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Marine Natural Products with Anti-HIV Activities in the Last Decade

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Abstract: Marine organisms have been proven to be excellent sources of biologically active compounds against HIV. This review gives an overview of 132 natural products from marine sources obtained during the last decade (2002–2011), which exhibit anti-HIV activity toward different biological targets. Sponges contribute more than half of all anti-HIV natural products from marine organisms, mainly as alkaloids and cyclic depsipeptides. In addition, some macromolecules are considered as potential anti-HIV agents, including lectins from algae and marine invertebrates, as well as sulfated polysaccharides from algae. In the reviewed marine natural products, many active ingredients act as HIV entry inhibitors, one class of new anti-HIV agents, and may be regarded as potential candidates for the development of novel anti-HIV agents. The other features of development in the marine original anti-HIV natural products in this ten years are also discussed.

Keywords: Anti-HIV, HIV entry inhibitors, last decade, marine organisms, natural products, sponges.

1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV) infection, is still one of the most challenging diseases today. The 2010 Joint United Nations Program on HIV/AIDS Report states that approximate 34 million people in the world are living with HIV. Although a vaccine is regarded as the last and only hope of solving the AIDS problem, a truly effective vaccine is actually far from being realized. Therefore, the development of effective, safe, and affordable anti-HIV drugs is still critical to save the lives of people who have been and will be infected by HIV.

Two major types of HIV have been identified so far, HIV-1 and HIV-2. HIV-1 is the cause of the worldwide epidemic and is most commonly referred to as HIV. The basic biological processes in the HIV-1 life cycle are now well established, and natural compounds targeting specific steps in this life cycle can be found [1]. According to the different targets, anti-HIV agents are classified under several categories: 1) HIV entry inhibitors, including attachment and fusion inhibitors, and chemokine receptor antagonists [chemokine receptor subtype 5 (CCR5) and CXC-specific receptor subtypes 4 (CXCR4) antagonists] [2, 3]; 2) HIV reverse transcriptase (RT) inhibitors, including nucleotide RT inhibitors and non-nucleotide RT inhibitors; 3) HIV integrase (IN) inhibitors; 4) HIV protease (PR) inhibitors; and 5) other HIV inhibitors, such as maturation inhibitors. Most clinical anti-HIV drugs are HIV RT and PR inhibitors, including the various combinations known as highly active antiretroviral therapy. However, the emergence of drug resistance, narrow spectrum of activity, and adverse effects have limited the therapeutic usefulness of several RT and PR inhibitors currently available in the market. Thus, the development of new classes of anti-HIV drugs targeting different stages of HIV replication is urgently needed [4].

In the past 30 years, thousands of novel compounds and their metabolites, with diverse biological activities ranging from anticancer to antiviral, have been isolated from various marine sources [5, 6]. With the rapid development of marine natural products research, marine organisms have been proven to be excellent sources of biologically active compounds against HIV.

Gochfeld *et al* [7] published an overview covering 107 marine natural products with anti-HIV activities reported before 2002 in *Mini Reviews in Medicinal Chemistry* in August 2003. In the next month, a similar review by Tziveleka [8] was published in *Current Topics in Medicinal Chemistry* covering 138 natural products, most of which were duplicates of those in the Gochfeld report. Reviews published after 2003 on this topic mainly focused on specific classes of compounds or specific origins [9, 10]. As reviewed of the annual "Marine natural products" in *Natural Product Reports*, the output of the new marine natural products has been increased rapidly in recent ten years, compared with those before 2002 [11-14]. The nine review papers published from 2004 to 2012 covered 7680 new marine natural products reported from 2002 to 2010 [11-19]. However, as can be observed, the marine natural products with anti-HIV activities reported in recent ten years have not been reviewed comprehensively.

Therefore, in our research of screening and discovery the anti-HIV constituents from marine organisms, marine natural products with anti-HIV activities reported during the last decade (2002–2011) are reviewed extensively. In this review, a total of 132 marine-derived anti-HIV constituents are summarized according to the origins of marine organisms, and the biological targets or acting sites of these anti-HIV constituents are focused on, together with brief structure-activity relationship discussion of some typical active constituents. The known marine natural products, whose anti-HIV activities been revealed for the first time or with new biological targets in the last decade, are also included. The salient features of development of the marine original anti-HIV natural products in this ten years are discussed. It is hoped that this review would be helpful to the discovery of the anti-HIV agents from marine organisms.

2. MARINE MICROBES

Secondary metabolites obtained from marine microorganisms, especially fungi and actinomycetes, have gained considerable attention because many of them are structurally unique and possess interesting biological as well as pharmacological properties.

The known cholesta-7,22-diene-3β,5α,6β-triol (**1**), obtained from a marine fungus *Trichoderma* sp. isolated from marine sediment in the South China Sea, was reported with its new activity. Compound **1** exhibited moderately inhibitive activity against HIV-1 PR (17.61% inhibition at 0.24 mM), but did not inhibit the HIV-1-induced cytopathic effect in MT-2 cells at 0.2 mM [20]. Compound **1** has also been isolated from the marine scallop *Patinopecten yessoensis* and bryozoan *Myriapora truncate* [21]. A breviane spiroditerpenoid brevione F (**2**), isolated from an extremely-tolerant marine fungus *Penicillium* sp. obtained from deep-sea sediment collected at a depth of 5115 m, displayed inhibitory effect on HIV-1 replication in C8166 cells, with an EC_{50} value (the half maximal effective concentration) of 14.7 μM [22]. An anti-HIV sorbicillinoid alkaloid named sorbicillactone A (**3**) was obtained from a marine-derived *Penicillium chrysogenum* strain isolated from the

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Mediterranean sponge *Ircinia fasciculata*. Compound **3** protected human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1 and inhibited the expression of viral proteins within the concentration range of 0.3–3.0 mg/mL [23]. A hexaketide derivative rezishanone (**4**) was obtained from the marine-derived fungus *Trichoderma viride*, which was isolated from the Caribbean sponge *Agelas dispar*. Compound **4** showed weak HIV-1 RT inhibitory activity (63.8% inhibition at 200 μg/mL) in ELISA-based assays [24].

Griseorhodin A (**5**), an aromatic polyketide produced by marine-derived bacterium *Streptomyces* sp. JP95, inhibited HIV RT similar to other rubromycins such as γ-rubromycin and heliquinomycin [25]. *Streptomyces* sp. JP95 is an isolate from the marine ascidian *Aplidium lenticulum*, which harbors a rich and diverse flora of actinomycetes [26]. Integramycin (**6**), a novel hexacyclic compound produced by marine actinomycete *Actinoplanes* sp. isolated from near-shore marine sediments, exhibited an IC_{50} value (the half maximal inhibitory concentration) of 4 μM against HIV-1 IN (strand transfer) [27]. A novel pentacyclic indolosesquiterpene xiamycin (**7**) obtained from marine-derived actinomycete *Streptomyces* sp. GT2002/1503, an endophyte from the mangrove plant *Bruguiera gymnorrhiza*, exhibited selective anti-HIV activity; it specifically blocked CCR5 (IC_{50} value 5–20 μg/mL) but had no effect on CXCR4 tropic HIV-1 infection [28].

3. MICROALGAE, ALGAE AND SEAWEEDS

3.1 Terpenoids

Two diterpenes, (6*R*)-6-hydroxydichotoma-3,14-diene-1,17-dial (**8**) and (6*R*)-6-acetoxidichotoma-3,14-diene-1,17-dial (**9**), isolated from the Brazilian marine brown alga *Dictyota menstrualis*, inhibited HIV-1 virus replication with EC_{50} values of 40 and 70 μM, respectively. They also reduced HIV-1 RT activity with IC_{50} values of 10 and 35 μM, respectively. Considering that neither **8** nor **9** affected cell viability or proliferation, the synthesis of proviral DNA is thus the specific target of the anti-HIV-1 activity of the diterpenes [29]. Kinetic behavior analyses of HIV-1 RT demonstrated that both diterpenes had similar mechanisms of inhibition of RNA-dependent DNA-polymerase activity [30]. The changes in the concentration of these two diterpenes at different life stages of *D. menstrualis* were also evaluated by gas chromatography-flame ionization detector [31].

The dollabelane diterpene named dolabelladienetriol (**10**; 8,10,18-trihydroxy-2,6-dolabelladiene), extracted from the brown alga *Dictyota pfaffii*, potently inhibited HIV-1 infection in primary cells *in vitro* by inhibiting the enzyme RT. Compound **10** also blocked HIV-1 replication (80% inhibition at 40 μM) at the post-transcriptional step [32, 33]. Studies of kinetic mode of action revealed that **10** is a non-nucleoside RT inhibitor acting as a noncompetitive inhibitor [34].

Three diterpene-benzoate natural products, bromophycolides A (**11**) and B, as well as debromophycolide A, with novel carbon skeletons and an unusual proposed biosynthesis, were isolated from extracts of the Fijian red alga *Callophycus serratus.* Only bromophycolide A (**11**) was isolated in sufficient yield for testing against HIV, revealing anti-HIV IC_{50} values of 9.1 and 9.8 μM against two HIV strains (UG/92/029 and 96USHIPS7) [35].

3.2 Phenols

Three flavones, thalassiolins A–C (**12**–**14**), with a sulfated β-glucose at the 7-position, were isolated from the Caribbean sea grass *Thalassia testudinum*. Compound **12** can inhibit HIV-1 IN terminal cleavage and strand transfer activities with IC_{50} values of 2.1 and 0.4 μM, respectively. Compounds **13** and **14** were less potent inhibitors, with IC_{50} values within the 30–100 μM range [36].

Several dimers of phenols obtained from brown algae showed effective anti-HIV activities. Two phlorotannins, 8,8'-bieckol (**15**) and 8,4'''-dieckol (**16**), which were isolated from the brown algae *Ecklonia cava* Kjellman, showed an inhibitory effect on HIV-1 RT and PR. The inhibition against RT of **15** with a biaryl linkage (IC_{50} = 0.5 μM) was 10-folds higher than that of **16** with a diphenyl ether linkage (IC_{50} = 5.3 μM), although these two phlorotannins are dimers of eckol. The kinetic mode studies of action revealed that **15** was a new non-nucleoside HIV-1 RT inhibitor [37]. Diphlorethohydroxycarmalol (**17**), derived from *Ishige okamurae* Yendo, exhibited inhibitory effects on HIV-1 RT and IN with IC_{50} values of 9.1 and 25.2 μM, respectively. However, **17** did not show inhibitory activity against HIV-1 PR [38]. 6,6'-Bieckol (**18**), one of the main phloroglucinol derivatives naturally occurring in *Ecklonia cava*, potently inhibited against HIV-1-induced syncytia formation, lytic effects, and viral p24 antigen production. Compound **18** selectively inhibited the activity of HIV-1 RT with an IC_{50} of 1.07 μM, and inhibited HIV-1 entry. Unlike most tannins, **18** did not exhibit cytotoxicity at concentrations that almost completely inhibited HIV-1 replication. Thus, the potentially effective **18** may be employed as an anti-HIV drug candidate [39].

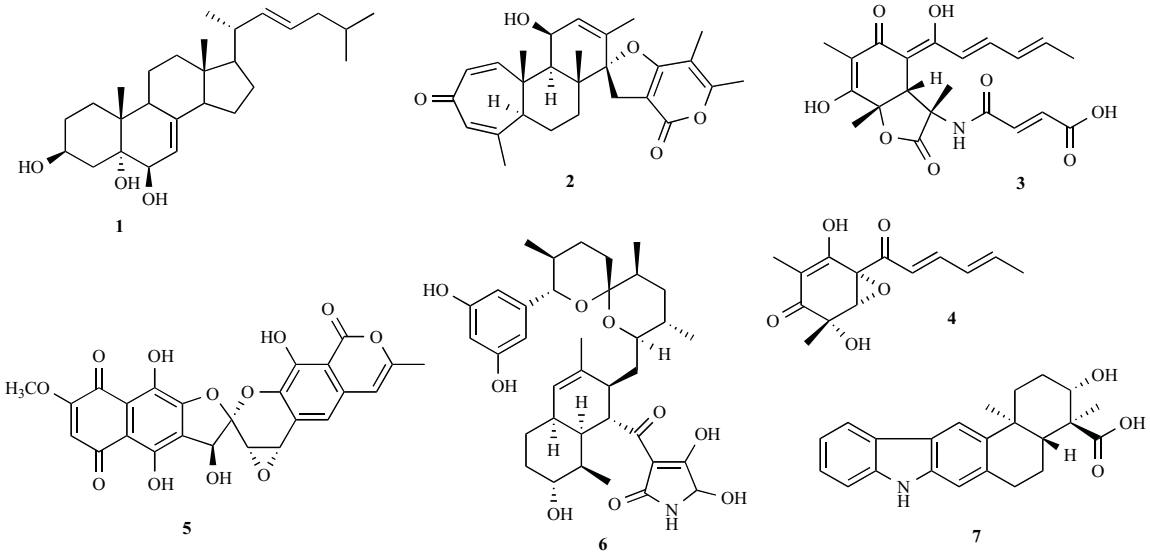


Fig. (1). Structures of **1**–**7** from marine microbes.

