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The Pharmacological Potential of Non-ribosomal Peptides from Marine Sponge and Tunicates

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Abstract

Marine biodiversity is recognized by a wide and unique array of fascinating structures. The complex associations of marine microorganisms, especially with sponges, bryozoans, and tunicates, make it extremely difficult to define the biosynthetic source of marine natural products or to deduce their ecological significance. Marine sponges and tunicates are important source of novel compounds for drug discovery and development. Majority of these compounds are nitrogen containing and belong to non-ribosomal peptide (NRPs) or mixed polyketide–NRP natural products. Several of these peptides are currently under trial for developing new drugs against various disease areas, including inflammatory, cancer, neurodegenerative disorders and infectious disease. This review features pharmacologically active NRPs from marine sponge and tunicates based on their biological activities.

Keywords: Marine ecosystem, sponge, tunicates, marine natural products, non-ribosomal peptides, pharmacology

Introduction

Nature provides a wide and structurally diverse array of active biomolecules that have proved vital for the development of novel pharmaceuticals. The marine world, covering more than 70 per cent of the Earth's surface, is the home of tremendous biodiversity. Due to very exigent oceanic environments, marine organisms have developed the capacity to produce unique compounds (Steele, 1985, Mehbub et al., 2014). This rich and unprecedented chemo diversity of marine natural products provides an unlimited resource of novel biomolecules in the field of drug development. The importance of marine metabolites in current drug research is driven by the fact, that during 1981–2002, around half of US FDA-approved drugs consisted of either marine metabolites or their synthetic analogues (Vinothkumar and Parameswaran, 2013). Interestingly, the majority of these natural products involved in clinical or preclinical trials are produced by invertebrates, that is, sponges, tunicates, bryozoans, or molluscs. Sixty per cent of these natural products belong to non-ribosomal peptide (NRP) families, which are biosynthesized by poly-functional mega-synthases called NRP synthetases (NRPSs) (Finking and Marahiel, 2004, Mehbub et al., 2014). The excellent binging properties, low off-target toxicity, and high stability of NRPs make them a promising molecule for development of new therapeutics. Currently, only a handful of NRPs are used as drug (Table 1).

Table 1 NRPs-based drugs in market

Compound	Biosynthetic class of agent	Source	Disease/molecular target	Reference
Polymyxin B	Polypeptides	*Bacillus polymyxa*	Antibiotic/Alters bacterial outer membrane	(Paulus and Gray, 1964)
Pristinamycin	Depsipeptide	*Streptomyces. pristinaespiralis*	Antibiotic/protein synthesis inhibitor	(de Crécy-Lagard et al., 1997)
Gramicidin	Linear pentadecapeptide	*Bacillus bovis*	Antibiotic/Alters bacterial outer membrane	(Kleinkauf and von Döhren, 1995)
Bacitracin	Cyclic peptide	*Bacillus subtilis*	Antibiotic/dephosphorylation of C55-isoprenyl pyrophosphate	(Johnson et al., 1945)
Capreomycin	Cyclic peptide	*Streptomyces capreolus*	Antibiotic/protein synthesis inhibitor	(Stark et al., 1962)
Teicoplanin	Glycopeptide	*Actinoplanes teichomyceticus*	Antibiotic/inhibit cell wall synthesis	(Somma et al., 1984)

Vancomycin	Glycopeptide	*Amycolatopsis orientalis*	Antibiotic/inhibit cell wall synthesis	(van Wageningen et al., 1998)
Cephalosporin C	β-lactam	*Acremonium* sp.	Antibiotic/Alters bacterial outer membrane	(Abraham and Newton, 1961)
Oritavancin	---	Semi synthetic	Antibiotic/disrupts the cell membrane	(Domenech et al., 2009)
Bleomycin	Hybrid peptide	*Streptomyces verticillus*	Antibiotic/inhibition of DNA synthesis	(Umezawa et al., 1966)
Daptomycin	Lipopeptide	*Streptomyces roseosporus*	Antibiotic/disrupts the cell membrane	(Miao et al., 2005)
Cyclosporine A	Cyclic peptide	*Tolypocladium inflatum*	Immunosuppressant /lower the activity of T cells	(Murthy et al., 1999)
Actinomycin D	Polypeptide	*Streptomyces* sp.	Antitumor/inhibit transcription	(Waksman and Woodruff, 1940)
Romidepsin	Depsipeptide	*Chromobacterium violaceum*	Antitumor/Histone deacetylase inhibitor	(Ueda et al., 1994)

Marine sponges (*Phylum porifera*) represent the most primitive multicellular animals, with origins dating back to the Precambrian (Hentschel et al., 2002). There are mainly 3 classes of sponges: *Calcarea* (5 orders and 24 families), *Demospongiae* (15 orders and 92 families), and *Hexactinellida* (6 orders and 20 families). There are about 9 000 described species of sponges and perhaps twice as many undescribed species are (Brusca et al., 1990) available in the ocean (Wörheide et al., 2005). Till date, more than 5 300 different natural products have been isolated from marine sponges, and each year more than 200 additional new metabolites are being discovered (Laport et al., 2009, Mehbub et al., 2014). Today, there are several sponge derived metabolites currently available in market and many in clinical studies (Table 2).

It is proposed that some of the bioactive compounds isolated from sponges are produced by functional enzyme clusters originated from the sponges and their associated microorganisms (Laport et al., 2009, Thomas et al., 2010). It has been observed that bacterial phyla such as *Proteobacteria*, *Nitrospira*, *Cyanobacteria*, *Bacteriodetes*, *Actinobacteria*, *Chloroflexi*, *Planctomycetes*, *Acidobacteria*, *Poribacteria*, and *Verrucomicrobia* besides members of the domain *Archaea* are most sponge-associated bacterial community (Hentschel et al., 2002, Olson and McCarthy, 2005). However, fungi and microalgae also symbiotically inhabit sponges. It has

been recognized that one host sponge can possess diverse symbionts. For example, unicellular heterotrophic bacteria, unicellular cyanobacteria, and filamentous heterotrophic bacteria all grow together in sponge *Theonella swinhoei* (Bewley et al., 1996). Likewise, a sponge belonging to *Aplysina* includes heterogeneous bacteria *Bacillus* sp., *Micrococcus* sp., *Arthrobacter* sp., *Vibrio* sp., *Pseudoalteromonas* sp., and so on (Hentschel et al., 2001). Sponge *Rhopaloeides odorabile has β-Proteobacteria, γ-Proteobacteria, Cytophaga, Actinobacteria*, *and* green sulphur bacteria (Webster et al., 2001). Beside this, species-specific symbiotic relationship has also been observed. For example, sponge *T. swinhoei* and δ-*proteobacteria* have shown a specific association (Schmidt et al., 2000). A species of α-*proteobacteria* dominates in sponge *R. odorabile* over various habitats but is not detected from seawater, which strongly suggests that the symbiont is species specific (Lee et al., 2001b). On the other hand, one symbiont occurs commonly in various sponges from different regions, so seems to possess a wide host range (Wilkinson et al., 1981). For example, cyanobacteria *Aphanocapsa* sp., *Phormidium* sp., or *Oscillatoria spongeliae* are found in numerous sponges (Wilkinson, 1978). Symbiotic associations between sponges and marine microorganisms might be involved in nutrient acquisition, stabilization of sponge skeleton, processing of metabolic waste, and secondary metabolite synthesis. It is assumed that symbiotic marine microorganisms harboured by sponges are the original producers of some of these bioactive compounds (Newman and Hill, 2006). For example, antibiotics polybrominated biphenyl ether isolated from the sponge *Dysidea herbacea* (Demospongiae) are actually produced by endosymbiotic cyanobacterium *O. spongeliae* (Unson et al., 1994). A symbiotic bacterium *Micrococcus* sp. produces diketopiperazines previously ascribed to the host sponge *Tedania ignis* (Stierle et al., 1988). Another symbiotic bacterium *Vibrio* sp. produces brominated biphenyl ethers formerly attributed to the host sponge *Dysidea* sp. (Elyakov et al., 1991). Symbiotic bacterium *Vibrio* sp. produces an anti-Bacillus peptide andrimid that was found in the sponge *Hyatella* sp. extract (Oclarit et al., 1994). Antimicrobial activity is detected in *Micrococcus luteus* isolated from the sponge *Xestospongia* sp. (Bultel-Poncé et al., 1998). Antimicrobial compounds such as quinolones and phosphatidyl glyceride are isolated from a *Pseudomonas* sp. collected at the surface of the sponge *Homophymia* sp. (Bultel-Poncé et al., 1999). However, the mutual mechanism between sponge and microbial associate, in compound production, is not well understood. Thus, it is extremely relevant to highlight the therapeutic potential of various secondary metabolites synthesized by the microbial flora inhabiting sponges. This is because they

96 open up the possibility of providing a continuous supply of the biologically active compounds by
97 laboratory cultivation of the producer (Thomas et al., 2010).
98
99 **Table 2** Sponge secondary metabolites that are FDA-approved agents in clinical trial (Mayer et al.,
100 2010, Newman and Cragg, 2016)

Compound	Biosynthetic class of agent	Source	Disease/molecular target	Clinical status
Cytarabine (Ara-C)	Nucleoside	*Cryptotethya crypta*	Cancer/DNA polymerase	FDA approved
Vidarabine (Ara-A)	Nucleoside	*C. crypta*	Antiviral viral/DNA polymerase I	FDA approved
Eribulin Mesylate (E7389)	Complex Polyketide	*Lissodendoryx sp.*	Cancer/microtubules	FDA approved
Hemiasterlin derivative (E7974)	Modified linear Tripeptide (NRPS-PKS)	*Cymbastella sp.*	Cancer/microtubules	Phase I
Discodermolide	Polyketide	*Discodermia dissolute*	Cancer/microtubules	Phase I
Bengamide derivative (LAF389)	Mixed PKS/NRP	*Jaspis sp.*	Cancer/methionine aminopeptidases	Phase I
Spongistatin 1	Macrocyclic lactone polyether	*Hyrtios erecta*	Cancer/microtubules	Preclinical
Manoalide	Sesterterpene	*Luffariella variabilis*	Inflammation/inhibition of Phospholipase A2	Preclinical
Salicylhalimides A	Polyketide	*Haliclona sp.*	Cancer/microtubules	Preclinical
Laulimalide	Polyketide	*Cacospongia mycofijiensis*	Cancer/microtubules	Preclinical
Peloruside A	Polyketide	*Mycale hentscheli*	Cancer/microtubules	Preclinical

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102 Tunicates include a wide variety of invertebrates that are classified within the *Phylum chordata*
103 based on presence of a larval notochord during early development. Tunicates contains about 2 150
104 described species that are divided into 4 classes: *Ascidiacea* (*Aplousoobranchia*, *Phlebobranchia*,

105 *Stolidobranchia*) *Thaliacea* (*Pyrosomida*, *Doliolida*, *Salpida*), *Appendicularia* (*Larvacea*), and
106 *Sorberacea* (Ruppert and Fox, 2004). Amongst these, *Ascidacea* (commonly known as the
107 ascidians) are highly studied given that their biologically active metabolites serve as antineoplastic
108 agents. Geranyl hydroquinone was first ascidian metabolite isolated from *Aplidium* sp. which
109 displayed chemo protective activity against some forms of leukemia, rous sarcoma, and mammary
110 carcinoma in test animals (Fenical, 1976) (Menna, 2009). Since then, ascidians are known as the
111 source of numerous marine natural products. The biologically active metabolites originated from
112 tunicates which are approved by FDA or in clinical trials along with their biological properties are
113 given in Table 3.
114 Tunicate secondary metabolites that are FDA-approved agents or in clinical trial (Mayer et al.,
115 2010, Newman and Cragg, 2016,)

Compound	**Biosynthetic class of agent**	**Source**	**Disease/molecular target area**	**Clinical status**
Trabectedin (ET-743) (EU registered only)	NRPS-derived alkaloid	*Ecteinascidia turbinata*	Cancer/minor groove of DNA	FDA approved
Plitidepsin (Aplidine)	Cyclic depsipeptide	*Aplidium albicans*	Cancer/Rac1 and JNK activation	Phase III
Trabectedin analog (PM01183)	NRPS alkaloid	*E. turbinata*	Cancer/minor groove of DNA, nucleotide excision repair	Phase I
Vitilevuamide	NRPS	*Didemnum cuculiferum* and *Polysyncranton lithostrotum*	Cancer/microtubules	Preclinical

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117 To date, significant biological activities, such as antimicrobial, anticancer, neurotoxic, and
118 antiprotozoal properties and their associated cellular targets have been reported for several NRPs
119 from the marine sponges and tunicates. These NRPs have unique structures as compared to those
120 from other sources. It is this attribute that makes marine sponge- and tunicate-derived NRPs
121 highly attractive as potential drug and molecular probes. In this review, the authors survey the
122 discoveries of NRPs derived from marine sponges and tunicates, which have shown *in vivo*
123 efficacy or potent *in vitro* activity against various human diseases. Our objective is to highlight
124 NRPs that have the greatest potential to be clinically useful. These are presented based on their

biological activities (Table 4). The details of sponge- and tunicate-derived NRPs along with biological properties is given Table 4.

Table 4 Biological activities of NRPs isolated from marine sponges and tunicates

NRPs	Chemical class	Origin	Disease/Target	Biological active value (IC_{50}/GI_{50}/ID_{50}/ED_{50})	Reference(s)
Miraziridine A (1)	Linear penta peptide	*Theonella* aff. *mirabilis*	Cancer/inhibit protease cathepsin B	1.4 µg/mL	(Nakao et al., 2000)
Haligramides A-B (2-3)	Cyclic hexapeptides	*Haliclona nigra*	Cancer / A-549 (lung) HCT-15(colon) SF-539 (CNS) SNB-19 (CNS)	5.17–15.6 µg/mL 3.89–8.82 µg/mL	(Rashid et al., 2000)
Prepatellamide A (4)	Cyclic peptide	*Lissoclinum patella*	Cancer/P388 murine leukemia cell lines	5 µg/mL	(Fu et al., 2000)
Tamandarins A-B (5-6)	Depsipeptides	*Didemnid ascidian*	Cancer/pancreatic carcinoma BX-PC3, prostatic cancer DU-145, head and neck carcinoma UMSCC10b	1.79, 2.00 µg/mL 1.36, 1.53 µg/mL 0.99, 1.76 µg/mL	(Vervoort et al., 2000)
Microsclerodermins F–I (7-10)	Cyclic peptides	*Microscleroderma* sp.	Cancer/HCT-116 cell line	1.8, 2.4, 1.0, and 1.1 µg/mL	(Qureshi et al., 2000)
Wainunuamide (11)	Cyclic hexapeptide	*Stylotella aurantium*	Cancer/A2780 ovarian, K562 leukaemia cancer cells	19.15 and 18.36 µg/mL	(Tabudravu et al., 2001)
Leucamide A (12)	Cyclic hexapeptide	*Leucetta microraphis*	Cancer / Tumor cell lines HM02, HepG2, Huh7	5.2 µg/mL 5.9 µg/mL 5.1µg/mL	(Kehraus et al., 2002)
Axinellin C (13)	Cyclic octapeptide	*S. aurantium*	Cancer / A2780 ovarian, K562 leukaemia cancer cells	13.17 and 4.46 mg/mL	(Tabudravu et al., 2002
Milnamide D (14)	Linear peptide	*Cymbastela* sp.	Cancer / HCT-116 cells	66nM	(Chevallier et al., 2003)
Kapakahines E–G (15-17)	----	*Cribrochalina olemda*	Cancer / P388 murine leukemia cells	5.0 µg/mL	(Nakao et al., 2003)
Didmolamides A- B (18-19)	Cyclic hexapeptides	*Didemnum molle*	Cancer Tumor cell lines (A549, HT29, and MEL28)	10-20 µg/mL	(Rudi et al., 2003)
Bistratamides E–J (20- 25)	Cyclic hexapeptides	*Lissoclinum bistratum*	Cancer / Human colon tumor (HCT-116) cell line	3, 7.9; 4, 28; 5, 5; 6, 1.7 7, 9; 8, 1 µg/mL	(Perez and Faulkner, 2003)
Milnamide C (26)	----	*Auletta* sp.	Cancer / MDA-MB-435 cancer cells	3.2 × 10-1 µg/mL	(Sonnenschein et al., 2004)

