Progress in the Chemistry of Organic Natural Products

A. Douglas Kinghorn · Heinz Falk
Simon Gibbons · Jun'ichi Kobayashi
Yoshinori Asakawa · Ji-Kai Liu *Editors*

111

Progress in the Chemistry of Organic Natural Products

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Volume 111

With contributions by

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Contents

Sesterterpenoids

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Contents

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1 Introduction

Sesterterpenoids are a relatively small group of natural products. Even though they belong to one of the largest families of natural products, the "terpenoids," only around 1000 natural sesterterpenoids have been reported [1–5]. Considering that over 80,000 terpenoids have already been isolated [6–8], the number of known sesterterpenoids is quite small. Moreover, in almost all cases, their biological role is unknown. However, sesterterpenoids have been isolated from many kinds of organisms (e.g., plants, bacteria, fungi, lichens, insects, marine sponges, and other marine organisms) [1–5]. This fact implies that various organisms have the potential to produce sesterterpenoids.

In this contribution, we will introduce the chemical structures of sesterterpenoids. Although the number of sesterterpenoids is not very large, they have a large variety of simple to complicated chemical structures. Herein, we have classified the sesterterpenoids based on the number of carbocyclic moieties in their chemical structures. In addition, we will also explain how the structure of each sesterterpenoid is formed in Nature.

2 What Are the Sesterterpenoids?

2.1 "Sesterterpenoids" Are Members of the "Terpenoids"

As mentioned above, the sesterterpenoids are a subgroup of the terpenoids. Therefore, we will start by briefly describing the terpenoids. Terpenoids are defined as a group of natural products composed of simple "C_5" units, called isoprene units (Fig. 1). Thus, terpenoids are also called "isoprenoids." In this definition, "C_5" means that a compound contains five carbon atoms. This notation will be frequently used in this chapter, and thus "C_{25}" refers to a compound containing 25 carbon atoms.

For example, the chemical structure of sesterbrasiliatriene (**1**), a type of terpenoid, contains five isoprene units (Fig. 2b) [9]. In another example, four isoprene units (b) constitute the chemical structure (a) of **2** (Fig. 3) [10].

The origins of the isoprene units are dimethylallyl pyrophosphate (DMAPP) (**3**) and isopentenyl pyrophosphate (IPP) (**4**) (Fig. 4) [6–8]. Both are widely distributed in Nature, and generated via two kinds of metabolic pathways, known as the MVA (mevalonate) and MEP (methylerythritol phosphate) pathways [11, 12].

The biosynthesis of all terpenoids starts from condensation reactions of **3** and **4** to yield polyprenyl diphosphates, which are important intermediates of terpenoids.

Fig. 1 Isoprene unit

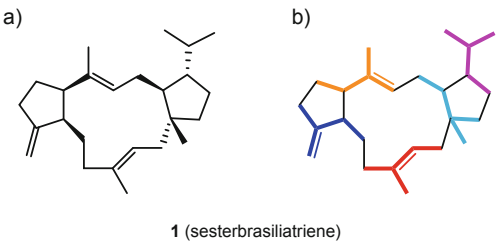


Fig. 2 Structure of **1**. The structure of **1** contains five isoprene units. Each isoprene unit is shown by bold lines with different colors

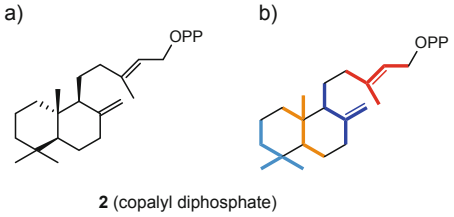


Fig. 3 Structure of **2**. The structure of **2** contains four isoprene units. Each isoprene unit is shown by bold lines with different colors

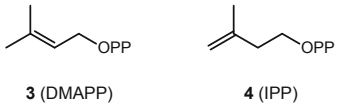


Fig. 4 Structures of dimethylallyl pyrophosphate (DMAPP) (**3**) and isopentenyl pyrophosphate (IPP) (**4**)

Each polyprenyl diphosphate is designated as follows: (C_{10}) geranyl diphosphate (GPP) (**5**), (C_{15}) farnesyl diphosphate (FPP) (**6**), (C_{20}) geranylgeranyl diphosphate (GGPP) (**7**), and (C_{25}) geranylfarnesyl diphosphate (GFPP) (**8**). These condensation reactions are catalyzed by enzymes called "prenyltransferases" (Fig. 5) [6–8].

In many cases, the polyprenyl diphosphates are subjected to cyclization reactions to form a carbocyclic moiety. These cyclization reactions are catalyzed by "terpene cyclases." Generally, the terpene cyclases are divided into two classes, "type 1" and "type 2," based on their catalytic mechanisms.

The type 1 terpene cyclases initiate the cyclization by heterolytic cleavage of the diphosphate moiety of the polyprenyl diphosphates. The heterolytic cleavage leads to the generation of cation intermediates, and the high energy of the cation intermediate is the driving force of the cyclization reaction. The cyclization reaction is finalized by either deprotonation or an attack by H_2O. For example, **1** is formed by a type 1 terpene cyclase (Fig. 6).

The other class of terpene cyclases is known as the "type 2" terpene cyclases. The type 2 terpene cyclases also generate cation intermediates to initiate the cyclization reaction. However, the strategy to generate the cation intermediate is different from that of the type 1 terpene cyclases. The type 2 terpene cyclases generate the cation intermediate via the protonation of a double bond of the polyprenyl diphosphates. For example, **2** is formed by a type 2 terpene cyclase (Fig. 7).

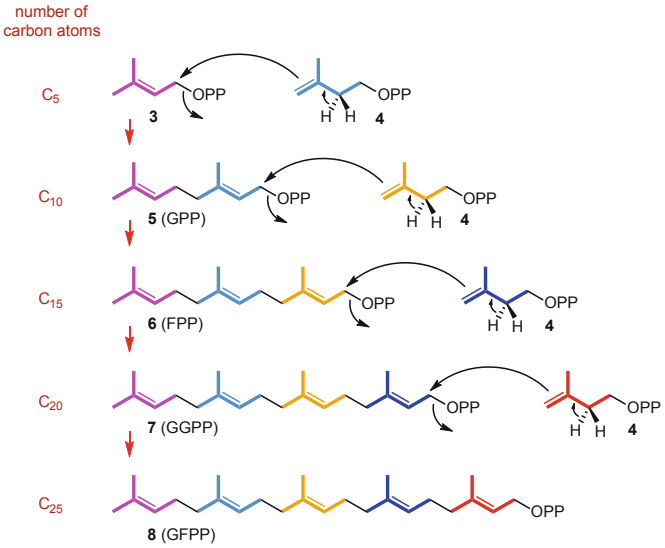


Fig. 5 Condensation reaction catalyzed by prenyltransferases to form polyprenyl diphosphates, and structures of **5**–**8**

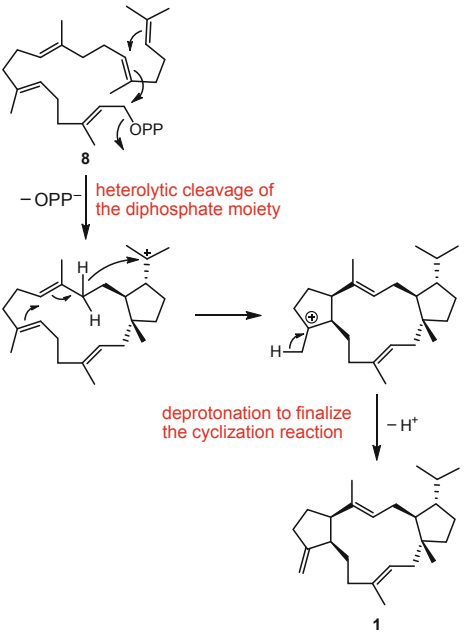


Fig. 6 Cyclization reaction to form sesterbrasiliatriene (**1**). This reaction is catalyzed by the type 1 terpene cyclase

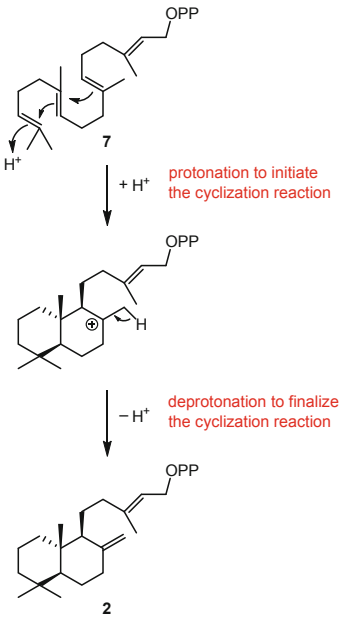


Fig. 7 Cyclization reaction to form **2**. This reaction is catalyzed by the type 2 terpene cyclase

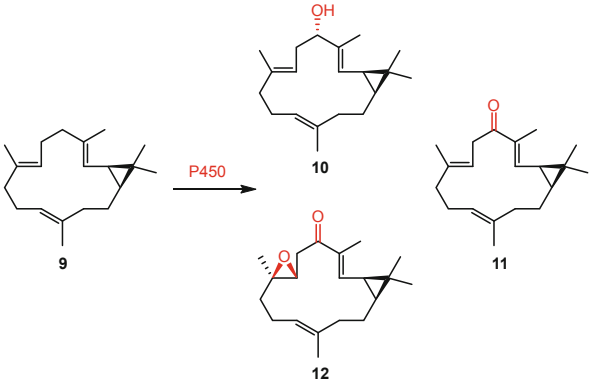


Fig. 8 Compound **9** could be oxidized by a cytochrome P450, forming **10**–**12**

After the fundamental carbon skeleton of the terpenoids is formed by the prenyltransferases and terpene cyclases, the intermediates of the terpenoids are converted into the final products by tailoring enzymes. A typical tailoring enzyme is cytochrome P450, which catalyzes an oxidation reaction. For instance, casbene (**9**) is converted to the oxidized products **10**–**12** by means of cytochrome P450 (Fig. 8) [13]. However, in addition to cytochrome P450, various other enzymes are also involved in the biosynthesis of terpenoids and expand their structural diversity.

For example, many kinds of tailoring enzymes (prenyltransferase, oxidase, aminotransferase, methyltransferase, sugar transferase, and ligase) are involved in the biosynthesis of brasilicardin A (**13**), a terpenoid with potent immunosuppressive

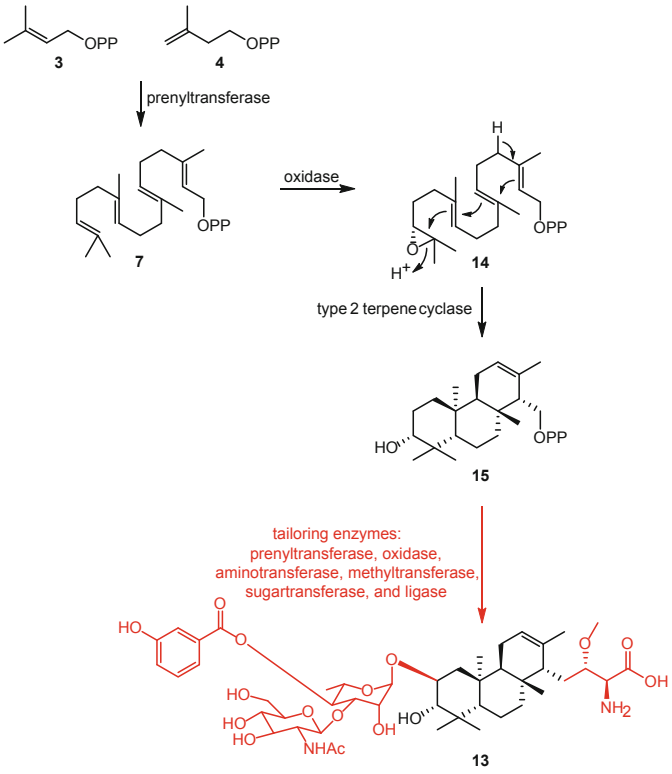


Fig. 9 Putative biosynthesis pathway of brasilicardin A (**13**). The functional groups of **13**, which might be generated by the tailoring enzymes, are shown in red

activity (Fig. 9). After the formation of **15** via **7** and **14**, these tailoring enzymes apparently convert **15** to **13** [14].

2.2 *Definition of "Sesterterpenoids"*

The terpenoids are classified by the chain lengths of the polyprenyl diphosphates used in their biosynthesis. In the case of the sesterterpenoids, they are defined as compounds that are biosynthesized via geranylfarnesyl diphosphate (GFPP) (**8**) (Fig. 10).

For example, preasperterpenoid A (**16**) is biosynthesized via **8** (Fig. 11) [9]. Thus, **16** is a sesterterpenoid. Actually, **1** is also a sesterterpenoid, while **2** is not, by considering their biosynthesis pathways (Figs. 6 and 7). Compounds **9**–**15** are also not sesterterpenoids (Figs. 8 and 9).

The other classes of terpenoids biosynthesized via different polyprenyl diphosphates are defined as follows: "hemiterpenoids" are from (C_5) **3** or **4**, "monoterpenoids" are from (C_{10}) **5**, "sesquiterpenoids" are from (C_{15}) **6**,

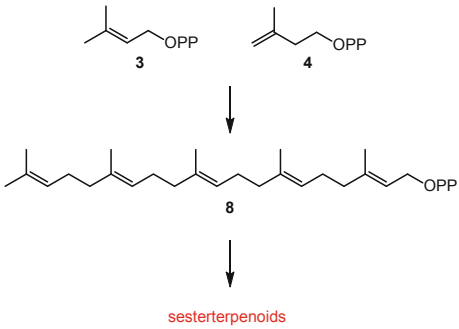


Fig. 10 Definition of sesterterpenoids. The genuine sesterterpenoids should be biosynthesized via **8**

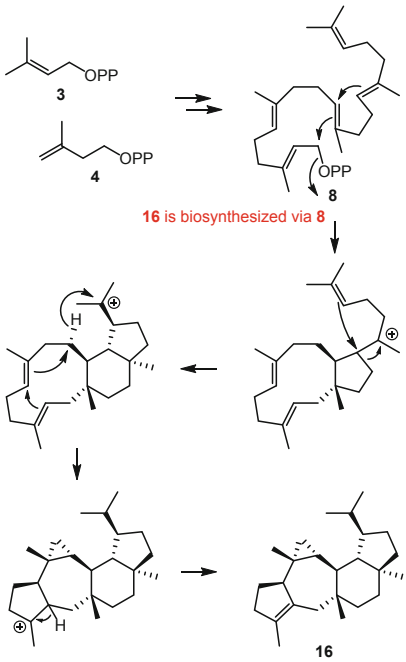


Fig. 11 Biosynthesis of preasperterpenoid A (**16**). Compound **16** is a sesterterpenoid, since **16** is biosynthesized via **8**

"diterpenoids" are from (C_{20}) **7**, and "triterpenoids" are from (C_{30}) squalene (**17**) (Fig. 12).

In contrast to **5**–**8**, **17** is generated by the condensation of two (C_{15}) **6** units. This condensation pattern is known as a tail-to-tail (Fig. 13b) linkage. The other polyprenyl diphosphates **5**–**8** exhibit only head-to-tail linkages (Fig. 13b).

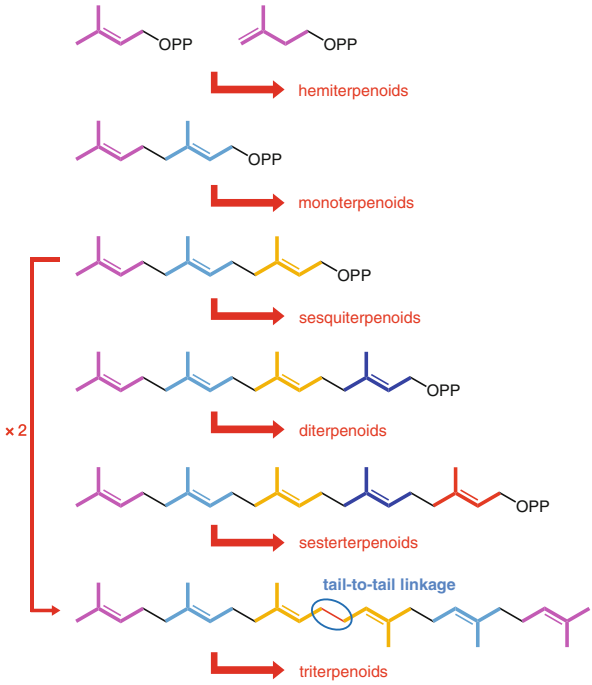


Fig. 12 Classification of the terpenoids

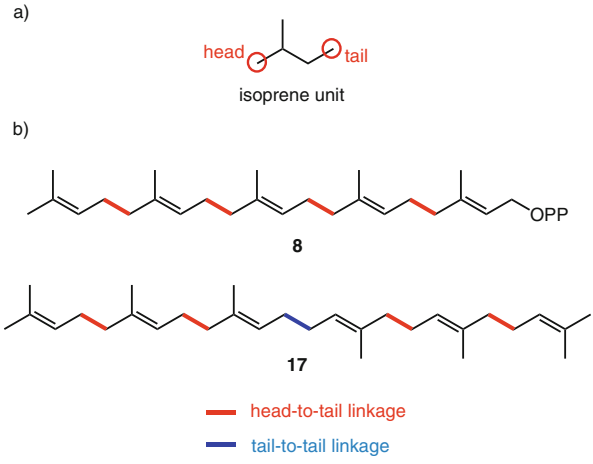


Fig. 13 (**a**) The "head" and "tail" positions in the isoprene unit. (**b**) Compound **8** is formed only by the "head-to-tail" condensation of isoprene units, while **17** is formed not only by the "head-to-tail" linkage but also by the "tail-to-tail" linkage

2.3 Natural Products Confused with Sesterterpenoids

Since all genuine sesterterpenoids should be derived from GFPP (**8**), the basic carbon skeletons of many sesterterpenoids are composed of 25 carbon atoms. However, it should be noted that not all compounds with basic carbon skeletons consisting of 25 carbon atoms are sesterterpenoids. Herein, we introduce examples of natural products that could be confused with sesterterpenoids. When determining whether a compound is a sesterterpenoid, it is essential to consider its biosynthetic origin.

2.3.1 Meroterpenoids

One example of natural products that could be confused with the sesterterpenoids is a group of meroterpenoids containing a C_{10} polyketide moiety (e.g., preterretonin A (**18**), protoaustinoid A (**19**), and andrastin E (**20**)) (Fig. 14) [15]. There are 25 carbon atoms in the basic carbon skeletons of these compounds. However, they are not biosynthesized via **8**, but are generated from a C_{15} terpenoid moiety and a C_{10} polyketide moiety. These C_{15} and C_{10} moieties are combined in their biosynthesis to form the C_{25} basic carbon skeleton.

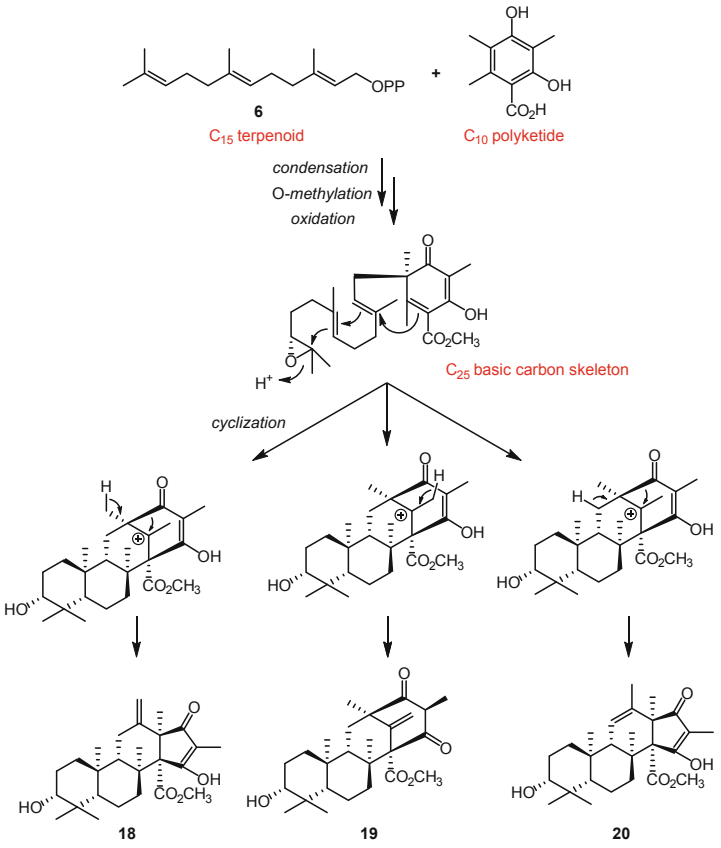


Fig. 14 Biosynthesis of **18**–**20**. In their basic carbon skeletons, there are 25 carbons. However, they are not sesterterpenoids

2.3.2 Highly Branched Isoprenoids

Compound **21** is a highly branched isoprenoid produced by the diatom *Rhizosolenia setigera* [16]. Five isoprene units are found readily in its structure (Fig. 15). Thus, **21** is a member of the terpenoids, and 25 carbon atoms exist in its basic carbon skeleton. However, **21** is not a sesterterpenoid, since **21** is not derived from the C_{25} polyprenyl diphosphate **8**, but from (C_{10}) **5** and (C_{15}) **6** (Fig. 16).

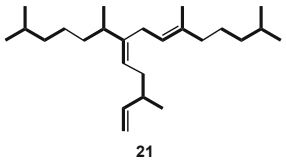


Fig. 15 Structure of **21**. The structure of **21** has five isoprene units, but **21** is not a sesterterpenoid. The isoprene units are shown by bold lines

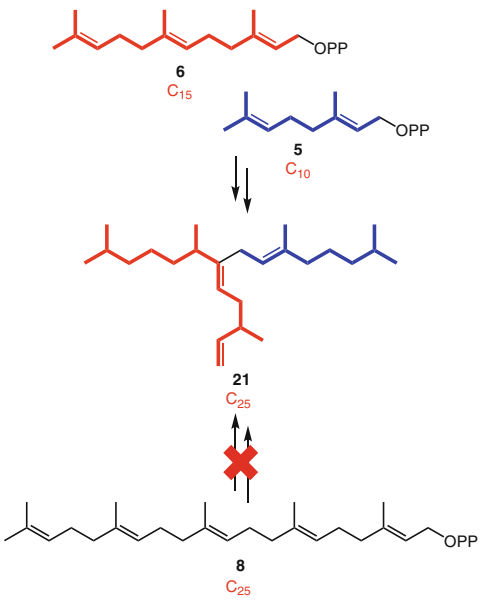


Fig. 16 Putative biosynthesis pathway of **21**. Compound **21** is biosynthesized from **5** and **6**, but not from **8**

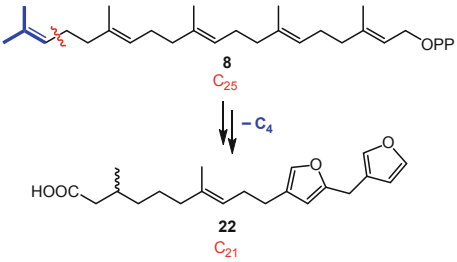


Fig. 17 Compound **22** is considered to be generated from **8**. The C_4 partial structure, which is shown by bold blue lines in **8**, is removed by the degradation reaction during the biosynthesis of **22**

2.3.3 Other Notable Points

The examples shown in Sects. 2.3.1 and 2.3.2 suggest that not all compounds with 25 carbon atoms are sesterterpenoids. However, it should also be noted that the basic carbon skeletons of some sesterterpenoids are composed of fewer than 25 carbons, due to a degradation reaction during their biosynthesis. For example, even though ircinin-3 (**22**) from the sponge *Ircinia oros* possesses only 21 carbon atoms, **22** is a sesterterpenoid (Fig. 17) [17].

3 Linear Sesterterpenoids

The linear sesterterpenoids do not possess a carbocyclic moiety. Thus, the terpene cyclases are not involved in their biosynthesis. The C_{25} polyprenyl chain of GFPP (**8**) is directly modified by tailoring enzymes to form a variety of linear sesterterpenoids.

One of the simplest linear sesterterpenoids is geranylfarnesol (**23**), discovered from the wax of the scale insect *Ceroplastes albolineatus* [18]. Another example of a simple linear sesterterpenoid is geranylnerolidol (**24**) from the fungus *Cochliobolus heterostrophus* [19]. The putative biosynthesis pathways of **23** and **24** should not be complicated, since the elimination of the diphosphate moiety and the attack of H_2O should be sufficient to form **23** and **24** from **8** (Fig. 18).

Actually, **23** and **24** are the simplest examples, and in many cases, further tailoring reactions occur to generate more functionalized linear sesterterpenoids. In spite of their simple basic carbon skeletons, many kinds of linear sesterterpenoids, especially from marine organisms, have been reported.

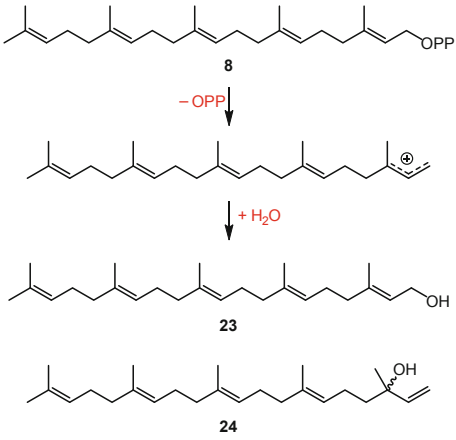


Fig. 18 Putative biosynthesis pathway of geranylfarnesol (**23**) and geranylnerolidol (**24**)

3.1 Linear Sesterterpenoids with a Furan Ring Moiety

A furan ring moiety is observed frequently in the structures of the linear sesterterpenoids. However, in almost all cases, the enzymes responsible for the formation of the furan moiety of the linear sesterterpenoids have not been identified. One example of a possible pathway for the biosynthesis of the furan skeleton is shown in Fig. 19. Other pathways for the formation of the furan ring could also be proposed as shown in Fig. 20.

As examples of linear sesterterpenoids with a furan ring moiety, furospongin-3 (**25**) and furospongin-4 (**26**) were isolated from the marine sponge *Spongia officinalis* (Plate 1) (Fig. 21) [17]. Another example is idiadione (**27**), which was discovered in a different sponge, *Spongia idia* (Fig. 21) [20]. An epoxyfuranosesterterpene carboxylic acid (**28**) was isolated from a Western Australian sponge *Spongia* sp. [21]. These linear sesterterpenoids possess one furan ring moiety in their structures. In addition, other tailoring reactions (e.g., oxidation, reduction, methyl ester formation) also seem to occur in their biosynthesis.

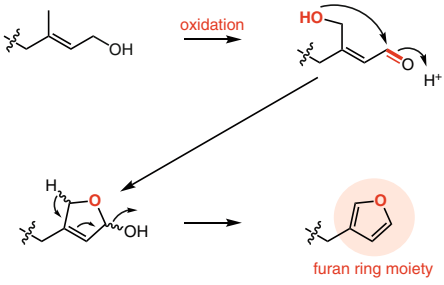


Fig. 19 One example of the proposed pathways for the formation of the furan moiety

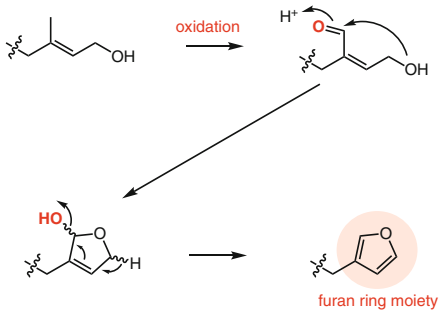


Fig. 20 Another pathway for the formation of the furan moiety

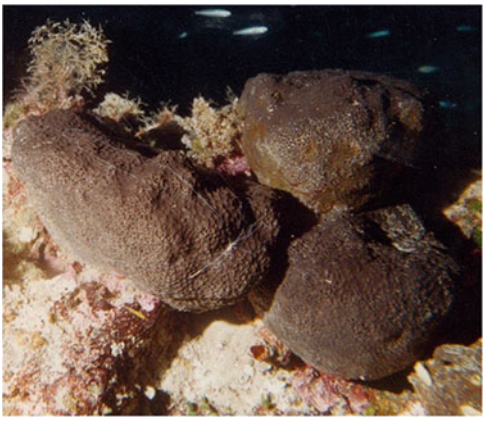


Plate 1 *Spongia officinalis*, Greece. Photograph courtesy E. Voultsiadou et al., Creative Commons 2.5

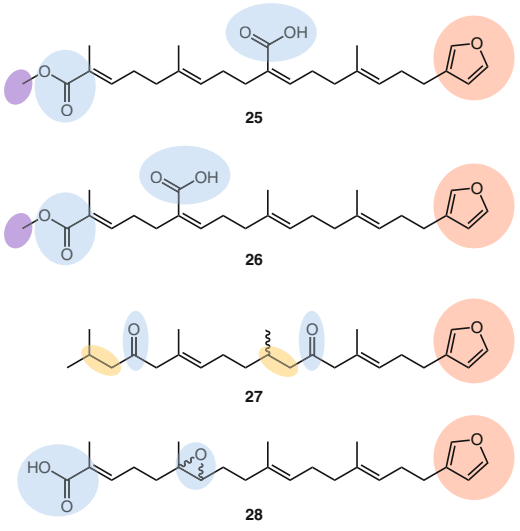


Fig. 21 Structures of **25**–**28**. The furan ring moieties are shown in red circles. The other functional groups, generated by oxidation, reduction, and methyl ester formation, are shown in blue, orange, and purple, respectively

3.2 *Linear Sesterterpenoids with a 2-Furanone Moiety*

Linear sesterterpenoids with a 2-furanone moiety also exist. The formation of the 2-furanone moiety should be similar to that of the furan ring moiety. Two possible pathways are shown in Figs. 22 and 23.

Two linear sesterterpenoids with a 2-furanone moiety, **29** and **30,** were isolated from the Caribbean sponge *Thorecta horridus* (Fig. 24) [22]. In particular, **29** possesses potent inflammatory activity, inducing histamine release (in vitro), and causes edema in rat paws (in vivo).

Compound **29** has also been reported from the Australian sponge *Luffariella geometrica*, and designated as luffarin Q [23]. Luffarin R (**31**) was also isolated from the same sponge (Fig. 25) [23]. Compound **31** possesses a γ-butyrolactone moiety in addition to the 2-furanone moiety.

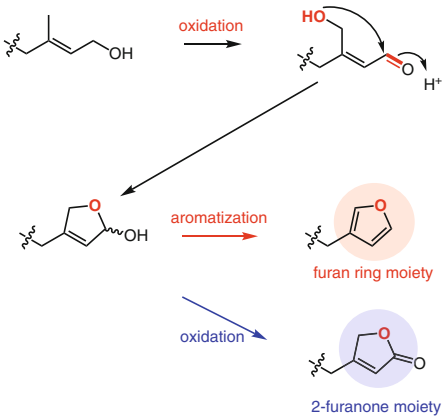


Fig. 22 Formation of the 2-furanone moiety

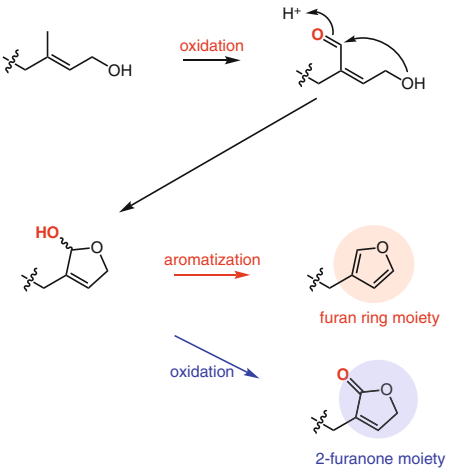


Fig. 23 An alternative pathway for the formation of the 2-furanone moiety

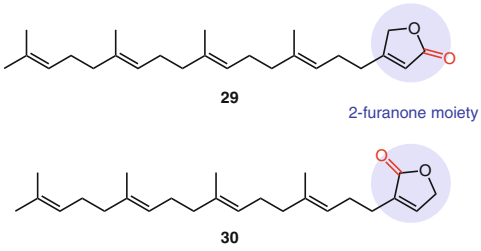


Fig. 24 Structures of **29** and **30**. The 2-furanone moieties are highlighted by blue circles

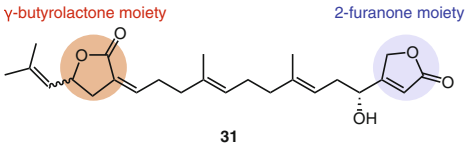


Fig. 25 Structure of luffarin R (**31**), which possesses not only the 2-furanone moiety but also a γ-butyrolactone moiety

3.3 Linear Sesterterpenoids with a Tetronic Acid Moiety

The tetronic acid moiety is present in numerous linear sesterterpenoids, and many of them exhibit bioactivities. The tetronic acid moiety seems to be generated by an oxidation of the 2-furanone moiety (Fig. 26).

For example, **32** was isolated from the Australian sponge *Psammocinia* sp. (Fig. 27) [24] and has antimicrobial activity. A similar compound, isopalinurin (**33**), was reported from the South Australian sponge, *Dysidea* sp. (Fig. 27) [25]. Compound **33** is known as a moderate protein phosphatase inhibitor. In addition to the tetronic acid moiety, **32** and **33** also possess a furan ring moiety.

Variabilin (**34**), an antimicrobial linear sesterterpene with a tetronic acid moiety (Fig. 28) [26], was isolated from the Okinawan sponge, *Amphidmedon* sp. Compound **34** possesses a stereocenter at the C-18 position, and the absolute configuration of this position was determined as (*S*) by the synthesis of the degradation product of **34** [26].

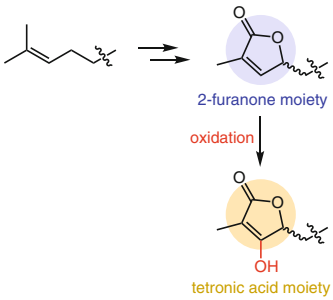


Fig. 26 Proposed pathway for the formation of the tetronic acid moiety

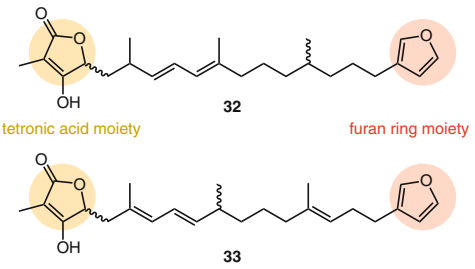


Fig. 27 Structures of **32** and **33**. The tetronic acid and furan ring moieties are highlighted by orange and red circles, respectively

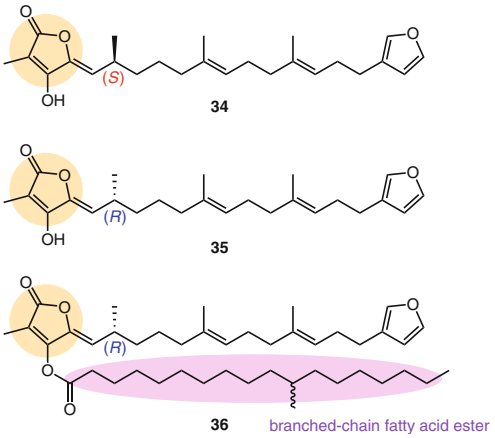


Fig. 28 Structures of **34**–**36**. The tetronic acid and branched-chain fatty acid ester are highlighted by orange and purple circles, respectively

An enantiomer of **34**, (18*R*)-variabilin (**35**), was isolated from the Caribbean sponge *Ircinia felix* (Fig. 28) [27]. Together with **35**, variabilin 11-methyloctadecanoate (**36**), a branched-chain fatty acid ester of **35**, was also isolated [28].

Compounds **32**–**36** possess not only a tetronic acid moiety but also a furan ring moiety. Actually, many linear sesterterpenoids with a tetronic acid moiety have a furan ring moiety, and some of them possess more than one furan ring moiety in their chemical structures. For example, spongionellin (**37**) [29], dehydrospongionellin (**38**) [29], ircinin-1 (**39**) [30, 31], and ircinin-2 (**40**) [30, 31] have two furan ring moieties, in addition to a tetronic acid moiety (Fig. 29). Compounds **37** and **38** are from a Japanese sponge, *Spongionella* sp., and both inhibit the cell division of fertilized starfish (*Asterina pectinifera*) eggs. Compounds **39** and **40** were isolated from the sponge *Ircinia oros*, collected in the Bay of Naples along the south-western coast of Italy [30], and another sponge *Ircinia* sp., collected from the Island of Bora Bora in French Polynesia [31].

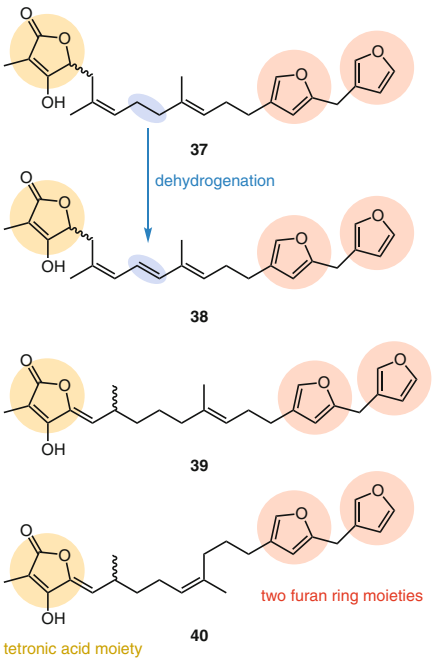


Fig. 29 Structures of **37**–**40**. The tetronic acid and furan ring moieties are highlighted by orange and red circles, respectively. Compounds **37**–**40** possess two furan ring moieties and one tetronic acid moiety

3.4 Degraded Linear Sesterterpenoids

As mentioned in Sect. 2.3.3, the numbers of carbon atoms in some sesterterpenoids are less than 25, because of degradation reactions in their biosynthesis. Herein, we introduce the "C_{21}" and "C_{24}" linear sesterterpenoids.

3.4.1 "C_{21}" Linear Sesterterpenoids

The C_{21} linear sesterterpenoids are one of the largest groups among the degraded linear sesterterpenoids. The C_{21} linear sesterterpenoids are considered to arise from the cleavage of the tetronic acid moiety, which was introduced in Sect. 3.3. This hypothesis is supported by the co-occurrence of the C_{21} linear sesterterpenoids (e.g. **22**, ircinin-4 (**41**)) and the corresponding linear sesterterpenoids with a tetronic acid moiety (e.g., **39** and **40**) (Figs. 17 and 30) [17]. A proposed mechanism of the degradation reaction is shown in Fig. 31 [1, 17]. Some sesterterpenoids with a tetronic acid moiety (e.g., **39** and **40**) possess a double bond, which is attached to the tetronic acid moiety (Figs. 30 and 31). Thus, when this tetronic acid moiety becomes an opened form, a reactive α-dicarbonyl moiety is generated, and the α-dicarbonyl moiety is cleaved. For example, a hydroperoxide compound, which could be formed by autoxidation, is capable of cleaving an α-dicarbonyl compound [32]. However, this is just one possible way, and further studies are required to reveal the mechanism leading to the formation of the C_{21} linear sesterterpenoids.

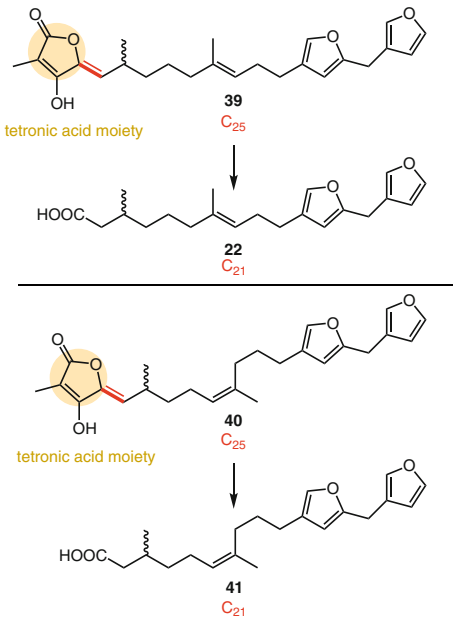


Fig. 30 Comparison of the structures of **22**, **41**, **39**, and **40**, which were all isolated from the same marine sponge, *Ircinia oros*. The double bonds attached to the tetronic acid moiety are highlighted by the bold red line. Compounds **22** and **41** are considered to be generated by the cleavage of **39** and **40**, respectively. The structure of **22** is also shown in Fig. 17, and the structures of **39** and **40** are also shown in Fig. 29

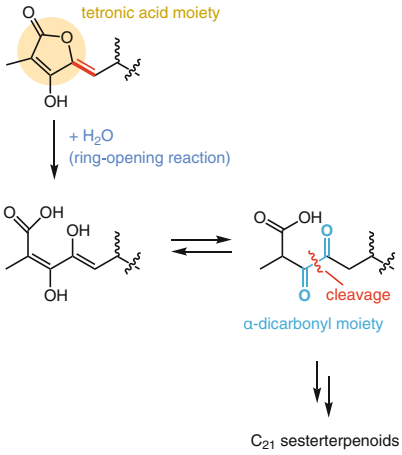


Fig. 31 Proposed mechanism leading to the formation of the C_{21} linear sesterterpenoids. Double bonds attached to the tetronic acid moiety are emphasized by bold red lines

Interestingly, many of the C_{21} linear sesterterpenoids possess furan ring moieties at both ends of their structures. For example, untenospongin C (**42**), obtained from an Okinawan sponge *Hippospongia* sp. (Fig. 32) [33], exhibited cytotoxicity against murine lymphoma L1210 cells (in vitro experiment). Another example is isonitenin (**43**) from the sponge *Spongia officinalis* collected at O Grove, Pontevedra, Spain (Fig. 32) [34]. Anhydrofurospongin-1 (**44**) [35] and furospongin-1 (**45**) [36] have been found in both the *Spongia officinalis* and *Hippospongia communis* sponges,

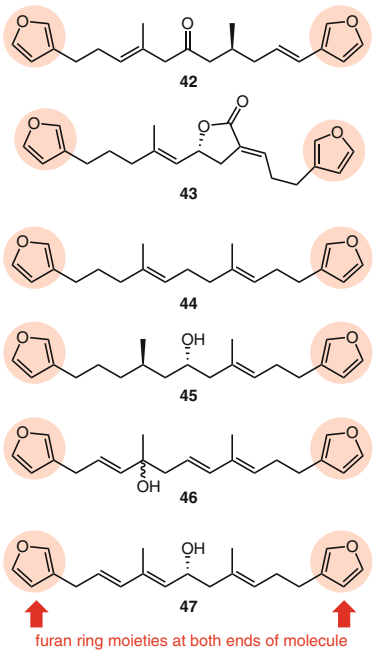


Fig. 32 Structures of **42**–**47**. These are C_{21} linear sesterterpenoids, with the furan ring moiety at both ends of their structures

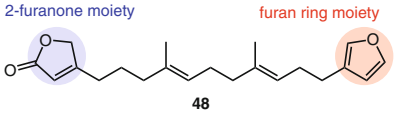


Fig. 33 Structure of furospongolide (**48**), which possesses one furan ring moiety and one 2-furanone moiety at the ends of the molecule

which were collected in the Bay of Naples, Italy (Fig. 32). In addition, **46** has been reported from a sponge *Spongia* sp. collected in Western Australia [37], and tetradehydrofurospongin-1 (**47**) has been found in both the *Leiosella* sp. and *Spongia* sp. sponges (Fig. 32) [37, 38].

On the other hand, furospongolide (**48**), from the sponge *Dysidea herbacea* (Fig. 33) [39], possesses one furan ring moiety and one 2-furanone moiety at the ends of the molecule.

3.4.2 "C_{24}" Linear Sesterterpenoids

The C_{24} linear sesterterpenoids are also considered to be formed from the linear sesterterpenoids with a tetronic acid moiety. In the case of the C_{24} linear

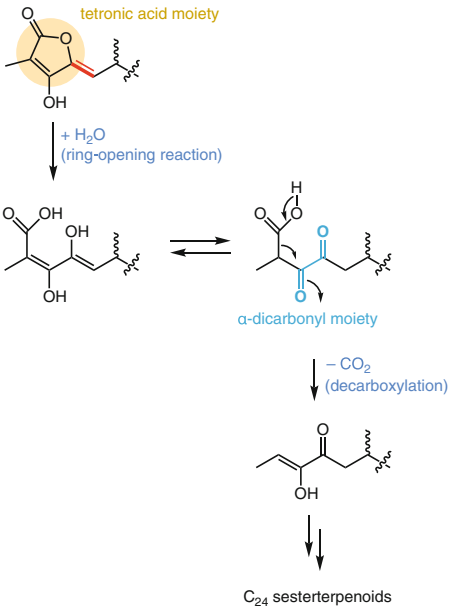


Fig. 34 Proposed mechanism leading to the formation of the C_{24} linear sesterterpenoids

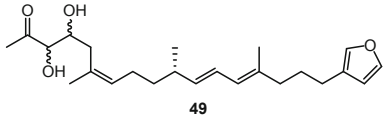


Fig. 35 Structure of sarcotin P (**49**)

sesterterpenoids, decarboxylation occurs to remove one carbon atom from the molecule (Fig. 34).

The C_{24} linear sesterterpenoids are exemplified by sarcotin P (**49**), from a sponge *Sarcotragus* sp. collected off Cheju Island, Korea (Fig. 35) [40]. Compound **49** might show toxicity to brine shrimp larvae, since this compound was isolated by a bioactivity-guided fractionation procedure that evaluated toxicity to brine shrimp larvae, although this was not confirmed.

