Review

Natural Products from Marine Invertebrates and Microorganisms in Brazil between 2004 and 2017: Still the Challenges, More Rewards

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The Brazilian marine biodiversity represents a unique, yet underexplored resource of biologically active compounds. This review provides an analysis of the development of marine natural products chemistry in Brazil within the period comprised between 2004 and 2017. Emphasis is directed towards marine invertebrate and marine microorganisms metabolites, including isolation, structure analysis, biosynthesis, bioactivities and total synthesis. An overview of the research on marine natural products by Brazilian researchers is also discussed, as well as perspectives for the development of the chemistry of marine natural products in Brazil.

Keywords: marine natural products, marine sponges, marine bacteria, marine fungi, marine alkaloids, marine polyketides

1. Introduction

The chemistry of natural products is a science well established in Brazil, spanned over 60 years and all over the country. Most of Brazilian natural product researchers devote efforts to the investigation of plant metabolites. From the beginning of the 21st century there has been a substantial growth of research on microbial natural products by Brazilian researchers,[1] and on marine natural products as well. The interest of Brazilian natural product chemists to investigate other sources than plants for the isolation of secondary metabolites are consequential to the chemical diversity of marine and microbial organisms. Clearly distinctive biosynthetic pathways arose from unrelated biological groups or from their respective associated microorganisms. Increasing evidences demonstrate that bacteria, cyanobacteria and fungi are now considered as the actual producers of many natural products first isolated from macroorganisms, both terrestrial[2,3] and marine.[4]

While the knowledge on the secondary metabolism interplay between micro- and macroorganisms is only starting to be deciphered, it seems clear that the approximate number of 300,000 secondary metabolites so far identified from all biological sources may represent only a tiny fraction of genes regulating the biosynthesis of natural products.[5] Unexpressed genes coding the biosynthesis of natural products appear to be the largest fraction of genomes encoding the biochemistry of natural products pathways. Thus, if the sciences of investigating natural products have expanded to unexpected boundaries in a very impressive rate since the advent of genomic tools, there is no need to say that much more remains to be done, particularly exploring new biological sources for the discovery of secondary metabolites. Among poorly known sources of natural products, Gram-negative bacteria are now under a more intense scrutiny, since these bacteria are capable of survive in many habitats and produce a series of antimicrobial molecules.[6] Additionally, the exciting discovery of a new marine biome at the mouth of the Amazon river provided a series of yet uninvestigated species of marine sponges and other marine invertebrates.[7]

The move of natural products chemistry in Brazil towards contemporary approaches to discover novel natural products has been slow, for various reasons. First, the lack of expertise on the use of genomic tools for the investigation of secondary metabolism is critical. This is a severe gap that must be faced in the current education of graduate students involved in natural products chemistry projects. Second, the need of closer collaborative efforts between chemists, pharmacologists and biologists, including microbiologists, is evident. There are still very few collaborative research efforts in Brazil involving bioassay-guided isolation, as well as the chemical synthesis and medicinal chemistry of

bioactive or chemically unique natural products. However, the most difficult challenge to address is the need to develop a truly innovative natural products science in Brazil. A new vision in the way of natural product chemistry has been performed is very much in need of consideration, since the country is still one with the highest biodiversity in the planet-remaining largely unexplored towards the identification of novel, biologically active natural products.[8]

The Brazilian marine environment is now under a more intense investigation by Brazilian natural product chemists, as shown by the exponential growth of research in this field. This review covers the literature on natural products chemistry of marine invertebrates and marine microorganisms published between 2004 and August 2017 by Brazilian researchers as corresponding authors. Research on algae natural products in Brazil has been the subject of two special issues of the Brazilian Journal of Pharmacognosy,[9] and therefore will not be herein discussed. A special issue of the same journal on marine natural products has been published in 2015.[10] Publications dealing with crude extracts or with only partially identified, bioactive or not, chemical entities or even primary metabolites, are not included as well.

2. Marine Microorganisms

As predicted in a previous review,[11] the investigation of marine-derived fungi and bacteria metabolites by Brazilian researchers has grown impressively during over the last decade. Collaborative efforts between microbiologists and chemists led to the discovery of a number of bioactive metabolites produced by marine-derived microbes. Investigation on the biosynthesis of marine-derived microbial

metabolites during this period is also noteworthy. The large majority of bacteria metabolites isolated by Brazilian researchers are derived from amino acids, while polyketides corresponds to up 50% for fungi secondary metabolites.

2.1. Bacteria

A sponge-associated strain of *Pseudomonas fluorescens* produced the known diketopiperazine cyclo-(*L*-Leu-*L*-Pro) (**1**, Figure 1).[12] Assignment of the absolute configuration was based on comparison with literature data, with no mention to a value of specific rotation. Cultures of *Streptomyces* sp. provided the known diketopiperazines (Figure 1) cyclo-(*L*-Phe-*trans*-4-OH-*L*-Pro) (**2**), cyclo-(*L*-Phe-*L*-Pro) (**3**) and cyclo-(*L*-Trp-*L*-Pro) (**4**). No mention to the experimental assignment of absolute configuration was provided.[13] Well-known prodigiosin (**5**), deoxycholic acid (**6**) and cholic acid (**7**) were isolated from cultures of *Pseudoalteromonas* sp. (Figure 1).[14] Since the production of sterols by bacteria is very unlikely,[15] growth media used in this investigation, namely starch casein agar, may contain sterols, thus compounds **6** and **7** may be media components.

The new 2(1*H*)-pyrazinones giovaninones A-D (**8-11**, Figure 1) were produced by a strain of *Streptomyces* sp. isolated from marine sediments.[16] Compounds were identified by analysis of spectroscopic data, using HPLC-SPE-NMR (high performance liquid chromatography-solid phase extraction-nuclear magnetic resonance) with a cryoprobe. No bioactivity data was reported for compounds **8-11**.

Bromotyrosine-derived verongidoic acid (**12**), 11-hydroxyaerothionin (**13**) and fistularin-3 (**14**) have been isolated from cultures of *Pseudovibrio denitrificans*
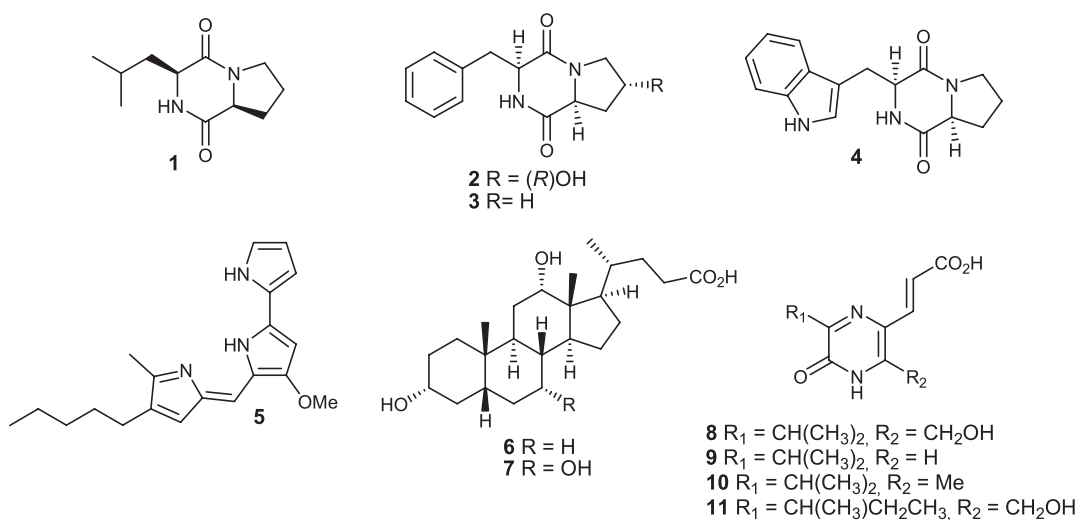

Figure 1. Structures of cyclo-(*L*-Leu- *L*-Pro) (**1**), cyclo-(*L*-Phe-*trans*-4-OH-*L*-Pro) (**2**), cyclo-(*L*-Phe- *L*-Pro) (**3**) cyclo-(*L*-Trp- *L*-Pro) (**4**), prodigiosin (**5**), deoxycholic acid (**6**), cholic acid (**7**) and of giovaninones A-D (**8-11**).

obtained from the sponge *Arenosclera brasiliensis* (Figure 2), and identified by analysis of spectroscopic data, including the assignment of absolute configuration by circular dichroism analysis.[17] The production of bromotyrosine-derived metabolites by a marine bacterium provided strong evidence that such metabolites are likely not produced by sponges, as it has been repeatedly assumed in the past.[18,19] The isolation of **12**-**14** from cultures of a *Pseudovibrio* Gram-negative bacterial strain illustrates the potential metabolic diversity of this particular group of marine bacteria, first described only ten years ago.[20]

Sponges harbor a high density of cyanobacteria and bacteria which may exceed those of surrounding seawater by up to three orders of magnitude.[18] The microbiome composition of *Aplysina* sponges, the main source of bromotyrosine-derived metabolites, is rather homogeneous within the genus,[21-23] but distinct to the environmental microbiome to which the sponges are exposed.[24] One of the unique characteristics of the microbiome of *Aplysina* sponges is the high diversity and abundance of bacteria belonging to "*Poribacteria*" and *Chloroflexi* clades,[19,21,22,25] bacterial groups which are considered true sponge symbionts[26] and that present the enzymatic machinery for the biosynthesis of secondary metabolites.[27,28] Based on evidences that marine sponges share microbiomes with similar composition, it is possible that horizontal gene transfer between marine sponge symbionts is common.[29] However, there is still no definitive evidences of exchange of genomic material between sponge-associated bacteria.[29,30] On the other hand, colonization of sponges by bacteria found in surrounding seawater has been repeatedly observed, indicating that a bacterial interchange between species is a real possibility.[26] Such evidences are supported by solid exprimental data indicating both vertically and horizontally bacterial transmission within and between sponge species.[21,22,26,31]

The importance of developing strategies for culturing marine bacteria, in particular sponge symbionts, must be stressed,[21,22,26,32] since the large majority of sponge-associated microbial strains are considered to be resistant to cultivation[26] or the secondary metabolism is difficult to be trigger. This is

not only particularly relevant for the correct assignment of a microbial production of secondary metabolites,[30] along to the knowledge of microbial physiology and ecology of sponge symbionts[22,26,31] but also for the detailed investigation of unique biosynthetic pathways which are not found elsewhere in nature but in sponges.

2.2. Marine-derived fungi

The destruxins [β-Me-Pro] destruxin E chlrohydrin (**15**), destruxin E chlorohydrin (**16**), pseudodestruxin C (**17**), [Phe³, *N*-Me-Val⁵] destruxin B (**18**), roseotoxin B (**19**), roseocardin (**20**), isariin (**21**) and isariin B (**22**) have been isolated from cultures of marine-derived *Beauveria felina*, obtained from the seaweed *Caulerpa* sp. (Figure 3). Cyclodepsipeptides **15** and **17** are new representatives of this class of metabolites. The structures of the metabolites have been established by analysis of spectroscopic data, while the absolute configuration of amino acids have been established by Marfey's analysis.[33,34] This class of cyclodepsipeptides very often present potent and diverse bioactivities, including antitumoral, antiviral, cytotoxic, immunosuppressant and antiproliferative. *Beauveria*, *Isaria* and *Metarrhizium* fungi are entomopathogenic as a result of producing insecticide destruxins and other cyclodepsipeptides.[35,36]

Metabolites of disctinct biosynthetic pathways, including (*E*)-1-(2,3-dihydro-1*H*-pyrrol-1-yl)-2-methyldec-8-ene-1,3-dione (**23**), 1-(2,3-dihydro-1*H*-pyrrol-1-yl)-2-methyldecene-1,3-dione (**24**), citrinalin A (**25**), B (**26**) and citrinin (**27**), have been obtained from the culture media of *Penicillium citrinum*, also isolated from *Caulerpa* sp. (Figure 4).[37] Biosynthetic investigations with the labelled precursors [Me-¹³C]-*L*-methionine, [1-¹³C]acetate, [1,2-¹³C]acetate, [U-¹³C₅]-*L*-proline and [U-¹³C₅]-*L*-ornithine established that pyrrol-polyketides **23** and **24** are biosynthesized via the formation of a polyketide chain condensed with an ornithine residue and a methionine-derived methyl group.[38] Similar experiments performed with [Me-¹³C]-*L*-methionine, [1-¹³C]-*D*-glucose, [U-¹³C anthranilic acid, [U-¹³C₅]-*L*-proline and
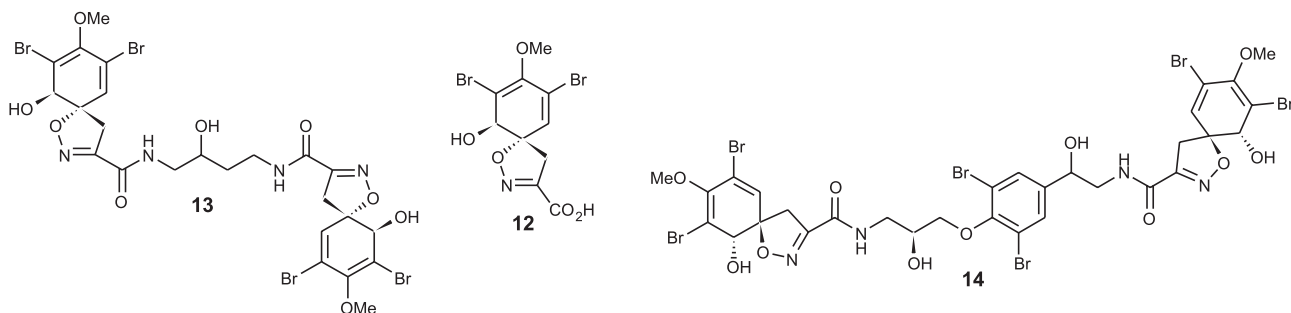

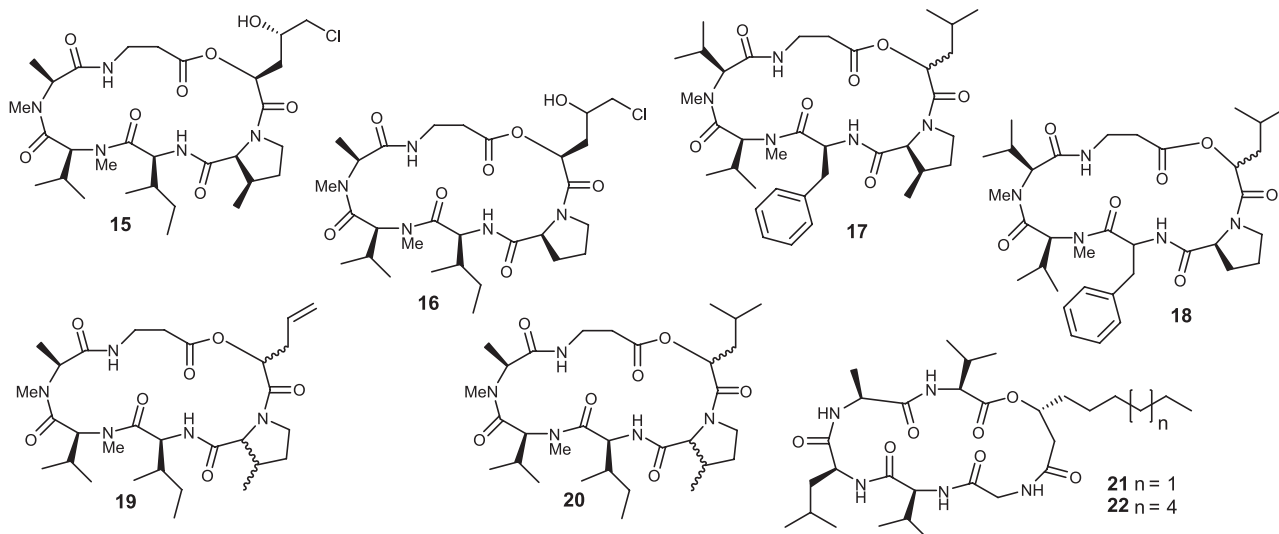**Figure 2.** Structures of verongidoic acid (**12**), 11-hydroxyaerothionin (**13**) and fistularin-3 (**14**).

Figure 3. Structures of [β-Me-Pro] destruxin E chlrohydrin (**15**), destruxin E chlorohydrin (**16**), pseudodestruxin C (**17**), [Phe³, *N*-Me-Val⁵] destruxin B (**18**), roseotoxin B (**19**), roseocardin (**20**), isariin (**21**) and isariin B (**22**).

[U-^{13}C$_5$]-*L*-ornithine indicated that citrinalins A (**25**) and B (**26**) are derived from a mixed biosynthetic pathway from isoprene units, ornithine and tryptophan, via anthranilic acid.[39] The isolation of citrinalin C (**28**) provided support for a biosynthetic pathway suggested for citrinalins (Scheme 1).

Meleagrine (**29**) and oxaline (**30**) were isolated from cultures of a strain of *P. oxalicum* obtained from marine sediments (Figure 4).[37] The biosynthesis of both **29** and **30** involves the intermediation of roquefortine L (**31**) (Scheme 2), itself a product of transformation of

roquefortine C (**32**) by oxaD, an efficient nitronase of *P. oxalicum* expressed heterologously by *E. coli*.[40]

A series of polyketide-derived and terpene-derived fungal metabolites have been isolated from cultures of different fungal strains (Figure 5). Cultures of *Penicillium* sp. isolated from the ascidian *Didemnum granulatum* presented 13-desoxy-phomenome (**33**), identified by analysis of spectroscopic data. Sponge-derived *P. raistrickii* produced norliquexanthone (**34**), while an algae-derived *Penicillium stecki* strain produced (*S*)-8-methoxy-3,5-dimethylisochroman-6-ol (**35**). Roridin A (**36**) has been
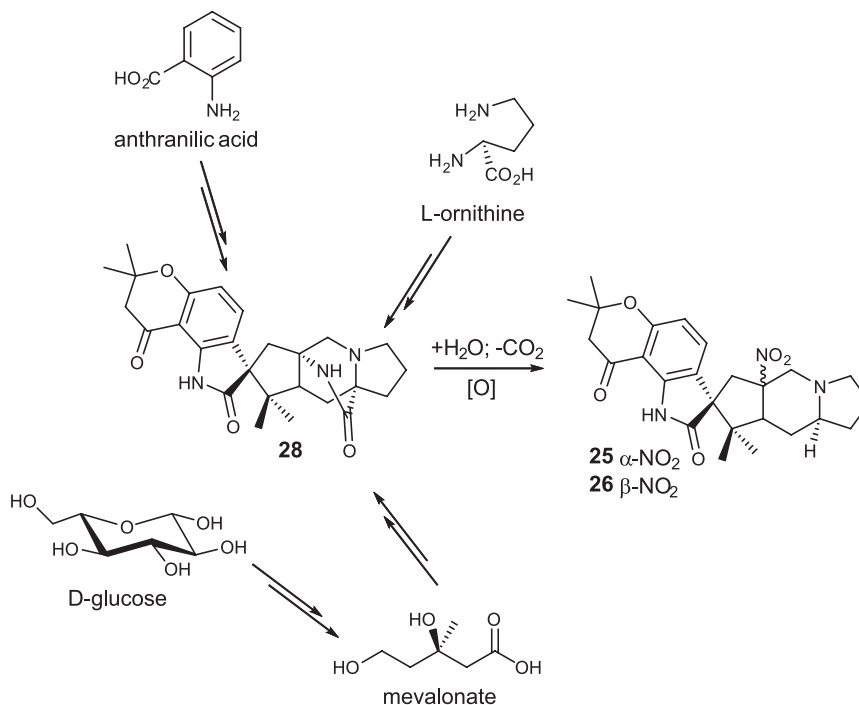
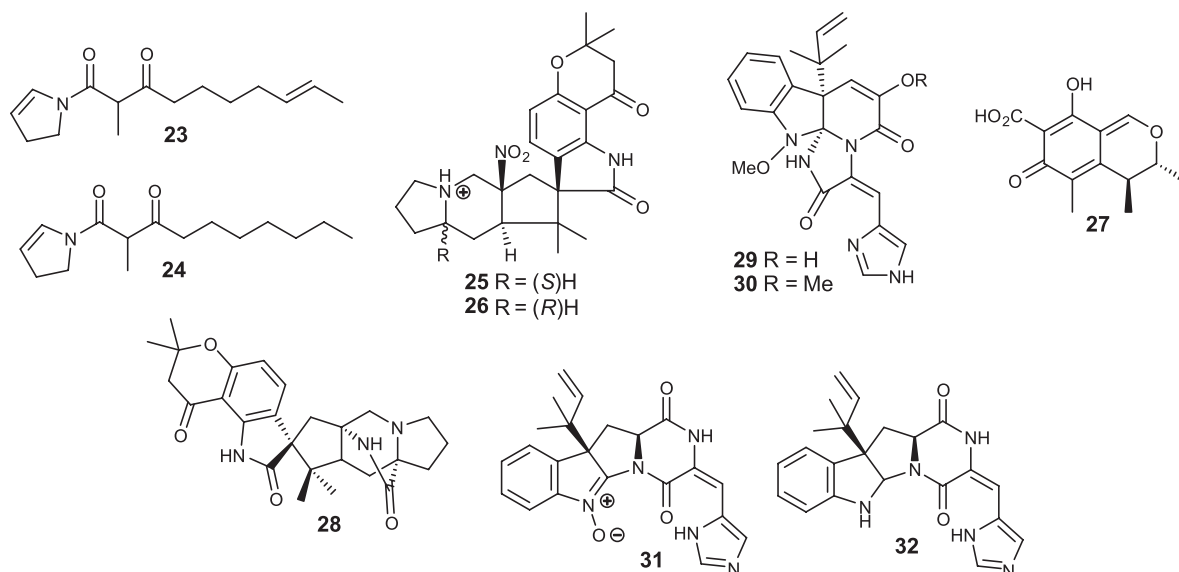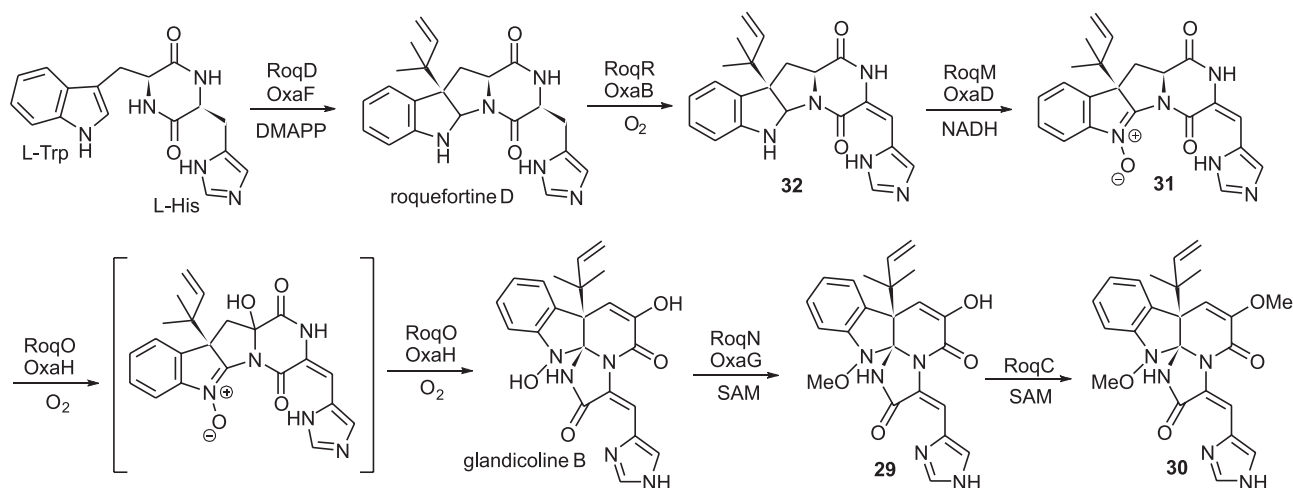
Scheme 1. Biosynthesis of citrinalins.[39]

