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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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 aminimidazole 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. Additionally, the linear pyrrole alkaloids lacking an aminimidazole 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. However, the initial structure of oroidin was not exactly right; afterwards the structure was reassigned based on a chemical synthesis. Subsequently, three closely related analogues, including the nonbrominated clathrodin (2) from the Caribbean A. clathrodes collected from Desecheo Island, the monobrominated hyme-nidin (3) and N-methylated derivative sventrin (4) from Bahamas A. sventres have been discovered. The simplest PIAs oroidin (1), clathrodin (2) and hynenidin (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. As a consequence, proline was strongly suggested as the precursor of the pyrrolyl moiety in 1–3, while the 2-aminimidazole 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. Biological evaluation revealed that compound 1 had a broad spectrum of bioactivities, including antibacterial, antifouling, antipredatory defense against reef fish, antimalarial, acetylcholinesterase inhibitory and radical scavenging, inhibitory action towards voltage-gated potassium channels, and inhibiting biofilm formation of pathogenic and marine environment derived bacteria. 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, while compound 3 was proved to be an inhibitor of the voltage-gated potassium channels, and compound 4 was feeding deterrent against omnivorous reef fish.

Keramadine (5), 9,10-dihydrokeramadine (6), 2-bromokeramadine (7) and 2-bromo-9,10-dihydrokeramadine (8) identified from Okinawan sponge Agelas sp., and debromokeramadine (9) from the Solomon Islands A. cf. mauritiana are oroidin congeners with an N-methylated aminimidazole 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. 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). In addition, a recent report on Okinawan sponges Agelas sp. described two closely related congeners, 9E-keramadine (10) and 9-hydroxydihydrooroidin (11).

From Fig. 2—four oroidin derivatives with an aminimidazolone 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 hydroxyl group in the central chain causes a marked reduction of the antihistaminic activity. Further biological researches suggested that compound 12 served as the primary chemical defense of Agelas sponges, while compound 13 emerged as an antimalarial lead compound with significant activity and low toxicity towards...
mammalian cells. 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. Recently, the study of A. ovoides collected near the Israeli Mediterranean coastline and Okinawan sponges Agelas sp. yielded E-dispacamidine (18) and 9-hydroxydihydrodispacamide (19), 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 Eniwetok Atoll A. mauritiana, while an Okinawan specimen of A. nakamura was the source of mukanadins A (dispacamide D, 15) and B (22), and chemical investigations of Mediterranean A. ovides, collected off the Tel Aviv coast, and the Okinawan Agelas sp. afforded mukanadins D (23) and F (24), 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. The Agelas sponges from the Xisha Islands in the South China Sea were demonstrated to contain 9-oxethyl-mukanadin F (25) from Agelas sp., the nonbrominated nakurine D (26) and a known congener 27 from A. nakamura and nemocheine H (28) from A. nemoechinata. Among which, compound 28 possessed cytotoxic activity against human leukemia cell K562 and human liver cell L-02 (IC50, 6.1 and 12.3 µM, respectively).

From Fig. 4—the sponges of the genus Agelas were also the source of a quite rare family of PIAs with a thiamine moiety. The first member of this family is the Fijian species A. mauritiana derived mauritamide A (29), which is an oroidin derivative having a thiamine methyl ester group. Two congeners, mauritamides B (30) and C (31) were detected in the Indonesian A. linnaei. Investigation of the chemistry of Mediterranean A. ooides 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 IC50 values ranging from 0.21 to 1.4 µM. A series of taunine containing PIAs, tauroacidins A (33) and C–E (34–36), nagelamides M (37), N (38), U (39) and V (40) were isolated from Okinawan Agelas sp., by Kobayashi’s group. Structurally, compound 37 possesses a unique 2-amino-octahydropropol(2,3-dijmidazole ring, while compounds 39 and 40 are the first example for a pyrrole alkaloid with a γ-lactam ring. Biosynthetically, compounds 37–40 could be derived from the same precursor (32) through oxidation and cyclization. In the bioassays, compound 33 not only exhibited tyrosine kinase inhibitory effect (IC50, 20 µg mL−1) but also had antibacterial activity against M. lutea (MIC, 8.0 µg mL−1), while compounds 37 and 38 had antimicrobial activity against

