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REVIEW ARTICLE

Chemistry and bioactivity of secondary metabolites from South China Sea marine fauna and flora: recent research advances and perspective

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Marine organisms often produce a variety of metabolites with unique structures and diverse biological activities that enable them to survive and struggle in the extremely challenging environment. During the last two decades, our group devoted great effort to the discovery of pharmaceutically interesting lead compounds from South China Sea marine plants and invertebrates. We discovered numerous marine secondary metabolites spanning a wide range of structural classes, various biosynthetic origins and various aspects of biological activities. In a series of reviews, we have summarized the bioactive natural products isolated from Chinese marine flora and fauna found during 2000–2012. The present review provides an updated summary covering our latest research progress and development in the last decade (2012–2022) highlighting the discovery of over 400 novel marine secondary metabolites with promising bioactivities from South China Sea marine organisms.

Keywords: marine natural products; biological activity; marine flora; sponges; soft corals; mollusks

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INTRODUCTION

The ocean supports vast habitats and serves as prolific resources for various living organisms. Given the uniqueness of ocean habitat, high concentration of salts, high pressure, low concentration of oxygen, and dark condition, marine organisms often produce highly potent metabolites with unique structures and diverse biological activities to enable them to survive and struggle in the extremely challenging environments. Since one of the first marine-derived drugs, cytarabine, was approved in 1969 by the U.S. Food and Drug Administration (FDA) for the treatment of leukemia, inspiring more and more scientists to devote great effort to the development of marine drugs [1]. In recent decades, the rapid development of the biotechnology has led to a new era of bioprospecting for marine natural products. The efficiency of drug discovery has been greatly improved as the revolutionary target screening methods were widely applicated. Several marine drugs and drug candidates in preclinical or clinical trials undoubtedly proved that marine natural products are important inspiration sources for drug development.

Located in tropical and subtropical areas, the South China Sea is an important geographic location yielding many novel marine natural products, most likely due to the remarkable biodiversity of coral reefs, which provide a suitable environment for the wide range of marine organisms. As a pioneer in the chemical investigation of Chinese marine organisms, our group, the only group in Shanghai Institute of Materia Medica (SIMM), has long been dedicating on the discovery of pharmaceutically interesting lead compounds from marine plants and invertebrates since 2000. We have continuously reported hundreds of marine compounds with novel structural skeletons from marine sponges, soft corals, marine algae and so on, resulting in numerous publications in reputable journals, and our research results have been serially invited reviews including *Chemical Reviews* [2, 3], *Natural Product Reports* [4–6], as well as *Acta Pharmacologica Sinica* [7]. As great recent progress on marine natural products has been achieved by our group, an update of the previous summary was highly urgent. On the occasion of the 90th anniversary of SIMM, we will take this opportunity to showcase the main research progress of our group in the past 10 years. In this review, it covers more than 100 literatures and summarize over 400 novel marine metabolites with interesting biological activities reported by our group since 2012. Some classic cases are described in detail.

CHEMICAL STUDIES ON MARINE PLANTS

Marine plants are primary producers playing important roles in the marine ecosystem. They are autotrophic organisms that use chlorophyll to produce organic nutrient in the ocean. There are many phyla of marine plants, ranging from low eukaryotic algae to higher seed plants. Our group has long been engaged in the chemical investigation of various marine algae and mangroves, because of their nutritional or medicinal values. In this section, it will mainly discuss the chemistry and bioactivity of structurally and biologically interesting metabolites from marine algae and mangrove plants discovered by our group.

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Marine algae

Marine algae comprise large number of simple organisms relying on photosynthesis. In general, algae can be classified into two main groups. The first one is the microalgae, which includes blue green algae, dinoflagellates, bacillariophyta, *etc*. The second group is macroalgae (seaweeds) which includes green, brown, and red algae. Most of our studies involve algae belonging to the phyla Chlorophyta, Phaeophyta, and Rhodophyta. A series of unusual compounds bearing unprecedented structures were identified in these taxa.

Caulerpa racemosa is a species of edible green alga belonging to the phylum Chlorophyta. It is commonly known as sea grapes and is mainly distributed in Guangdong Province, Guangxi Autonomous Region, Dongsha and Xisha Islands in China. *C. racemosa* is a kind of traditional Chinese medicine, which was first recorded in the *Compendium of Xinhua Materia Medica* for the treatment of various pains caused by qi stagnation and blood stasis. As part of our continuing studies on the chemical constituents of the *C. racemosa*, the green algae were collected from the coastline of Zhanjiang city, Guangdong Province, led to the isolation of two bisindole alkaloids, racemosins A (**1**) and B (**2**), and one well-known pigment caulerpin (S**1**) [8] (Fig. 1 and Supplementary Fig. S1). Compound **1** possesses a structurally unique *seco*-indolo[3,2-a]carbazole skeleton with two uncommon indolinenone units both conjugated with a methyl propenoate moiety, which represents the first example of a bisindole alkaloid with the *seco*-indolo[3,2-a] carbazole skeleton from nature. Comparing the chemical structures of **1** and **2**, it is easy to find that they are biogenetically related to each other with an unusual indolo[3,2-a] carbazole. In a neuroprotective assay, compound **1** significantly attenuated the $A\beta_{25-35}$-induced SH-SY5Y cell damage with a 14.6% increase in cell viability at the concentration of 10 μM, when compared to epigallocatechin gallate (16.57% increase at 10 μM) as the positive control.

Sargassum thunbergii belongs to the phylum Phaeophyta. As a common economic brown alga in coastal areas of China, *S. thunbergii* has strong reproductive capacity, which plays an important regulatory role in maintaining the balance of coastal ecosystem. It is well known that marine algae are ideal health food for diabetics. In our chemical and biological studies of the *S. thunbergii*, which were collected off the coast of Nanji Island, Zhejiang Province, China, resulting in the isolation of a new sterol thunberol (**3**). The compound exhibited significant inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), a potential drug target for the treatment of type-II diabetes, with the IC_{50} value of 2.24 μg/mL [9]. This result provided an inspiration for the development of marine algae products in the prevention of diabetes.

Red algae of the genus *Laurencia* are well-known for their ability to biosynthesize an astonishing variety of structurally unusual secondary metabolites. More than 1100 different metabolites have been characterized from approximately 80 species of this genus. Among them, cuparene-type, and laurane-type sesquiterpenoids are well-known and typical. Two chemical investigations of the red algae *L. okamurai* Yamada, which were collected off the coast of Nanji Island, Zhejiang Province in 2010 [10] and 2013 [11, 12], led to the isolation of a novel rearranged sesquiterpene *seco*-laurokamurone (**4**), six new laurane-type sesquiterpenes (**5**–**10**), one new laurokamurane-type sesquiterpene (**11**), one new bisabolane-type sesquiterpene (**12**) and three novel heterodimeric laurane-type sesquiterpenoids laurokamurols A–C (**13**–**15**) (Fig. 1). The absolute configurations of the new bis-sesquitepenoids (**13**–**15**), especially their axial chirality, were determined by extensive spectroscopic analyses and time-dependent density functional theory electronic circular dichroism (TDDFT-ECD) method. In bioassay, laurokamurols A–C (**13**–**15**) and the known related compounds showed promising PTP1B inhibitory activities

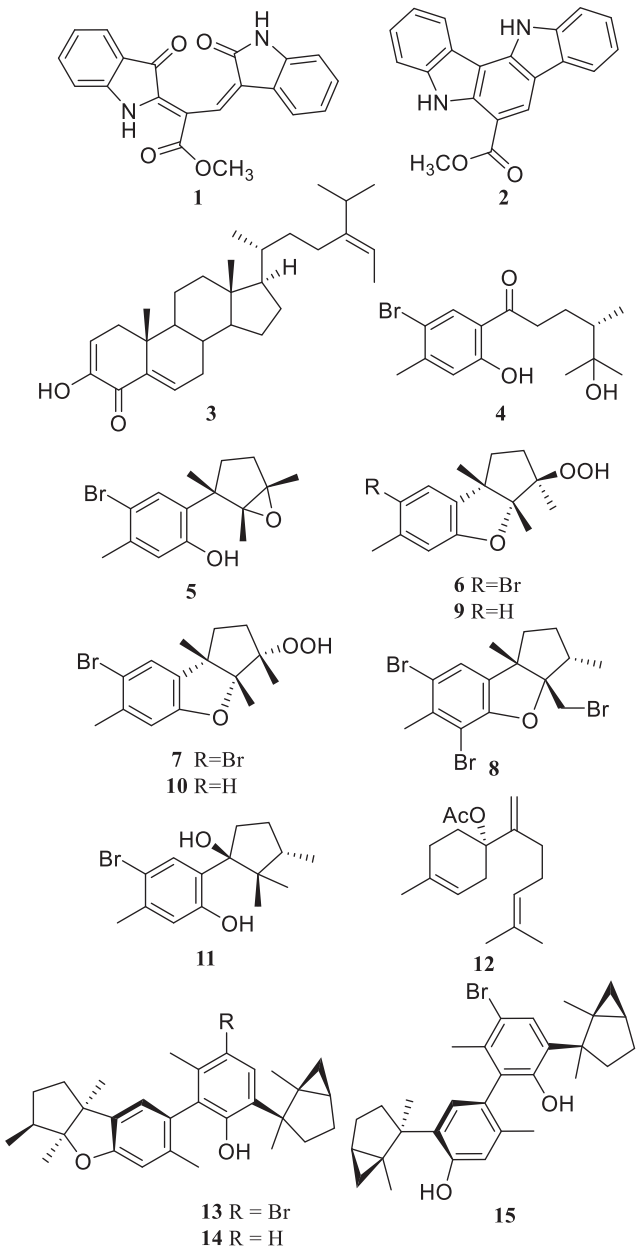


Fig. 1 Structures of new isolates from marine algae.

with the IC_{50} values ranging from 4.9 to 14.9 μg/mL [11, 12]. These biological components of the marine algae suggest the possible utilization as food additives with the functions for human healthcare, especially for anti-diabetic aspect.

Mangroves

Mangroves, mainly distributed in the tropical and subtropical tidelands, are distinct plant communities that have attracted as much curiosity and scientific attention for their salt-tolerant habits. This special ecosystem is usually found in Asia and Australia with diverse species. For example, more than 40% of mangrove forests are found along the Asian coasts, including the South China Sea Coast. In many countries, especially in China, the extracts and chemicals from mangroves are used mainly in folkloric medicine, as insecticides and piscicides and these practices continue to today. The chemical and biological studies of the plants are very important for deciphering the actual value of folkloric remedies.

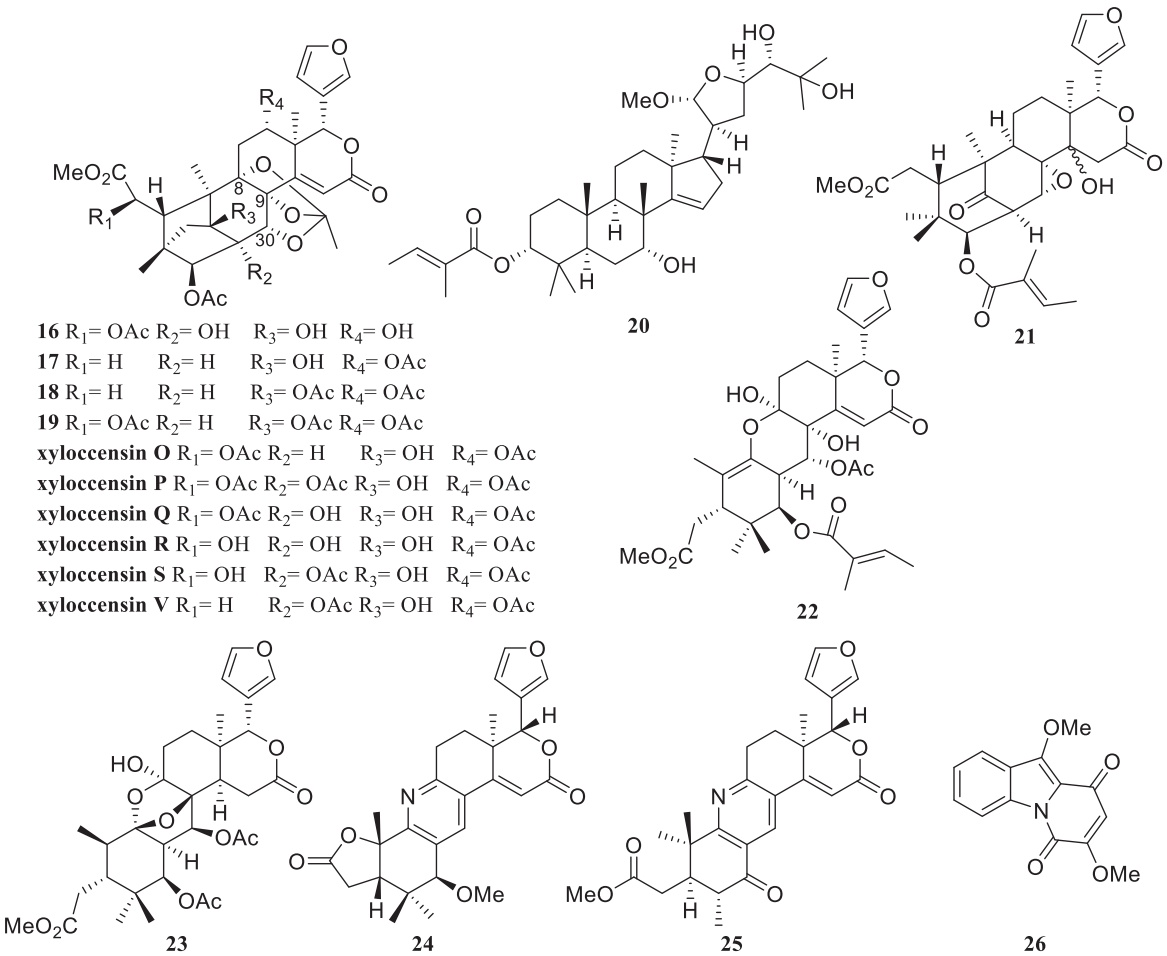


Fig. 2 Structures of representative compounds from mangroves.

