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EXPLORING MYXOBACTERIA FOR DRUGS

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ABSTRACT

Over the past two decades, there has been huge gain of interest towards research in Myxobacteria as a group towards the discovery of novel drugs. The latter includes antibacterial, antiviral, anticancer, immunosuppressive etc. To fight and combat many emerging diseases that confronts the human. Myxobacteria represent an interesting group of Gram negative prokaryotic microorganisms primarily due to exceptional changes in life cycle and predatory mode of life. Although, majority of the antibiotics has been obtained from Actinobacteria, in recent years, however, Myxobacteria became increasingly recognised as a rich yet underexplored resource of novel drugs, with the potential to combat the looming health threat posed by antibiotic resistance and other medical conditions. The diversity and unique structural properties of their secondary metabolites is what make these social microbes highly attractive for drug discovery. Various Myxobacterial drugs having antibacterial (glumirecins, disciformycins, chlorotonil, etangien, sorangicin, hyapyrones, roimatac ene, argyrins, cystobactamids etc.); both antibacterial and antifungal activities include hyapyrones, argyrins, chondrocholrens While aetheramide, etangien, ratjadon, sprirangiens etc. are reported to have antiviral activities. These are mainly considered for treating Hepatitis infections (labindoles, soraphen, lanyamycin), AIDS (aetheramide, sulfangolid, soraphen epithilon, sprirangiene etc). Many drugs of Myxobacterial origin are now being considered as therapeutic drugs for treating cancers, such as epithilone, disorazol, microsclerodermin, chondramides, saframyxin, microscleramidermin. Some other activities of the secondary metabolites derived from Myxobacteria are anti- malarial (**Chlorotonila**), immunosuppressive (**Argyrins**), insecticidal (macyranones, chondramides, benzamides, eliamid)) activities. A large variety of compounds however, have been reported to exhibit cytotoxic or cytostatic effects against eukaryotic cell lines. Future trend of research in this sector will involve developing methods and process to chemically modify them (by adding various groups) so as to make them applicable (i.e. no toxicity).

1. INTRODUCTION

Over the past two decades, the myxobacteria have become one of the most fascinating objects of microbiological research.[1] The myxobacteria (“Slime bacteria’’) are a group of bacteria that are predominantly found in soil which primarily feed on insoluble organic substances.[2] The two largest species of myxobacteria,are *Minicystis rosea* (bacterial genome over 16 million nucleotides) and *Sorangium cellulosum.*[3]

Myxobacteria are Gram negative in staining behaviour and taxonomically belong to deltaproteobacteria order within the class Proteobacteria. They are cosmopolitan in distribution and are reported from diverse ecological niches of the world, such as arctic tundra, temperate zones, tropical rain forests, deserts, acidic soils,[4] marine and saline environments,[5]and saline environments[5] and are even reported from caves.[6] Aerobic myxobacteria can be isolated from the natural sources such as, soil, bark, rotting wood, leaves of a trees, compost or dug of herbivores. Currently, one only facultative anaerobic bacterium (*Anaeromyxobacteria dehalogenans)* is reported in literature.[6]

They are interestingly fascinating due to their exceptional lifestyle, which not commonly reported in bacteria. These are as follows

1) Myxobacteria as a group have effectively made the transition from single cell to multicellular life, exhibiting multifacility cooperative behaviours and multicellular development comparable in sophistication to that seen in macroscopic social organisms.[7]

2) Under nutritionally starved/depleted conditions, they form multicellular biofilms called fruiting bodies, known as myxospores. Morphologically, these vary from simple mounds to convoluted three dimensional structures, within which some bacteria altruistically develop into non-reproductive cells, while others differentiate into resistant and reproductive spores.[8]

Myxobacteria are social predators, studied extensively for their potential to produce natural products. Their

predatory secretions have already been extensively exploited by pharmaceutical industry with over 100 core structure and 500 derivatives of novel antibiotics reported in the literature.[9] Myxobacteria produce a wide range of structurally diverse small molecules called secondary metabolites.[10] Although these natural products are important for health as antibiotics or other therapeutic values but their physiological functions to the producer organisms are still not known.[11]

Thus, how these microbes produce effective antibiotics in micromolar range for killing other compeating microbes in their natural habitats (Such as soil), is not clear. But in recent time, it is shown that antibiotics can significantly alter microbiological gene expression.[12] Elucidating the biological role of the secondary metabolites to the producers is a fundamental concern to understand their evolution and regulation, so as to develop informed strategies to optimize /engineer strains, and to find new isolates that make therapeutically useful products. Myxobacteria have interesting properties, that includes rich production of secondary metabolites and predatory behaviours.[13]

Predation involves the ability to more or glides to establish prey contact.Killing by myxobacteria appears to involve direct cell-cell contact. Killed and lysed preys are digested into small molecules for consumption.[14] Interestingly among the known myxobacterial secondary metabolites, about 20% have antibiotic activity. Upon starvation, vegetative cells of myxobacterial convert into myxospores.But when vegetative cells of myxobacteria encounter prey they are postulated to neutrilize them by the secretions of antibiotics and other hydrolytic enzymes. Extracellular digestion of the prey into small molecules allows nutrient uptake by myxobacteria.In support of this,the myxobacterial growth rate increases as well density increases when myxobacteria grown on macromolecular substrates,such as proteins.[15] This observation led to the notion that myxobacteria feed as microbial ‘wolfpacks’; i.e., higher cell density increases extracellular hydrolytic enzymes and antibiotic concentrations,thus allowing more efficient prey killing and digestion. Although this hypothesis seems resonable, it is also striking that a single myxobacteria can penetrate a prey microcolony and rapidly kill digest and consume it.[16]

This form of predation appears to depend on cell-cell contact.Thus myxobacteria are effective predators in packs or as lone cells. Myxobacterial predatory activity seems to require more than just the possession of specific antimicrobial metabolites[17] Over the last decade, however, the myxobacteria have emerged as a promising bioactive molecules. Myxobacterial natural products exhibit many unique structural features relative to other metabolites, as well as rare or novel modes of action, making them attractive lead structures for drug development.In addition, the complex biosynthesis of many of these compounds derivates significantly from established precedents in other bacteria.

Here in this review work I aim to summarize the secondary metabolites of myxobacteria that has therapeutic value and discuss briefly about their modes of action.

1. Why secondary metabolites of Myxobacteria are underappreciated?

In 1982, scientist Ronald Thaxter first identified the myxobacteria as a distinct group of oraganisms.Multiple features of myxobacterial microbiology (such as their peculiar behavioural and morphological charcteristics, basic physiology, biochemistry, genetics) help to studies their natural product producers.[18] Because myxobacteria divide very slowly under laboratory conditions (4h-14h doubling time) and most strains grow as lumps and flakes when first inoculated, with homogenous suspension produced only after weeks or months of repeated sub culturing. As full structure elucidation of natural products often requires fermentation scale growth of the producing organisms, these characteristics significantly impeded and continues to impact attempts to identify the myxobacterial secondary metabolome.

Genetic manipulation of the producing strains is so difficult because plating on solid medium hardly yield single colonies in high numbers, and when colonies emerge they grow very slowly (8-14 days). So, techniques developed for one strain often cannot be applied directly to another, even if the two strains are phylogenetically closely related and also no autonomously replicating plasmids for myxobacteria have been reported until recently,[19] and most strains exhibit natural multi-resistance to commonly antibiotics, hampering the identification of resistance markers.

2. Myxobacteria as multiple producer of secondary metabolites

Only a few microorganisms have been identified as good producers of natural products: yeasts, fungi and bacteria such as *bacillus*, the pseudomonads, actinobacteria, cyanobacteria, myxobacteria, and the insect pathogenic bacteria.[20] Mainly myxobacteria have been isolated from soil (Except some marine strains), the cells can move by gliding or creeping over surfaces,within the context of the swarm, they remain virtually stationary.[21] Therefore one resonable explanation for myxobacterial productivity is that they are simply ‘keeping up with the zones’-to protect its ecological niche in the highly competitive terrestrial environment, each species maintain an armament of antibacterial and antifungal agents. Compound production rates are typically highest in the exponential phase of growth.This behaviour contrasts with that of the actinobacteria,in which secondary metabolism correlates with the onset of the stationary phase.[21,22] The ability to not only fend off your neighbours but to actively kill them-if concentrations reached in the natural environments are sufficient-might be particularly useful for some myxobacterial strains such as *Myxococcus,*which are

capable of degrading proteins and even whole cells of other microorganisms, through excretion of exoenzymes.[23] Alternatively (or in addition), a major role of myxobacterial small molecules may be in modulating cell-cell interactions within the enormously complex soil communites.[23,24]

3. Myxobacterial secondary metabolites: A new source of medicine

Myxobacterial predatory activity seems to require more than just the possession of specific antimicrobial metabolites. Incorrect use in human medicine, incorrectly prescribed antibiotics extensive agricultural use and fast spread of resistant bacteria caused by increasing mobility led to substantial problems with multidrug resistant bacteria. Some of the most problematic germs are called ESKAPE panel-*Enterococcus facium, Stahylococcus aureus, Klebsiella pnemoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.* are mainly responsible for the nosocominal infections. Eligible countermeasures include the development of synthetic and semisynthetic drugs, evaluation of rediscovered drugs and the classical screen of natural secondary metabolites producers. Myxobacteria for instance are one of the promising natural product producers,but demanding with regard to isolation and large scale cultivation.[25] The majority of myxobacterial compounds are polyketides, non –ribosomal polypeptides and their hybrids, terpenoids, phenyl-propanoids,alkaloids.Many of these substances show promising activities against bacteria, viruses, fungi, cancer cell and immune cells,malaria respectively, as well as unusual modes of action.The global challengs of increased drug resistance has led to strong demand to increase the chemical diversity of antibiotics, especially to obtain drugs that overcome bacterial resistance through new modes of action. In recent times, various novel carbon skeletons with interesting bioactivities have been isolated from hitherto under explored taxa such as sorazolones and carolacton from *Sorangium cellulosum*, argyrins and tubulysins from *Archangium gephyra,*aetheramides from *Aetherobacter spp.,* disciformycins from *Pyxidicoccus fallax* and cystobactamids from *Cystobacter sp.,* etc.[26]

Many myxobacterial compounds exhibit antiviral, antibacterial or antifungal, and rarely but notable properties include anti-malarial, immunosuppressive, insecticidal and herbicidal activities,while a much more significant number of compounds exhibit cytotoxic or cytostatic effects against eukaryotic cell lines. The modes of action of various metabolites have been discussed following.

