Reviews

Naturally Occurring Proline Analogues

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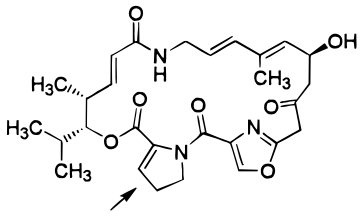
Introduction

Two earlier reviews (in 1966 and 1977) were published on the subject of proline analogs,[1,2] including both natural and synthetic compounds. The present review is restricted to naturally occurring compounds based upon the pyrrolidine-2-carboxylic acid structure, both as the free amino acids and embedded in larger structures, usually peptides (however, analogues incorporated by "directed biosynthesis" are not covered). Unlike the earlier reviews,[1,2] the present compilation does not include the compounds with other ring sizes such as azetidine-2-carboxylic acid and pipecolic acid. *N*-Substituted derivatives of proline itself are not included, but those of proline analogs are. The compounds reviewed are discussed in terms of source, structure, and biological activity (where relevant), but not synthesis.

1. Dehydroprolines

2,3-Dehydroproline. Although unstable under hydrolytic conditions, 2,3-dehydro-L-proline is a component of the cyclopeptolide antibiotic ostreogrycin A (**1**) from *Streptomyces ostreogriseus.*[3,4] The same compound from



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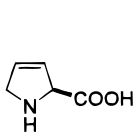
other strains of *Streptomyces* has been named mikamycin A, pristinamycin II_A, staphylomycin M_1, streptogramin A, syncothrecin A, synergistin A1, vernamycin A, virginiamycin M_1, etc., and is one of several congeners that display antimicrobial synergy with members of another class of antibiotics[5] (depsipeptides). Isotopic labeling experiments demonstrated that L-proline is the precursor of the 2,3-dehydroproline residue in virginiamycin M_1.[6]

3,4-Dehydroproline. 3,4-Dehydro-L-proline (**2**) was identified in hydrolysates of phomopsins A and B, mycotoxins from *Phomopsis leptostromiformis.*[7,8] Consumption of lupins infected with this fungus causes severe liver damage in cattle and sheep.[9] The phomopsins inhibit the polymerization of tubulin and depolymerize preformed microtubules.[10]

1,2-Dehydropyrrolidine-5-carboxylic Acid and Related Compounds. This compound (**3**) accumulates in culture filtrates of a proline-requiring mutant of *Escherichia coli.*[11]

Siderochelin A (**4**) is a ferrous iron chelating antibiotic from *Norcardia* species.[12]



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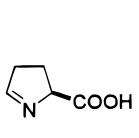

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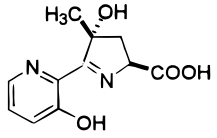

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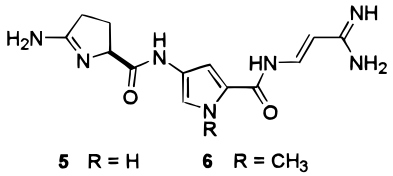
The antibiotics termed kikumycins A (**5**) and B (**6**)[13−15] (from *Streptomyces phaeochromogenes)*, noformicin (**7**)[16] (from *Nocardia formica*), and anthelvencin A (**8**)[17,18] (from *Streptomyces venezuelae*) have also been represented as having structures with the tautomeric 5-iminoprolyl moiety. These compounds have antimicrobial, and also antiviral activity, especially noformicin.[19,20] Their biological activity is exerted through binding to the minor groove of DNA.[21,22]



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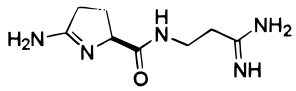

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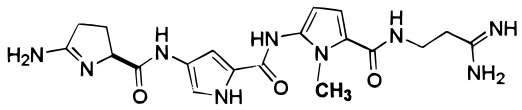

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2. Carbon-Substituted Prolines

A. 3-Substituted Prolines. 3-Methylproline. *cis*-3-Methyl-L-proline (**9**) was identified[23] in hydrolysates of the peptide antibiotic bottromycin A_2, a member of an antibiotic complex from *Streptomyces* species,[24] and from *Kitasatoa kauaiensie, Kitasatoa purpurea* and *Micromonospora chalcea.* Originally believed to be

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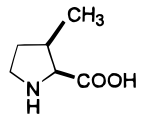
acyclic,[23,24] structural revisions[25,26] led to the cyclic structure. The bottromycins are active against Gram-positive bacteria and mycobacteria.[27]

trans-3-Methyl-L-proline (**10**) is a component of the mycotoxin, roseotoxin B, a cyclodepsipeptide elaborated by the fungus, *Trichotheceum roseum*.[28,29] Recently, a novel member of the destruxin family, destruxin A5, which has insecticidal activity, has been isolated from an undescribed species of fungus from the genus *Aschersonia*.[30] Destruxin A5 contains a 3-methylproline residue of unspecified stereochemistry. The striking structural similarity between the destruxins and roseotoxin B suggests that the 3-methylproline residue in destruxin A5 is *trans*.

3,4-Methanoproline. *cis*-3,4-Methano-L-proline (**11**) was isolated from the seeds of *Aesculus parviflora*,[31] and recently, from *Ephedra foeminea* and *Ephedra foliata*.[32]



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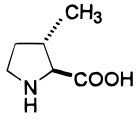

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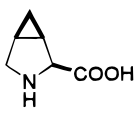

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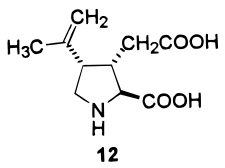
Kainic Acid. α-Kainic acid (**12**), originally named digenic acid, was isolated as the anthelmintic principle of *Diginea simplex*, along with its diastereoisomer, α-allokainic acid.[33] The structures of these two compounds were subsequently reported[34,35] and confirmed by X-ray crystallography.[36] They possess anthelmintic[37] and neurotoxic[38] activity, the latter via a potent neurotransmitting effect,[39] mediated through glutamate receptors. This activity enabled kainic acid to generate an animal model of Huntington's chorea in the rat.[40] The particular excitotoxic amino acid receptors affected by kainic acid have become known as kainate receptors. Kainic acid is a conformationally restricted analog of glutamic acid,[39] which is the molecular basis for this activity, as well as that of the related domoic acid and acromelic acids (see below). The neurotoxicity of kainic acid[41] and its applications in neurobiology[42] have been reviewed.



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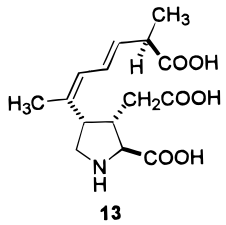

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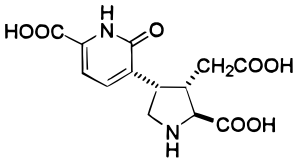
Domoic Acid. Domoic acid (**13**) was isolated from *Chondria armata*,[43] and the structures previously proposed[43,44] were subsequently revised.[45] The isomeric isodomoic acids A, B, and C, which differ structurally in the positions of the double bonds in the 4-substituent, and other related compounds (nordomoic acid and domoilactones A and B) were later obtained from the same source.[46] Like kainic acid, domoic acid possesses anthelmintic,[47] insecticidal,[48] and neuroexcitatory[49,50] activities. It was rediscovered in 1989 as the causative agent in a Canadian outbreak of shellfish poisoning traced to cultured mussels (*Mytilus edulis*).[51] The origin of the domoic acid found in the mussels was the diatom (*Nitzschia pungens*) upon which they fed.

