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REVIEW

Bioactive compounds from marine actinomycetes

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Abstract Actinomycetes are one of the most efficient groups of secondary metabolite producers and are very important from an industrial point of view. Among its various genera, *Streptomyces, Saccharopolyspora, Amycolatopsis, Micromonospora* and *Actinoplanes* are the major producers of commercially important biomolecules. Several species have been isolated and screened from the soil in the past decades. Consequently the chance of isolating a novel actinomycete strain from a terrestrial habitat, which would produce new biologically active metabolites, has reduced. The most relevant reason for discovering novel secondary metabolites is to circumvent the problem of resistant pathogens, which are no longer susceptible to the currently used drugs. Existence of actinomycetes has been reported in the hitherto untapped marine ecosystem. Marine actinomycetes are efficient producers of new secondary metabolites that show a range of biological activities including antibacterial, antifungal, anticancer, insecticidal and enzyme inhibition. Bioactive compounds from marine actinomycetes possess distinct chemical structures that may form the basis for synthesis of new drugs that could be used to combat resistant pathogens.

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Introduction

Microbial natural products are an important source of both existing and new drugs. Among the producers of commercially important metabolites, bacteria have proven to be a prolific source with a surprisingly small group of taxa accounting for the vast majority of compounds discovered till date [1]. Among these, Actinomycetes are the most economically and biotechnologically priceless prokaryotes. Representative genera of actinomycetes include *Streptomyces*, *Actinomyces, Arthrobacter, Corynebacterium, Frankia, Micrococcus, Micromonospora* and several others. Secondary metabolites produced by actinomycetes possess a wide range of biological activities [1–4]. The genus *Streptomyces* alone produces a large number of bioactive molecules [5–128]. It has an enormous biosynthetic potential that remains unchallenged without a potential competitor among other microbial groups. A large number of *Streptomyces* spp. have been isolated and screened from soil in the past several decades [129, 130]. Consequently the chances of isolating a novel *Streptomyces* strain from terrestrial habitats have diminished. Above 500 species of *Streptomyces* account for 70–80% of relevant secondary metabolites as shown in Table 1 [5–127], with small contributions from other genera, such as *Saccharopolyspora, Amycolatopsis, Micromonospora and Actinoplanes*. An important reason for discovering novel secondary metabolites is to circumvent the problem of resistant pathogens, which are no longer susceptible to the currently used drugs [131, 132]. The number of deaths due to these clever pathogenic organisms is on the rise. Secondary metabolites from marine

Table 1 Secondary metabolites produced by actinomycetes

S. No.	Compound	Source	Activity
1.	Erythromycin [5]	*Saccharopolyspora erythrae*	Antibacterial
2.	Rhamnose [6]	*Saccharopolyspora spinosa*	Essential component of insect control agent compound spinosad
3.	Zorbamycin [7]	*Streptomyces flavovirdis*	Antitumor
4.	Kanamycin [8]	*Streptomyces kanamyceticus* 12-6	Antibacterial
5.	Kanglemycin C (K-C) [9]	*Nocardia mediterranei* var. *kanglensis* 1747-64	Immunosuppressive
6.	Rapamycin [10]	*Streptomyces hygroscopicus*	Antifungal
7.	Pandavir (nigericin) [11]	*Streptomyces hygroscopicus*	Affects ion transport and ATPase activity
8.	FK520 Ascomycin [12]	*Streptomyces hygroscopicus* var. *ascomyceticus*	Antifungal, immunosuppressive, neutrophic
9.	Himastatin [13]	*Streptomyces hygroscopicus*	Antitumor
10.	Jinggangmycin [14]	*Streptomyces hygroscopicus*	Antifungal
11.	Oxytetracycline [15]	*Streptomyces rimosus*	Antibacterial
12.	Amphotericin B [16]	*Streptomyces nodosus*	Antifungal
13.	Asukamycin [17]	*Streptomyces nodosus* subsp. *asukaensis*	Antibacterial
14.	Tylosin [18]	*Streptomyces fradiae*	Antibacterial
15.	Urdamycin A [19]	*Streptomyces fradiae*	Antitumor
16.	Fosfomysin [20]	*Streptomyces fradiae*	Antibacterial
17.	CE-108 [21]	*Streptomyces diastaticus*	Antifungal
18.	Rimocidin [22]	*Streptomyces diastaticus* var. 108	Antifungal
19.	Shurimycins A and B [23]	*Streptomyces hygroscopicus*	Antibacterial, antifungal
20.	Chloramphenicol [24]	*Streptomyces venezuelae*	Antibacterial
21.	Rifamycin [25]	*Amycolatopsis mediterranei* U-32	Antibacterial
22.	Amythiamicins [26]	*Amycolatopsis* sp.	Antibacterial
23.	Cyclo (L-leucyl-l-prolyl) [27]	*Streptomyces* sp. KH614	Antileukemic, anti-VRE (vancomycin-resistant enterococci)
24.	Ipomicin [28]	*Streptomyces ipomoeae* group III	Antibacterial
25.	Streptomycin [29]	*Streptomyces griseus*	Antibacterial
26.	Valinomycin [30]	*Streptomyces griseus*	Mitochondrial toxin
27.	Griseorhodin [31]	*Streptomyces griseus* FCRC-57	Telomerase inhibitor
28.	Fredericamycin A [32]	*Streptomyces griseus* FCRC-48	Antitumor
29.	Capuramycin [33]	*Streptomyces griseus* SANK 60196	Antibacterial
30.	Frigocyclinone [34]	*Streptomyces griseus strain* NTK 97	Antibacterial
31.	Clorobiocin [35]	*Streptomyces coelicolor*	Inhibitor of bacterial gyrase
32.	Meilingmycin [36]	*Streptomyces nanchangensis*	Antiparasitic
33.	Nanchangmycin [36]	*Streptomyces nanchangensis*	Insecticidal
34.	Eremomycin [37, 38]	*Amycolatopsis orientalis* subsp. *eremomycini*	Antimicrobial
35.	Nikkomycins [39]	*Streptomyces ansochromogenus*	Antifungal
36.	Avilamycin A [40]	*Streptomyces viridochromogenes* Tu57	Antibacterial
37.	Tubelactomicin A [41]	*Nocardia* sp.	Antibacterial

Table 1 (***Continued***)