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Fig. 2 Chemical structures of 12–19.
Aspergillus niger (MIC, 33.3 μg mL⁻¹, each),³¹ and compound 39 was active against C. albicans (IC₅₀, 4 μg mL⁻¹).³²

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 (IC₅₀, 4 μg mL⁻¹).³³ Compound 42 (mukanadin G) with a tricyclic skeleton consisting of a fused tetrahydrobenzimidazoline and 2,5-dioxopyrrolidine moieties, was found to have antifungal activity against C. albicans and Cryptococcus neoformans (IC₅₀, 16 and 8.0 μg mL⁻¹, respectively).³⁴ Compound 43 (agelamin F) is the first example for a pyrrole alkaloid with the coexistence of aminoimidazole and pyridinium moieties.³⁵ 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).³⁶ The Okinawan A. nakamurai was the source of the unusual PIAs sharing a tetrahydrofurano[2,3-d]imidazolidin-2-one moiety, slagenins A–C (48–50), with 49 and 50 showing cytotoxic activity against routine leukemia L1210 cells (IC₅₀, 7.5 and 7.0 μg mL⁻¹, respectively).³⁷ 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.³⁸ Examination of Xisha Islands A. aff. nemoechinata led to the isolation of nemochelin A (52) bearing an uncommon cyclopentane-fused imidazole ring system.³⁹ Ageladine A (53) containing 2-aminoimidazolopyridine and agelain A (54) with 2-aminoimidazoletetrahydropyridinyl, were characterized from Kuchinoerabu-jima Island A. nakamurai³⁷ and thousand Islands A. linnaei,³⁸ 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.³⁷,³⁸

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),⁶ 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,³⁹,⁴⁰ while compound 56, 4,5-dibromopyrrole-2-methylcarboxylate, could mildly inhibit protein tyrosine phosphatase 1B (PTP1B),⁴¹ and compound 58, 4,5-dibromopyrrole-2-carboxamide, not only had the ability to promote larval metamorphosis of the ascidian Ciona savignyi³⁷ but also inhibited Pseudomonas aeruginosa PAO1 biofilms.³⁷ 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).⁴², 2,3-Dibromopyrrole (61) and 2,3-dibromo-5-methoxymethylpyrrole (62) were discovered from Agelas sp. without collection location data.⁴² The Papua New Guinean sponge A. nakamurai was the source of 5-bromopyrrole-2-carboxamide (63) and 5-bromopyrrole-2-(N-methoxymethyl)carboxamide (64) with 63 being active against some Gram-positive bacteria and fungi,⁴³ while 4-bromopyrrole-2-carboxylic acid (65) and 4-bromopyrrole-2-carboxamide (66) have been sourced from Menjangan Island specimen of A. nakamurai.⁴⁴ 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).⁴⁴ The species A. mauritiana from Enewetak Atoll could produce methyl N-methyl-4,5-dibromopyrrole-2-carboxylate (69).⁴⁵

From Fig. 7—agelone (70) and N-methylagelone (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.⁴⁶,⁴⁷ Manzacidin C (72), isolated from the Indonesian Agelas sp. collected from Likpan, is the first pyrrole alkaloid with a tetrahydropropyrimidine unit from Agelas sponges.⁷ In the bioactivity study, compound 70 displayed antiserotonergic activity tested in vitro on rat stomach fundus strip.⁴⁸ 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

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**Fig. 3** Chemical structures of 20–28.
a notable variation from the oroidin family. With no antibacterial or anticancer activity, compound 73 was a potent ligand and antagonist of several therapeutically relevant G protein-coupled receptors, the α1D and α2A adrenergic receptors and the H2 and H3 histamine receptors. 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-1H-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
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.

Compounds 74–77 were found to have mild cytotoxic activity against L5178Y mouse lymphoma cells (IC₅₀, 9.25–16.76 μM).

The sponges A. wiedenmayeri collected off the coast of Florida Keys and Okinawan Agelas sp. contained 4-bromopyrrole-2-carboxyhomoarginine (82) and mukanadin E (83), 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. Pyrrolosine (84), comprised by two symmetric 4,5-dibromopyrrole-2-carboxamide moieties was discovered from Mediterranean A. oroides, collected in Tel Aviv.