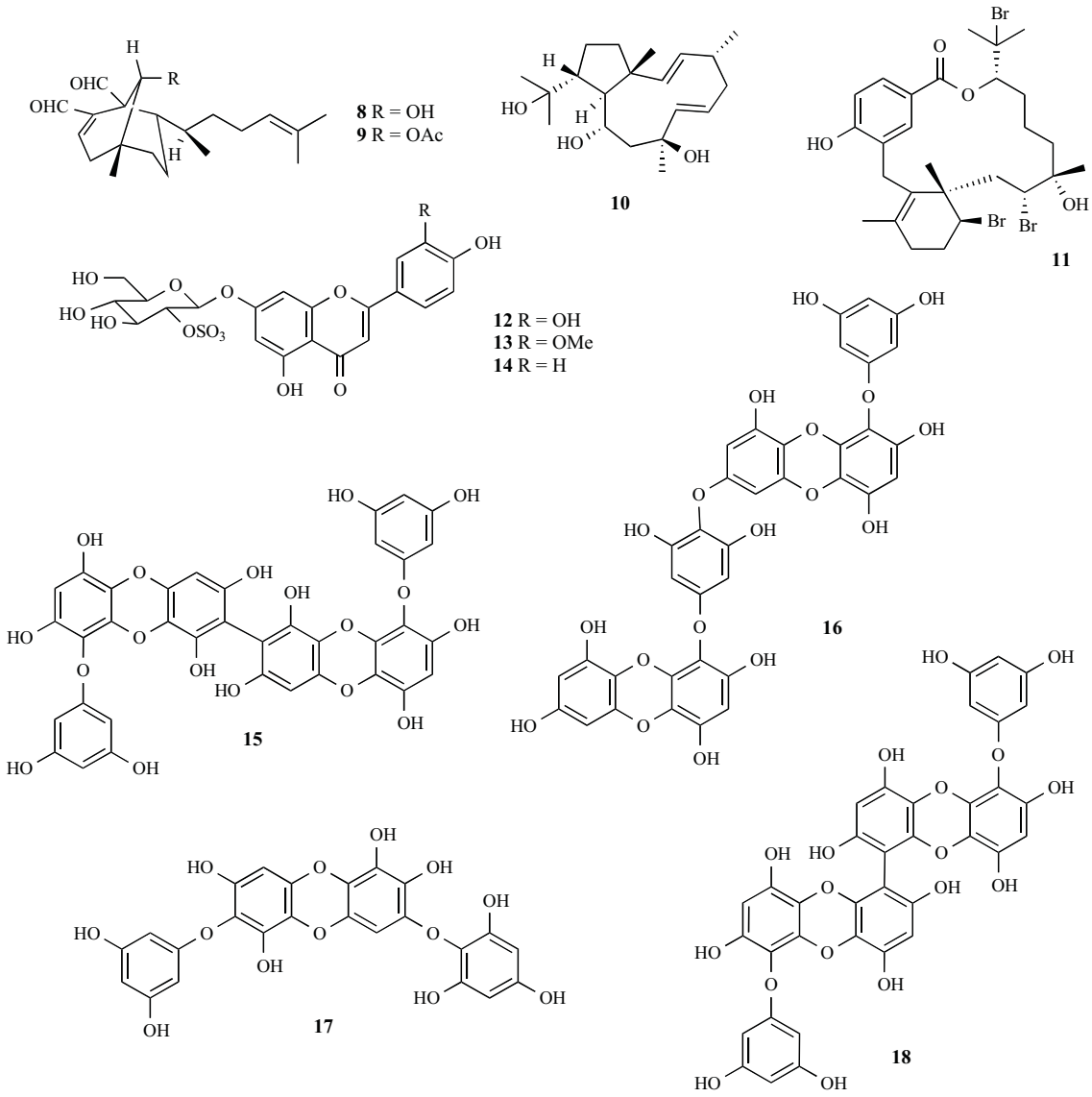


Fig. (2). Structures of **8**–**18** from microalgae, algae, or seaweeds.

3.3 Sulfated Polysaccharides

SPs comprise a complex group of macromolecules with a wide range of important biological activities, including anti-HIV activity.

Navicula directa is a diatom often collected at a sluice gate of deep-sea water. Naviculan (**19**, structure not shown), a sulfated polysaccharide isolated from *N. directa* as a novel antiviral agent, consisted of fucose, xylose, galactose, mannose, rhamnose, and other trace amounts of sugar moieties. Compound **19** showed an inhibitory effect on the formation of cell–cell fusion between HIV gp160- and CD4-expressing HeLa cells with an IC_{50} value of 53 μg/mL [40].

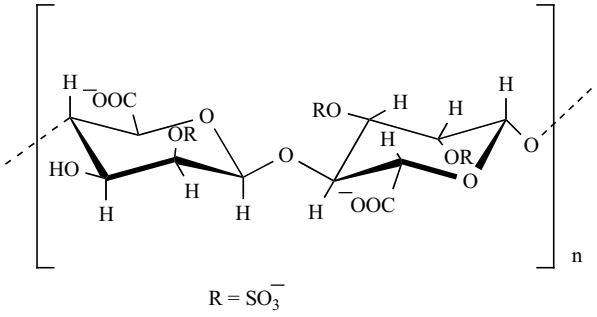
SPs from two red algae, *Sphaerococcus coronopifolius* (PSC, **20**, structure not shown) and *Boergeseniella thuyoides* (PBT, **21**, structure not shown), inhibited the replication of HIV at 12.5 μg/mL *in vitro* by directly controlling the appearance of new generations of virus and exerting potential virucidal effect. PSC (**20**) and PBT (**21**) were composed of galactose, 3,6-anhydrogalactose, uronics acids, and sulfate in ratios of 33.1%, 11.0%, 7.7%, and 24.0% (w/w), as well as 25.4%, 16.0%, 3.2%, and 7.6% (w/w), respectively [41].

The sulfated galactans GFP (**22**, structure not shown) extracted from the red algae *Grateloupia filicina* and GLPE (**23**, structure not shown) obtained from *Grateloupia longifolia* also showed antiretroviral activity *in vitro*. The sulfate ester groups were located at carbon 2 for GFP (**22**) as well as carbons 2 and 6 for GLPE (**23**). Both **22** and **23** showed potent anti-HIV-1 activities when added at the time of infection and 2 h post-infection (EC_{50} values, 0.010–0.003 μM; and EC_{90} values, 0.87–0.33 μM, respectively) with low cytotoxicity [42].

Galactofucan fraction EA1-20 (**24**, structure not shown) from the brown algae *Adenocystis utricularis* also exhibited anti-HIV-1 activity *in vitro* with IC_{50} values of 0.6 μg/mL [43], and sulfated fucans (**25**, structure not shown) from the seaweed species *Dictyota mertensii*, *Lobophora variegata*, *Spatoglossum schroederi*, and *Fucus vesiculosus* reportedly inhibited HIV RT [44].

Sulfated polymannuroguluronate (SPMG, **26**), a new form of sulfated polysaccharide extracted from brown algae with an average molecular mass of 8.0 kDa, is rich in 1,4-linked *β*-D-mannuronate and has an average of 1.5 sulfates and 1.0 carboxyl groups per sugar residue. Compound **26** exhibited both preventive and therapeutic potentials on HIV-1 entry [45, 46]. CD4 is considered to be the binding site of **26** in lymphocytes mediating its anti-AIDS activities [47]. The further study disclosed that SPMG-derived hexasaccharide residues represented the minimum sequence for binding to the gp120 molecule, and an octasaccharide was required for

minimum anti-HIV activity (representative structure of [ManA (2s)β1-4 ManA(2s/3s)]$_n$) [48]. SPMG (**26**) is a well-known novel anti-AIDS drug candidate now in phase II clinical trial.



26

Fig. (3). Structures of **26**.

The gel called Carraguard (**27**, structure not shown), a sulfated linear polysaccharide of D-galactose and 3,6-anhydro-D-galactose extracted from certain red algae (such as *Solieria chordalis* along the coasts of Brittany), has been shown to block HIV and other sexually transmitted diseases *in vitro* [49, 50]. However, phase III clinical trials of Carraguard (**27**) in South Africa did not show its efficacy in preventing the vaginal transmission of HIV [51].

3.4 Polypeptides

A number of lectins that bind high-mannose carbohydrates on the surface of viral envelopes were found to have antiviral activities [52]. Several studies have clearly shown that mannose-binding lectin (MBL) binds to HIV, which depended on the high-mannose glycans on gp120, whereas host cell glycans incorporated into virions did not contribute substantially to this interaction. Notably, MBL, given its specificity for the types of glycans abundant on gp120, interacted with all tested HIV strains [53]. Several algal lectins, such as griffithsin (GRFT), inhibited HIV-1 infection by binding to multiple mannose-rich glycans on the HIV-1 envelope glycoproteins [54, 55].

GRFT (**28**, structure not shown), a novel lectin isolated from the red algae *Griffithsia* sp. with a molecular weight of 12.7 kDa, displayed potent anti-HIV activity. GRFT potently inhibited the cytopathic effects of HIV-1 on T-lymphoblastic cells at 0.043 μM. GRFT also blocked cell–cell fusion between chronically infected and uninfected cells at sub-nanomolar concentrations [56].

A high mannose-binding lectin with preference for the cluster of α(1-2)-mannose from the green alga *Boodlea coacta* (BCA, **29**, structure not shown) was determined as a potent entry inhibitor of HIV-1. Compound **29** inhibited HIV-1 entry into host cells at an EC_{50} of 8.2 nM. A high association constant (3.71×10^8 M^{-1}) of **29** with the HIV envelope glycoprotein gp120 was demonstrated by surface plasmon resonance analysis [57].

A lectin, ESA-2 (**30**, structure not shown), from the red alga *Eucheuma serra* was also strictly specific for high mannose N-glycans and showed potent anti-HIV activity [58]. Compound **30** is structurally and evolutionary related to lectin *Oscillatoria agardhii* agglutinin (OAA) from the freshwater cyanobacterium *O. agardhii* NIES-204, and these lectins have recently been classified into a new lectin superfamily based on similarities in structure and carbohydrate-binding specificity [59].

4 SPONGES

4.1 Polyenynes

Five brominated polyacetylenic diols, diplynes A–E as well as three sulfated analogs, diplyne A 1-sulfate (**31**), diplyne C 1-sulfate (**32**), and 2-deoxydiplyne D sulfate (**33**), were isolated from the Philippine sponge *Diplastrella* sp. employing bioassay-guided fractionation using the HIV-1 IN inhibition assay. Diplynes A–E did not significantly inhibit IN (IC_{50} > 50 μg/mL), whereas the sulfated compounds (**31**–**33**) exhibited mild inhibition of HIV-1 IN (30 μg/mL to 90 μg/mL) [60]. Polyacetylenetriol (PAT, **34**), isolated from the Mediterranean sponge *Petrosia* sp., inhibited HIV-1 RT-associated DNA polymerase functions. RNA- and DNA-dependent DNA polymerases were strongly inhibited by **34** with IC_{50} values of 0.95 and 2.60 μM, respectively. Compound **34** showed selective inhibition of the DNA polymerase activities of HIV-1 RT, such that it did not affect the RNase H activity of HIV-1 RT [61]. Plakortide N (**35**), a new polyketide endoperoxide, was isolated from the marine sponge *Plakortis halichondrioides* collected in Puerto Rico [62]. Compound **35** exhibited anti-HIV activity in human peripheral blood mononuclear cells (PBMC) with an EC_{50} of 7.8 μM and EC_{90} (the 90% effective concentration) of 22.1 μM, but was remarkably cytotoxic to human T-lymphoma (CEM) and African green monkey kidney (*Vero*) cells [63].

