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BayeshERG: A Robust, Reliable, and Interpretable Deep Learning Model for Predicting hERG Channel Blockers

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Unintended inhibition of the human ether-à-go-go-related gene (hERG) ion channel by small molecules leads to severe cardiotoxicity. Several computational models have been developed to predict hERG channel blockage, including deep learning models; however, they lack robustness, reliability, and interpretability. Here, we developed a graph-based Bayesian deep learning model for hERG channel blocker prediction, named *BayeshERG*, which has robust predictive power, high reliability, and high resolution of interpretability. We conducted both internal and external validations for stringent evaluation, and we showed that our proposed model outperformed predictive performance and uncertainty calibration performance. Furthermore, we found that our model learned to focus on the essential substructures of hERG channel blockers via an attention mechanism. Lastly, we validated the prediction results of our model by conducting *in vitro* experiments and confirmed its high validity. In summary, BayeshERG could serve as a versatile tool for discovering hERG channel blockers and help maximize the possibility of successful drug discovery.