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Marine natural products targeting phospholipases A2

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Abstract

Phospholipases A₂ (PLA₂s) 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, PLA₂s have been considered as potential targets in anti-inflammatory drug discovery.

Marine natural products are a rich source of bioactive compounds, including PLA₂ inhibitors. Here, we review the properties of marine PLA₂ inhibitors identified since the first discovery of PLA₂ inhibitory activity in the marine natural product manoalide in the mid 1980's.

Keywords: anti-inflammatory; arachidonic acid; eicosanoids; marine natural product; membrane phospholipids; PLA₂

Abbreviations

5-HPTETE, 5-hydroperoxyeicosatetraenoic acid; COX, cyclooxygenase; cPLA₂, cytosolic PLA₂; IP₃, inositol 1,4,5-triphosphate; iPLA₂, calcium independent PLA₂; LOX, lipoxygenase; (Lp)PLA₂, lipoprotein-associated PLA₂; LT, leukotriene; NO, nitric oxide; PAF, platelet-activating factor; PG, prostaglandin; PLA₂, phospholipase A₂; PLC, phospholipase C; ROS, reactive oxygen species; sPLA₂, secretory PLA₂; TX, thromboxane

1. Introduction

Inflammation is the response of vascular tissues to harmful stimuli such as injury, pathogens, or irritants. While inflammation normally functions as a defense mechanism in higher animals, deregulated inflammation is implicated in a large number of diseases such as autoimmune diseases, allergies, asthma, rheumatoid arthritis, inflammatory bowel diseases, pelvic inflammatory diseases, glomerulonephritis, atherosclerosis, myocardial ischemia, and cancer [1-3]. The process of inflammation is controlled by a group of substances called chemical mediators [1]. Endogenous chemical mediators consist of vasoactive amines, cytokines, bradykinin, fibrin, complement components, eicosanoids, platelet activating factor (PAF), nitric oxide (NO), and neuropeptides [1]. Eicosanoids, in particular, play a critical role in virtually every step of inflammation. Eicosanoids, which comprise prostaglandins, prostacyclins, thromboxanes, and leukotrienes, are a family of oxygenated fatty acid metabolized by cyclooxygenases (COX) and lipoxygenases (LOX) from arachidonic acid [1]. Despite the extensive efforts invested in developing drugs that suppress the conversion of arachidonic acid into pro-inflammatory eicosanoids, the latter approach has been unsuccessful. Undesired side-effects resulting from the lack of specificity of COX and LOX are responsible for the failure of the concept [2]. As an alternative, the quest for inhibitors of phospholipases A₂ (PLA₂s), the enzymes that catalyze the hydrolysis of membrane phospholipids into arachidonic acid, has opened up a new research avenue in anti-inflammatory drug discovery [2, 4-6]. As a matter of fact, PLA₂s isolated from snake venom have been shown to induce all the inflammatory symptoms of snakebite such as acute pain, oedema, hypotension, hemorrhage, and neuromuscular junction blockage. Furthermore, rheumatoid arthritis, asthma, psoriasis, myocardial ischemia, and pancreatitis have all been shown to be associated with elevated levels of serum PLA₂. Lysophospholipids produced by PLA₂s have also been shown to induce gastric ulceration in rats, and to induce an inflammation similar to acute cholecystitis in the gall bladder mucosa [3]. Here, we review the properties of marine PLA₂ inhibitors identified since the first discovery of PLA₂ inhibitory activity in the marine natural product manoalide (**1**), 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.

