Actinobacteria and Myxobacteria—Two of the Most Important Bacterial Resources for Novel Antibiotics

Wiebke Landwehr, Corinna Wolf and Joachim Wink

Abstract Bacteria have been by far the most promising resource for antibiotics in the past decades and will in all undoubtedly remain an important resource of innovative bioactive natural products in the future. Actinobacteria have been screened for many years, whereas the Myxobacteria have been underestimated in the past. Even though Actinobacteria belong to the Gram-positive and Myxobacteria to the Gram-negative bacteria both groups have a number of similar characters, as they both have huge genomes with in some cases more than 10kB and a high GC content and they both can differentiate and have often cell cycles including the formation of spores. Actinobacteria have been used for the antibiotic research for many years, hence it is often discussed whether this resource has now been exhaustively exploited but most of the screening programs from pharmaceutical companies were basing on the cultivation mainly of members of the genus *Streptomyces* or Streptomyces like strains (e.g., some *Saccharopolyspora, Amycolatopsis* or *Actinomadura* species) by use of standard methods so that many of the so called "neglected" Actinobacteria were overlooked the whole time. The present review gives an overview on the state of the art regarding new bioactive compounds with a focus on the marine habitats. Furthermore, the evaluation of Myxobacteria in our ongoing search for novel anti-infectives is highlighted.

Contents

W. Landwehr · C. Wolf · J. Wink (✉)
Helmholtz Centre for Infection Research, Microbial Strain Collection,
Inhoffenstrasse 7, 38124 Braunschweig, Germany
e-mail: Joachim.wink@helmholtz-hzi.de

Current Topics in Microbiology and Immunology (2016) 398: 273–302
DOI 10.1007/82_2016_503

Published Online: 22 September 2016

1 Marine Actinobacteria

1.1 Introduction

Over the last years, the commercial natural product research came back into focus because "the pipeline for new antibiotics is running dangerously low" (Fenical and Jensen 2006). While the rate of newly discovered antibiotics from soil inhabiting Actinobacteria decreased, the rate of re-isolation increased (Fenical et al. 1999; Lam 2006). However, to further explore this promising source of novel bioactive secondary metabolites, new strains had to be isolated with alternative methods or in unexplored environments (Lam 2006). Therefore, not only isolation techniques, but also the sampling sites had to be altered. With 70 % of the earth surface and a microbial abundance of 10^6 per mL in sea water and 10^9 per mL in ocean bottom, oceans are the world's biggest environment (Fenical and Jensen 2006). However, not only sea water and sediments are microbial rich environments, also marine organisms, flora and fauna like sponges harbor abundant communities (Ward and Bora 2006).

1.2 Marine Actinobacteria?

Over a long time, it was not clear whether truly "marine" Actinobacteria really exist because of the fact that there has been a lot of re-isolation of terrestrial strains and known compounds (Moore et al. 2005). The explanation for this assumption was the wash-in from terrestrial spores into the sea (Goodfellow and Haynes 1984) and the sampling problems of marine samples which were taken mostly close to the coast (Fenical and Jensen 2006). However, in the year 1984, the first marine Actinobacterium was found: *Rhodococcus marinonscens* (Helmke and Weyland 1984). 7 Years later, in 1991, the first marine Actinobacteria genus "*Salinispora* spp." which obligately requires seawater for growth (Jensen et al. 1991) was published. But even with the application of DNA sequence-based methods and the corresponding ability to analyze the relationships between this genus and their terrestrial relatives, the first seawater-obligate Actinobacteria genus "*Salinospora"* (grammatically incorrect; corrected to *Salinispora*) was described in 2005 (Mincer et al. 2005) and its two species *Salinispora tropica* and *Salinispora arenicola* were published (Maldonado et al. 2005a). Moreover, with the help of the type strains of these species, which are actively growing in sediment samples, the metabolic

activity in the natural marine environment was demonstrated (Mincer et al. 2005). In addition to this finding, Fenical and Jensen (2006) also detected uncommon secondary metabolites produced by *Salinispora* strains and were inspired to further search for new groups of marine Actinobacteria. With the help of 16S analysis of the phylogenetic diversity as well as new cultivation approaches, Stach and Bull (2005) demonstrated that deep-sea sediments contained more than 1300 different actinobacterial operational taxonomical units which led to the assumption that there is a great opportunity to find novel species and genera. Fenical and Jensen (2006) cultivated diverse strains within six Actinobacteria families and many of them seemed to represent new taxa like *Salinispora* and *Mariniphilus* (Fig. 1). In addition to the taxonomic findings and therefore the demonstration of the existence of marine Actinobacteria, these strains turned out to be "excellent producers for secondary metabolites".

1.3 Where Can One Find Marine Actinobacteria?

The geographical origin of the new actinobacterial producer strains, published compounds and bioactivities of 67 % of marine natural products (up to 2003) was restricted to Japan, the Mediterranean as well as the Western Pacific Ocean (Blunt et al. 2007; Bull and Starch, 2007). However, because of the growing focus on the research on marine natural products, a dramatic rise of the published data from the China Sea was observed just one year later (Bull and Starch 2007). Marine Actinobacteria are present in diverse marine habitats, which are widespread over the ocean. These habitats are influenced by numerous geographical as well as physical parameters like temperature and salinity. Furthermore, they underlie geochemical impacts and ocean currents. But also ecosystems like salt marshes, wetlands, estuaries, continental shelves as well as the open ocean and the deep sea are habitats for specialized marine Actinobacteria (Ward and Bora 2006). The marine habitat starts with the sea surface microlayer, followed by the water column, from a few millimeters below the surface to more than 10,000 m depth, down to the sea floor with the micro- and macro-fauna and-flora, which were used as host for epibiosis and symbiosis, as well as the sea subfloor and deep biosphere. Within the habitat of the sea floor, varying sediments of varying geology, mineral nodule fields, carbonate mounds, cold seeps, hydrocarbon seeps, saturated brines, and hydrothermal vents were observed (Ward and Bora 2006).

The sea surface microlayer is an environment which is to date poorly characterized. However, some studies showed the existence of Actinobacteria and Proteobacteria within this habitat (Ward and Bora 2006). In the water column, together with the β- and δ-Proteobacteria, Firmicutes, Cytophaga-Flavobacter-Bacteriodes (CFGs) and Chlorobia, Actinobacteria belong to the mid-range of abundance. α- and γ-Proteobacteria dominated this habitat. Interestingly, theses compositions of strain collectives were also found in coastal and pelagic waters, despite differences in isolation techniques used and scale (Ward and Bora 2006).

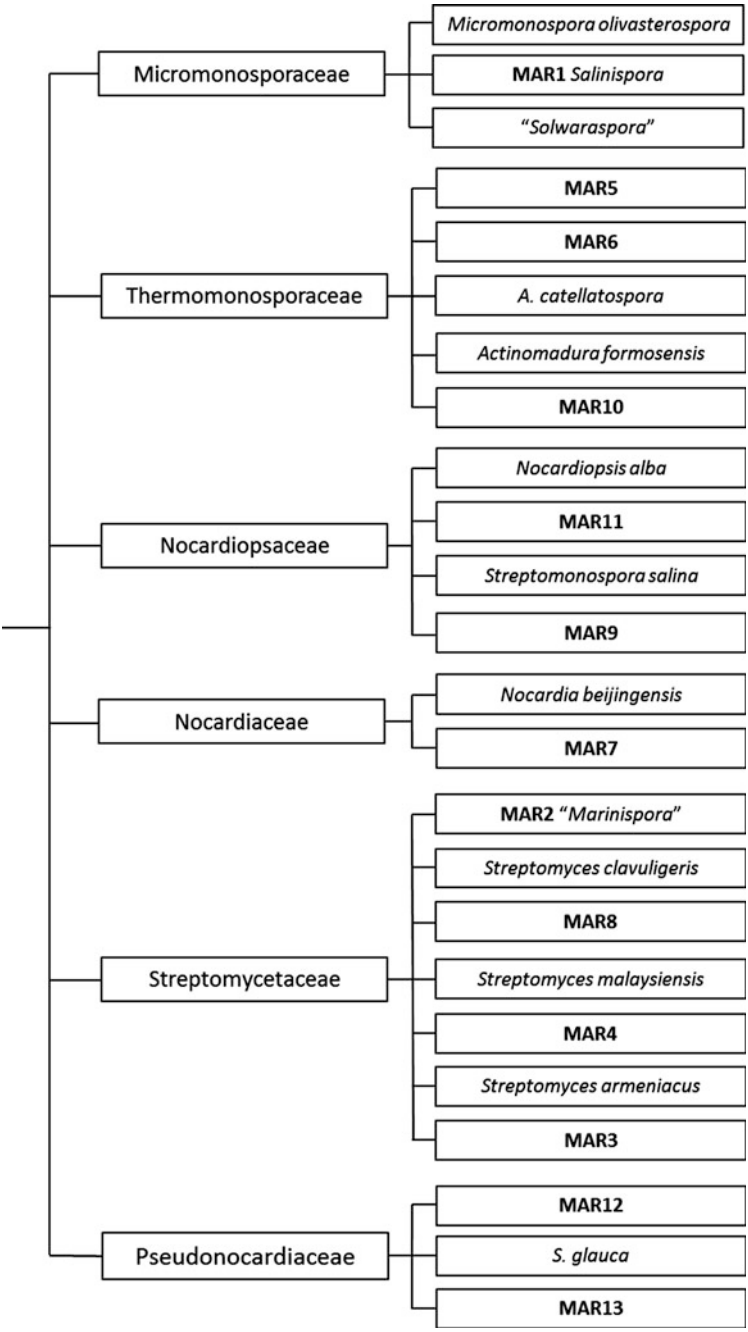

Fig. 1 Tree illustrating the phylogenetic relationships of 13 groups of marine-derived actinobacteria within six different families. The taxonomic status of the MAR groups is not really clear whereas it is known that they include numerous of new species. However, the MAR1 group was described as the genus *Salinispora* and the MAR2 group as the genus *Marinispora* (modified after Fenical and Jensen 2006)

Marine sediments are the best known source for the isolation of Actinobacteria from marine habitats. Studies on the 16S rRNA, to detect the phylogenetic diversity of Actinobacteria in marine sediments, showed that some deep-sea sediment contained up to 13,000 different actinobacterial operational taxonomic units which are forecast to belong to a large number of novel species and genera (Stach and Bull 2005). Also cultivation approaches of a range of depths and sediments (Maldonado et al. 2005b; Kim et al. 2004; Takami et al. 1997) illustrate the diversity and new insights in Actinobacteria classification (Maldonado et al. 2005a) and biogeography. These insights were used as inspirations for the isolation and recognition of novel marine Actinobacteria (Magarvey et al. 2004; Ward and Bora 2006). Furthermore, molecular studies on three different structural types of stromatolites ("organisms that have been present in the fossil record from greater than 3.5 billion years ago," cf. Ward and Bora 2006) ensured the presence 6–9 % of actinobacterial clones in the their complex mat community (Papineau et al. 2005).

However, there are not only the upper centimeters of marine sediments harboring Actinobacteria but also the below sea subfloor and the deep biosphere were found to be a natural habitat for these bacteria. Up to a depth of 800 m, a minor fraction of Actinobacteria were isolated (Stach et al. 2003; Inagaki et al. 2003) and molecular studies with specific primers showed a high actinobacterial diversity in clone libraries (Stach et al. 2003).

Moreover, marine Actinobacteria even live in marine organisms like many free swimming as well as sessile vertebrates and invertebrates. These organisms are mostly known to produce bioactive metabolites but these substances are often produced by symbiotic living microorganisms. The pufferfish, for example, was for a long time supposed to be the producer of the potent neurotoxin tetrodotoxin (TTX). However, to date this substance is known to be produced by numerous of marine organisms. Additionally, the production could also be correlated to many taxa of marine bacteria which live in symbiotic relationships with these organisms. In case of the pufferfish, a TTX-producing Actinobacteria (closely related to *Nocardiopsis dassonvillei*) and some TTX producing Bacillus strains were isolated out of its ovaries which are known to harbor high levels of TTX (Wu et al. 2005; Ward and Bora 2006). With the help of a sodium channel blocker assay using a mouse neuroblastoma cell culture bioassay, toxicity levels of 0.1–1.6 MU/g bacteria cells were observed [MU: amount of toxin which was expressed, calculated from the observed cell ratio (relationship between survival cell ratio and authentic TTX amount)] (Wu et al. 2005; Ward and Bora 2006). Furthermore, some TTX producing Actinobacteria like *Micrococcus* spp. and *Streptomyces* spp. were isolated out of deep sea and marine sediment (Do et al. 1990, 1991) which support the assumption that the symbiotic living organisms are responsible for the TTX production. However, to date the biosynthesis of TTX in bacteria or other organisms has not been described (Chau et al. 2011).

