The European Journal of Biomedical and Life Sciences 2025, No 3
ISSN 2310-5674

PREMIER Publishing
ppublishing.org

Section 3. Pharmacertic sciences

DOI:10.29013/EJBLS-25-3-30-45

COMPUTATIONAL IDENTIFICATION OF GPR119-TARGETED SMALL MOLECULES AS POTENTIAL THERAPIES FOR DIABETES MELLITUS

Alison Wang [1]

[1] Faculty of Arts and Sciences, Queens University

Cite: *Alison Wang. (2025). Computational Identification of Gpr119-Targeted Small Molecules as Potential Therapies For Diabetes Mellitus. The European Journal of Biomedical and Life Sciences 2025, No. 3.* https://doi.org/10.29013/EJBLS-25-3-30-45

Abstract

Type 2 diabetes mellitus (T2DM) is a global epidemic, accounting for over 90% of diabetes mellitus cases worldwide, in part due to inadequate treatment options. GPR119 is a protein receptor that stimulates insulin excretion and has the potential to revolutionise current T2DM care. In this study, we used computational methods to search for promising GPR119 agonists. Firstly, a test for binding sites in GPR119 was done using geometric, energetic-based, and machine-learning methods. Secondly, a pharmacophore map was generated and used to scan for potential small molecule agonists. Next, a molecular docking method was used to test the energetic favourability of selected molecules. The top compounds of this test then underwent virtual screening to determine their ADME profiles, and were then tested for toxicity. This study identified Z1275113833 to be the most promising candidate based on the above tests, warranting further exploration into its capabilities as a new GPR119-based treatment for T2DM. In addition, more computational tests to search for more potential agonists could be done.

Keywords: *Virtual Screening, Pharmacophore, Diabetes Mellitus, Molecular Docking*

1. Introduction

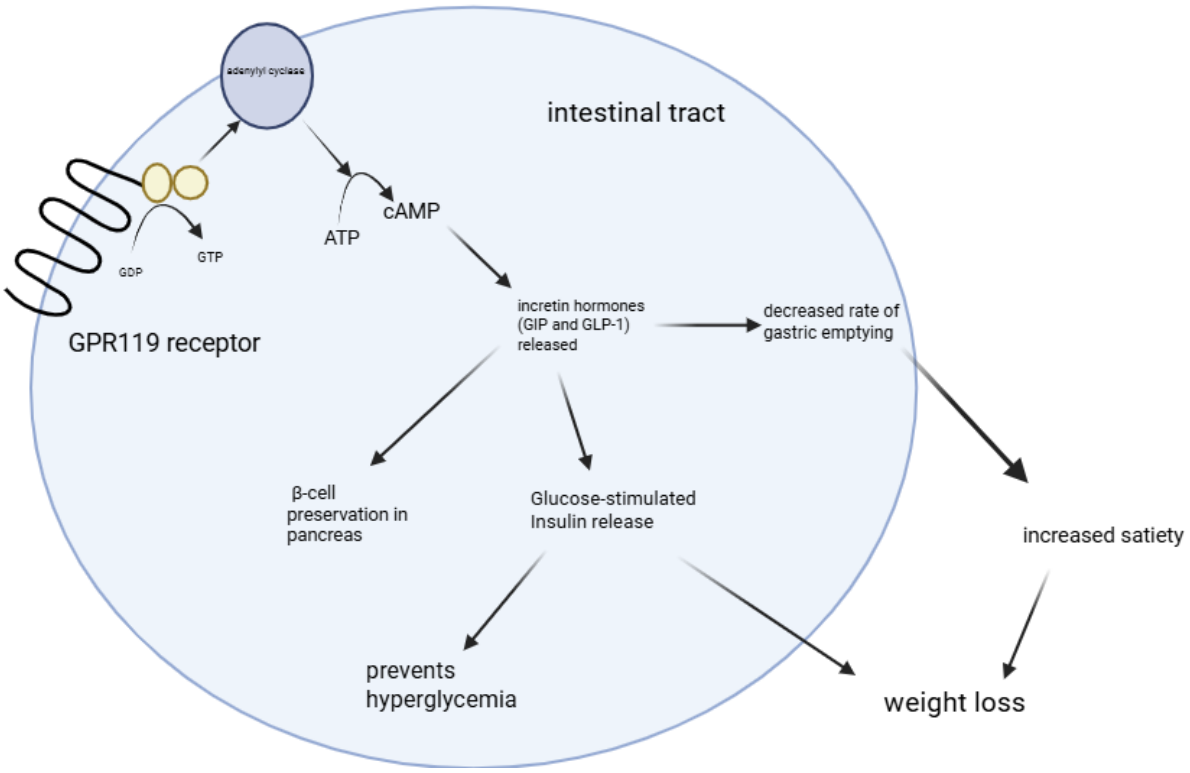
Diabetes mellitus (DM) is a chronic disease primarily characterised by sustained hyperglycemia (Petersmann et al., 2019). It currently affects over 589 million adults (aged 20–79), and is projected to affect over 852.5 million adults worldwide by 2050, over 90% of which are estimated to be type 2 diabetes mellitus (T2DM) (Diabetes Atlas, 2025). T2DM is characterised by increased insulin resistance, resulting in abnormal glucose metabolism and lack of insulin secretion. Especially concerning is the rise of early-onset T2DM (< 40 years), which obesity and genetics are the main risk factors of (Magliano et al., 2020; Ruze et al., 2023), which causes more severe complications and higher rates of β-cell deterioration (Magliano et al., 2020; Strati et al., 2024). Diabetes can lead to blindness, kidney failure, and nerve damage (Młynarska et al., 2025). Furthermore, an esti-