Figure 4. Structures of (*E*)-1-(2,3-dihydro-1*H*-pyrrol-1-yl)-2-methyldec-8-ene-1,3-dione (**23**), 1-(2,3-dihydro-1*H*-pyrrol-1-yl)-2-methyldecene-1,3-dione (**24**), citrinalin A (**25**), B (**26**), citrinin (**27**), citrinalin C (**28**), meleagrine (**29**), oxaline (**30**), roquefortine L (**31**) and roquefortine C (**32**).

Scheme 2. Biosynthesis of maleagrin (**29**) and oxaline (**30**) via roquefortine L (**31**).[40]

isolated from cultures of *Trichoderma* sp., while cultures of the fungus *P. paxilli* provided pyrenocine A (**37**), B (**38**) and the new pyrenocine J (**39**), identified by analysis of spectroscopic data.[41] Compound **37** displayed antiviral activity against Herpes Simplex virus type-1 (HSV-1) and avian metapneumovirus (AMPV) with EC_{50} at 4.2 and 63.27 µg mL^{-1}, respectively. Pyrenocine A (**37**) also showed cytotoxic activity (3-5 µg mL^{-1}).[42,43]

The marine-derived fungus *Phomopsis longicolla* obtained from the seaweed *Bostrychia radicans* produced the known 18-deoxycytochalasin H (**40**, Figure 6), mycophenolic acid (**41**, Figure 6) and dicerandrol C (**42**, Figure 6). Compound **42** displayed antimicrobial activity against *S. aureus* and *S. saprophyticus* with IC_{50} at 1.33 and 2.66 µM, respectively.[44]

Cultures of *Aspergillus* sp. isolated from the ascidian *Eudistoma vannamei* provided the known polyketides (*R*)-mellein (**43**, Figure 7), penicillic acid (**44**, Figure 7), *cis*-4-hydroxymellein (**45**, Figure 7) and *trans*-4-hydroxymellein (**46**, Figure 7). Compound **44** displayed moderate cytotoxic activity against MDA-MB-435 and HCT-8 with IC_{50} at 4.43 and 8.76 µg mL^{-1}, respectively.[45] A co-culture of marine-derived *Penicillium* sp. and *Trichoderma* sp. isolated from the marine sponges *Mycale angulosa* and *Geodia corticostylifera*, respectively, yielded two novel polyketides (Figure 7), (*Z*)-2-ethylhex-2-enedioic acid (**47**) and (*E*)-4-oxo-2-propylideneoct-7-enoic acid (**48**).[46]

A strain of *Aspergillus* sp. isolated from marine sediments produced the known metabolites pseurotins A (**49**, Figure 8), D (**50**, Figure 8), FD-838 (**51**, Figure 8), fumitremorgin C (**52**, Figure 8), 12,13-dihydroxy-
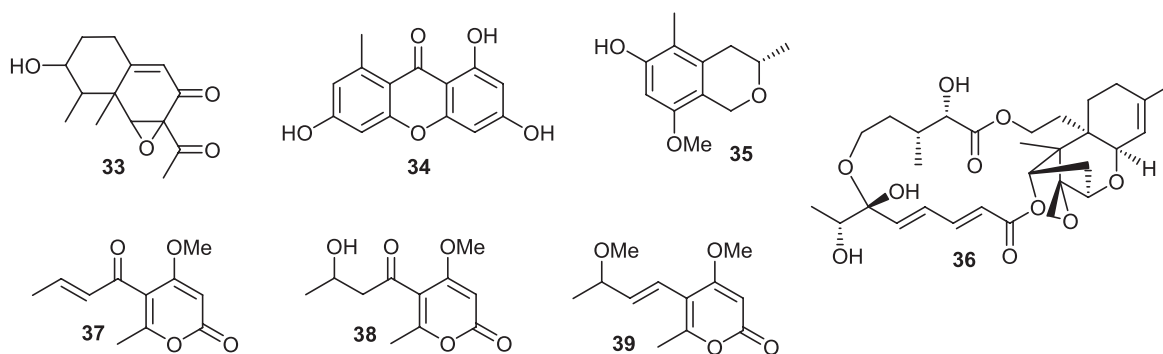
Figure 5. Structures of 13-desoxy-phomenome (**33**), norliquexanthone (**34**), (*S*)-8-methoxy-3,5-dimethylisochroman-6-ol (**35**), roridin A (**36**), pyrenocines A (**37**), B (**38**) and J (**39**).
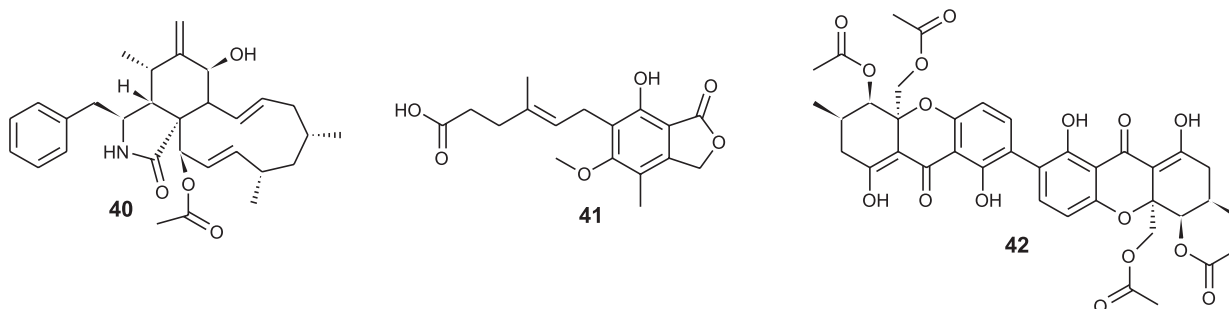

Figure 6. Structures of 18-deoxycytochalasin H (**40**), mycophenolic acid (**41**) and dicerandrol C (**42**).
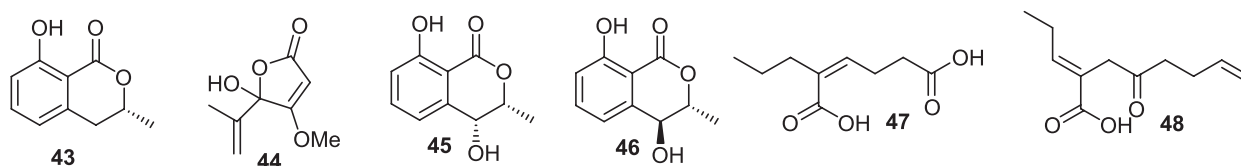
Figure 7. Structures of (*R*)-mellein (**43**), penicillic acid (**44**), *cis*-4-hydroxymellein (**45**), *trans*-4-hydroxymellein (**46**), (*Z*)-2-ethylhex-2-enedioic acid (**47**) and (*E*)-4-oxo-2-propylideneoct-7-enoic acid (**48**).

fumitremorgin C (**53**, Figure 8), methylsulochrin (**54**, Figure 8) and bis(dethio)bis(methylthio)gliotoxin (**55**, Figure 8). Compounds **52** and **53** displayed weak cytotoxic activity against HCT-116 cells with IC$_{50}$ at 15.17 and 4.53 µM, respectively.[47] The known cytochalasin D

(**56**, Figure 8) has been isolated from cultures of *Xylaria* sp. obtained from the seaweed *Bostrychia tenella*.[48]

The marine-derived fungus *Roussoella* sp. produced a novel polyketide named roussoelatide (**57**), which structure and absolute configuration were established by analysis
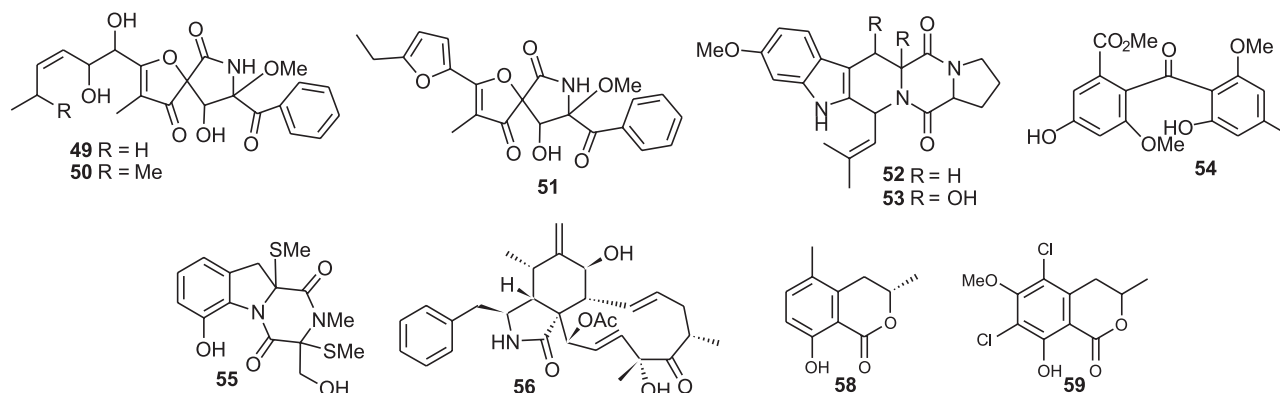

Figure 8. Structures of pseurotins A (**49**), B (**50**), FD-838 (**51**), fumitremorgin C (**52**), 12,13-dihydroxy-fumitremorgin C (**53**), methylsulochrin (**54**), bis(dethio) bis(methylthio)gliotoxin (**55**), cytochalasin D (**56**), 5-methylmellein (**58**) and 5,7-dichloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (**59**).

of spectroscopic data and X-ray diffraction analysis. Biosynthesis of **57** was investigated using ^{13}C-labeled sodium acetate, indicating a unique pathway including two Favorskii-like rearrangements and an intermolecular Diels-Alder reaction (Scheme 3).[49] The same marine-derived fungus produced the known compounds 5-methylmellein (**58**) and 5,7-dichloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (**59**)[43] (Figure 8).

A marine-derived *Penicillium* sp. strain isolated from the sponge *Dragmacidon reticulatum* (Figure 9) provided cultures with the known 15(*S*)-10,11-dehydrocurvularin (**60**) along with seven new compounds 15(*S*)-12-keto-10,11-dehydrocurvularin (**61**), 15(*S*)-*cis*-10,11-epoxycurvularin (**62**), 10(*R*),11(*R*),15(*S*),18(*S*)-cyclothiocuvularin A (**63**), 10(*S*),11(*S*),15(*S*),18(*R*)-cyclothiocuvularin B (**64**), the methyl ester (**65**), 15(*S*),18(*S*)-cyclosulfoxicurvularin (**66**) and its methyl ester (**67**). Structures were established by analysis of spectroscopic data and by X-ray diffraction analysis. Feeding experiments using ^{13}C-labelled *L*-cysteine indicated that compounds **63**-**65** are likely detoxification

products induced by overproduction of **60** in the presence of *L*-cysteine.[50]

Aspergillus sydowii isolated from the sponge *D. reticulatum* produced the known sydowic acid (**68**, Figure 10) in culture media. The new (−)-naphthoquinoneimine (**69**, Figure 10) along with seven known compounds (Figure 10), aurosperone A (**70**), aurosperone C (**71**), pyranonigrins B (**72**), C (**73**), pyrophen (**74**), leucomelone (**75**) and atromentin (**76**), have been isolated from culture media of *Aspergillus* sp. obtained from the ascidian *Didemnum ligulum*.

A marine-derived strain of the fungus *Penicillium glabrum* isolated from the same ascidian procuded in culture medium penicitrinone A (**77**, Figure 11), pinselin (**78**, Figure 11) and emodin (**79**, Figure 11), while a marine-derived *P. citrinum* produced **79**, quinolactacin B (**80**, Figure 11) and C (**81**, Figure 11), penicillenol A1 (**82**, Figure 11) and citreorosein (**83**, Figure 11). Three known metabolites, (+)-abscisic acid (**84**), 4-hydroxy-3-(3-methylbut-2-enyl)benzoic acid (**85**) and anofinic acid (**86**), and the new 2,3-dihydro-6,7-dihydroxy-2,2-dimethylchromen-4-one (**87**), were
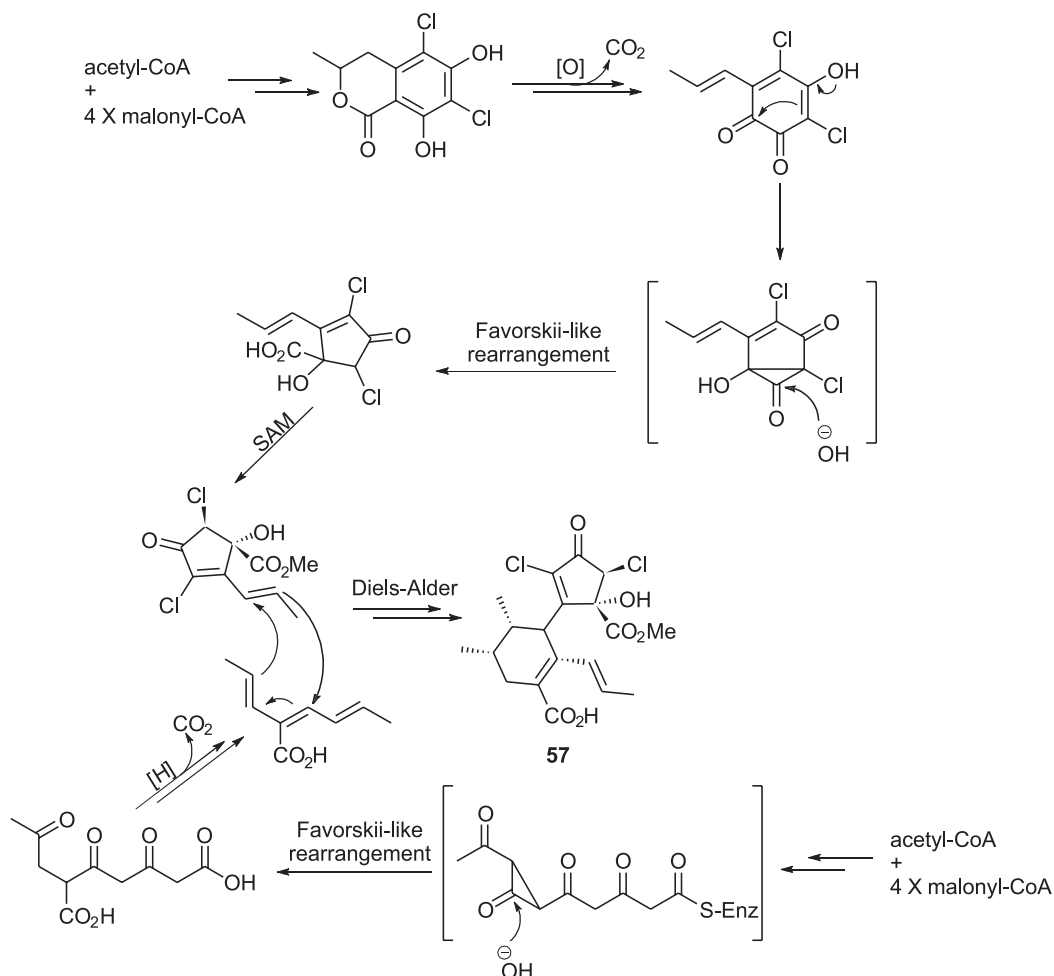
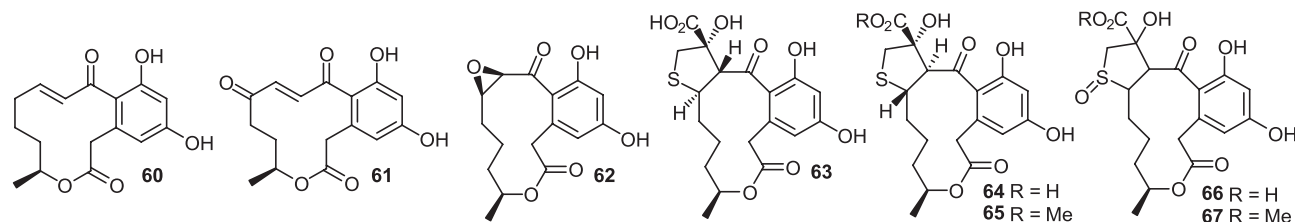**Scheme 3.** Biosynthesis of roussoellatide (**57**).[49]

Figure 9. Structures of 15(*S*)-10,11-dehydrocurvularin (**60**), 15(*S*)-12-keto-10,11-dehydrocurvularin (**61**), 15(*S*)-*cis*-10,11-epoxycurvularin (**62**), 10(*R*),11(*R*),15(*S*),18(*S*)-cyclothiocurvularin A (**63**), 10(*S*),11(*S*),15(*S*),18(*R*)-cyclothiocurvularin B (**64**), the methyl esther (**65**), 15(*S*),18(*S*)-cyclosulfoxicurvularin (**66**) and its methyl ester (**67**).
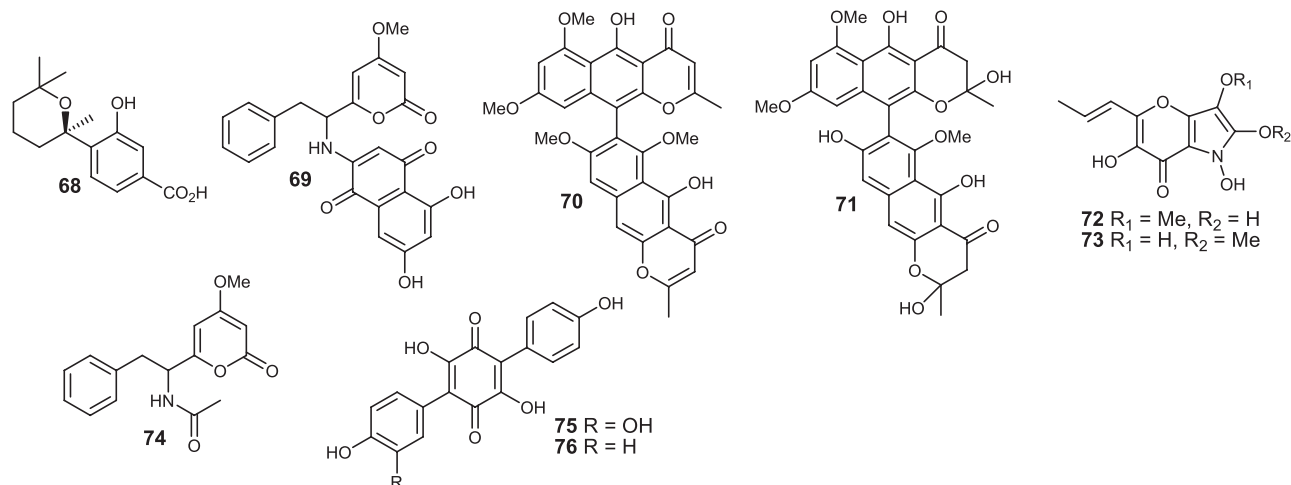

Figure 10. Structures of sydowic acid (**68**), (−)-naphthoquinoneimine (**69**) along with seven known compounds, aurosperone A (**70**), aurosperone C (**71**), pyranonigrins B (**72**), C (**73**), pyrophen (**74**), leucomelone (**75**) and atromentin (**76**).

isolated from cultures of *Cochliobolus* sp., isolated from the sponge *Mycale laxissima*. A strain of *Trichoderma* sp., also obtained from *M. laxissima*, produced in culture harzianopyridone (**88**, Figure 11). Compounds **69**, **79** and **83** displayed moderate antiviral activity. Harzianopyridone (**88**) was active against HSV-1 (EC$_{50}$ at 0.2 µg mL^{-1}) with low toxicity (34 µg mL^{-1}) and high selectivity. This compound also showed inhibition of virus HSV-1 KOS, an acyclovir resistant lineage. Compound **79** was active against hepatitis C virus at IC$_{50}$ 2.5 µg mL^{-1}.[43]

3. Marine Invertebrates

Marine invertebrates collected along the Brazilian coastline for chemical and pharmacological investigation have a large extension of redundancy with invertebrates collected in the past in the Caribbean region. Such redundancy led to the isolation of several known compounds, 70% of which are aminoacid-derived.

