Bulletin of Pharmaceutical Research 2025;15(2):199
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)
DOI: 10.21276/bpr.2025.15.2.3

RESEARCH PAPER

COMPUTATIONAL REPURPOSING OF FDA-APPROVED DRUGS AS GPR119 AGONISTS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS: A HOMOLOGY MODELING AND MOLECULAR DOCKING APPROACH

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Received: Jan 11, 2025 / Revised: Aug 30, 2025 / Accepted: Aug 31, 2025

Type-2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, beta-cell dysfunction, and hyperglycemia. G-protein-coupled receptor 119 (GPR119) is a promising therapeutic target, as its activation enhances insulin secretion and maintains glucose homeostasis with minimal adverse effects. Drug repurposing, leveraging FDA-approved drugs for new therapeutic indications, offers a cost-effective and time-efficient strategy to accelerate the drug discovery process. A 3D structure of the GPR119 receptor was developed using homology modeling and validated using Ramachandran plot analysis, ERRAT scores, and MolProbity metrics. FDA-approved drugs from the DrugBank database were prepared with the LigPrep tool, and the receptor's binding site was predicted using SiteMap. Molecular docking simulations were performed with the Glide module in Schrödinger, utilizing HTVS, SP, and XP protocols to assess binding interactions and rank potential agonists. The validated GPR119 model revealed a well-defined binding pocket conducive to ligand interactions. Docking studies identified Leuprolide (DB00007), Goserelin (DB00014), and Desmopressin (DB00035) as top-performing compounds, with docking scores of -11.132, -10.554, and -9.783 kcal/mol, respectively. These drugs demonstrated strong receptor-ligand interactions, including hydrogen bonding with critical residues indicative of their potential to activate GPR119. This study highlights the effectiveness of drug repurposing and computational techniques in identifying FDA-approved drugs with high potential as GPR119 agonists. The identified compounds, originally approved for conditions such as hormone regulation, represent promising candidates for further optimization and experimental validation in the treatment of T2DM. These findings underscore the potential of repurposing existing drugs to address unmet needs in diabetes management.

Key words: Homology modeling, Virtual screening, GPR119, Molecular docking, Diabetes.

INTRODUCTION

T2DM is a multifaceted and progressive metabolic disorder characterized by chronic hyperglycemia, primarily resulting from a combination of insulin resistance, impaired glucose tolerance, and, often, inadequate insulin secretion. It is a global health concern, contributing significantly to morbidity and mortality and posing a substantial economic burden on healthcare systems. Beyond its

physiological impacts, T2DM profoundly affects patients' quality of life, increasing the risk of cardiovascular complications, nephropathy, neuropathy, and retinopathy. Current therapeutic strategies for T2DM are primarily focused on glycemic control through mechanisms such as enhancing insulin sensitivity, stimulating insulin secretion, and delaying carbohydrate absorption. However, these approaches often come with limitations, including the risk of hypoglycemia, gastrointestinal disturbances, weight gain, and progressive beta-cell dysfunction. These drawbacks underscore the need for novel and more effective therapeutic agents [1-3].

Recent advances in diabetes research have identified G-protein-coupled receptor 119 (GPR119) as a promising therapeutic target for T2DM. GPR119, predominantly expressed in pancreatic beta cells and enteroendocrine cells, plays a critical role in glucose homeostasis. Upon activation by an agonist, GPR119 engages the Gs signaling pathway, leading to increased intracellular cyclic adenosine monophosphate (cAMP) levels. This cascade enhances insulin secretion, promotes the release of incretin hormones such as GLP-1 and GIP, and improves glucose tolerance. Additionally, GPR119 agonists have demonstrated potential in delaying gastric emptying and reducing body weight, offering multifaceted benefits for T2DM management. These attributes make GPR119 an attractive target for developing antidiabetic therapies with a reduced risk of adverse effects.

Despite its therapeutic potential, the structural biology of GPR119 remains underexplored due to the absence of an experimentally resolved 3D structure in the Protein Data Bank (PDB). This gap necessitates the use of computational approaches such as homology modeling to predict the receptor structure. Homology modeling is a well-established method that generates a 3D structural model of a protein based on its sequence similarity to a known template structure. A validated structural model of GPR119 provides critical insights into its active site architecture, enabling the identification of key interactions between the receptor and potential agonists.