Halogenated C_{24} linear sesterterpenoids also exist, and are exemplified by konakhin (**50**) [41], **51** [42], and **52** [42] (Fig. 36). Compound **50** was isolated from an unidentified sponge collected off the coast of Konakhè, near Dakar, Senegal, while **51** and **52** were obtained from a North Adriatic Sea collection of *Ircinia oros*.

A proposed mechanism leading to the formation of the halogenated C_{24} linear sesterterpenoids is shown in Fig. 37. In this pathway, after decarboxylation to form the C_{24} fundamental carbon skeleton, a halogenation reaction occurs.

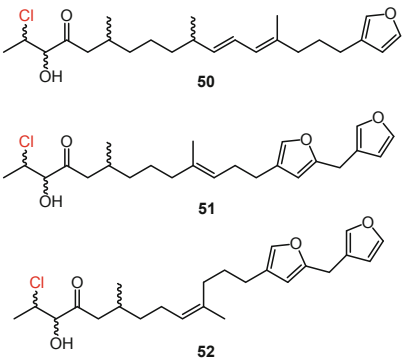


Fig. 36 Structures of **50**–**52**. Halogen atoms are shown in red

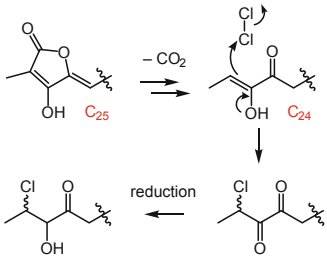


Fig. 37 Proposed mechanism leading to the formation of the halogenated C_{24} linear sesterterpenoids

3.5 Linear Sesterterpenoids Containing a Nitrogen Atom

All linear sesterterpenoids shown above (**22**–**52**) are composed of only carbon, hydrogen, and oxygen atoms. However, some linear sesterterpenoids contain a nitrogen atom, as exemplified by the ircinialactams (**53**–**55**) (Fig. 38) [43], purified

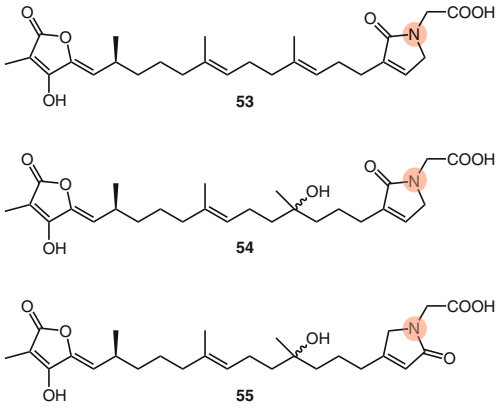


Fig. 38 Structures of the ircinialactams **53**–**55**, which contain a nitrogen atom in their structures

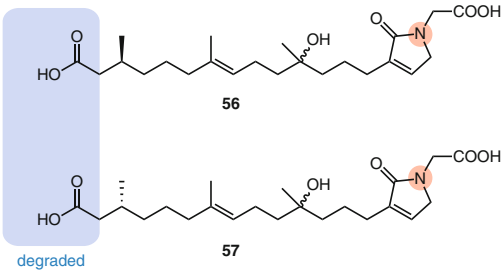


Fig. 39 Structures of **56** and **57**, which contain a nitrogen atom in their structures, and are members of the C_{21} linear sesterterpenoids

from Australian sponges of the family Irciniidae. From these sponges, the C_{21} degraded compounds, **56** and **57**, have also been isolated (Fig. 39) [43]. The proposed degradation mechanism is shown in Fig. 31. Compounds (**53**–**57**) are all modulators of glycine receptor chloride channels.

4 Monocarbocyclic Sesterterpenoids

In the biosynthesis of the monocarbocyclic sesterterpenoids, terpene cyclases are responsible for the formation of the carbocyclic moiety (Figs. 6 and 7). As mentioned above, there are two kinds of terpene cyclases, types 1 and 2. Each cyclase can generate a variety of characteristic basic carbon skeletons of sesterterpenoids.

4.1 Monocarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

4.1.1 14-Membered Ring

Monocarbocyclic sesterterpenoids constructed by the type 1 terpene cyclases are relatively rare. They are exemplified by ceriferol (**58**), ceriferic acid (**59**), ceriferol-I (**60**), 13-methoxycericerene (**61**), and ceriferol-II (**62**), which possess 14-membered ring systems (Fig. 40) [44–49]. They were isolated from the wax of the scale insect *Ceroplastes ceriferus*. In fact, scale insects are known as good sources of sesterterpenoids.

The mechanism of the 14-membered ring formation by the type 1 terpene cyclases is shown in Fig. 41. The cyclization reaction is initiated by the heterolytic cleavage of the diphosphate moiety of **8**, and then the cyclization is finalized by the deprotonation or the attack of H_2O.

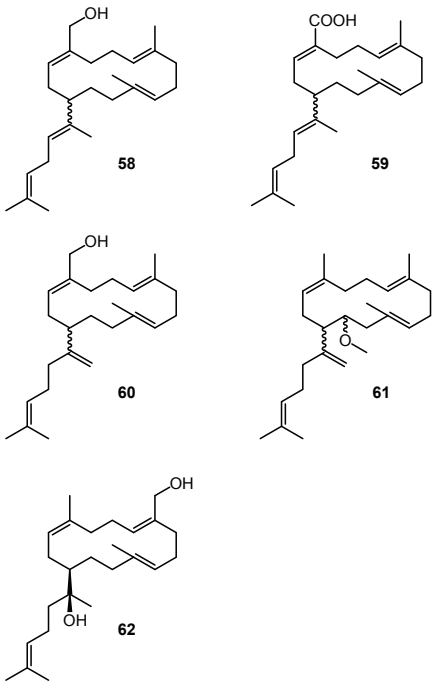


Fig. 40 Structures of **58**–**62**

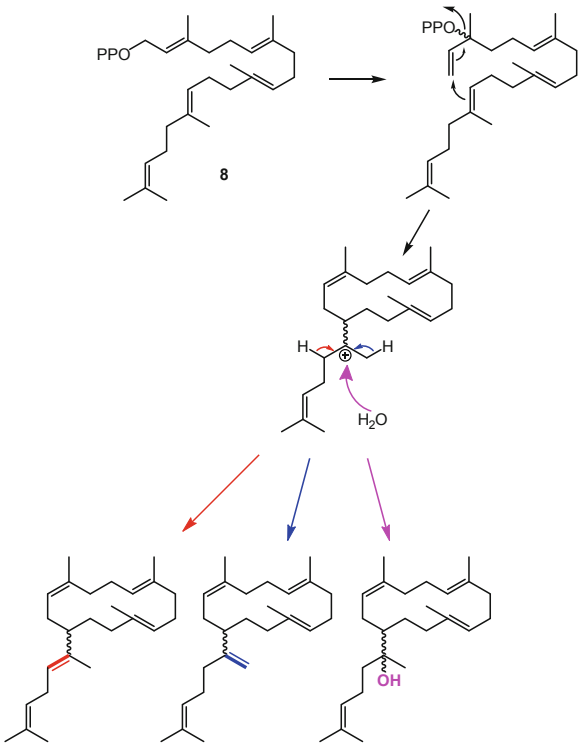


Fig. 41 The mechanism of 14-membered ring formation by the type 1 terpene cyclases

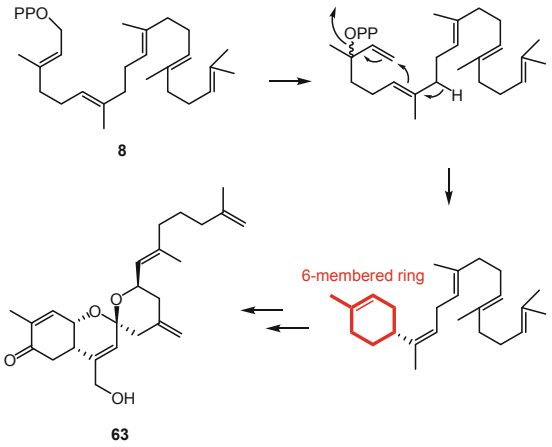


Fig. 42 Structure and formation of (–)-alotaketal A (**63**)

4.1.2 6-Membered Ring

The compound (−)-alotaketal A (**63**), which possesses a 6-membered ring system, was reported from a marine sponge, *Hamigera* sp., collected in Papua New Guinea (Fig. 42) [50], and is known to activate the cAMP cell signaling pathway. Its biosynthesis originates from geranylfarnesyl diphosphate (GFPP) (**8**).

4.2 Monocarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases

4.2.1 6-Membered Ring

The type 2 terpene cyclases also generate 6-membered ring systems. Moreover, most of the monocarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases possess a 6-membered ring. For example, **64** [51], **65** [51], luffariolide H (**66**) [52], and luffariolide J (**67**) [52] have been reported (Fig. 43). Compounds **64** and **65** were isolated from the sponge *Hyrtios* cf. *erecta*, collected at Nananu-I-Ra, Fiji. Compounds **66** and **67** were reported from an Okinawan marine sponge, *Luffariella* sp., and exhibit antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, and *Micrococcus luteus*.

Acantholide A (**68**) [53] and acantholide B (**69**) [53] also possess 6-membered rings (Fig. 44). They were isolated from an Indonesian sponge, *Acanthodendrilla* sp., and **69** has antimicrobial activities against *Staphylococcus aureus* and *Bacillus subtilis*.

A cyclization mechanism for the formation of the 6-membered rings of **64**–**69** is shown in Fig. 45. Since their basic carbon skeletons are formed by the type 2 terpene cyclases, the cyclization reaction is initiated by the protonation of the double bond of geranylfarnesyl diphosphate (GFPP) (**8**).

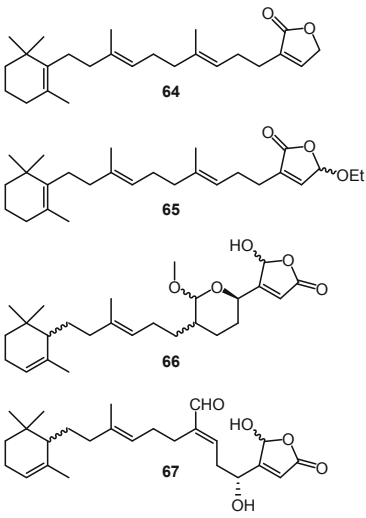


Fig. 43 Structures of **64**–**67**

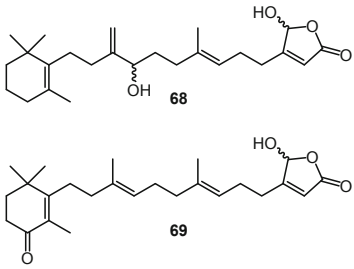


Fig. 44 Structures of acantholide A (**68**) and acantholide B (**69**)

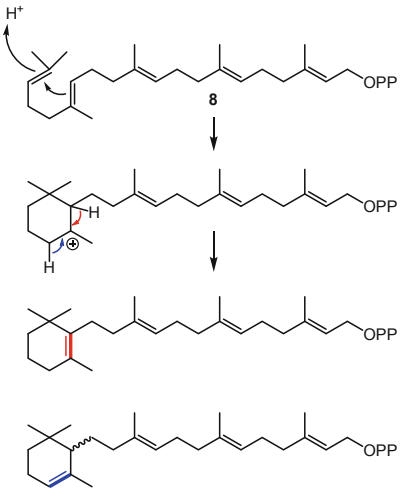


Fig. 45 Cyclization mechanism for the formation of the 6-membered rings of **64**–**69**

Another monocarbocyclic sesterterpenoid with a 6-membered ring is cyclolinteinone (**70**), isolated from the Caribbean sponge *Cacospongia linteiformis* (Fig. 46) [54]. The positions of the methyl groups on the 6-membered ring differentiate **70** from **64**–**69**. Compound **70** can downregulate the protein expression of an inducible NO synthase and cyclo-oxygenase-2 via the inhibition of NF-κB activation.

A cyclization reaction leading to the formation of the basic carbon skeleton of **70** is shown in Fig. 47. In this proposed mechanism, a 1,2-hydride shift and a 1,2-alkyl shift occur to change the position of the methyl group on the 6-membered ring, and then deprotonation finalizes the reaction.

The structures of cyclolinteinol (**71**) and cyclolinteinol acetate (**72**) are similar to that of **70** (Fig. 48) [55]. They were isolated from the Caribbean sponge *Cacospongia* cf. *linteiformis*.

Fig. 46 Structure of **70**

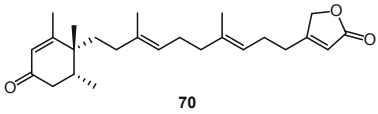


Fig. 47 Cyclization reaction leading to the formation of the basic carbon skeleton of **70**

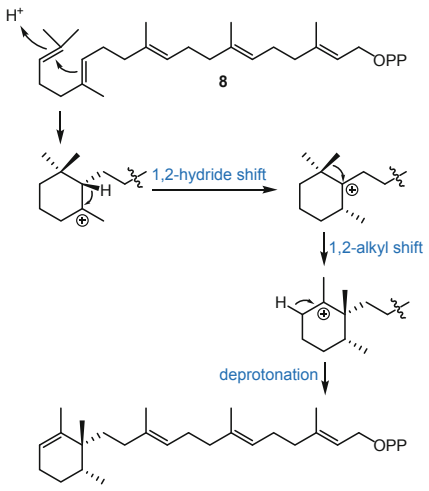
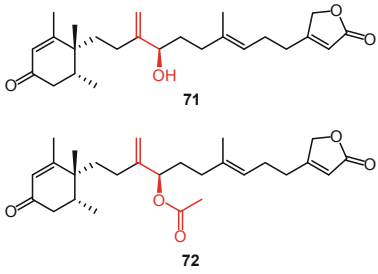


Fig. 48 Structures of cyclolinteinol (**71**) and cyclolinteinol acetate (**72**)



4.2.2 5-Membered Ring

Monocarbocyclic sesterterpenoids with 5-membered ring systems also exist. However, they are rare, as compared with the monocarbocyclic sesterterpenoids with 6-membered ring systems. Such sesterterpenoids are exemplified by 25-acetoxyluffariellins A and B (**73** and **74**) (Fig. 49) [56], isolated from the sponge *Luffariella variabilis* from the Great Barrier Reef, Australia. Notably, they are unstable in the sponge tissue, even though they are stable after isolation. Thus, the sponge apparently has some enzymes that can convert or degrade these compounds.

A proposed mechanism for the formation of the 5-membered ring system is shown in Fig. 50.

A different type of 5-membered ring is seen in the structures of acantholide D (**75**) and acantholide E (**76**) (Fig. 51) [53]. Actually, **75** and **76** were co-isolated with **68** and **69** from the Indonesian sponge, *Acanthodendrilla* sp. [53], and **76** exhibited cytotoxicity against the L5187Y mouse lymphoma cell line. A proposed cyclization mechanism for generating the basic carbon skeleton of **75** and **76** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 52.

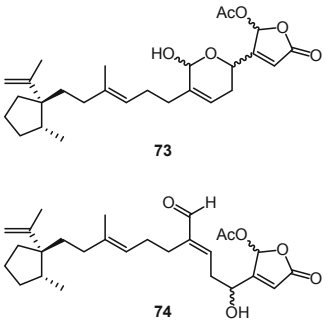


Fig. 49 Structures of 25-acetoxyluffariellins A (**73**) and B (**74**)

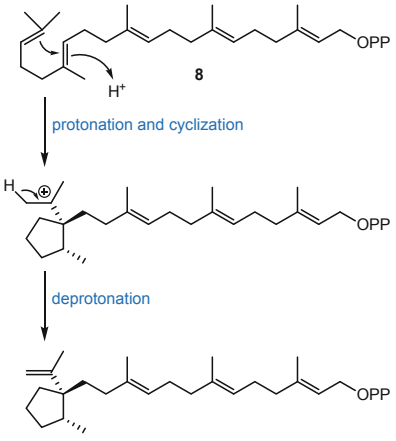


Fig. 50 Proposed mechanism for the formation of the 5-membered rings of **73** and **74**

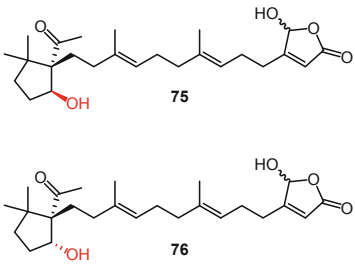


Fig. 51 Structures of acantholide D (**75**) and acantholide E (**76**)

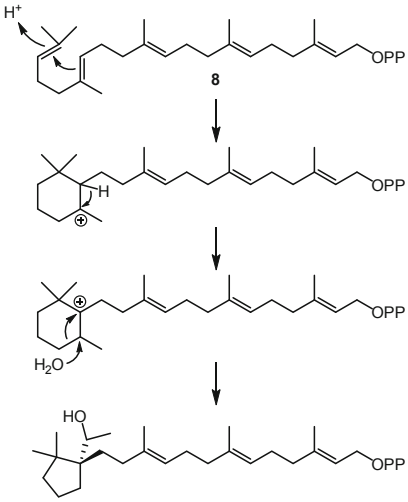


Fig. 52 Proposed cyclization mechanism for generating the basic carbon skeletons of acantholide D (**75**) and acantholide E (**76**)

5 Bicarbocyclic Sesterterpenoids

5.1 Bicarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

5.1.1 15/5-Membered Ring System

Bicarbocyclic sesterterpenoids, constructed by the type 1 terpene cyclases, have been reported from fungi. Terpestacin (**77**), a representative compound with a 15/5-membered ring system (Fig. 53) [57, 58], has been isolated from the fungi *Arthrinium* sp. [57] and *Phomopsis* sp. XZ-26 [58]. Compound **77** reportedly inhibits tumor angiogenesis by binding to the 13.4-kDa subunit of the mitochondrial complex III and suppresses hypoxia-induced reactive oxygen species production and cellular oxygen sensing [59].

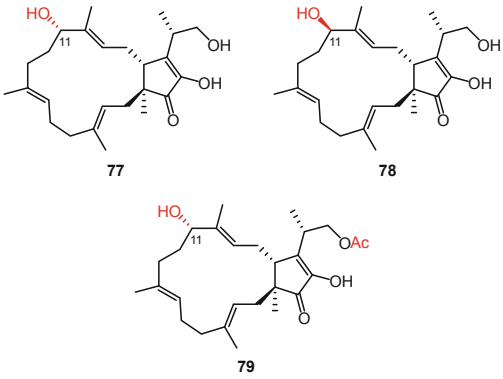


Fig. 53 Structures of **77**–**79**, which possess a 15/5-membered ring system

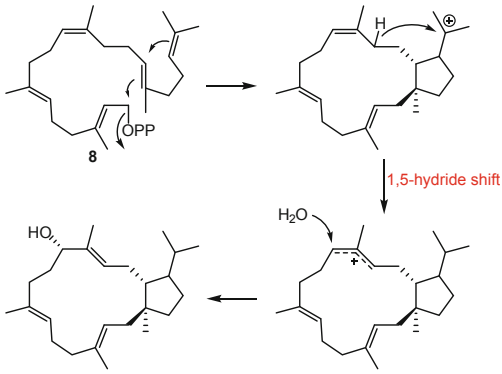


Fig. 54 Proposed cyclization mechanism for the formation of the 15/5-membered ring system

Interestingly, the compound known as "siccanol," isolated from the fungus *Bipolaris sorokiniana* NSDR-011, is also compound **77**. Even though "siccanol" was initially reported as 11-epiterpestacin (**78**), an epimer of **77** (Fig. 53) [60], the total synthesis of **78** revealed that "siccanol" was not **78**, but **77** [61].

Fusaproliferin (**79**), isolated from the fungus *Fusarium proliferatum*, also possesses the 15/5-membered ring system (Fig. 53) [62]. Compound **79** is an acetate ester of **77**, and the stereochemistry of **79** was established by a synthesis approach [63]. A proposed cyclization mechanism for the formation of the 15/5-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 54. This cyclization involves a 1,5-hydride shift, which is seen frequently in the type 1 cyclization reactions of sesterterpenoids.

5.1.2 12/6-Membered Ring System

Emericellene A (**80**) and related compounds have been reported from an endophytic fungus, *Emericella* sp. AST0036, collected from a healthy leaf of the plant

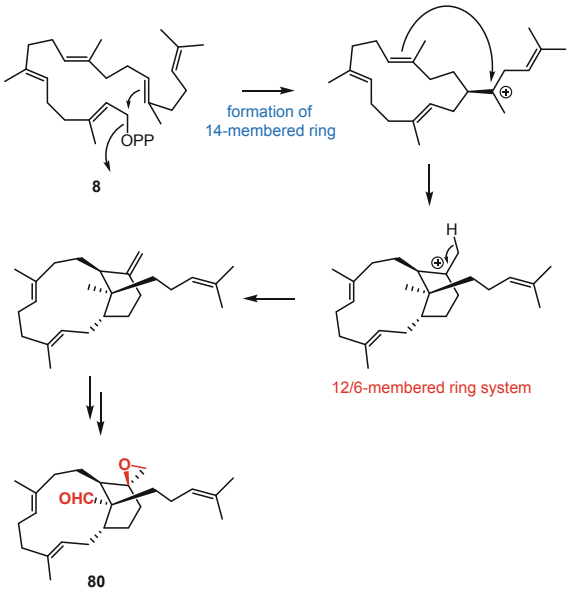


Fig. 55 Structure of mericellene A (**80**), and proposed cyclization mechanism for the formation of the 12/6-membered ring system

Astragalus lentiginosus (Fig. 55) [64]. Compound **80** possesses a 12/6-membered ring system. A proposed cyclization mechanism for generating the 12/6-membered ring system originating in geranylfarnesyl diphosphate (**8**) is shown in Fig. 55, and the formation of a 14-membered ring might be the first step in this reaction.

5.2 *Bicarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases*

The majority of bicarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases possess 6/6-membered ring systems. An example of the 6/6-membered ring formation starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 56.

Salvimirzacolide (**81**), with a 6/6-membered ring system, was isolated from the aerial parts of the plant *Salvia mirzayanii* (Fig. 57) [65]. Another example is salvileucolide methyl ester (**82**), which reportedly exists in the aerial parts of two Iranian *Salvia* species plants (Fig. 57) [66]. The structures of both **81** and **82** have been confirmed by X-ray crystallography.

In some cases, an alkyl shift occurs in the middle of the cyclization reaction. For example, the basic carbon skeleton of halisulfate-3 (**83**) is different from those of **81** and **82** (Fig. 58) [67]. Compound **83** is one of the metabolites of a sponge, *Ircinia* sp., which was collected in the Philippines. The cyclization reaction for the formation of the basic carbon skeleton of **83** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 59.

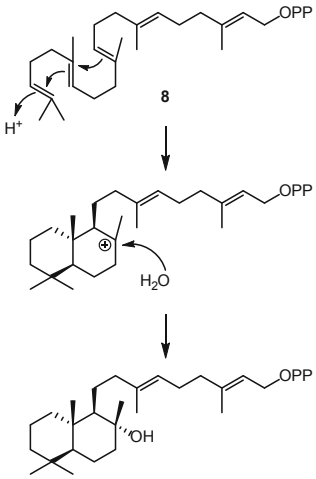


Fig. 56 One example of the 6/6-membered ring formation

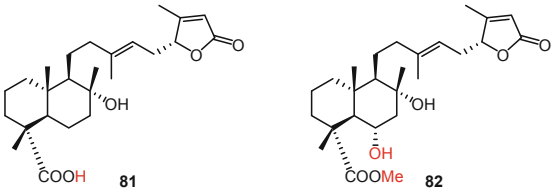


Fig. 57 Structures of salvimirzacolide (**81**) and salvileucolide methyl ester (**82**)

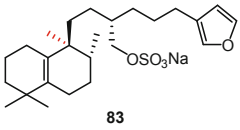


Fig. 58 Structure of halisulfate-3 (**83**)

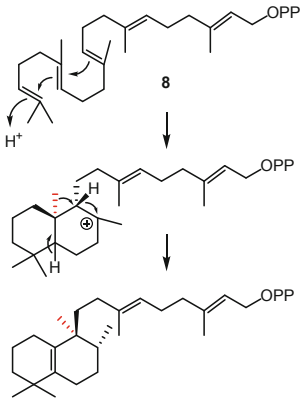


Fig. 59 Proposed cyclization mechanism to generate the basic carbon skeleton of **83**

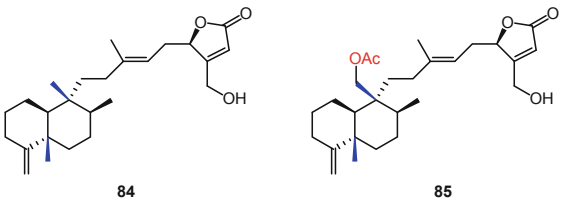


Fig. 60 Structures of thorectandrol A (**84**) and thorectandrol B (**85**)

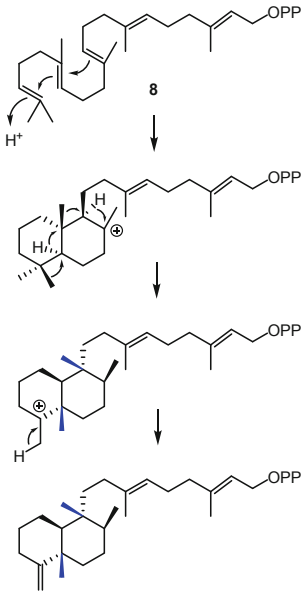


Fig. 61 Proposed cyclization mechanism for generating the basic carbon skeleton of **84** and **85**

Another example of an alkyl shift is found in the formation of thorectandrol A (**84**) and thorectandrol B (**85**) (Fig. 60) [68]. Compounds **84** and **85** were isolated from the sponge *Thorectandra* sp. collected in Palau, and both **84** and **85** inhibited the growth of the MALME-3M and MCF-7 cancer cells. A proposed cyclization mechanism for the formation of the basic carbon skeletons of **84** and **85** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 61. During this reaction, the alkyl shift occurs twice.

5.3 Other Bicarbocyclic Sesterterpenoids

Even though most of the carbocyclic moieties of sesterterpenoids are formed by the terpene cyclases, some carbocyclic structures are generated in a different manner. For example, the bicarbocyclic ring systems of (+)-wistarin (**86**) [69, 70] and (−)-wistarin (**87**) [71] would not be formed by the typical terpene cyclases (Fig. 62). Compound **87** is an enantiomer of **86**. Compound **86** was found in the sponge *Ircinia*

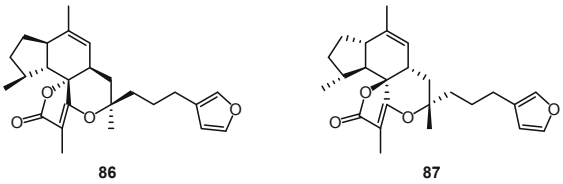


Fig. 62 Structures of (+)-wistarin (**86**) and (−)-wistarin (**87**)

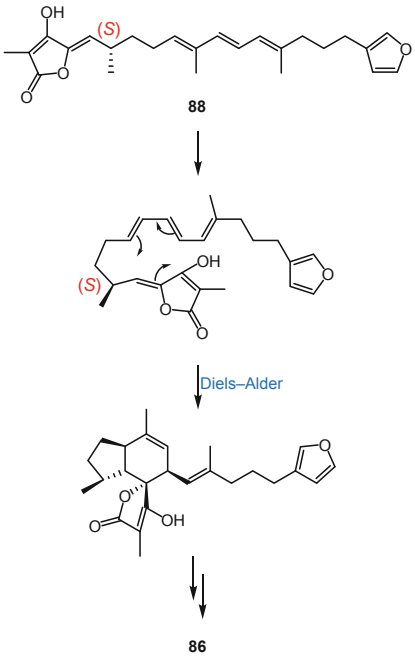


Fig. 63 Proposed mechanism to generate the basic carbon skeleton of **86**

wistarii from the Great Barrier Reef, Australia [69], while **87** was isolated from a sponge, *Ircinia* sp., collected at Hurghada, Red Sea, Egypt [71].

A proposed biosynthesis of **86** is shown in Fig. 63. Actually, **86** seems to be biosynthesized via a linear sesterterpenoid **88**, and the Diels–Alder reaction might occur to form the bicarbocyclic moiety of **86**. In the same manner, **87** should be formed via *ent*-**88**.

The biosynthesis pathway of ircinianin sulfate (**89**) (Fig. 64) [72] should be similar to that of **86**. Compound **89** is an unstable metabolite from the sponge *Ircinia wistarii*, collected from the Great Barrier Reef, Australia.

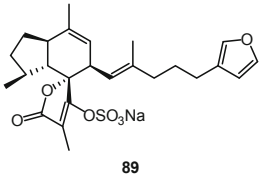


Fig. 64 Structure of ircinianin sulfate (**89**)

6 Tricarbocyclic Sesterterpenoids

A greater number of carbocyclic moieties increases the complexity of the structures of sesterterpenoids. Thus, sesterterpenoids with more than three carbocyclic rings exhibit considerable complexity. Moreover, the diversity of the basic carbon skeleton is also increased. Especially the type 1 terpene cyclases have great potential to generate various kinds of structures with more than three carbocyclic rings.

6.1 Tricarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

6.1.1 5/8/5-Membered Ring System

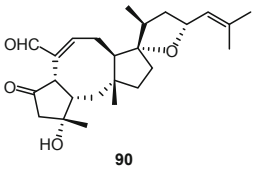
A tricarbocyclic sesterterpenoid with a 5/8/5-membered ring system (**90**), from the fungi *Ophiobolus miyabeanus* and *Helminthosporium oryzae*, was found initially and characterized by Japanese [73] and Italian [74] groups, independently. The Japanese group designated this compound as ophiobolin, while the Italian group named it cochliobolin. In order to avoid confusion, a joint paper from these two groups was published, and this compound was renamed ophiobolin A (**90**) (Fig. 65) [75].

Many derivatives of **90** have been reported, and they are called ophiobolin-type sesterterpenoids. Examples of the ophiobolin-type sesterterpenoids, ophiobolins B-M (**91**–**102**), are shown in Figs. 66 and 67 [19, 76–86]. Notably, the ophiobolin-type sesterterpenoids are known as bioactive compounds. For example, **90**, **91**, **92**, and **100** exhibited activity toward leukemia cells with the induction of apoptosis, at nanomolar concentrations [87].

A proposed cyclization mechanism for the formation of the 5/8/5-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 68. In this reaction, an 11/5-membered ring system first would be generated. Subsequently, a 1,5-hydride shift and the formation of another 5-membered ring would occur.

Epimers of many ophiobolins have also been reported, as exemplified by 6-epiophiobolin A (**103**) [88, 89], 6-epiophiobolin C (**104**) [85], 6-epiophiobolin I (**105**) [82], and 6-epiophiobolin K (**106**) [83] (Fig. 69).

Many ophiobolin-type sesterterpenoids have been described, and even now, the number of ophiobolin-type sesterterpenoids is increasing. For example, the new



90

Fig. 65 Structure of ophiobolin A (**90**)

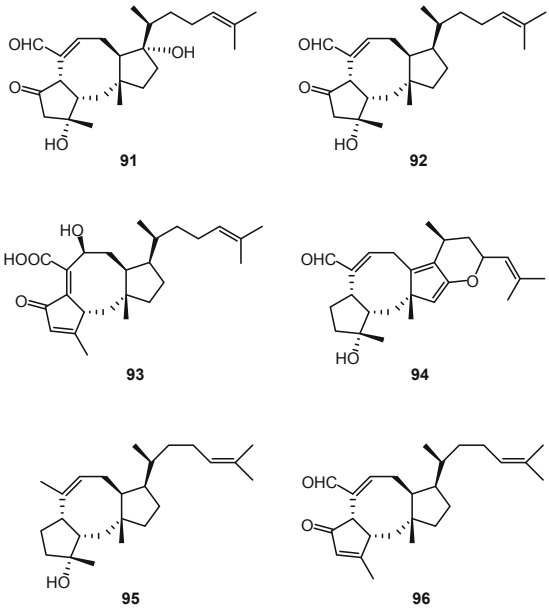


Fig. 66 Structures of **91**–**96**

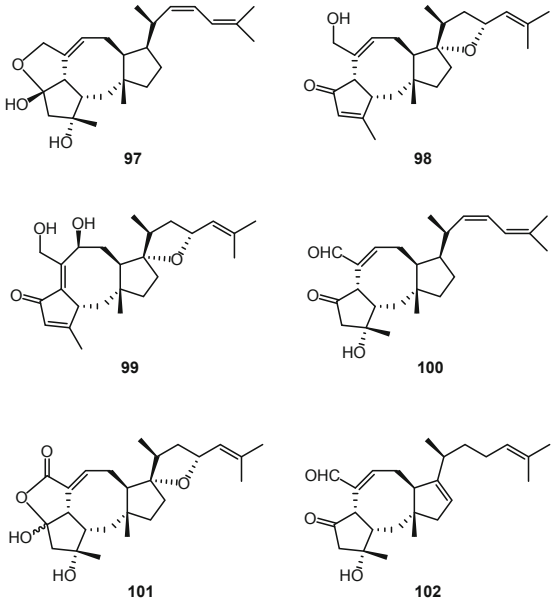


Fig. 67 Structures of **97**–**102**

ophiobolin-type sesterterpenoids, asperophiobolins A (**107**), and ten other related new sesterterpenoids were reported in 2019 (Fig. 70) [90]. They were isolated from cultures of a mangrove endophytic fungus, *Aspergillus* sp. ZJ-68.

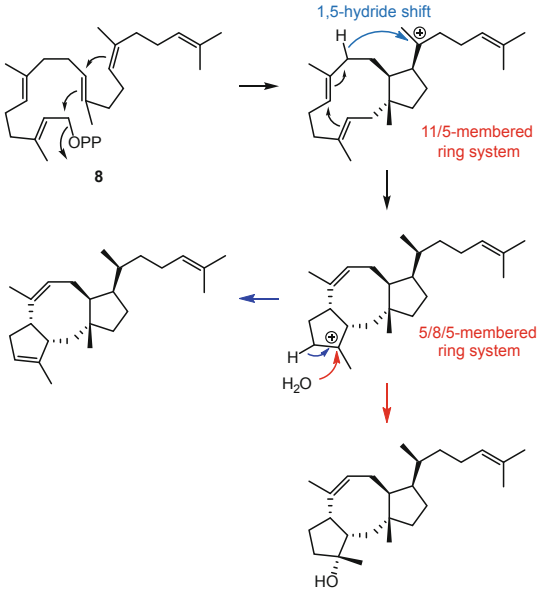


Fig. 68 Proposed cyclization mechanism for the formation of the 5/8/5-membered ring system

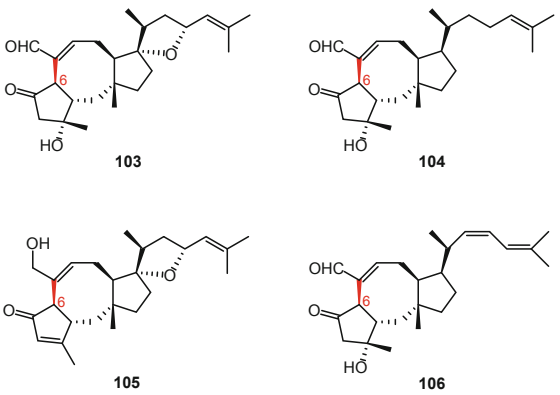


Fig. 69 Structures of **103**–**106**

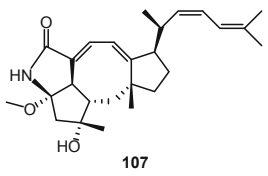


Fig. 70 Structure of asperophiobolin A (**107**)

6.1.2 5/12/5-Membered Ring System

Sesterterpenoids with 5/12/5-membered ring systems have been found in both a fungus and a plant. Variculanol (**108**) was isolated from the fungus *Aspergillus variecolor* [91], while nitinol (**109**) was reported from the plant *Gentianella nitida*, which is used in Peruvian folk medicine (Fig. 71) [92]. Compound **109** exhibits activity to enhance IL-2 gene expression in a human T cell line. A possible cyclization mechanism for the formation of the 5/12/5-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 72.

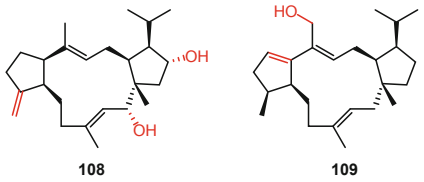


Fig. 71 Structures of variculanol (**108**) and nitinol (**109**)

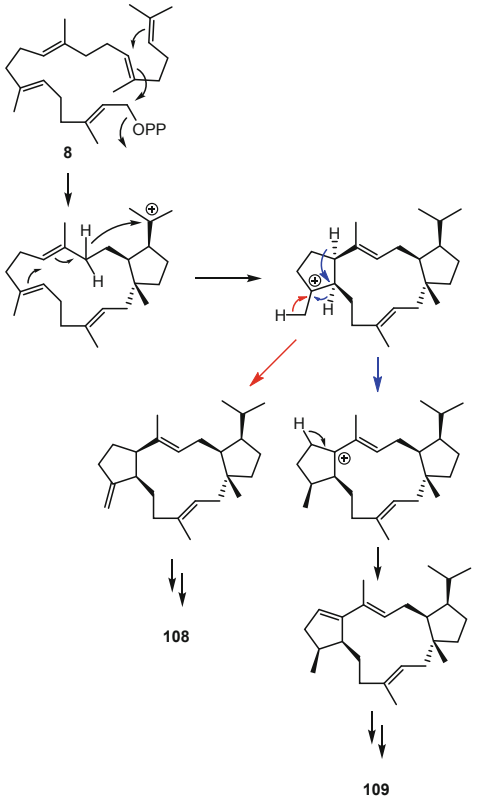


Fig. 72 Proposed cyclization mechanism for the formation of the 5/12/5-membered ring system

6.1.3 11/6/5-Membered Ring System

Two groups of sesterterpenoids possess 11/6/5-membered ring systems. One is exemplified by flocerol (**110**) and floceric acid (**111**) from the secretions of the scale insect *Ceroplastes floridensis*, an orchard pest collected in Osaka, Japan (Fig. 73) [93]. The other is exemplified by stellatic acid (**112**) (Fig. 73) [94], isolated from the metabolites of the fungus *Aspergillus stellatus*.

A proposed cyclization mechanism for the formation of the 11/6/5-membered ring systems of **110** and **111** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 74. At first, an 11/5-membered ring system is generated. Importantly, the configuration of one of the two double bonds in the 11-membered ring is (*Z*). Next, a ring expansion from a 5-membered ring to a 6-membered ring occurs, and at the

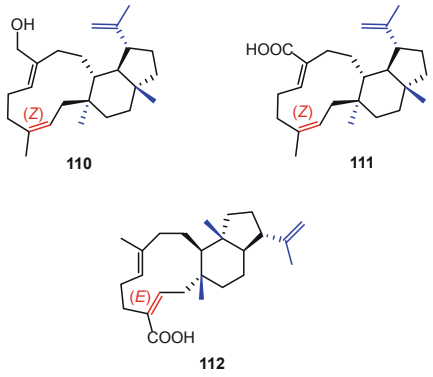


Fig. 73 Structures of **110**–**112**

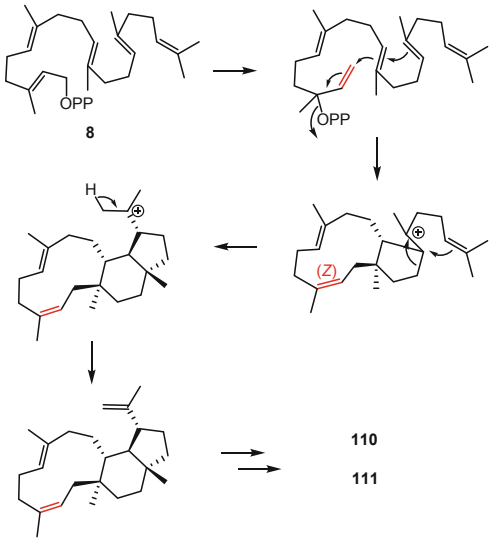


Fig. 74 Proposed cyclization mechanism for the formation of the 11/6/5-membered ring system of **110** and **111**

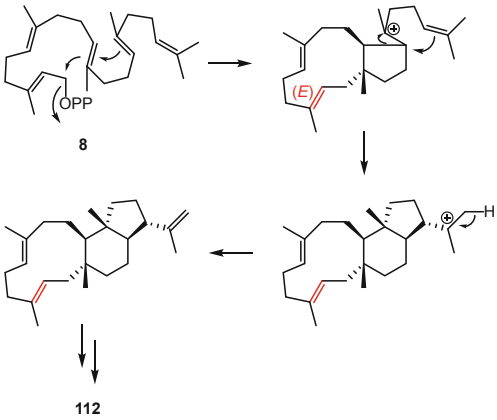


Fig. 75 Proposed cyclization mechanism for the formation of the 11/6/5-membered ring system of **112**

same time, a new 5-membered ring is generated to form the 11/6/5-membered ring system. Subsequently, deprotonation occurs to finalize the cyclization reaction.

A cyclization reaction for generating the basic carbon skeleton of **112** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 75. There are several differences between the reactions shown in Figs. 74 and 75. First, the configuration of both double bonds in the 11-membered ring is (*E*) in Fig. 75. Second, the ring expansion from the 5-membered ring to the 6-membered ring occurs in a different manner. These two differences result in the generation of two different types of 11/6/5-membered ring systems.

6.1.4 11/6/6-Membered Ring System

Floridenol (**113**) possesses an 11/6/6-membered ring (Fig. 76) [93] and was also isolated from the wax of the scale insect from which **110** and **111** were reported. The formation of the 11/6/6-membered ring system starting from geranylfarnesyl diphosphate (**8**) is illustrated in Fig. 77. The formation of **113** seems to have diverged from those of **110** and **111**.

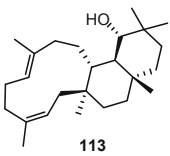


Fig. 76 Structure of floridenol (**113**)

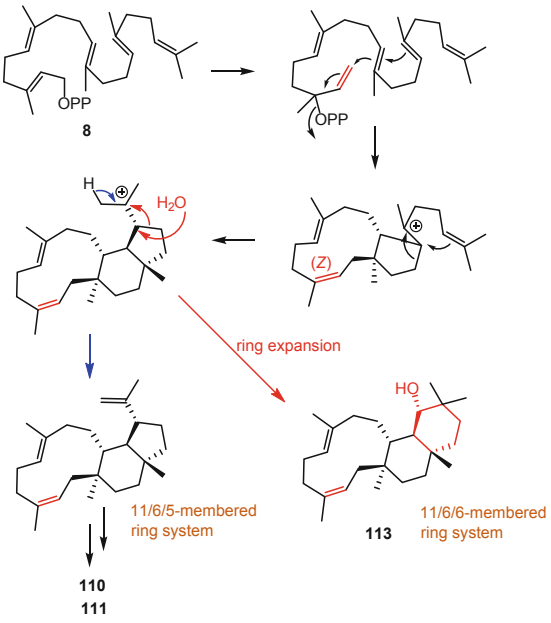


Fig. 77 Proposed cyclization mechanism for the formation of the 11/6/6-membered ring system of **113**

6.2 *Tricarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases*

6.2.1 6/6/6-Membered Ring Systems

Many tricarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases exhibit 6/6/6-membered ring systems. For example, suvanine (**114**) [95] and lintenolide F (**115**) [96] possess the 6/6/6-membered ring system (Fig. 78). Compound **114** was isolated from a sponge, *Ircinia* sp., and its chemical structure has been confirmed by the X-ray crystallography of its degradation product [95], while **115** was isolated from a Caribbean sponge, *Cacospongia* cf. *linteiformis* [96].

A proposed cyclization mechanism for the formation of the carbon skeleton of **114** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 79a, while the cyclization reaction for that of **115** is illustrated in Fig. 79b.

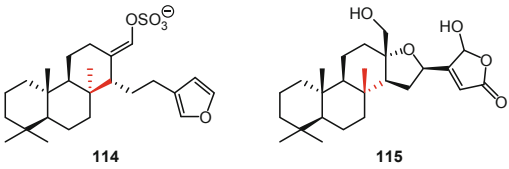


Fig. 78 Structures of suvanine (**114**) and lintenolide F (**115**)

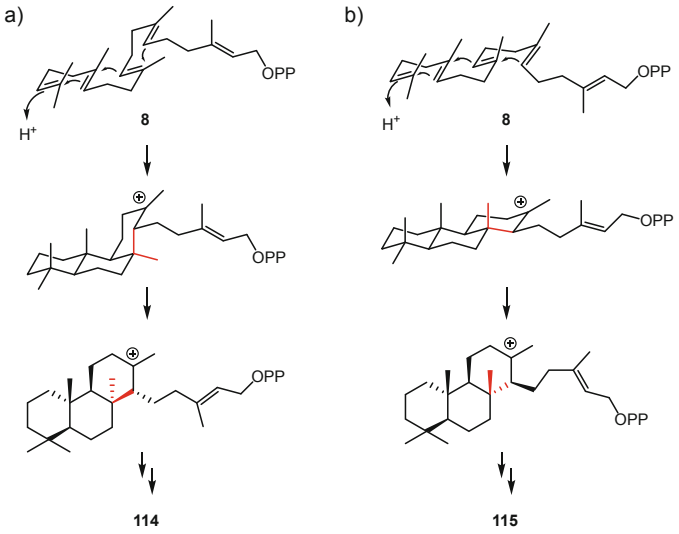


Fig. 79 Proposed cyclization mechanisms for the formation of the 6/6/6-membered ring systems of (**a**) **114** and (**b**) **115**

6.2.2 6/6/5-Membered Ring System

Hyrtiosal (**116**), which possesses a 6/6/5-membered ring system, was isolated from the Okinawan marine sponge *Hyrtios erectus*, collected at a coral reef off Ishigaki Island, Okinawa, Japan (Fig. 80) [97]. Compound **116** has been shown to inhibit the proliferation of KB cells. Its formation starting from geranylfarnesyl diphosphate (**8**) is illustrated in Fig. 80.

