs by cleaving their acetyl group at the *sn*-2 position. However, (Lp)PLA<sub>2</sub>s have become an important target in PLA<sub>2</sub> inhibitory drug discovery, as they are known to lead to coronary heart diseases [6]. iPLA<sub>2</sub>s have complex and still poorly understood implications in signalling pathways. iPLA<sub>2</sub>s play a role in bone formation, apoptosis, insulin secretion, sperm development, and axon regeneration [2, 6]. The present review focuses only on inhibitors of sPLA<sub>2</sub>s and

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cPLA<sub>2</sub>s. The latter two are present in most types of cells, and both of them are known to be implicated in inflammation through eicosanoid biosynthesis [6, 9-11].

As illustrated in **Figure 1**, PLA<sub>2</sub>s initiate the pro-inflammatory signaling cascade by catalyzing the hydrolysis of the *sn*-2 acyl ester bond of membrane phospholipids, leading to the release of the  $\omega$ -6 fatty acid arachidonic acid and of lysophospholipids [7]. Next, arachidonic acid is oxygenated into prostaglandin (PG) PGH<sub>2</sub> by COX, or into 5-hydroperoxyeicosatetraenoic acid (5-HPTETE) by LOX. The conversion of arachidonic acid to PGH<sub>2</sub> by COX occurs in two steps. First, two molecules of O<sub>2</sub> are added as two peroxide linkages, and a 5-membered carbon ring is formed near the middle of the fatty acid chain, leading to an unstable intermediate prostaglandin G (PGG<sub>2</sub>). One of the peroxide linkages then sheds a single oxygen atom to form the PGH<sub>2</sub> [1]. PGH<sub>2</sub> is the unstable precursor of PGD<sub>2</sub>, PGE<sub>2</sub>, PGI<sub>2</sub>, and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) [1]. PGE<sub>2</sub> and PGI<sub>2</sub> enhance edema formation and leukocyte infiltration by promoting blood flow in the inflamed region, and they stimulate the pain-inducing activity of bradykinin and autacoids. PGE<sub>2</sub> induces pain, heat, and fever. TXA<sub>2</sub> triggers platelet aggregation [1]. LOX converts arachidonic acid into lipid hydroxyperoxides that exert relevant functions as mediators of inflammation: 5-hydroperoxyeicosatetraenoic acid (5-HPTETE) is spontaneously reduced to 5-hydroxyeicosatetraenoic acid (5-HETE), which is further converted by 5-lipoxygenase to leukotriene A<sub>4</sub>. LTA<sub>4</sub> may be converted to LTB<sub>4</sub>. LTB<sub>4</sub> is a potent chemoattractant for polymorphonuclear leukocytes. It activates neutrophil functional responses, leading to the generation of free oxygen free radicals and to the release of lysosomal enzymes. LTB<sub>4</sub> also causes the adhesion and chemotaxis of leukocytes, it stimulates aggregation, enzyme release, generation of superoxide in neutrophils, and it makes blood vessels more permeable [10]. Eosinophils, mast cells, and alveolar macrophages use LTC<sub>4</sub> synthase to conjugate glutathione with LTA<sub>4</sub> to make LTC<sub>4</sub>, which is transported outside the cell where a glutamic acid moiety is removed to make LTD<sub>4</sub>. LTD<sub>4</sub> is then cleaved by dipeptidases to make LTE<sub>4</sub>. LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> play an important role in atherosclerosis, in asthma, in allergic rhinitis, and in inflammatory gastrointestinal diseases. Eicosanoids also activate the production of pro-inflammatory reactive oxygen species (ROS), nitric oxide (NO), and cytokines [3, 9, 10, 13, 14]. The lysophospholipids produced during the conversion of membrane phospholipids to arachidonic acid are a precursor for PAF. In addition,

lysophospholipids induce the activation and extravasion of pro-inflammatory leukocytes and activate the secretion of pro-inflammatory histamine by mast cells [7].

### 3. Marine PLA<sub>2</sub> inhibitors

PLA<sub>2</sub> activity has been reported in several marine organisms, including hard and soft corals, jellyfish, starfish, sea anemones, and soft corals, and marine snails [11, 12]. Hence, from an ecological perspective, it is not surprising that marine organisms have developed potent PLA<sub>2</sub> inhibitors, which may be used as chemical defences in their natural environment. Marine PLA<sub>2</sub> inhibitors reported to date are primarily terpenoids isolated from sponges, nudibranchs, and algae. Their chemical and biological properties are described below and summarized in **Table 1**. The chemical structures of the compounds are shown in **Figure 2**.

#### 3.1. PLA<sub>2</sub> inhibiting sesquiterpenes

One of the most investigated marine PLA<sub>2</sub> inhibitors is the merosesquiterpene bolinaquinone (**1**) isolated from the sponge *Dysidea* sp. Bolinaquinone (**1**) has been shown to inhibit the enzymatic activity of sPLA<sub>2</sub> with an IC<sub>50</sub> value of 100 nM [13]. While the inhibition of sPLA<sub>2</sub> by bolinaquinone (**1**) is very potent, it is not selective against this enzyme. Bolinaquinone **1** is known to also affects cPLA<sub>2</sub> [13-19]. Bolinaquinone (**1**) is known to reduce LTB<sub>4</sub> production in neutrophils and NO and PGE<sub>2</sub> production in macrophages [13-19]. Another, closely related sesquiterpenoid quinone, ilimaquinone (**2**) isolated from the sponge *Hippiospongia metachromia* [20], has also been shown to inhibit PLA<sub>2</sub> (IC<sub>75</sub> = 270 μM against bee venom sPLA<sub>2</sub>) [19]. The anti-psoriasis sesquiterpene hydroquinone avarol (**3**) and the sesquiterpene quinones avarone (**4**) and dysidine (**5**) isolated from the sponge *Dysidea avara* inhibit sPLA<sub>2</sub> activity and PGE<sub>2</sub> release in keratinocytes and in monocytes (IC<sub>50</sub> = 2 μM). Furthermore, avarol has been shown to reduce eicosanoid release and ROS generation in stimulated leukocytes [17-19]. Dysidiotronic acid (**6**) isolated from *Dysidea* sp. also inhibits sPLA<sub>2</sub> (IC<sub>50</sub> = 2.6 μM) [18, 19]. The sesquiterpene lactone cavernolide (**7**) isolated from the sponge *Fasciospongia cavernosa* inhibits sPLA<sub>2</sub> activation (IC<sub>50</sub> = 8.8 μM), as well as iNOS and COX-2 gene expression [18, 20, 21]. Amongst sesquiterpenes isolated from algae, rhipocephalin (**8**) extracted from the green alga *Rhipocephalus phoenix* has been shown to inhibit bee venom sPLA<sub>2</sub> (IC<sub>100</sub> = 4.1 μM),