Furthermore, marine invertebrates such as sponges were described as natural habitat for marine Actinobacteria. They are known over a long time to be a prolific source of bioactive substances. Because of the reason that they are sessile organisms, they use the bioactive metabolites as a kind of chemical defence (Hill 2004; Ward and Bora 2006). However, up to 35 % of sponge biomass is comprised of

microorganisms, which build an abundant microbial community (Hentschel et al. 2012; Webster and Taylor 2012; Steinert et al. 2014). Sponge-associated bacteria have been also frequently described as producers of bioactive natural products (Blunt et al. 2011, 2012, 2013). These communities include amongst other Actinobacteria also *Salinispora* and related strains (Hentschel et al. 2002).

1.4 Isolation of Marine Actinobacteria

To date, the most common sources for the isolation of marine Actinobacteria are sediments and sponges. However, as mentioned above, Actinobacteria were found almost everywhere in the marine environment. Because of the large amount of bacteria living in the marine sediment (10^9 bacteria per mL, Fenical and Jensen 2006), the cells have to be separated using diverse dilution or stamp techniques.

The common method for the isolation of marine Actinobacteria is very similar to the methods used to isolate terrestrial ones. On the one hand, sea mud can be directly spread over the agar media (Okami and Okazaki 1972) or the sediment samples may be diluted and treated with diverse methods as described below.

Some sediment samples were mixed with sterile sea water (Jensen et al. 1991; Mincer et al. 2002) or used as dried samples (Takizawa et al. 1993) before they were heated up between 6 and 60 min (Mincer et al. 2002; Jensen et al.1991, Takizawa et al. 1993) at about 50 °C. This heat-shock treatment should dispatch most non-spore forming bacteria to provide the slow growing Actinobacteria a selective benefit for growth. Such measures had to be taken to avoid that, as described in the concurrent paper of Karwehl and Stadler (2016) for fungi, the fast-growing strains in soil samples would inadvertently overgrow the more interesting, hitherto unexploited ones. Afterwards, the samples were diluted in several dilution steps and plated on different types of nutrient rich agar plates. Pathom-Aree et al. (2006) used sterile saline solution (Ringer's solution) to pre-incubate the sediment samples for 30 min before the dilution and the following inoculation on a range of different media and an incubation temperature of 55 °C for the isolation of new thermophilic Actinobacteria taxa.

Another dilution technique was described by Mincer et al. (2002) for the isolation of the first *Salinispora* species. In this study, in addition to the heat-shock dilution series approach, the wet sediment was air dried and afterwards pressed into a sterile form plug. This plug was used as a stamp to inoculate the agar plates by stamping the plug several times in a circular fashion onto the plate to cause a dilution of the sediment. This approach was used with and without a previously described heat-shock treatment.

For the isolation of "novel marine-derived Actinobacteria taxa" Magarvey et al. (2004) used a modification of the medium Stan21, which is normally used to isolate Myxobacteria from soil samples (Shimkets et al. 2004). Therefore, the yeast extract was eliminated and the distilled water was replaced by artificial sea water. After the media preparation and the addition of cycloheximide, filter paper disks were placed on the agar plates and the wet sediment was spotted on the surface of the cellulose. The plates were incubated afterwards for 30–90 days at 30 °C in a humidified

chamber. With this method they isolated some unknown marine Actinobacteria which cluster between the *Salinispora* clade and the genus *Micromonospora.*

One possibility for the isolation of marine Actinobacteria out of seawater is a simple filter technique. Okami and Okazaki (1972) described a method by which the seawater was centrifuged and filtered through a 0.3 µl pore size filter. The concentrated microorganisms on the filter were afterwards suspended in filtered sea water and plated on different isolation media.

To isolate Actinobacteria out of sponges several approaches are described. In classical isolation techniques, the sponge samples were directly stamped on isolation media or, in the dilution series method, sponge samples are crashed with a mortar, placed into sea water and after sedimentation, plated in different dilutions on specific sponge isolation agar (Mantalvo et al. 2005; Jiang et al. 2007). However, there are also some modifications of this method. Abdelmohsen et al. (2010) added the supernatant of crashed sponges (sponge extract) into the isolation media to rebuilt the natural environment. A further approach is the addition of both, "aqueous extract" like described before and "organic extract" where the sponge tissue was extracted with the help of hexane, dichlormethane and methanol. Finally, both studies demonstrated an enhanced number of novel isolated strains (Webster and Hill 2001; Selvin et al. 2004; Abdelmohsen et al. 2010). However, for all of these approaches, the sponges had to be harvested. To keep the sponges alive, Steinert et al. (2014) constructed a so called diffusion growth chamber (DGC). This chamber was built out of two combined centrifuge microfilter sections and was inoculated with different types of media. The media compositions differed in the amount of nutrients. Furthermore, every medium includes a small amount of sponge homogenate which was prepared out of a homogenized sponge sample in sterile sea water. After inoculation, the DGCs were directly inserted in the living sponge and retaken after 4 weeks of incubation (Fig. 2). Subsequently, one part of the inoculated media was plated on isolation media and the other part was used to inoculate new DGCs which were inserted into the same sponges. In this study, the authors showed that they were able to detect and cultivate more bacteria than using the classical direct plating method while the sponges stayed in their natural environment.

Most of the isolation media contained fungicidal agents like cycloheximide and nystatin to reduce fungal contamination as well as rifampicin and nalidixic acid to dispatch fast-growing Gram-negative bacteria. All plates were incubated between 2 and 6 weeks between room temperature and 28 °C.

1.5 Bioactive Substances Produced by Marine Actinobacteria

While we concentrate in this review on the bioactive secondary metabolites like antibiotics, cytotoxic agents and fungicides, marine Actinobacteria also produce melanins, enzymes, enzyme inhibitors, single cell proteins as well as probiotics which can be used for example in aquaculture (Manivasagan et al. 2013).

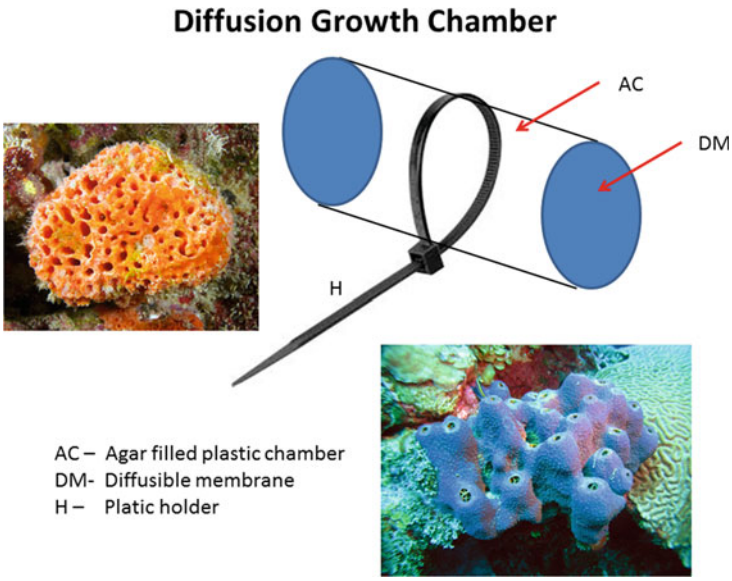

Fig. 2 Diffusion growth chamber (DGC) for in vivo cultivation of sponge-associated bacteria. Build-up of DGC out of two combined centrifuge microfilter sections with diffusible membranes (DM), inoculated with different types of media within the chamber (AC) and the plastic holder (H) for fixing within the sponge

Novel metabolites isolated from marine Actinobacteria include the antitumor agents chromomycins B, A2 and A3 from *Streptomyces coelicolor* (Lu et al. 2012), the antibacterial frigocyclinone from *Streptomyces griseus* (Bruntner et al. 2005), the antifungal and anticancer agents, daryamides from *Streptomyces* sp. (Sivakumar et al. 2007) and further ones as listed in Table 1. However, it becomes apparent that most of the producer strains were classified as *Streptomyces* species, which are common terrestrial bacteria. To date, "real new structures" were only isolated from the two genera of genuine marine Actinobacteria *Salinispora* and *Marinospora* (Manivasagan et al. 2013). Salinosporamides A and B (Fig. 3) are both produced by *Salinispora tropica*. These compounds are β-lactone-γ-lactams produced by a mixed PKS/NRPS biosynthesis. Salinosporamide A is an orally active proteasome inhibitor that induced apoptosis in multiple myeloma cells with mechanisms distinct from the commercial proteasome inhibitor anticancer drug Bortezomib (Chauhan et al. 2005). As NPI-0052, salinosporamide A entered as the first compound isolated out of an obligate marine organism, the clinical studies in multiple phase I trials for solid tumors, lymphoma, and multiple myeloma (http://www.nereuspharm.com/NPI-0052.shtml). The second compound, salinisporamide B, differs only in a lack of chorine and the subsequently less activity by a factor of 500 (Manivasagan et al. 2013). However, the terrestrial *Streptomyces* strain JS360 is the producer strain of the cinnabaramides A-G which are structurally close related to salinosporamide A (Stadler et al. 2007). These substances are also described as

Table 1 Examples of secondary metabolites produced by marine actinobacteria

Compound	Biological activity	Species/Isolate	Reference
1,8-Dihydroxy-2-ethyl-3 methylanthraquinone	Anticancer	*Streptomyces* sp.	Huang et al. (2006)
1-Hydroxy-1-norresistomycin	Antibacterial; anticancer	*Streptomyces chinaensis*	Gorajana et al. (2005) and Kock et al. (2005)
2-Allyloxyphenol	Antimycrobial; food preservative; oral desinfectant	*Streptomyces* sp.	Arumugam et al. (2010)
Abyssomycin C	Antibacterial (inhibition of PABA biosynthesis)	*Verrucosispora maris*	Bister et al. (2004)
Albidopyrone	Anticancer	*Streptomyces* sp.	Hohmann et al. (2009a)
Antracyclines	Anticancer	*Streptomyces galileus*	Fujii and Ebizuka (1997)
Arenicolides A-C	Mild anticancer activity	*Salinispora arenicola*	Jensen et al. (2007)
Arenimycin	Antibacterial; anticancer	*Salinispora arenicola*	Asolkar et al. (2006)
Aureoverticillactam	Anticancer	*Streptomyces aureoverticillatus*	Mitchell et al. (2004)
Avermectin	Antiparasitic	*Streptomyces avermitilis*	Burg et al. (1979)
Bafilomycin	ATPase-inhibitor of microorganisms, plant and animal cells	*Streptomyces griseus, Streptomyces halstedii*	Werner et al. (1984) and Frändberg et al. (2000)
Bisanthraquinone	Antibacterial	*Streptomyces* sp.	Socha et al. (2006)
Butenolides	Anticancer	*Streptoverticillium luteoverticillatum*	Li et al. (2006)
Carboxamycin	Antibacterial; anticancer	*Streptomyces* sp.	Hohmann et al. (2009b)
Chinikomycns	Anticancer	*Streptomyces* sp.	Li et al. (2005)
Chlaramphenicol	Antibacterial, inhibitor of protein biosynthesis	*Streptomyces venuzoelae*	Bewick et al. (1976)
Chlorodihydroquinones	Antibacterial; anticancer	*Novel Actinobacteria*	Soria-Mercado et al. (2005)
Cyanospraside A	Unknown	*Salinispora pacifica*	Jensen et al. (2007)
Cyclomarines	Antiinflammatory	*Streptomyces* sp., *Salinispora arenicola*	Schultz et al. (2008)

(continued)

Table 1 (continued)