Biosynthetic studies utilizing ^{13}C-labeled acetate established that domoic acid is derived from condensation of geranyl pyrophosphate with glutamic acid derived from an activated C_5 unit from the citric acid cycle.[52]

Acromelic Acids. Acromelic acids A (**14**) and B (**15**) were isolated from *Clitocybe acromelaga*[53] and found to be even more potent neuroexcitants than kainic or domoic acids.



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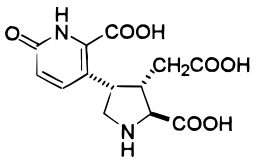

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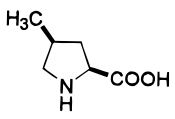
B. 4-Substituted Prolines. 4-Methylproline. *cis*-4-Methyl-L-proline (**16**) was discovered in hydrolysates of leucinostatins A (originally[54] termed antibiotic ICI 13959), B, C, and D, peptide antibiotics isolated from several *Paecilomyces* strains.[54−58] The structure of leucinostatin A was confirmed by X-ray crystallography.[59] A compound termed Antibiotic P168 was independently isolated from *Paecilomyces lilicanus* and found to be identical to leucinostatin A.[60] The leucinostatins have antitumor activity[55,58,61] as well as a wide antimicrobial spectrum against fungi, yeasts, and Gram-positive bacteria.[62] They act as uncouplers of oxidative phosphorylation.[57]

Free *trans*-4-methyl-L-proline (**17**) has been isolated from apples.[63,64] This amino acid is also a component of the monamycins,[65,66] depsipeptide antibiotics from *Streptomyces jamaicensis*, and griselimycin,[67,68] a depsipeptide antibiotic from *Streptomyces griseus* and *Streptomyces coelicus*. The monamycins are active against Gram-positive bacteria and have some immunosuppressant activity.[65] Griselimycin, which contains one proline and two 4-methylproline residues, is active against mycobacteria and Gram-positive microorganisms.[67] Minor griselimycin congeners were isolated with three proline residues, or three methylprolines, or the combination of two prolines and one methylproline.[69] *trans*-4-Methyl-L-proline is also a component of mycoplanecin A, a depsipeptide antibiotic from *Actinoplanes awajinensis*,[70−72] which is active against molds, yeasts and mycobacteria, including *Mycobacterium tuberculosis*.[71]



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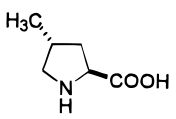

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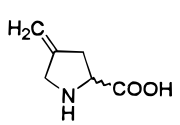

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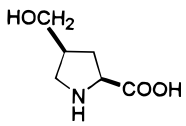

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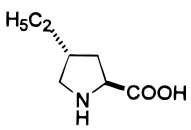

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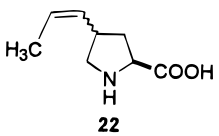

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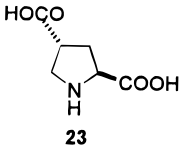

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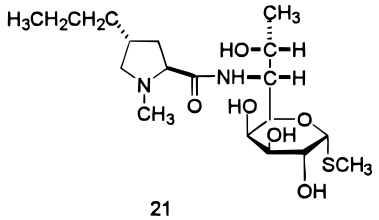
4-Methyleneproline. 4-Methylene-DL-proline (**18**) was isolated from the seeds of the loquat tree (*Eriobot-*

rya japonica)[73,74] and the plants *Raphiolepis indica* and *Afzelia bella*.[75]

4-(Hydroxymethyl)proline. Free *cis*-4-(hydroxymethyl)-L-proline (**19**) was found in several species of apples (*Malus pumila* and *Pyrus communis*).[76−78] It seems remarkable that the *cis* stereoisomer coexists with the *trans* isomer of the related 4-methylproline (see above). This amino acid has also been isolated from *Afzelia bella*.[75]

4-Ethylproline. *trans*-4-Ethyl-L-proline (**20**) is a component of the depsipeptide antibiotic mycoplanecin A[72] together with *trans*-4-methyl-L-proline (see above).

4-Propylproline. The clinically used broad spectrum antibiotic lincomycin (**21**) (from *Streptomyces lincolnensis*, *Streptomyces espinosus*, and *Streptomyces variabilis*) consists of *N*-methyl-*trans*-4-*n*-propyl-L-proline attached amide-wise to an aminosugar.[79−81] Lincomycin B (from *S. lincolnensis*) contains *N*-methyl-*trans*-4-ethyl-L-proline.[82] The lincomycins have been reviewed.[83]



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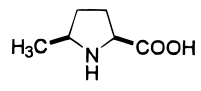
4-Propenylproline. 4-[(*Z*)-Prop-1-enyl]proline (**22**) of unreported streochemistry is a component of the peptide lactone antibiotic hormaomycin (from *Streptomyces griseoflavus*), which is active against some Gram-positive bacteria, especially *Arthrobacter* species.[84,85] It has potent aerial mycelium-inducing activity.[84]

4-Carboxyproline. Free *trans*-4-carboxy-L-proline (**23**) was isolated from the seeds of *Afzelia bella*.[75]

C. 5-Substituted Prolines. 5-Methylproline. *cis*-5-Methyl-L-proline (**24**) has been identified in hydrolysates of the chromodepsipeptide antibiotic, actinomycin Z_5 from *Streptomyces fradiae*.[86,87] 4-Keto-*cis*-5-methyl-L-proline and 2,3-*trans*-2,5-*cis*-3-hydroxy-5-methyl-L-proline are also found in actinomycins (see below, section 4). The actinomycins, which have antimicrobial and antitumor activity, have been reviewed.[88]

5-Carboxyproline. Free *trans*-5-carboxy-L-proline (**25**) was isolated from *Schizymenia dubyi*.[89]



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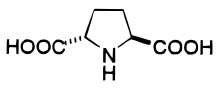

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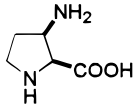
3. Nitrogen-Substituted Prolines

3-Aminoproline. *cis*-3-Amino-L-proline (**26**) was isolated from the fruit bodies of *Morchella esculenta*, *Morchella conica*, and *Morchella crassipes*.[90] Biosynthetic experiments demonstrated efficient conversion of L-proline into *cis*-3-amino-L-proline in the cultured mycelium of *M. esculenta*.[91] The dipeptide, γ-glutamyl-*cis*-3-amino-L-proline, was also found in *M. esculenta*.[92]



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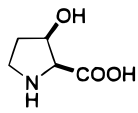
Noformicin, anthelvencin, and the kikumycins, which are 5-aminodehydroproline derivatives, are discussed in section 1.

