Investigating the inhibition mechanism and catalytic cycle of MbtI, the salicylate synthase from *Mycobacterium tuberculosis*

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According to the latest annual report published by the World Health Organisation, tuberculosis is the first cause of death from a single infectious agent worldwide. Moreover, the growing emergence of resistant strains of *Mycobacterium tuberculosis* (Mtb) poses a serious threat to the public's health. Therefore, the discovery of new antitubercular agents has still a critical importance.[1]

In this context, the mycobacterium-specific salicylate synthase MbtI has been recently validated as a promising pharmacological target. This Mg^{2+}-dependent enzyme is involved in the siderophore-mediated iron uptake, a key pathway for the survival and pathogenicity of Mtb in the host.[2]

A structure-based virtual screening allowed us to identify a competitive furan-based inhibitor of MbtI, which was taken as a starting point for a thorough structure-activity investigation. Our studies led to the development of potent enzymatic inhibitors, also exhibiting a promising antimycobacterial action.[3,4]

In an attempt to deeply understand the inhibition mechanism of this class of compounds, we performed biochemical investigations: these studies suggested the possibility of a Mg^{2+}-independent binding, despite the interaction with the catalytic metal had been a cornerstone of MbtI inhibition for years. Further computational analyses and experimental data seemed to support our hypothesis, but it was only with crystallisation studies that we obtained a definitive characterisation of the binding mode. Our structural investigations also provided new insights into the conformational shifts of the active site, in relation to the catalytic state of the enzyme.[5]

Overall, these results pave the way for the rational modification of our scaffold, which will hopefully lead to the obtainment of improved antitubercular candidates.

References

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