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]-1H-pyrrole-2-carboxamide (85) from A. mauritiana, 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.
nakamurines A–C (88–90) and E (91) along with seven known congeners 92–98 from *A. nakamurai*,44,45 nemochine C (99) and the previously reported 100 and 101 from *A. aff. nemochinata*.36 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.44,45

### 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 z-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.24 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: agelaspongins 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. Agelaspongins family

From Fig. 9—agelaspongins (104–109) are a family of tetracyclic PIAs usually found in *Agelas* sponges. Dibromoagelaspongion 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 dibromoagelaspongion 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, monobromoagelaspongion (106),77 while a further investigation of the Tel Aviv (East Mediterranean Sea) *A. oroides* yielded the optically active (−)-monobromoagelaspongion (107), (−)-11-deoxy-monobromoagelaspongion (108) and (−)-11-O-methylmonobromoagelaspongion (109).77 From a biosynthetic perspective, these dibromo- and monobromoagelaspongions were thought to be formed through cyclization and oxidation of oroidin/hymenidin.24,77,78

#### 2.2.2. Phakellin family

From Fig. 10—a series of phakellin family alkaloids (110–112) bearing a similar tetracyclic skeleton to that of agelaspongins, have been identified from *Agelas* sponges.
Dibromophakellin (110), previously described from the sponge *Phakellia abellate*, was obtained from Fijian *A. mauritiana*, 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). 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. Additionally, results of antifeedant activity of these phakellins against *Thalassoma bifasciatus* suggested that the isophakelline skeleton showed a higher activity than that of phakelline skeleton, and bromination increases the antifeedant activity.

Two *N*-methylated phakellin derivatives, (−)-7-*N*-methyl dibromophakellin (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 lipoxigenase isozymes (IC$_{50}$, 10.7 ± 1.3 μM). A racemic mixture, dibromohydroxyphakellin (116) purified from Thousand Islands *A. linnaei* is the first 12-OH analogue of the phakellin family alkaloids. The report on an Indonesian sponge *Agelas* sp. collected in North Sulawesi, included 5-bromophakelline (117), as well as the known cylindradine A (118), which was previously isolated from the sponge *Axinella cylindratus* and was found to display moderate inhibitory activity against the murine leukemia cell line P388. Dibromocantharillin (119), firstly described from the sponge *Pseudaxinyssa cantharella*, was later purified from the Kosrae Island *A. kosrae*. Compound 119 not only showed antifungal activity against *Cladosporium herbarum*, but also displayed a significant inhibitory effect towards glycogen synthase kinase 3β (IC$_{50}$, 3 μM). Another two congeners, 9-*N*-methycylindradine A (120) and 1-*N*-methylygibohlin (121), were isolated from Xisha Islands *A. nemoechinata*, together with the
known N-methyl dibromoisophakellin (122),\(^6\) which was firstly found in the sponge \textit{Stylissa caribica}.\(^7\)

2.2.3. \textit{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 \textit{A. dendromorpha}, a species that has rarely been studied to date.\(^8\)–\(^10\) These compounds structurally featured by a densely functionalized cyclopentane ring bearing four contiguous stereoergic 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 hydroxymide derivatives.\(^11\) In addition to powerful cytotoxicity against a wide range of human cancer cell lines,\(^12\)–\(^14\) agelastatin A (123) could also selectively inhibit glycogen synthase kinase-3B\(^15\) and was significantly toxic toward brine shrimp, larvae of beet army worm and corn rootworm.\(^16\) 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.\(^17\) 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.\(^18\)

