hERG blocking potential of acids and zwitterions characterized by three thresholds for acidity, size and reactivity

Ionization is a key factor in hERG K+ channel blocking, and acids and zwitterions are known to be less probable hERG blockers than bases and neutral compounds. However, a considerable number of acidic compounds block hERG, and the physico-chemical attributes which discriminate acidic blockers from acidic non-blockers have not been fully elucidated. We propose a rule for prediction of hERG blocking by acids and zwitterionic ampholytes based on thresholds for only three descriptors related to acidity, size and reactivity. The training set of 153 acids and zwitterionic ampholytes was predicted with a concordance of 91% by a decision tree based on the rule. Two external validations were performed with sets of 35 and 48 observations, respectively, both showing concordances of 91%. In addition, a global QSAR model of hERG blocking was constructed based on a large diverse training set of 1374 chemicals covering all ionization classes, externally validated showing high predictivity and compared to the decision tree. The decision tree was found to be superior for the acids and zwitterionic ampholytes classes.