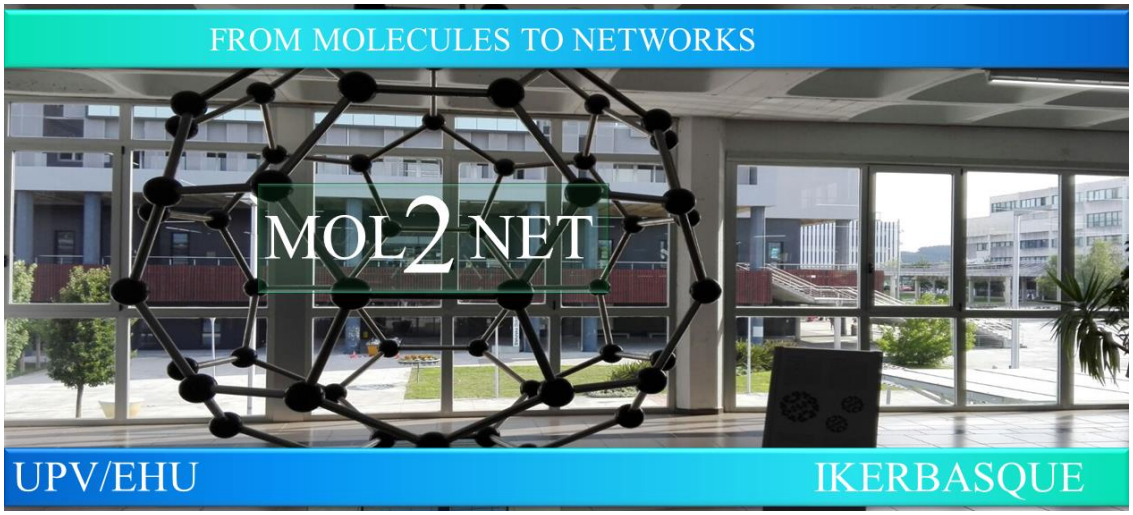
MOL2NET'21, Conference on Molecular, Biomedical & Computational Sciences and Engineering, 7th ed.

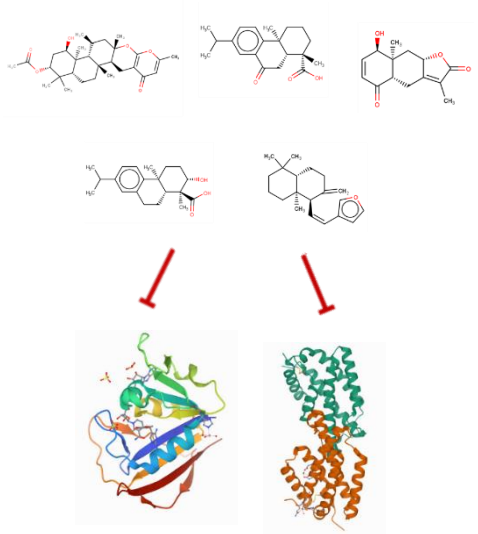


Molecular docking studies of terpenoids in *Mycobacterial tuberculosis* proteins

Emille Wannick Reinaldo da Silva [a], Teresa Carolliny Moreira Lustoza Rodrigues [a], Jéssica Paiva de Moura [a], Paulo Sérgio da Silva Pereira [a], Jeremias Justo Emídio [a], Igor Mikael Alves de Araújo [a], Alex France Messias Monteiro [a]

[a] Program of Natural and Synthetic Bioactive Products (PgPNSB), Health Sciences Center, Federal University of Paraíba, João Pessoa-PB, Brazil

Graphical Abstract



Abstract.

Since 2007, tuberculosis has been the leading cause of death from an infectious agent, ranking above HIV/AIDS. Thus, despite some progress in the pipeline of new drugs, the identification of new drugs for the treatment of TB is still urgent. The active and non-toxic molecules and the control molecule (rifampicin) were subjected to molecular docking using the Molegro Virtual Docker 6.0 (MVD) software with the proteins chorismate mutase and dihydrofolate reductase . Thus, this study evidenced interactions that favor the action of the compounds studied.

Introduction

Tuberculosis is an infectious disease chronic *Mycobacterium tuberculosis* by the microorganism. The global risks of infectious diseases, much is an entity of governmental and non-governmental institutions responsible for public health policies. As tuberculosis, as an infectious disease, remains one of the leading causes of death in the world, it requires effective monitoring, efficient and reliable diagnosis, screening and effective treatment (1,2,3).

