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Structure-Activity Relationship (SAR) Studies to Maximize the Activity of Compounds Isolated from Octocorals

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Additional information is available at the end of the chapter

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Abstract

This chapter presents some significant study cases on octocoral organisms (*Eunicea succinea*, *Eunicea mammosa*, *Eunicea knighti*, *Pseudoplexaura flagellosa*, *Eunicea laciniata*, *Antillogorgia elisabethae*, *Muricea austera*, *Paragorgia* sp., *Lobophyton* sp., *Sarcophyton glaucum* and *Sinularia lochmodes*) that have been identified as a source of promising bioactive compounds and whose results have further been used for studies on structure-activity relationship (SAR) as a strategy to increase the value of the activity initially detected. The scientific literature data discussed here were obtained with the SciFinder tool during the period 2000–2016 and from the additional results here presented for the biofilm inhibition activity of compounds and synthetic analogs for the cases related with *Eunicea knighti* and *Pseudoplexaura flagellosa* (until now unpublished data of the authors of this chapter).

Keywords: bioprospecting, marine natural products, octocorals, structure-activity relationship, synthetic and natural analogs, bioactivity

1. Introduction

Animals, plants and microorganisms of marine origin are suitable sources for the discovery and development of numerous medicines and industrial products. Among the 36 animal phyla described to date, 34 are represented in the marine environment, with about half being exclusively marine [1, 2]. Such statistics demonstrate the immense potential of marine biodiversity from which only a small percentage has been studied as a source of compounds useful to humans. The next few lines will briefly describe a very short history of marine natural

products drug discovery, until today one of the major fields of application of marine natural products (extensive reviews on the subject can be found in Refs. [3–8]).

Studies began in the early 1950s with the discovery of spongouridine and spongothymidine isolated from the marine sponge *Tehya crypta* [9–11], natural compounds later transformed by synthesis into vidarabine and cytarabine, respectively, and approved as drugs by the USA Food and Drug Administration (FDA) [3]: vidarabine as an anticancer agent in 1969, and cytarabine as an antiviral drug in 1976. Although the latter has recently been withdrawn from the market, it is still being used in ophthalmic treatments. However, it was only in the mid-1970s that the isolation of prostaglandins from octocoral species such as *Plexaura homomalla* [12], the structural determination of several of them and their application in human medicine encouraged many scientists to conduct research in this field. In such a way, by the end of the last century, thousands of compounds had been isolated as major metabolites of conspicuous marine organisms, easy to collect and easy to study.

Since then, thanks to tremendous efforts by scientists, to the improvement and easy access to better techniques of collection of organisms (snorkeling, scuba, submersibles, remote operated vehicles (ROVs)), to the discovery of modern techniques of chemical analysis and of biological activity, to the emergence of the “omic” approaches (genomics, proteomics, metabolomics, transcriptomics), to the recent genome mining approaches (exploitation of genome public data) for the discovery of new natural products, and to the use of molecular biology in the field of bioengineering, today approximately 25,000 bioactive marine compounds with novel structure are known, many of them with potential industrial use [13]. Focusing only on the pharmaceutical industry, 8 marine compounds approved by the FDA and/or by the European Medicines Agency (EMA) are on the market as therapeutic agents, 11 in different clinical phases, 1458 in the preclinical phase (the data on the compounds in the clinical and preclinical phases were taken as reported in recent references [3, 13, 14] and from A.M.S. Mayer’s website in the USA (<http://marinepharmacology.midwestern.edu>, accessed: 2017-01-30). In addition, there are many other compounds that remain in the laboratories of academic research groups or research centers waiting for the opportunity and adequate funding to enter the commonly so-called marine pharmaceutical pipeline, which allows them to start the path toward their conversion to new drugs.

Furthermore, it is worth mentioning that in parallel with the aforementioned studies, toward the first decade of the present century, numerous researchers turned their attention to look for new sources of bioactives, that is, marine microorganisms (cyanobacteria, marine fungi and other classes of Eubacteria) hoping to find new compounds and new activities, and because it began to be known that many compounds previously isolated from macroorganisms were actually produced by their associated microbes, as described in [4].

The aforementioned shows that marine organisms really are a fascinating source of molecules with unique structures and exploitable biological activity. The following are some of the compounds of marine origin established in the market as therapeutic agents or used as industrial products [3, 13, 14]: compounds used in cancer treatment such as cytarabine (CytosarU™, Depocyt™) (mentioned above), trabectedina (Yondelis™), complex tetrahydroisoquinoline alkaloid obtained from tunicate *Ecteinascidia turbinata*; Eribulin mesylate (Halaven™) isolated from sponge *Halichondria okadai*; Brentuximav vedotin (Adcetris™) isolated from sea hare

Dollabella auricularia and Plitidepsin (Aplidin™) isolated from ascidian *Aplidium albicans* which last year received an orphan drug designation by EMA and by FDA; compounds used as antivirals: vidarabin (Vira A™) (mentioned above), and the recent developed iota-carrageenane (carragelose™) obtained from red algae (ready to enter the market); compounds used to treat pain: ziconotide (Prial™) very powerful product, isolated from marine snail *Conus magnus* ziconotide (Prial™); compounds used in hypertriglyceridemia treatment: omega-3-acid ethyl esters (Lovaza®) and some other products such as the skin cream called Resilience™ whose active base is a crude extract of pseudopterosines and *seco*-pseudopterosines; and although these ingredients ran their race as antiinflammatories, they were unsuccessful in reaching the final stage; on the other hand, they retained their status as cosmeceutical products of great demand for the care of sun-induced skin irritations.

Among marine organisms source of bioactives, octocorals—a sub-class of Anthozoa—are a diverse group of colonial animals with 8 tentacle polyps and 8 internal mesenteries comprising about 3000 species (1.5% of all marine animals) of soft corals, gorgonians (sea fans, sea whips), sea pens and blue corals [15, 16] found throughout the world's oceans. They have proven to be a prolific source of natural products having new structures, many of them without terrestrial-counterpart with relevant biological activities, which have been arising enormous interest both in the academic world and in the industry in the last 50 years. The first publication on octocorals came out in 1958 [17]. Since then, many studies on metabolites from octocorals have been published in the chemical literature and biological activity and high-quality reviews have appeared on the subject. Among such important contributions, it is worth mentioning the article written by Coll in 1992 [18], the annual reviews initiated by Faulkner in 1984 until 2002 [6] and continued by Blunt and his New Zealand group since 2003 [7], as well as the reviews by Rodríguez in 1995 [19], Berrue and Kerr in 2009 [20], Berrue et al. in 2011 [21], Almeida et al. in 2014 [22], Hu et al. in 2015 [8] and by Lei et al. in 2016 [23]. According to all these published data, the chemical constituents of octocorals are mostly steroids, acetogenins, sesquiterpenes and numerous diterpenes (with at least 40 skeletal classes) and diterpenes glycosides (compounds unique to gorgonians), exhibiting biological activities such as ichthyotoxic, antimicrobial, anticancer or/and cytotoxic, antiviral, antiinflammatory, antiproliferative, feeding stimulation, feeding deterrent, antipredatory, antifouling, antileishmanial, antiplasmodial and antiHIV-1, among others.

All the studies mentioned above clearly show that the natural products from Cnidaria (mostly corals) and from Porifera (mostly sponges) accounting for 56.89% of the total reported marine bioactives [19] have become a very attractive source of study for scientists, with the added value of being exploited industrially, particularly in pharmacology. However, for a compound discovered in a laboratory to be transformed in an industrial product, it is first necessary to maximize its biological activity and face the big problem of the sustainable supply (as mentioned in the literature [13]: whatever the use given to the compound, *several grams to hundreds of grams are required for preclinical development, multikilogram quantities are needed for clinical phases and tons for industrial uses—figures that contrast with the minimum quantities isolated commonly in the research laboratories*).

These current problems are critical in the industrial development of natural products and have lead to the development of new alternate ways such as preparation of synthetic or hemisynthetic

analogs, among other applications, enhancing the activity and designing pharmacophores of lower complexity that can then be synthesized by faster and easier routes.

For this reason, this chapter aims to show some studies of the scientific literature in the last 15 years, where octocorals emerge as an excellent source of bioactive compounds and how the increase in their activity has been achieved through the use of the structure-activity relationship (SAR) strategy. This method has become a powerful tool for the discovery of new bioactive compounds and to promote the activity by converting bioactive compounds through synthesis into chemical analogs. Furthermore, we will discuss how the preparation of analogs could also be a way of helping the key current problem of material supply in a sustainable manner. Finally, we will present some recent unpublished experimental data from our laboratory where the isolation of terpenoids and some of their natural homologs from octocorals, and their conversion by chemical synthesis into compounds with higher biological activity have been a good strategy to achieve the aforementioned purposes.

2. SAR study cases in octocorals (2000–2016)

The studies highlighted in this item show the results of the literature survey using the SciFinder tool between 2000 and 2016, of some relevant studies reported, describing natural analogs and semi-synthetic derivatives prepared as a strategy to promote biological activity of compounds isolated from octocorals. The analyzed cases are chronologically organized throughout the chapter and each SAR study appears in the chemical literature grouped under subheadings with the name of the corresponding species. **Figure 1** presents some of octocoral species discussed here.