4. Oxygen-Substituted Prolines

A. 3-Substituted Prolines. 3-Hydroxyproline. Both *cis*- and *trans*-3-hydroxyprolines (**27** and **28**) are components of the cyclopeptide antibiotic telomycin, which was isolated from a *Streptomyces* species.[93] The structure originally proposed for telomycin[94] has since been revised.[95] A related compound, antibiotic AO 341B, has been isolated from *Streptomyces candidus*.[96,97] Like telomycin, it is active against Gram-positive microorganisms.

trans-3-Hydroxy-L-proline (**28**) was first isolated from hydrolysates of Mediterranean sponge,[98] and later from hydrolysates of the seeds of *Delonix regia*.[99,100] It has also been identified as a component of various collagens[101−103] and of *Candida*.[104] The free amino acid occurs in human urine, resulting from collagen metabolism.[105] This amino acid is also a component of pneumocandins B_0 and B_2, lipopeptide antibiotics from *Zalerion arboricola*.[106] These compounds are structurally related to the echinocandins (see below), but with 3-hydroxyproline replacing 3-hydroxy-4-methylproline.[107] They are active against *Candida*, like the echinocandins, and also against *Pneumocystis carinii*.[108]

Two isomeric 3-hydroxyproline betaines (L-*trans*- and D-*cis*-3-hydroxystachydrines, **29** and **30**) were isolated from *Courbonia virgata*,[109] and uncertainties regarding their absolute stereochemistry were settled by synthesis.[110,111]



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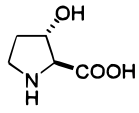

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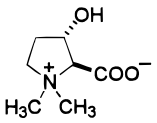

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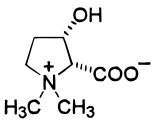

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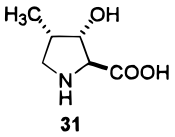
3-Hydroxy-4-methylproline. 2,3-*trans*-2,4-*trans*-3-Hydroxy-4-methyl-L-proline (**31**) was first identified in echinocandins B, C, and D, cyclic lipopeptide antibiotics isolated from *Aspergillus ruglosus* and *Aspergillus nidulans*.[112,113] The echinocandins have been reviewed.[114] This amino acid is also a component of the structurally related aculeacin A (from *Aspergillus aculeatus*),[115] mulundocandin (from *Aspergillus sydowi*),[116,117] and certain of the pneumocandins (A_0, A_1, A_2, A_3, and A_4).[107] This whole class of compounds is important because of the potent activity (in the subnanomolar range) against *Candida albicans*, a clinically significant pathogen. Biosynthetic studies on the pneumocandins (see also above under 3-hydroxyproline) revealed that, whereas L-leucine is the precursor of the 3-hydroxy-4-methylproline in these compounds, L-proline is the precursor of the *trans*-3-hydroxyproline that occupies the corresponding site in pneumocandins B_0 and B_2, as well as of the *trans*-4-hydroxyproline present in all of them.[118] Recently, the related water-soluble compounds WF11899 A, B, and C were isolated from *Coleophoma empetri*.[119]

3-Hydroxy-5-methylproline. 2,3-*trans*-2,5-*cis*-3-Hydroxy-5-methyl-L-proline (**32**) was identified in hydrolysates of the antitumor chromodepsipeptide antibiotic actinomycin Z_1 (from *Streptomyces fradiae*).[120,121] Oxygen substitution at the 3 position was unexpected in view of the presence of 4-hydroxyproline and 4-ketoproline in other actinomycins,[88] and of 4-keto-5-methylproline in the other peptide unit of this same actinomycin Z_1 (see below).



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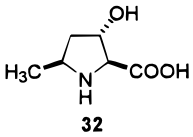
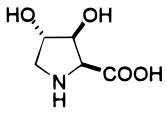


32

3,4-Dihydroxyproline. Three of the four possible diastereoisomers of this proline analog have been found to occur in nature. *2,3-cis*-3,4-*trans*-3,4-Dihydroxy-L-proline (**33**) was the first to be isolated, from hydrolysates of the protein component of the cell walls of the diatom *Navicula pelicullosa*.[122,123]

2,3-*trans*-3,4-*cis*-3,4-Dihydroxy-L-proline (**34**) was discovered in hydrolysates of an adhesive protein from the mussel *Mytilus edulis*.[124]

2,3-*trans*-3,4-*trans*-3,4-Dihydroxy-L-proline (**35**) is a component of the virotoxins from the mushroom *Amanita virosa*.[125]



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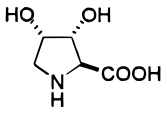

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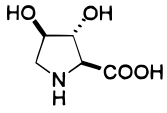
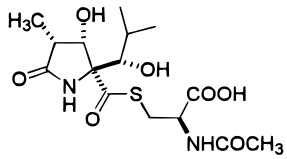


35

Dihydroxyproline of unspecified stereochemistry was found in the free amino acid pool of *Aspergillus tamarii*.[126]

Lactacystin. Lactacystin (**36**),[127,128] a derivative of 3-hydroxypyroglutamic acid, was isolated from *Streptomyces* sp. OM-6519, and its structure was recently confirmed by synthesis.[129] It is of interest as the first microbial metabolite found to possess neurotrophic activity.



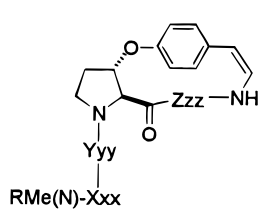
36

Cyclopeptide Alkaloids Containing 3-(Aryloxy)-prolyl Moieties. These compounds have been found to occur in two structural categories, **37** and **38**, as summarized in the Table 1.[130−140] They belong to a class of related compounds, not all of which contain a prolyl moiety.[141] Zizyphin,[142] for which a quite different structure incorporating a 4-(aryloxy)proline moiety was originally proposed,[143] has been renamed zizyphin A, and the revised structure is in accord with the other members of this class.[138]

B. 4-Substituted Prolines. 4-Hydroxyproline and its *N*- and *O*-Methyl Derivatives. *trans*-4-Hydroxy-L-proline (**39**) was first discovered[144] in gelatin hydrolysates in 1902 and has since been found in many other proteins, particularly collagens. During the biosynthesis of collagen, free hydroxyproline is not incorporated directly, but rather proline is converted to hydroxyproline in a bound form.[145] Free hydroxyproline has been detected in prunes,[146] *Galleria mellonella*,[147] and *Bacillus globigii*.[148] Hydroxyproline is also a component of actinomycin $X_{0\beta}$,[149] and of the pneumocandins[107] (see also above under 3-hydroxyproline and 3-hydroxy-4-methylproline). The biochemistry of hydroxyproline has been reviewed.[150]

Table 1. Cyclopeptide Alkaloids Containing 3-(Aryloxy)proline Moieties

	structure						
compd	code	R	Xxx	Yyy	Zzz	source	ref
Amphibine B	**37**	Me	Phe	Ile	Phe	*Ziziphus amphibia*	130
Amphibine C	**37**	Me	Leu	Ile	Phe	*Z. Amphibia*	130
Amphibine D	**37**	Me	Phe	Ile	Ile	*Z. amphibia*	130
Amphibine E	**37**	Me	Leu	Trp	Ile	*Z. amphibia*	130
Amphibine F	**37**	H	Ile	---	Phe	*Z. amphibia*	131
Amphibine G	**37**	Me	Trp	---	Leu	*Z. amphibia*	131
Amphibine H	**38**	Me	Ala	Val	Phe	*Z. amphibia*	131
Mauritin A	**37**	Me	Ala	Val	Phe	*Z. mauritania*	132
Mauritin B	**37**	Me	Ile	Val	Phe	*Z. mauritania*	132
Mauritine J	**37**	H	Leu	Trp	Ile	*Z. mauritania*	133
Mucronin D	**38**	Me	Phe	Leu	Ile	*Z. mucronata*	134
Mucronine J	**37**	Me	Leu	---	Ile	*Z. mucronata*	135
Nummuraline A	**38**	H	Phe	Leu	Ile	*Z. nummaralia*	136
Nummuraline B	**38**	H	Ala	Val	Phe	*Z. nummaralia*	136
Nummuraline C	**38**	Me	Phe	---	Leu	*Z. nummaralia*	136
Nummuraline F	**37**	Me	Gly	---	Ile	*Z. nummuralia*	137
Zizyphin A	**38**	Me	Ile	Ile	Pro	*Z. oenoplia*	138
Zizyphin B	**38**	H	Ile	Ile	Pro	*Z. oenoplia*	139
Zizyphin C	**38**	Me	Phe	Ile	Pro	*Z. oenoplia*	140



