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ORIGINAL ARTICLE

Multi-Target Virtual Screening Identifies Vorinostat and Benzquinamide as Promising Lead Compounds for Focal Segmental Glomerulosclerosis

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ABSTRACT

OBJECTIVE: The current study used a combined in silico drug discovery strategy to identify potential therapeutic targets for key pathways involved in FSGS.

METHODOLOGY: Disease-related proteins were selected, such as SAMD9L3, TEK (Tie2), and TGFB1. Protein sequences and structures of proteins were obtained from public databases, modelled with the aid of advanced structure prediction programs, and then prepared and validated computationally. A drug-like compound library with several drug-likeness criteria was searched and filtered on ZINC and PubChem databases. The SwissADME, Molsoft, and PAINS screening were conducted to assess Pharmacokinetics and toxicity, thereby maximizing desirable ADME and safety characteristics. PyRx, a combination of AutoDock Vina, was used to perform molecular Docking to compare the binding affinity and binding patterns of the chosen compounds with the target proteins.

This study was conducted at Government College University, Faisalabad, Pakistan, between 15 February 2025 and 10 August 2025

RESULTS: Many compounds showed good and consistent binding affinities with the target proteins, meaning that they can be used as lead candidates.

CONCLUSION: In general, the study provides a computational pipeline for the identification of potential drug-like molecules against the targets of FSGS and provides the basis for subsequent experimental validation and therapeutic development.

KEYWORDS: Renal failure, Pharmacokinetics, toxicity, Molecular Docking.

INTRODUCTION

Focal Segmental Glomerulosclerosis (FSGS) is an acute and progressive glomerular disease characterized by segmental scarring of part of the renal glomeruli, proteinuria, nephrotic syndrome, and progressive kidney failure[1]. It is one of the common causes of chronic kidney disease and end-stage renal failure in pediatrics and adults. The pathogenesis of FSGS is extremely complex, involving injury of the podocytes, destruction of the glomerular filtration barrier, immune deregulation, oxidative stress, and fibrotic signaling transduction. Such a consequence makes FSGS difficult to treat, further complicating the patient's response to current treatment[2].

The main treatment modalities for FSGS include corticosteroids, immunosuppressive reagents, and supportive therapies. However, these methods may be effective, but most patients develop an increase in steroid resistance or multiple relapses and harsh side effects. Additionally, traditional treatment usually aims to address symptoms or isolated physiological pathways, rather than the underlying molecular complexity of the disease[3].

In our study, the notion of multi-target drug discovery has proven an effective approach to complex diseases such as FSGS. As FSGS is associated with a complex of biological processes, including regulation of the podocyte cytoskeleton, inflammatory signaling, and glomerulonephritis, a multi-target approach is particularly applicable. These approaches have the potential to improve the results of the therapeutic process, as they can interrupt several pathogenic processes simultaneously and decrease the possibility of the development of a drug-resistant phenomenon[4,5].

The breakthroughs in computational biology and computer-aided drug design have drastically boosted the process of drug discovery. One of such method is molecular Docking, which is commonly used to predict the orientation and affinity of small molecules for their target proteins[6]. With the use of molecular Docking, it is possible to screen large libraries of compounds and perform a high-throughput virtual screening to focus on promising compounds before experimental work. Docking-based screening is also a potent method of screening compounds of polypharmacological interest when present in multiple targets[7].

There is a logical and effective approach of drug discovery using multi-target molecular Docking and screening of the ZINC database against FSGS-related targets. By selecting proteins implicated in the pathogenesis of podocyte dysfunction, inflammatory responses, and fibrotic remodeling, it is possible to computationally analyze how a single compound interacts with the different pathways of interest in disease. Lead molecules with high affinity and stable binding to multiple targets can be effective therapeutic agents with enhanced pharmacological properties[6].

This paper focuses on screening and ranking of ZINC database compounds using molecular Docking to identify multi-target therapeutic candidates for Focal Segmental Glomerulosclerosis (FSGS). The study aims to identify bioactive molecules that can regulate multiple disease-relevant pathways by targeting proteins involved in key pathogenic processes, namely podocyte injury, inflammatory signaling, and glomerular fibrosis. Overall, the objective is to produce promising lead compounds with good binding affinities and drug-like properties that can serve as a starting point for more extensive experimental studies and the development of more effective and safer therapeutic approaches to FSGS.

