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REVIEW

Metabolites from marine invertebrates and their symbiotic microorganisms: molecular diversity discovery, mining, and application

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Abstract

Metabolites from marine organisms have proven to be a rich source for the discovery of multiple potent bioactive molecules with diverse structures. In recent years, we initiated a program to investigate the diversity of the secondary metabolites from marine invertebrates and their symbiotic microorganisms collected from the South China Sea. In this review, representative cases are summarized focusing on molecular diversity, mining, and application of natural products from these marine organisms. To provide a comprehensive introduction to the field of marine natural products, we highlight typical molecules including their structures, chemical synthesis, bioactivities and mechanisms, structure–activity relationships as well as biogenesis. The mining of marine-derived microorganisms to produce novel secondary metabolites is also discussed through the OSMAC strategy and via partial chemical epigenetic modification. A broad prospectus has revealed a plethora of bioactive natural products with novel structures from marine organisms, especially from soft corals, gorgonians, sponges, and their symbiotic fungi and bacteria.

Keywords Marine invertebrates · Symbiotic microorganisms · Marine natural products · Molecular diversity · Bioactivities · Marine drugs

Introduction

The marine environment has been proven to be a rich source of new bioactive natural products for drug discovery. Coral reefs are among the most productive ecosystems and are a source of a large group of structurally unique biosynthetic products. To date, more than 40,000 marine natural products (MNPs) have been identified from various marine organisms, such as sponges, cnidarians, tunicates, molluscs, echinoderms, bryozoans, red algae, brown algae, green algae, and microorganisms (Carroll et al. 2019; Deshmukh et al. 2017; Jiménez 2018; Leal et al. 2016; Newman and Cragg 2016b). The upward trend in the discovery of new MNPs sourced from marine microorganisms continues unabated and now represents 57% of the total new MNPs reported in 2017 (Carroll et al. 2019). Based upon the putative biogenetic origins, these MNPs can be classified as polyketides, terpenoids, alkaloids, steroids, lactones, peptides, phenols, and lipids. Also, a large proportion of MNPs display interesting pharmaceutical activities, such as cytotoxic, antimicrobial, hypolipidemic, anti-inflammatory, antimalarial, analgesic, and antiasthmatic activities (According to the following

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websites: http://marinepharmacology.midwestern.edu; Jiménez 2018). Hence, MNPs are considered as an excellent and potentially valuable source for new chemical entities with novel structures and distinct mechanisms of action. To date, there have been 13 approved therapeutic agents that could be considered derivatives of MNPs (Altmann 2017; Jiménez 2018; Newman 2019; Pereira et al. 2019). Moreover, more than 30 MNP derivatives constitute the global marine pharmaceutical clinical pipeline in Phases III, II or I of drug development (According to the following websites: http://marinepharmacology.midwestern.edu; http://pharma.id.informa.com (accessed on August 6, 2019); Jiménez 2018; Newman 2019; Pereira et al. 2019). The significant potential for new drug development based on MNPs in all disease areas has been previously discussed (Newman and Cragg 2016a).

Marine invertebrates have proven to be a primary source of bioactive MNPs, as many serve as chemical defense tools against predators, competitors and other ecological pressures. It has been demonstrated that the true origin of most MNPs appears to be the microorganisms living in concert with invertebrates. Most invertebrates are sessile, soft-bodied and move slowly, and are thus subject to potential parasite predation and detrimental microbial colonization. Therefore, they require a complex arsenal of secondary metabolites produced by their symbiotic microorganisms to facilitate a form of chemical defense (Jiménez 2018; Wang et al. 2008). This is likely the reason why MNPs from marine invertebrates and their symbiotic microorganisms are a rich sources of diverse and bioactive secondary metabolites (Martins et al. 2014; Mayer et al. 2010; Newman and Cragg 2016b). The chemical ecology underlying invertebrate–microorganism interactions provides a great opportunity for natural product chemists to mine for novel drug discovery. Therefore, the invertebrates and the abundant microorganisms in their ecosystems have attracted widespread attention for producing novel structural metabolites with potential bioactive applications (Blunt et al. 2018).

In the recent decade, the China Sea, especially the South China Sea, has become a hot spot in searching for novel bioactive MNPs. The invertebrates including sponges, soft corals, gorgonians and tunicates are prolific in the coral reefs in the South China Sea, and the microorganisms associated with these invertebrates have been demonstrated as a distinctive source for new bioactive MNPs.

In recent years, we have initiated a research program to find biological active MNPs based on marine chemical ecology (Figs. 1, 2) (Hou et al. 2015, 2019a; Wang et al. 2008). A total of 709 MNPs including 307 new compounds have been obtained from marine invertebrates and their symbiotic microorganisms collected from the South China Sea. In this review, we summarize the representative 287 MNPs (Table 1) obtained by our group, highlighting multiple structural types of compounds and demonstrating discovery, diversity, compound mining, and bioactive application. The goal is to provide further inspiration for the discovery of bioactive MNPs and subsequent drugs development.

Fig. 1 Collection positions for marine invertebrates and microorganisms in the South China Sea. The red points represent the sampling sites

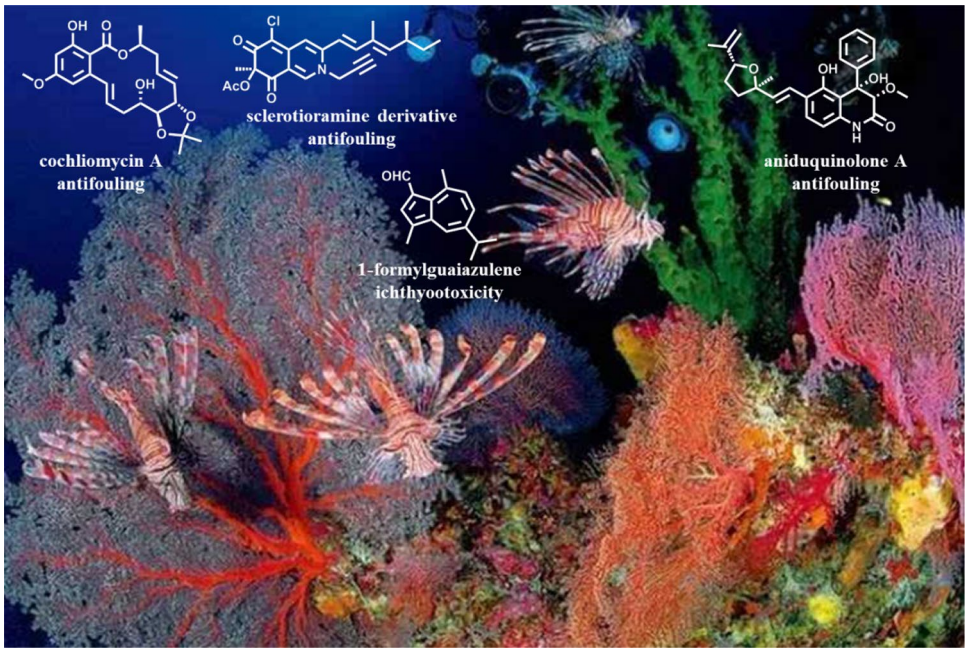

Fig. 2 The coral reef ecosystem and the chemical defensive metabolites with chemoecological effects

Macrocyclic lactones

Macrocyclic lactones derived from marine organisms have attracted much attention on account of their multiple potent biological activities including antitumor (Hirata and Uemura 1986; Isaka et al. 2002, 2009; Qi and Ma 2011; Suo et al. 2018), antifungal (Shier et al. 2001), and antimalarial activities (Isaka et al. 2009). For instance, caniferolides A and B, two glycosylated 36-membered polyol macrolides from marine-derived *Streptomyces* sp., showed pronounced antifungal activity (Perez-Victoria et al. 2019). Peloruside E, a macrolide from the New Zealand marine sponge *Mycale hentscheli*, displayed potent antiproliferative activity (Hong et al. 2018). As part of our current research, 88 macrolides with unique structures and significant biological properties have been obtained from marine invertebrates and their symbiotic microorganisms (Liu et al. 2014; Shao et al. 2011, 2015a, 2018). To obtain more valuable undiscovered natural compounds, multiple strategies and methods, including OSMAC and chemical epigenetic manipulation, were applied to microorganisms. Structural modification and chemical synthesis were performed to provide more derivatives, and the structure–activity relationships were discussed (Zhang et al. 2017). The molecular mechanisms of compounds with strong activities were also investigated (Wang et al. 2016).

Three new 14-membered resorcylic acid lactones (RALs), including compounds **1** and **2** (cochliomycins A and B) with a rare natural acetonide group and **3** (cochliomycin C) with a 5-chloro substituted lactone (Fig. 3), were isolated from the culture broth of *Cochliobolus lunatus* (M351) isolated from the gorgonian *Dichotella gemmacea* collected from the South China Sea (Shao et al. 2011). In an antifouling assay, compound **1** (cochliomycin A) showed significant antifouling activity against the barnacle *Amphibalanus* (=*Balanus*) *amphitrite* at nontoxic concentrations (EC_{50} = 1.2 μg/mL). Thus, compound **1** merits further investigation as a molecular model for the discovery of new antifouling molecules (Shao et al. 2011).

The molecular mechanism underlying antifouling activity of **1** against the cyprids of barnacle *A. amphitrite* has been investigated using the isobaric tags for the relative or absolute quantification (iTRAQ) labeling proteomic method (Wang et al. 2016). Differentially expressed proteins were examined by analyzing the changes in the proteome of *A. amphitrite* cyprids in response to **1** treatment. The results suggested that compound **1** affected the cytochrome P450, glutathione *S*-transferase (GST) and NO/cGMP pathways. The results of real-time PCR further demonstrated that the NO/cGMP pathway was activated in response to **1**. Larval settlement assays suggested that *S*-methylisothiourea sulfate (SMIS) and 1*H*-(1,2,4)oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) rescued cyprids from **1** (cochliomycin A)-induced inhibition of larval settlement. These findings supported the hypothesis that **1** inhibited barnacle larval settlement through stimulating the NO/cGMP pathway (Wang et al. 2016).

However, further research on compound **1** and its analogues was hindered by strain-specific variation of the strain *C. lunatus* (M351), especially altering metabolite profiles when re-cultured. Fortunately, another fungal strain *C. lunatus* (TA26-46) derived from the sea anemone *Palythoa haddoni* was also found to produce 14-membered RALs. Three new 14-membered RALs, **4**–**6** (cochliomycins D–F)

Table 1 Representative compounds and their original organisms

Compd.	Names	Original organisms	Species	Ref.
Macrocyclic lactones				
1-3	Cochliomycins A-C	Gorgonian-derived fungus	*C. lunatus* M351	Shao et al. (2011)
4-6	Cochliomycins D-F	Sea anemone-derived fungus	*C. lunatus* TA26-46	Liu et al. (2014)
7	(7'*E*)-6'-Oxozeaenol			
8	Deoxy-aigialomycin C			
9	LL-Z1640-2			
9a	Acetonide derivative of **9**			
10	Zeaenol			
11	LL-Z1640-1			
12	Paecilomycin F			
13	Aigialomycin B			
14-29	Derivatives from **9** and **10**	Semisynthetic		Zhang et al. (2017)
30	5-Bromozeaenol	Sea anemone-derived fungus	*C. lunatus* TA26-46	Zhang et al. (2014)
31	3,5-Dibromozeaenol			
32	Borrelidin	Sponge-derived actinomycete; gorgonian-derived fungus	*S. rochei* MB037; *R. similis* 35	Yu et al. (2019)
33-35	Borrelidins F, J, K			
36	Bastimolide A	Cyanobacterium	*O. hirsute*	Shao et al. (2015a)
36a	Nona-p-nitrobenzoate derivative of 32			
37	Bastimolide B			Shao et al. (2018)
38	2-(*E*)-Bastimolide A			
Anthraquinones				
39	4a-*epi*-9α-Methoxydihydrodeoxybostrycin	Sea anemone-derived fungus	*Nigrospora* sp. ZJ-2010006	Yang et al. (2012)
40	10-Deoxybostrycin			
41	Nigrosporin B			
42	9α-Hydroxydihydrodesoxybostrycin			
43	9α-Hydroxyhalorosellinia A			
44	4-Deoxybostrycin			
45	Bostrycin			
46	3,5,8-Trihydroxy-7-methoxy-2 -methylanthracene-9,10-dione			
47	Austrocortirubin			
44a, 45a, 46a–46g, 47a	Acetyl derivatives of **44-47**	Semisynthetic		
48-51	Tetrahydroaltersolanols C-F	Soft coral-derived fungus	*Alternaria* sp. ZJ-2008003	Zheng et al. (2012)
52	Dihydroaltersolanol A			
53-57	Alterporriol N-R			
Azaphilones				
58-60	Pinophilins D-F	Gorgonian-derived fungus	*P. pinophilum* XS-20090E18	Zhao et al. (2015a)
61	Sch 1385568			
62	Pinophilin B			
63	Sch 725680			
64	(−)-Mitorubrin			
65	(−)-Mitorubrinol			

Table 1 (continued)

66	(−)-Mitorubrinic acid			
67-68	Penicilazaphilones D and E	Sponge-derived fungus	*P. sclerotiorum*	Wang et al. (2018)
69	(+)-Sclerotiorin			
70	Geumsanol C			
71	WB			
72	Geumsanol G			
73-102	Sclerotioramine derivatives of **69**	Semisynthetic		Wei et al. (2017)
Alkaloids				
103	(±)-Pestaloxazine A	Soft coral-derived fungus	*Pestalotiopsis* sp.	Jia et al. (2015)
104	Aniduquinolone A	Gorgonian coral-derived fungus	*Scopulariopsis* sp.	Shao et al. (2015b)
105-106	Aflaquinolones A and D			
107	6-Deoxyaflaquinolone E			
108-109	Aflaquinolones F and G			
110	22-*O*-(N-Me-*L*-valyl)-Aflaquinolone B	Gorgonian-derive d fungus	*Aspergillus* sp.	Chen et al. (2014a)
111	22-*O*-(N-Me-*L*-valyl)-21-epi-Aflaquinolone B			
112	Di(1*H*-indol-3-yl)methane	Bacterium	*P. denitrificans* UST4-50	Wang et al. (2015a)
113	Vibrindole A			
114	3,3'-Di-1*H*-indol-3-yl-1,2-propandiol			
115	Tri(1*H*-indol-3-yl)methane			
116	1,2,2-Tri(1H-indol-3-yl) ethanone			
117	Arsindoline A			
118	3, 3'-(Phenylmethylene) bis-1*H*-indole			
119	(4-(Di(1*H*-indol-3-yl)methyl) phenol (DIM-Ph-4-OH)			
120	2-(Phenyl(2-phenyl-1*H*-indol-3-yl)methyl)malon onitrile	Synthetic		Wen et al. (2015)
121	4-Hydroxy-3-(phenyl(2-phenyl-1*H*-indol-3-yl)me thyl)-2*H*-chromen-2-one			
122	4-(Phenyl(2-phenyl-1*H*-indol-3-yl)methyl)phenol			
123	2-Phenyl-3-(phenyl(2,4,6-trimethoxyphenyl)meth yl)-1*H*-indole			
Terpenoids				
124	Aspergiterpenoid A	Sponge-derived fungus	*Aspergillus* sp. ZJ-2008004	Li et al. (2012a)
125	(–)-Sydonol			
126	(–)-Sydonic acid			
127	(–)-5-(Hydroxymethyl)-2-(2',6',6'-trimethyltetrah ydro-2*H*-pyran-2-yl)phenol			
128-138	Carteriofenones A-K	Sponge	*C. foliascens*	Cao et al. (2015)
139-141	Euplexaurenes A-C	Gorgonian	*Euplexaura* sp. GXWZ-05	Cao et al. (2017)
142	Anthogorgiene P			
143-144	Ochracenoids A and B	Gorgonian	*A. ochracea*	Zheng et al. (2014)
145	1-Formylguaiazulene			
146	1-formyl-4-methyl-7-isopropylazulene			
147	Ketolactone			
148	3,8-Dimethyl-5-isopropyl-6-formylindenone			
149-154	Lobophytumins A-F	Soft coral	*S. compacta*	Li et al. (2011)
155	(–)-Germacrene D			
156	Sarcophytol-A	Soft coral	*S. infundibuliforme*	Wang et al. (2011b)
157	Sarcophytol-A acetate			
158	Sarcophytol-H			
159	Sarcophytonolid-J			

Table 1 (continued)

160	Sarcophytol B	Soft coral	*Sarcophyton* sp.	Cao et al. (2013)
161	Juncin P	Gorgonian	*D. fragilis*	Zhou et al. (2011)
162	Junceellolide D			
Steroids				
163-166	Echrebsteroids A-D	Gorgonian	*E. rebekka*	Cao et al. (2014)
167	15*β*-Hydroxypregna-1,4,20-trien-3-one	Gorgonian	*Carijoa* sp.	Zhao et al. (2013)
168	15*β*-Acetoxypregna1,4,20-trien-3-one			
169	18-Acetoxypregna-1,4,20-trien-3-one			
170	Pregna-1,4,20-trien3-one			
171-182	Subergorgiaols A-L	Gorgonian	*S. rubra*	Sun et al. (2015)
183	Astrogorgiadiol			
184-186	Calicoferols C, F, A			
187	(3*S*,23*R*,24*S*)-Ergost-5-ene-3*β*,23*α*,25-triol	Soft coral	*Sinularia* sp.	Li et al. (2012b)
188	(24*S*)-Ergostane-6-acetate-3*β*,5*α*,6*β*,25-tetraol			
189	(24*S*)-Ergostane-6-acetate-3*β*,6*β*,12*β*,25-tetraol			
190	24-Methylenecholestane-3*β*,5*α*,6*β*-triol-6-monoacetate			
191-193	Topsensterols A-C	Sponge	*Topsentia* sp.	Chen et al. (2016)
194	3*α*-Hydroxy-7-ene-6,20-dione	Gorgonian-derived fungus	*Cladosporium* sp. WZ-2008-0042	Yu et al. (2018)
195	5*α*, 8*α*-Epidioxy-ergosta-6,9,22*E*-triene3*β*-ol			
196	5*α*,8*α*-Epidioxy-ergosta-6,22*E*-dien-3*β*-ol			
197	Ergosta-7,22*E*-diene-3*β*,5*α*,6*β*-triol			
198	3*β*,5*α*-Dihydroxy-6*β*-methoxyergosta7,22-diene			
199	Ergosterol peroxide			
200	Stigma-5-en-3-*O*-*β*-glucopyranoside			
Phenylpropanoids				
201-203	Penicimarins A-C	Sponge-derived fungus	*Penicillium* sp. MWZ14-4	Qi et al. (2013)
204-205	Aspergillumarins B and A			
206-208	Penicimarins D-F			
209	Sescandelin B			
210	5,6,8-Trihydroxy-4-(1'-hydroxyethyl)isocoumarin			
211-222	Corynechromones A-L	Sponge-derived fungus	*C. cassiicola* XS-20090017	Zhao et al. (2015b)
223-234	(±)-Eurotiumides A-G	Gorgonian-derived fungus	*Eurotium* sp. XS-200900E6	Chen et al. (2014b)
Peptides				
235-237	Chrysogeamides A-C	Gorgonian coral-derived fungus	*P. chrysogenum* TA01-16	Hou et al. (2019b)
238-239	Scopularides A and B			
240-244	Hrysogeamides D-H			
245-247	Asperversiamides A-C	Coral-derived fungus	*A. versicolor* CHNSCLM-0063	Hou et al. (2019c)
248	Penilumamide	Gorgonian-derived fungus	*Aspergillus* sp. XS-20090B15	Chen et al. (2014c)
249-251	Penilumamides B-D			
252	Asperpeptide A			
Phenyl Ether Derivatives				
253	Cordyol D	Gorgonian-derived fungus	*Aspergillus* sp. XS-20090066	Chen et al. (2013b)
254	3,3'-*O*-Dimethyl-violaceol-I			
255	Cordyol C			
256	4-Methoxycarbonyl-diorcinol			
257	Cordyol E			
258	Diorcinol			
256a, 258a-25	Derivative of **256** and **258**	Semisynthetic		

Table 1 (continued)

8g				
259-261	Phomaethers A-C	Gorgonian-derived fungus	*Phoma* sp. TA07-1	Shi et al. (2017)
262	2,3'-Dihydroxy-4-methoxy-5',6-dimethyl diphenyl ether			
263	Talaromycin C	Gorgonian-derived fungus	*Talaromyces* sp.	Chen et al. (2015)
264	Purpactin C'			
265	Pencillide		*P. pinophilum* XS-20090E18	Zhao et al. (2015a)
266	Purpactin A			
267	Tenellic acid A methyl ester		*Talaromyces* sp.	Chen et al. (2015)

together with eight known analogues **1** (cochliomycin A), **7** ((7′*E*)-6′-oxozeaenol), **8** (deoxy-aigialomycin C), **9** (LL-Z1640-2), **10** (zeaenol), **11** (LL-Z1640-1), **12** (paecilomycin F) and **13** (aigialomycin B) (Fig. 3) were obtained (Liu et al. 2014). Compounds **4**, **6**–**9**, and the acetonide derivative **9a** displayed strong anti-larval settlement activity against *B. amphitrite* (EC_{50} = 1.82 to 22.5 μg/mL; $LC_{50}/EC_{50} > 50$), suggesting that they might be promising environmentally benign antifouling agents (Liu et al. 2014).