and caulerpyne (**9**) produced by the green alga *Caulerpa prolifera* inhibits bee venom sPLA<sub>2</sub> activity with an IC<sub>92</sub> value of 4.2 μM [21].

### 3.2. PLA<sub>2</sub> inhibiting diterpenes

The diterpenes gracilin A (**10**), aplyroseol 1 (**11**), and 12-acetoxytetrahydroaplysulphurin 1 (**12**) isolated from *Aplysilla* sp. sponges [22], and dendrillolide A (**13**) and norrisolide (**14**) isolated from the sponge *Dendrilla* sp. inhibit bee venom sPLA<sub>2</sub> with IC<sub>50</sub> values around 5 μM [20]. They all contain a masked 1,4-dialdehyde function, which has been suggested to play a key role in their bioactivity [20]. The meroditerpene epitaondiol (**15**) isolated from the brown alga *Styopodium flabelliforme* inhibits TXB<sub>2</sub> production by potently inhibiting human sPLA<sub>2</sub> (IC<sub>50</sub> = 3.8 μM) [19, 23]. The tetra- and bicyclic diterpenes phomactins A-C (**16-18**) isolated from the marine fungus *Phoma* sp. are potent PAF antagonists. While the precise mode of action of **16-18** remains poorly understood, it is likely that these three compounds may act as PAF antagonists by inhibiting cPLA<sub>2</sub>s or by activating (Lp)PLA<sub>2</sub> [9, 23, 24]. The arabidose-containing diterpene fuscocide B (**19**) isolated from the gorgonian *Eunicea fusca* has not been reported as a PLA<sub>2</sub> inhibitor, but it has been shown to inhibit the conversion of arachidonic acid to LTB<sub>4</sub> by inhibiting 5-LO (IC<sub>50</sub> = 18 μM) [18, 25].

### 3.3. PLA<sub>2</sub> inhibiting sesterterpenes

Sesterterpenes have an outstanding potential as anti-inflammatory compounds. The sesterterpene manoalide (**20**), which was isolated for the first time in the early 1980s from the sponge *Luffariella variabilis* by Scheuer *et al.* [26], became the first marine natural product reported as PLA<sub>2</sub> inhibitor, and it remains, to date, the most investigated marine PLA<sub>2</sub> antagonist. The PLA<sub>2</sub> inhibiting properties of manoalide (**20**) were discovered simultaneously by research groups lead by Edward Dennis [4] and by Robert Jacobs [5] at the universities of San Diego and Santa Barbara, respectively, in the mid 1980's. Both groups confirmed that PLA<sub>2</sub> inhibition was responsible for the previously observed potent anti-inflammatory properties of manoalide (**20**) [8, 14, 15, 18, 27, 28]. Like bolinaquinone (**1**), manoalide (**20**) is a non-specific inhibitor of PLA<sub>2</sub>s [27]. Manoalide (**20**) inhibits human sPLA<sub>2</sub> (IC<sub>50</sub> = 1.7 μM); snake venom sPLA<sub>2</sub> (IC<sub>50</sub> = 0.03 μM); and cPLA<sub>2</sub> (IC<sub>50</sub> = 10 μM) [8, 14,

15, 18, 27, 28]. Manoalide (**20**) has been shown to inhibit cPLA<sub>2</sub> (IC<sub>50</sub> = 10 μM) and phospholipase C [27]. Mechanistic studies revealed that the PLA<sub>2</sub> inhibitory activity of manoalide (**20**) results from the irreversible binding of two of the compound's masked aldehyde groups (the α-hydroxydihydropyran ring and the γ-hydroxybutenolide ring) to lysine residues at the active site of PLA<sub>2</sub> [15, 28-30]. Manoalide (**20**) was licensed to Allergan Pharmaceuticals and reached Phase II clinical trials as a topical antipsoriatic, its development was however, discontinued due to formulation problems [14, 28]. In addition to manoalide (**20**), several analogues of the molecule have been isolated from sponges belonging to the genus *Luffariella*, as well from other sponges. The major manoalide analogues include secomanoalide (**21**), which has the same potency as manoalide (**20**), luffariellolide (**22**) (IC<sub>50</sub> = 230 nM against bee venom sPLA<sub>2</sub>), luffariellins A (**23**) and B (**24**) (IC<sub>50</sub> = 60 nM against bee venom sPLA<sub>2</sub>), and luffolide (**25**) (IC<sub>50</sub> = 40 nM against bee venom sPLA<sub>2</sub>) [20]. Manoalide analogues have also been isolated from nudibranchs of the *Chromodoris* genus, which prey primarily on *Luffariella* sp. sponges [29]. Noteworthy, the nudibranch derived compounds, which include luffariellins C (**26**) and D (**27**), and deoxymanoalide (**28**) (IC<sub>50</sub> = 0.2 μM against snake venom PLA<sub>2</sub>) and deoxysecomanoalide (**29**) (IC<sub>50</sub> = 0.5 μM against snake venom PLA<sub>2</sub>), are all reduced (deoxy) counterparts of spongean manoalide analogues, and their PLA<sub>2</sub> inhibitory activity is a ten-fold weaker than the ones observed in the sponges [29, 30]. Other PLA<sub>2</sub> inhibiting sesterterpenes isolated from various marine sponges include cacospongiolide B (**30**) (IC<sub>50</sub> = 300 nM against human and bee venom sPLA<sub>2</sub>), cyclolinteinone (**31**) (IC<sub>50</sub> = 25 μM against bee venom sPLA<sub>2</sub>), variabilin (**32**) (IC<sub>50</sub> = 6.9 μM against human sPLA<sub>2</sub> and cPLA<sub>2</sub>), halistanol sulphate 1 (**33**) (IC<sub>50</sub> = 16 μg/mL against bee venom sPLA<sub>2</sub>), petrosaspongiolide M (**34**) (IC<sub>50</sub> = 1.6 μM against human sPLA<sub>2</sub>; 0.6 μM against bee venom PLA<sub>2</sub>), scalaradial (**35**) (IC<sub>50</sub> = 1.6 nM against bee sPLA<sub>2</sub> and cPLA<sub>2</sub>), aplyolide (**36**) (IC<sub>50</sub> = 10.5 μM against human sPLA<sub>2</sub>), palinurin (**37**) (IC<sub>50</sub> = 50 μM against bee venom sPLA<sub>2</sub>), palauolol (**38**) (IC<sub>50</sub> = 0.8 μg/mL against bee venom sPLA<sub>2</sub>), and palauolide (**39**) (IC<sub>50</sub> = 0.8 μg/mL against bee venom sPLA<sub>2</sub>) [12, 14, 18, 20, 31-34]. Molecular modelling studies have revealed that petrosaspongiolide M (**34**) inhibits PLA<sub>2</sub> *via* a non-covalent recognition between petrosaspongiolide M (**34**) and the enzyme, followed by a nucleophilic attack by the PLA<sub>2</sub> N-terminus onto the masked aldehyde at C-25 of the pharmacophoric γ-

