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AI-Driven De Novo Design and Development of Nontoxic DYRK1A Inhibitors

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Abstract-

Dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) is implicated in several human diseases, including DYRK1A syndrome, cancer, and neurodegenerative disorders such as Alzheimer’s disease, making it a relevant therapeutic target. In this study, we combine artificial intelligence with traditional drug discovery methods to design nontoxic DYRK1A inhibitors. An ensemble QSAR model was used to predict binding affinities, while a directed message passing neural network evaluated toxicity. Novel compounds were generated using a hierarchical graph-based generative model and subsequently refined through molecular docking, chemical synthesis, and experimental validation. This pipeline led to the identification of pyrazolyl-1H-pyrrolo[2,3-b]pyridine 1 as a potent inhibitor, from which a new derivative series was developed. Enzymatic assays confirmed nanomolar DYRK1A inhibition, and additional assays demonstrated antioxidant and anti-inflammatory properties. Overall, the resulting compounds exhibit strong DYRK1A inhibition and favorable pharmacological profiles.

Index Terms- AI-driven drug design, Molecular generative models, DYRK1A inhibition

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