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Hafizur Rahman
Chowdhury Kamrul Hasan
Musfique Ahmed
M Ali Hossain
Department of
Environmental Science,
School of Environmental
Science and Management,
Independent University,
Bangladesh, Plot 16 Block
B, Aftabuddin Ahmed Road,
Bashundhara R/A, Dhaka,
Bangladesh.

Kazi Didarul Islam
Biotechnology and Genetic
Engineering Discipline,
Khulna University, Khulna-
9208, Bangladesh.

Correspondence:
Hafizur Rahman
Department of
Environmental Science,
School of Environmental
Science and Management,
Independent University,
Bangladesh, Plot 16 Block
B, Aftabuddin Ahmed
Road, Bashundhara R/A,
Dhaka, Bangladesh.

Promising natural products against nosocomial infections

**Hafizur Rahman, Chowdhury Kamrul Hasan, Musfique Ahmed,
Kazi Didarul Islam, M Ali Hossain**

Abstract

Globally, increasing drug resistance among nosocomial infections is a growing concern for medicine, which demands effective therapeutic regimes. Along with existing major scaffolds, namely penicillin, cephalosporin, quinolones, macrolides and tetracyclines, exploring new antibiotics with novel scaffold is a pressing necessity to combat multi-drug resistant pathogens causing hospital associated infections. Therefore, this review is intended to present the latest advances in the process of drug development from natural sources. The review shows that nature can provide a variety of scaffolds, though variability in the effectiveness exists among them. Consequently, an endeavour to isolate and characterize more potential antibiotics from nature is extremely important. In this aspect, the marine environment could be a promising source as it has been comparatively ignored to date.

Keywords: Natural products, nosocomial, bacteria, drug resistant

1. Introduction

Since the first use of penicillin in the mid-twentieth century, antibiotic resistance developed rapidly in some bacteria such as *Staphylococcus aureus*. Over the last several decades, a shift in the etiology of more easily treated pathogens has increased toward more antimicrobial resistant pathogens with fewer options for therapy. Infections from antimicrobial-resistant bacteria increase the cost of health care, cause higher morbidity and mortality, and lengthen hospital stays compared to infections from organisms susceptible to common, inexpensive antimicrobials. Along with the bacterial resistance to antimicrobial agents, hospitalization of immune-compromised patients, invasive diagnosis, treatment and care practices, and certain hospital environment favoring pathogens cumulatively contribute to nosocomial infections. Nosocomial infections, also called hospital acquired infections, are infections acquired during hospital care, which are not present or incubating at admission. A comprehensive WHO study report highlights the great impact of nosocomial infection burden in high-, middle- and low-income countries^[1].

The emergence of resistance to antimicrobial agents is a global public health problem, particularly in pathogens causing nosocomial infection. Surveillance data, reported by the National Nosocomial Infections Surveillance System for January-December 2003 compared with 1998-2002 as well as for 1993-97 compared with January-November 1998, show a continuing increase in antimicrobial resistant pathogens associated with nosocomial infections in intensive care unit (ICU) patients from the US hospitals.^[2] The increase is particularly marked for vancomycin-resistant enterococci (VRE), methicillin-resistant *S. aureus* (MRSA), third generation cephalosporin-resistant *Escherichia coli*, imipenem-resistant *Pseudomonas aeruginosa* and quinolone-resistant *P. aeruginosa*. The worldwide emergence of resistance against antimicrobials has prompted the search for novel antimicrobials both from natural origin and organic synthesis.

Here we review the novel antimicrobials against nosocomial infections reported from terrestrial plants and marine organisms.

2. Microorganisms involved in nosocomial infection

A diverse range of pathogens of viral, bacterial and fungal origin may cause nosocomial infections; however, bacteria are the most common and significant nosocomial pathogens.

2.1 Gram-positive pathogens

A battery of Gram-positive bacteria has clearly re-emerged as important causative agents worldwide for nosocomial infections in the past three decades. *Clostridium difficile*, an anaerobic spore-forming bacillus, was first detected in 1935 in healthy newborn and subsequently in 1978 was identified as the primary cause of pseudomembranous colitis in patients treated with antibiotics. *C. difficile* infection (CDI) is the leading cause of antibiotic-associated diarrhea and a seriously problematic nosocomial infection. Staphylococci, including the coagulase-negative staphylococci and MRSA along with VRE account for approximately one-third of all blood-stream infections and as much as 50% of nosocomial blood-stream infections [3].

2.2 Gram-negative pathogens

P. aeruginosa is a Gram-negative, aerobic, coccobacillus, opportunistic human pathogen that causes pneumonia, septic shock, urinary tract infection, gastrointestinal infection as well as skin and soft tissue infections. It is a leading cause of nosocomial infection and is responsible for 10% of all hospital-acquired infections. Enterobacteriaceae is a large family of Gram-negative bacteria that includes, along with many harmless symbionts, many of the familiar pathogens. *E. coli*, *Klebsiella pneumonia* and *Enterobacter* are three important nosocomial pathogens belonging to this family. Bacteremia, respiratory tract infection and urinary tract infection are the most common manifestation of the Enterobacteriaceae infection. These four above-mentioned Gram-negative pathogens accounted for 30% of all nosocomial infections [4].

3. Natural compounds effective against *Clostridium difficile*

Diarrhoea in hospitalized patients is mainly caused by *C. difficile* infection (CDI), [5] which may occur from asymptomatic colonization to fulminant, even severe colitis. Broad spectrum antibiotics, e.g. metronidazole or oral vancomycin (Figure 1), are commonly used for the treatment of CDI. However, half of the CDI-infected patients exhibit unmanageable or persistent *C. difficile* associated diarrhoea, which is even more prevalent among older patients [6]. Here, the main attempt is to provide a progress report on the search for potential anti-*C. difficile* compounds from natural products. There are a few, but promising, drug candidates being investigated, in the hope of combating the progression of *C. difficile* infection.

3.1 Vancomycin

Over the last thirty years, vancomycin, a glycopeptide antibiotic, isolating from *Amycolatopsis orientalis*, has been a good option for treating ingrained gram-positive bacterial infections [7], demonstrating MIC ranging from 0.125 to 2 mg/L [8, 9]. Although *Leuconostoc* sp. and some lactobacilli are thought to be generally resistant to vancomycin [10-12], a

substantial number of studies suggest that the frequency of resistant to the anti-microbial has increased significantly [13-19], which is further substantiated by a study reporting 55 clinical isolates of *Enterococcus faecium* and *E. faecalis* which are resistant to high concentrations of vancomycin (MICs, >128 mg/L) [20]. Consequently, while searching for new drugs which may be capable of inhibiting VRE, researchers around the world have been able to isolate some vancomycin derivatives.

Studies show that anti-bacterial activities have been manifested by several vancomycin derivatives namely A51568 factors A and B, [21] the M43 group of antibiotics, [22] A82846 factors A, B, and C, [23] orienticins, [24] chloroorienticins, [25] eremomycin, [26] and MM45289 [27]. Eremomycin, a novel antibiotic, isolating at the Institute of New Antibiotics, the USSR Academy of Medical Sciences from the culture fluid of actinomycete INA-238, differs from vancomycin by the carbohydrate composition and structure of tri-phenoxytriaminotricarboxylic acid. Research indicates that its antibacterial spectrum is reported to be close to ristomycin and vancomycin. On the contrary, it is possible that eremomycin may demonstrate 2-10 times higher activity than those compounds [28].

3.2 Daptomycin

Daptomycin (Figure 4), isolated from *Streptomyces roseoporus*, shows bactericidal activity against resistant Gram-positive bacteria including *C. Difficile* [29, 30]. It is a branched non-ribosomally assembled acidic cyclic lipopeptide [31]. The MIC for daptomycin against *C. difficile* is ≥ 1 mg/L [32]. It causes bacterial cytoplasmic membrane disruption as well as membrane potential dissipation [33]. Additionally, it displays bactericidal activity against a variety of antibiotic-resistant Gram-positive pathogens, such as VRE, MRSA, glycopeptide-intermediate *S. aureus*, and *Streptococcus pneumoniae* [34, 35]. Studies indicate that daptomycin not only oligomerizes daptomycin peptide into transmembrane pores but also helps release intracellular ions causing rapid cell death [36, 37]. Moreover, it is an approved drug for skin infections caused by Gram-positive pathogens and staphylococcal sepsis [38]. On the other hand, daptomycin (4 mg/kg of body weight) is less effective than ceftriaxone in a rat model infected with MRSA pneumonia. However, it is more effective in the case of hematogenous pneumonia caused by *S. aureus* [39, 40].

3.3 Rifamycin SV

Rifamycin SV (Figure 2A), isolated from a strain of *Streptomyces mediterranei* demonstrates activity against *C. difficile* with MIC₅₀ values ranging from 32-128 mg/L [41, 42]. One study, based on MIC, shows that rifamycin SV is 11 times less effective than metronidazole [43]. However, several semi-synthetic derivatives of rifamycin have shown more potent activity against *C. Difficile* [44].

3.4 Penicillin G

Penicillin G (Figure 3), isolated from cultures of *Penicillium chrysogenum*, shows activity against *C. difficile* (MIC₅₀ values ranging from 1-8 mg/L) [45]. Besides, Penicillin G (benzylpenicillin) is used for many treatments, such as, gonorrhoea, meningitis, aspiration pneumonia, lung abscess, community-acquired pneumonia, syphilis and septicemia in children [46].

