



## UNUSUAL FATTY ACIDS INCORPORATED INTO NATURAL PEPTIDES DERIVED FROM SEAWEEDS AND INVERTEBRATES

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### ABSTRACT

This review is a first comprehensive survey focuses on the unique, unusual and rare fatty acids incorporated into natural peptides derived from seaweeds and invertebrates. Fatty acids incorporated into lipopeptides are of particular interest because many of them display important biological activities and possess antibacterial, antimicrobial, antifungal, antitumour, phototoxic, HIV-inhibitory, or immunosuppressive properties. There is no doubt that they are of great interest, especially for the medical chemistry and pharmaceutical industries. This review presents structures and describes cytotoxic activities of more than 100 unusual fatty acids incorporated into natural lipopeptides isolated from seaweeds and invertebrates.

**KEYWORDS:** Fatty acids, lipopeptides, peptides, seaweeds, sponges, mollusks, tunicate.

### 1. INTRODUCTION

Bioactive lipid compounds are molecules from natural sources that have been biologically assayed for activities in a number of key therapeutic areas.<sup>[1,18]</sup> Some bioactive lipids have been linked to good health for many years and it appears that bioactive food components can alter gene expression to influence a host of cellular events, thereby influencing health outcomes or providing beneficial antioxidant or enzyme-inhibitory activities.<sup>[19,29]</sup>

Many algae and invertebrate species have long been used as human food, animal fodder and sources of valuable substances, including lipids. Marine seaweeds and invertebrates are rich in unusual lipids, phospholipids, glycolipids and polyunsaturated fatty acids and are of potential value as sources of essential fatty acids, important in the nutrition of humans and animals.<sup>[1,18,30,39]</sup>

Scanning over 25,000 structures of natural peptides including with lipophilic moiety which have been isolated from various organisms, we observed that these compounds in absolute majority (over 80%) contained fragments of saturated fatty acids (C<sub>6:0</sub> - C<sub>26:0</sub>), about 15% *iso*-, *anteiso*- and *neo*- saturated fatty acids (C<sub>6:0</sub> - C<sub>24:0</sub>), about 4-5% unsaturated fatty acid. The few exceptions of fatty acids not included in this review are amine fatty (carboxylic) acids and those mentioned above. Rare and unusual fatty acids constitute just about one percent.

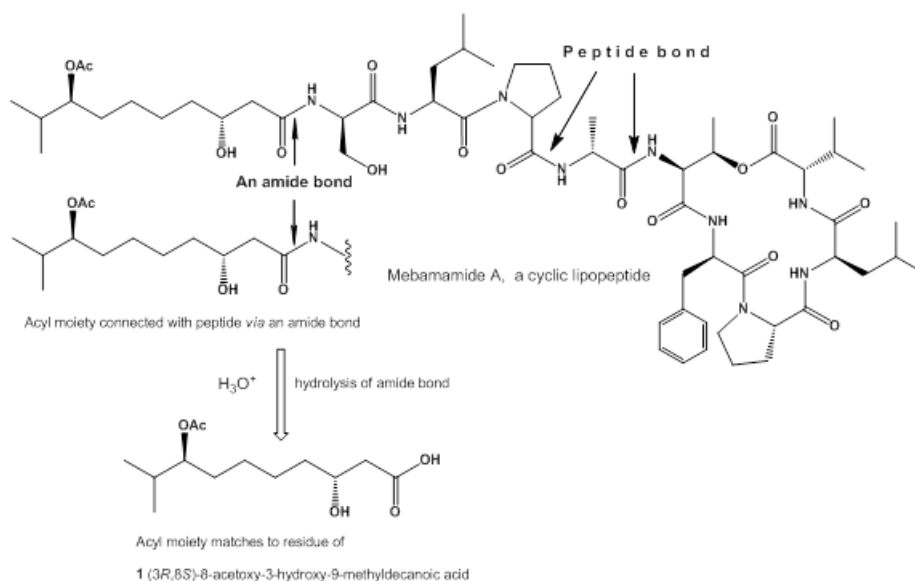
In these comprehensive analysis, we would indicate rare and unusual fatty acids been incorporated into natural peptides of seaweeds and invertebrates. These lipopeptides showed impressive biological activities, with applications in the field of crop protection, human health, medicine and lipid chemistry and biochemistry. This review is dedicated to the unusual fatty acids incorporated into the natural peptides of algae and invertebrates.

### 2. FATTY ACIDS DERIVED FROM SEAWEEDS LIPOPEPTIDES

Seaweeds are a phylogenetically diverse group of aquatic plants. They comprise evolutionary distant lineages belonging to three main taxonomic groups (Chlorophyta, Phaeophyta and Rhodophyta).<sup>[40]</sup> Marine macrophytes have attracted interest due to the interesting biological activities they possess, including antimicrobial, antiviral, anti-inflammatory and immunotropic properties.<sup>[41,46]</sup> Seaweeds have been recognized as a source of potentially valuable and recoverable bioactive substances.<sup>[3,5,7,8-13]</sup> These features may be related to the high content of different glycolipids, phospholipids, which along with fatty acids, are the main polar lipids of marine macrophytes.<sup>[3,5,7,31,36]</sup>

There are a large number of reviews on the use of algae as food and related biological activity.<sup>[4,6,30,39,41,46]</sup> However, there are no articles devoted to fatty acids derived from algae lipopeptides.

Examples of cyclic lipopeptides isolated from green alga are shown in Figure 1. Fatty acids described in this text were formed by hydrolysis of the amide bond.

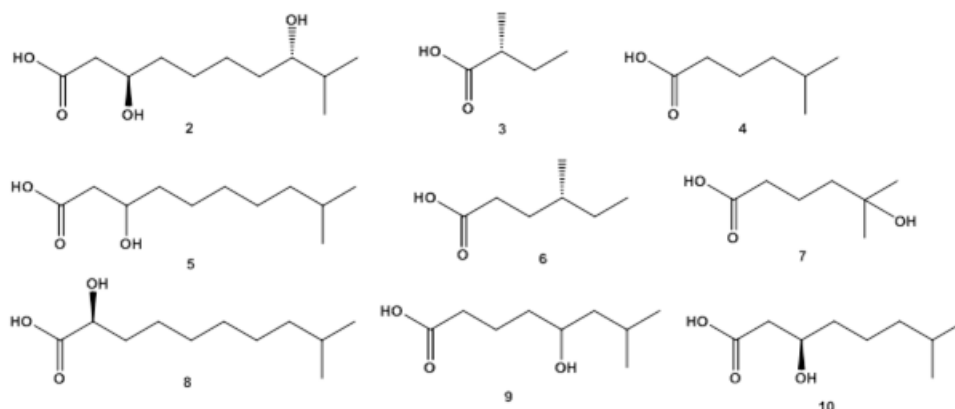


**Fig. 1.** Graphical display of the chemical structure of green alga *Derbesia marina* lipopeptide and the free fatty acid formed by hydrolysis of the amide bond.

Mebamamide A and B, lipopeptides with four D-amino acid residues and a 3,8-dihydroxy-9-methyldecanoic acid residue, were isolated from the green alga *Derbesia marina*. 100  $\mu\text{M}$  Mebamamide B can induce the differentiation of HL60 cells into macrophage-like cells.<sup>[47]</sup> Mebamamide A contained fatty acid [1] and mebamamide B contained (3*R*,8*S*)-3,8-dihydroxy-9-methyldecanoic acid [2].

