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Design of novel camphane-based derivatives with antimycobacterial activity

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ABSTRACT

Although tuberculosis (TB) continues to be one of the leading infectious disease killers globally, it is curable and preventable. Despite the existence of safe, well tolerated and effective drugs used in the TB treatment, the interest in new entities, combinations and regimens increases during the last 10 years. Recently, we reported for a new class of anti-TB agents – camphane-based derivatives with nanomolar activity against *Mycobacterium tuberculosis* strains. The quantitative structure–activity relationship (QSAR) study on 12 compounds revealed several structural requirements for antimycobacterial activity: two hydrogen bond donors, two or three rings and no large branched substituents. Here, we describe the design of a set of nine novel camphane-based derivatives following these requirements. The compounds were synthesized and tested against *M. tuberculosis* strain H37Rv. Four of them showed activities in the nanomolar range, significantly higher than the activities in the initial set. The QSAR study based on all 21 derivatives pointed to two main structural requirements for anti-TB activity: two hydrogen bond donors and a side chain with aromatic ring.

1. Introduction

Tuberculosis (TB) remains a leading infectious disease killer globally. In Africa, TB is the biggest killer of people with HIV/AIDS [1]. One third of the world's population is thought to have been infected with *Mycobacterium tuberculosis* [2] but about 90% of them have asymptomatic, latent TB infections. TB is curable and preventable. Bacille Calmette Guerin (BCG) is the only vaccine available today for protection against tuberculosis [3]. It is most effective in protecting children from the disease. Many strains of tuberculosis resist the drugs mostly used to treat the disease. People with active tuberculosis must take several types of medications for many months to eradicate the infection and to prevent the development of antibiotic resistance [4].

After 40 years of neglect, encouraging advances have been made in TB drug research and development during the last 10 years, resulting in nine compounds currently under clinical development and more than 20 new chemical entities in preclinical research [5]. New drugs and drug combinations are needed that have strong, bactericidal activity against various strains of *M. tuberculosis*.

When the target is known, structure-based methods as docking, molecular dynamics simulations, virtual screening, de novo design, are effective in lead identification and lead optimization [6]. When the initial information comes from a whole-cell experiment, ligand-based methods as pharmacophore search, 2D and 3D QSAR studies, fingerprints and similarity search, are helpful in the design of new ligands [6]. The advances in the chase of new anti-TB drugs have been recently reviewed [7]. The ligand-based methods are involved actively [8–18] but the structure-based methods targeting specific *M. tuberculosis* enzymes also take place [19–22].

Recently, we synthesized a series of novel camphane-based derivatives and tested them against two *M. tuberculosis* strains: strain H37Rv and multi-drug resistant strain 43 [23]. All of them were active against strain H37Rv with *MIC* values in the micro- and nanomolar range. Three derivatives showed also activity against MDR strain 43 with *MIC* values in the micromolar range. A detailed QSAR study was conducted and the following 2D-QSAR model was derived:

$$pMIC = 0.592knotp - 0.445SHHBd - 0.683nrings + 12.992,$$

$$n = 12, \quad r^2 = 0.875, \quad SEE = 0.290, \quad F = 18.58, \quad q^2 = 0.675$$

The structures of the compounds, their experimental *MIC* and *pMIC* ($-\log MIC$) are given in Table 1. In Table 1 also are given the values of the descriptors presented in the model and the calculated *pMIC* and *MIC*. The descriptor *knotp* relates to intermolecular accessibility [24]. Negative *knotp* values correspond to large molecules

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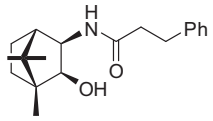
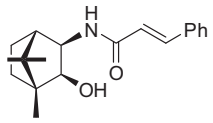
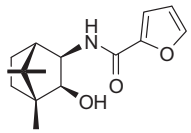
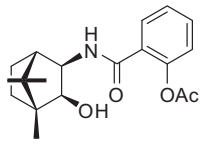
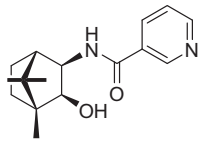
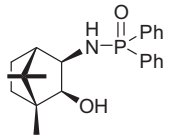
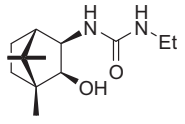
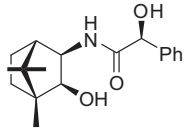
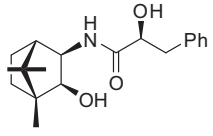
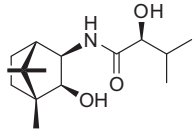
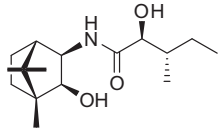
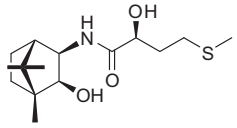
Table 1
Structure, experimental *MIC*s, molecular descriptors and calculated *MIC*s of the training set.

Cmpd.[a]	Structure	*MIC(exp)* (μM)	*pMIC(exp)*	*knotp*	*SHHBd*	*nrings*	*pMIC(calc)*	Residual
1 (**3a**)		0.33	6.481	−4.109	4.327	3	6.584	−0.103
2 (**3b**)		0.33	6.481	−4.109	4.382	3	6.559	−0.078
3 (**3c**)		0.38	6.420	−4.385	4.432	3	6.373	0.047
4 (**3d**)		0.30	6.523	−4.475	4.523	3	6.280	0.243
5 (**3e**)		0.36	6.444	−4.385	4.416	3	6.381	0.063
6 (**4**)		13.55	4.868	−5.506	4.553	4	4.941	−0.073
7 (**5**)		0.41	6.387	−3.880	6.026	2	6.646	−0.259
8 (**9a**)		16.50	4.783	−4.810	7.105	3	4.932	−0.149
9 (**9b**)		6.30	5.201	−4.606	7.049	3	5.078	0.124
10 (**9c**)		0.74	6.131	−4.784	6.899	2	5.722	0.409
11 (**9d**)		7.06	5.151	−4.907	6.915	2	5.643	−0.492
12 (**9e**)		0.66	6.180	−4.434	6.939	2	5.912	0.268

[a] The compounds ID according to Ref. [23] are given in parenthesis.