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Review

Marine *Streptomyces*-Derived Novel Alkaloids Discovered in the Past Decade

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Abstract: Natural alkaloids of actinomycetes origin and synthetic derivatives have always been among the important suppliers of small-molecule drugs. Among their biological sources, *Streptomyces* is the highest and most extensively researched genus. Marine-derived *Streptomyces* strains harbor unconventional metabolic pathways and have been demonstrated to be efficient producers of biologically active alkaloids since more than 60% of these compounds exhibit valuable activity such as antibacterial, antitumor, anti-inflammatory activity, etc. This review comprehensively summarizes novel alkaloids produced by marine *Streptomyces* discovered in the past decade, focusing on their structural features, biological activity and pharmacological mechanisms. Future perspectives on the discovery and development of novel alkaloids from marine *Streptomyces* are also provided.

Keywords: marine *Streptomyces*; alkaloid; secondary metabolite; discovery; development

1. Introduction

The Extensive marine habitats differ greatly from the land in terms of temperature, pressure and inorganic salt content thereby providing a wealth of ecological and biogenetic diversity [1]. Benefiting from technological advances in deep-sea resource extraction and microbial culture methods, the number of new microbial species with unique metabolisms is constantly expanding in recent years [2]. Natural products of marine microbial origin are more likely to have novel skeletons and significant pharmacological activity [3]. It is estimated that at least 30,000 compounds with therapeutic potential have been isolated from marine microorganisms [4]. Actinomycetes are one of the largest phyla of bacterial groups and are ubiquitous in both terrestrial and marine ecosystems [5]. Their biosynthetic gene clusters (BGCs) have well-known talents in the metabolization of complex natural products [6]. *Streptomyces*, as the most numerous and advanced genus of actinomycetes, is the source of 60% natural antibiotics, and classic examples widely are used in clinical practice including erythromycin, streptomycin and rifamycin [7,8]. In the past thirty years, the number of novel metabolites produced by marine *Streptomyces* as a percentage of the total source has increased from 23.0% to 40.1% per decade (Figure 1), suggesting these *Streptomyces* strains play a more and more important role in the production of new natural products.

Alkaloids are the main chemical constituents in secondary metabolites of actinomycetes and one of the most druggability types of compounds [9]. Most of these nitrogen-containing molecules have complex ring structures with promising pharmacological activity [10]. With the technical development of microbial genomics and metabonomics, the biosynthetic potential of marine *Streptomyces* had been deeply explored in the past decade. By extensive literature search and analysis, this review firstly provides a comprehensive overview of all new alkaloids produced by marine *Streptomyces* strains reported between January 2013 and June 2023. According to their chemical structures, these novel metabolites (**1**-**259**) are grouped into nine types including indole, pyrrole, oxazole and thiazole, pyridine, pyrazine and piperazine, phenazine and phenoxazine, indolizidine

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and pyrrolizidine, amide and miscellaneous alkaloids, and are respectively introduced as followings. Detailed information for these substances is summarized in Table S1.

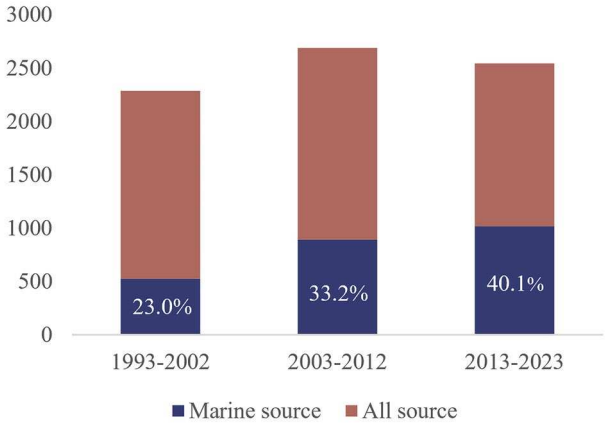

Figure 1. Source and statistics of new compounds from *Streptomyces* over the past three decades.

2. Indoles

Indoles are bicyclic alkaloids that usually use tryptophan or tryptamine as biosynthetic precursors [11]. They are common and growing rapidly in the secondary metabolites of marine-derived microorganisms with a wide range of biological activities [12]. Compounds **1-56** have been described as indole alkaloid derivatives of marine *Streptomyces* origin including bisindole, indole sesquiterpenoid and other miscellaneous indole.

2.1. Bisindoles

Bisindole alkaloids represent a family formed by the oxidation and polymerization of two L-tryptophan molecules, which have more pronounced biological activities compared to the indole monomer structure [13]. These alkaloids have been reported to have cytotoxic, antibacterial and antiviral activities, among which the well-known molecules are the anticancer compound staurosporine and chlorinated bisindole rebeccamycin [14].

2.1.1. Staurosporines

The potent protein kinase C (PKC) inhibitor (IC_{50} = 2.7 nM) staurosporine containing indolo[2,3-*a*]carbazole structure was firstly discovered from *S. staurosporeus* in 1977 [15]. Lately several analogues had been isolated and approved for clinical use, such as midostaurin and lestaurtinib [16,17]. Compounds **1**-**4** (Figure 2) were also marine *Streptomyces*-derived staurosporine derivatives and were shown to have significant selective inhibition of Rho-associated protein kinase (ROCK2), PKC and Brution tyrosine kinase (BTK) [18,19]. Biosynthesis study indicated that the C-N bond linking the aglycone and deoxysugar moiety of staurosporine is catalyzed by cytochrome P450 enzymes, and holyrine A is a biosynthetic intermediate of C-5′ and N-12 unformed C-N bonds [20]. Twelve novel holyrine A derivatives (**5-16,** Figure 2) were isolated from five marine-derived *Streptomyces* sp. strains [19,21–23]. All compounds strongly or moderately exhibited cytotoxic and enzyme inhibitory activity with IC_{50} values ranged from 0.0057 to 16.6 μM. When cultured in liquid medium with 5-hydroxy-*L*-tryptophan precursors, strain *Streptomyces* sp. OUCMDZ-3118 could produce a new analogue 3-hydroxy-K252d (**17,** Figure 2), which demonstrated cytotoxicity against A549 and MCF-7 cell lines with IC_{50} values of 1.2 ± 0.05 μM, 1.6 ± 0.09 μM,respectively [24].

Moreover, six staurosporine derivatives named streptocarbazoles C-H (**18-23,** Figure 2) were extracted from *Streptomyces* sp. DT-A65, DT-A61 and OUCMDZ-5380 [19,23,25]. Streptocarbazoles D and E rarely contained a hydroxyl group at the C-3 position. Compound **20** inhibited PC3 cell line with an IC_{50} value of 5.6 μM, while compounds **21-23** inhibited acute myeloid leukemia cell line MV4-11 (IC_{50} = 0.81-1.88 μM). In addition, strain DT-A61 collected another staurosporine analogue (**24,**

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Figure 2**)**, which exhibited extremely potent cytotoxic activity against PC3 cells with an IC_{50} value of 0.16 Mm [19]. Compounds with a glycosyl unit double-linked to the aromatic aglycone by two C-N bonds (similar to staurosporine) showed better biological activity.

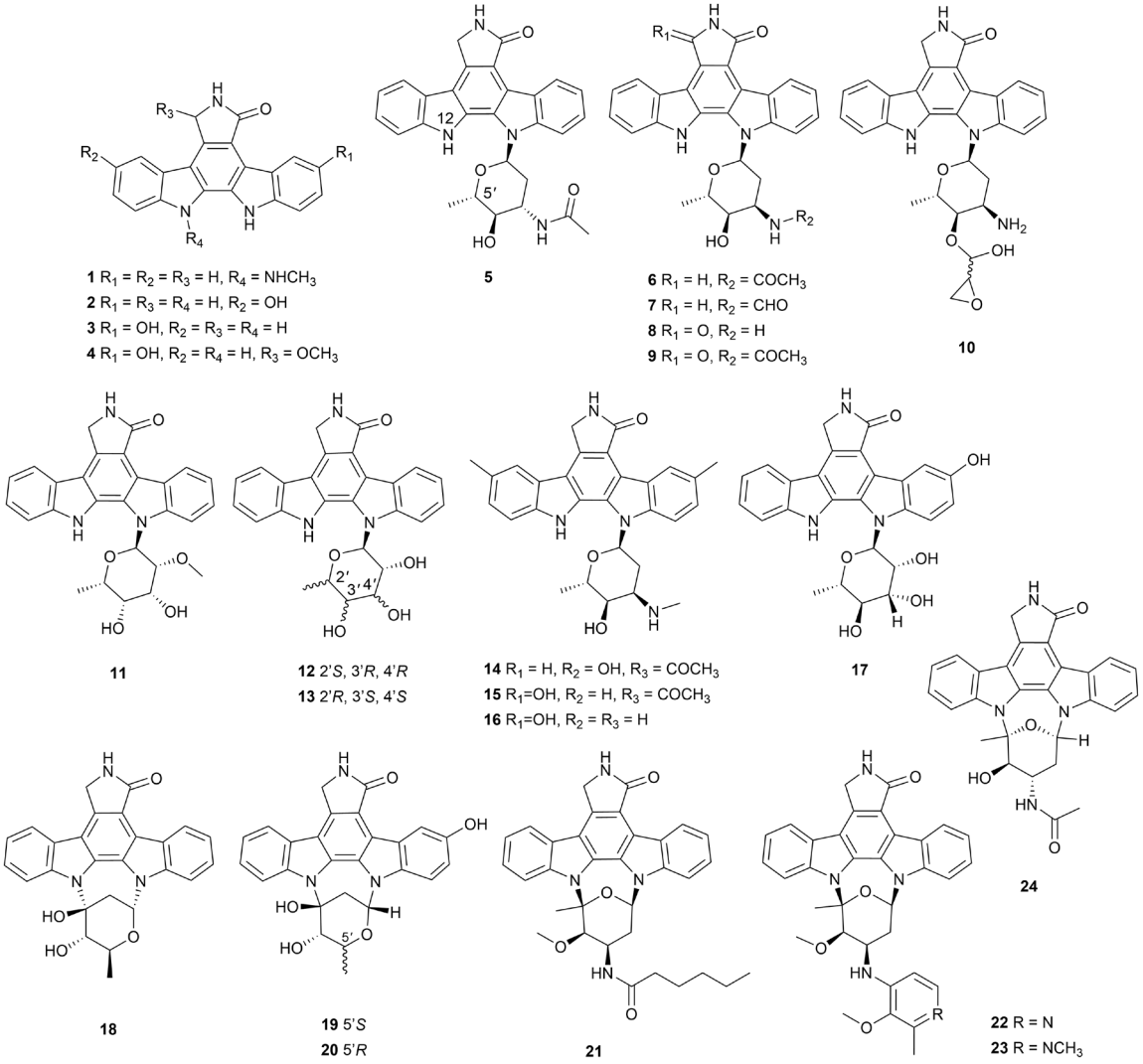

Figure 2. Chemical structures of compounds **1-24** isolated from marine *Streptomyces*.

2.1.2. Halogenated bisindoles

To the best of our knowledge, all bisindoles from marine *Streptomyces* are chlorinated (**25-39,** Figure 3). Indimicins A−E (**25-29**) and lynamicins F-G (**30** and **31**) were obtained from a deep-sea-derived *Streptomyces* sp. SCSIO 03032 by solid phase extraction with XAD-16 resin [26]. These compounds had unusual 1′,3′-dimethyl-2′-hydroindole structures. In order to characterize the function of gene *spmH* which was predicted to be an L-Trp 5-halogenase, the authors inactivated this gene in strain SCSIO 03032 and obtained four new bisindole without halogen substituent named spiroindimicins G-H (**32-33**) and indimicins F-G (**34-35**) [27]. It was confirmed that *spmH* functioned as halogenase and acted in early biosynthesis using L-Trp as substrate. Compounds **32** and **33** showed various degrees of cytotoxicity against four cancer cell lines (SF-268, MCF-7, HepG2 and A549). Indimicin B (**26**) was seen to have antitumor activity only against MCF-7 cell line with an IC_{50} value of 10.0 μM.