mated 3.4 billion deaths worldwide arose due to DM in the past year (Diabetes Atlas, 2025).

Current medications for T2DM can be categorised into 10 classes: 1) Biguanides, 2) Glucagon-like peptide 1 (GLP-1) and dual GLP-1 and gastric inhibitory peptide (GIP) receptor agonists, 3) Dipeptidyl peptidase 4 (DPP-4) inhibitors, 4) Sodium-glucose cotransporter 2 (SGLT2) inhibitors, 5) Sulfonylureas, 6) Thiazolidinediones (TZDs), 7) Alpha glucosidase inhibitors, 8) Meglitinides, 9) Dopamine-2 agonists, 10) Bile acid sequestrants (Feingold, 2000; Ganesan et al., 2025). The most commonly administered drug is Metformin, which inhibits synthesis of glucose in the liver (Apostolova et al., 2020) and has marginal weight loss capabilities (Yerevanian & Soukas, 2019). Medication can be administered both orally and via injection, with oral administration being preferred (Manaithiya et al., 2021).

No orally administered drug has the capability to both improve glucose tolerance and induce weight loss (Manaithiya et al., 2021; Zhao et al., 2021). One of the leading causes of T2DM is obesity (Ruze et al., 2023), so drugs that target both blood sugar levels and induce weight loss would revolutionise current T2DM care (Manaithiya et al., 2021; Zhao et al., 2021). Therefore, new treatment options that can achieve all three are desirable. In addition, despite the large number of different available medications, the proportion of T2DM patients achieving glycated hemoglobin A1C targets have remained relatively unchanged or decreased across both the US and Canada (Carls et al., 2017; Leiter et al., 2019). A 2021 multinational survey looking into what percentage of T2DM patients were meeting the glycated hemoglobin A1C goals found that only about 39.1% of patients were on target, suggesting that current T2DM treatment options are inadequate (Lautsch et al., 2022).

Figure 1.1 *Signalling pathway of GPR119 illustrating the overall effects and benefits for T2DM patients. (Zhao et al., 2021). This figure was made using Biorender*



GPR119 is a G-coupled protein receptor (GCPR) that primarily works to stimulate the release of incretin hormones, controlling glucose-stimulated insulin secretion (GSIS) (Manaithiya et al., 2021). Primarily expressed in the pancreas, fetal liver, and in certain intestinal tract tissues (Chu et al., 2007; Manaithiya et al., 2021; Soga et al., 2005), GPR119 causes GSIS through two mechanisms: secretion of GIP and GLP-1

(Panaro et al., 2017), and promotion of it in β-cells in the pancreas (Zhao et al., 2021). Both GLP-1 and GIP are anti-hyperglycemic agents, and decrease the rate of gastric emptying, lowering appetite (Zander et al., 2002).

