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# Bioactive Marine Secondary Metabolites Isolation in China and Total Synthesis Progress of the known Marine Biomolecules by Chinese Scientists: A Review

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# ABSTRACT

In the past few decades, most Chinese researchers focused on terrestrial biological resources investigation. But during the last few years, marine organisms have received great attention. Due to the surviving environment, marine organisms are quite different from terrestrial ones. Especially for marine secondary metabolites, many of them have been found to be surprisingly effective as leading compounds. This review covers bioactive marine secondary metabolites isolation in China and total synthesis progress of several representative marine biomolecules by Chinese scientists in 2010-2015.

Keywords: Marine organisms, Streptomyces sp., Antibiotics

### INTRODUCTION

Natural products play an important role in new chemical entities discovery. Over 25% New Chemical Entities NCEs are natural products or derived from natural products [1]. Although both terrestrial and marine organisms are pivotal sources for NCEs discovery, marine organisms have received more attention in recent years. Marine natural products are new sources for drug discovery. A huge number of biologically active products have been isolated from marine organisms and each year numerous compounds with an array of biological activities are reported [2].

The marine world is extremely complex and contains a huge diversity of life forms, turning it into a rich natural resource of biologically active compounds. Most marine organisms live in stressful habitats exposed to extreme conditions. In order to adapt to such environment, they produce and accumulate a large number of fascinating and structurally complex secondary metabolites, which cannot be found easily in other organisms [3]. Due to the extraordinary surviving ecosystem, marine organisms are quite special and marine secondary metabolites they produce are usually for nutrition or defense. But incredibly, many scientists have found that numerous marine secondary metabolites have biological activities including antitumor, antiviral, antimicrobial, anti-inflammatory, etc. [4-8]. Furthermore, a large number of marine products have been evaluated in the preclinical or clinical pipeline and several biomolecules have been approved for clinical use which substantially means marine drug investigation is not just on paper [9].

In the past few decades, most Chinese researchers focused on terrestrial biological resources investigation. But during the last five years, research on natural products derived from marine organisms increased tremendously. Many excellent contributions are very important for marine drug investigation. Plenty of bioactive compounds were isolated and some of them may become promising candidates in future. In addition, some significantly important achievements on the total synthesis of bioactive marine molecules also would be quite meaningful for marine drug production.

Due to the limited space, this review only covers bioactive marine secondary metabolites isolation in China and total synthesis progress of several representative marine biomolecules by Chinese scientists in 2010-2015.

#### Anticancer secondary metabolites

Despite the significant progress of treatment and diagnosis, cancer is still one of the most dangerous diseases all over the world [10]. And thus, one of the major research objectives on marine natural products is to discover new anticancer molecules. Through traditional cytotoxicity evaluation experiments against cancer cell lines, the inhibitory activities of target compounds were determined and used for validating anticancer ability. Surprisingly, a number of excellent potent cytotoxic compounds were isolated and some important structure-activity relationships (SAR) had been summarized. Probably novel active pharmaceutical compounds will be generated from them in future.

In 2011, two new natural sterols (1-2) were identified from marine bryozoan *Cryptosula pallasiana*. Both of them exhibited moderate cytotoxicity to HL-60 cells [11]. In 2012, three new polyhydroxysterols, named as muriflasteroids A–C (3-5), were discovered from the South China Sea gorgonian *Muriceopsis flavida*, all of them were validated to show moderate cytotoxic activities towards A549 and M63 cell lines [12]. In 2013, three new polyhydroxylated steroids, (6-8), were isolated from the soft coral *Sarcophyton sp*. which was collected from the South China Sea. Compound 7 and 8 exhibited marked activities against human leukemia K562 cell lines with IC<sub>50</sub> values of 9.9 and 10.1  $\mu$ M, respectively. Compound 6 exhibited marked activity against human myeloid leukemia HL-60 tumor cell lines with IC<sub>50</sub> value of 9.3  $\mu$ M [13]. Eight new sterol derivatives were found which would be very important for sterol natural products profiling. In addition to the antitumor activity discovery, we may conclude from the results that the side chain at C-17 of sterol scaffold is probably the key influencing factor for the antitumor performance which still needs to be investigated deeply in the future.



Fungus Talaromyces flavus was isolated from the leaves of *Sonneratia apetala*, which were collected on the coastal saltmarsh of the South China Sea. Chemical investigations of its products resulted in the discovery of four new norsesquiterpene peroxides, **talaperoxides A-D** (9-12), and one known analogue, **steperoxide B** (13). After evaluating *in vitro* against human cancer cell lines MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3,

**talaperoxides B** and **D** were proved to show cytotoxicity toward these five cancer cell lines with IC<sub>50</sub> values ranging from 0.70 to 2.78 µg/mL. In particular, talaperoxide D exihibited excellent inhibitory activities on MDA-MB-435, HepG2, and PC-3 with IC<sub>50</sub> values of 0.91, 0.90, and 0.70 µg/mL, respectively. Notably, **talaperoxides B** and **D**, which possessed the *R* configuration at C-7, showed more potent cytotoxicity than the others with the *S* configuration at C-7. These results indicated that the *R* configuration at C-7 might contribute more to the cytotoxic activity. Additionally, **steperoxide B**, with a hydroxyl group at C-3, displayed better inhibitory activities than compound 1 (with an acetoxy group at C-3) and compound 3 (with a 3-carbonyl group at C-3) , implying that the hydroxy group at C-3 probably may have important influence on the cytotoxic activity [14].



Strain SCSIO 01299 is a marine actinomycete member of the genus *Pseudonocardia*, isolated from deepsea sediment of the South China Sea. Chemical investigation of its products afforded three new diazaanthraquinone derivatives Pseudonocardians A–C. Pseudonocardians A (**14**) and B (**15**) exhibited excellent cytotoxic activities against three tumor cell lines of SF-268, MCF-7 and NCI-H460 with IC<sub>50</sub> values ranging from 0.021 to 0.209  $\mu$ M, which probably means a promising broad spectrum antitumor scaffold discovering [15]. Five new bipyridine alkaloids and a new phenylpyridine alkaloid, named as caerulomycins F-K, along with five known analogues, were isolated from the marine-derived actinomycete *Actinoalloteichus cyanogriseus* WH1-2216-6. Caerulomycin I (**16**) was found to be potent inhibitors against K562 cell lines, with IC<sub>50</sub> value of 0.37 $\mu$ M, which possibility led to the discovery of a selective inhibitor against K562 [16].



Streptomyces sp. W007 is one of Streptomyces species distributing widely in marine habitats. Screening the fermentation broth of marine *Streptomyces sp.* W007 resulted in a new anthracene derivative (17), which showed cytotoxicity against human lung adenocarcinoma cell line A549. Interestingly, this compound showed stronger cytotoxicity at low concentration but weaker cytotoxicity at high concentration unlike normal cytotoxic biomolecule such as adriamycin. The mechanism of this compound might be selectively inducing apoptosis in human lung adenocarcinoma cell line A549 while sparing other cells [17]. Although most researchers focused on potent inhibitors exploring, this anthracene derivative discovering will probably lead to a new direction for investigating scaffolds with selective inhibitory effects and little side effects [18].



In 2012, Cheng-Bin Cui et al. [19] found two new drimenyl cyclohexenone derivatives, named as purpurogemutantin (18) and purpurogemutantidin (19), from a bioactive mutant BD-1-6 obtained by random diethyl sulfate (DES) mutagenesis of a marine-derived Penicillium purpurogenum G59. Purpurogenutantin moderately inhibited human cancer K562, HL-60, HeLa, BGC-823 and MCF-7 cells with IC<sub>50</sub> values ranging from 13.4 to 33.0 µM. Purpurogemutantidin also moderately inhibited human cancer HeLa, BGC-823 and MCF-7 cells, but surprisingly selectively inhibited human cancer K562 and HL-60 with IC<sub>50</sub> values of 0.93 and 2.48 µM, respectively [18] And then in 2014, their group developed a practical strategy for microbial chemists to access silent metabolites in fungi and used a marine-derived fungus Penicillium purpurogenum G59 and a modified diethyl sulphate mutagenesis procedure to successfully discover four new antitumor compounds named penicimutanolone (20), penicimutanin A (21), penicimutanin B (22), and penicimutatin. Penicimutanolone, penicimutanin A and penicimutanin B inhibited several human cancer cell lines including K562, HL-60, HeLa, BGC-823 and MCF-7 with IC50 values lower than 20 µM [19]. Subsequently, seven new lipopeptides, penicimutalides A-G, were isolated from the antitumor fungal mutant AD-2-1 obtained by diethyl sulfate mutagenesis of a marine-derived Penicillium purpurogenum G59. Penicimutalides G (23) inhibited human cancer K562, HL-60, HeLa, BGC-823, and MCF-7 cells to varying extents [20]. From their excellent mutagenesis investigation, we may conclude that diethyl sulfate mutagenesis of Penicillium purpurogenum G59 is a promising method for antitumor candidates discovering.