Compound	Biological activity	Species/Isolate	Reference
Daryamides	Antifungal; anticancer	*Streptomyces* sp.	Sivakumar et al. (2007)
Dermacozines	Anticancer, radical scavenging	*Dermacoccus* sp.	Abdel-Mageed et al. (2010)
Diazepinomicin	Anticancer	*Micromonospora* sp.	Charan et al. (2004)
Enterocin	Bacteriostatic	*Streptomyces maritimus*	Piel et al. (2000) Max-Planck Inst., Jena
Essramycin	Antibacterial	*Streptomyces* sp.	El-Gendy et al. (2008)
Frigocyclinone	Antibacterial	*Streptomyces griseus*	Bruntner et al. (2005)
Glaciapyrroles	Antibacterial	*Streptomyces* sp.	Macherla et al. (2005)
Hygromycin	Antimicrobial, immunosuppressive	*Streptomyces hygroscopicus*	Omura et al. (1987), Uyeda et al. (2001)
Lajollamycin	Antibacterial	*Streptomyces nodosus*	Manam et al. (2005)
Lincomycin	Antibacterial, inhibitor of protein biosynthesis	*Streptomyces lincolnensis*	Peschke et al. (2006)
Lynamicins	Antibacterial	*Marinispora* sp.	McArthur et al. (2008)
Mansouramycins	Anticancer	*Streptomyces* sp.	Hawas et al. (2009)
Marinomycin A-D	Antimicrobial, anticancer	*Marinispora*	Kwon et al. (2006)
Mechercharmycins	Anticancer	*Thermoactinomyces* sp.	Kanoh et al. (2005)
Mitomycin C	Anticancer, binds to double stranded DNA	*Streptomyces lavendulae*	Mao et al. (1999)
ML-449	Anticancer	*Streptomyces* sp.	Jørgensen et al. (2010)
Pacificanones A and B	Antibacterial	*Salinispora pacifica*	Oh et al. (2008)
Piericidins	Anticancer	*Streptomyces* sp.	Hayakawa et al. (2007)
Proximicins	Antibacterial; anticancer	*Verrucosispora* sp.	Fiedler et al. (2008)
Rapamycin	Immunosuppressive, antifungal	*Streptomyces hygroscopicus*	Vezina et al. (1975)

(continued)

Table 1 (continued)

Compound	Biological activity	Species/Isolate	Reference
Resistoflavin methyl ester	Antibacterial; anti-oxidative	*Streptomyces* sp.	Kock et al. (2005)
Salinamides	Antiinflammatory	*Streptomyces* sp.	Moore et al. (1999)
Saliniketal	Cancer cemoprevention	*Salinispora arenicola*	Jensen et al. (2007)
Salinispyrone	Unknown	*Salinispora pacifica*	Jensen et al. (2007)
Salinispyrone A&B	Mild anticancer activity	*Salinispora pacifica*	Oh et al. (2008)
Salinosproramide A	Anticancer; antimalarial	*Salinispora tropica*	Jensen et al. (2007) and Prudhomme et al. (2008)
Salinosporamide B and C	Anticancer	*Salinispora tropica*	Williams et al. (2005)
Sesquiterpene	Unknown	*Streptomyces* sp.	Wu et al. (2006)
Staurosporine	Antitumor; phycotoxicity	*Streptomyces* sp.	Wu et al. (2006)
Streptokordin	Antitumor	*Streptomyces* sp.	Jeong et al. (2006)
Streptomycin	Antimicrobial	*Streptomyces griseus*	Egan et al. (1998)
Streptozotocin	Diabetogenic	*Streptomyces achromogenes*	Herr et al. (1967)
Tetracyclines	Antimicrobial	*Streptomyces achromogenes, Streptomyces rimosus*	Saleh et al. (1985) and Hansen et al. (2001)
Thiocoraline	Anticancer	*Micromonospora* spp.	Perez Baz et al. (1997)
Tirandamycins	Antibacterial	*Streptomyces* sp.	Carlson et al. (2009)
TP-1161	Antibacterial (inhibition of protein synthesis)	*Nocardiopsis* sp.	Engelhardt et al. (2010)
Valinomycin	Isophor, toxic for Pro- and Eukaryotes	*Streptomyces griseus*	Andersson et al. (1998)
ZHD-0501	Anticancer	*Actinomadura* sp.	Han et al. (2003)
Elaiomycins B and C	Anticancer	*Streptomyces* sp. BK 190	Helaly et al. (2011)
N-(2-hydroxyphenyl)-2phenazinamine (NHP)	Anticancer, antifungal	*Nocardia dassonvillei*	Gao et al. (2012)

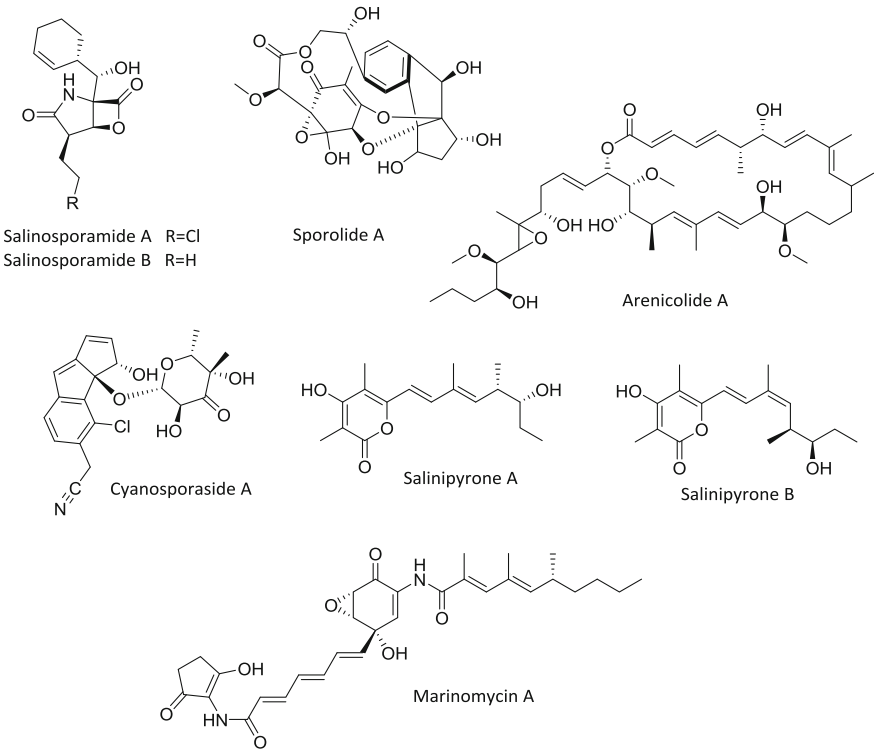

Fig. 3 Examples of new bioactive compounds and their corresponding structures produced by novel genera of marine actinobacteria

strong proteasome inhibitors. However, Rachid et al. (2011) detected a significantly weaker cytotoxic effect then caused by salinosporamide A. Other unprecedented substances produced by *Salinispora tropica* are sporolide A, arenicolide A, cyanosporaside A, and salinipyrone A (Fig. 3). Even though, the salinipyrones A and B (Fig. 3) were first isolated out of the obligate marine Actinobacterium *Salinispora pacifica* (Oh et al. 2008). Both substance did not show antibiotic activity against drug resistance human pathogens, however a moderate cytotoxic activity was detected (Jensen et al. 2007; Manivasagan et al. 2013).

Marinomycin A (Fig. 3), produced by a *Marinophilus* strain (Kwon et al. 2006), is a new polyene macrolide with a high toxicity to tumor cells and antibiotic effect against vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*.

In conclusion, the discovery of the new marine Actinobacteria genera *Salinispora* and *Marinophilus* could be directly correlated to the new and unprecedented compounds with new structures and partially new modes of action. Like described before, molecular studies indicate a great potential for the isolation

of novel genera of marine Actinobacteria. However, new isolation techniques will have to be established and unexplored environments have to be sampled to avoid re-isolations of bacteria out of known genera producing common compounds.

2 Myxobacteria—The Underestimated Bacterial Resource

2.1 History of Myxobacteria

The first myxobacterium was discovered in 1809 by the German botanist H.F. Link and named *Polyangium vitellinum*, but erroneously it was characterized as fungus because of the characteristic fungi-like life cycle (Link 1809). It took many years, until 1892, until Roland Thaxter identified these organisms as bacteria (Thaxter 1892). Actually, the order of Myxococcales consists of 55 species including 28 genera (Fig. 4) and differentiates from other Gram-negative prokaryotes by the mutuality to have a special life cycle.

Myxobacteria belong to the δ-subgroup of proteobacteria and therefore are Gram-negative. The vegetative cells are rod-shaped with the ability to glide over

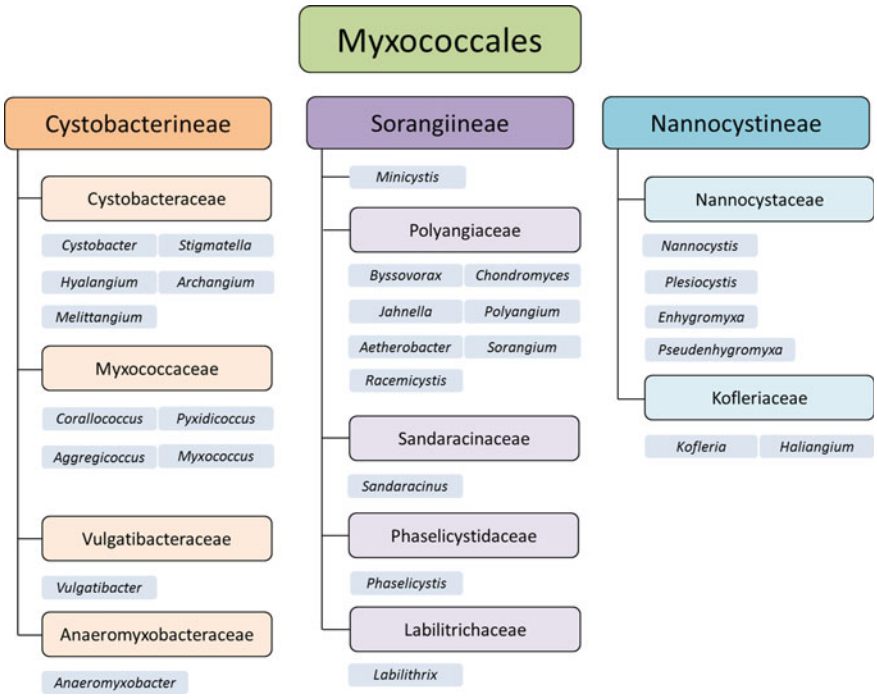

Fig. 4 Current taxonomy of the order Myxococcales

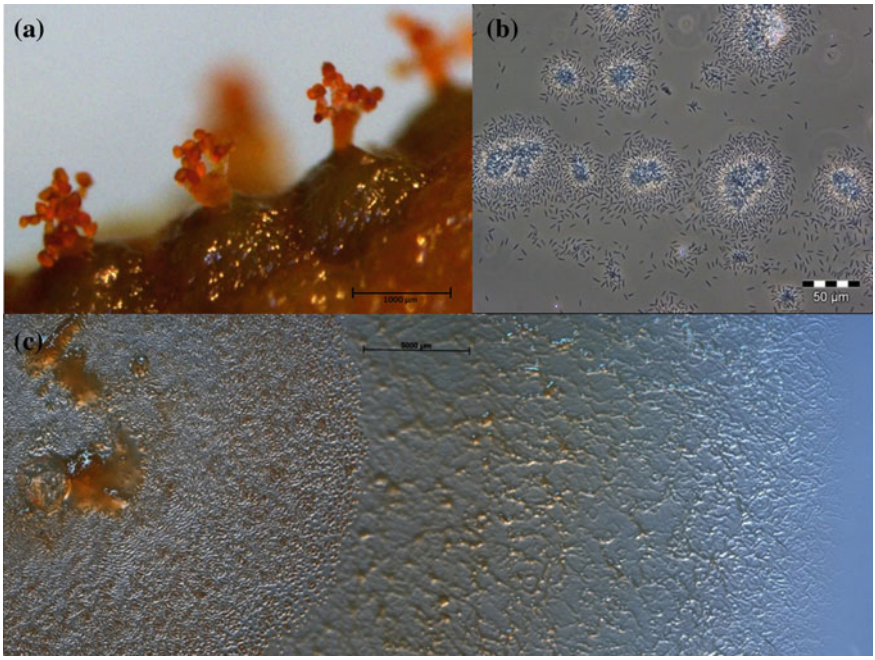

Fig. 5 **a** Fruiting bodies of *Stigmatella aurantiaca* (bar = 1000 µm); **b** Cells of *Myxococcus virescens* (bar = 50 µm); **c** Swarming of *Corallococcus coralloides* (bar = 5000 µm)

solid surfaces and form some kind of multicellular, species-specific "fruiting-bodies" under starvation conditions without access to a sufficient nutrient storage (Reichenbach et al. 1988) (Fig. 5). Those fruiting bodies can comprise up to 10^5 individuals and show a wide range of differences between the genera and species referring their height, shape and color, which mostly varies from yellow, orange or red until brown or even black (Reichenbach 1983; Garcia and Müller 2014a, b, c, d, e).

