Marine Microbes-Derived Anti-Bacterial Agents

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Abstract: This review covers natural products isolated from marine microorganisms including bacteria, fungi and actinomycetes published in the recent years. The emphasis is mainly about new compounds, together with their anti-bacterial activities, source organisms and country of origin, biosynthetic studies as well as the mechanisms involved in their anti-bacterial activities.

Keywords: Marine microorganism, bacteria, fungi, actinomycetes, natural products, antibacterial activity, marine antibiotics, co-culture.

1. INTRODUCTION

Almost three quarters of the earth's surface is covered by seas and oceans, whose resources are varied and vast and partly comprise of fish, shellfish, other animals, algae, and microorganisms *etc*. Since marine organisms live in a significantly different environment from those of terrestrial ones, it is reasonable to suppose that their secondary metabolites will differ in chemical structures and pharmacological activities considerably [1-5]. The rapid growth in chemistry of marine organisms and marine derived natural compounds over the past five decades has led to the discovery of a surprisingly large number of novel structures, some of which have been in different clinical studies (Table **1**) [6-10].

As people abuse the most commonly prescribed antibiotics, such as penicillin and cefoperazone *etc*, bacteria have rapidly turn resistant to them [23-25]. Thus bacterial infection, particularly from some MDR (Multi-drug resistant) strains, such as MRSA (Methicillin-resistant *Staphylococcus aureus*), remains a serious threat to human lives [26-28]. Consequently the identification and development of novel anti-bacterial agents is of paramount importance to human health [29]. For example, cephalosporin was the first marine antibiotic obtained by fermentation of genetically modified *Cephalosporium acremonium*.

Marine microbiology is developing quickly in several countries with a distinct focus on bioactive secondary metabolites. Analysis of the secondary metabolites of the marine microbes up to 2008 indicated that 30% of marine natural products have antibacterial activities towards many MDR strains. In this review, the anti-bacterial natural products isolated from marine microbes from 2004 to 2008 were reviewed.

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2. BACTERIA

A novel compound named zafrin (**1**, Fig. **1**) was isolated from a crude extract of a marine bacterium identified as *Pseudomonas stutzeri.* It was the first time discovered that *P. stutzeri* produced an antibiotic. Zafrin was active against several human pathogenic strains, including *S. aureus* and *Salmonella typhi*. The MIC (minimal inhibitory concentration) was between 50 μg/mL and 75 μg/mL for Gram-positive bacteria while between 75 μg/mL and 125 μg/mL for Gram-negative bacteria. Uzair *et al* studied further about the zafrin's mechanism of against *Bacillus subtilis.* Some preliminary experiments showed that its lysis pattern resembled that of nisin (50 μg/mL), which disrupted the cell membrane. So it was proposed that zafrin's mode of action was *via* the disruption of cytoplasmic membrane for its hydrophobic and lipophilic chemical structure. The experiment showed that the killing rate of zafrin was faster than ampicillin, vancomycin or tetracycline, which also suggested a different action mode of this compound [30].

Ariakemicins A **2** and B **3** (Fig. **1**), which were unusual linear hybrid polyketide-nonribosomal peptide antibiotics, were discovered from the fermentation extract of marine gliding bacterium *Rapidithrix* sp. isolated from the muddy land alongside the Ariake Island Sea in southwest Japan. The antibiotic mixture selectively inhibited the growth of Gram-positive bacteria, among which *S. aureus* was the most affected. From the structures of compound **2** and **3** that incorporate 3-hydroxy-4-methoxyphenyl and 5-methyloxazole rings along with unsaturated polyketide chain, it could be deduced that they were siphonazoles from *Herpetosiphon* sp. [31], a marine gliding bacterium belonging to phylum *Chloroflexi* [32].

A new lipopeptide antibiotic Tauramamide **4** and its ethyl ester **5** (Fig. **2**) were produced by cultures of the marine bacterial isolate *Brevibacillus laterosporus* PNG276 obtained from tissues of an unidentified tube worm collected off the

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Table 1. Marine-Derived Compounds Launched and in Clinical Trials Since 2005

Lead compound	Name	Source	Action mechanism	Development status	Company	Indication	Ref
Ziconotide	Prialt	conotoxin	**calcium channel blocker**	launched	Elan	pain	[11]
Xen-2174	χ-MrIA	conotoxin	**norepinephrine transporter inhibitor**	Phase I/IIa		Cancer pain	[12]
Tro-dusquemine(MSI-1436)	Tro-dusquemine(MSI-1436)	Dogfish shark *Squalus acanthias*	**protein tyrosine phosphatase 1B inhibitor**	Phase I	Genaera	Type II diabetics	[13]
Plitidepsin (aplidin)	Plitidepsin (aplidin)	Ascidian	**VEGF/VEGFR1 inhibitor, G1/G2 phase cell cycle inhibitor**	Phase II	PharmaMar	Cancer	[14]
Halichondrin B	Eribulin (E7389, NSC-707389)	Sponge	**tubulin assembly inhibitor**	Phase II/III	Eisai	Cancer	[15]
Hemiasterlin	E7974		**tubulin assembly inhibitor**	Phase I	Eisai	Cancer	[16]
Psammaplin A	Panobinostat (LBH-589)		**HDAC inhibitor**	Phase I/II/III	Novartis	Cancer	[17]
Bryostatin	Bryostatin 1		**protein kinase C inhibitor**	Phase I/II	NCI	Cancer	[18]
Jorumycin	Zalypsis (PM00104/50)	Nudibranch *Jorunna funebris*	**DNA binding and transcriptional activity**	Phase I	PharmaMar	Cancer	[19]
Dolastatin 15	Tasidotin (synthadotin, ILX-651)	Cyano-bacteria	**tubulin assembly inhibitor**	Phase II	Genzyme	Cancer	[20]
Dolastatin 10	Soblidotin (YHI-501, TZT-1027, auristatin PE)	Cyano-bacteria	**tubulin assembly inhibitor**	Phase II under preparation	Yakult Honsha (ASKA Pharmaceutical)	Cancer	[21]
Kahalalide F	Kahalalide F	Green algae	**alter lysosomal membrane function**	Phase II	PharmaMar	Cancer	[22]
	PM02734		**alter lysosomal membrane function**	Phase I	PharmaMar		

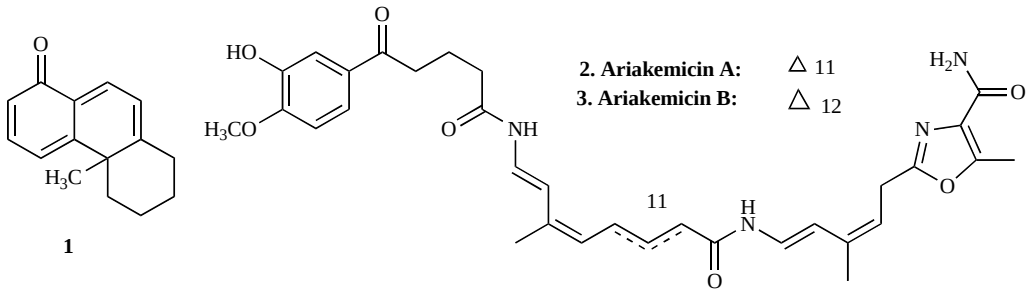

Fig. (1). The structures of compound **1-3**.

coast of Loloata Island, Papua New Guinea. Both of the compounds showed potent and selective activities against an important Gram-positive human pathogen *Enterococcus* sp., while compound **5** showed relatively weaker activity against MRSA. Tauramamide **4** was a new lipopeptide antibiotic that contained five amino acids, in which Tyr and Leu had the D configuration, while Arg, Trp, and Ser were L configuration, while compoud **5** was acylated at its N-terminus, which were both hallmarks of a non-ribosomal peptide synthase biosynthetic origin [33].