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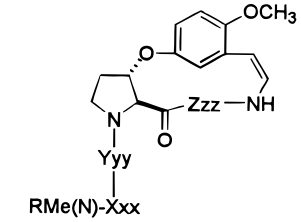
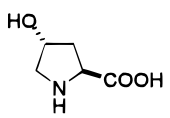


38

The free *cis* isomer, *allo*-4-hydroxy-L-proline (**40**), was isolated from sandal (*Santalum album*)[151,152] and was obtained from fermentations of the microorganisms *Heliocerus oryzae* and *Acrocylindrium oryzae*.[153] This amino acid was also found in hydrolysates of the toxic cyclopeptides phalloidin, phallicidin, and amanitin from *Amanita phalloides* and *Agaricus phalloides*.[154−157] More recently, it was identified as a component of two structurally related lipopeptides from *Lyngbya majuscula:* majusculamide D (**41**), which is cytotoxic,[158] and microcolin A (**42**), which has immunosuppressive, antileukemic,[159] and protein kinase C inhibitory[160] properties.



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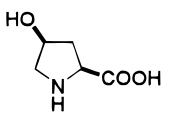

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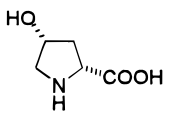

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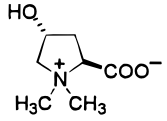

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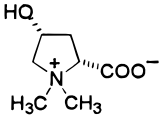
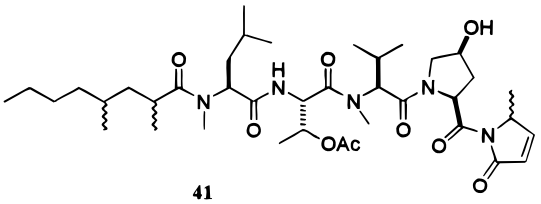


45

allo-4-Hydroxy-D-proline (**43**) was isolated from hydrolysates of the cyclodepsipeptide viridogrisein,[161,162]

a broad-spectrum antibiotic subsequently found to be identical with etamycin,[163] of which the structure was later determined.[164]

The betaines of hydroxy-L-proline (**44**) and *allo*-hydroxy-D-proline (**45**) (termed betonicine and turicine, respectively) coexist in *Betonica officinalis* and *Stachys sylvatica*.[165] Probably the isolation of turicine results from the ready C-2 epimerization of betonicine.[166] Betonicine is also found in *Marrubium vulgare*.[167]



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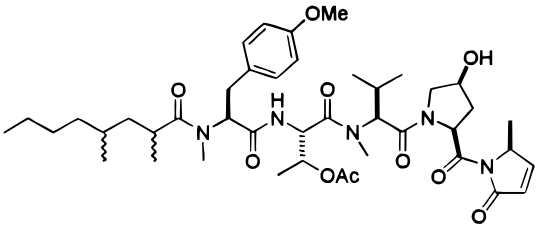


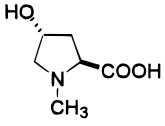
42

N-Methyl-*trans*-4-hydroxy-L-proline (**46**) has been isolated from various plants, including *Croton gobouga*,[168] *Afromosia elata*,[169] and *Celaenodendron mexicanum*.[170]

N-Methyl-*trans*-4-methoxy-L-proline (**47**) was isolated from *Petiveria alliacea*.[171]

4-Keto-L-proline. 4-Keto-L-proline (**48**) was found to be a component of actinomycins X_2[172] and X_{1a}[173] from *Streptomyces chrysomallus*. Because it is largely destroyed during hydrolysis, it was identified following prior reduction to 4-hydroxyproline. Later, 4-ketoproline itself was identified in unreduced hydrolysates.[174] 4-Ketoproline is also a component of the antibiotic echinocandin B[112] together with 3-hydroxy-4-methylproline (see above).

4-Keto-5-methylproline. 4-Keto-*cis*-5-methyl-L-proline (**49**) has been identified as a component of actinomycins Z_1[175] and Z_5[86] from *Streptomyces fradiae*.



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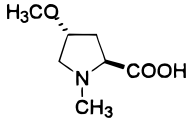

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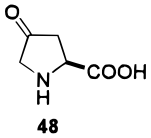

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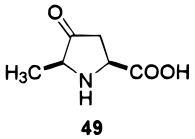
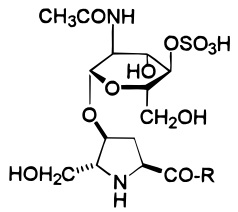


49

Bulgecins. Bulgecins A, B, and C (**50**−**52**), are aminoglycoside antibiotics isolated from *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*.[176,177] They induce bulge formation (a morphological change) in Gram-negative bacteria in synergy with β-lactam antibiotics and enhance the latter's lytic activity.[178] The 2,4-*cis*-2,5-*trans*-4-hydroxy-5-(hydroxymethyl)prolyl moiety of the bulgecins is termed bulgecinine.



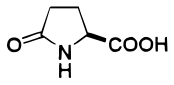
50 R = $NHCH_2CH_2SO_3H$

51 R = $NHCH_2CH_2COOH$

52 R = OH

C. 5-Substituted Prolines. 5-Keto-L-proline (Pyroglutamic Acid). Pyroglutamic acid (**53**), the biochemistry of which has been reviewed,[179] occurs in various animal tissues[180] and is the *N*-terminal residue of several neuropeptide hormones.[181] It is an orally active glutamatergic agonist.[182]

2,3-Dimethyl-5-ketoproline. 2,3-*trans*-2,4-*trans*-3,4-Dimethylpyroglutamic acid (**54**) is the N-terminal component of callipeltin B, a cytotoxic peptide lactone from *Callipelta* sp. (sponge).[183]



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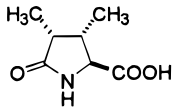


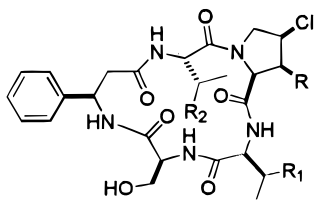
54

5. Chlorine-Substituted Prolines

3,4-Dichloroproline. 3,4-Dichloro-L-proline of unspecified relative stereochemistry was tentatively identified as a component of the toxic metabolite islanditoxin (from *Penicillium islandicum*)[184] on the basis of degradation to L-proline (by hydrogenation) and to pyrrole-2-carboxylic acid (by alkali).[185] Independently, a toxic cyclopeptide was isolated from the same organism and named cyclochlorotine;[186] its structure was determined by X-ray crystallography.[187] This structure incorporates a *cis*,*cis*-3,4-dichloro-L-proline residue. Since the source and the amino acid composition of the two toxins are the same, and the amino acid sequences reported differ only slightly, they are probably identical.