1 hydroxybutenolide ring of petrosaspongiolide M (**34**) [30, 32, 35, 36].  
2 Petrosaspongiolide M (**34**) also inhibits the expression of iNOS and COX-2, and, as a  
3 result, the production of NO and PGE<sub>2</sub>, respectively, and NF-κB activation [30, 32-  
4 35]. Studies performed by Monti *et al.* have revealed that, although scalaradial (**35**)  
5 does bind covalently to bee venom PLA<sub>2</sub>, the key step in the PLA<sub>2</sub> inhibitory activity  
6 of scalaradial (**35**) is, as observed with petrosaspongiolide M (**34**), its nonvalent  
7 binding to the enzyme's active site [33]. The furanosesterterpene palinurin (**37**)  
8 isolated from the sponge *Ircinia echinata* has been shown to inhibit TXB<sub>2</sub> (IC<sub>50</sub> = 5  
9 μM), and the furan ring is thought to be the pharmacophore of the molecule [36]. The  
10 sesterterpenes cladocoran A (**40**) and B (**41**) isolated from the coral *Cladocora*  
11 *cespitosa* inhibit sPLA<sub>2</sub> (IC<sub>50</sub> = 0.78 μM and 1.95 μM, respectively) [37]. Cladocoran  
12 A (**40**) and B (**41**) caught the attention of Miyako *et al.* because of their possession of  
13 a γ-hydroxybutenolide moiety as in manoalide (**20**) and cacospongiolide B (**30**).  
14 Interestingly, studies on diastereoisomers of cladocoran A (**40**) and B (**41**) revealed  
15 that the presence of a γ-hydroxybutenolide moiety itself is not sufficient for PLA<sub>2</sub>  
16 inhibitory activity, and that the size and shape of the molecule also play critical roles  
17 towards the compounds' potency [37].  
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### 3.4. Non-terpenoid marine PLA<sub>2</sub> inhibitors

33 The bromohydroquinones cymopol (**42**) and cyclocymopol (**43**) isolated from  
34 the green alga *Cymopolia barbata* inhibit bee venom sPLA<sub>2</sub> activity with IC<sub>98</sub> values  
35 of 4.7 and 3.4 μM, respectively [21]. The pyridinium alkaloids spongidines A-D (**44**-  
36 **47**) isolated from the sponge *Spongia* sp. inhibit human sPLA<sub>2</sub> (IC<sub>50</sub> = 10 μM) [38], and the  
37 bromophenols vidalol A (**48**) and B (**49**) isolated from the red alga *Vidilia obtusiloba*  
38 inhibit bee venom sPLA<sub>2</sub> (IC<sub>50</sub> = 1.6 μg/mL) despite lacking a γ-hydroxybutenolide or  
39 masked 1,4-dialdehyde group [20]. Finally, one of the most recently discovered  
40 marine PLA<sub>2</sub> inhibitors, namely the methoxylated fatty acid 7-methoxy-9-  
41 methylhexadeca-4,8-dienoic acid (MMHDA) (**50**) isolated from the brown alga *Ishige*  
42 *okamurae* has been shown to inhibit bacterial PLA<sub>2</sub> (IC<sub>50</sub> = 2 μg/mL) [39].  
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## 4. Future perspectives and concluding remarks