Two non-typical bisindole spiroindimicins E and F (**36** and **37**) were purified from the metabolites of strain MP131-18 with cluster 36 being predicted to be the gene cluster responsible for bisindole biosynthesis [28]. Only compound **36** showed weak activity against *B. subtilis*. In addition, *Streptomyces* sp. SCSIO 11791 produced two new chlorinated bisindoles (**38** and **39**) which displayed

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moderate cytotoxicity against four tumor cells with IC_{50} values ranging from 2.9 μM to 19.4 μM [29]. Compound **38** additionally exhibited cytotoxic activity against MDA-MB-231 and NCI-H460 cell lines as well as inhibition of Gram-positive bacteria. The structure-activity relationship suggested that the substitution of C-6″ position by the chlorine atom was more beneficial to the biological activity.

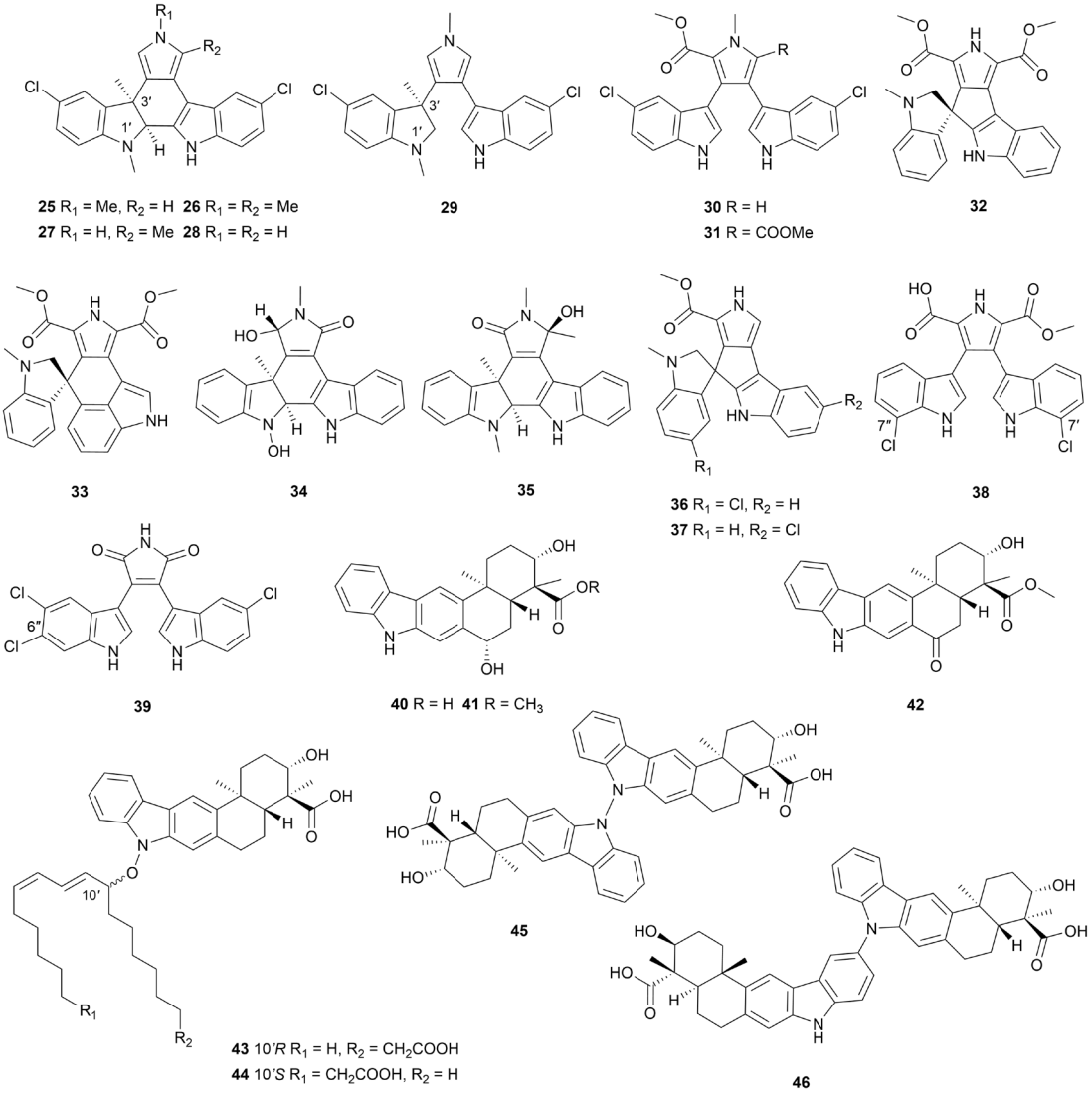

Figure 3. Chemical structures of compounds **25-46** isolated from marine *Streptomyces*.

2.2. Indole sesquiterpenoids

The first bacterial-derived indole sesquiterpenoid alkaloid named xiamycin was isolated from an endophytic *Streptomyces* sp. from *B. gymnorrhiza* in 2010 [30]. In recent years, compounds of this family have been found in marine *Streptomyces*, and attracted attention because of their plant pathogen antibacterial activity, anti-HIV and anti-tumor activity [31].

Xiamycins C-E (**40-42,** Figure 3) were isolated from *Streptomyces* sp. HK-18 [32]. Compounds **41** and **42** exhibited strong activity against the replication of porcine epidemic diarrhea virus (PEDV) in a dose-dependent manner with EC_{50} value of 0.93 μM and 2.89 μM, respectively. The mechanism of action was inhibited the synthesis of key structural proteins for PEDV to prevent virus replication. The methyl ester was important functional group to maintain activity. In 2023, the team overexpressed the *orf2011* gene encoding the LuxR family regulator in the *Streptomyces* sp. HK-18 [33]. The mutant strain afforded two new members of the xiamycins family containing an N-O bone linked aliphatic chain structure named lipoxiamycins A and B (**43** and **44,** Figure 3), as well as increased the production of xiamycins dimers dixiamycins A and C (**45** and **46,** Figure 3). The results

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of anti-inflammatory experiments showed that compounds **43** and **45** could significantly inhibit the production of lipopolysaccharide-induced NO, with IC_{50} values of 9.89 ± 0.92 μM and 4.12 ± 0.22 μM, respectively.

2.3. Other indoles

The first novel naturally derived indolinone-naphthofuran alkaloids, (±)-Pratensilins A-C (**47-49,** Figure 4), was isolated from *Streptomyces* pratensis KCB-132 obtained from a marine sediment, Bohai Sea, China [34]. After adding 50 μM of lanthanum chloride to the liquid medium, a new indolinone-naphthofuran analogue (±)-Pratensilin D (**50,** Figure 4) was detected in the metabolites [35]. (-)-Pratensilin D (**50**) exhibited more potent biological activity against Gram-positive bacteria, yeast and five human cancer cell lines. In addition, compound **47** displayed moderate cytotoxicity against eight human cancer cell lines (IC_{50} = 2.4 μM-67.4 μM). The isolation of three novel anthranilate-containing alkaloids, anthranosides A−C (**51-53,** Figure 4), were reported from a sponge-derived *Streptomyces* sp. CMN-62 (Naozhou Island, China) [36]. Only anthranoside C (**53)** exhibited a 171 μM IC_{50} against the influenza A H_1N_1 virus. Four novel indole alkaloids streptoindoles A-D (**54-57,** Figure 4) were ob3tained from *Streptomyces* sp. ZZ1118 rice solid medium derived from a gut sample of marine shrimp (*Penaeus* sp.) [37]. Compound **56** potently inhibited *E. coli* and *C. albicans* (MIC = 7 μg/mL) and compound **57** was weakly active against MRSA only (MIC = 25 μg/mL). Compounds **54** and **55** were effective against all three pathogens with MIC values of 7-25 μg/mL.

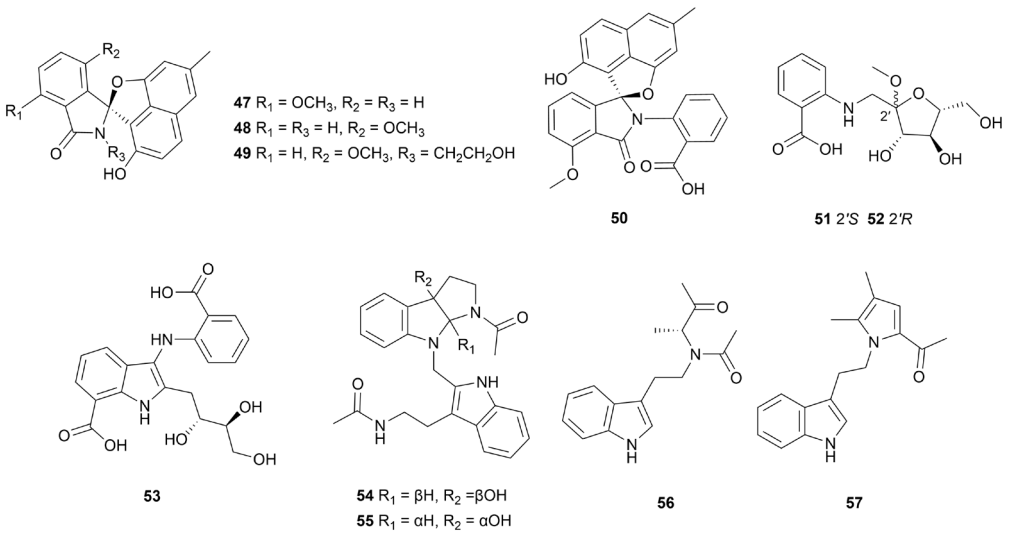

Figure 4. Chemical structures of compounds **47-57** isolated from marine *Streptomyces*.

3. Pyrroles

Due to structural similarity between pyrroles and endogenous substances in the human body such as nucleotides and easy formation of hydrogen bonds, pyrrole alkaloids have more potential to be designed as lead compounds [38]. Marine pyrrole derivatives usually have more unique structures and significant pharmacological activities such as antimicrobial, antiproliferative, anti-inflammatory and antiviral activities [39].

3.1. Pyrrolones and pyrrolidones

This part describes the cases in which pyrrole or pyrrolidine pentacyclic rings are replaced by carbonyl groups. The formed pyrrolone and pyrrolidone structures are crucial heterocyclic pharmacophores in medicinal chemistry with significant biological activities [40]. The tirandamycins are a class of bacterial RNA polymerases (RNAPs) inhibitors containing dienoyl tetramic acid and 2,4-pyrrolidinedione structures [41]. Two new tirandamycin analogues tirandamycin K and isotirandamycin B (**58** and **59,** Figure 5), together with two known derivatives (**60** and **61,** Figure 5)

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were produced from marine *Streptomyces* strains [42,43]. Compound **58** was the first linear tirandamycin derivative which avoided bicyclic ketal ring formation due to the inability of the C-9S hydroxyl group to be nucleophilic attacked by C-13. In the pathogenic bacterial inhibitory activity assay, compounds **59-61** showed obvious antibacterial activity against *S. agalactiae* with MIC values of 2.5-5.0 μg/mL. However, compound **58** was inactive, therefore the authors deduced that the bicyclic ketal ring moiety was a necessary RNA polymerase target.