4.2 Terpenes

Cyanthiwigin B (**36**), isolated from the Jamaican sponge *Myrmekioderma styx* together with other 26 homogeneous diterpenes, exhibited moderate activity against HIV-1 with an EC_{50} of 42.1 μM. The C-8 ketone group seemed important to anti-HIV-1 activity because only **36** exhibited anti-HIV-1 activity whereas the other cyanthiwigins without C-8 ketone group were inactive [64]. Hyrtiosal (**37**), a sesterterpenoid from the marine sponge *Hyrtios erectus*, inhibited HIV-1 IN binding to viral DNA at an IC_{50} of 9.60 μM by a new inhibitor binding site of the HIV-1 N-terminal domain at Ser17, Trp19, and Lys34 [65]. A new C22 furanoterpenoid, designated as dehydrofurodendin (**38**), isolated from a Madagascan sponge of the genus *Lendenfeldia*, was found to be a potent inhibitor of HIV-1 RT-associated DNA polymerase activities. The IC_{50} values calculated from dose–response curves were 3.2 and 5.6 μM for the RNA- and DNA-directed DNA polymerase functions, respectively. Compound **38** displayed inhibitive capacity against the RNase H activity of HIV-1 RT, albeit to a lesser extent, with an IC_{50} value of 29.5 μM [66].

Four sesquiterpenoid (hydro)quinones, isosemnonorthoquinone (**39**), ilimaquinone (**40**), smenospongine (**41**), and smenotronic acid (**42**), isolated from the South China Sea sponge *Dysidea arenaria*, displayed weak or moderate inhibitory activities on HIV-1 RT, with IC_{50} values of 239.7, 16.4, 176.1, and 130.4 μM, respectively [67]. A new pentacyclic sulfated hydroquinone named phuklona sulfate (**43**), apparently triterpene-derived, was isolated from the marine sponge *Haliclona* sp. collected near Phuket Island, Thailand, and its anti-HIV activity was evaluated by the classical cell-based cytoprotection assay established by National Cancer Institute (NCI) [68]. The NCI assay showed modest cytoprotection against HIV of **43** with an EC_{50} of 30 μg/mL and IC_{50} of 117 μg/mL [69].

4.3 Alkaloids

Aaptamine (**44**) and isoaaptamine (**45**) isolated from the sponge *Aaptos nigra*, together with several semisynthetic aaptamine derivatives, were tested for anti-HIV-1 and other activities. Although **44** and **45** showed significantly improved activities against HIV-1 in human PBM cells with EC_{50} values of 8.9 and 7.7 μM, respectively, their cytotoxicities against PBM, T-lymphoblastoid (CEM), and *Vero* cell lines were high (IC_{50} < 1.0, 3.3, and 23.1 μM for **44**, as well as 1.1, 1.4, 2.1 μM for **45**), respectively [70]. The structure-activity relationship (SAR) of the side-chain attachment at the C9 hydroxyl position of **45** for anti-HIV-1 activity was also investigated [71].

Ten pyrroloquinoline alkaloids from the Indopacific sponge *Zyzzya fuliginosa* were tested for activities of inhibiting HIV-1

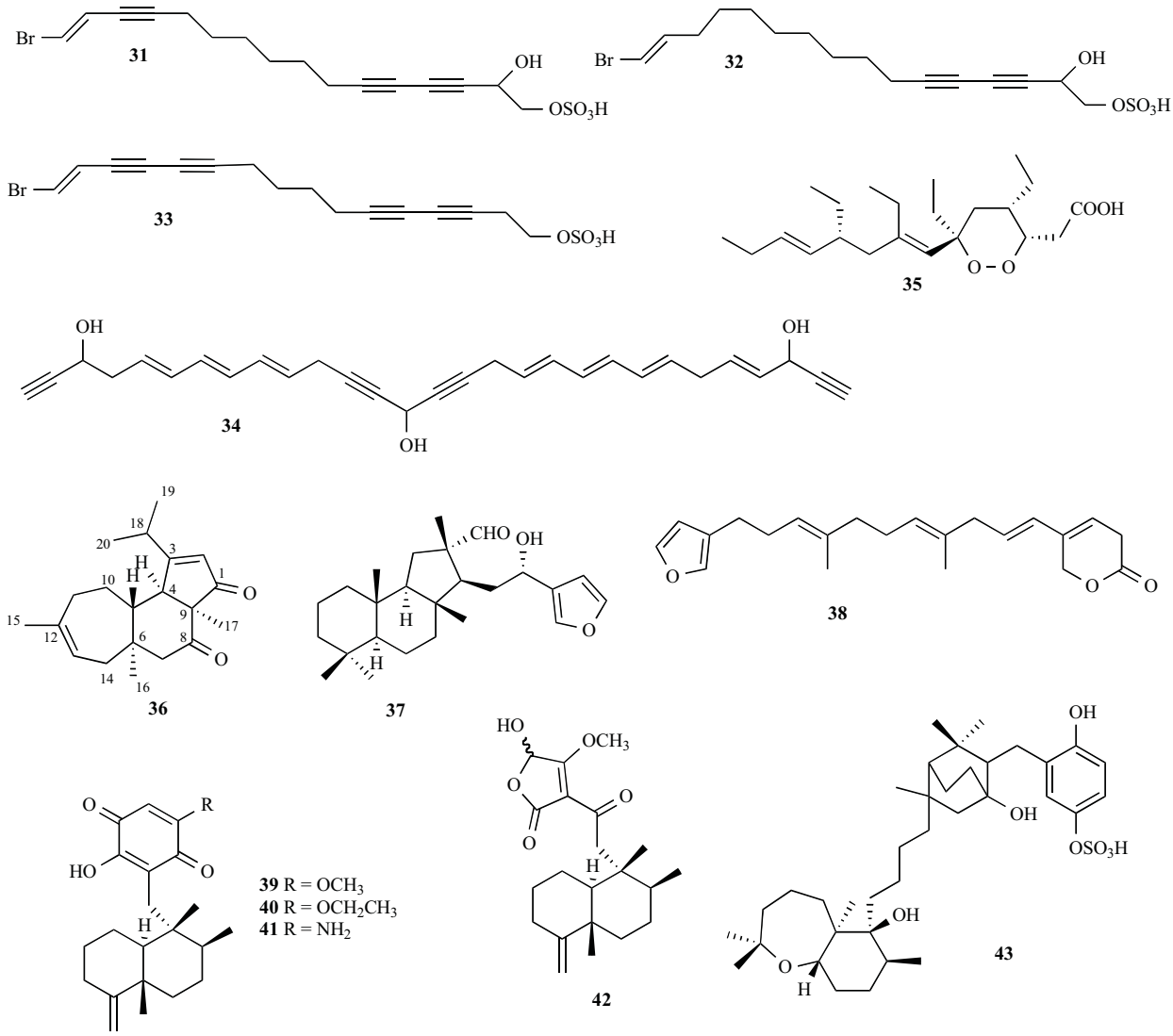


Fig. (4). Structures of **31**–**43** from sponges.

envelope-mediated cell fusion. Isobatzelline C (**46**) as well as makaluvamines A (**47**) and H (**48**) appeared to affect fusion potently as detected by the complete absence of α-galactosidase activity at concentrations less than 1 μg/mL. Dose-response experiments yielded IC_{50} values of ~200 nM for **46** and ~5 μM for **47** and **48** [72]. Ancorinolates A (**49**) and C (**50**), two unusual sulfamate indoles isolated from the sponge *Ancorina* sp., showed weak HIV-inhibitory activities (EC_{50} = 10.7 and 10.6 μg/mL, respectively) in a tetrazolium salt (XTT)-based anti-cytopathicity assay [73]. Three bisindole alkaloids, coscinamides A–C (**51–53**), with partial cytoprotective activities against HIV in the NCI assay, were isolated from an extract of the marine sponge *Coscinaderma* sp. collected in Papua, New Guinea [74, 75].

The marine sponge *Petrosia similis* afforded two compounds that were bis-quinolizidine alkaloids, petrosin (**54**) and petrosin A (**55**), which showed anti-HIV inhibition with IC_{50} values of 41.3 and 52.9 μM, respectively. MAGI cell assays indicated that the compounds inhibited the early steps of HIV replication. In an extracellular HIV-1 RT inhibition assay, **54** and **55** inhibited HIV-1 RT at IC_{50} values of 10.6 and 14.8 μM [76].

The pentacyclic guanidine alkaloids crambescidin 826 (**56**), crambescidin 800 (**57**), and fromiamycalin (**58**), isolated from the marine sponge *Monanchora* sp., inhibited HIV-1 envelope-mediated fusion (to block gp120-CD4 interactions) *in vitro* with IC_{50} values of 1–3 μM. Another guanidine alkaloid, dehydrocrambine A (**59**), from the same sponge showed weaker inhibition with an IC_{50} of 35 μM. In the extent of HIV-1 fusion in time-delayed experiments, **57** was added to the mixture of HIV-1 envelope-expressing cells and CXCR4 or CCR5 expressing cells after 15, 30, 45, 60, and 90 min. When fusion proceeded for 60 min or more prior to the addition of **57**, no protection was observed [77]. More polycyclic guanidine alkaloids from the sponge *Monanchora unguifera* and their activities against HIV-1 were tested. Ptilomycalin A (**60**) and crambescidin 800 (**57**) exhibited potent activities against HIV-1 virus with EC_{50} (EC_{90}) values of 0.011 (0.046) and 0.04 (0.12) μM, respectively. In contrast, dehydrobatzelladine C (**61**) as well as batzelladines C (**62**), L (**63**), M (**64**), and N (**65**) were less active with EC_{50} values of 1.6–7.7 μM and EC_{90} values of 7.1–25.6 μM [78]. Another study reported other synthetic guanidine alkaloid analogs that inhibited HIV-1 envelope glycoprotein-mediated cell–cell fusion [79], as well as HIV-1 protein Nef interactions with p53, actin, and $p56^{lck}$ [80].

Manzamine alkaloids from the Indonesian sponge of *Acanthostrongylophora* genus and *Petrosiidae* genus were tested for their anti-HIV-1 activities, and all of them showed anti-HIV-1 activities. In last decade, fifteen manzamine alkaloids (**66**–**80**) were tested and showed significant or moderate anti-HIV-1 activity with EC_{50} of 0.59~22.2 μM as listed in (Table **1**) [81-84].

