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The future of structure-based drug discovery, identifying novel inhibitors as anti-gonococcal drugs : The curious case of Glutamate racemase

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Background

Neisseria gonorrhoeae, has developed resistance to most of the drugs and hence declared as ‘Superbug’. Glutamate racemase (MurI) considered as an important drug target for its role in bacterial cell wall synthesis. Therefore, identification of novel drugs for the treatment of gonorrhea is urgently required.

Aim/Methods

The amino acid sequence of MurI from Neisseria gonorrhoeae (YP_208550) was retrieved from NCBI. Homology model was generated by Modeller programme of Discovery Studio. Best model was selected based on DOPE score and PDF energy score and further verified. Receptor binding site was identified after superimposition of template structure and modelled structure. Best pose was selected and receptor-ligand pharmacophore model was generated. Virtual screening was performed, best hits were selected based on ADMET profile and further refined.

Results

The best homology model generated was selected based on the verify score of 107.93. Validation of the selected model by Ramachandran plot showed 214 residues (91.8%) fall in most favored region. Root-mean-squared deviation (RMSD) of 0.2475 A 0 was generated by superimposition of query and template structures. Six pharmacophores were generated using best docking pose between D-glutamate and MurI. Virtual screening with ZINC library was done. 586 hits so obtained were filtered by fit value of 3.51 which resulted in 268 hits. These were subjected to energy minimization and docking to obtain the best hits.

Conclusions

The study identifies potential compounds that interact with active site of MurI protein, opening new avenues for the treatment option against multi-drug resistant strains.

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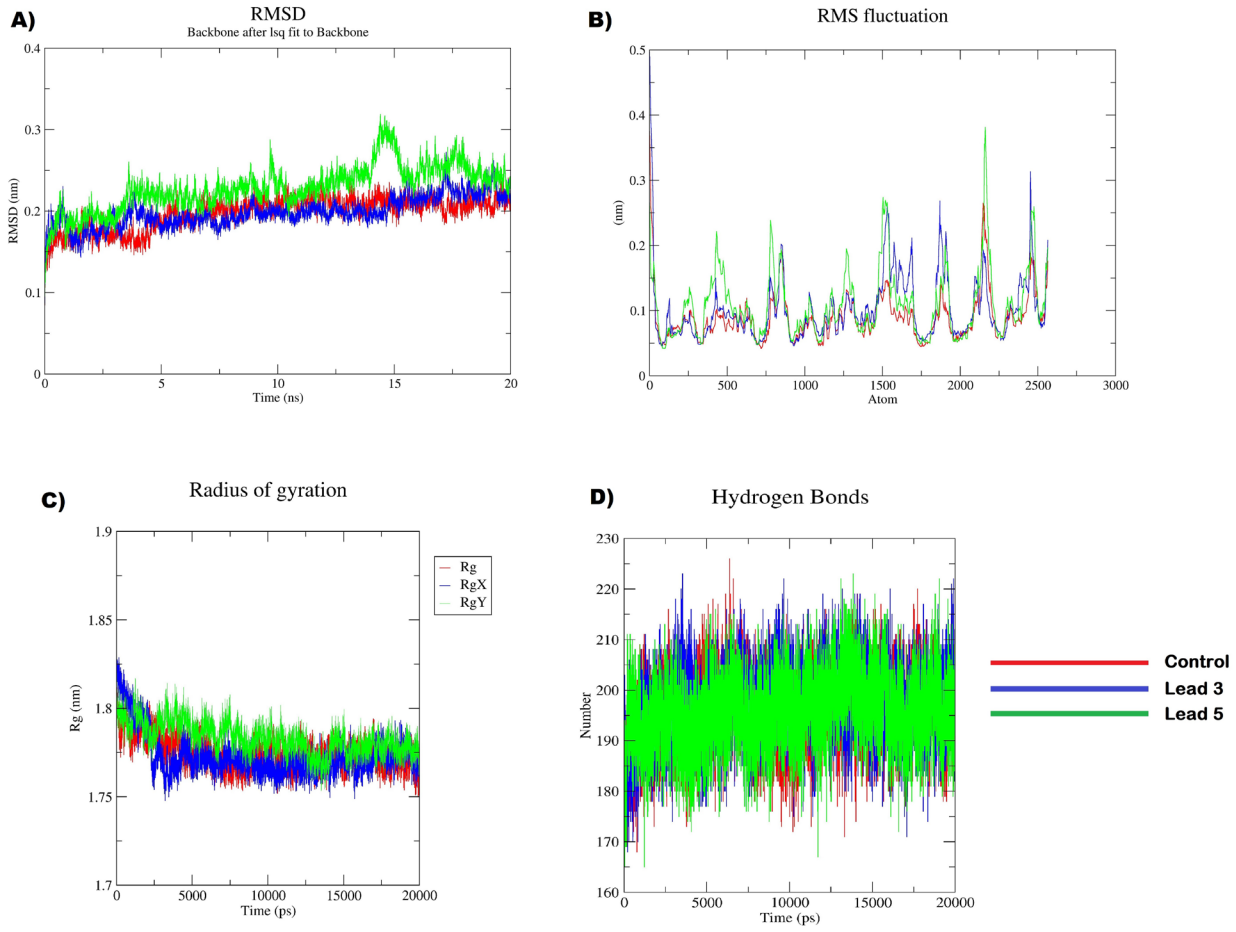
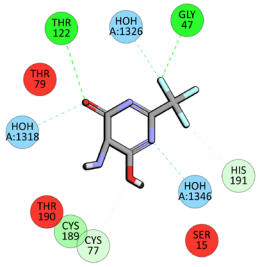
Supplemental Document Upload

Molecular Dynamics Simulation study of two novel inhibitors identified through computational screening



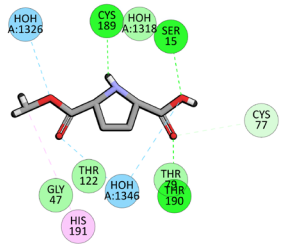
Molecular Interaction analysis of five top compounds identified through high-throughput virtual screening

A)



Lead1

B)



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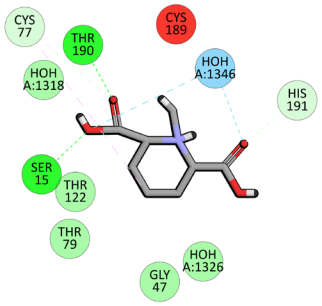

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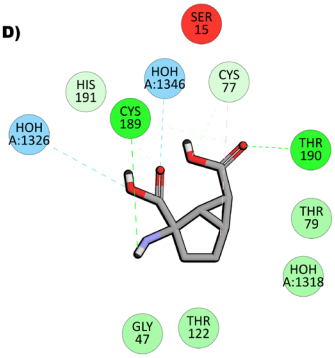

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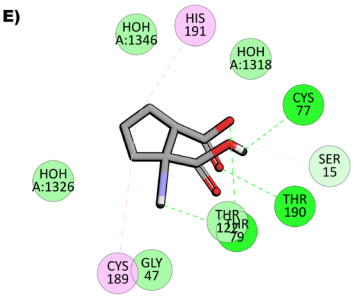

Lead5