

Marine dinoflagellates as a source of new bioactive structures

Arnaud Cousseau, Raffaele Siano, Ian Probert, Stéphane Bach, Mohamed Mehiri

▶ **To cite this version:**

Arnaud Cousseau, Raffaele Siano, Ian Probert, Stéphane Bach, Mohamed Mehiri. Marine dinoflagellates as a source of new bioactive structures. Studies in Natural Products Chemistry, 65, 2022, Bioactive Natural Products, 10.1016/B978-0-12-817905-5.00004-4 . hal-03867411

HAL Id: hal-03867411
https://hal.science/hal-03867411

Submitted on 30 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Studies in Natural Products Chemistry
(Bioactive Natural Products)
ELSEVIER SCIENCE PUBLISHERS - AMSTERDAM

Marine Dinoflagellates as source of new bioactive structures

Arnaud Cousseau [1,2], Raffaele Siano [3], Ian Probert [4], Stéphane Bach [2], Mohamed Mehiri [1]

[1] University Nice Côte d'Azur, CNRS, Nice Institute of Chemistry, UMR 7272, Marine Natural Products Team, Nice 60103, France.

[2] UPMC, CNRS, USR3151, Kinase Inhibitor Specialized Screening facility - KISS*f*, Station Biologique, Roscoff 29688, France.

[3] Ifremer, Center of Brest, French Institute of Research for the Exploitation of the Sea, Dynamics of Coastal Ecosystems - DYNECO/Pelagos, Plouzané 29280, France.

[4] UPMC, CNRS, FR2424, Roscoff Culture Collection - RCC, Station Biologique, Roscoff 29688, France (http://www.roscoff-culture-collection.org/).

Abstract

Dinoflagellates are an extremely diverse group of unicellular eukaryotes that represent an important part of marine plankton communities. Amongst other secondary metabolites, these microorganisms are known to produce potent toxins such as the saxitoxins, which can affect marine fauna and ultimately humans who consume seafood in which these toxins have accumulated. The extreme biodiversity of dinoflagellates undoubtedly mirrors an inexhaustible reservoir of compounds, yet the chemodiversity of dinoflagellates is still poorly studied, due in part to constraints linked to the difficulty of isolating and cultivated these organisms. Nevertheless, a number of new dinoflagellate secondary metabolites have been described in recent years. Here we review these new advances in the isolation and characterization of bioactive metabolites from dinoflagellates, some of which might be of therapeutic interest in human health applications.

Keyword: Microalgae, dinoflagellates, chemodiversity, phycotoxins, bioassays.

Plan

1. **Introduction** 3
2. **Chemical diversity sorted by genus** 4
   - ***2.1. Amphidinium*** 8
     - **2.1.1. Amphidinins** 8
     - **2.1.2. Amphidinols** 9
     - **2.1.3. Amphirionin** 11
       - **2.1.3.1. Amphirionin-2** 11
       - **2.1.3.2. Amphirionin-4** 11
       - **2.1.3.3. Amphirionin-5** 12
     - **2.1.4. Iriomoteolide** 12
       - **2.1.4.1. Iriomoteolide-1a, 1b et 1c** 13
       - **2.1.4.2. Iriomoteolide-2a** 14
       - **2.1.4.3. Iriomoteolide-3a et 3b** 14
       - **2.1.4.4. Iriomoteolide-4a** 15
       - **2.1.4.5. Iriomoteolide-5a** 15
       - **2.1.4.6. Iriomoteolide-9a** 16
       - **2.1.4.7. Iriomoteolide-10a** 16
       - **2.1.4.8. Iriomoteolide-11a** 17
       - **2.1.4.9. Iriomoteolide-12a** 17
     - **2.1.5. Amdigenol** 18
   - ***2.2. Azadinium*** 19
     - ***2.2.1.*** **Azapiracids** 19
   - ***2.3. Dinophysis*** 20
     - **2.3.1. Acuminolide** 21
   - ***2.4. Gambierdiscus*** 21
     - **2.4.1. Gambierone** 21
     - **2.4.2. Gambieroxide** 22
   - ***2.5. Karlodinium*** 23
     - **2.5.1. Karlotoxin** 23
     - **2.5.2. Karmitoxin** 24
   - **2.6.** ***Ostreopsis*** 24
   - ***2.7. Prorocentrum*** 25
     - **2.7.1. Prorocentin** 26
     - **2.7.2. Belizentrin** 26
     - **2.7.3. Limaol** 26

27

2.8. Vulcanodinium 27
2.8.1. Pinnatoxin 27
2.8.2. Portimine 28
3. Conclusion 29
Acknowledgments 30
Abbreviations 30
Reference 30

1. Introduction

Dinoflagellates (Dinoflagellata, Alveolata) are a lineage of protists that are ecologically important components of marine and freshwater microbial communities. To date, about 2400 species of dinoflagellate belonging to 260 genera have been described [1], making this one of the most diverse protist lineages. Approximately half of dinoflagellate species are photosynthetic, therefore being considered as microalgae. Most photosynthetic dinoflagellates have reddish brown chloroplasts containing chlorophylls a and c2, beta-carotene and a group of unique xanthophylls including peridinin. Some, however, contain golden brown or green chloroplasts originating from independent tertiary endosymbiotic events. Dinoflagellates characteristically possess two dissimilar flagella, one of which (the transverse flagellum) lies in a groove around the cell (the cingulum) and the other that beats posteriorly (longitudinal flagellum). Dinoflagellates have a complex cell covering called an amphiesma composed of a series of membranes, flattened 'amphiesmal vesicles' and related structures. In many dinoflagellates these support overlapping cellulose plates to create a sort of armour called the theca (as opposed to 'athecate' or 'naked' dinoflagellates). Most dinoflagellates have a peculiar form of nucleus, called a dinokaryon, in which the permanently condensed chromosomes are attached to the nuclear membrane. Most dinoflagellates are pelagic, but many benthic forms exist, and some dinoflagellates, such as the genera *Symbiodinium* [2–4], *Pelagodinium* [5], *Brandtodinium* [6] (can form symbiotic relationships with invertebrate animals or other protists). Dinoflagellates are a rich source of bioactive compounds. Many dinoflagellates are well known producers of toxins that can be harmful to humans via syndromes like Paralytic Shellfish Poisoning (PSP) [7–11], Neurotoxic Shellfish Poisoning (NSP) [12–14], Azaspiracid Shellfish Poisoning (AZP) [15,16], Diarrheic Shellfish Poisoning (DSP) [17] and Ciguatera Fish Poisoning (CFP) [18,19]. These metabolites are generally

detected because of their bioaccumulation through the marine food-chain into marine organisms including fish, crustaceans and mollusks, which are consumed by humans. It is known that these neurotoxins interact with specific neurotransmitter receptors or voltage-sensitive ion channels [20]. Voltage-gated Na^+, Ca^{2+}, and K^+ ion channels lead to the generation of electrical signals involved in muscle contraction, hormone secretion, sensing of the environment, processing of information in the brain and nervous output from the brain [21]. It is therefore important to obtain information on the molecular structure of these metabolites in order to attempt to develop means to regulate/control their effects. Other dinoflagellate metabolites may have beneficial biological properties, such as amphidinol macrolides that have been shown to exhibit anti-bacterial and anti-fungal activities [22]. The constraints for isolation and characterization of new molecules produced by dinoflagellates remain cumbersome. Most significantly, large-scale cultivation of dinoflagellates to obtain sufficient biomass for purification and characterization of new molecules is relatively complicated because of (i) their relatively low growth rate, and (ii) the difficulty of attaining high cell density in culture. In addition, some heterotrophic or mixotrophic species cannot be cultivated in monoclonal or axenic culture conditions, being dependent on acquisition of eukaryotic or bacterial prey. The extreme biodiversity of dinoflagellates means that they undoubtedly represent a huge potential reservoir of compounds to be discovered and/or molecularly characterized. Interest in this potential source of bioactive compounds is reflected in the recent use of cutting edge technologies for the characterization of chemical structures, leading to a growing number of new secondary metabolites from dinoflagellates having been described. A set of these metabolite structures was selected in this review to highlight these recent advances.

2. Chemical diversity sorted by genus

The present review can be considered as an update of the previous chapter "*Bioactive metabolites from marine dinoflagellates"* in *Comprehensive Natural Products II: Chemistry and Biology (2010)*. In light of the vast and diverse chemical reservoir produced by dinoflagellates, this review is not intended to be exhaustive. Rather, we provide here an overview of new advances on the isolation and the structural characterization of metabolites from dinoflagellates that have been shown to exhibit bioactivities of potential interest for applications related to human health (**Table 1**).

Table 1. Selected set of metabolites characterized from dinoflagellates.

Dinoflagellates (Genus)	Metabolites	Chemical class		Biological Activity	Reference
Amphidinium	Amphidinin A **(1)**	**Polyketides**	Antifungal/Antibacterial	***Bacillus subtilis:*** MIC of 16 μg/mL ***Aspergillus niger:*** IC_{50} of 4 μg/mL	[23,24]
	Amphidinin C **(2)**			***Staphylococcus aureus:*** MIC of 32 μg/mL ***Bacillus subtilis:*** MIC of 32 μg/mL ***Aspergillus niger:*** IC_{50} of 12 μg/mL ***Trichophyton mentagrophytes:*** IC_{50} of 16 μg/mL	[25]
	Amphidinin D **(3)**			***Trichophyton mentagrophytes:*** IC_{50} of 16 μg/mL	[25]
	Amphidinin E **(4)**			***Staphylococcus aureus:*** MIC of 32 μg/mL ***Bacillus subtilis:*** MIC of 32 μg/mL ***Aspergillus niger:*** IC_{50} of 16 μg/mL ***Trichophyton mentagrophytes:*** IC_{50} of 16 μg/mL	[25]
	Amphidinin F **(5)**			***Trichophyton mentagrophytes:*** IC_{50} of 16 μg/mL	[25]
	Amphidinin G **(7)**			***Trichophyton mentagrophytes:*** IC_{50} of 8 μg/mL	[23,24]
	Amphidinol 17 **(9)**	**Polyketides**	Hemolytic Activity	EC_{50} of 4.9 μM in a hemolytic assay	[26]
	Amphidinol 18 **(10)**		Antifungal	***Candida albicans:*** IC_{50} of 9 μg/mL	[27]
	Amphidinol 19 **(11)**		-	-	[27]
	Amphidinol 20 **(12)**		Hemolytic Activity	EC_{50} of 3 μM in a hemolytic assay	[28]
	Amphidinol 21 **(13)**		-	-	[28]
	Amphirionin-2 **(14)**	**Polyketides**	Cytotoxicity/Toxic	**Caco-2**: IC_{50} 0.1 μg/mL; **A549**: IC_{50} 0.1 μg/mL T/C 120% at dose of 0.5mg/kg **(Murine tumor)**	[29]
	Amphirionin-4 **(15)**		Cells proliferation activity	950% proliferation propotion of **ST-2** cells at 0.1 ng/mL.	[30]
	Amphirionin-5 **(16)**			282% proliferation propotion of **ST-2** cells at 320% proliferation propotion of **MC3T3-E1** cells at 10 ng/mL.	[31]

Dinoflagellates (Genus)	Metabolites	Chemical class		Biological Activity	Reference
Amphidinium	Iriomoteolides-1a **(17)**	**Macrolides**	Cytotoxicity	**DG-75**: IC_{50} of 0.004μg/mL	[32]
	Iriomoteolides-1b **(18)**			**DG-75**: IC_{50} of 0.9μg/mL	[32]
	Iriomoteolides-1c **(19)**			**DG-75**: IC_{50} of 0.004μg/mL	[32]
	Iriomoteolides-2 **(20)**			**DG-75**: IC_{50} of 0.006μg/mL; **HeLa**: IC_{50} of 0.03μM	[33]
	Iriomoteolides-3a **(21)**			**DG-75**: IC_{50} of 0.08μg/mL	[34]
	Iriomoteolides-3b **(22)**			**DG-75**: IC_{50} of 0.02μg/mL	[34]
	Iriomoteolides-4 **(23)**			**DG-75**: IC_{50} of 0.8μg/mL	[35]
	Iriomoteolides-5 **(24)**			**DG-75**: IC_{50} of 1μg/mL	[35]
	Iriomoteolides-9 **(25)**			**Hela**: IC_{50} of 15mM	[36]
	Iriomoteolides-10 **(26)**			**DG-75**: IC_{50} of 1.5 μM; **HeLa**: IC_{50} of 1.5μM **MH134**: IC_{50} of 3.3μM	[37]
	Iriomoteolides-11 **(27)**			**DG-75**: IC_{50} of 1.5 μM; **HeLa**: IC_{50} of 2μM	[36]
	Iriomoteolides-12 **(28)**			**DG-75**: IC_{50} of 50μM	[37]
	Amdigenol-A **(29)**	**Polyketides**	ND	ND	[38]
	Amdigenol-E **(30)**		ND	ND	[39]
	Amdigenol-G **(31)**		ND	ND	[39]
Azadinium	Azaspiracids-33 **(33)**	**Polyether**	Cytotoxic	**TIB-152**: EC_{50} of 5.2 nM	[16]
	Azaspiracids-34 **(34)**			**TIB-152**: EC_{50} of 0.2 nM	[16]
	Azaspiracids-36 **(35)**			**TIB-152**: EC_{50} of 1.70 nM	[40]
	Azaspiracids-37 **(36)**			**TIB-152**: EC_{50} of 0.85 nM	[40]
Dinophysis	Acuminolide-A **(37)**	**Polyether**	ATPase activity	250% ATPase activity in skeletal muscles at 1μM	[41]

