ABSTRACT

Tuberculosis (TB) is a deep public health concern worldwide worsened by reported multi drug-resistant (MDR) and extensively drug- resistant (XDR) strains of Mycobacterium tuberculosis, the causative agent of the disease. A new class of thiadiazole inhibitors were reported to inhibit the enoyl-acyl transporter protein reductase (InhA) of Mycobacterium tuberculosis (MTb). We performed here the computer-aided molecular design of novel thiadiazole (TDZ) inhibitors of InhA by in situ modifying the reference crystal structure of (S)-1-(5-((1-(2,6-difluorobenzyl)-1H-pyrazol-3-yl)amino)-1,3,4-thiadiazol-2-yl)-1-(4methylthiazol-2-yl)ethanol-InhA (PDB code: 4BQP). Thus a training set of 15 hybrids with known inhibition potency (IC_{50}^{exp}) was selected to establish a one-descriptor quantitative structure-activity relationship (QSAR) model resulting in a linear correlation between the Gibbs free energy (GFE) during the formation of the InhA-TDZ complex and IC_{50}^{exp})

($pIC_{50}^{exp} = -0{,}29x\Delta\Delta G_{com} + 8{,}13$; n=15; $R^2 = 0.92$; $R_{xv}^2 = 0.91$; F-test of 142.6;

$\sigma = 0.21$; $\alpha > 95\%$; $R^2 - R_{xv}^2 = 0.01$). The 3D pharmacophore model (PH4) generated from the active conformations of TDZs ($pIC_{50}^{exp} = 0.93 \times pIC_{50}^{pred} + 0{,}47$; $n = 15$; $R^2 = 0.97$; $R_{xv}^2 = 0.94$; F-test of 215.45; $\sigma = 0.17$; $\alpha > 98\ \%$;

$R^2 - R_{xv}^2 = 0.03$) served as a virtual screening tool for new analogs from a virtual library (VL). The combination of molecular modeling and PH4 in silico screening of VL resulted in the identification of novel potent antitubercular agent candidates with favorable pharmacokinetic profiles of which the six best hits predicted inhibitory potencies IC_{50}^{pred} in the sub nanomolar range $(0.1 - 0.2)\ nM$.

Keywords: Tuberculosis; enoyl-acyl carrier protein reductase (InhA); molecular modeling; QSAR models; pharmacophore; combinatorial library; ADME properties prediction.