S. No.	Compound	Source	Activity
38.	Benzanthrins A and B [42]	*Nocardia lurida*	Antibacterial
39.	Azureomycins A and B [43]	*Pseudonocardia azurea* nov. sp.	Antibacterial
40.	Nogalamycin [44]	*Streptomyces nogalater*	Antibacterial
41.	Aclacinomycin A (aclarubicin) [45]	*Streptomyces galilaeus*	Antitumor
42.	Cinerubin R [46]	*Streptomyces eurythermus*	Antibacterial
43.	Scopafungin [47]	*Streptomyces hygroscopicus* var. *enhygrus* var. nova UC-2397	Antifungal, antibacterial
44.	Spiramycin [48]	*Streptomyces ambofaciens*	Antibacterial
45.	Pristinamycin I [49]	*Streptomyces pristinaespiralis*	Antibacterial
46.	Lankacidin [50]	*Streptomyces rochei*	Antibacterial
47.	Lankamycin [50]	*Streptomyces rochei*	Antibacterial
48.	Actinomycin C [51]	*Streptomyces chrysomallus*	Antitumor
49.	Duanomycin [52]	*Streptomyces* sp.	Antitumor
50.	Midecamycin [53]	*Streptomyces mycarofaciens*	Antibacterial
51.	Avermectin [54]	*Streptomyces avermitilis*	Anthelminthic
52.	Oligomycin [55]	*Streptomyces avermitilis*	Cell growth inhibitor
53.	Resormycin [56]	*Streptomyces platensis*	Herbicidal, antifungal
54.	Ileumycin [57]	*Streptomyces lavendulae*	Antifungal
55.	Mitomycin C [58]	*Streptomyces lavendulae*	Antitumor
56.	Lomofungin [59]	*Streptomyces lomodensis*	Antifungal, antibacterial
57.	Kalafungin [60]	*Streptomyces tanashiensis* strain Kala UC5063	Antifungal, antibacterial, antiprotozoal
58.	Thiamycins [61]	*Streptomyces michiganensis* var. *amylolyticus* var. nova	Anthelminthic, antiprotozoal
59.	Axenomycins [62]	*Streptomyces lisandri* nov. sp.	Anthelminthic, antiprotozoal, antifungal
60.	Neihumicin [63]	*Micromonospora neihuensis*	Cytotoxic
61.	Fortimicin A (Astromicin) [64]	*Micromonospora olivasterospora*	Antibacterial
62.	Gentamicin [65]	*Micromonospora purpurea* var. *violaceae*	Antibacterial
63.	Tetracycline [66]	*Streptomyces aureofaciens*	Antibacterial
64.	Monomycin [67, 68]	*Actinomyces circulatus* var. *monomycini*	Antibacterial
65.	PC-766 B [69]	*Nocardia brasiliensis*	Antioxidant
66.	Medecamycin [70, 71]	*Streptomyces mycarofaciens*	Antibacterial
67.	Dunaimycins [72]	*Streptomyces diastatochromogenes*	Immunosuppressive, antimicrobial
68.	Novobiocin [73]	*Streptomyces niveus*	Antibacterial
69.	Carminomycin [74]	*Actinomadura carminata*	Antitumor
70.	Maduramycins [75]	*Actinomadura rubra*	Antibacterial
71.	MM461156 [76]	*Actinomadura pelletieri*	Antiviral, antibacterial
72.	Verucopeptin [77]	*Actinomadura verrucosospora*	Antitumor
73.	Saptomycins [78]	*Streptomyces* sp. HP 530	Antitumor, antimicrobial
74.	Oxaprapalines B, D, G [79]	*Streptomyces* sp. G324	Antitumor
75.	Lavendamycin [80]	*Streptomyces lavendulae*	Antitumor
76.	Chlorocarcins A, B, C [81]	*Streptomyces lavendulae* No. 314	Antitumor, antibacterial

Table 1 (***Continued***)

S. No.	Compound	Source	Activity
77.	Mimosamycins [81]	*Streptomyces lavendulae* No. 314	Antibacterial
78.	Lavendomycin [82]	*Streptomyces lavendulae*	Antibacterial
79.	Sohbumycin [83]	*Streptomyces* sp. 82-85	Antitumor, antibacterial
80.	Furaquinocins C, D, E, F, G, H [84]	*Streptomyces* sp. KO 3988	Antitumor
81.	Arizonins A1 and B1 [85]	*Actinoplanes arizonaensis* sp. nov.	Antibacterial
82.	Coloradocin [86]	*Actinoplanes coloradoensis* sp. nov.	Antibacterial
83.	Teichomycins [87]	*Actinoplanes teichomyceticus* nov. sp.	Antibacterial
84.	Lipiarmycin [88]	*Actinoplanes deccanensis* nov. sp.	Antibacterial
85.	Candiplanecin [89]	*Ampullariella reguralis* subsp. *mannitophila* subsp. nov.	Antifungal
86.	Victomycin [90]	*Streptosporangium violaceochromogenes* nov. sp.	Antitumor, antibacterial
87.	Maggiemycin and anhydromaggiemycin [91]	*Streptomyces* sp.	Antitumor
88.	Gilvusmycin [92]	*Streptomyces* sp.	Antitumor
89.	Kazusamycin [93]	*Streptomyces* sp.	Antitumor
90.	Okicenone [94]	*Streptomyces* sp.	Antitumor
91.	Hydramycin [95]	*Streptomyces violaceus*	Antitumor
92.	Musacin C [96]	*Streptomyces griseovirdis*	Anthelminthic, antiviral
93.	Kanchanamycins [97]	*Streptomyces olivaceus*	Antifungal, antibacterial
94.	Elloramycin [98]	*Streptomyces olivaceus*	Antitumor
95.	Fattiviracin A1 [99]	*Streptomyces microflavus*	Antiviral
96.	FK 506 [100]	*Streptomyces tsukubaensis*	Antiviral
97.	Retamycin [101]	*Streptomyces olindensis*	Antitumor
98.	Manumycin [102]	*Streptomyces parvulus*	Antitumor, enzyme inhibitory
99.	Granaticin [103, 104]	*Streptomyces thermoviolaceus*	Antibacterial
100.	Pimaricin [105]	*Streptomyces natalensis*	Antifungal
101.	Virginiamycin M [106, 107]	*Streptomyces virginae*	Antibacterial
102.	Daptomycin (commercialized as Cubicin) [108]	*Streptomyces roseosporus*	Antibacterial
103.	Enduracidin [109]	*Streptomyces fungicidicus* B5477	Antibacterial
104.	Apramycin [110]	*Streptomyces tenebrabrius* UD2	Antibacterial
105.	Mithramycin [111]	*Streptomyces argillaceus*	Antitumor
106.	Blasticidin S [112]	*Streptomyces griseochromogenes*	Antifungal
107.	Leptomycin [113]	*Streptomyces lividans*	Antifungal, antitumor
108.	Landomycin E [114]	*Streptomyces globisporus*	Antitumor
109.	Phenalinolactones A–D [115]	*Streptomyces* sp.	Antibacterial
110.	Pipalamycin [116]	*Sreptomyces* sp.	Apoptosis inducer, antibacterial
111.	Biphenomycin A and B [117]	*Streptomyces griseorubiginosus*	Antibacterial
112.	Streptocidins A–D [118]	*Streptomyces* sp. Tu6071	Antibacterial
113.	Zelkovamycin [119]	*Streptomyces* sp. K96-0670	Antibacterial
114.	Methylsulfomycin I [120]	*Streptomyces* sp. RSP9	Antibacterial

Table 1 (***Continued***)

S. No.	Compound	Source	Activity
115.	YM-216391 [121]	*Streptomyces nobilis*	Anticancer
116.	RP-1776 [122]	*Streptomyces* sp.	Inhibit binding of platelet derived growth factor to its receptor
117.	RS-22 A, B and C [123]	*Streptomyces violaceusniger*	Antifungal, antibacterial
118.	Vicenistatin [124]	*Streptomyces* sp. Tu6239	Antitumor
119.	Ripromycin [125]	*Streptomyces* sp.	Antibacterial, antitumor
120.	Vinylamycin [126]	*Streptomyces* sp.	Antibacterial
121.	Cephamycin C [127]	*Streptomyces lactamdurans*	Antibacterial

actinomycetes may form the basis for the synthesis of novel therapeutic drugs, which may be efficient to combat a range of resistant microbes [133, 134].

