Developments in the Synthesis and Biological Activity of Glycyl-L-Histydyl-L-Lysine Derivatives

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Abstract: Three decades of extensive research on biological activity of natural tripeptide Gly-His-Lys has established the substructure for development of its novel derivatives which give hope for widening the application in the field of medicine and dermatology. Synthetic approaches to obtain Gly-His-Lys and its modifications provide both classical solution method and solid phase peptide synthesis, usage of different protecting groups and methods of peptide bond formation. In our present review, we emphasize on the methods of the synthesis described in the literature and present the aspects of Gly-His-Lys structure modifications that played a key role in scientific research.

Keywords: Copper peptides, dermatology, Glycyl-L-Histydyl-L-Lysine, Gly-His-Lys analogues, hydrophobic derivatives, medicine, polymeric derivatives.

1. INTRODUCTION

Glycyl-L-Histydyl-L-Lysine is a natural sequence, presents in the extracellular matrix protein, mainly in the α-II-chain of human collagen or SPARC. It is liberated during the episodes of tissue damage by action of proteolysis [1, 2]. Its beneficial actions in many organs and tissues, including nervous tissue, skin, hair follicles, bone, gastric, intestinal linings and the liver, have been discovered since 1973. The mechanism of its activity is also associated with the function as a transporter of ionic copper (II) (and other metal ions) which facilitates copper uptake into cells. It became recognized as a growth factor for a variety of cells, exhibiting wound healing, anti-inflammatory, antioxidant and regenerative actions [3-8].

Gly-His-Lys attained the widespread use in the field of dermatology and cosmetology and still has constituted the object of interests in dermatological and medical research. Recent study has also revealed gene regulating activity of Gly-His-Lys, suggesting that it could belong to class of epigenetic modifiers with protective and restorative actions. It was proved to down regulate the genes overexpressed in metastatic colon cancer and became promising neuroprotective agent capable of preventing the development of common age-associated neurodegenerative disorders [9-11].

In spite of a wide range of Gly-His-Lys biological activities, the literature presented a lot of modifications of peptide. The reason of the modifications is connected with the parameters such as stability, solubility, potency, bioavailability, toxicity and transdermal delivery system. The modifications let control these parameters and lead to increased possibility of therapeutical applications.

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In this paper, we present a development in the synthesis and biological activity of Glycyl-L-Histydyl-L-Lysine derivatives.

2. SYNTHESIS OF GLYCYL-L-HISTYDYL-L-LYSINE DERIVATIVES

Both classical solution method and solid phase peptide synthesis were used to obtain Gly-His-Lys and its derivatives. The authors exhibited different protecting groups and coupling reagents in the synthesis that ensured different yields and purity of the compounds. The most interesting solutions were reported and depicted in this chapter.

2.1. Solution Phase Peptide Synthesis

Dalcol *et al.* [12] described the classical method of peptide synthesis where coupling reaction between Z-L-His(Boc)-OH **(1)** and L-Lys(Tos)-OMe **(2)** was carried out by anhydride method using ethyl chloroformate. After catalytic hydrogenation, further coupling with Boc-Gly-OH **(4)** was done by mixed anhydride method (pivaloyl chloride) to give Boc-Gly-L-His(Boc)-L-Lys(Tos)-OMe **(5)**. Tripeptide **(7a)** was obtained after deblocking protecting groups with the yield of 21% as shown in (Scheme **1**). No racemization process was occurred, which was excluded by chiral phase chromatography of volatilized hydrolysate.

Arul *et al.* [13, 14] also proposed the solution phase synthesis of two *N*-terminal Gly-His-Lys derivatives in accordance with DCC/HOBt strategy (Bodansky, 1984). In the final step of the synthesis, a part of Boc-Gly-His-L-Lys(Z)-OH **(8)** was treated with HCl/ethyl acetate and then acylated by Opf ester of biotin **(9)** in the presence of TEA. Both derivatives, Boc-Gly-His-Lys **(10)** and Bio-Gly-His-Lys **(11)**, were obtained after hydrogenation over palladium/carbon under hydrogen.

Connato *et al.* [15] described a synthesis where Z-Gly-OSu **(12)** and L-Spi·HCl **(13)** or Z-Gly-OH **(15)** and HCl·H-

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