In the course of our ongoing research for bioactive metabolites from mangrove plants, we investigated the twigs and leaves of *Xylocarpus granatum* (Meliaceae), collected from the seashore of Dongzhai, Hainan Province, China, resulting in the isolation of four new 8,9,30-phragmalin orthoesters (**16**–**19**), along with six related known compounds, namely xyloccensins O–S and V [13]. It is worth mentioning that the absolute configurations of xyloccensins O–S and V were revised via X-ray diffraction analysis and TDDFT-ECD calculation. Later, 6-*O*-acetyl xylocarpin D (**S2**) [14], 1,2-dihydro-3*α*-hydroxy-turranolide (**S3**) [14] and xylogranatumines A–G (**S4**–**S8**, **20**, and **S9**) [15] were also successively isolated and determined (Fig. 2 and Supplementary Fig. S2). Biogenetically, these interesting molecules might be derived from hainangranatumin D, a limonoid previously isolated from *X. granatum*. In bioassay, xylogranatumine F (**20**) exhibited weak cytotoxic activity against A549 tumor cells with inhibition of 54.2% at the concentration of 10 μM.

Besides, some new tetranortritepenoids (**21**–**23** and **S10**–**S12**) (Fig. 2 and Supplementary Fig. S2) were discovered and determined by detailed spectroscopic analysis. Among them, the absolute configuration of 9-*epi*xylogranatin A (**22**) was determined by TDDFT-ECD calculation. Xylogranatumin A (**23**) represents the first example of the 9,10-*seco* limonoid with an unprecedented B ring bearing an oxygen bridge between C-1 and C-8 [14]. Xylogranatopyridines A and B (**24** and **25**) were two new pyridine-containing limonoids, their structures were elucidated unambiguously by single-crystal X-ray diffraction analysis. In addition, xylogranatopyridine A (**24**) was found to be the first limonoid to show inhibitory activity against PTP1B with the IC_{50} value of 22.9 μM [16].

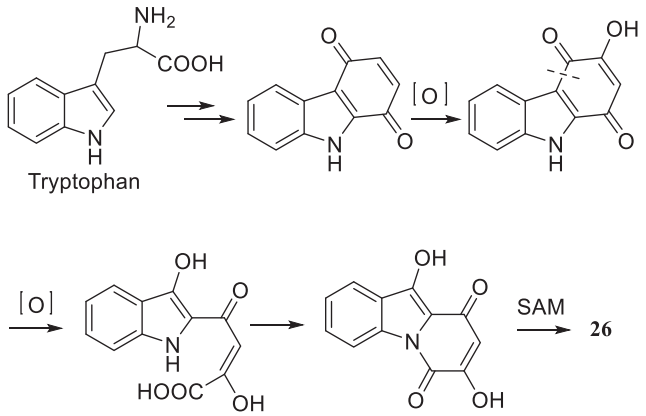
Acanthus ilicifolius Linn. (Acanthaceae), a gregarious shrub, widely distributed in coastal regions of southeastern China. It has long been used as a traditional Chinese medicine for treatment against rheumatism, paralysis, and asthma. Chemical investigation of the leaves and stems of *A. ilicifolius* Linn., collected at the Zhanjiang mangrove national nature reserve, Guangdong Province, China, led to the isolation of one new pyrido[1,2-a]indole alkaloid acanthiline A (**26**) (Fig. 2) [17]. A plausible biosynthetic pathway for **26** from tryptophan was proposed as shown in Scheme 1.

CHEMICAL STUDIES ON MARINE INVERTEBRATES

Marine invertebrates have been categorized into over 30 phyla. Most marine invertebrates lack physical protection in the form of an exoskeleton, for example, spines, stings, or shells. Therefore, marine organisms developed unique metabolic pathways and, thus, the capability to produce a wide variety of toxic chemicals to mediate spatial competition as well as to prevent parasitism and predation. According to our study, marine sponges, soft corals, and mollusks are the most productive invertebrates contributing numerous biomolecules.

Sponges

Sponges (phylum Porifera) are the most primitive of multicellular animals evolved from about 600 million years ago, and one of



Scheme 1 Possible biosynthesis of acanthiline A (**26**) in *Acanthus ilicifolius*.

the most important reef-building organisms in benthic biomes worldwide. Sponges, which are nerveless and muscleless, are simple in structure but diverse in variety. Over the past decade, a series of chemical investigations of the sponge samples collected from the South China Sea were conducted by our group.

For instance, a new isomalabaricane triterpene, stellettin N (**S13**) [18], was isolated from the marine sponge *Stelletta* sp. from Hainan Province. A novel sesquiterpene pyridine alkaloid fasciospyrinadine (**S14**) [19] was isolated from the sponge *Fasciospongia* sp. collected from Weizhou Island, Guangxi Autonomous Region. Two new indole alkaloids (**S15** and **S16**) [20], and one new *β*-carboline alkaloid (**S17**) [20] were isolated from the Hainan marine sponge *Hyrtios erecta* (Supplementary Fig. S3).

Sponges of the genus *Xestospongia* are rich sources of brominated polyunsaturated lipids. This type of secondary metabolites always exhibited various biological activities ranging from antitumoral, antibacterial, and antifungal, to inhibite pancreatic lipase and HIV-1 integrase [3]. A library of novel brominated polyunsaturated lipids was found and confirmed from the chemical investigation of marine sponge *X. testudinaria*. Xestonarienes A–H (**S18**–**S25**) [21] (Supplementary Fig. S4) and methyl (*E*, *E*)-14,14-dibromo-4,6,13-tetradecatrienoate (**S26**) [22] were isolated from sponge *X. testudinaria* (collected at Weizhou Island, Guangxi Autonomous Region, China). Another new compound xestonariene I (**S27**) [23] was obtained from sponge *X. testudinaria* collected at Ximao Island, in 2014. Brominated polyunsaturated lipids represent a new class of inhibitors of pancreatic lipase (PL), an essential enzyme for efficient fat digestion, since the ethyl xestospongic ester (**27**) [21] and methyl 22-bromo-(17*E*,21*E*)-docosa-17,21-diene-9,11,19-triynoate (**28**) [23] exhibited significant inhibitory activity against PL with the IC_{50} values of 3.11 μM and 0.61 μM, respectively. The result was comparable to that of the positive control orlistat ($IC_{50} = 0.78$ μM). For structure-activity relationships (SAR) analysis, a terminal (*E*)-enyne functionality, a diyne within the chain, and methyl ester group are the key functional groups for sustaining the activity of this kind of structure. In addition, another known compounds methyl 18-bromo-(17*Z*)-octadeca-l7-ene-5,7,15-triynoate (**29**) [22] and a new steroidal ketone (**30**) [24] (Fig. 3) from the animal exhibited significant inhibitory activity against PTP1B with the IC_{50} values of 5.30 μM and 4.27 μM, respectively. Ursolic acid was served as a positive control, and its IC_{50} value was 2.39 μM.

Six new 3-alkylpyridine alkaloids, topsendines A–F (**S28**–**S33**) [25], were isolated from Hainan sponge *Topsentia* sp. Two new 5-alkylpyrrole-2-carboxaldehyde derivatives, mycalenitrile-15 (**31**) and mycalenitrile-16 (**S34**) [26], along with five known related

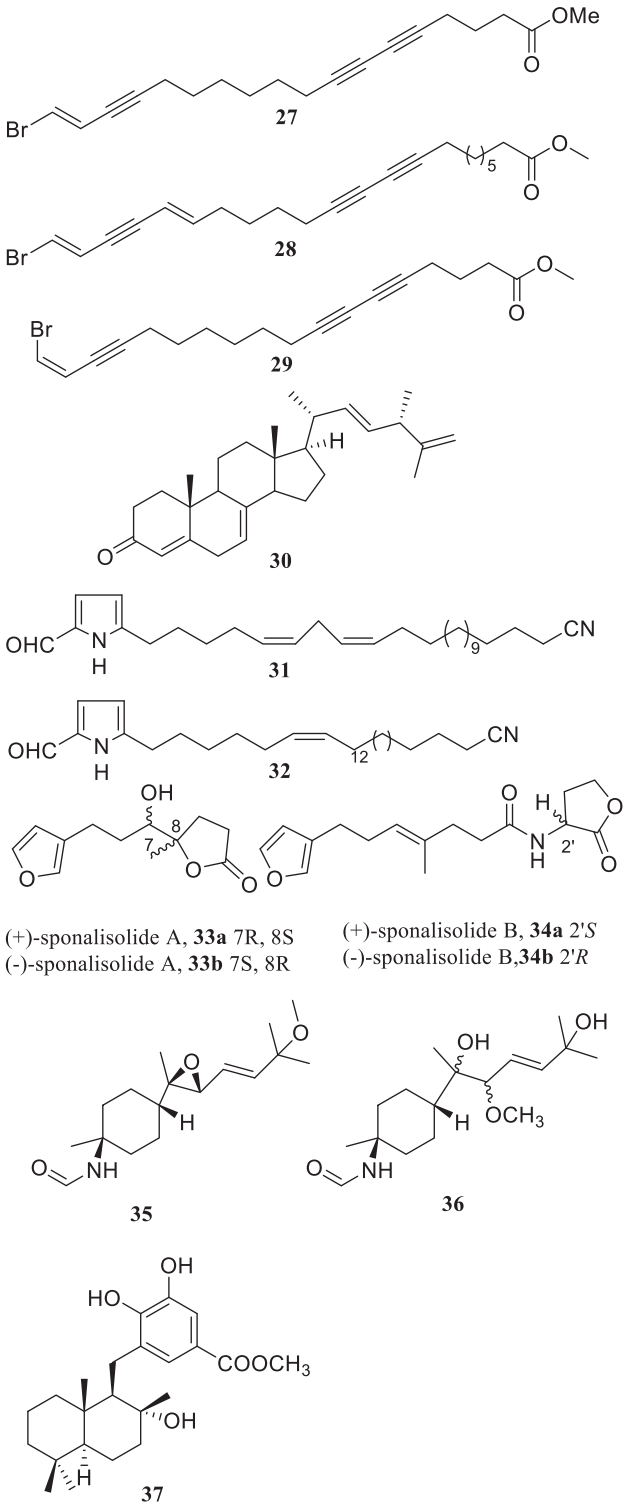
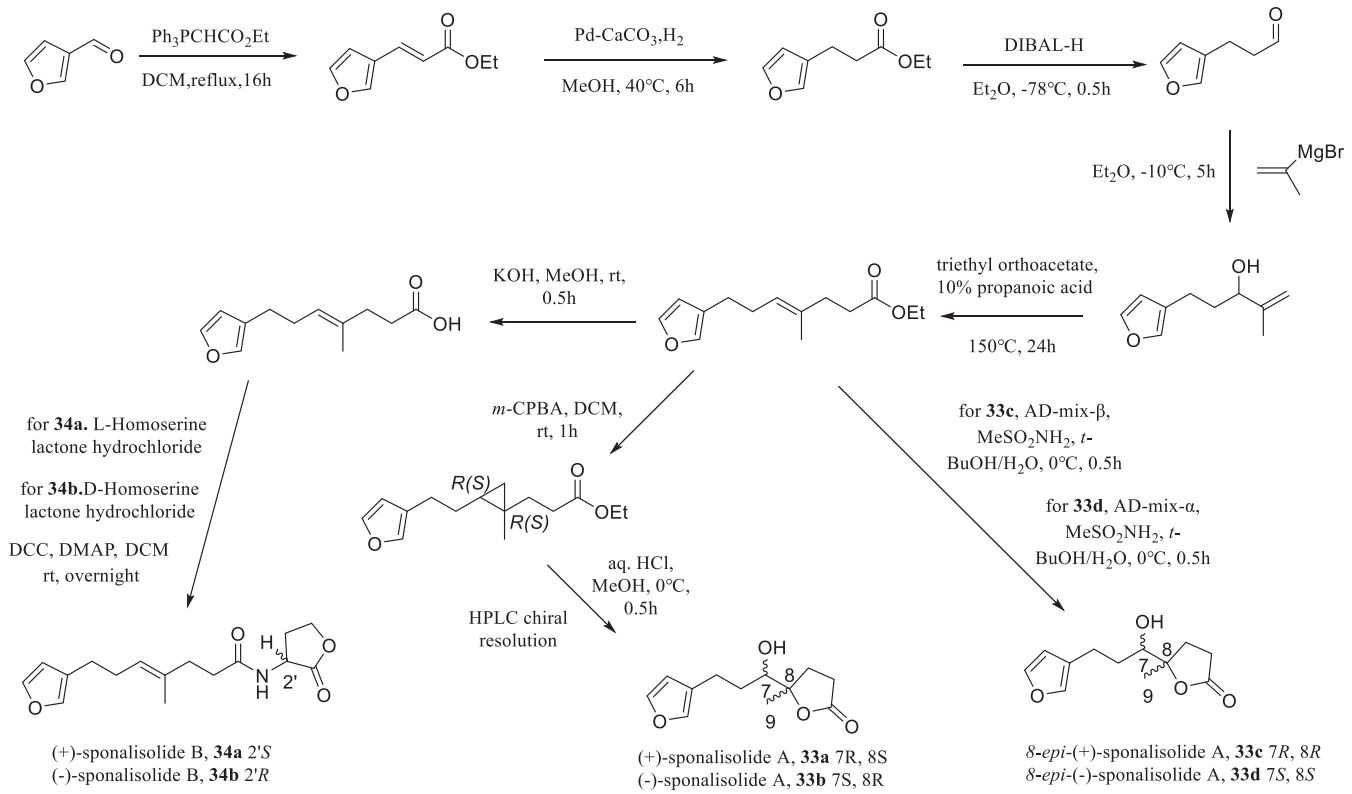


Fig. 3 Structures of new bioactive isolates from sponges.

ones, were isolated from the marine sponge *Mycale lissochela* (Fig. 3 and Supplementary Fig. S5). In bioassay, the new compound **31** and the known compound (6′Z)-5-(23′-cyano-6′-tricosenyl)pyrrole-2-carboxaldehyde (**32**) [26] (Fig. 3) exhibited significant PTP1B inhibitory activities with the IC_{50} values of 8.6 and 3.1 μM, respectively, which are comparable with the positive control ursolic acid ($IC_{50} = 3.6$ μM). A preliminary SAR analysis revealed that the unsaturated aliphatic side chain was potentially necessary for PTP1B inhibitory activity.