2.2.4. \textit{Longamide family.} From Fig. 12—the most common structural class of \textit{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 \textit{A. longissima}, collected from Little San Salvador Island.\(^19\) Soon afterwards, the same research group found a mixture of enantiomers, longamide B (129), having moderate antibacterial activity against \textit{B. subtilis} and \textit{S. aureus}, from another Little San Salvador Island species \textit{A. dispers}.\(^20\) A follow-up antiprotozoal activity screening revealed that 129 was a promising trypanocidal and anti-leishmanial agent, with narrower therapeutic windows, while 128 was completely inactive against any protozoan parasite.\(^21\) The monobrominated mukanadin C (130) and nonbrominated nemoechine B (131), were racemates obtained from the Okinawan \textit{A. nakamura} and the Xisha Islands \textit{Agelas} aff. nemoechinata, respectively.\(^22\)–\(^24\) The Indonesian \textit{A. nakamura} collected from the Menjangan Island produced longamide C (132).\(^25\) Bioassay-guided fractionation of the extract of the Xisha Islands \textit{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 \textit{Acanthella carteri} collected from Hanish Islands\(^26\) and \textit{A. ceylonica} collected near the Mandapam coast,\(^27\) respectively. In the experiment of antimicrobial activity, compound 137 possessed mild antibacterial activity against \textit{B. subtilis}.\(^28\) Furthermore, the individual enantiomers (+)-(9S,10R)-133, (−)-S-134, (+)-R-135, (−)-R-136 and (+)-R-137 exhibited significant antifungal activity against \textit{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...
individual enantiomers \((\pm)-(9R,10S)-133\), \((\pm)-R-134\), \((-)-S-135\), \((-)-S-136\) and \((-)-S-137\).\(^{43}\)

The longamide family also includes compounds 138–143, featured by a pyrrololotetopiperazine 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 pyrrololotetopiperazine derivatives with a hydantoin ring, namely agesamides A (139) and B (140).\(^{50}\) 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. 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. 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. Several years later, the di- and debromo analogues (145 and 146), and monoxygenated analogues of sceptrin with an aminoimidazoline 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*. 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. 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. Oxsceptrin (148) and ageliferins (149–151) were a potent actomyosin ATPase activator. As an anti-biofilm substance, compound 150 had the ability to inhibit the growth of marine bacteria with adhering properties. Compounds 150 and 151 could also inhibit voltage-operated, but not store-operated calcium entry in phaeochromocytoma PC12 cells. Additionally, Compounds 144, 145, 150 and 151 were revealed to be potent feeding deterrents against fish predation. The first sceptrin-type alkaloid without bromine substitution was debromosceptrin (152), isolated from the Caribbean *A. conifera* collected in Belize.

The sceptrin derivatives with only one aminomidazole ring in the molecule, nakamuric acid (153) and its corresponding methyl ester (154), without the assignment of absolute configuration, were obtained from *A. nakamura*, collected near the island of Ambon, and both the compounds were shown to be active against the bacteria *B. subtilis*. 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 aminimidazole substitution, agelestes A (156) and B (157), along with (9S,10R,9'S,10'R)-nakamuric acid (158), of which the

Fig. 13 Chemical structures of 144–160.
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. A purple elongated species that has rarely been studied to date, identified as *A. kosrae*, collected from Kosrae Island, was revealed to produce dioxygenptin (159) and ageletse C (160). Compound 159, the dioxygenated form of scepfrin 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.

From Fig. 14—two unusual benzocyclobutane-containing natural products, benzosceptrin A (161) from Solomon Islands *A. cf. mauritiana*, and its brominated analogue benzosceptrin C (162) from both the Okinawan *Agelas* sp. and New Caledonian *A. dendromorpha*, 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*. 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 scepfrin-like alkaloids, compound 163 was constructed by two monomers with a linkage between C-11 in aminoimidazolinone unit and C-15’ in the aminoimidazolide unit. Biological studies have identified that compound 163 could inhibit larval metamorphosis of the barnacle *Balanus Amphitrite* (ED₅₀, 15 μg mL⁻¹), and exhibit moderate antibacterial activity against *Flavobacterium marinotopicum*.