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Given the critical role of inflammation in diseases, identifying and developing novel anti-inflammatory drug candidates is of great importance in drug discovery. PLA<sub>2</sub>s play a very important role in inflammation, and they are hence regarded as an interesting target for anti-inflammatory drugs. Fifty marine natural products and counting have been identified as potent PLA<sub>2</sub> inhibitors. Although the quest for novel marine PLA<sub>2</sub> inhibitors faded a little during the 1990's, the last three years have been associated with a fresh spark of enthusiasm into this field of research. Additionally, significant progress has been made recently in the classification and characterization of the different families of phospholipases, and in the understanding of the biochemistry and biology of PLA<sub>2</sub>s. We can therefore expect a high number of novel, highly promising PLA<sub>2</sub> inhibitors to be developed over the next few years, from marine sources, as well as from terrestrial organisms or synthetically produced. Researchers working in this field of research are still facing some major challenges, as they need to find compounds that express high levels of specificity to the PLA<sub>2</sub>s that they are inhibiting. The development of a thorough understanding of the chemical and biological properties of the various types of PLA<sub>2</sub>s, and of their specificity to various diseases, is also a critical point that needs to be addressed, as is the precise understanding of the mechanism of action of PLA<sub>2</sub>-targeting drug candidates. Only recently have the specific biological roles of the different classes of PLA<sub>2</sub>s, and of the different isoforms within these classes, started to become understood, and even though a relatively large number of marine natural products have been tested for their PLA<sub>2</sub> inhibitory effects, most of them have only been screened against a single class of PLA<sub>2</sub>s. For the tested compounds to become potential drug candidates, or to become useful research tools in fundamental biology, it is absolutely critical to screen their bioactivity against each one of the four PLA<sub>2</sub> classes, and against various PLA<sub>2</sub> isoforms, and to establish the specificity of the compounds for their target PLA<sub>2</sub>. Specific PLA<sub>2</sub> inhibitors are indeed more likely to be bioactive at lower concentrations than non-specific inhibitors, and they are less prone to induce undesired side-effects [8]. Amongst the marine natural products included in the present review article, bolinaquinone (**1**) and manoalide (**20**) and its analogues have been shown to potently inhibit PLA<sub>2</sub>s, but in a non-specific manner. Manoalide (**20**) has been valued as a potential drug candidate, and it has been taken forward to clinical trials, but it had to be dropped due to formulation problems. To our knowledge, the sesterterpenes palauolol (**38**) and palauolide (**39**) have only been

1 evaluated for their potential to inhibit bee venom sPLA<sub>2</sub>. Yet, their IC<sub>50</sub> values were  
2 rather promising, and if the compounds' bioactivity could be shown to be paralleled  
3 with a good level of specificity, then **38** and **39** could potentially be considered as  
4 promising drug candidates, based on their PLA<sub>2</sub> inhibiting properties. Finally, when  
5 considering PLA<sub>2</sub>-inhibiting compounds to be taken forward into more advanced  
6 studies, it is important to make sure that the compounds in question do not completely  
7 abolish the PLA<sub>2</sub> activity. Instead, they should only bring PLA<sub>2</sub> activity down to the  
8 basal level, as some vital cellular housekeeping depends on basal levels of PLA<sub>2</sub>  
9 activity.  
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### 18 **Acknowledgements**

19  
20 The authors thank C. Cerella for a critical reading. M. Diederich's research at  
21 the Laboratoire de Biologie Moléculaire et Cellulaire du Cancer (LBMCC) is  
22 financially supported by "Recherche Cancer et Sang" foundation, by «Recherches  
23 Scientifiques Luxembourg» asbl, by «Een Häerz fir Kriibskrank Kanner» association,  
24 the Action Lions "Vaincre le Cancer" Luxembourg, The Fonds National de la  
25 Recherche Luxembourg, Televie Luxembourg and the Foundation for Scientific  
26 Cooperation between Germany and Luxemburg is thanked for additional support.  
27 Further support was received from the European Union (ITN "RedCat" 215009 and  
28 Interreg IVa project "Corena").  
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## 5. Legends to figures

### Figure 1. The PLA<sub>2</sub>-mediated inflammation signaling cascade

cPLA<sub>2</sub>s are calcium-dependent enzymes activated by extra-cellular stimulations from pathogens, tissue injury, or physical or chemical stresses. The cytosolic concentrations of calcium required for PLA<sub>2</sub> activation result from the cleavage of phospholipids into IP<sub>3</sub> by PLC, followed by the binding of IP<sub>3</sub> to calcium channels in the endoplasmic reticulum. PLA<sub>2</sub>s hydrolyze the *sn*-2 acyl ester bond of membrane phospholipids, which leads to the release of arachidonic acid and lysophospholipids. Arachidonic acid is oxygenated into PGH<sub>2</sub> by COX, or into 5-HPTETE by LOX. PGH<sub>2</sub> is the unstable precursor of PGD<sub>2</sub>, PGE<sub>2</sub>, PGI<sub>2</sub>, and thromboxane A<sub>2</sub> (TXA<sub>2</sub>). PGE<sub>2</sub> and PGI<sub>2</sub> enhance edema formation, pain induction, and fever development. TXA<sub>2</sub> triggers platelet aggregation. LOX converts arachidonic acid into 5-HPTETE, which is spontaneously reduces to 5-HETE, and then to leukotriene A<sub>4</sub>. LTA<sub>4</sub> may be converted to LTB<sub>4</sub>, a potent chemoattractant for polymorphonuclear leukocytes. Eosinophils, mast cells, and alveolar macrophages conjugate glutathione with LTA<sub>4</sub> to make LTC<sub>4</sub>, which is transported outside the cell where a glutamic acid moiety is removed to make LTD<sub>4</sub>. LTD<sub>4</sub> is then cleaved by dipeptidases to make LTE<sub>4</sub>. LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> play an important role in atherosclerosis, asthma, allergic rhinitis, and inflammatory gastrointestinal diseases. The lysophospholipids produced during the conversion of membrane phospholipids to arachidonic acid are a precursor for PAF.