3.1. Marine sponges

The new bis-piperidine alkaloid ingenamine G (**89**, Figure 12) has been isolated from the marine sponge

Pachychalina alcaloidifera. Ingenamine G (**89**) displayed cytotoxic activity against HCT-8 (colon), B16 (leukemia) and MCF-7 (breast) at 8.6, 9.8 and 11.3 µg mL^{-1}, respectively.[51] Investigation on the cytotoxic mechanism-of-action of compound **89** indicated that it promotes DNA-damage, especially in S-phase of the cell-cycle.[52] Ingenamine G also displayed antibacterial action with IC$_{50}$ at 105.0, 75.0, 10-50 and 8.0 µg mL^{-1} against *Staphylococcus aureus*, *Escherichia coli*, *S. aureus* oxacillin-resistant and *Mycobacterium tuberculosis*, respectively.

The *n*-BuOH extract of *P. alcaloidifera* yielded a mixture of eleven 3-alkylpyridine compounds, cyclostellettamines A-I, K and L (**90-100**), among which alkaloids **96-100** are new representatives of this class. Cyclostellettamines **90-100** were identified by high performance liquid chromatography-mass spectrometry (HPLC-MS/MS) analyses.[51] The antimicrobial activity of **90-100** were also investigated, suggesting that the distance between the two pyridinium moieties of cyclostellettamines are important for the antibacterial activity against different pathogenic bacterial and fungal strains.[53] Futher studies on the secondary metabolites from *P. alcaloidifera* led to the isolation of mandangamine F (**101**, Figure 12), haliclonacyclamine (**102**, Figure 12), arenosclerin D (**103**, Figure 12) and E (**104**, Figure 12). All these
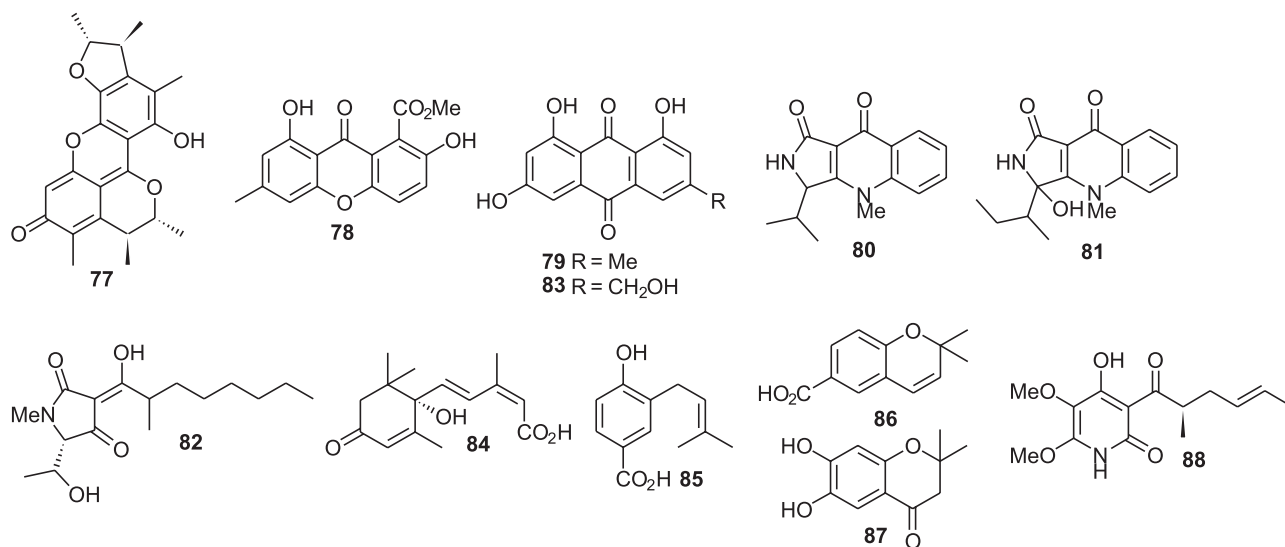
Figure 11. Structures of penicitrinone A (**77**), pinselin (**78**), emodin (**79**), quinolactacin B (**80**) and C (**81**), penicillenol A1 (**82**), citreorosein (**83**), (+)-abscisic acid (**84**), 4-hydroxy-3-(3-methylbut-2-enyl)benzoic acid (**85**), anofinic acid (**86**), new 2,3-dihydro-6,7-dihydroxy-2,2-dimethylchromen-4-one (**87**) and harzianopyridone (**88**).

alkaloids presented moderated cytotoxic activity against SF295, MDA-MD435, HCT8 and HL60 cell lineages.[54]

The polycyclic aromatic alkaloid 4-methylaaptamine (**105**, Figure 13) was isolated from the extract of *Aaptos aaptos* and displayed anti-viral activity by inhibiting the replication of HSV-1.[55] The sponge *Haliclona tubifera* provided the known halisphingosine A (**106**, Figure 13) and the new halisphingosine B (**107**, Figure 13), long-chain sphingoid bases derivatives, which possess an uncommon *L*-threo configuration for this class of natural products.[56] Cyclic alkylpyridine oligomers (Figure 13) haliotoxin (**108**) and amphitoxin (**109**) have been isolated from the

marine sponge *Amphimedon* sp. and displayed antifungal activity against *Aspergillus flavus*, a storage contaminant fungus affecting for commercial agricultural products. The mixture of **108** and **109** showed a MIC (minimum inhibitory concentration) in the range of 1.9-15.6 µg mL^{-1} and MFC (minimum fungicidal concentration) between 3.9-31.3 µg mL^{-1} against eleven strains of *A. flavus*.[57]

The sponge *Cliona delitrix* yielded the neurotransmitter serotonin (**110**, Figure 14).[58] Four known halogenated depsipeptides (Figure 14), geodiamolides A (**111**), B (**112**), H (**113**) and I (**114**) have been isolated from the MeOH extract of *Geodia corticostylifera*.[59] Geodiamolides are
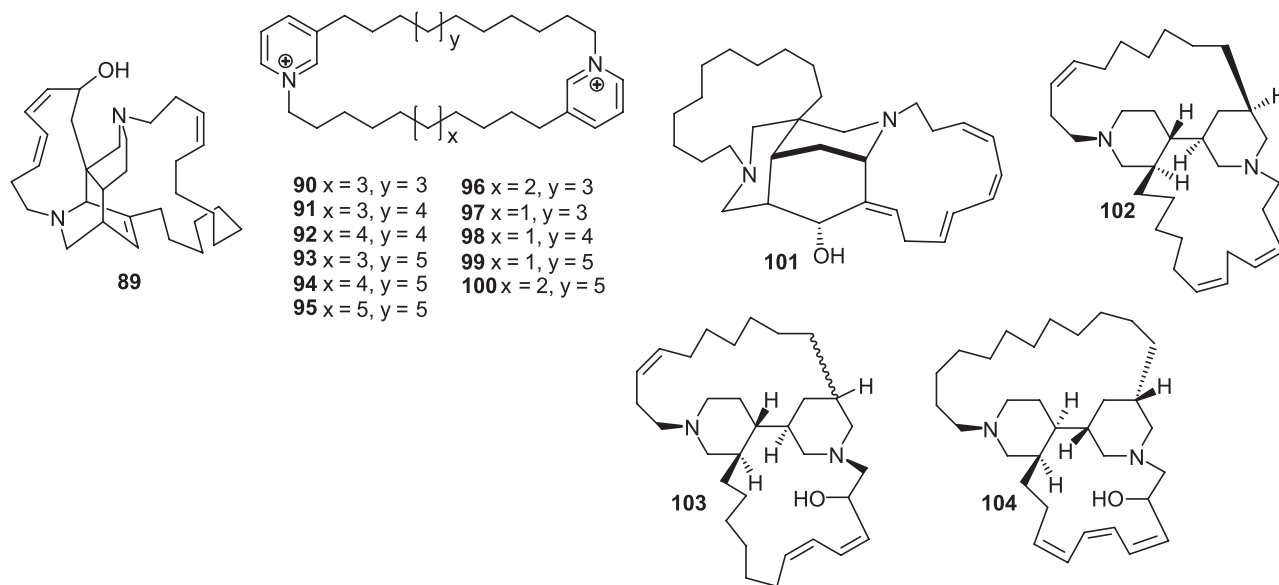

Figure 12. Structures of ingenamine G (**89**), cyclostellettamines A-I, K and L (**90-100**), mandangamine F (**101**), haliclonacyclamine (**102**), arenosclerins D (**103**) and E (**104**).
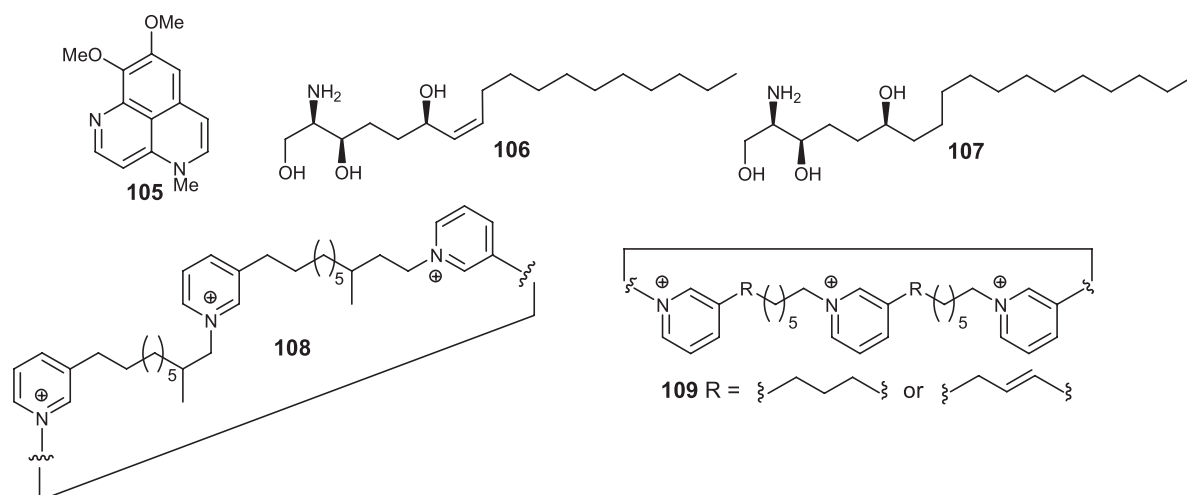
Figure 13. Structures of 4-methylaaptamine (**105**), halisphingosine A (**106**), halisphingosine B (**107**), haliotoxin (**108**) and amphitoxin (**109**).

known to disassemble actin microfilaments.[60] In the case of compounds **111**-**114**, they presented antiproliferative activity against breast cancer cells, with EC_{50} ranging among 9.82 and 115.3 nM, and did not affect healthy cells.[59]

Guanidine alkaloids isolated from marine sponges are unique for their chemical structures and biological activities.[61-68] The extract of the sponge *Monanchora* aff. *arbuscula* provided isoptilocaulin (**115**, Figure 15), which displayed antimicrobial activity against *S. aureus* oxacillin-resistant at 1.3 μg mL⁻¹.[69] Mirabilin B (**116**, Figure 15), 8β-hydroxyptilocaulin (**117**, Figure 15),

ptilocaulin (**118**, Figure 15) and the 8β and 8α-epimers mixture of 8-hydroxymirabilin (**119**-**120**, Figure 15) have been obtained from *M. arbuscula*. Alkaloids **117** and **118** presented weak cytotoxic activity against HL60 at 7.89 and 5.77 μM, HCT-8 at 19.0 and 17.69 μM and MDA-MB-435 at 11.34 and 7.58 μM, respectively. Ptilocaulin (**118**) induces apoptosis in HL60 cell lineage.[70]

Further investigations on the minor compounds of *M. arbuscula* extract led to the isolation of monalidine A (**121**, Figure 15), arbusculidine A (**122**, Figure 15), batzellamide A (**123**, Figure 16), hemibatzelladine J (**124**,
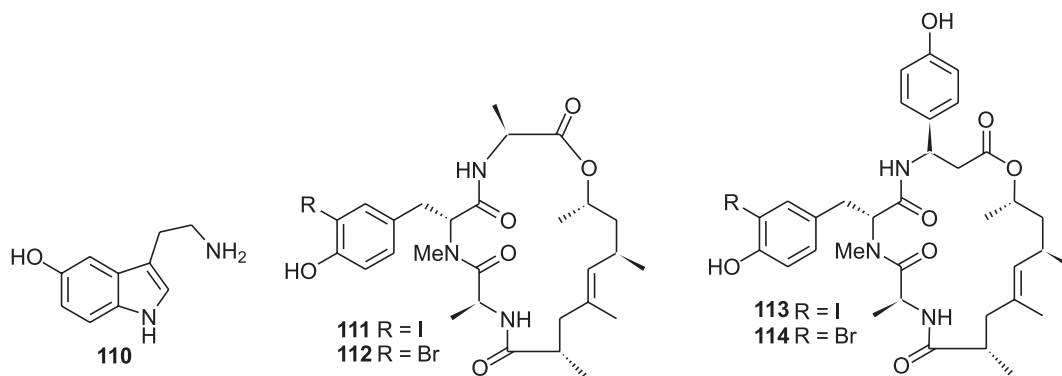

Figure 14. Structures of serotonin (**110**), geodiamolides A (**111**), B (**112**), H (**113**) and I (**114**).
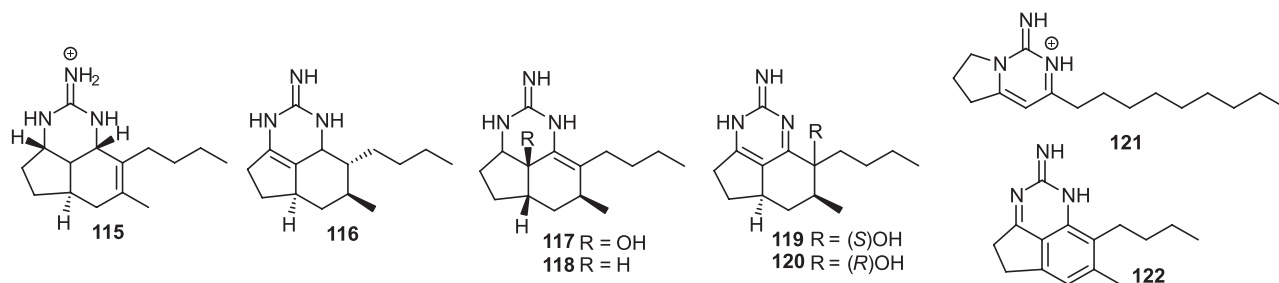

Figure 15. Structures of isoptilocaulin (**115**), mirabilin B (**116**), 8β-hydroxyptilocaulin (**117**), ptilocaulin (**118**), of the 8β and 8α-epimers mixture of 8-hydroxymirabilin (**119**-**120**), monalidine A (**121**) and arbusculidine A (**122**).
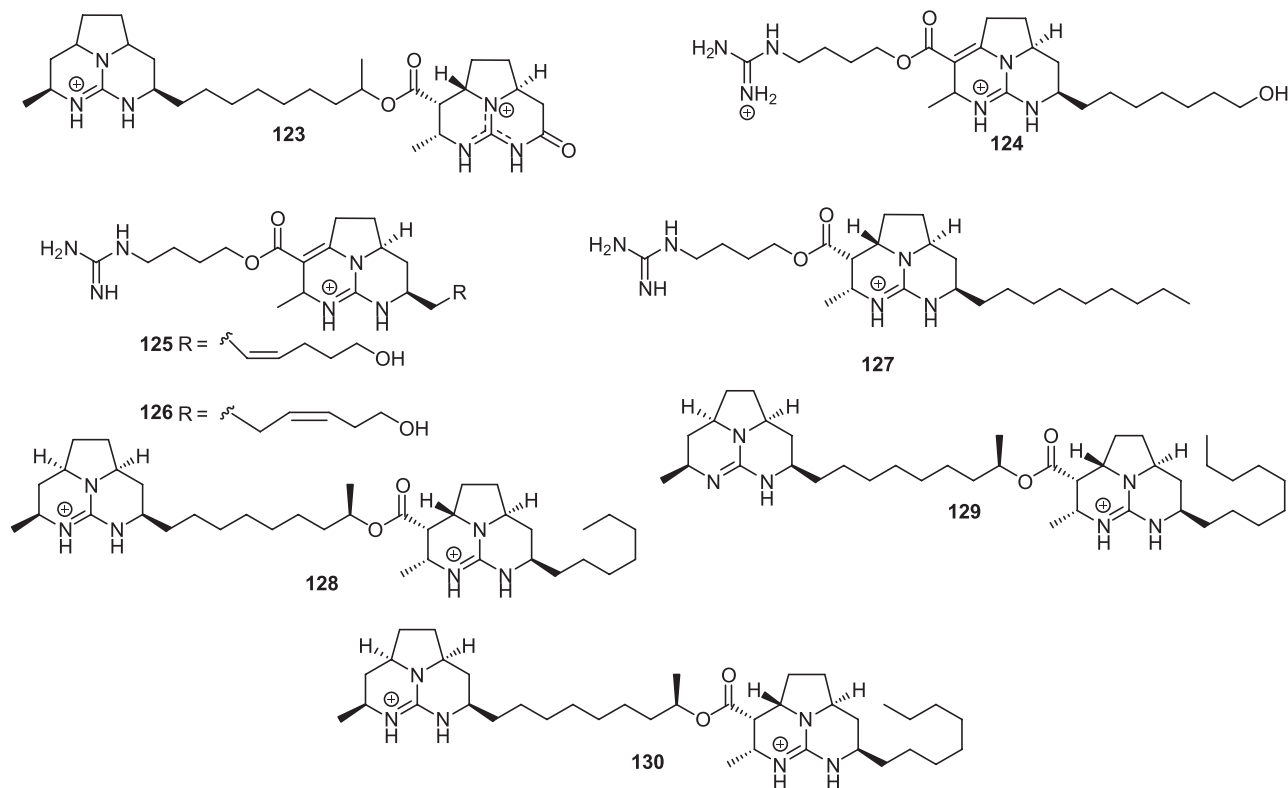
Figure 16. Structures of batzellamide A (**123**), hemibatzelladine J (**124**), Δ[19]-hemibatzelladine J (**125**), Δ[20]-hemibatzelladine J (**126**), batzelladines D (**127**), F (**128**), L (**129**) and nor-L (**130**).