The known synthetic compound 1-methyl-1,4-dihydroquinoline **6** (Fig. **2**) was isolated from a natural source for the first time, which produced by *P. aeruginosa* isolated from ribbonfish (Baluchistan coast, Pakistan), and showed good spectra of activities which inhibited *Vibrio*

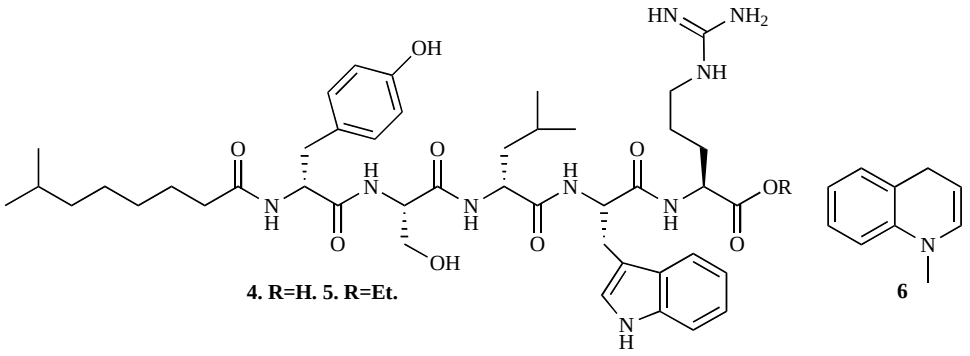

Fig. (2). The structures of compound **4-6**.

alginolyticus, *Shewanella putrifacians*, *Escherichia coli*, *B. subtilis*, MRSA, MSSA(Methicillin-sensitive *Staphylococcus aureus*), *S. epidermidis* sp, etc. Its MIC for Gram-positive bacteria ranged from 50 μg/mL to 75 μg/mL and for Gram-negative bacteria ranged from 75 μg/mL to 100 μg/mL [34].

The salt-tolerant actinobacteria which grow in 200 g/L NaCl isolated from the sediment from the Bay of Bengal produced an active compound **7** (Fig. **3**), which was inhibitory to three Gram-positive and three Gram-negative MDR bacteria, seven non-clinical Gram-positive, four Gram-negative bacteria and five fungi (MIC: 3.5-4.0 μg/mL) [35]. The *Streptomyces* species isolated from sediment (Laguna de Terminos, Gulf of Mexico) yielded Gutingimycin **8** and trioxacarcins D–F **9–11** (Fig. **3**) [36, 37]. The absolute configuration of gutingimycin **8** was determined by X-ray analysis [38], while the absolute configurations of compound **9-11** were determined by consulting the X-ray of gutingimycin **8** and the known stereochemistry of L-trioxacarcins A and B. The trioxacarcins and gutingimycin **8** exhibited strong antibacterial activities against a range of test organisms, while trioxacarcin A and trioxacarcin D **9** were also potently antiplasmodial [39].

A deep-sea sediment (Ayu Trough, western Pacific Ocean) *Streptomyces* sp. yielded the cytotoxic streptokordin **12** [40]. A *Streptomyces* strain separated from sediment (Laguna de Terminos, Gulf of Mexico) produced anthraquinones **13** and **14** (Fig. **3**) [41], both of which displayed moderate activities against *S. aureus* and *Streptomyces viridochromogenes*. Cultivation of the obligate marine *Streptomyces* strain CNQ-418 isolated from a sediment sample collected near La Jolla, CA, at a depth of 51 m, furnished the marinopyrroles A **15** and B **16** (Fig. **3**) [42]. Though configurationally stable at room temperature, M-(-)-marinopyrrole A racemized at elevated temperatures and yielded the non-natural P-(+)-atropo-enantiomer. The compounds displayed noteworthy activities in antimicrobial bioassays. For example, compound **15** and **16** showed MIC values less than 2 μmol/L against MRSA. A new strain of *Halomonas* sp. (Bacterial) isolated from seawater (East Frisian Wadden Sea, Germany), when cultured with the addition of anthranilic acid to the medium, produced a different secondary metabolite pattern including the new 2-aminophenoxazin-3-one derivatives **17–19** (Fig. **3**). Of these, **17** and **18** were good inhibitors to Gram-positive bacteria [43].

A new 24-membered ring lactone, macrolactin S **20** (Fig. **3**), together with macrolactin A and macrolactin B, were isolated in our laborarory from a culture broth of marine *Bacillus* sp., which derived from sea sediment of East China Sea [44, 45]. They all exhibited antimicrobial and antifungal activities, of which macrolactin S **20** was the most potent one. Macrolactin S **20** inhibited the growth of *E. coli* with a MIC value of 0.2 μg/mL, while inhibited the growth of *S. aureus* and *B. subtilis* with MIC values of 0.7 μg/mL and 100 μg/mL, respectively. Besides, there are some other natural products from the marine bacteria with weak antibacterial activities collected in Table **2** (Fig. **4**).

3. FUNGI

The marine-derived fungus *Emericella* sp., which was isolated from the surface of a green alga of the genus *Halimeda* at Madang Bay in Papua New Guinea, produced emericellamides A **40** and B **41** (Fig. **5**), when co-cultivated with the marine actinomycete *Salinispora arenicola* isolated from a sediment sample collected from Bahamas. Compounds **40** and **41** showed modest antibacterial activities against MRSA with MIC values of 3.8 μmol/L and 6.0 μmol/L, respectively. They appeared to be derived from two distinct biosynthetic pathways. The amino acid components clearly derived from nonribosomal peptide synthetase pathways, while the 3-hydroxy acids (HDMD and HTMD) derived from an apparent PKS (Polyketide synthase) origin. The HDMD unit has previously been reported as a component of a fungal peptide.

The relative configurations of chiral centers in HDMD (emericellamide A, **40**) were identical to those in the HDMD component of a lipodepsipeptide previously isolated from the marine-derived fungus *Hypoxylon oceanicum,* but the absolute configurations of those compounds were opposite [55]. The HTMD component of emericellamide B **41** has not been reported as a component of a lipopeptide previously. This chain extended unit may derive from the incorporation of an additional methylmalonyl building block (C-24, C-25, and C-34) in PKS chain elongation process [56].

Compounds **42-44** (Fig. **6**) with antimicrobial activities were obtained from the fungal strain *Fusarium* sp. (section *Liseola*) FH-146 isolated from driftwood collected from the Oga Peninsula, Akita, Japan. Among these compounds, fusapyrone (**43**) was less potent than **42** against *Aspergillus clavatus*. The behavior of **43** and **44** indicated that their activities were related to the change of the pyrone ring moiety.

