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Marine Bacterial Metabolites

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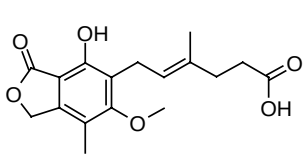
In the past few years, a remarkable number of structurally unique and highly active metabolites has been published from marine bacteria, and especially marine actinomycetes have shown an impressive metabolic capacity. If these bacterial isolates are really indigenous to the marine environment is, however, often not proven. After decades of research mainly on terrestrial microbes, the yearly output of the marine research has passed now its terrestrial counterpart. This chapter summarizes the development of the marine microbial research since the year 2000.

In spite of the long and successful history of antibiotics of terrestrial origin, the search for marine microbial metabolites is even today a nearly untouched subject. The very first antibiotic – mycophenolic acid (**1**) from a *Penicillium* spp. (Bentley, 2000) – was described as early as 1896 and has even found medical application long before the discovery of penicillin; the first marine antibiotic, pentabromopseudilin (**2**), was described more than half a century later (Burkholder *et al.*, 1966; Hanessian *et al.*, 1966; Lovel, 1966; Andersen *et al.*, 1974). The reason for this unexpected fact is among others certainly the assumption of the past decades, that sea water is nearly sterile and that even microbes due to terrestrial pollutions cannot survive for long in the sea. It is now a fact, however, that the water column of the oceans contains on the average 10^4 – 10^6 bacteria/ml, that is an estimated global weight of at least 10^{12} tons at a weight of 1 pg/bacterium and a volume of 1.35 10^9 km^3 of the oceans!



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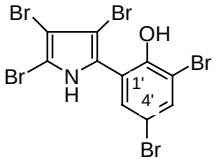

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Due to the often poor physiological status of sea water bacteria and/or to the cultivation methods used, only a very small bacterial fraction of about 1% is usually cultured. However, during the last few years this percentage could be raised considerably by the development of fascinating novel strategies for cultivation and detection (Zengler 2002).

In spite (or because?) of the tremendous success of the past secondary metabolite research, the number of terrestrial antibiotics seems currently to approach a saturation curve with an apparent limit in the near future. The increasing number of duplications and the urgent demand for new leading structures in pharmacology has enforced the search for metabolites in so far untouched habitats like deserts, caves, hot springs, the polar ice and – the oceans. And although most of the so far investigated bacteria from the sea may not be truly marine, the number of newly discovered metabolites from these resources is indeed growing exponentially (Fig. 1). This will certainly continue, as not more than 12 % of the bacteria in the marine habitat seem to be known so far (Bull *et al.*, 1992). Since 2000, nearly 250 marine bacterial metabolites have been described. It should be stated, that in the same period the number of metabolites from terrestrial bacteria was less than 150!

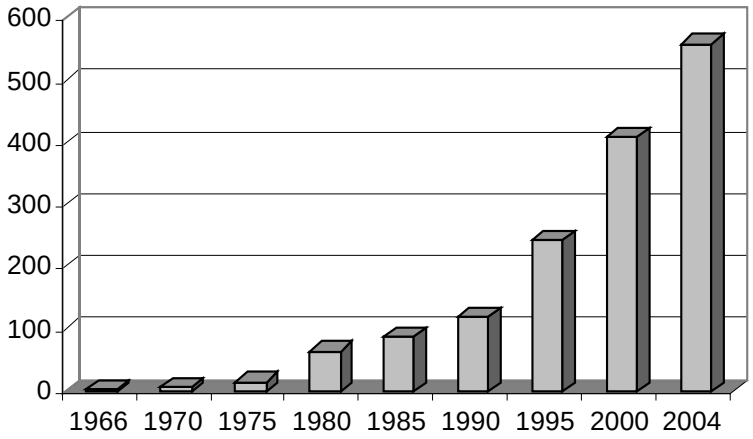
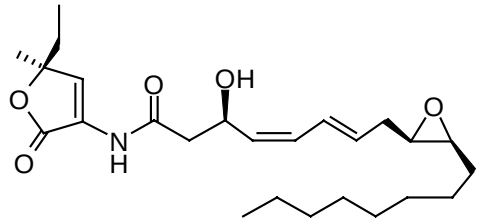


Figure 1: Annual increase of published marine bacterial metabolites, according to AntiBase (Laatsch, 1994-2005)

The definition of a truly marine bacterium is somewhat difficult. Certain species and even genera have not been found in terrestrial surroundings so far, e.g. the *Roseobacter* clade or the genus *Pseudoalteromonas* (see below). Sea water and/or sodium requirements are unequivocal physiological characteristics of autochthonous marine bacteria, however, bacteria with broad salt tolerances may also be active members in some marine environments. Many marine bacteria use a respiratory chain-linked sodium dependent NADH:quinone reductase instead of the common proton-coupled enzyme e.g. *Salinospora* spp.), and korormycin (**3**) (Yoshikawa *et al.*, 1997) from a marine *Vibrio alginolyticus*, a specific inhibitor of this enzyme (Yoshikawa *et al.*, 1999), may be a tool to identify such sodium-dependent bacteria.



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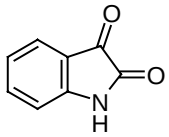
Only a few metabolites have been described from marine bacteria with sodium requirement. Not all bacteria in the sea have, however, the same surrounding and certainly also not the same requirements. A restriction to sodium-dependent bacteria would therefore be too narrow for practical use. Also the production of bromine-containing compounds is not sufficient, as also terrestrial bacteria were shown to synthesize bromoorganics in the presence of bromide (Hochlowski *et al.*, 1997). For the statistics of Table 2, a broader definition was used therefore, which was firstly given by Fenical (Jensen *et al.*, 1996): Marine bacteria are microorganisms which were isolated from the marine habitat and which are functionally reproductive under typical marine conditions. It is obvious that this description may also include terrestrial contaminants if they tolerate the 3.4 % salt concentration of the oceans. Most streptomycetes do so, and according to K. Schaumann from the Alfred-Wegener Institute in Bremerhaven, it might be advisable to name most marine microorganisms better as "isolates from a marine habitat".

There are obviously differences between the physical, chemical and biological characteristics of the marine and the terrestrial environment (Scheuer, 1990). One of the most intriguing factors is the strong mutual, epibiotic and even symbiotic interaction of microbes with higher forms of life in the sea, the majority of which is uniquely marine: In the oceans, nearly every surface is covered by microorganisms, and for a few cases, chemical interactions have been proven. One of the earliest examples is probably the presence of an *Alteromonas* sp. on the embryos of the shrimp *Palaemon macrodactylus*: These bacteria are producing isatine (**4**), a long-known synthetic product, which showed now a reasonable antifungal activity and protects the eggs successfully against the pathogenic fungus *Lagenidium callinectes* (Gil-Turnes *et al.*, 1989).



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It was argued that ecological pressure and selection can rapidly produce specially adapted strains under marine conditions; the development of resistance against medically used antibiotics is a related well-known parallel. The reverse process is, unfortunately, also frequently observed. Meant is not the loss of biodiversity, which certainly also could happen on the microbial level, e.g. if the host of certain symbiotic bacteria is extinguished. More frequently observed is the loss of certain chemotypes inside a bacterial cluster under laboratory conditions: Artificial nutrient compositions are obviously lacking certain trigger substances or stress factors, and it is a common experience that bacterial cultures are rapidly loosing their metabolic capabilities under laboratory conditions if they are too often sub-cultured. The process itself is due to a loss of plasmids or just a selection of clones without needless capabilities and well understood. What we do not know, however, is a reliable technique to avoid this. We are also still at the beginning to understand mutual interactions between bacteria and their hosts or among each others, especially in the sea.

The structures of metabolites published in the past years have been summarized most comprehensively by Fenical (1993), in the annual reviews on marine natural products by Faulkner (2000), and recently by Blunt *et al.* (2003, 2004). This article is focussed therefore on some technical aspects and on the chemistry of marine bacteria of the past four years only.

Isolation and Fermentation of Marine Bacteria

The isolation of bacteria with special capabilities is generally rather an art than a technique. Samples are treated with heat or antibiotics and cultures are kept on different carbon and nitrogen sources, and especially a selection for slowly growing organisms is made. General techniques are summarized in ”The Prokaryotes” (Dworkin *et al.*, 2005) and other handbooks of systematics (Wagenitz 2003, Berger *et al.* 1997).

While the isolation of pure cultures is predominantly a task of microbiologists, their bulk fermentation is already part of their chemical investigation. The search for metabolites with useful properties, the screening, goes parallel with the search for optimal conditions of their

production. The genom of e.g. a streptomycete has a size of up to 8 mega-base pairs (Mbps). As only approximately 4 Mbps are needed for the basic life processes and up to 100 kbps are needed to synthesize a simple polyketide antibiotic like **12**, at least 40 products can be expected from each of the expected 20.000 streptomycetes (Omura *et al.*, 2001). Usually, the number of isolated metabolites is, however, much lower. So it is obvious that we could make much more use of the metabolic capacities of the organisms under investigation, if silent genes could be switched on by added trigger substances or other influences. A few of these factors are known, however, due to their selectivity, they cannot be applied generally.

In most experiments, the search for optimal growth conditions is a matter of trial and error, starting with a standard broth composition and some (often secret) additives. In our laboratory, M_2^+ medium (Maskey *et al.*, 2002e), a composition of glucose, yeast extract and malt extract in diluted (50%) artificial sea water containing trace elements (Biabani *et al.*, 1998) gave good results with marine streptomycetes and bacteria of the free water column. Other compositions are on the basis of oatmeal, peptone, fish flour or chitin (crab shell powder). It should be mentioned that natural seawater contains already a high background of various biological activities and is not suitable if biological tests will be applied on the extracts.

The optimisation of chemical properties concerns usually an increase of the yield and sometimes also the number of metabolites and requires the search for suitable growth factors, the feeding of biosynthetic precursors or the generation and selection of mutants and high-production clones, respectively. Variation of pH and temperature, certain inorganic salts and a variety of carbon and nitrogen sources are commonly used, among others. Typical marine additives are algal extracts: The borine-containing aplasmomycin was formed by *Streptomyces griseus* ss-20 (FERM-p 3448) only in the presence of "Kobu cha", a commercial Japanes algal product (Fenical, 1993). Recently, however, we were able to isolate various aplasmomycins from the marine *Streptomyces* isolate Mei22 also without any additives. This indicates that general rules do not exist.

Screening

Published results show that in a screening for drug development by interactions with special receptors, the hit rate is as low as 10.000:1 ≈ 20.000:1, leading to the industrial high throughput screening as a logical consequence. Even very high sample numbers can be handled now easily, however, this advantage goes in parallel with an increasing number of disadvantages: The flood of data is getting more and more anonymous and only yes/no decisions are obtained, individual observations are impossible and side effects are getting lost.

In contrast to this expensive industrial „vertical screening“, at universities a broad „horizontal screening“ makes more sense: Tests just with one or two fungi, a yeast, a Gram-positive and a Gram-negative bacterium, a microalga and the brine shrimp test are supplying sufficient information about antibiotic, antifungal, phyto- and cytotoxic activity to decide if more detailed tests should follow or not.

Optimisation of Culture Conditions by Genetic Algorithms

A random variation of culture conditions will seldomly reach the best nutrient broth compositions, and a systematic variation of all parameters ends up in an unrealistic number of experiments. As especially about marine bacteria more information with respect to the carbon and nitrogen sources and many other factors is needed, mathematical approaches are making sense. A most suitable method has been developed years ago and has found many technical applications, however, is not often used in fermentations: the optimisation by genetic algorithms.

The rapid development of computers gave rise for a new definition of information as a function of self-organisation: The whole evolution of living beings can be understood as a tendency to optimise storage and processing of relevant information (Stonier, 1991; Hosp, 1994). If a system has no way for variations, there is also no way for development (Grzeganek, 2003).

The natural evolution is an ongoing experiment where the genetic information is continuously optimised. The progress of this evolutionary optimisation is achieved by mutation and recombination and controlled by a steady selection, resulting in the best fit of a population. Evolutionary algorithms (EA) are using these biological mechanisms of evolution to solve nonlinear-polynomical problems for technical applications (Coveney *et al.*, 1995; Merkl *et al.* 2003).

The mathematical basis of EA has a strong correlation to evolutionary biology: The genetic pattern of an organism is defined by its genotype, and the phenotype is the sum of the resulting visible properties (caterpillar and butterfly are having the same genes). If in EA the genotype corresponds to the encoding of parameters responsible for the fitness, the phenotype is then the decoded fitness value of the solution. The "genetic information" of a cultivation experiment (e.g. the broth composition) is digitised as a matrix, changes are achieved by bit manipulations (Adolf, 2001), similar as in artificial neuronal networks (McNeill *et al.*, 1994). Within the various EAs, genetic algorithms (GA) are among the most stable optimisation routines and deliver a solution, even if all other statistical methods fail due to a high number of parameters (Albertz, 1989; Bäck, 1996).

By copying the biological evolution process of selection, mutation and crossover, the GA will find a solution, which is better than the starting condition. Repetition of this procedure will approach to the global (!) optimum by stepwise improvements until a termination condition is fulfilled (Bäck, 1996).

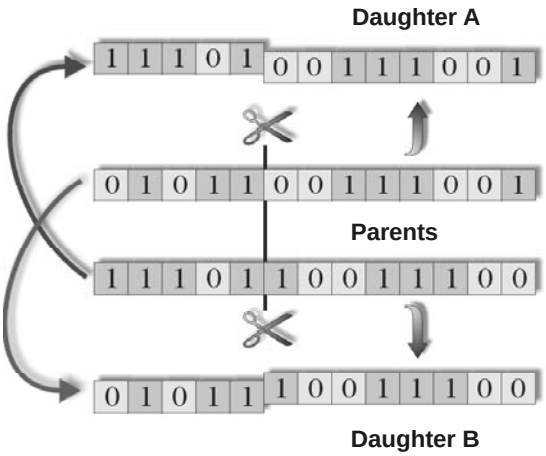
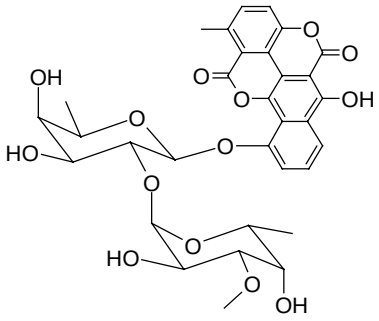


Figure 2. Mixing of the genetic material during a simple *crossover* process

In the case of a fermentation optimisation, a set of plausible nutrient compositions is defined as starting conditions. Each composition is encoded as a binary string, the “gene”. The sum of these genes are forming the gene pool of the respective experiment. After the parallel fermentation of different compositions in a small scale, the biochemical result (phenotype, e.g. the activity, the concentration of certain compounds or the cell mass) is validated. The binary strings (genes) of selected positive experiments are now subjected to "genetic manipulations" resulting in a first daughter generation. A second fermentation is performed, the phenotypes are again determined, and so on.

The number of repetitions (generations), the probability of mutations, recombinations, the number of individuals and their mortality are speed and quality determining factors. They do not obey general rules and have to be experimentally adopted to the problem in question (Clemens *et al.*, 1996; Adolf, 2001).

For the optimisation of culture conditions, we used the program GALOP (Genetic Algorithm for the Optimisation of Processes, Möllney *et al.*, 1998), where a complex influence on the selection and optimisation procedure is possible. For the example of a Streptomycete GW27/1179, a nutrient broth consisting of glucose, maltose and yeast extract in artificial sea water was found to produce chartreusin (**5**) in low yield. As a stress factor, calcium chloride was added, which has an influence on the morphogenesis of microorganisms (Goodwin *et al.*, 1979, 1985, 1992), and also effects many other cellular functions. To optimise the concentration of these four constituents, in each generation 15 individuals (15 inoculated Erlenmeyer flasks each with 50 ml nutrient broth) were fermented for 3 days and extracted using a standard protocol. The **5** concentration of each extract was determined by HPLC.



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An increase of the $CaCl_2$ concentration and reduction of the other constituents afforded a fourfold increase in the production of **5**. As in the third generation, the $CaCl_2$ concentration is again decreasing, obviously only a local maximum was reached (Table 1), and after the fifth generation, an increase of more than 700 % was obtained (Fig. 3). It should be stated that the number of parameters is theoretically not limited so that e.g. various carbon and nitrogen sources or stress factors can be tested simultaneously.

Table 1. The best individuals of five subsequent generations, according to the **5** concentration.

Generation	Maltose [g/l]	Glucose [g/l]	Yeast extr. [g/l]	$CaCl_2$ [g/l]	concentration of 5
1	8.1	7.9	1.9	0.3	5.7
2	3.1	5.8	0.6	1.7	22.8
3	9.0	8.8	7.5	0.4	31.5
4	5.8	8.2	4.1	1.3	38.9
5	1.6	8.5	3.9	2.0	42.1

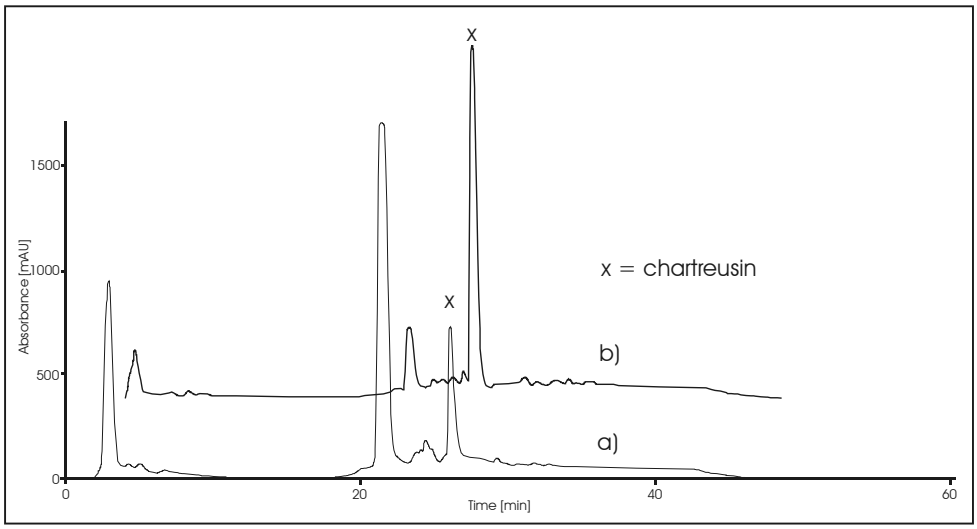


Figure 3. HPLC chromatograms of the best individuals of *S*. sp. GW27/1179 for the production of chartreusin (**5**) in a) generation II and b) generation V, registered at λ = 260 nm.

Isolation and Separation Techniques

There is certainly no principal difference between the work-up procedures of terrestrial and marine bacteria, and therefore the following technical hints concern both groups.

For most medical applications a certain polarity profile is needed which can be described by the octanol/water coefficient, i.e. by the extractability with organic solvents and the Nernst equation. Many bioactive compounds can be extracted with ethyl acetate or at least butanol, however, highly polar compounds like sugars, certain polyhydroxy acids, amino acids and many peptides remain in the water phase. There are two ways also to extract at least some of these compounds: 1. the solid phase extraction with e.g. activated charcoal, lipophilised silica gel or special adsorber resins (mostly Amberlite® XAD-16 or Mitsubishi DIAION® HP20), or 2. the lyophilisation of the whole culture broth and then the extraction with a solvent of higher polarity like water-saturated ethyl acetate or even methanol.

In a few examples the metabolite in question can be precipitated directly from the crude extract; in all other cases, a sequence of separation steps is necessary. If a solid-phase extraction had been used, an elution by a methanol/water gradient of decreasing polarity can be used for a pre-separation. If a solvent-extraction was applied and larger amounts have to be handled, defatting is advisable as the first step. For this purpose, the extract is distributed between methanol and cyclohexane. The latter solvent is more suitable than hexane or petrol ether, which are also in use. Hexane is toxic and expensive, and both solvents contain contaminations of higher boiling alkanes, which are later on difficult to remove from the extract. Cyclohexane is not causing these problems.

For compounds of low or moderate polarity, the further separation steps may include column chromatography on silica gel, size-exclusion chromatography on Sephadex LH-20, HPLC with a wide variety of phases, and solvent/solvent distributions like high speed counter-current chromatography (HSCCC) and other techniques. For highly polar compounds, ion exchange chromatography, preparative electrophoresis and hydrophilic Sephadex are suitable. It is obvious that the separation processes have to be monitored, e.g. by the biological activity, by spectroscopic methods (mostly used are UV, MS, NMR, CD), TLC in combination with spray reagents (anisaldehyde/sulphuric acid for a wide range of compounds, Ehrlich´s reagent for indole derivatives, the chlorine/o,o´-dianisidine reaction for amides, especially peptides, ninhydrin for amino acids and peptides, aniline phthalate for carbohydrates, etc.).