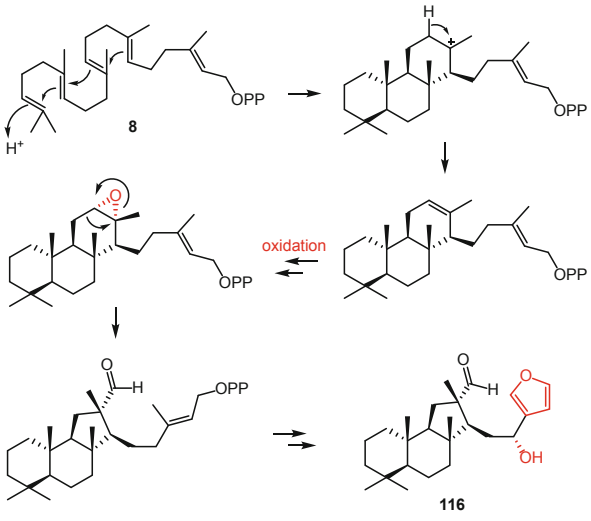


Fig. 80 Structure of hyrtiosal (**116**), and possible cyclization mechanism for the formation of the 6/6/5-membered ring system

6.2.3 3/6/6-Membered Ring System

Cacospongionolide (**117**), with a 3/6/6-membered ring system (Fig. 81) [98, 99], was isolated as a potent antitumor and ichthyotoxic agent from the sponge *Cacospongia mollior*, collected in the Northern Adriatic Sea. The chemical structure of **117** has been confirmed by the X-ray crystallography of its acetyl derivative.

A proposed cyclization mechanism for the formation of the 3/6/6-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 82. One methyl group of **8**, highlighted with a red color in Fig. 82, might be involved in the formation of the cyclopropane ring of **117**.

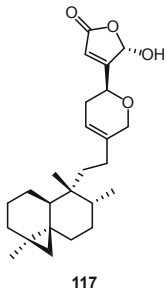


Fig. 81 Structure of cacospongionolide (**117**)

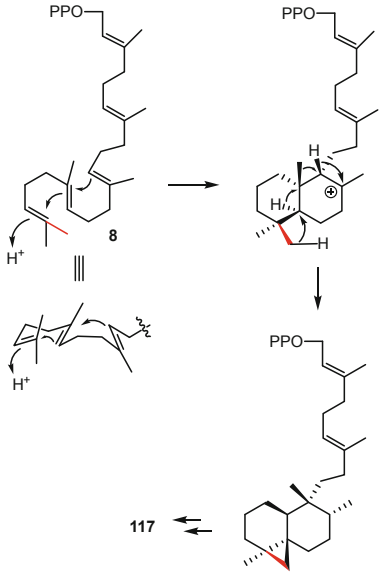


Fig. 82 Proposed cyclization mechanism for the formation of the 3/6/6-membered ring system of **117**

6.2.4 6/5/4-Membered Ring System

Lintenone (**118**) is a representative sesterterpenoid with a 6/5/4-membered ring system (Fig. 83) [100]. Compound **118** was isolated from a Caribbean sponge, *Cacospongia* cf. *linteiformis*, and possesses potent ichthyotoxicity and antifeedant properties.

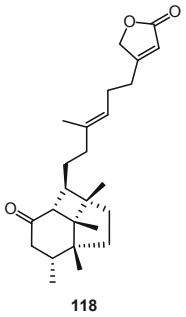


Fig. 83 Structure of lintenone (**118**)

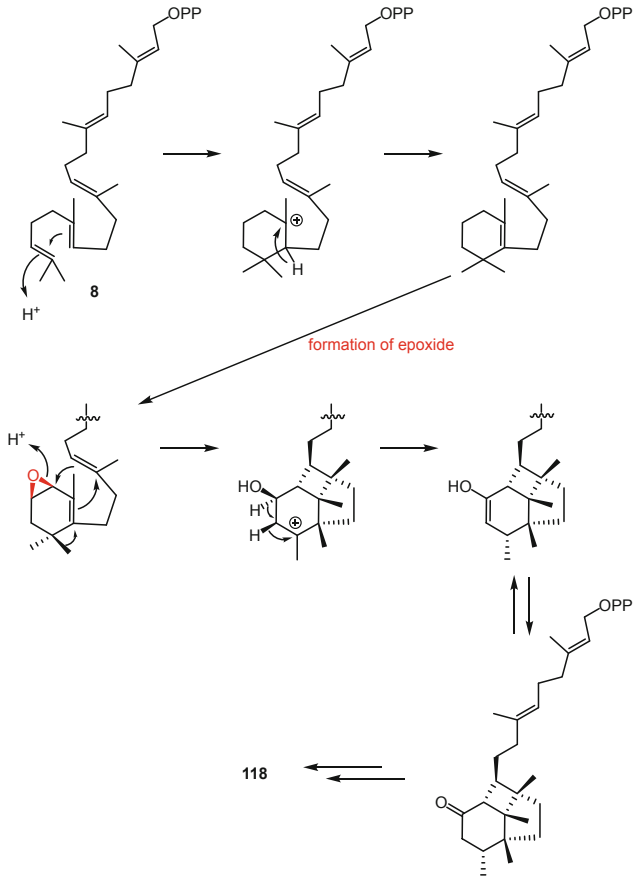


Fig. 84 Proposed cyclization mechanism for the formation of the 6/5/4-membered ring system of **118**

One possible mechanism for the formation of the 6/5/4-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 84 [3]. In this proposal, the cyclization reactions occur twice to generate the characteristic 6/5/4-

membered ring system. After a 6-membered ring is formed by the first cyclization reaction, an epoxide might be generated by tailoring enzymes. The second cyclization reaction would then be initiated by the protonation of the epoxide.

6.3 *Tricarbocyclic Sesterterpenoids Constructed by Both Type 1 and 2 Terpene Cyclases*

In some sesterterpenoids, the type 1 and 2 terpene cyclases seem to work together to form the complex basic carbon skeleton, and many such sesterterpenoids have been isolated from marine organisms [101].

One example is ansellone A (**119**), isolated from the nudibranch *Cadlina luteromarginata* and a sponge, *Phorbas* sp. (Fig. 85) [102]. Analyses revealed that **119** activates the cAMP signaling pathway. In the proposed biosynthesis pathway, at first the type 1 cyclization starting from geranylfarnesyl diphosphate (**8**) occurs, and then the type 2 cyclization reactions form the basic carbon skeleton of **119** (Fig. 85) [101].

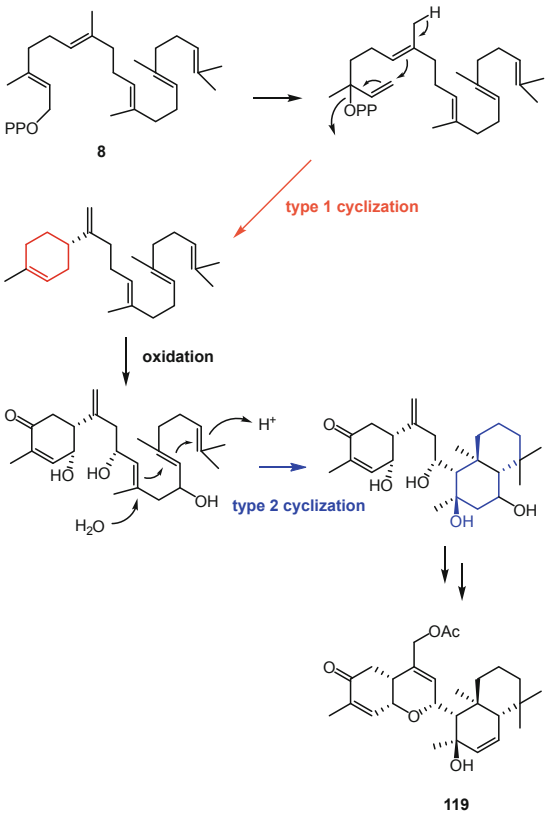


Fig. 85 Proposed biosynthesis pathway of ansellone A (**119**)

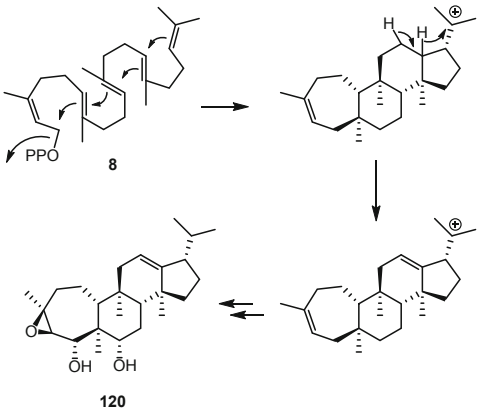


Fig. 86 Structure of aspergilloxide (**120**), and possible cyclization reaction for the formation of the 7/6/6/5-membered ring system

7 Tetracarbocyclic Sesterterpenoids

7.1 Tetracarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

7.1.1 7/6/6/5-Membered Ring System

Aspergilloxide (**120**), isolated from a fungus, *Aspergillus* sp., has a 7/6/6/5-membered ring system (Fig. 86) [103]. A possible cyclization reaction to form the basic carbon skeleton starting from geranylfarnesyl diphosphate (**8**) is also shown in Fig. 86.

7.1.2 5/8/6/6-Membered Ring System

Asperterpenol A (**121**) and a derivative have been reported from a mangrove endophytic fungus, *Aspergillus* sp. 085242 (Fig. 87) [104]. Compound **121** is an acetylcholinesterase inhibitor. Their tetracarbocyclic skeletons would be formed starting from geranylfarnesyl diphosphate (**8**) as shown in Fig. 87.

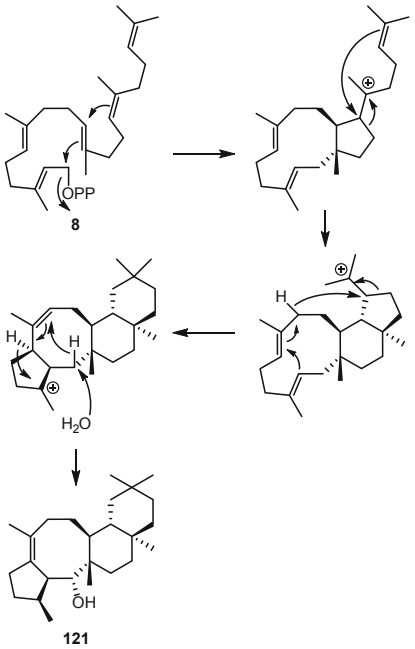


Fig. 87 Structure of asperterpenol A (**121**), and possible cyclization reaction for the formation of the 5/8/6/6-membered ring system

7.1.3 5/8/6/5-Membered Ring System

There are two types of 5/8/6/5-ring systems. One is exemplified by variecolin (**122**), which has been isolated from some fungi, including *Aspergillus variecolor* MF138 [105], *Emericella purpurea* [106], and *Emericella aurantio-brunnea* [107] (Fig. 88). Compound **122** possesses immunosuppressive activity, and the formation of its 5/8/6/5-membered ring system is shown in Fig. 88. In this reaction, an 11/6/5-membered ring system is first formed from geranylfarnesyl diphosphate (**8**), and then protonation occurs to start a second round of cyclization, and the 5/8/6/5-membered ring system is generated.

The other type of 5/8/6/5-membered ring systems is exemplified by aleurodiscal (**123**), from the corticioid fungus *Aleurodiscus mirabilis* [108], and nitidasin (**124**), from the plant *Gentianella nitida* [109, 110] (Fig. 89). The formation of the 5/8/6/5-membered ring systems of **123** and **124** is initiated by generating a 15/5-membered ring system (Fig. 89), while that of **122** starts from the generation of the 11/5-membered ring system (Fig. 88).

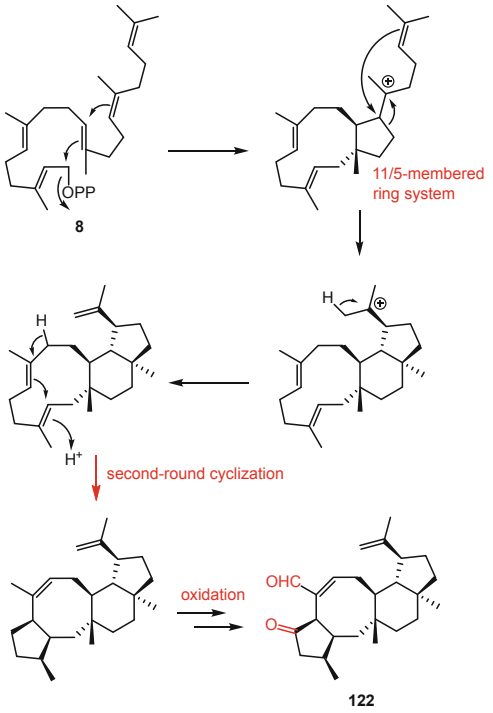


Fig. 88 Structure of variecolin (**122**), and possible cyclization reaction for the formation of the 5/8/6/5-membered ring system of **122**

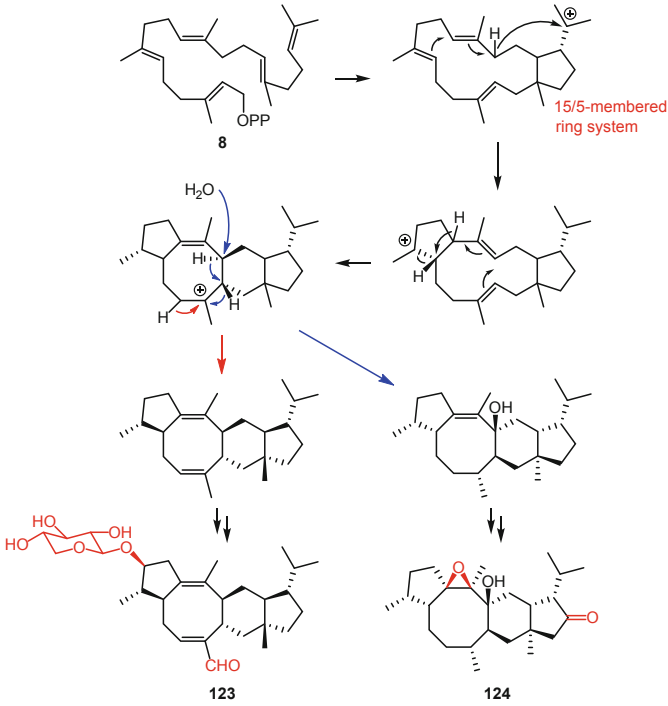


Fig. 89 Structures of aleurodiscal (**123**) and nitidasin (**124**), and possible cyclization reaction for the formation of the 5/8/6/5-membered ring systems of **123** and **124**

7.1.4 5/5/6/5- and 5/6/6/5-Membered Ring Systems

The 5/5/6/5-membered ring system is exemplified by mangicol A (**125**) [111], while the 5/6/6/5-membered ring system is found in the structure of neomangicol A (**126**) (Fig. 90) [112]. A proposed cyclization mechanism for the formation of the 5/5/6/5-membered ring systems is shown in Fig. 91. Since both **125** and **126** were isolated from the same fungus, *Fusarium heterosporum*, it is proposed that the 5/6/6/5-membered ring system of **126** is generated starting from geranylfarnesyl diphosphate (**8**) by the conversion of a precursor possessing the 5/5/6/5-membered ring system [111].

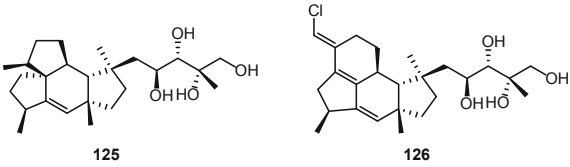


Fig. 90 Structures of mangicol A (**125**) and neomangicol A (**126**)

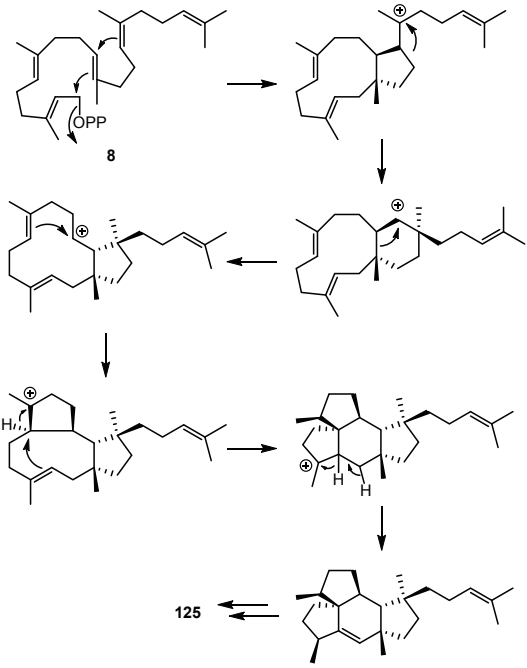


Fig. 91 Possible cyclization reaction for the formation of the 5/5/6/5-membered ring system of mangicol A (**125**)

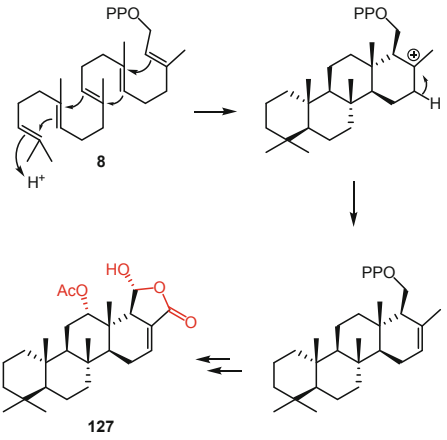


Fig. 92 Structure of scalarin (**127**), and possible cyclization reaction for the formation of the 6/6/6/6-membered ring system of **127**

7.2 *Tetracarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases*

7.2.1 6/6/6/6-Membered Ring System

Most tetracarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases exhibit a 6/6/6/6-membered ring system and are among the most common sesterterpenoids. Scalarin (**127**) was the first of this type of compound to be isolated [113, 114]. The chemical structure of **127** and a cyclization mechanism for the formation of the 6/6/6/6-membered ring system starting from geranylfarnesyl diphosphate (**8**) are shown in Fig. 92.

7.2.2 6/6/5/7-Membered Ring System

Salmahyrtisol A (**128**) [115] and hippospongide A (**129**) (Fig. 93) [116] possess a 6/6/5/7-membered ring system. Compounds **128** and **129** were isolated from the sponges *Hyrtios erecta* from the Red Sea and *Hippospongia* sp. from coral reefs off the coast of Tai-tung, Taiwan, respectively. From these two sponges, **116** with a

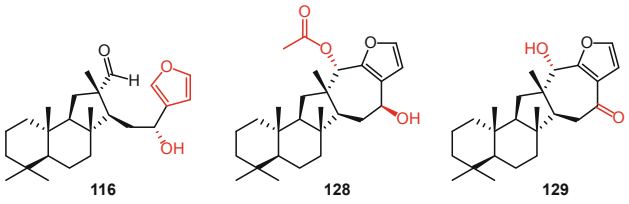


Fig. 93 Structures of **116**, **128**, and **129**. The structure of **116** is also shown in Fig. 80. Compound **116** is a possible intermediate of **128** and **129**

6/6/5-membered ring system has also been isolated. Considering the structural relationship among **128**, **129**, and **116**, **116** might be a biosynthetic intermediate of **128** and **129**.

8 Pentacarbocyclic Sesterterpenoids

Pentacarbocyclic sesterterpenoids are rare, and the complexity of their structures is quite high. In particular, the type 1 terpene cyclases are known to generate fascinating pentacarbocyclic skeletons.

8.1 Pentacarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

8.1.1 5/6/5/6/5-Membered Ring System

Peniroquesine A (**130**) and its derivatives, which possess 5/6/5/6/5-membered ring systems, have been isolated from the fungus *Penicillium roqueforti* YJ-14 (Fig. 94) [117]. Compound **130** is a potent inhibitor of nitric oxide production in

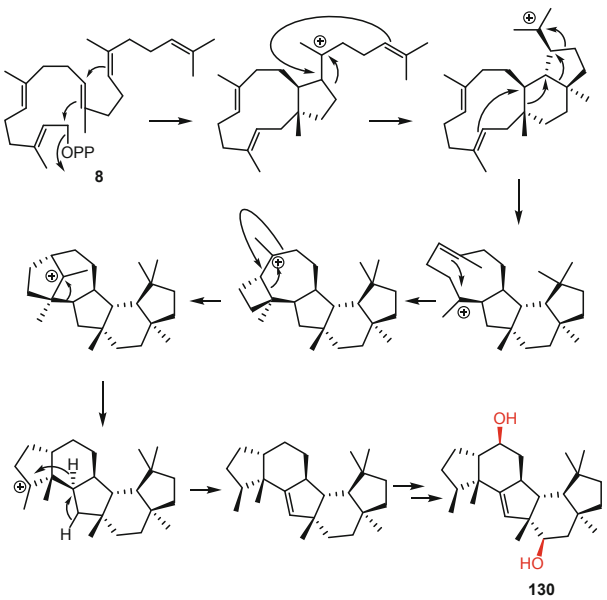


Fig. 94 Structure of peniroquesine A (**130**), and possible cyclization reaction for the formation of the 5/6/5/6/5-membered ring system

LPS-activated RAW264.7 macrophages. During the proposed cyclization reaction for the formation of the 5/6/5/6/5-membered ring system starting from geranylfarnesyl diphosphate (**8**), several complex rearrangements could occur (Fig. 94).

8.1.2 5/7/3/6/5-Membered Ring System

Asperterpenoid A (**131**), with a 5/7/3/6/5-membered ring system, has been isolated from a mangrove endophytic fungus, *Aspergillus* sp. 16-5c (Fig. 95) [118]. Compound **131** is a strong inhibitor of *Mycobacterium tuberculosis* protein tyrosine phosphatase B. Its formation from geranylfarnesyl diphosphate (**8**) is illustrated in Fig. 95.

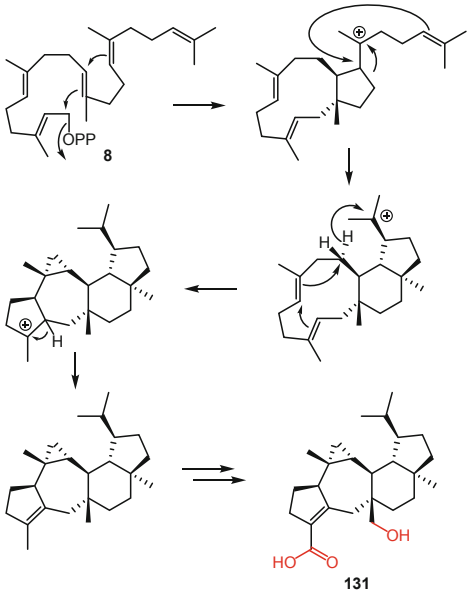


Fig. 95 Structure of asperterpenoid A (**131**), and possible cyclization reaction for the formation of the 5/7/3/6/5-membered ring system of **131**

8.1.3 5/3/7/6/5- and 5/4/7/6/5-Membered Ring Systems

Aspterpenacid A (**132**) [119] has a 5/3/7/6/5-membered ring system, while astellatol (**133**) [120] possesses a 5/4/7/6/5-membered ring system (Fig. 96). Compounds **132** and **133** were isolated from the fungi *Aspergillus terreus* H010 and *Aspergillus variecolor*, respectively. Proposed pathways for the formation of the 5/4/7/6/5- and 5/3/7/6/5-membered ring systems starting from geranylfarnesyl diphosphate (**8**) are also shown in Fig. 96.

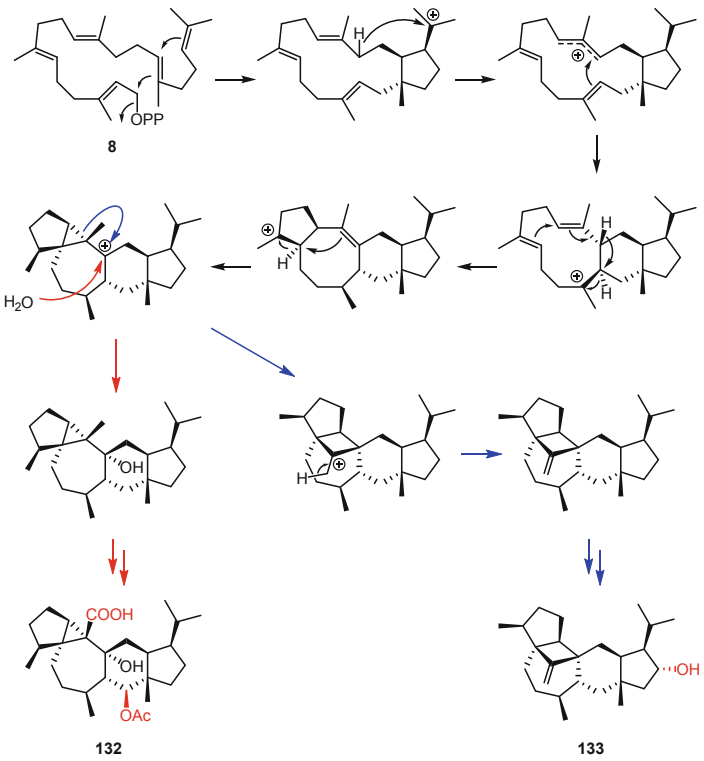


Fig. 96 Structures of **132** and **133**, and possible cyclization reactions for the formation of the basic carbon skeletons of **132** and **133**

8.1.4 5/5/5/6/5-Membered Ring System

Retigeranic acid A (**134**) [121, 122], retigeran-11-ol (**135**) [123], and 4-hydroxyretigeran-11-ol (**136**) [123] possess 5/5/5/6/5-membered ring systems, which originate from geranylfarnesyl diphosphate (**8**) (Fig. 97). Compounds **135** and **136** were isolated from the lichen *Leprocaulon microscopicum*. Compound **134** was isolated from lichens of the *Lobaria retigera* group (Plate 2), and **134** reportedly exists as a mixture with retigeranic acid B (**137**), an epimer of **134**, in Nature (Fig. 98) [124].

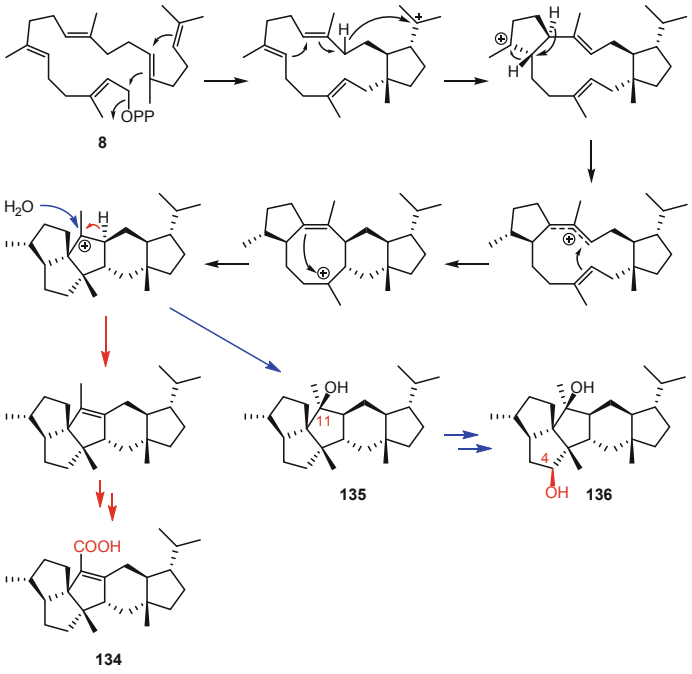


Fig. 97 Structures of **134**–**136**, and possible cyclization reactions for the formation of the basic carbon skeleton of **134**–**136**

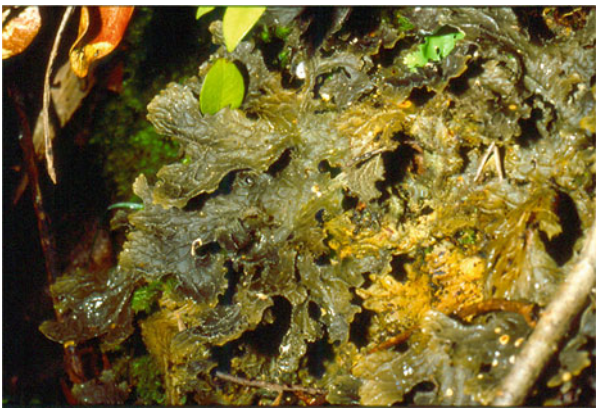
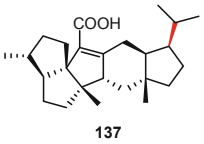


Plate 2 *Lobaria retigera* (Bory) Trevisan, Maungataniwha Ecological District. Photograph courtesy D. J. Galloway, CCBY Auckland Museum, Creative Commons 4.0



137

Fig. 98 Structure of retigeranic acid B (**137**)

9 Hexacarbocyclic Sesterterpenoids

Niduterpenoid A (**138**) and niduterpenoid B (**139**) possess hexacarbocyclic 5/5/5/5/3/5-membered ring systems (Fig. 99) [125]. Both compounds were isolated from *Aspergillus nidulans*. Compound **138** lacks cytotoxicity, but abrogates 17-estradiol-induced cell proliferation. The cyclization reaction for the formation of the hexacarbocyclic system starting from geranylfarnesyl diphosphate (**8**) is quite complicated, as shown in Fig. 100. After the formation of the intermediate **A**, with a 5/5/5/6/5-membered ring system, further rearrangements occur to form the hexacarbocyclic structure. Notably, the 5/5/5/6/5-membered ring system of the intermediate **A** is distinct from those of **134**–**137** (Figs. 97 and 98).

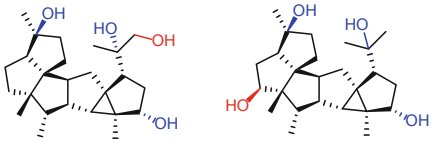


Fig. 99 Structures of niduterpenoid A (**138**) and niduterpenoid B (**139**)

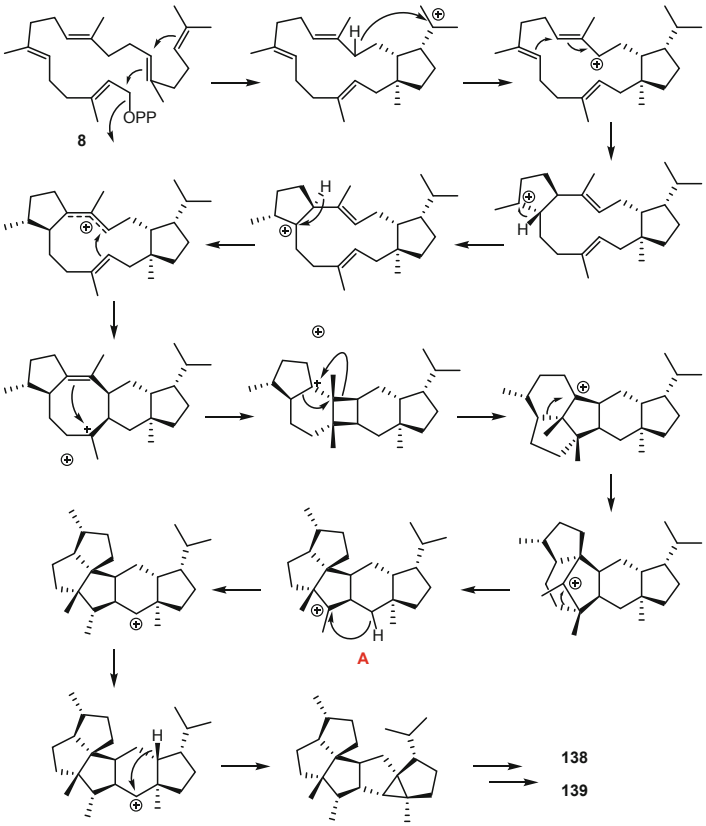


Fig. 100 Possible cyclization reactions for the formation of the hexacarbocyclic skeleton of **138** and **139**. The intermediate **A** possesses a 5/5/5/6/5-membered ring system, which is distinct from that of **134**–**137**

10 Sesterterpenoids Found by a Genome-Based Approach

Recently, a genome-based approach to the search for novel sesterterpenoids has been reported [126, 127]. As in a typical search for new natural products, researchers extract mixtures of compounds from natural sources and search for new compounds in the crude extracts. However, in the genome-based approach, investigators extract the genomic DNA from such natural resources and perform genome sequencing. From the obtained genomic data, a search is made for genes that could be involved in sesterterpenoid biosynthesis. These genes are expressed inducibly utilizing genetic engineering techniques. If the expressed genes are responsible for the formation of unknown sesterterpenoids, then these new sesterterpenoids can be isolated. By utilizing this approach, several new sesterterpenoids have been identified from fungi, plants, and bacteria.

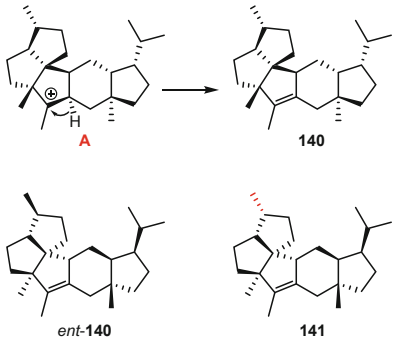


Fig. 101 Structures of quiannulatene (**140**), *ent*-**140**, and boleracene (**141**), and formation of **140**. The formation of intermediate **A** is shown in Fig. 100

10.1 5/5/5/6/5-Membered Ring System

A genome-based approach generated quiannulatene (**140**), with a 5/5/5/6/5-membered ring system (Fig. 101) [128]. The gene responsible for the production of **140** was found from the genomic data of the fungus *Emericella variecolor* NBRC 32302. Notably, the 5/5/5/6/5-membered ring system of **140** is different from those of **134**–**137** (Figs. 97 and 98). It is proposed that **140** is generated by the deprotonation of the intermediate **A** in Fig. 100. The detailed cyclization mechanism leading to the formation of **140** has been investigated by both computational approaches [129, 130] and isotope labeling experiments [128]. From the plant *Arabidopsis thaliana*, a gene for the biosynthesis of *ent*-**140** has also been found [131]. In addition, from the plant *Brassica oleracea*, a gene for the production of boleracene (**141**) has been identified (Fig. 101) [131]. The stereochemistry of **141** is different from those of **140** and *ent*-**140**.

10.2 5/8/6/5-Membered Ring System

Compound Bm2 (**142**) [132] and sesterfisherol (**143**), with a 5/8/6/5-membered ring system, were also discovered by the genome-based approach (Fig. 102) [133, 134]. The genes responsible for the production of **142** and **143** were found in the genomes of the fungi *Bipolaris maydis* ATCC48331 and *Neosartorya fischeri*, respectively. In fact, **123** and **124**, which were mentioned in Sect. 7.1.3, also possess similar 5/8/6/5-membered ring systems (Figs. 89 and 102). However, the stereochemistry and positions of the double bonds of **142**, **143**, **123**, and **124** are different from each other. A possible cyclization reaction starting from geranylfarnesyl diphosphate (**8**) leading to the formation of **142** and **143** is shown in Fig. 103.

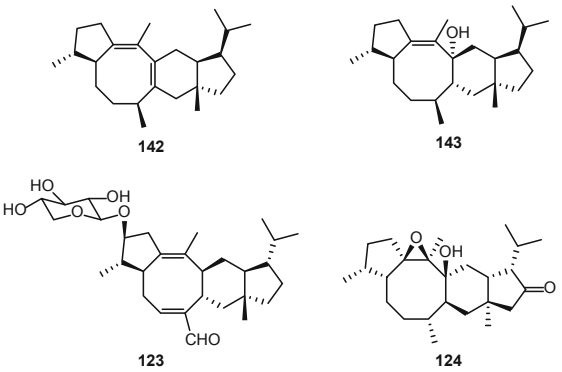


Fig. 102 Structures of **142**, **143**, and **123** and **124**

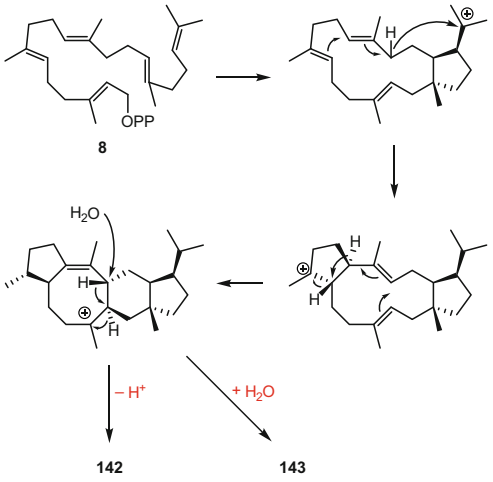


Fig. 103 Formation of **142** and **143**

10.3 11/6/5-Membered Ring Systems

(+)-Thalianatriene (**144**), which is also known as (+)-arathanatriene, possesses an 11/6/5-membered ring system (Fig. 104) [131, 135]. The gene encoding the synthase of **144** has been identified in the *Arabidopsis thaliana* genome. In addition, a gene involved in the production of a related compound, caprutriene (**145**), has been found in the genome of the plant *Capsella rubella* [131].

In Sect. 6.1.3, two kinds of 11/6/5-membered ring systems were introduced. However, the 11/6/5-membered ring systems of **144** and **145** are different from the two known 11/6/5-membered ring systems. The formation of **144** and **145** from geranylfarnesyl diphosphate (**8**) starts from the generation of a 15/5-membered ring system (Fig. 105), while the formation of the other two 11/6/5-membered ring systems is initiated by the formation of the 11/5-membered ring system (Figs. 74 and 75).

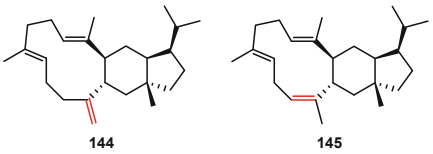


Fig. 104 Structures of (+)-thalianatriene (**144**) and caprutriene (**145**)

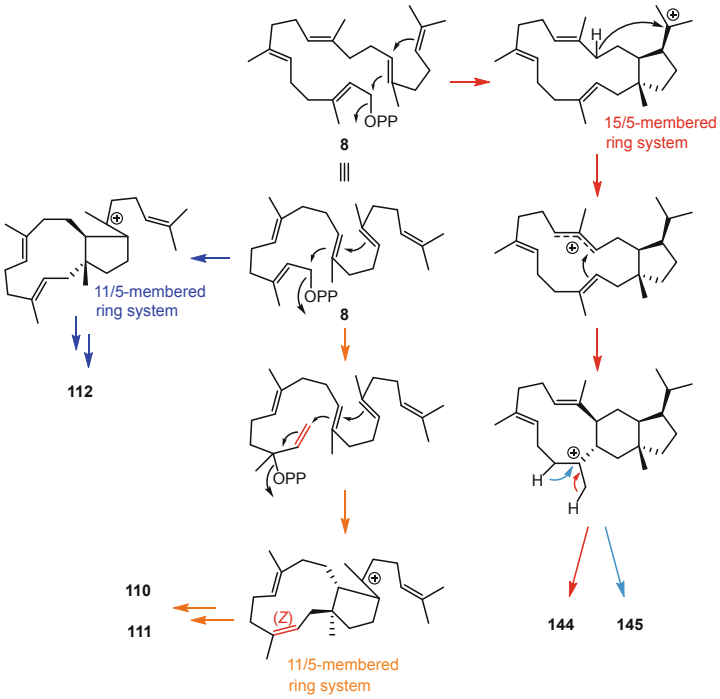


Fig. 105 Formation of **144** and **145**, and comparison with those of **110**–**112**

10.4 6/6/7/5- and 6/11/5-Membered Ring Systems

A sesterterpene synthase, identified from the genetic data of the plant *Capsella rubella*, was found to produce (−)-caprudiene A (**146**), (−)-caprutriene B (**147**), and (+)-caprutriene C (**148**) (Fig. 106) [136]. Compound **146** possesses a 6/6/7/5-membered ring system, while **147** and **148** have 6/11/5-membered ring systems. In addition to **146**–**148**, this enzyme also produces (+)-brassitetraene A (**149**) and (+)-brassitetraene B (**150**) with 15/5-membered ring systems. In fact, **149** and **150** are considered as intermediates of **146**–**148**. Thus, after the formation of **149** and **150** starting from geranylfarnesyl diphosphate (**8**), a second round of cyclization,

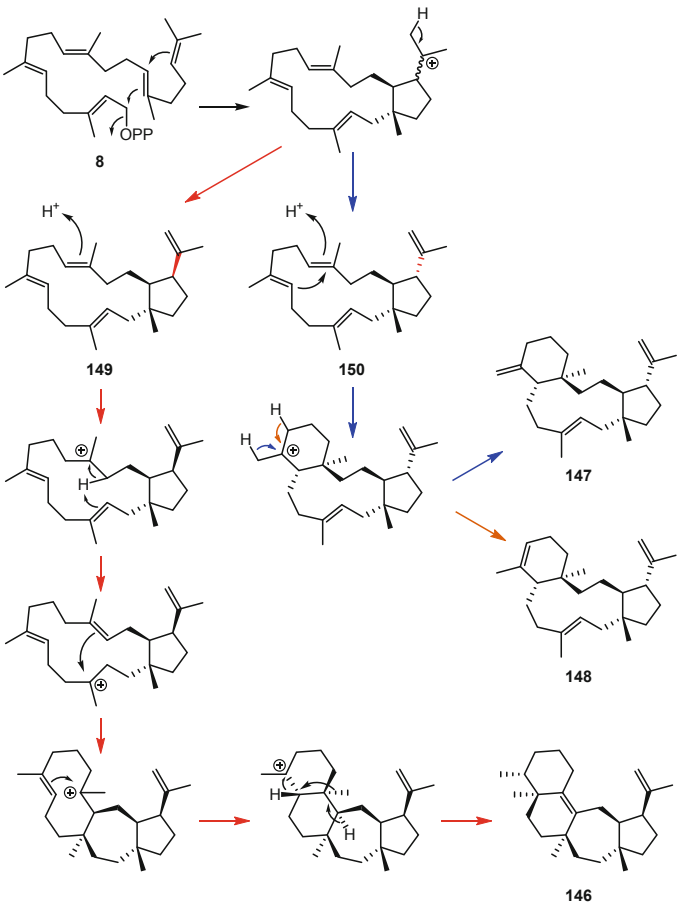


Fig. 106 Structures and formation of **146–150**

initiated by the protonation of **149** and **150**, occurs to form **146–148**. Other genes for the production of related sesterterpenoids with a 6/6/7/5-membered ring system have also been found in the genomes of the plants *Arabidopsis thaliana* and *Brassica rapa* [136].

10.5 5/4/5- and 4/5/5-Membered Ring Systems

A terpene cyclase designated as "spata-13,17-diene synthase" was found in the marine bacterium *Streptomyces xinghaiensis* by the genome-based approach [137]. This enzyme has the potential to produce prenylspata-13,17-diene (**151**), geranylkelsoene (**152**), and other C_{15} sesqui- and C_{20} di-terpenoids. Compound

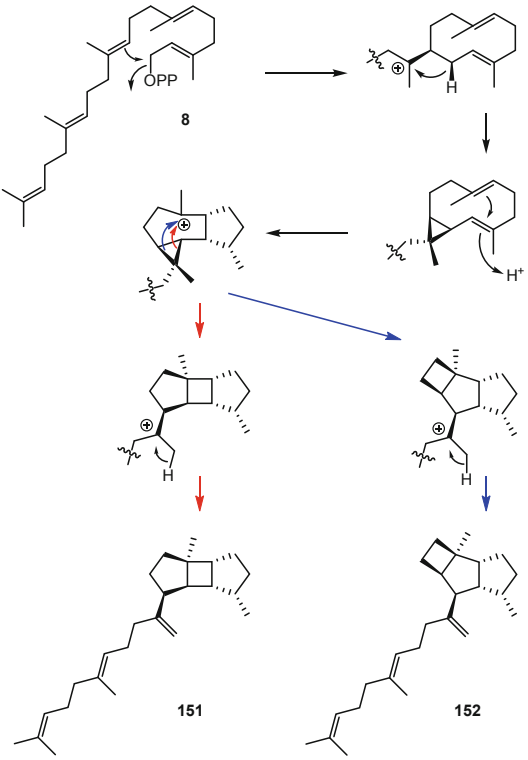


Fig. 107 Structures and formation of prenylspata-13,17-diene (**151**) and geranylkelsoene (**152**)

151 possesses a 5/4/5-membered ring system, while **152** has a 4/5/5-membered ring system (Fig. 107).

10.6 6/8/6/5-Membered Ring System

Astellifadiene (**153**) is a sesterterpenoid with a 6/8/6/5-membered ring system (Fig. 108) [138]. The formation of the 6/8/6/5-membered ring system from geranylfarnesyl diphosphate (**8**) requires two cyclization reactions. In the first cyclization, an 11/6/5-membered ring is generated, and then deprotonation finalizes the reaction. Next, protonation occurs to initiate the second round of cyclization, and the basic carbon skeleton of **153** is formed. The gene for the biosynthesis of **153** has been found in the genome of the fungus *Emericella variecolor* NBRC 32302.