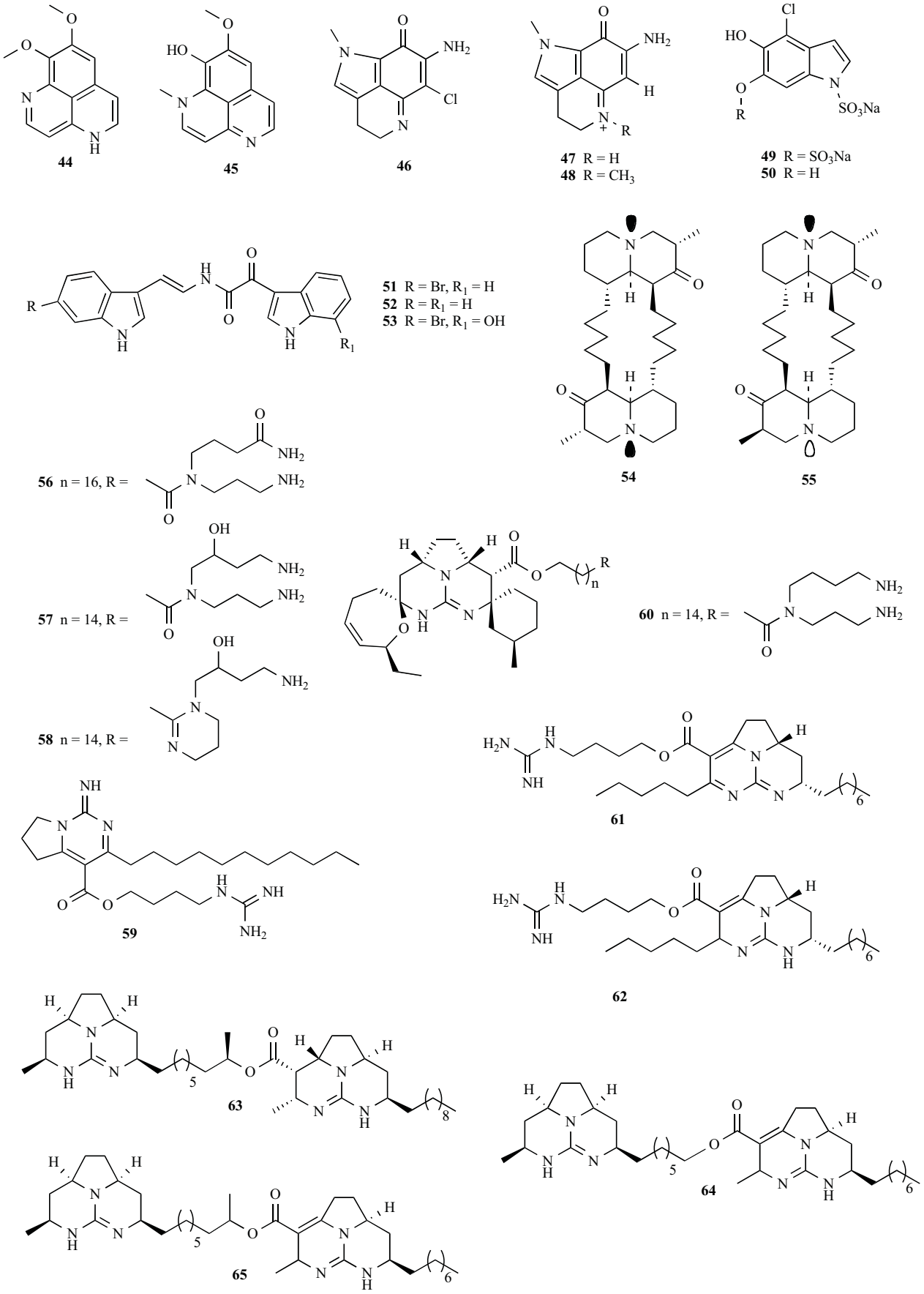


Fig. (5). Structures of **44**–**65** from sponges.

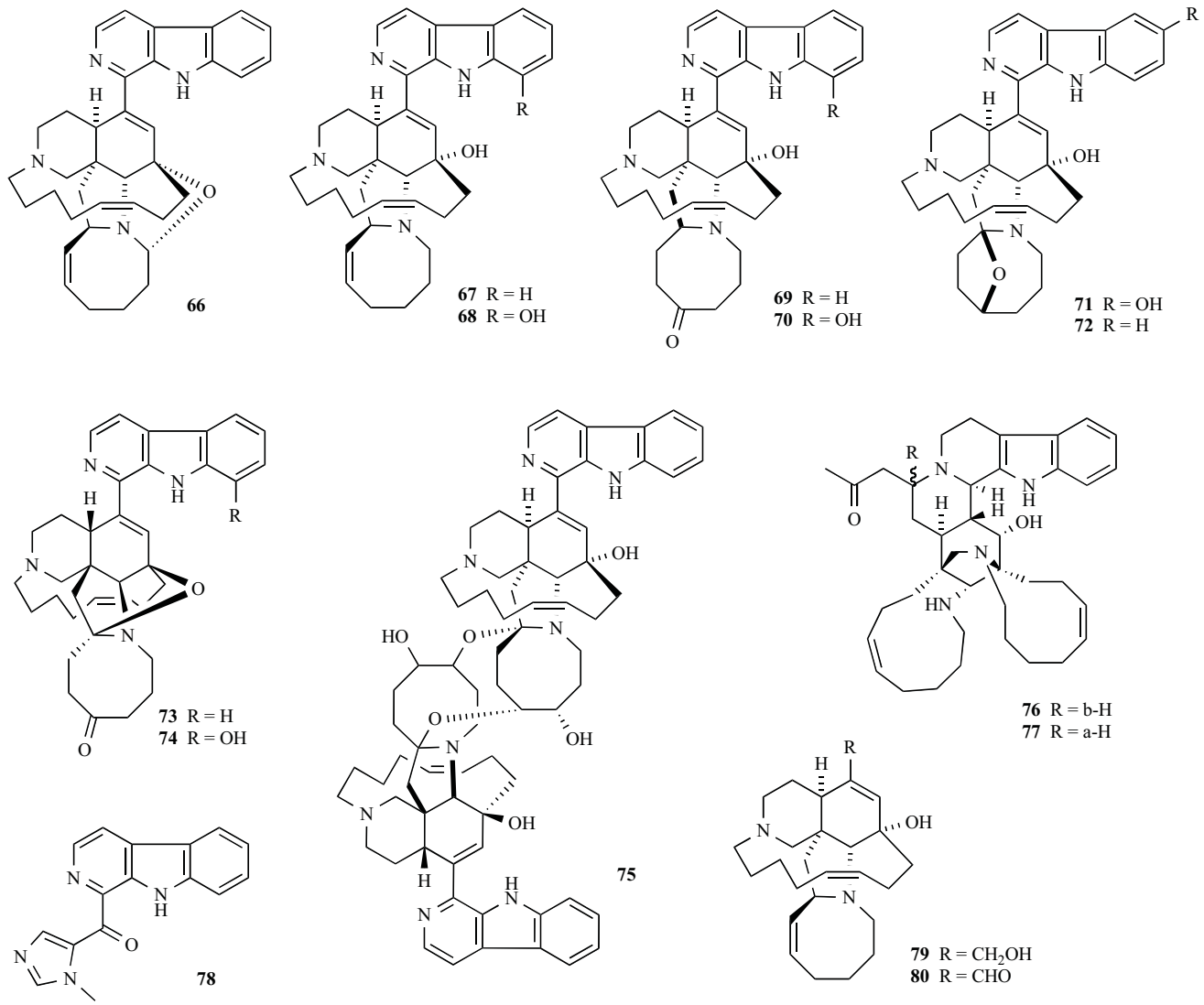


Fig. (6). Structures of **66**–**80** from sponges.

Table 1. Sponge Original Manzamine Alkaloids with Anti-HIV-1 Activities.

Manzamine alkaloids	EC_{50} (μM)	Ref.
12,28-Oxamanamine A (**66**)	22.2	[81, 82]
Manzamine A (**67**)	4.2	[81-83]
8-Hydroxymanzamine A (**68**)	0.59	[81-83]
Manzamines E (**69**)	13.1	[81-83]
Manzamines F (**70**)	7.3	[81-83]
Manzamine X (**71**)	2.3	[83]
6-Deoxymanzamine X (**72**)	1.6	[81, 83]
ent-12,34-Oxamanzamines F (**73**)	14.9	[81, 82]
ent-12,34-Oxamanzamines E (**74**)	17.5	[81, 82]
neo-Kauluamine (**75**)	2.3	[81, 83]
Manadomanzamines A (**76**)	7.0	[84]
Manadomanzamines B (**77**)	16.5	[84]
Xestomanzamine A (**78**)	11.2	[84]
Ircinol A (**79**)	4.3	[81, 83]
Ircinal A (**80**)	6.8	[81, 83]

Manzamine A (**67**) exhibited significant anti-HIV activity, whereas 12,28-oxamanzamine A (**66**), the oxidative cyclization product of manzamine A, did not show notable activity. To understand better the SAR and possible steric effects contributing to this oxidation, molecular modeling was performed. The results suggested that anti-HIV activity may be closely related to N-27 and the conformation of the N27-C34 eight-membered ring. Oral and intravenous pharmacokinetic studies of **67** in rats indicated that it had low metabolic clearance, a reasonably long pharmacokinetic half-life, and good absolute oral bioavailability at 20.6%. Hence, **67** can be subjected to further preclinical assessment and possible development [81].

Fifteen new DOPA [2-amino-3-(3',4'-dihydroxyphenyl) propionic acid]-derived pyrrole alkaloids named baculiferins A–O (**81**–**95**) were isolated from the Chinese marine sponge *Iotrochota baculifera*. Most of them were found to possess potent inhibitory activities against the HIV-1 IIIB virus, which had been encoded in MT4 (IC_{50} = 1.4–8.4 μg/mL) and HeLa-CD4-LTR-β-gal cell line (IC_{50} < 0.1–4.4 μg/mL). Baculiferins containing an N-acetic acid group, as found in **92** and **93**, had potent binding affinities toward both the Vif (viral infectivity factor of HIV-1) and APOBEC3G (an innate intracellular anti-viral factor). The lactam-type alkaloids **89** and **90** possessed potent affinities toward gp41 (Table **2**) [85].

A new sulfur-containing guanidino derivative, halichondria sulfonic acid (**96**), isolated from the marine sponge *Halichondria rugosa* Ridley & Dendy collected from the South China Sea, exhibited activity against HIV-1 with EC_{50} = 29 μg/mL and IC_{50} > 200 μg/mL [86].

4.4 Cyclic Depsipeptides

A series of potent HIV inhibitory cyclic depsipeptides has been described from a number of marine sponges, and the structural characteristics of this family of cyclic peptides include various unusual amino acid residues and unique N-terminal polyketide-derived moieties.

Papuamide A (**97**), a representative marine-derived cyclic depsipeptide from the Papua New Guinea sponges *Theonella mirabilis* and *Theonella swinhoei*, were reported to have cytoprotective activity against HIV-1 *in vitro* at the end of last century [87]. Continuous research showed that **97** acted as an entry inhibitor by preventing the HIV infection of host cells, and that this inhibition was not specific to the CCR5 or CXCR4 tropic virus. The inhibition of **97** did not target the key proteins involved in the viral entry process, such as binding to CD4 or HIV gp120. Compound **97** was also able to inhibit HIV pseudotype viruses expressing envelope glycoproteins from vesicular stomatitis virus or amphotropic murine leukemia virus, indicating that the mechanism of viral entry inhibition was not HIV-1 envelope glycoprotein specific. Time-delayed addition studies on the pseudotype viruses showed that **97** inhibited viral infection only at the initial stage of the viral life cycle [88]. At similar concentrations to **97**, papuamide B (**98**) also inhibited viral entry [88]. The total synthesis of **98** had been reported, and this synthesis opened the door for the elaboration of related natural products and their analogs, prompting SAR studies on these potent anti-HIV agents [89].

Papuamide A (**97**) shares many chemical features with this group, including an aliphatic tail, depsipeptide cyclization, a 3,4-dimethylglutamine residue, and an available tyrosine hydroxyl group glycosylated in mirabamides. Three new cyclic depsipeptides termed mirabamides A, C, and D (**99**, **100**, and **101**), isolated from the marine sponge *Siliquariaspongia mirabilis*, showed potent HIV-1 fusion-inhibiting activities at the early stages of HIV-1 entry. Compound **99** inhibited HIV-1 in neutralization and fusion assays with IC_{50} values between 40 and 140 nM, as did **100** and **101** (IC_{50} values between 140 nM and 1.3 μM for **100**, as well as 190 nM and 3.9 μM for **101**). Two new entities in mirabamides, including 4-chlorohomoproline (in **99** and **100)** and the unusual glycosylated amino acid *β*-methoxytyrosine 4′-*O*-α-L-rhamnopyranoside (in **99** and **101**), along with a rare N-terminal aliphatic hydroxy acid, proved useful for anti-HIV SAR studies [90]. Four other homogenous depsipeptides, mirabamides E–H (**102–105**), from the sponge *Stelletta clavosa* also showed strong inhibition of HIV-1 in a neutralization assay with IC_{50} values of 121, 62, 68, and 41 nM, respectively [91]. The primary feature that distinguished **102–105** from **99–101** was the presence of 2-amino-2-butenoic acid in place of threonine. The anti-HIV assay results suggested that this change improved activity, as evidenced by the twofold increase in potency of mirabamide G (**104**) compared with mirabamide C (**100**) [91].

Two new cyclic depsipeptides, neamphamide A (**106**) and homophymine A (**107**), both containing 11 amino acid residues and an amide-linked 3-hydroxy-2,4,6-trimethylheptanoic acid moiety, were isolated from a Papua New Guinea sponge *Neamphius huxleyi* and a New Caledonian sponge *Homophymia* sp., respectively. In a cell-

Table 2. The Anti-HIV-1 IIIB Activities of Baculiferins on MT-4 and MAGI Cells and their Binding Capacities (RU) Toward the Recombinant Proteins of Vif, APOBEC3G and gp41 [85].

