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# Anticancer potential of secondary metabolites from marine actinomycetes

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## Abstract

*Actinomycetes are the most effective microorganism antagonists. Marine actinomycetes, which may be found in shallow to deep sea sediments, have proven to be an excellent source for research. Streptomyces, Saccharopolyspora, Amycolatopsis, Micromonospora, and Actinoplanes are the major producers of commercially relevant biomolecules among its various species. Because of its extraordinary diversity and severe conditions, the marine environment attracts special attention when looking for new sources of commercially essential items; it is known to produce metabolic products of great value. Marine actinomycetes are significant for industry since they are one of the most efficient classes of secondary metabolite producers. Actinomycetes isolated from the marine environment are currently receiving a lot of interest because of the structural diversity and distinct biological activities of their secondary metabolites. They are effective producers of novel secondary metabolites with antibacterial, antifungal, anticancer, antitumor, cytotoxic, cytostatic, anti-inflammatory, anti-parasitic, anti-malaria, antiviral, antioxidant, anti-angiogenesis, and other biological actions. Marine actinomycetes are extremely promising, yielding high-quality, value-added products that will usher in a new era of bioactive compounds with medicinal and biotechnological applications. In this review, we list and describe secondary metabolites from marine actinomycetes that will be used for anticancer activity.*

***Keywords***

Marine actinomycetes, Secondary metabolites, Anti-cancer activity, Anti-cancer potential compounds, Cancer cell lines

## 1. INTRODUCTION

Actinomycetes are a type of gram-positive bacteria that are known for their ability to produce spores and create mycelia structures. Scientists, pharmaceutical companies, and agricultural companies are all interested in these bacteria because they serve as rich reservoirs of therapeutic antibiotics [1]. They are primarily aerobic and have a wide distribution of soils. Their DNA has a GC composition of 57–75%. The ability of actinomycetes to manufacture antibiotics is their most important feature [2]. Indeed, many of the currently known antibiotics, such as streptomycin, gentamycin, rifamycin, and erythromycin, come from actinomycetes. They are found in soil, fresh water, and marine environments [3]. Actinomycetes provided many important bioactive compounds of high commercial value and were screened for new bioactive substances [4]. Due to their potential to create a wide range of secondary metabolites, such as antibiotics, anticancer agents, immunosuppressive agents, cosmetics, vitamins, nutritional materials, herbicides, pesticides, anti-parasitic agents, and enzymes, these bacteria constitute an important category of microorganisms [5]. Microbial secondary metabolites have attracted a lot of interest because of their important biological functions, notably in terms of human health benefits. The biosynthesis of these secondary metabolites via metabolic engineering and industrial biotechnology has a number of advantages over traditional biomass extraction methods. Marine bacteria are microorganisms that produce unique and innovative secondary metabolites and have interesting biological activity. Actinomycetes, like other species of marine bacteria, play an important role in the pharmaceutical and medical industries because of their ability to produce secondary metabolites with a wide range of chemical structures and biological activities. Thousands of bioactive compounds have been identified and described, with many of them being turned into medications for a variety of ailments in the human, veterinary, and agricultural sectors [6]. Microorganisms have been found to create around 23,000 bioactive secondary metabolites. Over 10,000 of these compounds are produced by actinomycetes, accounting for roughly 45 percent of all bioactive microbial metabolites discovered. *Streptomyces* species create around 7600 compounds among actinomycetes [7]. As the number of novel bioactive compounds found from terrestrial actinomycetes decreased, it was recognized that actinomycetes from marine sediments could be useful for isolating novel strains capable of producing a diverse range of secondary metabolites [8]. However, it has been identified whether actinomycetes are a component of the marine microbial community seen in sediment samples, or if they are simply taken out to sea in the form of resistant spores from terrestrial ecosystems [9]. It has been reported that marine actinomycetes not only have several new species, but also plenty of novel structures with potent bioactivities [10]. Several novel bioactive compounds have been identified in aquatic actinomycetes, such as rifamycin, which was discovered in *Micromonospora* sp. [11], salinosporamide-A, an anticancer metabolite from *Salinispora* sp. [12], marinomycins from *Marinophilus* sp. [13], abyssomicin-C from *Verrucosispora* sp., and marinopyrroles from *Streptomyces* sp. [14].