1. Antiviral activity

Viral infections including human immunodeficiency virus (HIV), cytomegalo virus (CMV), hepatitis B virus (HBV) and hepatitis C virus (HCV) pose an ongoing threat to human health due to lack of therapeutic agents.The drug used to treat or manage HIV tends to increase the pathogenesis of HBV and HCV. Myxobacteria are in the focus of this review since they produce numerous structurally and functionally unique bioactive molecules, which have been screened for antiviral effect. More so, some have been found to have an unusual broad-spectrum antiviral activity.[27]

Human immunodeficiency virus (HIV) is a lentivirus of the retroviridae family. HIV targets the immune cells,and reverse transcribes its single–stranded RNA (ssRNA) genome, integrating into the host chromosomal DNA.The virus's high antigenic diversity and multiple mechanisms to avert recognition by the human immune system thus posing a challenge to host defence and treatment.[28] Various assays have been developed and used to identify the molecules with anti-HIV activity; based design of a small molecules CD-4 antagonist with broad spectrum anti- HIV 1activity,structure based identification of small molecules antiviral compounds targeted to the gp41 core structure of the human immunodeficiency virus type 1,[29] and identification of HIV inhibition by high throughput (HTP) two step assay.The HTP assay has been study on myxobacterial derived molecules with success due to the ability to screen a large number of molecules in a short period. [30]

Sulfangolids, the first sulfate esters containing a series of secondary metabolites produced by several strains of *Sorangium cellulosum.* Sulfangolid C(1),Soraphen F(2), Epothilon D(3) and Spriangium(4) showed impressive activity, with EC 50 values in the nM range with a selectivity index value greater than 15 (SI>15) in the high throughput two step infectivity assay. The soraphen have been reported as acetyl coA carboxylate transferase inhibitors, while the epithilones stabilize microtubulin of macrophages. Metabolites 3 and 4 are reported to decelerate the phosphorylation and degradation of inhibitor of kappa βα. The preliminary compounds are identified as anti-HIV activity.[1-5]

Rhizopodin(6) from *Myxococcus stipitatus* was identified as interesting two steps HTP assay likely because of its modes of action. HIV cell to cell transmission is the primary route of HIV infection in naive cells in vivo. Actin filaments are known to be essential for virological synapse formation, therefore virus synapses are interfered by Rhizopodin,which is a known actin inhibitor Disorazol,tubulysin and stigmatellin variants were also reported to have mild anti-HIV activity.

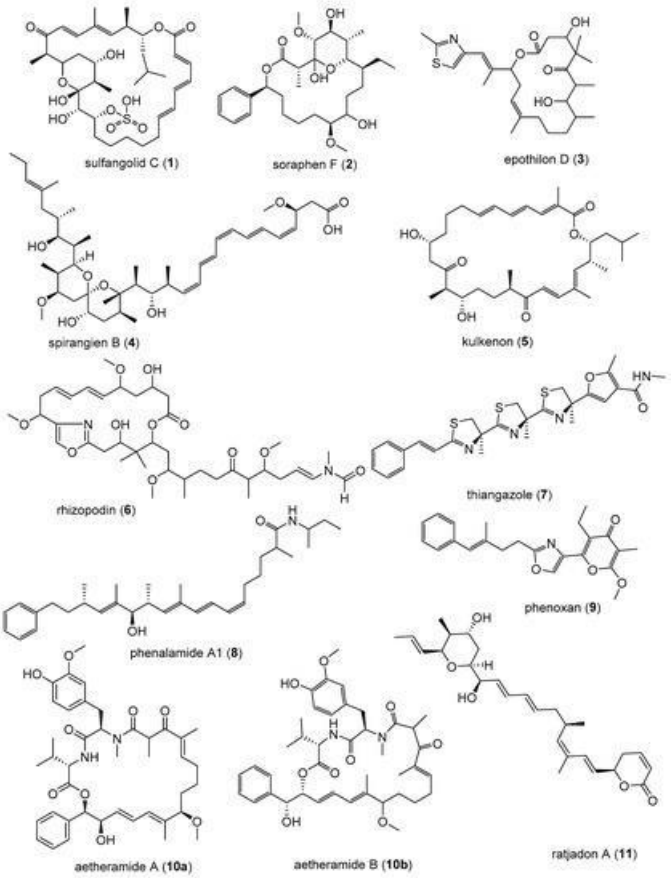


Fig. 1: Myxobacterial-derived compounds with activity against HIV.[27]

Thiangazole(7), Phenalamide A1(8) and Phenoxan(9) isolated from two strains of *Polyangium sp.*,*Myxococcus stipitatus* strain Mx s40 were reported to have anti HIV activity as they all revealed high EC50 value of 8 and 9 in the nanaomolar range,whereas Thiangazole(7) had an impressing EC50 value in the picomolar range making it a possible lead compound for anti-HIV therapy.[32]

Aetheramide A(10a) and aetramide(10b) are containing a polyketide moiety and two amino acids residues, isolated from the recently described genus *Aetherobacter*, inhibited HIV- 1 infection with IC50 value of 0.015 & 0.018μM respectively.[33,34]

Ratjadon A(11), an α-pyrone metabolite isolated from *Sorangium cellulosum* (strain Soce 360),was reported to inhibit HIV infection by blocking the Rev/CRM1-mediated nuclear export pathway,CRM1-Rev complex is an attractive target for the development of new antiviral drugs because the nuclear export of unspliced and partially spliced HIV-1 m-RNA is mediated by the recognition of a leucine rich nuclear export signal (NES) in the HIV Rev protein by the host protein CRM1/exprotein 1.[35] Despite 11 being reported to exhibit a strong anti-HIV actively, it has allowed selectivity due to toxic effect; its low SI value limits its uses a therapeutic drug. More studies with derivatives of its need to be done. Even the active metabolites that cannot realistically be further developed as drug candidates because they are too toxic could be attain a better understanding of the invasion mechanism of HIV, or for development of synthetic analogues that mimic these compounds without causing toxicity.[35] Another viral infections, Human cytomegalovirus (HCMV), belongs to β-herpes virus family, with a high prevalence, infecting up to 80% of the general population usually asymptomatic in healthy people and disease associated with HCMV include glandular fever and pneumonia. HCMV is also an important pathogen in organ transplant patients responsible for significant morbidity and mortality in organ transplant recipients and a major cause of disease in patients with HIV infection.[36]

Several anti-HCMV drugs such as Ganciclovir, Forscarnet, Cidoforvir and Fomivirsen,[37] were reported to have low potency, poor bio-availability, and adverse side effects and also drug resistances were reported to emerge. Hence, there has been a renewed interest in search of new inhibitors of HCMV.[27,38] A class of myxobacterial compounds Myxochelin,belonging to a larger group of natural products, siderophores,were isolated from several strains of myxobacteria which produced siderophore, secondary metabolites produced by some microorganisms under iron-limiting conditions and uptake the iron.[39] Other siderophore isolated from myxobacteria includes nannochelins and hylachelins.Myxochelin A(12a)was initially isolated from the culture broth of *Angiococcus disciformis* (strain

An D30), Myxochelins B, C, D, E, F are also synthesized later.[40]

The corresponding biosynthetic gene clusters that are responsible for siderophore production have been identified in *Stigmatella aurantica (*Sga 15), *Sorangium cellulosum (*Soce 56),[41] and *Nanocystis exedens*(21a-21c) and *Hyalangium minitum*(20a-20c).[41] Myxochelins C (12c)inhibited HCMV with an IC 50 value of 0.7µg/ml.[42] In particular, the known myxobacterial derived siderophore,such as nannochelins,hyalachelins and all other myxochelin analogues should be screened for various antiviral activites specially anti-HCMV, and should be studied for structure activity relationship for possible discovery of more potent antivirals.[38]

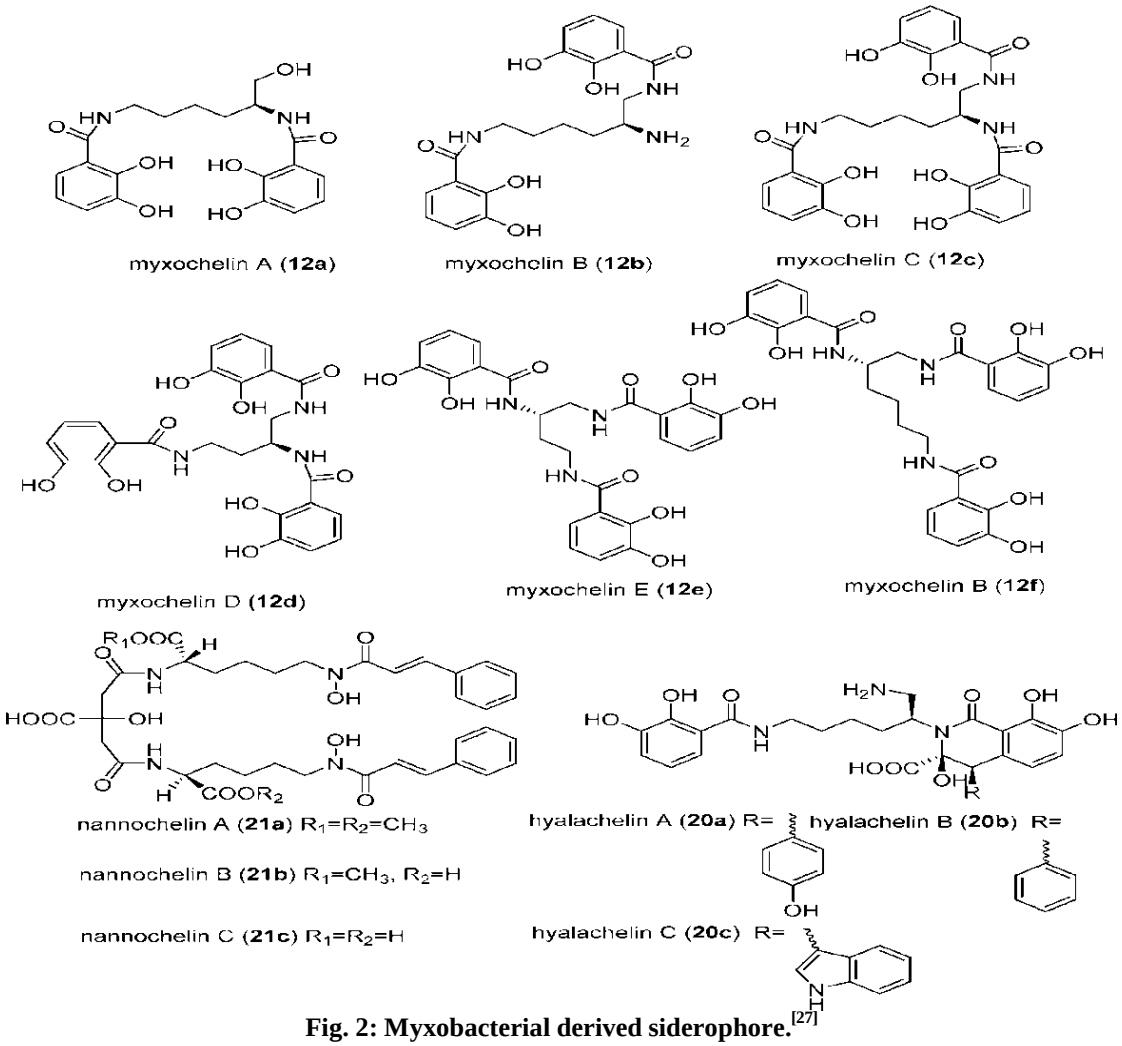
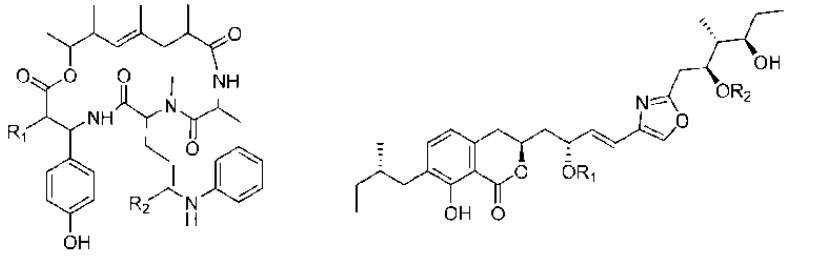


Fig. 2: Myxobacterial derived siderophore.[27]

Another dangerous virus disease, Ebola haemorrhagic fever is caused by the Ebola virus (EBOV), a single stranded RNA enveloped virus belonging to the family Filo viridae. EVB first appeared in 1976 in the simultaneous out breaks, one in Nzara, South Sudan and the other in Yambuku, the democratic republic of Congo, the Ebola river, from which the disease takes its name. EVB case fatality rate is around 50%, with different cases.[43] Various metabolites from myxobacteria were screened for EBOV inhibition by an assay with a surrogate system using Ebola envelops glycoprotein GP-pseudotyped lentiviral vectors. GP-psedotyped lentiviral vectors were used as tools to investigate the entry process of the viruses, enabling studies without the need of using the native Ebola virus reducing the safety level from the highest level 4 to level 2.[44] Chondramides,a class of compounds known to interfere with actin, were isolated from a myxobacterium belonging to the genus Chondromyces.[45] which are reported to inhibit the EBOV-GP mediated transduction with impressive IC 50 values 24-42 Nm. Other promising hits were the noricumazoles, a family of polyketaides from *Sorangium cellulosum*, such as noricumazole A(14a) was found to inhibit EBOV-GP with an IC 50 value of 0.33µM. Norcumzoles are known to be[44,46] pottassium channels blockers.

