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hERG PHARMACOPHORE MODELS AS CARDIAC TOXICITY PREDICTION TOOLS: IDENTIFICATION OF CHANNEL BLOCKERS OF NATURAL ORIGIN

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ABSTRACT

The human ether-a-go-go-related gene (hERG) channel plays a critical role in cardiac action potential repolarization. hERG block can lead to arrhythmia, and increased incidence of sudden death. Association of in silico and experimental approaches has been suggested as the foundation of a cost-effective preclinical evaluation of the cardiotoxic risks of drug candidates. Although several drugs have been withdrawn from the market for this reason, it has just recently been of interest to assess the potential cardiotoxic risks of botanicals. The goal of this study was to design, experimentally validate and apply a virtual screening workflow to identify novel hERG channel blockers, with a special focus on the investigation of natural products. A ligand-based pharmacophore model collection was developed and theoretically evaluated against databases of known hERG blockers from the literature and drug-like decoys. The best models were then used for virtual screening of compound libraries. Fifty chemically diverse compounds were selected from the hitlists for bioactivity testing on Xenopus laevis oocytes and HEK 293 cells using patch clamp techniques. This campaign identified 20 unknown hERG blockers, including highly potent compounds, active at the submicromolar range. The experimental confirmation that the models developed in this study can accurately predict hERG block by previously unknown compounds of natural origin is of special interest. These models are currently implemented as prediction tools in a larger ongoing EU-project (hERGscreen), aiming at target-oriented identification and isolation of hERG channel blockers from highly consumed botanicals.

Keywords: hERG; pharmacophore models; virtual screening; patch clamp; cardiac toxicity.