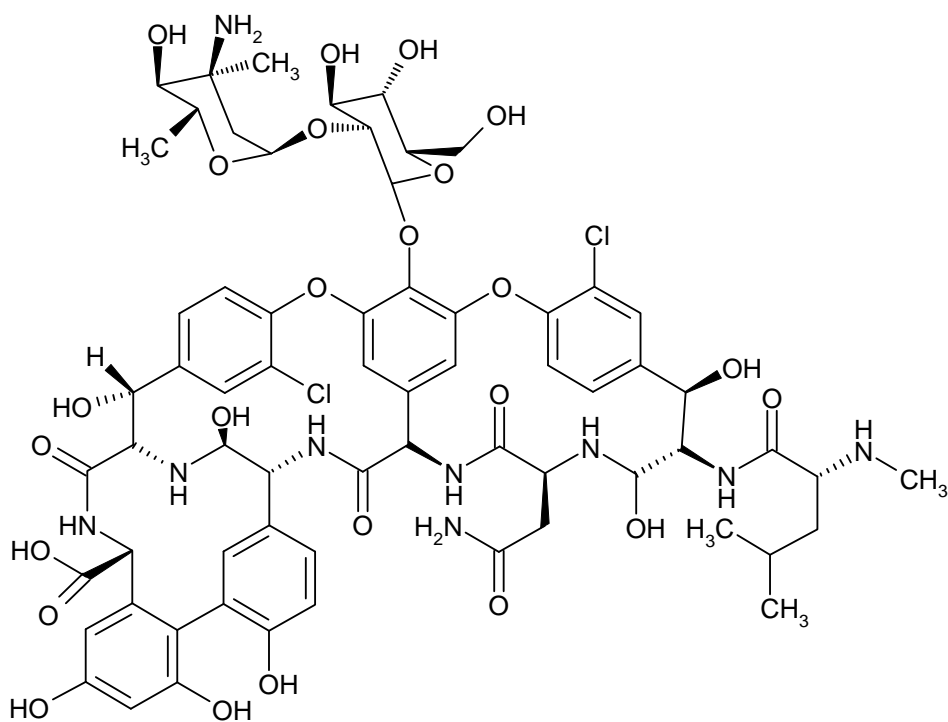


Fig 1: Structure of vancomycin

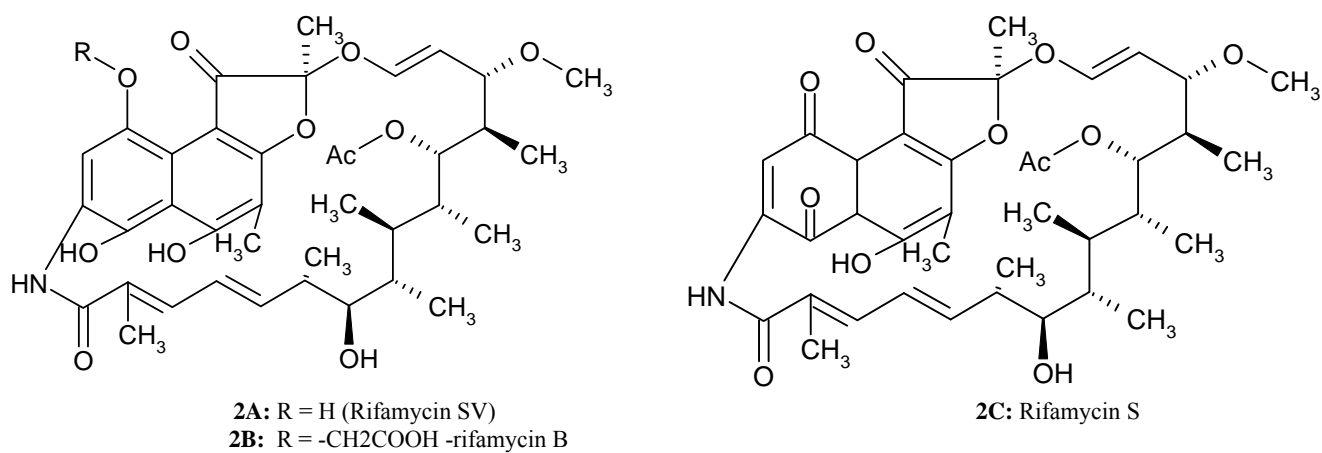


Fig 2: Structures of rifamycins 2 A-C

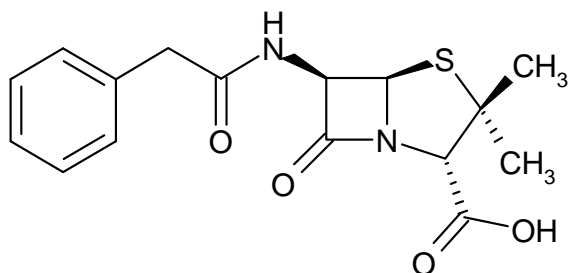


Fig 3: Structure of penicillin G

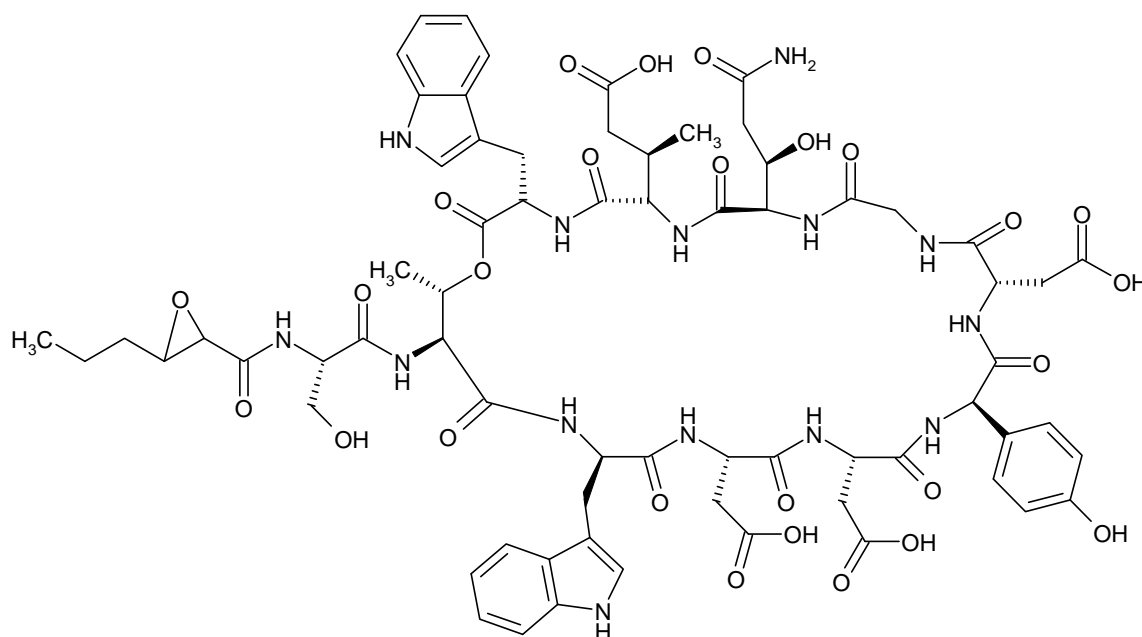


Fig 4: Structure of daptomycin

4. Natural Products against Multi-drug Resistant Gram-negative Pathogens

Although the threat of Gram-negative pathogens is not as prevalent as that of Gram-positive pathogens (e.g. MRSA and VRE), a few potent antibiotics have been developed and approved against them^[47]. Nevertheless Gram-negative drug resistant pathogens show increasing trend, and the available treatment has been proved to be ineffective in combating them^[48]. This is further substantiated by the fact that tough and serious Gram-negative pathogens are commonly found in hospitals with severe threat being posed by the three Gram-negative pathogens, namely *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*^[24]. The discussion that follows highlights some of the most common and potent natural products effective against those three bacteria.

4.1 Colistin

Recently, antibiotic polymyxin derivative colistin, (polymyxin E1 – Figure 6) which is well known for its nephrotoxicity and neurotoxicity, has appeared as a rescue therapy against *K. pneumoniae* in ICU^[49]. It also expresses activity against almost all Gram-negative pathogens including *P. aeruginosa*, and *A. Baumannii*^[50]. It is a cyclic polypeptide, first isolated in Japan at 1947, from the Gram-positive strain *Bacillus polymyxa* and was clinically available at 1959. Colistin consists of a number of closely related decapeptides. Furthermore, the structure of colistin is consisted of acyclic heptapeptide moiety as well as an acetylated *N* terminus fatty acid side chain^[51, 52]. Two types of colistin derivatives exist: colistin A (polymyxin E1-Figure 6) and colistin B (polymyxin E2), which contain the same amino acids but differ in their fatty acid side chain (colistin A contains 6-methyl-octanoic acid, whereas colistin B contains 6-methyl-heptanoic acid). It has been reported that they show bactericidal characteristics towards Gram-

negative pathogens through a detergent-like mechanism^[53]. MICs of colistin ranged from 1 to 4 mg/L against *P. aeruginosa*, *K. pneumoniae* and *A. baumannii*^[54]. Several studies focus on the effectiveness of colistins against Gram-negative pathogens. For example, it can inhibit *P. Aeruginosa*, which may easily infect cystic fibrosis patients^[55, 56]. Moreover, the Clinical and Laboratory Standards Institute of USA has published activity result for polymyxin B in 2007 against *P. aeruginosa*, *Acinetobacter* and *Enterobacteriaceae* representative. Although *P. aeruginosa* manifests susceptibility to polymyxin B at MIC ≤ 2 mg/L, it shows resistance to the same with MIC ≥ 8 mg/L. On the contrary, the resistance to *A. baumannii* and *Enterobacteriaceae* has been manifested at MIC ≥ 4 mg/L^[57, 58]. While polymyxin B and E differ in the amino acid components, they disrupt membrane permeability of Gram-negative bacteria leading to cell death^[59, 60].

4.2 Fosfomycin

A broad band antibiotic fosfomycin (Figure 5), isolated from a *Streptomyces* sp., shows activity (MIC ≤ 64 mg/L) against *E. coli*, *K. pneumoniae* and lower urinary tract infections caused by extended-spectrum β -lactamase-producing *E. coli*^[61]. Besides, UDP-*N*-acetylglucosamine enol-pyruvate transferase enzyme is inactivated by fosfomycin that ultimately slows down bacterial cell wall biogenesis^[62, 63].

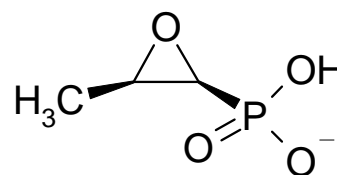


Fig 5: Structure of fosfomycin.

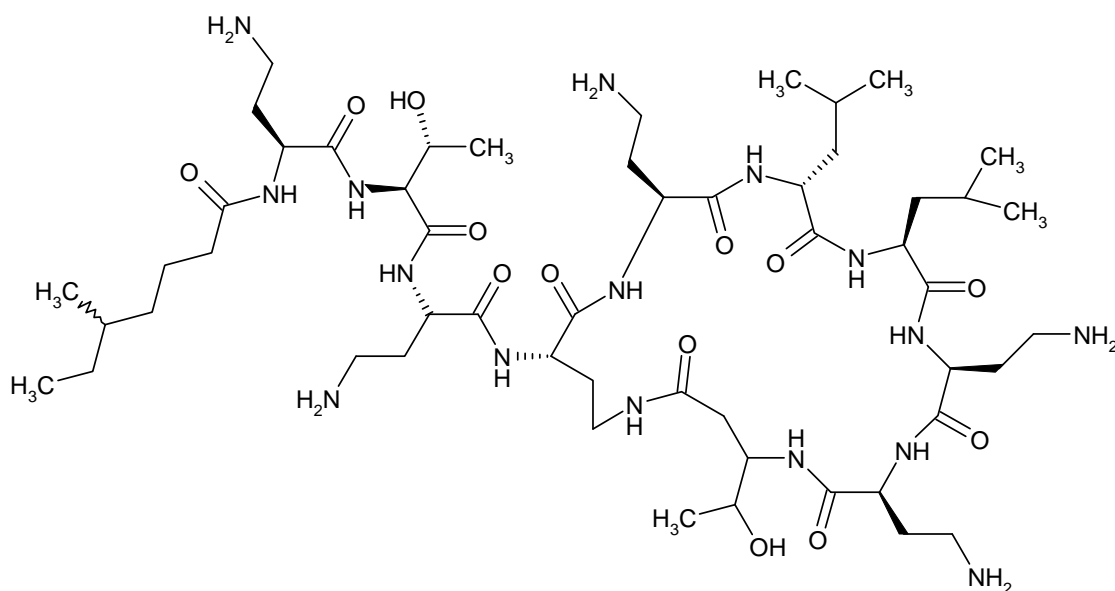


Fig 6: Structure of polymyxin E1

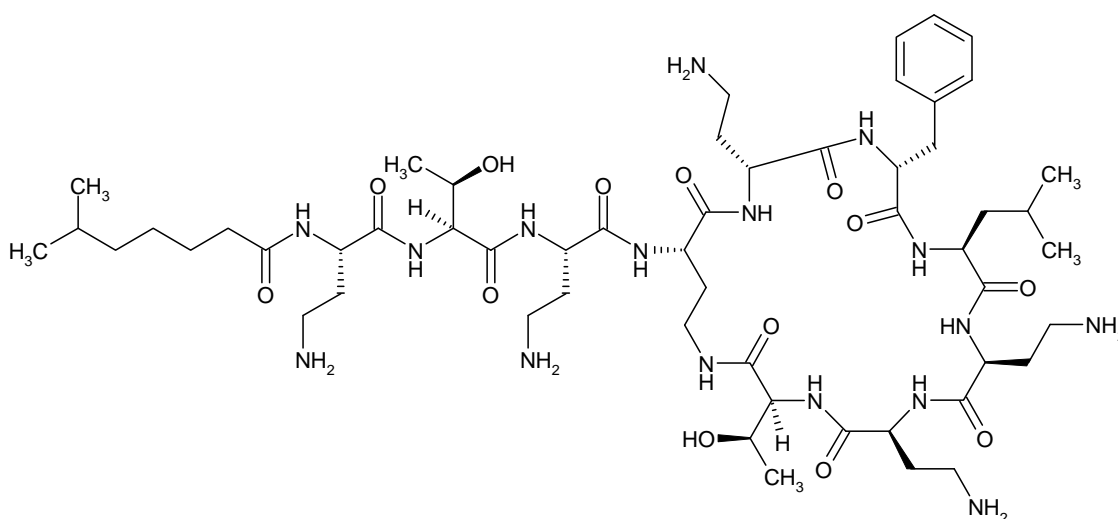


Fig 7: Structure of polymyxin B

4.3 Carbapenems and Bromoageliferin

Searching for new anti-biotics against *P. Aeruginosa* seems logical because of its severe pathogenesis and its resistance to conventional drugs. Its nature of pathogenicity is advocated by a study describing that *P. Aeruginosa* targets immune-compromised patients, causing varieties of infections, such as pneumonia, urinary tract infection, bacteremia, and wound infection. Moreover, a known secondary metabolite phenazine-1-carboxylic acid produced by *P. aeruginosa* has several actions that could mutate host immune and build inflammatory relationship, contributing to bacterial pathogenesis [64]. On the other hand, through mutation and inheritance, it has acquired the ability of resistance to major antibiotics, practically more potential for avoiding the actions of antibiotics than any other microorganism [65]. In view of these, Carbapenems (e.g. meropenem, imipenem etc.), which are derived synthetically from a natural compound thienamycin (Figure 8), originally isolated from *Streptomyces cattleya* by Merck in 1976, have been used for the treatment of *P. aeruginosa* infections [66, 67]. Due to extreme unstability of thienamycin in aqueous solution, it is considered to be ineffective drug against

bacterial infections. Therefore, stable derivatives like carbapenems have been developed. In addition to that, a brominated pyrrole alkaloid, bromoageliferin (Figure 9), isolated from the marine sponge *Agelas conifer*, shows modest activity (>153.99 mg/L) against *P. aeruginosa* and *A. Baumannii* [68]. In whole-cell patch clamp experiments, bromoageliferin reduces voltage-dependent calcium access in PC12 cells with half maximal concentration 2.04 mg/L [69].