GPR119 aids T2DM patients by stimulating GSIS, which can help them maintain blood glucose levels after meals (Manaithiya et al., 2021). There are several benefits of a potential GPR119 based treatment above currently available medications for T2DM patients (Nema et al., 2024). Firstly, it has demonstrated the potential to impede β-cell deterioration in the Islets of Langerhans (Kim et al., 2021; Zhao et al., 2021). Secondly, it has both strong anti-hyperglycemic and noticeable weight loss effects (Overton et al., 2008). Studies have found that when GPR119 agonists are used in conjunction with a DPP-4 inhibitor, which prevents the breakdown of GLP-1 and GIP, the issue of rapid degradation of incretin hormones can be addressed, increasing the usefulness of potential drugs (Ansarullah et al., 2013; Hryciw et al., 2024).

GPR119 has a number of endogenous lipid-based ligands such as oleoylethanolamide (OEA) (Ning et al., 2008) and lysophosphatidylcholine (LPC) (Drzazga et al., 2014). Many synthetic agents have been developed, which have demonstrated varying efficacies when studied as potential T2DM treatments (Kim et al., 2021; Manaithiya et al., 2021). No potential agonists have reached past phase II clinical trial stage, most having been cancelled due to a lack of effective hyperglycemic control (Hu et al., 2024). AR231453 was the first synthetic agent created, showing mixed results when given orally to wild type, GLP-1 receptor knockout, and GIP receptor knockout mice (Flock et al., 2011; Hu et al., 2024). However, no further study into it is currently being conducted. Another promising agent, DS-8500a, showed a higher degree of efficacy, however, study into it was also cancelled (Hryciw et al., 2024). Successive synthetic agents have shown only modest capabilities to reduce hyperglycemia in T2DM patients (Hu et al., 2024; Flock et al., 2011). There are no currently available T2DM treatments involving GPR119 agonists (Hryciw et al., 2024; Hu et al., 2024), warranting further study.

2. Methodology

2.1. Determining amount and viability of binding sites on GPR119

2.1.1. Geometric based virtual screening to determine number and suitability of binding sites using DoGSiteScorer

To determine the number of binding sites capable of supporting small molecule agonists, the DoGSiteScorer was used, accessed at: https://proteins.plus/. First, the structure of GPR119 was determined using the Protein Data Bank (PDB) (PDB code 7XZ5). On the Proteins Plus website, the PDB code was entered. Next, the DoGSiteScorer tool was selected. Maintaining the default selections. The website then used the Difference of Gaussian (DoG) method to calculate results and produced the number of binding sites, their sizes, their surface areas, and assigned them a score in terms of viability.

2.1.2. Energetic-based method to determine number and viability of binding sites using FT site

To determine the number of binding sites energetically capable of binding to small molecule agonists, the FT site was used, accessed at: https://ftsite.bu.edu/. The PDB ID, 7XZ5, was entered into the appropriate field. FT site used empirical free energy functions to find energetically favourable binding sites around the protein target. Next, consensus clusters found from multiple iterations of the previous step were ranked in terms of total interactions and probes. FT site generated a.PSE file, which was read using PyMO L.

2.1.3. Machine learning based method to assess number and viability of binding sites using Prankweb

A machine learning algorithm, Prankweb, was further used to determine the number and viability of binding sites for small molecule agonists, accessed at: https://prankweb.cz/. The input method was selected as 'Experimental Structure,' then the PDB code, 7XZ5, was entered. Both 'Use original structure' and 'use conservation' were selected. Prankweb generated a model of GPR119, a list of binding sites, the average number of residues, and gave each a score.