Noticeably, besides significant antifouling activity, compound **9** (LL-Z1640-2) produced by *C. lunatus* (TA26-46) exhibited promising inhibitory activity against phytopathogenic fungal strain *Pestalotia calabae*, with a minimum inhibitory concentration (MIC) value of 0.39 μmol/L, 25-fold stronger than that of the positive control, ketoconazole (MIC = 10 μmol/L) (Liu et al. 2014). A fungicide whole plant assay suggested that **9** exhibited pronounced activity on the phytopathogenic fungus *Plasmopara viticola* preventative test at 6×10^{-6} and concentration-dependent activity on the phytopathogenic fungus *Phytophthora infestans* preventative application at 200, 60, and 20×10^{-6}. Compound **9** could be considered as a promising new natural fungicide lead (Liu et al. 2014).

Further optimization of fermentation conditions of fungus *C. lunatus* (TA26-46) led to the isolation of two major natural products **9** (LL-Z1640-2) and **10** (zeaenol) (Fig. 3) with multi-gram quantities (Zhang et al. 2017). By one or two steps, we semi-synthesized six trace natural compounds **1** (cochliomycin A), **3** (cochliomycin C) (Fig. 3), **4** (cochliomycin D), **5** (cochliomycin E), **6** (cochliomycin F) and **7** ((7′*E*)-6′-oxozeaenol) (Fig. 3), and a series of derivatives **14**–**29** (Fig. 4) from compounds **9** and **10** with high yields (65–95%) (Zhang et al. 2017). Compounds **14**–**16** displayed potent antiplasmodial activity against *P. falciparum* (IC_{50} = 1.84, 8.36, and 6.95 μmol/L, respectively). The acetoxy groups and acetonide functionality might contribute to the antiplasmodial activity (Fig. 5). However, the chlorine atom has a negative effect on the activity. Very importantly, **14** and **15** were non-toxic with very safety and high therapeutic indices ($CC_{50}/IC_{50} > 180$), and thus represent potential promising leads for antiplasmodial drug discovery. In addition, 2-OH was found to be an important functionality for reducing toxicity. Only **14** showed antileishmanial activity against *Leishmania donovani* (IC_{50} = 9.22 μmol/L). Most of the enone RALs showed high antileishmanial efficacy but poor therapeutic indices, suggesting that the *cis* or *trans*-functionality has a contribution to toxicity, and their antileishmanial activities may well be related to their toxicity (Fig. 5). Furthermore, **14** and **15** also displayed antiplasmodial activity against the neglected Chagas' disease causing *Trypanosoma cruzi* (IC_{50} = 11.9 and 17.2 μmol/L, respectively) (Zhang et al. 2017).

It should be noted that many gene clusters in marine-derived fungi for the production of undiscovered secondary metabolites generally remain unexpressed under common laboratory culture conditions. In order to obtain uncharacterized metabolites, the chemical epigenetic perturbation method was applied to *C. lunatus* (TA26-46) to manipulate the silent fungal genes. Two new 14-membered RALs characterized with bromine substitution, **30** (5-bromozeaenol) and **31** (3,5-dibromozeaenol) (Fig. 6), were obtained from the culture treated with histone deacetylase inhibitor, sodium butyrate (Zhang et al. 2014). Compounds **30** and **31** represent the first examples of naturally occurring brominated RALs.

Facing the challenges of discovery repetition and silent biosynthetic pathways, only limited mining approaches were applied in our work to date. As well known, microorganisms are easily manipulated on the genetic level. With gene sequencing technology blooming, genetic techniques and bioinformatics algorithms will continue to provide more opportunities for disclosing the novel pathways within marine microorganisms to then enable exploration of the untapped valuable bioactive molecules encoded within.

Furthermore, co-culturing as an effective method to induce production of novel secondary metabolites from two interacting microbial strains was applied to mine macrocyclic lactones. In single strain cultivation, the sponge-derived actinomycete *Streptomyces rochei* MB037 could produce two 18-membered macrolides, **32** (borrelidin) and **33** (borrelidin F) (Yu et al. 2019). Interestingly, in the co-culture of

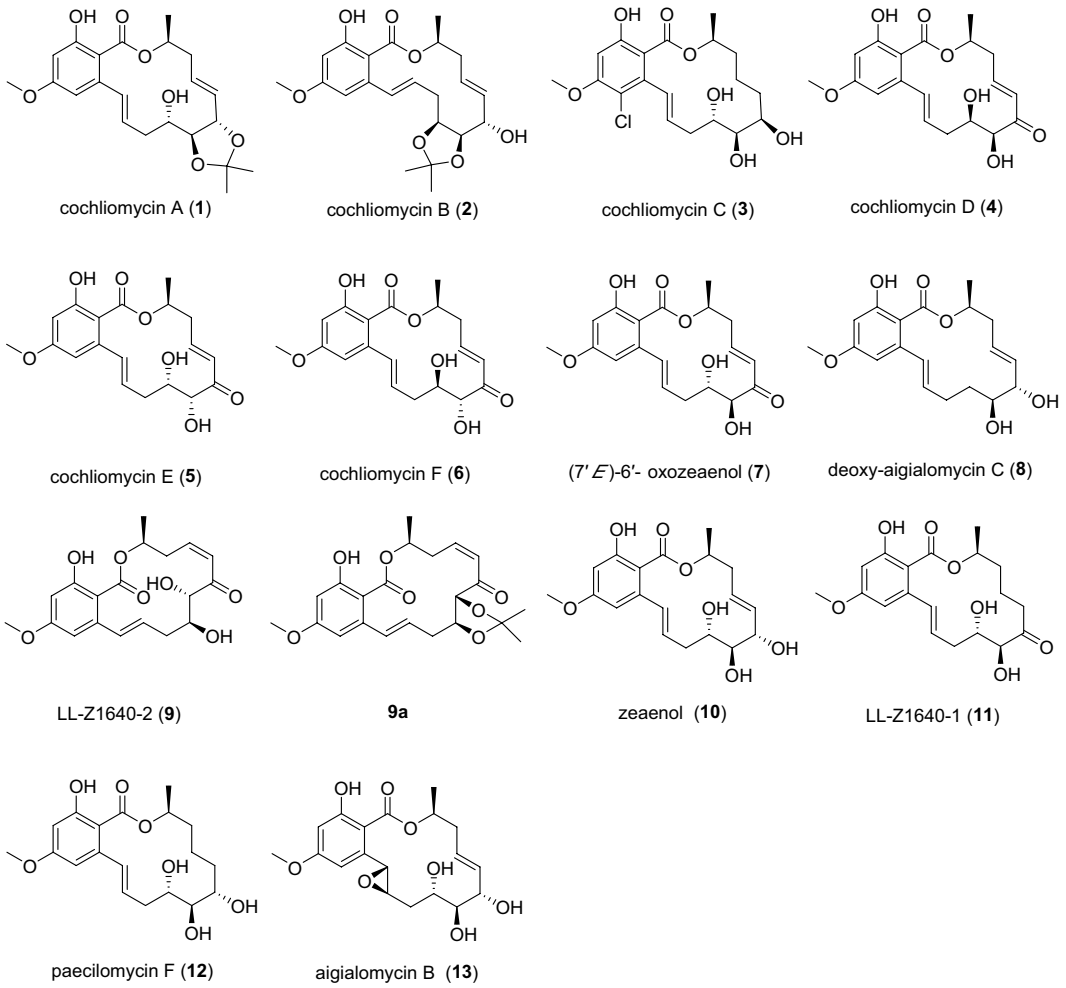

Fig. 3 14-Membered resorcylic acid lactones from the gorgonian-derived fungus *C. lunatus* (M351) (**1**–**3**) and the sea anemone-derived fungus *C. lunatus* (TA26-46) (**4**–**13**)

S. rochei MB037 and the gorgonian-derived fungus *Rhinocladiella similis* 35, besides macrolides **32** and **33**, *S. rochei* MB037 was induced to produce two new fatty acids with a rare nitrile group, **34** (borrelidin J) and **35** (borrelidin K) (Fig. 7) (Yu et al. 2019), which are structurally related to borrelidins. Compounds **34** and **35** were derived from the actinomycete *S. rochei* MB037, suggesting that the silent hydrolytic enzyme genes for hydrolyzing lactone in the borrelidin macrolides could be activated by the co-culture approach. Notably, both **34** and **35**, obtained only in co-culture, exhibited stronger antibacterial activities against methicillin-resistant *S. aureus* than **32** and **33**.

In addition to marine invertebrates and their symbiotic microorganisms, macrolides were also obtained from marine-derived bacteria. Compound **36** (bastimolide A) (Fig. 8), a polyhydroxy macrolide with a 40-membered ring, was obtained from a new genus of the tropical marine cyanobacterium *Okeania hirsute* (Shao et al. 2015a). Its complete structure and absolute configuration were unambiguously identified by X-ray diffraction analysis of the nona-*p*-nitrobenzoate derivative **36a** (Fig. 8). Compound **36** is a complex 40-membered macrolactone with repeating 1,5-diol and 1,3-diol groups as well as a *t*-butyl group moiety which is quite rare among natural products. Compound **36** showed strong antimalarial activity against four resistant strains of *P. falciparum* (IC_{50} = 80 to 270 nmol/L), including TM90-C2A (chloroquine, mefloquine, and pyrimethamine resistant), TM90-C2B (chloroquine, mefloquine, pyrimethamine, and atovaquone resistant), W2 (chloroquine and pyrimethamine resistant), and TM91-C235 (chloroquine, mefloquine, and pyrimethamine resistant). Although this compound displayed toxicity to the host Vero cells (IC_{50} = 2.1 μmol/L), it still represents a potentially promising lead for antimalarial drug discovery (Shao et al. 2015a).

After discovery of the potent antimalarial 40-membered macrolide, continued investigation of the biologically-active and structurally-complex polyketides from *O. hirsuta* led to the isolation of a novel analogue **37** (bastimolide

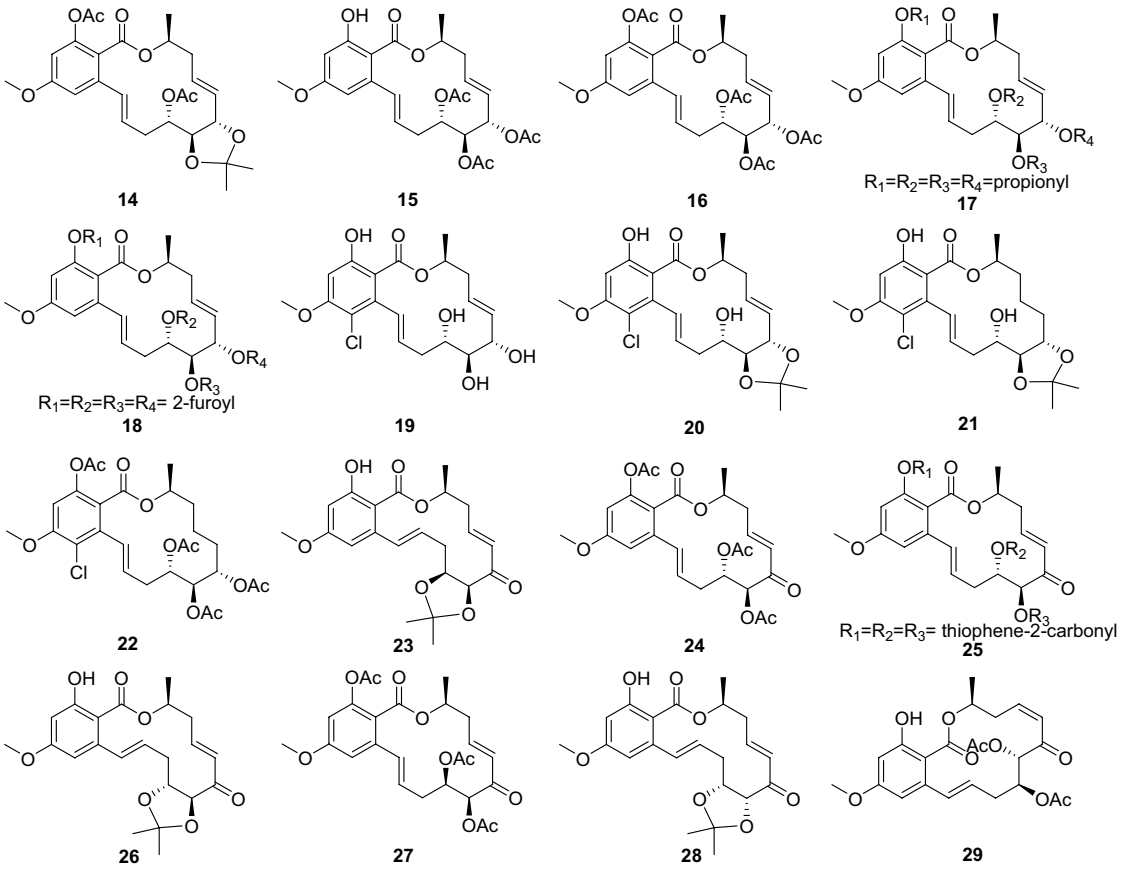

Fig. 4 Semisynthesized resorcylic acid lactone derivatives

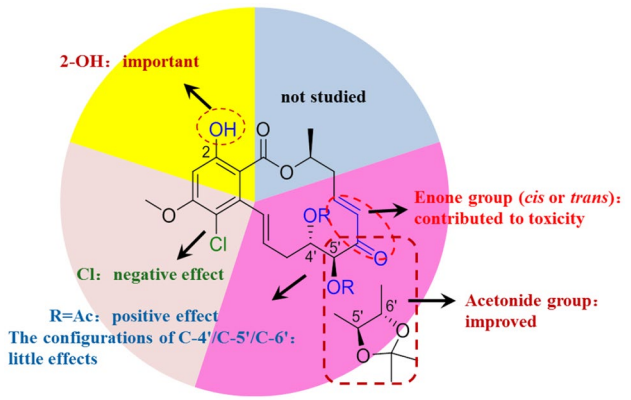

Fig. 5 The structure–activity relationships of resorcylic acid lactones

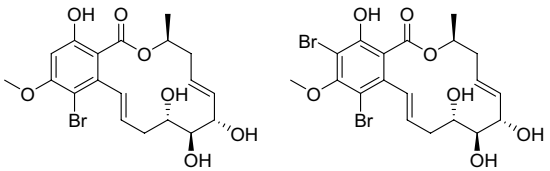

Fig. 6 Brominated resorcylic acid lactones from the sea anemone-derived fungus *C. lunatus* (TA26-46) by chemical epigenetic manipulation

B) (Fig. 9), a 24-membered macrolide characterized by a long aliphatic chain with polyhydroxy groups and bearing a unique terminal tert-butyl group (Shao et al. 2018). A methanolysis mechanism for **36** is proposed and one unexpected isomerization product of the C_2–C_3 double bond, **38** (2-(*E*)-bastimolide A) (Fig. 9), was also obtained. The natural product **37** showed pronounced antimalarial activity against chloroquine-sensitive *P. falciparum* strain HB3 ($EC_{50} = 5.72 \pm 0.65$ μmol/L). Compound **38** showed even stronger antimalarial potency with an EC_{50} value of 1.41 ± 0.47 μmol/L. Thus, the bastimolides show considerable antimalarial activity and represent an intriguing new class of antimalarial agents (Shao et al. 2018).

Anthraquinones

The diverse activities of anthraquinones isolated from marine-derived fungi with cytotoxic (Chen et al. 2013a; Xie et al. 2010; Zhu et al. 2012), antiviral (Huang et al. 2017), antioxidant (Li et al. 2016) and other activities have attracted many interests for drug discovery. For example, SZ-685C, a hydroanthraquinone isolated from the marine-derived *Halorosellinia* fungus, exhibited potent cytotoxic activity (Chen et al. 2013a; Xie et al. 2010; Zhu et al. 2012). In our investigation of bioactive anthraquinone derivatives from marine-derived fungi (Yang et al. 2012; Zheng et al. 2012), a total of 54 anthraquinone monomers and dimers have been isolated from *Nigrospora* sp., *Alternaria* sp. and other fungal genera. Analysis of anthraquinones with various chemical structures possessing interesting biological activities revealed the key structural features required for their activities.

Nine anthraquinone derivatives were obtained from a sea anemone-derived fungus *Nigrospora* sp. ZJ-2010006, including two new hydroanthraquinone analogues, **39** (4a-*epi*-9α-methoxydihydrodeoxybostrycin) and **40** (10-deoxybostrycin), together with seven known anthraquinone derivatives **41** (nigrosporin B), **42** (9α-hydroxydihydrodesoxybostrycin), **43** (9α-hydroxyhalorosellinia A), **44** (4-deoxybostrycin), **45** (bostrycin), **46** (3,5,8-trihydroxy-7-methoxy-2-methylanthracene-9,10-dione), **47** (austrocortirubin) (Fig. 10). Ten acetyl derivatives (**44a**, **45a**, **46a**–**46g**, **47a**) (Fig. 10) were prepared by structural modification (Yang et al. 2012). Compound **39** represents the first case of a hydroanthraquinone with a 9-OMe group. Notably, **40** displayed significant antibacterial activity against *Bacillus subtilis* (MIC = 625 nmol/L). Compound **41** exhibited promising antibacterial activity against *B. subtilis* and *B. cereus* (MICs = 312 nmol/L). Additionally, the derivative **44a** showed pronounced inhibitory activity against *B. cereus* (MIC = 48.8 nmol/L), 25-fold stronger than that of ciprofloxacin (MIC = 1250 nmol/L). These results demonstrated that hydroanthraquinone derivatives might be a promising source for antimicrobial agent discovery.