## 2. Secondary metabolites from marine actinomycetes

Marine actinomycetes are known to have the ability to produce a wide variety of secondary metabolites. Indeed, each strain of actinomycetes is likely to have the genetic potential for the production of 10–20 secondary metabolites. About 23,000 antibiotics have been discovered by microorganisms. It has been estimated that approximately 10,000 of them have been isolated from actinomycetes. Actinomycetes, especially those of the genus *Streptomyces*, can develop a wide range of secondary metabolites as bioactive compounds, including antibiotics. Among other microbial groups, this one has a large biosynthetic potential that has yet to be matched. The enormous diversity of metabolites, as well as their underutilization, is the primary reason for researchers' interest in identifying new ones [15].

## 3. Anticancer activity of marine actinomycetes

Breast cancer is the second most common cause of cancer death in women, and it is still one of the most serious human health problems [16]. Surgery, radiotherapy, immunotherapy, and chemotherapy are all therapeutic strategies for cancer treatment [17]. When combined, each technique is valuable in its own right. When combined, they provide a more effective treatment for tumors. Many of the antitumor compounds derived from marine drugs are derived from marine actinomycetes, and these metabolites play an important role in the identification of pharmaceutical compounds [18]. Currently, it appears that there have been only a few studies focused on finding bioactive compounds derived from marine actinomycetes to be used as anticancer agents as well as agents against infectious organisms.

As indicated in the table, marine actinomycetes have proven to be excellent producers of novel secondary metabolites, which show a range of biological activity that is anticancer. The chemical structure of secondary metabolites produced by marine actinomycetes can be used to classify them.

| S.NO | CHEMICAL GROUP | COMPOUND | SPECIES | ACTIVITY |
|---|---|---|---|---|
| 1 | Alkaloid | K252c and arcyriaflavin A [19] | Z (2) 0392 | Anticancer |
| 2 | Alkaloid | Lodopyridone [20] | *Saccharomonospora* .sp | Anticancer |
| 3 | Alkaloids | ULDF4 and ULDF5 [21] | *Streptomyces bingchenggensis* | Anticancer |
| 4 | Piperazine | 1-acetyl-4-4(hydroxyphenyl)piperazine [22] | *Nocardiopsis* sp. SCA30 | Anticancer |
| 5 | Diketopiperazine | Nocazines F and G [23] | *Nocardiopsis* sp. YIM M13066 | Anticancer |

| | | | | |
|---|---|---|---|---|
| 6 | Polyketide | Saliniketal A, saliniketal B [24,25] | *Salinispora arenicola* | Anticancer |
| 7 | Polyketide | Daryamides [26] | *Streptomyces* sp. CNQ-085 | Anticancer |
| 8 | Peptide | Thiocoraline [27] | *Micromonospora* | Anticancer |
| 9 | Peptide | Piperazimycins [28] | *Streptomyces* sp. | Anticancer |
| 10 | Peptide | Urukthapelstatin [29] | *Mechercharimyces asporophorigenes* YM11-542 | Anticancer |
| 11 | Caprolactone | R-10-methyl-6-undecanolide (6R,10S)-10-methyl-6-dodeconolide [30] | *Streptomyces* sp. B6007 | anticancer |
| 12 | Butenolide | Butenolide [31] | *Streptoverticillium luteoverticillatum* | Anticancer |
| 13 | Polycyclic xanthone | IB-00208 [32] | *Actinomadura* | Anticancer |
| 14 | Piericidin | Piericidins C7 and C8 [33] | *Streptomyces* | Anticancer |
| 15 | Quinone | Tetracenomycin D [34] | *Streptomyces corchorusii* AUBN(1)/7 | Anticancer |
| 16 | Quinone | Resistoflavine [35,36] | *Streptomyces chibaensis* AUBN(1)/7 | Anticancer |
| 17 | Quinone | Chlorinated dihydroquinones [37] | CNQ-525 | Anticancer |
| 18 | Macrolide | Marinomycins [38] | *Marinispora* | Anticancer |
| 19 | Manumycin | Chinikomycins A and B [39] | *Streptomyces* sp. | Anticancer |

| | | | | |
|---|---|---|---|---|
| | derivatives | | M045 | |
| 20 | Methylpyridine | Streptokordin [40] | *Streptomyces* sp. KORDI-3238 | Anticancer |
| 21 | Gamma lactam beta lactone | Salinosporamide A [41,25] | *Salinispora tropica* | Anticancer |
| 22 | Macrocyclic lactam | Aureoverticillactam [42] | *Streptomyces aureoverticillaris* | Anticancer |

**1.Alkaloids**

1. A marine actinomycete Z (2)0392, produces two indolocarbazole alkaloids, K252c (Fig.1) and Arcyriaflavin A (Fig.2). Both of these alkaloids have moderate cytotoxicity and induce apoptosis in the K562 cell line. This is the first time indolocarbazole alkaloids have been shown to induce apoptosis in K562 cancer cells [19].