Depending on the source organism and its origin and the investigated structures, 90 % or more of all isolated metabolites may already be known. It is extremely important therefore to eliminate these doublettes as early as possible, a process, which is called dereplication. The earliest possible stage to detect known metabolites is the investigation of the producing organisms itself by MS methods, e.g. by MALDI/TOF (Erhard *et al.*, 1998, 2001). If high resolution is applied and MS/MS fragmentation patterns are known from reference measurements, this technique gains some reliability.

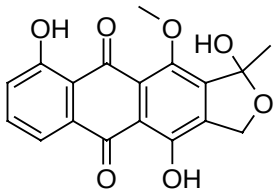
Extracts can be investigated by the same method, which is further enhanced by including additional dimensions, e.g. the HPLC retention time and UV data. Corresponding HPLC/UV databases are widely used and even commercially available (Fiedler, 1993), an HPLC/MS-

MS/UV database is applied for dereplication in our group (Oka *et al.*, 2004). While investigations by means of MS daughter ions or the spectral fitting of UV data require the availability of reference compounds to measure the basic data set at least once under identical conditions, NMR measurements are delivering *ab initio* results which can be compared directly with the literature even prior to a full structure elucidation. Proton and carbon NMR spectra can be easily translated into a set of substructures, which can be used for a fragment search in suitable data bases. It is even more important that in structure-based data collections also those structures can be searched, which are obviously not present in the compound under investigation, to reduce the size of the answer set. The Chemical Abstracts are in practice not applicable for this purpose, for a search with simple fragments will usually result in a system overflow. More suitable are the Dictionary of Natural Products on CD ROM (2005), which covers more than 170.000 entries and includes mainly terrestrial metabolites, and Marinlit (Blunt *et al.*, 2005), a database of solely marine natural products including those from sponges and higher forms of life (presently ~15.000 entries). AntiBase (Laatsch, 1994-2005) (31.000 entries) was developed in our laboratory and is specially designed for the dereplication of terrestrial and marine *microbial* products (including those from fungi and algae) by means of structural features, UV and NMR data. The Umezawa Database (2005) is a related product, however, without NMR data and a smaller data set. Berdy´s BNPD was worldwide the first electronic inhouse database, however, was limited to the DOS operation system and had therefore restricted search capacities; it is not further supported. Some of these databases have been reviewed recently (Buckingham *et al.*, 1997; Gringard *et al.*, 1995).

A dereplication with AntiBase may proceed in the following way: The ^{1}H and ^{13}C NMR data of a yellow, green fluorescent compound showed 3 methine signals between δ 95-100 which were interpreted as acetal functions, 2 aliphatic ketone signals beyond δ 200 and 3 methoxy groups (3H signals between 3.6-4.0), and gave signals of an aromatic system. The substructure search in AntiBase successively step by step with 3 O-CH-O groups, 2 acetone fragments (aliphatic ketone substructure), 3 methoxy groups and a benzene ring afforded only 15 hits out of ~31.000 entries. As there was no typical colour reaction with sodium hydroxide, *peri*-hydroxyquinones were excluded, which left five trioxacarcin derivatives and one member of the hibarimicin group. Only one of them, trioxacarcin A (**47a**) had the observed mass of *m/*z = 876.

After the dereplication step and the final purification, structure elucidation is performed usually on the basis of 2D NMR data and simple chemical derivatisation. It should be stated that completely new skeletons are extremely rare and certainly do not occur worldwide more than a few times per year among bacterial constituents. The result of a structure elucidation should be re-examined carefully therefore, if no related skeletons can be found in the literature. Databases like AntiBase can assist also this process:

A low-molecular weight compound (probably *m/z* = 342) from a streptomycete showed benzene signals of three protons in a row, a C_q-methyl, a methoxy and an isolated methylene group. The colour reaction with sodium hydroxide and the 1H NMR spectrum indicated a quinone with two chelated *peri*-hydroxy groups. Only two compounds were found with these data, but mass and expected spectra were not fitting, and so the metabolite was probably new. The compound was finally elucidated as the quinone **6** and named fuchurmycin B (Barckhausen *et al.*, 1999).



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Recently Described Metabolites from Marine Bacteria

Most marine bacterial metabolites have been isolated from species of the genus *Streptomyces* and *Alteromonas/Pseudoalteromonas* (the genus *Altermonas* was revised 1995 by Gauthier *et al*., and most of the previous *Alteromonas* species were transferred to the new genus *Pseudoalteromonas*) (Table 2). However, also the search for further hot spots in other taxonomic branches is making sense. In the following part, recent results from the literature and our own work are summarised.

Table 2. Number M of published metabolites from marine bacteria according to their taxonomic origin since 1966 (Laatsch, 1994-2005)

Genus	**M**	**Genus**	**M**	**Genus**	**M**[a]
Streptomyces	241	*Janibacter*	9	*Brevibacterium*	2
unidentified bacteria	65	*Microbacterium*	9	*Chrysobacter*	2
Alteromonas	47	*Actinomadura*	8	*Enterobacter*	2
Bacillus	37	*Marinobacter*	7	*Pelagiobacter*	2
Vibrio	29	*Salinospora*	7	*Blastobacter*	1
Pseudomonas	28	*Flavobacterium*	6	*Chainia*	1
Actinomyces	25	*Micrococcus*	6	*Cyclobacterium*	1
Pseudoalteromonas	25	*Halomonas*	5	*Deleya*	1
Cytophaga	19	*Ruegeria*	4	*Enterococcus*	1
Micromonospora	19	*Halobacillus*	3	*Erythrobacter*	1
Myxobacteria	17	*Nocardiopsis*	3	*Flexibacter*	1
Chromobacterium	15	*Oceanibulbus*	3	*Maduramyces*	1
Agrobacterium	14	*Alcaligenes*	2	*Photobacterium*	1

Metabolites from Streptomycetes

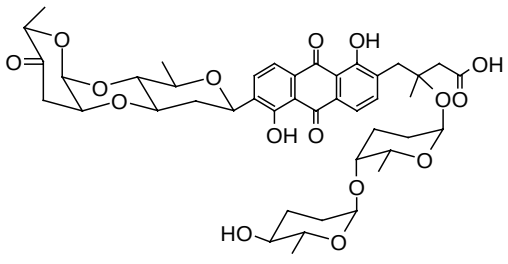
Quinones

Streptomycetes are filamentous actinomycetes and members of the Gram-positive eubacteria. Actinomycetes isolated from soil are the most important source of terrestrial metabolites, and the same situation is found in the marine habitat.

For a long time actinomycetes were considered to be rare or even non-existent in the sea. They are rare, indeed, in the free water column but they could be proven regularly in marine sediments even remote from land (Weyland 1969) although actinomycetes are not as abundant in marine as in terrestrial samples. Due to the work of Okami and co-workers at the Institute of Microbial Chemistry in Tokyo in Japan and the pioneering work of Weyland at the AWI in Bremerhaven (Berg *et al.*, 1981, Weyland 1981, Weyland 1984, Weyland 1986, Helmke *et al.*, 1984, Weyland *et al.* 1988) and others (e.g. Jensen et al., 1991), we have some knowledge about the occurrence of the different actinomycete types and their possible role in the marine environment. We know that the density of streptomycetes is decreasing with increasing distance from the shore. It cannot be excluded therefore, that at least some *Streptomyces* isolates may be terrestrial contaminants. This may explain that no obvious differences in the structures of metabolites from marine and terrestrial streptomycetes were found and that the percentage of halogen compounds is even less than in terrestrial bacteria! Representatives of the actinomycete genus *Salinospora* occur also preferably in coastal waters, nevertheless, these types are unequivocally indigenous marine organisms indicated by their sea water dependence (Pathirana *et al.* 1992). An active role of the actinomycete *Rhodococcus marinonascens* in offshore sediments is also unquestioned. However, *Rhodococci* strains are in general less attractive with respect to secondary metabolite formation but to bioremediation.

The density of rare actinomycetes e.g. *Actinoplanes*, *Rhodococcus* or *Actinomadura*, is obviously increasing in sediments of the open sea, which may be understood as an indication of a truly marine origin, so that also differences in their metabolism can be expected. And indeed, the marine *Salinosporae* have been delivering a number of fascinating structures in the recent past.

Streptomycetes are especially rich in biologically highly active quinones, and as these compounds are easily detected, it is not surprising that also many marine quinones have been described. Recent examples are the complex C-glycosides himalomycins (Maskey *et al.*, 2003a) A (**7**) and B (**8**), anthraquinones with the rare fridamycin E chromophor, a precursor of the anthracycline antibiotics. They were isolated from *Streptomyces* sp. B6921 isolated from a litoral sample from Mauritius and are showing strong antibacterial activity.



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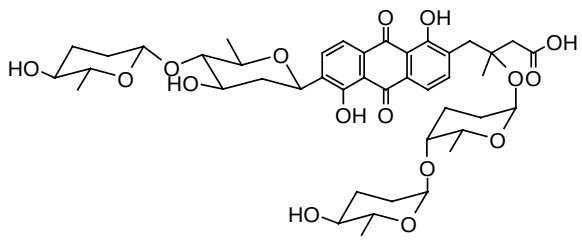

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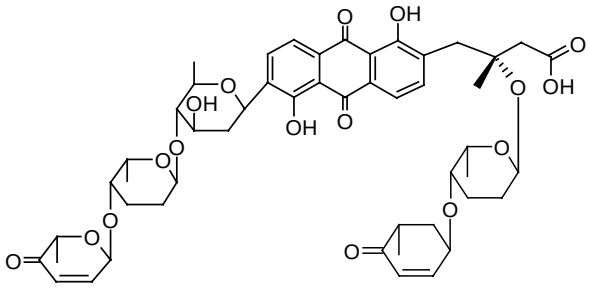
From the same strain, vineomycin C, an inhibitor of the inducible nitric oxide synthase (Alvi *et al.*, 2000), and vineomycin B2 (**9**) were isolated. The lipophilic part of the extract consisted interestingly to 80 % of the ethyl glycoside **10a/b** (K. Vossler, H. Laatsch, unpublished results), which were volatile enough for GC/MS investigations (Stritzke, 2003). It is still unknown if **10a/b** were formed during the isolation, or originated already during fermentation.



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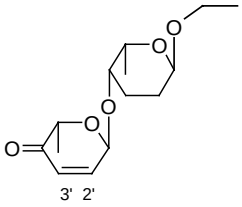
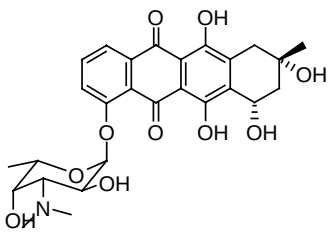


10a
10b: 2',3'-dihydro

Komodoquinone A (**11**) and its chromophor, komodoquinone B (**12**), are belonging to the anthracycline antibiotics, a large group with nearly 500 members. They have been isolated from *Streptomyces* sp. KS3 using a test for neuritogenic activity (Itoh *et al.*, 2003).



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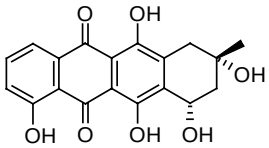
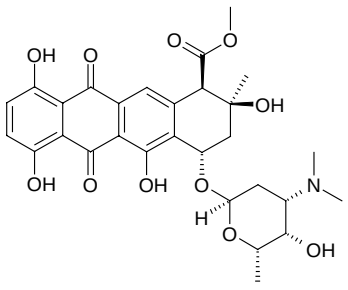


12

With nearly 500 members, the anthracyclines are forming one of the largest groups of antibiotics from actinomycetes. Most of them are highly glycosylated and exhibit strong antitumor activity doxorubicin (adriamycin) being a well-known example. Phipps *et al*. (2004) described recently four new rhodosaminosides 1-hydroxyauramycin T (**13**), 1-hydroxysulfurmycin T (**14**) and the diastereomeric (7S*9S*10R*)- and (7R*9R*10R*)-pyrromycins (**15a, 15b**), which showed the expected cytotoxicity against a P-388 cell line. It is remarkable, that the streptomycete produced monoglycosides with several variations in the aglycon; the previously described 'normal' pyrromycin had the (7S,9R,10R)-configuration (Brockmann, 1959, 1963).



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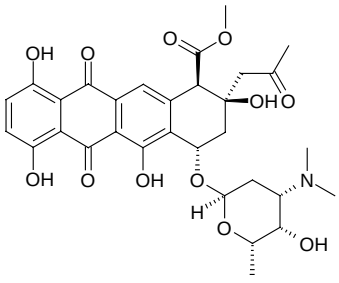

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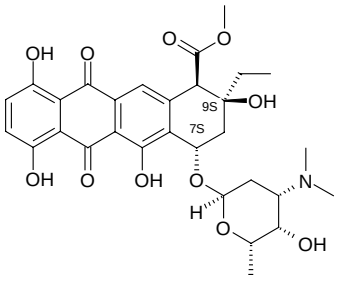
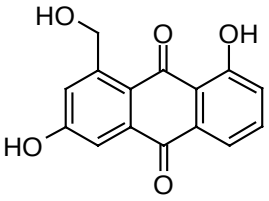


15a
15b: 7R,9R

At least 40 simple quinones with the skeleton of aloesaponarin II have been obtained from streptomycetes. New from a streptomycete from the Yellow Sea are the hydroxymethyl-quinone **16** (Laatsch, unpublished results) and the flavomarins A (**17a**) and B (**17b**), which were

isolated from *S.* sp. B1108 together with bafilomycins, feigrisolides, lactoquinomycin and the insect quinone deoxyerythrolaccin (Abdelfattah, 2003).



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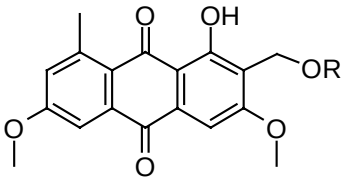
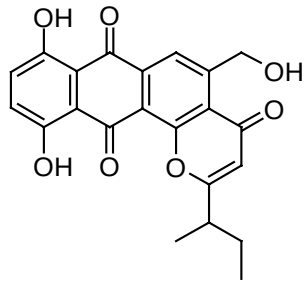


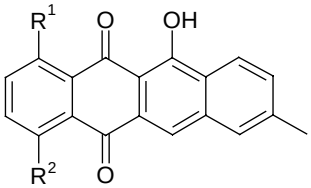
17a: R = Me
17b: R = H



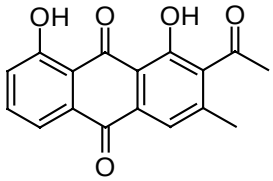
18

From *Streptomyces* sp. B5543, the new espicufolins A and B (**18**) (Abdelfattah, 2003) and several related but known indomycinones were isolated.

A *Streptomyces* sp. Mei 6-1,2 from the German North Sea delivered among others a series of simple anthra- and tetracenequinones **19a/b - 20**; **19a** was already known from synthesis (Laatsch, unpublished results).

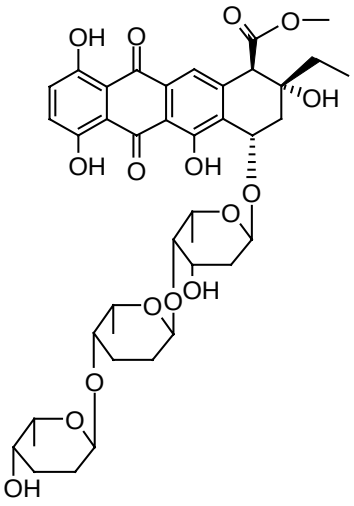


19a: R^1 = H, R^2 = OH
19b: R^1 = OH, R^2 = H



20

Also anthracyclines are not a domain of terrestrial bacteria, cinerubin K (**21**) (Laatsch, unpublished results) from *Streptomyces* sp. B9054, cinerubin M (**22**), **135** and **136** from *S.* sp. B8904 (Shaaban, 2004) being recent examples. The unusual glycocarbaminate fragments in **135** and **136** are typical for the bleomycin group, however, rare in other antibiotics; the only related quinones are rubomycin H and F (Fomicheva *et al.*, 1992).



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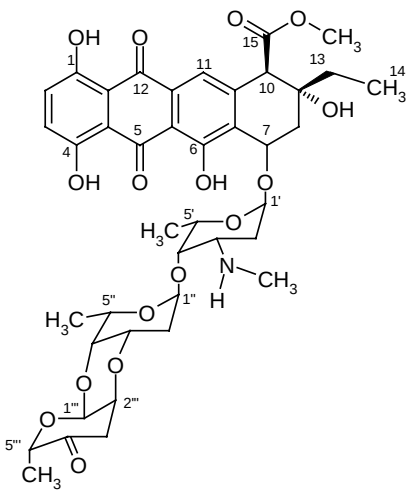
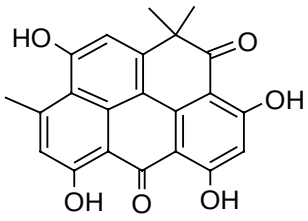


22

Only three benzopyrene quinones have been isolated from nature so far, resistomycin (**23**) (Brockmann *et al.*, 1954), resistoflavine (**24a**) (Eckhardt *et al.*, 1970) and its temptatively assigned methyl ether **24b** (Laatsch, unpublished results); the former two have been isolated from terrestrial as well as marine streptomycetes. 1-Hydroxy-1-norresistomycin (**25**) (Kock, 2005) has now been obtained as a trace component from an isolate B8005. The same compound was recently isolated from a genetically modified streptomycete (Hertweck, 2004).



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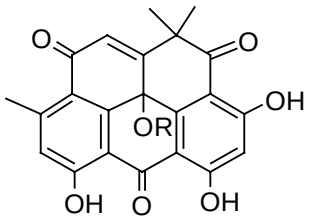
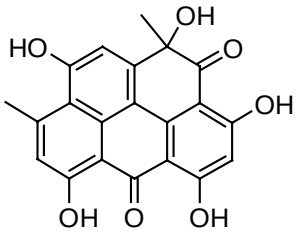
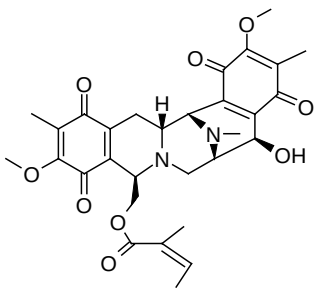


24a: R = H
24b: R = Me



25

The renieramycins A-D (A = **26**) are complex heterocyclic quinones from the marine sponges *Haliclona* sp., *Cribrochalina* sp., and *Reniera* sp., which differ in the ether residues at the quinone rings. It is highly fascinating that the closely related compounds **27** - **31** have now been isolated from a marine streptomycete isolated from a sponge (Saito *et al.*, 2000). They differ from **26** in the substitution at the central bicyclus and also in the (preliminarily assigned) stereochemistry. It can be speculated that the renieramycins are formed by a symbiotic microorganism and perhaps just only modified by the sponge.



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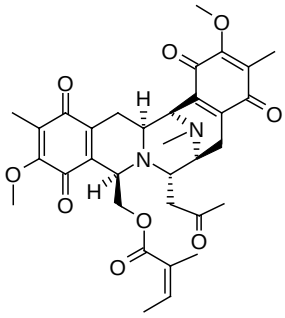

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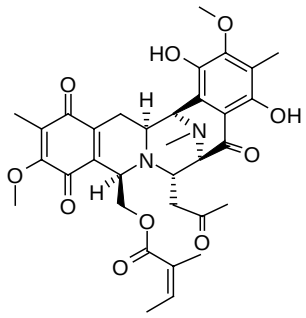

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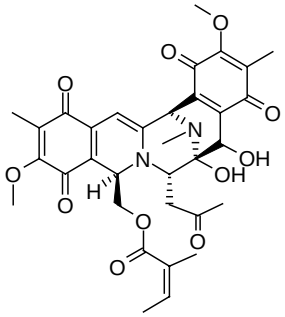

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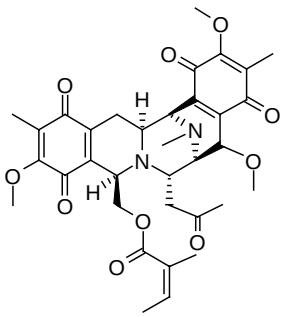

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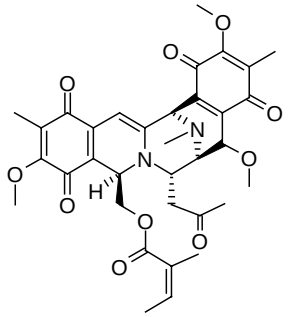
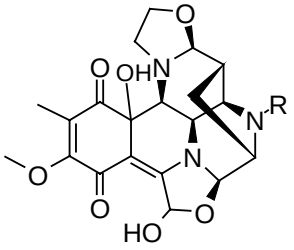


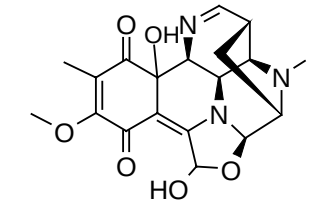
31

The isoquinolinequinones aclidinomycin B (= 12c-hydroxyaclidinomycin A (**32a**), **C** (**33**) and D (**32b**) (Cang *et al.*, 2001) were isolated by Thorwest (Thorwest *et al.*, 2001) from a marine streptomycete; they resemble the antibacterial and cytotoxic metabolites naphthyridinomycin A (**34**) (Kluepfel *et al.*, 1975) and the bioxalomycins, e.g. β_1 (**35**). The latter was

isolated from the marine *Streptomyces viridostaticus* subsp. littus (LL-31F508) (Zaccardi *et al.*, 1994; Bernan *et al.*, 1994).



