# Integrative Subtractive Genomics and Structure-Based Screening Reveal CheR as a Promising Therapeutic Target in *Leptospira interrogans*

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## Abstract

*Leptospira interrogans*, the primary causative agent of leptospirosis, poses a significant global health threat due to its ability to survive in diverse environments and establish severe infections in humans. To facilitate the discovery of novel therapeutic targets, a comprehensive subtractive genomics approach was applied to the *L. interrogans* proteome. This systematic workflow enabled the removal of host homologs, non-essential proteins, and redundant metabolic components, ultimately yielding a refined set of pathogen-specific, essential proteins suitable for drug targeting. Among these, **CheR**, a chemotaxis methyltransferase, was identified as a high-value target due to its critical role in methylation-dependent signal adaptation and its involvement in the chemotaxis-driven virulence of *L. interrogans*. The absence human homologs further strengthened its suitability as a selective therapeutic target. Following target prioritization, structure-based computational methods were employed to identify potential inhibitors of CheR. High-throughput virtual screening, molecular docking, and detailed interaction analyses were conducted to evaluate the binding affinity and active-site compatibility of screened compounds. The top-ranked molecules demonstrated strong and stable interactions with CheR, revealing promising scaffolds for future lead optimization. Overall, this study integrates subtractive genomics with advanced *in silico* drug discovery tools, providing a robust framework for identifying novel drug targets and inhibitors against *L. interrogans* and highlighting CheR as a compelling candidate for anti-leptospiral therapeutic development.

**Keywords:** *Leptospira interrogans*; chemotaxis methyltransferase; molecular docking; virtual screening; drug target;