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# QSAR-ENHANCED REINFORCEMENT LEARNING APPROACH FOR NOVEL SYK INHIBITOR DISCOVERY

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**Introduction.** Spleen tyrosine kinase (Syk) is a non-receptor tyrosine kinase expressed in various immune cells that plays a critical role in inflammatory responses [1]. Its hyperactivation is implicated in a broad spectrum of diseases, including autoimmune, allergic, and autoinflammatory conditions, as well as certain cancers and cardiovascular diseases, making Syk an attractive therapeutic target [2, 3]. Immune thrombocytopenia (ITP), a rare autoimmune disorder, represents a significant unmet medical need for effective Syk inhibitors. While several treatment options exist for ITP, Syk inhibition offers a promising approach for long-term disease management [4]. However, the development of potent and safe Syk inhibitors faces challenges ranging from avoiding off-target effects to limited clinical efficacy [5]. Fostamatinib, the only drug currently approved for ITP treatment from Syk inhibitors class, has encountered limitations due to safety concerns and a lack of robust efficacy data [6]. In this regard, search for an optimal Syk inhibitors is still underway [7].

**Main part.** The application of computational methods and machine learning is transforming biomedical research and drug development [8]. Two primary approaches for identification of promising compounds are screening existing drug-like databases and *de novo* design of molecules with desired properties [9]. Available data on Syk inhibitors supports the use of computational methods for developing novel compounds. Previous studies have applied virtual screening with pharmacophore modeling [10], molecular docking [11] and machine learning approaches [12] to identify potential inhibitors. However, generative *de novo* design for Syk inhibitors remains unexplored. Inspired by the success of RL-based methodologies, this study presents an approach to the design of new Syk inhibitors by enhancing the FREED++ deep reinforcement learning model, demonstrating how generative algorithms can be tailored for targeted drug discovery.

Our computational workflow comprises several key steps. Initially, we compiled a database of known Syk inhibitors. Using this data, we developed a QSAR model employing a stacking ensemble of machine learning algorithms to predict the biological activities of Syk inhibitors. Subsequently, we utilized the FREED++ generative model, which leverages reinforcement learning, to design novel inhibitors. To explicitly take into account the target properties of Syk inhibitors we adapted the reward function of FREED++ with our QSAR model, advancing the capabilities of the original generative approach. Finally, we applied stringent drug-likeness criteria and high predicted potency thresholds to select the most promising generated molecules. From over 78,000 generated molecules, 139 compounds met stringent drug-likeness criteria and exhibited high predicted potency. These novel candidates displayed favorable molecular properties and structural novelty compared to known Syk inhibitors, suggesting potential for improved efficacy and reduced side effects.

**Conclusion.** In this study, we successfully applied a novel approach combining deep reinforcement learning with QSAR predictive model to design new potential Syk inhibitors. We obtained a set of 139 promising candidate molecules with high predicted activity and favorable drug-like properties. Moreover, our approach establishes a versatile framework for accelerated drug discovery, particularly valuable for rare disease therapeutics development.

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