EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 12
66-84
Year: 2017

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

***Valery M. Dembitsky**

National Scientific Center of Marine Biology, Vladivostok, 690041, Russia.

***Corresponding Author: Valery M. Dembitsky**
National Scientific Center of Marine Biology, Vladivostok, 690041, Russia.

Article Received on 08/10/2017 **Article Revised on 28/10/2017** **Article Accepted on 18/11/2017**

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.[1,18] 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.[19,29]

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.[1,18,30,39]

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 ($C_{6:0}$ - $C_{26:0}$), about 15% *iso*-, *anteiso*- and *neo*- saturated fatty acids ($C_{6:0}$ - $C_{24:0}$), 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 linages belonging to three main taxonomic groups (Chlorophyta, Phaeophyta and Rhodophyta).[40] Marine macrophytes have attracted interest due to the interesting biological activities they possess, including antimicrobial, antiviral, anti-inflammatory and immunotropic properties.[41,46] Seaweeds have been recognized as a source of potentially valuable and recoverable bioactive substances.[3,5,7,8-13] 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.[3,5,7,31,36]

There are a large number of reviews on the use of algae as food and related biological activity.[4,6,30,39,41,46] 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.

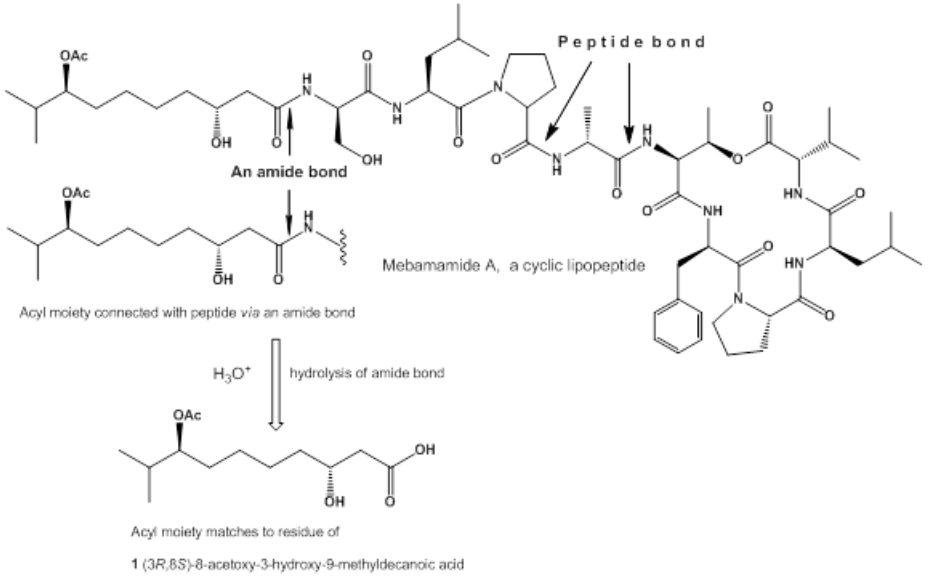

Fig. 1. Graphical display of the chemical structure of green alga *Derbesia marina lipopeptide* and the free fatty acid formed by hydrolysis of the amide bond.

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 μM Mebamamide B can induce the differentiation of HL60 cells into macrophage-like cells.[47] 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.[48,52] 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.[48] (*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.).

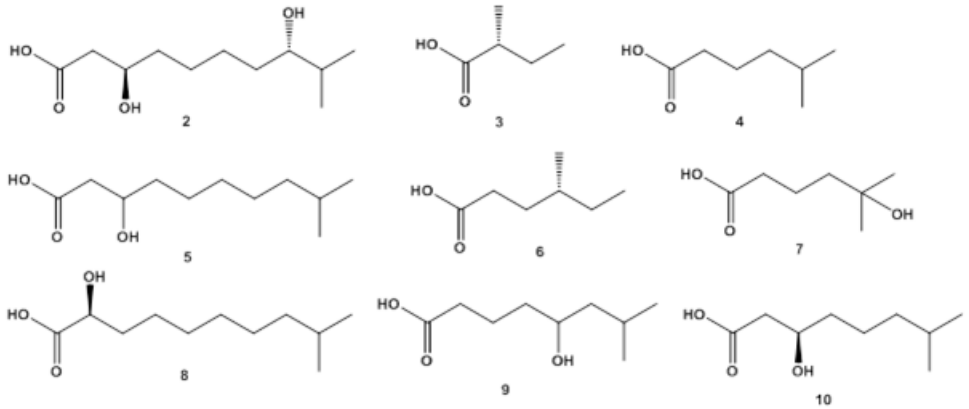

Fig. 2. Fatty acids were incorporated into lipopeptides of seaweeds.

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.[53,54] 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.[4,6,9,13,15,38,39,55,71]

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.[72,73] 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.[74,75] It also inhibited the enzymatic activity of cathepsin B with an IC_{50} value of 2 □M. Rare fatty acid (**11**) has also been previously isolated from an ascomycete: *Streptomyces* MD 398-A1.[76,77] 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 1.5×10^4 M^{-1} s^{-1}. Theonella species have been shown to be a source of anti-protease and anti-HIV secondary metabolites.[73] 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.[59] The aziridine-containing compounds have been of interest as both immuno-modulatory and anticancer agents since the late 1950s.[78]

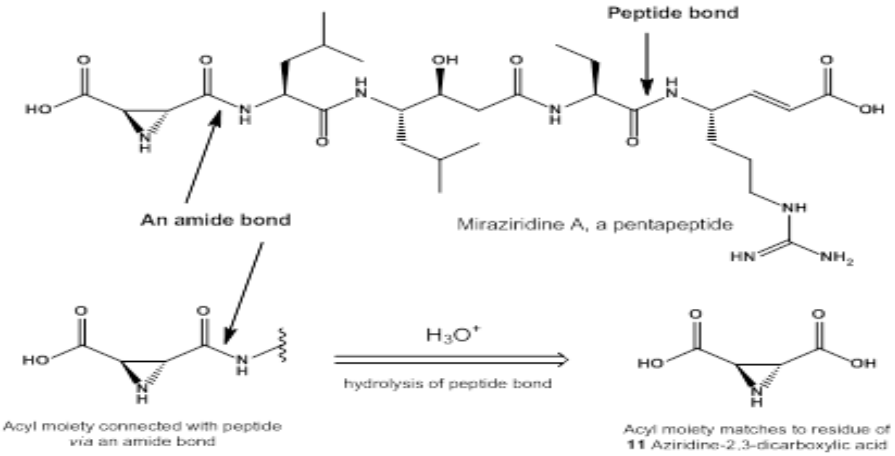

Fig. 3. Graphical display of the chemical structure of lipopeptide isolated from marine sponge *Theonella* aff. *mirabilis* and the free fatty acid formed by hydrolysis of the amide bond.

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.[16] Neo fatty acids and their derivatives have different biological activities, including anticarcinogenic, antifungal, antibacterial, antimicrobial and others.[16,79]

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.[80] 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**].[80]

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.[81] 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,[82] and chondropsin D.[83] 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.[84]

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, l-3-ureidoalanine, E-dehydronorvaline and d-citrulline. MTT assays against P388 and HeLa cells revealed that all three compounds had moderate cytotoxicity.[85,86] 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.[87] The only difference between the two peptides is the N-terminus acyl moiety. Their structures also contain the unusual residues (2*R*,3*R*)-β-methoxytyrosine, (3*S*,4*R*)-3,4-dimethyl-l-glutamine, (2*S*,3*S*)-2,3-diamino-butyric acid, (2*R*,3*S*)-β-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.[87]

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, □-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_{50} 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.[88-91]

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 □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.[92,94]

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.[95,97] The same fatty acid contains jasplakinolide D, M, Q and R1.[98,100] 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.[101,104] The serine residue in geodiamolides L-P and R had not been previously found in this family of compounds.[95] 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-β-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 μg/mL.[105] Similar peptides have been reported from various sponges.[106] 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.[101,104,107]

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.[108]

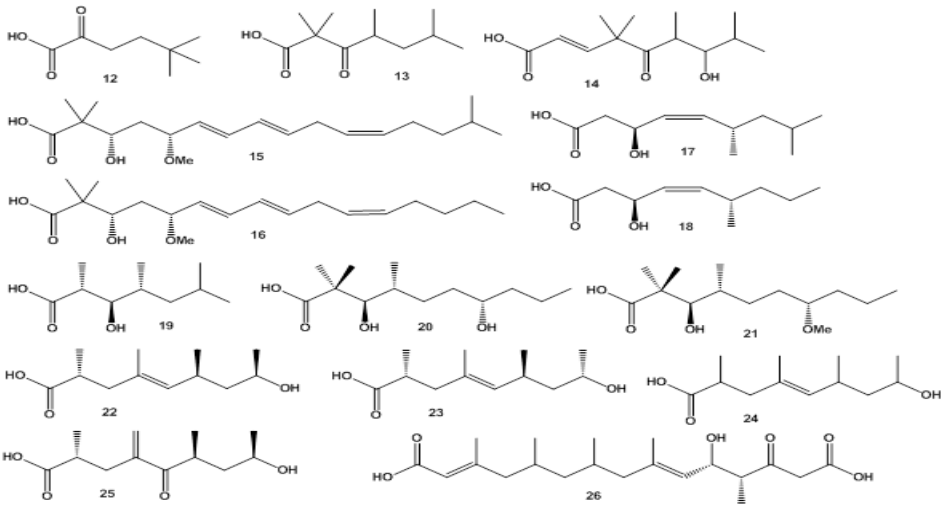

Fig. 4. Neo-, branched, saturated and unsaturated fatty acids isolated from sponge lipopeptides.