	Anti-HIV-1 IIIB, IC_{50} (μg/mL)		Binding capacities (RU, baculiferins 20 μg/mL)		
	MT-4 cells	MAGI cells	Vif	APOBEC3G	gp41
81	7.6	3.7	110.7	170.6	17.1
82	2.2	1.3	152.4	89.7	12.9
83	8.4	1.2	296.4	885.9	115.8
85–86	4.6	2.7	361.9	991.5	108.7
87	3.2	4.4	446.8	571.8	125.1
88	1.4	1.3	259	578.5	76.2
89	/	/	638.4	/	1351.0
90	/	/	528.9	765.4	1485.4
91	5.5	< 0.4	448.4	/	523.3
92	7.0	4.1	1983.2	2170.7	469.0
93	5.0	0.2	1897.0	2463.5	379.7
94	4.4	< 0.1	596.8	/	952.9

/: Not detected

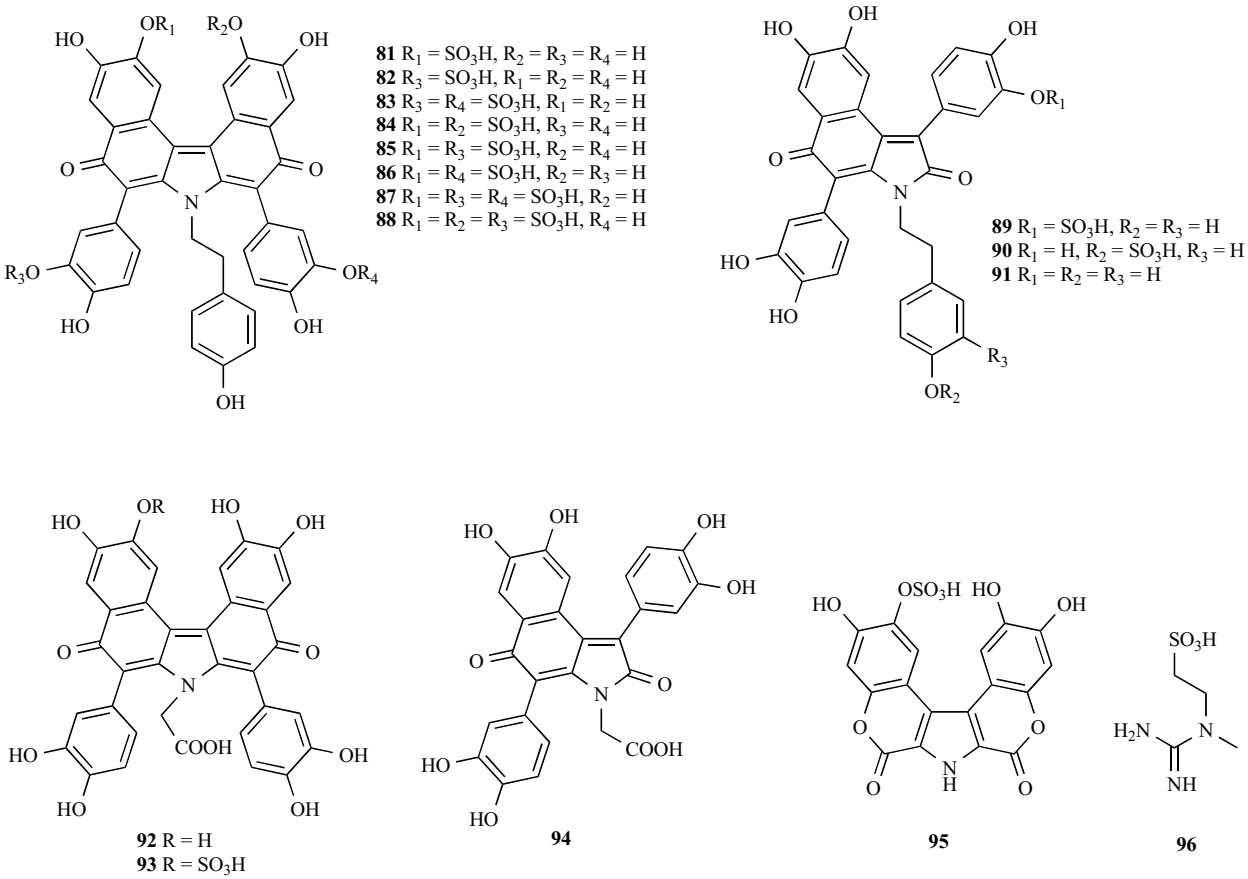


Fig. (7). Structures of **81**–**96** from sponges.

based XTT assay, **106** and **107** exhibited potent cytoprotective activities against HIV-1 infection with an EC_{50} of approximately 28 and 75 nM, respectively [92, 93].

Six new depsipeptides, celebesides A–C and theopapuamides B–D, were isolated from the sponge *S. mirabilis*. Celebeside A (**108**) neutralized HIV-1 in a single-round infectivity (inhibits HIV-1 entry) assay with an IC_{50} value of 1.9 ± 0.4 μg/mL, whereas the nonphosphorylated celebeside C was inactive at concentrations as high as 50 μg/mL. Theopapuamide B (**109**) was active in the neutralization assay with an IC_{50} value of 0.8 ± 0.3 μg/mL [94].

Cyclic koshikamides F (**110**) and H (**111**) were isolated from different deep-water specimens of *T. swinhoei* and *Theonella cupola*. These two koshikamides, with 17-residue depsipeptides containing a 10-residue macrolactone, inhibited HIV-1 entry against a CCR5-using viral envelope with IC_{50} values of 2.3 and 5.5 μM, respectively, whereas their linear counterparts (such as koshikamide C) were inactive [95] .

The novel structural features and anti-HIV activities of these peptidic metabolites have generated considerable interest. However, obtaining sufficient quantities of these metabolites for pharmacological and toxicological testing in natural resources is difficult. Therefore, the structural determination and total syntheses of these natural compounds are required. Progress on the synthesis and study of potential drugs based on cyclic peptides and depsipeptides has been extensively reviewed [96, 97].

4.5 Other Macromolecules

A novel actin-depolymerizing marine toxin, mycalolide B (**112**, structure not shown), first isolated from the sponge *Mycale* sp. [98], blocked the production of HIV-1 from primarily infected T-lymphoblastoid and clonically infected monocytoid cells in a concentration-dependent manner. Compound **112** did not disturb the synthesis of viral proteins, but rather inhibited the transport processes of HIV-1 in the host cells [99].

The anti-HIV activities of 23 polysaccharide pellets from the marine sponges *Erylus discophorus*, *Cliona celata*, and *Stelletta* sp. collected in the Northeastern Atlantic were tested. *Stelletta* sp. pellets, although quite rich in polysaccharides (up to 97.3%), showed only modest bioactivity (<36% HIV-1 inhibition). *E. discophorus* pellets were among the richest in terms of polysaccharide content (up to 98%), and the most active against HIV-1 (up to 95% inhibition). Chromatographic fractionation of the polysaccharide pellets obtained from a specimen of *Erylus discophorus* (B161) yielded only modestly active fractions. However, it can be inferred that the active molecule is most probably a high-molecular-weight sulfated polysaccharide (>2000 kDa) whose possible mechanism is the prevention of viral attachment and entry (fusion inhibitor) [100].

5. OTHER MARINE ANIMALS

5.1 Small Molecules

Lamellarin α-20 sulfate (**113**), isolated from an unidentified ascidian collected from the Arabian Sea coast of India, was known for its inhibition of HIV-1 IN in 1999 [101]. Another study reported that **113** was a selective inhibitor of HIV IN both *in vitro* and *in vivo*, and SAR studies showed that the sulfate group was critical for the HIV-1 IN-inhibiting activity of **113** [102, 103]. The total synthesis of **113** and some of its analogs was reported [104], and recent research on **113** as well as other lamellarin sulfates showed good correlation between the inhibitory effects on HIV-1 infection and

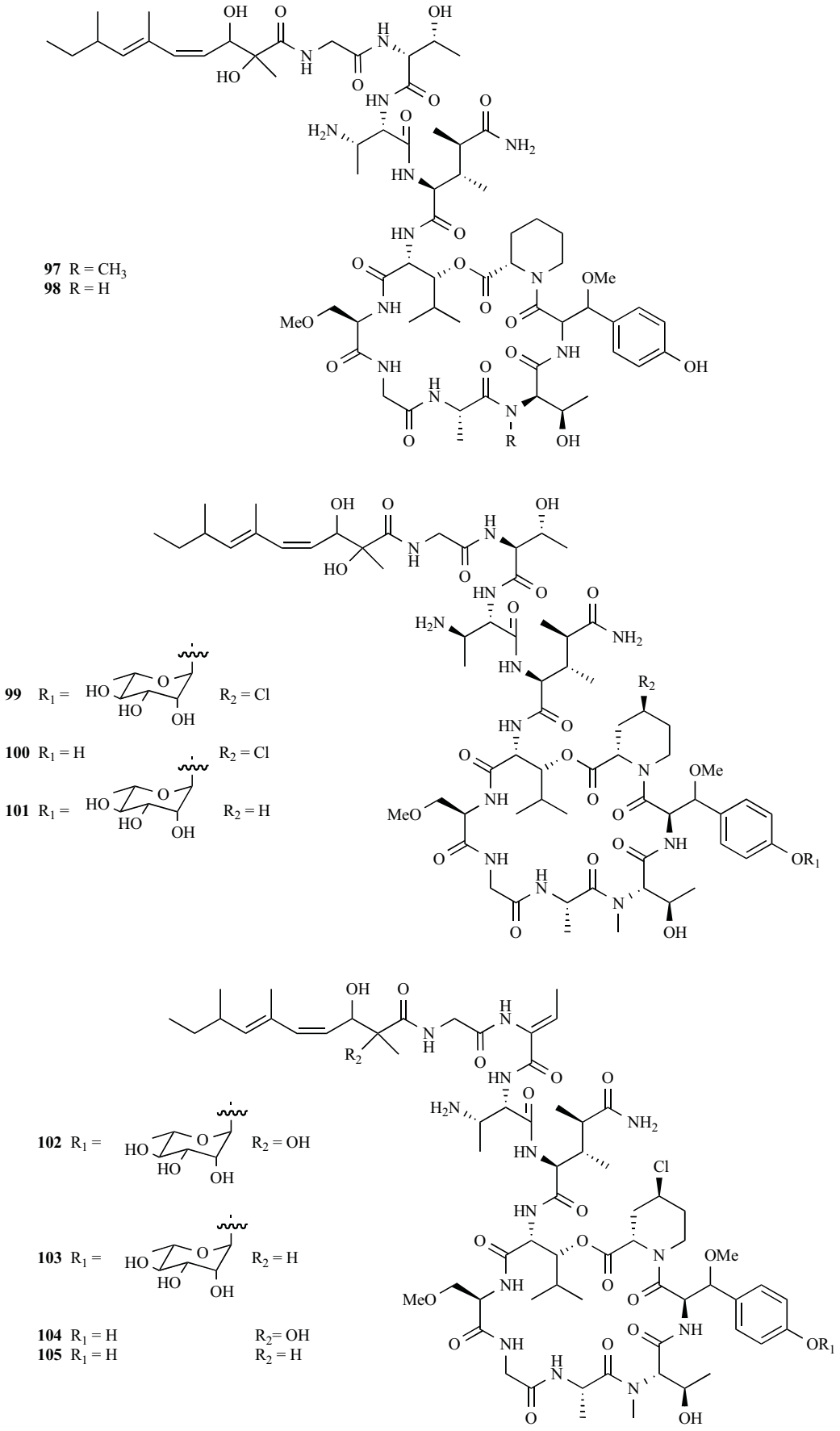


Fig. (8). Structures of **97**–**105** from sponges.

