



Category: Bioinformatics

# Computational attempts for synthesis of potent antibacterial sulfamethoxazole-monocyclic terpenes conjugates

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## Abstract

To develop 6 conjugate agents of the moribund antibiotic sulfamethoxazole (SMZ) joined to 6 individual monoterpenes, followed by protocols of medicinal chemistry as potent antibacterials, against multidrug resistant (MDR) human gruesome pathogenic bacteria. Antibacterial activities of the proposed conjugates were ascertained by the 'prediction of activity spectra of substances' (PASS) program. Drug-likeness parameters and toxicity profiles of conjugates were standardized with the Lipinski rule of five, using cheminformatic tools, Molsoft, molinspiration, OSIRIS and ProTox. Antibacterial activities of individual chemicals and conjugates were examined by targeting the bacterial folic acid biosynthesis enzyme, dihydropteroate synthases (DHPSs) of bacteria, *Bacillus anthracis*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*, with 3D structures of DHPSs from protein data bank. According to the PASS program, biological spectral values of conjugate-2, conjugate-5 and conjugate-6 were ascertained effective with 'probably active' or 'Pa' value > 0.5, for anti-infective and anti-tuberculosic activities. Using molecular docking against 5 cited bacterial DHPSs, effective docking scores of 6 monoterpenes in the specified decreasing order (kcal/mol): -9.72 (eugenol against *B. anthracis*), -9.61 (eugenol against *S. pneumoniae*), -9.42 (safrol, against *B. anthracis*), -9.39 (thymol, against *M. tuberculosis*), -9.34 (myristicin, against *S. pneumoniae*) and -9.29 (thymol, against *B. anthracis*); whereas the lowest docking score of SMZ was -8.46 kcal/mol against *S. aureus* DHPS. Similarly, effective docking scores of conjugates were as specified (kcal/mol.): -10.80 (conjugate-4 consisting SMZ + safrol, against *M. tuberculosis*), -10.78 (conjugate-5 consisting SMZ + thymol, against *M. tuberculosis*), -10.60 (conjugate-5 against *B. anthracis*), -10.26 (conjugate-2 consisting SMZ + eugenol, against *M. tuberculosis*), -10.25 (conjugate-5, against *S. aureus*) and -10.19 (conjugate-2 against *S. pneumoniae*). Conjugates-2 and -5 were the most effective antibacterials based on Lipinski rule of five with lethal doses 3471 and 3500 mg/kg, respectively and toxicity class levels. Conjugate-2 and conjugate-5 were more effective than individual monoterpenes and SMZ, against pathogenic bacteria. Synthesis, characterization and *in vitro* antibacterial study with acute toxicity testing for Wister rat model of the conjugate-5 could land at success in the recorded computational trial and it could be promoted for synthesis in the control of MDR bacteria.

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