Scleritodermin A (27)	Cyclic peptide	*Scleritoderma nodosum*	Cancer	< 2 µM	(Schmidt et al., 2004)
Microcionamides A-B (28-29)	----	*Clathria abietina*	Cancer / Human breast tumor cell lines MCF-7 and SKBR-3	125 and 98 nM 177 and 172 nM	(Davis et al., 2004)
Kendarimide A (30)	Linear peptide	*Haliclona* sp.	Cancer / KB-C2 cells	---	(Aoki et al., 2004)
Phakellistatin 14 (31)	Cycloheptapeptide	*Phakellia* sp.	Cancer / Murine lymphocytic leukemia P388 cell line	5 µg/mL	(Pettit and Tan, 2005)
Polytheonamides A-B (32-33)	Polypeptides	*T. swinhoei*	Cancer / P388 murine leukemia cells	78, 68 pg/mL	(Hamada et al., 2005)
Neopetrosiamides A- B (34-35)	Tricyclic peptides	*Neopetrosia* sp.	Cancer	6 µg/mL	(Williams et al., 2005)
Seragamides A–F (36-37)	Depsipeptides	*Suberites japonicus*	Cancer	0.01, 0.02, 0.01, 0.01, and 0.04 mg/mL	(Tanaka et al., 2006)
Theopapuamide (38)	Cyclic depsipeptide	*T. swinhoei*	Cancer / CEM-TART HCT-116 cell lines	0.5 µM 0.9 µM	(Ratnayake et al., 2006)
Azumamide A- E (39- 47)	Cyclotetrapeptides	*Mycale izuensis*	Cancer	---	(Maulucci et al., 2007)
Callyaerin G (48)	Cyclic peptide	*Callyspongia aerizusa*	Cancer / Mouse lymphoma cell line (L5178Y) and HeLa cells	0.53 and 5.4 ug/mL	(Ibrahim et al., 2008)
Stylopeptide 2 (49)	Cyclodecapeptide	*Stylotella* sp.	Cancer / BT-549 and HS 578T breast cancer cell lines	----	(Brennan et al., 2008)
Ciliatamides A-C (50-52)	Lipopeptides	*Aaptos ciliata*	Cancer / HeLa cells	50, 4.5, and 50 µg/mL	(Nakao et al., 2008)
Diazonamides C–E (53-55)	Macrocyclic peptides	*Diazona* sp.	Cancer / Human tumor cell lines (A549, HT29, MDA-MB 231)	2.2, 2.9, 8.0µg/mL 1.8, 2.9, 5.2 µg/mL 2.2, 3.1, 9.0 µg/mL	(Fernández et al., 2008)
Rolloamide A- B (56-57)	Cyclic heptapeptides	*Eurypon laughlini*	Cancer	0.4–5.8 µM	(Williams et al., 2009)
Euryjanicin A (58)	Cycloheptapeptide	*Prosuberites laughlini*	Cancer	---	(Vicente et al., 2009)
Callyaerin A–F (59-64) and H (65)	Cyclic peptides	*C. aerizusa*	Cancer / L5178Y cell line	0.39 and 0.48 µM	(Ibrahim et al., 2010)
Papuamides E-F	Depsipeptides	*Melophlus* sp.	Cancer / Brine shrimp	92 and 106 µg/mL	(Prasad et al., 2011)

(66-67)					
Stylissamide X (68)	Octapeptide	*Stylissa* sp.	Cancer / HeLa cells	0.1 µM to 10 µM	(Arai et al., 2012)
Gombamide A (69)	Hexapeptide	*Clathria gombawuiensis*	Cancer / K562 and A549 cell lines	6.9 and 7.1 µM	(Woo et al., 2013)
Microspinosamide (70)	Cyclic depsipeptide	*Sidonops microspinosa*	HIV	0.2 µg/mL	(Rashid et al., 2001)
Neamphamide A (71)	Cyclic depsipeptide	*Neamphius huxleyi*	HIV	8 nM	(Oku et al., 2004)
Mirabamides A-D (72-75)	Cyclic depsipeptide	*Siliquariaspongia mirabilis*	HIV	40 and 140 nM, 140 nM and 1.3 µM 190 nM and 3.9 µM	(Plaza et al., 2007)
Homophymine A (76)	Cyclodepsipeptide	*Homophymia* sp.	HIV / PBMC cell line	75 nM	(Zampella et al., 2008b
Celebeside A-C (77-79)	Depsipeptides	*S.mirabilis*	HIV / Colon carcinoma (HCT-116) cells	2.1 and 4.0 µg/mL 1.9 ± 0.4 µg/mL	(Plaza et al., 2008)
Theopapuamides B–D (80-82					
Mutremdamide A (83) Koshikamides C-H (84-89)	Cyclic depsipeptide	*Theonella* sp.	HIV	2.3 and 5.5 µM	(Plaza et al., 2010)
Ceratospongamide (90)	Cyclic heptapeptide	*Sigmadocia symbiotica*	Inflammation	32 nM	(Tan et al., 2000)
Halipeptin A-B (91-92)	Cyclic depsipeptide	*Haliclona* sp.	Inflammation	300 µg/kg (i.p.)	(Randazzo et al., 2001
Perthamide C-D (93-94)	Cyclopeptide	*T. swinhoei*	Inflammation	---	(Festa et al., 2009)
Solomonamide A-B (95-96)	Cyclic peptide	*T. swinhoei*	Inflammation	---	(Festa et al., 2011)
Stylissatin A (97)	Cyclic peptide	*Stylissa massa*	Murine macrophage RAW264.7	87 µM	(Kita et al., 2013)
Dicynthaurin (98)	----	*Halocynthia aurantium*	Antimicrobial	---	(Lee et al., 2001a)
Nagahamide A (99)	Depsipeptide	*T. swinhoei*	Antibacterial	---	(Okada et al., 2002)

Plicatamide (100)	Octapeptide	*Styela plicata*	Antimicrobial	---	(Tincu et al., 2003)
Callipeltins F-I (101-104)	----	*Latrunculia* sp.	Antifungal / *Candida albicans*	10−4 M	(Sepe et al., 2006)
Callipeltins J-M (105-108)	----	*Latrunculia* sp.	Antifungal / *Candida albicans*	4−10 M	(D'Auria et al., 2007)
Citronamides A- B (109-110)	----	*Citronia astra*	Antifungal / *Saccharomyces cerevisiae*	8 µg/mL	(Carroll et al., 2009)
Renieramide (111)	Cyclic tripeptide	*Reniera* sp.	----	---	(Ciasullo et al., 2002)
Phoriospongins A-B (112-113)	Depsipeptide	*Phoriospongia* sp. and *Callyspongia bilamellata*	Nematocidal / *Haemonchus contortus*	100, 194 µg/mL	(Capon et al., 2002)

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Anticancer NRPs from Marine Sponges and Tunicates (Figures 1–6)

Sponge *Theonella* aff. *mirabilis* was the source of linear penta peptide Miraziridine A **(1)**, which showed inhibitory activity on cathepsin B with an IC_{50} value of 1.4 µg/mL (Nakao et al., 2000). Two cyclic hexapeptides, Haligramides A **(2)** and B **(3)**, were isolated from an aqueous extract of the sponge *H. nigra*. Both compounds exhibited cytotoxicity against various cell lines. Haligramide A exhibited cytotoxicity against A-549, HCT-15, SF-539, SNB-19 cell line with IC_{50} values of 5.17, 15.62, 9.00 and 9.08 µg/mL respectively. Haligramide B, was found to be more active than Haligramide A against A-549, HCT-15, SF-539, SNB-19 cell line with IC_{50} values of 3.89, 8.82, 5.01 and 6.56 µg/mL respectively (Rashid et al., 2000).

A cyclic peptide, Prepatellamide A **(4)** was isolated from the cytotoxic extracts of *L. patella*. The crude extract of this ascidian showed cytotoxicity against P388 murine leukemia cell lines with IC_{50} = ~5 µg/mL (Fu et al., 2000). Naturally occurring depsipeptides, Tamandarins A and B **(5 and 6)** were discovered from a Brazilian ascidian of the family *Didemnidae* and were cytotoxic against various human cancer cell lines including pancreatic carcinoma BX-PC3, IC_{50} = 1.79, 2.00 µg/mL, prostatic cancer DU-145, IC_{50} = 1.36, 1.53 µg /mL, head and neck carcinoma UMSCC10b, IC_{50} = 0.99, 1.7 6µg/mL, respectively (Vervoort et al., 2000). *Microscleroderma* sp. from Palau gave 4 new cyclic peptides, Microsclerodermins F–I **(7–10)**, all of which inhibited the growth of *C. albicans* with MIC value of 1.5 µg, 3 µg, 12 µg, and 25 µg per disk, respectively, and also showed cytotoxicity against the HCT-116 cell line with IC_{50} value of 1.8 µg/mL, 2.4 µg/mL, 1.0 µg/mL, and 1.1 µg/mL, respectively (Qureshi et al., 2000).

A histidine-containing proline-rich cyclic heptapeptide, Wainunuamide **(11)**, was isolated from the Fijian marine sponge *S. aurantium*. Compound **(11)** exhibited weak cytotoxic activity against A2780 ovarian tumour and K562 leukaemia cancer cells with ID_{50} of 19.15 and 18.36 µg/mL, respectively (Tabudravu et al., 2001). The Australian marine sponge *L. microraphis* was the source of a bioactive cyclic heptapeptide, Leucamide A **(12)**. Compound **(12)** inhibited the growth of the 3 tumour cell lines HM02 (gastric, GI_{50} =5.2 µg/mL), HepG2 (liver, GI_{50} =5.9 µg/mL), and Huh7 (liver, GI_{50} = 5.1 µg/mL) (Kehraus et al., 2002). The Fijian collection of marine sponge *S. aurantium* gave a proline-rich cyclic octapeptide, Axinellin C **(13)** (cyclo [Thr1-Val2-Pro3-Trp4-Pro5-Phe6-Pro7-Leu8]). Axinellin C displayed weak cytotoxicity against A2780 ovarian tumour

and K562 leukaemia cancer cells with ID_{50s} of 13.17 and 4.46 mg/mL, respectively (Tabudravu et al., 2002). The crude extract of a marine sponge *Cymbastela* sp. (Papua New Guinea) gave a cytotoxic peptide Milnamide D **(14)**. Milnamide D was found to exhibit cytotoxicity against HCT-116 at IC_{50} value of 66 nM and inhibition of tubulin polymerization at IC_{50} of 16 µM (Chevallier et al., 2003).

Investigation of marine sponge *C. olemda* yielded 3 new Kapakahines E–G **(15–17)**. Only kapakahines E was found to display moderate cytotoxic against P388 murine leukemia cells at IC_{50} of 5.0 µg/mL (Nakao et al., 2003). Two novel cyclic hexapeptides, Didmolamides A-B **(18 and 19)** were isolated from ascidian *D. molle* (Madagascar). Both peptides showed mild cytotoxicity against tumour cell lines (Lung—A549, Colon—HT29, and Skin—MEL28) with IC_{50} values of 10–20 µg/mL (Rudi et al., 2003). The Philippines ascidian *L. bistratum* was the source of 6 cyclic hexapeptides, Bistratamides E-J **(20–25)**. Bistratamides E-J showed weak to moderate activity against the human colon tumour (HCT-116) cell line (IC_{50}'s: 3, 7.9; 4, 28; 5, 5; 6, 1.7; 7, 9; 8, 1 µg/mL, respectively) (Perez and Faulkner, 2003). Milnamide C **(26)** was isolated from *Auletta* sp., which showed significantly activity against MDA-MB-435 breast cancer cells with IC_{50} values of 3.2×10^{-1} µg/mL (Sonnenschein et al., 2004).

Scleritodermin A **(27)** A new cyclic peptide was isolated from the Lithistid Sponge *S. nodosum*. Scleritodermin A, inhibited tubulin polymerization and demonstrated significant *in vitro* cytotoxicity against a panel of human tumor cell lines ($IC50 < 2$ µM), including colon carcinoma HCT116, ovarian carcinoma A2780, and breast carcinoma SKBR3 (Schmidt et al., 2004).

Microcionamides A **(28)** and B **(29)** were isolated from the Philippine marine sponge *Clathria* (Thalysias) *abietina*. Both compounds displayed significant cytotoxicity towards human breast tumour cell lines MCF-7 and SKBR-3 with IC_{50} of 125 and 98 nM for compound **(28)** and 177 and 172 nM for compound **(29)**, respectively (Davis et al., 2004). Methanol extract of an Indonesian marine sponge of *Haliclona* sp. gave a linear peptide Kendarimide A **(30)**. This peptide reversed P-glycoprotein-mediated multi-drug resistance in mammalian cells (Aoki et al., 2004).

Cycloheptapeptide, Phakellistatin 14 **(31)**, was isolated from *Phakellia* sp., (Chuuk, Federated States of Micronesia). Compound 31 exhibited cytotoxic activity against the murine lymphocytic leukemia P388 cell line at ED_{50} of 5 µg/mL (Pettit and Tan, 2005). The marine sponge *T. swinhoei* was found to produce highly cytotoxic polypeptides Polytheonamides A and B **(32–33)**

with 48 amino acid residues. Both compounds were found to be cytotoxic against P388 murine leukemia cells with IC_{50} values of 78, 68 pg/mL, respectively (Hamada et al., 2005). Two diastereomeric tricyclic peptides Neopetrosiamdes A **(34)** and B **(35)** have been isolated from the marine sponge *Neopetrosia* sp. collected in Papua New Guinea. These peptides inhibited amoeboid invasion of human tumour cells at 6 µg/mL (Williams et al., 2005). Six new depsipeptides, Seragamides A–F **(36–41)** were isolated from sponge *S. japonicas* (Okinawan). Except seragamide F, all seragamides have showed multinuclei formation in NBT-T2 cells at 0.01, 0.02, 0.01, 0.01, and 0.04 mg/mL, respectively. Compound **(36)** also promotes the polymerization of G-actin and stabilizes F-actin filaments (Tanaka et al., 2006). *Theonella swinhoei* from Papua New Guinea gave a cyclic depsipeptide, Theopapuamide **(42)**. This peptide contains several unusual amino acid residues such as β-methoxyasparagine, 4-amino-5-methyl-2, 3, 5-trihydroxy-hexanoic acid, and also contains an amide linked fatty acid moiety, 3-hydroxy-2, 4, 6-trimethyl-octanoic acid (Htoa) with cytotoxicity against CEM-TART (EC_{50} = 0.5 µM) and HCT-116 (EC_{50}= 0.9 µM) cell lines (Ratnayake et al., 2006).