Existence of cousins of terrestrial actinomycetes has been reported in the relatively untapped marine ecosystem. The immense diversity of this habitat along with it's underexploitation is the fundamental reason for attracting researchers towards it for discovering novel metabolite producers. Actinomycetes comprise about 10% of the bacteria colonizing marine aggregates and can be isolated from marine sediments [135]. Many actinomycete isolates from deep oceans contain non-ribosomal polyketide synthetase (NRPS) and polyketide synthetase (PKS) pathways, the hallmarks of secondary metabolite production [136]. There is an occurrence of distinct rare genera in the marine ecosystem as evidenced by the taxonomic description of the first marine actinomycete *Rhodococcus marinonascens* [137]. Actinomycetes have also been isolated from free swimming as well as sessile marine vertebrates and invertebrates [135]. Unusual actinomycetes belonging to *Micrococceae*, *Dermatophilaceae* and *Gordoniaceae*, have been isolated from sponges [133]. Tetrodotoxin-producing actinomycete has been isolated from puffer fish ovaries [138], the organism was found to be most closely related to *Nocardiopsis dassonvillei.*

Researchers are finding new genera from marine environments on a regular basis and discovering new metabolite producers never reported earlier. Actinomycete genera identified by cultural and molecular techniques from different marine ecological niches include *Actinomadura, Actinosynnema, Amycolatopsis, Arthrobacter, Blastococcus, Brachybacterium, Corynebacterium, Dietzia, Frankia, Frigoribacterium, Geodermatophilus, Gordonia, Kitasatospora, Micromonospora, Micrococcus, Microbacterium, Mycobacterium, Nocardioides, Nocardiopsis, Nonomurea, Psuedonocardia, Rhodococcus, Saccharopolyspora, Salinispora, Serinicoccus, Solwaraspora, Streptomyces, Streptosporangium, Tsukamurella, Turicella, Verrucosispora and Williamsia* [135]. Inspite of improvements being made in the cultural methods for the isolation of rare marine actinomycetes, many of these organisms still remain unculturable and have to be detected by using molecular techniques [139, 140]. Metagenomic methods are useful for characterizing microbes that cannot be cultivated and can also be used to isolate their genes [141].

Secondary metabolites from marine actinomycetes

Marine actinomycetes have proven to be efficient producers of new secondary metabolites as shown in Table 2 [142–182], which show a range of biological activities such as antifungal, antitumor, antibacterial, immunosuppressive, insecticidal and enzyme inhibition, to name a few.

Secondary metabolites produced by marine actinomycetes can be classified on the basis of their chemical structure as follows:

1. Terpenes and terpenoids

The most chemically diverse pool of secondary metabolites in nature is constituted by terpenes [183]. In 1956, novobiocin was isolated as the first antibiotic with a terpenoid side chain from *Streptomyces niveus* [184]. After this, the list of these compounds isolated from soil actinomycetes has increased as listed in Table 3 [185–193].

Terpenes are not only produced by the soil actinomycetes but also from the marine habitants as evidenced by the following compounds:

I. Azamerone [142] is a meroterpenoid produced by a new marine bacterium related to the genus *Streptomyces*. It appears to be the first natural product with a phthalazione ring (Fig. 1).
II. Three new pyrrolosesquiterpenes, glaciapyrroles A, B and C [143] are produced by a *Streptomyces* strain (NPSOO 8187). These compounds show antibacterial

Table 2 Bioactive compounds produced by marine actinomycetes

S. No.	Chemical group	Compound	Source	Activity
1.	Meroterpenoid	Azamerone [142]	*Streptomyces* sp.	None
2.	Pyrrolosesquiterpenes	Glaciapyrroles A, B and C [143]	*Streptomyces* sp. NPS008187	Antibacterial
3.	Amorphane sesquiterpenes [144]	10α, 15-dihydroxyamorph-4-en-3-one, 10α, 11-dihydroxyamorph-4-ene and 5α, 10α, 11-trihydroxyamorphan-3-one [144]	*Streptomyces* sp. M491	None
4.	Sesquiterpene	Neomarinone [145]	Strain CNH-099	Cytotoxic
5.	Polyketide	Saliniketal A, saliniketal B [146, 147]	*Salinispora arenicola*	Anticancer
6.	Polyketide	Abyssomicin C [148]	*Verrucosispora*	Antibacterial
7.	Polyketide	SBR-22 [149]	*Steptomyces psommoticus* BT408	Antibacterial
8.	Polyketide	Daryamides [150]	*Streptomyces* sp. CNQ-085	Anticancer, antifungal
9.	Polyketide	Actinofuranones A and B [151]	*Streptomyces* sp.	Cytotoxic
10.	Peptide	Mechercharmycins [152]	*Thermoactinomyces* sp.	Antitumor
11.	Peptide	Thiocoraline [153]	*Micromonospora*	Anticancer, antibacterial
12.	Peptide	CyclomarinA [154]	*Streptomyces* sp.	Anti-inflammatory, antiviral
13.	Peptide	Piperazimycins [155]	*Streptomyces* sp.	Anticancer
14.	Peptide	Dehydroxynocardamine and desmethylenylnocardamine [156]	*Streptomyces* sp.	Enzyme sortase B inhibitor
15.	Peptide	Urukthapelstatin [157]	*Mechercharimyces asporophorigenes* YM11-542	Anticancer
16.	Peptide	Salinamides A and B [158]	*Streptomyces* sp.	Antibacterial, anti-inflammatory
17.	Caprolactone	R-10-methyl-6-undecanolide (6R,10S)-10-methyl-6-dodeconolide [159]	*Streptomyces* sp. B6007	Phytotoxic, anticancer
18.	Butenolide	Butenolide [160]	*Streptoverticillium luteoverticillatum*	Anticancer
19.	Polycyclic xanthone	IB-00208 [161]	*Actinomadura*	Anticancer, antibacterial
20.	Piericidin	Piericidins C7 and C8 [162]	*Streptomyces*	Anticancer
21.	Quinone	Resistomycin [163]	*Streptomyces corchorusii* AUBN(1)/7	Antiviral
22.	Quinone	Tetracenomycin D [164]	*Streptomyces corchorusii* AUBN(1)/7	Anticancer, antibacterial
23.	Quinone	Resistoflavine [165, 166]	*Streptomyces chibaensis* AUBN(1)/7	Anticancer, antibacterial
24.	Quinone	Komodoquinone A [167]	*Streptomyces* sp. K53	Neuritogenic activity
25.	Quinone	Himalomycins A and B [168]	*Streptomyces* sp. B6921	Antibacterial
26.	Quinone	Helquinoline [169]	*Janibacter limosus*	Antibacterial
27.	Quinone	Chlorinated dihydroquinones [170]	CNQ-525	Anticancer, antibacterial
28.	Macrolide	Chalcomycin A [144]	*Streptomyces* sp. M491	None
29.	Macrolide	Arenicolide A [147, 171]	*Salinispora arenicola*	Antibacterial
30.	Macrolide	Marinomycins [172]	*Marinispora*	Anticancer, antibacterial

Table 2 (***Continued***)

S. No.	Chemical group	Compound	Source	Activity
31.	Alkaloid	K252c and arcyriaflavin A [173]	Z (2)0392	Anticancer
32.	Ester	Bonactin [174]	*Streptomyces* sp. BD21-2	Antibacterial, antifungal
33.	Manumycin derivatives	Chinikomycins A and B [175]	*Streptomyces* sp. M045	Anticancer
34.	Complex compounds	Trioxacarcins [176]	*Streptomyces ochraceus* and *Streptomyces bottropensis*	Anticancer, antimalarial
35.	Methylpyridine	Streptokordin [177]	*Streptomyces* sp. KORDI-3238	Anticancer
36.	Gamma lactam beta lactone	Salinosporamide A [147, 178]	*Salinispora tropica*	Anticancer
37.	Macrocyclic lactam	Aureoverticillactam [179]	*Streptomyces aureoverticillaris*	Anticancer
38.	Enzyme inhibitor	Alpha-amylase inhibitor [180]	*Streptomyces corchorusii* subsp. *rhodomarinus* subsp. nov	Enzyme Inhibition
39.	Enzyme inhibitor	Pyrostatins A and B [181]	*Streptomyces* sp. SA-3501	N-acetyl-beta-glucosaminidase inhibition
40.	Enzyme inhibitor	Pyrizinostatin [182]	*Streptomyces* sp. SA-2289	Pyroglutamyl peptidase inhibition

