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Review

Tetramic and tetronic acids: An update on new derivatives and biological aspects

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Abstract—Significant developments in the isolation of tetramic acids and tetronic acids, in the elucidation of their biosyntheses and their biological activities and in laboratory syntheses are reviewed with a focus on those derivatives with medicinal and pharmacological relevance. Important new members of the title compound families isolated since the year 2000 are covered as well as new biological aspects of some earlier congeners.

Contents

1. Introduction

The heterocyclic core of tetramic acids (i.e., pyrrolidine-2,4-diones) **1** is a recurrent motif among natural products originating from a variety of marine and terrestrial species such as sponges, cyanobacteria, bacteria and fungi. Their study has experienced a renaissance due to the high incidence of biological activities and because of their challenging structural complexity. A steadily increasing number of reports have been dealing with the isolation of new derivatives, with aspects of their biosyntheses and their medicinal potential as well as with the refinement of synthetic strategies including parallel and combinatorial approaches. Several reviews appeared over the last 20 years. In 1993, Henning et al. published a compilation mainly of general methods for the synthesis and conversion of these compounds.[1] The biological properties of representative natural tetramic acids had already been assessed by Rosen.[2] A review by Royles covered all aspects of tetramic acid chemistry and was seminal in bringing the subject to the attention of a wider audience of chemists, biologists and physicians.[3] In 2003, two comprehensive overviews of the structures, biosyntheses and pharmacological properties

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of tetramates were published by Ghisalberti[4] and Gossauer.[5] Since then the number of natural derivatives has risen to well over 150 and further progress was made towards an understanding of their biosyntheses and multi-facetted bioactivity. *O*-Analogous tetronic acids (i.e., dihydrofuran-2,4-diones) **2** were isolated from bacteria, moulds, algae, fungi, lichens and sponges. The spectrum of their physiological activities is as broad as that of tetramic acids with a focus on antibiotic, antiviral and antineoplastic properties. Two comprehensive summaries of their chemistry and biology appeared recently.[6,7] As with the tetramic acids, the most frequent and pharmacologically most interesting derivatives are those featuring 3-acyl residues. This has been explained by their ability to chelate biochemically indispensable metal ions and to mimick phosphate groups in the binding site of kinases and phosphatases. Several hundred naturally occurring tetronic acids and 4-O-substituted derivatives (i.e., tetronates) are known to date.

This review provides a concise update on new developments in the field, concerning recently isolated derivatives and their biosynthesis, as well as new laboratory syntheses and pharmacological aspects.

2. General aspects of structure and biosynthesis

The structural features of the title compounds were discussed in some detail in the above-mentioned reviews and are only very briefly summarised here. Tetramic acids normally exist predominantly in the 2,4-diketo form while the more strongly acidic tetronic acids usually prefer the enolised 4-hydroxy-butenolide tautomer (Fig. 1). 3-Acyltetramic acids **3** can in principle form nine different tautomers, out of which only four are normally detectable in solution, namely, two pairs of rapidly interconverting internal tautomers **3a/3b** and **3c/3d**. The interconversion of the external tautomers, that is, of **3a/3b** into **3c/3d** proceeds more slowly on the NMR time scale since requiring a C–C bond rotation. For simple 3-acyltetramic acids, Steyn et al. found the exo-enol **c** to be the prevailing tautomer in solution and in the crystalline state.[8,9] For instance, the 3-acetyl-5-isopropyltetramic acid **3** ($R^3 = CH_3$, $R^5 = i$-Pr) was shown by ^{13}C NMR spectroscopy to be a mixture of tautomers of ratio **a/b/c/d** = 5:15:80:0.[8] However, certain substituents R^5 or residues other than hydrogen at the N-atom may change the ratio of tautomers considerably.[10] For instance, N-acylated 3-acyltetramic acids prefer the **a** tautomer.[11] 3-Acyltetronic acids **4** also normally exist as mixtures of up to four tautomers similar to **3a**–**d**.[12] In protic polar solvents such as methanol the tautomers **4a/4b** predominate by far, whereas **4c/4d** are the major tautomers in DMSO.[13]

As a consequence, chelate complexes of 3-acyltetronic acids contain the metal ion sandwiched between the enolic oxygen of the 3-acyl group and the 4-oxygen atom, while the congenerous 3-acyltetramic acids coordinate the metals through their 3-acyl and 2-carbonyl oxygen atoms. Metal chelation seems to be crucial for the stability of some natural tetramic and tetronic acids as well as for their transport in biological tissues and across membranes (Fig. 2). In some cases the bioactivity of tetramic and tetronic acids was shown to be dependent on metal chelation. For instance, tenuazonic acid (TA-H; **5**) was isolated as a mixture of calcium and magnesium complexes, $Ca(TA)_2$ and $Mg(TA)_2$, from *Phoma sorghina*, a fungus implicated in the aetiology of onyalai, a haematologic disorder affecting Black African populations south of the Sahara.[14] Other complexes of defined stoichiometry were isolated, for example, $Cu(TA)_2$, $Ni(TA)_2$ and $Fe(TA)_3$.[15,16] The complex $Cu(TA)_2 \times H_2O$ was shown by X-ray single crystal structure analysis to contain the tenuazonate coordinating via 2-*O* and the 3-acyl oxygen atoms.[17] Binding constants for the complex $Fe(TA)_3$ and analogues thereof lie in the range of 10^{-29}M.[18] The 3-palmitoyl-5-hydroxymethyltetronic acid RK-682 (**6**) was also isolated as the respective calcium or sodium chelate complexes from various strains of *Actinomycetes* and *Streptomycetes*.[19] It inhibits HIV-1 protease and various other protein tyrosine phosphatases and dual-specificity phosphatases such as VHR (vaccinia VH-1 related phosphatase) and cdc25B which is a key enzyme for cell cycle progression.[20] By comprehensive structure–activity relationship studies the essential interactions between 3-acyl-5-hydroxy-

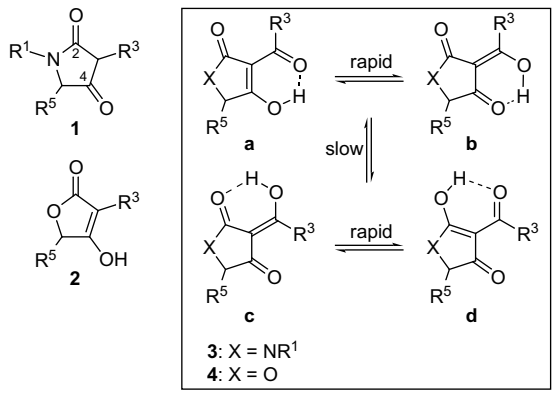


Figure 1. Major tautomers of tetramic acids **1**, tetronic acids **2**, 3-acyltetramic acids **3** and 3-acyltetronic acids **4**.

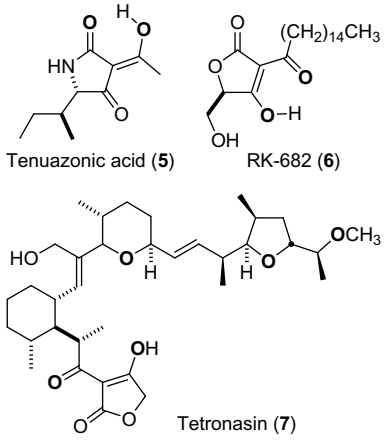
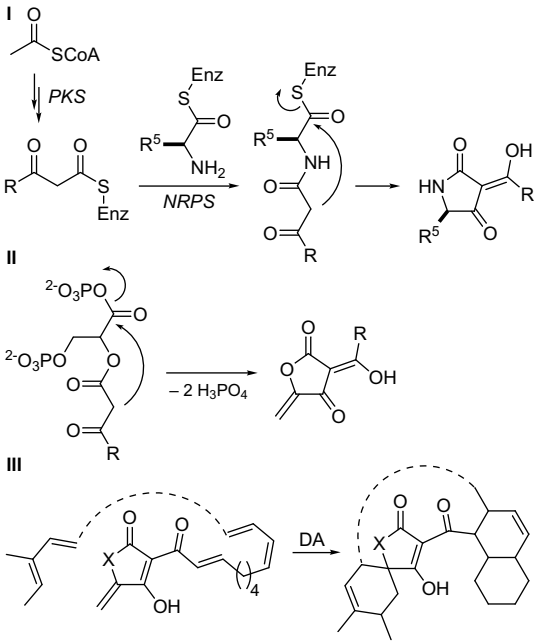


Figure 2. A 3-acyltetramic acid and 3-acyltetronic acids isolated as metal chelate complexes.

methyltetronic acids such as RK-682 and the active site in the phosphatases could be pinpointed.[21] The *Streptomyces* metabolite tetronasin (**7**) is a polyether ionophore antibiotic that coordinates metal cations octahedrally by its 3-acyltetronate oxygen atoms together with those of the methoxy and the tetrahydropyranyl and -furanyl groups in the side-arm attached to C3. Such octahedral complexes are relatively stable and get internalised into cells through channels, pores or receptors in membranes.[22]

3-Acyltetramic and -tetronic acids are typical hybrid secondary metabolites originating from polyketide and α-amino or α-hydroxy acid precursors that are built up and connected by the concerted actions of polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPS). The lactam ring is finally closed between C3 and C4 either enzymatically or spontaneously in the cytoplasm. This principle has recently been recognised at a genetic level.[23] In general, fungal tetramic acids are assembled by iterative PKS–NRPS hybrids that gain flexibility in producing structurally altered carbon frameworks by point mutations and deletions.[24] In contrast, bacterial PKS are large proteins consisting of repeated modules, each of which usually carries a set of catalytic domains for chain extension and modification and adds a single building block to the growing polyketide chain.[25] Unlike type I fatty acid synthases of animals and some bacteria which act iteratively and use a constant set of domains to produce a fully reduced carbon chain after each extension cycle, the domain structure of bacterial PKS modules is variable. Module and domain swaps can give rise to a wide range of optional intermediates. Piel et al. have lately assessed the PKS gene diversity in marine sponges and their bacterial symbionts.[26] The biosynthesis of a number of tetronic acids was deduced from feeding experiments with the respective ^{2}H- and ^{13}C-labelled fatty acids and potential C_2O-precursors.[27,28] According to these and resembling the blueprint for the construction of tetramic acids, the C2–C3 segment of the tetronic acid core almost always stems from acetate, a homologous fatty acid or from malonate while the O–C5–C4 string is provided by a suitable activated α-hydroxy carboxylate such as 1,3-bisphosphoglycerate[29] in the case of RK-682 (**6**). An alternative biosynthetic route to 3-acyltetramic acids from *N*-acylhomoserine lactones (AHL) has been reported by Janda et al.[18] AHL are so-called quorum-sensing molecules produced by certain Gram-negative bacteria (e.g., *Pseudomonas aeruginosa*) to control and initiate cell density dependent processes such as biofilm formation. AHL producing species seem to gain a competitive advantage in mixed communities owing to the fact that *N*-(3-oxoalkanoyl)homoserine lactones are spontaneously converted into antimicrobial and siderophoric 3-acyltetramic acids under physiological conditions. A simplified sketch of the standard biosynthetic route to 3-acyltetramic acids is depicted in Scheme 1**I**. Three extensions leading to the important subclasses of 5-alkylidene (**II**) and 3-decalinoyl and macrocyclic 5-spiro tetramic/tetronic acids (**III**) are also shown. Type I PKS can produce linear *E*,*E*-conjugated polyene and *E*-enone systems. In the case of hepta- to nona-ketides these can undergo enzymatic [4 + 2] cycloadditions yielding 3-decalinoyl derivatives. If the latter carry a 5-alkylidene group, a second cyclohexene moiety may arise from either an intra- or intermolecular Diels–Alder reaction with a suitable 1,3-diene fragment. The biosynthetic Diels–Alder reaction usually affords a single diastereoisomer which for the decalin system is the *trans* isomer.[30]

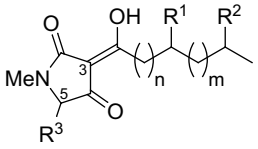


Scheme 1. Biosynthetic routes to the main classes of 3-acyltetramic and 3-acyltetronic acids.