2. The PLA₂-mediated inflammation signaling cascade

PLA₂s 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 PLA₂s have been characterized to date. They are grouped into four families: secreted PLA₂s (sPLA₂s), cytosolic PLA₂s (cPLA₂s), lipoprotein associated PLA₂s ((Lp)PLA₂), and calcium-independent PLA₂s (iPLA₂s) [2, 5, 6]. The calcium-dependent sPLA₂s 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 sPLA₂s involves a nucleophilic attack onto the phospholipid's *sn*-2 bond. While the role of sPLA₂s in inflammation remains poorly understood, it has been suggested that sPLA₂s induce an increase in cPLA₂-dependent eicosanoid release, and that they synergize with other pro-inflammatory mediators [2, 6]. cPLA₂s are 85 kDa enzymes containing a serine and an aspartic acid residue in the active site. Noteworthy, cPLA₂s are the only PLA₂s with specificity for arachidonic acid at the phospholipase *sn*-2 position. cPLA₂s 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 PLA₂ activation result from the cleavage of phospholipids into inositol 1,4,5-triphosphate (IP₃) by phospholipase C (PLC), followed by the binding of IP₃ 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, cPLA₂s 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 cPLA₂-specific drug candidates [7-9]. Unlike cPLA₂s, (Lp)PLA₂s, 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)PLA₂s have become an important target in PLA₂ inhibitory drug discovery, as they are known to lead to coronary heart diseases [6]. iPLA₂s have complex and still poorly understood implications in signalling pathways. iPLA₂s play a role in bone formation, apoptosis, insulin secretion, sperm development, and axon regeneration [2, 6]. The present review focuses only on inhibitors of sPLA₂s and

cPLA₂s. 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**, PLA₂s 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 ω -6 fatty acid arachidonic acid and of lysophospholipids [7]. Next, arachidonic acid is oxygenated into prostaglandin (PG) PGH₂ by COX, or into 5-hydroperoxyeicosatetraenoic acid (5-HPTETE) by LOX. The conversion of arachidonic acid to PGH₂ by COX occurs in two steps. First, two molecules of O₂ 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 (PGG₂). One of the peroxide linkages then sheds a single oxygen atom to form the PGH₂ [1]. PGH₂ is the unstable precursor of PGD₂, PGE₂, PGI₂, and thromboxane A₂ (TXA₂) [1]. PGE₂ and PGI₂ 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. PGE₂ induces pain, heat, and fever. TXA₂ 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 A₄. LTA₄ may be converted to LTB₄. LTB₄ 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. LTB₄ 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 LTC₄ synthase to conjugate glutathione with LTA₄ to make LTC₄, which is transported outside the cell where a glutamic acid moiety is removed to make LTD₄. LTD₄ is then cleaved by dipeptidases to make LTE₄. LTC₄, LTD₄, and LTE₄ 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 PLA₂ inhibitors

PLA₂ 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 PLA₂ inhibitors, which may be used as chemical defences in their natural environment. Marine PLA₂ 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. PLA₂ inhibiting sesquiterpenes

One of the most investigated marine PLA₂ inhibitors is the meros sesquiterpene bolinaquinone (**1**) isolated from the sponge *Dysidea* sp. Bolinaquinone (**1**) has been shown to inhibit the enzymatic activity of sPLA₂ with an IC₅₀ value of 100 nM [13]. While the inhibition of sPLA₂ by bolinaquinone (**1**) is very potent, it is not selective against this enzyme. Bolinaquinone **1** is known to also affects cPLA₂ [13-19]. Bolinaquinone (**1**) is known to reduce LTB₄ production in neutrophils and NO and PGE₂ 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 PLA₂ (IC₇₅ = 270 µM against bee venom sPLA₂) [19]. The anti-psoriasis sesquiterpene hydroquinone avarol (**3**) and the sesquiterpene quinones avarone (**4**) and dysidine (**5**) isolated from the sponge *Dysidea avara* inhibit sPLA₂ activity and PGE₂ release in keratinocytes and in monocytes (IC₅₀ = 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 sPLA₂ (IC₅₀ = 2.6 µM) [18, 19]. The sesquiterpene lactone cavernolide (**7**) isolated from the sponge *Fasciospongia cavernosa* inhibits sPLA₂ activation (IC₅₀ = 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 sPLA₂ (IC₁₀₀ = 4.1 µM),

and caulerpyne (**9**) produced by the green alga *Caulerpa prolifera* inhibits bee venom sPLA₂ activity with an IC₉₂ value of 4.2 μM [21].

3.2. PLA₂ 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 sPLA₂ with IC₅₀ 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 TXB₂ production by potently inhibiting human sPLA₂ (IC₅₀ = 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 cPLA₂s or by activating (Lp)PLA₂ [9, 23, 24]. The arabidose-containing diterpene fuscoid B (**19**) isolated from the gorgonian *Eunicea fusca* has not been reported as a PLA₂ inhibitor, but it has been shown to inhibit the conversion of arachidonic acid to LTB₄ by inhibiting 5-LO (IC₅₀ = 18 μM) [18, 25].

