MOLECULAR DOCKING STUDY OF FDA-APPROVED DRUGS TO INHIBIT THE BACTERIAL RIBOSOME

Beril Ates, Merve Yuce, Ozge Kurkcuoglu Levitas, and Fethiye Aylin Sungur

Department of Chemical Engineering, Istanbul Technical University, 34469, Istanbul, Turkey; Computational Science and Engineering Division, Informatics Institute, Istanbul Technical University, 34469, Istanbul, Turkey
Email: atesb18@itu.edu.tr

Abstract

Ribosomes are large macromolecular complexes responsible for cellular protein synthesis. It consists of two subunits; called 30S small and 50S large subunits in bacteria, involving antibiotic binding regions. This macromolecular machine is one of the significant targets of conventional antibiotics because protein synthesis can be stopped by targeting functional sites in the ribosome. For instance, several antibiotics target the decoding center responsible for deciphering the genetic code, as well as mRNA corridor on the 30S subunit. However, antibiotic resistance is a growing threat, and new molecules are urgently needed to be developed. This computational work aims to find new potential inhibitors of *E. coli* ribosome from FDA-approved drug library. First, 30S subunit used as the target is obtained from the crystal structure of *E. coli* 70S ribosome (PDB ID: 4v64). 30S small subunit is prepared in Protein Preparation Wizard, ligands are prepared in LigPrep module of Maestro. Standard (SP) and extra precision (XP) docking scoring protocols are performed in Glide and binding free energies of hit compounds are calculated using Prime MM/GBSA module. SP and XP docking scores of the ligand bound to the crystal structure are determined and then used as reference values to select the hit compounds. According to the results, several antibiotics such as framycetin and amikacin that already target 30S have the highest binding free energy scores, verifying our approach. Antibiotics, hormone agonists, antidiuretic hormones, and drugs used for the treatment of tumors and obesity are determined as promising against bacterial ribosomes. Generally, hit compounds make hydrogen bonds with nucleotides C1403, C1404, G1491, A1492, A1493, G1494, U1495 and G1497 next to the decoding center. In the light of these results, proposed hit molecules and their interactions can be also useful for pharmacophore design and guide further experimental studies.

Keywords: ribosome, molecular docking, pharmacophore