3. Tetramic acids

3.1. Simple 3-acyltetramic acids

New properties were reported of the long known phytotoxin L-tenuazonic acid (**5**) originally isolated from cultures of *Alternaria alternata* and proved to be the causal agent of brown leaf spot disease of *Eupatorium adenophorum*. It was now disclosed in the culture extract of *Ulocladium* sp. HKI 0226 as new inducer of the morphogenesis and formation of reddish polyketides such as fusarubin by *Fusarium culmorum*.[31] It was also found in the extracts of two fungal strains, *Alternaria brassicicola* and *Alternaria raphani*, isolated from pollen collected from beehives and identified as an inhibitor of *Paenibacillus* larvae, the causal agent of American foulbrood, a honeybees' disease. L-Tenuazonic acid showed a MIC of 32 μg/mL, comparable with that of oxytetracycline, an antibiotic currently used for the prevention of this disease.[32] Results from chlorophyll fluorescence revealed that **5** can block electron flow from Q_A to Q_B at the photosystem II acceptor site. Based on studies with D1-mutants of *Chlamydomonas reinhardtii*, the no. 256 amino acid was found to play a key role in its binding to the Q_B-niche. The results of competitive displacement with [^{14}C]atrazine combined with the JIP-test showed that **5** should be considered as a new type of photosystem II inhibitor because it has a binding behav-



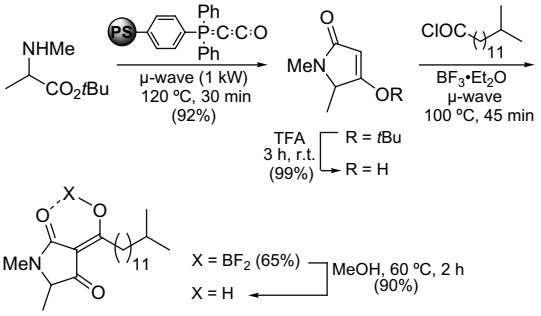
Melophlins

melophlin	R^3	R^1	R^2	n	m
A (**8a**)	H	H	H	12	0
B (**8b**)	(5S)-Me	Me	H	2	6
C (**8c**)	Me	Me	H	3	5
D (**8d**)	H	H	H	11	0
E (**8e**)	H	H	Me	11	0
F (**8f**)	H	Me	H	11	0
G (**8g**)	H	H	H	10	0
H (**8h**)	H	H	Me	10	0
I (**8i**)	H	Me	H	10	0
J (**8j**)	Me	H	H	10	0
K (**8k**)	H	H	Me	9	0
L (**8l**)	Me	H	H	9	0
M (**8m**)	Me	H	H	8	0
N (**8n**)	Me	H	Me	8	0
O (**8o**)	Me	Me	H	8	0
P (**8p**)	Me	H	H	12	0
Q (**8q**)	Me	H	Me	10	0
R (**8r**)	Me	Me	H	10	0
S (**8s**)	Me	Me	H	3	8

Figure 3. Known naturally occurring melophlins (**8**).

iour within Q_B-niche different from that of other known inhibitors.[33]

The melophlins (**8**) are *N*-methyl-3-acyltetramic acids that differ only in the substituents at C5 (H or Me) of the pyrrolidine-2,4-dione core and in the chain length (C_{12} to C_{16}) and branching of the 3-acyl residue (Fig. 3). Melophlins A (**8a**) and B (**8b**) were isolated by Kobayashi et al. from the Indonesian sponge *Melophlus sarasinorum* collected at Spermonde Islands and were shown to be cytotoxic against HL-60 cells at 0.2 and 0.4 μg/mL, respectively, and to arrest NIH/3T3 cells in the G_1 phase of the cell cycle at 1–5 μg/mL.[34] Proksch et al. obtained another 13 congeners, melophlins C–O (**8c**–**o**), from the same sponge collected near Makassar.[35] In 2006, Namikoshi et al. reported the extraction of the melophlins P–S (**8p**–**s**) from a specimen of *Melophlus sarasinorum* harvested in Palau.[36] Melophlins C, E, G, H, I, M, N and O were reported to exert no cytotoxicity in HL-60, HeLa or TF-1 cells, but melophlin C proved antibacterial in *Bacillus subtilis* and *Staphylococcus aureus* and antifungal in *Candida albicans*.[35] Another study by Namikoshi et al. of 11 melophlins including the set of the four isolated latest revealed that only melophlins H and O were modestly active in Chinese hamster lung fibroblasts V79 and none out of 11 had any impact on the level of cytokine IL-8 in PMA-stimulated HL-60 cells.[37] A structure–activity study by Schobert et al. of seven structurally diverse melophlins revealed that melophlins B, C, P, Q and R which share a 5-methyl residue are distinctly antibacterial, mainly in Gram-positive bacteria.[38] In this study, melophlins B, C and R, which have methyl branched 3-acyl side chains in common, inhibited the growth of murine L929 fibroblasts and cells of A-498 kidney cancer and KB-3-1 HeLa cervix carcinoma at $IC_{50} < 10$ μM. Melophlin Q, also methyl branched, specifically inhibited A-498 cells at $IC_{50} = 3.4$ μM. The position of the methyl branch was found decisive for the magnitude of the antiproliferative effect of the melophlin couples B/C and R/Q. Schobert et al. also published the first syntheses of melophlins A–C, G,[39] and P–R[38]that were based on the microwave-assisted Wittig cyclisation of the respective α-amino esters with

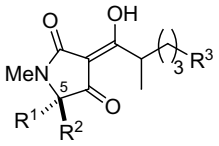


Scheme 2. Four-step synthesis of melophlin Q (**8q**).[38]

the polystyrene-bound cumulated ylide Ph_3PCCO[40] followed by a 3-acylation of the resulting tetramic acid (Scheme 2).

Six new tetramic acid derivatives **9**, structurally closely related to the melophlins, were recently isolated as yellow oils from *Penicillium* sp. GQ-7, an endophytic fungus associated with *Aegiceras corniculatum* (Fig. 4).[41] They were dubbed penicillenols A_1 (**9a**), A_2 (**9b**), B_1 (**9c**), B_2 (**9d**), C_1 (**9e**) and C_2 (**9f**). The configurations at C-5 were inferred as being *S* for **9a** and **9e** and *R* for **9b** and **9f** from CD and NMR spectra. Configurations at exocyclic stereogenic centres remained unspecified. The penicillenols were tested for cytotoxicity in cell lines of A549 human lung carcinoma, BEL7402 human hepatocellular carcinoma, murine leukaemia P388 and human leukaemia HL-60. Significant activity (MTT, 24 h) was only found for penicillenols A_1 (**9a**) and B_1 (**9c**) in HL-60 cells with IC_{50} values of 0.76 and 3.20 μM, respectively. Compounds **9b**–**f** were inactive ($IC_{50} > 100$ μM) in A549, BEL7402 and P388 cells, derivatives **9e** and **9f** also in HL-60.

The 1,3-bisacyltetramic acid reutericyclin ((5*R*)-**10**) was first obtained from a sourdough isolate of *Lactobacillus reuteri* by Jung et al.[42] It exhibits antibiotic activity against a wide variety of Gram-positive bacteria, including common sourdough lactic acid bacteria, the pathogenic bacteria *Staphylococcus aureus*, *Listeria innocua*, as well as the opportunistic pathogen *Enterococcus faecium*. The MIC range from 0.006 to 2.5 mg/L. Reutericyclin in excess is bactericidal. It was also shown to

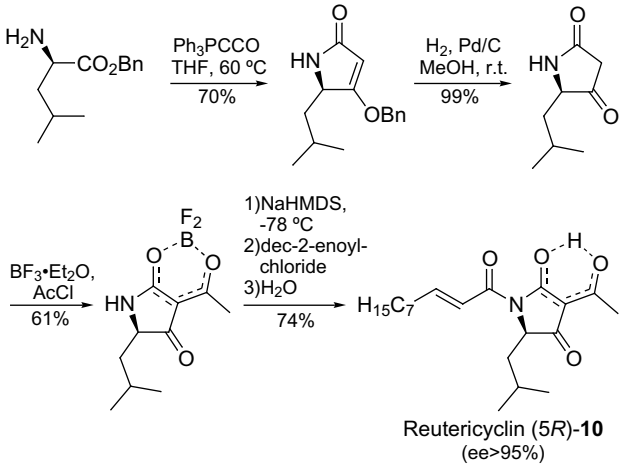


penicillenol	R^1	R^2	R^3
A_1 (**9a**)	CH(Me)OH	H	*n*-pr
A_2 (**9b**)	H	CH(Me)OH	*n*-pr
B_1 (**9c**)	(*Z*)-MeC=		*n*-pr
B_2 (**9d**)	(*E*)-MeC=		*n*-pr
C_1 (**9e**)	CH(Me)OH	H	(*E*)-CH=CHMe
C_2 (**9f**)	H	CH(Me)OH	(*E*)-CH=CHMe

Figure 4. Penicillenols **9** as isolated from *Penicillium* sp. GQ-7.

inhibit the growth of *Salmonella* and *Helicobacter*, the causative agent of stomach ulcer. There is no cross-resistance with vancomycin and methicillin. Gram-negative enteric bacteria are resistant to reutericyclin and yeasts and fungi are not inhibited. It is also not toxic in humans or animals. Mechanistically (5*R*)-**10** acts as a proton–ionophore targeting the cellular membrane. It translocates protons across the cytoplasmic membrane which lowers the transmembrane pH gradient. This mode of action is more reminiscent of that of weak organic acids, for example, sorbic or acetic acid, than of other naturally occurring tetramates.[43] Reutericyclin-producing *L. reuteri* strains have been proposed as a biopreservative for food. The Jung group published two syntheses of **10**. The first one[44] submitted an *N*-dec-2-enoylleucine to the condensation–cyclisation reaction with Meldrum's acid as described by Jouin et al.[45] The 3-acetyl group was introduced last with acetyl chloride and catalytic amounts of $TiCl_4$ which led to racemization at C5. In the second[46] synthesis of **10**, *N*-acetoacetylleucinate was cyclised under basic Lacey-Dieckmann conditions.[47] The resulting 3-acetyl-5-isobutyltetramic acid was finally deprotonated with BuLi and N-acylated with dec-2-enoyl chloride to leave (5*R*)-**10** in an optical purity of 80% ee. A four-step synthesis of enantiomerically pure (ee > 95%) (5*R*)-**10** from D-leucine benzyl ester was published by Schobert et al.[48] Wittig cyclisation with Ph_3PCCO afforded the 4-*O*-benzyl tetramate, which was hydrogenolytically debenzylated. The resulting tetramic acid crystallised as the pure keto tautomer from ethyl acetate. It was treated with an excess both of BF_3–etherate and acetyl chloride to give the stable BF_2–chelate complex of the corresponding 3-acetyltetramic acid. Deprotonation at the nitrogen atom with sodium disilazanide (NaHMDS) for 5 min at −78 °C in THF solution followed by immediate quenching with *E*-dec-2-enoylchloride and final aqueous work-up produced pure (5*R*)-reutericyclin (Scheme 3).

Pachydermin (**11**), an unusual oxalylated tetramic acid, has been isolated from the New Zealand basidiomycete *Chamonixia pachydermis* (Boletaceae) as a mixture of sodium and potassium salts.[49] The free acid is prone



Scheme 3. Synthesis of reutericyclin ((5*R*)-**10**).[48]

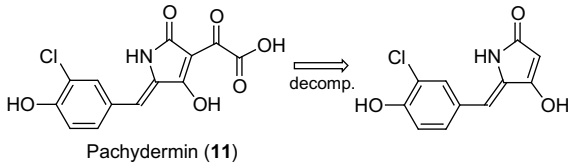


Figure 5. 3-Oxalyltetramic acid pachydermin (**11**) and a thermal decomposition product.

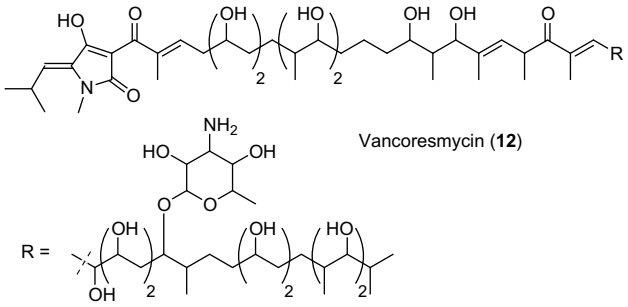


Figure 6. Vancoresmycin (**12**).

to degradation under acidic conditions (Fig. 5). The structure of **11** was inferred from that of the more stable degradation product 5-(3-chloro-4-hydroxybenzylidene)tetramic acid. The latter exhibited moderate antibacterial activity against *Bacillus subtilis* in agar diffusion tests. It remained unclear whether this decomposition product is also formed in vivo as a response to injury of the fruiting body or predatory attack.

Vancoresmycin (**12**), a new tetramic acid derivative of as yet unknown absolute configuration, has been isolated from the fermentation broth of the actinomycete *Amycolatopsis* sp. ST 101170 (Fig. 6).[50] A striking characteristic of this compound is the highly oxygenated long alkyl chain. It exhibited potent antibiotic activity against Gram-positive bacteria, including *Staphylococcus aureus* (MIC < 0.04 μg/mL), *Enterococcus faecalis* (MIC = 0.3 μg/mL) and against vancomycin-resistant strains, like *Enterococcus* spp. Inhibition effects against Gram-negative bacteria and antifungal activity were not observed.

3.2. 3-Oligoenoyltetramic acids

α-Lipomycin (**13**), a yellow-red lipophilic tetramic acid inhibits the growth of Gram-positive bacteria, for example, *Bacillus* sp., *Arthrobacter* sp., *Clostridium pasteurianum*, *Brevibacterium flavum*, *Staphylococcus aureus* and *S. viridochromogenes*. It was originally obtained as a metabolite of strain *S. aureofaciens* Tü117 which was isolated from a Venezuelan soil sample.[51] While its precise mechanism of action is yet unknown, early test results concerning the influence of **13** on the synthesis of RNA, DNA and murein suggested the bacterial membrane to be the actual target.[52] The observations that α-lipomycin increased the permeability of artificial membranes and that various lipids antagonised its activity further corroborated this assumption. The gene cluster

responsible for the biosynthesis of α-lipomycin by *S. aureofaciens* Tü117 was localised and sequentially analysed in 2005. It is ca. 67 kb large and comprises 22 genes with 28 open frames.[53] Active genes of this cluster code for polyketide synthases organised in eight modules, a non-ribosomal peptide synthetase, a type II thioesterase, a methyl transferase, a carboxypeptidase and six putative enzymes dealing with the synthesis of the D-digitoxose moiety as the chief protagonists in the biosynthesis of **13**. The corresponding starting materials are isobutyl-CoA (polyketide starter unit), methylmalonyl-CoA (first two extender units), malonyl-CoA (further extender units), glutamate and D-glucose (Fig. 7).