The green alga *Bryopsis pennata* or *B. plumosa* and the sacoglossan mollusc *Elysia rufescens*, which feeds on the alga, have been extensively investigated for their biologically active natural products including depsipeptides.<sup>[48,52]</sup> Thus far, 24 cyclic depsipeptides, (kahalalides A–F, *iso*-KF, 5-OHKF, K, O–S, R', S', W and Y) and five linear depsipeptides (kahalalides G, H, J, V and X) have been isolated from the green alga *B. pennata* or the herbivorous marine mollusks *Elysia rufescens*, *E. ornata*, or *E. grandifolia*. The kahalalides

show highly promising biological activities including antiviral, antimalarial and primarily anticancer properties. KF and *iso*-KF reveal significant *in vitro* and *in vivo* antitumour activity against various cell lines. These exhibit highly diverse biological properties, including cytotoxic and antitumour, antimicrobial, antileishmanial and immunosuppressive activities.<sup>[48]</sup> (*R*)-2-methylbutanoic acid [3] was incorporated into kahalalide A and 5-methylhexanoic acid [4] was found in structure of kahalalides B, F, G, O, R2 and S2. 3-hydroxy-9-methyldecanoic acid [5] was found in kahalalides E, H, J, K and Y. (*R*)-4-methylhexanoic acid [6], 5-hydroxy-5-methylhexanoic acid [7], (*S*)-2-hydroxy-9-methyldecanoic acid [8], 5-hydroxy-7-methyloctanoic acid [9] and (*R*)-3-hydroxy-7-methyloctanoic acid [10] were incorporated into *iso*-kahalalide F, 5-OH-kahalalide F, kahalalide P and Q, kahalalide R1 and S1 and kahalalide V, respectively (Fig. 2.).



**Fig. 2.** Fatty acids were incorporated into lipopeptides of seaweeds.

### 3. FATTY ACIDS DERIVED FROM SPONGE LIPOPEPTIDES

Marine and freshwater sponges belonging to the class Demospongiae are very fertile host invertebrates for diverse symbiotic microorganisms.<sup>[53,54]</sup> They are simple multicellular “living fossil” organisms attached to solid substrates in benthic habitats. Both marine and freshwater sponges are filter feeders: numerous tiny pores on the surface allow water to enter and circulate through a series of canals where microorganisms and organic particles are filtered out and eaten. Sponges have been excellent sources for bioactive natural products such as halogenated fatty acids, terpenoids and alkaloids.<sup>[4,6,9,13,15,38,39,55,71]</sup>

Miraziridine A, a natural pentapeptide isolated from the marine sponge *Theonella* aff. *mirabilis*, contains a rare (2*R*,3*R*)-aziridine-2,3-dicarboxylic acid (**11**, Fig. 3) residue.<sup>[72,73]</sup> Isolated metabolite (**11**) allows for a simultaneous inhibition of the proteolytic activity of

trypsin-like serine proteases, papain-like cysteine proteases and pepsin-like aspartyl proteases. Therefore, this unique compound represents a blueprint for the design of class-spanning protease inhibitors.<sup>[74,75]</sup> It also inhibited the enzymatic activity of cathepsin B with an IC<sub>50</sub> value of 2 μM. Rare fatty acid (**11**) has also been previously isolated from an ascomycete: *Streptomyces* MD 398-A1.<sup>[76,77]</sup> A similar peptide isolated from the Red Sea sponge *Theonella swinhoei* (order Lithistida), is a potent cathepsin B inhibitor with a second-order rate constant of  $1.5 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ . *Theonella* species have been shown to be a source of anti-protease and anti-HIV secondary metabolites.<sup>[73]</sup> Aziridine alkaloids also belong to a rare and somewhat neglected group of natural products that are known to play a seminal role in the secondary metabolism of some microorganisms, plants and various marine organisms.<sup>[59]</sup> The aziridine-containing compounds have been of interest as both immuno-modulatory and anticancer agents since the late 1950s.<sup>[78]</sup>

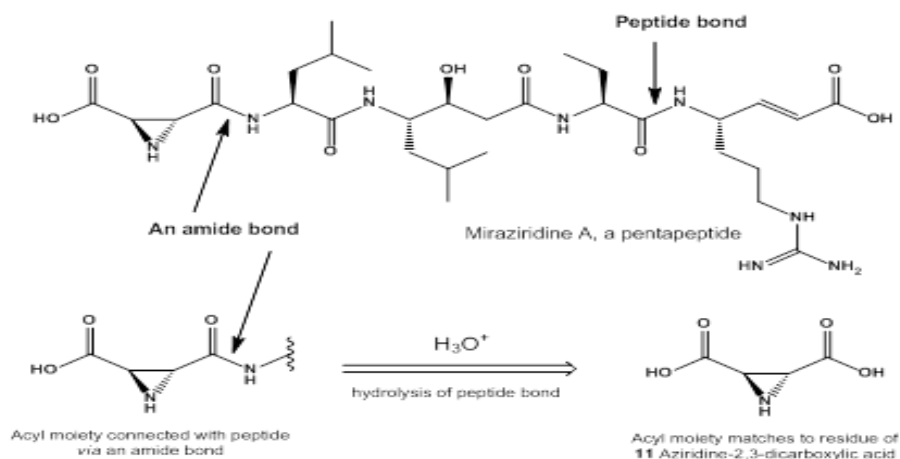


Fig. 3. Graphical display of the chemical structure of lipopeptide isolated from marine sponge *Theonella* aff. *mirabilis* and the free fatty acid formed by hydrolysis of the amide bond.

#### 3.1. BRANCHED, SATURATED AND UNSATURATED FATTY ACIDS DERIVED FROM SPONGE LIPOPEPTIDES

Neo fatty (carboxylic) acids, neo alkanes and their analogues and derivatives have been isolated from cyanobacteria, algae, fungi, microorganisms, plants, marine invertebrates and other living organisms.<sup>[16]</sup> Neo fatty acids and their derivatives have different biological activities, including anticarcinogenic, antifungal, antibacterial, antimicrobial and others.<sup>[16,79]</sup>

The unique polytheonamides A and B are highly cytotoxic polypeptides 48 amino acid residues long isolated from the marine sponge *Theonella swinhoei*. Polytheonamide A is an epimer of polytheonamide B differing only in the stereochemistry of the sulfoxide of the 44th residue.<sup>[80]</sup> Polytheonamides A and B are quite unusual in that one peptide molecule contains nine amino acids with *tert*-butyl units. Both *linear* polypeptides contain rare fatty acid neo 5,5-dimethyl-2-oxohexanoic acid [**12**].<sup>[80]</sup>

Yaku'amides A and B are two linear peptides containing several dehydro amino acids and β-hydroxy amino acids. These rare metabolites isolated from the Japanese sponge *Ceratopsia* sp were active against P388 murine leukemia cells.<sup>[81]</sup> Among these, Yaku'amide A has been reported to display a unique mode of action against a panel of 39 cancer cell lines. Yaku'amides A and B contain 2,2,4,6-tetramethyl-3-oxoheptanoic acid [**13**].

(*E*)-7-hydroxy-4,4,6,8-tetramethyl-5-oxonon-2-enoic acid [**14**] was present in the lipopeptides poecillastrin A and B,<sup>[82]</sup> and chondropsin D.<sup>[83]</sup> A deep-water (350 m) collection of a *Poecillastra* species (Grand Bahama Is., Bahamas) yielded the potently cytotoxic poecillastrins B and C, which are related to the chondropsins. The closely related poecillastrin D was isolated from *Jaspis serpentina* (Oshimashinsone, Japan) and was also potently cytotoxic.<sup>[84]</sup>

Three lipodepsipeptides, lipodiscamides A-C, from the marine sponge *Discodermia kiiensis* were characterized.

These structurally rare cyclic lipodepsipeptides have an unprecedented dilactone macrocycle and thus represent a new family of lipopeptides. They are the only lipopeptides bearing 4(*S*)-hydroxy-*trans*-2-enoate and noncanonical amino acids, 1-3-ureidoalanine, E-dehydronorvaline and d-citrulline. MTT assays against P388 and HeLa cells revealed that all three compounds had moderate cytotoxicity.<sup>[85,86]</sup> Lipodiscamides A and C contain (3*S*,5*R*,6*E*,8*E*,11*Z*)-3-hydroxy-5-methoxy-2,2,15-trimethyl-hexadeca-6,8,11-trienoic acid [15] and lipodiscamide B contains fatty acid [16].

