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REVIEW

Recent progresses in marine microbial-derived antiviral natural products

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Abstract Viruses have always been a class of pathogenic microorganisms that threaten the health and safety of human life worldwide. However, for a long time, the treatment of viral infections has been slow to develop, and only a few antiviral drugs have been using clinically. Compared with these from terrestrial environments, marine-derived microorganisms can produce active substances with more novel structures and unique functions. From 2015 to 2019, 89 antiviral compounds of 8 structural classes have been isolated from marine microorganisms, of which 35 exhibit anti-H1N1 activity. This review surveys systematically marine microbial-derived natural products with antiviral activity and illustrates the impact of these compounds on antiviral drug discovery research.

Keywords Antiviral activity · Marine microorganism · Marine natural products · Structure–activity relationships

Introduction

Since viral diseases (such as HIV, H1N1, HSV, etc.) have always been seriously threatening human life and health, antiviral compounds are continuously special attention. Some existing viral diseases including AIDS, hepatitis B, influenza and other diseases that can cause millions of deaths every year have not been able to be eradicated completely. New viral diseases such as coronavirus are beginning to sweep the world, and related medical treatments are under investigation (Barlow et al. 2020; Li et al. 2020). Considering the importance of marine compounds in antiviral activity, the potency of some marine natural products to target SARS CoV-2 main protease (Mpro) (PDB ID 6MO3) was investigated (Khan et al. 2020) and reported the molecular docking analysis of 2019-nCoV inhibition by antiviral compounds from marine natural resources (Vijayaraj et al. 2020). Recent scientific studies triumphantly reported new antiviral agents, which generally inhibit the virus replication cycle through affecting the important host cell factor(s) for virus replication and/or viral elements (Lou et al. 2014). Despite the rapid development in antiviral pharmaceuticals over the past few decades, the emergence of recombinant viruses, drug resistance, and cell toxicity make it an urgent need to develop new antiviral agents with higher efficiency and lower toxicity (Moghadamtousi et al. 2015).

The oceans, with their unique aquatic environment and rich biodiversity, have proven to be a plentiful source of diverse natural products with significant antimicrobial, antiviral, antimalarial, antitumor, anti-inflammatory, and anti-oxidant activities (Hou et al. 2019). Since the exploration of marine microorganisms began in the 1960s, marine microorganisms have gradually become a new field of natural product research. Approximately 150 to 200 new compounds of alkaloids, sesquiterpenoids, polyketides, and

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others are obtained from marine fungi annually (Moghadamtousi et al. 2015). In recent years, with the popularity of genomic sequencing information and genome mining analysis, more and more drugs have been discovered from the marine environment, which will have a significant impact on the discovery of new natural products (Zhao 2011). With the continuous development of technologies for marine microbial research, synthetic biological approaches also provide a total of possible biological activities for the secondary metabolites of marine microbes (Seghal Kiran et al. 2018). All of these indicate that natural products derived from marine microorganisms will continue to play a pivotal role in drug discovery and development.

Marine microorganisms are known producers of antiviral agents and may provide unlimited biological resources for the production of therapeutic drugs for the treatment and control of viral diseases in humans, ever more novel compounds with potential as pharmaceuticals, which have strong potential market value (Bhadury et al. 2006). Currently, more than 200 natural products with promising levels of anti-HIV activity have been isolated from marine organisms, following bioassay-guided protocols (Yasuhara-Bell and Lu 2010). Halovirs A–E, isolated from the marine fungus *Scytidium* sp., exhibit potent antiviral activity against HSV-1 with ED_{50} values of 1.1, 3.5, 2.2, 2.0 and 3.1 μM, respectively (Rowley et al. 2003). Stachyflin, a novel terpenoid isolated from the fungus *Stachybotrvs* sp., shows significant antiviral activity against H1N1 with an IC_{50} value of 0.003 μM, which is much better than anti-H1N1 drugs amantadine and zanamivir (with IC_{50} values of 5.3 and 0.75 μM, respectively) (Minagawa et al. 2002a, b). This highlights the important role of marine natural products in the discovery of new antiviral agents.

In recent reviews on the same topic, some focused on specific compounds or compound categories (Goh et al. 2020), some were related to the biological activity of marine natural products (Deshmukh et al. 2017), some focused on biological or geographic regions (Pech-Puch et al. 2020), and others were more general. Since the marine antiviral natural products discovered recently have not been studied systematically in recent years, we summarize here the research progresses of these antiviral natural compounds from marine microorganisms published in the past five years and discuss the research status of marine microbial-derived antiviral compounds in this period including 89 compounds in 60 references. Compounds with effective antiviral activity will be described in detail.

Marine microbial-derived antiviral compounds

The following section describes antiviral compounds from marine microbial resources. The compounds are organized according to their chemical structural classes namely alkaloids, quinones, peptides, polyketones, pyrones, sterols, terpenoids, and others.

Alkaloids

Alkaloids are an important class of basic nitrogen-containing natural organic compounds that are abundant in animals and plants. In recent decades, tetramic acids have attracted researcher's attention, their chemical and biosynthetic methods have also been widely reported (Henning and Gelbin 1993; Schobert and Schlenk 2008). Even so, the natural products containing decalin ring that appear frequently in microorganisms also show different biological activities (Li et al. 2014). Recently, several tetramic acid derivatives containing a decalin ring with antiviral biological activity, trichobotrysins A (**1**), B (**2**) and D (**3**) (Sun et al. 2015), were obtained from a fermentation broth of the fungal strain *Trichobotrys effuse* derived from the deep-sea sediment collected from the South China Sea. These compounds were shown to have activity against HSV-1 with IC_{50} values of 3.08, 9.37 and 3.12 μM, respectively.

Neosartoryadins A (**4**) and B (**5**) (Yu et al. 2015), were isolated from the endophytic fungus *Neosartorya udagawae*. They have a common unique pyrido [2,1-*b*]-quinazoline framework and a tetrahydrofuran ring, and the quinazoline is conjugated with a pyridine ring. Such compounds were first isolated from *Aspergillus fumigates* in 1992 (Numata et al. 1992). Using the cytopathic effect (CPE) inhibition assay to evaluate their antiviral activity, both **4** and **5** exhibited antiviral activity against H1N1 with IC_{50} values of 66 and 58 μM, respectively (ribavirin as positive control, $IC_{50} = 94$ μM). Biosynthetically, these compounds may derive from an assembly by L-tryptophan, ATA, L-valine, and 2-aminoisobutyric acid (Aib).

Pyrazine heterocycle is an important pharmacophore present as a basic scaffold in various clinical drugs with a wide range of pharmacological and therapeutic activities, such as antitumor, anti-inflammatory, antithrombotic, anti-diabetic, and anti-tubercular (Dolezal and Zitko 2012; Miniyar et al. 2013). Trypilepyrazinol (**6**) (Li et al. 2019b) isolated from marine-derived fungus *Penicillium* sp. is characterized by a pyrazine motif and has a broad spectrum of antiviral activity against human immunodeficiency virus (HIV) and hepatitis C virus (HCV) with IC_{50} values of 4.6 and 7.7 μM, respectively.

Raistrickindole A (**7**) and raistrickin (**8**) (Li et al. 2019a) were isolated from the marine-derived fungus *Penicillium raistrickii*. Both **7** and **8** showed anti-HCV activity *in vitro* with EC_{50} values of 5.7 and 7.0 μM, respectively (as compared to 0.05 μM of the positive control VX-950). Compound **7** had an unusual pyrazino[1′,2′:2,3]-[1,2] oxazino[6,5-*b*]indole tetraheterocyclic ring system, and this

novel structure provides more possibilities for the discovery of antiviral compounds.

9(10H)-Acridanone (**9**) (Manimaran et al. 2018) (Fig. 1) was extracted from *Streptomyces fradiae* strain VITMK2, isolated from marine soil sediment sample collected from the mangrove forest region of Pichavaram, Tamil Nadu, India. The shrimp infected with WSSV and treated with **9** (500 µg, 250 µg, and 125 µg) showed survival rates of 88.89%, 83.33% and 55.56%, respectively. Docking of the compound with VP26 and VP28 of WSSV drug target proteins showed the least binding energy of − 5.71 kcal/mol and − 5.21 kcal/mol, respectively, predicting the strong interaction of the compound with VP26 and VP28.

