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SYNTHESIS AND BIOLOGICAL APPLICATION OF A SHORT PEPTIDOMIMETICS BASED ON BACTERIAL CELL WALL PEPTIDOGLYCAN MONOMER

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INTRODUCTION

Bacterial peptidoglycan (PG) (Figure 1.) plays a vital role in both bacterial viability and in the response of human physiology to bacterial infection. A large number of novel synthetic compounds representing smaller parts of original peptidoglycan molecules have been synthesized and found to possess versatile biological activity [1]. Peptidoglycan monomer (PGM) was isolated from the cell wall of the non-pathogenic bacterium *B. divaricatum* by a procedure described in the literature, and its significant immunomodulating activity was confirmed [2]. It was previously reported that bacterial cell wall fragments play important roles in the immune response of higher organisms against bacterial infections, and mediate the innate immune response. Furthermore, it is known that bacterial cell wall biosynthesis is a major target of antibiotics, including beta-lactam and glycopeptide antibiotics, such as vancomycin, which represent the last line of defense against antimicrobial resistance (AMR). Hence, based on the facts that peptides are increasingly becoming key therapeutic agents for a wide range of applications and that the introduction of triazolyl or lipidic moieties into the peptides as well as cyclization could stabilize the molecule to hydrolysis, oxidation, or reduction [3], the new PGM peptidomimetics are designed. The structure and conformation of the PGM molecule in solution, in DMSO, and in an aqueous medium, were studied in detail through molecular modeling and chemical calculations and were confirmed by ^{1}H NMR spectroscopy [4] (Figure 2.). Numerous PGM derivatives with an adamantane moiety, the amino acid tyrosine [5], and adamantyltripeptides have been synthesized. All the derivatizations were performed on the amino group present in the side chain of diaminopimelic acid. Still, no cyclic derivative has been synthesized, nor has a new functional group been introduced to the C-terminal end of the peptide.

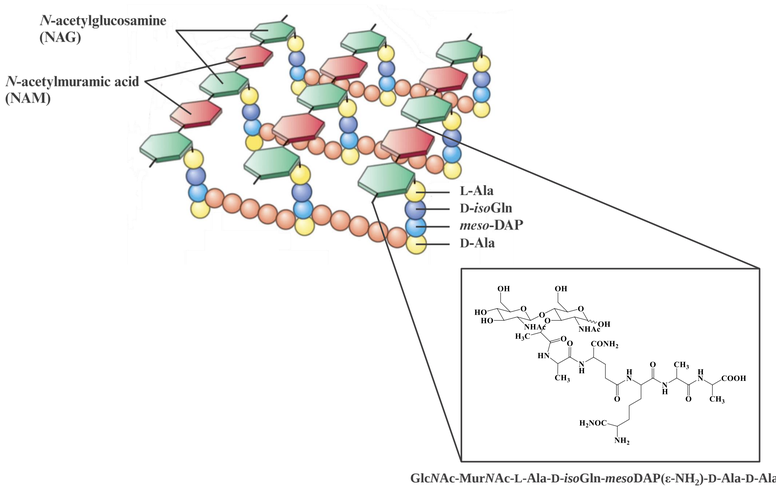

Figure 1. Schematic representation of bacterial peptidoglycan.

AIM

The aim of the present study is the synthesis of new peptidomimetics of the peptidoglycan monomer (PGM), Glc*N*Ac-Mur*N*Ac-L-Ala-D-*iso*Gln-*meso*DAP(ε-NH_2)-D-Ala-D-Ala, cyclic derivative (tail-to-side chain cyclization of Tyr-PGM), cyTyr-PGM (Figure 3.), and lipophilic derivative, PGM-DOPE (Figure 4.).

