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SYNTHESIS AND ANTISTAPHYLOCOCCAL ACTIVITY OF NEMATOPHIN AND ITS ANALOGS

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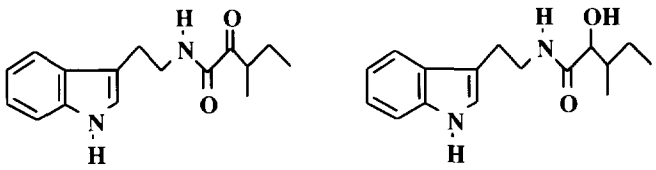
Abstract: Nematophin, a novel antibiotic from *Xenorhabdus nematophilus*, and its analogs were synthesized, and their biological activity was evaluated. It was demonstrated that the conjugated carbonyl acyl group in nematophin and its analogs is essential for their antistaphylococcal bioactivity. © 1997 Elsevier Science Ltd.

Bacteria develop resistance to antibiotics in a variety of ways, such as by chromosomal mutation, genetic transformation, transduction (bacteriophage), or plasmid conjugation.[1] *Staphylococcus* spp. are a particular challenge to antibiotics research because they have developed drug resistant strains that have chronic and sometimes lethal consequences. Methicillin-resistant *S. aureus* (MRSA) is resistant not only to virtually all β-lactam antibiotics but also to other antibiotics such as erythromycin, fusidic acid, tetracycline, minocycline, streptomycin, spectinomycin, sulfonamides, and even to disinfectants and to toxic metals such as cadmium and mercury.[2] The emergence of MRSA as a major problem worldwide has been countered by vancomycin, but its increased use has created vancomycin resistance in other species, such as *Enterococcus* spp.. Consequently, novel compounds, preferable ones that use new mechanisms of action, are urgently needed to control this important group of bacteria.

Recently a novel antibiotic, namely nematophin **1**, has been isolated from the culture broth of *Xenorhabdus nematophilus* (Enterobacteriaceae), a bacterial symbiont of the entomopathogenic nematode, *Steinernema carpocapsae*. This compound has been proven to be highly active against both wild and drug-resistant strains of *S. aureus*.[3] A closely related compound from the same source, 3-indoleethyl (3'-methyl-2'-hydroxy)pentanamide **11** (Figure 1), was inactive.[4] Consequently, it is important and interesting to understand the structure–bioactivity relationship of nematophin and its derivatives. In this paper, we report our results on the chemical synthesis of nematophin and its derivatives and on the evaluation of their antistaphylococcal activity.



1 **11**

Figure 1: Structures of natural products **1** and **11** isolated from *Xenorhabdus nematophilus*

Nematophin **1** itself was readily synthesized by amidation of tryptamine and 3-methyl-2-oxo-pentanoic acid with dicyclohexylcarbodiimide (DCC). Similarly, compounds **2**, **3**, **4**, and **5**, with a side chain on the acid part different from that of nematophin, were synthesized from tryptamine and the corresponding acids, and compounds **6**, **7**, and **8**, with a different substitute on the indole ring of nematophin, were synthesized from sodium 3-methyl-2-oxo-pentanoate and the corresponding substituted tryptamine hydrochloride (Scheme 1). Compound **9** was synthesized from 3-indoleethanol and 3-methyl-2-oxo-pentanoic acid. Another derivative, **10** was produced through the reaction of **1** and methoxylamine hydrochloride[5] and purified by HPLC. Once purified and characterized, the bioactivity of the above synthesized compounds was evaluated using a wild strain, ATCC29213, of *S. aureus* and the method described previously.[6] The results are summarized in Table 1.

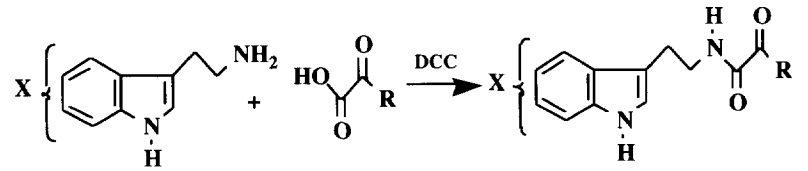
Table 1: Minimum Inhibitory Concentrations (MIC) of the derivatives of nematophin on *Staphylococcus aureus* ATCC29213 strain

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
MIC (μg/ml)	0.7	100	100	3	0.7	3	3	0.7	25	>100	>100

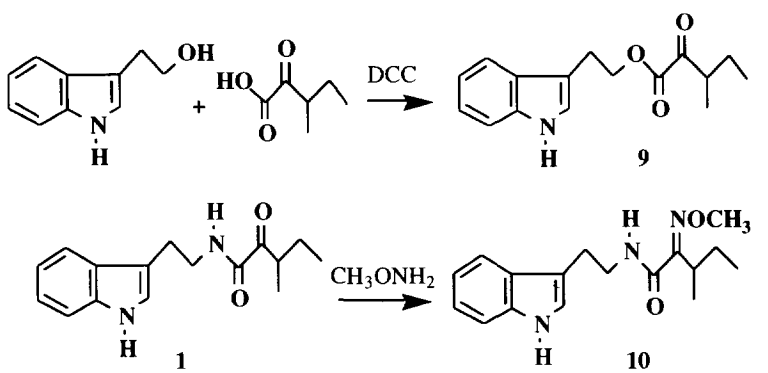
All the derivatives with a α-carbonyl acyl group, **1**–**9**, have demonstrated their activity against *S. aureus*. When the α-carbonyl acyl group was transferred to the corresponding α-methoximino acyl group as in compound **10**, or was reduced to the corresponding α-hydroxy acyl group as in compound **11**, the bioactivity disappeared or was dramatically decreased. Clearly, the α-carbonyl acyl group is essential for the associated antibacterial activity.

The substitutes on the indole ring system as shown in compounds **1**, **6**, **7**, and **8**, have some effect on the bioactivity, but this effect appears to be very limited. This suggests that the ring system could be further modified to improve its solubility and/or bioavailability without losing its bioactivity. Further, the indole ring

may be substituted with other rings which have demonstrated bioactivity so as to dramatically increase the compound's overall antibacterial activity.



X=H	R=$CH(CH_3)CH_2CH_3$	1
X=H	R=CH_3	2
X=H	R=CH_2CH_3	3
X=H	R=$CH(CH_3)_2$	4
X=H	R=$CH_2CH(CH_3)CH_3$	5
X=5-methyl	R=$CH(CH_3)CH_2CH_3$	6
X=5-methoxy	R-$CH(CH_3)CH_2CH_3$	7
X=6-fluoro	R-$CH(CH_3)CH_2CH_3$	8



Scheme 1: Synthesis of nematophin and its derivatives

Changes in the side chain have a significant effect on the bioactivity. The compounds with a branched chain, namely **1**, **4**, and **5**, were more active than those with a straight chain, namely **2** and **3**. This is scientifically interesting and is helpful in the design of additional antibiotics. As well, the results demonstrate that the change of an amide group, as in compound **1**, to the corresponding ester group, as in compound **9**, decreased the bioactivity to a certain extent, and this discovery could lead to many additional bioactive compounds with quite different characteristics.

In conclusion, this study of the structure–bioactivity relationship of nematophin and its derivatives has demonstrated that the conjugated carbonyl acyl functional group is essential for the bioactivity of nematophin and its derivatives, the side chain on the acid part has a significant effect on the bioactivity, and the substitute on the indole ring has a relatively small effect. These results provide useful information that may help in the development of related antibiotics.

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