STUDY OF MARINE-DERIVED ANTI-MYCOBACTERIUM COMPOUNDS: A REVIEW

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ABSTRACT

Mycobacterium tuberculosis exerts an enormous burden on public health globally, killing approximately 2 million people every year. The shortcomings of currently available drugs, the emergence of drug resistant strains, and the difficulty in treating latent TB, all contribute to this crisis. Marine pharmacology during 2009–2011 remained a global enterprise, with researchers from 35 countries including the United States, contributing to the preclinical pharmacology of 262 marine compounds which are part of the preclinical pharmaceutical pipeline. Natural products represent an outstanding source of compounds that play an important role in the treatment of human diseases. Due to the importance of nature as a source of new drug candidates, the aim of this review is to highlight on the marine natural products, which exhibit anti-tuberculosis activity.

Keyword: Mycobacterium, Tuberculosis activity, natural products, MIC.

No:of References : 46

INTRODUCTION

The ocean covers more than 70% of the planet surface and its complicated ecosystems offer vast biodiversities. The long term natural selection force faced by the rich fauna and flora favours those which could produce secondary metabolites that are used to fend off competition, predation and parasitism. The effort of acquiring natural compounds for disease treatment started in 1970s and great progress has been made over the past four decades. Many marine natural compounds are isolated from cone snails, corals, sponges, sea squirts, marine worms, bryozoans, sea slug, and sharks. These drugs are used for treating cancer, fungal infection, tuberculosis, nematode infection, malarial infection, bacterial infection, viral infection, pain management and inflammation control. The natural compounds currently under clinical trials are very limited and the potential to discover more potent drugs from the seas could be expected.

Mycobacterium tuberculosis (identified in 1882 by R. Koch) mainly affects and damages the lungs, but it may spread across almost any tissue or organ of the body. At present, the accepted treatment of TB involves a combination of the first-line drugs, isoniazid, pyrazinamide, ethambutol and rifampicin given in combination over 6–9 months. The combinations are very important to prevent the emergence of multiple drug-resistant organisms, which would lead to an ineffective treatment. This problem has become serious as M. tuberculosis developed resistance against both the first line and the second line drugs leading to an emergence of multi drug resistant and extensive drug resistant strains of M. tuberculosis all over the world [1, 2].

Tuberculosis (TB) is a vicious disease that has infected man since the earliest of times. TB became a worldwide problem between 1985 and1992 when the number of TB cases increased, particularly in people infected with the HIV virus. Another problem that increased TB cases is multidrug-resistant tuberculosis (MDR TB) due to inconsistent or partial treatment. Although a vaccine (BCG) and effective chemotherapy against TB were available 50 years ago, TB was declared a global emergency in 1993[3]. Over the past 10 years, the area of tuberculosis therapy has undergone a basic change in emphasis for drug therapy. The increase of tuberculosis coinciding with the AIDS epidemic has resulted in additional drug-resistant isolates of *Mycobacterium tuberculosis* [4,5]. HIV infection has increased the incidence of tuberculosis by causing immune suppression, which enables latent infection to clinically progress [6].The risk of developing tuberculosis among AIDS patients is over 100 times higher than among normal individuals [7]. Tuberculosis is a unique serious disease in that unlike other diseases associated with AIDS, it may be spread by airborne transmission to adults and children who are not at risk of AIDS[7,8].Tuberculosis (TB) is an infection transmitted through the air caused by the bacterium.

In this context, marine natural products became a powerful source of new anti-TB compounds for newer anti-tuberculosis drugs. Marine derived bioactive compounds offer a great hope

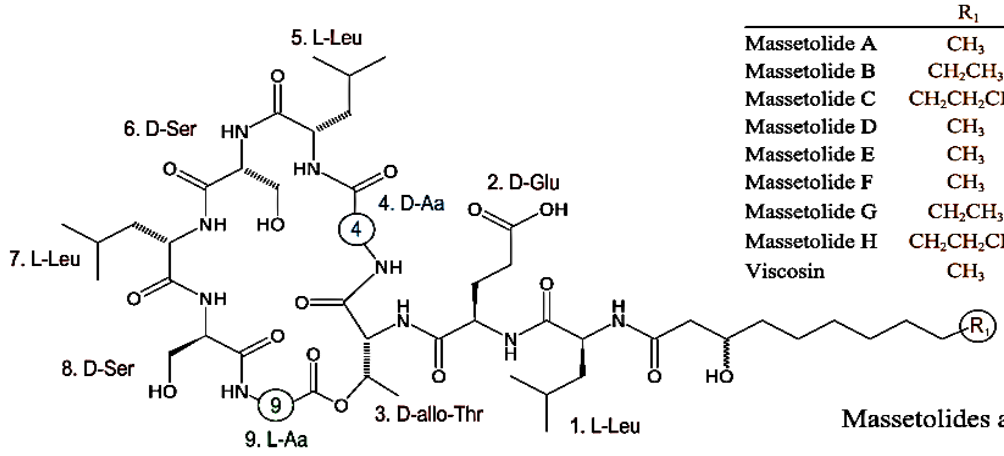
to fulfil the needs and hold great promise as therapeutics in the treatment of human diseases. Marine organisms have evolved biochemical and physiological mechanisms that include the production of secondary metabolites meant for self-protection against infection, predation and competition. In this light, marine natural products emerged as a powerful source of new anti-TB compounds.