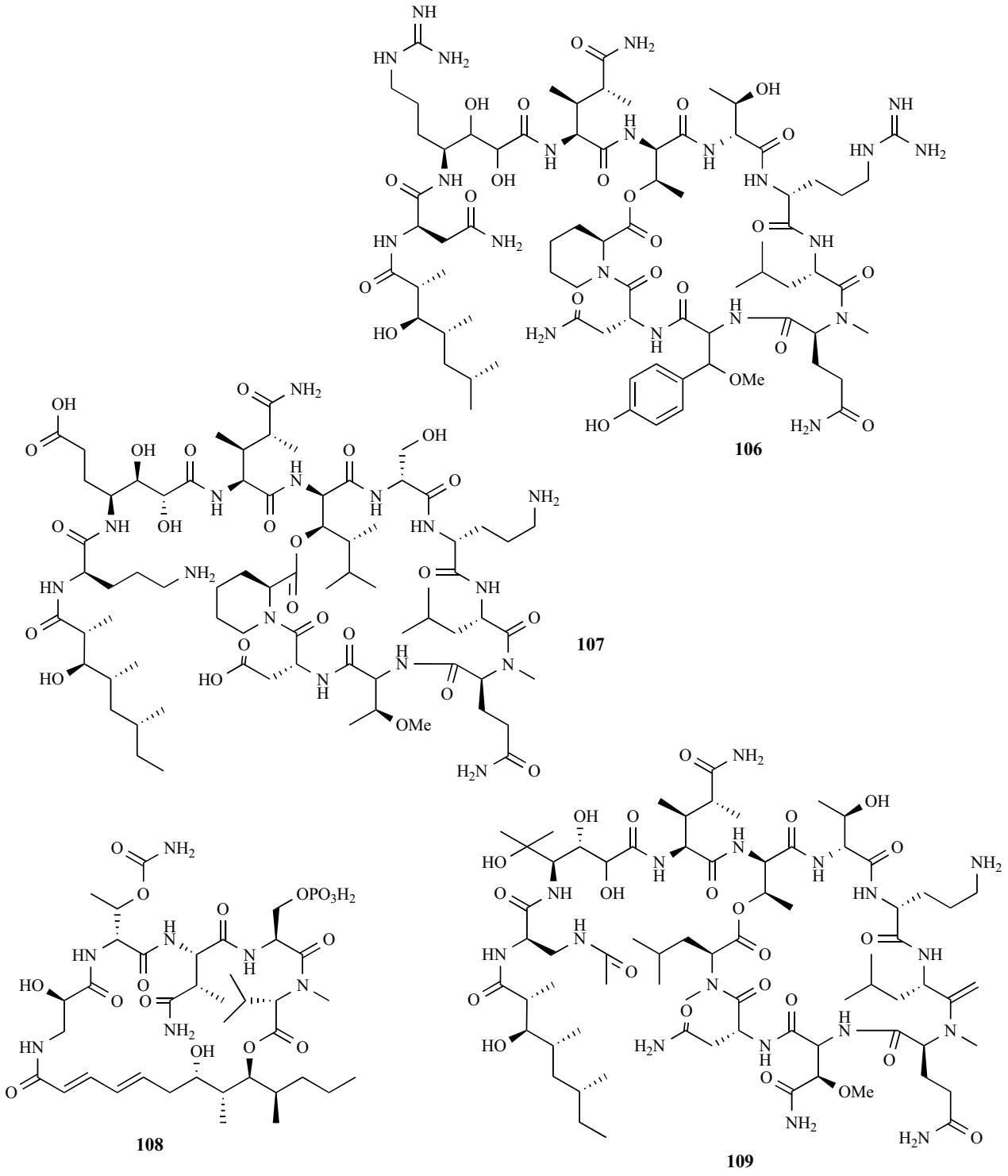


Fig. (9). Structures of **106**–**109** from sponges.

HIV-1 envelope glycoprotein-mediated cell–cell fusion. This finding suggested that the mechanism of action of **113** and other lamellarin sulfates were entry inhibition and not than IN inhibition [105].

Polyisoprenoids named didemnaketals A and B isolated from a Palauan ascidian *Didemnum* sp. with unclear stereochemistry showed inhibitory activity to HIV-1 PR [106]. The relative and absolute stereochemistry of didemnaketal B (**114**) was determined using a combination of degradation and derivatization experiments, chiral shift methods, and comparison of fragments to known compounds in further studies [107].

Two triterpene glycosides **115** and **116** isolated from the sea cucumber *Telenata ananas* collected from the Andaman and Nicobar Islands (India) exhibited inhibitory activity (K_i) of 30 and 5.1μM, respectively, in a chemokine receptor subtype 5 (CCR5) assay. Both compounds did not show any significant inhibition in a CXCR2 assay at 50 μM, suggesting their selectivity for the CCR5 receptor [108].

Macrocyclic lactone bryostatin-5 (**117**), one of the bryostatins first isolated from the marine organism *Bugula neritina*, can block stromal cell-derived factor-1-induced chemotaxis via the

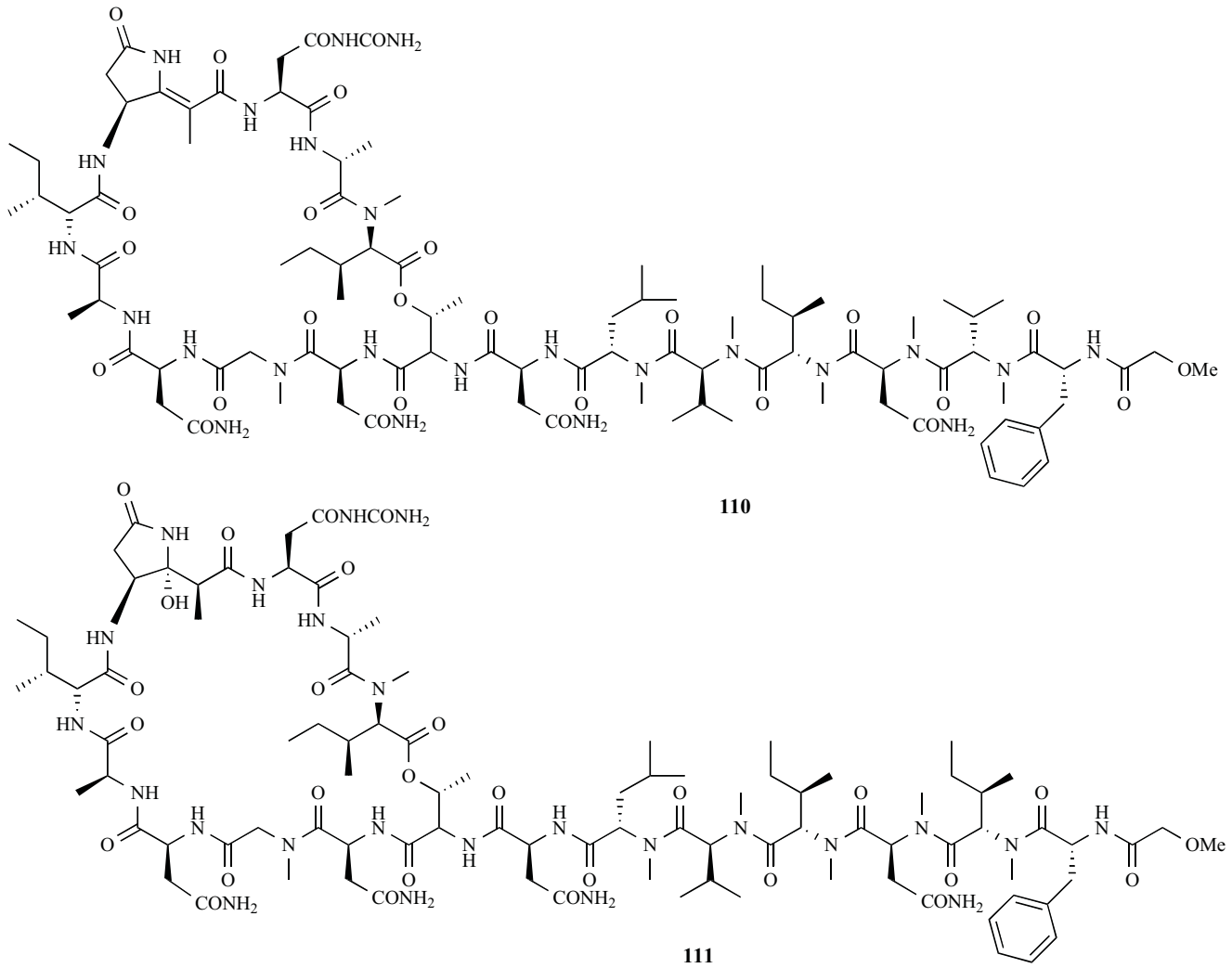


Fig. (10). Structures of **110**–**111** from sponges.

desensitization and downregulation of cell surface CXCR4 receptor, one of the principal coreceptors for the CD4-mediated HIV infection of T cells [109]. Bryostatin-1 (**118**), another bryostatin from *B. neritina* clinically used as an anti-cancer agent, also revealed anti-HIV activity against R5- and X4-tropic viruses in a receptor-independent manner, and partly via transient decrease in CD4/CXCR4 expression. The dual role of **118** inhibiting acute HIV-1 infection and reactivating latent HIV via a novel PKC pathway without T-cell activation and cytotoxicity may be a beneficial adjunct to the treatment of HIV [110, 111].

5.2 Peptides and Polypeptides

Mollamide B (**119**), a cyclic hexapeptide isolated from the Indonesian tunicate *Didemnum molle*, exhibited marginal activity against HIV-1 in human PBM cells with an EC_{50} value of 48.7 μM *in vitro* [112]. A hexapeptide (**120**, structure not shown) with a mass of 683 Da separated from aqueous extracts of a marine worm *Eunicidae* sp. inhibited HIV-1 IN with an IC_{50} value of 30 μM. The proposed structure of Asp-Leu-Hse-His-Ala-Gln (**120**) was the first example of a natural peptide containing an amino acid homoserine residue [113]. Peptide fragments P (**121**, structure not shown) and Q (**122**, structure not shown) of 19 amino acids, isolated from the Mediterranean mussel *Mytilus galloprovincialis*, prevented HIV-1 infestation at 20 μM under a simple phenotypic assay for drug susceptibility of HIV-1 using a CCR5 and CXCR4-expressing HeLa/CD4 cell clone (MAGIC-5B) [114, 115].

Lectins have the potential to block the binding of HIV to target cells, preventing HIV infection and dissemination. In recent years, marine invertebrates have gained interest as new sources of unusual lectins, some of which are considered potential anti-HIV agents.

CVL (**123**, structure not shown), a 30 kDa β-galactose-specific lectin isolated from the marine worm *Chaetopterus variopedatus*, inhibited the cytopathic effect induced by HIV-1 and the production of viral p24 antigen at the early stage of virus replication with EC_{50} = 0.0043 and 0.057 μM, respectively. CVL also blocked the cell–cell fusion process of HIV-infected and uninfected cells with an EC_{50} value of 0.073 μM. Finally, CVL was shown to abort 86% and 21% of HIV-1 entry into host cells at concentrations of 0.33 and 0.07 μM, respectively [116].

Five other lectins isolated from marine invertebrates were also reported to exhibit anti HIV-1 activity *in vitro* [117]. The lectins DTL (**124**, structure not shown) and DTL-A (**125**, structure not shown) were isolated from the ascidium *Didemnum ternatanum*. DTL, a GlcNAc-specific lectin with a shorter carbohydrate-binding site, was revealed to possess hybrid-type N-chains rather than carbohydrate chains of the complex and highly mannose type. DTL-A, a GlcNAc/GalNAc and heparin-binding lectin, can be used to detect glycoproteins containing α-bound residues of GlcNAc/GalNAc and some SPs due to the peculiarities of its carbohydrate specificity. The Ca^{2+}-independent lectins SVL-1 (**126**, structure not shown) and SVL-2 (**127**, structure not shown) were obtained from the marine worm *Serpula vermicularis*. Compound **126** was a mannan-binding