Quinones

Quinones are a class of aromatic organic compounds with two double bonds and a six-carbon atom cyclic diketone structure. They are often found in nature as pigments in animals, plants, and microorganisms. Two anthraquinones, aspergilols H (**10**) and I (**11**) (Huang et al. 2017), were isolated from fungus *Aspergillus versicolor* derived from the deep-sea sediment sample collected from the South China Sea. In vitro antiviral assay indicated that these compounds showed significant anti-HSV-1 activity with EC_{50} values of 4.68, 6.25 µM and CC50 values of 108.6, 50.7 µM, respectively (The corresponding EC50 and CC50 values of positive control acyclovir were 3.0 and > 1000 µM, respectively).

A citrinin dimer, seco-penicitrinol A (**12**) (Yang et al. 2018) was isolated from the extracts of the coculture of two marine algal-derived endophytic fungal strains *Aspergillus sydowii* and *Penicillium citrinum*. Compound **12** showed inhibitory activity towards influenza neuraminidase in vitro with an IC_{50} value of 24.7 µM (oseltamivir as positive control, $IC_{50} = 3.6$ µM).

Two anthraquinone derivatives, (–)-2′*R*-1-hydroxyisorhodoptilometrin (**13**) and methyl 6,8-dihydroxy-3-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**14**) (Jin et al. 2017) (Fig. 2) were isolated from the acidic fermentation broth (pH 2.5) of *Penicillium* sp. OUCMDZ-4736 collected from the sediment around roots of mangrove (*Acanthus ilicifolius*). Low pH induced the fungus producing abundant and diverse secondary metabolites. Compared with the positive control lamivudine, **13** showed stronger anti-hepatitis B virus activity by inhibiting HBsAg and HBeAg secretion in HepG2.2.15 cells.

Actinomycetes isolated from mangrove ecosystem plays an important role in protecting human health by having the

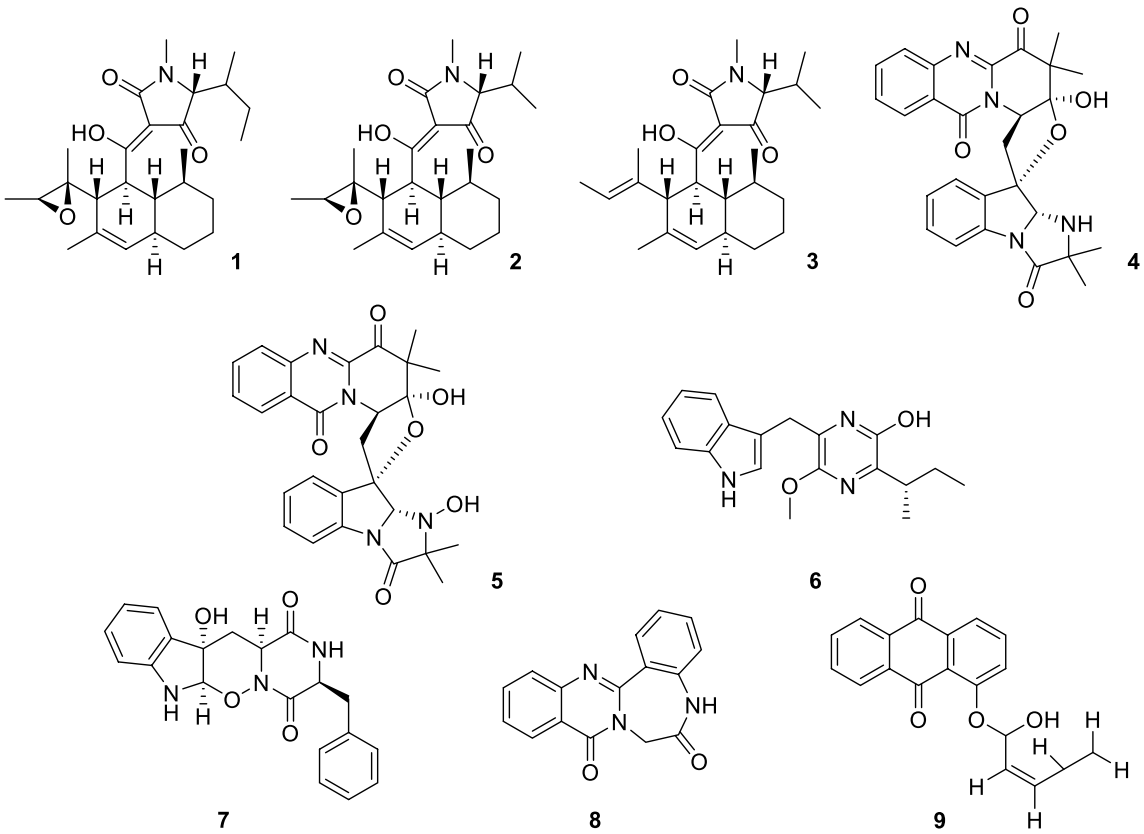


Fig. 1 Chemical structures of **1–9**

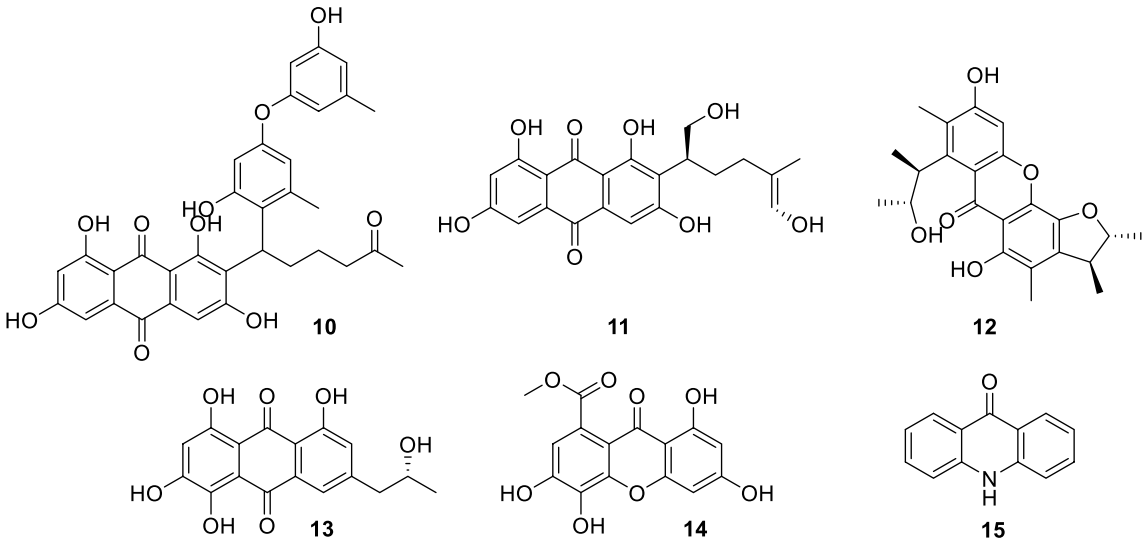


Fig. 2 Chemical structures of **11**–**15**

antagonistic activity against disease causing microorganisms. A novel bioactive compound, (Z)-1-((1-hydroxypenta-2,4-dien-1-yl)oxy)anthracene-9,10-dione (**15**) (Avilala et al. 2018) extracted from *Nocardia alba* KC710971 showed antiviral activity against two poultry viruses NDV and IBDV.