Scheme 2 Biomimetic synthetic route of **33** and **34**.

Nitrogenous sesquiterpenoids with cyanide, isocyanide, isothiocyanate, or formamide functionalities, are the secondary metabolites seldom discovered from nature. According to the reports, they were mainly found to exist in the sponges of the order Axinellida. As expected, two new highly oxidized formamidobisabolene sesquiterpenes (**S35** and **S36**) [27], together with four new uncommon nitrogenous eudesmane-type sesquiterpenes, axiriabilines A–D (**S37**–**S40**) [28], were isolated from a Hainan sponge *Axinyssa variabilis*. The absolute configurations of compounds **S37** and **S40** were determined by TDDFT-ECD calculation.

Spongian diterpenes are a family of isoprenoid natural products displaying parent 6,6,6,5-tetracyclic ring system. Aside from their role as eco-physiological mediators, a broad range of pharmaceutically relevant biological activities such as cytotoxic, antifungal, antiviral, and other biological activity, have been reported for spongian diterpenes, making them attractive targets for chemists. Our group has isolated a series of spongian diterpenes from sponge *Spongia officinalis* including new compounds, 3-nor-spongiolide A (**S41**), spongiolides A and B (**S42** and **S43**) [29], as well as two rare new furan butanolides sponalisolides A and B (**33** and **34**) (Fig. 3 and Supplementary Fig. S6) [30]. Compounds **33** and **34** were further separated to their corresponding enantiomers **33a**/**33b** and **34a**/**34b**, respectively. The absolute configurations of **S41**–**S43** were determined by ECD calculations, whereas the absolute configuration of two pairs of enantiomeric compounds (**33a**/**33b** and **34a**/**34b**) was unambiguously established by biomimetic total synthesis. The synthetic route involved a key Johnson-Claisen rearrangement and a lactone cyclization after epoxidation or dihydroxylation (Scheme 2). The natural products (**33a**/**33b** and **34a**/**34b**) (Fig. 3) exhibited the anti-quorum sensing activity to the bacteria *Pseudomonas aeruginosa*.

Sponges were the first invertebrates shown to contain sterols. They have been shown to have the most diverse array of novel sterols. In our study, two new C29 steroids with an unusual *α*-keto-enol functionality bearing A-ring, xidaosterols A (**S44**) and B (**S45**) [31], and two new bis-quinolizidine alkaloids, neopetrosiasins A (**S46**) and B (**S47**) [32], possessing *cis*- and *trans*-quinolizidine nuclei, were isolated from the sponge *Neopetrosia chaliniformis* (Supplementary Fig. S7). The structures of **S46** and **S47** were unambiguously determined by extensive spectroscopic data and single-crystal X-ray analyses. Besides, chemical study of a Hainan sponge *Halichondria* sp. resulted in the isolation of three new sterols, halichsterols A–C (**S48**–**S50**) (Supplementary Fig. S7) [33]. Compounds **S44** and **S45** belong to a small group of steroids that are always found as intermediates in synthesis but also exist in some marine benthic invertebrates. Meanwhile, neopetrosiasins A (**S46**) and B (**S47**) are macrocyclic diamine alkaloids, which are a class of structurally interesting marine natural products mainly occurring in sponges. They are regarded to be biogenetically derived from bis-3-alkylpyridine or reduced bis-3-alkylpridine units.

Formamidobisabolene-based sesquiterpenes are a small group of structurally unusual natural products only found from marine sponges and nudibranchs. A chemical study of the marine sponge *Halichondria sp*. resulted in the isolation of eight new formamidobisabolene-based sesquiterpenes (**35**, **36**, and **S51**–**S56**) (Fig. 3 and Supplementary Fig. S8) [34]. In bioassay, halichine C (**35**) and halichine D (**36**) (Fig. 3) displayed significant inhibitory effect on LPS-induced NO production in BV-2 microglial cells at 10 μM.

Metabolites of mixed sesquiterpene and quinone or hydroquinone biosynthesis are common in marine sponges. For instance, xishaeleganins A–D (**S57**, **37**, **S58**, and **S59**) [35] were isolated from the Xisha marine sponge *Dactylospongia elegans* (Fig. 3 and Supplementary Fig. S8). Their structural variation mainly focuses on the degree of oxygenation and substitution to the aromatic ring. In addition, xishaeleganins B (**37**) (Fig. 3) showed significant antibacterial activity against *Staphylococcus*

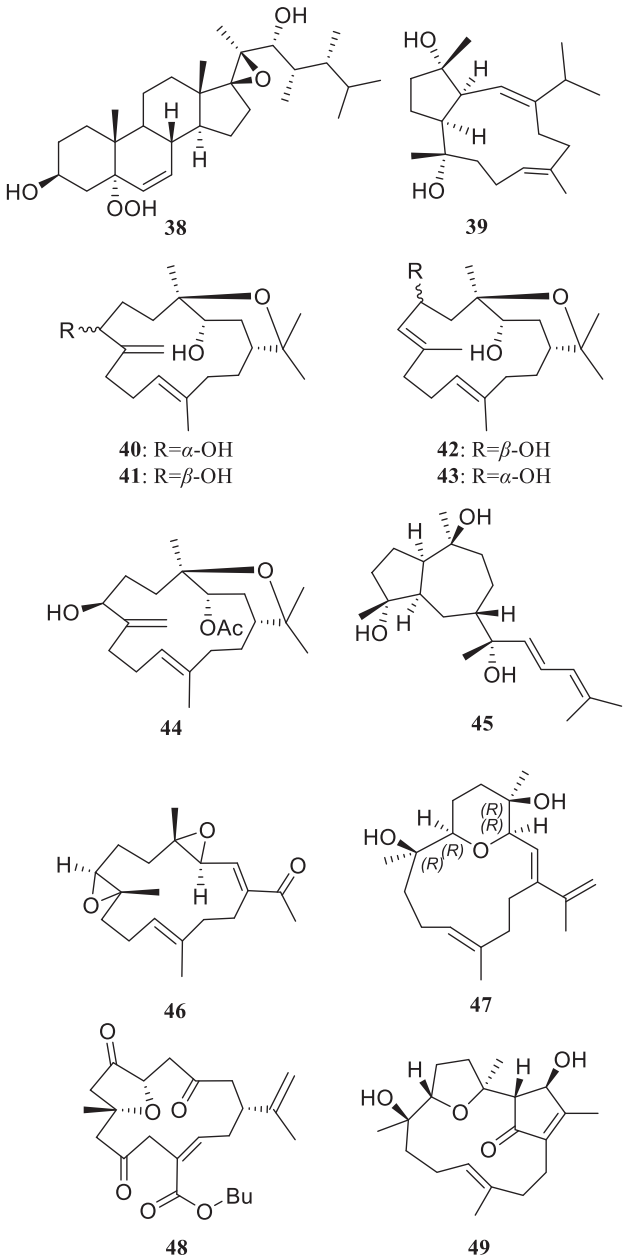


Fig. 4 Structures of representative compounds from soft corals of *Lobophytum*.

aureus, with minimum inhibitory concentration (MIC) value of 1.5 μg/mL, which is comparable with that of positive control vancomycin (MIC: 1.0 μg/mL).

Soft corals (Alcyonacea)

Corals are the common group of sessile invertebrates in the ocean. Secondary metabolites from corals have great diversity because these sessile organisms need exceptional chemical weapons for potential parasite predation and microbial colonization. Our group has a great interest in soft corals and has been persistently studying on them for over 20 years. In this section, we will illustrate our mainly achievements on soft corals in the past 10 years.

During the investigation of the soft corals *Lobophytum* sp. collected at Ximao Island, Hainan Province, China, in October 2013, two unusual steroids, (22*R*,23*S*)-3*β*-hydroxy-23-methyl-17,20-epoxyergost-5-en-22-yl acetate (**S60**) and (22*R*,23*S*)-5-hydroperoxy-23-methyl-5*α*-17,20-epoxyergost-6-ene-3*β*,22-diol (**38**), were obtained (Fig. 4 and Supplementary Fig. S9) [36]. The chemical structure including the absolute configuration of compound **S60** was further confirmed via chemical correlation with the related known one (**S61**). In bioassay, compound **38** showed considerable NF-κB inhibitory activity with the IC_{50} value of 8.96 μg/mL. Considering the surprising structural properties and biological activity of these compounds, we resampled *Lobophytum* sp. from Weizhou Island, in May 2015. The chemical study of the second collection led to the isolation of four new polyhydroxylated steroids (**S62**–**S65**) (Supplementary Fig. S9) [37], together with three new capnosane-type diterpenoids (**39**, **S66**, and **S67**) (Fig. 4 and Supplementary Fig. S10) [38]. It is worth mentioning that capnosane-type diterpenoid is a group of uncommon derivatives. This is the first report of capnosanes from the *Lobophytum* sp. [38]. In addition, nine new bicyclic cembranoid ethers, lobophytolins A–I (**40**–**44** and **S68**–**S71**), and one new prenylated-guiane-type diterpene lobophytolin J (**45**) have been isolated from the soft coral *Lobophytum* sp. (collected off Xisha Island, Hainan province, China) (Fig. 4 and Supplementary Fig. S11) [39, 40]. Quantum mechanical (QM)-NMR method was successfully used to complete the stereochemical assignment of **40**–**45** and **S68**–**S71** with the DP4 + and the i*J*/d*J*-DP4 approaches. In the cases of **40** and **41**, the application of *J*-DP4 displayed better performance than DP4 + method in the assignment of relative configurations of multi-stereogenic centers, which was supported by X-ray crystallography [40]. The absolute configuration of lobophytolin H (**44**) was determined by the application of the modified Mosher's method and chemical transformation. In bioassay, lobophytolin D (**43**) (Fig. 4) exhibited promising cytotoxicity against HT-29, Capan-1, A549, and SNU-398 human cancer cell lines with the IC_{50} values of 4.52, 6.62, 5.17, and 6.15 μM, respectively [39].

In the chemical study of the soft coral *L. crassum* (collected off Ximao Island, in May 2014), a series of polyoxygenated cembranoids, lobophycrasins A–D (**46**, **47**, **S72**, and **S73**), (-)-humilisin A (**S74**), lobocrassins G and H (**S75** and **48**), 6-oxocembrene-A (**S76**), and 14-*epi*-lobophytolide B (**S77**), were isolated and identified (Fig. 4 and Supplementary Fig. S12) [41, 42]. Among them, compound **46** is a C-16 norcembranoid and **48** is a C-4 norcembranoid. In addition, the structure of lobocrasol (**49**) was firmly revised based on X-ray diffraction analysis. By comparing the major chemical components in the soft corals of *Lobophytum* collected four times, their metabolites type varied widely, which may be caused by the geographical and seasonal factors of the collection, as well as interspecies differences.

The soft corals of *Sinularia* are well known as a produce factory of terpenoids, and in our ongoing research on this genus for the past decade, they were the most productive source for searching of novel compounds. For example, five different types of novel terpenoids, sinulatumolins A–E (**50**, **S78**, and **51**–**53**), were isolated from the South China Sea soft coral *S. tumulosa* [43]. Sinulatumolin A (**50**) represented the first example of sesquiterpene bearing an eight-membered cyclic peroxide ring from soft coral, and **51** represented the second furanosesquiterpenoid with a 2-methylfuran-3(2H)-one moiety (Fig. 5). In the anti-inflammatory activity evaluation, compounds **50** and **51**–**53** displayed significant TNF-α inhibitory activity with the IC_{50} values of 7.5, 2.6, 5.5, and 3.6 μM, respectively, being comparable with that of the positive control dexamethasone (IC_{50} = 8.7 μM). Six novel asteriscanoids, sinuhumesins A–F (**54**, and **S79**–**S83**) and two rare polycyclic merosesquiterpenoids, (+)-9-*epi*-verrubenzospirolactone (**55**) and (–)-9-*epi*-verrubenzospirolactone (**56**), were isolated from Hainan soft coral *S. humesi* [44]. Compounds **55** and **56** were a pair of enantiomers further separated by chiral HPLC. Sinuhirtins A (**57**) and B (**S84**) were two new uncommon norhumulene-type norsesquiterpenoids isolated from the soft coral *S. hirta* (Fig. 5 and Supplementary Fig. S13) [45].