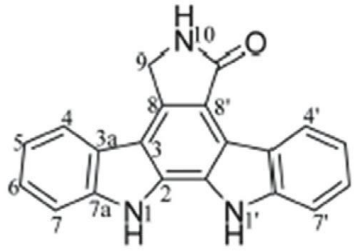

**Fig. 1** K252c

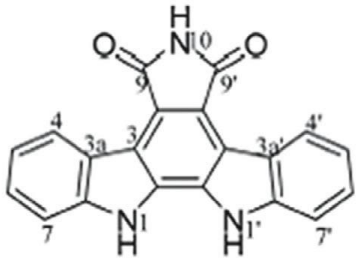

**Fig. 2** Arcyriaflavin A

2. Lodopyridone (Fig.3) is a modified alkaloid with an unprecedented carbon skeleton. Lodopyridon was produced by *Saccharomonospora caesia* sp. strain CNQ490. HCT-116 human colon cancer cells are cytotoxic to loxopyridone [20].

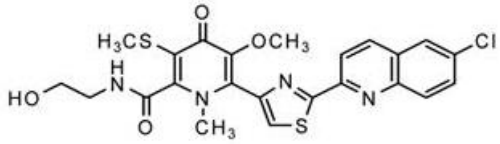

**Fig. 3** lodopyridone

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3. ULDF4 (Fig. 4) and ULDF5 (Fig. 5) compounds are derived from *Streptomyces bingchenggensis*. ULDF4 and ULDF5 exhibit cytotoxicity against K562 human acute myelocytic leukaemia, cervical carcinoma, human gastric carcinoma, MCF-7 breast adenocarcinoma, and human acute promyelocytic leukemia [21].

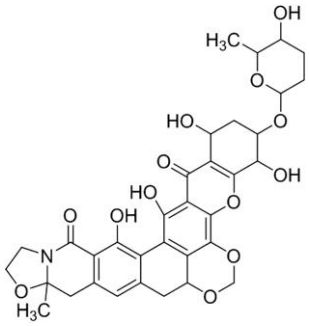

**Fig. 4** ULDF4

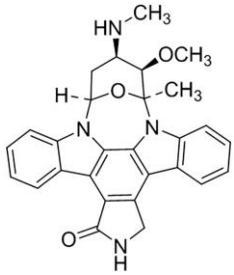

**Fig. 5** ULDF5

## 2. Piperazine

4. 1-acetyl-4-4(hydroxyphenyl)piperazine(Fig.6)is a secondary metabolite isolated from *Nocardiopsis* sp. SCA30 marine actinomycetes. 1-acetyl-4-4(hydroxyphenyl) Piperazine demonstrated anticancer activity against HCT 15, HT 29, MCF 7, and MDA-MB 468 cell lines [22].

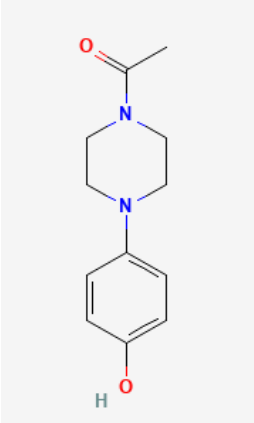

**Fig. 6** 1-acetyl-4-4(hydroxyphenyl)piperazine

## 3. Diketopiperazine

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5. Nocazines F(Fig.7)and G, isolated from the deep-sea sediment *Nocardiopsis* sp. YIM M13066, exhibited broad-spectrum and excellent cytotoxicity against a panel of cancer cell lines PC3, H1299, HL7702, HeLa, MCF-7, and U251 [23].