These metabolites will give insights into the EBOV infection mechanism, rather than being used as drugs, because the modes of actions are expected to side effects.



13 14

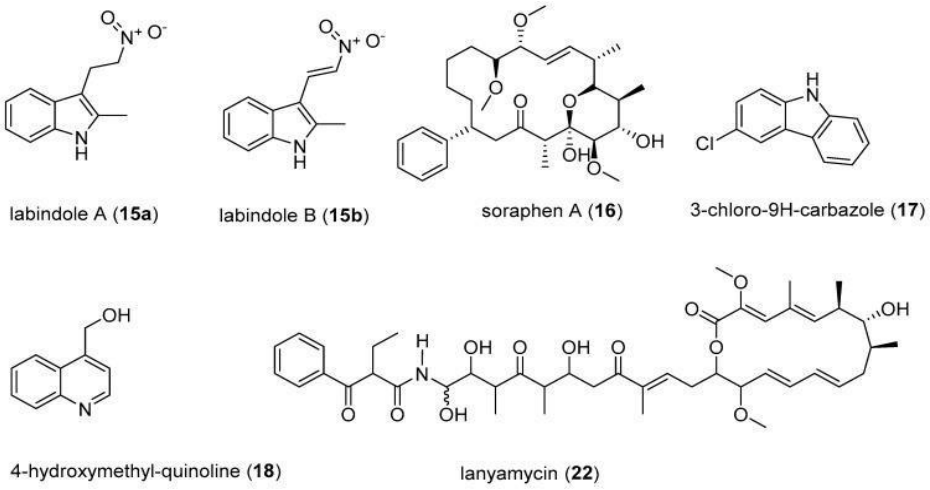
chondramide A (**13a**) R_1=OCH_3, R_2= H
chondramide B (**13b**) R_1=OCH_3, R_2= C
chondramide C (**13c**) R_1= H, R_2= H
chondramide D (**13d**) R_1= H, R_2= Cl

noricumazol A (**14a**) R_1= H, R_2 =H
noricumazol B (**14b**) R_1= H, R_2 = Alpha-D-arabino-Furanosyl
noricumazol C (**14c**) R_1= Beta-D-arabino-g uco-Pyranosyl, R_2 =H

Fig. 3: Antiviral compounds for Ebola virus from myxobacteria.[27]

Another viral infections, hepatitis C virus (HCV)is an enveloped,single stranded RNA virus with positive polarity (ss(+) RNA) and transmitted by blood to blood contacts, such as through intravenous injections, blood transfusion and various exposure contaminants or body fluids, including saliva or semen.[47] HCV and hepatitis B virus (HBV) infection are the major causes of hepatocellular carcinoma (HCC)associated with cirrhosis, currently no products are avaliable to prevent HCV infection.[48] However,treatment is complicated by HIV-HCV/HBC co- infections with drug-drug interactions between anti-HIV and anti-HCV drugs, resulting in serious side effects and can lead to death of patient.[49] The discovery of broad-spectrum antivirals may play an essential role in overcoming this challenge.

The recently isolated compounds from *Labilithrrix luteola*, labindoles A(15a) and B(15b)(fig:4)have been reported to have moderately inhibited HCV.[48] Interestingly the labindoles were said to have no toxicity, anti-bacterial or anti-fungal activities. Also 3-chloro- 9H-cabazole (17) and 4-hydroxymethyl-quinoline (18) (fig4) isolated from *Labilithrix luteola* were reported to have a strong inhibition of HCV.[48] However, recent studies have suggested that soraphen A(16) (fig:4) inhibits HCV replication in HCV cell culture models expressing sub-genomic and full-length replicons as well as a cell culture-adapted virus with an IC 50 value of 5n M. The HCV assay involved the development of sub-genomic replicons that replicons that replicate autonoumously in the human hepatoma cell line Huh-7 to be able to screen for anti-HCV activity.The subgenomic replicons are genetic materials from HCV, which represent the actual invasion and replication of HCV on the liver cells.Furthermore,16 is known to depolymerise the acetyl-CoA carboxylase (ACC) complexes into less active dimers.[50] The mechanism of action of 16 is a valuable probe to study the roles of ACC polymerization and enzymatic activity in viral pathogenesis.[50] Various minor structure alterations og 16 did not affect the antiviral activity. Owing to the fact that soraphens inhibit both HIV and HCV, it has been proposed that the broad-spectrum activity of 16 could be due to targeting commonly used host factors or pathways necessary for viral replication.[51] Another recently isolated myxobacteria-derived secondary metabolite, lanyamycin(22) (Fig. 4.) from *Sorangium cellulosum(*strain Soce 481)moderately inhibited HCV with IC 50 value of 11.8µM.[51] The macrolide[22] is closely related to the bafilomycins, a class of secondary metabolites from actinobacteria.[52]



labindole A (**15a**) labindole B (**15b**) soraphen A (**16**) 3-chloro-9H-carbazole (**17**)

4-hydroxymethyl-quinoline (**18**) lanyamycin (**22**)

Fig. 4: Myxobacterial-derived secondary metabolites use as antiviral drugs to treat HCV.

2. Antibacterial activity

As persistance challenge in clinical antibiotic use in resistance development,this combined with the abandonment of antibiotics drug discovery by most pharmaceutical companies, has led to a public health concern about the availability of efficacious antibiotics.[53] Historically, microbial natural products have been primary source of clinical antibiotics, one such group comprises the myxobacteria where up to 10% of their genomes can encode secondary metabolites pathway.[54] Importantly, myxobacterial natural products often have novel structures and activities, and also they are rich source for new drugs, particularly antibiotics,which are worthy of pursuit.

1. Antibiotic TA

It was solated from producer strain *Myxococcus xanthus* (from Tel Aviv), also known as myxovirescin, megovalicin or M-230B, is a promising lead compounds has a novel structure consisting of 28 membered macrolactone.[55] TA is a rapid bactericidal agents and has activity against many Gram negative and some Gram-positive bacteria. Antibacterial activity is specific, as TA shows no toxicity toward fungi, protozoa, eukaryotic cells,rodents or even humans.[56,57] TA, has also exhibits unusually high adhesive properties toward biological and abiotic materials, so, TA has been proposed for the treatment or prevention of bioflim infections, such as peridontal disease or infection derived indwelling medical services.[58] Mainly, type ii signal peptidase (LspA) was first targeted to the TA because universally found in bacteria and broadly essential in the Gram-negative bacteria. But in Gram-positive bacteria, LspA appears to be conditionally essential or non-essential and plays an important role in virulence factors are lipoprotein LspA is absent in eukaryotic cells, which eliminates any concerns about target based toxicity in animals.[59]

2. Glumirecenis

These were were found from the predactory myxobacterium, *Pyxidicoccus fallax* HKI 727. Chemically, Glumirecins form a novel class of antibiotics, together with the disciformycins, which were discovered in a different *P.fallax* strain the distinctive 12- membered macrolide scaffold in these natural products features an arabinose moiety, which is only rarely observed in bacterial polyketides. The two forms of Glumirecins A and B,have main differences in their structures with or without of an isovalerate subtituent comparison with the bioactivity data of the disciformycins suggests that the is ovalerate moiety is mainly responsible for the antibacterial activity.Due to their potent effects against human pathogenic Staphylococci as well as negligible toxicity, Glumirecins A and Disciformycin B have become a promising candidate compounds for the design of new antibiotics.[59]

3. Myxopyronins

Myxopyronins were first reported in 1983 from a culture of *Myxococcus fulvus* Mxf 50 and structurally related Corallopyronins were found in different strains of *Corallopyronins coralloides.* Myxopyronins and corallopyronins share a common scaffold composed of a central pyrone ring carrying two flexible side-chains. Structurally differences in the western side chains,which ranges from 10(Myxopyronins A)up to 18 carbon atoms (Corallopyronins B).[60] Myxopyronins and corallopyronins turned out to be highly active against Gram-positive bacteria with MIC values between 0.1 and 1.0µg/ml for *Staphylococcus aureus*,whereas their inhibitory effects on Gram-negative strains are in general much weaker. Gram-negative bacteria of the genus *Wolbachia*, which have emerged as a new target for filariasis control consititute a significant exception.[61] Myxopyronins and corallopyronins are inhibited on of prokaryotic RNA polymerase as mode of action.[62] During early stages of transcriptional initiation,the RNAp clamp possesses an opened from in order to allow binding of the promoter DNA to the active center cleft.At late transcriptional initiation and elongation,the clamp changes into a cosed position to retain the DNA inside the active region, Myxopyronins and corallopyronins prevent the opening of the clamp.[63]

4. Althiomycin

It was initially discovered in cultures of *Streptomyces althioticus* but it also reported from strains of *Myxococcusvirescens, M. xanthus* and *Cystobacter fuscus.*[64] The pentapeptide is broadly active against Gram-positive as well as Gram-negative bacteria and also inhibit the bacterial protein synthesis. Its inhibit the 50s subunit of the ribosome and where althiomycin interferes with the peptidyl transferase reaction.[65] The althiomycin biosynthetic gene cluster was recently identified in *M.xanthus* DK897 by a combination of retrobiosyntetic analysis and gene inactivation.Two open reading frames (ORFs) encoding for a non-ribosomal peptide synthetase (NRPS) and NRPS/polyketide synthase (PKS) hybrid were found to be involved in the assembly of the core structure.Furthermore,the sreactions and drug resistance.[66]

5. Cystobactamids

These antibiotics were recently isolated from a *Cystobacter sp.* and represent a novel class of NRPS-derived antimicrobial peptides. Cystobactmids 919-1 and 919-2 display an unusual aromatic scaffold composed of p-nitrobenzoic acid and four p-aminobenzoic acid (PABA) derived moieties. The latter vary in their oxidation and substitution pattern, which may even comprise rare isopropoxy groups.The two unmodified PABA residues in the compounds 919- 1 and 919-2 are connected via an iso-β-methoxyasparagine or a β-methoxyaspargine unit, respectively. In contrast, the tripeptide cysobactmid 507 seems to be either biosynthetic by product or a degradation fragment of its larger congeners. Especially derivatives 919- 2,possesses

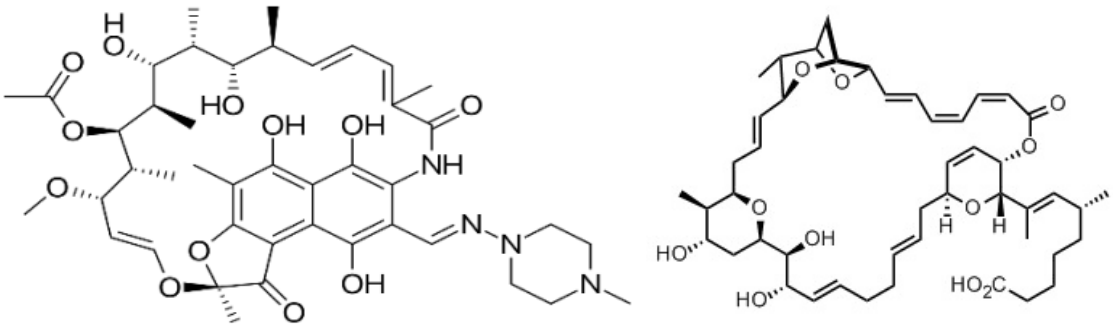
strong inhibitory effects on the growth Gram-positive and Gram-negative bacteria. Analysis of the cystobactamids biosynthesis gene clusters led to the identification of a gene coding a putative resistance factors. Subsequent assays confirmed that the cystobactamids acts on the DNA replication of bacteria by inhibit the DNA gyrase.[67]

