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Anti-mycobacterial peroxides: A new class of agents for development against tuberculosis

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Abstract:
Background: With few exceptions, existing tuberculosis drugs were developed many years ago and resistance profiles have emerged. This has created a need for new drugs with discrete modes of action. There is evidence that tuberculosis (like other bacteria) is susceptible to oxidative pressure and this has yet to be properly utilised as a therapeutic approach in a manner similar to that which has proven highly successful in malaria therapy. Objective: To develop an alternative approach to the incorporation of bacterial siderophores that results in the creation of antitubercular peroxidic leads for subsequent development as novel agents against tuberculosis. Methods: Eight novel peroxides were prepared and the antitubercular activity (H37Rv) was compared to existing artemisinin derivatives in vitro. The potential for toxicity was evaluated against the L6 rat skeletal myoblast and HeLa cervical cancer lines in vitro. Results: The addition of a pyrimidinyl residue to an artemisinin or, preferably, a tetraoxane peroxidic structure results in antitubercular activity in vitro. The same effect is not observed in the absence of the pyrimidine or with other heteroaromatic substituents. Conclusion: The incorporation of a pyrimidinyl residue adjacent to the peroxidic function in an organic peroxide results in anti-tubercular activity in an otherwise inactive peroxidic compound. This will be a useful approach for creating oxidative drugs to target tuberculosis.