Dinoflagellates (Genus)	Metabolites	Chemical class		Biological Activity	Reference
Gambierdiscus	Gambierone **(38)**	**Polyether**	Ladder-shaped toxin	A slight cytosolic Ca^{2+} increase was observed (at 30 nM to **SH-SY5Y**)	[42]
	Gambieroxide **(40)**	**Polyether**	ND	ND	[43]
Karlodinium	Karlotoxin-1a **(42)**	**Polyketides**	Hemolytic Activity	EC_{50} of 63 nM in a hemolytic assay	[44]
	Karlotoxin-1b **(43)**			EC_{50} of 56 nM in a hemolytic assay	[45]
	Karlotoxin-1c **(44)**			EC_{50} of 300 nM in a hemolytic assay	[45]
	Karlotoxin-2 **(45)**			-	[45]
	Karlotoxin-3a **(46)**			EC_{50} of 200 nM in a hemolytic assay	[45]
	Karlotoxin-3b **(47)**			EC_{50} of 110 nM in a hemolytic assay	[45]
	Karlotoxin-3c **(48)**			EC_{50} of 2400 nM in a hemolytic assay	[45]
	Karmitoxin **(49)**	**Polyketides**	Toxic	**RTgill-W1:** LC_{50} of 125 ± 1nM ***Aciarta tonsa* (copepod):** LC_{50} of 400 ± 100nM	[46]
Ostreopsis	Ostreol-A **(50)**	**Polyketides**	Toxic	***Artemia salina:*** LD_{50} of 0.9 µg/mL.	[47]
	Ostreol-B **(51)**		Cytotoxic	**HepG2:** IC_{50} of 4.8 µM ; **HCT-116:** IC_{50} of 0.1 µM **Neuro2a:** IC_{50} of 0.9 µM	[48]
Prorocentrum	Prorocentin-1 **(52)**	**Polyketides**	Cytotoxic	**DLD-1**: IC_{50} of 16.7µg/mL **RPMI7951**: IC_{50} of 83.6µg/mL	[49]
	Prorocentin-4 **(53)**		-	-	[50]
	Belizentrin **(54)**	**Macrolides**	Neurotoxic	50% reduction in maximum neuronal survival after 24 h EC_{50} was estimated at 193 ± 7 nM.	[51]
	Limaol **(55)**	**Polyketides**	Cytotoxic	**HepG2:** IC_{50} of 3.7 µM ; **HCT-116:** IC_{50} of 7.3 µM **Neuro2a:** IC_{50} of 9.6 µM	[52]
Vulcanodinium	Pinnatoxin-E **(56)**	**Macrolides**	Toxic	LD_{50} of 57.0µg/kg **(mice by intraperitoneal injection)**	[53]
	Pinnatoxin-F **(57)**			LD_{50} of 12.7µg/kg **(mice by intraperitoneal injection)**	[53]
	Pinnatoxin-G **(58)**			LD_{50} of 48.0µg/kg **(mice by intraperitoneal injection)**	[53]
	Pinnatoxin-H **(59)**			LD_{50} of 67µg/kg (**mice by intraperitoneal injection)**	[54]

Footnote: Statistics: IC_{50} half maximal inhibitory concentration, EC_{50} median effective concentration, MIC minimum inhibitory concentration, T/C Treatment to control (comparative tumor size between treated tumor and control tumor), LD_{50} median lethal dose. **Cell lines:** A549 lung carcinomatous tissue, Caco-2 human epithelial colorectal adenocarcinoma, DG-75 human B-lymphocyte; HeLa human cervix adenocarconoma ST-2 bone marrow-derived stroma, MC3T3-E1 osteoblastic, SH-SY5Y Neuroblastoma, RTgill-W1 trout epithelial cell line, HepG2 liver hepatocellular, HCT-116 colorectal carcinoma, Neuro2a mouse neuroblastoma, DLD-1 colorectal adenocarcinoma, RPM1751 Human Malignant Melanoma.

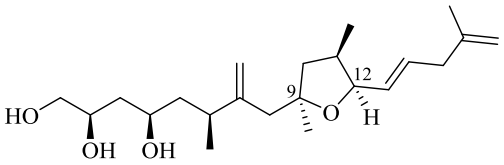
2.1. Amphidinium

Amphidinium is a widespread dinoflagellates genus, found in both free-living and benthic states in temperate and tropical marine waters. *Amphidinium* species are often amongst the most abundant dinoflagellates in benthic ecosystems [55]. Over 100 species have been described in this genus [1]. These dinoflagellates are known producers of several families of bioactive macrolides including amphidinolides [56], amphidinols [22,27,57–60], colopsinols [61], luteophanols [62,63] and amdigenols [38,39]. Furthermore, this genus also produces characteristic linear polyketides such as amphidinins [23–25] and amphirionins [29–31].

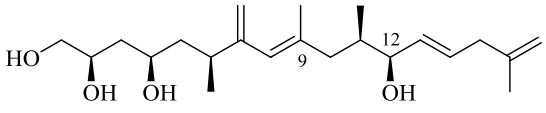
2.1.1. Amphidinin

Amphidinins are a family of cytotoxic linear polyketides isolated from the marine dinoflagellate *Amphidinium.* Since 2010, six amphidinins have been isolated, the structures of which are illustrated in **Figure 1**. The first amphidinin **(1)** was isolated in 1994 from a symbiotic strain of *Amphidinium sp.* [64]. **(1)** is composed of 17 linear carbons that form a tetrahydrofuran ring. This long backbone is substituted by different chemical groups including 3 hydroxy groups, 2 olefins, 1 methylene and 4 methyls. The absolute configurations of the six stereogenic centers was solved in 2014 [23].

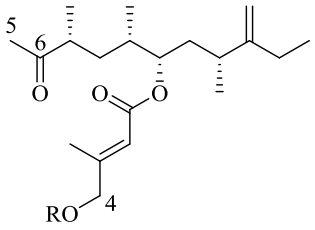
In 2014, four new amphidinins: C-F **(2-5)** were isolated from the same culture of symbiotic *Amphidinium sp.*. The structures of these planar molecules are very similar. **(4-5)** have a hydroxyl on position 6 which is replaced by a ketone group on **(2-3)**. Substituents on C_4 introduce also a structural diversity: **(2)** and **(4)** have an hydroxyl group in this position while **(3)** and **(5)** have a ribofuranosyl group [25]. In 2015, another linear polyketide was isolated from the same species: Amphidinin G **(7)**. This metabolite is directly related to amphidinin A **(1)**. **(7)** was expected to be a precursor of amphidinin A **(1)**. In fact, **(1)** is obtained by the formation of tetrahydrofuran ring by the addition of hydroxyl group at C_{12} to an olefinic carbon at C_9 of **(7)**. These molecules are directly associated with another metabolite produced by *Amphidinium*: amphidinolide Q **(6)** [46]. This metabolite corresponds to the cyclization of **(2)** on positions **4-5**.



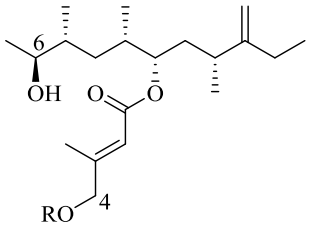
Amphidinin A **(1)**



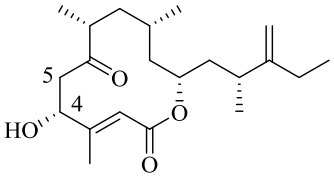
Amphidinin G **(7)**



Amphidinin C **(2)** R = H
Amphidinin D **(3)** R = alpha-D-ribofuranosyl



Amphidinin E **(4)** R = H
Amphidinin F **(5)** R = alpha-D-ribofuranosyl



Amphidinolide Q **(6)**

Figure 1. Structures of amphidinins A,C-G and amphidinolide Q (**1**-**7**).

Amphidinins have been tested for their cytotoxicity, anti-fungal and anti-bacterial activities. Only compound **(5)** showed modest cytotoxicity against murine lymphoma P388 cells (IC_{50} of 5.8 μg/mL). The majority of compounds were active against the *Trichophyton mentagrophytes* fungus (IC_{50} of 8 μg/mL **(8)** IC_{50} of 16 μg/mL **(2-4)** and 32 μg/mL **(5-6)**). Amphidinin A **(1),** C **(2)** and E **(4)** showed antimicrobial activities against *Bacillus subtilis* (MIC 16 μg/mL **(1)** and 32 μg/mL **(2)(4)**) and *Aspergillus niger* (IC_{50} of 4 μg/mL, IC_{50} of 12 μg/mL, IC_{50} of 16 μg/mL, respectively) [11]. Only amphidinin C **(2)** and E **(4)** exhibited activity against *Staphylococcus aureus* (MIC 32 μg/mL for both).

2.1.2. Amphidinols

Amphidinols form a group of polyhydroxylated and polyunsaturated polyketides very characteristic of dinoflagellates from the genus *Amphidinium.* The first member of the series: AM 1 **(8) (Figure 2)** was isolated from *Amphidinium klebsii* in 1991 [57]. These secondary metabolites are constituted by 2 tetrahydropyran rings linked by a short C6 chain [45,65]. Structural modifications occur at the two ends that contain respectively a polyunsaturated

alkyl chain and a long irregular polyhydroxylated chain. In 2017, 21 amphidinols have been described [22,27,57–60]. Only metabolites isolated between 2010-2017 are described here. Amphidinol 17 (AM17; **9**) was isolated from a Bahamas strain of *Amphidinium carterae* [26]. This compound is characterized by the presence of a polyol arm shorter than other amphidinols [26]. Moreover, the polyunsaturated alkyl chain also has one less double bond. Nevertheless, this metabolite did not exhibit an antifungal activity [26].

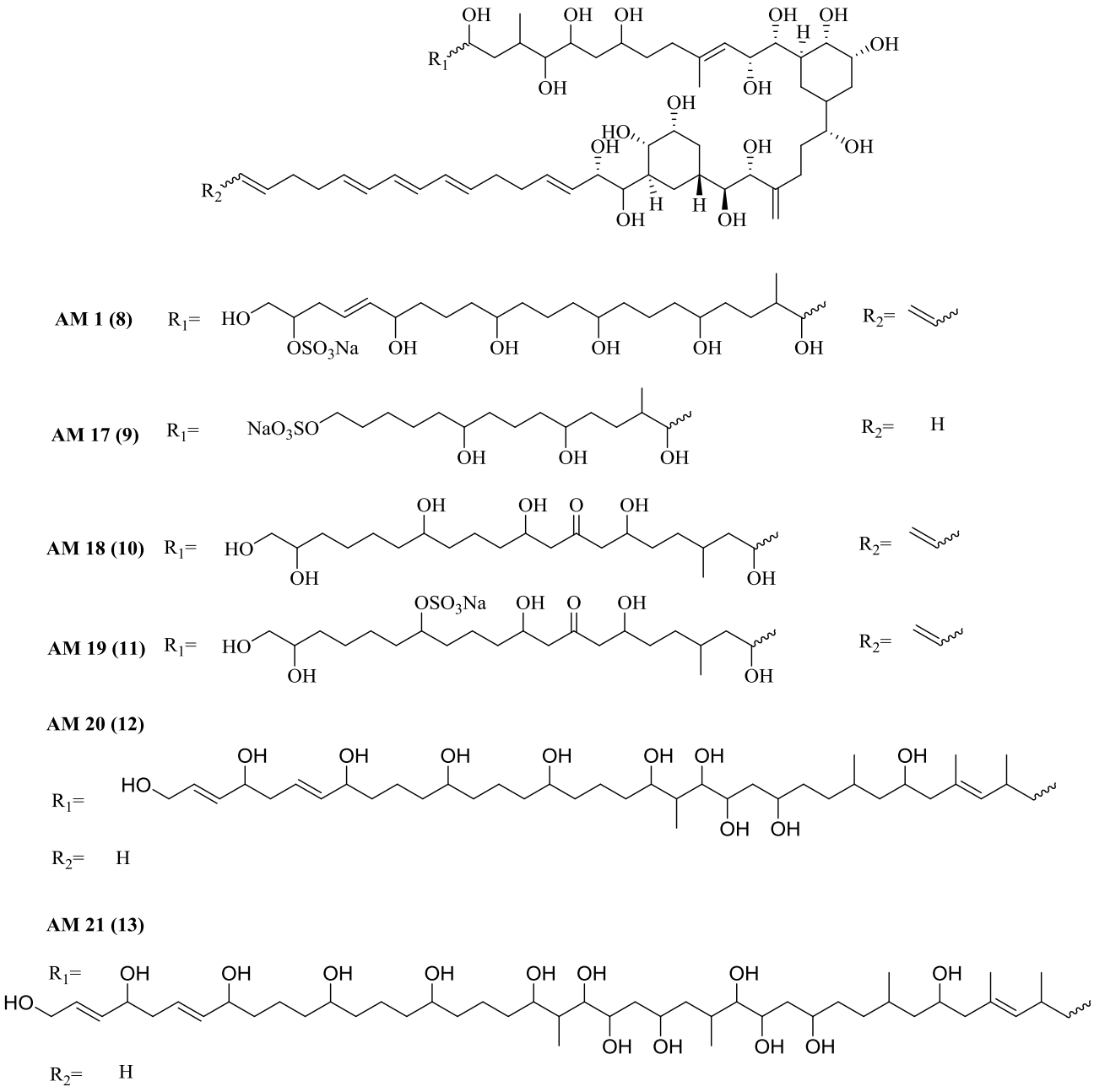


Figure 2. Structures of novel amphidinols 17-21 (**9**-**13**).