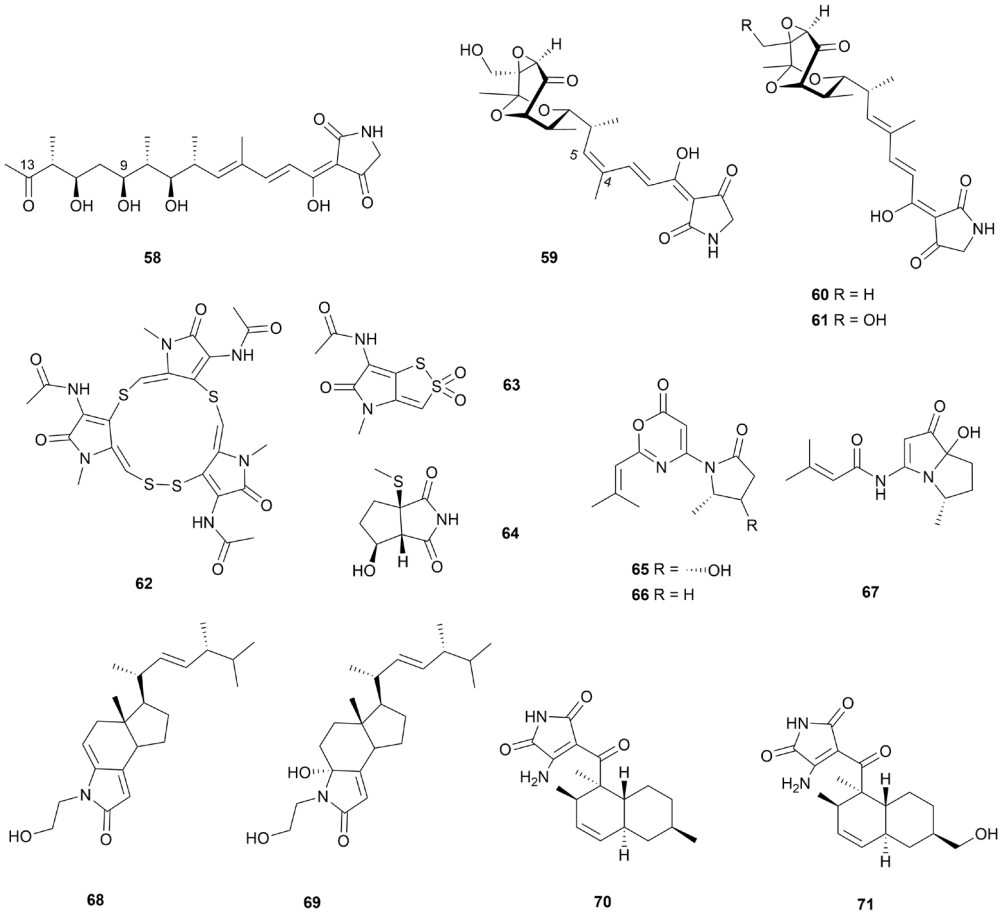

Figure 5. Chemical structures of compounds **58-71** isolated from marine *Streptomyces*.

Three sulfur substituents-containing pyrrolizidine alkaloids (**62-64,** Figure 5) were discovered from two marine *Streptomyces* [44,45]. Thiolopyrrolone A (**62**) gave a novel macrocyclic skeleton and also inhibited Bacille Calmette–Guérin (BCG), *M. tuberculosis*, and *S. aureus* with MIC values of 10, 10 and 100 μg/mL, respectively. Bacillimide (**64**) had a rare cyclopenta[c]pyrrole-1,3-dione structure bearing a methylsulfide group. This novel pyrrolidone alkaloid was an ICL enzyme moderate inhibitor under C_2-carbon-utilizing conditions, demonstrating an IC_{50} value of 44.24 μM against *C. albicans*. In addition, *Streptomyces* sp. KMF-004 yielded two unusual pyrrolidinyl-oxazinone alkaloids, Salinazinones A and B (**65** and **66,** Figure 5) [46]. Compound **66** showed an inhibitory effect on LPS-induced NO production by BV-2 microglia cells (IC_{50} values of 17.7 μM). The authors speculated that the oxazinone structure was synthesized by amide cyclization and gave a possible biosynthetic intermediate named bohemamine D (**67**). Anandins A and B (**68** and **69,** Figure 5) as two unique pyrrolidone-containing steroidal alkaloids were isolated from *Streptomyces anandii* H41-59 derived from mangrove sediments [47]. The compound **68** showed moderate inhibitory effects against cancer cell lines MCF-7, SF-268 and NCI-H460 (IC_{50} = 7.5-7.9 μg/mL, respectively). Two new pyrrolidone derivatives ligiamycins A and B (**70** and **71,** Figure 5) were obtained by co-culture of two marine-derived strains *Streptomyces* sp. GET02.ST and *Achromobacter* sp. GET02.AC [48]. Biological evaluation showed that the compound **70** exhibited the moderate effects against *S. aureus* and *S.*

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enterica (both MIC values of 16 μg/mL), while compound **71** was cytotoxic against HCT116 cancer cells (IC_{50} = 20.1 μM).

3.2. Pyrrolobenzodiazepines

Pyrrolo[1,4]benzodiazepines (PBDs) are tricyclic alkaloids which can be divided into [2,1-*c*][1,4], [1,2-*a*][1,4] and [1,2-*d*][1,4] structural types according to the different positions of the pyrrole ring binding [49]. Natural PBDs were originally derived from *Streptomyces* as DNA alkylating antitumor drugs, and the classical representatives are anthramycin, sibiromycin and tomaymycin [50]. A new pyrrolobenzodiazepine alkaloid, oxoprothracarcin (**72,** Figure 6), was produced by *Streptomyces* sp. M10946 obtained from the mangrove sediment [51]. The new compound had antiproliferative effects against MDA-MB-231 cells and A549 cells at a concentration of 10 μM, with growth inhibition rates of 10.2% and 7.3%. In another study one new PBDs derivative 7-methoxy-8-hydroxy cycloanthranilylproline (**73,** Figure 6) along with a known analogue cycloanthranilylproline (**74,** Figure 6) were isolated from marine-derived *Streptomyces cacaoi* 14CM034 [52]. The MIC values of the compounds for several common pathogens were ranging from 8.75 to 32 μg/mL including *E. coli*, MRSA, *E. faecium*, *P.aeruginosa* and *C. albicans*.

3.3. Ansamycins

Ansamycins are a class of important macrocyclic lactam alkaloids obtained mainly from actinomycetes, of which the more representative include the anti-tuberculosis drug laofomycin, Hsp90 inhibitor Geldamycin and anticancer drug ansamitocin P-3 [53]. According to the different aromatic cores, ansamycins can be divided into benzene series and naphthalene series [54]. Hygrocins is a subclassification of naphthalenic ansamycins, whose amides are 5-membered or 7-membered nitrogen heterocycles [55]. After knocking out the gene *gdmAI* responsible for the synthesis of the high-yield ansamycin analogue geldanamycin in *Streptomyces* sp. LZ35, four new compounds hygrocins C−F (**75-78,** Figure 6) were purified [56]. In 2015, this team modified the strain LZ35 again by overexpress *hgc1*, a LAL-type activator specific for the biosynthesis process of hygrocins [57]. The mutant strain then produced three new hygrocins derivatives, hygrocins H–J (**79-81,** Figure 6). Compounds **75**, **76**, **78** and **79** were exhibited to be cytotoxic to MDA-MB-231, PC3 and HeLa cell lines with IC_{50} values of 0.5-5.0 μM. *Streptomyces* sp. ZZ1956 afforded nine new compounds named hygrocins K–S (**82-90,** Figure 6) [58]. Compounds **85**, **88** and **89** showed antiproliferative activity against human glioma U87MG and U251 cells with IC_{50} values of 7.04-10.46 μM. In addition, compounds **85**, **86** and **89** displayed antibacterial activity against MASA and *E. coli* (MIC = 8-24 μg/mL).

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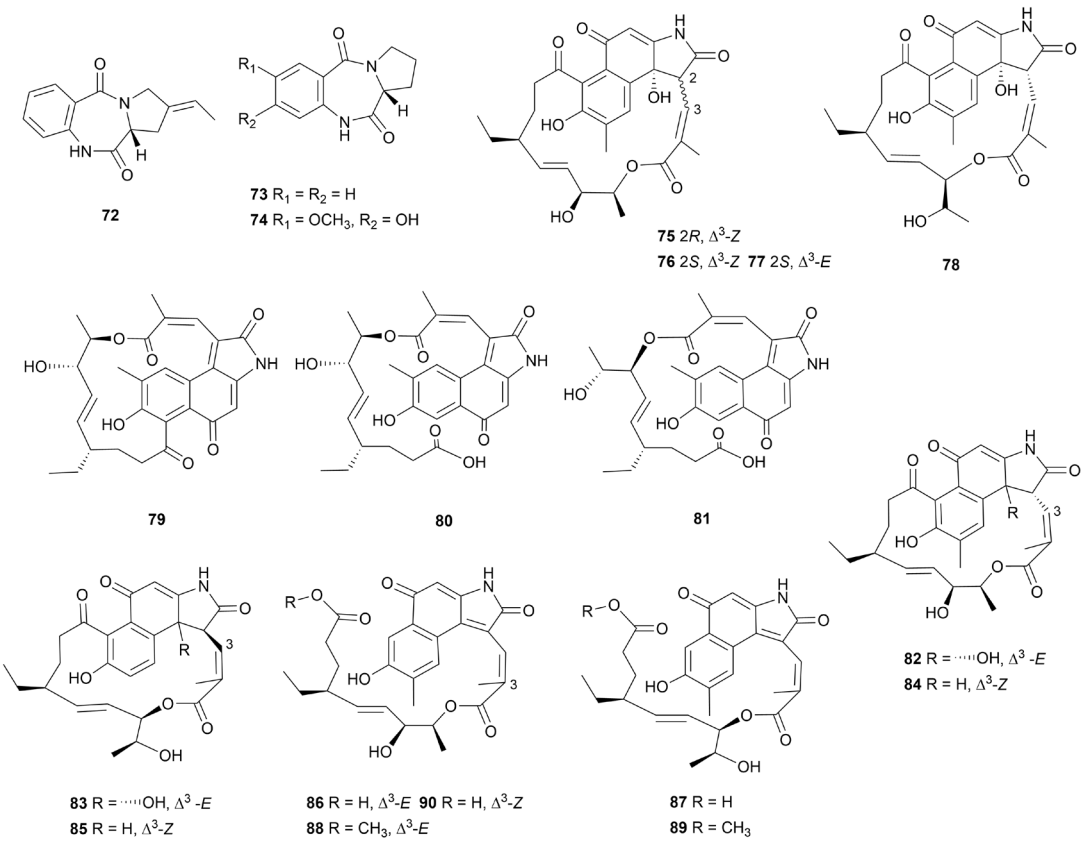

Figure 6. Chemical structures of compounds **72-90** isolated from marine *Streptomyces*.

Three ansamycin derivatives of novel skeletons, ansalactams B-D (**91-93,** Figure 7), were isolated from marine sediment-derived *Streptomycetes* sp. CNH189 [59]. Antibacterial activity tests showed that compounds **91-93** had weak inhibitory activity against MRSA with MIC values of 31.2, 31.2, and 62.5 μg/mL, respectively. A chemical study of the strain *Streptomyces* sp. KFD18 produced four new ansamycin analogues named divergolides T–W (**94-97,** Figure 7) [60]. All compounds showed various degrees of cytotoxic activity against cancer cell lines SGC-7901, K562, Hela and A549 with **94** exhibiting the most promising inhibitory effect with IC_{50} values of 2.8-14.9 μM.