32a: R = CH_3
32b: R = H



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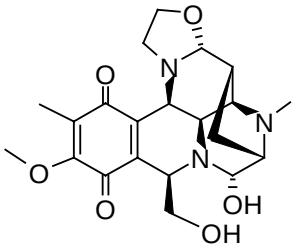
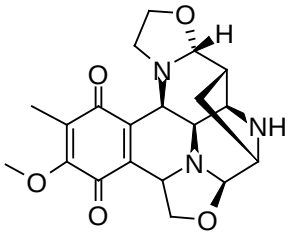
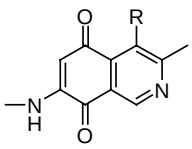


34

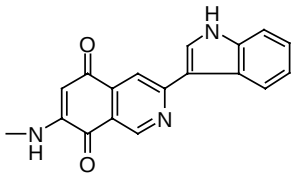


35

From various marine streptomycetes, we have isolated recently the mansouramycins **36** – **41** (Speitling, 1998; Fotso *et al.*, submitted 2005). These isoquinolinequinones resemble the spongal cribrostatins (Pettit *et al.*, 1992; 2000; Sandoval *et al.*, 2004) from the blue marine sponge *Cribrochalina* sp. (e.g. cribrostatin 6, **43**), the caulibugulones (Milanowski *et al.*, 2004) from the marine bryozoon *Caulibugula intermis* (caulibugulone A, **44**) and the related renierones (Sandoval *et al.*, 2004; Kitahara *et al.*, 1985) from the sponges *Reniera*, *Petrosia*, and *Haliclona* sp. All these isoquinolinequinones are showing a pronounced cytotoxicity with IC_{50} values down to 30 ng/ml and are active against viruses, bacteria and malaria as well. From *S.* sp. B1848, also 6-hydroxyisatin (**42**) was obtained.



36a: R = H
36b: R = Me



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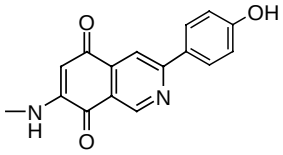

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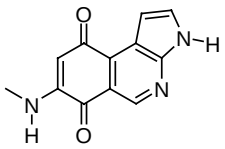

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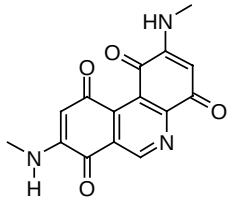

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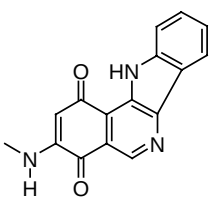

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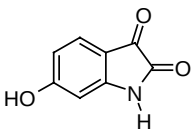

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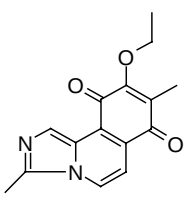

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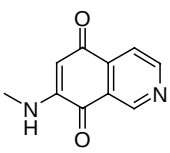
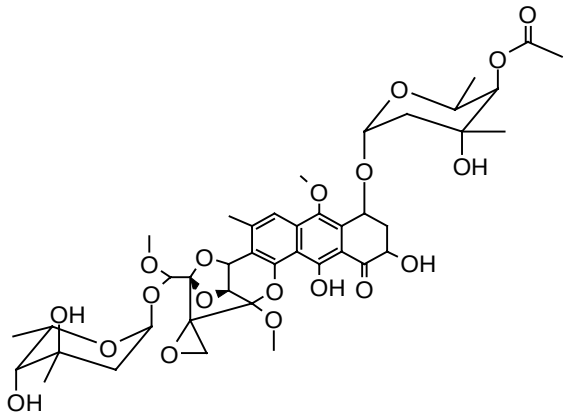


44

The 12 members of the LL-D49194 complex (e.g. LL-D49194η, **45**) are highly oxygenated quinone derivatives, which have been isolated from the terrestrial *Streptomyces vinaceus-drappus* (Maiese *et al.*, 1990). It is very surprising that the trioxacarcins **47a** - **47f** from the marine *S.* sp. B8652 are derivatives of the same aglycone where, however, a sugar residue and one of the acetal methoxyls have changed places. Some of these trioxacarcins had been obtained previously from a terrestrial streptomycete (Shirahata *et al.*, 1981). We observed now a so far unknown strong antiplasmodial activity of the trioxacarcins (Maskey *et al.*, 2004a). Gutingimycin (**47g**), the trioxacarcins (**47a** - **47f**) and also the previously described chromophor **46** (parimycin) (Maskey *et al.*, 2002a) are displaying a characteristic green UV fluorescence on TLC, which is due to the 2,3-dihydroquinizarin skeleton.



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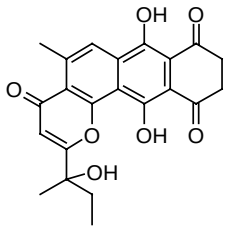

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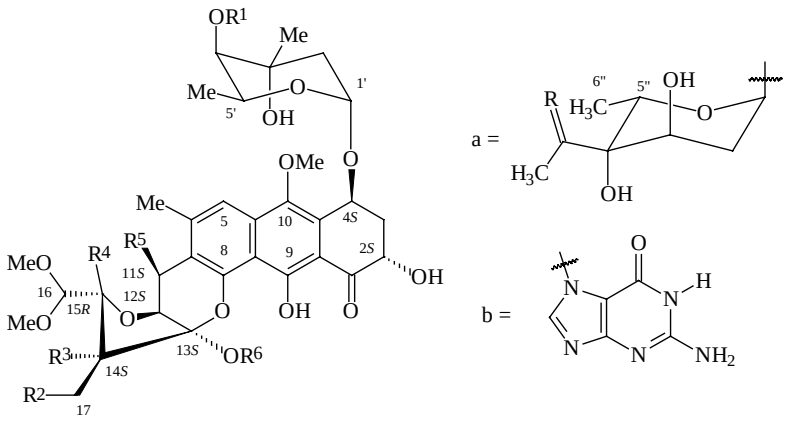
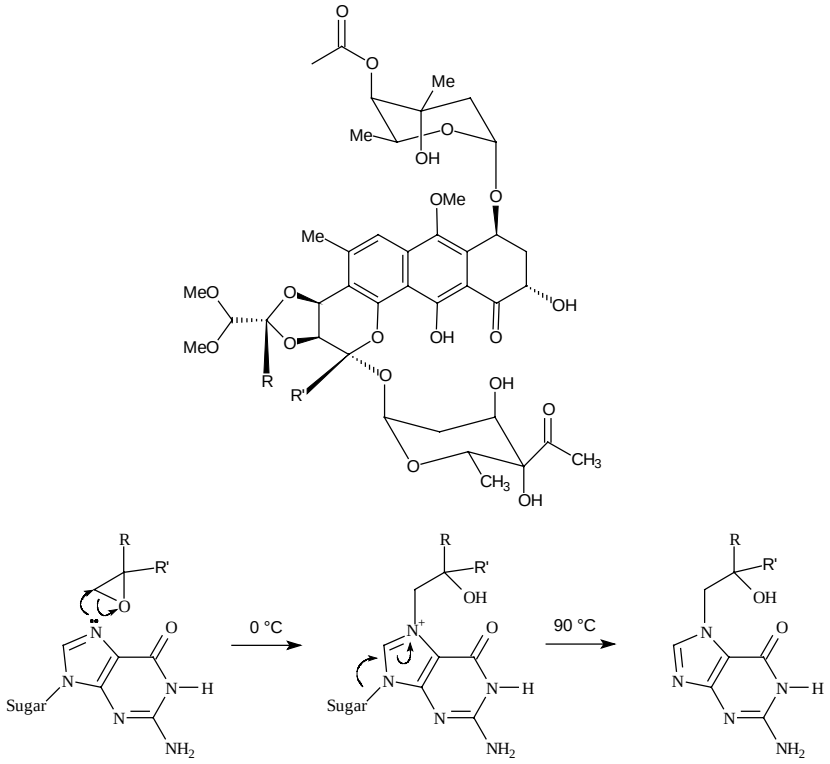


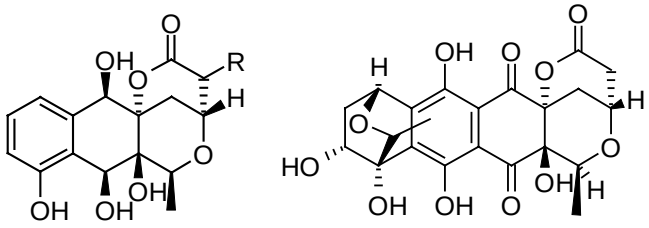
47a: $R^1 = COCH_3$; R^2-$R^3 = R^4$-$R^5 = O$; R^6 = a: R = O
47b: $R^1 = COCH_3$; $R^2 = R^3 = OH$; R^4-$R^5 = O$; R^6 = a: R = O
47c: $R^1 = COCH_3$; R^2-$R^3 = R^4$-$R^5 = O$; R^6 = a: R = OH, H
47d: $R^1 = H$; R^2-$R^3 = R^4$-$R^5 = O$; R^6 = a: R = O
47e: $R^1 = COCH_3$; $R^2 = R^3 = R^4 = R^5 = OH$; $R^6 = H$
47f: $R^1 = COCH_3$; $R^2 = R^3 = R^4 = R^5 = OH$; R^6 = a; R = O
47g: $R^1 = COCH_3$; R^2 = b; $R^3 = OH$; R^4-$R^5 = O$; R^6 = a: R = O

The high cytotoxicity of trioxacarcin A (**47a**) is due to the cleavage of DNA: **47a** forms a MS-detectable complex at guanine containing DNA/RNA positions, which decays under opening of the N-glycosidic bond and liberation of the conjugate **47g**. This compound, gutingimycin, was isolated as a major component from B8652.



47a + guanine **47g**

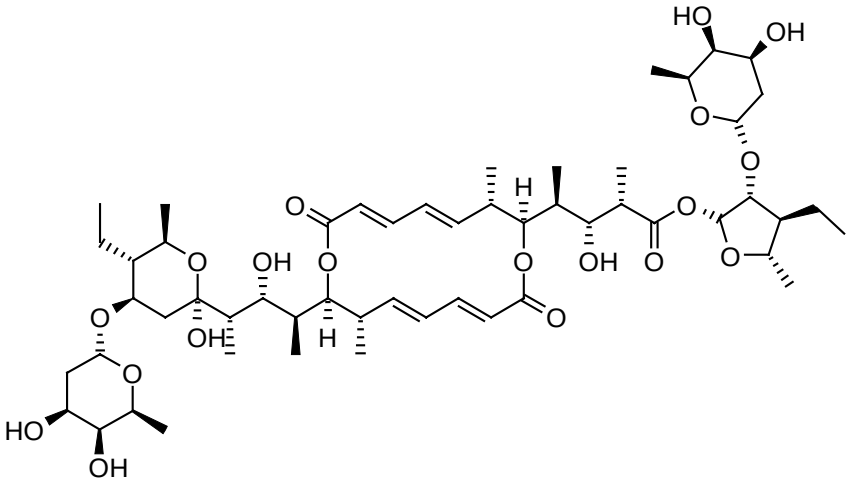
Compound **48a** from the actinomycete ACT 7617 is an unusual quinone derivative as well (Laatsch, unpublished results); it is a hydroxy-luisol A (**48b)**, related with nanaomycin aE and has also some similarity with granaticin C (**49**).



48a: R = OH **49**
48b: R = H

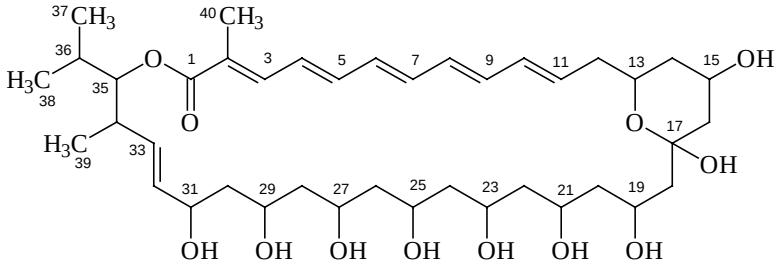
Polyenes

Polyene macrolides are a typical domain of streptomycetes and rare actinomycetes, all compounds of this type were isolated from these organisms. Halichoblelide (**50**), a new member of the efomycin/elaiophylin group from *Streptomyces hygroscopicus* isolated from fish, is a further marine example, which shows, however, potent cytotoxicity instead of the antifungal activity of the larger polyenes (Yamada *et al.*, 2002).



50

The antifungal oxopentaen-macrolide dhanyabadomycin (**51**) (Maskey, 2001) from *S.* strain B 8905 had been isolated previously as TG-488 from terrestrial streptomycetes, however, was not published in detail (Takahashi *et al.*, 1995).



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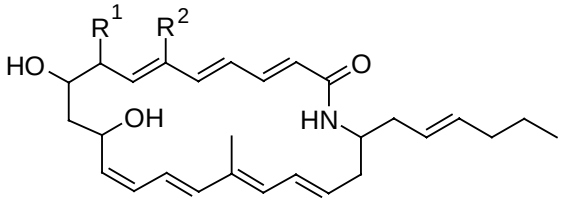
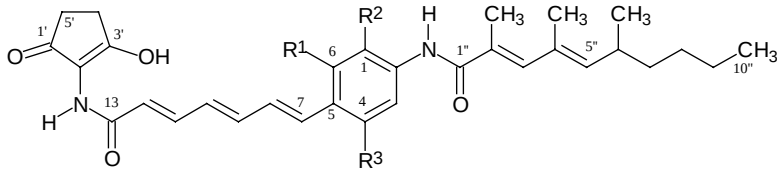


52a: R^1 = OH, R^2 = H
52b: R^1 = OH, R^2 = Me
52c: R^1 = H, R^2 = Me

Aureoverticillactam (**52a**) (Mitchell *et al.*, 2004), a novel 22-membered macrocyclic lactam from the marine actinomycete *Streptomyces aureoverticillatus*, is a demethyl-BE-14106 (**52b**) from a terrestrial streptomycete and is also related with GT-32B (**52c**). All these polyene macrolactams exhibited a strong cytotoxicity.

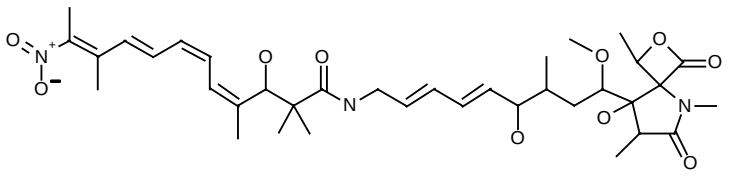
A streptomycete M045 from the sediment of Jiaozhou Bay in China produced the chinikomycins (**53a**) and B (**53b**) (Li *et al.*, 2005) A, unusual chlorinated rearrangement products of manumycin with some structural similarity with 64-p-ABA-2 (**53c**), which was obtained by precursor-directed biosynthesis (Zeeck *et al.*, 1993). They exhibited antitumor activity against

different human cancer cell lines (IC_{50} = 5.6-5.9 µg/ml), however, were inactive in antiviral, antimicrobial, and phytotoxicity tests.



53a: R_1 = Cl, R_2 = R_3 = OH
53b: quinone form of **53a**
53c: R_1 = R_2 = R_3 = H

A very unusual polyen is nitrated ß-lactone lajollamycin (**54**) from a marine *Streptomyces nodosus* strain NPS007994 (Manam *et al*., 2005), which is nearly an isomer of 16-methyloxazolomycin (**55**) from a terrestrial streptomycete (Ryu et al., 1999).



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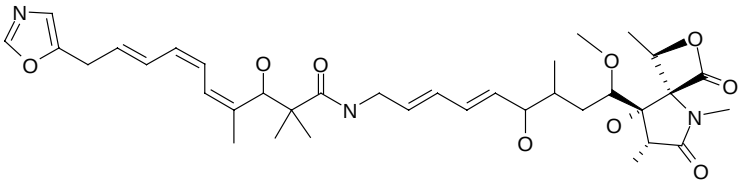
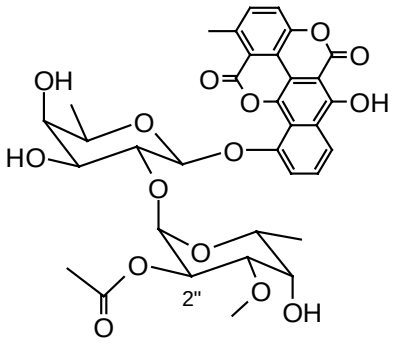


55

Macrolides and other Lactones

A similar intensive greenish fluorescence as in the trioxacarcins is also displayed by chartreusin (**5**), a compound which is not only antibacterially active, but shows also a very promising antitumor-activity against different human cell lines (McGovren *et al.*, 1977), a fact that has stimulated the search for related compounds. The marine streptomycete isolates B5525 and B5342 produced chartreusin (**5**) in high yields of 10-90 mg/l, in addition to 2-methyl-3-hexen-2,5-diole (**58**), phenylacetic acid, streptazolin (Drautz *et al.*, 1981), and 5-hydroxy-5-methylhex-3-en-2-one (**58b**) (Speitling, 1998). Two trace components were identified as the monoacetates **56** and **57**. While one of the monoacetates showed a normal acetate methyl signal at δ = 1.97, the corresponding 2''-signal in the minor component **56** was extremely upfield shifted to δ = 1.39, an effect which was accounted to the influence of the aromatic ring system. Even stronger upfield shifts with signals at δ = 0.81 and 0.71, respectively, were observed for the 2''-acetate groups in the tetra- and pentaacetates (Maskey *et al.*, 2002b).



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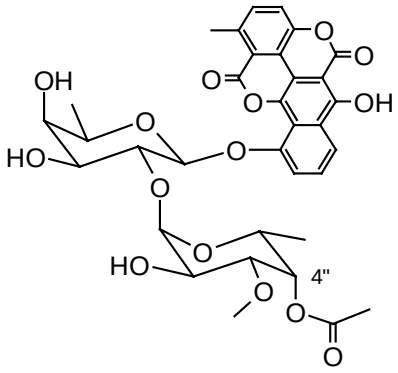

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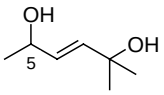
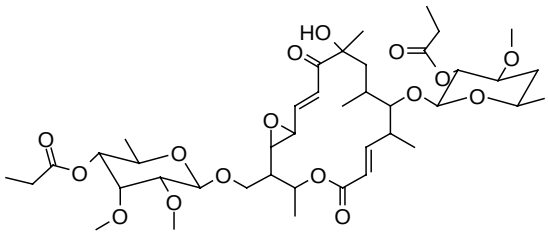


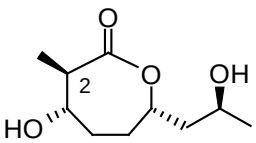
58a
58b: CO instead of 5-OH



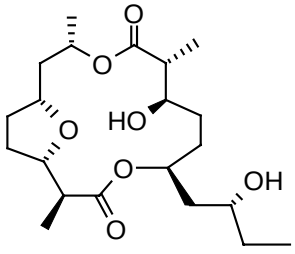
59a
59b

Complex aliphatic lactones are very common among streptomycetes: examples are the uncounted natural and synthetically modified erythromycins, many of which are having clinical applications. A 16- instead of a 14-membered lacton is found in chalcomycin B (**47b**) (Maskey *et al.*, 2002c) from *Streptomyces* sp. B7064, which shows a high antibiotic and moderate phycotoxic activity, similar to that of chalcomycin A (**59a**).

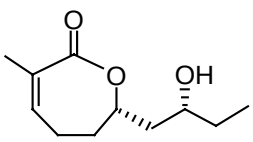
Smaller lactones occur very frequently in terrestrial streptomycetes. Recent examples are the feigrisolides A (**60a**), B (**60b**), and C (**61**) from *Streptomyces griseus* (Tang *et al.*, 2000), which were also found in many marine streptomycetes, together with further minor metabolites, e.g. feigrisolide E (**62**) from *S.* sp. B5375 (Laatsch, unpublished results). Attempts to synthesize two of the feigrisolides have been published recently: The stereochemistry of **60b** is obviously wrong, as synthetic and natural product were not identical; the correct stereochemistry is still unknown (Sharma *et al*., 2004). For feigrisolide C (**61**), even an open acid structure **63** was suggested based on the synthesis (Kim et al., 2005a,b), so that the planar structure of the chiral feigrisolide C is now identical with that of the racemic bonactin (Schumacher *et al*., 2003). As the authors of the old structure **61** claimed, however, to be able to distinguish a lactone and a free acid, also the structure of feigrisolide C is still under debate.