2.1. *Eunicea succinea* and *Eunicea mammosa*

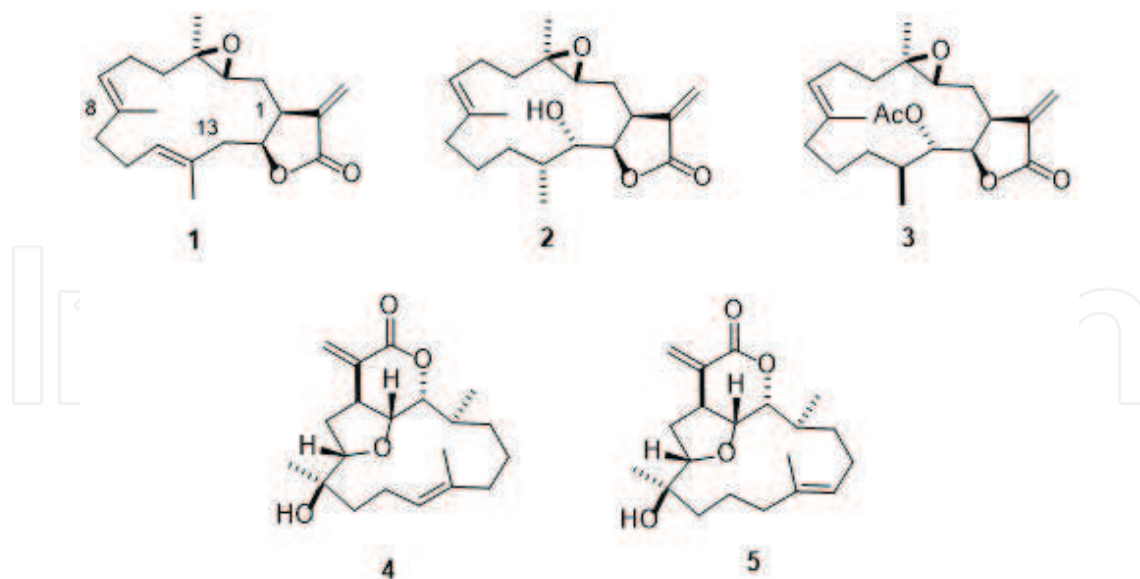
Octocorals of the *Eunicea* genus are one of the most interesting gorgonians because they are a source of abundant and diverse cembranoids and dolabellane diterpenoids, including some glycosylated [20]. On the Scopus database, there are more than 56 search results of chemical studies on *Eunicea* species. Biological activities described for cembranoids isolated from *Eunicea* extracts include antiplasmodial, quorum sensing inhibition, antiviral and cytotoxic activity against several cancer cell lines [20]. It has been described that cembranolides containing cyclic ethers possess potent antileukemic activities [24], that is, euniolide **1**, 12,13-bisepieupalmerin **2** and eupalmerin acetate **3** cembranoids, isolated in large quantities from *E. succinea* and *E. mammosa*, collected in shallow waters of Mona Island (Puerto Rico). These natural compounds showed strong cytotoxic activity against several cell lines, being the oxygenated C-13 compounds (**2** and **3**) more active than the euniolide **1** [25].

In 2000, Puerto Rican scientists [25] synthesized a series of unusual analogs of natural cembranolides **1–3** containing cyclic ether ring systems. They conducted some saponification reactions using KOH from euniolide **1** to obtain eight derivatives, including the well-known

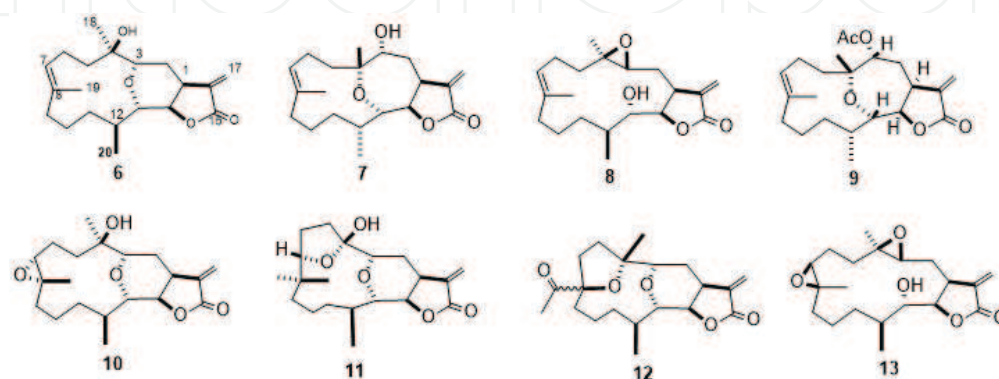


Figure 1. Some octocorals reviewed in this chapter in relation to the SAR studies of their active isolated metabolites.

crassin acetate; from compound 2 to obtain five derivatives and from compound 3 to obtain four compounds. Natural compound 3 was also treated with CH_2N_2 , Ac_2O , photolysis, ozonolysis and H_2O_2 to obtain 18 more derivatives. In this way, the authors obtained a large variety of structural diverse diterpenoids with multiple oxygen bridges, nitrogen atoms and hydroxyl groups. Finally, the 3 natural compounds together with 11 derivatives were tested in the NCI-60 human tumor cell line screen. Natural compounds 1 and 2 had strong cytotoxic activity (IC_{50} values of 0.1–43 $\mu\text{g}/\text{ml}$) while eupalmerin acetate 3 showed to be less active (IC_{50} values from 0.3 to 16 $\mu\text{g}/\text{mL}$). Unfortunately, the synthetic compounds screened were less cytotoxic than the natural diterpenoids prototypes, only α -methylene- δ -lactones 4 and 5 obtained from 2 and 3, respectively, showed a characteristic pattern of differential cytotoxicity and were approximately equipotent than the natural products from which they were obtained.

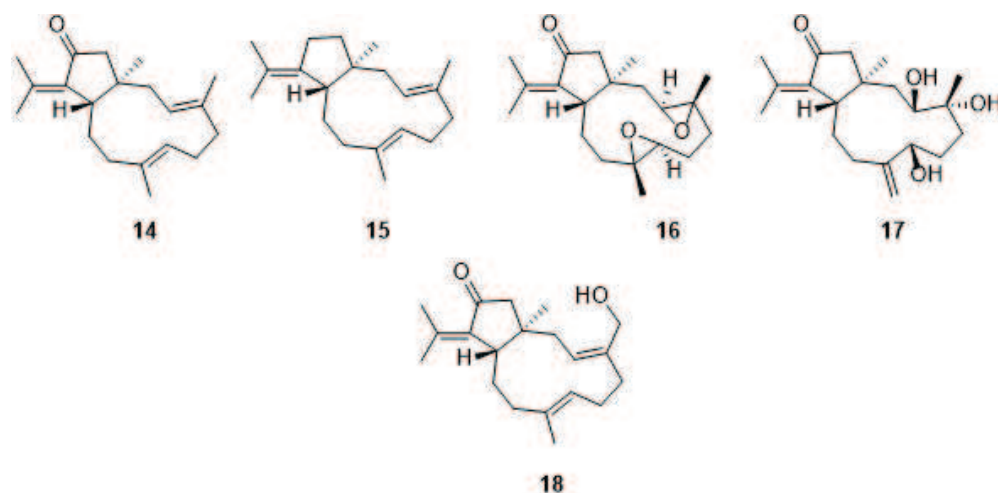


Cembranoids 12-epieunicin **6**, 4-epijeunicin **7** and 13-epieupalmerin **8** were isolated from gorgonian octocoral *E. mammosa* collected in Bahamas, and their structure and their anticancer activity were determined [26]. Compounds **6** and **7** showed moderate cytotoxic activity with A549 (human lung carcinoma), H116 (human colon carcinoma), PSN1 (human pancreatic adenocarcinoma) and T98G (human caucasian glioblastoma); in contrast the activity of compound **8** was higher (IC_{50} ranging from 0.5 to 5 $\mu\text{g/ml}$). In order to evaluate structure-activity relationships, analogs **9**–**13** were prepared by chemical transformations of the natural compounds and their activity were evaluated in the same mentioned assays. The chemical modifications introduced to the natural compounds potentiated the activity (excepting in compound **10**), being the most active and selective compound **13** against A-549, H116 and PSNI. It is noteworthy that synthetic analogs **11** and **13** exhibited greater potential than their parent natural products. According to the mentioned results, it could be said that the introduction of cyclic ether linkages across the cembrane skeleton enhances the activity, as well as the introduction of an extra epoxide, that is, in compound **13**, significantly increases the activity against H116 and PSN1 ($IC_{50} = 5 \mu\text{g/ml}$ in **8** to $IC_{50} = 0.5 \mu\text{g/ml}$ in **13**). These results suggest, as mentioned by the authors of this study [26], that the analogs of this series appear to be attractive targets for the development of antitumor agents.



2.2. *Eunicea laciniata*

As there is not much published information about the antiviral activity of dolabellanes isolated from soft corals, in 2014 Colombian and Brazilian researchers studied the dolabellanes diterpenoids 13-keto-1(R),11(S)-dolabella-3(E),7(E),12(18)-triene (**14**) and β -araneosene (**15**) for their antiviral properties. These diterpenoids were isolated in multigram scale from the Caribbean octocoral *E. laciniata* collected at Santa Marta bay. The antiviral data showed that they exhibited low antiHIV-1 activity and low toxicity. Supported by the fact that oxygenated dolabellanes, isolated from brown algae, showed good antiviral activity [27, 28], the authors of this article obtained derivatives **16–18** by epoxidation, by epoxide opening and by allylic oxidation, respectively. These oxygenated compounds showed significant improvement in the antiHIV-1 potency (100-fold) [29]. Their high antiviral activity, along with their low cytotoxicity, makes them promising antiviral compounds, and is a good example of the usefulness of this strategy to improve the biological activity of marine natural products. Currently, the researchers are obtaining more oxygenated dolabellane derivatives in a continuous work to improve the antiviral activity of natural dolabellanes.



2.3. *Eunicea knighti* and *Pseudoplexaura flagellosa*

In this section, we show our recent published results on quorum sensing inhibition (QSI) and our until now unpublished biofilm inhibition data, related as antipathogenic activity of natural compounds isolated from *E. knighti* and *P. flagellosa* and some of their synthetic analogs prepared in our laboratory. However, first we would like to provide an introduction on bacterial biofilms, quorum sensing inhibition and their relationship with the recently used term antipathogenic activity.

Quorum sensing (QS) is defined as a phenomenon related to the gene expression of bacteria in function of the density of their population, allowing the synchronization of phenotypes through bacterial communication. Recently, quorum sensing has been recognized as one of the main factors that regulates phenotypes such as bioluminescence, transfer of tumor-

inducing plasmids (Ti plasmids), antibiotic production, swarming motility, biofilm maturation (assembled bacterial communities that coordinate themselves for the expression of different phenotypes that change over time and with the environment) and the production of virulence factors [30]. Many bacteria do not express virulence factors until the population density is high enough to overwhelm host defense and establish infection. Compounds with QS inhibitory activity are capable of preventing bacterial communication and suppress some virulence factors. These compounds have been termed as antipathogenic drugs [30]. Furthermore, some QS inhibitor makes biofilms susceptible to antimicrobial treatments and can reduce mortality and virulence in experimental models of infection. Thus, compounds with QSI and biofilm inhibition activity can be considered as leads to antipathogenic drugs [30].