Complementary to homology modeling, molecular docking is a powerful tool for understanding receptor-ligand interactions. It predicts the binding affinity and interaction patterns of potential drug candidates, providing a structural basis for assessing their activity as GPR119 agonists. Virtual screening further accelerates this process by allowing the rapid evaluation of extensive compound libraries to identify promising candidates for drug development. Together, these computational techniques streamline the drug discovery process, offering cost-effective and efficient alternatives to traditional experimental approaches.

Drug repurposing, a strategy that identifies new therapeutic uses for existing FDA-approved drugs, has gained significant traction in the pharmaceutical industry. By leveraging the safety and pharmacokinetic profiles of existing drugs, repurposing reduces the time, cost, and risk associated with drug development. In the context of this study, drug repurposing was employed to screen FDA-approved drugs as potential GPR119 agonists. This approach not only aligns with the goal of accelerating antidiabetic drug discovery but also holds promise for uncovering novel therapeutic applications of known drugs, thereby addressing the unmet clinical needs of T2DM patients [4-5].

MATERIALS AND METHODS

Homology modeling

To address the absence of experimentally resolved 3D structures for the G-protein-coupled receptor 119 (GPR119) in public repositories such as the Protein Data Bank (PDB), homology modeling was employed to predict its 3D structure. This computational approach leverages sequence similarities between GPR119 and proteins with known structures to construct a reliable model. The amino acid sequence of GPR119 was retrieved from the National Center for Biotechnology Information (NCBI) database in FASTA format. The Swiss-Model server was used to generate the receptor 3D structure, utilizing homologous templates identified in the Swiss-Model Template Library (SMTL). Based on their high sequence identity and Global Model Quality Estimate (GMQE) scores, PDB structures were selected as templates (**Table 1**). The model construction involved transferring conserved atomic coordinates from the selected templates to the target sequence.

The generated models were rigorously validated using computational tools, including QMEAN scores, Ramachandran plot analysis, and Errat scores, to ensure high structural and stereochemical quality. Among the models evaluated, Model 1 was identified as the most reliable (**Table 2**) [6-9].

Table 1. PDB hits predicted by Swiss model

PDB ID	GMQE	QMEAND	METHOD
8vhf	0.84	0.83 ± 0.05	CryoEM
7xz6	0.83	0.81 ± 0.05	CryoEM
7wcm	0.82	0.81 ± 0.05	CryoEM
7wcn	0.82	0.80 ± 0.05	CryoEM
8zr5	0.81	0.81 ± 0.05	CryoEM

Table 2. Models Predicted by Swiss model webservers

Generated model	Ramachandran score	Errat	MolProbity score	Clash score
MODEL 1	**96.60 %**	**95.4545**	**1.03**	**0.42**
MODEL 2	97.65%	94.8630	0.72	0.42
MODEL 3	97.28%	90.2439	0.90	0.85
MODEL 4	94.56%	93.7063	0.95	0.21
MODEL 5	97.59%	89.0459	0.90	1.07

To enhance the accuracy and utility of the initial GPR119 model for applications such as molecular docking, structural refinement was carried out using GalaxyWEB, a computational server designed for protein structure optimization. The refinement process involved reducing steric clashes, improving hydrogen bonding patterns, and optimizing side-chain orientations. Among the analyzed protein models, MODEL 4 was identified as the most reliable due to its optimal balance of structural similarity and stereochemical quality. MODEL 4 achieved a high GDT-HA score of 0.9840, reflecting excellent alignment with the reference structure, and an RMSD value of 0.302, indicating minimal atomic positional deviations. Furthermore, it recorded the lowest MolProbity score (1.334), which evaluates overall model quality by considering steric clashes, rotamer accuracy, and backbone geometry (**Table 3**).

Table 3. Refinement of best protein model

Model	GDT-HA	RMSD	MolProbity	Clash score	Poor rotamers	Rama favored
Initial	1.0000	0.000	1.639	4.1	2.0	96.6
MODEL 1	0.9814	0.299	1.482	9.0	0.4	99.0
MODEL 2	0.9755	0.330	1.393	7.2	0.4	99.3
MODEL 3	0.9899	0.286	1.445	8.2	0.0	99.0
MODEL 4	**0.9840**	**0.302**	**1.334**	**6.1**	**0.0**	**99.0**
MODEL 5	0.9814	0.323	1.393	7.2	0.8	99.3

Additional validation metrics further supported the choice of MODEL 4. It exhibited the best clash score (6.1), indicating minimal atomic clashes, and no poor rotamers (0.0%), confirming optimal side-chain conformations. Moreover, 99.0% of its residues were located within the favored regions of the Ramachandran plot, affirming excellent backbone geometry. While other models, such as MODEL 2, performed marginally better in individual metrics like Ramachandran favored regions (99.3%), MODEL 4 provided the most consistent and reliable structure across multiple quality parameters [7].

