

QSAR MODELS DEVELOPMENT FOR INHIBITORS OF
MYCOBACTERIUM TUBERCULOSIS EIS PROTEINCarla C. R. de Mendonça (PG),¹ Edeildo F. S. Júnior (Prof).^{1*}

ccmendonca10@hotmail.com;

¹ Federal University of Alagoas (UFAL);

Keywords: QSAR, Tuberculosis, Eis Protein, Mycobacterium tuberculosis.

ABSTRACT

According to the World Health Organization, Tuberculosis is the second leading infectious disease to result in deaths, behind only COVID-19. Although there are several forms of treatment available, the Multidrug-resistant (MDR-TB) and extremely drug-resistant (XDR-TB) strains are among the most lethal and signal the importance of studying new drugs and pharmacological targets. One of the promising pharmacological targets is Eis Protein (Enhanced Intracellular Survival). The literature shows its connection with bacterial resistance through the acetylation of some antibiotics and inhibition of autophagy by manipulating the production of anti-inflammatory genes. Therefore, this work aimed to build Quantitative structure–activity relationship (QSAR) models using Eis Protein inhibitor molecules, so that the equations obtained can guide the synthesis of molecules with good predicted inhibitory activity. The methodology used consisted of building a library of inhibitors from articles obtained from the following databases: Google Scholar, ScienceDirect, Scopus, PubMed, Pubchem; selection of articles with a group of molecules with the same biological parameter test (IC_{50}) and structural similarity; molecules were designed in MarvinSketch version 24.1.2 and the model was built and validated using the QSARINS program. The search in the databases resulted in 9 articles, two of which were used to build the model NGO et al., 2018 and PUNETHA et al., 2020 totaling 105 molecules. After failed attempts to obtain a valid model using all molecules, 60 were selected, 20 active (pIC_{50} = 6.6 – 7.5), moderate (pIC_{50} = 5.6 – 6.6) and inactive (pIC_{50} = 3.6-5.6). With this group, it was possible to obtain 4 QSAR models using 1D/2D/3D descriptors. The models obtained values for validation: A (R^2 =0.84 Q^2_{LOO} =0.78 R^2_{ext} =0.81), B (R^2 =0.83 Q^2_{LOO} =0.78 R^2_{ext} =0.82), C (R^2 =0.69 Q^2_{LOO} =0.62 R^2_{ext} =0.82), D (R^2 =0.68 Q^2_{LOO} =0.63 R^2_{ext} =0.80). Descriptors obtained were AATS7e, ATSC1v, MATS5s, GATS4c, SsssN, SRW9, JGI9, CIC5 and ATSC2e. Equations and validations by Y-Scramble are available in figure 1. Therefore, this study was able to develop and validate QSAR models to inhibit the Eis Protein, thereby obtaining descriptors that demonstrate the structure-activity relationship of the molecules. This information can be used for the rational design of a new series of promising molecules for the treatment of Tuberculosis.

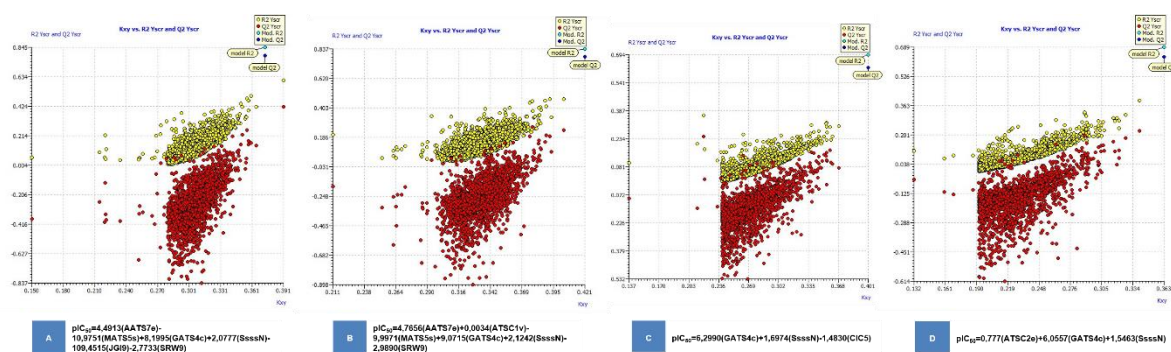


Figure 1. Y-Scramble and Equations of the four QSAR models (A,B,C,D). The yellow and red spheres represent R^2 and Q^2 of the random models respectively. The light blue and purple spheres represent R^2 and Q^2 of the model.