Chemical and Pharmacological Significance of Natural Guanidines from Marine Invertebrates

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Abstract: Natural Guanidines from marine invertebrates represent a group of bioactive secondary metabolites that revealed prominent pharmacological activities such as antimicrobial, antiproliferative, analgesic, and anticoagulant properties. Acyclovir (Zovirax®), the first guanidine-derived pharmaceutical for the treatment of herpes infections since late 1970s, was synthesized based on a marine arabinosyl nucleoside, spongosine. Recently, ziconotide (Prialt®), a synthetic form of the marine-derived peptide (ω-conotoxin MVIIA) comprising a guanidine moiety, has been approved for the treatment of chronic pain. This review surveys over 130 compounds of guanidine-containing secondary metabolites from marine invertebrates with emphasis on their pharmacological significance and structure-activity relationships.

Keywords: Guanidine, marine invertebrates, antimicrobial, antiproliferative, anticoagulant.

1. INTRODUCTION

Although the diversity of life in the terrestrial environment is extraordinary, the greatest biodiversity is in the world's oceans, with 34 of the 36 known phyla of life represented [1, 2]. Based on the chemical, biological, and ecological diversity of the marine ecosystem, the oceans are considered as unique resources for a diverse array of natural products. These natural products are produced primarily by marine invertebrates such as sponges, tunicates, bryozoans, molluscs, and also by marine bacteria and cyanobacteria. Exploration of marine natural products has contributed to the discovery of compounds showing potent activities including antiproliferative, analgesia, anti-inflammatory, and antiviral activities.

Recently, the first marine-derived compound that succeeded to enter the pharmaceutical market was ziconotide (ω-conotoxin MVIIA/Prialt®; Elan Pharmaceuticals, Fig. **1**), a peptide originally discovered in a tropical cone snail *Conus magus*, which was approved in the United States in December 2004 for the treatment of severe and chronic pain [3]. Then, in October 2007, trabectedin (ET-743/Yondelis®; Pharmamar, Fig. **1**), first isolated from the Caribbean tunicate *Ecteinascidia turbinata*, became the first marine anticancer drug approved in the European Union [3].

Natural guanidines represent a group of natural products with a wide distribution in the marine ecosystem. They are produced by a vast array of marine invertebrates, marine cyanobacteria in addition to terrestrial organisms. Guanidine alkaloids from marine invertebrates were first reviewed by Chevolot [4] and more recently in a series of reviews by Berlinck that included their occurrence in all natural sources [5-10].

This review attempts to survey the major guanidine-containing natural products including pyrimidine derivatives, acyclic guanidines, bromopyrrole, bromotyrosine and peptides, obtained recently from marine invertebrates with a particular attention placed on their occurrence, biological activities, and their potency to inspire for new drug leads.

Reviews on natural guanidines from marine invertebrates that highlight isolation, synthesis, and pharmacological properties, such as "Neurotoxic alkaloids: Saxitoxin and its analogues" [11], "Halogenated indole alkaloids from marine invertebrates" [12], "Variolins and related alkaloids" [13] and "Aplysinopsins - marine indole alkaloids: Chemistry, bioactivity and ecological significance" [14] have been recently published.

2. PYRIMIDINE DERIVATIVES

In 1994, the isolation and structural elucidation of the variolins were reported from the Antarctic sponge *Kirkpatrickia varialosa* in the Blunt, Munro, and Faulkner laboratories [15, 16]. Variolins are the first natural products, either terrestrial or marine, that feature a pyrido[3',2':4,5]pyrrolo [1,2-*c*]pyrimidine moiety bearing a heterocyclic substituent at C-5 in variolins A (**1**), B (**2**), and *N*(3')-methyltetrahydrovariolin B (**3**) (Fig. **2**). The naturally rare chemical skeleton of variolins has made them an interesting class of alkaloids from both structural and biogenetic viewpoints. Variolins are considered as guanidine-containing alkaloids in which the guanidine moiety is found in the guise of a 2-aminopyrimidine ring [17, 18].

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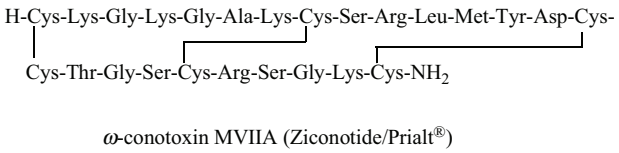
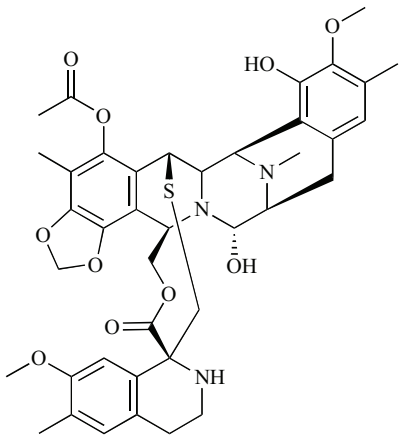


ω-conotoxin MVIIA (Ziconotide/Prialt®)



Trabectedin (ET-743/Yondelis®)

Fig. (1). Structures of *ω*-conotoxin MVIIA (ziconotide) and trabectedin (ET-743).

The isolated congeners include variolins A (**1**), B (**2**), *N*(3')-methyltetrahydrovariolin B (**3**), in addition to variolin D (**4**) which was considered as an artifact produced by oxidation of the variolins during the extraction process. From the initial isolation studies of variolins, they exhibited a potent cytotoxic activity against P388 murine leukemia cell line, with variolin B (**2**) as the most active congener (IC_{50} = 0.72 μM), whereas compounds **1** and **3** revealed only modest activities and variolin D (**4**) was completely inactive against the same cell line indicating that the presence of 2-aminopyrimidine moiety at C-5 is essential for activity. However, variolin B (**2**) proved to be more effective against Herpes simplex type I viruses, whereas it was inactive against a range of bacteria and fungi [15, 16].

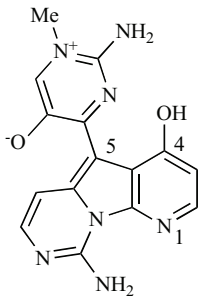
In 1996, variolin B (**2**) was found to be an efficient activator of apoptosis, showing potent cytotoxic activity against a variety of human cancer cell lines, including those overexpressing *p*-glycoprotein (*pgp*), a cell efflux pump responsible for the resistance of cancerous cells to multiple chemotherapy agents. These findings have placed a considerable interest on the synthesis of variolins which lead to the first total synthesis of variolin B (**2**) in 2001 [19, 20], in addition to the synthetic derivative, deoxyvariolin B (**5**) [21-23]. Cytotoxicity studies indicated that both **2** and **5** possessed similar levels of cytotoxic activities with IC_{50} values of 50-100 μM against a variety of cell lines [13]. However, further in-depth studies investigating the mechanism of cytotoxic activity have preferentially utilized deoxyvariolin B (**5**) because of its improved stability and water solubility compared to the natural product.

Both variolin B (**2**) and deoxyvariolin B (**5**) were found to affect cell cycle progression through inhibiting cyclin-dependent kinases with IC_{50} values in the micromolar range [13]. Further understanding of the interaction between variolin B (**2**) and a variety of cylcin-dependent kinases was provided by Meijer and co-workers [24, 25]. The results of this assay (Table **1**) revealed a preferential inhibition of CDK1 and CDK2 over CDK4 and CDK7 by variolin B. However, the inhibition of CDK9 (IC_{50} = 26 nM) was found to be more pronounced than that of either CDK1 (IC_{50} = 60 nM) or CDK2 (IC_{50} = 80 nM).

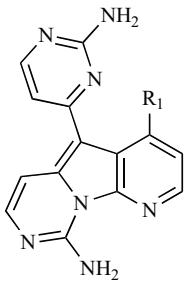
Meridianins are another example of aromatic guanidine alkaloids which were first isolated from the marine ascidian

Table 1. Effects of Variolin B (2) and Merialins (13-20) on Protein Kinases (IC_{50} in μM) [25]

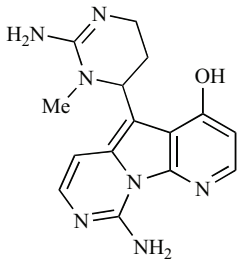
Compd	CDK1/cyclin B	CDK2/ cyclin A	CDK5/p25	CDK9/ cyclin T	GSK-3*α/β*	CK1	DYRK1A
Variolin B (**2**)	0.06	0.08	0.09	0.026	0.07	0.005	0.08
Merialin 1 (**13**)	0.78	0.09	0.51	0.026	0.63	0.2	0.13
Merialin 2 (**14**)	0.057	0.018	0.05	0.018	0.40	0.05	0.035
Merialin 3 (**15**)	0.17	0.011	0.17	0.006	0.23	0.2	0.029
Merialin 4 (**16**)	0.01	0.007	0.005	0.007	0.03	0.1	0.032
Merialin 5 (**17**)	0.007	0.003	0.003	0.0056	0.025	0.2	0.037
Merialin 8 (**18**)	1.20	1.80	5.50	1.20	4.60	2.30	1.20
Merialin 10 (**19**)	0.24	0.06	0.23	0.05	2.00	3.00	0.13
Merialin 11 (**20**)	2.20	1.30	0.68	1.00	30.0	1.30	0.3



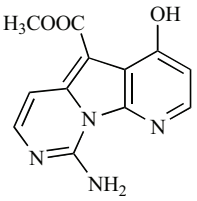
Variolin A (**1**)



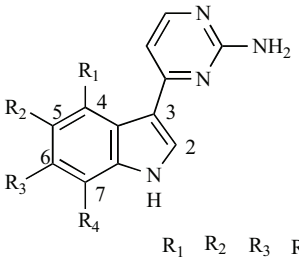
Variolin B (**2**) OH
Deoxyvariolin B (**5**) H



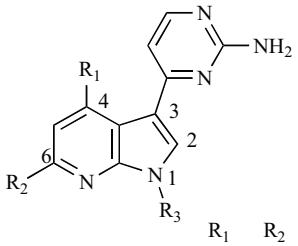
N(3')-Methyltetrahydrovariolin B (**3**)



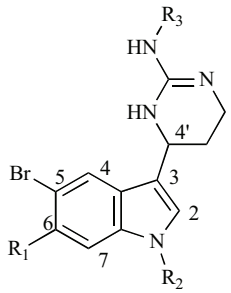
Variolin D (**4**)



	R_1	R_2	R_3	R_4
Meridianin A (**6**)	OH	H	H	H
Meridianin B (**7**)	OH	H	Br	H
Meridianin C (**8**)	H	Br	H	H
Meridianin D (**9**)	H	H	Br	H
Meridianin E (**10**)	OH	H	H	Br
Meridianin F (**11**)	H	Br	Br	H
Meridianin G (**12**)	H	H	H	H



	R_1	R_2	R_3
Meriolin 1 (**13**)	H	H	H
Meriolin 2 (**14**)	OH	H	H
Meriolin 3 (**15**)	OMe	H	H
Meriolin 4 (**16**)	OEt	H	H
Meriolin 5 (**17**)	OPr	H	H
Meriolin 8 (**18**)	OH	H	Me
Meriolin 10 (**19**)	Cl	H	H
Meriolin 11 (**20**)	H	Br	H



	R_1	R_2	R_3
Aplicyanin A (**21**)	H	H	H
Aplicyanin B (**22**)	H	H	Ac
Aplicyanin C (**23**)	H	OMe	H
Aplicyanin D (**24**)	H	OMe	Ac
Aplicyanin E (**25**)	Br	OMe	H
Aplicyanin F (**26**)	Br	OMe	Ac

Fig. (2). Structures of **1**-**26**.

Aplidium meridianum [26]. Structurally, meridianins share a brominated and/or hydroxylated indole nucleus substituted at C-3 by a 2-aminopyrimidine moiety. Seven congeners, meridianins A-G (**6**-**12**, Fig. **2**) have been reported to date. Meridianins have been described as potent inhibitors of various protein kinases with meridianins B (**7**) and E (**10**) as the most potent congeners (Table **2**) [27].

Protein phosphorylation constitutes one of the major mechanisms regulating most aspects of cell life, whereas abnormal phosphorylation is a cause or a consequence of diseases. Among the 518 protein kinases encoded in the human genome, cyclin-dependent kinases (CDK) have attracted considerable interest due to their role in many essential physiological pathways and numerous abnormalities in multiple human diseases, especially cancer and neurodegenerative diseases such as *Alzheimer*'s and *Parkinson*'s diseases [24, 25, 28].

Investigation of the structure-activity relationships (SAR) of meridianins revealed that a bromine substitution on position 7 of the indole moiety and a hydroxyl on position 4 provide the best inhibitory activity against CDK1 and CDK5 (Table **2**). A single bromine substitution at position 5 or 6 significantly increases the inhibitory activity while two bromine atoms as in meridianin F (**11**) partially reduce the inhibitory potency. Shifting the 2-aminopyrimidine from position 3 to position 2 inactivates the inhibitory activity as in isomeridianins C and G compared to their respective congeners meridianins C (**8**) and G (**12**). The hydroxyl group in position 4 seems to be important for the inhibitory activity, but much less so when a bromine substitution is present (compare meridianins B and D).

In cytotoxicity assay against U937 (myeloid leukemia) and LMM3 (murine mammalian adenocarcinoma) cell lines, meridianins C (**8**), E (**10**) and F (**11**) were the most potent congeners with IC_{50} values of 2.7 and 9.3 μM for **8**; 9.8 and 11.1 μM for **10**; and 0.2 and 1.4 μM for **11**, respectively [27].

The structural skeleton of variolins and meridianins has inspired the synthesis of a new class of 7-azaindole-containing analogues, meriolins (**13**-**20**, Fig. **2**), which feature a 3-(pyrimidin-4-yl)-7-azaindole core. Meriolins displayed inhibitory activity towards CDKs (especially CDK2 and CDK9) when tested, together with variolin B (**2**) as a reference, against seven purified protein kinases (Table **1**). The complex structures of pCDK2/cyclin A with each of variolin B (**2**), meriolin 3 (**15**), and meriolin 5 (**17**) have been determined by X-ray crystallography, which disclosed that they bind to the ATP-binding site of the kinase, but in different orientations [13, 24, 25]. SAR studies together with the crystal structure have provided some mechanistic explanation of meriolins on their CDK target [25]. The two nitrogens within the pyrrolo[2,3-*b*]pyridine ring in meriolin 5

Table 2. Effects of Meridianins (6-12) on the Activity of a Selection of Protein Kinases (IC_{50} in μM) [27]

Compd	CDK1/ cyclin B	CDK5/p25	PKA	PKG	GSK-3-β	CK1
Meridianin A (**6**)	2.50	3.00	11.00	200.00	1.30	nt
Meridianin B (**7**)	1.50	1.00	0.21	1.00	0.50	1.00
Meridianin C (**8**)	3.00	6.00	0.70	0.40	2.00	30.00
Meridianin D (**9**)	13.00	5.50	1.00	0.80	2.50	100.00
Meridianin E (**10**)	0.18	0.15	0.09	0.60	2.50	0.40
Meridianin F (**11**)	20.00	20.00	3.20	0.60	2.00	nt
Meridianin G (**12**)	150.00	140.00	120.00	400.00	350.00	nt

nt: not tested.

(**17**) bind *via* hydrogen bonding to the CDK2 hinge region. Therefore, these positions are anticipated to tolerate little variation as confirmed by the loss of potency upon addition of a methyl group at the pyrrole N*H* (compare meriolins 2 and 8). In case of meriolin 11 (**20**), addition of a bromine atom at C-5 leads to a drop in inhibitory activity for almost all tested protein kinases, in particular against CDK9 and GSK-3, while CDK1, CDK2, and CDK5 are less affected by the bromine substitution of the inhibitor. Moreover, the addition of a chlorine atom at C-4 in meriolin 10 (**19**) leads to a decreased potency compared to the non-halogenated meriolin 1 (**13**). The hydroxyl substituent at C-4 results in an increase in inhibitory activity against all tested protein kinases, whereas alkylation of this hydroxyl group similarly increased the inhibitory activity proportional to the alkyl chain length (compare meriolins 1-5). These observations conclusively suggest that variolins, meridianins, and meriolins constitute new CDK inhibitory scaffold with promising antiproliferative activity.

Aplicyanins A-F (**21**-**26**, Fig. **2**) represent a recently reported family of aromatic guanidine alkaloids which were isolated from the Antarctic tunicate *Aplidium cyaneum* [29]. In contrast to the planar pyrimidine ring in the meridianins, aplicyanins (**21**-**26**) contain a 6-tetrahydropyrimidine substituent at C-3 which imparts a stereocenter at C-4'. Some aplicyanin congeners exhibited significant cytotoxic activity when tested against three human tumor cell lines: A549 lung, HT-29 colon, and MDA-MB-231 breast cancer cells and they also revealed antimitotic activity [29]. These bioactivities have placed higher scientific interest toward the chemical synthesis of aplicyanins which resulted in a successful total synthesis of (±) aplicyanins A, B, and E in addition to 17 further analogues as well [30]. All natural and synthetic aplicyanins were assessed for both cytotoxicity and antimitotic activities. Results (Table **3**) demonstrated that both cytotoxicity and antimitotic properties in the submicromolar range were found for aplicyanins B (**22**), D (**24**), and F (**26**), whereas aplicyanins A (**21**) and C (**23**) proved to be inactive at the highest concentrations tested and aplicyanin E (**25**) displayed only mild cytotoxic properties [29].