Structure–activity relationship analysis revealed that the introduction of the 4-OH/9-OH/10-OH groups had little effect on antibacterial activity (Fig. 11). Interestingly, transforming from a hydroxy group at C-3 to an acetoxy

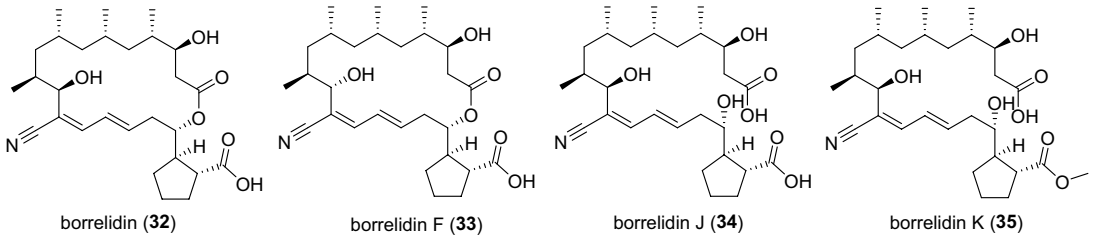

Fig. 7 18-Membered macrolides and structurally related fatty acids from the co-culture of the sponge-derived actinomycete *S. rochei* MB037 and the gorgonian-derived fungus *Rhinocladiella similis* 35

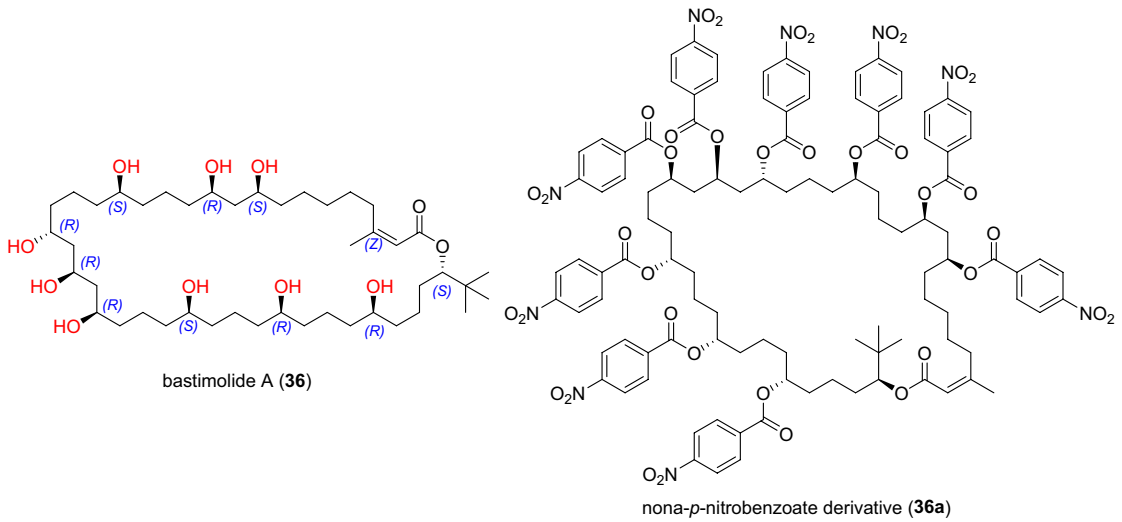

Fig. 8 Polyhydroxy macrolides from the cyanobacterium *O. hirsute*

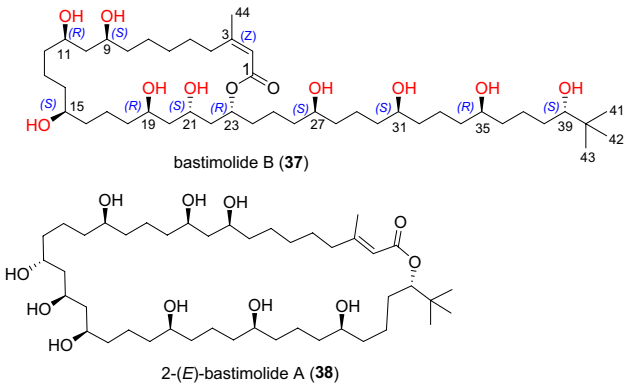

Fig. 9 Bastimolide B and isomerization product of bastimolide A from the cyanobacterium *O. hirsute*

group significantly increased selective antibacterial activity. The cycloaliphatic ring has a positive contribution to the antibacterial activity. Additionally, an aromatic B ring may be necessary for the antibacterial activity (Yang et al. 2012).

Ten anthraquinone derivatives were isolated from the culture of *Sarcophyton* soft coral-derived fungus *Alternaria* sp. ZJ-2008003 collected from the South China Sea, including five new hydroanthraquinone derivatives, **48**–**51** (tetrahydroaltersolanols C–F) and **52** (dihydroaltersolanol A), and five new alterporriol-type anthranoid dimers, **53**–**57** (alterporriols N–R) (Fig. 12) (Zheng et al. 2012). Compound **54** (alterporriol O) was the first isolated alterporriol dimer with a C-4–C-4′ linkage. Compound **48** (tetrahydroaltersolanol C) and **56** (alterporriol Q) showed antiviral activity against the Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) (IC_{50} = 65 and 22 μmol/L, respectively). Compound **55** (alterporriol P) exhibited cytotoxic activity against the PC-3 and HCT-116 cell lines (IC_{50} = 6.4 and 8.6 μmol/L, respectively) (Zheng et al. 2012).

Azaphilones

The azaphilone molecules are a structurally variable family of fungal polyketide metabolites with a highly oxygenated pyranoquinone bicyclic core and exhibiting multiple bioactivities such as cytotoxic (Yamada et al. 2008), antimicrobial (Che et al. 2002), antiviral (Wang et al. 2011a), and anti-inflammatory (Yasukawa et al. 2008) activities. For instance, sclerketide C, an azaphilone analogous isolated from gorgonian-derived fungus *Penicillium sclerotiorin* CHNSCLM-0013, exhibited significant anti-inflammatory activity (Liu et al. 2019). Pleosporalone B from the culture of marine-derived fungus *Pleosporales* sp. CF09-1 and penicilazaphilone C from *Penicillium sclerotiorum* M-22 displayed potent antimicrobial activities (Cao et al. 2019; Zhou et al. 2016). Azaphilones have attracted much attention due to their fascinating structural features and distinguished bioactivities (Wei et al. 2017). Our previous work on metabolites produced by symbiotic microorganisms of marine invertebrates found 48 azaphilones, including 37 new compounds, many of which were reported to exhibit antifouling and antiviral activities (Wang et al. 2018; Wei et al. 2017; Zhao et al. 2015a). Desiring promising antifouling molecules, a one-step semisynthetic method was applied to discover more new azaphilonoids derivatives.

A series of azaphilone derivatives were isolated from the gorgonian-derived fungal strain, *Penicillium pinophilum* XS-20090E18, collected from the Xisha Islands coral reef, including three new azaphilone derivatives **58**–**60** (pinophilins D–F), together with six known azaphilone derivatives **61** (Sch 1385568), **62** (pinophilin B), **63** (Sch 725680), **64** ((−)-mitorubrin), **65** ((−)-mitorubrinol) and **66** ((−)-mitorubrinic acid) (Fig. 13) (Zhao et al. 2015a). However, none of the obtained azaphilone derivatives showed antifouling, cytotoxic, or topoisomerase I (Topo I) inhibitory activity (Zhao et al. 2015a).

Six azaphilone derivatives were isolated from the sponge-derived fungus *Penicillium sclerotiorum*, including two new azaphilones **67** and **68** (penicilazaphilones D and E), together with four known analogs, **69** ((+)-sclerotiorin), **70** (geumsanol C), **71** (WB (CAS No. 1701443-52-8, 6*H*-2-benzopyran-6-one,5-chloro-3-[(1*E*,3*R*,4*R*,5*S*)-3,4-dihydroxy-3,5-dimethyl-1-hepten-1-yl]-1,7,8,8a-tetrahydro-7,8-dihydroxy-7-methyl-,(-7*R*,8*R*,8a*S*)) and **72** (geumsanol G) (Fig. 14) (Wang et al. 2018). Compound **67** was the second reported azaphilone with a C4 aliphatic side chain, and **68** was the first azaphilone with a tetrahydrofuran ring at C-3. Compound **69** demonstrated antiviral activity against HSV (IC_{50} = 19.5 μmol/L) and EV71 (IC_{50} = 132 μmol/L), 16- and 3-fold stronger than the positive control ribavirin, respectively (Wang et al. 2018).

On account of the significant bioactivities of **69** ((+)-sclerotiorin), 30 sclerotioramine derivatives **73**–**102** has been semi-synthesized from **69** by a one-step reaction (Fig. 15) (Wei et al. 2017). Most of them except **77**, **78**, **79**, **83**, and **99** showed strong anti-barnacle settlement activity against *B. amphitrite*. The aromatic amino-derivatives **84**–**88**, **90**–**92**, **94**, **96**–**98**, and **100**–**102** demonstrated potent antifouling activity; while only two aliphatic amino-derivatives **76** and **101** displayed antifouling activity. It should be noted that **76** and **101** showed promising activity (EC_{50} = 0.94 and 0.47 μg/mL, respectively) stronger than that of the commercial biocide Sea-Nine 211™ (EC_{50} = 1.2 μg/mL). Meanwhile, compounds **76** and **101** possess high therapeutic ratios (LC_{50}/EC_{50} 53.2 and 106.4, respectively), indicating that they may be antifouling candidates with low-toxicity for the development of new environmentally benign antifoulants (Wei et al. 2017).

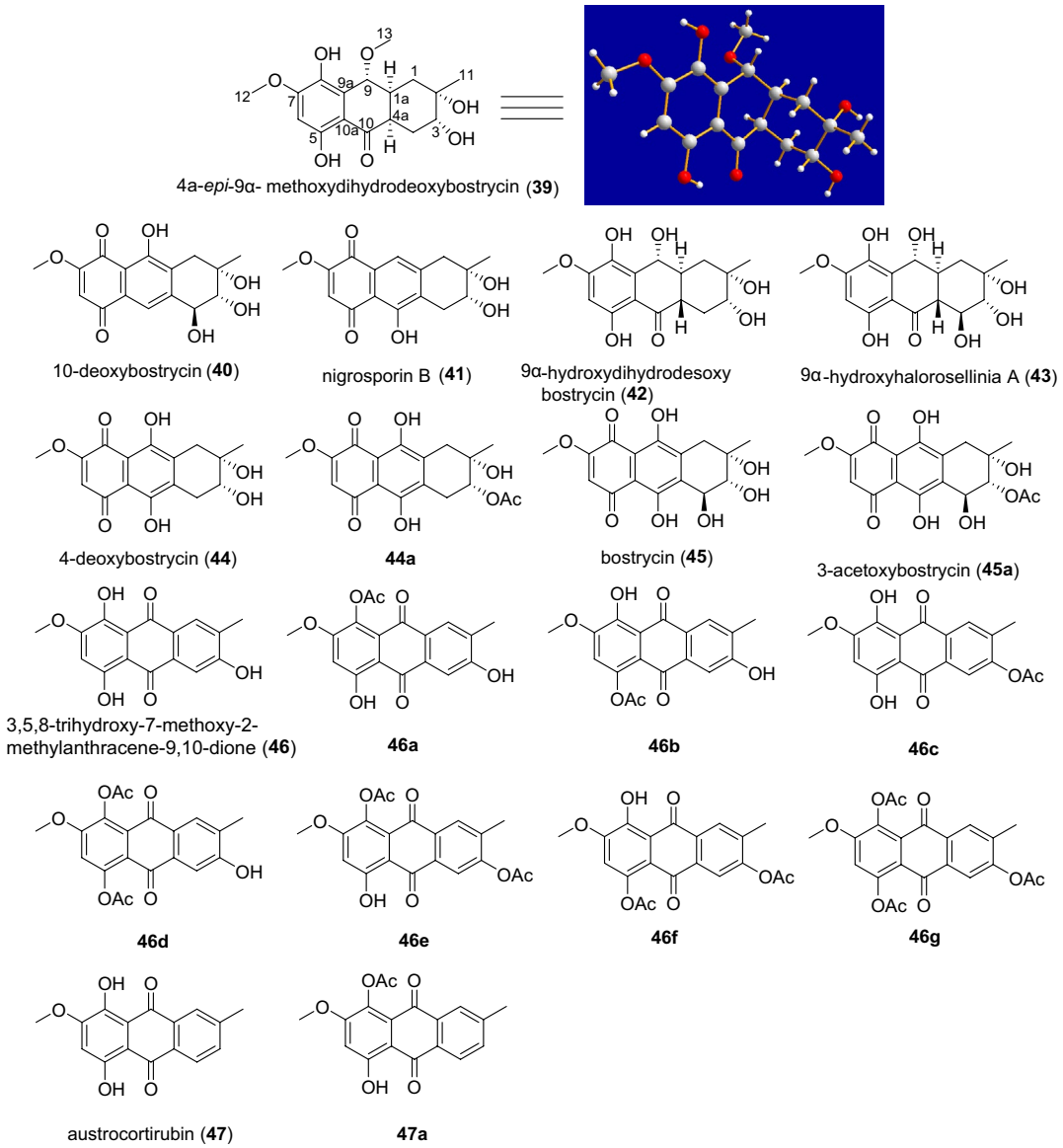

Fig. 10 Anthraquinone derivatives from the sea anemone-derived fungus *Nigrospora* sp. ZJ-2010006

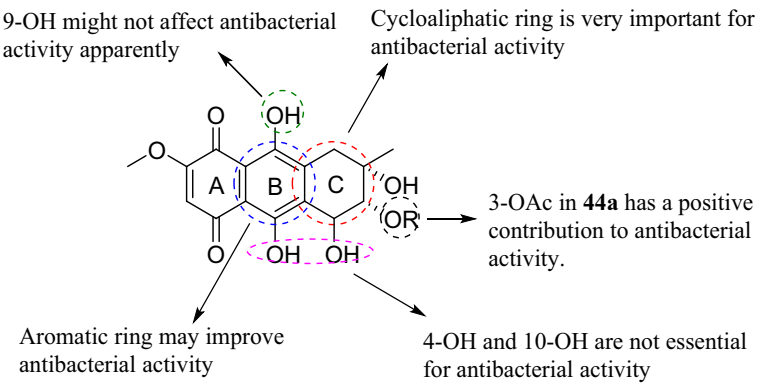

Fig. 11 Antibacterial structure–activity relationships for hydroanthraquinone derivatives

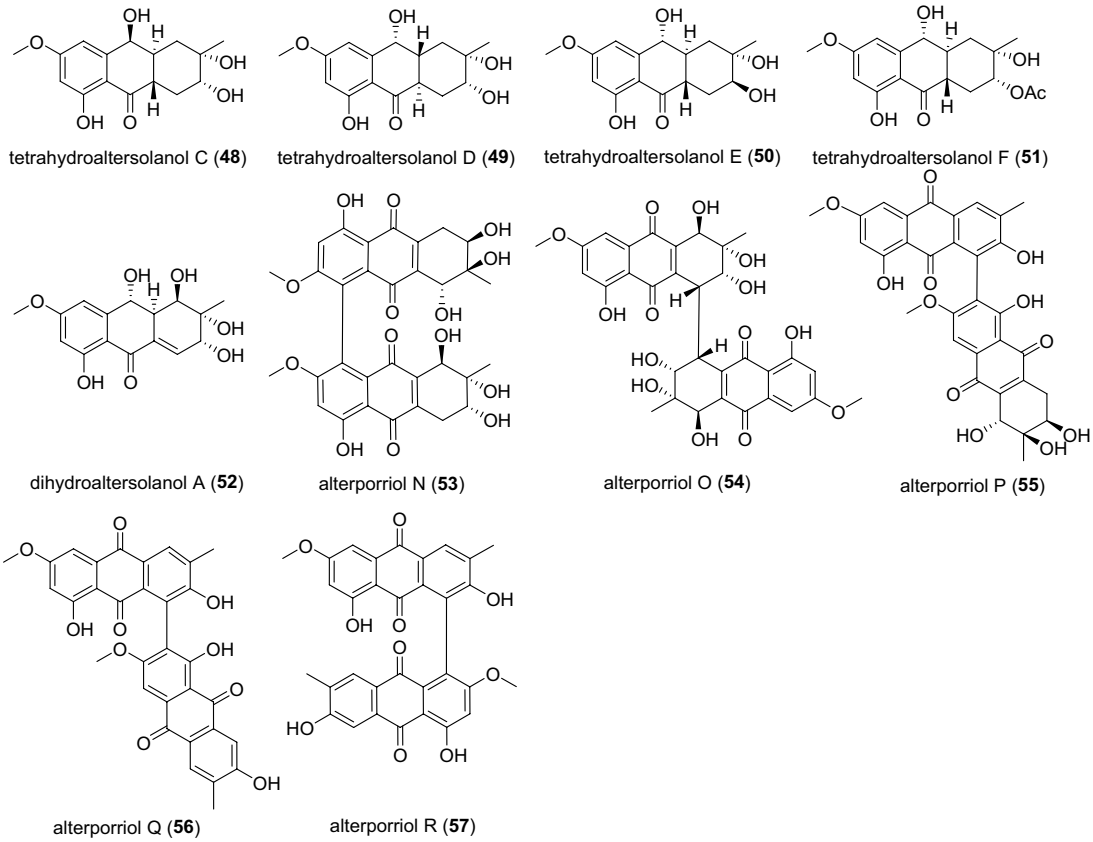

Fig. 12 Anthraquinone monomers and dimers from the soft coral-derived fungus *Alternaria* sp. ZJ-2008003

Alkaloids

Marine-derived alkaloids represent a class of compounds with particularly privileged structures, which have been frequently encountered in a vast number of pharmaceuticals as well as agrochemicals (Bandini and Eichholzer 2009; Hibino and Choshi 2001; Humphrey and Kuethe 2006; Kochanowska-Karamyan and Hamann 2010; Lounasmaa and Tolvanen 2000). For example, raistrickindole A, an indole diketopiperazine alkaloid obtained from the marine-derived fungus *Penicillium raistrickii*, displayed antiviral activity against the hepatitis C virus (Li et al. 2019a). Agelastatin A, a bromopyrrole marine alkaloid isolated from the Mexican sponge, *Agelas* sp., exhibited strong antineoplastic activity (Pettit et al. 2005). Our group has isolated more than 100 alkaloids with promising biological activities from diverse fungal strains derived from marine invertebrates (Chen et al. 2014a; Jia et al. 2015; Shao et al. 2015b; Wang et al. 2015a). To obtain significant antibacterial compounds, efficient and environmental friendly methods for synthesis of unsymmetrical bisindolylmethanes or triarylmethane were developed (Wen et al. 2015).

Compound **103** ((+)- and (−)-pestaloxazine A) (Fig. 16), a pair of new enantiomeric alkaloid dimers with an unprecedented symmetric spiro[oxazinane-piperazinedione] skeleton, were isolated from a soft coral-derived fungus *Pestalotiopsis* sp. (Jia et al. 2015). A plausible biosynthetic pathway for **103** was proposed starting from two molecules of L-ornithine (Fig. 17). The piperazinedione intermediate **103a** is produced by double dehydration. The oxidation results in the presence of the N-oxide **103b**, and the key racemic intermediates (±)-**103c** are achieved by intermolecular nucleophilic attack at the same face. The condensation between **103c** and **103d** gives the final product (±)-**103**. The epimer (2*R*,2′*S* or 2*S*,2′*R*) of (±)-**103**, a mesomer, was not observed, indicating that the production of **103** in the fungus was regulated by enzymes with selective catalytic functions. Compound **103** exhibited potent and selective antiviral activity against Enterovirus 71 (EV71) ($IC_{50} = 14.2 \pm 1.3$ μmol/L), 18-fold more potent than the positive control ribavirin ($IC_{50} = 256.1 \pm 15.1$ μmol/L). Therefore, **103** could be considered as a promising antiviral agent (Jia et al. 2015).