The refined and validated MODEL 4 was subsequently employed in molecular docking studies to explore ligand-binding interactions with GPR119. This high-fidelity model serves as a foundational resource for advancing the understanding of GPR119 structural and functional properties, as well as for the rational design of antidiabetic drug candidates targeting this receptor. By leveraging computational tools and rigorous validation protocols, this study successfully developed a structurally accurate homology model of GPR119 (**Figure 1**) paving the way for innovative therapeutic strategies in diabetes management [10-12].

Molecular docking

Molecular docking was employed to investigate ligand-receptor interactions and identify potential agonists for GPR119. The refined 3D structure of GPR119, developed through homology modeling and validated using robust quality metrics, served as the receptor model for

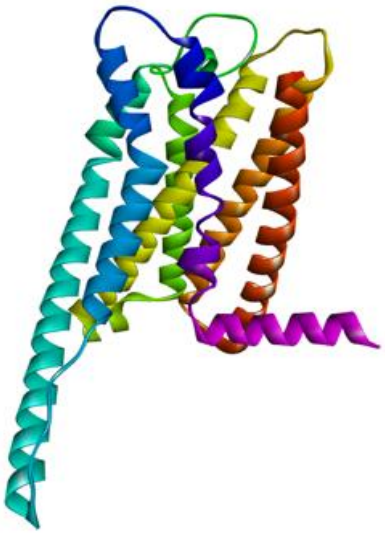

Fig. 1. Schematic representation of Best refined model by GalaxyWEB

docking studies. FDA-approved drugs were exclusively selected from the DrugBank database, ensuring a focus on compounds with established safety and pharmacokinetic profiles, aligning with the objectives of drug repurposing. Ligand preparation was carried out using Schrödinger LigPrep tool, which generated 3D structures, optimized geometries, and assigned appropriate ionization states at physiological pH (7.4).

Since the binding site of GPR119 is not experimentally characterized, SiteMap was utilized to predict potential ligand-binding pockets. The receptor surface was analyzed for critical features, including hydrophobicity, hydrogen bond donor/acceptor sites, pocket depth, and volume. Multiple SiteMap analyses were performed, and the binding pocket with the highest draggability score was selected for further studies. A receptor grid was generated using the OPLS_2005 force field, with the predicted binding site serving as the grid centre for docking simulations.

Docking simulations were conducted using the Glide module in Schrödinger Maestro v13.5, employing three levels of precision: HTVS (High-Throughput Virtual Screening) for initial ligand screening, SP (Standard Precision) for a balance of speed and accuracy, and XP (Extra Precision) for detailed interaction analysis. The XP docking protocol provided the most reliable results, allowing for an in-depth evaluation of ligand-receptor interactions. Docking scores were calculated, and the top-performing ligands were analyzed for their binding affinities and interaction patterns, with particular attention to critical residues which play a key role in GPR119 activation.

The docking poses and receptor-ligand interactions were visualized (**Figure 2, 3**) using Schrödinger Maestro. Detailed analyses of the interaction patterns revealed key binding features, including hydrogen bonds that contribute to ligand affinity and specificity. This workflow, integrating receptor modeling, ligand preparation, binding site prediction, and docking simulations, offers a robust and systematic approach to identifying FDA-approved drugs as potential GPR119 agonists. The study highlights the utility of computational methods in rational drug design, paving the way for repurposing existing drugs for the treatment of Type 2 Diabetes Mellitus [8-21].

