Next-Gen Antibiotics Targeting the Shikimate Pathway

In view of the antibiotic resistance crisis, identifying new targets to establish robust intervention strategies is urgently needed. Targeting the shikimate pathway is a highly promising approach, as exemplified by the blockbuster herbicide glyphosate.

BACKGROUND

The shikimate pathway is vital to bacteria, fungi, apicomplexa, and plants but absent in mammals. The pathway comprises seven enzymes, and its inhibition is detrimental to the organism, as exemplified by the highly efficient herbicide glyphosate, which inhibits the sixth enzyme of this pathway. Therefore, the enzymes of the shikimate pathway are highly promising targets for intervention strategies, especially considering the current antibiotic resistance crisis. Potent inhibitors of these targets, including chorismate synthase—the last enzyme of the shikimate pathway, would represent antibiotics (but also antimycotics/fungicides) insusceptible to existing resistance mechanisms.

TECHNOLOGY

We identified promising inhibitors of chorismite synthase by extensive virtual and experimental screening. The currently most promising lead compound is the azo dye PH011669, exhibiting a dissociation constant (*K*d) and 50% inhibitory constant (IC_{50}) value of 1.1 ± 0.1 and 10 ± 1 µM, respectively, against chorismate synthase from *Paracoccidioides brasiliensis*, a dimorphic fungus responsible for the most systemic mycosis in Latin America. The compound also exhibits micromolar affinity towards chorismate synthases from at least 17 other organisms.
We use X-ray crystallography combined with computational methods (molecular docking and molecular dynamics) for structure-based rational drug design and optimization of our current lead compound, including the elucidation of the mode of inhibition.

OFFER

We offer the development and optimization of potent chorismate synthase inhibitors that have the potential to become the next-generation antibiotics. The intellectual property and compounds developed in our project would fully belong to our investor/industrial partner.

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DEVELOPMENT STATUS:
Technology Readiness Level 2-5
(Technology validated in lab)

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