Marine-Derived Anti-mycobacterium Compounds

The oceans, with their unique and wide range of biodiversity, producing unusual metabolites, emerge as good candidatesfor new anti-tuberculosis agents. The interest and study of marine natural products against *M. tuberculosis* started with Andersen et al. [3] and Hamman et al. [4].

Andersen and co-workers reported the *in vitro* anti-TB activity of massetolide A (MIC = 5–10 µg/ml) and viscosin (MIC = 10–20 µg/ml) [9] that are cyclic depsipeptides isolated from cultures of two *Pseudomonas* species of marinealga and tube worm, respectively [9].

MIC - It is defined as the minimal inhibitory concentration of an antibiotic that inhibits a bacterium.

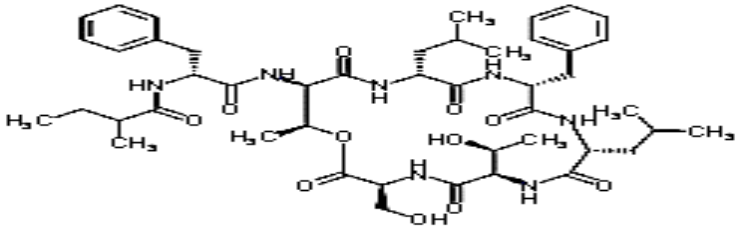


	R_1	4. D-Aa	9. L-Aa
Massetolide A	CH_3	allo-Ile	Ile
Massetolide B	CH_2CH_3	allo-Ile	Ile
Massetolide C	$CH_2CH_2CH_3$	allo-Ile	Ile
Massetolide D	CH_3	allo-Ile	Leu
Massetolide E	CH_3	Val	Val
Massetolide F	CH_3	Val	Leu
Massetolide G	CH_2CH_3	Val	Ile
Massetolide H	$CH_2CH_2CH_3$	Val	Ile
Viscosin	CH_3	Val	Ile