Azumamide A-E **(43–47)** carboxylic acid containing histone deacetylase (HDAC) inhibitor cyclotetrapeptides were recovered from the sponge *M. izuensis.* Compound (47) only displayed human histone deacetylase inhibitory activity (Maulucci et al., 2007). An Indonesian sponge *C. aerizusa* gave a new cyclic peptide named Callyaerin G **(48)** with cytotoxic activity against mouse lymphoma cell line (L5178Y) and HeLa cells with ED_{50}(s) of 0.53 and 5.4 ug/mL, respectively (Ibrahim et al., 2008). The Papua New Guinea marine sponge *Stylotella* sp. was found to produce a new proline-rich cyclodecapeptide, Stylopeptide 2 **(49)**. Compound **(49)** inhibited growth of BT-549 and HS 578T 2 breast cancer cell lines by 77 per cent and 56 per cent, respectively (Brennan et al., 2008). Bioactive lipopeptides Ciliatamides A-C **(50–52)** were isolated from the deep-sea sponge *A. ciliate*. Ciliatamides A-B have showed anti-leishmanial activity at 10 µg/mL with 50 per cent and 45.5 per cent growth inhibition, respectively. Ciliatamides A-C also inhibited growth of HeLa cells with IC_{50} values of 50, 4.5, and 50 µg/mL, respectively (Nakao et al., 2008).

The marine ascidian *Diazona* sp. (Indonesia) gave 3 new macrocyclic peptides, Diazonamides C–E **(53–55)**. All the isolated peptides displayed moderate cytotoxicity against a panel of 3 human tumour cell lines (IC_{50}'s: A549 = 2.2, 2.9, 8.0 µg/mL; HT29 = 1.8, 2.9, 5.2 µg/mL; MDA-MB-231 = 2.2, 3.1, 9.0 µg/mL) (Fernández et al., 2008). Dominican marine sponge *E. laughlini* gave 2 cyclic heptapeptides, Rolloamides A **(56)** and B **(57)**. Rolloamide A displayed significant growth

suppression against several cancer cells (prostate, breast, ovarian, glioma, and renal) with IC_{50}'s of 0.4–5.8 µM (Williams et al., 2009). Proline-containing cycloheptapeptide, Euryjanicin A **(58)** was extracted from the marine sponge *P. laughlini* (Vicente et al., 2009). Bioassay guided extraction of the sponge *C. aerizusa* (Ambon, Indonesia) revealed 7 new cytotoxic cyclic peptides Callyaerins A–F **(59–64)** and H **(65)**. All peptides have showed cytotoxicity activity, however, callyaerins E and H exhibited strong activity against the L5178Y lymphoma cell line with ED_{50} values of 0.39 and 0.48 µM, respectively (Ibrahim et al., 2010).

An undescribed sponge of the genus *Melophlus* sp. (Karumolum, Russell Is., Solomon Is.) yielded 2 depsipeptides, Papuamides E **(66)** and F **(67),** which were cytotoxic against brine shrimp with LD_{50} values between 92 and 106 µg/mL (Prasad et al., 2011). A proline-rich octapeptide Stylissamide X **(68)** isolated from an Indonesian marine sponge of *Stylissa* sp. inhibited HeLa cells in the concentration ranging from 0.1 µM to 10 µM through wound-healing assay (Arai et al., 2012). The marine sponge *C. gombawuiensis* collected from Korean waters gave a disulphide-linked hexapeptide, Gombamide A **(69)**. Gombamide A showed weak cytotoxic activity against the K562 and A549 cell lines with LC_{50} values of 6.9 and 7.1 µM, respectively, as well as moderate inhibitory activity against Na+/K+-ATPase with an LC_{50} value of 17.8 µM (Woo et al., 2013).

Anti-HIV Agents (Figures 7 and 8)

The marine sponge *S. microspinosa* was the source of a cyclic depsipeptide Microspinosamide **(70) ,** inhibited HIV-1 infection with an EC_{50} value of approximately 0.2 µg/mL (Rashid et al., 2001). A Papua New Guinea collection of the marine sponge *N. huxleyi* has been shown to produce a new HIV-inhibitory cyclic depsipeptide, Neamphamide A **(71)**. Neamphamide A displayed potent cytoprotective activity against HIV-1 infection with EC_{50} value of approximately 28 nM (Oku et al., 2004). Four cyclic depsipeptides, Mirabamides A–D **(72–75)**, were isolated from the marine sponge *S. mirabilis*. Mirabamides A, C and D inhibited HIV-1 fusion (Mirabamides A IC_{50} values between 40 and 140 nM: Mirabamides C IC_{50} values between 140 nM and 1.3 µM : and Mirabamides D IC_{50} values between 190 nM and 3.9 µM). Mirabamides A–C also inhibited the growth of *B. subtilis* and *C. albicans* at 1–5 µg/disk (Plaza et al., 2007).

The marine sponge *Homophymia* sp was the source of an anti-HIV cyclodepsipeptide, Homophymine A **(76)**. This peptide inhibited the infection of HIV-1 in PBMC cell line with an IC_{50} of 75 nM (Zampella et al., 2008b). Six depsipeptides Celebesides A-C **(77–79)** and

Theopapuamides B-D **(80–82)** were isolated from an Indonesian sponge *S. mirabilis*. Compound (77) neutralized HIV-1 with an IC_{50} value of 1.9 ± 0.4 µg/mL, while the non-phosphorylated analogue Celebeside C was inactive at concentrations as high as 50 µg/mL. Theopapuamides A-C displayed cytotoxicity against human colon carcinoma (HCT-116) cells with IC_{50} values between 2.1 and 4.0 µg/mL, and antifungal activity against wild type and amphotericin B-resistant strains of *C. albicans* at 1–5 µg/disk (Plaza et al., 2008). The deep-water specimens of *T. swinhoei* and *Theonella cupola* (Mutremdiu Reef, Palau) gave sulphated cyclic depsipeptide, Mutremdamide A **(83)** and 6 N-methylated peptides Koshikamides C–H **(84–89)**. Cyclic koshikamides F and H inhibited HIV-1 entry at IC_{50} values of 2.3 and 5.5 µM, respectively, while their linear counterparts were inactive (Plaza et al., 2010).

Anti-Inflammatory NRPs (Figure 9)

Marine sponge *S. symbiotica* collected from Biaro Island, Indonesia, along with its symbiont marine red alga (Rhodophyta) *Ceratodictyon spongiosum* gave thiazole-containing cyclic heptapeptide, Ceratospongamide **(90)**. Compound **(90)** consist of two l-phenylalanine residues, one (l-isoleucine)-l-methyloxazoline residue, one l-proline residue, and one (l-proline) thiazole residue. The trans-isomer of ceratospongamide exhibits potent inhibition of sPLA2 expression in a cell-based model for anti-inflammation at ED_{50} 32 nM (Tan et al., 2000). Two cyclic depsipeptides, Halipeptins A and B **(91 and 92)** were obtained from marine sponge *Haliclona* sp. Only halipeptins A displayed *in vivo* potent anti-inflammatory activity (mice at the dose of 300 µg/kg [i.p.]) (Randazzo et al., 2001). A Solomon Lithistid sponge *T. swinhoei* was the source of two new cyclopeptides Perthamides C and D with potent anti-inflammatory **(93 and 94)** (Festa et al., 2009). Cyclic peptides, Solomonamides A and B **(95 and 96)**, were separate out from the marine sponge *T. swinhoei*; however, only compound **(86)** showed anti-inflammatory activity (Festa et al., 2011). The marine sponge *S. massa* produced a cyclic peptide Stylissatin A **(97)** that inhibited nitric oxide production in LPS-stimulated murine macrophage RAW264.7 cells with an IC_{50} value of 87 µM (Kita et al., 2013).

Antimicrobial Agents (Figure 10)

The solitary tunicate, *H. aurantium*, was the source of a novel antimicrobial peptide Dicynthaurin **(98)** (Lee et al., 2001a). An antibacterial depsipeptide, Nagahamide A **(99)**, was discovered from the marine sponge *T. swinhoei* (Okada et al., 2002). An antimicrobial octapeptide peptide Plicatamide **(100)** ((Phe-Phe-His-Leu-His-Phe-His-dcΔDOPA), where dcΔDOPA represents decarboxy-(E)-α, β-dehydro-3, 4-dihydroxyphenylalanine, was isolated from *S. plicata* (Tincu et al., 2003). The marine sponge *Latrunculia* sp., (Vanuatu Islands) was the source of four new antifungal peptides, Callipeltins F–I **(101–104)**. Callipeltins F–I inhibit the growth of *C. albicans* (ATCC24433) with a MIC value of 10^{-4} M (Sepe et al., 2006). Four new peptides, Callipeltins J–M **(105–108)**, were isolated from the marine sponge *Latrunculia* sp. However only Callipeltins J and K inhibited the growth of *C. albicans* with MIC values of ca. 4^{-10} M (D'Auria et al., 2007). Two new linear tetrapeptides, Citronamides A **(109)** and B **(110)**, were isolated from the Australian sponge *C. astra*. Only citronamides A showed moderate antifungal activity against *Saccharomyces cerevisiae* at MIC value of 8 µg/mL (Carroll et al., 2009).

Miscellaneous (Figure 11)

A cyclic tripeptide Renieramide **(111)** was isolated from Vanuatu collection of sponge *Reniera* sp. that showed immunomodulating activity in preliminary tests (Ciasullo et al., 2002). Two nematocidal depsipeptides, Phoriospongin A and B **(112 and 113)**, have been isolated from Australian marine sponges *Phoriospongia* sp. and *C. bilamellata*. Both compounds have displayed significant nematocidal activity against *H. contortus* (LD_{99} =100, 194 µg/mL, respectively) (Capon et al., 2002).

Biological Aspects, Challenges, and Future Perspectives

Like their structural diversity, metabolites produced from marine sponges and tunicates bind to a variety of cellular targets to elicit their effects. Numerous articles published in recent years highlighting the significance of these metabolites in disease control, the details of their biological significance from molecular recognition perspective have been rather scarce. Although some promising leads have been obtained, the discovery of their cellular targets, molecular interactions, and adverse effects are lacking. In cases where the therapeutic potential has been reported, details

of a proper screening approach to identify nucleic acid or protein targets are missing. However, some established metabolites from these sources (see Tables 1 and 2) and their derivatives have been examined extensively and their molecular targets are varied. One of the earliest examples in this class is FDA-approved drug Ara-C (cytarabine), which is known to elicit anticancer properties by inhibiting the functions of DNA polymerase (Furth and Cohen, 1968), which ultimately results in stalling DNA synthesis. Another FDA approved related compound Ara-A(vidarabine), which is known to have antiviral properties (active against herpes simplex and varicella zoster viruses), targets viral DNA polymerase (Chadwick et al., 1978) by functioning as mimic of natural nucleotides. Both Ara-C and Ara-A resemble natural cytidine and adenine nucleosides where the structural differences are in the sugar components of the two (arabinose versus deoxyribose). The natural nucleoside mimics Ara-A and Ara-C are easily phosphorylated as their triphosphate derivatives by kinases and act as terminators of DNA synthesis. Ara-A is also known to impede 3′-end processing of pre-mRNAs by inhibiting cleavage and polyadenylation (Ghoshal and Jacob, 1991, Rose and Jacob, 1978).

Several other molecules that are either FDA approved or in early stages of clinical trials have been identified as anticancer agents with microtubules as their primary molecular targets. The predominance of natural metabolites being microtubule binding agents has been hypothesized as evolutionary response to predation by plants and animals (Dumontet and Jordan, 2010). Some of these molecules, such as discodermolide, are among the first non-taxane stabilizers of microtubules (Mooberry et al., 2004). The microtubule stabilizers act by enhancing microtubule polymerization at high concentrations. Discodermolide has been known to bind to tubulin dimers in a stoichiometric ratio. Competitive binding experiments have shown that it blocks taxol binding and is a much stronger binder of microtubules than taxol (Kowalski et al., 1997). The microtubule binding of Tau proteins is interfered by discodermolide (Kar et al., 2003). Similarly, laulimalide showed properties very similar to paclitaxel where it helped in enhancing tubulin assembly (Gapud et al., 2004). However, laulimalide modulation of microtubule assembly in *C. elegans* is dose dependent where it stabilization effects were observed only at concentrations higher than 100 nM (Bajaj and Srayko, 2013).

The antiviral effect of homophymine A has been established by measuring the reverse transcriptase activity in HIV-infected primary peripheral blood mononuclear cells (Zampella et al., 2008a). The

reverse transcriptase activity is exhibited by 2 classes of molecules: one that directly competes with natural nucleotide triphosphates and the other that either directly blocks the catalytic reactions or by allosteric binding that leads to structural changes in the viral enzyme. Since homophymine A lacks structural features to act as mimics of natural nucleotide triphosphates, it is likely to impede the catalytic activity of the enzyme by direct binding.

A tunicate-derived metabolite trabectedin (ET-743) uses DNA binding to exert its anticancer properties. Trabectin binds to the GC rich regions in the B-DNA where it uses its carbolinamine moiety to form adduct with the exocylic amine (N-2) of guanine (Pommier et al., 1996) and covers 3 base pairs during this process (Marco et al., 2006). Unlike B-DNA minor groove binders, such as Hoechst 33258, which binds snugly along the minor groove curvature with high-affinity (Haq et al., 1997), trabectedin only uses part of its structure to make necessary contacts for the antitumor action (D'Incalci and Galmarini, 2010).

Despite these advances in determining the mode of their binding, a large number of recently discovered metabolites are still not explored to assess it functional capabilities. In the past, well-known anti-retroviral drug zidovudine, which was initially thought to be functionally inert, turned out as excellent therapeutic agent. Such discoveries are possible only when a rational screening design is aimed to asses it full potential as a drug. For example, compounds that have structural regions favourable for protein binding should be screened against all potential protein targets. Similarly, compounds that show preference towards nucleic acid binding should be screened using assays such as competition dialysis that establish a preferential nucleic acid target. Such approaches not only determine the best target for a particular compound but also shed light to its secondary targets, which may be helpful in dealing with toxicity issues. Current target design of marine and tunicate metabolites clearly need to take these approaches.

Some of the metabolites that have weaker binding to a target or have poor bioavailability can be improved by nano-encapsulation techniques. Additionally, DNA binding metabolites can be chemically modified to enhance their affinity using multi-recognition of the target (Willis and Arya, 2010), which has led to remarkable enhancement in the affinity of double,(Arya et al., 2003), triple (Arya and Willis, 2003), and four-stranded DNA helical structures (Ranjan et al., 2013).

Conclusion

Extreme environment of the ocean plays a vital role in exploring and studying marine bio-resources and their bio-actives. The large biodiversity of the sea serves as an untapped resource for developing potential drugs with promising pharmacological activities. The significance of marine-derived secondary metabolites has recently been corroborated by introduction of Prialt and Yondelis to the market. In the past three decades, numerous NRPs with unique chemical structures and varied biological activities have been discovered from marine sponges and tunicates as described above. In addition, some of them exhibit strong potential to be developed as a new drug. However, none of the NRPs highlighted in this review have been successfully marketed as therapeutics. To translate bioactivity of these important compounds into therapeutically significant outcomes, it is crucial to further unravel their modes of action and measure their toxicity. Since the majority of these studies have been focused on *in vitro* bioassays and elucidation of the chemical structures only, a complete examination of their biological target selectivity is required. Nevertheless, large-scale production of these NRPs for clinical use is a real challenge. Therefore, environmentally sound and economically feasible alternatives are required. To counter these challenges, many strategies have been established.