In 2011, Wen Zhang et al. [21] discovered 13 new briarane diterpenoids, gemmacolides G-M [21], gemmacolides N-S [22], from the South China Sea gorgonian *Dichotella gemmacea*. In the *in vitro* bioassay, gemmacolide J (24) exhibited excellent inhibitory activity against A549 tumor cell lines with  $<1.4 \mu$ M IC<sub>50</sub> value, superior to the positive control Adriamycin [21]. In 2012, their group discovered another six new briarane diterpenoids, gemmacolides T–Y from the South China Sea gorgonian *Dichotella gemmacea*. And gemmacolides V (25) and Y (26) were found to show potent growth inhibitory activity towards tumor cell lines of A549 and MG63, even stronger than that of Adriamycin [23]. In 2013, their group identified 18 new 11,20-epoxy-3*Z*,5*E*-dien briaranes, gemmacolides AA–AR, from the same source. By testing the bioactivity, gemmacolide AH (27) exhibited good inhibition activity against A549 and MG63 cell lines with IC<sub>50</sub> values of 5.0 and 5.0  $\mu$ M, respectively [24]. And in 2014, their group isolated another 7 new briarane diterpenoids, gemmacolides AS-AY, from that source again. In the preliminary *in vitro* bioassays, Gemmacolide AW (28) showed potential growth inhibitory activity against MG63 cells with IC<sub>50</sub> value of 7.2  $\mu$ M [25]. According to their results, South China Sea gorgonian *Dichotella gemmacea* probably is another excellent source for structurally diverse and biologically active antitumor biomolecules.



Ethyl acetate extracts of strain *Acrostalagmus luteoalbus* SCSIO F457 originated from a deep-sea sediment exhibited good cytotoxic activity. Chemical investigation of the extracts led to the isolation of two new indole diketopiperazines, named as luteoalbusins A–B (**29-30**), along with eight known ones. All of them were evaluated for their cytotoxic activities against SF-268, MCF-7, NCI-H460, and HepG-2 cell lines. And Luteoalbusins A–B was found to have more potent cytotoxicity than the others and cisplatin, with IC<sub>50</sub> values ranging from 0.23-1.31  $\mu$ M. Further analysis of the active data and structural characteristics of target compounds indicated that similar structure but different number of sulfur atom would possibly influence the cytotoxicities [26].



29-30 (29.n=2, 30.n=3)

Three new resveratrol derivatives, resveratrodehydes A–C (**31-33**), were yielded from the mangrove endophytic fungus *Alternaria sp.* R6. Resveratrodehyde A and B exhibited cytotoxic activities against MDA-MB-435 and HCT-116 cell lines (IC<sub>50</sub> < 10  $\mu$ M) and moderate cytotoxic activities against HepG2. Resveratrodehyde C exhibited moderate cytotoxic activities against human cancer cell lines including MDA-MB-435, HepG2, and HCT-116 [27]. Not only the compounds with good cytotoxic activities are meaningful, but also the phenomenon that formyl group on the C-2 and C-3 would significantly influence the antitumor effect of resveratrol is important for resveratrol structure-activity relationship investigation.



Nine new aaptamine derivatives, together with three known related compounds, were discovered from the South China Sea sponge *Aaptos aaptos*. The cytotoxic activities of the compounds were evaluated against various human cancer cell lines. And compound **34** and **35** were found to exihibit excellent cytotoxic activities

against HL60, K562, HepG2, KB, and MCF-7, with  $IC_{50}$  values ranging from 0.11 to 2.3  $\mu$ M, even superior to famous antitumor drug paclitaxel. Because of the significant cytotoxicities, both compounds should be investigated in more detail to develop a comprehensive understanding to their cell growth inhibition characteristics and related mechanisms [28].



In 2015, a strong inhibitor with broad spectrum was obtained by Yongxiang Song et al. [29]. They isolated two new C-glycoside angucyclines, marangucycline A and marangucycline B, from deep-sea sediment strain *Streptomyces sp.* SCSIO 11594. Notably, marangucycline B (**36**) bearing a keto-sugar displayed significant cytotoxicity against four cancer cell lines A594, CNE2, HepG2, MCF-7 with IC<sub>50</sub> values ranging from 0.24 to 0.56  $\mu$ M, superior to traditional anticancer drug cisplatin. In addition, the IC<sub>50</sub> value (3.67)  $\mu$ M was determined when testing non-cancerous hepatic cell line HL7702, validating the cancer cell selectivity of marangucycline B [29].



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Additionally, some other marine derived compounds were also isolated and proved to be effective antitumor biomolecules. Brevione I (37) was found to show good cytotoxic effects against MCF-7 cells comparable to the positive control cisplatin, with IC<sub>50</sub> values of 7.44  $\mu$ M [30]. Chondrosterin A (38) was validated to have marked cytotoxic activities against cancer cell lines A549, CNE2, and LoVo with IC<sub>50</sub> values of 2.45, 4.95, and 5.47 µM, respectively [31]. Penipacid A (39) and E (40) exhibited good inhibitory activity against human colon cancer RKO cell line with an IC<sub>50</sub> values of 8.4 and 9.7  $\mu$ M, respectively [32]. Sarcophyolide B (41) showed significant inhibitory effect against human ovarian carcinoma cell line A2780 with IC<sub>50</sub> value of 2.92  $\mu$ M, even much better than the positive control Taxol with IC<sub>50</sub> value of 14.45  $\mu$ M [33]. Engyodontiumone H (42) which was similar to the known compound AGI-B4 exhibited significant selective cytotoxicity against human histiocytic lymphoma U937 cell line with IC<sub>50</sub> value of 4.9 µM and moderate cytotoxicity against Hela, MCF-7, HepG2 and Huh7 cell lines [34]. Aspergilone A (43) was proved to exhibit selective cytotoxicity toward HL-60 human promyelocytic leukemia, MCF-7 human breast adenocarcinoma and A-549 human lung carcinoma cell lines with IC<sub>50</sub> values of 3.2, 25.0 and 37.0  $\mu$ g/mL, respectively [35]. Penicinoline (44) showed potential cytotoxicity in vitro toward 95-D and HepG2 cell lines with  $IC_{50}$  values of 0.57 and 6.5 µg/mL, respectively [36]. Cytochalasins Z21 and Z22 (45-46) exhibited modest cytotoxic activities against A-549 cell lines with  $IC_{50}$  values of 8.2 and 20.0, respectively [37]. Venezueline B (47) was proved to show moderate cytotoxic activities against HCT-8, BGC-823, A549, A2780 and NIH-H460 cell lines, with IC<sub>50</sub> values ranging from 5.74 to 9.67 µM [38]. Sumalarins A-C (48-50) were testified to have potential cytotoxicity against seven tumor cell lines including Du145, HeLa, Huh 7, MCF-7, NCI-H460, SGC-7901 and SW1990, with IC<sub>50</sub> values ranging from 3.8 to 11  $\mu$ M [39] Phomazine B (51) was found to display cytotoxicity against MGC-803, with IC<sub>50</sub> value of 8.5  $\mu$ M [40]. Cytoglobosins C and D (52-53) exhibited marked cytotoxic activity against A-549 tumor cell line, with IC<sub>50</sub> values of 2.26 and 2.55 µM, respectively [41] Suberitines B and D (54-55) showed potent cytotoxicity against P388 cell lines, with IC<sub>50</sub> values of 1.8 and 3.5  $\mu$ M, respectively [42].

Streptocarbazol A (56) was validated to present potential cytotoxic effects on the HL-60 and A-549 cell lines with  $IC_{50}$  values of 1.4 and 5.0  $\mu$ M, respectively [43].

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#### Antimicrobial secondary metabolites

Since the discovery of penicillin in 1928, plenty of studies, mainly on soil-derived bacteria and fungi, demonstrate that microorganisms are rich sources for bioactive substances discovering, such as antimicrobial agents [44]. But the growing need for new antimicrobial candidates to control emerging diseases inspires a great number of scientists to explore the oceans for new antimicrobial compounds. Throughout the years, great efforts have been devoted aiming at the isolation of new metabolites from marine organisms.