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.[109,110] They are similar in structure to the previously published antiviral marine cyclodepsipeptides callipeltin A,[111,112] neamphamide A,[113,114] papuamides,[115,116] theopapuamides[117] and mirabamides.[118] Homophymine A was cytotoxic against uninfected PBMC cells with an IC_{50} of 1.19 μM, 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.[109-118] (2*S*,3*S*,4*S*,6*S*)-3-hydroxy-2,4,6-trimethyl-octanoic 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*.[115,116] (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.[118] *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.[118] These □-OMe tyrosine-containing peptides were potent inhibitors of HIV-1 fusion and shed light on the role of the □-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-trimethyloctanoic acid [**33**] was isolated from mirabamides A–D[118] and neamphamide D.[119]

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

Theopapuamide A is a cytotoxic undecapeptide isolated from *Theonella swinhoei* collected off Milne Bay, Papua New Guinea.[123] It is the first natural peptide containing *β*-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 μM, respectively. In 2009, theopapuamide A was reported along with six new cyclic peptides, theopapuamides B–D[117] and celebesides A–C, from an extract of *Siliquariaspongia mirabilis* collected off Sulawesi Island, Indonesia. Theopapuamides B–D and celebesides A–C were tested against HCT-116 cells and had IC_{50} values of 2.5, 1.3, 9.9 and >31 μM, respectively.[117] (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 celebeside 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 celebeside B.[117]

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.[124] 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**].[124]

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.[125,126] Psymberin has structural similarities to the pederin family metabolites. [127,128] The potent cytotoxicty and unique structural features of psymberin make it a promising lead for therapeutic development.[129] 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.[125,130]

Sponges in the *Jaspidae* family have proved to be a prolific source of bioactive natural products.[131-134] 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.[131-134]

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_{50} value of 0.27 μM and was not cytotoxic to several other cell lines tested.[135,137]

Poecillastrin A, a new polyketide-derived macrolide lactam, was isolated from a deep-water collection of the marine sponge *Poecillastra*.[138] Poecillastrin D was isolated together with poecillastrin C from the deep-sea sponge, *Japsis serpentine*.[139] These compounds showed 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**].[138-140]

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.[141] 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.[141,144]

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 □-methoxyasparagine and 4-amino-5-methyl-2,3,5-trihydroxyhexanoic acid is unprecedented in natural peptides.[145] 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_{50} values of 0.5 and 0.9 □M, respectively.[145] Geodiamolide TA is a cytotoxic peptide isolated from the marine sponge *Hemiasterella minor*.[146]

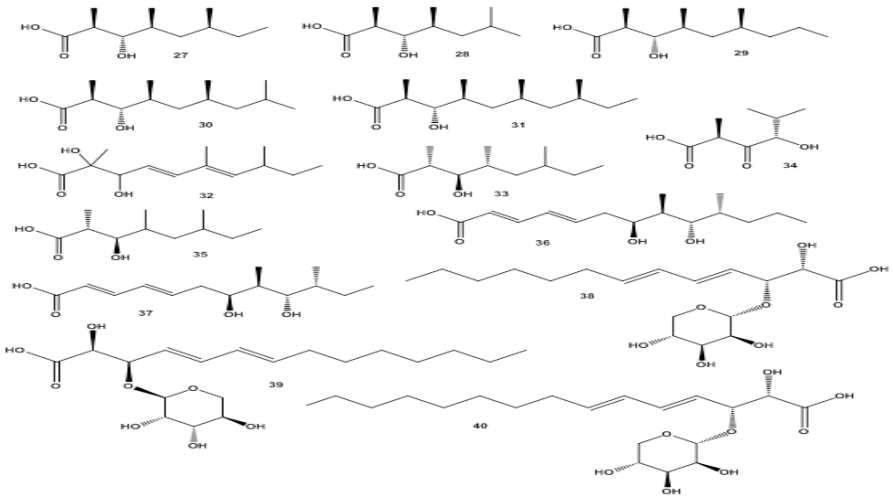

Fig. 5. Hydroxy branched fatty acids from lipopeptides of the sponge species.

In 2008 and 2009, Zampella and co-workers described ten cyclodepsipeptides, named homophymines A–E and A1–E1[109,110] 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**].[109,110]

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.[147]

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*.[148]

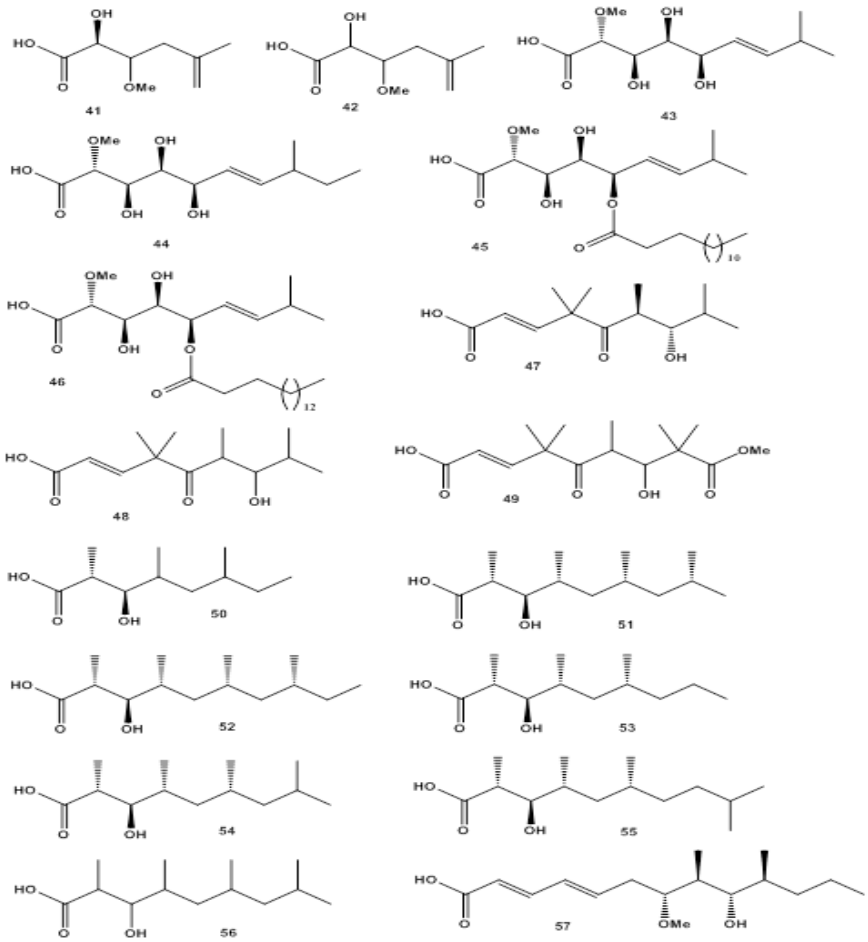

Fig. 6. Saturated, unsaturated and branched fatty acids from sponge lipopeptides.

3.2. HALOGENETED FATTY ACIDS OF SPONGE LIPOPEPTIDES

Several chlorinated fatty acids have been isolated from lipopeptides and other metabolites of marine sponges.[4] 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**].[149-152] 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**].[153] *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.[154] The same acid also contained the herbaceamide A. Fatty acid [**63**] was isolated from chlorinated peptides found in the marine sponge *Dysidea* sp.[155]

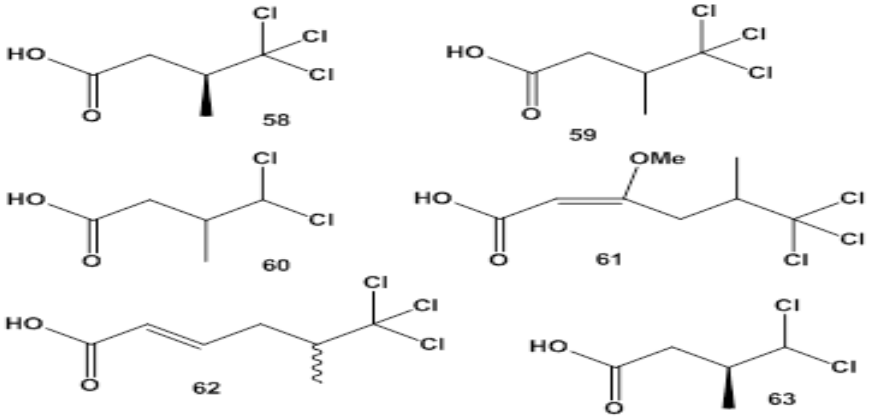

Fig. 7. Halogenated fatty acids from sponge lipopeptides.