Chemical synthesis of these NRPs is among the first strategies to be used. However, the structural complexity limits its chemical synthesis and has resulted in only a few successful achievements (e.g., analgesic drug ziconotide) (Olivera, 2000). A second strategy uses screening the pharmacological significance of NRPs and subsequently attempting to define the critical pharmacophore that can result in practical drugs based on a marine prototype via chemical synthesis, degradation, modification, or a combination of these. Aquaculture of the source organisms has also been used to secure a sustainable supply of active compound(s). However, in most cases, the biomass currently generated is still far the requirement from an industrial perspective (Mendola, 2000). Identification and large-scale culturing of true producers that are known to thrive within the tissues of marine invertebrates (sponge or tunicate) is an intriguing strategy. However, to date only 5 per cent or less of the symbiotic microbes present in marine specimens can be cultivated under standard conditions. Consequently, molecular approaches such as transfer of biosynthetic gene clusters to a vector suitable for large-scale fermentation could be used to avoid obstacles in culturing symbiotic bacteria. Enzyme technology and solid-phase peptide synthesis offer particularly promising alternatives to generate variety of unique peptides

401 using native peptide as a template. Besides, combinations of chemical synthesis and biosynthetic
402 technologies have potential to accelerate the discovery of novel drugs derived from sponge and
403 their microbial association in future.
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References

ABRAHAM, E. & NEWTON, G. 1961. The structure of cephalosporin C. *Biochemical Journal,* 79**,** 377.

AOKI, S., CAO, L., MATSUI, K., RACHMAT, R., AKIYAMA, S.-I. & KOBAYASHI, M. 2004. Kendarimide A, a novel peptide reversing P-glycoprotein-mediated multidrug resistance in tumor cells, from a marine sponge of Haliclona sp. *Tetrahedron,* 60**,** 7053-7059.

ARAI, M., YAMANO, Y., FUJITA, M., SETIAWAN, A. & KOBAYASHI, M. 2012. Stylissamide X, a new proline-rich cyclic octapeptide as an inhibitor of cell migration, from an Indonesian marine sponge of Stylissa sp. *Bioorganic & medicinal chemistry letters,* 22**,** 1818-1821.

ARYA, D. P. & WILLIS, B. 2003. Reaching into the Major Groove of B-DNA: Synthesis and Nucleic Acid Binding of a Neomycin−Hoechst 33258 Conjugate. *Journal of the American Chemical Society,* 125**,** 12398-12399.

ARYA, D. P., XUE, L. & TENNANT, P. 2003. Combining the Best in Triplex Recognition: Synthesis and Nucleic Acid Binding of a BQQ−Neomycin Conjugate. *Journal of the American Chemical Society,* 125**,** 8070-8071.

BAJAJ, M. & SRAYKO, M. 2013. Laulimalide Induces Dose-Dependent Modulation of Microtubule Behaviour in the <italic>C. elegans</italic> Embryo. *PLoS ONE,* 8**,** e71889.

BEWLEY, C., HOLLAND, N. & FAULKNER, D. 1996. Two classes of metabolites fromTheonella swinhoei are localized in distinct populations of bacterial symbionts. *Experientia,* 52**,** 716-722.

BRENNAN, M. R., COSTELLO, C. E., MALEKNIA, S. D., PETTIT, G. R. & ERICKSON, K. L. 2008. Stylopeptide 2, a Proline-Rich Cyclodecapeptide from the Sponge Stylotella sp.⊥#. *Journal of natural products,* 71**,** 453-456.

BRUSCA, R. C., BRUSCA, G. J. & HAVER, N. J. 1990. *Invertebrates*, Sinauer Associates Sunderland, Massachusetts.

BULTEL-PONCÉ, V., BERGE, J.-P., DEBITUS, C., NICOLAS, J.-L. & GUYOT, M. 1999. Metabolites from the sponge-associated bacterium Pseudomonas species. *Marine Biotechnology,* 1**,** 384-390.

BULTEL-PONCÉ, V., DEBITUS, C., BERGE, J.-P., CERCEAU, C. & GUYOT, M. 1998. Metabolites from the sponge-associated bacterium Micrococcus luteus. *Journal of marine biotechnology,* 6**,** 233-236.

CAPON, R. J., FORD, J., LACEY, E., GILL, J. H., HEILAND, K. & FRIEDEL, T. 2002. Phoriospongin A and B: Two New Nematocidal Depsipeptides from the Australian Marine Sponges Phoriospongia sp. and Callyspongia b ilamellata. *Journal of natural products,* 65**,** 358-363.

CARROLL, A. R., DUFFY, S. & AVERY, V. M. 2009. Citronamides A and B, tetrapeptides from the australian sponge Citronia astra. *Journal of natural products,* 72**,** 764-768.

CHADWICK, R. G., BASSENDINE, M. F., CRAWFORD, E. M., THOMAS, H. C. & SHERLOCK, S. 1978. Hbsag-Positive Chronic Liver Disease: Inhibition Of DNA Polymerase Activity By Vidarabine. *The British Medical Journal,* 2**,** 531-533.

CHEVALLIER, C., RICHARDSON, A. D., EDLER, M. C., HAMEL, E., HARPER, M. K. & IRELAND, C. M. 2003. A new cytotoxic and tubulin-interactive milnamide derivative from a marine sponge Cymbastela sp. *Organic letters,* 5**,** 3737-3739.

CIASULLO, L., CASAPULLO, A., CUTIGNANO, A., BIFULCO, G., DEBITUS, C., HOOPER, J., GOMEZ-PALOMA, L. & RICCIO, R. 2002. Renieramide, a cyclic tripeptide from the Vanuatu sponge Reniera n. sp. *Journal of natural products,* 65**,** 407-410.

D'AURIA, M. V., SEPE, V., D'ORSI, R., BELLOTTA, F., DEBITUS, C. & ZAMPELLA, A. 2007. Isolation and structural elucidation of callipeltins J–M: antifungal peptides from the marine sponge Latrunculia sp. *Tetrahedron,* 63**,** 131-140.

D'INCALCI, M. & GALMARINI, C. M. 2010. A Review of Trabectedin (ET-743): A Unique Mechanism of Action. *Molecular Cancer Therapeutics,* 9**,** 2157-2163.

DAVIS, R. A., MANGALINDAN, G. C., BOJO, Z. P., ANTEMANO, R. R., RODRIGUEZ, N. O., CONCEPCION, G. P., SAMSON, S. C., DE GUZMAN, D., CRUZ, L. J. & TASDEMIR, D. 2004. Microcionamides A and B, bioactive peptides from the Philippine sponge Clathria (Thalysias) abietina. *The Journal of organic chemistry,* 69**,** 4170-4176.

DE CRÉCY-LAGARD, V., BLANC, V., GIL, P., NAUDIN, L., LORENZON, S., FAMECHON, A., BAMAS-JACQUES, N., CROUZET, J. & THIBAUT, D. 1997. Pristinamycin I biosynthesis in Streptomyces pristinaespiralis: molecular characterization of the first two structural peptide synthetase genes. *Journal of bacteriology,* 179**,** 705-713.

DOMENECH, O., FRANCIUS, G., TULKENS, P. M., VAN BAMBEKE, F., DUFRÊNE, Y. & MINGEOT-LECLERCQ, M.-P. 2009. Interactions of oritavancin, a new lipoglycopeptide derived from vancomycin, with phospholipid bilayers: effect on membrane permeability and nanoscale lipid membrane organization. *Biochimica et Biophysica Acta (BBA)-Biomembranes,* 1788**,** 1832-1840.

DUMONTET, C. & JORDAN, M. A. 2010. Microtubule-binding agents: a dynamic field of cancer therapeutics. *Nat Rev Drug Discov,* 9**,** 790-803.

ELYAKOV, G., KUZNETSOVA, T., MIKHAILOV, V., MALTSEV, I., VOINOV, V. & FEDOREYEV, S. 1991. Brominated diphenyl ethers from a marine bacterium associated with the spongeDysidea sp. *Experientia,* 47**,** 632-633.

FENICAL, W. 1976. Geranyl hydroquinone, a cancer-protective agent from the tunicate Aplidium species. *Food Drugs Sea Proc,* 4**,** 388-394.

FERNÁNDEZ, R., MARTÍN, M. J., RODRÍGUEZ-ACEBES, R., REYES, F., FRANCESCH, A. & CUEVAS, C. 2008. Diazonamides C–E, new cytotoxic metabolites from the ascidian Diazona sp. *Tetrahedron Letters,* 49**,** 2283-2285.

FESTA, C., DE MARINO, S., SEPE, V., D'AURIA, M. V., BIFULCO, G., DÉBITUS, C., BUCCI, M., VELLECCO, V. & ZAMPELLA, A. 2011. Solomonamides A and B, new anti-inflammatory peptides from Theonella swinhoei. *Organic letters,* 13**,** 1532-1535.

FESTA, C., DE MARINO, S., SEPE, V., MONTI, M. C., LUCIANO, P., D'AURIA, M. V., DÉBITUS, C., BUCCI, M., VELLECCO, V. & ZAMPELLA, A. 2009. Perthamides C and D, two new potent anti-inflammatory cyclopeptides from a Solomon Lithistid sponge Theonella swinhoei. *Tetrahedron,* 65**,** 10424-10429.

FINKING, R. & MARAHIEL, M. A. 2004. Biosynthesis of nonribosomal peptides1. *Annu Rev Microbiol,* 58**,** 453-88.

FU, X., SU, J. & ZENG, L. 2000. Prepatellamide A, a new cyclic peptide from the ascidianLissoclinum patella. *Science in China Series B: Chemistry,* 43**,** 643-648.

FURTH, J. J. & COHEN, S. S. 1968. Inhibition of Mammalian DNA Polymerase by the 5'-Triphosphate of 1-β-d-Arabinofuranosylcytosine and the 5'-Triphosphate of 9-β-d-Arabinofuranosyladenine. *Cancer Research,* 28**,** 2061-2067.

GAPUD, E. J., BAI, R., GHOSH, A. K. & HAMEL, E. 2004. Laulimalide and Paclitaxel: A Comparison of Their Effects on Tubulin Assembly and Their Synergistic Action When Present Simultaneously. *Molecular Pharmacology,* 66**,** 113-121.

GHOSHAL, K. & JACOB, S. T. 1991. Ara-ATP impairs 3'-end processing of pre-mRNAs by inhibiting both cleavage and polyadenylation. *Nucleic Acids Research,* 19**,** 5871-5875.

HAMADA, T., MATSUNAGA, S., YANO, G. & FUSETANI, N. 2005. Polytheonamides A and B, Highly Cytotoxic, Linear Polypeptides with Unprecedented Structural Features, from the Marine Sponge, Theonella s winhoei. *Journal of the American Chemical Society,* 127**,** 110-118.

HAQ, I., LADBURY, J. E., CHOWDHRY, B. Z., JENKINS, T. C. & CHAIRES, J. B. 1997. Specific binding of hoechst 33258 to the d(CGCAAATTTGCG)2 duplex: calorimetric and spectroscopic studies1. *Journal of Molecular Biology,* 271**,** 244-257.

HENTSCHEL, U., HOPKE, J., HORN, M., FRIEDRICH, A. B., WAGNER, M., HACKER, J. & MOORE, B. S. 2002. Molecular evidence for a uniform microbial community in sponges from different oceans. *Applied and Environmental Microbiology,* 68**,** 4431-4440.

HENTSCHEL, U., SCHMID, M., WAGNER, M., FIESELER, L., GERNERT, C. & HACKER, J. 2001. Isolation and phylogenetic analysis of bacteria with antimicrobial activities from the Mediterranean sponges Aplysina aerophoba and Aplysina cavernicola. *FEMS Microbiology Ecology,* 35**,** 305-312.

IBRAHIM, S. R., EDRADA-EBEL, R., MOHAMED, G. A., YOUSSEF, D. T., WRAY, V. & PROKSCH, P. 2008. Callyaerin G, a new cytotoxic cyclic peptide from the marine sponge Callyspongia aerizusa. *Arkivoc,* 12**,** 164-171. DOI: http://dx.doi.org/10.3998/ark.5550190.0009.c18

IBRAHIM, S. R., MIN, C. C., TEUSCHER, F., EBEL, R., KAKOSCHKE, C., LIN, W., WRAY, V., EDRADA-EBEL, R. & PROKSCH, P. 2010. Callyaerins A–F and H, new cytotoxic cyclic peptides from the Indonesian marine sponge Callyspongia aerizusa. *Bioorganic & medicinal chemistry,* 18**,** 4947-4956.

JOHNSON, B. A., ANKER, H. & MELENEY, F. L. 1945. Bacitracin: a new antibiotic produced by a member of the B. subtilis group. *Science,* 102**,** 376-377.

KAR, S., FLORENCE, G. J., PATERSON, I. & AMOS, L. A. 2003. Discodermolide interferes with the binding of tau protein to microtubules. *FEBS Letters,* 539**,** 34-36.

KEHRAUS, S., KÖNIG, G. M., WRIGHT, A. D. & WOERHEIDE, G. 2002. Leucamide A: A new cytotoxic heptapeptide from the Australian sponge Leucetta microraphis. *The Journal of organic chemistry,* 67**,** 4989-4992.

KITA, M., GISE, B., KAWAMURA, A. & KIGOSHI, H. 2013. Stylissatin A, a cyclic peptide that inhibits nitric oxide production from the marine sponge Stylissa massa. *Tetrahedron Letters,* 54**,** 6826-6828.

KLEINKAUF, H. & VON DÖHREN, H. 1995. The nonribosomal peptide biosynthetic system—on the origins of structural diversity of peptides, cyclopeptides and related compounds. *Antonie van Leeuwenhoek,* 67**,** 229-242.

KOWALSKI, R. J., GIANNAKAKOU, P., GUNASEKERA, S. P., LONGLEY, R. E., DAY, B. W. & HAMEL, E. 1997. The Microtubule-Stabilizing Agent Discodermolide Competitively Inhibits the Binding of Paclitaxel (Taxol) to Tubulin Polymers, Enhances Tubulin Nucleation Reactions More Potently than Paclitaxel, and Inhibits the Growth of Paclitaxel-Resistant Cells. *Molecular Pharmacology,* 52**,** 613-622.

LAPORT, M., SANTOS, O. & MURICY, G. 2009. Marine sponges: potential sources of new antimicrobial drugs. *Current pharmaceutical biotechnology,* 10**,** 86-105.

LEE, I. H., LEE, Y. S., KIM, C. H., KIM, C. R., HONG, T., MENZEL, L., BOO, L. M., POHL, J., SHERMAN, M. A. & WARING, A. 2001a. Dicynthaurin: an antimicrobial peptide from hemocytes of the solitary tunicate, Halocynthia aurantium. *Biochimica et Biophysica Acta (BBA)-General Subjects,* 1527**,** 141-148.

LEE, Y. K., LEE, J.-H. & LEE, H. K. 2001b. Microbial symbiosis in marine sponges. *JOURNAL OF MICROBIOLOGY-SEOUL-,* 39**,** 254-264.

MARCO, E., DAVID-CORDONNIER, M.-H., BAILLY, C., CUEVAS, C. & GAGO, F. 2006. Further Insight into the DNA Recognition Mechanism of Trabectedin from the Differential Affinity of Its Demethylated Analogue Ecteinascidin ET729 for the Triplet DNA Binding Site CGA. *Journal of Medicinal Chemistry,* 49**,** 6925-6929.

MAULUCCI, N., CHINI, M. G., DI MICCO, S., IZZO, I., CAFARO, E., RUSSO, A., GALLINARI, P., PAOLINI, C., NARDI, M. C. & CASAPULLO, A. 2007. Molecular insights into azumamide E histone deacetylases inhibitory activity. *Journal of the American Chemical Society,* 129**,** 3007-3012.

Mayer, A.M., Glaser, K.B., Cuevas, C., Jacobs, R.S., Kem, W., Little, R.D., and McIntosh, J.M.,Newman, D.J., Potts, B.C. and Shuster, D.E. (2010).The odyssey of marine pharmaceuticals: a current pipeline perspective. *Trends Pharmacol Sci.* 31(6):255-265. doi: 10.1016/j.tips.2010.02.005.