6. Aurachins

It is new quinolone alkaloids which were isolated from the myxobacterium *Stigmatellin auraurica* strain Sga15. It mainly block the electron transport specifically complex 1 (ubiquinone, oxidoreductase). It has been described to produce two structurally unrelated antibiotics such as stigmatellin and a mixture of myxalamids. This strain produces a third group of biologically active compounds (formly Sga 15A, B, C, D). Aurachins, mainly active against numerous Gram-positive bacteria. In general, the aurachins C and D were more active than the Aurachins, B and A.Only some coryne-form bacteria were similarly sensitive to Aurachins A and C. [68]

7. Compounds of Myxobacterial origin having inhibitory action on Eiukaryotic Transcription & Translation Processes

Eubacterial RNA polymerase (RNAP), the enzyme responsible for transcription of DNA into RNA, is the target of several low molecular weight inhibitors, best known is Rifampicin (Rif). But in recent time, bacterial strains resistant to rifampicin arise with appreciable frequency and compromise treatment of the disesase. Sorangicin A (Sor), a new macrolide polyether antibiotics, isolated from myxobacterium *Sorangium cellulosum*, that shown a potent inhibitors of bacterial, but not eukaryotic RNAPs. Despite the lack of apparent chemical similarity between Sor and Rif, Sor was observed to inhibit transcription initiation,but not elongation.



Rifampicin **Sorangicin A**

Fig. 5: Chemical formulas for RNAP inhibitors rifampicin and sorangicin A.

A. Sorangicin, occupies the same RNAP β subunit pocket as rifampicin, with an almost overlap of RNAP binding determinants, and that sorangicin inhibits trancription by the same mechanism as rifampicin. On the other hand, while Rifampicin binding and inhibition are very sensitive to amino acid substtitutions that would be excepted to alter the shape of the antibiotic binding pocket, Sorangicin is able to bind and inhibit these rifampicin resistant RNAPs effectively.[70]

B. Ripostatins A-C was first isolated from myxobacterium *Sorangium cellulosum* Soce377. Ripostatins A and B are 14 member macrolides with three 2,5,8 positioned double bonds, whereas Ripostatins C is a non-cyclised derivative but biologically inactive.[71] Ripostatins A and B only showed nearly the same antibacterial activity against Gram-positive bacteria, mainly *S. aureus* strains,and towards *E. coli* tolC with MICs in the range of about 1µg m L.Furthermore,it was found that no cross-resistance occurs between Ripostatins and rifampicin or sorangicin.[71] Indeed,Ripostatins A,was effective against rifampicin-resistant bacteria harbouring point mutations in the *rpoB* gene sequence coding for their RNAP.

C. Myxovalargins A and the derivatives B and C were obtanied from *Myxococcus fulvus* Mx f65. These compounds are linear peptides consisting of 14 amino acids, and hydrolysis proved that many of these are non-proteinogenic.[72] The antibiotic spectrum of Myxovalargins (a mixture of the different myxovalargins containing 90% myxovalargins A was studies) is prominent against Gram-positive bacteria with MICs ranging from 0.3µg mL against *Micrococcus luteus* up to 5µg mL. Toward *Corneybacterium mediolanum.*[72] All Gram- negative bacteria were only inhibited at significantly higher concentrations (MIC of 6µg ml against *E.coli).* The mode of action underlying the describe antibiotic effects can be separated into two different mechanisms. At low concentrations myxovalargin A inhibits instantaneously bacterial protein synthesis, whereas at higher concentrations or upon prolonged incubation, cell membranes are damaged[72] In cell free *E. coli*. system protein synthesis only inhibited, ifmyxovalargin A was added prior to the reaction start. This observation and continuing experiments with ribosomes led to the suggestion that myxovalargin acts at the A site of the ribosome. Due to cytotoxicity along with the fact that eukaryotic ribosomes were not inhibited an

additional biological effect proposed. It was found that at higher concentrations myxovalargin A interacted with membranes, resulting in cell lysis.This activity was obervedwhen applying to *Bacillus* cells,but also with erthrocytes, and may be the reason for the toxicity obesrved in mice. [72]

D. Angiolam A, is a lactum-lactone antibiotic from *Angiococcus disciformis* An D30. The antibiotic activity profile was found to be very narrow and bacteriostatic, in that only some members of the Gram-positive bacillaceae, including anaerobic *Clostridium perfringens*, were senstive. Gram-negative were in general resistant, except of *E.coli* mutants with increased permeability. Itb was reported to interfare with protein synthesis.[73]

E. Etnangien, was isolated from two *Sorangium cellulosum* strains designated as So ce750 and So ce1045. It is chemically characterized by a 22-membered, polyhydroxylated macrolide ring bearing a polyunsaturated C_{21} carboxylated side chains with two aliphatic hydroxy groups.[74] Etangien is effective against a broad panel of Gram-positive bacteria,some belonging to the Corneybacteria like *Nocardia corallia* and mycobacteria.Of special note is its antibiotic activity against rifampicin-resistant *S.aureus*.Investigation of the DNA,RNA and protein synthesis of etnangien treated Micrococcus luteus cells revealed an inhibitory effect on the formation of all these macromolecules.Inhibition assays purified RNAP and DNA polymerase and reverse transcriptase showed comparable dose-effect curves,with a maximal inhibition reached at 60µg ml^{-1}. The reverse transcriptase of Moloney murine leukemia virus was the most sensitive virus with a nearly complete inhibition at 5µg ml^{-1}.Analogs of etnangium with an absent or a shortened polyene side chain, or a contracted macrocycle lost their antibiotic activity, whereas the activity of the carboxy-methyl ester analogs comparable with that of the natural products.[74]

F. Carolactone A type of macrolides antibiotic was isolated from the *Sorangium cellulosum* stranis So ce960. The structural characteristics are a 12-membered lactone ring with two secondary hydroxyl functions at C-17 and C-18,and a terminal carboxyl group at the side chains.[75] Especially worthwhile mentioning is the antibiotic activity of carolacton against *E. coli* strain tolC,with an MIC of 0.06µg ml^{-1}, and its influence on biofilm formation. The main focus in further investigations was placed on the activity of carolactone against the carries and endocarditic associated bacterium *Streptococcus mutants*. The latter is able to form biofilms and proved to be sensitive towards carolactone. At a concentration of 5 ng ml^{-1} 33% of the cells in the biofilm died,whereas a concentration of 25 ng ml^{-1} resulted in 66% dead cells.[75] The inhibition of biofilms in nanomolar concentrations implied that carolacton addresses a primary target, present only in a few copies per cell.[76] A time related profile of the transcriptional response of *Streptococcus mutants* to carolacton treatment indicated the regulation of genes with an impact on biofilm formation, autolysis, cell shape, cell division, and pyrimidine and histidine metabolism.The investigation of correlated two-component signal transduction systems(TCS) revealed that carolacton mainly interacts with the serine/ threonine protein kinase (STPK) PknB.[76] The summing up, recent insights into the mode of action of carolacton indicated that this compound interferes with the STPK PknB and hence with PknB-mediated signalling.This in turn influences pyrimidine biosynthesis,cell-wall and biofilm formation,as well as the ComDE mediated bacteriocin production.The alterations in cell wall composition result in weakend cell walls,leading to loss integrity at low pH and leakage of cytoplasmatic proteins and DNA,and finally cause of cell death. [75,76]

G. Chondrochlorens,was isolated from *Chondromyces crocatus*,two chloro-hydroxy- styryl amides,the characteristics styrene moiety of which is linked by an amide bond with a 14 –membered aliphatic side chain.Chondrochlorens A and B differ merely concerning the methoxy or ethoxy functionality at C-2,respectively.[77] Chondrochlorens A was assyaed for its biological activity in agar diffusion test using 20µg of 31 on a 6mm paper disk. Only a weak antibiotic effect against *M. Luteus* (13 mm inhition zone) was found. *B. subtilis* and S.aureus were hardly affected.Pre- chondrochloren with a carboxyl group at C1´and no carbon-carbon double bond between C1´and C2´ showed at 30µg/disk agar diffusion assay no inhibition zone against *B.subtilis* and *M.luteus.* In comparison, chondrochlorensB produced an inhibition zone 17 and 14 mm, respectively. [77]

H. Indiacens A and B, from *Sandaracinus amylolyticus* strain NOSO-4T, a recently characterized new myxobacterial genus, two 3-formylindol derivatives were isolated, i. e. Indiacens A, and Indiacens B, whereby the latter represents the chlorinated derivatives of Indiacens A.[78] It showed antibiotic activity against Gram-positive and Gram-negative bacteria. However, the antibiotic effects were mostly moderate.[78]

I. Maracin A and Maracen A were isolated in 1998 from *Sorangium cellulosum* strain Soce 880 and Soce1128, respectively. Characteristics for maracin A is the unusual ethynyl-trans-vinyl ether moiety, which is replaced in maracen A by an α-chlorovinyl group.A screening of the National Insititute of Allergy and Infectious Diseases aiming to find compound against Mycobacterium tuberculosis

showed an in vitro activity of maracinA and maracen A of IC_{99} <12.5µg ml^{-1}. So far nothing is reported concerning in vivo studies, also no mode of action studies were published.An in vitro assessment of toxicity using the mouse fibroblast cell line L929 showed no cytotoxic effects up to a concentration of 24µg ml^{-1}.[79]

8. Nannochelins

These are siderophores isolated from Nannocystis exedens strain Na e485 and belong structurally to the citrate-hydroxamate family.[80] In the nannnochelins the carboxyl groups of the citric acid moiety are linked to an N-Ɛ-cinnamoyl hydroxy-L-lysine (-methyl-ester). The three described derivatives are nannochelins A, B, andC and differ in the methylation state of their carboxyl groups. Thus, nannochelinsA mainly isolated from nannochelins BorC in isolation process. NannochelinsB, which is represent the main product.[81] Several Gram-positive bacteria mainly, *Bacillus sp*. were inhibited by some of the nannochelins in agar diffusion tests.Since the nannochelins are siderophore, their mode of action remains even more obscure, since bacterial growth stimulation may be suggested especially for those bacteria which are able to use these siderophores for iron-uptake, e. g., mycobacteria. This mechanism could be used as a new form of drug delivery utilizing the pathogenic organism's own iron transport system. Thus, these compounds represent interesting structures for the development of conjugates,consisting of a lethal drug covalently attachted to a siderophore.[81]

9. Roimatacene

It is a polyenic carboxylic acid, isolated from a myxobacteria Cystobacter ferrugineus cb G35 was challenging, due to chemical instability. The metabolite harbours an acrylic acid residue, two α-polyunsaturated alcohol groups, atertiary alcohol, and a several conjugated double-bonds;in all together resulting in oxygen-light sensitivity.[82] Unlike most other myxobacterial antibiotically active compounds,which show by their majority active against Gram-positive bacteria, roimatacene was found active against the Gram-negative bacteria such as *E.coli*. Activity against *E.coli* and *Pseudomonas sp.* was in the moderate range.[82] It has little cell toxicity, but antimicrobial activity was not performed due to its chemical instabilty. This is of special interest in the view of the selective activity against Gram-negative bacteria, a field in which new lead structures and targets are extremely desirable.[82]