Tirandalydigin (**14a**) is a tetramic acid of the tirandamycin–streptolydigin type and was isolated from *Streptomyces tirandis* subsp. *umidus* strain AB-1006A-9.[54] It exhibits an antimicrobial spectrum similar to those of tirandamycin A and streptolydigin (**14b**). Compound **14a** is active against a number of anaerobes, for example, *Bacteroides fragilis* (MIC = 0.5 μg/mL), while its activity against aerobes is much lower. *Streptococci*, including *S. pyogenes* 930 CONST (MIC = 3.1 μg/mL) and *S. bovis* A5169 (MIC = 12.5 μg/mL), are sensitive to tirandalydigin whereas the efficacy against *Enterococci* (MIC > 16 μg/mL) and *Legionellae* (MIC > 32 μg/mL) is only moderate. Compounds **14a** and **14b** both inhibit bacterial DNA-directed RNA-polymerase.[55] Recently the mechanism of this process was revealed.[56] Bacterial RNA polymerase (RNAP) has two binding and one allosteric determinants that can bind to streptolydigin. The RNAP–streptolydigin complex is no longer able to cycle between the straight-bridge-helix and the bent-bridge-helix conformational states of the RNAP active centre. This conformational change of the allosteric determinant of the bridge helix disfavours and possibly excludes backtracked states and so the translocation. Total syntheses of **14a** and **14b** were published in 2005, based upon the synthesis of streptolic acid (**15**) by Ireland and Smith.[57] Miyashita's retrosynthetic strategy is outlined in Scheme 4.[58] The tetramic acid moiety of **14** was built up according to Ley et al.[59] Streptolic acid was converted into the corresponding β-ketothiolester which was submitted to a silver mediated aminolysis reaction with a protected glycinate. Dieckmann-cyclisation of the resulting β-ketoamide with sodium methoxide in methanol afforded tirandalydigin. The 2,6-dioxabicyclononane precursor **16** was stereoselectively prepared employing the three-step Ito-Saeguso method[60]: preparation of the silyl enolether of ketone **17**, cyclopropanation with Et_2Zn and CH_2I_2 and finally treatment with $FeCl_3$. **17** was obtained by acid-catalysed intramolecular acetalisation of **18** which in turn was prepared in several steps from the chiral precursor **19**.

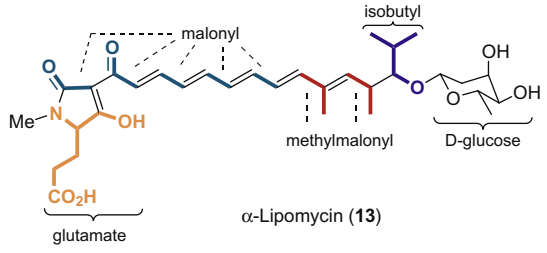
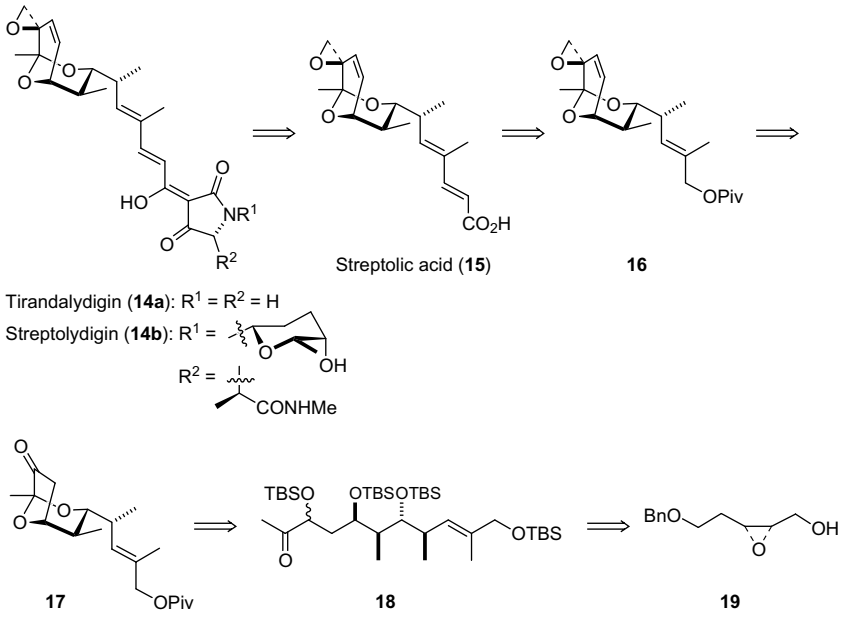
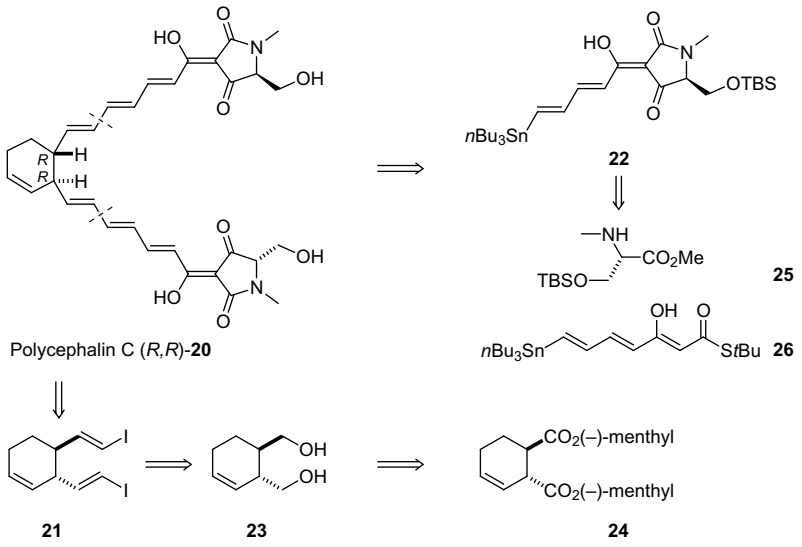


Figure 7. Biosynthetic assembly of α-lipomycin (**13**).

Polycephalin C (**20**) is a recently isolated metabolite of the fungus *Physarum polycephalum* featuring two trienoyltetramic acid units connected by a *trans* 3,4-disubstituted cyclohexene ring.[61] Physarorubinic acids A and B are the biosynthetic precursors of **20** and they are also responsible for the yellow colour of the wild-type plasmodia.[61] The first total synthesis of **20** was published by Ley et al. (Scheme 5).[62] It was built up from two major fragments, a bisvinyl iodide **21** and a stanny-



Scheme 4. Retrosynthetic approach to tirandalydigin (**14a**).[58]



Scheme 5. Retrosynthetic approach to polycephalin C (**20**).[62]

lated dienoyltetramic acid **22**, which were connected by a double Stille coupling. Fragment **21** was constructed from cyclohexene diol **23** via a 1,4-dioxidation and a double Takai reaction. Diol **23** was prepared from Diels–Alder adduct **24** by double bond manipulation and exhaustive reduction. Tetramic acid **22** was prepared in two steps, a silver mediated aminolysis reaction between the protected (*S*)-serine methyl ester **25** and the stannylated β-ketothiolester **26** followed by a Lacey-Dieckmann condensation of the resulting β-ketoamide. In contrast to the earlier reports,[61] Ley et al. showed the natural product to be *R*,*R*-configured at the ring junction.[62]

3.3. 3-Decalinoyltetramic acids

No total syntheses of members of this subgroup have been reported so far. The structurally novel hexacyclic tetramic acid integramycin (**27**) was isolated from *Actinoplanes* sp. and found to inhibit recombinant HIV-1 integrase strand transfer reaction with an IC_{50} value of 4 μM (Fig. 8).[63]

Equisetin (**28**) is also a member of the subgroup of tetramic acids being produced by moulds or fungi and featuring bicyclic sesquiterpenoid 3-acyl residues. It was first isolated in 1974 from the white mould *Fusarium equiseti*.[64] Equisetin exhibits antibiotic and HIV inhibitory activity, cytotoxicity and mammalian DNA binding.[65–67] The total synthesis of **28** was already reported by Ley et al.[68] and Danishefsky et al.[65]

Trichosetin (**29**), the *N*-desmethyl homolog of equisetin, was recently isolated from the dual culture of *Trichoderma harzianum* H14 and *Catharanthus roseus* callus.[69] It shows a remarkable activity against Gram-positive bacteria, such as *Staphylococcus aureus* and *Bacillus subtilis*.[70] The phytotoxicity of trichosetin was examined in seedling growth assays.[71] **29** inhibited root and shoot growth of all five plant species tested by damaging the cell membrane, as evidenced by the dose-dependent increase in electrolyte leakage and lipid peroxidation. It also has damaging effects on mitochondria. The biosynthetic origin of the carbon atoms in trichosetin was determined by feeding experiments with ^{13}C-labelled precursors, for example, 1-^{13}C, 2-^{13}C or 1,2-^{13}C acetate.[70] According to these, trichosetin originates from two separate biogenetic units, an octaketide intermediate directly derived from eight intact acetate units joined in a head-to-tail fashion and the amino acid serine (Fig. 9).

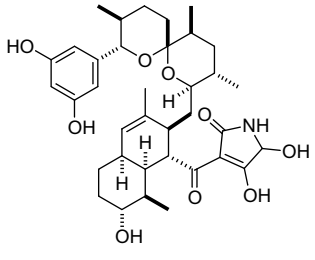


Figure 8. Structure of integramycin (**27**).

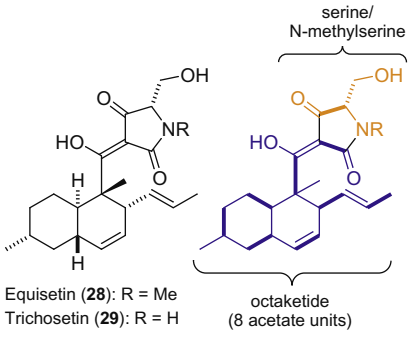


Figure 9. Structures and biosynthetic origin of equisetin (**28**) and trichosetin (**29**). Bold bonds in the right formula represent ^{13}C-labelled acetate units.

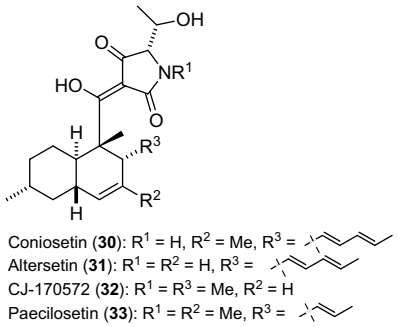


Figure 10. Structures of coniosetin (**30**), altersetin (**31**), CJ-170572 (**32**) and paecilosetin (**33**).

Coniosetin (**30**), altersetin (**31**), CJ-17572 (**32**) and paecilosetin (**33**) are structurally related to equisetin (Fig. 10). Coniosetin was found in cultures of the ascomycete *Coniochaeta ellipsoidea* DSM 13856 and it showed a pronounced antimicrobial effect.[72] Like altersetin and CJ-17572 it was strongly active against Gram-positive bacteria such as *Stapyhlococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae*, but inactive against Gram-negative bacteria. Coniosetin also inhibited the growth of various *Streptococci*, including erythromycin resistant and penicillin resistant strains such as a clinically isolated multi-drug resistant *Staphylococcus aureus* (MIC = 0.3 μg/mL) and *Enterococci* (MIC = 2.5 μg/mL). Coniosetin is two to three times more toxic than amphothericin B under the same conditions. It also inhibits the yeast *Candida albicans* at a concentration of 3.1 μg/mL. Cultures of endophytic *Alternaria* spp. were found to produce the structurally related antibiotic altersetin (**31**) which possesses a spectrum of bioactivity quite similar to that of equisetin.[73] CJ-17572 (**32**) was isolated in 2002 from the fungus *Pezicula* sp. CL11877. It inhibited the growth of multi-drug resistant *Staphylococcus aureus* and *Enterococcus faecalis* with IC_{50} values of 10 and 20 μg/mL, respectively.[74] **32** was also cytotoxic against HeLa cancer cells at an IC_{90} of 7.1 μg/mL. Paecilosetin (**33**) and a recently characterised *N*-hydroxypyridone, farinosone B, were the two major metabolites isolated from the fungus *Paecilomyces farinosus*.[75] Both compounds proved cytotoxic against the P388 tumour cell line with IC_{50} values of 3.1 and 1.1 μg/mL, respectively. Paecilosetin was also antimicrobially active in agar diffusion assays with *Bacillus subtilis* and the fungi *Cladosporium resinae* and *Trichophyton mentagrophytes*.

TPU-0037 A–D (**34a–d**) are newly isolated congeners of lydicamycin (**35**) produced by *Streptomyces platensis* TP-A0598 (Fig. 11).[76] These antibiotics have the longest side chain found so far in the group of 3-decalinoyltetramic acids. They all possess remarkable antimicrobial activities against Gram-positive bacteria, including *Staphylococcus aureus* F597 (MRSA) and *Bacillus subtilis* ATCC6633, but showed no activities against Gram-negative bacteria and yeasts. **34c** exhibited the most potent anti-MRSA activity in this group of compounds (MIC 3.13 μg/mL).

3.4. Macrocyclic tetramic acids

HSAF (heat-stable antifungal factor; **36**), a secondary metabolite produced by the bacterium *Lysobacter enzymogenes* strain C3 when kept in nutritionally limited media such as 10% TSB, is highly active against a wide range of fungi by a novel and unique mode of action. It disrupts the biosynthesis of a distinct group of sphingolipids crucial for the polarised growth of filamentous fungi.[77] Structurewise, HSAF is closely related to the natural products discodermide (**37**), ikarugamycin (**38**), and capsimycin (**39**) with which it shares the 17-membered macrolactam ring (Fig. 12). Like HSAF, discodermide is antifungal, particularly against *Candida albicans*, and also cytotoxic. It was isolated from the Carribean deep-sea sponge *Discoderma dissoluta*.[78] Ikarugamycin, a metabolite of *Streptomyces phaeochromogenes* var *ikaruganensin*, is an antibiotic and antiprotozoal bearing a 5,5,6-tricyclic system on the macrolactam.[79] The antifungal *Streptomyces* metabolite capsimycin also features a similar structure.[80]

As the first study of the genetic basis for the synthesis of macrocyclic tetramates, the genetic locus responsible for the biosynthesis of HSAF was recently identified.[81] HSAF is produced by a complex comprising a hybrid polyketide synthase and non-ribosomal peptide synthase (PKS–NRPS), a sterol desaturase, a ferredoxin reductase and an arginase with hydroxyornithine stemming from arginine and several hexaketides being the starting materials (Scheme 6). HSAF is identical to dihydromaltophilin (a.k.a. A90931a) previously isolated from *Streptomyces* sp.[82]

Cylindramide (**40**) was originally isolated in 1993 by Fusetani et al. from the marine sponge *Halichondria cylindrata* Tanita and Hoshino.[83] It is structurally akin to

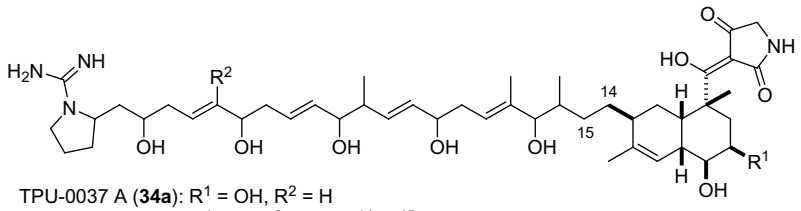


Figure 11. Structures of TPU-0037 derivatives (**34**) and lydicamycin (**35**).