Figure 16), Δ[19]-hemibatzelladine J (**125**, Figure 16) and Δ[20]-hemibatzelladine J (**126**, Figure 16), along with the known batzelladines D (**127**, Figure 16), F (**128**, Figure 16), L (**129**, Figure 16) and nor-L (**130**, Figure 16). Alkaloids **126**-**129** presented potent antiparasitic activity against *Trypanosoma cruzi* and *Leishmania* (*L.*) *infantum*,[71] while **129** also showed antifungal activity against *A. flavus* with MIC 1.9-7.8 μM mL^{-1} and MFC 3.9-15.6 μg mL^{-1}.[57]

Bromotyrosine-derived sponge metabolites are some of the very first natural products isolated from marine sponges. In the past, these metabolites were considered as chemotaxonomic markers for sponges belonging to the order Verongida.[72] However, the isolation of several of these metabolites from many sources other than sponges within the order Verongida[17,73] challenged previous assumptions on the actual origin of these metabolites.[17]

The MeOH extract of the sponge *Verongula gigantea* yielded the known (Figure 17) 2-(3,5-dibromo-4-methoxyphenyl)-*N,N,N*-dimethylethanammonium (**131**) and 2,6-dibromo-4-(2-(trimethylammonium)ethyl)phenol (**132**).[58] Further investigation on the metabolites of the marine sponge *Aplysina caissara* led to the isolation of the new agelocaissarines A1 (**133**, Figure 17), A2 (**134**, Figure 17), B1 (**135**, Figure 17), B2 (**136**, Figure 17) and caissarine C (**137**, Figure 17), together with the known 11-hydroxyaerothionin

(**13**, Figure 2) and fistularin-3 (**14**, Figure 2).[74] Compound **14**, 11-deoxyfistularin-3 (**138**) and the new 2-(3-amino-2,4-dibromo-6-hydroxyphenyl)acetic acid (**139**) have been isolated from *A. cauliformis* (Figure 17). Bromotyrosines **14**, **138** and **139** displayed antituberculosis activity against *Mycobacterium tuberculosis* at 7.1, 7.3 and 49 μM, respectively.[73] The new 3-(3,5-dibromo-4-methoxyphenyl-2-methoxy-*N*-methylpropan-1-ammonium (**140**, Figure 17) was isolated from the sponge *Pachychalina* sp., the only Haplosclerida sponge source of a bromotyrosine-derived compound.[73] The MeOH extract of *Aplysina* sp. provided **131**, (3',5'-dibromo-4'-ethoxy-1'-hydroxy-4'-methoxycycloexa-2',5'-dienyle)acetamide (**141**, Figure 17), aeroplysinin-2 (**142**, Figure 17), ethyl ester of 2,4-dibromo-1-hydroxy-3-methoxy-6-oxa-3-azaspiro [4.5]dec-2,4,8-trieno-8-carboxylate (**143**, Figure 17) and (*R**,*S**)-[3,5-dibromo-4-(2-oxo-5-oxazolidinyl) methoxyphenyl]-2-oxazolidinone (**144**, Figure 17).[69]

The chemical profile of *Aplysina fulva* collected in different locations along the Brazilian coastline was investigated (Figure 18). *A. fulva* collected at Angra dos Reis, Rio de Janeiro State, Brazil, yielded **14**, **144** and cavernicolins-1 (**145**) and -2 (**146**). *A. fulva* sampled in Salvador, Bahia State, provided the new bromotyrosine aplysinafulvin (**147**), along with **148**, 11-oxoaerothionin (**149**)
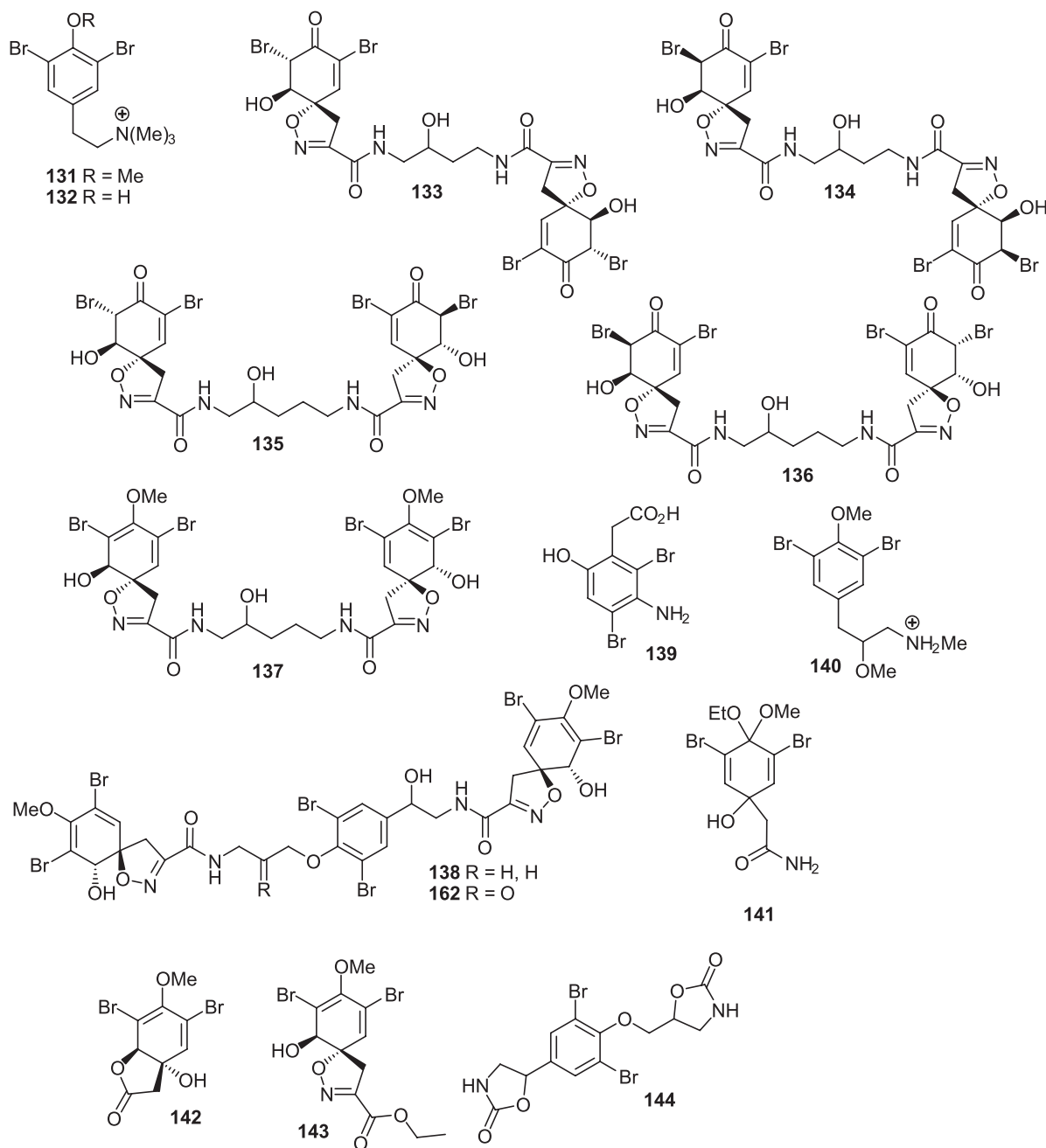
Figure 17. Structures of 2-(3,5-dibromo-4-methoxyphenyl)-*N,N,N*-dimethylethanammonium (**131**), 2,6-dibromo-4-(2-(trimethylammonium)ethyl)phenol (**132**), agelocaissarines A1 (**133**), A2 (**134**), B1 (**135**), B2 (**136**), caissarine C (**137**), 11-deoxyfistularin-3 (**138**), 2-(3-amino-2,4-dibromo-6-hydroxyphenyl)acetic acid (**139**), 3-(3,5-dibromo-4-methoxyphenyl-2-methoxy-*N*-methylpropan-1-ammonium (**140**), (3',5'-dibromo-4'-ethoxy-1'-hydroxy-4'-methoxycycloexa-2',5'-dienyle)acetamide (**141**), aeroplysinin-2 (**142**), ethyl of 2,4-dibromo-1-hydroxy-3-methoxy-6-oxa-3-azaspiro[4.5]dec-2,4,8-trieno-8-carboxylate (**143**) and (*R**,*S**)-[3,5-dibromo-4-(2-oxo-5-oxazolidinyl)methoxyphenyl]-2-oxazolidinone (**144**).

and 11-oxo-12-hydroxyaerothionin (**150**). Aerothionin (**151**) have been isolated from *A. fulva* collected at São Sebastião, São Paulo State, while **144**, **152**, **153** and subereatensin (**154**) have been isolated from an Arraial do Cabo sample of *A. fulva*, Rio de Janeiro State. Simultaneously, *A. fulva* from J Reef, Florida (USA) was investigated and yielded **13**, homoaerothionin (**155**), aerophobin-1 (**156**), aerophobin-2 (**157**), aplysinamisin-1 (**158**), aeroplysinin-1

(**159**) and 2-(3,5-dibromo-1-hydroxy-4-oxocyclohexa-2,5-dienyl)acetamide (**160**). All samples of *A. fulva* consistently presented bromotyrosine-derived metabolites.[72]

Investigation of the sponge *A. fistularis* yielded **14**, **131**, **142**, **149**-**151**, verongidoic acid (**12**, Figure 2), its methyl esther (**161**, Figure 18) and 11-ketofistularin-3 (**162**, Figure 18). Compound **162** inhibited the growth of *M. tuberculosis* at 16 mg mL^{-1}.[75] Bromotyrosine **149**

was further investigated as an anti-inflammatory agent in the presence of lipopolysaccharide, a component of cell-wall that triggers the inflammatory response. The assay showed that **149** supressed NO_2 and iNOS (inducible nitric oxide synthase) expression, as well as cytokine and prostaglandin E2, responsible for the proinflammatory and immunoregulatory properties.[76] Investigation of an *Aplysina* sp. provided **14**, while from *A. solangeae* compounds **13**, **150** and 11,12-hydroxiaerothionin (**163**, Figure 18) have been isolated.[77] A distinct investigation on *A. fistularis* yielded **131**, aplysfistularine (**164**, Figure 18), aplysterol (**165**, Figure 19) and 24,28-didehydroaplysterol (**166**, Figure 19). The salt **131** inhibited human DNA topoisomerase II-a at concentration of 100 μM.[78]

Investigation of the MeOH extract of *Petromica citrina* provided halistanol (**167**, Figure 19) and halistanol sulfate C (**168**, Figure 19).[79] Compounds **167** and **168** presented inhibitory effects on the replication of the Herpes Simplex Virus type 1 (HSV-1, KOSstrain), with IC_{50} at 5.63 μg mL^{-1} (selectivity index (SI) = 2.46) and 6.09 μg mL^{-1} (SI = 1.95), respectively, while the fraction that contained these compounds as the major constituents displayed antiviral activity with IC_{50} at 2.87 μg mL^{-1} (SI = 15.33), suggesting that the anti-HSV-1 activity of the fraction is possibly related

to the synergistic effects of compounds **167** and **168**.[79] The known pyrodysinoic acid (**169**) and three new nitrogen-containing terpenes, isopyrodysinoic acid (**170**), 13-hydroxyisopyrodysinoic acid (**171**) and pyrodisinoic acid B (**172**) have been isolated from *Dysidea robusta*.[80]

Three novel dissulfated meroterpenoids (Figure 20), ilhabelanol (**173**), ilhabrene (**174**) and isoakaterpin (**175**) have been obtained from the MeOH extract of *Callyspongia* sp., and presented a novel carbon skeleton. Isoakaterpin (**175**) inhibits *Leishmania* spp. adenine phosphoribosyl transferase with IC_{50} at 1.05 μM, which compromises the parasite metabolism.[81]

Halistanol sulfate A (**176**, Figure 20) was isolated from the MeOH extract of the sponge *Petromica ciocalyptoides*. Compound **176** has also been obtained from *Topsentia ophiraphidites*, first isolated from the marine sponge *Halichondria* cf. *moorei* in 1981.[69] Furodysinin (**177**, Figure 20) and 9α,11α-epoxicholest-7-en-3β,5α,6α,10-tetrol-6-acetate (**178**, Figure 20) have been isolated from *Dysidea* sp.[75] Investigation of *Ircinia felix* MeOH extract led to the isolation of 4*H*-pyran-2-ol-acetate (**179**, Figure 20) as probably an isolation artifact formed by the cyclization of pentanodial by a nucleophilic attack from an acetate anion followed by dehydration and oxidation.[58]
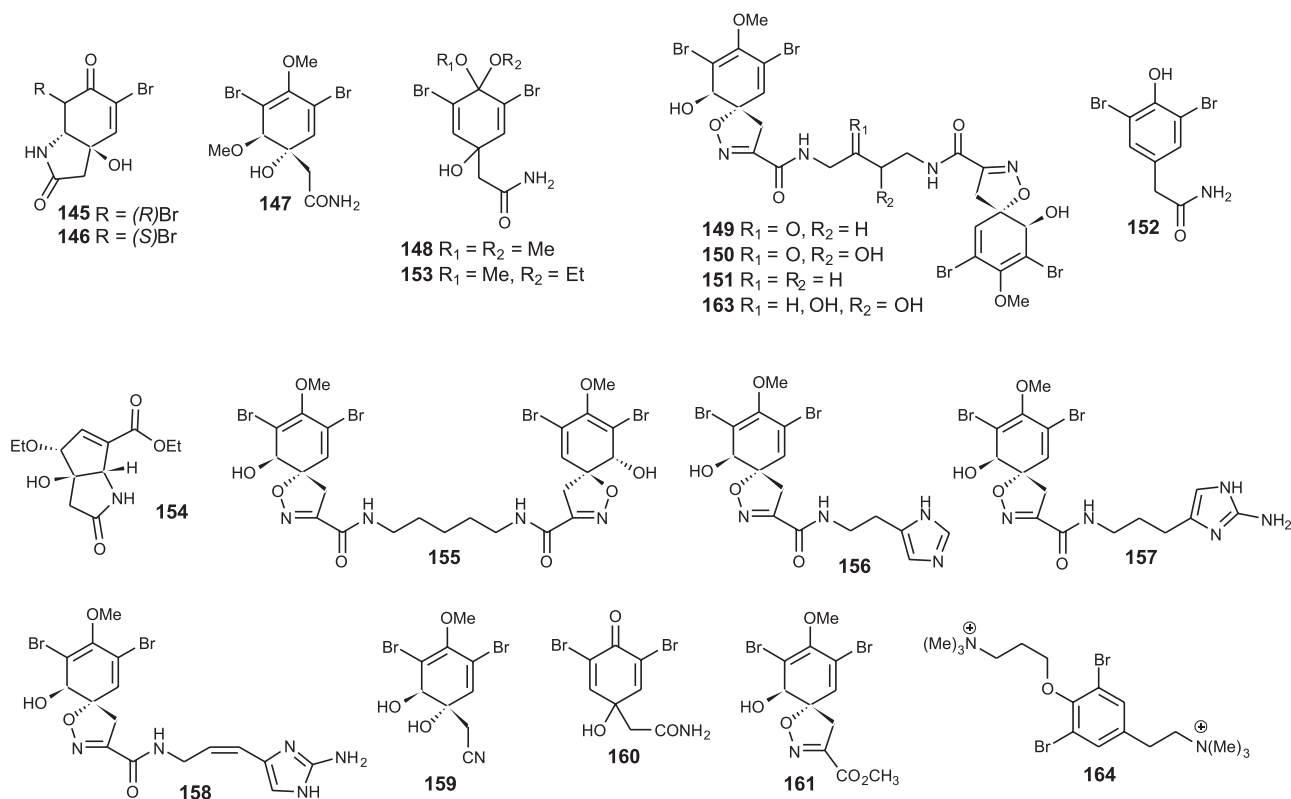

Figure 18. Structures of cavernicolins-1 (**145**) and -2 (**146**), aplysinafulvin (**147**), along with the dimethylketal **148**, 11-oxoaerothionin (**149**), 11-oxo-12-hydroxyaerothionin (**150**), aerothionin (**151**), the phenol **152**, the mixed ketal **153**, subereatensin (**154**), homoaerothionin (**155**), aerophobin-1 (**156**) aerophobin-2 (**157**), aplysinamisin-1 (**158**), aeroplysinin-1 (**159**), 2-(3,5-dibromo-1-hydroxy-4-oxocyclohexa-2,5-dienyl)acetamide (**160**), the methyl ester of verongidoic acid (**161**), 11-ketofistularin-3 (**162**), 11,12-hydroxiaerothionin (**163**) and aplysfistularine (**164**).
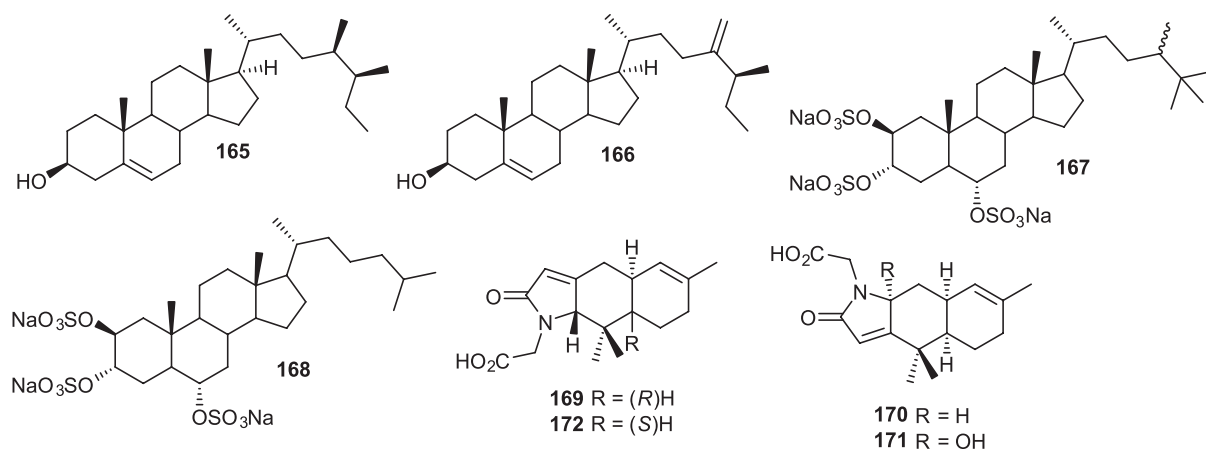
Figure 19. Structures of aplysterol (**165**), 24,28-didehydroaplysterol (**166**), halistanol (**167**), halistanol sulfate C (**168**), pyrodysinoic acid (**169**), isopyrodysinoic acid (**170**), 13-hydroxyisopyrodysinoic acid (**171**) and pyrodisinoic acid B (**172**).