These results clearly suggest a key role for the presence of the acetyl group with regard to the biological activity of the aplicyanins. However, (±)-aplicyanin B was as active as its corresponding natural product in all three tested cell lines, the racemic (±)-aplicyanin E maintained activity only towards the MDA-MB-231 cell line which may imply that one enantiomer is more active than the other. Interestingly, racemic (±)-aplicyanin A exhibited activity in the submicro-

Table 3. Cytotoxicity of Aplicyanins to Three Human Tumor Cell Lines (GI_{50} Values Reported in μM) and Antimitotic Activity (IC_{50}, μM) [29, 30]

Compound	Cell Lines			Antimitotic Activity
	A-549	HT-29	MDA-MB-231	
Aplicyanin B (**22**)	0.66	0.39	0.42	1.19
Aplicyanin D (**24**)	0.63	0.33	0.41	1.09
Aplicyanin E (**25**)	8.70	7.96	7.96	nt
Aplicyanin F (**26**)	1.31	0.47	0.81	0.18–0.036
(±)-Aplicyanin A	0.27	0.11	0.27	nt
(±)-Aplicyanin B	0.51	0.33	0.98	nt
(±)-Aplicyanin E	na	na	10.9	nt

nt: not tested; na: not active.

molar range, despite the inactivity of the corresponding naturally occuring congener (Table **3**) [30].

3. ACYCLIC GUANIDINES

Tubastrine (**27**, Fig. **3**) is the parent compound of this group of marine natural guanidines which was firstly isolated from the Okinawan hard coral *Tubastraea aurea* and showed antiviral activity against Herpes simplex virus [31]. Then, it has been isolated from the ascidian *Dendrodoa grossularia* collected off Red Nev, Orkney Islands (UK) as an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase [32]. Recently, tubastrine was isolated as monomer together with five dimer congeners, orthidines A-E (**28**-**32**), from the New Zealand ascidian *Aplidium orthium* [33].

Orthidines A-E (**28**-**32**, Fig. **3**) together with tubastrine (**27**) were tested for anti-inflammatory activity. Results revealed that tubastrine and all orthidines, except orthidine D (**31**), inhibited the *in vitro* production of superoxide by phorbol-12-myristate-13-acetate (PMA)-stimulated human neutrophils in a dose dependent manner with IC_{50}'s of 10-36 μM and this was also associated with *in vivo* inhibition (30-70%) of superoxide production by neutrophils in a murine model of gouty inflammation at a dose of 25 μmol/kg [33].

Recently, leptoclinidamines A-C have been reported as three new indole alkaloids from the Australian ascidian *Leptoclinides durus* [34]. Both leptoclinidamines A (**33**) and B (**34**) (Fig. **3**) feature an indoleglyoxylic acid attached to an L-arginine while the third congener comprises the naturally rare 1,3-dimethyl-5-(methylthio)histidine attached to a 6-bromoindole-3-carboxylic acid. Leptoclinidamines A-C were assessed for antimalarial, antitrypanosomal, and cytotoxic activities, but none of them was found to be bioactive [34].

4. APLYSINOPSINS

Aplysinopsin (**35**, Fig. **4**) was firstly isolated by Kazlauskas and co-workers in 1977 from eight Indo-Pacific sponge species of the genus *Aplysinopsis* [35]. Aplysinopsins are widely distributed in the Pacific, Indonesia, Caribbean, and Mediterranean regions. Structurally, aplysinopsins (**35**-**46**, Fig. **4**) comprise a 6-bromoindole moiety, and an iminoimidazolidinone or imidazolidinedione system. They mainly differ in the bromination pattern of the indole ring, either at C-5, C-6 or both, the structure of the iminoimidazolidinone ring, including the number and pattern of *N*-methylation, and the existence and configuration of the C-8-C-1' double bond either (*Z*)- or (*E*)-isomers, however, it has been observed that (*Z*)-aplysinopsins are generally less abundant than the (*E*)-isomers [36, 37]. Aplysinopsin-like dimers such as tubastrindoles A-C (**47**-**49**, Fig. **4**) [38] and 6-bromo-2'-de-*N*-methylaplysinopsin dimer (**50**, Fig. **4**) [39] have also been reported as marine natural products from two different sponge species of the genus *Tubastraea*.

Aplysinopsins, especially 6-bromoaplysinopsin (**39**), exhibit cytotoxicity toward tumor cell lines, in addition to other activities such as antiplasmodial and antimicrobial activity, as for compounds **35**, **38** and **39** and the dimer **50** [14]. However, effects related to neurotransmission modulation pose the most significant pharmacological property of aplysinopsins which potentially influence monamine oxidase (MAO) and nitric oxide synthase (NOS) activities in addition to modulating serotonin (5HT) receptors [14].

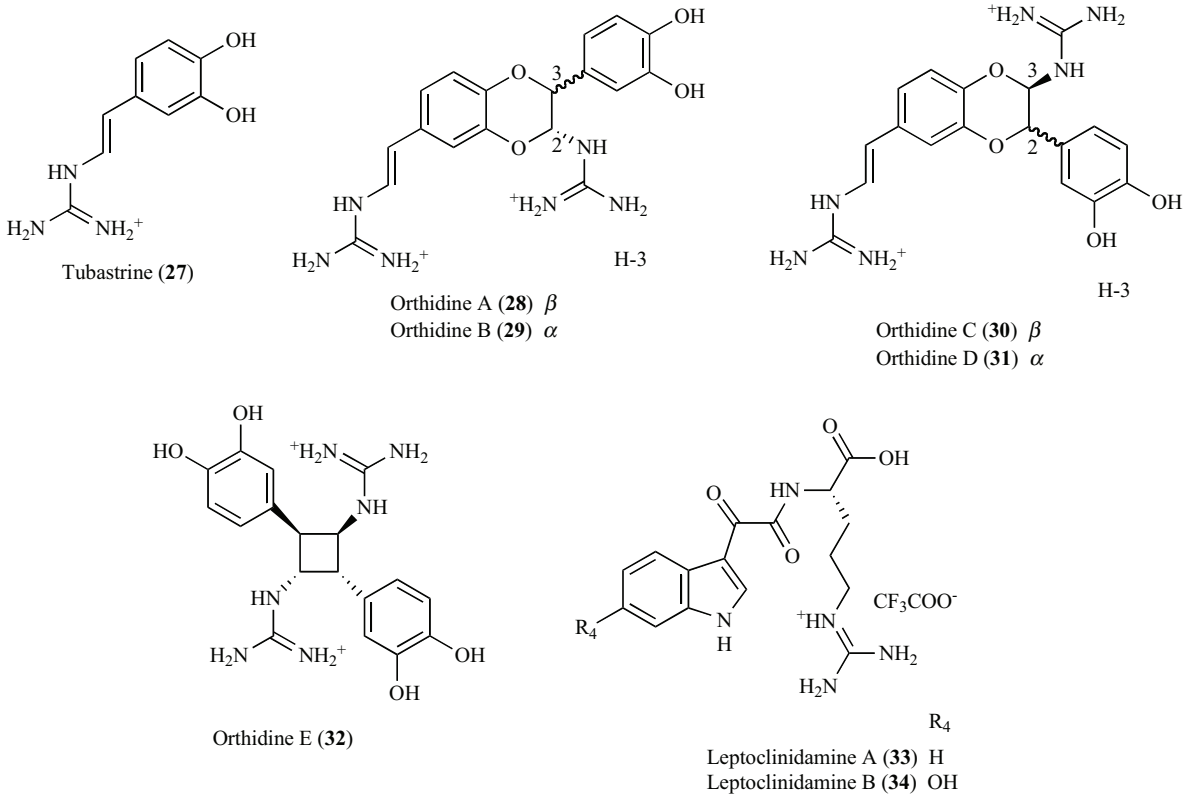
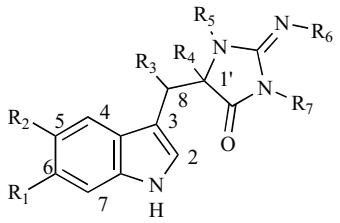
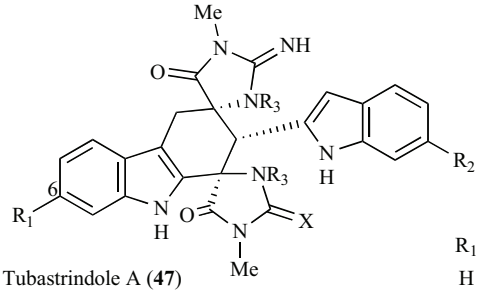


Fig. (3). Structures of **27**-**34**.



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Aplysinopsin (**35**)	H	H	$\Delta^{8,1'}$		Me	H	Me
N-3'-methylaplysinopsin (**36**)	H	H	$\Delta^{8,1'}$		Me	Me	Me
N-3'-ethylaplysinopsin (**37**)	H	H	$\Delta^{8,1'}$		Me	Et	Me
6-Bromo-2'-de-*N*-methylaplysinopsin (**38**)	Br	H	$\Delta^{8,1'}$		H	H	Me
6-Bromoaplysinopsin (**39**)	Br	H	$\Delta^{8,1'}$		Me	H	Me
6-Bromo-4'-de-*N*-methylaplysinopsin (**40**)	Br	H	$\Delta^{8,1'}$		Me	H	H
6-Bromo-4'-demethyl-3'-*N*-methylaplysinopsin (**41**)	Br	H	$\Delta^{8,1'}$		H	Me	Me
5,6-Dibromo-2'-demethylaplysinospin (**42**)	Br	Br	$\Delta^{8,1'}$		H	H	Me
6-Bromo-1',8-dihydroaplysinopsin (**43**)	Br	H	H	H	Me	H	Me
6-Bromo-1'-hydroxy-1',8-dihydroaplysinopsin (**44**)	Br	H	H	OH	Me	H	Me
6-Bromo-1'-methoxy-1',8-dihydroaplysinopsin (**45**)	Br	H	H	OMe	Me	H	Me
6-Bromo-1'-ethoxy-1',8-dihydroaplysinopsin (**46**)	Br	H	H	OEt	Me	H	Me



	R_1	R_2	R_3	X
Tubastrindole A (**47**)	H	Br	Me	NH
Tubastrindole B (**48**)	H	H	Me	NH
Tubastrindole C (**49**)	H	H	Me	O
6-Bromo-2'-de-*N*-methylaplysinopsin dimer (**50**)	Br	Br	H	NH

Fig. (4). Structures of **35**-**50**.

6-Bromo-2'-de-*N*-methylaplysinopsin (**38**) and 6-bromoaplysinopsin (**39**), isolated from the Jamaican sponge *Smenospongia aurea*, displaced high-affinity [^{3}H] antagonistic properties against cloned human serotonin 5-HT_2 receptor subtypes, whereas **38** showed more than 40-fold selectivity for the 5-HT_{2C} ove the 5-HT_{2A} receptor subtypes [40].

Structure-activity comparisons of the aplysinopsins reveal a role of the R_1, R_5, and R_6 functional groups at positions 6, 2', and 3', respectively, with regard to binding to human 5-HT_2 receptors. First, the length of the alkyl chain at R_6 appears to be important for aplysinopsins binding to serotonin receptors. For example, compounds **36** and **37** are identical except that *N*-3'-ethylaplysinopsin (**37**) has an ethyl group at the R_6 position and it has measurable binding activity, while *N*-3'-methylaplysinopsin (**36**) has no detectable binding activity. Second, the bromination at position R_1 seems important not only for binding activity but also for their selective binding to the 5-HT_{2C} receptor substype. Third, methylation at the R_5 position facilitates selective binding to the 5-HT_{2A} receptor subtype. However, more compounds will be required to clearly define these SARs [40].

5. BROMOPYRROLE DERIVATIVES

Bromopyrrole guanidine-containing alkaloids comprise a group of marine natural products produced particularly by marine sponges. Oroidin (**51**, Fig. **5**), the parent compound of this group, was first reported from the marine sponge *Agelas oroides* in 1971 [41] and it is considered as the key precursor for this group, since many bromopyrrole alkaloids with pyrrole-imidazole unit can be considered as metabolic derivatives of the $C_{11}N_5$ skeleton of oroidin (**51**).

Since the first report of oroidin (**51**) in 1971 to date, more than 150 further bromopyrrole alkaloids, with a wide variety of structures and interesting bioactivities, have been isolated from more than twenty different sponge taxa from different genera belonging mainly to the families Agelasidae, Axinellidae, and Halichondridae [42]. Their deterrence against predators is of ecological significance as revealed for the Caribbean reef sponges of the genus *Agelas* [43, 44].

Bromopyrrole guanidine-containing derivatives are of interest due to their potential pharmacological activities including antiproliferative, antimicrobial, and immunosuppressive properties which have drawn attention of organic chem-

ists towards their total syntheses especially during the last decade. These synthetic efforts resulted in successful total syntheses of many bromopyrrole alkaloids such as dimeric pyrrole-imidazole alkaloids including sceptrin, oxysceptrin and ageliferin [45]; nagelamides D [46] and E [45]; and hymenialdisine analogues [47].

Hymenidin (2-debromooroidin) (**52**), clathrodin (2,3-debromooroidin) (**53**), and sventrin (pyrrole *N*-methyloroidin) (**54**) (Fig. **5**) were reported from an Okinawan marine sponge of the genus *Hymeniacidon* [48], from the Caribbean sponges *Agelas clathrodes* [49], and *A. sventres* [50], respectively. The bromination pattern of the pyrrole moiety was found to influence the bioactivities of these compounds (*e.g.* in the feeding assay, hymenidin (2-debromooroidin) (**52**) showed lower deterrence against fishes as compared to oroidin) [51].

N-methylation of pyrrole moiety in sventrin (**54**) reduced fish feeding deterrency [50]. The reduction of voltage-dependent calcium elevation in PC12 cells was found to be directly proportional to the number of bromine atoms associated with the pyrrole ring in oroidin and hymenidin [52]. In addition, oroidin (**51**), hymenidin (**52**), and clathrodin (**53**) exhibited potential anticholinergic and antiserotonergic activities [48, 50].

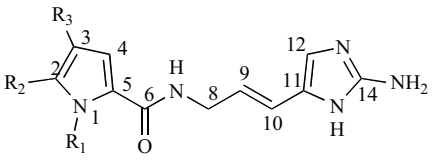
Dispacamides A-D (**55**-**58**, Fig. **5**) were purified from four different species of the genus *Agelas* namely *A. longissima*, *A. clathrodes*, *A. conifer*, and *A. dispar* [53, 54]. Dispacamides feature an alkylidene glycocyamidine formed by oxidation of the 2-aminoimidazole moiety in oroidin. Dispacamide A (**55**) and B (**56**) differ from oroidin (**51**) and hymenidin (**52**), respectively, regarding both the presence of an aminoimidazolone moiety and the position of the double-bond in the amine side chain. Compounds (**55** and **56**) were inactive with regard to anticholinergic or antiserotonergic activity.

On the other hand, all dispacamides showed a pronounced *in vivo* antihistaminic activity on the guinea pig ileum through a reversible non-competitive binding to histamine receptors, with dispacamide A (**55**) being the most active derivative [53]. Dispacamide C (**57**) and D (**58**) exhibited mild antihistaminic activity in comparison which implied the importance of the hydroxyl group on the side chain and also indicated that its orientation resulted in a notable reduction of antihistaminic activity [54]. Recently, debromodispacamides B and D were reported from *Agelas mauritiana* collected off the Solomon Islands [55].

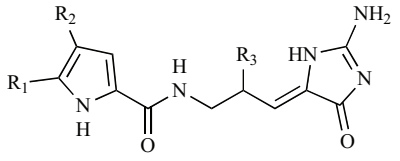
Mauritamide A, the first bromopyrrole alkaloid featuring a rare taurine moiety, was isolated from the Fijian sponge *Agelas mauritiana* [56]. Other examples of bromopyrrole guanidine-containing metabolites with taurine moiety are tauroacidin A (**59**) and B (**60**) (Fig. **5**), isolated from an Okinawan *Hymeniacidon* sp. [57], taurodispacamide (**61**), isolated from the Mediterranean sponge *Agelas oroides* [58], and its debromo derivative (**62**), isolated from *Axinella verrucosa* [59]. Diverse pharmacological activities have been reported for these four compounds (**59**-**62**). Tauroacidins A (**59**) and B (**60**) inhibited EGF receptor kinase and *c-erb*B-2 kinase activities (IC_{50}= 38 and 44.5 μM, respectively) [57]. Taurodispacamide (**61**) further exhibited significant antihistaminic activity [58] while its debromo derivative (**62**) revealed potential neuroprotection by acting as glutamate and serotonin antagonist [59].

Polycyclic bromopyrrole alkaloids are thought to be biosynthetically derived from the parent compound, oroidin (**51**), through formation of one (or more) C-C or C-N bonds. Polycyclic bromopyrrole alkaloids can be divided into five major classes based on the oroidin atoms involved in the cylcizations (Fig. **6**) [58].

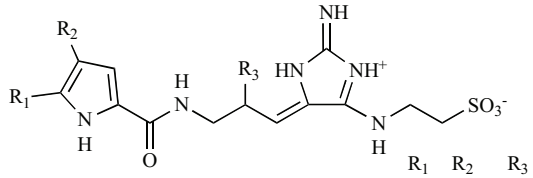
(10*Z*)-Debromohymenialdisine (**63**), (10*Z*)-hymenialdisine (**64**), and (10*Z*)-3-bromohymenialdisine (**65**) (Fig. **6**) express the first cyclization mode of oroidin which takes



	R_1	R_2	R_3
Oroidin (**51**)	H	Br	Br
Hymenidin (2-Debromooroidin) (**52**)	H	H	Br
Clathrodin (2,3-Dirbromooroidin) (**53**)	H	H	H
Sventrin (pyrrole-*N*-methyloroidin) (**54**)	Me	Br	Br



	R_1	R_2	R_3
Dispacamide A (**55**)	Br	Br	H
Dispacamide B (**56**)	H	Br	H
Dispacamide C (**57**)	Br	Br	OH
Dispacamide D (**58**)	H	Br	OH



	R_1	R_2	R_3
Tauroacidin A (**59**)	Br	Br	OH
Tauroacidin B (**60**)	H	Br	OH
Taurodispacamide (**61**)	Br	Br	H
2-Debromotaurodispacamide (**62**)	Me	Br	H

Fig. (5). Structures of **51**-**62**.