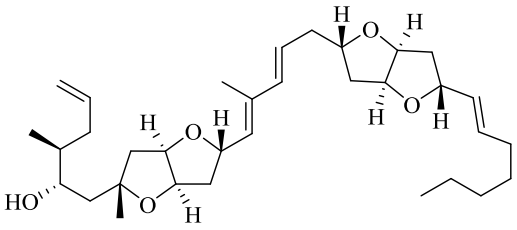
In 2017, a new antifungal amphidinol, AM18 (**10**), and a sulfate analogue, AM 19 (**11**),

were isolated from *Amphidinium carterae* [27]. The main difference from AM17 is on the hydroxyl chain with 15 hydroxyl groups (14 for **(10)**) and 1 ketone group**.** From a bioactivity point of view, AM18 (**10**) showed moderate antifungal activity against *Candida albicans* (9 μg/mL)[27]. The addition of a sulfate group reduces the antifungal activity of the compounds. Two other amphidinols have recently been isolated and characterized: AM20 (**12**) and AM21 (**13**), with the longest polyol chain for compound (**13**) [28]. The dose dependency of hemolysis of AM17 (**9)**, AM20 (**12**) and AM21 (**13**) were determined using human red blood cells but only (**9)** and (**12**) were active (EC_{50} of 4.9 μM and 3 μM, respectively) [26,28]. Additionally, AM20 and AM21 were tested for their antifungal activity on *Aspergillus niger* but no activity was found [28].

2.1.3. Amphirionin

2.1.3.1. Amphirionin-2

Amphirionin-2 **(14)** is a polyketide consisting of a linear C30 carbon chain. This is the first *Amphidinium* polyketide possessing a hexahydrofuro[3,2-b]furan moiety [29]. Amphirionin-2 **(14)** showed a modest cytotoxicity against human colon carcinoma (IC_{50} of 0.1μg/mL) and human lung adenocarcinoma (IC_{50} of 0.6μg/mL). The cytotoxicity against human cervix adenocarcinoma Hela cells was also determined, but proved to be low with a 20% growth inhibition at 1 μg/mL. In addition **(14)** exhibited activity against an *in vivo* murine tumor (T/C (Treatment to control) 120% at a dose of 0.5 mg/kg). A surface plasmon resonance assay was used to demonstrate an interaction of amphirionin-2 **(14)** with the actin cytoskeleton [29].

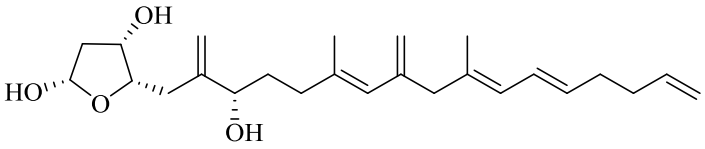


Amphirionin-2 **(14)**

2.1.3.2. Amphirionin-4

A linear polyketide, amphirionin-4 **(15)**, was isolated (0.0031% of dry weight) from cultivated cells of *Amphidinium* [30]. This polyketide consists of a linear C22 carbon chain forming a tetrahydrofuran ring. This linear chain is substituted by 3 hydroxyl groups, with 2

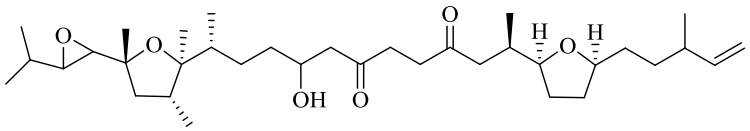
on the cycle. Compound **(15)** exhibited potent proliferation-promoting activity on murine bone marrow stromal ST-2 cells with a value of 950% at a concentration of 0.1 ng/mL [30].



Amphirionin-4 **(15)**

2.1.3.3. Amphirionin-5

Amphirionin-5 **(16)** was isolated from *Amphidinium* in 2014 [31]**.** This metabolite is a linear C28 polyketide forming 2 tetrahydrofuran rings and containing 2 ketone groups, 1 epoxide and 1 hydroxyl group. Like **(14)** and **(15)**, amphirionin-5 **(16)** promotes cell proliferation: a treatment with 10 ng/mL of **(16)** resulted in a 282% increase in the proliferation of murine bone-marrow derived stromal ST-2 cells and 320% increase in the proliferation of murine osteoblastic MC3T3-E1 cells [30].



Amphirionin-5 **(16)**

2.1.4. Iriomoteolides

Table 2. Lactone ring size and cytotoxicity for iriomoteolides. The various reported IC_{50} are mentioned in the table.

Iriomoteolides	Lactone size	Cytotoxicity activity		Reference
		Human B-lymphocyte cells	Human adenocarcinoma HeLa cells	
Iriomoteolides-1a	**20**	0.004 µg/mL		[32]
Iriomoteolides-1b	**20**	0.9 µg/mL		[32]
Iriomoteolides-1c	**20**	0.004 µg/mL		[32]
Iriomoteolides-2	**23**	0.006 µg/mL	0.03 µg/mL	[33]
Iriomoteolides-3a	**15**	0.08 µg/mL		[34]
Iriomoteolides-3b	**15**	0.02 µg/mL		[34]
Iriomoteolides-4	**16**	0.8 µg/mL		[35]
Iriomoteolides-5	**20**	1 µg/mL		[35]
Iriomoteolides-9	**15**		15 mM	[36]
Iriomoteolides-10	**21**	1,5 µM	1,5 µM	[37]
Iriomoteolides-11	**19**	1,5 µM	2 µM	[36]
Iriomoteolides-12	**12**	50 µM		[37]

Iriomoteolides are macrolides directly related to amphidinolides that are produced by *Amphidinium* species. They have a variety of backbone skeletons and different size macrolactone rings **(Table 2)**. All iriomoteolides contain a vicinal carbon branch, but they differ in the number of hydroxyl groups and methylene units. Most iriomoteolides are potent cytotoxic compounds and with putative antitumor activity **(Table 2)**.

2.1.4.1. Iriomoteolide-1a, 1b and 1c

Iriomoteolides-1a, b and c **(17-19)** are 20-membered macrolides isolated from *Amphidinium sp*.. Iriomoteolide-1a **(17)** has a six-membered hemiacetal ring, a methylene group and 4 hydroxyl groups [32]. It has a hydroxyl group at C_9 and a ketone at C_{13} conjugated with an E-double bond. Iriomoteolide-1c **(19)** is considered a homologue of **(17)** with a 4-hydroxy-3-methylpentyl side chain instead of a 3-hydroxy-2-methylbutyl side chain [32]. Iriomoteolide-1a, b and c **(17-19)** exhibited potent cytotoxicity against human B-lymphocytes with a value of IC_{50} of 0.004 μg/mL for **(17)** and **(19)**.

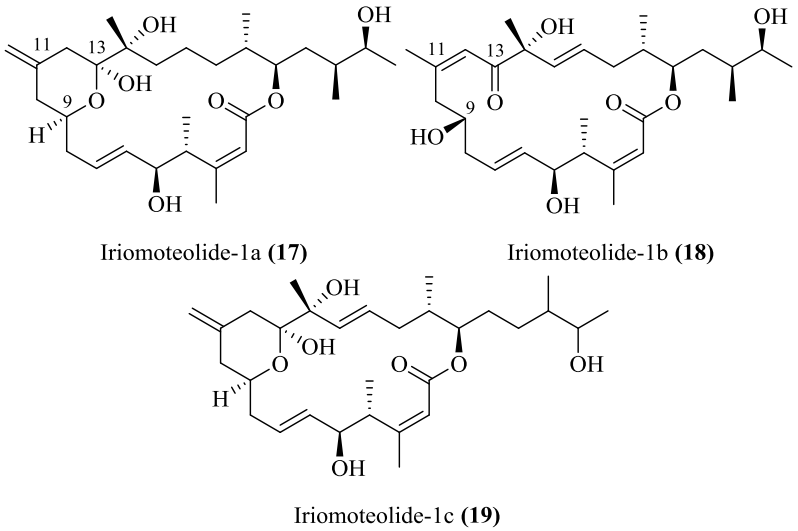
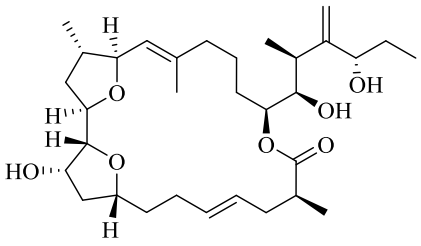


Figure 3. Structures of iriomoteolides-1a, 1b and 1c. (**17**-**19**).

However, the IC_{50} value (0.9 μg/mL) of iriomoteolide-1b **(18)** against human B lymphocytes was weak compared to **(17)** and **(19)** [32]. This result suggests that the six-membered hemiacetal ring (C_9–C_{13}) and/or the methylene unit (C_{11}) in iriomoteolide-1a **(17)** is important for cytotoxic activity.

2.1.4.2. Iriomoteolide-2a

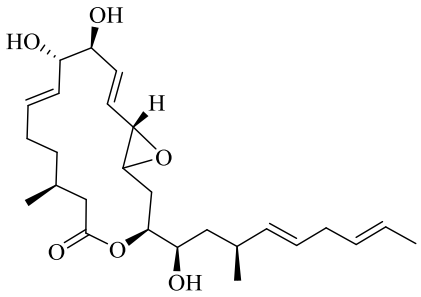
Iriomoteolide-2a **(20)** is the first reported natural product possessing a 23-membered macrolactone ring consisting of a polyketide chain with 2 tetrahydrofuran rings [29]. **(20)** exhibited potent cytotoxicity against human B-lymphocyte DG-75 cells (IC_{50} of 0.006 μg/mL) and human cervix adenocarcinoma HeLa cells (IC_{50} of 0.03 μg/mL) [29]. Moreover, this compound exhibited activity against murine tumor *in vivo* (T/C 132%) at a dose of 0.2 mg/kg [29].



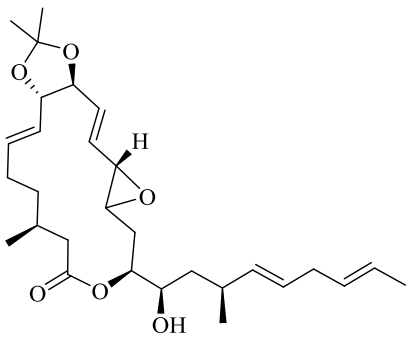
Iriomoteolide-2a **(20)**

2.1.4.3. Iriomoteolide-3a et 3b

Iriomoteolide-3a **(21)** and its 7,8-oisopropylidene derivative **(22) (Figure 4)** are 15-membered macrolides with an allyl epoxide, 3 hydroxyl groups and 2 methyl groups [34]. Although two classes of 15-membered macrolides (amphidinolides J and O) have been isolated from the symbiotic dinoflagellate *Amphidinium*, the carbon chain length and oxygen-substituted positions for **(21)** are quite different from those of these known 15-membered macrolides [34,66]. A cell-based screening on cytotoxicity and antiviral activities showed that iriomoteolide-3a **(21)** and iriomoteolide-3b **(22)** are potently cytotoxic against human B-lymphocyte DG-75 cells (IC_{50} of 0.08 and 0.02 μg/ mL, respectively) and Raji cells (IC_{50} of 0.05 and 0.02 μg/mL, respectively) [34].



Iriomoteolide-3a **(21)**



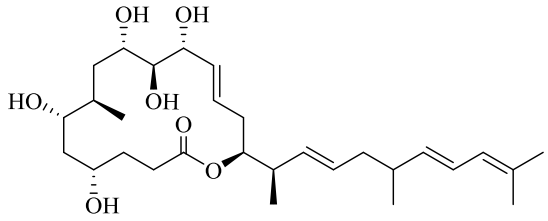
Iriomoteolide-3b **(22)**

Figure 4. Structures of iriomoteolides-3a and b. (**21**-**22**).

2.1.4.4. Iriomoteolide-4a

Iriomoteolide-4a **(23)** is a 16-membered macrolide possessing 5 hydroxyl groups and substituted by an isoprene chain on the side chain. This metabolite is the second *Amphidinium* macrolide with a 16-membered macrocyclic ring [35].

.

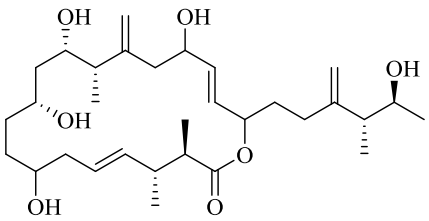


Iriomoteolide-4a **(23)**

Iriomoteolide-4a (23) was tested *in vitro* for the capacity to inhibit the growth of tumor cells: (23) showed a moderate toxicity against human B-lymphocyte DG-75 cells with an IC_{50} of 0.8 µg/mL [35].

2.1.4.5. Iriomoteolide-5a

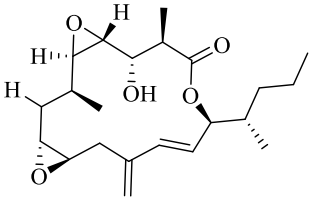
Iriomoteolide-5a **(24)** is a 20-membered macrolide with a unique carbon skeleton associated with five hydroxyl groups [35]. Although two classes of 20-membered macrolides (amphidinolides A [67] and U [68]) had been isolated from the symbiotic dinoflagellate *Amphidinium*, the carbon chain length and C1-branches of **(24)** are different from those of these macrolides. Iriomoteolide-5a **(24)** exhibited moderate toxicity against human B-lymphocyte DG-75 cells with an IC_{50} of 1 µg/mL [35].