3.4. Other pyrroles

Chlorizidine A (**98,** Figure 7), biosynthesized based on the NRPS-PKS pathway, was an unprecedented alkaloid containing chlorinated 5H-pyrrolo[2,1-*a*]isoindol-5-one fragment [61]. It exhibited an IC_{50} value of 3.2-4.9 μM against the HCT-116 adenocarcinoma cell line with the pyrrole isoindolone ring moiety as a key pharmacophore. Isolated from marine sediment samples, the *S. zhaozhouensis* 208DD-064 produced two new halogenated pyrroles, streptopyrroles B and C (**99** and **100,** Figure 7) [62]. Compounds **99** and **100** showed promising activity of three Gram-positive bacteria (MIC = 0.7-2.9 μM) with inverse correlation to the number of halogen substituents. Moreover, streptopyrrole B (**99**) exhibited moderate activity against six cancer cell lines. Three novel pyrrole ether compounds of the indanomycin family (**101-104,** Figure 7) were isolated from *S. antibioticus* PTZ0016 extracts based on antimicrobial activity [63]. Biological evaluation showed that compounds **101-104** inhibited the growth of *S. aureus* with MIC values of 4.0-8.0 μg/ml. Nitricquinomycins A-C (**105-107,** Figure 7) is the first example of naphthopyrrolediones derivatives containing angolosamine moiety [64]. Compound **107** was significantly effective against A2780 cell lines (IC_{50} = 4.77 μM) and exhibited moderate activities against *E. coli*, *S. aureus* and *C. albicans* (MIC values of 20-40 μM). Isolated from a deep-sea floor, the *Streptomyces* sp. GGS53 produced two new pyrrolosesquiterpenes glaciapyrroles, D and E (**108** and **109,** Figure 7) [65]. Influenza A viruses were used to infect Mardin–

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Darby canine kidney cells and **109** exhibited significant antiviral activity, resulting in the reduction of the viral titer by 70%.

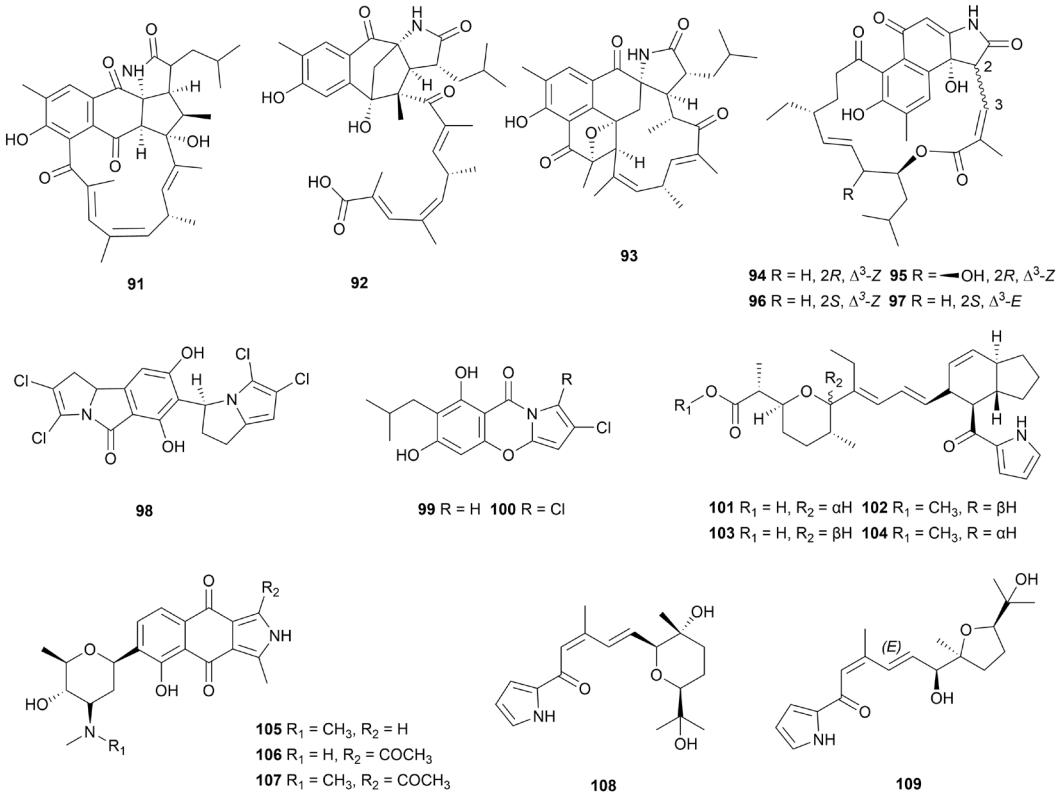

Figure 7. Chemical structures of compounds **91-109** isolated from marine *Streptomyces*.

4. Oxazoles and thiazoles

Oxazole and thiazole rings exhibit a wide range of pharmacological activities such as antiproliferative, anti-inflammatory and antimicrobial activity by binding non-covalently to many enzyme and receptor targets [66,67]. Most of these alkaloids have been mentioned in other chapters, and this chapter summarizes the remaining five compounds **110-114** (Figure 8). Under LC-MS/MS molecular networking guidance, five novel siderophores containing oxazole or thiazole rings were isolated from *S. diastaticus* NBU2966 collected form marine sponge Axinellida sp., named pulicatin J (**110**), thiazostatin C (**111**), methyl thiazostatin B (**112**), spoxazomicin E (**113**) and streptochelin A (**114**) [68]. Compounds **110-114** were inactive against *S. aureus*, MRSA, *B. subtilis* and *P. aeruginosa*.

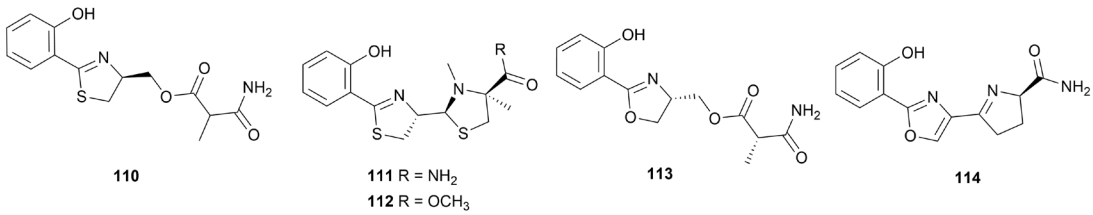

Figure 8. Chemical structures of compounds **110-114** isolated from marine *Streptomyces*.

5. Pyridines

Pyridine alkaloids are a class of important skeletons for maintaining the pharmacological activity of drugs [69]. This chapter summarizes pyridine and its derivatives of marine *Streptomyces* sp. including pyridone, benzopyridine (quinoline) and the saturated variant piperidine.

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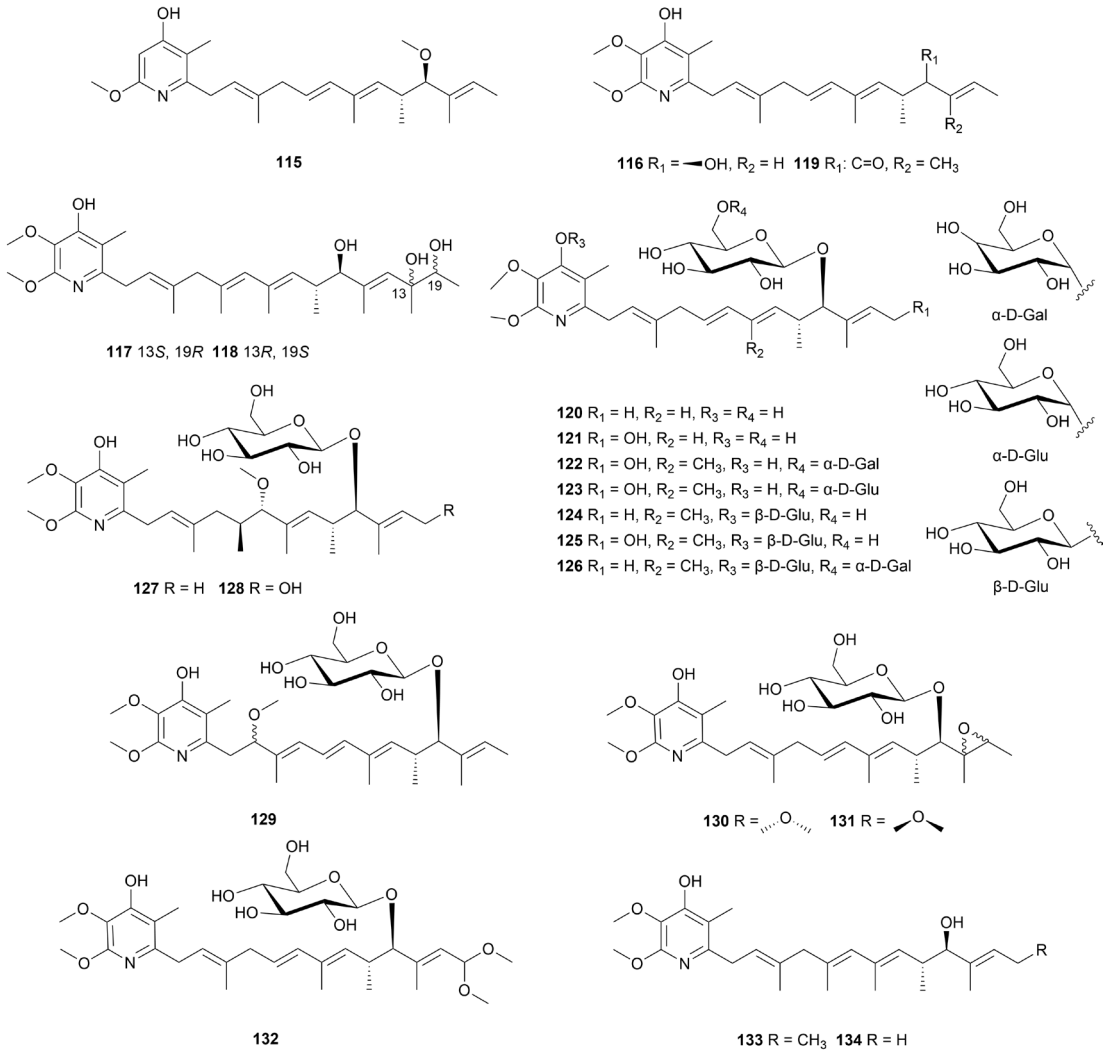

Figure 9. Chemical structures of compounds **115-134** isolated from marine *Streptomyces*.

5.1. Piericidins

Piericidins are a class of 4-pyridinol alkaloids decorated with methylated polyene side chains, mostly isolated from actinomycetes of soil, marine or bio-symbiotic origin [70]. Due to structural similarities with coenzyme Q, some piericidins exhibit NADH−ubiquinone oxidoreductase inhibitory activity [71]. Moreover, insecticidal, cytotoxic and bactericidal effects of piericidins had been reported. When a mangrove soil-derived *Streptomyces* sp. CHQ-64 was knocked out of the gene *rdmF*, a positive regulatory gene for reedsmycins (polyol polyene macrolides), one mutant strain was shown to produce a new piericidin analog (**115,** Figure 9), which displayed prominent cytotoxicity against the HeLa, NB4, A549 and H1975 cell lines (IC_{50} values of 0.003-0.56 μM). Seventeen piericidin derivatives (**116-132,** Figure 9) purified from *S. psammoticus* SCSIO NS126 from mangrove sediment samples showed strong or moderate activity against renal cell (RCC) carcinoma cell line ACHN with IC_{50} values of 0.31-60 μM [73]. Molecular mechanisms suggested that the peroxiredoxin 1 (PRDX1) as an anti-RCC target to decrease the level of reactive oxygen species in cells through increased expression. Piericidin A5 (**133**) together with G1 (**134**) produced by strain SCSIO 40063 exhibited antitumor activity against SF-268, MCF-7, HepG2 and A549 tumor cell lines with IC_{50} values ranging from 10.0 to 12.7 μM [74].