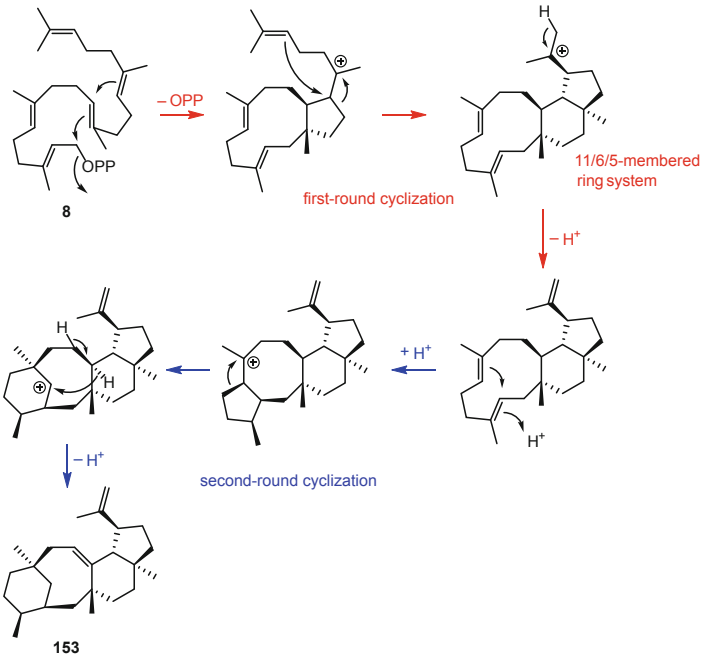


Fig. 108 Structure and formation of astellifadiene (**153**)

10.7 5/12/5-Membered Ring System

Sesterbrasiliatriene (**1**) [9], betaestacin I (**154**) [132], and Bm1 (**155**) [132] have 5/12/5-membered ring systems (Fig. 109) and were found by the genome-based

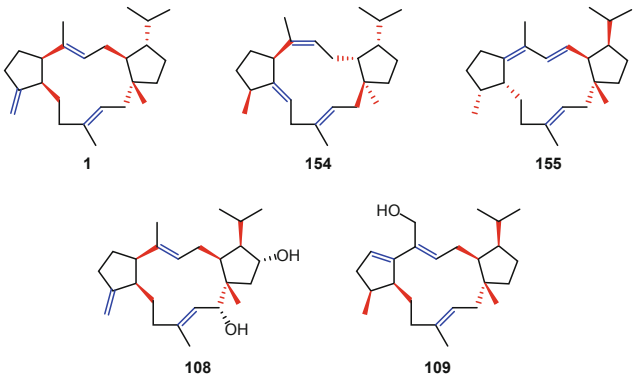


Fig. 109 Structures of **1**, **154**, **155**, **108**, and **109**. Compounds **1**, **154**, and **155** were discovered by a genome-based approach. Structures of **108** and **109** are also shown in Fig. 71

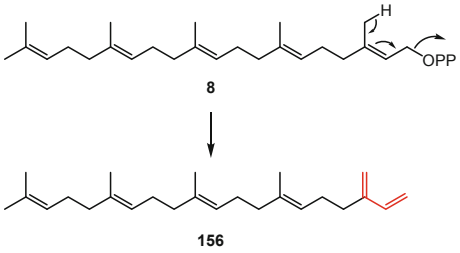


Fig. 110 Structure and formation of β-geranylfarnesene (**156**)

approach. The genes responsible for the production of **1**, **154**, and **155** are from the fungi *Penicillium brasilianum* NBRC 6234, *Phoma betae* PS-13, and *Bipolaris maydis* ATCC48331, respectively. Of these, **108** and **109** with 5/12/5-membered ring systems were isolated from Nature, as mentioned in Sect. 6.1.2. However, the configurations and positions of the double bonds of **1**, **154**, **155**, **108**, and **109** are different from each other.

10.8 Genes for the Formation of a Linear Sesterterpenoid

Genes for the biosynthesis of linear sesterterpenoids have also been found. For example, a gene from the bacterium *Bacillus clausii* encodes an enzyme that can transform geranylfarnesyl diphosphate (**8**) into a linear sesterterpene, hydrocarbon β-geranylfarnesene (**156**) (Fig. 110) [139].

10.9 Genes Encoding a Membrane-Bound Sesterterpene Cyclase

The typical terpene cyclases, which catalyze type 1 terpene cyclization reactions, are soluble proteins. However, there are also membrane-bound terpene cyclases for type 1 cyclization reactions, and they are referred to as UbiA-type terpene cyclases. A gene encoding a UbiA-type terpene cyclase involved in the biosynthesis of sesterterpenoids has been found in the bacterium *Streptomyces somaliensis* [140]. This enzyme can convert geranylfarnesyl diphosphate (**8**) to somaliensenes A (**157**) and B (**158**) (Fig. 111).

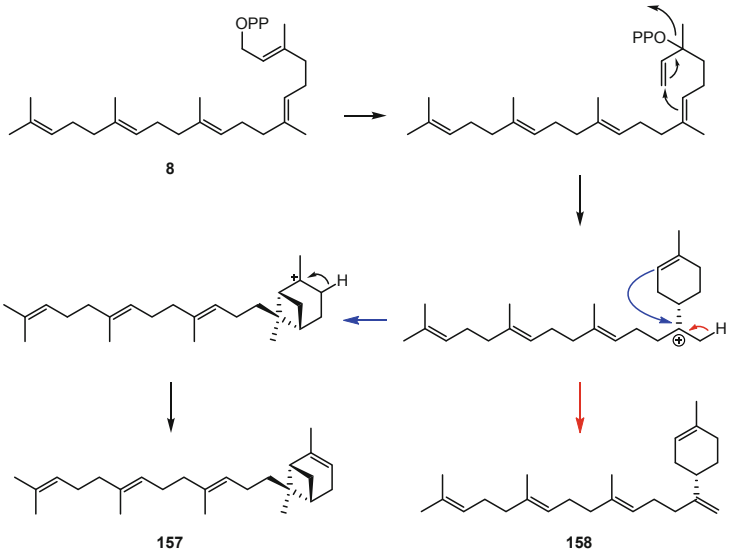


Fig. 111 Structures and formation of somaliensenes A (**157**) and B (**158**)

10.10 A Sesterterpenoid Produced by an Artificially Engineered Enzyme

In many cases, fungal sesterterpene synthases (C_{25}) and diterpene synthases (C_{20}) exist as chimeric enzymes, composed of a terpene cyclase and a prenyltransferase [126, 127]. In other words, the terpene cyclase and the prenyltransferase are linked together (Fig. 112). The reactions catalyzed by these two enzymes are shown in Figs. 5–7. The fusion of these two enzymes is considered to provide a catalytic

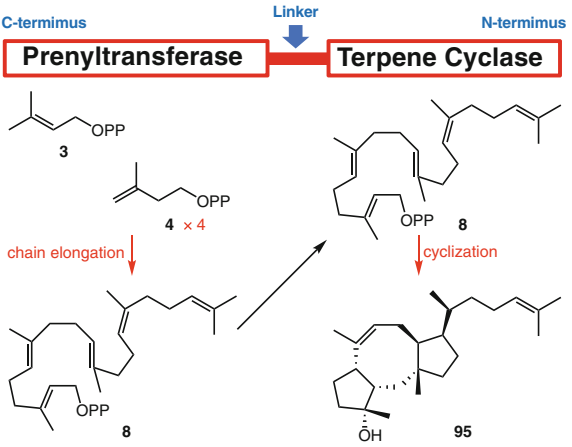


Fig. 112 Constitution of the fungal chimeric diterpene synthase and sesterterpene synthase. The chimeric terpene synthase consists of two domains. The C-terminal domain possesses the prenyltransferase activity, while the N-terminal domain exhibits the terpene cyclase activity

advantage, because the physical proximity of the active sites of the two enzymes can enhance product flux [141, 142]. Polyprenyl diphosphates **7** and **8**, which are produced by the prenyltransferase, could be efficiently moved into the active site of the terpene cyclase if these enzymes are linked together, namely, exist near each other.

The prenyltransferase domain of the fungal diterpene synthase (C_{20}) might produce mainly the (C_{20}) polyprenyl diphosphate **7**, while that of sesterterpene synthase might yield primarily the (C_{25}) version **8**. Therefore, even when the terpene cyclase domain of a fungal diterpene cyclase has the potential to cyclize not only **7** but also **8**, the major products of the enzyme should be diterpenes (C_{20}), because the prenyltransferase domain supplies principally (C_{20}) **7**, not (C_{25}) **8**, to the terpene cyclase domain.

Accordingly, a protein engineering experiment, in which the prenyltransferase domain of a fungal diterpene synthase is exchanged with that of a sesterterpene synthase, could enable the terpene cyclase domain of the diterpene synthase to produce sesterterpenoids, since the prenyltransferase domain of the sesterterpene synthases can supply a sufficient amount of **8**.

A protein engineering experiment based on this hypothesis has been reported [143]. This study utilized a fungal diterpene cyclase, designated as EvVS. The wild-type EvVS produces only C_{20} variediene (**159**). However, after its prenyltransferase domain was exchanged artificially with that of a sesterterpene synthase by genetic engineering, this enzyme produced a sesterterpene, (2*E*)-α-cericerene (**160**) (Figs. 113 and 114). A similar approach using a different fungal diterpene synthase has also been reported [144].

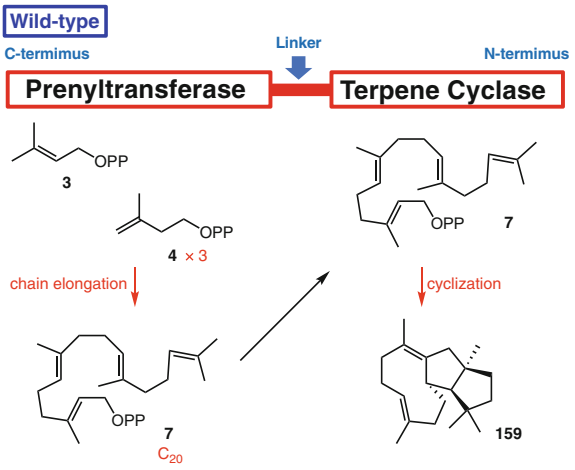


Fig. 113 Reaction catalyzed by the wild-type fungal diterpene synthase (EvVS), which produces **159**. Since the prenyltransferase domain of this enzyme mainly produces **7**, the terpene cyclase domain primarily accepts **7**. Thus, only the cyclized diterpene **159** is produced by the wild-type EvVS

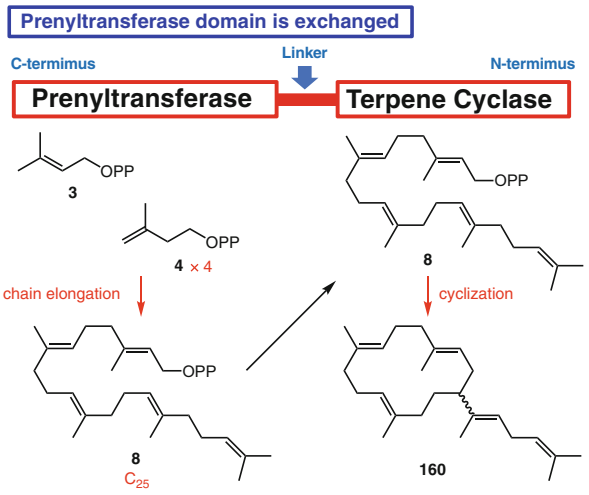


Fig. 114 Reaction catalyzed by the engineered EvVS. The prenyltransferase domain of EvVS was exchanged with that of a sesterterpene synthase. In the case of the engineered EvVS, **8** is primarily supplied to the terpene cyclase domain. Therefore, the terpene cyclase domain starts to accept **8** and produces the cyclized sesterterpene **160**

10.11 Tailoring Enzymes for the Derivatization of Sesterterpenoids

In addition to the enzymes responsible for the formation of the basic carbon skeletons of the sesterterpenoids, modification enzymes, which can attach a functional group to these compounds, have been found by the genome-based approach. For example, from the fungus *Talaromyces wortmannii* ATCC 26942, a cytochrome P450, which can convert **131** to a new sesterterpenoid, asperterpenoid C (**161**), has been identified (Fig. 115) [145]. The cytochrome P450 catalyzes an oxidation reaction and attaches a hydroxy group to **131**.

Another example refers to the tailoring enzymes for the derivatization of **154** [146]. Analyses revealed that three cytochrome P450s, from the fungi *Phoma betae* and *Colletotrichum orbiculare*, are involved in the conversion of **154** into the new sesterterpenoids **162**–**168** (Fig. 116).

In addition, cytochrome P450s for the formation of new sesterterpenoids, quiannulatic acid (**169**) and sesterfisheric acid (**170**), have also been identified (Fig. 117) [128, 133].

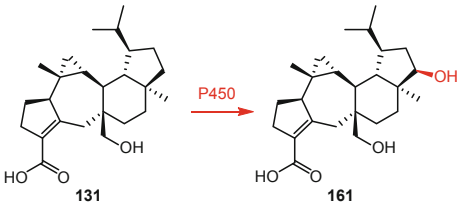


Fig. 115 Structure and formation of asperterpenoid C (**161**). The structure of **131** is also shown in Fig. 95

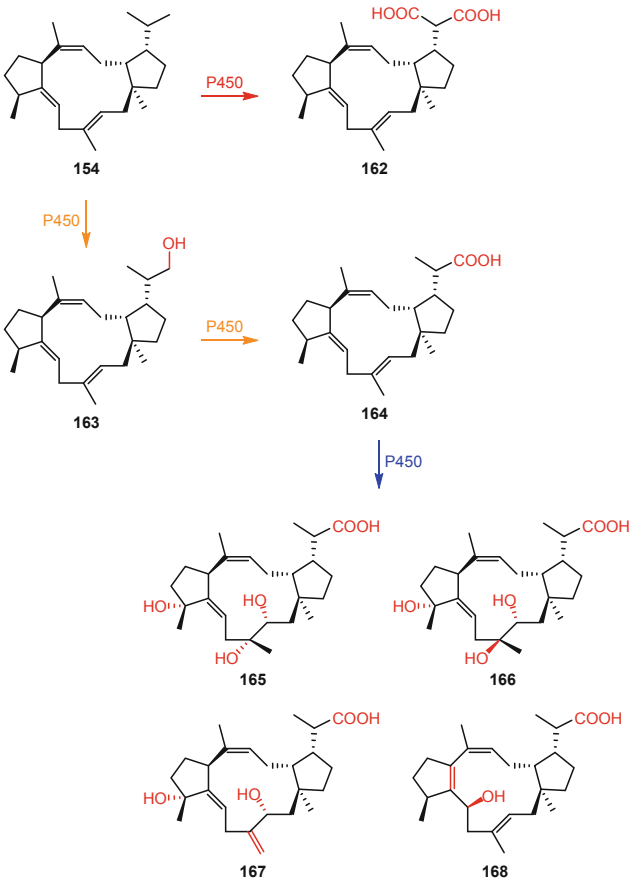


Fig. 116 Structures and formation of **162–168**. Reactions catalyzed by different enzymes are shown by arrows with different colors. The structure of **154** is also shown in Fig. 109

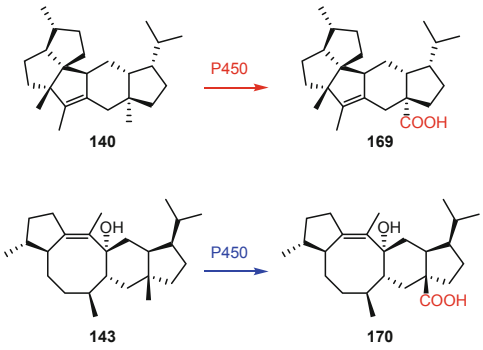


Fig. 117 Structures and formation of **169** and **170**. The structures of **140** and **143** are also shown in Figs. 101 and 102

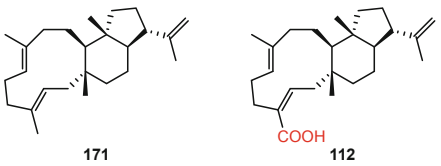


Fig. 118 Structures of **171** and **112**. The structure of **112** is also shown in Fig. 73

10.12 Genes for the Biosynthesis of Known Sesterterpenoids or Their Precursors

The genome-based approach has also identified the genes involved in the biosynthesis of known sesterterpenoids. Herein, such examples are introduced. Importantly, in many cases, the genome-based approach enables the isolation of the biosynthetic precursors of the known sesterterpenoids, which have never been isolated from Nature.

10.12.1 Stellatic Acid

The gene for the production of stellata-2,6,19-triene (**171**) was found in the genome from the fungus *Emericella variecolor* NBRC 32302 (Fig. 118) [147]. In fact, **170** is a biosynthetic precursor of stellatic acid (**112**) and has not been reported from natural sources. Moreover, a cytochrome P450 for the conversion of **170** into **112** has also been identified from the same fungal strain.

10.12.2 Ophiobolin F

A gene encoding a sesterterpene synthase for the production of ophiobolin F (**95**) has been found in the genome from the fungus *Aspergillus clavatus* (Figs. 66 and 112) [148]. Indeed, this enzyme is the first example of a sesterterpene synthase.

The gene for the biosynthesis of **95** has also been found in the genome from the fungus *Aspergillus ustus* 094102, and the genes responsible for the accumulation of **95** in this fungus have been investigated in detail [149, 150]. Based on this information, the production of **95** in *Escherichia coli* has been accomplished [151].

10.12.3 Mangicol A

The gene encoding a sesterterpene synthase for the production of mangicdiene (**172**) has been found in the genome from the fungus *Fusarium graminearum* J1-012 (Fig. 119) [152]. Compound **172** is considered to be a biosynthetic intermediate of mangicol A (**125**).

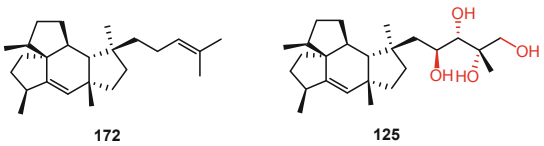


Fig. 119 Structures of **172** and **125**. The structure of **125** is also shown in Fig. 90

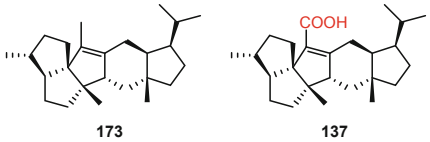


Fig. 120 Structures of **173** and **137**. The structure of **137** is also shown in Fig. 98

10.12.4 Retigeranic Acid B

The gene for the biosynthesis of retigeranin B (**173**) has been found in the genome from the plant *Arabidopsis thaliana* (Fig. 120) [131, 135]. Compound **173** is considered to be a biosynthetic intermediate of retigeranic acid B (**137**).

10.12.5 Astellatol

The gene for the production of astellatene (**174**) has been identified in the genome from the plant *Arabidopsis thaliana* (Fig. 121) [131]. Compound **174** might be a precursor of astellatol (**133**). Incidentally, the genes for the production of **174** (Fig. 121) and *ent*-**140** (Fig. 101) reportedly play an important role in the root microbiota assembly of the plant [153]. This is one of the few examples of an investigation into the biological roles of sesterterpenoids.

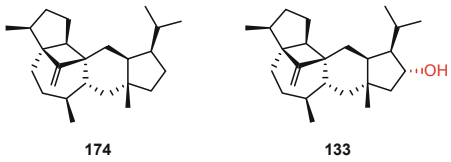


Fig. 121 Structures of **174** and **133**. The structure of **133** is also shown in Fig. 96

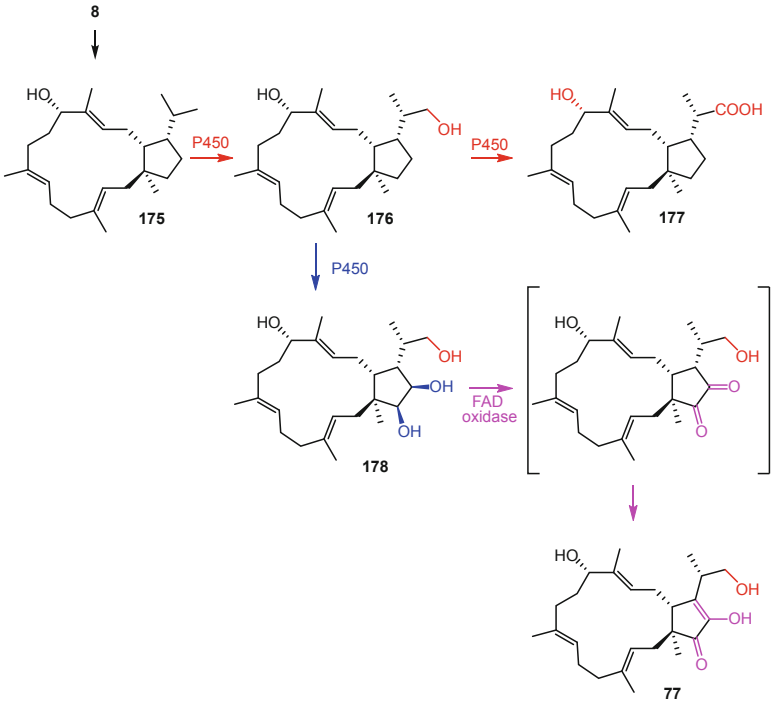


Fig. 122 Structures and formation of **175**–**178**, and **77**. The structure of **77** is also shown in Fig. 53

10.12.6 Terpestacin

Four genes for the biosynthesis of terpestacin (**77**) have been identified in the genome from the fungus *Bipolaris maydis* [132, 154]. One of the four genes encodes a sesterterpene synthase that produces **175**. The other three genes encode oxidases, two cytochrome P450s, and a single flavin-dependent oxidase. These oxidases could convert **175** into **176**, **177**, **178**, and **77** (Fig. 122).

11 Conclusions

This contribution provides an overview of the chemical structures of sesterterpenoids. Even though only relatively few sesterterpenoids are known, their structures are quite fascinating. In particular, the complexity of polycarbocyclic sesterterpenoids is quite high. There are many stereocenters in their structures, and their stereochemistry is well controlled during the cyclization reactions leading to the formation of their basic carbon skeletons. Moreover, many sesterterpenoids are known as bioactive compounds.

Considering that some sesterterpenoids with novel chemical structures have been reported very recently, we can look forward to many exciting discoveries of unknown sesterterpenoids in the near future. Therefore, the present authors believe that it is worthwhile maintaining a sharp focus on sesterterpenoid research.

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Secondary Metabolites from Marine-Derived Fungi from China

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Contents

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1 Introduction

Natural products play a major role in the discovery of lead compounds for the development of drugs to treat human diseases [1]. Marine ecosystems, covering almost 70% of the earth's surface, represent an important source of chemical and biological diversity [2], and have already contributed to the development of new drugs such as Trabectedin®, an antitumor alkaloid for the treatment of soft tissue sarcoma and ovarian cancer obtained from the tunicate *Ecteinascidia turbinata*; Eribulin®, a macrolide to treat metastatic breast cancer derived from halichondrin B found in sponges of the genus *Halichondria*; and Vidarabine®, an antiviral nucleoside against herpes simplex virus isolated from the Caribbean sponge *Tethya crypta*, just to name a few [3]. Whereas marine natural product research had in the beginning focused mainly on marine macroorganisms such as algae, sponges, tunicates, and others as sources of new bioactive compounds, recent years have seen a growing emphasis on marine microorganisms as potential sources of new drug leads. This is exemplified by salinosporamide A (produced by the marine bacteria *Salinispora tropica* and *S. arenicola*) as an inhibitor of the proteasome and plinabulin (a synthetic analogue of halimide obtained from the seaweed fungus *Aspergillus*) as an inhibitor of tubulin polymerization [3]. In addition to marine-derived bacteria, marine-derived fungi are gaining considerable attention due to their capability of producing structurally unique bioactive secondary metabolites [4, 5].

The population of China has been using Traditional Chinese Medicine (TCM), inclusive of medicinal plants, animals, and minerals, to treat various kinds of diseases for thousands of years. Prof. Youyou Tu was awarded the Nobel Prize in Physiology or Medicine in 2015 for her contribution to the discovery of artemisinin for the treatment of malaria, representing a great achievement of natural product research in China [6]. In the 1980s, Prof. Kanghou Long, the pioneer of marine natural product research in China, reported methyl isosartortuoate, a novel tetracyclic tetraterpenoid from the soft coral *Sarcophyton tortuosum*, and subergorgic acid, a novel tricyclopentanoid cardiotoxin from the gorgonian *Subergorgia suberosa* [7, 8]. This marked the start of marine natural product research in China even though the pace of this field of Chinese science was still slow for the next two decades to come. Since the beginning of the new millennium, however, more and more Chinese scientists have turned their attention to marine natural product research. Recent reviews regarding the temporal and geographic distribution of marine natural products have highlighted the rise of marine natural product research in China and the substantial increase in discoveries of new marine natural products from marine microorganisms over time [9–11].

Since 2001, more than 1000 new compounds have been isolated from marine-derived fungi from China including fungi from seawater, sediment, marine animals, and marine plants, such as algae and mangrove plants. Advances in the study of secondary metabolites from mangrove-derived fungi from the South China Sea that were published between 2008 and mid-2013 have been reviewed [12]. Bioactive compounds from marine-derived bacteria and fungi by China-based research groups starting from 2009 have likewise been reviewed [13]. In this contribution, the authors focus exclusively on new compounds reported from marine-derived fungi that are associated with organisms, such as algae, sponges, corals, and other marine animals from Chinese waters, but we have excluded deliberately fungi from sediment, seawater, mangrove plants, or taxonomically unidentified sources in order to avoid overlap with other reviews from recent years. The host organisms from which fungi were isolated and their geographical origin, the media used for cultivation, and the bioactivities of the isolated compounds (whenever reported) are given herein. This contribution includes 613 marine fungal metabolites and 176 references from 2001 to 2017. The various compounds are classified into eight sections and various subsections according to their structural classes.

2 Polyketides

2.1 Macrolides

The fungal strain *Cochliobolus lunatus* M351 was isolated from inner parts of the gorgonian *Dichotella gemmacea*, which was collected from the Weizhou coral reef in the South China Sea. Cultivation of this fungus in liquid glucose yeast peptone (GPY) medium yielded three 14-membered resorcylic acid lactones, cochliomycins A−C (**1**–**3**). Cochliomycin A (**1**) (Fig. 1) showed significant antifouling activity against larval settlement of the barnacle *Balanus amphitrite* with an EC_{50} value of 3 μ*M* and a pronounced difference between inhibition of larval settlement and toxicity ($LC_{50}/EC_{50} > 16.7$), suggesting that the compound might be useful as a environmentally benign antifouling agent. Cochliomycin A (**1**) also exhibited moderate antibacterial activity against *Staphylococcus aureus* with an inhibition zone of 11 mm at a concentration of 50 μg/cm^3 in an agar plate diffusion assay [14]. Three further resorcylic acid lactones, cochliomycins D−F (**4**–**6**), were isolated from solid rice medium fermentation of *Cochliobolus lunatus* TA26–46, which was obtained from inner parts of the sea anemone *Palythoa haddoni*, collected from the Weizhou coral reef in the South China Sea. Cochliomycins D and F (**4** and **6**) exhibited potent antifouling activity against larval settlement of *B. amphitrite* with EC_{50} values of 48 and 18 μ*M* [15]. Furthermore, epigenetic manipulation was applied by cultivating the fungal strain in starch medium with the addition of histone deacetylase inhibitors (sodium butyrate or suberoylanilide hydroxamic acid), resulting in the production of two additional resorcylic acid lactone derivatives with bromine substitution, namely, 5-bromozeaenol (**7**) and 3,5-dibromozeaenol (**8**) [16]. *Pseudallescheria ellipsoidea*

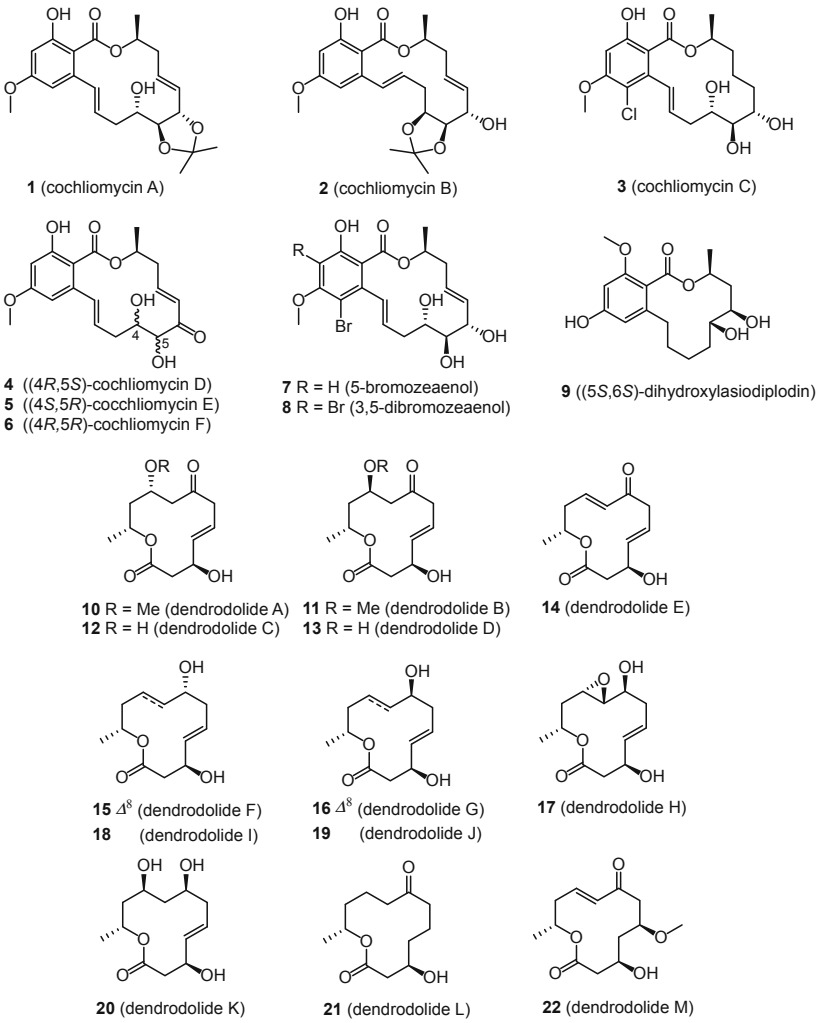


Fig. 1 Structures of macrolides

F42-3 was obtained from the soft coral *Lobophytum crassum* collected from Sanya National Coral Reef Reserve. Liquid GPY medium fermentation of this fungus yielded a 12-membered lactone, (5*S*,6*S*)-dihydroxylasiodiplodin (**9**) [17]. Thirteen 12-membered macrolides, dendrodolides A−M (**10**–**22**), were isolated from the solid agar medium fermentation of *Dendrodochium* sp., a fungus associated with the sea cucumber *Holothuria nobilis*, which was collected in the South China Sea. Dendrodolides A−E, G−I, K, and L (**10**–**14**, **16**–**18**, **20**, and **21**) exhibited weak growth inhibitory activity against SMMC-7721 and HCT116 tumor cells, whereas none of the isolated compounds displayed activity against A549 tumor cells (Fig. 1) [18].

2.2 α-Pyrones Including Isocoumarins

The fungus *Neosartorya pseudofischeri* was obtained from the inner tissue of the starfish *Acanthaster planci* collected from the Hainan Sanya National Coral Reef Reserve. Fermentation of this fungus in liquid GPY medium gave 6,8-dihydroxy-3-[(1*E*,3*E*)-penta-1,3-dien-1-yl]isochroman-1-one (**23**) (Fig. 2) [19]. The halotolerant endophytic fungus *Aspergillus* sp. F00785 was obtained from the marine alga *Enteromorpha prolifera* collected in Jinjiang Saltern, Fujian Province. Three asperentin-type compounds including 6-*O*-α-D-ribosylasperentin (**24**), 6-*O*-α-D-ribosyl-8-*O*-methylasperentin (**25**), and 5-hydroxy-6-*O*-methylasperentin (**26**) were isolated following fermentation of this fungus in potato dextrose agar (PDA)

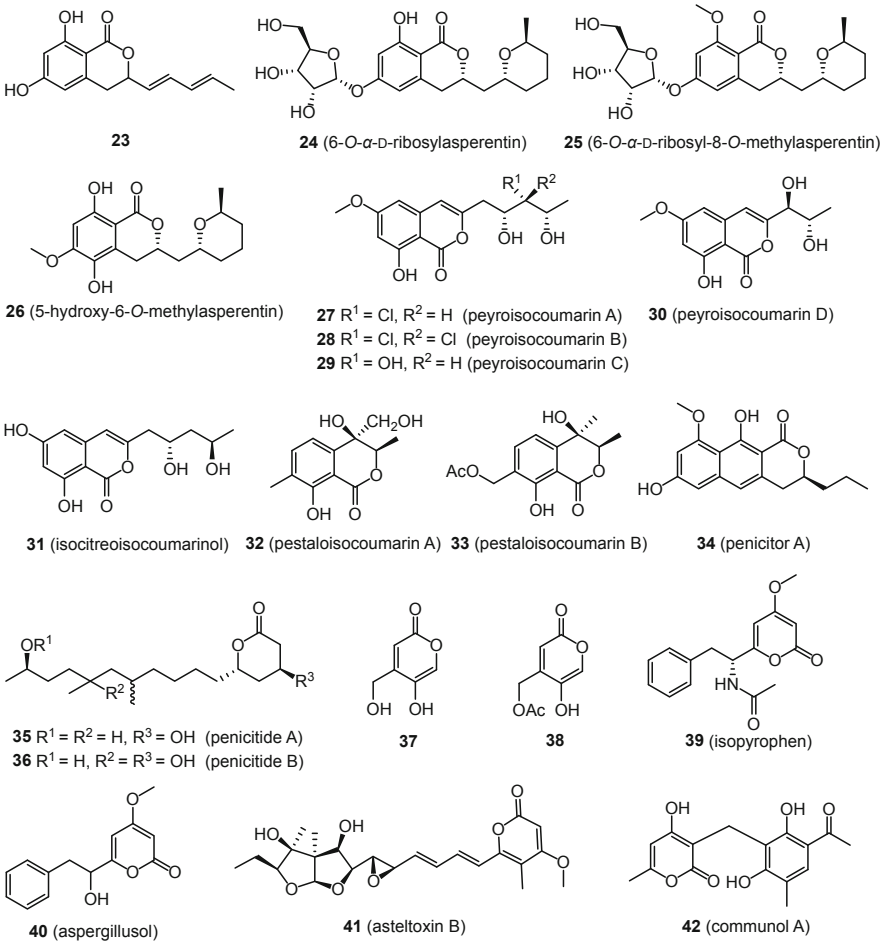


Fig. 2 Structures of α-pyrones including isocoumarins (part 1)

medium. Compounds **24** and **25** were reported as the first members of this group containing D-ribofuranose bound via an α-glycosidic linkage [20]. Five isocoumarins, peyroisocoumarins A–D (**27**–**30**) and isocitreoisocoumarinol (**31**), were isolated from the solid rice fermentation of *Peyronellaea glomerata* XSB-01-15 that was obtained from the finger sponge *Amphimedon* sp. collected from Yongxing Island, Hainan Province. Among them, peyroisocoumarins A and B (**27** and **28**) were characterized by the presence of a chlorine atom in the pentane side chain, which is unusual for isocoumarin derivatives. An antioxidant response element reporter assay (ARE) revealed that peyroisocoumarins A, B, and D (**27**, **28**, and **30**) exhibited potent ARE activation in HepG2C8 cells [21]. Solid rice culture fermentation of *Pestalotiopsis heterocornis*, which was obtained from the sponge *Phakellia fusca* collected from the Xisha Islands, gave two isocoumarins pestaloisocoumarins A and B (**32** and **33**). Pestaloisocoumarins A and B (**32** and **33**) showed weak antibacterial activities against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* with *MIC* values ranging from 90 to 210 μ*M* [22]. Penicitor A (**34**) was isolated from solid rice medium fermentation of *Penicillium* sp. SCS-KFD08 that was associated with the marine worm *Sipunculus nudus* collected from Haikou Bay [23]. The fungal stain *Penicillium chrysogenum* QEN-24S was isolated from the inner tissue of the marine red alga *Laurencia* sp. collected from Weizhou Island in the South China Sea. From the solid rice culture of this fungus, two polyketide derivatives penicitides A and B (**35** and **36**) both featuring a unique 10-hydroxy- or 7,10-dihydroxy-5,7-dimethylundecyl moiety were obtained. Penicitide A (**35**) displayed moderate antifungal activity against *Alternaria brassicae* with an inhibition zone of 6 mm in diameter at a concentration of 20 μg/disk and also possessed cytotoxicity against the HepG2 cell line with an IC_{50} value of 32 μg/cm^3 [24]. Two 5-hydroxy-2-pyrone derivatives, 4-hydroxymethyl-5-hydroxy-2*H*-pyran-2-one (**37**) and (5-hydroxy-2-oxo-2*H*-pyran-4-yl) methyl acetate (**38**), were isolated from artificial seawater-containing liquid medium fermentation of *Aspergillus flavus* c-f-3, an endophyte obtained from the marine alga *Enteromorpha tubulosa* collected at Putian Pinghai. Compound **37** induced the production of cAMP in GPR12-transfected cells, including CHO (Chinese hamster ovary cells) and HEK293 (human embryonic kidney cells), in a dose-dependent manner, indicating compound **37** to be a possible ligand for GPR12 [25]. Two phenethyl-α-pyrone derivatives, isopyrophen (**39**) and aspergillusol (**40**), were obtained from the GPY medium fermentation of *Aspergillus niger* EN-13 that was isolated from the marine brown alga *Colpomenia sinuosa* collected along the Qingdao coastline [26]. The fungal strain *Aspergillus* sp. SCSGAF 0076 was isolated from the gorgonian *Melitodes squamata* collected in Sanya, Hainan Province. Following cultivation of this fungus in liquid medium containing 3.0% sea salt, asteltoxin B (**41**) was isolated [27]. Communol A (**42**) was isolated from the liquid GPY medium fermentation of *Penicillium commune* 518, as obtained from the gorgonian *Muricella abnormalis* collected from Danzhou, Hainan Province. Communol A (**42**) showed moderate antimicrobial activities against *Escherichia coli* and *Enterobacter aerogenes* with *MIC* values of 4.1 and 16.4 μ*M* (Fig. 2) [28].

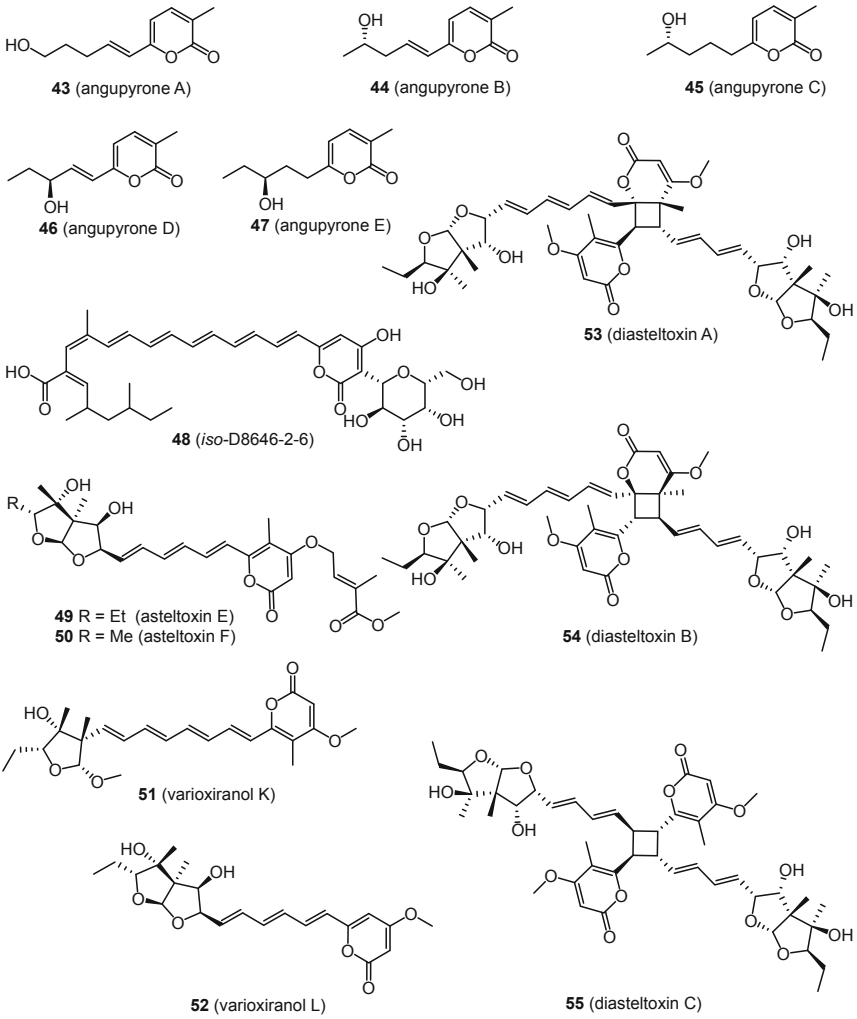


Fig. 3 Structures of α-pyrones including isocoumarins (part 2)

The fungal strain *Truncatella angustata* XSB-01-43 was isolated from the finger sponge *Amphimedon* sp. collected near Yongxing Island, Hainan Province. Chromatographic workup of the antioxidant extract obtained from the solid rice fermentation of *T. angustata* resulted in the isolation of five α-pyrone-based analogues, angupyrones A–E (**43**–**47**) (Fig. 3), which showed moderate ARE activation in HepG2C8 cells [29]. Fermentation in a seawater-containing liquid medium of *Epicoccum* sp. JJY40, obtained from the sponge *Callyspongia* sp. collected offshore at Sanya, Hainan Province, led to the isolation of a pyronepolyene C-glucoside, *iso*-D8646-2-6 (**48**). Compound **48** has a unique C-3-pyranosyl 4-hydroxypyrone

structure with a long side chain that is rare in Nature, and it was also the first C-3-pyranosyl 4-hydroxypyrone derivative to be isolated from a sponge-derived fungus. The glucoside *iso*-D8646-2-6 (**48**) showed anti-influenza A viral (H1N1) activity with an IC_{50} value of 91.5 μ*M*, while ribavirin as a positive control had an IC_{50} value of 114.8 μ*M*. Compound **48** was also found to possess weak NF-κB inhibitory activity with an IC_{50} value of 40.0 μ*M* [30].

Asteltoxins E and F (**49** and **50**) were isolated from the solid rice medium fermentation of *Aspergillus* sp. SCSIO XWS02F40 that was obtained from the sponge *Callyspongia* sp. collected from the sea area near Xuwen County, Guangdong Province. Asteltoxins E and F (**49** and **50**) showed significant activity against H3N2 cells with IC_{50} values of 6.2 and 8.9 μ*M*. In addition, asteltoxin E (**49**) also exhibited inhibitory activity against the H1N1 virus with an IC_{50} value of 3.5 μ*M* [31]. The fungal strain *Emericella variecolor* XSA-07-2 was obtained from the sponge *Cinachyrella* sp. collected from Yongxing Island in the South China Sea. Chemical examination of the EtOAc extract of *E. variecolor* cultured on solid rice medium yielded varioxiranols K and L (**51** and **52**). Cytotoxic activities of both compounds were evaluated against different tumor cell lines including human colon carcinoma (HCT-116), liver hepatocellular carcinoma (HepG2), gastric cancer (BGC-823), lung cancer stem cells (NCI-H1650), and human ovarian cancer (A2780) cells.

Varioxiranol K (**51**) showed significant effects against the tumor cell lines HCT-116 (IC_{50} 3.5 μ*M*), HepG2 (IC_{50} 8.8 μ*M*), BGC-823 (IC_{50} 4.2 μ*M*), and NCI-H1650 (IC_{50} 2.8 μ*M*), while varioxiranol L (**52**) showed selective inhibitory activity toward HCT-116 (IC_{50} 2.0 μ*M*), BGC-823 (IC_{50} 5.0 μ*M*), and NCI-H1650 cells (IC_{50} 2.2 μ*M*) [32]. Diethyl sulfate was added as a chemical mutagen to the fungus *E. variecolor* XSA-07-2 in order to activate silent fungal metabolite pathways of this fungus. Fresh fungal spores in 50% (*v*/*v*) DMSO were treated with 1% (*v*/*v*) diethyl sulfate at 4°C for 1 day, and single colony isolates resulting from the treated spores were collected. A mutant of *E. variecolor* XSA-07-2-M3 that produced asteltoxin (absent in the wild strain) was obtained. Chromatographic separation following solid rice medium fermentation of the mutant resulted in the isolation of three further novel asteltoxin-bearing dimers, diasteltoxins A−C (**53**–**55**), which were characterized structurally by a [2+2] cycloaddition of asteltoxin. This was the first report of a [2+2] cycloaddition occurring in marine fungi. Diasteltoxins A−C (**53**–**55**) showed significant inhibition of thioredoxin reductase (TrxR) with IC_{50} values of 12.8, 11.1, and 7.2 μ*M*, respectively, suggesting that these compounds may act as regulators of tumor progression and metastasis (Fig. 3) [33].