Iriomoteolide-5a **(24)**

2.1.4.6. Iriomoteolide-9a

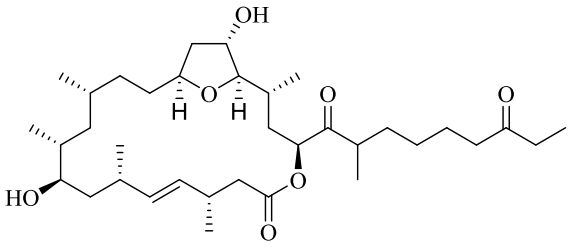
Iriomoteolide-9a **(25)** is another macrolide isolated from *Amphidinium* in 2017. It is a 15-membered macrolide with 2 epoxy rings, 4 methyl groups, and 1 hydroxyl group [36]. Several 15-membered macrolides had previously been isolated such as amphidinolides O and P [66] and iriomoteolide-3a [34]. This molecule is only slightly cytotoxic against human cervix adenocarcinoma HeLa cells with an IC_{50} of 15 mM [36].



Iriomoteolide-9a **(25)**

2.1.4.7. Iriomoteolide-10a

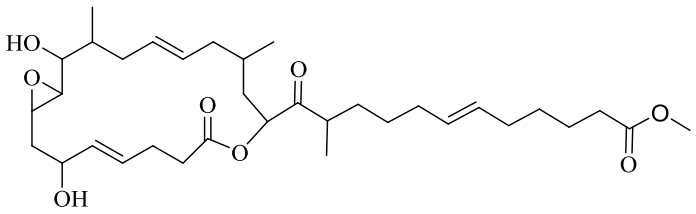
Iriomoteolide-10a **(26)** is the first 21-membered macrolide containing 1 tetrahydrofuran ring, 2 hydroxyl groups, 6 methyl groups and 2 ketone groups on the C1-carbon chain [37]. Iriomoteolide-10a **(26)** exhibited cytotoxic activity against human cervix adenocarcinoma HeLa (IC_{50} of 1.5 μM), human B-lymphocyte DG-75 cells (IC_{50} of 1.5 μM), and murine hepatocellular carcinoma MH134 cells (IC_{50} of 3.3 μM) [37].



Iriomoteolide-10a **(26)**

2.1.4.8. Iriomoteolide-11a

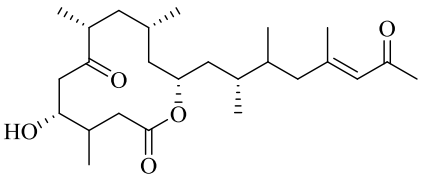
Iriomoteolide-11a **(27)** is a unique 19-membered macrolide possessing a methyl carboxylic group and an exo-ketone on side chains in addition to 1 epoxy ring, 3 methyl groups, 2 hydroxyl groups [36]. Compound **(27)** exhibited cytotoxic activity against human cervix adenocarcinoma HeLa cells with an IC_{50} of 2μM. Moreover, experiments using SPR revealed that compounds **(25)** and **(27)** are able to interact with actin [36].



Iriomoteolide-11a **(27)**

2.1.4.9. Iriomoteolide-12a

Irimoteolide-12a **(28)** is one of the smaller macrolides produced by *Amphidinium* with a 12-membered lactone ring [37] possessing 2 ketone groups, 1 hydroxyl group and 6 methyl groups. This metabolite can be directly associated to amphidinolide Q macrolides. Compound **(28)** showed moderate cytotoxicity against DG-75 cells (IC_{50} of 50μM) [37].



Iriomoteolide-12a **(28)**

2.1.5. Amdigenol

The polyol compound amdigenol A **(29)**, isolated from the dinoflagellate *Amphidinium* sp., consists of a C98-linear carbon backbone likely formed linearly by 2 amphidinol analogs [38]. In 2014, two other polyols were isolated from *Amphidinium* sp.. Amdigenol G **(31)** is a typical amphidinol analog with 2 linear carbon side chains connected to the core portion. Its structure is similar to that of luteophanol-A [69], but an oxymethine and a methylene (C43 and C47) position are switched [39]. In amdigenol E [39], the carbon chain is inserted between the 2 tetrahydropyrans, also possessing 2 epoxide groups. Amdigenols A **(29)**, E **(30)**, and G **(31)** inhibited an increase of the intracellular Ca^{2+} concentration in differentiated IMR-32 neuroblastoma cells. The effect on Ca^{2+} concentration was observed in the presence of amdigenols A, E, and G at 10 μM for **(29)** and 40μM for **(30)** and **(31)** [38,39]. The amdigenols were tested for their antimicrobial activity against

Streptomyces aureus, *Escherichia coli* and *Pseudomonas aeruginosa*, but did not show inhibition [38,39].

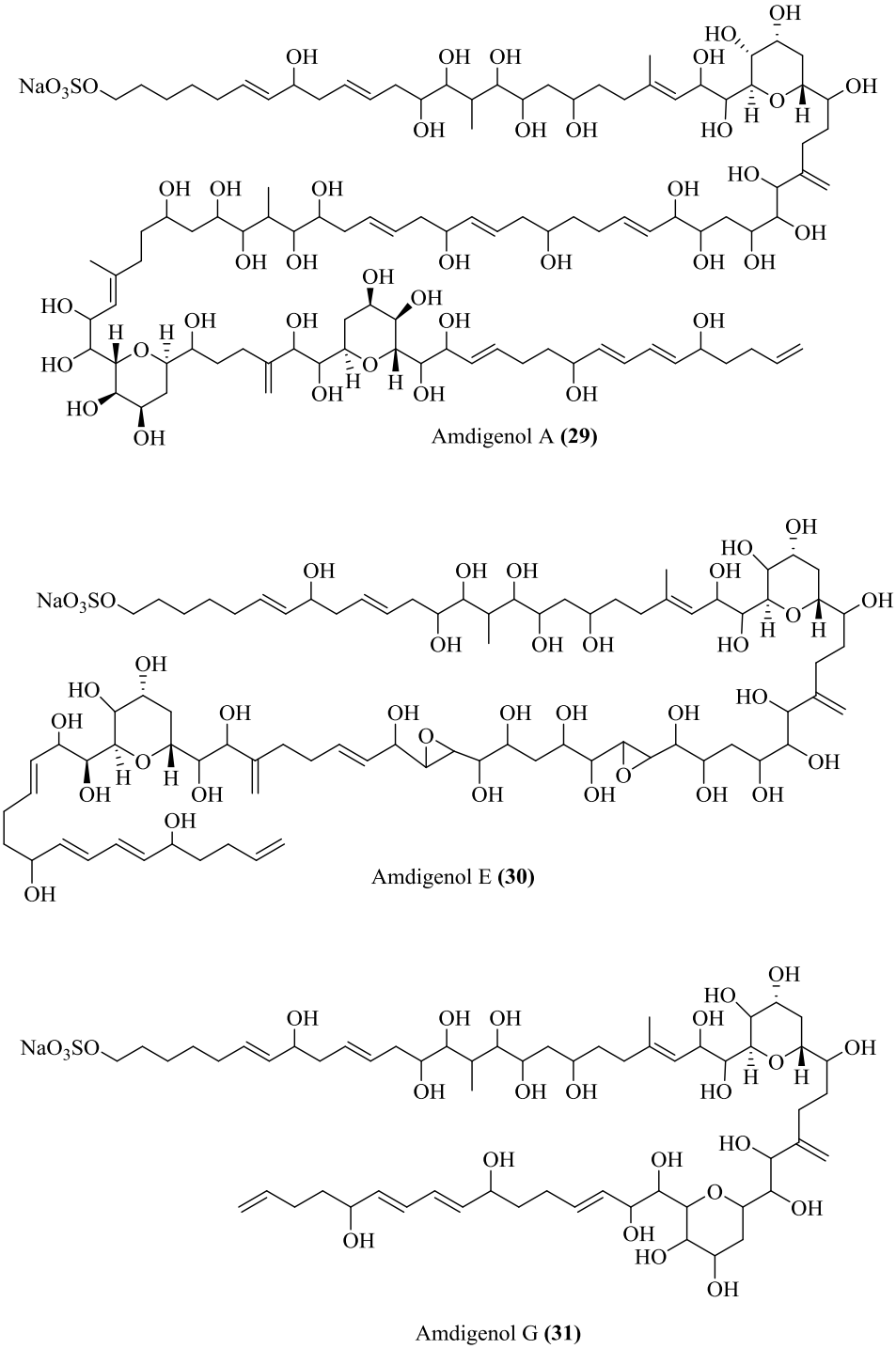


Figure 6. Structures of amdigenol A (**29**), E (**30**) and G (**31**).

2.2. Azadinium

2.2.1. **Azapiracids**

Azaspiracids (AZA) are a family of marine lipophilic polyether metabolites having 2 spiro-ring assemblies, a cyclic amine and a carboxylic acid functionality at one terminus [48]. They were first detected in 1995 following human illness following ingestion of contaminated mussels (*Mytilus edulis)* from Ireland. In 2009, a novel dinoflagellate species, *Azadinium spinosum*, was identified and described as the source of AZA production [15]. Several AZA-related structures were subsequently isolated from other *Azadinium* species: *A. poporum*, *A. dexteroporum*, and *A. spinosum* [16]. However, the genus *Azadinium* is not the only producer of Azaspiracids. Recently, the *Amphidomataceae* lineage was also shown to produce Azaspiracids. Specifically, *Amphidoma languida* has been found to produce a novel toxin belonging to the azaspiracids and implicated in a molluscan contamination event in the southern Atlantic coast [70].

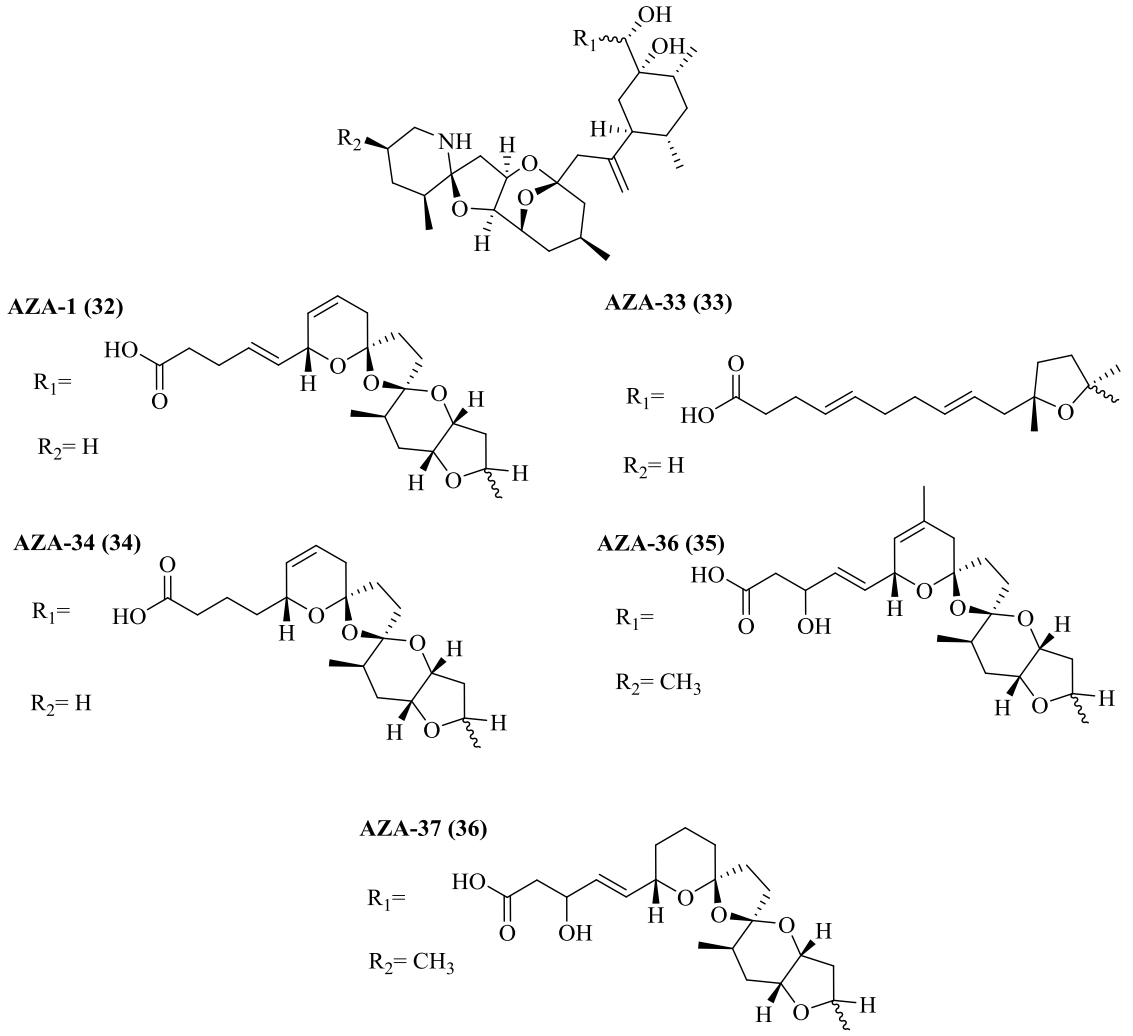


Figure 7. Structures of novel azaspiracids (AZA1, AZA 33, 34, 36, 37) **(36-41)**.