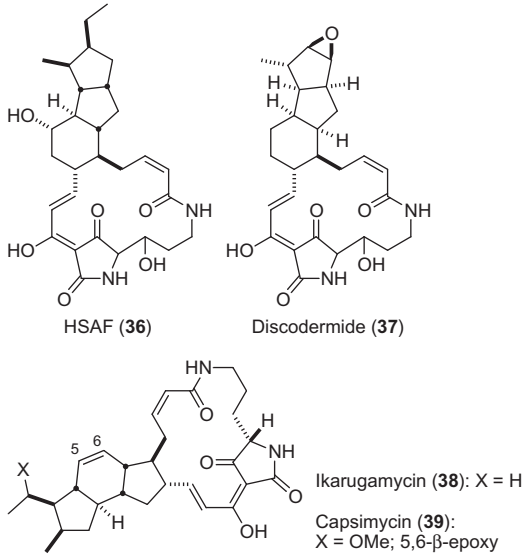
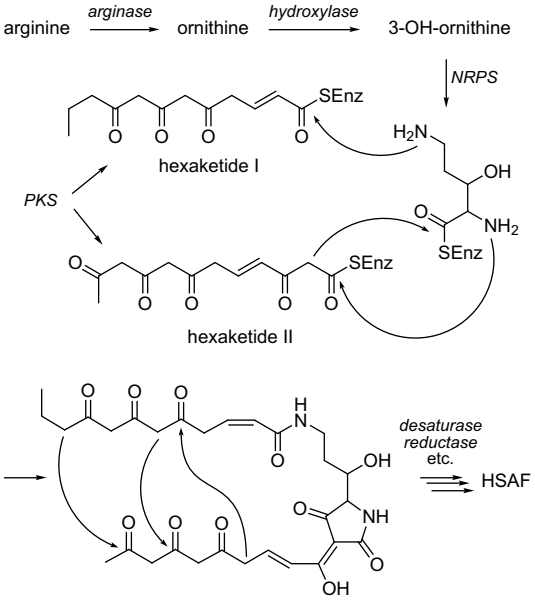
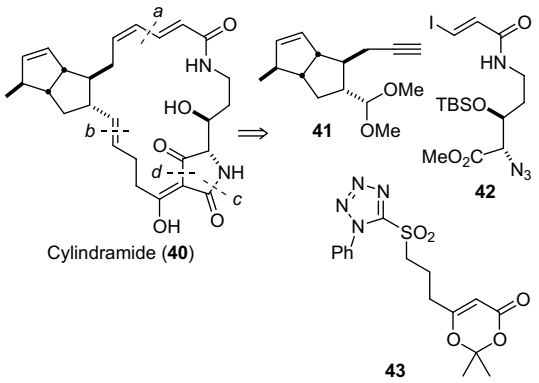


Figure 12. Structures of HSAF (**36**), discodermide (**37**), ikarugamycin (**38**) and capsimycin (**39**).



Scheme 6. Biosynthetic pathway to HSAF (**36**).[81]

aburatubolactams A and **C** and like these very likely of bacterial origin.[84] It exhibited cytotoxicity against B16 melanoma cells with an IC_{50} of 0.8 μg/mL. Geodin A, a didehydro derivative of **40**, was isolated as a magnesium salt from an Australian marine sponge of *Geodia* sp. and found nematocidal in vitro.[85] The first total synthesis of **40** was published by Laschat et al., together with the assignment of its absolute stereochemistry by means of comparison with the natural product.[86] The retrosynthetic strategy is outlined in Scheme 7. The target compound was built up from three components: a substituted pentalene **41**, a β-hydroxy-ornithine derivative **42**, and a dioxinone with tetrazolylsulfone terminus **43**. Assemblage of these fragments was achieved by Sonogashira coupling of precursors **41** and **42** (connec-



Scheme 7. Retrosynthetic approach to cylindramide (**40**) by Laschat et al.[86]

tion step *a*), Julia-Kocienski olefination between tetrazolyl sulfone **43** and the aldehyde function in the resulting coupling product (connection step *b*), macrolactamization (connection step *c*) by reaction of an amine, as obtained by Staudinger reduction of the azide group introduced with **42**, with the dioxinone stemming from **43** and Lacey-Dieckmann condensation to form the tetramic acid unit (step *d*). Cylindramide was thus obtained as a 53%:26% mixture of the natural isomer and the 2-epimer, that could be separated on an RP-C18 phase. Shortly after Laschat, Phillips et al disclosed another total synthesis key steps of which were metathesis and HWE reactions to put the C=C double bonds in place and two lactamizations reminiscent of Laschats approach.[87]

Macrocidins A and **B** (**44a**,**b**) are unique 3-acyltetramic acids, both structurewise and with respect to their biological activities (Fig. 13). They were isolated in 2003 by Graupner et al. as phytotoxic metabolites from liquid cultures of the fungus *Phoma macrostoma* Montagne [family *Sphaeropsidacaea*] which is a weak plant pathogen or wound parasite with a ubiquitous distribution.[88] It causes chlorotic leaf spots and necrosis on woody and herbaceous plants, and black rot of artichoke leaves. The macrocidins were the first examples of naturally occurring acyltetramic acids containing a tyrosine unit. As part of a macrocyclic ring the latter confers rigidity to the molecule which fact was corroborated by NMR studies. An X-ray single crystal structure analysis of **44a** was also reported by the Graupner group. While the macrocylic skeleton of the macrocidins has been already synthesised,[89] a total synthesis of these tetramic

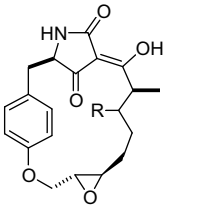


Figure 13. Structures of macrocidins (**44**).

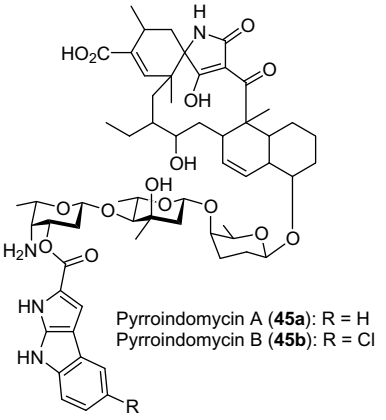


Figure 14. Structures of pyrroindomycins (**45**).

acids is still missing. Biological testing on greenhouse-grown weeds [sunflower (*Helianthus annuus*), giant foxtail (*Setaria faberi*), ivy leaf morning glory (*Ipomoea hederaceae*), wild oat (*Avena fatua*) and barnyard grass (*Echinochloa crusgalli*)] revealed a pronounced chlorosis and growth inhibition in broadleaf weeds but not in the grass weed. The mode of action remained unknown. The bleaching and stunting appeared primarily in the new growth of susceptible weeds, which suggested these compounds were phloem mobile.

Pyrroindomycins A and **B** (**45a,b**) were isolated from *Streptomyces rugosporus* LL-42D005 by Ding et al. They are composed of an unusual pyrroloindole group linked to a deoxytrisaccharide and a tetramic acid containing moiety (Fig. 14).[90,91] Pyrroindomycins A and B exhibit good to excellent in vitro activity against Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* strains but only poor activity against Gram-negative bacteria. Pyrroindomycin A (**45a**) is generally more active than the chlorinated derivative pyrroindomycin B (**45b**).[92] Biosynthetic precursor of the indole portion of pyrroindomycin B is tryptophan. A regioselective tryptophan 5-halogenase was recently found to be involved in pyrroindomycin biosynthesis in *Streptomyces rugosporus* LL-42D005.[93]

3.5. Alkaloid and peptidic tetramic acids

Cyclopiazonic acid (**46**) is a toxic indole tetramic acid produced by numerous *Penicillium* and *Aspergillus* species some of which infect commodities (Fig. 15).[94] Its toxicity in rodents (ingested $LC_{50} \sim 30$ mg/kg) is believed to stem from its ability to inhibit Ca^{2+}-dependent ATPase.[95] Structures at a resolution of 2.65 Å of **46**

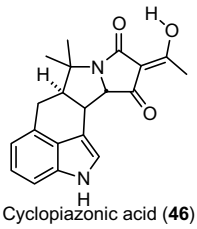


Figure 15. Structure of cyclopiazonic acid (**46**).

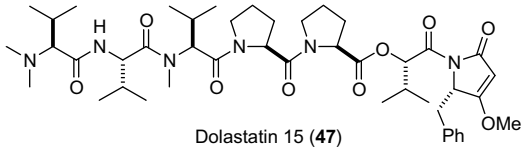


Figure 16. Structure of dolastatin 15 (**47**).

bound to the calcium access channel of this enzyme were published very recently.[96] **46** causes weight loss, diarrhea, degeneration and necrosis of the muscles and viscera and convulsion and death in rodents, birds, dogs and swine. It has also been implicated in two acute mycotoxicoses in humans: 'Koudua poisoning', for which the kodo millet produced symptoms of giddiness and nausea in man[97] and 'Turkey X disease'.[98] In vitro studies with cultured skeletal muscle cells, sarcoplasmic reticulum vesicles cells and membrane preparations indicated that cyclopiazonic acid interacts with cell membrane processes by three apparently distinct modes.[99–101] Apart from its inhibition of the ATPase of cardiac, smooth and skeletal muscle sarcoplasmic reticulum and the endoplasmic reticulum of animal cells it causes electric charge alterations on the intracellular surface of plasma and possibly the mitochondrial membranes in intact or permeabilised renal, liver and muscle cells. In addition, it has an antioxidant activity as evidenced by the ability to prevent increases in thiobarbituric acid positive substances (used to estimate the extent of lipid peroxidation) of cell membranes in renal and muscle cells.

The dolastatin family of natural products includes a series of linear and cyclic antineoplastic and/or cytostatic peptides. They were initially isolated from the sea hare *Dolabella auricularia*.[102] Some derivatives were later also found in strains of *Lyngbya majuscula* implying that at least some metabolites isolated from *D. auricularia* have a cyanobacterial origin.[103] One of the most potent members of this family, dolastatin 15 (**47**), includes a tetramate as its terminal moiety (Fig. 16). It induces apoptosis via cell cycle arrest at the G2/M checkpoint and activation of both mitochondrial- and Fas(CD95)/Fas-L(CD95-L)-mediated pathways. It is also antiangiogenic. LU 103793, a synthetic analogue of **47** is currently undergoing clinical phase III studies in patients with metastatic breast cancer. The dolastatins including **47** bind weakly to the 'Vinca domain' of tubulin and disrupt microtubule formation. By a similar mechanism they also block the growth and development of malarial parasites, for example, **47** with an IC_{50} (72 h) = 200 nM against *P. falciparum*. The cytotoxic effects of these agents were similar to those of vinblastine but different from those of paclitaxel.[104]

4. Tetronic acids

4.1. Simple 3,5-disubstituted tetronic acids

The biosynthesis of agglomerin A (**48a**) (Fig. 17), originally isolated from the fermentation broth of *Enterobac-*

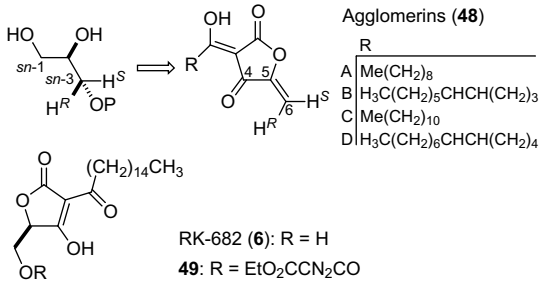


Figure 17. Structures of agglomerins (**48**) and RK-682 (**6**).

ter agglomerans PB-6042,[105] was elucidated by Fujimoto et al. by feeding/NMR experiments.[106] Feeding of [1-^{13}C]acetate to *E. agglomerans* PB-6042 resulted in the ^{13}C enrichment at C1′, C3′, C5′, C7′ and C9′ of the side chain of **48a**, indicating that the fragment C4–C5–C6 is not derived from acetate. Feeding of [1,3-$^{13}C_2$]glycerol afforded **48a** enriched at C4 and C6. Feeding of *sn*-(3*R*)- and *sn*-(3*S*)-[3-^{2}H]glycerols resulted in an agglomerin A with pro-*R* and pro-*S* hydrogens at *sn*-C3 of glycerol incorporated stereospecifically as the 6*E* and 6*Z* hydrogens, respectively. Hence, the immediate biosynthetic precursor of the C4–C5–C6 fragment of **48a** is not pyruvate but 1,3-bisphosphoglyceric acid or its biological equivalent. Agglomerins A–D are antibiotics mainly active against anaerobic bacteria, both Gram-positive and Gram-negative. MIC (μg/mL) values typical of agglomerin A (**48a**) are 3.13 (*C. difficile*; *B. fragilis*; *B. vulgatus*; *Streptococcus constellatus*) or 6.25 (*Eubacterium limosum*; *B. longum*; *B. melaninogenicus*; *F. nucleatum*; *F. necrophorum*).[105a] Compound **48a** has been synthesised by various groups.[107,108]