3.3. PLA₂ 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 PLA₂ inhibitor, and it remains, to date, the most investigated marine PLA₂ antagonist. The PLA₂ 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 PLA₂ 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 PLA₂s [27]. Manoalide (**20**) inhibits human sPLA₂ (IC₅₀ = 1.7 μM); snake venom sPLA₂ (IC₅₀ = 0.03 μM); and cPLA₂ (IC₅₀ = 10 μM) [8, 14,

15, 18, 27, 28]. Manoalide (**20**) has been shown to inhibit cPLA₂ (IC₅₀ = 10 μM) and phospholipase C [27]. Mechanistic studies revealed that the PLA₂ 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 PLA₂ [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 secomanalide (**21**), which has the same potency as manoalide (**20**), luffariellolide (**22**) (IC₅₀ = 230 nM against bee venom sPLA₂), luffariellins A (**23**) and B (**24**) (IC₅₀ = 60 nM against bee venom sPLA₂), and luffolide (**25**) (IC₅₀ = 40 nM against bee venom sPLA₂) [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**) (IC₅₀ = 0.2 μM against snake venom PLA₂) and deoxysecomanalide (**29**) (IC₅₀ = 0.5 μM against snake venom PLA₂), are all reduced (deoxy) counterparts of spongean manoalide analogues, and their PLA₂ inhibitory activity is a ten-fold weaker than the ones observed in the sponges [29, 30]. Other PLA₂ inhibiting sesterterpenes isolated from various marine sponges include cacospongiolide B (**30**) (IC₅₀ = 300 nM against human and bee venom sPLA₂), cyclolinteinone (**31**) (IC₅₀ = 25 μM against bee venom sPLA₂), variabilin (**32**) (IC₅₀ = 6.9 μM against human sPLA₂ and cPLA₂), halistanol sulphate 1 (**33**) (IC₅₀ = 16 μg/mL against bee venom sPLA₂), petrosaspongiolide M (**34**) (IC₅₀ = 1.6 μM against human sPLA₂; 0.6 μM against bee venom PLA₂), scalaradial (**35**) (IC₅₀ = 1.6 nM against bee sPLA₂ and cPLA₂), aplyolide (**36**) (IC₅₀ = 10.5 μM against human sPLA₂), palinurin (**37**) (IC₅₀ = 50 μM against bee venom sPLA₂), palauolol (**38**) (IC₅₀ = 0.8 μg/mL against bee venom sPLA₂), and palauolide (**39**) (IC₅₀ = 0.8 μg/mL against bee venom sPLA₂) [12, 14, 18, 20, 31-34]. Molecular modelling studies have revealed that petrosaspongiolide M (**34**) inhibits PLA₂ *via* a non-covalent recognition between petrosaspongiolide M (**34**) and the enzyme, followed by a nucleophilic attack by the PLA₂ N-terminus onto the masked aldehyde at C-25 of the pharmacophoric γ-

hydroxybutenolide ring of petrosaspongiolide M (**34**) [30, 32, 35, 36]. Petrosaspongiolide M (**34**) also inhibits the expression of iNOS and COX-2, and, as a result, the production of NO and PGE₂, respectively, and NF-κB activation [30, 32-35]. Studies performed by Monti *et al.* have revealed that, although scalaradial (**35**) does bind covalently to bee venom PLA₂, the key step in the PLA₂ inhibitory activity of scalaradial (**35**) is, as observed with petrosaspongiolide M (**34**), its nonvalent binding to the enzyme's active site [33]. The furanosesterterpene palinurin (**37**) isolated from the sponge *Ircinia echinata* has been shown to inhibit TXB₂ (IC₅₀ = 5 μM), and the furan ring is thought to be the pharmacophore of the molecule [36]. The sesterterpenes cladocoran A (**40**) and B (**41**) isolated from the coral *Cladocora cespitosa* inhibit sPLA₂ (IC₅₀ = 0.78 μM and 1.95 μM, respectively) [37]. Cladocoran A (**40**) and B (**41**) caught the attention of Miyako *et al.* because of their possession of a γ-hydroxybutenolide moiety as in manoalide (**20**) and cacospongiolide B (**30**). Interestingly, studies on diastereoisomers of cladocoran A (**40**) and B (**41**) revealed that the presence of a γ-hydroxybutenolide moiety itself is not sufficient for PLA₂ inhibitory activity, and that the size and shape of the molecule also play critical roles towards the compounds' potency [37].

