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Quantitative structure activity relationship and docking studies on imidazole derivatives as P-glycoprotein inhibitors

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Background and Aims: P-glycoprotein (P-gp), one of the important transporters in cells has significant role in multidrug resistance (MDR). P-gp inhibitors are potent compounds at overcoming MDR in cancer and epilepsy therapies. Quantitative structure activity relationship (QSAR) methods are extensively used to predict the biological activity of new compounds in drug design process. The aim of this study is to rationalize biological activity for a set of imidazole derivatives as P-gp inhibitors based on linear and non-linear QSAR methods.
Methods: A dataset of 51 imidazole derivatives of P-gp inhibitors were selected for QSAR and docking studies. To this end, the molecular descriptors were calculated using DRAGON software and then genetic algorithm coupled partial least squares (GA-PLS) as well as stepwise regression or enhanced replacement method (ERM) were used for descriptor selection in order to be used in linear model i.e. multiple linear regression (MLR) and non-linear models i.e. support vector machines (SVM) and artificial neural network (ANN) methods. In order to investigate the mode of interaction(s) of the studied P-gp inhibitors and P-gp, the inhibitors were docked onto the binding site of protein using MOE program and interaction(s) analyzed.
Results: Among the different 2D-QSAR approaches used in this work, the results showed that the best model was obtained by ANN method with mean square error (MSE) value of 0.075. The result of docking study was analyzed and mode of interactions between ligands and receptor were identified.
Conclusions: The result of this investigation demonstrated that non linear methods perform well compared to linear methods in predicting the biological activity of P-gp inhibitors. The result of docking study was in agreement with those obtained by 2D-QSAR models. The results of the current study can be used in drug development where P-gp inhibitors are involved

Keywords: P-glycoprotein; QSAR; Docking