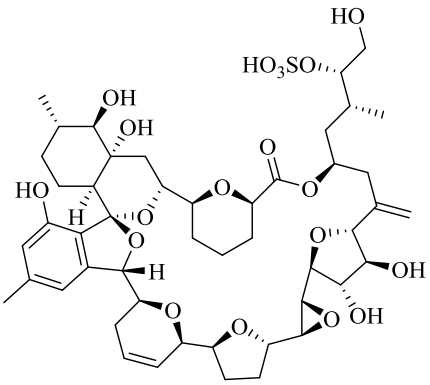
In 2015, three new azaspiracids were isolated from *Azadinium spinosum* (AZA-33 **(33)**, AZA-34 **(34)** and AZA-35). These compounds differ significantly at the carboxyl end of the molecule from known AZA analogues. The cytotoxicity of two analogues was tested on Jurkat T-lymphocyte cells, revealing that AZA-33 **(33)** and AZA-34 **(34)** are less and more toxic respectively compared to AZA-1 **(32)** [16]. New structures from *Azadinium poporum* were identified to be 3-hydroxy-8-methyl-39-demethyl-azaspiracid-1 (AZA-36 **(35)**) and 3-hydroxy-7,8-dihydro-39-demethyl-azaspiracid-1 (AZA-37 **(36)**). Compound **(35)** was found to be less toxic to T-lymphocyte cells (EC_{50} of 1.70 nM) compared to **(36)** (EC_{50} of 0.85 nM) and **(31)** (EC_{50} of 0.28 nM) [16]. From a structure-activity point of view, the addition of a hydroxyl function or the addition of a methyl on the heterocycle would decrease the activity, whereas decrease of the aliphatic chain length would increase the bioactivity.

2.3. Dinophysis

Over 50 species have been described in the genus *Dinophysis* [1], some of which are well-known harmful dinoflagellates. *Dinophysis* has received special attention because it can seriously impact the bivalve culturing industry when DSP toxins that it produces, such as okadaic acid (OA) [17], dinophysistoxin (DTX) [71,72] and pectenotoxin (PTX) [72], are found in commercialized mussels. These compounds have already been well-characterized and described in the literature, but a new macrolide, Acuminolide [41] was described from *Dinophysis* in 2014.

2.3.1. Acuminolide

Acuminolide-A **(37)** is a new 33-membered polyether macrolide isolated from the dinoflagellate *Dinophysis acuminata*. This compound is composed of 2 tetrahydrofurans, 2 dihydropyrans, 1 dihydroisobenzofuran, 1 octahydroisochromene, and 1 epoxide [41]. This compound did not show any cytotoxicity against four cancer cell lines [41].



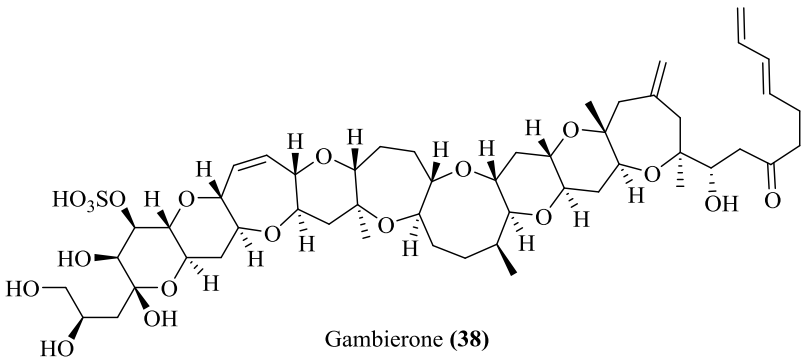
Acuminolide-A **(37)**

2.4. Gambierdiscus

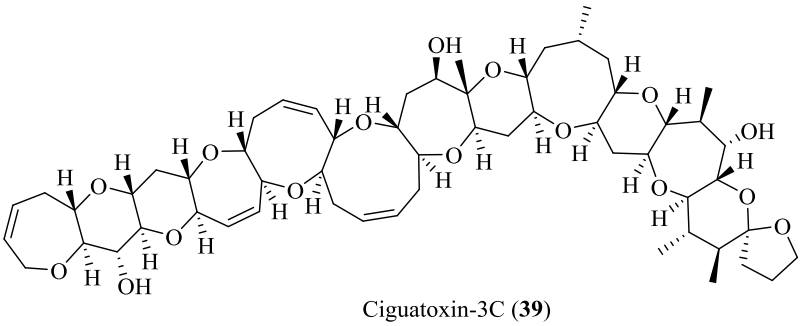
Eleven species have been described in the genus *Gambierdiscus* [1] which is one of the most extensively studied dinoflagellate genera. These dinoflagellates are well-known producers of hazardous metabolites such as ciguatoxin [73], gambieric acid [74], and maitotoxin [75–78]. Since 2010, two novel families of compounds have been described from these dinoflagellates: gambierone [42] and gambieroxide [43].

2.4.1. Gambierone

Isolated from *Gambierdiscus belizeanus*, gambierone **(38)** is a new macrolide described in 2017 [42]. The structure of this compound features an unprecedented polyether skeleton and an unusual right-hand side chain. Its relative configuration was fully determined by interpretation of several NMR analyses. The succession of cycles is very different from that of ciguatoxin, but compound **(38)** has a molecular formula and biological activity similar to those of ciguatoxin-3C **(39)** [79].



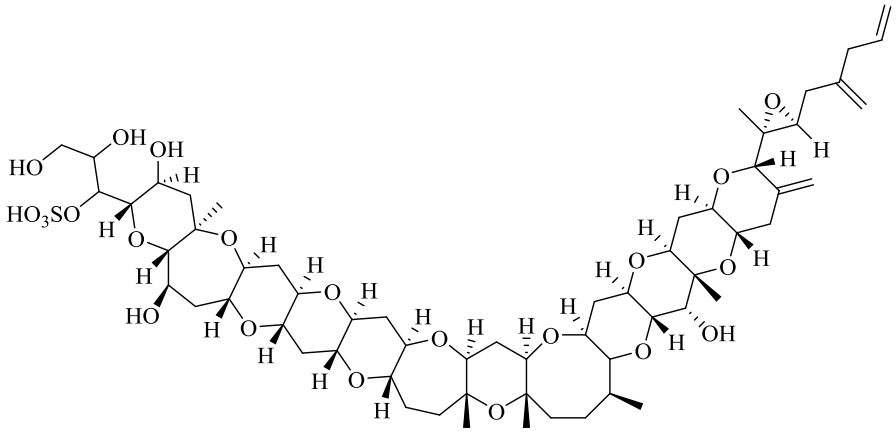
Gambierone **(38)**



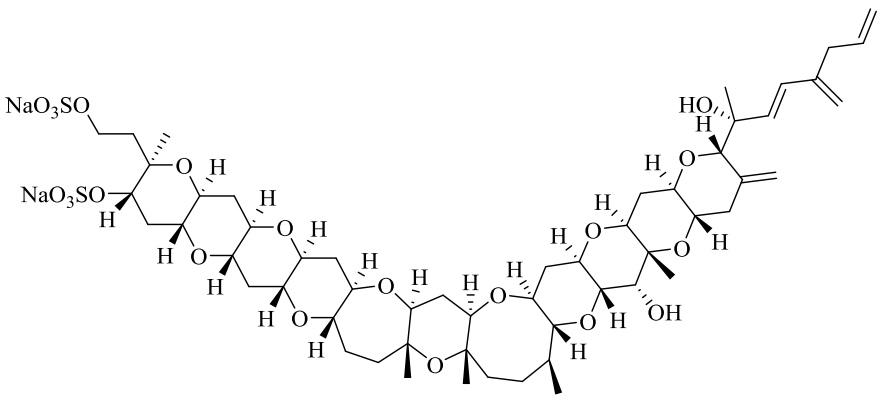
Ciguatoxin-3C (**39**)

2.4.2. Gambieroxide

A novel epoxy polyether compound named gambieroxide **(40)** was isolated from the benthic dinoflagellate *Gambierdiscus toxicus*. It is intriguing that the chemical structure of **(40)** is similar to that of yessotoxin (YTX) (**41**) produced by the dinoflagellate *Protoceratium reticulatum* [43], which is phylogenetically distant from *Gambierdiscus*. The bioactivity of this metabolite has not been studied, but from a structural point of view it is likely to show similar biological properties to YTX (**41**) [43].



Gambieroxide **(40)**



Yessotoxin (**41**)

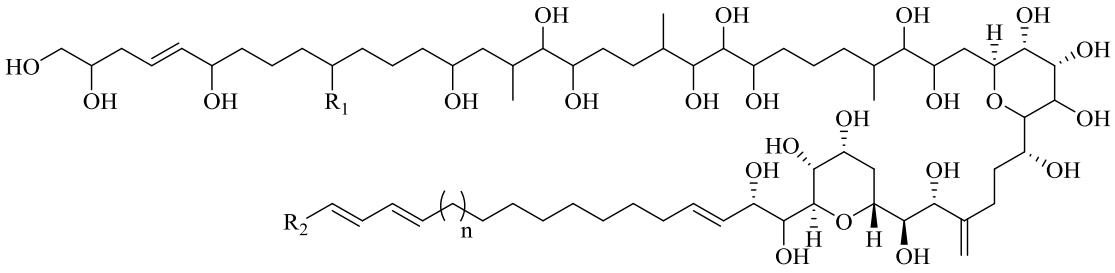
2.5. Karlodinium

The genus *Karlodinium,* which only contains 12 described species [1,80], is known to produce karlotoxins [45] and karmitoxins [46] which act as anti-grazing or allelopathic compounds.

2.5.1. Karlotoxin

The karlotoxins (**Figure 8**) **(42-48)** represent a class of metabolites that are structurally close to the amphidinols [44,45] produced by *Amphidinium*, having three distinct regions: (i) a polyol arm with variable hydroxylation and methylation, (ii) a hinge region containing 2 ether rings, (iii) and a lipophilic arm that often includes conjugated trienes in amphidinols [22,27,57,58]. Note here that the terminal diene is chlorinated in several karlotoxins [45]. Three types of karlotoxins, type-1 **(42-44)**, type-2 **(45)** and type-3 **(46-48)**, have been described, differing in the length of the lipophilic arm. Several analogues also exist, with a sulfate group replacing a hydroxyl group or variable terminal chlorination of the lipophilic chain [45] (**Figure 8**).

Various biological activities have been reported for these metabolites, including hemolytic properties [45]. The length of the lipophilic arm appears to modulate their hemolytic activity. Sulfated compounds have lower activity, whereas the presence of a chloric group on the C-terminal increases the hemolytic activity.

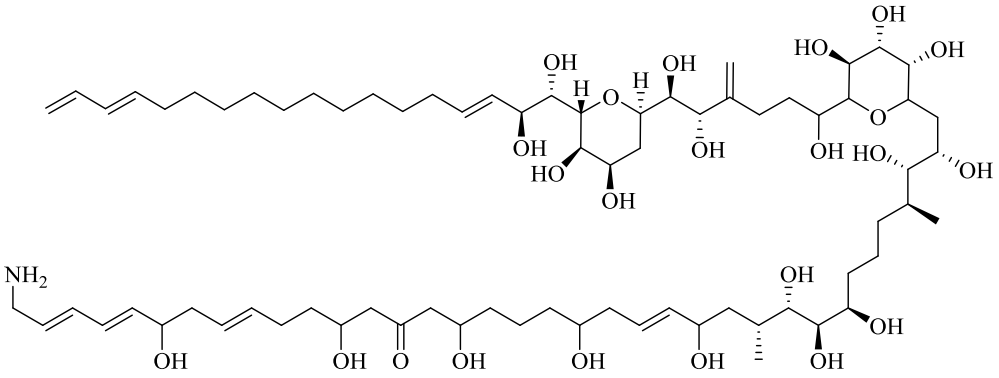


Name	n	R_1	R_2	Hemolytic Activity EC_{50} (nM)
KmTx 1a (42)	**3**	OH	H	63
KmTx 1b (43)	**3**	OH	Cl	56
KmTx 1c (44)	**3**	OSO_3H	H	300
KmTx 2 (45)	**1**	OH	Cl	NB
KmTx 3a (46)	**2**	OH	H	200
KmTx 3b (47)	**2**	OH	Cl	110
KmTx 3c (48)	**2**	OSO_3H	H	2400

Figure 8. Structures of karlotoxins (KmTxs).

2.5.2. Karmitoxin

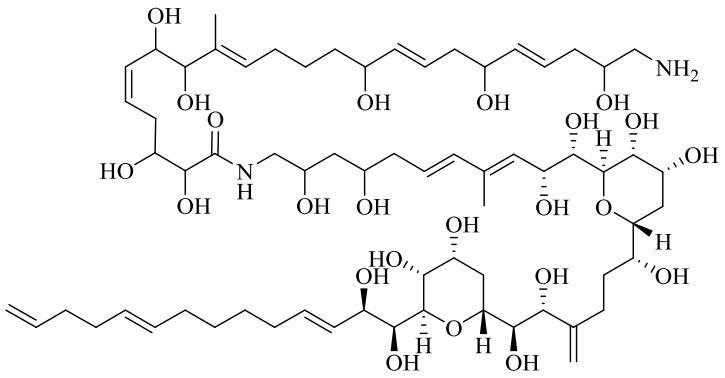
Karmitoxin (**49**) is a macrolide isolated in 2016 from the dinoflagellate *Karlodinium armiger*. Its structure is related to those of the amphidinols and karlotoxins. Karmitoxin (**49**) differs by having a longer aliphatic chain with a primary amine at the end [46]. Compound (**49**) exhibited cytotoxic activity against RTgill-W1 cells from the fish *Oncorhynchus mykiss* (LC_{50} of 125 nM) and toxicity to copepods has also been observed (LC_{50} of 400 nM) [46].