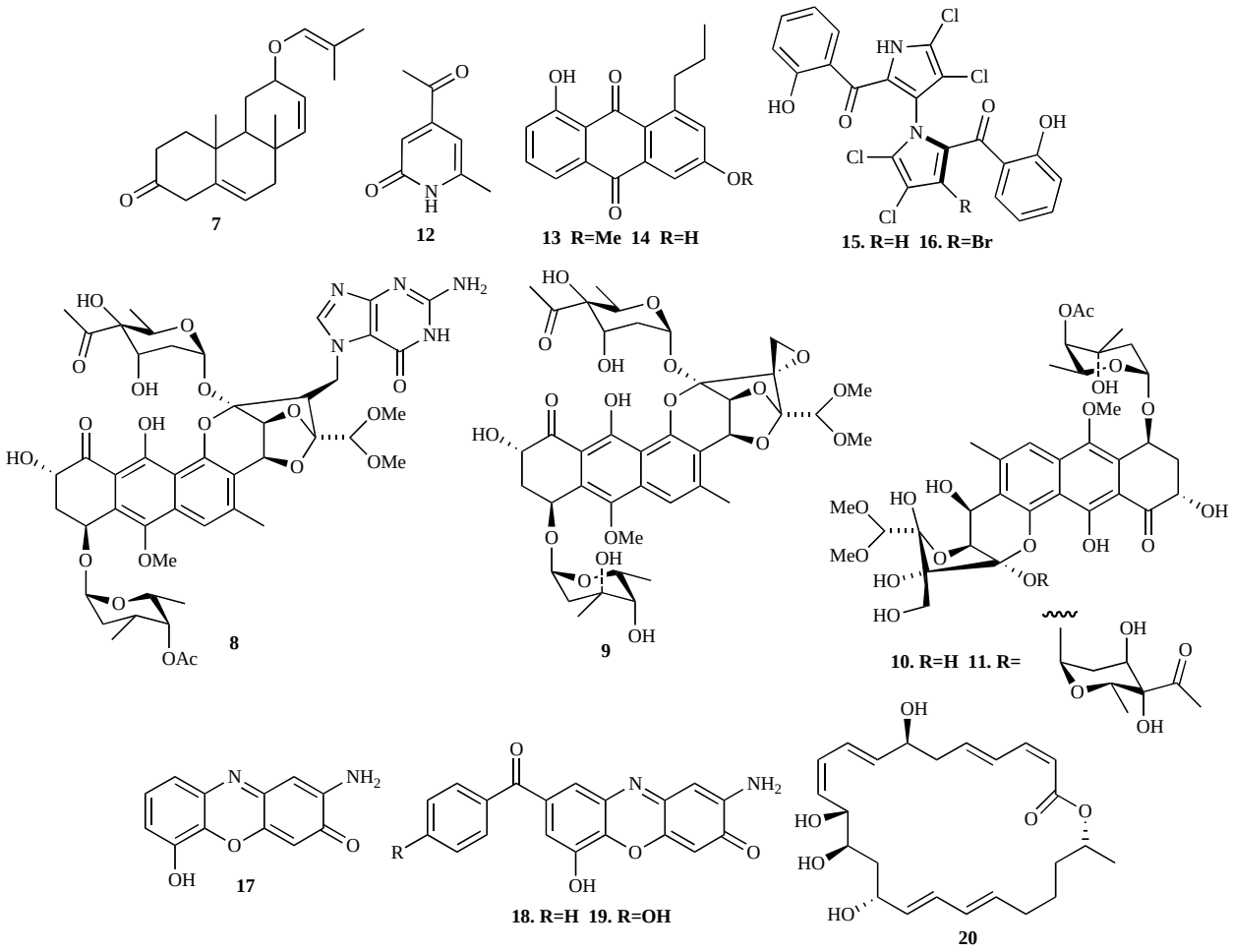

Fig. (3). The structures of compound **7-20**.

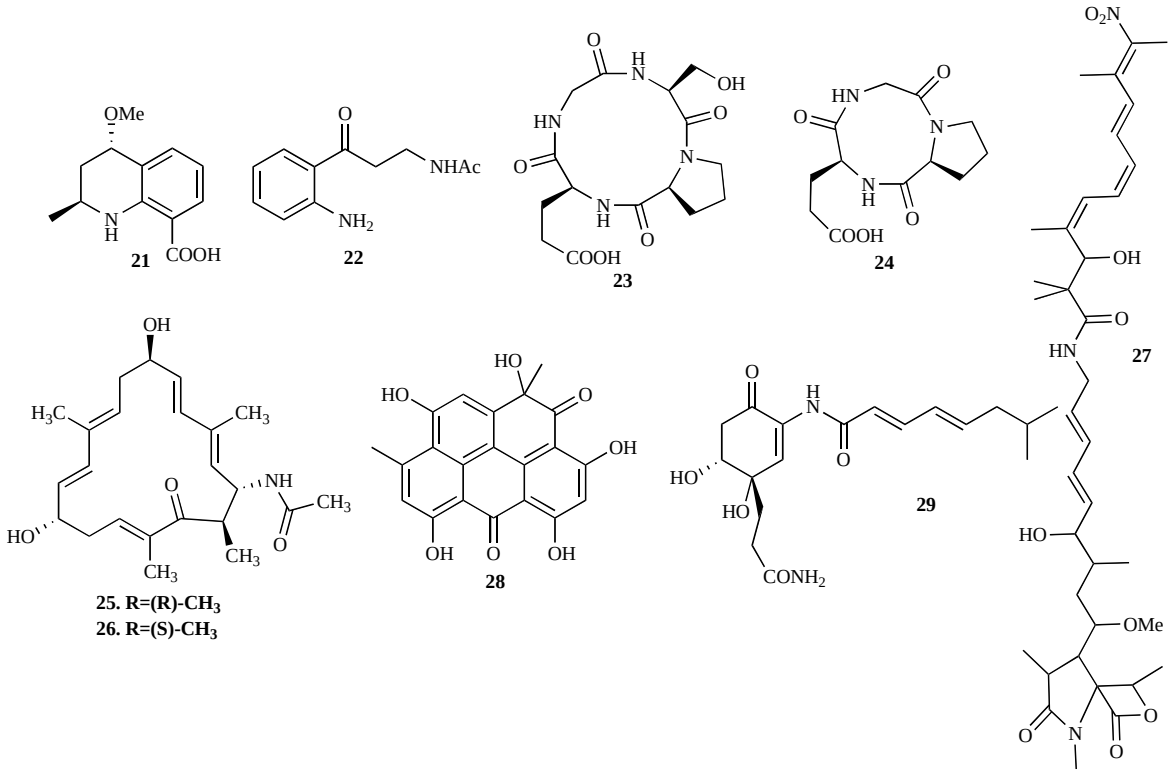

Fig. (4). contd.…

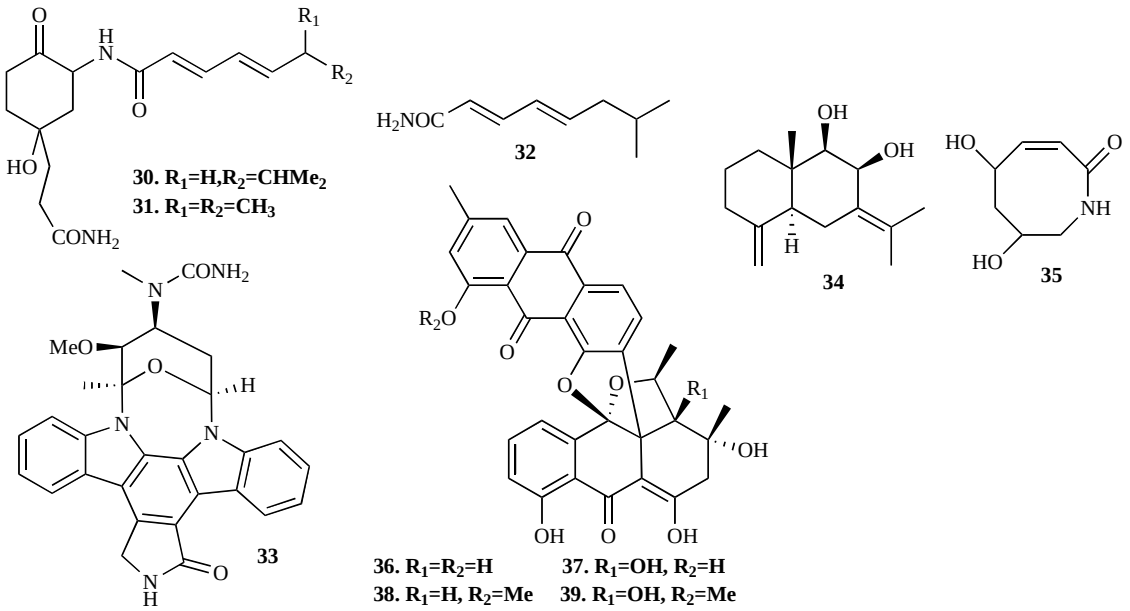

Fig. (4). The structures of compound **21-39** listed in Table **2**.

