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Novel synthetic scaffold for anti tuberculosis drugs

Keywords

Tuberculosis, Natural product, *Mycobacterium tuberculosis*, Drug discovery, Pyridomycin, InhA

Summary

The invention enables the synthesis of a range of novel tuberculosis drugs. A versatile synthetic scaffold derived from the natural product pyridomycin is the basis for novel drugs in the treatment of tuberculosis.

Background

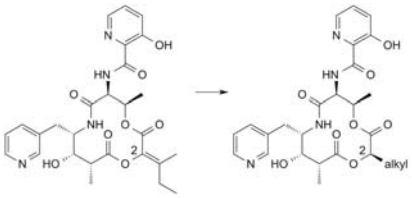
Tuberculosis is a frequently fatal disease that causes more than 1.4 million deaths annually. Due to co-morbidity with AIDS and the emergence of multi drug-resistant and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) there is an urgent need for new anti tuberculosis drugs. In particular, current combination therapy is insufficient to eliminate XDR *M. tuberculosis*.
Pyridomycin is a bacterial natural product that exhibits significant *in vitro* anti tubercular activity and low systemic toxicity in mice. The compound inhibits the enzyme InhA (the target of the clinically used anti tuberculosis drug isoniazid) in a novel manner and shows no cross-resistance with known anti InhA drugs. The structure of pyridomycin includes a complex chemical entity (an enol ester moiety) which impedes easy synthetic access to pharmaceutically improved structures of the natural product.

Patent Status

- Patent pending

Invention

A solution to the synthetic accessibility problem is the modification of the enol ester part of natural product pyridomycin by saturation of the bond extruding from the macrocycle C2. The novel scaffold (Fig. 1) retains most of the anti *M. tuberculosis* activity of the natural product and enables synthetic access to a range of additional chemical modifications. Thereby, the lead structure can be optimized with regard to its anti *M. tuberculosis* activity and pharmacokinetic profile.



Pyridomycin Novel Scaffold

Figure 1: Pyridomycin (left) and the novel scaffold (right) with an alkyl residue in the lower right part of the molecule. The heterocycle at the top can be attached in the last step of the synthesis process and can therefore be replaced by other moieties in a straightforward manner.

Features & Benefits

- Enables a greater variety of structures for anti tuberculosis compounds
- Novel chemical entities with a minimal IC against *M. tuberculosis* of 0.7 to 1.5 µg/mL
- Compounds act on clinically validated drug target (InhA) and show no cross-resistance with existing drugs
- Compared to the natural product lead, reduced chemical complexity but conserved anti *M. tuberculosis* activity
- Straightforward synthesis process

Field of Application

- Treatment of *M. tuberculosis* infections
- Mycobacterial drug discovery

References & Institute

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