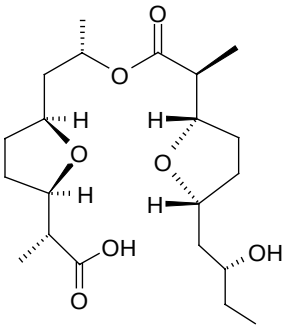
60a
60b: opposite config. at C-2'



61

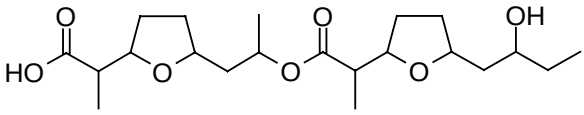


62

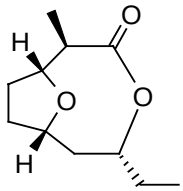


63

On ESI MS measurements, some of the feigrisolide fractions are showing indeed a typical molecular weight distributions as of a polymer, and it is plausible that lactones as **60a** can yield a mixture of oligomers on work-up. The antifungal and antibacterial bonactin (**64**) (Schumacher *et al.*, 2003) from *S.* sp. BD21-2 is such a linear dimer of nonactic and homononactic cid, and the isolation of higher isomers would not be surprising.



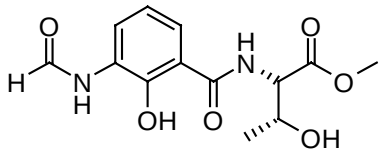
64



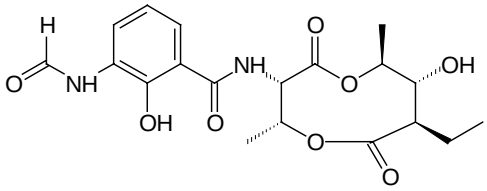
65

Nonactic and homononactic acids are building blocks of more than 50 antibiotics like pamamycins, feigrisolides C (**61**) and E (**62**), macrotetrolides and others. Borolactin A (**65**) Shin *et al.*, 2001) is a new monomeric lactone of homononactic acid, which we recently re-isolated from the marine *S.* sp. B5375.

The antibiotically inactive N-formylantimycic acid methyl ester (**66**) (Seo *et al.*, 2001) is the major constituent of the bislactones of the antimycin and urauchimycin series and was now isolated for the first time as a natural product from *S.* sp. M03033. It is also part of the new urauchimycin C (**67**) from *S.* sp. B175 (Schiebel *et al.*, 2005).



66

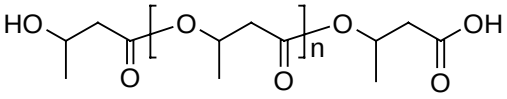


67

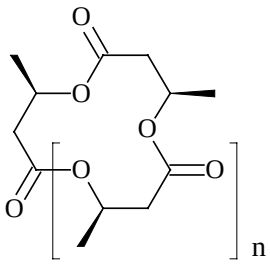
Polyhydroxybutyric acid (sPHB, **69a**) is a very common energy storage material of bacteria (and also often found in marine streptomycetes), which is of commercial interest as biodegradable plastic material. It was surprising now to find for the first time low-molecular weight polyhydroxybutyric acids **69b** (Maskey *et al.*, 2002d) with 8-20 repetition units and a main component **69b** with n = 13. According to Seebach's hypothesis (Seebach *et al.*, 1995), such oligomers may be channel-forming (cPHB), in contrast to the high-polymeric storage sPHB.

From most strains, sPHB *or* cPHB were isolated, and only in a few cases both were found together.

Crude PHBs are obtained easily as insoluble residues, if ethyl acetate extracts of fermentations are dissoved in methanol. It should be mentioned that EI mass spectra of both PHBs are displaying only fragment ions as for small homologues so that the impression may result that the dimer **70** (n = 0) (Fujimoto *et al.*, 1998) or the trimeric pinnatifolide (**70**, n = 1) from the red alga *Laurencia pinnatifida* (Viqar *et al.*, 1991) is present; also CI delivers incomplete results, so that ESI or MALDI TOF are the methods of choice.

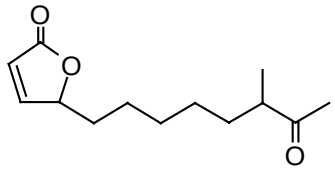


69a: n ≈ 50.000
69b: n = 8-20

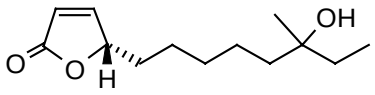


70

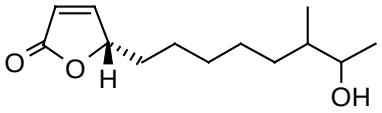
Most microbial butenolides are substituted at the double bond. So far, only 12 metabolites are 2,3-unsubstituted, **71** - **76** being recent examples (Mukku *et al.*, 2000; Cho *et al.*, 2001; Laatsch, unpublished results). Not much is known about their biological function.



71



72



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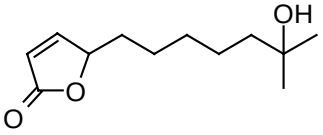

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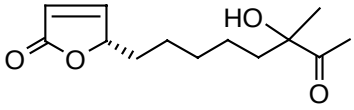

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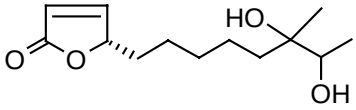
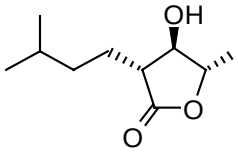


76

The number of the reduced low-molecular butyrolactones is much higher, and more is known about their biological relevance: Some are autoregulators and initiate pigment or antibiotic production, and also antibiotic or antiviral activity was reported. The butyrolides **77** - **79** have been isolated recently from a marine streptomycete (Cho *et al.*, 2001).



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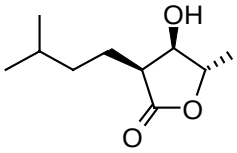

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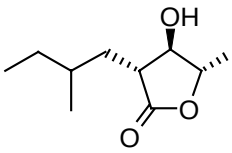

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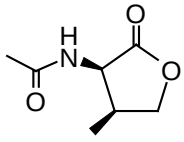
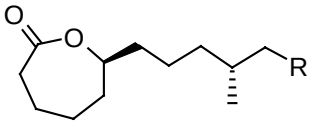


80

The related acylamino-butyrolides (acyl-homoserinlactones) have got much more attention due to their function as quorum sensing molecules. After γ-hydroxynorvaline lactone, N-acetyl-γ-hydroxyvaline lactone (**80**) provides now the third type of a 3-substituted homoserinelactone from bacteria (Hernandez *et al.*, 2000a).

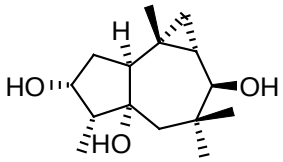
Simple seven-membered lactones are relatively rare in nature, in contrast to their frequently occurring six-membered homologues. The feigrisolides **60a**, **60b** and **62** have already been mentioned; (6*R*)-10-methyl-6-undecanolide (**81a**) and (6*R*,10*S*)-10-methyl-6-dodecanolide (**81b**) are recent examples from a marine *Streptomyces albogriseolus* isolate B6007 (Stritzke *et al.*, 2004). Both lactones showed a weak antifungal and a pronounced antitumor activity.



81a: R = H
81b: R = Me

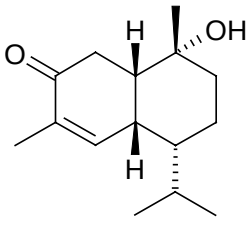
Terpenes

Terpenes are believed to be rare in bacteria and are more typical constituents of fungi. A number of sesquiterpenes has, however, been found among the odour components of *S. citreus* (Pollak *et al.*, 1996) and other streptomycetes. Africantriol (**82**) from *Streptomyces* sp. GT 061115 is another bacterial example (Hu *et al.*, 2003), although this compound has been isolated previously from the marine invertebrate *Lemnalia africana*.

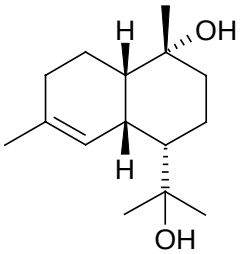


82

The chemical investigation of the marine-derived *Streptomyce*s sp. QD491 from Qingdao coast (China) delivered four sesquiterpenes, namely 10α-hydroxyamorph-4-en-3-one (**83**), 10α,11-dihydroxyamorph-4-ene (**84**), 10α,14-dihydroxyamorph-4-en-3-one (**85**), 8α,10α,11-triydroxyamorphan-3-one (**86**), and some trivial compounds (Wu et al., 2005); **84** had previously been obtained from *Taiwania cryptomerioides* Hayata. It exhibited moderate activity in the brine shrimp lethality test [He *et al*., 1997].



83



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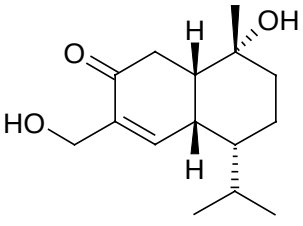

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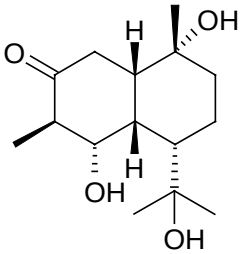
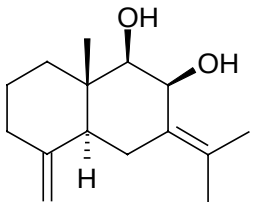


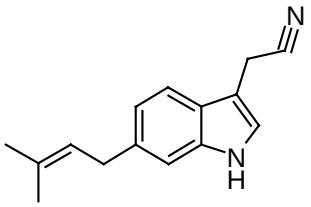
86

From the staurosporine producing streptomycete QD518 from the same shore in China, selina-4(14),7(11)-diene-8,9-diol (**87**) was obtained [Wu *et al*., 2005].

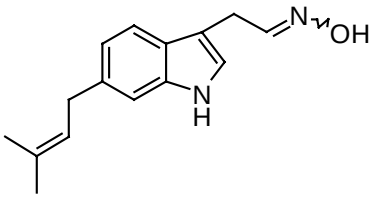


87

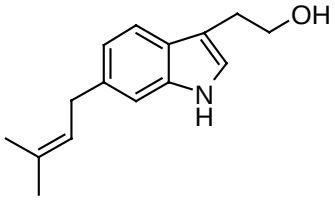
Recently, the cytotoxic indoles **88** - **90** having isoprenoid side chains were reported (Sanchez Lopez *et al.*, 2003). They were produced by *Streptomyces* sp. BL-49-58-005 isolated from marine invertebrates, and are obviously products of a mixed biosynthesis. The nitril **88** can be derived by dehydratation of the oxime **89**, whose hydrolysis and reduction would deliver **90**.



88

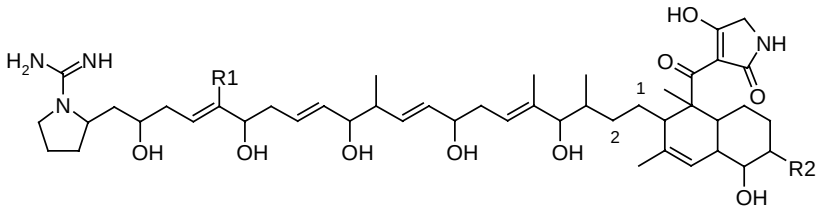


89



90

The irregular methylation pattern of the TPU-0037 components (**91a** - **91d**) (Furumai *et al.*, 2002) with an interesting activity against methicillin resistant *Staphylococcus aureus* strains from a marine *Streptomyces platensis* isolate TP-A0598 indicates that these compounds are certainly not terpenoids. Although the nitrogen containing terminal octahydronaphthalene unit occurs in at least 10 *Streptomyces* metabolites, this structural element is more typical for fungi like *Alternaria*, *Fusarium*, *Phoma* spp. and others. It is one of the rare cases where the bacterial and fungal metabolism results in related structures, and it should be of interest if also the gene sequences of their synthases reflect these similarities.

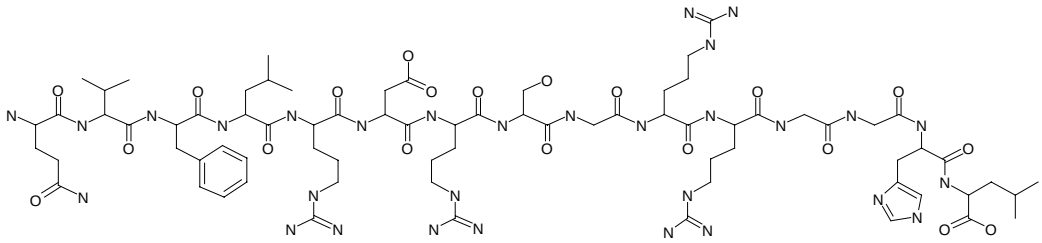


91a: R^1 = H, R^2 = OH; TPU-0037-A
91b: R^1 = Me, R^2 = H, $\Delta^{1,2}$; TPU-0037-B
91c: R^1 = H, R^2 = H; TPU-0037-C
91d: R^1 = Me, R^2 = H; TPU-0037-D

Peptides

Most of the about 500 *Streptomyces* peptides are cyclic and contain further rare structural elements such as chromophors or uncommon amino acids. In this respect, the puromycin re-

sistance proteins **92** - **94** from *Streptomyces* sp. AP77 are quite normal (Woo *et al.*, 2002). They show activity against *Pythium porphyrae*.



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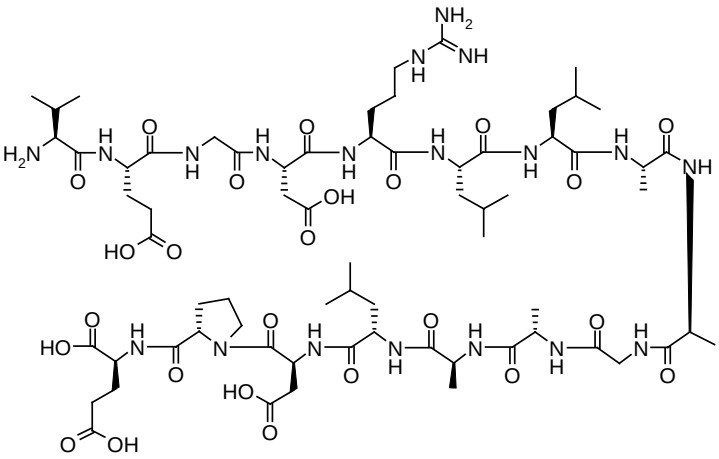

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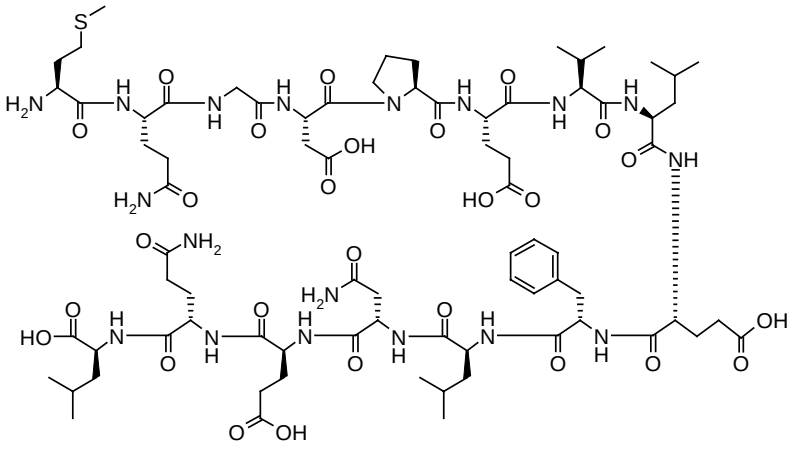
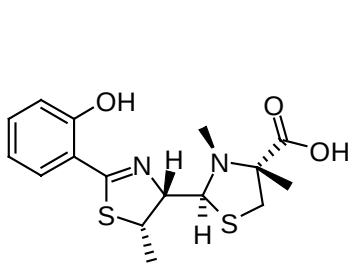


94

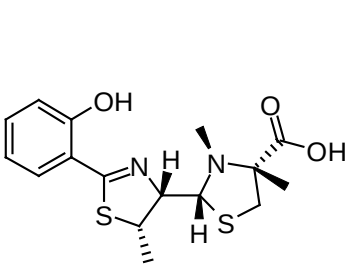
Heterocycles

While the bithiazolyl structural element is found often in a broad variety of microorganisms and even in cyanobacteria, the hexahydrobithiazolyl core of the antibiotics watasemycins A (**94a**) and B (**94b**) from *Streptomyces* sp. TP-A0597 is fairly rare in nature (Sasaki *et al.*, 2002). It can be assumed that **94a** and **94b** are good ligands of iron(III) and bivalent metals, in

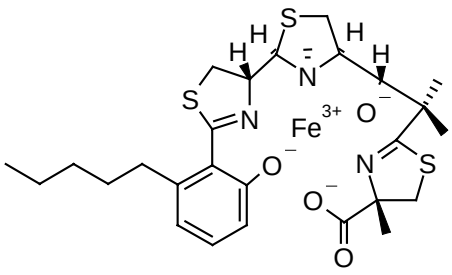
parallel to the closely related micacocidin C (**96**) from a terrestrial *Pseudomonas* sp. (Kobayashi *et al.*, 1998a,b).



95a

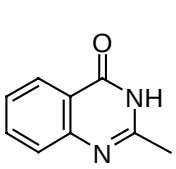


95b



96

Small heterocyclic compounds like the quinazolines **97** and **98** are found frequently (Speitling, 1998; Schroeder, 2002) and are not restricted to the marine habitat (Maskey *et al.*, 2004b).



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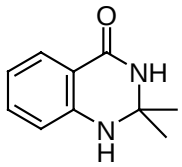
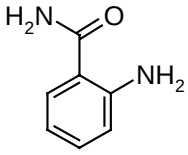


98

Others

Two glycolipids (**155**) from marine streptomycetes are mentioned below. Also a number of small molecules (**99 - 103)** (Laatsch, unpublished results) belonging to different metabolic pathways was isolated from various sources, where no obvious biological activity is known (Maskey, 2001; Shaaban *et al.*, 2002). If these compounds are shunt products, side products of the primary metabolism or just metabolic waste, has still to be found out.



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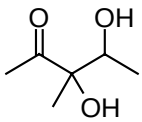

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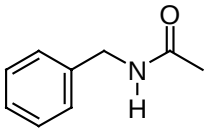

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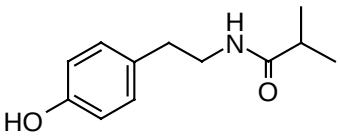

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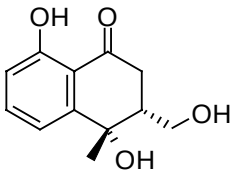
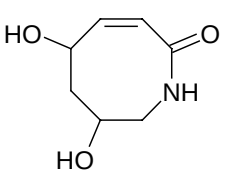


103

From the producer of the selinane **87**, the simple 5,7-dihydroxy-5,6,7,8-tetrahydroazocin-2(*1H*)-one (**104**) was obtained [Wu et al., 2005]. It is the first azocin-2-one from micro-organisms and remarkably unstable: On standing in chloroform, a quantitative transformation into 1,2-dihydro-pyrrolizin-3-one (**105**) and the trimer **106** was observed, probably due to the influence of HCl, which induces a transannular reaction of **104**.



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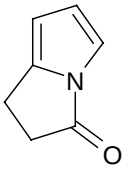

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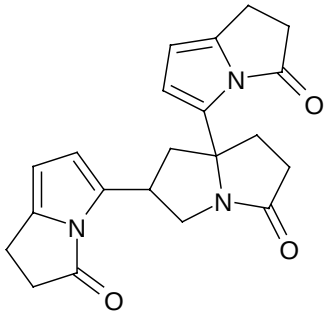
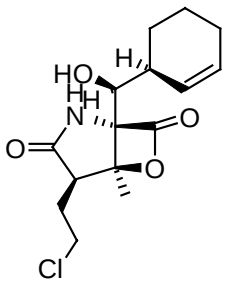


106

Rare Actinomycetes

***Salinospora* sp.**

Morphologically indistinguishable from the *Micromonosporae* are strains of the new sea water dependent genus *Salinospora* (Fenical *et al.*, 2002), which can be differentiated only by means of genetic markers. The first species was found by cytotoxicity screenings, which lead to the salinosporamides (Feling *et al.*, 2003; Fenical *et al.*, 2002) A (**107**), B (**108**) and E (**111**), novel ß-lactones with some relation only to omuralide (**114**) from *Streptomyces lactacystinaeus* (Tomoda *et al.*, 2000). Due to the high reactivity of the strained ß-lactone ring, the other salinosporamides (C, **109**; D, **110**; F, **112**; G, **113**) are formed as artifacts during work-up (Fenical, 2003). Salinosporamide A (**107**) is active against colon cancer in the remarkable low concentration of 10 ng/ml.