According to a 2019 World Health Organization (WHO) estimate report, there was an agreement with the Report of 1.2 million deaths among HIV-negative people in 2018, and a 251,000 deaths among HIV-positive people. Since 2007, tuberculosis has been the leading cause of death from an infectious agent, ranking above HIV/AIDS. Brazil ranked 18th in number of TB cases, representing 0.9% of cases worldwide and 33% of estimated cases in the Americas. In 2016, the disease incidence coefficient was 32.4 cases per 100,000 inhabitants (4,5,6).

The *Mycobacterium* genome may contain and other structural modifications that may modify the action commonly used to inhibit it. The emergence of resistance makes disease control measures more complicated. Thus, despite some progress in the pipeline of new drugs, the identification of new drugs for the treatment of TB is still urgent (7,8,9).

Materials and Methods

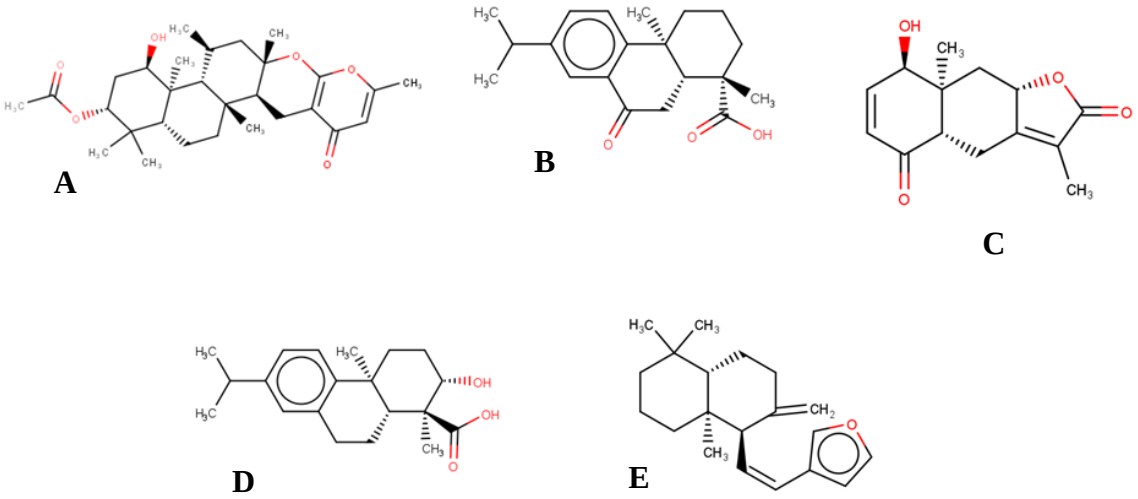
The three-dimensional structures of 10 terpenoids were designed using the HyperChem 7.5 TM software (RMS 0.1 kcal.Å-1.mol-1 in 800 cycles) and using MM+ molecular mechanics. Subsequently, a new geometry optimization based on the semi-empirical AM1 method was performed. The optimized structures were subjected to conformational analysis using KNIME Analytics Platform 3.7 software.

The terpenes considered active were then imported into the OSIRIS DataWarrior software. In this way, it was possible to predict the mutagenicity, carcinogenicity, toxic effect on the reproductive system and tissue irritability of these substances.

The active and non-toxic molecules and the control molecule (rifampicin) were subjected to molecular docking using the Molegro Virtual Docker 6.0 (MVD) software with the proteins chorismate mutase (PDB ID: 2FP1) and dihydrofolate reductase (PDB ID: 6NNE). These enzymes were imported from the Protein Data Bank (PDB) in the Molegro Virtual Docker (MVD) 6.0 program. The Moldock scor algorithm was used as a scoring function in predicting the best interaction between ligand and receptor.

Results and Discussion

After optimizing and verifying the toxicity parameters of the 10 terpenoids, only 5 molecules showed activity for the model and were considered non-toxic. Therefore, these compounds were imported into the Molegro Virtual Docker software to verify their interactions with two proteins present in *M. tuberculosis* (chorismate mutase - 2FP1 and dihydrofolate reductase - 6NNE)



For the enzyme chorismate mutase (2FP1), compound "A" showed hydrogen interactions with residues of Ser111, Ser179, Arg112, Leu180, and steric interactions with residues of Arg183, Leu180, Asp115, Ser111, and Ser179. For compound "B" hydrogen interactions with Ser111, Arg112, Ser179, Asp115, Ser114, Arg183 and steric interactions with Asp115, Arg183, Ser111, Leu180, Asp178 were observed. Compound "C" made hydrogen interactions with residues of Ser179, Arg112, Ser111, Arg183, Ser114, Asp115, and interacted sterically with Asp115, Arg183, Ser111, Leu180 and Asp178. The compound "D" presented 3 hydrogen interactions with Ser111, Ser114, Ser111 and 3 steric interactions with Ser111, Asp115, Arg183. The terpenoid "E" showed only steric interactions with residues of Asp115, Leu180, Ser111. According to the Moldock scoring algorithm, the substance that showed the best interaction with the 2FP1 enzyme was compound A (-104.41) which showed a value very close to the control, rifampicin (-105.54).