In 2011, Shu-Shan Gao et al. [45] investigated an endophytic fungus Penicillium chrysogenum QEN-24S, isolated from an unidentified marine red algal species of the genus Laurencia. Five secondary metabolites were discovered and four of them are new compounds including penicimonoterpene (57). Among them, penicimonoterpene displayed significant activity against pathogen *A. brassicae*, with an inhibition zone of 17 mm in diameter at the concentration of 20  $\mu$ g/disk.



In 2012, from a spent broth of marine-derived actinomycete *Streptomyces lusitanus*, two new antimycin A analogues, antimycin B1 (**58**) and antimycin B2 (**59**) were yielded. Antimycin B2 was found to show moderate antibacterial activities against *S. aureus, L. hongkongensis* and *B. subtilis*. Notably, its activity against *L. hongkongensis* was much stronger than streptomycin. Besides, Antimycin B1 did not show any activities against these three bacterial strains demonstrating the importance of phenyl group at C-1" for the antibacterial activity [46].



Three new polyketides, woodylides A–C (**60-62**), were isolated from the ethanol extract of the South China Sea sponge Plakortis simplex. Woodylide A and C showed antifungal activity against fungi Cryptococcus neoformans with  $IC_{50}$  values of 3.67 and 10.85 µg/mL respectively. While woodylide B, bearing an ethyl group at C-8, was inactive even tested at a higher concentration, indicating the importance of substituent at C-8 for the antifungal activity [47].



Marine Streptomyces fradiae strain PTZ0025 yielded four Capoamycin-type antibiotics and two polyene acids. Four new compounds, fradimycins A and B (**63-64**) and fradic acids A and B, were characterized. Fradimycins A and B showed potent antibacterial activity against Staphylococcus aureus with a minimal inhibitory concentration (MIC) of 6.0 and 2.0  $\mu$ g/mL, respectively. Interestingly, Fradimycins A and B also significantly inhibited cell growth of colon cancer and glioma with IC<sub>50</sub> values ranging from 0.13 to 6.46  $\mu$ M. The results demonstrated that Fradimycins A and B would be promising bioactive candidates with both of potent antimicrobial and antitumor activities [48].



Ling-Li Liu et al. [49] obtained four new polycyclic antibiotics, citreamicin  $\theta$  A (**65**), citreamicin  $\theta$  B (**66**), citreaglycon A (**67**), and dehydrocitreaglycon A (**68**), from marine-derived Streptomyces caelestis. Citreamicin  $\theta$  A, citreamicin  $\theta$  B and citreaglycon A were proved to exhibit low MIC values of 0.25, 0.25, and 8.0 µg/mL, respectively, against methicillin-resistant *Staphylococcus aureus* ATCC 43300. And all of the four compounds exhibited potent antibacterial activity against *B. subtillis* 769, *S. haemolyticus* UST950701-004 and *S. aureus* UST950701-005. Besides, citreamicin  $\theta$  A and citreamicin  $\theta$  B displayed at least ten-fold stronger antibacterial activity than citreaglycon A and dehydrocitreaglycon A, might be critical for antibacterial activity [49].



In 2013, seven new polyoxygenated steroids (1-7), together with seven known analogues (8-14), were found from the South China Sea soft coral, *Sarcophyton sp.* These compounds except steroid 5 displayed potent

antibacterial and antifungal bioactivities in the *in vitro* bioassay, against *Escherichia coli, Bacillus megaterium*, *Microbotryum violaceum* and *Septoria tritici*. Preliminary SAR analysis implies that the substituents at position 11 and 17 are crucial for both antibacterial and antifungal activities. Besides, the terminal double bond and the cyclopropane side chain seem to be responsible for bioactivity diversity [50].





The fermentation extract of South China Sea sediment-derived actinomycete, identified as *Streptomyces niveus* SCSIO 3406, showed antibacterial activity against methicillin-resistant *Staphylococcus epidermidis* (MRSE) shhs-E1. Chemical investigation of the fermentation broth afforded four new sesquiterpenoid naphthoquinones, marfuraquinocins A–D (**83-86**), and two new geranylated phenazines, phenaziterpenes A and B (**87-88**). Marfuraquinocins A, C and D exhibited antibacterial activities against *Staphylococcus aureus* ATCC 29213 with equivalent MIC values of 8.0  $\mu$ g/mL. Marfuraquinocins C and D showed antibacterial activity against methicillin-resistant *Staphylococcus epidermidis* (MRSE) shhs-E1 with MIC values of 8.0  $\mu$ g/mL. Besides, marfuraquinocins A and C were found to inhibit a NCI-H460 cancer cell line with IC<sub>50</sub> values of 3.7 and 4.4  $\mu$ M, respectively [51].



Hippolachnin A (89), a polyketide possessing an unprecedented carbon skeleton with a four-membered ring, was discovered from the South China Sea sponge *Hippospongia lachne*. It was evaluated for antifungal activity against seven pathogenic fungi and Hippolachnin A exhibited potent antifungal activity against Cryptococcus neoformans, Trichophyton rubrum, and Microsporum gypseum, with MIC value of 0.41  $\mu$ M for all three species and modest activity against four other fungi strains. The results showed that hippolachnin A would be a promising new leading compound for antifungal therapy [52].



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The strain SCSIO 01127, isolated from the South China Sea sediment, was identified as a member of Streptomyces by the 16S rDNA sequence analysis. Two new spirotetronate antibiotics lobophorins E (94) and F (95), along with two known analogs lobophorins A (90) and B (91), were isolated from Streptomyces sp. SCSIO 01127. Antibacterial activities of four lobophorins were evaluated against S.aureus ATCC 29213, E. faecalis ATCC 29212 and B. thuringensis SCSIO BT01. Lobophorins E and F exhibited activities against B. thuringensis SCSIO BT01 with MIC values of 8 and 2 µg/ml, respectively. Besides, Lobophorin F also exhibited antibacterial activities against the other two strains and potent antitumor activities against SF-268, MCF-7 and NCI-H460 cell lines [53]. A newly isolated Actinomycetes strain, designated as MS100061, was discovered to exhibit strong anti-Mycobacterium bovis Bacillus Calmette-Guérin (BCG) activity. Chemical investigation afforded a new spirotetronate, lobophorin G (96), together with two known compounds, lobophorins A and B. All of them were testified antibiotic activity and they exhibited potent anti-BCG activity with MIC values of 1.56, 1.56, and 0.78 µg/ml, respectively. Furthermore, all of them exhibited antibacterial activity against Bacillus subtilis with MIC values of 3.125, 12.5 and 1.56 µg/ml, respectively [54]. Strain 12A35 was isolated from a deep-sea sediment collected from the South China Sea. Chemical investigation of its fermentation culture resulted in two new spirotetronate antibiotics, lobophorins H (97) and I (98), along with three known analogues. Notably, lobophorin H showed similar antibacterial activity to ampicillin against B. subtilis CMCC63501, with MIC value of 1.57 µg/mL. Lobophorin B also showed excellent antibacterial activity against B. subtilis CMCC63501 with MIC value of 3.13 µg/mL [55]. Interestingly, from the sponge-associated actinomycete, Streptomyces carnosus strain AZS17, two new kijanimicin derivatives, lobophorins C (92) and D (93) were discovered and found to show selective cytotoxicity against human liver cancer cell line 7402 and human breast cancer cells MDA-MB 435 [56]. On the basis of lobophorins series investigation, a new functional scaffold probably would appear as leading structure for both of excellent antitumor and antibacterial candidates investigation and trigger more in-depth research in the future.



In 2014, Siwen Niu et al. [57] identified 15 new depsidone-based analogues named spiromastixones A-O from the fermentation broth of a deep-sea Spiromastix sp. fungus. All of them exhibited significant inhibition 50

against gram-positive bacteria including *Staphylococcus aureus, Bacillus thuringiensis*, and *Bacillus subtilis* with MIC values ranging from 0.125 to 8.0 µg/mL. Besides, spiromastixones F–J displayed potent inhibitory effects against methicillin-resistant bacterial strains of *S. aureus*, even much better than that of the clinical medicine levofloxacin. Spiromastixones F–J also showed comparable inhibitory effects with levofloxacin against *S. epidermidis* (MRSE). Furthermore, spiromastixone J also surprisingly inhibited the growth of the vancomycin-resistant bacteria *Enterococcus faecalis* and *E. faecium* (VRE), which levofloxacin showed almost no activity against. The excellent inhibitory effect of spiromastixone J (99) suggests that it may be a potent leading compound to treat multidrug-resistant bacterial infections. Most importantly, the selective inhibition against gram-positive bacteria demonstrates that spiromastixones may become promising leading compounds for treating gram-positive related diseases [57].