10. Sorangioadenosine

It was isolated from Sorangium cellulosum strain KM1003 and represents a nucleoside substituted with a sesquiterpene.The molecule thus consists of three distinct units: (i) the heteroaromatic adenosine;(ii) the pentose sugar D-ribofuranose; and (iii) a bicyclic sesquiterpen of the eudesmane-type.The determination of MIC values showed sorangiadenosine to moderately inhibit Gram-positive bacteria, e. g. the MIC value against *M. luteus* IFC 12708 and *S. aureus* ATCC6538p were 6.25 and 25µg ml^{-1}, respectively. The growth of *E. coli* cells are not inhibited.[83]

11. Sulfangolids

These are with the sulfangolids the first sulphate ester containing secondary metabolites from myxobacteria were isolated from different *Sorangium cellulosum* strains (e.g. So ce666, So ce192, So ce1375).They are macrolides with a prominent conjugated triene or teranene moiety. Sulfangolid B carries an additional methoxy group, compared to sulfangolid A, whereas, a most prominent feature of sulfangolid C is a six-membered semi-ketal ring, a ketal ring is also present in sulfangolids D, even though not as a hemiketal.The antibiotic spectrum of sulfangolids C active against Gram-positive bacteria was observed. In case of *S. aureus, B.subtilis*, and *Norcardia corallina* 10µg/disc of sulfangolids resulted in an inhibition zone of 8-10 mm,while no inhibition zone was observed for *E.coli* tolC.[84]

12. Salimyxin B And Enhygrolide A

Reported from marine myxobacteria *Enhygromyxa salina* strains SWB005 and SWB007, showed inhibitory activity toward the non-pathogenic *Arthrobacter crisallopoietes* with MIC values of 8 and 4µg ml^{-1}, respectively.[85] Another compound isolated from same strain(SWB007)named as Salimabromide posseses a new carbon skeleton, consisting of four rings,including a highly brominated benzene ring,a furano lactone residue, and a cyclohexane ring, bridged by a seven-membered cyclic moiety. The antibiotic was moderate with an MIC against *A. cristallopoietes* of 16µg ml^{-1}.[86]

13. Hyapyrone B

Although initially isolated from myxobacterium Hyalangium minutum strain Hym- 3. Polypropionate compounds with a pyranone moiety. Its best antibiotic activites were observed against Gram-positive bacteria *N.flava* with an MIC value of ~ 33µg/ml.[87]

14. Ajudazols

It is a mitochondrial transport inhibitor that was isolated from *Chondromyces crocatus*. It was minor activity against Gram-positive bacteria.[88] In presence of ajudazols all cytochoromes remains oxidized state. This indicated that the site of inhibition of ajudazols is on the substrate site of cytochrome B, can be reduced either by NADH via complex I (NADH: ubiquinone oxidoreductase)or by succinate.

15. Saframyxin Mx1

Is a natural antibiotic isolated from myxobacterium *Myxococcus xanthus* strain Mx 48. It is particularly active against Gram-positive bacteria, but also is a rather efficient inhibitor of several Gram-negative bacteria and halobacteria. The effects of this antibiotic was mainly inhibited the DNA, RNA, protein synthesis. At a

concentration of 0.5µg/ml all three syntheses were inhibited completely.[89]

16. Pyrrolnitrin

Was isolated from myxobacteria *Myxococcus fulvus*, *Cystobacter ferrugineus* etc., chemically substituted with 3-phenyl pyrrole derivatives containing two chlorine atoms and a nitro group. Bacterial growth inhibition by pyrrolnitrin forms complex with phospholipids of cell membrane that eventually cease cellular respiration. Furthermore, pyrrolnitirn causes leakage inside the cells and impairs synthesis of protein, DNA, RNA.[90]

17. Antibiotics from myxobacterial lower respiratory infection treatment

In 2019, it was estimated that 2.5 million[91] people die from lower respiratory tract infections annually. Pulmonary infections represent a serious health risk for today's society and specially children,aged people, aged five years and younger.[92] Lung infection is a frequent complication,for patients with cystic fibrosis (CF),an inherited, systematic disorder caused by a mutation in the cystic fibrosis transmembrane regulator channels.[93] CF lung disease is characterized by the accumulation of thick mucus in the airway, which favours lung inflammation and persistent, chronic bacterial infection, *Staphylococcus aureus.*[94] Besides being able to form biofilms, it is known that *S. Aureus* can also invade professional and non-professional phagocytes and is able to survive intracellularly by escaping the endosomal pathway into the cytoplasm.[95] The antibiotics currently avaliable on the market are not optimal for treating intrecellular infections,as most of them need higher concentration and alonger therapy time to induce a positive effects.Generally free antibiotics (e. g., aminoglycoside)are unable to erudate intracellular infection due to their hydrophillic characteristics and high polarity,which prevent their permeations into the mammalian cells.[96]

Myxobacteria are potent producers of antimicrobial compounds and they are non-pathogenic to humans. Outer membrane vesicle(OMV) are nanoparticles shed from the outer membrane of Gram-negative myxobacteria have been shown to be involved intercolony communication but also as predactory weapons against other bacteria.Myxobacterial OMVs with inherent antimicrobial properties due their cystobactmid cargo are topoisomerase inhibitors that have been potent antimicrobial activity.[97] Myxobacterial strains *Cystobacter velatus* cbv34 and *Cystobacter ferungineus* cbfe23 for the production of natural antibacterial OMVs and analyze their potential for uptake by mammalian cells and erudiction of intracellular *S. Aureus* and also releaseof TNF-alpha,IL-8,IL-6,IL-1 beta by both OMVs of cbfe23OMVs.[91] From a report work, found that outer membreane vesicles(OMVs) that are naturally antimicrobial to target intracellular infections and also effect on the macrophage and cell lines to prevent the Staphylococcal infection.

3. Antifungal activity

A. Ambruticin, is the first antibiotic from myxobacteria, Isolated from in a strain *Sorangium cellulosum*. It was interested because of their antifungal effects, which were quite impressive. They are active against mainly fungi (ascomycetes, zygomycetes, oomycetes, deuteromycetes), important pathogens of plants, a nimal and humans. But on the other hand, *Sporothrix schenckii*, *Cryptococcus neoformans*, *Candid albicans*, and many other fungi turuned out to be resistant, so that ambruticin is clearly selective. Mechanism of action of this compound was studied but without coclusive result.Some results showed may be ambruticin reduces carbohydrate utilization leading to a decrease in energy production;as a result breakdown of energy-dependent transport e.g.,of amino acids.[98]

B. Crocacins,a new secondary metabolites that isolated from the myxobacterial *Chondromyces crocatus* strain Cm c3 produced,a potent activity against a wide spectrum yeast and fungi. As crocacin moderately inhibited of the growth of a few Gram-positive bacteria and was a potent inhibitor of the growth of several yeasts and fungi. In the presence of crocacins, only cytochrome b of complex III became reduced, whereas the cytochrome aa_3 and $c+c_1$ remained oxidized state. So, crocacin inhibited the electron flow within the cytochrome bc_1 segement of the respiratory chain. The binding of certain complex III inhibitors to cytochrome b, inhibit the bacterial growth by blocking their energy flow.[69] Aurachins,[68] it has higher concentrations also weak the fungi and yeasts also.

C. New polyketide antibiotics,isolated from two myxobacteria *Stigmatella aurantica* and *Archangium gephyra*, strain Ar10844 named as Aurafuron Aand B. Aurafuron mainly active against filamentous fungi, both compounds shows cytotoxicity against the mouse fibroblast cell line L929.But its mode of action still unknown.[99]

D. Another novel secondary metabolite, Phenoxan isolated from a myxobacteria *Polyangium spec*., strain PI VO19. It is another antifungal drug which showing that phenoxan is a powerful inhibitor of the eukaryotic respiratory chain at the site of complex I,i.e., NADH: Ubiquinone oxidoreductase. Mainly the site of action of phenoxan is on the substrate site of cytochrome b also inhitited cytochrome b only when NADH as a electron donor.[100]

E. New antifungal activites detected a new compound, named Cyrmenins isolated from myxobacteria *Cystobacter armeniaca* Cb a24 and *Archanigium gephyra* Ar 9944. The cyrmenins had no effect on bacteria but highly effect on fungi. The most active compound was crymenin A with an IC_{50} of 27ng/ml.

The site of inhibition within the electron transport chain, in the presence of crymenin,only cytochrome b of complex III became reduced, whereas the cytochromes aa_3 and cc_1 remained oxidized state.This indicated that crymenin inhibited the electron flow within the cytochrome bc_1 segment of the respiratory chain.[101]

F. *Nannocystis pusila* strain Ari7, was produced a secondary metabolite named as Pyrronazols A,which have antifungal activity. This compound shows antifungal activity against *Mucor hiemalis* with a minimum inhibitory concentration of 33 µg/ml but no antibacterial activity.[103]

G. The structurally related unique leupyrrins A_1, A_2, B_1,B_2,C and D as major secondary metabolites isolated from myxobacterium *Sorangium cellulosum* strain So ce705. Leupyrrins A1 only shows good antifungal activity against different fungi, yeasts and moderate toxicity against mouse fibroblasts. The mode of action was investigated with *Rhodotortulaglutinis.* Measurement of DNA, RNA, and protein syntheses by incorporation of[methyl-^{3}H]thymine,[2-^{14}C]uracil, and [U-^{14} C]protein hydrolysate came to a complete stop after 30min all of three macromolecules at 2.5µg/ml of leupyrrins.No of inhibition of the respiratory chain or disruption of membranes measured as release UV absorbing material ,could be observed. But how this be accomplished without membrane disruption and how this effect can correlated with the observed much faster termination of the DNA,RNA,and protein biosynthesis is currently under investigation.[104]

H. Melithiazol, a new antifungal isolated from myxobacteria *Melittangium lichnicola* (Me l26 and Me l46), *Archangium gephyra* Ar 7747, *Myxococcus stipitatus* Mx s64. The melithazols, myxothiozole.[100] cystothiazoles,[99] were the group contains a β- methoxyacrylate(MOA) system as a terminal segment so this are termed as MOA-inhibitors. The melithazols had no effect on bacteria but highly antifungal activity. The site of inhibition within the electron transport chain, presence of melithazol A, only cytochrome b of complex iii become reduced, whereas the cytochromes cc_1 and aa_3 remained in oxidized state, this indicated that the compounds inhibited the electron flow within cytochrome bc_1 segment of the repiratory chain between b and cytochrome cc_1. The melithiazol and cystothiazols turned out to be less toxic than myxothiazolA. In contrast, myxothiazol which is an amide, the melithiazols and cystothiazols are methy esters so reduced its toxicity level.[108]

I. Argyrins, another myxobacterial compound isolated from *Archangium* and *Cystobacter*. It has highly active against fungi and yeasts.[109]

J. Geophyronic acid was isolated from myxobacterium *Archangium gephyra* Ar3895 that inhibit mainly protein synthesis in the translational initiation phase. It active against all type of yeasts and filamentous fungi, MIC value for yeasts were generally lower than those for molds.[110]

K. From *Sorangium cellulosum* strain So ce12, isolated a new compound consisting of a macrocyclic ring with two oxazole rings named as disorazol A, highly effective aganist fungi belonging to the group ascomycetes, deuteromycetes, zygomycetes, basidiomycetes, etc. Mainly inhibited the RNA synthesis, but this is not appears to influence DNA dependent RNA polymerase II. But interfers with specifically with RNA polymerase I and III.