From the gorgonian coral-derived fungus *Scopulariopsis* sp., six dihydroquinolin-2-one-containing alkaloids were isolated, including three

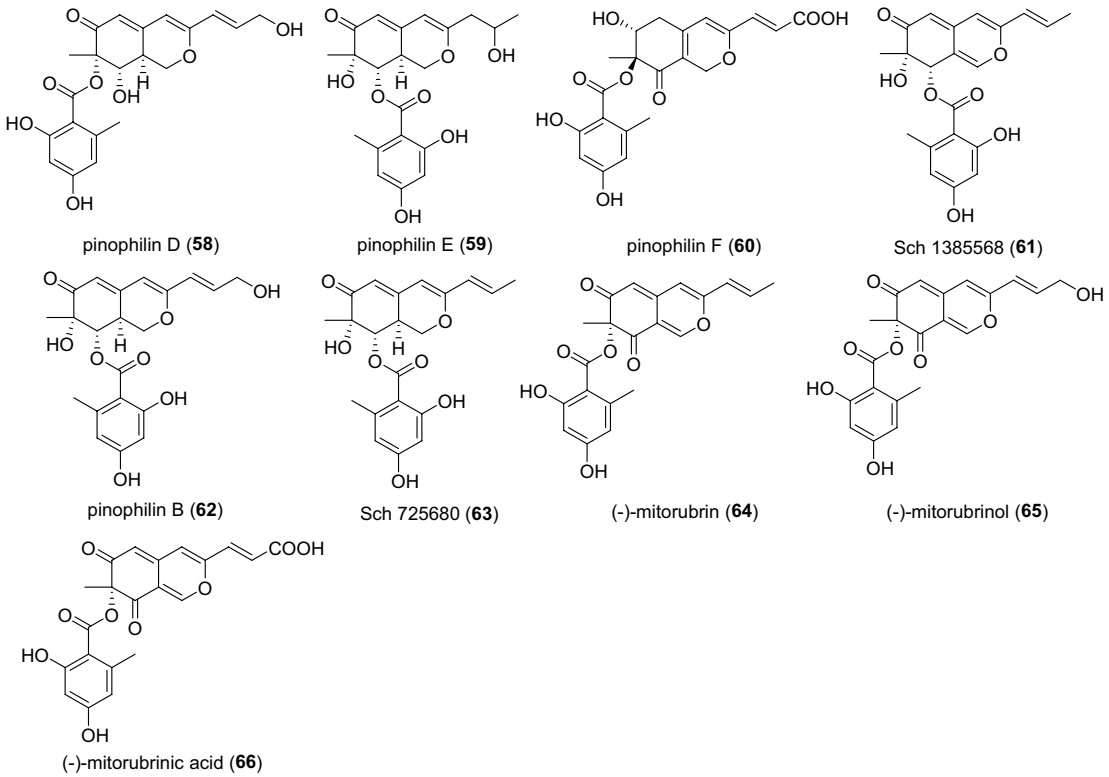

Fig. 13 Azaphilone derivatives from the gorgonian-derived fungus *P. pinophilum* XS-20090E18

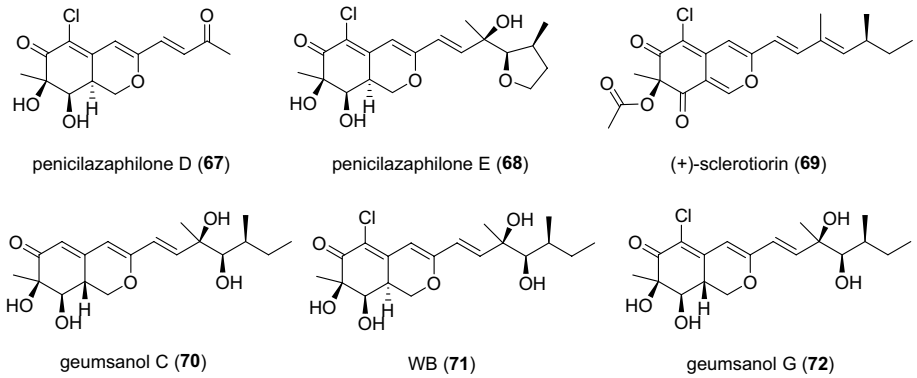

Fig. 14 Azaphilone derivatives from the sponge-derived fungus *P. sclerotiorum*

4-phenyl-3,4-dihydroquinolin-2(1*H*)-one alkaloids containing a monoterpenoid moiety, **104** (aniduquinolone A), **105** (aflaquinolone A), **106** (aflaquinolone D), and three 4-phenyl-3,4-dihydroquinolin-2(1*H*)-one alkaloids, **107** (6-deoxyaflaquinolone E), **108** (aflaquinolone F), **109** (aflaquinolone G) (Fig. 18) (Shao et al. 2015b). These dihydroquinolin-2-one-containing alkaloids except **109** exhibited significant anti-larval settlement activity against *B. amphitrite*. This is the first report on the antifouling activity for quinolin alkaloids. In particular, compound **104** showed highly potent antifouling activity against *B. amphitrit* at a picomolar level (EC_{50} = 17.5 pmol/L), 249,000-fold stronger than that of Sea-Nine 211™ (EC_{50} 4.36 μmol/L). Particularly, **104** displayed a high therapeutic ratio (LC_{50}/EC_{50} = 1200). Therefore, it represents a structural class for discovery of effective, non-toxic, environmentally friendly antifouling agents (Shao et al. 2015b).

From the mycelia of a gorgonian-derived *Aspergillus* sp. fungus, two new prenylated dihydroquinolone derivatives, **110** (22-*O*-(*N*-Me-*L*-valyl)-aflaquinolone B) and **111** (22-*O*-(*N*-Me-*L*-valyl)-21-*epi*-aflaquinolone B), and two known analogues, **105** and **106** (aflaquinolones A and D) (Fig. 19), were obtained (Chen et al. 2014a). Compounds **110** and **111** possess an unusual esterification of *N*-Me-*L*-Val to the side chain prenyl group. It is worth noting that compound

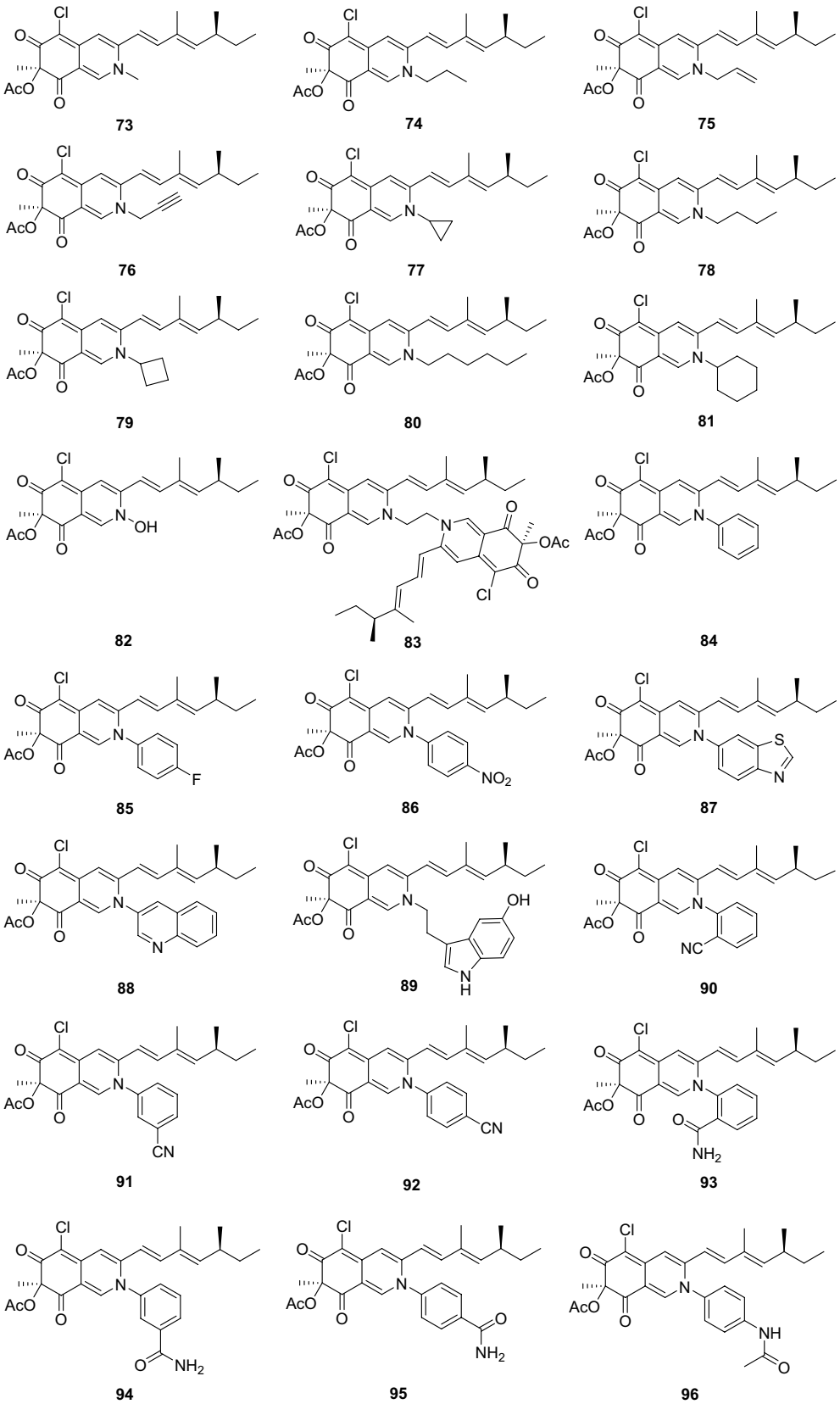

Fig. 15 Semisynthetic azaphilone derivatives from the natural compound (+)-sclerotiorin (**69**)

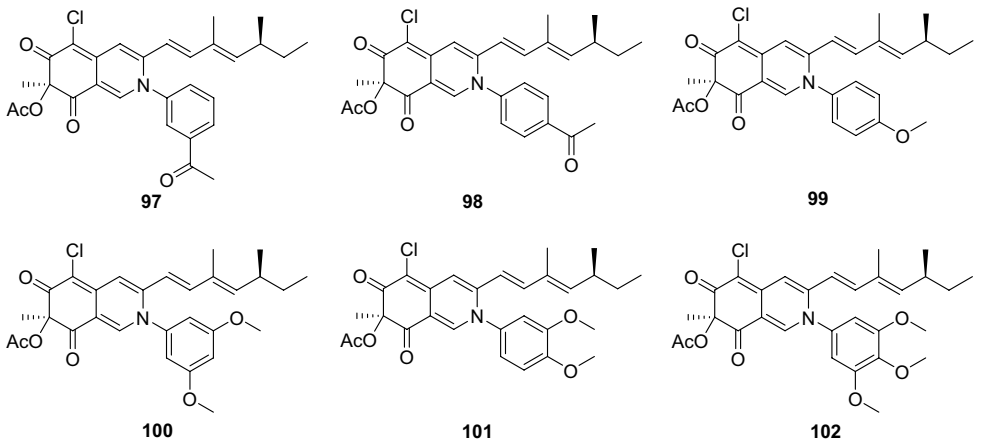

Fig. 15 (continued)

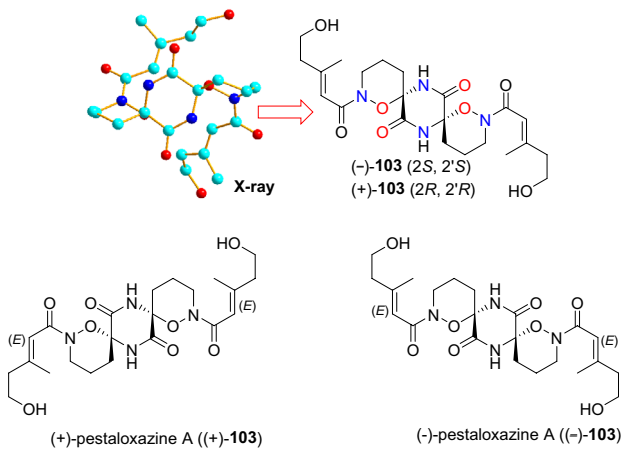

Fig. 16 Enantiomeric alkaloid dimers with an symmetric spiro[oxazinane-piperazinedione] skeleton from the soft coral-derived fungus *Pestalotiopsis* sp.

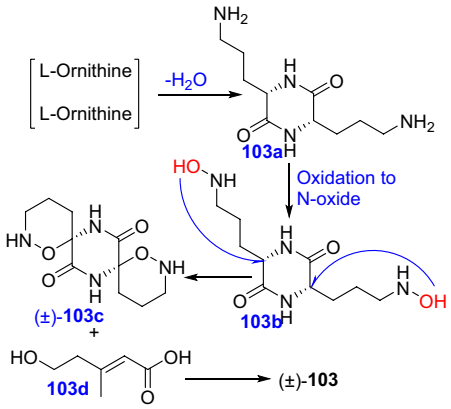

Fig. 17 Plausible biosynthetic pathway to **103**

111 exhibited outstanding anti-RSV (Human respiratory syncytial virus (RSV)) activity (IC_{50} = 42 nmol/L), 500-fold more potent than that of ribavirin (IC_{50} = 20 μmol/L) and showed a comparatively higher therapeutic ratio (TC_{50}/IC_{50} = 520). This is the first report of prenylated dihydroquinolone derivatives with potent antiviral activity (Chen et al. 2014a).

Eight indol alkaloids were isolated from the bacterium *Pseudovibrio denitrificans* strain UST4-50 derived from an unidentified ascidian, including a diindol-3-ylmethane (DIM), **112** (di(1*H*-indol-3-yl)methane), and several analogues, **113** (vibrindole A), **114** (3,3′-di-1*H*-indol-3-yl-1,2-propandiol), **115** (tri(1*H*-indol-3-yl)methane), **116** (1,2,2-tri(1*H*-indol-3-yl) ethanone), **117** (arsindoline A), **118** (3, 3′-(phenylmethylene) bis-1*H*-indole), and **119** (4-(di(1*H*-indol-3-yl)methyl) phenol (DIM-Ph-4-OH)) (Fig. 20) (Wang et al. 2015a). All DIMs showed low-toxic anti-larval settlement activity against *B. amphitrite* (EC_{50} = 18.57 to 1.86 μmol/L; LC_{50}/EC_{50} > 15). Structure–activity relationship analysis revealed that 3,3′-diindolylmethylene and Ph-C1‴ phenolic hydroxyl were necessary for the activity. A field test of **112** over a period of 5 months further confirmed its antifouling activity comparable to Sea-Nine 211™ (Wang et al. 2015a). DIMs could be considered promising candidates as environmentally friendly antifouling agents owing to their simple structures, excellent activities, and low toxicities against marine target organisms.

The bisindole derivatives manifest significant biological activities, while the synthesis method for unsymmetrical bisindolylmethanes or triarylmethanes still remains a great challenge (Abe et al. 2013; Fu et al. 2013; Ma and Yu 2005; Yu and Yu 2009; Zhu et al. 2002). In our study, an efficient S_N1-type reaction was developed for 3-indolylmethanols with miscellaneous nucleophiles, featuring catalyst-free, low cost, wide substrate scope and mild reaction conditions (Figs. 21, 22). This approach provides an efficient and environmental friendly method for synthesis of diverse

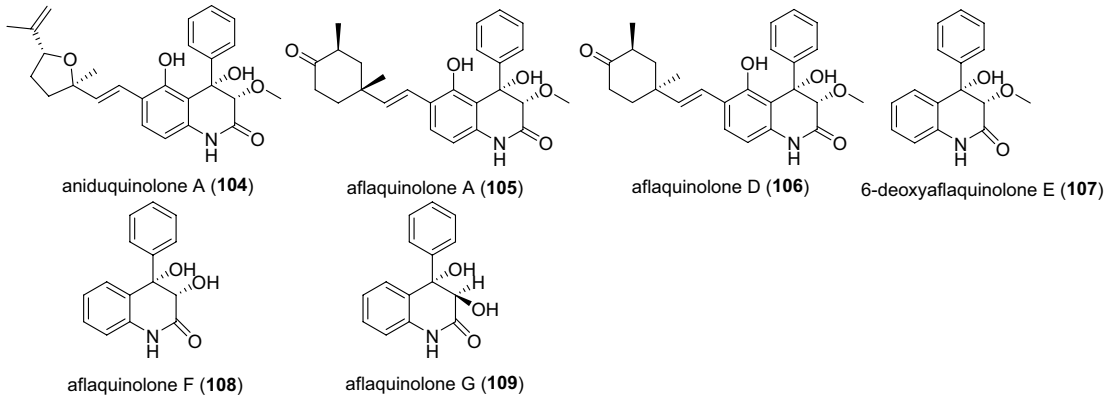

Fig. 18 Dihydroquinolin-2-one-containing alkaloids from the gorgonian coral-derived fungus *Scopulariopsis* sp.

3-substituted indolyl derivatives as well as unsymmetrical bisindolylmethanes and triarylmethanes (Wen et al. 2015).

As part of our continuous work in this area, versatile 3-substitued indolyl derivatives were synthesized in high yields, including unsymmetrical diarylmethanes and triarylmethanes. Among them, compounds **120** (2-(phenyl(2-phenyl-1*H*-indol-3-yl)methyl)malononitrile), **121** (4-hydroxy-3-(phenyl(2-phenyl-1*H*-indol-3-yl)methyl)-2*H*-chromen-2-one), **122** (4-(phenyl(2-phenyl-1*H*-indol-3-yl)methyl)phenol) and **123** (2-phenyl-3-(phenyl(2,4,6-trimethoxyphenyl)methyl)-1*H*-indole) (Fig. 23) exhibited antibacterial activities against *B. megaterium* and *M. lysodeikticus*. In particular, **121** and **122** displayed antibacterial activities against *B. megaterium* (MIC = 13.5 and 8.36 μmol/L, respectively). In addition, **120**, **121** and **122** exhibited potent antibacterial activities against *M. lysodeikticus* (MIC = 2.10, 3.35 and 4.18 μmol/L, respectively). These synthetic compounds could be considered as promising lead compounds for further investigation and application (Wen et al. 2015).

Terpenoids

Terpenoids constitute a class of broadly active natural products isolated from a diverse range of marine organisms. For example, 11*R*-methoxy-5,9,13-proharzitrien3-ol, obtained from an endophytic fungus *Trichoderma harzianum* X-5 derived from the marine brown alga *Laminaria japonica*, displayed growth inhibition of some marine phytoplankton species (Song et al. 2018). Nakijinol G, a meroterpenoid obtained from a sponge *Hyrtios* sp. collected from the South China Sea, showed protein tyrosine phosphatase (PTP1B) inhibitory activity (Wang et al. 2017). Trichodermanin C, a diterpenes obtained from a fungal strain *Trichoderma harzianum* OUPS-111D-4 derived from sponge *Halichondria okadai*, exhibited significant cytotoxic activity (Yamada et al. 2017). In our ongoing research on the marine invertebrates and their symboitic microorgnisms, 101 terpenoids including 43 new compounds with novel structures were isolated, which exhibited antibacterial, cytotoxic and antifouling activities (Cao et al. 2015, 2017; Li et al. 2012a).