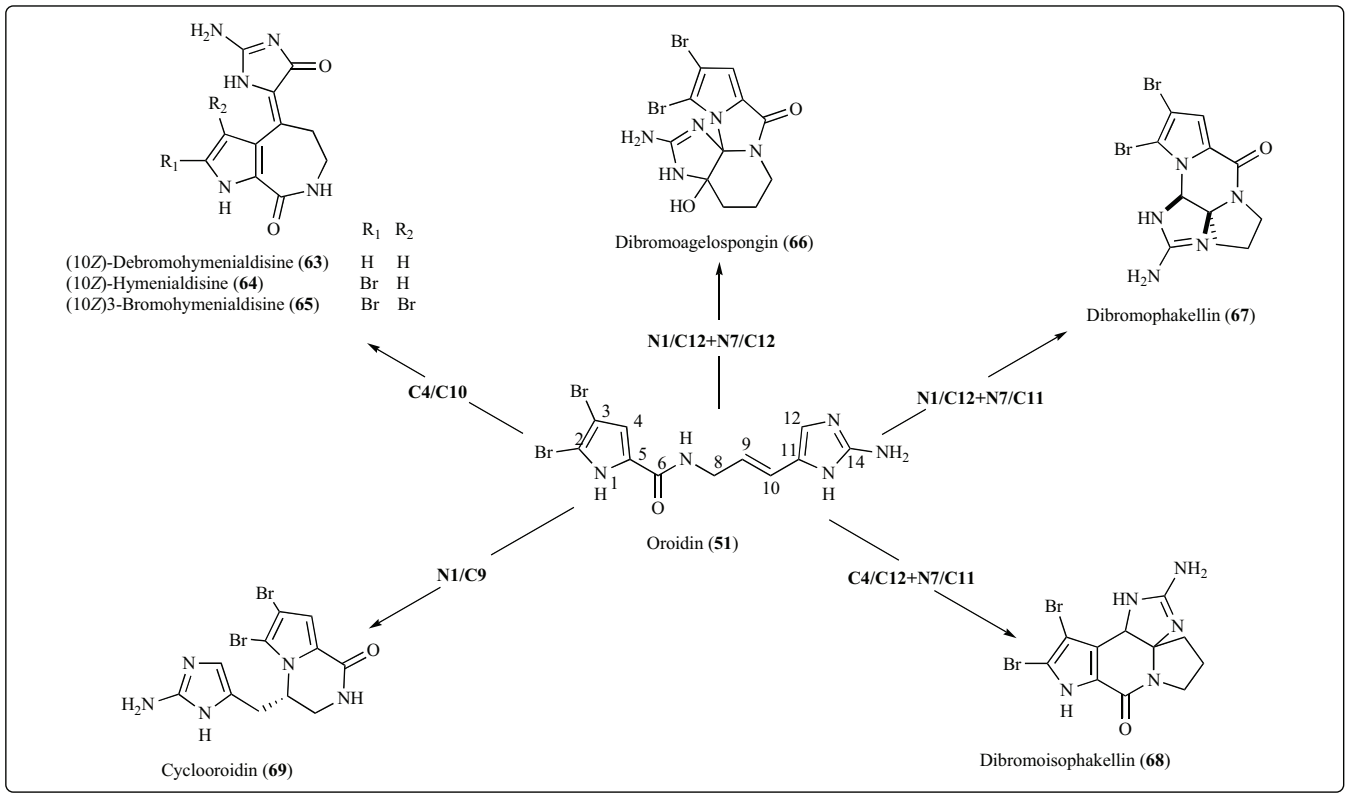


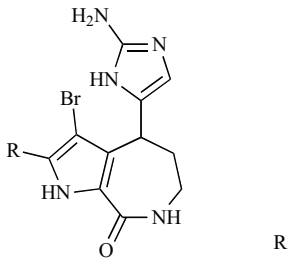
Fig. (6). An overview of cyclization modes of the oroidin skeleton and their products [58].

place between **C4** and **C10**. Compound (**63**) was first reported from the Great Barrier Reef sponge *Phakellia* sp. in 1980 [60] while (10*Z*)-hymenialdisine (**64**) was isolated two years later from different sponge genera including *Acanthella*, *Axinella*, and *Hymeniacidon* [61-63]. (10*Z*)-3-Bromohymenialdisine (**65**) was first purified from a tropical collection of the marine sponge *Axinella carteri* [64]. The (*E*) isomers of debromohymenialdisine and hymenialdisine have also been isolated from the marine sponge *Stylotella aurantium* from Palau [65]. All compounds (**63**-**65**) were subjected to cytotoxicity and insecticidal assays. In a cytotoxicity (MTT) assay, (10*Z*)-debromohymenialdisine (**63**) was the most active compound against mouse lymphoma L5178Y cells (IC_{50} value of 1.8 μg/mL (4.1 μM)) [64] while (10*Z*)-hymenialdisine (**64**) and (10*Z*)-3-bromohymenialdisine (**65**) revealed IC_{50} of 12.0 and 9.7 μM, respectively. Both **63** and **64** exhibited insecticidal activity towards larvae of the pest insect *Spodoptera littoralis* (LD_{50} values of 88 and 125 ppm, respectively), whereas (10*Z*)-debromohymenialdisine (**65**) proved to be inactive in this assay [64].

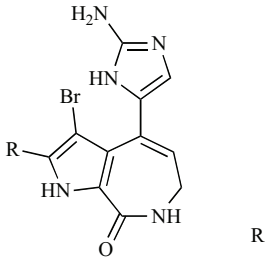
Hymenin (**70**, Fig. **7**) was isolated from *Hymeniacidon* sp. as an α-adrenoceptor antagonist, and also showed antibacterial activity against *Bacillus subtilis* and *Escherichia coli* [66]. Another hymenin analogue named stevensine (=odiline) (**72**, Fig. **7**), differing in the presence of a double bond between **C9** and **C10**, was isolated from *Pseudaxynissa cantharella* [67]. 2-Debrominated derivatives of both hymenin (**71**) and stevensine (**73**) (Fig. **7**) were isolated from the Indopacific sponge *Stylissa carteri* [68]. Stevensine (**72**) was proven to play a major role in the chemical defense of the reef sponge *Axinella corrugata* against predators [69].

Hymenialdisine together with its derivatives are of interest due to their potent inhibitory activity of several protein kinases such as CDKs, GSK-3β, CK1 and Chk1 which are crucial for regulating vital cellular functions such as gene expression, cellular proliferation, membrane transport and apoptosis [70, 71]. Inhibiting these kinases plays an important role in the treatment of diseases like *Alzheimer*'s disease, type II diabetes and cancer [47, 72]. Hymenialdisines also inhibited formation of several pro-inflammatory cytokines (IL-1, IL-2, IL-6, and NO) through inhibition of the NF-κB signaling pathway [70] which is potential for treatment of serious inflammatory conditions such as rheumatoid arthritis and osteoarthritis or for treatment of cancer.

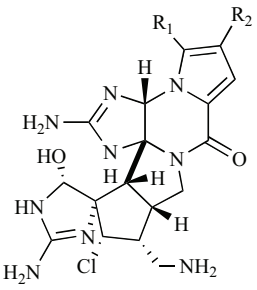
In 2009, a comprehensive review summarized all known hymenialdisines, their chemical synthesis and their protein kinase inhibitory activities [73]. The conclusion was that i) halogenation at R_1 and R_2 of the pyrrole ring does not significantly influence the activity of these compounds, ii) pyrrole derivatives appear to be more potent inhibitors than indole analogues which resulted in up to a 4-fold reduction in activity, iii) the existence of an aminoimidazolone ring, particularly the guanidine moiety, is crucial for the activity, and iv) a change in the geometry of the double bond (either (*E*) or (*Z*)) does not influence the activity. Modification of the amino group dramatically decreased activity possibly due to steric hindrance and loss of hydrogen bonding. Hymenin (**70**), with an aminoimidazole ring, exhibited lower kinase



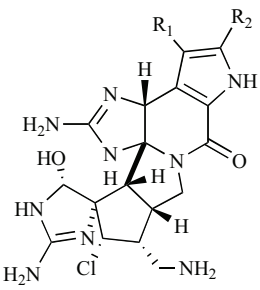
	R
Hymenin (**70**)	Br
2-Debromohymenin (**71**)	H



	R
Stevensine (**72**)	Br
2-Debromostevensine (**73**)	H



	R_1	R_2
Palau'amine (**74**)	H	H
4-Bromopalau'amine (**75**)	H	Br
4,5-Dibromopalau'amine (**76**)	Br	Br



	R_1	R_2
Styloguanidine (**77**)	H	H
3-Bromostyloguanidine (**78**)	H	Br
2,3-Dibromostyloguanidine (**79**)	Br	Br

Fig. (7). Structures of **70**-**79**.

inhibitory activity compared to hymenialdisine analogues [73].

Dibromoagelospongin (**66**, Fig. **6**), isolated from the marine sponge *Agelas* sp. collected off the Tanzanian coasts, represents to the best of our knowledge the only reported example of the second cyclization mode, occuring between both **N1** and **N7** with **C12** [74]. Dibromoagelospongin (**66**) is closely related to dibromophakellin (**67**, Fig. **6**), isolated from the marine sponge *Phakellia flabellata* in 1971 by Sharma *et al*. [75], in which **N7** is bonded to **C11** instead. Afterwards, several other phakellins have been reported from *Pseudaxynissa cantharella* [67] and *Agelas* sp. [76]. In 1997 a further derivative, phakellistatin, which differs from **67** in having a urea-type carbonyl instead of amino group present in the guanidine moiety, was purified from the Indian Ocean sponge *Phakellia mauritiana* [77]. Phakellistatin exhibited potent cytotoxic activity against a panel of human cancer cell lines (IC_{50} values from 0.3 to 0.4 μM) [77].

The next cyclization mode of oroidin (**51**) occurs between **N7**/**C11** and **C4**/**C12** affording a class of compounds known as isophakellins, from which dibromoisophakellin (**68**, Fig. **6**) was first isolated the marine sponge *Acanthella carteri* [78]. The compounds of this class differ from the phakellins in the linkage of imidazole **C12** with **C4** instead of **N1**.

The group of phakellins and isophakellins include other structurally complex metabolites known as palau'amines (**74**-**76**, Fig. **7**) or styloguanidines (**77**-**79**, Fig. **7**), respectively. In each of these compounds, the corresponding basic skeleton of either phakellin or isophakellin is conjugated with an aminoimidazolyl propene unit.

Palau'amines (**74**-**76**) were isolated from *Stylotella agminata* collected in the Western Caroline Island [79] and from the Belau sponge *Stylotella aurantium* [80]. Palau'amine exhibited potent antiproliferative activity against a panel cancer cell lines with IC_{50} values from 0.24 to 24.0 μM in addition to antibacterial, antifungal and immunosuppressive activities [79, 80]. In addition to palau'amines, styloguanidines (**77**-**79**) were obtained from the marine sponge *Stylotella aurantium* collected in the Yap Sea. The compounds were found to inhibit chitinase, a key enzyme involved for example in the ecdysis of insects and crustaceans. The inhibiton of chitinase affects the settlement of barnacles and hence could be a potential target for antifouling agents [81].

In a recent study, 14 bromopyrrole alkaloids, of which 8 featured guanidine moiety in their structures, were screened *in vitro* for their antiprotozoan activity against two *Trypanosoma* species (*T. brucei rhodesiense* and *T. cruzi*), *Leishmania donovani*, and multi-drug resistant K1 strain of *Plasmodium falciparum* [82]. Interestingly, only 4,5-dibromopalau'amine (**76**) exhibited a selective activity against African trypanosome, *T. brucei rhodesiense* with IC_{50} of 0.8 μM but not against American trypanosome, *T. cruzi* (IC_{50} = 119 μM) [82]. Furthermore, the highest activities against *Leishmania donovani* and *P. falciparum* were also shown by **76** with IC_{50}'s of 1.9, and 2.6 μM, respectively [82]. However, in the cytotoxicity assay against mammalian L6 cells, 4,5-dibromopalau'amine (**76**) was associated with toxicity (IC_{50} of 7.7 μM) which diminishes its therapeutic index as antitrypanosomal or antileishmanial agent, but it can still inspire to further synthetic derivatives aiming at improving its therapeutic index.

Moreover, spongiacidin B, *E* isomer of hymenialdisine (**64**) with bromine substituent at C-3 instead, and dispacamide B (**56**) exhibited potent antiplasmodial activities (IC_{50} of 3.4 and 4.1 μM, respectively) but with much lower cytotoxicity imparting a therapeutic index of more than 30 for both [82] and hence, they can be considered as probable lead candidates.

The last proposed cyclization mode of oroidin (**51**) occurs between **N1** and **C9** (Fig. **6**), affording cyclooroidin (**69**) which was firstly reported in 2000 from the Mediterranean sponge *Agelas oroides* [58].

Dimeric bromopyrrole alkaloids were isolated from the Caribbean sponge *Agelas sceptrum* in 1981 which hence gave the name "sceptrin" to one of the metabolites (**80**, Fig. **8**) [83]. Historically, sceptrin (**80**) is considered as the prototype compound of this group and it represents a symmetrical dimer of hymenin (2-debromooroidin) (**52**). Sceptrin (**80**) exhibited a wide range of bioactivities such as antimicrobial activity against different bacterial and fungal pathogens [83]. Moreover, it revealed antiviral [84], antimuscarinic [50], and antihistaminic activities [54]. In addition to the genus *Agelas*, dimeric bromopyrrole alkaloids were also isolated from other genera of marine sponges including *Stylissa* [85, 86], *Axinella* [87], and *Hymeniacidon* [88]. Among this group of dimeric alkaloids, two series can be identified which include ageliferins and nagelamides.

Ageliferin (**81**), 2-bromoagliferin (**82**), and 2,2'-dibromoageliferin (**83**) (Fig. **8**) were first reported from *Agelas conifera* and *A*. cf. *mauritiana* in 1989 by Rinehart [89]. Then, their detailed structural elucidation and stereochemistry were reported in 1990 by Kobayashi *et al*. [90]. Both 2-bromoagliferin (**82**) and 2,2'-dibromoageliferin (**83**) reduced voltage dependent calcium entry in PC12 cells which leads to vasorelaxation [91]. Seven further ageliferin derivatives, methylated at one or at several of the pyrrole nitrogens, together with the formerly isolated 2-bromo- (**82**) and 2,2'-dibromoageliferin (**83**) were isolated from the Micronesian marine sponge *Astrosclera willeyana* [92].

Nagelamides are fifteen dimeric bromopyrrole guanidine-containing congeners including nagelamides A-H [93], J-L [94, 95], and O-R [96, 97]. All of them were isolated from different collections of the Okinawan marine sponge *Agelas* sp. collected off Seragaki beach by Kobayashi *et al*. [93-97].

Nagelamides A-D (**84**-**87**, Fig. **8**) are dimerized *via* a C-C bond between **C10** and **C15'**, whereas nagelamides E-G were found to be diastereomers of ageliferin (**81**), 2-bromoagelifern (**82**), and 2,2'-dibromoageliferin (**83**), respectively.

Amongst the isolated nagelamides, nagelamide J (**88**) is the first bromopyrrole alkaloid featuring a cylcopentane ring fused to an amino-imidazole ring [94], whereas, nagelamide L (**89**) was defined as a unique dimeric bromopyrrole alkaloid possessing an ester linkage [95]. Nagelamide Q (**90**) is a rare dimeric bromopyrrole alkaloid with a pyrrolidine ring, while nagelamide R (**91**) was the first bromopyrrole alkaloid with an oxazoline ring [97].

All nagelamides have been screened for antimicrobial activity against a wide range of bacterial and fungal pathogens including *Bacillus subtilis*, *Escherichia coli*, *Micrococcus luteus*, *Staphylococcus aureus*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, *Candida albicans*, and *Aspergillus niger*. Results revealed that most of the nagelamides displayed antimicrobial activity with MIC values between 7.7 and 38.4 μM [93-97]. In addition, nagelamides A, G, and H exhibited also inhibitory activity against protein phosphatase 2A, a major serine/threonine protein phosphatase involved in cellular growth and potentially in cancer development, with IC_{50} values of 48, 13, and 46 μM, respectively [93].

6. BROMOTYROSINE DERIVATIVES

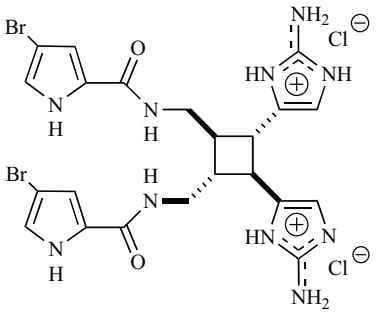
Aerophobin-2 (**92**, Fig. **9**), the parent bromotyrosine metabolite comprising a guanidine moiety, was first isolated from the marine sponge *Verongia* (= *Aplysina*) *aerophoba* in 1983 [98]. Ten years later, two structurally related metabolites, aplysinamisin-1 (**93**) and aplysinamisin-2 (**94**) (Fig. **9**) were isolated from the Caribbean *Aplysina cauliformis* collected in Puerto Rico [99].

Aplysinamisin-1 (**93**) and -2 (**94**) (Fig. **9**) showed *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* within the concentration range of 50-100 μg/disc. However, in the *in vitro* cytotoxicity assay against human breast (MCF-7) and T cell leukemia (CCRF-CEM) cell lines, both compounds **93** and **94** did not exhibit significant activity ($IC_{50} > 50\mu$g/mL) [99]. Interestingly, only aplysinamisin-2 (**94**) showed selective activity against human colon (HCT-116) cell line (IC_{50} = 19.6 μM) [99].