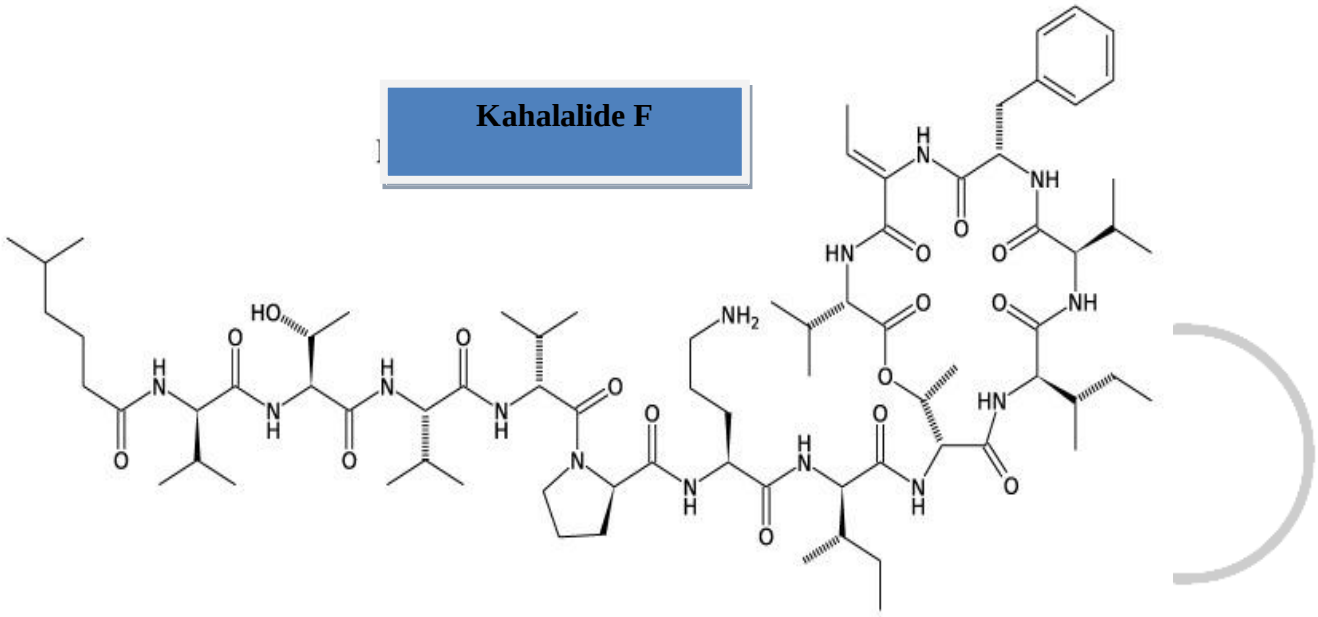
Massetolides and viscosin

Hamman and co-workers identified anti-TB activity in two known polypeptides isolated from the sacoglossan mollusk *Elysia rufescens*Kahalalide A and F [10,11]. The Kahalalide A has demonstrated important *in vitro* activity, inhibiting 83% *M. tuberculosis* growth (H37Rv), at 12µg/ml. It is the third example of antimycobacterial tuberculosis activity for a marine-derived peptide, after massetolide A and viscosin. and the Kahalalide F, inhibiting 67%*M. tuberculosis* growth (H37Rv), at the same concentration.

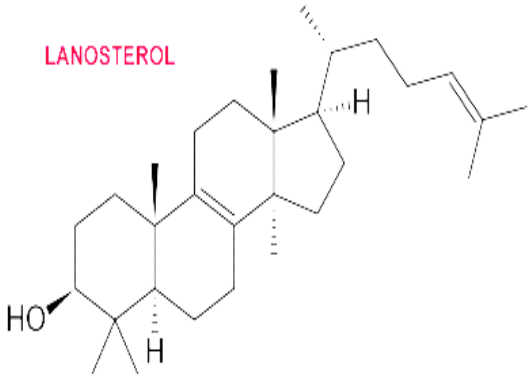
Kahalalide A



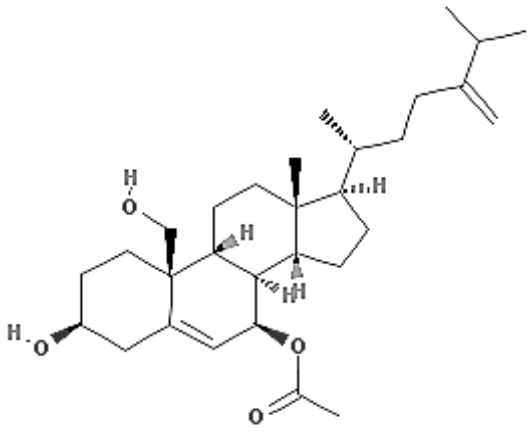
Kahalalide F



Hamann and co-workers also made an important contribution by testing *in vitro* activities against *M.tuberculosis*, with marine natural products and semi synthetic molecules from different classes, in the total of 48 compounds. As examples of the compounds tested by Hamann and his group, the C-19 hydroxysteroids linosterol, nephalsterol B and C were isolated from red sea *Nepthea* sp. [12,13]. The natural products linosterol and nephalsterol C had MICs of 3.13 and 12.5 µg/ml inhibiting 90 and 96%of the growth of *M. tuberculosis* (H37Rv). However, nephalsterol B inhibited only 69% at the same concentration, which indicated that C-7 hydroxylation could reduce the activity. When C-7 hydroxyl was blocked by an acetate group as in the case of nephalsterol C or when it was absent as in linosterol , an improvement of the biological activity was observed. Hamann and his group were the first to identify antimycobacterial activity in this class of compounds.