In the last 10 years, many researchers have focused their studies on marine metabolites, mainly from octocorals [31], that exhibit antipathogenic activity, which involve, as mentioned, QSI and biofilm inhibition activity. As previously described by Tello and colleagues in 2009, 2011 and 2012 [32–34], octocorals *E. knighti* and *P. flagellosa* collected in Santa Marta Bay (Colombian Caribbean Sea) were extracted with organic solvents followed by fractionation on vacuum column chromatography and reverse-phase HPLC to afford 16 pure compounds, and their stereostructures were elucidated by means of spectroscopic features. Their activity as QS inhibitors was evaluated against *Chromobacterium violaceum* (ATCC 31532)—a recognized biosensor using a standard disk-diffusion assay, following the parameters described by Tello et al. 2012 [34] and 2013 [35]. Whatman filter paper disks (5.2 mm diameter) were initially sterilized and then loaded with 2.5, 5.0, 7.5, 15.0 and 30.0 µg/disk of each compound. The disks were placed on agar dishes plated with 100 µL of *C. violaceum* culture grown in trypticase soy broth (106 cfu/mL, 0.5 Mac Farland) and finally the agar plates were incubated for 48 h at 26°C. This QSI assay is based on inhibition of QS pigment production (violet color) without interfering with bacterial growth. Kojic acid was used as a positive control, as it is a known inhibitor of quorum sensing systems [34, 35]. The biofilm inhibition assay was performed on polystyrene multi-well plates (96 wells), the pre-inoculates of the bacterial strains *Vibrio harveyi*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were grown in the Luria-Bertani (LB) culture medium with an optical density (OD) of 0.2–0.3 A at 600 nm. All pure compounds were evaluated at five different concentrations (0.5, 1.0, 2.5, 10.0 and 100.0 ppm). Finally, each well was filled with LB culture medium up to 200 µL. Control of growth inhibition was monitored by measuring the absorbance of each well at 621 nm before and after incubation as was described by Tello and colleagues in 2013 [36]. Biofilm inhibitory activity is reported in **Table 1**, as IC₅₀ (ppm).

Based on the results of QS inhibition (QSI) and biofilm inhibition, on their high amounts in the gorgonians and on the diverse reactive functional groups present in their structures (e.g. epoxide groups in the C-7 and C-8, hydroxy groups in the C-2 and C-18, reactive double bonds between the C-3/C-4 and C-11/C-12, and keto or hydroxy reactive groups in C-3, C-6 and C-11) six of the natural compounds were selected as lead compounds to improve their QSI activity and to establish their biofilm inhibition activity via preparation of synthetic analogs using regioselective, straightforward and reproducible reactions such as epoxide ring opening, oxidations, treatment with iodine, photochemicals, methylation and acetylation, and synthesis of cyclic hemiketals [35]. In total, we had in hand 50 cembranoids (natural and synthetic) which were assayed for their QSI and biofilm inhibition activities. The results displayed in **Table 1**

Assay	Biofilm Inhibition IC ₅₀ (ppm) ^a			Quorum sensing Inhibition ^b
	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	<i>Vibrio harveyi</i>	(μg/disk) ^c
Compounds				<i>Chromobacterium violaceum</i>
19	5.0	0.01	80.2	—
20	12.8	0.3	>100.0	—
21	52.9	15.7	7.8	—
22	3.7	1.8	5.8	2.5
23	23.8	11.7	17.3	5.0
24	56.1	2.2	>100.0	2.5
25	4.0	10.1	17.1	—
26	4.5	10.0	69.7	—
27	11.5	>100.0	11.0	7.5
28	17.2	>100.0	>100.0	—
29	9.2	20.9	0.3	—
30	6.4	1.0	>100.0	7.5
31	12.2	5.7	9.5	30.0
32	6.8	1.4	53.8	—
33	10.1	2.0	0.3	—
34	50.0	1.3	9.8	7.5
35	8.3	3.2	1.0	15.2
36	4.1	0.01	>100.0	—
37	9.3	0.8	>100.0	7.5
38	14.7	0.5	>100.0	—
39	52.3	3.2	21.4	7.5
40	37.4	0.13	34.5	—
41	57.3	0.04	1.2	7.5
42	21.6	1.3	16.8	7.5
43	49.8	35.5	>100.0	—
44	>100.0	>100.0	>100.0	—
45	>100.0	>100.0	>100.0	—
46	52.5	0.03	53.1	7.5
47	56.0	3.1	>100.0	7.5
48	>100.0	1.2	>100.0	—
49	>100.0	>100.0	>100.0	30.0
50	>100.0	0.8	>100.0	—
51	>100.0	8.5	>100.0	—
52	>100.0	0.6	>100.0	30.0

Assay	Biofilm Inhibition IC ₅₀ (ppm) ^a			Quorum sensing Inhibition ^b (µg/disk) ^c
	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	<i>Vibrio harveyi</i>	<i>Chromobacterium violaceum</i>
53	47.2	0.01	6.2	7.5
54	46.2	0.02	62.5	30.0
55	51.4	0.07	14.5	30.0
56	>100.0	20.0	10.4	—
57	>100.0	81.5	>100.0	—
58	>100.0	>100.0	>100.0	—
59	33.6	3.1	38.3	—
60	28.5	0.3	2.6	—
61	43.5	4.2	52.5	—
62	>100.0	2.1	>100.0	—
63	>100.0	>100.0	>100.0	15.0
64	>100.0	>100.0	>100.0	7.5
65	>100.0	>100.0	>100.0	30.0
66	>100.0	>100.0	84.4	—
67	>100.0	>100.0	>100.0	7.5
68	>100.0	>100.0	>100.0	—
Kojic acid	17.2	24.7	>100.0	90.0
Solvent	NI	NI	NI	NI

^aConcentration that inhibits 50% of the biofilm. ND, not determined; NI, no inhibition of biofilm.

^bThe activity was measured taking into account the inhibition of the violet pigment.

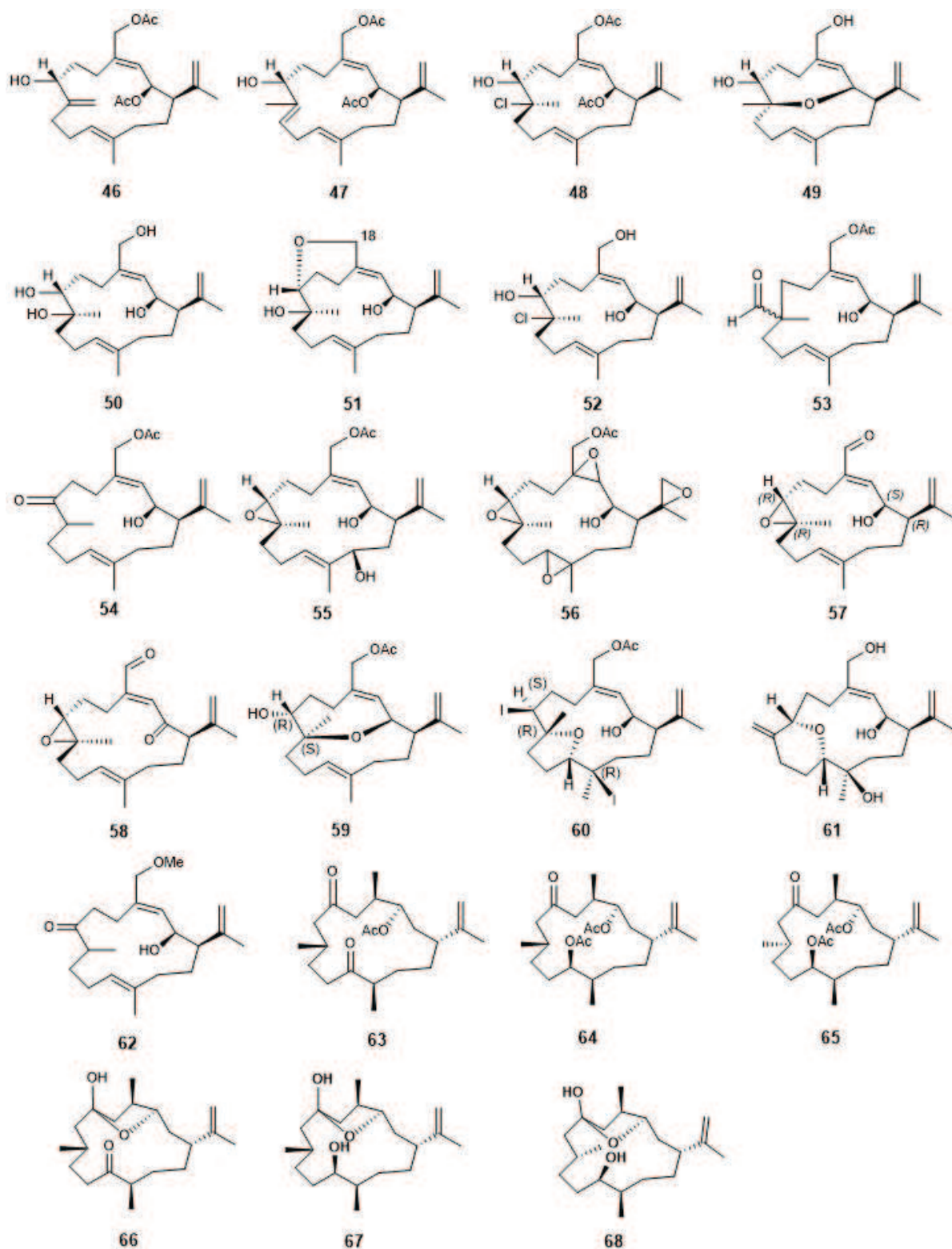
^cMinimum amount required in µg per disc of compound to inhibit the production of violet pigment. There is no inhibition zone even at 30 µg per disk.