3.3. MISCELLANEOUS FATTY ACIDS FROM SPONGE LIPOPEPTIDES

Arenastatin A with (5S,6S,7S,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*.[156,158] 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.[159,160] However, arestatin 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.[161,163]

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.[164,166] Onnamide A contains (*S*)-2-hydroxy-2-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-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-2H-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-2H-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*.[164,166]

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.[167] 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-Δ-3-pyrroline, a sulfated glyceric acid, (*R*)-2-methoxy-3-(sulfooxy) propanoic acid [**69**] and D-leucine, assembled through three peptide linkages.[168] Dysinosin A inhibited factor VIIa at a Ki of 108 nM and thrombin at a Ki of 452 nM. The identification of the 1-N-amidino-Δ-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.[169,170] An additional three products, dysinosins B−D, were isolated from the sponge *Lamellodysidea chlorea*. 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**].[169,170]

The lithistid sponge *Scleritoderma nodosum* contains a cyclic peptide, scleritodermin A, the structure of which incorporates l-proline, l-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.[171,172] 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.[173-175]

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.[176,177]

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 □-hydroxy acids as well as □-methoxy-phenylalanine residues.[178,179]

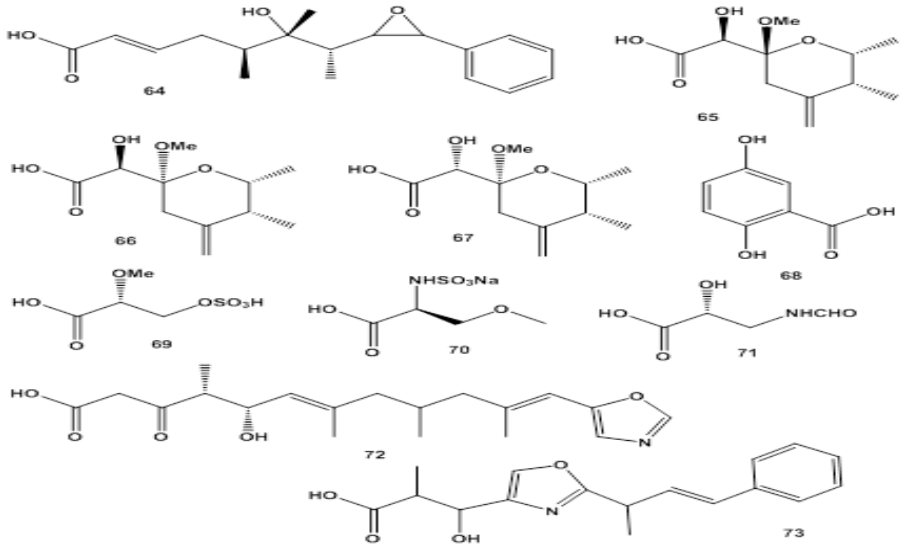

Fig. 7. Miscellaneous fatty acids from sponge lipopeptides.

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.[180-182] Bioactive marine compounds belong to very diverse structural classes, including polyketides, terpenes, steroids and lipopeptides.[182]

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_{50} values ranging from 4.2 to 59.1 nM) indicating cancer cell selectivity.[183]

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_{50} values of 0.7 and 2.1 μg/mL, respectively. Kulolide caused morphological changes in rat 3Y1 fibroblast cells at the concentration of 50 Mm.[184] Kulolide 2 from *Ph. speciosa* contained (S)-3-hydroxy-2,2-dimethyloct-7-enoic acid [**76**].[185] Kulomoopunalide-2 from *Ph. speciosa* contained (2*R*,3*S*)-3-hydroxy-2-methyloct-7-ynoic acid [**77**].[186]

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

Two cyclic depsipeptides, kahalalide R and S together with two known congeners, kahalalides F and D, were isolated from the mollusc *Elysia grandifolia*.[189] 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.[190]

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-trimethyl-undeca-2,8-dienoic acid [**82**], is a 26-membered cyclodepsipeptide that has been isolated from the Japanese sea hare *Dolabella auricularia*.[191]

An antineoplastic agent, depsipeptide dolastatin 13, with 3-hydroxy-2-methoxy-propanoic acid [**83**], was isolated from the sea hare *Dolabella auricularia*.[192] 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_{50} of 1.8 ng/mL.[193]

Dolastain C, a depsipeptide exhibiting weak cytotoxicity, was isolated from the Japanese sea hare *Dolabella auricularia* and contained (2S,3R)-2-(dimethylamino)-3-methylpentanoic acid [**85**].[194] 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.[195] 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_{50} values of 1.0 and 5.3 g/mL, respectively. Nordolastatin G is a congener that has the same absolute stereochemistry as that of dolastatin G.[196] 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.[197,198] 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_{50} 2.7×10^{-3} and 7.5×10^{-2} µg/mL, respectively.[199] 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_{50} of 0.39 µg/mL for the non-small cell lung cancer NCI-H460.[200]

The cytotoxic, cyclic depsipeptide (-)-doliculide with (2S,3S,5S,6S,8S)-6,8-dihydroxy-2,3,5,9-tetramethyldecanoic acid [**91**, Fig. 8] was isolated by Ishiwata et al.[201,202] 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.[203]

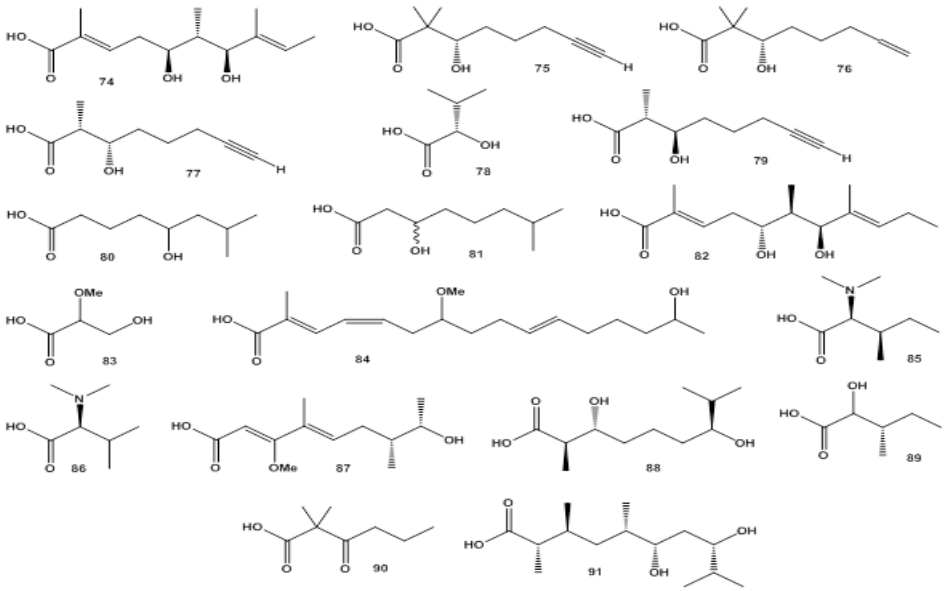

Fig. 8. Lipopeptide fatty acids from Molluscs.

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.[204,205] 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.[206,207] ET-743 is a tetrahydro-isoquiniline alkaloid and acts by selective alkylation of guanine residues in the DNA minor groove[208,209] and also interacts with nuclear proteins.[210] In Europe and the United States ET-743 is currently in phase II clinical trials.[210,211] 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).[212,213] Four minor congeners, sagittamides C–F were isolated from Didemnid ascidia that were previously identified to contain sagittamides A and B.[212-214] 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.[215] 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.[216,217] 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*.[218] 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.[219,220] 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 35R absolute configuration for eudistomide B.[221] Both compounds contained the same fatty acid [**104**].

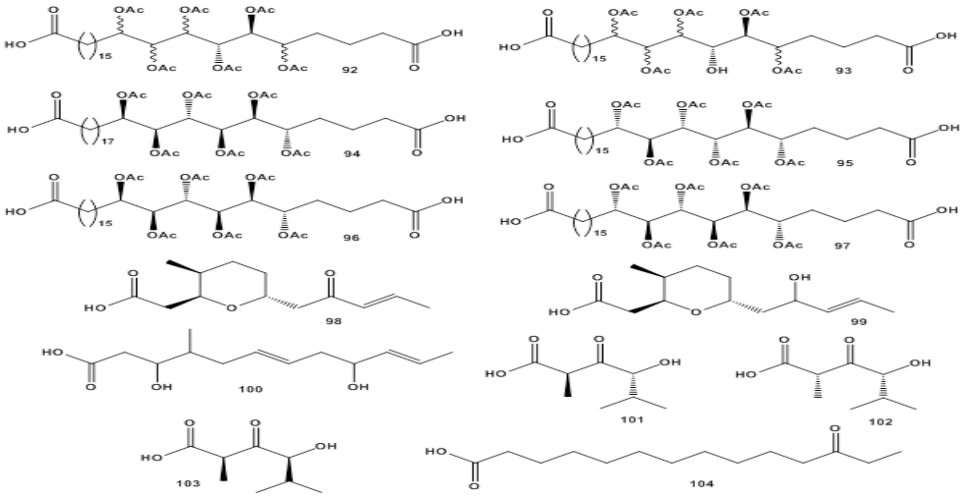

Fig. 9. Fatty acids from Tunicate lipopeptides.

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.