In 2015, Siwen Niu et al. [58] obtained another 11 new polyphenols namely spiromastols A–K from the same source again. Spiromastols A–C (**100-102**) exhibited potent inhibitory effects against several bacterial strains, including *Xanthomanes vesicatoria*, *Pseudomonas lachrymans*, *Agrobacterium tumefaciens*, *Ralstonia solanacearum*, *Bacillus thuringensis*, *Staphylococcus aureus* and *Bacillus subtilis*, with MIC values ranging from 0.25 to 4  $\mu$ g/mL. Analysis of the SAR revealed that antibacterial activities meanly depended on the substitution in rings A and B. Especially when compared to Spiromastols D–F (**103-105**), it was found that the adding of carboxylic acid at C-1 and missing of chloride at C-3 and C-5' led to no activities against those bacterial strains [58].



#### 100-105

Five new sulfide diketopiperazine derivatives, penicibrocazines A–E (**106-110**), along with a known congener, were found from the culture extract of Penicillium brocae MA-231, an endophytic fungus obtained from the fresh tissue of the marine mangrove plant Avicennia marina. Penicibrocazines C–D and congener showed potent activity against *Staphylococcus aureus*, with MIC values of 0.25, 8.0, and 0.25  $\mu$ g/mL, respectively, which were comparable to chloromycetin. Besides, Penicibrocazine C also showed excellent activity against *Micrococcus luteus* with MIC value of 0.25  $\mu$ g/mL, which was much stronger than chloromycetin. Moreover, Penicibrocazines B, D and E exhibited marked activity superior to amphotericin B against plant pathogen *Gaeumannomyces graminis* with MIC values of 0.25, 8.0 and 0.25  $\mu$ g/mL, respectively. Interestingly, after preliminary SAR analysis, it was found that, the double bonds at C-6 and C-6', S-methyl group at C-2' and keto groups at C-5/5' would be probably related to the antimicrobial activity of penicibrocazines [59].



#### 106-110

In addition, some other marine derived compounds were also found and testified to have antimicrobial activities. In 2012, guignardone I (111) was isolated from the endophytic fungus A1 of the mangrove plant Scyphiphora hydrophyllacea and found to show marked antibacterial activity against Escherichia coli, Vibrio anguillarum and Vibrio parahaemolyticus with the MIC values of 5.0, 10.0 and 20.0 µM, respectively [60]. Cristatumin A (112) was identified from the culture extract of Eurotium cristatum EN-220 and validated to show modest antibacterial activity against Escherichia coli [61]. In 2013, a new antibacterial chlorinated benzophenone derivative,  $(\pm)$ -pestalachloride D (113) was found from the marine-derived fungus Pestalotiopsis sp. which was collected from Yongxing Island in the South China Sea. (±)-pestalachloride D was proved to exhibit moderate antibacterial activity [62]. Pinodiketopiperazine A (114) was obtained from the marine sediment-derived fungus Penicillium pinophilum SD-272 and displayed inhibitory activity against Escherichia coli, causing 10.0 mm zones of inhibition at 20 µg/disk [63]. In 2014, felinone B (115) was discovered from Beauveria felina EN-135, a Marine-Derived Entomopathogenic Fungus, and exhibited modest inhibitory activity against P. aeruginosa with an MIC value of  $32 \mu g/mL$  [64]. Symphyocladin G (116) was discovered from the collection of the marine red alga Symphyocladia latiuscula and found to exhibit potential antifungal activity against Candida albicans (ATCC 10231) with an MIC value of 10  $\mu$ g/mL [65]. Three new  $\alpha$ -pyrones, nocapyrones E-G (117-119), were isolated from the marine-derived actinomycete Nocardiopsis dassonvillei HR10-5 and they showed moderate antimicrobial activity against Bacillus subtilis with MIC values of 26, 14, and 12 µM, respectively [66]. Chemical investigation of a marine-derived fungus Nigrospora sp., isolated from an unidentified sea anemone, yielded 10-deoxybostrycin (120), which was found to show strong antibacterial activity against B. subtilis with an MIC value of 625nM [67]. Two new 9,11-secosteroidal glycosides, namely, sinularosides A and B (121-122), were isolated from the South China Sea soft coral Sinularia humilis Ofwegen and proved to exhibit marked antifungal activity against Microbotryum violaceum and Septoria tritici, antibacterial activity against the Gram-positive bacterium Bacillus megaterium, and moderate inhibitory activity against the microalga Chlorella fusca [68].





#### Anti-inflammatory secondary metabolites

Inflammation is a kind of common clinical pathologic process and part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Anti-inflammatory effect refers to the specific property of a drug or treatment that may help to reduce or eliminate inflammation. Many steroids, NSAIDs, herbal medicines, etc., are widely used for the treatment of inflammation. Besides, marine derived bioactive compounds also play an important role in treating or controlling inflammation [3]. Recently, important advances in anti-inflammatory compounds isolation have been made and probably will lead to the discovery of new candidates with promising anti-inflammatory activity.

In 2010, a structurally unique symmetric sulfur-containing biscembranoid, thioflexibilolide A (123) was isolated from the soft coral Sinularia flexibilis. It was found that at 10  $\mu$ M thioflexibilolide A significantly reduced the iNOS expression to 26.2  $\pm$  11.2% but did not show cytotoxicity against microglial cells. Besides, thioflexibilolide A also exhibited significant neuroprotective activity [69].



In 2010, Wenhan Lin et al. [70] discovered seven new biscembranoids, lobophytones A-G, together with three known biscembranes from the Chinese soft coral Lobophytum pauciflorum. Lobophytone D (124) was found to show significantly inhibition towards lipopolysaccharide (LPS)-induced nitric oxide (NO) in mouse peritoneal macrophage with IC<sub>50</sub> value of 4.70  $\mu$ M, while the other compounds showed weak activities [70]. In the same year, their group identified another seven new biscembranoids, named as lobophytones H-N [71], five new biscembranoids named as lobophytones O–S [72] and a new monomeric cembrane lobophytone T [72] from the same source. Lobophytones Q was proved to present significant inhibition against lipopolysaccharide - induced nitric oxide production in mouse peritoneal macrophages with IC<sub>50</sub> = 2.8  $\mu$ M. Besides, Lobophytones Q (125) and T (126) exhibited marked inhibition against *Staphylococcus aureus*, *S. pneumoniae*, and Saccharomyces cerevisiae with the inhibitory rates around 90% at 20  $\mu$ g/mL [72]. In the next year, their group obtained seven new biscembranoids, named as lobophytones U–Z1, together with methyl sartortuoate and nyalolide from that source again. All of the seven new biscembranoids inhibited NO production in mouse peritoneal macrophages ranging from 2.6 to 5.2  $\mu$ M. Besides, the antibiotic test indicated that lobophytone U (127) exhibited significant inhibition against *S. aureus* (IC<sub>50</sub>=18.7 ± 0.6  $\mu$ M) and *S. pneumoniae* (IC<sub>50</sub>=19.8 ± 0.8  $\mu$ M) [73].



Thirteen new thiodiketopiperazines, named epicoccin I, ent-epicoccin G, and epicoccins J-T, together with six known diketopiperazines, were isolated from the EtOAc extract of a culture of endophytic fungus Epicoccum nigrum. Ent-epicoccin G (**128**), epicoccin O (**129**) and epicoccin S (**130**) showed potent anti-inflammatory activities *in vitro* against the release of  $\beta$ -glucuronidase in rat polymorphonuclear leukocytes induced by platelet-activating factor, with IC<sub>50</sub> values of 3.07, 4.16 and 4.95  $\mu$ M, respectively [74].



