



Computational modeling of some oxazolyl thiosemicarbazone derivatives against multidrug-resistant tuberculosis via 2-QSAR and molecular docking simulation



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INTRODUCTION

Tuberculosis (TB) remains the leading cause of mortality because of a bacterial pathogen, *Mycobacterium tuberculosis*. It is estimated that 8.2 million new TB cases occurred worldwide in the year 2000, with approximately 1.8 million deaths in the same year, and more than 95% of those were in developing countries. The reemergence of TB infection is complicated by an increase in cases that are resistant to conventional antitubercular drug therapy; isoniazid and rifampin, the two most potent TB drugs. Thus, new drugs are necessary to overcome the current problems of therapy. In the course to discover new compounds employed in the chemotherapy of tuberculosis, we identified oxazolyl thiosemicarbazones derivatives that inhibited in vitro MTB and multidrug resistant *Mycobacterium tuberculosis* (MDR-TB).

RESULTS AND DISCUSSION

QSAR equation relating the experimental IC_{50} values were tested for this model. However the regression equation that best correlates the calculated molecular descriptors with the experimental activities was obtained as:

$$pIC_{50}^{exp} = -\log_{10} IC_{50} = 5.49106 - 1.74799 (XlogP) + 0.22879 (XlogP)^2 - 0.05990 (MR) + 0.01103 (2DPSA) - 0.05169 (Dipole) + 0.02341 (E) - 0.01094 (MTD) - 0.21408 (\eta) + 1.52955 (\omega)$$

$$pIC_{50}^{pred} = -\log_{10} IC_{50}^{pred} = 0.955286 pIC_{50}^{exp} + 0.0112285$$

CONCLUSION AND PRESPECTIVE

This work presents a QSAR study of a series of 20 oxazolyl Thiosemicarbazone derivatives for their activity against MDR-TB activities. The developed models: multiple linear regression, are validated internally and externally which shows that they have a good predictive power as well as a better statistical significance. Five descriptors used showed a better correlation with studied activity.

The correlation coefficient obtained $r^2 = 0.9553$, given the relationship between the activity and the calculated molecular descriptors of the 16 molecules in the training set, and $F = 21.3644$.

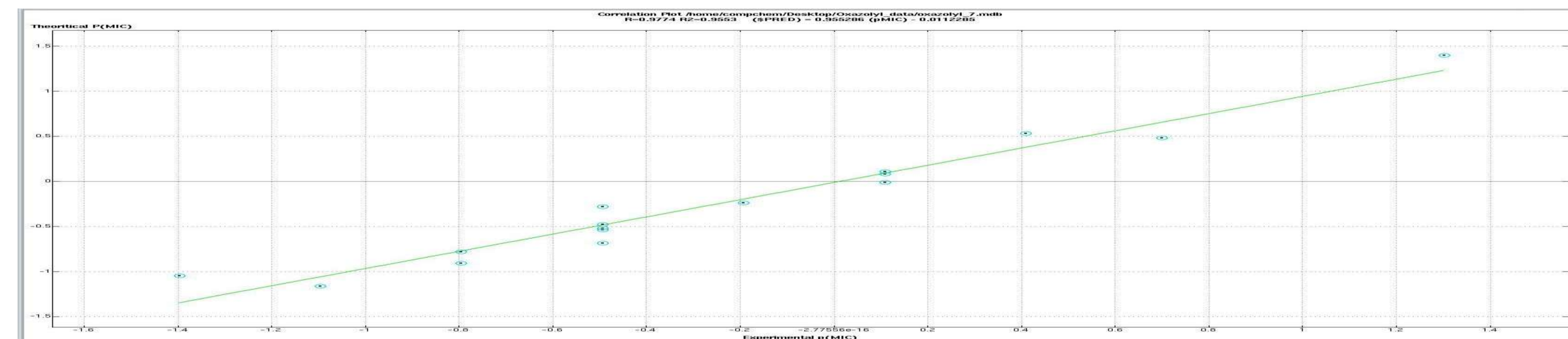
The high correlation coefficient, r^2 , indicates the robustness and internal predictivity of the derived QSAR model.

RESULTS AND DISCUSSION

The validation of QSAR model was realized using the cross-validation method with the cross validation coefficient calculated according to the formula

$$Q^2 = 1 - \frac{\sum (pIC_{50}^{exp} - pIC_{50}^{pred})^2}{\sum (pIC_{50}^{exp} - pIC_{50}^{mean})^2} = 0.45$$

The cross validated value Q^2 is 0.4571 for the QSAR model, which suggest good prediction for the MDR-TB activities of the test set. A plot of theoretical versus experimental values of the training set molecules shows good linearity as shown in figure 1



Plot of predicted activity versus experimental activity of training set molecules in the QSAR model.