REFERENCES

1. Dembitsky VM. Lipids of lichens. Prog. Lipid Res, 1992; 31: 373-397.
2. Dembitsky VM. Lipids of bryophytes. Prog. Lipid Res, 1993; 32: 281-356.
3. Dembitsky VM. Betaine ether-linked glycerolipids: Chemistry and biology. Prog. Lipid Res, 1996; 35: 1-51.
4. Dembitsky VM, Srebnik M. Natural halogenated fatty acids: their analogues and derivatives. Prog. Lipid Res, 2002; 41: 315-367.
5. Dembitsky VM, Levitsky DO. Arsenolipids. Prog. Lipid Res, 2004; 43: 403-348.
6. Dembitsky V., Maoka T. Allenic and cumulenic lipids. Prog. Lipid Res, 2007; 46: 328-375.
7. Kuklev DV, Dembitsky VM. Epoxy acetylenic lipids: Their analogues and derivatives. Prog. Lipid Res, 2014; 56: 67-391.
8. Dembitsky VM. Astonishing diversity of natural surfactants: 1. Glycosides of fatty acids and alcohols. Lipids, 2004; 39: 933-953.
9. Dembitsky VM. Astonishing diversity of natural surfactants: 2. Polyether glycosidic ionophores and macrocyclic glycosides. Lipids, 2005; 40: 219-248.
10. Dembitsky VM. Astonishing diversity of natural surfactants: 3. Carotenoid glycosides and isoprenoid glycolipids. Lipids, 2005; 40: 535-557.
11. Dembitsky VM. Astonishing diversity of natural surfactants: 4. Fatty acid amide glycosides, their analogs and derivatives. Lipids, 2005; 40: 641-660.
12. Dembitsky VM. Astonishing diversity of natural surfactants: 5. Biologically active glycosides of aromatic metabolites. Lipids, 2005; 40: 869-900.
13. Dembitsky VM. Astonishing diversity of natural surfactants: 6. Biologically active marine and terrestrial alkaloid glycosides. Lipids, 2005; 40: 1081-1105.
14. Dembitsky VM. Astonishing diversity of natural surfactants: 7. Biologically active hemi- and monoterpenoid glycosides. Lipids, 2006; 41: 1-27.
15. Dembitsky VM. Anticancer activity of natural and synthetic acetylenic lipids. Lipids, 2006; 41: 883-924.
16. Dembitsky VM. Natural neo acids and neo alkanes: their analogs and derivatives. Lipids, 2006; 41: 309-340.
17. Hanus LO, Goldshlag P, Dembitsky VM. Identification of cyclopropyl fatty acids in walnut (Juglans regia L.) oil. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech. Repub, 2008; 152: 41-45.
18. Kilimnik A, Kuklev DV, Dembitsky VM. Anitumor acetylenic lipids. Mathews J. Pharm. Sci, 2016; 1(1): 005.
19. Benes LB, Bassi NS, Davidson MH. Omega-3 carboxylic acids monotherapy and combination with statins in the management of dyslipidemia. Vasc. Health Risk Manag, 2016; 12: 481-490.
20. Filippatos TD, Klouras E, Barkas F, Elisaf M. Cholesteryl ester transfer protein inhibitors: challenges and perspectives. Expert Rev. Cardiovasc. Ther, 2016; 14: 953-962.
21. Wascher TC, Paulweber B, Toplak H, Säly CH, *et al*., Lipids - Diagnosis and therapy in diabetes mellitus. Wien Klin. Wochenschr, 2016; 128 Suppl 2: S68-S70.
22. Zhou P, Zhao J. Structure, inhibition, and regulation of essential lipid A enzymes. Biochim. Biophys. Acta, 2016; S1388: 30331-30336.
23. Kadhum AA, Shamma MN. Edible lipids modification processes: A review. Crit. Rev. Food Sci. Nutr, 2017; 57: 48-58.
24. Yao J, Rock CO. Bacterial fatty acid metabolism in modern antibiotic discovery. Biochim. Biophys. Acta, 2016; S1388: 30260-30268.
25. Spassieva S, Bieberich E. Lysosphingolipids and sphingolipidoses: Psychosine in Krabbe's disease. J. Neurosci. Res, 2016; 94: 974-981.
26. PrakashG, Agrawal R, Natung T. Role of lipids in retinal vascular and macular disorders. Indian J. Clin. Biochem, 2017; 32: 3-8.
27. Perez-Matos MC, Morales-Alvarez MC, Mendivil CO. Lipids: A suitable therapeutic target in diabetic neuropathy? J. Diabetes Res, 2017; 6943851.
28. Michalak A, Mosińska P, Fichna J. Polyunsaturated fatty acids and their derivatives: therapeutic value for inflammatory, functional gastrointestinal disorders and colorectal cancer. Front. Pharmacol, 2016; 7: 459.
29. Perrotti F, Rosa C, Cicalini I, Sacchetta P, *et al*., Advances in lipidomics for cancer biomarkers discovery. Int. J. Mol. Sci, 2016; 17: E1992.
30. Fernando, I.P., Nah JW, Jeon YJ. Potential anti-inflammatory natural products from marine algae. Environ. Toxicol. Pharmacol, 2016; 48: 22-30.
31. Dembitsky VM, Pechenkina-Shubina EE, Rozentsvet OA. Glycolipids and fatty acids of some seaweeds and marine grasses from the Black Sea. Phytochemistry, 1991; 30: 2279-2283.
32. Dembitsky VM, Pechenkina-Shubina EE, Rozentsvet OA. Glycolipids, phospholipids and fatty acids of brown algae species. Phytochemistry, 1990; 29: 3417-3421.
33. Kalisch B, Dörmann P, Hölzl G. DGDG and glycolipids in plants and algae. Subcell. Biochem,

2016; 86: 51-83.
34. Barbosa M, P. alentão P, Andrade PB. Biologically active oxylipins from enzymatic and nonenzymatic routes in macroalgae. Mar Drugs, 2016; 14: 23-28.
35. Abdul QA, Choi RJ, Jung HA, Choi JS. Health benefit of fucosterol from marine algae: a review. J. Sci. Food Agric, 2016; 96: 1856-1866.
36. Zitzelsberger C, Buchbauer G. Essential Oils as "A Cry for Help". A Review. Nat. Prod. Commun, 2005; 10: 1127-1138.
37. Hanuš LO, Levitsky DO, Shkrob I, Dembitsky VM. Plasmalogens, fatty acids and alkyl glyceryl ethers of marine and freshwater clams and mussels. Food Chem, 2009; 116: 491-498.
38. Dembitsky VM. Chemistry and biodiversity of the biologically active natural glycosides. Chem. Biodiver, 2004; 1(5): 673-781.
39. Dembitsky VM, Rezanka T, Srebnik M. Lipid compounds of freshwater sponges: family Spongillidae, class Demospongiae. Chem. Phys. Lipids, 2003; 123: 117-155.
40. Williams SL, Smith JE. A global review of the distribution, taxonomy, and impacts of introduced seaweeds. Ann. Rev. Ecol. Evol. Syst, 2007; 38: 327-359.
41. Pérez MJ, Falqué E, Domínguez H. Antimicrobial action of compounds from marine seaweed. Mar Drugs, 2016; 14(3): E52. doi: 10.3390/md14030052.
42. Maciel E, Costa Leal M, Lillebø AI, Domingues P, Domingues MR, Calado R. Bioprospecting of marine macrophytes using MS-based lipidomics as a new approach. Mar Drugs, 2016; 14: E49. doi: 10.3390/md14030049.
43. Plouguerné E, da Gama BA, Pereira RC, Barreto-Bergter E. Glycolipids from seaweeds and their potential biotechnological applications. Front. Cell Infect. Microbiol, 2014; 4: 174-189.
44. Moussavou G, Kwak DH, Obiang-Obonou BW, *et al*., Anticancer effects of different seaweeds on human colon and breast cancers. Mar Drugs, 2014; 12: 4898-4911.
45. Yende SR, Harle UN, Chaugule BB. Therapeutic potential and health benefits of Sargassum species. Pharmacogn. Rev, 2014; 8: 1-7.
46. Wijesinghe WA, Jeon YJ. Exploiting biological activities of brown seaweed Ecklonia cava for potential industrial applications: a review. Int. J. Food Sci. Nutr, 2012; 63: 225-235.
47. Iwasaki A, Ohno O, Sumimoto S, *et al*., Mebamamides A and B, cyclic lipopeptides isolated from the green alga Derbesia marina. J. Nat. Prod, 2015; 78: 901–908.
48. Pelay-Gimeno M, Tulla-Puche J, Albericio F. "Head-to-Side-Chain" cyclodepsi-peptides of marine origin. Mar. Drugs, 2013; 11: 1693-1717.
49. Hamann MT, Scheuer PJ. Kahalalide F: a bioactive depsipeptide from the sacoglossan mollusk Elysia rufescens and the green alga Bryopsis sp. J. Am. Chem. Soc, 1993; 115: 5825–5826.
50. Hamann MT, Otto CS, Scheuer PJ, Dunbar DC. Kahalalides: bioactive peptides from a marine mollusk Elysia rufescens and its algal diet Bryopsis sp. J. Org. Chem, 1996; 61: 6594-6600.
51. Goetz G, Nakao Y, Scheuer PJ. Two acyclic kahalalides from the sacoglossan mollusk Elysia rufescens. J. Nat. Prod, 1997; 60: 562–567.
52. Dmitrenok A, Iwashita T, Nakajima T, et al., New cyclic depsipeptides from the green alga Bryopsis species; application of a carboxypeptidase hydrolysis reaction to the structure determination. Tetrahedron, 2006; 62: 1301–1308.
53. Thacker RW, Freeman CJ. Sponge-microbe symbioses: recent advances and new directions. Adv. Mar. Biol, 2012; 62: 57-111.
54. Webster NS, Thomas T. The Sponge Hologenome. MBIO, 2016; 7: e00135-16.
55. Sagar S, Kaur M, Minneman KP. Antiviral lead compounds from marine sponges. Mar Drugs, 2010; 8: 2619-2638.
56. Dembitsky VM. Bioactive cyclobutane-containing alkaloids. J. Nat. Med, 2008; 62: 1-33.
57. Dembitsky VM, Gloriozova TA, Poroikov VV. Novel antitumor agents: marine sponge alkaloids, their synthetic analogs and derivatives. Mini Rev. Med. Chem, 2005; 5: 319-336.
58. Dembitsky VM. Bioactive peroxides as potential therapeutic agents. Eur. J. Med. Chem, 2008; 43: 223-251.
59. Ismail FMD, Levitsky DO, Dembitsky VM. Aziridine alkaloids as potential therapeutic agents. Eur. J. Med. Chem, 2009; 44: 3373-3387.
60. Dembitsky VM, Gloriozova TA, Poroikov VV. Natural peroxy anticancer agents. Mini Rev. Med. Chem, 2007; 7: 571-589.
61. Dembitsky VM. Bromo-and iodo-containing alkaloids from marine microorganisms and sponges. Russ. J. Bioorg. Chem, 2002; 28: 170-182.
62. Sergeiko A, Poroikov VV, Hanuš LO, Dembitsky VM. Cyclobutane-containing alkaloids: origin, synthesis, and biological activities. Open Med. Chem, 2008; J. 2: 26-37.
63. Dembitsky VM. Biogenic iodine and iodine-containing metabolites. Nat. Prod. Commun, 2006; 1: 139-175.
64. Kuklev DV, Domb AJ, Dembitsky VM. Bioactive acetylenic metabolites. Phytomedicine, 2013; 20: 1145-1159.
65. Dembitsky VM, Gloriozova TA, Poroikov VV. Naturally occurring plant isoquinoline N-oxide alkaloids: Their pharmacological and SAR activities. Phytomedicine, 2015; 22: 183-202.
66. Dembitsky VM, Gloriozova TA, Poroikov VV. Pharmacological and predicted activities of natural azo compounds. Nat. Prod. Bioprospec, 2017; 7: 151-169.
67. LevitskyDO, Gloriozova TA, Poroikov VV, Dembitsky VM. Naturally occurring isocyano/isothiocyanato compounds: Their pharmacological and SAR activities. Mathews J. Pharm. Sci, 2016; 1(1): 003.