Table 2. The Natural Products from the Marine Microbes with Weak Antibacterial Activity

Source	Location	Bacterial Species	Metabolite	Biological activity	Ref
	North Sea	*Janibacter limosus*	Helquinoline **21**, *N*-acetylkynuramine **22**	moderate activity against *B. subtilis*, *Streptococcus viridochromogenes* and *S. aureus*	[46]
sponge	Gulf of Naples, Italy	*Ruegeria*	cyclic peptides **23** and **24**	moderate activity against *B. subtilis.*	[47]
marine sediment	Gejae Island, Korea	*Hahlella chejuensis*	chejuenolides A **25** and B **26**	inactive at 200 μg/disk against *B. subtilis*, *S. aureus*, and *Candida albicans*	[48]
marine sediment	Scripps Canyon, California	*Streptomyces nodosus*	Lajollamycin **27**	active against both drug-sensitive and drug-resistant Gram positive microorganisms	[49]
different cultures of sediment	Laguna de Terminos, Gulf of Mexico, Bay of Bengal, India	*Streptomyces, Streptomyces chibaensis*	1-hydroxy-1-norresistomycin **28**	activity against *E. coli*, *S. aureus* and *Streptomyces viridochromogenes*	[50-51]
marine sediment	San Diego, California	*Streptomyces*	daryamides A–C **29**–**31**, (2*E*,4*E*)-7-methylocta-2,4-dienoic acid amide **32**	weak activity against *Candida albicans*.	[52]
sediment	Jiaozhou Bay, China	*Streptomyces*	Astaurosporine **33**, sesquiterpene **34**, alkaloid 5,7-dihydroxy-5,6, 7,8-tetrahydro-1*H*-azocin-2-one **35**	weak activity against *Streptomyces viridochromogenes*	[53]
Cyanobacterium	La Parguera, Puerto Rico	*Streptomyces*	bisanthraquinone compounds **36**-**39**	strong activity against MRSA, but less strong activity against VREF	[54]

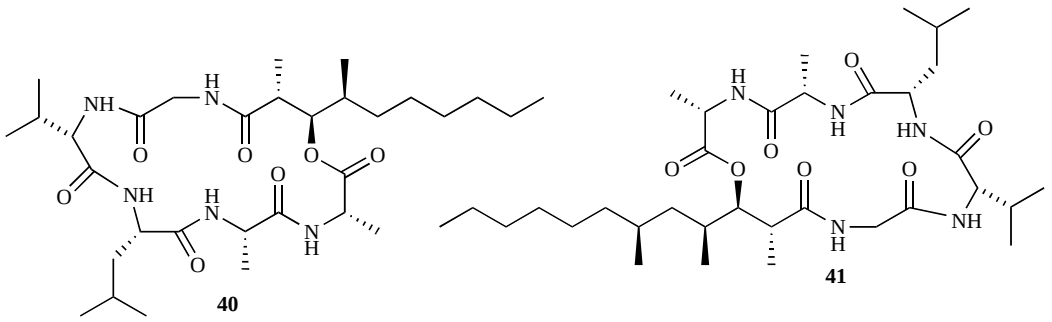

Fig. (5). The structures of emericellamides A **40** and B **41**.

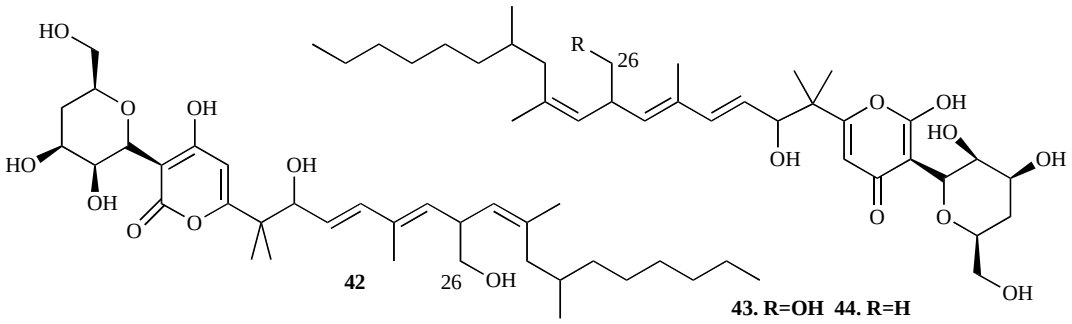

Fig. (6). The structures of compounds **42-44** isolated from the fungal strain *Fusarium* sp.

The fact that the antimicrobial activity of **43** was lower than that of **44** also suggested that the presence of a hydroxyl group at position 26 might be important for their antimicrobial activities [57].

The endophytic *Emericella nidulans*, which was isolated from a green alga (Sardinia, Mediterranean Sea), produced the prenylated polyketides arugosins G **45** and H **46** (Fig. **7**). Arugosin H **46**, a co-occuring metabolite of sterigmatocystin, was active against the fungus *Mycotypha microspora* and the green alga *Chlorella fusca* [58]. A new antibacterial dioxopiperazine, dehydroxy*bis*dethio*bis*(methylthio)gliotoxin **47**, and two previously described *bis*dethio*bis*(methyl-thio)gliotoxin **48** and gliotoxin **49** (Fig. **7**), have been isolated from the broth of a marine-derived fungus of the genus *Pseudallescheria*, which was isolated from the surface of the marine brown alga *Agarum cribrosum* that collected in the Uljin, Gyeongbuk Province, Korea. Compounds **47-49** exhibited potent antibacterial activities against the MRSA and MDR *S.aureus* with MIC values of 31.2 μg/mL, 31.2 μg/mL, and 1.0 μg/mL, respectively [59].

Three new diketopiperazine alkaloids, which were named 6-methoxyspirotryprostatin B **50**, 18-oxotryprostatin A **51** and 14-hydroxyterezine **52**, an oxaspiro[4.4] lactam-14-norpseurotin A **53**, and a 29-nordammarane triterpenoid 6,16-diacetoxy-25-hydroxy-3,7-dioxy-29-nordammara-1,17(20)-dien-21-oic acid **54** (Fig. **8**), as well as 12 known compounds, were isolated from the ethyl acetate extract of a marine-derived fungal strain, *Aspergillus sydowi* PFW1-13, which was isolated from a driftwood sample (PFW1) that collected at the beach of Baishamen, Hainan, China. Compounds **53** and **54** displayed significant antimicrobial activities against *E. coli*, *B. subtilis*, and *Micrococcus lysoleikticus*. The MIC values of compounds **53** and **54** against these three bacterial were 3.74 μ mol/L and 14.97 μ mol/L (against *E. coli*), 7.49 μ mol/L and 10.65 μ mol/L (against *B. subtilis*), 5.33 μ mol/L and 10.65 μ mol/L (against *Micrococcus lysoleikticus*), respectively [60].