In 2010, 'Pharma Mar' isolated two "head-to-side-chain" cyclodepsipeptides, stellatolides A and B, from a marine sponge of the family Ancorinidae, genus *Ecionemia*, species *Ecionemia acervus* collected in Tulear, Madagascar.<sup>[87]</sup> The only difference between the two peptides is the N-terminus acyl moiety. Their structures also contain the unusual residues (2*R*,3*R*)- $\beta$ -methoxytyrosine, (3*S*,4*R*)-3,4-dimethyl-L-glutamine, (2*S*,3*S*)-2,3-diamino-butyric acid, (2*R*,3*S*)- $\beta$ -hydroxyasparagine and the terminating moieties 3-hydroxy-6,8-dimethylnon-(4*Z*)-enoic acid or 3-hydroxy-6-methylnon-(4*Z*)-enoic acid. Both compounds have proven to display strong anti-proliferative activity against three human cancer cell lines (Lung-NSCLC A549, Colon HT-29 and Breast MDA-MB-231). (3*S*,6*S*,*Z*)-3-hydroxy-6,8-dimethylnon-4-enoic acid [17], and (3*S*,6*S*,*Z*)-3-hydroxy-6-methylnon-4-enoic acid [18] was isolated from stellatolide A.<sup>[87]</sup>

A HIV-inhibitory cyclic depsipeptide was isolated from a Papua New Guinea collection of the marine sponge *Neamphius huxleyi*. Neamphamide A contains 11 amino acid residues and an amide-linked 3-hydroxy-2,4,6-trimethylheptanoic acid moiety. The amino acid constituents were identified as L-Leu, L-NMeGln, D-Arg, D- and L-Asn, two residues of D-allo-Thr, L-homoproline, (3*S*,4*R*)-3,4-dimethyl-L-glutamine,  $\beta$ -methoxytyrosine and 4-amino-7-guanidino-2,3-dihydroxyheptanoic acid. In a cell-based XTT assay, neamphamide A exhibited potent cytoprotective activity against HIV-1 infection with an EC<sub>50</sub> of approximately 28 nM. (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid [19] is present in neamphamide A, B and C.<sup>[88-91]</sup>

Two metabolites, halipeptins A and B, have been isolated from the marine sponge *Haliclona* sp. Halipeptin A, a 17-membered cyclic depsipeptide was found to possess very potent anti-inflammatory activity *in vivo*, causing approximately 60% inhibition of oedema in mice at a dosage of 300  $\mu$ g/kg (i.p.). (3*R*,4*R*,7*S*)-3,7-dihydroxy-2,2,4-trimethyldecanoic acid [20] from halipeptin B and C, (3*R*,4*R*,7*S*)-3-hydroxy-7-methoxy-2,2,4-trimethyldecanoic acid [21] from halipeptin A and D.<sup>[92,94]</sup>

Six depsipeptides, seragamides A–F, have been isolated as cytotoxic metabolites from the Okinawan sponge *Suberites japonicus*. Seragamide A promotes the

polymerization of G-actin and stabilizes F-actin filaments. (2*R*,6*S*,8*R*,*E*)-8-hydroxy-2,4,6-trimethylnon-4-enoic acid [22] has been isolated from all seragamides A–F.<sup>[95,97]</sup> The same fatty acid contains jasplakinolide D, M, Q and R1.<sup>[98,100]</sup> Eight cyclic depsipeptides, geodiamolides J–P and R, have been isolated from the marine sponge *Cymbastela* sp. collected in Papua New Guinea. Geodiamolides A and B were isolated from *Geodia* sp., and geodiamolide D was isolated from *Pseudoaxinyssa* sp. sponges.<sup>[101,104]</sup> The serine residue in geodiamolides L–P and R had not been previously found in this family of compounds.<sup>[95]</sup> Jaspamide (jasplakinolide) with (2*R*,6*S*,8*S*,*E*)-8-hydroxy-2,4,6-trimethylnon-4-enoic acid [23], a cyclic depsipeptide comprised of such unusual amino acids as *N*-methyl-2-bromo-D-tryptophan and L- $\beta$ -tyrosine and isolated from Fijian sponges of the genus *Jaspis*, was fungicidal against *C. albicans* with both an MIC and a minimal lethal concentration of 25  $\mu$ g/mL.<sup>[105]</sup> Similar peptides have been reported from various sponges.<sup>[106]</sup> Cytotoxic peptides, jaspamide and geodiamolide TA with (*E*)-8-hydroxy-2,4,6-trimethylnon-4-enoic acid [24], have been isolated from the sponge *Hemiasterella minor*. Geodiamolides J, K, and jaspamide B contained (2*R*,6*S*,8*R*)-8-hydroxy-2,6-dimethyl-4-methylene-5-oxononanoic acid [25], were isolated as minor metabolites of a *Cymbastela* sp. from Papua New Guinea.<sup>[101,104,107]</sup>

The lipodepsipeptide taumycin B, with (2*E*,9*E*,11*S*,12*R*)-11-hydroxy-3,5,7,9,12-pentamethyl-13-oxopentadeca-2,9-dienedioic acid [26, Fig. 4], has been isolated from the Madagascar sponge *Fascaplysinopsis* sp.<sup>[108]</sup>

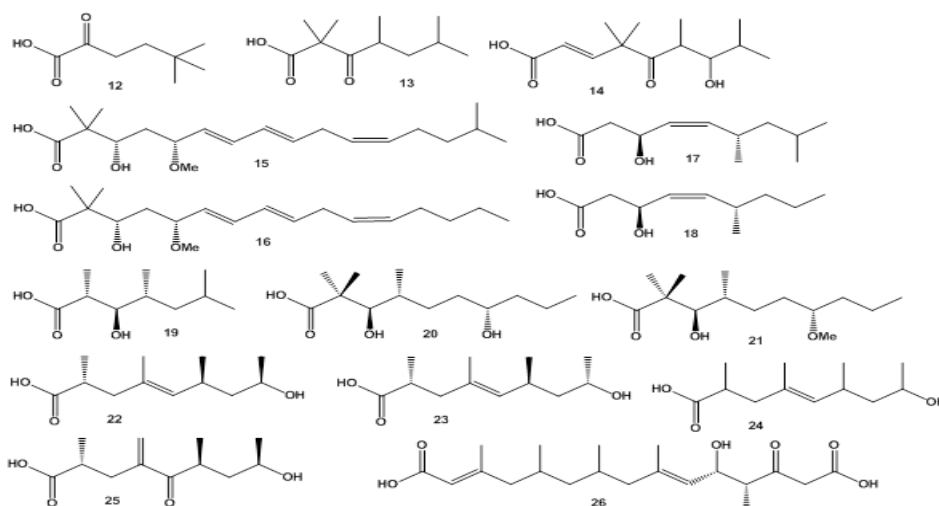


Fig. 4. Neo-, branched, saturated and unsaturated fatty acids isolated from sponge lipopeptides.

Homophymines A–E and A1–E1 are a series of cyclodepsipeptides isolated from *Homophymia* sp. collected from shallow waters off the east coast of New Caledonia.<sup>[109,110]</sup> They are similar in structure to the previously published antiviral marine cyclodepsipeptides callipeltin A,<sup>[111,112]</sup> neamphamide A,<sup>[113,114]</sup> papuamides,<sup>[115,116]</sup> theopapuamides<sup>[117]</sup> and mirabamides.<sup>[118]</sup> Homophymine A was cytotoxic against uninfected PBMC cells with an  $IC_{50}$  of 1.19  $\mu$ M, but it was almost sixteen times more effective against infected cells and exhibited potent cytotoxicity with  $IC_{50}$  values ranging from 2 to 100 nM. These compounds were most potent against the PC3 human prostate adenocarcinoma and the SK-OV3 human ovarian adenocarcinoma cell lines.<sup>[109–118]</sup> (2*S*,3*S*,4*S*,6*S*)-3-hydroxy-2,4,6-trimethyloctanoic acid [27] was isolated from homophymines A and A1, (2*S*,3*S*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid [28] from homophymines B and B1, (2*S*,3*S*,4*S*,6*S*)-3-hydroxy-2,4,6-trimethylnonanoic acid [29] from homophymines C and C1, (2*S*,3*S*,4*S*,6*S*)-3-hydroxy-2,4,6,8-tetramethylnonanoic acid [30] from homophymines D and D1 and (2*S*,3*S*,4*S*,6*S*,8*S*)-3-hydroxy-2,4,6,8-tetramethyldecanoic acid [31] from homophymines E and E1.