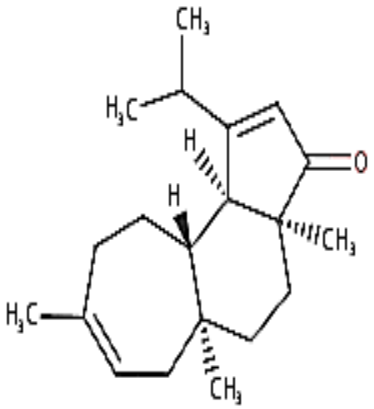


LINOSTEROL



Nephalsterol C

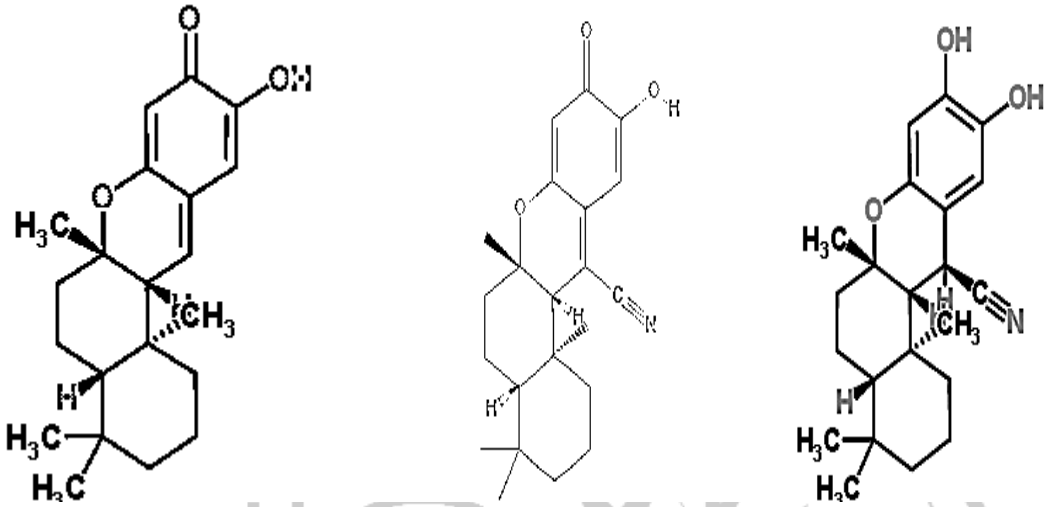
Hamman and co-workers also isolated 27 diterpenes called cyanthiwigins from Jamaican sponge *Mymekioderma styx*[14], which have been tested against *M. tuberculosis*. However, the best result was the moderate activity of cyanthiwigin (C)[15] with 50% of inhibition at 6.25 µg/ml.



Cyanthiwigin C

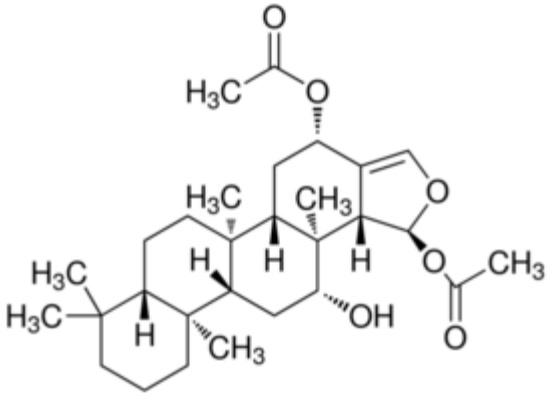
Hamman, Nasu, Zjawiony and co-workers identified Puupehenone , 15-cyanopuupehenone, puupehedione, 15-oxopuupehenol , 15a-methylpuupehenol and 15a-cyanopuupehenol compounds which are natural sesquiterpene-shikimate derived metabolites or semisynthetic derivatives of puupehenone, which is

isolated from sponges of the orders Verongida and Dictyoceratida. [16-18] Puupehenone , 15-cyanopuupehenone, and 15α-cyanopuupehenol induced 99, 90, and 96% inhibition of *M. tuberculosis* (H37Rv) growth, respectively. Puupehenone shows an MIC of 12.5 mg/mL and an IC50 of 2.0 mg/mL. Clearly, the quinone-methide system in ring D of puupehenone is essential for activity. Compounds with substitution or addition of cyano functionality at position C-15 retain activity and show reduced toxicity. On the other hand the 15 oxo- or methyl derivatives were shown to be inactive.



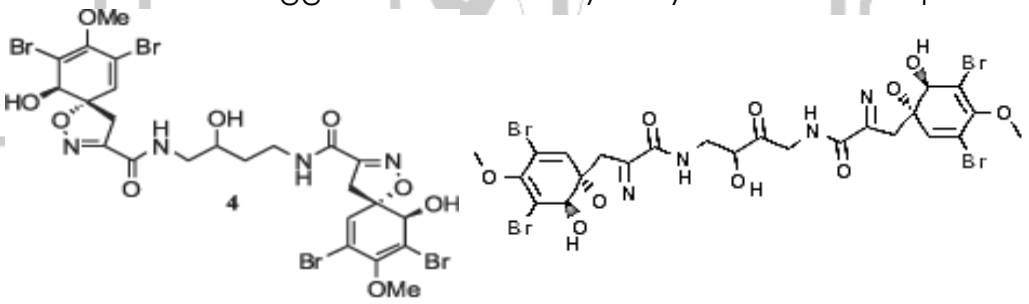
Puupehenone	15-Cyanopuupehenone	15α-Cyanopuupehenol

Kazlauskas and co-workers isolated Heteronemin a scalarin-type sesterterpene from the sponge *Heteronema erecta [19]* and recently *K. A. El Sayed et al and coworkers* isolated Heteronemin from a Red Sea sponge [20]. Heteronemin displayed a 99% inhibition of *M. tuberculosis* (H37Rv) with an MIC 6.25 mg/mL and IC50 1.3 mg/mL. This is the first report of anti-TB activity for the scalarin-type sesterterpene class of compounds. The high cytotoxicity of these compounds prohibited further testing; however, microbial or chemical modifications of these compounds may produce more active derivatives with less toxicity.