2.2. Virtual screening for small molecule agonists using a pharmacophore map generated by Pharmit and using the Enamine chemical library

2.2.1. Generating a pharmacophore map of GPR119

To generate a pharmacophore map, Pharmit (accessed at: https://pharmit.csb.pitt.edu/) was used. The PDB code of GPR119, 7XZ5, was entered into the appropriate box. LSC was selected from the drop-down menu. Binding site waters were ignored.

2.2.2. Scanning the Enamine database to determine potential small molecule agonists

Six binding sites were removed. Enamine was selected as the chemical library for all three trials. Data on the top five molecules that Pharmit identified as the best matches for the pharmacophore was then extracted. The process of was repeated with six different binding interactions being removed. It was repeated two more times, each with another six binding interactions removed, and the top five compounds from each trial were kept. The binding interactions analysed for the three trials are compared in Table 3.2.2. Some initial tests were done to show that the arrangement for the third trial yielded lower RMSD values than other arrangements before it was chosen. Pharmit then compared the pharmacophore map of interactions with binding sites on chemicals in the database and ranked them by their root mean squared deviation.

2.3. Virtual screening of free energy of binding interactions of identified potential agonists via molecular docking using Swissdock

In order to ascertain the free energy of the binding interactions between potential agonists and GPR119, Swissdock (accessed at: https://swissdock.ch/) was used. The SMILES for each ligand were obtained from the MCULE database (accessed at: https://mcule.com/) and inputted into the appropriate box. Next, the PDB code for GPR119, 7XZ5, was inputted. The R-Glucose-dependent insulinotropic receptor chain was selected, and 'none' was selected for heteroatoms. Then the parameters for the box were set as follows: box centre (98 Å, 118 Å, 94 Å), box size (45 Å, 44 Å, 67Å) for each. Swissdock estimated the energy of interactions between the ligand and GPR119 to determine favourable binding sites.

2.4. Screening to determine ADME profile of top five molecules using SwissADME

Using the top five compounds identified by Swissdock, the ADME profiles of selected molecules were obtained using SwissADME (accessed at: http://www.swissadme.ch/). The SMILES for each ligand obtained in 2.3. were input into the text box. SwissADME outputted a number of parameters, of which a selection were selected to test for Lipinski's rules, GI permeability, and BBB permeability.

2.5. Virtual toxicological screening of top compounds using ProTox-3.0

Next, the SMILES of the top compounds were entered into ProTox-3.0 (accessed at: https://tox.charite.de/protox3/index.php?site=home#). When prompted to choose what kinds of toxicity to test for, 'All' was chosen. ProTox-3.0 identified which areas the compounds sleceted were active toxins towards and calculated how their toxicity measured up against current FDA-approved drugs in each category. The top two compounds identified from the proceeding tests were tested.

3.Results and Discussion

3.1. Determining amount and viability of binding sites on GPR119

3.1.1. Geometric based virtual screening to determine number and suitability of binding sites using DoGSiteScorer

Figure 3.1.1. *Geometric-based binding site screening done by Proteins Plus using the 3D shape of GPR119 (PDB code 7XZ5). The various binding sites are depicted by coloured highlights over the structure of the protein receptor*

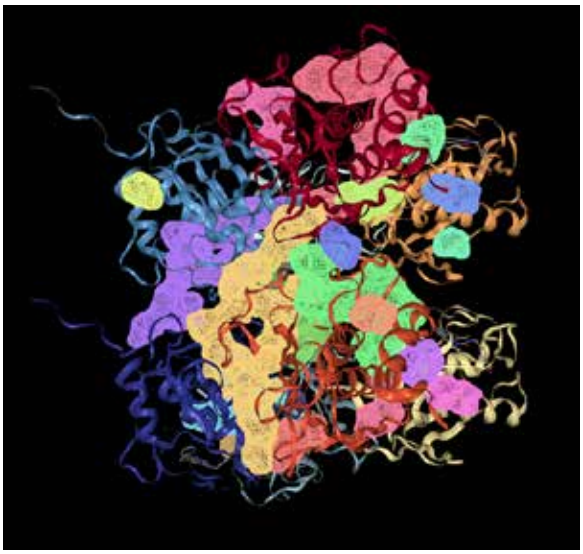


Table 3.1.1. *Pocket name, colour of highlight shown in Figure 3.1.1. above, volume, surface area, and drug score of the various pockets discovered on GPR119 that had a Drug score above 0.5 (PDB code 7XZ5) by DoGSiteScorer*