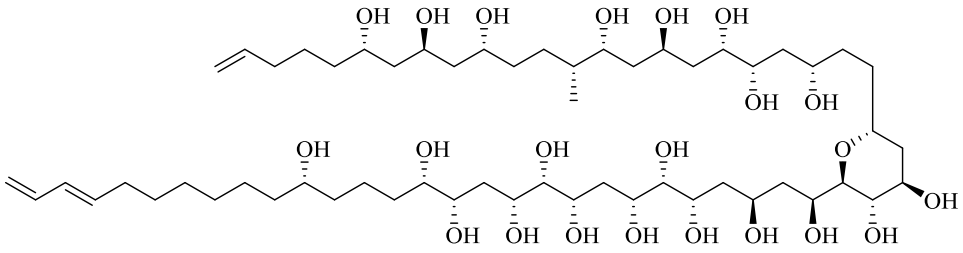
Karmitoxin **(49)**

2.6. Ostreopsis

Ostreopsis species are epiphytic benthic dinoflagellates, and some species are harmful to marine organisms (and to humans). Many studies have reported that these organisms produce the potent biotoxins palytoxin [81] and ovatoxin [82]. In 2013, 2 macrolides, specifically ostreols, were isolated and described from *Ostreopsis ovata* [47,48]. These new polyhydroxyl chain compounds are called Ostreol A (**50**) and B (**51**).



Ostreol A (**50**)



Ostreol B (**51**)

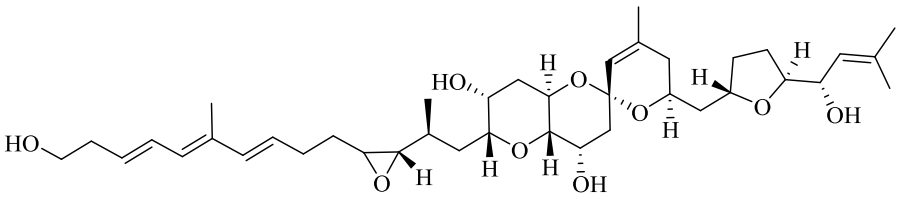
The former has 3 linear polyhydroxyls separated by 2 tetrahydropyrane like amphidinols or karlotoxins. The specificity is the presence of a primary amino group, an amide bond and a double bond. Ostreol A (**50**) was determined to have *in vitro* cytotoxicity against *Artemia salina* with a LD_{50} value of 0.9 μg/mL [47]. Ostreol B (**51**) is structurally different from Ostreol A (**50**) which contains only a hydroxyl function at number 21 and only 1 tetrahydropyran [48]. Ostreol B was shown to exhibit moderate cytotoxicity against hepatocarcinoma HepG2 (IC_{50} of 4.8 μM), neuroblastoma Neuro-2a (IC_{50} of 0.1 μM) and colon cancer HCT-116 (IC_{50} of 0.9 μM) cell lines [48].

2.7. Prorocentrum

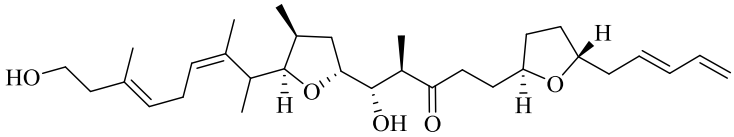
Prorocentrum is well-known for producing DSP toxins. Apart from these compounds, skeletally diverse bioactive compounds have also been isolated from cultured *Prorocentrum* species, including prorocentrolide [83], hoffmanniolide [84], prorocentin [49, 50], formosalides A and B [85], belizentrin [51], belizeanolide [86] and limaol [52].

2.7.1. Prorocentin

Prorocentins 1 and 4 (**52-53**) are linear polyketides produced by *Prorocentrum* sp. and *Prorocentrum lima*, respectively [50]. Prorocentin-1 (**52**) exhibited a moderate cytotoxic activity against the human colon adenocarcinoma cell line DLD-1 (IC_{50} = 16.7 µg/mL) and the human malignant melanoma cell line RPMI-7951 (IC_{50} = 83.6 µg/mL) [49]. By contrast, prorocentin-4 (**53**) was not cytotoxic when tested on the same cell lines.



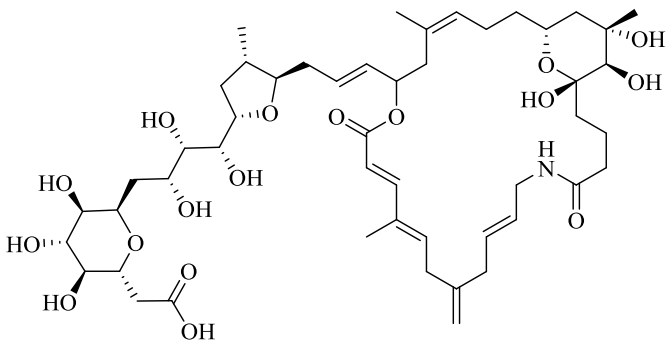
Prorocentin 1 **(52)**



Prorocentin 4 **(53)**

2.7.2. Belizentrin

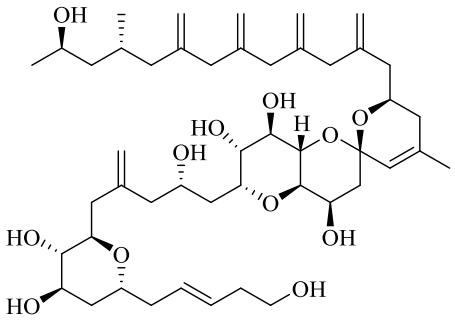
Belizentrin (**54**) is a 25-membered polyketide-derived macrocycle isolated from the marine dinoflagellate *Prorocentrum belizeanum* [51]. This macrolide is composed of an unsaturated 25-membered cycle containing 2 hydroxyls. This ring is substituted by a linear chain with 6 hydroxyls and 1 carboxylic acid moiety at the end of the chain. Several biological experiments have been performed on belizentrin (**54**), revealing toxicity against several neublastoma cell lines (EC_{50} approximately 200 nM) [51].



Belizentrin **(54)**

2.7.3. Limaol

Limaol (**55**) is a linear polyketide isolated from the benthic marine dinoflagellate *Prorocentrum lima*. Limaol (**55**) is constituted by a long aliphatic chain with 4 terahydropyran and 8 hydroxyl groups. From a biological point of view, limaol (**55**) exhibited moderate cytotoxicity against three tumoral cell lines: HepG2 (hepatocellular carcinoma), HCT-116 (colon adenocarcinoma), and Neuro2a (neuroblastoma) with EC_{50}s of 3.7, 7.3 and 9.6 μM, respectively [52].



Limaol **(55)**

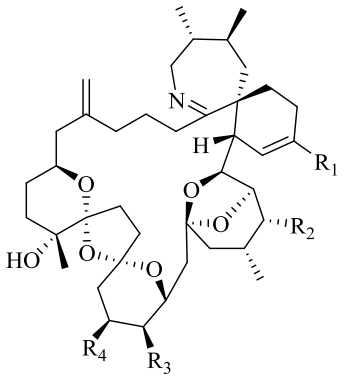
2.8. Vulcanodinium

The dinoflagellate genus *Vulcanodinium*, first described in 2010, is found in many locations around the world, including Australia, Japan, China, France and Hawaii [53,87]. *Vulcanodinium* is a producer of a potent neurotoxin, pinnatoxin [53,54], and of the macrolide, portimine [88].

2.8.1. Pinnatoxin

In 1995, a potent neurotoxin called Pinnatoxin, a polycyclic ether with a spiroimine function, was isolated from an Okinawan bivalve [89]. Since this discovery, several Pinnatoxin analogues have been isolated and characterized [90]. It was only in 2010 that *Vulcanodinium rugosum* was recognized as a producer of pinnatoxin E (**56**), F (**57**) and G (**58**) [53]. In 2014, a new Pinnatoxin H (**59**) was isolated from *V. rugosum.* (**59**) shares close structural similarities with other pinnatoxins, having an identical carbon skeleton but harboring different substituents [54]. The LD_{50} value of (**59**) in mice by intraperitoneal injection was 67 μg/kg and by gavage was 163 μg/kg [54], similar to the values for other

pinnatoxin compounds.



Pinnatoxin E **(56)** R_1= R_2= H R_3= OH R_4= CH_3

Pinnatoxin F **(57)** R_1= COOH OH R_2= H R_3= OH R_4= CH_3

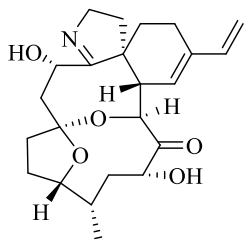
Pinnatoxin G **(58)** R_1= O O R_2= H R_3= OH R_4= CH_3

Pinnatoxin H **(59)** R_1= R_2= OH R_3= H R_4= H

Figure 9. Structures of Pinnatoxins from *Vulcanodinium rugosum*

2.8.2. Portimine

A five-membered cyclic imine called portimine (**60**) was isolated from *Vulcanodinium rugosum* [88]. This compound shares some similarities with pinnatoxins: a spiro-linked cyclicimine and a polycyclic ether backbone. Compared to pinnatoxins, portimine (**60**) exhibited relatively low toxicity on mice, but higher toxicity on P388 mouse leukemia cells (EC_{50} of 2.7 nM) by inducing cell death in an apoptotic manner [88].



Portimine (**60**)

3. Concluding remarks

Dinoflagellates have developed unique biosynthetic pathways leading to the production of sophisticated and specific metabolites, many of which are likely involved in protection mechanisms in the highly competitive environment in which the cells live. The set of bioactive molecules so far known to be produced by dinoflagellates includes various polyketide compounds such as amphidinols, lutheophanol and ostreols, as well as macrolides including acuminolide and iriomoteolides. It is noteworthy that these molecules have been isolated from a very broad diversity of species, including members of most of the main dinoflagellate families: Gymnodiniales (*Amphidinium*, *Karlodinium*), Peridiniales (*Vulcanodinium*), Gonyaulacales (*Gambierdiscus*, *Ostropsis*), Prorocentrales (Prorocentrum) and Dinophysiales (*Dinophysis*). Phylogenetic trends in metabolite structure may exist (as would appear to be the case for example for the structural similarity between amphidinols and karlotoxins which are both produced by members of the Gymnodiniales), but much more data on other dinoflagellate species would be required to assess whether these trends are robust (which might lead to development of a certain degree of predictive capability). It should be noted that a huge number of metabolites have been found firstly into macro-organisms as fishes, sponges and crustaceans derived of the bioaccumulation or molecular transfer pro-symbiotic with microorganisms. It is very likely that other marines compounds described is initially derived from dinoflagellates. The interest will be to determine the real producer of bioactive metabolites to be controlled or promoted. However, the discovery and characterization of new metabolites from dinoflagellates is the result of a long process including: (i) isolation of culture strains and their characterization; (ii) scale-up from laboratory scale cultivation (from mL up to 100L) to production scale (up to several m^3); (iii) extraction, fractionation and structural elucidation of metabolites; (iv) screening of the purified compounds using disease-relevant assays. Despite some of the recently discovered natural products from dinoflagellates being too toxic, the majority have potential therapeutic value as anti-cancer, anti-fungal and/or anti-bacterial agents. The road from identification of an interesting bioactivity to marketable product is long and restrictive, involving for example intensive medicinal chemistry studies in order to improve the efficiency and selectivity of products, but there are numerous examples of successful development of natural products, such as the multi-kinase inhibitor Midostaurin (Rydapt, Novartis Pharmaceuticals, Inc.), approved in 2017 in the EU and USA for the treatment of FMS-like tyrosine kinase 3 (FLT3)

mutation-positive acute myeloid leukemia [92]. Midostaurin is an indolocarbazole and a direct derivative of staurosporin, a natural alkaloid purified from the bacterium *Streptomyces staurosporeus* (first described in 1977). This natural product, considered as a "pan-kinase" inhibitor (high- affinity inhibitor of nearly all mammalian protein kinases), and its derivatives were under investigation for decades before reaching the market for cancer treatment in combination notably with the marine natural product, cytarabin [91]. With current technological advances, notably in bioinformatics, mass spectrometry, and microfluidics for miniaturization of high-throughput screening assays, a growing number of metabolites from microorganisms will be isolated and characterized, and in this context we hope that the present review highlights the potential potency of dinoflagellate metabolites for human therapeutics. Specific new cultivation techniques will be needed as a key step towards further exploring this potential, and further efforts should be made to influence the induction of metabolite synthesis (via the use of specific culture media and/or co-cultures with several organisms for example) in order to reveal minor compounds. Pharmaceutical companies need access to new chemical diversity. We believe that the development of dinoflagellates as producers of high value chemicals will pave the way for promising new therapeutic applications.

Acknowledgments

The authors thank the Cancéropôle Grand-Ouest (axis: Nature sea products in cancer treatment), the GIS IBiSA (Infrastructures en Biologie Santé et Agronomie, France) and Biogenouest (western France life science and environment core facility network) for supporting the KISS*f* screening facility (Roscoff, France). AC, SB, MM and IP are supported by the ANR/Investissements d'Avenir program via the OCEANOMICs project (grant #ANR-11-BTBR-0008).