A detailed investigation of extracts from the sponge *Plakortis angulospiculatus* led the isolation of the new plakortenone (**180**, Figure 21), together with the known plakortin (**181**, Figure 21), plakortide P (**182**, Figure 21), (2Z,6R,8R,9E)-methyl 3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate (**183**, Figure 21), spongosoritin (**184**, Figure 21) and (2E,6R,8S)-methyl 3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**185**, Figure 21). Compound **182** presented a potent antiparasitic activity against *Leishmania chagasi* and *Trypanosoma cruzi*.[82]

Futher investigations on *P. angulospiculatus* provided (Figure 22) the new 7,8-dihydroplakortide E (**186**), a diastereoisomer of plakortide H (**187**) and **188**, together with seven known polyketides, 6-desmethyl-6-ethyl-spongosoritin A (**189**), 6-desmethyl-6-ethyl-9,10-dihydrospongosoritin A (**190**), spongosoritin A (**191**),

9,10-dihydrospongosoritin A (**192**), **193**, **194** and plakortide P (**182**). Compounds **182**, **187**, **189**, **190** and **193** presented cytotoxic activity agains HCT-116, PC-3M and MRC-5 cell lineages with IC_{50} between 0.2-10 μM, while **189** and **190** induce a G_0/G_1 arrest, compounds **182**, **187** and **193** delivered G_2/M arrest and accumulation of mitotic figures without affecting the microtubules.[83]

The extracts obtained from the sponge *Darwinella* cf. *oxeata* yielded four new rearranged diterpenoids (Figure 23), oxeatine (**195**) and oxeatamides H-J (**196**-**198**), along with the known metabolites oxeatamide A (**199**), the methyl ester of oxeatamide A (**200**), and membranolide (**201**). Compound **195** has a new heterocyclic skeleton and **198** have an *N*-methyl urea group included in a γ-lactam moiety. Compounds **197** and **201** were detected by UPLC-qTOF (ultra-performance
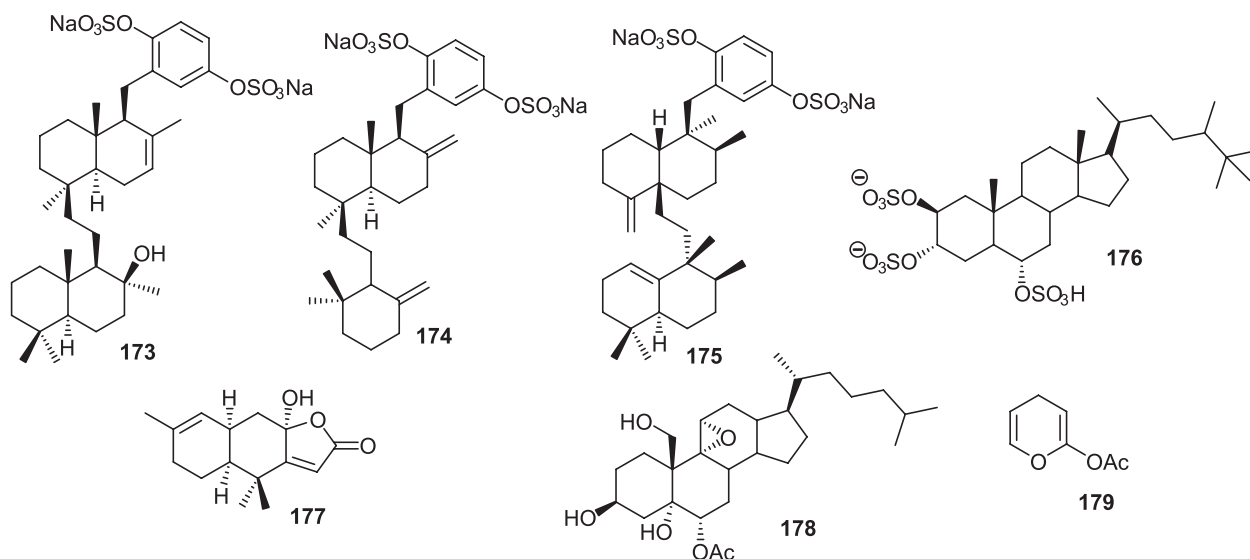

Figure 20. Structures of ilhabelanol (**173**), ilhabrene (**174**), isoakaterpin (**175**), halistanol sulfate A (**176**), furodysinin (**177**), 9α,11α-epoxicholest-7-en-3β,5α,6α,10-tetrol-6-acetate (**178**) and of 4*H*-pyran-2-ol-acetate (**179**).
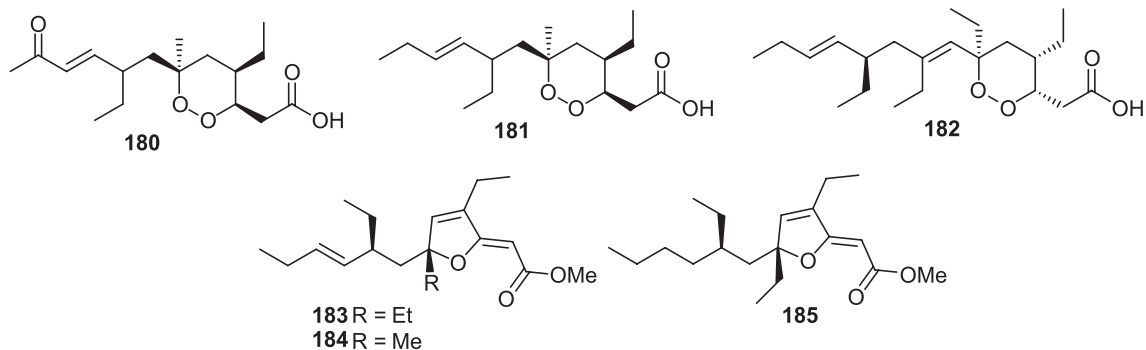
Figure 21. Structures of plakortenone (**180**), plakortin (**181**), plakortide P (**182**), (2Z,6R,8R,9E)-methyl 3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate (**183**), spongosoritin (**184**) and (2E,6R,8S)-methyl 3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**185**).
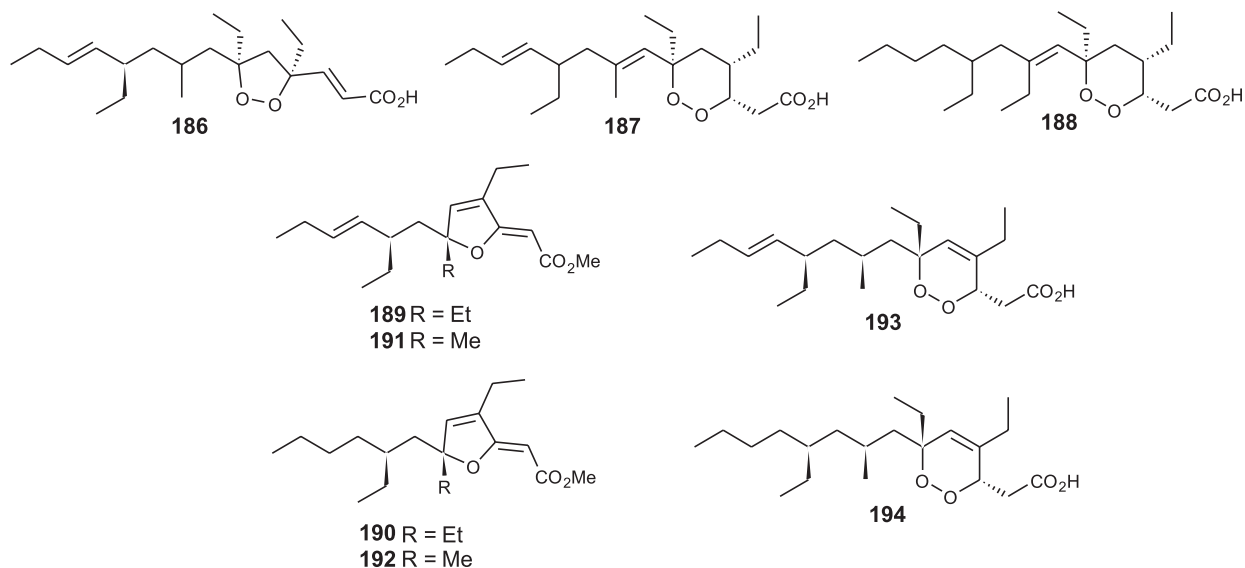

Figure 22. Structures of 7,8-dihydroplakortide E (**186**), a diastereoisomer of plakortide H (**187**), polyketide **188**, 6-desmethyl-6-ethyl-spongosoritin A (**189**), 6-desmethyl-6-ethyl-9,10-dihydrospongosoritin A (**190**), spongosoritin A (**191**), 9,10-dihydrospongosoritin A (**192**), and of polyketides **193** and **194**.

liquid chromatography-quadrupole/time of flight mass spectrometry) analysis in the mantle of the nudibranch *Felimida grahami*, a predator of *D. oxeata*.[84]

3.2. Corals

The steroid 18-acetoxypregna-1,4,20-trien-3-one (**202**, Figure 24) has been isolated from the octocoral *Carijoa riisei* and displayed weak cytotoxic activity against the cell lines SF295 (brain), MDA-MD435 (breast), HCT-8 (colon) and HL60 (leukemia) with IC_{50} at 14.4, 23.1, 22.0 and 12.4 µg mL^{-1}, respectively.[69] The new hemiketal steroid 23-keto-cladiellin A (**203**, Figure 24) was isolated from the soft coral *Chromonephthea braziliensis*. Compound **203** presented antifeeding activity against several species of fishes, properties that justifies the success of the invasion by this exotic octocoral in the Brazilian coast.[85] A new series of sterols (Figure 24) named punicinols A (**204**), B (**205**), C (**206**), D (**207**) and E (**208**), has been isolated from

the gorgonian *Leptogorgia punicea*. Compounds **204-208** presented cytotoxic activity against A549 lung cancer cell lineage at 9.6, 9.7, 35.9, 73.3 and 35.8 µM, respectively. The potent cytotoxic activity of **204** and **205** has been assigned to the absence of the double bond at the side chain.[86]

Chemical investigation of the gorgonian *Pseudopterogorgia rigida* yielded perezone (**209**, Figure 25), triacetyl perezone (**210**, Figure 25) and the epimeric mixture of 2-((2R)-5-hydroxy-6-methylhept-6-en-2-yl)-5-methylbenzenene-1,4-diol (**211** and **212**, Figure 25). This group of quinoidal structures presented cytotoxic activity against various cancer cell lineages. Compound **209** was the most active with IC_{50} at 8.7 µM (HL60, leukemia), 17.9 µM (HCT-8, colon), 15.4 µM (SF295, brain), 22.0 µM (MDA-MD435, breast), 13.2 µM (MDA-MD231, breast), 25.2 µM (MX1, breast), 24.2 µM (B16, murine melanoma), 11.5 µM (J774 murine macrophage) and 16.3 µM (L929, murine fibroblast).[87] Amphidinolide P (**213**, Figure 25) and its 3-*O*-methyl derivative (**214**, Figure 25) have been isolated
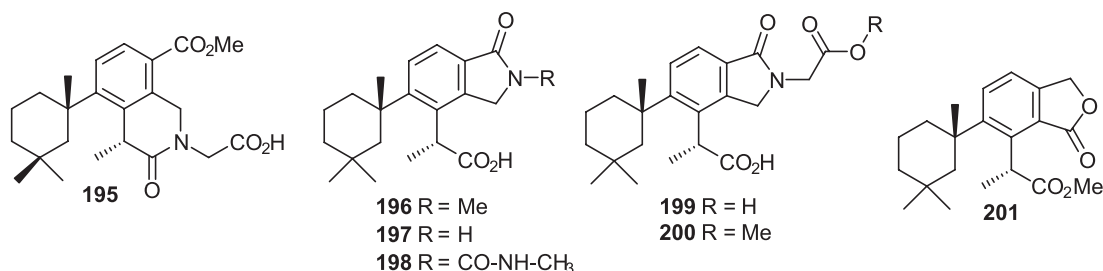
Figure 23. Structures of oxeatine (**195**) and oxeatamides H-J (**196-198**), oxeatamide A (**199**), the methyl ester of oxeatamide A (**200**), and membranolide (**201**).
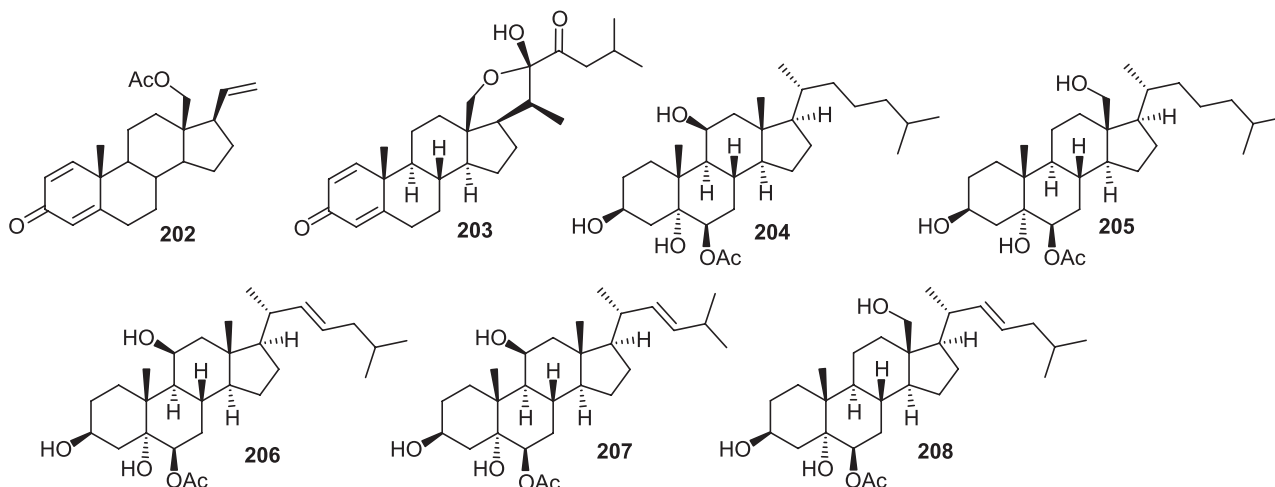

Figure 24. Structures of 18-acetoxypregna-1,4,20-trien-3-one (**202**), 23-keto-cladiellin A (**203**), punicinols A (**204**), B (**205**), C (**206**), D (**207**) and E (**208**).
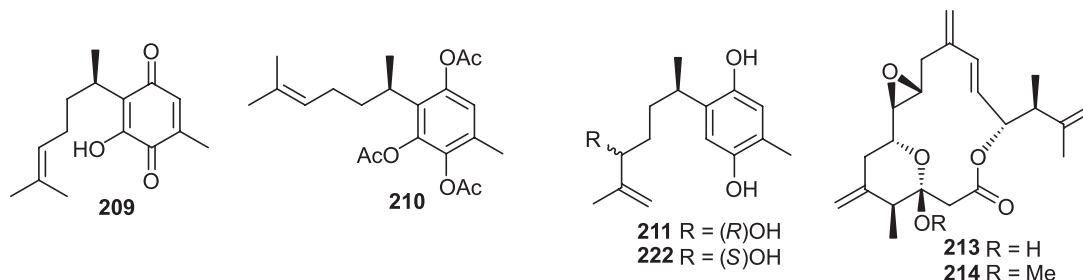

Figure 25. Structures of perezone (**209**), triacetyl perezone (**210**) of the epimeric mixture of 2-((2*R*)-5-hydroxy-6-methylhept-6-en-2-yl)-5-methylbenzenene-1,4-diol (**211** and **212**), amphidinolide P (**213**) and its 3-*O*-methyl derivative (**214**).

from the octocoral *Stragulum bicolor*. Compound **214** is probably an artifact of isolation.[88]

3.3. Bryozoans

Investigation of the MeOH extract of the bryozoan *Bugula dentata* led to the isolation of tambjamines A (**215**, Figure 26), B (**216**, Figure 26), C (**217**, Figure 26), D (**218**, Figure 26), K (**219**, Figure 26), 5'-bromo-4-methoxy-2,2'-pyrrol-5-carboxyaldehyde (**220**, Figure 26) along with the new tambjamine J1 (**221**, Figure 26).[89] The alkaloid 2,5,6-tribromo-*N*-methylgramine (**222**, Figure 26) has been obtained from the bryozoan *Zoobotryon verticillatum* (*Amathia verticillata*).[89] Re-investigation of extracts

obtained from different samples of *Amathia verticillata* provided the new alkaloid 2,6-dibromo-*N*-methylgramine (**223**, Figure 26), together with **222**.[90]

3.4. Mollusks

Very often shell-less marine mollusks accumulate metabolites captured from preys, which can be invertebrates such as sponges, ascidians, bryozoans, soft-corals and other mollusks. Such metabolites are considered as chemical defenses of the soft-bodied, frequently beautifully colored nudibranchs.

The bis-pyrrole alkaloids (Figure 26) tambjamines A (**215**) and D (**217**) have been isolated from the nudibranch *Tambja*
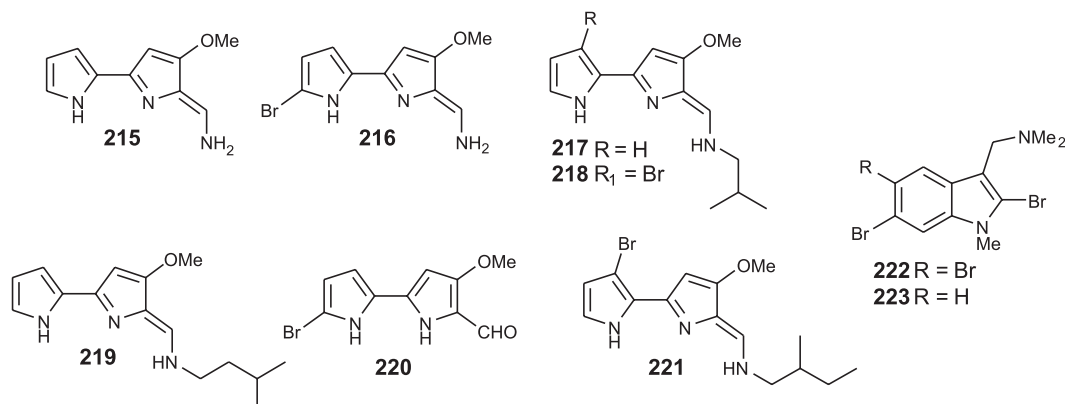
Figure 26. Structures of tambjamines A (**215**), B (**216**), C (**217**), D (**218**), K (**219**), 5'-bromo-4-methoxy-2,2'-pyrrol-5-carboxyaldehyde (**220**), tambjamine J1 (**221**), 2,5,6-tribromo-*N*-methylgramine (**222**) and of 2,6-dibromo-*N*-methylgramine (**223**).

eliora. Compound **217** displayed cytotoxic activity cells lines CEM (leukemia), HL60 (leukemia), MCF-7 (breast), HCT-8 (colon) and B16 (leukemia) with IC$_{50}$ at 12.2, 13.2, 13.2, 10.8 and 6.7 μg mL^{-1}, respectively.[58] The nudibranch *T. stegosauriformis* is the predator of the bryozoan *B. dentata*, and accumulates tambjamine alkaloids (Figure 26) found in tissues of the bryozoan, such as tambjamines C (**216**) and K (**219**). The alkaloid **223** isolated from the bryozoan *Zoobotryon verticillatum* (*Amathia verticillata*) has also been isolated from the nudibranch *Okenia zoobotryon*. Extracts of the nudibranch *Hypselodoris lajensis* provided the diterpene furodysinin (**177**, Figure 20), previously isolated only from marine sponges.[89]

Extracts of the sea slug *Pleurobranchus areolatus* yielded the modified diketopiperazines **224** and **225** (Figure 27), as well as, four new modified rodriguesines (Figure 27), rodriguesic acid (**226**), its hydroxamate (**227**), and the corresponding methyl esters **228** and **229**.[91] Amphidinolide P (**213**, Figure 25) has been isolated from the nudibranch *Marionia limceana* which preys on the coral *S. bicolor*.[88]

3.5. Ascidians

Colonial ascidians are members of Tunicata phylum which are the most often investigated towards the discovery of bioactive secondary metabolites. A large number of ascidians natural products are alkaloids and NRPS-derived peptides, some of which are produced by the associated microflora such as *Prochloron*.[92,93]

From the ascidian *Clavelina oblonga* the new aminoalcohol (2*S*,3*R*)-2-aminododecan-3-ol (**230**, Figure 28) has been isolated together with the known bis-oxazolidinone **144**, previously reported only from Verongid sponges. The absolute stereochemistry of **230** was determined after derivatization and circular dichroism analysis. Compound **230** displayed antifungal activity against *Candida albicans* and *C. glabrata* with MIC at 0.7 and 30.0 μg mL^{-1}, respectively.[94] The new polyunsaturated alcohol 3*Z*,6*Z*,9*Z*-dodecatrien-1-ol (**231**, Figure 28) have been obtained from *Botrylloides giganteum*.[58]

Investigation of the extract from *Didemnum ligulum* yielded asterubin (**232**, Figure 28) and *N*,*N*-dimethyl-*O*-methylethanolamine (**233**, Figure 28).[69] Extracts of the ascidian *Didemnum* sp. provided the highly modified diketopiperazines (Figure 28) rodriguesine A (**224**) and B (**225**). Rodriguesines *N*-acetyl derivatives **234** and **235**, respectively, have been obtained from another sample of the same ascidian collected at the same location.[95] Structure of compounds **224**, **225**, **234** and **235** has been established by analysis of spectroscopic data, while absolute configuration has been established by Marfey's method.

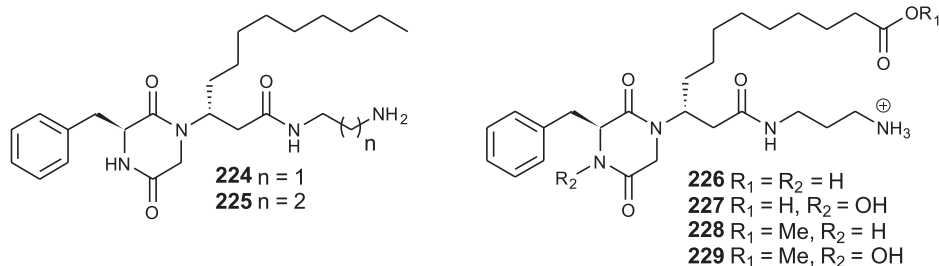Investigation of an aqueous MeOH extract of the ascidian *Eudistoma vannamei* yielded two new

Figure 27. Structures of rodriguesines A (**224**) and B (**225**), rodriguesic acid (**226**), its hydroxamate (**227**), and of the corresponding methyl esters **228** and **229**.
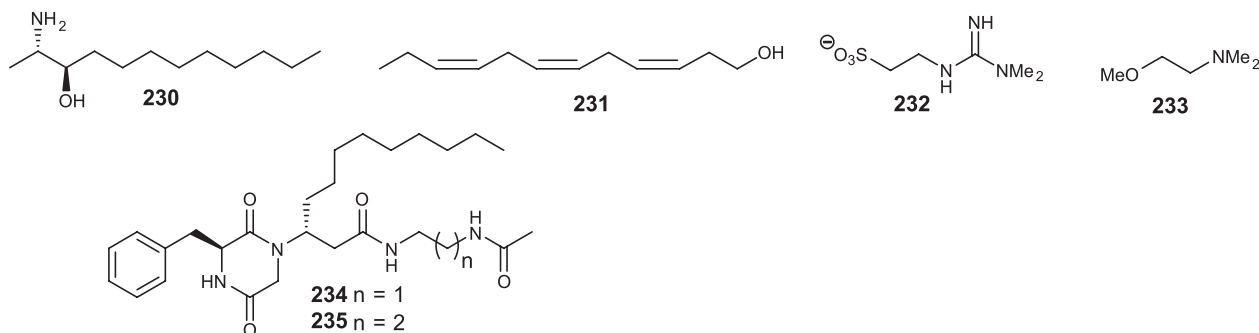
Figure 28. Structures of (2*S*,3*R*)-2-aminododecan-3-ol (**230**), 3*Z*,6*Z*,9*Z*-dodecatrien-1-ol (**231**), asterubin (**232**), *N*,*N*-dimethyl-*O*-methylethanolamine (**233**), and of rodriguesines *N*-acetyl derivatives **234** and **235**.

staurosporine derivatives, 2-hydroxy-7-oxostaurosporine (**236**, Figure 29) and 3-hydroxy-7-oxostaurosporine (**237**, Figure 29). The mixture of **236** and **237** displayed cytotoxic activity across a panel of tumor cell lines with IC_{50} values in the range of 10.3-144.47 nM and was 14 times more cytotoxic than staurosporine (**238**).[96] The occurrence of such alkaloids in *E. vannamei* may be correlated to the presence of associated biota, such as *Streptomyces* bacteria. In the light of to this hypothesis, marine microorganisms associated with *E. vannamei* were recovered and cultured. One strain of *Streptomyces* sp. was able to generate staurosporine (**238**), detected by LC-MS/MS analysis, while none of the hydroxy-7-oxo derivatives were detected.[97]
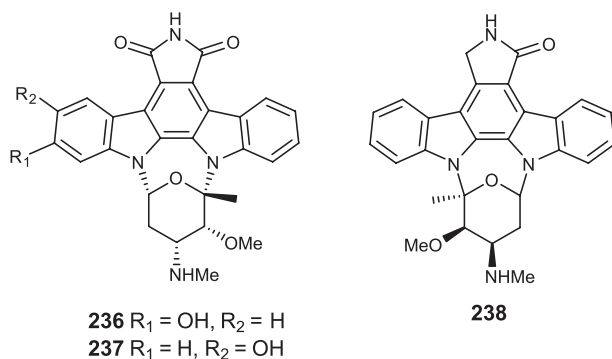

Figure 29. Structures of 2-hydroxy-7-oxostaurosporine (**236**), 3-hydroxy-7-oxostaurosporine (**247**) and of staurosporine (**238**).