5.2. Quinolines

Quinolines have been designed as important skeletons in drug structures for more than two centuries [75]. Classic examples are quinine, the first effective antimalarial drug in history, and broad-

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spectrum antibiotic fluoroquinolone [76]. This subsection overviews quinoline alkaloids of marine *Streptomyces* sp. origin and their derivatives isoquinolines and quinolones. Compounds **135-142** (Figure 10) were identified as simple quinoline alkaloids purified from marine *Streptomyces*. Strain CNP975 produced two rare quinoline derivatives containing 3-hydroxyquinaldic acid (3HQA) fragments, named actinoquinolines A and B (**135** and **136**) with stronger inhibitory activity against cyclooxygenases-2 (IC_{50} of 2.13 and 1.42 μM, respectively) compared to cyclooxygenases-1 (IC_{50} of 7.6 and 4.9 μM, respectively) [77]. Three new amino acid-substituted quinoline derivatives (**137-139**) were isolated by *S. cyaneofuscatus* M-157 collected from coral samples which contained serine, glutamine and cysteine residues unit, respectively [78]. Only compound **137** displayed weak cytotoxicity against human tumor cell line HepG2 with IC_{50} value of 51.5 μM. Diazaquinomycins E-G (**140-142**) were novel diazaanthracene alkaloids and compound **140** had cytotoxic activity against the ovarian cancer cell line OVCAR5 by upregulating the cell cycle inhibitor p21 and impairing DNA (IC_{50} value of 9.0 μM) [79]. Antichlamydial activity-guided purification of a novel chlorinated quinolone ageloline A (**143,** Figure 10) from *Streptomyces* sp. SBT345 collected from the Mediterranean sponge *Agelas oroides* [80]. Compound **143** dose-dependently exhibited inhibition of *Chlamydia trachomatis* growth (IC_{50} value of 9.54 ± 0.36 μM) by inhibiting reactive oxygen species (ROS) production during the early stages of infection. The high-yield extract medium of strain B1848 afforded three new isoquinolinequinone alkaloids mansouramycins E–G (**144-146,** Figure 10) [81]. In a cytotoxicity assay against 36 tumor cells, compound **145** exhibited selective moderate cytotoxic activity (mean IC_{50} value of 7.92 μM) while compound **144** exhibited weak effect.

5.3. Other pyridines

Two new pyridine derivatives, strepchazolins A and B (**147** and **148,** Figure 10), was purified from *S. chartreusis* NA02069 [82]. Compound **147** inhibited a 64.0 μM MIC value against *B. subtilis* and a 50.6 μM IC_{50} value against acetylcholinesterase. Compound **148** was inactive, indicating that steric configuration affected biological activity. Isolated from a marine mud sample, *Streptomyces* sp. ZZ741 afforded ten novel glutarimide analogues named streptoglutarimides A–J (**149-158,** Figure 10) [83]. All new analogues were effective against MRSA (MIC = 9-11 μg/mL), *E. coli* (MIC = 8-12 μg/mL) and *C. albicans* (MIC = 8-20 μg/mL). Moreover, **156** displayed promising antiproliferative activity against glioma cells U87MG and U251 with IC_{50} values of 3.8 ± 0.6 μM and 1.5 ± 0.1 μM, respectively.

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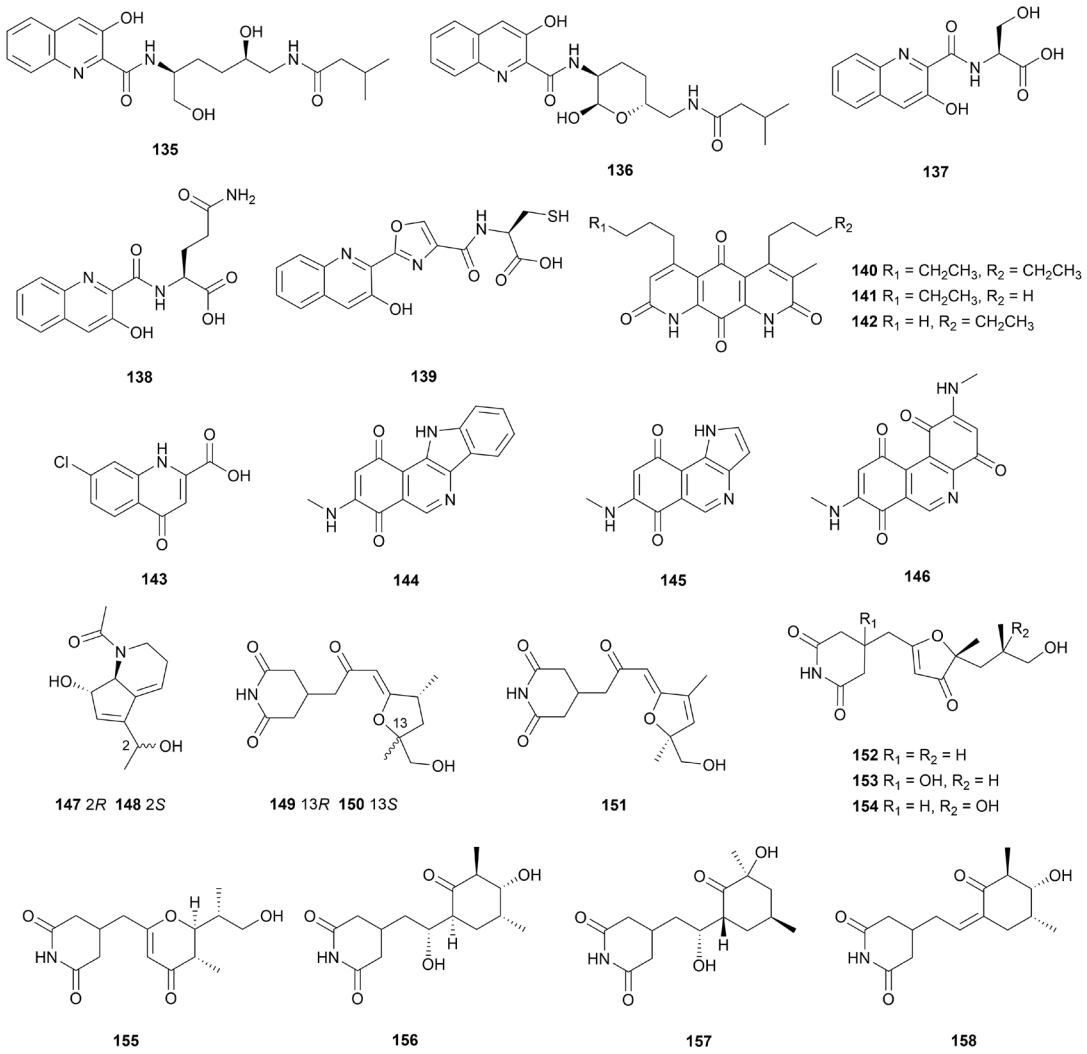

Figure 10. Chemical structures of compounds **135-158** isolated from marine *Streptomyces*.

6. Pyrazines and piperazines

6.1. Pyrazines

Owing to both nitrogen atoms acting as hydrogen bonding acceptors and the structure being conducive to nucleophilic reaction, pyrazine is often used as a classical pharmacophore.[84] Pyrazine derivatives have been reported for applications as antitumor drugs, diuretics, anti-inflammatory and anti-infective drugs [85]. Griseusrazin A (**159**, Figure 11) was isolated from a strain *S. griseus* subsp. *griseus* 09-0144 and activated the expression of heme oxygenase 1 which inhibits the upstream NF-κB pathway [86]. Therefore, it could down-regulate the expression of related enzymes iNOS and COX-2 at the transcriptional level as well as the production of inflammatory mediators NO and PGE_2. Compounds **160-162** (Figure 11) were purified by *Streptomyces* sp. Did-27 isolated from the marine tunicate *Didemnum* sp., from which **160** and **162** showed weak cytotoxicity against HCT-116 and MCF-7 cancer cell lines with IC_{50} of 25-35 μg/mL [87]. Collected from a sample of coastal soil from Zhoushan Islands, China, the *Streptomyces* sp. ZZ446 afforded four new pyrazinones of streptopyrazinones A-D (**163-166**, Figure 11) [88]. These compounds exhibit a 35.0-60.0 μg/mL MIC values against *C. albicans* and 58.0-65.0 μg/mL MIC values against MRSA.

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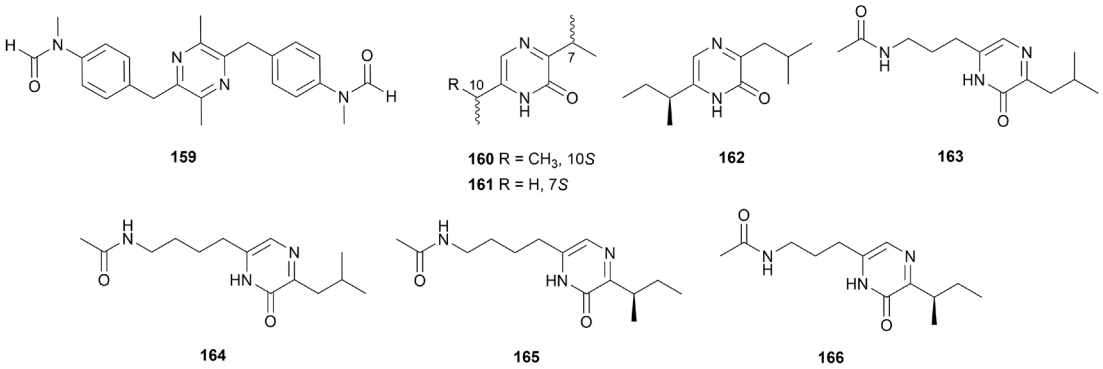

Figure 11. Chemical structures of compounds **159-166** isolated from marine *Streptomyces*.

6.2. Diketopiperazines

Piperazine alkaloids of biological origin are most commonly of the 2,5-diketopiperazines (2,5-DKPs) type, with a cyclodipeptide structure formed by condensation of two amino acids [89]. These simple dipeptides reported for multiple biological activities have a flexible skeleton with multiple chiral centers and four hydrogen bonding sites [90].

A variety of 2,5-DKPs alkaloids (**167-176**, Figure 12) had been produced by several marine-derived *Streptomyces*. Compounds **167-169** were condensed with leucine and phenylalanine residues and purified by a *Streptomyces* sp. MNU FJ-36 obtained from the intestinal fabric of *Katsuwonus* sp. [91]. All compounds were weakly inhibitory to A549 and HCT-116 cell lines. Streptodiketopiperazines A (**170**) and B (**171**) containing phenylalanine residues were isolated from the Mariana Trench source *Streptomyces* sp. SY1965 [92]. Biological evaluation showed that the novel compounds showed weak antifungal activity against *C. albicans* (MIC = 42-47 μg/mL). A new 2,5-DKPs dimer naseseazine C (**172**) had moderate inhibitory activity against chloroquine-sensitive *Plasmodium falciparum* (average IC_{50} value = 3.52 ± 1.2 μM) [93]. This dimer was connected by an unconventional C-6′/C-3 linkage and thus promoted antimalarial activity. Actinozine A (**173**) and cyclo(2-OH-D-Pro-L-Leu) (**174**) as two new 2,5-DKP alkaloids were purified from S*treptomyces* sp. Call-36 isolated from the Red Sea sponge *Callyspongia* sp. [94]. Compound **173** had a special hydroperoxy moiety on the proline residue. Antimicrobial assays against *S. aureus* and *C. albicans* revealed that **173** and **174** showed inhibition zones of 16-23 mm. Furthermore, a novel glycosylated 2,5-DKP (**175**) and its aglycone (**176**) showed inhibitory activity against MRSA, *E. coli* and *C. albicans* (MIC = 26.0-37.0 μg/mL) [95].