METHODOLOGY

Selection of FSGS-associated molecular targets

FSGS is a genetic condition [disease causes] characterized by progressively worsening glycosuria, accompanied by the loss of filtration cysts in kidney tubules. The proteins linked to Focal Segmental Glomerulosclerosis (FSGS) were chosen according to previous evidence that includes 20 genes related to the disease: *NRP1, NRP2, TEK, FN1, SERPINE1, DUSP1, TRPC6, SAMD3, TGFB1, JUN, KDR, HIF1A, CRB2, A2M, ICAM1, RHOA, TNF, CCL2, CD40LG*, and *ATF3*. Protein sequences of the proteins were retrieved from databases such as the National Centre of Biotechnology Information (NCBI) and UniProt, and only high-quality records were used. Sequences were downloaded in FASTA format and filtered for the presence of isoforms, functional domains, and other features of interest, with duplicates and uncertain records removed. Given their centrality in key pathogenic pathways such as fibrosis, endothelial stability, and the immune response, SAMD9L3, TEK, and TGFB1 were selected as potential therapeutic targets for FSGS.

This study was conducted at Government College University, Faisalabad, Pakistan, between 15 February 2025 and 10 August 2025.

Protein structure retrieval and preparation

Three-dimensional structures that must be resolved experimentally have been sourced from the Protein Data Bank, whereas proteins lacking structural data have been modelled using AlphaFold or SWISS-MODEL. The preparation of all protein structures was done using PyMOL and UCSF Chimera through the removal of non-protein molecules, addition of hydrogen atoms, reconstruction of any missing residues, and energy refinements. The completed protein models were stored in PDB format and further used to analyze protein-protein interactions, perform molecular Docking, and conduct pathway-based studies to understand the molecular mechanisms of FSGS.

Drug-like Compounds Library Retrieval

The pharmacological screen and discussion of potential therapeutic candidates of Focal Segmental Glomerulosclerosis (FSGS) were developed by identifying small molecules through searches and screening of the ZINC and PubChem databases, which contain a wide range of structural and biological annotations. Keywords were used to search databases of major molecular processes implicated in FSGS[8]. The compounds and remedies retrieved were filtered according to the Rule of Five of Lipinski to select molecules with excellent oral bioavailability, based on molecular weight, hydrogen bond donors and acceptors, and lipophilicity[9]. To facilitate the computation of the screened compounds, such as molecular Docking, three-dimensional structures of the compounds were obtained in the form of SDF and MOL2 files. The drug-like subset of ZINC was selected specifically for its chemical suitability for drug development. In contrast, PubChem was used to access complementary information on biological activity, target classes, and predicted mechanisms of action. The completed library of compounds was further used to perform virtual screening against priority protein targets in FSGS, such as SAMD3, TGFB1, and TEK, and downstream molecular Docking and ADMET profiling were performed to measure binding affinity and pharmacokinetic behavior[10].

Screening of drug-like compounds library

In silico ADME screening of the drug-like compounds retrieved from ZINC and PubChem was performed using SwissADME, a freely available web server developed by the Swiss Institute of Bioinformatics. The key drug-likeness and oral bioavailability characteristics,

such as the Lipinski Rule of Five (molecular weight, hydrogen bond donors and acceptors, and lipophilicity), Veber criteria (topological polar surface area and the number of rotatable bonds), and Ghose filters (total atoms and the molar refractivity), were predicted using SwissADME, which allowed the systematic removal of those compounds that had poor properties. Moreover, pharmacokinetic properties, including gastrointestinal absorption, blood-brain barrier permeability, and P-glycoprotein substrate potential, were also measured to assess safety and bioavailability. The visualization of membrane permeability and brain access to compounds was performed using a graphical model from SwissADME to aid in compound prioritization. Any molecule that violated more than one of the larger rules was eliminated, leaving a set of high-quality candidates with desirable ADME properties, which were then subjected to molecular Docking and further validation through FSGS-associated protein targets.