MEHBUB, M. F., LEI, J., FRANCO, C. & ZHANG, W. 2014. Marine Sponge Derived Natural Products between 2001 and 2010: Trends and Opportunities for Discovery of Bioactives. *Marine drugs,* 12**,** 4539-4577.

MENDOLA, D. 2000. Aquacultural production of bryostatin 1 and ecteinascidin 743.

MENNA, M. 2009. Antitumor potential of natural products from Mediterranean ascidians. *Phytochemistry Reviews,* 8**,** 461-472.

MIAO, V., COEFFET-LEGAL, M.-F., BRIAN, P., BROST, R., PENN, J., WHITING, A., MARTIN, S., FORD, R., PARR, I. & BOUCHARD, M. 2005. Daptomycin biosynthesis in Streptomyces roseosporus: cloning and analysis of the gene cluster and revision of peptide stereochemistry. *Microbiology,* 151**,** 1507-1523.

MOOBERRY, S. L., RANDALL-HLUBEK, D. A., LEAL, R. M., HEGDE, S. G., HUBBARD, R. D., ZHANG, L. & WENDER, P. A. 2004. Microtubule-stabilizing agents based on designed laulimalide analogues. *Proceedings of the National Academy of Sciences of the United States of America,* 101**,** 8803-8808.

MURTHY, M. R., MOHAN, E. & SADHUKHAN, A. 1999. Cyclosporin-A production by Tolypocladium inflatum using solid state fermentation. *Process Biochemistry,* 34**,** 269-280.

NAKAO, Y., FUJITA, M., WARABI, K., MATSUNAGA, S. & FUSETANI, N. 2000. Miraziridine A, a novel cysteine protease inhibitor from the marine sponge Theonella aff. mirabilis 1. *Journal of the American Chemical Society,* 122**,** 10462-10463.

NAKAO, Y., KAWATSU, S., OKAMOTO, C., OKAMOTO, M., MATSUMOTO, Y., MATSUNAGA, S., VAN SOEST, R. W. & FUSETANI, N. 2008. Ciliatamides A− C, Bioactive Lipopeptides from the Deep-Sea Sponge Aaptos ciliata#. *Journal of natural products,* 71**,** 469-472.

NAKAO, Y., KUO, J., YOSHIDA, W. Y., KELLY, M. & SCHEUER, P. J. 2003. More Kapakahines from the Marine Sponge Cribrochalina o lemda. *Organic letters,* 5**,** 1387-1390.

NEWMAN, D. J. & CRAGG, G. M. 2016. Natural products as sources of new drugs from 1981 to 2014. *Journal of natural products,* 79**,** 629-661.

NEWMAN, D. J. & HILL, R. T. 2006. New drugs from marine microbes: the tide is turning. *Journal of Industrial Microbiology and Biotechnology,* 33**,** 539-544.

OCLARIT, J., OKADA, H., OHTA, S., KAMINURA, K., YAMAOKA, Y., IIZUKA, T., MIYASHIRO, S. & IKEGAMI, S. 1994. Anti-bacillus substance in the marine sponge, Hyatella species, produced by an associated Vibrio species bacterium. *Microbios,* 78**,** 7.

OKADA, Y., MATSUNAGA, S., VAN SOEST, R. W. & FUSETANI, N. 2002. Nagahamide A, an Antibacterial Depsipeptide from the Marine Sponge Theonella swinhoei 1. *Organic letters,* 4**,** 3039-3042.

OKU, N., GUSTAFSON, K. R., CARTNER, L. K., WILSON, J. A., SHIGEMATSU, N., HESS, S., PANNELL, L. K., BOYD, M. R. & MCMAHON, J. B. 2004. Neamphamide A, a new HIV-inhibitory depsipeptide from the Papua New Guinea marine sponge Neamphius huxleyi. *Journal of natural products,* 67**,** 1407-1411.

OLIVERA, B. M. 2000. ω-Conotoxin MVIIA: from marine snail venom to analgesic drug.

OLSON, J. B. & MCCARTHY, P. J. 2005. Associated bacterial communities of two deep-water sponges. *Aquatic microbial ecology,* 39**,** 47-55.

PAULUS, H. & GRAY, E. 1964. The biosynthesis of polymyxin B by growing cultures of Bacillus polymyxa. *Journal of Biological Chemistry,* 239**,** 865-871.

PEREZ, L. J. & FAULKNER, D. J. 2003. Bistratamides EJ, Modified Cyclic Hexapeptides from the Philippines Ascidian Lissoclinum b istratum. *Journal of natural products,* 66**,** 247-250.
PETTIT, G. R. & TAN, R. 2005. Isolation and Structure of Phakellistatin 14 from the Western Pacific Marine Sponge Phakellia sp., 1. *Journal of natural products,* 68**,** 60-63.
PLAZA, A., BIFULCO, G., KEFFER, J. L., LLOYD, J. R., BAKER, H. L. & BEWLEY, C. A. 2008. Celebesides A− C and Theopapuamides B− D, Depsipeptides from an Indonesian Sponge That Inhibit HIV-1 Entry. *The Journal of organic chemistry,* 74**,** 504-512.
PLAZA, A., BIFULCO, G., MASULLO, M., LLOYD, J. R., KEFFER, J. L., COLIN, P. L., HOOPER, J. N., BELL, L. J. & BEWLEY, C. A. 2010. Mutremdamide A and Koshikamides C− H, Peptide Inhibitors of HIV-1 Entry from Different Theonella Species. *The Journal of organic chemistry,* 75**,** 4344-4355.
PLAZA, A., GUSTCHINA, E., BAKER, H. L., KELLY, M. & BEWLEY, C. A. 2007. Mirabamides A–D, depsipeptides from the sponge Siliquariaspongia mirabilis that inhibit HIV-1 fusion. *Journal of natural products,* 70**,** 1753-1760.
POMMIER, Y., KOHLHAGEN, G., BAILLY, C., WARING, M., MAZUMDER, A. & KOHN, K. W. 1996. DNA Sequence- and Structure-Selective Alkylation of Guanine N2 in the DNA Minor Groove by Ecteinascidin 743, a Potent Antitumor Compound from the Caribbean Tunicate Ecteinascidia turbinata. *Biochemistry,* 35**,** 13303-13309.
PRASAD, P., AALBERSBERG, W., FEUSSNER, K.-D. & VAN WAGONER, R. M. 2011. Papuamides E and F, cytotoxic depsipeptides from the marine sponge Melophlus sp. *Tetrahedron,* 67**,** 8529-8531.
QURESHI, A., COLIN, P. L. & FAULKNER, D. J. 2000. Microsclerodermins F–I, antitumor and antifungal cyclic peptides from the Lithistid sponge Microscleroderma sp. *Tetrahedron,* 56**,** 3679-3685.
RANDAZZO, A., BIFULCO, G., GIANNINI, C., BUCCI, M., DEBITUS, C., CIRINO, G. & GOMEZ-PALOMA, L. 2001. Halipeptins A and B: two novel potent anti-inflammatory cyclic depsipeptides from the Vanuatu marine sponge Haliclona species. *Journal of the American Chemical Society,* 123**,** 10870-10876.
RANJAN, N., DAVIS, E., XUE, L. & ARYA, D. P. 2013. Dual recognition of the human telomeric G-quadruplex by a neomycin-anthraquinone conjugate. *Chemical Communications,* 49**,** 5796-5798.
RASHID, M. A., GUSTAFSON, K. R., BOSWELL, J. L. & BOYD, M. R. 2000. Haligramides A and B, two new cytotoxic hexapeptides from the marine sponge Haliclona nigra. *Journal of natural products,* 63**,** 956-959.
RASHID, M. A., GUSTAFSON, K. R., CARTNER, L. K., SHIGEMATSU, N., PANNELL, L. K. & BOYD, M. R. 2001. Microspinosamide, a New HIV-Inhibitory Cyclic Depsipeptide from the Marine Sponge Sidonops m icrospinosa 1. *Journal of natural products,* 64**,** 117-121.
RATNAYAKE, A. S., BUGNI, T. S., FENG, X., HARPER, M. K., SKALICKY, J. J., MOHAMMED, K. A., ANDJELIC, C. D., BARROWS, L. R. & IRELAND, C. M. 2006. Theopapuamide, a cyclic depsipeptide from a Papua New Guinea lithistid sponge Theonella swinhoei. *Journal of natural products,* 69**,** 1582-1586.
ROSE, K. M. & JACOB, S. T. 1978. Selective inhibition of RNA polyadenylation by Ara-ATP in vitro: A possible mechanism for antiviral action of Ara-A. *Biochemical and Biophysical Research Communications,* 81**,** 1418-1424.
RUDI, A., CHILL, L., AKNIN, M. & KASHMAN, Y. 2003. Didmolamide A and B, Two New Cyclic Hexapeptides from the Marine Ascidian Didemnum m olle. *Journal of natural products,* 66**,** 575-577.
RUPPERT, E. & FOX, R. 2004. Invertebrate zoology: a functional evolutionary approach (of RD Barnes' Invertebrate zoology). *Brooks/Cole, Belmont, CA*.

SCHMIDT, E. W., OBRAZTSOVA, A., DAVIDSON, S., FAULKNER, D. & HAYGOOD, M. 2000. Identification of the antifungal peptide-containing symbiont of the marine sponge Theonella swinhoei as a novel δ-proteobacterium,"Candidatus Entotheonella palauensis". *Marine Biology,* 136**,** 969-977.

SCHMIDT, E. W., RAVENTOS-SUAREZ, C., BIFANO, M., MENENDEZ, A. T., FAIRCHILD, C. R. & FAULKNER, D. J. 2004. Scleritodermin A, a Cytotoxic Cyclic Peptide from the Lithistid Sponge Scleritoderma n odosum. *Journal of natural products,* 67**,** 475-478.

SEPE, V., D'ORSI, R., BORBONE, N., D'AURIA, M. V., BIFULCO, G., MONTI, M. C., CATANIA, A. & ZAMPELLA, A. 2006. Callipeltins F–I: new antifungal peptides from the marine sponge Latrunculia sp. *Tetrahedron,* 62**,** 833-840.

SOMMA, S., GASTALDO, L. & CORTI, A. 1984. Teicoplanin, a new antibiotic from Actinoplanes teichomyceticus nov. sp. *Antimicrobial agents and chemotherapy,* 26**,** 917-923.

SONNENSCHEIN, R. N., FARIAS, J. J., TENNEY, K., MOOBERRY, S. L., LOBKOVSKY, E., CLARDY, J. & CREWS, P. 2004. A further study of the cytotoxic constituents of a milnamide-producing sponge. *Organic letters,* 6**,** 779-782.

STARK, W., HIGGENS, C., WOLFE, R., HOEHN, M. & MCGUIRE, J. 1962. Capreomycin, a new antimycobacterial agent produced by Streptomyces capreolus sp. n. *Antimicrobial Agents and Chemotherapy,* 1962**,** 596-606.

STEELE, J. H. 1985. A comparison of terrestrial and marine ecological systems. *Nature,* 313**,** 355-358.

STIERLE, A., CARDELLINA II, J. & SINGLETON, F. 1988. A marineMicrococcus produces metabolites ascribed to the spongeTedania ignis. *Experientia,* 44**,** 1021-1021.

TABUDRAVU, J., MORRIS, L. A., KETTENES-VAN DEN BOSCH, J. J. & JASPARS, M. 2001. Wainunuamide, a histidine-containing proline-rich cyclic heptapeptide isolated from the Fijian marine sponge Stylotella aurantium. *Tetrahedron Letters,* 42**,** 9273-9276.

TABUDRAVU, J. N., MORRIS, L. A., KETTENES-VAN DEN BOSCH, J. J. & JASPARS, M. 2002. Axinellin C, a proline-rich cyclic octapeptide isolated from the Fijian marine sponge Stylotella aurantium. *Tetrahedron,* 58**,** 7863-7868.

TAN, L. T., WILLIAMSON, R. T., GERWICK, W. H., WATTS, K. S., MCGOUGH, K. & JACOBS, R. 2000. cis, cis- and trans, trans-Ceratospongamide, New Bioactive Cyclic Heptapeptides from the Indonesian Red Alga Ceratodictyon s pongiosum and Symbiotic Sponge Sigmadocia s ymbiotica. *The Journal of organic chemistry,* 65**,** 419-425.

TANAKA, C., TANAKA, J., BOLLAND, R. F., MARRIOTT, G. & HIGA, T. 2006. Seragamides A–F, new actin-targeting depsipeptides from the sponge Suberites japonicus Thiele. *Tetrahedron,* 62**,** 3536-3542.

THOMAS, T. R. A., KAVLEKAR, D. P. & LOKABHARATHI, P. A. 2010. Marine drugs from sponge-microbe association—A review. *Marine Drugs,* 8**,** 1417-1468.

TINCU, J. A., MENZEL, L. P., AZIMOV, R., SANDS, J., HONG, T., WARING, A. J., TAYLOR, S. W. & LEHRER, R. I. 2003. Plicatamide, an antimicrobial octapeptide from Styela plicata hemocytes. *Journal of Biological Chemistry,* 278**,** 13546-13553.

UEDA, H., NAKAJIMA, H., HORI, Y., FUJITA, T., NISHIMURA, M., GOTO, T. & OKUHARA, M. 1994. FR901228, a novel antitumor bicyclic depsipeptide produced by Chromobacterium violaceum No. 968. I. Taxonomy, fermentation, isolation, physico-chemical and biological properties, and antitumor activity. *The Journal of antibiotics,* 47**,** 301-310.

UMEZAWA, H., MAEDA, K., TAKEUCHI, T. & OKAMI, Y. 1966. New antibiotics, bleomycin A and B. *The Journal of antibiotics,* 19**,** 200.

UNSON, M., HOLLAND, N. & FAULKNER, D. 1994. A brominated secondary metabolite synthesized by the cyanobacterial symbiont of a marine sponge and accumulation of the crystalline metabolite in the sponge tissue. *Marine Biology,* 119**,** 1-11.

VAN WAGENINGEN, A. A., KIRKPATRICK, P. N., WILLIAMS, D. H., HARRIS, B. R., KERSHAW, J. K., LENNARD, N. J., JONES, M., JONES, S. J. & SOLENBERG, P. J. 1998. Sequencing and analysis of genes involved in the biosynthesis of a vancomycin group antibiotic. *Chemistry & biology,* 5**,** 155-162.

VERVOORT, H., FENICAL, W. & EPIFANIO, R. D. A. 2000. Tamandarins A and B: New cytotoxic depsipeptides from a Brazilian ascidian of the family Didemnidae. *The Journal of organic chemistry,* 65**,** 782-792.

VICENTE, J., VERA, B., RODRÍGUEZ, A. D., RODRÍGUEZ-ESCUDERO, I. & RAPTIS, R. G. 2009. Euryjanicin A: a new cycloheptapeptide from the Caribbean marine sponge Prosuberites laughlini. *Tetrahedron letters,* 50**,** 4571-4574.

VINOTHKUMAR, S. & PARAMESWARAN, P. 2013. Recent advances in marine drug research. *Biotechnology advances,* 31**,** 1826-1845.

WAKSMAN, S. A. & WOODRUFF, H. B. 1940. Bacteriostatic and Bactericidal Substances Produced by a Soil Actinomyces. *Experimental Biology and Medicine,* 45**,** 609-614.

WEBSTER, N. S., WILSON, K. J., BLACKALL, L. L. & HILL, R. T. 2001. Phylogenetic diversity of bacteria associated with the marine sponge Rhopaloeides odorabile. *Applied and environmental microbiology,* 67**,** 434-444.