Table 3 Terpenes produced by soil actinomycetes

S. No.	Compound	Source	Activity
1.	Pentalenolactone I [185, 186]	*Streptomyces filipinensis*	Antibacterial, immunosupprressive
2.	Lavanduquinocin [185, 187]	*Streptomyces viridochromogenes*	Neuronal cell protection
3.	Napyradiomycins [185, 188]	*Chiana rubra*	Antibacterial
4.	Spirocardins A and B [185, 189]	*Nocardia* sp. SANK 64282	Antibacterial
5.	Benthocyanin A [185, 190]	*Streptomyces prunicolor*	Radical scavenger
6.	Benzastatin C [185, 191]	*Streptomyces nitrosporeus*	Antiviral
7.	Carquinostatin B [185, 192]	*Streptomyces exfoliatus*	Neuronal cell protection
8.	Moenomycin [185, 193]	*Streptomyces bambergensis*	Antibacterial

activities. Structures of glaciapyrroles A, B and C are shown in Fig. 2.

III. Amorphane sesquiterpenes [144] (Fig. 3) namely 10α,15-dihydroxyamorph-4-en-3-one, 10α,11-dihydr -oxyamorph-4-ene and 5α,10α,11-trihydroxyamor phan-3-one are produced by *Streptomyces* sp. M491. This is the first report of these sesquiterpenes from bacteria.

IV. Neomarinone [145], a novel metabolite possessing a new sesquiterpene and polyketide-derived carbon skeleton and several derivatives of the marinone class of naphthoquinone antibiotics are produced by a taxonomically novel marine actinomycete (strain CNH-099). These bioactive molecules show moderate cytotoxicity towards human cancer cells.

2. Polyketides

I. Saliniketal A (Fig. 4) and saliniketal B [146, 147], produced by *Salinispora arenicola,* are inhibitors of ornithine decarboxylase biosynthesis. Inhibition of ornithine decarboxylase production is an important strategy in the control of cancer since high levels of this enzyme lead to uncontrolled proliferation of cells. The Saliniketals are partly related in structure to the rifamycins.

II. Abyssomicin C [148] (Fig. 5) is a polycyclic polyketide produced by *Verrucosispora*. It targets p-aminobenzoate (PABA) biosynthesis and therefore inhibits folic acid biosynthesis at an early stage as compared to the well-known synthetic sulpha drugs.

The abyssomicins are the first known bacterial secondary metabolites that can inhibit the biosynthesis of PABA. Targeting PABA production is an attractive strategy for arresting microbial growth since PABA directly leads to the production of folic acid, which is a precursor of purine biosynthesis. Humans lack this pathway; therefore the strategy will not be harmful to humans. Abyssomicin C shows antibacterial activity against gram-positive bacteria as well as clinical isolates of multiple resistant and vancomycin-resistant *Staphylococcus aureus*. Abyssomicin C and its analogues thus have a high potential to be developed as antibacterial agents against drug-resistant pathogens.

III. A marine inhabitant known as *Streptomyces psommoticus* produces antibiotic SBR-22 [149]. It shows antibacterial activity against methicillin-resistant *Staphylococcus aureus.*

IV. Daryamides [150] (Fig. 6) are cytotoxic polyketides isolated from culture broth of a *Streptomyces* strain, CNQ-085. These bioactive compounds show weak to moderate cytotoxicity against the human colon carcinoma cell line HCT-116 and very weak antifungal activities against *Candida albicans.*

V. Actinofuranones A and B [151] (Fig. 7) are isolated from the fermentation broth of a marine bacterium related to *Streptomyces* genus. Actinofuranones A and B show weak *in vitro* cytotoxicity against mouse splenocyte T-cells and macrophages.

3. Peptides

I. Mechercharmycins [152] are new bioactive compounds obtained from marine-derived *Thermoactinomyces* sp. YM3-251. The cyclic structure of mechercharmycin A