Peptides

Peptides are short chains of between 2 and 50 amino acids, linked by peptide bonds. Chains of less than 10 or 15 amino acids are called oligopeptides, and include dipeptides, tripeptides, and tetrapeptides. A class of thiodiketopiperazine-type alkaloids, eutypellazines A–L (**16**–**27**) (Niu et al. 2017) (Fig. 3), were extracted from deep-sea derived fungus *Eutypella* sp. collected from the South Atlantic Ocean. In vitro antiviral experiments showed that these compounds have antiviral activities and low cytotoxicity ($CC_{50} > 100$ μM). Compound **20** showed the strongest inhibitory effect on HIV-1 with an IC_{50} value of 3.2 ± 0.4 μM and the rest (**16**–**19** and **21**–**27**) demonstrated IC_{50} values of anti-HIV activity 14.8 ± 1.2, 11.5 ± 0.8, 10.7 ± 1.3, 8.5 ± 0.5, 16.6 ± 0.5, 18.2 ± 1.3, 13.3 ± 0.6, 6.7 ± 2.1, 4.9 ± 1.1, 5.8 ± 0.7, and 5.9 ± 0.9 μM, respectively. Structure–activity relationships (SAR) indicated that these analogues with thiomethyl group at C-2/C-2′ (**19** and **20**) showed more active than those with sulfide bridge (**16**–**18** and **21**–**23**) in the pentacyclic thiodiketopiperazines. A comparison of the inhibitory effect between **19** and **20** revealed a double bond at C-6′/C-7′ in **20** enhancing the activity. In regard to **24**–**27**, the analogues with thiomethyl group at C-2/C-2′ (**25**) showed stronger effect than those with hydroxyl substitution (**25**–**26**), whereas the analogue with methoxy/hydroxyl substitution at C-2/C-2′ dramatically reduced the activity. Another study indicated that **25** showed the reactivation on latent HIV-1 transcription with a dose-dependent manner, whereas the remaining compounds exerted inactive in a dose of 100 μM. Compound **25** had the reactivation activity at 80 μM, which is comparable to the positive control of prostratin (5 μM) and SAHA (2.5 μM).

Rubrumlines A–O (**28**–**42**) (Chen et al. 2015) (Fig. 4) is a class of prenylated indole diketopiperazines isolated from marine-derived fungus *Eurotium rubrum*. Antiviral tests showed that they all have weak anti-influenza A/WSN/33 virus activity. Structure–activity relationships (SAR) indicated that **28**–**42** exhibited a variety of antiviral activities dependent on the substituent groups and the olefinic location at diketopiperazine unit. The analogues with a saturated C_8–C_9 bond (**33**–**34**, **37** and **40**–**42**) exerted weak antiviral effects. For the analogues with a $\Delta^{8,9}$ bond, **31** with a $\Delta^{12,15}$ unit at the diketopiperazine moiety instead of alanine unit such as **28**–**30**, **35** and **36** significantly enhanced the antiviral activity. The analogues with a hydroxy group at C-15 of alanine unit (**37**–**38**) and with a ketone at C-12 (**39**) exhibited weak antiviral effects. Rubrumline N (**41**) with a MeO group at C-8 increased antiviral effect in comparison with rubrumline M (**40**) in which an OH group was substituted at C-8. The analogues with an isoprenyl unit in indole ring displayed stronger cytotoxic effects than those linked by an oxygenated isoprenyl unit (**28**–**29** and **35**–**36**) at a dose of 100 μM.

A pair of enantiomeric alkaloid dimers, (+)-and (−)-pestaloxazine A (**43** and **44**) (Jia et al. 2015b) (Fig. 5), with an unprecedented symmetric spiro-[oxazinane-piperazinedione] skeleton consisting of 22 carbons and 12 heteroatoms, were isolated from a fungus *Pestalotiopsis* sp., derived from a soft coral. Pestaloxazine A belongs to the

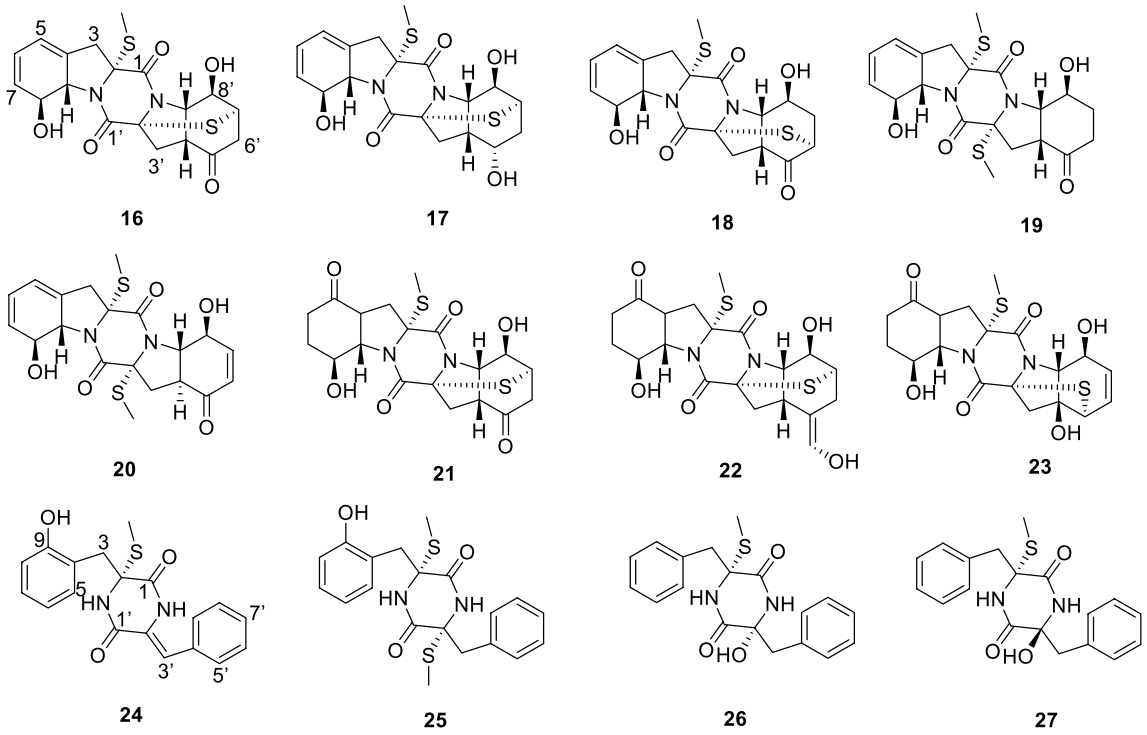


Fig. 3 Chemical structures of **16**–**27**

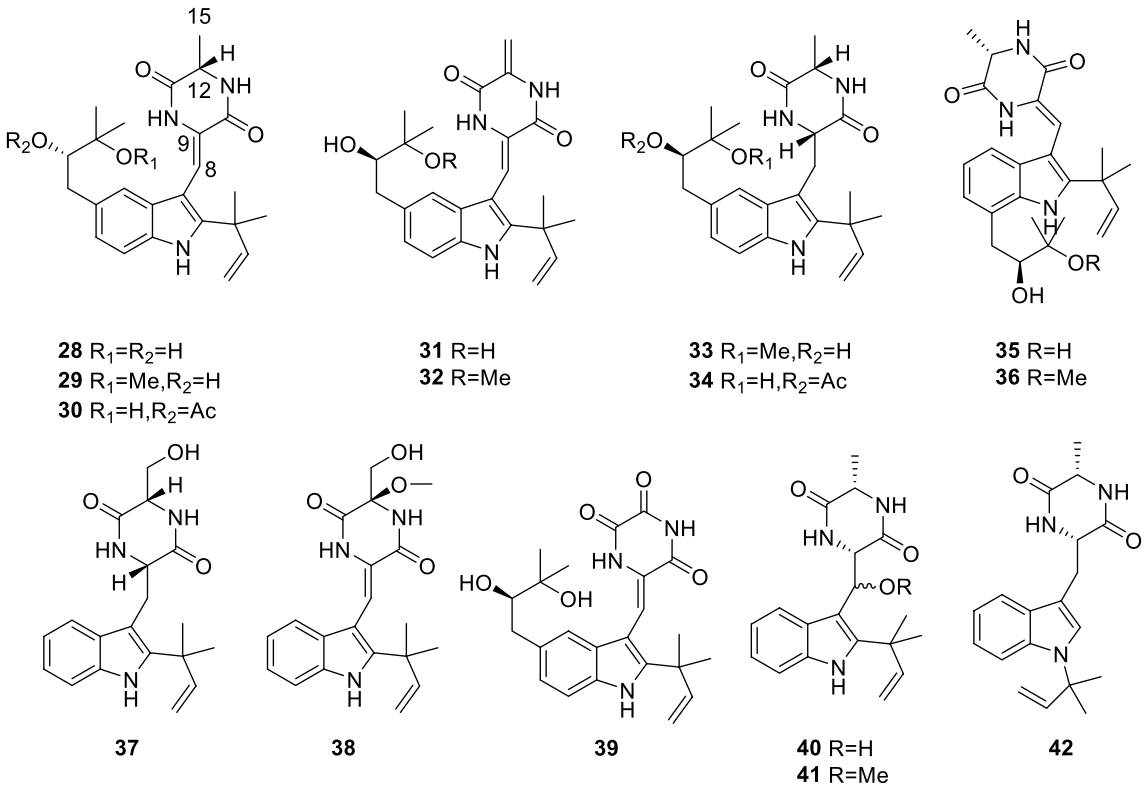
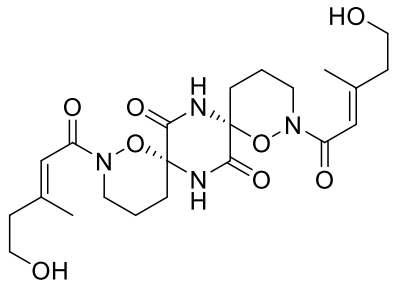