Molecular Docking and virtual screening

The molecular docking technique was carried out with the help of the program PyRx (AutoDock Vina) to assess the binding affinities of the selected drug-like compounds to the known FSGS-related target proteins (TGFB1, SAMPDLB3, and TEK) involved in disease-related signaling and vascular regulation. Favorable drug-like properties were used to select a set of prioritized ligands (CID5161, CID5311, CID5578, CID754, CID2342, CID4788, CID13730, CID6432465, and CID_91886385) and to set up ligand structures in Open Babel, which is an embedded functionality of PyRx. The docking simulations were conducted by characterizing grid boxes covering the predicted active sites in each protein, with the ligand allowed to of flexible. Binding affinities and interaction profiles were determined using AutoDock Vina scoring, which is used to bring about stable protein-ligand complexes due to the presence of hydrogen bond interactions, as well as hydrophobic interactions. All in all, the docking findings have revealed several compounds with suitable binding energies and the potential to serve as lead candidates for further experimentation in FSGS drug discovery applications[11].

Prediction of Drug-like properties

There was an evaluation of physicochemical properties, drug-likeness, and toxicity potential of the highest-ranked compounds using the SwissADME online platform[12]. (The drug-like properties were evaluated using the main parameters, such as molecular weight (MW < 500 Da), the hydrogen bond donors (HBD ≤ 5), hydrogen bond acceptors (HBA ≤ 10), and lipophilicity (logP ≤ 5). Further, Molsoft was used of compare compounds with drug-like properties to those without. Potential toxicity was also analyzed using PAINS screening to identify toxicophoric substructures associated with adverse biological outcomes, including carcinogenicity and hepatotoxicity, thereby ensuring that safe and pharmacologically viable candidates are selected for follow-up[13].

RESULTS

Structural evaluation of target protein

The choice of possible therapeutic targets as potential treatment of Focal Segmental Glomerulosclerosis (FSGS) was based on the roles of SAMD9L3, TEK, and TGFB1 in the dysfunction of podocytes, instability of the endothelium, inflammation, and fibrotic remodeling of the glomerulus. SAMD9L3 has been involved in cellular stress responses and innate immunity, and recent data have shown an association between its differentiation and podocyte impairment, as well as inflammation typical of FSGS. TEK (Tie2), an endothelial receptor that plays a crucial role in angiogenesis and glomerular capillary stability, contributes to proteinuria and renal fibrosis when its signalling is disrupted. TGFβ1 is a key mediator of renal fibrosis and stimulates the accumulation of extra cells, mesenchymal cell growth, and calcium-dependent cell-to-mesenchymal conversion in podocytes, and is commonly expressed in FSGS patients. Whenever possible, three-dimensional structures of these proteins were obtained from the Protein Data Bank and predicted by SWISS-MODEL and AlphaFold. The optimal, energy-minimized structures were identified and evaluated using Ramachandran plot analysis to explore essential functional domains that could serve as potential binding sites, which were then used as stable targets to enable molecular Docking and identify inhibitors that would reduce the progression of FSGS.

Molecular Docking Analysis

Molecular Docking is a popular method of computer modelling used to predict the binding orientation and affinity of small molecules to a target protein, and this technique can help in structure-based drug design. The procedure approximates the free energy of binding by measuring key interaction forces, including hydrogen bonding, electrostatics, van der Waals interactions, desolvation effects, and torsional energy. Due to its effectiveness in identifying potential lead products, molecular Docking is widely used in drug discovery, and both natural and drug-like products are increasingly considered as drug targets[14]. In this study, molecular Docking was employed to assess the binding energies of selected drug-like molecules with target proteins to identify promising inhibitors for further drug development. The top 3 Residues Docking of drug-like compounds with SAMD9L3 are shown in **Table I**. The top three docking results of drug-like compounds with TGFBD1 are shown in **Table II**; the top three docking results of drug-like compounds with TEK are shown in **Table III**, and the top three drug-like compounds with 3 target proteins are revealed in **Table IV**.

Table I: Top 3 Residues Docking of drug-like compound with SAMD9L3

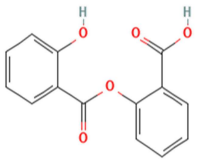
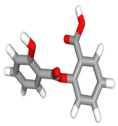
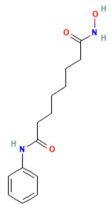
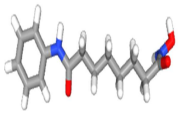
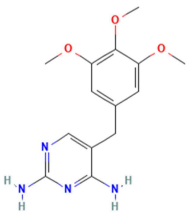
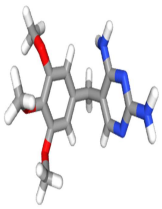
Drug-like Compounds Name	PubChem ID	2D structure	3D structure	Binding Energy	Residues Interacting
Salsalate	5161			-7.6	THR: B330 ASN: B331 ARG: B296 THR:294 LEU: B258
Vorinostat	5311			-7.7	LEU: A435 LEU: A313 ILE: A299
Trimethoprim	5578			-7.5	LEU: A233 GLU: A234 GLN: A241 SER: A240 TYR: A282

