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Secondary metabolites from marine sponges of the genus *Agelas*: a comprehensive update insight on structural diversity and bioactivity

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As one of the most common marine sponges in tropical and subtropical oceans, the sponges of the genus *Agelas*, have emerged as unique and yet under-investigated pools for discovery of natural products with fabulous molecular diversity and myriad interesting biological activities. The present review highlights the chemical structure and biological activity of 355 compounds that have been isolated and characterized from the members of *Agelas* sponges, over the period of about five decades (from 1971 to November 2021). For a better understanding, these numerous compounds are firstly classified and presented according to their carbon skeleton as well as their biosynthetic origins. Relevant summaries focusing on the source organism and the associated bioactivity of these compounds belonging to different chemical classes are also provided. This review highlights sponges of the genus *Agelas* as exciting source for discovery of intriguing natural compounds.

1. Introduction

Natural products have historically served as potential sources of lead compounds for drug development.[1] Under physically variable and competitive environments, marine sponges have necessitated the evolution of thorough metabolic capability to produce diverse physiologically active secondary metabolites. About 9500 new compounds have been isolated from marine sponges during the period of 1950 to 2019, most of them exhibiting a wide range of biological activities.[2,3] As one of the most common sponges in tropical and subtropical areas around the world, marine sponges of the genus *Agelas* (class Demospongiae, order Agelasida, family Agelasidae), include to date 36 valid species, and knowledge of its species continues to expand.[4] The reasons for us discussing this genus of sponges are the chemical richness and interesting biological activity of their secondary metabolites as well as the wide geographical distribution in the global ocean, especially in the Okinawa Sea, the Caribbean Sea and the South China Sea. Many of these metabolites are of mixed biogenetic origin, as illustrated by alkaloids (especially pyrrole alkaloids and terpenoid alkaloids), glycosphingolipids, sterols, carotenoids, and so on. Although Zhang *et al.* have reviewed the 291 secondary metabolites isolated from *Agelas* sponges according to their biological sources,[5] few reports have analysed the structure and chemical classification of the diverse *Agelas*-derived natural products. In order to better illustrate the intriguing chemistry and biology of these natural products and rationally exploit the resources of *Agelas* sponges, the 355 compounds isolated from *Agelas* sponges, covering the period from 1971 to November 2021, are systematically categorized and grouped into several families according to their carbon skeleton as well as biosynthetic origins, and their sources and a wide range of bioactivities are also summarized.

2. Pyrrole alkaloids

As a fascinating group of a large variety of secondary metabolites produced by *Agelas* sponges, pyrrole alkaloids are of historic importance in marine natural products chemistry due to their high chemodiversity and interesting bioactivities. Structurally, most of them share a bromo- or debromopyrrole-2-carboxamide core with diverse linear side chains (linear pyrrole alkaloids) and fused cyclic systems (fused cyclic pyrrole alkaloids). Furthermore, the monomers can dimerize to give a large variety of dimers (dimeric pyrrole alkaloids). It is interesting to note that, despite their structural diversity, the biosynthetic origin of these pyrrole alkaloids can be traced back to a small number of possible precursors. According to the stunning logic of nature, only a few fundamental amino acids, including proline and lysine, are necessary to construct the simple pyrrole alkaloids (*e.g.*, oroidin), which are building blocks to form complex pyrrole alkaloids with various molecular architectures.[6]

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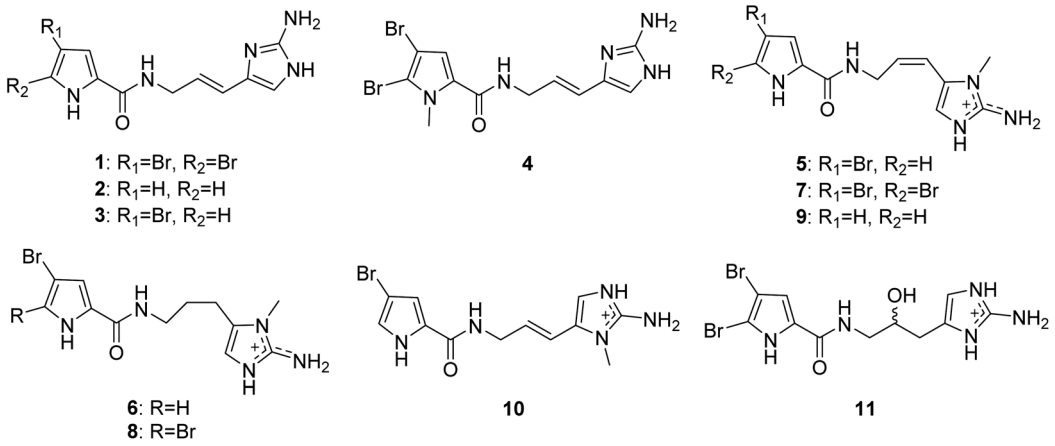


Fig. 1 Chemical structures of **1–11**.

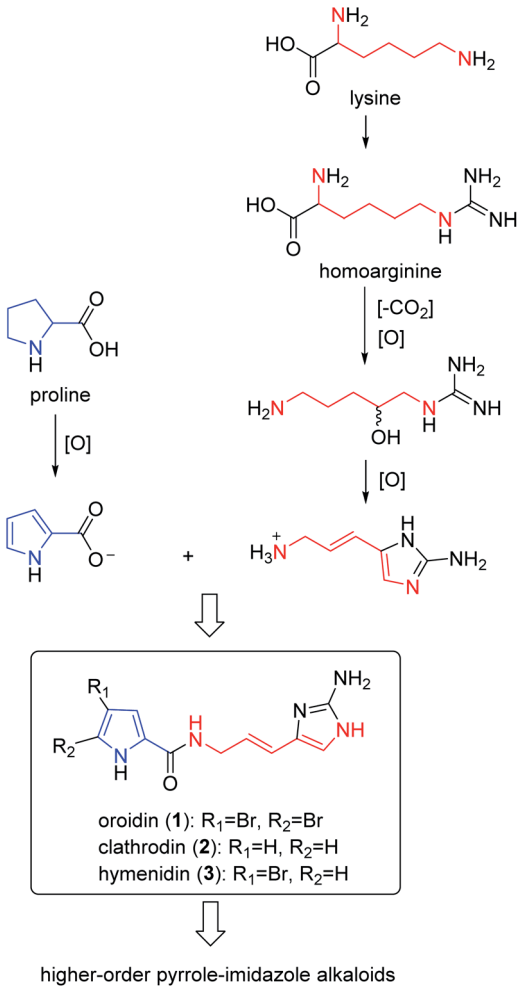
2.1. Linear pyrrole alkaloids

Most of the linear pyrrole alkaloids are pyrrole-imidazole alkaloids (PIAs) constructed by the bromo- or debromopyrrole-2-carboxamide core connected with an aminoimidazole group through an aliphatic segment. These chemically interesting alkaloids, produced exclusively by marine sponges, have been regarded as useful chemotaxonomic markers for axinellid sponges that were once allied with the Agelasida, such as the sponges of the genus *Agelas*, *Axinella*, *Acanthella*, *Hymeniacidon*, *Phakellia* and *Pseudaxinyssa*.[7] Additionally, the linear pyrrole alkaloids lacking an aminoimidazole moiety in the molecules have also been reported from *Agelas* sponges.

2.1.1. Pyrrole-imidazole alkaloids (PIAs). From Fig. 1—the first member of the PIAs to be isolated was oroidin (**1**), initially from *A. oroides* collected in the bay of Naples in 1971.[8] However, the initial structure of oroidin was not exactly right; afterwards the structure was reassigned based on a chemical synthesis.[9] Subsequently, three closely related analogues, including the nonbrominated clathrodin (**2**) from the Caribbean *A. clathrodes* collected from Desecheo Island,[10] the monobrominated hymenidin (**3**) and *N*-methylated derivative sventrin (**4**) from Bahamas *A. sventres*[11] have been discovered. The simplest PIAs oroidin (**1**), clathrodin (**2**) and hymenidin (**3**), the structures of which differ only in bromine content, often served as the key monomeric building blocks to biosynthesize a large variety of chemically complex PIAs with amazing molecular diversity. Several lines of investigation aimed at understanding the origin and the reactivity of the precursors **1–3** and possible pathways for their conversion to higher-order PIAs have been undertaken.[6] As a consequence, proline was strongly suggested as the precursor of the pyrrolyl moiety in **1–3**, while the 2-aminoimidazole part of **1–3** was thought to originate from lysine (Scheme 1). These biosynthesis speculations on PIAs have been demonstrated by feeding experiments with radioisotopes, precursor-guided mining and detection of marine sponge metabolomes, and *de novo* synthesis using cell-free enzyme preparations.[12–15] Biological evaluation revealed that compound **1** had a broad spectrum of bioactivities, including antibacterial,[16] antifouling,[17] antipredatory defense against reef fish,[18–20] antimalarial,[21] acetylcholinesterase inhibitory and radical scavenging,[22] inhibitory action towards voltage-gated potassium channels,[23] and inhibiting biofilm formation of pathogenic and marine environment derived bacteria.[24–27] Compound **2** exhibited cytotoxicity against Chinese hamster ovary (CHO)-K1 cells (ED_{50}, 1.33 μg mL^{-1}), blocking activity against cholinergic receptors on the isolated frog skeletal muscle, and modulatory effect on voltage-gated sodium and potassium channels,[10,23,28] while compound **3** was proved to be an inhibitor of the voltage-gated potassium channels,[23] and compound **4** was feeding deterrent against omnivorous reef fish.[11]

Keramadine (**5**),[29] 9,10-dihydrokeramadine (**6**),[30] 2-bromokeramadine (**7**) and 2-bromo-9,10-dihydrokeramadine (**8**) identified from Okinawan sponge *Agelas* sp.,[31] and debromokeramadine (**9**) from the Solomon Islands *A.* cf. *mauritiana*[32] are oroidin congeners with an *N*-methylated aminoimidazole moiety. It is worth noting that in contrast to *E* configuration of the vinylic double bond in oroidin and many other analogues, *Z* configuration is characteristic of compounds **5–9**.[32] Biological studies have identified that compound **5** was an effective antagonist of serotonergic receptors, and had antibacterial activities against *Bacillus subtilis*, *Staphylococcus aureus* and *Micrococcus luteus* (MIC, 40, 35 and 4.0 μg mL^{-1}, respectively).[29,31,33] In addition, a recent report on Okinawan sponges *Agelas* sp. described two closely related congeners, 9*E*-keramadine (**10**) and 9-hydroxydihydrooroidin (**11**).[34]

From Fig. 2—four oroidin derivatives with an aminoimidazolone moiety, dispacamides A–D (**12–15**), were reported from Caribbean species *A. dispar*, *A. clathrodes*, *A. longissima* and *A. conifer*, collected from Little San Salvador Island, by Fattorusso's group. All the four compounds were evaluated for the antihistaminic activity on the guinea pig ileum, with compounds **12** and **13** being more potent than **14** and **15**, indicating the insertion of a hydroxylic group in the central chain causes a marked reduction of the antihistaminic activity.[35,36] Further biological researches suggested that compound **12** served as the primary chemical defense of *Agelas* sponges,[37] while compound **13** emerged as an antimalarial lead compound with significant activity and low toxicity towards



Scheme 1 Origin of the building blocks oroidin (1), clathrodin (2) and hymenidin (3) from amino acid precursors.

mammalian cells.[38] Two nonbrominated analogues, debromodispacamides B (**16**) and D (**17**), were purified from the Solomon Islands collection of *A. mauritiana*, and a biomimetic one-step reaction gave the chiral form of the natural product stereoselectively.[39] Recently, the study of *A. oroides* collected near the Israeli Mediterranean coastline and Okinawan sponges *Agelas* sp. yielded *E*-dispacamide (**18**)[27] and 9-hydroxydihydrodispacamide (**19**),[34] respectively.

From Fig. 3—further examples of *Agelas*-derived PIAs were oroidin derivatives with a hydantoin unit (**20–28**). Midpacamide (**20**) and 5-debromomidpacamide (**21**) were obtained from the Enewetak Atoll *A. mauritiana*,[40] while an Okinawan specimen of *A. nakamurai* was the source of mukanadins A (dispacamide D, **15**) and B (**22**),[41] and chemical investigations of Mediterranean *A. oroides*, collected off the Tel Aviv coast, and the Okinawan *Agelas* sp. afforded mukanadins D (**23**)[27] and F (**24**),[42] respectively. It should be noted that unlike the usually encountered racemic or scalemic mixtures of PIAs, compound **24** was isolated as a single enantiomer with the absolute configuration established using Mosher's esters.[42] The *Agelas* sponges from the Xisha Islands in the South China Sea were demonstrated to contain 9-oxethyl-mukanadin F (**25**) from *Agelas* sp.,[43] the nonbrominated nakamurine D (**26**) and a known congener **27** from *A. nakamurai*[44,45] and nemoechine H (**28**) from *A. nemoechinata*.[46] Among which, compound **28** possessed cytotoxic activity against human leukemia cell K562 and human liver cell L-02 (IC_{50}, 6.1 and 12.3 μM, respectively).[46]

From Fig. 4—the sponges of the genus *Agelas* were also the source of a quite rare family of PIAs with a taurine moiety. The first member of this family is the Fijian species *A. mauritiana* derived mauritamide A (**29**), which is an oroidin derivative having a taurine methyl ester group.[47] Two congeners, mauritamides B (**30**) and C (**31**) were detected in the Indonesian *A. linnaei*.[48] Investigation of the chemistry of Mediterranean *A. oroides* afforded taurodispacamide A (**32**), which displayed a good antihistaminic activity tested on the isolated guinea pig ileum and antimicrobial activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* with IC_{50} values ranging from 0.21 to 1.4 μM.[16,49] A series of taurine containing PIAs, tauroacidins A (**33**) and C–E (**34–36**),[31,50] nagelamides M (**37**), N (**38**),[51] U (**39**) and V (**40**)[52] were isolated from Okinawan *Agelas* sp., by Kobayashi's group. Structurally, compound **37** possesses a unique 2-aminooctahydropyrrolo[2,3-*d*]imidazole ring,[51] while compounds **39** and **40** are the first example for a pyrrole alkaloid with a γ-lactam ring.[52] Biosynthetically, compounds **37–40** could be derived from the same precursor (**32**) through oxidation and cyclization.[51,52] In the bioassays, compound **33** not only exhibited tyrosine kinase inhibitory effect (IC_{50}, 20 μg mL^{-1}) but also had antibacterial activity against *M. luteus* (MIC, 8.0 μg mL^{-1}),[31,53] while compounds **37** and **38** had antimicrobial activity against

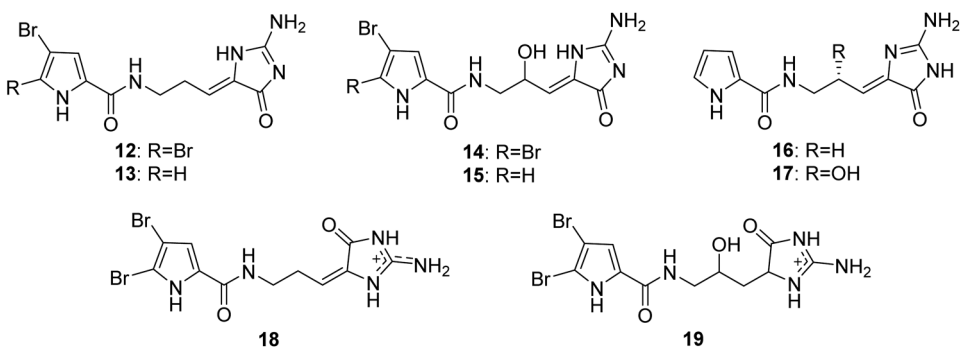


Fig. 2 Chemical structures of **12–19**.