2.3 γ-Pyrones Including Xanthones and Chromones

The fungus *Penicillium citrinum* SCSGAF 0167 was obtained from the gorgonian *Echinogorgia aurantiaca* collected from Sanya, Hainan Province. 2,11-Dihydroxy-1-methoxycarbonyl-9-carboxylxanthone (**56**) (Fig. 4) was isolated following

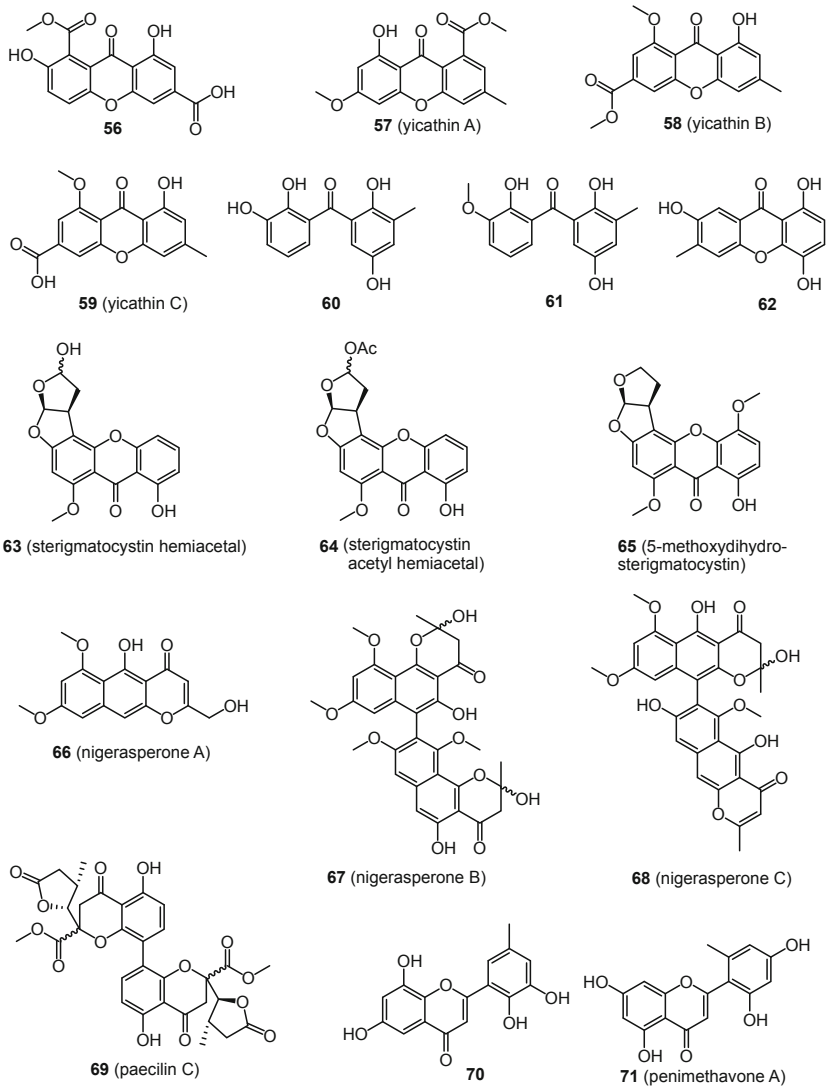


Fig. 4 Structures of γ-pyrones including xanthones and chromones (part 1)

fermentation of this fungus in liquid medium containing sea salt [34]. Three xanthone derivatives, yicathins A−C (**57**–**59**), were isolated from the liquid potato dextrose broth (PDB) medium fermentation of *Aspergillus wentii* pt-1, an endophyte obtained from the marine red alga *Gymnogongrus flabelliformis* that was collected from the coast of Pingtan Island. In antibacterial and antifungal bioassays, yicathin B (**58**) was active against *Escherichia coli* (inhibition diameter 9 mm) while yicathin C (**59**) inhibited *Escherichia coli*, *Staphylococcus aureus*, and *Colletotrichum*

lagenarium with inhibition diameters of 12, 8, and 11 mm, respectively, at a concentration of 10 μg/disk [35].

Solid rice culture fermentation of *Talaromyces islandicus* EN-501, isolated from the marine red alga *Laurencia okamurai* collected off the coast at Qingdao, yielded two diphenylketones, 2,2′,3,5′-tetrahydroxy-3′-methylbenzophenone (**60**) and 2,2′,5′-trihydroxy-3-methoxy-3′-methylbenzophenone (**61**), as well as a xanthone, 1,4,7-trihydroxy-6-methylxanthone (**62**). The joint isolation of benzophenones and xanthones from the same fungal strain supports the biogenesis of xanthones via a benzophenone intermediate. Compounds **60–62** exhibited potent antioxidative activities against DPPH (1,1-diphenyl-2-picrylhydrazyl) and ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonate)) radicals with IC_{50} values ranging from 3 to 27 μ*M*, more potent than the positive controls BHT (butylated hydroxytoluene) and ascorbic acid. Compound **60** also showed moderate inhibitory activities against several pathogenic bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus, Vibrio alginolyticus, V. harveyi,* and *V. parahaemolyticus*) with *MIC* values ranging from 15 to 30 μ*M* [36]. The fungus *Aspergillus versicolor* MF359 was obtained from the marine sponge *Hymeniacidon perleve* collected from the Bohai Sea. Cultivation of *A. versicolor* on solid rice medium containing artificial seawater gave the hemiacetal sterigmatocystin (**63**), the acetyl-hemiacetal sterigmatocystin (**64**), and 5-methoxydihydrosterigmatocystin (**65**). Compound **63** represented the first example of a sterigmatocystin hemiacetal in Nature. Compound **65** exhibited antibacterial activities against *Staphylococcus aureus* and *Bacillus subtilis* with *MIC* values of 35 and 9 μ*M*, respectively [37].

Three naphtho-γ-pyrones, nigerasperones A−C (**66–68**), were isolated from a liquid GPY medium culture of *Aspergillus niger* EN-13, an endophytic fungus obtained from the marine brown alga *Colpomenia sinuosa* collected at the Qingdao coastline. Nigerasperone C (**68**) showed antifungal activity against *Candida albicans* with an inhibition diameter of 9 mm, which was compared with a positive control, amphotericin B, having an inhibition diameter of 12 mm. Nigerasperone C (**68**) also showed weak DPPH-scavenging activity with a scavenging ratio of 41.6% at a concentration 50 μg/cm^3, compared to 80.4% by the positive control BHT [38]. The fungus *Penicillium* sp. SCSGAF 0023 was obtained from the gorgonian *Dichotella gemmacea* that was collected from Sanya, Hainan Province. Culturing this fungus on liquid potato dextrose agar medium yielded paecilin C (**69**) and 6,8,5′6′-tetrahydroxy-3′-methylflavone (**70**). Compound **70** showed antifouling activity against *Balanus amphitrite* larval settlement with an EC_{50} value of 22 μ*M* and low toxicity with LC_{50}/EC_{50} ratio > 14.9 [39]. A novel flavone, penimethavone A (**71**), possessing a rare methyl group in ring B, was isolated from the solid rice medium fermentation of *Penicillium chrysogenum*, and was obtained from the gorgonian *Carijoa* sp. collected from the South China Sea. Penimethavone A (**71**) showed selective and moderate cytotoxicity against cervical cancer (HeLa) and rhabdomyosarcoma cell lines with IC_{50} values of 8.4 and 8.2 μ*M* (Fig. 4) [40].

The fungus *Penicillium oxalicum* SCSGAF 0023 was isolated from the gorgonian *Muricella flexuosa* collected from Sanya, Hainan Province. PDA liquid medium fermentation of this fungus yielded five chromones including four

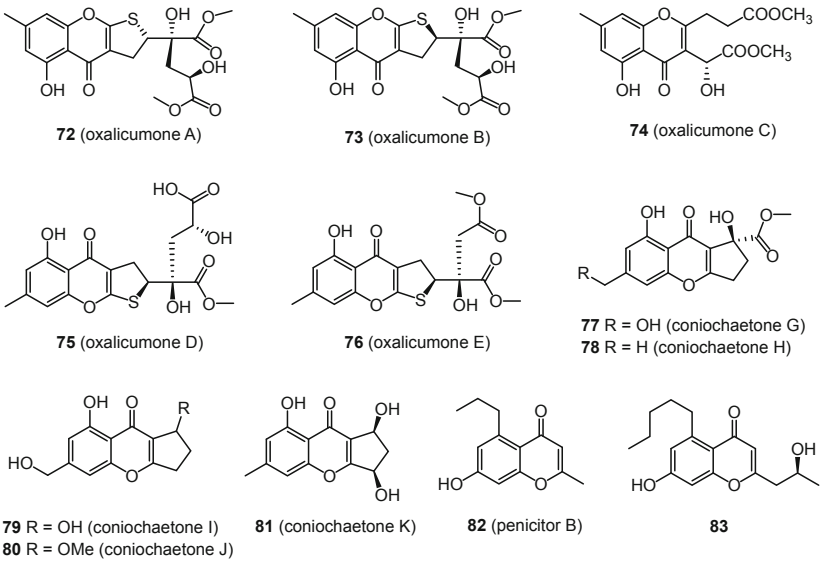


Fig. 5 Structures of γ-pyrones including xanthones and chromones (part 2)

dihydrothiophene-condensed congeners, oxalicumones A−E (**72–76**) (Fig. 5), as well as five cyclopentane-condensed chromones, coniochaetones G−K (**77–81**). Oxalicumone A (**72**) showed cytotoxicity against the A375 and SW-620 cell lines with IC_{50} values of 11.7 and 22.6 μ*M*, while its (*R*)-MTPA ester displayed cytotoxicity against the A375, SW-620, and HeLa carcinoma cell lines with IC_{50} values of 8.9, 7.8, and 18.4 μ*M*, respectively [41]. Oxalicumones D and E (**75** and **76**) exhibited significant cytotoxicity against eight tested cell lines (H1975, U937, K562, BGC823, MOLT-4, MCF-7, HL60, and Huh-7) with IC_{50} values all below 10 μ*M* [42, 43]. Penicitor B (**82**) was isolated from the solid rice medium fermentation of *Penicillium* sp. SCS-KFD08 associated with the marine worm *Sipunculus nudus* from Haikou Bay. Penicitor B (**82**) exhibited anti-quorum sensing activity at a dose of 50 μg/well in the *Chromobacterium violaceum* CV026 well diffusion assay [23]. 7-Hydroxy-2-(2-hydroxypropyl)-5-pentylchromone (**83**) was obtained from the solid rice medium fermentation of *Aspergillus* sp. SCSIO XWS02F40 that was associated with the sponge *Callyspongia* sp. collected from the sea near Xuwen County, Guangdong Province. The pentylbenzene moiety of compound **83** is rare in Nature (Fig. 5) [31].

2.4 Anthraquinones and Hydroanthraquinones

Cultivation of *Aspergillus versicolor* EN-7, which was isolated from the brown alga *Sargassum thunbergii* collected along the Qingdao coastline of Shandong Province,

in GPY medium gave the anthraquinone derivative 6,8-di-*O*-methylaverantin (**84**) (Fig. 6). Compound **84** showed weak antibacterial activity against *Escherichia coli* with an inhibition diameter of 7 mm at 20 μg/disk [44]. The fungal strain *Talaromyces islandicus* EN-501 was obtained from the marine red alga *Laurencia okamurai* collected at Qingdao. Fermentation of this fungus on seawater-containing solid rice medium yielded five hydroanthraquinone derivatives,

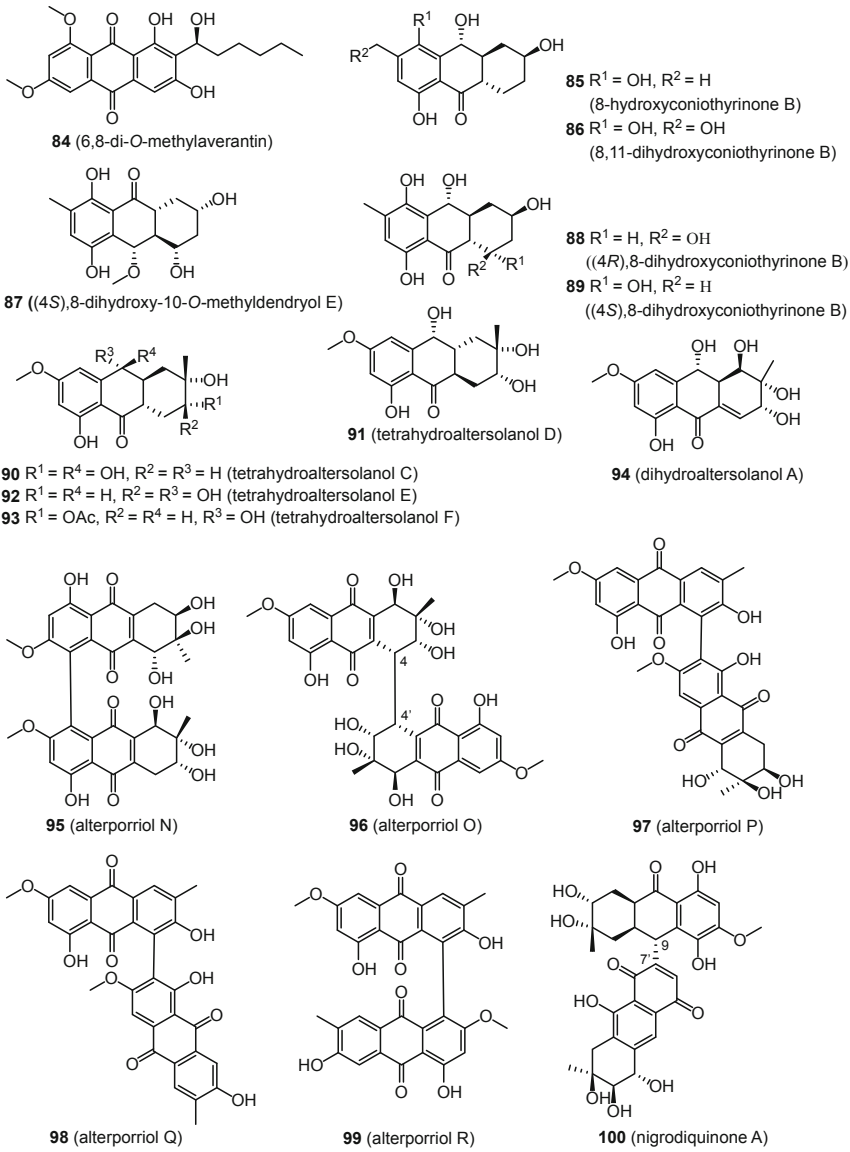


Fig. 6 Structures of anthraquinones and hydroanthraquinones

8-hydroxyconiothyrinone B (**85**), 8,11-dihydroxyconiothyrinone B (**86**), (4*S*),8-dihydroxy-10-*O*-methyldendryol E (**87**), (4*R*),8-dihydroxyconiothyrinone B (**88**), and (4*S*),8-dihydroxyconiothyrinone B (**89**). Compounds **85**–**89** showed inhibitory activity against *Staphylococcus aureus* with *MIC* values ranging from 7 to 26 μ*M*. In the antioxidant assay, compounds **85**–**89** displayed DPPH radical-scavenging activity with IC_{50} values ranging from 12 to 52 μ*M*, somewhat more potent than that of BHT, a well-known antioxidant (IC_{50} 61 μ*M*). In addition, compounds **85**–**89** showed moderate ABTS radical-scavenging activity with IC_{50} values ranging from 8.3 to 34 μ*M*, comparable to the positive control ascorbic acid (IC_{50} 16 μ*M*) [45]. Five hydroanthraquinone derivatives, tetrahydroaltersolanols C−F (**90**–**93**) and dihydroaltersolanol A (**94**), together with five alterporriol-type anthranoid dimers, alterporriols N−R (**95**–**99**), were isolated from the potato glucose liquid medium fermentation of *Alternaria* sp. ZJ-2008003, a fungus obtained from the soft coral *Sarcophyton* sp. collected from the Weizhou coral reef in the South China Sea. Alterporriol O (**96**) represents the first alterporriol dimer with a C-4–C-4′ linkage. Tetrahydroaltersolanol C (**90**) and alterporriol Q (**98**) exhibited antiviral activity against the porcine reproductive and respiratory syndrome virus (PRRSV) with IC_{50} values of 65 and 39 μ*M*. Alterporriol P (**97**) showed cytotoxic activity against the PC-3 and HCT-116 cell lines with IC_{50} values of 6.4 and 8.6 μ*M* [46]. The fungal strain *Nigrospora* sp. was isolated from the zoanthid *Palythoa haddoni* collected from the Weizhou coral reefs in the South China Sea. Fermentation of this fungus in potato glucose liquid medium gave the hydroanthraquinone dimer nigrodiquinone A (**100**) featuring the rare C-9–C-7′ linkage (Fig. 6) [47].

2.5 Other Aromatic Polyketides

The endophytic fungus *Cladosporium cladosporioides* EN-399 (Plate 1) was isolated from the marine red alga *Laurencia okamurai* (Plate 2) collected from Qingdao.

From the rice solid medium culture of *C. cladosporioides*, five cladosporol derivatives, cladosporols F−J (**101**–**105**) (Fig. 7), were obtained. Cladosporol H (**103**) showed significant cytotoxicity against the A549, Huh7, and LM3 cell lines with IC_{50} values of 5.0, 1.0, and 4.1 μ*M*, respectively, while cladosporol I (**104**) showed activity against the H446 lung cancer cell line with an IC_{50} value of 4.0 μ*M* [48]. The red alga *Laurencia* sp. collected from Weizhou Island in the South China Sea yielded two fungal strains, *Alternaria alternata* and *Penicillium chrysogenum* QEN-24S. Two perylene derivatives, 7-*epi*-8-hydroxyaltertoxin I (**106**) and 6-*epi*-stemphytriol (**107**), were obtained from seawater-containing liquid GPY medium fermentation of *A. alternata* [49], while 2-(2,4-dihydroxy-6-methylbenzoyl)-glycerol (**108**) was isolated from the solid rice culture of *P. chrysogenum* [24].

The fungus *Pleosporales* sp. was isolated from the green alga *Enteromorpha clathrata* collected from the South China Sea in Hainan Province. From Czapek's liquid medium fermentation of this fungus, pleosporallin E (**109**) was obtained,

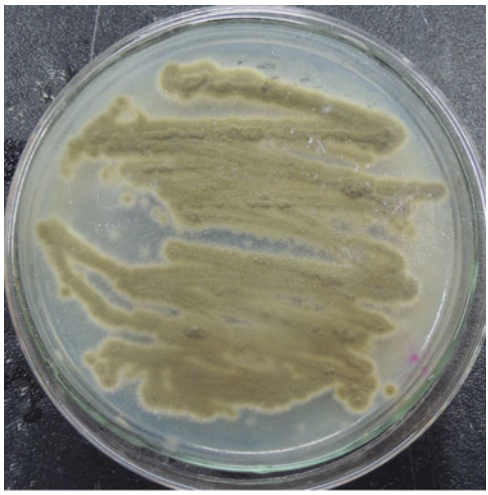


Plate 1 *Cladosporium cladosporioides* EN-399 isolated from *Laurencia okamurai*

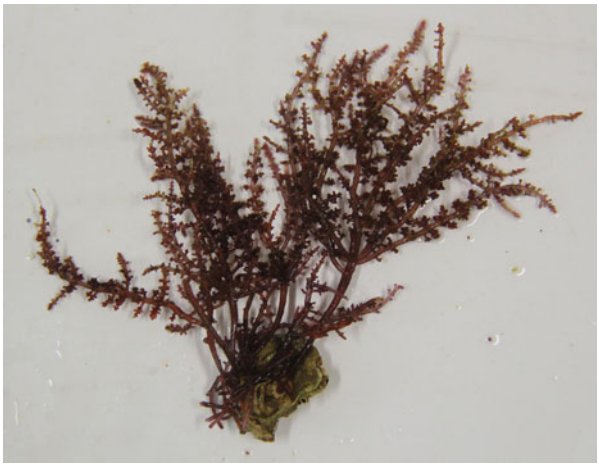


Plate 2 The marine red alga *Laurencia okamurai*

which showed antimicrobial activity against *Candida albicans* with an *MIC* value of 7.4 μg/cm^3 [50]. Two fungal strains, *Dichotomomyces* sp. L-8 and *Dichotomomyces cejpii* F31-1, were obtained from the inner tissue of the soft coral *Lobophytum crassum* collected from Hainan Sanya National Coral Reef Reserve. The sea salt-containing GPY liquid fermentation of *Dichotomomyces* sp. yielded dichotones A and B (**110** and **111**) [51]. By adding L-tryptophan and L-phenylalanine to the GPY liquid medium fermentation of *D. cejpii*, dichocetide A (**112**) was obtained [52].

The fungus *Pestalotiopsis* sp. ZJ-2009-7-6 was obtained from the soft coral *Sarcophyton* sp. collected from Yongxing Island in the South China Sea. From the solid rice culture of this fungus following addition of sea salt, a phthalide derivative, pestalotiolide A (**113**), was obtained, which exhibited significant activity against the

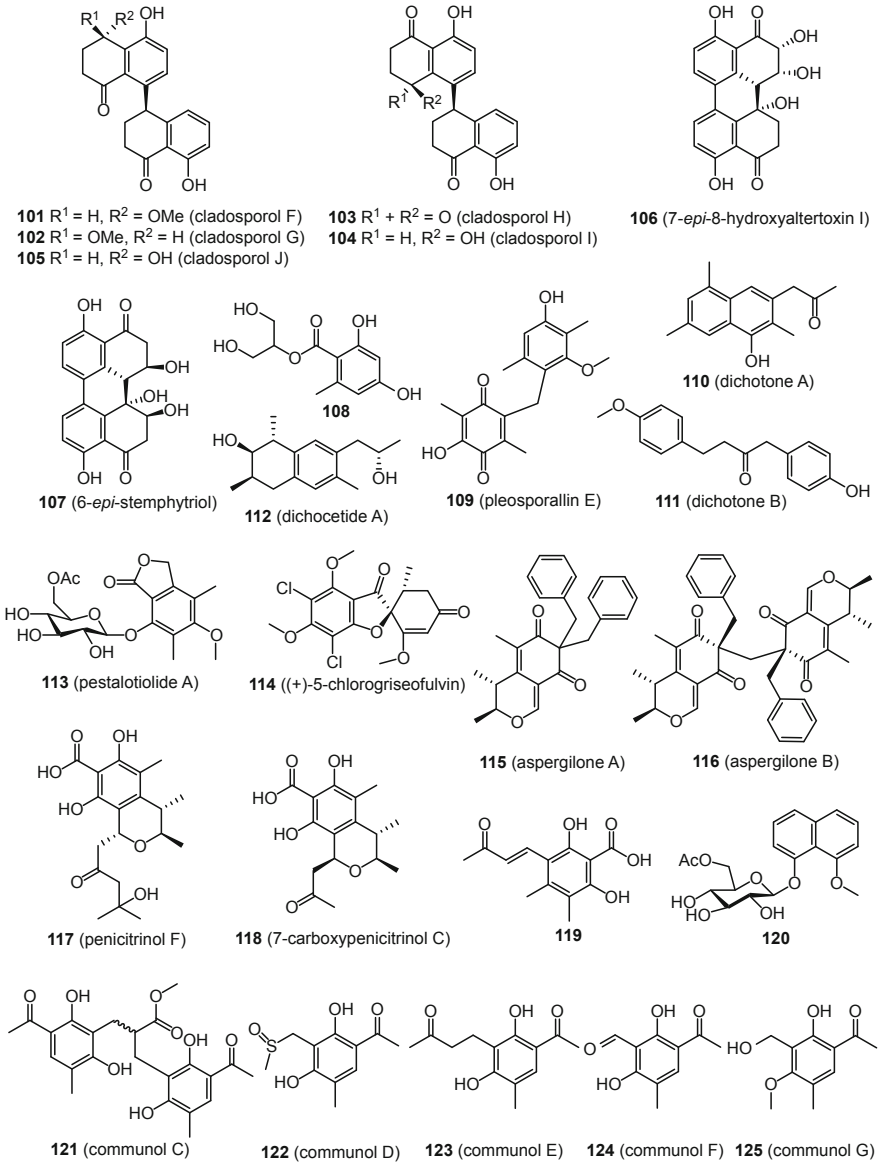


Fig. 7 Structures of other aromatic polyketides (part 1)

EV71 virus, with an IC_{50} value of 27.7 μ*M*, and was compared to the positive control ribavirin (IC_{50} 418.0 μ*M*) [53]. The fungus *Arthrinium* sp. was isolated from a piece of fresh tissue of the gorgonian *Anthogorgia caerulea* collected from the South China Sea. Cultivation of this fungus in GPY seawater liquid medium gave (+)-5-chlorogriseofulvin (**114**), exhibiting lethality against the brine shrimp *Artemia salina*

with an LC_{50} value of 65 μ*M* [54]. Aspergilones A and B (**115** and **116**), two novel benzylazaphilone derivatives, were isolated from the GPY seawater liquid medium fermentation of *Aspergillus* sp., as obtained from the gorgonian *Dichotella gemmacea* collected in the South China Sea. Aspergilone A (**115**) exhibited cytotoxicity against HL-60 human promyelocytic leukemia cells with an IC_{50} value of 8.2 μ*M*, but showed weak cytotoxicity against the MCF-7 human breast adenocarcinoma and A-549 human lung carcinoma cell lines with IC_{50} values of 64 and 95 μ*M* [55].

The fungal strain Xylariaceae sp. SCSGAF0086 was obtained from the gorgonian *Melitodes squamata* collected from the South China Sea. Fermentation of Xylariaceae sp. in liquid PDB medium yielded four polyketides, penicitrinol F (**117**), 7-carboxypenicitrinol C (**118**), 2,6-dihydroxy-4,5-dimethyl-3-(3-oxo-1-butenyl) benzoic acid (**119**), and 8-methoxy-1-naphthyl 6′-*O*-acetyl-*β*-glucopyranoside (**120**) [56]. Five aromatic polyketides, communols C−G (**121**–**125**), were obtained from the liquid GPY medium fermentation of *Penicillium commune* 518, a marine-derived fungus isolated from the gorgonian *Muricella abnormalis* collected from Danzhou, Hainan Province. Communol D (**122**) represented the first naturally occurring aromatic polyketide with a sulfoxide group from marine fungi. Communol F (**124**) was active in an antimicrobial test against *Escherichia coli* with an *MIC* value of 6.4 μ*M* (Fig. 7) [28].

The fungus *Emericella variecolor* XSA-07-2 was obtained from the marine sponge *Cinachyrella* sp., which was collected from Yongxing Island in the South China Sea. The solid rice culture of *E. variecolor* yielded five polyketide derivatives, varioxiranols A−E (**126**–**130**) (Fig. 8) [57]. (*S*)-Dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone (**131**) was obtained from the GPY liquid medium fermentation of *Simplicillium* sp. YZ-11, which was isolated from the sponge *Hymeniacidon perleve* collected from Dalian, Liaoning Province [58]. The fungus *Pestalotiopsis heterocornis* XWS03F09 was obtained from the sponge *Phakellia fusca*, as collected from the Xisha Islands, Hainan Province. The solid rice culture of this fungus yielded five polyketide derivatives, heterocornols A−E (**132**–**136**) [59]. Ten resorcinol derivatives, hansfordiols A–J (**137**–**146**), were isolated from the solid rice medium fermentation of *Hansfordia sinuosae* WGCA-23-3A, a fungus derived from the sponge *Niphates* sp. collected from the South China Sea (Fig. 8) [60].

From the inner tissue of the starfish *Acanthaster planci* collected from the Hainan Sanya National Coral Reef Reserve, three fungal strains, *Pseudallescheria boydii*, *Neosartorya pseudofischeri*, and *Trichoderma* sp., were obtained. The GPY liquid culture of *P. boydii* yielded two isobenzofuranone derivatives, pseudaboydins A and B (**147** and **148**) (Fig. 9). Pseudaboydin A (**147**) showed weak cytotoxicity against the HONE1 human nasopharyngeal carcinoma cell line, the SUNE1 human nasopharyngeal carcinoma cell line, and the GLC82 human glandular lung cancer cell line, with IC_{50} values of 37.1, 46.5, and 87.2 μ*M*, respectively [61]. The sea salt-containing GPY liquid medium cultivation of *N. pseudofischeri* gave 5-formyl-6-hydroxy-8-isopropyl-2-naphthoic acid (**149**) [19].

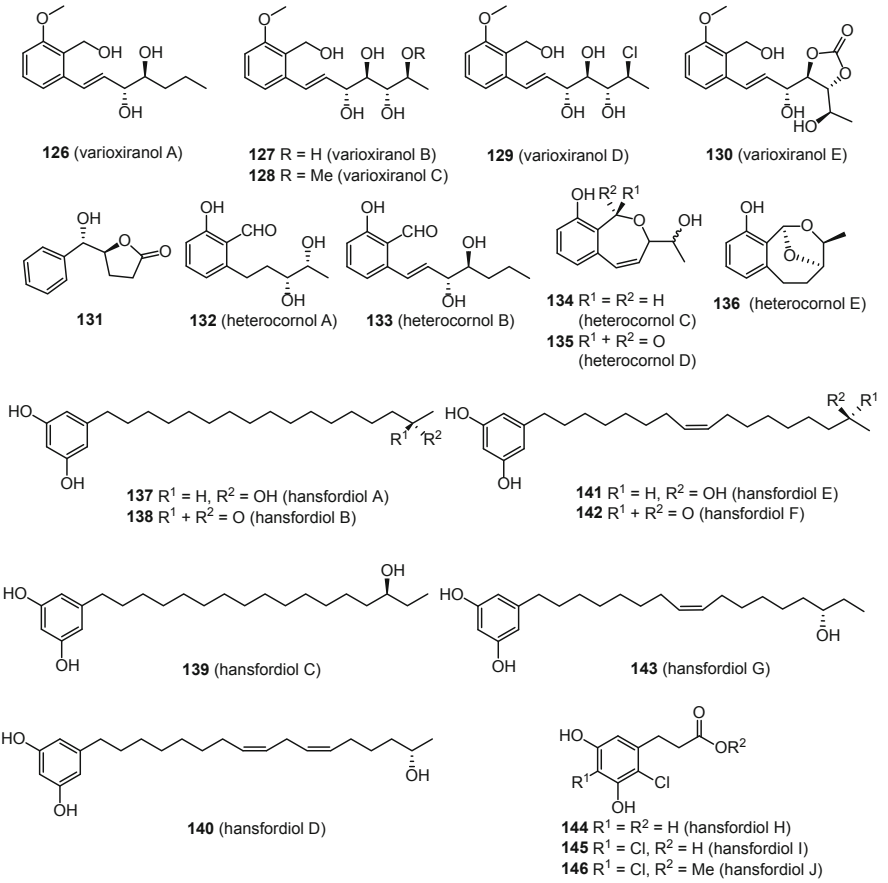


Fig. 8 Structures of other aromatic polyketides (part 2)

Two sorbicillinoid analogues, (4′*Z*)-sorbicillin (**150**) and (2*S*)-2,3-dihydro-7-hydroxy-6-methyl-2-[(*E*)-prop-1-enyl]-chroman-4-one (**151**), were obtained from the GPY liquid medium fermentation of *Trichoderma* sp. Compound **151** showed cytotoxicity against the MCF-7 human breast cancer cell line with an IC_{50} value of 7.8 μ*M* [62]. The biomalt solid agar medium fermentation of *Torula herbarum*, as obtained from the viscera of the sea hare *Notarchus leachii cirrosus* collected from Beihai, Guangxi Province, yielded the novel heptaketide, herbarone (**152**), as well as *ent*-astropaquinones B and C (**153** and **154**) [63]. The fungus *Cochliobolus lunatus* TA26–46 was obtained from the fresh inner part of the sea anemone *Palythoa haddoni* collected from the Weizhou coral reef in the South China Sea. From starch medium fermentation of this fungus, a series of diethylene glycol phthalate esters, cochphthesters A−G (**155**–**161**), were isolated, representing the first examples of naturally occurring phthalate ester oligomers (Fig. 9) [64].

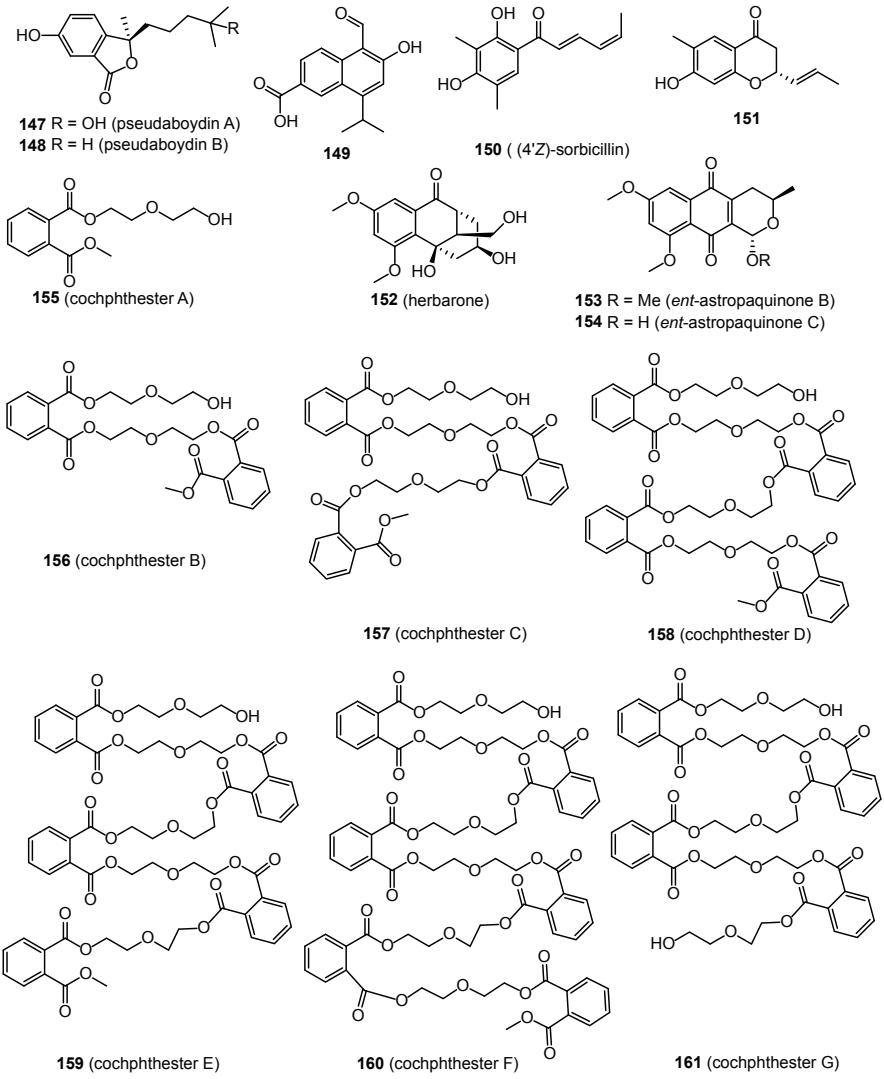


Fig. 9 Structures of other aromatic polyketides (part 3)

2.6 Other Polyketides

Penicitrinols G and H (**162** and **163**) (Fig. 10) were isolated from the liquid glucose, yeast, and malt (GYM) medium cultivation of *Penicillium citrinum* SCSGAF0167, as obtained from the gorgonian *Echinogorgia aurantiaca* collected from Sanya, Hainan Province [34]. Xylariaceae sp. SCSGAF0086 was obtained from the gorgonian *Melitodes squamata* collected from the South China Sea. The liquid PDB

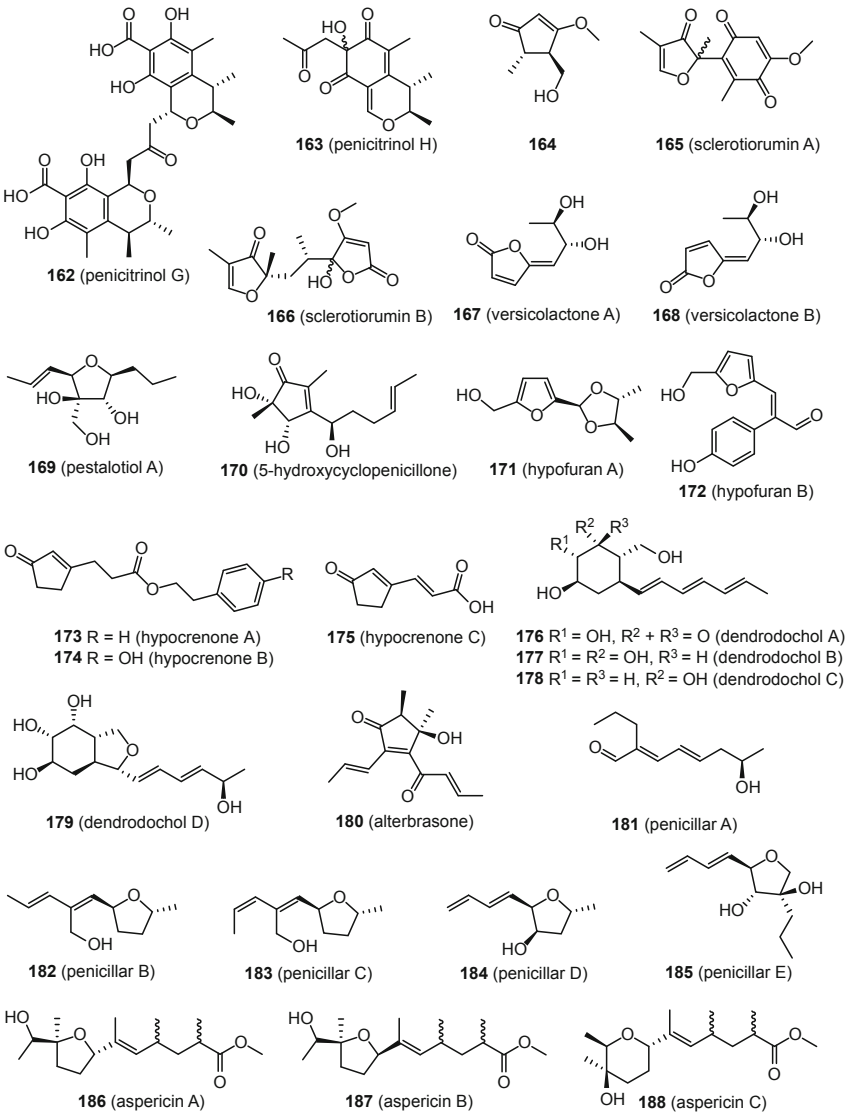


Fig. 10 Structures of other polyketides

medium fermentation of Xylariaceae sp. yielded 4-(hydroxymethyl)-3-methoxy-5-methylcyclopent-2-enone (**164**) [56]. The fungi *Penicillium citrinum* SCSGAF0052 and *Aspergillus sclerotiorum* SCSGAF0053 were obtained from the gorgonian *Muricella flexuosa* collected from Sanya, Hainan Province. Co-culture of both fungi in liquid glucose-starch-peptone medium with the addition of sea salt yielded sclerotiorumins A and B (**165** and **166**) [65]. Versicolactones A and B (**167** and **168**) were isolated from the liquid sorbitol-maltose-yeast extract medium fermentation of

Aspergillus versicolor LCJ-5-4, a fungus derived from the soft coral *Cladiella* sp. collected from Lingao, Hainan Province [66]. The fungal strain *Pestalotiopsis heterocornis* was obtained from a piece of fresh tissue from the inner part of the soft coral *Sarcophyton* sp. collected from Yongxing Island in the South China Sea. When cultivated on solid rice medium with sea salt, *P. heterocornis* yielded a phthalide derivative, pestalotiol A (**169**) [22].

The fungus *Trichoderma* sp. HPQJ-34 was obtained from the marine sponge *Hymeniacidon perleve* collected at Dongji Island, Zhejiang Province. *Trichoderma* sp. was cultivated in a liquid PDB medium to give a cyclopentenone, 5-hydroxycyclopenicillone (**170**). Compound **170** scavenged 2,2-diphenyl-1-picrylhydrazyl free radicals, decreased β-amyloid fibrillization in vitro, and significantly reduced H_2O_2-induced neurotoxicity in SH-SY5Y cells [67]. From the tissue of the sponge *Phakellia fusca* collected from Yongxing Island in the South China Sea, the fungus *Hypocrea koningii* PF04 was obtained. The PDA seawater liquid medium cultivation of this fungus gave two furan derivatives, hypofurans A and B (**171** and **172**), as well as three cyclopentenone derivatives, hypocrenones A–C (**173**–**175**). Hypofuran A (**171**) displayed antibacterial activity against *Staphylococcus aureus* ATCC25923 (*MIC* 32 μg/cm^3) and showed DPPH radical-scavenging capacity (IC_{50} 27.4 μg/cm^3) [68].

Cultivation of *Dendrodochium* sp., which was obtained from the sea cucumber *Holothuria nobilis* collected from the South China Sea, on biomalt solid agar medium, yielded four cyclohexanol analogues, dendrodochols A−D (**176**–**179**). Dendrodochols A and C (**176** and **178**) exhibited antifungal activities against several *Candida* strains, *Cryptococcus neoformans* and *Trichophyton rubrum*, with MIC_{80} values between 8 and 16 μg/cm^3 [69]. Alterbrasone (**180**) was obtained from the fermentation of *Alternaria brassicae* 93, a fungal stain derived from the marine crinoid *Comanthina schlegelii* collected from the South China Sea [70]. Penicillars A−E (**181**–**185**) were isolated from the rice medium culture of *Penicillium* sp. SCS-KFD08, a fungus associated with the marine worm *Sipunculus nudus* collected from the Haikou Bay [71]. Fermentation of *Rhizopus* sp. 2-PDA-61 that was obtained from the marine bryozoan *Bugula* sp. collected in Jiaozhou Bay, using liquid seawater-containing medium, produced three furan and pyran derivatives, aspericins A–C (**186**–**188**). Aspericin C (**188**) exhibited cytotoxicity against the P388, A549, HL-60, and BEL-7420 cell lines with IC_{50} values of 14.6, 61.4, 7.1, and 24.2 μ*M* (Fig. 10) [72].

3 Meroterpenes and Prenylated Polyketides

3.1 Merosesquiterpenes

The fungal strain *Stachybotrys chartarum* 952 was isolated from the marine crinoid *Himerometra magnipinna* collected from Xuwen Coral Reef Nature Reserve in Guangdong Province. Cultivation of *S. chartarum* on solid rice medium gave

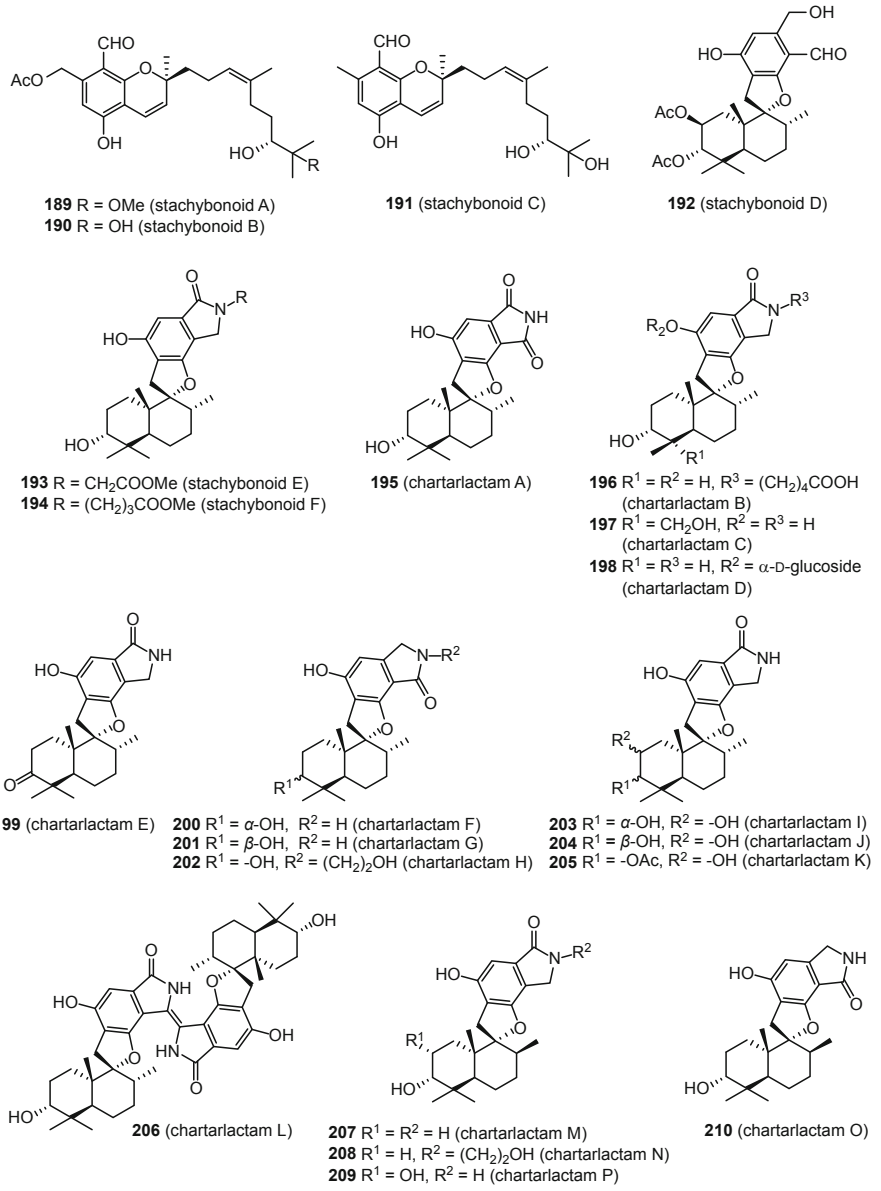


Fig. 11 Structures of merosesquiterpenes (part 1)

stachybonoid A (**189**), while cultivation of this fungus in PDB medium yielded stachybonoids B–F (**190**–**194**) (Fig. 11). Stachybonoid A (**189**) was reported to reduce the expression of the dengue virus protein prM in a dose-dependent manner, while stachybonoid F (**194**) showed an inhibitory effect with regard to the production of NO with an IC_{50} value of 27.2 μ*M* [73].