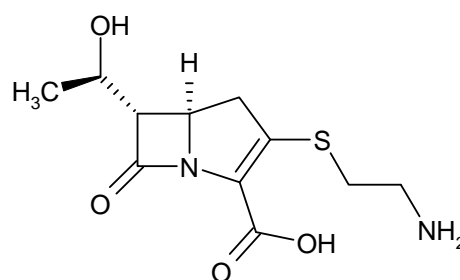


Fig 8: Structure of thienamycin

4.4 Oroidin and Microsphaerins D

Since *A. baumannii* is considered to be a growing concern for ICU patients [70, 71] as well as its resistance to most antibiotics [72], studies focus on exploring potent antimicrobials that are capable of inhibiting the pathogen, commonly exist on either wet or dry places for long-standing periods [73] and can be found in around one fourth of all hospital swabs [74]. This along with its bio-film producing ability allows it to survive for prolonged periods, which create problems for total disinfection of hospital or medical instruments [75]. A marine-derived sponge (*Agelas sventres*) provides an active metabolite, named oroidin that restrained the action and role of Pdr5 which encodes a multi-drug transporter allowing *Saccharomyces cerevisiae* to be multidrug resistant. Oroidin shows activity against *A. baumannii* and *P. aeruginosa* at >61.60 mg/L concentration. This finding may assist in the discovery of new drugs against pathogenic yeast and fungi [76]. In addition, oroidin displays fish-deterrent activity as well as inhibits bacteria to attach on the surface cell [77, 78]. Another derivative of oroidin (Figure 10A), named dihydrosventrin (Figure 10B), isolated from the same source, has been proved to be more effective against *A. baumannii* and *P. Aeruginosa* [79]. Another study isolates benzophenone dimers, microsphaerins D (Figure 11) from the fungus *Microsphaeropsis* sp., which displays antibacterial activities against *P. aeruginosa*, *K. pneumoniae* and *E. coli* with MIC (50 mg/L) [80].

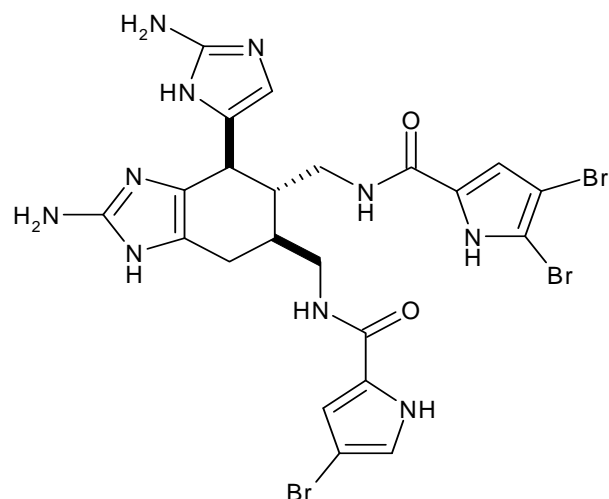
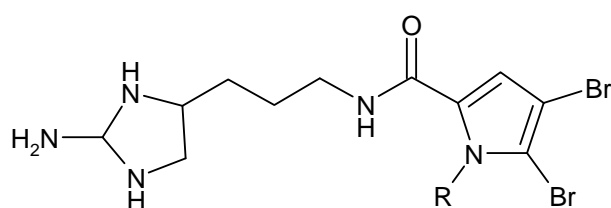


Fig 9: Structure of Bromogeliferin



10 A: R = H oroidin and 10 B: R = CH₃ dihydrosventrin

Fig 10: Structure of oroidin (10 A) and dihydrosventrin (10 B)

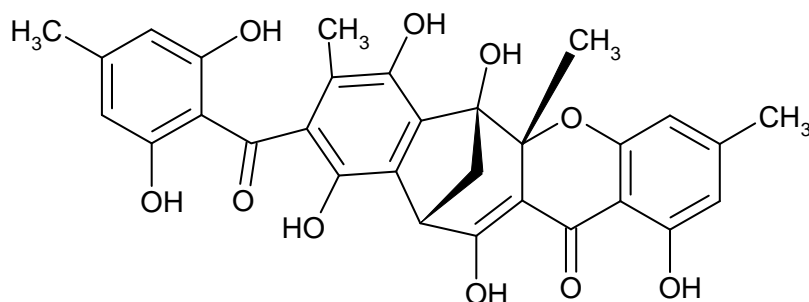


Fig 11: Structure microsphaerins D

5. Natural Compounds against MRSA and VRE

Methicillin resistant *S. aureus* (MRSA) is considered to be the main threat among all of the hospital-acquired infectious diseases, leading to several thousand deaths and 3 to 4 billion dollar expenditure in the USA alone [81]. Vancomycin-resistant isolates of *S. aureus* or *Enterococcus* (VRSA and VRE) are not as common as MRSA but are a growing concern because of the absence of effective antibiotics [82, 83]. The remarkable increase in the occurrence of bacterial antibiotic resistance by MRSA and VRE creates a severe health hazard worldwide [84]. Presently, vancomycin or a combination of linezolid and streptogramin are commonly used for the MRSA infections though there is a gradual increase of resistance against these antibiotics [85, 86]. A substantial review paper covers marine micro-organisms, delivering a variety of natural compounds against MRSA and VRE [87]. So, in this review, marine micro-organism derived secondary metabolites against MRSA/VRE will not be included. However, the following review will focus on some

compounds isolated from other marine organisms along with terrestrial plants.

5.1 Pestalone and 7-deacetoxyanuthone A

A halogenated benzophenone “Pestalone” (Figure 12 A), isolated from a marine fungus *Pestalotia* sp., exhibits high activity against MRSA (MIC = 0.037 mg/L) and VRE (MIC = 0.078 mg/L) [88]. It should be mentioned here that the production of pestalone relates to co-cultured fermentation process with a marine bacterium strain CNJ-328, initiated by the competition between the fungus and the bacterial strain [89]. Moreover, pestalone displays modest in vitro cytotoxicity against 60 human tumour cell line screen (mean GI₅₀ = 1.85 mg/L) [65]. Another marine-derived fungus (*Penicillium* sp.) delivers a polyoxygenated farnesyl cyclohexenone compound, named 7-deacetoxyanuthone A (Figure 12 B), which shows moderate in vitro activity against MRSA (MIC= 50 mg/L) as well as mild anti-tumour activity [90].

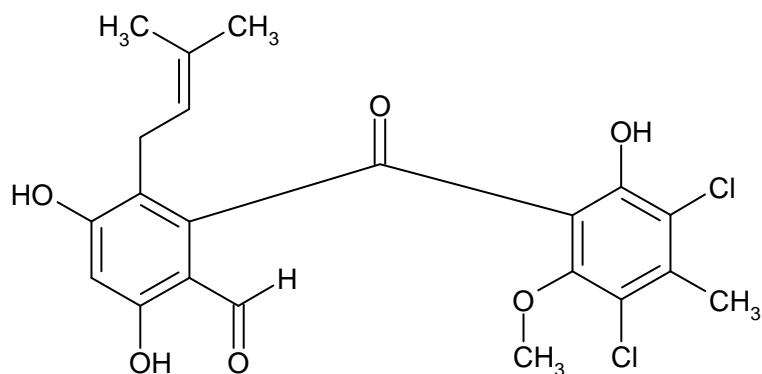


Fig 12 A: Structure of pestalone

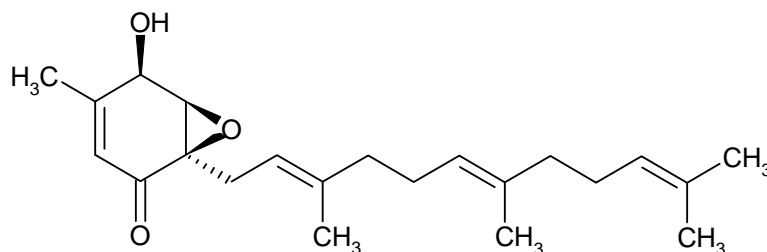


Fig 12 B: Structure of 7-deacetoxyanuthone

5.2 Enniatin B and Dioxopiperazine

While Enniatin B (Figure 13), a cyclodepsipeptide isolated from *Fusarium* sp., shows potent antibacterial activity against MRSA (2.5 mg/L) and VRE (2.5 mg/L) [63, 91], the anthracene glycosides, asperflavin (Figure 14 A) and ribofuranoside (Figure 14 B), isolated from the marine-derived fungus *Microsporium* sp., exhibits moderate effectivity against MRSA (MIC 50 mg/L) [92]. Since enniatin B possesses ionophoric properties, it displays antimicrobial, anthelmintic, cytotoxic and phytotoxic activities against

several cancer cell lines [93]. However, occurrence of enniatin B as food contaminants [93] requires further investigation of its toxicity [94]. Another study identifies three anti-MRSA dioxopiperazine compounds from a marine-derived fungus of the genus *Pseudallescheria*, which include dehydroxy-*bis*-dethio-*bis*-(methyl-dethio) gliotoxin (Figure 15A), *bisdethiobis* (methylthio) gliotoxin (Figure 15 B) and gliotoxin (Figure 15 C), demonstrating activity against MRSA with MIC values of 31.2, 31.2, and 1.0 mg/L, respectively [95].

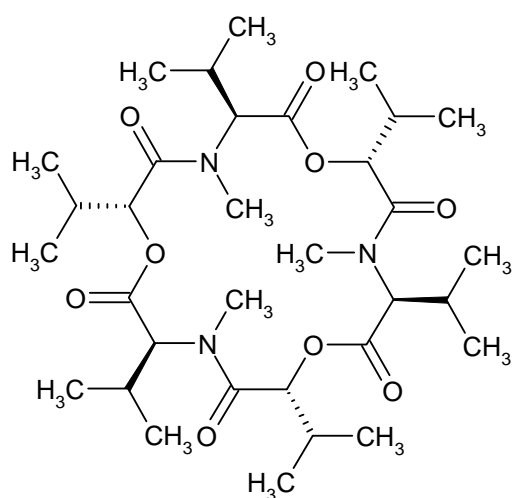
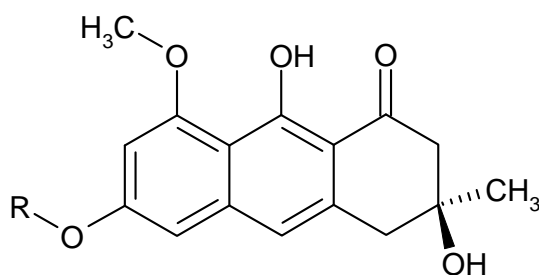
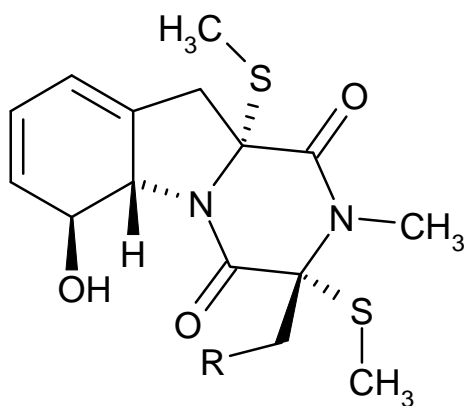


Fig 13: Structure of enniatin B

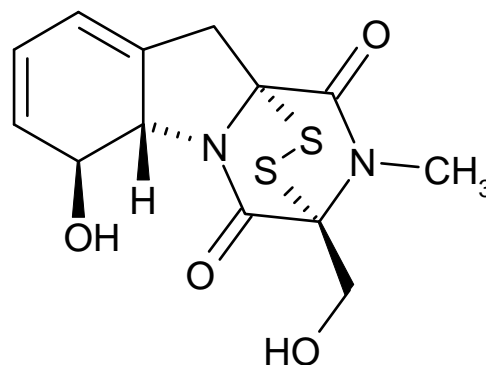


14 A: R = H for asperflavin
14 B: R = α -D-ribofuranose Asperflavin ribofuranoside

Fig 14: Structure of asperflavin (14 A) and asperflavin ribofuranoside (14 B)



15 A: R = H, 15 B: R = OH



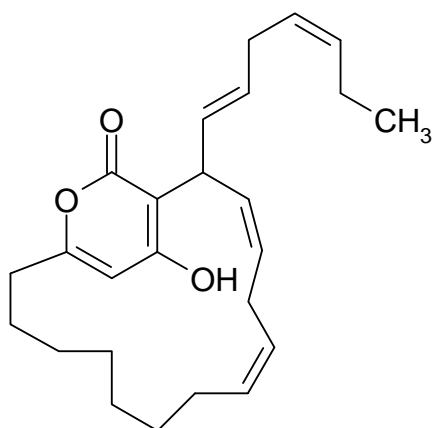
15 C

Fig 15: Structure of dehydroxybisdethiobis- (methylthio) gliotoxin (**15 A**), bisdethiobis (methylthio) gliotoxin (**15 B**), and gliotoxin (**15 C**).