Table II: Top Three Dockings of drug-like compounds with TGFBD1

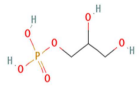
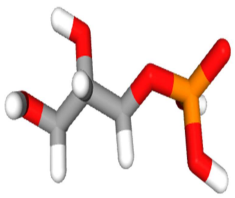
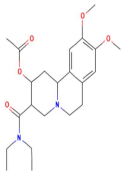
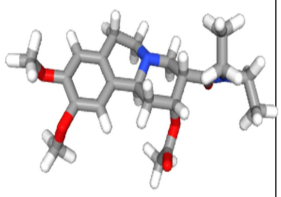
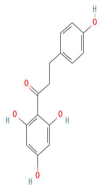
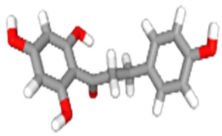
Drug-like Compounds Name	PubChem ID	2D structure	3D structure	Binding Energy	Residues Interacting
Glycerophosphoric	754			-5.1	GLY: B295 PRO: 296 1LE: A7 LEU: B294
Benziquenamide	2342			-6.9	PRO: A336 GLU: A333 PRO: A334 LEU: A335
phloriten	4788			-6.8	LYS: B15 LEU: B11 ALA: B324

Table III: Top Three Docking of drug-like compounds with TEK

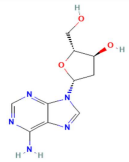
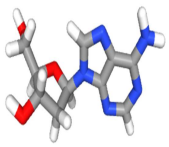
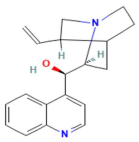
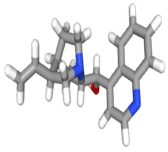
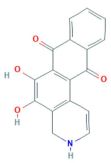
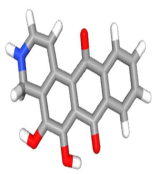
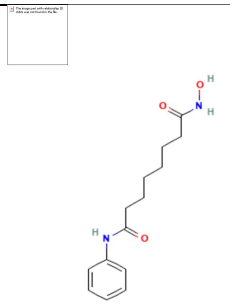
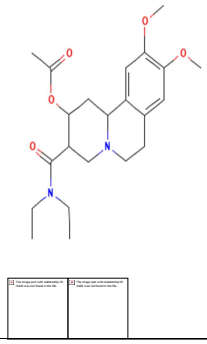
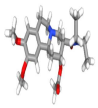
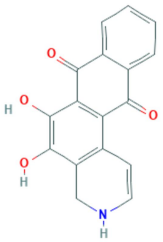
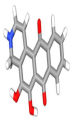
Drug-like Compounds Name	PubChem ID	2D structure	3D structure	Binding Energy	Residues interacting
2'-Deoxyadenosine	13730			-5.7	VAL: A14 ALA: A16 LEU: A19
(8alpha,9R)-Cinchonan-9-ol	6432465			-6.0	GLN: A67 ARG: A40 LEU: A51 ARG: A63
5,6-Dihydroxy-3,4-dihydronaphtho[2,3-f]isoquinoline-7,12-dione	91886385			-6.3	ASP: A82 THR: A86 VAL: A83

Table IV: Top 3 drug-like compounds with 3 target proteins

Drug-like Compounds Name	PubChem ID	2D structure	3D structure	Binding Energy	Residues interacting
Vorinostat	5311			-7.7	ILE: A299 LEU: A313 LEU: A435
Benzquinamide	2342			-6.9	PRO: A336 PRO: A334 GLU: A333
5,6-Dihydroxy-3,4-dihydronaptho[2,3-f]isoquinoline-7,12-dione	91886385			-6.3	ASP: A82 THR: A86 VAL:A83

Drug-like properties of Top Compounds

The compound is predicted with reference to the drug-like character with the help of a rule set which is applied to the structure to determine the drug-likeness. Drug-likeness regulations comprise a set of rules governing the structural characteristics of substances. These are used of rapidly approximate drug-like molecule characteristics. The SwissADME software was also used further to assess the drug-like properties of the target compounds. Docking analysis has been performed to identify how target proteins interact with drug-like compounds, providing statistical information on their binding affinities and possible molecular interactions[15].

