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Antimycobacterial activity of chiral aminoalcohols with camphane scaffold

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ABSTRACT

A series of aminoalcohols were synthesized by reaction of aminolysis of camphor derived oxiranes with chosen amines. The compounds were evaluated for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv. Ten of the new structures show much higher activity than the classical anti-TB drug ethambutol. Some of the most active compounds were tested against MDR strain 43, and four of them demonstrated excellent activities with MICs 0.27–0.72 μM. The cytotoxicity of representative exerting antimycobacterial activity compounds was assessed. Quantitative structure–activity relationship (QSAR) model is derived to estimate the contribution of each structural fragment to the activity. The camphane-based aminoalcohols are promising lead compounds for further development of novel antimycobacterial agents.

1. Introduction

Mycobacterium tuberculosis (MTB) infects latently one-third of the world's population causing approximately 9 million cases of active disease each year [1]. The WHO-recommended anti-TB therapy involves four drugs: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), but the emergence of multi drug-resistant bacteria (MDR TB) against which the first-line drugs have become ineffective, requires treatment for up to two years with more toxic, less active and more expensive drugs. The latter usually involve any first-line drugs to which the strain is still susceptible and alternative or second-line drugs [2]. The long current drug regimen, the emergence of drug resistant strains and HIV co-infection necessitate the urgent development of new and effective anti-TB drugs.

The synthesis and activity of EMB (Fig. 1. **I**) was first reported by Wilkinson and coworkers [3]. Despite the relatively modest MIC of 10 μM, EMB is a useful addition to tuberculosis chemotherapy, in part because of its very low toxicity and relatively few side-effects. Based on structure–activity relationship (SAR) studies it appeared that crucial for its activity is the distance between the two nitrogens, the presence of β-aminoalcohol motifs, and the small side chains [4]. Lately, the occurrence of a 'better ethambutol' has been systematically investigated through virtual screening or a combinatorial approach [5,6]. Several 1,2-diamines, such as SQ 109 (Fig. 1. **II**), displaying improved antimycobacterial potencies and promising pharmacokinetic properties have thus been reported [7]. It is very likely that the highly lipophilic adamantane structure was integral for the antitubercular activity.

Camphor and its derivatives are of particular importance among the numerous monoterpenoids. Camphor is a readily available and inexpensive chiral source for the synthesis of a variety of structurally diverse compounds [8,9]. Inspired by the β-aminoalcohol fragment in the molecule of EMB and the analogy of the camphane scaffold as a compact lipophilic moiety to the adamantyl fragment in SQ 109, we dedicated our efforts towards the development of camphor derived structures. Recently, we have accomplished a practical synthesis of new β-amido-alcohols and amido-diols on the base of 3-*exo*-aminoisoborneol (Fig. 1. **III**) and isobornylamine (Fig. 1. **IV**) [10,11]. Some of the compounds show 25 times higher antimycobacterial activity than EMB.

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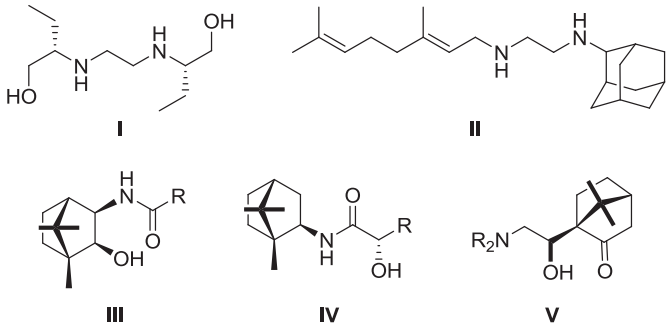


Fig. 1. Structures of ethambutol (**I**), SQ 109 (**II**), 3-*exo*-aminoisoborneol based amido-alcohols (**III**), isobornylamine based amido-alcohols (**IV**), camphor derived amino-alcohols (**V**).

Encouraged by these observations, we expanded the approach to the synthesis of aminoalcohols possessing a camphane skeleton (Fig. 1. **V**). Here, we report the synthesis, antimycobacterial activity and cytotoxicity of 21 compounds and derive a QSAR model to estimate the contribution of each structural fragment to the activity. Thus, we continue the exploration of camphane based structures as a novel class of anti-TB compounds.

2. Results and discussion

2.1. Chemistry

Commercially available 10-camphorsulfonyl chloride **1** was selected as the key (+)-camphor-derived starting compound. Its reaction with diazomethane and triethylamine followed by elimination of sulphur dioxide afforded 7,7-dimethyl-1-vinyl-norbornan-2-on in 77% yield [12]. Subsequent epoxidation using 3-chloroperbenzoic acid led to diastereoisomeric mixtures of oxiranes **2a** and **2b** (Scheme 1) [13].