Recently, a series of related cyclopeptides named astins A−C (**55**−**57**), which possess antitumor activity, have been isolated from *Aster tataricus*.[188] These compounds have the same ring size (16) as islanditoxin and cyclochlorotine and share some of the amino acids, including *cis*,*cis*-3,4-dichloro-L-proline.[189] However, the astins adopt a conformation different from that of cyclochlorotine, for example, incorporating a *cis* X-Pro-(Cl_2) peptide bond.[190,191] Dechlorinated derivatives of the astins lack the antitumor activity of the parent compounds.[192]

3-Hydroxy-4-chloroproline. *cis, cis*-3-Hydroxy-4-chloro-L-proline was identified as a component of astin I (**58**) from *Aster tataricus*.[193]



55 R = Cl, R_1 = H, R_2 = OH

56 R = Cl, R_1 = OH, R_2 = H

57 R = Cl, R_1 = R_2 = H

58 R = OH, R_1 = R_2 = H

References and Notes

(1) Mauger, A. B.; Witkop, B. *Chem. Rev.* **1966**, *66*, 47−86.

(2) Mauger, A. B. In *Chemistry and Biochemistry of Amino Acids, Peptides and* Proteins; Weinstein, B., Ed.; Marcel Dekker: New York, 1977; pp 179−240.
(3) Delpierre, G. R.; Eastwood, F. W.; Gream, G. E.; Kingston, D. G. I.; Sarin, P. S.; Todd, Lord; Williams, D. H. *J. Chem. Soc. C* **1966**, 1653−1669.
(4) Kingston, D. G. I.; Todd, Lord; Williams, D. H. *J. Chem. Soc. C* **1966**, 1669−1676.
(5) Ball, S.; Boothroyd, B.; Lees, K. A.; Raper, A. H.; Smith, E. L. *Biochem. J.* **1958**, 24P.
(6) Kingston, D. G. I.; Kolpak, M. X.; LeFevre, J. W.; Borup-Grotchmann, I. *J. Am. Chem. Soc.* **1983**, *105*, 5106−5110.
(7) Culvenor, C. C. J.; Beck, A. B.; Clarke, M.; Cockrum, P. A.; Edgar, J. A.; Frahn, J. L.; Jago, M. V.; Lanigan, G. W.; Payne, A. L.; Peterson, J. E.; Petterson, D. S.; Smith, L. W.; White, R. R. *Aust. J. Biol. Sci.* **1977**, *30*, 269−277.
(8) Culvenor, C. C. J.; Cockrum, P. A.; Edgar, J. A.; Frahn, J. L.; Gorst-Allman, C. P.; Jones, A. J.; Marasas, W. F. O.; Murray, K. E.; Smith, L. W.; Steyn, P. S.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 1259−1262.
(9) Edgar, J. A.; Frahn, J. L.; Cockrum, P. A.; Culvenor, C. C. J. *Bioact. Mol.* **1986**, *1*, 169−184.
(10) Tonsing, E. M.; Steyn, P. S.; Osborn, M.; Weber, K. *Eur. J. Cell Biol.* **1984**, *35*, 156−164.
(11) Vogel, H. J.; Davis, B. D. *J. Am. Chem. Soc.* **1952**, *74*, 109−112.
(12) Liu, W.-C.; Fisher, S. M.; Wells, J. C.; Ricca, C. S.; Principe, P. A.; Trejo, W. H.; Bonner, D. P.; Gougoutos, J. Z.; Toeplitz, B. K.; Sykes, R. B. *J. Antibiot.* **1981**, *34*, 791−799.
(13) Kikuchi, M.; Kumagai, K.; Ishida, N.; Ito, Y.; Yamaguchi, T.; Furumai, T.; Okuda, T. *J. Antibiot. Ser. A* **1965**, *18*, 243−250.
(14) Peck, R. L.; Shafer, H. M.; Wolf, F. J. U.S. Pat. 2,804,463, 1957.
(15) Taikaishi, T.; Sugawara, Y.; Suzuki, M. *Tetrahedron Lett.* **1972**, 1873−1876.
(16) Harris, D. A.; Woodruff, H. B. *Antibiot. Annu.* **1953**−**1954**, 609−614.
(17) Probst, G. W.; Hoehn, M. M.; Woods, B. L. *Antimicrob. Agents Chemother.* **1965**, 789−795.
(18) Lee, M.; Coulter, D. M.; Lown, J. W. *J. Org. Chem.* **1988**, *53*, 1855−1859.
(19) McClelland, L. *Antimicrob. Agents Chemother.* **1953**−**1954**, 615−621.
(20) Sidwell, R. W.; Dixon, G. J.; Sellers, S. M.; Schabel, F. M. *Appl. Microbiol.* **1968**, *16*, 370−392.
(21) Zimmer, C.; Wahnert, U. *Prog. Biophys. Mol. Biol.* **1986**, *47*, 31−112.
(22) Sapse, A. M.; Feng, W.; Fugler-Domenico, L.; Kabir, S.; Joseph, T.; Lown, J. W. *J. Biomol. Struct. Dyn.* **1993**, *10*, 709−726.
(23) Nakamura, S.; Chikaike, T.; Yonehara, H.; Umezawa, H. *Chem. Pharm. Bull.* **1965**, *13*, 599−602.
(24) Waisvisz, J. M.; van der Hoeven, M. G.; van Peppen, J.; Zwennis, W. C. M. *J. Am. Chem. Soc.* **1957**, *79*, 4520−4521.
(25) Takahashi, Y; Naganawa, H.; Takita, T.; Umezawa, H.; Nakamura, S. *J. Antibiot.* **1976**, *29*, 1120−1123.
(26) Schipper, D. *J. Antibiot.* **1983**, *36*, 1076−1077.
(27) Nakamura, S.; Chikaike, T.; Yonehara, H.; Umezawa, H. *J. Antibiotics Ser. A* **1965**, *18*, 47−52 and 60−61.
(28) Engstrom, G. W.; DeLance, J. V.; Richard, J. L.; Baetz, A. L. *J. Agric. Food Chem.* **1975**, *23*, 244−253.
(29) Springer, J. P.; Cole, R. J.; Dorner, J. W.; Cox, R. H.; Richard, J. L.; Barnes, C. L.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 2388−2392.
(30) Krasnoff, S. B.; Gibson, D. M.; Belofsky, G. N.; Gloer, K. B.; Gloer, J. B. *J. Nat. Prod.* **1996**, *59*, 485−489.
(31) Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, R. C. *Phytochemistry* **1969**, *8*, 437−443.
(32) Starratt, A. N.; Caveney, S. *Phytochemistry* **1995**, *40*, 479−481.
(33) Murakami, S.; Takemoto, T.; Shimizu, Z.; Daigo, K. *Jpn. J. Pharm. Chem.* **1953**, *25*, 571−574.
(34) Murakami, S.; Takemoto, T.; Tei, Z.; Daigo, K. *J. Pharm. Soc. Jpn.* **1955**, *75*, 869−873.
(35) Murakami, S.; Takemoto, T.; Tei, Z.; Daigo, K. *J. Pharm. Soc. Jpn.* **1955**, *75*, 1255−1257.
(36) Nitta, I.; Watase, H.; Tomiie, Y. *Nature (London)* **1958**, *181*, 761−762.
(37) Murakami, S.; Takemoto, T.; Shimizu, Z.; Daigo, K. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1055−1057.
(38) Nadler, J. V. *Life Sci.* **1979**, *24*, 289−300.
(39) Johnston, G. A. R.; Curtis, D. R.; Davies, J.; McCulloch, R. M. *Nature (London)* **1974**, *248*, 804−805.
(40) Coyle, J. T.; Schwarcz, R. *Nature (London)* **1976**, *263*, 244−246.
(41) Coyle, J. T. *Ciba Found. Symp.* **1987**, *126*, 186−203.
(42) McGreer, E. G.; Olney, J. W.; McGreer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven Press: New York, 1978.