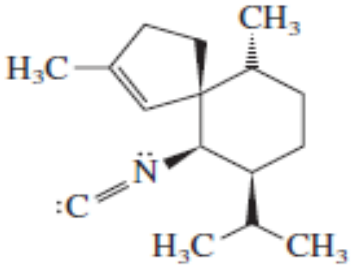
Heteronemin

Aerothionins are a group of brominated spirocyclohexadienylis oxazolines isolated from Verongid sponges.[21-24] Both 11-hydroxyaerothionin and 11-oxo-12 *epi*-hydroxyaerothionin induced 70 and 60% inhibition respectively, of *M. tuberculosis* growth while 11-oxoaerothionin induced no inhibition at all . This suggests that hydroxylation at positions 11 or 12 is essential for the activity of these compounds. Despite the moderate activity and their low cytotoxicity and common occurrence in Verongid sponges suggest that they could be possible leads if additional chemical or microbial hydroxylation is accomplished.



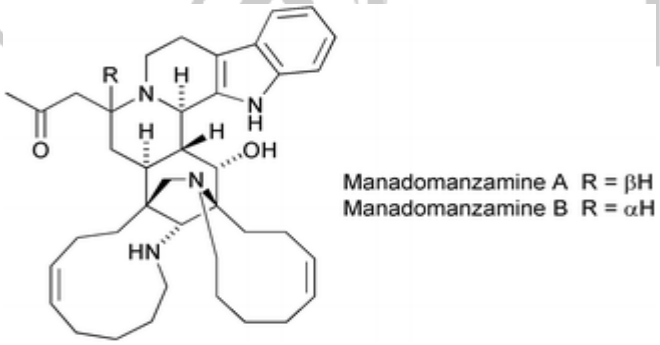
11-hydroxyaerothionin **11-oxo-12 *epi*-hydroxyaerothionin**

Konig and co-workers who have tested 39 different marine natural products representatives of different classes, such as terpenes, aliphatics, aromatics, alkaloids and andsterols[25]. In this context, the most promising compound reported in the Konig study was axisonitrile-3 (MIC = 2.0 µg/ml) isolated from the sponge *Acanthella klethra* with no toxicity to Vero cells at concentrations < 200µg/ml. [25]



Axisonitrile-3

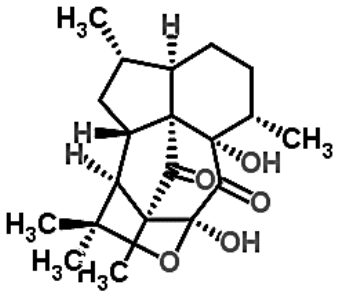
Higa and co-workers in 1986 reported Manzamines , β-carbolines alkaloids from the Okinawan sponge genus *Haliclona*. This class of compounds possesses a diverse range of bioactivities, such as antibacterial[26], cytotoxic[27], and malaria activity[28]. In the search for new types of anti-TB agents, Hamman and co-workers have isolated and tested new manzanines from Indonesian sponges [29]. As examples, the two novel alkaloids called manadomanzamines A and B isolated from Indonesian sponge *Acanthostrongylophora* sp. (Haploscilerida:Petrosiidae)[30] exhibited strong activity against *M. tuberculosis* with MIC values of 1.9 and 1.5µg/ml, respectively. These two alkaloids also exhibited significant activity against human immunodeficiency virus (HIV-1) with EC50 values of 7.0 and 16.5 µg/ml, respectively, and moderate activity against several AIDS opportunist infections.

