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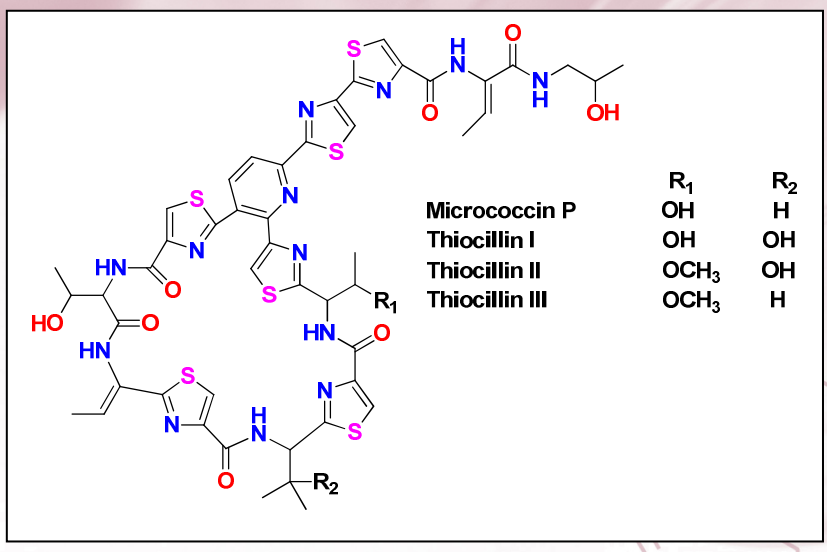
Thiopeptides

Unusual Macrocycles

In 1948 Su isolated the antibiotic micrococcin M from a *Micrococcus* sp. recovered from sewage. Micrococcin M was the first reported member of an unusual family of cyclic peptides incorporating thiazoles and other simple heterocycles as constituent amino acids. Although that producing culture was lost to science a *Bacillus pumilus* strain isolated in 1955 was found to be identical. However, given the technical limitations for structure proofs of such complex molecules, at the time it was conservatively named micrococcin P_1. Close analogues, the thiocillins, were isolated from *Bacillus badius* at Shionogi Laboratories in 1976 and together these analogues are smallest macrocyles of the class.



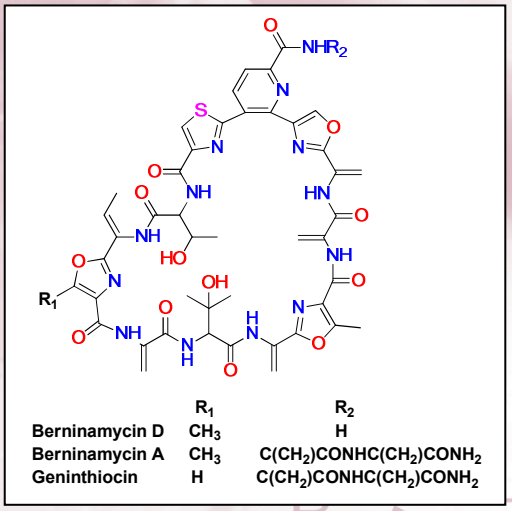
	R_1	R_2
Micrococcin P	OH	H
Thiocillin I	OH	OH
Thiocillin II	OCH_3	OH
Thiocillin III	OCH_3	H

The thiopeptides have been produced by a number of G+ve bacteria including Bacillus, Streptomyces and less common genera, such as Amycolatopsis, Micromonspora, Planobispora, Planomonospora and Sebekia. The class is classified into four families according to their central heterocyclic domain with analogues with analogues within the class displaying different bioprofiles, varying from highly selective antibiotics to highly selective antitumor actives.

The larger monocyclic thiopeptides includes geninthiocin, berninomycin A, which contain an extended didehydroalanyl side chain, absent in berninomycin D.

These metabolites show selective antibiotic activity against G+ve bacteria and have been shown to be inducers of tipA, a gene controlling regulators of bacterial transcription.

Induction of tipA is also shared by the more complex bicyclic thiopeptides, siomycin and thiostrepton. It is believed the metabolites share a common "face" responsible for induction.