Fig. 4 Chemical structures of **28**–**42**



43 (RR) (+)-pestaloxazine A
44 (SS) (–)-pestaloxazine A

Fig. 5 Chemical structures of **43–44**

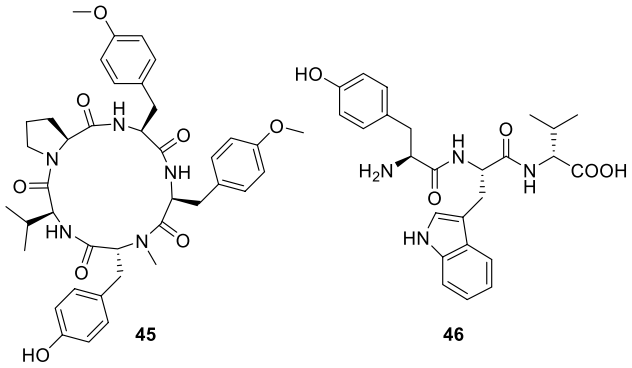


Fig. 6 Chemical structures of **45–46**

mixed polyketide-cyclo-dipeptide class of natural products (often referred to as a PKS-NRPS hybrid). According to the anti-EV71 assay in vitro, **43**, **44**, and their enantiomeric mixtures showed antiviral biological activity with IC_{50} values of 14.2 ± 1.3, 69.1 ± 3.1, and 16.0 ± 0.8 μM, respectively. It is worth noting that the antiviral activity of **43** is about 18-fold higher than that of ribavirin (IC_{50} = 256.1 ± 15.1 μM). In addition, their selectivity index (SI) for anti-EV71 activity is different, indicating that the stereochemistry of the spiro center may contribute to the antiviral activity and selectivity indices. Pestaloxazine A has a unique structural skeleton including its symmetric spiro [oxazinane-piper-azinedione] skeleton and two unique hemiaminal and oxazinane groups, and 10 of the 22 carbon atoms are oxygenation or nitrification which also contributes to the special structure.

Two linear peptides, namely aspergillipeptides D (**45**) and E (**46**) (Ma et al. 2017) (Fig. 6), were isolated from a culture broth of marine gorgonian-derived fungus *Aspergillus* sp. obtained from the China South Sea gorgonian *Melitodes squamata*. Compounds **45** and **46** showed evident antiviral activity against herpes simplex virus type 1 (HSV-1) with IC_{50} values of 9.5 and 19.8 μM under their non-cytotoxic concentrations against a Vero cell line, respectively. In addition, **45** had antiviral activity against acyclovir-resistant clinical isolates of HSV-1-106 and HSV-1-153 at concentration of 12.5 μM with about 50% inhibition rate.

Polyketones

Polyketones are a class of secondary metabolites produced by bacteria, fungi, plants, and animals. These substances are not necessary for the growth and development of organisms, but can be used for defense or intercellular communication. Asteltoxins E (**47**) and F (**48**) (Tian et al. 2015) (Fig. 7) discovered from marine-derived fungus *Aspergillus* sp. Compounds **47** and **48** showed significant activity against H3N2 with the prominent IC_{50} values of 6.2 ± 0.08 and 8.9 ± 0.3 μM, respectively. In addition, asteltoxin E also exhibited inhibitory activity against H1N1 with an IC_{50} value of 3.5 ± 1.3 μM.

Pestalotiolide A (**49**) (Jia et al. 2015a) was a phthalide derivative obtained from marine-derived fungus *Pestalotiopsis* sp. Compared to the positive control ribavirin (IC_{50} = 418.0 μM), **49** exhibited significant anti-EV71 activity in vitro with an IC_{50} value of 27.7 μM. Structure–activity relationships (SAR) indicated that the glycosidation of 7-OH significantly increased anti-EV71 activity and the acetylation of 6′-OH also increased anti-EV71 activity. The acetoxy group at C-6′ had a positive contribution to anti-EV71 activity as well.

Isoprenylated cyclohexanols, truncateol M (**50**) (Zhao et al. 2015), was isolated from the solid culture of the

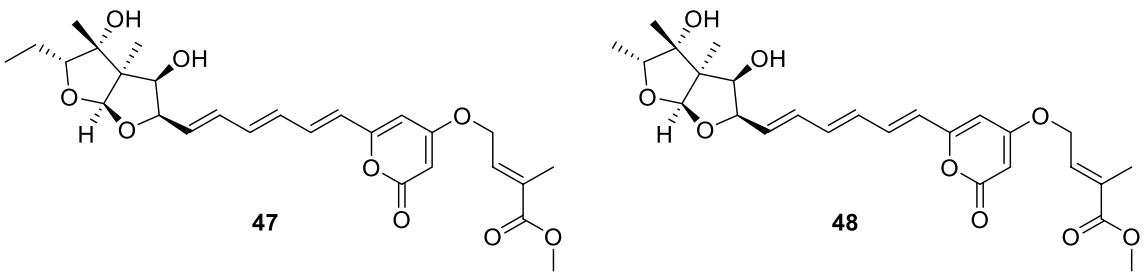
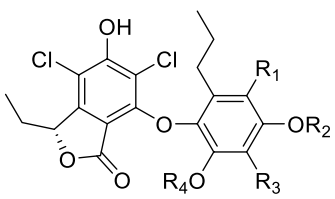


Fig. 7 Chemical structures of **47–48**

sponge-associated fungus *Truncatella angustata* obtained from a finger sponge *Amphimedon* sp. collected from the bay of Yongxing Island in the South China Sea was fermented. The potential mechanism for **50** to suppress influenza infection by targeting virion assembly/release step to exert an effective inhibitory effect. The inhibitory effect of **50** on the H1N1 virus was almost six-fold more potent than OSV with an IC_{50} value of 8.8 μM (oseltamivir (OSV) as positive control, IC_{50} = 46.5 μM).

A new chromone, coniochaetone J (**51**) (Liu et al. 2017a) (Fig. 8), was isolated from deep-sea derived sediment fungus *Penicillium* sp. Compound **51** exhibited weak anti-EV71 activity in vitro with an IC_{50} value of 81.6 μM (ribavirin as positive control, IC_{50} = 0.6 μM).