Four new bisabolane-type sesquiterpenoids were separated from the culture of *Aspergillus* sp. (ZJ-2008004) derived from the sponge *Xestospongia testudinaria*, including **124** (aspergiterpenoid A), **125** ((−)-sydonol), **126** ((−)-sydonic acid), and **127** ((−)-5-(hydroxymethyl)-2-(2′,6′,6′-trimethyltetrahydro-2*H*-pyran-2-yl)phenol) (Fig. 24) (Li et al. 2012a). All are optically active compounds. Compound **125** displayed potent inhibitory activity against *S. albus* and *M. tetragenus* (MIC = 5.00 and 1.25 μmol/L, respectively), and **127** on *S. albus* and *B. subtilis* (MIC = 5.00 and 2.50 μmol/L, respectively). Compound **126** showed strong inhibiting activity against four pathogenic bacteria *B. subtilis*, *Sarcina lutea* (MIC = 2.50 μmol/L), *E. coli* and *M. tetragenus* and uniquely against two marine bacteria (*V. parahaemolyticus* and *V. anguillarum*) (Li et al. 2012a).

Eleven new scalarane sesterterpenoids were isolated from the sponge *Carteriospongia foliascens*, including

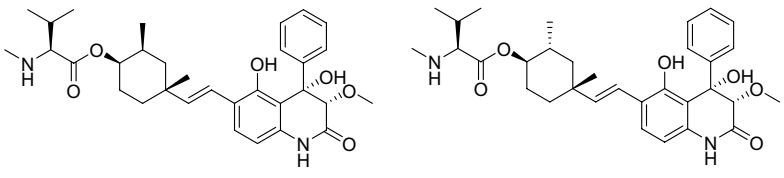

Fig. 19 Prenylated dihydroquinolone derivatives from the gorgonian-derived fungus *Aspergillus* sp.

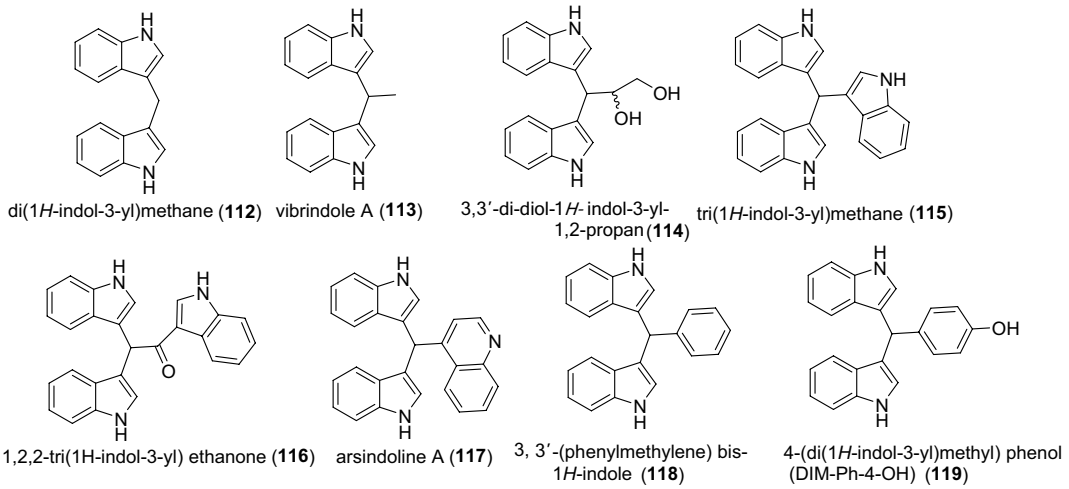

Fig. 20 Diindol-3-ylmethanes from the ascidian-derived bacterium *P. denitrificans* UST4-50

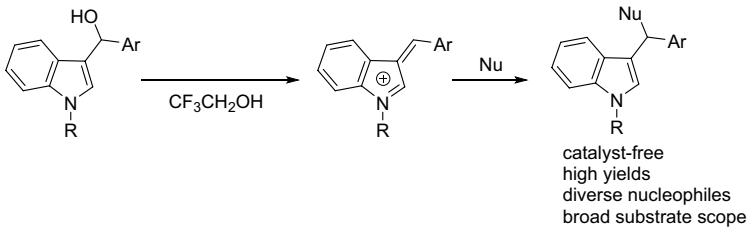

Fig. 21 Reaction of 3-indolylmethanol with diverse nucleophiles

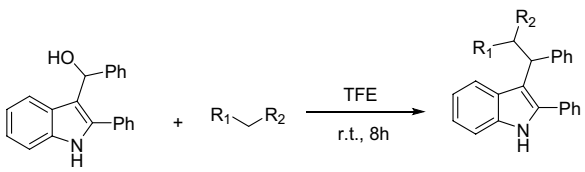

Fig. 22 The active methylene compounds used as nucleophiles

three 20,24-bishomo-25-norscalaranes, **128**–**130** (carteriofenones A–C), and eight 20,24-bishomoscalaranes, **131**–**138** (carteriofenones D–K) (Fig. 25) (Cao et al. 2015). Scalarane sesterterpenoids with 4-methylpentanate or pentanoate substituents at the C-12 position were reported for the first time. Compounds **132**–**135** (carteriofenones E–H) represented rare naturally occurring scalarane sesterterpenoids with a cyclobutane ring. Specifically, the 18-carboxylic scalarane sesterterpenoid **131** displayed strong cytotoxicity against P388, HT-29, and A549 cell lines (IC_{50} = 0.96, 1.43 and 3.72 μmol/L, respectively). Whereas, **130** without the 18-carboxy was inactive, indicating that the carboxyl group at C-18 might be an indispensable functional group for activity. Additionally, **131** was also found to display brine shrimp lethality towards *Artemia salina* (LC_{50} = 5.80 μmol/L)

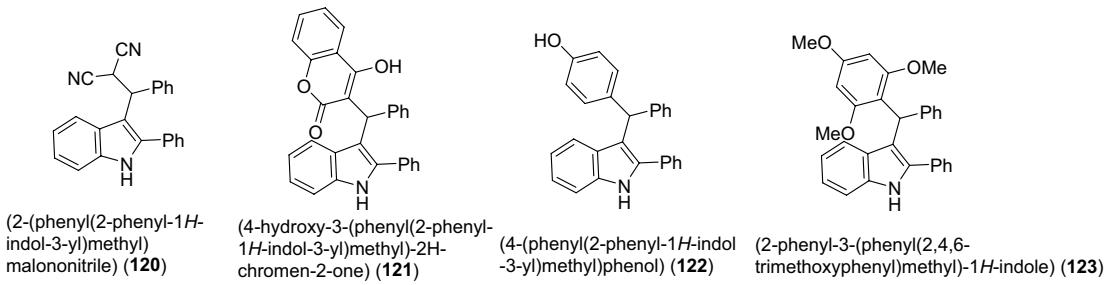

Fig. 23 3-Substitued indolyl derivatives synthesized from di(1*H*-indol-3-yl)methane

and anti-larval settlement activity against *B. amphitrite* (EC_{50} = 2.50 μmol/L) (Cao et al. 2015).

From the gorgonian *Euplexaura* sp. GXWZ-05, three new serrulatane-type diterpenoids, **139–141** (euplexaurenes A–C), and a known metabolite, **142** (anthogorgiene P) (Fig. 26), were isolated (Cao et al. 2017). The absolute configurations of C-11 in **139–142** were difficult to determine by common methods due to the high conformational flexibility of the eight-carbon aliphatic chain attached at C-4. By vibrational circular dichroism (VCD), their absolute configurations were determined. Compounds **139–142** displayed selective cytotoxic activities against the human laryngeal carcinoma (Hep-2) cell line (IC_{50} = 1.95, 7.80, 13.6 and 5.85 μmol/L, respectively) (Cao et al. 2017).

Six sesquiterpenoids were obtained from the gorgonian *Anthogorgia ochracea,* including two new guaiazulene-based analogues, **143** and **144** (ochracenoids A and B), along with four known analogues **145** (1-formylguaiazulene), **146** (1-formyl-4-methyl-7-isopropylazulene), **147** (ketolactone), and **148** (3,8-dimethyl-5-isopropyl-6-formylindenone) (Fig. 27) (Zheng et al. 2014). Compound **143** is a rare guaiazulene-based analogue possessing a unique C_{16} skeleton. Compound **145** exhibited strong ichthyootoxicity with the antiproliferative effects on several aspects of embryo development in zebrafish *Danio rerio*, including coagulated eggs (48 h), notochord malformation (72 h), and embryo death (72 h) with the EC_{50} values of 3.98, 6.50, and 7.39 μmol/L, respectively (Zheng et al. 2014).

Six diterpenoids were found from the soft coral *Sinularia compacta*, including two new prenylgermacrane type diterpenoids, **149–150** (lobophytumins A–B), two new prenyleudesmane type diterpenoids, **151–152** (lobophytumins C–D), and two new spatane type diterpenoids, **153–154** (lobophytumins E–F) (Fig. 28) (Li et al. 2011). Although structures of **149–154** are formally quite different, they are biogenetically related to each other. Sesquiterpene compound **155** ((−)-germacrene D) is considered as their common precursor (Faulkner 1984). A plausible biogenetic pathway for **149–154** was proposed (Fig. 29). It is worth noting that prenylgermacrane and prenyleudesmane diterpenes are quite rare in soft coral. This is the first report of spatane type diterpenoids from a soft coral source (Li et al. 2011).

Additionally, multiple known diterpenoids were obtained and showed various bioactivities. From the soft coral *Sarcophyton infundibuliforme*, four known cembrene diterpenoids were obtained, including **156** (sarcophytol-A), **157** (sarcophytol-A acetate), **158** (sarcophytol-H) and **159** (sarcophytonolid-J) (Wang et al. 2011b) (Fig. 30). These compounds exhibited strong anti-larval settlement activity against *B. amphitrite* (EC_{50} = 2.25, 1.75, 8.13 and 7.50 μg/mL, respectively) (Wang et al. 2011b). From a soft coral *Sarcophyton* sp., a cembranoid diterpene **160** (sarcophytol B) was isolated. This compound displayed antibacterial activity against *B. cereus*, *S. albus* and *V. parahaemolyticus* (MIC = 3.13, 1.56, and 0.50 μmol/L, respectively) (Cao et al. 2013). Briarane type diterpenoids **161** (juncin P) and **162** (junceellolide D) isolated from the gorgonian *Dichotella fragilis* (Ridleg) exhibited potent antifouling activity (EC_{50} = 0.80 and 0.77 μg/mL, respectively) (Zhou et al. 2011).

Steroids

Steroid derivatives from marine organisms are noted for diverse unusual structures with multiple potent biological properties. For instance, petasitosterone B, a steroid isolated from a Formosan marine soft coral *Umbellulifera petasites* exhibited promising anti-inflammatory activity (Huang et al. 2016). Two 9,11-secosteroidal glycosides, sinularosides A and B, isolated from the South China Sea soft coral *Sinularia humilis*, exhibited potent antimicrobial activity (Sun et al. 2012). In our previous reports, 86 steroidal compounds were obtained from marine invertebrates and their symbiotic fungi, which exhibited cytotoxic, antiviral and antibacterial activities (Cao et al. 2014; Sun et al. 2015; Zhao et al. 2013).

From the gorgonian *Echinogorgia rebekka*, four new steroids with an acetoxy linked at the end of the side chain, **163–166** (echrebsteroids A–D) (Fig. 31) were isolated (Cao et al. 2014). Among them, **164** and **165** were a pair of new C-25 epimers of 26-acetoxy steroids, representing the first reported separation of C-25 epimers of 26-acetoxy steroids. Compound **165** exhibited pronounced antiviral activity against RSV (IC_{50} = 0.19 μmol/L) and a comparatively higher therapeutic ratio (TC_{50}/IC_{50} = 128), suggesting that

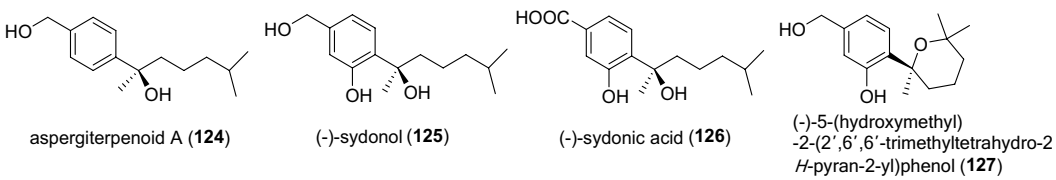

Fig. 24 Bisabolane-type sesquiterpenoids from the sponge-derived fungus *Aspergillus* sp.

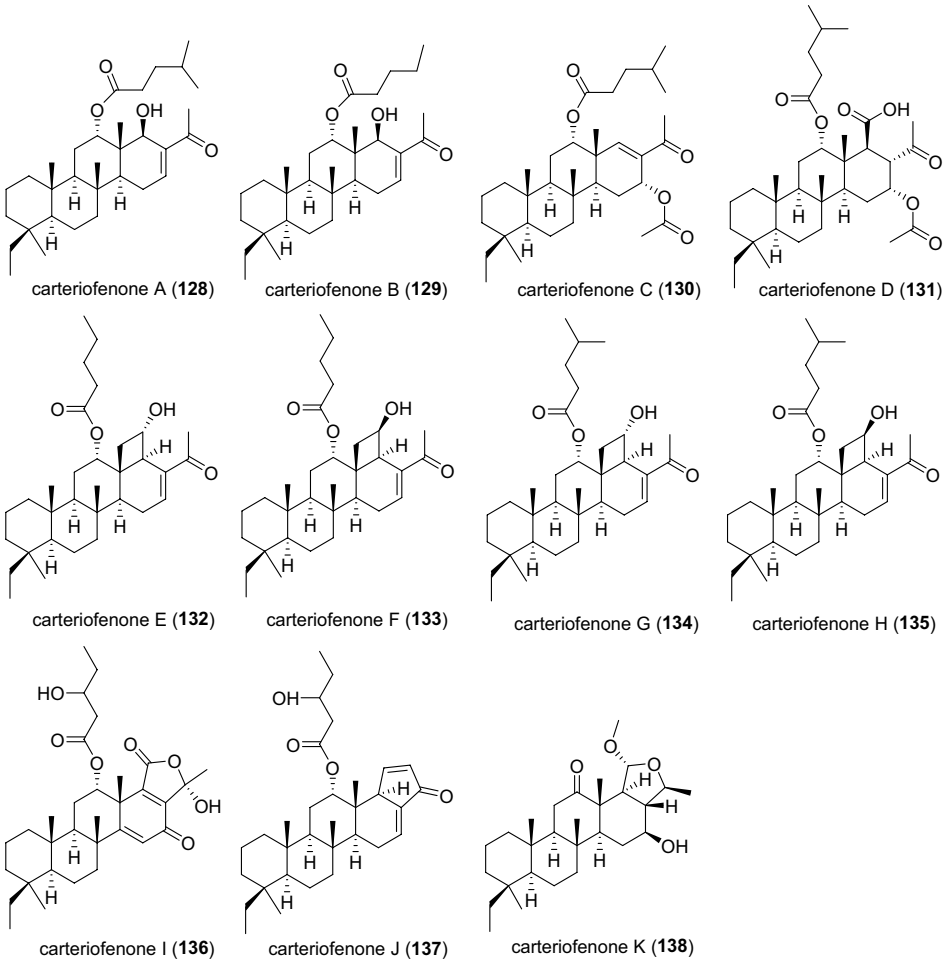

Fig. 25 Scalarane sesterterpenoids from the sponge *C. foliascens*

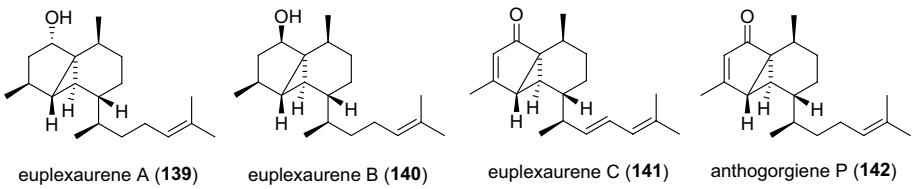

Fig. 26 Serrulatane-type diterpenoids from the gorgonian *Euplexaura* sp. GXWZ-05

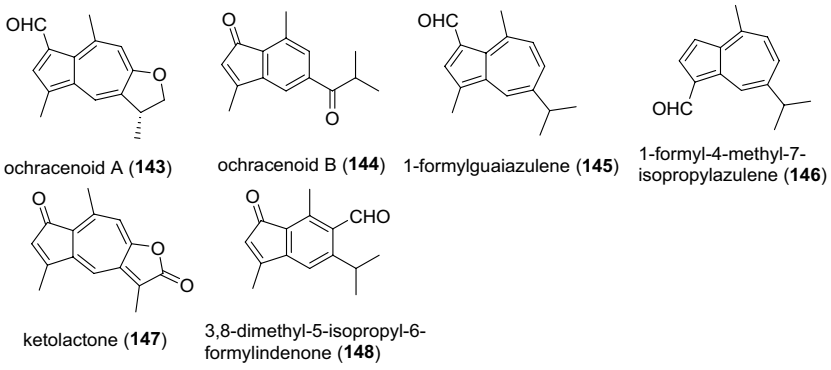

Fig. 27 Guaiazulene-based analogues from the gorgonian *A. ochracea*

it could be considered as a potential antiviral agent (Cao et al. 2014).