In 2010, Wan-Yu Lin et al. [75] obtained five new cembranoids, sarcocrassocolides A-E, along with three known cembranoids, from a Formosan soft coral Sarcophyton crassocaule. Sarcocrassocolides A-D (131-134), sarcocrassolide and 13-acetoxysarcocrassolide significantly reduced the levels of iNOS protein to  $13.7 \pm 5.2\%$ ,  $13.3 \pm 5.0\%$ ,  $4.6 \pm 1.3\%$ ,  $7.0 \pm 3.1\%$ ,  $1.1 \pm 0.9\%$  and  $6.2 \pm 0.5\%$ , respectively. Furthermore, at the same concentration, successfold could strongly reduce COX-2 expression  $(3.9 \pm 2.3\%)$  with LPS treatment [75]. Next year, they discovered another seven new cembranoids, sarcocrassocolides F-L from Sarcophyton crassocaule. All of them were found to inhibit the expression of the iNOS protein and display significant antiinflammatory activity in LPS-stimulated RAW264.7 macrophage cells. By testing at a concentration of 10 µM, sarcocrassocolides F-L were found to significantly reduce the levels of iNOS protein. Besides, some of the sarcocrassocolides also showed cytoxicity against MCF-7 OR carcinoma cell lines, with IC<sub>50</sub> value less than 10  $\mu$ M. Furthermore, also at 10  $\mu$ M, Sarcocrassocolide I (135) could effectively reduce COX-2 expression with LPS treatment, indicating that it might be a promising anti-inflammatory leading compound because of the excellent inhibitory activity on the expression of both iNOS and COX-2 proteins [76]. And in the next two years, their group found other six new cembranoids, sarcocrassocolides M-R, from that source again [77,78]. All of them were proved to show significant effect on inhibiting the expression of the iNOS protein which further demonstrated the excellent anti-inflammatory activities of cembranoids.



In 2013, six new casbane diterpenoids, named as sinularcasbanes A–F, along with six known analogues, were yielded from a South China Sea soft coral, Sinularia sp. Sinularcasbane B and E (**136-137**) showed good inhibitory activity against lipopolysaccharide (LPS)-induced nitric oxide production in mouse peritoneal macrophages with IC<sub>50</sub> values of 8.3 and 5.4  $\mu$ M, respectively [79], In the same year, Yonghong Liu et al. identified four new sesquiterpenes, sinularianins C–F, together with known sinularianins A and B from the same source. Sinularianin A and D (**138-139**) exhibited a potential inhibitory effect against NF- $\kappa$ B activation at 10

 $\mu$ g/mL and the inhibitory ratio was 41.3% and 43.0%, respectively [80]. In 2014, Yonghong Liu et al. [81] isolated another eight new compounds, sinulolides A–H, along with two known compounds, α-methoxy-2,3-dimethyl-butenolide and sinularone D from that soft coral source again. At the concentration of 10  $\mu$ g/mL, sinulolide E (**140**) and sinularone D (**141**) exhibited moderate effects for inhibition of NF-κB activation [81]. Based on the results, South China Sea soft coral, *Sinularia sp.* possibly would be an excellent source for anti-inflammatory compounds production and isolation.



In 2015, two new briarane-type diterpenoids, briarenolide K and L were purified from an octocoral which was identified as Briareum sp. Through the *in vitro* anti-inflammatory activity test, the regulation of the proinflammatory iNOS and COX-2 protein expression of LPS-stimulated RAW264.7 macrophage cells was evaluated. At the concentration of 10  $\mu$ M, briarenolide K and L (**142-143**) were found to significantly reduce the levels of iNOS to 23.67% ± 1.86% and 31.71% ± 8.75%, respectively. Briarenolide K and L might be promising anti-inflammatory agents in the future, because of their excellent inhibitory effect on iNOS expression and no cytotoxicity to RAW264.7 macrophage cells [82].



### Antidaibetic and antivirus secondary metabolites

Diabetes mellitus is a debilitating and sometimes life threatening disorder with increasing incidence throughout the world. The International Diabetes Federation predicted that the number of people with diabetes would rise from 266 million in 2011 to 552 million by 2030 [83]. In addition to diabetes, some diseases related to virus are also serious and easily cause millions of deaths, such as H1N1 influenza virus, which emerged and rapidly spread worldwide, causing excess mortality in children and young adults [84]. The development of new drugs for use against diabetes and virus is therefore urgently needed.

 $\alpha$ -glucosidase is one of the fundamental target enzymes for the treatment of type-2 diabetes [85]. Several reversible inhibitors are currently used clinically to control blood glucose levels of patients, but it is still necessary to search for new  $\alpha$ -glucosidase inhibitors for further drug development. Eurotium rubrum SH-823 is a fungus obtained from a *Sarcophyton sp.* soft coral collected from the South China Sea. EtOAc extract of the fungal fermentation on rice exhibited significant  $\alpha$ -glucosidase inhibitory activity. Chemical investigation of the

bioactive extract afforded two new sulfur-containing benzofurans, named as, eurothiocin A and B, along with five known compounds, zinniol, butyrolactone I, aspernolide D, vermistatin, and methoxyvermistatin. The  $\alpha$ glucosidase inhibitory effects of the isolates were compared with the clinical  $\alpha$ -glucosidase inhibitor acarbose. As a result, eurothic in A and B (144-145) were the most active, and showed more potent inhibitory effect ( $IC_{50}$ = 17.1 and 42.6  $\mu$ M, respectively) than acarbose (IC<sub>50</sub> = 376.7  $\mu$ M). Furthermore, kinetic studies were carried out by the Lineweaver-Burk plot method for determining the inhibition type. The results indicated that both of them were competitive inhibitors of  $\alpha$ -glucosidase which probably led to promising antidiabetic candidates discovering [86]. The ethyl acetate extract from the fungus, Epicoccum sp. HS-1, associated with Apostichopus japonicus, showed  $\alpha$ -glucosidase inhibition activity. Chemical investigation of the extract resulted in one new isopimarane diterpene (146), together with two known compounds, 11-deoxydiaporthein A and isopimara-8(14),15-diene. All of them were tested for their *in vitro* inhibitory activities against  $\alpha$ -glucosidase and isopimarane diterpene was found to exhibit excellent effective inhibitory activity, with IC<sub>50</sub> value of  $4.6 \pm 0.1$  $\mu$ M, superior to that of the positive resveratrol(IC<sub>50</sub>= 31.2 ± 4.4  $\mu$ M) [87]. Besides, three new vermistatin derivatives (147-149), along with five known vermistatin analogues, were discovered from the culture of the mangrove endophytic fungus Penicillium sp. HN29-3B1. Compounds 147 and 149 exhibited potential  $\alpha$ glucosidase inhibitory activity with IC<sub>50</sub> values of  $9.5 \pm 1.2$  and  $8.0 \pm 1.5 \mu$ M, respectively [88].



Protein tyrosine phosphatase 1B (PTP1B), as a therapeutic target for the treatment of Type-II diabetes, has been the intensive researching topic over the past decade. Approximately 300 natural PTP1B inhibitors have been isolated and characterized from various natural resources, many of which are originated from marine [89]. Several new PTP1B inhibitors have been discovered recently. Five new sesterterpenoids, were isolated from the sponge Hippospongia lachne off Yongxing Island in the South China Sea. To further confirm the original PTP1B activity from the crude fraction of the sponge, all of them were evaluated *in vitro* for PTP1B inhibitory activity. Compound **150** and **151** exhibited PTP1B inhibitory activities with  $IC_{50}$  values of 5.2 and 8.7  $\mu$ M, which were the most potent compounds isolated from marine sponges of the genus Hippospongia relevant to PTP1B inhibitory activity [90]. Another PTP1B inhibitor was isolated from the South China Sea sponge Dysidea avara, named as Dysidavarone A (**152**). It was found to show marked inhibitory activity on protein tyrosine phosphatase 1B (PTP1B) with IC<sub>50</sub> value of 9.98  $\mu$ M [91]. All of them are meaningful for PTP1B inhibitors profiling and also important for therapeutic investigation for the treatment of type II diabetes.



Taiwanese Octocoral I. hippuris was collected at Orchid Island and its acetone extract exhibited antiviral activity against human cytomegalovirus HCMV. Bioactivity-guided fractionation afforded five polyoxygenated

steroids: hipposterone M–O, hipposterol G and hippuristeroketal A. Hipposterone N (**153**) exhibited significant inhibitory activity against HCMV, with an EC<sub>50</sub> value of 6.0  $\mu$ g/mL [92].



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Streptomyces sp. FXJ7.328 was isolated from marine sediment and the ethyl acetate extract of fermentation broth exhibited antivirus activity against H1N1 influenza virus. Chemical investigation of the extract led to the discovery of five new diketopiperazine derivatives and another five known analogues. After testing for antivirus effects with Ribavirin as the positive control (IC<sub>50</sub>=38.8  $\mu$ M), Compounds **154**, **155** and **156** displayed potent activity against H1N1 virus with the IC<sub>50</sub> values of 41.5 ± 4.5, 28.9 ± 2.2 and 6.8 ± 1.5  $\mu$ M, respectively. And SAR analysis showed that phenyl group with its substituent at C-15 and the substituent of diketopiperazine at C-6 would be important for the antivirus activity against H1N1 [93]. Besides, Chemical investigation of the extract of the strain Cladosporium sphaerospermum 2005-01-E3 led to the discovery of another anti-H1N1 compound, named as Cladosin C (**157**). It exhibited modest activity with an IC<sub>50</sub>=276  $\mu$ M against the influenza A H1N1 virus [94].