RK-682 ((5*R*)-**6**) was isolated as the corresponding tetronate salts with different countercations from the strains *Actinomycetes* DSM 7357 by a CIBA-GEIGY group,[19,109] from *Streptomyces* sp. 88-682 by a RIKEN group[20] and from *Streptomyces* sp. AL-462 by a TAKEDA group.[110] It was found to inhibit HIV-1 protease[109] and various protein tyrosine kinases and phosphatases[111] presumably by acting as a phosphate mimic. Early stereoselective syntheses by the TAKEDA group[110] and others[112] served to ascertain the absolute configuration of the natural products. Recently, a library of congeners of **6** with diversity in the 3- and the 5-residues was built up via a Lacey-Dieckmann based solution-phase synthesis and screened for inhibition of the phosphatases VHR (vaccinia VH-1 related phosphatase) and cdc25B which is a key enzyme for cell cycle progression.[20,113] A few general structure–activity relationships were observed: (1) long-chain hydrophobic substituents at C3 were not as critical for cdc25b inhibition as for that of VHR. (2) O-substitution at the α-position of the C3-acyl group was unfavourable for cdc25B inhibition compared to that of VHR. (3) A long-chain hydrophobic substituent at C5 increased inhibition of cdc25B, an effect opposite to that seen in the case of VHR. Library member **49** exhibited a particularly strong inhibition of cdc25B (IC_{50} = 0.4 μM) and a 30-fold preference for cdc25B compared to VHR. Other structural variations have also been published.[114]

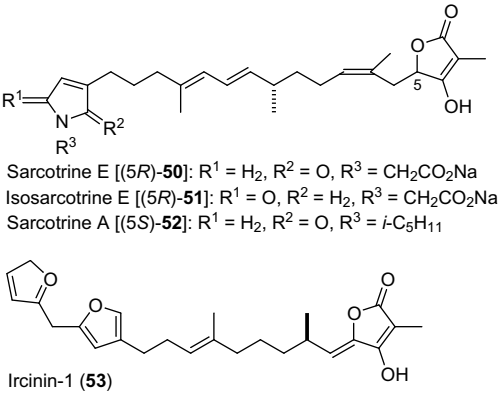
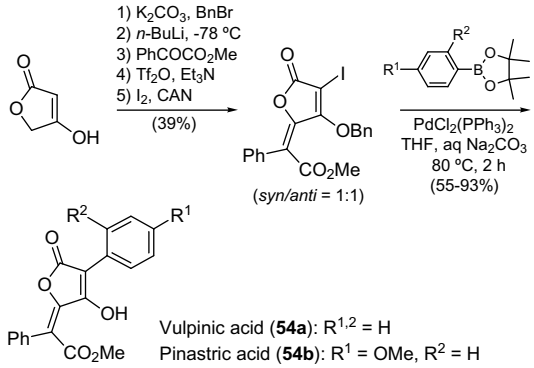


Figure 18. Structures of sarcotrines A (**52**) and E (**50**), isosarcotrine E (**51**) and ircinin-1 (**53**).

Recently, (5*R*)-**6** was prepared in solution and on a solid support from (2*R*)-glycerates in only five steps and ca. 40% overall yield.[108]

Two new pyrrolosesterterpenes, sarcotrine E (**50**) and isosarcotrine E (**51**) were isolated from a sponge *Sarcotragus* species, collected off the coast of Jeju Island, Korea (Fig. 18). They were suggested as a chemotaxonomic marker for this sponge.[115] Natural congeners such as sarcotrine A (**52**) and its (5*R*)-epimer forming upon prolonged standing of **52** exhibited distinct cytotoxicities against a panel of five tumour cell lines (A549, SK-OV-3, SK-Mel-2, XF498, HCT15) with IC_{50} values ranging from 3.4 to 4.3 μg/mL.[116] Sponges of the genus *Sarcotragus* had been reported earlier to contain structurally similar furanosesterterpene tetronic acids such as variabilin and derivatives thereof.[117] Sponges of various *Ircinia* species were also found to produce furanosesterterpene tetronic acids, for example, variabilin, felixinine, strobilinine and ircinines.[118] In a thorough study ircinin-1 (**53**) specifically inhibited cell proliferation and exhibited a cytotoxic, apoptosis inducing effect on human SK-Mel-2 melanoma cells. Mechanistically, it arrested the cell cycle progression during the G_1 to S-phase transition which was associated with a marked decrease in the protein expression of D-type cyclins and their activating partners Cdk 4 and 6 with concomitant inductions of $p21^{WAF1/CIP1}$ and $p27^{KIP1}$.[119]

A new synthesis of vulpinic acids (**54**) with mixed aryl residues was published in 2007.[120] Tetronic acid was converted in a few steps to an iodide. Suzuki–Miyaura cross-coupling of this with various arylboronates afforded a collection of vulpinic acids, among them two natural products, vulpinic (**54a**) and pinastric acid (Scheme 8). Vulpinic acids represent a substantial subclass of 5-alkylidenetetronic acids occurring mainly as colour pigments in a wide variety of lichens and fungi. The parent vulpinic acid exhibits diverse biological activities, and lichens containing it have a strong history of medicinal use. For example, Eskimos[121] and people of Northern Europe have used such lichens to poison the wolf[121,122] and fox.[122,123] In central Europe, members of the genus *Cetraria*, which is known to produce



Scheme 8. Synthesis of mixed-aryl vulpinic acids (**54**) by Le Gall et al.[120]

54a, have been used as laxatives and have been taken for coughing, including that associated with tuberculosis.[123,124] A comprehensive overview of the structural variance of vulpinic acids and synthetic approaches towards them was provided by Zografos and Georgiadis.[7]

Artapetalin A (**55**), a 5-methylene-3-hexadeca-*Z*7, *Z*10,*Z*13-trienyltetronic acid was isolated from the aerial parts of the plant *Artabotrys hexapetalus* [(L.f.) Bhandari] (Annonaceae) which is widely distributed in southern China, and is used in traditional Chinese medicine for the treatment of malaria and scrofula (Fig. 19). The authors suggested the biosynthesis of **55** to start from α-linolenic acid and pyruvic acid.[125]

Pesthetoxin (**56**) is a leaf necrosis inducing metabolite of the grey blight fungus *Pestalotiopsis theae* which regularly infects tea crops.[126] It was synthesised by cyclising benzyl α-hydroxyoctanoate with the cumulated ylide Ph_3PCCO, debenzylating the resulting benzyltetronate and treating the so-formed tetronic acid with another equivalent of Ph_3PCCO to give the corresponding 3-acylylidated tetronic acid. Saponification of the ylide function liberated pesthetoxin in ca 60% overall yield (Scheme 9).[48]

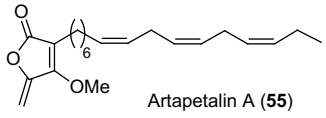
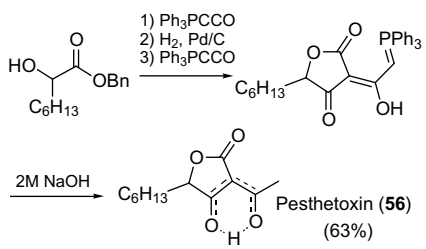


Figure 19. Structure of artapetalin A (**55**).



Scheme 9. Synthesis of pesthetoxin (**56**).[48]

4.2. 5-Spirotetronic acids

Tetrocarcins (**57**) constitute a growing class of spirotetronic acids with activities against some Gram-negative bacteria (e.g., *Bacillus subtilis*).[127] Tetrocarcin A (**57a**) showed activity against cells of sarcoma 180, P-388 leukemia and B16 melanoma.[128] Mechanistically, it selectively inhibited the mitochondrial functions of the Bcl-2 family of antiapoptotic proteins at one-digit micromolar concentrations. In addition, it induced up-regulation of heat-shock proteins involved in the endoplasmic reticulum stress-induced apoptotic pathway. Two new members with similar properties, aristostatin A (**58a**) and aristostatin B (**58b**), were isolated in 2000[129] and were shown to inhibit growth of human squamous cell carcinoma cells by inducing apoptosis (Fig. 20). Exposure of human AMC HN-4 cells to aristostatin A produced dose-dependent apoptosis featuring the expected markers (morphological features and DNA fragmentation), caspase-3 activation, loss of mitochondrial transmembrane potential, release of cytochrome *c* into cytosol, and generation of reactive oxygen species.[130] The aglycone of the tetrocarcins, (+)-tetronolide, which is also found in kijanolide and chlorothricolide[131] was recently synthesised by Boeckman Jr. et al. by connecting two major precursors via a ketene-trapping/intramolecular [4 + 2] cycloaddition strategy.[132] The structurally akin lobophorins A and **B**, isolated from fermentation broths of a marine bacterium recovered from the surface of the Caribbean brown alga *Lobophora variegata* (Dictyotales) were found to be potent inhibitors of topical PMA-induced oedema in the mouse ear assay when administered either topically or IP.[133]

Versipelostatin (**59**), a metabolite of *Streptomyces versipellis* 4083-SVS6, was discovered[134] in the course of a screening programme for modulators of protein GRP78, a molecular chaperone in endoplasmic reticulum (ER) that associates transiently with incipient proteins as they traverse the ER and that aids in their folding and transport.[135–137] The GRP78 protein is also induced under various stress conditions such as glucose starvation, inhibition of protein glycosylation and suppression of the ER-calcium-ATPase pump.[138,139] The

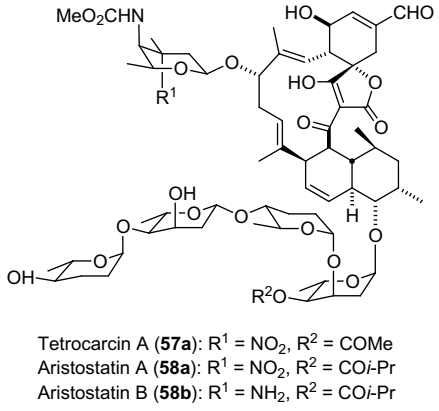
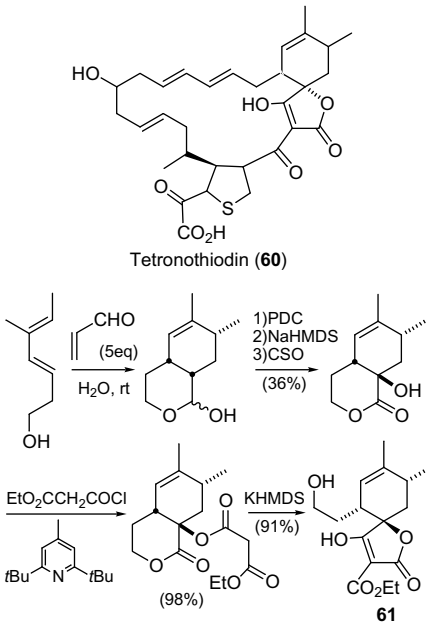


Figure 20. Structures of tetrocarcin A (**57a**) and aristostatins A (**58a**) and B (**58b**).

enhancement of ER stress response is generally a hallmark of tumours resistant against chemotherapy and hypoxic stress.[140] Overexpression of GRP78 enables tumour cells to grow under hypoxic and glucose starved conditions, which is typical of the core of solid tumours.[141] Versipelostatin is a potent down-regulator of the *grp78* gene and inhibits the expression of GRP78 induced by a variety of ER stress signals. It also exhibits limited cytotoxic activity against various cancer cell lines. The biosynthesis of **59** was elucidated on a non-genetic level by feeding/NMR experiments (Fig. 21).[142] *Streptomyces versipellis* 4083-SVS6 was cultivated in the presence of either [1-^{13}C]acetate, or [1,2-$^{13}C_2$]acetate, or [3-^{13}C]propionate, or [1,2,3-$^{13}C_3$] glycerol as polyketide precursors. The conclusion based upon the corresponding ^{13}C NMR spectra was that the α-acyltetronic acid moiety of **59** is composed of an acetate and a glycerol unit and that only glycerol, which might be converted to glyceric acid but not pyruvic acid, was utilised as the intermediate in the biosynthesis of the C_3 unit of the α-acyltetronic acid moiety. Feeding experiments with pyruvic acid and succinic acid suggested that downstream metabolites of glycerol do not revert to be precursors of this unit. The polyketide chain of **59** is built up from acetate, propionate and glycerol precursors. The precise order of connection of these fragments is still unclear as are the genes responsible for the biosynthesis of **59**.

Tetronothiodin(**60**) is an antagonist of the brain-type cholecystokinin (CCK-B) receptors. These receptors are widely distributed in the brain and have been shown to cause appetite,[143] pain[144] and anxiety.[145] The natural ligand CCK is a 33 amino acid peptide that functions as a gastrointestinal hormone having a variety of effects including pancreatic exocrine secretion, stimulation of gut motility and gallbladder contraction.[146] Tetronothiodin was isolated from *Streptomyces* sp. NR0489 and its structure was assigned on the basis of detailed spectroscopic analysis rather than by crystallography. The relative stereochemistry therefore remained unconfirmed.[147] Isomer **61** of the oxaspirobicyclic tetronic acid unit of **60**, diastereoisomeric at the spiro centre, has been synthesised in five steps by Page et al. (Scheme 10).[148] Diels–Alder reaction of a dienol with acrolein afforded the lactol endo-cycloadduct in a diastereoisomeric ratio of 2:1 at the hydroxy group. It was oxidised to the corresponding lactone which in turn was α-hydroxylated



Scheme 10. Tetronothiodin (**60**) and synthesis of an isomer **61** of the tetronic acid unit by Page et al.[148]

with sodium bis(trimethylsilyl)amide (NaHMDS)/(1*S*)-(+)-(10-camphorsulfonyl) oxaziridine (CSO). The resulting diastereomerically pure hydroxylactone was treated with excess ethyl malonyl chloride in the presence of 2,6-di-*t*-butyl-6-methylpyridine. The acylated product was finally Dieckmann cyclised with potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C to furnish **61** in 91% yield.