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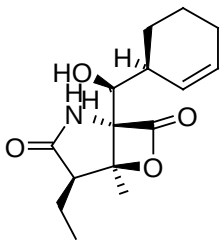

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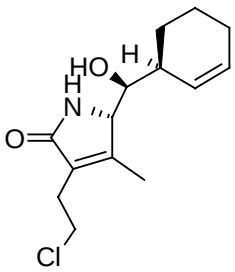

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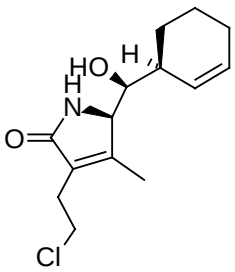

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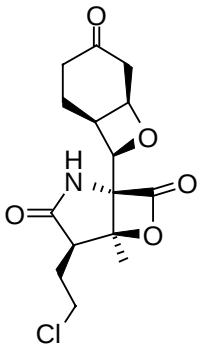

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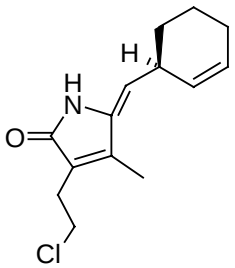

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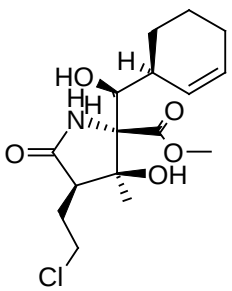

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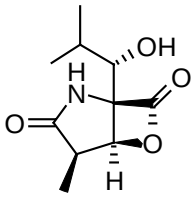
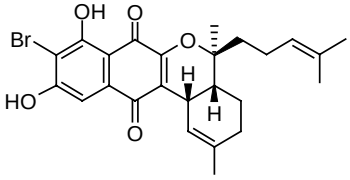


114

Another marine filamentous bacterium (strain CNH-099) delivered several partially brominated and moderately cytotoxic naphthoquinones with a terpenoid ring extension (Hardt *et al.*, 2000), namely isomarinone (**115**), hydroxydebromomarinone (**116a**), methoxydebromomarinone (**116b**), and neomarinone (**117**). Only the terrestrial naphterpines and naphthgeranines are similar (Wessels *et al.*, 1991; Shinya *et al.*, 1992).



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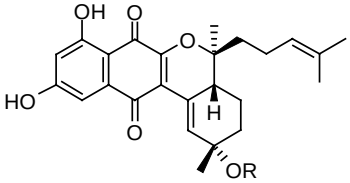
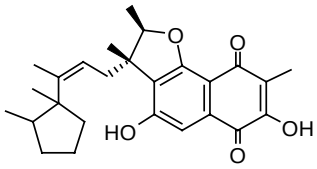
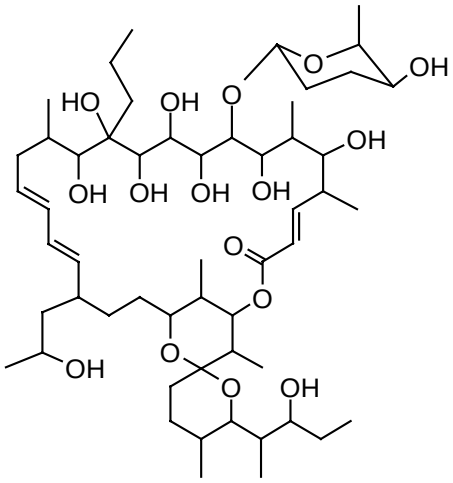


116a: R = H
116b: R = Me

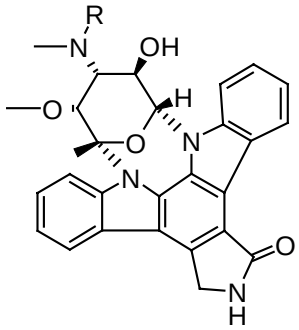


117

The cytotoxic IB-96212 (**118**) from *Micromonospora* sp. L-25-ES25-008 is a common oligomycin derivative (Canedo *et al.*, 2000; Fernandez-Chimeno *et al.*, 2000),



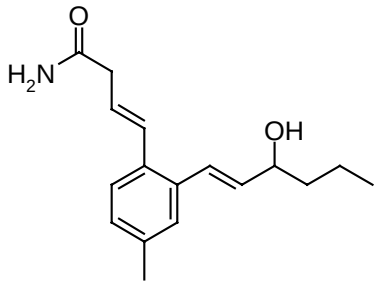
118

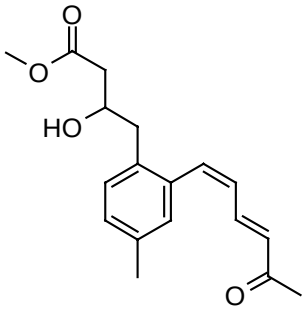


119a: R = H
119b: R = Me

and also staurosporines are frequently found in terrestrial and marine streptomycetes. It can be speculated therefore that the staurosporines found in ascidians as *Eudistoma* sp. are synthesized by microbial symbionts and are just accumulated or modified by the host (Schupp *et al.*, 1999). It is of interest that two new derivatives, 5'-hydroxystaurosporine (**119a**) and 4'-N-methyl-5'-hydroxystaurosporine (**119b**) have now been isolated from *Micromonospora* sp. L-31-CLCO-002 (Hernandez *et al.*, 2000b).

Compounds related with the recently described marine lorneamides A (**120a**) and B (**120b**) (Capon *et al.*, 2000) are the terrestrial serpentemycins (Vertesy *et al.*, 2004), serpentene, demetric acid, the marine ester **121** (Grzeganek, 2003), and the rubrenoic acids, the latter from the marine *Alteromonas rubra* (Holland *et al.*, 1984). All these compounds displayed a weak antibacterial activity, the rubrenoic acids were also bronchodilatators.

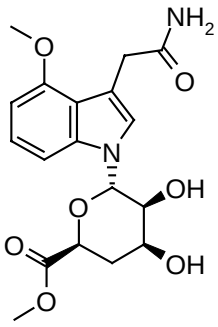




120a
120b: CO instead of OH

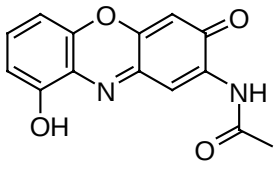
121

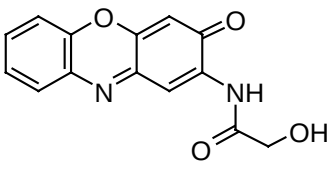
Kahakamide A (**122a**) (Schumacher *et al.*, 2001) from *Nocardiopsis dassonvillei* is the 4-methoxy derivative of neosidomycin from *S. hygroscopicus* and formally the partial hydrolysis product of the nitril SF-2140 from *Actinomadura albolutea* sf-2140 (FERM-p 5704), kahakamide B (**122b**) is the corresponding amide of **122a**. All these compounds are fascinating, as two very rare structural elements are coming together, the 4-methoxy indole, and the indole-N-glycoside. The kahakamides are having a weak antibacterial activity.

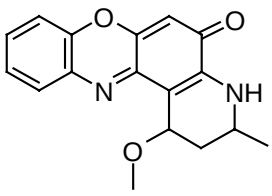


122a: R = Me
122b: R = NH_2

The orange phenoxazin-3-one chromophor of the chandrananimycins A-C (**123** - **125**) (Maskey *et al.*, 2003b) originates biosynthetically from an oxidative coupling of two molecules *o*-aminophenol and further derivatisation. Compounds of this type are rather common in bacteria, the actinomycins among them have certainly found the strongest interest (Mauger *et al.*, 2005, in press). The chandrananimycins from *Actinomadura* sp. M045 have a significant cytotoxicity (IC_{70} < 2 µg/ml), **125** is in addition antibiotically active.

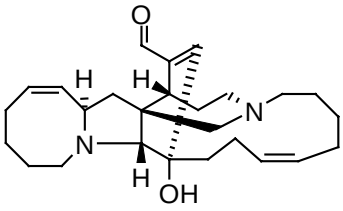




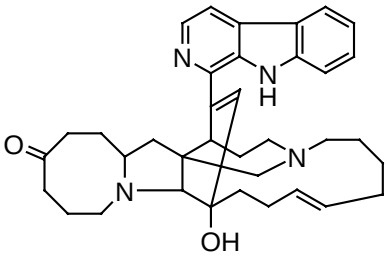


123 **124** **125**

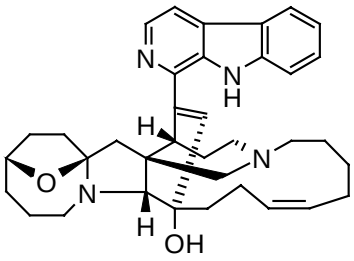
Ircinal (**126a**), ircinol (**126b**), several manzamines (**127** - **130**), and neokauluamine (**131**) have been obtained from the same marine *Micromonospora* sp. M42 isolated from a sponge (Hill *et al.*, 2004). The co-existence of these compounds indicates that the ß-carboline derivatives **127** - **130** are formed from ircinal (**126a**) and tryptamines *via* Pictet-Spengler reactions.



126a
126b: OH instead of CHO



127



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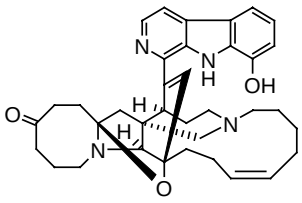

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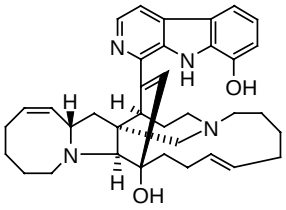

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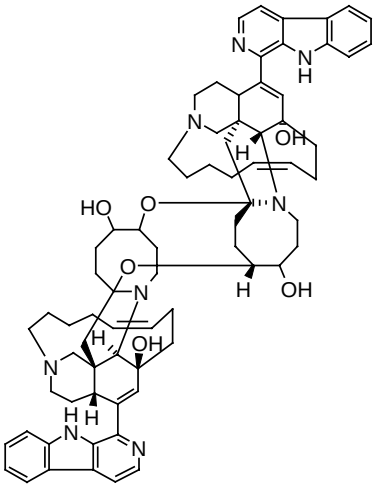
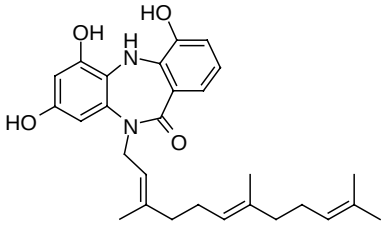


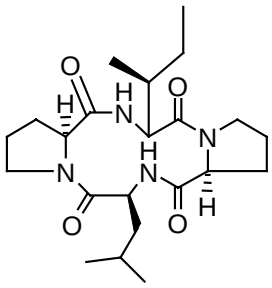
131

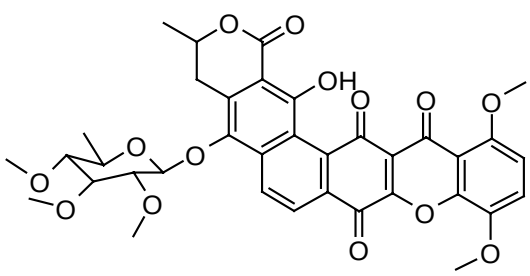
About 100 diazepines have been isolated from microbial sources, however, bacterial dibenzodiazepines were unknown so far. A first compound of this type, diazepinomicin (**132**) has been isolated now from a *Micromonospora* strain (Charan *et al.*, 2004). Interestingly, the dibenzodiazepine core is linked to a farnesyl side chain.



132

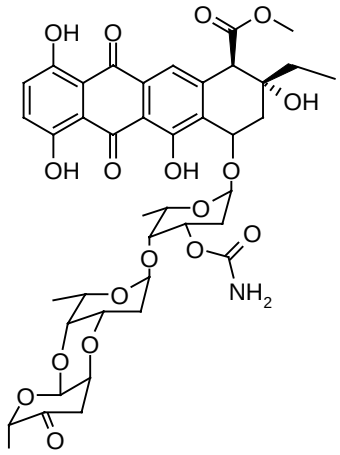
Whereas the tetrapeptide **133** from a *Nocardiopsis* sp. is one of about 40 microbial tetrapeptides and a sequence isomer of fenestine A from the sponge *Leucophloeus fenestrata*,

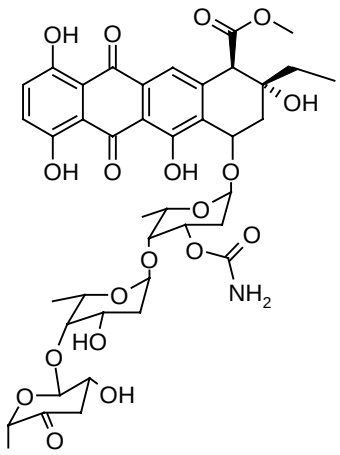




133 **134**

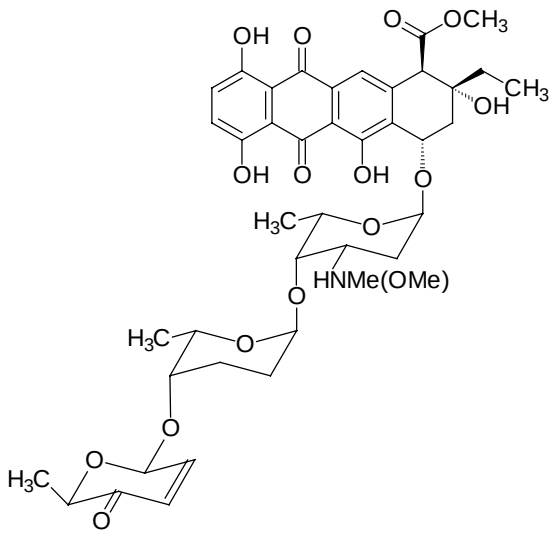
the cytotoxic and antibacterial quinone IB-00208 (**134)** from an *Actinomadura* sp. is unique so far (Malet-Cascon *et al.*, 2003). The next parallels are the terrestrial cervinomycins and the citreamicins.

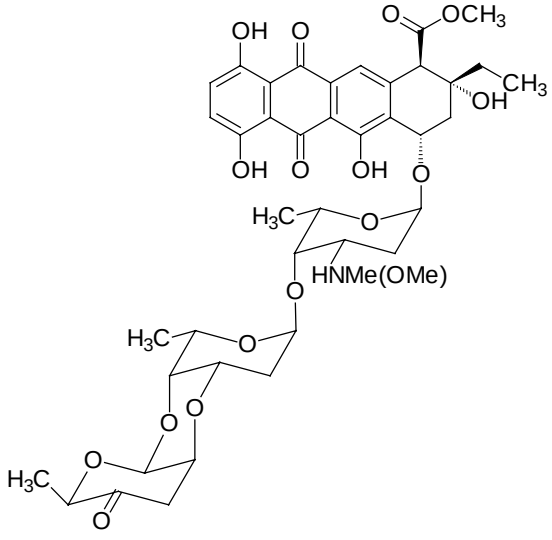




135 **136**

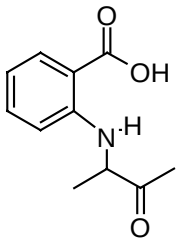
Kadamycin A (**137**) with the novel hydroxylamino sugar kadamalose is a *nor*-N-methoxy-cinerubin R, and kadamycin B (**138**) is the corresponding spartanamycin A derivative (Maskey *et al.*, 2005). The only other hydroxylaminosugar-glycoside is dactylocycline A from a *Dactylosporangium* sp. (Tymiak *et al.*, 1992; Wells *et al.*, 1992). Hydroxylamino sugars may be precursors of the various nitroso and nitro sugar derivatives as in dactylocycline B.





137 **138**

The 3-amino-2-butanone residue in barycine (**139**, 2-(1-methyl-2-oxo-propylamino)-benzoic acid) from *Streptomyces* sp. B6005 is extremely rare among the microbial metabolites and was found so far only in maniwamycin A (Nakayama *et al.*, 1989) and 7-(1-methyl-2-oxopropyl)streptonigrin (Wang *et al.*, 2002).



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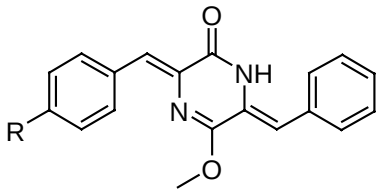


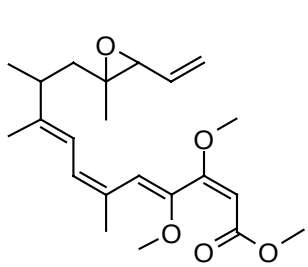
140a: R = OMe
140b: R = H

The new methoxy derivative methoxyneihumicin (**140a**) has been obtained from an uncharacterised marine bacterium NPS0002/0014 (Macherla *et al.*, 2002), which might be related with *Micromonospora neihuensis*, the producer of the cytotoxic and antifungal neihumicin (**140b**) (Wu *et al.*, 1988; Yang *et al.*, 1988).

Marine gliding Bacteria and Myxomycetes

Especially due to the work of Hoefle and Reichenbach it is known that gliding bacteria (especially myxobacteria and myxomycetes) are extremely potent producers of highly active and structurally unique natural products. It was an obvious idea therefore, also to investigate such types isolated from marine samples. Only very few reports, however, were published so far.

The linear antifungal tetranes haliangicin A – D (**141 - 145**) from the NaCl requiring myxobacteria *Haliangium leuteum* AJ13395 seem not to have further parallels (Fudou *et al.*, 2001; Kundim *et al.*, 2003), and also the diterpenoid verrucosan derivatives **146a,b - 148** from *Saprospira grandis* (ATCC 23116) belonging to the CFB cluster are unique (Spyere *et al.*, 2003).



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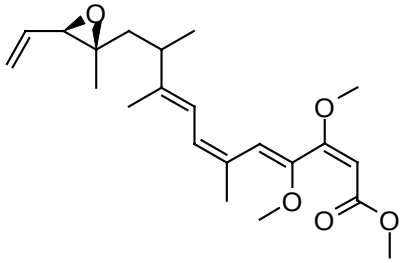

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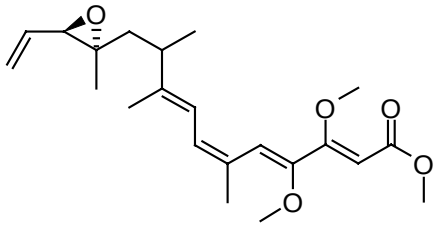

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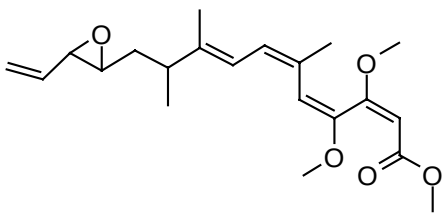

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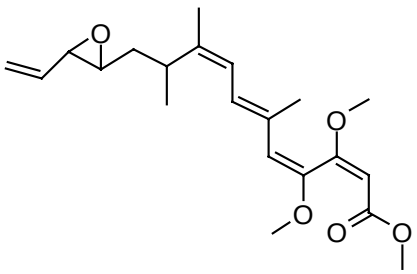

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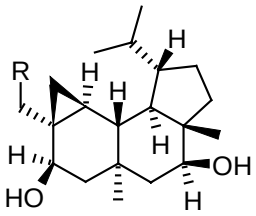
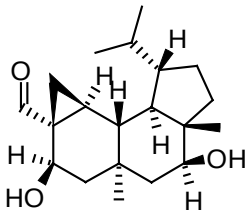


146a: R = H
146b: R = OH



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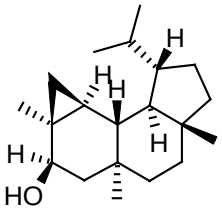
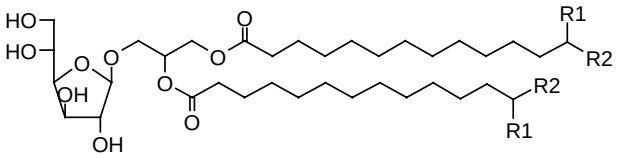


148

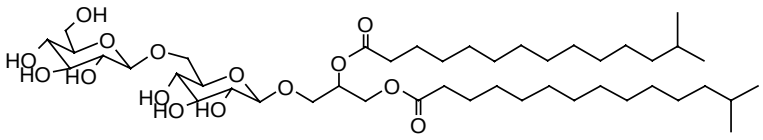
Other Marine Bacteria

Among the metabolites from marine bacteria not belonging to actinomycetes or myxomycetes, two large groups can be distinguished, the peptides and the glycolipids. Wicke *et al.* (2000) isolated from a microbacterium isolated from a Mediterranean sponge a complex mixture **149a – 153** of diacylglyceroglycosides, which differ in the sugar part and the acyl pattern. The monosaccharides **149a/b** were identified as glucofuranosides, whereas the disaccharides are gentiobiosyl-diglycerides (**150**) or glucopyranosyl-mannopyranosides (**151 - 153**) with α- or β-configuration. Similar (**154**, Lurtz *et al.*, 2002) or identical compounds have also been isolated from other sources, e.g. from *Bacillus pumilus* associated with the ascidian *Halocynthia aurantium* (Kalinovskaya *et al.*, 2000).