A strain of *Aspergillus* sp., which was isolated from the surface of the marine brown alga *Sargassum horneri* that collected in Gadeok Island, Busan, Korea, produced com-

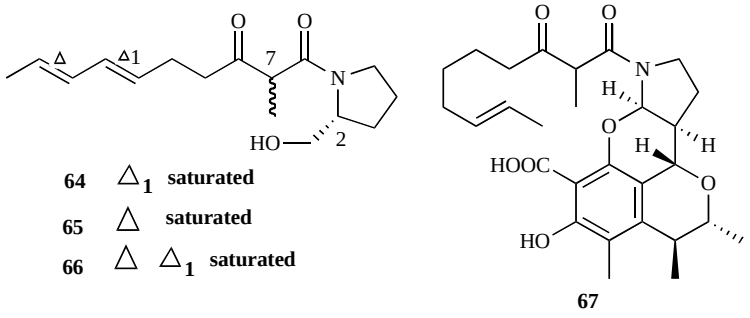

Fig. (7). The structures of compounds **45-49**.

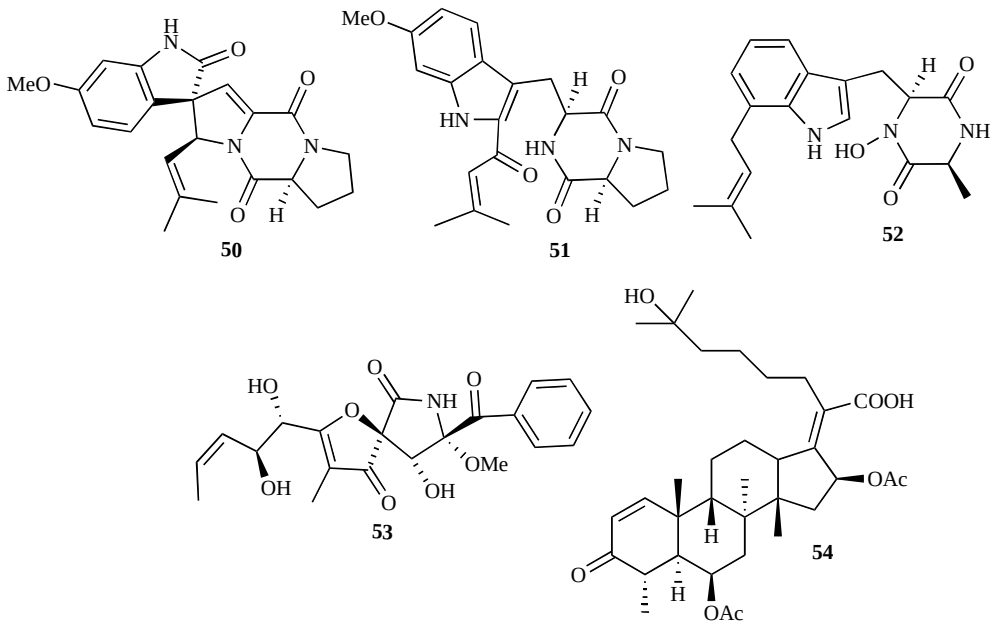

Fig. (8). The structures of compounds **50-54** isolated from the fungal strain *Aspergillus sydowi* PFW1-13.

pounds **55-57** (Fig. **9**). They all exhibited a mild antibacterial activities against *S. aureus*, MRSA, and MDRSA (Multi-drug resistant *Staphylococcus aureus*). The MIC values for each strain were as follows: both compounds **55** and **57**, 62.5 μg/mL for all strains; compound **56**, 32.5 μg/ mL for *S. aureus* and MRSA and 62.5 μg/mL for MDRSA [61].

Four new metabolites, which were named nigrospoxydons A-C (**58**, **59**, **60**) and nigrosporapyrone **61** (Fig. **9**), were isolated together with nine known compounds from the fungus *Nigrospora* sp. PSU-F5, which was isolated from sea fan that collected at 8°39′9″ N, 97°38′27″ E, 60 feet deep near Similan Island, Thailand. However, only compound **58** showed activities against *S. aureus* with the MIC value of 64 μg/mL [62].

Chlorohydroaspyrones A **62** and B **63** (Fig. **9**), which were identified as antibacterial aspyrone derivatives, were isolated from marine fungus *Exophiala*. The MIC values of each strain were as follows: compound **62** showed 62.5 μg/mL against *S. aureus* and 125 μg/mL against MRSA as well as MDRSA; compound **63** showed 62.5 μg/mL against *S. aureus* as well as MRSA and 125 μg/mL against MDRSA [63].

Scalusamides A-C (**64**, **65**, **66)** (Fig. **10**), indentified as pyrrolidine alkaloids, originated from *Penicillium citrinum* which was isolated from the parrot fish *Scalus ovifrons* (HedoCape, Okinawa). The absolute configuration of C-2 was established as (*R*) form, while all three compounds showed to be epimeric isomers at C-7. Scalusamide A **64** showed weak antifungal activity against *Cryptococcus neoformans*

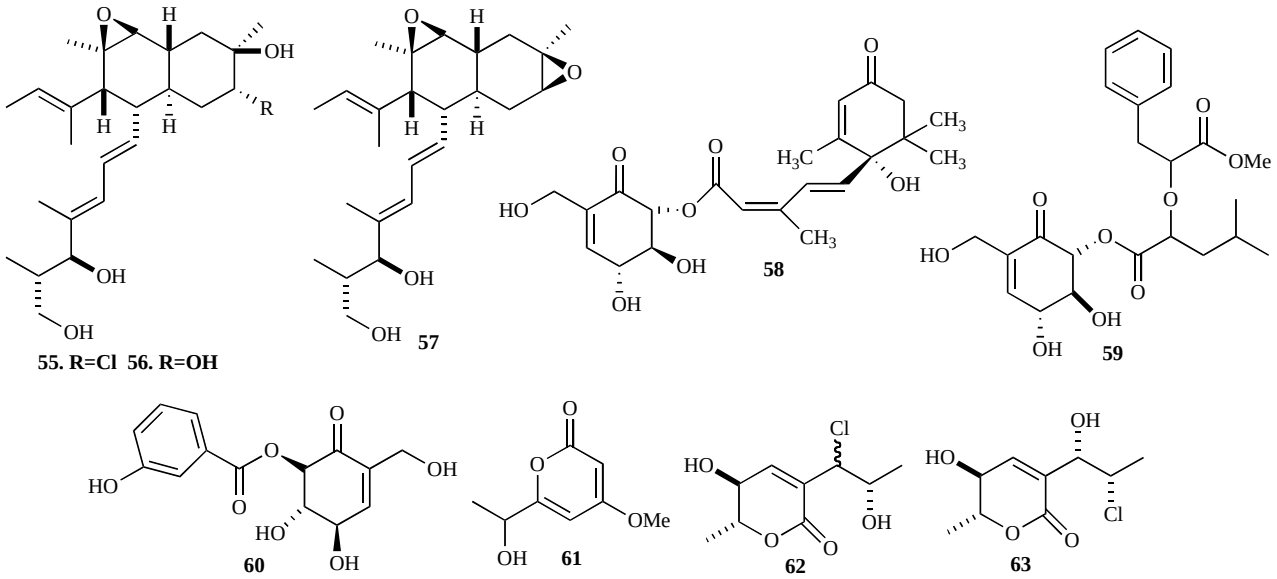

Fig. (9). The structures of compounds **55-63**.

