TOWARD COMPUTER-AIDED DESIGN OF CATALYTIC AMINOGLYCOSIDE – "A WOLF IN SHEEP'S CLOTHING"

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The growing resistance of bacteria to traditional antibiotics has driven the search for innovative strategies to combat pathogenic bacteria. One promising approach to address this issue is the development of catalytic antibiotics. Catalytic antibiotics bind specifically to their biological target, like conventional antibiotics, but also inactivate it through catalytic degradation. This approach would decrease the required drug dosage, thereby reducing side effects, overcome existing resistance mechanisms, and mitigate the emergence of new resistance.
We present two classes of antibiotics for which we have attempted to create a catalytic drug: aminoglycosides and fluoroquinolones. Aminoglycosides target bacterial ribosomes, while fluoroquinolones inhibit DNA topoisomerases, both through reversible non-covalent binding in their standard modes of action. The catalytic mechanism of these antibiotics is based on the hydrolysis of RNA and DNA phosphodiester bonds at their respective binding sites, leading to the irreversible deactivation of the molecular target.
So far, developing an effective ribonuclease among aminoglycoside derivatives has proven challenging [1]. To better understand these difficulties, we solved the cryo-EM structure of the lead aminoglycoside-warhead compound bound to the *E. coli* ribosome and performed molecular dynamics simulations of this complex. We found that the catalytic warhead was unable to induce the in-line conformation of the rRNA backbone required in the classical mechanism of rRNA hydrolysis.
In parallel research on fluoroquinolones [2-4], we found that the 1,4,7-triazacyclononane (TACN) moiety with a guanidinoethyl sidechain in its metal-free form efficiently cleaves DNA under physiological conditions. Since the mechanism of DNA cleavage by TACN warhead does not require a significant conformational change of the DNA backbone, we hypothesized that integrating the TACN-guanidinoethyl moiety within an aminoglycoside scaffold might enable hydrolytic cleavage of rRNA in a similar manner. In addition, by employing a metal-free catalytic warhead, the proposed strategy circumvents the issues linked to metallic compounds, such as loss of nuclease activity under physiological conditions [2-4].
We discuss how modern computational methods and tools can facilitate the rational design of aminoglycosides with ribonuclease capabilities, presenting a promising direction for future research in combating antibiotic resistance.

References:
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