Papuamide A is representative of a class of marine-derived cyclic depsipeptides reported to have cytoprotective activity against HIV-1 *in vitro*.<sup>[115,116]</sup> (4*E*,6*E*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienoic acid [32] was isolated from Papuamide A–D and mirabamides A–D.<sup>[118]</sup> *Siliquariaspongia mirabilis* (Chuuk Lagoon, Micronesia) contained mirabamides A–D and though the configuration of the amino acids and sugars were determined, the stereochemistry of the 2,3-dihydroxy-2,6,8-trimethyldecadienoic acid moiety remains unresolved.<sup>[118]</sup> These  $\square$ -OMe tyrosine-containing peptides were potent inhibitors of HIV-1 fusion and shed light on the role of the  $\square$ -Me tyrosine moiety in HIV-1 fusion inhibition activity of the related papuamides, callipeltins and neamphamides. (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyldecanoic acid [33] was isolated from mirabamides A–D<sup>[118]</sup> and neamphamide D.<sup>[119]</sup>

The didemmins, which are potent cytotoxins and immunosuppressive agents were isolated from *Trididemnum solidu*. All didemnin A, B and C contained (2*S*,4*S*)-4-hydroxy-2,5-dimethyl-3-oxohexanoic acid [34].<sup>[120,122]</sup>

Theopapuamide A is a cytotoxic undecapeptide isolated from *Theonella swinhoei* collected off Milne Bay, Papua New Guinea.<sup>[123]</sup> It is the first natural peptide containing  $\beta$ -methoxyasparagine and 4-amino-5-methyl-2,3,5-trihydroxyhexanoic acid residues. It was tested in the CEM-TART (T-cells that express both HIV-1 tat and rev) and HCT-116 colorectal carcinoma cell lines with  $IC_{50}$  values of 0.5 and 0.9  $\mu$ M, respectively. In 2009, theopapuamide A was reported along with six new cyclic peptides, theopapuamides B–D<sup>[117]</sup> and celesbesides A–C, from an extract of *Siliquariaspongia mirabilis* collected off Sulawesi Island, Indonesia. Theopapuamides B–D and celesbesides A–C were tested against HCT-116 cells and had  $IC_{50}$  values of 2.5, 1.3, 9.9 and >31  $\mu$ M, respectively.<sup>[117]</sup> (2*R*,3*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid [35] was isolated from undecapeptides theopapuamide A–D, (2*E*,4*E*,7*S*,8*R*,9*S*,10*R*)-7,9-dihydroxy-8,10-dimethyltrideca-2,4-dienoic acid [36] was isolated from celesbeside A and C and (2*E*,4*E*,7*S*,8*R*,9*S*,10*R*)-7,9-dihydroxy-8,10-dimethyldodeca-2,4-dienoic acid [37] was isolated from celesbeside B.<sup>[117]</sup>

The lithistid sponge *Aciculites orientalis* contains three cyclic peptides, aciculitins A–C, which are identical except for homologous lipid residues. The aciculitins consist of a bicyclic peptide that contains an unusual histidino-tyrosine bridge. Attached to the bicyclic peptide are C13–C15 2,3-dihydroxy-4,6-dienoic acids bearing D-lyxose at the 3-position. The aciculitins inhibited the growth of *Candida albicans* and were cytotoxic toward the HCT-116 cell line.<sup>[124]</sup> Aciculitins A–C are a homologous series of antifungal and cytotoxic bicyclic peptides that were isolated from *Aciculites orientalis* from the Philippines. Aciculitins A–C inhibited the growth of *Candida albicans* and were cytotoxic toward

the HCT-116 cell line. Aciculitin A contains fatty acid [38], aciculitin B contains fatty acid [39] and aciculitin C contains fatty acid [40].<sup>[124]</sup>

Bioassay-guided fractionation of the sponge *Psammocinia* sp. identified psymberin, also known as irciniastatin A, which has 5*S*,8*S*,9*S*,11*R*,13*R*,15*S*,16*R*,17*R* stereochemistry.<sup>[125,126]</sup> Psymberin has structural similarities to the pederin family metabolites.<sup>[127,128]</sup> The potent cytotoxicity and unique structural features of psymberin make it a promising lead for therapeutic development.<sup>[129]</sup> A very potent cytotoxin, psymberin, which is related to the pederin family of metabolites, was obtained from a series of Papua New Guinean collections of *Psammocinia* species and the keto analogue irciniastatin B was isolated from *Ircinia ramosa* (Borneo). (2*S*)-2-hydroxy-3-methoxy-5-methylhex-5-enoic acid [31] was found in psymberin and 2-hydroxy-3-methoxy-5-methylhex-5-enoic acid [32] was present in irciniastatin B.<sup>[125,130]</sup>

Sponges in the *Jaspidae* family have proved to be a prolific source of bioactive natural products.<sup>[131-134]</sup> Among these, the bengamides and the bengazoles stand out by virtue of their unprecedented molecular architectures and impressive biological profiles, including antitumour, antibiotic and anthelmintic properties. As a consequence, intense research has been devoted to these compounds from both chemical and biological standpoints. Bengamides A-E, G, H, J, L, M, O, Y and Z contain (2*R*,3*R*,4*S*,5*R*,*E*)-3,4,5-trihydroxy-2-methoxy-8-methylnon-6-enoic acid [33], bengamides E' and F' contain (2*R*,3*R*,4*S*,5*R*,*E*)-3,4,5-trihydroxy-2-methoxy-8-methyldec-6-enoic acid [34], bengamides P and Q contain (2*R*,3*R*,4*R*,5*R*,*E*)-3,4-dihydroxy-2-methoxy-8-methyl-5-(tetradecanoyloxy)non-6-enoic acid [35] and (2*R*,3*R*,4*R*,5*R*,*E*)-3,4-dihydroxy-2-methoxy-8-methyl-5-(palmitoyloxy)non-6-enoic acid [36] was found in bengamide R.<sup>[131-134]</sup>

Mirabalin, initially reported as mirabilin with (6*S*,7*S*,*E*)-7-hydroxy-4,4,6,8-tetramethyl-5-oxonon-2-enoic acid

[37], was isolated from *Siliquariaspongia mirabilis* collected southeast of Chuuk lagoon in the Federated States of Micronesia. Mirabalin inhibited the growth of the HCT-116 cell line with an IC<sub>50</sub> value of 0.27 μM and was not cytotoxic to several other cell lines tested.<sup>[135,137]</sup>

Poecillastrin A, a new polyketide-derived macrolide lactam, was isolated from a deep-water collection of the marine sponge *Poecillastra*.<sup>[138]</sup> Poecillastrin D was isolated together with poecillastrin C from the deep-sea sponge, *Japsis serpentine*.<sup>[139]</sup> These compounds showed a potent cytotoxicity against various tumour cell lines. Both poecillastrins C and D contain (*E*)-7-hydroxy-4,4,6,8-tetramethyl-5-oxonon-2-enoic acid [38].<sup>[138-140]</sup>

Anti-proliferative bioassay-guided fractionation of an aqueous extract of the marine sponge *Chondropsis* sp. provided two macrolides, chondropsins A and B. The chondropsins define an unprecedented class of polyunsaturated, polyhydroxylated, 35-membered macrocycles, which incorporate both lactone and lactam functional groups. The chondropsins therefore represent an interesting lead for cancer therapeutics research.<sup>[141]</sup> Chondropsin A, B and D and deoxychondropsin A contain (*E*)-7-hydroxy-9-methoxy-4,4,6,8,8-pentamethyl-5,9-dioxonon-2-enoic acid [39] and (*E*)-7-hydroxy-4,4,6,8-tetramethyl-5-oxonon-2-enoic acid [38] was found in chondropsin C.<sup>[141,144]</sup>

Theopapuamide, a cytotoxic peptide, has been isolated from the lithistid sponge *Theonella swinhoei* from Papua New Guinea. The undecapeptide contains several unusual amino acid residues, of which the occurrence of  $\beta$ -methoxyasparagine and 4-amino-5-methyl-2,3,5-trihydroxyhexanoic acid is unprecedented in natural peptides.<sup>[145]</sup> Theopapuamides A-D contain an amide-linked fatty acid moiety, (2*R*,3*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid [40, Fig. 5]. Theopapuamide was cytotoxic against CEM-TART and HCT-116 cell lines, with EC<sub>50</sub> values of 0.5 and 0.9 μM, respectively.<sup>[145]</sup> Geodiamolide TA is a cytotoxic peptide isolated from the marine sponge *Hemisterella minor*.<sup>[146]</sup>