4. Total Synthesis of Marine Natural Products in Brazil

In the first and sole review on the synthesis of marine metabolites by Brazilian organic synthesis chemists, Prof Alphonse Kelecom reviewed the synthesis of twenty-three metabolites, the large majority being terpenes.[98] Synthesis of alkaloids and polyketides have also been included. The present coverage attempts to comprehensively update Prof Kelecom's review, organized by biological source and biogenetic grounds. Only total syntheses of

natural products have been herein considered, including syntheses that enabled structural re-assignments of natural products. Partial syntheses, formal syntheses, syntheses of "unnatural" natural products and of natural product derivatives are explicitly omitted.

4.1. Total synthesis of marine microbe metabolites

The antibiotic pentabromopseudilin (**239**) is considered the first secondary metabolite isolated from cultures of a marine bacterium, namely *Pseudomonas bromoutilis*[99] and *Chromobacterium* sp.[100] Schwalm *et al*.[101] synthesis of **239** (Scheme 4) proceeded from the *ortho*-methoxy benzenediazonium salt **240** converted into the 2-arylpyrroline **241** in 78% yield after optimization. The product **241** was converted into the 2-substituted protected pyrrole **242** by oxidation with DDQ in almost quantitative yield. Deprotection of both pyrrole and phenol groups to give **243** was accomplished in excellent yields, followed by bromination with pyridine/HBr to give the natural product **239** in 28% overall yield.

Enhygrolide A (**244**) was isolated from cultures of the marine myxobacterium *Enhygromyxa salina*, and displayed antibiotic activity against *Arthrobacter crystallopoietes*.[102] The synthesis of **244** (Scheme 5)[103] was accomplished from the condensation of tetronic acid **245** with *para*-methoxybenzaldehyde (**246**) using Hantzch ester **247** as hydride source and *L*-proline as catalyst. Esterification of the product **248** with pivaloyl chloride under basic conditions provided **249** which underwent alkylation with isobutyl magnesium bromide to give **250**. Condensation with benzaldehyde followed by phenol deprotection gave enhygrolide A (**244**) in 54% overall yield.

The total synthesis of coibacins A (**251**) and B (**252**) have been completed and allowed the revision of the stereochemistry (Scheme 6).[104] Coibacins were first isolated from the cyanobacterium *Oscillatoria* sp. and displayed cytotoxic and anti-Leishmanial activity.[105] The highly convergent strategy involved the preparation of four
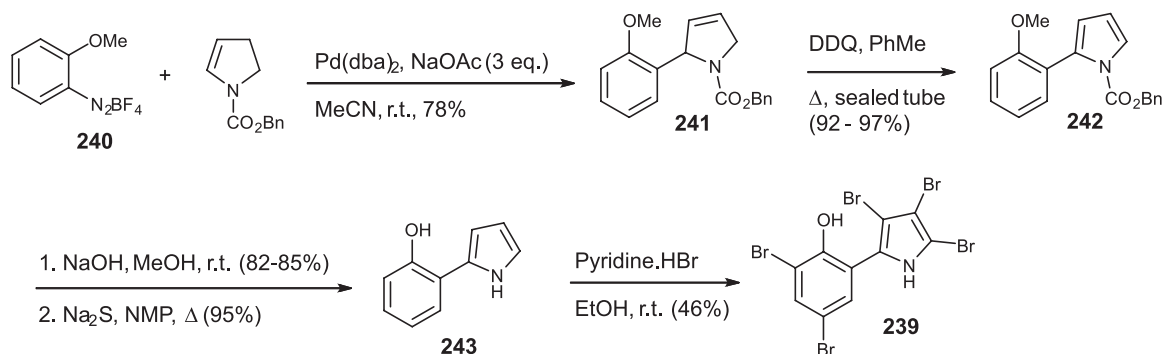
Scheme 4. Total synthesis of pentabromopseudilin (**139**).[101]
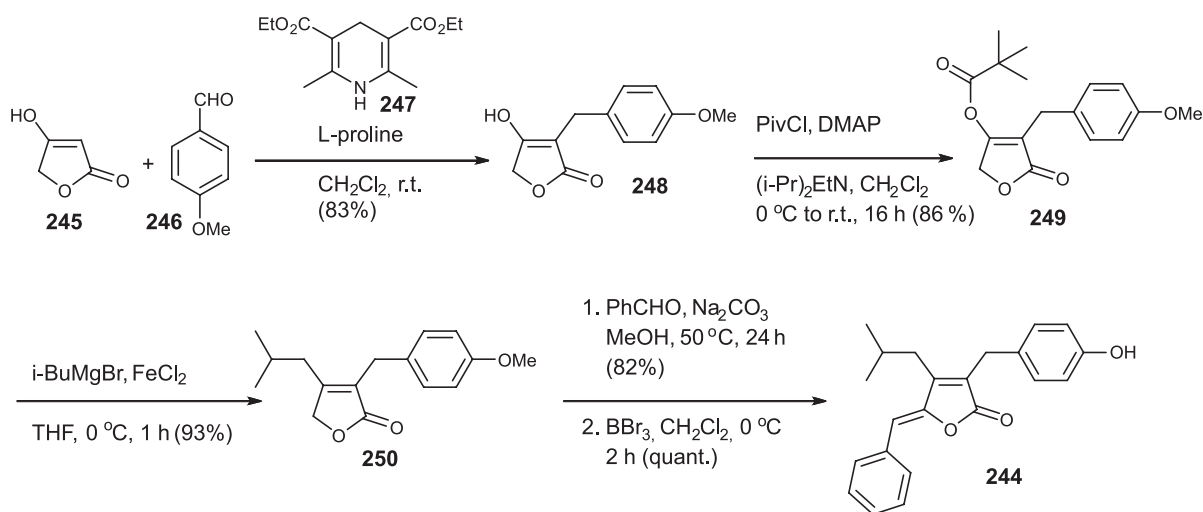
**Scheme 5.** Total synthesis of enhygrolide A (**244**).[102]

intermediates, **257**, **263**, **265** and **269**. The preparation of ketal **257** started by protection of the epoxyalcohol **253**, followed by esterification of alcohol **254** and metatesis reaction with Grubbs I catalyst, to afford the lactone **255** in 58% yield over four steps. Reduction with DIBALH and formation of the ketal group was followed by the alcohol deprotection and oxidation to give the chiral ketal **257** in 72% over four additional steps. The synthesis of phosphonium salt **263** was achieved from the diol **258** via two tandem oxidation/Wittig olefinations, followed by the diester **260** reduction and monoprotection. The phosphonium salt **263** was then prepared by usual interconversions. The overall yield for the preparation of **263** from **258** was 32%. Coupling of **257** with **263**, followed by the alcohol deprotection and oxidation to the corresponding aldehyde gave **265** in 60% over two steps. Next, preparation of the cyclopropane moiety involved a Charette asymmetric cyclopropanation of *trans*-crotyl alcohol (**266**) using a borolane-based ligand. The product **267** was reacted with 2-mercaptobenzothiazole in the presence of diisopropyl azodicarboxylate to give **268** in a Mitsunobu-type reaction. Oxidation of the mercaptane **268**

with ammonium molybdate and oxygen peroxide yielded the suitable sulfone **269** in 39% over three steps. Coupling aldehyde **265** with the sulfone **269** was achieved in the presence of sodium hexamethyldisilazide. The product **270** was subjected to oxidation with pyridinium chlorocromate to afford a mixture of geometric isomers resulting from the Wittig reactions, which could be efficiently separated by HPLC. Analysis of the products obtained indicated that (5*S*,16*R*,18*R*)-**251** was the enantiomer of natural coibacin A, which had, then, its stereochemistry redefined. The synthetic strategy developed for the synthesis of coibacin A enabled the preparation of all its stereoisomers. Coibacin B (**252**) was prepared by a very similar approach to that of coibacin A (**251**).

The total synthesis of lyngbyabellin M (**271**),[106] a metabolite isolated from the cyanobacterium *Moorea bouilloni*,[107] has been achieved using a highly convergent approach (Scheme 7). The first fragment **274** was prepared from (*S*)-1-ethoxy-1-oxobutan-2-aminium chloride (**272**) and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**273**) in a three-step reaction sequence. The second fragment **280** was synthezised from *L*-valine (**275**),

starting by the preparation of the thioamide **276** which was coupled with ethyl 3-bromo-2-oxopropanoate (**277**) in the

presence of 2-ethyloxirane (**278**). The product **279** was deacetylated with dibutyltin oxide to give the thiazole **280**.
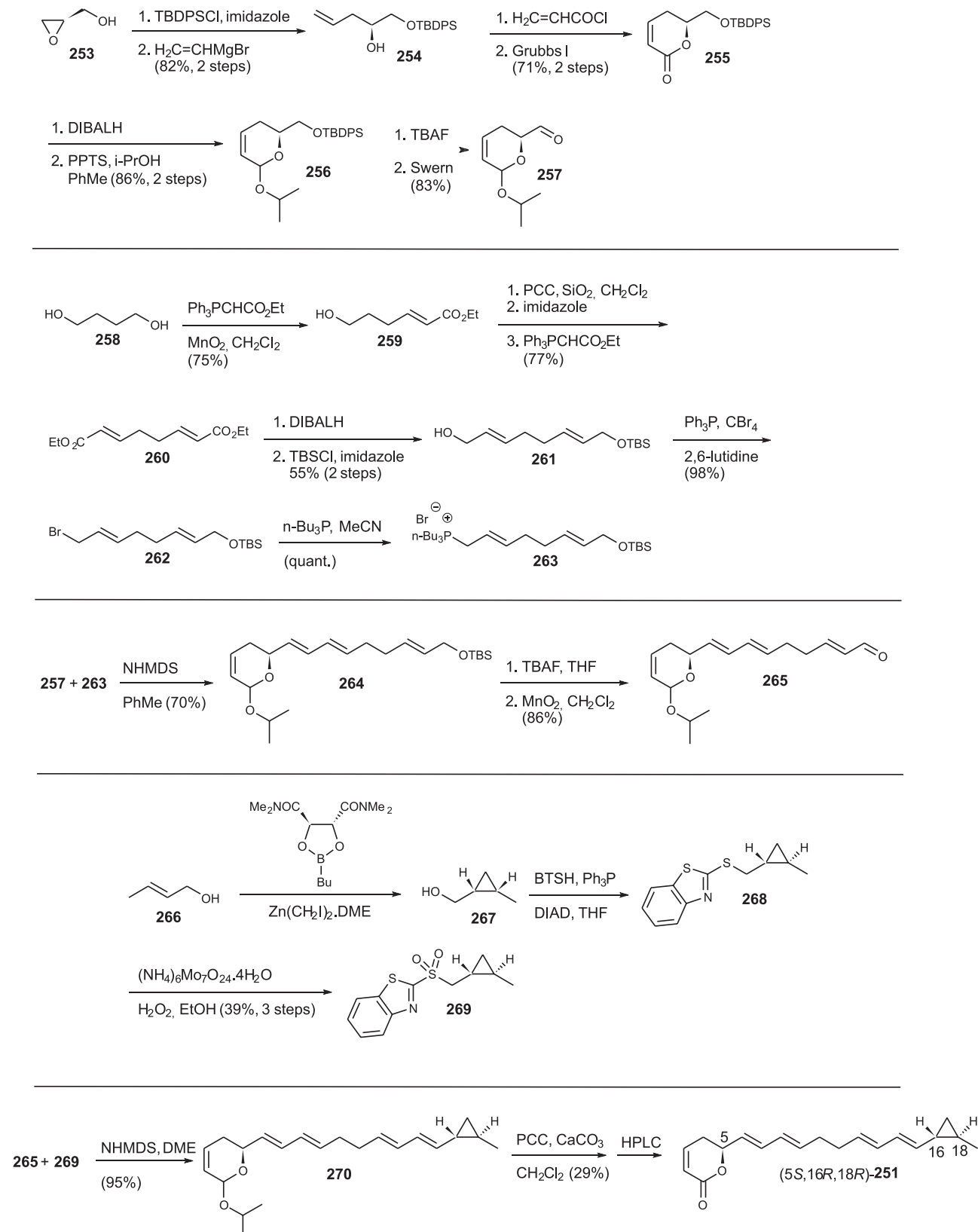
Scheme 6. Total synthesis of coibacin A [(5*S*, 16*R*, 18*R*)-**251**].[104]

The preparation of 5,5-dichlorohexanal (**284**) involved the conversion of hex-5-en-2-one (**281**) to its corresponding hydrazone followed by oxidation in the presence of copper chloride to give **282**. Hydroboration-oxidation followed by oxidation of the alcohol **283** gave **284**. Reaction of **284** with

the chiral propionate ester **285** provided the ester **286** which was hydrolysed to **287**. The absolute configuration of **287** was confirmed by its conversion to the corresponding diol (by reduction of the acid with LiAlH$_4$), followed by conversion to the corresponding acetonide with 2,2-dimethoxypropane
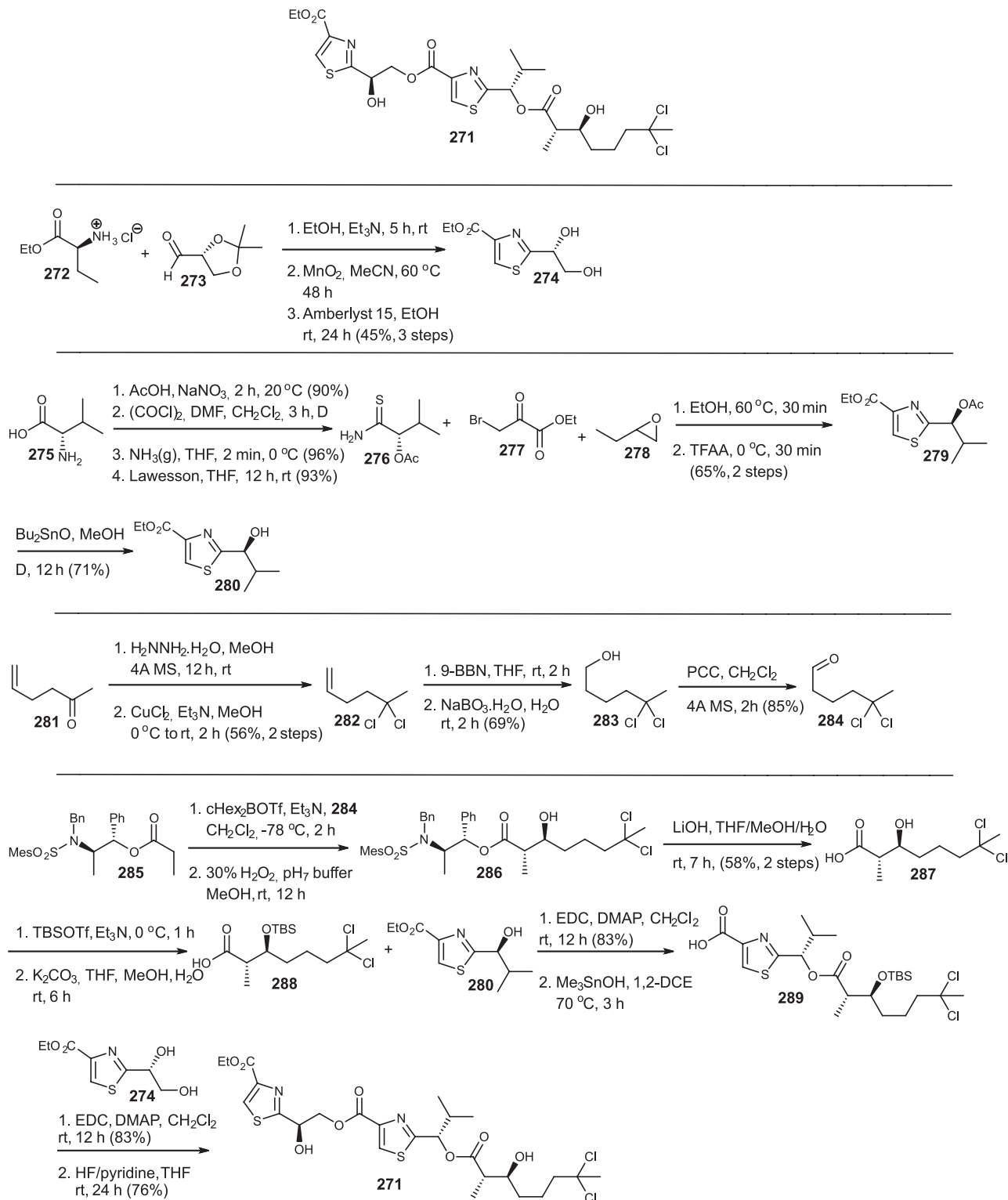
Scheme 7. Total synthesis of lyngbyabellin M (**271**).[106]

with concomitant Mosher ester analysis. After the alcohol protection of **287**, the product was coupled with **280** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and DMAP, followed by ethyl ester hydrolysis with hydroxymethyltin to provide **289**. Intermediate **289** was coupled with **274** also using EDC and DMAP, followed by the alcohol deprotection, to give lyngbyabellin M (**271**). Although the spectroscopic data of both synthetic and natural **271** compared almost exactly, the specific rotation of synthetic **271** {$[\alpha]_D^{25}$ +12 (*c* 0.5, MeOH)} had an opposite signal relatively to the natural product, $[\alpha]_D^{25}$ −4.5 (*c* 0.5, MeOH).

### 4.2. Total synthesis of metabolites from marine invertebrates

### 4.2.1. Marine sponges

4.2.1.1. Alkaloids

The brominated alkaloids 3-bromoverongiaquinol (**290**) and 5-monobromocavernicolin (**291**), previously isolated from the sponge *Aplysina cavernicola*,[108] have been synthezised (Scheme 8).[109] Starting from

para-benzoquinone (**292**), which reacted with the lithium enolate of *N,O*-bistrimethylsilylacetamide (**293**) to give the mixture of protected and unprotected amides **294** and **295**. The mixture of **294** and **295** were first brominated then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeCN to provide **290** and **291** in 47 and 20% yield, respectively.