Within the fruiting bodies, the vegetative cells transform to short, so called myxospores, often enclosed in sporangioles. Because of desiccation resistance, myxospores are able to survive in unfavorable environmental conditions for many years (Reichenbach et al. 2006a, b). Myxobacteria can be found in large populations on many substrates in nature all over the world, e.g., soil, rotting wood, and other habitats. Due to their nutritional requirements, myxobacteria can be divided into two ecological groups that are also in agreement with their phylogeny. Predators use other bacteria or yeasts as food source, and cellulose decomposers, belonging to the genera *Sorangium* and *Byssovorax*, decompose organic materials by producing different types of lytic exoenzymes (Reichenbach et al. 1988; Reichenbach et al. 2006a, b).

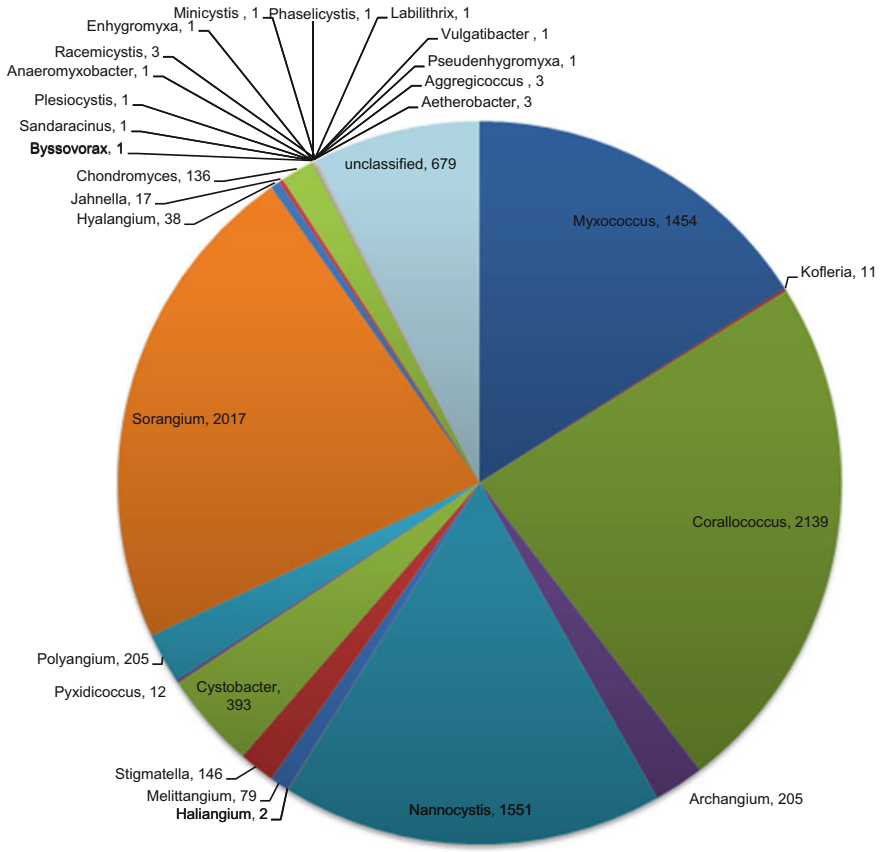

Fig. 6 Number of strains at the HZI

Another important and interesting feature of myxobacteria is their ability to produce a broad range of structurally diverse secondary metabolites, many of them with bioactivity. The working group Microbial Strain Collection at the Helmholtz-Center for Infection Research (HZI) in Braunschweig, has the largest collection of myxobacteria worldwide with more than 9000 strains, including all validly described type strains (Fig. 6).

The major part of the collection is represented by species of the frequently occurring genera *Corallococcus*, *Myxococcus*, *Nannocystis,* and *Sorangium* (Gerth et al. 2003). *Chondromyces*, *Myxococcus,* and *Sorangium* are producers of most of the interesting natural products, consequently they became enriched in the collection (Fig. 7).

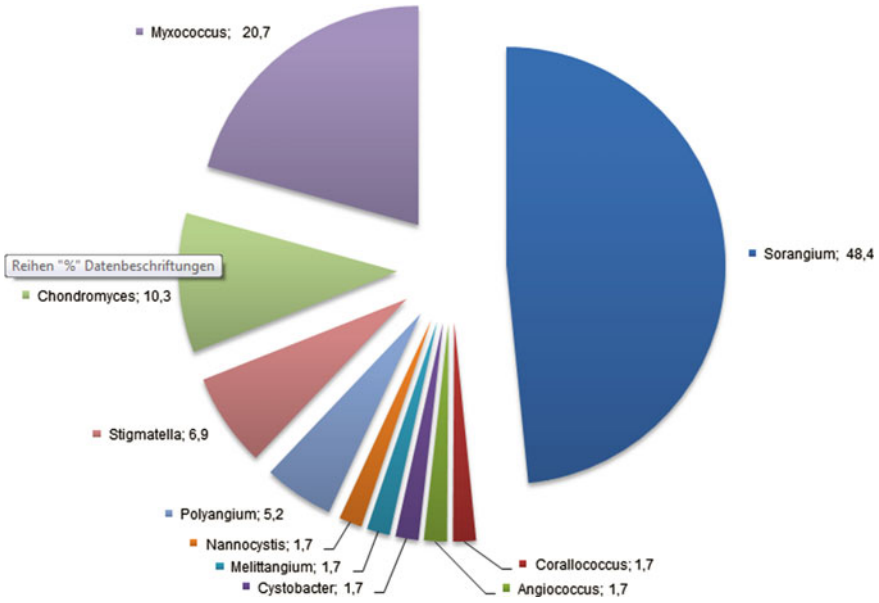

Fig. 7 Percentage of genera in the producers of our novel secondary metabolites from myxobacteria (modified according to Gerth et al. 2003)

2.2 Isolation Methods

To find new bioactive substances, it seems reasonable to exploit new producer organisms and to insert these novel species and genera in the latest taxonomic classification (Müller and Wink 2014). It is necessary to use basic routine methods (Dawid 2000; Shimkets et al. 2006) as well as new approaches (Garcia et al. 2009; Mohr et al. 2015) for the isolation and cultivation of potential and interesting new producer strains.

In general, myxobacteria are characterized as mesophilic soil organisms which prefer a temperature of 30° and a neutral pH. Nevertheless, also acidophilic (Brockman and Boyd 1963), alkaliphilic (Hook 1977) and psychrophilic (Dawid et al. 1988) species were found in the last decades, demonstrating the enormous adaptability of myxobacteria even to extreme uncomfortable habitats. Myxobacteria can also be found in marine, saline habitats, for example *Haliangium ochraceum* and *Haliangium tepidum* (Iizuka et al. 1998). To isolate new myxobacterial strains from different biotopes, environmental samples (e.g., soil, sand, dead wood, bark, leaves, compost) were treated by a standardized procedure. For soil samples, an amount of 50–150 g of sample is collected in 1–5 cm depth below the surface in sterile vials. Before the enrichment on different plates, the sample has to be air dried

and characterized concerning different parameters like color, size, grain, content, and acidity (Dawid 2000). Commonly, different types of plates are used for the enrichment of a wide range especially of myxobacteria species referring to the methods of Reichenbach et al. (2006). Living *E. coli* cells on water agar are suitable as the feed organism for predatory myxobacteria (Shimkets et al. 2006). Many soil bacteria are able to degrade dead, but not living, microorganisms. Furthermore, most soil bacteria grow faster than myxobacteria. Using living bait organisms, myxobacteria have an advantage in comparison to other, not or less swarming, competitors (Garcia et al. 2009). To enrich and isolate specifically cellulose degrading myxobacteria, mineral salt agar Stan 21 is used. Sterile filter paper is placed on the top of the agar and serves as food source (Shimkets et al. 2006). The plates are normally incubated at 30° over a period of several weeks, until the visually striking myxobacteria can be seen with the naked eye. The following isolation, purification, and identification of new strains are carried out on VY/2 plates, containing yeast as nutrient source (Dawid 2000). It is supposed, that the preparation of the medium, combining the important characteristics like in the natural habitats of myxobacteria, leads to high advantage finding novel strains. For example, novel strains were isolated by growing at room temperature (23°) as well as under white light or sun light exposure and on acidic or saline agar plates (Mohr et al. 2015; Garcia et al. 2009). The identification of the facultative anaerobic genus *Anaeromyxobacter* (Sanford et al. 2002) leads to the assumption, that different air conditions tried within the isolation procedures can reveal facultative anaerobic and microaerophilic species (Garcia et al. 2009). Culture-independent methods, like clone bank analyzes, revealed that there is a high number of new potential producer species (Mohr et al. 2015). The development of new cultivation methods is important to find the best growth conditions for all these different types of uncultivated myxobacteria.

The procedure of the standardized screening method, developed at the HZI, starts with the cultivation of a new isolated strain in different liquid complete media (each 100 ml) with different C- and N-sources. The bacteria are cultivated at 30 °C and shaking (180 rpm) 7–14 days. Myxobacteria secrete the secondary metabolites out of the cells into their environment, in this case into the medium. To bind the metabolites and thereby preventing a feedback inhibition or a degradation of the metabolite by a producer strain, XAD16 adsorber resin is added to the culture. After sieving, the resin, and the adsorbed compounds are extracted with acetone, evaporated and finally eluted with methanol, resulting in a raw extract of a 1:100 concentration which is used for further analyzes (Reichenbach and Höfle 1993). However, it is necessary to find the best growth conditions and to optimize the specific production rate for each producer strain, as well as an economic justifiable fermentation process has to be established.

To investigate the effect of a crude extract from a new potential myxobacterial producer strain against different pathogens with clinical importance and to find the active principle, the working group Microbial Strain Collection at the HZI use a dereplication system, which is a combination of a biological activity assay and a chemical screening with liquid chromatography-high resolution mass spectrometry

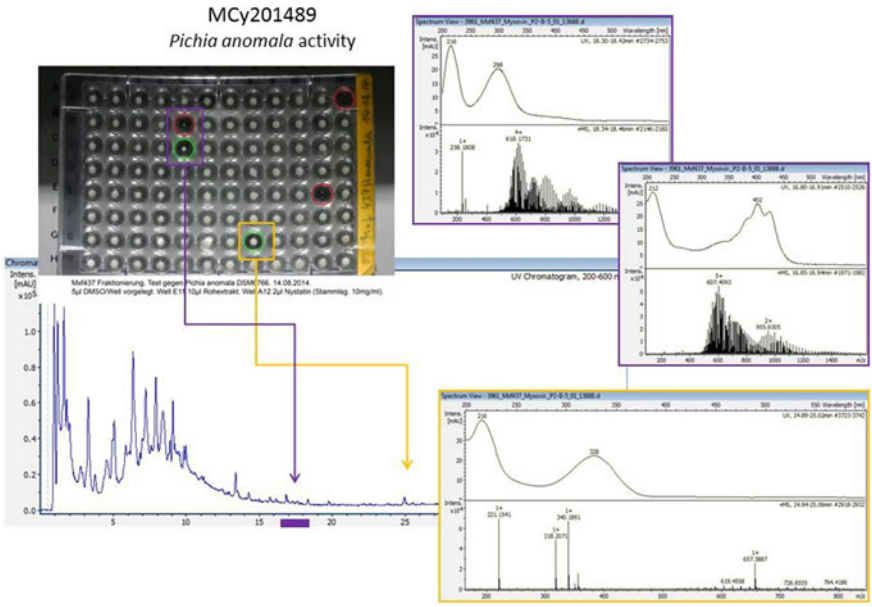

Fig. 8 Combination of activity assay and HPLC-MS

(LC/HRMS). First, the minimum inhibitory concentration (MIC) of the extract is determined by the use of a microtiter plate based serial dilution assay containing different Gram-positive and Gram-negative bacteria as well as fungi to assess selectivity. After semipreparative high performance liquid chromatography (HPLC), the inhibitory effect of the fractionated extract is examined against the affected organisms and further analyzed by ultra-high resolution-time of flight mass spectrometry (UHR-TOF-MS) regarding molecular masses and molecular formulae (Fig. 8). These obtained molecular features are matched against known myxobacterial compounds from the in-house database (Myxobase) or Dictionary of Natural Products (Taylor and Francis Group 2016). The strategy consisting of the use of the different methods above gives possibilities to find and identify new bioactive substances from myxobacteria.