A class of phenolic lactones, spiromastilactones B, D–G, I–J and L (**52–59**) (Niu et al. 2016) (Fig. 9), were isolated from a deep-sea derived fungus *Spiromastix* sp. An antiviral assay revealed that these compounds show inhibitory activity against WSN influenza virus with low cytotoxicity. Among them, **54** and **55** have strong antiviral activity, even higher than their positive control compounds (oseltamivir, 10.0 μM and amantadine, 13.0 μM) with IC_{50} values of 6.0 ± 0.2 and 11.4 ± 1.3 μM, respectively. The remaining compounds have weak antiviral activity against WSN influenza virus with IC_{50} values of 16.2 ± 0.6, 27.6 ± 0.4, 30.7 ± 1.7, 74.9 ± 4.9, 38.2 ± 2.1, and 22.6 ± 0.9 μM, respectively. In addition, spiromastilactone D displayed the most potent activity by inhibiting a panel of influenza A and B viruses. Mechanistic studies indicated that spiromastilactone D binds to the hemagglutinin protein (HA) and disrupts the interaction of HA-sialic acid receptor, which is essential for the attachment and entry of all influenza viruses. In addition, **54** also showed modest inhibition on viral genome replication. These findings, in association with the inhibitory effects against a panel of influenza virus strains and less induction of drug resistance, suggested that the spiromastilactone entity may be an attracting scaffold for development of a new class of influenza virus inhibitors. Structure–activity relationships indicated that chlorination at either 3′ or 5′ or methylation of the 2′-hydroxyl group all enhanced the antiviral activity significantly. Simultaneous methylation of the 2′-hydroxyl group and chlorination at either 3′ or 5′ further enhance their potency against the WSN virus. However,



52 R_1=Cl,R_2=R_4=Me,R_3=H
53 R_1=Cl,R_2=R_3=H,R_4=Me
54 R_1=R_2=H,R_3=Cl,R_4=Me
55 R_1=Cl,R_2=R_3=R_4=H
56 R_1=R_2=R_4=H,R_3=Cl
57 R_1=R_2=R_3=H,R_4=Me
58 R_1=R_3=Cl,R_2=Me,R_4=H
59 R_1=R_3=Cl,R_2=H,R_4=Me

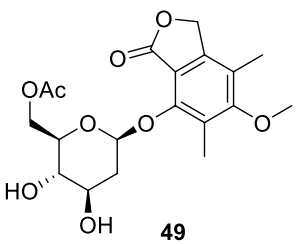
Fig. 9 Chemical structures of **52–59**

chlorination at both 3′ and 5′ with the 2′-hydroxyl group either methylated or not decreased substantially the antiviral activity. Further, methylation of the 2′-hydroxyl group seems likely to be critical since the methylated derivatives were all more potent than their parent compounds. In contrast, methylation of 4′-hydroxyl group seems detrimental to the antiviral activity. Clearly, mono-methylation and mono-chlorination rather than di-methylation and/or di-chlorination of spiromastilactone promoted the antiviral activity, **54** exerting the most potent.

Two phenolic polyketides, wailupemycin J (**60**) and *R*-Wailupemycin K (**61**) were isolated and identified from the fermentation broth of *Streptomyces* sp. associated with the marine green algae, *Enteromorpha prolifera* (Liu et al. 2017b). Compounds **60** and **61** at a concentration of 50 μg/mL showed anti-H1N1 virus activity with 47.8% and 42.5% inhibitions, respectively (positive control ribavirin, 45.3% inhibition). Regrettably, the IC_{50} values of **60** and **61** were not obtained due to the lack of quantity.

Abyssomicin monomers designated neoabyssomicin D (**62**) (Huang et al. 2018) (Fig. 10) was discovered from the marine-derived *Streptomyces koyangensis*. Compound **62** exhibited mild antiviral activity against herpes simplex virus at a concentration of 10 μM, the percentage of virus replication is low (31 ± 10%). Structurally as a representative of a novel abyssomicin skeleton, **62** contains a unique 8/5/5/7 tetracyclic core. The biosynthetic pathway may be that the internal Michael addition reaction at C-16 of abyssomicin 4 with the enolate formed by deprotonation at C-8 would yield abyssomicin 5 (Leon et al. 2015). The hydroxy group at C-9 can be eliminated in tandem with the cleavage of the C-10/C-11 bond, leading to the generation of the intermediate with a C-9/C-10 double bond. An aldol

Fig. 8 Chemical structures of **49–51**



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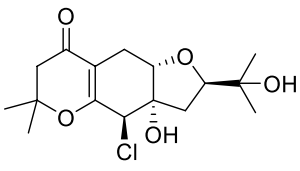

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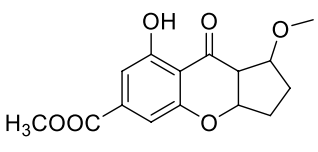
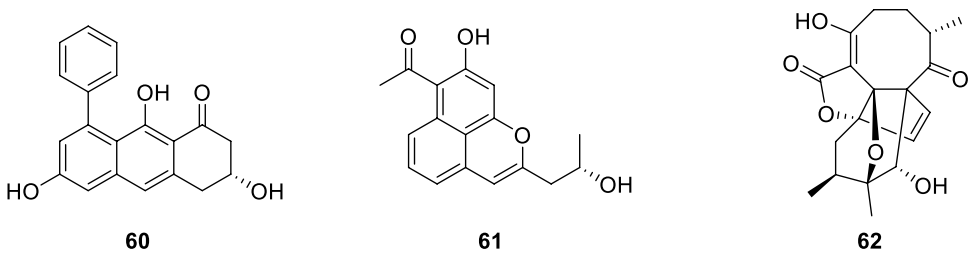


51

Fig. 10 Chemical structures of **60–62**



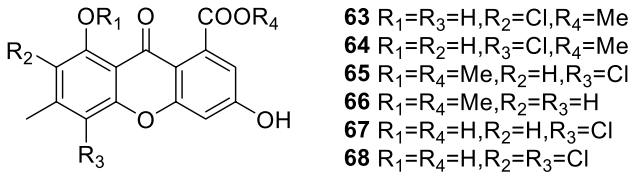


Fig. 11 Chemical structures of **63–68**

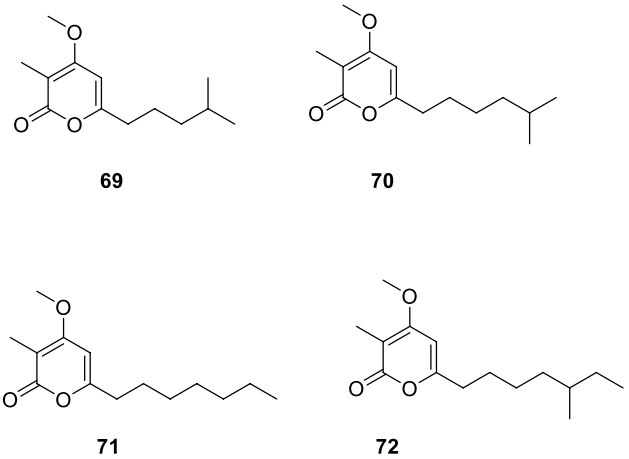


Fig. 12 Chemical structures of **69–72**

reaction between a C-8 enolate and C-11 yields a new seven-membered ring to give this compound.

Pyrones

Pyrones are a class of heterocyclic chemical compounds. They contain an unsaturated six-membered ring with one oxygen atom and a ketone functional group. There are two isomers denoted as 2-pyrone and 4-pyrone. Methyl-(2-chloro-l,6-dihydroxy-3-methylxanthone)-8-carboxylate (**63**), methyl-(4-chloro-l,6-dihydroxy-3-methylxanthone)-8-carboxylate (**64**), methyl-(4-chloro-6-hydroxy-1-methoxy-3-methylxanthone)-8-carboxylate (**65**), methyl-(6-hydroxy-1-methoxy-3-methylxanthone)-8-carboxylate (**66**), 4-chloro-1,6-dihydroxy-3-methylxanthone-8-carboxylic acid (**67**), and 2,4-dichloro-1,6-dihydroxy-3-methylxanthone-8-carboxylic acid (**68**) (Kang et al. 2018) (Fig. 11) were isolated from the coastal saline soil-derived *Aspergillus iizukae* by application of an OSMAC approach. Compound **64** exhibited strong antiviral activities against H1N1, HSV-1, and HSV-2 with IC_{50} values of 44.6, 21.4, and 76.7 μM, respectively (ribavirin as the positive controls of H1N1 and acyclovir as the positive control of HSV-1 and HSV-2). The preliminary structure-activity relationships of **63–68** showed that the hydroxy group at C-1 and the methyl carboxylate group at C-8 essentially contributed to the anti-H1N1, anti-HSV-1, and anti-HSV-2 activities, and the position of the chlorine atom in ring A would affect the antiviral activities. Additionally, it seemed that methylation of the hydroxy group at C-1 or replacement of methyl carboxylate at C-8 by carboxylic acid, to a large extent, lower the antiviral effect.