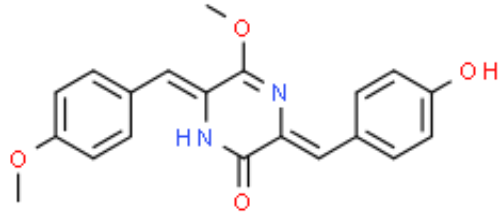


**Fig. 7** Nocazines F

## 4.Polyketides

6. *Salinispora arenicola* produces saliniketal A (Fig. 8) and B, which are inhibitors of ornithine decarboxylase production. Because high levels of this enzyme lead to uncontrolled cell proliferation, inhibiting ornithine decarboxylase synthesis is an essential technique in cancer control. The structure of the saliniketals is similar to that of the rifamycins [24, 25].

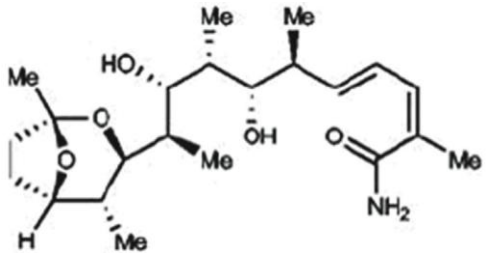


**Fig. 8** Saliniketal A

7. Daryamides (Fig. 9) are cytotoxic polyketides isolated from CNQ-085 *Streptomyces* culture broth. The human colon cancer cell line HCT116 is cytotoxic to these bioactive compounds in a mild to limited manner [26].

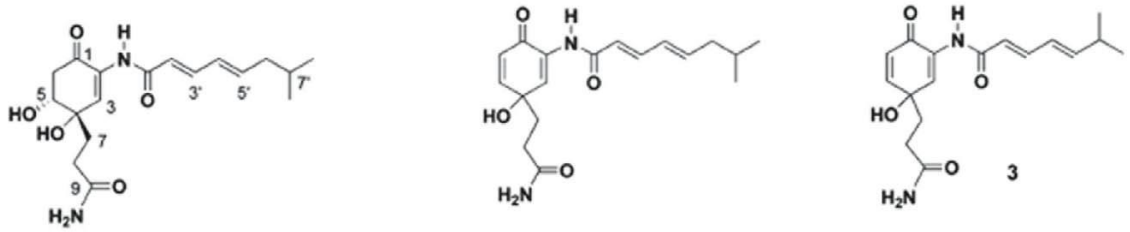


**Fig. 9** Daryamides A, B and C

## 5. Peptides

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8. *Micromonospora* has produced a novel depsipeptide called thiocoraline (Fig. 10). When treated with the compound, cell lines such as P-388, A-549, and MEL showed significant cytotoxicity [27].

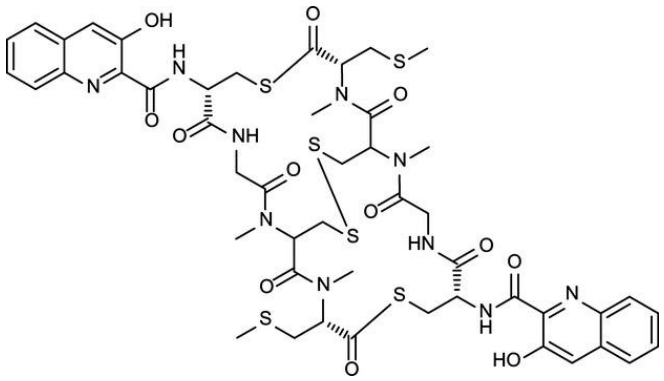

**Fig.10** Thiocoraline

9. Piperazimycins (Fig.11) are cytotoxic hexadepsipeptides discovered in the fermentation broth of *Streptomyces* sp. Piperazimycin A has significant cytotoxicity in vitro against a variety of cancer cell types [28].