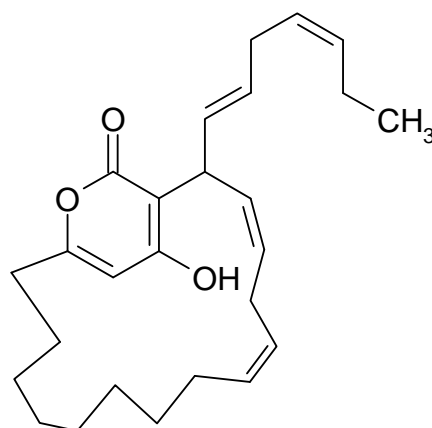
5.3 Neurymenolides

Anti MRSA α -pyrone macrolides, neurymenolides A (Figure 16 A) and B (Figure 16 B) were isolated from the Fijian red alga *Neurymenia fraxinifolia*. Neurymenolide A exists as interchanging atropisomers due to restricted rotation about the α -pyrone ring system. Neurymenolide A exhibits better

activity against MRSA (IC_{50} of 0.65 mg/L), VRE (IC_{50} of 1.39 mg/L) than neurymenolide B, recommending that the size or conformational restriction may have a role for the activity [96]. Furthermore, two anti-MRSA compounds (Figure 17 A & B) have been isolated from a culture of an endophyte *Penicillium* sp [97, 98].

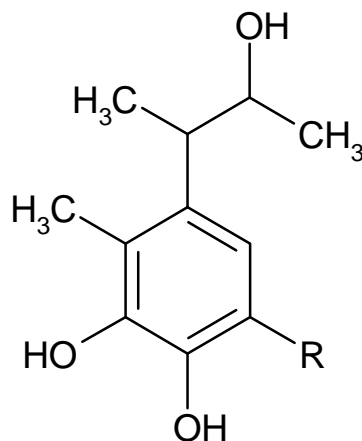


16 A



16 B

Fig 16: Structure of Neurymenolide A (**16 A**) and Neurymenolide B (**16 B**)



17 A: R = Me, 17 B: R = Ac

Fig 17: Structure of compounds 17 A & B

5.4 Trichoderamide B and Farnesol

A dipeptide trichoderamide B (Figure 18), isolated from a marine-derived fungus *Trichoderma virens*, exhibits potent activity (0.32mg/L) against MRSA and VRE. This compound also shows activity against HCT-116 human colon carcinoma in the same concentration as mentioned [99]. An isoprenoid Farnesol (Figure 19), common in many aromatic plants, has shown significant synergistic effects

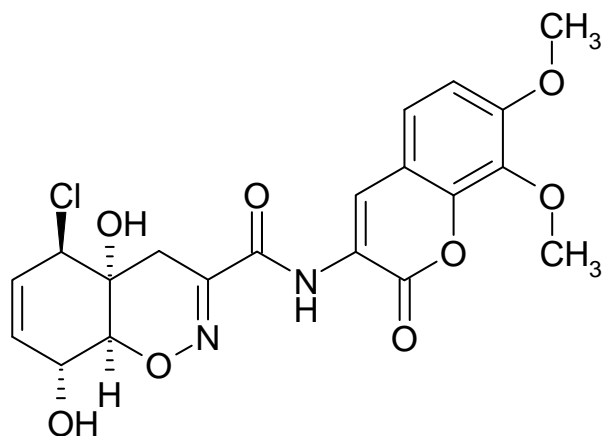


Fig 18: Structure of trichoderamide B

5.5 Xanaleric Acids, Stilbene and Kaempferol

A study shows that endophytic fungus *Alternaria* sp., found in China, is believed to be a potential source of two xanaleric acids I (Figure 20 A) and II (Figure 20 B), displaying low antibiotic activity against MRSA with MICs 125 mg/L and 250 mg/L, respectively [101]. Conversely, stilbene (*E*)-3-hydroxy-5-methoxystilbene (Figure 21), a promising plant-derived antimicrobial, isolated from the leaves of *Comptonia peregrine*, shows potent activity against a variety of pathogens, such as MRSA (MIC 32 mg/L) VRE (16 mg/L), *Bacillus anthracis* (MIC 8 mg/L) and

when used with β -lactam antibiotics (e.g. ampicillin, oxacillin, cefoxitin, bacitracin, teicoplanin etc.) against MRSA through retardation of cell wall biosynthesis by reducing free C₅₅ lipid carrier, followed by inhibition of murein monomer precursor transport across the cell membrane [100]

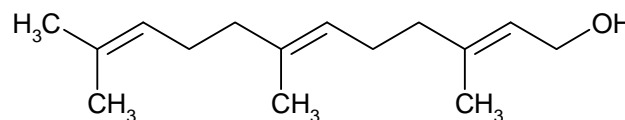


Fig 19: Structure of farnesol

Mycobacterium bovis (26 mg/L) [102]. Furthermore, an American sycamore, plant *Platanus occidentalis* delivers four potent and selective anti-MRSA secondary metabolites, which include kaempferol 3-*O*-*R*-*L*-(2'',3''-*di-Ep*-coumaroyl) rhamnoside (Figure 22 A) (IC₅₀ = 2.0 mg/L), kaempferol 3-*O*-*R*-*L*-(2''-*E-p*-coumaroyl-3''-*Z-p*-coumaroyl) rhamnoside (Figure 22 B) (IC₅₀ = 0.8 mg/L), kaempferol 3-*O*-*R*-*L*-(2''-*Z-p*-coumaroyl-3''-*E-p*-coumaroyl) rhamnoside (Figure 22 C) (IC₅₀ = 0.7 mg/L), and kaempferol 3-*O*-*R*-*L*-(2'',3''-*di-Z-p*-coumaroyl) rhamnoside (Figure 22 D) (IC₅₀ = 0.4 mg/L) [103].

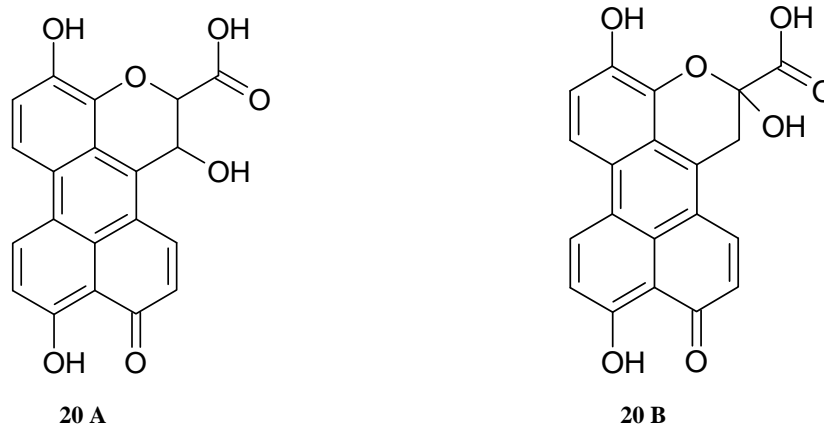


Fig 20: Structure of xanaleric acid I (20 A) and II (20 B)

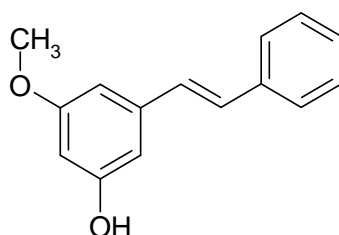
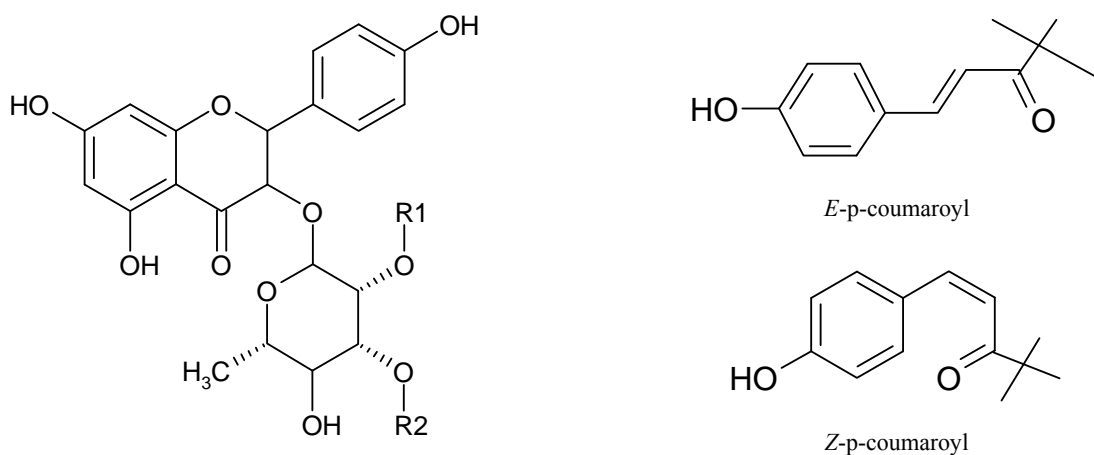


Fig 21: Structure of (*E*)-3-hydroxy-5-methoxystilbene



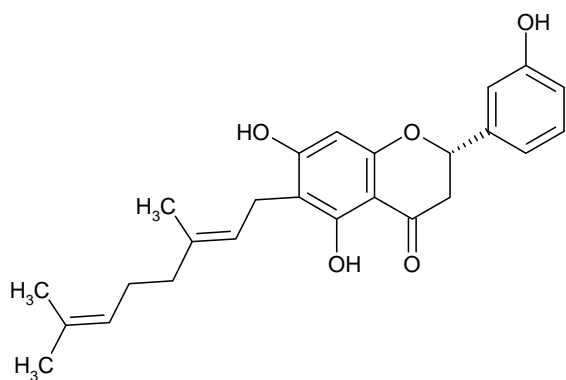
22 A: R1 =R2= *E*-p-coumaroyl, **22 B:** R1 = *E*-p-coumaroyl, R2= *Z*-p-coumaroyl
22 C: R1 = *Z*-p-coumaroyl, R2= *E*-p-coumaroyl, **22 D:** R1 =R2= *Z*-p-coumaroyl

Fig 22: Structure of kaempferols (**22 A-C**)

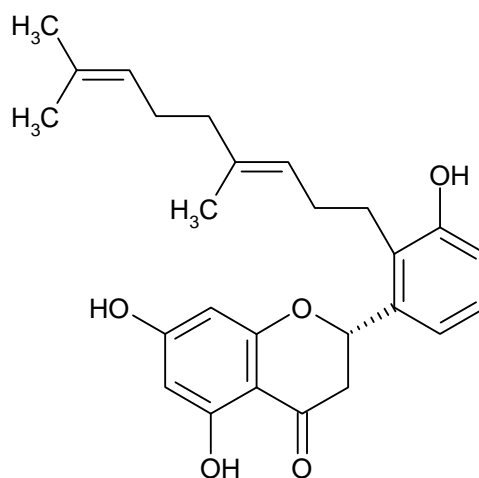
5.6 Propolin, Magnolol, Honokiol, and α -Mangostin

It has been reported that propolin C (Figure 23 A) and propolin D (Figure 23 B), isolated from propolis, exhibit potent activity against MRSA with MICs 8–32 $\mu\text{g/L}$ and 8–16 mg/L, respectively [104]. Another study isolates magnolol (Figure 24 A) and honokiol (Figure 24 B) from the medicinal plant *Magnolia officinalis*, which show potential activities against VRE and MRSA at MIC 6.25–25

mg/L. Additionally, both compounds exhibit potential cytotoxic properties against human ovarian adenocarcinoma, hepatocellular and carcinoma cervical epitheloid carcinoma cell lines at 3.3–13.3 mg/L [105]. Besides, the stem bark of a south east Asian plant *Garcinia mangostana* L. delivers α -Mangostin (Figure 25) which shows activities against VRE (6.25 mg/L) and MRSA (6.25-12.5 mg/L) [106].