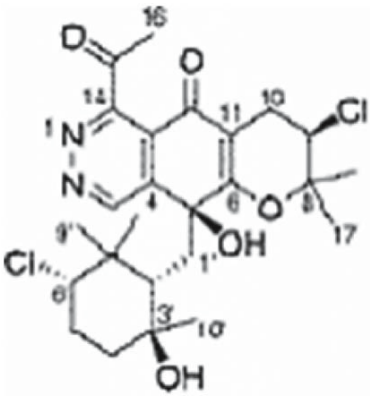


Fig. 1 Azamerone

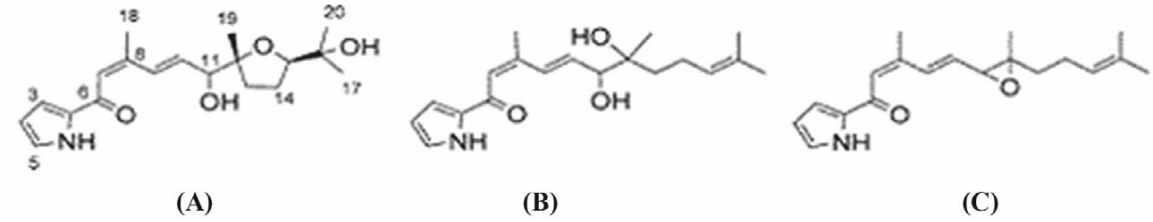


Fig. 2 Glaciapyrroles A, B, C

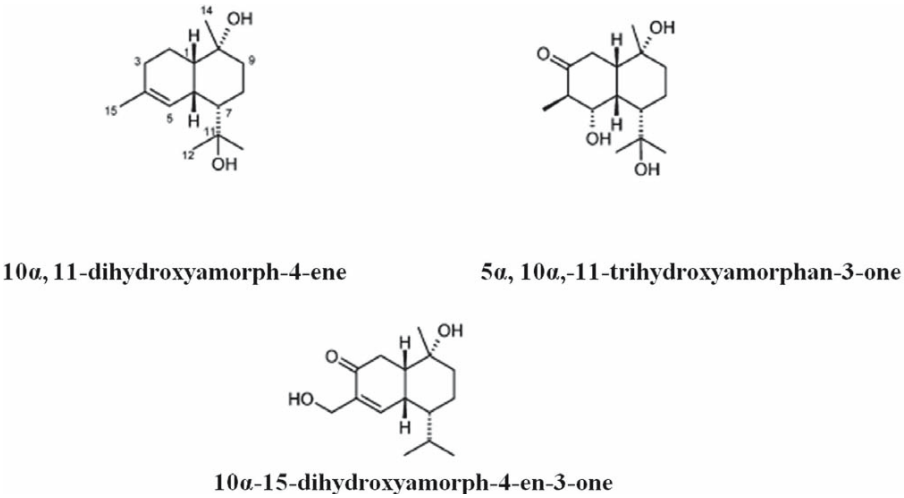


Fig. 3 Amorphane sesquiterpenes

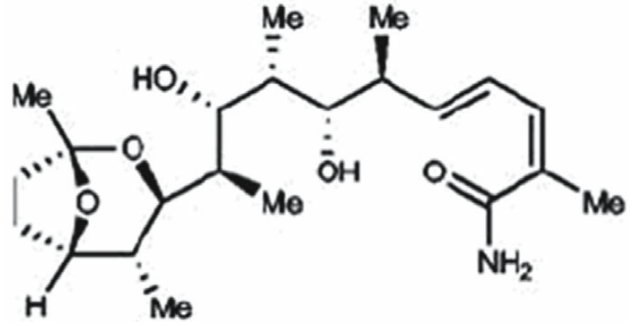


Fig. 4 Saliniketal A

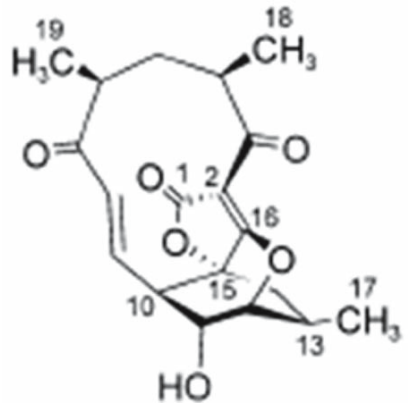


Fig. 5 Abyssomicin C

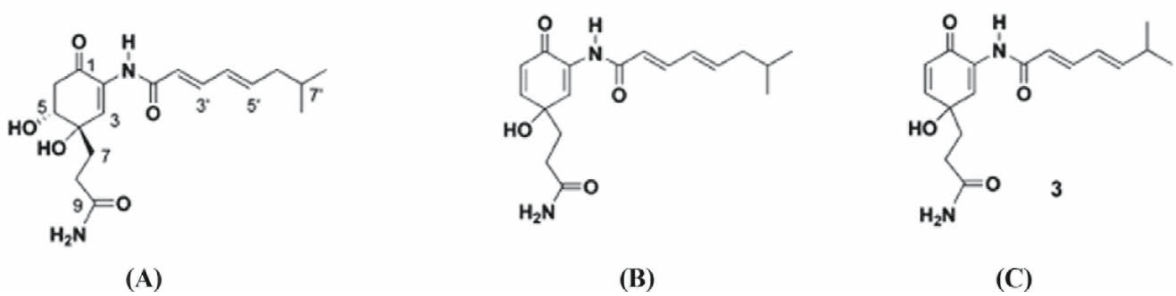


Fig. 6 Daryamides A, B and C

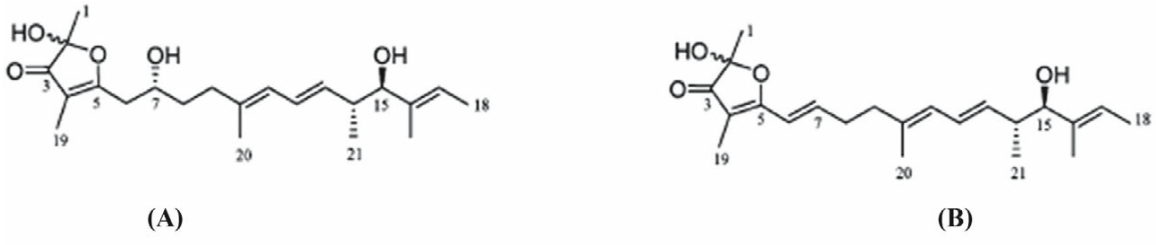


Fig. 7 Actinofuranones A and B

(Fig. 8) is essential for its strong antitumor activity, since the related compound mechercharmycin B (Fig. 9) does not show such an activity.

II. Thiocoraline [153] is a new depsipeptide isolated from *Micromonospora.* It shows potent cytotoxicity against P-388, A-549 and MEL cell lines, and also a strong antimicrobial activity against gram-positive microorganisms. This compound binds to supercoiled DNA and inhibits RNA synthesis.

III. Cyclomarins A-C [154] (Fig. 10) are cyclic peptides produced by a *Streptomyces* sp. They show anti-inflammatory and antiviral activities.

IV. Piperazimycins [155] (Fig. 11) are cytotoxic hexadepsipeptides isolated from the fermentation broth of a *Streptomyces* sp. Piperazimycin A exhibits potent *in vitro* cytotoxicity against multiple tumor cell lines.

V. Two cyclic peptides dehydroxynocardamine [156] and desmethylenylnocardamine [156] along with nocardamine have been isolated from a *Streptomyces* sp. which has been obtained from an unidentified marine sponge. These new compounds exhibit weak inhibition against the enzyme sortase B.

VI. Urukthapelstatin A [157] is a novel cyclic peptide produced by the thermoactinomycete bacterium *Mechercharimyces asporophorigenes* YM11-542. It inhibits the growth of human lung cancer A54 cells and shows cytotoxicity against a range of human cancer cell lines.

