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Identification and further development of thiazolidinones spiro-fused to indolin-2-ones as potent and selective inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase B

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ABSTRACT

Tuberculosis continues to be a major cause of morbidity and mortality throughout the world. Protein tyrosine phosphatases from *Mycobacterium tuberculosis* are attractive targets for developing novel strategies in battling tuberculosis due to their role in the intracellular survival of *M. tuberculosis* in various infection models. Here, we report on the identification and further development of thiazolidinones spiro-fused to indolin-2-ones as a new class of potent and selective inhibitors of *M. tuberculosis* protein tyrosine phosphatase B. Detailed structure–activity relationship (SAR) studies revealed that a nitro-substituted 2-oxoindole core together with a dihalogenated anilide and a halogenated *N*-benzyl moiety are essential for strong inhibitory activity against MptpB (*M. tuberculosis* protein tyrosine phosphatase B). Small structural modification of the identified compounds led to significant improvement of compound solubility and cell permeability retaining inhibitory activity in the micromolar range. The configuration of the spiro-center was found to be crucial for the inhibitory activity and the separation of the racemate revealed the *R*-(−)-enantiomers as the biologically active component. The reported MptpB inhibitors show excellent selectivity against a selected panel of protein tyrosine phosphatases, including MptpA (*M. tuberculosis* protein tyrosine phosphatase A), PTP1B (protein tyrosine phosphatase 1B), SHP-2 (Src homology 2 domain-containing protein tyrosine phosphatase), PTPN2, h-PTPβ (human protein tyrosine phosphatase β), and VHR (*Vaccinia virus* VH1-related dual-specific protein phosphatase) and further highlight the identified thiazolidinones spiro-fused to indolin-2-ones as a promising class of new compounds that might prove useful for chemical biology research to dissect MptpB function and eventually foster the development of next generation antibiotics.

1. Introduction

Tuberculosis (TB) continues to be a major cause of morbidity and mortality throughout the world. According to the World Health Organization, one-third of the world's population is infected with *Mycobacterium tuberculosis* and about 35 million people are expected to die from TB in the first 20 years of this century.[1] Because of the increasing occurrence of drug-resistant mycobacteria and the need of the extended use of current drugs, new targets and drugs for therapeutic interventions are in high demand. *M. tuberculosis* protein tyrosine phosphatase A (MptpA) and MptpB are two enzymes secreted by growing mycobacteria and believed to mediate *M. tuberculosis* survival in macrophages by dephosphorylation of host proteins that are involved in the interferon signaling, which represents a crucial pathway of the immune system.[2] The genetic knock-out of MptpB suppresses growth of *M. tuberculosis* in activated macrophages and guinea pigs and suggests that MptpA/B could qualify as potential drug targets in the treatment of TB.[3] The importance of MptpB to the intracellular survival of *M. tuberculosis* was recently confirmed by two independent studies in which specific inhibitors directed against MptpB were shown to impair mycobacterial survival in murine macrophages.[4] Since MptpB has no direct human orthologues, inhibitors active against MptpB might not only prove useful as probe molecules in chemical biology research to dissect the functional role of phosphatases in cell invasion, but also offer unique opportunities for the development of new antitubercular drugs.

Compounds with anti MptpA and MptpB activity have been successfully identified and characterized in vitro.[5] In particular, the

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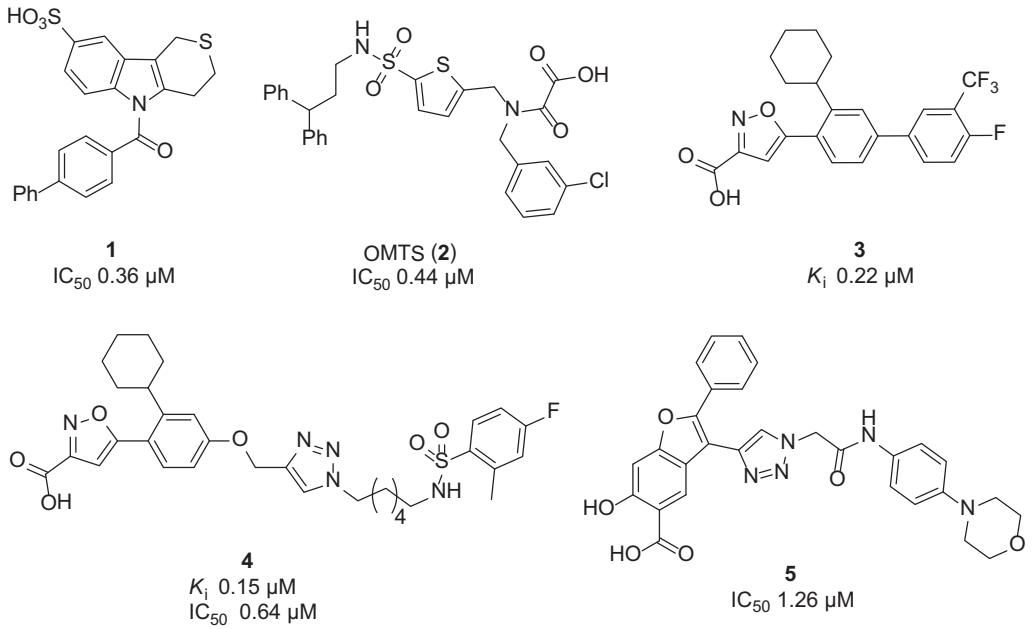