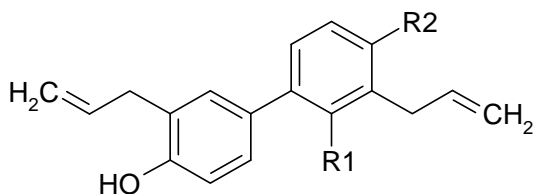


23 A



23 B

Fig 23: Structure of Propolin C (**23 A**) and propolin D (**23 B**)



24 A: R1 = OH, R2 = H and **24 B:** R1 = H, R2 = OH

Fig 24: Structure of magnolol (**24 A**) and honokiol (**24 B**)

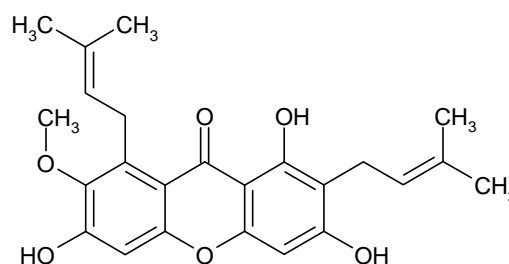


Fig 25: Structure of α -Mangostin

5.7 GE2270 A and Panduratin A

One study reports thiopeptide-based natural product GE2270 A (Figure 26), isolated from the fermentation of *Planobispora rosea* ATCC 53773, a strain of the rarest genera of actinomycetes, which exhibits potential activity

against MRSA and VRE (< 1 mg/L) [107]. Another study discusses a natural chalcone compound panduratin A (Figure 27), isolated from the plant *Kaempferia pandurata* Roxb, shows high potency against MRSA at MIC 1 mg/L [108].

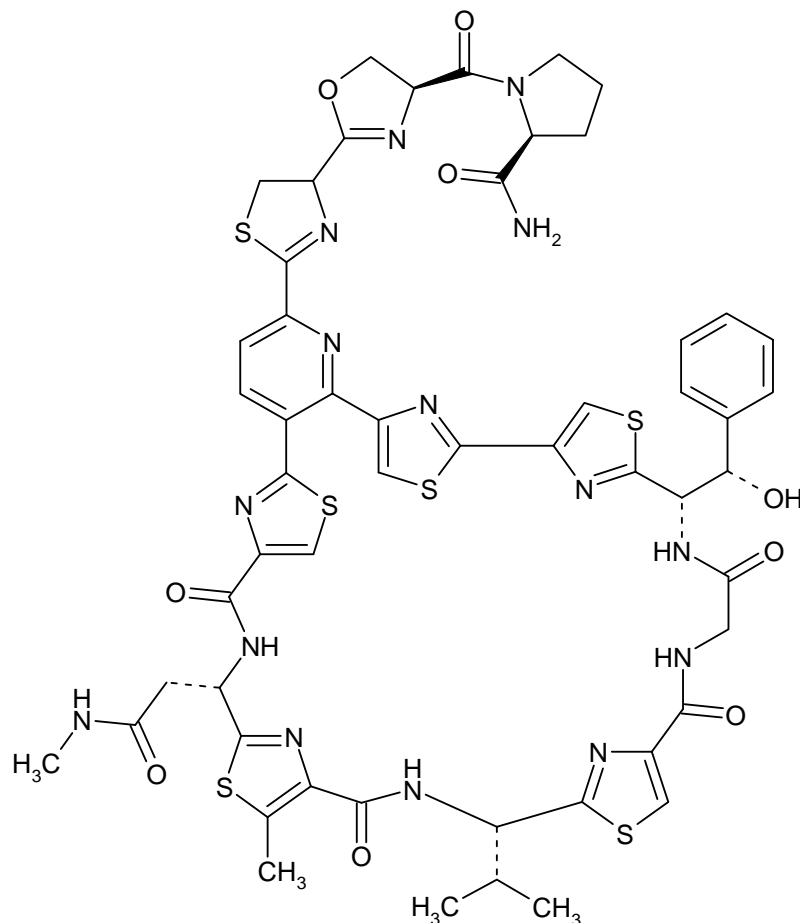


Fig 26: Structure of GE2270 A

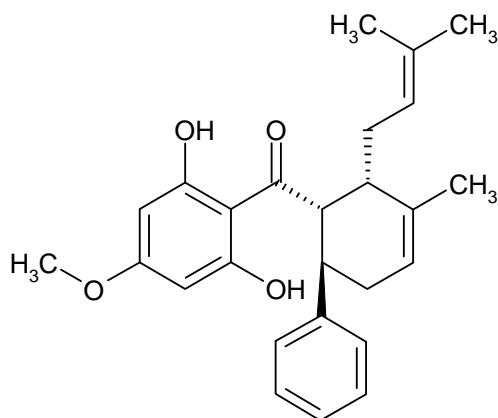


Fig 27: Structure of panduratin A

5.8 2-(2', 4'-Dibromophenoxy)-4, 6-dibromophenol and flavonoids kaempferol

The marine sponge *Dysidea granulose*, native to the Indian Ocean, produces 2-(2',4'-Dibromophenoxy)-4,6-dibromophenol (Figure 28) which displays potent *in-vitro* antibacterial activity against MRSA and VRE at the MIC

range of 0.12-2.5 mg/L [109]. Two flavonoids kaempferol 3-O- α -L-(2'',4''-di-*E*-p-coumaroyl)-rhamnoside (Figure 29 A) and kaempferol 3-O- α -L-(2''-*Z*-p-coumaroyl-4''-*E*-p-coumaroyl)-rhamnoside (Figure 29 B), isolated from *Laurus nobilis* L. (Lauraceae) leaves, show antibacterial activity against MRSA (MIC = 1-2 mg/L) [110].

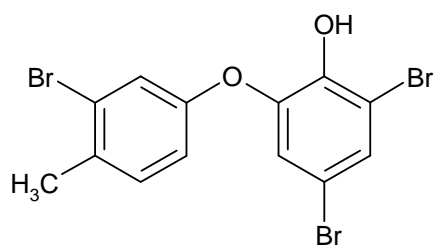
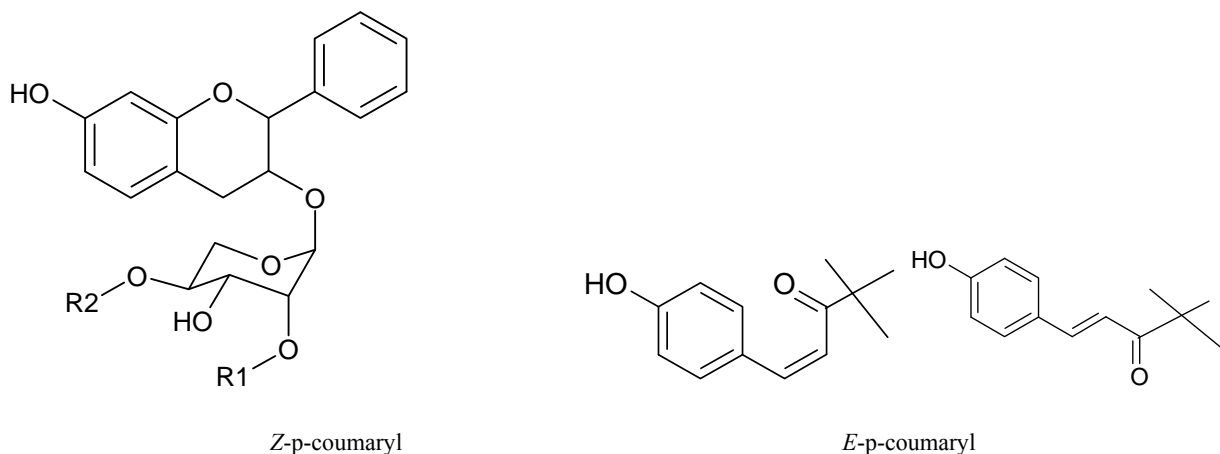


Fig 28: Structure of 2-(2', 4'-Dibromophenoxy)-4, 6-dibromophenol



29 A: R1 = R2 = Z-p-coumaryl and **29 B:** R1 = Z-p-coumaryl R2 = E -p-coumaryl

Fig 29: Structure of kaempferol from *Laurus nobilis* L.

5.9 Abietane diterpenoids, 2-arylbenzofuran, and pumilicin

Two novel abietane diterpenoids, hanagokenol A (Figure 30 A) and B (Figure 30 B), isolated from *Cladonia rangiferina*, display antimicrobial activity against MRSA (100 mg/L) and VRE (100 mg/L) [111]. While pumilicin 4 (molecular weight: 1994.62 Dalton), a novel bacteriocin, isolated from *B. Pumilus*, is reported to be bacteriostasis at low dosage (3.32

$\times 10^{-17}$ mg/L), it presents bactericidal effect at high dosage (1.33×10^{-16} mg/L) to both MRSA and VRE [112]. A 2-arylbenzofuran compound, named Chalcomoracin (Figure 31), was isolated from the leaf phytoalexine of mulberry tree, exhibits high antibacterial activity against MRSA (MIC 0.78 mg/L) [113] another study describes plant-derived 2-arylbenzofurans, exhibiting anti-MRSA (MIC₈₀ = 3.13 mg/L) properties [114].

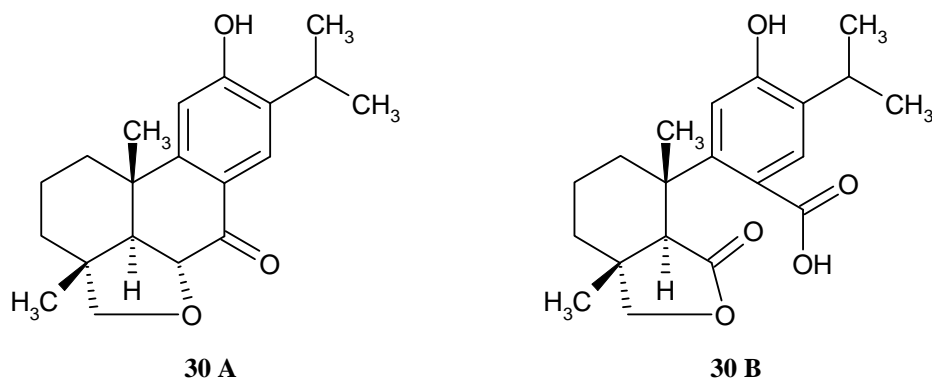


Fig 30: Structure of hanagokenol A (30A) and B (30B)

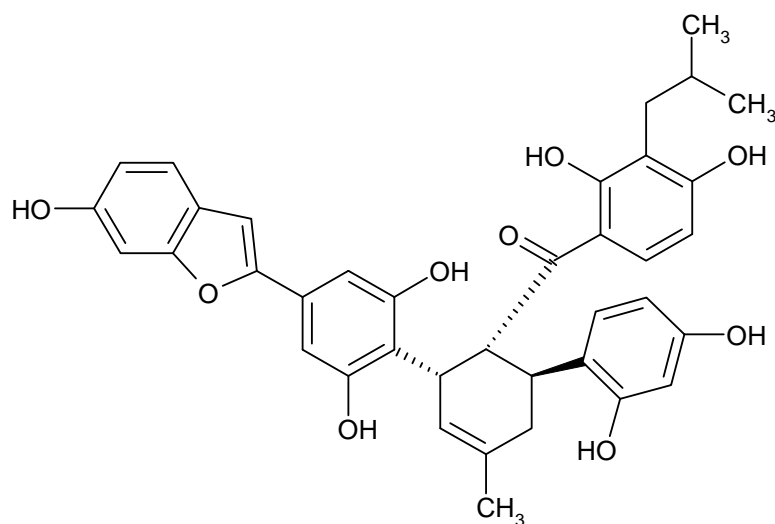


Fig 31: Structure of chalcomoracin

5.10 Triterpene, Alkannin, Guanacastepene, and Pterocarpan

A triterpene, $1\beta, 3\beta$ -dihydroxyurs-12-en-27-oic acid (Figure 32) isolated from the Argentinian plant *Caiophora coronata*, displays activity against MRSA and VRE with MIC 4 mg/L [115]. Extracts from *Arnebia euchroma*, leading to the isolation of alkannin (Figure 33) and its derivatives (e.g. enantiomer and shikonin), are found to be active against MRSA (MIC 1.56 - 3.13 mg/L) and VRE (MIC = 6.25 mg/L) [116]. A fungal culture, collected from the branch of a

Daphnopsis Americana, leading to the isolation of Guanacastepene (I) that shows activity against MRSA and VRE. Moreover, it (Figure 34) produces 11 and 17 mm zones against MRSA and VRE with 100 μ g in agar diffusion assays [117]. One research explains four pterocarpan anti-MRSA compounds, namely sandwicensin (Figure 35 A), erythribyssin A (Figure 35 B), erythrabissin I (Figure 35 C) and eryvarin D (Figure 35 D), isolated from the stems of *Erythrina fusca* Lour., with MICs of 16, 32, 64 mg/L, respectively [118].