(43) Takemoto, T.; Daigo, K. *Chem. Pharm. Bull.* **1958**, *6*, 578−580.
(44) Takemoto, T.; Daigo, K.; Kondo, Y.; Kondo, K. *Yakugaku Zasshi* **1966**, *86*, 874−877.
(45) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511−3513.
(46) Maeda, M.; Kodama, T.; Tanaka, T.; Yoshizumi, H.; Takemoto, T.; Nomoto,Y.; Fujita, T. *Chem. Pharm. Bull.* **1986**, *34*, 4892−4895.
(47) Daigo, K. *Yakugaku Zasshi* **1959**, *79*, 350−353.
(48) Maeda, M.; Kodama, T.; Tanaka, T.; Ohfune, Y.; Nomoto, K.; Nishimura, K.; Fujita, T. *J. Pestic. Sci.* **1984**, *9*, 27−32.
(49) Zaczek, R.; Coyle, J. T. *Neurophamacol.* **1982**, *21*, 15−26.
(50) Kizer, J. S.; Nemeroff, C. B.; Youngblood, W. W. *Pharmacol. Rev.* **1978**, *29*, 301−318.
(51) Wright, J. L. C.; Boyd, R. K.; de Freitas, A. S. W.; Falk, M.; Foxhall, R. A.; Jamieson, W. D.; Laycock, M. V.; McCulloch, A. W.; McInnes, A. G.; Odense, P.; Pathak, V. P.; Quilliam, M. A.; Ragan, M. A.; Sim, P. G.; Thibault, P.; Walter, J. A.; Gilgan, M.; Richard, D. J. A.; Dewar, D. *Can. J. Chem.* **1989**, *67*, 481−490.
(52) Douglas, D. J.; Ramsey, U. P.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1992**, 714−716.
(53) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939−942.
(54) Kenner, G. W.; Sheppard, R. C. *Nature (London)* **1958**, *181*, 48.
(55) Arai, T.; Mikami, Y.; Fukushima, K.; Utsumi, T.; Yazawa, K. *J. Antibiot.* **1973**, *26*, 157−161.
(56) Fukushima, K.; Arai, T.; Mori, Y.; Tsuboi, M.; Suzuki, M. *J. Antibiot.* **1983**, *36*, 1606−1612 and 1613−1630.
(57) Stroh, J. G.; Rinehart, K. L.; Cook, J. C.; Kihara, T.; Suzuki, M.; Arai, T. *J. Am. Chem. Soc.* **1986**, *108*, 858−859.
(58) Mori, Y.; Tsuboi, M.; Suzuki, M.; Fukushima, K.; Arai, T. *J. Antibiot.* **1982**, *35*, 543−544.
(59) Cerrini, S.; Lamda, D.; Scatturin, A.; Ughetto, G. *Biopolymers* **1989**, *28*, 409−420.
(60) Isogai, A.; Suzuki, A.; Tamura, S.; Higashikawa, S.; Kuyama, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1405−1411.
(61) Ishiguro, K.; Arai, T. *Antimicrob. Agents Chemother.* **1976**, *9*, 893−898.
(62) Isogai, A.; Suzuki, A.; Higashikawa, S.; Kuyama, S.; Tamura, S. *Agric. Biol. Chem.* **1981**, *45*, 1023−1024.
(63) Hulme, A. C.; Arthington, W. *Nature (London)* **1952**, *170*, 659−660.
(64) Hulme, A. C.; Arthington, W. *Nature (London)* **1954**, *173*, 588−589.
(65) Hassall, C. H.; Magnus, K. E. *Nature (London)* **1959**, *184*, 1223−1224.
(66) Hassall, C. H.; Morton, R. B.; Ogihara, Y.; Phillips, D. A. S. *J. Chem. Soc. C* **1971**, 526−532.
(67) Terlain, B.; Thomas, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2349−2356.
(68) Terlain, B.; Thomas, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2357−2362.
(69) Terlain, B.; Thomas, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2363−2365.
(70) Torikata, A.; Enokita, R.; Okazaki, T.; Nakajima, M.; Iwado, S.; Haneishi, T.; Arai, M. *J. Antibiot.* **1983**, *36*, 957−960.
(71) Nakajima, M.; Torikata, A.; Ichikawa, Y.; Katayama, T.; Shiraishi, A.; Haneishi, T.; Arai, M. *J. Antibiot.* **1983**, *36*, 961−966.
(72) Nakajima, M.; Torikata, A.; Tamaoki, H.; Haneishi, T.; Arai, M.; Kinoshita, T.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 967−975.
(73) Gray, D. O.; Fowden, L. *Nature (London)* **1962**, *193*, 1285−1286.
(74) Gray, D. O.; Fowden, L. *Phytochemistry* **1972**, *11*, 745−750.
(75) Welter, A.; Marlier, M.; Dardenne, G. *Phytochemistry* **1978**, *17*, 131−134.
(76) Hulme, A. C. *Nature (London)* **1954**, *174*, 1055−1056.
(77) Urbach, G. *Nature (London)* **1955**, *175*, 170−171.
(78) Burroughs, L. F. *J. Sci. Food. Agric.* **1957**, *8*, 122−131.
(79) Mason, D. J.; Dietz, A.; DeBoer, C. *Antimicrob. Agents Chemother.* **1962**, 554−559.
(80) Herr, R. R.; Bergy, M. E. *Antimicrob. Agents Chemother.* **1962**, 560−564.
(81) Hoeksema, H.; Bannister, B.; Birkenmeyer, R. D.; Kagan, F.; Magerlein, B. J.; MacKellar, F. A.; Schroeder, W.; Slomp, G.; Herr, R. R. *J. Am. Chem. Soc.* **1964**, *86*, 4223−4224.
(82) Argudelis, A. D.; Fox, J. A.; Mason, D. J.; Eble, T. E. *J. Am. Chem. Soc.* **1964**, *86*, 5044−5045.
(83) Eble, T. E. *J. Chromatogr. Libr.* **1978**, *15*, 231−271.
(84) Andres, N.; Wolf, H.; Zähner, H.; Rössner, E.; Zeeck, A.; König, W. A.; Sinnwell, V. *Helv. Chim. Acta* **1989**, *72*, 426−437.
(85) Rössner, E.; Zeek, A.; König, W. A. *Angew. Chem.* **1990**, *102*, 84−85.
(86) Brockmann, H.; Stähler, E. A. *Tetrahedron Lett.* **1973**, 2567−2570.
(87) Katz, E.; Mason, K. T.; Mauger, A. B. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 819−826.
(88) Mauger, A. B. *Top. Antibiot. Chem.* **1980**, *5*, 224−306.
(89) Impellizzeri, G.; Mangiafico, S.; Oriente, G.; Piatelli, M.; Sciuto, S. *Phytochemistry* **1975**, *14*, 1549−1557.
(90) Hatanaka, S.-I. *Phytochemistry* **1969**, *8*, 1305−1308.
(91) Hatanaka, S.-I. *Sci. Pap. Coll. Gen. Educ., Univ. Tokyo* **1976**, *26*, 33−38.
(92) Moriguchi, M.; Kimura, K.; Hatanaka, S.-I. *Trans. Mycol. Soc. Jpn.* **1983**, *24*, 191−195.
(93) Misiek, M.; Fardig, O. B.; Gourevich, A.; Johnson, D. L.; Hooper, I. R.; Lein, J. *Antibiot. Annu.* **1957**−**1958**, 852−855.
(94) Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462−470.
(95) Katrukha, G. S.; Maevskaya, S. N.; Silaev, A. B.; Lomonosov, M. V. *Bioorg. Khim.* **1977**, *3*, 422−423.
(96) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shu, P.; Swift, M. E.; Porter, J. N.; Redin, G. *Antimicrob. Agents Chemother.* **1966**, 587−590.