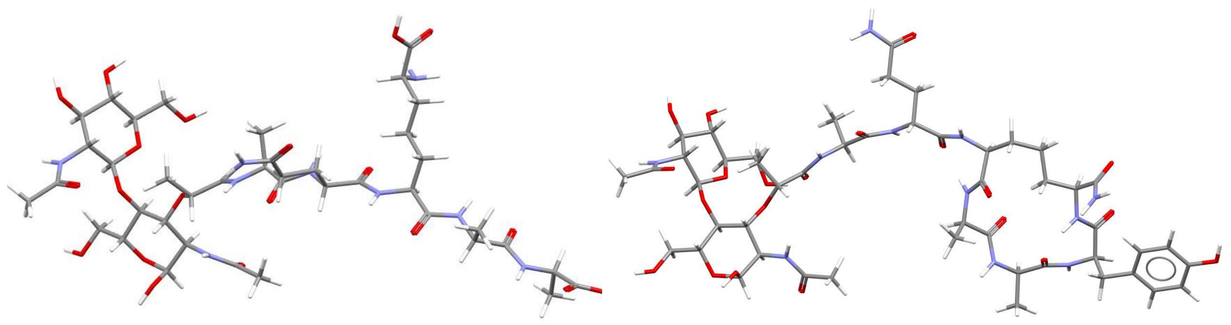

Figure 2. Minimized chemical structure of PGM [4] and designed cyTyr-PGM derivative.

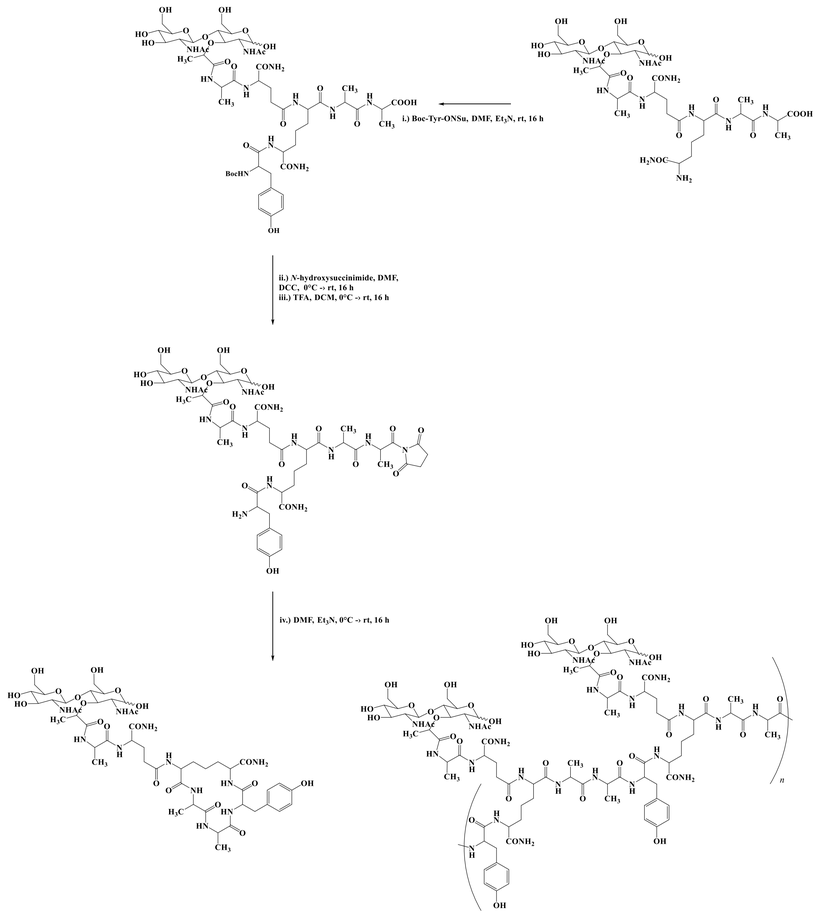

Figure 3. Synthesis route for the cyclic derivative of peptidoglycan monomer, cyTyr-PGM.

