New Sulphonamide-peptide Hybrid Molecules as Potential PBP 2a Ligands and Methicillin Resistant *Staphylococcus aureus* Actives

Abstract

Penicillin-binding protein 2a (PbP 2a) expression accounts for the insusceptibility of methicillin-resistant *Staphylocuccus aureus* (MRSA) to β-lactam antibiotics. In this research, we employed computational strategies to challenge PbP 2a with series of fifty-five 'ala-ala' and 'ala-pro' sulphonamide-dipeptides. The binding stability of two compounds (labeled: **10i** and **10n**) with theoretical K_i in nM and μM ranges, for PbP 2a active and allosteric sites respectively, were investigated using molecular dynamics simulations. In addition, the results of the sensitivity of four strains of MRSA for compounds **10i** and **10n** obtained revealed the compounds at 10 μg/ml caused two isolates (S4 and S10) to revert to being susceptible. Finally, a reliable binding conformation of both compounds in the two binding sites of PbP 2a are described to provide a rationale for structure-activity optimization of this series.