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N-Benzyl-4-((heteroaryl)methyl)benzamides :A New Class of Direct NADH- Dependent 2-trans Enoyl-Acyl Carrier Protein Reductase(InhA) Inhibitors with Antitubercular Activity

Wednesday, 30 January 2019 17:40 (20 minutes)

We have carried out a computational structure-based design of new potent N-Benzyl-4-((heteroaryl)methyl)benzamides(BHMB) inhibitors of enoyl-acyl carrier protein

reductase (InhA) of Mycobacterium tuberculosis (MTb). Three-dimensional (3D) models of InhA-BHMBx complexes were prepared by in situ modification of the crystal structure of InhA-BHMB1 (Protein Data Bank (PDB) entry code: 4QXM), the reference compound of a training set of 19 BHMBs with known experimental inhibitory potencies (IC50

exp). First, we
built a gas phase quantitative structure-activity relationships (QSAR) model, linearly correlating the computed enthalpy of the InhA-BHMB complex formation and the IC50
exp
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Further, taking into account the solvent effect and loss of inhibitor entropy upon enzyme binding led to a QSAR model with a superior linear correlation between computed Gibbs free energies (ΔΔGcom) of InhA-BHMB complex formation and IC50
exp (pIC50
exp = -0.237ΔΔGcom +

7.8783, R
2 = 0.97), which was further validated with a 3D-QSAR pharmacophore model generation (PH4).

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