Four new abyssomicins E, G, H and *atrop*-C have been isolated and characterised since the 2006 in-depth review by Zografos and Georgiadis (Fig. 22).[7] Abyssomicin E (**62**) features a C_{19} skeleton and was isolated from *Streptomyces* sp. (HKI0381).[149] It is the first compound of this class, the absolute stereochemistry of which was directly established by single-crystal X-ray diffraction study using anomalous dispersion with copper radiation. The oxygenation at the carbon atom next to the carbonyl group is a structural variation that is otherwise not found in this compound class. Abyssomicins G (**63**), H (**64**) and *atrop*-C (*a*-**65**) were isolated from the marine *Verrucosispora* strain AB-18-032, a new member of this rare actinomycete genus.[150] *a*-**65** was found to be half as

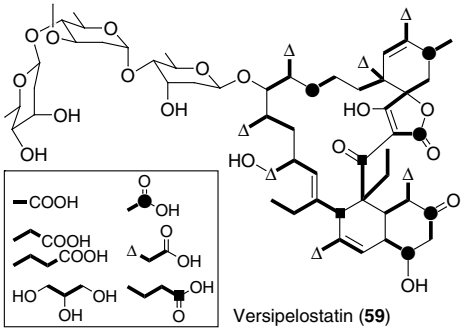


Figure 21. Biosynthetic origin of versipelostatin (**59**).

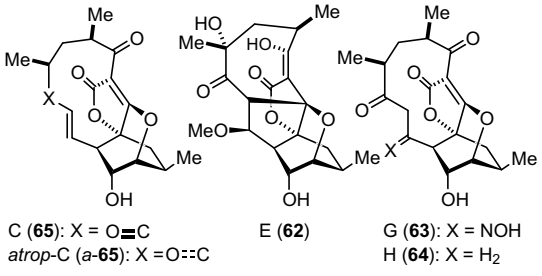


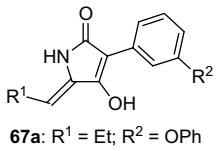
Figure 22. Structures of abyssomicins C (**65**), E (**62**), G (**63**), H (**64**) and *atrop*-C (**65**).

active again as an inhibitor of the *p*-aminobenzoate biosynthesis when compared with the longer known abyssomicin C (**65**).[151a] Both are strongly active against Gram-positive bacteria, including multi-resistant clinical isolates of *Staphylococcus aureus*.[151b] The mechanism of action is thought to imply an irreversible binding to the chorismate mutase via Michael addition to the enone acceptor system. This would also explain the inactivity of abyssomicins B, D, G, H and E lacking such a Michael system. Little is known about the biosynthesis of the abyssomicins which most likely should be similar to that of the kijanimicin-type antibiotics.

5. Synthetic derivatives with tailored biological properties

Tetronic, tetramic and N-substituted tetramic acids that can inhibit β-secretase (BACE-1) were recently identified using a solid-phase synthesis approach.[152,153] They were synthesised by loading of Fmoc-protected amino acids onto Wang resin, followed by N-deprotection, amidation and base catalysed cleavage from the resin with concomitant cyclisation to deliver compounds of general structure **66**, as depicted in Scheme 11. In this way, a small library was synthesised and the compounds screened in a FRET assay for BACE-1 inhibition. One of the most potent compounds isolated was **66a**, which had a moderate IC_{50} of 60 μM. BACE-1 is a member of the pepsin family of aspartyl proteases that has a crucial role in the abnormal cleavage of the β-amyloid precursor protein (β-APP) leading to the formation of β-amyloidpeptides (Aβ) and thence of amyloid plaques which are believed to be responsible in part for the onset of Alzheimer's disease (AD). Recent reports have demonstrated a direct correlation between increased BACE-1 activity and Aβ production in AD brain tissue.[154]

3-Aryl-5-alkylidenetetramic acids **67** have been designed as novel glycine site *N-methyl-*D*-aspartate (NMDA) receptor* antagonists with affinities for the strychnine insensitive glycine site as good as IC_{50} = 0.7 μM (vs. [^{3}H]-L-689,560) and binding constant K_B = 6.15 μM (inhibition of NMDA-induced depolarisation in rat cortical slices) in the case of **67a** (Fig. 23).[155] There is evidence that antagonists acting at the glycine site may



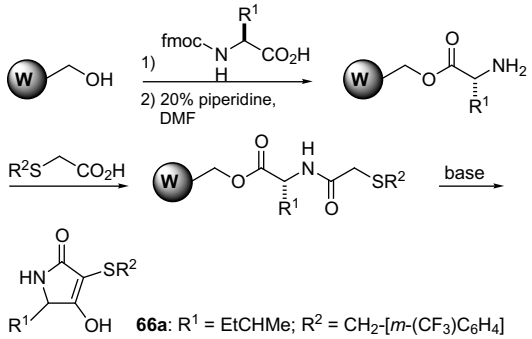
67a: R^1 = Et; R^2 = OPh

Figure 23. Structure of NMDA receptor antagonist **67a**.

have a superior side effect profile over uncompetitive antagonists such as dizocilpine (MK-801).[156] NMDA antagonists are of potential use in the treatment of neurological diseases.

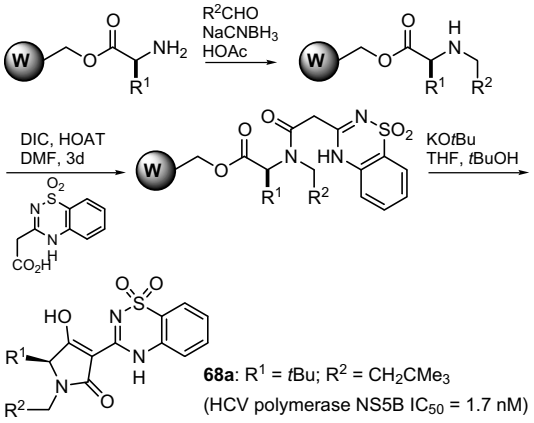
An efficient asymmetric solid-phase synthesis of benzothiadiazine substituted tetramic acids that are potent inhibitors of the *hepatitis C virus RNA-dependent RNA polymerase* was reported by Evans et al.[157] Reminiscent of the above sequence leading to compounds **66**, it started from commercially available chiral Fmoc-protected α-amino acids loaded onto Wang resin (Scheme 12). Fmoc removal, reductive amination followed by amide bond formation, and base-catalysed Dieckmann cyclisation with simultaneous cleavage from the resin provided the desired products **68**.

The ability of various synthetic 3-dienoyltetramic acids **69** to inhibit bacterial *DNA gyrase* was investigated by Rosen et al. back in 1989.[158] Out of a library of 33 compounds with variance in the residues at C5, N and at the terminal C=C bond those derivatives inhibited supercoiling by DNA gyrase isolated from *E. coli* H560 most effectively which bore only H atoms at C5 and three non-H substituents at the terminal double bond. Using norfloxacin as a standard (IC_{50} = 1 μg/mL), IC_{50}values were obtained for these derivatives ranging from 3 to 60 μg/mL which is superior to the efficacy of the natural tetramic acid inhibitor BU2313B[159] (IC_{50} ca. 100 μg/mL). β-Napthyl derivative **69b** was studied further and was found to show no cross-resistance with quinolones (inhibitors of DNA gyrase subunit A), coumermycin (inhibitor of DNA gyrase subunit B), or tirandamycin (Fig. 24). The quinolones and coumermycin were the only reported inhibitors of DNA gyrase at that time.



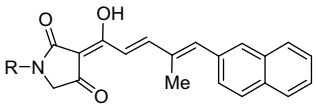
66a: R^1 = EtCHMe; R^2 = CH_2-[*m*-(CF_3)C_6H_4]

Scheme 11. Solid-phase synthesis of β-secretase inhibitory tetramic acids.[153]



68a: R^1 = *t*Bu; R^2 = CH_2CMe_3
(HCV polymerase NS5B IC_{50} = 1.7 nM)

Scheme 12. Solid-phase synthesis of HCV RNA polymerase inhibitor **68a**.[157]



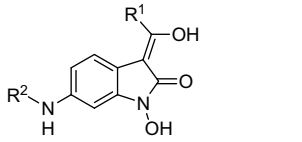
69a: R = H (IC_{50} = 3.5 μg/mL)
69b: R = Me (IC_{50} = 10.3 μg/mL)

Figure 24. Structures of DNA gyrase inhibitors **69**.

Based on a pharmacophore model emphasising the ligand interaction with two catalytic metal ions in the active site, a new class of *influenza endonuclease inhibitors* **70** with vinylogous tetramic acid structure was synthesised (Fig. 25). The most active compound **70a** in a library of 131 analogues exhibited an IC_{50} = 3 μM in cap-dependent transcription assays using RNP (RNA + nucleoprotein) purified from influenza A/PR/8/34 virus.[160]

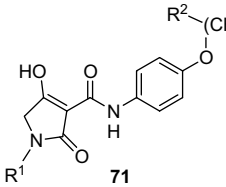
A series of tetramic acid based inhibitors of *plasminogen activator inhibitor-1 (PAI-1)* was synthesised and evaluated (Fig. 26).[161] Some of derivatives **71** showed excellent potency against PAI-1. Plasminogen activators (PAs) are serine proteases that control the conversion of the zymogen, plasminogen, to the active enzyme plasmin. Plasminogen activator inhibitor (PAI-1), a member of the serpin superfamily of protease inhibitors, is the major physiological inhibitor of PAs. Several studies have linked increased PAI-1 activity with thromboembolic disease[162] and with a poor prognosis in a variety of cancers.[163] It is believed to play a role in angiogenesis, invasion and metastasis.[164]

Losigamone ((±)-5(*R,S*)-5-(2-chlorophenyl) hydroxymethyl-4-methoxy(5*H*)-furan-2-one) **72** is an experimental *anticonvulsant* drug undergoing phase III clinical trials in patients with partial and secondary generalised seizures (Fig. 27). The drug has a good efficacy against experimentally induced seizures in rat and mice[165] and depresses various forms of epileptiform activity



70: R^1 = Me, Et, Ph; R^2 = acyl, carbamoyl, sulfonyl
70a: R^1 = Ph; R^2 = (*m*-CO_2H)C_6H_4-NHCO

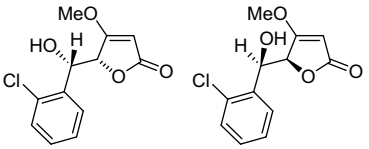
Figure 25. Structure of influenza endonuclease inhibitors **70**.



71

R^1	R^2	IC_{50} (μM)
4-Cl-Ph	CO_2H	5.00 ± 3.00
4-Cl-Ph	CO_2Me	> 50
4-Cl-Ph	tetrazole	0.69 ± 0.06
4-Me-Ph	CO_2H	1.95 ± 0.37
4-Me-Ph	tetrazole	0.89 ± 0.17

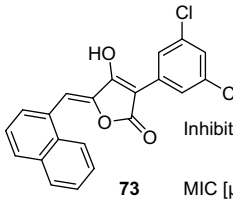
Figure 26. Structure of PAI-1 inhibitors **71**.



AO-242; (+)-*threo* AO-294; (–)-*threo*

Losigamone (**72**)

Figure 27. Structure of losigamone (**72**).



Inhibition of *E. coli* MurB: K_d = 40 nM; IC_{50} = 21 μM

73 MIC [μg mL^{-1}]: 1–2 (*S. aureus*) 2 (*E. coli*)

Figure 28. Structure of inhibitor **73** of bacterial peptidoglycan biosynthesis.

in vitro, such as low Mg^{2+} induced epileptiform activity and low Ca^{2+} induced epileptiform discharges. It decreases the frequency of spontaneous action potentials and suppresses repetitive firing of neurons.[166] Losigamone is a racemic mixture of two *threo* isomers. Both in vitro and in vivo experiments confirmed that their pharmacological activity profiles are not identical and suggested that excitatory amino acid mediated processes are involved in the mode of action of (+)-*threo*losigamone whereas (−)-*threo*losigamone does not possess such properties. For the treatment of neurological conditions involving exaggerated excitatory amino acid function the use of (+)-*threo*losigamone might therefore be most effective clinically.[167]

A pathway screen targeting multiple *muramyl peptide synthesis inhibitors* identified the 3-aryl-5-naphthylmethylidenetetronic acids series. Its optimization based on IC_{50}, K_d and MIC values led to potent inhibitors of bacterial peptidoglycan biosynthesis such as **73** (Fig. 28). One compound was co-crystallised in the active site of *E. coli* MurB (PDB Code: 2Q85, RCSB 043269).[168]

Acknowledgment

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References and notes

1. Henning, H.-G.; Gelbin, A. *Adv. Heterocycl. Chem.* **1993**, *57*, 139–185.
2. Rosen, T. *Drugs Future* **1989**, *14*, 153–163.
3. Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981–2001.
4. Ghisalberti, E. L. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, 2003; Vol. 28/1, pp 109–163.