68. Mioso R, Marante FJ, Bezerra RS, *et al*., Cytotoxic compounds derived from marine sponges. A review (2010-2012). Molecules, 2017; 22: E208.
69. Daletos G, Ancheeva E, Chaidir C, Kalscheuer R, Proksch R. Antimycobacterial metabolites from marine invertebrates. Arch. Pharm. (Weinheim), 2016; 349: 763-773.
70. Anjum K, Abbas SQ, Shah SA, Akhter N, Batool S, Hassan SS. Marine sponges as a drug treasure. Biomol. Ther. (Seoul), 2016; 24: 347-362.
71. Gammone MA, Riccioni G, Galvano F, D'Orazio N. Novel therapeutic strategies against cancer: Marine-derived drugs may be the answer? Anticancer Agents Med. Chem, 2016; 16: 1549-1557.
72. Nakao Y, Fujita M, Warabi K, Matsunaga S, Fusetani N. Miraziridine A, a novel cysteine protease inhibitor from the marine sponge Theonella aff. Mirabilis. J. Am. Chem. Soc, 2000; 122: 10462-10463.
73. Tabares P, Degel B, Schaschke N, Hentschel U, Schirmeister T. Identification of the protease inhibitor miraziridine A in the Red sea sponge Theonella swinhoei. Pharmacog. Res, 2012; 4: 63-66.
74. Schaschke N. Miraziridine A: natures blueprint towards protease class-spanning inhibitors. Bioorg. Med. Chem. Lett, 2004; 14: 855-857.
75. Konno H. Synthesis of bioactive natural products as protein inhibitors. Biosci. Biotechnol. Biochem, 2012; 76: 1257-1261.
76. Naganawa H, Usui N, Takita T, Hamada M, Umezawa H. S-2,3-dicarboxy-aziridine: A new metabolite from a Streptomyces. J. Antib. (Tokyo), 1975; 28: 828-829.
77. Zwanenburg B, Thijs L. Aziridine and azirine carboxylic esters. Pure Appl. Chem, 1996; 68: 735-738.
78. Oettel H, Wilhelm G. Wege zur chemotherapic des krebses. Arzneimittel-Forsch, 1954; 4: 681-703.
79. Dembitsky VM, Gloriozova TA, Poroikov V.V. Natural steroids containing a tertiary butyl group and their biological activities. European J. Biomed. Pharm. Sci, 2017; 4(11): 32-58.
80. Hamada T, Matsunaga S, Yano G, Fusetani N. Polytheonamides A and B, highly cytotoxic, linear polypeptides with unprecedented structural features, from the marine sponge, Theonella swinhoei. J. Am. Chem. Soc, 2005; 127: 110–118.
81. Ueoka R, Ise Y, Ohtsuka S, Okada S, Yamori T, Matsunaga S. Yaku'amides A and B, cytotoxic linear peptides rich in dehydroamino acids from the marine sponge Ceratopsion sp. J. Am. Chem. Soc, 2010; 132: 17692–17694.
82. Takada K, Choi BW, Rashid MA, Gamble WR, *et al*., Structural assignment of poecillastrins B and C, macrolide lactams from the deep-water Caribbean sponge Poecillastra species. J. Nat. Prod, 2007; 70: 428-431.
83. Rashid MA, Cantrell CL, Gustafson KR, Boyd MR. Chondropsin D, a new 37-membered-ring macrolide lactam from the marine sponge Chondropsis species. J. Nat. Prod, 2001; 64: 1341-1344.
84. Takemoto D, Takekawa Y, Soest RW, Fusetani N, Matsunaga S. Poecillastrin D: a new cytotoxin of the chondropsin class from marine sponge Jaspis serpentina. Biosci. Biotechnol. Biochem, 2007; 71: 2697-700.
85. Tan KC, Wakimoto T, Abe I. Lipodiscamides A-C, new cytotoxic lipopeptides from Discodermia kiiensis. Org. Lett, 2014; 16: 3256-3259.
86. Tan KC, Wakimoto T, Abe I. Sulfoureido lipopeptides from the marine sponge Discodermia kiiensis. J. Nat. Prod, 2016; 79: 2418-2422.
87. Martín MJ, Rodríguez-Acebes R, García-Ramos Y, Martínez V, et al. Stellatolides, a new cyclodepsipeptide family from the sponge Ecionemia acervus: isolation, solid-phase total synthesis, and full structural assignment of stellatolide A. J. Am. Chem. Soc, 2014; 136: 6754-6762.
88. Oku N, Gustafson KR, Cartner LK, Wilson JA, *et al*., Neamphamide A, a new HIV-inhibitory depsipeptide from the Papua New Guinea marine sponge Neamphius huxleyi. J. Nat. Prod, 2004; 67: 1407-1411.
89. Oku N, Krishnamoorthy R, Benson AG, Ferguson RL, *et al*., Complete stereochemistry of neamphamide A and absolute configuration of the beta-methoxytyrosine residue in papuamide B. J. Org. Chem, 2005; 70: 6842-6847.
90. Yamano Y, Arai M, Kobayashi M. Neamphamide B, new cyclic depsipeptide, as an anti-dormant mycobacterial substance from a Japanese marine sponge of Neamphius sp. Bioorg. Med. Chem. Lett, 2012; 22: 4877-4881.
91. Tran TD, Pham NB, Fechner G, Zencak D, *et al*., Cytotoxic cyclic depsipeptides from the Australian marine sponge Neamphius huxleyi. J. Nat. Prod, 2012; 75: 2200-2208.
92. Randazzo A, Bifulco G, Giannini C, Bucci M, et al., Halipeptins A and B: two novel potent anti-inflammatory cyclic depsipeptides from the Vanuatu marine sponge Haliclona species. J. Am. Chem. Soc, 2001; 123: 10870-10876.
93. Nicolaou KC, Lizos DE, Kim DW, Schlawe D, *et al*., Total synthesis and biological evaluation of halipeptins A and D and analogues. J. Am. Chem. Soc, 2006; 128: 4460-44670.
94. Yu S, Pan X, Ma D. Asymmetric total syntheses of marine cyclic depsipeptide halipeptins A-D. Chem, 2006; 12: 6572-84.
95. Tanaka C, Tanaka J, Bolland RF, Marriott G, Higa T. Seragamides A–F, new actin-targeting depsipeptides from the sponge Suberites japonicus Thiele. Tetrahedron, 2006; 62: 3536–3542.
96. Mayer AMS, Gustafson KR. Marine pharmacology in 2005-6: Antitumour and cytotoxic compounds. Eur. J. Cancer, 2008; 44: 2357–2387.
97. Mehbub MF, Lei J, Franco C, Zhang W. Marine sponge derived natural products between 2001 and