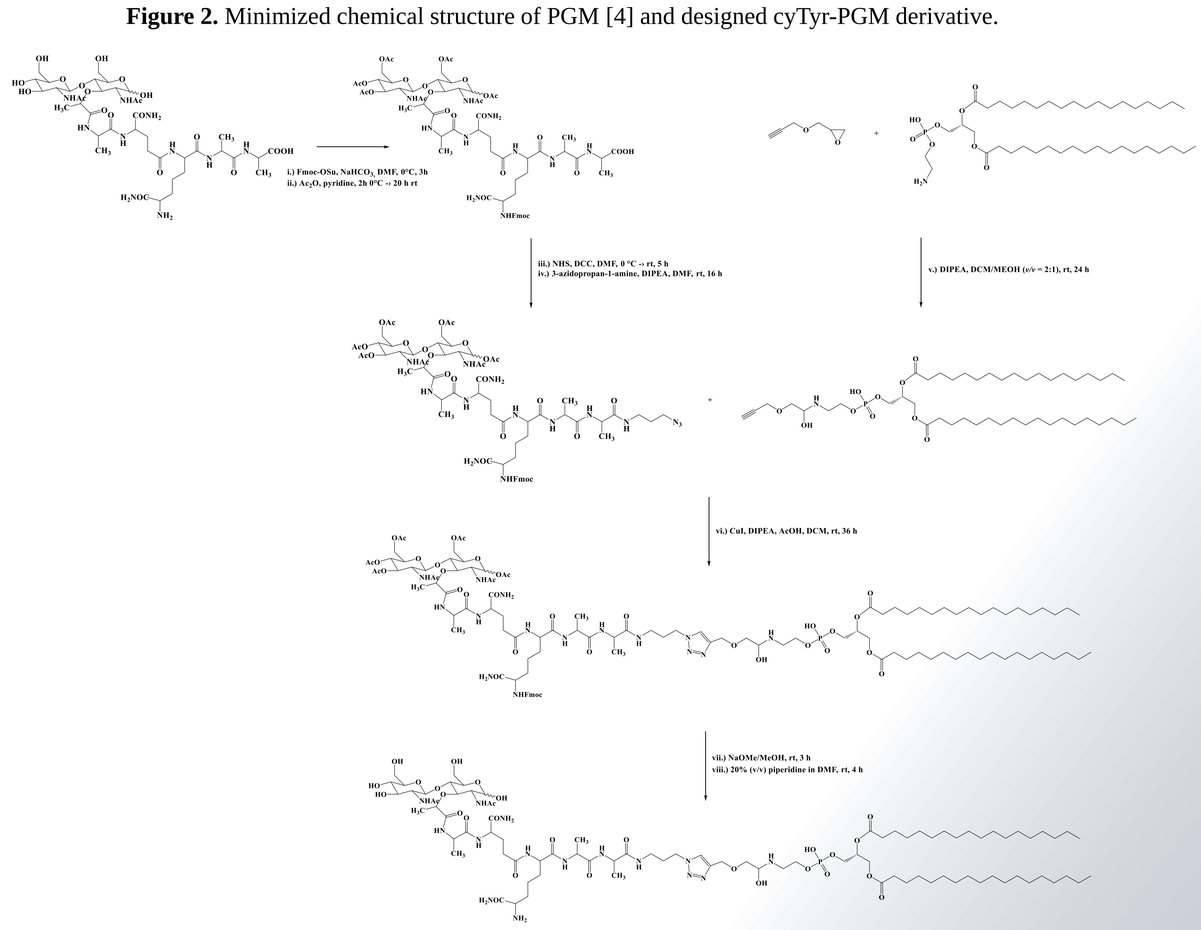

Figure 4. Synthesis route for the lipophilic derivative of peptidoglycan monomer, PGM-DOPE.

METHODS

The design of new peptidomimetics is carried out using molecular modeling and chemical calculations using a numerical/graphical workstation HP-620 (Linux) equipped with a software package for molecular modeling (MM) and molecular dynamics (MD) *Sybyl*-X (Tripos Inc. Certara). The peptidomimetics were synthesized in solution. PGM-DOPE synthesis is carried out by cycloaddition catalyzed by copper(I) ions, which leads to the formation of 1,4-disubstituted 1,2,3-triazoles under very mild reaction conditions. For the design of cyclic peptidomimetics, obtained clusters of conformations with minimum energy were analyzed, and tyrosine-PGM was selected as the starting molecule for cyclization. DCC and NHS crosslinking agents were used for introducing “zero-length” amide cross-links between a carboxylic group of terminal D-Ala and the amino group of tyrosine which is attached to *meso*DAP in the molecule Tyr-PGM. In the cyclization reaction, along with the cyclization of the tetrapeptide, polymerization was observed. The described synthetic protocols should be optimized and the antibacterial and immunostimulating effects of the synthesized peptidomimetics should be tested.

CONCLUSION

- ❑ Design of peptidomimetics by molecular modeling and structure optimization with particular emphasis on the possibility of cyclization of the peptide part of the PGM molecule is performed
- ❑ The protocol for the introduction of new substituents by the click-chemistry method at the carboxyl end of the peptide part of the PGM is established and PGM-DOPE is synthesized
- ❑ The synthetic route using copper(I)-catalyzed azide-alkyne cycloaddition for the synthesis of triazolyl-containing PGM-DOPE peptidomimetic was developed
- ❑ The preliminary protocol for tail-to-side chain cyclization of the Tyr-PGM molecule is established

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