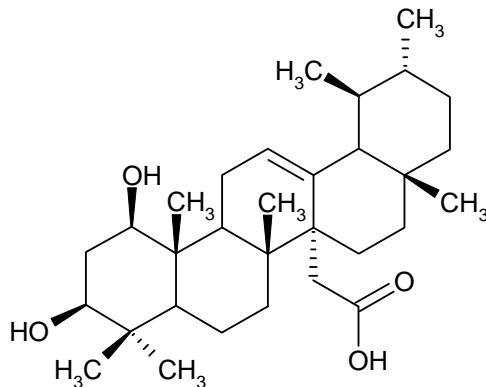


Fig 32: Structure of triterpene, $1\beta, 3\beta$ -dihydroxyurs-12-en-27-oic

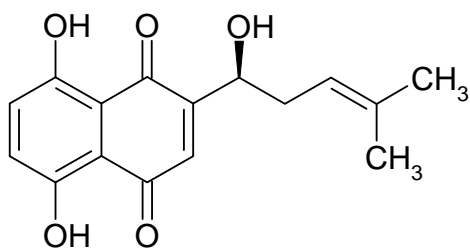


Fig 33: Structure of alkannin

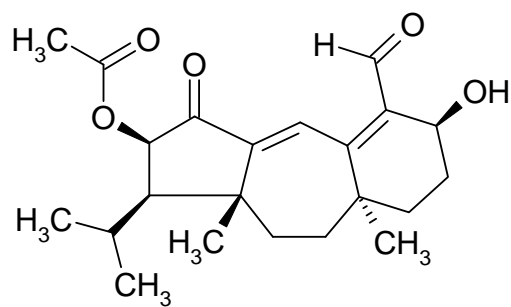
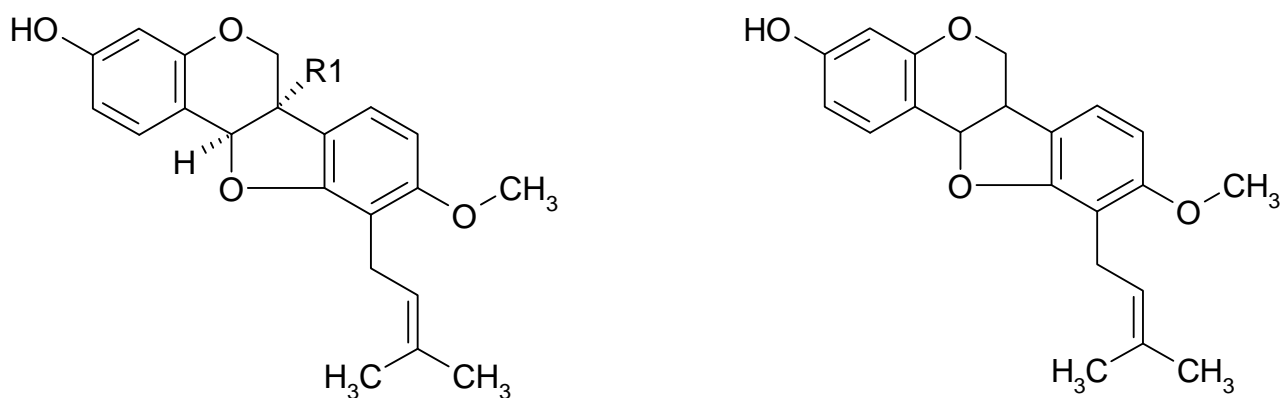


Fig 34: Structure of guanacastepene



35 A: R1 = H, 35 B: R1 = OMe, 35 C: R1 = OH

35 D

Fig 35: Structure of pterocarpan (35 A-D)

5.11 Sorocenols, Polyketide chaxamycin D, Crossbyanol B and Sepicanin A

Two sorocenols G (Figure 36) and H (Figure 37), isolating from *Sorocea muriculata*, show considerable and selective activity against MRSA with IC_{50} values of 1.5 and 0.5 μ M, respectively [119]. It has been reported that *Streptomyces* sp. strain C34, leading to the isolation of ansamycin-type polyketide chaxamycin D (Figure 38), shows a selective antibacterial activity against MRSA (1-3 mg/L) [120]. Another

study identifies that marine cyanobacterium *Leptolyngbya crossbyana* is a potential source of heptabrominated polyphenolic ether, crossbyanol B (Figure 39), showing antibiotic activity against MRSA with an MIC value of 2.0-3.9 mg/L [121]. A geranyl flavanone, sepicanin A (Figure 40), isolating from *Artocarpus sepicanus*, exhibits a potent and selective activity against MRSA (IC_{50} = 1.4 μ M) and (MIC = 2.9 μ M) [122].

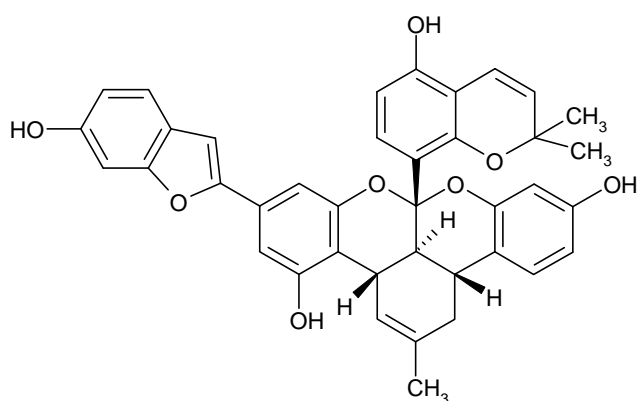


Fig 36: Structure of sorocenols G

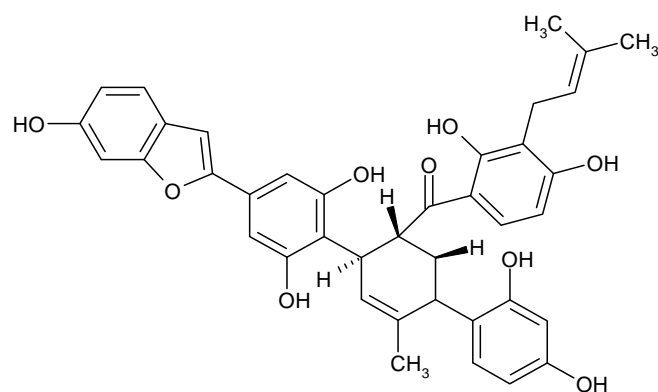


Fig 37: Structure of sorocenols H

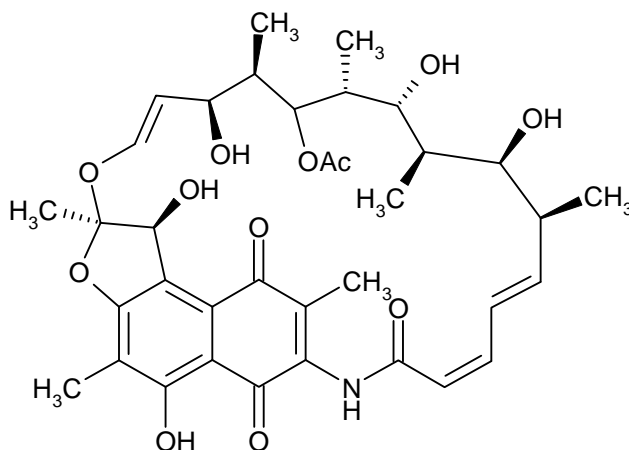


Fig 38: Structure of Chaxamycin D

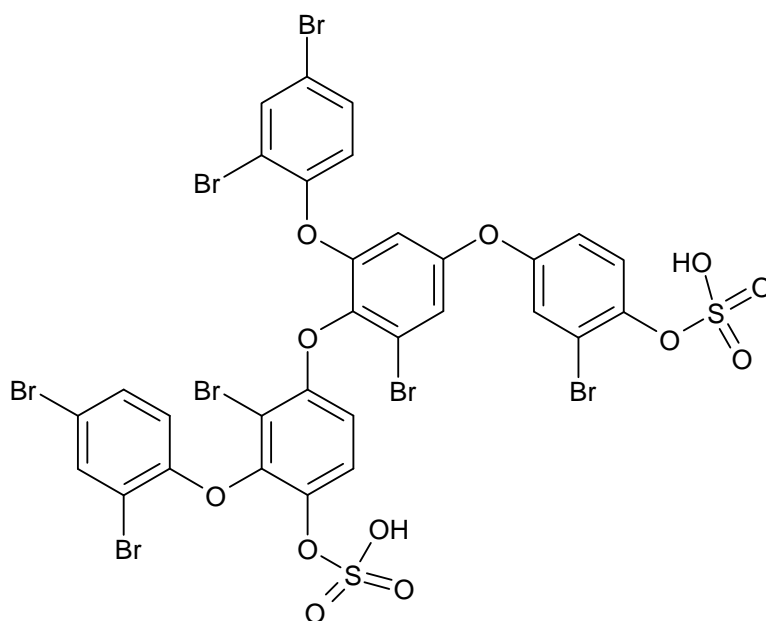


Fig 39: Structure of crossbyanol B

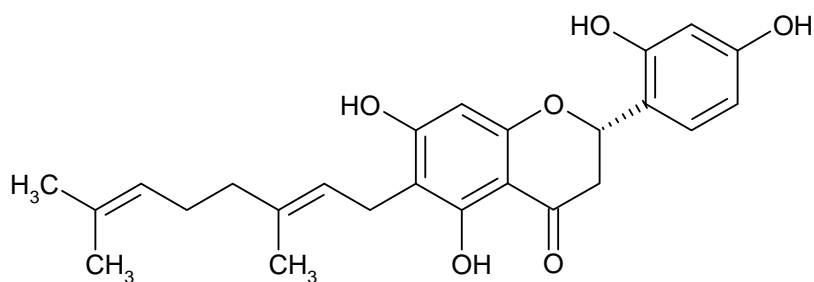


Fig 40: Structure of Sepicanin A

5.12 Norselic acid and Rhodomyrtone

The norselic acid A (Figure 41), isolating from sponge *Crella* sp., shows activity against MRSA and VRE [123]. The crude extract of *Rhodomyrtus tomentosa* (Aiton) Hassk, leading to the isolation of rhodomyrtone [6, 8-dihydroxy-2, 2, 4, 4-tetramethyl-7-(3-methyl-1-oxobutyl)-9-(2-methylpropyl)-4, 9-dihydro-1H-xanthene-1,3 (2H)-di-one] (Figure 42), shows

considerable activity against MRSA (MIC 0.39 - 0.78 mg/L) [124]. On the other hand, the extract from the whole herb of *Plectranthus ernstii*, leading to the isolation of diterpenoid *rel*-15(ζ), 16-epoxy-7α-hydroxypimar-8, 14-ene (Figure 43), displays moderate activity against MRSA with MIC of 32 mg/L [125].