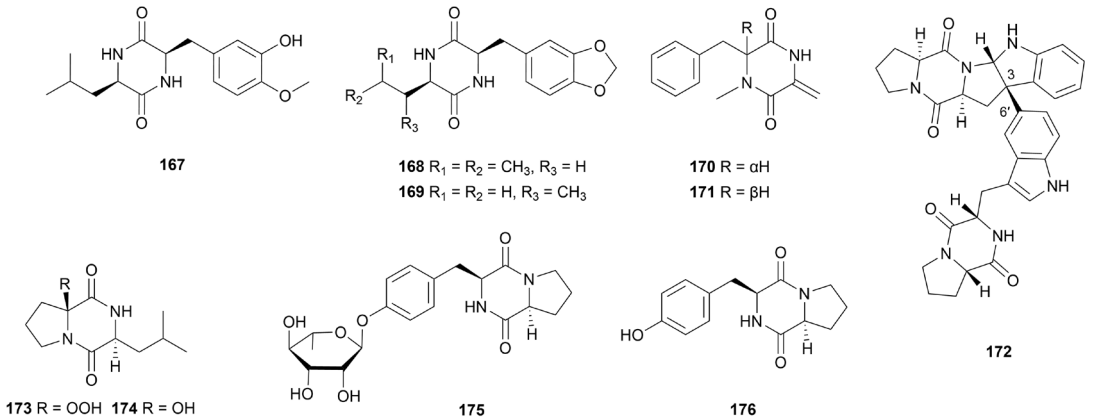

Figure 12. Chemical structures of compounds **167-176** isolated from marine *Streptomyces*.

7. Phenazines and phenoxazines

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This type of natural products are mainly derived from secondary metabolites of *Streptomyces* and *Pseudomonas* isolated from soil or marine habitats [96]. Most of the phenazine-containing alkaloids are characterized by promising biological activities such as antibacterial, antiviral, antitumor and antiparasitic effects [97]. In addition, phenoxazines are a class of phenazine derivatives whose structural cores are replaced by the oxazine ring.

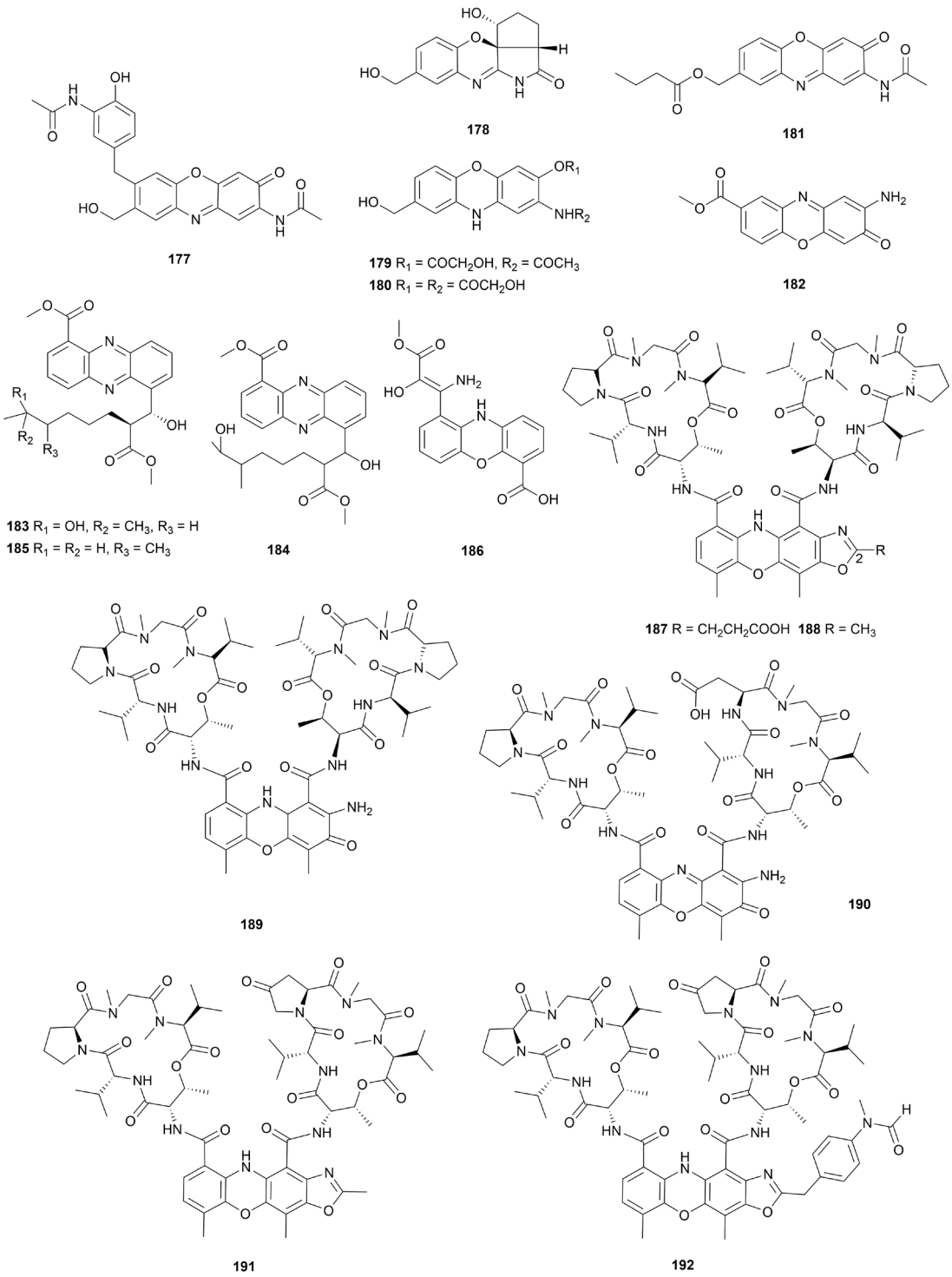

Figure 13. Chemical structures of compounds **177-192** isolated from marine *Streptomyces*.

Six novel antitumor phenoxazines venezuelines A–E (**177-181**, Figure 13) and maroxazinone (**182**, Figure 13) was isolated from two sediments-derived *Streptomyces* [98,99]. Compound **178** showed moderate antitumor activity against five cancer cell lines with IC_{50} values of 5.74-9.67 μM

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and weak activity against human hepatoma cell Bel 7042 (IC_{50} >10 μM). Notably, the cytotoxicity of this compound may be explained by significant upregulation of the orphan nuclear receptor Nur77 (apoptosis-associated) expression. **182** showed moderate antiproliferative activity against MCF7, HEPG2 and HCT116 cell lines with IC_{50} values of 4.32, 2.90 and 8.51 μg/mL, respectively. Sponges can host microorganisms colonization due to their porous structure, therefore the metabolites of sponge symbiotic microorganisms are important sources of marine natural products [100]. *Streptomyces* sp. HB202 was isolated from the sponge *Halichondria panicea* and yielded three new phenazine alkaloids streptophenazines I-K (**183-185**, Figure 13) [101]. These compounds inhibited the activity of inflammatory response associated enzyme phosphodiesterase (PDE 4B) with IC_{50} values ranging from 11.6 to 12.2 μM. In addition, compound **185** had antibacterial activity against *B. subtilis* and *S. epidermidis* (IC_{50} = 21.6 ± 6.8 μM and 14.5 ± 2.0 μM, respectively). One new phenoxazine derivative named strepoxazine A (**186**, Figure 13) was produced by a strain SBT345 obtained from the Mediterranean sponge *Agelas oroides* [102]. The IC_{50} value for strepoxazine A against promyelocytic leukemia cells HL-60 was 16 μg/mL.

Actinomycin analogues (**187-192**, Figure 13) are a class of novel tetracyclic 5H-oxazolo[4,5-b]phenoxazine alkaloids [103,104]. Neo-actinomycin A (**187**) exhibited promising cytotoxic activity against HCT116 and A549 cancer cell lines (IC_{50} = 38.7 nM and 65.8 nM, respectively), as well as the biosynthetic pathways of **187** and **188** were the condensation of actinomycin D (**189**) with α-ketoglutarate or pyruvate. Actimomycin S (**190**) and neo-actinomycins C-D (**191-192**) were bacteriostatic against five common pathogenic bacteria (MIC = 2.5-80.0 μg/mL) and exhibited potent cytotoxic activity against HepG2 liver carcinoma cell line by blocking the G0/G1 phase cell cycle.

8. Indolizidines and pyrrolizidines

8.1. Indolizidines

Indolizidine were reported to have broad biological activity such as antitumor activity, anti-infective system disease and anti-inflammatory activity [105]. Most indolizidine are obtained from plants and animals, rarely from microbial sources [106]. Only cyclizidine type of indolizidine alkaloids from marine Streptomyces sp. have been reported in the last ten years.

Eight indolizidine alkaloids cyclizidine B-I (**193-200**, Figure 14) were detected in the EtOAc extracts of a strain *Streptomyces* sp. HNA39 [107]. Cyclizidine C (**194**) showed the most promising activity against PC-3 and HCT-116 cancer cell lines with IC_{50} values of 0.52 ± 0.03 μM and 8.3 ± 0.1 μM, respectively. Moreover, compounds **194**, **197**, **199** and **200** exhibited moderate inhibitory activities against protein kinase ROCK2. In another report, a low-yielding indolizidine named cyclizidine J (**201**, Figure 14) was detected from strain HNA39 [108]. This compound had an uncommon chlorine atom substitution at the C-8 position. However, **201** lacked inhibitory activity against cancer cell line PC-3 and protein kinase. Stress culture of marine hydrothermal vent actinomycetes with heavy metal ions can activate silent biosynthetic pathways [109]. After addition of 100 μmol/L Ni^{2+} to the medium of metal-resistant *Streptomyces* sp. WU20, a new cyclizidine analogue (**202**, Figure 14) that was absent before addition was purified [110]. The authors hypothesized that the ring opening of the five-membered ring in the structure of alkaloid **202** was due to the inhibition of normal biosynthesis by heavy metal stress. Compound **202** was bacteriostatic against *B. subtilis* with MIC of around 32 μg/mL.

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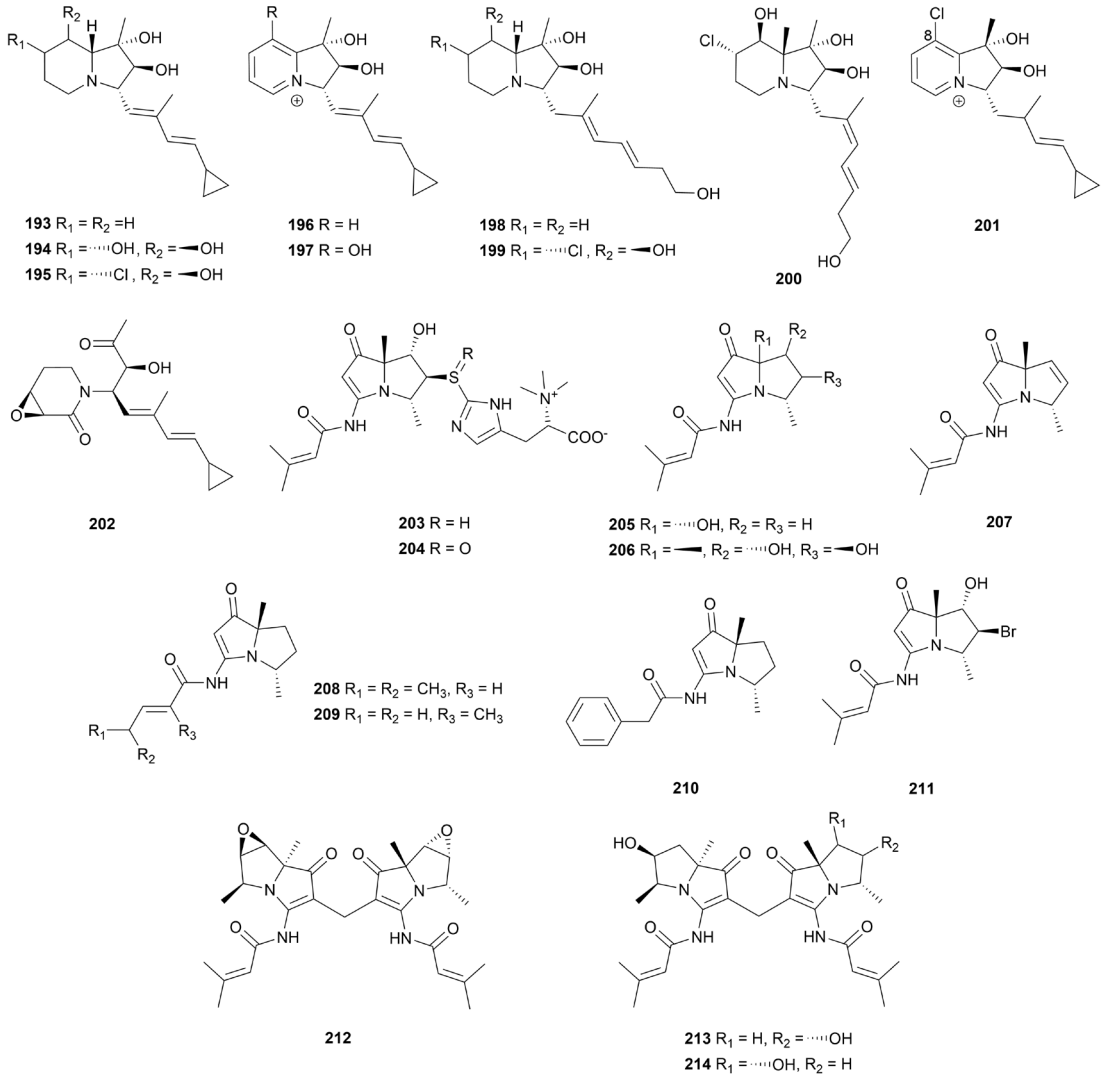