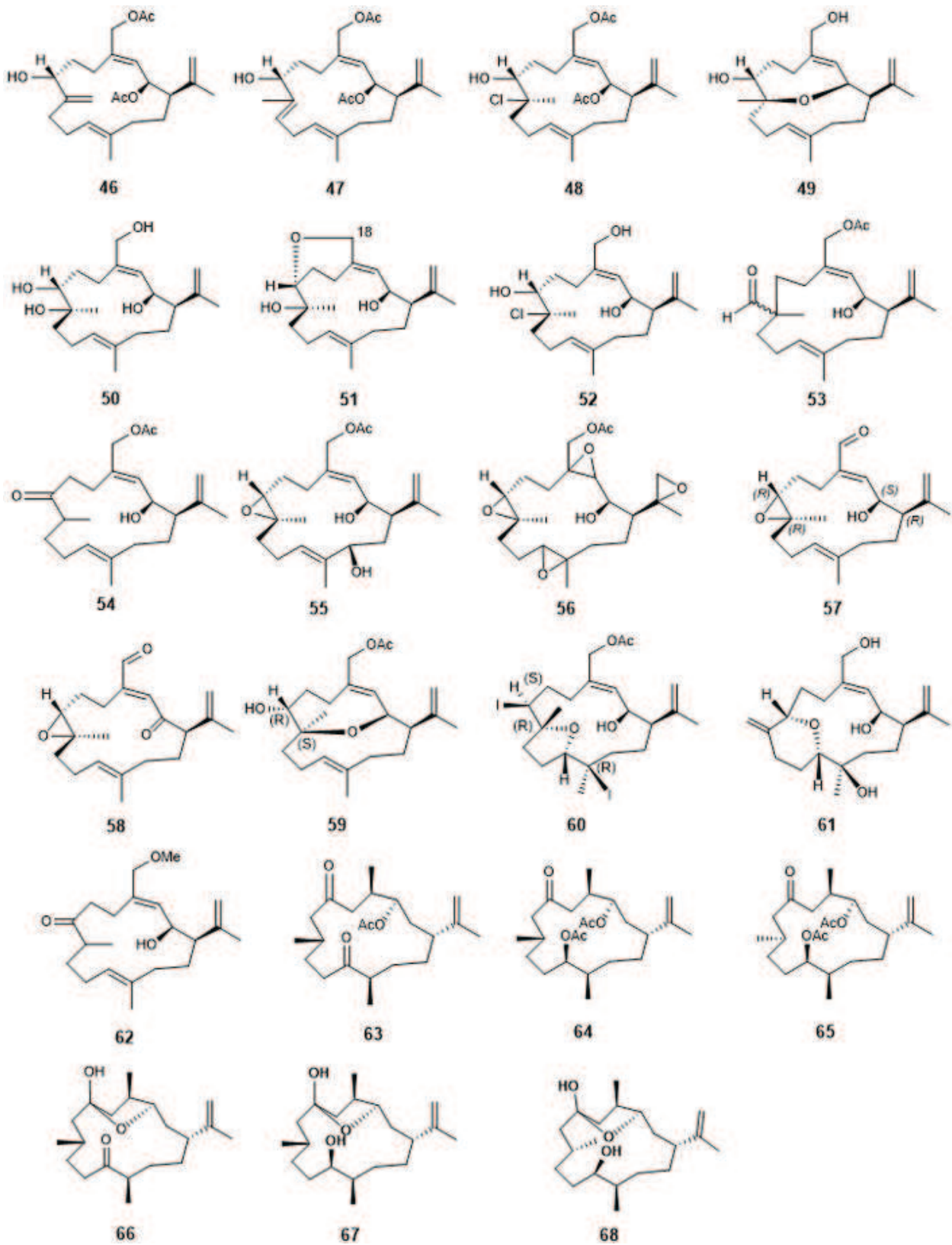
Table 1. IC₅₀ of natural and synthetic analogs (50 cembranoids) in the bacterial biofilm and quorum sensing inhibition assays.

estimate the correlation between QS and biofilm inhibition, demonstrating the potential antipathogenic effect of the 50 cembranoids evaluated, as discussed below.

The results demonstrated that half of the synthetic tested cembranoid analogs showed QSI activity without toxicity against the biosensor bacteria, results worth being highlighted, mainly because 16 active synthetic analogs were obtained from 5 non-active natural compounds (in QSI bioassay). The synthetic compounds with the best QSI activity were **22** (2.5 µg/disk), **23** (5.0 µg/disk) and **24** (2.5 µg/disk), presenting similar structure features, scilicet: C-7R hydroxy methine group, a double bond with *E* configuration between C-8 and C-9, and an acetyl group at C-18. The above allows us to infer that the presence of a *E*-hydroxy allylic moiety is highly relevant for the activity [33]. It is worth noting that the three synthetic

cembranoids (22, 23, and 24) were obtained from three natural inactive natural cembranoids (19, 20 and 21, respectively). Finally, these compounds were not able to inhibit the *C. violaceum* growth, thus, it suggests that inhibition on violacein pigment production is triggered by the disruption of QS systems. Therefore, there is no selective pressure for the development of resistance in bacteria.





The biofilm inhibition results showed that half of the synthetic analogs inhibited the formation of biofilm in the three bacterial strains used at concentrations lower than 100.0 ppm. It was found that several compounds that did not exhibit QSI did not show inhibition of biofilm formation either in the three biosensor strains evaluated, for example, compounds **44**, **45**, **58** and **68**; however it was not a generalized trend. Otherwise, all compounds having QSI showed inhibition of bacterial biofilm in at least one of the three strains used, except for compounds **49**, **63–65** and **66**. It was also evident that some of the synthetic analogs showed better biofilm inhibition activity than their natural precursors used as leads (**19–21**, **25**, **27** and **28**), in several cases achieving or increasing the activity. It was observed that most of the synthetic cembranoid type analogs exhibited an excellent activity to inhibit the formation of biofilm against Gram-positive *S. aureus* bacteria, although good results were also obtained against Gram-negative bacteria *P. aeruginosa* and *V. harveyi*.

In particular, 9 synthetic analogs inhibited *S. aureus* bacteria at concentrations less than 1.0 ppm, 10 inhibited the same strain at concentrations between 1.0 and 10.0 ppm and 5 between 10.0 and 100.0 ppm (**Table 1**). The compounds that showed the best potency against this biosensor strain were **40**, **41**, **46**, **50**, **52–54** and **60**, out of which compounds **41** (0.04 ppm), **46** (0.003 ppm), **53** (0.01 ppm), **54** (0.02 ppm) and **55** (0.07 ppm) were the most potent ones since they were up to 2000 times more active than the recognized kojic acid QS inhibitor, which presented an IC_{50} of 24.7 ppm. Against *P. aeruginosa* bacterium, only compound **22** (3.7 ppm) had a lower IC_{50} value than kojic acid (17.2 ppm), but it is important to mention that 16 synthetic cembranoids analogs had IC_{50} values between 10.0 and 100.0 ppm. Finally, four synthetic analogs (**22**, **41**, **53** and **60**) were shown to be active at concentrations lower than 10.0 ppm against *V. harveyi* bacteria, being compounds **41** and **60** the most active with IC_{50} values of 1.2 and 2.6 ppm, respectively. In addition, 11 compounds had IC_{50} values between 10.0 and 100.0 ppm, being still more active than the positive control used, which had an IC_{50} value greater than 100.0 ppm against this biosensor strain. It is noteworthy that biofilm inhibition was achieved in all cases without interruption of bacterial growth in the strains used, even at the highest concentration evaluated (100.0 ppm). The fact that compounds **22**, **24**, **39**, **41**, **42**, **46**, **47**, **51–54** showed biofilm and QSI activity suggests that these compounds interfere in bacterial communication, preventing the development or maturation of bacterial biofilm and successive development of bacterial communities, and therefore may serve as potential antibiotics.

It is worth highlighting that the comparison of the results of the bacterial biofilm inhibition with the results found in the literature showed that the synthetic cembranoids analogs present an excellent activity and low toxicity compared to other natural products reported, for example, oroidin had an IC_{50} of 0.26 ppm against *P. aeruginosa* and an IC_{50} of 35.0 ppm against *Acinetobacter baumannii*, dictiol C inhibited the formation of biofilm in the bacterial strain *Pseudoalteromonas* sp. D41 at an IC_{50} of 9.2 ppm and finally agelasine D oxime showed an MIC of 0.027 ppm against *Staphylococcus epidermis*. These IC_{50} values were higher than those reported by us here for some of the synthetic analogs against the *S. aureus* biosensor bacteria, for example, compound **41** (0.04 ppm), compound **46** (0.03 ppm), compound **53** (0.01 ppm), compound **54** (0.02 ppm) and compound **55** (0.07 ppm) (**Table 1**).

Some considerations about the structure-activity relationship of the compounds evaluated in this bioassay must be taken into account, for example, the presence of an electronegative group on C-7 (in most of the compounds “oxygen”) is highly relevant for the activity, since the most active compounds presented this functionality. Also, the formation of a double bond with *E*-configuration between carbons C-8 and C-9 is one of the most important rearrangements to increase or induce biofilm inhibitory activity, since its absence or formation of the *Z*-isomer decreases the activity, the presence of an electronegative group on C-2 and C-18 (oxygen) enhances this activity, as can be observed in all active compounds in this bioassay, except for compound **23**. Finally, the formation of an exomethylene between carbons C-8 and C-19 also has a positive effect on the activity, as can be seen in compounds **39** and **46**.

In summary, six natural compounds were selected as lead compounds (**19–21**, **25**, **27** and **28**) in an attempt to induce or enhance their antipathogenic activity by selectively applied chemical transformations at different active sites of the cembrane nucleus. Thus, 33 analogs of cembranoids (**22–24**, **39–68**) were obtained, being half of them remarkably active in the QSI bioassay against the *C. violaceum* biosensor strain and in the bacterial biofilm inhibition against *P. aeruginosa*, *S. aureus* and *V. harveyi* strains, all without interfering the bacterial growth. Finally, a select group of structurally related cembranoids (**23**, **23**, **39–42**, **46**, **53–55**) were obtained as QS and bacterial biofilm inhibitors, making them excellent candidates to be used as antipathogenic drugs by the pharmaceutical industry, since the relationship between biofilm inhibitors and QS inhibitors is often associated with potent antipathogenic agents.