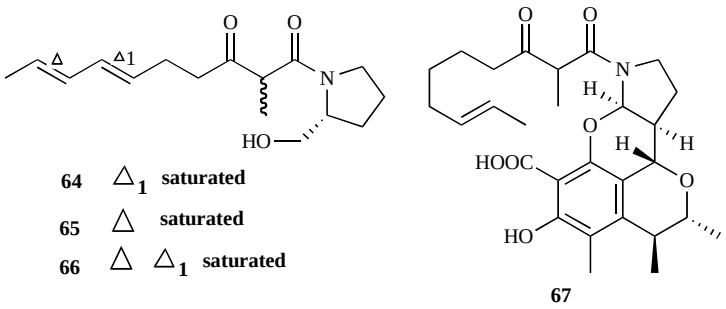

Fig. (10). The structures of compounds **64-67**.

and antibacterial activity against *Micrococcus luteus* [64]. A tetracyclic alkaloid perinadine A **67** (Fig. **10**), was also discovered from *Penicillium citrinum*, which showed a weak activity against murine leukaemia L1210 cells and antibacterial activity against *M. luteus* and *B. subtilis* [65].

Two new dimeric naphtho-γ-pyrones **68** and **69** (Fig. **11**) together with eight known analogues were isolated from the ethyl acetate extract of the fungal strain WZ-4-11 of *A. carbonarius*, which was isolated from marine sediments that collected from Weizhou Island, Guangxi Province, China. Compounds **68** and **69** showed weak antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv, with their MIC values of 43.0 and 21.5 μmol/L respectively. These results strongly indicated that the presence of conjugated carbon double bonds in pyrane rings was crucial for their activities [66]. Besides, there were also some other natural products from the marine fungus with weak antibacterial activities listed in Table **3** (Fig. **12**).

4. ACTINOMYCETES

In natural sea water containing media, the Marine actinomycete strain NPS008920, a member of the new genus *Marinispora*, which was isolated from a sediment sample collected in Cocos Lagoon Guam, produced a series of novel 2-alkylidene-5-alkyl-4-oxazolidinones, lipoxazolidinone A **99**, B **100**, and C **101** (Fig. **13**). Compound **99** showed broad spectrum activity, with MIC values ranging from 0.5 μg/mL to 5 μg/mL against Gram-positive bacteria while 12 μg/mL against two strains of *Haemophilus influenzae*. The antibacterial spectrum and potency of compound **99** were similar to the commercially available antibiotic linezolid (Zyvox) [76]. Compounds **100** and **101** also showed broad spectrum antibacterial activity, albeit with lesser overall potency than **99**.

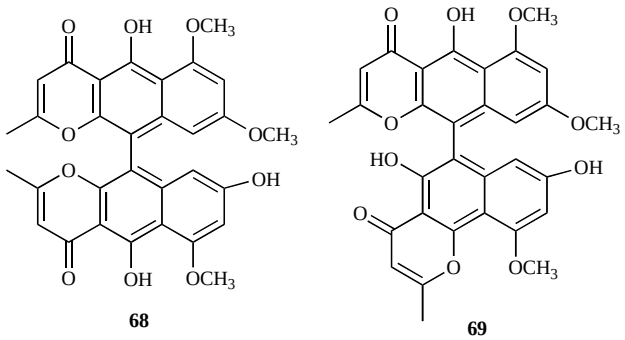

Fig. (11). The structures of new dimeric naphtha-γ-pyrones compounds **68** and **69**.

In contrast, hydrolysis of the amide bond of the 4-oxazolidinone ring of compound **99** resulted in the loss of antibacterial activity, which suggested the importance of an intact oxazolidinone ring system [77].

Cultivation of the actinomycete "*Marinispora*" yielded the macrodiolide antibiotics marinomycins A-D (**102-105)** (Fig. **14**). The all-(*E*) isomer marinomycin A **102** slowly photoisomerised to marinomycins B **103** and C **104**. In the absence of light, marinomycin A **102** was the predominant metabolite isolated with only small quantities of marinomycins B **103** and C **104**. This suggested that compound **102** may be the only natural product produced; however it has not been proven rigorously. Given the propensity of compound **102** to photoisomerise, it was postulated that an all-(*E*) isomer of **105** was possibly another true natural product in that series as well. All marinomycins exhibited antibacterial activities against MRSA, and marinomycin A **102** was also active against VREF (vancomycin-resistant *Enterococcus faecium*) and *C. albicans* [78].

A series of chlorinated bisindole pyrroles, lynamicins A-E (**106-110**) (Fig. **15**), were discovered from a novel marine actinomycete named NPS12745, which was isolated from marine sediment that collected off the coast of San Diego, California. The antimicrobial spectrums of these compounds were evaluated against a panel of 11 pathogens. The results demonstrated that these substances possess broad-spectrum activity against both Gram positive and Gram negative organisms. Significantly, compounds **106-110** were active against drug-resistant pathogens such as MRSA and VREF, which suggested potential usage in the treatment of nosocomial infections. In the meanwhile, their moderate activity against *Streptococci* and *Haemophilus* may indicate some potential usage in treating community-acquired infections. Based on the structures of compounds **106-110**, the scientists suggested that these compounds may derive from two units of tryptophan. The biosynthetic pathway of the related bisindole pyrrole, chromopyrrolic acid, also supported the hypothesis that the core bisindole pyrrole skeleton was tryptophan-derived [79]. However, the precursor amino acids were modified in the final natural products where the indole rings were substituted with chlorine. This series of compounds were exemplary of the unique chemotypes that may obtain from marine environment, which was well known for giving rise to chlorinated natural products that are not produced by terrestrial organisms [80].