Corismato Mutase (2FP1)	
Composto	**MolDock score**
A	-104.41
B	-69.22
C	-61.37
D	-66.51
E	-83.83
controle	-105.54

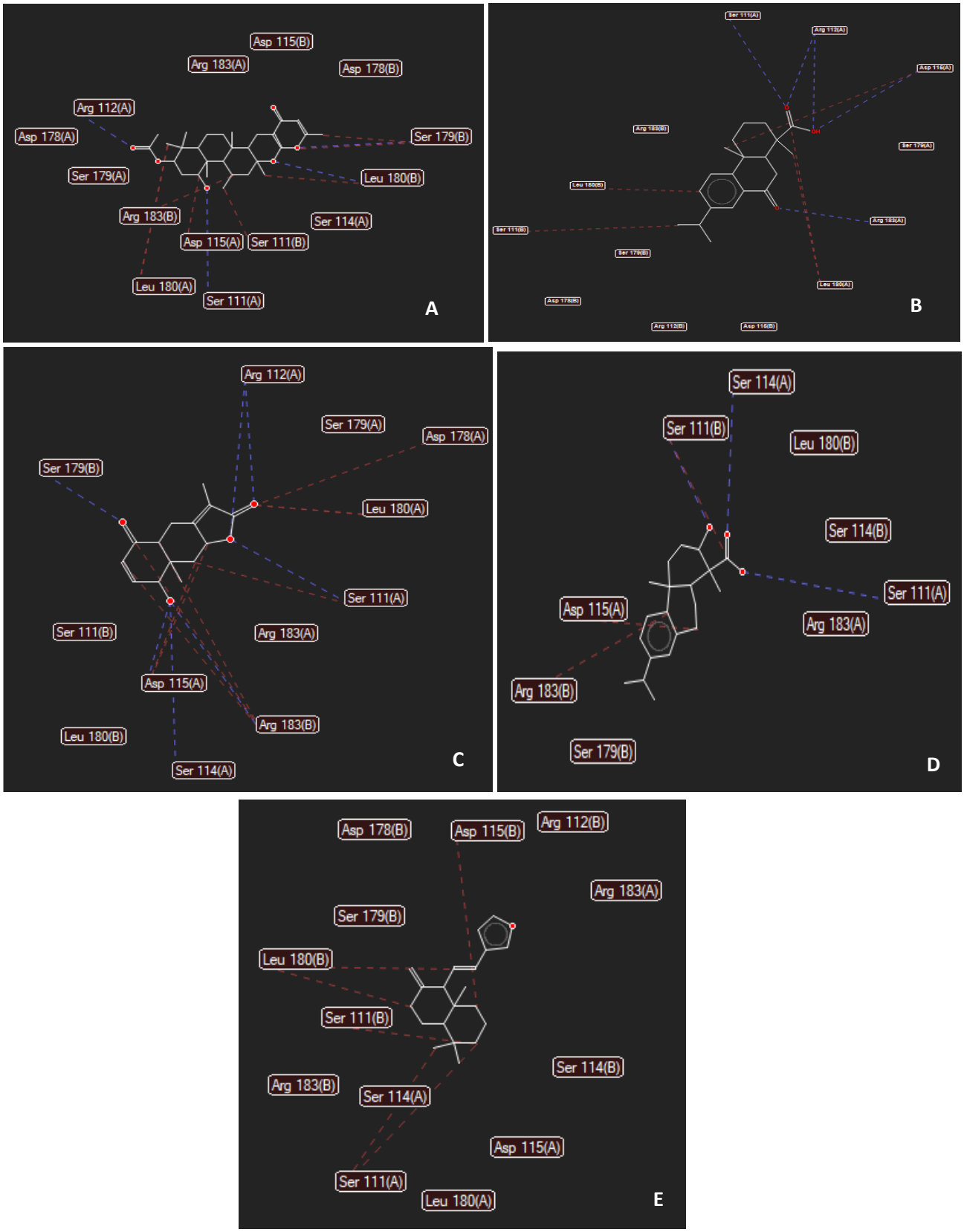
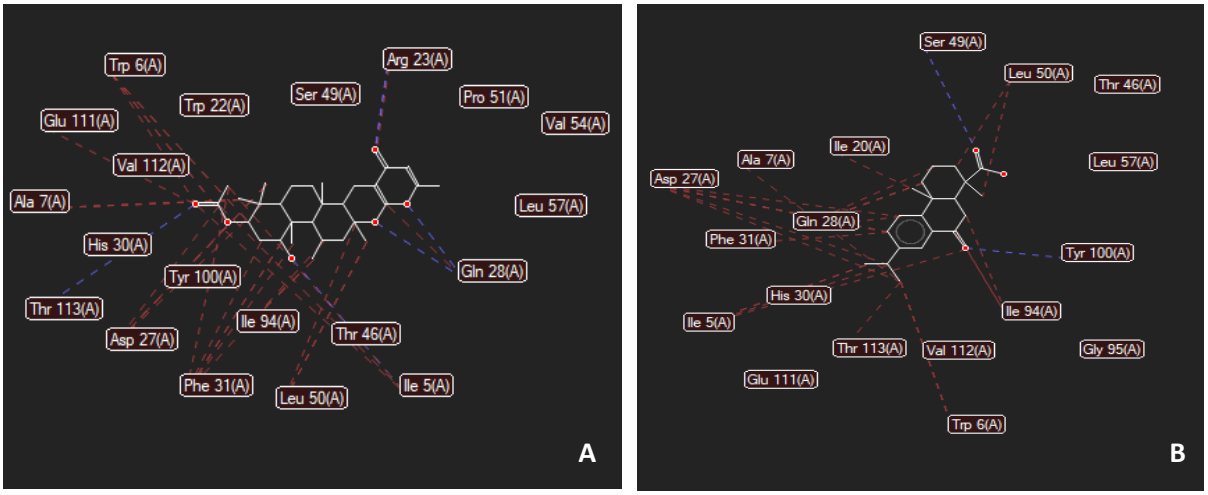