Aspergillus niger (MIC, 33.3 μg mL^{-1}, each),[51] and compound **39** was active against *C. albicans* (IC_{50}, 4 μg mL^{-1}).[52]

From Fig. 5—three unique PIAs **41–43** were identified from the prolific Okinawan *Agelas* sponges, which were proved to be a rich source of structurally intriguing compounds. Compound **41** (nagelamide W) is the first monomeric pyrrole alkaloid containing two aminoimidazole units in the molecule, and exhibited antimicrobial activity against *C. albicans* (IC_{50}, 4 μg mL^{-1}).[52] Compound **42** (mukanadin G) with a tricyclic skeleton consisting of a fused tetrahydrobenzaminoimidazole and 2,5-dioxopyrrolidine moieties, was found to have antifungal activity against *C. albicans* and *Cryptococcus neoformans* (IC_{50}, 16 and 8.0 μg mL^{-1}, respectively).[31] Compound **43** (agelamadin F) is the first example for a pyrrole alkaloid with the coexistence of aminoimidazole and pyridinium moieties.[50] In a further study of Caribbean *Agelas* specimens collected from Little San Salvador Island, Fattorusso's group discovered two pairs of diastereomeric bromopyrrole alkaloids sharing an uncommon *N*-methylimidazolinium moiety, clathramides A (**44**) and B (**45**) from *A. clathrodes*, and clathramides C (**46**) and D (**47**) from *A. dispar*. All the four clathramides (**44–47**) displayed moderate antifungal activity against *A. niger* (100 μg of the mixture caused a zone of inhibition of 7–8 mm).[33,54] The Okinawan *A. nakamurai* was the source of the unusual PIAs sharing a tetrabydrofuro[2,3-*d*]imidazolidin-2-one moiety, slagenins A–C (**48–50**), with **49** and **50** showing cytotoxic activity against routine leukemia L1210 cells (IC_{50}, 7.5 and 7.0 μg mL^{-1}, respectively).[55] Recently, slagenin D (**51**), presenting opposite absolute configuration of stereogenic centers relative to those of slagenin A (**48**), was discovered from Mediterranean *A. oroides*, collected in Tel Aviv.[27] Examination of Xisha Islands *A.* aff. *nemoechinata* led to the isolation of nemoechine A (**52**) bearing an uncommon cyclopentane-fused imidazole ring system.[56] Ageladine A (**53**) containing 2-aminoimidazolopyridine and agelanin A (**54**) with 2-aminoimidazolo-tetrahydropyridinol, were characterized from Kuchinoerabu-jima Island *A. nakamurai*[57] and Thousand Islands *A. linnaei*,[48] respectively. In addition to the important pharmacological activity as antiangiogenic compound and metallo-protease inhibitor, compound **53** was a reliable and stable fluorescent pH sensor, implying utility as a membrane permeable dye.[57,58]

2.1.2. Pyrrole alkaloids without an imidazole moiety. From Fig. 6—the first investigation of the constituents of *A. oroides* collected in the bay of Naples identified the pyrrole alkaloids without an imidazole moiety (**55–58**),[8] which were common metabolites encountered in *Agelas* species and had many bioactivities. Compound **55**, 4,5-dibromopyrrole-2-carboxylic acid, displayed immunosuppressive effect and feeding deterrent activity towards reef fishes,[18,59] while compound **56**, 4,5-dibromopyrrole-2-methylcarboxylate, could mildly inhibit protein tyrosine phosphatase 1B (PTP1B),[60] and compound **58**, 4,5-dibromopyrrole-2-carboxamide, not only had the ability to promote larval metamorphosis of the ascidian *Ciona savignyi*[17] but also inhibited *Pseudomonas aeruginosa* PAO1 biofilms.[27] A study of Great Barrier Reef collection of *A. oroides* resulted in the isolation of pyrrole-2-carboxamide (**59**) and *N*-formyl-pyrrole-2-carboxamide (**60**).[61] 2,3-Dibromopyrrole (**61**) and 2,3-dibromo-5-methoxymethylpyrrole (**62**) were discovered from *Agelas* sp. without collection location data.[62] The Papua New Guinean sponge *A. nakamurai* was the source of 5-bromopyrrole-2-carboamide (**63**) and 5-bromopyrrole-2-(-*N*-methoxymethyl)carboxamide (**64**) with **63** being active against some Gram-positive bacteria and fungi,[63] while 4-bromopyrrole-2-carboxylic acid (**65**) and 4-bromopyrrole-2-carboxamide (**66**) have been sourced from Menjangan Island specimen of *A. nakamurai*.[48] The first report of a chemical study on Caribbean *A. cerebrum* collected from Cuba, concluded 5-bromopyrrole-2-carboxylic acid (**67**) and 3,4-bromopyrrole-2-carboxylic acid (**68**).[64] The species *A. mauritiana* from Enewetak Atoll could produce methyl *N*-methyl-4,5-dibromopyrrole-2-carboxylate (**69**).[40]

From Fig. 7—agelongine (**70**) and *N*-methylagelongine (**71**), obtained from San Salvador Island specimens of *A. longissima* and *A. citrina*, respectively, contain an uncommon pyridinium ring in place of the imidazole nucleus as usually found in PIAs.[65,66] Manzacidin C (**72**), isolated from the Indonesian *Agelas* sp. collected from Likpan, is the first pyrrole alkaloid with a tetrahydropyrimidine unit from *Agelas* sponges.[67] In the bioactivity study, compound **70** displayed antiserotonergic activity tested *in vitro* on rat stomach fundus strip.[66] The chemistry study on Caribbean *A. dispar* collected near the Venezuelan island La Blanquilla yielded dispyrin (**73**), which is featured with a rare bromopyrrole tyramine motif and represent

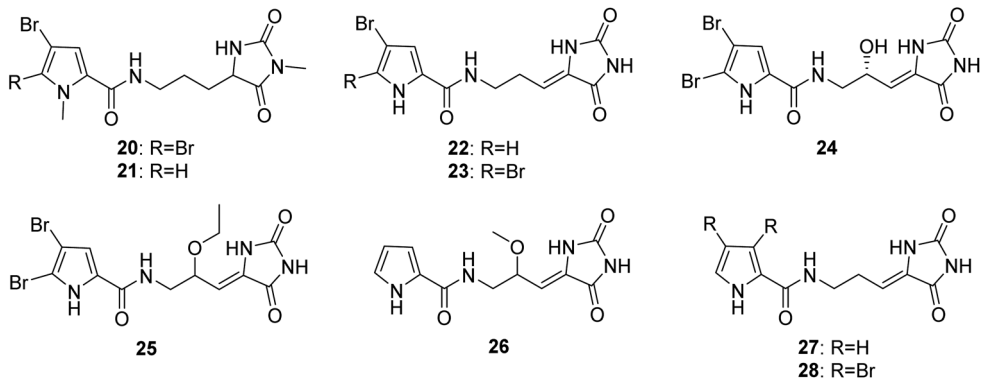


Fig. 3 Chemical structures of **20–28**.

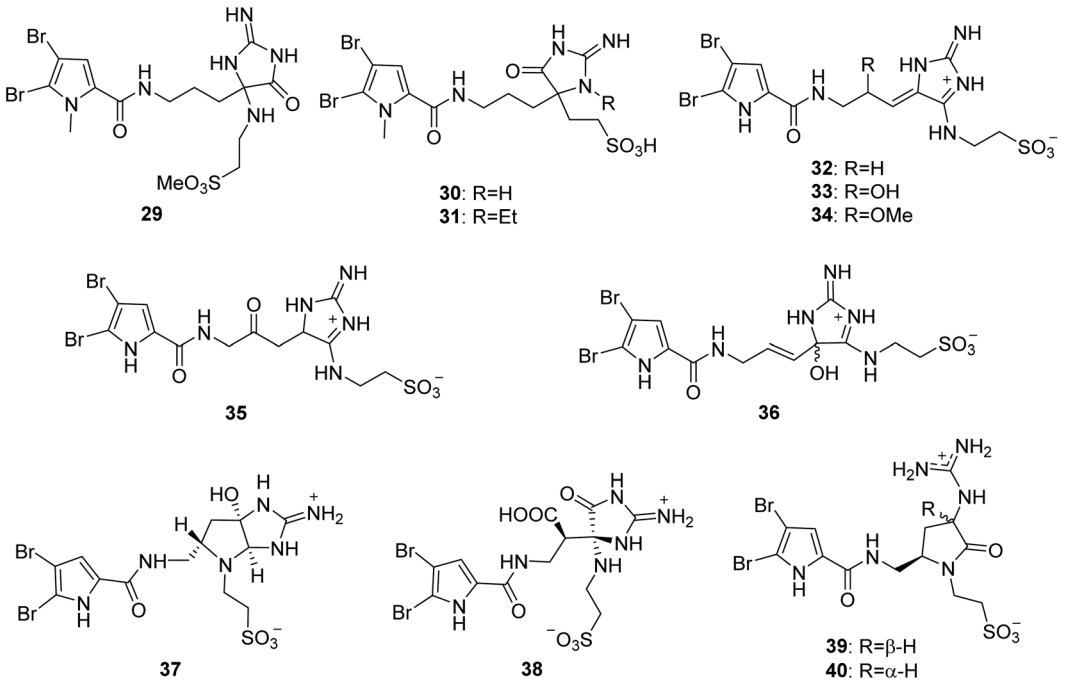


Fig. 4 Chemical structures of 29–40.

a notable variation from the oroidin family.[68] With no antibacterial or anticancer activity, compound 73 was a potent ligand and antagonist of several therapeutically relevant G protein-coupled receptors, the α_{1D} and α_{2A} adrenergic receptors and the H2 and H3 histamine receptors.[69,70] The Indonesian specimen *A. linnaei* collected from Thousand Islands could produce a number of linear pyrrole alkaloids without an imidazole moiety, including agelanesins A–D (74–77), *N*-methyl-4,5-dibromopyrrole-2-carboxylic acid (78), butanoic acid derivative of 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxamide (79), agelanin B (80), and mauritamide D (81). Compounds 74–77 are the first naturally occurring compounds featuring a halogenated tyramine unit linked to a brominated pyrrole unit. Furthermore, replacement of the bromine functionality by an

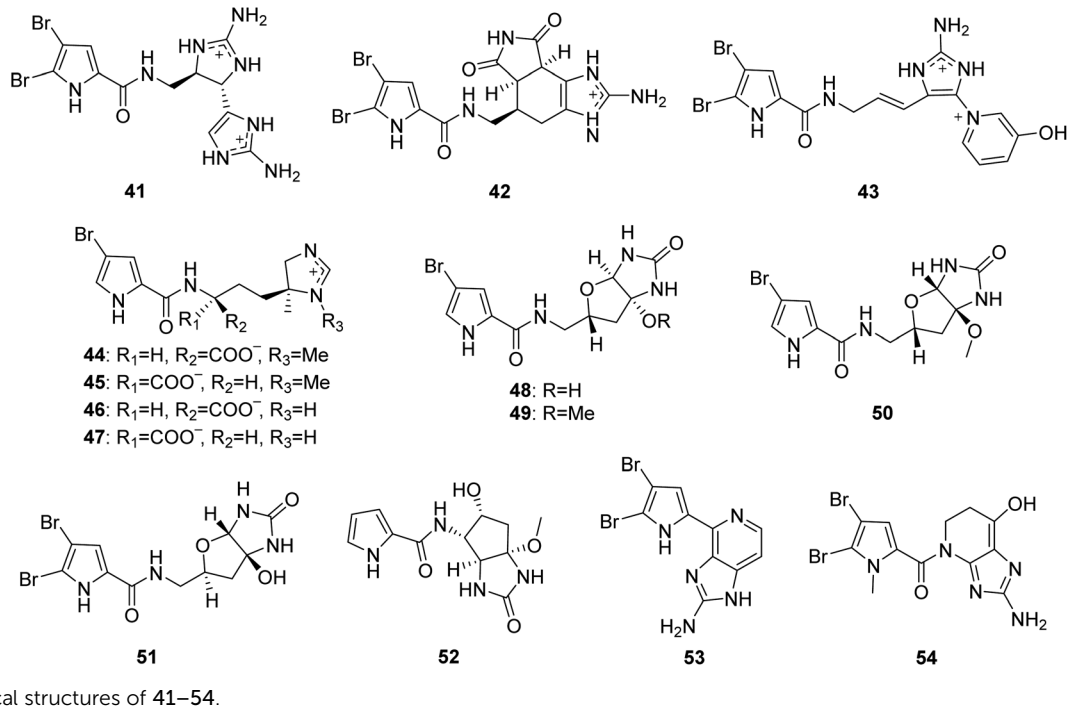


Fig. 5 Chemical structures of 41–54.

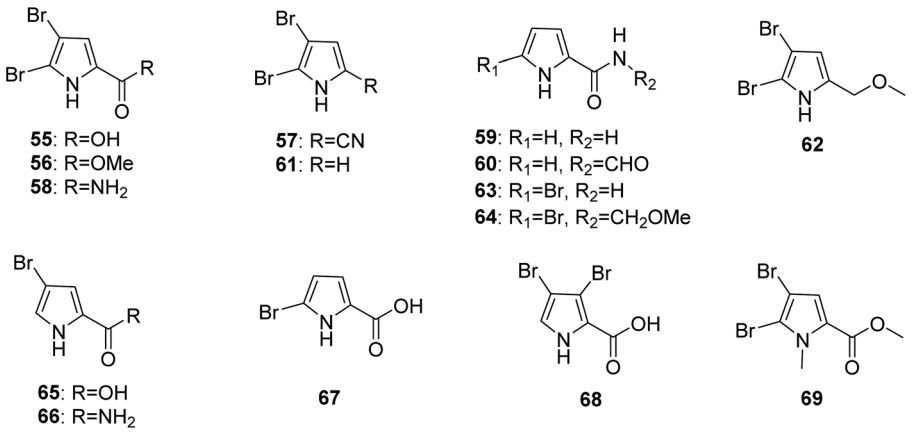


Fig. 6 Chemical structures of 55–69.

iodine residue in the tyramine moiety as found in 75 and 77 makes these compounds even more attractive. Among halogenated natural products, iodo-alkaloids are known as very rare compounds due to the fact that most reported halogenases catalyze reactions with chlorine and bromine donors.[71] Compounds 74–77 were found to have mild cytotoxic activity against L5178Y mouse lymphoma cells (IC_{50}, 9.25–16.76 μM).[48] The sponges *A. wiedenmayeri* collected off the coast of Florida Keys and Okinawan *Agelas* sp. contained 4-bromopyrrole-2-carboxyhomoarginine (**82**)[72] and mukanadin E (**83**),[42] respectively. Compound **82** is of interest because it does not correspond to the proposed biosynthesis of the oroidin-like alkaloids and may be alternatively a biosynthetic precursor of oroidin/hymenidin related alkaloids.[72] Pyrrolosine (**84**), comprised by two symmetric 4,5-dibromopyrrole-2-carboxamide moieties was discovered from Mediterranean *A. oroides*, collected in Tel Aviv.[27]

From Fig. 8—*Agelas* sponges from the Xisha Islands were an excellent source of structurally novel pyrrole alkaloids without an imidazole moiety, including 4-bromo-*N*-(butoxymethyl)-1*H*-pyrrole-2-carboxamide (**85**) from *A. mauritiana*,[73] 3-oxethyl-4-[1-(4,5-dibromopyrrole-2-yl)-formamido]-butanoic acid methyl ester (**86**) and 2-oxethyl-3-[1-(4,5-dibromopyrrole-2-yl)-formamido]-methyl propionate (**87**) from *Agelas* sp.,[43]

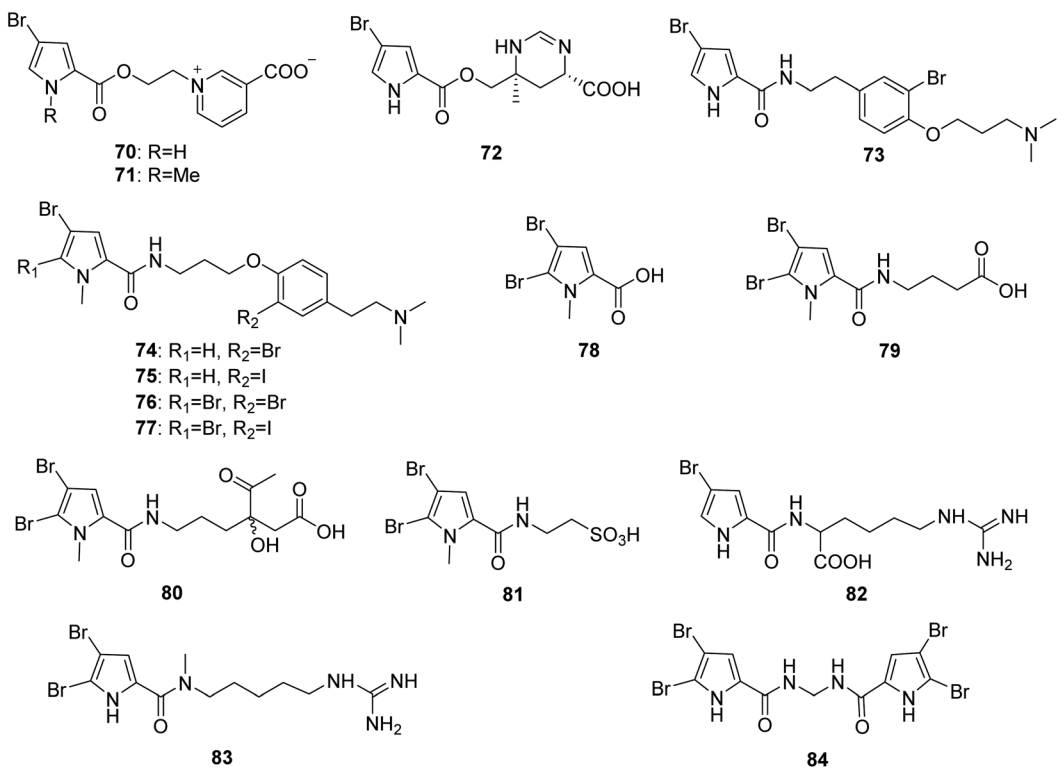


Fig. 7 Chemical structures of 70–84.