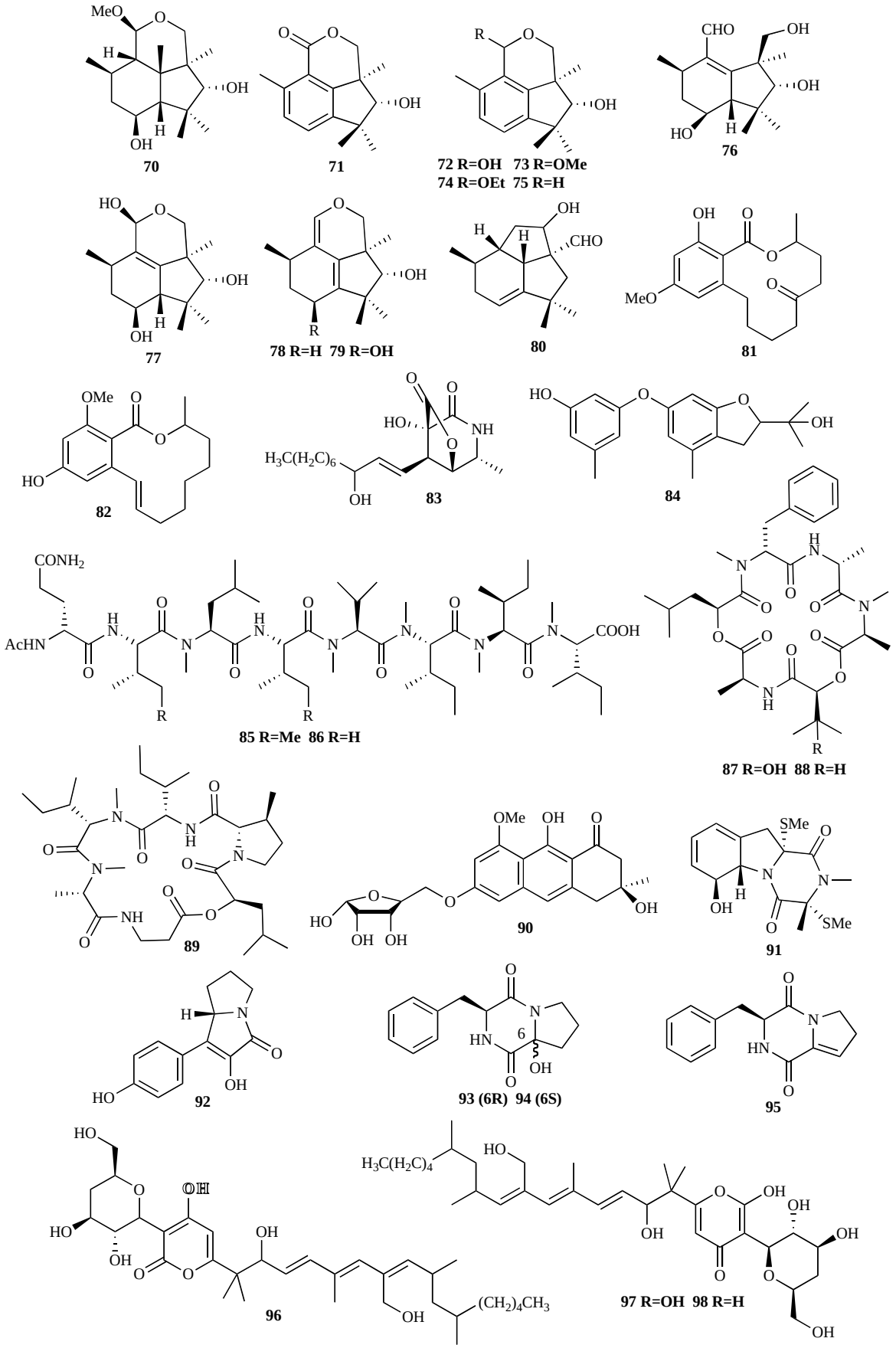

Fig. (12). The structures of compound **70-98** listed in Table **3**.

Table 3. The Natural Products from the Marine Fungus with Weak Antibacterial Activity

Source	Location	Fungus Species	Metabolite	Biological activity	Ref.
associated with a red algal *Polysiphonia* species	Ahrenshoop Baltic Sea	*Geniculosporum*	botryane compounds **70**–**80**	some displayed modest growth inhibition of alga, bacteria and fungi	[67]
cultured endophytic fungus from the brown alga *Sargassum* sp.	Zhanjiang Sea, China		12-membered ring lactones **81** and **82**	both showed varying levels of antibacterial activity	[68]
sea mud	Awajishima Is., Japan	*Acremonium*	awajanomycin **83** dihydrobenzofuran derivative **84**	**83** had moderate antibacterial and antifungal activity	[69]
Teichaxinella sponge	Papua New Guinea	*Acremonium*	highly *N*-methylated linear octapeptides **85** and **86**	Octapeptide **85** was active against *Staphylococcus epidermidis*	[70]
sponge *Ianthella* sp.	Guango, Papua New Guinea		Cyclic depsipeptides, guangomides A **87** and B **88**, a destruxin derivative, homodescartin **89**	Guangomides A **87** and B **88** displayed weak antibacterial activity against *S. epidermidis* and *Enterococcus durans*	[71]
Red alga *Lomentaria catenata*	Ulsan City, Korea	*Microsporum*	asperflavin ribofuranoside **90**	**90** displayed moderate activity against MRSA and MDRSA	[72]
the surface of the brown alga *Agarum cribosum*	Uljin, Korea	*Pseudallescheria*	dioxopiperazine alkaloid **91**	**91** displayed activity against MRSA and MDRSA	[73]
sediment	Gulf of Mexico	*Chromocleista*	*p*-hydroxy phenopyrrozin **92** diketopiperazines **93**-**95**	**92** displayed moderate activity against *C. albicans*	[74]
separated from driftwood	Oga Peninsula, Japan	*Fusarium*	neofusapyrone **96**, fusapyrone **97** and deoxyfusapyrone **98**	some displayed moderate activity against *A.clavatus*	[75]

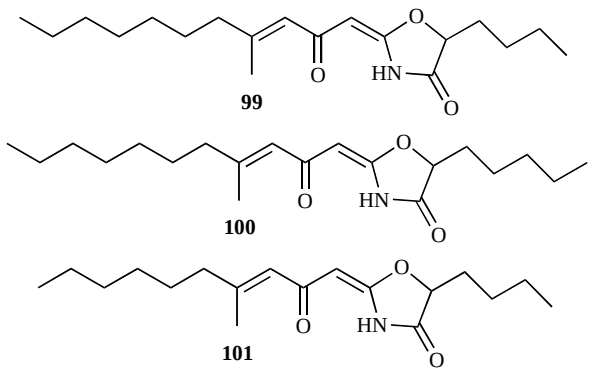

Fig. (13). The structures of compound **99**-**101** isolated from marine actinomycete.

An actinomycete, *Verrucosispora* sp. (deep sediment, Sea of Japan), yielded the abyssomicins B-D (**111-113)** (Fig. **16**), whose structures and relative stereochemistries were supported by X-ray analyses. The absolute stereochemistry of abyssomicin D **113** was determined by Mosher and Helmchen methods. Through the structural analogy, abyssomicins B **111** and C **112** were assumed to share the same stereochemistry [81]. Besides, abyssomicin C **112**, which was strongly active against Gram-positive bacteria, was identified as an inhibitor of the pathway between chorismic and para-aminobenzoic acids [82].

A new genus of actinomycete from deep water sediment (La Jolla, California) yielded four chlorinated dihydroquinones (**114-117**) (Fig. **16**). All compounds of **114-117** displayed significant activities against MRSA (MIC < 2.0 μg/mL), while compounds **114**, **115** and **117** displayed significant activities against VREF (MIC < 4.0 μg/mL) [83]. An actinomycete, *Micromonospora* sp. obtained from *Didemnum proliferum* (Shishijima Is., Japan), produced the dibenzodiazepine alkaloid, diazepinomicin **118** (Fig. **16**), which exhibited modest antimicrobial activity against selected Gram-positive bacteria [84].