### Figure 2. Molecular structure of marine PLA<sub>2</sub> inhibitors.

**Table 1. Bioactivity of marine PLA2 inhibitors.**

Compound	Source organism	target PLA <sub>2</sub>	IC <sub>50</sub> (μM)	References
<u>Sesquiterpenes</u>				
bolinaquinone <b>1</b>	<i>Dysidea</i> sp. (S)	non-specific	0.1	[13]
ilimaquinone <b>2</b>	<i>Hippiospongia metachromia</i> (S)	bee venom sPLA <sub>2</sub>	< 270	[19, 20]
avarol <b>3</b>	<i>D. avara</i> (S)	sPLA <sub>2</sub>	2	[17-19]
avarone <b>4</b>	<i>D. avara</i> (S)	sPLA <sub>2</sub>	2	[17-19]
dysidine <b>5</b>	<i>D. avara</i> (S)	sPLA <sub>2</sub>	2	[16-19]
dysidiotronic acid <b>6</b>	<i>D. avara</i> (S)	sPLA <sub>2</sub>	2.6	[18, 19]
cavernolide <b>7</b>	<i>Fasciospongia cavernosa</i> (sponge)	sPLA <sub>2</sub>	8.8	[16, 18, 20, 21]
rhipocephalin <b>8</b>	<i>Rhipocephalus phoenix</i> (GA)	bee venom sPLA <sub>2</sub>	> 4.0	[21]
caulerpyne <b>9</b>	<i>Caulerpa prolifera</i> (GA)	bee venom sPLA <sub>2</sub>	> 4.0	[21]
<u>Diterpenes</u>				
gracilin A <b>10</b>	<i>Aplysilla</i> sp. (S)	bee venom sPLA <sub>2</sub>	5	[20]
aplyroseol 1 <b>11</b>	<i>Aplysilla</i> sp. (S)	bee venom sPLA <sub>2</sub>	5	[20]
12-acetoxytetrahydro-aplysulphurin1 <b>12</b>	<i>Aplysilla</i> sp. (S)	bee venom sPLA <sub>2</sub>	5	[20]
dendrillolide A <b>13</b>	<i>Dendrilla</i> sp. (S)	bee venom sPLA <sub>2</sub>	5	[20]
norrisolide <b>14</b>	<i>Dendrilla</i> sp. (S)	bee venom sPLA <sub>2</sub>	5	[20]
epitaondiol <b>15</b>	<i>Styopodium flabelliforme</i> (BA)	human sPLA <sub>2</sub>	3.8	[19, 23]
<u>Sesterterpenes</u>				
manoalide <b>20</b>	<i>Luffariella variabilis</i> (S)	human sPLA <sub>2</sub> : snake venom sPLA <sub>2</sub> : cPLA <sub>2</sub> :	1.7 10	[4, 5, 27, 29, 30]
secomanoalide <b>21</b>	<i>L. variabilis</i> (S)	snake venom sPLA <sub>2</sub> :	< 0.1	[20, 29, 30]
luffariellolide <b>22</b>	<i>L. variabilis</i> (S)	bee venom sPLA <sub>2</sub>	0.2	[20, 29, 30]
luffariellin A-B <b>23-24</b>	<i>L. variabilis</i> (S)	bee venom sPLA <sub>2</sub>	0.06	[20, 29, 30]
luffolide <b>25</b>	<i>L. variabilis</i> (S)	bee venom sPLA <sub>2</sub>	0.04	[20, 29, 30]

1	luffariellin C-D <b>26-27</b>	<i>Chromodoris</i> sp. (N)	snake venom sPLA <sub>2</sub>	0.2	[29, 30]
2	deoxymanoalide <b>28</b>	<i>Chromodoris</i> sp. (N)	snake venom sPLA <sub>2</sub>	0.2	[29, 30]
3	deoxyseco-	<i>Chromodoris</i> sp.	snake venom		
4	manoalide <b>29</b>	(N)	sPLA <sub>2</sub>	0.5	[29, 30]
5	cacospongiolide B <b>30</b>	<i>Fasciospongia</i> <i>cavernosa</i> (S)	human and bee venom sPLA <sub>2</sub>	0.3	[29, 30]
6	cyclolinteinone <b>31</b>	<i>Cacospongia</i> <i>linteiformis</i> (S)	bee venom sPLA <sub>2</sub>	25	[29, 30]
7	variabilin <b>32</b>	various sponges	human sPLA <sub>2</sub> and cPLA <sub>2</sub>	6.9	[29, 30]
8	halistanol sulphate 1	<i>Halichondria</i> sp.	bee venom		[18, 20, 29,
9	<b>33</b>	(S)	sPLA <sub>2</sub>	50	30]
10	petrosaspongiolide M	<i>Petrosaspongia</i>	human and		
11	<b>34</b>	<i>nigra</i> (S)	bee venom sPLA <sub>2</sub>	0.6	[18, 29, 30]
12	scalaradial <b>35</b>	<i>Cacospongia</i> <i>mollior</i> (S)	bee venom sPLA <sub>2</sub> and cPLA <sub>2</sub>	0.6	[18, 20, 29, 30]
13	aplyolide <b>36</b>	<i>Aplysinopsis</i> <i>elegans</i> (S)	human sPLA <sub>2</sub>	10.5	[18]
14	palinurin <b>37</b>	<i>Ircinia echinata</i> (S)	bee venom sPLA <sub>2</sub>	50	[18, 29, 30]
15	palauolol <b>38</b>	<i>Fascaplysinopsis</i> sp. (S)	bee venom sPLA <sub>2</sub>	0.8	[18, 29, 30]
16	palauolide <b>39</b>	<i>Fascaplysinopsis</i> sp. (S)	bee venom sPLA <sub>2</sub>	0.8	[18, 29, 30]
17	cladocorans	<i>Cladocora</i>			
18	A-B <b>40-41</b>	<i>cespitosa</i> (C)	sPLA <sub>2</sub>	< 2.0	[37]
19	<u>Bromohydroquinones</u>				
20	cymopol <b>42</b>	<i>Cymopolia barbata</i> (GA)	bee venom sPLA <sub>2</sub>	> 4.7	[21]
21	cyclocymopol <b>43</b>	<i>Cymopolia barbata</i> (GA)	bee venom sPLA <sub>2</sub>	> 3.7	[21]
22	<u>Alkaloids</u>				
23	spongidine A-D <b>44-47</b>	<i>Spongia</i> sp. (S)	human sPLA <sub>2</sub>	10	[38]
24	<u>Bromophenols</u>				
25	vidalol A-B <b>48-49</b>	<i>Vidilia obtusaloba</i> (RA)	bee venom sPLA <sub>2</sub>	5	[20]
26	<u>Methoxylated fatty</u>				
27	acid				
28	MMHDA <b>50</b>	<i>Ishige okamurae</i> (BA)	bacterial PLA <sub>2</sub>	2	[39]

BA, brown alga; C, coral, F, fungus; GA, green alga; N, nudibranch; N.A., not available; RA, red alga; S, sponge