The synthesis of the alkaloid (+)-*trans*-trikentrin A (**296**), isolated from the sponge *Trikentrion flabelliforme*,[110] has been accomplished (Scheme 9).[111] 7-Bromo-4-ethyl-1*H*-indole (**297**) was first protected and then subjected to a Heck coupling with methyl crotonate to give **298**, which was reduced at the double bond and de-racemized using a lipase hydrolyis with Amano OS-CII enzyme, a formulation of *Pseudomonas cepacia* lipase immobilized on a ceramic substrate, to give **299**. This intermediate was subjected to a Kowalski homologation towards **300**, which was then cyclized using a Friedel-Crafts like acylation, to provide **301**. After indole nitrogen re-protection with Boc, the ketone was reduced and dehydrated to prepare the substrate **302** for a ring contraction with thallium trinitrate trihydrate and NaBH₄. The product **303** was detosylated and
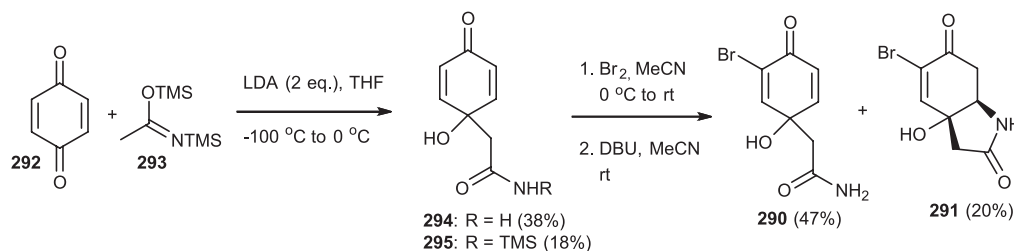
Scheme 8. Syntheses of 3-bromoverongiaquinol (**290**) and 5-monobromocavernicolin (**291**).[109]
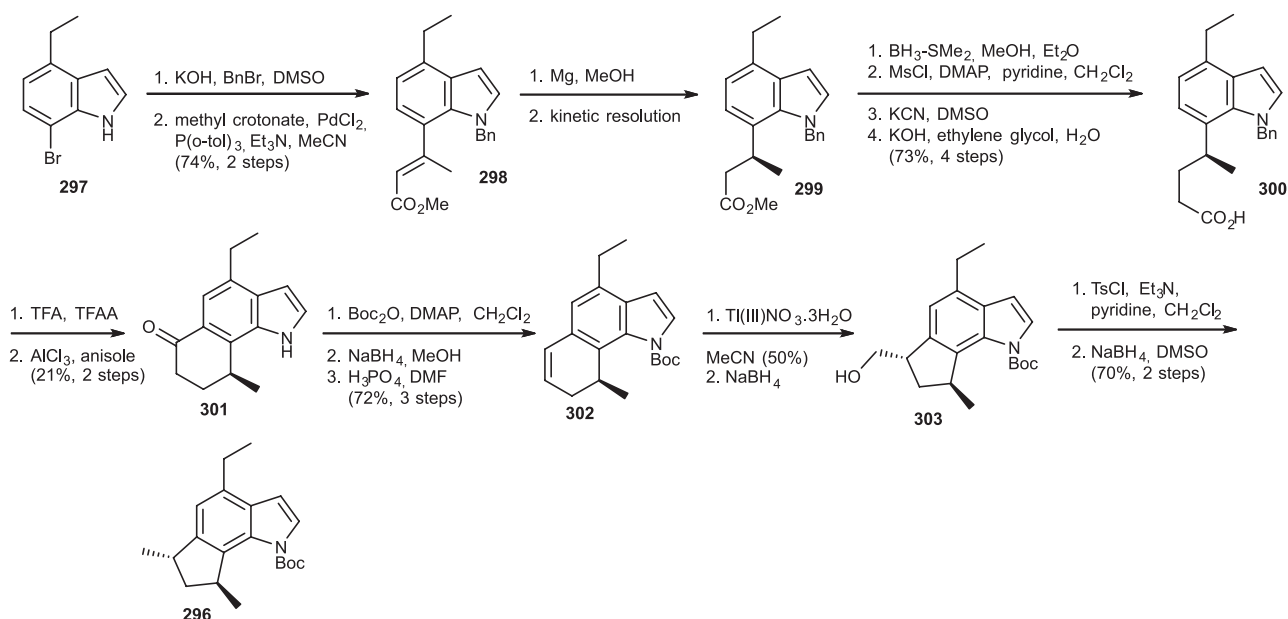
Scheme 9. Synthesis of (+)-*trans*-trikentrin A (**296**).[111]

N-deprotected to afford the natural product **296** in 70% over two steps. The natural product (+)-*trans*-triketrin A (**296**) displayed very good cytotoxic activity on breast (MCF-7), ovarian resistant (NCI-ADR/RES), ovarian (OVCAR-3) and prostate (PC-3) cancer cell lines, with IC_{50} at 2.8, 2.5, 3.1 and 6.6 mg mL^{-1}, respectively.

The pyrimidine alkaloid monalidine (**121**), isolated form the sponge *Monanchora arbuscula*,[71] has been synthesized in four steps (Scheme 10),[71] starting with a base-catalyzed Claisen condensation between undecan-2-one (**304**) and dihydrofuran-2(3*H*)-one (**305**). The product obtained (**306**) was condensed with guanidine hydrochloride (**307**) in the presence of potassium *tert*-butoxide, to give the pyrimidine **308**. Reaction of **308** under Mitsonobu-like conditions provided the alkaloid **121** identical to the natural product.[71]

4.2.1.2. Aromatic derivatives

A convergent synthesis of metachromin A (**309**), previously isolated from the sponge *Hippospongia metachromia*,[112] has been completed (Scheme 11).[113] Synthesis of the non-aromatic fragment **310** started by alkylation of the trimethylsilylenol ether derived from 2,6-dimethylcyclohexanone (**311**) with methyl vinyl ketone (**312**). The product (**313**) was protected with 2,2-dimethyl-1,3-propanediol (**314**) before a Wittig olefination followed by the ketone deprotection, to give **310**. The synthesis of the aromatic moiety **316** started with the transformation of the chloride **317** into the carboxylic acid **318**, which was then reduced and protected to give **319**. The protected alcohol **319** was then oxidized and acetoxylated to yield **320** before transformation of the protected alcohol in the phosphonate **316**. Both **310** and **316** were then coupled via a Horner-Wadsworth-Emmons reaction, to yield the precursor of the natural product **309**, which was obtained after the reduction of esters and oxidation of the hydroquinone.

An inhibitor of the SARS-coronavirus 3CL protease, esculetin-4-carboxylic acid ethyl ester (**322**) isolated from the sponge *Axinella* cf. *corrugata*,[114] has been synthesized in three steps (Scheme 12).[114] Baeyer-Villiger oxidation of 3-hydroxy-4-methoxybenzaldehyde (**323**) was followed by condensation of the formyl ester **324** with the sodium

derivative of diethyl oxalacetate (**325**) to give ethyl scopoletin-4-carboxylate (**326**), which was transformed into the natural product **322** after removal of the methyl group with boron tribromide. Esculetin-4-carboxylic acid ethyl ester (**322**) inhibited recombinant 3CL^{pro} *in vitro* with ID_{50} of 46 mmol L^{-1}. The same compound inhibited SARS-CoV replication in Vero cells with EC_{50} of 112 mmol L^{-1}, with no cytotoxic activity.[114]

4.2.1.3. Polyketides

A synthesis of callystatin A (**327**), a potently cytotoxic complex polyketide isolated from the sponge *Callyspongia truncata* in minute amounts (1 mg from 100 kg of sponge),[115] has been developed (Scheme 13)[116] in preparing three fragments, **328**, **329** and **330**, for subsequent coupling. Fragment **328** was synthesized from the chiral diol ester **331** by *tert*-butylsilyl (TBS)-protection, followed by ester reduction to the corresponding aldehyde, which was condensed with ethyl 2-((bis(*o*-tolyloxy))phosphoryl) acetate to give the unsaturated ester **332** in a 94:6 *Z/E* selectivity. The ester was converted to the chiral lactone by treatment with DIBALH for the ester reduction, a Dowex resin for the alcohols deprotection, followed by a MnO$_2$ oxidation to provide the lactone **333**. Protection of the primary alcohol with TBS, then reduction of the lactone carbonyl group and treatment of the lactol with i-PrOH and catalytic PPTS provided the desired ketal **328**. The second fragment was the phosphonium salt **329**, synthesized from methyl (*R*)-3-hydroxy-2-methylpropanoate (**334**), first by alcohol protection, then ester reduction followed by a Swern oxidation to provide the aldehyde **335**. This aldehyde was coupled with the β-ketophosphonate **336** to yield the unsaturated ester **337**. Ester reduction with DIBALH, followed by alcohol substitution by bromine and subsequent substitution by tributylphosphine provided the suitable phosphonium salt **329**. Coupling of **328** and **329** in the presence of ((methylsulfinyl)methyl)lithium gave the conjugated diene **339** in excellent yield (82%) and with a 95:5 *E/Z* stereoselectivity. Primary alcohol deprotection followed by functional group interconversions (FGI) to its corresponding iodide **340** was accomplished in 90%
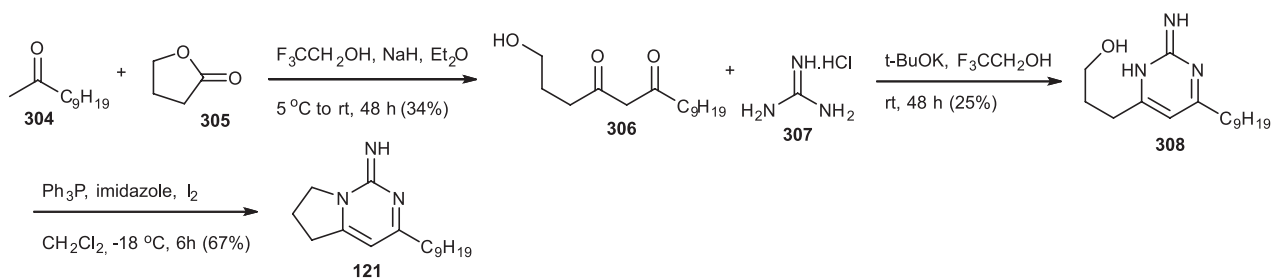
Scheme 10. Total synthesis of monalidine (**121**).[71]
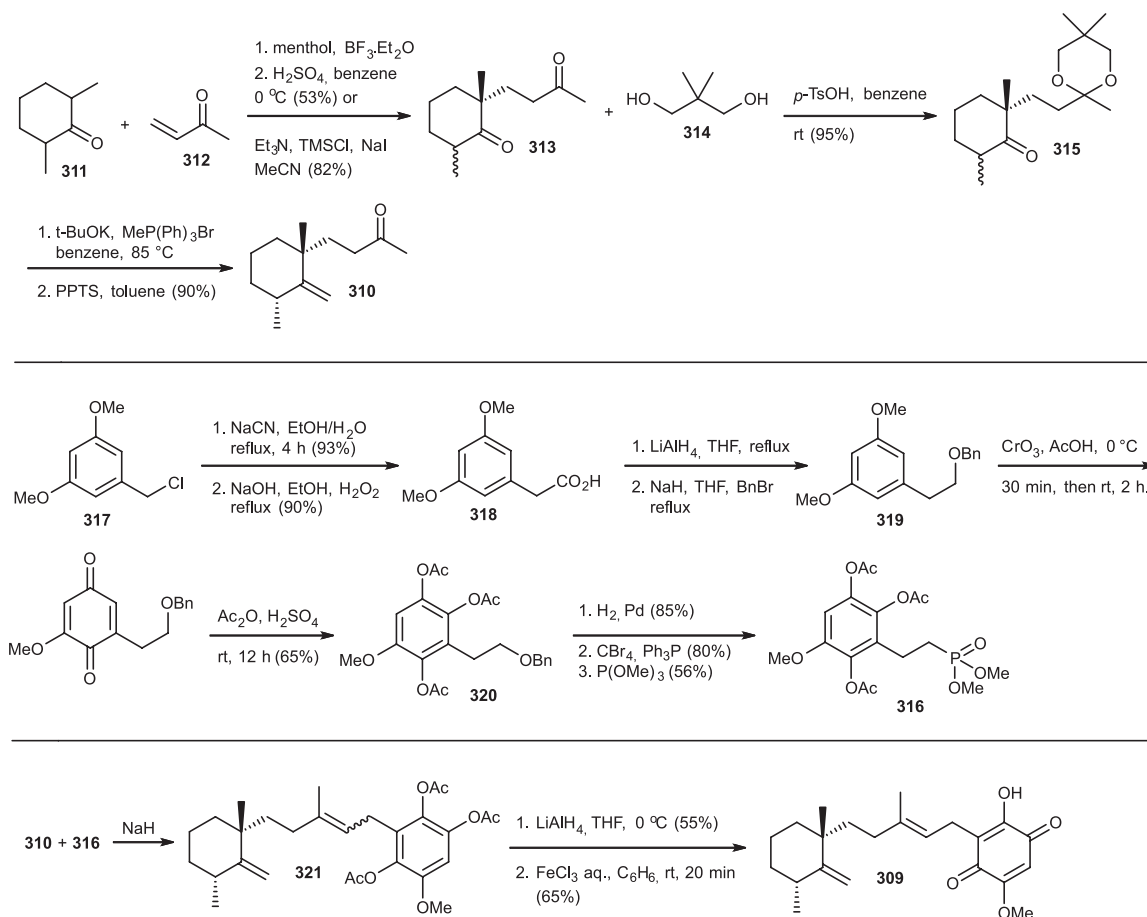
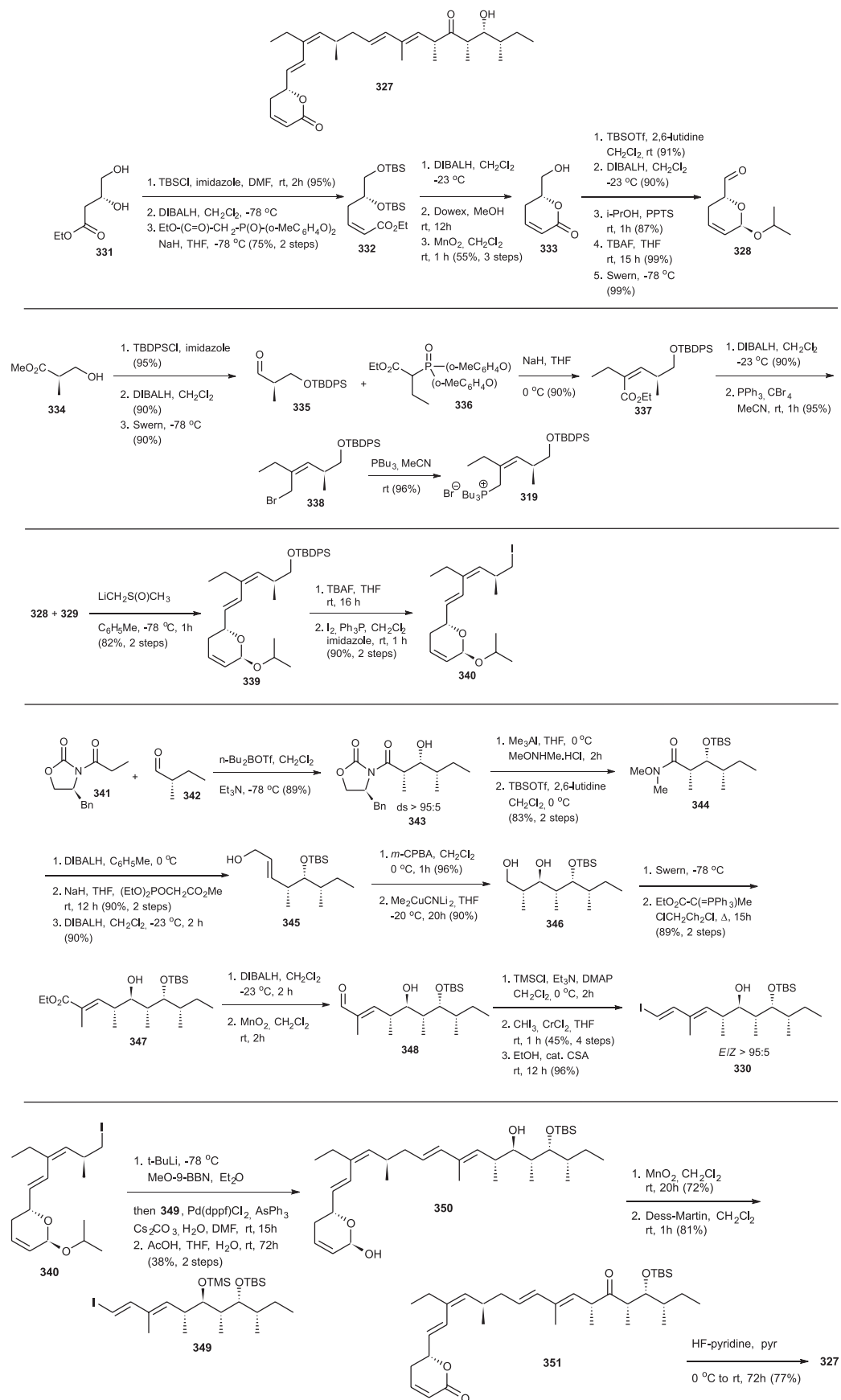**Scheme 11.** Total synthesis of synthesis of metachromin A (**309**).[113]
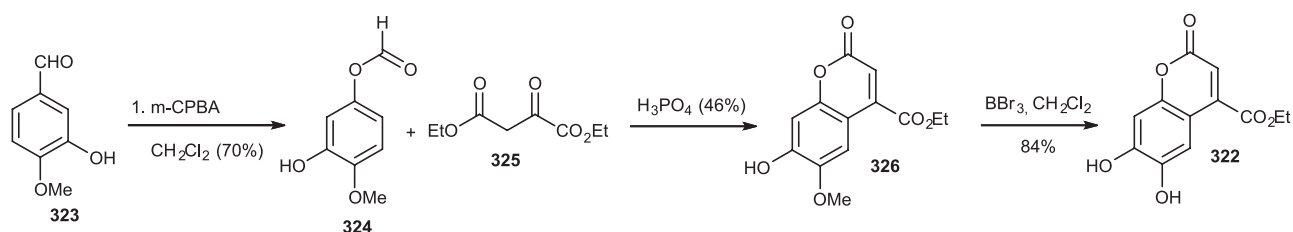
Scheme 12. Total synthesis of esculetin-4-carboxylic acid ethyl ester (**322**).[114]

yield in two steps. The third fragment **330** was synthezised through the longer sequence, starting by coupling **341** and **342** in 89% yield and 95:5 diastereoselectivity. Conversion of the oxazolidinone **343** to its corresponding Weinreb's amide and alcohol protection led to **344**, which was then converted to the alcohol **345** by amide reduction to its corresponding aldehyde before condensation with methyl 2-(diethoxyphosphoryl)acetate and reduction of the ester formed. The allylic alcohol **345** was converted to its epoxide before alkylation with Me$_2$CuCNLi$_2$ to give the diol **346**. Oxidation of the primary alcohol followed by coupling with EtO$_2$C−C(=PPh$_3$)Me gave the unsaturated ester **347** which was reduced and oxidized to the aldehyde **348**. Protection of the alcohol, conversion of the aldehyde

to its corresponding vinyl iodide and alcohol deprotection provided the third fragment **330** for the synthesis of callystatin in 21% overall yield from **341**. Coupling of **340** with **330** (the TBS protected **330**) in the presence of *t*-BuLi and MeO-9-BBN to provide a boronate intermediate in order to be subjected to a palladium-catalyzed cross-coupling led to the formation of the pentaene **350** in 38% yield. Final FGIs followed by alcohol deprotection gave callystatin A (**327**) in 3.5% overall yield.