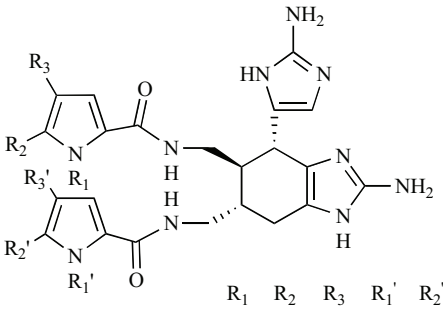
Purealidin A (**95**, Fig. **9**) is the parent compound of a group of bromotyrosine-derived alkaloids including seventeen additional purealidins (B-H and J-S) that were isolated from different collections of the Okinawan sponge *Psammaplysilla purea* [100-105] except for purealidin S that were obtained from the Fijian sponge *Druinella* sp. [106]. Amongst the isolated purealidins, only two congeners, purealidins A (**95**) and L (**96**) (Fig. **9**), feature a guanidine moiety.

In the *in vitro* cytotoxicity assay against murine leukemia L1210 cells, only purealidin A (**95**) exhibited significant activity with IC_{50} value of 2.1 μM [100]. Later, a related derivative trivially named caissarine A (**97**, Fig. **9**) was isolated from a Brazilian collection of the marine sponge *Aplysina caissara* [107].

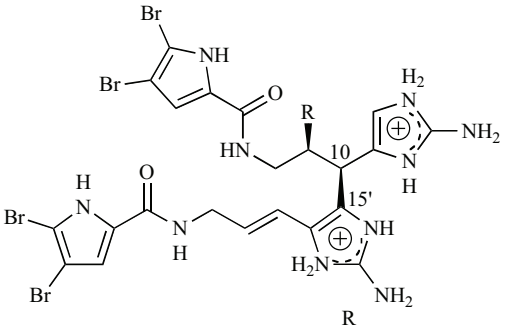
Antithrombotics (= anticoagulants) are potential pharmaceuticals used for treatment of thrombotic disorders particularly myocardial infarction, angina, pulmonary embolism and cerebrovascular incidences. The conventional antithrombotic therapy is carried out by intravenous administration of heparin as a loading dose followed by oral treatment with warfarin to retain the anticoagulant effect. In addition to be indirect and nonspecific inhibitors of coagulation serine proteases, both heparin and warfarin require very careful and costly monitoring to ensure safe therapeutic drug levels over treatment duration due to the high risk of bleeding.



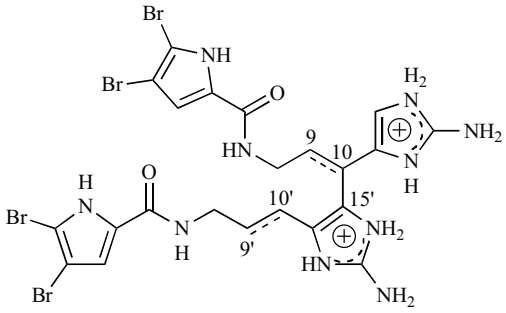
Sceptrin (**80**)



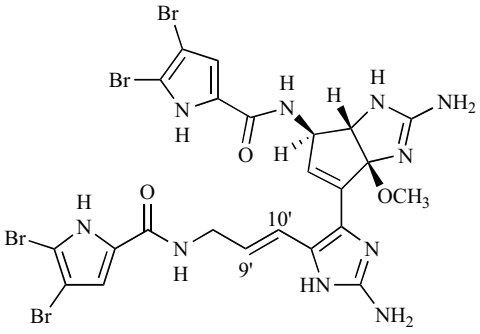
	R_1	R_2	R_3	R_1'	R_2'	R_3'
Ageliferin (**81**)	H	H	Br	H	H	Br
2-Bromoageliferin (**82**)	H	Br	Br	H	H	Br
2,2'-Dibromoageliferin (**83**)	H	Br	Br	H	Br	Br



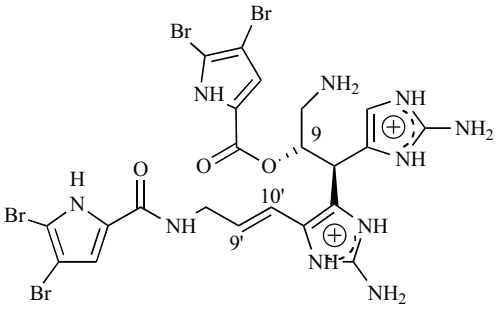
Nagelamide A (**84**) H
Nagelamide B (**85**) OH



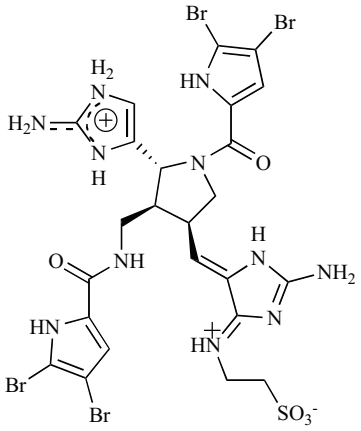
Nagelamide C (**86**) $\Delta^{9(10),9'(10')}$
Nagelamide D (**87**) 9,9',10,10'-tetrahydro



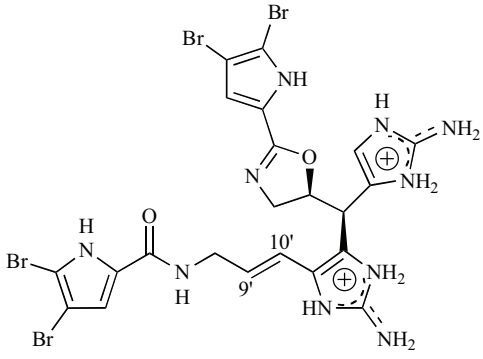
Nagelamide J (**88**)



Nagelamide L (**89**)

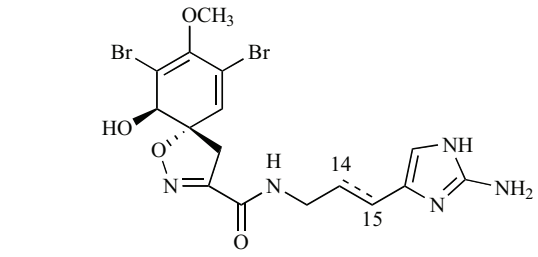


Nagelamide Q (**90**)

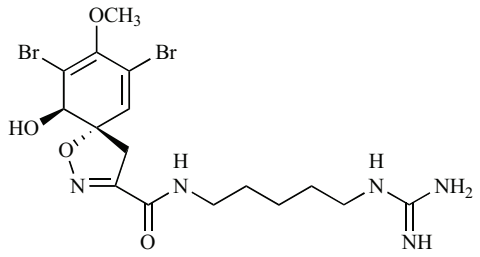


Nagelamide R (**91**)

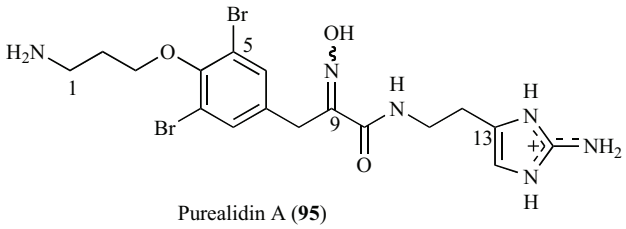
Fig. (8). Structures of **80**-**91**.



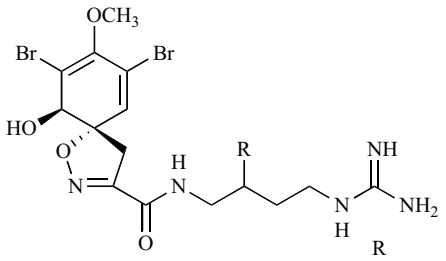
Aerophobin-2 (**92**) 14,15-dihydro
Aplysinamisin-1 (**93**) $\Delta^{14(15)}$



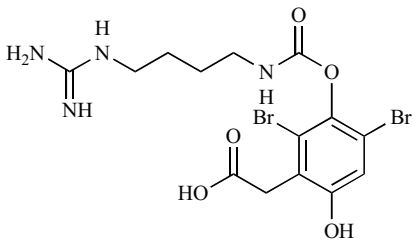
Aplysinamisin-2 (**94**)



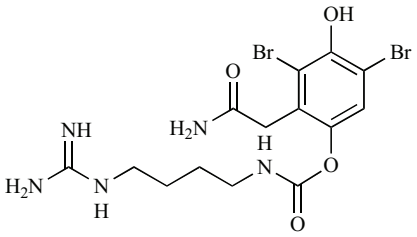
Purealidin A (**95**)



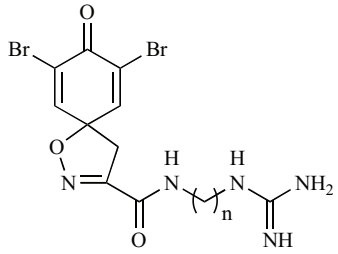
Purealidin L (**96**) H
Caissarine A (**97**) OH



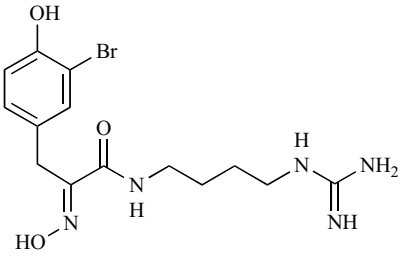
Clavatadine A (**98**)



Clavatadine B (**99**)



Clavatadine C (**100**) n = 4
Clavatadine D (**101**) n = 5



Clavatadine E (**102**)

Fig. (9). Structures of **92**-**102**.

Therefore, enormous efforts focused on new plausible drug candidates with an improved efficacy-to-safety index compared to heparin and warfarin. Factor XIa (FXIa) is a trypsin-like serine protease that plays a major role in the amplification phase of the coagulation cascade and in maintaining clot integrity. FXIa is a unique target as its specific inhibitors might inhibit thrombosis without intimate interruption of normal hemostasis and thus, might prevent or minimize the risks of hemostatic complications.

To fulfill this aim, a series of bromotyrosine-derived alkaloids were isolated from two different collections of the Australian Verongid sponge *Suberea clavata* by Buchanan *et al*. and trivially named as clavatadine A-E (**98**-**102**, Fig. **9**) [108, 109]. All clavatadines were assessed for their inhibitory activities against factor XIa. Only clavatadines A (**98**) and B (**99**) inhibited selectively FXIa with IC_{50} values of 1.3 and 27 μM, respectively [108], whereas other clavatadines showed only weak inhibitory activity (17-37 %) against FXIa at concentrations up to 222 μM [109]. The crystal structure and molecular docking of clavatadine (**98**) helped understanding SARs. Clavatadine A (**98**) can approach/bind in the S1-S1' pocket of FXIa by favorable interactions with Asp189 at its guanidine group of one end and the free carboxylate to either Arg37D or Lys192 of the other end. This results in a close contact between the side chain of Ser195 and the carbamate group of **98**, which eventually leads to the covalent binding with FXIa. In addition, clavatadine B (**99**)

was more than one order of magnitude less potent than **98**, most probably due to weaker interactions between its amide group and either Arg37D or Lys192, compared to the carboxylate moiety in clavatadine A (**98**) [108].

7. PEPTIDE GUANIDINES

Bioactive peptides from marine invertebrates are an interesting subject for both marine natural product chemists and pharmacologists. They comprise a considerable sector of marine natural products research. Most bioactive peptides are obtained from marine sponges and they disclose unique structures compared to those from other sources. Marine peptides are often cyclic or linear peptides featuring unusual amino acids which are either rare or even absent in terrestrial and microbial peptides. Moreover, marine peptides possess uncommon linkages between amino acids such as kapakahines isolated from a Pohnpei sponge *Cribrochalina olemda* [110-112].

Discodermin A (**103**, Fig. **10**) was the first bioactive peptide guanidine isolated from the marine sponge *Discodermia kiiensis* collected at Shikine Island (Japan) [113, 114]. Three additional discodermins B-D (**104**-**106**, Fig. **10**) were isolated from the same sponge extract [115] whereas bioassay-guided fractionation of the extract of *D. kiiensis* collected off Atami in the Gulf of Sagami (Japan) resulted in the isolation of discodermin E [116]. Structurally, discodermin E showed a D-kynurenine residue instead of a D-Trp residue and a reversed sequence of the 12^{th} and 13^{th} residues from the *N*-terminus in comparison to discodermin A (**103**) [116]. Besides discodermin E, three further peptide congeners, discodermins F-H (**107**-**109**, Fig. **10**), were obtained from the latter sponge extract [117].

In addition to discodermins A-H, the structurally related discobahamins A and B [118], polydiscamides A-D [119, 120] and halicylindramides A-E [121, 122] have been reported from marine sponges of the genera *Discodermia*, *Iricina* and *Halichondria*, respectively. They constitute a group of bioactive peptides including 13 to 14 proteinogenic as well as rare amino acid residues with a macrocyclic ring formed by lactonization of a threonine moiety with the carboxy terminal of the peptide chain. An exception is halicylindramide E (**110**, Fig. **10**) which is a linear peptide composed of 11 amino acids.

Discodermins A-D (**103**-**106**) exhibited *in vitro* antibacterial activity [113-116]. Afterwards, discodermins A-D were disclosed to be potent inhibitors of phospholipase A_2 (PLA_2) and **103** inhibited the tumor promotion activity of okadaic acid [116]. Moreover, discodermins F-H (**107**-**109**) exhibited antiproliferative activity against P388 murine leukemia cells with IC_{50} values of 0.6, 0.23, and 0.6 μM, respectively [117], whereas discobahamins A and B revealed weak antifungal activity against *Candida albicans* [118]. Polydiscamide A inhibited the proliferation of human lung cancer A549 cell line (IC_{50} = 0.4 μM) *in vitro* and the growth of *Bacillus subtilis* (MIC of 1.8 μM) [119]. Interestingly, polydiscamides B-D acted as pain modulators by activating the sensory neuron-specific G protein coupled receptors (SNSRs), which are expressed solely in dorsal root ganglia [123]. Previous studies showed that SNSRs are key players in both acute and persistent pain [124].

Based on the highly restricted distribution of SNSRs in the body, ligands that interact with these receptors may potentially modulate pain with very few side effects [120]. Interestingly, polydiscamides B-D showed potent agonist activity against human SNSR with EC_{50} values of 1.26, 3.57, and 2.80 μM [120] and they were the unprecedented examples of non-endogenous compounds with human SNSR agonist activity. Therefore, they could potentially be modified for pharmaceutical application as pain modulators.

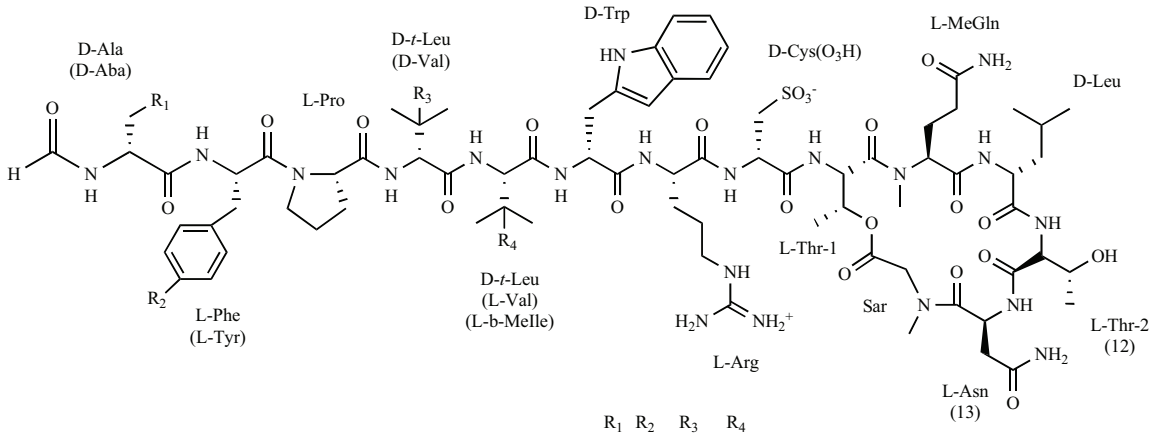
Halicylindramides A-D, possessing D-Phe and L-BrPhe instead of D-Leu and L-Phe (or L-Tyr) present in discodermins, respectively, revealed antifungal activity against *Mortierella ramanniana* at 7.5 μg/disk as well as antiproliferative activity against P388 murine leukemia cells with IC_{50} values of 0.3, 0.1, 0.01, and 1.2 μM, respectively [121, 122].

Dysinosins A-D (**111**-**114**, Fig. **10**) have been isolated from marine sponges belonging to the family Dysideidae [125, 126]. Dysinosin A (**111**) was first reported from a new genus of sponges found near Lizard Island (Australia) [125], whereas, it was reisolated together with three further dysinosins, B-D, from the Australian marine sponge *Lamellodysidea chlorea* [126]. Structurally, dysinosins are related to the cyanobacterial metabolites aeruginosins [127-129]. Aeruginosin 98-A (**115**, Fig. **10**) was reported in 1994, as a thrombin and trypsin inhibitor from the cyanobacterium *Microcystis aeruginosa* [127]. Not surprisingly, dysinosins A-D exhibited similar inhibitory activity against thrombin (IC_{50} values of 0.17->5.1 μM) and factor VIIa (IC_{50} values of 0.09-1.32 μM) [125, 126].

