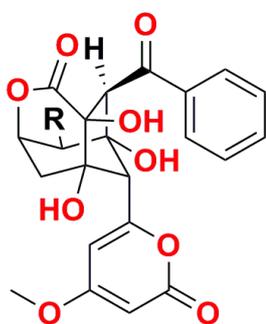


## Enterocins

### Unknown Mode of Action

In 1976, researchers at Fugisawa Pharmaceutical Co. in Japan discovered a novel antibiotic from two species of *Streptomyces*, *S. viridochromogenes* and *S. candidus*. The metabolite named **enterocin** was an unusual caged aliphatic with benzoyl and pyranone pendants. Unusually among *Streptomyces* metabolites, **enterocin** possesses broad spectrum G+ve and G-ve antibacterial activity.



**Enterocin**

**Deoxyenterocin**

**Enterocin-5-arachidate**  $\text{OCO}(\text{CH}_2)_{18}\text{CH}_3$

**Enterocin-5-behenate**  $\text{OCO}(\text{CH}_2)_{20}\text{CH}_3$

R  
OH

H

Interestingly, **enterocin** is known to act synergistically with both streptomycin and chloramphenicol. Despite these synergies **enterocin** has not been extensively investigated.

#### A future scaffold

In an unusual twist, Fenical & Jensen from SCRIPPS reported a Western Australian ascidian, *Didemnum* sp. that may have shown us the future direction of this class. The ascidian contained low levels of **enterocin** but high levels of a less polar analogue, **5-deoxyenterocin**, and two highly hydrophobic esters, **enterocin behenate** and **enterocin arachidate**. The fatty acids were enzymically coupled through the chemically accessible 5-position. While the isolation of the symbiotic *Streptomyces* was not achieved, **enterocin** production from marine *Streptomyces* is documented.

It has been the genetics of **enterocin** production in another species, "*S. maritimus*", rather than the pharmacology that has received literature prominence. Working to describe the biosynthetic route required to generate a caged structure, Moore and colleagues reported a number of intermediates

belonging to the wailupemycin class leading to a route for production of biosynthetic unnatural analogues.

#### Rare microbes

Producers of **enterocin** are very rare with only 10 examples in our collection, occurring with an incidence of ~1 in 50,000 cultures. At BioAustralis we isolate **enterocin** and **5-deoxyenterocin** from MST-MA9095, an unidentified marine *Streptomyces* culture isolated from a sponge collected at a depth of 5m off Sorrento in Victoria.

#### The opportunities

The mode of action, selectivity of more modern resistant strains, analogue synthesis and structure-activity relationships, and interaction with other classes antibiotics have never been investigated.

1. Enterocin, a new antibiotic. Miyairi N. et al. *J. Antibiot.* **1976**, 29, 227.
2. Isolation and microbial antibiotics from a marine ascidian of the genus *Didemnum*. Kang H. et al. *J. Org. Chem.* **1996**, 61, 1543.
3. Natural metabolic diversity encoded by the enterocin biosynthesis gene cluster. Piel J. et al. *J. Am. Chem. Soc.* **2000**, 122, 5415.
4. *In Vitro* biosynthesis of unnatural enterocin and wailupemycin polyketides. Kalaitzis J. A. J. et al. *Nat. Prod.* **2009**, 72, 469.

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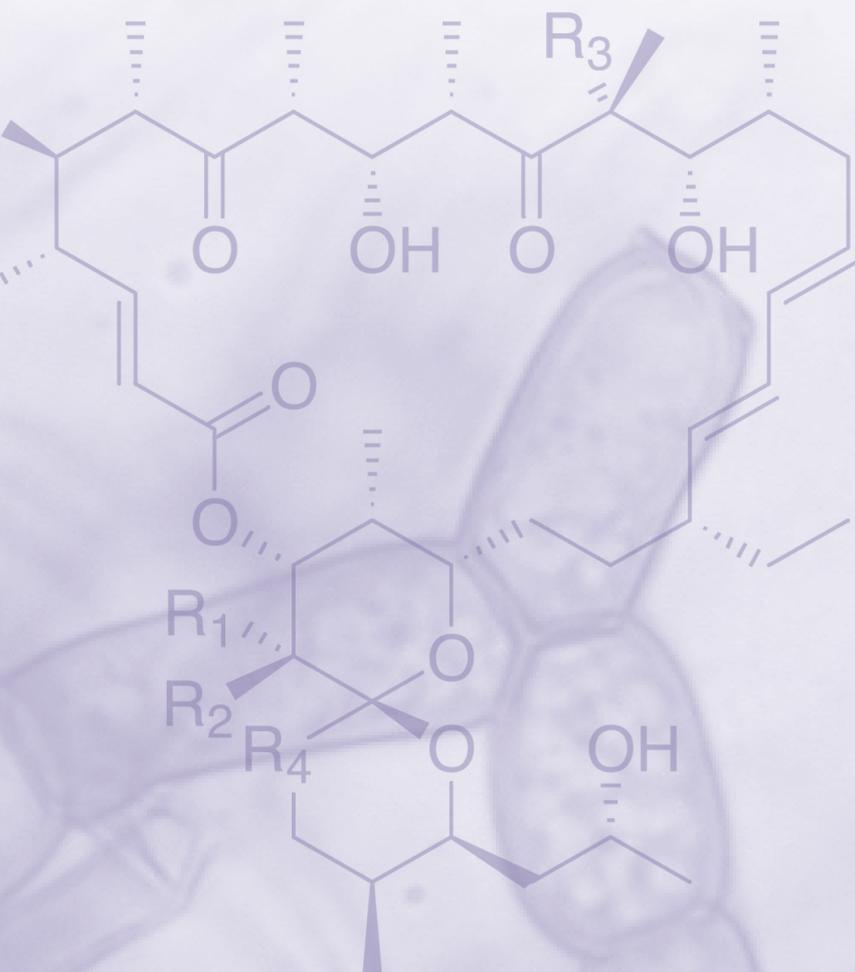
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