3.4. Non-terpenoid marine PLA₂ inhibitors

The bromohydroquinones cymopol (**42**) and cyclocymopol (**43**) isolated from the green alga *Cymopolia barbata* inhibit bee venom sPLA₂ activity with IC₉₈ values of 4.7 and 3.4 μM, respectively [21]. The pyridinium alkaloids spongidines A-D (**44-47**) isolated from the sponge *Spongia* sp. inhibit human sPLA₂ (IC₅₀ = 10 μM) [38], and the bromophenols vidalol A (**48**) and B (**49**) isolated from the red alga *Vidilia obtusiloba* inhibit bee venom sPLA₂ (IC₅₀ = 1.6 μg/mL) despite lacking a γ-hydroxybutenolide or masked 1,4-dialdehyde group [20]. Finally, one of the most recently discovered marine PLA₂ inhibitors, namely the methoxylated fatty acid 7-methoxy-9-methylhexadeca-4,8-dienoic acid (MMHDA) (**50**) isolated from the brown alga *Ishige okamurae* has been shown to inhibit bacterial PLA₂ (IC₅₀ = 2 μg/mL) [39].

4. Future perspectives and concluding remarks

Given the critical role of inflammation in diseases, identifying and developing novel anti-inflammatory drug candidates is of great importance in drug discovery. PLA₂s 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 PLA₂ inhibitors. Although the quest for novel marine PLA₂ 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 PLA₂s. We can therefore expect a high number of novel, highly promising PLA₂ 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 PLA₂s that they are inhibiting. The development of a thorough understanding of the chemical and biological properties of the various types of PLA₂s, 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 PLA₂-targeting drug candidates. Only recently have the specific biological roles of the different classes of PLA₂s, 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 PLA₂ inhibitory effects, most of them have only been screened against a single class of PLA₂s. 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 PLA₂ classes, and against various PLA₂ isoforms, and to establish the specificity of the compounds for their target PLA₂. Specific PLA₂ 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 PLA₂s, 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 sPLA₂. Yet, their IC₅₀ 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 PLA₂ inhibiting properties. Finally, when
5 considering PLA₂-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 PLA₂ activity. Instead, they should only bring PLA₂ activity down to the
8 basal level, as some vital cellular housekeeping depends on basal levels of PLA₂
9 activity.
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5. Legends to figures

Figure 1. The PLA₂-mediated inflammation signaling cascade

cPLA₂s 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 PLA₂ activation result from the cleavage of phospholipids into IP₃ by PLC, followed by the binding of IP₃ to calcium channels in the endoplasmic reticulum. PLA₂s 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 PGH₂ by COX, or into 5-HPTETE by LOX. PGH₂ is the unstable precursor of PGD₂, PGE₂, PGI₂, and thromboxane A₂ (TXA₂). PGE₂ and PGI₂ enhance edema formation, pain induction, and fever development. TXA₂ triggers platelet aggregation. LOX converts arachidonic acid into 5-HPTETE, which is spontaneously reduces to 5-HETE, and then to leukotriene A₄. LTA₄ may be converted to LTB₄, a potent chemoattractant for polymorphonuclear leukocytes. Eosinophils, mast cells, and alveolar macrophages conjugate glutathione with LTA₄ to make LTC₄, which is transported outside the cell where a glutamic acid moiety is removed to make LTD₄. LTD₄ is then cleaved by dipeptidases to make LTE₄. LTC₄, LTD₄, and LTE₄ 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 PLA₂ inhibitors.

Table 1. Bioactivity of marine PLA2 inhibitors.

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

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

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

5. Bibliography

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Figure 1

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 manolide

28 R = H deoxymanolide

21 R₁ = CHO, R₂ = OH, R₃ = OH secomanolide

22 R₁ = CH₃, R₂ = H, R₃ = OH luffariellolide

29 R₁ = CHO, R₂ = OH, R₃ = H deoxysecomanolide

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 scalaradial

36 aplyolide A

37 palinurin

38 palaulol

39 palaulide

40 R = CH₃COOH cladocoran A

41 R = H cladocoran B

42 cymopol

43 cyclocymopol

44 R = CH₃ spongidine A

45 R = CH₂OCH₃ spongidine B

46 spongidine C

47 spongidine D

48 vidalol A

49 vidalol B

50 MMHDA