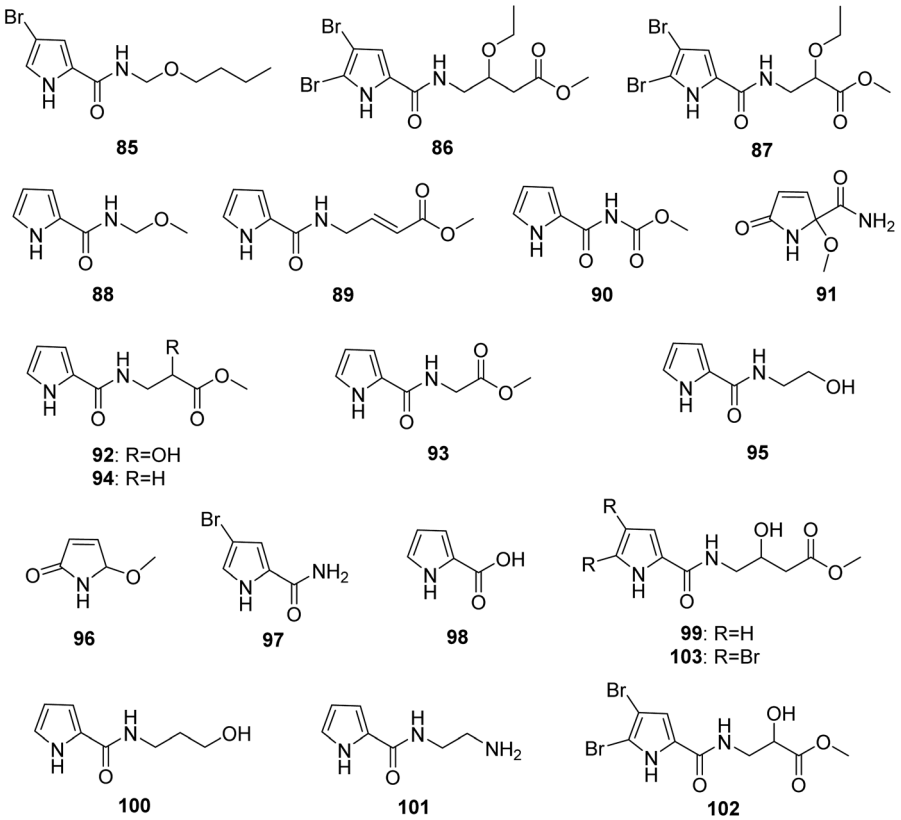


Fig. 8 Chemical structures of 85–103.

nakamurines A–C (**88–90**) and E (**91**) along with seven known congeners **92–98** from *A. nakamurai*,[44,45] nemoechine C (**99**) and the previously reported **100** and **101** from *A.* aff. *nemoechinata*.[56] Besides, exploration for specialized metabolites of Okinawan *Agelas* sp. resulted in isolation of two analogues, agesasines A (**102**) and B (**103**).[34]

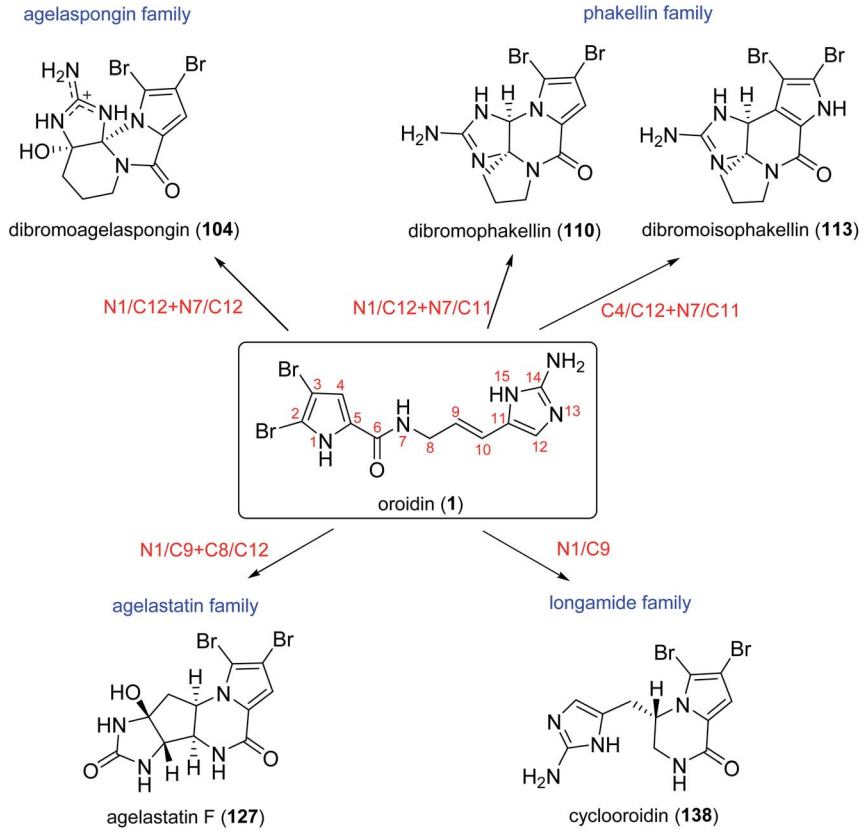
Among pyrrole alkaloids without an aminoimidazole moiety, the simple pyrroles (such as compounds **55–69** and **96–98**) may serve as precursors or intermediates involved in biosynthesis of this family of alkaloids, whereas other compounds containing an ester group at the end of the side chain (such as the Xisha Islands derived compounds **86**, **87**, **89**, **90**, **92–94** and **99**, and the Okinawa derived compounds **102** and **103**) might be artifacts during the extraction and isolation process.[34,43]

2.2. Fused cyclic pyrrole alkaloids

By analysing the structures of fused cyclic pyrrole alkaloids, we can easily find that the position of fusion usually occurred between C-1 and C-2, with the fused ring being five- or six-membered. Additionally, these alkaloids often share a carbonyl moiety in α-position to the bridgehead atom. These common structural features are attributed to the similar biosynthetic origin of these metabolites, which may be formed by oroidin (**1**) and its analogues through cyclization and oxidation processes.[74] With the amazing biosynthesis capacity, the sponges could produce an array of fused cyclic pyrrole alkaloids with diverse structure frameworks. According to different oroidin atoms involved in the linkage formation, these compounds can be classified into four groups: agelaspongin family (N1/C12 + N7/C12), phakellin family (N1/C12 + N7/C11 or C4/C12 + N7/C11), agelastatin family (N1/C9 + C8/C12) and longamide family (N1/C9) (Scheme 2).

2.2.1. Agelaspongin family. From Fig. 9—agelaspongins (**104–109**) are a family of tetracyclic PIAs usually found in *Agelas* sponges. Dibromoagelaspongin hydrochloride (**104**), the structure of which has been elucidated by X-ray analysis, was characterized from the Tanzania sea *Agelas* sp.,[75] and was later found to have the ability to stimulate growth of seedling roots of wheat *Triticum aestivum* L.[76] The Caribbean specimen of *A. dispar*, collected near the Venezuelan island La Blanquilla, could metabolize dibromoagelaspongin methyl ether (**105**).[68] LC-MS based metabolomics study of *A. oroides* collected from West Mediterranean Sea revealed that this sample contained a racemic monobromo analogue, monobromoagelaspongin (**106**),[77] while a further investigation of the Tel Aviv (East Mediterranean Sea) *A. oroides* yielded the optically active (−)-monobromoagelaspongin (**107**), (−)-11-deoxy-monobromoagelaspongin (**108**) and (−)-11-*O*-methylmonobromoagelaspongin (**109**).[27] From a biosynthetic perspective, these dibromo- and monobromoagelaspongins were thought to be formed through cyclization and oxidation of oroidin/hymenidin.[74,77,78]

2.2.2. Phakellin family. From Fig. 10—a series of phakellin family alkaloids (**110–122**) bearing a similar tetracyclic skeleton to that of agelaspongins, have been identified from *Agelas* sponges.



Scheme 2 The four groups of fused cyclic pyrrole alkaloids formed by different cyclization modes of oroidin (1).

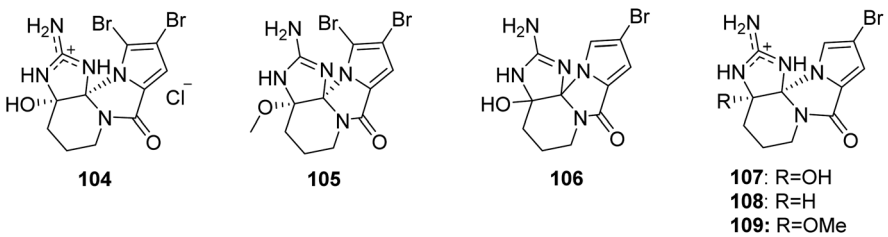


Fig. 9 Chemical structures of 104–109.

Dibromophakellin (**110**), previously described from the sponge *Phakellia flabellate*,[79] was obtained from Fijian *A. mauritiana*,[47] while an examination of the extract of Caribbean *Agelas* sp. collected off Sweetings Cay resulted in isolation of monobromoisophakellin (**111**), along with previously reported monobromophakellin (**112**) and dibromoisophakellin (**113**).[80] An antibiofilm assay of the four phakellins (**110–113**) indicated that dibromophakellin and dibromoisophakellin significantly reduced the biofilm formation of *E. coli*, which was more active than the analogues with monobromo substitution.[25] Additionally, results of antifeedant activity of these phakellins against *Thalassoma bifasciatum* suggested that the isophakelline skeleton showed a higher activity than that of phakelline skeleton, and bromination increases the antifeedant activity.[80] Two *N*-methylated phakellin derivatives, (−)-7-*N*-methyldibromophakellin (**114**) and 7-*N*-methylmonobromophakellin (**115**) from Papua New Guinean *Agelas* sp., were obtained using a combination of bioassay- and LC-MS guided fractionation. Compound **114** had moderate inhibitory effect towards 12-human lipoxygenase isozymes (IC_{50}, 10.7 ± 1.3 μM).[81] A racemic mixture, dibromohydroxyphakellin (**116**) purified from Thousand Islands *A. linnaei* is the first 12-OH analogue of the phakellin family alkaloids.[48] The report on an Indonesian sponge *Agelas* sp. collected in North Sulawesi, included 5-bromophakelline (**117**), as well as the known cylindradine A (**118**),[60] which was previously isolated from the sponge *Axinella cylindratus* and was found to display moderate inhibitory activity against the murine leukemia cell line P388.[82] Dibromocantharillin (**119**), firstly described from the sponge *Pseudaxinyssa cantharella*,[83] was later purified from the Kosrae Island *A. kosrae*.[84] Compound **119** not only showed antifungal activity against *Cladosporium herbarum*,[85] but also displayed a significant inhibitory effect towards glycogen synthase kinase 3β (IC_{50}, 3 μM).[86] Another two congeners, 9-*N*-methylcylindradine A (**120**) and 1-*N*-methylugibohlin (**121**), were isolated from Xisha Islands *A. nemoechinata*, together with the

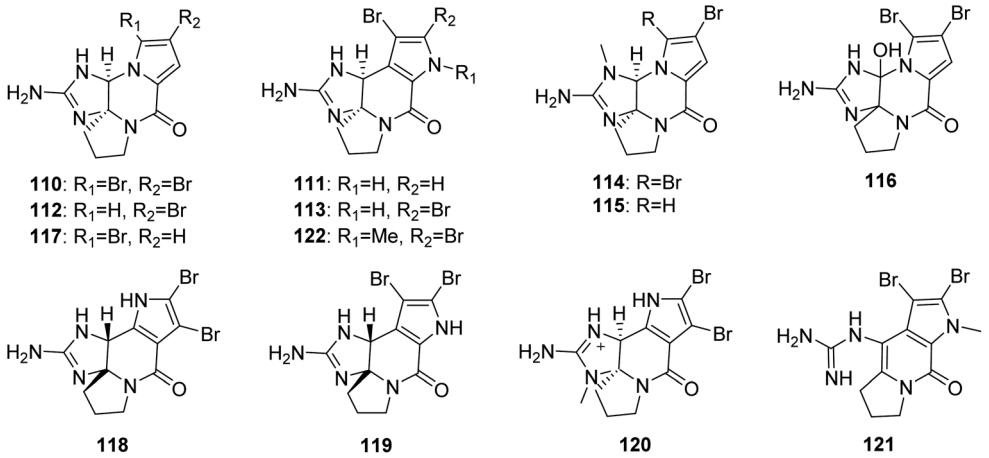


Fig. 10 Chemical structures of **110–122**.

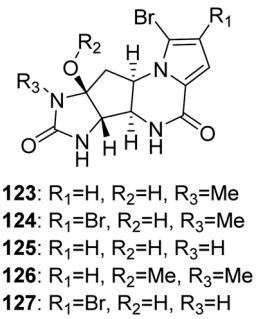


Fig. 11 Chemical structures of **123–127**.

known *N*-methyldibromoisophakellin (**122**),[46] which was firstly found in the sponge *Stylissa caribica*.[87]

2.2.3. Agelastatin family. From Fig. 11—as a most unusual member of fused cyclic pyrrole alkaloids, agelastatins A (**123**), B (**124**) and D–F (**125–127**) were discovered from New Caledonian *A. dendromorpha*, a species that has rarely been studied to date.[88–90] These compounds structurally featured by a densely functionalized cyclopentane ring bearing four contiguous stereogenic centers substituted with nitrogen functionalities, and their conformational preference and absolute configuration were determined *via* combined molecular modelling, nuclear magnetic resonance, and exciton splitting for diamide and hydroxyamide derivatives.[88] In addition to powerful cytotoxicity against a wide range of human cancer cell lines,[89,91] agelastatin A (**123**) could also selectively inhibit glycogen synthase kinase-3β[92] and was significantly toxic toward brine shrimp, larvae of beet army worm and corn rootworm.[93] Comparative bioassays with semisynthetic derivatives showed that for high cytotoxic activity of **123**, the unsubstituted OH–C(8a), H–N(5), and H–N(6) moieties are needed in the natural B/D transoid configuration.[94] For biogenetic considerations, the agelastatin skeleton could be derived from oroidin/hymenidin through subtle tautomerization and the dual reactivity induced by the 2-aminoimidazole portion of the structure.[74]

2.2.4. Longamide family. From Fig. 12—the most common structural class of *Agelas*-derived fused cyclic pyrrole alkaloids were longamide family alkaloids, which are characterized by a pyrroloketopiperazine nucleus and could be derived from the cyclization of an oxidized oroidin-like fragment. A typical bicyclic pyrrole alkaloid, longamide (**128**) with moderate antibacterial activity was discovered in *A. longissima*, collected from Little San Salvador Island.[95] Soon afterwards, the same research group found a mixture of enantiomers, longamide B (**129**), having moderate antibacterial activity against *B. subtilis* and *S. aureus*, from another Little San Salvador Island species *A. dispar*.[33] A follow-up antiprotozoal activity screening revealed that **129** was a promising trypanocidal and antileishmanial agent, with narrower therapeutic windows, while **128** was completely inactive against any protozoan parasite.[38] The monobrominated mukanadin C (**130**) and nonbrominated nemoechine B (**131**), were racemates obtained from the Okinawan *A. nakamurai* and the Xisha Islands *Agelas* aff. *nemoechinata*, respectively.[41,56] The Indonesian *A. nakamurai* collected from the Menjangan Island produced longamide C (**132**).[48] Bioassay-guided fractionation of the extract of the Xisha Islands *Agelas* sp. afforded another three new longamide family alkaloids, (±)-longamides D–F (**133–135**), together with the known (±)-hanishin (**136**) and (±)-longamide B methyl ester (**137**), previously discovered in the sponge *Acanthella carteri* collected from Hanish Islands[96] and *A. ceylonica* collected near the Mandapam coast,[97] respectively. In the experiment of antimicrobial activity, compound **137** possessed mild antibacterial activity against *B. subtitles*.[97] Furthermore, the individual enantiomers (+)-(9*S*,10*R*)-**133**, (−)-*S*-**134**, (+)-*R*-**135**, (+)-*R*-**136** and (+)-*R*-**137** exhibited significant antifungal activity against *C. albicans*, whereas no activity was observed for some linear pyrrole alkaloids, suggesting that the pyrroloketopiperazine core positively affected the antifungal activity. In addition, the conclusion that the absolute configuration at C-9 of the intramolecular cyclized metabolites had an appreciable effect on the antifungal activity was reached, owing to the fact that no antifungal activity was found for

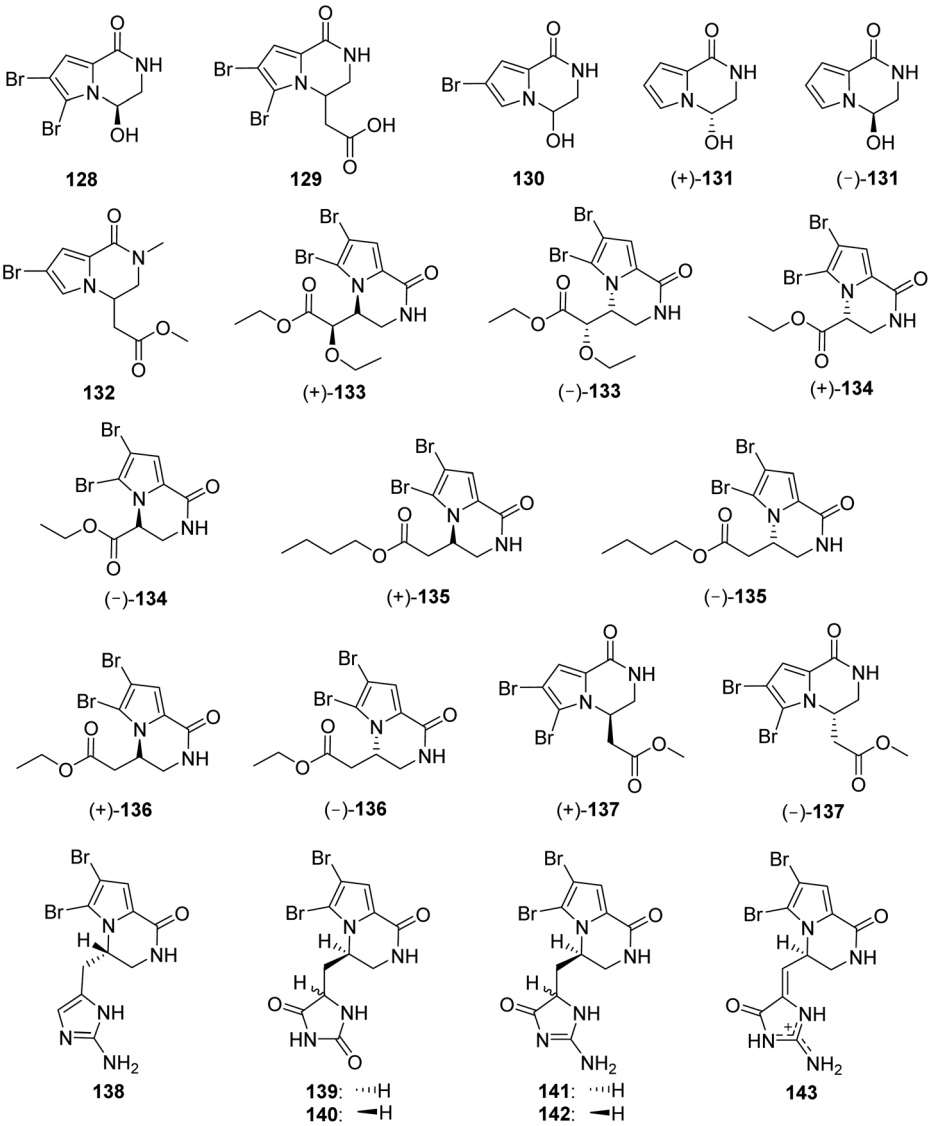


Fig. 12 Chemical structures of 128–143.

individual enantiomers (−)-(9*R*,10*S*)-**133**, (+)-*R*-**134**, (−)-*S*-**135**, (−)-*S*-**136** and (−)-*S*-**137**.[43]

The longamide family also includes compounds **138–143**, featured by a pyrroloketopiperazine nucleus linked with an additional aminoimidazole/aminoimidazolone/hydantoin moiety. Cyclooroidin (**138**), bearing a methylenaminoimidazole unit was isolated from Mediterranean *A. oroides*.[49] Diffusion-ordered NMR spectroscopy was applied for constituent analysis of crude pyrrole fractions from the Okinawan *Agelas* sp., resulting in the detection and isolation of two new stereoisomeric pyrroloketopiperazine derivatives with a hydantoin ring, namely agesamides A (**139**) and B (**140**).[98] The congeners having a methylenaminoimidazolone unit, agesamines A (**141**) and B (**142**), were obtained as an inseparable epimeric mixture from Indonesian *Agelas* sp.,[67] while a chemical investigation of the Mediterranean *A. oroides* yielded agesamine C (**143**).[27]