Figure 14. Chemical structures of compounds **193-214** isolated from marine *Streptomyces*.

8.2. Pyrrolizidines

Pyrrolizidines are mainly derived from plants as toxic components of chemical defense [111]. Bacterial-derived pyrrolizidines have been reported less frequently, with a total of 12 species and about 60 compounds of this class identified as of 2021 [112]。 These Pyrrolizidines are commonly biosynthesized by multidomain NRPS genes clusters as well as post-modified by FAD-dependent monooxygenases [113].

Bohemamine is a rare pyrrolizidine subtype derived only from actinomycetes [114]. The fermentation broth of a strain *S. spinoverrucosus* SNB-048 purified two new bohemamine-type pyrrolizidines named spithioneines A and B (**203** and **204**, Figure 14) with rare ergothioneine moiety [115]. In the same year, six new derivatives bohemamines D–I (**205-210**, Figure 14) were again isolated from strain SNB-048 [116]. Unfortunately, none of the compounds showed significant activity. Tracing the cytotoxic activity of *S. spinoverrucosus* SNB-032 metabolites led to the isolation of a novel bohemamine analogue 5-Br-bohemamine C (**211**, Figure 14), as well as three new dimeric bohemamines dibohemamines A–C (**212-214**, Figure 14) [117]. The authors confirmed that dimer formation is a non-enzymatic Baylis-Hillman addition reaction of monomeric compounds using formaldehyde in the medium. Compounds **213** and **214** exhibited potent cytotoxicity against NSCLC cell line A549 with IC_{50} values of 0.140 and 0.145 μM, respectively. In addition, compound **214** showed moderate activity against HCC1171 cell line (IC_{50} = 1.2 μM).

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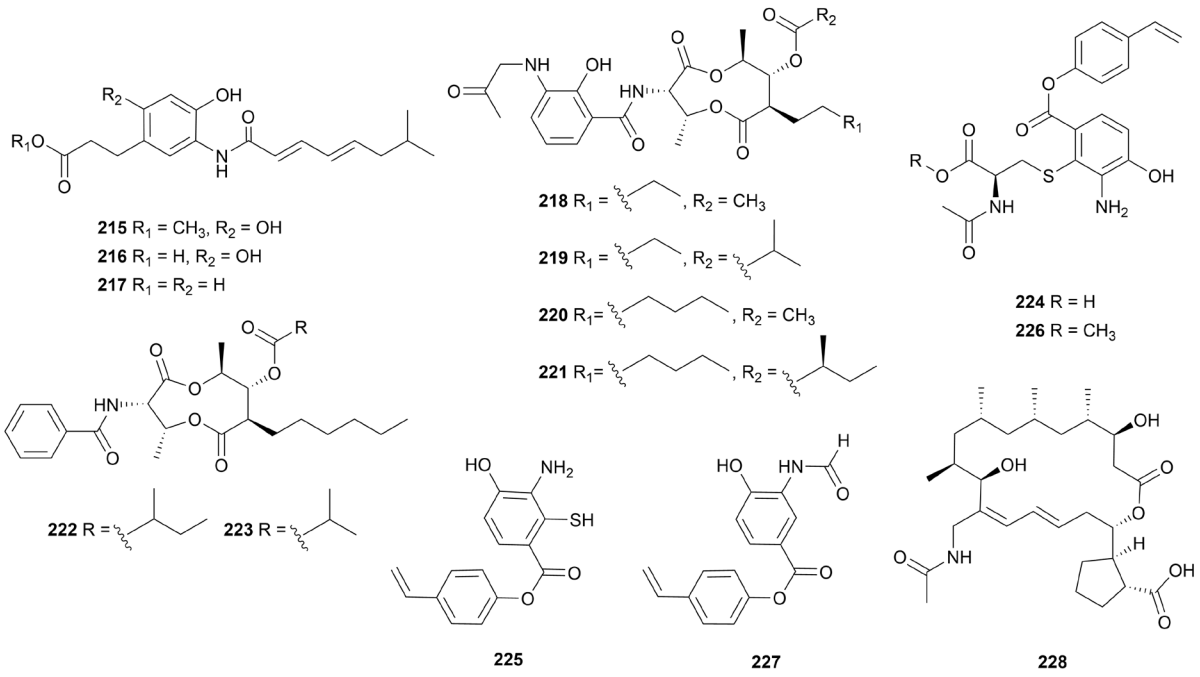

Figure 15. Chemical structures of compounds **215-228** isolated from marine *Streptomyces*.

9. Amides

9.1. Linear amides

Marine sediment-derived *Streptomyces* sp. SNE-011 afforded three novel acylated arylamine alkaloids named carpatamides A-C (**215-217**, Figure 15) [118]. Compounds **215** and **217** displayed positive activity against HCC366, A549 and HCC44 cell lines (IC_{50} = 2.2-8.4 μM). For compound **216**, the authors hypothesized that the reason for its inactivity was the inability to pass through the cell membrane. Antimycin is an antibiotic with antibacterial, insecticidal and anticancer activity consisting of a rare nine-membered dilactone core [119]. Antimycins E-H (**218-221**, Figure 15) were isolated from *Streptomyces* sp. THS-55, which showed extremely significant cytotoxic activity against HeLa cell line (IC_{50} < 0.1 μM) by down-regulating the levels of E6/E7 oncoproteins [120]. The potency was dependent on the long-chain substituent of R_2 and the acyl group of R_3. In addition, neoantimycins A and B (**222** and **223**, Figure 15) were isolated from *S. antibioticus* and exhibited weak cytotoxic activity against SF-268 cancer cell line [121]. Bagremycin is a phenol ester formed from *p*-hydroxystyrene and *p*-hydroxybenzoic acid with antimicrobial activity [122]. Bagremycins C and D (**224** and **225**, Figure 15) were isolated in 2017 from *Streptomyces* sp. Q22 [123]. The following year, novel bagremycins F and G (**226** and **227**, Figure 15) were again purified from coastal mud-sourced *Streptomyces* sp. ZZ745 [124]. Compound **224** inhibited the G_0/G_1 cell cycle in four glioma cells (U87MG, U251, SHG44 and C6) with IC_{50} values of 2.2 to 6.4 μM. Furthermore, compounds **226** and **227** showed 41.8 and 67.1 μM MIC values against *E. coli*. One new N-acetyl macrolide analogue N-acetylborrelidin B (**228**, Figure 15) was detected by a strain *S. mutabilis* MII with stronger activity against *Staphylococcus warneri* (18 mm zone of inhibition) [125].

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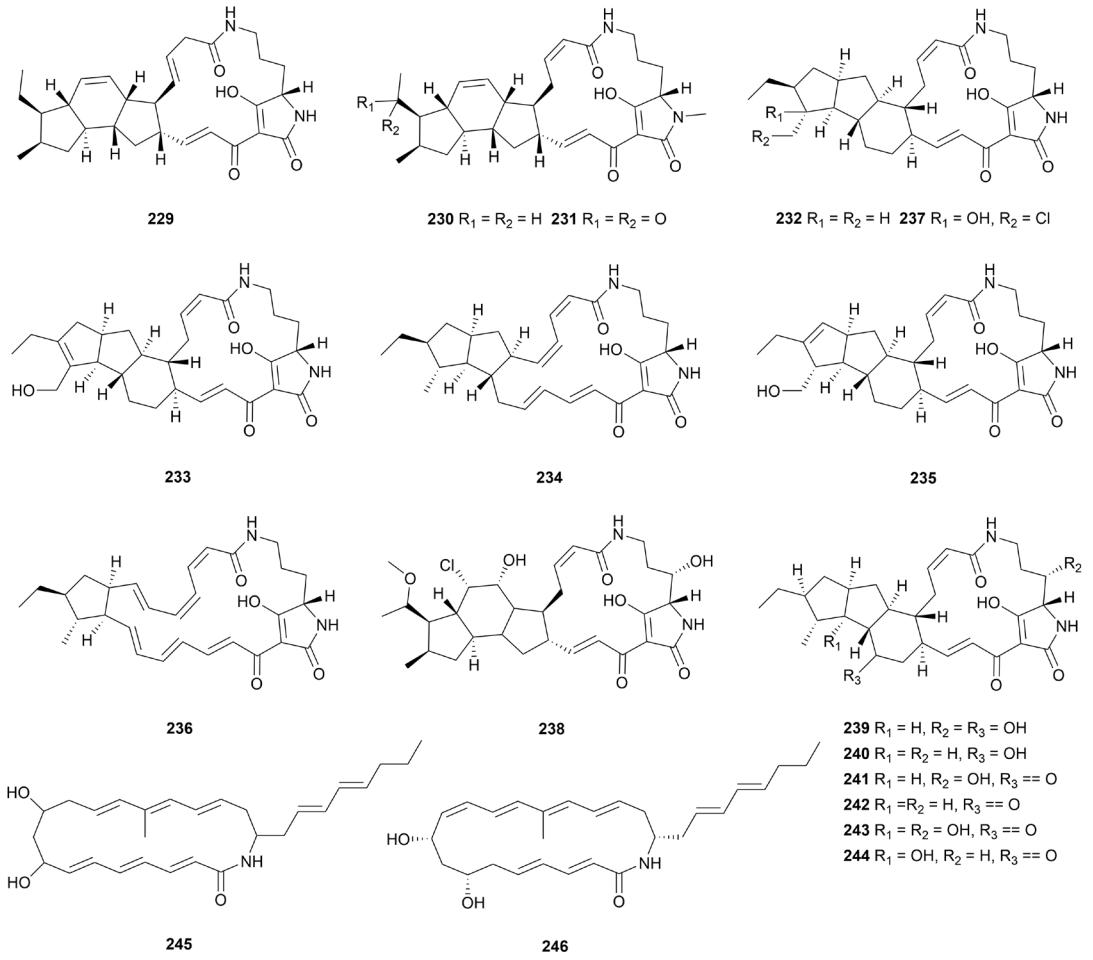

Figure 16. Chemical structures of compounds **229-246** isolated from marine *Streptomyces*.