Figura 1. Interações de hidrogênio e interações estéricas entre os compostos A-E com 2FP1.

For the enzyme dihydrofolate reductase (6NNE), compound “A” showed hydrogen interactions with residues of Arg23, Gln28, Ile5, Thr113, and steric interactions with residues of Arg23, Gln28, Ile5, Leu50, Phe31, Asp27, Ala7, Glu119, Trp6. In compound “B” hydrogen interactions were observed with Ile94, Leu50, Trp6(A), Thr113, Ile5, His30, Phe31, Gln28, Asp27, Ala7, Ile20. Compound “C” made hydrogen interactions with residues of Asp27, Gln28, Tyr100, and steric interactions with Leu50, Gln28, Asp27, Phe31, Ile5, Trp6, Ile94. Compound “D” showed 2 hydrogen interactions with Ser49 and Gln28 and steric interactions with Leu50, Gln28, Trp6, Phe31, Asp27, Ile5. The “E” molecule showed, again, only steric interactions, this time with residues of Trp6, Ile5, Ile20, Gln28 and Leu50. As for the 2FP1 enzyme, the molecule with the best ligand-receptor interaction in the 6NNE protein was compound A (-93.55).

Diidrofolato redutase (6NNE)	
Composto	**MolDock score**
A	-93.55
B	-84.54
C	-66.12
D	-67.57
E	-76.35
controle	-130.36