The lysophosphatidyl inositols 1 and 2 (**155**) were obtained from streptomycetes (Cho *et al*., 1999), however, the phosphatidyl glycerol **156** with an interesting cyclopropanated acid was found in a marine *Pseudomonas* sp. from the sponge *Homophymia* sp. (Bultel-Ponce 1999). The more complex 1,3-diphosphatidylglycerols (Wicke *et al.*, 2000) **157** and **158** have been isolated from the a *Microbacterium* sp. (actinomycete); they exhibited a strong antitumor activity.



149a: $R^1 = R^2 = Me$
149b: $R^1 = H$, $R^2 = Et$



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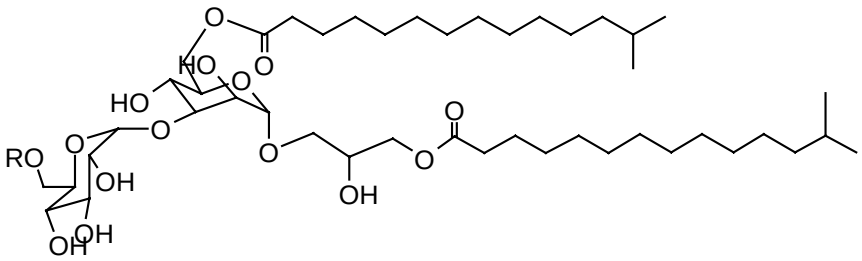
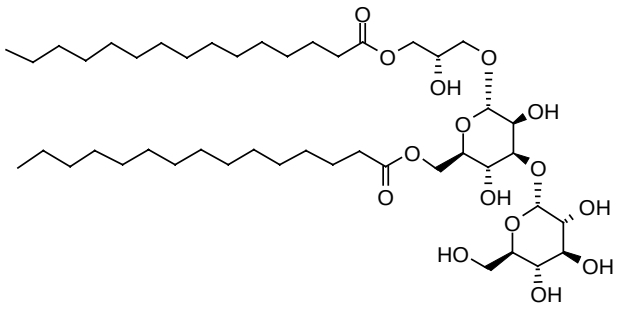


151a: R = H

151b: R = Ac



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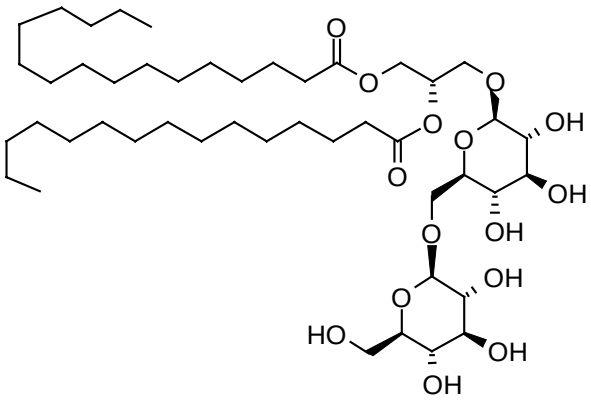

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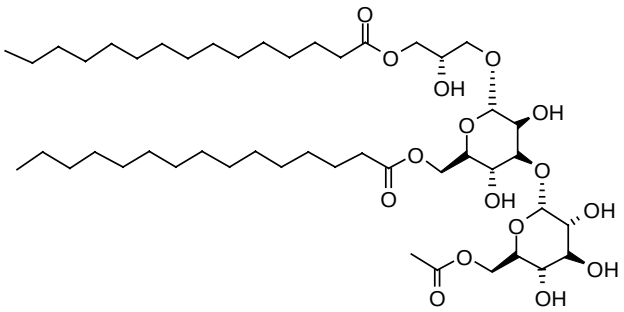

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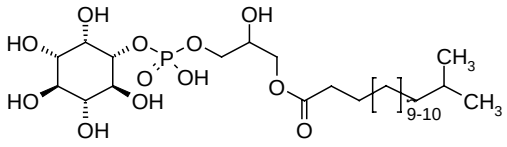

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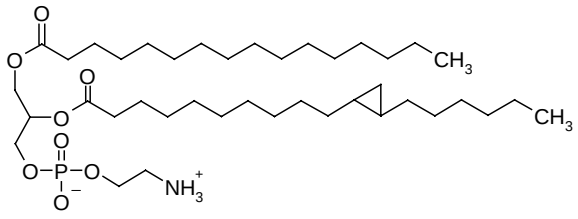

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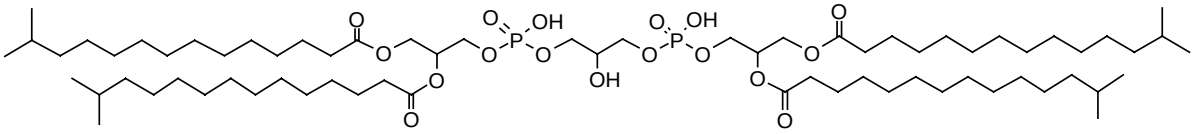

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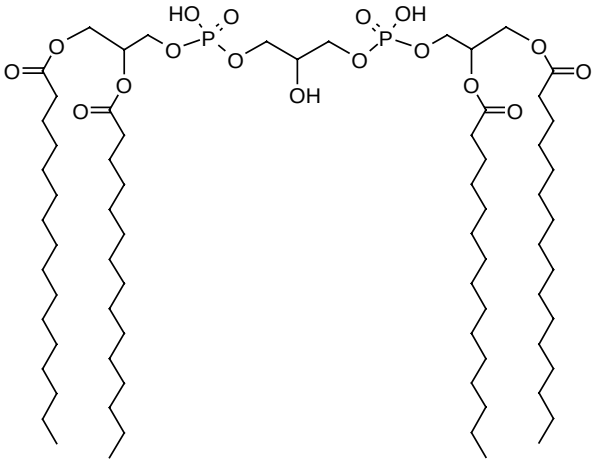
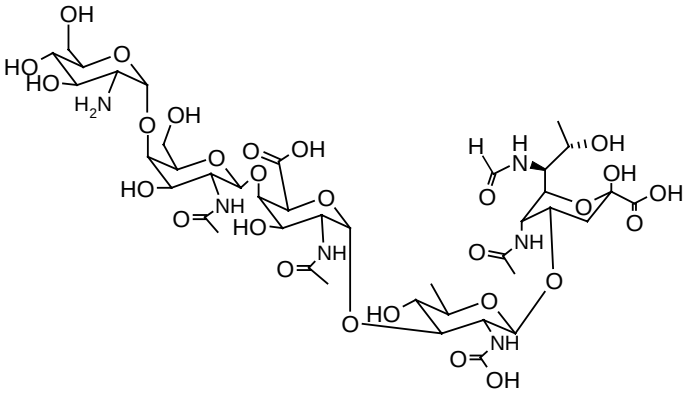


158

The acidic polysaccharide **159** was obtained from a marine *Pseudoalteromonas distincta* strain KMM 638 isolated from a sponge (Muldoon *et al.*, 2001), the O-specific polysaccharide **160** comes from *Alteromonas marinoglutinosa* NCIMIB 1770 (Komandrova *et al.*, 2001).



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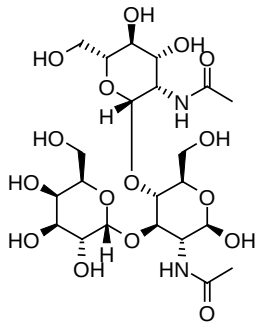
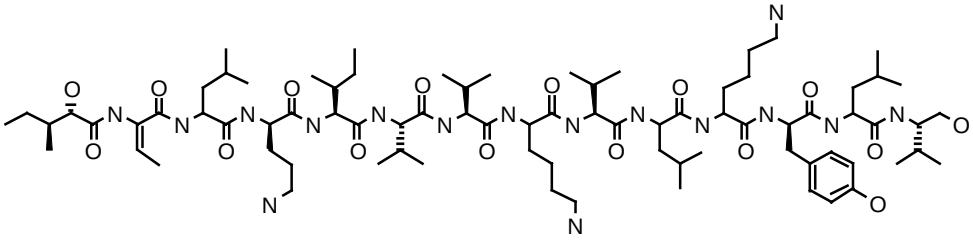


160

The recently published bacterial peptides can be summarised into three groups, the linear acylpeptides, the cyclopeptides and some very sulfur-rich thiazolylpeptides. The dehydropep-

tide bogorol A (**161**) from a *Bacillus* sp. is active against methicillin resistant *Staphylococcus aureus* and vancomycin resistant enterococci (Barsby *et al.*, 2001), the N-acylated aquachelins A-D (**162a-d**) from the marine bacterium *Halomonas aquamarina* strain DS40M3 are novel siderophores (Martinez *et al.*, 2000).



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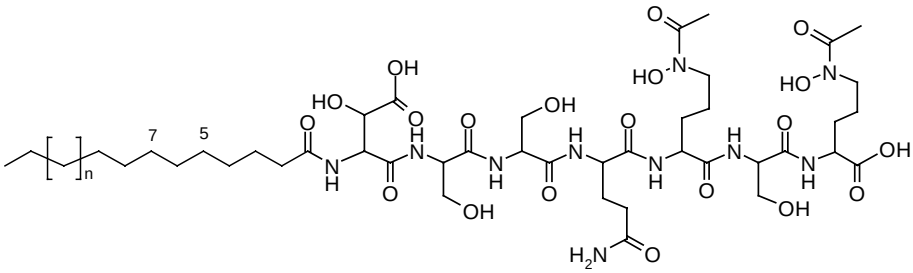
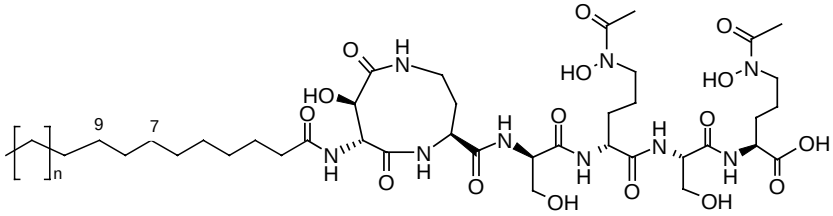


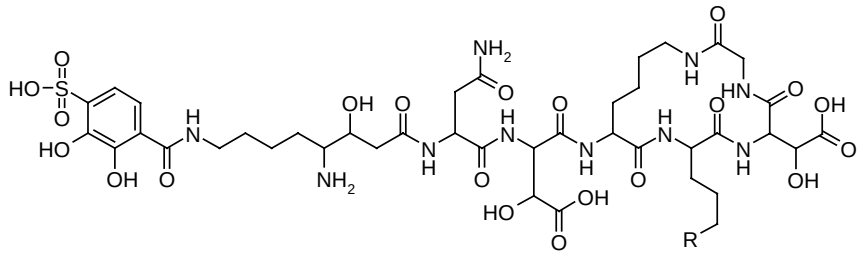
162 a: n = 1, *cis*-$\Delta^{5,6}$
162b: n = 1
162c: n = 3, *cis*-$\Delta^{7,8}$
162d: n = 3

The marinobactins A-C, D1, D2, and E (**163a - f**) from the new genus *Marinobacter* resemble the aquachelins, however, are characterised by a unique α,γ-cyclodipeptide core of ß-hydroxyaspartic acid and 2,4-diaminobutyric acid (Martinez *et al.*, 2000). They are siderophores as well.



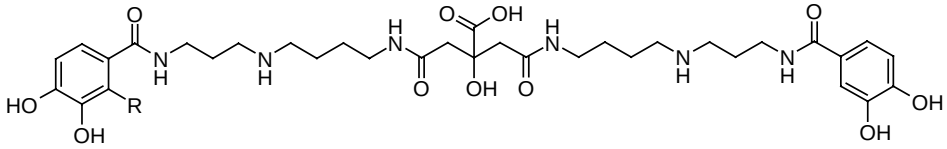
163a : n = 1
163b : n = 3, *cis*-$\Delta^{7,8}$
163c : n = 3
163d : n = 5, *cis*-$\Delta^{9,10}$
163e : n = 5, *cis*-$\Delta^{7,8}$
163f : n = 5

The pseudoalterobactins A (**164a**) and B (**164b**) are siderophores from the marine *Pseudoalteromonas* sp. KP20-4 (Kanoh *et al.*, 2003). Their carboxybenzene sulfonic acid residue is unique in nature.



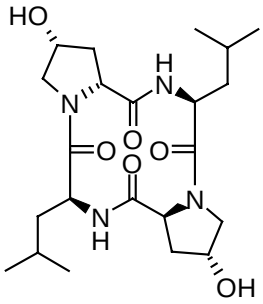
164a: R = CH_2-NH_2
164b: R = NH-C(=NH)-NH_2

Petrobactin (**165a**) from *Marinobacter hydrocarbonoclasticus* is certainly not a peptide, however, has some similarity with **164a** (Barbeau *et al.*, 2002; Bergeron *et al.*, 2003). The combination of the chelating properties of citric acid with a second chelator is rather common in nature and found e.g. in aerobactin, schizokinen, actinoferrin, etc. The combination with a catechol siderophor, however, is unique so far. Petrobactin sulfonate (**165b**) has been recently isolated from the oil-degrading marine bacterium *Marinobacter hydrocarbonoclasticus* (Hickford et al., 2004).



165a: R = H
165b: R = SO_3H

The cyclopeptide **166** (Mitova *et al.*, 2003) from a *Pseudomonas* sp. from the sponge *Ircinia muscarum* and the weakly cytotoxic halolitoralins A (**167**), B (**168**) and C (**169**) from *Halobacillus litoralis* YS3106 resemble the previously discussed peptides (Yang *et al.*, 2002). Their structures were elucidated by extended NMR, MS and chiral HPLC measurements.



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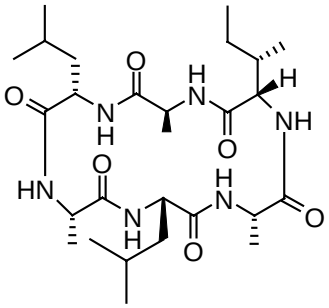

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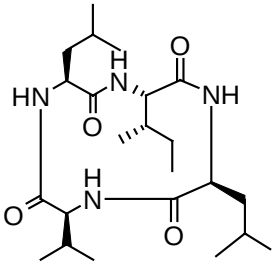

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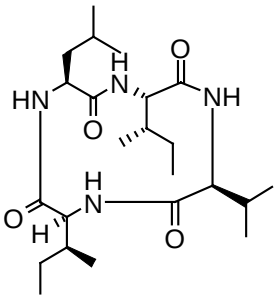

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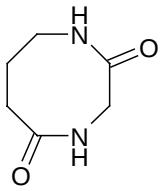

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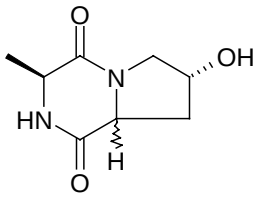

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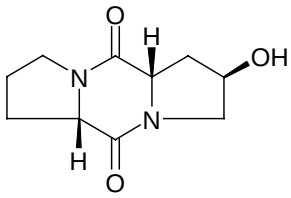

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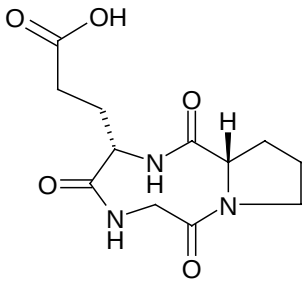

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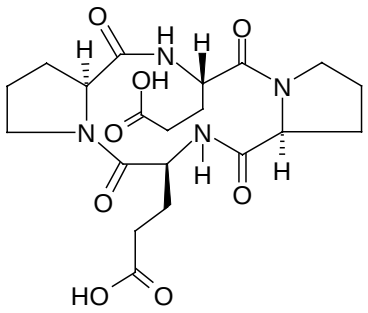

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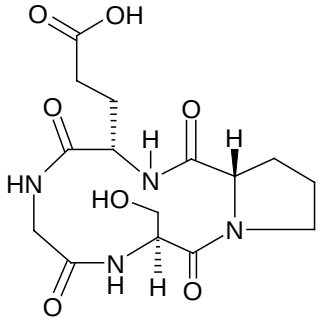
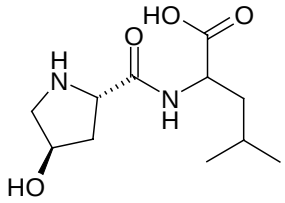


175

Mitova *et al*. (2004) described recently a further series of cyclopeptides **170** - **175**. Besides **170**, all of them contain proline or hydroxyproline, which may give rise to the idea that nutrient constituents were incorporated. This may also be valid for the dipeptide **176** and the ornithine derivative **177** (Hernandez, 2004).



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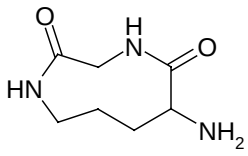

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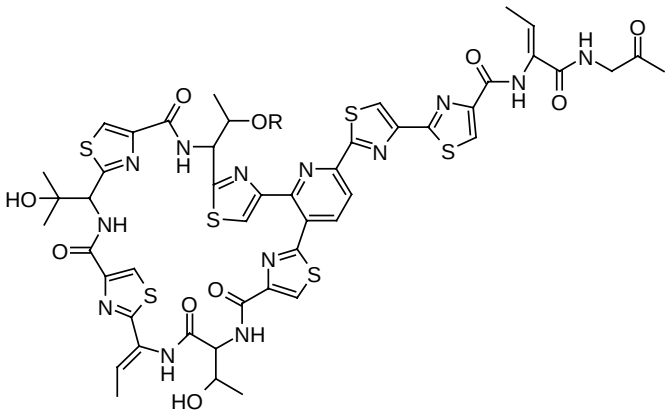
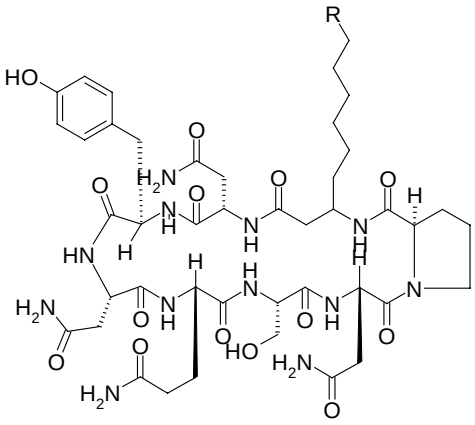


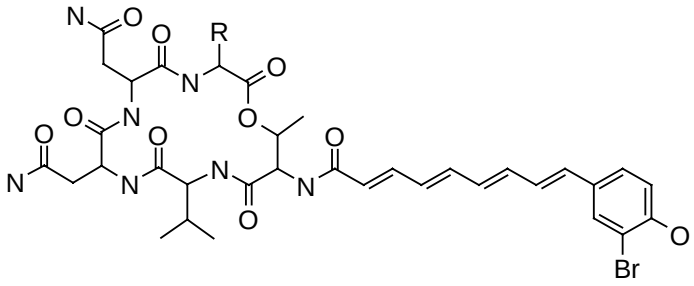
178a: R = H
178b: R = Me



179a: R = *n*-C_5H_{11}
179b: R = Et
179c: R = 2-Bu

The mixirins A-C (**179a** – **179c**) from a marine *Bacillus* sp. are related to the iturins, however, in the latter, Ser and Pro have changed places (Zhang *et al*., 2004). The long-chain β-aminoacyl residue is a common constituent of many further cyclopeptides, e.g. the bacillomycins and mycosubtilins.

From a further bacillus (*B. cereus* QN03323 from a marine sponge), the thiazolyl-dehydropeptides YM-266183 (**178a**) and YM-266184 (**178b**) were isolated. They are new members of a large group of related compounds, which are widespread over various bacterial taxa (Nagai *et al.*, 2003; Suzumura *et al.*, 2003) and are highly active against Gram-positive bacteria, however, not against Gram-negative microbes.

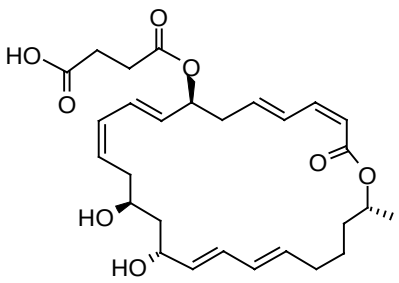


180a: R = *i*-Bu
180b: R = 2-Bu

Two unusual chrompeptides alterochromide A and B (**180a**/**b**) were isolated as an inseparable mixture from a *Pseudoalteromonas piscicida* strain KMM 636 isolated from the sponge *Fascaplysinopsis reticulata* collected at the Greet Barier Reef (Speitling *et al.*, 2005). The only related chromopeptide is (the halogen-free) myxochromide A from a terrestrial myxomycete (Trowitzsch-Kienast *et al.*, 1993).