2010: Trends and opportunities for discovery of bioactivities. Mar Drugs, 2014; 12: 4539–4577.
98. Holzinger A. Jasplakinolide: an actin-specific reagent that promotes actin polymerization. Meth. Mol. Biol, 2009; 586: 71-87.
99. Noro JC, Kalaitzis JA, Neilan BA. Bioactive natural products from Papua New Guinea marine sponges. Chem. Biodivers, 2012; 9: 2077-2095.
100. Trendowski M. Exploiting the cytoskeletal filaments of neoplastic cells to potentiate a novel therapeutic approach. Biochim. Biophys. Acta, 2014; 1846: 599-616.
101. White JD, Amedio JC, Jr. Total synthesis of geodiamolide A, a novel cyclodepsipeptide of marine origin. J. Org. Chem, 1989; 54: 736–738.
102. Rao AVR, Gurjar MK, Nallaganchu BR, Bhandari A. Studies on cyclodepsipeptides - Part I: A stereoselective synthesis of C12 polyketide unit (C1–C8) present in Jaspamide and Geodiamolide A–F. Tetrahedron Lett, 1993; 34: 7081-7084.
103. Tinto WF, Lough AJ, McLean S, Reynolds WF, Yu M, Chan WR. Geodiamolides H and I, further cyclodepsipeptides from the marine sponge Geodia sp. Tetrahedron, 1998; 54: 4451-4458.
104. Laus G. Biological activities of natural halogen compounds. Stud. Nat. Prod. Chem, 2001; 25F: 757-809.
105. Scott VR, Boehme R, Matthews TR. New class of antifungal agents: jasplakinolide, a cyclodepsipeptide from the marine sponge, Jaspis species. Antimicrob. Agents Chemother, 1988; 32: 1154-1157.
106. Molinski F. Anti-infective agents. Curr. Med. Chem, 2004; 3: 197–220.
107. Braekman JC, Daloze D, Moussiaux B, Riccio R. Jaspamide from the marine sponge Jaspis johnstoni. J. Nat. Prod, 1987; 50: 994–995.
108. Bishara A, Rudi A, Aknin M, Neumann D, Ben-Califa N, *et al*., Taumycins A and B, two bioactive lipodepsipeptides from the Madagascar sponge Fascaplysinopsis sp. Org. Lett, 2008; 10: 4307–4309.
109. Zampella A, Sepe V, Bellotta F, Luciano P, et al. Homophymines B-E and A1-E1, a family of bioactive cyclodepsipeptides from the sponge Homophymia sp. Org. Biomol. Chem, 2009; 7: 4037-4044.
110. Zampella A, Sepe V, Luciano P, Bellotta F, et al. Homophymine A, an anti-HIV cyclodepsipeptide from the sponge Homophymia sp. J. Org. Chem, 2008; 73: 5319–5327.
111. Trevisi L, Bova S, Cargnelli G, Danieli-Betto D, *et al*., Callipeltin A, a cyclic depsipeptide inhibitor of the cardiac sodium-calcium exchanger and positive inotropic agent. Biochem. Biophys. Res. Commun, 2000; 279: 219-222.
112. Trevisi L, Cargnelli G, Ceolotto G, Papparella I, *et al*., Callipeltin A: sodium ionophore effect and tension development in vascular smooth muscle. Biochem. Pharmacol, 2004; 68: 1331-1338.
113. Oku N, Gustafson KR, Cartner LK, Wilson JA, *et al*., Neamphamide A, a new HIV-inhibitory depsipeptide from the Papua New Guinea marine sponge Neamphius huxleyi. J. Nat. Prod, 2004; 67: 1407-1411.
114. Noro JC, Kalaitzis JA, Neilan BA. Bioactive natural products from Papua New Guinea marine sponges. Chem. Biodivers, 2012; 9: 2077-2095.
115. Ford PW, Gustafson KR, McKee TC, Shigematsu N, *et al*., Papuamides A−D, HIV-inhibitory and cytotoxic depsipeptides from the sponges Theonella mirabilis and Theonella swinhoei collected in Papua New Guinea. J. Am. Chem. Soc, 1999; 121: 5899–5909.
116. Prasad P, Aalbersberg W, Feussner KD, Van Wagoner RM. Papuamides E and F, cytotoxic depsipeptides from the marine sponge Melophlus sp. Tetrahedron, 2011; 67: 8529-8531.
117. Plaza A, Bifulco G, Keffer JL, Lloyd JR, *et al*., Celebesides A-C and theopapuamides B-D, depsipeptides from an Indonesian sponge that inhibit HIV-1 entry. J. Org. Chem 2009; 74: 504-512.
118. Plaza A, Gustchina E, Baker HL, Kelly M, Bewley CA. Mirabamides A-D, depsipeptides from the sponge Siliquariaspongia mirabilis that inhibit HIV-1 fusion. J. Nat. Prod, 2007; 70: 1753-1760.
119. Tran TD, Pham NB, Fechner G, Zencak D, *et al*., Cytotoxic cyclic depsipeptides from the Australian marine sponge Neamphius huxleyi. J. Nat. Prod, 2012; 75: 2200-2208.
120. Rinehart KL, Kishore V, Bible KC, Sakai R, *et al*., Didemnins and tunichlorin: novel natural products from the marine tunicate Trididemnum solidum. J. Nat. Prod, 1988; 51: 1-21.
121. Hossain MB, van der Helm D, Antel J, *et al*., Crystal and molecular structure of didemnin B, an antiviral and cytotoxic depsipeptide. Proc. Natl. Acad. Sci. USA, 1988; 85: 4118-4122.
122. Hossain MB, Van Der Helm D, Antel J, Sheldrick GM, *et al*., Crystal and molecular structure of didemnin A, an antiviral depsipeptide. Int. J. Pept. Protein. Res, 1996; 47: 20-27.
123. Ratnayake AS, Bugni TS, Feng X, Harper MK, et al., Theopapuamide, a cyclic depsipeptide from a Papua New Guinea lithistid sponge Theonella swinhoei. J. Nat. Prod, 2006; 69: 1582-1586.
124. Bewley CA, He H, Williams DH, Faulkner DJ. Aciculitins A−C: cytotoxic and antifungal cyclic peptides from the lithistid sponge Aciculites orientalis. J. Am. Chem. Soc, 1996; 118: 4314–4321.
125. Uesugi S, Watanabe T, Imaizumi T, Ota Y, Yoshida K, *et al*., Total synthesis and biological evaluation of irciniastatin A (a.k.a. Psymberin) and irciniastatin B. Org. Chem, 2015; 80: 12333-123350.
126. Crimmins MT, Stevens JM, Schaaf GM, Total synthesis of irciniastatin A (Psymberin). Org. Lett, 2009; 11: 3990–3993.
127. Fisch KM, Gurgui C, Heycke N, van der Sar SA, et al., Polyketide assembly lines of uncultivated sponge symbionts from structure-based gene targeting. Nat.