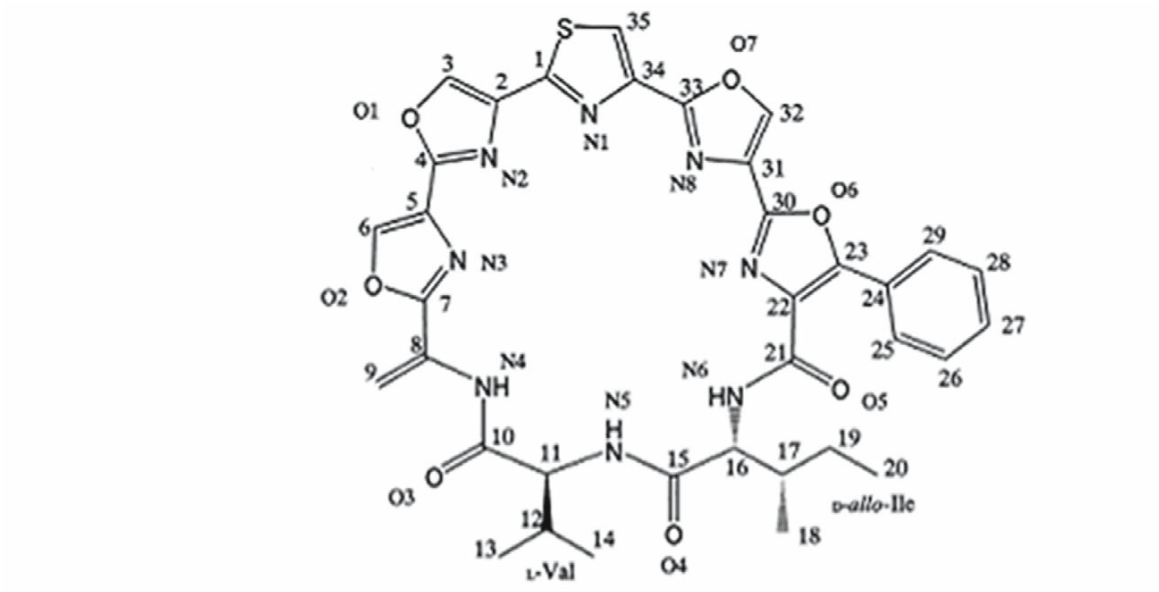


Fig. 8 Mechercharmycin A

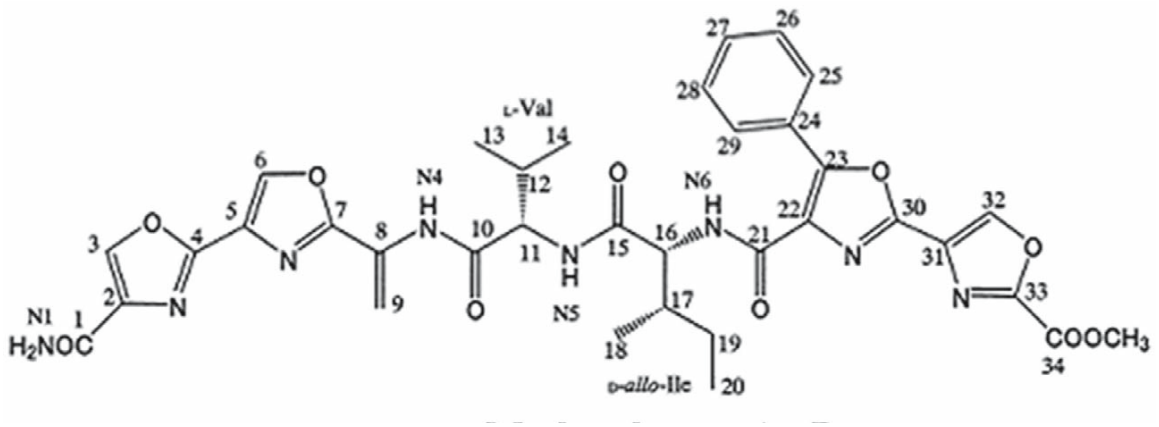


Fig. 9 Mechercharmycin B

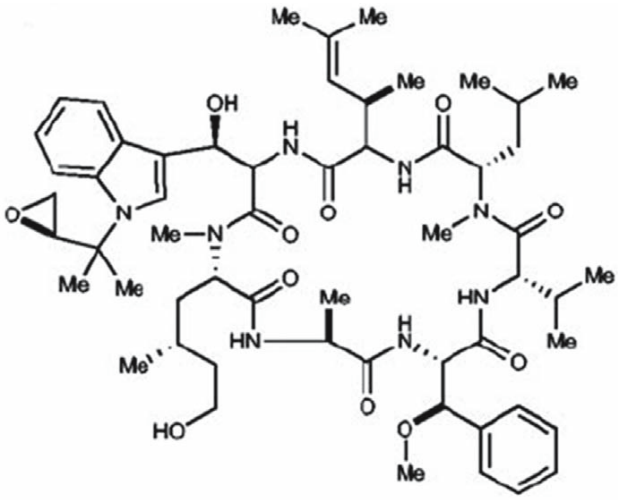


Fig. 10 Cyclomarin A

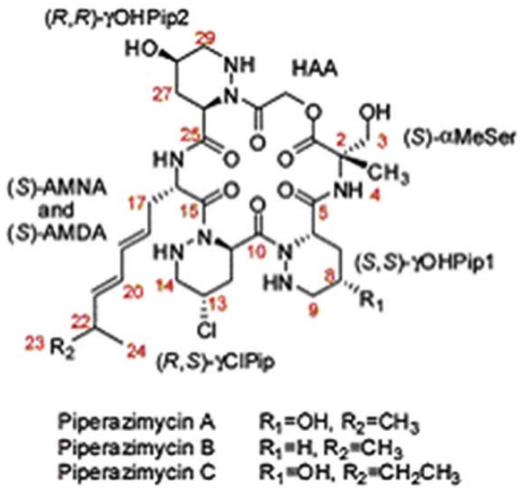


Fig. 11 Piperazimycins

VII. Salinamides [158] A and B are bicyclic depsipeptides produced by a *Streptomyces* sp., CNB-091, isolated from jelly fish *Cassiopeia xamachana*. These metabolites are useful as antibiotic and anti-inflammatory agents.

4. Caprolactones

Two new caprolactones R-10-methyl-6-undecanolide and (6R,10S)-10-methyl-6-dodeconolide [159] are produced by a marine *Streptomyces* sp. isolate B6007. These caprolactones show a moderate phytotoxicity and low cytotoxocity against cancer cells.

5. Butenolides

Streptoverticillium luteoverticillatum produces four butenolides [160]. These butenolides show cytotoxicity against the murine lymphoma P388 and human leukemia K562 cell lines. This is the first report of isolation of butenolides from the marine ecosystem, which possess cytotoxic activity.

6. Polycyclic xanthones

IB-00208 [161] is a polycyclic xanthone isolated from the culture of *Actinomadura.* This compound possesses cytotoxicity against tumor cell lines and bactericidal activity against gram-positive bacteria.

7. Piericidins

Piericidins C7 and C8 [162] show selective cytotoxicity against rat glia cells transformed with the adenovirus EIA gene and neuro-2a mouse neuroblastoma cells. These compounds are produced by a marine *Streptomyces* sp.

8. Quinones

I. Resistomycin [163] (Fig. 12), an antibiotic related to quinones, is produced by *Streptomyces corchorusii* AUBN(1)/7. This is an inhibitor of HIV-1 protease.

II. Tetracenomycin D [164] (Fig. 13) is an anthraquinone antibiotic also produced by *Streptomyces corchorusii* AUBN(1)/7. It shows cytotoxicity against cell line HMO2 (gastric adenocarcinoma) and HepG2 (hepatic carcinoma) and possesses weak antibacterial activities against gram-positive and gram-negative bacteria.

III. Resistoflavine [165, 166] (Fig. 14) is produced by *Streptomyces chibaensis* AUBN(1)/7. It shows cytotoxicity against cell line HMO2 (gastric adenocarcinoma) and HepG2 (hepatic carcinoma) and possesses weak antibacterial activities against gram-positive and gram-negative bacteria.

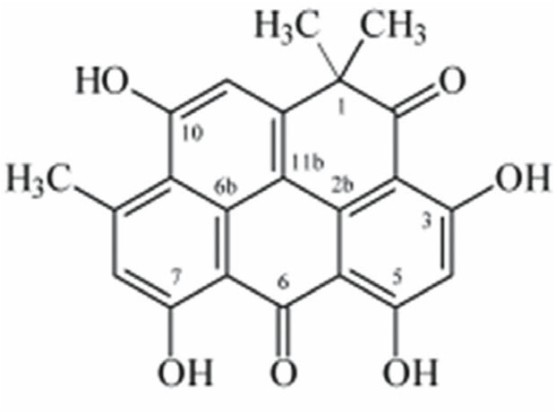


Fig. 12 Resistomycin

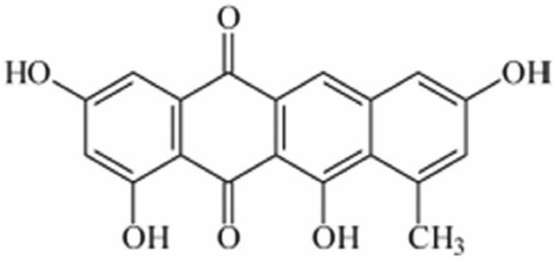


Fig. 13 Tetracenomycin D

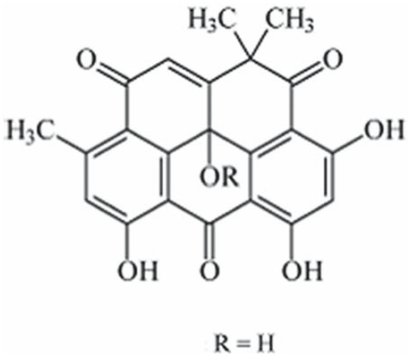


Fig. 14 Resistoflavine

IV. Komodoquinone A [167] (Fig. 15) is a neuritogenic anthracycline isolated from the fermentation broth of a marine *Streptomyces* sp. K53. It induces cell differentiation in the neuroblastoma cell line, Neuro2A and arrests cell cycle at the G1 phase.