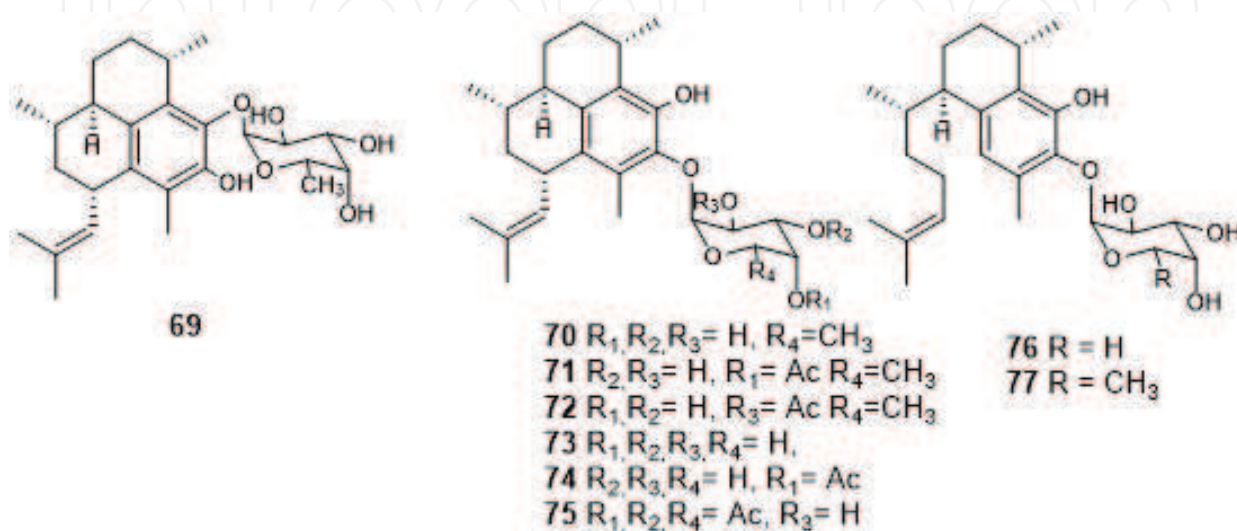
2.4. *Antilloorgia elisabethae* (Syn. *Pseudopterogorgia elisabethae* [37])

Pseudopterოსins, *seco*-pseudopterოსins and amphilectosins constitute an important class of diterpene glycosides found in the gorgonian *Antilloorgia elisabethae* [37] (known before as *Pseudopterogorgia elisabethae*), except for *seco*-pseudopterოსins A-D isolated from *Pseudopterogorgia* Kallo, collected from different regions of the Caribbean (Bahamas, Bermudas, Florida, Providencia and San Andrés). The pseudopterოსins were discovered first by Fenical et al. in the late 1980s [38, 39] and since then numerous members of the scientific community have been involved in this attractive area finding many other compounds of this kind, most of them with potent biological activity [40, 41], that is, antiinflammatory and analgesic, wound healing, antibacterial, anticancer, antiviral, antimalaria and antituberculosis, in *in vitro* and *in vivo* assays with a new mechanism of action. Very recently, a protection of synaptic function and potential as a neuromodulatory agent for PsA has also been reported [42]. In addition, those compounds have demonstrated efficacy in Phase II clinical trials as an antiinflammatory and wound healing agents and are the first commercial licensed natural product for use as an additive in Estée Lauder skin care and cosmetic products. To date, 31 pseudopterოსins, 11 *seco*-pseudopterოსins and 2 amphilectosins are known from nature. A recent review about this topic can be consulted in [21].

We have had a special interest in pseudopterოსins G, and P-U, 3-*O*-acetyl-PsU, *seco*-Ps J and *seco*-Ps K isolated by Duque and collaborators [43–45] from specimens of *P. elisabethae* collected at Providencia Island. After their isolation and chemical structure determination, we soon discovered their high chemical diversity (natural analogs) and their potent therapeutic activity [46–48] (antiinflammatory, cytotoxic and antimicrobial activity).

Their antiinflammatory activity was evaluated by us using *in vitro* experiments as myeloperoxidase (MPO) assay, nitric oxide release (cell-based assay) and scavenger activity on this radical [46]. Our results reported in [46] showed that compounds PsG, PsK, PsP, PsQ, PsS, PsT, PsU and *seco*-PsK are promising molecules with an interesting and potent antiinflammatory activity. In our experiments, they displayed more potent action than indomethacin, a clinical drug used currently to treat inflammation and with different mechanism of action. Furthermore, the results for the different MPO inhibition values obtained provided us with preliminary insights toward their structure-activity relationship, that is, the activity depends on the kind of sugar moiety, on whether sugar moiety is in a free form or acetylated, on the acetylation position within the sugar moiety and on the glycosylation position. In addition, regarding the results of NO release in J-774 cell-based assay, we found a greater activity for the pseudopterosins than for the *seco*-pseudopterosins, clearly showing that the non-glycosylation improves the inhibition of NO release. And finally, by comparing the different NO inhibition values for individual compounds, the inhibitory activity apparently depends on the glycosylation position, on the stereochemistry of the aglycone and on the type of the skeleton. For example, the amphilectane skeleton (PsP) has more inhibitory activity than the serrulatane skeleton (*seco*-PsK). However, more experiments are needed in order to support structure-activity relationships among these kinds of compounds.

The results of the cytotoxicity of the natural homologous compounds PsG, PsP, PsQ, PsS, PsT, PsU, 3-O-acetyl-PsU, *seco*-PsJ and *seco*-PsK (69–77), evaluated using human cancer cell lines (HeLa, PC-3, HCT116 and MCF-7) showed moderate and non-selectivity activity between the lines used. After examining the mentioned cytotoxic activity results, it could be seen that some SARs were evident. According to the results that we have published in [47], the position of glycosylation on the terpene skeleton appears to affect the inhibitory activity profile, for example, PsG (glycosylated in C-9 with fucopyranose) is more active than PsP (glycosylated in C-10 with fucopyranose). Further, the type of sugar moiety also influences the activity, for instance, PsP, which is glycosylated with fucopyranose, is more active than PsT, which is glycosylated with arabinopyranose. Likewise, PsQ (C-4' mono-acetylated fucose as sugar moiety) is more active than PsU (C-4' mono-acetylated arabinose as sugar moiety), and *seco*-PsK (non-acetylated fucose as sugar moiety) is more active than *seco*-PsJ (mono-acetylated arabinose as sugar moiety).



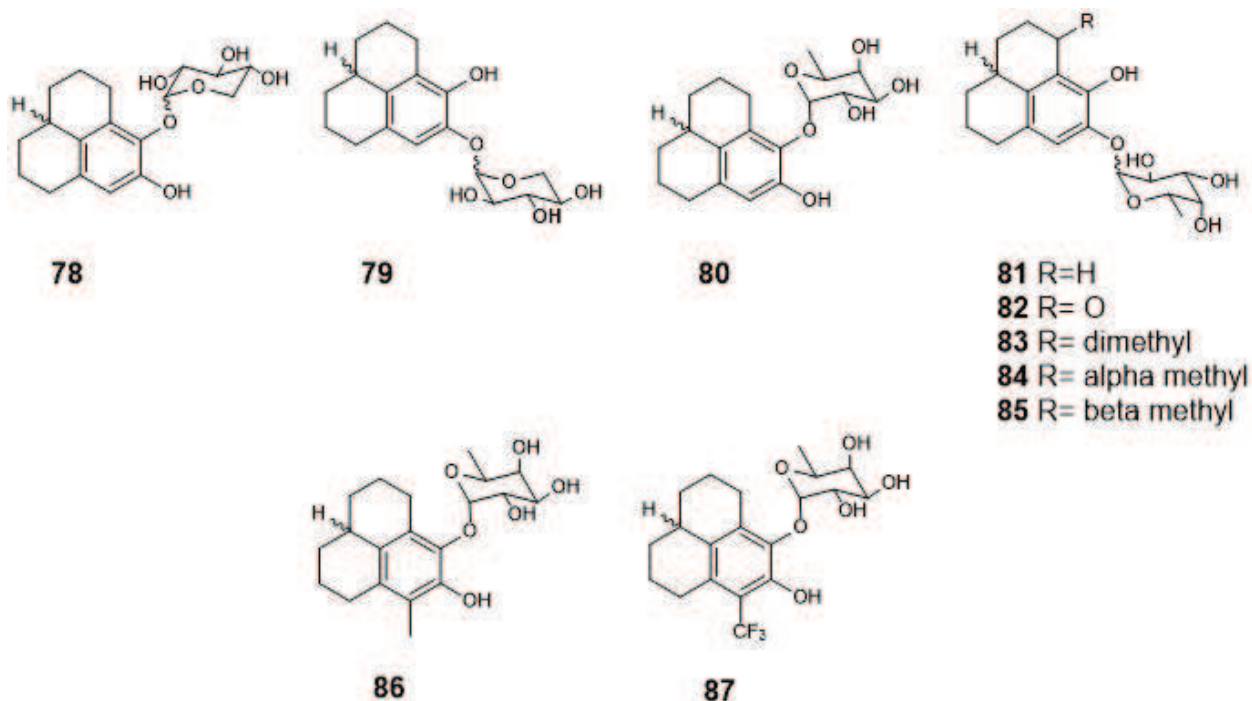
Regarding the antimicrobial activity for the natural homologous **69–77**, we found good and selective activity against Gram-positive bacteria, *Staphylococcus aureus* and *Enterobacter faecalis*, being the most active PsG, PsU, PsQ, PsS and *seco*-PsK. Additionally, they did not show activity against the Gram-negative bacteria or the yeast used in our assay and, more importantly, their antimicrobial potency was comparable to the reference drug vancomycin. In examining our just mentioned data, published in [47], the following SARs could be noted: fucopyranose glycosilation at C-9 instead at C-10 seems to increase the activity (PsG vs. PsP); arabinopyranose instead of fucopyranose glycosilation favors the activity (PsT vs. PsP); likewise, mono-acetylated arabinose as sugar moiety increases the activity (PsU vs. PsQ and PsS (mono-acetylated fucose as sugar moiety)). In contrast, this behavior initially observed in pseudopterosins is not consistent when the results are applied to the *seco*-pseudopterosins *seco*-Psk (glycosilated with fucopyranose), which is more active than *seco*-PsJ (glycosilated with arabinopyranose).