#### Total synthesis of secondary metabolites

Not only the discovery and identification of marine bioactive secondary metabolites are important, but also the preparation and production methods of excellent biomolecules are meaningful. Hence, the total synthesis, especially the first total synthesis of natural complex bioactive structures, plays a pivotal role in marine science investigation, leading to more practical and hopeful candidates.

During the last few decades, a great number of cyclopeptides, cyclic depsipeptides and linear peptides were discovered and validated to display a wide range of biological activities. Thus, total synthesis research on natural peptides has increased tremendously in recent years due to the urgent demand. Grassypeptolide, obtained from Lyngbya confervoides, was proved to be a potential anticancer cyclodepsipeptide [95]. The excellent anticancer activity of grassypeptolide attracted great attention of Zhengshuang Xu et al. [96]. They successfully achieved first total synthesis of grassypeptolide in 17 steps with an overall 11.3% yield. Fragments a1 and a2 with approximately equal complexity were chosen as key intermidiates for final assembly. Fragment a2 was hydrolized with lithium hydroxide and then underwent a PyAOP-mediated coupling reaction with Cbz deprotecting fragment a1. After simultaneous removal of the tert-butyl ester and Boc-protecting group, the afforded linear precursor a3 was immediately activated by BOPC15 in the presence of 2,6-lutidine to

successfully obtain cyclodepsipeptide a4 in 72% yield. Then, after Troc protection and TBS deprotection, thioamide a5 was treated with diethylaminosulfur trifluoride (DAST) in CH2Cl2 at -78°C and the cyclized product a6 was achieved which was then treated with activated zinc and aqueous NH4OAc in THF to afford the final grassypeptolide (Figure 1) [96].



Figure 1: Total synthesis of grassypeptolide

Viequeamide A is a natural cyclic depsipeptide isolated from a marine cyanobacterium *Rivularia sp.* It was proved to be significantly toxic against H460 human lung cancer cell lines, with an IC<sub>50</sub> value of 60 nM, turning it into a new target molecule for total synthesis [97]. The first total synthesis of viequeamide A was accomplished by Dongyu Wang et al. [98]. In view of the reduced steric hindrance, formation of the N-MeVal–Thr peptide bond was chosen for the final macrocyclization instead of Thr-(3*S*)-Dhoya. And viequeamide A was partitioned and started from three fragments, the tripeptide b1, dipeptide b2, and ester b4. After removal of the O-allyl group in b1 and N-Boc protection in b2, pentapeptide b3 was yielded through condensation under the standard peptide bond-forming conditions. And then, removal of the allyl protecting group in b4 afforded a corresponding acid intermediate, which was condensed with the liberated primary amine from pentapeptide b3, successfully leading to amide b5. After sequential removal of the allyl group and the Fmoc group, cyclic peptide b6 was assembled through macrocyclization under the standard conditions in 41% yield. Finally, viequeamide A (Figure 2) was obtained after deprotection [98].



Figure 2: Total synthesis of viequeamide A

# Zhiyu Zhang and Yan Sun

Lagunamide A was isolated from the marine cyanobacterium *Lyngbya majuscula* collected in Pulau Hantu Beser, Singapore. It exhibited significant cytotoxic activity against P388 murine leukemia cell lines with  $IC_{50}$  value of 6.4 nM and potent antimalarial property against Plasmodium falciparum with  $IC_{50}$  value of 0.19  $\mu$ M [99]. Zhengshuang Xu et al. [96] finished the first total synthesis of lagunamide A. The tetrapeptide c3 and triester c4 were chosen to be the crucial intermidiates. Coupling of dipeptides c1 and c2 using HATU3 catalyst gave tetrapeptide c3 in 84% yield. Aldehyde c5 was homologated by Horner–Wadsworth–Emmons condensation to produce  $\alpha$ ,  $\beta$ -unsaturated ester c6.



Figure 3: Total synthesis of lagunamide A

Then after deprotecting and coupling with Fmoc-N-Me–Ala–Cl in the presence of DMAP in toluene, triester c4 was successfully synthesized. The final assembly started from removal of the Fmoc of triester c4 and underwent a HATU-mediated coupling reaction with the corresponding acid of tetrapeptide c3. The afforded precursor c7 was deprotected and immediately activated by HATU to successfully produce Lagunamide A (Figure 3) which was also used to correct stereochemical configuration of the natural product [100].

Jianrong Han et al. [101] accomplished first total synthesis of micromide (Figure 4) by assembling seven fragments, namely, N-Me-Gly-thiazole, N-Me-Phe, N-Me-Ile, Val, N-Me-Val, Phe, and 3-methoxyhexanoic acid. Fragments d1 and d2 were coupled to give compound d3 which was treated with mercaptoacetic acid in DMF under basic conditions to produce d4. And then d4 was coupled to yield dipeptide d5, which was deprotected and transformed to d6 via coupling with L-N-Boc-Val using DIPEA as base in the presence of HATU and TFA treatment.



Figure 4: Total synthesis of micromide

Next, d-N-o-Ns-N-Me-Val chloride was coupled with d6 and through several post-treatment steps d7 was achieved. The fragment (R)-3-methoxyhexanoic acid was produced by asymmetric hydrogenation of a  $\beta$ -keto ester using a RuCl<sub>3</sub>/(R)-MeO-BIPHEP catalyst system and then methylation together with hydrolysis. Finally, fragment d7 was coupled with the corresponding acid under HATU activation to successfully give micromide [101].

 $\beta$ -Carbolines belong to a large family of indole alkaloids and their unique rigid heterocyclic skeletons lead to special bioactivities, such as CDK inhibition and DNA intercalation. In 2010, Puyong Zhang et al. [102] finished the first total synthesis of a marine alkaloid hyrtiosulawesine. 5-methoxyindole e1 was chosen as the starting material and after reacting with oxalyl chloride 5-methoxyindole-3-glyoxyloyl chloride e2 was prepared. Then treatment with tributyltin in anhydrous ethyl acetate produced the key intermidiate 5-methoxyindole-3-glyoxal e3. Another key intermidiate e4 also was synthesized from 5-methoxyindole via Vilsmeier–Haack reaction, Henry reaction, double-bond reduction and nitro reduction. Then, acetic acid catalyzed Pictet-Spengler cyclization of intermidiates e3 and e4 led to dehydrogenated b-carboline product e5. Final demethylation in the presence of BBr3 afforded hyrtiosulawesine successfully (Figure 5) [102].



Figure 5: Total synthesis of hyrtiosulawesine

In 2011, Puyong Zhang et al. [102] accomplished the first total synthesis of another two marine alkaloid pityriacitrin and pityriacitrin B (Figure 6). Starting from the condensation of oxalyl chloride and indole led to intermidiate indole-3-glyoxyloyl chloride f2. Then after treating with tributyltin in anhydrous ethyl acetate at room temperature, corresponding indole-3-glyoxal f3 was produced. Finally intermidiate f3 was transformed to pityriacitrin B, via Pictet-Spengler cyclization reaction with L-tryptophan [103].



Figure 6: Total synthesis of pityriacitrin and pityriacitrin B

Cyanthiwigin diterpenoids belong to a growing family of cyathane natural products with over 30 members and many of them possess antitumor or antimicrobial activities [104]. Their interesting structures and biological activities have attracted considerable synthetic efforts. Cheng Wang et al. [105] developed a more general and flexible strategy to achieve the first total synthesis of cyanthiwigins A, C, H and a concise synthesis of cyanthiwigin G. After retrosynthetic analysis, a common intermediate g1 was needed and cis-Hydrindanone g2 was found to be crucial for the assembly of g1. But cis-Hydrindanone g2 was not easily synthesized by hypothesized Diels-Alder reaction. A modified [4+2] reaction was built by incorporating a sequential Michael addition followed by oxonium ion-promoted cyclization and after decarboxylation with Raney Nickel cis-Hydrindanone g2 was successfully synthesized. And then, cis-Hydrindanone g2 was used to construct the cycloheptene ring and the stereocenters of g1 through a series of carbocycle-forming reactions, including stereospecific 1,4-addition, alkylation, and ring-closing metathesis. Finally, intermediate g1 was transformed to cyanthiwigins A, C, G, and H, through several common reactions, including reduction, dehydroxylation, oxidation, deprotection, addition and rearrangement (Figure 7) [105].