5. Gossauer, A. Monopyrrolic natural compounds including tetramic acid derivatives. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer: Wien New York, 2003; Vol. 86, pp 1–188.
6. Tejedor, D.; Garcia-Tellado, F. *Org. Prep. Proced. Int.* **2004**, *36*, 35–59.
7. Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157–3188.
8. Steyn, P. S.; Wessels, P. L. *Tetrahedron Lett.* **1978**, *47*, 4707–4710.
9. Nolte, M. J.; Steyn, P. S.; Wessels, P. L. *J. Chem. Soc. Perkin 1* **1980**, 1057–1065.
10. Barkley, J. V.; Markopoulos, J.; Igglessi-Markopoulou, O. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1057–1065.
11. Shimshock, S. J.; DeShong, P. *Stud. Nat. Prod. Chem.* **1994**, *14*, 97–141.
12. Saito, K.; Yamaguchi, T.; Tsujimoto, T.; Yuki, H. *J. Heterocycl. Chem.* **1976**, *13*, 533–537.
13. Saito, K.; Yamaguchi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 651–652.
14. Steyn, P. S.; Rabie, C. J. *Phytochemistry* **1976**, *15*, 1977–1979.
15. (a) Lebrun, M. H.; Duvert, P.; Gaudemer, F.; Gaudemer, A.; Deballon, C.; Boucly, P. *J. Inorg. Biochem.* **1985**, *24*, 167–181; (b) Lebrun, M. H.; Nicolas, L.; Boutar, M.; Gaudemer, F.; Ranomenjanahary, S.; Gaudemer, A. *Phytochemistry* **1988**, *27*, 77–84.
16. Fujita, M.; Nakao, Y.; Matsunaga, S.; Seiki, M.; Itoh, H.; van Soest, R. W. M.; Fusetani, N. *Tetrahedron* **2001**, *57*, 1229–1234.
17. Dippenaar, A.; Holzapfel, C. W.; Boeyens, J. C. A. *J. Cryst. Mol. Struct.* **1978**, *7*, 189.
18. Kaufmann, G. F.; Sartorio, R.; Lee, S.; Rogers, C. J.; Meijler, M. M.; Moss, J. A.; Clapham, B.; Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 309–314.
19. Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H.-B.; Peter, H. H.; Roesel, J. *J. Antibiot.* **1994**, *47*, 136–142.
20. Hamaguchi, T.; Sudo, T.; Osada, H. *FEBS Lett.* **1995**, *372*, 54–58.
21. Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Usui, T.; Ueda, K.; Osada, H. *J. Med. Chem.* **2001**, *44*, 3216–3222.
22. (a) Davies, D. H.; Norris, G. L. F. GB Patent 2.027.013, 1980; (b) Davies, D. H.; Snape, E. W.; Suter, P. J.; King, T. J.; Falshaw, C. P. *J. Chem. Soc. Chem. Commun.* **1981**, 1073–1074.
23. Schwarzer, D.; Finking, R.; Marahiel, M. A. *Nat. Prod. Rep.* **2003**, *20*, 275–287.
24. Sims, J. W.; Fillmore, J. P.; Warner, D. D.; Schmidt, E. W. *Chem. Commun.* **2005**, *2*, 186–188.
25. Staunton, J.; Weissman, K. *Nat. Prod. Rep.* **2001**, *18*, 380–416.
26. Fieseler, L.; Hentschel, U.; Grozdanov, L.; Schirmer, A.; Wen, G.; Platzer, M.; Hrvatin, S.; Butzke, D.; Zimmermann, K.; Piel, J. *Appl. Environ. Microbiol.* **2007**, *73*, 2144–2155.
27. Bentley, R.; Bhate, D. S.; Keil, J. G. *J. Biol. Chem.* **1962**, *237*, 859–866.
28. Sekiyama, Y.; Fujimoto, Y.; Hasumi, K.; Endo, A. *J. Org. Chem.* **2001**, *66*, 5649–5654.
29. Sun, Y.; Hong, H.; Gillies, F.; Spencer, J. B.; Leadlay, P. F. *ChemBioChem*, 2007, doi: doi:10.1002/cbic.200700492.
30. (a) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365–394; (b) Ichihara, A.; Oikawa, H. The Diels–Alder reaction in biosynthesis of polyketide phytotoxin. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: Amsterdam, 1999; Vol. 1, p 367.
31. Schlegel, B.; Schmidtke, M.; Dörfelt, H.; Kleinwächter, P.; Gräfe, U. *J. Basic Microbiol.* **2001**, *41*, 179–183.
32. Gallardo, G. L.; Penia, N. I.; Chacana, P.; Terzolo, H. R.; Cabrera, G. M. *World J. Microbiol. Biotechnol.* **2004**, *20*, 609–612.
33. Chen, S.; Xu, X.; Dai, X.; Yang, C.; Qiang, S. *Biochim. Biophys. Acta* **2007**, *1767*, 306–318.
34. Aoki, S.; Higuchi, K.; Ye, Y.; Satari, R.; Kobayashi, M. *Tetrahedron* **2000**, *56*, 1833–1836.
35. Wang, C.-Y.; Wang, B.-G.; Wiryowidagdo, S.; Wray, V.; van Soest, R.; Steube, K. G.; Guan, H.-S.; Proksch, P.; Ebel, R. *J. Nat. Prod.* **2003**, *66*, 51–56.
36. Xu, J.; Hasegawa, M.; Harada, K.-I.; Kobayashi, H.; Nagai, H.; Namikoshi, M. *Chem. Pharm. Bull.* **2006**, *54*, 852–854.
37. Oda, T.; Fujita, A.; Xu, M.; Mochizuki, M.; Namikoshi, M. *Marine Drugs* **2007**, *5*, 1–5.
38. Biersack, B.; Diestel, R.; Jagusch, C.; Rapp, G.; Sasse, F.; Schobert, R. *Bioorg. Med. Chem.*, submitted for publication.
39. Schobert, R.; Jagusch, C. *Tetrahedron* **2005**, *61*, 2301–2307.
40. Schobert, R.; Jagusch, C.; Melanophy, C.; Mullen, G. *Org. Biomol. Chem.* **2004**, *2*, 3524–3529.
41. Lin, Z.-J.; Lu, Z.-Y.; Zhu, T.-J.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M. *Chem. Pharm. Bull.* **2008**, *56*, 217–221.
42. (a) Gänzle, M. G.; Höltzel, A.; Walter, J.; Jung, G.; Hammes, W. P. *Appl. Environ. Microbiol.* **2000**, *66*, 4325–4333; (b) Höltzel, A.; Gänzle, M. G.; Nicholson, G. J.; Hammes, W. P.; Jung, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2766–2768.
43. (a) Gänzle, M. G. *Appl. Microbiol. Biotechnol.* **2004**, *64*, 326–332; (b) Gänzle, M. G.; Vogel, R. F. *Appl. Environ. Microbiol.* **2003**, *69*, 1305–1307.
44. Marquardt, U.; Schmid, D.; Jung, G. *Synlett* **2000**, *8*, 1131–1132.
45. Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1177.
46. Böhme, R.; Jung, G.; Breitmaier, E. *Helv. Chim. Acta* **2005**, *88*, 2841–2873.
47. Lacey, R. N. *J. Chem. Soc.* **1954**, 850–854.
48. Schobert, R.; Dietrich, M.; Mullen, G.; Urbina-Gonzales, J. M. *Synthesis* **2006**, 3902–3914.
49. Lang, G.; Cole, A. L. J.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2006**, *69*, 151–153.
50. Hopmann, C.; Kurz, M.; Brönstrup, M.; Wink, J.; LeBeller, D. *Tetrahedron Lett.* **2002**, *43*, 435–438.
51. Kunze, B.; Schabacher, K.; Zahner, H.; Zeeck, A. *Arch. Microbiol.* **1972**, *86*, 147–174.
52. Kunze, B. Lipomycine, neue polyenartige Antibiotika aus *Streptomyces aureofaciens*: Untersuchungen zur Wirkungsweise. PhD thesis, Universität Tübingen, Germany, 1975.
53. Bihlmaier, C. Polyenantibiotika aus Streptomyceten – Molekularbiologische Untersuchungen zur Biosynthe-se von Simocyclinon und α-Lipomycin. PhD thesis, Albert-Ludwigs Universität, Freiburg, Germany, 2005.
54. Karwowski, J. P.; Jackson, M.; Theriault, R. J.; Barlow, T. G.; Coen, L.; Hensey, D. M.; Humphrey, P. E. *J. Antibiot.* **1992**, *45*, 1125–1132.
55. Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225–4236.
56. Tuske, S.; Sarafianos, S. G.; Wang, X.; Hudson, B.; Sineva, E.; Mukhopadhyay, J.; Birktoft, J. J.; Leroy, O.; Ismail, S.; Clark, A. D., Jr.; Dharia, C.; Napoli, A.;

Laptenko, O.; Lee, J.; Borukhov, S.; Ebright, R. H.; Arnold, E. *Cell* **2005**, *122*, 541–552.
57. Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854–860.
58. Iwata, Y.; Maekawara, N.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1532–1536.
59. Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145–1174.
60. Ito, Y.; Fuji, S.; Saeguso, T. *J. Org. Chem.* **1976**, *41*, 2073–2074.
61. Nowak, A.; Steffan, B. *Angew. Chem. Int. Ed.* **1998**, *37*, 3139–3141.
62. Longbottom, D. A.; Morrison, A. J.; Dixon, D. J.; Ley, S. V. *Tetrahedron* **2003**, *59*, 6955–6966.
63. Sing, S. B.; Zink, D. L.; Heimbach, B.; Genilloud, O.; Teran, A.; Silverman, K. C.; Lingham, R. B.; Felock, P.; Hazuda, D. J. *Org. Lett.* **2002**, *4*, 1123–1126.
64. Burmeister, H. R.; Bennet, G. A.; Vesonder, R. F.; Hesseltine, C. W. *J. Antimicrob. Agents Chemother.* **1974**, *5*, 634–639.
65. Turos, E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231–8236.
66. Singh, S. B.; Zink, D. L.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Hazuda, D. J. *Tetrahedron Lett.* **1998**, *39*, 2243–2246.
67. Vesonder, R. F.; Tjarks, L. W.; Rohwedder, W. K.; Burmeister, H. R.; Laugal, J. A. *J. Antimicrob. Agents Chemother.* **1979**, *32*, 750–761.
68. Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Lett.* **2000**, *2*, 3611–3613.
69. Marfori, E. C.; Kajiyama, S.; Fukusaki, E.; Kobayashi, A. *Z. Naturforsch.* **2002**, *57c*, 465–470.
70. Marfori, E. C.; Bamba, T.; Kajiyama, S.; Fukusaki, E.; Kobayashi, A. *Tetrahedron* **2002**, *58*, 6655–6658.
71. Marfori, E. C.; Bamba, T.; Kajiyama, S.; Fukusaki, E.; Kobayashi, A. *Phytochemistry* **2003**, *62*, 715–721.
72. Segeth, M. P.; Bonnefoy, A.; Brönstrup, M.; Knauf, M.; Schummer, D.; Toti, L.; Vertesy, L.; Wetzel-Raynal, M.-C.; Wink, J.; Seibert, G. *J. Antibiot.* **2003**, *56*, 114–122.
73. Hellwig, V.; Grothe, T.; Mayer-Bartschmid, A.; Endermann, R.; Geschke, F.-R.; Henkel, T.; Stadler, M. *J. Antibiot.* **2002**, *55*, 881–892.
74. Sugie, Y.; Dekker, K. A.; Inagaki, T.; Kim, Y.-J.; Sakakibara, T.; Sakemi, S.; Sugiura, A.; Brennan, L.; Duigman, J.; Sutcliffe, J. A.; Kojima, Y. *J. Antibiot.* **2002**, *55*, 19–24.
75. Lang, G.; Blunt, J. W.; Cummings, N. J.; Cole, A. L. J.; Munro, M. H. G. *J. Nat. Prod.* **2005**, *68*, 810–811.
76. Furumai, T.; Eto, K.; Sasaki, T.; Higuchi, H.; Onaka, H.; Saito, N.; Fujita, T.; Naoki, H.; Igarashi, Y. *J. Antibiot.* **2002**, *55*, 873–880.
77. Sullivan, R. F.; Holtman, M. A.; Zylstra, G. J.; White, F.; Kobayashi, D. Y. Y. *J. Appl. Microbiol.* **2003**, *94*, 1079–1086.
78. Gunasekera, S. P.; Gunasekera, M.; McCarthy, P. *J. Org. Chem.* **1991**, *56*, 4830–4833.
79. Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sasaki, H. *J. Antibiot.* **1972**, *25*, 271–280.
80. Aizawa, S.; Akutsa, H.; Satomi, T.; Nagatsu, T.; Taguchi, R.; Seino, A. *J. Antibiot.* **1979**, *32*, 193–196.
81. Yu, F.; Zaleta-Rivera, K.; Zhu, X.; Huffman, J.; Millet, J. C.; Harris, S. D.; Yuen, G.; Li, X.; Du, L. *Antimicrob. Agents Chemother.* **2007**, *51*, 64–72.
82. (a) Graupner, P. R.; Thornburgh, S.; Mathieson, J. T.; Chapin, E. L.; Kemmitt, G. M.; Brown, J. M.; Snipes, C. E. *J. Antibiot.* **1997**, *50*, 1015–1019; for maltophilin see: (b) Jakobi, M.; Winkelmann, G.; Kaiser, D.; Kempter, C.; Jung, G.; Berg, G.; Bahl, H. *J. Antibiot.* **1996**, *49*, 1101–1104.
83. Kanazawa, S.; Fusetani, N.; Matsunaga, S. *Tetrahedron Lett.* **1993**, *34*, 1065–1068.
84. Bae, M.-A.; Yamada, K.; Ijuin, Y.; Tsuji, T.; Yazawea, K.; Tomono, Y.; Uemura, D. *Heterocycl. Commun.* **1996**, *2*, 315–318.
85. Capon, R. J.; Skene, C.; Lacey, E.; Gill, J. H.; Wadsworth, D.; Friedel, T. *J. Nat. Prod.* **1999**, *62*, 1256–1259.
86. (a) Cramer, N.; Buchweiz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem. Eur. J.* **2006**, *12*, 2488–2503; (b) Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 820–822.
87. Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094–1095.
88. Graupner, P. R.; Carr, A.; Clancy, E.; Gilbert, J.; Bailey, K. L.; Derby, J.-A.; Gerwick, B. C. *J. Nat. Prod.* **2003**, *66*, 1558–1561.
89. Ramana, C. V.; Mondal, M. A.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 4061–4064.
90. Ding, W.; Williams, D. R.; Northcote, P.; Seigal, M. M.; Tsao, R.; Ashcroft, J.; Morton, G. O.; Alluri, M.; Abbanat, D.; Maiese, W. M.; Ellestad, G. A. *J. Antibiot.* **1994**, *47*, 1250–1257.
91. Singh, M. P.; Petersen, N. V.; Mroczenski-Widley, M.; Maiese, W. M.; Greenstein, M.; Steinberg, D. A. *J. Antibiot.* **1994**, *47*, 1258–1265.
92. Abbanat, D.; Maiese, W. M.; Greenstein, M. *J. Antibiot.* **1999**, *52*, 117–126.
93. Zehner, S.; Kotzsch, A.; Bister, B.; Süssmuth, R. D.; Mendez, C.; Salas, J. A.; van Pée, K.-H. *Chem. Biol.* **2005**, *12*, 445–452.
94. Holzapfel, C. W. *Tetrahedron* **1968**, *24*, 2101–2119.
95. Siedler, N. W.; Iona, I.; Vegh, M.; Martonsi, A. *J. Biol. Chem.* **1989**, *264*, 17816–17823.
96. Moncoq, K.; Trieber, C. A.; Young, H. S. *J. Biol. Chem.* **2007**, *282*, 9748–9757.
97. Rao, B. L.; Husain, A. *Mycopathologia* **1985**, *89*, 177–180.
98. Cole, R. J. *Mycotoxin Res.* **1986**, *2*, 3–7.
99. Riley, R. T.; Goeger, D. E.; Yoo, H.; Showker, J. L. *Toxicol. Appl. Pharmacol.* **1992**, *114*, 261–267.
100. (a) Goeger, D. E.; Riley, R. T.; Domer, J. W.; Cole, R. J. *Biochem. Pharmacol.* **1988**, *37*, 978–981; (b) Goeger, D. E.; Riley, R. T. *Biochem. Pharmacol.* **1989**, *38*, 3995–4003.
101. Riley, R. T.; Showker, J. L. *Toxicol. Appl. Pharmacol.* **1991**, *109*, 108–126.
102. Pettit, G. R.; Kamano, Y.; Dufresne, C.; Cerny, R. L.; Herald, C. L.; Schmidt, J. M. *J. Org. Chem.* **1989**, *54*, 6005–6006.
103. Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **1999**, *62*, 1702–1706.
104. Fennell, B. J.; Carolan, S.; Pettit, G. R.; Bell, A. *J. Antimicrob. Chemother.* **2003**, *51*, 833–841.
105. (a) Shoji, J.; Sakazaki, R.; Hattori, T.; Matsumoto, K.; Uotani, N.; Yoshida, T. *J. Antibiot.* **1989**, *42*, 1729–1733; (b) Terui, Y.; Sakazaki, R.; Shoji, J. *J. Antibiot.* **1990**, *43*, 1245–1253; (c) Sakazaki, R.; Shoji, J. *J. Antibiot.* **1990**, *43*, 1245–1253; (d) Yoshida, T.; Hattori, T.; Matsumoto, K.; Terui, Y.; Shoji, J. EP 0 365 329 A2, JP 266575, 1988.
106. Mashimo, Y.; Sekiyama, Y.; Araya, H.; Fujimoto, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 649–651.
107. Ley, S. V.; Trudell, M. L.; Wadsworth, D. J. *Tetrahedron* **1991**, *47*, 8285–8296.
108. Jagusch, C.; Schobert, R. *J. Org. Chem.* **2005**, *70*, 6129–6132.