	R_1	R_2
Berninamycin D	CH_3	H
Berninamycin A	CH_3	$C(CH_2)CONHC(CH_2)CONH_2$
Geninthiocin	H	$C(CH_2)CONHC(CH_2)CONH_2$

The use thiopeptides for regulation of bacterial transcription appears to have a mammalian counterpart, with siomycin shown to be a potent inhibitor of the oncogenic transcription factor, forkhead box M1 (FoxM1). The reduced transcription activity was reflected in the down regulation of FoxM1 and effected on down stream genes – Cdc25B, Survivin and CENPB. In vitro, siomycin was demonstrated to inhibit FoxM1 induced cell growth on soft agar and selectively kill transformed but not normal cells.

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Several analogues in the class have been developed for use as therapeutic agents with thiostrepton and nosiheptide receiving limited use in animal health.

While the thiopeptides have been recently reviewed the class has seen little semi-synthetic optimisation to exploit selectivity between binding to bacterial and mammalian targets.

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3. Microbial metabolites with tipA promoter inducing activity. II. Geninthiocin, a novel thiopeptide produced by *Streptomyces* sp. DD84. Yun B-S. et al. *J. Antibiot.* **1994**, 47, 969.
4. Berninamycin. I. The structure of berninamycinic acid. Liesch, J.M. et al., *J.Am.Chem.Soc*. **1976**, 98, 299.
5. Mode of action of berninamycin. An inhibitor of protein biosynthesis. Reusser F. *Biochem.* **1969**, 8, 3303.
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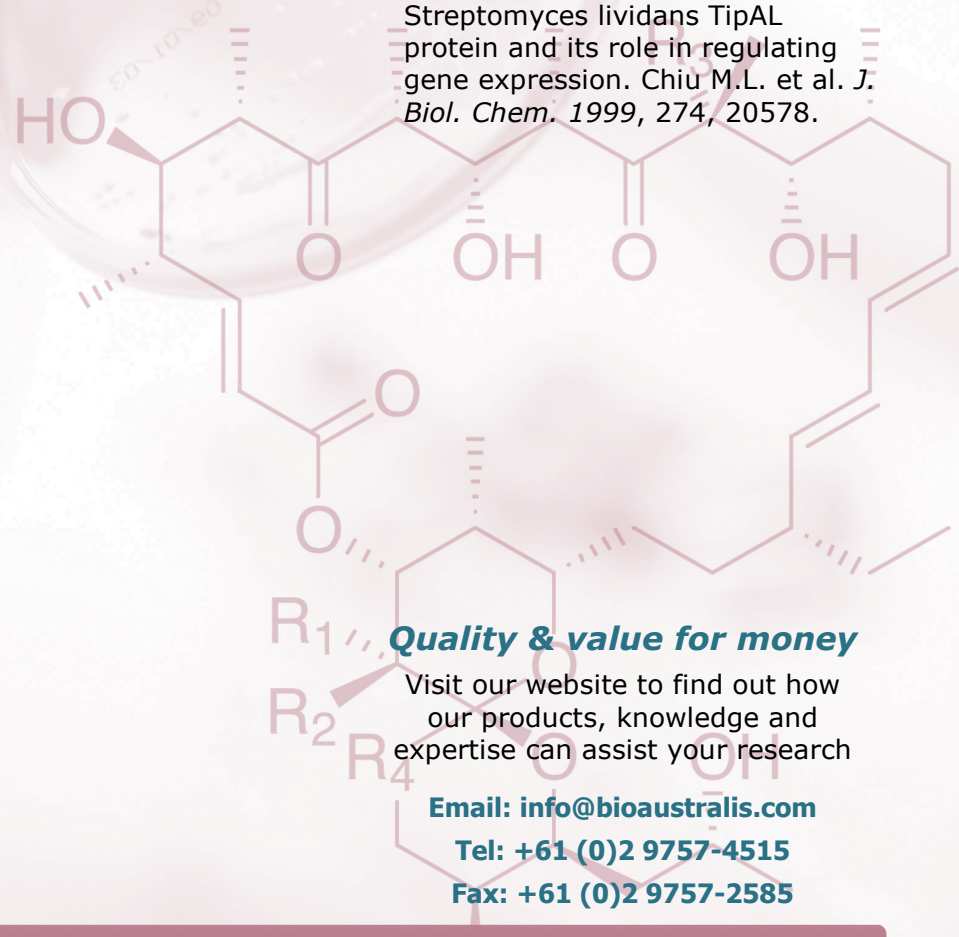

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