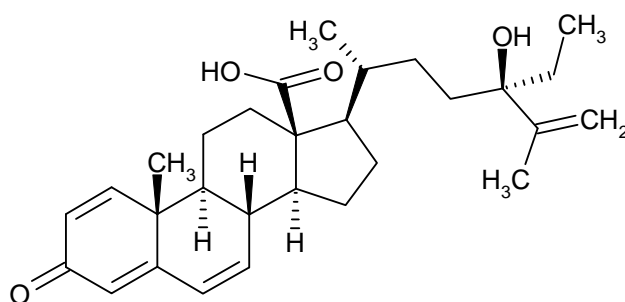


Fig 41: Structure of norselic acid A

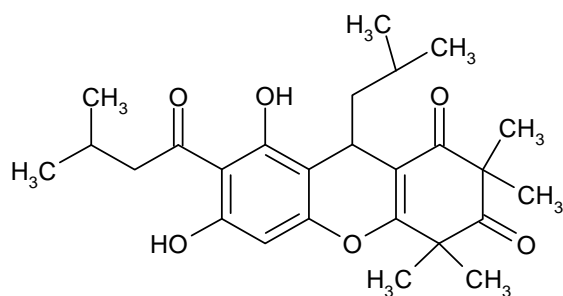


Fig 42: Structure of rhodomyrtonone

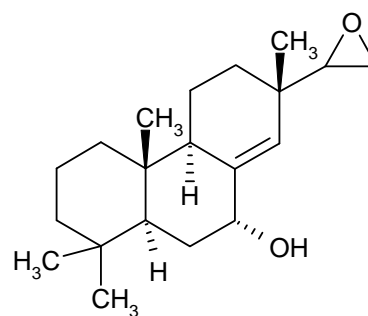
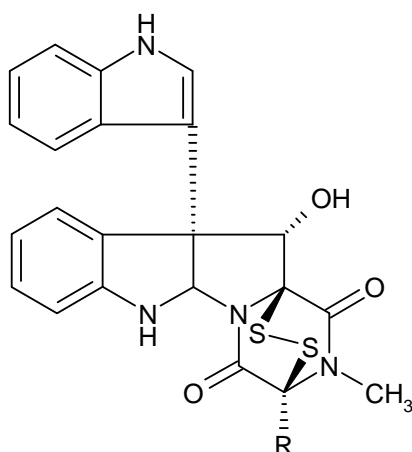


Fig 43: Structure of *rel*-15(ζ), 16-epoxy-7α-hydroxypimar-8,14-ene

5.13 Benzophenone Dimers, epidithiodioxopiperazine, fusidane triterpene and stemphone

Several studies indicate that fungus provides a considerable number of compounds capable of inhibiting pathogens causing nosocomial infections. For example, the fungus *Microsphaeropsis* sp., is reported to be an important source of novel benzophenone dimers, microsphaerins D (Figure 11), which display potent antibacterial activities, against MRSA (1 mg/L) [57]. Furthermore, two epidithiodioxopiperazine compounds, bionectins A (Figure 44 A) and B (Figure 44 B), isolating from the liquid

fermentation cultures of the fungus *B. byssicola* F120, express antibacterial activity against MRSA with MIC 10-30 mg/L [126]. Another species of mitosporic fungus *Acremonium crotonigenum* is a source of a fusidane triterpene, 16-deacetoxy-7-β-hydroxy-fusidic acid (Figure 45) that presents activity against MRSA strains with MIC value 16 mg/L [127]. Besides, stemphone C (Figure 46), isolating from a fungal strain *Aspergillus* sp. FKI-2136, functions as a potentiator of imipenem activity against MRSA with MIC value ranging from (0.03-16) mg/L [128].



44 A: R= H and **44 B:** R= CH (OH) CH₃

Fig 44: Structure of bionectins A (**44 A**), B (**44 B**)

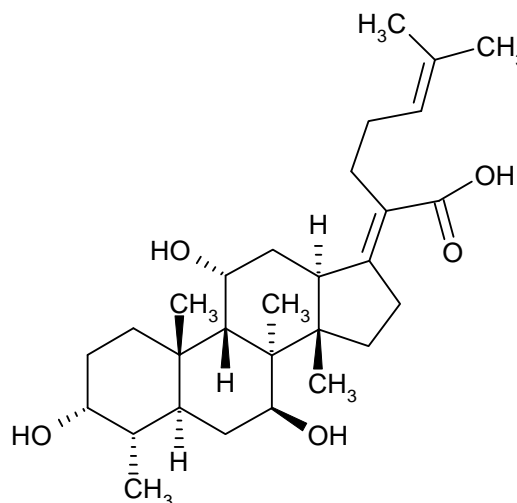


Fig 45: Structure of fusidane triterpene, 16-deacetoxy-7-β-hydroxy-fusidic acid

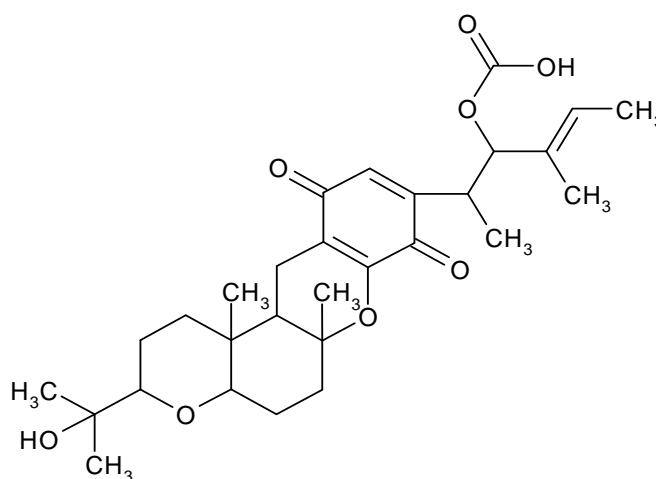
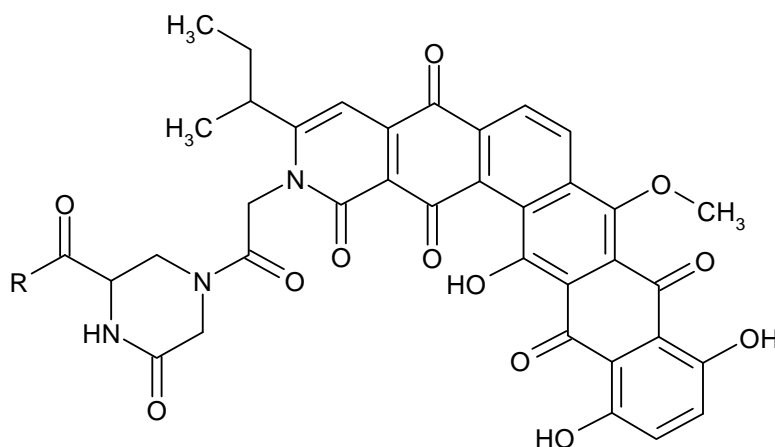


Fig 46: Structure of stemphone C

5.14 TLN-05220, TLN-05223, and TPPaiC

The antibiotics TLN-05220 (Figure 47 A) and TLN-05223 (Figure 47 B), bearing six fused rings starting with a 2-pyridone moiety, isolating from the strain *Micromonospora polytota*, have been proved to be effective against MRSA (MIC 1 mg/L) and VRE (MIC 1-3 mg/L) [129]. Another strain

Lysobacter sp. BMK333-48F3 produces a novel compound TPPaiC (Figure 48), which is a tri-propeptin conjugated with a branched chain fatty acid. The compound exhibits high and selective activity against MRSA (MIC 0.39-3.13 mg/L) and VRE (MIC 6.25-25 mg/L) [130].



47 A: TLN-05220 R = H and **47 B:** TLN-05223 R = Me

Fig 47: Structure of TLN-05220 (**47 A**) and TLN-05223 (**47 B**)

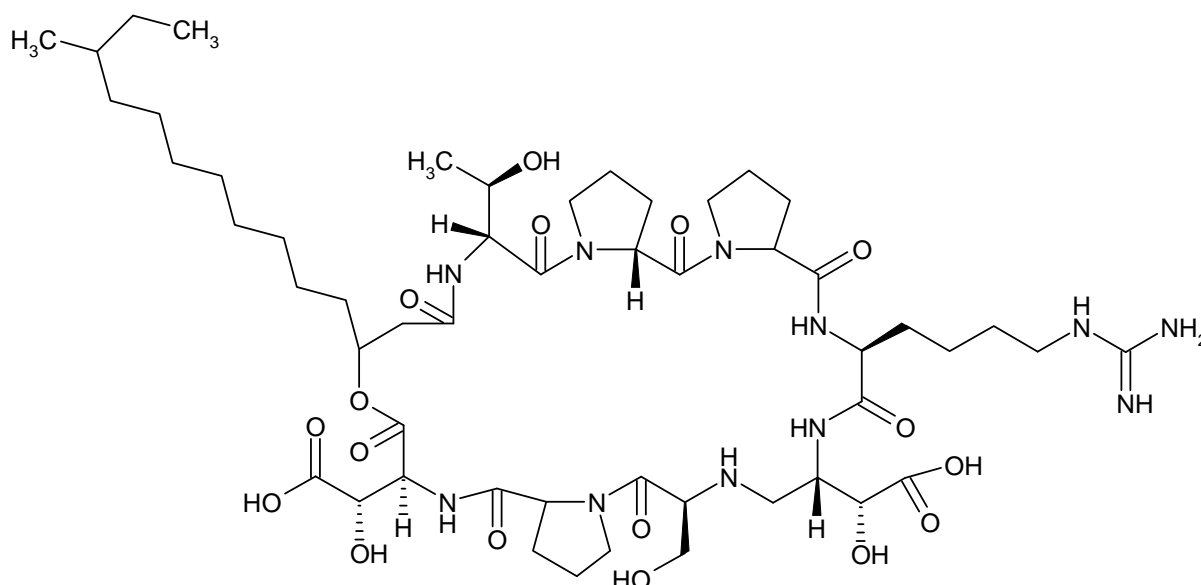


Fig 48: Structure of the TPPaiC

5.15 Pargamicin A, Viridicatumtoxin B, Cyslabdan, WAP-8294A2, and Decatromicins A

An actinomycete strain ML1-hF4 produces a cyclic hexapeptide, pargamicin A (Figure 49) that shows potent antibacterial activity against MRSA (MIC 0.39-0.78 mg/L) and VRE (MIC 0.39 mg/L) [131]. Viridicatumtoxin B (Figure 50), isolating from the liquid culture of *Penicillium* sp. FR11, is a tetracycline derivative with potent activity against MRSA and VRE with a MIC 0.5 mg/L, which is comparable to the MIC of vancomycin and much more potent than that of tetracycline [132]. Research shows that the effectiveness of β -

lactam antibiotic imipenem increases from 16 to 0.015 mg/L against MRSA, when used in combination with a natural product cyslabdan (Figure 51) that has been extracted from *Streptomyces* sp. K04-0144 [133]. A peptide antibiotic, WAP-8294A2 (Figure 52), isolating from *Lysobacter* sp., displays *in vivo* activity in mice against MRSA (MIC 0.78 mg/L) and VRE (MIC 6.25 mg/L) infections [134]. The strain *Actinomadura* sp. MK73-NF4 produces the antibiotics decatromicins A (Figure 53 A) and B (Figure 53 B) that strongly inhibit the growth of MRSA with MICs of 1.90 mg/L and 0.80 mg/L, respectively [135].