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 (IC₅₀, 48, 13 and 46 μM, respectively). 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). Nagelamide I (172), a symmetric dimer of hymedinid, 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, while nagelamide J (173) represents the first pyrrole derivative with a cyclopentane-fused aminoimidazole system, nagelamide K (174) possesses a rare piperidinoiminoimidazolone ring with an aminoimidazolide ring and a taurine unit, and nagelamide L (175) is a unique dimeric pyrrole alkaloid containing an ester linkage. 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), while compounds 174 and 175 were able to inhibit the growth of *M. luteus* (MIC, both 16.7 μg mL⁻¹). Further studies on the Okinawan *Agelas* sponges, also by Kobayashi’s group, have yielded nagelamides O–R (177–180). The structure of compound 177 is notable for bearing an uncommon perhydrocyclopenta-imidazo-azolo-imidazole carbon skeleton, while 179 contains a rare pyrrolidine ring, and 180 is the first example of bromopyrrole alkaloid having an oxazoline ring. Compound 177 was found to have weak antibacterial activity against *B. subtilis*, *M. luteus* and *S. aureus* (MIC, 33.3 μg mL⁻¹, each), 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). Two non-brominated congeners, nagelamides S (181) and T (182), biogenetically starting from clathrodin were sourced from Solomon Islands collection of *A. cf. mauritiana*. Kobayashi’s group carried out a continued study on Okinawan *Agelas* sp., yielding three new structurally intriguing pyrrole-imidazole carbon dimers, nagelamides X–Z (183–185). The racemates 183 and 184 both possess a rare tricyclic skeleton consisting of spiro-bonded tetrahydrobenzoinimidazolide and aminoimidazolide 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 IC₅₀ of 185 for *C. albicans* was 0.25 μg mL⁻¹).
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.
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. 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.

From Fig. 17—Kobayashi’s group also obtained five unique unsymmetrical pyrrole-imidazole dimers, agelamadins A–E (191–195), from the Okinawan Agelas sp. 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 (IC₅₀, 8.0 and 4.0 μg mL⁻¹, respectively). 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). 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. 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 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.

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, 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-methyladennium terpenoids (i.e., agelasines, agelines, nemoehines) and terpenoids

![Scheme 3](image-url)  
**Scheme 3** Origin of labdane, halimane and clerodane diterpenoid skeletons from geranylgeranyl diphosphate (GGPP).

![Fig. 18](image-url)  
**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). In contrast to the structural variety of the 9-N-methyladeninium terpenoid, only 10 terpenoids of hypotaurocyamine have been reported to date.

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 \(\text{Na}^+,\text{K}^+\)-ATPase inhibitors. In contrast to the presence of the unusual adenine in the structure made these compounds attractive targets in biological and chemical research.
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. 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*, 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.

![Chemical structures of 231–248.](image-url)
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. A brominated analogue of 205, named agelasine G (206), exhibiting cytotoxic activity against murine lymphoma L1210 cells (IC50, 3.1 μg mL−1), was obtained from Okinawan Agelas sp. 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. Agelasines H (207) and I (208), both bearing a clerodane skeleton, were discovered from Agelas sp., collected at Yap Island. 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 IC50 values of 6.6, 8.3 and 18 μM, and a low cytotoxicity on MCF7 human breast cancer cells.

From Fig. 19—a study on Pohnpei collection of A. mauritiana afforded epi-agelasine C (212), which was an antifouling substance active against macroalgae. 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. The Eniwetak species A. mauritiana gave agelasimines A (213) and B (214), as well as an unusual purino-diterpene (215), the structure of which was determined by X-ray analysis. Compounds 213 and 214 not only had cytotoxic effect on L1210 leukemia cells, but also served as smooth muscle relaxants, Ca2+ channel antagonists and α1 adrenergic blockers. Chemical investigation of Indonesian A. nakamurai collected from Menjangan Island yielded (−)-agelasine D (216) and its analogue 217. Compound 217 was originally proposed as an oxime derivative and revised later as a formamide derivative of 216, thus renamed agelamide. Both compounds 216 and 217 exhibited cytotoxicity against L5178Y mouse lymphoma cells (IC50, 4.03 and 12.5 μM, respectively), and were toxic to the larvae rather than just...
inhibiting settlement of *Balanus improvisus* in an antifouling bioassay. Additionally, the therapeutic potential of agelamide (217) as a natural radiosensitizer in hepatocellular carcinoma models has been also revealed. 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-
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* (IC₅₀, 3.0 μg mL⁻¹) as well as mild cytotoxicity against Jurkat cells (IC₅₀, 25 μg mL⁻¹). 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* and *A. citrina*, 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 bromopyrrole 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.
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.\(^{153}\) 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 \(\mu\)M), and also inhibited the growth of a panel of methicillin-resistant S. aureus clinical isolates (MIC\(_{so}\), 1–2 \(\mu\)g 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 adenosine 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 \(\mu\)g mL\(^{-1}\), respectively).\(^{44}\) Another Xisha Islands specimen of A. aff. nemochinata 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 \(\mu\)M) and Jurkat cell lines (IC\(_{50}\), 17.1 \(\mu\)M), respectively.\(^{26,149}\) A bioassy-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.\(^{154}\) Newly discovered agelasine derivatives included agelasaines 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.\(^{155}\)