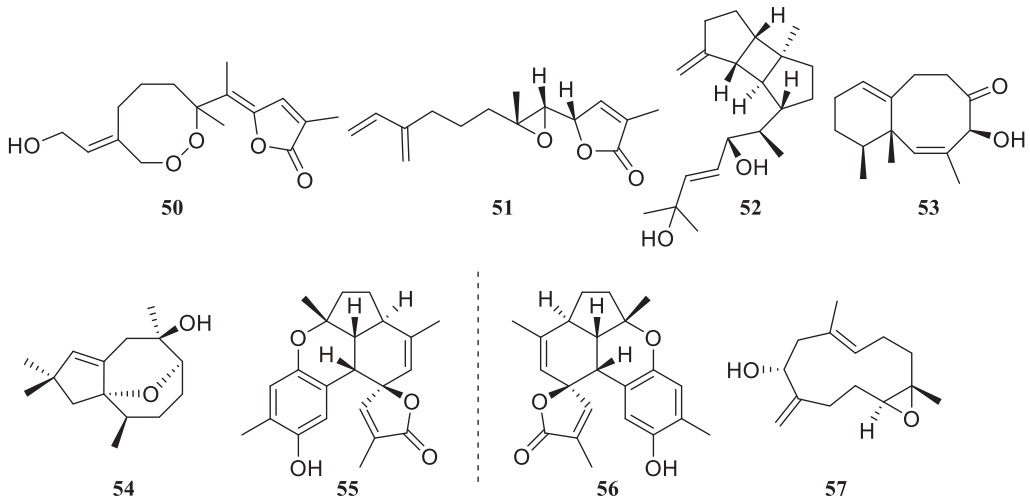


Fig. 5 Structures of representative sesquiterpenoids from soft corals of *Sinularia*.

Cembrane-type diterpenoids are one class of the conspicuous secondary metabolites widely distributed in the soft corals. The intriguing patterns of different substitutions diversify types of cembranoids. Six novel *α*-methylene-*δ*-lactone-bearing cembranoids (**58** and **S85**–**S89**), together with one 15-membered macrocyclic diterpenoid (**59**), and one rare biscembranoid (**60**) were isolated from the soft coral *S. flexibilis* [46]. The structure of **60** was unambiguously confirmed by X-ray diffraction analyses. Epoxyfexibilene (**59**) represents the second flexitilane-type diterpenoid discovered from marine sources. Sinulafexiolide L (**60**) is the third member of the rare cembrane dimer connected through a C–C single bond (Fig. 6). The chemical investigation of soft coral *S. flexibilis* collected off the coastline of Hainan Island led to the isolation of three new cembranoid esters, xidaosinularides A–C (**61**, **S90**, and **S91**), featuring an n-butyl alcohol moiety [47]. It is worth noting that not only the butyl ester group at C-16 was uncommon, but also the configuration at C-1 position was an unusual *β*-oriented. According to the Tursch's empirical rule, isopropyl moieties of cembranoids from Alcyonacean soft corals are always *α*-oriented, while those from Gorgonacean corals are always *β*-oriented. Besides, a novel norditerpenoid, sinusiaetone A (**62**), featuring an unprecedented bicyclo[11.3.0]hexadecane carbon skeleton, and two new polyoxygenated cembranoids, sinusiaeolide A (**S92**) and sinusiaesin A (**S93**), were isolated from the Hainan soft coral *S. siaesensis* (Fig. 6 and Supplementary Fig. S14) [48]. These compounds (**62**, **S92**, and **S93**) displayed a significant inhibitory activity against lipopolysaccharide-induced inflammation in BV-2 microglial cells.

The study of soft corals *Sinularia* sp., which were collected from the Xisha Island, led to the isolation of four new cembranoids (**63**, **S94**, **64**, and **S95**) [49]. The absolute configuration of **63** was established by X-ray diffraction analysis. Compounds **63** and **64** (Fig. 6) displayed moderate inhibitory activity against $A\beta_{42}$ aggregation without cytotoxicity, suggesting that these cembranoids as new anti-Aβ aggregation agents, provided a novel chemical scaffold for anti-Alzheimer's disease drug discovery.

Four other new cembranoids, sinulacrassins A−C (**S96**, **65** and **S97**) and ent-xishaflavalin G (**S98**), have been discovered from *S. crassa* [50]. The present results highlighted the unusual coexistence of *α* (**S97** and **S98**) and *β* (**S96** and **65**) configurations of C-1 in cembranoids from soft coral in the Order Alcyonacea. As mentioned above, Tursch's empirical rule is generally accepted and applied for deducing the absolute configuration of C-1 in cembranoids. However, in view of the reports regarding the co-existence of 1-*α* and 1-*β* series of cembranoids from Order Alcyonacea, we have to use this empirical rule more carefully. The bioassay results revealed that compound **65** (Fig. 6) was a novel *α*-glucosidase inhibitor with the IC_{50} value of 10.65 μM [50]. In the study of soft corals *S. scabra* (collected off Xigu Island, Hainan Province) [51, 52], six new cembranoids (**66**–**69**, **S99**, and **S100**) and one new polycyclic furanobutenolide-derived norcembranoid (**S101**) [52] were isolated and determined (Fig. 6 and Supplementary Fig. S15). Xiguscabrate B (**66**), xiguscabrols A and B (**67** and **68**), and 8-*epi*-xiguscabrol B (**69**) (Fig. 6) exhibited strong inhibitory activity on the proliferation of ConA-induced T lymphocyte cells with the IC_{50} values ranging from 2.3–8.4 μM [51]. The result gave an inspiration for the discovery of novel immunosuppressive agents.

In addition, a series of novel cembranoids (**S102**–**S111**) with hydroxyl or epoxy substitutions were discovered by the chemical study on the soft coral *S. nanolobata* [53, 54]. The absolute stereochemistry of ximaonanolobatin A (**S102**) was determined by X-ray diffraction analysis. The absolute configuration of ximaonanolobatin B (**S103**) was established by QM-NMR calculations and chemical transformation, whereas the absolute configuration of ximaonanolobatin C (**S104**) was determined using the modified Mosher's method. A detailed chemical investigation of soft coral *S. humilis* led to the isolation of other four new cembranoids (**70** and **S112**–**S114**), together with two new uncommon diterpenoids humilisins E and F (**71** and **72**) (Fig. 6 and Supplementary Fig. S16) [55]. Humilisin A (**70**) was a distinct cembranoid with an ether linkage between C-3 and C-7, and was firstly reported by our group. In bioassay, Compound **72** (Fig. 6) displayed a significant inhibitory effect on LPS-induced inflammatory response (NO production) in BV-2 microglial cells.

Casbane diterpenes are featured by the presence of a dimethyl-cyclopropyl moiety fused to the 14-membered ring, which are extremely rare in nature and marine organisms. From South China Sea soft corals, a series of novel casbane-type diterpenoids were obtained, which greatly expanded the diversity and complexity of casbane family. For example, three rare casbane diterpenoids with an uncommon 8,10-peroxide bridge, sinuereperoxides A–C (**73**–**75**), together with other six new casbanes (**76**–**79**, **S115**, and **S116**) were isolated from the soft coral *S. erecta* [56, 57]. Their structures and absolute configurations of **73**–**75** (Fig. 7) were determined by X-ray diffraction analysis, whereas the absolute configurations of **76**–**79**, **S115**, and **S116** were determined by TDDFT-ECD calculations. In bioassay, compounds **73**, **75** and **79** (Fig. 7)

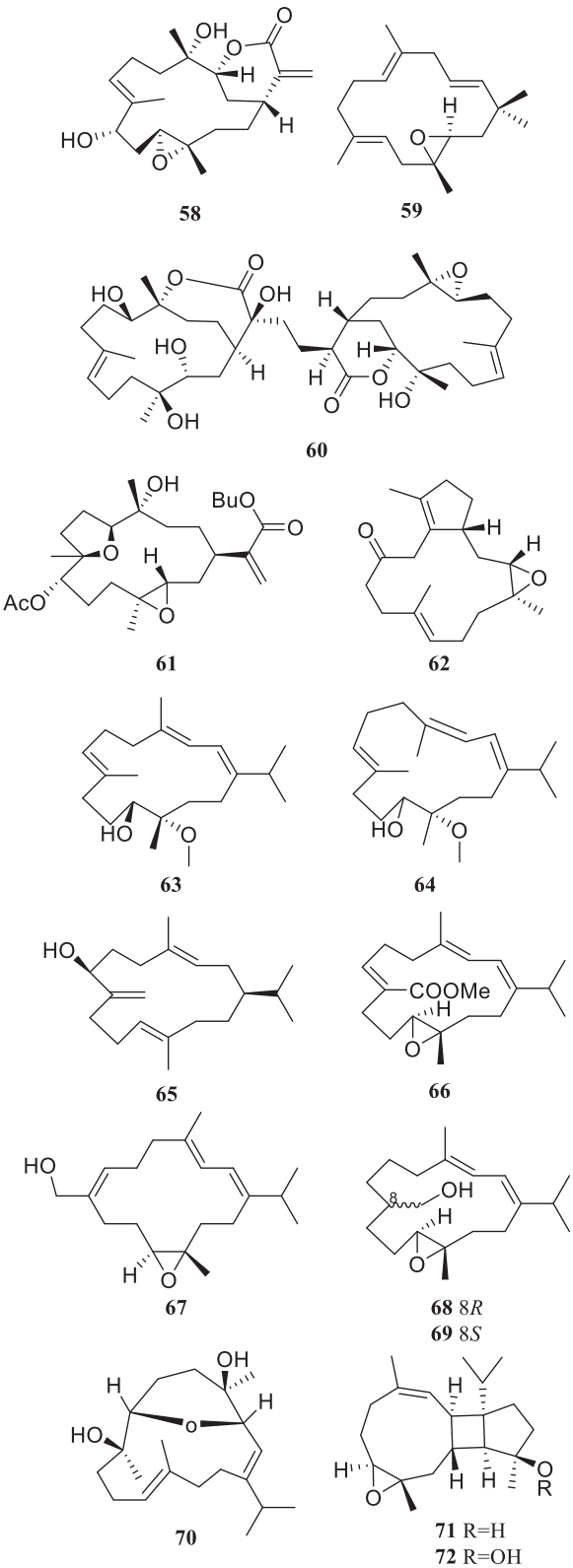


Fig. 6 Structures of representative Cembrane diterpenoids and related rare diterpenoids (**62**, **71** and **72**) from soft corals of *Sinularia*.

exhibited considerable anti-inflammatory activity by inhibition of TNF-α release, with the IC_{50} values of 10.6 μM, 33.8 μM and 5 μM, respectively. The chemical study on the soft coral *S. crassa* also led to the isolation and characterization of eleven new

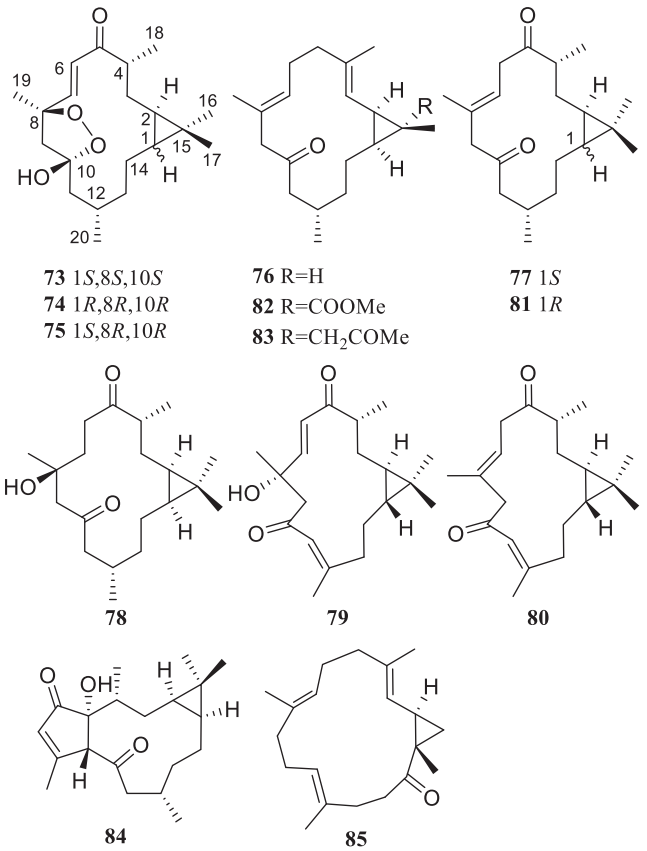
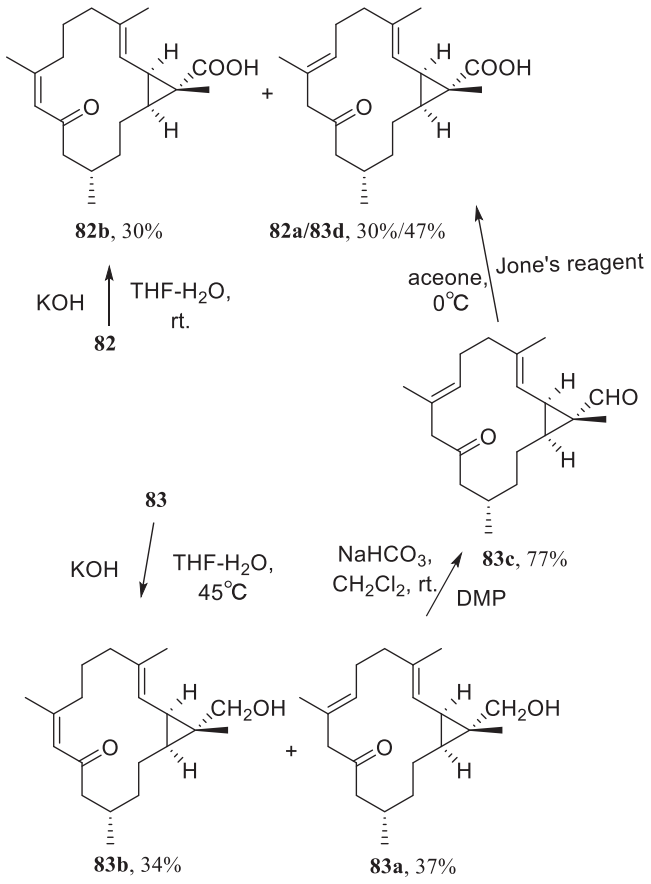