WILKINSON, C. 1978. Microbial associations in sponges. III. Ultrastructure of the in situ associations in coral reef sponges. *Marine Biology,* 49**,** 177-185.

WILKINSON, C. R., NOWAK, M., AUSTIN, B. & COLWELL, R. R. 1981. Specificity of bacterial symbionts in Mediterranean and Great Barrier Reef sponges. *Microbial ecology,* 7**,** 13-21.

WILLIAMS, D. E., AUSTIN, P., DIAZ-MARRERO, A. R., SOEST, R. V., MATAINAHO, T., ROSKELLEY, C. D., ROBERGE, M. & ANDERSEN, R. J. 2005. Neopetrosiamides, peptides from the marine sponge Neopetrosia sp. that inhibit amoeboid invasion by human tumor cells. *Organic letters,* 7**,** 4173-4176.

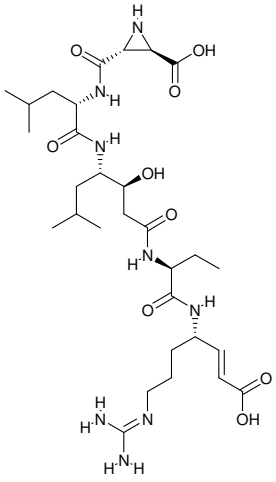
WILLIAMS, D. E., YU, K., BEHRISCH, H. W., VAN SOEST, R. & ANDERSEN, R. J. 2009. Rolloamides A and B, cytotoxic cyclic heptapeptides isolated from the Caribbean marine sponge Eurypon laughlini. *Journal of natural products,* 72**,** 1253-1257.

WILLIS, B. & ARYA, D. P. 2010. Triple Recognition of B-DNA by a Neomycin−Hoechst 33258−Pyrene Conjugate. *Biochemistry,* 49**,** 452-469.

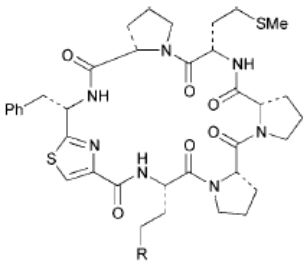
WOO, J.-K., JEON, J.-E., KIM, C.-K., SIM, C. J., OH, D.-C., OH, K.-B. & SHIN, J. 2013. Gombamide A, a Cyclic Thiopeptide from the Sponge Clathria gombawuiensis. *Journal of natural products,* 76**,** 1380-1383.

WÖRHEIDE, G., SOLÉ-CAVA, A. M. & HOOPER, J. N. 2005. Biodiversity, molecular ecology and phylogeography of marine sponges: patterns, implications and outlooks. *Integrative and Comparative Biology,* 45**,** 377-385.

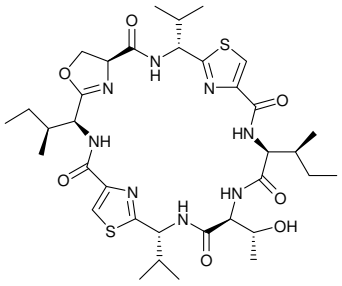
ZAMPELLA, A., SEPE, V., LUCIANO, P., BELLOTTA, F., MONTI, M. C., D'AURIA, M. V., JEPSEN, T., PETEK, S., ADELINE, M.-T., LAPRÉVÔTE, O., AUBERTIN, A.-M., DEBITUS, C., POUPAT, C. & AHOND, A. 2008. Homophymine A, an Anti-HIV Cyclodepsipeptide from the Sponge Homophymia sp. *The Journal of Organic Chemistry,* 73**,** 5319-5327.



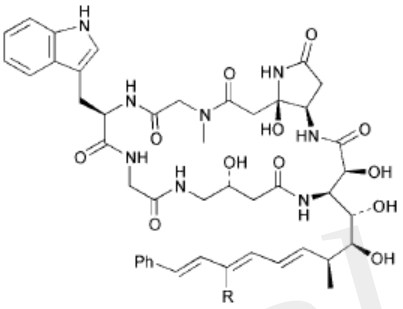
Miraziridine A (1)



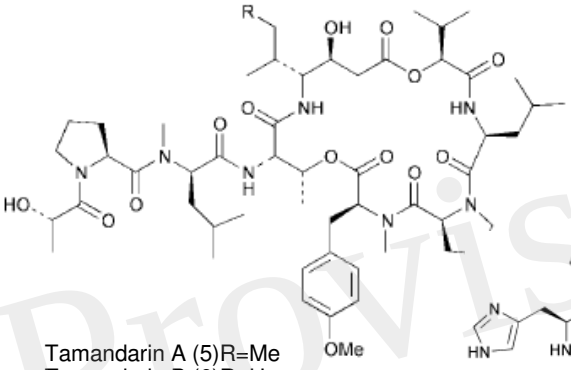
Haligramide A (2)(R)= SMe
Haligramide B (3)(R)= S(O)Me



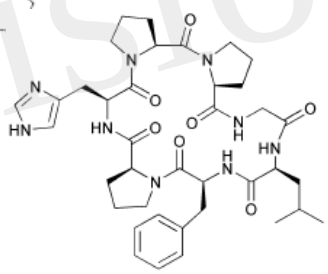
Prepatellamide A (4)



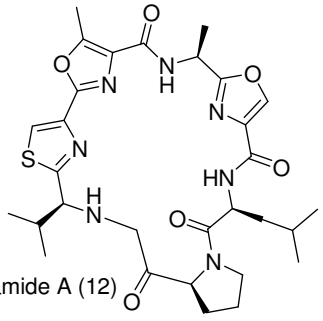
Microsclerodermin F (7)(R)= H
Microsclerodermin G(8)(R)= Me



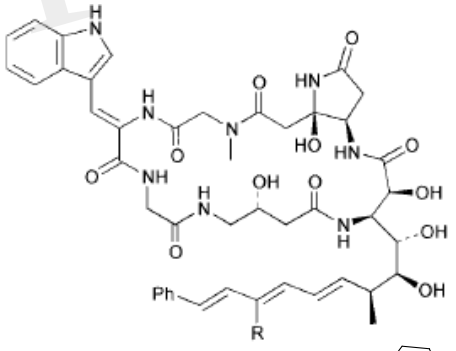
Tamandarin A (5)R=Me
Tamandarin B (6)R=H



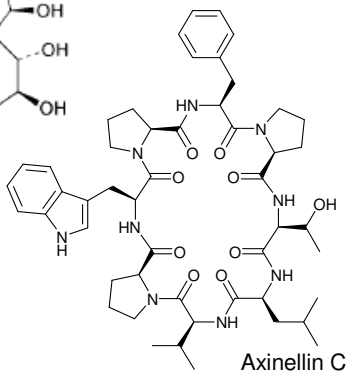
Wainunuamide (11)



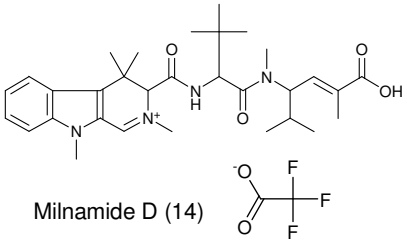
Leucamide A (12)



Microsclerodermin H (9)(R)= H
Microsclerodermin I (10)(R)= Me



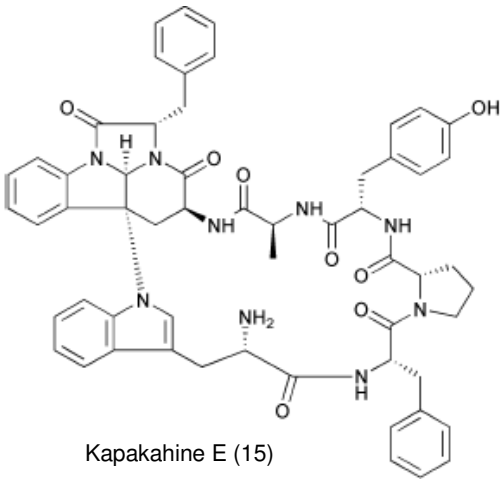
Axinellin C (13)



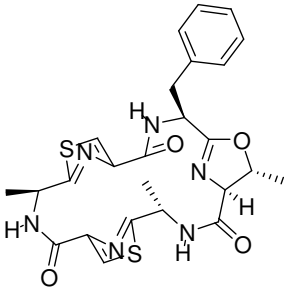
Milnamide D (14)

725

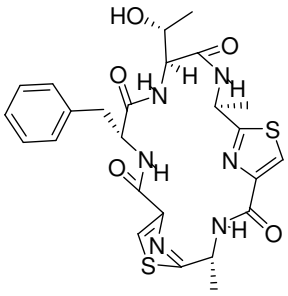
726 **Figure 1** Structures of anticancer non-ribosomal peptides (1–14)



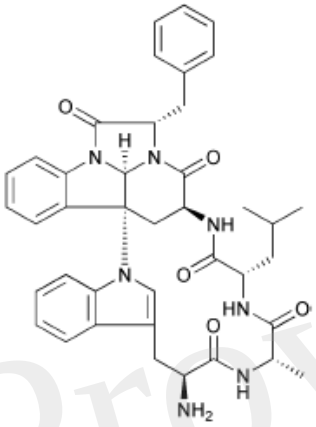
Kapakahine E (15)



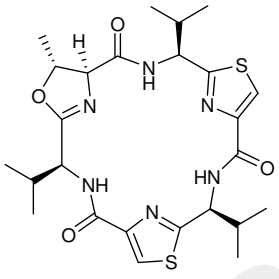
Didmolamide A (18)



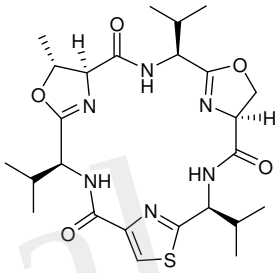
Didmolamide B (19)



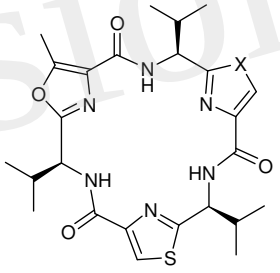
Kapakahine F (16)



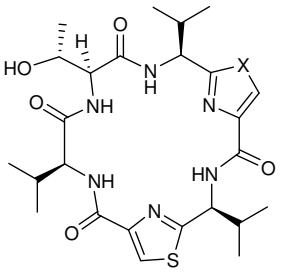
Bistratamide E (20)



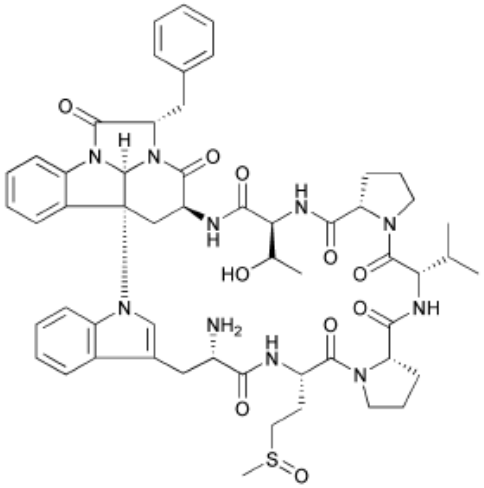
Bistratamide F(21)



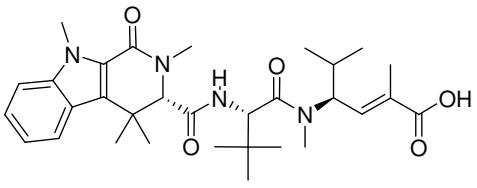
Bistratamide G(22) X=O
Bistratamide H(23) X=S



Bistratamide I(24) X=O
BistratamideJ(25) X=S



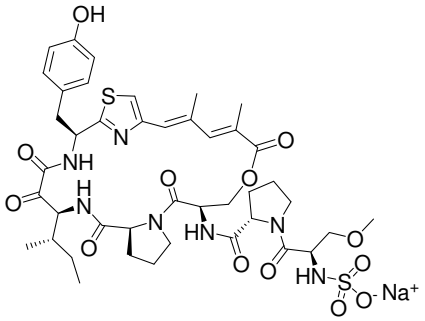
Kapakahine G (17)



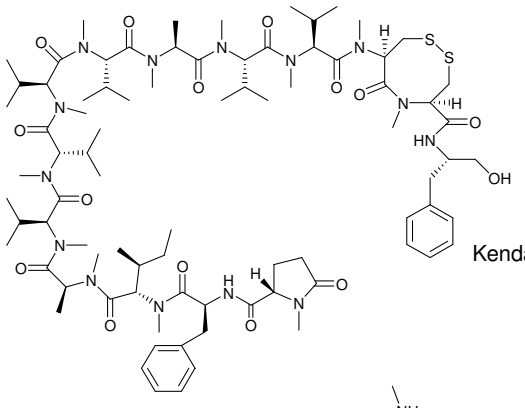
Milnamide C (26)

727

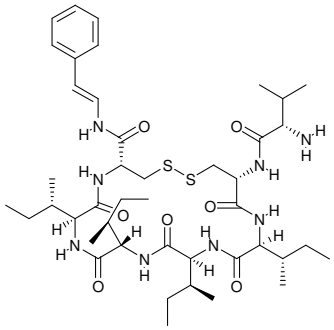
728 **Figure 2** Structures of anticancer non-ribosomal peptides (15–26)



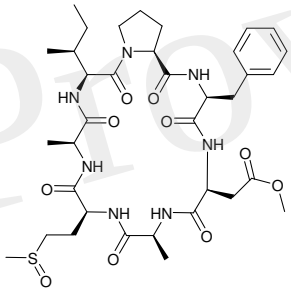
Scleritodermin A (27)



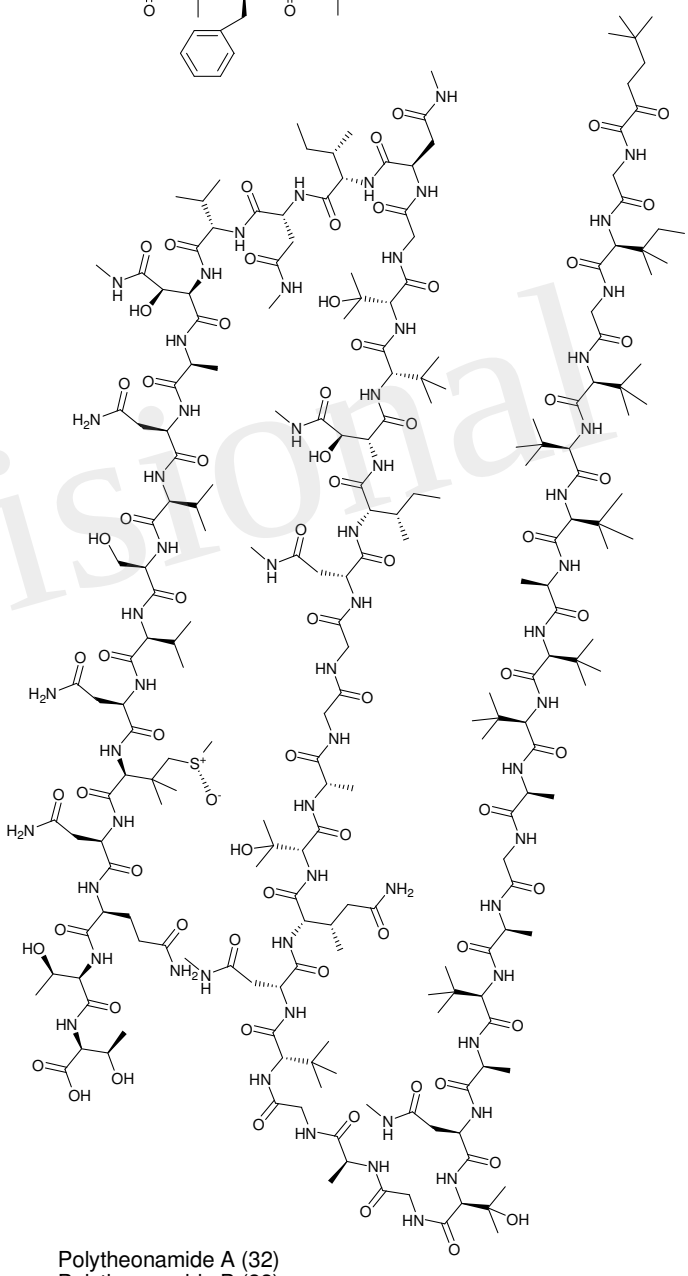
Kendarimide A (30)



