

Structure-based optimization and discovery of novel 1,3,5-triazine derivatives as bacterial translation inhibitor with favourable metabolic fate

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Introduction

We have recently moved into an era not just of multiple resistant bacteria but of totally resistant pathogens, which now include vancomycin-resistant *enterococci*, carbapenem-resistant *Acinetobacter baumannii*, vancomycin-resistant MRSA and, very recently, NDM-1. Thus, increased incidence of bacterial resistance to currently available antibiotics necessitates the discovery and introduction of new and effective drugs. In our earlier studies, we have discovered a potent antibacterial lead molecule from 1,3,5-triazine (first generation) and its subsequent optimization till its tenth generation results much more advanced analogue with enhanced activity and less toxicity [1].

Objectives

Present study deals with the advancement of novel derivatives of 1,3,5-triazines to increase its efficacy and potency to make them viable drug candidate (eleventh generation).

Methods

The synthesis of analogues was achieved by means of S_NAr reaction utilizing distinguished amines. These molecules were then subjected to antibacterial screening against pathogenic Gram-positive and Gram-negative micro-organisms. MetaPrint2D-React from University of Cambridge, UK was utilized for the prediction of metabolites of the compounds.

Results

Entire set of derivatives demonstrated excellent antibacterial activity ($1.56 - 25 \mu\text{g ml}^{-1}$), and in some instance

found equipotent to cefixime as standard. The molecular docking study on eubacterial ribosomal decoding A site (*Escherichia coli* 16S rRNA A site) confirmed the stability of target compounds into the inner groove of active site by making close H-bonds with highly conserved residues, e.g. Ade38, Gua37, Ade39, and Gua40. Moreover, the most active compound 7e, in MetaPrint2D-React study was not found to be deactivated by human metabolic process, which conform the utility of designed molecules.

Conclusion

We have discovered an another novel 1,3,5-triazine analogs as potent antibacterial agent through structure-based optimization of our defined lead.

Disclosure of interest

None declared.

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Reference

1. Singh B, Bhat HR, Kumawat MK, Singh UP: Structure-guided discovery of 1,3,5-triazine-pyrazole conjugates as antibacterial and antibiofilm agents against pathogens causing human diseases with favourable metabolic fate. *Bioorganic & Medicinal Chemistry Letters* 2014, **24**:3321-3325.

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