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.\(^{155}\) In addition to antispasmodic activity, compound 249 was also revealed to have antimicrobial effect against C. albicans, B. subtilis and S. aureus.\(^{155,157}\) 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.\(^{155}\) The Caribbean A. clathodes has been reported to yield three antibacterial analogues, (−)-agelasidine A (252), (−)-age- lasidine 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 \(\mu\)g 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.\(^{156}\) The Xisha Islands A. mauritiana and A. nakamurai were found to produce (+)-2-oxo-agelasidine C (257)\(^{73}\) and isogelasidine B (258),\(^{44}\) respectively. Compound 258 showed mild cytotoxic activities against HL-60 and K562 cell lines (IC\(_{50}\), 33.0 and 39.2 \(\mu\)M, respectively), as well as potent antifungal activities against C. albicans (MIC, 2.34 \(\mu\)g mL\(^{-1}\)).\(^{44}\)
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 clarnhamnose (271) is a tetraglycosylated α-galactosylglycosphingolipid, containing an unusual γ-rhamnose unit in the sugar head,163 while clarnhodolides A-C (272–274) and isoclathroside 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 antiproliferative, as well as trypanocidal and leishmanicidal activities without cytotoxicity towards mammalian cells.171 The Bahamas *A. flabelliforis* 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⁻¹.172 Another examples of *Agelas*-derived sterols are 299–301 produced by Caribbean *A. schmidti*,173,174 ecdeysterone (302) and ajugasterone C (303) contained in Little Salvador Island *A. dispar*,175 and 304–307 derived from Jamaican *A. sceptrum*.176

6. Carotenoids
From Fig. 25—four carotenoids, namely α-carotene (308), isorenieratene (309), triketontrirhodin (310) and zeaxanthin (311), were identified from West Indies *A. schmidti*,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 agelorin A (314) and B (315), and 11-epi-fistularin-3 (316),177 along with two volatile compounds, 2,4,6,6-tetramethyl-3(6H)-pyridone (317) and 2,2,6,6-tetramethyl-4-piperidine (318),178 while one imidazole derivative (319), taurine (320) and the fatty acids (321–324) were isolated from the Northern Aegean Sea collection of *A. oroides*,179 and the Mediterranean *A. oroides* contained several amino-acid derivatives, namely zwitriciono zoonoomin (325), N,N,N-trimethyl-β-alanin (326), 3-(2-aminoethyll)-11-dimethyleura (327), homarine (328), norzoonoomin (329) and (–)-equinobetaine (330).177 Compounds 319–324 showed antiplasmodial, trypanocidal and leishmanicidal activities.180 The Caribbean *A. dispar* could metabolize three new betaine alkaloids, called amino zoonoomin (331), pyridinebetaine A (332) and pyridinebettein A (333), along with the known zoonoomin (325), homarine (328), trignonelline (333) 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 Salvador Island has resulted in 3,7-dimethylisouguinine (336) being reported.180 The Xisha Islands *A. clathrodes* was revealed to contain 337–339, with 338 exhibiting moderate cytotoxicity against cancer cell line SGC7901 (IC₅₀, 13.2 μg mL⁻¹).178 The identification of four brominated phospholipid fatty acids 340–343 from the Caribbean *Agelas* sp.178 and an anti-mycobacterial bifunctionalized sphingolipid, leucettamol A (344), detected in another unclassified Indonesian *Agelas* specimen181 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 gracilothere A–C (348–350) from Amami–oshima Island *A. gracilis*,182 together with nemocehioxide A (351) and 352–355 from Xisha Islands *A. aff. nemoechinata*.183 Bioactivity tests indicated that compounds 348–350 showed antimalarial activity against *Plasmodium falciparum* (IC₅₀, 0.5–10 μg mL⁻¹), whereas 349 also possessed antileishmanial activity.184