Microcionamide A (28)E
Microcionamide B (29)Z



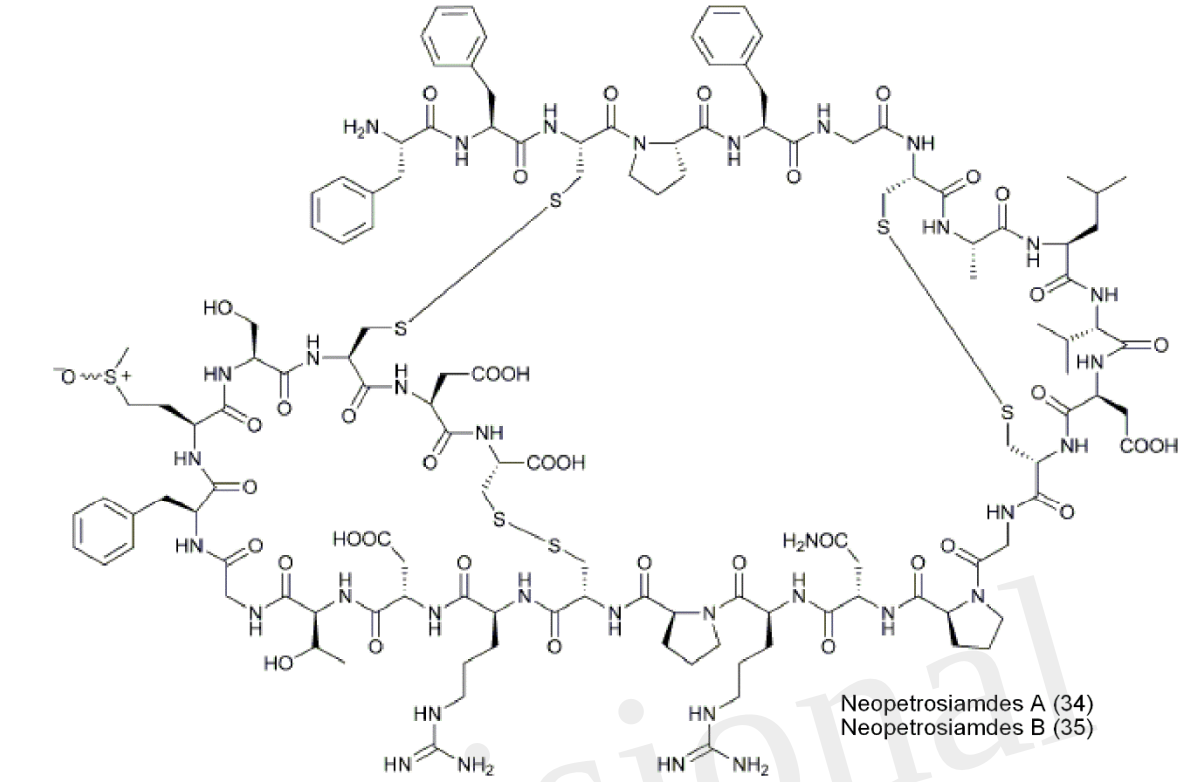
Phakellistatin 14 (31)



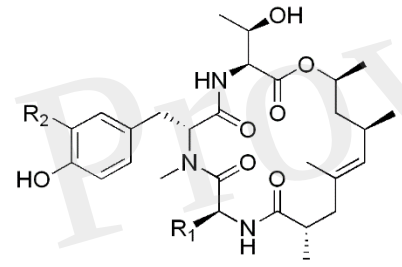
Polytheonamide A (32)
Polytheonamide B (33)

729

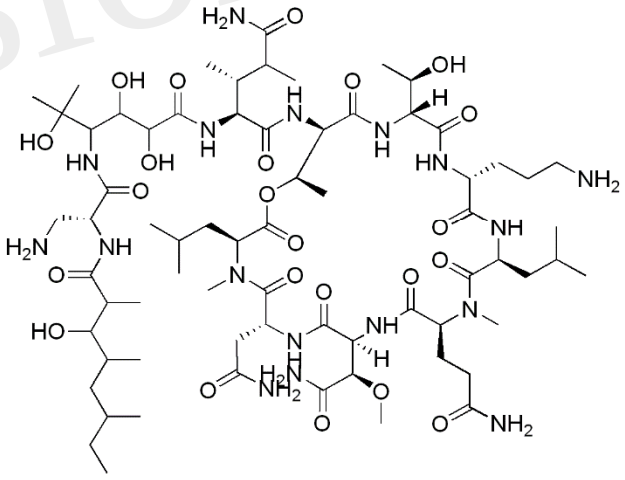
730 **Figure 3** Structures of anticancer non-ribosomal peptides (27–33)



Neopetrosiamdes A (34)
Neopetrosiamdes B (35)

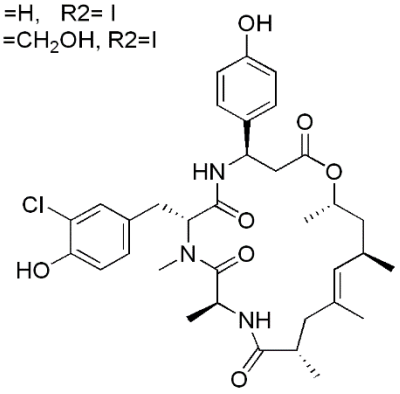


Seragamide A (36) R1=Me, R2=I
Seragamide B (37) R1=Me, R2=Br
Seragamide C (38) R1=Me, R2=Cl
Seragamide D (39) R1=H, R2= I
Seragamide E (40) R1=CH_2OH, R2=I



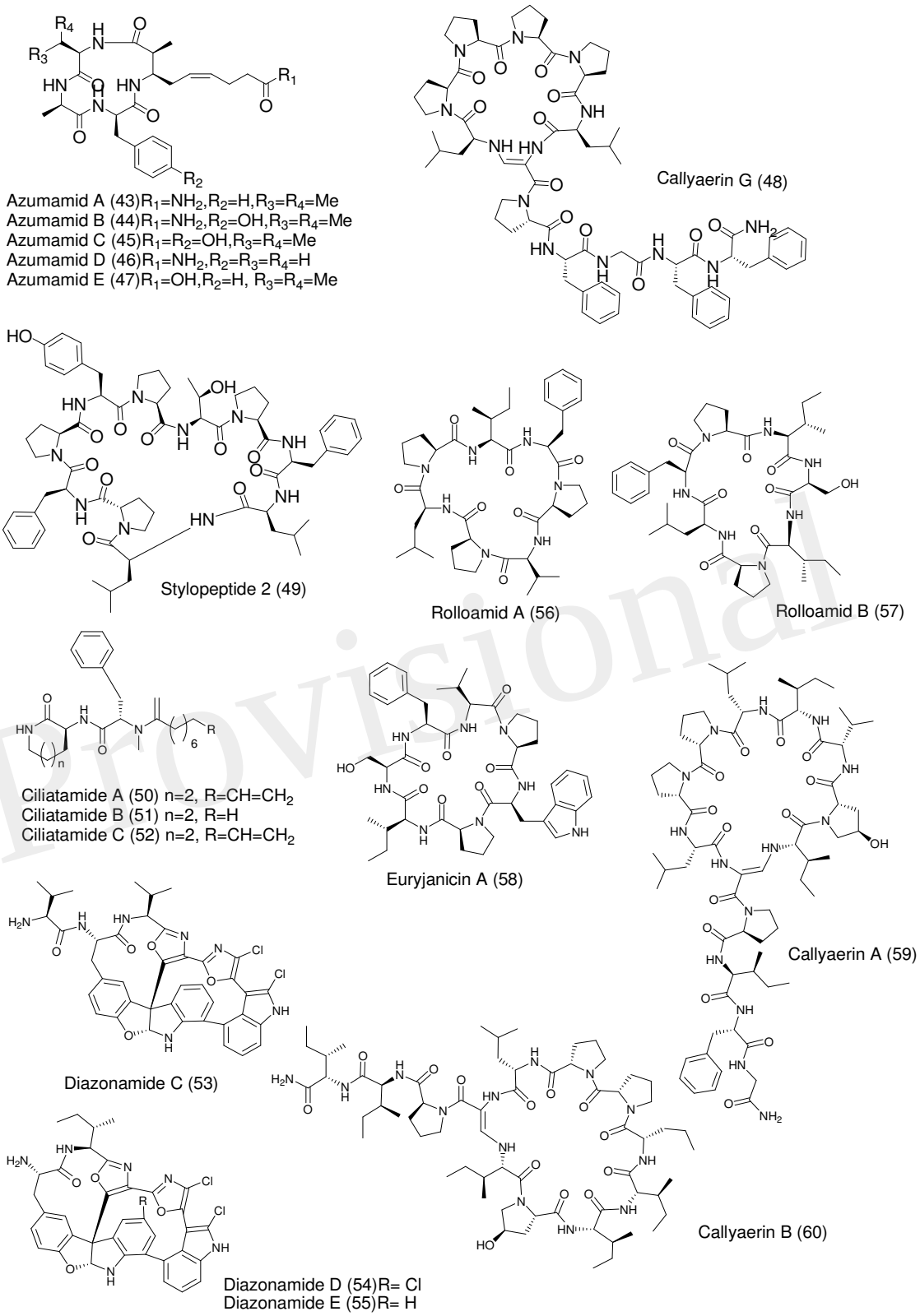
Theopapuamide (42)

Seragamide F (41)



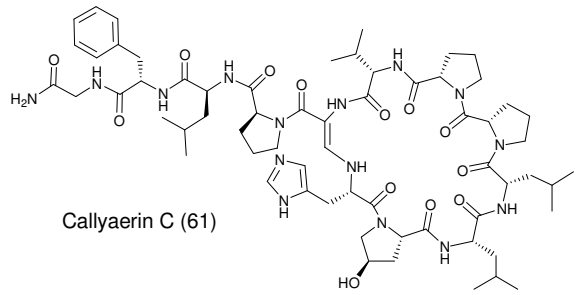
731

732 **Figure 4** Structures of anticancer non-ribosomal peptides (34–42)

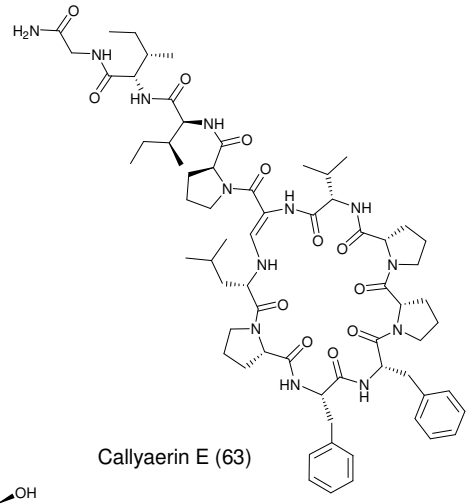


733

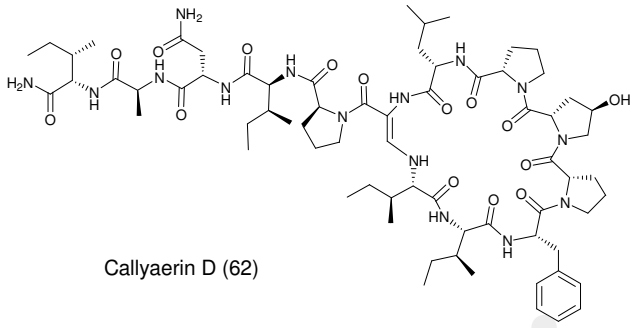
734 **Figure 5** Structures of anticancer non-ribosomal peptides (43–60)



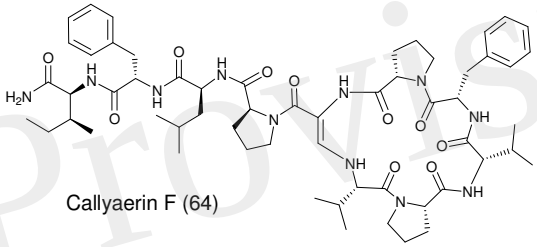
Callyaerin C (61)



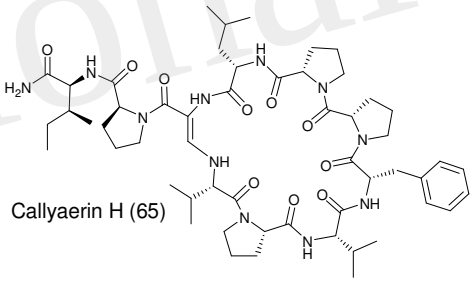
Callyaerin E (63)



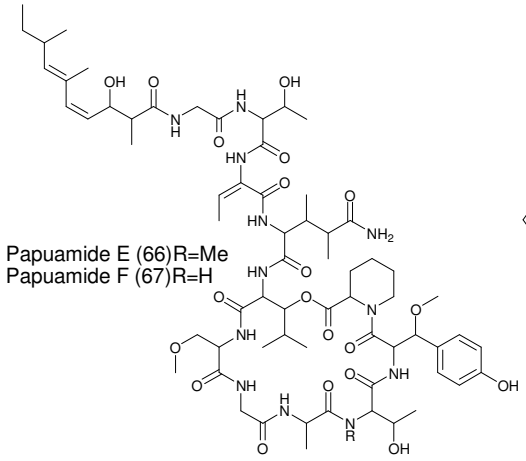
Callyaerin D (62)



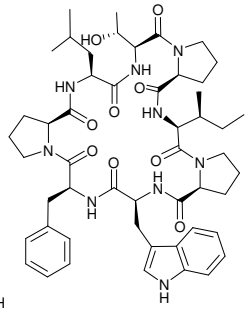
Callyaerin F (64)



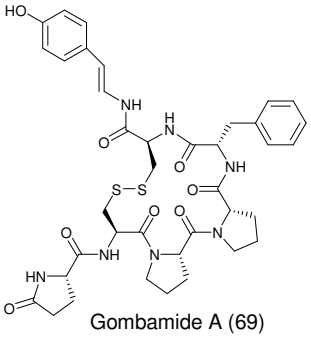
Callyaerin H (65)