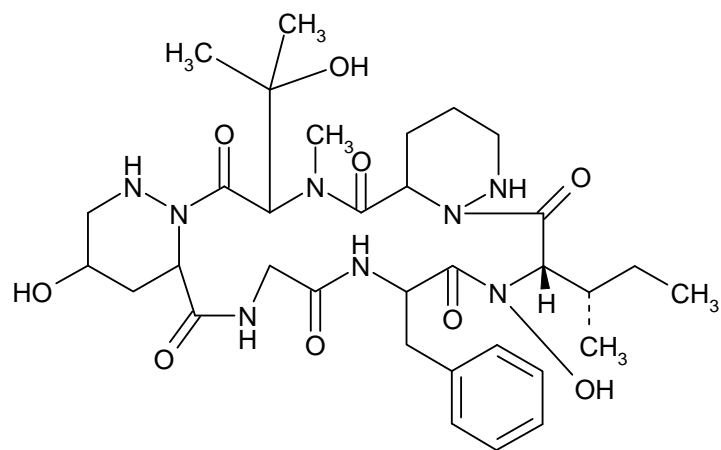


Fig 49: Structure of pargamicin A

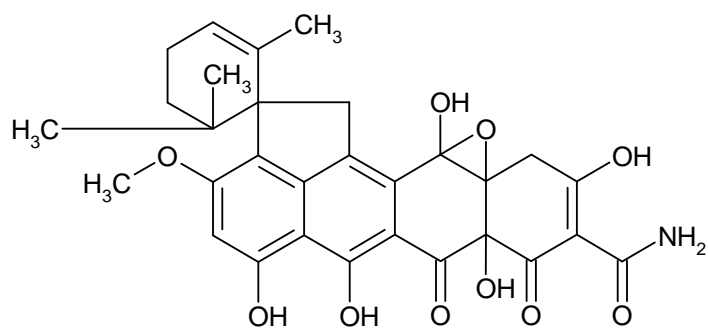


Fig 50: Structure of viridicatumtoxin B

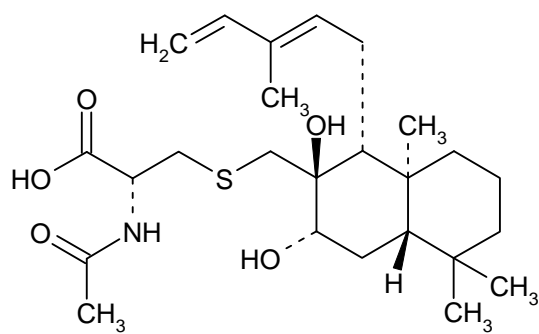


Fig 51: Structure of cyslabdan

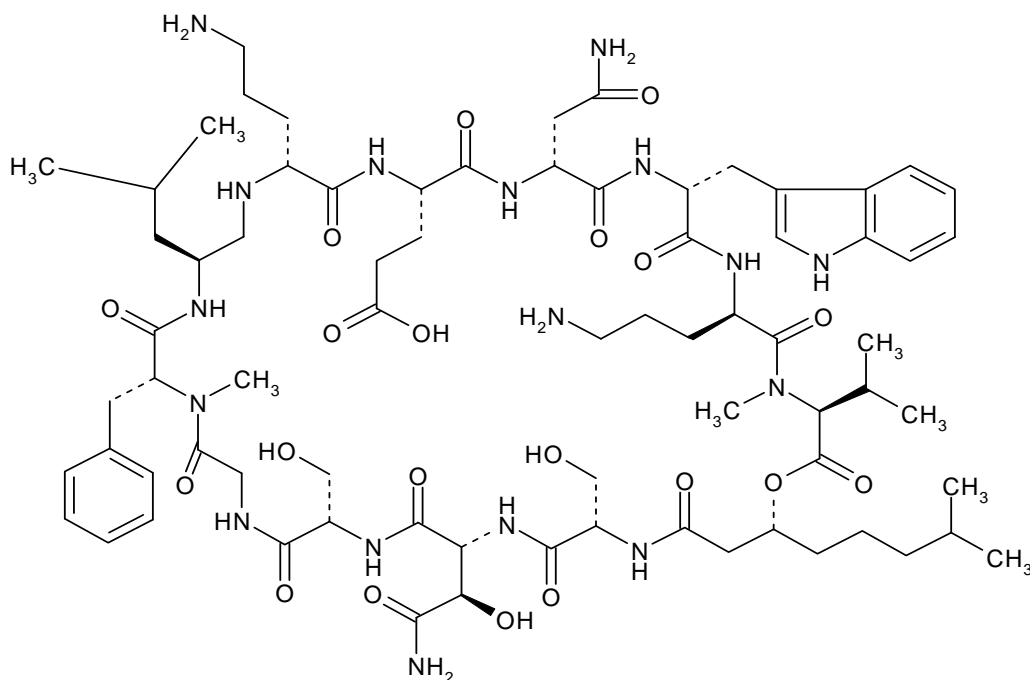
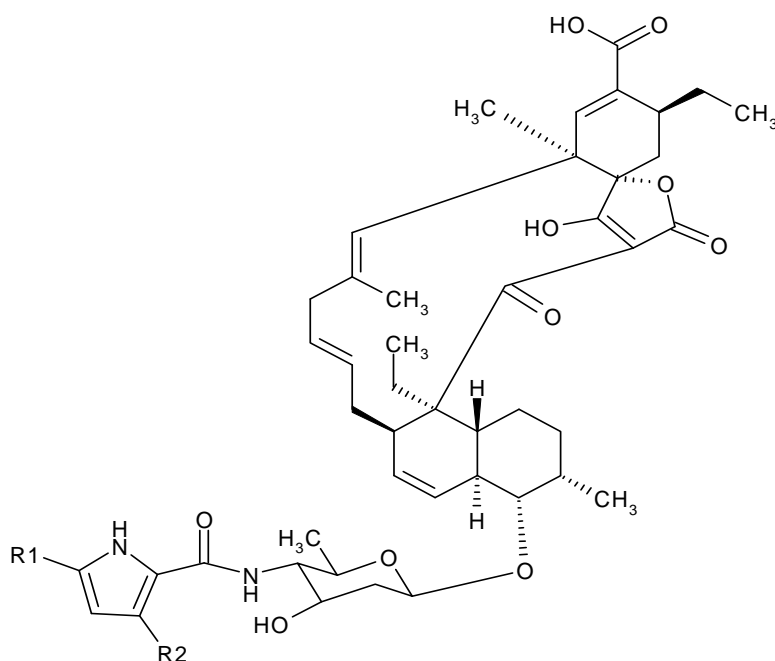


Fig 52: Structure of WAP-8294A2



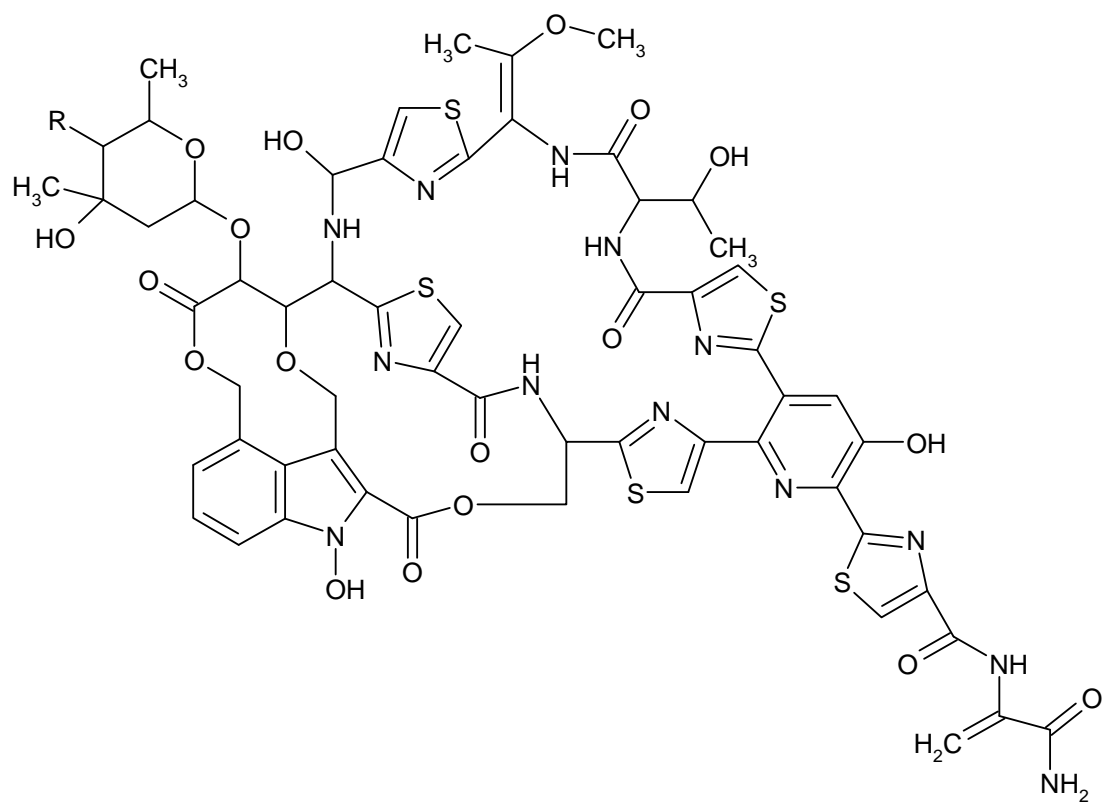
decatromicins A (**53 A**): R1 = H, R2 = Cl
 decatromicins B (**53 B**): R1 = Cl, R2 = Cl

Fig 53: Structure of decatromicins A (**53 A**) and B(**53 B**)

5.16 MJ347-81F4 and Pyrroindomycins

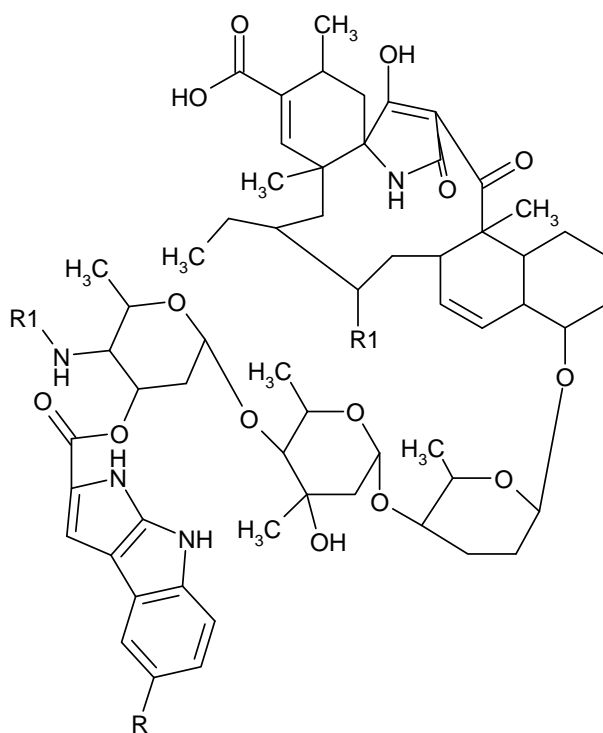
Fermentation of *Amycolatopsis* sp. of the large family of *Amycolatopsis*, leading to the isolation of two relevant cyclic thiazolyl peptide antibiotics MJ347-81F4 A (Figure 54 A) and B (Figure 54 B) which display potent *in vitro* activity against MRSA and VRE with MIC values ranging from 0.006 to 0.1 mg/L [136]. A bacterial strain LL-42D005

(*Streptomyces rugosporus*) produces two un-saturated pyrroindole moiety, containing pyrroindomycins A (Figure 55 A) and B (Figure 55 B) which display potent antimicrobial activities against MRSA(0.06-0.12 mg/L and 0.12-0.50 mg/L, respectively) and VRE (0.25-0.50 and 0.25-1 mg/L respectively) [137, 138].



MJ347-81F4 A (**54 A**): R = N(CH₃)₂
 MJ347-81F4 B (**54 B**): R = NHCH₃

Fig 54: Structure of MJ347-81F4 A (**54 A**) and B (**54 B**)



pyrroindomycins A (**55 A**): R = Cl, R1 = -CoCH₃
 pyrroindomycins B (**55 B**): R = Cl, R1 = H

Fig 55: Structure of pyrroindomycins A (**55 A**) and B (**55 B**)

Discussion

It has been reported that more than two-thirds of clinically-used antibiotics are natural products ^[139] being effective against variety of microbes. The review demonstrates that most of the natural compounds like Vancomycin, Daptomycin, Colistins show high potentiality against *Clostridium difficile* except Rifamycin SV which requires comparatively high dose of MIC to perform effectively (Table 1). On the other hand, natural products which work well against Gram-negative Pathogens require reasonably high concentration of MIC. Compounds like Bromogeliferi and Oridin show modest activity in more than 200 mg/L whereas Dihydroventrin and Microsphaerins D are effective with 50 mg/L (Table 1). Natural compounds like Microsphaerins, Gliotoxin, kaemferols, GE-22702 A, Panduratin A, 1, 3- dihydroxyurs-12-en-27-oic acid, Chaxamycin etc. have been effective against MRSA while Xanalteric acid, Hanagokenol A and B, Guanacastepene are relatively less potential against the same. Some of the active compounds such as Pyrroindomycins, MJ347-81F4, Viridicatumto, Sorocinol G & H, Rhodomyrton etc. show considerable effectiveness against both MRSA and VRE in very low MICs (<1 mg/L) (Table 1).

Although most of the scaffolds are originated from natural sources ^[140] and subsequent tailoring of existing scaffolds have been reported to be ineffective against nosocomial infections or multi-drug resistant bacteria, initiatives to invest in exploring new scaffolds from natural sources are few ^[141]. The reasons behind such decline relates to increasing rate of scaffold rediscovery ^[142] and the accompanying difficulty in finding new antibiotics ^[2]. However, due to the revival of interest on natural antimicrobials in the last two decades, we have witnessed the development of new antibiotics based on novel scaffolds. Recently approved lipopeptide antibiotic daptomycin is an example of such endeavour. Classical approaches for screening novel antimicrobials should continue aided with improvement in screening platforms, new cultivation techniques, direct isolation of metabolites from environmental samples, genome mining for cryptic metabolic pathways, metagenomics and last but not least, modification of natural scaffolds.

6. Conclusions

Although numerous pathogens display resistance to conventional antimicrobials, the review focuses on those microbes which cause nosocomial infections including both Gram positive and Gram negative bacteria. While a number of drugs have so far been developed from natural sources (e.g. terrestrial plants and marine organisms), there is a great deal of variability in the effectiveness, demonstrating low, moderate, and potent activity against pathogens causing nosocomial infections. Since the rate of emergence of nosocomial infections shows increasing trend, intensive research should continue to explore potential terrestrial plants and marine organisms, which can offer promising and more potent drugs than existing antimicrobials with a view to containing global health problems related to nosocomial infections

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