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MOLECULAR MODELING OF NUCLEOTIDE DERIVATIVES OF 2,5-DIHYDROFURAN-2,5-DIOL FOR EVALUATION OF POTENTIAL ANTITUBERCULAR ACTIVITY

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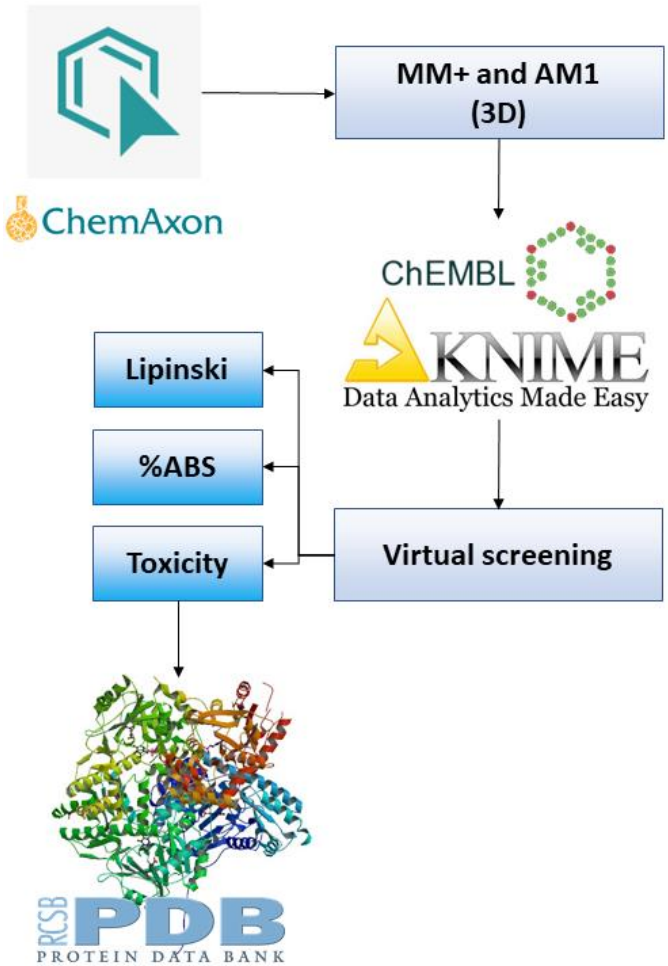
Graphical Abstract



Abstract.

Tuberculosis is a disease caused by bacterial infection, which mainly compromises the respiratory system leading to death if left untreated. Currently the treatment is efficient, although bacterial resistance has been hindering and even prevented the progress of treatment for many patients. The transmission medium should be in several areas or direct contact with contaminated body fluids. Many therapeutic targets are addressed in research involving rational planning of new drugs with antitubercular activity, always in search of more efficient bioactive and with increasingly reduced toxicity. Thus, this work consists of an in silico proposition through the molecular modeling of nucleotide compounds against tuberculosis. For the development of this research were used chemoinformatics tools for structural design, optimization, virtual screening taking into account Lipinski rule, absorption rate and cytotoxicity risks. Finally, a molecular docking study was conducted to know the existing ligand-receptor interactions and to compare them with those of the drugs used as controls for this research. Finally, it is possible to perceive the existence of promising molecules for the antitubercular activity of synthetic nucleosides.

Introduction

The bacteria *Mycobacterium tuberculosis* is responsible for the pathology known as tuberculosis, which is one of the top 10 causes of death in the world, according to the World Health Organization (WHO) in 2017 about 10 million people contracted the disease, of which 1.6 million died last year. The bacterial infection in its primary form compromises the lungs, however, it is possible to reach the brain, bones, heart, kidneys and other organ of the human body. The form of transmission is mainly through the air, where infected people cough, sneeze or spit spreading the bacteria, leaving it available to contaminate new individuals. [1,2,3,4]

Tuberculosis is treatable with the aid of antibiotics and avoided from childhood with the aid of the vaccine BCG (Bacillus Calmette-Guérin), however, studies show that 82% of tuberculosis cases the bacterium develops resistance to first-line drugs such as rifampicin, due to this problem, research in the field of pharmaceutical sciences is necessary to make new bioactive available to treat the disease. Some authors have developed studies on the use of nucleoside / nucleotide analogues as antitubercular bioactive and have shown good results that have made this class of synthetic compounds promising drug candidates in the fight against *M. tuberculosis*. [5,6,7]

Knowing the potential activity against tuberculosis of nucleotides, the objective of this study is the molecular modeling with the use of several computational tools for the theoretical proposition of some derivatives of 2,5-dihidroxyfuran-2,5-diol with adenine against tuberculosis-causing bacteria. For the initial part of this research, a model of activity prediction was developed in the KNIME, thus, nucleotides that were active against the model were subjected to a virtual screening and molecular docking, as well as the drugs used as controls: pyrazinamide, ethambutol, rifabutin, amikacin, levofloxacin, ethionamide and protionamide.