Low-Molecular Weight Compounds

At least 17 macrolactines are known from a deep-sea *Bacillus*. Some members of this series were already isolated in 1989 by Gustafson *et al.* (1989), further compounds were added in 2000 (**181**, **182**) (Jaruchoktaweechai *et al.*, 2000) and 2001 (**183** - **189**) (Nagao *et al.*, 2001). All macrolactins exhibit a weak antibacterial activity.



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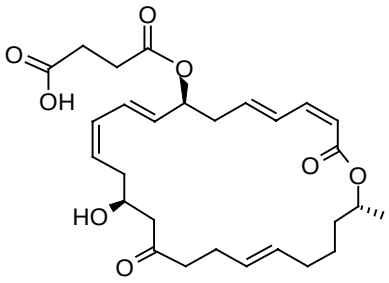

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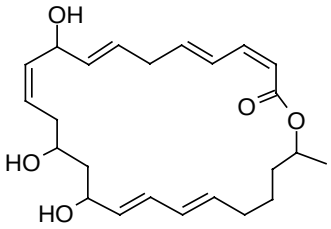

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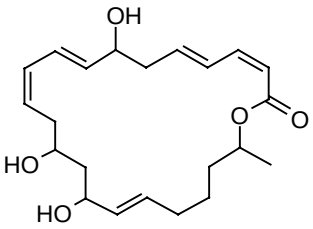

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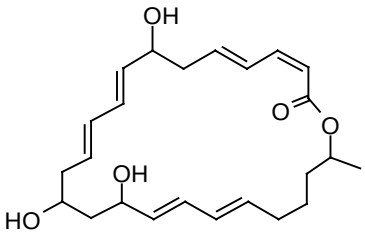

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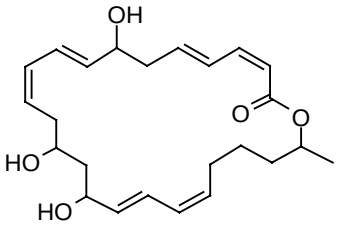

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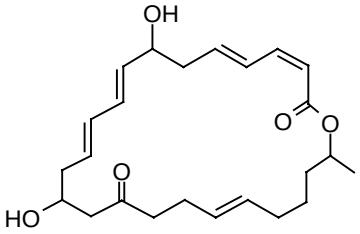

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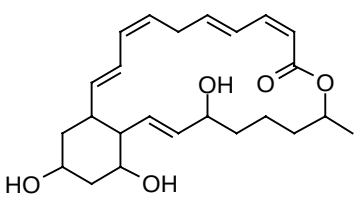

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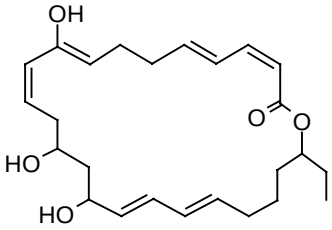
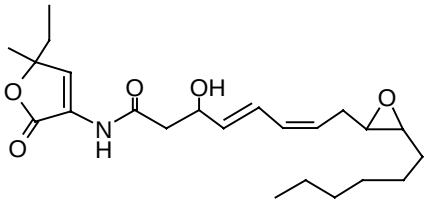


189

Further korormicins **190** – **194** have been isolated from a marine *Pseudoalteromonas* sp. F-420 (Yoshikawa *et al.*, 2003). As **3**, they are selective inhibitors of the primary sodium pump and are active against obligate marine Gram-negative bacteria. It is of interest that **193** contains bromine.



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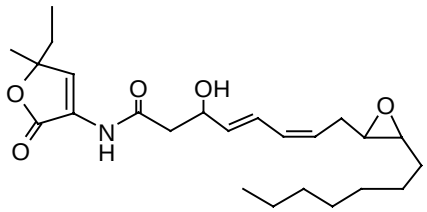

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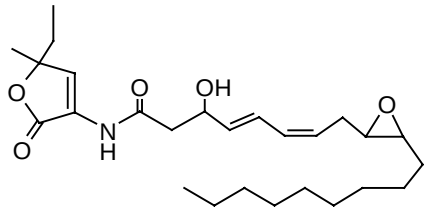

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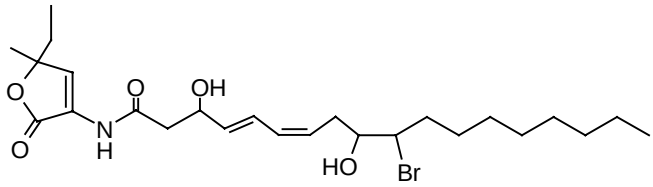

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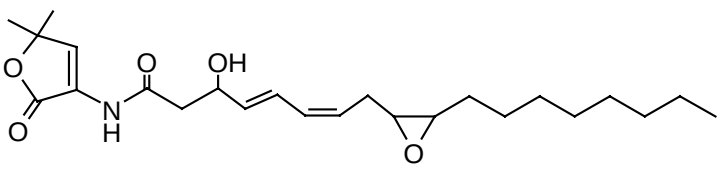

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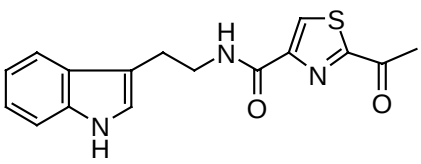
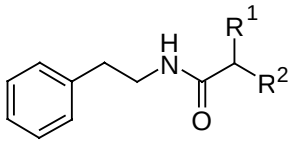


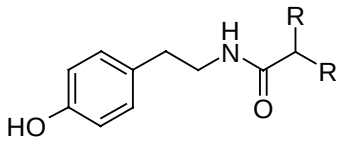
195

Acyl-thiazolylcarboxamides had been found before only in the few bacitracins from *Bacillus subtilis* and *B. lichenformis*. The recently described simple derivative bacillamide (**195**) from another *Bacillus* sp. showed a reasonable activity against the dinoflagellate *Cochlodinium polykrikoides* with an LC_{50} value of 3.2 µg/ml (Jeong *et al.*, 2003).

A number of ß-phenylethylamides **196a - f** had been isolated from a marine *Bacterium* sp. GBF 102b (Maskey *et al.*, 2002e), and later on, these and further amides **196g - k** were obtained from many other marine and also terrestrial bacteria (Stritzke, 2003 and unpubl. results). It was surprising that these simple compounds showed a pronounced phycotoxicity (MIC 12.5 µg/ml) and even more, that closely related compounds had been patented as herbicides long ago (Zaweski, 1965; Kirino *et al.*, 1983).



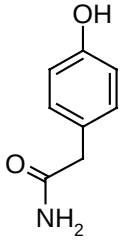
196	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**I**	**j**	**k**
R^1	H	H	Me	H	H	Me	H	H	H	H	H
R^2	H	Me	Me	*i*-Pr	*n*-Bu	Et	Et	*n*-Pr	*i*-Bu	2-MeBu	*i*-Pent



197	**a**	**b**	**c**	**d**	**e**
R^1	H	H	H	Me	H
R^2	H	Me	*i*-Pr	Et	*i*-Bu

In contrast to most of the phenylethyl amides, the corresponding acyltyramines **197a-e** (Stritzke, 2003 and unpubl. results) from the North Sea bacterium Hel 11 were already known also from plants, the isobutyramide **102** from a streptomycete had been already described above. The amide **197b** is a moderate inhibitor of the porcine aldose reductase (Bahn *et al.*, 1998).

A further simple amide **198** was obtained from *Cytophaga* sp. strain AM13.1 (Shaaban *et al.*, 2002) and the marine *Vibrio parahaemolyticus* Bio249 (Veluri *et al.*, 2003).



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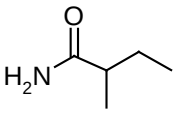

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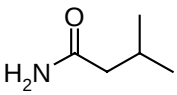
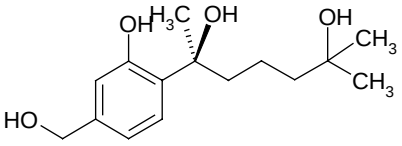


200

Small aliphatic compounds are certainly frequently occurring, however, difficult to isolate if other methods than GC are used. The amides **199** and **200** were obtained from *Cytophaga marinoflava* strain AM13,1 (Shaaban, 2004).

The isolation of the phenolic bisabolane sesquiterpenoid curcutetraol (**201**) is somewhat unexpected for a bacterium, as this type of compounds is typical for fungi. And indeed, Mülhaupt *et al*. (2005) isolated the same compound also from a marine fungus CNC-979. The corresponding acid, sydonic acid (**202**), is known from the terrestrial *Aspergillus sydowi*; also a cyclic form, sydowic acid, is known (Hamasaki *et al*., 1978).



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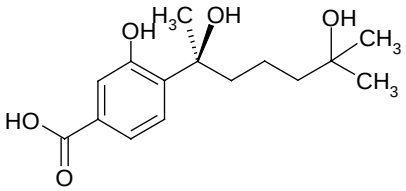
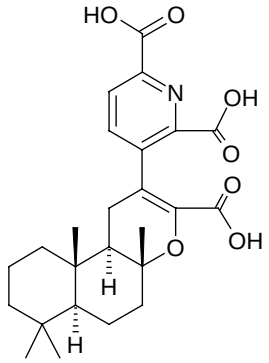


202

The combination of a diterpenoid basic structure with a pyridine ring is characteristic for fungi as well. Thallusin (**203**) with its labdane unit was isolated from an epiphytic marine Cytophaga so. YM2-23. With an activity of as low as 1 attogram/ml, it is probably the most active algal morphogenesisi inducer differentiation ever described (Matsuo *et al*., 2005). The similarity with a series of fungal metabolites such as Pyripyropene-E (**204**) is obvious (Tomoda *et al*., 1995). A related biological activity was, however, not reported for these compounds.



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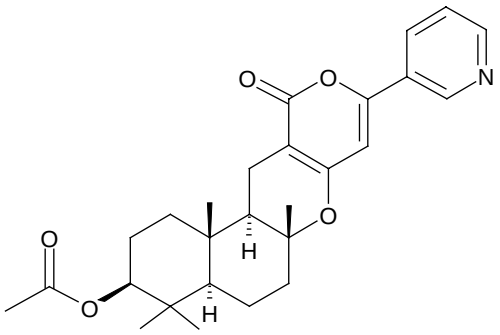
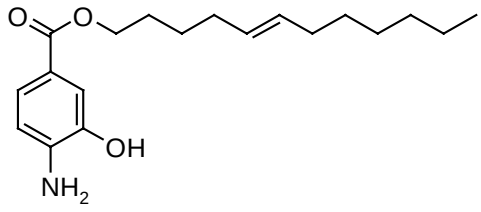


204

Three remarkable esters B-5354a-c (**205** - **207**) have been isolated from *Ruegeria* sp. SNAK 71896 and shown to be sphingosine kinase inhibitors (Kono *et al.*, 2000a,b). It should be mentioned that only one further occurrence of 4-amino-3-hydroxybenzoic acid (notonesomycin A) was reported before (Sasaki *et al.*, 1986a,b).



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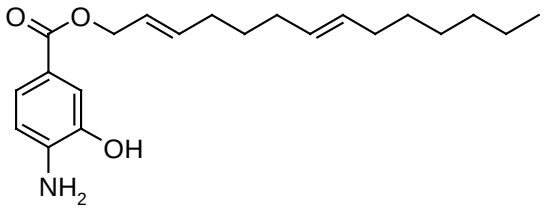

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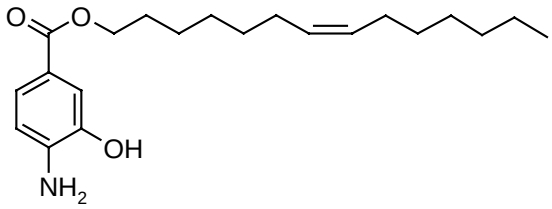
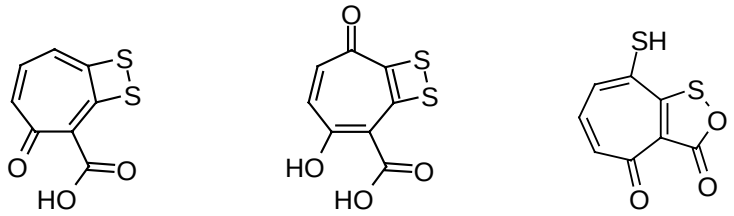


207

The *Roseobacter* clade seems to be specific marine and showed an interesting metabolic capacity in the past. Another impressive structure is that of the antibacterial tropodithietic acid (**208**), whose remarkable four-membered disulfide bridge was confirmed by X-ray analysis (Brinkhoff *et al.*, 2004; Liang, 2003). Isomers of **208** from a marine *Agrobacterium* and various *Pseudomonas* spp. have been described previously (Kawano *et al.*, 1997; 1998) as troposulfenin (**210**) and the tautomeric thioketone thiotropocin (Tsubotani *et al.*, 1984; Kintaka *et al.*, 1984; Cane *et al.*, 1992), respectively. Their structures should be revised now into **208** (Liang *et al.*, unpublished). A minor component of strain T5 was identified as the hydroxytropodithietic acid **209** (Liang, 2003).



208 **209** **210**

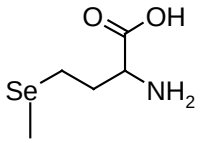
Thiazoloethanol (**211**a) has been isolated from an unidentified marine bacterium (M. Thorwest, A. Zeeck, unpublished). The corresponding methyl derivative sulfurol (**211b**) is a flavour component of *Boletales* (Rapior *et al.*, 1997) and part of vitamin B_1.

211a: R = H;
211b: R = Me

212

Another simple sulphur compound is the thioester **212**, an activated ester from the new species *Oceanibulbus indolifex* Hel 45 (Wagner-Döbler, 2004). This compound is new in nature, however, had been obtained previously by synthesis.

In the presence of selenomethionine (**213**) or selenoethionine (**214**), the selene-resistant marine *Bacillus* sp. No. 14 produced selenohomocystine (**215**), which is antibiotically active (Imada *et al.*, 2002).



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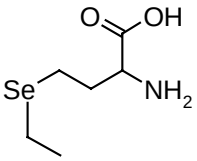

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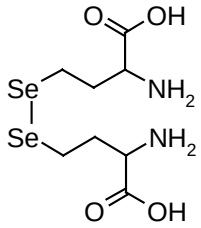
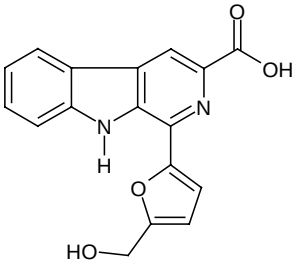


215

ß-Carbolines, among them some alkaloids of the harman group, have been firstly isolated from plants, however, are known now also from many other sources. They are formed by condensation of tryptamines amines with carbonyl compounds and cyclisation of the intermediate imines, a sequence, which is called Pictet-Spengler reaction. Phenethylamines deliver correspondingly isoquinolines. Some complex examples were obtained from streptomycetes, but as arylethylamines are degradation products of the amino acids phenylalanine, tyrosine and tryptophane, similar structures were also formed in other bacteria.

Flazin (**216**) was isolated first from Japanese sake and soy sauce and is the Pictet-Spengler product (after subsequent dehydrogenation) of tryptophane and furfural (Gessner *et al.*, 1988). The new ß-carbolin **217** can be derived in the same way from the naturally occurring 4-hydroxy-2-keto-butyraldehyde (Sparkes *et al.*, 1969); both ß-carbolines were obtained from an unidentified North Sea bacterium Bio215 (Shaaban, 2004).



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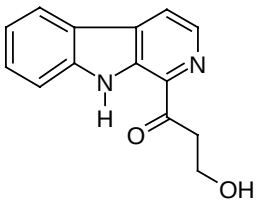
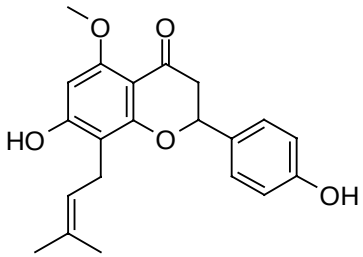


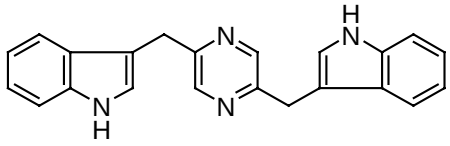
217

There are only a few examples that plant metabolites also occur in bacteria, the prenylated flavanone isoxanthohumol (**218**) from the North Sea isolate PIC009 being a new one (Shaaban, 2004). This compound was isolated first from the roots of *Sophora flavescens* (Kang *et al.*, 2000), however, occurs also in hop and is an inhibitor of cyclooxygenases and lipoxygenase, has estrogenic, trypanocidal and antiviral properties and may have a potential as cancer chemopreventive agent.



218

The list of simple pyrazine derivatives has been extended by the new member **219** from *Cytophaga* sp. AM13.1, which was inactive against bacteria, fungi or algae (Shaaban *et al.*, 2002).



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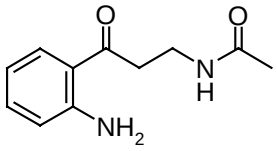
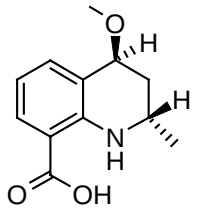


220

Under oxidative conditions, indole derivatives may undergo a ring opening which delivers *o*-formylaminobenzenes and, after hydrolysis, the anilines. N-Acetylkynuramine (**220**), an oxidative degradation product of the bacterial metabolite N-acetyltryptamine, has now been isolated for the first time from a microorganism (*Janibacter limosus* Hel 1 from the German North Sea). From the same strain, the isoquinoline helquinolin (**221**) was isolated, which showed a selective activity against Gram-positive bacteria (Asolkar *et al.*, 2004).

Methyl quinoline-2-one-4-carboxylate (**222**) was isolated together with nicotinamide (**223**) from a bacterium of the free water column Hel59b (Shaaban, 2004); other quinolones have been described previously (Bultel-Ponce *et al*., 1999). The yellow 2-methyl-pyrimidine-5-carboxamide **224** has been isolated from another unidentified marine bacterium (Thorwest *et al.*, 2001). Related structures are part of the bleomycins and the boxazomycins; **224** is also a sub-structure of vitamin B_1.



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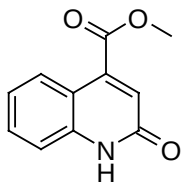

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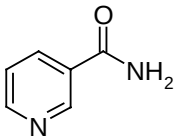

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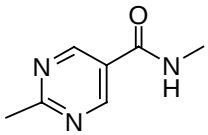
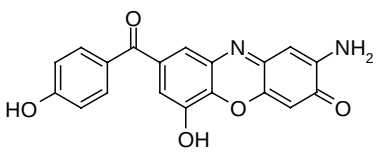


224

A *Halomonas* sp. (strain RK 3771) from the North Sea turned out to be a talented producer of many amino acid-derived metabolites, e.g. isatin and some known indole derivatives, diketopiperazines, various new 2-aminophenoxazones (e.g. **225**), and – for the first time from nature – 7-hydroxy-2*H*-benzo[1,4]thiazin-3-one (**226**) and the previously undescribed 3,4-di-(4'-hydroxyphenyl)pyrrole-2,5-dicarboxylic acid (**227**) (Liang, pers. communication). The unusual acetal **228** has been obtained from *Vibrio angustum* S14 (de Nys *et al.*, 2001).



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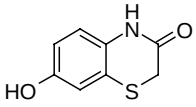

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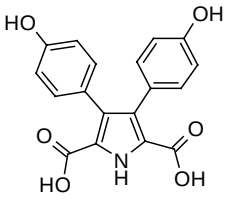

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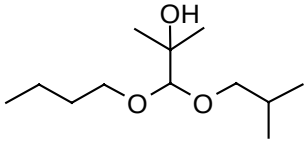
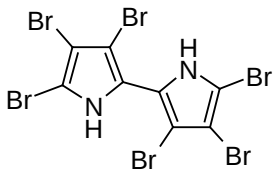


228

Feeding experiments of *Alteromonas violaceus* with [3,5-$^{13}C_2$]*p*-hydroxybenzoic acid or [2-^{13}C]proline resulted in a pentabromopseudilin (**2**) with a symmetrical isotope distribution on C-1',3' and C-2,5, respectively, which confirmed that also the pyrrole precursor must be symmetrical (Laatsch *et al.*, 1994; Peschke *et al.*, 2005). If both rings are connected *via* phenol oxidation, also the symmetrical dimers should be obtained, and this is the case, indeed. While hexabromobipyrrole (**229**) is known for long (Burckholder *et al.*, 1966; Hanessian *et al.*, 1966; Lovel *et al.*, 1966), feeding experiments delivered now also the brominated biphenol **230** (Laatsch, unpublished results). This compound has recently been described from *Pseudoalteromonas phenolica* sp. nov. O-BC30T and was shown to have a remarkable activity against a methicillin-resistant *Staphylococcus aureus* strain (Isnansetyo *et al.*, 2003). Monomeric halogen phenols like **231** and **232** have been obtained only in feeding experiments with *Alteromonas luteo-violaceus* or from algae so far (Laatsch, unpublished results).