Additionally, it is important to mention that in our experiments published in Ref. [48], we assayed pseudopterosins and *seco*-pseudopterosins (natural analogs **69–77**) as antifouling agents against marine bacteria isolated from heavily fouled marine surfaces. These compounds at a 30 µg dose showed moderately to highly active against all Gram-positive microfouling bacteria assayed, and non-active against the Gram-negative bacteria used. Tetracycline and kanamycin reference antibiotics used in the assay showed similar values of activity with doses of 30 µg as well. Furthermore, we performed assays of natural compounds **69–77**, kanamycin and tetracycline on bacterial growth and on biofilm disruption (% of inhibition) of *Pseudomonas putida* IsoF used as a positive control for biofilm formation and of six marine bacterial strains associated with fouled surfaces. The natural analogs tested showed no activity (did not inhibit bacterial growth and did not promote biofilm formation) against Gram-negative bacteria *Pseudomonas putida* Iso F, *Alteromona Macleodii* and *Ochrobactrum pseudopgringonense* strains 1 and 2. In contrast, they inhibited both growth and biofilm formation of Gram-positive bacteria (*Oceanobacillus iheyensis*, *Bacillus* sp. and *Kocuria* sp.).

Finally, it is worth mentioning the many studies carried out using the chemical synthesis (total synthesis and semi-synthesis) in order to increase the activity and to solve at least partly the problem of the sustainable supply of pseudopterosins. Those studies were conducted by Broka in 1988, Corey in 1989, 1990, 1998 and 2000, McCombie in 1990 and 1991, Buszek in 1995, Schmalz in 1997, Kociensk in 2001, and Harroweven in 2004 (complete information on this topic can be found cited and widely commented in Ref. [21]). Unfortunately, the mentioned syntheses have not yet been used, perhaps due to the complexity or/and non-economically ways of the synthetic routes applied. However, those efforts have provided information on improvement of their biological activity, pharmacophore and mechanism of action. Moreover, it is worth noting that semi-synthetic alkoxy or phenoxy substitution such as ether and acetate derivatives of pseudopterosins are under patent protection [21].

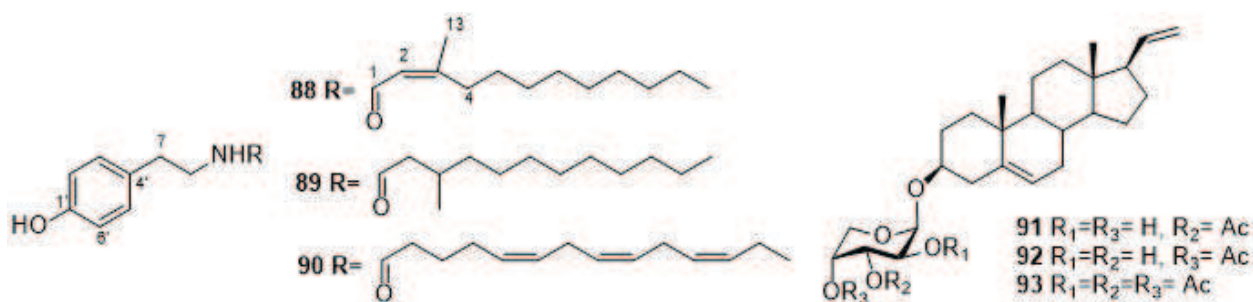
At this point, we want to mention the recent studies reported in [40] where simplified synthetic analogs of pseudopterosins **78–87** were prepared by Fenical and colleagues using a new and efficient synthesis taking into account the following general structural modifications: degree of substitution of the hexahydrophenalone core, different configurations at C-4 and at C-7, and several sugar moieties and place of the glycosidation. Nine of the 10 compounds evaluated as

racemic mixtures were active in the mouse-ear assay (the most active one was twice more active than PsA) and no statistical differences were identified among compounds. Additionally, the synthetic route involving only six steps leads to derivatives without substituents at C-1 and C-3 (reducing the number of stereoisomers) and allows for the preparation of multigram amounts of them.

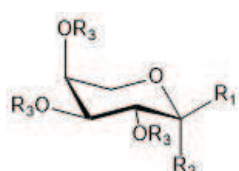


2.5. *Muricea austera*

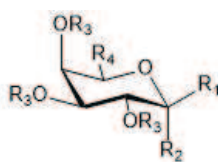
Specimens of *Muricea austera* were collected in the Pacific coast of Panama during an expedition of the Smithsonian Tropical Research Institute [49]. The MeOH extract of *M. austera* showed *in vitro* activity against chloroquine-resistant *Plasmodium falciparum*. Bioassay-guided fractionation using vacuum liquid chromatography followed by flash chromatography and normal-phase HPLC purification yielded six compounds: three tyramine derivatives (**88–90**) and three steroidal pregnane glycosides (**91–93**). The structures of the compounds were determined based on their spectroscopic data. Several synthetic analogs were obtained under basic hydrolysis and perbenzoylation reactions. All natural compounds and synthetic analogs were evaluated against a drug-resistant *Plasmodium falciparum* and intracellular form of *Trypanosoma cruzi*.



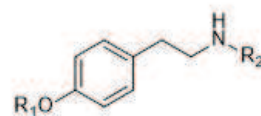
Natural compounds **88–92** showed moderate activity, being compounds **88** (IC_{50} 36 μ M), **89** (IC_{50} 45 μ M) and **90** (IC_{50} 45 μ M) the most active ones. The antiplasmodial activity of glycosides **91** and **92** (IC_{50} 67 and 80 μ M) was increased in their peracetylated natural analog **99** (IC_{50} 28 μ M) [49]. Arabinopyranosides synthetic analogs **94** and **95** were also evaluated, showing that perbenzoylated derivatives **94** (IC_{50} 35 μ M) and **95** (IC_{50} 21 μ M) were more active against *P. falciparum* than natural compounds **91** and **92**. The antiplasmodial activity of analogs with stereochemistry as D-arabinopyranose **96** and **97** and D-galactosides **98** and **99** were also evaluated. Interestingly, compounds **96–98** displayed antiplasmodial activity, being compound **98** (IC_{50} 29 μ M) the most active one, while perbenzoylated methyl β -D-galactoside **99** was inactive.



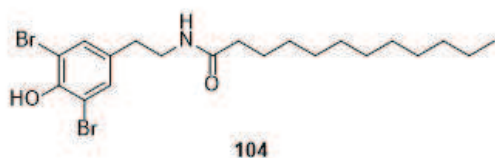
94 $R_1 = H$, $R_2 = OMe$, $R_3 = Bz$
95 $R_1 = OMe$, $R_2 = H$, $R_3 = Bz$



96 $R_1 = H$, $R_2 = OMe$, $R_3 = Bz$, $R_4 = CH_3$
97 $R_1 = OMe$, $R_2 = H$, $R_3 = Bz$, $R_4 = CH_3$
98 $R_1 = H$, $R_2 = OMe$, $R_3 = Bz$, $R_4 = CH_2OBz$
99 $R_1 = OMe$, $R_2 = H$, $R_3 = Bz$, $R_4 = CH_2OBz$



100 $R_1 = H$, $R_2 = CO(CH_2)_8CH_3$
101 $R_1 = H$, $R_2 = CO(CH_2)_{10}CH_3$
102 $R_1 = H$, $R_2 = CO(CH_2)_{12}CH_3$
103 $R_1 = H$, $R_2 = CO(CH_2)_{10}CHOH(CH_2)_5CH_3$



Given the antiplasmodial activity displayed by natural tyramine derivatives **88** (IC_{50} 36 μ M), **89** (IC_{50} 45 μ M) and **90** (IC_{50} 38 μ M), thirteen synthetic analogs were evaluated. The results indicated that the derivatives with a fatty acid moiety **100** (IC_{50} 72 μ M), **101** (IC_{50} 47 μ M) and **102** (IC_{50} 34 μ M) showed similar activity to those of their natural analogs **88–90**, suggesting that the increasing of the number of carbons of the fatty acid chain produces an increase in the activity, while the presence of polar groups decreases the activity as in compound **103** (IC_{50} 62 μ M). Finally, the presence of a bromine group on the tyramine aromatic ring as in **104** (IC_{50} 17 μ M) substantially enhances the antiplasmodial activity [49].

