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In vitro studies of antimicrobial activity of Gly-His-Lys conjugates as potential and promising candidates for therapeutics in skin and tissue infections

Monika Kukowska *, Magdalena Kukowska-Kaszuba, Krystyna Dzierzbicka

Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, 11/12 G. Narutowicza Street, 80-233 Gdansk, Poland

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ABSTRACT

In this Letter, we presented in vitro studies of antimicrobial activity of Gly-His-Lys conjugates that are important point in preliminary biological evaluation of their potential application in skin and tissue therapies. The novel compounds include the conjugation of fatty acids with a modification of the amino acid sequence in the primary structure of Gly-His-Lys (**6i**). All the compounds exhibited strong to moderate activity. Compound **1d** had the most potent antimicrobial activity at MIC ranges 31.3–125.0 μg/mL (against *Escherichia coli* spp. and *Staphylococcus aureus* spp.), 375.0–500.0 μg/mL (against *Pseudomonas aeruginosa* spp.). Conjugate **5b** expressed activity against *Staphylococcus aureus* spp. and *Escherichia coli* spp. at MIC ranges 250.0–500.0 μg/mL and 62.5–125.0 μg/mL, respectively. Both conjugates **1d** and **5b** possessed rapid bactericidal activity against Gram-positive bacteria at 2MIC or 4MIC. Conjugates **1b–c**, **1e**, **2a–b** and **4b** showed noticeable effect against both Gram-positive and Gram-negative bacteria. Compounds **1d**, **1e** and **2e** were the most active against fungus.

The interesting achievement in therapy of skin and tissue infections is the use of endogenous peptidic antibiotics.[1–3] The peptidic compounds are essential due to the natural origin and low incidence of bacterial resistance. They possess a broad spectrum of antimicrobial,[2,3] immunomodulatory[4] and strong repairing activities.[2,4] One of the recently marketed drug is daptomycin (a cycle lipopeptide) which possesses really strong activity and low resistance in treating skin and tissue infections caused by Gram-positive cocci (mainly *Staphylococcus* spp. and *Streptococcus* spp.).[5–7] Many experimental works proved surprisingly high activity of oligopeptides against different microorganisms. Moreover, they are also active against biofilm formation.[8,9] The activity is also potentiated by fatty acid chain linked to the *N*-terminal end of peptide.[10]

Known as lipids, fatty acids are the second group of compounds, that are involved in both physical and immunologic function barriers of the skin. They have been known for nearly several decades for their antimicrobial activity and played a direct role in innate immune defense against epidermal infections.[11–13] Fatty acids also possess antimicrobial activity especially against Gram-positive cocci (*Micrococci* spp., *Staphylococci* spp., *Streptococci* spp.), *Propionibacterium acnes*, and yeast (*Candida albicans*), rather than Gram-negative bacteria such as *Escherichia coli* spp. and *Pseudomonas aeruginosa* spp.[12–17]

Therefore research involving the possibility of their application for therapy of skin infections is still widely discussed. One of the major advantages of this group of compounds is the ability to decrease the development of bacterial resistance in comparison with conventional antibiotics used in treatment of skin lesions and vast array of wounds.[18–20]

Additionally, it was proved that the highest level of biological activity among the saturated fatty acids and their derivatives is represented by lauric acid. It also assuages in in vivo studies the effect of inflammation-related infections[1,21,22] and has a great potential in treatment of acne.[14,15]

In spite of the fact that most fatty acids possess a very strong activity and a low toxicity, especially at higher concentration in comparison with the conventional antibiotics, it makes them very attractive candidates for further modifications.[21] It is also well known that the effective topical therapeutics with antimicrobial activity should selectively target microorganisms, killing bacteria and other microbes, with minimal adverse on healthy cells. Many fatty acid–oligopeptide conjugates exhibit improved biological activity with low cytotoxic activity.[8,23] However, they represent a relatively new group of compounds and the data on their activity are limited to in vitro and in vivo studies. Their amphipathic structure seems to be required for membrane binding. The length of

* Corresponding author. Tel.: +48 58 347 20 54; fax: +48 58 347 26 94.
E-mail address: m-kukowska@wp.pl (M. Kukowska).

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