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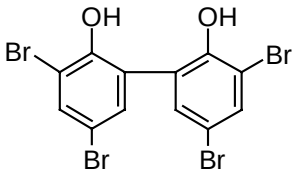

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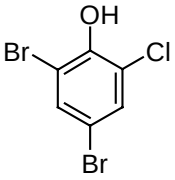

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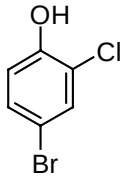
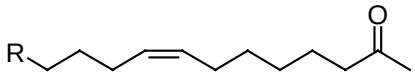
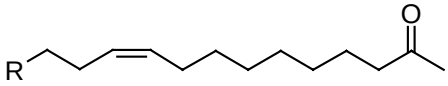


232

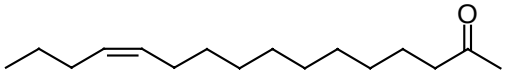
While the characteristic earthy odour of actinomycetes is due to geosmin, the often very unpleasant smell of other bacteria has not found much attention. Dickschat has performed head space analyses of marine *Cytophaga* spp. and detected a number of mostly unsaturated methyl ketones **233 - 236** by GC/MS (Dickschat, 2003). Interestingly, most of these compounds were also found in the flavour of the gliding bacterium *Myxococcus xanthus*.



233a: R = *n*-Pr
233b: R = *i*-Pr
233c: R = *i*-Bu
233d: R = 2-Bu
233e: R = *n*-Bu



234a: R = *i*-Pr
234b: R = *n*-Pr



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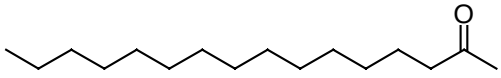


236

It is obvious from the summary above, that in compounds from bacteria other than actinomycetales, especially those of the free water column or the German Wadden Sea, peptides and other aliphatic compounds dominate. Certain other structures like quinones or polyenes are extremely rare, not only in the recent past. Most compounds are of low molecular weight and cover a wide polarity range, as metabolic profiling by HPLC/MS showed (Fig. 4). In contrast, extracts of marine streptomycetes for comparison showed masses in the range of 400-1200, a narrow polarity profile and less background noise.

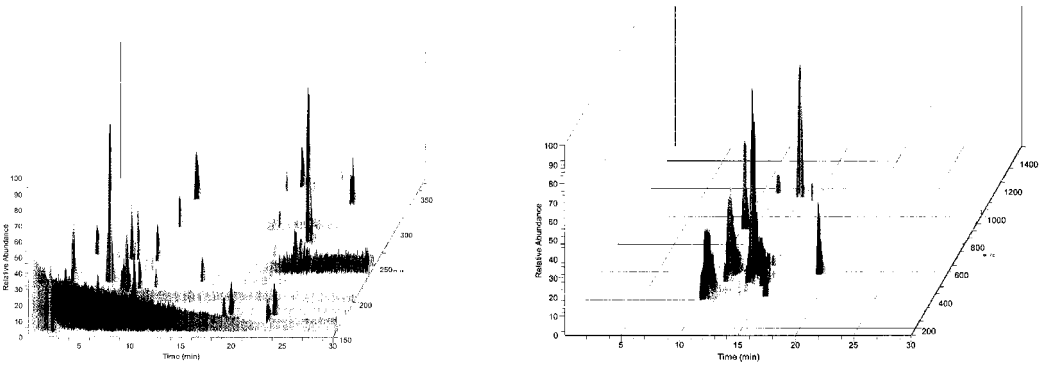


Figure 4. 3D-HPLC/MS profile of extracts from the North Sea bacterium Hel53 (left) and a marine streptomycete isolate (right)

Bacteria of the Polar Sea Ice and Other Cold Habitats

It has been discussed above that the complexity of metabolite patterns of bacteria may decrease rapidly, if the environmental pressure is reduced, e.g. by repeated sub-cultivation in a monoculture. Oppositely, certain metabolites may be formed only in the presence of trigger substances, a situation which was interpreted as a chemical defence in the case of antibiotics, but can also be understood as a vivid chemical communication in life communities. Further examples were reported recently (Yakovleva *et al.,* 1986). These mutualistic and commensalic interactions can be expected in megadiversity places (hot spots like the Great Barrier Reef), however, dense bacterial populations were found surprisingly also in the sea ice of the polar regions (Staley *et al.,* 1999).

A few antarctic isolates from rocky grounds have already been chemically investigated, and compounds, which resemble plastic additives have been obtained (see below). Bacteria from polar sea ice, however, have never been chemically investigated before. Other than tap water, freezing sea water is not forming a dense matter, but a sponge-like skeleton of ice crystals with brine channels in between, which are in connection with the sea water on the bottom. This material is translucent enough that in a depth of about 2 m below the surface a dense population of algae is found. The chlorophyll concentration may be higher than 2000 mg/m^3, which is even more than in tropical oceans at algal blooms (Spindler *et al.,* 1991).

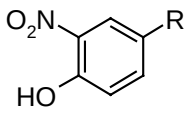
These green or brown microalgae and diatoms are associated with a high variety of morphologically unique bacteria, which had not been inspected chemically before. The ratio of viable to total bacterial counts is extraordinarily high with sea ice samples. Percentages up to 80% could be determined with some Antarctic winter sea ice samples (Helmke *et al.*, 1995). Furthermore most of the bacterial sea ice diversity turned out to be cultivatable (Brinkmeyer *et al.* 2003).

About 90% of the polar sea-ice bacteria are strictly cold adapted (psychrophilic) (Helmke *et al.*, 1995) and must be handled and maintained permanently at temperatures below 10 °C. Their growth optima are at about 10 to 15 °C (Helmke *et al.*, 2004); generation times can vary from about 5 days at -5 °C up to about 10 h at 10 °C. The mass fermentation which is needed if isolation and structure elucidation of metabolites are intended, required growth periods of

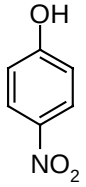
4-6 weeks therefore. The temperature range of the psychrotolerant bacterial component is clearly broader and extends from about -5° up to more than 30°C.

Most metabolites isolated so far from sea ice bacteria were obviously derived from the amino acid pathways: Simple indoles like tyramine, tyrosol, N-acetyl tryptamine, and again N-acetylkynuramine (**220**), were isolated (Schroeder, 2002). Unique metabolites or metabolic capabilities, however, were rare. A very recent example of potent capabilities was an isolate of a flavobacterium T436 (gene bank accession no. AF 468417) from Arctic sea ice, which showed 98% homology with the 16S rRNA of *Salegentibacter holothuriorum* and formed an unprecedented variety of more than 20 nitro and dinitro compounds (**237a-d** to **246**) (Schuhmann, 2005). Some of these metabolites had already been isolated from other sources or were synthesized, but were never found naturally in this complexity. Of special interest are the halogenated nitro compounds **242e** and **242f** which indicate that the producer possesses also halogenases or haloperoxidases. If the tryptamine derivative **246** is formed *via* an amino-pyrrole precursor related to **247**, or by cyclization of **245**, has to be further explored.

Nothing is known about the biosynthesis of these compounds so far, and it cannot be excluded that they are formed by oxidation of amino precursors, similarly as in pyrrolnitrin (**247**) or chloramphenicol. The formation of **244a** may indicate that also another pathway exists: the nitration of a nitrogen-free precursor **244b** with inorganic nitrate as the nitrogen source as in **248** (Carter *et al.*, 1987, 1989). The daidzein (**244b**) needed for this reaction is commonly present in the culture broth if soybean flour or malt extract are used for fermentation.



237a: R = CO_2H
237b: R = CH_2CO_2H
237c: R = CH_2CO_2Me
237d: R = CH_2CH_2OH
237d: R = CH_2CH_2NHAc
237d: R = $CH_2CH_2\ CO_2H$
237d: R = $CH=CHNO_2$



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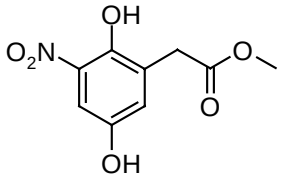

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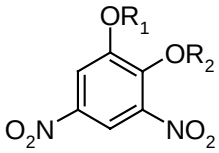
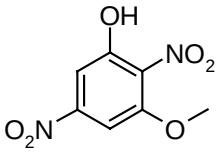


240a: R^1 = H, R^2 = Me
240b: R^1 = Me, R^2 = H



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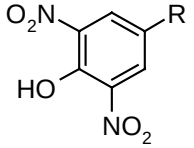
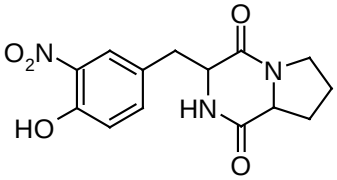


242a: R = CH_2CO_2He
242b: R = CH_2CO_2Me
242c: R = $CH_2CH_2CO_2H$
242d: R = $CHClCH_2CO_2Me$
242e: R = CH_2CH_2Cl
242f: R = CH_2CH_2NHAc



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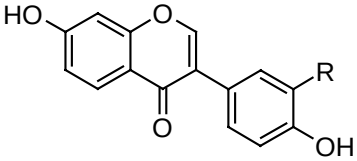
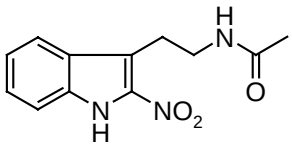


244a: R = NO_2
244b: R = H



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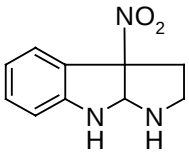

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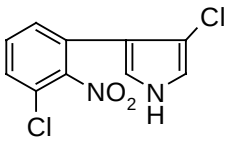

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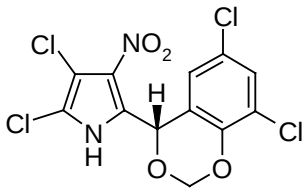

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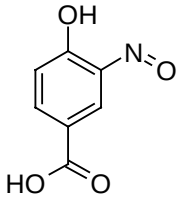
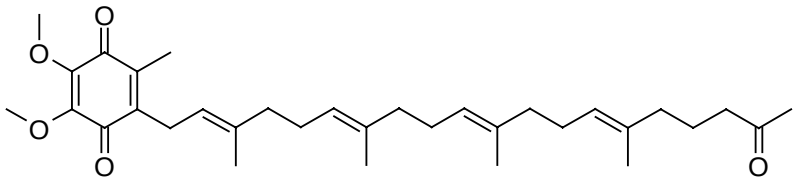


249

It has also to be further investigated if the nitro compounds could be formed by oxidation of the corresponding nitroso precursors. Nitrosophenols like **249** have been isolated from different bacterial sources and were shown to be iron chelators. It can be assumed that in the case of *Flavobacterium* sp. T436, precursors of the nitro compounds were synthesized for the same purpose, however, were oxidized by haloperoxidases.

Prenylated ubiquinones are very widespread among microorganisms and may serve as taxonomic markers. Side chains with a terminal acetone fragment as in **251** and **250** from *Pseudoalteromonas* sp. T268 (99% homology of 16S rRNA) are, however, very unusual (Schuhmann, 2005).



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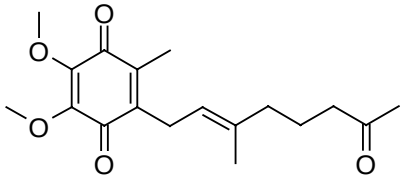

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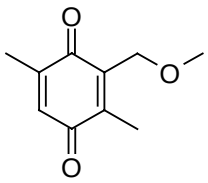

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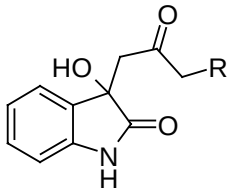
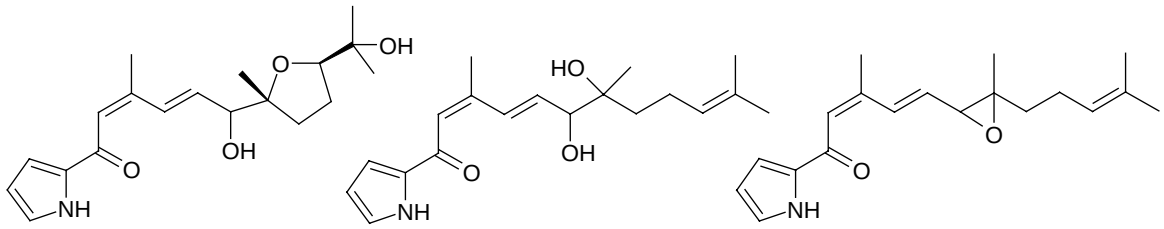


253a: R = Me
253b: R = H

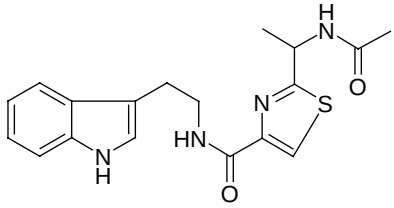
From the same strain, the benzoquinone **252** and the indolones **253a** and **253b** were isolated (Schuhmann, 2005). The latter had been obtained by Fenical (2001) before and is also formed easily in a solution of isatin (**4**) in acetone at room temperature.

Streptomycetes are rare in the polar habitats and seems to be isolated only from solid supports. Recent examples from Antarctica are the glaciapyrroles A-C (**254**-**256**) from a *Streptomyces* sp. NPS 008187 (Macherla *et al*., 2005). The konjugated pyrroloketone fragment is very rare amongst microbial products and was found so far only embedded in two few cytochalasans or as substructure of condensed ring systems.



254 **255** **256**

Microbiaeratin (**257**) is the acetate an antibiotic TM-64 previously isolated from a *Thermoactinomyces* sp. The isolation from penguin excrements explains that the strain is thermophilic with an optimal growth temperature at 45 °C (Ivanova *et al*., 2005).



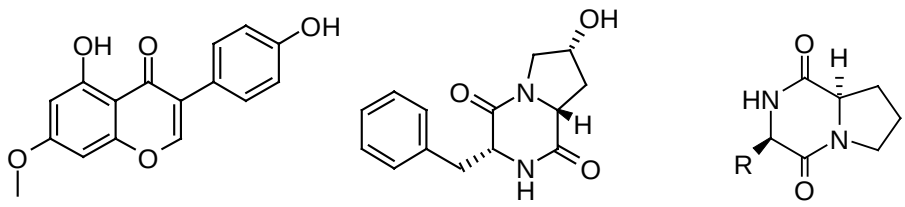
257

Bacterial Products of Uncertain Biogenetic Origin

In most cases, for the mass fermentation of microorganisms complex media are used. It is obvious that also some of their constituents may be isolated and miss-interpreted as bacterial products, or will be modified in the bacterial metabolism as in a precursor-directed biosynthesis. Fats and peptides from fish meal, and the isoflavones daidzein (**244b**) and genistein from soybean flour are well-known examples; 7-O-methylgenisteine (**258**) from *Streptomyces* sp. B 4244 may result from such a precursor (Maskey *et al.*, 2003c).

Another group of frequently isolated compounds are the diketopiperazines. Most microbial examples contain proline or hydroxyproline, and as these amino acids occur in a high concentration in meat extract and as also these cyclodipeptides are already formed during sterilisation of the culture medium, some may be artefacts. On the other hand, even in recent articles (Trischmann *et al.*, 2004; De Rosa *et al.*, 2003) a pronounced and selective antibiotic activity is claimed which, however, could not be confirmed in all cases with material from other sources or synthesis.

It has been shown now that the D,D-diketopiperazines may have a high selective antibiotic activity, while the L,L-derivatives do not (Fdhila *et al.*, 2003). The D,D-piperazinediones **259** - **260** from marine bacteria were found to be highly active against *Vibrio anguillarum*. In most other cases, the configuration of these diketopiperazines has not been determined.

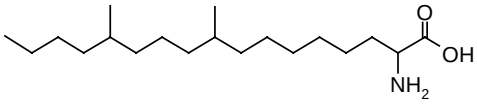


258 **259**: R = *i*-Pr **260a**: R = *i*-Pr

260b: R = *i*-Bu
260c: R = 2-Bu
260d: R = Bzl

In the period of this report, several other compounds have been reported which may have an abiotic origin due to non-enzymatic reactions during work-up, modification of nutrient components or even pollution with xenobiotics as in the case of dioctyl phthalate. A biosynthetic origin cannot be excluded in all cases, however has to be proven carefully by further experiments, best by investigation of the biosynthesis.

The arctic *Streptomyces* sp. 1010 (Ivanova *et al.*, 2001) contained the novel 2-amino-9,13-dimethyl heptadecanoic acid (**261**) and additionally the polyphenylether **262** and hexanedioic acid dioctyl ester (**263**). Compounds related with the latter are the many glycopeptides of the vancomycin type and especially the polyphenyl ethers isolated from brown algae by Glombitza *et al*. (1985).



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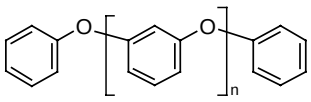
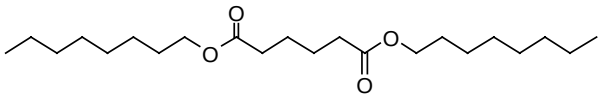


262: n = 3



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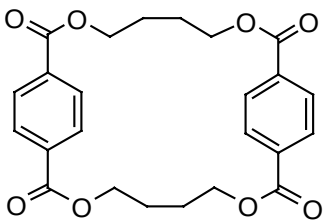
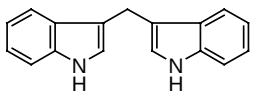
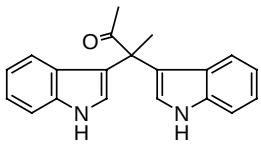


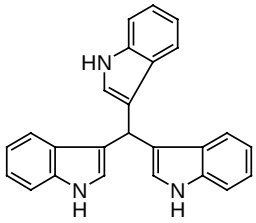
264

Pharacine (Shaaban *et al.*, 2002) (**264**), a cyclic terephthalate, was isolated as a trace component from *Cytophaga* sp. AM13.1. It was previously known as a degradation product of certain polyesters, where it is found as mixture with higher homologues. Although the fermentation result was reproducible, only one further strain formed **264** so far, and higher oligomers as by the pyrolysis of terephthalates were not obtained, a confirmation as a natural product would need biosynthetic investigations.

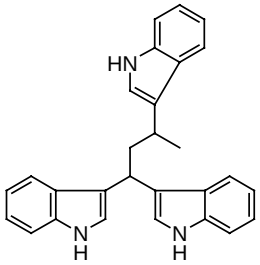
A case of its own is the isolation of the indole derivatives **265** - **267** from *Vibrio parahaemolyticus* Bio249 (Veluri *et al.*, 2003). All these compounds are formal condensation products of simple aliphatic aldehydes or ketones with indole, and the ketone **266** e.g. is obtained indeed easily by reaction of indole with diacetyl. Indole is a main product of the isolate Bio249, however, some of the condensation products (but not all) are already present in fresh extracts from agar plates.

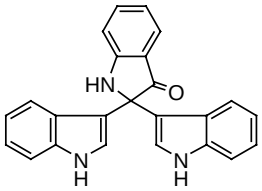


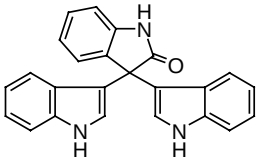




265 **266** **267**

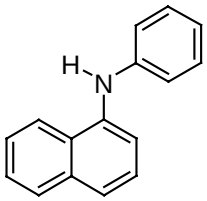


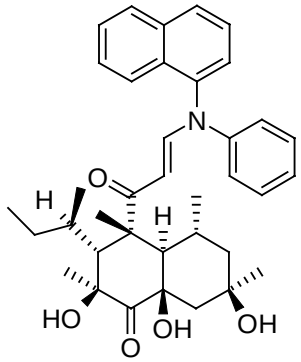




268 **269** **270**

Unexpected is the unequivocal identification of N-phenyl-1-naphthylamine (**271**) as a natural product from a streptomycete B8335 (Shaaban, 2004). This compound has been used as an antioxidant and fluorescent dye in tissue cultures, however, occurs only a second time in nature as a substructure in 10-hydroxy-18-N-1-naphthyl-N-phenylaminobetaenone (**272**) (Ebel, 2002); also the isomeric 2-naphthyl-N-phenylaminobetaenon has been described (Brauers *et al.*, 2000).





271 **272**

During the past four years, nearly 250 new metabolites have been isolated from marine bacteria, and many of them have been patented due to their relevant biological activities. Interestingly, in the same period much less compounds have been published from bacteria of terrestrial origin. This relation confirms again the importance of the marine habitat for natural product chemistry and is a strong incentive for further investigations.

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