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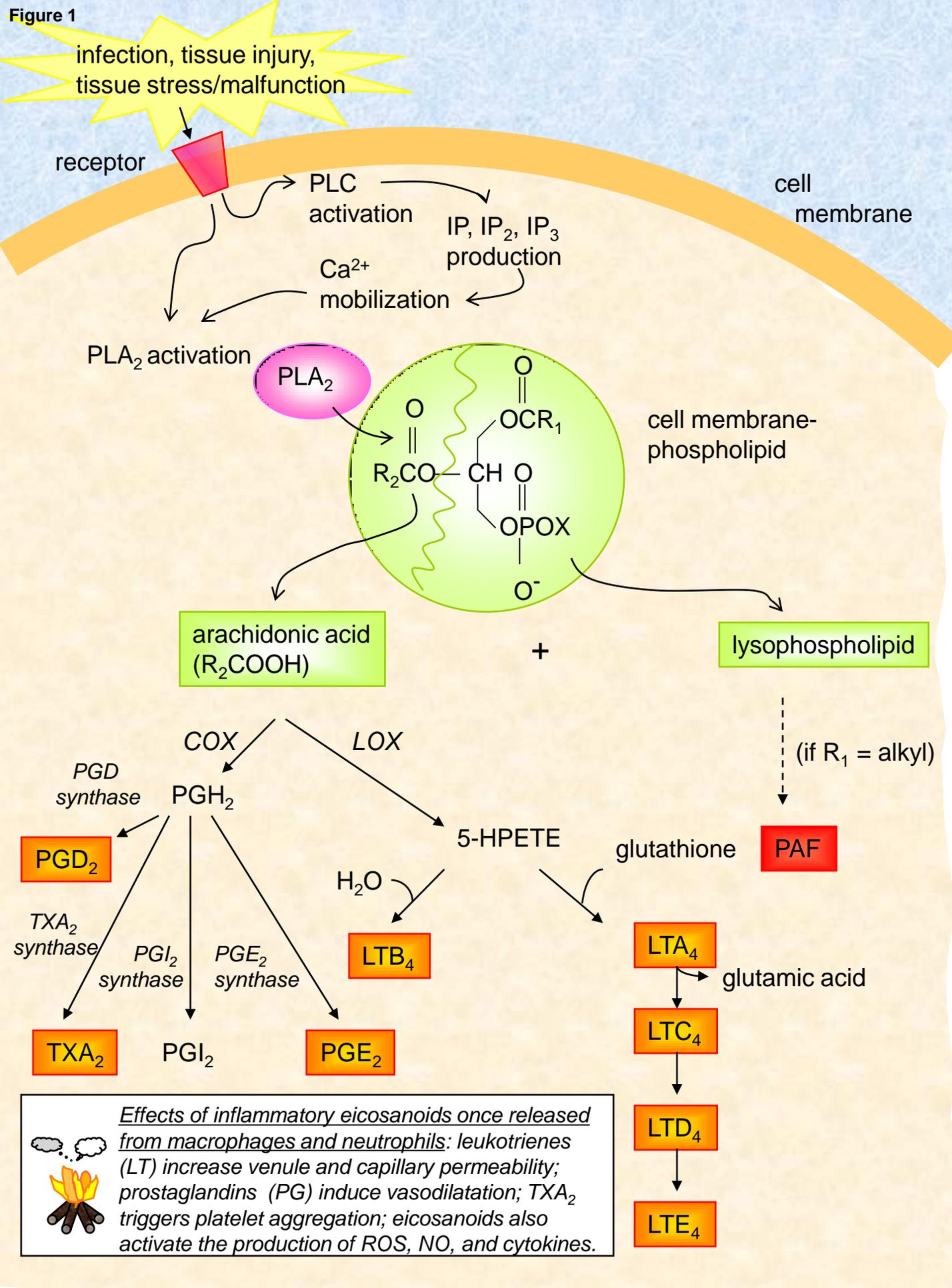
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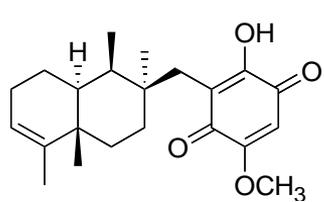
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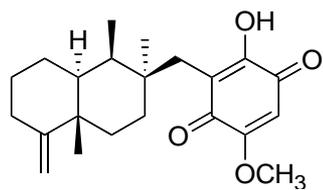
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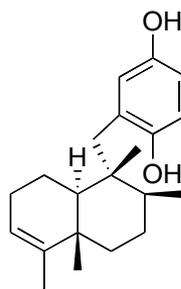
**Figure 2**