4.2.2. Corals

A synthesis of racemic pathylactone A (**352**), isolated from the soft coral *Paralemnalia thyrsoides*,[117] was developed (Scheme 14)[118] from 2-methylcyclohex-2-en-1-one (**353**) by

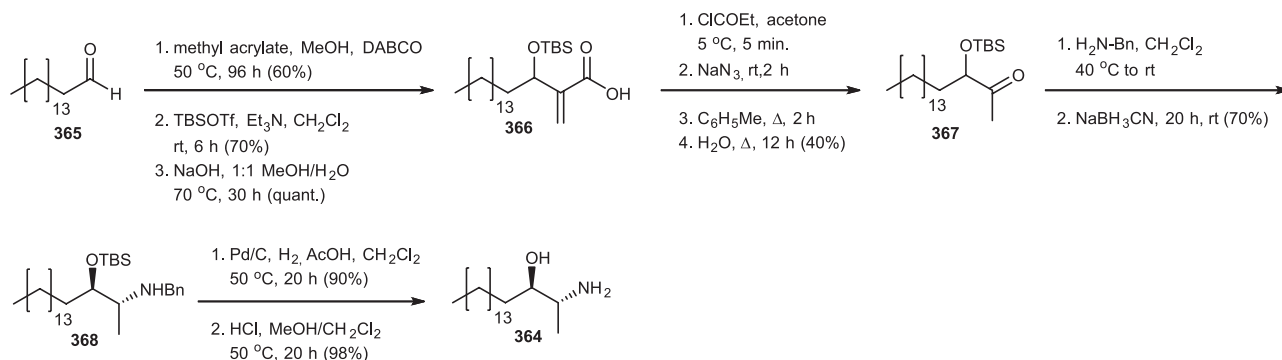**Scheme 13.** Total synthesis of callystatin A (**327**).[116]
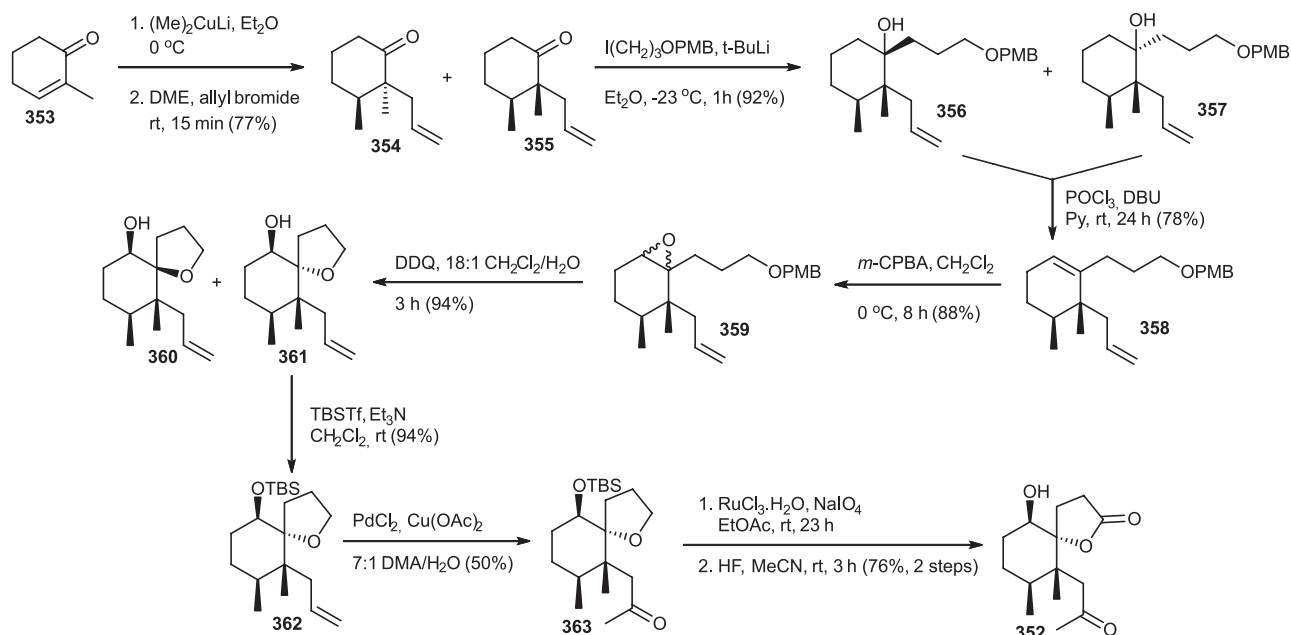
Scheme 14. Total synthesis of racemic pathylactone A (**352**).[118]

alkylation with the Gilman reagent then with allyl bromide, to give a 1:4 mixture of stereoisomers **354** and **355**. Intermediate **355** was further alkylated with 1-((3-iodopropoxy)methyl)-4-methoxybenzene to give the mixture of alcohols **356** and **357** which was transformed into the alkene **358** with POCl$_3$ and DBU. Double dond epoxidation followed by cyclization provided a mixture of tetrahydrofurans **360** and **361**. Alcohol protection and double bond cleavage on the stereoisomer **361** gave the ketone **363** which was transformed into the natural product **352** after oxidation of the tetrahydrofuran ring into its respective lactone followed by alcohol deprotection. Careful analysis of the NMR data obtained by the authors for synthetic **352** indicated that the original report on its isolation presented some misassignments, particularly for the carbinolic group.

4.2.3. Mollusks

A synthesis of racemic spisulosine (**364**), previously isolated from the clam *Spisula polynyma*, was achieved

(Scheme 15).[119] Palmitaldehyde (**365**) was subjected to a Morita-Baylis-Hillman reaction with methyl acrylate and 1,4-diazabicyclo[2.2.2]octane (DABCO), to provide the corresponding alcohol-conjugated ester, which was protected and hydrolysed to give **366**. The acid **366** was subjected to a Curtius rearrangement to give the acyloin **367** in 40% in a four-step reaction sequence. Condensation of **367** with benzylamine and mild reduction with NaBH$_3$CN gave the protected amine **368**. Deprotection of both benzyl and sylil groups led to the natural product **364** in 10% overall yield.

4.2.4. Ascidians

Polycitrin A (**369**), isolated previously from the ascidian *Polycitor africanus*,[120] has been synthezised using a Heck arylation as the key step (Scheme 16).[121] Palladium-mediated Heck arylation between maleic anhydride with the tetrafluoroborate salt of diazonium **371** gave anhydride **372** in 46% yield after the deprotection of phenol groups.

Scheme 15. Total synthesis of racemic spisulosine (**364**).[119]
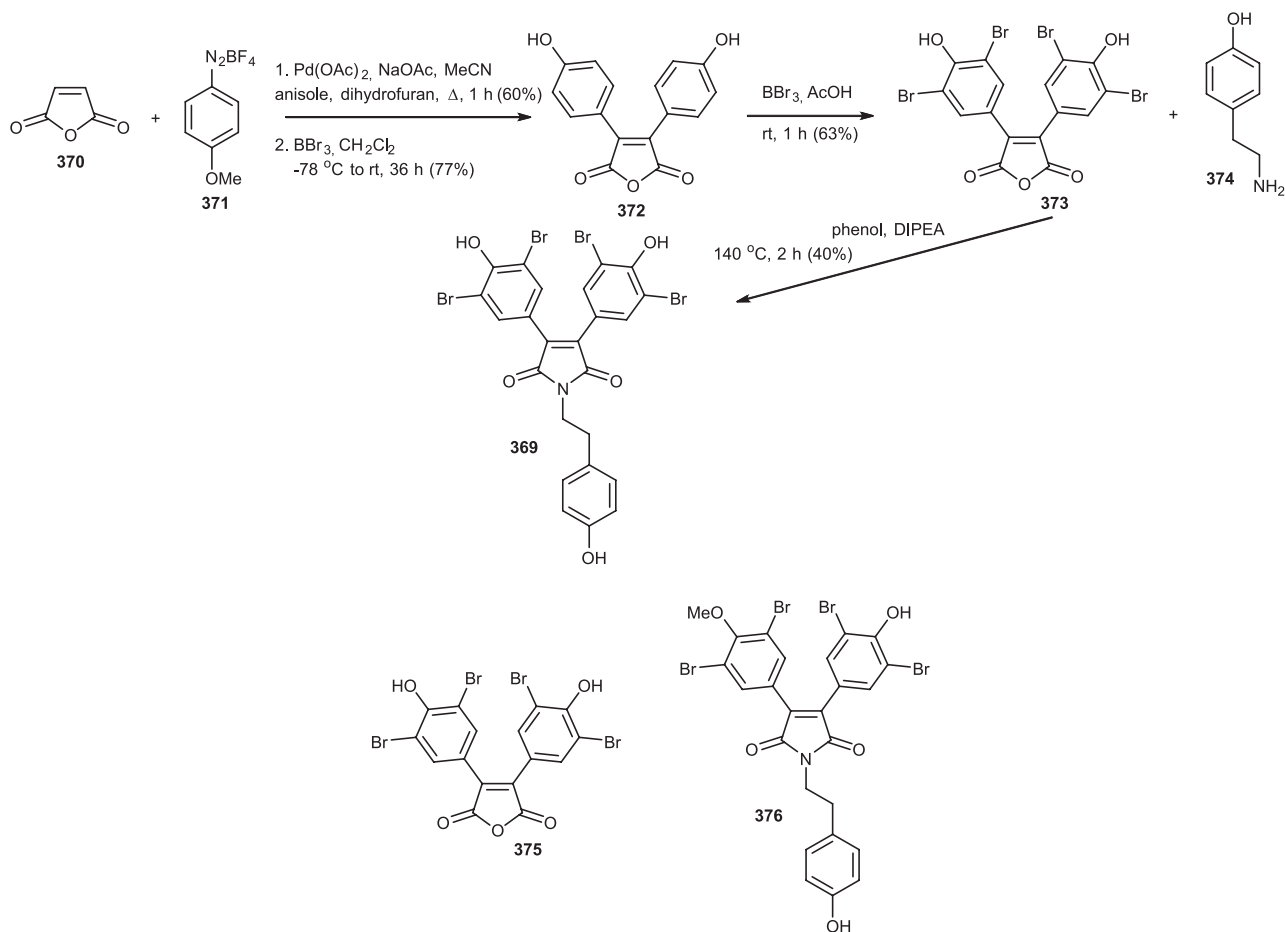
Scheme 16. Total synthesis of polycitrin A (**369**).[121]

Bromination of **372** followed by coupling of product **373** with tyramine (**374**) provided the natural product **369** in 12% overall yield. A related and improved synthesis for polycitrin A (**369**), as well as for prepolycitrin (**375**) and polycitrin B (**376**), has been subsequently developed.[122]

Rubrolides are butenolides which have been first isolated from the ascidian *Ritterella rubra*.[123] Recently a unified synthesis of rubrolides B, I, K and O has been developed (the synthesis of rubrolide B, **377**, is illustrated in Scheme 17).[124] Suzuki coupling of the lactone **378** with the
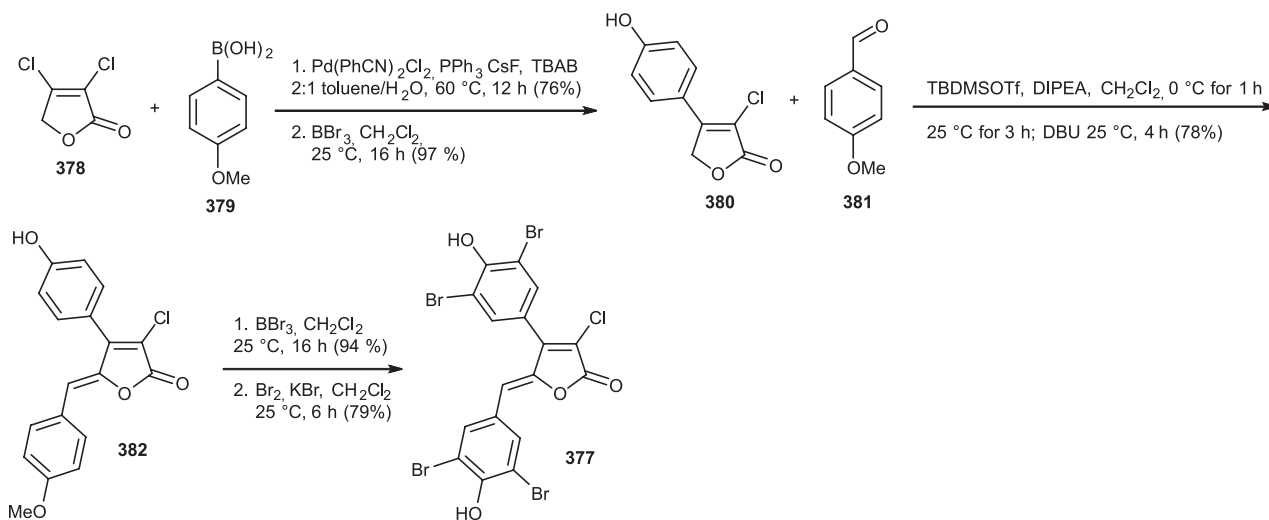
Scheme 17. Total synthesis of synthesis of rubrolide B (**377**).[124]

boronic aromatic derivative **379** gave the product **380** in very good yield (73%) after deprotection. The aromatic lactone **380** was then coupled with *para*-methoxybenzaldehyde (**381**) to afford intermediate **382**. Deprotection of the phenol group followed by perbromination of both benzene moieties led to the natural product **377** in 42% overall yield from **378**.

These remarkable total syntheses by Brazilian organic synthetic chemists represent major achievements, during a period of limited financial support for research by Brazilian Federal funding agencies. Sadly, the real challenge of total synthesis of natural products in Brazil is currently being pursued by only very few research groups of organic chemists, most of which are senior researchers. Therefore, we expect a diminishing number of total syntheses of marine natural products achievements by Brazilian chemists in the forthcoming years.

5. Marine Natural Products in Brazil: Present and Future

The current interest by Brazilian natural product scientists to investigate marine natural products is justified by the fact that secondary metabolites isolated from marine organisms present a chemical diversity which is very distinct of terrestrial plants. Such interest is evident when we consider the number of isolated compounds, both known and new, and in the number of articles published within the period covered in the present review (Figures 30 and 31). This change of perspective by Brazilian natural product scientists towards marine natural products is considered very positive. Nature is virtually an infinite source of structurally exquisite compounds, most of which are biologically active. Biological sources are very abundant in Brazil, both terrestrial and marine. New

strategies and bioassays, the use of modern and sensitive tools for dereplication and prioritization, searching for minor metabolites, are approaches that should be envisaged for the discovery of new natural compounds, from any biological source.

As previously predicted,[11] research on marine microbial secondary metabolites expanded significantly during the 2004-2017 period (Figure 31). This is certainly also associated to the chemical novelty of secondary metabolites produced by marine-derived strains, the relatively easy access to marine microbes when compared to marine invertebrate collections and the possibility to obtain large amounts of material for investigation by microbial culturing. Marine-derived fungi have been explored more extensively than marine-derived bacteria by Brazilian natural product chemists. It seems that fungi are more friendly to manipulate, to grow and to produce secondary metabolites of interest. This trend is in agreement with perspectives presented by Blunt and collaborators.[125-139]

Marine sponges continue to be the main source of marine natural products in Brazil, a trend that follows the overall interest by marine natural product chemists all around the world.[125-139] Marine sponges are prolific in providing unique bioactive chemicals, many of which appear to be produced by associated microorganisms. As shown in Figure 32, alkaloids comprise the main group of marine secondary metabolites isolated by Brazilian researchers, followed by metabolites of mixed biosynthetic origin, polyketides and terpenes. Peptides are the least group of metabolites isolated, even including common diketopiperazines in this class of compounds. The distribution of metabolites of distinct biosynthetic pathways follow the usual distribution of marine natural products from the organisms of origin. Such patterns have been consistently observed over the
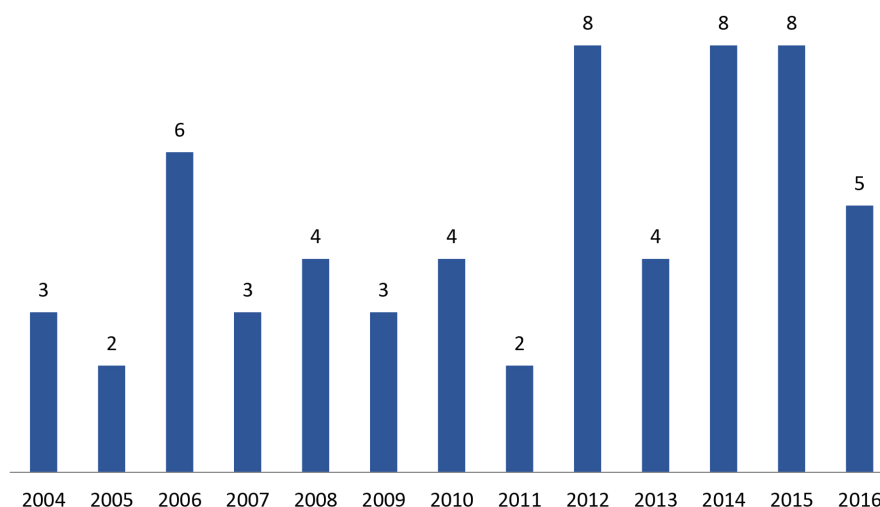
Figure 30. Articles on marine natural products published by Brazilian researchers as corresponding authors between January 2004 and August 2017.
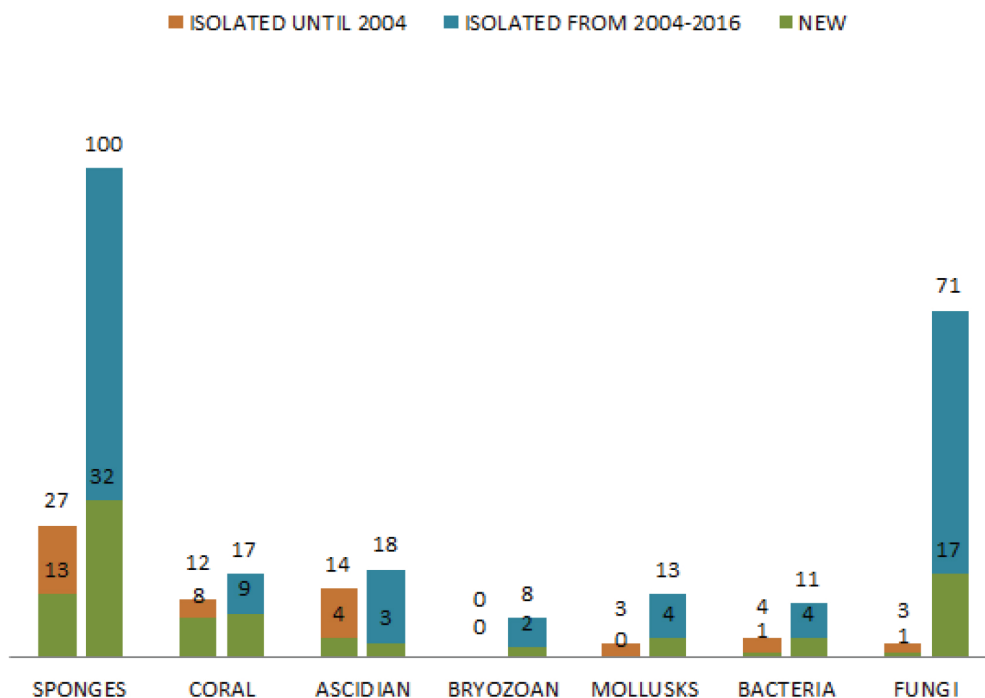
Figure 31. Number of marine natural products *per* biological group isolated by Brazilian researchers as corresponding authors.
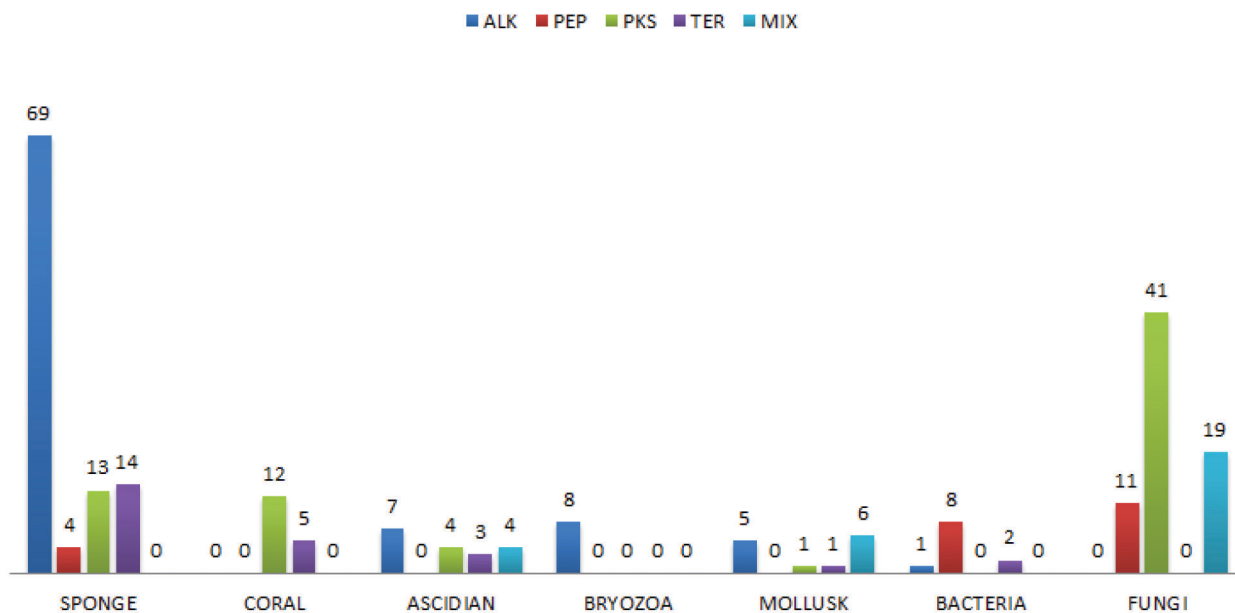
Figure 32. Biogenetic origin of marine natural products isolated by Brazilian researchers as corresponding authors.

years.[125-139] Although an analysis of bioactivities has not been herein included, it sounds as illogical to correlate bioactivities to certain classes of metabolites or organisms. This is because the reported bioactivities are the author's choice rather than a comprehensive assessment of a bioactivity for each particular compound.

Perspectives for the development of marine natural products in Brazil indicate it as a promising venue.

Challenges include the access to minor and water-soluble metabolites, which are difficult to handle. Difficulties related to complex structure determination of novel minor metabolites are also evident. Additional problems to be circumvented include the re-isolation of known compounds and the chemical isolation of culture media components when dealing with marine microbes. Much expertise should be developed aiming to overcome such issues and promote a

sounding capacity building and science of utmost quality, as marine natural products has shown to be since its origins in the 1950's. As for microbial natural products,[1] the chemistry of marine natural products in Brazil is still in its infancy. It is expected to grow to its maturity in the forthcoming years, resulting from the development of multidisciplinary projects. Marine natural products chemistry in Brazil should be well developed in order to deserve its current designation-marine bioproducts from the blue Amazon.

Acknowledgments

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