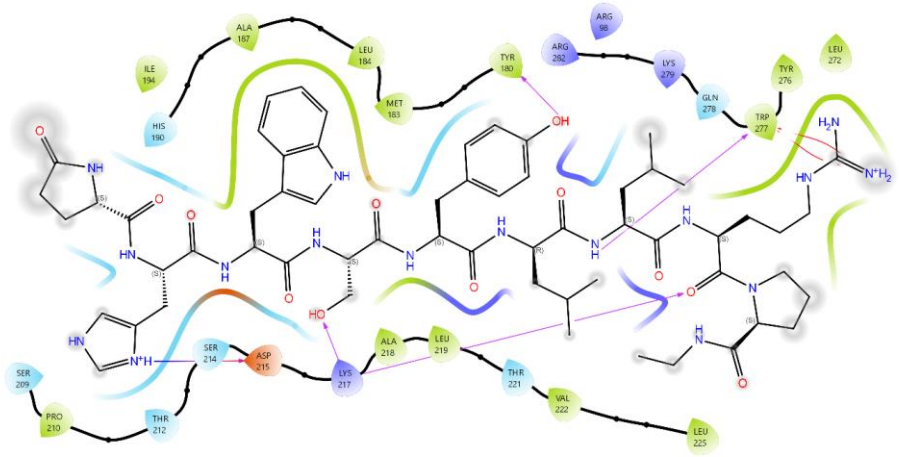

Fig. 2. 2D-drug receptor interaction of top ranked compound (Leuprolide)

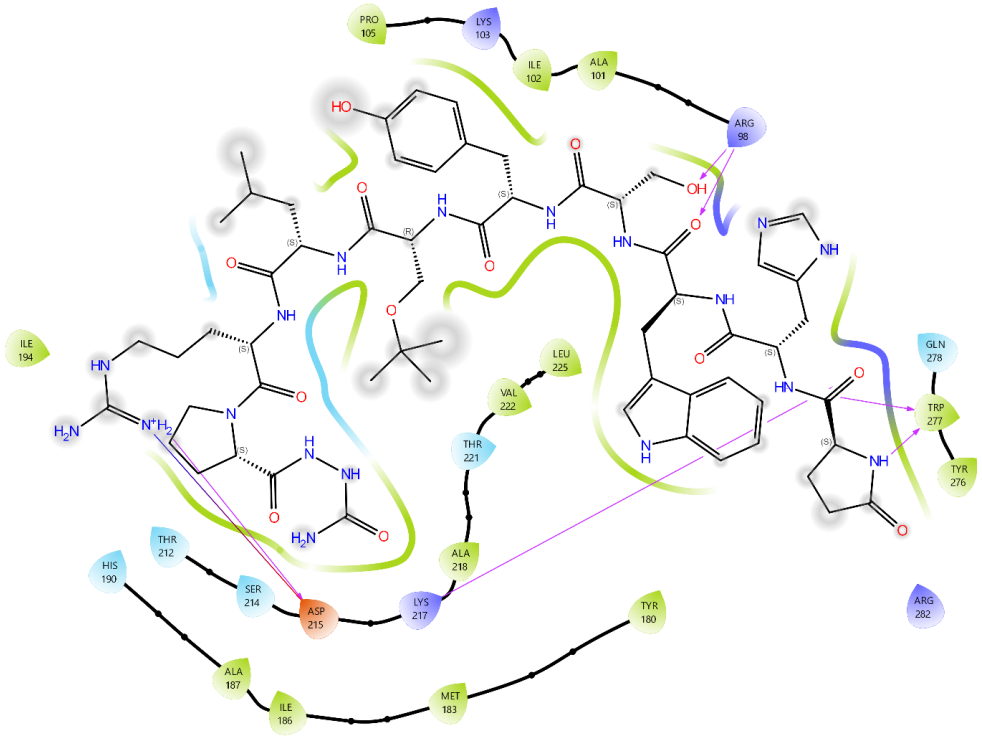

Fig. 3. 2D-drug receptor interaction of top ranked compound (Goserelin)

RESULTS AND DISCUSSION

Homology modeling and validation

The absence of a resolved 3D structure for GPR119 necessitated the use of homology modeling, a computational approach that predicts a protein 3D structure based on known templates. Using the Swiss-Model server, the amino acid sequence of GPR119 was modelled, leveraging sequence similarities with structural templates from the PDB. Among the five generated models, MODEL 1 was identified as the most reliable. It achieved a Ramachandran favored score an Errat score (**Table 2**) reflecting a high level of geometric and stereochemical accuracy.