Figure 7: Total synthesis of cyanthiwigins A, C, G, and H

Lingzhiol, which was reported to be an important candidate for the study and treatment of diabetic nephropathy, attracted the attention of Zhen Yang et al. [106] They developed the first asymmetric total synthesis strategy of (-)-lingzhiol in 17 steps. The key step was the [4.3.0]-bicyclic ring moiety construction and they used the homopropargyl alcohol h1, which was treated with [RhCl(CO)<sub>2</sub>]<sub>2</sub> (5 mol%) at 85°C under an atmosphere of CO in ClCH<sub>2</sub>CH<sub>2</sub>Cl, to successfully afford intermidiate h2 with [4.3.0]-bicyclic ring moiety through [3+2] cycloaddition. Subsequently, intermidiate h2 was transformed to (-)-lingzhiol through reductive lactonization, allylic oxidation and benzylic oxidation (Figure 8).



Figure 8: Total synthesis of (-)-lingzhiol

Fengying Zhang et al. [107] finished the first asymmetric total synthesis of the bisindole marine alkaloid (+)-dragmacidin D. The route started from ortho-iodoaniline i1 which was used to build indole i3 via Pd-catalyzed annulation with butaldehyde i2. And then, indole i3 was transformed to intermidate i4 through Evans' oxazolidinone chiral auxiliary induced asymmetric conjugate addition. After a classical three-step sequence to

form the central pyrazinone ring, and a modified Chen's method to install the aminoimidazole moiety, (+)-dragmacidin D was successfully achieved (Figure 9).



Figure 9: Total synthesis of (+)-dragmacidin D

The first total synthesis of marine natural product,  $(\pm)$ -marinopyrrole A, was accomplished via a nine-step reaction strategy by Rongshi Li et al. [108] in an overall yield of 30%. 2-ethoxycarbonyl-3-aminopyrrole j1 and R-ketone ester j2 were chosen as the starting materials and via a TsOH-catalyzed condensation and cyclization bis-pyrrole skeleton j3 was formed. After three steps reduction and oxidation reactions, dialdehyde j4 was obtained which was transformed to diol j5 through addition reaction with Grignard reagent. But diol j5 was unstable and easily turned into oxazepine j6. To avoid this, the crude j5 was directly subjected to oxidation by CrO3 in anhydrous pyridine at room temperature to successfully furnish diketone j7 in 69% yield. After deprotection of the Ts group, NCS chlorination and demethylation, ( $\pm$ )-marinopyrrole A was afforded finally (Figure 10) [108].



Figure 10: Total synthesis of marinopyrrole A

Zhen-Yu Yang et al. [109] finished the first total synthesis of Clavulactone (Figure 11) which started from the known enantiopure epoxide k1. Rearrangement of epoxide k1 under Yamamoto's conditions led to aldehyde k2 which was transformed to trans-cyclopentanol k3 with SmI<sub>3</sub> as the most suitable catalyst. After oxidation, protection, substitution and reduction, enone k4 was obtained. Wittig olefination of enone k4 with methoxymethyltriphenylphosphonium chloride yielded dienes k5 which underwent hetero-Diels–Alder reaction to give adduct k6 with pyran ring. After reduction with  $Et_3SiH$  and reversal with NaHMDS, bicyclic intermediate k7 was synthesized. After several reduction, hydrolization and substitution reactions, precursor k8 was afforded. The intramolecular SN<sub>2</sub> alkylation of k8 in the presence of NaHMDS under highly diluted conditions was smoothly accomplished and subsequent release of the ketone functionality led to the tricyclic skeleton k9. Final conversion of tricyclic enone k9 to clavulactone was achieved via Michael addition of Me<sub>2</sub>CuLi·LiCN and PCC-mediated chemoselective allylic C (sp3)-H oxidation [109].



Figure 11: Total synthesis of clavulactone

Mandelalide A is an excellent antitumor glycosylated macrolide which was found from a new species of Lissoclinum ascidian, collected from Algoa Bay, South Africa [110]. Zhengshuang Xu et al. [96] accomplished its total synthesis via two subunits, 15 and 16, through Suzuki coupling and Horner-Wadsworth-Emmons (HWE) macrocyclization. For synthesizing subunit 15, Alcohol 11 was homologated into allylic alcohol 12 in 91% yield, by a three-step sequence including Dess-Martin oxidation, HWE olefination, and reduction with DIBAL-H. After treating with iodine in acetonitrile, 2,5-cis-disubstituted tetrahydrofuran 13 was obtained which was transformed to diol l4 through several steps including Dess-Martin oxidation and selective dihydroxylation. The primary alcohol of 14 was protected and condensed with dimethylphosphonoacetic acid under the Yamaguchi conditions to afford phosphonate 15 in 88% yield. For synthesizing subunit 16, Prins cyclization of aldehyde 17 and homoallylic alcohol 18 was finished over 2 steps. And after hydrogenolysis, protection and three-step sequence, terminal alkyne 19 was transformed to subunit 16 with dicyclohexylborane-mediated hydroboration and DDQ treatment. Then, fragments assembly started between vinyl boronate 16 with vinyl iodide 15 according to Suzuki reaction. After selectively oxidization using the Piancatelli protocol and intramolecular HWE reaction, aglycone 110 was afforded and coupled with L-rhamnose-derived thioglycosyl donor according to Kahne glycosylation through sulfoxide activation. Next final global desilylation successfully led to Mandelalide A (Figure 12) [111].



Figure 12: Total synthesis of mandelalide A

(+)-awajanomycin was isolated from the marine-derived fungus *Acremonium sp.* AWA16-1, collected from sea mud off Awajishima island in Japan, and found to be cytotoxic against A549 cells [112]. Rui Fu et al. [113] accomplished the first total synthesis of (+)-awajanomycin by assembling  $\gamma$ -lactone- $\delta$ -lactam core m1 and the lipid side chain m2. The building block m3 was chosen as the key intermidiate for the synthesis of  $\gamma$ -lactone- $\delta$ -lactam core m1. After O-Silylation, m3 was obtained which was treated with MeMgI in CH<sub>2</sub>Cl<sub>2</sub> to produce adducts and subjected to BF<sub>3</sub>•OEt<sub>2</sub>-mediated Et<sub>3</sub>SiH reduction for obtaining lactam m4. Through cleaving the N-allyl group with RhCl<sub>3</sub> hydrate in refluxing n-propanol and N-Boc protecting, lactam m5 was afforded. Then introduction of a double bond by phenylselenylation followed by oxidative elimination led to compound m6 which was desilylated to give requisite amide. After extensive investigations, the requisite amide was successfully transformed to C,O-bis-methoxycarbonylated compounds m7 and m8 in 89: 11 diastereomeric ratio using vinylmagnesium bromide as the vinylation reagent and HMPA as a cosolvent. Then, through treating with sodium hydride and the Davis' oxaziridine, deprotecting of the N-Boc and condensation in the presence of K<sub>2</sub>CO<sub>3</sub>, segment m1 was successfully afforded. Finally, cross-coupling of segment m1 with segment m2 catalyzed by Grubbs' second generation catalyst accomplished the synthesis of (+)-awajanomycin (Figure 13).



Figure 13: Total synthesis of (+)-awajanomycin

Bin-Gui Wang et al. [114] accomplished the first total synthesis of marine-derived penicimonoterpene after its isolation from the endophytic isolate of the fungus, Penicillium chrysogenum QEN-24S in 2011 [45]. Reformatsky reaction was a key step for obtaining the key intermidiate n4. Although 3 routes could lead to intermidiate n4, routes 1-2 were found to be uneconomic because of the poor yield and by-products formation. In Route III, the Reformatsky reaction of 6-methylhept-5-en-2-one with BrCH<sub>2</sub>COOCH<sub>3</sub> yielded n1 in 85% yield. Then treatment of Compound n1 with t-BuOOH and SeO<sub>2</sub> led to aldehyde n2 and alcohol n3, and n2

could be converted to n3 by NaBH4 reduction. Intermediate n4 was produced in 85% yield by saponification of n3 with no protection of the tertiary hydroxyl group. Finally intermidiate n4 was transformed to penicimonoterpene via acylation reaction (Figure 14) [114].