L. Previous discussed myxobacterial strain *Chondromyces crocatus* produced two secondary metabolite Chondrocholren A and B that have high antifungal properties.[77]

M. Another antifungal property detected from the secondary metabolite of myxobacteria *Sorangium cellulosum* So ce360, named as Ratjadon.This compound does not inhibited any bacteria, but some yeasts and fungi were very sensitive to the compound. The oomycets Phytophthora drechsleri was inhibited at 40 ng/ml. However, ratjadon caused striking changes in yeast morphology. The cells become elongated and sometimes began to branch like a fungal mycelium, the cell cytotoxicity is very high.[111]

N. Ajudazol.[88] described earlier;with 40µ ajudazols/disc, in ajudazol B incompletely inhibited the growth of the following fungi:*Botrytis cinerea*, *Trichoderma koningii*, *Giberella fujikuroi*, *Ustilago maydis* etc.

O. From the myxobacterium *Sorangium cellulosum* strain So ce26, a novel group of highly active antifungal metabolites was isolated, named as Soraphen. After the potential of Soraphen $A_{1\alpha}$ was selected for its good activity against a variety of yeasts and fungi. It was found that the soraphens also exhibit a novel mode of action, inhibits fungal acetyl–coA carboxylase and thus interferes with lipid synthesis eventually killing the fungus.[112]

P. Pedain A and B, were isolated from the cell mass of the myxobacterium *Chondromyces pediculatus*, as antifungal activity. The 24-membered cyclic hexapeptides composed of a variable tryptophan residue, glycine, sarcosine and three unusual hydroxy β-and γ-amino acids. The main component pedein A, strongly inhibited the growthof inhibition. MIC for *Rhodotorula glutinis* was 0.6µg/ml, and for both *Saccharomyces cerevisiae* and *Candidi albicans* 1.6 µg/ml, and for *Ustilogo maydis* 3.1

µg/ml and show weak cytotoxicity with an IC_{50} of 1.1 µg/ml.[113]

Q. During a screening of gliding bacteria for new antibiotics, the myxobacterium *Stigmatella aurantiaca* strain Sg a15, active against filamentous fungi and yeasts named as stigamellin. But the antibiotic proved highly toxic for animals.In S.cerevisiae RNA and protein synthesis, measured as incorporation of uracil and of leucine into trichloroacetic acid insoluble material, stopped immediately upon the addition of stigmatellin to the culture. Several sensitive organisms became resistant to stigmatellin, when grown in presence of glucose. When glucose was addes to a culture which had been blocked before with stigmatellin, growth resumed after a delay of a few hours.[114]

R. Pyrrolnitrin,[90] the inhibitory spectrum of compound was described for yeasts and fungi. The phycomycetes, *Mucor hiemalis* and *Rhizopus stolonifer* proved particularly sensitive and were completely inhibited by 0.1~0.2 µg/ml.The effect was a fungistatic one.[115]

S. Cruentaren, a novel macrolide isolated from *Byssovorax cruenta*, strongly inhibited the growth of yeasts and filamentous fungi and shows high cytotoxicity. A minor co-metabolite of cruentaren A,named cruentaren B,and identified as a six membered lactone isomer of cruentaren A,showed only marginal cytotoxicity and no antifungal activity.Cruentaren A inhibited F_0F_1 mitochondrial ATP-hydrolysis in submitochondrial particles of fungi and yeasts.[116]

T. *Sorangium cellulosum* So ce90,isolated a novel group of antifungal and highly cytotoxic compounds named spriangien A and B.Sprinagien was tested for biological activity in agar diffusion assays against a broad spectrum of yeasts and fungi (e.g.,diameters of inhibition zones: *Pichia membranaefaciens* 24mm, *Rhodotortula glutins* 19mm, *Botrytis cinerea* 11 nm).[117]

U. Another antifungal compounds from myxobacteria Haliangicin from *Haliangium sp*., inhibition site of fungi electron flow of respiration complex III and cytotoxic effects observed.[118] Chlorotonil[48] and icumazol[46] compounds isolated from *S.cellulosum Soce1525* and *S.cellulosum So ce701* shows antifungal property. Only icumazol inhibit NADH oxidation in electron flow but chlorotonil function still unknown. Aetheramide[28] and Hyapyrones,[87] indiacen.[78] Epothilone,[129] (also anticancer property)from *S. cellulosum*,. Macyranones[119] from *C.fuscus* Mcy9118 as proteosome inhibitor, microsclerodermin[120] from *Jahnella* sp. and *Sorangium* sp., myxlamides from *S.aurantiaca* (inhibit respiration complex I) shows antifungal activity. Nannocystin,[80] Chondramides[45] acts as antifungal activity by blocks translational elongation factor 1α.

4. Myxobacterial antibiotics active against both bacteria & Fungi

A. Hyaladione was isolated from myxobacterium *Hyalagium minutum*, a novel S-methyl cyclohexadiene-dione. It have broad spectrum activity against bacteria (inhibited methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* with an MIC value 0.83 and 8.5µg/ml) and fungi and also cytotoxicity reported.[102]

B. Myxothiazol, a new antibiotic isolated from *Myxococcus fulvus* strain Mx f16. It was active against numerous fungi and a few Gram-positive bacteria (high concentrations of the antibiotic were requried to inhibit growth of *Staphylococccus aureus* at 10µg/ml). There was no inhibition of yeasts and Gram-negativebacteria. The antibiotic effect of myxothiazol on *Mucor. hiemalis* is fungistatic, for the number of viablecells remained constant over along time when sporangiospores were incubated in the presence of 10µg of myxothiazol/ml. But it is highly toxic to the eukaryotic cells.It is an inbitors of the mitochondrail cytochrome bc_1 complex.[105,106]

C. New bithiazole type antibiotics,cystothiazolsA and B have been isolated from myxobacterium *Cystobacter fucus*.The cystothiazols active against all type of fungi (MICs were measured by serial dilution media ranging from 0.1to 6.3µ/ml) but inactive against on bacteria.Although such a tendency of acitivity was same as that of myxothiazol,the potency of cystothiazol A was mostly higher.Since mode of action of myxothiazol is known to be the inhibition of NADH oxidation of submitochondrial membrane fraction, the effect of both antibiotics cystothiazol A and B showed comparable activity. Thus,the does required for 50% inhibition of cystothiazol A and myxothiazol were 1.8 and 2.1µM, respective and also less toxic than myxothiazol.[107]

5. Antimalarial and Antiparasitic activity

Malarial is the most important parasite disease worldwide,causing by Plasmodium spp. in humans,Plasmodium flaciparum is responsible for almost all severe and fatal cases.[121] In the past,a particularly powerful way to find new chemotherapeutics against infections disease was by characterizing and derivatizations.[122] The soil dwelling myxobacteria are a rich source of biologically active compounds such as chlorine-containing metabolite Chrontonil A,which have antimalerial or antiplamodial activity.Chrotonil A, a tricyclic macrolide produced by *Sorangium cellulosum*.[123] Chrontonil A, mainly arrested parasite developing in the ring trophozoites stages and schizonts stage in the blood smear and it acts more quickly than the previous antimalerial drugs (chloroquine and artesunate).

It reduces the biomass of the parasite and generation of the parasite toxins immediately upon contact with the parasite. It has low toxicity and administrated orally.In addition it is active against the transmission stages of the parasite.Improved derivatives and dose regimens are required prior to clinical development but at this stage,it is already evident that chrontonil A has unique features.[122,124] Macryranones A shows a potent antiparasitic activity against Trypanosoma brucei rhodesiense,the causative agents of the african sleeping sickness and against extracellular grown amastigotes Leishmania donovani is lost in the intracellular amastigote assay tested upto a concentration of 30 µM.[119] Eliamid another compound treated soil nematodes (Panagrellus spec.) with 5 µg/ml was lethal to all animals.[125] Hyafurone,[87] shows antiparasitic activity against *Trypanosoma bruceir rhodesiense, Trypanosoma cruzi, Leishmania donovani, plasmodium falciparum* etc.

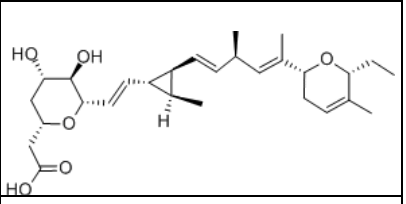
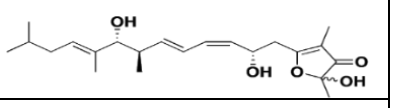
6. Place all anticancer together

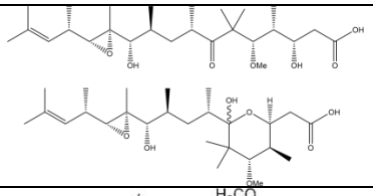
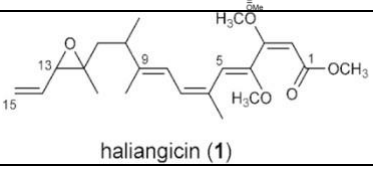
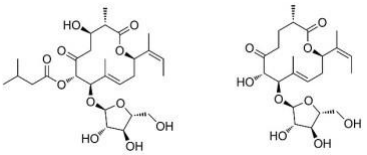
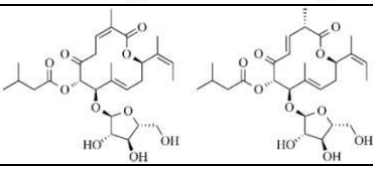
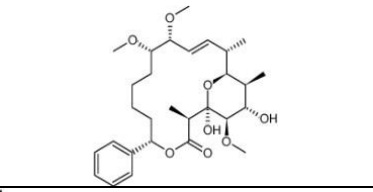
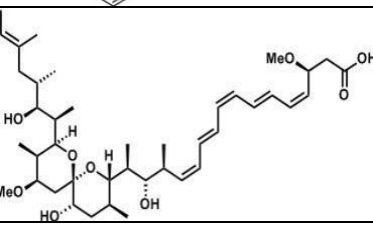
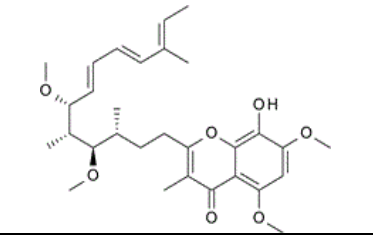
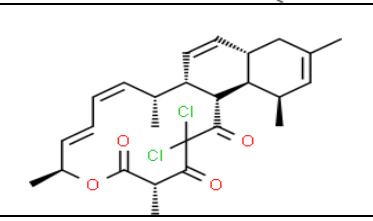
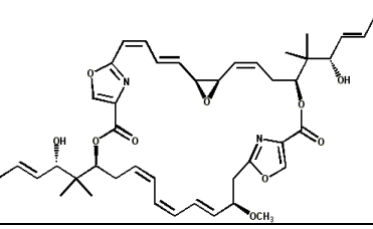
Anticancer property;Nannocystin A, isolated from myxobacteria *Nannocystis* sp.MB1016 active antiproliferative action against a panel of 472 cell lines and targets eukaryotic translational elongation factor 1 and shows a potential use for such chemical agents as cancer therapeutics.[126] The biological evalution of **Eliamid**[125] with a panel of transformed cell lines showed a specific cystostatic action on human lymphoma and cervix carcinoma cell cultures. **Argyrins B** also inhibited cell differentiation rather than cell proliferation or alternatively might exert selective inhibition of proliferation of only certain cell types. The **benzamides** another compound isolated from myxobacterium *M.virescens* which resulted in an optimized derivatives taht combined high cellular potency in the nanomolar range with high metabolic stability, which translated to an improved half-life in mice and an antitumor effiacy in a melanoma mouse model.It reduces also obesity. [127] In a recent report shows that **Disorazol c** was shown to exhibit antiproliferative activity against a wide range of tumor cells and to cause both premature cellular senecscence and apoptosis. Mode of action demonstrated that, uniquely amoung anti-mitotic agents**, disorazol** A inhibits tubulin polymerization and leads to depletion of microtubules in equal measure. This perturbation to the microtubule network results in the cell cycle arrest at the G2/M checkpoint and induction of the apoptotic cell death cascade.[128] **Epothilones**, isolated from *Sorangium cellulosum* interacts with the eukaryotic cytoskeleton and is about to approved for breast cancer and colon cancer cancer treatment. These are a class of potential caner drugs,like taxanes, they prevent cancer cells from dividing by interfering with tubulin.Epothilones A to F have been identified and cancer cell lines and in human cancer patients indicate superior efficacy to the taxanes,their mechanism of action similar, but their chemical structure is simpler. Due to their better water solubility,cremophores (solubilizing agents used for Paclitaxel which can affect cardiac function and cause severe hypersensitivity) are not needed and mainly inhibited the microtubule Function (the ability of epothilonee to inhibit spindle function is generally attributed to its suppression of microtubule dynamics.