Fig. 1. Structures of selected MptpB inhibitors, IC_{50} or K_i values are given.

application of biology-oriented synthesis (BIOS) approaches resulted in the identification of indole derivative **1** (Fig. 1), as potent and specific inhibitor of MptpB.[6] Recently Alber et al. reported the development of a potent and selective (oxalylamino-methylene)-thiophene sulfonamide inhibitor for MptpB (**2**) (OMTS).[7] Compound **2** shows an IC_{50} value of 440±50 nM and >60-fold selectivity for MptpB over six human PTPs. Application of a substrate-based fragment approach resulted in the discovery of the isoxazole **3**, which is one of the most potent MptpB inhibitors known from literature to date (K_i of 220 nM).[8] Using the structure of isoxazole **3** as a starting point, Yao et al. recently synthesized and screened a click chemistry-based library of MptpB inhibitors and identified **4** as the most active representative with a K_i value of 0.15 μM for MptpB but only moderate selectivity when screened against PTP1B, TCPTP (T-cell protein tyrosine phosphatase), Yop-H (*Yersinia* protein tyrosine phosphatase), and LMW-PTP (low molecular weight protein tyrosine phosphatase).[9] Recently Zhou et al. identified a potent and selective MptpB inhibitor **5** with significant cellular activity, from a combinatorial library of bidentate benzofuran salicylic acid derivatives assembled by click chemistry.[4b]

Remarkably, the aforementioned inhibitors all contain highly polar acidic groups that are highly ionized at physiologic pH and can be expected to display exceedingly poor cell permeability and low oral bioavailability. Indeed, compound **4** is not cell permeable or its cell permeability cannot be determined.[9] After all, the discovery of potent cell permeable and orally bioavailable MptpB inhibitors is a challenging task of medicinal chemistry research. New inhibitor classes with good selectivity profiles and improved pharmacological properties are therefore in high demand.

Recently we communicated on the identification of the indolin-2-on-3-spirothiazolidinones as a novel class of potent and selective inhibitors of MptpB.[10] In the present study we present detailed systematic structure–activity relationship (SAR) studies, investigations of the inhibition profiles, and biochemical evaluation toward the mode of action of the early discovered compounds as well as molecular docking study.

2. Results and discussion

Using enzyme activity assays we screened a library of 40,000 compounds to discover inhibitors of MptpB.[6a] In a 384-well HTS format we used *p*-nitrophenyl phosphate (*p*-NPP) as the substrate and identified **6**–**9** as a series of compounds that perturbed substrate hydrolysis by MptpB in the mid-micromolar range (Fig. 2).

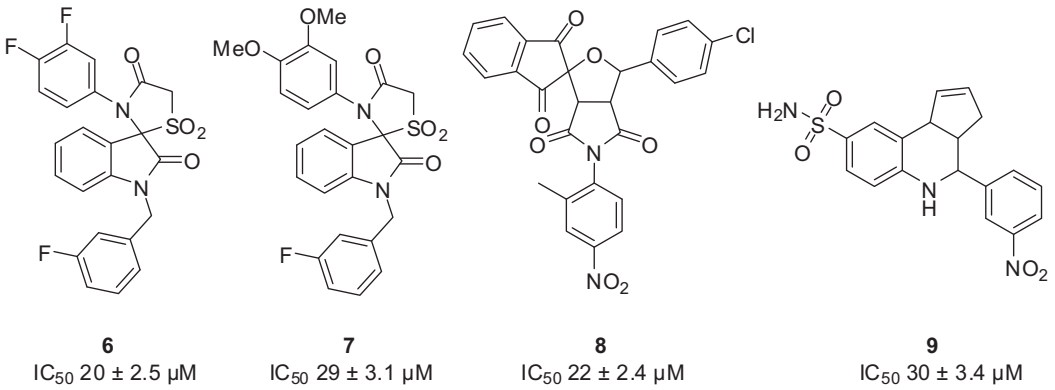

Fig. 2. Structures and IC_{50} values of primary hits derived from HTS against MptpB.