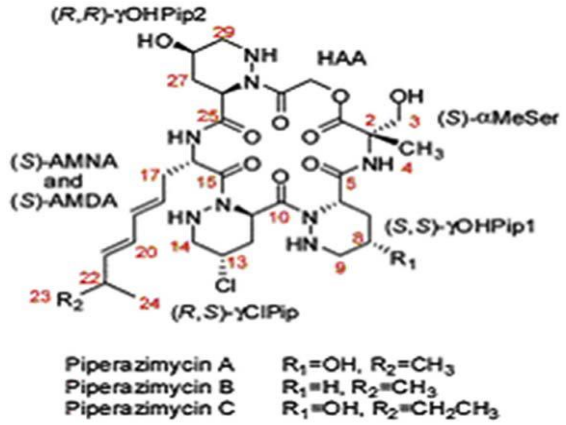


**Fig.11** Piperazimycins

10. Urukthapelstatin A (Fig.12)is a new cyclic peptide generated by *Mechercharimyces asporophorigenes* YM11-542, a thermo actinomycete bacteria. It demonstrates cytotoxicity against a variety of human cancer cell lines and suppresses the growth of human lung cancer A54 cells [29].

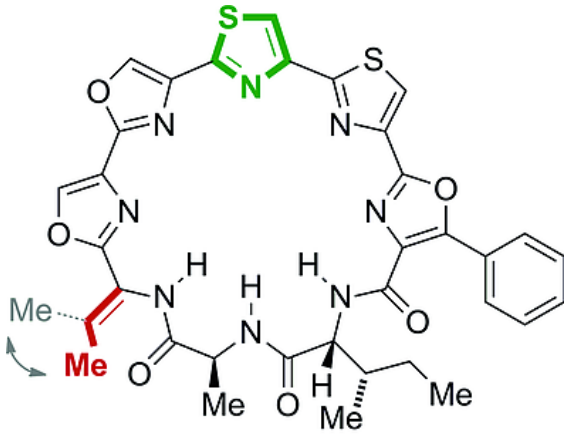

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**Fig.12** Urukthapelstatin A

### 6. Caprolactones

11. A marine *Streptomyces* sp. isolate *B6007* produces two novel caprolactones, R-10-methyl-6-undecanolide and (6R, 10S)-10-methyl-6-dodeconolide (Fig.13). These caprolactones have moderate phytotoxicity and low cytotoxocity when it comes to cancer cells [30].

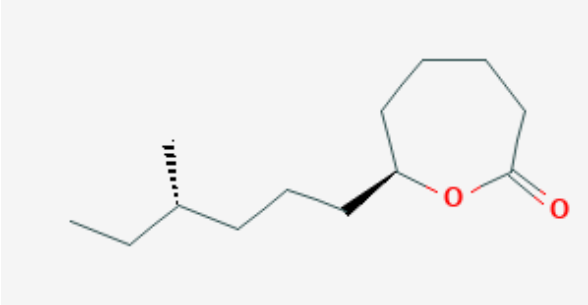


**Fig.13** (6R,10S)-10-methyl-6-dodeconolide

### 7. Butenolides

12. *Streptoverticillium luteoverticillatum* produces four butenolides (Fig. 14). The murine lymphoma P388 and human leukaemia K562 cell lines are also cytotoxic to these butenolides. This is the first time that butenolides with cytotoxic activity have been isolated from the marine environment [31].

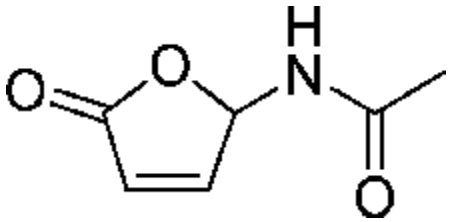


**Fig.14** butenolide

### 8. Polycyclic xanthones

13. IB-00208 (Fig. 15) is a polycyclic xanthone derived from *Actinomadura* culture. This compound is cytotoxic to cancerous cell lines [32].

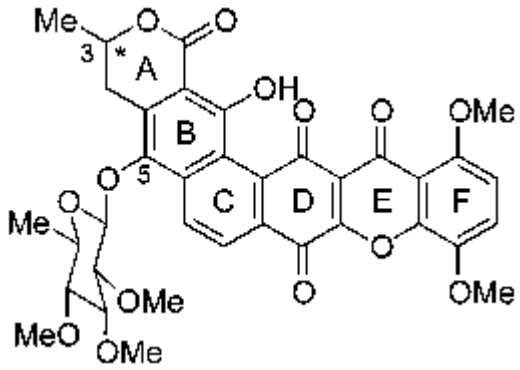


**Fig.15** IB-00208

### 9. Piericidins

14. Piericidins C7 and C8 (Fig. 16) show specific cytotoxicity against neuro-2a mouse neuroblastoma cells and rat glia cells transformed with the adenovirus EIA gene. A marine *Streptomyces* sp. produces these compounds [33].