DISCUSSION

Focal Segmental Glomerulosclerosis (FSGS) is a complex kidney disease of multifactorial aetiology, characterized by podocyte damage, endothelial dysfunction, inflammation, and advanced fibrosis[16]. The existing treatment modalities are not very effective, and innovative approaches that address multiple pathogenic mechanisms simultaneously are required. This paper employed a multi-target in silico screening of identify drug-like candidate molecules that interact with important proteins related to FSGS, namely SAMD9L3, TEK, and TGFB1, which have been reported to play key roles in disease pathogenesis[17].

TGFB1 is also considered a major mediator of renal fibrosis and glomerulosclerosis, as its excessive activity drives harmful mechanisms, including the accumulation of extracellular matrix and permanent glomerular damage[18]. The docked compounds were a good indication of binding interactions with TGFB1, with benzquinamide and phloridzin being notable, with stable interactions with key residues of the protein, suggesting their potential to inhibit fibrotic signaling[19].

TEK is an endothelial receptor tyrosine kinase that preserves the glomerular capillary integrity and vascular stability. Proteinuria and progression of chronic kidney disease are associated with dysregulation of TEK[20]. The analysis identified a range of compounds with moderate to high affinity for TEK, with 5,6-dihydroxy-3,4-dihydronaphtho-isoquinoline derivatives being the best candidates to influence TEK signaling, which might be useful for restoring endothelial activity and alleviating glomerular injury[21].

SAMD9L3, an immune regulation and cellular stress response factor, has shown promise as a target in FSGS, but its role is less well described than those of TGFB1 and TEK. The Docking of compounds such as vorinostat and salsalate indicated high binding affinities with SAMD9L3, with vorinostat exhibiting the best affinity and binding patterns across different targets, and it is reportedly a prospective lead molecule for multi-target therapeutic approaches[22,23].

The discussion justifies the use of polypharmacological methods of address the interrelated nature of FSGS pathophysiology, rather than conventional single-pathway therapies. Drugs that target several of the FSGS-related proteins have stronger therapeutic potential as they treat fibrosis, inflammation, and endothelial dysfunction[24].

Along with molecular Docking, drug-likeness and Pharmacokinetics also play a very important role during early drug discovery. The highest-ranking compounds met major drug-likeness criteria and exhibited good ADME properties. They lack PAINS warning signs and toxicophoric frameworks, which support their appropriateness for subsequent pharmacological development[25].

The research has identified some limitations, such as the inability of molecular Docking to represent protein flexibility or the dynamic environment in vivo, as it is static. Biological efficacy is not necessarily reflected in predictions of binding affinities. Hence, the results are encouraging but should be formulated of hypotheses awaiting confirmation through in vitro and in vivo testing to determine the clinical significance and safety of the identified compounds.

CONCLUSION

The combined computational approach used in the present research provided a methodical and effective framework of identifying potential therapeutic candidates in the case of Focal Segmental Glomerulosclerosis (FSGS). This method was an integrative approach comprising the retrieval and preparation of disease-relevant target proteins, virtual screening of drug-like compounds, ADME and toxicity profiling, and molecular Docking to analyze protein-ligand interactions at the molecular level. Stringent filtering has been applied using drug-likeness rules and pharmacokinetic parameters, which were suitable to select candidates of high quality with good safety and bioavailability attributes. Molecular Docking also helped to explain the binding affinities and stability of interactions of particular compounds with the most interesting FSGS-associated proteins, which proved to be potential leads for future development. In general, the approach will provide a powerful in silico pipeline that can reduce large chemical libraries to develop viable drug leads and provide a strong basis for further validating the leads in experimental/therapeutic development against FSGS.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Sehrish: Manuscript writing, Editing
Akram M: Study design, Concept, and Supervision
Aslam S: Manuscript editing, Data analysis
Ahmad B: Critical Review and Editing
Waryah YM: Critical Review and Supervision
Ujjan AH: Critical Review and Supervision

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