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Design and development of novel inhibitors for the treatment of latent tuberculosis

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ABSTRACT

Objective/background: "The captain of all these men of death", is the apt sobriquet for the age-old disease tuberculosis (TB). Despite the availability of many drugs, cases of increasing resistance in the forms of multi-drug and extensively drug-resistant TB and persistence [characteristic of *Mycobacterium tuberculosis* (MTB)] make the eradication of TB a nightmare. Approval of bedaquiline by the Food and Drug Administration focused attention on quinoline scaffolds for development of new anti-TB agents. Lysine ε-aminotransferase (LAT) in MTB plays a pivotal role in regulating amino acid synthesis, which in turn affects mycobacterial persistence. Here, developed quinoline inhibitors that targeted LAT with an objective to eliminate dormant forms of mycobacterium.

Methods: Using e-pharmacophore approaches, quinolone (PBD: 2CJD) leads were found to inhibit lysine binding to LAT. To investigate structural activity relationships, 21 analogues were synthesized and characterized based on the identified lead molecules.

Results: Among the derivatives, *N*-(pyridin-2-yl methyl)-2-(4-(quinolin-4-yl) piperazin-1-yl) acetamide was identified as a potent molecule, with an IC_{50} for LAT of 1.04 μM. In nutrient-starved and zebra fish models, this molecule exhibited logarithmic reductions of 2.1- and 2.2-fold, respectively, at a concentration of 10 μg/mL. The compound also exhibited good activity against persistent forms of mycobacteria (biofilm model), showing logarithmic reduction of 2.8-fold. Additionally, the hit molecule showed concentration-dependent kill kinetics against dormant forms of mycobacteria, and were devoid of cytotoxicity against RAW cell lines 264.7 at concentrations of 50 μM.

Conclusion: Our results indicated that the hit molecule showed activity against both active and persistent forms of infection, which is ideal for new anti-TB agents. This molecule requires further pharmacokinetic and dynamic screening for development as new drug candidate.

Conflicts of interest

All authors declare no conflicts of interest.

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