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Structure-Activity Relationship for Inhibition of HERG Potassium Channel

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The human ether-a-go-go related gene (HERG) protein forms the ion channel responsible for IKr, and its blockade is a significant contributor to prolongation of the QT interval. In this study, a 2D-QSAR model was developed to elucidate structural factors affecting HERG channel blockade. The IC_{50} values of 104 compounds with diverse structures were collected from literature. By taking consideration of structural diversities, the 104 compounds were divided into two sets: 84 compounds for the training set, and 20 compounds for the test set. Statistics of the final model were R^2=0.647, RMSE=0.835, and F=36.1 for the training set, and R^2=0.679 and RMSE=0.865 for the test set. Statistically significant descriptors were clogP, TPSA, diameter, and the total surface area of atoms having partial charges in the range from -0.25 to -0.20. This model is practically helpful in the design of new drug candidate before synthesis.