(97) Whaley, H. A.; Patterson, E. L.; Kunstmann, M. P.; Bohonos, N. *Antimicrob. Agents Chemother.* **1966**, 591−594.
(98) Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 2824−2831
(99) Sung, M. L.; Fowden, L. *Phytochemistry* **1968**, *7*, 2061−2063.
(100) Szymanovicz, G.; Mercier, O.; Randoux, A.; Borel, J. P. *Biochim.* **1978**, *60*, 499−503.
(101) Ogle, J. D.; Arlinghaus, B.; Logan, M. A. *J. Biol. Chem.* **1962**, *237*, 3667−3673.
(102) Piez, K. A.; Eigner, E. A.; Lewis, M. S. *Biochemistry* **1963**, *2*, 58−66.
(103) Fujiwara, S.; Nagai, Y. *J. Biochem.* **1981**, *89*, 1397−1401.
(104) Kerese, J. *Szeszipar* **1971**, *19*, 77−78.
(105) Weiss, M.-T.; Weninger, M.; Hausler, J.; Lubec, G. *Padiatrie Padagogie* **1988**, *23*, 9−14.
(106) Schwartz, R. E.; Sesin, D. F.; Joshua, H.; Wilson, K. E.; Kempf, A. J.; Goklen, K. A.; Kuehner, D.; Gailliot, P.; Gleason, C.; White, R.; Inamine, E.; Bills, G.; Salmon, P.; Zitano, L. *J. Antibiot.* **1992**, *45*, 1853−1866.
(107) Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Smith, J. L.; Wichmann, C. F.; Schwartz, R. E. *J. Antibiot.* **1992**, *45*, 1875−1885.
(108) Schmatz, D. M.; Abruzzo, G.; Powles, M. A.; McFadden, D. C.; Balkovec, J. M.; Black, R. M.; Nollstadt, K.; Bartizal, K. *J. Antibiot.* **1992**, *45*, 1886−1891.
(109) Cornforth, J. W.; Henry, A. J. *J. Chem. Soc.* **1952**, 597−601.
(110) Sakiyama, F.; Irreverre, F.; Friess, S. L.; Witkop, B. *J. Am. Chem. Soc.* **1964**, *86*, 1842−1844.
(111) Sheehan, J. C.; Kuhn, R. R. *J. Org. Chem.* **1964**, *29*, 2008−2009.
(112) Benz, F.; Knüsel, F.; Nüesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459−2477.
(113) Koyama, G. *Helv. Chim. Acta* **1974**, *57*, 2477−2483.
(114) Hammond, M. L. *Clin. Dermatol.* **1993**, *7*, 395−420.
(115) Mizuno, K.; Yagi, A.; Satoi, S.; Takada, M.; Hayashi, M.; Asano, K.; Matsuda, T. *J. Antibiot.* **1977**, *30*, 297−302.
(116) Roy, K.; Mukhopadhyay, T.; Reddy, G. C. S.; Desikan, K. R.; Ganguli, B. N. *J. Antibiot.* **1987**, *40*, 275−280.
(117) Mukhopadhyay, T.; Ganguli, B. N.; Fehlhaber, H. W.; Kogler, H.; Vertesy, L. *J. Antibiot.* **1987**, *40*, 281−289.
(118) Adefarati, A. A.; Hensens, O. D.; Jones, E. T. T.; Tkacz, J. S. *J. Antibiot.* **1992**, *45*, 1953−1957.
(119) Iwamoto, T.; Fujie, A.; Sakamoto, K.; Tsurumi, Y.; Shigematsu, N.; Yamashita, M.; Hashimoto, S.; Okuhara, M.; Kohsaka, M. *J. Antibiot.* **1994**, *47*, 1084−1091.
(120) Katz, E.; Mason, K. T.; Mauger, A. B. *Biochem. Biophys. Res. Commun.* **1975**, *63*, 502−508.
(121) Mauger, A. B.; Stuart, O. A.; Katz, E.; Mason, K. T. *J. Org. Chem.* **1977**, *42*, 1000−1005.
(122) Nakajima, T.; Vocani, B. E. *Science* **1969**, *164*, 1400−1401.
(123) Karle, I. L.; Daly, J. W.; Witkop, B. *Science* **1969**, *164*, 1401−1402.
(124) Taylor, S. W.; Waite, J. H.; Ross, M. M.; Shabanowitz, J.; Hunt, D. F. *J. Am. Chem. Soc.* **1994**, *116*, 10803−10804.
(125) Baku, A.; Faulstich, H.; Wieland, T.; Dabrowski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2370−2371.
(126) Razak, A. A.; Ramadan, S. E.; Haroun, B. M.; Lashine, I. *J. Collect. Sci. King Saud Univ.* **1985**, *16*, 41−48.
(127) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113−116.
(128) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117−118.
(129) Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139−2140.
(130) Tschesche, R.; Kauβmann, E. U.; Fehlhaber, H.-W. *Chem. Ber.* **1972**, *105*, 3094−3105.
(131) Tschesche, R.; Spilles, C.; Eckhardt, G. *Chem. Ber.* **1974**, *107*, 686−697.
(132) Tschesche, R.; Wilhelm, H.; Fehlhaber, H. W. *Tetrahedron Lett.* **1972**, 2609−2612.
(133) Jossang, A.; Zahir, A.; Diakite, D. *Phytochemistry* **1996**, *42*, 565−567.
(134) Tschesche, R.; David, S. T.; Uhlendorf, J.; Fehlhaber, H.-W. *Chem. Ber.* **1972**, *105*, 3106−3114.
(135) Auvin, C.; Lezenven, F.; Blond, A.; Augeven-Bour, I.; Pousset, J.-L.; Bodo, B.; Camara, J. *J. Nat. Prod.* **1996**, *59*, 676−678.
(136) Tschesche, R.; Miana, G. A.; Eckhardt, G. *Chem. Ber.* **1974**, *107*, 3180−3185.
(137) Tschsche, R.; Elgamal, M.; Miana, G. A.; Eckhardt, G. *Tetrahedron* **1975**, *31*, 2944−2947.
(138) Tschesche, R.; Kauβmann, E. U.; Eckhardt, G. *Tetrahedron Lett.* **1973**, 2577−2580.
(139) Pailer, M.; Haslinger, E.; Zbiral, E. *Monatsh. Chem.* **1969**, *100*, 1608−1612.
(140) Cassels, B. K.; Eckhardt, G.; Kaussmann, E.-U.; Tschesche, R. *Tetrahedron* **1974**, *30*, 2461−2466.
(141) Warnhoff, E. W. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 162−203.
(142) Ménard, E. L.; Müller, J. M.; Thomas, A. F.; Bhatnagar, S. S.; Dastoor, N. J. *Helv. Chim. Acta* **1963**, *46*, 1801−1811.
(143) Zbiral, E.; Menard, E. L.; Muller, J. M. *Helv. Chim. Acta* **1965**, *48*, 404−431.