Fig. 7 Structures of representative Casbane diterpenoids and related rare diterpenoids (**84** and **85**) from soft corals of *Sinularia*.

casbane-type diterpenoids, sinucrassins A–K (**80**, **81**, and **S117**–**S125**) [58]. Among them, the absolute configurations of **80** and **81** were determined by X-ray diffraction analysis, whereas the absolute configurations of **S122**–**S125** were determined by TDDFT-ECD calculations. The general rule that diagnostic ^{13}C NMR chemical shifts of the geminal methyls are very close in the *trans*-isomer, while very distinct in the *cis*-isomer, are helpful to determine the relative configurations of C-1/C-2 in casbanes. Other two new casbanes (**82** and **83**) [59] with the oxidation at C-16 were isolated from soft coral *S. nanolobata* (Fig. 7). Through a series of chemical reactions, compound **83** was eventually associated with **82** (Scheme 3). Therefore, its stereochemistry was further confirmed same as that of **82**, which had been unambiguously determined by a successful performance of X-ray crystallography. In the anti-inflammatory assay, compounds **82a**, **83**, and **83a** displayed inhibitory activity on NO production against LPS-induced inflammation-related BV-2 microglial cells at the concentration of 20 μM, which were comparable to that of the positive control resveratrol [59].

Interestingly, sinueretone A (**84**), featuring an unprecedented tricyclo[12.1.0.0^{5,9}]pentadecane carbon framework, and sinunanolobatone A (**85**), featuring an unprecedented bicyclo[13.1.0] pentadecane carbon framework, were also isolated from the soft coral *S. erecta* and *S. nanolobata*, respectively (Fig. 7) [56, 59]. Combined with the biosynthesis of cembrane-type and casbane-type diterpenes from geranylgeranyl pyrophosphate [60], the biosynthetic connection of these diterpenoids was described as shown in Scheme 4. In addition, compound **85** displayed inhibitory activity on NO production against LPS-induced inflammation-related BV-2 microglial cells at the concentration of 20 μM. It significantly reduced the mRNA transcription levels of the

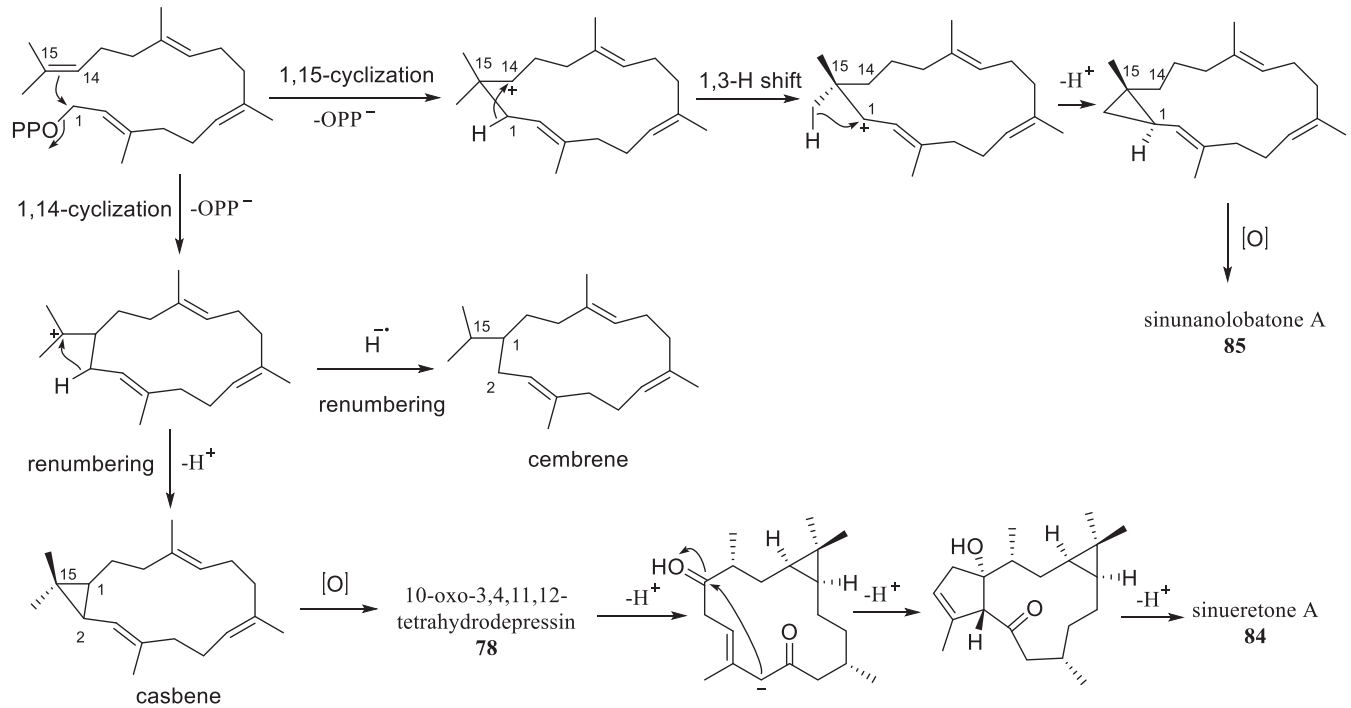
pro-inflammatory cytokines IL-6 and IL-1β in LPS stimulated BV-2 microglial cells, which further demonstrated the anti-inflammatory effect of compound **85** [59].



Scheme 3 Chemical correlation of compounds **82** and **83**.

Moreover, some low abundance diterpenoids were discovered occasionally. For example, three complex polyoxygenated possessing uncommon tetradecahydro2,13:6,9-diepoxybenzo[10]annulene scaffold, namely ximaoornatins A–C (**86**–**88**), and one new eunicellin-type diterpene, litophynin K (**89**) (Fig. 8), were isolated from the soft coral *S. ornate* [61]. Sinuhumilol A (**90**) was a new capnosane-type diterpenoid isolated from the soft coral *S. humilis* [62]. The chemical investigation of the Xisha soft coral *S. polydactyla* has led to the isolation of another new capnosane-type diterpenoid sinulacetate (**91**), as well as a new prenyleudesmane-type diterpene sinupol (**92**), three new lobane-type diterpenes 13-methoxyloba-8,10,15(16),17(18)-tetraene (**93**), 8,10,13(15)*Z*,16*E*-lobatetraene (**94**), and 19-hydroxy-lobatetraene (**95**) (Fig. 8). It is noteworthy that three new diterpenes with new structural skeleton, xishacorenes A–C (**96**–**98**) (Fig. 8), featuring an undescribed bicyclo[3.3.1]nonane nucleus bearing 1-vinyl and 13-[(*E*)-4-methylpenta1,3-dien-1-yl] alkyl chains, were also discovered from the *S. polydactyla* [63–65]. The bioassay results showed sinulacetate (**91**) and sinupol (**92**) exhibited promising PTP1B inhibitory activities [63]. Xishacorenes A–C (**96**–**98**) exhibited a dose-dependent promotion effect on the ConA-induced T lymphocyte proliferation [65]. In addition, the fascinating molecular architectures and potential pharmaceutical applications of **96**–**98** have attracted considerable interest of synthetic chemists for total chemical syntheses. Sarpong group have successively completed the total synthesis of (-)-xishacorene B from (*R*)-carvone, as well as bio-inspired synthesis of xishacorenes A–C from fuscol [66–69]. Moreover, they have described immunomodulatory activity studies of fuscol and xishacorenes. These observations suggest that hydrophilicity of the xishacorenes should be enhanced to improve the immunomodulatory potency [67].

(2*β*,3*β*,4*α*,5*α*,8*β*)-4-methylergost-24(28)-ene-2,3,8-triol (**S126**) and (3*β*,7*α*)-24-methyl-7-hydroperoxycholest-5,24(28)-diene-3-ol (**S127**) were two new steroids isolated from the soft coral *S. depressa* Tixier-Durivault (collected off Lingshui Bay, Hainan Province) [70]. Three new oxygenated steroids, sinulasterols A–C (**S128**–**S130**), were also isolated from the soft coral *S. depressa* (collected off Ximao Island) [71]. Among them, Sinulasterols A and B (**S128** and **S129**) are featured with unusual C-18 oxygenated



Scheme 4 The plausible biosynthetic connection of cembranes, casbanes, sinueretone A (**84**) and sinunanolobatone A (**85**).

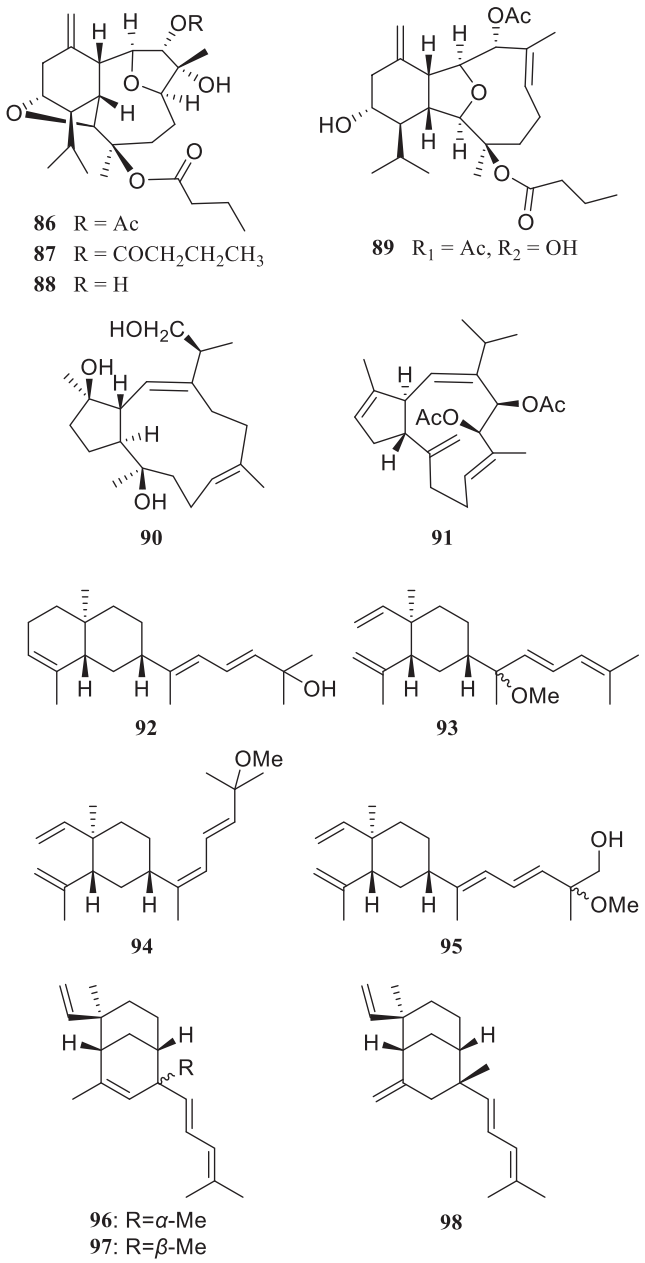


Fig. 8 Structures of other uncommon diterpenoids (**86**–**98**) from soft corals of *Sinularia*.

patterns. Two new polyhydroxylated steroids, 7*α*-hydroxy-crassarosterol A (**S131**) and 11-acetoxy-7*α*-hydroxycrassarosterol A (**S132**), were derived from the soft corals *S. flexibilis* [72] (Supplementary Fig. S18). The stereochemistry of **S132** was established same as that of **S131** through chemical conversion. In the study of soft coral *Sinularia* sp. collected from the Xisha Islands, two new highly oxygenated ergostane-type sterols (**99** and **100**) (Fig. 9) were isolated and identified [73]. In bioassays, **99** and **100** showed antiproliferative activity against a panel of cancer cell lines, including MDA-MB-436, A549, Hep3B, HT-29, and H157 cell lines. Besides, Western blot assay showed that **99** increases the expression of Bax and down-regulates the expression of Bcl-2 [73], which suggests compound **99** exhibited the anticancer potential by initiating apoptosis process. A new 5*α*,8*α*-epidioxysterol, yalongsterol A (**S133**), was isolated from the soft coral *Sinularia* sp. that was collected off Yalong Bay, Hainan

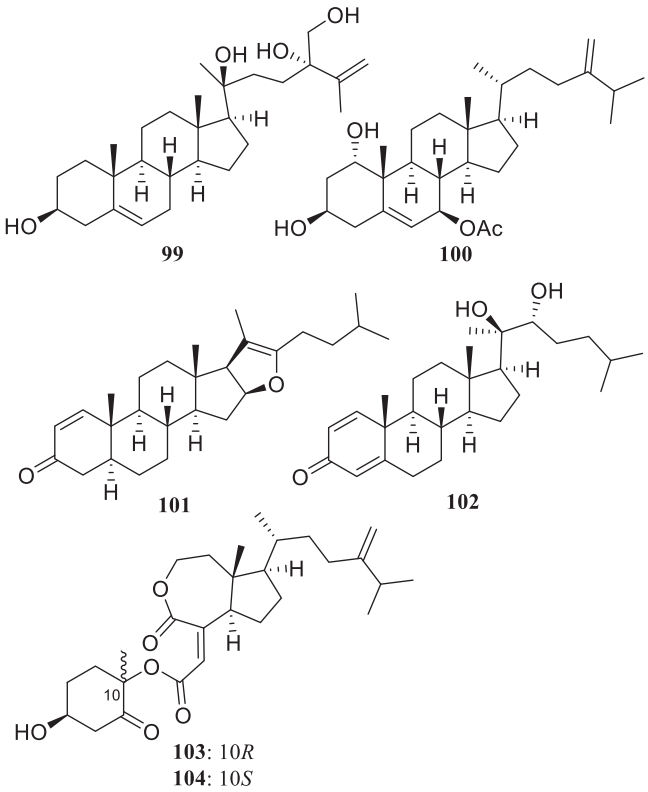


Fig. 9 Structures of novel representative steroids from soft corals of *Sinularia*.

