Exploiting Plasmid-Mediated Resistance: Discovery of Small-Molecule Inhibitors for the Artificial Activation of the Kid-Kis Toxin-Antitoxin System in Plasmid R1

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Antibiotic resistance is one of the leading challenges to public health today, and a primary contributor to the rapid rise of resistance is plasmids, which facilitate the spread of multi-drug resistance genes within bacterial populations through horizontal gene transfer. Therefore, plasmids are critical targets to prevent the rapid spread of antibiotic resistance. In particular, low-copy number plasmids often contain toxin-antitoxin systems that act lethally when activated, so due to the role of toxin-antitoxin systems in facilitating internal cell death, the disruption of the protein-protein interaction between the toxin and the antitoxin may be a promising novel target for antibiotic development. Key interacting regions of the Kid-Kis toxin-antitoxin interaction were identified as binding sites for the de-novo design of small-molecule inhibitors using the webserver LEA3D. To predict the activity of novel inhibitors, a QSAR classification model was constructed with OCHEM using published experimental data on a related system. The most promising inhibitors with drug-like properties were molecules targeting the Glu66 to Arg72 region of the Kis antitoxin, as four out of five inhibitors were classified as active compounds. Calculations for Gibbs free energy ($p=0.000000252$) and pKd ($p=0.000459$) showed statistically significant binding affinity compared to control molecules with no known affinity for the target, representing a significant binding specificity towards the target interaction region. In the fight against antibiotic resistance, the design of small-molecule inhibitors targeting toxin-antitoxin systems may be an important discovery for the selective targeting of plasmid-mediated resistance through the application of internal mechanisms toward antibiotic development.

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