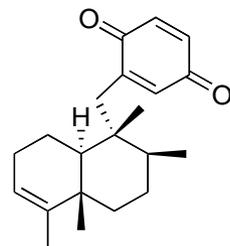
**1 bolinaquinone**



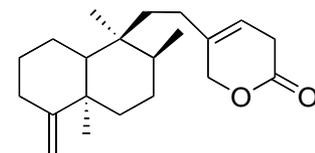
**2 ilimaquinone**



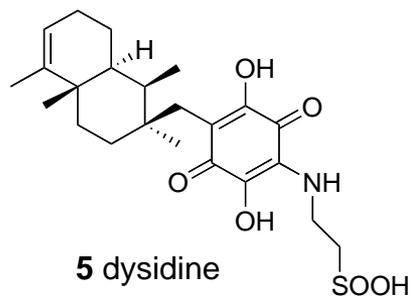
**3 avarol**



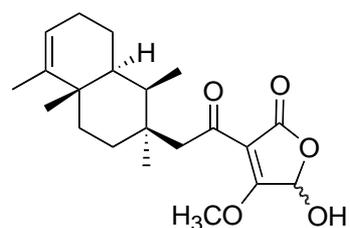
**4 avarone**



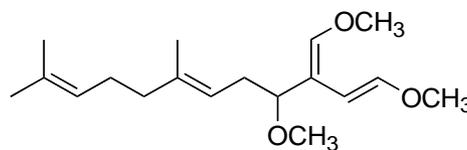
**7 cavernolide**



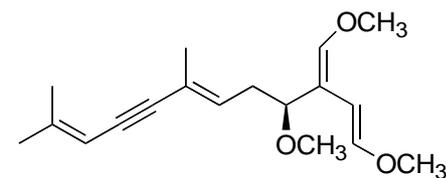
**5 dysidine**



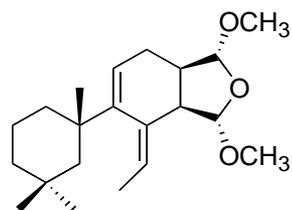
**6 dysidiotronic acid**



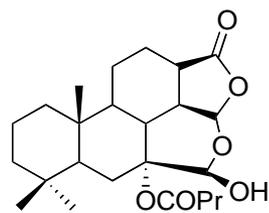
**8 rhipocephalin**



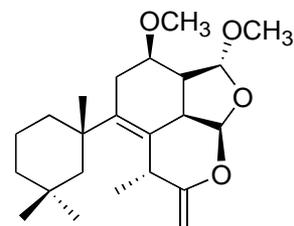
**9 caulerpyne**



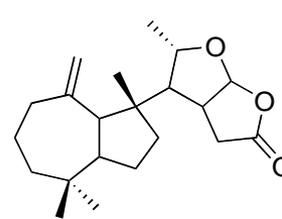
**10 gracilin A**



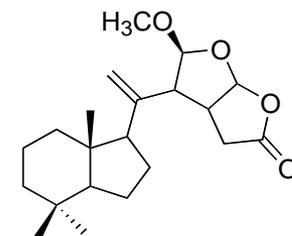
**11 aplyroseol 1**



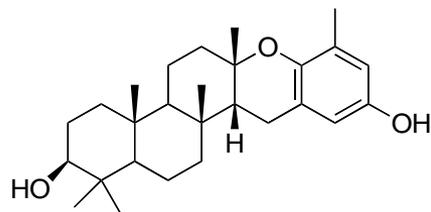
**12 12-acetoxytetrahydroxyaplysulphurin 1**



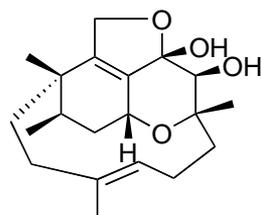
**13 dendrillolide A**



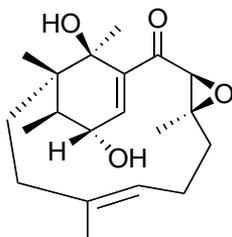
**14 norrisolide**



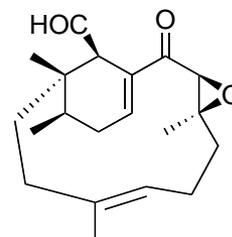
**15 epitaondiol**



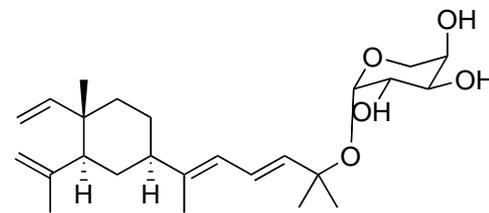
**16 phomactin A**



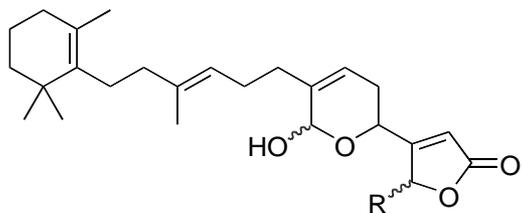
**17 phomactin B**



**18 phomactin C**

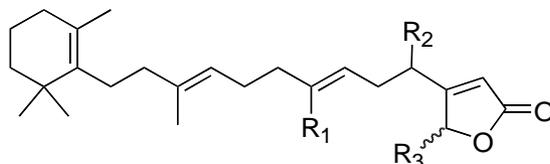


**19 fucoside B**



**20** R = OH manoalide

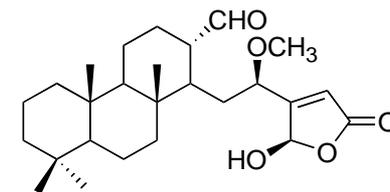
**28** R = H deoxymanoalide



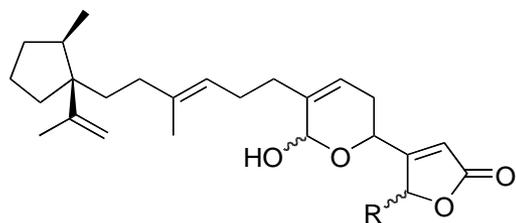
**21** R<sub>1</sub> = CHO, R<sub>2</sub> = OH, R<sub>3</sub> = OH secomanoalide

