

In silico* Driven Design and Synthesis of New Chalcone-Like Lead Compounds Active Against *Mycobacterium tuberculosis

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Abstract

In this work we designed, synthesized, and identified new potent chalcone-like lead compounds active against *M. tuberculosis*.

Introduction

Tuberculosis (TB) remains a global pandemic, being the major cause of death by infectious diseases¹. This situation is worsened due to the lack of health care, co-infection with HIV, and the emergence of resistant strains. Therefore, new anti-TB drugs active against *Mycobacterium tuberculosis* (*M. tb*) resistant strains and that could shorten the treatment regimen are urgently needed. In this study, we report the *in silico* driven design of new chalcone-like compounds using SAR rules QSAR models. Then, we synthesized the designed hits and performed the experimental evaluation on replicating and nonreplicating *M. tb* strains.

Results and Discussion

We developed SAR rules using matched molecular pair analysis (MMPA) approach and designed new chalcones using the information from the SAR analysis and bioisosteric replacement strategy. Then, binary QSAR models were developed using a large dataset of 604 chalcones collected from the literature, to rationalize which compounds would be synthesized. The QSAR models were developed combining four types of fingerprints and four different machine learning methods, and were rigorously validated using 5-fold cross-validation strategy. This approach led to highly externally predictive models (correct classification rate values ranging between 0.73 – 0.94 and coverage of 0.73 – 0.94). Developed models were used in the most conservative way for selection of more promising designed hits. As a result, 30 virtual hits were selected, synthesized and experimentally evaluated against *M. tb* H37Rv strain. Ten compounds exhibited submicromolar activity against the replicating mycobacteria on microplate assay blue alamar (MABA) (< 1 μ M) and nonreplicating mycobacteria on low recovery assay (LORA) (< 10

μ M). The most potent compound showed MIC values of 0.19 μ M and 1.73 μ M for MABA and LORA, respectively. We also tested the compounds against six other microorganisms of the genus *Mycobacterium*, presenting MIC values between 0.21-8.92 μ M. The cytotoxicity assay in Vero cells demonstrated that the compounds have selectivity index (SI) values between 41-454, therefore highly selective for bacteria when compared with mammalian cells. We also predicted the potential of blockage of hERG channels using the web server Pred-hERG². The compounds were predicted as non-blockers by binary prediction (probability >50%) and by multiclass prediction (probability >46%). Further, we developed continuous QSAR models using MIC data from our compounds and retrieved from literature, in order to analyze the positive and negative contributions of each fragment for the anti-TB activity. This approach led to highly externally predictive models (CCC ranging between 0.85-0.94 and Q² of 0.75-0.82). A consensus model was built for mechanistic interpretation. The fragments furan, NO₂, NO₂ aromatic, pyridine, thiophen, Br aromatic and CO ketone presented positive contribution, which corroborate with some of SAR results obtained using the MMPA approach.

Conclusion

The combination of SAR rules and QSAR modeling was useful to guide the synthesis of new optimized compounds and consequently, led to the identification of 10 new chalcone-like scaffolds with potent anti-TB activity and low cytotoxicity in mammalian cells. The designed new anti-TB compounds are promising new leads for pre-clinical studies.

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WHO. Global tuberculosis report 2015 (WHO): http://www.who.int/tb/publications/global_report/en/

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