Mycobacterium tuberculosis Tryptophan Synthase as a target for novel antitubercular drugs

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Mycobacterium tuberculosis Tryptophan Synthase (TrpAB) is an essential enzyme for bacterial growth absent in human, thus considered an interesting target for drug development. TrpAB is a heterotetramer of two alpha and two beta subunits; alpha-subunits hydrolyse indole-3-glycerol phosphate into glyceraldehyde-3-phosphate and indole, while beta-subunits condensate indole and L-Serine into L-Tryptophan.
GSK3778839 (GSK839) is a potent antitubercular compound active against Mtb clinical isolates, without cross-resistance with other antitubercular drugs and low Frequency or Resistance. Sequencing of resistant mutants suggested the involvement of TrpAB in GSK839 mechanism of action. To confirm this hypothesis, the effects of GSK839 have been evaluated against the recombinant enzyme, showing a specific inhibition of the beta-subunits without affecting the alpha-reaction. An in-depth characterization revealed a mixed uncompetitive inhibitor behaviour, with a Ki value of 0.25 ± 0.01 μM and residence time of 1.5 minutes. To confirm the suitability of TrpAB as druggable target, different chemical class inhibitors have been evaluated against both reactions. Some compounds showed a moderate inhibition of both enzyme activities without specificity against one of the two reactions, possibly affecting the allosteric regulation rather than a specific active site. This study confirmed the TrpAB enzyme as feasible drug target opening the possibility to the development of different chemotypes.
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