Abbreviations

AM: Amphidinol
AMP: Amphidinolide
ASP: Amnesic shellfish poisoning

AZA: Azaspiracid

CTX: Ciguatoxins

CFP: Ciguatera fish poisoning

DSP: Diarrheic shellfish poisoning

EC_{50}: Half maximal effective concentration

GI_{50}: Half maximal inhibition of cell proliferation

GTX: Gonyautoxins

IC_{50}: Half maximal inhibitory concentration

KmTx: Karlotoxin

LD_{50}: Median Lethal Dose

MTX: Maitotoxin

NSP: Neurotoxic shellfish poisoning

OA: Okadaic acid

PTX: Palytoxin

PSP: Paralytic shellfish poisoning

STX: Saxitoxin

YTX: Yessotoxin

References

[1] Gómez F. A checklist and classification of living dinoflagellates (Dinoflagellata, Alveolata). Cicimar Oceanides 2012;27:65–140.

[2] Revel J, Massi L, Mehiri M, Boutoute M, Mayzaud P, Capron L, et al. Differential distribution of lipids in epidermis, gastrodermis and hosted Symbiodinium in the sea anemone Anemonia viridis. Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology 2016;191:140–51. doi:10.1016/j.cbpa.2015.10.017.

[3] Freeman C, Stoner E, Easson C, Matterson K, Baker D. Symbiont carbon and nitrogen assimilation in the Cassiopea–Symbiodinium mutualism. Marine Ecology Progress Series 2016;544:281–6. doi:10.3354/meps11605.

[4] Tonk L, Sampayo EM, Chai A, Schrameyer V, Hoegh-Guldberg O. *Symbiodinium* (Dinophyceae) community patterns in invertebrate hosts from inshore marginal reefs of the southern Great Barrier Reef, Australia. Journal of Phycology 2017;53:589–600. doi:10.1111/jpy.12523.

[5] Siano R, Montresor M, Probert I, Not F, de Vargas C. Pelagodinium gen. nov. and P. béii comb. nov., a Dinoflagellate Symbiont of Planktonic Foraminifera. Protist 2010;161:385–99. doi:10.1016/j.protis.2010.01.002.

[6] Probert I, Siano R, Poirier C, Decelle J, Biard T, Tuji A, et al. *B randtodinium* gen. nov. and *B . nutricula* comb. Nov. (Dinophyceae), a dinoflagellate commonly found in symbiosis with polycystine radiolarians. Journal of Phycology 2014;50:388–99. doi:10.1111/jpy.12174.

[7] Lefebvre KA. Characterization of Intracellular and Extracellular Saxitoxin Levels in Both Field and Cultured Alexandrium spp. Samples from Sequim Bay, Washington. Marine Drugs 2008;6:103–16. doi:10.3390/md20080006.
[8] Orr R, Stüken A, Murray S, Jakobsen K. Evolution and Distribution of Saxitoxin Biosynthesis in Dinoflagellates. Marine Drugs 2013;11:2814–28. doi:10.3390/md11082814.
[9] Wiese M, D'Agostino PM, Mihali TK, Moffitt MC, Neilan BA. Neurotoxic Alkaloids: Saxitoxin and Its Analogs. Marine Drugs 2010;8:2185–211. doi:10.3390/md8072185.
[10] Landsberg JH, Hall S, Johannessen JN, White KD, Conrad SM, Abbott JP, et al. Saxitoxin Puffer Fish Poisoning in the United States, with the First Report of Pyrodinium bahamense as the Putative Toxin Source. Environmental Health Perspectives 2006;114:1502–7. doi:10.1289/ehp.8998.
[11] Cusick K, Sayler G. An Overview on the Marine Neurotoxin, Saxitoxin: Genetics, Molecular Targets, Methods of Detection and Ecological Functions. Marine Drugs 2013;11:991–1018. doi:10.3390/md11040991.
[12] Rein KS, Baden DG, Gawley RE. Conformational analysis of the sodium channel modulator, brevetoxin A, comparison with brevetoxin B conformations, and a hypothesis about the common pharmacophore of the" site 5" toxins. The Journal of Organic Chemistry 1994;59:2101–2106.
[13] McCall J, Elliott E, Bourdelais A. A New Cytotoxicity Assay for Brevetoxins Using Fluorescence Microscopy. Marine Drugs 2014;12:4868–82. doi:10.3390/md12094868.
[14] Walsh CJ, Leggett SR, Carter BJ, Colle C. Effects of brevetoxin exposure on the immune system of loggerhead sea turtles. Aquatic Toxicology 2010;97:293–303. doi:10.1016/j.aquatox.2009.12.014.
[15] Krock B, Tillmann U, John U, Cembella AD. Characterization of azaspiracids in plankton size-fractions and isolation of an azaspiracid-producing dinoflagellate from the North Sea. Harmful Algae 2009;8:254–63. doi:10.1016/j.hal.2008.06.003.
[16] Kilcoyne J, Nulty C, Jauffrais T, McCarron P, Herve F, Foley B, et al. Isolation, Structure Elucidation, Relative LC-MS Response, and in Vitro Toxicity of Azaspiracids from the Dinoflagellate *Azadinium spinosum*. Journal of Natural Products 2014;77:2465–74. doi:10.1021/np500555k.
[17] Cembella AD. Occurrence of okadaic acid, a major diarrheic shellfish toxin, in natural populations ofDinophysis spp. from the eastern coast of North America. Journal of Applied Phycology 1989;1:307.
[18] Friedman MA. Ciguatera Fish Poisoning: Treatment, Prevention and Management. Marine Drugs 2008;6:456–79. doi:10.3390/md20080022.
[19] Yasumoto, T., Nakajima, I., Bagnis, R., Adachi, R. Finding of a dinoflagellate as a likely culprit of ciguatera. Nippon Suisan Gakkaishi 1977;43:1021–6.
[20] Botana LM, editor. Seafood and freshwater toxins: pharmacology, physiology, and detection. New York, NY: Marcel Dekker; 2000.
[21] Catterall WA, Cestèle S, Yarov-Yarovoy V, Yu FH, Konoki K, Scheuer T. Voltage-gated ion channels and gating modifier toxins. Toxicon 2007;49:124–41. doi:10.1016/j.toxicon.2006.09.022.
[22] Houdai T, Matsuoka S, Murata M, Satake M, Ota S, Oshima Y, et al. Acetate labeling patterns of dinoflagellate polyketides, amphidinols 2, 3 and 4. Tetrahedron 2001;57:5551–5555.
[23] Iwai T, Kubota T, Kobayashi J. Absolute Configuration of Amphidinin A. Journal of Natural Products 2014;77:1541–4. doi:10.1021/np5003065.
[24] Kubota T, Iwai T, Ishiyama H, Sakai K, Gonoi T, Kobayashi J. Amphidinin G, a putative biosynthetic precursor of amphidinin A from marine dinoflagellate Amphidinium sp. Tetrahedron Letters 2015;56:990–3. doi:10.1016/j.tetlet.2015.01.058.
[25] Kubota T, Iwai T, Sakai K, Gonoi T, Kobayashi J. Amphidinins C–F, Amphidinolide Q Analogues from Marine Dinoflagellate *Amphidinium* sp. Organic Letters 2014;16:5624–7. doi:10.1021/ol502685z.

[26] Meng Y, Van Wagoner RM, Misner I, Tomas C, Wright JLC. Structure and Biosynthesis of Amphidinol 17, a Hemolytic Compound from *Amphidinium carterae* ⊥. Journal of Natural Products 2010;73:409–15. doi:10.1021/np900616q.
[27] Nuzzo G, Cutignano A, Sardo A, Fontana A. Antifungal Amphidinol 18 and Its 7-Sulfate Derivative from the Marine Dinoflagellate *Amphidinium carterae*. Journal of Natural Products 2014;77:1524–7. doi:10.1021/np500275x.
[28] Satake M, Cornelio K, Hanashima S, Malabed R, Murata M, Matsumori N, et al. Structures of the Largest Amphidinol Homologues from the Dinoflagellate *Amphidinium carterae* and Structure–Activity Relationships. Journal of Natural Products 2017;80:2883–8. doi:10.1021/acs.jnatprod.7b00345.
[29] Kumagai K, Minamida M, Akakabe M, Tsuda M, Konishi Y, Tominaga A, et al. Amphirionin-2, a novel linear polyketide with potent cytotoxic activity from a marine dinoflagellate Amphidinium species. Bioorganic & Medicinal Chemistry Letters 2015;25:635–8. doi:10.1016/j.bmcl.2014.12.003.
[30] Minamida M, Kumagai K, Ulanova D, Akakabe M, Konishi Y, Tominaga A, et al. Amphirionin-4 with Potent Proliferation-Promoting Activity on Bone Marrow Stromal Cells from a Marine Dinoflagellate *Amphidinium* Species. Organic Letters 2014;16:4858–61. doi:10.1021/ol5023504.
[31] Akakabe M, Kumagai K, Tsuda M, Konishi Y, Tominaga A, Tsuda M, et al. Amphirionin-5, a novel linear polyketide from a cultured marine dinoflagellate Amphidinium species with a potent cell proliferation-promoting activity. Tetrahedron Letters 2014;55:3491–4. doi:10.1016/j.tetlet.2014.04.086.
[32] Tsuda M, Oguchi K, Iwamoto R, Okamoto Y, Fukushi E, Kawabata J, et al. Iriomoteolides-1b and -1c, 20-Membered Macrolides from a Marine Dinoflagellate *Amphidinium* Species. Journal of Natural Products 2007;70:1661–3. doi:10.1021/np0702537.
[33] Tsuda M, Kumagai K, Masuda A, Fukushi E, Kawabata J. Iriomoteolide-2a, a Cytotoxic 23-Membered Macrolide from Marine Benthic Dinoflagellate Amphidinium Species. HETEROCYCLES 2015;91:265. doi:10.3987/COM-14-13132.
[34] Oguchi K, Tsuda M, Iwamoto R, Okamoto Y, Kobayashi J 'ichi, Fukushi E, et al. Iriomoteolide-3a, a Cytotoxic 15-Membered Macrolide from a Marine Dinoflagellate *Amphidinium* Species. The Journal of Organic Chemistry 2008;73:1567–70. doi:10.1021/jo702440s.
[35] Kumagai K, Tsuda M, Fukushi E, Kawabata J. Iriomoteolides-4A and -5A, Hydrophilic Macrolides from Marine Dinoflagellate Amphidinium species. HETEROCYCLES 2013;87:2615. doi:10.3987/COM-13-12841.
[36] Kumagai K, Tsuda M, Fukushi E, Kawabata J, Masuda A, Tsuda M. Iriomoteolides-9a and 11a: two new odd-numbered macrolides from the marine dinoflagellate Amphidinium species. Journal of Natural Medicines 2017;71:506–12. doi:10.1007/s11418-017-1080-y.
[37] Akakabe M, Kumagai K, Tsuda M, Konishi Y, Tominaga A, Kaneno D, et al. Iriomoteolides-10a and 12a, cytotoxic macrolides from marine dinoflagellate Amphidinium species. Chemical and Pharmaceutical Bulletin 2016;64:1019–1023.
[38] Inuzuka T, Yamamoto Y, Yamada K, Uemura D. Amdigenol A, a long carbon-backbone polyol compound, produced by the marine dinoflagellate Amphidinium sp. Tetrahedron Letters 2012;53:239–42. doi:10.1016/j.tetlet.2011.11.033.
[39] Inuzuka T, Yamada K, Uemura D. Amdigenols E and G, long carbon-chain polyol compounds, isolated from the marine dinoflagellate Amphidinium sp. Tetrahedron Letters 2014;55:6319–23. doi:10.1016/j.tetlet.2014.09.094.
[40] Krock B, Tillmann U, Potvin É, Jeong H, Drebing W, Kilcoyne J, et al. Structure Elucidation and in Vitro Toxicity of New Azaspiracids Isolated from the Marine Dinoflagellate Azadinium poporum. Marine Drugs 2015;13:6687–702. doi:10.3390/md13116687.
[41] Hwang BS, Kim HS, Yih W, Jeong EJ, Rho J-R. Acuminolide A: Structure and Bioactivity of a New Polyether Macrolide from Dinoflagellate *Dinophysis acuminata*. Organic Letters 2014;16:5362–5. doi:10.1021/ol502567g.