2.3 Genetical Potential

The genomes of myxobacteria belong to the largest ever found in bacteria. The genome of the *Sorangium* strain So ce56, for example, consists of more than 13,000 base pairs and includes seventeen secondary metabolite gene clusters (Schneiker et al. 2007) and the genome of *M. xanthus* comprises at least around 9000 base pairs (Goldman et al. 2006). It is suggested that this large genome size is connected to the

extraordinary and complex life cycle of myxobacteria. In contrast to other bacteria, they need a much more complex genetic constitution to demonstrate their special social behavior including swarming and culminating fruiting bodies. Within these enormously large genomes, there probably exists a high capacity concerning to the unlimited number of unknown and promising secondary metabolites (Wenzel and Müller 2009).

It is hardly possible to figure out the potential of a strain to produce bioactive substances only by phenotypic and biochemic analyzes, because some metabolites cannot be detected due to the applied extraction and detection methods (Wenzel and Müller 2009). Therefore, our research is focusing on the discovery of biosynthetic pathways and the connected gene clusters of novel, potentially anti-infective natural compounds as well as the full genome sequences of scientific interesting bacteria strains. With this information, it might become easier to find possibilities for enhancing the production of known metabolites as well as activating unused "silent" genes for novel substances (Müller and Wink 2014). The genome mining approach is based on the genome sequences, which are used to predict synthesized compounds with the help of bioinformatics analyzes. The recovered genetic information can lead to specific inducing of the supposed biosynthetic gene clusters that encode for new bioactive products (Müller and Wink 2014).

2.4 *Pharmaceutically Important Secondary Metabolites*

Myxobacteria are a rich source of novel and unique secondary metabolites, mainly polyketides and nonribosomal polypetides. Many of these metabolites show antibiotic activities and are urgently needed as new drugs for a broad range of applications. These skills probably evolved because of the natural competition between different kinds of organisms in varying habitats. For example, the cellulose degrading members of the genus Sorangium have to combat other cellulose degraders sharing the same habitat like fungi which also use wood (cellulose) as nutrient source, whereas proteolytic myxobacteria need to stand up to other degraders of decaying organic material (Gerth et al. 2003). The existence of a link between the production of biological active secondary metabolites and microbial predation is supposed, because about 20 % of the known myxobacterial compounds show antibiotic effects. The importance of secondary metabolites derived from natural producers should not be underestimated, because they are the source of almost 50 % of most important medications for humans (Demain 1999).

The scientific interest for myxobacteria increased already in the year 1947, when it was shown that a strain of *Myxococcus virescens* has a significant inhibitory effect on the growth of *Staphylococcus aureus* (Oxford 1947). In the following years many research groups all over the world tried to find the active compounds by optimizing the growth conditions. It was believed for a long time that it is very difficult to cultivate myxobacteria in liquid medium and that these organisms are somewhat problematic with regard to their axenic growth in general (Reichenbach

and Höfle 1993). The breakthrough in discovering antibiotic substances from myxobacteria happened in 1977 by elucidation of the complete chemical structure of the potent antifungal secondary metabolite ambruticin, produced by *Sorangium cellulosum* (Connor et al. 1977; Ringel et al. 1977). Next to the use as antibiotic or antifungal drug, biologically active secondary metabolites can also be used as antiparasitic, antiviral and antitumor drugs in human and veterinary medicine and also as insecticides, acaricides, and herbicides. They can act, e.g., as inhibitors of carboxylases, polymerases, or mitochondrial respiration as well as inhibitors of eukaryotic protein synthesis (Weissmann and Müller 2009). Furthermore, also antidiabetic, antimalarial, antihypertensive, antihypercholesterolemic, insuline-sensitizing, and immunoregulatory characteristics can be attributed to microbial products (Grabley and Thiericke 1999; Schreurs et al. 2009; Berod et al. 2014). A molecule with biological effects can also work as a model for a synthetic production to get a higher output under better economic conditions (Reichenbach and Höfle 1993). More than 100 new and important myxobacterial core structures have been discovered (Garcia et al. 2009), some of them are summarized in Table 2. Another important ability of myxobacteria is the production of polyunsaturated fatty acids (PUFAs) like eicosaoentaenoic acid (EPA) and docosahexaenoic acid (DHA), which play an important role in food industry and for pharmaceutical applications (Garcia et al. 2011; Gemperlein et al. 2016).

Table 2 Important compounds and their biological activity found in myxobacteria

Compound	Activity	Mode of action	Species	Reference
Ambruticin	Antifungal	Interfere with high-osmolarity glycerol (HOG) signaling pathway	*S. cellulosum*	Ringel et al. (1977); Connor et al. (1977) Vetcher et al. (2013)
Aurachins	Antibacterial	Block NADH oxidation	*S. aurantiaca*	Kunze et al. (1987)
Chrondramide	Antifungal/ cytostatic	Interfere with actine polymerisation	*C. crocatus*	Kunze et al. (1995)
Crocacin	Antibacterial	Inhibits electron transport	*C. crocatus*	Kunze et al. (1994)
Cystobactamids	Antibacterial	Inhibit type II topoisomerase	*Cystobacter sp.*	Baumann et al. (2014)
Cystothiazol	Antifungal/ cytostatic	Inhibits submitochondrial NADH oxidation	*C. fuscus*	Ojika et al. (1998)
Disciformycins	Antibacterial	n/a	*P. fallax*	Surup et al. (2014)
Epothilones	Cytotoxic	Inhibition of microtubule function	*S. cellulosum*	Gerth et al. (1996)
Etnangien	Antibacterial	Inhibits nucleic acid polymerases	*S. cellulosum*	Irschik et al. (2007)

(continued)

Table 2 (continued)

Compound	Activity	Mode of action	Species	Reference
Melithiazols	Antibacterial	Inhibit NADH oxidation	*M. lichenicola, A. gephyra, M. stipitatus*	Sasse et al. (1999)
Myxothiazol	Antifungal	Inhibits electron transport	*M. fulvus*	Gerth et al. (1980)
Myxovalargin	Antibacterial	Inhibits protein synthesis and damages cell membranes	*M. fulvus*	Irschik et al. (1983) Irschik and Reichenbach (1985)
Myxovirescin	Antibacterial	Inhibition of signal peptidase	*M. virescens*	Gerth et al. (1982)
Rhizopodin	Cytostatic	Alteration of protein phosphorilation	*M. stipitatus*	Sasse et al. (1993)
Ripostatin	Antibacterial	Inhibits RNA polymerase	*S. cellulosum*	Irschik et al. (1995)
Sorangicin	Antibacterial	Inhibits RNA polymerase	*S. cellulosum*	Irschik et al. (1987)
Soraphens	Antifungal, antiviral, Cancerocidal, Immunoregulatory, Insulin-sensitizing	Inhibit acetyl-CoA carboxylase	*S. cellulosum*	Gerth et al. (1994) Schreurs et al. (2009) Martinez et al. (2013) Berod et al. (2014) Corominas-Faja et al. (2014) Koutsoudakis et al. (2015)
Stigmatellin	Antibacterial	Inhibits electron transport	*S. aurantiaca*	Kunze et al. (1984)

Furthermore, the natural compounds can also work as a basic structure for chemical modifications which can lead to an exploitation in the pharmaceutical area. Epothilones A and B, for example, were originally found in a *Sorangium cellulosum* strain and are distinguished by antifungal and cytotoxic activity (Gerth et al. 1996). Meanwhile, there are modified versions of these molecules already used in the active treatment against different types of cancer or are present in clinical trials. Until epothilones were discovered, the common medication for advanced and early-stage breast cancer was taxanes, anthracyclines, and capecetabine, but these agents are often subjected to a multidrug-resistance, which has a natural origin in the patient. It is suggested that there is an overexpression of efflux pumps and other proteins serving as efflux pumps, so that the anticancer agents can be removed very easy out of the targeted cancer cell (Egerton 2008). In fact, this resistance limits dramatically the chances of success within a therapy (Burger et al. 2003). As an effective alternative to the chemotherapies with taxanes and

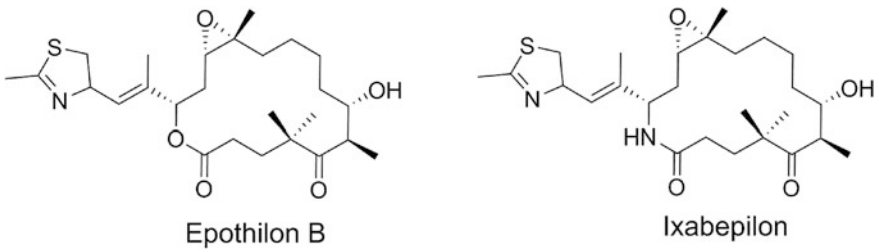

Fig. 9 Chemical structures of epothilon B and ixabepilon

anthracyclines, the semi-synthetic epothilone derivative ixabepilone (Ixempra®) was developed in October 2007 for monotherapie of different stages of breast cancer (Fig. 9) (Reichenbach and Höfle 2008). In contrast to the other available pharmaceuticals referring to this disease, ixabepilone is just low affected by multidrug-resistant mechanisms and consequently offers a chance to eliminate the tumor cells effectively (Pivot et al. 2007).

References

Abdel-Mageed WM, Milne BF, Wagner M, Schumacher M, Sandor P, Pathom-Aree W, Goodfellow M, Bull AT, Horikoshi K, Ebel R, Diederich M, Fiedler HP, Jaspars M (2010) Dermacozines, a new phenazine family from deep-sea dermacocci isolated from a Mariana Trench sediment. Org Biomol Chem 8:2352–2362

Abdelmohsen UR, Pimentel-Elardo SM, Hanora A, Radwan M, Abou-El-Ela SH, Ahmed S, Hentschel U (2010) Isolation, phylogenetic analysis and anti-infective activity screening of marine sponge-associated actinomycetes. Mar Drugs 8:399–412

Andersson M, Mikkola R, Kroppenstedt R, Rainey F, Peltola J, Helin J et al (1998) The mitochondrial toxin produced by *Streptomyces griseus* strains isolated from an indoor environment is valinomycin. Appl Environ Microbiol 64:4767–4773

Arumugam M, Mitra A, Jaisankar P, Dasgupta S, Sen T, Gachhui R et al (2010) Isolation of an unusual metabolite 2-allyloxyphenol from a marine actinobacterium, its biological activities and applications. Appl Microbiol Biotechnol 86:109–117

Asolkar RN, Jensen PR, Kauffman CA, Fenical W, Daryamides AC (2006) Weakly cytotoxic polyketides from a marine-derived actinomycete of the genus *Streptomyces* strain CNQ-085. J Nat Prod 69:1756–1759

Baumann S, Herrmann J, Raju R, Steinmetz H, Mohr KI, Hüttel S, Harmrolfs K, Stadler M, Müller R (2014) Cystobactamids: myxobacterial topoisomerase inhibitors exhibiting potent antibacterial activity. Angew Chem Int Ed Engl 53:14605–14609

Berod L, Friedrich C, Nandan A, Freitag J, Hagemann S, Harmrolfs K, Sandouk A, Hesse C, Castro CN, Bähre H, Tschirner SK, Gorinski N, Gohmert M, Mayer CT, Huehn J, Ponimaskin E, Abraham WR, Müller R, Lochner M, Sparwasser T (2014) De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. Nat Med 20:1327–1333