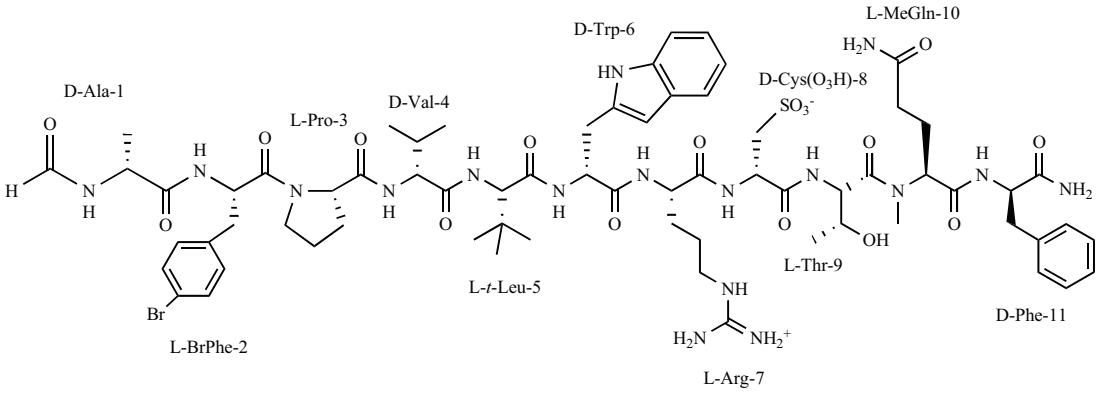
Dysinosins A-D (**111**-**114**) were further investigated to assess their SARs. The X-ray structural analysis of dysinosin A (**111**) exhibited a hydrogen bonding network forming the dysinosin-A-thrombin complex [125]. The presence of a sugar unit at C-13 in dysinosin B (**112**) slightly increased the inhibitory activity against factor VIIa in comparison to either dysinosins A (**111**) or C (**113**) (0.09 μM compared to 0.108 and 0.124 μM, respectively). However, selectivity relative to thrombin decreased to 1.9 (for **112**) compared to 4.2 (for **111**) and 4.4 (for **113**) [126]. Desulfated dysinosin D (**114**) was shown to be 10-fold less potent against both factor VIIa and thrombin in comparison to other sulfated dysinosins, indicating the importance of the sulfate group [126].

Hymenamides (A-K) are cyclic peptides that were obtained from the Okinawan marine sponge *Hymeniacidon* sp. [130-133]. Hymenamides A (**116**, Fig. **11**) and B were reported in 1994 and only the latter revealed cytotoxic activity against L1210 murine leukemia and KB human epidermoid carcinoma cell lines (IC_{50} values of 3.8 and 7.2 μM, respectively) [130].

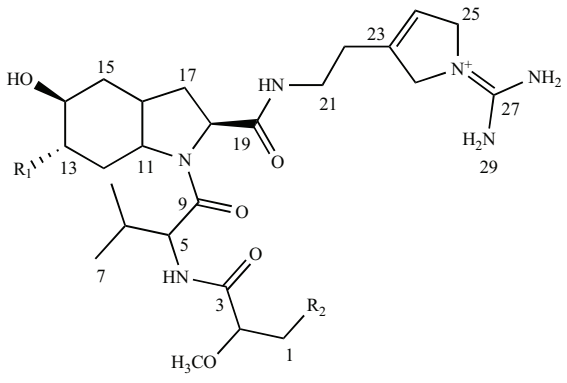
Cyclotheonamides A (**117**) and B (**118**) (Fig. **11**) are cyclic peptides featuring unusual amino acid residues, i.e. vinylogous tyrosine (V-Tyr), α-ketohomoarginine (K-Arg), and β-linked-diaminopropionic acid (Dpr) which were isolated from the marine sponge *Theonella swinhoei* (Japan) [134] together with two additional congeners C and D [135]. Cyclotheonamide E was obtained from a morphologically different specimen of *Theonella swinhoei* [135]. Chemical investigation of the marine sponge *Theonella* sp. collected off

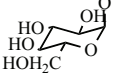


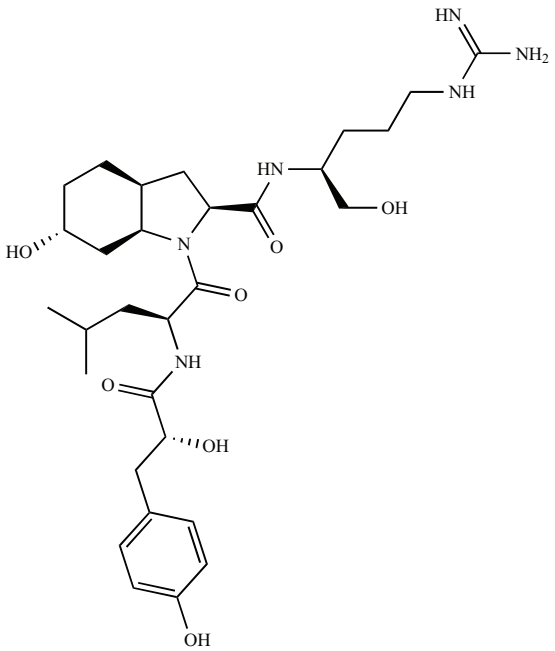
	R_1	R_2	R_3	R_4
Discodermin A (**103**)	H	H	Me	Me
Discodermin B (**104**)	H	H	H	Me
Discodermin C (**105**)	H	H	Me	H
Discodermin D (**106**)	H	H	H	H
Discodermin F (**107**)	H	H	Me	Et
Discodermin G (**108**)	Me	H	Me	Me
Discodermin H (**109**)	H	OH	Me	Me



Halicylindramide E (**110**)



	R_1	R_2	R_3
Dysinosin A (**111**)	OH	$CH(Me)_2$	OSO_3^-
Dysinosin B (**112**)		$CH_2CH(Me)_2$	OSO_3^-
Dysinosin C (**113**)	OH	$CH_2CH(Me)_2$	OSO_3^-
Dysinosin D (**114**)	OH	$CH_2CH(Me)_2$	OSO_3^-

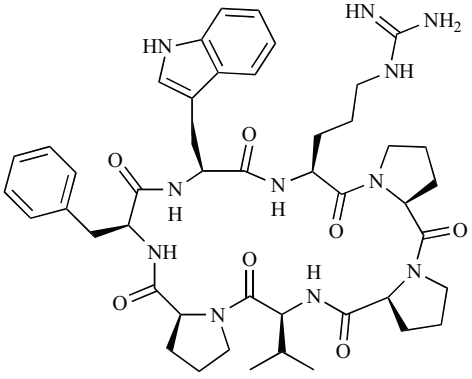


Aeruginosin 98-A (**115**)

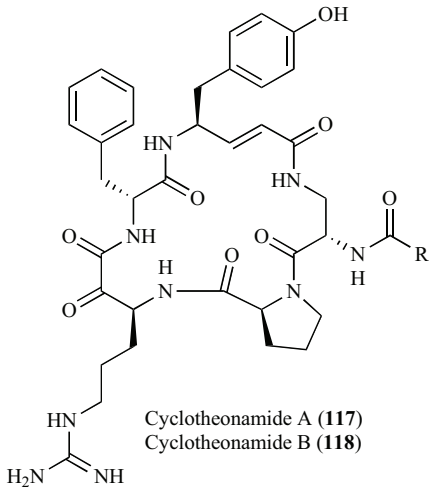
Fig. (10). Structures of **103-115**.

Tanegashima Island resulted in the isolation of cyclotheonamides E2 and E3 [136] while cyclotheonamides E4 and E5 were obtained from the Okinawan marine sponge *Ircinia* sp. [137].

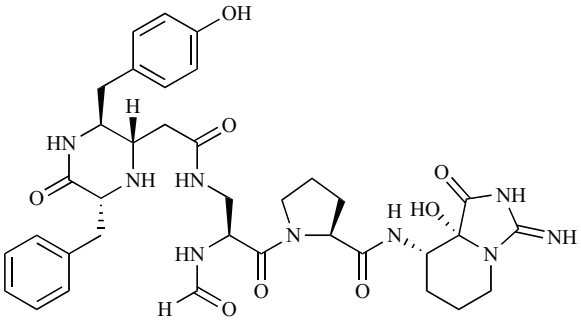
All cyclotheonamides (A-E) and (E2-E5) potentially inhibited serine proteases such as thrombin, trypsin and plasmin [134-137]. Their mode of action was investigated by X-ray crystallography of the complex between cyclotheonamide A (**117**) and human α-thrombin. Conclusively, it revealed that (1) the binding of cyclotheonamide A to the catalytic triad of the enzyme is achieved through forming a network of hydrogen bonds between the α-keto group of the K-Arg residue and the hydroxyl group of Ser195 of the enzyme, (2) V-Tyr residue proved to be involved in the bonding mechanism, and (3) cyclotheonamide D which possesses D-Leu instead of D-Phe in **117** showed comparable activity against thrombin, thus a further hydrophobic amino acid can replace D-Phe [135]. However, a comparative X-ray study against human α-thrombin and bovine β-trypsin disclosed that cyclotheonamide A (**117**) inhibited trypsin stronger than thrombin (IC_{50} = 16 and 23 nM, respectively) [136]. These results were substantiated to the more favourable (a) aromatic interaction of the D-Phe in **117** with Tyr39 and Phe41 in trypsin than with Glu39 and Leu41 in thrombin and (b) interaction of *N*-formyl Dpr residue with Gly174 and Gln175 in trypsin than Ile174 and Arg175 in thrombin [136].



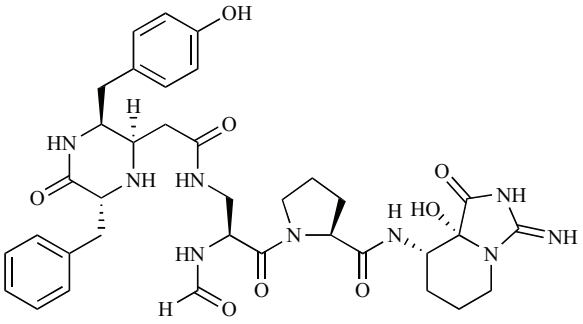
Hymenamide A (**116**)



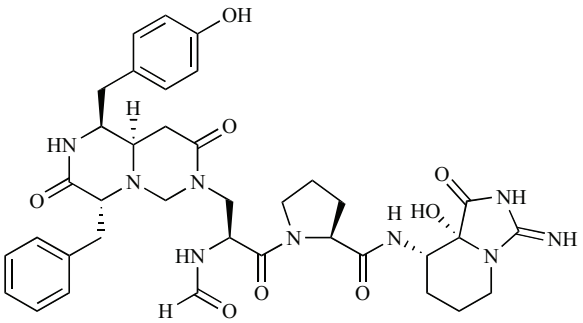
Cyclotheonamide A (**117**)
Cyclotheonamide B (**118**)



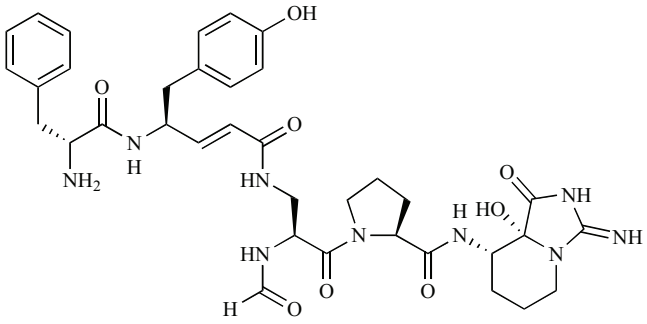
Pseudotheonamide A_1 (**119**)



Pseudotheonamide A_2 (**120**)



Pseudotheonamide B_2 (**121**)

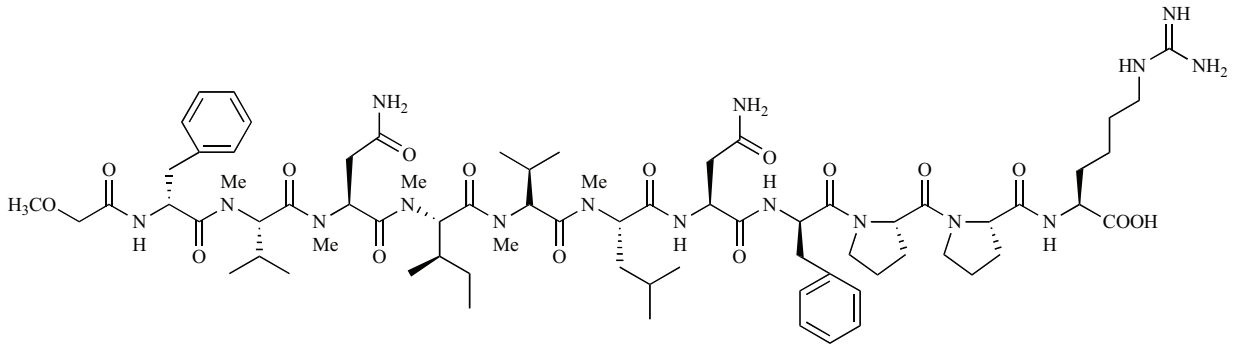


Pseudotheonamide C (**122**)

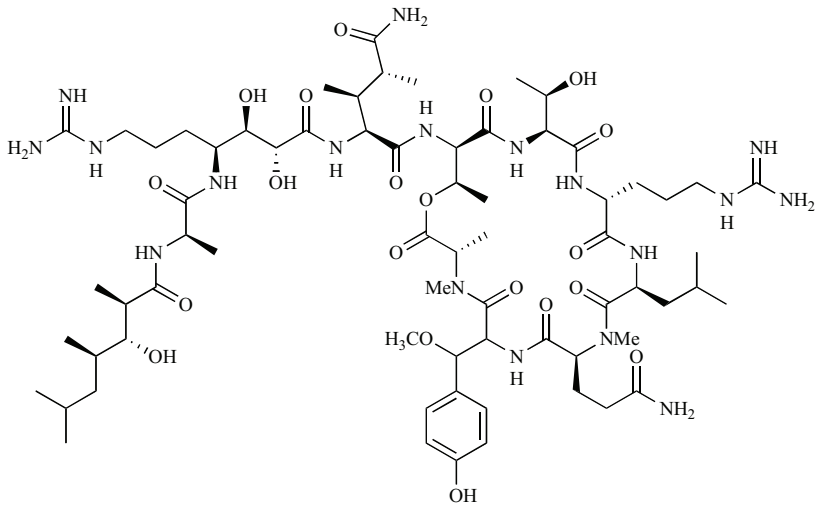
Fig. (11). Structures of **116-122**.

Following these findings, the marine sponge *T. swinhoei* has been thoroughly investigated and from a specimen of this sponge collected off Hachijo-jima Island in 1993, pseudotheonamides A_1, A_2, B_2, C, D, and dihydrocyclotheonamide A were purified [136].

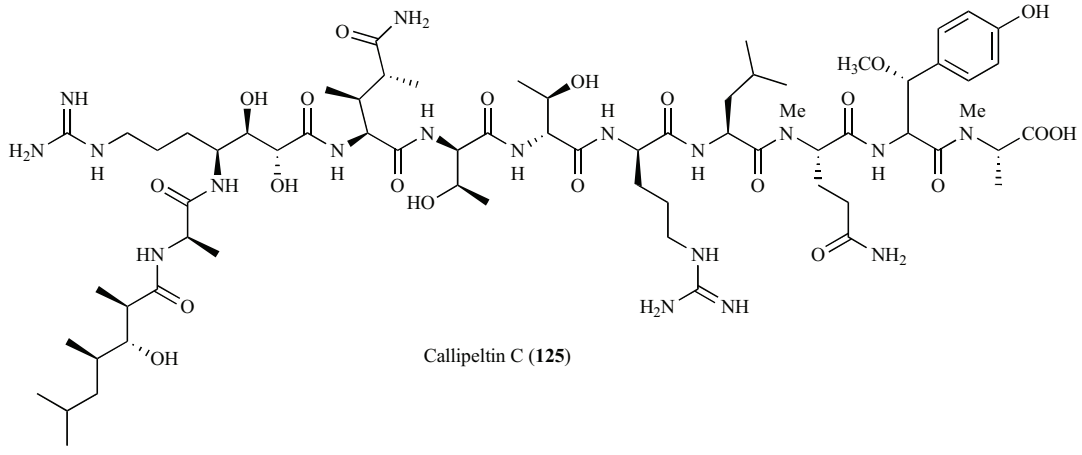
Pseudotheonamides A_1 (**119**), A_2 (**120**), and B_2 (**121**) (Fig. **11**) are linear pentapeptides comprising the rare piperazinone and piperidinoiminoimidazolone ring systems, while pseudotheonamide C (**122**, Fig. **11**) features V-Tyr instead of a piperazinone ring. Pseudotheonamide D, a tetrapeptide lacking a *C*-terminal K-Arg unit and dihydrocyclotheonamide A, is a reduction product of cyclotheonamide A (**117**). Pseudotheonamides A_1 (**119**), A_2 (**120**), B_2 (**121**), C (**122**), D, and dihydrocyclotheonamide A inhibited thrombin with IC_{50} values of 1.0, 3.0, 1.3, 0.19, 1.4, and 0.33 μM, respectively whereas they inhibited trypsin with IC_{50} values of 4.5, >10, 6.2, 3.8, >10, and 6.7 μM, respectively [138]. According to the SAR study of cyclotheonamides, potent inhibition of serine proteases is related to the presence of the α-



Koshikamide A_2 (**123**)



Callipeltin A (**124**)



Callipeltin C (**125**)

Fig. (12). Structures of **123**-**125**.

keto group of K-Arg residue [134-137]. Therefore, it is not surprising that pseudotheonamides, in which the α-keto group was either modified or missing, showed only moderate inhibitory activity against serine proteases [138].

Conclusively, both cyclotheonamides and pseudotheonamides inhibit serine proteases including trypsin and thrombin. These results suggested that cyclotheonamides and pseudotheonamides may be valuable candidates for treatment of asthma and other inflammatory disorders of the respiratory tract in addition to coagulatory disorders [137].