Province [74]. Two new steroids featuring a different C-20 side chain, ximaosteroids E (**101**) and F (**102**) (Fig. 9), were discovered from the soft coral *Sinularia* sp. (collected off the coast of the Ximao Island), with significant cytotoxicity against the HL-60 tumor cells with the IC_{50} values of 1.79 and 4.03 μM, respectively [75]. In addition, a pair of epimers of novel highly degraded steroid derivatives, namely erectsterates A and B (**103** and **104**) (Fig. 9), have been also obtained under the chemical investigation of soft coral *S. erecta* [76]. Their structures were established by extensive spectroscopic analysis and deduction from biosynthesis route. The B ring of steroidal nucleus was completely broken by twice cleavages of C-C bonds, and then the C ring was oxidized by Baeyer-Villiger reaction to form an unprecedented seven-membered lactone moiety in ring C of steroid, and then, the A ring and C ring were connected by an ester bond.

Sarcophyton is a genus of soft corals in the family Alcyoniidae. As a hardy and dominant soft coral genus in many coral reef areas of China, they are the main source of biscembranoids (Fig. 10) generated by Diels-Alder cycloaddition. During our ongoing search for these compounds, many species in this genus were systematically investigated. Four new biscembranoids, bislatumlides C–F (**105**, **S134**–**S136**), were isolated from the Hainan soft coral *S. latum* [77]. The absolute configurations of bislatumlides C and E (**105** and **106**) were determined by TDDFT-ECD calculation, which resulted in the confirmation of the absolute configurations of **S134-S137** by comparison of the CD spectra. The Scheme 5 illustrated the formation of these biscembranoids. Briefly, the $\Delta^{1(2)}$ double bond in the *α*,*β*-unsaturated *γ*-lactone ring as a dienophile group was reacted with a trisubstituted conjugated $\Delta^{21(34)}/\Delta^{35(36)}$-butadiene moiety. An endo-cycloaddition generated **105**, **S134**, **S136**, and **S137**, whereas an exo-cycloaddition produced **106** and **S135**.

Because of the complexity of the dimeric cembranoids, some confusions were inevitable. For instance, the structure of methyl tortuoate D was firstly isolated and reported as **107a**. However, in

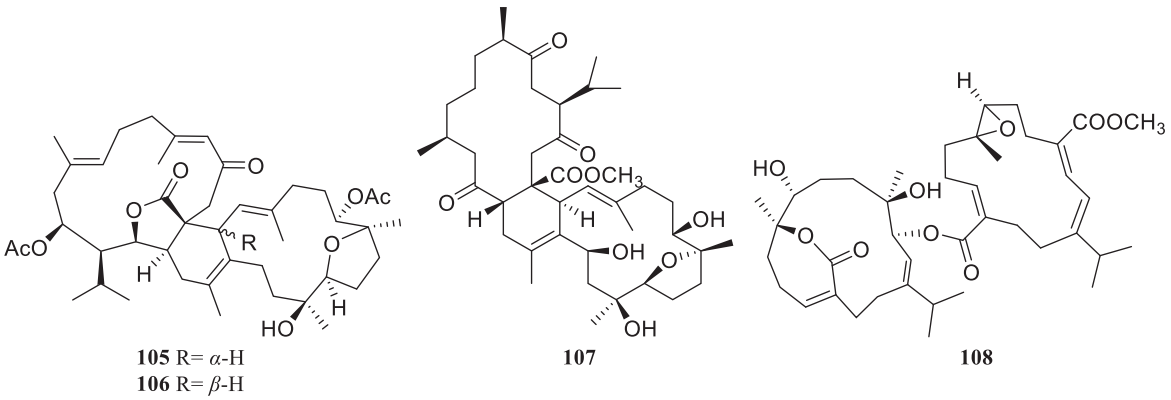
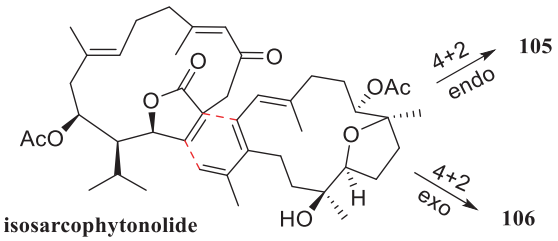


Fig. 10 Structures of novel representative biocembranoids from soft corals of *Sarcophyton*.



Scheme 5 The plausible endo/exo-Diels-Alder Cycloaddition.

our study of the Hainan soft coral *S. tortuosum*, the planar structure of tortuoate D was identified as **107** [78]. In addition, lobophytone K (**107b**) isolated from Hainan soft coral *L. pauciflorum* by Lin et al., was proved to be the same compound as **107** and **107a** by our group through an extensive analysis and comparison of their NMR data and the optical rotation values. Later, other five novel biscembranoids (**S138**–**S142**) were also isolated from the soft coral *S. tortuosum* (Supplementary Fig. S19) [79]. In bioassay, ximaolides I (**S139**), and K (**S141**) exhibited significant inhibition activity against LPS-induced TNF-α release in RAW264.7 macrophages.

The study of *S. trocheliophorum* Marenzeller also led to the discovery of an unprecedented biscembranoid bissartrolide (**108**) (Fig. 10). Unlike the dimers mentioned above, it was formed by an esterification rather than a Diels-Alder reaction. The sartrolides A–G (**109**, **110**, and **S143**–**S147**) (Supplementary Fig. S20) were a series of novel cembranolides containing *α,β*-unsaturated *ε*-lactone that were also obtained from the *S. trocheliophorum* [80]. The sartrolides differed from each other at the partial structure from C-1 to C-8 with various substitutions. Sarcophytonolides N–R (**111** and **S148**–**S151**) (Supplementary Fig. S20) were another group of novel cembranolides isolated from the soft coral *S. trocheliophorum* Marenzeller, their structures have been elucidated by detailed spectroscopic analysis [81]. Sarcophytonolide N (**109**) (Fig. 11) showed significant inhibitory activity toward PTP1B enzyme with the IC_{50} value of 5.95 μM. In addition, the chemical investigation of this soft coral also yielded two new unprecedented diterpenoids (**112** and **113**) possessing a tetradecahydrocyclopenta[3′,4′]cyclobuta[1′,2′:4,5]-cyclonona[1,2-b]oxirene ring system, along with their probable biogenetic precursor, sarcophytonolide M (**114**). Two new sarsolenane diterpenes, dihydrosarsolenone (**115**), methyl dihydrosarsolenoneate (**116**), and two new capnosane diterpenes, sarsolilides B (**117**) and C (**118**) were discovered from the same species 1 year later [82, 83]. It is worth noting that compound **113** and **117** exhibited significant inhibitory activity against PTP1B, which were comparable to the positive control oleanolic acid [82]. In

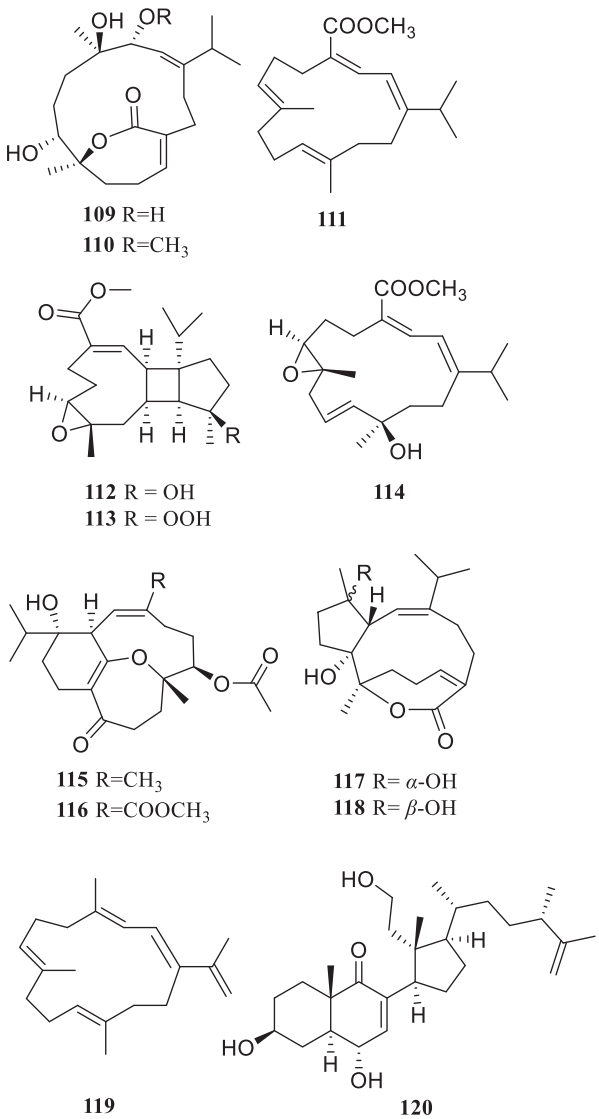


Fig. 11 Structures of some representative compounds from soft corals of *Sarcophyton*.

order to examine whether seasonal factors can lead to differences in metabolites of the same species, the soft corals *S. trocheliophorum* Marenzeller were recollected in different season, resulting in two hydrocarbon cembranoids, yalongenes

A (**119**) and B (**S152**) [84]. Yalongene A (**119**) (Fig. 11) showed a significant cytoprotective activity on H_2O_2 induced SH-SY5Y cell injury model at the concentration of 1 μM. In the further investigations of soft corals *S. trocheliophorum*, a new 9,11-secosteroid (**120**) [72], three new capnosane-type diterpenoids (**S153**–**S155**) [85], together with a set of new cembranoids (**S156**–**S181**) [86–90] were isolated and characterized. Interestingly, sarcophytrols M–U (**S165**–**S173**) exhibit a variety of cyclization patterns, including furan, pyran, oxepane, or peroxyl rings, which provide in-depth understanding of the diversity of cyclized cembranoids [87]. Sartrolides H–J (**S177**–**S179**) were distinguished by an unusual *α*,*β*-unsaturated *ε*-lactone (Supplementary Fig. S20) [89]. The discovery of these highly oxidative cembranoids enriched the family of cembranoids derived from the soft coral *S. trocheliophorum*.

The chemical study on other species of the genus *Sarcophyton* was also very productive. Sixteen new cembranoids (**S182**–**S197**) were isolated from the soft coral *S. ehrenbergi* [91, 92]. Their structures including absolute configurations were established by a combination of detailed spectroscopic analysis, comparison with reported data, modified Mosher's method, TDDFT-ECD calculations and/or X-ray diffraction analysis. Sarcoehrenolides A–E (**S182**–**S186**) are featured by an *α*,*β*-unsaturated *γ*-lactone moiety at C-6 to C-19 (Supplementary Fig. S21) [91]. In the TNF-α inhibitory biotest, compound **S183** exhibited a potent inhibitory activity with the IC_{50} value of 8.5 μM, which was analogous to the positive control dexamethasone (IC_{50} = 8.7 μM) [91]. Ximaoglaucumins A – F (**S198**–**S203**) [93], and ximaocembrols A, B and (±)-ximaocembrol C (**S204**–**S207**) [94], were isolated from the soft corals *S. glaucum* and *S. crassocaule*, respectively. Although the determination of the stereochemistry of cembranoids is always a challenging task without suitable single crystals, a series of reliable approaches including extensive spectroscopic analysis, quantum chemical calculations, modified Mosher's method, and Snatzke's method were applied in combination. Finally, their stereochemistry was unambiguously confirmed as shown in Supplementary Fig. S22. In the case of *S. mililatensis*, a novel diterpenoid, sarcomililate A (**121**), possessing an unprecedented tricyclo[11.3.0.0^{2,16}]-hexadecane scaffold, as well as its possible biogenic precursors, sarcomililatols A and B (**122** and **123**) (Fig. 12), was isolated from the samples collected from Hainan Province [95]. The chemical structure including absolute configuration of **121** was unambiguously determined by a combination of residual dipolar coupling (RDC)-based NMR analysis, TDDFT-ECD calculation, and Snatzke's method. The absolute configuration of **121** was further confirmed by a comparison with **122**, whose absolute configuration was determined by X-ray diffraction. The plausible biogenetic relationship of **121** – **123** was depicted in Scheme 6, which further corroborated the confirmation of absolute configuration of **121** and **123**. The study of *S. infundibuliforme* also led to the discovery of two new nitrogenous diterpenoids, sarinfacetamides A (**124**) and B (**125**), featuring an uncommon tricyclo[6.3.1.0^{1,5}]dodecane scaffold (Fig. 12). As shown in Scheme 7, a plausible biosynthetic pathway for **124** and **125** from co-isolated known compound nanolobatin B was also proposed. Moreover, sarinfacetamide A (**124**) exhibited an interesting promotion effect on the ConA-induced T lymphocyte proliferation with a proliferation rate of 36.18% at the concentration of 10 μM [96].