Bewick M, Williams S, Veltkamp C (1976) Growth and ultrastructure of *Streptomyces venezuelae* during chloramphenicol production. Microbios 16:191–199

Bister B, Bischoff D, Ströbele M, Riedlinger J, Reicke A, Wolter F, Bull AT, Zähner H, Fiedler HP, Süssmuth RD (2004) Abyssomicin C-A—polycyclic antibiotic from a marine

Verrucosispora strain as an inhibitor of the p-aminobenzoic acid/tetrahydrofolate biosynthesis pathway. Angew Chem Int Ed Engl 43:2574–2576
Blunt JW, Copp BR, Hu WP, Munro MH, Northcote PT, Prinsep MR (2007) Marine natural products. Nat Prod Rep 24:31–86
Blunt JW, Copp BR, Munro MHG, Northcote PT, Prinsep MR (2011) Marine natural products. Nat Prod Rep 28:196–268
Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR (2012) Marine natural products. Nat Prod Rep 29:144–222
Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR (2013) Marine natural products. Nat Prod Rep 30:237–323
Brockman ER, Boyd WL (1963) Myxobacteria from soils of the Alaskan and Canadian Arctic. J Bacteriol 86:605–606
Bruntner C, Binder T, Pathom-Aree W, Goodfellow M, Bull AT, Potterat O et al (2005) Frigocyclinone, a novel angucyclinone antibiotic produced by a *Streptomyces griseus* strain from Antarctica. J Antibiot 58:346–349
Bull AT, Starch JEM (2007) Marine actinobacteria: new opportunities for natural product search and discovery. Trends in Microbiol 15:491–499
Burg RW, Miller BM, Baker EE, Birnbaum J, Currie SA, Hartman R et al (1997) Avermectins, new family of potent anthelmintic agents: producing organism and fermentation. Antimicrob Agents Chemother 15:361–367
Burger H, Foekens JA, Look MP, Meijer-van Gelder ME, Klijn JG, Wiemer EA, Stoter G, Nooter K (2003) RNA expression of breast cancer resistance protein, lung resistance-related protein, multidrug resistance-associated proteins 1 and 2, and multidrug resistance gene 1 in breast cancer: correlation with chemotherapeutic response. Clin Cancer Res 9:827–836
Carlson JC, Li S, Burr DA, Sherman DH (2009) Isolation and characterization of tirandamycins from a marine-derived *Streptomyces* sp. J Nat Prod 72:2076–2079
Charan RD, Schlingmann G, Janso J, Bernan V, Feng X, Carter GT (2004) Diazepinomicin, a new antimicrobial alkaloid from a marine *Micromonospora* sp. J Nat Prod 67:1431–1433
Chau R, Kalaitzis JA, Neilan BA (2011) On the origins and biosynthesis of tetrodotoxin. Aqua Toxicol 104:61–72
Chauhan D, Catley L, Li G, Podar K, Hideshima T, Velankar M et al (2005) A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from Bortezomib. Cancer Cell 8:407–419
Connor DT, Greenough RC, Strandtmann M (1977) W-7783, a unique antifungal antibiotic. J Org Chem 42:3664–3669
Corominas-Faja B, Cuyàs E, Gumuzio J, Bosch-Barrera J, Leis O, Martin ÁG, Menendez JA (2014) Chemical inhibition of acetyl-CoA carboxylase suppresses self-renewal growth of cancer stem cells. Oncotarget 5:8306–8316
Dawid W (1978) Fruchtkörperbildene Myxobakterien in Böden Brasiliens. Z Allg Mikrobiol 34:333–335
Dawid W, Gallikowski CA, Hirsch P (1988) 3.8 Psychrophilic myxobacteria from antarctic soils. Polarforschung 58:271–278 (Alfred Wegener Institute for Polar and Marine Research & German Society of Polar Research, Bremerhaven)
Demain A (1999) Pharmaceutically active secondary metabolites of microorganisms. Appl Microbiol Biotechnol 52:455–463
Do H, Kogure K, Simidu U (1990) Identification of deep-sea-sediment bacteria which produce tetrodotoxin. Appl Environ Microbiol 56:1162
Do H, Kogure K, Imada C, Noguchi T, Ohwada K, Simidu U (1991) Tetrodotoxin production of actinomycetes isolated from marine sediment. J Appl Microbiol 70:464–468
Egan S, Wiener P, Kallifidas D, Wellington EMH (1998) Transfer of streptomycin biosynthesis gene clusters within streptomycetes isolated from soil. Appl Environ Microbiol 64:5061–5063
Egerton N (2008) Ixabepilone (ixempra), a therapeutic option for locally advanced or metastatic breast cancer. P T 33:523–531

El-Gendy MM, Shaaban M, Shaaban KA, El-Bondkly AM, Laatsch H (2008) Essramycin: a first triazolopyrimidine antibiotic isolated from nature. J Antibiot 61:149–157

Engelhardt K, Degnes KF, Kemmler M, Bredholt H, Fjaervik E, Klinkenberg G, Sletta H, Ellingsen TE, Zotchev SB (2010) Production of a new thiopeptide antibiotic, TP-1161, by a marine *Nocardiopsis* species. Appl Environ Microbiol 76:4969–4976

Fenical W, Jensen P (2006) Developing a new resource for drug discovery: marine actinomycete bacteria. Nature Chem Biol 2:666–673

Fenical W, Baden D, Burg M, de Goyet CV, Grimes JD, Katz M, Marcus NH, Pomponi S, Rhines P, Tester P, Vena J (1999) Marine derived pharmaceuticals and related bioactive compounds. In: Fenical W (ed) From monsoons to microbes: understanding the ocean's role in human health, National Academies Press, pp 71–86

Fiedler HP, Bruntner C, Riedlinger J, Bull AT, Knutsen G, Goodfellow M, Jones A, Maldonado L, Pathom-Aree W, Beil W, Schneider K, Keller S, Sussmuth RD (2008) Proximicin A, B and C, novel aminofuran antibiotic and anticancer compounds isolated from marine strains of the actinomycete *Verrucosispora*. J Antibiot 61:158–163

Frändberg E, Petersson C, Lundgren LN, Schnürer J (2000) *Streptomyces halstedii* K122 produces the antifungal compounds bafilomycin B1 and C1. Can J Microbiol 46:753–758

Fujii I, Ebizuka Y (1997) Anthracycline biosynthesis in *Streptomyces galilaeus*. Chem Rev 97:2511–2524

Gao X, Lu Y, Xing Y, Ma Y, Lu J, Bao W, Wang Y, Xi T (2012) A novel anticancer and antifungus phenazine derivative from a marine actinomycete BM-17. Microbiol Res 167:616–622

Garcia RO, Müller R (2014a) The family haliangiaceae. In: Rosenberg E, DeLong EF, Lory S, Stackebrandt E, Thompson F (eds) The prokaryotes deltaproteobacteria and epsilonproteobacteria, Springer, pp 173–181

Garcia RO, Müller R (2014b) The family myxococcaceae. In: Rosenberg E, DeLong EF, Lory S, Stackebrandt E, Thompson F (eds) The prokaryotes deltaproteobacteria and epsilonproteobacteria, Springer, pp 192–212

Garcia RO, Müller R (2014c) The family nannocystaceae. In: Rosenberg E, DeLong EF, Lory S, Stackebrandt E, Thompson F (eds) The prokaryotes deltaproteobacteria and epsilonproteobacteria, Springer, pp 213–229

Garcia RO, Müller R (2014d) The family phaselicastaceae. In: Rosenberg E, DeLong EF, Lory S, Stackebrandt E, Thompson F (eds) The prokaryotes deltaproteobacteria and epsilonproteobacteria, Springer, pp 239–245

Garcia RO, Müller R (2014e) The family polyangiaceae In: Rosenberg E, DeLong EF, Lory S, Stackebrandt E, Thompson F (eds) The prokaryotes deltaproteobacteria and epsilonproteobacteria, Springer, pp 247–279

Garcia RO, Krug D, Müller R (2009) Discovering natural products from myxobacteria with emphasis on rare producer strains in combination with improved analytical methods. Methods Enzymol 458:59–91

Garcia R, Pistorius D, Stadler M, Müller R (2011) Fatty acid-related phylogeny of myxobacteria as an approach to discover polyunsaturated omega-3/6 fatty acids. J Bacteriol 139:1930–1942

Gemperlein K, Zipf G, Bernauer HS, Müller R, Wenzel SC (2016) Metabolic engineering of *Pseudomonas putida* for production of docosahexaenoic acid based on a myxobacterial PUFA synthase. Metab 33:98–108

Gerth K, Irschik H, Reichenbach H, Trowitzsch W (1980) Myxothiazol, an antibiotic from *Myxococcus fulvus* (myxobacterales). I. Cultivation, isolation, physico-chemical and biological properties. J Antibiot 33:1474–1479 Tokyo

Gerth K, Pradella S, Perlova O, Beyer S, Müller R (2003) Myxobacteria: proficient producers of novel natural products with various biological activities–past and future biotechnological aspects with the focus on the genus *Sorangium*. J Biotechnol 106:233–253

Gerth K, Ischik H, Reichenbach H, Trowitzsch WPG (1982) The myxovirescins, a family of antibiotics from *Myxococcus virescens* (myxobacterales). J Antibiot 35:1454–1459

Gerth K, Bedorf N, Irschik H, Höfle G, Reichenbach H (1994) The soraphens: a family of novel antifungal compounds from *Sorangium cellulosum* (Myxobacteria). I. Soraphen A1 alpha: fermentation, isolation, biological properties. J Antibiot 47:23–31

Gerth K, Bedorf N, Irschik H, Höfle G, Reichenbach H (1996) Epothilons A and B: antifungal and cytotoxic compounds from *Sorangium cellulosum* (myxobacteria) production, physico-chemical and biological properties. J Antibiot 49:560–563

Goldman BS, Nierman WC, Kaiser D, Slater SC, Durkin AS, Eisen JA, Ronning CM, Barbazuk WB, Blanchard M, Field C, Halling C, Hinkle G, Iartchuk O, Kim HS, Mackenzie C, Madupu R, Miller N, Shvartsbeyn A, Sullivan SA, Vaudin M, Wiegand R, Kaplan HB (2006) Evolution of sensory complexity recorded in a myxobacterial genome. Proc Natl Atlac Sci USA 103:15200–15205

Goodfellow M, Haynes JA (1984) Actinomycetes in marine sediments. In: Ortiz-Ortiz L, Bojalil LF, Yakoleff V (eds) Biological, biochemical, and biomedical aspects of actinomycetes. Academic Press, New York, pp 453–472

Gorajana A, Kurada BV, Peela S, Jangam P, Vinjamuri S, Poluri E et al (2005) 1-Hydroxy-1-norresistomycin, a new cytotoxic compound from a marine actinomycete, *Streptomyces chibaensis* AUBN1/7. J Antibiot 58:526–529

Grabley S, Thiericke R (1999) The impact of natural products on drug discovery. Drug discovery from nature, Springer, pp 3–37

Han SK, Nedashkovskaya OI, Mikhailov VV, Kim SB, Bae KS (2003) *Salinibacterium amurskyense* gen. nov., sp. nov., a novel genus of the family microbacteriaceae from the marine environment. Int J Syst Evol Microbiol 53:2061–2066

Hansen LH, Ferrari B, Sørensen AH, Veal D, Sørensen S (2001) Detection of oxytetracycline production by *Streptomyces rimosus* in soil microcosmos by combining whole cell biosensors and flow cytometry. Appl Environ Microbiol 67:239–244

Hawas UW, Shaaban M, Shaaban KA, Speitling M, Maier A, Kelter G, Fiebig HH, Meiners M, Helmke E, Laatsch H (2009) Mansouramycins A-D, cytotoxic isoquinolinequinones from a marine streptomycete. J Nat Prod 72:2120–2124

Hayakawa Y, Shirasaki S, Shiba S, Kawasaki T, Matsuo Y, Adachi K et al (2007) Piericidins C7 and C8, new cytotoxic antibiotics produced by a marine *Streptomyces* sp. J Antibiot 60:196–200

Helaly SE, Pesic A, Fiedler HP, Süßmuth RD (2011) Elaiomycins B and C: Alkylhydrazide antibiotics from *Streptomyces* sp. BK 190. Org Lett 13:1052–1055

