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In Silico Evaluation of Diketopiperazine (DPK) Derivatives as Potential Inhibitors for G-Protein-Coupled Receptors (GPCRs)

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Background:

G-protein-coupled receptors (GPCRs) are membrane proteins that mediate key physiological processes by converting extracellular signals into intracellular responses. The β2-Adrenergic Receptor (β2-AR) regulates smooth muscle relaxation, bronchodilation, and cardiovascular function, making it a key target for treating hypertension and asthma. Diketopiperazines (DPKs), the simplest cyclic peptides, offer a promising approach to modulating receptor activity with potentially fewer side effects than small-molecule inhibitors [1-3]

Results:

Among the five compounds, tryptophan-proline diketopiperazine (compound 3) showed the highest binding affinity (-5.89 kcal/mol) with two hydrogen bonds. Tryptophan's aromaticity enables strong π-π stacking, while proline's rigidity ensures optimal receptor binding, further stabilized by hydrophobic interactions.

	Name	Binding Energy (Kcal/mol)	No. H bond
1	2_5_Piperazinedione	-3.00	2
2	Alanine diketopiperazine	-3.70	2
3	Tryptophan_proline diketopiperazine	-5.89	2
4	Diketopiperazine	-2.95	2
5	Histidylproline diketopiperazine	-5.13	2

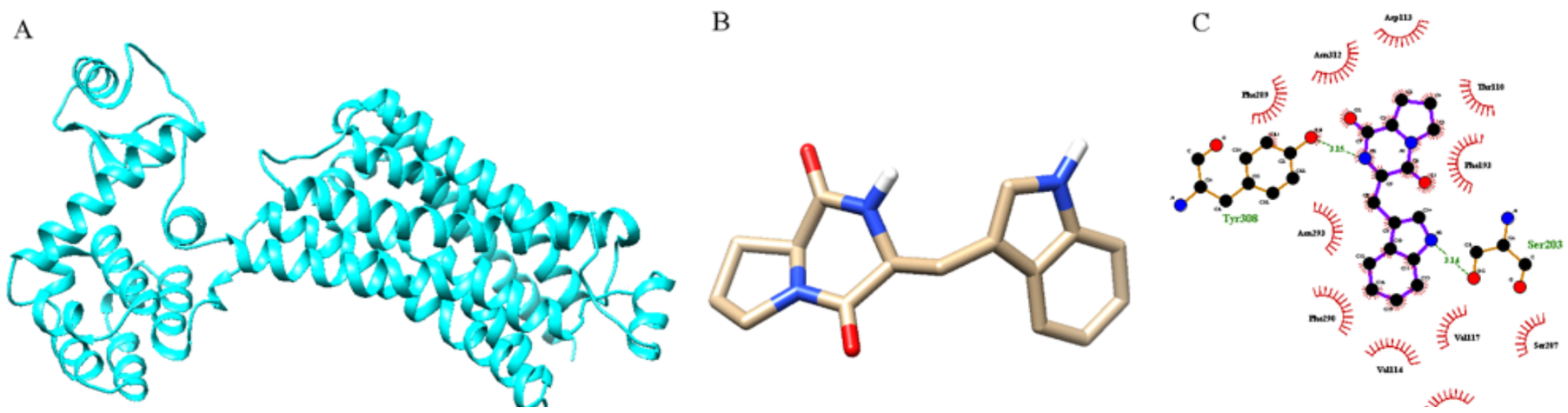

Figure. A, β2-Adrenergic Receptor, B. Tryptophan_proline diketopiperazine, and C. Interaction of Ligand-Protein via DimPlot, Ser203 and Tyr308 have H.bond with the ligand.

Methods:

In this study, five DPK derivatives were obtained from PubChem and evaluated for their binding affinity to 3D structure of β2-AR (PDB ID = 2RH1) through molecular docking studies using Autodock 4.6 and MGLTools. Each compound's binding energy and hydrogen bond formation were assessed to determine their interaction efficiency [4,5].

Conclusion:

This study highlights tryptophan-proline diketopiperazine as a promising β2-AR inhibitor. Its aromaticity and rigidity enhance receptor binding, offering insights for designing peptide-based GPCR inhibitors with improved specificity and fewer side effects.

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[2] Bojarska, J., 2021. A Global Review on Short Peptides: Frontiers and Perspectives
[3] Sammes, P.G.1957. Naturally occurring 2,5-dioxopiperazines and related compounds.
[4] Cherezov V, 2007 High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor.
[5] Morris, G. M.2009.Autodock4 and AutoDockTools4: automated docking with selective receptor flexibility.