Chem. Biol, 2009; 5: 494-501.
128. Cardani C, Ghiringhelli D, Mondelli R, Quilico A. The structure of pederin. Tetrahedron Lett, 1965; 6: 2537-2545.
129. Cichewicz RH, Valeriote FA, Crews P. Psymberin, a potent sponge-derived cytotoxin from Psammocinia distantly related to the pederin family. Org. Lett, 2004; 6: 1951-1954.
130. An C, Jurica JA, Walsh SP, Hoye AT, Smith AB, 3rd. Total synthesis of (+)-irciniastatin A (a.k.a. psymberin) and (-)-irciniastatin B. J. Org. Chem, 2013; 78: 4278-4296.
131. García-Ruiz C, Sarabia F. Chemistry and biology of bengamides and bengazoles, bioactive natural products from Jaspis sponges. Mar. Drugs, 2014; 12: 1580–1622.
132. Quinoa E, Adamczeski M, Crews P, Bakus GJ. Bengamides, heterocyclic anthelmintics from a Jaspidae marine sponge. J. Org. Chem, 1986; 51: 4494–4497.
133. Quiñoà E, Adamczeski M, Crews P. Bengamides, heterocyclic anthelminthics from a jaspidae marine sponge. J. Org. Chem, 1986; 51: 4497–4498.
134. Groweiss A, Newcomer JJ, O'Keefe BR, *et al*., Cytotoxic metabolites from an Australian collection of the sponge Jaspis species. J. Nat. Prod, 1999; 62: 1691–1693.
135. Plaza A, Baker HL, Bewley CA. Mirabalin, an antitumor macrolide lactam from the marine sponge Siliquariaspongia mirabilis. J. Nat. Prod, 2008; 71: 473-477.
136. Plaza A, Baker HL, Bewley CA. Mirabalin, an antitumor macrolide lactam from the marine sponge Siliquariaspongia mirabilis. J. Nat. Prod, 2009; 72: 324–324.
137. Cornil J, Echeverria PG, Reymond S, *et al*., Synthetic studies toward the C14–C29 fragment of mirabalin. Org. Lett, 2016; 18: 4534–4537.
138. Rashid MA, Cantrell CL, Gustafson KR, Boyd MR. Chondropsin D, a new 37-membered-ring macrolide lactam from the marine sponge Chondropsis species. J. Nat. Prod, 2001; 64: 1341-1344.
139. Takemoto D, Takekawa Y, van Soest RWM, Fusetani N, *et al*., Poecillastrin D: A new cytotoxin of the chondropsin class from marine sponge Jaspis serpentine. Biosci. Biotechnol. Biochem, 2007; 71: 2697–2700.
140. Takada K, Choi BW, Rashid MA, Gamble WR, *et al*., Structural assignment of poecillastrins B and C, macrolide lactams from the deep-water Caribbean sponge Poecillastra species. J. Nat. Prod, 2007; 70: 428-431.
141. Cantrell CL, Gustafson KR, Cecere MR, Pannell LK, Boyd MR. Chondropsins A and B: novel tumor cell growth-inhibitory macrolide lactams from the marine sponge Chondropsis sp. J. Am. Chem. Soc, 2000; 122: 8825–8829.
142. Boyd MR, Gustafson KR. Chondropsin-class antitumor V-ATPase inhibitor compounds, compositions and methods of use thereof. US Patent: 8609716 B2. Dec 17, 2013.
143. Bowman EJ, Gustafson KR, Bowman BJ, Boyd MR. Identification of a new chondropsin class of antitumor compound that selectively inhibits V-ATPases. J. Biol. Chem, 2003; 278: 44147-44152.
144. Chevallier C, Laprévote O, Bignon J, Debitus C, *et al*., Isolation of cytotoxic chondropsins, macrolide lactams from the New-Caledonian marine sponge Psammoclemma sp. and electrospray ion trap multiple stage MS study of these macrolides. Nat. Prod. Res, 2004; 18: 479-484.
145. Ratnayake AS, Bugni TS, Feng X, Harper MK, *et al*., Theopapuamide, a cyclic depsipeptide from a Papua New Guinea lithistid sponge Theonella swinhoei. J. Nat. Prod, 2006; 69: 1582-1586.
146. Talpir R., Benayahu Y, Kashman Y, Pannell L, Schleyer M. Hemiasterlin and geodiamolide TA; two new cytotoxic peptides from the marine sponge Hemiasterella minor (Kirkpatrick). Tetrahedron Lett, 1994; 35: 4453–4456.
147. Coello L, Reyes F, Martín MJ, Cuevas C, Fernández R. Isolation and structures of pipecolidepsins A and B, cytotoxic cyclic depsipeptides from the Madagascan sponge Homophymia lamellosa. J. Nat. Prod, 2014; 77: 298-303.
148. Okada Y, Matsunaga S, van Soest RW, Fusetani N. Nagahamide A, an antibacterial depsipeptide from the marine sponge Theonella swinhoei. Org. Lett, 2002; 4: 3039-3042.
149. Williard PG, De Laszlo SE. Total synthesis of (+)-dysidin, a marine metabolite containing an N-acyl-O-methyltetramic acid. J. Org. Chem, 1984; 49: 3489–3493.
150. Van Sande J, Deneubourg F, Beauwens R, Braekman JC, *et al*., Inhibition of iodide transport in thyroid cells by dysidenin, a marine toxin and some of its analogs. Mol. Pharmacol, 1990; 37: 583-589.
151. Vroye L, Beauwens R, Van Sande J, Daloze D, *et al*., The Na+-I- cotransporter of the thyroid: characterisation of new inhibitors. Pflugers Arch, 1998; 435: 259-266.
152. MacMillan JB, Trousdale EK, Molinski TF. Structure of (-)-neodysidenin from Dysidea herbacea. Implications for biosynthesis of 5,5,5-trichloroleucine peptides. Org. Lett, 2000; 2: 2721-2713.
153. Harrigan GG, Goetz GH, Luesch H, *et al*., Dysideaprolines A-F and barbaleucamides A-B, novel polychlorinated compounds from a Dysidea species. J. Nat. Prod, 2001; 64: 1133-1138.
154. MacMillan JB, Molinski TF. Herbacic acid, a simple prototype of 5,5,5-trichloroleucine metabolites from the sponge Dysidea herbacea. J. Nat. Prod, 2000; 63: 155-157.
155. Lee GM, Molinski TF. Herbaceamide, a chlorinated N-acyl amino ester from the marine sponge, Dysidea herbacea. Tetrahedron Lett, 1992; 33: 7671-7674.
156. Kobayashi M, Aoki S, Ohyabu N, Kurosu M, *et al*., Arenastatin A, a potent cytotoxic depsipeptide from the okinawan marine sponge Dysidea arenaria.

Tetrahedron Lett, 1994; 35: 7969–7972.
157. Kobayashi M, Wang W, Ohyabu N, Kurosu M, Kitagawa I. Improved total synthesis and structure-activity relationship of arenastatin A, a potent cytotoxic spongean depsipeptide. Chem. Pharm. Bull. (Tokyo), 1995; 43: 1598-1600.
158. Murakami N, Tamura S, Koyama K, Sugimoto M, *et al*., New analogue of arenastatin A, a potent cytotoxic spongean depsipeptide, with anti-tumor activity. Bioorg. Med. Chem. Lett, 2004; 14: 2597-2601.
159. Koiso Y, Morita K, Kobayashi M, Wang W, *et al*., Effects of arenastatin A and its synthetic analogs on microtubule assembly. Chem. Biol. Interact, 1996; 102: 183–191.
160. Morita K, Koiso Y, Hashimoto Y, Kobayashi M, *et al*., Interaction of arenastatin A with porcine brain tubulin. Biol. Pharm. Bull, 1997; 20: 171–174.
161. Murakami N, Wang W, Tamura S, Kobayashi M. Synthesis and biological property of carba and 20-deoxo analogues of arenastatin A. Bioorg. Med. Chem. Lett, 2000; 10: 1823-1826.
162. Andavan GS, Lemmens-Gruber R. Cyclodepsipeptides from marine sponges: natural agents for drug research. Mar. Drugs, 2010; 8: 810-834.
163. Singh R, Sharma M, Joshi P, Rawat DS. Clinical status of anti-cancer agents derived from marine sources. Anticancer Agents Med. Chem, 2008; 8: 603-617.
164. Sakemi S, Ichiba T, Kohmoto S, Saucy G, Higa T. Isolation and structure elucidation of onnamide A, a new bioactive metabolite of a marine sponge, Theonella sp. J. Am. Chem. Soc, 1988; 110: 4851–4853.
165. Matsunaga S, Fusetani N, Nakao Y. Eight new cytotoxic metabolites closely related to onnamide A from two marine sponges of the genus Theonella. Tetrahedron, 1992; 48: 8369–8376.
166. Lee KH, Nishimura S, Matsunaga S, Fusetani N, *et al*., Inhibition of protein synthesis and activation of stress-activated protein kinases by onnamide A and theopederin B, antitumor marine natural products. Cancer Sci, 2005; 96: 357-364.
167. Chill L, Kashman Y, Schleyer M. Oriamide, a new cytotoxic cyclic peptide containing a novel amino acid from the marine sponge Theonella sp. Tetrahedron, 1997; 53: 16147–16152.
168. Carroll AR, Pierens GK, Fechner G, De Almeida Leone P, *et al*., Dysinosin A: a novel inhibitor of Factor VIIa and thrombin from a new genus and species of Australian sponge of the family Dysideidae. J. Am. Chem. Soc, 2002; 124: 13340-13341.
169. Carroll AR, Buchanan MS, Edser A, Hyde E, *et al*., Dysinosins B-D, inhibitors of factor VIIa and thrombin from the Australian sponge Lamellodysidea chlorea. J. Nat. Prod, 2004; 67: 1291-1294.
170. Tiwari A, Gupta S, Srivastava S, Srivastava R, Rawat AK. A ClpP protein model as tuberculosis target for screening marine compounds. Bioinformation, 2010; 4: 405-408.
171. Schmidt EW, Raventos-Suarez C, Bifano M, Menendez AT, *et al*., Scleritodermin A, a cytotoxic cyclic peptide from the lithistid sponge Scleritoderma nodosum. J. Nat. Prod, 2004; 67: 475-458.
172. Chen YT, Tang CL, Ma WP, Gao LX, Wei Y, *et al*., Design, synthesis and biological evaluation of novel 2-ethyl-5-phenylthiazole-4-carboxamide derivatives as protein tyrosine phosphatase 1B inhibitors with improved cellular efficacy. Eur. J. Med. Chem, 2013; 69: 399-412.
173. Kobayashi J, Sato M, Ishibashi M, Shigemori H, *et al*., Keramamide A, a novel peptide from the Okinawan marine sponge Theonella sp. J. Chem. Soc. Perkin Trans 1, 1991; 2609-2611.
174. Kimura M, Wakimoto T, Egami Y, Tan KC, Ise Y, Abe I. Calyxamides A and B, cytotoxic cyclic peptides from the marine sponge Discodermia calyx. J. Nat. Prod, 2012; 75: 290-294.
175. Smith DR, Uria AR, Helfrich EJ, Milbredt D, van Pee KH, *et al*., An unusual flavin-dependent halogenase from the metagenome of the marine sponge Theonella swinhoei WA. ACS Chem. Biol, 2017; DOI: 10.1021/acschembio.6b01115.
176. Bishara A, Rudi A, Aknin M, Neumann D, *et al*., Taumycins A and B, two bioactive lipodepsipeptides from the Madagascar sponge Fascaplysinopsis sp. Org. Lett, 2008; 10: 4307–4309.
177. De Gruyter JN, Maio WA. The taumycin A macrocycle: asymmetric total synthesis and revision of relative stereochemistry. Org. Lett, 2014; 16: 5196–5199.
178. Toda H, Tozyo T, Terui Y, Hayashi F. Discokiolides. cytotoxic cyclic depsipeptides from the marine sponge Discodermia kiiensis. Chem. Lett, 1992; 431-434.
179. Kim HS, Kim HS, Lee JYJ. Synthetic studies on discokiolide BKor. Chem. Soc, 1996; 40: 692-698.
180. Jimeno JM. A clinical armamentarium of marine-derived anti-cancer compounds. Anticancer Drugs, 2002; S1: S15-S19.
181. De Zoysa M. Medicinal benefits of marine invertebrates: sources for discovering natural drug candidates. Adv. Food Nutr. Res, 2012; 65: 153-169.
182. Lazcano-Pérez F, Román-González SA, Sánchez-Puig N, Arreguin-Espinosa R. Bioactive peptides from marine organisms: a short overview. Protein Pept. Lett, 2012; 19: 700-707.
183. Nakao Y, Yoshida WY, Takada Y, Kimura J, *et al*., Kulokekahilide-2, a cytotoxic depsipeptide from a cephalaspidean mollusk Philinopsis speciose. J. Nat. Prod, 2004; 67: 1332–1340.
184. Reese MT, Gulavita NK, Nakao Y, Hamann MT, *et al*., Kulolide: A cytotoxic depsipeptide from a cephalaspidean mollusk, Philinopsis speciose. J. Am. Chem. Soc, 1996; 118: 11081–11084.
185. Nakao Y, Szabo WY, Baker CM, Scheuer PJ. More