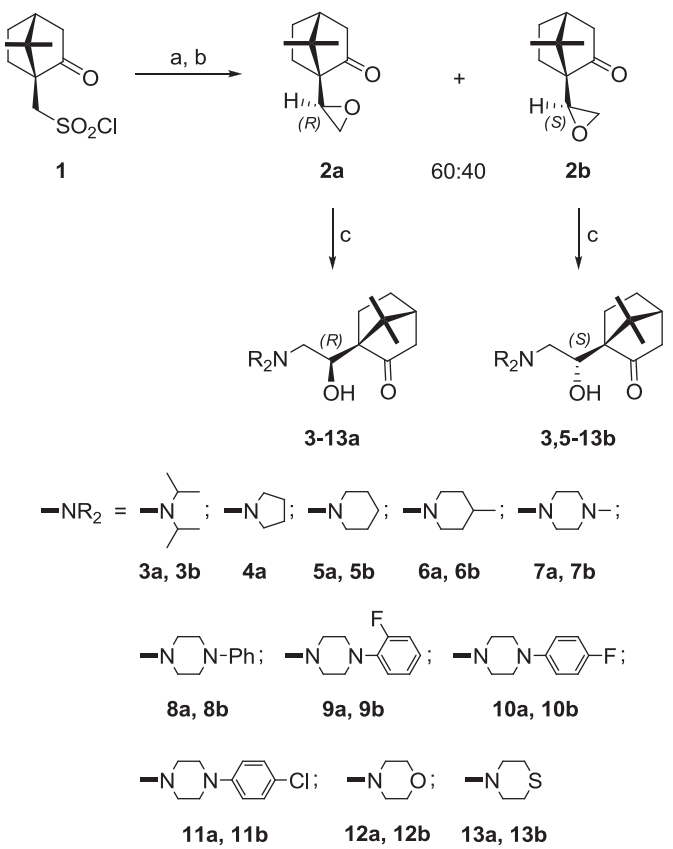
Both oxiranes **2a** and **2b** were isolated as pure diastereoisomers, after chromatographic separation, in 52% and 33% yield respectively [13]. In our previous work we determined the configuration of the newly formed stereogenic centre by advanced NMR experiments and X-ray crystallography [13]. The two products **2a** and **2b** were then converted into aminoalcohols by aminolysis with excess of secondary amines at 50 °C in acetonitrile in the presence of $LiClO_4$ (Scheme 1). The synthesis of compounds **3a,b**–**6a,b** was reported in our previous work considering their use as chiral ligands for asymmetric Zn-mediated catalysis [13]. The initial antimycobacterial activity testing of these compounds directed us towards the creation of a small library of camphane based aminoalcohols and evaluation of their biological properties. The aminolytic cleavage of the oxirane ring with various amines containing groups with pharmacophore properties afforded 14 new compounds **7a,b**–**13a,b**. Consequently, 21 compounds were synthesised and tested for the antimycobacterial activity reported herein.

The aminoalcohols were obtained in very good to excellent yields as summarized in Table 1. All compounds were characterized by NMR spectroscopy, MS data, $[\alpha]_D^{20}$ and elemental analysis.

2.2. Antimycobacterial activity

All synthesized camphane-based aminoalcohols were evaluated for their *in vitro* activity against *M. tuberculosis* H37Rv using the method of Canetti (Table 2). Ten of these compounds have shown excellent activity, between 10 and 27 times higher than that of EMB, used as reference (Table 2). The most active compounds possess diisopropyl, piperidine, methylpiperidine, morpholine and fluoro or chloro substituted N-phenylpiperazine moieties. As evident from the calculated log *P* values, most of the compounds are lipophilic and thus have low water solubility (Table 2). However, the compounds possess amino groups, which allow their transformation into corresponding water soluble ammonium salts. The combination of these two features conditions good cell permeability and facilitates preparation of pharmaceutical forms for various applications.

The diisopropylamine and piperidine derived aminoalcohols with *R*-configuration (**3a** and **5a**) exhibited high activity against *M. tuberculosis* H37Rv with MICs of 0.37 and 0.38 μM. The isomers with *S*-configuration **3b** and **5b** gave low activity. Interestingly, both isomers derived from 4-methyl-piperidine **6a,b** demonstrated excellent activity with MIC values of 0.36 and 0.72 μM, respectively. On the other hand, introducing of N-Me-piperazine **7a,b** and N-phenyl-piperazine **8a,b** fragments in the structure of the aminoalcohols resulted in activity lower than that of EMB. Various substituted piperazines (N-*o*-F-phenyl **9a,b**, N-*p*-F-phenyl **10a,b**, N-*p*-Cl-phenyl **11a,b**) were also used as pharmacophores in combination with camphane moiety. The *o*-F-phenyl- and *p*-F-phenyl-piperazine derivatives **9a**,**b**, and **10a**,**b** exhibited extremely high activity for both isomers: MICs of 0.28 μM. In the case of *p*-Cl-phenyl-piperazine, the more active isomer was the one with *S*-configuration **11b**, MIC 0.27 μM. The *R*-isomer **11a** displayed potency comparable to EMB. The morpholine derived aminoalcohol with *R*-configuration **12a** showed excellent MIC of 0.37 μM, while the *S*-isomer **12b** had low activity. The thiomorpholine derivatives **13a,b** were not active.



Scheme 1. Synthesis of aminoalcohols **3a** and **3b**: (a) Et_3N, CH_2N_2, 95 °C, 77%; (b) MCPBA, CH_2Cl_2, 53% **2a** and 32% **2b;** (c) HNR_2, $LiClO_4$, up to 99%.