Heterologous expression of the type III polyketide synthase (PKS) gene vioA in marine-derived *Streptomyces youssoufiensis* led to production of violapyrones (VLPs) Q–T (**69–72**) (Hou et al. 2018) (Fig. 12). Besides, **69–72** showed anti-H1N1 activity with IC_{50} values of 58.8, 64.9, 30.6, and 68.4 μM, respectively. Compounds **69–72** also revealed anti-H3N2 activity with IC_{50} values of 95.0, 63.9, 45.3, and 72.8 μM, respectively. Preliminary structure–activity relationships research demonstrated that all the methylated compounds displayed stronger anti-virus activity than their non-methylated counterparts, among which **71** showed the best activities. Methylation of 4-OH has a negative effect on the anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activity, with methylated VLPs displaying decreased (**70**) or abolished (**71** and **72**) activities in comparison with each of their non-methylated counterparts. Results suggested that methylation at 4-OH of these compounds enhanced anti-virus activity but reduced anti-MRSA activity.

Sterols

Sterols, also known as steroid alcohols, are a subgroup of the steroids and an important class of organic molecules. They occur naturally in plants, animals, and fungi, and can be also produced by some bacteria. A new pregnane, 3α-hydroxy-7-ene-6,20-dione (**73**) (Yu et al. 2017) was obtained from the fungus *Cladosporium* sp. cultured from a gorgonian *Dichotella gemmacea* collected from the South China Sea. This compound has a rare configuration of 3α-OH that is different from most of pregnanes. Compound **73** showed antiviral activity against the respiratory syncytial virus (RSV) with

the IC_{50} value of 0.12 μM. Cladosporisteroid B (**74**) (Pang et al. 2018), a highly oxygenated sterol, was also isolated from the culture extracts of sponge-derived fungus *Cladosporium* sp. and exhibited weak inhibitory activity against H3N2 with an IC_{50} value of 16.2 μM.

A new ergostane analogue, 3*β*-hydroxyergosta-8,14,24(28)-trien-7-one (**75**) (Li et al. 2019b) (Fig. 13), was isolated and characterized from the marine-derived fungus *Penicillium* sp. IMB17-046. Compound **75** displayed broad-spectrum antiviral activities against different types of viruses, showed anti-HIV activity with an IC_{50} value of 3.5 μM and potent anti-IAV activity with an IC_{50} value of 0.5 μM, that is 300-fold stronger than ribavirin.

Terpenoids

Terpenoids are volatile substances distributed in the animal and plant kingdom, especially in essential oils of plants, and are important chemical components of natural medicine. Talaromyolide D (**76**) (Cao et al. 2019) was isolated from a marine fungus *Talaromyces* sp. Compound **76** displayed potent antiviral activity against pseudorabies virus (PRV) with a CC_{50} value of 3.35 μM.

Two new meroterpenoids, chrodrimanins K (**77**) and N (**78**) (Kong et al. 2017) were discovered from the fermentation broth of *Penicillium* sp. collected from a marine worm of Haikou Bay, China. Compounds **77** and **78** displayed anti-H1N1 activity with IC_{50} values of 74 and 58 μM, respectively.

A new meroterpenoid, stachybonoid A (**79**) (Zhang et al. 2017), was discovered from the crinoid-derived fungus *Stachybotrys chartarum*, a crinoid (*Himerometra magnipinna*) isolated from Xuwen Coral Reef Nature Reserve, Zhanjiang city, Guangdong Province, China. Compound **79** displayed inhibitory activity against the replication of dengue virus (DENV). Biosynthetically, orsellinic acid and farnesyl diphosphate underwent addition to form the intermediate ilicicolin B. Then, the terminal olefin bond in the prenyl group of ilicicolin B was epoxidized to obtain another intermediate. When the aromatic hydroxyl group was connected to the C-3 of the prenyl group by electrophilic addition, **79** was obtained.

Stachybogrisephenone B (**80**) (Qin et al. 2014) (Fig. 14) was discovered from the cultures of sponge-derived fungus *Stachybotry* sp. Compound **80** showed activity against intestinal virus EV71 with an IC_{50} value of 30.1 μM (ribavirin as positive control, $IC_{50} = 0.60$ μM).

Others

Isoprenylated cyclohexanols, truncateols C (**81**), E (**82**) (Zhao et al. 2015), O (**83**) and P (**84**) (Zhao et al. 2018), were isolated from the marine-derived fungus *Truncatella angustata* collected from the South China Sea. Compounds **81** and **82** showed anti-H1N1 activities with IC_{50} values of 55 and 63.5 μM, respectively (the IC_{50} value of the positive control, oseltamivir was 46.5 μM). Compound **83** exhibited significant inhibition toward both HIV-1 and H1N1 virus with IC_{50} values of 39.0 ± 1.2 and 30.4 ± 0.4 μM, respectively. Compound **84** showed anti-HIV-1 activity with an IC_{50} value of 16.1 ± 0.7 μM. Due to lower cytotoxicity ($CC_{50} > 100$ μM), these compounds could be considered as potential anti-HIV lead compounds in comparison with the positive control efavirenz ($CC_{50} > 40.6$ μM).

A hexahydrobenzopyran derivative, cytosporin L (**85**) (Liao et al. 2017), was isolated from the marine-derived fungus *Eutypella* sp. collected from the South China Sea. Compound **85** obviously inhibited the respiratory syncytial virus (RSV) with the IC_{50} value of 72.01 μM (ribavirin as positive control).

New salicyloid derivative, vaccinol J (**86**) (Wang et al. 2017), was discovered from *Pestalotiopsis vaccinii* endogenous with the mangrove plant *Kandelia candel* (L.) Druce (Rhizophoraceae). Compound **86** was a salicyloid derivative that containing 2-methylfuran moiety and