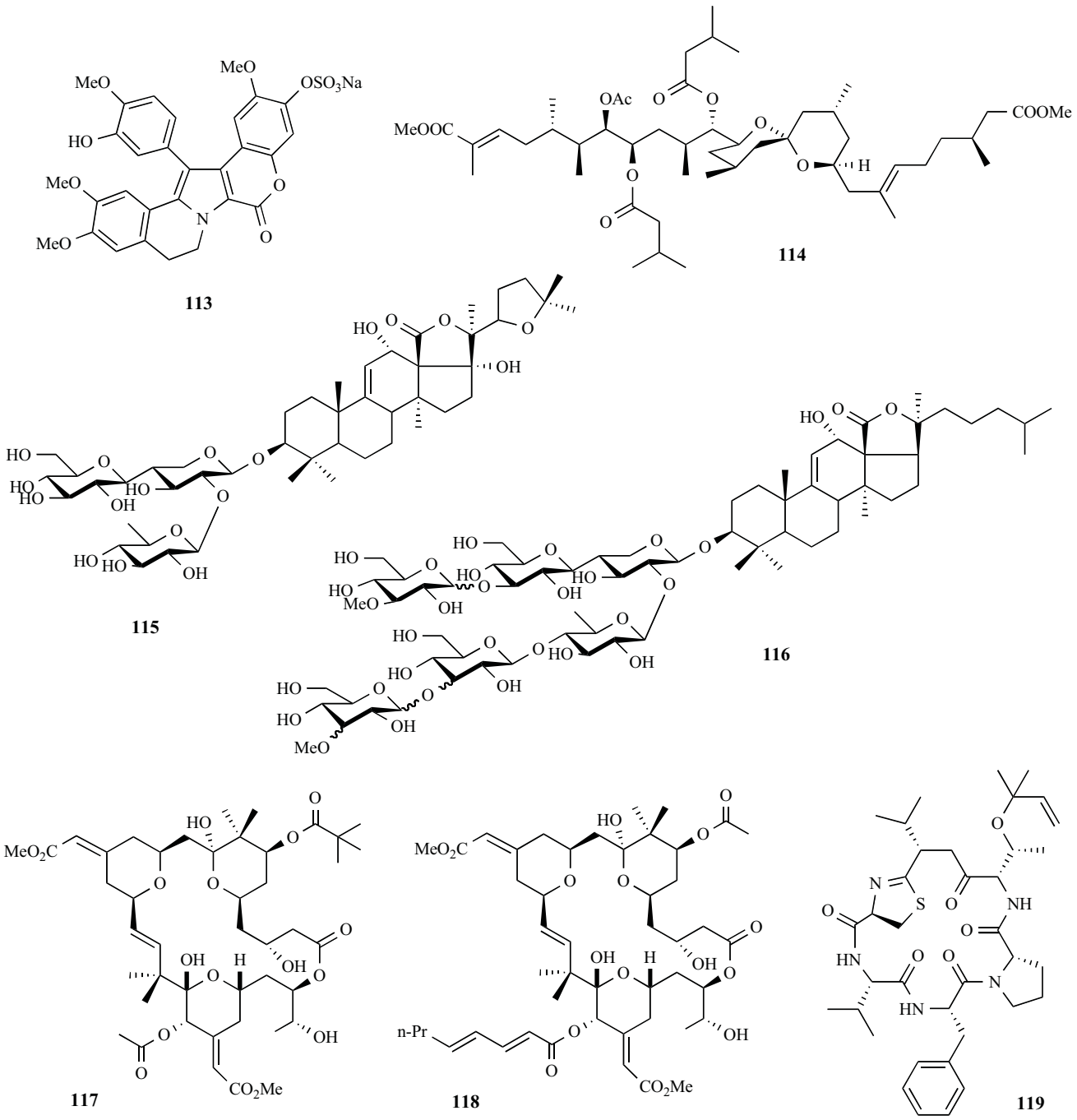


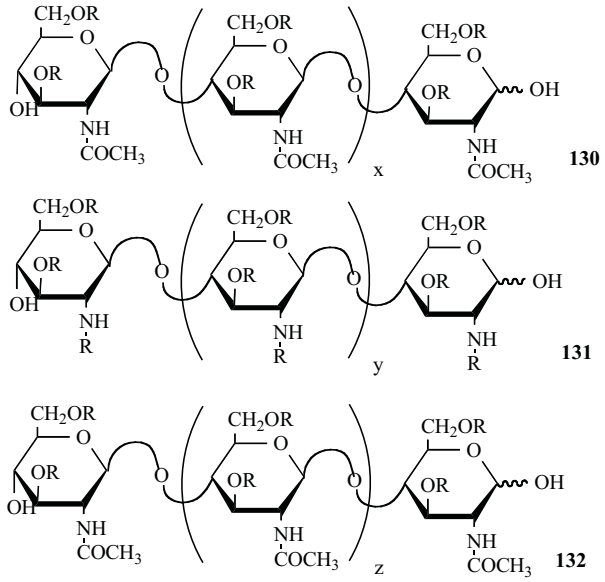
Fig. (11). Structures of **113**–**119** from other marine animals.

lectin with a molecular mass of 65 kDa, whereas **127** was a GlcNAc-specific lectin with a molecular mass of 50 kDa [118]. CGL (**128**, structure not shown), a lectin isolated from the mussel *Crenomytilus grayanus*, exhibited a very high affinity to mucin-type glycoproteins. Lectins **124**, **125**, **127**, and **128** inhibited HIV-1 IIIB-induced syncytium formation in C8166 cells with EC_{50} values of 0.002, 0.36, 0.15, and 27.88 μg/mL, respectively. These lectins, **124**–**128**, were confirmed to inhibit virus replication effectively at EC_{50} values of 0.006, 0.59, 89.1, 0.23, and 45.7 μg/mL, respectively. Among them, **124**, **125**, and **128** displayed activity against cellular fusion between the H9/HIV-1 chronically infected cells and C8166 uninfected cells at the following concentrations (EC_{50}): 1.37, 6.97, and 35.12 μg/mL, respectively. DTL (**124**) may be regarded as a potential candidate for the development of novel antiviral agents [117].

5.3 Polysaccharides

Chitin, a long-chain polymer of N-acetylglucosamine, is widely distributed as the principle component of living organisms such as insects, fungi, crustaceans, and invertebrates. Chitosan, a partially deacetylated polymer of N-acetylglucosamine, is produced commercially by the deacetylation of chitin [119]. Aminoethyl-chitosan (**129**, structure not shown), prepared from 50% deacetylated chitosan, showed activity against HIV-1 with an IC_{50} value of 17 μg/mL [120]. Sulfated chitin (**130**) and chitosan (**131**) had a variety of biological functions, including anti-HIV-1 [121]. Sulfated chitooligosaccharide (SCOS, **132**), which was synthesized by a random sulfation reaction, reportedly possessed anti-HIV activity at low molecular weights (3–5 kDa). Compound **132** exhibited inhibitory activities on viral entry and viral-cell fusion by blocking the bind-

ing between HIV-1 gp120 and CD4 cell surface receptor. These observations indicated that **132** may be a novel candidate for the development of anti-HIV-1 agents [122].



R = H or SO_3H, x > y, y >> z

Fig. (12). Structures of polysaccharides **130**–**132**.

CONCLUSION AND PERSPECTIVES

In the last decade (2002–2011), 132 anti-HIV natural products were obtained from marine organisms, which was quantitatively equal to the total of those reported before 2002, based on another two reviews in 2003 (Table **3**). Among these anti-HIV bioactive marine natural products, both before or after 2002, more than half were derived from marine sponges [14]. Sponge-derived alkaloids and cyclic depsipeptides were demonstrated to be good resources of anti-HIV agents. For example, sponge original manzamine alkaloids were attractive with their anti-HIV activities. Meanwhile the SAR and pharmacokinetic studies of them suggested manzamine A (**67**) could be subjected to further preclinical assessment and possible development [81]. Notably, some macromolecules, such as lectins from algae and marine invertebrates and SPs from algae, were also considered as potential anti-HIV agents, such as SPMG (**26**), a well-known novel anti-AIDS drug candidate now in phase II clinical trial [48].

In this review, the biological targets or acting sites of anti-HIV constituents are given focus, and are listed in (Table **4**). Most of anti-HIV constituents reported before 2002 were HIV RT and PR inhibitors, which contributed to the majority of clinical applications today, together with their various combinations. Due to the drug-resistance and adverse effects of HIV RT and PR inhibitors, the new classes of anti-HIV agents, HIV IN inhibitors and entry inhibitors, have become attractive in recent years [123]. Among all the marine original anti-HIV constituents in this review, 7 HIV IN inhibitors were discovered and 37 compounds (or constituents) showed anti-HIV activities at the HIV entry process, or blocked

Table 3. Number of Marine Natural Products According to the Marine Organisms Resources and Chemical Classes in Present and previous Reviews.

Resources and chemical classes	This review (2002–2011)	Gochfeld [7]# (Before 2002)	Tziveleka [8] (Before 2002)
Total Number	132	107	138
1. Microbes	7	/	4
2. Microalgae, Algae and Seaweed	23	10	25
Terpenes	4	/	4
Phenols	7	/	/
Sulfoglycolipids and lipids	/	3	11
Polysaccharides	9	5	8
Polypeptidess	3	2	2
3. Sponge	82	84	76
Polyenynes	5	3	10
Lactones	/	7	/
Sterol	/	15	11
Phenols	/	7	6
Terpenes	8	22	20
Alkaloids	52	23	22
Cyclic depsipeptides	15	5	4
Polysaccharides	1	1	1
Proteins	1	1	2
4. Other Marine Animals	20	13	33
Sterol	/	/	12
Other Small Molecules	6	8	14
Peptides and Polypeptides	10	3	5
Polysaccharides	4	2	2

There is one reference in 2002 in this review, which has been excluded in this table.

Table 4. The Chemical Types of the Reviewed Marine Natural Products and their Anti-HIV Activities Towards Different Targets.

Chemical Type	Compounds	Origin of marine organisms	Anti-HIV activity	Ref.
Polyenyne	Diplyne A 1-sulfate (**31**)	Sponge: *Diplastrella* sp.	Inhibit HIV IN	[60]
	Diplyne C 1-sulfate (**32**)			
	2-Deoxydiplyne D sulfate (**33**)			
	Polyacetylenetriol (**34**)	Sponge: *Petrosia* sp.	Inhibit HIV RT	[61]
	Plakortide N (**35**)	Sponge: *Plakortis* Sponge	Anti-HIV	[63]
Phenol	Rezishanone (**4**)	Fungus: *Trichoderma viride*	Inhibit HIV RT	[24]
	Griseorhodin A (**5**)	Actinomycete: *Streptomyces* sp.	Inhibit HIV RT	[26]
	Thalassiolin A (**12**)	Seaweed: *Thalassia testudinum*	Inhibit HIV IN	[36]
	Thalassiolin B (**13**)			
	Thalassiolin C (**14**)			
	8,8'-Bieckol (**15**)	Brown alga: *Ecklonia cava*	Inhibit HIV RT and PR	[37]
	8,4'''-Dieckol (**16**)			
	Diphlorethohydroxycarmalol (**17**)	Brown alga: *Ishige okamurae*	Inhibit HIV RT and IN	[38]
	6,6'-Bieckol (**18**)	Brown alga: *Ecklonia cava*	Inhibit HIV RT and HIV-1 entry	[39]
Sterol	Cholesta-7,22-diene-3b,5a,6b-triol (**1**)	Fungus: *Trichoderma* sp.	Inhibit HIV PR	[20]
Terpenoid	Breviones F (**2**)	Fungus: *Penicillium* sp.	Inhibit HIV replication in C8166 cells	[22]
	(6*R*)-6-Hydroxydichotoma-3,14-diene-1,17-dial (**8**)	Brown alga: *Dictyota menstrualis*	Inhibit HIV RT	[29]
	(6*R*)-6-Acetoxidichotoma-3,14-diene-1,17-dial (**9**)			
	Dolabelladienetriol (**10**)	Brown alga: *Dictyota pfaffii*	Inhibit HIV RT	[34]
	Bromophycolides A (**11**)	Red algae: *Callophycus serratus*	Anti-HIV for HIV strains UG/92/029 and 96USHIPS7	[35]
	Cyanthiwigin B (**36**)	Sponge: *Myrmekioderma styx*	Anti-HIV	[64]
	Hyrtiosal (**37**)	Sponge: *Hyrtios erectus*	Inhibit HIV IN	[65]
	Dehydrofurodendin (**38**)	Sponge: genus *Lendenfeldia*	Inhibit HIV RT	[66]
	Isosemnonorthoquinone (**39**)	Sponge: *Dysidea arenaria*	Inhibit HIV RT	[67]
	Ilimaquinone (**40**)			
	Smenospongine (**41**)			
	Smenotronic acid (**42**)			
	Phuklona sulfate (**43**)	Sponge: *Haliclona* sp.	Anti-HIV	[69]
	Didemnaketals B (**114**)	Ascidian: *Didemnum* sp.	Inhibit HIV-1 PR	[106]
	Triterpene glycoside 1 (**115**)	Sea cucumber: *Telenata Ananas*	Inhibits HIV-1 entry: selectivity binds to CCR5	[108]
	Triterpene glycoside 2 (**116**)			
Alkaloid	Sorbicillactone A (**3**)	Fungus: *Penicillium chrysogenum*	Protect H9 cells against HIV-1 and inhibit the viral proteins expression	[23]
	Integramycin (**6**)	Actinomycete: *Actinoplanes* sp.	Inhibit HIV IN	[27]
	Xiamycin (**7**)	Actinomycete: *Streptomyces* sp.	Inhibit HIV entry: blocks CCR5	[28]
	Aaptamine (**44**)	Sponge: *Aaptos nigra*	Anti-HIV	[70]
	Isoaaptamine (**45**)			
	Isobatzelline C (**46**)	Sponge: *Zyzzya fuliginosa*	Inhibiting HIV-1 Env-mediated cell fusion	[72]
	Makaluvamines A (**47**)			
	Makaluvamines H (**48**)			
	Ancorinolate A (**49**)	Sponge: *Ancorina* sp.	Anti-HIV	[73]
	Ancorinolate C (**50**)			
	Coscinamide A (**51**)	Sponge: *Coscinaderma* sp.	Anti-HIV	[74, 75]
	Coscinamide B (**52**)			
	Coscinamide C (**53**)			

(Table 4) contd….