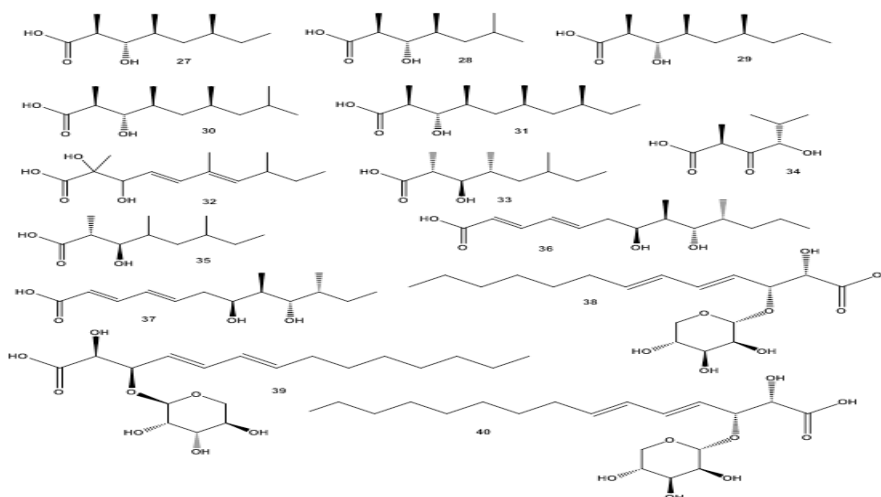


Fig. 5. Hydroxy branched fatty acids from lipopeptides of the sponge species.

In 2008 and 2009, Zampella and co-workers described ten cyclodepsipeptides, named homophymines A–E and A1–E1<sup>[109,110]</sup> isolated from the marine sponge *Homophymia*, in the order Lithistida, collected in New Caledonia. All the members described so far exhibit potent cytotoxic activity. Furthermore, the isolated member, homophymine A, also displays considerable cytoprotective activity against HIV-1 infection at very low concentrations. (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6,8-tetramethylnonanoic acid [51] is found in homophymines B and B1, (2*R*,3*R*,4*R*,6*R*,8*R*)-3-hydroxy-2,4,6,8-tetramethyldecanoic acid [52] in homophymines A and A1. Homophymines C and C1 contain (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethylnonanoic acid [53], homophymines D and D1 contain (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6,8-tetramethyl-nonanoic acid [54] and

homophymines E and E1 contain (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6,9-tetramethyldecanoic acid [55].<sup>[109,110]</sup>

The cyclic depsipeptides, pipecolidepsins A and B, have been isolated from the sponge *Homophymia lamellosa* collected off the coast of Madagascar. Pipecolidepsins A and B displayed cytotoxic activity against a panel of different human tumour cell lines. Pipecolidepsins A and B contain fatty acid [27] and 3-hydroxy-2,4,6,8-tetramethylnonanoic acid [56] found in pipecolidepsin C.<sup>[147]</sup>

An antibacterial depsipeptide, nagahamide A with (2*E*,4*E*,7*R*,8*S*,9*S*,10*S*)-9-hydroxy-7-methoxy-8,10-dimethyltrideca-2,4-dienoic acid [57, Fig. 6], has been isolated from the marine sponge *Theonella swinhoei*.<sup>[148]</sup>

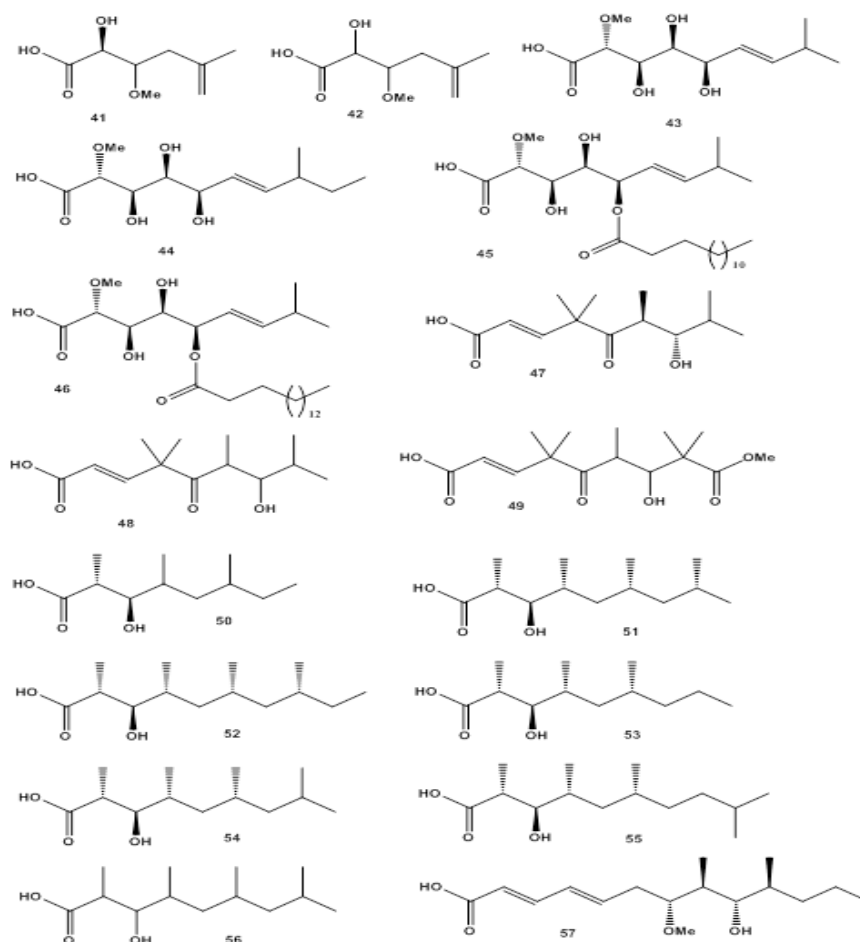


Fig. 6. Saturated, unsaturated and branched fatty acids from sponge lipopeptides.

### 3.2. HALOGENATED FATTY ACIDS OF SPONGE LIPOPEPTIDES

Several chlorinated fatty acids have been isolated from lipopeptides and other metabolites of marine sponges.<sup>[4]</sup> The sponge *Lamellodysidea* (syn. *Dysidea*) herbacea contains a series of polychlorinated peptides, such as dysidin and dysidenin. Both compounds contained (*S*)-4,4,4-trichloro-3-methylbutanoic acid [58].<sup>[149-152]</sup> An undescribed species of *Dysidea* collected in the Philippines yielded the proline-derived dysideaprolines A–F with fatty acids [59 and 60] together with the enol-

ether containing barbaleucamides A and B, which contained (*E*)-6,6,6-trichloro-3-methoxy-5-methylhex-2-enoic acid [61].<sup>[153]</sup> *Dysidea herbacea*, collected at Harrier Reef on the Great Barrier Reef, contains the metabolite herbacic acid [(*E*)-6,6,6-trichloro-5-methylhex-2-enoic acid, 62] as the major trichloroleucine metabolite. Herbacic acid appears to be an early product of direct free-radical chlorination of leucine and is a prototype for further transformation of the free carboxylic acid group and generation of complex trichloromethyl metabolites, including natural products

of the dysidenin family.<sup>[154]</sup> The same acid also contained the herbaceamide A. Fatty acid [63] was isolated from

chlorinated peptides found in the marine sponge *Dysidea* sp.<sup>[155]</sup>

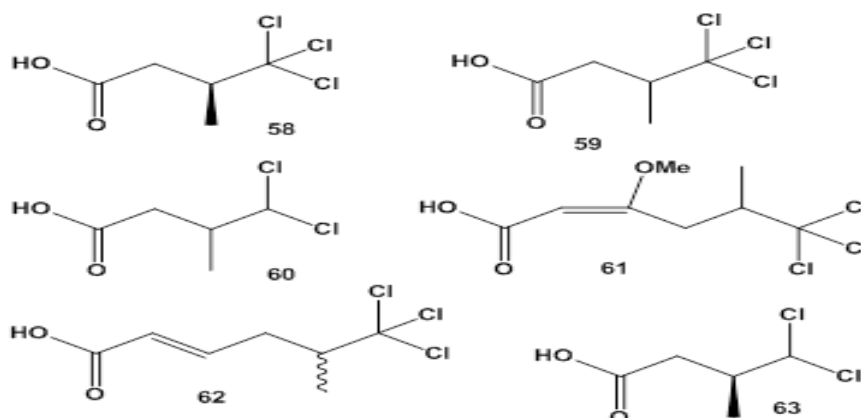


Fig. 7. Halogenated fatty acids from sponge lipopeptides.