From a gorgonian *Carijoa* sp., four pregnane steroid were isolated, including a new pregnane steroid, **167** (15β-hydroxypregna-1,4,20-trien-3-one), and three known analogues **168** (15β-acetoxypregna1,4,20-trien-3-one), **169** (18-acetoxypregna-1,4,20-trien-3-one), and **170** (pregna-1,4,20-trien3-one) (Fig. 32), all with rare 3-one dienones (Zhao et al. 2013). Compounds **167**, **169** and **170** displayed cytotoxicity against human hepatoma cell line Bel-7402 (IC_{50} = 9.33, 11.02 and 18.68 μmol/L, respectively). Additionally, **167** exhibited potent antibacterial activity against *S. aureus*, *S. albus*, *E. coli*, *V. parahaemolyticus* and *Nocardia brasiliensis* (MIC = 0.063, 1.00,

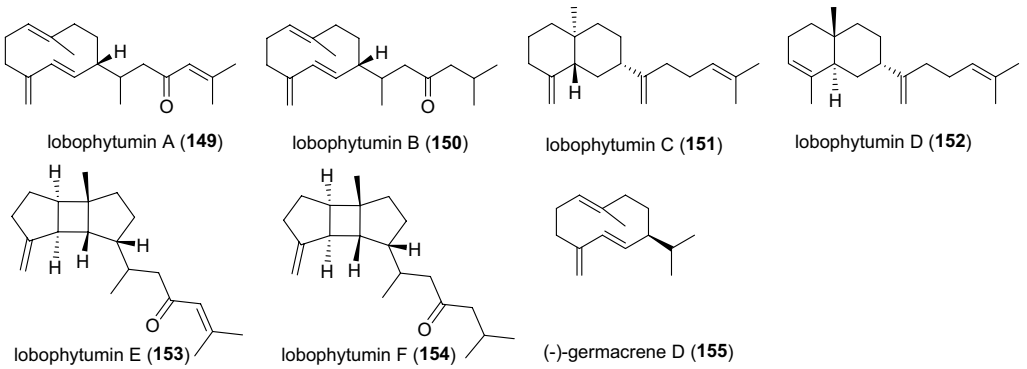

Fig. 28 Diterpenoids from the soft coral *S. compacta*

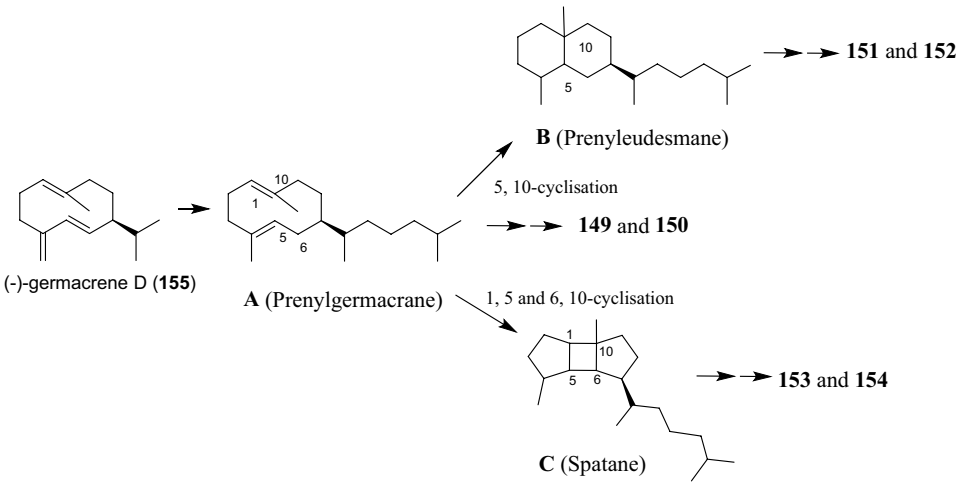

Fig. 29 Plausible biosynthetic correlations between three extended sesquiterpenoid skeleton diterpenoids

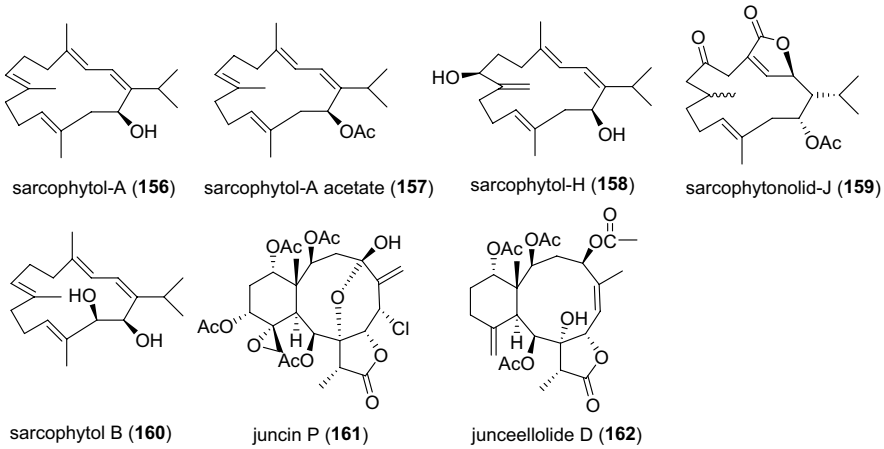

Fig. 30 Cembrene diterpenoids and briarane diterpenoids from the soft coral *S. infundibuliforme* and *Sarcophyton* sp. and gorgonian *D. fragilis*

1.00, 4.00, and 0.500 μmol/L, respectively), and displayed excellent inhibitory activity against *Pseudomonas putida* (MIC = 31 nmol/L), fivefold stronger than that of ciprofloxacin (MIC = 156 nmol/L). Compound **168** showed very strong antibacterial activity against pathogenic bacteria *Tetragenococcus halophilus* (MIC = 312 nmol/L). While **169** demonstrated strong antibacterial activity against *B. cereus*, *S. aureus* and *T. halophilus* (MIC = 2.50, 0.156, and 1.25 μmol/L, respectively) (Zhao et al. 2013).

From the gorgonian *Subergorgia rubra*, sixteen secosteroids were obtained, including twelve new 9,10-secosteroids **171–182** (subergorgiaols A–L), along with four known analogues **183** (astrogorgiadiol), **184** (calicoferol C), **185** (calicoferol F), **186** (calicoferol A) (Fig. 33) (Sun et al. 2015). Among them, compounds **171–182**, with a series of different aliphatic side chains, represent the first examples of 9,10-secosteroids bearing a hydroxy group at C-8, which are 8-OH derivatives of astrogorgiadiols/calicoferols. Compound **174** showed selective strong cytotoxicity against the cervical carcinoma cell line (CaSki) (IC_{50} = 2.4 μmol/L). Additionally, **176** displayed toxicity toward brine shrimp *A. salina* (LC_{50} = 2.0 μmol/L) (Sun et al. 2015).

Four polyoxygenated sterols were separated from a soft coral *Sinularia* sp., including **187** ((3*S*,23*R*,24*S*)-ergost-5-ene-3β,23α,25-triol), **188** ((24*S*)-ergostane-6-acetate-3β,5α,6β,25-tetraol), **189** ((24*S*)-ergostane-6-acetate-3β,6β,12β,25-tetraol) and **190** (24-methylenecholestane-3β,5α,6β-triol-6-monoacetate) (Fig. 34) (Li et al. 2012b). Compound **190** showed moderate cytotoxicity against the K562 cell line (IC_{50} = 3.18 μmol/L) and also demonstrated potent lethality toward brine shrimp *A. salina* (LC_{50} = 0.96 μmol/L).

Chemical investigation of sponge *Topsentia* sp. led to the isolation of three novel polyhydroxylated sterol derivatives, **191–193** (topsensterols A–C), with novel 2β,3α,4β,6α-tetrahydroxy-14α-methyl $\Delta^{9(11)}$ steroidal core and rare side chains (Fig. 35) (Chen et al. 2016). The differences between them were mainly existed in the respective aliphatic side chains. Compound **192** demonstrated significant cytotoxicity against human gastric carcinoma cell line SGC-7901 (IC_{50} = 8.0 μmol/L). While **193**

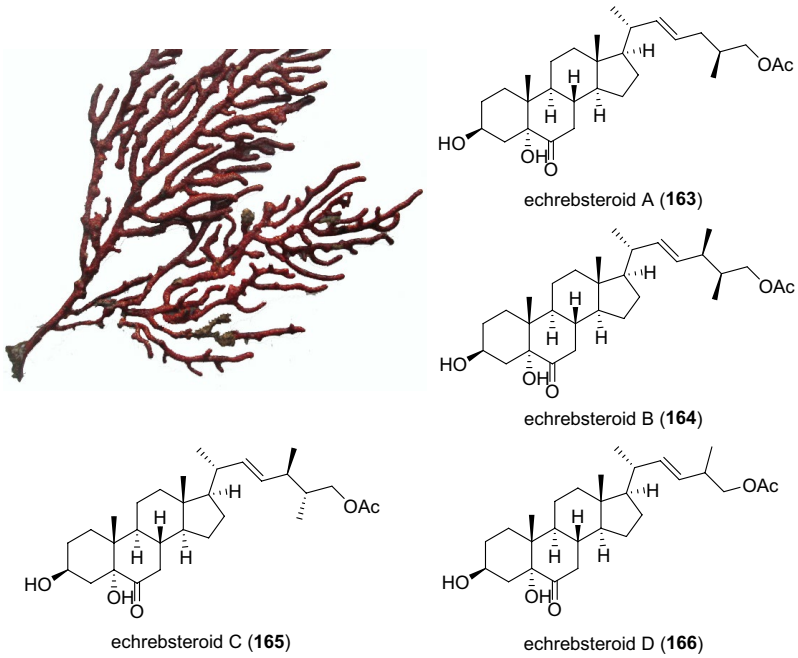

Fig. 31 Steroids with 26-acetoxy from the gorgonian *E. rebekka*

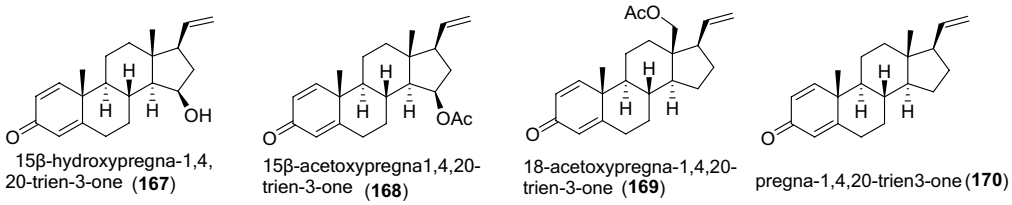

Fig. 32 Pregnane steroids from the gorgonian *E. rebekka*

showed cytotoxicity against human erythroleukemia cell line K562 (IC_{50} = 6.0 μmol/L) (Chen et al. 2016).

Six steroids and one steroidal glycoside were isolated from the fungal strain *Cladosporium* sp. WZ-2008-0042 separated from the gorgonian *Dichotella gemmacea*, including a new pregnane, **194** (3*α*-hydroxy-7-ene-6,20-dione), five known steroids **195** (5*α*, 8*α*-epidioxy-ergosta-6,9,22*E*-triene3*β*-ol), **196** (5*α*,8*α*-epidioxy-ergosta-6,22*E*-dien-3*β*-ol), **197** (ergosta-7,22*E*-diene-3*β*,5*α*,6*β*-triol), **198** (3*β*,5*α*-dihydroxy-6*β*-methoxyergosta7,22-diene), **199** (ergosterol peroxide), along with one known steroidal glycoside **200** (stigma-5-en-3-*O*-*β*-glucopyranoside) (Fig. 36) (Yu et al. 2018). Compounds **194**–**196** and **198** exhibited potential antiviral activity against RSV virus (IC_{50} = 0.11 to 0.17 mmol/L; TC_{50}/IC_{50} = 5.18 to 9.92).

Phenylpropanoids

Phenylpropanoids contain many chemical structure types, such as chromone, coumarin, flavone and lignin, which possess various biological activities including antioxidant, cytotoxic, antimicrobial, and enzyme inhibitory activities. For example, arthone C, a chromone derivative isolated from a deep-sea-derived fungus *Arthrinium* sp., exhibited potent antioxidant activity (Bao et al. 2018). Two tetracyclic coumarin derivatives and two coumarin dimers isolated from the marine-derived fungus *Eurotium rubrum* showed significant tyrosinase inhibitory activity (Kamauchi et al. 2018). In our previous studies, 80 phenylpropanoid compounds with 54 new compounds were obtained, which showed antifouling, antibacterial and cytotoxic activities (Qi et al. 2013; Zhao

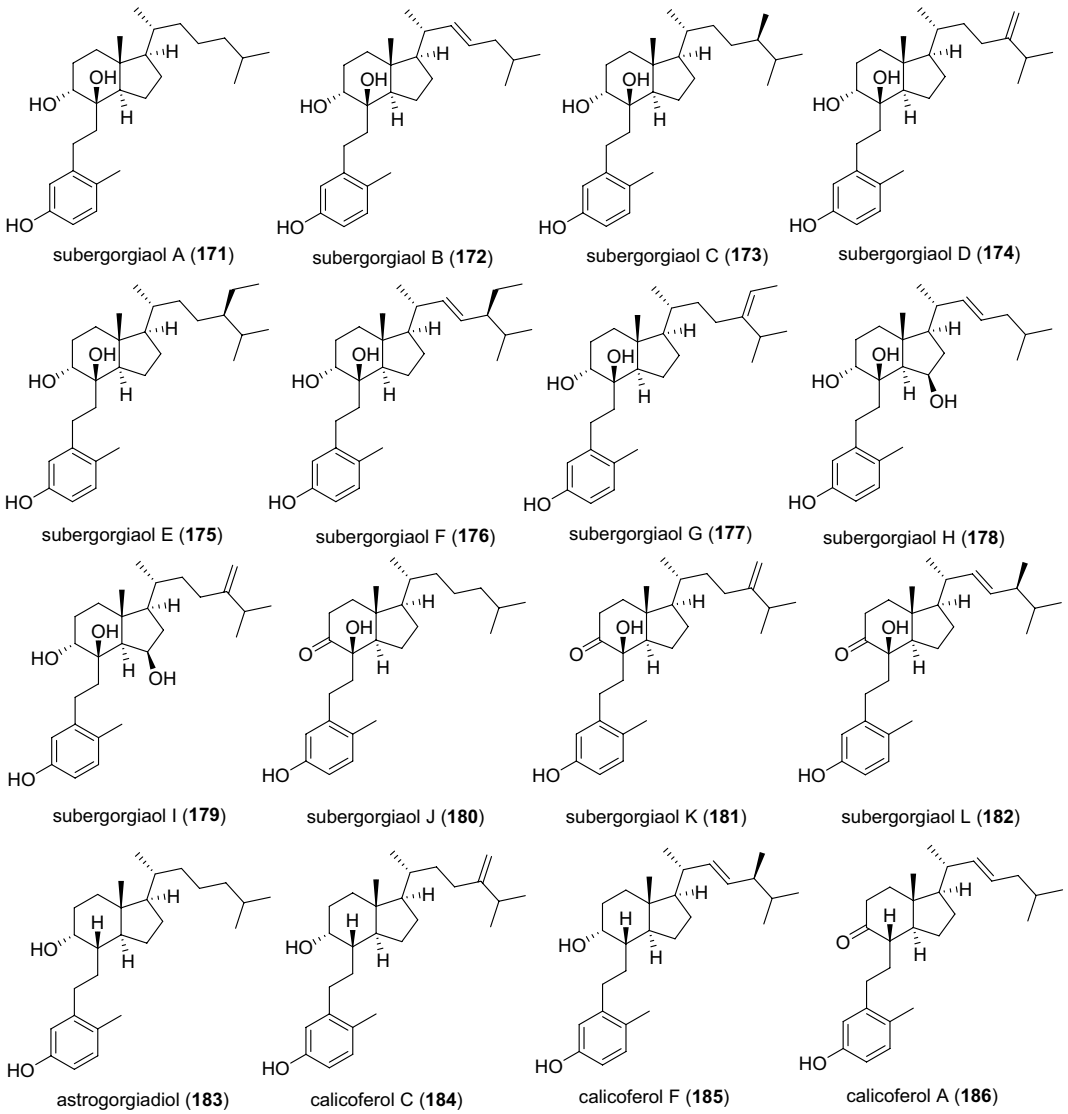

Fig. 33 9,10-Secosteroids from the gorgonian *S. rubra*

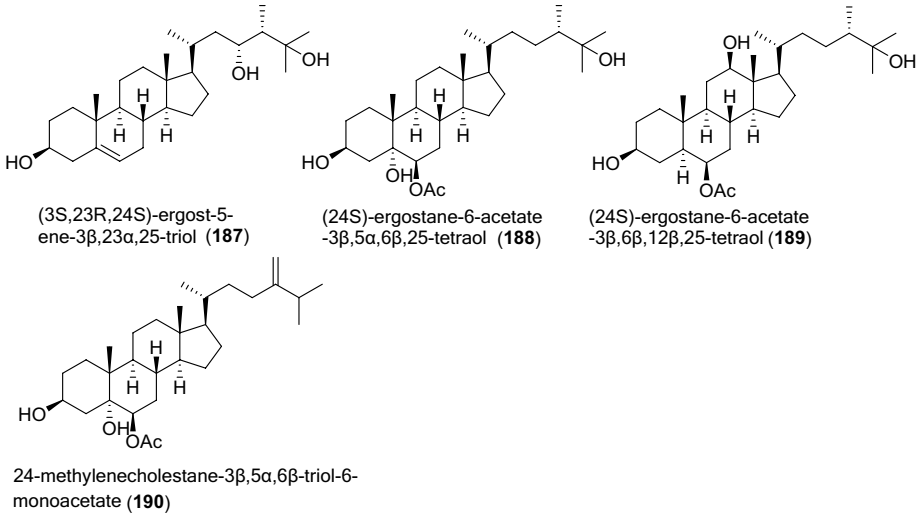

Fig. 34 Polyoxygenated sterols from the soft coral *Sinularia* sp.

et al. 2015b). These findings provide further insight into the chemical diversity and biological activities of this class of MNPs.

Ten isocoumarins were isolated from the sponge-derived fungus *Penicillium* sp. MWZ14-4, including three new hydroisocoumarins, **201**–**203** (penicimarins A-C), three new isocoumarins, **206**–**208** (penicimarins D–F), together with four known isocoumarin derivatives **204** (aspergillumarin B), **205** (aspergillumarin A), **209** (sescandelin B), and **210** (5,6,8-trihydroxy-4-(1′-hydroxyethyl)isocoumarin) (Fig. 37) (Qi et al. 2013). Compound **201** represents a rare naturally occurring isocoumarin derivative with 4-substitution but no substituent at the 3-position.

Twelve new chromone derivatives, **211–222** (corynechromones A–L) (Fig. 38), were obtained from the sponge-derived fungus *Corynespora cassiicola* XS-200900I7 (Zhao et al. 2015b). These are the first chromone derivatives reported from the genus *Corynespora*. The absolute configurations of **211–220** were determined by the modified Mosher's method and TDDFT ECD calculations along with comparison of their CD spectra. Interestingly, **211/212**, **213/214**, **215/216**, and **217/218** were pairs of epimers at C-2. A biogenetic pathway of the isolated chromone derivatives was proposed (Fig. 39). The different cyclization pathways from an uncyclized α,β-unsaturated ketone precursor may lead to production of the octalactones (Ebrahim et al. 2012, 2013). Alternatively, the decalactones may be produced by ester formation with the distal hydroxy group. A possible non-enzymatic cyclization route may be involved to form the epimeric pairs. A Michael reaction can occur with the nucleophile attacking from either face, leading to the formation of the epimeric pairs (Zhao et al. 2015b).

From a gorgonian-derived fungus *Eurotium* sp. XS-200900E6, five pairs of new dihydroisocoumarin enantiomers, **223**–**232** ((±)-eurotiumides A–E), together with two related racemates, **233** and **234** ((±)-eurotiumides F and G), were isolated, all of them are rare dihydroisocoumarin derivatives with a methoxy at C-4 (Fig. 40) (Chen et al. 2014b). The (+)- and (−)-eurotiumides B and D with *cis* configurations of H-3/H-4 demonstrated significant anti-larval settlement activity against *B. amphitrite* (EC_{50} = 0.7 to 2.3 μg/mL; $LC_{50}/EC_{50} > 15$), indicating that they could be considered as promising environmentally benign antifouling agents. Additionally, **223**, **224**, **225**, and **226** displayed significant antibacterial activities against *S. epidermidis* (MICs = 0.39 to 0.78 μmol/L), and **223** and **224** showed remarkable activities against *B. cereus* (MICs = 0.39 and 0.78 μmol/L, respectively). All of the tested compounds, especially **223** and **224**, exhibited strong inhibitory activities against two marine bacteria, *V. anguillarum* and *V. parahaemolyticus* (Chen et al. 2014b).

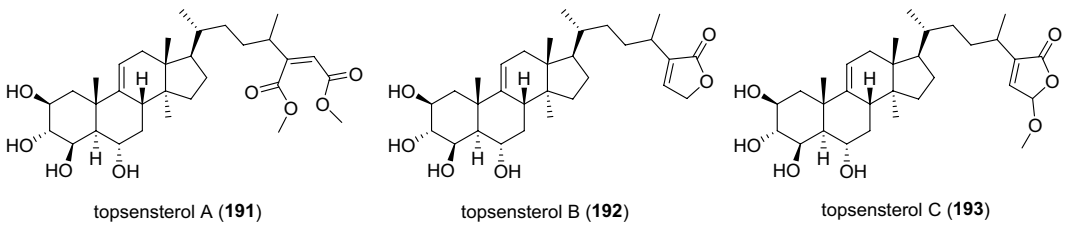

Fig. 35 Polyhydroxylated sterol derivatives from the sponge *Topsentia* sp.

