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Molecular Docking and Structure-Based Pharmacophore Modelling Discover New TRPC5 Inhibitors for Focal Segmental Glomerulosclerosis

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Objectives : Podocyte dysfunction is a hallmark of focal segmental glomerulosclerosis (FSGS), a leading cause of end-stage renal disease. A promising therapeutic target, the Transient Receptor Potential Cation Channel Subfamily C Member 5 (TRPC5) is implicated in mediating altered podocyte permeability in FSGS.
Methods : To find new TRPC5 inhibitors, we used a structure-based pharmacophore modelling technique. Based on Clemizole's binding to the TRPC5 crystal structure (PDB ID: 7D4P), a pharmacophore model was created. Using Pharmit, this model was utilised to screen the ZINC database, giving compounds with Clemizole-like binding poses priority. Compound selection was then improved through the use of molecular docking.
Results : Three lead compounds, ZINC1625179, ZINC225886464, and ZINC225886466, were found by virtual screening and docking. These compounds showed favourable binding energies of -8.3 kcal/mol, -9.0 kcal/mol, and -9.2 kcal/mol, respectively. These substances showed possible inhibitory activity by exhibiting binding positions within the TRPC5 binding site that were comparable to those of clemizole.
Conclusions : By using a structure-based virtual screening method, this study was able to successfully identify three novel compounds as putative TRPC5 inhibitors. These substances are encouraging candidates for FSGS treatments.Future work will involve Molecular Dynamics (MD) simulations to assess protein-ligand complex stability and further characterize binding interactions. In vitro and in vivo studies are warranted to validate the efficacy of these compounds in modulating TRPC5 activity and mitigating FSGS progression.

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Compound Name	ZINC ID	Binding Energy (kcal/mol)	Interaction
Clemizole	N/A	-8.3	For pharmacophore modelling, a control compound
Compound 1	ZINC1625179	-8.3	Lead compound chosen through molecular docking and virtual screening
Compound 2	ZINC225886464	-9.0	Lead compound chosen through molecular docking and virtual screening
Compound 3	ZINC225886466	-9.2	Lead compound chosen through molecular docking and virtual screening

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