Koshikamide A_1 and A_2 (**123**, Fig. **12**) are two linear peptides isolated from the sponge *Theonella* sp. collected off Koshiki-jima Island (Japan) [139, 140]. Koshikamide A_2 (**123**) exhibited cytotoxicity against P388 murine leukemia cells *in vitro* with an IC_{50} value of 4.6 μM [140].

Callipeltins represent a group of marine peptides with unusual structural features and remarkable biological activities, isolated from the marine sponges *Callipelta* sp. [141, 142] and *Latrunculia* sp. [143-145]. Callipeltin A (**124**, Fig. **12**) is the prototype compound of this class which includes 12 further congeners (B-M). Apart from the cyclic congeners, callipeltins A and B, all the other callipeltins are linear derivatives structurally related to callipeltin C (**125**, Fig. **12**) which in turn represents the acyclic counterpart of callipeltin A (**124**).

The most distinctive structural characteristic of callipeltins is the existence of several non-proteinogenic units while from a biological point of view, callipeltin A displays a broad range of bioactivities, including antiviral, antifungal, and cytotoxic activity against a panel of human tumor cell lines and regulatory activity of the myocardial force of contractions [141-147].

The unusual structural features of callipeltins and the interesting biological activities have attracted considerable interest from the synthetic chemistry community. As a result, all non-proteinogenic units in this group of metabolites, namely (3*S*,4*R*)-3,4-dimethyl-L-pyroglutamic acid (the *N*-terminus unit in callipeltin B) [148], (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid [149], (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid [150] linked to the *N*-terminus of callipeltins A, C, D and F-I; and (*R*)-β-methoxy-D-tyrosine were synthesized in a stereoselective manner [151].

Anchinopeptolide A (**126**, Fig. **13**), a dimeric peptide guanidine alkaloid, was isolated from the marine sponge *Anchinoe tenacior* (order Poecilosclerida, family Demospongiae) collected in the Mediterranean Sea along the coasts of Tunisia [152]. The structural elucidation of **126** indicated for each monomer the presence of a C-terminal *trans*-4-hydroxystirylamino residue linked to L-alanine, which in turn is bound to an arginine-derived 5-guanidino-2-hydroxyl-pentanoyl residue.

From the same sponge collection, three further anchinopeptolides B-D (**127-129**, Fig. **13**) together with cycloanchinopeptolide C (**130**), were postulated to be produced from anchinopeptolide C (**128**) by a head-to-head intramolecular [2+2] cycloaddition reaction [153]. At a concentration of 5.0 μg/mL, only anchinopeptolides B-D (**127-129**) were able to significantly displace specific ligands from somatostatin, human B_2 bradykynin, and neuropeptide Y receptors [153].

Among the sacoglossans, *Elysia rufescens* and more recently *E. ornata* are known to accumulate toxic cyclic depsipeptides from their green algal diet *Bryopsis* sp. [154]. These metabolites are called kahalalides which is based on the location of the first collection of the sacoglossan mollusk *Elysia rufescens* at Kahala Bay bear Black Point, Oahu. Kahalalides show very promising biological activity, including antiviral, antimalarial, and primarily antiproliferative properties [154]. Structurally, kahalalides comprise cyclic and linear peptides or depsipeptides, ranging from a C_{31} tripeptide to a C_{75} tridecapeptide.

Among these, kahalalides C (**131**) and D (**132**) (Fig. **13**) were the first kahalalide congeners incorporating a guanidine moiety in the form of L-arginine amino acid which were obtained from the sacoglossan mollusk *Elysia rufescens* collected in 1991 [155]. Recently, three further guanidine-containing congeners, namely kahalalides V (**133**), W (**134**), and X (**135**) (Fig. **13**) were isolated from new specimens of *E. rufescens* collected from the waters of Kahala Bay near Black Point (Oahu) [156].

None of the guanidine-containing kahalalide congeners (**131-135**) did elicit any biological activities when subjected to cytotoxicity, antibacterial, antifungal and antiparasitic assays [155]. However, in preliminary tests using a rodent forced swim test model, kahalalide D (**132**) appreared to have some activity in the control of depression without noticeable toxicity [156]. Further reevaluation of its antidepressant activity, revealed that it does not yield consistent antidepressant-like actions in the forced swim test [156].

CONCLUDING REMARKS AND PERSPECTIVES

Natural guanidines from marine invertebrates constitute an interesting category of marine natural products illustrating both structural diversity and pharmacological activity. Structurally, natural guanidines range from simple pyrimidine derivatives to peptide or polyketide-derived guanidines. The pharmacological activity of natural guanidines includes a vast array of bioactivities such as antimicrobial, antiviral, cytotoxicity, anticoagulant, pain modulator, and protein kinase inhibitory activities.

Both features of guanidine-containing natural products have drawn the research interest of natural product chemists toward the isolation of further natural guanidine derivatives which may help in discovering a pharmaceutical lead which can help in development of a marine-derived medication to treat and/or prevent serious diseases.

Although, some success has been achieved in launching natural guanidine-inspired pharmaceuticals, more efforts are still required to isolate and find out further marine drug candidates from the oceans.

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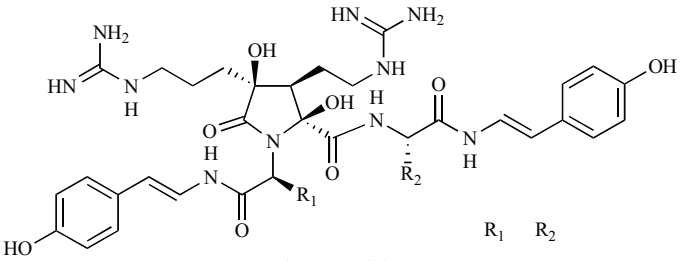
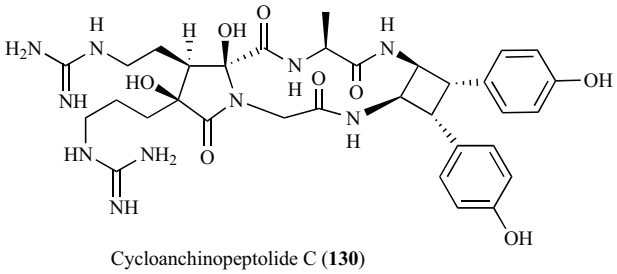
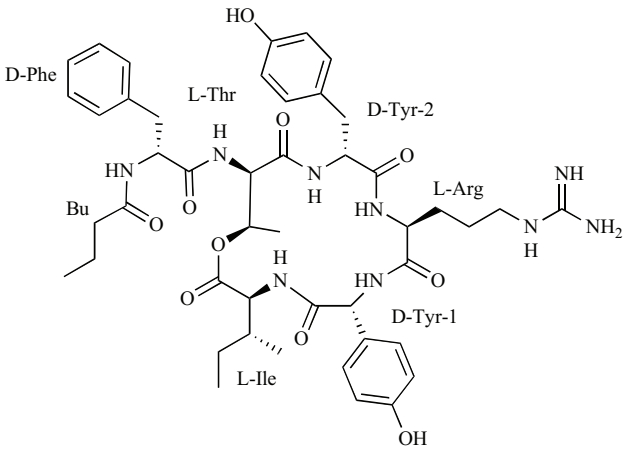


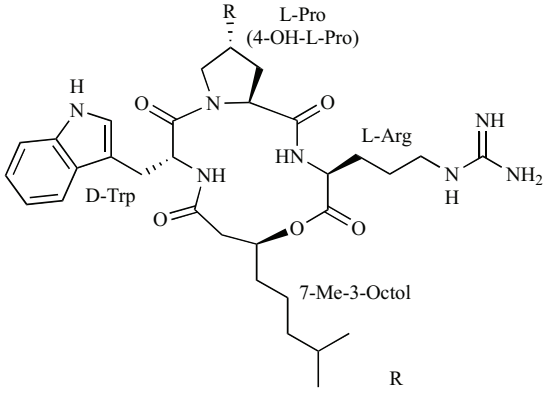
	R_1	R_2
Anchinopeptolide A (**126**)	Me	Me
Anchinopeptolide B (**127**)	Me	H
Anchinopeptolide C (**128**)	H	Me
Anchinopeptolide D (**129**)	H	H



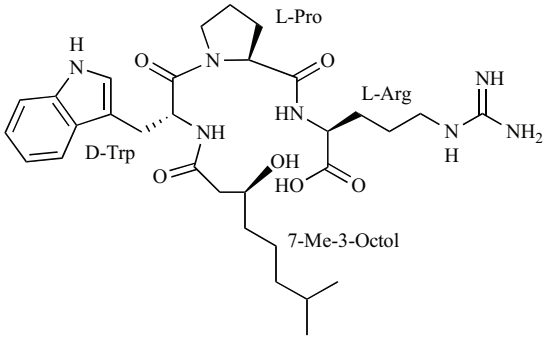
Cycloanchinopeptolide C (**130**)



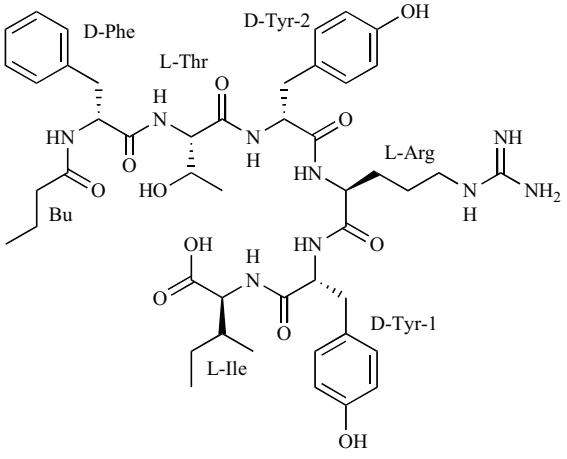
Kahalalide C (**131**)



Kahalalide D (**132**)	H
Kahalalide W (**134**)	OH



Kahalalide V (**133**)



Kahalalide X (**135**)

Fig. (13). Structures of **126**-**135**.

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REFERENCES

[1] Jimeno, J.M. A clinical armamentarium of marine-derived anticancer compounds. *Anticancer Drugs*, **2002**, *13*, S15-19.

[2] Pomponi, S.A. The bioprocess-technological potential of the sea. *J. Biotechnol.*, **1999**, *70*, 5-13.

[3] Molinski, T.F.; Dalisay, D.S.; Lievens, S.L.; Saludes, J.P. Drug development from marine natural products. *Nat. Rev. Drug Discov.*, **2009**, *8*, 69-85.

[4] Chevolot, L. In: *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P.J., Ed.; Academic Press: London, **1981**; Vol. *4*, pp. 53-91.

[5] Berlinck, R.G.S. Natural guanidine derivatives. *Nat. Prod. Rep.*, **1999**, *16*, 339-365.

[6] Berlinck, R.G.S. Natural guanidine derivatives. *Nat. Prod. Rep.*, **2002**, *19*, 617-649.

[7] Berlinck, R.G.S.; Kossuga, M.H. Natural guanidine derivatives. *Nat. Prod. Rep.*, **2005**, *22*, 516-550.

[8] Berlinck, R.G.S.; Kossuga, M.H. In: *Modern Alkaloids*; Fattorusso, E.; Taglialatela-Scafati, O., Ed.; Wiley-VCH Verlag: Weinheim, **2008**, pp. 305-337.

[9] Berlinck, R.G.S.; Burtoloso, A.C.B.; Kossuga, M.H. The chemistry and biology of organic guanidine derivatives. *Nat. Prod. Rep.*, **2008**, *25*, 919-954.

[10] Berlinck, R.G.S.; Burtoloso, A.C.B.; Trindade-Silva, A.E.; Romminger, S.; Morais, R.P.; Bandeira, K.; Mizuno, C.M. The chemistry and biology of organic guanidine derivatives. *Nat. Prod. Rep.*, **2010**, *27*, 1871-1907.

[11] Wiese, M.; D'Agostino, P.M.D.; Mihali, T.K.; Moffitt, M.C.; Neilan, B.A. Neurotoxic alkaloids: Saxitoxin and its analogues. *Mar. Drugs*, **2010**, *8*, 2185-2211.

[12] Pauletti, P.M.; Cintra, L.S.; Braguine, C.G.; da Silva Filho, A.A.; e Silva, M.L.A.; Cunha, W.R.; Januário, A.H. Halogenated indole alkaloids from marine invertebrates. *Mar. Drugs*, **2010**, *8*, 1526-1549.

[13] Walker, S.R.; Carter, E.J.; Huff, B.C.; Morris, J.C. Variolins and related alkaloids. *Chem. Rev.*, **2009**, *109*, 3080-3098.

[14] Bialonska, D.; Zjawiony, J.K. Aplysinopsins - Marine indole alkaloids: Chemistry, bioactivity and ecological significance. *Mar. Drugs*, **2009**, *7*, 166-183.

[15] Perry, N.B.; Ettouati, L.; Litaudon, M.; Blunt, J.W.; Munro, M.H.G.; Parkin, S.; Hope, H. Alkaloids from the Antarctic sponge *Kirkpatrickia varialosa*. Part 1: Variolin B, a new antitumor and antiviral compound. *Tetrahedron*, **1994**, *50*, 3987-3992.

[16] Trimurtulu, G.; Faulkner, D.J.; Perry, N.B.; Ettouati, L.; Litaudon, M.; Blunt, J.W.; Munro, M.H.G.; Jameson, G.B. Alkaloids from the Antarctic sponge *Kirkpatrickia varialosa*. Part 2: Variolin A and N(3')-methyltetrahydrovariolin B. *Tetrahedron*, **1994**, *50*, 3993-4000.

[17] Urban, S.; Hickford, S.J.H.; Blunt, J.W.; Munro, M.H.G. Bioactive marine alkaloids. *Curr. Org. Chem.*, **2000**, *4*, 765-807.

[18] Fresneda, P.M.; Delgado, S.; Francesch, A.; Manzanares, I.; Cuevas, C.; Molina, P. Synthesis and cytotoxic evaluation of new derivatives of the marine alkaloid variolin B. *J. Med. Chem.*, **2006**, *49*, 1217-1221.

[19] Anderson, R.J.; Morris, J.C. Studies toward the total synthesis of the variolins: rapid entry to the core structure. *Tetrahedron Lett.*, **2001**, *42*, 311-313.

[20] Anderson, R.J.; Morris, J.C. Total synthesis of variolin B. *Tetrahedron Lett.*, **2001**, *42*, 8697-8699.

[21] Álvarez, M.; Fernández, D.; Joule, J.A. Synthesis of deoxyvariolin B. *Tetrahedron Lett.*, **2001**, *42*, 315-317.

[22] Ahaidar, A.; Fernández, D.; Danelón, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J.A.; Álvarez, M. Total syntheses of variolin B and deoxyvariolin B. *J. Org. Chem.*, **2003**, *68*, 10020-10029.

[23] Anderson, R.J.; Hill, J.B.; Morris, J.C. Concise total syntheses of variolin B and deoxyvariolin B. *J. Org. Chem.*, **2005**, *70*, 6204-6212.

[24] Bettayeb, K.; Tirado, O.M.; Marionneau-Lambot, S.; Ferandin, Y.; Lozach, O.; Morris, J.C.; Mateo-Lozano, S.; Drueckes, P.; Schächtele, C.; Kubbutat, M.H.G.; Liger, F.; Marquet, B.; Joseph, B.; Echalier, A.; Endicott, J.A.; Notario, V.; Meijer, L. Meriolins, a new class of cell death-inducing kinase inhibitors with enhanced selectivity for cyclin-dependent kinases. *Cancer Res.*, **2007**, *67*, 8325-8334.

[25] Echalier, A.; Bettayeb, K.; Ferandin, Y.; Lozach, O.; Clément, M.; Valette, A.; Liger, F.; Marquet, B.; Morris, J.C.; Endicott, J.A.; Joseph, B.; Meijer, L. Meriolins (3-(pyrimidin-4-yl)-7-azaindoles): Synthesis, kinase inhibitory activity, cellular effects, and structure of a CDK2/Cyclin A/meriolin complex. *J. Med. Chem.*, **2008**, *51*, 737-751.

[26] Franco, L.H.; Joffé, E.B.deK.; Puricelli, L.; Tatian, M.; Seldes, A.M.; Palermo, J.A. Indole alkaloids from the tunicate *Aplidium meridianum*. *J. Nat. Prod.*, **1998**, *61*, 1130-1132.

[27] Gompel, M.; Leost, M.; Joffe, E.B.deK.; Puricelli, L.; Franco, L.H.; Palermo, J.; Meijer, L. Meridianins, a new family of protein kinase inhibitors isolated from the ascidian *Aplidium meridianum*. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 1703-1707.

[28] Cohen, P. Protein kinases-the major drug targets of the twenty-first century? *Nat. Rev. Drug Discov.*, **2002**, *1*, 309-315.

[29] Reyes, F.; Fernández, R.; Rodríguez, A.; Francesch, A.; Taboada, S.; Conxita, Á.; Cuevas, C. Aplicyanins A-F, new cytotoxic bromoindole derivatives from the marine tunicate *Aplidium cyaneum*. *Tetrahedron*, **2008**, *64*, 5119-5123.

[30] Šíša, M.; Pla, D.; Altuna, M.; Francesch, A.; Cuevas, C.; Albericio, F.; Álvarez, M. Total synthesis and antiproliferative activity screening of (±)-aplicyanins A, B and E and related analogues. *J. Med. Chem.*, **2009**, *52*, 6217-6223.

[31] Sakai, R.; Higa, T. Tubastrine, a new guanidinostyrene from the coral *Tubastraea aurea*. *Chem. Lett.*, **1987**, 127-128.