109. Roggo, B. E.; Hug, P.; Moss, S.; Raschdorf, F.; Peter, H. H. *J. Antibiot.* **1994**, *47*, 143–147.
110. Shinagawa, S.; Muroi, M.; Itoh, T. Jpn. Kokai Tokkyo Koho JP 05-43568, 1993.
111. Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Morisaki, N.; Hashimoto, Y. *Chem. Pharm. Bull.* **2001**, *49*, 206–212.
112. Sodeoka, M.; Sampe, R.; Kagamizono, T.; Osada, H. *Tetrahedron Lett.* **1996**, *37*, 8775–8778.
113. Osada, H.; Shimizu, S.; Sodeoka, M.; Hirai, T.; Ishida, K. Jpn. Kokai Tokkyo Koho JP 2003-270049, CAN 142:148769, 2005.
114. Usui, T.; Kojima, S.; Kidokoro, S.; Ueda, K.; Osada, H.; Sodeoka *Chem. Biol.* **2001**, *8*, 1209–1220.
115. Liu, Y.; Jung, J. H.; Zhang, S. *Biochem. Syst. Ecol.* **2006**, *34*, 774–776.
116. Liu, Y.; Hong, J.; Lee, C.-O.; Im, K. S.; Kim, N. D.; Choi, J. S.; Jung, J. H. *J. Nat. Prod.* **2002**, *65*, 1307–1314.
117. (a) Perry, N. B.; Battershill, C. N.; Blunt, J. W.; Fenwick, G. D.; Munro, M. H. G.; Bergquist, P. R. *Biochem. Syst. Ecol.* **1987**, *15*, 373–376; (b) Barrow, C. J.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B. *J. Nat. Prod.* **1988**, *51*, 275–281.
118. Pawlik, J. R.; McFall, G.; Zea, S. *J. Chem. Ecol.* **2002**, *28*, 1103–1115.
119. Choi, H. J.; Choi, Y. H.; Yee, S.-B.; Im, E.; Jung, J. H.; Kim, N. D. *Mol. Carcinog.* **2005**, *44*, 162–173.
120. Willis, C.; Bodio, E.; Bourdreux, Y.; Billaud, C.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 6421–6424.
121. Foden, F. R.; McCormick, J.; O'Mant, D. M. *J. Med. Chem.* **1975**, *18*, 199–203.
122. Söderberg, U. *Acta Physiol. Scand.* **1952**, *27*, 97–98.
123. Vartia, K. O. In *The Lichens*; Ahmadjian, V., Hale, M. E., Eds.; Academic Press: New York, 1973; pp 548–551, Chapter 17.
124. Richardson, D. H. S. *The Vanishing Lichens*; Hafner Press: New York, 1974, p 99.
125. Wong, H.-F.; Brown, G. D. *Phytochemistry* **2002**, *59*, 99–104.
126. Kimura, J.; Kouge, A.; Nakamura, K.; Koshino, H.; Uzawa, J.; Fujioka, S.; Kawano, T. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1624–1626.
127. (a) Tomita, F.; Tamaoki, T.; Shirahata, K.; Kasai, M.; Morimoto, M.; Ohkubo, S.; Mineura, K.; Ishii, S. *J. Antibiot.* **1980**, *33*, 668–670; (b) Tomita, F.; Tamaoki, T. *J. Antibiot.* **1980**, *33*, 940–945.
128. (a) Nakashima, T.; Miura, M.; Hara, M. *Cancer Res.* **2000**, *60*, 1229–1235; (b) Hara, T.; Omura-Minamisawa, M.; Chao, C.; Nakagami, Y.; Ito, M.; Inoue, T. *Int. J. Radiat. Oncol. Biol. Phys.* **2005**, *61*, 517–528.
129. Tinhofer, I.; Anether, G.; Senfter, M.; Pfaller, K.; Bernhardt, D.; Hara, M.; Greil, R. *FASEB J* **2002**, *16*, 1295–1297.
130. Kim, Y.-H.; Shin, H. C.; Song, D. W.; Lee, S.-H.; Furumai, T.; Park, J.-W.; Kwon, T. K. *Biochem. Biophys. Res. Commun.* **2003**, *309*, 449–456.
131. Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419.
132. Boeckman, R. K., Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, T. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572–10588.
133. Jiang, Z.-D.; Jensen, P. R.; Fenical, W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2003–2006.
134. Park, H.-R.; Furihata, K.; Hayakawa, Y.; Shinya, K. *Tetrahedron Lett.* **2002**, *43*, 6941–6945.
135. Kaufman, R. J. *Genes Dev.* **1999**, 1211–1233.
136. Yoshida, H.; Haze, K.; Yanagi, H.; Yura, T.; Mori, K. *J. Biol. Chem.* **1998**, *273*, 33741–33749.
137. Roy, B.; Lee, A. S. *Nucleic Acids Res.* **1999**, *27*, 1437–1443.
138. Wang, Y.; Shen, J.; Arenzana, N.; Tirasophon, W.; Kaufman, R. J.; Prywes, R. *J. Biol. Chem.* **2000**, *275*, 27013–27020.
139. Clapham, D. E. *Cell* **1995**, *80*, 259–268.
140. Katschinski, D. M.; Jacobson, E. L.; Wiedmann, G. J.; Robins, H. I. *J. Cancer Res. Clin. Oncol.* **2001**, *127*, 425–435.
141. Yun, J.; Tomida, A.; Nagata, K.; Tsuruo, T. *Oncol. Res.* **1995**, *7*, 583–590.
142. Chijiwa, S.; Park, H.-R.; Furihata, K.; Ogata, M.; Endo, T.; Kuzuyama, T.; Hayakawa, Y.; Shinya, K. *Tetrahedron Lett.* **2003**, *44*, 5897–5900.
143. Dourish, C. T.; Rycroft, W.; Iversen, S. D. *Science* **1989**, *245*, 1509–1511.
144. Dourish, C. T.; O'Neil, M. F.; Coughlan, J.; Kitchener, S. J.; Hawley, D.; Iversen, S. D. *Eur. J. Pharmacol.* **1990**, *176*, 35–44.
145. Ravard, S.; Dourish, C. T. *Trends Pharmacol. Sci.* **1990**, *11*, 271–273.
146. Kuwahara, T.; Kudoh, T.; Nagase, H.; Takamiya, M.; Nakano, A.; Ohtsuka, T.; Yoshizaki, H.; Arisawa, M. *Eur. J. Pharmacol.* **1992**, *221*, 99–105.
147. Murayama, T.; Matsumori, Y.; Iwata, N.; Ito, M.; Taniguchi, T.; Chihara, K.; Matsui, T. *Jap. J. Cancer Res.* **1996**, *87*, 743–750.
148. Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, 1022–1024.
149. Niu, X.-M.; Li, S.-H.; Görls, H.; Schollmeyer, D.; Hilliger, M.; Grabley, S.; Sattler, I. *Org. Lett.* **2007**, *9*, 2437–2440.
150. Keller, S.; Nicholson, G.; Drahl, C.; Sorensen, E.; Fiedler, H.-P.; Süssmuth, R. D. *J. Antibiot.* **2007**, *60*, 391–394.
151. (a) Keller, S.; Schadt, H. S.; Örtel, I.; Süssmuth, R. D. *Angew. Chem.* **2007**, *119*, 8433–8435; (b) Riedlinger, J.; Reicke, A.; Zähner, H.; Krismer, B.; Bull, A. T.; Maldonado, L. A.; Ward, A. C.; Goodfellow, M.; Bister, B.; Bischoff, D.; Süssmuth, R. D.; Fiedler, H.-P. *J. Antibiot.* **2004**, *57*, 271–279.
152. Edwards, P. *Drug Discovery Today* **2007**, *12*, 345–346.
153. Larbig, G.; Schmidt, B. *J. Comb. Chem.* **2006**, *8*, 480–490.
154. Li, R.; Lindholm, K.; Yang, L.-B.; Yue, X.; Citron, M.; Yan, R.; Beach, T.; Sue, L.; Sabbagh, M.; Cai, H.; Wong, P.; Price, D.; She, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 3632–3637.
155. Mawer, I. M.; Kulagowski, J. J.; Leeson, P. D.; Grimwood, S.; Marshall, G. R. *Bioorg. Med. Chem. Lett.* **1995**, *22*, 2643–2648.
156. Leeson, P. D.; Iversen, L. L. *J. Med. Chem.* **1994**, *37*, 4053–4067.
157. Evans, K. A.; Chai, D.; Graybill, T. L.; Burton, G.; Sarisky, R. T.; Lin-Goerke, J.; Johnston, V. K.; Riveroa, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2205–2208.
158. Rosen, T.; Fernandes, P. B.; Marovich, M. A.; Shen, L.; Mao, J.; Pernet, A. G. *J. Med. Chem.* **1989**, *32*, 1062–1069.
159. Tsukiura, H.; Tomita, K.; Hanada, M.; Kobaru, S.; Tsunakawa, M.; Fujisawa, K.-I.; Kawaguchi, H. *J. Antibiot.* **1980**, *33*, 157–165.
160. Parkes, K. E. B.; Ermert, P.; Fässler, J.; Ives, J.; Martin, J. A.; Merrett, J. H.; Obrecht, D.; Williams, G.; Klumpp, K. *J. Med. Chem.* **2003**, *46*, 1153–1164.
161. Folkes, A.; Brown, S. D.; Canne, L. E.; Chan, J.; Engelhardt, E.; Epshteyn, S.; Faint, R.; Golec, J.; Hanel,

A.; Kearney, P.; Leahy, J. W.; Mac, M.; Matthews, D.; Prisbylla, M. P.; Sanderson, J.; Simon, R. J.; Tesfai, Z.; Vicker, N.; Wang, S.; Webb, R. R.; Charlton, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1063–1066.
162. Dawson, S.; Henney, A. *Atherosclerosis* **1992**, *95*, 105–117.
163. Pappot, H.; Gardsvoll, H.; Rømer, J.; Pedersen, A.; Grøndahl-Hansen, J.; Pyke, C.; Brünner, N. *Biol. Chem. Hoppe-Seyler* **1995**, *376*, 259–267.
164. Bajou, K.; Noel, A.; Gerard, R. D.; Masson, V.; Brunner, N.; Holst-Hansen, C.; Skobe, M.; Fusenig, N. E.; Carmeliet, P.; Collen, D.; Foidart, J. M. *Nat. Med.* **1998**, *4*, 923–928.
165. Zhang, C. L.; Chatterjee, S.; Stein, U.; Heinemann, U. *Naunyn Schmiedebergs Arch. Pharmacol.* **1992**, *345*, 85–92.
166. (a) Gebhardt, C.; Breustedt, J. M.; Noldner, M.; Chatterjee, S. S.; Heinemann, U. *Brain Res.* **2001**, *920*, 27–31; (b) Draguhn, A.; Jungclaus, M.; Sokolowa, S.; Heinemann, U. *Eur. J. Pharmacol.* **1997**, *325*, 245–251.
167. Jones, F. A.; Davies, J. A. *Br. J. Pharmacol.* **1999**, *128*, 1223–1228.
168. Mansour, T. S.; Caufield, C. E.; Rasmussen, B.; Chopra, R.; Krishnamurthy, G.; Morris, K. M.; Svenson, K.; Bard, J.; Smeltzer, C.; Naughton, S.; Antane, S.; Yang, Y. J.; Severin, A.; Quagliato, D.; Petersen, P. J.; Singh, G. *ChemMedChem* **2007**, *2*, 1414–1417.

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