### 3.3. MISCELLANEOUS FATTY ACIDS FROM SPONGE LIPOPEPTIDES

Arenastatin A with (5*S*,6*S*,7*S*,*E*)-6-hydroxy-5,6-dimethyl-7-(3-phenyloxiran-2-yl)oct-2-enoic acid [64] has been isolated from the Okinawan marine sponge *Dysidea arenaria*.<sup>[156,158]</sup> The cyclodepsipeptide was shown to have extremely potent cytotoxic activity ( $IC_{50} = 5$  pg/mL) against KB 3-1 cells. Cytotoxicity is caused by inhibition of microtubule assembly through binding to the rhizoxin/maytansine site on tubulin.<sup>[159,160]</sup> However, arenastatin A was found to exhibit only marginal *in vivo* anti-tumour activity after intravenous administration due to rapid metabolism of the 15,20-ester linkage. Analogue was found to show sufficient stability in serum and moderate levels of cytotoxicity ( $IC_{50} = 6$  ng/mL). However, it was almost insoluble in polar solvents, thus it could not be applied for *in vivo* biological evaluation.<sup>[161,163]</sup>

Cytotoxic compounds were isolated along with onnamide A from a marine sponge *Theonella* sp. collected at Hachijo Island. All compounds were highly cytotoxic against the P388 cell line.<sup>[164,166]</sup> Onnamide A contains (*S*)-2-hydroxy-2-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2*H*-pyran-2-yl)acetic acid [65], onnamide B contains (*S*)-2-hydroxy-2-((2*S*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylene-tetrahydro-2*H*-pyran-2-yl) acetic acid [66] and onnamide C contains (*R*)-2-hydroxy-2-((2*S*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2*H*-pyran-2-yl)acetic acid [67]. Onnamide A was first isolated from the Okinawan marine sponge *Theonella swinhoei* as an antiviral constituent. Onnamide A exhibits cytotoxicity by inhibiting protein synthesis in eukaryotes as does the structurally related compound pederin, isolated from the blister beetle *Paederus fuscipes*. Four onnamide A analogues, 21,22-dihydroxyonnamides A1–A4 contained fatty acid [65] and were isolated from an Okinawan collection of *Theonella swinhoei*.<sup>[164,166]</sup>

A cyclic peptide with 2,5-dihydroxybenzoic acid [68], oriamide containing the 4-propenoyl-2-tyrosylthiazole

amino acid, was isolated from the marine sponge *Theonella* sp. collected in Sodwana Bay.<sup>[167]</sup> The marine natural product dysinosin A has also been isolated from a genus and species of sponge of the family *Dysideidae* found near Lizard Island, North Queensland (Australia). Dysinosin A is a potent inhibitor of the blood coagulation cascade factor VIIa and an inhibitor of the serine protease thrombin. Among the distinctive features of dysinosin A are the presence of a 5,6-dihydroxy-octahydroindole-2-carboxylic acid, 3-amino-ethyl 1-*N*-amidino- $\Delta$ -3-pyrroline, a sulfated glyceric acid, (*R*)-2-methoxy-3-(sulfoxy) propanoic acid [69] and D-leucine, assembled through three peptide linkages.<sup>[168]</sup> Dysinosin A inhibited factor VIIa at a  $K_i$  of 108 nM and thrombin at a  $K_i$  of 452 nM. The identification of the 1-*N*-amidino- $\Delta$ -3-pyrroline and 5,6-dihydroxy-octahydroindole-2-carboxylic acid as the P1 and P2 moieties, respectively, should pave the way for the design and synthesis of new structure-based inhibitors.<sup>[169,170]</sup> An additional three products, dysinosins B–D, were isolated from the sponge *Lamellodysidea chloreia*. These compounds are inhibitors of the blood coagulation cascade serine proteases factor VIIa and thrombin. The analogues, dysinosins B–D, allowed identification of two structural motifs within the structures that contribute to binding to factor VIIa and thrombin. Dysinosins B and C contained fatty acid [69].<sup>[169,170]</sup>

The lithistid sponge *Scleritoderma nodosum* contains a cyclic peptide, scleritodermin A, the structure of which incorporates 1-proline, 1-serine and keto-*allo*-isoleucine units, as well as a novel conjugated thiazole moiety and *O*-methyl-*N*-sulfoserine. Scleritodermin A with sodium (*S*)-(1-carboxy-2-methoxyethyl)sulfamate [70] inhibited tubulin polymerization and showed significant *in vitro* cytotoxicity against human tumour cell lines.<sup>[171,172]</sup> The bioactive peptide, keramamide A, has been isolated from the Okinawan marine sponge *Theonella* sp. and the structure established as a unique hexapeptide containing a hitherto-unknown amino acid 6-chloro-5-hydroxy-*N*-methyltryptophan and possessing an unusual ureido



bond. (*R*)-3-formamido-2-hydroxypropanoic acid [71] was found in keramamides A, J, K, H and G.<sup>[173-175]</sup>

The lipodepsipeptide taumycin A, with (4*R*,5*S*,6*E*,11*E*)-5-hydroxy-4,7,9,11-tetramethyl-12-(oxazol-5-yl)-3-oxododeca-6,11-dienoic acid [72], has been isolated from the Madagascar sponge *Fascaplysinopsis* sp. Lipodepsipeptide was toxic to brine shrimp larvae and taumycin A (1 Mm) inhibited growth of the human UT-7

toxic to a leukemic cell line.<sup>[176,177]</sup>

Sponge *Discodermia kiiensis* had yielded the unrelated cyclic depsipeptides, discokiolide A-C, with (E)-3-hydroxy-2-methyl-3-(2-(4-phenylbut-3-en-2-yl)oxazol-4-yl)propanoic acid [73]. These peptides had unusual  $\alpha$ -hydroxy acids as well as  $\alpha$ -methoxy-phenylalanine residues.<sup>[178,179]</sup>

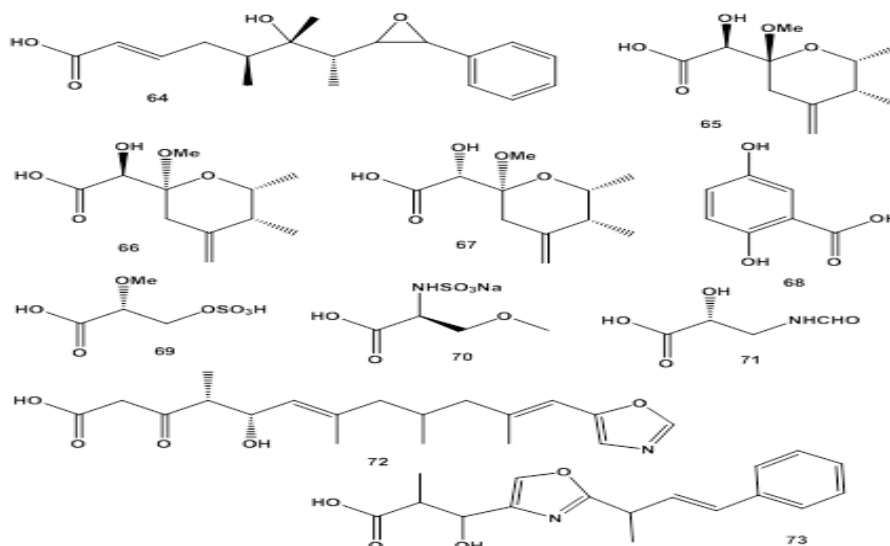


Fig. 7. Miscellaneous fatty acids from sponge lipopeptides.