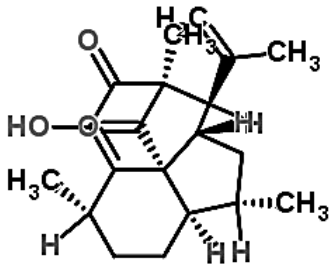


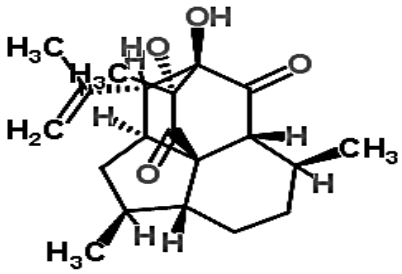
Manadomanzamines A

Rodrigues and coworkers gave an important contribution towards the search for new natural products against TB. They have purified and identified the natural products elisapterosin B , elisabethin A [31], cumbiasin A and B [32], and colombiasin A [33] . These compounds have similar carbocyclic skeletons and they were isolated from an extract of the West Indian corals gorgonianoctocoral

Pseudopterogorgia elisabethae Bayer (order Gorgonacea, family Gorgoniidae, phylum Cnideria) from the waters near San Andréas Islands, Colombia, showing potent activity against *M.tuberculosis*. The elisapterosin B has been found to have potent inhibitory activity against *M.tuberculosis* H37Rv at a concentration of 12.3 µg/ml[31]. In the case of cumbiasin A and B , they display mild *in vitro* activity against H37Rv, 6.25 and 12.5 µg/ml, respectively, and both compounds caused 17% growth inhibition of *M. tuberculosis*[33].

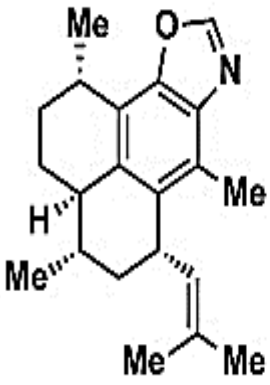


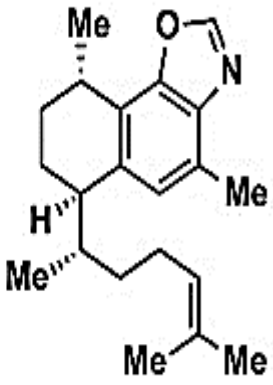


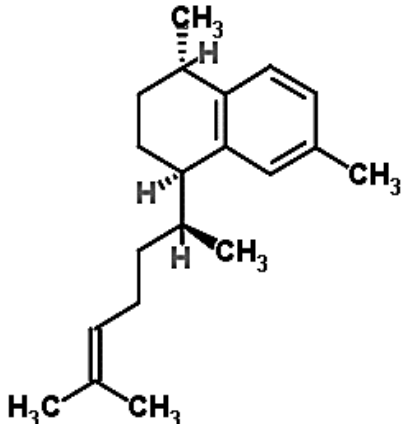


Elisabethin A **Elisabethin B** **Cumbiasin A**

Rodrigues and coworkers from the same source of *P. Elisabethae* also showed activity against *M. tuberculosis*. The three benzoxazole diterpene alkaloids, pseudopteroxazole,homopseudopteroxazole, and seco-pseudopteroxazole [34] had potent to moderate inhibitory activity against *M. tuberculosis* H37Rv (97, 88, and 66%), respectively, at a concentration of 12.5 µg/ml. Another example is the two serrulatane-based diterpenes, erogorgiaene and 7-hydroxyerogorgiaene,which induced 96 and 77% inhibition of *M. tuberculosis* H37Rv at concentrations of 12.5 and 6.25 µg/ml,respectively. The biological results indicated that the oxazole moiety is not essential for activity [34].

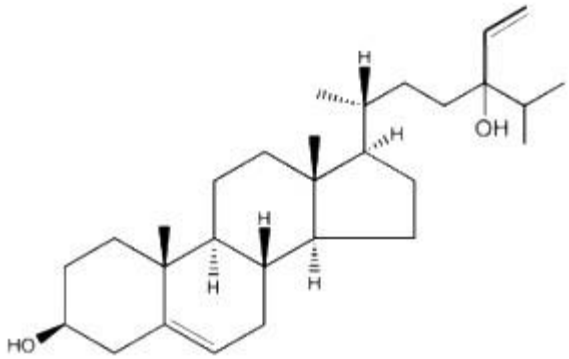






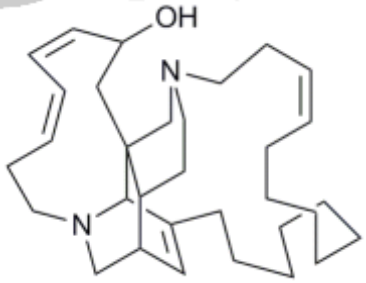
Pseudopteroxazole ***Seco*-pseudopteroxazole** **Erogorgiaene**

Timmermann and co-workers isolated the phytosterol saringosterol from the Chileanbrown algae *Lessonia nigrescens Bory* (*Phaeophyta, Laminariales*)[35], showed potent anti-TB activity against the H37Rv strain of *M. tuberculosis*. The 24*S* epimer of saringosterol presented MIC values of 0.125 µg/ml, eight times more active than their epimer 24*R* (1.0 µg/ml), indicating the importance of the hydroxyl position for biological activity. Due to its specific activity and low toxicity, this class of compounds could be a good target for the development of new TB drugs [35].