Figure 14: Total synthesis of penicimonoterpene

4-amino-7-(5'-deoxy- $\beta$ -D-xylofuranosyl)-5-iodo-pyrrolo [2,3-d]pyrimidine was first isolated in 2008, from an ascidan, *Diplosoma sp.* It was proved to cause complete inhibition of cell division in fertilized sea urchin eggs at 1 µg/mL concentration [115]. Qiang Xiao et al. [116] accomplished its first total synthesis. 5-Deoxy-Dxylose glycosylation acceptor o3 was produced starting from D-xylose o1. After sulfuric acid-catalyzed acetalation and selectively tosylation with p-toluenesulfonyl chloride, monotosylate o2 was afforded which underwent reduction, subsequent benzoylation and acetylation to give acceptor o3. Final assembly accomplished by Vorbrüggen glycosylation of 5-iodo-7H-pyrrolo [2,3-d]pyrimidine with acceptor o3. Then after deprotection and amination reaction target nucleoside was obtained successfully (Figure 15) [116].



Figure 15: Total synthesis of 4-amino-7-(5'-deoxy-β-D-xylofuranosyl)-5-iodo-pyrrolo [2,3-d]pyrimidine

Besides, some other modifying total synthsis strageties are also impressive and make sense for the practical production of marine drugs. Zhai Hongbin et al. [117] focused on improving the synthetic method of (-)-nakadomarin A and successfully provided a novel total synthesis strategy with practicality and efficiency. Enzyne p1 was found to be the key intermidiate which was transformed to the core tetracycle p2 with PtCl<sub>2</sub> in toluene under cascade reaction. And after saturation of C8-C9 double bond via a three step protocol, compound p3 was used to afford dienol p4 via five step reaction sequence. Facile RCM of p4 took place in the presence of Grubb's second generation catalyst to obtain pentacycle p5. Then, after four step reaction sequence and treating with Grubb's first generation catalyst, final RCM was smoothly accomplished. And after reduction with Red-Al, (-)-nakadomarin A was achieved successfully in 85% yield (Figure 16) [117].



Figure 16: Total synthesis of (-)-nakadomarin A

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Zhanzhu Liu et al. [118] focused on the total synthesis of (-)-Saframycin A (Figure 17) which started from L-tyrosine. It was transformed to N-Cbz-protected 1,2,3,4-tetrahydroisoquinoline moiety q1 and N-Boc protected amino acid moiety q2 through several normal steps. The obtained two intermidiates were coupled to give compound q3, which was used to build the pentacyclic skeleton of compound q4 via the stereospecific intramolecular Pictet-Spengler reaction. Final oxidation of the phenolic hydroxyl groups afforded (-)-Saframycin A and the total 24 steps gave an overall yield of 9.7%.



Figure 17: Total synthesis of (-)-saframycin A

The lamellarins and related pyrrole-derived alkaloids were found to exhibit promising biological activities such as antitumor, antibiotic, antioxidant and HIV-1 integrase inhibition activities [119]. Their fascinating novel structures and interesting biological activities stimulated considerable synthetic efforts. Yanxing Jia et al. [120] developed a concise total synthesis method of lamellarins D, H, and R and ningalin B which started from the corresponding aldehydes and amines. An AgOAc mediated oxidative coupling reaction of aldehyde r1 and amine r2 led to the key intermediate pyrrole r3 which was used to construct acid r4 by Vilsmeier-Haack reaction and Lindgren oxidation. And next acid r4 could be tranformed to lactone r5 through Pb(OAc)4-mediated oxidative lactonization. Finally, lactone r5 turned into lamellarins D and H, via Kita's oxidation to form the pyrrole-arene C-C bond, DDQ oxidation, and selective deprotection. Alternatively, treatment of lactone r5 with BBr3 produced ningalin B. Besides, lamellarin R was also synthesized by the similar way (Figure 18).



Figure 18: Total synthesis of lamellarins D and H

(+)-Tanikolide is a brine-shrimp toxin and antifungal marine metabolite isolated from the lipid extract of the cyanobacterium Lyngbya majuscule on Tanikely Island, Madagascar. Its potent biological activity attracted

the interest of Hua Yang et al. [121]. Enantiospecific total synthesis was accomplished by starting with the known compound  $\alpha,\beta$ -unsaturated ester s1. It was reduced with LAH to give allylic alcohol s2. But allylic alcohol s2 was not efficiently transformed to compound s5 according to Meisenheimer rearrangement like assumption, because the undesired s8 was produced mostly. Instead, treatment of s2 with acetic anhydride was utilized and the acetoxy-protected s3 was synthesized in quantitative yield which was successfully rearranged to give s4 under mCPBA condition. After transesterification with methanol and Pd/C-catalyzed hydrogenation, triol s6 was afforded which could be directly oxidized to (+)-tanikolide in 30% yield under NaClO/NaClO<sub>2</sub>/TEMPO condition. Alternatively, protecting triol s6 as acetonide s7 and then oxidating with NaClO/NaClO<sub>2</sub>/TEMPO followed by one-pot deprotection of acetonide with aq. HCl, led to (+)-Tanikolide in excellent yield (89%). The improvement of yield probably related to the avoidence of oxidation of non-target primary hydroxyl group (Figure 19).



Figure 19: Total synthesis of (+)-tanikolide

Rigidin E with calmodulin antagonistic activity was first isolated from Papua New Guinea tunicate *Eudistoma sp.* [122]. For improving the synthetic efficiency of Rigidin E et al. [123] accomplished another total synthesis route. Methanesulfonamide t1 and Knoevenagel adduct t2 are key intermidiates for final assembly. Regioselective bromination of acetophenone t3 and subsequent amination with hexamethylenetetramine led to 2-Amino-acetophenone t4. Then after treating with methanesulfonyl chloride methanesulfonamide t1 was produced. After Knoevenagel condensation of 2-cyano-N-methylacetamide t5 and 4-(benzyloxy)benzaldehyde t6, 3-(4-(benzyloxy)phenyl)-2-cyano-N-methylacrylamide t2 was obtained. Methanesulfonamide t1 and Knoevenagel adduct t2 underwent a cascade Michael addition/intermolecular cyclization to afford intermediate t7. Finally, through triphosgene/I2 catalyzed cyclization and deprotection of benzyl groups, rigidin E was successfully synthesized (Figure 20) [123].



Figure 20: Total synthesis of Rigidin E

# CONCLUSION

Marine-derived organisms constitute a promising source of unique secondary metabolites with considerable pharmaceutical and therapeutical potentials. A great number of excellent compounds with diverse bioactivities have been discovered and validated. Most biological assays focus on cytotoxic and antimicrobial activities investigation as demonstrated throughout the literature. Examples mentioned in this review including Pseudonocardians A-B [15], Luteoalbusins A–B [26], Marangucycline B [29], Fradimycins A-B [48], citreamicin  $\theta$  A-B [49], Hippolachnin A [52], should trigger more intensive efforts to reveal the mechanisms and explore further pharmacological applications.

Besides, biological screens for marine natural secondary metabolites should be broadened to afford more specific and rarely noticed biological activities. Inflammation and diabetes are also worldwide chronic diseases leading to millions of deaths every year, although less papers concern the corresponding activities of marine natural products investigation. But biomolecules like Thioflexibilolide A [69], Lobophytones [70-73], Sarcocrassocolides [75-78], Eurothiocin A-B [86], deserve more attention considering their excellent potentials for the therapy of lifethreatening chronic diseases.

Indeed, isolation and characterization of marine bioactive secondary metabolites are important for new pharmaceutical candidates profiling and screening. But after approving for clinical use, the occuring problem is how to achieve the target structure-complex compound in sufficient amount for practical application. Traditional isolation from marine natural organisms is not sustainable due to the relative limitation of resources. Total synthesis starting from simpler pieces is one of the excellent tools for shooting this trouble. The first total synthesis of peptides [96,98,100,101], alkaloids [102,103,107] and some other molecules with outstanding bioactivities has been accomplished which is quite meaningful for building actual production routes. Some other modified total synthesis strategies [117,118,120,121,123], also should be noticed in light of improving the generality and reproducibility.

Marine natural products investigation still has a huge unexploited potential, and there is no doubt that more bioactive molecules will be discovered and synthesized in the future. But the significant advantages and disadvantages of marine natural secondary metabolites as drug candidates for development still need to be explored deeply because the world is always facing serious situation against various diseases and novel therapeutic entities that can make a substantial contribution to the treatment and precaution are urgently needed.

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