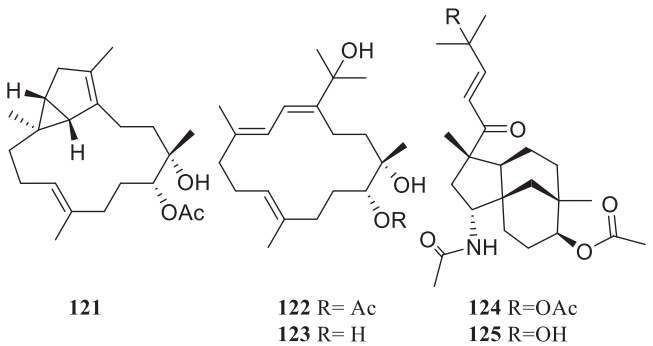
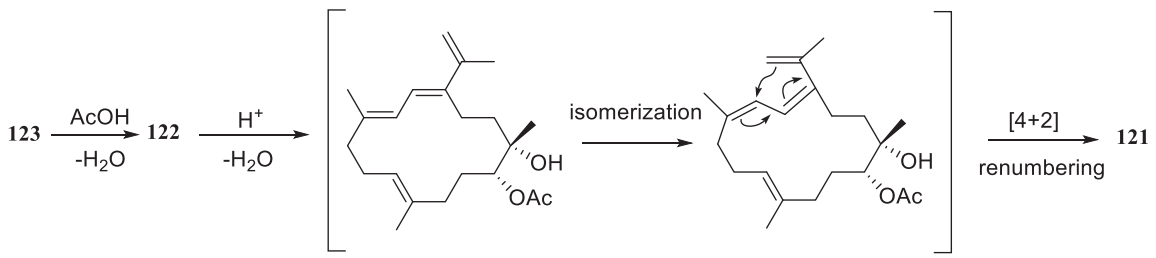


Fig. 12 Structures of compounds **121**–**125**.

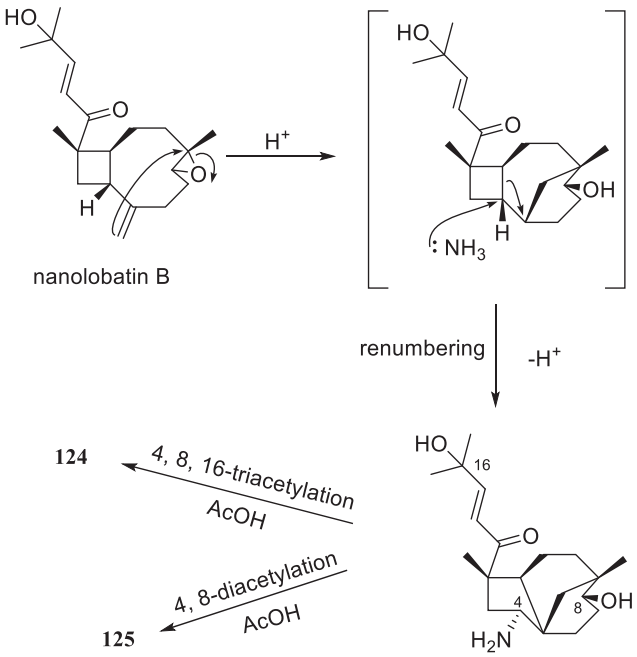
As mentioned above, the soft corals of Genera *Lobophytum*, *Sinularia*, and *Sarcophyton* are dominant cnidaria inhabiting South China Sea and consequently being extensive resources in the subject of marine natural product chemistry. Apart them, there are also some relatively less populated soft corals, such as *Litophyton nigrum, Lemnalia flava, Clavularia viridis, Cladiella krempfi*, and *Klyxum flaccidum* being collected and chemical investigation. The chemical investigation of the Xisha soft coral *L. nigrum* has resulted in the isolation of eight new nardosinane-type sesquiterpenoids (**126**, **127**, and **S208**–**S213**), four new neolemnane-type sesquiterpenoids (**128**, **129**, **S214**, and **S215**), as well as one uncommon sesquiterpenoid dimer (**130**) (Fig. 13 and Supplementary Fig. S23) [97–99]. Notably, linardosinene A (**126**) and lineolemnene D (**129**) represent uncommon nornardosinane and seconeolemnane sesquiterpenoids, respectively [97]. In addition, the bioassay results indicated that the compound (**127**) exhibited potent PTP1B inhibitory activity (IC_{50} = 0.67 μg/mL) compared to the positive control [99].

A detailed chemical investigation of the Xisha soft coral *L. flava* led to the acquisition of four new nardosinane-type sesquiterpenoids (**S216** – **S219**), a new neolemnane-type sesquiterpenoid (**S220**), a new sesquiterpenoid (**S221**), and two new cembranoids (**S222** and **S223**) (Supplementary Fig. S24) [100, 101]. Unlike xishaflavalin E (**S220**), the xishaflavalin F (**S221**) featured an uncommon 6/9 fused bicyclic skeleton. One point to note is that the discovery of cembrane-type diterpenes from the genus *Lemnalia* was reported for the first time [100].

Another Xisha soft coral *C. viridis* has been well studied, and finally yielded two new trinor-guaiane sesquiterpenes (**S224** and **S225**) [102], four new halogenated laurane-type sesquiterpenoids (**131** – **133** and **S226**) [103], one new aromadendrane-type sesquiterpenoid (**S227**) [103], and thirteen dolabellane-type diterpenoids (**134** and **S228**–**S239**) [104] (Fig. 13 and Supplementary Fig. S25). Among them, *ent*-laurenisol (**133**), and clalaurenol B (**S226**) had also been produced by the soft coral *L. flava* [103]. The structure including absolute configuration of



Scheme 6 Proposed biosynthetic pathway of compound **121**.



Scheme 7 Proposed biosynthetic pathway of compounds **124** and **125**.

clavuridin B (**S224**), clavurol F (**S235**) and clavirolide I (**S239**) was directly determined by X-ray diffraction analysis [102, 105]. Most notably, clavuperoxylides A and B (**S231** and **S232**) and clavufuranolides A – C (**S236**–**S238**) exhibited the structural diversity of the dolabellanes comprising peroxyl group, novel peroxide bridge, and tetrahydrofuran ring [105]. In bioassay, sesquiterpenoids isobromolaurenisol (**131**), clalaurenol A (**132**), *ent*-laurenisol (**133**) and clavurol E (**134**) exhibited significant inhibitory activities against PTP1B [105]. Meanwhile, **131** – **133** (Fig. 13) showed potential anti-inflammatory activity in vitro by inhibiting the NF-κB signaling pathway [103].

Our investigation on the chemical constituents of the soft coral *C. krempfi*, collected off the Weizhou Island, yielded seven new eunicellin-based diterpenoids (**S240**–**S243**, and **135**–**137**) [106, 107]. It is well known that eunicellins represent the largest class of 2,11-cyclized cembranoids and share a common 15-oxatricyclo[6.6.1.$0^{2,7}$]pentadecane system [5]. By a network of chemical conversions of **S240**–**S243** and **135**, together with detailed spectroscopic analysis and comparison, the stereostructures of these isolates were all elucidated (Supplementary Fig. S26). In bioassay, **135**–**137** (Fig. 13) displayed moderate anti-inflammatory effect [106]. In addition, twenty polyoxygenated eunicellin diterpenoids (**138** and **S244**–**S262**), and two novel polyoxygenated diterpenoids, klyflaccilides A (**139**) and B (**140**) (Fig. 13 and Supplementary Fig. S26), featuring an uncommon 6/5/8/3 tetracyclic ring system, were isolated from the Hainan soft coral *K. flaccidum* [108, 109]. It was reasonable to speculate

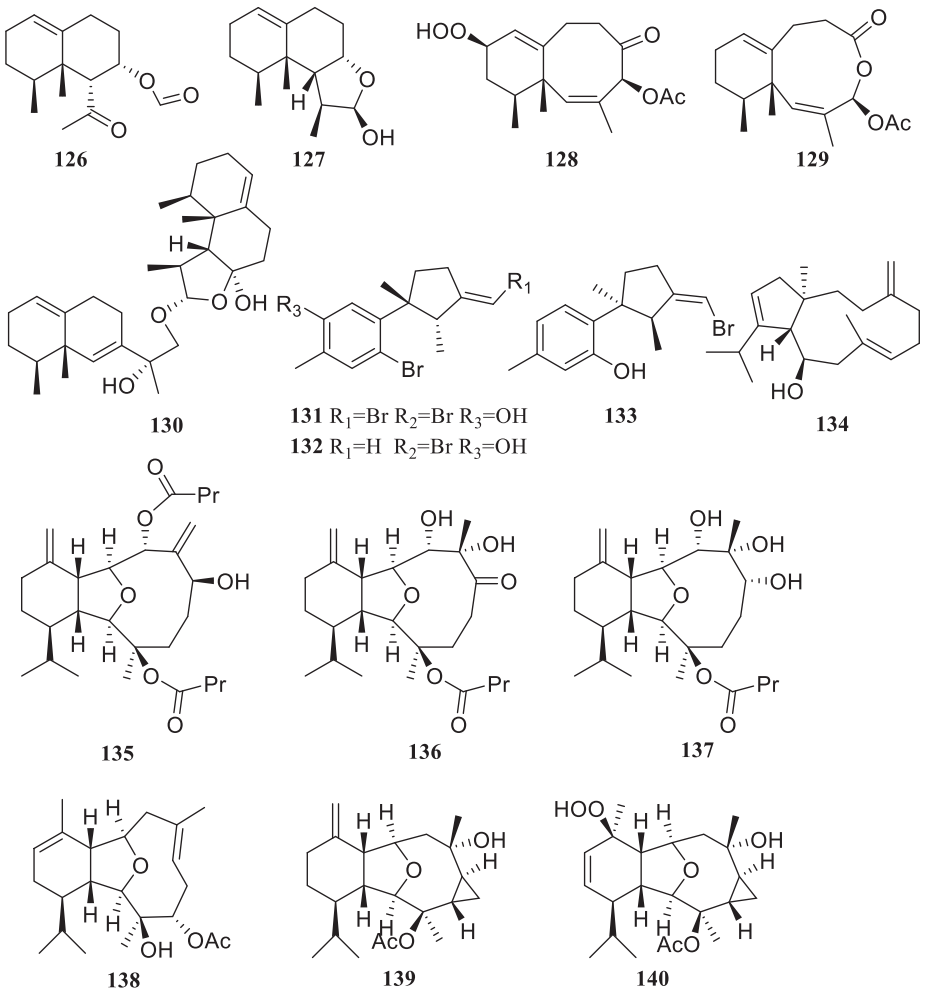


Fig. 13 Structures of representative compounds from soft corals *Litophyton nigrum, Lemnalia flava, Clavularia viridis, Cladiella krempfi*, and *Klyxum flaccidum*.

that **139** and **140** were derived from klyflaccilin A (**138**) based on the common fragment [109].

Mollusks

Marine mollusks, belonging to the second largest invertebrate phylum (Mollusca), comprise a group of shelled and shell-less soft bodied animals that are not only highly diverse in size and anatomical structure, but also in their behavior and habitat. Marine mollusks usually produce structurally diverse polyketides, polypropionates terpenes, and nitrogenous metabolites as chemical defense, which may be attributed to the predator-prey relationship between mollusks and algae, sponges, and corals. Nudibranchs are a family of Opisthobranchia, which are most extensively studied from the natural product chemistry point of view. Many of them are slow-moving, brightly colored, and shell-less slug, and appear to be free of predation causing great interest to biologists, chemists, pharmacologists.

In the several studies [110–112] of the South China Sea nudibranch *Jorunna funebris* and its possible sponge-prey *Xestospongia* sp., a series of isoquinolinequinone alkaloids, including four renieramycin-type bistetrahydroisoquinolinequinone alkaloids, fennebricins A–D (**S263** and **141**–**143**), and *N*-formyl-1,2-dihydrorenierol (**144**), were isolated and elucidated as new compounds (Fig. 14 and Supplementary Fig. S27). **S263** and **141** are structurally related to the ecteinascidins and the saframycins that are two groups of promising antimicrobial and antitumor alkaloids. However, since these two compounds were only available in trace amount and were relatively unstable, their bioactivity have been unable to determine. But in the case of **142** and **143**, they showed strong NF-κB inhibitory activity, indicating a promising anti-inflammatory potential. Very interestingly, we have isolated multiple metabolites occurred simultaneously in both mollusk *J. funebris* and its associated prey, the sponge *Xestospongia sp*., suggesting the prey-predator relationship between the two animals.