[32] Barenbrock, J.S.; Köck, M. Screening enzyme-inhibitory activity in several ascidian species from Orkney Islands using protein tyrosine kinase (PTK) bioassay-guided fractionation. *J. Biotechnol.*, **2005**, *117*, 225-232.

[33] Pearce, A.N.; Chia, E.W.; Berridge, M.V.; Maas, E.W.; Page, M.J.; Harper, J.L.; Webb, V.L.; Copp, B.R. Orthidines A-E, tubastrine, 3,4-dimethoxyphenethyl-β-guanidine, and 1,14-sperminedihomovanillamide: potential anti-inflammatory alkaloids isolated from the New Zealand ascidian *Aplidium orthium* that act as inhibitors of neutrophil respiratory burst. *Tetrahedron*, **2008**, *64*, 5748-5755.

[34] Carroll, A.R.; Avery, V.M. Leptoclinidamines A-C, indole alkaloids from the Australian ascidian *Leptoclinides durus*. *J. Nat. Prod.*, **2009**, *72*, 696-699.

[35] Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. Aplysinopsin, a new tryptophan derivative from a sponge. *Tetrahedron Lett.*, **1977**, *18*, 61-64.

[36] Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. Novel aplysinopsin-type alkaloids from Scleractinian corals of the family Dendrophylliidae of the Mediterranean and the Philippines. Configurational-assignment criteria, stereospecific synthesis, and photoisomerization. *Helv. Chim. Acta*, **1988**, *71*, 773-782.

[37] Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. Aplysinopsin-type alkaloids from *Dendrophyllia* sp., a Scleractinian coral of the family Dendrophylliidae of the Philippines. Facile photochemical (*Z*/*E*) photoisomerization and thermal reversal. *Helv. Chim. Acta*, **1989**, *72*, 1444-1450.

[38] Iwagawa, T.; Miyazaki, M.; Okamura, H.; Nakatani, M.; Doe, M.; Takemura, K. Three novel bis(indole) alkaloids from a stony coral, *Tubastraea* sp. *Tetrahedron Lett.*, **2003**, *44*, 2533-2535.

[39] Koh, E.G.L.; Sweatman, H. Chemical warfare among scleractinians: bioactive natural products from Tubastraea faulkneri Wells kill larvae of potential competitors. *J. Exp. Mar. Biol. Ecol.*, **2000**, *251*, 141-160.

[40] Hu, J.-F.; Schetz, J.A.; Kelly, M.; Peng, J.-N.; Ang, K.K.H.; Flotow, H.; Leong, C.Y.; Ng, S.B.; Buss, A.D.; Wilkins, S.P.; Harmann, M.T. New antiinfective and human 5-HT_2 receptor binding natural and semisynthetic compounds from the Jamaican sponge *Smenospongia aurea*. *J. Nat. Prod.*, **2002**, *65*, 476-480.

[41] Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. New bromopyrrole derivatives from the sponge *Agelas oroides*. *J. Chem. Soc. D Chem. Commun.*, **1971**, 1129-1130.

[42] Braeckman, J.C.; Daloze, Q.; Stoller, C.; van Soest, R.W. Chemotaxonomy of *Agelas* (Porifera: Demospongiae). *Biochem. Syst. Ecol.*, **1992**, *20*, 417-430.

[43] Wilson, D.M.; Puyama, M.; Fenical, W.; Pawlik, J.R. Chemical defense of the Caribbean reef sponge *Axinella corrugata* against predatory fishes. *J. Chem. Ecol.*, **1999**, *25*, 2811-2823.

[44] Lindel, T.; Hoffmann, H.; Hochguertel, M.; Pawlik, J.R. Structure-activity relationship of inhibition of fish feeding by sponge-derived and pyrrole-imidazole alkaloids. *J. Chem. Ecol.*, **2000**, *26*, 1477-1496.

[45] O'Malley, D.P.; Li, K.; Maue, M.; Zografos, A.L.; Baran, P.S. Total synthesis of dimeric pyrrole-imidazole alkaloids: sceptrin, ageliferin, nagelamide E, oxysceptrin, nakamuric acid, and the axinellamine carbon skeleton. *J. Am. Chem. Soc.*, **2007**, *129*, 4762-4775.

[46] Bhandari, M.R.; Sivappa, R.; Lovely, C.J. Total synthesis of the putative structure of nagelamide D. *Org. Lett.*, **2009**, *11*, 1535-1538.

[47] Nikoulina, S.E.; Ciaraldi, T.P.; Mudaliar, S.; Mohideen, P.; Carter, L.; Henry, R.R. Potential role of glycogen synthase kinase-3 in skeletal muscle insulin resistance of type 2 diabetes. *Diabetes*, **2000**, *49*, 263-271.

[48] Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. A novel antagonist of serotonergic receptors, hymenidin, isolated from the Okinawan marine sponge *Hymeniacidon* sp. *Experientia*, **1986**, *42*, 1176-1177.

[49] Morales, J.J.; Rodriguez, A.D. The structure of clathrodin, a novel alkaloid isolated from the Caribbean sea sponge *Agelas clathrodes*. *J. Nat. Prod.*, **1991**, *54*, 629-631.

[50] Rosa, R.; Silva, W.; de Motta, G.E.; Rodriguez, A.D.; Morales, J.J.; Ortiz, M. Anti-muscarinic activity of a family of $C_{11}N_5$ compounds isolated from *Agelas* sponges. *Experientia*, **1992**, *48*, 885-887.

[51] Assmann, M.; Zea, S.; Köck, M. Sventrin, a new bromopyrrole alkaloid from the Caribbean sponge *Agelas sventres*. *J. Nat. Prod.*, **2001**, *64*, 1593-1595.

[52] Bickmeyer, U.; Drechsler, C.; Köck, M.; Assmann, M. Brominated pyrrole alkaloids from marine *Agelas* sponges reduce depolarization-induced cellular calcium elevation. *Toxicon*, **2004**, *44*, 45-51.

[53] Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. Dispacamides, anti-histamine alkaloids from Caribbean *Agelas* sponges. *Tetrahedron Lett.*, **1996**, *7*, 3587-3590.

[54] Cafieri, F.; Carnuccio, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Vallefuoco, T. Anti-histaminic activity of bromopyrrole alkaloids isolated from Caribbean *Agelas* sponges. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 2283-2288.

[55] Vergne, C.; Appenzeller, J.; Ratinaud, C.; Martin, M.T.; Debitus, C.; Zaparucha, A.; Al-Mourabit, A. Debromodispacamides B and D: isolation from the marine sponge *Agelas mauritiana* and stereoselective synthesis using a biomimetic proline route. *Org. Lett.*, **2008**, *10*, 493-496.

[56] Jimenez, C.; Crews, P. Mauritamide A and accompanying oroidin alkaloids from the sponge *Agelas mauritiana*. *Tetrahedron Lett.*, **1994**, *35*, 1375-1378.

[57] Kobayashi, J.; Inaba, K.; Tsuda, M. Tauroacidins A and B, new bromopyrrole alkaloids possessing a taurine residue from *Hymeniacidon* sponge. *Tetrahedron*, **1997**, *53*, 16679-16682.

[58] Fattorusso, E.; Taglialatela-Scafati, O. Two novel pyrrole-imidazole alkaloids from the Mediterranean sponge *Agelas oroides*. *Tetrahedron Lett.*, **2000**, *41*, 9917-9922.

[59] Aiello, A.; D'Esposito, M.; Fattorusso, E.; Menna, M.; Müller W.E.G.; Pervoic-Ottstadt, S.; Schroeder, H.C. Novel bioactive bromopyrrole alkaloids from the Mediterranean sponge *Axinella verrucosa*. *Bioorg. Med. Chem.*, **2006**, *14*, 17-24.

[60] Sharma, G.M.; Buyer, J.S.; Pomerantz, M.W. Characterization of a yellow compound isolated from the marine sponge *Phakellia flabellate*. *J. Chem. Soc. Chem. Commun.*, **1980**, *10*, 435-436.

[61] Mattia, C.A.; Mazzarella, L.; Puliti, R. 4-(2-Amino-4-oxo-2-imidazolin-5-ylidene)-2-bromo-4,5,6,7-tetrahydropyrrolo-[2,3-C] azepine -8-one Methanol solvate-a new bromo compound from the sponge *Acanthella aurantiaca*. *Acta Crystallogr., Sec. B, Struct. Sci.*, **1982**, *38*, 2513-2515.

[62] Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. Isolation and X-ray crystal structure of a novel bromo compound from two marine sponges. *Tetrahedron Lett.*, **1982**, *23*, 767-768.

[63] Kitagawa, I.; Kobayashi, J.; Kitanaka, K.; Kido, M.; Kyogoku, Y. Marine natural products. XII. On the chemical constituents of the Okinawan marine sponge *Hymeniacidon aldis*. *Chem. Pharm. Bull.*, **1983**, *3*, 2321-2328.

[64] Supriyono, A.; Schwarz, B.; Wray, V.; Witte, L.; Müller, W.E.G.; van Soest, R.; Sumaryono, W.; Proksch, P. Bioactive alkaloids from the tropical marine sponge *Axinella carteri*. *Z. Naturforsch.*, **1995**, *50c*, 669-674.

[65] Williams, D.H.; Faulkner, D.J. Isomers and tautomers of hymenialdisine and debromohymenialdisine. *Nat. Prod. Lett.*, **1996**, *9*, 57-64.

[66] Kobayashi, J.; Ohizumi, Y.; Nakamura, H., Hirata, Y.; Wakamatsu, K.; Miyazawa, T. Hymenin, an α-adrenoceptor blocking agent from the Okinawan marine sponge *Hymeniacidon* sp. *Experientia*, **1986**, *42*, 1064-1065.

[67] De Nanteuil, G.; Ahond, A.; Guilhem, J.; Poupat, C.; Tran Huu Dau, E.; Potier, P.; Pusset, M.; Pusset, J.; Laboute, P. Marine invertebrate of Neo-Caledonian V. Isolation and identification of the metabolites of the new Caledonian sponge *Pseudaxinyssa cantharella*. *Tetrahedron*, **1985**, *41*, 6019-6033.

[68] Eder, C.; Proksch, P.; Wray, V.; Steube, K.; Bringmann, G.; van Soest, R.W.M.; Sudarsono; Ferdinandus, E.; Pattisina, L.A.; Wiryowidagdo, S.; Moka, W. New alkaloids from the Indopacific sponge *Stylissa carteri*. *J. Nat. Prod.*, **1999**, *62*, 184-187.

[69] Wilson, D.M.; Puyana, M.; Fenical, W.; Pawlik, J.R. Chemical defense of the Caribbean reef sponge *Axinella corrugata* against predatory fishes. *J. Chem. Ecol.*, **1999**, *25*, 2811-2823.

[70] Meijer, L.; Thunnissen, A.M.W.H.; White, A.W.; Garnier, M.; Nikolic, M.; Tsai, L.H.; Walter, J.; Cleverley, K.E.; Salinas, P.C.; Wu, Y.Z.; Biernat, J.; Mandelkow, E.M.; Kim, S.H.; Pettit, G.R. Inhibition of cyclin-dependent kinases, GSK-3 beta and CK1 by hymenialdisine, a marine sponge constituent. *Chem. Biol.*, **2000**, *7*, 51-63.

[71] Sharma, V.; Lansdell, T.A.; Jin, G.; Tepe, J.J. Inhibition of cytokine production by hymenialdisine derivatives. *J. Med. Chem.*, **2004**, *47*, 3700-3703.

[72] Martinez, A.; Castro, A.; Dorronsoro, I.; Alonso, M. Glycogen synthase kinase (GSK-3) inhibitors as new promising drugs for diabetes, neurodegeneration, cancer and inflammation. *Med. Res. Rev.*, **2002**, *22*, 373-384.

[73] Nguyen, T.N.T.; Tepe, J.J. Preparation of hymenialdisine, analogues and their evaluation as kinase inhibitors. *Curr. Med. Chem.*, **2009**, *16*, 3122-3143.

[74] Fedoreyev, S.A.; Ilyin, S.G.; Utkina, N.K.; Maximov, O.B.; Reshetnyak, M.V.; Antipin, M.Y.; Struchkov, Y.T. The structure of dibromoagelospongin - a novel bromine-containing guanidine derivative from the marine sponge *Agelas* sp. *Tetrahedron*, **1989**, *45*, 3487-3492.

[75] Sharma, G.M.; Burkholder, P.R. Structure of dibromophakellin, a new bromine-containing alkaloid from the marine sponge *Phakellia flabellate*. *J. Chem. Soc. D Chem. Commun.*, **1971**, *3*, 151-152.

[76] Gautschi, J.T.; Whitman, S.; Holman, T.R.; Crews, P. An analysis of phakellin and oroidin structure stimulated by further study of an *Agelas* sponge. *J. Nat. Prod.*, **2004**, *67*, 1256-1261.

[77] Pettit, G.R.; McNulty, J.; Herald, D.L.; Doubek, D.L.; Chapuis, J.C.; Schmidt, J.M.; Tackett, L.P.; Boyd, M.R. Antineoplastic agents. 362. Isolation and X-ray crystal structure of dibromophakellistatin from the Indian Ocean sponge *Phakellia mauritiana*. *J. Nat. Prod.*, **1997**, *60*, 180-183.

[78] Fedoreyev, S.A.; Utkina, N.K.; Ilyin, S.G.; Reshetnyak, M.V.; Maximov, O.B. The structure of dibromoisophakellin from the marine sponge *Acanthella carteri*. *Tetrahedron Lett.*, **1986**, *27*, 3177-3180.

[79] Kinnel, R.B.; Gehrken, H.P.; Scheuer, P.J. Palau'amine: a cytotoxic and immunosuppressive hexacyclic bisguanidine antibiotic from the sponge *Stylotella agminata*. *J. Am. Chem. Soc.*, **1993**, *115*, 3376-3377.

[80] Kinnel, R.B.; Gehrken, H.P.; Swali, R.; Skoropowski, G.; Scheuer, P.J. Palau'amine and its congeners: a family of bioactive bisguanidines from the marine sponge *Stylotella aurantium*. *J. Org. Chem.*, **1998**, *63*, 3281-3286.

[81] Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. Styloguanidines, new chitinase inhibitors from the marine sponge *Stylotella aurantium*. *Tetrahedron Lett.*, **1995**, *36*, 2133-2136.

[82] Scala, F.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O.; Tierney, M.; Kaiser, M.; Tasdemir, D. Bromopyrrole alkaloids as lead compounds against protozoan parasites. *Mar. Drugs*, **2010**, *8*, 2162-2174.

[83] Walker, R.P.; Faulkner, D.J. Sceptrin, an antimicrobial agent from the sponge *Agelas sceptrum*. *J. Am. Chem. Soc.*, **1981**, *103*, 6772-6773.

[84] Keifer, P.A.; Schwartz, R.E.; Koker, M.E.S.; Hughes, R.G.; Jr.; Rittschof, D.; Rinehart, K.L. Bioactive bromopyrrole metabolites from the Caribbean sponge *Agelas conifera*. *J. Org. Chem.*, **1991**, *56*, 2965-2975.

[85] Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R.W.M.; Fusetani, N. Massadine, a novel geranylgeranyl transferase type I inhibitor from the marine sponge *Stylissa* aff. *massa*. *Org. Lett.*, **2003**, *5*, 2255-2257.

[86] Grube, A.; Köck, M. Stylissadines A and B: the first tetrameric pyrrole-imidazole alkaloids. *Org. Lett.*, **2006**, *8*, 4675-4678.

[87] Urban, S.; Leone, P.deA.; Carroll, A.R.; Fechner, G.A.; Smith, J.; Hooper, J.N.A.; Quinn, R.J. Axinellamines A-D, novel imidazo-azolo-imidazole alkaloids from the Australian marine sponge *Axinella* sp. *J. Org. Chem.*, **1999**, *64*, 731-735.

[88] Kobayashi, J.; Suzuki, M.; Tsuda, M. Konbu'acidin A, a new bromopyrrole alkaloid with cdk4 inhibitory activity from *Hymeniacidon* sponge. *Tetrahedron*, **1997**, *53*, 15681-15684.

[89] Rinehart, K.L. Biologically active marine natural products. *Pure Appl. Chem.*, **1989**, *61*, 525-528.

[90] Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. Ageliferins, potent actomyosin ATPase activators from the Okinawan marine sponge *Agelas* sp. *Tetrahedron*, **1990**, *46*, 5579-5586.

[91] Bickmeyer, U. Bromoageliferin and dibromoageliferin, secondary metabolites from the marine sponge *Agelas conifera*, inhibit voltage-operated, but not store-operated calcium entry in PC12 cells. *Toxicon*, **2005**, *45*, 627-632.

[92] Williams, D.H.; Faulkner, D.J. *N*-methylated ageliferins from the sponge *Astrosclera willeyana* from Pohnepi. *Tetrahedron*, **1996**, *52*, 5381-5390.

[93] Endo, T.; Tsuda, M.; Okada, T.; Mitsuhashi, S.; Shima, H.; Kikuchi, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. Nagelamides A-H, new dimeric bromopyrrole alkaloids from marine sponge *Agelas* species. *J. Nat. Prod.*, **2004**, *67*, 1262-1267.

[94] Araki, A.; Tsuda, M.; Kubota, T.; Mikami, Y.; Fromont, J.; Kobayashi, J. Nagelamide J, a novel dimeric bromopyrrole alkaloid from a sponge *Agelas* species. *Org. Lett.*, **2007**, *9*, 2369-2371.

[95] Araki, A.; Kubota, T.; Tsuda, M.; Mikami, Y.; Fromont, J.; Kobayashi, J. Nagelamides K and L, dimeric bromopyrrole alkaloids from sponge *Agelas* species. *Org. Lett.*, **2008**, *10*, 2099-2102.