9.2. Macrolactams

Macrolactams are a class of macrocyclic compounds in which amide units are integrated into a polyketide skeleton above twelve carbons [126]. These compounds often contain an azacyclic core skeleton or azacyclic substituent modifications that result in alkalinity [127].

Polycyclic tetramate macrolactams (PTMs) is a polycyclic macrolactam example encoded by the PKS/NRPS heterozygous gene cluster [128]. Three new PTMs (**229-231**, Figure 16) were purified from *S. zhaozhouensis* CA-185989 [129]. Compounds **229** and **230** had the most promising activity against MRSA, *C. albicans* and *A. fumigatus* (MIC = 1-8 μg/mL). The addition of the strong promoter *ermE**p to the PTM gene cluster of the deep-sea derived *S. pactum* SCSIO 02999 activated the generation of six novel antitumor active PTMs, pactamides A-F (**232-237**, Figure 16) [130]. The highest active compound **232** exhibited 0.24-0.51 μM IC_{50} values against four cancer cell lines. The study also verified that *PtmC* was a bifunctional cyclase acting on the formation of five-membered rings within the PTMs. In addition, some atypical structural PTMs (Figure 16) with moderate cytotoxic activity such as chlorinated derivatives chlokamycin (**238**) and H-10/H-11 *trans*-oriented PTM (**239-244**) have been reported in recent years from marine *Streptomyces* metabolites [131,132].

Moreover, a novel simple macrolactam JBIR-150 (**245**, Figure 16) was isolated from a strain OPMA00071 in 2018 [133]. Biological evaluation showed that **245** was cytotoxic against human malignant mesothelioma MESO-1 (IC_{50} = 2.3 μM) and human T-lymphoma Jurkat cells (IC_{50} = 0.9 μM). Another similar structure compound muanlactam (**246**, Figure 16) was targeted for purification from *Streptomyces* sp. MA159 through combined genomic library and spectral characterization [134]. The IC_{50} value for compound **246** against HCT116 cell line was 1.58 μM. *Streptomyces* sp. OUCMDZ-4348 is an extreme habitat microbe obtained from Antarctica and two novel bicyclic macrolactams named cyclamenols E and F (**247** and **248**, Figure 17) were isolated from this strain [135]. Only compound

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247 exhibited a moderate IC_{50} value (9.8 μM) against the gastric carcinoma cell line N87. Another polar actinomyces *S. somaliensis* 1107 was isolated four new macrocyclic lactam containing furan rings named somalactams A-D (**249-252**, Figure 17) [136]. Compound **249** was shown to have anti-inflammatory activity and inhibited LPS-stimulated release of inflammatory cytokines.

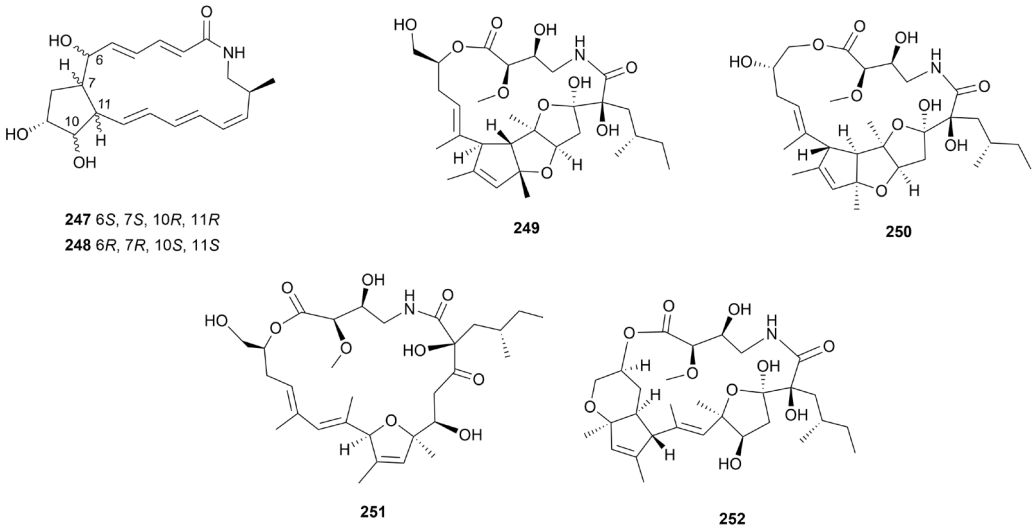

Figure 17. Chemical structures of compounds **247-252** isolated from marine *Streptomyces*.

10. Miscellaneous alkaloids

Niphimycin (NM) is a class of guanidylpolyol macrolide antibiotics with extensive antibacterial activity against fungi and Gram-positive bacteria [137]. A type I PKS BGC (named *npm*) associated with NMs biosynthesis was found in *Streptomyces* sp. IMB7-145 and four novel niphimycins derivatives，niphimycins C−E (**253-255**, Figure 18) and 17-O-methyl-niphimycin (**256**, Figure 18) were then isolated [138]. Compounds **253, 255** and **256** showed antibacterial activity against MRSA and VRE with MIC values of 8-64 μg/mL and also exhibited cytotoxic activity against the human HeLa cancer cell line. Moreover, compound **253** exhibited additional significant anti-*M. tuberculosis* activity (MIC = 32 μg/mL) and significantly inhibited the growth of the phytopathogenic fungus *Fusarium oxysporum* f. sp.*cubense* (EC_{50} = 1.20 μg/mL) [139]. Compound **253** was supplemented with cytotoxic activity against nasopharyngeal carcinoma cell lines TW03 and 5-8F (IC_{50} = 12.24 μg/mL and 9.44 μg/mL, respectively) [140].

Antartin (**257**, Figure 18) as a new zizaane-type sesquiterpene was isolated from a strain *Streptomyces* sp. SCO736 which showed promising cytotoxic activity against twelve human cancer cells with 50% growth inhibition (GI_{50}) of 4-8 μg/mL and inhibited the production of solid lung tumor cells [141]. *Streptomyces* sp. SCSIO 40020 afforded two new phenylhydrazone derivatives penzonemycins A–B (**258-259**, Figure 18) [142]. The hydrazone moiety of compounds was synthesized by a non-enzymatic Japp−Klingemann coupling reaction. Antitumor activity assays against cancer cell lines SF-268, MCF-7, A549 and HepG-2 with compound **258** showed IC_{50} values ranging from 30.44 to 61.92 μM.

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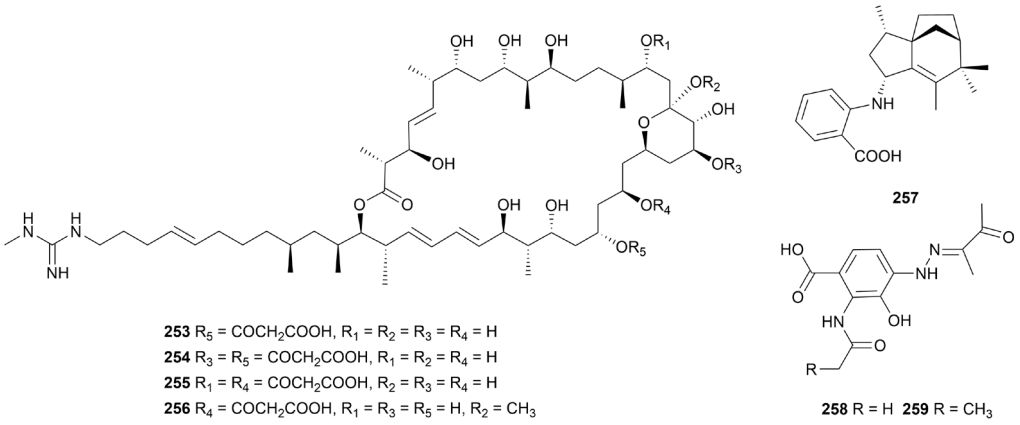

253 $R_5 = COCH_2COOH$, $R_1 = R_2 = R_3 = R_4 = H$
254 $R_3 = R_5 = COCH_2COOH$, $R_1 = R_2 = R_4 = H$
255 $R_1 = R_4 = COCH_2COOH$, $R_2 = R_3 = R_4 = H$
256 $R_4 = COCH_2COOH$, $R_1 = R_3 = R_5 = H$, $R_2 = CH_3$

Figure 18. Chemical structures of compounds **253-259** isolated from marine *Streptomyces*.

11. Conclusion and future perspectives

Metabolic pathways of microorganisms in special habitats have increased potential to biosynthesize unique metabolites due to the need of adapting to extreme environments. Marine-derived *Streptomyces* as a potent producer of bioactive alkaloids becomes a new frontier in natural product research. This review summarizes the discovery of more than 200 new alkaloids in marine *Streptomyces* in the last decade, and some of these metabolites have the potential to be developed into drug leads. The proportion of each type suggests that indoles and pyrroles are particularly prolific in marine-derived *Streptomyces* (Figure 19a). Microbial strains isolated from marine sediments have a numerical advantage, which may be explained by advances in diving sampling techniques (Figure 19b). In addition, with gene sequencing and gene cluster information prediction methods being widely used in silent biosynthetic gene cluster mining, the number of new compounds had a short-lived upward trend, but has fallen back in the last two years (Figure 19c). These data analyses are useful for scholars who work on marine microorganisms in choosing research directions.

Although the strategies for the isolation of marine microbial metabolites have been revolutionized over the past decades, there are still difficulties to overcome. Traditional means of separating natural products are subject to randomization. The efficient isolation of novel natural products and removal of inactive known compounds has been a thorny issue hindering the development of natural medicinal chemistry. Annotation of BGCs as well as the LC-MS/MS-based metabolite structure prediction methods will remain hot research topics in this field in the future. BGCs of marine microorganisms often have low or no expression under routine laboratory culture conditions. BGCs activation techniques such as OSMAC strategy, strain co-culture, ribosome engineering, heterologous expression of gene clusters and overexpression/knockout of regulatory genes and ribosome engineering provide methodological references to break this bottleneck. In addition to the discovery of these therapeutic agents, it is crucial to solve the problem of compound supply. Currently, in addition to the total synthesis route design of natural products, the modification of industrial production strains using genetic engineering approaches and optimization of microbial fermentation and extraction as well as purification processes at various level should be employed in preparation of these substances.

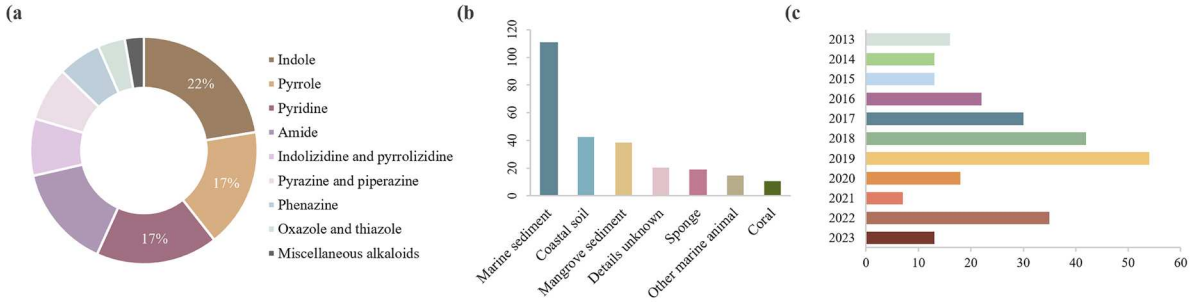

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Figure 19. (**a**) Structural classes of marine *Streptomyces*-derived alkaloids reported in 2013- June 2023. (**b**) Taxonomic data on the origin of marine *Streptomyces*. (**c**) Statistics on the number of new alkaloids reported in 2013- June 2023.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Detailed information for new alkaloids from marine *Streptomyces* discovered in 2013-June 2023.

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