Papuamide E (66)R=Me
Papuamide F (67)R=H



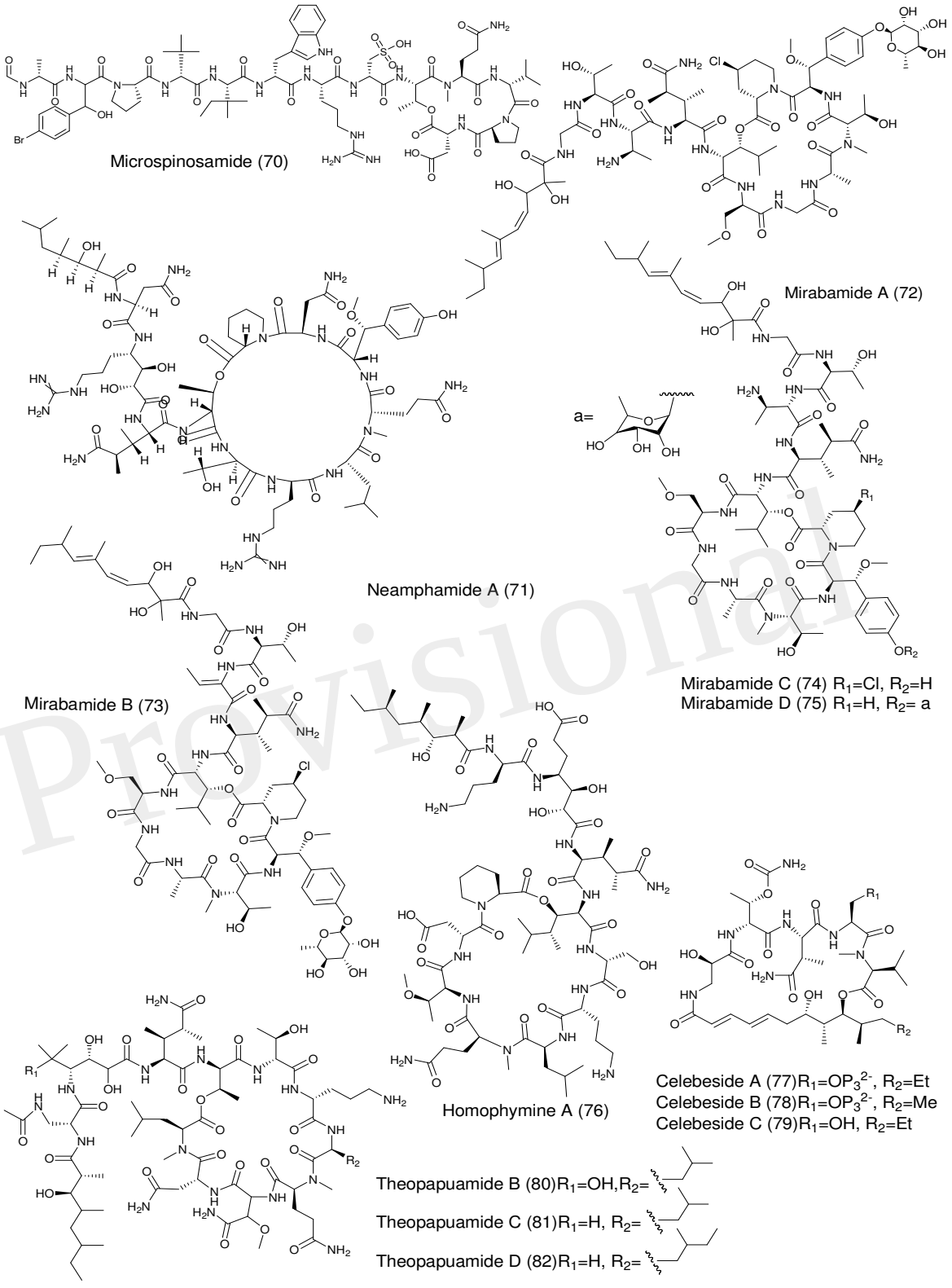
Stylissamide X (68)



Gombamide A (69)

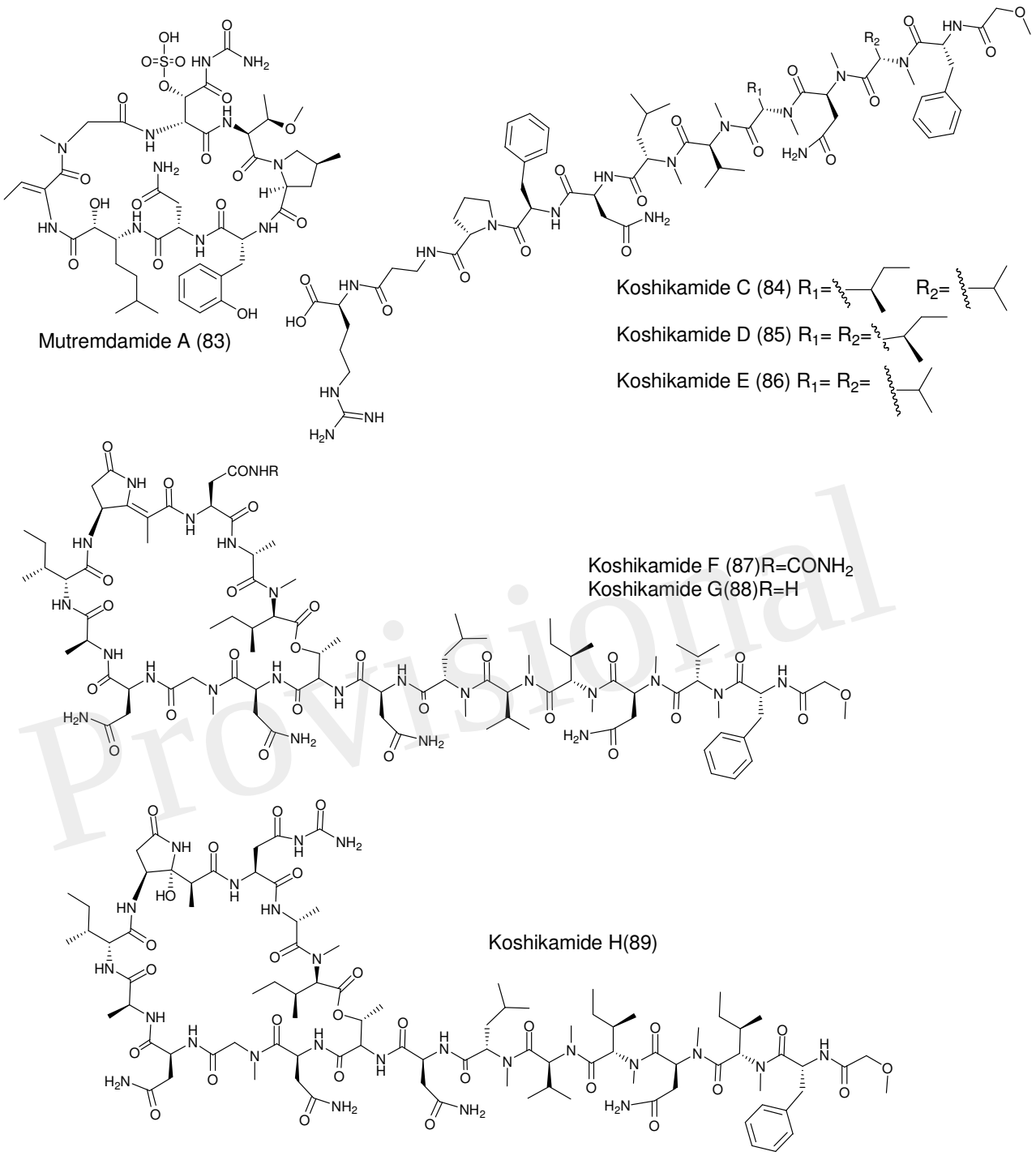
735

736 **Figure 6** Structures of anticancer non-ribosomal peptides (61–69)



737

738 **Figure 7** Structures of non-ribosomal peptides with anti-HIV activity (70–82)



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741 **Figure 8** Structures of non-ribosomal peptides with anti-HIV activity (83–89)

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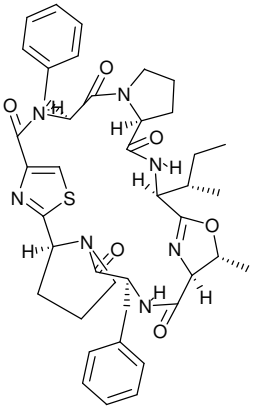
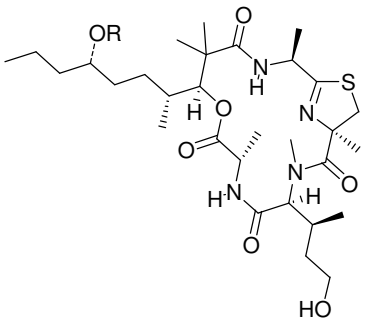
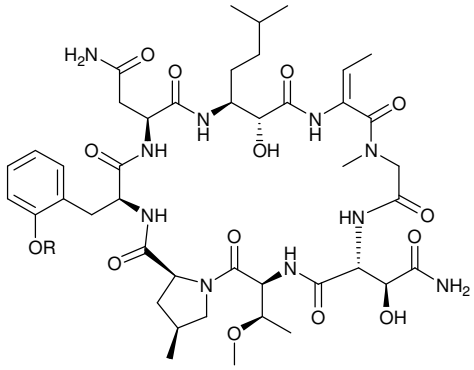


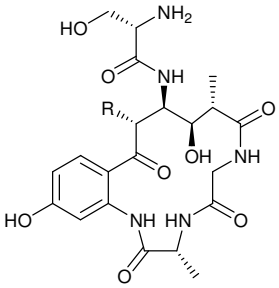
Ceratospongamide (90)



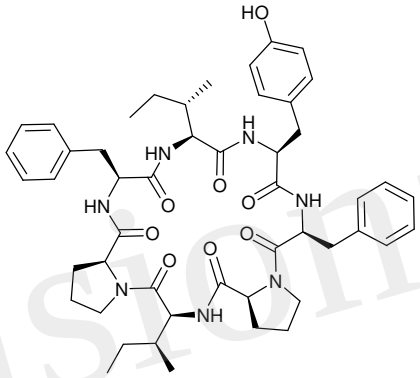
Halipeptin A (91) R= Me
Halipeptin B (92) R=H



Perthamide C (93)R=OH
Perthamide D (94)R=H



Solomonamide A (95)R=OH
Solomonamide B (96)R=H



Stylissatin A (97)

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744

745 **Figure 9** Structures of non-ribosomal peptides with anti-inflammatory activity (90–97)

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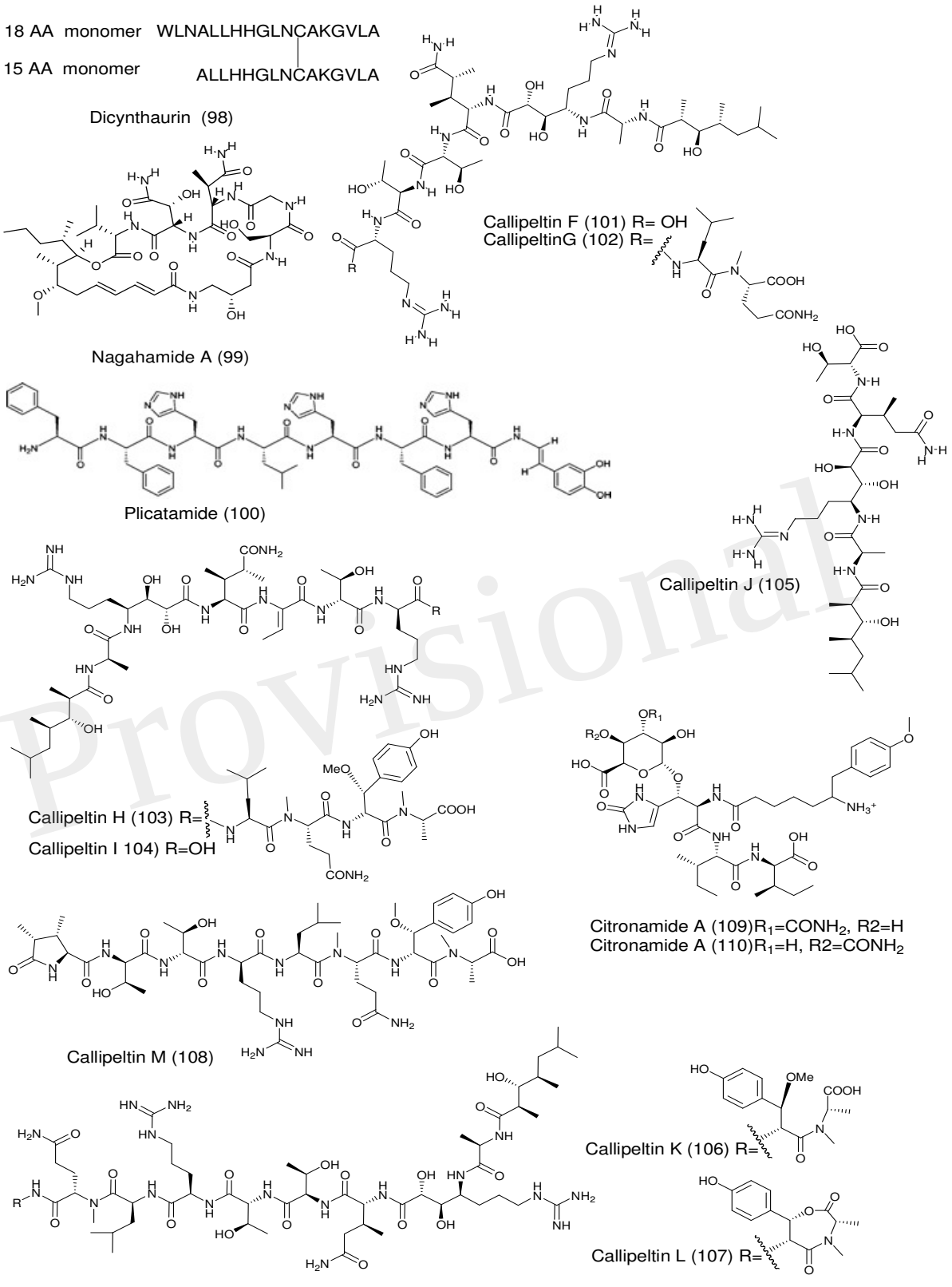
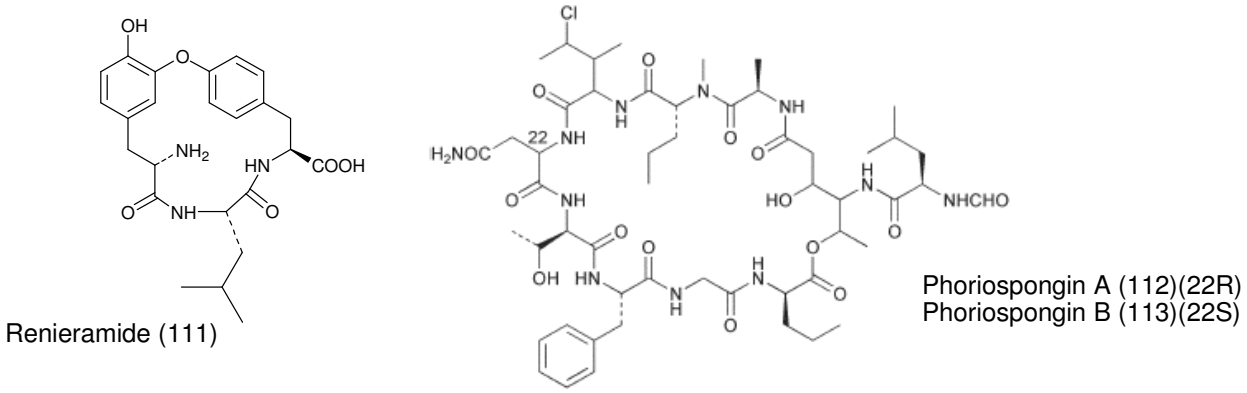


747

748 **Figure 10** Structures of antimicrobial non-ribosomal peptides (98–110)



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751 **Figure 11** Structures of non-ribosomal peptides with (98–110)