[96] Yasuda, T.; Araki, A.; Kubota, T.; Ito, J.; Mikami, Y.; Fromont, J.; Kobayashi, J. Bromopyrrole alkaloids from marine sponge of the genus *Agelas*. *J. Nat. Prod.*, **2009**, *72*, 488-491.

[97] Araki, A.; Kubota, T.; Aoyama, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. Nagelamides Q and R, novel dimeric bromopyrrole alkaloids from sponges *Agelas* sp. *Org. Lett.*, **2009**, *11*, 1785-1788.

[98] Cimino, G.; De Rosa, S.; De Stefano, S.; Self, R.; Sodano, G. The bromo compounds of the true sponge *Verongia aerophoba*. *Tetrahedron Lett.*, **1983**, *24*, 3029-3032.

[99] Rodríguez, A.D.; Piña, I.C. The structures of aplysinamisins I, II, and III: New bromotyrosine-derived alkaloids from the Caribbean sponge *Aplysina cauliformis*. *J. Nat. Prod.*, **1993**, *56*, 907-914.

[100] Ishibashi, M.; Tsuda, M.; Ohizumi, Y.; Sasaki, T.; Kobayashi, J. Purealidin A, a new cytotoxic bromotyrosine-derived alkaloid from the Okinawan marine sponge *Psammaplysilla purea*. *Experientia*, **1991**, *47*, 299-300.

[101] Kobayashi, J.; Tsuda, M.; Agemi, K.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. Purealidins B and C, new bromotyrosine alkaloids from the Okinawan marine sponge *Psammaplysilla purea*. *Tetrahedron*, **1991**, *47*, 6617-6622.

[102] Tsuda, M.; Shigemori, H.; Ishibashi, M.; Kobayashi, J. Purealidin D, a new pyridine alkaloid from the Okinawan marine sponge *Psammaplysilla purea*. *Tetrahedron Lett.*, **1992**, *33*, 2597-2598.

[103] Tsuda, M.; Shigemori, H.; Ishibashi, M.; Kobayashi, J. Purealidins E-G, new bromotyrosine alkaloids from the Okinawan marine sponge *Psammaplysilla purea*. *J. Nat. Prod.*, **1992**, *55*, 1325-1327.

[104] Kobayashi, J.; Honma, K.; Tsuda, M.; Kosaka, T. Lipopurealidins D and E and purealidin H, new bromotyrosine alkaloids from the Okinawan marine sponge *Psammaplysilla purea*. *J. Nat. Prod.*, **1995**, *58*, 467-470.

[105] Kobayashi, J.; Honma, H.; Sasaki, T.; Tsuda, M. Purealidins J-R, new bromotyrosine alkaloids from the Okinawan marine sponge *Psammaplysilla purea*. *Chem. Pharm. Bull.*, **1995**, *43*, 403-407.

[106] Tabudravu, J.N.; Jaspars, M. Purealidin S and purpuramine J, bromotyrosine alkaloids from the Fijian marine sponge *Druinella* sp. *J. Nat. Prod.*, **2002**, *65*, 1798-1801.

[107] De Lira, T.O.; Berlinck, R.G.S.; Nascimento, G.G.F.; Hajdu, E. Further dibromotyrosine-derived metabolites from the marine sponge *Aplysina caissara*. *J. Braz. Chem. Soc.*, **2006**, *17*, 1233-1240.

[108] Buchanan, M.S.; Carroll, A.R.; Wessling, D.; Jobling, M.; Avery, V.M.; Davis, R.A.; Feng, Y.; Xue, Y.; Oester, L.; Fex, T.; Deinum, J.; Hooper, J.N.A.; Quinn, R.J. Clavatadine A, a natural product with selective recognition and irreversible inhibition of Factor XIa. *J. Med. Chem.*, **2008**, *51*, 3583-3587.

[109] Buchanan, M.S.; Carroll, A.R.; Wessling, D.; Jobling, M.; Avery, V.M.; Davis, R.A.; Feng, Y.; Hooper, J.N.A.; Quinn, R.J. Clavatadines C-E, guanidine alkaloids from the Australian sponge *Suberea clavata*. *J. Nat. Prod.*, **2009**, *72*, 973-975.

[110] Nakao, Y.; Yeung, B.K.S.; Yoshida, W.Y.; Scheuer, P.J. Kapakahine B: a cyclic hexapeptide with an α-carboline ring system from the marine sponge *Cribrochalina olemda*. *J. Am. Chem. Soc.*, **1995**, *117*, 8271-8272.

[111] Yeung, B.K.S.; Nakao, Y.; Kinnel, R.B.; Carney, J.R.; Yoshida, W.Y.; Scheuer, P.J.; Kelly-Borges, M. The kapakahines, cyclic peptides from the marine sponge *Cribrochalina olemda*. *J. Org. Chem.*, **1996**, *61*, 7168-7173.

[112] Nakao, Y.; Kuo, J.; Yoshida, W.Y.; Kelly, M.; Scheuer, P.J. More kapakahines from the marine sponge *Cribrochalina olemda*. *Org. Lett.*, **2003**, *5*, 1387-1390.

[113] Matsunaga, S.; Fusetani, N.; Konosu, S. Bioactive marine metabolites VI. Structure elucidation of discodermin A, and antimicrobial peptide from the marine sponge *Discodermia kiiensis*. *Tetrahedron Lett.*, **1984**, *25*, 5165-5168.

[114] Matsunaga, S.; Fusetani, N.; Konosu, S. Bioactive marine metabolites IV. Isolation and the amino acid composition of discodermin A, an antimicrobial peptide, from the marine sponge *Discodermia kiiensis*. *J. Nat. Prod.*, **1985**, *48*, 236-241.

[115] Matsunaga, S.; Fusetani, N.; Konosu, S. Bioactive marine metabolites VII. Structures of discodermins B, C, and D, antimicrobial peptides from the marine sponge *Discodermia kiiensis*. *Tetrahedron Lett.*, **1985**, *26*, 855-856.

[116] Ryu, G.; Matsunaga, S.; Fusetani, N. Discodermin E, a cytotoxic and antimicrobial tetradecapeptide, from the marine sponge *Discodermia kiiensis*. *Tetrahedron Lett.*, **1994**, *35*, 8251-8254.

[117] Ryu, G.; Matsunaga, S.; Fusetani, N. Discodermins F-H, cytotoxic and antimicrobial tetradecapeptides, from the marine sponge *Discodermia kiiensis*: structure revision of discodermins A-D. *Tetrahedron*, **1994**, *50*, 13409-13416.

[118] Gunasekera, S.P.; Pomponi, S.A.; McCarthy, P.J. Discobahamins A and B, new peptides from the Bahamian deep water marine sponge *Discodermia* sp. *J. Nat. Prod.*, **1994**, *57*, 79-83.

[119] Gulavita, N.K.; Gunasekera, S.P.; Pomponi, S.A.; Robinson, E.V. Polydiscamide A: a new bioactive depsipeptide from the marine sponge *Discodermia* sp. *J. Org. Chem.*, **1992**, *57*, 1767-1772.

[120] Feng, Y.; Carroll, A.R.; Pass, D.M.; Archbold, J.K.; Avery, V.M.; Quinn, R.J. Polydiscamides B-D from a marine sponge *Ircinia* sp. as potent human sensory neuron-specific G protein coupled receptor agonists. *J. Nat. Prod.*, **2008**, *71*, 8-11.

[121] Li, H.; Matsunaga, S.; Fusetani, N. Halicylindramides A-C, antifungal and cytotoxic depsipeptides from the marine sponge *Halichondria cylindrata*. *J. Med. Chem.*, **1995**, *38*, 338-343.

[122] Li, H.; Matsunaga, S.; Fusetani, N. Halicylindramides D and E, antifungal peptides from the marine sponge *Halichondria cylindrata*. *J. Nat. Prod.*, **1996**, *59*, 163-166.

[123] Dong, X.; Han, S.; Zylka, M.J.; Simon, M.I.; Anderson, D.J. A diverse family of GPCRs expressed in specific subsets of nociceptive sensory neurons. *Cell*, **2001**, *106*, 619-632.

[124] Simonin, F.; Kieffer, B.L. Two faces for an opioid peptide-and more receptors for pain research. *Nat. Neurosci.*, **2002**, *5*, 185-186.

[125] Carroll, A.R., Pierens, G.K.; Fechner, G.; de Almeida, L.P.; Ngo, A.; Simpson, M.; Hyde, E.; Hooper, J.N.A.; Bostroem, S.L.; Musil, D.; Quinn, R.J. 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.

[126] Carroll, A.R.; Buchanan, M.S.; Edser, A.; Hyde, E.; Simpson, M.; Quinn, R.J. Dysinosins B-D, inhibitors of factor VIIa and thrombin from the Australian sponge *Lamellodysidea chlorea*. *J. Nat. Prod.*, **2004**, *67*, 1291-1294.

[127] Ishida, K.; Okita, Y.; Matsuda, H.; Okino, T.; Murakami, M. Aeruginosins, protease inhibitors from the cyanobacterium *Microcystis aeruginosa*. *Tetrahedron*, **1999**, *55*, 10971-10988.

[128] Matsuda, H.; Okino, T.; Murakami, M.; Yamaguchi, K. Aeruginosins 102-A and B, new thrombin inhibitors from the cyanobacterium *Microcystis viridis* (NIES-102). *Tetrahedron*, **1996**, *52*, 14501-14506.

[129] Murakami, M.; Ishida, K.; Okino, T.; Okita, Y.; Matsuda, H.; Yamaguchi, K. Aeruginosins 98-A and B, trypsin inhibitors from the blue-green alga *Microcystis aeruginosa* (NIES-98). *Tetrahedron Lett.*, **1995**, *36*, 2785-2788.

[130] Kobayashi, J.; Tsuda, M.; Nakamura, T.; Mikami, Y.; Shigemori, H. Hymenamides A and B, new proline-rich cyclic heptapeptides from the Okinawan marine sponge *Hymeniacidon* sp. *Tetrahedron*, **1993**, *49*, 2391-2402.

[131] Tsuda, M.; Shigemori, H.; Mikami, Y.; Kobayashi, J. Hymenamides C-E, new cyclic heptapeptides with two proline residues from the Okinawan marine sponge *Hymeniacidon* sp. *Tetrahedron*, **1993**, *49*, 6785-6796.

[132] Kobayashi, J.; Nakamura, T.; Tsuda, M. Hymenamide F, new cyclic heptapeptide from marine sponge *Hymeniacidon* sp. *Tetrahedron*, **1996**, *52*, 6355-6360.

[133] Tsuda, M.; Sasaki, T.; Kobayashi, J. Hymenamides G, H, J, and K, four new cyclid octapeptides from the Okinawan marine sponge *Hymeniacidon* sp. *Tetrahedron*, **1994**, *50*, 4667-4680.

[134] Fusetani, N.; Matsunaga, S. Cyclotheonamides, potent thrombin inhibitors, from a marine sponge *Theonella* sp. *J. Am. Chem. Soc.*, **1990**, *112*, 7053-7054.

[135] Nakao, Y.; Matsunaga, S.; Fusetani, N. Three more cyclotheonamides, C, D, and E, potent thrombin inhibitors from the marine sponge *Theonella swinhoei*. *Bioorg. Med. Chem.*, **1995**, *3*, 1115-1122.

[136] Nakao, Y.; Oku, N.; Matsunaga, S.; Fusetani, N. Cyclotheonamides E2 and E3, new potent serine protease inhibitors from the marine sponge of the genus *Theonella*. *J. Nat. Prod.*, **1998**, *61*, 667-670.

[137] Murakami, Y.; Takei, M.; Shindo, K.; Kitazume, C.; Tanaka, J.; Higa, T.; Fukamachi, H. Cyclotheonamides E4 and E5, new potent tryptase inhibitors from an *Ircinia* species of sponge. *J. Nat. Prod.*, **2002**, *65*, 259-261.

[138] Nakao, Y.; Masuda, A.; Matsunaga, S.; Fusetani, N. Pseudotheonamides, serine protease inhibitors from the marine sponge *Theonella swinhoei*. *J. Am. Chem. Soc.*, **1999**, *121*, 2425-2431.

[139] Fusetani, N.; Warabi, K.; Nogata, Y.; Nakao, Y.; Matsunaga, S.; van Soest, R.R.M. Koshikamide A_1, a new cytotoxic linear peptide isolated from a marine sponge, *Theonella* sp. *Tetrahedron Lett.*, **1999**, *40*, 4687-4690.

[140] Araki, T.; Matsunaga, S.; Fusetani, N. Koshikamide A_2, a cytotoxic linear undecapeptide isolated from a marine sponge of *Theonella* sp. *Biosci. Biotechnol. Biochem.*, **2005**, *69*, 1318-1322.

[141] Zampella, A.; D'Auria, M.V.; Paloma, L.G.; Casapullo, A.; Minale, L.; Debitus, C.; Henin, Y. Callipeltin A, an anti-HIV cyclic depsipeptide from the New Caledonian Lithistida sponge *Callipelta* sp. *J. Am. Chem. Soc.*, **1996**, *118*, 6202-6209.

[142] D'Auria, M.V.; Zampella, A.; Paloma, L.G.; Minale, L.; Debitus, C.; Roussakis, C.; Le Bert, V. Callipeltins B and C; bioactive peptides from a marine Lithistida sponge *Callipelta* sp. *Tetrahedron*, **1996**, *52*, 9589-9596.

[143] Zampella, A.; Randazzo, A.; Borbone, N.; Luciani, S.; Trevisi, L.; Debitus, C.; D'Auria, M.V. Isolation of callipeltins A-C and of two new open-chain derivatives of callipeltin A from the marine sponge *Latrunculia* sp. A revision of the stereostructure of callipeltins. *Tetrahedron Lett.*, **2002**, *43*, 6163-6166.

[144] Sepe, V.; D'Orsi, R.; Borbone, N.; D'Auria, M.V.; Bifulco, G.; Monti, M.C.; Catania, A.; Zampella, A. Callipeltins F-I: new antifungal peptides from the marine sponge *Latrunculia* sp. *Tetrahedron*, **2006**, *62*, 833-840.

[145] D'Auria, M.V.; Sepe, V.; D'Orsi, R.; Bellotta, F.; Debitus, C.; Zampella, A. Isolation and structural elucidation of callipeltins J-M: antifungal peptides from the marine sponge *Latrunculia* sp. *Tetrahedron*, **2007**, *63*, 131-140.

[146] Trevisi, L.; Bova, S.; Cargnelli, G.; Danieli-Betto, D.; Floreani, M.; Germinario, E.; D'Auria, M.V.; Luciani, S. Callipeltin A, a cyclic depsipeptide inhibitor of the cardiac sodium-calcium exchanger and positive inotropic agent. *Biochem. Biophys. Res. Commun.*, **2000**, *279*, 219-222.

[147] Trevisi, L.; Cargnelli, G.; Ceolotto, G.; Papparella, I.; Semplicini, A.; Zampella, A.; D'Auria, M.V.; Luciani, S. Callipeltin A: sodium ionophore effect and tension development in vascular smooth muscle. *Biochem. Pharmacol.*, **2004**, *68*, 1331-1338.

[148] Acevedo, C.M.; Kogut, E.F.; Lipton, M.A. Synthesis and analysis of the sterically constrained L-glutamine analogueues (3*S*,4*R*)-3,4-dimethyl-L-glutamine and (3*S*,4*R*)-3,4-dimethyl-L-pyroglutamic acid. *Tetrahedron*, **2001**, *57*, 6353-6359.

[149] Chandrasekhar, S.; Ramachandar, T.; Venkateswara Rao, B. Chiron approach to callipeltin A: first synthesis of fully protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyhepatonic acid. *Tetrahedron: Assymetry*, **2001**, *12*, 2315-2321.

[150] Guerlavais, V.; Carroll, P.J.; Joullié, M.M. Progress towards the total synthesis of callipeltin A. Asymmetric synthesis of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid. *Tetrahedron: Assymetry*, **2002**, *13*, 675-680.

[151] Okamoto, N.; Hara, O.; Makino, K.; Hamada, Y. Diastereoselective synthesis of all stereoisomers of *β*-methoxytyrosine, a component of papuamides. *J. Org. Chem.*, **2002**, *67*, 9210-9215.

[152] Casapullo, A.; Finamore, E.; Minale, L.; Zollo, F. A dimeric peptide alkaloid of a completely new type, anchinopeptolide A, from the marine sponge *Anchinoe tenacior*. *Tetrahedron Lett.*, **1993**, *34*, 6297-6300.

[153] Casapullo, A.; Minale, L.; Zollo, F.; Lavayre, J. Four new dimeric peptide alkaloids, anchinopeptolides B-D, and cycloanchinopeptolide C, congeners of anchinopeptolide A, from the Mediterranean marine sponge *Anchinoe tenacior*. *J. Nat. Prod.*, **1994**, *57*, 1227-1233.

[154] Fontana, A.; Ciavatta, M.L.; D'souza, L.; Mollo, E.; Naik, C.G.; Parameswaran, P.S.; Wahidulla, S.; Cimino, G. Selected chemo-ecological studies of marine opisthobranchs from Indian coasts. *J. Indian Inst. Sci.*, **2001**, *81*, 403-415.

[155] Hamann, M.T.; Otto, C.S.; Scheuer, P.J.; Dunbar, D.C. Kahalalides: Bioactive peptides from a marine mollusk *Elysia rufescens* and its algal diet *Bryopsis* sp. *J. Org. Chem.*, **1996**, *61*, 6594-6600.

[156] Rao, K.V.; Na, M.K.; Cook, J.C.; Peng, J.; Matsumoto, R.; Hamann, M.T. Kahalalides V-Y isolated from a Hawaiian collection of the sacoglossan mollusk *Elysia rufescens*. *J. Nat. Prod.*, **2008**, *71*, 772-778.

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