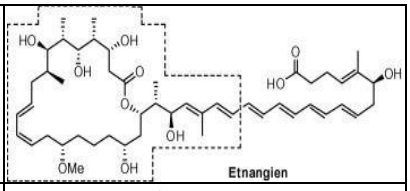
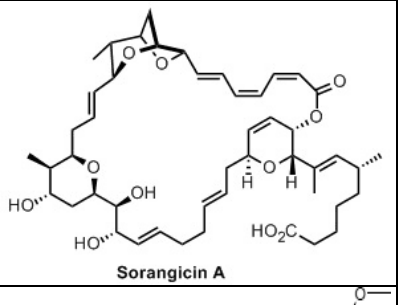
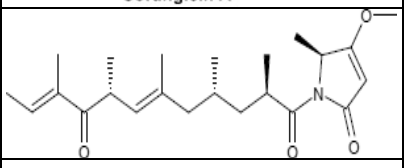
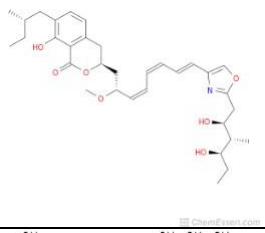
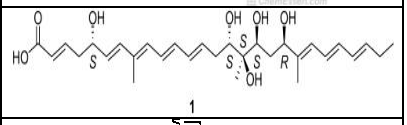
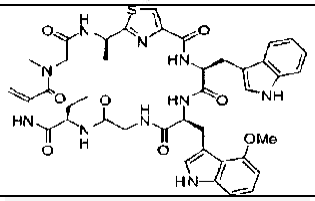
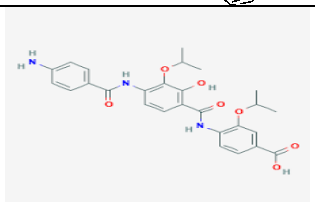
7. Immunosuppression activity; Argrins[109]

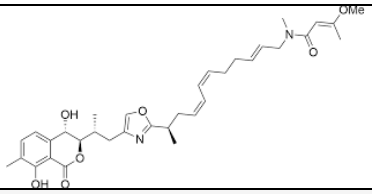
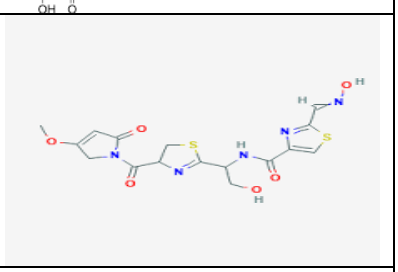
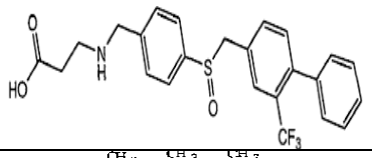
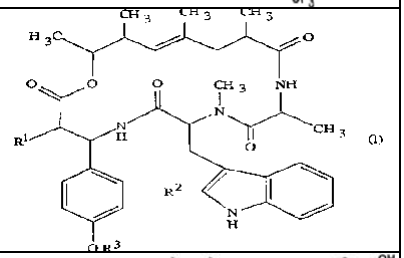
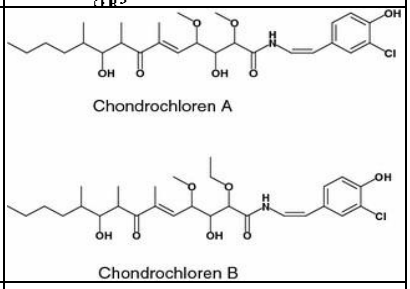
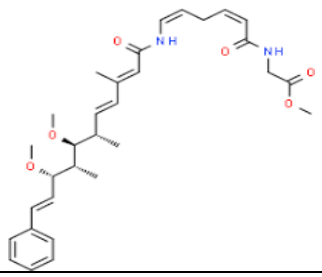
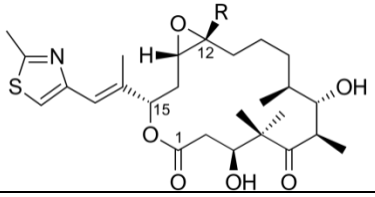
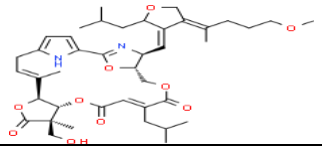
B was found to be a very active immunosuppressant. Several autoimmune disease are mediated by autoantibody production from B-cells. In addition T-cell independent antibody-mediated rejection is a major obstacle to soild organ xenotransplantation, because production of xenogenic antibodies is a key event during both, the hyperacute and acute rejection phase of xenotransplantation. Thus drugs are selectively inhibit antibody formation by B-cells can be effective in certain autoimmune diseases.Argyrins B inhibited the T-cell independent B-cell responses of murine B –cells and blocked alloantigen –induced proliferation of murine T cells at submicromolar concentrations.Antibody production of SAC or CD4OL- stimulated human B –cells was even more powerfullly inhibited with IC_{50} values in the low nanomolar range. Therefore, Argrins might bear potential for the disease and for xenoplantation. Moreover, argyrins blocked the alloantigen-induced murine mixed lymphocytes reaction suggesting a possible use in allo-transplantation as well.

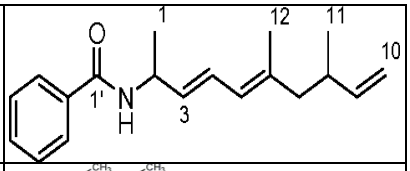
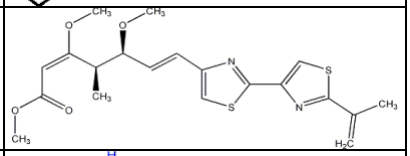
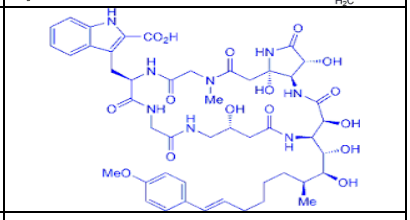
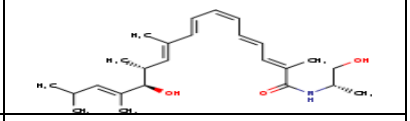
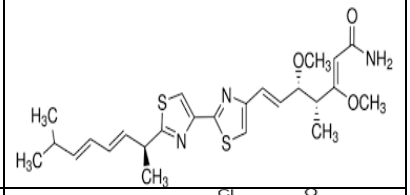
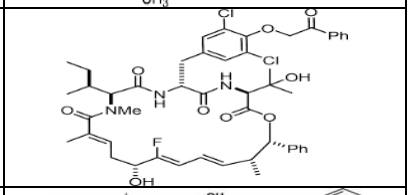
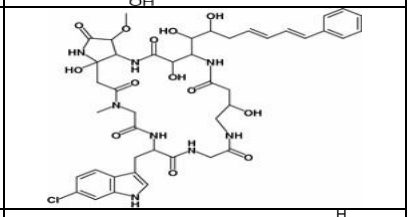
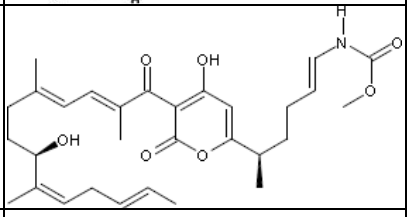
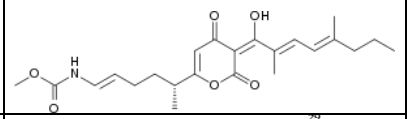
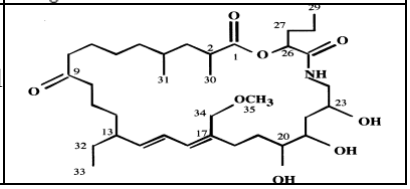
Table Comprehensive overview of antimicrobial metabolites known to be produced by Myxobacteria.

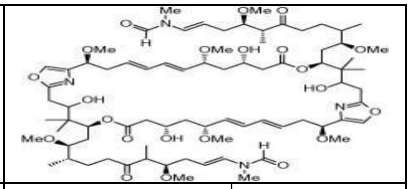
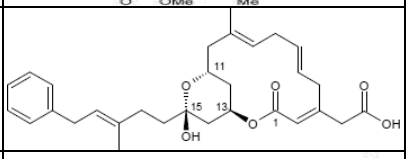
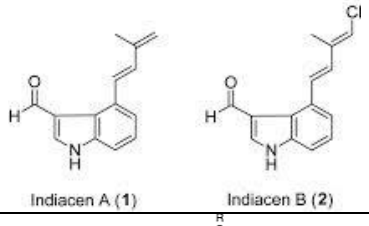
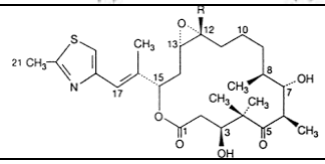
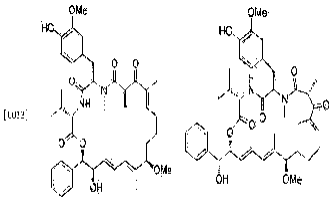
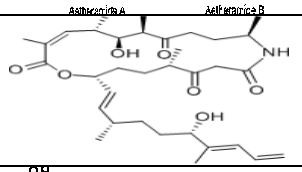
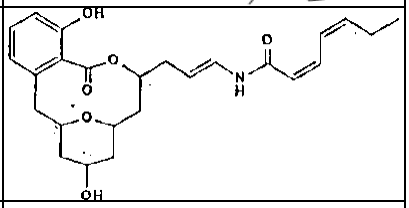
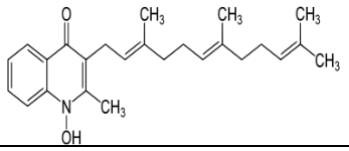
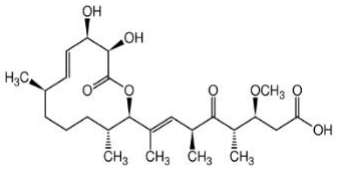
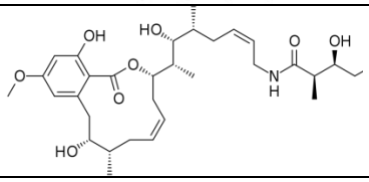
Compound	Producers	Bioactivity	Molecular target	Structure
Ambruticins	*Sorangium cellulosum* So ce 10	Antifungal	Osmoregulation via HOG pathway	
Aurafurons	*Stigmatella aurantica, Archangium gephyra*	Antifungal	Unknown	
Gephyronic acid	*A. gephyra* Ar3895, *Cystobacter violaceus*	Antifungal	Protein synthesis	