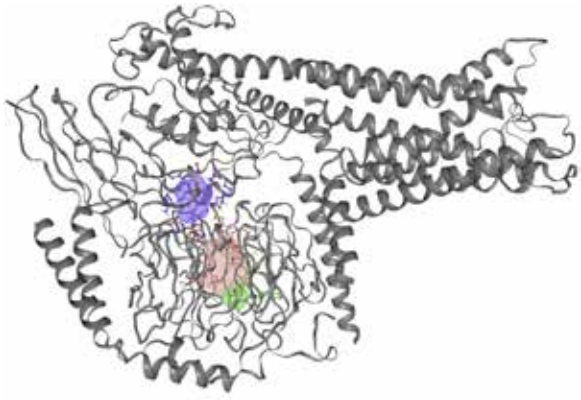
Binding Site Name	P_3	P_1	P_2	P_0	P_5	P_4	P_6	P_8	P_7	P_11
Colour	Orange	Dark Purple	Dark Green	Yellow	Lime Green	Blue	Magenta	Orange	Blue-Green	Pink
Volume (Å^3)	769.5	983.01	936.11	1082.97	581.08	732.06	577.17	331.17	370.66	212.69
Surface Area (Å^2)	670.8	931.51	1240.59	1616.21	828.58	889.3	890.35	499.33	640.19	483.3
Drug Score	0.84	0.82	0.82	0.79	0.79	0.78	0.75	0.73	0.73	0.61

A total of 25 ligand binding sites were identified by Proteins Plus, ranging in size from 1616.21Å2 to 71.48Å2. There were ten different binding sites with drug scores above 0.50, indicating that GPR119 has a relatively large number of binding sites defined as 'druggable' by DoGSiteScorer. The highest drug score identified was 0.84, with seven of the ten druggable binding sites having scores above 0.75. This method is incomplete, as it does not account for energetic barriers to ligand binding, likely overinflating the number of viable binding sites discovered.

3.1.2 Energetic-based method to determine number and viability of binding sites using FT site

FT site identified 3 different ligand binding sites shown below as orange, green, and blue highlights. FT site did not provide precise data on how druggable each of the binding sites were, but ranked them from most druggable to least. There were less binding sites discovered by FT site, DoGSiteScorer having found ten. Site one, shown in orange, was the most druggable, and site three, shown as purple, was the least druggable. This result indicates ligand binding viability but does not provide information on the exact druggability of each. These results must be used in conjunction with further methods to corroborate and enhance the usefulness of results. (Brenke et al., 2009; Jones et al., 2022; Kozakov et al., 2015; Ngan et al., 2012).

Figure 3.1.2. *Energetic-based method for determining binding sites done by FT site and shown on the 3D structure of GPR119 (PDB code 7XZ5) in coloured highlights*



With both DoGSiteScorer and FT site having high accuracy, the discrepancy between how many binding sites each identified

is interesting. It is unclear whether or not the binding sites indicated by the FT site result are the same as those indicated by the DoGSiteScorer. Therefore, the two results cannot independently verify one another.

Table 3.1.2. *Binding sites on GPR119 (PDB code 7XZ5), where the colour of highlight portraying each site in the image generated by FT site's assessment of binding sites and druggability*

Binding Site	1	2	3
Colour	Orange	Green	Purple

3.1.3. Machine learning based method to assess number and viability of binding sites using Prankweb

Prankweb identified 19 different binding sites and assigned each a druggability score. The highest score given was 33.73, indicating an extremely high likelihood of being druggable given that a score above 2.0 is considered good. 8 different binding sites were indicated to have good scores by Prankweb, suggesting that GPR119 has a very high number of druggable binding sites. Prankweb detected a number in between that of DoGSiteScorer and FT site. However, the results given by Prankweb cannot be corroborated with either of the other two results given, meaning that it is unclear whether or not the sites identified by Prankweb are the same as those identified by FT site and DoGSiteScorer.

