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Developing a lead compound for the inhibition of bacterial DNA Gyrase

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Purpose: As reported by the Centers of Disease Control (CDC), multi-drug resistance bacteria have an estimated cost of $40 billion on health-care systems globally. In the past 20 years, developments of therapeutics aimed at killing infectious strains of bacteria have been very limited. Bacterial DNA gyrase is a complex enzyme that is used to relieve strain from DNA unwinding and introduces supercoils for various cellular processes including DNA compaction, replication and transcription. Inhibition of bacterial DNA gyrase provides an avenue to develop compounds that can be optimized for clinical applications. The present study focuses on using computational predictions, synthetic chemistry and in vitro enzymatic activity assays to search for a lead compound.

Methods: The rationale for the study employs molecular dynamic simulations and binding energy calculations to predict potential lead compounds from a library containing 800 substituted pyrrole and thiophene analogues. The cumulative binding energy predictions and ligand interactions with binding pocket residues were used to select 25 compounds. These compounds were then tested in *in vitro* DNA supercoiling assays.

Results: *In silico* predictions demonstrated favorability of compounds to interact with the ATPase binding site of Gyrase subunit B. Ligand binding scores suggested a preference for tetrazole-substituted thiophenes that adopted pi-stacking interactions with hydrophobic side chains and formed hydrogen bonds with donor side chains. In vitro DNA supercoiling assays indicated dose-dependent reduction of supercoiling activity of DNA gyrase at a concentration of 80 μM for compounds 0599, 0607 and 0608.

Conclusions: Molecular modeling predictions were able to select compounds that inhibit bacterial DNA gyrase in vitro. Computational chemistry and synthetic approaches are being used to optimize analogues of top compounds.

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