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Multi-algorithm based machine learning and structural pattern studies for hERG ion channel blockers mediated cardiotoxicity prediction

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ABSTRACT

The development of novel bioactive molecules without hERG ion channel blocking activities is one of the important tasks for the drug discovery scientists. Both experimental and *in silico* techniques are applied for screening/assaying of novel molecules and existing molecules against hERG ion channel to study its cardiotoxicity. Hence, in the present investigation, QSAR and multialgorithm based classification analysis such as Random Forest (RF), Decision Tree (DT), Support Vector Machine (SVM) and Naive Bayesian (BN) were performed on the data set possessed hERG ion channel blocking activity using different variable (MOE-descriptors and MACCS Fingerprints). The models developed with the MLR and the machine learning techniques provided significant results which were confirmed by their acceptable statistical parameter values. Further, the sum of ranking differences (SRDs) calculated for the models showed that the Model 6-MOE, Model 7-MOE, Model 4-SVM, Model 7-SVM and Model 9-SVM are having smaller SRD values and are placed as top ranked models. The MOE-descriptors and the MACCS Fingerprints contributed in these models revealed that the volume-surface area properties, negative charge on the vdW surface area, number of fluorine atom, number of aromatic ring/atoms, less number of oxygen and hydrogen bonding and donor atoms are contributed for the activity. Furthermore the MACCS Fingerprints such as MACCSFP42, MACCSFP85, MACCSFP122 and MACCSFP139 also explain the polarity of the compounds. The structural pattern analysis with the MACCS Fingerprint revealed that the aromatic rings responsible for hydrophobicity, halogen and heteroatoms provide polarity to the compounds and the asymmetric carbon make the compounds are highly flexible. These studies concluded that the derived results can be used for prediction of hERG ion channel blocking activity of novel molecules.

1. Introduction

Warmke and Ganetzky have first identified the human ether-a-go-go-related gene (hERG), which encodes the K^+ channel protein (Kv 11.1) that causes repolarization of the cardiac action potential (AP) [1–3]. When the hERG ion channel function is blocked by bioactive molecules especially non-cardiovascular acting drugs, prolong the AP duration (APD) that suppress premature ventricular contraction (effective refractory period) lead to long QT syndrome-2 (LQTS-2) (“torsades de pointes”) [4,5]. The Committee of Proprietary Medicinal Products, in 1997 (Committee of Proprietary Medicinal Products/986/96 (1997) and ICH S7B (2005)) constituted by European Pharmaceutical Regulatory Authority recommended to evaluate hERG ion channel blocking activity of new chemical entities [6,7]. Furthermore, a recent report showed that administration of multiple medications such as anti-malarial or anti-viral drugs for the treatment of SARS-CoV2 (COVID-19) can cause QT prolongation, because some combined medications may be synergistic rather than simply additive in hERG ion channel blocking action. Beside the cardiotoxic effect of these blockers, the hERG ion channel blockers are used for the treatment of cardiac arrhythmia (class III antiarrhythmics) [8,9].

The discovery of novel bioactive molecules and screening of existing (repurposing) pharmacologically active molecules on new pharmacological targets may be affected by their action on hERG ion channel. It has observed that both *in silico* and experimental (electrophysiology and biochemical) screening assays can be a valuable tools to evaluate the hERG ion channel blocking action of any molecules. The utilization of these approaches can significantly help to reduce the adverse drug reaction and toxicity related attrition and late level failure of medicines in clinical trials [10,11].

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