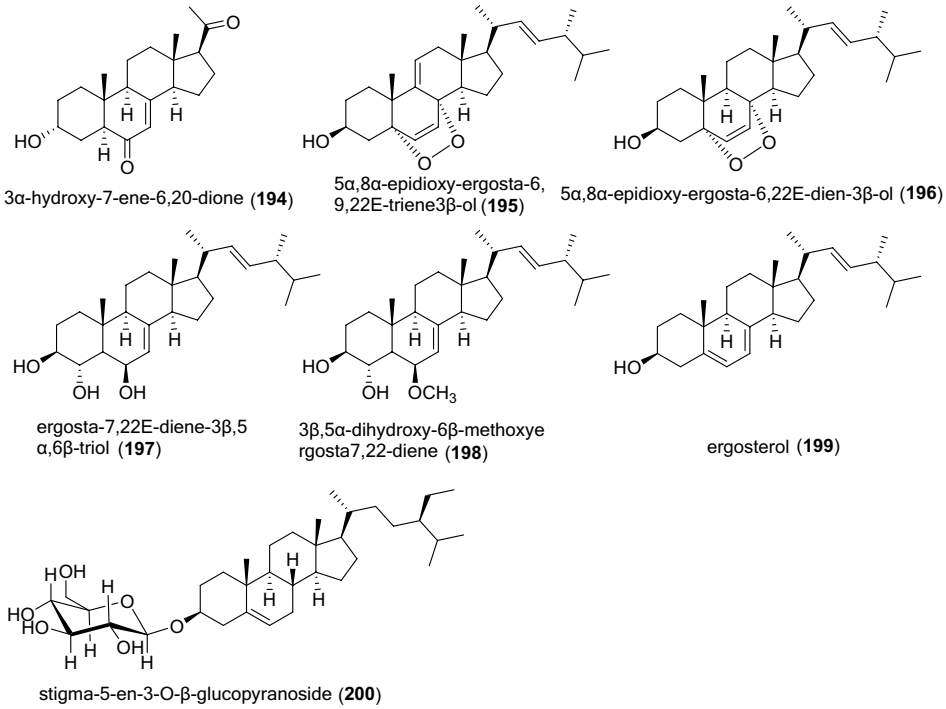

Fig. 36 Steroids and steroidal glycoside from the gorgonian-derived fungus *Cladosporium* sp. WZ-2008-0042

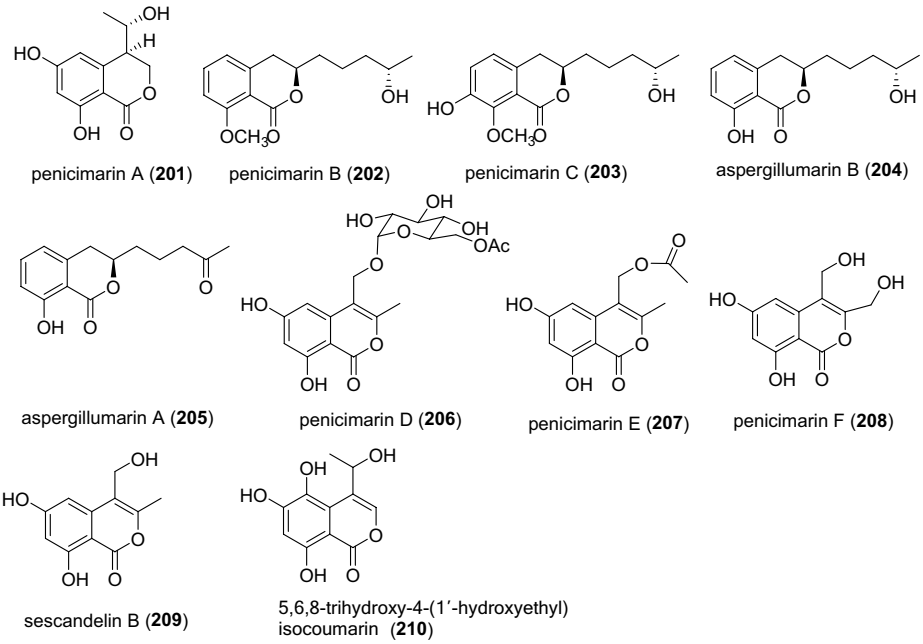

Fig. 37 Isocoumarins from the sponge-derived fungus *Penicillium* sp. MWZ14-4

Peptides

Peptides isolated from many marine species present various biological activities, such as antimicrobial, antiviral, antitumor, antioxidative and cardioprotective activities. For instance, mirabamide A, a cyclic depsipeptide obtained from the sponge *Siliquariaspongia mirabilis*, showed potent inhibitory activity on HIV-1 fusion (Plaza et al. 2007). Reniochalistatin E, an octapeptide isolated and characterized from the marine sponge *Reniochalina stalagmitis*, displayed significant cytotoxic activity (Zhan et al. 2014). In our studies, a total of 34 peptides were identified, of which more than half are cyclopeptides involved in 18 new peptides (Chen et al. 2014c; Hou et al. 2019b, 2019c). Particularly, LC–MS/MS-dependent molecular networking and ^{1}H NMR techniques were applied in order to identify new peptides.

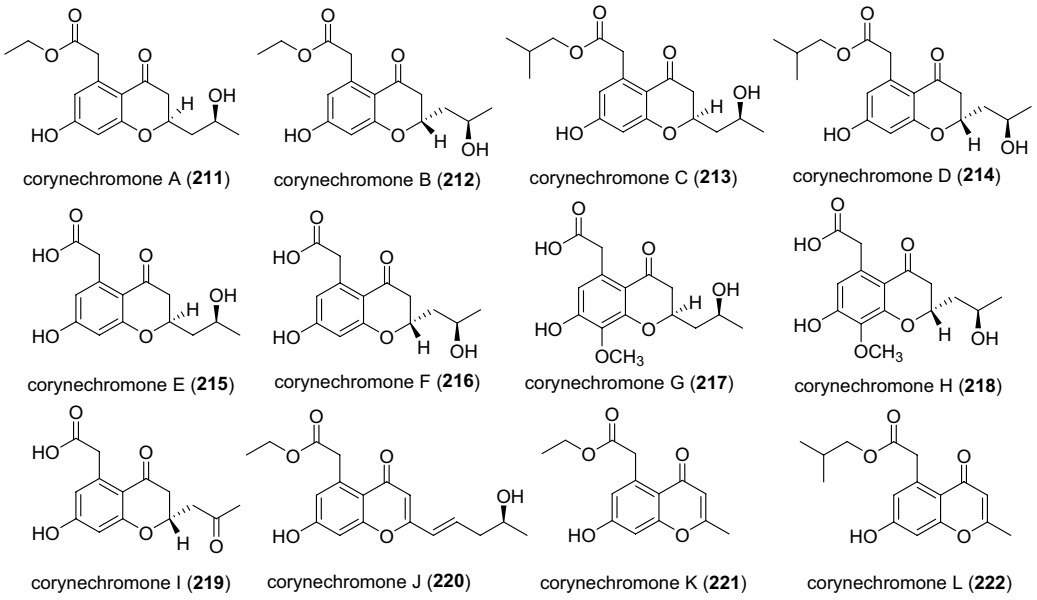

Fig. 38 Chromone derivatives from the sponge-derived fungus *C. cassiicola* XS-200900I7

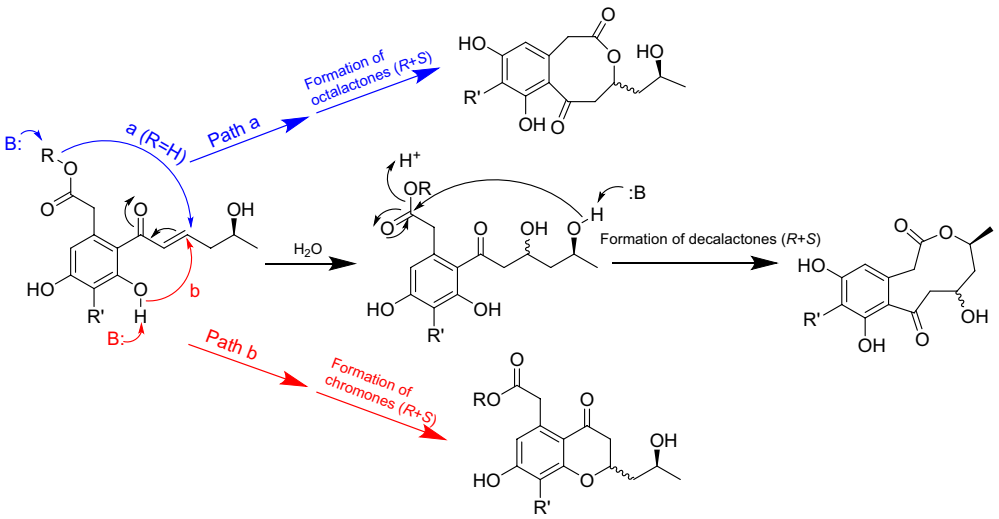

Fig. 39 Proposed biogenetic pathway for corynechromones, octalactones and decalactones

The strategy of molecular networking based on MS/MS cheminformatics could shed light on structural relationships and accelerate the dereplication of molecules in crude extracts to mine new molecules. Based on integrating LC–MS/MS-dependent molecular networking and ^{1}H NMR techniques, the targeted identification of ten cyclohexadepsipeptides were achieved from the gorgonian coral-derived fungus *Penicillium chrysogenum* (TA01-16) (Fig. 41), including the new compounds **235**–**237** (chrysogeamides A–C) and **240**–**244** (hrysogeamides D–H), as well as the known compounds **238** and **239** (scopularides A and B) (Fig. 42) (Hou et al. 2019b). These cyclohexadepsipeptides contain the same *D*-Leu fragment, and **235** and **242** are reported for the first time featuring a 3-hydroxy-4-methylhexanoic acid (HMHA) moiety of cyclodepsipeptides. Interestingly, isotope labelling feeding experiments demonstrated that $^{13}C_1$-*L*-Leu was transformed into $^{13}C_1$-*D*-Leu moiety in **238** and **239** indicating that *D*-Leu in these molecules may be epimerized from *L*-Leu by a leucine racemase. Compounds **235**–**239** displayed selective activity in promoting angiogenesis toward the *Tg (Flk1: EGFP)* transgenic zebra fish *D. rerio* embryo (Hou et al. 2019b).

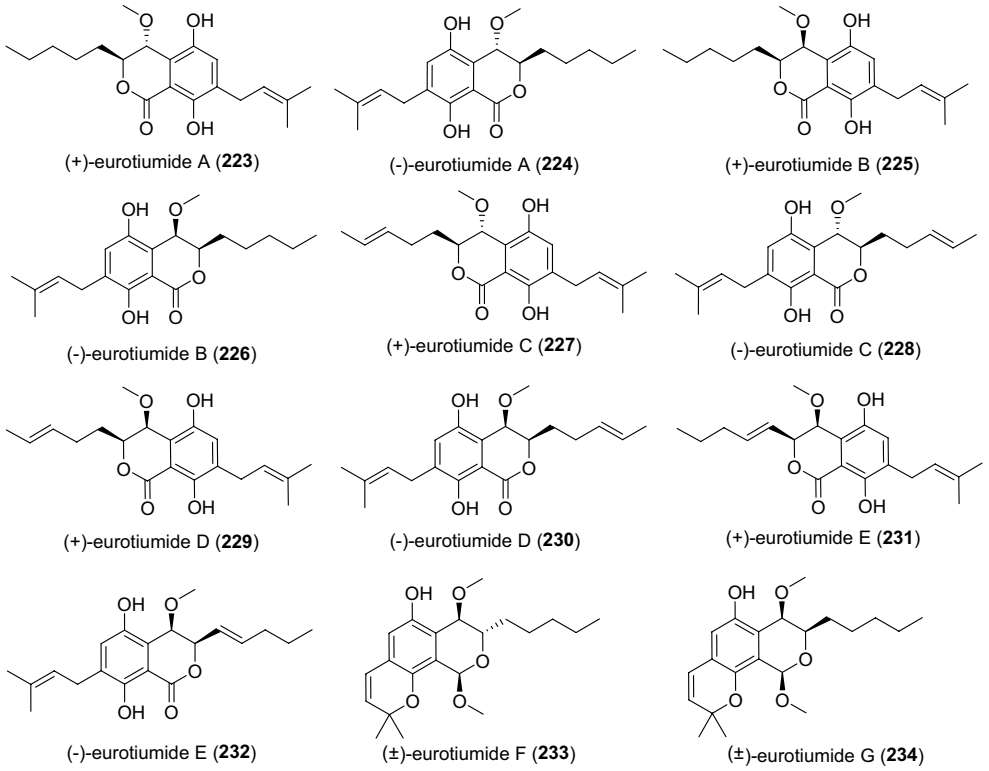

Fig. 40 Dihydroisocoumarin enantiomers from the gorgonian-derived fungus *Eurotium* sp. XS-200900E6

Applying molecular networking techniques, three new cycloheptapeptides, **245**–**247** (asperversiamides A–C) (Fig. 43), were isolated from the coral-derived fungus *Aspergillus versicolor* (CHNSCLM-0063) (Hou et al. 2019c). Their complete structures including configuration were confirmed by total synthesis. These compounds showed strong inhibitory activity against *Mycobacterium marinum* (MICs = 23.4, 81.2, 87.5 μmol/L, respectively), demonstrating valuable application potential in treating *M. marinum* infection (Hou et al. 2019c).

Until now, the molecular networking approach has only been applied to mine the undiscovered cycloheptapeptides from marine-derived fungus in our research on MNPs. Undoubtedly, the molecular networking strategy based on LC–MS/MS and relevant data libraries should be considered an effectively targeted isolation technique to speed the discovery of new cryptic secondary metabolites. It is worth applying the molecular networking approach to exploit novel molecules from the pools of MNPs in extracts from marine organisms.

From the gorgonian-derived fungus *Aspergillus* sp. XS-20090B15, four lumazine peptides, **248** (penilumamide) and **249–251** (penilumamides B–D), together with a cyclic pentapeptide, **252** (asperpeptide A) (Fig. 44), were isolated (Chen et al. 2014c). Penilumamide B (**249**) was obtained from a feeding culture experiment with L-methionine. Compounds **249**–**251** are rare lumazine peptides, of which **248** and **250** are formed from **249** by oxidation of the L-methionine residue. The cyclic pentapeptide (**252**) exhibited antibacterial activity against *B. cereus* and *S. epidermidis* (MICs = 12.5 μmol/L) (Chen et al. 2014c).

Phenyl ether derivatives

An increasing number of marine-derived phenyl ether derivatives with novel structures have been reported with diverse biological activities, including antimicrobial, antitumor, cardiotonic, antidiabetic, antiinflammatory and antiviral activities. For instance, 4-carbglyceryl-3,30-dihydroxy-5,50-dimethyldiphenyl ether, a diphenyl ether isolated from the deep-sea-derived fungus *Aspergillus versicolor* SCSIO 41502 showed potent antifouling activity (Huang et al. 2017). A series of antibacterial polybrominated diphenyl ethers were isolated from the Indonesian sponge *Lamellodysidea herbacea* (Hanif et al. 2007). In our studies, 35 phenyl ether derivatives were obtained in all, among them 9 compounds were first reported, showing antibacterial, antifouling and cytotoxic activities (Chen et al. 2013b; Shi et al. 2017). To clarify the structure–activity relationships, chemical synthesis was performed (Chen et al. 2013b).

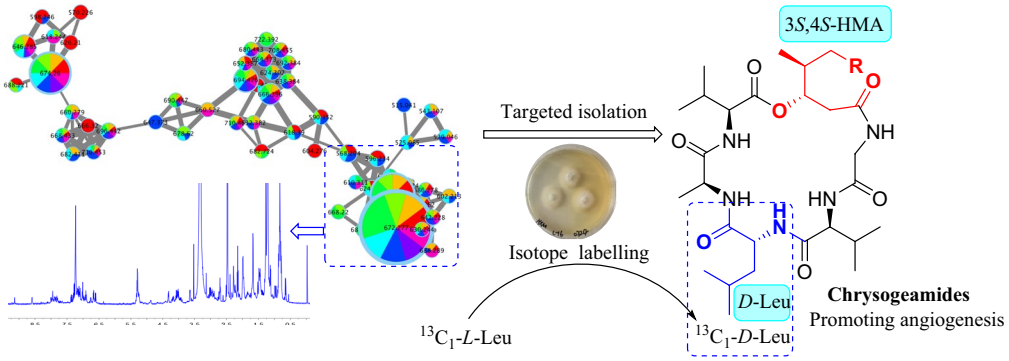

Fig. 41 The conceptual framework of LC–MS/MS-dependent molecular networking to target the isolation of new compounds

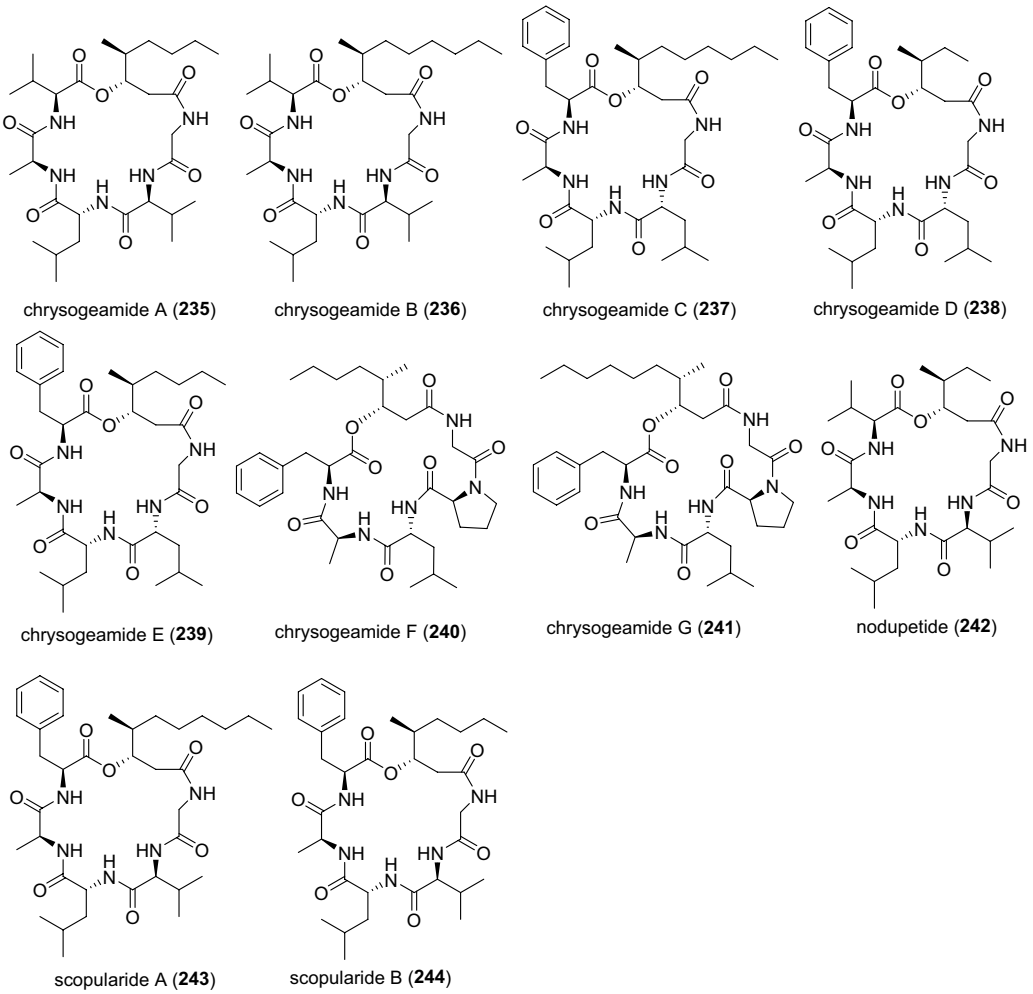

Fig. 42 Cyclohexadepsipeptides from the gorgonian coral-derived fungus *P. chrysogenum* (TA01-16)

Six phenyl ether derivatives were obtained from *Aspergillus* sp. XS-20090066 isolated from the gorgonian *Dichotella gemmacea*, including two new phenyl ether derivatives, **253** and **257** (cordyols D and E), together with 4 known analogue compounds **254** (3,3′-*O*-dimethyl-violaceol-I), **255** (cordyol C), **256** (4-methoxycarbonyl-diorcinol), and **258** (diorcinol) (Fig. 45) (Chen et al. 2013b). Among them, **256** displayed significant antibacterial activity against *S.*

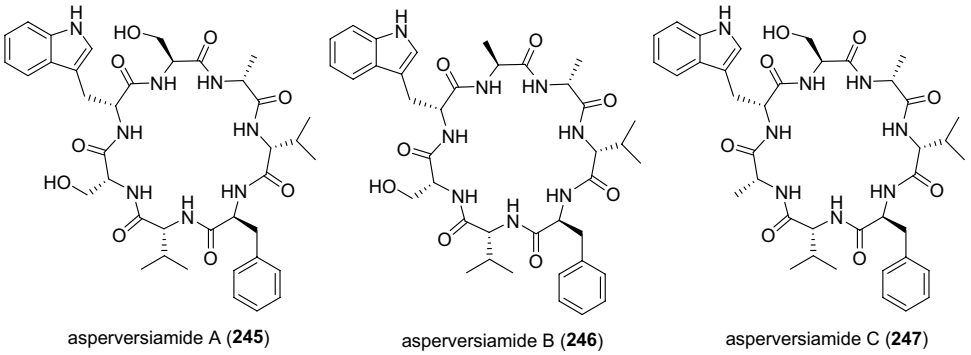

Fig. 43 Cycloheptapeptides from the coral-derived fungus *A. versicolor* (CHNSCLM-0063)

epidermidis (MIC = 2.71 μmol/L). A series of derivatives (**256a**, **258a**–**258g**) were designed and synthesized for the study of structure–activity relationships, suggesting that one free hydroxy plays a critical role for antibacterial activity. In particular, **258g** exhibited the strongest antibacterial activity toward *S. epidermidis* (MIC = 0.556 μmol/L). These results revealed that the ester functionality or bromination could increase antibacterial activity, but the simultaneous presence of both the ester and brominated benzene ring caused a loss of activity (Chen et al. 2013b).