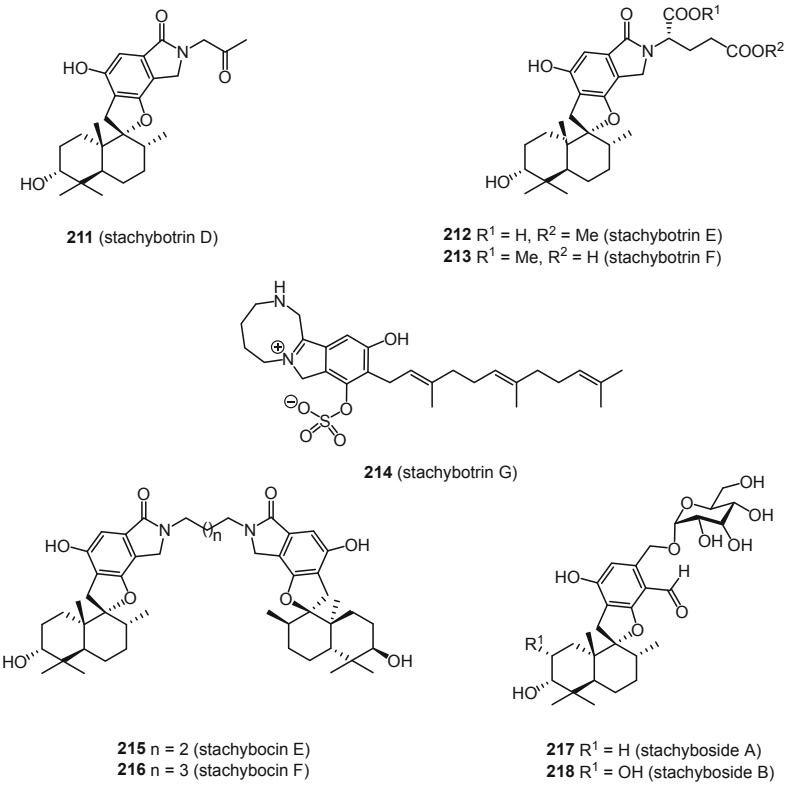


Fig. 12 Structures of merosesquiterpenes (part 2)

Chemical examination of the solid rice culture of *Stachybotrys chartarum* WGC-25C-6, which was obtained from the sponge *Niphates recondita* collected from the inner coral reef near Weizhou Island in Beibuwan Bay, Guangxi Province, resulted in the isolation of sixteen phenylspirodrimanes, chartarlactams A−P (**195**–**210**). When tested at a concentration of 10 μ*M* in the HepG2 cell model, chartarlactams D−F, K, L, N, and O (**198**–**200**, **205**, **206**, **208**, and **209**) displayed potent lipid-lowering activities as assessed by Oil Red O staining. Chartarlactams E, F, K, and O (**199**, **200**, **205**, and **209**) resulted in strong inhibition of intracellular triglyceride levels, while chartarlactams D−F and N (**198**–**200** and **208**) dramatically reduced total cholesterol levels [74]. *Stachybotrys chartarum* MXH-X73, as obtained from the sponge *Xestospongia testudinaris* collected at Xisha Island, produced stachybotrins D−G (**211**–**214**) (Fig. 12), stachybocins E and F (**215** and **216**), and stachybosides A and B (**217** and **218**) when cultivated in liquid seawater-containing medium. Stachybotrin D (**211**) exhibited inhibitory effects on HIV-1 replication against wild-type and five NNRTI-resistant strains with EC_{50} values ranging from 7.0 to 23.8 μ*M* [75, 76].

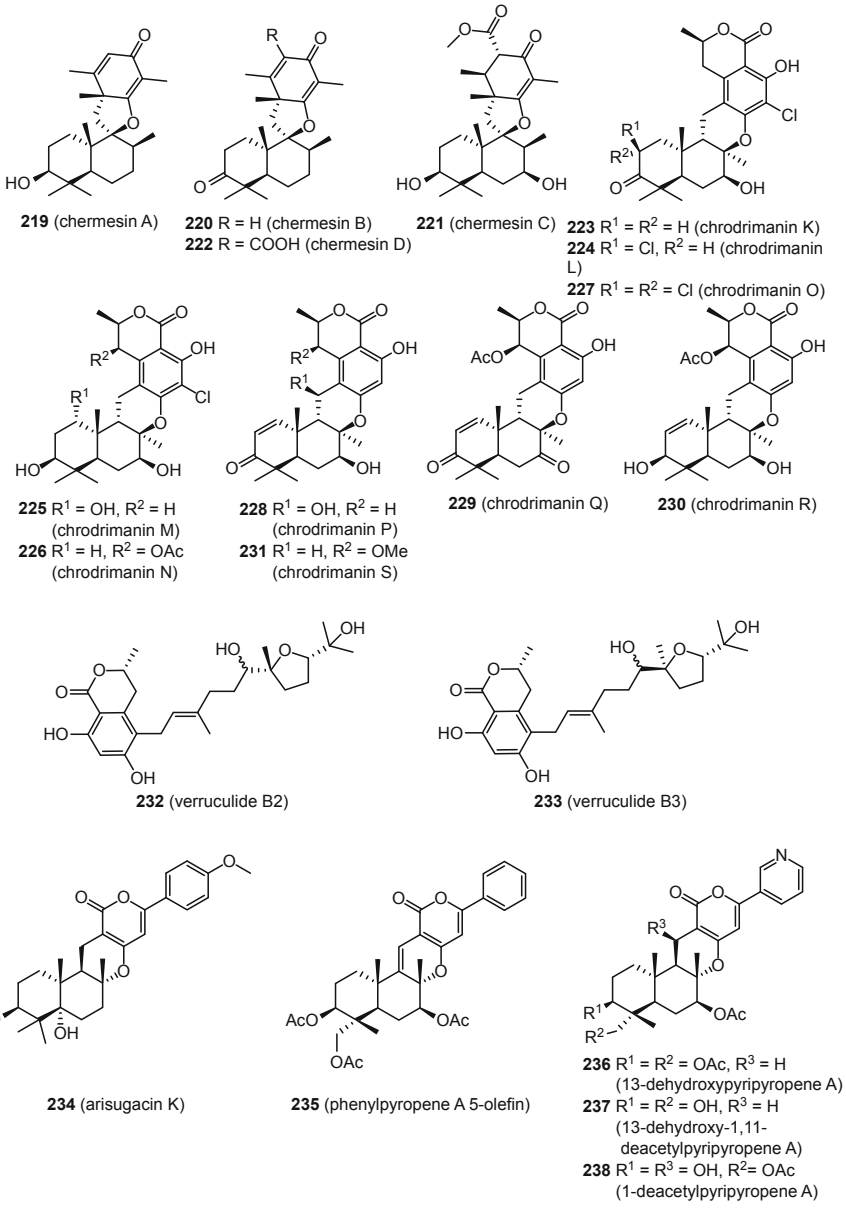


Fig. 13 Structures of merosesquiterpenes (part 3)

Four spiromeroterpenoids, chermesins A–D (**219**–**222**) (Fig. 13), were isolated from the solid rice culture extract of *Penicillium chermesinum* EN-480, an endophyte obtained from the inner tissue of the marine red alga *Pterocladiella tenuis* collected at Rongcheng, Shandong Province. Chermesins A and B (**219** and **220**)

exhibited antimicrobial activities against *Candida albicans*, *Escherichia coli*, *Micrococcus luteus*, and *Vibrio alginolyticus* with *MIC* values ranging from 8 to 64 μg/cm^3, whereas chermesin D (**222**) showed only weak activity against *E. coli*, having an *MIC* value of 64 μg/cm^3 [77]. Fermentation of *Penicillium* sp. SCS-KFD09W isolated from the marine worm *Sipunculus nudus* from Haikou Bay in liquid GYM medium yielded eleven meroterpenes, chrodrimanins K–S (**223**–**231**) and verruculides B2 and B3 (**232** and **233**). Chrodrimanins K and N (**223** and **226**) showed anti-H1N1 activity with IC_{50} values of 74 and 58 μ*M*. Chrodrimanins O and R (**227** and **230**) exhibited inhibitory activity of protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 71.6 and 62.5 μ*M*. Verruculide B2 (**232**) displayed weak antibacterial activity against *Staphylococcus aureus* with an *MIC* of 32 μg/cm^3 [78, 79].

Arisugacin K (**234**) was isolated from the PDB culture of *Penicillium echinulatum* pt-4, an endophytic fungus obtained from fresh tissue of the marine red alga *Chondrus ocellatus* collected from the coast of Pingtan Island. Arisugacin K (**234**) showed inhibitory activity against *Escherichia coli* with an inhibition diameter of 8 mm at 30 μg/disk in the agar plate diffusion assay [80]. The fungus *Neosartorya pseudofischeri* was obtained from the starfish *Acanthaster planci* collected from the South China Sea. 5-Olefin-phenylpyropene A (**235**) and 13-dehydroxypyripyropene A (**236**) were isolated from the liquid medium culture of *N. pseudofischeri* [19]. The fungal strain *Fusarium lateritium* 2016F18-1 was obtained from the sponge *Phyllospongia foliascens* collected from Hainan Sanya National Coral Reef Reserve. Two pyripyropenes, 13-dehydroxy-1,11-deacetylpyripyropene A (**237**) and 1-deacetylpyripyropene A (**238**), were isolated following fermentation of this fungus in liquid GPY medium [81].

Fermentation of *Aspergillus terreus*, which was obtained from the South China Sea gorgonian *Echinogorgia aurantiaca*, on solid rice medium, yielded three meroterpenoids, territrems D and E (**239** and **240**) and 11a-dehydroxyisoterreulactone A (**241**) (Fig. 14). Territrems D and E (**239** and **240**) showed strong inhibitory activity against acetylcholinesterase with IC_{50} values of 4.2 and 4.5 n*M*, respectively. Territrem D (**239**) was also tested for antifouling activity toward larvae of the barnacle *Balanus amphitrite* with an EC_{50} value of 25.2 μ*M*. 11a-Dehydroxyisoterreulactone A (**241**) showed weak antiviral activity against HSV-1 with an IC_{50} value of 35.8 μ*M* [82]. Pleosporallins A–D (**242**–**245**) were obtained from *Pleosporales* sp., an endophytic fungus derived from the marine alga *Enteromorpha clathrata* collected from the South China Sea in Hainan Province following fermentation of this fungus in Czapek's liquid medium. Pleosporallins A–C (**242**–**244**) showed moderate inhibitory activities against the stimulation of IL-6 in RAW264.7 cells, whereas pleosporallin D (**245**) exhibited antibacterial activity against *Clavibacter michiganense* subsp. *sepedonicus* with an *MIC* value of 9.5 μg/cm^3 [50]. Cultivation of *Lophiostoma* sp. ZJ, as isolated from the inner part of the fresh soft coral *Sarcophyton* sp. collected from the Weizhou Island coral reef in the South China Sea, using potato glucose liquid medium, yielded craterellin D (**246**) [83].

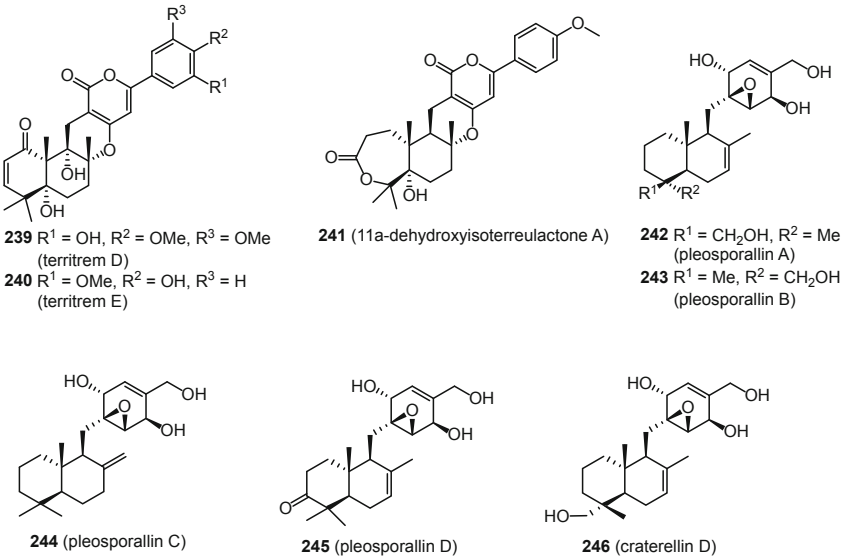
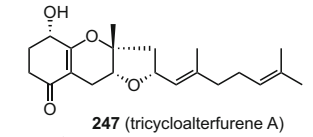


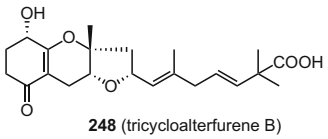
Fig. 14 Structures of merosesquiterpenes (part 4)

Fermentation of *Alternaria alternata* k21-1, a fungus obtained from the surface of the marine red alga *Lomentaria hakodatensis* collected from Kongdong Island, in liquid PDB medium yielded four tetrahydrofuran-bearing meroterpenes, tricycloalterfurenes A−D (**247**–**250**) (Fig. 15) [84]. Another *Alternaria* strain (*Alternaria* sp. JJY-32) was obtained from the sponge *Callyspongia* sp. collected off the coast of Hainan Island. Fermentation of this fungus in PDB medium yielded thirteen meroterpenoids with diverse ring systems, including tricycloalterarenes A−C (**251**–**253**), bicycloalternarenes A−F (**254**–**259**), and monocycloalterarenes A−D (**260**–**263**). The compounds were tested for their NF-κB inhibitory activities in RAW264.7 cells, but showed only weak bioactivities with IC_{50} values ranging from 39 to 85 μ*M* [85]. 1,2-Dihydroterretonin F (**264**) was produced in PDB medium with addition of seawater by *Aspergillus ustus* cf-42, an endophyte obtained from the fresh tissue of the marine green alga *Codium fragile* collected from Zhoushan Island [86].

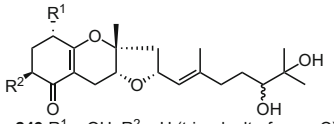
The fungal strain *Aspergillus* sp. ZL0-1b14 was obtained from the marine green alga *Enteromorpha* sp. collected in the Jinjiang Dongshi salt pan, Fujian Province. Aspertetranones A−D (**265**–**268**), four highly oxygenated triketide-sesquiterpenoid meroterpenes, were isolated following cultivation of this fungus on solid PDA medium containing 20% NaCl. Aspertetranone D (**268**) suppressed the production of IL-6 (69% inhibition at 40 μ*M*) in LPS-stimulated RAW264.7 macrophages [87]. The digestive gland of the crab *Xenograpsus testudinatus* collected from the Kueishantao hydrothermal vents off Taiwan yielded *Aspergillus* sp. WU 243. A novel hybrid polyketide-terpenoid, aspergstressin (**269**), was induced by adding cobalt to the PDB medium employed for fermentation of this fungus (Fig. 15) [88].



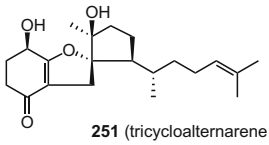
247 (tricycloalterfurene A)



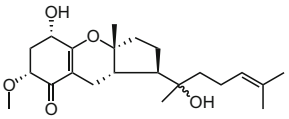
248 (tricycloalterfurene B)



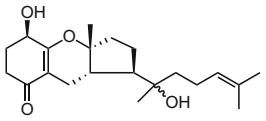
249 R^1 = OH, R^2 = H (tricycloalterfurene C)
250 R^1 = H, R^2 = OH (tricycloalterfurene D)



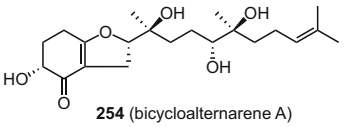
251 (tricycloalternarene A)



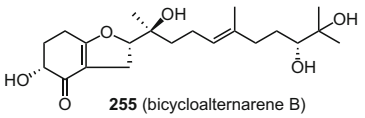
252 (tricycloalternarene B)



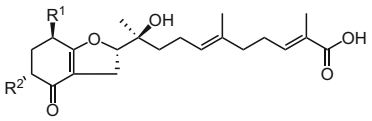
253 (tricycloalternarene C)



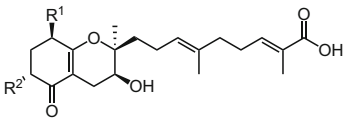
254 (bicycloalternarene A)



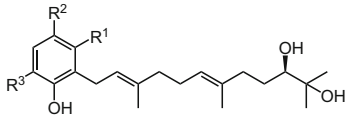
255 (bicycloalternarene B)



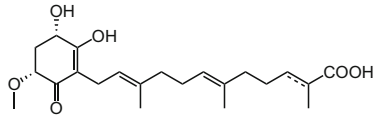
256 R^1 = OH, R^2 = H (bicycloalternarene C)
257 R^1 = H, R^2 = OH (bicycloalternarene D)



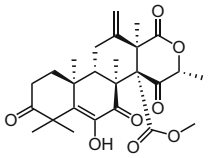
258 R^1 = H, R^2 = OH (bicycloalternarene E)
259 R^1 = OH, R^2 = H (bicycloalternarene F)



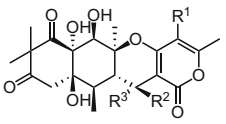
260 R^1 = OH, R^2 = OMe, R^3 = H (monocycloalternarene A)
261 R^1 = H, R^2 = COOH, R^3 = OH (monocycloalternarene B)



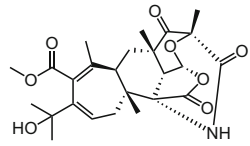
262 (monocycloalternarene C)
263 Δ (monocycloalternarene D)



264 (1,2-dihydroterretonin F)



265 R^1 = Me, R^2 + R^3 = O (aspertetranone A)
266 R^1 = Me, R^2 = R^3 = H (aspertetranone B)
267 R^1 = H, R^2 + R^3 = O (aspertetranone C)
268 R^1 = Me, R^2 = H, R^3 = OH (aspertetranone D)



269 (aspergstressin)

Fig. 15 Structures of merosesquiterpenes (part 5)

3.2 Other Meroterpenes and Prenylated Polyketides

The fungus *Penicillium oxalicum*, obtained from the green alga *Codium fragile* collected from the Qingdao coastline, produced 15-hydroxydecaturin A (**270**) (Fig. 16) following fermentation of the fungus on solid rice medium

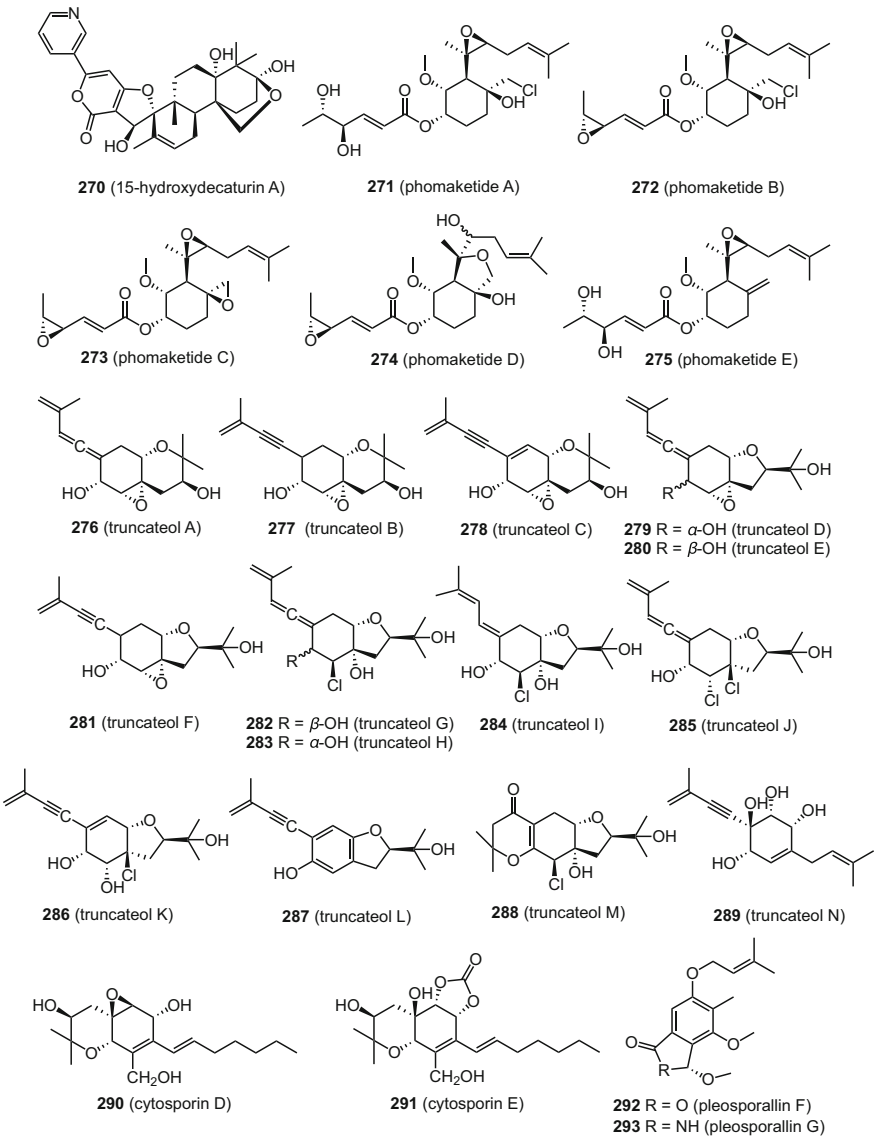


Fig. 16 Structures of other meroterpenes and prenylated polyketides (part 1)

[89]. Phomaketides A–E (**271**–**275**) were obtained from the liquid YPD medium fermentation broth and mycelium of *Phoma* sp. NTOU4195, an endophytic fungus isolated from the marine red alga *Pterocladiella capillacea* collected in the intertidal zone of northern Taiwan. Phomaketide A (**271**) exhibited potent antiangiogenic activity by suppressing the tube formation of human endothelial progenitor cells with an IC_{50} value of 8.1 μ*M*, while phomaketide C (**273**) showed selective inhibitory activity of LPS-induced NO production in RAW264.7 macrophages with an IC_{50} value of 8.8 μ*M* [90]. The fungal strain *Truncatella angustata* was obtained from the finger sponge *Amphimedon* sp. collected from a reef at Yongxing Island, Hainan Province. Fermentation of *T. angustata* on solid rice medium yielded fourteen isoprenylated cyclohexanols, truncateols A–N (**276**–**289**). Truncateol M (**288**) inhibited replication of the H1N1 virus (IC_{50} 8.8 μ*M*) possibly by targeting virion assembly/release steps [91]. Cytosporins D and E (**290** and **291**) were isolated from the malt extract broth of *Eutypella scoparia* ICB-OBX, an organism obtained from the surface of the marine pulmonate *Onchidium* sp. collected in the intertidal zone along the coast of Lingshui County, Hainan Province [92]. Pleosporallins F and G (**292** and **293**) were obtained from *Pleosporales* sp., an endophyte from the marine alga *Enteromorpha clathrata* collected in the South China Sea in Hainan Province, following cultivation of the fungus in liquid Czapek's medium (Fig. 16) [50].

The sponge-associated fungus *Emericella variecolor* XSA-07-2 was obtained from *Cinachyrella* sp. collected from Yongxing Island in the South China Sea. Fermentation of this fungus on solid rice medium with sterilized artificial seawater yielded five hybrid PKS-isoprenoid metabolites, varioxiranols F, G, I, and J (**294**–**297**) (Fig. 17), and 19-*O*-methyl-22-methoxypre-shamixanthone (**298**) [57]. Varioxiranols I and J (**296** and **297**) displayed significant cytotoxicity against the HCT-116, BGC-823, NCI-H1650, and A2780 cancer cell lines with IC_{50} values ranging from 5.2 to 9.2 μ*M* [32]. Seven prenylated polyketide derivatives, heterocornols F−L (**299**–**305**), were obtained from the solid rice medium culture of *Pestalotiopsis heterocornis*, which was isolated from the sponge *Phakellia fusca* collected from the Xisha Islands, Hainan Province. Heterocornols F−H (**299**–**301**) exhibited weak cytotoxicity against a human gastric carcinoma cell line (BGC-823), a human large-cell lung carcinoma cell line (H460), a human prostate cancer cell line (PC-3), and a human hepatocellular carcinoma cell line (SMMC-7721), with IC_{50} values ranging from 15.0 to 83.5 μ*M*. The compounds furthermore showed antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* with *MIC* values ranging from 25 to 100 μg/cm^3 [59].

Fermentation on solid rice medium of *Pestalotiopsis* sp. ZJ-2009-7-6, obtained from the soft coral *Sarcophyton* sp. collected from Yongxing Island in the South China Sea, yielded the chlorinated benzophenone derivatives, (±)-pestalachlorides D−F (**306**–**308**). Pestalachloride D (**306**) was obtained as a racemic mixture and exhibited antibacterial activity against *Escherichia coli*, *Vibrio anguillarum*, and *Vibrio parahaemolyticus* with *MIC* values of 5.0, 10.0, and 20.0 μ*M*, respectively [93]. Pestalachlorides E and F (**307** and **308**) were likewise found to be racemic and displayed atropisomerism. Both compounds showed potent antifouling activity against settlement of larvae of the barnacle *Balanus amphitrite* at nontoxic

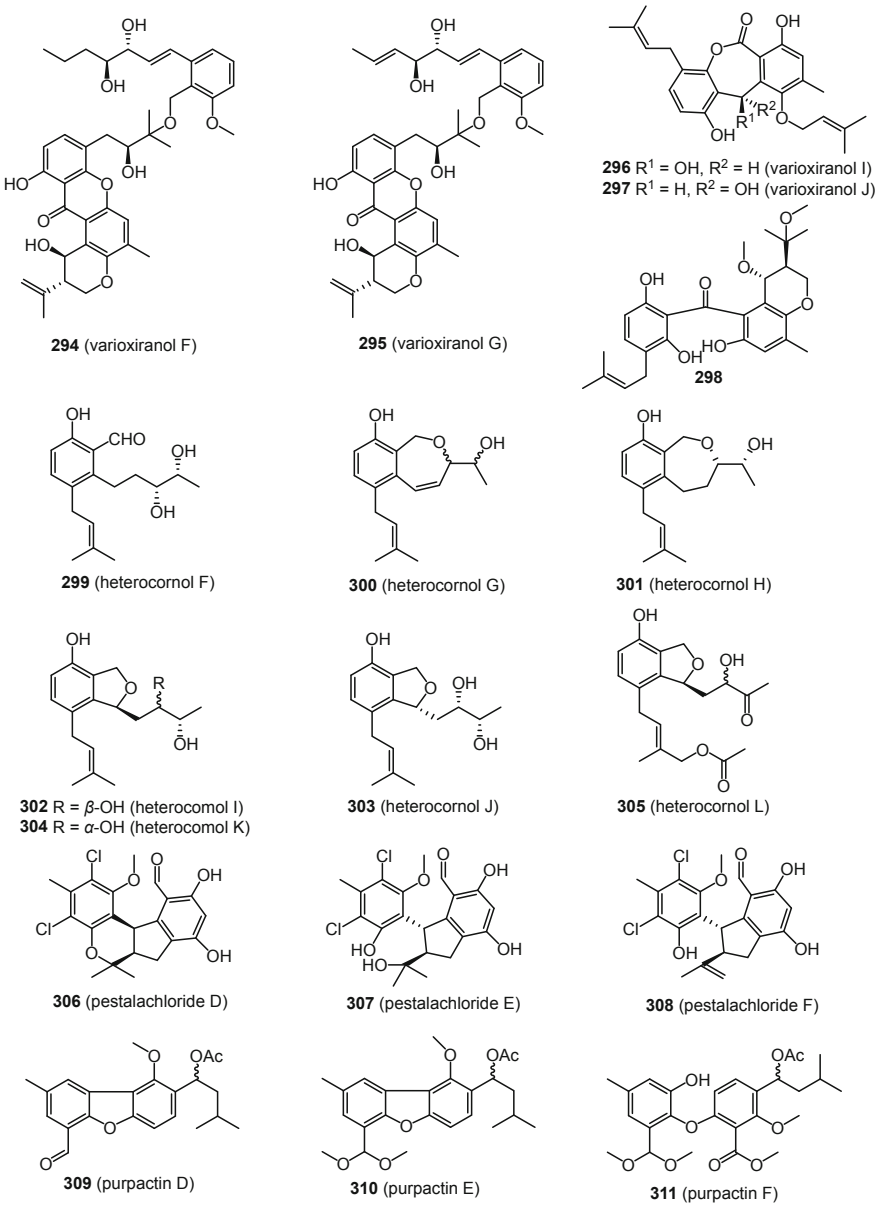


Fig. 17 Structures of other meroterpenes and prenylated polyketides (part 2)

concentrations with EC_{50} values of 1.7 and 0.6 μg/cm^3, respectively [94]. Liquid potato glucose medium fermentation of *Talaromyces* sp., a gorgonian-derived fungus from *Subergorgia suberosa* collected from the South China Sea, yielded three diphenyl ether derivatives, purpactins D–F (**309**–**311**) (Fig. 17) [95].

4 Terpenes

4.1 Sesquiterpenes

The most frequently reported terpenes from marine fungi are sesquiterpenes. Their distribution among fungi is diverse and there is no clear focus of accumulation in a particular fungal genus. The fungal strain *Penicillium* sp. SCS-KFD08 was isolated from the marine worm *Sipunculus nudus* collected from Haikou Bay, Hainan. The sesquiterpene aculene E (**312**) (Fig. 18) was obtained from solid rice medium fermentation of this fungus and showed quorum-sensing inhibition against *Chromobacterium violaceum* CV026 at a concentration of 50 μg/well [23]. *Neosartorya pseudofischeri* was isolated from the inner tissue of the starfish *Acanthaster planci* collected from Hainan Sanya National Coral Reef Reserve. Fermentation of this fungus in liquid GPY medium yielded deacetylsesquiterpene (**313**), showing more potent cytotoxicity against the Sf9 cell line from the fall armyworm *Spodoptera frugiperda* at a concentration of 50 mg/dm^3 than the positive control rotenone [19]. Isopolisin B (**314**) was obtained from a solid rice culture of *Pestalotiopsis heterocornis*, as isolated from the sponge *Phakellia fusca* collected from the Xisha Islands in the South China Sea [22]. *Pestalotiopsis* sp. Z233 was isolated from a marine alga *Sargassum horneri*, which was obtained from the

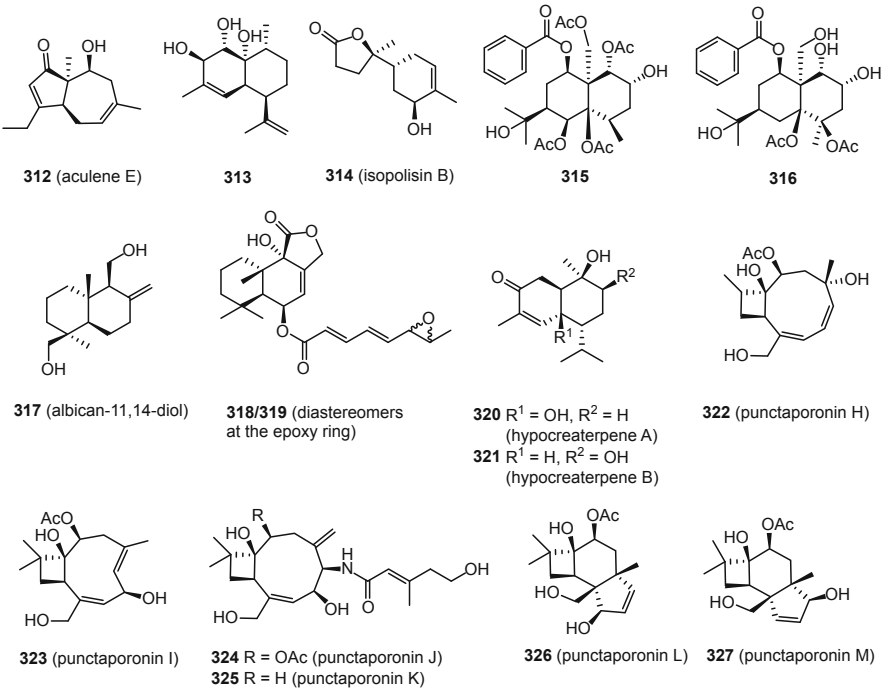


Fig. 18 Structures of sesquiterpenes (part 1)

seashore at Wenzhou. Two eudesmane-type sesquiterpenes (**315** and **316**) were isolated from the mycelia of this fungus following addition of 50 μ*M* $CuCl_2$ to the liquid medium composed of sucrose, yeast extract, silkworm chrysalis, and seawater. The compounds showed tyrosinase inhibitory activity with IC_{50} values of 14.8 and 22.3 μ*M*, respectively, comparable to the positive control kojic acid (IC_{50} 21.2 μ*M*) [96]. The fungal strain *Aspergillus versicolor* dl29 was isolated from the marine green alga *Codium fragile*, which was collected off the coast of Dalian. Fermentation of this fungus in liquid potato dextrose broth medium yielded the sesquiterpene albican-1,14-diol (**317**). Albican-1,14-diol (**317**) exhibited antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* at a concentration of 30 μg/disk with inhibitory diameters of 7 and 10 mm, respectively [97]. Two sesquiterpenes diastereomers, (6-strobilactone-B) esters of (*E*,*E*)-6,7-epoxy-2,4-octadienoic acids (**318** and **319**), were produced in liquid PDB medium by *Aspergillus ustus* cf-42, which was isolated from the marine green alga *Codium fragile* collected from Zhoushan Island [86]. Two adinane sesquiterpenes, hypocreaterpenes A and B (**320** and **321**), were obtained from the liquid GPY medium fermentation of *Hypocreales* sp. HLS-104 that was isolated from the sponge *Gelliodes carnosa* [98]. The sponge *Niphates* sp. collected in the South China Sea yielded the fungus *Hansfordia sinuosae*. Fermentation of this fungus on solid rice medium led to the isolation of six caryophyllene-type sesquiterpenes, punctaporonins H−M (**322–327**). These compounds were tested for oleic acid-induced lipid accumulation in HepG2 liver cells. Punctaporonin K (**325**) reduced the intracellular level of triglycerides and total cholesterol in a dose-dependent manner, comparable to the positive control lovastatin (Fig. 18) [99].

Pseudallescheria boydii was isolated from the inner tissue of the soft coral *Lobophytum crassum* collected from the Hainan Sanya National Coral Reef Reserve. Fermentation of *P. boydii* in liquid GSY medium yielded two aromadendrane sesquiterpene diastereomers, pseuboydones A and B (**328** and **329**) (Fig. 19), which are the first aromadendranes reported from marine fungi [100]. Six additional aromadendrane sesquiterpenes, scedogiines A−F (**330–335**), were obtained from the liquid GPY medium cultivation of *Scedosporium dehoogii* F41-4, which was isolated from the sponge *Phyllospongia foliascens* collected from Sanya National Coral Reef Reserve [101]. The fungus *Chondrostereum* sp. was isolated from the inner tissue of the soft coral *Sarcophyton tortuosum*, which was collected from Sanya Bay off the South China Sea. Fermentation of this fungus in liquid PDB medium yielded five triquinane sesquiterpenes, chondrosterins A−E (**336–340**), and two hirsutane sesquiterpenes, chondrosterin F (**341**) and hirsutanol E (**342**). Further fermentation of the fungus in the same medium with the addition of glycerol as carbon source furnished two additional hirsutane sesquiterpenes, chondrosterins I and J (**343** and **344**), while fermentation in liquid GPY medium afforded three additional triquinane sesquiterpenes, chondrosterins K−M (**345–347**). Chondrosterin A (**336**) showed significant cytotoxic activity against the A549, CNE2, and LoVo cancer cell lines with IC_{50} values of 2.5, 4.9, and 5.5 μ*M*, respectively. In turn, chondrosterin J (**344**) exhibited potent cytotoxicity against the CNE1 and CNE2 cancer cell lines with IC_{50} values of 1.3 and 0.6 μ*M*,

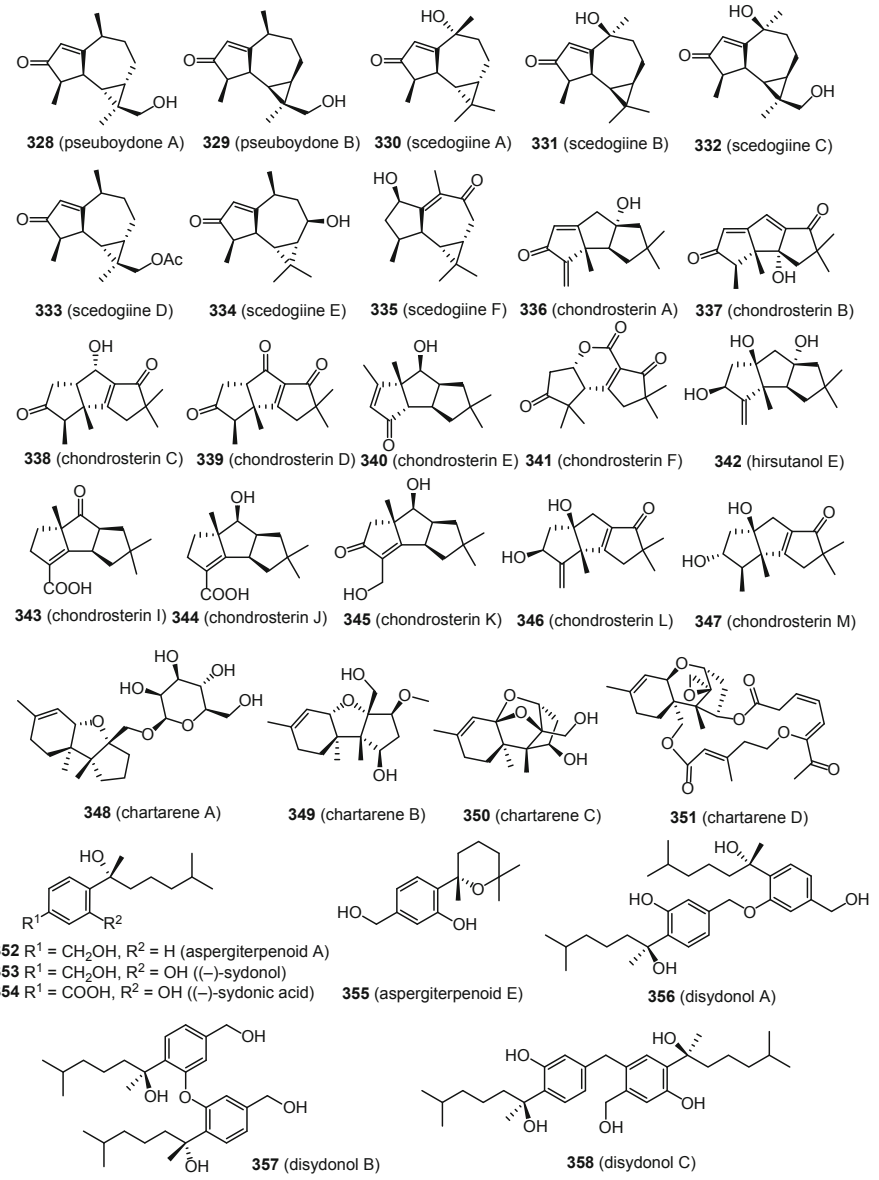


Fig. 19 Structures of sesquiterpenes (part 2)

respectively, whereas chondrosterin K−M (**345**–**347**) showed moderate cytotoxic potency against a panel of cancer cell lines (CNE1, CNE2, HONE1, SUNE1, A549, GLC82, and HL7702) with IC_{50} values ranging from 12 to 59 μ*M* [102–106].

The fungus *Stachybotrys chartarum* WGC-25C-6 was isolated from the sponge *Niphates recondita*, collected from the inner coral reef in Beibuwan Bay.

Fermentation of *S. chartarum* on solid rice medium produced four trichothecene-based sesquiterpenes, chartarenes A−D (**348**–**351**). These compounds were tested against a panel of human cancer cell lines (HCT-116, HepG2, BGC-823, NCI-H1655, and A2780) and exhibited potent cytotoxicity against most of these cell lines with IC_{50} values ranging from 0.6 to 10 μ*M*. Chartarene B (**349**) was selectively cytotoxic to HCT-116 cells with an IC_{50} value of 5.6 μ*M* [107]. Aromatic bisabolane derivatives were reported from a strain of *Aspergillus* sp. that was isolated from the inner tissue of the sponge *Xestospongia testudinaria* collected from the Weizhou coral reef in the South China Sea. The broth of liquid GPY medium fermentation yielded four bisabolane sesquiterpenes (**352**–**355**) and three dimers, disydonols A−C (**356**–**358**). Compounds **352**–**355** were tested for their antibacterial activity against *Staphylococcus albus*, *Bacillus subtilis*, *B. cereus*, *Sarcina lutea*, *Escherichia coli*, *Micrococcus tetragenus*, *Vibrio parahaemolyticus*, and *V. anguillarum*. Each compound showed activity against one or several strains with *MIC* values between 1.3 and 20.0 μ*M*. Disydonols A and C (**356** and **358**) exhibited cytotoxicity against the HepG-2 human hepatoma and Caski human cervical cell lines, with IC_{50} values of 19.1 and 25.5 μ*M* and 6.0 and 21.0 μ*M*, respectively (Fig. 19) [108, 109].

4.2 Diterpenes

The fungal strain *Trichoderma citrinoviride* cf-27 was isolated from the marine brown alga *Dictyopteris prolifera* collected from Zhoushan. Fermentation of *T. citrinoviride* on solid rice medium yielded a diterpene, trichocitrin (**359**) (Fig. 20). In an antibacterial disk diffusion assay, trichocitrin (**359**) exhibited an 8 mm inhibition zone against *Escherichia coli* at a concentration of 20 μg/disk. Furthermore, it showed 54.1% growth inhibition against the microalga *Prorocentrum donghaiense* at a concentration of 80 μg/cm^3 [19]. Seven antranone diterpenes (**360**–**366**) were obtained from a solid rice culture of *Stachybotrys chartarum* 952, isolated from the crinoid *Himerometra magnipinna* collected in the Zhanjiang Mangrove National Nature Reserve [110].

Two cyclopiane diterpenes, conidiogenones H and I (**367** and **368**), were isolated from solid rice fermentation of *Penicillium chrysogenum* QEN-24S, a fungus obtained from the inner tissue of the marine red alga *Laurencia* sp. collected from Weizhou Island in the South China Sea [111]. From the liquid GPY medium fermentation of *Epicoccum* sp. isolated from the sea cucumber *Apostichopus japonicus*, one isopimarane diterpene (**369**) and three pimarane diterpenes (**370**–**372**) were isolated. Compound **369** exhibited α-glucosidase inhibitory activity with an IC_{50} value of 4.6 μ*M*, while **370** showed cytotoxicity against the KB and KBv200 human cancer cell lines with IC_{50} values of 10.1 and 6.8 μ*M*, respectively [112, 113]. A strain of *Trichoderma erinaceum* was isolated from the inner tissue of the starfish *Acanthaster planci* collected from Sanya National Coral Reef Reserve. Liquid GPY medium fermentation of this fungus yielded a diterpene lactone,

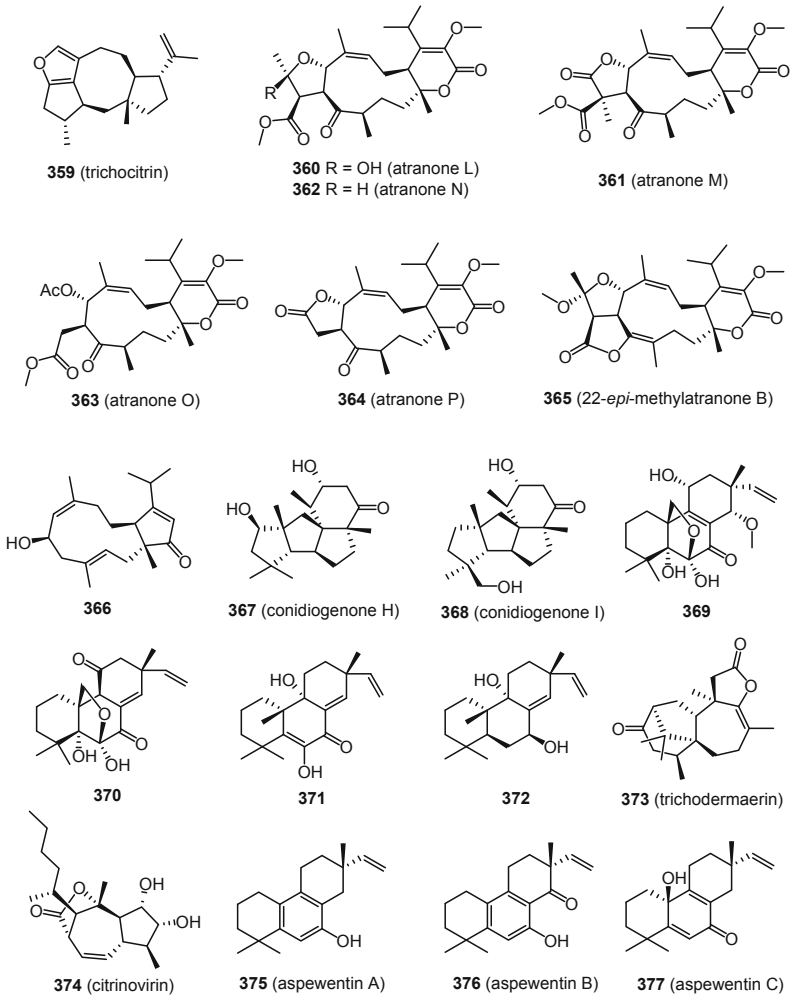


Fig. 20 Structures of diterpenes

trichodermaerin (**373**) [114]. Fermentation on solid rice medium of *Trichoderma citrinoviride* cf-27, isolated from the marine brown alga *Dictyopteris prolifera* collected from Zhoushan, yielded a *nor*-diterpene, citrinovirin (**374**). Citrinovirin (**374**) inhibited the growth of *Staphylococcus aureus* with an *MIC* value of 38.5 μ*M* [115]. The fungal strain *Aspergillus wentii* na-3 was isolated from the marine brown alga *Sargassum fusiforme* collected from Nanao Island. Cultivation of this fungus in liquid medium containing suberoylanilide hydroxamic acid yielded three *nor*-diterpenes, aspewentins A−C (**375**–**377**). These compounds were tested for their growth inhibition against marine zooplankton (*Artemia salina*) and against three marine phytoplankton species (*Chattonella marina*, *Heterosigma akashiwo*, and

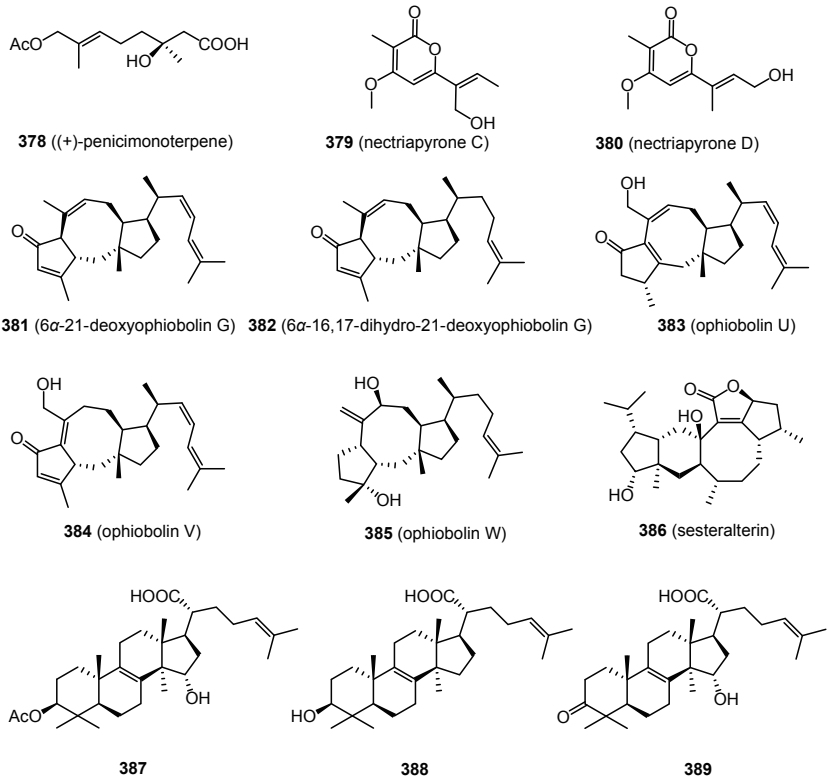
Alexandrium sp.). Aspewentins A−C (**375**–**377**) proved to be toxic to all three phytoplankton species with LC_{50} values ranging from 0.8 to 34.4 μ*M*, while only aspewentin B (**376**) was lethal to *A. salina* with an LC_{50} value of 6.4 μ*M* (Fig. 20) [116].