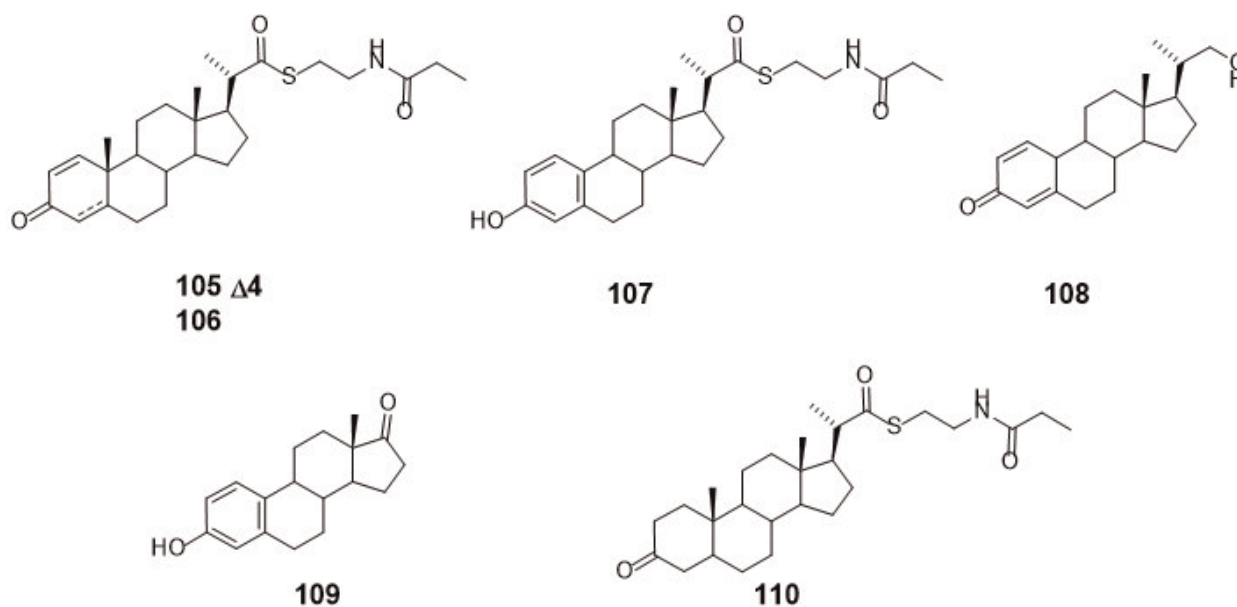
2.6. *Paragorgia* sp.

The octocoral genus *Paragorgia* has been barely studied; however, some diterpenoids and steroids were reported in 1984 [50]. In 2008, Spanish researchers collected *Paragorgia* sp. by bottom trawling near the Madagascar Island at a depth of 790 m. The sample was extracted with isopropanol, and a bioguided isolation procedure allowed to isolate three novel cytotoxic steroids derivatives named parathioesters A-C **105–107**. The structures incorporate an A-ring with different degrees of unsaturation, and a side chain containing both a thioester and an acetamide groups. These structural novelties do not have precedents in marine natural products chemistry [51]. Natural compounds **105–107** displayed cytotoxic properties against

colon (HT-29), lung (A-549) and breast (MDA-MB-231) tumor cell lines with GI_{50} values in the micromolar range. Interestingly, parathio steroid B **106** showed a selective cytotoxicity against HT-29 with a GI_{50} of 6.5 μ M. Related compounds were detected in an aerobic degradation study of bile acid cholate by a *Pseudomonas* sp. [52].

In addition the authors obtained by simple and fast synthesis in the laboratory, the three natural products **105–107**, starting from commercially available 20-(hydroxymethyl)-pregnan-1,4-dien-3-one **108** and (+)-estrone **109**. The synthesis includes oxidation of C-20 hydroxymethylene to carboxylic acid followed by thioesterification of the carboxylic acid with N-acetylcysteamine. The unsaturation pattern of A-ring at **106** was obtained by Birch reduction of **108** followed by bromination at C-2 and subsequent dehydrohalogenation.

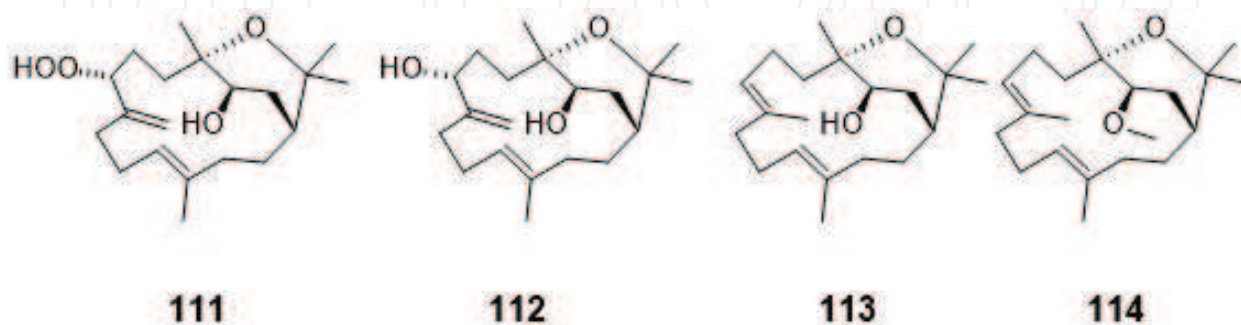
Furthermore, to obtain different synthetic analogs, the authors used $XCH_2CH_2NHCOCH_3$ ($X = O$ or NH) instead of sulfur derivate and prepared analogs with different oxidation patterns at the A-ring. In this way, more than 20 steroids were prepared. These analogs were assayed for their cytotoxic activity against HT-29, A-549 and MDA-MB-231 cell lines. Analog **110** showed to be more active than natural products (GI_{50} MDA-MB-231: 39 μ M; A-549: 79 μ M; HT-29: 72 μ M); this compound has no double bonds at A-ring and neither thioester at side chain. Structure-activity relationship studies [51] showed that the presence of $XCH_2CH_2NHCOCH_3$ moiety ($X = S, O$ and N) in the side chain is essential for the antiproliferative activity, and that a low oxidation degree on an A-ring results in a higher bioactivity.



2.7. *Lobophytum* sp.

Colonies of *Lobophytum* sp. collected in 2006 in Siladen (North Sulawesi, Indonesia) were extracted with MeOH:CHCl₃. The organic extract was chromatographed by MPLC and the obtained fractions were further purified by analytical HPLC to obtain six cembranoids [53]. All compounds were evaluated for cell growth inhibitory activity against three different cell lines:

H9c2 (cardiacmyoblasts), C6 (glioma) and HeLa (epithelial carcinoma). One of the isolated compounds, decaryiol D **111**, showed a significant activity against C6 glioma cell line (IC_{50} 40 μ M) compared with the structurally related decaryiol B **112** which was inactive. This fact indicated that the growth inhibitory activity of **111** should be attributed to the presence of the hydroperoxy group in this molecule. Based on the availability of high amounts of decaryiol **113**, it was subjected to several reactions (acetylations, oxidations and epoxidations) to obtain six semi-synthetic derivatives with the purpose of extending the structure-activity relationship knowledge.

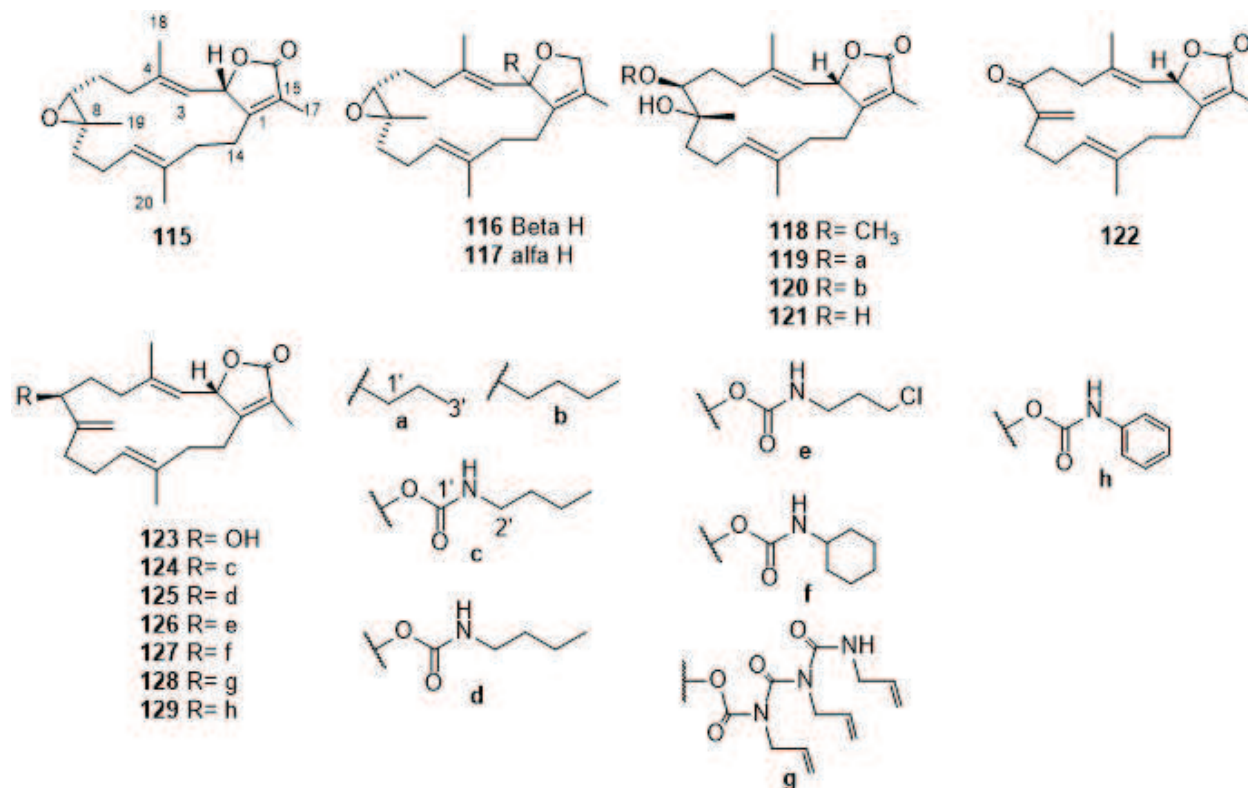


The six synthetic cembranoids were also evaluated against the same cell lines and the results showed that the derivative O-methyl decaryiol **114** was more active against C6 glioma cell line (IC_{50} of 8 μ M) than the natural compound and it also presented a selectivity as it was inactive against HeLa and practically inactive against the non-tumor H9c2 cell line [53]. These results allowed to establish that minor structural changes on the cembranoid skeleton of decaryiol can radically affect the activity and selectivity as cell growth inhibitors.