Figure 3.1.3. *Machine learning based analysis of binding sites of GPR119 (PDB code 7XZ5) discovered by Prankweb and shown through coloured highlights on the 3D structure. The residues in the different binding sites are shown through coloured highlights on the structure*

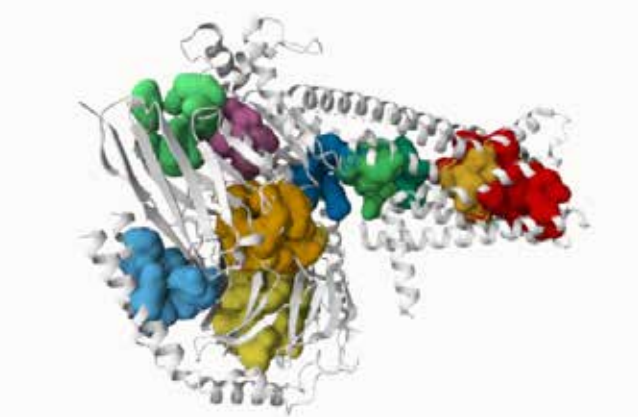


Table 3.1.3. *Binding sites of GPR119 (PDB code 7XZ5) discovered by Prankweb depicted by rank, score, number of residues, and average conservation*

Rank of binding site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Score	33.7	25.0	5.74	3.17	2.7	2.62	2.38	2.3	1.98	1.94	1.92	1.64	1.3	1.23	1.2	1.1	1.07	0.81	0.52
Number of residues	27	41	18	15	9	12	11	9	8	12	9	9	5	8	8	5	4	5	5
Average conservation	1.0	0.6	0.5	1.5	1.5	0.5	1.9	2.4	1.6	1.0	1.8	1.9	2.7	0.75	1.7	2.4	2.2	1.4	1.3

3.2. Virtual screening for small molecule agonists using a pharmacophore map generated by Pharmit and using the Enamine chemical library

3.2.1. Generating a pharmacophore map of GPR119 (PDB code 7XZ5) using Pharmit

A total of 10 different binding interactions were discovered by Pharmit: two hydrogen-acceptor interactions, one negative ion interaction, and seven hydrophobic interactions. GPR119 has a very high number of potential agonist binding sites, making it difficult to search for small molecule agonists that could interact with all of them. This necessitates for some to be removed before the selected chemical database is scanned.

Figure 3.2.1. *Pharmacophore map generated by Pharmit of GPR119 (PDB code 7XZ5) depicting the 10 binding interactions, with the specific type shown through colour. Red indicates a negative ion interaction, yellow depicts hydrogen accepting interactions, and green indicates hydrophobic interactions. One of the yellow interactions is layered underneath the red interaction*

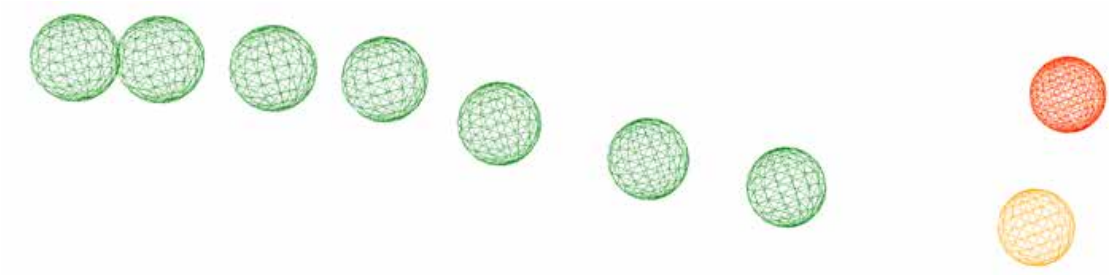


Table 3.2.1. *Types and number of binding interactions found for GPR119 (PDB code 7XZ5) by Pharmit, and the representative colour on the pharmacophore map shown above*