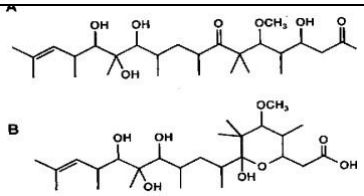
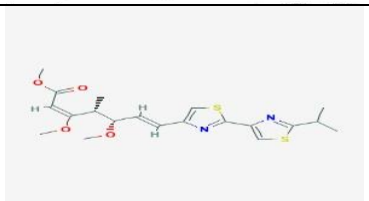
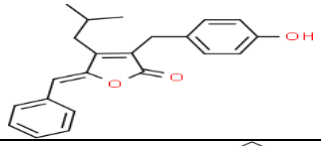
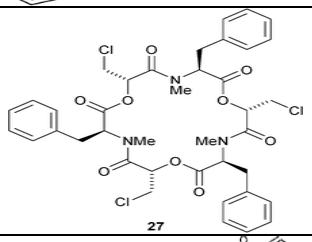
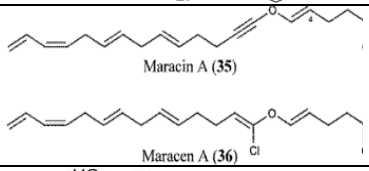
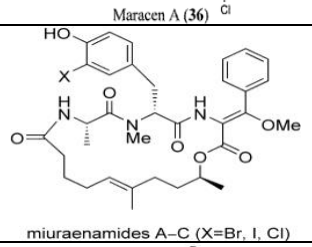
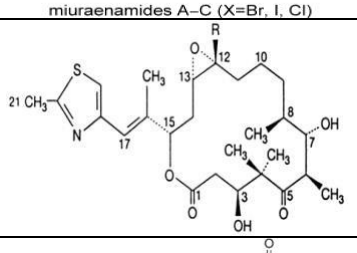
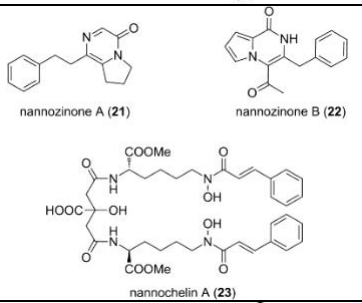
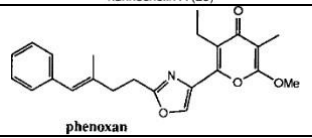
	Cb vi76			
Halinagicin	*Haliangium sp.*	Antifungal	Respiration complex III	 haliangicin (**1**)
Glumirecins	*Pyxidicoccus fallax*	Antibacterial	Unknown	
Disciformyci ns	*P .fallax*	Antibacterial	Unknown	
Soraphen	*S.cellulosum* Soce26	Antifungal, anticancer, a nt-iviral	Acetyl – CoA carboxylase	
Sprinangien	*S.cellulosum* Soce90	Antifungal ,antiviral	Unknown	
Stigmatellin	*s.aurantica*	Antifungal	Respiration complex I	
Chlorotonil	*S.cellulosum* So ce1525	Antibacterial, antiprotozoa l	Unknown	
Diasorazol	*S. cellulosum* So ce12	Antifungal, anticancer	Tubulin	

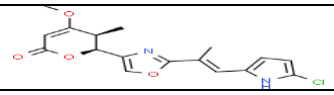
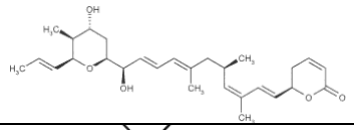
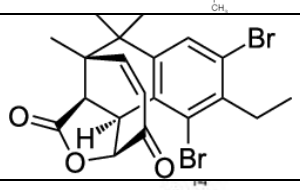
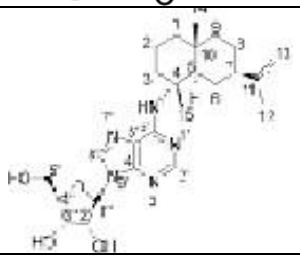
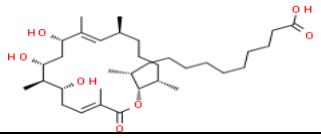
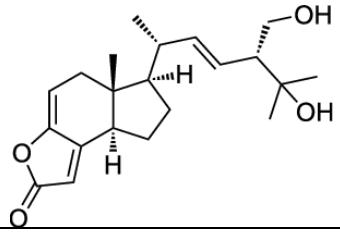
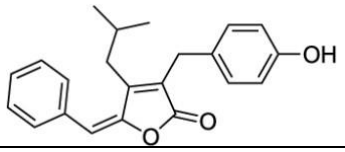
Etnangien	*S. cellulosum*	Antibacterial, antiviral	RNA Polymerase	 Etnangien
Sorangicin	*S.cellulosum*	Antibacterial	RNA Polymerase	 Sorangicin A
Eliamid	*S.cellulosum*	Antifungal,a ntihelmintic	Mitochondri al repiratoryco mplex I	
Hyapyrones	*Hyalangium minutum*	Antibacterial, antifungal	Unknown	Unknown
Icumazol	*S.cellulosum* So ce701	Antifungal	NADH oxidation	
Roimatacene	*Cystobacter ferrugineus* Cb G35	Antibacterial	Unknown	 1
Argyrins	*A.gephyra*	Antibacterial, antifungal	Elongation factor G	
Cystobactami des	*Cystobacter sp*.Cbv34	Antibacterial	TypeII topoisomera se	
Saframycin Mx1	*Myxococcus xanthus* DM504/15	Antibacterial, antitumor	DNA	
Ajudazol	*Chondromyce s crocatus* Cm c5	Antifungal	Unknown	

				
Althiomycin	*M. xanthus, Cysto bacter fuscus*	Antibacterial	peptidyltran sferase	
Benzamides	*Myxococcus virescens* ST200611	Antibacterial, antihelmintic, anti-inflammatory	Methionine aminopeptid ase	
Chondramide s	*C.crocatus* Cm c5	Antifungal, a ntitumor, anti parasite	Actin cytoskeleton	
Chondrochlo ren	D. crocatus Cm c5	Antibacterial, antifungal	Unknown	
Crocacin	C. crocatus Cm c5	Antifungal	Respiration complexIII	
Epothilone	*S.cellulosum*	Antifungal	Tubulin	
leupyrrin	*S.cellulosum So ce690*	Antifungal	DNA,RNA, Protein synthesis	

Macyranones	*C.fuscus Mcy9118*	Antifungal, antiparasitei c.	Proteosome	
Melithiazol	*Melittangium lichenicola Me146*	Antifungal	Respiration complex I	
Microsclerod ermin	*Jahella sp.,Chondromyces sp., Sorangium sp.*	Antifungal, antitumor.	Unknown	
Myxalamid	*S.aurantica Sga15*	Antifungal	Repiration complexI	
Myxothiazol	*S.aurantica DW4/3-1*	Antifungal	Respiration complexIII	
Nannocystin	*Nannocystis sp.*	Antifungal	Translation elongation factor 1α	
Pedein	*Chondromyces pediculatus Cmp3*	Antifungal	Cell membrane	
Corallopyron in	*Corallococcus coralloides*	Antibacterial	RNA Polymrerase	
Myxopyronin	*M. fuscus Mx f50*	Antibacterial	RNA Polymerase	
Myxovirescins	*Myxococcus sp.*	Antibacterial	Type IIsignal peptidase	

Rhizopidin	*S.aurantica Sg a15*	Antifungal	Actin cytoskeleton	
Ripostatin	*S.cellulosum So ce377*	Antibacterial, antifungal	RNA Polymerase	
Indiacens	*Sandaracinus amylolyticus*	Antibacterial, antifungal	Unknown	
Pyrrolnitrin	*M.fulvus*	Antibacterial, antifungal	Repiratory electron transport system	
Aetheramide	*Aetherobacter rufus SBSr00*	Antifungal, a ntiviral	Unknown	
Angiolum	*Angiococcus disformisAn d30*	Antibacterial	Protein synthesis	
Apicularen	*Chondromyces sp.*	Antibacterial	Vacuolar ATP protease	
Aurachin	*S.aurantica Sg a15*	Antibacterial, antifungal	Respiration complex I and III	
Carolacton	*S.cellulosum So ce960*	Antibacterial	Serine/threonine protein kinase PknB Biofilm formation	
Cruentaren	*Byssovorax cruenta*	Antifungal	Mitochondrial F_0F_1- ATPase	

Cyrmenin	*Cystobacter armeniaca, A.gephyra*	Antifungal	Respiration complex III	
Cystothiazole	*C.fucus*	Antifungal	Respiration complex III	
Enhygrolide	*Enhygromyx a salina*	Antibacterial	Unknown	
Hyaladione	*Hyalagium minutum*	Antibacterial, antifungal	Unknown	
Maracin /maracen	*S .cellulosum*	Antibacterial	unknown	
Miuraenamide	*Paraliomyxa miuraensis*	Antifungal	Respiration complex III	
Myxovalargin	*M .fulvus*	Antibacterial	Protein synthesis	
Nannozinone A	*Nannocystis pusila*	Antibacterial	Unknown	
Phenoxan	*Polyangium sp.*	Antifungal	Repiration complex I	
Pyrronazol A	*Nannocytis pusila*	Antifungal	Unknown	

				
Ratjadon	*S .cellulosum*	Antifungal, antiviral	Exportoin 1(CRM1)	
Salimabromide	*E .salina*	Antibacterial	Unknown	
Sorangioadenosine	*S .cellulosum*	Antibacterial	Unkown	
Sorangiolid	*S. cellulosum*	Antibacterial	Cell memebrane	
Sorazionones A, B	*S. cellulosum*	Antibacterial	Unknown	Not known
Salimyxin B	*E.salina*	Antibacterial	Unknown	
Enhygrolide A	*E .salina*	Antibacterial	Unknown	

8. CONCLUSION AND OUTLOOK

Natural products have always played a significant role in drug discovery for treated human diseases. Drugs developed from myxobacteria have ignited a hope to offer novel mechanisms to fight some of the most debilitating disease such as HIV, Cancer, other viral, bacterial and protozoal disease. In the last six years, many new published scafflod of natural products from various classes have been added to the family of compounds isolated from myxobacteria.In addition, the mode of action of compounds are described and is currently under extensive investigation and a good number of these are being assessed in preclinical studies. Recently, a myxobacterial secondary metabolite, epithilone is already at work in the clinical trial.

The high hit-rate for these natural products, combined with the the fact that have likely only scratched the surface of myxobacterial secondary metabolism, makes it likely that these microorganisms will provide us with many new drugs leads in the future. In the meantime, the structures will continue to function as useful chemical genetics tools for unvelling the complex workings of biological processes in prokaryotic and eukaryotic cells. Bright future awaits pharmaceutical industry developing new drugs from antimicrobial lead compounds obtained from myxobacteria. The progress is slow, but surely drug manufacturing units have strated showing interest in implementation natural myxobacterial sources for drug developing.

Understanding the biology of antibiotic production as a lifesaver for humans and other animals, may lead to improved strategies to discover new antibiotics and perhaps optimize production yields and variant discovery. These research areas should be pursued,as

myxobacteria are well endowed to produce secondary metabolites, some of which have great therapeutic potencial.

9. Future trend of research

Despite their proven potential to assemble antimicrobial specialized metabolites also anticancer and antiprotozoal as well, the production of antibiotics by Gram-negative myxobacteria remains understudied.Traditionally, drug discovery efforts in Gram- negatives have focused on myxobacteria, the overwhelming majority of microorganisms are difficult to isolate from the environment and/or cultivate under laboratory conditions. It is likely that additional myxobacterial metabolites will reach the clinic to treat cancer or malaria. The future of myxobacterial natural products research looks very promising indeed.

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