peptides and other diverse constituents of the marine mollusk Philinopsis speciose. J. Org. Chem, 1998; 63: 3272–3280.
186. Liu Y. Mechanism of action of seven marine-derived natural products. Thesis. University of Hawaii at Manoa, 2014; 47 pp.
187. Rodríguez J, Fernández R, Quiñoá E, Riguera R. Onchidin: a cytotoxic depsipeptide with C 2 symmetry from a marine mollusk. Tetrahedron Lett, 1994; 35: 9239-9242.
188. Fernández R, Rodríguez J, Quiñoá E, Riguera R, *et al*., Onchidin B: A new cyclodepsipeptide from the mollusc Onchidium sp. J. Am. Chem. Soc, 1996; 118: 11635–11643.
189. Tilvi S, Naik CG. Tandem mass spectrometry of kahalalides: identification of two new cyclic depsipeptides, kahalalide R and S from Elysia grandifolia. J. Mass. Spectr, 2007; 42: 70–80.
190. Faircloth G, del Carmen Cuevas Marchante M. Kahalalide F and ES285: Potent anticancer agents from marine molluscs. Molluscs, 2006; 43: 363-379.
191. Suenaga K, Mutou T, Shibata T, Itoh T, Kigoshi H, Yamada K. Isolation and stereostructure of aurilide, a novel cyclodepsipeptide from the Japanese sea hare Dolabella auricularia. Tetrahedron Lett, 1996; 37: 6771–6774.
192. Pettit GR, Kamano Y, Herald CL, Dufresne C, et al., Antineoplastic agent. 174. Isolation and structure of the cytostatic depsipeptide dolastatin 13 from the sea hare Dolabella auricularia. J. Am. Chem. Soc, 1989; 111: 5015–5017.
193. Pettit GR, Kamano Y, Herald CL, Dufresne C, *et al*., Antineoplastic agents. 190. Isolation and structure of the cyclodepsipeptide dolastatin 14. J. Org. Chem, 1990; 55: 2989–2990.
194. Sone H, Nemoto T, Ojika M, Yamada K. Isolation, structure, and synthesis of dolastatin C, a new depsipeptide from the sea hare Dolabella auricularia. Tetrahedron Lett, 1993; 34: 8445–8448.
195. Sone H, Shibata T, Fujita T, Ojika M, Yamada K. Dolastatin H and isodolastatin H, potent cytotoxic peptides from the sea hare Dolabella auricularia: isolation, stereostructures and synthesis. J. Am. Chem. Soc, 1996; 118: 1874–1880.
196. Mutou T, Kondo T, Ojika M, Yamada K. Isolation and stereostructures of dolastatin G and nordolastatin G, cytotoxic 35-membered cyclodepsipeptides from the Japanese sea hare Dolabella auricularia. J. Org. Chem, 1996; 61: 6340-6345.
197. Oda T, Crane ZD, Dicus CW, Sufi BA, Bates RB. Dolastatin 11 connects two long-pitch strands in F-actin to stabilize microfilaments. J. Mol. Biol, 2003; 328: 319-324.
198. Bai R, Verdier-Pinard P, Gangwar S, Stessman CC, *et al*., Dolastatin 11, a marine depsipeptide, arrests cells at cytokinesis and induces hyperpolymerization of purified actin. Mol. Pharmacol, 2001; 59: 462-469.
199. Pettit GR, Kamano Y, Kizu H, Dufresne C, Herald CL, *et al*., Isolation and structure of the cell growth inhibitory depsipeptides dolastatins 11 and 12. Heterocycles, 1989; 28: 553-558.
200. Pettit GR, Xu J-P, Hogan F, Schmidt JM. Antineoplastic agents 370. Isolation and structure of dolastatin 18. Bioorg. Med. Chem. Lett, 1997; 7: 827-832.
201. Ishiwata H, Nemoto T, Ojika M, Yamada K. Isolation and stereostructure of doliculide, a cytotoxic cyclodepsipeptide from the Japanese sea hare Dolabella auricularia. J. Org. Chem, 1994; 59: 4710–4711.
202. Ishiwata H, Sone H, Kigoshi H, Yamada K. Total synthesis of doliculide, a potent cytotoxic cyclodepsipeptide from the Japanese sea hare Dolabella auricularia. J. Org. Chem, 1994; 59: 4712–4713.
203. Bai R, Covell DG, Liu C, Ghosh AK, Hamel E. (-)-Doliculide, a new macrocyclic depsipeptide enhancer of actin assembly. J. Biol. Chem, 2002; 277: 32165-32171.
204. Crews P, Manes LV, Boehler M. Jasplakinolide, a cyclodepsipeptide from the marine sponge, Jaspis sp. Tetrahedron Lett, 1986; 27: 2797-2800.
205. Rinehart KL. Antitumor compounds from tunicates. Med. Res. Rev, 2000; 20: 1-27.
206. Chun HG, Davies B, Hoth D, Suffness M, Plowman J, *et al*., Didemnin B. The first marine compound entering clinical trials as an antineoplastic agent. Invest. New Drugs, 1986; 4: 279-284.
207. Weiss GR, Arteaga CL, Brown TD, Craig JB, Harman GS, *et al*., New anticancer agents. Cancer Chemother. Biol. Response Modif, 1988; 10: 85-116.
208. Dembitsky VM, Gloriozova TA, Poroikov VV, Chlorinated plant steroids and their biological activities. Int. J. Curr. Res. Biosci. Plant Biol, 2017; 4(11): 70-85.
209. Le VH, Inai M, Williams RM, Kan T. Ecteinascidins. A review of the chemistry, biology and clinical utility of potent tetrahydroisoquinoline antitumor antibiotics. Nat. Prod. Rep, 2015; 32: 328-347.
210. Zewail-Foote M, Hurley LH. Ecteinascidin 743: a minor groove alkylator that bends DNA toward the major groove. J. Med. Chem, 1999; 42: 2493-2497.
211. Takebayashi Y, Pourquier P, Zimonjic DB, Nakayama K, *et al*., Antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair. Nat. Med, 2001; 7: 961-966.
212. Lievens SC, Molinski TF. Sagittamides A and B. Polyacetoxy long-chain acyl amino acids from a Didemnid ascidian. Org. Lett, 2005; 7: 2281–2284.
213. Schuetz A, Junker J, Leonov A, Lange OF, Molinski TF, Griesinger C. Stereochemistry of sagittamide A from residual dipolar coupling enhanced NMR. J. Am. Chem. Soc, 2007; 129: 15114–15115.
214. Humbert A, Plé K, Harakat D, Martinez A, Haudrechy A. A further contribution to the study of

sagittamide A: synthesis of a pivotal intermediate belonging to a rare L-series. Molecules, 2012; 17: 7709-7721.
215. Biard JF, Roussakis C, Kornprobst JM, Gouiffes-Barbin D, Verbist JF, *et al*., Bistramides A, B, C, D, and K: A new class of bioactive cyclic polyethers from Lissoclinum bistratum. J. Nat. Prod, 1994; 57: 1336–1345.
216. Riou D, Roussakis C, Robillard N, Biard JF, Verbist JF. Bistramide A-induced irreversible arrest of cell proliferation in a non-small-cell bronchopulmonary carcinoma is similar to induction of terminal maturation. Biol. Cell, 1993; 77: 261-264.
217. Statsuk AV, Bai R, Baryza JL, Verma VA, Hamel E, Wender PA, Kozmin SA. Actin is the primary cellular receptor of bistramide A. Nat. Chem. Biol, 2005; 1: 383-388.
218. Rinehart KL, Jr, Gloer JB, Hughes RG, Jr, Renis HE, *et al*., Didemnins: antiviral and antitumor depsipeptides from a caribbean tunicate. Science, 1981; 212(4497): 933-935.
219. Crampton SL, Adams EG, Kuentzel SL, Li LH, *et al*., Biochemical and cellular effects of didemnins A and B. Cancer Res, 1984; 44: 1796-1801.
220. Lee J, Currano JN, Carroll PJ, Joullié MM. Didemnins, tamandarins and related natural products. Nat. Prod. Rep, 2012; 29: 404-424.
221. Whitson EL. Ratnayake AS, Bugni TS, Harper MK, Ireland CM. Isolation, structure elucidation and synthesis of eudistomides A and B, lipopeptides from a Fijian ascidian Eudistoma sp. J. Org. Chem, 2009; 74: 1156-1162.