4.3 Other Terpenes

Monoterpenes are rarely reported from fungi. (+)-Penicimonoterpene ((3*S*,6*E*)-8-acetoxy-3-hydroxy-3,7-dimeethyl-6-octenoic acid) (**378**) (Fig. 21) was obtained from the solid rice medium fermentation of *Penicillium chrysogenum* QEN-24S. The fungus was isolated from the inner tissue of a marine red alga *Laurencia* sp. collected from Weizhou Island in the South China Sea. (+)-Penicimonoterpene (**378**) showed antifungal activity against *Aspergillus brassicae* in a disk diffusion assay with an inhibitory zone of 17 mm at 20 μg/disk [24]. Two monoterpenoid alpha-pyrones, nectriapyrones C and D (**379** and **380**), were produced on solid rice medium by *Nectria* sp., obtained from the marine sponge *Gelliodas carnosa* from the South China Sea [117].

During the time frame covered in this contribution, two publications reported six sesterterpenes from fungi from China. In both cases, the producing fungi were derived from marine algae. The endophyte *Aspergillus ustus* cf-42 was isolated from *Codium fragile* when collected from Zhoushan Island. Five sesterterpenes, 6α-21-deoxyophiobolin G (**381**), 6α-16,17-dihydro-21-deoxyophiobolin G (**382**), and ophiobolins U−W (**383**–**385**), were isolated from liquid PDB medium fermentation of this fungus. Ophiobolin U (**383**) showed antibacterial activity in a disk diffusion assay against *Escherichia coli* and *Staphylococcus aureus* with inhibitory zones of 15 and 10 mm, respectively [86]. The second sesterterpene-producing fungal endophyte *Alternaria alternata* k21-1 covered in this contribution was isolated from the surface of the marine red alga *Lomentaria hakodatensis* collected from Kongdong Island. Liquid PDB medium fermentation of *A. alternata* yielded sesteralterin (**386**). Sesteralterin (**386**) was evaluated for its toxicity against three phytoplankton species (*Chattonella marina*, *Heterosigma akashiwo*, and *Prorocentrum donghaiense*) and was reported as being moderately active at a dose of 250 μ*M* with growth inhibition ranging between 41 and 69% [84].

The only report of fungal triterpenes in this contribution is from the starfish-associated fungus *Ceriporia lacerata*, which was isolated from the inner tissue of *Acanthaster planci* collected from Sanya National Coral Reef Reserve. Fermentation of *C. lacerata* in liquid GPY medium yielded three lanostane triterpenes (**387**–**389**) (Fig. 21) [118].



378 ((+)-penicimonoterpene) **379** (nectriapyrone C) **380** (nectriapyrone D)

381 (6*α*-21-deoxyophiobolin G) **382** (6*α*-16,17-dihydro-21-deoxyophiobolin G) **383** (ophiobolin U)

384 (ophiobolin V) **385** (ophiobolin W) **386** (sesteralterin)

387 **388** **389**

Fig. 21 Structures of other terpenes

5 Steroids

Ergosterimide (**390**) (Fig. 22), a natural Diels–Alder adduct of ergosterol and maleimide, was obtained from a 2.4% artificial sea salt-containing GPY medium fermentation of *Aspergillus niger* EN-13, a fungal endophyte that was isolated from fresh tissue of the marine brown alga *Colpomenia sinuosa* collected off the Qingdao coastline [119]. Fermentation of *Aspergillus ochraceus* EN-31, which was isolated from the marine brown alga *Sargassum kjellmanianum* collected from the Dalian coastline, in a sea salt-containing liquid medium, yielded a pentalactone-containing norsteroid, 7-*nor*-ergosterolide (**391**), together with two steroids, 3*β*,11*α*-dihydroxyergosta-8,24(28)-dien-7-one (**392**) and 3*β*-hydroxyergosta-8,24(28)-dien-7-one (**393**). 7-*nor*-Ergosterolide (**391**) displayed cytotoxicity against the NCI-H460, SMMC-7721, and SW1990 cell lines with IC_{50} values of 12.1, 16.9, and 67.6 μ*M*, respectively, while compound **392** showed only weak cytotoxicity against the SMMC-7721 cell line with an IC_{50} value of 65.4 μ*M* [120].

The endophyte *Aspergillus versicolor* pt20 was isolated from the marine brown alga *Sargassum thunbergii* collected from Pingtan Island. Fermentation of this

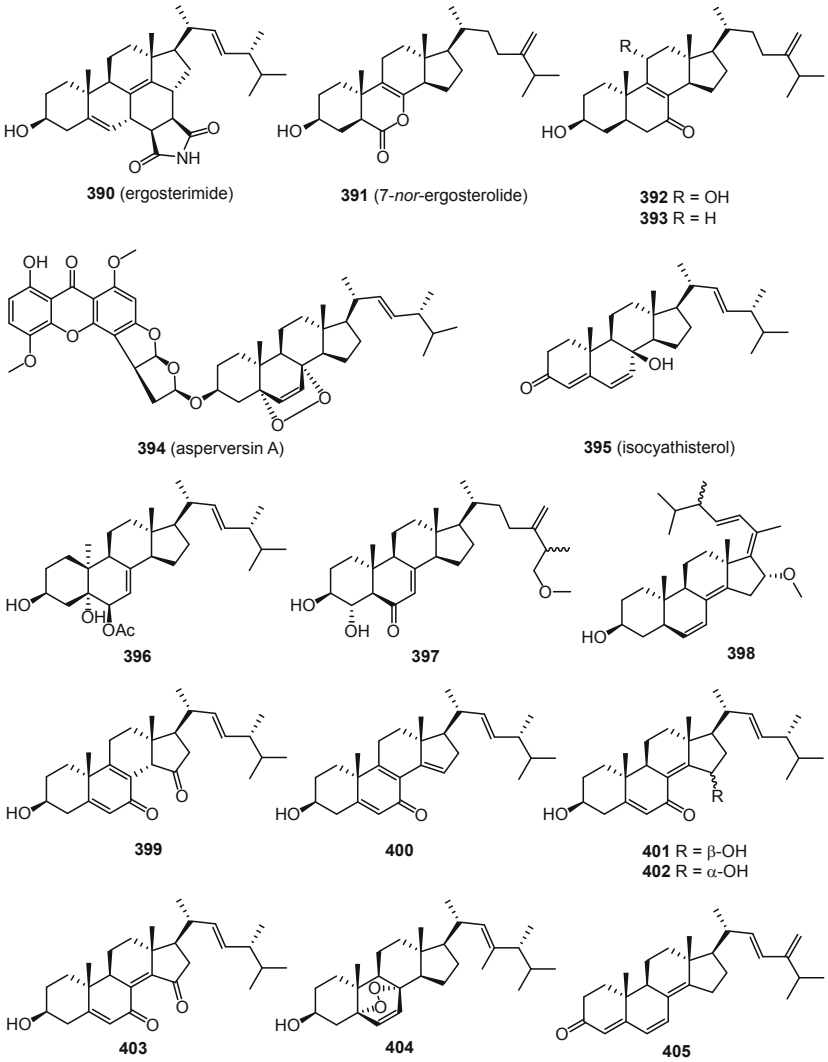


Fig. 22 Structures of steroids

fungus in PDB medium gave asperversin A (**394**) [121]. Isocyathisterol (**395**) was produced in a PDB culture of *Aspergillus ustus* that was isolated from the marine green alga *Codium fragile* collected from Zhoushan Island. Isocyathisterol (**395**) exhibited antibacterial activity in a Petri dish assay against *Escherichia coli* and *Staphylococcus aureus* with inhibitory diameters of 7 and 6 mm, respectively, at a dose of 30 μg/disk [122]. The endophytic fungal strain *Eurotium rubrum* cf-14 was isolated from the marine green alga *Codium fragile* collected off the coast of Yantai.

Fermentation of *E. rubrum* in PDB medium yielded 3β,5α-dihydroxy-10α-methyl-6β-acetoxy-ergosta-7,22-diene (**396**) [123].

The fungus *Aspergillus flavus* cf-5 was isolated from the marine red alga *Corallina officinali*s collected off the coast of Yantai. Fermentation of this fungus in PDB medium yielded 3β,4α-dihydroxy-26-methoxyergosta-7,24(28)-dien-6-one (**397**). Compound **397** possessed low inhibitory activity against AChE (inhibitory rate 10.3% at 100 μg/cm^3) [124]. Asporyergosterol (**398**) was obtained from the PDB culture of *Aspergillus oryzae* cf-2, which was isolated from the marine red alga *Heterosiphonia japonica* collected off the coast of Yantai [125]. The fungus *Rhizopus* sp., isolated from the marine bryozoan *Bugula* sp. collected in Jiaozhou Bay, was reported to produce six ergosterol derivatives, including 3β-hydroxy-(22*E*,24*R*)-ergosta-5,8,22-trien-7,15-dione (**399**), 3α-hydroxy-(22*E*,24*R*)-ergosta-5,8,14,22-tetraen-7-one (**400**), 3β,15β-dihydroxy-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7-one (**401**), 3β,15α-dihydroxy-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7-one (**402**), 3β-hydroxy-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7,15-dione (**403**), and 5α,8α-epidioxy-23,(24*R*)-dimethylcholesta-6,9(11),22-trien-3β-ol (**404**) when cultured in liquid GYM medium. Compounds **399**–**404** showed significant cytotoxicity against P388 cells and HL-60 cells with IC_{50} values below 10 μ*M* [126]. A highly conjugated steroid, (22*E*)-ergosta-4,6,8(14),22,24(28)-pentaen-3-one (**405**), was obtained from the liquid PDA medium culture of *Aspergillus* sp., which was isolated from the inner part of the gorgonian *Muricella abnormalis* collected from the Xisha Islands coral reef of the South China Sea. Compound **405** inhibited barnacle larval settlement with an EC_{50} value of 47.2 μ*M* (Fig. 22) [127].

6 Peptides Including Diketopiperazines

6.1 Diketopiperazines

Aspergillus versicolor pt20 was obtained from the brown alga *Sargassum thunbergii*, which was collected from Pingtan Island. The diketopiperazine 9ξ-*O*-2(2,3-dimethylbut-3enyl)brevianamide Q (**406**) (Fig. 23) was isolated from fermentation of this fungus in liquid potato dextrose medium [121]. The endophytic fungus *Eurotium cristatum* EN-220 was isolated from the brown alga *Sargassum thunbergii* collected from the coast of Qingdao. Fermentation of *E. cristatum* on solid rice medium yielded cristatumins A−D (**407**–**410**), while addition of 0.6% peptone to solid rice medium gave four additional indole diketopiperazines (**411**–**414**). Compounds **408** and **412** showed weak toxic activity in a brine shrimp assay (*Artemia salina*) with LD_{50} values of 156 and 46 μ*M* [128, 129]. Epoxyisoechinulin A (**415**) was obtained from soybean medium fermentation of *Aspergillus ruber*, which was isolated from the crinoid *Himerometra magnipinna* collected from the coral reef national reserve at Xuwen, Zhanjiang City, in Guangdong Province [130].

Fermentation on solid rice medium of *Aspergillus* sp. XS-20090066, isolated from the gorgonian *Dichotella gemmacea* collected from the Xisha Islands coral

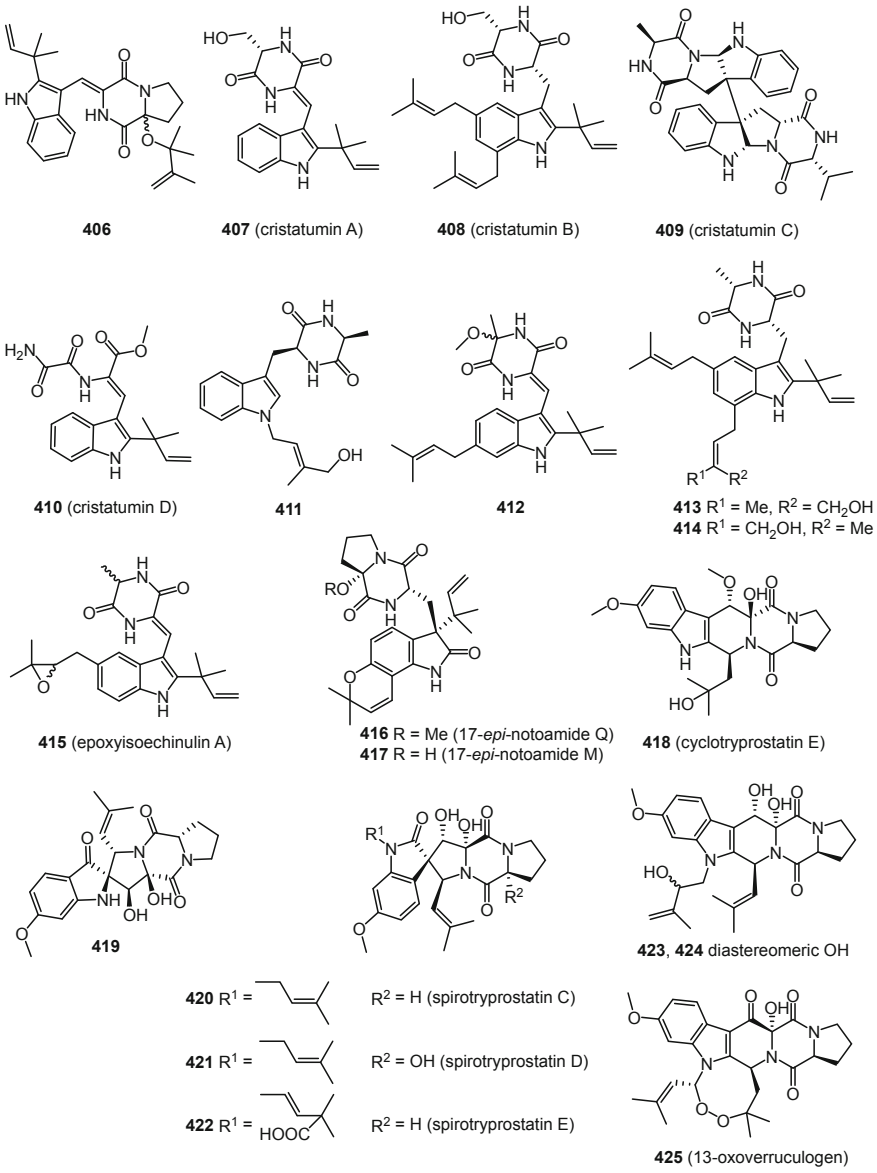


Fig. 23 Structures of diketopiperazines (part 1)

reef, yielded two indole diketopiperazines, 17-*epi*-notamides Q and M (**416** and **417**) [131]. The fungus *Aspergillus sydowii* SCSIO 00305 was purified from the gorgonian *Verrucella umbraculum* collected from Sanya, Hainan Province. The indole diketopiperazine cyclotryprostatin E (**418**) was isolated from the mycelium of liquid GYM medium fermentation of this fungus [132]. A strain of *Aspergillus fumigatus*

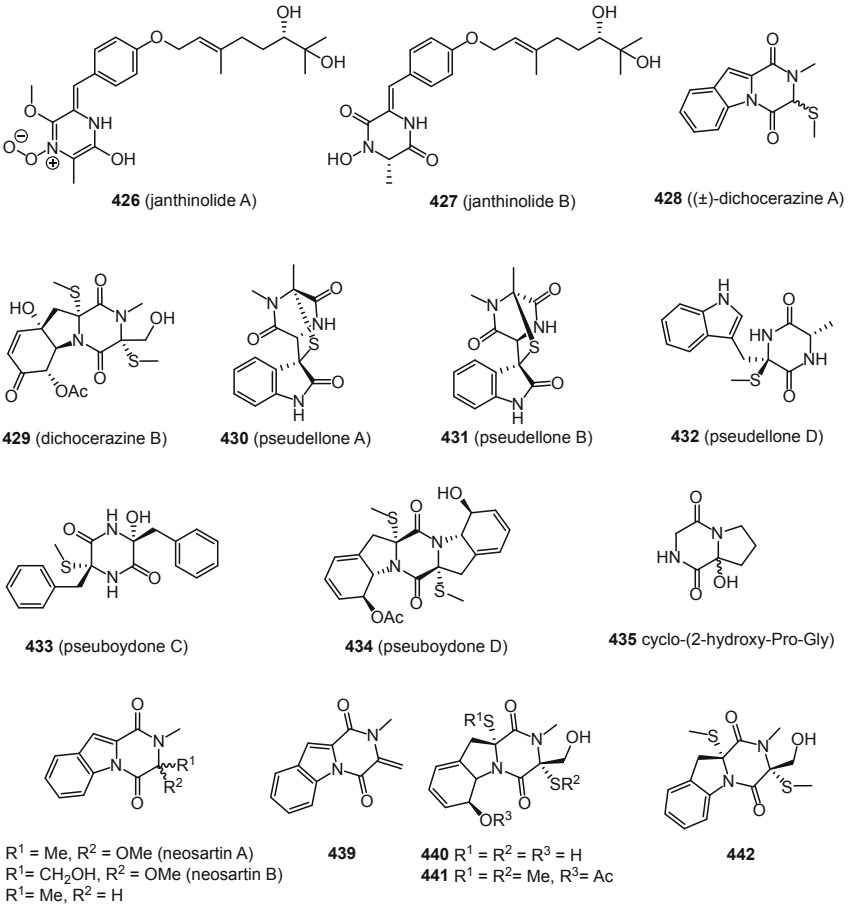


Fig. 24 Structures of diketopiperazines (part 2)

was obtained from the sea cucumber *Stichopus japonicus* that was collected from Lingshan Island, Qingdao, Shandong Province. Liquid GYM medium fermentation of *A. fumigatus* yielded seven prenylated indole diketopiperazines (**419**–**425**). Compound **422** was active against the MOLT-4, HL-60, and A-549 cell lines with IC_{50} values of 3.1, 2.3, and 3.1 μ*M*, respectively. Compound **423** was active against two further cell lines, HEL-60 and BEL-7402, with IC_{50} values of 3.4 and 7.0 μ*M*, respectively. Compounds **424** and **425** were active against the HL-60 cell line with IC_{50} values of 5.4 and 1.9 μ*M* (Fig. 23) [133].

The fungal strain *Penicillium janthinellum* was isolated from the soft coral *Dendronephthya* sp. collected in the South China Sea. Two 2,5-piperazinediones, janthinolides A and B (**426** and **427**) (Fig. 24), were obtained from the mycelium of liquid potato extract medium fermentation of *P. janthinellum* [134]. The fungus *Dichotomomyces cejpii* from the soft coral *Lobophytum crassum* collected from the

Sanya National Coral Reef Reserve gave dichocerazines A and B (**428** and **429**), when the fungus was fermented in L-tryptophan- and L-phenylalanine-enriched liquid medium [52]. Fermentation of *Pseudallescheria ellipsoidea* F42−3 in liquid GPY medium, as isolated from the inner tissue of the soft coral *Lobophytum crassum* collected from the Sanya National Coral Reef Reserve, yielded pseudellones A, B, and D (**430**–**432**) containing unusual monosulfide bridges [17, 135].

The fungus *Pseudallescheria boydii* was isolated from the soft coral *Lobophytum crassum* collected from the Sanya National Coral Reef Reserve. Fermentation of *P. boydii* in liquid GSY medium afforded pseuboydones C and D (**433** and **434**). Pseuboydone C (**433**) showed significant cytotoxicity against the insect-derived cell line Sf9 with an IC_{50} value of 0.7 μ*M* [100]. Cyclo-(2-hydroxy-Pro-Gly) (**435**) was obtained from liquid medium fermentation of the fungus *Simplicillium* sp. YZ-11, as isolated from the marine sponge *Hymeniacidon perleve* collected from Dalian in Liaoning Province [58]. The fungus *Neosartorya pseudofischeri* was isolated from the inner tissue of the starfish *Acanthaster planci* collected from Sanya National Coral Reef Reserve. Liquid GPY medium fermentation of this fungus gave neosartins A and B (**436** and **437**) in addition to five additional diketopiperazines (**438**–**442**) that were not previously known as natural products. Compound **439** exhibited cytotoxicity against the human colon cancer cell line HCT-116 with an IC_{50} value of 10.3 μ*M*. Compound **440** displayed antibacterial activity against *Staphylococcus aureus* with an *MIC* value of 1.5 μ*M* and showed cytotoxicity against the HEK-293 human embryonic kidney cell line and the human HCT-116 and RKO colon cancer cell lines, with IC_{50} values of 1.3, 0.4, and 0.4 μ*M*, respectively (Fig. 24) [136].

6.2 Peptides

A strain of *Aspergillus* sp. was isolated from the gorgonian *Melitodes squamata* collected from Sanya in the South China Sea. Seven peptides were obtained from the sea salt-containing fermentation broth of this fungus, including three cyclic tetrapeptides, aspergillipeptides A−C (**443**–**445**) (Fig. 25), a cyclic pentapeptide, aspergillipeptide D (**446**), and three linear tetrapeptides, aspergillipeptides E−G (**447**–**449**). Aspergillipeptides D and E (**446** and **447**) showed antiviral activity against *Herpes simplex* virus type 1 (HSV-1) with IC_{50} values of 9.5 and 19.8 μ*M*, respectively. Aspergillipeptide D (**446**) also exhibited activity against two acyclovir-resistant clinical isolates with an IC_{50} value of 12.5 μ*M* in each case [27, 137].

A further strain of *Aspergillus* sp. was isolated from the inner tissue of the gorgonian *Muricella abnormalis* that was collected from the Xisha Islands coral reef in the South China Sea. From potato glucose liquid medium fermentation of this fungus, the cyclic pentapeptide asperpeptide A (**450**) and two lumazine peptides penilumamides C and D (**451** and **452**) were isolated. Feeding of L-methionine during fermentation additionally yielded penilumamide B (**453**). Asperpeptide A (**450**) showed antibacterial activity against *Bacillus cereus* and *Staphylococcus*

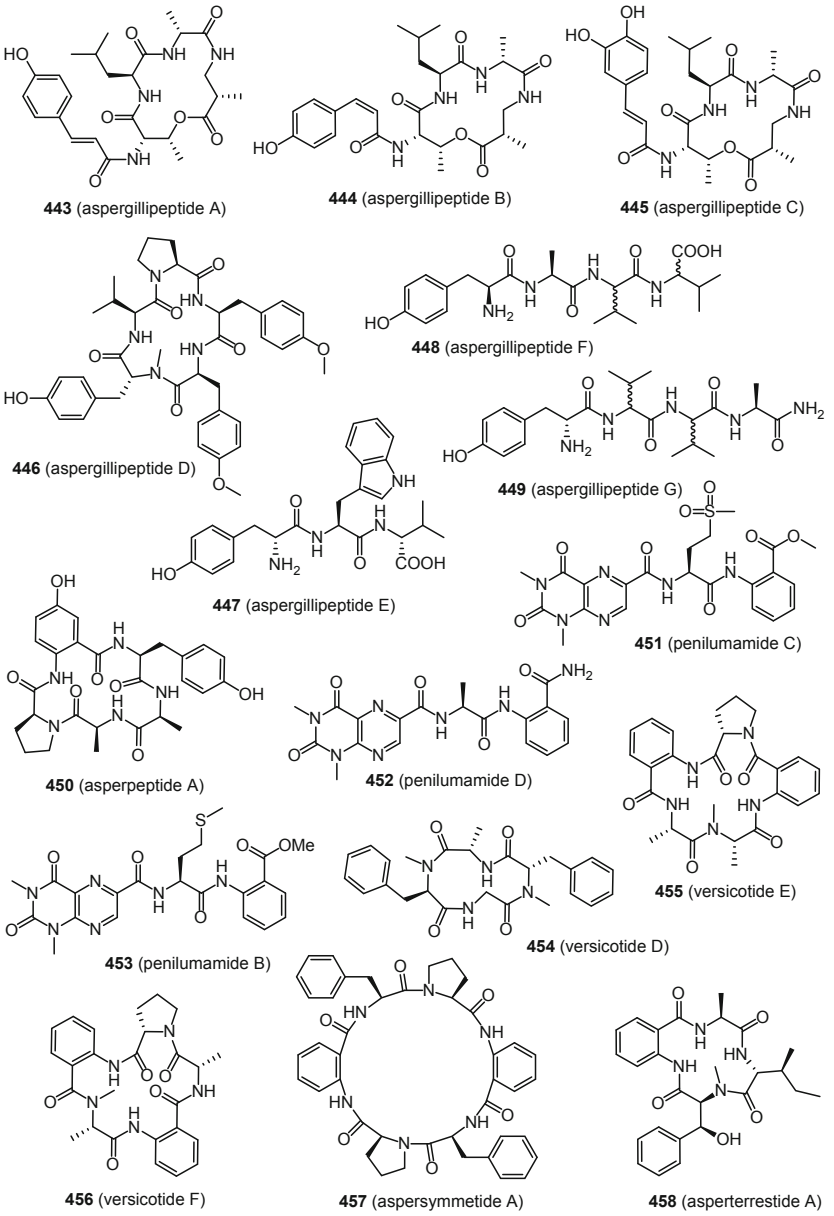


Fig. 25 Structures of peptides (part 1)

epidermidis with *MIC* values of 12.5 μ*M* against both bacteria [138]. Fermentation on solid rice medium of *Aspergillus versicolor*, isolated from the gorgonian *Pseudopterogorgia* sp. collected in the South China Sea, yielded a cyclic tetrapeptide, versicotide D (**454**) and two cyclic pentapeptides, versicotides E and

F (**455** and **456**). Versicotides D−F (**454–456**) showed cholesterol-lowering effects at a dose of 10 μ*M*, comparable to simvastatin through the regulation of cholesterol efflux to HDL in RAW264.7 macrophages. The mechanism of action was explained through promotion of the target genes ABCG1 and LXRa and a decrease in critical scavenger receptors CD36 and SR-1/SR-2 [139]. A further fungal strain of *Aspergillus versicolor* was isolated from the gorgonian *Carijoa* sp. collected from the Weizhou coral reefs in the South China Sea. Solid rice medium fermentation of this fungus gave a cyclic hexapeptide, aspersymmetide A (**457**) [140]. The fungal strain *Aspergillus terreus* was isolated from the gorgonian *Echinogorgia aurantiaca* collected from Sanya, Hainan Province. An unusual cyclic tetrapeptide, asperterrestide A (**458**), containing anthranilic acid and 3-OH-*N*-Me-Phe moieties, was obtained from fermentation of this fungus in liquid medium composed of maltose, NaCl, sorbitol, and yeast extract. Asperterrestide A (**458**) exhibited cytotoxic activity against the U937 and MOLT4 human carcinoma cell lines with IC_{50} values of 6.4 and 6.2 μ*M*, respectively, and also displayed antiviral activity against the H1N1 and H3N2 influenza viral strains, having IC_{50} values of 15.0 and 8.1 μ*M* (Fig. 25) [141].

A strain of *Aspergillus versicolor* was isolated from the soft coral *Cladiella* sp. collected from Lingao, Hainan Province. Three cyclopentapeptides, versicoloritides A−C (**459–461**) (Fig. 26), were obtained following fermentation of this fungus in liquid medium composed of sea salt, sorbitol, maltose, and yeast extract [66]. The fungus *Aspergillus clavatus* was isolated from the shell of the crab *Xenograpsus testudinatus* collected from hydrothermal vents in Kueishantao near Taiwan. From the mycelium and broth obtained from a cultivation of the fungus in liquid potato medium, two anthranilic acid-containing cyclic depsipeptides, clavatusides A and B (**462** and **463**), were isolated, while cultivation in a zinc-enriched medium yielded the cyclic pentapeptide clavatuside C (**464**). Clavatusides A and B (**462** and **463**) suppressed the proliferation of the HepG2, SMMC-7721, and Bel-7402 hepatocellular carcinoma cell lines in a dose- and time-dependent manner with IC_{50} values ranging between 32 and 64 μ*M*. Clavatuside B (**463**) was also active against several other human cancer cell lines including pancreatic cancer (Panc-1), gastric cancer (MGC-803), colorectal cancer (SW-480), retinoblastoma (WERI-Rb-1), and prostate cancer (PC3) cell lines in a dose-dependent manner with IC_{50} values ranging between 32 and 42 μ*M* [142, 143].

A cyclic tetrapeptide (**465**), containing the unusual amino acids 3-aminoacrylic acid and 3-methoxyanthranilic acid, was isolated from the solid rice medium fermentation of *Aspergillus flavipes* obtained from the gut of the marine isopod *Ligia oceanica* collected in Zhoushan, Zhejiang Province [144]. A strain of *Nigrospora oryzae* was obtained from the inner tissue of the sponge *Phakellia fusca* collected from Yongxing Island in the South China Sea. Fermentation of this fungus in liquid PDA medium yielded three cyclohexadepsipeptides, oryzamides A−C (**466–468**), and two isolation artifacts, oryzamides D and E (**469** and **470**), which are methionine sulfoxide diastereomers. Oryzamides A−E (**466–470**) all possess a rare 3-hydroxy-4-methyldecanoic acid moiety (Fig. 26) [145].

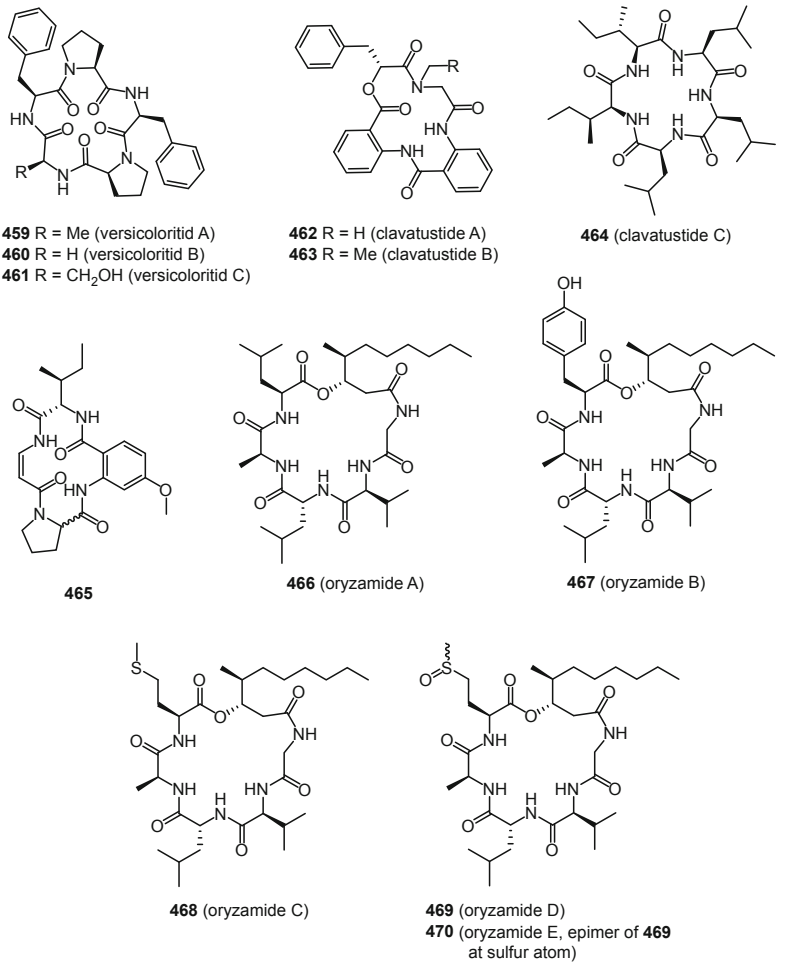


Fig. 26 Structures of peptides (part 2)

7 Alkaloids

7.1 Indole Alkaloids

Seven cytochalasans, cytoglobosins A−G (**471**–**477**) (Fig. 27), were obtained from the liquid potato dextrose broth medium cultivation of *Chaetomium globosum* QEN-14, an endophyte derived from the green alga *Ulva pertusa* collected on the Qingdao coastline. Cytoglobosins C and D (**473** and **474**) exhibited cytotoxicity against the A549 cell line with IC_{50} values of 2.3 and 2.6 μ*M* [146]. The fungus *Penicillium* sp. AS-79 was isolated from fresh tissue of the sea anemone *Haliplanella luciae* that was also sourced from the Qingdao coastline. Fermentation

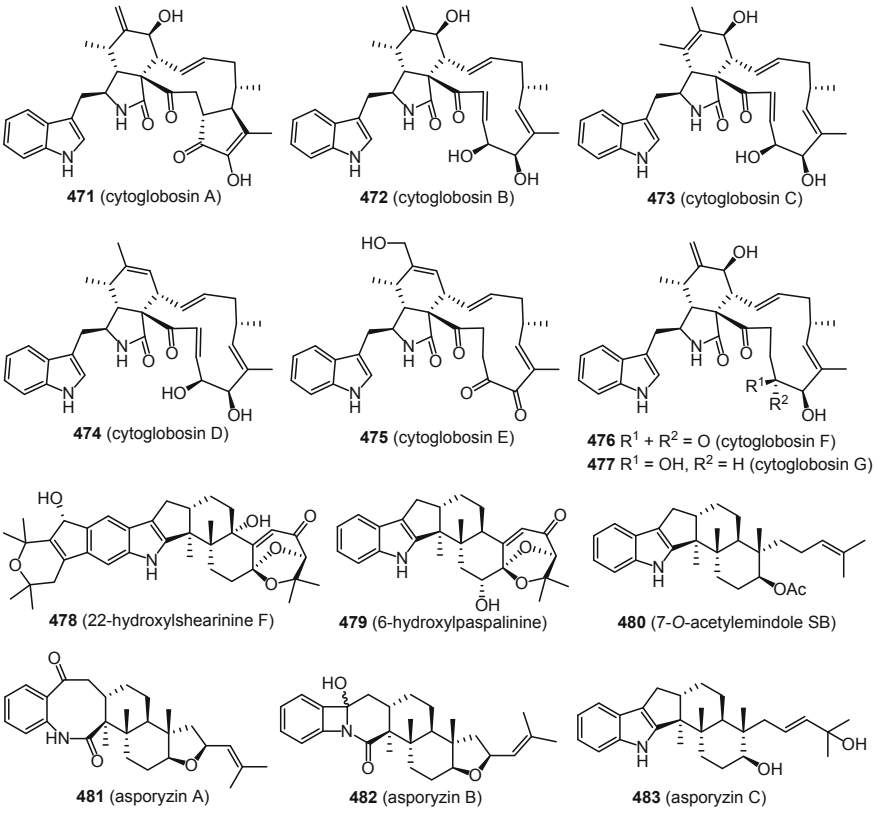


Fig. 27 Structures of indole alkaloids (part 1)

of this fungus on solid rice medium yielded three indole diterpenoids, 22-hydroxylshearinine F (**478**), 6-hydroxylpaspalinine (**479**), and 7-*O*-acetylemindole SB (**480**) [147]. Three further indole diterpene derivatives, asporyzins A−C (**481**–**483**), were isolated from the liquid PDB medium fermentation of *Aspergillus oryzae* as obtained from the marine red alga *Heterosiphonia japonica* [148].

The red alga *Polysiphonia scopulorum* collected from the Yantai coastline yielded *Aspergillus nidulans* EN-330. Two indole diterpenoids, 19-hydroxypenitrem A (**484**) and 19-hydroxypenitrem E (**485**), were obtained following fermentation of *A. nidulans* in liquid PDB medium (Fig. 28). 19-Hydroxypenitrem A (**484**) and 19-hydroxypenitrem E (**485**) displayed toxicity against brine shrimp (*Artemia salina*) with LD_{50} values of 3.2 and 4.6 μ*M*, respectively, more potent than that of the positive control colchicine with an LD_{50} value of 10.7 μ*M*. In addition, 19-hydroxypenitrem A (**484**) exhibited moderate antimicrobial activities against aquatic (*Edwardsiella tarda* and *Vibrio anguillarum*) and human pathogens (*Escherichia coli* and *Staphylococcus aureus*) with IC_{50} values of 16, 16,

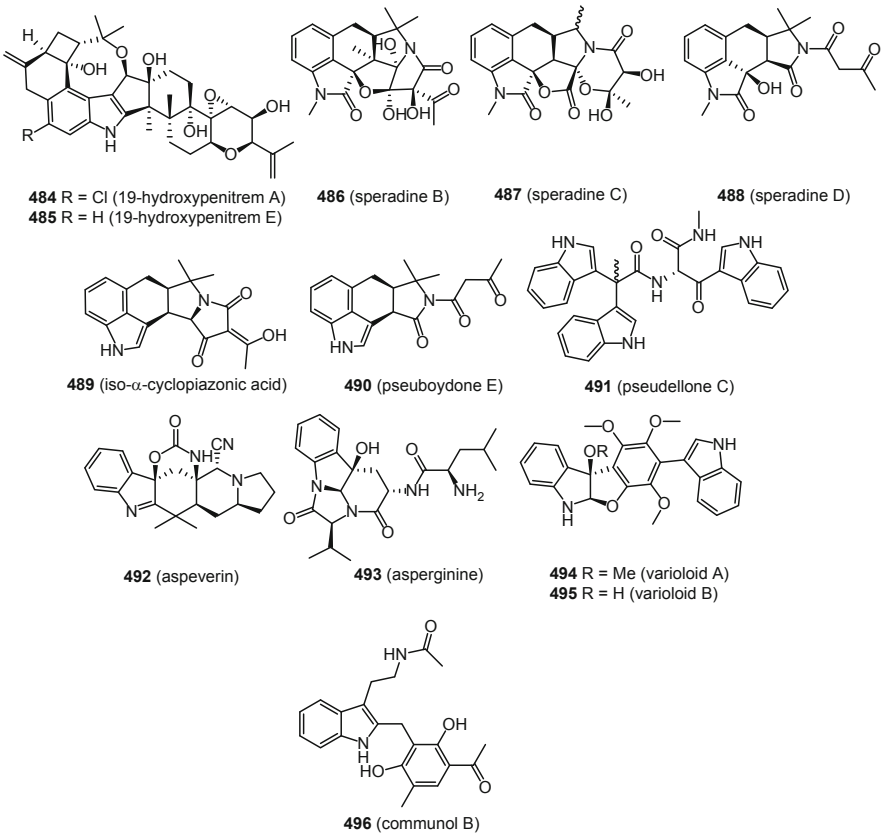


Fig. 28 Structures of indole alkaloids (part 2)

16, and 32 μg/cm^3 [149]. The fungal strain *Aspergillus flavus* MXH-X104 was obtained from the sponge *Agelas* aff. *nemoechinata* collected at the Xisha Islands. The seawater-containing liquid medium cultivation of this fungus yielded three oxygenated cyclopiazonic acid alkaloids, speradines B−D (**486**–**488**) [150]. Another strain of *Aspergillus flavus* coded c-f-3 was obtained from the green alga *Enteromorpha tubulosa* collected at Putian Pingha. Fermentation in liquid GYM medium gave iso-α-cyclopiazonic acid (**489**) [151]. From the soft coral *Lobophytum crassum* collected at the Hainan Sanya National Coral Reef Reserve, two fungal strains, *Pseudallescheria boydii* F19-1 and *P. ellipsoidea* F42−3, were obtained. *P. boydii* gave the cyclopiazonic acid analogue, pseuboydone E (**490**), when cultivated in liquid GSY medium [61], while *P. ellipsoidea* when grown in liquid GPY medium yielded pseudellone C (**491**), which possesses a unique skeleton with a 2,2-di(3-indolyl)-1-propone fragment attached to a tryptophan derivative via an amide bond [135].

A novel carbamate- and cyano-containing alkaloid, aspeverin (**492**), was isolated from the liquid PDB medium fermentation of *Aspergillus versicolor* dl-29, as

obtained from the green alga *Codium fragile* collected from the coast of Dalian. Aspeverin (**492**) inhibited growth of the marine phytoplankton *Heterosigma akashiwo* with EC_{50} values of 6.3 and 3.4 μg/cm^3 after 24 and 96 h, respectively [152]. When grown on solid 2216E medium, *Aspergillus* sp. Z-4, a gut-derived fungus from the marine isopod *Ligia oceanica* collected in Zhoushan, Zhejiang Province, gave asperginine (**493**) [153]. The fermentation in liquid PDB medium of *Paecilomyces variotii* EN-291, an endophyte obtained from the red alga *Grateloupia turuturu*, yielded two indole alkaloids varioloids A and B (**494** and **495**). Both compounds exhibited cytotoxicity against the A549, HCT116, and HepG2 cell lines with IC_{50} values ranging from 2.6 to 8.2 μg/cm^3 [154]. Communol B (**496**) was isolated from a liquid GPY medium cultivation of *Penicillium commune* 518, a fungus associated with the gorgonian *Muricella abnormalis* collected in Danzhou, Hainan Province (Fig. 28) [28].

7.2 Quinolone and Quinazoline Derivatives

The fungal strain *Aspergillus* sp. XS-20090B15 was derived from the gorgonian *Muricella abnormalis* collected in the South China Sea. Solid rice fermentation of this fungus led to the isolation of two prenylated dihydroquinolone derivatives, 22-*O*-(*N*-methyl-L-valyl)aflaquinolone B and 22-*O*-(*N*-methyl-L-valyl)-21-*epi*-aflaquinolone B (**497** and **498**) (Fig. 29). Compound **498** showed significant antiviral activity against the human respiratory syncytial virus (RSV) with an IC_{50} value of 42 n*M*, approximately 500-fold more potent than that of the positive control ribavirin (IC_{50} 20 μ*M*). The compound furthermore showed a high therapeutic ratio (TC_{50}/IC_{50} = 520), whereas its 21-epimer **497** exhibited no antiviral activity, suggesting that the configuration of the cyclohexane unit plays a key role in the anti-RSV activity [155].