[42] Rodríguez I, Genta-Jouve G, Alfonso C, Calabro K, Alonso E, Sánchez JA, et al. Gambierone, a Ladder-Shaped Polyether from the Dinoflagellate *Gambierdiscus belizeanus*. Organic Letters 2015;17:2392–5. doi:10.1021/acs.orglett.5b00902.
[43] Watanabe R, Uchida H, Suzuki T, Matsushima R, Nagae M, Toyohara Y, et al. Gambieroxide, a novel epoxy polyether compound from the dinoflagellate Gambierdiscus toxicus GTP2 strain. Tetrahedron 2013;69:10299–303. doi:10.1016/j.tet.2013.10.022.
[44] Van Wagoner RM, Deeds JR, Satake M, Ribeiro AA, Place AR, Wright JLC. Isolation and characterization of karlotoxin 1, a new amphipathic toxin from Karlodinium veneficum. Tetrahedron Letters 2008;49:6457–61. doi:10.1016/j.tetlet.2008.08.103.
[45] Van Wagoner RM, Deeds JR, Tatters AO, Place AR, Tomas CR, Wright JLC. Structure and Relative Potency of Several Karlotoxins from *Karlodinium veneficum*. Journal of Natural Products 2010;73:1360–5. doi:10.1021/np100158r.
[46] Rasmussen SA, Binzer SB, Hoeck C, Meier S, de Medeiros LS, Andersen NG, et al. Karmitoxin: An Amine-Containing Polyhydroxy-Polyene Toxin from the Marine Dinoflagellate *Karlodinium armiger*. Journal of Natural Products 2017;80:1287–93. doi:10.1021/acs.jnatprod.6b00860.
[47] Hwang BS, Yoon EY, Kim HS, Yih W, Park JY, Jeong HJ, et al. Ostreol A: A new cytotoxic compound isolated from the epiphytic dinoflagellate Ostreopsis cf. ovata from the coastal waters of Jeju Island, Korea. Bioorganic & Medicinal Chemistry Letters 2013;23:3023–7. doi:10.1016/j.bmcl.2013.03.020.
[48] Hwang BS, Yoon EY, Jeong EJ, Park J, Kim E-H, Rho J-R. Determination of the Absolute Configuration of Polyhydroxy Compound Ostreol B Isolated from the Dinoflagellate *Ostreopsis* cf. *ovata*. The Journal of Organic Chemistry 2018;83:194–202. doi:10.1021/acs.joc.7b02569.
[49] Lu C-K, Chou H-N, Lee C-K, Lee T-H. Prorocentin, a New Polyketide from the Marine Dinoflagellate *Prorocentrum l ima*. Organic Letters 2005;7:3893–6. doi:10.1021/ol051300u.
[50] Lu C-K, Chen Y-M, Wang S-H. Prorocentin-4, a novel linear polyketide from a marine dinoflagellate Prorocentrum sp. Tetrahedron Letters 2010;51:6911–4. doi:10.1016/j.tetlet.2010.10.116.
[51] Domínguez HJ, Napolitano JG, Fernández-Sánchez MT, Cabrera-García D, Novelli A, Norte M, et al. Belizentrin, a Highly Bioactive Macrocycle from the Dinoflagellate *Prorocentrum belizeanum*. Organic Letters 2014;16:4546–9. doi:10.1021/ol502102f.
[52] Yang AR, Lee S, Yoo YD, Kim HS, Jeong EJ, Rho J-R. Limaol: A Polyketide from the Benthic Marine Dinoflagellate *Prorocentrum lima*. Journal of Natural Products 2017;80:1688–92. doi:10.1021/acs.jnatprod.7b00127.
[53] Rhodes L, Smith K, Selwood A, McNabb P, Munday R, Suda S, et al. Dinoflagellate Vulcanodinium rugosum identified as the causative organism of pinnatoxins in Australia, New Zealand and Japan. Phycologia 2011;50:624–8. doi:10.2216/11-19.1.
[54] Selwood AI, Wilkins AL, Munday R, Gu H, Smith KF, Rhodes LL, et al. Pinnatoxin H: a new pinnatoxin analogue from a South China Sea Vulcanodinium rugosum isolate. Tetrahedron Letters 2014;55:5508–10. doi:10.1016/j.tetlet.2014.08.056.
[55] Murray SA, Garby T, Hoppenrath M, Neilan BA. Genetic Diversity, Morphological Uniformity and Polyketide Production in Dinoflagellates (Amphidinium, Dinoflagellata). PLoS ONE 2012;7:e38253. doi:10.1371/journal.pone.0038253.
[56] Nuzzo G, Gomes BA, Luongo E, Torres MCM, Santos EA, Cutignano A, et al. Dinoflagellate-Related Amphidinolides from the Brazilian Octocoral *Stragulum bicolor*. Journal of Natural Products 2016;79:1881–5. doi:10.1021/acs.jnatprod.6b00259.
[57] Satake M, Murata M, Yasumoto T, Fujita T, Naoki H. Amphidinol, a polyhydroxy-polyene antifungal agent with an unprecedented structure, from a marine dinoflagellate, Amphidinium klebsii. Journal of the American Chemical Society 1991;113:9859–9861.
[58] Morsy N, Matsuoka S, Houdai T, Matsumori N, Adachi S, Murata M, et al. Isolation and structure elucidation of a new amphidinol with a truncated polyhydroxyl chain from Amphidinium klebsii. Tetrahedron 2005;61:8606–10. doi:10.1016/j.tet.2005.07.004.

[59] Morsy N, Houdai T, Matsuoka S, Matsumori N, Adachi S, Oishi T, et al. Structures of new amphidinols with truncated polyhydroxyl chain and their membrane-permeabilizing activities. Bioorganic & Medicinal Chemistry 2006;14:6548–54. doi:10.1016/j.bmc.2006.06.012.
[60] Echigoya R, Rhodes L, Oshima Y, Satake M. The structures of five new antifungal and hemolytic amphidinol analogs from Amphidinium carterae collected in New Zealand. Harmful Algae 2005;4:383–9. doi:10.1016/j.hal.2004.07.004.
[61] Kubota T, Tsuda M, Takahashi M, Ishibashi M, Naoki H, Kobayashi J. Colopsinols B and C, new long chain polyhydroxy compounds from cultured marine dinoflagellate Amphidinium sp. Journal of the Chemical Society, Perkin Transactions 1 1999:3483–3487.
[62] Kubota, T, Masaahi Tsuda, Yukiko Doi, Ayako Takahashi, Hiroko Nakamlehi, Masami Ishibashi, et al. Luteophanois B and C, New Polyhydroxyi Compounds from Marine Dinoflageilate Amphidinium sp. Tetrahedron Letters 1998;54:14455–67.
[63] Takaaki Kubota, Ayako Takahashi, Masashi Tsuda, Jun'ichi Kobayashi. Luteophanol D, New Polyhydroxyl Metabolite from Marine Dinoflagellate Amphidinium sp. Marine Drugs 2005;3:113–8.
[64] Kobayashi J 'ichi, Yamaguchi N, Ishibashi M. Amphidinin A, a novel amphidinolide-related metabolite from the cultured marine dinoflagellate Amphidinium sp. Tetrahedron Letters 1994;35:7049–7050.
[65] Swasono RT, Mouri R, Morsy N, Matsumori N, Oishi T, Murata M. Sterol effect on interaction between amphidinol 3 and liposomal membrane as evidenced by surface plasmon resonance. Bioorganic & Medicinal Chemistry Letters 2010;20:2215–8. doi:10.1016/j.bmcl.2010.02.025.
[66] Ishibashi M, Takahashi M, Kobayashi J 'ichi. Amphidinolides O and P, novel 15-membered macrolides from the dinoflagellate Amphidinium sp.: analysis of the relative stereochemistry and stable solution conformation. The Journal of Organic Chemistry 1995;60:6062–6066.
[67] Kobayashi J 'ichi. Pharmacologically active metabolites from symbiotic microalgae in Okinawan marine invertebrates. Journal of Natural Products 1989;52:225–238.
[68] Tsuda M, Endo T, Kobayashi J 'ichi. Amphidinolide U, novel 20-membered macrolide from marine dinoflagellate amphidinium sp. Tetrahedron 1999;55:14565–14570.
[69] Doi Y, Ishibashi M, Nakamichi H, Kosaka T, Ishikawa T, Kobayashi J 'ichi. Luteophanol A, a new polyhydroxyl compound from symbiotic marine dinoflagellate Amphidinium sp. The Journal of Organic Chemistry 1997;62:3820–3823.
[70] Tillmann U, Jaén D, Fernández L, Gottschling M, Witt M, Blanco J, et al. Amphidoma languida (Amphidomatacea, Dinophyceae) with a novel azaspiracid toxin profile identified as the cause of molluscan contamination at the Atlantic coast of southern Spain. Harmful Algae 2017;62:113–26. doi:10.1016/j.hal.2016.12.001.
[71] Huhn J, Jeffrey PD, Larsen K, Rundberget T, Rise F, Cox NR, et al. A Structural Basis for the Reduced Toxicity of Dinophysistoxin-2. Chemical Research in Toxicology 2009;22:1782–6. doi:10.1021/tx9001622.
[72] Kamiyama T, Suzuki T. Production of dinophysistoxin-1 and pectenotoxin-2 by a culture of Dinophysis acuminata (Dinophyceae). Harmful Algae 2009;8:312–7. doi:10.1016/j.hal.2008.07.003.
[73] Murata M, Legrand AM, Ishibashi Y, Fukui M, Yasumoto T. Structures and configurations of ciguatoxin from the moray eel Gymnothorax javanicus and its likely precursor from the dinoflagellate Gambierdiscus toxicus. Journal of the American Chemical Society 1990;112:4380–4386.
[74] Holmes MJ, Lewis RJ, Gillespie NC. Toxicity of Australian and French Polynesian strains of Gambierdiscus toxicus (Dinophyceae) grown in culture: characterization of a new type of maitotoxin. Toxicon 1990;28:1159–1172.
[75] Michael J. Holmes, Richard J. Lewis. Purification and Characten'sation of Large and Small Maitotoxins From Cultured Gambierdiscus toxicus. Natural Toxins 1994;2:64–72.
[76] Murata M, Naoki H, Iwashita T, Matsunaga S, Sasaki M, Yokoyama A, et al. Structure of maitotoxin. Journal of the American Chemical Society 1993;115:2060–2062.

[77] Pisapia F, Sibat M, Herrenknecht C, Lhaute K, Gaiani G, Ferron P-J, et al. Maitotoxin-4, a Novel MTX Analog Produced by Gambierdiscus excentricus. Marine Drugs 2017;15:220. doi:10.3390/md15070220.
[78] Kakizaki A, Takahashi M, Akagi H, Tachikawa E, Yamamoto T, Taira E, et al. Ca2+ channel activating action of maitotoxin in cultured brainstem neurons. European Journal of Pharmacology 2006;536:223–31. doi:10.1016/j.ejphar.2006.02.052.
[79] Satake M, Fukui M, Legrand A-M, Cruchet P, Yasumoto T. Isolation and structures of new ciguatoxin analogs, 2, 3-dihydroxyCTX3C and 51-hydroxyCTX3C, accumulated in tropical reef fish. Tetrahedron Letters 1998;39:1197–1198.
[80] Nézan E, Siano R, Boulben S, Six C, Bilien G, Chèze K, et al. Genetic diversity of the harmful family Kareniaceae (Gymnodiniales, Dinophyceae) in France, with the description of Karlodinium gentienii sp. nov.: A new potentially toxic dinoflagellate. Harmful Algae 2014;40:75–91. doi:10.1016/j.hal.2014.10.006.
[81] Ramos V, Vasconcelos V. Palytoxin and Analogs: Biological and Ecological Effects. Marine Drugs 2010;8:2021–37. doi:10.3390/md8072021.
[82] Ciminiello P, Dell'Aversano C, Dello Iacovo E, Fattorusso E, Forino M, Grauso L, et al. Isolation and Structure Elucidation of Ovatoxin-a, the Major Toxin Produced by Ostreopsis ovata. Journal of the American Chemical Society 2012;134:1869–75. doi:10.1021/ja210784u.
[83] Hu T, DeFreitas AS, Curtis JM, Oshima Y, Walter JA, Wright JL. Isolation and structure of prorocentrolide B, a fast-acting toxin from Prorocentrum maculosum. Journal of Natural Products 1996;59:1010–1014.
[84] Tingmo Hu, Jonathan M. Curtis, John A. Walter, Jeffrey L. C. Wright. Hoffmanniolide: a Novel Macrolide from Prorocentrum hoffmannianum. Tetrahedron Letters 1999;40:3977–80.
[85] Lu C-K, Chen Y-M, Wang S-H, Wu Y-Y, Cheng Y-M. Formosalides A and B, cytotoxic 17-membered ring macrolides from a marine dinoflagellate Prorocentrum sp. Tetrahedron Letters 2009;50:1825–7. doi:10.1016/j.tetlet.2009.02.013.
[86] Napolitano JG, Norte M, Padrón JM, Fernández JJ, Hernández Daranas A. Belizeanolide, a Cytotoxic Macrolide from the Dinoflagellate *Prorocentrum belizeanum*. Angewandte Chemie International Edition 2009;48:796–9. doi:10.1002/anie.200804023.
[87] Zeng N, Gu H, Smith K, Rhodes L, Selwood A, Yang W. The first report of *Vulcanodinium rugosum* (Dinophyceae) from the South China Sea with a focus on the life cycle. New Zealand Journal of Marine and Freshwater Research 2012;46:511–21. doi:10.1080/00288330.2012.719911.
[88] Selwood AI, Wilkins AL, Munday R, Shi F, Rhodes LL, Holland PT. Portimine: a bioactive metabolite from the benthic dinoflagellate Vulcanodinium rugosum. Tetrahedron Letters 2013;54:4705–7. doi:10.1016/j.tetlet.2013.06.098.
[89] Uemura D, Chou T, Haino T, Nagatsu A, Fukuzawa S, Zheng S, et al. Pinnatoxin A: a toxic amphoteric macrocycle from the Okinawan bivalve Pinna muricata. Journal of the American Chemical Society 1995;117:1155–1156.
[90] Selwood AI, Miles CO, Wilkins AL, van Ginkel R, Munday R, Rise F, et al. Isolation, Structural Determination and Acute Toxicity of Pinnatoxins E, F and G. Journal of Agricultural and Food Chemistry 2010;58:6532–42. doi:10.1021/jf100267a.
[91] Levis M. Midostaurin approved for FLT3-mutated AML. Blood 2017;129:3403–6. doi:10.1182/blood-2017-05-782292.
[92] Rasko JEJ, Hughes TP. 2017. First Approved Kinase Inhibitor for AML. Cell. 2017 Nov 16;171(5):981. doi: 10.1016/j.cell.2017.11.007.PMID:29149610