Refinement of the best model

To further enhance the quality of MODEL.4, it underwent refinement using the GalaxyWEB server, which optimized hydrogen bonding, side-chain orientations, and steric interactions. Post-refinement analysis showed improvements in key metrics, reinforcing the model suitability for downstream applications. MODEL.4 GDT-HA score of 0.9840 and RMSD of 0.302 demonstrate its close alignment with the reference structure and minimal atomic deviations. These characteristics establish MODEL 4 as the best candidate for studying protein-ligand interactions.

Insights from validation metrics

Validation of MODEL 4 using comparative metrics against other generated models highlighted its superior quality. While some models, such as MODEL 2, excelled in specific parameters like Ramachandran favored regions (99.3%), MODEL 4 provided a more holistic blend of high-quality features, including minimal steric clashes and optimal backbone geometry. The data is summarized in **Table 4**, where MODEL 4 consistently performs well across all parameters.

By providing a high-fidelity model of GPR119, this work lays the foundation for detailed molecular docking studies, which can elucidate the binding modes of FDA-approved drug molecules and novel ligands. The integration of advanced computational methodologies enhances the accuracy and applicability of these findings, contributing to the broader field of diabetes drug discovery.

The docking results reveal that Leuprolide (DrugBank ID: DB00007), Goserelin (DrugBank ID: DB00014), and Desmopressin (DrugBank ID: DB00035) exhibit robust binding affinities with docking scores of -11.1323, -10.5548, and -8.4924 kcal/mol, respectively.

These scores indicate strong receptor-ligand interactions, suggesting their potential as repurposed GPR119 agonists. Leuprolide and

Table 4. Top-scoring FDA-approved compounds and their docking metrics

S. No.	Compound name	DrugBank ID	Docking score (Kcal/mol)
1	Leuprolide	DB00007	-11.1323
2	Goserelin	DB00014	-10.5548
3	Desmopressin	DB00035	-8.4924
4	Pentagastin	DB00183	-8.36163
5	Dotatate	DB14554	-8.1163
6	Histrelin	DB06788	-8.03948
7	Indium In-111 pentetreotide	DB11835	-7.85251
8	Gonadorelin	DB00644	-7.84958
9	Gallium Ga-68 gozetotide	DB16019	-7.83196
10	Kaolin	DB01575	-7.78942
11	Sincalide	DB09142	-7.68973
12	Buserelin	DB06719	-7.617
13	Lypressin	DB14642	-7.54376
14	Caspofungin	DB00520	-7.4271
15	Sacubitril	DB09292	-7.285

Goserelin, traditionally used as gonadotropin-releasing hormone agonists for treating hormone-sensitive cancers and reproductive disorders, might exert beneficial effects on glucose homeostasis by activating GPR119. Similarly, desmopressin, a synthetic analog of vasopressin used in diabetes insipidus and bleeding disorders, could also leverage GPR119-mediated pathways to improve insulin secretion and glycemic control. The promising docking outcomes underscore the potential of these FDA-approved drugs to modulate GPR119 activity, offering a cost-effective approach to diabetes management while expanding their therapeutic repertoire.

Future implications

Future research could involve *in vitro* and *in vivo* validation of the top-ranking compounds to confirm their agonistic activity on GPR119 and their therapeutic efficacy in clinical settings. Experimental validation using techniques such as molecular dynamics simulations (MDS) to assess the stability of receptor-ligand complexes, surface plasmon resonance (SPR) for binding kinetics, cellular assays for functional activity, and animal models for metabolic effects will be essential to bridge the gap between computational predictions and actual biological outcomes.

CONCLUSION

This study successfully employed homology modeling and molecular docking to explore the potential of FDA-approved drugs as GPR119 agonists, providing a promising avenue for the treatment of T2DM. Docking studies identified several FDA-approved drugs, including Leuprolide, Goserelin, and Desmopressin, as top-ranking candidates with robust binding affinities and strong receptor-ligand interactions. Leuprolide, with the highest docking score of -11.1323 kcal/mol, and Goserelin, with -10.5548 kcal/mol, displayed interactions indicative of their potential to modulate GPR119 activity. Desmopressin, known for its use in diabetes insipidus, also showed promising docking scores, suggesting a potential role in enhancing glucose homeostasis. These findings emphasize the feasibility of drug repurposing to accelerate therapeutic development, minimizing the time and cost associated with *de novo* drug design.

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