5. CONCLUSIONS

Marine microorganisms are important sources that produce the secondary metabolites with different structures in association with the diverse environments they live. Deeply research on marine microorganisms and use of biotransformation and biotechnological methods could help to obtain potent candidates for the treatment of diseases. Nowadays, more and more novel bioactive marine derived compounds have been discovered. In this paper, 118 new discovered marine natural products, including many important novel

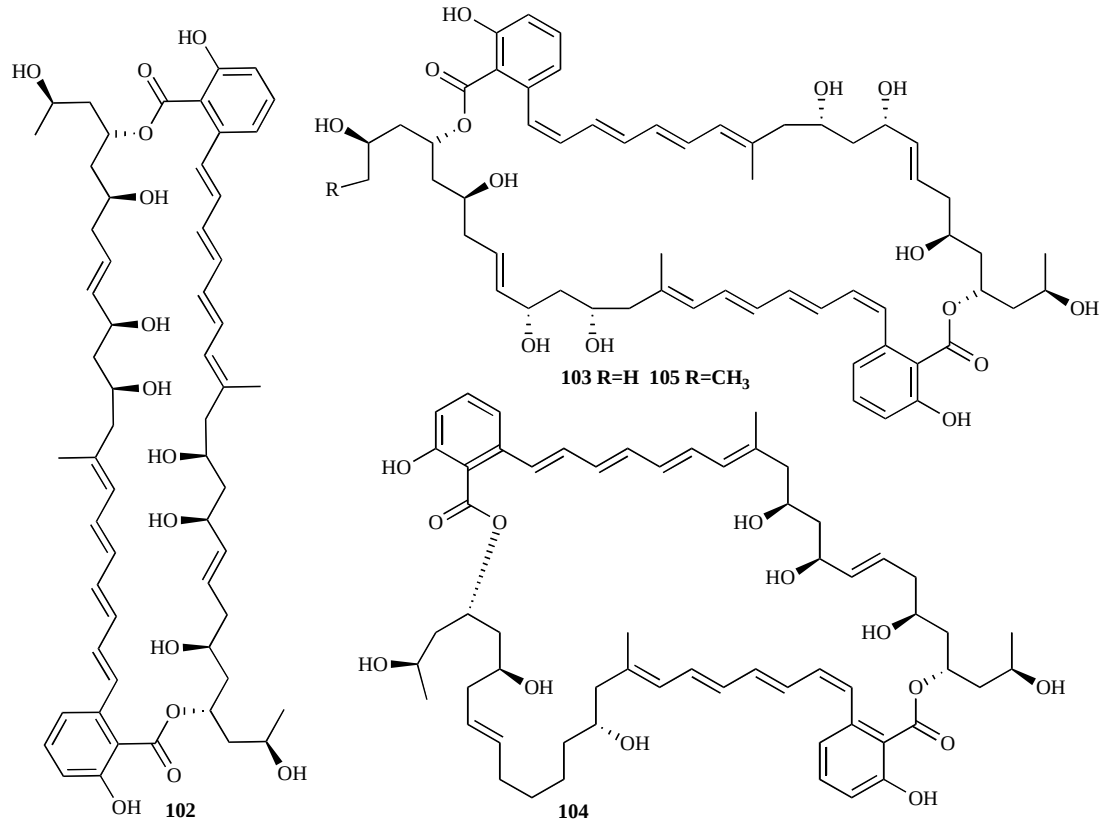

Fig. (14). The structures of compound **102**-**105** isolated from marine actinomycete "*Marinispora*".

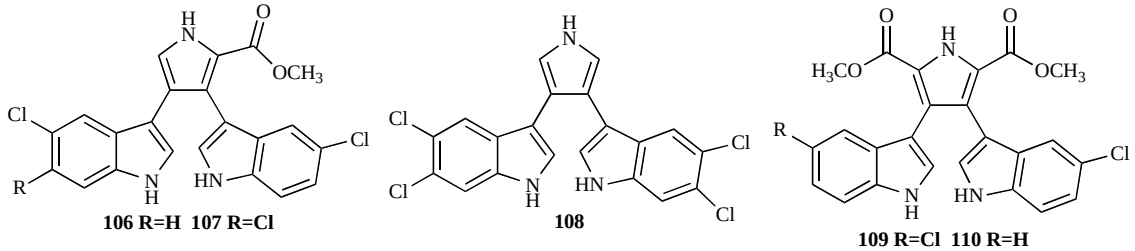

Fig. (15). The structures of chlorinated bisindole pyrroles, lynamicins A-E **106**-**110**.

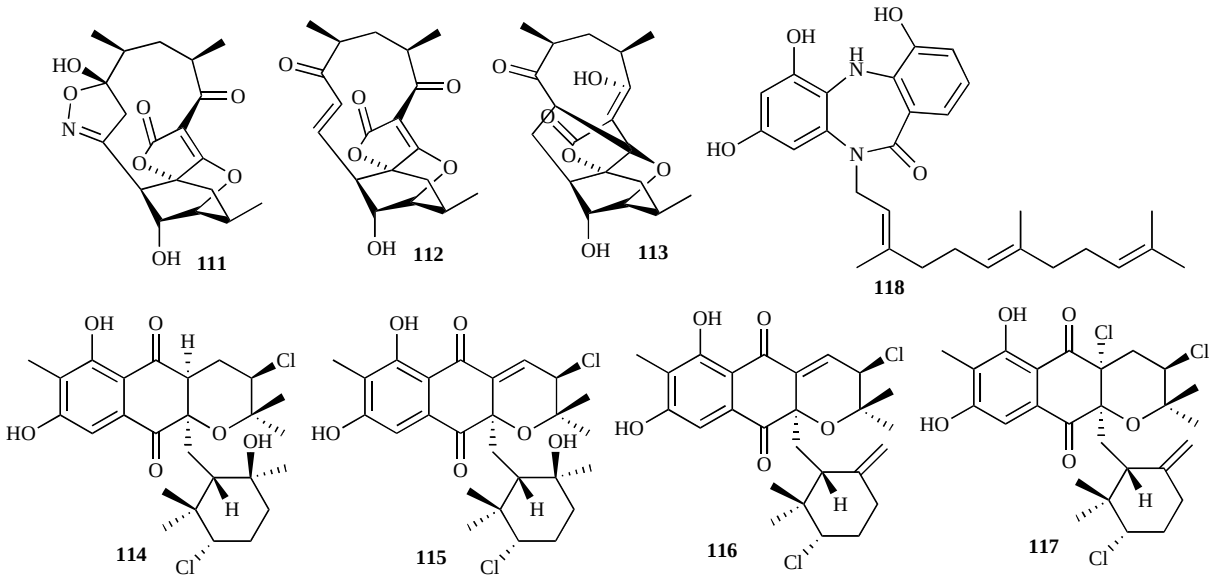

Fig. (16). The structures of compounds **111**-**118**.

scaffolds, were reviewed. Among these new structures, 92 compounds showed various antibacterial activities.

In the near future, research of marine natural products will be still an attractive research filed to scientists. It is time to use of microbial genome mining and searching for natural products in relatively untapped sources, thus expanding our ability to find novel, potent and selective drug leads. Besides, given that microorganisms interact with each other in the natural environment and these interactions are, arguably, the driving force to produce necessary secondary metabolites, simulating microbial habitats by culturing two different microbial strains in one culture vessel (i.e., co-culture) would seem to be an effective way to harvest new molecules.

Only a tiny fraction of microbial world has been explored yet. The recent achievements of genomic sciences, coupled with advancements in genetic engineering of secondary metabolite biosynthesis in marine microbes, are beginning to impact the discovery of antibiotics.

ACKNOWLEDGEMENTS

The work was supported by National Hi-tech R&D Program to Dr. B. Jiao (2007AA091501), Dr. X. Liu (2006AA09Z416) and Dr. Q. Xu (2006AA09Z425).

ABBREVIATIONS

MDR = Multi-drug resistant

MRSA = Methicillin-resistant *Staphylococcus aureus*

MDRSA = Multi-drug resistant *Staphylococcus aureus*

MIC = Minimal inhibitory concentration

MSSA = Methicillin-sensitive *Staphylococcus aureus*

PKS = Polyketide synthase

VREF = Vancomycin-resistant *Enterococcus faecium*

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Received: April 30, 2010 Revised: July 27, 2010 Accepted: July 30, 2010