2.3. Dimeric pyrrole alkaloids

The dimeric pyrrole alkaloids are a growing class of alkaloids with exotic connectivity, unique structure, high nitrogen content, and exciting bioactivities. Structurally, some dimers were formed by cyclization of two monomers through a unique cyclic skeleton, such as cyclobutane, cyclohexene and pyrrolidine group, the others in which both monomers were linked by a single chemical bond, including C-8–C-15′, C-10–C-15′, C-11–C-15′ and C-15–C-15′. Although the biosynthesis of the complex pyrrole alkaloid dimers has been a subject of long debates, it is generally agreed that these metabolites could be derived from the three simple monomers (**1–3**) through oxidation, cyclization and dimerization reactions. For example, sceptrins featured by a cyclobutane core skeleton could be formed by [2 + 2] cycloaddition of the corresponding monomers, while ageliferins with a cyclohexene-based skeleton are formally the [4 + 2] cycloaddition products. Even after more than 40 years of research, the chemical diversity of dimer pyrrole alkaloids is

still expanding, which have attracted many researchers to explore their biogenetic origin and structural relations.[99]

From Fig. 13—the study of *A. sceptrum* collected at Glover Reef afforded the first natural pyrrole-imidazole dimer, named sceptrin (**144**), which was generated from two molecules of hymenidin through a cyclobutane frame.[100] However, until 2014, the mismatched chirality of sceptrin (**144**) was corrected by the intramolecular cycloaddition reaction in asymmetric syntheses, which was confirmed by the new crystal structure of sceptrin.[101] Several years later, the di- and debromo analogues (**145** and **146**), and monooxygenated analogues of sceptrin with an aminoimidazolinone moiety (**147** and **148**), together with three structurally unique dimers, ageliferin (**149**), bromoageliferin (**150**) and dibromoageliferin (**151**), were identified both from Caribbean sponges *A. conifera* and *A.* cf. *mauritiana*.[102,103] The ageliferins (**149–151**) with a rare cyclohexene-based skeleton were considered to be formed by [4 + 2] cycloaddition, although sceptrin-like alkaloids seem to be derived from [2 + 2] cycloaddition. In light of the revision of the absolute stereochemistry of **144**, the absolute stereochemistry of **149–151** was also reversed.[101] These metabolites were endowed with many valuable bioactivities. Compounds **144–151** were shown to be antiviral and antimicrobial and were active in barnacle settlement and biochemical prophage induction assays.[102,104,105] Oxysceptrin (**148**) and ageliferins (**149–151**) were a potent actomyosin ATPase activator.[106,107] As an anti-biofilm substance, compound **150** had the ability to inhibit the growth of marine bacteria with adhering properties.[108] Compounds **150** and **151** could also inhibit voltage-operated, but not store-operated calcium entry in phaeochromocytoma PC12 cells.[109] Additionally, Compounds **144**, **145**, **150** and **151** were revealed to be potent feeding deterrents against fish predation.[19] The first sceptrin-type alkaloid without bromine substitution was debromosceptrin (**152**), isolated from the Caribbean *A. conifer* collected in Belize.[110]

The sceptrin derivatives with only one aminoimidazole ring in the molecule, nakamuric acid (**153**) and its corresponding methyl ester (**154**), without the assignment of absolute configuration, were obtained from *A. nakamurai*, collected near the island of Ambon, and both the compounds were shown to be active against the bacteria *B. subtilis*.[105] A chemical investigation of *Agelas* sp. collected from Xisha Islands afforded several dimers, including hexazosceptrin (**155**) with a rare cyclohexane-fused-cyclobutane skeleton, two sceptrin derivatives without any aminoimidazole substitution, agelestes A (**156**) and B (**157**), along with (9*S*,10*R*,9′*S*,10′*R*)-nakamuric acid (**158**), of which the

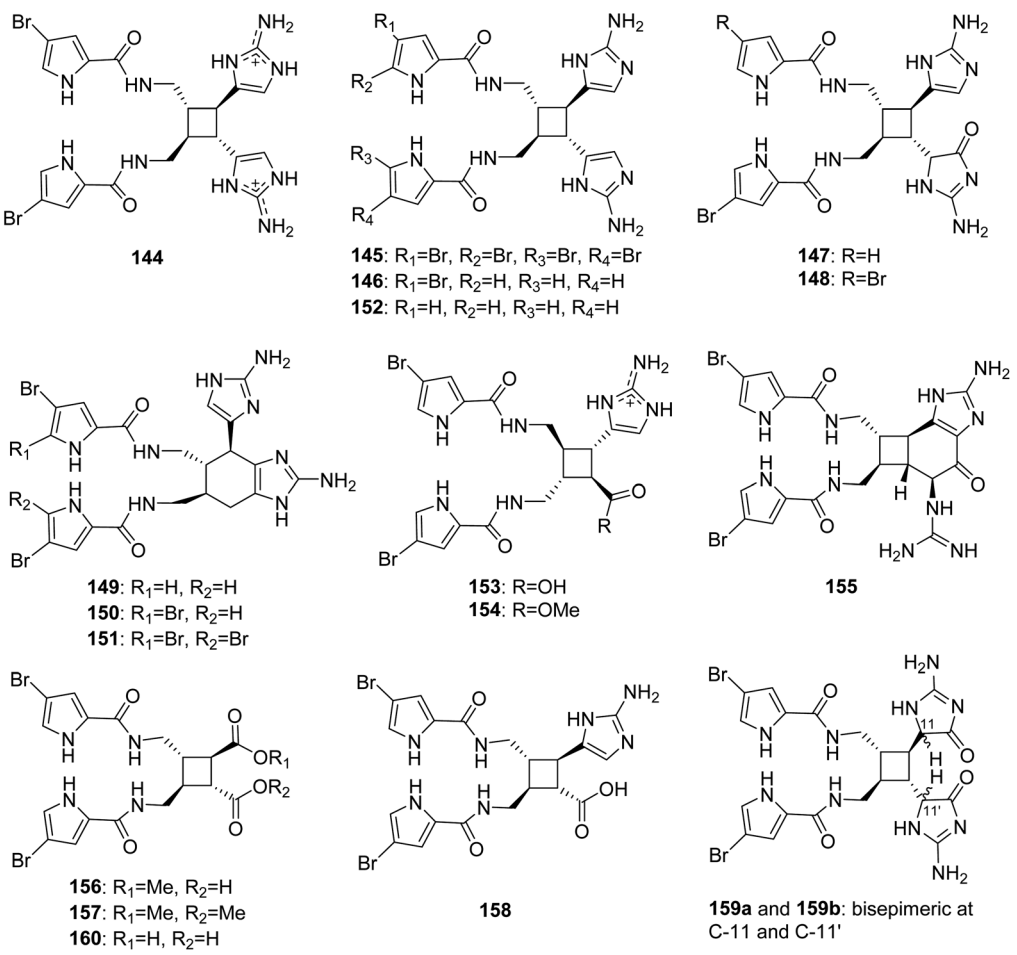
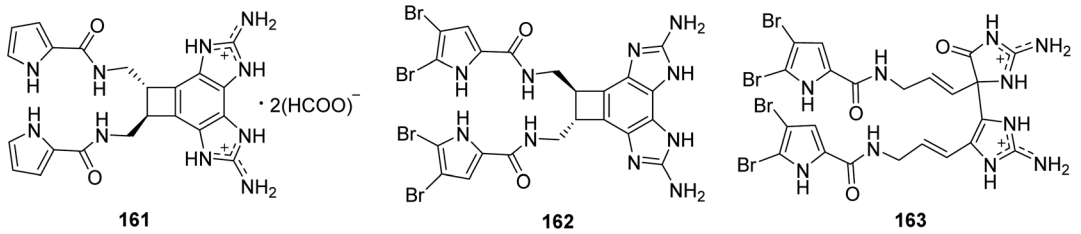


Fig. 13 Chemical structures of **144–160**.



161 162 163

Fig. 14 Chemical structures of **161–163**.

absolute configuration was assigned for the first time by comparison of experimental and calculated electronic circular dichroism (ECD). A subsequent bioactivity evaluation revealed that compounds **155** and **158** had moderate antimicrobial activity against *S. aureus* with the same MIC value of 16 μg mL^{-1}.[111] A purple elongated species that has rarely been studied to date, identified as *A. kosrae*, collected from Kosrae Island, was revealed to produce dioxysceptrin (**159**) and ageleste C (**160**). Compound **159**, the dioxygenated form of sceptrin with two aminoimidazolinone moieties, was found to exist as a mixture of α-amido epimers and the absolute configuration was determined by ECD calculation. Both compounds **159** and **160** exhibited weak cytotoxicity against several cancer cell lines (including K562, A549, HCT116, MDA-MB-231, SNU 638 and SK-Hep-1). In addition, compounds **159** and **160** displayed moderate antiangiogenic and isocitrate lyase inhibitory activities, respectively.[84]

From Fig. 14—two unusual benzocyclobutane-containing natural products, benzosceptrin A (**161**) from Solomon Islands *A.* cf. *mauritiana*,[112] and its brominated analogue benzosceptrin C (**162**) from both the Okinawan *Agelas* sp.[113] and New Caledonian *A. dendromorpha*,[90] have been identified. The bioactivities study revealed that compound **162** not only had antimicrobial activity against some pathogenic and environmental bacteria, quorum sensing inhibitory activity against *Chromobacterium violaceum*, but also inhibited the biofilm formation in *Pseudomonas aeruginosa* PAO1.[27,113] Bioassay-guided isolation of extract from *A. mauritiana* collected off Hachijo-jima Island, led to the isolation of a new type of oxygenated oroidin dimer, mauritiamine (**163**), obtained as a racemate. Unlike the dimerization through a cyclobutane group for sceptrin-like alkaloids, compound **163** was constructed by two monomers with a linkage between C-11 in aminoimidazolinone unit and C-15′ in the aminoimidazole unit. Biological studies have identified that compound **163** could inhibit larval metamorphosis of the barnacle *Balanus Amphitrite* (ED_{50}, 15 μg mL^{-1}), and exhibit moderate antibacterial activity against *Flavobacterium marinotypicum*.[17]

From Fig. 15—twenty-two dimeric PIAs named nagelamides (**164–185**) have been identified from *Agelas* sponges. The Okinawan *Agelas* sp. was the source of nagelamides A–H (**164–171**). Of which, nagelamides A–D (**164–167**) were generated by two oroidin-type subunits through a single bond between C-10 and C-15′, while nagelamide H (**171**) with a taurine residue has a C-11–C-15′ linkage similar to **163**. In the bioactivity assays, compounds **164–171** exhibited antibacterial activity against *M. luteus*, *B. subtilis* and *E. coli* (MIC, 2.08–33.3 μg mL^{-1}). Compounds **164**, **170** and **171** also inhibited protein phosphatase type 2A (IC_{50}, 48, 13 and 46 μM, respectively).[30] In addition, from the Okinawan collections of *Agelas* sp., the same research group obtained nagelamides I–L (**172–175**) and 2,2-didebromonagelamide B (**176**).[114–116] Nagelamide I (**172**), a symmetric dimer of hymenidin, is the first example of PIAs consisting of two subunits connected with an uncommon connection of single bond between C-15 and C-15′ in the imidazole rings,[114] while nagelamide J (**173**) represents the first pyrrole derivative with a cyclopentane-fused aminoimidazole system,[115] nagelamide K (**174**) possesses a rare piperidinoiminoimidazolone ring with an aminoimidazole ring and a taurine unit, and nagelamide L (**175**) is a unique dimeric pyrrole alkaloid containing an ester linkage.[116] Results of bioactivity tests suggested that compound **173** exhibited antimicrobial activity against *S. aureus* and *C. neoformans* (MIC, 8.35 and 16.7 μg mL^{-1}, respectively),[115] while compounds **174** and **175** were able to inhibit the growth of *M. luteus* (MIC, both 16.7 μg mL^{-1}).[116] Further studies on the Okinawan *Agelas* sponges, also by Kobayashi's group, have yielded nagelamides O–R (**177–180**).[42,117] The structure of compound **177** is notable for bearing an uncommon perhydrocyclopenta-imidazo-azolo-imidazole carbon skeleton,[42] while **179** contains a rare pyrrolidine ring, and **180** is the first example of bromopyrrole alkaloid having an oxazoline ring.[117] Compound **177** was found to have weak antibacterial activity against *B. subtilis*, *M. luteus* and *S. aureus* (MIC, 33.3 μg mL^{-1}, each),[42] while compounds **179** and **180** were active against *B. subtilis*, *T. mentagrophytes*, *C. neoformans*, *C. albicans* and *A. niger* (MIC, 6–13 μg mL^{-1}).[117] Two non-brominated congeners, nagelamides S (**181**) and T (**182**), biogenetically starting from clathrodin were sourced from Solomon Islands collection of *A.* cf. *mauritiana*.[112] Kobayashi's group carried out a continued study on Okinawan *Agelas* sp., yielding three new structurally intriguing pyrrole-imidazole dimers, nagelamides X–Z (**183–185**). The racemates **183** and **184** both possess a rare tricyclic skeleton consisting of spiro-bonded tetrahydrobenzaminoimidazole and amino-imidazolidine moieties and seem to be derived from oroidin and taurodispacamide A by [4 + 2] cycloaddition, while compound **185**, with the connectivity of C-8 to C-15′ between each oroidin unit, is the first pyrrole alkaloid involving the C-8 position in dimerization. Compounds **183–185** exhibited antimicrobial activities against some bacteria and fungi, with compound **185** being the most potent (the IC_{50} of **185** for *C. albicans* was 0.25 μg mL^{-1}).[118]

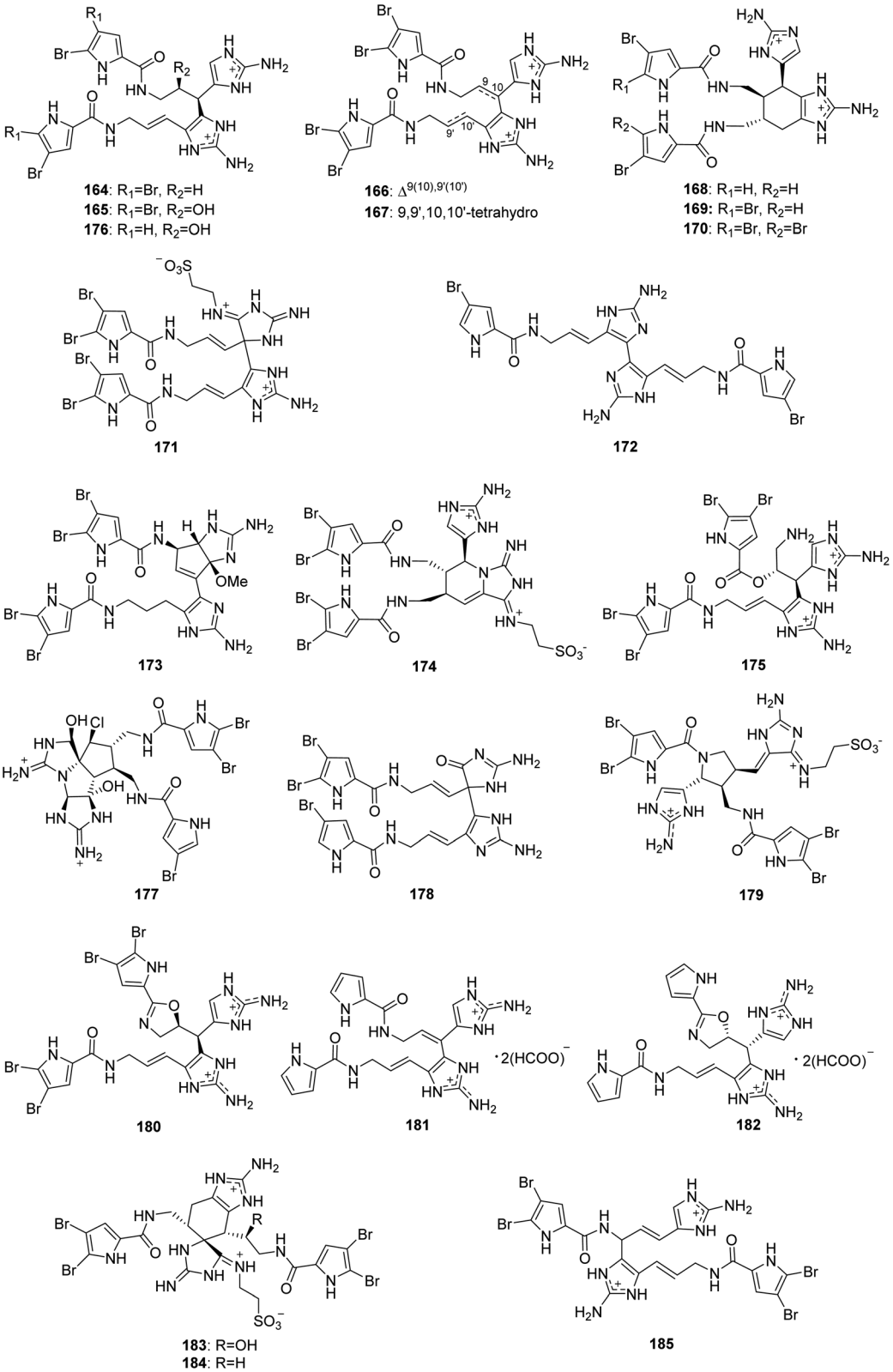


Fig. 15 Chemical structures of **164–185**.