Helmke E, Weyland H (1984) *Rhodococcus marinonascens* sp. nov., an actinomycete from the sea. Int J Syst Bacteriol 34:127–138

Hentschel U, Hopke J, Horn M, Friedrich AB, Wagner M, Hacker J, Moore BS (2002) Molecular evidence for a uniform microbial community in sponges from different oceans. Appl Environ Microbiol 68:4431–4440

Hentschel U, Piel J, Degnan SM, Taylor MW (2012) Genomic insights into marine sponge microbiome. Nat Rev Microbiol 10:641–654

Herr RR, Jahnke HK, Argoudelis AD (1967) Structure of streptozotocin. J Am Chem Soc 89:4808–4809

Hill RT (2004) Microbes from marine sponges: a treasure trove of biodiversity for natural products discovery. In: Bull AT (ed) Microbial diversity and bioprospecting, ASM Press, pp. 225–231

Hohmann C, Schneider K, Bruntner C, Brown R, Jones AL, Goodfellow M, Krämer M, Imhoff JF, Nicholson G, Fiedler HP, Süssmuth RD (2009a) Albidopyrone, a new alpha-pyrone-containing metabolite from marine-derived *Streptomyces* sp. NTK 227. J Antibiot 62:75–79

Hohmann C, Schneider K, Bruntner C, Irran E, Nicholson G, Bull AT et al (2009b) Caboxamycin, a new antibiotic of the benzoxazole family produced by the deep-sea strain *Streptomyces* sp. NTK 937. J Antibiot 62:99–104

Hook LA (1977) Distribution of myxobacters in aquatic habitats of an alkaline bog. Appl Environ Microbiol 34:333–335

Huang YF, Tian L, Fu HW, Hua HM, Pei YH (2006) One new anthraquinone from marine *Streptomyces* sp. FX-58. Nat Prod Res 20:1207–1210

Iizuka T, Jojima Y, Fudou R, Yamanaka S (1998) Isolation of myxobacteria from the marine environment. FEMS Microbiol Lett 169:317–322

Inagaki F, Suzuki M, Takai K, Oida H, Sakamoto T, Aoki K, Nealson KH, Horikoshi K (2003) Microbial communities associated with geological horizons in coastal subseafloor sediments from the Sea of Okhotsk. Appl Environ Microbiol 69:7224–7235

Irschik H, Reichenbach H (1985) The mechanism of action of myxovalargin A, a peptide antibiotic from *Myxococcus fulvus*. J Antibiot 38:1237–1245 Tokyo

Irschik H, Gerth K, Kemmer T, Steinmetz H, Reichenbach H (1983) The myxovalargins, new peptide antibiotics from *Myxococcus fulvus* (Myxobacterales). I. Cultivation, isolation, and some chemical and biological properties. J Antibiot 36:6–12 Tokyo

Irschik H, Jansen R, Gerth K, Höfle G, Reichenbach H (1987) The sorangicins, novel and powerful inhibitors of eubacterial RNA polymerase isolated from myxobacteria. J Antibiot 0:7–13 (Tokyo)

Irschik H, Augustiniak H, Gerth K, Höfle G, Reichenbach H (1995) The ripostatins, novel inhibitors of eubacterial RNA polymerase isolated from myxobacteria. J Antibiot 48:787–792 Tokyo

Irschik H, Schummer D, Höfle G, Reichenbach H, Steinmetz H, Jansen R (2007) Etnangien, a macrolide-polyene antibiotic from *Sorangium cellulosum* that inhibits nucleic acid polymerases. J Nat Prod 70:1060–1063

Jensen PR, Dwight R, Fenical W (1991) Distribution of actinomycetes in near-shore tropical marine sediments. Appl Environ Microbiol 57:1102–1108

Jensen PR, Williams PG, Oh DC, Zeigler L, Fenical W (2007) Species-specific secondary metabolite production in marine actinomycetes of the genus *Salinispora*. Appl Environ Microbiol 73:1146–1152

Jeong SY, Shin HJ, Kim TS, Lee HS, Park S, Kim HM (2006) Streptokordin, a new cytotoxic compound of the methylpyridine class from a marine-derived *Streptomyces* sp. KORDI-3238. J Antibiot 59:234–240

Jiang S, Sun W, Chen M, Dai S, Zhang L, Liu Y, Lee KJ, Li X (2007) Diversity of culturable actinobacteria isolated from marine sponge *Haliclona* sp. Antonie Van Leeuwenhoek 92:405–416

Jørgensen H, Degnes KF, Dikiy A, Fjaervik E, Klinkenberg G, Zotchev SB (2010) Insights into the evolution of macrolactam biosynthesis through cloning and comparative analysis of the biosynthetic gene cluster for a novel macrocyclic lactam, ML-449. Appl Environ Microbiol 76:283–293

Kanoh K, Matsuo Y, Adachi K, Imagawa H, Nishizawa M, Shizuri Y (2005) Mechercharmycins A and B, cytotoxic substances from marine-derived Thermoactinomyces sp. YM3-251. J Antibiot 58:289–292

Karwehl S, Stadler M (2016) Exploitation of fungal biodiversity for discovery of novel antibiotics. Curr Top Microbiol Immunol, in press (doi: 10.1007/82_2016_496)

Kim SB, Oh HM, Kang H, Park SS, Chun J (2004) Remarkable bacterial diversity in the tidal flat sediment as revealed by 16S rDNA analysis. J Microbiol Biotechnol 14:205–211

Kock I, Maskey RP, Biabani MAF, Helmke E, Laatsch H (2005) 1-Hydroxy-1-norresistomycin and resistoflavin methyl ether: new antibiotics from marine-derived streptomycetes. J Antibiot 58:530–535

Koutsoudakis G, Romero-Brey I, Berger C, Pérez-Vilaró G, Monteiro Perin P, Vondran FW, Kalesse M, Harmrolfs K, Müller R, Martinez JP, Pietschmann T, Bartenschlager R, Brönstrup M, Meyerhans A, Díez J (2015) Soraphen A: a broad-spectrum antiviral natural product with potent anti-hepatitis C virus activity. J Hepatol 63:813–821

Kunze B, Kemmer T, Höfle G, Reichenbach H (1984) Stigmatellin, a new antibiotic from *Stigmatella aurantiaca* (Myxobacterales). I. Production, physico-chemical and biological properties. J Antibiot 37:454–461 Tokyo

Kunze B, Höfle G, Reichenbach H (1987) The aurachins, new quinoline antibiotics from myxobacteria: production, physico-chemical and biological properties. J Antibiot 40:258–265 Tokyo

Kunze B, Jansen R, Höfle G, Reichenbach H (1994) Crocacin, a new electron transport inhibitor from *Chondromyces crocatus* (myxobacteria). Production, isolation, physico-chemical and biological properties. J Antibiot 47:881–886 Tokyo

Kunze B, Jansen R, Sasse F, Höfle G, Reichenbach H (1995) Chondramides A approximately D, new antifungal and cytostatic depsipeptides from *Chondromyces crocatus* (myxobacteria). Production, physico-chemical and biological properties. J Antibiot 48:1262–1266 Tokyo

Kwon HC et al (2006) Marinomycins A-D, antitumor-antibiotics of a new structure class from a marine actinomycete of the recently discovered genus "*Marinospora*". J Am Chem Soc 128:1622–1632

Lam KS (2006) Discovery of novel metabolites from marine actinomycetes. Curr Opin Microbiol 9:245–251

Li DH, Zhu TJ, Liu HB, Fang YC, Gu QQ, Zhu WM (2006) Four butenolides are novel cytotoxic compounds isolated from the marine-derived bacterium, *Streptoverticillium luteoverticillatum* 11014. Arch Pharmacal Res 29:624–626

Li F, Maskey RP, Qin S, Sattler I, Fiebig HH, Maier A et al (2005) Chinikomycins A and B: isolation structure elucidation, and biological activity of novel antibiotics from a marine *Streptomyces* sp. isolate M045. J Nat Prod 68:349–353

Link HF (1809) Observations in Ordines plantarum naturales. Dissertatio prima, complectens Anandrarum ordines Epiphytas, Mucedines Gastomycos et Fungos. Der Geselllschaft Naturforschender Freunde zu Berlin Magazin für die neuesten Entdeckungen in der gesamten Naturkunde 3:1–42

Lu J, Ma Y, Liang J, Xing Y, Xi T, Lu Y (2012) Aureolic acids from a marine-derived *Streptomyces* sp. WBF16. Microbiol Res 167:590–595

Macherla VR, Liu J, Bellows C, Teisan S, Nicholson B, Lam KS et al (2005) Glaciapyrroles A, B and C, pyrrolosesquiterpenes from a Streptomyces sp. isolated from an Alaskan marine sediment. J Nat Prod 68:780–783

Magarvey NA, Keller JM, Bernan V, Dworkin M, Sherman DH (2004) Isolation and characterization of novel marine-derived actinomycete taxa rich in bioactive metabolites. Appl Environ Microbiol 70:7520–7529

Maldonado LA, Fenical W, Jensen PR, Kauffman CA, Mincer TJ, Bull AT, Ward AC, Goodfellow M (2005a) *Salinispora arenicola* gen. nov., sp nov and *Salinispora tropica* sp nov., obligate marine actinomycetes belonging to the family micromonosporaceae. Int J Syst Evol Microbiol 55:1759–1766

Maldonado LA, Starch JEM, Pathom-Aree W, Ward AC, Bill AT, Goodfellow M (2005b) The diversity of cultivable actinobacteria in geographically widespread marine sediments. Antonie Van Leeuwenhoek 87:11–18

Manam RR, Teisan S, White DJ, Nishino T, Grodberg J, Neuteboom STC et al (2005) Lajollamycin, a nitro-tetraene spiro-b-lactone-g-lactam antibiotic from the marine actinomycete *Streptomyces nodosus*. J Nat Prod 68:240–243

Mao Y, Varoglu M, Sherman DH (1999) Molecular characterization and analysis of the biosynthetic gene cluster for the antitumor antibiotic mitomycin C from *Streptomyces lavendulae* NRRL 2564. Chem Biol 6:251–263

Martinez JP, Hinkelmann B, Fleta-Soriano E, Steinmetz H, Jansen R, Diez J, Frank R, Sasse F, Meyerhans A (2013) Identification of myxobacteria-derived HIV inhibitors by a high-throughput two-step infectivity assay. Microb Cell Fact 12:85

Manivasagan P, Venkatesan J, Sivakumar K, Kim S-K (2013) Marine actinobacterial metabolites: Current status and future perspectives. Microbiol Res 168:311–332

Mantalvo NF, Mohamed NM, Enticknap JJ, Hill RT (2005) Novel actinobacteria from marine sponges. Antonie Van Leeuwenhoek 87:29–36

McArthur KA, Mitchell SS, Tsueng G, Rheingold A, White DJ, Grodberg J, Lam KS, Potts BC (2008) Lynamicins A-E, chlorinated bisindole pyrrole antibiotics from a novel marine actinomycete. J Nat Prod 71:1732–1737

Mincer TJ, Jensen PR, Kauffman CA, Fenical W (2002) Widespread and persistent populations of a major new marine actinomycete taxon in ocean sediments. Appl Environ Microbiol 68:5005–5011

Mincer TJ, Fenical W, Jensen PR (2005) Culture-dependent and culture-independent diversity within the obligate marine actinomycete genus *Salinispora*. Appl Environ Microbiol 71:7019–7028

Mitchell SS, Nicholson B, Teisan S, Lam KS, Potts BC (2004) Aureoverticillactam, a novel 22-atom macrocyclic lactam from the marine actinomycete *Streptomyces aureoverticillatus*. J Nat Prod 67:1400–1402

Mohr KI, Stechling M, Wink J, Wilharm E, Stadler M (2015) Comparison of myxobacterial diversity and evaluation of isolation success in two niches: Kiritimati Island and German compost. Microbiologyopen 5:268–278

Moore BS, Trischman JA, Seng D, Kho D, Jensen PR, Fenical W (1999) Salinamides, antiinflammatory depsipeptides from a marine streptomycete. J Org Chem 64:1145–1150

Moore BS, Kalaitzis JA, Xiang L (2005) Exploiting marine actinomycete biosynthetic pathways for drug discovery. Antonie Van Leeuwenhoek 87:49–57