The study on two South China Sea nudibranchs *Phyllidiella pustulosa* and *Phyllidia coelestis*, as well as their possible sponge-prey *Acanthella cavernosa* led to the isolation of nitrogenous cadinane-type sesquiterpenoid xidaoisocyanate A (**145**), one new naturally occurring nitrogen-containing kalihinane-type diterpenoid bisformamidokalihinol A (**146**), along with other known nitrogenous terpenoids [113]. By comparison of the typical isolates from the three animals, as well as the previous investigation of the marine sponge *A. variabilis* from the same sea area, the interesting predator-prey relationship between two nudibranchs and two sponges were considered reasonably. We have also investigated nudibranch *Hexabranchus sanguineus* and its possible sponge-prey *A. cavernosa*. Fifteen new nitrogenous sesquiterpenoids, namely ximaocavernosins A–O (**S264**–**S276**, **147**, and **148**) (Fig. 14 and Supplementary Fig. S28), together with other known related compounds were isolated [114]. And a detailed investigation of the Weizhou nudibranch *Glossodoris atromarginata* yielded a new spongian-type diterpene (**149**) (Fig. 14) [115]. In short, the results of above studies suggest that nudibranchs perhaps accumulate the useful dietary metabolites from the sponges, especially those toxic isocyanide derivatives, to be employed as their own chemical defensive agents for surviving in the harsh marine environment.

It is noteworthy that the research of another mollusk of Opisthobranchia has yielded significant findings. From a chemical perspective, the marine sacoglossan *Placobranchus ocellatus* were collected from the shallow water of Ximao Island, producing a series of racemic non-γ-pyrone polyketides with novel skeletons, ocellatusones A–D (**150**–**153**) (Fig. 15) [116], characterized by

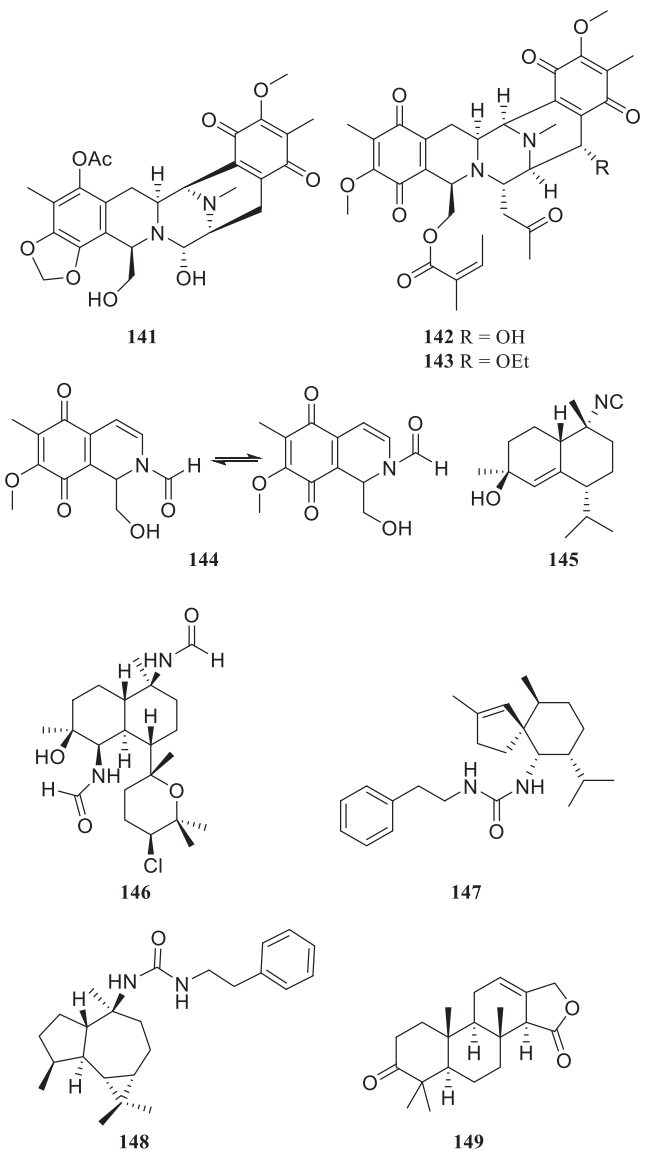


Fig. 14 Structures of representative compounds from nudibranches.

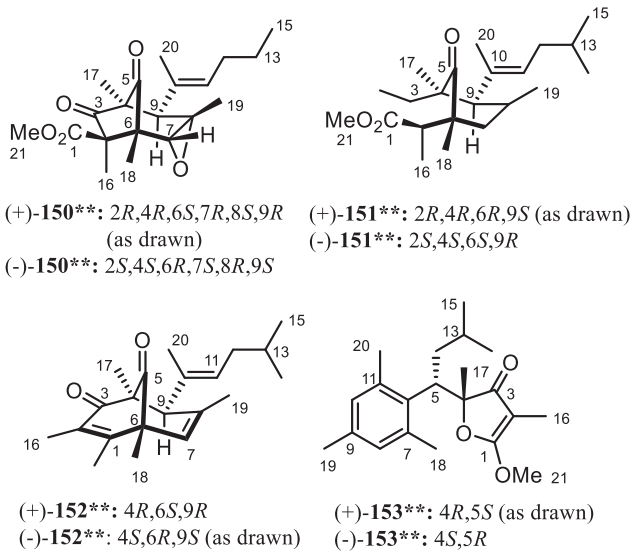
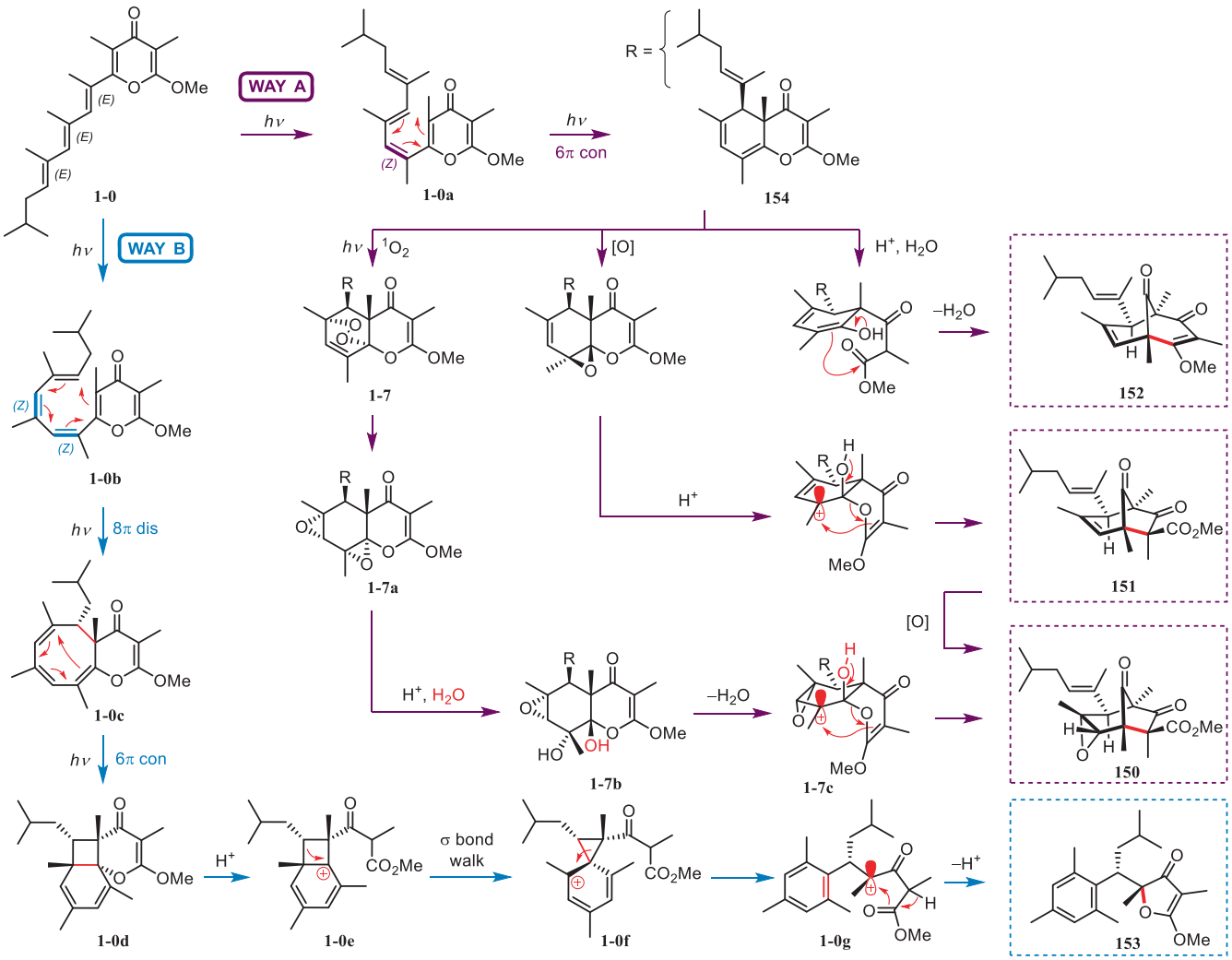


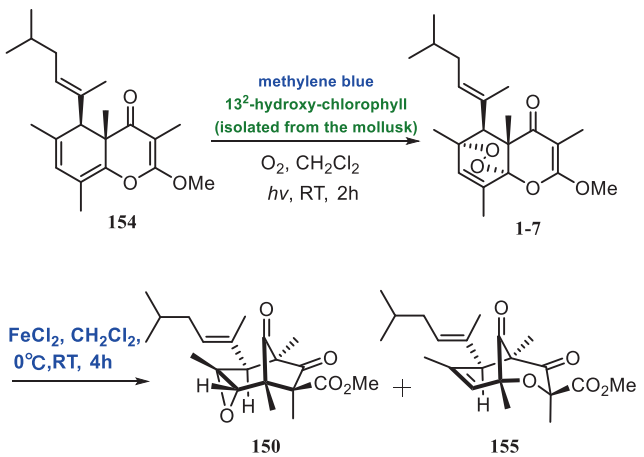
Fig. 15 Structures of compounds **150**–**153** isolated from the marine sacoglossan *Placobranchus ocellatus*.



Scheme 8 Proposed photobiosynthetic pathway towards novel polyketides **150**–**153**.

abicyclo[3.2.1]octane (**150**, **151**), a bicyclo[3.3.1]nonane (**152**) and a mesitylene-substituted dimethylfuran-3(2H)-one core (**153**). Some algae-feeding marine sacoglossan mollusks possess the capabilities to photosynthesize through the phenomenon of kleptoplasty. For example, the biosynthesis of the common metabolites, such as γ-pyrone-containing polypropionates, involved photoinduced cyclization. After a literature research on γ-pyrone-containing polypropionates, we have proposed a photobiosynthetic pathway towards these novel polyketides **150**–**153** (Scheme 8). As expected, the proposed rearrangement through an unprecedented acid induced cascade reaction was further confirmed by successful biomimetic semisynthesis of ocellatusone A (**150**) from natural precursor **154** (Scheme 9). In addition, the by-product **155** generated from the reaction is also present in the crude extract of the mollusk.

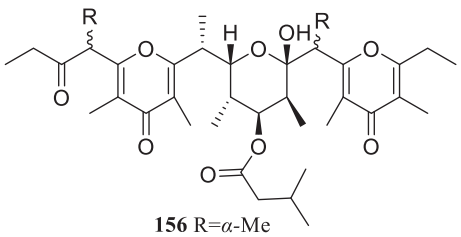
As mentioned above, the marine pulmonate *Onchidium* sp. should be of capacity to photosynthesize as it feeds mainly on benthic algae. The discovery of bis-γ-pyrone polypropionates from the animal is strong supporting evidence for the suspicion. Briefly, a dozen of bis-γ-pyrone polypropionates including three new members, 16-*epi*-onchidione (**156**) [117], 4-*epi*-onchidione (**157**) [117], and 4,16-di-*epi*-onchidiol (**158**) [118] were identified from *Onchidium* sp. (Fig. 16). Many of isolates exhibited a wide range of cytotoxicity [117], implying that the animal photosynthesizes these compounds for chemical defense against predators and survival from the harsh environment.



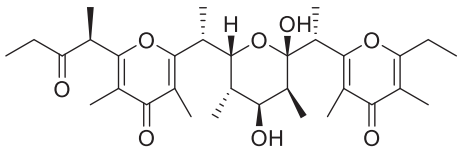
Scheme 9 Biomimetic semisynthesis of ocellatusone A (**150**) from natural precursor **154**.

CONCLUSION

This review summarizes representative substances from Chinese marine plants and invertebrates discovered by our group in the past decade. These structurally and biologically interesting marine metabolites, along with the rapid development of



156 R=α-Me
157 R=β-Me



158

Fig. 16 Structures of compounds **156**–**158** isolated from the marine pulmonate *Onchidium* sp.

the technologies on the high-throughput biological screening, their total syntheses and SAR analyses, would greatly benefit the discovery of pharmaceutically interesting lead compounds. Recent years, more and more attentions have been focused on the chemistry and biology of the microorganisms derived from marine plants and invertebrates, resulting in the discovery of a large number of bioactive secondary metabolites. Therefore, the application of multidisciplinary field, including genome mining, biosynthesis, and isotope labeling, will be effective ways to understand the origin and the biosynthetic pathway of the bioactive metabolites, and then, illustrate the relationship between the marine plants, invertebrates, and their associated microorganisms. Furthermore, with the advances of molecular biology, it will greatly increase the speed of finding pharmacological targets for these active molecules.

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ADDITIONAL INFORMATION

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