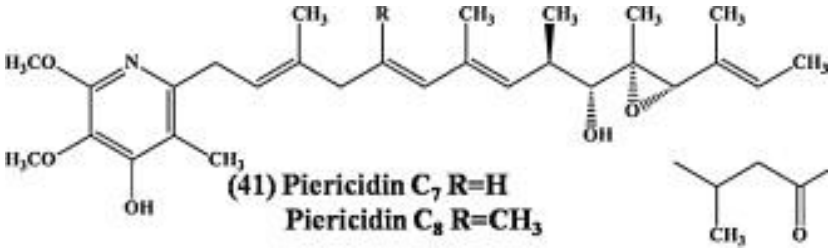


**Fig.16** Piericidins C7 and C8

## 10.Quinone

15. *Streptomyces corchorusii* AUBN (1)/7 also produces tetracenomycin D (Fig. 17). It's an anthraquinone antibiotic. It is cytotoxic to the HMO2 (gastric cancer) and HepG2 cell lines (hepatic carcinoma) [34].

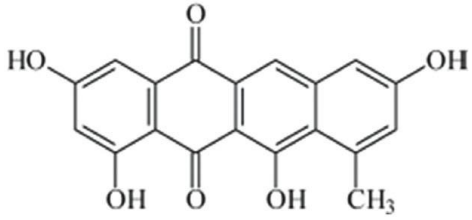

**Fig. 17** Tetracenomycin D

16. *Streptomyces chibaensis* AUBN (1)/7 produces resistoflavine (Fig. 18). It is cytotoxic to the HMO2 (gastric cancer) and HepG2 cell lines (hepatic carcinoma) [35, 36].

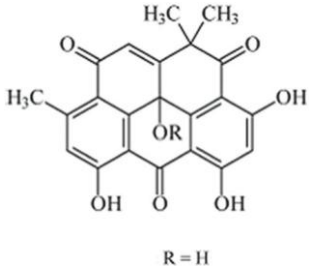


**Fig. 18** Resistoflavine

17. *CNQ-525* belongs to the *Streptomycetaceae* family, where it belongs to a new genus (tentatively designated MAR4) that produces three new chlorinated dihydroquinones (Fig. 19). These compounds have new carbon skeletons, yet they are connected to several previously described napyradiomycin metabolites. Cancer cells are cytotoxic when exposed to the metabolites [37].

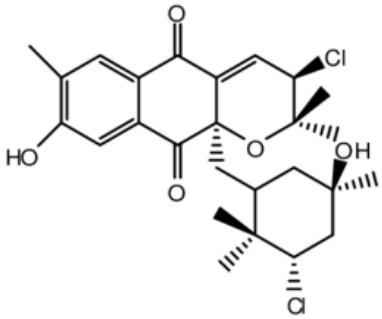

**Fig. 19** chlorinated dihydroquinones

## 11.Macrolide

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18. Marinomycins (Fig. 20) are macrolides that look like polyenes. These compounds are produced by the marine genus *Marinispora* and are effective anticancer antibiotics with moderate activity against a number of human cancer cell lines [38].

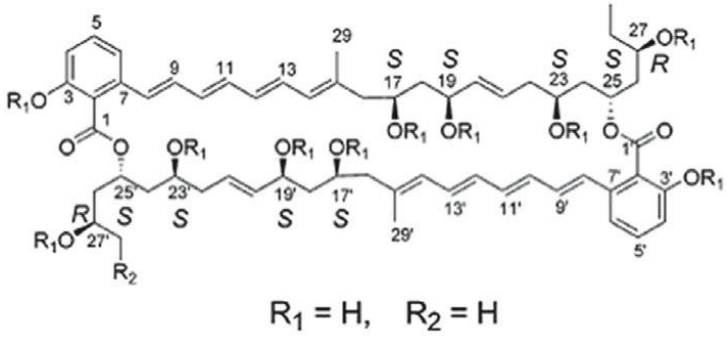


**Fig. 20** Marinomycin A

## 12.Chinikomycins

19. Chinikomycin derivatives A (Fig. 21) are aromatic manumycin derivatives that contain chlorine. They have anticancer properties against a variety of human cancer cell types. These compounds are produced by *Streptomyces* sp. isolate *MO45* [39].