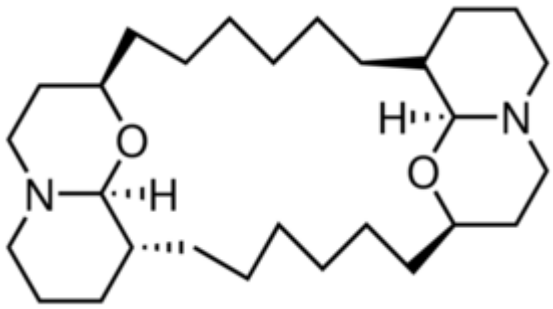
Saringosterol

Berlinck and co-workers isolated ingenamine G from methanol extract of the marine sponge *Pachychalina* sp[36] which showed biological activity against *M. tuberculosis* (H37Rv) at 8 µg/ml .



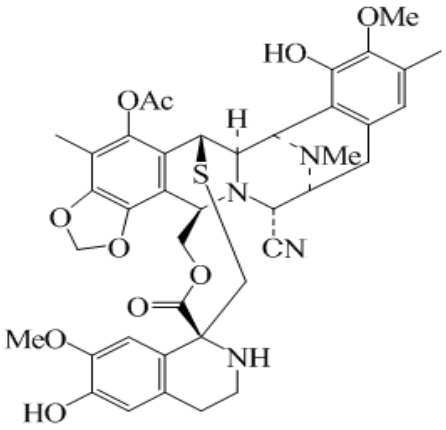
Ingenamine G

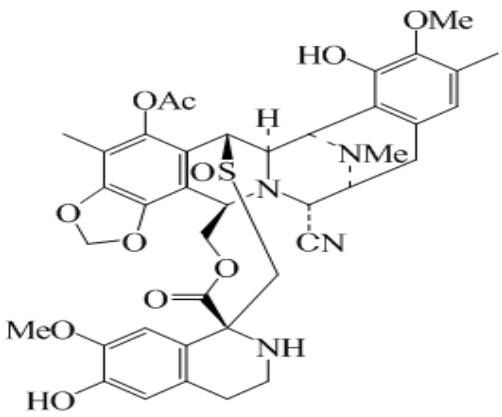
Orabi and co-workers [24] identified potent anti-TB activity in (+)-araguspongine C (MIC = 3.94µg/ml) [37], a natural product isolated from red sea specimens of *Xestospongia exigua* [38]. This class of compound possesses diverse important biological activities such as vasodilatation [39], cytotoxicity[40], antifungal and vasoactive intestinal peptide inhibition activity[41].



Araguspongin

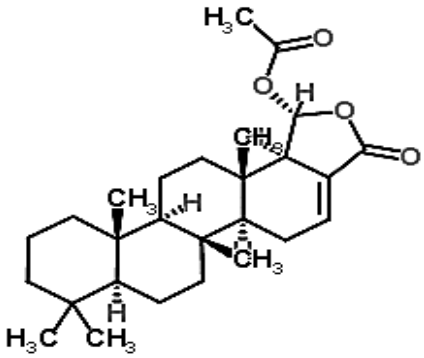
Suwanborirux and co-workers isolated Ecteinascidins 770 **and** 786 from Thaitunicate *Ecteinascidia thurstoni*[42]. This class of compounds showed potent cytotoxic activity with the ecteinascidin 743 under phase II clinical trials in the treatment of cancer [43]. Suwanborirux and his group found potent anti-TB activity against *M. tuberculosis* (H37Rv) in ecteinascidins 770 and 786 with MIC values of 0.13 and 2.0 µg/ml, respectively [42].



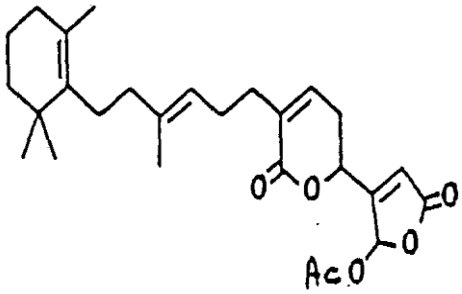


Ecteinascidins 770 **Ecteinascidins 786e C**

Plubrukarn and co-workers isolated and tested different sesterpenes from Thai sponge B *Brachiaster* sp. against *M. tuberculosis* (H37Rv). For example, 12-deacetoxyscalarin 19-acetate and themanoalide 25-acetate with MIC values of 4 and 7 µg/ml respectively [44].