#### 4. FATTY ACIDS DERIVED FROM MOLLUSCA LIPOPEPTIDES

Marine molluscs, mainly gastropod species, are a rich source for natural bioactive compounds. In recent years, advances in sea collection and aquaculture technology has allowed a significant number of compounds derived from marine molluscs to enter preclinical and early clinical evaluation as potential anticancer agents.<sup>[180-182]</sup> Bioactive marine compounds belong to very diverse structural classes, including polyketides, terpenes, steroids and lipopeptides.<sup>[182]</sup>

A cytotoxic depsipeptide, kulokekahilide-2 with (2*E*,5*S*,6*S*,7*S*,8*E*)-5,7-dihydroxy-2,6,8-trimethyldeca-2,8-dienoic acid [74], was isolated from a cephalaspidean mollusc, *Philinopsis speciosa*. Kulokekahilide-2 showed potent cytotoxicity against several cell lines (P388, SK-OV-3, MDA-MB-435 and A-10 with IC<sub>50</sub> values ranging from 4.2 to 59.1 nM) indicating cancer cell selectivity.<sup>[183]</sup>

Kulolide 1, a cyclic depsipeptide, was isolated from the same mollusc, *Ph. speciosa*. Kulolide is made up of five amino acid residues, one each of l-Ala, l-Pro and N-Me-d-Val, two of l-Val and two carboxylic acids: l-3-phenyllactic acid and the unprecedented (*S*)-3-hydroxy-2,2-dimethyloct-7-ynoic acid [75]. Kulolide was active against L-1210 leukemia cells and P388 murine leukemia cells at IC<sub>50</sub> values of 0.7 and 2.1  $\mu$ g/mL, respectively. Kulolide caused morphological changes in rat 3Y1 fibroblast cells at the concentration of 50 Mm.<sup>[184]</sup>

Kulolide 2 from *Ph. speciosa* contained (*S*)-3-hydroxy-2,2-dimethyloct-7-enoic acid [76].<sup>[185]</sup> Kulomoopunalide-2 from *Ph. speciosa* contained (2*R*,3*S*)-3-hydroxy-2-methyloct-7-ynoic acid [77].<sup>[186]</sup>

Onchidin A is a cytotoxic depsipeptide isolated from the pulmonate mollusc *Onchidium* sp. Onchidin contains a  $\beta$ -amino acid: 3-amino-2-methyloct-7-ynoic and (*S*)-2-hydroxy-3-methylbutanoic acids [78].<sup>[187]</sup> Onchidin B is a cyclic depsipeptide isolated from the pulmonate mollusc *Onchidium* sp. It contains four  $\alpha$ -amino acids [two units of N-methyl valine, two units of proline, four  $\alpha$ -hydroxy acids [two 2-hydroxyisovaleric acids, two 2-hydroxy-3-methylpentanoic acid moieties] and two units of the  $\beta$ -hydroxy acid: 3-hydroxy-2-methyloct-7-ynoic acid [79].<sup>[188]</sup>

Two cyclic depsipeptides, kahalalide R and S together with two known congeners, kahalalides F and D, were isolated from the mollusc *Elysia grandifolia*.<sup>[189]</sup> Kahalalide S1 contained 5-hydroxy-7-methyloctanoic acid [80], kahalalide F contained 5-methylhexanoic acid and kahalalide D contained 3-hydroxy-7-methyloctanoic acid [81]. Cyclic depsipeptides had antiproliferative activity against several cell lines, including MCF-7, PC12, HeLa, L1578Y and H4IIE. Kahalalide F was isolated from the mollusks *Elysia rufescens* and the bivalve mollusc *Spisula polynyma* and from the green alga *Bryopsis* sp.<sup>[190]</sup>

Sea hares, belonging to the order Opisthobranchia (Gastropoda), are mollusks that have attracted many researchers who are interested in the chemical defence mechanisms of these soft, "shell-less" snails. Aurilide with (2*E*,5*R*,6*R*,7*S*,8*E*)-5,7-dihydroxy-2,6,8-trimethylundeca-2,8-dienoic acid [82], is a 26-membered cyclodepsipeptide that has been isolated from the Japanese sea hare *Dolabella auricularia*.<sup>[191]</sup>

An antineoplastic agent, depsipeptide dolastatin 13, with 3-hydroxy-2-methoxy-propanoic acid [83], was isolated from the sea hare *Dolabella auricularia*.<sup>[192]</sup> A cytostatic depsipeptide, designated dolastatin 14, with (2*E*,4*Z*,10*E*)-15-hydroxy-7-methoxy-2-methylhexadeca-2,4,10-trienoic acid [84], was isolated from the Indian Ocean shell-less mollusc *Dolabella auricularia*. Dolastatin 14 inhibited growth of PS leukemia cells with an ED<sub>50</sub> of 1.8 ng/mL.<sup>[193]</sup>

Dolastatin C, a depsipeptide exhibiting weak cytotoxicity, was isolated from the Japanese sea hare *Dolabella auricularia* and contained (2*S*,3*R*)-2-(dimethylamino)-3-methylpentanoic acid [85].<sup>[194]</sup> Two cytotoxic compounds, designated dolastatin H and isodolastatin H, have been isolated from the Japanese sea hare *Dolabella auricularia*. *In vivo* antitumour activity against murine P388 leukemia was evaluated and it was shown that isodolastatin H antitumour activity was a little weaker than that of dolastatin 10.<sup>[195]</sup> Dolastatin H, isodolastatin H and dolastatin 10 contained (*S*)-2-(dimethylamino)-3-methylbutanoic acid [86].

A bioassay-directed fractionation of the cytotoxic constituents of the Japanese sea hare *Dolabella auricularia* resulted in the isolation of two 35-membered depsipeptides: dolastatin G and nordolastatin G, which showed cytotoxicity against HeLa S cells with IC<sub>50</sub> values of 1.0 and 5.3 μg/mL, respectively. Nordolastatin G is a congener that has the same absolute

stereochemistry as that of dolastatin G.<sup>[196]</sup> Both depsipeptides contained (2*Z*,4*E*,7*R*,8*S*)-8-hydroxy-3-methoxy-4,7-dimethylnona-2,4-dienoic [87] and (2*R*,3*R*,7*S*)-3,7-dihydroxy-2,8-dimethylnonanoic acids [88].

Dolastatin 11, a drug isolated from the Indian Ocean sea hare *Dolabella auricularia*, arrests cytokinesis *in vivo* and increases the amount of F-actin to stabilize F-actin *in vitro*, like phalloidin and jasplakinolide.<sup>[197,198]</sup> Two antineoplastic cyclic depsipeptides, designated dolastatin 11 and dolastatin 12, were isolated from the Indian Ocean sea hare *Dolabella auricularia*. Dolastatins 11 and 12 inhibited growth of the PS leukemia with ED<sub>50</sub> 2.7 × 10<sup>-3</sup> and 7.5 × 10<sup>-2</sup> μg/mL, respectively.<sup>[199]</sup> Both cyclic depsipeptides contained (3*S*)-2-hydroxy-3-methylpentanoic acid [89].

Bioassay-guided separation of cancer cell growth inhibitory fractions derived from the sea hare *Dolabella auricularia* obtained in Papua New Guinea led to the isolation of the thiazole-containing peptide, dolastatin 18. Dolastatin 18 with 2,2-dimethyl-3-oxohexanoic acid [90] was found to inhibit a selection of cancer cell lines, among which dolastatin had a GI<sub>50</sub> of 0.39 μg/mL for the non-small cell lung cancer NCI-H460.<sup>[200]</sup>

The cytotoxic, cyclic depsipeptide (-)-doliculide with (2*S*,3*S*,5*S*,6*S*,8*S*)-6,8-dihydroxy-2,3,5,9-tetramethyldecanoic acid [91, Fig. 8] was isolated by Ishiwata et al.<sup>[201,202]</sup> from the sea hare *Dolabella auricularia* collected in Japanese waters, but the mechanism of action of the depsipeptide is not known. In these biochemical assays (-)-doliculide and jasplakinolide were quantitatively virtually identical in their behaviours. Similar effects have also been reported with a series of depsipeptides known as chondramides.<sup>[203]</sup>