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
| Compound | Species | Local of collection | Bioactivity | Ref. |
|----------|---------|---------------------|-------------|------|
| **Pyrrrole alkaloids** | | | | |
| 1 | A. oroides | Naples | Broad spectrum<sup>a</sup> | 8, 9 and 16–27 |
| 2 | A. clathrodes | Desecheo Island | Broad spectrum<sup>a</sup> | 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<sup>b</sup> | 30 and 31 |
| 9 | A. cf. mauritiana | Solomon Islands | NR | 32 |
| 10, 11 | Agelas sp. | Okinawa | NR | 34 |
| 12 | A. clathrodes, A. dispar, A. longissima, A. conifera | Little San Salvador Island | Antihistaminic, antipredatory | 35–37 |
| 13 | | | 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 | 54 |
| 41 | | | Antimicrobial | 55 |
| 42 | Agelas sp. | Okinawa | Antimicrobial | 31 |
| 43 | Agelas sp. | Okinawa | Antimicrobial | 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 | A. oroides | Tel Aviv | Cytotoxic | 27 |
| 51 | A. aff. nemoechinata | Xisha Islands | NR | 56 |
| 52 | A. nakamurai | Kuchinoerabu-jima Island | Antiangiogenic, fluorescent pH sensor | 57 and 58 |
| 53 | A. linnaei | Thousand Islands | NR | 48 |
| 54 | A. oroides | Naples | Immunosuppressive, antipredatory | 8, 18 and 59 |
| 55 | | | Inhibitor of protein tyrosine phosphatase | 8 and 60 |
| 56 | | | NR | 8 |
| 57 | | | Promoter of ascidian larval metamorphosis, inhibitor of bacterial biofilm | 17 and 27 |
| 58 | | | NR | 61 |
| 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 |
| 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 |
| 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    | A. wiedenmayeri | Florida Keys | NR | 72 |
| 82       | Agelas sp. | Okinawa | NR | 42 |
| 83       | A. ovoides | 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. ovoides | West Mediterranean | NR | 77 |
| 107–109  | A. ovoides | 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      | 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  | A. longissima | Little San Salvador Island | Antibacterial | 95 |
| 128      | A. dispar | Little San Salvador Island | Antibacterial, trypanocidal, antileishmanial | 33 and 38 |
| 129      | A. longissima | 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      | A. ovoides | Mediterranean | Antifungal, antifungal | 49 |
| 138      | Agelas sp. | Okinawa | NR | 98 |
| 139, 140 | Agelas sp. | Indonesia | NR | 67 |
| 143      | A. ovoides | 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 | A. conifera | Belize | Antibacterial | 110 |
| 158, 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. nakamura | Okinawa             | Inhibitor of Na⁺,K⁺-ATPase | 126–128 |
|          |         |                     | 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 | Eniwetok          | Broad spectrum | 140 and 142 |
| 215      |         |                     | NR          | 141 |
| 216      | A. nakamura | Menjangan Island   | Cytotoxic, antifouling | 48 |
| 217      |         |                     | Cytotoxic, antifouling, radiosensitizer | 48 and 144 |
| 218      | Agelas sp. | Papua New Guinea   | Trypanocidal, cytotoxic | 130 |
| 219–221  | A. nakamura | Papua New Guinea   | NR          | 145 |
| 222      | A. citrina | Caribbean Sea      | NR          | 146 |
| 223      | Agelas sp. | Okinawa            | Antimicrobial | 147 |
| 228      |         |                     | NR          |     |
| 229, 230 |         |                     | Antimicrobial |     |
| 231–233  | A. nakamura | Okinawa             | Antibacterial | 135 |
| 234–237  | A. mauritiana | Xisha Islands   | NR          | 73 and 148 |
| 238      |         |                     | Antibacterial |     |
| 239      |         |                     | NR          |     |
| 240      |         |                     | Antibacterial, antileishmanial |     |
| 241      | A. nakamura | 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. nakamura | 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. nakamura | Xisha Islands       | Cytotoxic, antifungal | 44 |
| 259      | A. nakamura | Okinawa            | NR          | 156 |
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

Table 1 (Contd.)

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

*See main text for the bioactivities. *b Not reported.
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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