3-Methoxyviridicatol (**499**), a 2-quinolinone derivative, was obtained from liquid potato sucrose medium fermentation of *Penicillium crustosum* AP2T1, a fungus derived from the fresh gill tissue of the shark *Isurus oxyrinchus* that was captured by fishermen in the Wenzhou marine area of Zhejiang Province [156]. When grown in liquid medium composed of sorbitol, yeast extract, maltose, and NaCl, the gorgonian-derived fungus *Aspergillus terreus* SCSGAF0162, which was obtained from *Echinogorgia aurantiaca* collected from Sanya, Hainan Province, yielded terremide C (**500**) [141]. A cyclopenin derivative, 9-hydroxy-3-methoxyviridicatin (**501**), and four quinazoline derivatives, versicomides A−D (**502**–**505**), were obtained from the liquid potato dextrose fermentation of *Aspergillus versicolor* XZ-4, derived from the crab *Xenograpsus testudinatus* collected from Kueishantao, Taiwan. 9-Hydroxy-3-methoxyviridicatin (**501**) exhibited inhibitory activities against *Escherichia coli* with a *MIC* value of 32 μg/cm^3 [157]. Another fungal strain of *Aspergillus versicolor* coded LZD-14-1 was obtained from the gorgonian *Pseudopterogorgia* sp. collected from the South China Sea. Fermentation of this fungus on solid rice medium resulted in the isolation of eleven fumiquinazoline-type

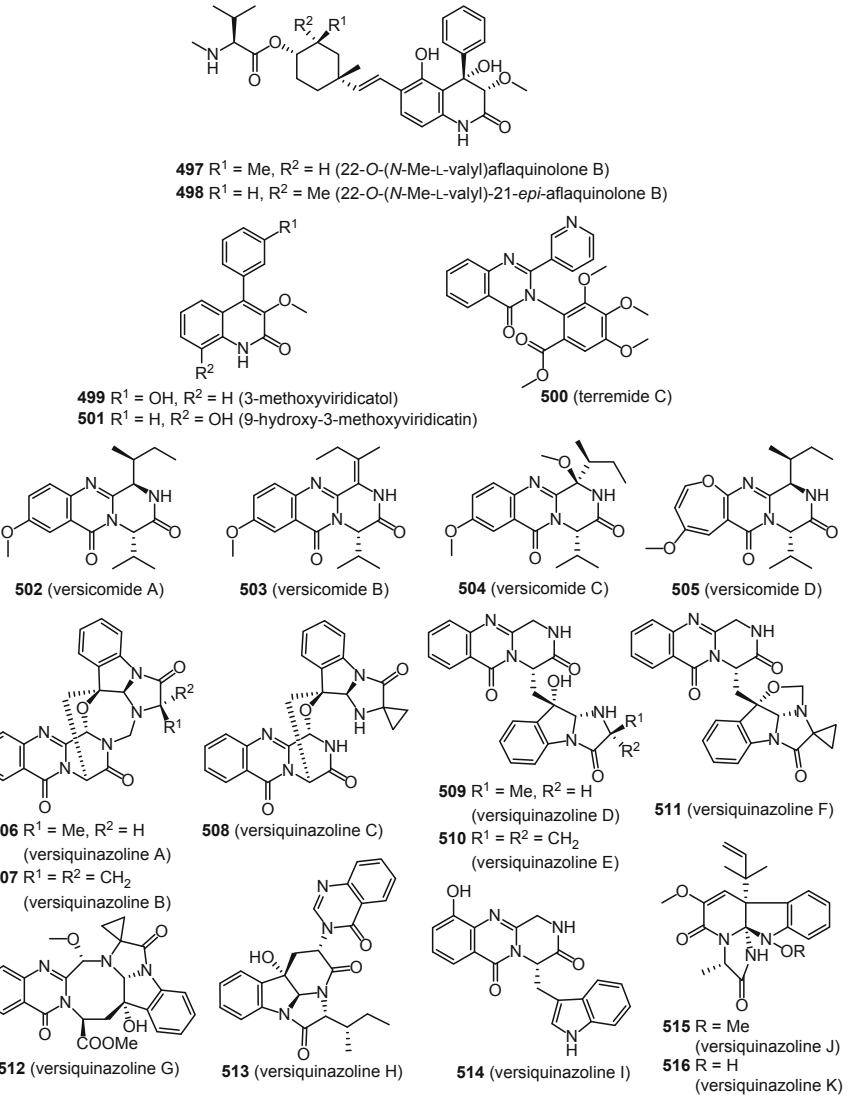


Fig. 29 Structures of quinolone and quinazoline derivatives (part 1)

alkaloids, versiquinazolines A−K (**506**–**516**). Versiquinazolines A, B, G, and K (**506**, **507**, **512**, and **516**) displayed inhibitory activities against thioredoxin with IC_{50} values of 20, 12, 13, and 13 μ*M*, respectively (Fig. 29) [158].

Fumiquinazoline L (**517**) (Fig. 30) was obtained from the liquid glucose potato medium fermentation of *Scopulariopsis* sp. TA01-33, a fungus associated with the gorgonian *Carijoa* sp. collected from the Weizhou coral reef in the South China Sea [159]. Neosartin C (**518**) was isolated from the liquid GPY medium cultivation of

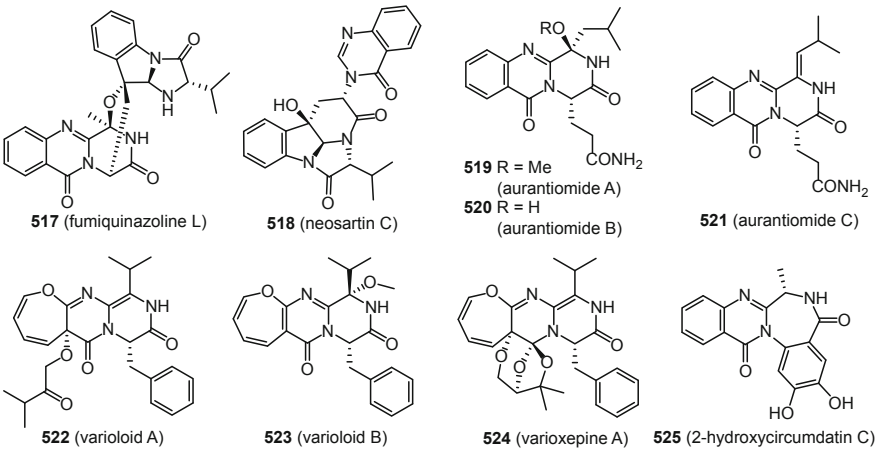


Fig. 30 Structures of quinolone and quinazoline derivatives (part 2)

Neosartorya pseudofischeri 2014F27-1, as obtained from the sea star *Acanthaster planci* collected from the Hainan Sanya National Coral Reef Reserve [136]. The fungus *Penicillium aurantiogriseum* SP0-19 was obtained from the sponge *Mycale plumosa* in Jiaozhou Bay, Qingdao. Cultivation of *P. aurantiogriseum* in liquid GYM medium yielded three quinazoline alkaloids, aurantiomides A−C (**519–521**) [160]. The red alga *Grateloupia turuturu* collected from the coast of Qingdao yielded *Paecilomyces variotii* EN-291. When cultivated in liquid PDB medium, this fungus gave three oxepine-containing alkaloids, varioloids A and B (**522** and **523**) and varioxepine A (**524**), showing antifungal activity against the plant pathogenic fungus *Fusarium graminearum* with *MIC* values of 8, 4, and 4 μg/cm^3, respectively [161, 162]. A benzodiazepine derivative, 2-hydroxycircumdatin C (**525**), was obtained from *Aspergillus ochraceus* 301, an endophytic fungus derived from the brown alga *Sargassum kjellmanianum* collected from the Dalian coastline, following fermentation of the fungus in liquid medium containing seawater, sorbitol, maltose, monosodium glutamate, and yeast extract. 2-Hydroxycircumdatin C (**525**) exhibited DPPH radical-scavenging activity with an IC_{50} value of 9.9 μ*M* (Fig. 30) [163].

7.3 Phenylalanine Derivatives

The fungus *Arthrinium arundinis* ZSDS1-F3 was obtained from the sponge *Phakellia fusca* collected from Xisha Islands. Four cytochalasins, arthriniumnins A−D (**526–529**) (Fig. 31), were reported when *A. arundinis* was cultivated in liquid medium composed of sorbitol, maltose, and yeast extract [164]. The soft coral *Sarcophyton* sp. gathered from the Weizhou coral reef in the South China Sea

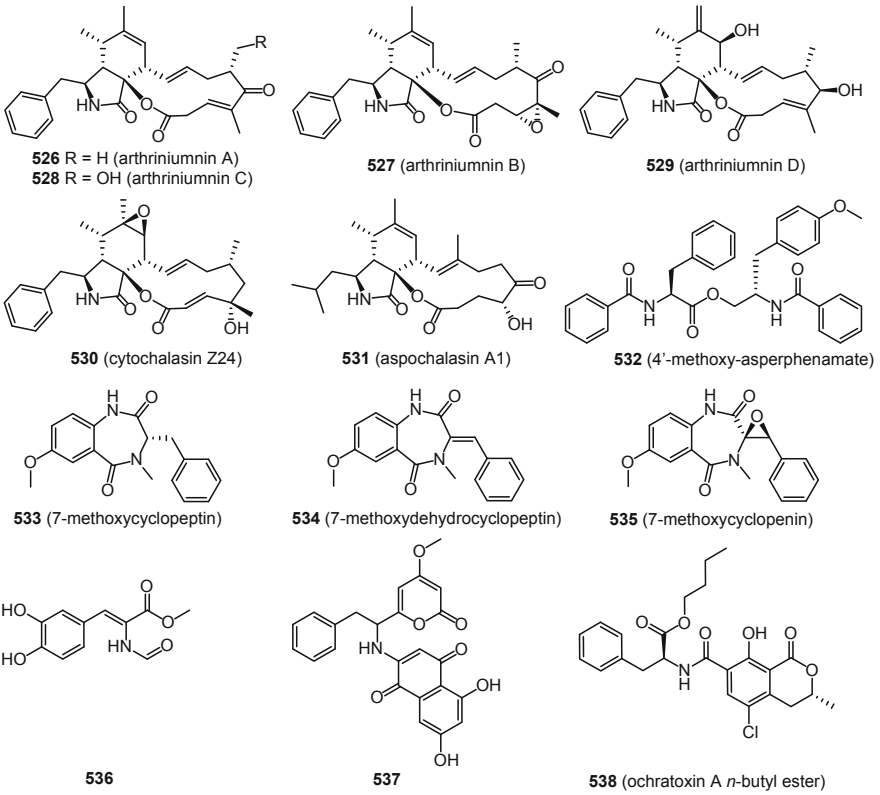


Fig. 31 Structures of phenylalanine derivatives

yielded the fungal strain *Aspergillus elegans* ZJ-2008010. Fermentation of this fungus in liquid potato glucose medium resulted in the isolation of two cytochalasins, cytochalasin Z24 (**530**) and aspochalasin A1 (**531**), in addition to a phenylalanine derivative, 4′-*O*-methyl-asperphenamate (**532**). 4′-*O*-Methyl-asperphenamate (**532**) exhibited selective antibacterial activity against *Staphylococcus epidermidis* with an IC_{50} value of 10 μ*M* [165]. Three cyclopenin derivatives, 7-methoxycyclopeptin (**533**), 7-methoxydehydrocyclopeptin (**534**), and 7-methoxycyclopenin (**535**), were obtained following cultivation of *Aspergillus versicolor* XZ-4, a crab-derived fungus from *Xenograpsus testudinatus* collected from Kueishantao, Taiwan, in liquid potato dextrose medium. 7-Methoxycyclopeptin (**533**) and 7-methoxycyclopenin (**535**) exhibited antibacterial activity against *Escherichia coli* with *MIC* values of 32 μg/cm^3 for both [157].

Following fermentation of *Penicillium oxalicum* EN-290, an endophytic fungus derived from the marine alga *Codium fragile* collected from the Qingdao coastline, in liquid potato dextrose medium, the phenolic enamide, methyl (*Z*)-3-(3,4-dihydroxyphenyl)-2-formamidoacrylate (**536**), was obtained. Compound **536** showed antimicrobial activities against *Staphylococcus aureus* and *Vibrio*

parahaemolyticus with *MIC* values of 2.0 and 16.0 μg/cm^3, respectively, comparable to those of the positive control, chloromycetin, having *MIC* values of 4.0 and 2.0 μg/cm^3, respectively [89]. Fermentation in liquid GPY medium of *Aspergillus niger* EN-13, as isolated from the marine brown alga *Colpomenia sinuosa* collected in Qingdao, resulted in the purification of a naphthoquinoneimine derivative, 5,7-dihydroxy-2-[1-(4-methoxy-6-oxo-6*H*-pyran-2-yl)-2-phenylethylamino]-[1,4] naphthoquinone (**537**). Compound **537** exhibited antifungal activity against *Candida albicans* with an inhibitory zone of 10 mm at a dose of 20 μg/well [166]. Ochratoxin A *n*-butyl ester (**538**) was isolated from the liquid GYM medium fermentation of *Aspergillus* sp. SCSGAF0093 obtained from the gorgonian *Melitodes squamata* collected from the South China Sea near Sanya City, Hainan Province. In the brine shrimp lethality assay, ochratoxin A *n*-butyl ester (**538**) showed activity with an LC_{50} value of 4.1 μ*M* (Fig. 31) [167].

7.4 Other Alkaloids

The fungal strain *Aspergillus* sp. Z-4 was derived from the gut of the marine isopod *Ligia oceanica* collected at the seaside at Dinghai in Zhoushan, Zhejiang Province. Cultivation of this fungus in liquid 2216E medium yielded three aspochalasin derivatives, aspochalasin V (**539**) (Fig. 32), aspochalasin W (**540**), and aspochalazine A (**541**). Aspochalasins V and W (**539** and **540**) were the first examples of methylthio-substituted aspochalasin, while aspochalazine A (**541**) was the first reported aspochalasin derivative with an azabicyclo ring system. Aspochalasin V (**539**) exhibited moderate cytotoxicity against the PC3 and HCT116 prostate cancer cell lines with IC_{50} values of 30.4 and 39.2 μ*M* [168, 169]. The sponge *Phakellia fusca* collected from Xisha Islands yielded *Arthrinium arundinis* ZSDS1-F3. Cultivation of this fungus in liquid medium composed of sorbitol, maltose, MSG, and yeast extract led to the isolation of three 4-hydroxy-2-pyridone alkaloids, arthpyrones A−C (**542**–**544**). Arthpyrone C (**544**) exhibited significant AChE inhibitory activity with an IC_{50} value of 0.8 μ*M* [170].

Pseurotins A_1 and A_2 (**545** and **546**) were obtained from the liquid GYM medium fermentation of *Aspergillus fumigatus* WFZ-25, a holothurian-derived fungus from *Stichopus japonicus* collected from Lingshan Island, Qingdao [171]. Pseurotins A_3 and G (**547** and **548**) were isolated from the liquid PDB medium cultivation of *Phoma* sp. NTOU 4195 that was obtained from the red alga *Pterocladiella capillacea* sampled in the intertidal zone of northern Taiwan. Pseurotin G (**548**) displayed antiangiogenic activity in human endothelial progenitor cells with an IC_{50} value of 16.7 μ*M* [90].

Eight isoindolinone-type alkaloids, chartarutines A−H (**549**–**556**), were isolated from the solid rice medium fermentation of *Stachybotrys chartarum* WGC-25C-6, a sponge-derived fungus obtained from *Niphates recondite* collected from the inner coral reef in Beibuwan Bay, Guangxi Province. Chartarutines B, G, and H (**550**, **555**, and **556**) exhibited significant inhibitory effects against HIV replication in a

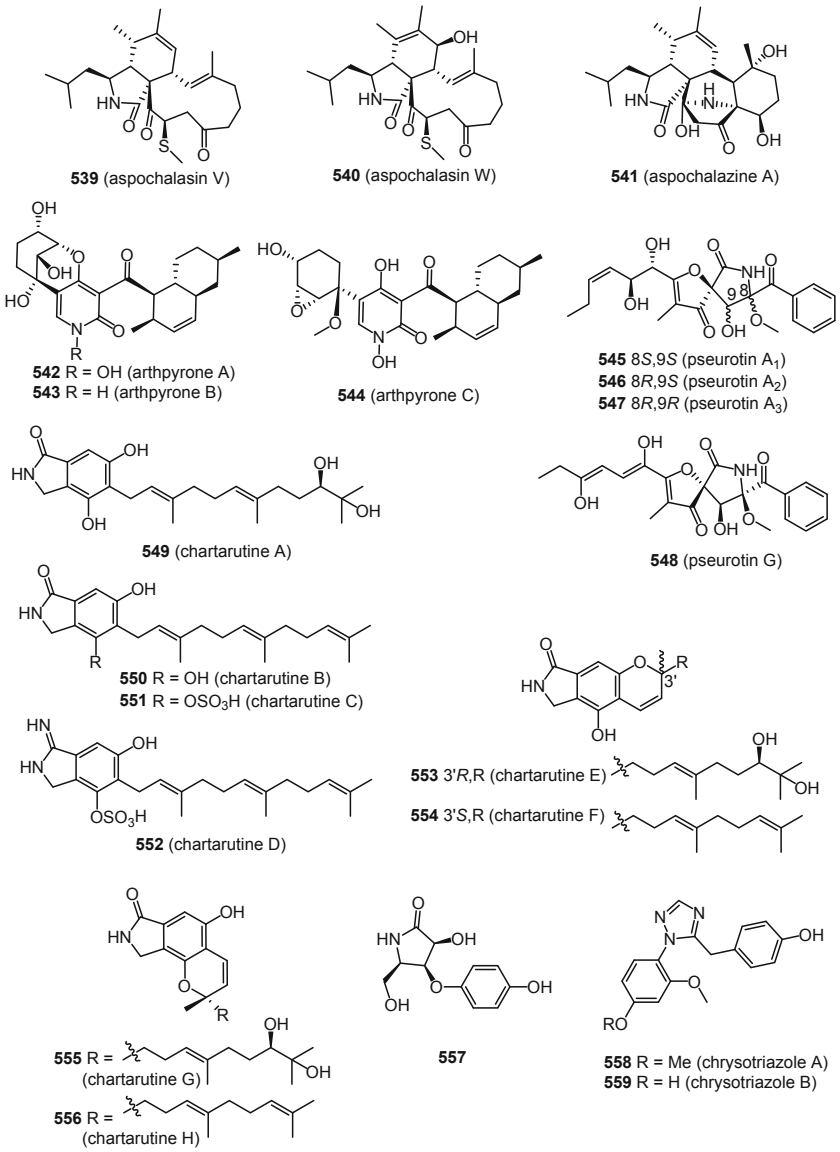


Fig. 32 Structures of other alkaloids (part 1)

one-cycle infection assay with IC_{50} values of 4.9, 5.6, and 5.6 μ*M*, respectively [172]. The fungal strain *Gibberella zeae* cf-18 was obtained from the marine green alga *Codium fragile* collected off the coast of Yantai. Cultivation of *G. zeae* in liquid PDB medium gave a pyrrolidinone derivative, 3-hydroxy-5-(hydroxymethyl)-4-(4-′-hydroxyphenoxy)pyrrolidin-2-one (**557**) [173]. Two triazoles, chrysotriazoles A and B (**558** and **559**), were isolated from the liquid MH_2 medium fermentation of

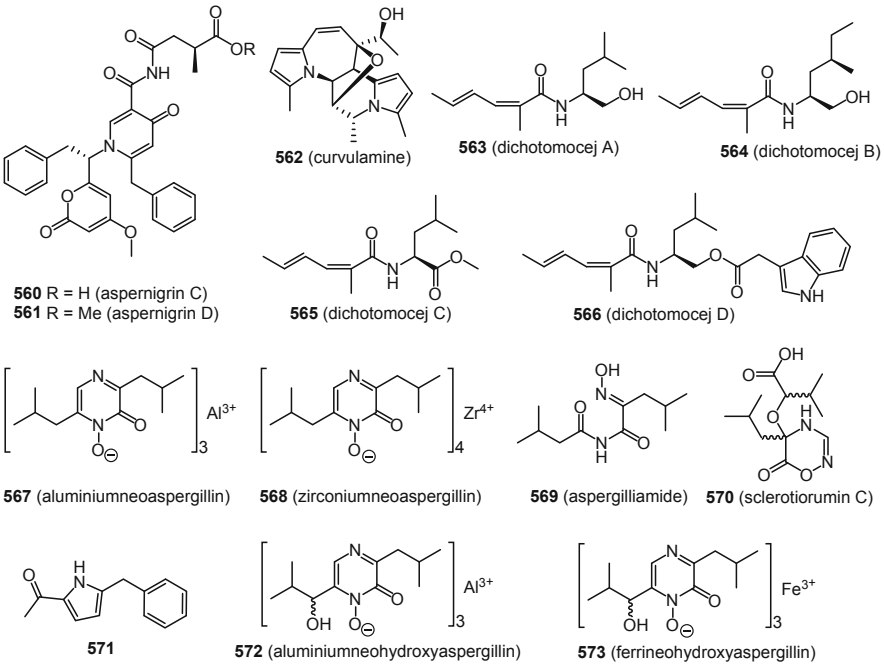


Fig. 33 Structures of other alkaloids (part 2)

Penicillium chrysogenum EN-118, an endophyte obtained from the marine alga *Sargassum palladium* collected from Fujian Province [174].

Cultivation in liquid MPY medium of *Aspergillus niger* SCSIO Jcsw6F30, obtained from the marine alga *Sargassum* sp. collected in Yongxing Island, South China Sea, yielded two 2-benzylpyridin-4-one containing metabolites, aspernigrins C and D (**560** and **561**) (Fig. 33). Aspernigrin C (**560**) showed anti-HIV-1 activity with an IC_{50} value of 4.7 μ*M* [175]. From the gut of the white croaker *Argyrosomus argentatus* collected from the Yellow Sea near Lvsi Port, the fungus *Curvularia* sp. IFB-Z10 was obtained. Fermentation of this fungus in modified Czapek's medium yielded a hitherto unprecedented alkaloid, curvulamine (**562**). Curvulamine (**562**) exhibited strong antibacterial activities against patient-derived pathogens *Veillonella parvula*, *Streptococcus* sp., *Bacteroides vulgatus*, and *Peptostreptococcus* sp. with *MIC* values of 0.37 μ*M* for each microbe and were more potent than the positive control tinidazole [176]. When grown in liquid GPY medium, the fungal strain *Dichotomomyces cejpii* F31-1, as obtained from the soft coral *Lobophytum crissum* collected from Hainan Sanya National Coral Reef Reserve, yielded four amides, dichotomocejs A−D (**563–566**). Dichotomocej A (**563**) showed moderate cytotoxicity against the RD human rhabdomyosarcoma cell line with an IC_{50} value of 39.1 μ*M* [51].

The fungal strain *Aspergillus* sp. SCSGAF0093 was obtained from the gorgonian *Melitodes squamata* collected from the South China Sea near Sanya City, Hainan

Province. Cultivation of this fungus in liquid GYM medium led to the isolation of three mycotoxins, aluminiumneoaspergillin (**567**), zirconiumneoaspergillin (**568**), and aspergilliamide (**569**). Zirconiumneoaspergillin (**568**) was the first reported zirconium complex obtained from Nature. Aluminiumneoaspergillin (**567**) and zirconiumneoaspergillin (**568**) displayed brine shrimp lethality with LC_{50} values of 6.6 and 10.8 μ*M*, respectively [167].

From the gorgonian *Muricella flexuosa* collected from Sanya, Hainan Province, two fungal strains *Penicillium citrinum* SCSGAF 0052 and *Aspergillus sclerotiorum* SCSGAF 0053 were obtained. Co-culture of these two fungi in liquid glucose-starch-peptone medium yielded a oxadiazin derivative sclerotiorumin C (**570**), a pyrrole derivative 1-(4-benzyl-1*H*-pyrrol-3-yl)ethanone (**571**), and two complexes of neoaspergillic acid aluminiumneohydroxyaspergillin (**572**) and ferrineohydroxyaspergillin (**573**). Sclerotiorumin C (**570**) was the first natural 1,2,4-oxadiazin-6-one. Aluminiumneohydroxyaspergillin (**572**) exhibited selective cytotoxicity against the U937 human histiocytic lymphoma cell line (IC_{50}, 4.2 μ*M*) and toxicity toward brine shrimp (LC_{50} 6.1 μ*M*) (Fig. 33) [65].

8 Shikimate-Derived Compounds

The fungus *Aspergillus terreus* OUCMDZ-1925 was obtained from the viscera of the fish *Chelon haematocheilus* from the Yellow River Delta. Fermentation of this fungus in liquid glucose yeast extract medium furnished rubrolides R and S (**574** and **575**) (Fig. 34). Rubrolide R (**574**) showed weak antioxidative activity (IC_{50} 1.3 m*M*) with regard to ABTS radicals compared to those of two postive controls including trolox (IC_{50} 2.0 m*M*) and ascorbic acid (IC_{50} 2.9 m*M*). Rubrolide S (**575**) exhibited somewhat more potent anti-influenza A (H_1N_1) activity (IC_{50} value of 87.1 μ*M*) than the positive control ribavirin (IC_{50} value of 118.8 μ*M*). Both rubrolides R and S (**574** and **575**) displayed cytotoxicity against the K562 cell line with IC_{50} values of 12.8 and 10.9 μ*M*, respectively [177]. A further strain of *Aspergillus terreus* coded SCSGAF0162 was obtained from the tissue of the gorgonian *Echinogorgia aurantiaca* collected from Sanya, Hainan Province. Fermentation of this fungus in liquid yeast extract medium gave aspernolide E (**576**) [56], whereas cultivation on solid rice medium yielded isobutyrolactones V and II (**577** and **578**). Isobutyrolactone II (**578**) showed antiviral activity toward HSV-1 virus with an IC_{50} value of 21.8 μg/cm^3, stronger than that of the positive control acyclovir (IC_{50} value of 34.5 μg/cm^3) [82].

The butenolides butyrolactone IX (**579**) and aspulvinone O (**580**) were isolated from the PDB medium fermentation of *Paecilomyces variotii* EN-291, an endophyte obtained from the red alga *Grateloupia turuturu* collected from the coast of Qingdao [178].

From the inner tissue of the sponge *Phakellia fusca* collected from Yongxing Island, two fungal strains *Aspergillus versicolor* 16F-11 and *Hypocrea koningii* PF04 were obtained. When cultivated in liquid PDB medium, *A. versicolor* yielded

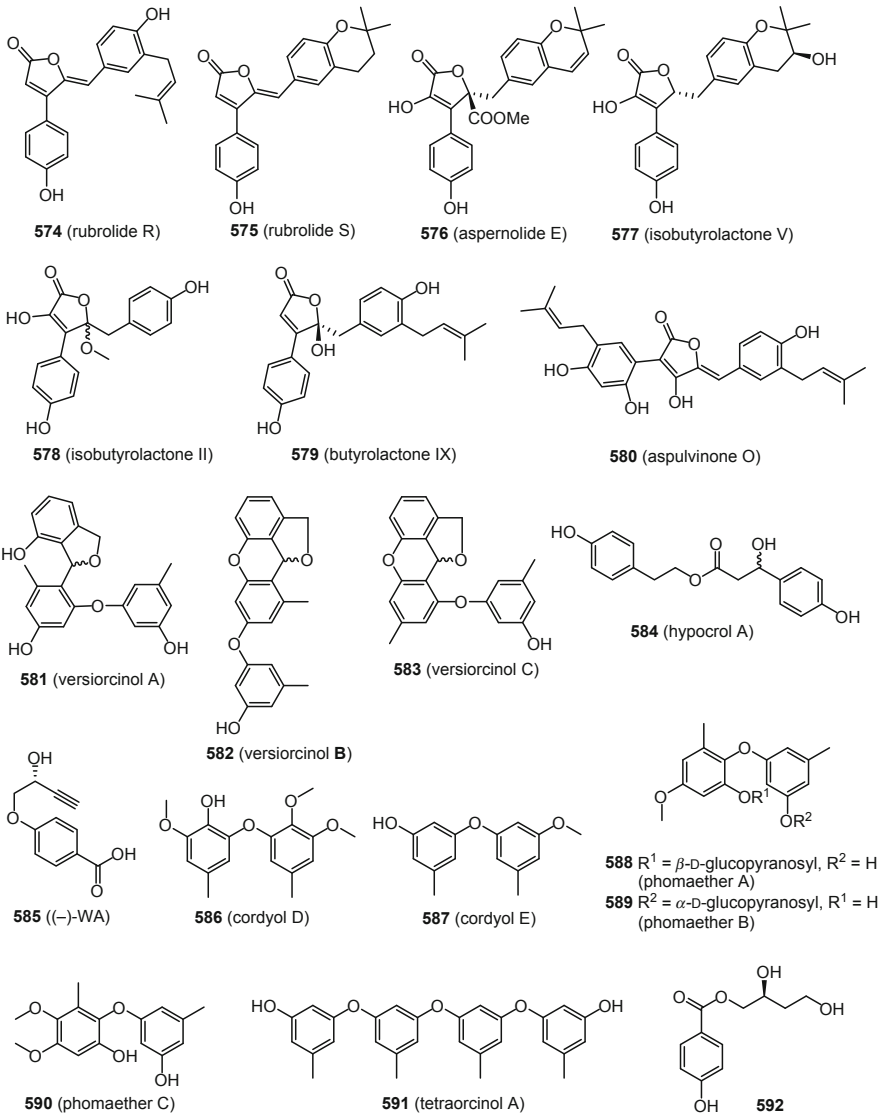


Fig. 34 Structures of shikimate-derived compounds

three racemic diorcinol monoethers, versiorcinols A–C (**581**–**583**) [179], while *H. koningii* gave a tyrosol derivative, hypocrol A (**584**). Hypocrol A (**584**) showed weak antioxidant activity in the DPPH radical-scavenging assay with an IC_{50} value of 48.5 μg/cm^3 [180]. The fungus *Penicillium polonicum* AP2T1 was obtained from gills of the shark *Isurus oxyrinchus* from the Wenzhou sea area of Zhejiang Province. An acetylenic aromatic ether, (−)-WA (**585**), was obtained from fermentation

of *P. polonicum* in potato sucrose broth containing natural sea salt. The ether (−)-WA (**585**) showed antimicrobial activities against *Bacillus subtilis* and *Escherichia coli* with inhibition zones of 8 and 9 mm in diameter in an agar plate diffusion assay, respectively [181]. Two phenyl ether derivatives, cordyols D and E (**586** and **587**), were isolated from *Aspergillus* sp. XS-20090066, a gorgonian-derived fungus from *Dichotella gemmacea* collected from the Xisha Islands coral reef in the South China Sea, when the fungus was cultivated on seawater-containing rice medium [131].

The fungal strain *Phoma* sp. TA07-1 was obtained from the gorgonian *Dichotella gemmacea* collected from the Weizhou coral reef in the South China Sea. Solid rice medium fermentation of this fungus yielded phomaethers A–C (**588–590**). Phomaethers A and B (**588** and **589**) were the first examples of diphenyl glycoside derivatives from coral-derived fungi. Phomaethers A and C (**588** and **590**) exhibited antibacterial activities against *Staphylococcus albus*, *S. aureus*, and *Escherichia coli* with *MIC* values ranging from 0.3 to 5 μ*M* [182]. *Aspergillus versicolor* LCJ-5-4 was isolated from the coral *Cladiella* sp. collected from Lingao, Hainan Province. The liquid yeast extract medium fermentation of *A. versicolor* afforded an orcinol tetramer, tetraorcinol A (**591**). Tetraorcinol A (**591**) exhibited weak antioxidative activity against DPPH radicals, with an IC_{50} value of 67 μ*M*, while ascorbic acid (vitamin C) served as a positive control (IC_{50} 22 μ*M*) [66]. The liquid medium broth of *Penicillium aurantiogriseum*, which was obtained from the sponge *Mycale plumosa* collected at Qingdao, yielded (*S*)-2,4-dihydroxy-1-butyl(4-hydroxy)benzoate (**592**). Compound **592** showed cytotoxicity against tsFT210 cells with an inhibitory effect observed at 8.0 μg/cm^3 (Fig. 34) [183].

9 Lipids

From the mycelium of *Aspergillus flavipes*, obtained from the sea anemone *Anthopleura xanthogrammica* collected at a beach in Qingdao, two cerebrosides, flavicerebrosides A and B (**593** and **594**) (Fig. 35), were isolated. Both compounds exhibited cytotoxicity against the KB cell line with IC_{50} values of 20.7 and 14.3 μg/cm^3 [184]. Asperamides A and B (**595** and **596**), a sphingolipid and its corresponding glycosphingolipid, were isolated from the liquid GPY medium fermentation of *Aspergillus niger* EN-13, an endophyte from the marine brown alga *Colpomenia sinuosa* collected along the Qingdao coastline of Shandong Province. Asperamide A (**595**) displayed antifungal activity against *Candida albicans* with an inhibitory zone of 12 mm in diameter, equal to that of the positive control, amphotericin B [185]. The fungal strain *Aspergillus flavus* cf-5 was isolated from the marine red alga *Corallina officinalis* collected off the coast of Yantai. The PDB medium fermentation of this fungus afforded a oxylipin, (8*E*,12*Z*)-10,11-dihydroxyoctadeca-8,12-dienoic acid (**597**) [124]. 4,5-Ditridecyl-octanedioic acid (**598**) was produced during liquid PDA medium cultivation of *Myrothecium* sp. Z16, a fungus associated with the white croaker *Argyrosomus argentatus* collected from the Yellow Sea near Lvsi Port [186]. The fungus *Aspergillus candidus* HDf2 was

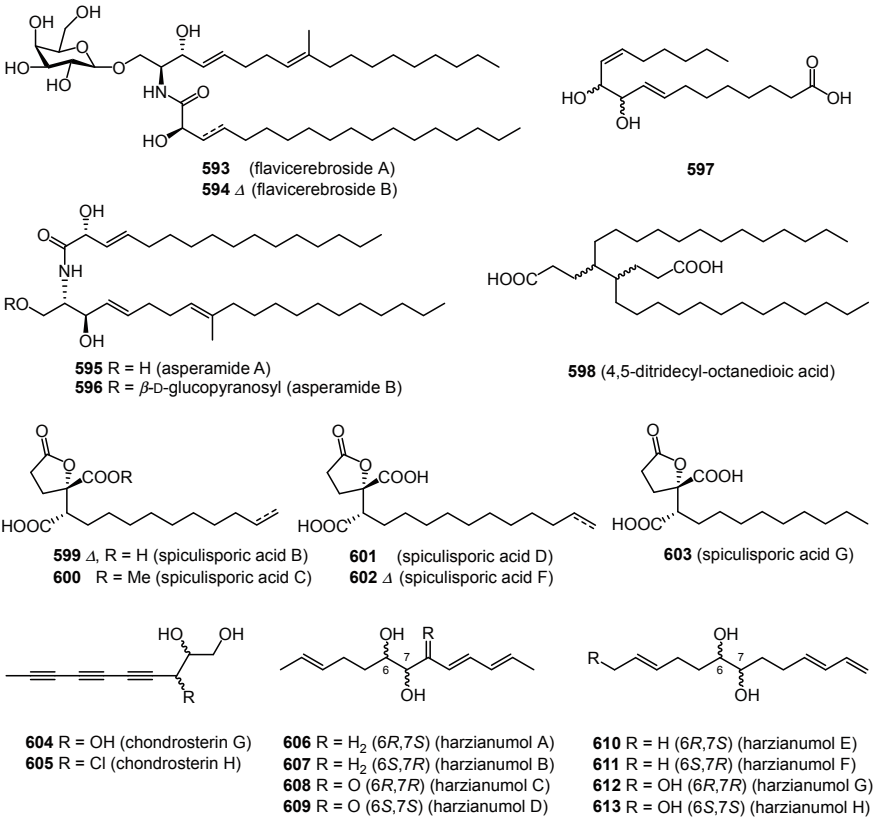


Fig. 35 Structures of lipids

derived from the sea urchin *Anthocidaris crassispina* collected from the seashore of Qionghai, Hainan. Three γ-butenolide derivatives, spiculisporic acids B–D (**599**–**601**), were isolated from the solid MEA medium fermentation of *A. candidus*. Spiculisporic acids B–D (**599**–**601**) showed no cytotoxicity against SGC-7901 and SPC-A-1 cell lines, but displayed antibacterial activity against *Staphylococcus aureus* with inhibition zones of 10, 12, and 12 mm at a concentration of 20 mg/cm^3, while the diameter of inhibition zone of the positive control (streptomycin sulfate) was 24 mm at the same concentration level [187]. Two additional derivatives, spiculisporic acids F and G (**602** and **603**), were obtained when this fungus was cultivated in liquid PDB medium. Both compounds **602** and **603** exhibited antibacterial activity against Gram-positive *Staphylococcus aureus* and Gram-negative *Pseudomonas solanacearum* but did not show cytotoxicity against the two cancer cell lines, SGC-7901 and SPC-A-1. The inhibitory diameters of spiculisporic acid F (**602**) against *S. aureus* and *P. solanacearum* in the filter paper disk diffusion assay at doses of 20 mg/cm^3 were 12 and 9 mm, respectively. The inhibitory diameters of spiculisporic acid G (**603**) against *S. aureus* and

P. solanacearum were 10 and 8 mm, respectively, while that of the positive control was 27 mm for *S. aureus* (streptomycin sulfate) and 24 mm for *P. solanacearum* (kanamycin) [188]. Two linear polyacetylenes, chondrosterins G–H (**604** and **605**), were obtained from liquid PDB medium fermentation of *Chondrostereum* sp. SF002, a coral-derived fungus from *Sarcophyton tortuosum* collected from the Hainan Sanya National Coral Reef Reserve [104]. The fungus *Trichoderma harzianum* HNS-15-3 was obtained from the sponge *Petrospongia nigra* collected from the South China Sea. Fermentation of this fungus on solid rice medium afforded four pairs of C_{13} lipid enantiomers, harzianumols A–H (**606–613**) (Fig. 35) [189].

10 Conclusions

This contribution covers 613 new natural products from marine-derived fungi obtained from various organisms including algae, sponges, corals, and other organisms that occur in Chinese marine habitats, focusing on the period from 2001 to 2017. The genera *Aspergillus* (170 new natural products, 28%) and *Penicillium* (70 new natural products, 11%) were the main fungal sources of new natural products during the time period covered (Fig. 36a). In terms of fungal origin, sponges (184 new natural products, 30%) were the most abundant sources of new natural products, followed by corals (154 new natural products, 25%) and algae (130 new natural products, 21%) (Fig. 36b). Altogether, 37% of new natural products covered in this contribution displayed various bioactivities. The major bioactivities reported were cytotoxicity, antimicrobial activity, and antiviral activity, which accounted for 13%, 9%, and 3% of all natural products covered in this contribution (including compounds with no published bioactivity) (Fig. 36c) or 34%, 25%, and 9% of all natural products with published bioactivity (Fig. 36d), respectively.

Figure 37a gives an overview of new natural products based on their structural classes. Polyketides (188 new natural products, 31%) play a dominant role, and if prenylated polyketides and nitrogen-containing polyketides (included in meroterpenes and alkaloids in this contribution, respectively) are taken into account, their total number exceeds 50%. Nitrogen-containing compounds including peptides (65 new natural products, 10%) and alkaloids (103 new natural products, 17%) were the second largest group.

The correlation between origin of marine-derived fungi and structural classes of compounds was also analyzed (Fig. 37b). Polyketides (33 new natural products, 25%), alkaloids (29 new natural products, 22%), and meroterpenes (26 new natural products, 20%) were the three largest structural types of new natural products reported from algicolous fungi. Meroterpenes (65 new natural products, 35%) were the most common new natural products found in sponge-derived fungi, followed by polyketides (51 new natural products, 28%) and terpenes (28 new natural products, 15%). In coral-associated fungi, the percentage of nitrogen-

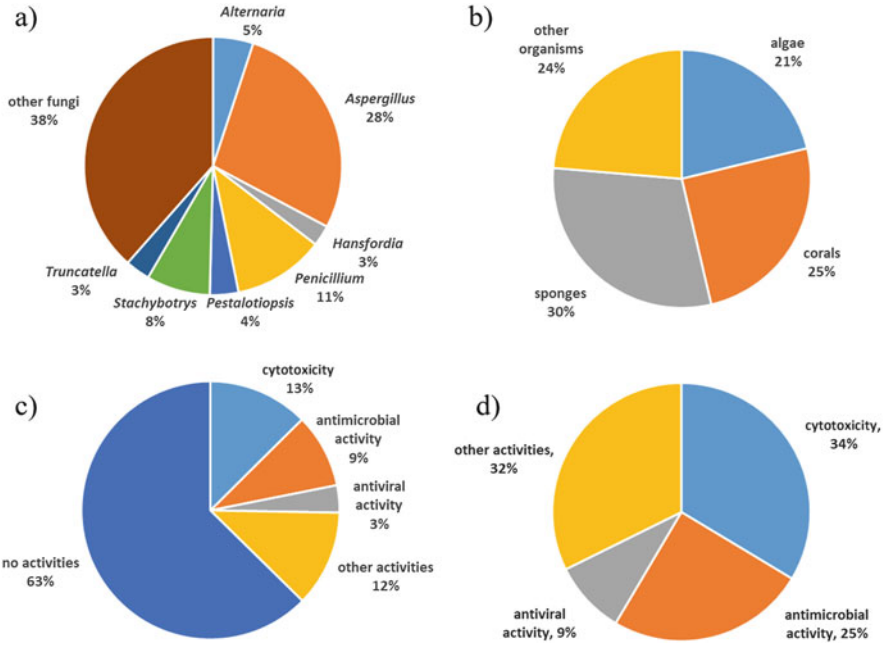


Fig. 36 (**a**) Percentage of new natural products according to fungal taxonomy; (**b**) Percentage of new natural products by fungal origin; (**c**) Percentage of new natural products by bioactivity out of all new natural products; (**d**) Percentage of new natural products by bioactivity out of all bioactive new natural products

containing new natural products including alkaloids (33 new natural products, 21%) and peptides (31 new natural products, 20%) was in comparison higher than that of polyketides (54 new natural products, 35%).

The number of new natural products reported from marine-derived fungi from China as well as the total number of publications mostly from groups from China devoted to this field has shown a sharp increase especially within the last decade (Fig. 38), which emphasizes the growing attention of Chinese natural product research to the marine environment as source of structurally unique bioactive metabolites. Compared to other countries like the USA or Japan where marine natural product research has already been a productive field of science for at least the last 40 years [190], this is a fairly recent development in China where the emphasis on terrestrial sources of natural products such as plants used in TCM (Traditional Chinese Medicine) has been far more prominent historically. Over the last few years, we have seen an impressive flow of publications of Chinese groups not only devoted to natural products from marine-derived fungi but also to bioactive compounds from other marine macro- and microorganisms. This underscores the growing importance of marine natural product research in China. Whereas in many countries of the Western world natural product research in general is declining due to

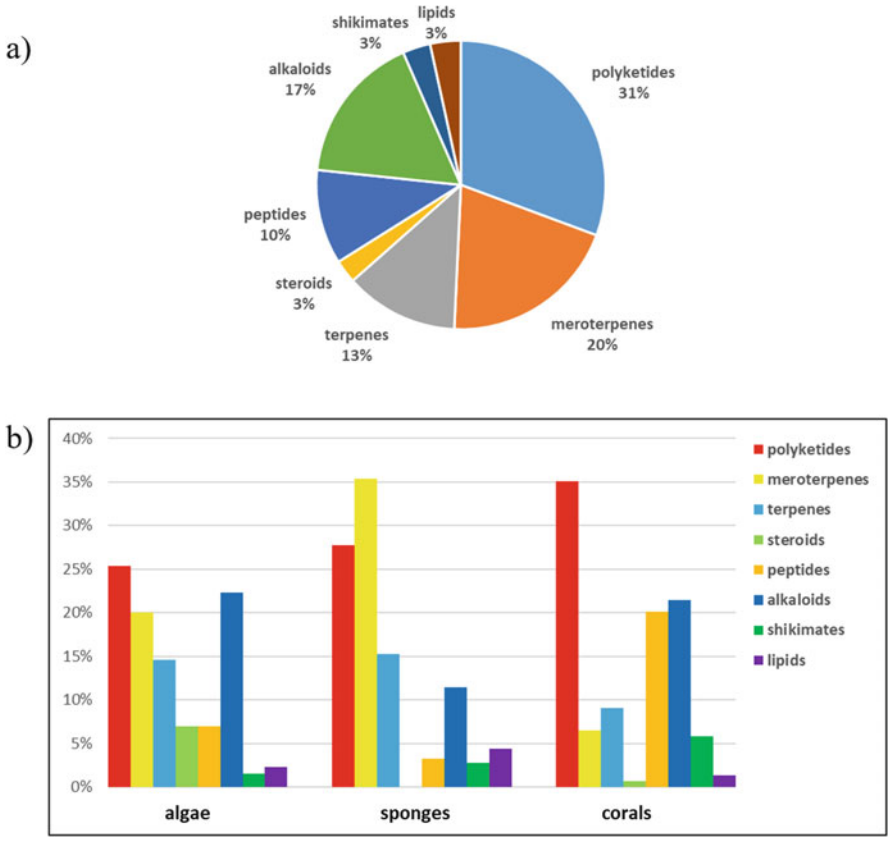


Fig. 37 (**a**) Percentage of new natural products by structural classes; (**b**) Percentage of new natural products of different structural classes by fungal origin

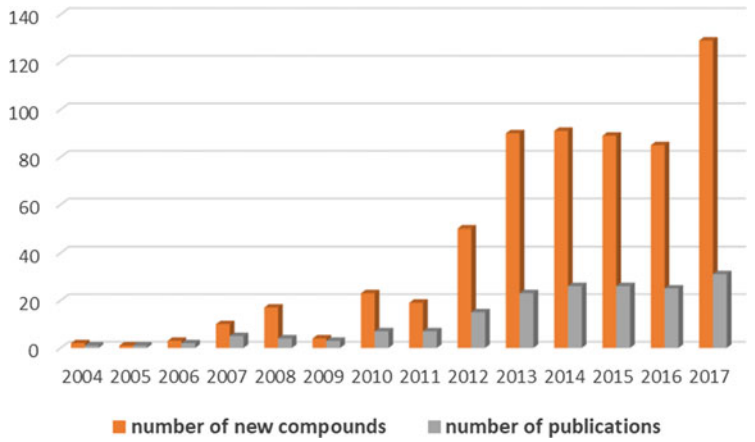


Fig. 38 Number of new natural products from Chinese marine-derived fungi and publications from 2004 to 2017

various reasons, the Chinese input to this field has been steadily growing over the last few years as seen by the increasing number of publications from Chinese groups in specialized technical journals devoted to this area. It can be expected that this trend will continue in the years to come.

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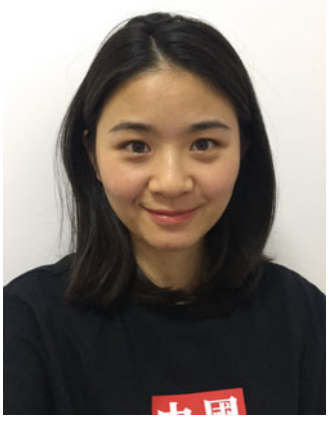

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