From Fig. 16—the specimen *A. citrina* collected at San Salvador in the Bahamas was revealed to metabolize four hymenidin-type dimers that have different linkages between each monomeric unit, namely citrinamines A–D (**186–189**). Compounds **186** and **187** are closely related to **163** in which the monomeric units are connected by a single bond between C-11

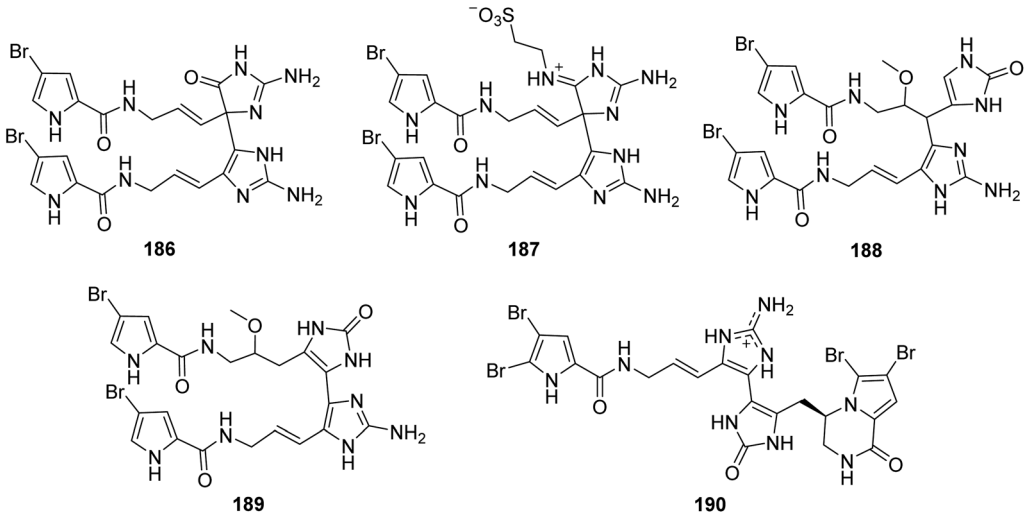


Fig. 16 Chemical structures of **186–190**.

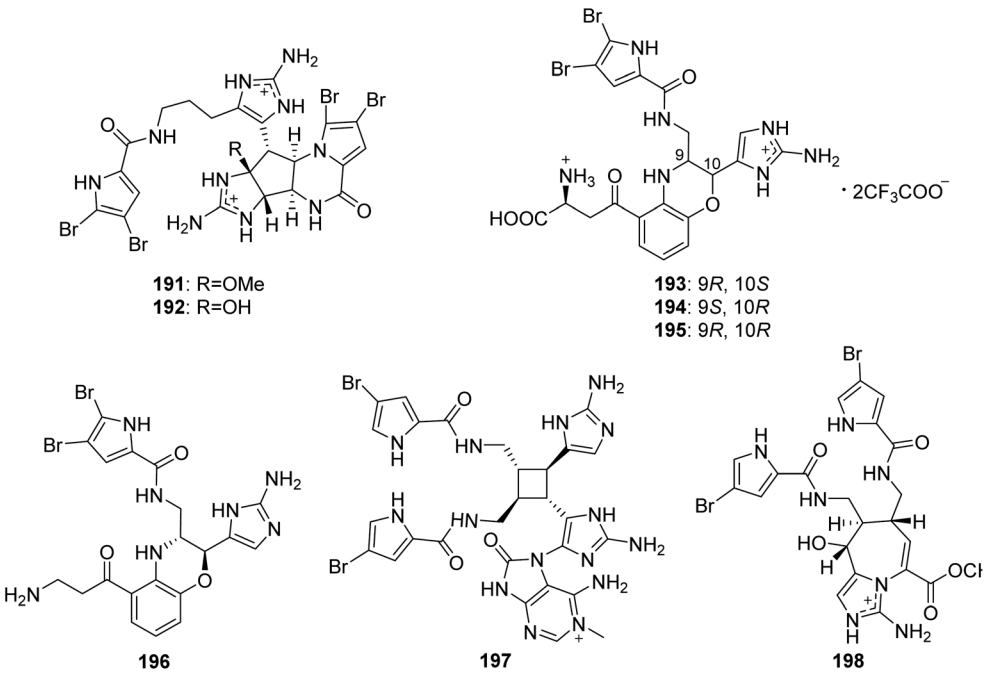


Fig. 17 Chemical structures of **191–198**.

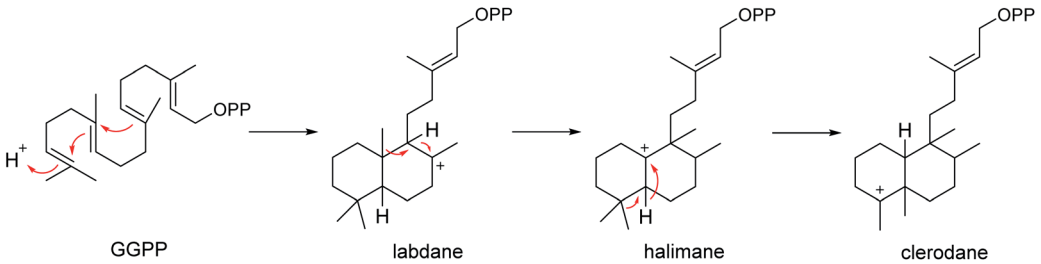
and C-15′. Whereas compounds **188** and **189** show a different connection of the two monomeric hymenidin units (C-10/C-15′ and C-15/C-15′, respectively). In antimicrobial assays, the inhibitory effect against *Mycobacterium phlei* were observed for **187–189**, while there was also an activity of **188** against *M. luteus*.[65] The Mediterranean Sea *A. oroides*, collected off the Tel Aviv coast, contained another dimeric pyrrole alkaloid with a linkage of C-15 and C-15′ between each monomeric unit, namely dioroidamide A (**190**), which was constructed by the co-isolated linear monomer oroidin and fused cyclic monomer agesamine C derivative.[27]

From Fig. 17—Kobayashi's group also obtained five unique unsymmetrical pyrrole-imidazole dimers, agelamadins A–E (**191–195**), from the Okinawan *Agelas* sp.[119,120] Of which, the racemates **191** and **192**, with an agelastatin-like tetracyclic subunit and an oroidin-like linear subunit in common, exhibited antimicrobial activity against *B. subtilis* (MIC, 16 μg mL^{-1}, each), *M. luteus* (MIC, 4.0 and 8.0 μg mL^{-1}, respectively) and *C. neoformans* (IC_{50}, 8.0 and 4.0 μg mL^{-1}, respectively).[119] The stereoisomeric **193–195** possess hybrid structures of oroidin and 3-hydroxykynurenine connected through a dihydro-1,4-oxazine moiety and their structure and absolute configuration were elucidated on the basis of spectroscopic analysis as well as

application of a phenylglycine methyl ester method and ECD calculation. Biosynthetically, compounds **193–195** have been emerged as the first example for pyrrole alkaloids comprising oroidin and a tryptophan derivative to be reported. In antimicrobial screening, compounds **193** and **195** showed antimicrobial activity against *C. neoformans* (IC_{50}, 32 μg mL^{-1}, each).[120] A closely related compound, decarboxyagelamadin C (**196**) has been sourced from Bahamas *A. sceptrum*, together with 15′-oxoadenosceptrin (**197**), which is the first pyrrole-imidazole derivative to incorporate adenine.[121] Another unusual dimer, agelanemoechine (**198**), with an unprecedented imidazo [1,5-*a*] azepin nucleus was isolated from Xisha Islands *A. nemoechinata*. A possible biogenetic pathway of compound **198** was proposed starting from sceptrin through a key step of ring expansion reaction by rearrangement, which was different from the [2 + 2] and [4 + 2] cycloaddition encountered in the previously reported pyrrole alkaloid dimers. It is also worth noting that compound **198** showed a strong *in vivo* promoting angiogenesis activity in a zebrafish model.[122]

3. Terpenoid alkaloids

Since Cullen and Devlin reported the isolation of agelasine, a quaternary 9-*N*-methyladenine derivative of an unidentified diterpene as a constituent of *A. dispar* in 1975,[123] a number of unusual terpenoid alkaloids characterized by a polar functionality attached to a terpenoid moiety, have been found from *Agelas* sponges. Included among these were 9-*N*-methyladeninium terpenoids (*i.e.*, agelasines, agelines, nemoechines) and terpenoids



Scheme 3 Origin of labdane, halimane and clerodane diterpenoid skeletons from geranylgeranyl diphosphate (GGPP).

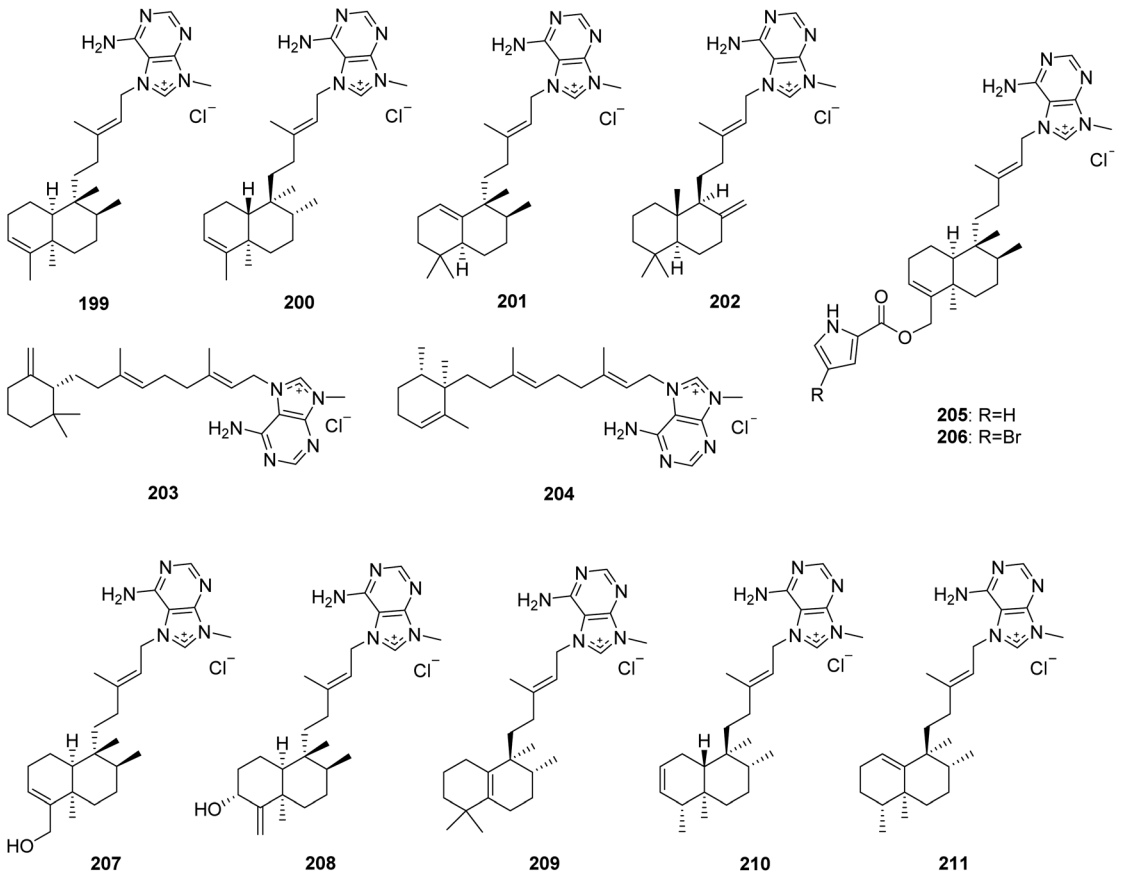


Fig. 18 Chemical structures of **199–211**.

of hypotaurocyamine (*i.e.*, agelasidines). The former usually carry a bicyclic diterpenoid skeleton (including clerodane, labdane and halimane) connected to the methyladenine moiety, while the latter featured by a branched diterpene with a hypotaurocyamine group. As the members of diterpenes, the 9-*N*-methyladeninium terpenoids likely arise from *E*,*E*,*E*-geranylgeranyl diphosphate (GGPP) to form the bicyclic diterpenoid moiety (Scheme 3).[124,125] The presence of the unusual adenine in the structure made these compounds attractive targets in biological and chemical research. Recently there has been enormous interest in the bioactivities of 9-*N*-methyladeninium terpenoids owing to their noteworthy biological activities, including cytotoxic and antimicrobial activity and their action as Na^+,K^+-ATPase inhibitors.[124] In contrast to the structural variety of the 9-*N*-methyladeninium terpenoid, only 10 terpenoids of hypotaurocyamine have been reported to date.

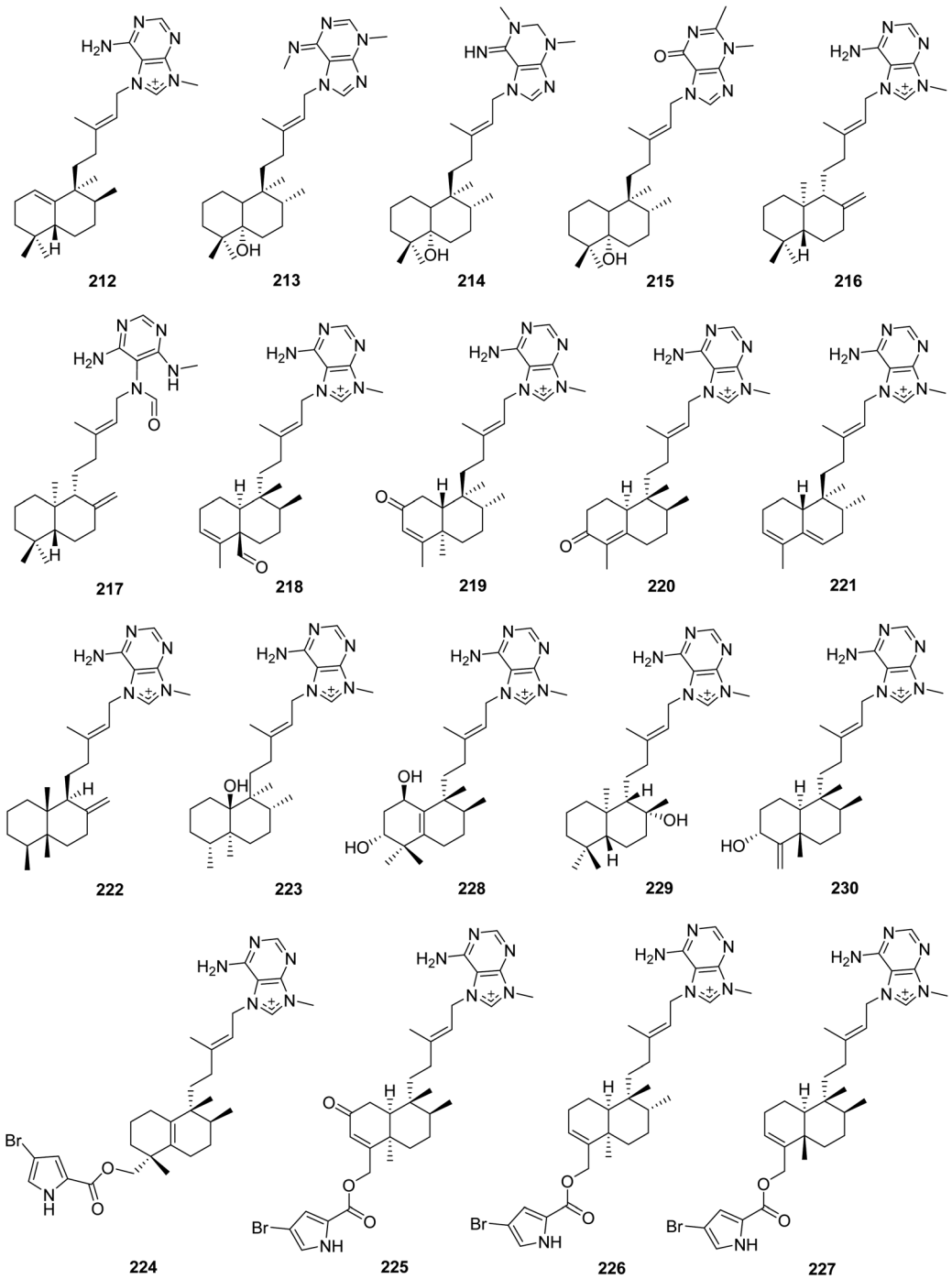


Fig. 19 Chemical structures of 212–230.

