Virtual screening cascade in search for novel purine-derivated MurD inhibitors as antibacterial agents

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Introduction: UDP-N-acetylmuramoylalanine glutamate ligase (MurD) is one of the emerging targets for the next-generation of anti-bacterial agents. Along with other members of the amide ligases (MurC-F) family, MurD inhibits the synthesis of peptidoglycan – key bacterial metabolite, essential for bacterial growth. In addition, the anti-bacterial action of MurC-F is indeed very promiscuous, as this metabolic pathway is common for multiple bacterial strains and so the inhibitor of a single enzyme can be multipotent antibacterial agent.[1]

Results and Discussion: Herein, we developed a virtual screening protocol oriented at identification of the new MurD inhibitors with purine scaffold. A number of organic synthesis schemes along with the databases of accessible building blocks were used for enumeration of combinatorial library of synthetically accessible compounds. This chemical subspace was used as an input for the multistep virtual screening (VS) protocol utilizing the previously developed methodology.[2,3] The VS cascade consisted of physicochemistry, ADME and pharmacophore filters, as well as the docking protocol. All stages were optimized to maximize the screening parameters in the retrospective experiments.

Conclusion: Compounds returned by the screening cascade were carefully analyzed (visual inspection) and the most promising ones were selected for future synthesis and *in vitro* evaluation.

References

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