2.8. *Sarcophyton glaucum*

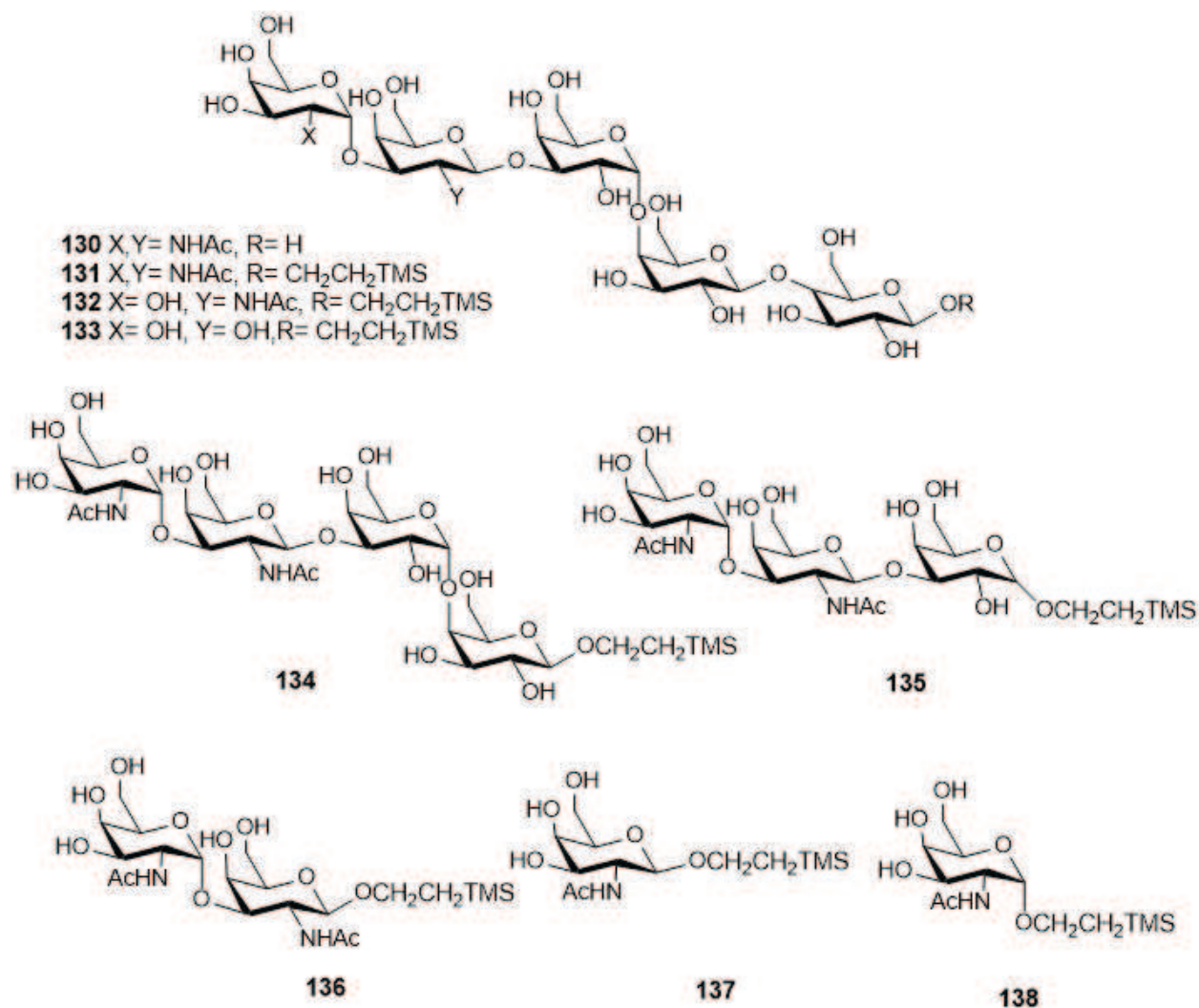
Sarcophine **115** is a bioactive cembranoid diterpenes with anticancer activity isolated by Kashman group in 1974 [54, 55] from the Red Sea soft coral *Sarcophyton glaucum*. Continued studies of structure-activity relationship as mentioned in Hassan et al., 2011 [56] suggested the importance of functional groups at C-7/C-8 and the opening of the ring lactone to increase the activity. In addition, later experiments confirmed the importance of macrocyclic double bonds to the mentioned activity, and showed that bromination of sarcophine **115** improved the antiproliferative activity against malignant breast cancer cells. Further experiments through the oxidation of **115**, which resulted in the formation of (+)-sarcophytoxin B exhibiting antiproliferative activity, suggested that C-7/C-8 epoxide is not required for the activity. Thus far, the reported studies clearly demonstrate the need to further optimize the epoxide functionality of sarcophine in relation to its anticancer activity. Then, more experiments [56] were done in the direction of measuring the activity of natural analogs 16-deoxysarcophine **116** and 2-epi-16-deoxysarcophine **117**, and of compounds **118–129** prepared via etherification and carbamoylation of **115** at C-7/C-8. The C-7 ether and carbamate functionalities can be taken as different examples of the introduction of hydrogen bonding donor and hydrogen bonding acceptor and π -aromatic groups at this position to examine their binding affinities toward their molecule target. The analogs thus prepared were subjected to evaluation of their ability to inhibit the proliferation and migration of the human metastatic prostate cancer PC-3 and

breast cancer MDA-MB-231 cell lines using MTT and wound healing assays. Most analogs exhibited enhance antimigration activity and lack of cytotoxicity toward the cancer cells.



2.9. *Sinularia lochmodes*

An interesting example related to the topic of this chapter is the one published by Tanaka et al. in 2013 [57]. This study mentions lectin SLL-2 isolated from octocoral *Sinularia lochmodes* as an important mediator in the symbiotic relationship of this animal with its zooxanthellae (the symbiotic microalgae *Symbiodinium*) on which the coral depends for energy and nutrients. This lectin SLL-2 influences the transformation of *Symbiodinium* cells into a non-flagellated coccoid form from a flagellated-swimming form. In addition, Forssman antigen pentasaccharide GalNAc α (1,3)GalNAc β (1,3)Gal α (1,4)Gal β (1,4)Glc **130** was also identified as a ligand of lectin SLL-2 [58]. The authors, Tanaka et al. in [57], oriented their work in terms of structure-activity relationship. Thus, the synthesis and biological evaluation of Forssman antigen pentasaccharide and some derivatives obtained by using a one-pot glycosylation and polymer-assisted deprotection were assessed. For the evaluation of the biological activity they used the analysis of the increase or decrease that occurs when oligosaccharides (**131**, **132**, **133** pentasaccharide derivatives of **130**, protected with 2-trimethylsilylethyl group at the reducing end and protected analogs **134–138**) bind to the fluorescent-labeled lectin SLL-2. The results revealed that the affinity of oligosaccharides for SLL-2 was dependent on the number of sugar units in the oligosaccharide and on the NHAc substituents [57]. Modification of the GalNAc unit to a Gal unit reduced the binding affinity to SLL-2. These results indicated that SLL-2 not only recognized the acetamide group at the non-reducing end of the Forssman antigen, but also the sugar units at the reducing end. In addition, α -GalNAc **138** showed a stronger affinity than that of β -GalNAc **137**, comparable to that of tetrasaccharide **134**.



3. Conclusions

As we have shown throughout this chapter, there is no doubt that chemical synthesis plays an important role in the bioprospection of chemical compounds isolated from octocorals, either in the production of the bioactive natural product (supply a natural product), facilitating the further ways of its development as a drug and its subsequent commercialization or in the obtaining of a series of analogs that undoubtedly reveal important features on the interaction of the bioactive molecule and its target, allowing the chemists of marine natural products to change at convenience the activity and toxicity initially detected in the isolated compounds and sometimes even to reach the establishment of the pharmacophore. However, it is also a fact that this strategy has important limitations to consider, among them that the chemical reactions used must be efficient, with the fewest possible steps, economical viable option, easy to perform and to supply products with significant values of biological activity and without by-side toxicity.

The studies using the strategy analyzed in this chapter, suggest in most cases that the natural compounds can be potential scaffolds for the design of potent bioactive leads against different biological targets. In addition, the results indicate that a subtle structural change on the lead compounds can dramatically affect the activity and the selectivity of the structure against the different activities evaluated. The above corroborate that the assessment of the synthetic analogs of this chapter appear to be attractive targets for the development of new anticancer, antiinflammatory, antiviral, antimicrobial, antileishmanial, antiplasmodial and antipathogenic agents. However, this strategy should be accompanied by in silico studies that allow to establish the mechanisms of interaction between the proteins involved in the different biological activities mentioned above with the substrates (natural and synthetic analogs). Thus, the work will be carried out in a more effective way, translating into shorter times and in an adequate investment of resources used in this strategy.

It is important to highlight in this section that for the case of the octocorals *E. knighti* and *P. flagellosa* six natural compounds selected as lead compounds based on their activity values in the QSI and biofilm inhibition assays and on the variety of reactive functional groups present in their cembrane nucleus, selective chemical transformations were used with the purpose of inducing or enhancing antipathogenic properties. As a result, 33 cembrane analogs were obtained, half of them being remarkably more active than the naturals in the bioassays used, without interfering with bacterial growth, which lead us to assume that the inhibition of the phenotype expression is caused by disruption of the bacterial communication (QS) system. The latter is noteworthy, because avoiding the bactericidal effect, there is no selective pressure in the bacteria to develop resistance to this type of compounds.

As for *A. elisabethae*, the work shown above evidenced the importance of the pseudopterosins and seco-pseudopterosins isolated from this octocoral collected in the North Caribbean Sea (Bahamas) and in the South Caribbean Sea (Providencia Island), not only in relationship with their novel chemical structure but also for their potent antiinflammatory, cytotoxic and selective antimicrobial activity against Gram-positive bacteria. The efforts of many well-known researchers using the total synthesis of pseudopterosins and the SAR studies described by us in this chapter for natural homologs, allow us to conclude that despite all the research done for about 30 years, the development of these compounds as drugs or as active ingredients in cosmetic creams needs to be continued. Particularly, the supply issue (currently the key point) needs the development of more efficient and commercially viable syntheses or more SAR works aiming the elucidation of the pharmacophore responsible for the activity. In relation to the latter, it is important to emphasize that if we can determine the nature of the pharmacophore there would be no need to synthesize the entire molecule but to achieve by synthesis a partial structure that retains the biological activity, as tried by Fenical and coworkers [40] in their interesting work of the 2010 year.

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