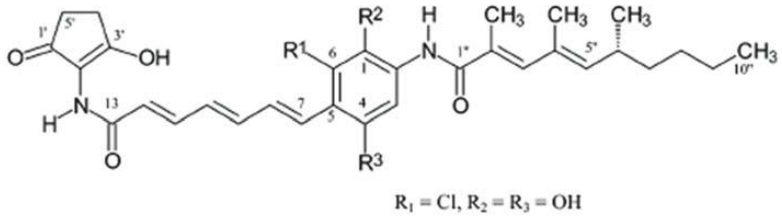


**Fig. 21** Chinikomycins A

## 13.Methylpyridine

20. Streptokordin (Fig.22), a novel cytotoxic methylpyridine compound, was discovered in the *Streptomyces* sp. KORDI-3238 culture broth. It has a high level of cytotoxicity against a variety of human cancer cell types [40].

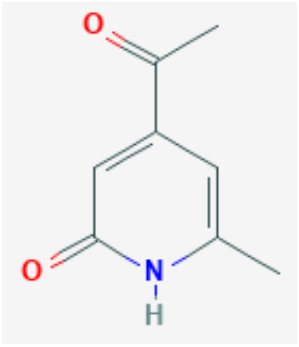

**Fig. 22** Streptokordin

## 14.Lactam

21. *Salinispora tropica*, which is found in oceanic sediments, produces salinosporamide A (Fig.23). Salinosporamide A is a strong proteasome inhibitor that has progressed to phase I of human clinical studies for the treatment of multiple myeloma [41, 25].

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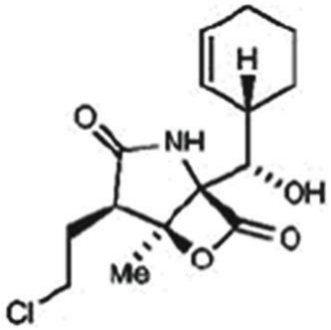


**Fig. 23** Salinosporamide A

22. *Streptomyces aureoverticillaris* produces aureoverticillactam (Fig. 24), a new 22-atom macrocyclic lactam. It has been shown to be cytotoxic against a variety of cancer cell lines. Lactams from marine actinomycetes are known as "aureoverticillactams." However, aureoverticillactam has been shown to be cytotoxic to cancer cells [42].

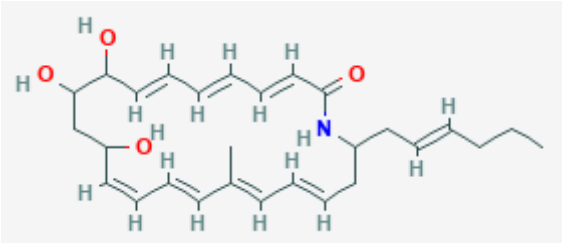

**Fig. 24** Aureoverticillactam

## Conclusion

The growing interest in natural products, particularly those derived from marine species, as well as the established ability of marine actinomycetes to synthesis a wide range of compounds, has pushed marine actinomycetes into the focus of intensive research. For drug discovery from marine actinomycetes, it appears that two key parallel techniques will be explored. One will be based on the development of novel and improved isolation and cultivation techniques in order to expand the diversity of cultivable isolates reduce cultivation time to obtain meaningful cell mass, and increase yields and secondary metabolite production. Because actinomycetes are so different, and each species may have unique requirements not only for growth but also for the synthesis of secondary metabolites, this method will necessitate a lot of new and creative thinking. Its primary benefit is that, if successful, it will result in the development of a molecule whose structure, novelty, and biological activity can all be evaluated immediately. For scientists, finding potent secondary metabolite producers like actinomycetes is an exciting and demanding platform. Recent culture-independent research has revealed that rare actinomycetes can still be found in large numbers in the marine environment.

The primary focus should be on applying cutting-edge translational research, such as transferring the results of biomolecule discovery or synthesis to industry bench-tops and clinics. Successful collaboration between research biologists or chemists and pharmaceutical industries can lead to the discovery of new, highly

effective medicines. Salinosporamide A (Marizomib) is a compound produced from marine rare actinomycetes that has progressed through phase trials of human clinical studies for the treatment of multiple myeloma.

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