3.1. 9-*N*-Methyladeninium terpenoids

From Fig. 18—agelasines A–F (**199–204**), possessing inhibitory effects against Na^+,K^+-ATPase, were isolated from Okinawan *A. nakamurai*, and their structures were solved by a comprehensive combination of spectral data and chemical conversions to establish the absolute configurations.[126–128] Compounds **199** and **200** have a bicyclic clerodane diterpenoid moiety, while **201** and **202** possess a halimane and labdane diterpenoid skeleton, respectively, and **203** and **204** are unusual monocyclic diterpenoids of 9-*N*-methyladeninium. An additional bioactivity study suggested that compound **203** had antituberculosis activity against *Mycobacterium tuberculosis*,[129] while compound **204** displayed a wide range of bioactivities including antimicrobial effect against *S. aureus*, *B. subtilis* and *C. albicans*, toxicity to goldfish *Carassius auratus*, antituberculosis activity against drug resistant *M. tuberculosis*, antitrypanosomal action against *Trypanosoma brucei*, as well as cytotoxicity against Jurkat

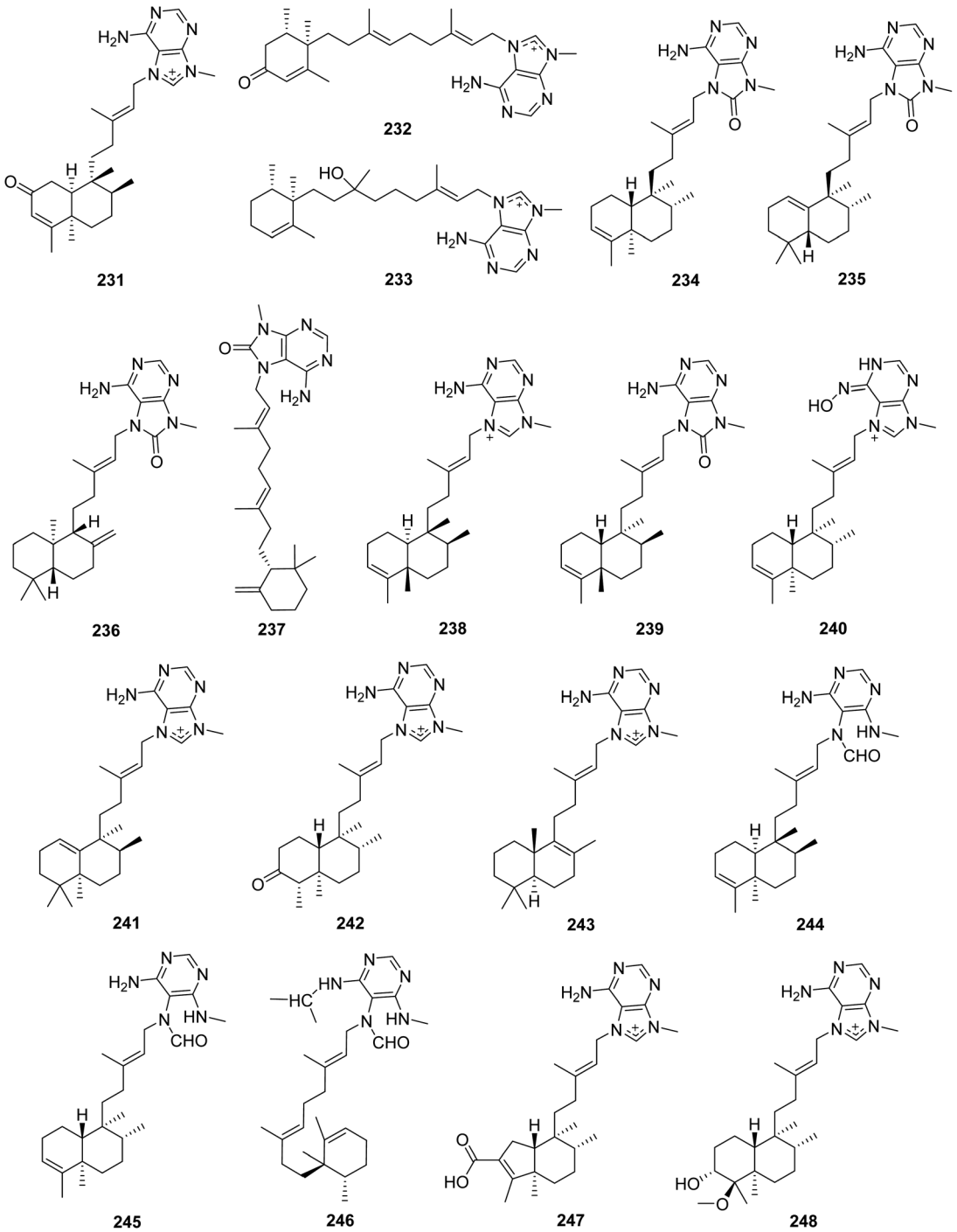


Fig. 20 Chemical structures of **231–248**.

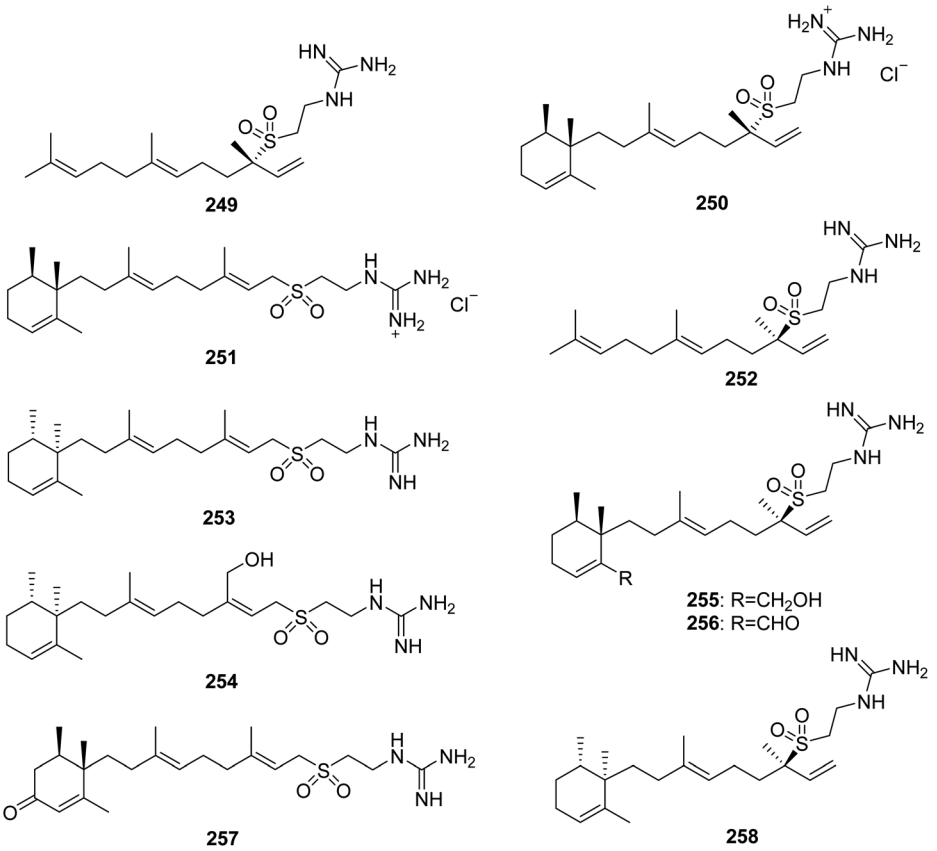


Fig. 21 Chemical structures of 249–258.

cells.[130,131] The specimen of *Agelas* sp. collected at Palau was found to yield agelines A (agelasine F, **204**) and B (**205**). It is interesting to note that the latter compound showed clerodane diterpene merged with a pyrrole ring, not yet encountered in the family of 9-*N*-methyladeninium terpenoid alkaloids.[132] A brominated analogue of **205**, named agelasine G (**206**), exhibiting cytotoxic activity against murine lymphoma L1210 cells (IC_{50}, 3.1 μg mL^{-1}), was obtained from Okinawan *Agelas* sp.[133] Further studies have identified compound **206** as being able to activate the insulin signaling pathway in Huh-7 human hepatoma cells by inhibiting PTP1B activity, while **205** exerted no inhibitory effect against PTP1B, suggesting that a Br atom plays a prominent role in the inhibition of PTP1B activity.[134,135] Agelasines H (**207**) and I (**208**), both bearing a clerodane skeleton, were discovered from *Agelas* sp., collected at Yap Island.[136] The Solomon Islands specimen of *A.* cf. *mauritiana* could metabolize agelasines J–L (**209–211**). Compound **209** possesses a halimane diterpenoid moiety, while compounds **210** and **211** are clerodane diterpenoid alkaloids. All the three metabolites (**209–211**) displayed antimalarial activity against *Plasmodium falciparum* with respective IC_{50} values of 6.6, 8.3 and 18 μM, and a low cytotoxicity on MCF7 human breast cancer cells.[137]

From Fig. 19—a study on Pohnpei collection of *A. mauritiana* afforded epi-agelasine C (**212**), which was an antifouling substance active against macroalgae.[138] The stereochemistry and absolute configuration of the halimane diterpenoid portion in compound **212** and the isomer agelasine C (**201**) were later reversed on the basis of chemical synthesis.[139] The Eniwetak species *A. mauritiana* gave agelasimines A (**213**) and B (**214**),[140] as well as an unusual purino-diterpene (**215**), the structure of which was determined by X-ray analysis.[141] Compounds **213** and **214** not only had cytotoxic effect on L1210 leukemia cells, but also served as smooth muscle relaxants, Ca^{2+} channel antagonists and α1 adrenergic blockers.[140,142] Chemical investigation of Indonesian *A. nakamurai* collected from Menjangan Island yielded (−)-agelasine D (**216**) and its analogue **217**.[48] Compound **217** was originally proposed as an oxime derivative and revised later as a formamide derivative of **216**, thus renamed agelamide.[143,144] Both compounds **216** and **217** exhibited cytotoxicity against L5178Y mouse lymphoma cells (IC_{50}, 4.03 and 12.5 μM, respectively), and were toxic to the larvae rather than just

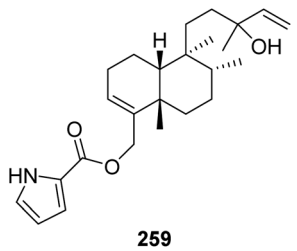


Fig. 22 Chemical structure of 259.

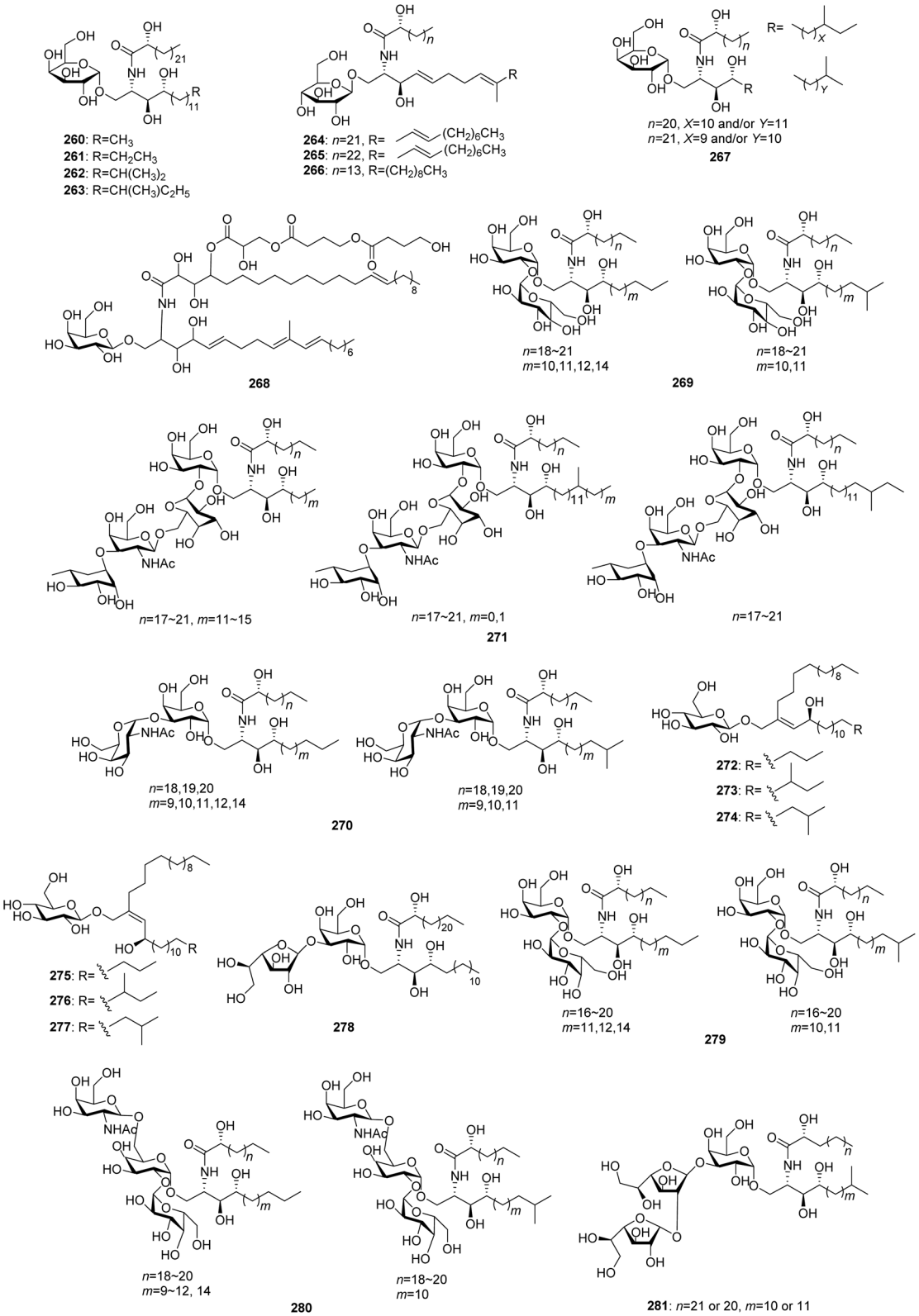


Fig. 23 Chemical structures of 260–281.

inhibiting settlement of *Balanus improvisus* in an antifouling bioassay.[48] Additionally, the therapeutic potential of agelamide (**217**) as a natural radiosensitizer in hepatocellular carcinoma models has been also revealed.[144] The specimen *Agelas* sp. from Papua New Guinea was the source of another two agelasines with a clerodane diterpenoid moiety, agelasine M (**218**) and 2-

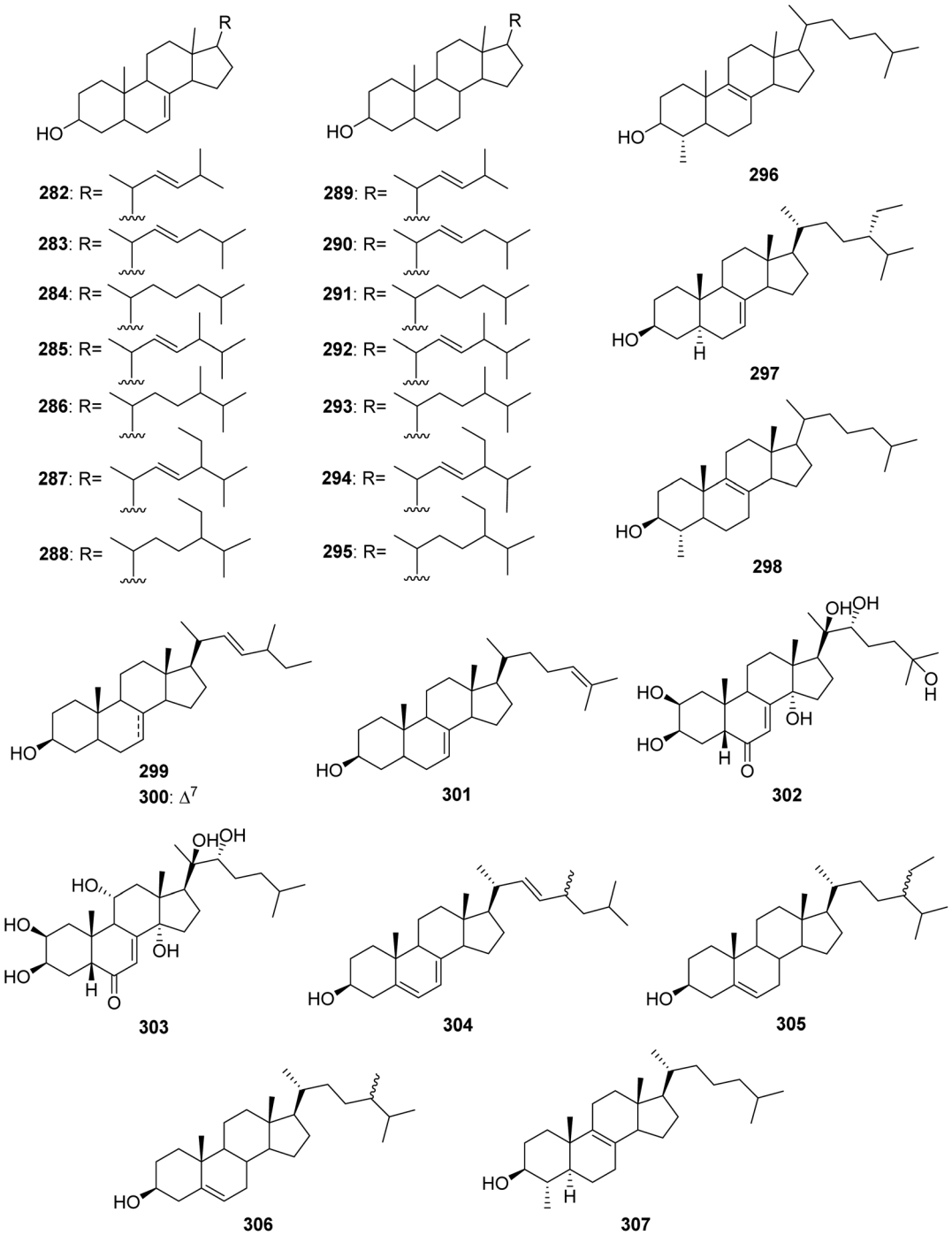


Fig. 24 Chemical structures of 282–307.

oxo-agelasine B (**219**), along with the unusual norditerpenoid-agelasines, gelasines A (**220**) and B (**221**), among which compound **218** possessed significant inhibitory action against *T. brucei* (IC_{50}, 3.0 μg mL^{-1}) as well as mild cytotoxicity against Jurkat cells (IC_{50}, 25 μg mL^{-1}).[130] An unusual thelepogane diterpene alkaloid (**222**) and agelasine N (**223**) with a hydroxy-substituted clerodane diterpenoid scaffold were reported from Papua New Guinean collections of *A. nakamurai*[145] and *A. citrina*,[146] respectively. Subsequently, Kobayashi's group described the isolation of agelasines O–U (**224–230**) from Okinawan *Agelas* sp. and the antimicrobial activity of compounds **224–227** and **229**. The structures of **224–227** are notable for being 9-*N*-methyladenine diterpene alkaloids consisting of a bromo-pyrrole unit. In terms of the diterpenoid part, compound **224** has a halimane skeleton, while compounds **225–227** are clerodane diterpenoids. Compounds **228–230** contain a halimane, labdane, and clerodane skeleton, respectively.[147]