Chemical Type	Compounds	Origin of marine organisms	Anti-HIV activity	Ref.
	Petrosin (**54**)	Sponge: *Petrosia similis*	Inhibited early steps of HIV replication; inhibit HIV-1 RT	[76]
	Petrosin A (**55**)			
	Crambescidin 826 (**56**)	Sponge: *Monanchora* sp.	Inhibiting HIV-1 Env-mediated cell fusion: block gp120-CD4 interactions	[77]
	Crambescidin 800 (**57**)			
	Fromiamycalin (**58**)			
	Dehydrocrambine A (**59**)			
	Ptilomycalin A (**60**)	Sponge: *Monanchora unguifera*	Anti-HIV	[78]
	Dehydrobatzelladine C (**61**)			
	Batzelladine C (**62**)			
	Batzelladine L (**63**)			
	Batzelladine M (**64**)			
	Batzelladine N (**65**)			
	12,28-Oxamanamine A (**66**)	Sponge: *Acanthostrongylophora* genus and *Petrosiidae* genus	Anti-HIV	[81-83]
	Manzamine A (**67**)			
	8-Hydroxymanzamine A (**68**)			
	Manzamine E (**69**)			
	Manzamine F (**70**)			
	Manzamine X (**71**)			
	6-Deoxymanzamine X (**72**)			
	ent-12,34-Oxamanzamines F (**73**)			
	ent-12,34-Oxamanzamine E (**74**)			
	neo-Kauluamine (**75**)			
	Manadomanzamine A (**76**)	Sponge: *Acanthostrongylophora* sp.	Anti-HIV	[84]
	Manadomanzamine B (**77**)			
	Xestomanzamine A (**78**)			
	Ircinol A (**79**)	Sponge: *Acanthostrongylophora* genus and *Petrosiidae* genus	Anti-HIV	[81, 83]
	Ircinal A (**80**)			
	Baculiferin A (**81**)	Sponge: *Iotrochota baculifera*	Anti-HIV	[85]
	Baculiferin B (**82**)			
	Baculiferin C (**83**)			
	Baculiferin D (**84**)			
	Baculiferin E (**85**)			
	Baculiferin F (**86**)			
	Baculiferin G (**87**)			
	Baculiferin H (**88**)			
	Baculiferin I (**89**)		Inhibit of HIV-1 entry: binds to gp41	
	Baculiferin J (**90**)			
	Baculiferin K (**91**)		Anti-HIV	
	Baculiferin L (**92**)		Inhibit of HIV-1 entry: binds to Vif and APOBEC3G	
	Baculiferin M (**93**)			
	Baculiferin N (**94**)		Anti-HIV	
	Baculiferin O (**95**)			
	Halichondria sulfonic acid (**96**)	Sponge: *Halichondria rugosa*	Anti-HIV	[86]
	Lamellarin α-20 sulfate (**113**)	Ascidian	inhibitor of HIV IN and HIV-1 Env-mediated cell–cell fusion	[101, 102, 105]
Macrolide	Bryostatin-5 (**117**)	Bryozoan: *Bugula neritina*	Inhibits HIV-1 entry: binds to CXCR4	[109]
	Bryostatin-1 (**118**)			[110]
Peptide	Mollamide B (**119**)	Tunicate: *Didemnum molle*	Anti-HIV	[112]

(Table 4) contd….

Chemical Type	Compounds	Origin of marine organisms	Anti-HIV activity	Ref.
	Asp-Leu-Hse-His-Ala-Gln (**120**)	Marine worm: *Eunicidae* sp.	Inhibit HIV-1 IN	[113]
	Fragment P (**121**)	Mussel: *Mytilus galloprovincialis*	Anti-HIV	[114, 115]
	Fragment Q (**122**)			
Depsipeptide	Papuamide A (**97**)		Inhibit of HIV-1 entry: binds both the X4 and R5	[87]
	Papuamide B (**98**)			
	Mirabamide A (**99**)	Sponge: *Siliquariaspongia mirabilis*	Inhibiting HIV-1 cell fusion	[90]
	Mirabamide C (**100**)			
	Mirabamide D (**101**)			
	Mirabamide E (**102**)	Sponge: *Stelletta clavosa*	Anti-HIV	[91]
	Mirabamide F (**103**)			
	Mirabamide G (**104**)			
	Mirabamide H (**105**)			
	Neamphamide A (**106**)	Sponge: *Neamphius huxleyi*	Anti-HIV	[92]
	Homophymine A (**107**)	Sponge: *Homophymia* sp	Anti-HIV	[93]
	Celebeside A (**108**)	Sponge: *Siliquariaspongia mirabilis*	Inhibits HIV-1 entry	[94]
	Theopapuamide B (**109**)			
	Koshikamide F (**110**)	Sponge: *Theonella swinhoei* and *Theonella cupola*	Inhibits HIV-1 entry: binds to CCR5	[95]
	Koshikamide H (**111**)			
Polypeptide	GRFT (**28**)	Red algae: *Griffithsia* sp	Inhibited HIV-1 on T-lymphoblastic cells; Inhibit cell–cell fusion	[56]
	BCA (**29**)	Green alga: *Boodlea coacta*	Inhibit of HIV-1 entry: binds to gp120	[57]
	ESA-2 (**30**)	Red algae: *Eucheuma serra*	Anti-HIV	[58]
	Mycalolide B (**112**)	Sponge: *Mycale* sp	Inhibit the transport processes of HIV-1	[98]
	CVL (**123**)	Marine worm: *Chaetopterus variopedatus*	Inhibit virus replication and block the cell–cell fusion	[116]
	DTL (**124**)	Ascidian: *Didemnum ternatanum*	Inhibit virus replication and block cell fusion	[117]
	DTL-A (**125**)			
	SVL-1 (**126**)	Marine worm: *Serpula vermicularis*	Inhibit virus replication	
	SVL-2 (**127**)			
	CGL (**128**)	Mussel: *Crenomytilus grayanus*	Inhibit virus replicationand block cell fusion	
Polysaccharide	Naviculan (**19**)	Diatom: *Navicula directa*	Inhibit cell–cell fusion	[40]
	PSC (**20**)	Red algae: *Sphaerococcus coronopifolius*	Inhibit HIV-1 replication	[41]
	PBT (**21**)	Red algae: *Boergeseniella thuyoides*		
	GFP (**22**)	Red algae: *Grateloupia filicina*	Anti-HIV	[42]
	GLPE (**23**)	Red algae: *Grateloupia longifolia*		
	Galactofucan fractions (**24**)	Brown alga: *Adenocystis utricularis*	Anti-HIV	[43]
	Sulfated fucans (**25**)	Seaweed: *Dictyota mertensii*, *Lobophora variegata*, *Spatoglossum schroederi* and *Fucus vesiculosus*	Inhibit HIV RT	
	SPMG (**26**)	Brown alga	Inhibit of HIV-1 entry: binds to CD4	[45-47]
	Carraguard (**27**)	Red alga: *Solieria chordalis*	Anti-HIV	[49]
	Aminoethyl-chitosan (**129**)		Anti-HIV	[120]
	Sulfated chitin (**130**)			[121]
	Sulfated chitosan (**131**)			
	Sulfated chitooligosaccharide (**132**)		Inhibits HIV-1 entry: binding between gp120 and CD4 cell surface receptor	[122]

HIV-1 cell–cell fusion targeting envelope glycoproteins or cell surface receptors. For example, recent research on lamellarin α-20 sulfate (**113**), known for its inhibition of HIV-1 IN, showed good correlation between the inhibitory effects on HIV-1 infection and HIV-1 envelope glycoprotein-mediated cell–cell fusion, as well as other lamellarin sulfates. These results suggested that lamellarin sulfates have a novel anti-HIV-1 activity besides the previously reported integrase activity inhibition, possibly at a viral entry step of HIV-1 replication. The finding of the new mechanism of anti-HIV of the lamellarin sulfates makes them more promising to be new lead anti-HIV agents [105].

The first anti-HIV drug as entry inhibitor licensed by the US FDA in 2003, T-20 showed promising in treating HIV/AIDS patients who failed to respond to current RT and PR inhibitors. However, as a polypeptide drug, T-20 has several limitations, such as lack of oral availability and high cost of production. Therefore, the development of small-molecule non-peptidic HIV entry inhibitors is more promising [4]. High-throughput screening (HTS) assays for screening HIV entry inhibitors targeting envelope glycoproteins (gp120/gp41) [124-126] and cell surface receptors (CD4/ CCR5/CXCR4) [127] were developed and optimized in the last decade. A novel target-specific HTS assay for identifying inhibitors of gp120 interaction with dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) was reported and considered useful in screening HIV entry inhibitors [125]. A number of small-molecule HIV entry inhibitors were identified in natural or synthetic compounds [128-131]. With the increasing number of HIV entry inhibitors being developed, more diversified combinations of anti-HIV drugs can be designed, e.g., combinations of HIV entry inhibitors targeting distinct sites in HIV envelope glycoproteins or in the cellular receptors, and/or with RT and PR inhibitors, as well as with newly developed anti-HIV drugs like IN inhibitors or maturation inhibitors [132]. These combinations should be expected to be significantly synergistic against HIV infection, resulting in reduced adverse effects and delayed emergence of drug resistance.

The decade's worth of extensive researches covered in this review revealed that significant progress was achieved in the discovery of marine-origin anti-HIV agents. Nevertheless, there are several questions worthy of consideration, especially in two aspects below. First, the number of marine-origin anti-HIV natural products obtained in the last decade is approximately equal to the number reported for about three decades before 2002. However, this number still lags behind that of anti-HIV natural products from terrestrial plants [1]. Particularly, most of the discovered small-molecule HIV entry inhibitors, which have been focused on in recent years, are originate from terrestrial plants and soil microbes [2, 3]. Second, natural products with novel structures are viable sources of new bioactive constituents. The probability of discovering novel bioactive compounds from marine organisms is continuously increasing, whereas the probability is declining with regard to terrestrial sources. More than 1000 new marine natural products are annually identified in recent years [11-13]. However, compared to the larger number of previously known natural products found to be active in various assays, fewer new compounds have been discovered with anti-HIV potential within the period covered in this review.

The progress of marine-origin anti-HIV agents in the last decade depended on the development of marine natural product chemistry. There is no report on the large-scale or systematic anti-HIV screening in marine natural products, and a few marine natural products studies guided by anti-HIV activities. Therefore, the discovery of anti-HIV agents is not as remarkable as those of anticancer and antibiotic agents of marine origin. Anti-HIV screening tests are also not as popular as cytotoxicity or antibacterial tests, and most newly discovered compounds are still untested for their anti-HIV activities. Notably, interest in the discovery of new anti-HIV targets and in the development of new screening methods considerably increased in the past decade [4]. Consequently, many new anti-HIV constituents were discovered from known natural products. Nevertheless, the widespread use of screening assays for new targets needs time.

In conclusion, numerous marine-origin anti-HIV agents are still waiting to be discovered. Finding the new natural products in new marine living resources, particularly those living in deep-sea and special marine environments, is still one of the important approaches to find new active agents. Moreover, screening anti-HIV activities in the existing marine natural product library, as well as semi-synthetic modifications of anti-HIV natural products, needs to be continued to discover anti-HIV agents, especially toward new targets (e.g., HIV envelope glycoproteins or cell surface receptors). These endeavors require close cooperation among researchers of marine natural products and anti-HIV screening. This cooperation is key to the greater progress of marine-origin anti-HIV agents discovery in the next decade.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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