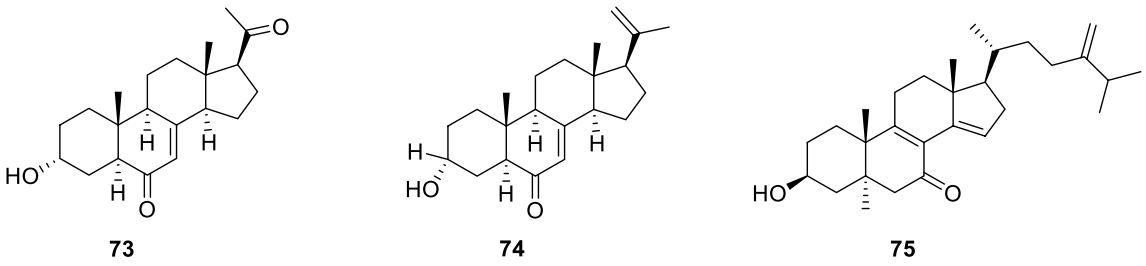


Fig. 13 Chemical structures of **73**–**75**

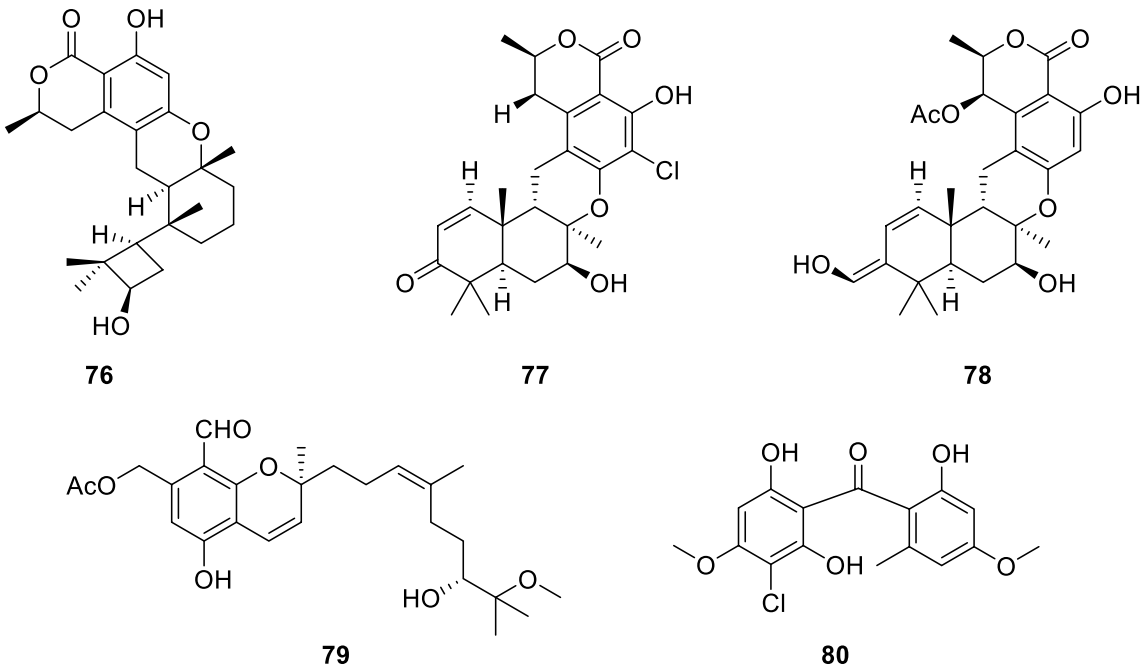


Fig. 14 Chemical structures of **76–80**

showed anti-enterovirus 71 (EV71) activity in vitro with an IC_{50} value of 30.7 μM (ribavirin as positive control, IC_{50} = 177.0 μM).

A new citrinin monomer, namely penicitrinol L (**87**) (Yang et al. 2018), was discovered from the extracts of the coculture of two marine algal-derived endophytic fungal strains *Aspergillus sydowii* and *Penicillium citrinum*. Compound **87** has the influenza neuraminidase (H5N1) inhibitory activity in vitro with an IC_{50} value of 41.5 μM.

A new anthranilic acid, anthranoside C (**88**) (Che et al. 2018), was isolated from a marine sponge-derived actinomycete *Streptomyces* sp. Compound **88** possessed a unique indole-containing scaffold and showed anti-influenza H1N1 virus activity with an IC_{50} value of 171 μM (ribavirin as positive control, IC_{50} = 133 μM). Biosynthetically, the compound may derive from an assembly by ATA and D-glucose. Structurally, **88** was comprised of ATA moiety and polyol units.

A new butenolide derivative, (4*S*)-10-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide (**89**) (Huang et al. 2019) (Fig. 15), was isolated from marine-derived *Streptomyces koyangensis*. Compound **89** displayed mild antiviral activity against herpes simplex virus with an EC_{50} value of 25.4 μM, which was characterized by an octyl substitution on C-position.

Conclusions and outlooks

The explosive growth of global drug resistance has prompted drug research and development institutions to actively seek new antiviral drugs, especially the recent global outbreak of new coronary pneumonia, which has promoted enthusiasm for antiviral drug research unprecedented. Although there are many challenges in the exploration and development of marine microorganisms, many significant antiviral activity compounds have been obtained from marine microorganisms, and it is expected that marine microorganisms will continue to be a good source of antiviral drugs, especially the novel, highly effective, low-toxic antiviral natural products.

This review surveys natural products systematically with antiviral activity derived from marine microorganisms, and clarifies the antiviral activities of these compounds

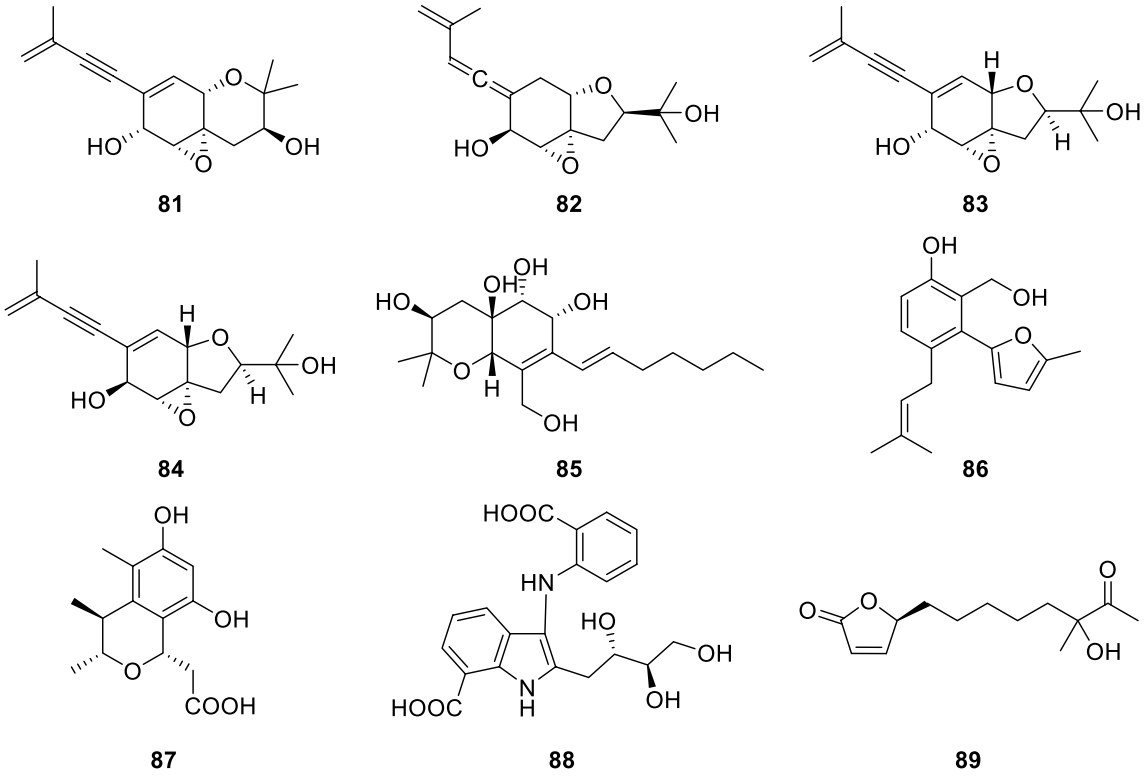


Fig. 15 Chemical structures of **81–89**

and related research progresses. In the literature spanning 2015–2019, marine microbial-derived natural products have made important progress in the study of antiviral lead compounds. A total of 89 secondary metabolites have been found, of which more than 30 have potent antiviral activities. Two secondary metabolites, trypilepyrazinol (**6**) and 3β-hydroxyergosta-8,14,24(28)-trien-7-one (**75**) showed potent broad-spectrum (HIV, HCV) antiviral activities worthy of further study (Table 1). Many significant antiviral activity compounds have been obtained from marine microorganisms, and it is expected that marine microorganisms will continue to be a good source of antivirals. The biological profiles of these leads provide hope for the discovery of highly effective and low-toxicity agents.