(144) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 2660−2665.
(145) Stetten, M. R. *J. Biol. Chem.* **1949**, *181*, 31−37.
(146) Joslyn, M. A.; Stepka, W. *Food Res.* **1949**, *14*, 459−467.
(147) Auclair, J. L.; Dubreuil, R. *Can. J. Zool.* **1952**, *30*, 109−113.
(148) Davis, F. L.; Williams, O. B. *J. Bacteriol.* **1952**, *64*, 766−767.
(149) Brockmann, H.; Pampus, G.; Manegold, J. H. *Chem. Ber.* **1959**, *92*, 1294− 1302.
(150) Kuttan, R.; Radhakrishnan, A. N. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1973**, *37*, 273−347.
(151) Radhakrishnan, A. N.; Giri, K. V. *Biochem. J.* **1954**, *58*, 57−61.
(152) Radhakrishnan, A. N. *Indian J. Chem.* **1963**, *2*, 88−90.
(153) Matsuoka, T.; Furuya, K.; Serizawa, N. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1747−1748.
(154) Lynen, F.; Wieland, U. *Liebigs Ann. Chem.* **1937**, *533*, 93−117.
(155) Wieland, H.; Witkop, B. *Liebigs Ann. Chem.* **1940**, *543*, 171−183.
(156) Wieland, T. *Helv. Chim. Acta* **1961**, *44*, 919−926.
(157) Wieland, T. *Pure Appl. Chem.* **1963**, *6*, 339−349.
(158) Moore, R. E.; Entzeroth, M. *Phytochemistry* **1988**, *27*, 3101−3103.
(159) Koehn, F. E.; Longley, R. E.; Reed, J. K. *J. Nat. Prod.* **1992**, *55*, 613−619.
(160) Koehn, F. E.; McConnell, O. J.; Longley, R. E.; Sennett, S. H.; Reed, J. K. *J. Med. Chem.* **1994**, *37*, 3181−3186.
(161) Bartz, Q. R.; Standiford, J.; Mold, J. D.; Johannessen, D. W.; Ryder, A.; Maretzki, A.; Haskell, T. H. *Antibiot. Annu.* **1954**−**1955**, *2*, 728−783.
(162) Haskell, T. H.; Maretzki, A.; Bartz, Q. R. *Antibiot. Annu.* **1954**−**1955**, *2*, 784−789.
(163) Heinemann, B.; Gourevitch, A.; Lein, J.; Johnson, D. L.; Kaplan, M. A.; Vanas, D.; Hooper, I. R. *Antibiot. Annu.* **1954**−**1955**, *2*, 728−732.
(164) Sheehan, J. C.; Zachau, H. G.; Lawson, W. B. *J. Am. Chem. Soc.* **1958**, *80*, 3349−3355.
(165) Kueng, A.; Trier, G. *Z. Physiol. Chem.* **1913**, *85*, 209−216.
(166) Patchett, A. A.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *79*, 185−192.
(167) Paudler, W. W.; Wagner, S. *Chem. Ind. (London)* **1963**, 1693−1694.
(168) Goodson, J. A.; Clewer, H. W. B. *J. Chem. Soc.* **1919**, *115*, 923−933.
(169) Morgan, J. W. W. *Chem. Ind. (London)* **1964**, 542−543.
(170) Castañeda, P.; Bahena, A.; García, E.; Chávez, D.; Mata, R.; Gutiérrez, A. *J. Nat. Prod.* **1993**, *56*, 1575−1579.
(171) de Sousa, J. R.; Demuna, A. J.; Pinheiro, J. A.; Breitmaier, E.; Cassels, B. K. *Phytochemistry* **1990**, *29*, 3653−3655.
(172) Brockmann, H.; Manegold, J. H. *Chem. Ber.* **1960**, *93*, 2971−2982.
(173) Brockmann, H.; Manegold, J. H. *Chem. Ber.* **1962**, *95*, 1081−1093.
(174) Diegelman, R., Mauger, A.; Katz, E. *J. Antibiot.* **1969**, *22*, 85−87.
(175) Brockmann, H.; Manegold, J. H. *Z. Physiol. Chem.* **1965**, *343*, 86−100.
(176) Shinagawa, S.; Kasahara, F.; Wada, Y.; Harada, S.; Asai, M. *Tetrahedron* **1984**, *40*, 3465−3470.
(177) Shinagawa, S.; Maki, M.; Kintaka, K.; Imada, A.; Asai, M. *J. Antibiot.* **1985**, *38*, 17−23.
(178) Imada, A.; Kintaka, K.; Nakao, M.; Shinagawa, S. *J. Antibiot.* **1982**, *35*, 1400−1403.
(179) van der Werf, P.; Meister, A. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 519−556.
(180) Meister, A. *Life Sci.* **1974**, *15*, 177−190.
(181) Gainer, H.; Brownstein, M. J. In *Basic Neurochemistry*; Siegel, G. J., Albers, R. W., Agranoff, B. W., Katzman, R., Ed.; Little Brown & Co.: Boston, 1981; pp 269−296.
(182) Moret, C.; Briley, M. *Trends Pharmacol. Sci.* **1988**, *9*, 278−279.
(183) D'Auria, M. V.; Zampella, A.; Paloma, L. G.; Minale, L.; Debitus, C.; Roussakis, C.; Le Bert, V. *Tetrahedron* **1996**, *52*, 9589−9596.
(184) Marumo, S.; Sumiki, Y. *J. Agr. Chem. Soc. Jpn.* **1955**, *29*, 305.
(185) Marumo, S. *Bull. Agric. Chem. Soc. Jpn.* **1959**, *23*, 428−437.
(186) Tatsuno, T.; Tsukioka, M.; Sakai, Y.; Suzuki, Y.; Asami, Y. *Pharm. Bull.* **1955**, *3*, 476−477.
(187) Yoshioka, H.; Nakatsu, K.; Sato, M.; Tatsuno, T. *Chem. Lett.* **1973**, 1319−1322.
(188) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 992−993.
(189) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Tetrahedron* **1995**, *51*, 1121−1132.
(190) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H. *Tetrahedron* **1994**, *50*, 11613−11622.
(191) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1995**, *43*, 1395−1397.
(192) Morita, H.; Nagashima, S.; Uchiumi, Y.; Kuroki, O.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1996**, *44*, 1026−1032.
(193) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H. *Chem. Lett.* **1994**, 2009−2010.

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