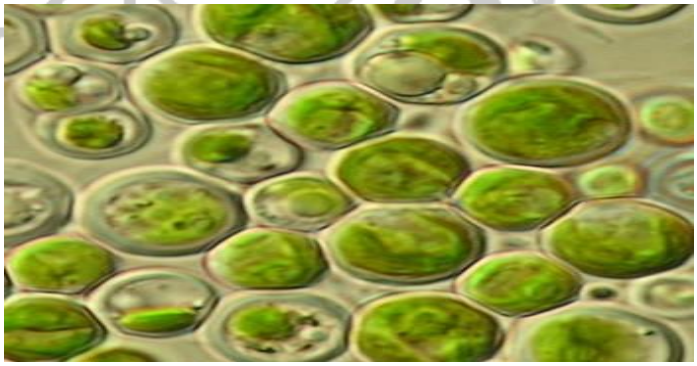


12-Deacetoxyscalarin



19-acetateManoalide 25-acetate

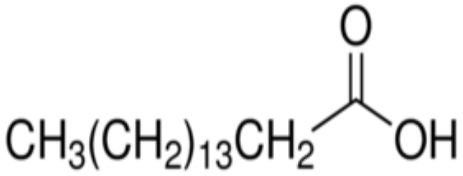
S Prakash and B Valentin Bhimba collected algal inoculum of chlorella marina, Isochrysis galbana, Tetraselmis sp., Nannochloropsis occulata, Dicarteria inorta and Chromulina freibergensis from Cental Marine Fisheries Research Institute (CMFRI) at Tuticorin. The selected resistant strains of mycobacterium tuberculosis were screened for bioactive compounds extracted from marine microalgae and Isochrysis galbana has been found rich in bioactive compounds than the other algal species. Maximum antimicrobials were obtained from butanol extract of Isochrysis galbana [44]. The minimum inhibitory concentration is 50-60µg/mL against mycobacterium tuberculosis, for Tetraselmis sp. it is 70-80µg/mL and for chlorella marina it is 80-90µg/mL.

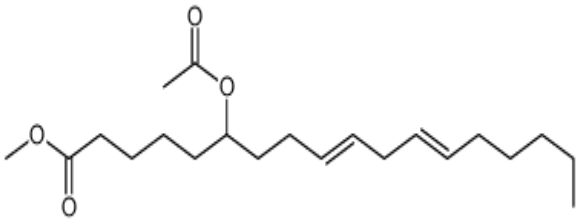


Isochrysis galbana

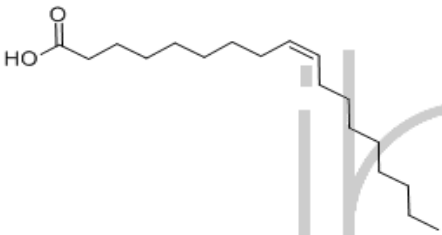
Muthusamy Ravichandiran and co-workers worked on Sepiella inermis (S. inermis). The cuttlefish produces a dark ink secreted by its ink gland for its defence. The ink of cuttlefish was identified as a potential source of bioactive compounds and it is a traditional Chinese medicine. Cuttlefish is found to contain antibacterial, antifungal, antiseptic, platelet aggregation, haem-agglutination and cytotoxic properties. Methanol and chloroform ink extracts of S. Inermis showed methanol extract to be

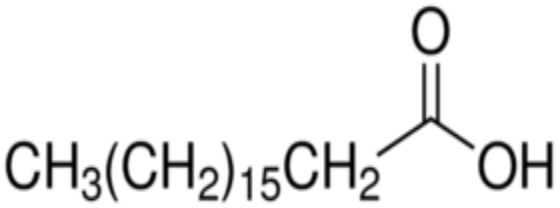
more potent than chloroform extract [46]. Methanol ink extract of S. inermis revealed the presence of omega fatty acids like hexadecanoic acid 9, 12-octadecadienoic acid, 9-octadecenoic acid and octadecanoic acid and exhibited significant inhibitory effect against M. tuberculosis at the concentration of 64 µg/mL with the observed inhibition of 14 CFU when compared to chloroform extract [46].





Hexadecanoic acid **9, 12-Octadecadienoic acid**





9-Octadecenoic acid **Octadecanoic acid**

Conclusion

The vast diversity of marine fauna and flora offer human beings the last frontier to explore the existence of potential drugs for use in disease treatment. The marine environment clearly holds an enormous potential for providing new leads for the development of antimycobacterium agents. These newly identified structural classes are active against *M. tuberculosis* action and are better treatments for resistant strains. Progression of studies in this direction could definitely help to develop some pharmaceutically important bioactive natural products from marine.

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