The antiviral compounds derived from marine microorganisms described herein can be divided into 8 biosynthetic categories; alkaloids, quinones, peptides, polyketones, pyrones, sterols, terpenoids and others (Fig. 16). Among them, peptides are the most group of secondary metabolites with potentially useful activities. Figure 17 shows that 10 viruses including H1N1, HIV, HSV, H3N2, EV71, HCV, RSV, H5N1, HBV and DENV were used as screening viruses for the antiviral activities of the compounds. In addition, most antiviral compounds showed anti-H1N1 activity, followed by anti-HIV and anti-HSV activities. Only one compound exhibited anti-DENV activity. Truncateol M (**50**) showed potent anti-H1N1 activity, eutypellazines E (**20**), I–K (**24–27**) and 3β-hydroxyergosta-8,14,24(28)-trien-7-one (**75**) exhibited promising anti-HIV activity, trichobotrysins A (**1**) and D (**3**), aspergilols H (**10**) and I (**11**) had strong anti-HSV activity. Asteltoxins E (**47**) and F (**48**) showed anti-H3N2 activity, trypilepyrazinol (**6**), raistrickindole A (**7**) and raistrickin (**8**) exhibited potent anti-HCV activity. These provide guidance for the later screening of antiviral activity of new compounds.

In summary, marine natural products are an important source of discovery of lead compounds and drug candidates for antiviral drugs. Nevertheless, it is undeniable that the current research and development of marine natural products still face bottlenecks. First, it is difficult to

Table 1 Recent progresses in marine-derived antiviral natural products

Type	No	Source	Active compound	
			No	Level
Alkaloids	**1–3**	*Trichobotrys effuse*	**1–3**	POTENT (HSV-1)
	4, **5**	*Neosartorya udagawae*	**4**, **5**	Moderate (H1N1)
	6	*Penicillium* sp.	**6**	Potent (HIV, HCV)
	7, **8**	*Penicillium raistrickii*	**7**, **8**	Potent (HCV)
	9	*Streptomyces fradiae* strain VITMK2	**9**	Potent (WSSV)
Quinones	**10**, **11**	*Aspergillus versicolor*	**10**, **11**	Significant (HSV-1)
	12	*Aspergillus sydowii* and *Penicillium citrinum*	**12**	Weak (H5N1)
	13, **14**	*Penicillium* sp.	**13**	Potent (HBV)
			14	Significant (HBV)
	15	*Nocardia alba* KC710971	**15**	Moderate (NDV)
				Moderate (IBDV)
Peptides	**16–27**	*Eutypella* sp.	**16–27**	Significant (HIV-1)
	28–42	*Eurotium rubrum*	**28–42**	Weak (H1N1)
	43, **44**	*Pestalotiopsis* sp.	**43**, **44**	Potent (EV71)
	45, **46**	*Aspergillus* sp.	**45**, **46**	Potent (HSV-1)
Polyketones	**47**	*Aspergillus* sp.	**47**	Potent (H3N2, H1N1)
	48	*Aspergillus* sp.	**48**	Potent (H3N2)
	49	*Pestalotiopsis* sp.	**49**	Potent (EV71)
	50	*Truncatella angustata*	**50**	Potent (H1N1)
	51	*Penicillium* sp.	**51**	Weak (EV71)
	52–59	*Spiromastix* sp.	**52–54**	Strong (H1N1)
			55, **56**, **58**, **59**	Moderate (H1N1)
			57	Weak (H1N1)
	60, 61	*Streptomyces* sp.	**60**, **61**	Moderate (H1N1)
	62	*Streptomyces koyangensis*	**62**	Low (HSV)
Pyrones	**63–68**	*Aspergillus iizukae*	**63**	Potent (HSV-1)
				Weak (H1N1, HSV-2)
			64	Potent (H1N1, HSV-1, HSV-2)
			65, **67**, **68**	Weak HSV-1
			66	Weak (HSV-1, HSV-2)
	69–72	*Streptomyces youssoufiensis*	**69–72**	Moderate (H1N1, H3N2)
Sterols	**73**, **74**	*Cladosporium* sp.	**73**	Potent (RSV)
			74	Weak (H3N2)
	75	*Penicillium* sp.	**75**	Potent (HIV, IAV)
Terpenoids	**76**	*Talaromyces* sp.	**76**	Potent (PRV)
	77–78	*Penicillium* sp.	**77–78**	Weak (H1N1)
	79	*Stachybotrys chartarum*	**79**	Significant (DENV)
	80	*Stachybotry* sp.	**80**	Moderate (EV71)
Others	**81–84**	*Truncatella angustata*	**81**, **82**	Moderate (H1N1)
			83	Potent (H1N1)
				Weak (HIV)
			84	Weak (HIV)
	85	*Eutypella* sp.	**85**	Moderate (RSV)
	86	*Pestalotiopsis vaccinii*	**86**	Moderate (EV71)
	87	*Aspergillus sydowii* and *Penicillium citrinum*	**87**	Weak (H5N1)
	88	*Streptomyces* sp.	**88**	Low (H1N1)
	89	*Streptomyces koyangensis*	**89**	Mild (HSV)

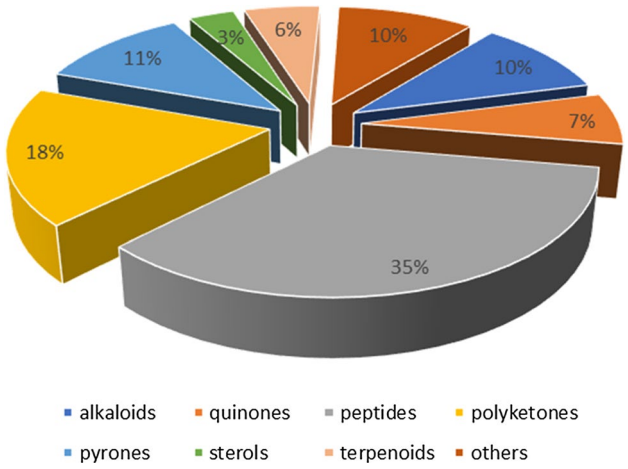


Fig. 16 The type of marine microbial-derived antiviral compounds

apply screening techniques to obtain lead compounds. Second, it is difficult to fully synthesize complex marine natural products. The most important thing is that most active marine natural products are limited to in vitro cell experiments, and few animals in vivo and clinical trials because of the limited availability of natural products. Today's rapidly evolving technologies and an increasing understanding of the molecular processes and mechanisms of secondary metabolite production will continue to increase the possibility of extracting natural products from marine microorganisms. By using marine natural product compound libraries and computing virtual screening can quickly obtain good active lead compounds; explore the synthetic route of complex products by fusing artificial intelligence technology with the total synthesis of natural products; finally, promote the activity evaluation of high-activity and low-toxic natural products and conduct animal experiments.

The purpose of this review is to help interested readers understand the current status of marine-derived antiviral compounds, and in the process identify areas for further research that may accelerate the development of more effective and selective drugs to treat this global disease.

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Compliance with Ethical Standards

Conflict of interest The authors declared no conflict of interest.

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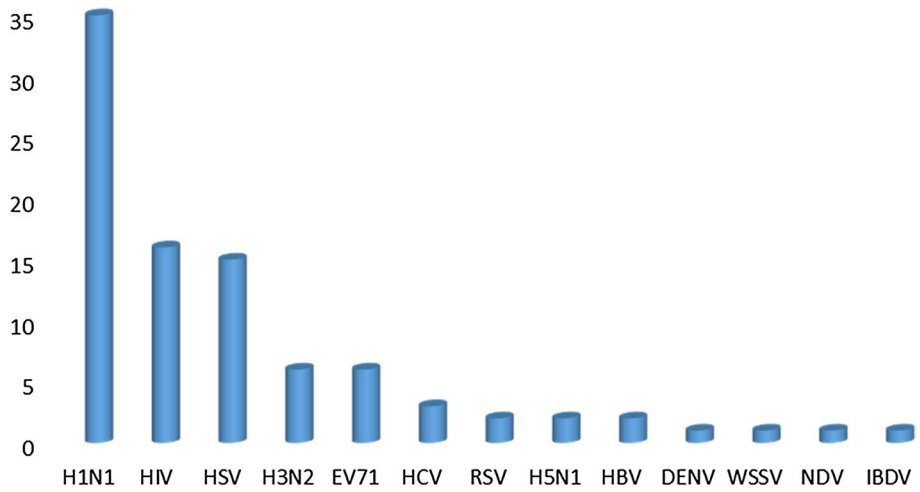

Fig. 17 Marine microbial-derived compounds with antiviral activity

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