V. Himalomycins A and B [168] (Fig. 16) are two new quinone antibiotics from a *Streptomyces* isolate, B6921. Himalomycins exhibit strong antibacterial activity against *Bacillus subtilis, Streptomyces*

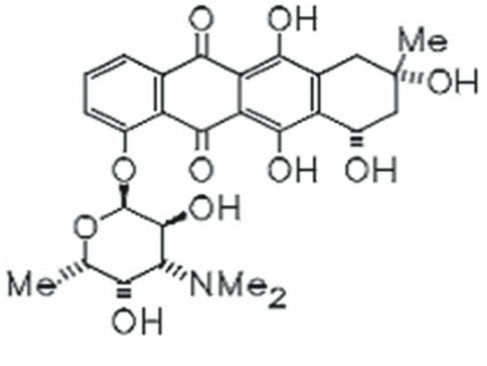


Fig. 15 Komodoquinone A

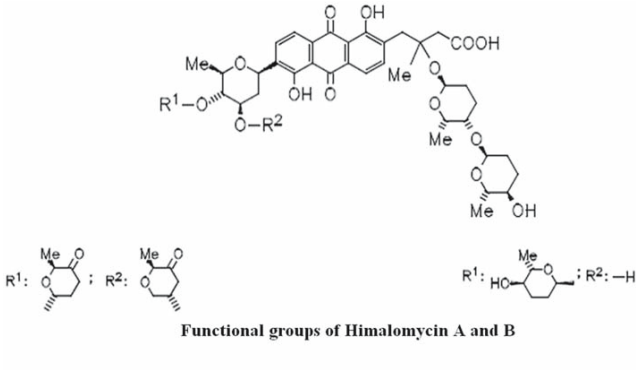


Fig. 16 Himalomycins A and B

viridochromogenes, Staphylococcus aureus and *Escherichia coli.*

VI. Helquinolines [169] (Fig. 17) are new tetrahydroquinoline antibiotic isolated from culture broth of *Janibacter limosus*. Helquinoline shows moderate activity against *Bacillus subtilis, Streptomyces virdochromogenes* Tu57 *and Staphylococcus aureus.*

VII. CNQ-525 is a member of a new genus (tentatively called MAR4) within the family Streptomycetaceae, which produces three novel chlorinated dihydroquinones [170]. These compounds possess new carbon skeletons but are related to several previously reported metabolites of the napyradiomycin class. The metabolites possess significant antibiotic properties and cytotoxicity against cancer cells.

9. Macrolides

I. *Streptomyces* sp. M491 is a marine actinobacterium that produces a macrolide antibiotic named Chalcomycin A [144] (Fig. 18) and also some terpenes.

II. Some strains of *Salinispora arenicola* produce a series of macrolides exemplified by Arenicolide [147, 171]

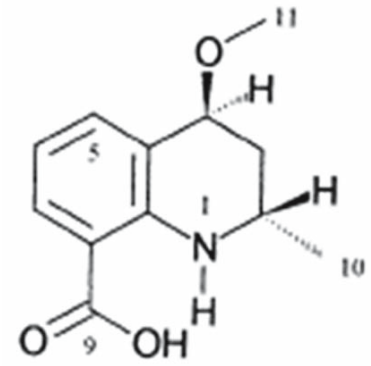


Fig. 17 Helquinoline

(Fig. 19). These possess weak antibacterial activities against drug-resistant bacteria.

III. Marinomycins [172] (Fig. 20) are polyene-like macrolides. A marine *Marinispora* produces these compounds, which are potent antitumor antibiotics with moderate activities against selected human tumors and drug-resistant bacterial pathogens. Marinomycin A inhibits the growth of human pathogenic bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium.* These polyenes are highly photoreactive and undergo isomerization even at room light because of which their use in clinics as potential drugs has been discontinued. In spite of being polyenes, marinomycins however, do not shows antifungal activities typically associated with other polyene antibiotics.

10. Alkaloids

Two indolocarbazole alkaloids, K252c [173] (Fig. 21) and Arcyriaflavin A [173] (Fig. 22) are produced by a marine actinomycete Z(2)0392. Both of these alkaloids possess moderate cytotoxicity against the K562 cell line and induce apoptosis. This is the first report of the significant apoptosis inducing effect of indolocarbazole alkaloids against K562 cancer cells.

11. Esters

Bonactin [174] (Fig. 23) is an antimicrobial ester. Bonactin displays antimicrobial activity against gram-positive and gram-negative bacteria as well as against several fungi. Bonactin is produced by *Streptomyces* sp. BD21-2.

12. Chinikomycins

Chinikomycins A (Fig. 24) and B [175] are chlorine-containing aromatic manumycin derivatives. They exhibit antitumor activity against different human cancer cell lines,

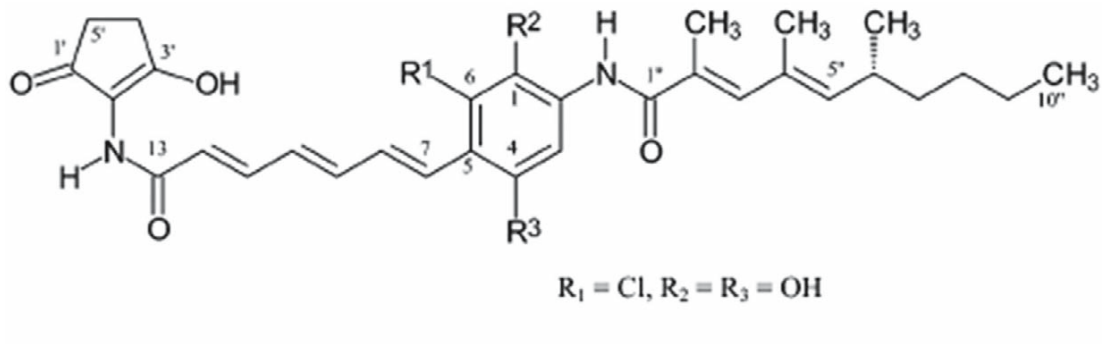


Fig. 18 Chalcomycin A

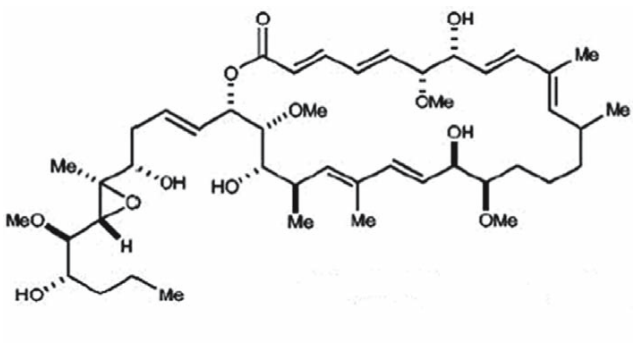


Fig. 19 Arenicolide A

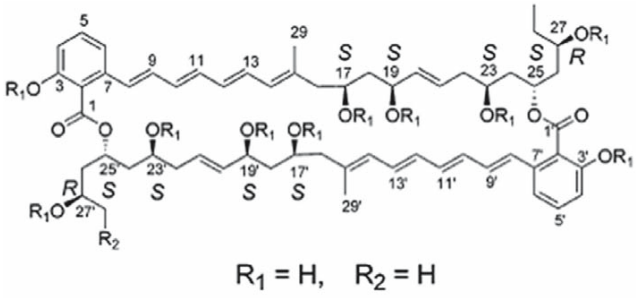


Fig. 20 Marinomycin A

but are inactive as antiviral, antimicrobial and phytotoxic agents. These compounds are produced by *Streptomyces* sp. isolate MO45.