Materials and Methods

The nucleotide molecules together with the drugs used as controls were designed using the software Marvin Sketch 18.21 [8,9] of ChemAxon© to obtain their 2D structures, then they were imported into the software HyperChemTM (RMS 0.1 kcal.mol^{-1}.Å^{-1} in 600 cycles) [10,11] to obtain their structures in 3D and, optimization through the methods of molecular and semi-empirical mechanics. [12,13,14]

These molecules were submitted to a classificatory model of prediction of activity developed in the KNIME Analytics Platform 3.7 [15,16] (https://doi.org/10.6084/m9.figshare.7445666.v2) in which it was used for its creation the molecules of the database of chemical structures ChEMBL (https://www.ebi.ac.uk/chembl) [17,18], as well as the descriptors generated in the software CDK Descriptor Calculator 1.4.8 (http://www.rguha.net/code/java/cdkdesc.html). [19,20]

The molecules approved in the prediction model were subjected to a continuous virtual screening of the series of compounds studied, thus, the molecules were imported into the software OSIRIS DataWarrior 4.7.3 (http://www.openmolecules.org) [21,21] to analyze cytotoxicity risks in four parameters (mutagenicity, carcinogenicity, irritability in the skin and effect on the reproductive system), considering only the molecules that presented no risk in any of the presented parameters.

Following the virtual screening of the non-toxic molecules, Lipinski's rule and absorption rate (%ABS = 109-0.345*TPSA) [22,23], being considered the derivatives that presented oral absorption rate greater than the lowest rate among the controls used and at most a violation of the Lipinski rule.

Finally, the molecules approved in the virtual screening were submitted to molecular docking with the software Molegro Virtual Docker 6.0 (MVD) [24,25] using the crystalline proteins of *Mycobacterium tuberculosis* PDB ID 5VRN corresponding to InhA with 2.55Å of resolution, and protein PDB ID 5YHV corresponding aminotransferase with 2,7Å, both with the respective inhibitors complexed together with the protein.

Results and Discussion

25 nucleotide analogs were submitted to the model of prediction of biological activity, all of which presented activity according to the model that presented ROC curve of 0.913, accuracy of 0.813 and Matthews coefficient equal to 0.627, with these statistical data it is possible to perceive that the model created showed good predictability of the molecules tested, it is worth noting that all the structures presented within the applicability domain of the model, guaranteeing the reliability of the results of the classifying model of antitubercular prediction.

According to the prediction of cytotoxicity risks performed for the 25 molecules that present activity against the model, none presented risks in any of the four parameters analyzed by OSIRIS. Considering Lipinski's rule as a virtual screening parameter, the molecules, seven molecules analyzed had two violations, so, with the others, the oral absorption rate (% ABS) was calculated, all of which presented a higher rate than the lowest rate among the controls (amikacin - %ABS = -5.52).

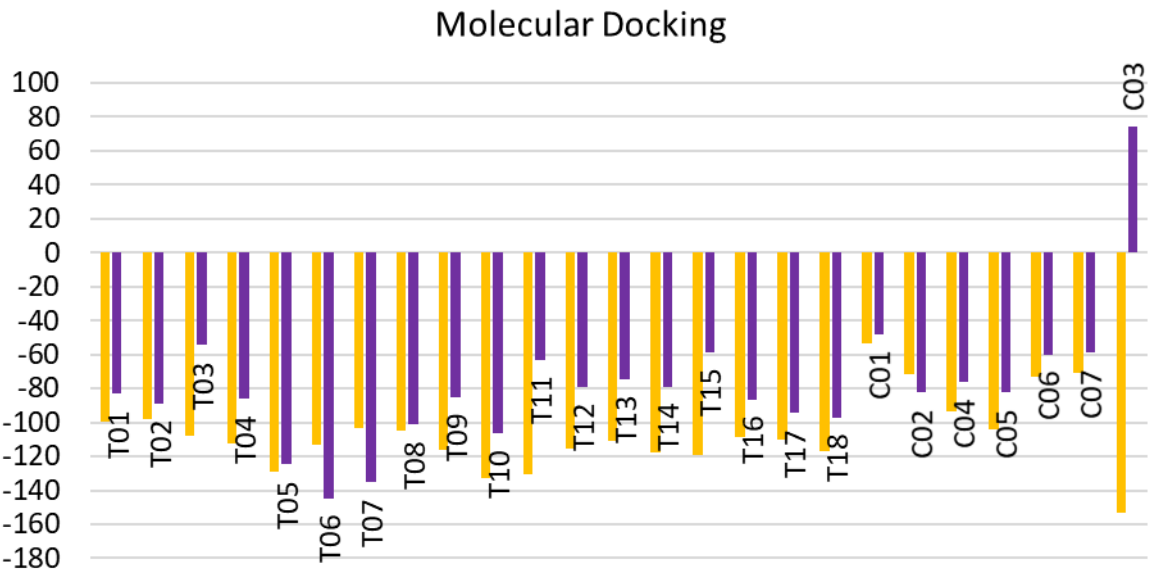


Figure 1. Molecular docking energies [kcal.mol^{-1}]. Orange column corresponds to protein PDB ID 5VRN and purple column corresponds to protein PDB ID 5YHV.

With the results already reported, the 18 compounds used were subjected to molecular docking with the proteins of M. tuberculosis together with the controls, for the PDB ID 5VRN protein the energies ranged from -53.2479 kcal.mol^{-1} to -153.401 kcal.mol^{-1}, to protein PDB ID 5YHV is 74.3982 kcal.mol^{-1} to -144.5640 kcal.mol^{-1}.

15 of the 18 derivatives presented better MolDockScore values than 6 of the 7 controls used, and the 18 compounds studied presented better molecular docking results than: C01, C02, C04, C06 and C07

for the 5VRN protein. For the 5YHV protein, 12 of the 18 derivatives had better energy than the 7 controls and all presented better results than the C01 and C03, as shown in Figure 1.

Conclusions

Other studies are needed to propose a prototype to the antitubercular drug, however, this research is important to draw attention to the possibility of new bioactive drugs with action against tuberculosis. As this study it is possible to notice that of the series used in this work, 18 compounds presented better results than the 25 initially considered, which the molecules can be seen in the supplementary material.

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