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Abstract

Computational Design of New Teixobactin Analogues as Inhibitors of Lipid II Flippase MurJ †

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Abstract: The peptidoglycan (PG) cell wall is an essential component of the bacterial cell structure, and crippling its synthesis is one of the most successful strategies in the continuing war against pathogenic bacteria. MurJ is a member of the multidrug/oligosaccharidyl-lipid/polysaccharide (MOP) flippase superfamily which is critically required for the synthesis of PG from lipid II. Teixobactin (TXB) is a recently discovered, promising macrocyclic depsipeptide natural antibiotic. TXB is claimed to "kill pathogens without detectable resistance" and is considered a possible "paving stone toward a new class of antibiotics". In the context of the current antibiotic resistance crisis, the rapid development of a plethora of TXB analogs with improved pharmacokinetics/pharmacodynamics (PK/PD) is a critical challenge. This study focuses on the computational design of new TXB analog prototypes—disruptors of PG cell wall biosynthesis by the inhibition of MurJ. A combinatorial library was generated in silico using a set of three scaffolds based on the TXB structure and a selected list of building blocks in order to avoid the molecular obesity issue and minimize the potential toxicity concerns and health risks. TXB and the combinatorial library were virtually screened with adequate drug-likeness filters and PK/PD models. The safest drug candidates were docked with PyRx v.0.9.7 against the crystal structure of MurJ. What was found was that 26 virtual analogs had better binding affinities than TXB against MurJ. Overall, the proposed computational drug design approach for novel antibiotics might be a useful asset for medicinal chemists and translational pharmacologists.

Keywords: antibacterials; in silico; molecular docking; pharmacodynamics; pharmacokinetics

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