13. Trioxacarcins

Trioxacarcins [176] (Fig. 25) are complex compounds showing high antibacterial activity against gram-positive and gram-negative bacteria, and some of them show high antitumor and antimalarial activities as well. Trioxacarcin A also exhibits antifungal activities. Trioxacarcin A, B and C are obtained from *Streptomyces ochraceus* and *Streptomyces bottropensis*. Some of these compounds possess extremely high antiplasmodial activity, which is comparable to that shown by artemisinin, the most active compound against the pathogen of malaria. The producers of trioxacarcins also biosynthesize the related metabolite, gutingimycin.

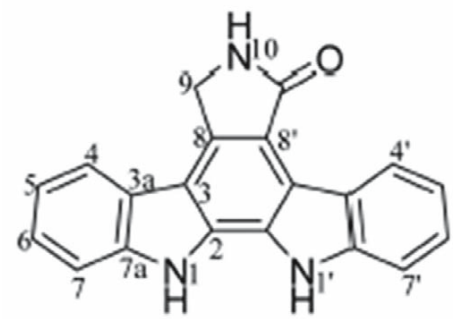
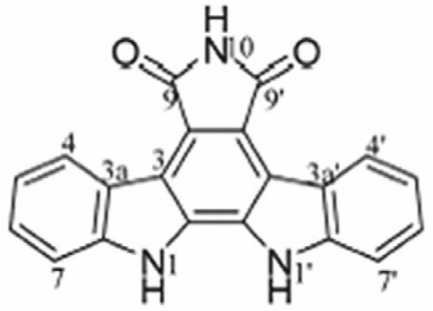


Fig. 21 K252c



Figs. 22 Arcyriaflavin A

14. Methylpyridine

Streptokordin [177] a new cytotoxic compound of the methylpyridine class is isolated from the cultural broth of *Streptomyces* sp. KORDI-3238. It exhibits significant cytotoxicity against several human cancer cell lines but shows no growth inhibition against various microorganisms, including bacteria and fungi.

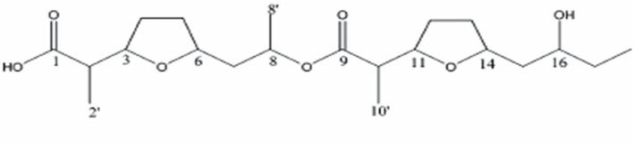


Fig. 23 Bonactin

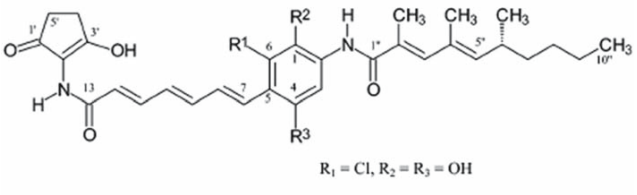


Fig. 24 Chinikomycin A

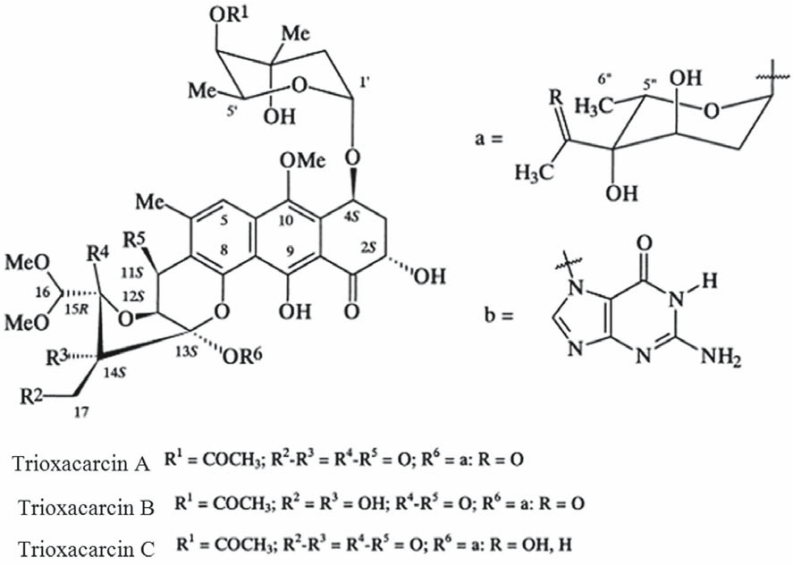


Fig. 25 Trioxacarcins

15. Lactams

I. Salinosporamide A [147, 178] (Fig. 26) is produced by *Salinispora tropica* which is found in oceanic sediments. Salinosporamide A is a potent proteasome inhibitor used as an anticancer agent that has entered phase I of the human clinical trials for the treatment of multiple myeloma. It inhibits proteasome activity by covalently modifying the active site threonine residues of the 20S proteasome.

II. Aureoverticillactam, a novel 22-atom macrocyclic lactam [179] is isolated from *Streptomyces aureoverticillaris*. It shows cytotoxicity against various tumor cell lines.

Salinosporamide A and aureoverticillactam are lactams from marine actinomycetes. These are distinct from β-lactam compounds which contain a four-membered β-lactam ring. The structure of β-lactam second ring allows these compounds to be classified into penicillins, cephalosporins, clavams, carbapenes and monobactans [194]. Most β-lactam compounds inhibit bacterial cell wall synthesis but others behave as β-lactamase inhibitors (e.g. cluvalanic acid) and even as antifungal agents (e.g. some clavams) [194], however salinosporamide A and aureoverticillactam show cytotoxicity against cancer cells.

16. Enzyme inhibitors

Some of the enzymes inhibitors reported from marine actinomycetes include:

I. Alpha amylase inhibitor from *Streptomyces corchorusii* subsp. *rhodomarinus*. subsp. nov [180].

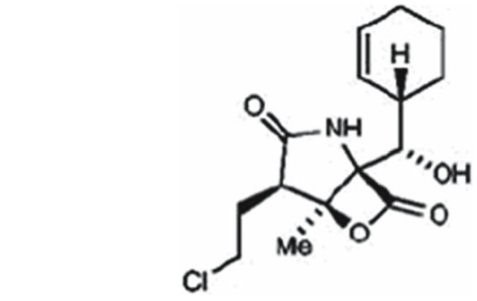


Fig. 26 Salinosporamide A

II. Pyrostatins A and B are inhibitors of n-acetyl-beta-glucosaminidase, produced by *Streptomyces* sp. SA-3501 [181].

III. Pyrizinostatin is an inhibitor of pyroglutamyl peptidase, isolated from culture of *Streptomyces* sp. SA-2289 [182].

Conclusion

Secondary metabolites produced from marine actinomycetes have distinct chemical structures, which may form the basis for the synthesis of new drugs. *Salinispora* alone produces a wide range of metabolites having different biological activities [146, 147, 171, 178]. Enrichment and selective isolation methods can also be used to isolate rare actinomycetes from marine ecological niches having the potential to biosynthesize novel bioactive compounds [140, 195–197]. A great hurdle however, in the search of these actinomycetes is that more than 90% of the organisms remain uncultivable under laboratory conditions. To explore the genomic diversity of the marine ecosystem and estimate their biosynthetic capability, the techniques of metagenomics can be used. Turbomycin is one of the first antibiotics to be discovered by metagenomics [198]. Isolation of long-chain acyltyrosine antibiotics from metagenomic libraries has also been reported [199]. Genes encoding enzymes responsible for the synthesis of secondary metabolites, are usually clustered on a contiguous piece of DNA. For expression of a single antibiotic there is a need for a large size DNA, which is a major challenge when DNA is isolated from soil, having high concentrations of humus and heavy metals as contaminants [200, 201]. But large insert metagenomic libraries can be prepared from marine samples with ease. By designing a suitable vector, which can accommodate large size inserts, it is possible to isolate novel bioactive compounds from marine unculturable actinomycetes [200, 201].

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