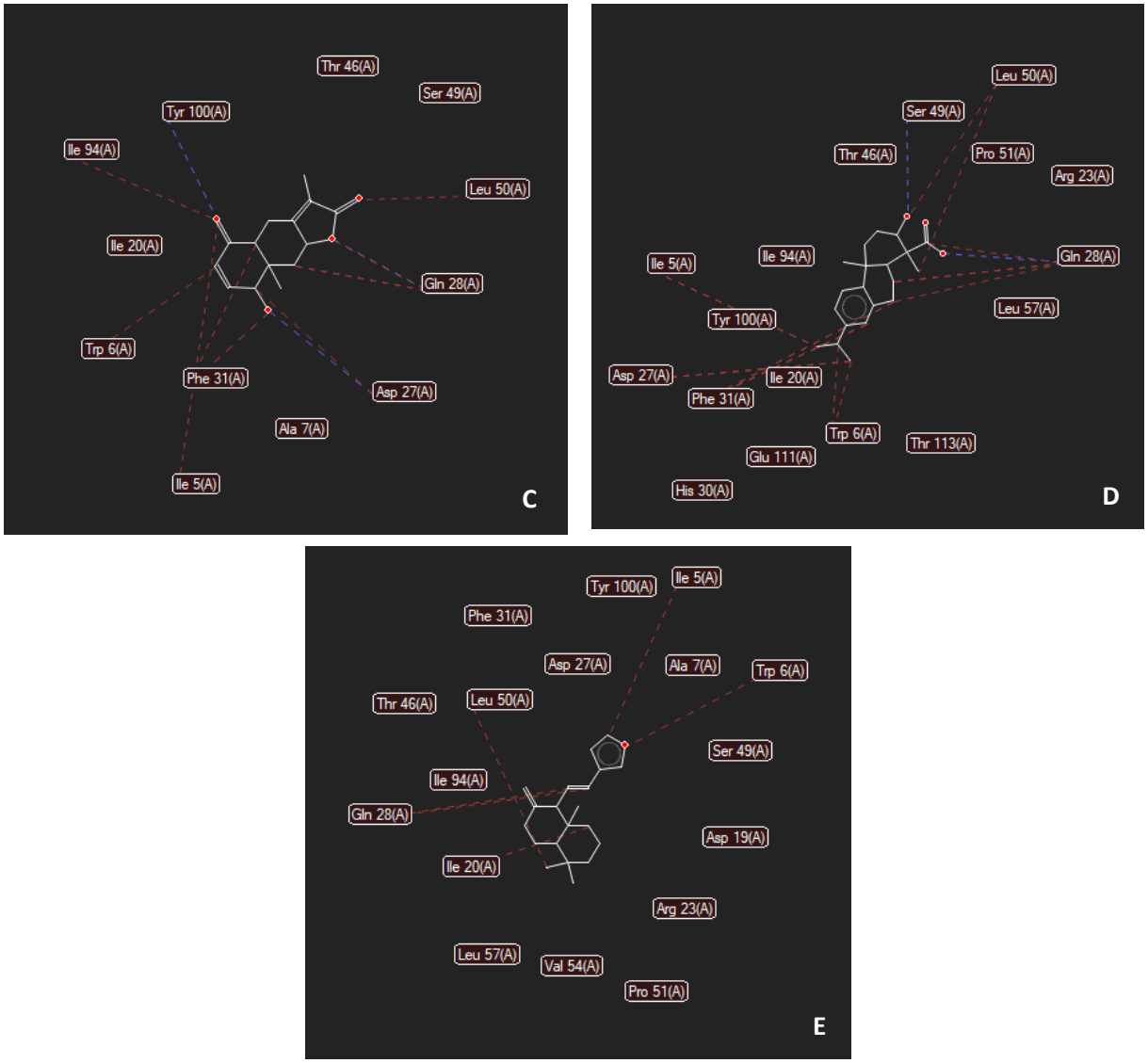


Figura 2. Interações de hidrogênio e interações estéricas entre os compostos A-E com 6NNE.

Conclusions

In this study, 5 terpenes in the enzymes dihydrofolate reductase (6NNE) and chorismate mutase (2FP1) were analyzed by molecular docking. Compounds A and E showed a better interaction for the 2FP1 protein, while molecules B, C and D have greater interaction with 6NNE. In addition, these compounds did not show toxicity parameters. Therefore, this study appears as an aid in the search for new pharmacological targets and new drug candidates that may have activity against *M. tuberculosis* and, thus, help in the fight against tuberculosis.

References

1. Lawn, S. D.; Zumla, A. I. Tuberculosis. **Lancet**, v. 378, p. 57-72, 2011.
2. Spitaleri, A.; Ghodousi, A.; Miotto, P. Whole genome sequencing in *Mycobacterium tuberculosis*. **Ann Transl Med**, v. 7, p. 19, 2019.

3. Wu, D.; Wu, T.; Liu, Q.; Yang, Z. The SARS-CoV-2 outbreak: What we know. **Int. J. Infect. Dis.**, v. 94, p. 44-48, 2020.

4. World Health Organization. Global Tuberculosis Report 2019. Switzerland Geneva: **World Health Organization**; 2019.

5. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Perspectivas brasileiras para o fim da tuberculose como problema de saúde pública. **Boletim Epidemiológico**, v. 47, p. 1-15, 2016.

6. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Indicadores prioritários para o monitoramento do Plano Nacional pelo fim da tuberculose como problema de saúde pública no Brasil. **Boletim Epidemiológico**, v. 48, p. 1-11, 2017.

7. Zhang, Y.; Yew, W. Mechanisms of drug resistance in *Mycobacterium tuberculosis*: update 2015. **Int. J. Tuberc**. **Lung Dis.**, v. 19, p. 1276–1289, 2015.

8. World Health Organization. Global Health Estimates 2016: deaths by cause, age, sex, by country and by region, 2000-2016. Geneva: **World Health Organization**; 2018.