From Fig. 20—three new agelasine derivatives, 2-oxoagelasine A (**231**), 2-oxoagelasine F (**232**) and 10-hydro-9-hydroxyagelasine F (**233**), together with series of known agelasines were isolated from Okinawan *A. nakamurai*. Compound **233** was found to inhibit the growth of *Mycobacterium smegmatis*, while the 2-oxoagelasines (**231** and **232**) exhibited markedly reduced activity against *M. smegmatis*, indicating that oxidation at the C-2 position of diterpenoid moiety was unfavorable for antimycobacterial activity of 9-*N*-methyladenine diterpenes.[135] The alkaloid constituents of *A. mauritiana* collected from Xisha Islands were described and consisted of four 8′-oxo agelasines, namely (−)-8′-oxo-agelasines B–E (**234–237**), accompanied by (+)-agelasine B (**238**), agelasine V (**239**), and an oxime derivative ageloxime B (**240**). Further biological studies have identified that compound **238** exhibited moderate cytotoxicity toward the cancer cell lines PC9, A549, HepG2, MCF-7 and U937 (IC_{50}, 4.49–14.07 μM), and also inhibited the growth of a panel of methicillin-resistant *S. aureus* clinical isolates (MIC_{90}, 1–2 μg mL^{-1}), while compound **240** showed antimicrobial activity against *Cryptococcus neoformans*, *S. aureus* and methicillin-resistant *S. aureus* and antileishmanial activity against *Leishmania donovani*. A subsequent structure–activity relationship analysis for 9-*N*-methyladenine diterpene alkaloids revealed that the presence of carbonyl at C-8′ in adenine can reduce antibacterial and cytotoxic activities.[73,148] The species *A. nakamurai*, also collected from Xisha Islands could metabolize isoagelasine C (**241**), showing mild cytotoxic activities against HL-60, K562 and HCT-116 tumor cell lines as well as antimicrobial activities against *C. albicans* and *Proteusbacillus vulgaris* (MIC, 4.69 and 18.75 μg mL^{-1}, respectively).[44] Another Xisha Islands specimen of *A.* aff. *nemoechinata* produced nemoechines D ((−)-8′-oxo-agelasine B, **234**), F (**242**) and G (**243**), with nemoechines D (**234**) and G (**243**) possessing cytotoxicity against HL-60 (IC_{50}, 9.9 μM) and Jurkat cell lines (IC_{50}, 17.1 μM), respectively.[56,149] A bioassay-directed separation of the extract of *A. axifera*, collected from the Republic of Palau, allowed the identification of three unusual diterpenes with a seco-methyladenine moiety, axistatins 1–3 (**244–246**), which were found to inhibit the growth of a panel of murine and human cancer cells as well as some bacteria and fungi.[150] Newly discovered agelasine derivatives included agelamasines A (**247**) and B (**248**), isolated from Okinawan *Agelas* sp. What's interesting is that compound **247**, which may be generated from agelasine B (**200**) *via* oxidative cleavage followed by aldol condensation, featured by a rearranged (4 → 2)-*abeo*-clerodane diterpene skeleton that has no precedent in marine derived diterpene alkaloids.[151]

3.2. Terpenoids of hypotaurocyamine

From Fig. 21—the first hypotaurocyamine terpenoid from natural source was agelasidine A (**249**) isolated from Okinawan *Agelas* sp., and the structure of this acyclic sesquiterpene with a guanidinylethysulfone unit was established by spectral analysis and chemical degradation.[152] In addition to antispasmodic activity, compound **249** was also revealed to have antimicrobial effect against *C. albicans*, *B. subtilis* and *S. aureus*.[132,152] A study on physiologically active metabolites of Okinawan *A. nakamurai*, by the same research group, resulted in the isolation of agelasidines B (**250**) and C (**251**), which were both found to have inhibitory effects on growth of microorganisms, contractile responses of smooth muscle and enzymic reactions of Na^+,K^+-ATPase.[153] The Caribbean *A. clathodes* has been reported to yield three antibacterial analogues, (−)-agelasidine A (**252**), (−)-agelasidine C (**253**) and (−)-agelasidine D (**254**). The latter two compounds had potent cytotoxicity against CHO-K1 cells (respective ED_{50}, 5.70 and 2.21 μg mL^{-1}).[154,155] Agelasidines E (**255**) and F (**256**) were discovered in another Caribbean specimen of *A. citrina*, and their absolute configurations were established by quantitative measurements of molar rotations based on van't Hoff's principle of optical superposition.[146] The Xisha Islands *A. mauritiana* and *A. nakamurai* were found to produce (+)-2-oxo-agelasidine C (**257**)[73] and isoagelasidine B (**258**),[44] respectively. Compound **258** showed mild cytotoxic activities against HL-60 and K562 cell lines (IC_{50}, 33.0 and 39.2 μM, respectively), as well as potent antifungal activities against *C. albicans* (MIC, 2.34 μg mL^{-1}).[44]

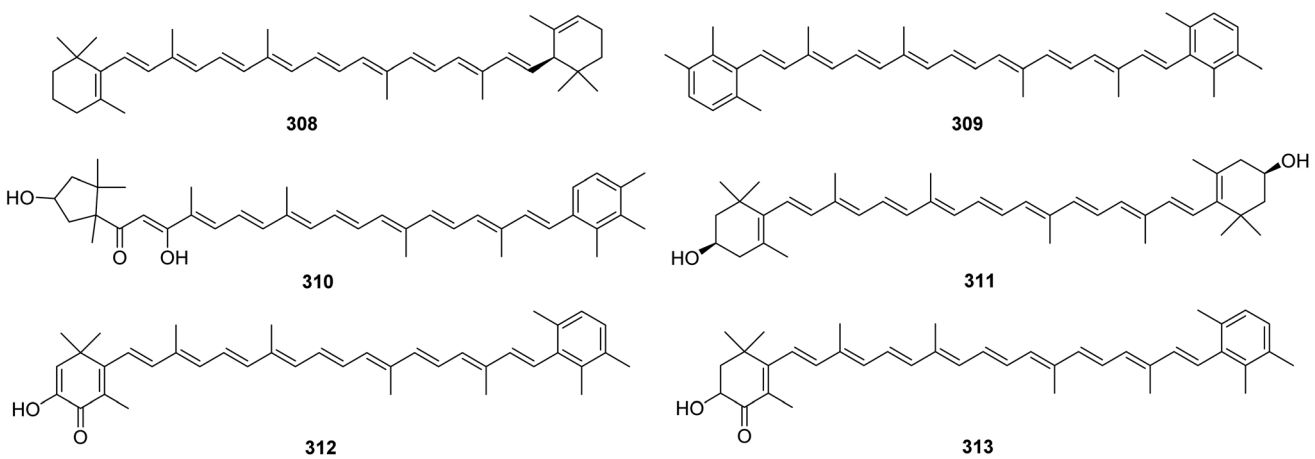


Fig. 25 Chemical structures of 308–313.

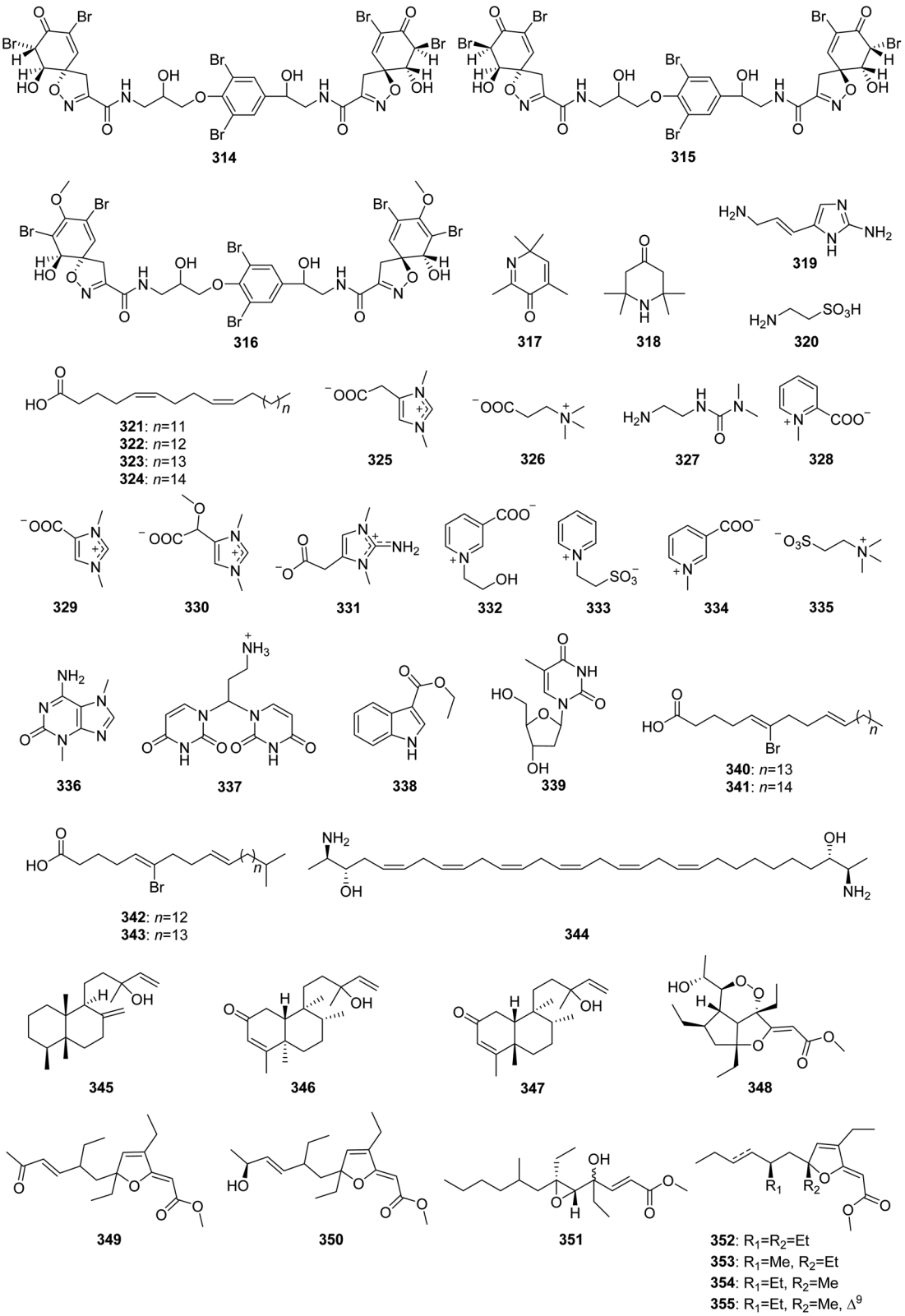


Fig. 26 Chemical structures of 314–355.

3.3. Other terpenoid alkaloids

From Fig. 22—the sponge *A. nakamurai*, collected from Okinawa, metabolized a rare pyrrole-containing diterpene, named nakamurol D (**259**).[156]

4. Glycosphingolipids

From Fig. 23—the sponges belonging to the genus *Agelas* have the ability to synthesize a variety of unique glycosphingolipids (**260–281**). Eight agelasphins (**260–267**), with their absolute configuration elucidated by total synthesis, were isolated from the Okinawan *A. mauritiana* as active substances prolonging the life span of mice intraperitoneally inoculated with B16 mouse melanoma cells. These glycosphingolipids represent the first example of galactosylceramides containing an α-galactosyl linkage,[157,158] and compound **262** has been served as a lead compound for further clinical application.[159,160] The Puerto Rico collection of *A. conifera* was the source of β-galactosphingolipid coniferoside (**268**)[161] and a mixture of homologs **269**.[162] Investigation of the glycosphingolipid composition of the Caribbean *A. clathrodes* revealed the presence of **270–277**,[163–165] of which clarhamnoside (**271**) is a tetraglycosylated α-galactoglycosphingolipid, containing an unusual L-rhamnose unit in the sugar head,[163] while clathrosides A–C (**272–274**) and isoclathrosides A–C (**275–277**) are glycosides of a very-long-chain alcohol derived from fatty acids, a new class of glycolipids that appears to be characteristic of marine sponges.[164] Additional research described by the same research group involved the congeners **278** and **279** from Caribbean *A. longissima*,[166,167] and an immunomodulating compound **280** from the San Salvador Island *A. dispar*.[168] A human cancer cell line bioassay-directed investigation of the Papua New Guinean *Agelas* sp. led to isolation of agelagalastatin (**281**), which is the first example of a natural product containing a digalactofuranosyl unit.[169]

5. Sterols

From Fig. 24—the species *A. oroides* was found to produce a group of sterols, including **282–296** from Naples specimen,[170] and the Northern Aegean Sea derived **297**, which exhibited antiplasmodial, as well as trypanocidal and leishmanicidal activities without cytotoxicity towards mammalian cells.[21] The Bahamas *A. flabelliformis* was shown to contain **298**, which was highly active in suppression of the response of murine splenocytes in the two-way mixed lymphocyte reaction with no associated toxicity when tested in a concentration range of 2.0 to 62.5 μg mL^{-1}.[59] Another examples of *Agelas*-derived sterols are **299–301** produced by Caribbean *A. schmidtii*,[171] ecdysterone (**302**) and ajugasterone C (**303**) contained in Little San Salvador Island *A. dispar*,[33] and **304–307** derived from Jamaican *A. sceptrum*.[172]

6. Carotenoids

From Fig. 25—four carotenoids, namely α-carotene (**308**), isorenieratene (**309**), trikentriorhodin (**310**) and zeaxanthin (**311**), were identified from West Indies *A. schmidtii*,[173] while the Kagoshima *A. mauritiana* was the source of isotedanin (**312**) and isoclathriaxanthin (**313**).[174]

7. Other types

From Fig. 26—an investigation of the chemistry of Great Barrier Reef *A. oroides* afforded three antibacterial fistularin-3 derivatives, including agelorins A (**314**) and B (**315**), and 11-*epi*-fistularin-3 (**316**),[175] along with two volatile compounds, 2,4,6,6-tetramethyl-3(6*H*)-pyridone (**317**) and 2,2,6,6-tetramethyl-4-piperidone (**318**),[176] while one imidazole derivative (**319**), taurine (**320**) and the fatty acids (**321–324**) were isolated from the Northern Aegean Sea collection of *A. oroides*,[21] and the Mediterranean *A. oroides* contained several amino-acid derivatives, namely zwitterionic zooanemonin (**325**), *N*,*N*,*N*-trimetyl-β-alanin (**326**), 3-(2-aminoethyl)-11-dimethylurea (**327**), homarine (**328**), norzooanemonin (**329**) and (−)-equinobetaine (**330**).[77] Compounds **319–324** showed antiplasmodial, trypanocidal and leishmanicidal activities.[21] The Caribbean *A. dispar* could metabolize three new betaine alkaloids, called aminozooanemonin (**331**), pyridinebetaine A (**332**) and pyridinebetaine B (**333**), along with the known zooanemonin (**325**), homarine (**328**), trigonelline (**334**) and *N*,*N*,*N*-trimethyltaurine (**335**), with **331** and **332** showing antibacterial activity against *B. subtilis* and *S. aureus* (MIC, 2.5–8 μg mL^{-1}).[177] A study of *A. longissima* collected in Little San Salvador Island has resulted in 3,7-dimethylisoguanine (**336**) being reported.[95] The Xisha Islands *A. clathrodes* was revealed to contain **337–339**, with **338** exhibiting moderate cytotoxicity against cancer cell line SGC7901 (IC_{50}, 13.2 μg mL^{-1}).[178] The identification of four brominated phospholipid fatty acids **340–343** from the Caribbean *Agelas* sp.[179] and an anti-mycobacterial bisfunctionalized sphingolipid, leucettamol A (**344**), detected in another unclassified Indonesian *Agelas* specimen[180] have been also achieved. The Okinawan *A. nakamurai* produced three uncommon diterpenoids, nakamurols A–C (**345–347**).[156] In addition, some *Agelas* sponges were also found to metabolize polyketides, represented by gracilioethers A–C (**348–350**) from Amami-oshima Island *A. gracilis*,[181] together with nemoechioxide A (**351**) and **352–355** from Xisha Islands *A.* aff. *nemoechinata*.[56] Bioactivity tests indicated that compounds **348–350** showed antimalarial activity against *Plasmodium falciparum* (IC_{50}, 0.5–10 μg mL^{-1}), whereas **349** also possessed antileishmanial activity.[181]

8. Conclusions

Secondary metabolites isolated from marine sponges of the genus *Agelas*, from their first discovery to date, present an interesting case which has stimulated research advancements in the field of marine natural products. This review highlights the chemical diversity and biological activities of the 355 compounds isolated from *Agelas* sponges over the nearly five decades from 1971 to November 2021, covering 20 identified species and unclassified *Agelas* sp. (Table 1). The species *A. oroides* (15%), *A. nakamurai* (13%) and *A. mauritiana* (11%) are predominant producers of these diverse compounds, while the

Table 1 Secondary metabolites isolated from *Agelas* sponges and their bioactivities

Compound	Species	Local of collection	Bioactivity	Ref.
Pyrrole alkaloids				
1	*A. oroides*	Naples	Broad spectrum[a]	8, 9 and 16–27
2	*A. clathrodes*	Desecheo Island	Broad spectrum	10, 23 and 28
3	*A. sventres*	Bahamas	Inhibitor of potassium channel	11 and 23
4			Antipredatory	11
5	*Agelas* sp.	Okinawa	Serotonergic receptors antagonist, antibacterial	29, 31 and 33
6–8			NR[b]	30 and 31
9	*A.* cf. *mauritiana*	Solomon Islands	NR	32
10, 11	*Agelas* sp.	Okinawa	NR	34
12	*A. clathrodes*, *A. dispar*,	Little San Salvador Island	Antihistaminic, antipredatory	35–37
13	*A. longissima*, *A. conifer*		Antihistaminic, antimalarial	35, 36 and 38
14, 15			Antihistaminic	36
16, 17	*A. mauritiana*	Solomon Islands	NR	39
18	*A. oroides*	Israeli Mediterranean	NR	27
19	*Agelas* sp.	Okinawa	NR	34
20, 21	*A. mauritiana*	Enewetak Atoll	NR	40
22	*A. nakamurai*	Okinawa	NR	41
23	*A. oroides*	Tel Aviv	NR	27
24	*Agelas* sp.	Okinawa	NR	42
25	*Agelas* sp.	Xisha Islands	NR	43
26, 27	*A. nakamurai*	Xisha Islands	NR	44 and 45
28	*A. nemoechinata*	Xisha Islands	Cytotoxic	46
29	*A. mauritiana*	Fijian	NR	47
30, 31	*A. linnaei*	Indonesia	NR	48
32	*A. oroides*	Mediterranean	Antihistaminic, antimicrobial	16 and 49
33	*Agelas* sp.	Okinawa	Inhibitor of tyrosine kinase, antibacterial	31 and 53
34–36	*Agelas* sp.	Okinawa	NR	31 and 50
37, 38	*Agelas* sp.	Okinawa	Antimicrobial	51
39	*Agelas* sp.	Okinawa	Antimicrobial	52
40			NR	
41			Antimicrobial	
42	*Agelas* sp.	Okinawa	Antimicrobial	31
43	*Agelas* sp.	Okinawa	NR	50
44, 45	*A. clathrodes*	Little San Salvador Island	Antifungal	54
46, 47	*A. dispar*	Little San Salvador Island	Antifungal	33
48	*A. nakamurai*	Okinawa	NR	55
49, 50			Cytotoxic	
51	*A. oroides*	Tel Aviv	NR	27
52	*A.* aff. *nemoechinata*	Xisha Islands	NR	56
53	*A. nakamurai*	Kuchinoerabu-jima Island	Antiangiogenic, fluorescent pH sensor	57 and 58
54	*A. linnaei*	Thousand Islands	NR	48
55	*A. oroides*	Naples	Immunosuppressive, antipredatory	8, 18 and 59
56			Inhibitor of protein tyrosine phosphatase	8 and 60
57			NR	8
58			Promotor of ascidian larval metamorphosis, inhibitor of bacterial biofilm	17 and 27
59, 60	*A. oroides*	Great Barrier Reef	NR	61
61, 62	*Agelas* sp.	NR	NR	62
63, 64	*A. nakamurai*	Papua New Guinea	Antimicrobial	63
			NR	
65, 66	*A. nakamurai*	Menjangan Island	NR	48
67, 68	*A. cerebrum*	Cuba	NR	64
69	*A. mauritiana*	Enewetak Atoll	NR	40
70	*A. longissima*	San Salvador Island	Antiserotonergic	66
71	*A. citrina*	San Salvador Island	NR	65
72	*Agelas* sp.	Likpan	NR	67