**22** R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = H, R<sub>3</sub> = OH luffariellolide

**29** R<sub>1</sub> = CHO, R<sub>2</sub> = OH, R<sub>3</sub> = H deoxysecomanoalide

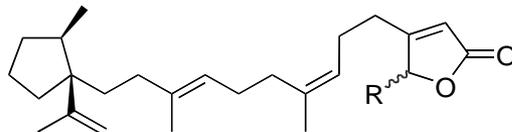


**25** luffolide



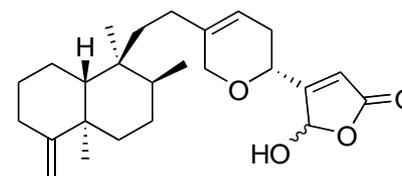
**23** R = OH luffariellin A

**26** R = H luffariellin C

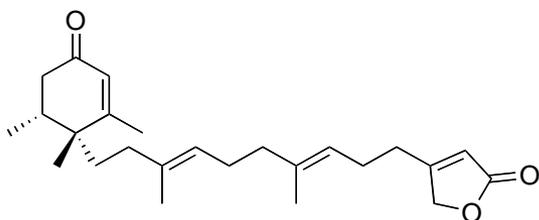


**24** R = OH luffariellin B

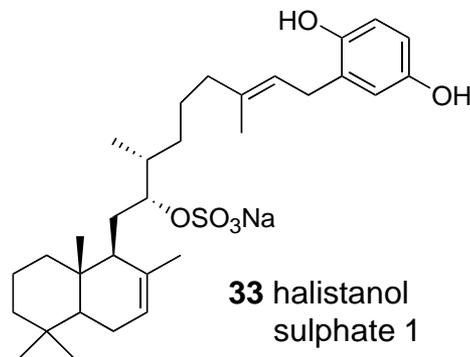
**27** R = H luffariellin D



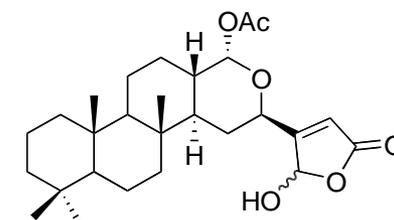
**30** cacospongiolide B



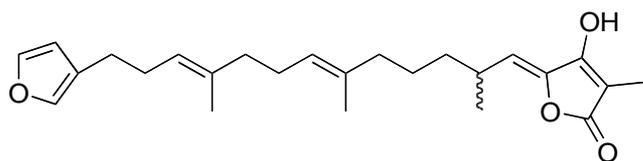
**31** cyclolinteinone



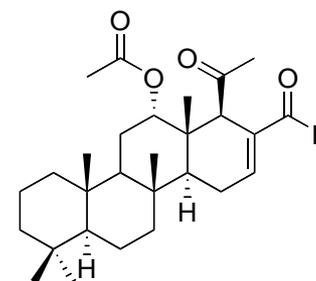
**33** halistanol  
sulphate 1



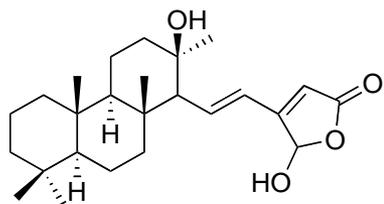
**34** petrosaspongiolide M



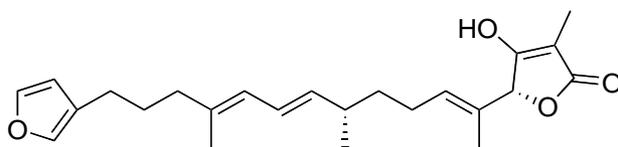
**32** variabilin



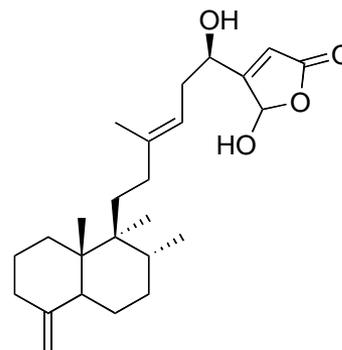
**35** scalarial



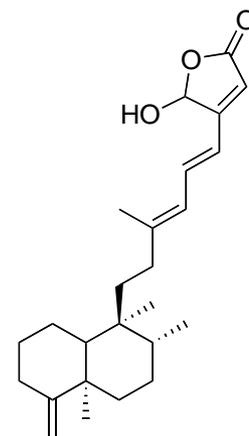
**36** alyolide A



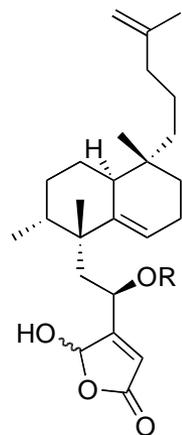
**37** palinurin



**38** palaulol

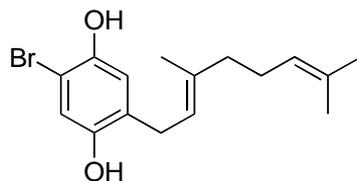


**39** palaulide

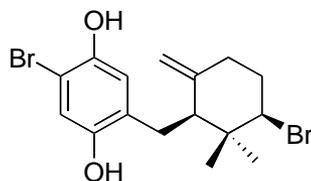


**40** R = CH<sub>3</sub>COOH cladocoran A

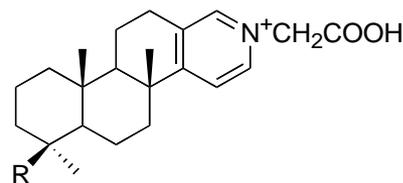
**41** R = H cladocoran B



**42** cymopol

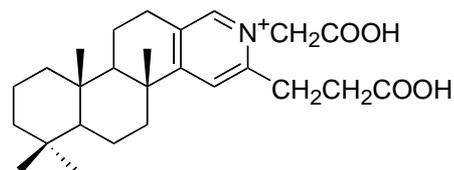


**43** cyclocymopol

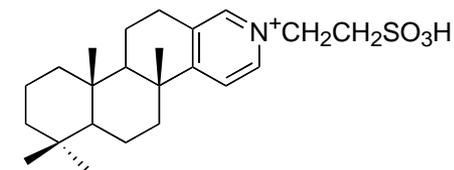


**44** R = CH<sub>3</sub> spongidine A

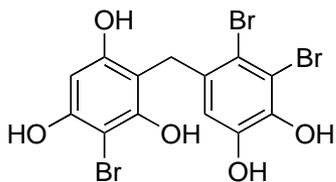
**45** R = CH<sub>2</sub>OCH<sub>3</sub> spongidine B



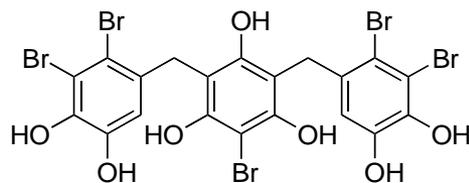
**46** spongidine C



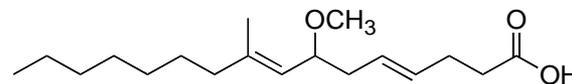
**47** spongidine D



**48** vidalol A



**49** vidalol B



**50** MMHDA