Two new diphenyl glycosides, **259**—**260** (phomaethers A–B), one new diphenyl ether derivative, **261** (phomaether C), and one known diphenyl ether analog, **262** (2,3′-dihydroxy-4-methoxy-5′,6-dimethyl diphenyl ether) (Fig. 46), were isolated from a gorgonian-derived fungus *Phoma* sp. (TA07-1) (Shi et al. 2017). It was the first report to find diphenyl glycoside derivatives from coral-derived fungi. Compounds **259**, **261**, **262** exhibited potent antibacterial activities, indicating that they might be developed as promising antibacterial agents. Specifically, **259** showed remarkable antibacterial activity against *S. albus, S. aureus*, *E. coli* and *V. parahaemolyticus* (MICs = 0.312 to 0.625 μmol/L; minimum bactericidal concentrations (MBCs) = 0.625 to 2.50 μmol/L). Compound **261** displayed significant antibacterial activity to *S. albus*, *S. aureus* and *E. coli* (MICs = 0.312 to 1.25 μmol/L; MBCs = 0.625 to 5.00 μmol/L). Notably, **262** demonstrated strong antibacterial activity against all the tested pathogenic bacteria (MICs and MBCs = 0.156 to 5.00 μmol/L) (Shi et al. 2017).

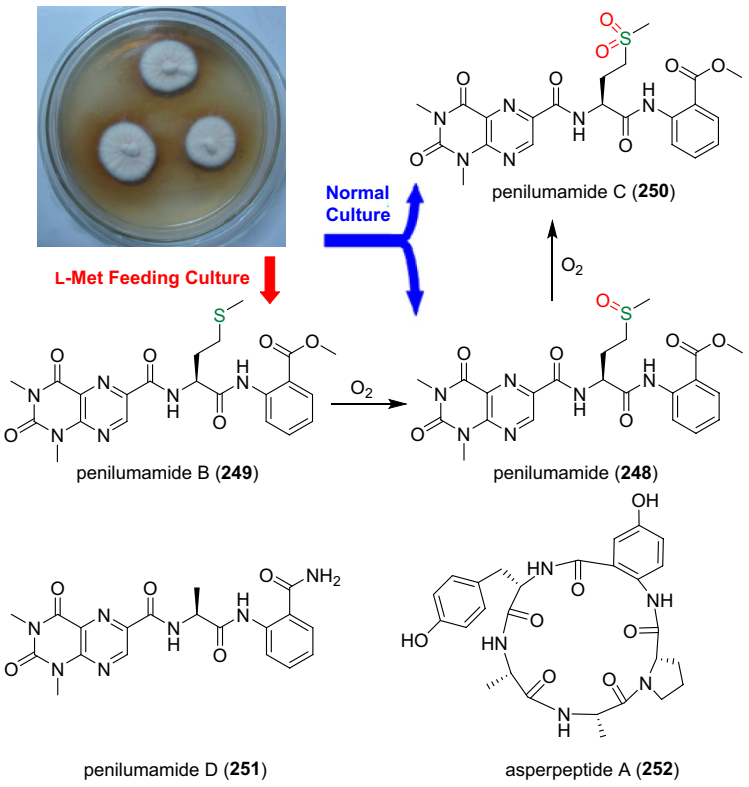

Fig. 44 Lumazine peptides and cyclic pentapeptide from gorgonian-derived fungus *Aspergillus* sp. XS-20090B15

Besides those indicated above, other phenyl ether derivatives, obtained from various fungi including *Penicillium pinophilum*, *Talaromyces* sp. and *Aspergillus elegans* isolated from gorgonian and soft coral, also exhibited anti-larval settlement activity against *B. amphitrite* and cytotoxic activity towards the tested human cell lines (Chen et al. 2015; Zhao et al. 2015a). For instance, diphenyl ether derivatives **263** (talaromycin C), **264** (purpactin C′), **265** (pencillide) and **266** (purpactin A) (Fig. 47) displayed strong anti-larval settlement activity against *B. amphitrite* (EC_{50} = 2.2–4.8 μg/mL). Compound **267** (tenellic acid A methyl ester) (Fig. 47) showed remarkable cytotoxicity towards human cell lines HepG2, Hep3B, MCF-7/ADR, PC-3, and HCT-116 (IC_{50} = 4.3–9.8 μmol/L) (Chen et al. 2015).

In summary, our research on the discovery of MNPs resulted in the discovery of diverse structures from soft corals, gorgonians, sponges, tunicates, anemones and their symbiotic microorganisms collected from the South China Sea. Based on our findings, the statistical analysis of 709 MNPs including 307 new compounds demonstrated that the proportions of terpenoids, alkaloids, steroids, and macrocyclic lactones are larger than that of other structures (Fig. 48). It is also revealed that macrocyclic lactones, azaphilones and phenylpropanoids are the most potential classes for the discovery of novel MNPs (Fig. 48). In terms of biological activities, more than half of the obtained MNPs displayed tested biological activities, with the most frequent findings as antibacterial, antifouling, and cytotoxic activities (Fig. 49). Interestingly, many of the active MNPs exhibited multiple bioactivities, for example, MNPs with antiviral activities usually displayed cytotoxic activities, while MNPs with antibacterial activities commonly showed cytotoxic and antifouling activities. It is worth noting that more than 40 compounds were found to exhibit potent activities even stronger than the positive controls. Particularly, the macrocyclic

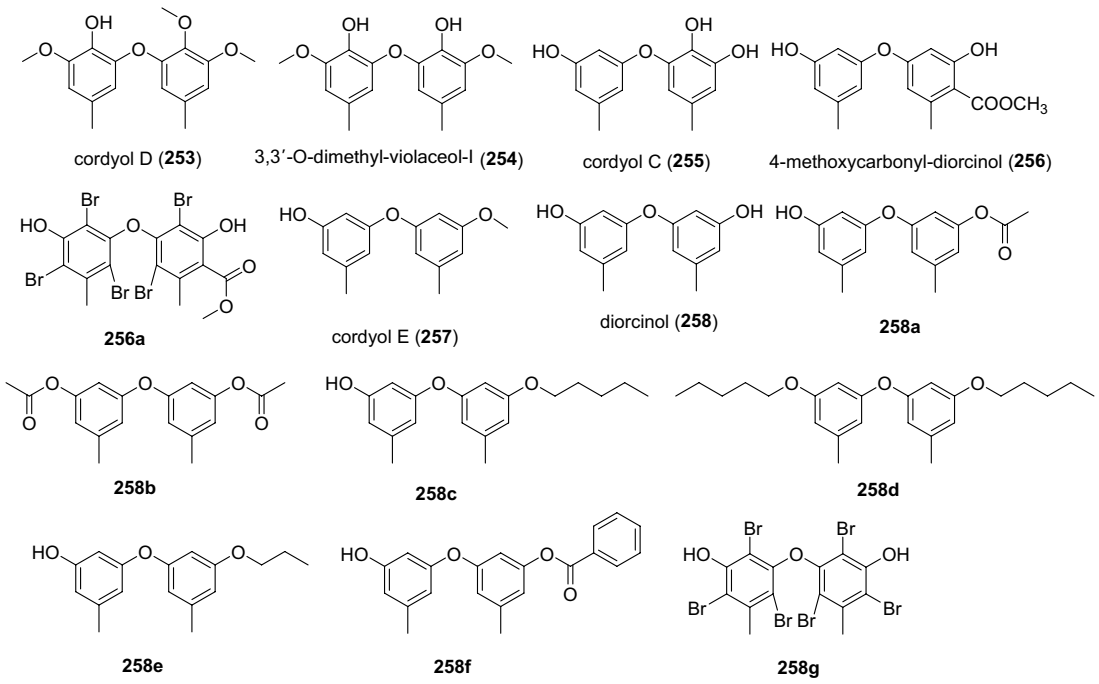

Fig. 45 Phenyl ether derivatives from the gorgonian-derived fungus *Aspergillus* sp. XS-20090066

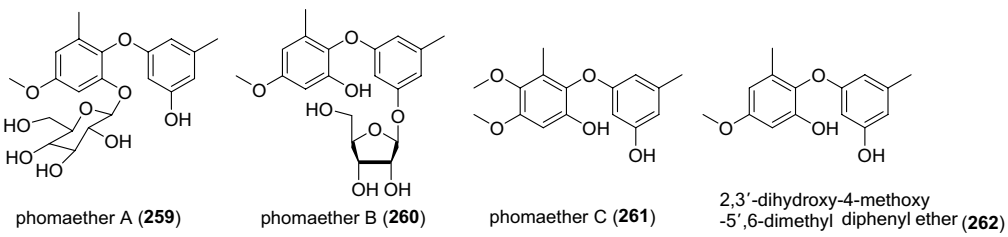

Fig. 46 Diphenyl glycosides and diphenyl ether derivatives from the gorgonian-derived fungus *Phoma* sp. (TA07-1)

lactone cochliomycin A (**1**), the azaphilone sclerotioramine derivative (**101**), and the alkaloid aniduquinolone A (**104**) may be candidates for efficient antifouling agents, and the macrocyclic lactone bastimolide A (**36**), the anthraquinones nigrosporin B (**41**), and the steroid echrebsteroid C (**165**) might be promising lead compounds for further development of antimalarial, antibiotic, and antiviral drugs.

The South China Sea possesses rich and unique species resources, with more than 95% of the invertebrates mainly existing in the coral reefs in this sea area in China (Zhang et al. 2006). Not surprisingly, many investigations on marine invertebrates and their symbiotic microorganisms target this "biodiversity hotspot" as the center of sample collection. It should be mentioned that the diverse abundance of MNPs derived from marine invertebrates and their symbiotic microorganisms from the South China Sea were discovered and studied. In recent decades, research on the diversity of MNPs discovered from the South China Sea by other Chinese researchers has been well underway. These groundbreaking research efforts contributed to the discovery of a great number of novel and promising bioactive molecules usually from such sources as sponges (Gui et al. 2019; Jiao et al. 2019; Wang et al. 2015b), corals (Li et al. 2019b; Wu et al. 2019), bryozoans (Yu et al. 2015), and associated microorganisms (Cheng et al. 2016; Nong et al. 2016). Regarding the abundance of MNPs with diverse structures and a wealth of biological activities, we believe that only the proverbial "tip of the iceberg" has been explored from the South China Sea, and the resulting novel active metabolites with potential pharmacology applications are worthy of further exploration.

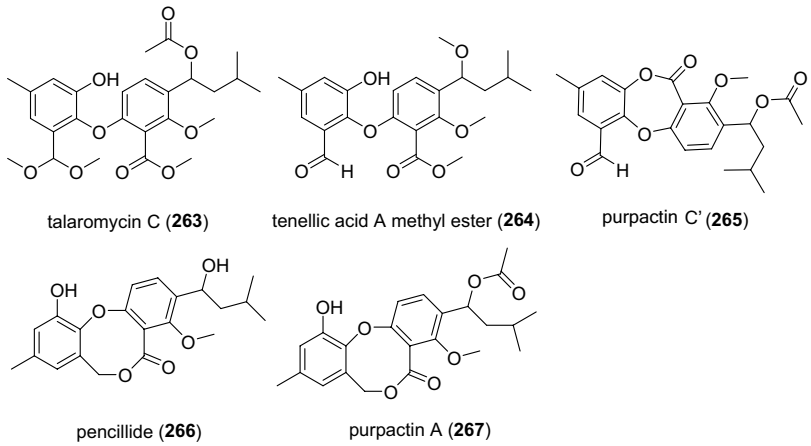

Fig. 47 Diphenyl ether derivatives from the gorgonian-derived fungus *Talaromyces* sp.

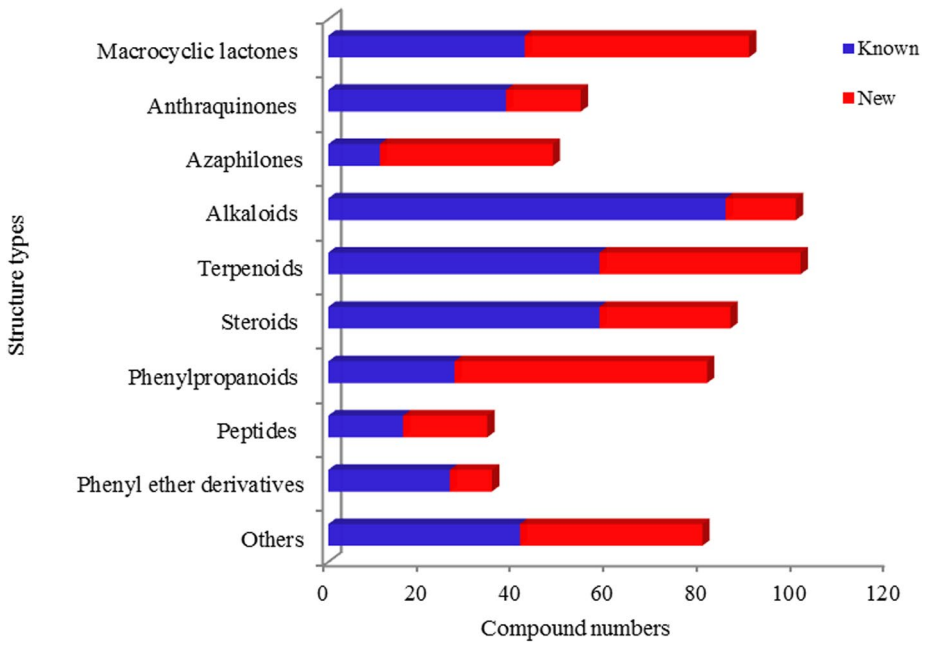

Fig. 48 The distribution of MNPs obtained from marine invertebrates and their symbiotic microorganisms

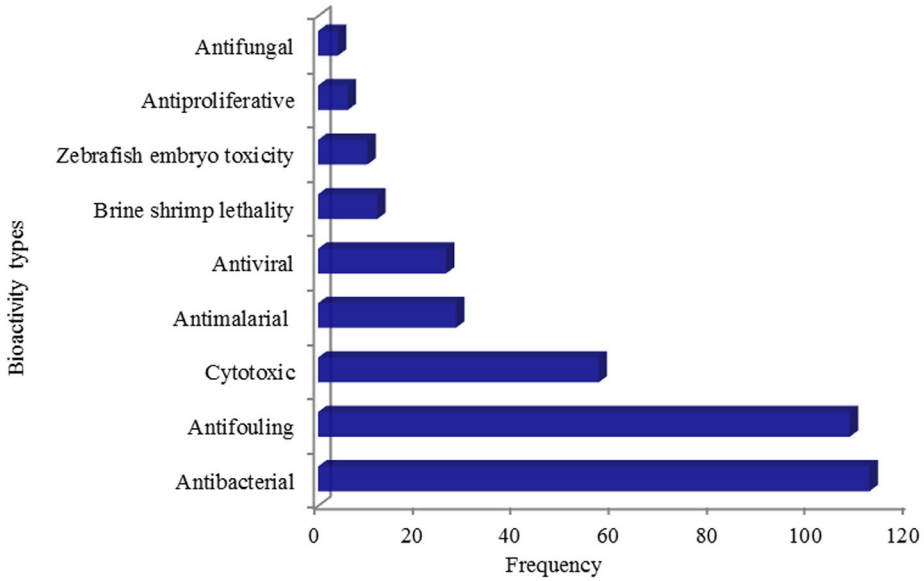

Fig. 49 The frequency of MNPs based on diverse biological activities

Conclusion

In this review, we exemplified nine types of structurally unique MNPs including macrocyclic lactones, anthraquinones, azaphilones, alkaloids, terpenoids, steroids, phenylpropanoids, peptides, and phenyl ether derivatives obtained from marine invertebrates and their symbiotic microorganisms. Our research provides several typical representative MNPs from marine invertebrates, especially sponges, soft corals, gorgonian corals, and their symbiotic microorganisms (mainly fungi). These MNPs display various potent bioactivities involved in not only chemoecological effects such as antifouling, ichthyootoxic, and brine shrimp lethal activities but also pharmaceutical activities including antibacterial, antiviral, fungicidal, cytotoxic, and antimalarial activities. Our studies demonstrate that MNPs derived from marine invertebrates and their symbiotic microorganisms in the South China Sea are a prolific resource for the discovery of bioactive MNPs. It could be expected that the symbiotic microorganisms associated with marine invertebrates have great potential as a significant source of structurally interesting molecules. It should be noted that the application of multiple discovery strategies and methods could effectively promote the exploitation of novel MNPs with diverse structures. In our study, different methodological approaches, including single culture, OSMAC, chemical epigenetic manipulation, co-culture, structural modification and chemical synthesis, have been applied in the search for new MNPs. Among them, co-culture, structural modification and chemical synthesis were found to be effective approaches to obtain potential bioactive MNPs. Particularly, LC–MS/MS-dependent molecular networking has been applied as a promising approach to dereplicate complex natural product mixtures, contributing to the targeted isolation of a series of new compounds. It is anticipated that future genetic techniques and bioinformatics tools, especially metagenomic approaches, genome mining, and heterologue biosynthesis, could accelerate the exploration and accessibility of remaining undiscovered MNPs with novel structures and promising bioactivities from marine microorganisms.

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Author contributions LL and YYZ collected the data and wrote the paper; CLS and CYW designed, directed and revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and human rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

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