Table 1 (*Contd.*)

Compound	Species	Local of collection	Bioactivity	Ref.
73	*A. dispar*	Venezuelan island La Blanquilla	Ligand and antagonist of several receptors	68–70
74–77	*A. linnaei*	Thousand Islands	Cytotoxic	48
78–81			NR	
82	*A. wiedenmayeri*	Florida Keys	NR	72
83	*Agelas* sp.	Okinawa	NR	42
84	*A. oroides*	Tel Aviv	NR	27
85	*A. mauritiana*	Xisha Islands	NR	73
86, 87	*Agelas* sp.	Xisha Islands	NR	43
88–98	*A. nakamurai*	Xisha Islands	NR	44 and 45
99–101	*A.* aff. *nemoechinata*	Xisha Islands	NR	56
102, 103	*Agelas* sp.	Okinawa	NR	34
104	*Agelas* sp.	Tanzania sea	Stimulator of wheat roots growth	75 and 76
105	*A. dispar*	Venezuelan island La Blanquilla	NR	68
106	*A. oroides*	West Mediterranean	NR	77
107–109	*A. oroides*	Tel Aviv	NR	27
110	*A. mauritiana*	Fijian	Inhibitor of bacterial biofilm, antipredatory	25, 47 and 79
111–113	*Agelas* sp.	Sweetings Cay	Inhibitor of bacterial biofilm, antipredatory	25 and 80
114	*Agelas* sp.	Papua New Guinea	Inhibitor of lipoxygenase isozymes	81
115			NR	
116	*A. linnaei*	Thousand Islands	NR	48
117, 118	*Agelas* sp.	North Sulawesi	Cytotoxic	60 and 82
119	*A. kosrae*	Kosrae Island	Antifungal, inhibitor of glycogen synthase kinase	84 and 85
120–122	*A. nemoechinata*	Xisha Islands	NR	46
123	*A. dendromorpha*	New Caledonia	Cytotoxic, inhibitor of glycogen synthase kinase, toxic towards arthropods	88, 89 and 91–93
124–127			NR	88 and 90
128	*A. longissima*	Little San Salvador Island	Antibacterial	95
129	*A. dispar*	Little San Salvador Island	Antibacterial, trypanocidal, antileishmanial	33 and 38
130	*A. nakamurai*	Okinawa	NR	41
131	*Agelas* aff. *nemoechinata*	Xisha Islands	NR	56
132	*A. nakamurai*	Menjangan Island	NR	48
133–136	*Agelas* sp.	Xisha Islands	antifungal	43
137			Antibacterial, antifungal	
138	*A. oroides*	Mediterranean	NR	49
139, 140	*Agelas* sp.	Okinawa	NR	98
141, 142	*Agelas* sp.	Indonesia	NR	67
143	*A. oroides*	Mediterranean	NR	27
144	*A. sceptrum*	Glover Reef	Broad spectrum	19, 100, 101, 104 and 105
145–151	*A. conifera*	Caribbean	Broad spectrum	19, 102 and 103
152	*A. conifera*	Belize	NR	110
153, 154	*A. nakamurai*	Island of Ambon	Antibacterial	105
155	*Agelas* sp.	Xisha Islands	Antibacterial	111
156, 157			NR	
158			Antibacterial	
159, 160	*A. kosrae*	Kosrae Island	Cytotoxic, antiangiogenic, inhibitor of isocitrate lyase	84
161	*A.* cf. *mauritiana*	Solomon Islands	NR	112
162	*Agelas* sp.	Okinawa	Antibacterial, quorum sensing inhibitory, inhibitor of bacterial biofilm	27 and 113
163	*A. mauritiana*	Hachijo-jima Island	Antifouling, antibacterial	17
164	*Agelas* sp.	Okinawa	Antibacterial, inhibitor of protein phosphatase	30

Table 1 (*Contd.*)

Compound	Species	Local of collection	Bioactivity	Ref.
165–169			Antibacterial	
170, 171			Antibacterial, inhibitor of protein phosphatase	
172	*Agelas* sp.	Okinawa	NR	114–116
173–175			Antimicrobial	
176			NR	
177	*Agelas* sp.	Okinawa	Antibacterial	42 and 117
178			NR	
179, 180			Antimicrobial	
181, 182	*Agelas* cf. *mauritiana*	Solomon Islands	NR	112
183–185	*Agelas* sp.	Okinawa	Antimicrobial	118
186	*A. citrina*	San Salvador	NR	65
187–189			Antimicrobial	
190	*A. oroides*	Tel Aviv	NR	27
191–195	*Agelas* sp.	Okinawa	Antimicrobial	119 and 120
196, 197	*A. sceptrum*	Bahamas	NR	121
198	*A. nemoechinata*	Xisha Islands	Proangiogenic	122
Terpenoid alkaloids				
199–202	*A. nakamurai*	Okinawa	Inhibitor of Na^+,K^+-ATPase	126–128
203			Inhibitor of Na^+,K^+-ATPase, antituberculosis	126–129
204			Broad spectrum	126–128, 130 and 131
205	*Agelas* sp.	Palau	NR	132
206	*Agelas* sp.	Okinawa	Cytotoxic, inhibitor of protein tyrosine phosphatase	133 and 134
207, 208	*Agelas* sp.	Yap Island	NR	136
209–211	*A.* cf. *mauritiana*	Solomon Islands	Antimalarial, cytotoxic	137
212	*A. mauritiana*	Pohnpei	Antifouling	138
213, 214	*A. mauritiana*	Eniwetak	Broad spectrum	140 and 142
215			NR	141
216	*A. nakamurai*	Menjangan Island	Cytotoxic, antifouling	48
217			Cytotoxic, antifouling, radiosensitizer	48 and 144
218	*Agelas* sp.	Papua New Guinea	Trypanocidal, cytotoxic	130
219–221			NR	
222	*A. nakamurai*	Papua New Guinea	NR	145
223	*A. citrina*	Caribbean Sea	NR	146
224–227	*Agelas* sp.	Okinawa	Antimicrobial	147
228			NR	
229, 230			Antimicrobial	
231–233	*A. nakamurai*	Okinawa	Antibacterial	135
234–237	*A. mauritiana*	Xisha Islands	NR	73 and 148
238			Cytotoxic, antibacterial	
239			NR	
240			Antibacterial, antileishmanial	
241	*A. nakamurai*	Xisha Islands	Cytotoxic, antimicrobial	44
242	*A.* aff. *nemoechinata*	Xisha Islands	NR	149
243			Cytotoxic	
244–246	*A. axifera*	Republic of Palau	Cytotoxic, antimicrobial	150
247, 248	*Agelas* sp.	Okinawa	NR	151
249	*Agelas* sp.	Okinawa	Antispasmodic, antimicrobial	132 and 152
250, 251	*A. nakamurai*	Okinawa	Smooth muscle relaxant, inhibitor of Na^+,K^+-ATPase	153
252	*A. clathodes*	Caribbean	NR	154 and 155
253, 254			Cytotoxic	
255, 256	*A. citrina*	Caribbean	NR	146
257	*A. mauritiana*	Xisha Islands	NR	73
258	*A. nakamurai*	Xisha Islands	Cytotoxic, antifungal	44
259	*A. nakamurai*	Okinawa	NR	156

Table 1 (*Contd.*)

Compound	Species	Local of collection	Bioactivity	Ref.
Glycosphingolipids				
260–267	*A. mauritiana*	Okinawa	Cytotoxic	157 and 158
268, 269	*A. conifera*	Puerto Rico	NR	161 and 162
270–277	*A. clathrodes*	Caribbean	NR	163–165
278, 279	*A. longissima*	Caribbean	NR	166 and 167
280	*A. dispar*	San Salvador Island	Immunoactivating	168
281	*Agelas* sp.	Papua New Guinea	NR	169
Sterols				
282–296	*A. oroides*	Naples	NR	170
297	*A. oroides*	Northern Aegean Sea	Antiplasmodial, trypanocidal, leishmanicidal	21
298	*A. flabelliformis*	Bahamas	Immunosuppressive	59
299–301	*A. schmidtii*	Caribbean	NR	171
302, 303	*A. dispar*	Little San Salvador Island	NR	33
304–307	*A. sceptrum*	Jamaica	NR	172
Carotenoids				
308–311	*A. schmidtii*	West Indies	NR	173
312, 313	*A. mauritiana*	Kagoshima	NR	174
Other types				
314, 315	*A. oroides*	Great Barrier Reef	Antibacterial	175
316			Antibacterial, cytotoxic	
317, 318			NR	176
319–324	*A. oroides*	Northern Aegean Sea	Trypanocidal, antiplasmodial, leishmanicidal	21
325–330	*A. oroides*	Mediterranean	NR	77
331, 332	*A. dispar*	Caribbean	Antibacterial	177
333–335			NR	
336	*A. longissima*	Little San Salvador Island	NR	95
337	*A. clathrodes*	South China Sea	NR	178
338			Cytotoxic	
339			NR	
340–343	*Agelas* sp.	Caribbean	NR	179
344	*Agelas* sp.	Indonesia	Anti-mycobacterial	180
345–347	*A. nakamurai*	Okinawa	NR	156
348	*A. gracilis*	Amami-oshima Island	Antimalarial	181
349			Antimalarial, antileishmanial	
350			Antimalarial	
351–355	*A.* aff. *nemoechinata*	Xisha Islands	NR	56

[a] See main text for the bioactivities. [b] Not reported.

unclassified *Agelas* sp. are the source of 28% of the secondary metabolites from this genus (Fig. 27).

Pyrrole alkaloids are widely distributed in *Agelas* sponges and accounted for 56% of *Agelas*-derived secondary metabolites (198/355). The number of new members discovered still increases. The biogenetic key metabolite oroidin, which could be derived from proline and lysine, functions as basis of structural diversity on the skeleton level by undergoing cyclization, oxidation and dimerization to form an array of structurally complex pyrrole alkaloids. These pyrrole alkaloids can be classified as three structural types: linear pyrrole alkaloids, fused cyclic pyrrole alkaloids and dimeric pyrrole alkaloids, which account for about 52, 20 and 28% of the total pyrrole alkaloids, respectively. Another represented structural class is terpenoid alkaloids, with 17% of *Agelas*-derived secondary metabolites. In contrast to the structural variety of pyrrole alkaloids, only 61 terpenoid alkaloids have been reported to date, covering the species *A. nakamurai* (28%), *A. mauritiana* (25%), *A. axifera* (5%), *A. citrina* (5%), *A. clathrodes* (5%) and *A. nemoechinata* (3%). The remaining 29% were obtained from unclassified *Agelas* species (Fig. 27). These unusual terpenoid alkaloids mainly include 9-*N*-methyladeninium terpenoids and terpenoids of hypotaurocyamine, which account for about 82 and 16% of the total terpenoid alkaloids, respectively. It should be noted that, no terpenoid alkaloids have been found from the most prolific species *A. oroides*, which mainly metabolized

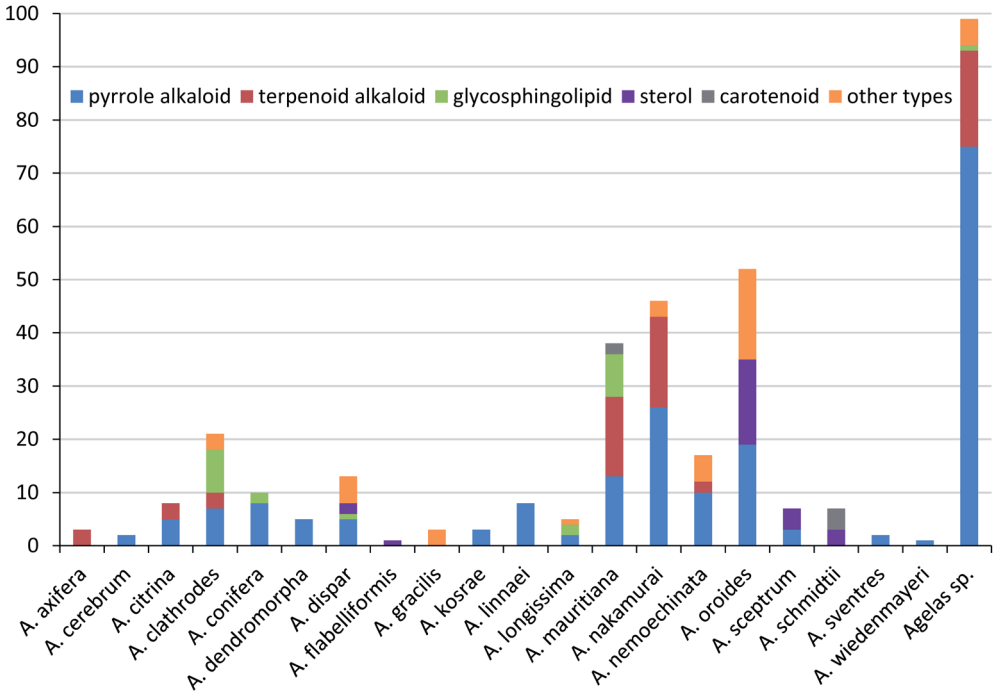


Fig. 27 *Agelas* species distribution of isolated compounds belonging to the several chemical classes.

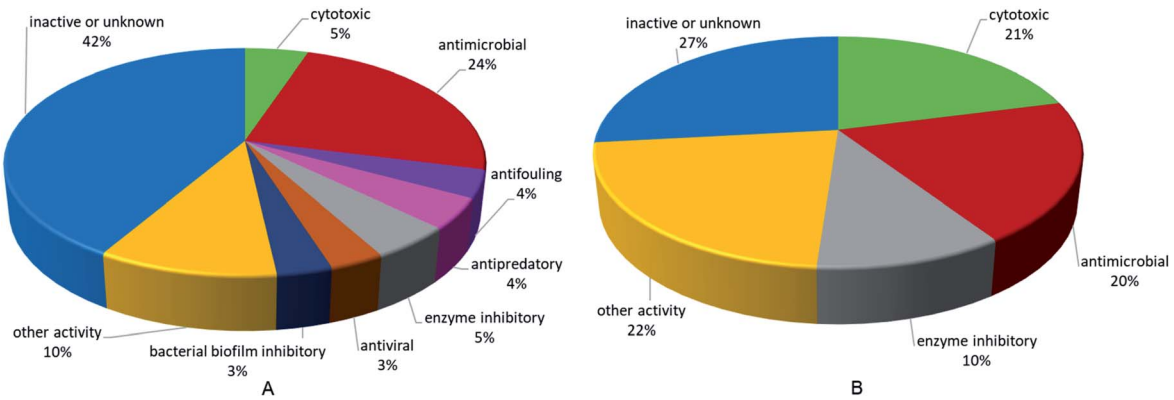


Fig. 28 Bioactivity distribution of *Agelas*-derived pyrrole alkaloids (A) and terpenoid alkaloids (B).

pyrrole alkaloids, sterol and other types. In addition, the species *A. clathrodes* and *A. mauritiana* were also the source of nearly 73% of glycosphingolipids. The reasons for the biosynthesis of such characteristic metabolites within the multiple sponge species of the genus *Agelas* remains puzzling and deserves further study.

This review also involves the biological activities of 355 compounds. Bioactivity distribution of the pyrrole alkaloids and terpenoid alkaloids, which are the most important and representative secondary metabolites from *Agelas* sponges, revealed that the two families of alkaloids have different emphases on activity (Fig. 28). In terms of pyrrole alkaloids, the most prevalent activity was antimicrobial activity, which have been expressed by about 24% of the compounds. There were also pyrrole alkaloids endowed with various activities, including cytotoxic, enzyme inhibitory, antifouling, antiviral, bacterial biofilm inhibitory, and other activities (*e.g.*, antihistaminic, antimalarial, antiangiogenic, proangiogenic, trypanocidal, antileishmanial and immunosuppressive effects). As for terpenoid alkaloids, about 21% were reported for cytotoxic activity, about 20% for antimicrobial activity, about 10% for enzyme inhibitory activity, and 22% for other activities, such as trypanocidal, antimalarial, antileishmanial and antispasmodic activities.

Although these *Agelas*-derived secondary metabolites, especially pyrrole alkaloids and terpenoid alkaloids, are of historic importance in marine natural products chemistry, the unavailability of large amounts of natural alkaloids, challenges for purification due to numerous similar analogues, and structural and configurational complexity restricting efficient

chemical synthesis have hindered further application in drug research and development. In recent years, with the increasing development of oceanographic science and spectroscopy technology, new intriguing *Agelas*-derived alkaloids are reported every year, making these marine sponges of this genus some of the most attractive targets for lead compounds discovery, worthy of further exploration. These findings, in conjunction with synthetic chemistry and biology, offer the potential to discover valuable molecules for future development in medicinal applications.

Conflicts of interest

There are no conflicts to declare.

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