Müller R, Wink J (2014) Future potential for anti-infectives from bacteria—how to exploit biodiversity and genomic potential. Int J Med Microbiol 304:3–13

Oh DC, Gontang EA, Kauffman CA, Jensen PR, Fenical W (2008) Salinipyrones and pacificanones, mixed-precursor polyketides from the marine actinomycete salinispora pacifica. J Nat Prod 71:570–575

Ojika M, Suzuki Y, Tsukamoto A, Sakagami Y, Fudou R, Yoshimura T, Yamanaka S (1998) Cystothiazoles A and B, new bithiazole-type antibiotics from the myxobacterium *Cystobacter fuscus*. J Antibiot 51:275–281 Tokyo

Okami Y, Okazaki T (1972) Studies on marine microorganisms. J Antibiot 25:456–460

Omura S, Nakagawa A, Fujimoto T, Saito K, Otoguro K, Walsh JC et al (1987) Hygromycin A, an antitreponemal substance. I. Screening method and therapeutic effect for *Treponema hyodysenteriae*-caused infection in CF-1 mice. J Antibiot 40:1619

Oxford AE (1947) Observations concerning the growth and metabolic activities of myxococci in a simple protein-free liquid medium. J Bacteriol 53:129–138

Papineau D, Walker JJ, Mojzsis SJ, Pace NR (2005) Composition and structure of microbial communities from stromatolites of Hamelin Pool in Shark Bay, Western Australia. Appl Environ Microbiol 71:4822–4832

Pathom-Aree W, Stach JEM, Ward AC, Horikoshi K, Bull AT, Goodfellow M (2006) Diversity of actinomycetes isolated from challenger deep sediment (10,898 m) from the Mariana Trench. Extremophiles 10:181–189

Perez Baz J, Cañedo LM, Fernández Puentes JL, Silva Elipe MV (1997) Thiocoraline, a novel depsipeptide with antitumor activity produced by a marine *Micromonospora*. II. Physico-chemical properties and structure determination. J Antibiot 50:738–741

Peschke U, Schmidt H, Zhang HZ, Piepersberg W (2006) Molecular characterization of the lincomycin-production gene cluster of *Streptomyces lincolnensis* 78–11. Mol Microbiol 16:1137–1156

Piel J, Hertweck C, Shipley PR, Hunt DM, Newman MS, Moore BS (2000) Cloning, sequencing and analysis of the enterocin biosynthesis gene cluster from the marine isolate '*Streptomyces maritimus*': evidence for the derailment of an aromatic polyketide synthase. Chem Biol 7:943–955

Pivot X, Dufresne A, Villanueva C (2007) Efficacy and safety of ixabepilone, a novel epothilone analogue. Clin Breast Canc 7:543–549

Prudhomme J, McDaniel E, Ponts N, Bertani S, Fenical W, Jensen P et al (2008) Marine actinomycetes: a new source of compounds against the human malaria parasite. PLoS ONE 3:2335

Rachid S, Huo L, Herrmann J, Stadler M, Köpcke B, Bitzer J, Müller R (2011) Mining the cinnabaramide biosynthetic pathway to generate novel proteasome inhibitors. ChemBioChem 12:922–931

Reichenbach H (1983) A simple method for the purification of myxobacteria. J Microbiol Methods 1:77–79

Reichenbach H, Höfle G (1993) Biologically active secondary metabolites from myxobacteria. Biotech Adv 11:219–277

Reichenbach H, Gerth K, Irschik H, Kunze B, Höfle G (1988) Myxobacteria: a source of new antibiotics. Trends Biotechnol 6:115–121

Reichenbach H, Lang E, Schumann P, Spröer C (2006a) *Byssovorax cruenta* gen. nov., sp. nov., nom. rev., an cellulose-degrading myxobacterium: rediscovery of '*Myxococcus cruentus'* Thaxter 1897. Int J Syst Evol Microbiol 56:2357–2363

Reichenbach H, Dworkin M, Shimkets LJ (2006) The myxobacteria In: Dworkin M, Falkow S, Rosenberg E, Schleifer K.-H. Stackebrandt E (eds) The prokaryotes,Springer, Berlin, vol 7, pp. 31–115

Reichenbach H, Höfle G (2008) Discovery and development of the epothilones: a novel class of antineoplastic drugs. Drugs R D 9:1–10

Ringel SM, Greenough RC, Roemer S (1977) Ambruticin (W7783), a new antifungal antibiotic. J Antibiot 30:371–375

Saleh EA, Mahmoud SAZ, El-Haddad ME, Abdel-Fatah MK (1985) Purification and identification of *Streptomyces aureofaciens* ID13 antibiotic. Zentralblatt für Mikrobiologie 140:325–332

Sanford RA, Cole JR, Tiedje JM (2002) Characterization and description of *Anaeromyxobacter dehalogenans* gen. nov., sp. nov., an aryl-halorespiring facultative anaerobic myxobacterium. Appl Environ Microbiol 68:893–900

Sasse F, Steinmetz H, Höfle G, Reichenbach H (1993) Rhizopodin, a new compound from *Myxococcus stipitatus* (myxobacteria) causes formation of rhizopodia-like structures in animal cell cultures. Production, isolation, physico-chemical and biological properties. J Antibiot 46:741–748

Sasse F, Böhlendorf B, Herrmann M, Kunze B, Forche E, Steinmetz H, Höfle G, Reichenbach H (1999) Melithiazols, new beta-methoxyacrylate inhibitors of the respiratory chain isolated from myxobacteria. Production, isolation, physico-chemical and biological properties. J Antibiot 52:721–729

Selvin J, Joseph S, Asha KRT, Manjusha WA, Sangeetha VS, Jayaseema DM, Antony MC, Denslin Vinitha AJ (2004) Antibacterial potential of antagonistic *Streptomyces* sp. isolated from marine sponge *Dendrilla nigra*. FEMS Microbiol Ecol 50:117–122

Schneiker S, Perlova O, Kaiser O, Gerth K, Alici A, Altmeyer MO, Bartels D, Bekel T, Beyer S, Bode E, Bode HB, Bolten CJ, Choudhuri JV, Doss S, Elnakady YA, Frank B, Gaigalat L, Goesmann A, Groeger C, Gross F, Jelsbak L, Jelsbak L, Kalinowski J, Kegler C, Knauber T, Konietzny S, Kopp M, Krause L, Krug D, Linke B, Mahmud T, Martinez-Arias R, McHardy AC, Merai M, Meyer F, Mormann S, Muñoz-Dorado J, Perez J, Pradella S, Rachid S, Raddatz G, Rosenau F, Rückert C, Sasse F, Scharfe M, Schuster SC, Suen G, Treuner-Lange A, Velicer GJ, Vorhölter FJ, Weissman KJ, Welch RD, Wenzel SC, Whitworth DE, Wilhelm S, Wittmann C, Blöcker H, Pühler A, Müller R (2007) Complete genome sequence of the myxobacterium *Sorangium cellulosum*. Nat Biotechnol 25:1281–1289

Schreurs M, Van Dijk TH, Gerding A, Havinga R, Reijngoud DJ, Kuipers F (2009) Soraphen, an inhibitor of the acetyl-CoA carboxylase system, improves peripheral insulin sensitivity in mice fed a high-fat diet. Diabetes Obes Metab 11:987–991

Schultz AW, Oh DC, Carney JR, Williamson RT, Udwary DW, Jensen PR, Gould SJ, Fenical W, Moore BS (2008) Biosynthesis and structures of cyclomarins and cyclomarazines, prenylated cyclic peptides of marine actinobacterial origin. J Am Chem Soc 130:4507–4516

Shimkets LJ, Dworkin M, Reichbach H (2004) The myxobacteria, 3rd edn. Springer, New York

Sivakumar K, Sahu MK, Thangaradjou T, Kannan L (2007) Research on marine actinobacteria in India. Ind J Microbiol 47:186–196

Socha AM, LaPlante KL, Rowley DC (2006) New bisanthraquinone antibiotics and semisynthetic derivatives with potent activity against clinical *Staphylococcus aureus* and *Enterococcus faecium* isolates. Bioorganic Med Chem 14:8446–8454

Soria-Mercado IE, Prieto-Davo A, Jensen PR, Fenical W (2005) Antibiotic terpenoid chloro-dihydroquinones from a new marine actinomycete. J Nat Prod 68:904–910
Stach JEM, Bull AT (2005) Estimating and comparing the diversity of marine actinobacteria. Antonie Van Leeuwenhoek 87:3–9
Stach JEM, Maldonado LA, Masson DG, Ward AC, Goodfellow M, Bull AT (2003) Statistical approaches to estimating bacterial diversity in marine sediments. Appl Environ Microbiol 69:6189–6200
Stadler M, Bitzer J, Mayer-Bartschmid A, Müller H, Benet-Buchholz J, Gantner F, Tichy HV, Reinemer P, Bacon KB (2007) Cinnabaramides A-G: analogues of lactacystin and salinosporamide from a terrestrial streptomycete. J Nat Prod 70:246–252
Steinert G, Whitfield S, Taylor MW, Thoms C, Schupp PJ (2014) Application of diffusion growth chambers for the cultivation of marine sponge-associated bacteria. Mar Biotechnol 16:594–603 Springer
Surup F, Viehrig K, Mohr KI, Herrmann J, Jansen R, Müller R (2014) Disciformycins A and B: 12-membered macrolide glycoside antibiotics from the myxobacterium *Pyxidicoccus fallax* active against multiresistant staphylococci. Angew Chem Int Ed 53:13588–13591
Takami H, Inoue A, Fuji F, Horikoshi K (1997) Microbial flora in the deepest sea mud of the Mariana Trench. FEMS Microbiol Lett 152:279–285
Takizawa M, Colwell RR, Hill RT (1993) Isolation and diversity of actinomycetes in the Chesapeake Bay. Appl Environm Micobiol 59:997–1002
Taylor and Francis Group (2016) Dictionary of natural products (online)
Thaxter R (1892) On the myxobacteriaceae, a new order of schizomycetes. Bot Gaz 17:389–406
Uyeda M, Mizukami M, Yokomizo K, Suzuki K, Pentalenolactone I (2001) Hygromycin A. immunosuppressants produced by *Streptomyces filipinensis* and *Streptomyces hygroscopicus*. Biosci Biotechnol Biochem 65:1252–1254
Vetcher L, Menzella HG, Kudo T, Motoyama T, Katz L (2013) The antifungal polyketide ambruticin targets the HOG pathway. Antimicrob Agents Chemother 51:3734–3736
Vezina C, Kudelski A, Sehgal S (1975) Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. J Antibiot 28:721–726
Ward AC, Bora N (2006) Diversity and biogeography of marine actinobacteria. Curr Opin Microbiol 9:279–286
Webster NS, Hill RT (2001) The culturable microbial community of the great barrier reef sponge Rhopaloeides odorabile. Appl Environ Microbiol 138:843–851
Webster NS, Taylor MW (2012) Marine sponges and their microbial symbionts: love and other relationships. Environ Microbiol 14:335–346
Weissmann KJ, Müller R (2009) A brief tour of myxobacterial secondary metabolism. Bioorg Med Chem 17:2121–2136
Wenzel SC, Müller R (2009) The impact of genomics on the exploitation of the myxobacterial secondary metabolome. Nat Prod Rep 26:1385–1407
Werner G, Hagenmaier H, Drautz H, Baumgartner A, Zähner H (1984) Metabolic products of microorganisms. bafilomycins, a new group of macrolide antibiotics. Production, isolation, chemical structure and biological activity. J Antibiot 37:110–117
Williams PG, Buchanan GO, Feling RH, Kauffman CA, Jensen PR, Fenical W (2005) New cytotoxic Salinosporamides from the marine actinomycete Salinispora tropica. J Org Chem 70:6196–6203
Wu SJ, Fotso S, Li F, Qin S, Kelter T, Fiebig HH et al (2006) 39-N-carboxamidostaurosporine and selina-4(14),7(11)-diene-8,9-diol, new metabolites from a marine *Streptomyces* sp. J Antibiot 59:331–337
Wu Z, Xie L, Xia G, Zhang J, Nie Y, Hu J, Wang S, Zhang R (2005) A new tetrodotoxin-producing actinomycete, *Nocardiopsis dassonvillei*, isolated from the ovaries of pufferfish *Fugu rubripes*. Taxoicon 45:851–859