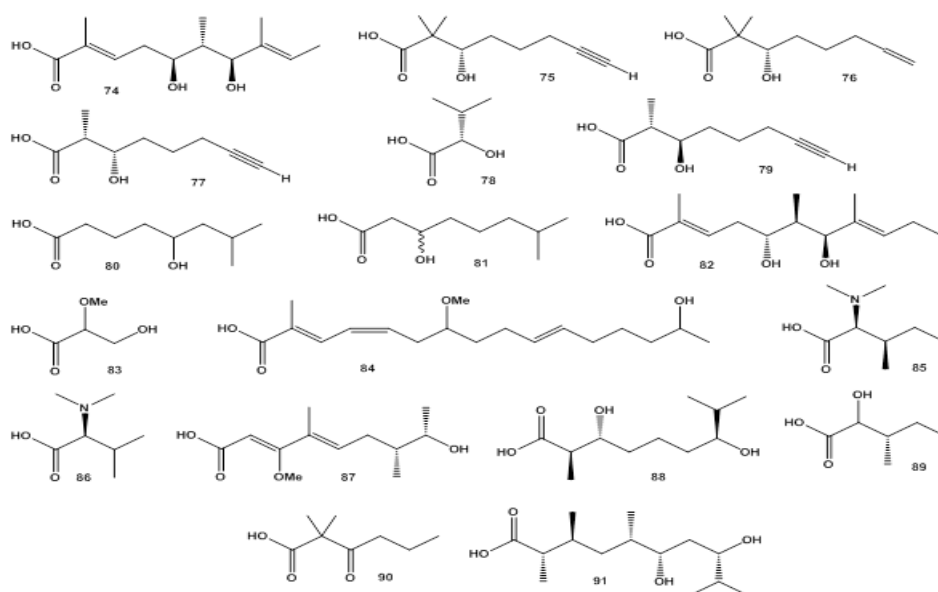


Fig. 8. Lipopeptide fatty acids from Molluscs.

## 5. FATTY ACIDS FROM TUNICATE LIPOPEPTIDES

The first anticancer product, didemnin B, is a cyclic depsipeptide isolated from the tunicate *Trididemnum solidum*. Preliminary results showed partial activity against non-Hodgkin's lymphoma.<sup>[204,205]</sup> It can inhibit protein synthesis and arrest the G1 cell-cycle phase. There are number of ecteinascidins that have been isolated from the marine tunicate *Ecteinascidia turbinata*. One of these ecteinascidins (ET-743) was selected for clinical trials and antitumour effects have been observed in phase I studies.<sup>[206,207]</sup> ET-743 is a tetrahydro-isoquiniline alkaloid and acts by selective alkylation of guanine residues in the DNA minor groove<sup>[208,209]</sup> and also interacts with nuclear proteins.<sup>[210]</sup> In Europe and the United States ET-743 is currently in phase II clinical trials.<sup>[210,211]</sup> The dolastatins are a class of peptides obtained from the Indian Ocean, *Dolabella auricularia*. Sagittamide A and B have been isolated from a tropical tunicate (Pohnpei, Micronesia).<sup>[212,213]</sup> Four minor congeners, sagittamides C–F were isolated from Didemnid ascidia that were previously identified to contain sagittamides A and B.<sup>[212-214]</sup> Sagittamides A–F each have different fatty acids [92–97], respectively.

Four cyclic polyethers, bistramides B, C, D and K, which are closely related to the previously reported bistramide A from the New Caledonian urochordata *Lissoclinum bistratum* have been isolated and characterized. Cytofluorimetric analysis with bistramide K showed a complete block of NSCLC-N6 cells in the G1 phase. Bistramide D and particularly, bistramide K are less toxic than bistramides A, B and C and are thereby effective *in vivo* against NSCLC-N6.<sup>[215]</sup> Bistramides A, D and K are capable of inducing *in vitro* terminal differentiation of cells from a non-small cell broncho-pulmonary carcinoma (NSCLCN6), but present different *in vitro* toxicities.<sup>[216,217]</sup> Bistramides A–C contained fatty acid [98], bistramide D contained fatty acid [99] and bistramide K contained fatty acid [100].

Extracts of samples of a Caribbean tunicate (ascidian, sea squirt) of the family Didemnidae at low concentrations inhibit *in vitro* growth of DNA and RNA viruses as well as L1210 leukemic cells. The active compounds isolated from the tunicate, didemnins A, B and C, are depsipeptides and didemnin B (a derivative of didemnin A) is the component active at the lowest concentration in inhibiting viral replication *in vitro* and P388 leukemia *in vivo*.<sup>[218]</sup> Didemnins are a class of cyclic depsipeptides in which didemnin A is the major component, didemnin B the minor component and a trace of didemnin C is present. Didemnin B was more potent than was didemnin A against B16 melanoma and P388 leukemia *in vivo* and B was also approximately 20 times more cytotoxic than was didemnin A *in vitro*. Therefore, didemnin B was studied in greater detail for its biochemical and cellular effects. Didemnin B inhibited the *in vitro* growth of B16 more than L1210 and V-79 cells (human foreskin fibroblast) greater than Chinese hamster ovary cells. Chinese hamster ovary cells were not killed even at 25,000 ng/mL. Mitotic cells were the least sensitive to didemnin B and cells became more sensitive as they progressed into G1 and S phase.<sup>[219,220]</sup> Didemnins A, B and D contained (2*R*,4*R*)-4-hydroxy-2,5-dimethyl-3-oxohexanoic [101], (2*S*,4*R*)-4-hydroxy-2,5-dimethyl-3-oxohexanoic [102] and (2*R*,4*S*)-4-hydroxy-2,5-dimethyl-3-oxohexanoic [103] acids, respectively.

Eudistomides A and B, two cyclic peptides are the first ascidian-derived peptides cyclized solely by a disulfide bridge, were isolated from a Fijian ascidian *Eudistoma* sp. These five-residue cystine-linked cyclic peptides are flanked by a C-terminal methyl ester and a 12-oxo- or 12-hydroxy-tetradecanoyl moiety. Enantioselective lipase-catalysed hydrolysis of a mixture of C-35 acetoxy epimers indicated a 3*S*R absolute configuration for eudistomide B.<sup>[221]</sup> Both compounds contained the same fatty acid [104].

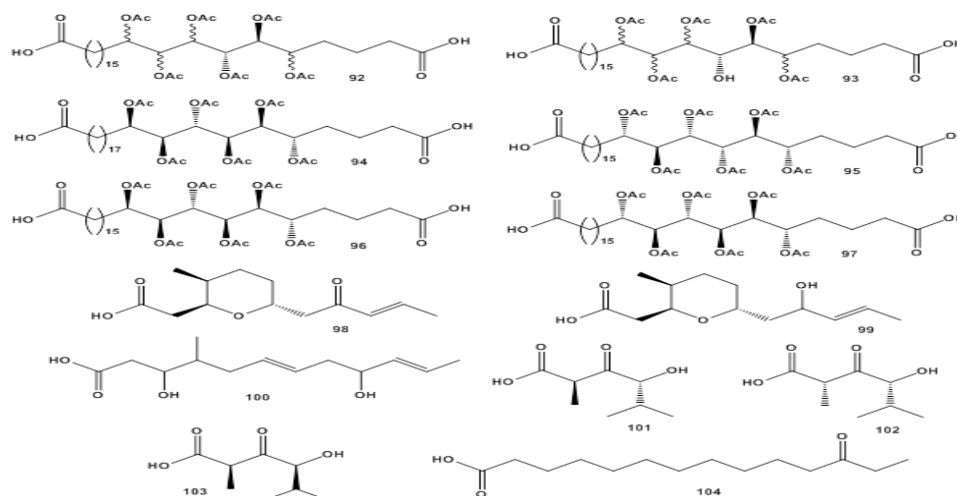


Fig. 9. Fatty acids from Tunicate lipopeptides.

**CONCLUDING REMARKS**

Natural lipopeptides are active surface biological metabolites produced by a wide variety of seaweeds and invertebrates. They are characterized by high structural diversity and the ability to decrease the surface and interfacial tension at the surface and interface, respectively. Additionally, their ability to form pores and destabilize biological membrane permits their use as antibacterial, antiviral, antitumor, hemolytic and insecticide agents. Fatty acids as an active fragment of lipopeptides, is extremely of great interest to medicinal chemists and pharmaceutical industry. Without doubt, other important new lipopeptides and with their *unique* and/or unusual fatty acid moiety possessing important biological activities will be discovered in the future.

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