Type of interaction	Hydrogen accepting	Negative ion	Hydrophobic
Number of interactions found for GPR119	2	1	7
Representative colour	Yellow	Red	Green

3.2.2. Scanning the Enamine database to determine potential small molecule agonists

Table 3.2.2. *The four binding interactions used in the analysis of the pharmacophore map of GPR119 (PDB Code 7XZ5) for trial numbers 1, 2, and 3 described in Section 2.2. Red indicates a negative ion interaction, yellow depicts hydrogen accepting interactions, and green indicates hydrophobic interactions. There is a yellow interaction layered underneath the red one*

Trial number	1	2	3
Interactions used			

For the first trial, Pharmit identified 2621 088 different hits for this specific set of binding interactions on GPR 119 out of 60516 302 total conformations of 4177 328 molecules scanned. Among these, 7 had RMSD values below 0.02, indicating a large

number of promising potential agonists. Furthermore, 834 molecules had RMSD values below 0.1. The most promising molecule found had an RMSD value of 0.010, indicating a very close match with the pharmacophore map generated by Pharmit. The top five molecules identified, their structures, their size, and their RMSD values can be found in Table 3.2.2. The RMSD values ranged from 0.010 to 0.018, indicating that all five are candidates for potential agonists. In addition, there was a good variety of different binding interactions, which points to this result giving promising agonist candidates. Pharmacophore maps ideally contain at least one hydrophobic binding interaction and two hydrogen acceptors (Abdel-Rahman & Gabr, 2024). These results influenced the binding interactions chosen for each search for potential agonists. The interactions used are shown above in Table 3.2.2.

For the second trial, Pharmit identified 757283 hits of the Enamine inventory. The RMSD values were also higher for this arrangement, as the lowest value was 0.033. There was a lower level of variance in the RMSD values between these five compounds, ranging from 0.033 to 0.038, when compared with the values in 3.2.2., suggesting that they have relatively more equal chances of being agonists. There was also good variety in the binding interactions selected for this test.

For the third trial, a total of 1612 266 hits were identified by Pharmit. This is a promising result, as the RMSD value of the top five compounds are all relatively low, although on average they are slightly higher than those obtained in the first trial. The values are still indicative of an extremely high degree of overlap between the potential agonists and the pharmacophore obtained from GPR119. This trial only used one hydrogen accepting interaction and multiple more hydrophobic reactions, however, the RMSD values being so low suggests a high degree of interaction.

Table 3.2.3. *The top five most overlapping small molecule agonists found for GPR119 (PDB code 7XZ5) using four of the ten binding interactions identified by Pharmit, as well as the calculated RMSD value. The selected binding sites can be seen in Figure 3.2.2.*

Name	Z202499044	Z18360185	Z73747989	Z57728534	Z56891512
Structure					
RMSD Value	0.010	0.015	0.016	0.016	0.018

Table 3.2.4. *The top five most overlapping small molecule agonists found for GPR119 (PDB code 7XZ5) using four of the ten binding interactions identified by Pharmit, as well as the calculated RMSD value. The selected binding sites can be seen in Figure 3.2.3.*

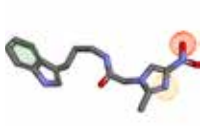
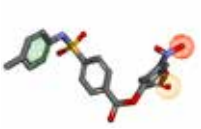
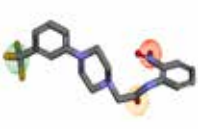
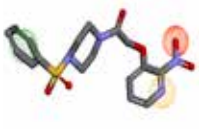
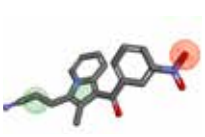
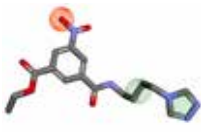
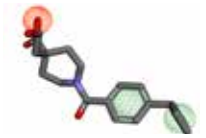
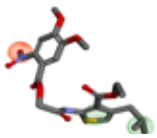
Name	Z1151811424	Z18338344	Z31000072	Z24778861	Z131263998
Structure					
RMSD Value	0.033	0.034	0.034	0.037	0.038

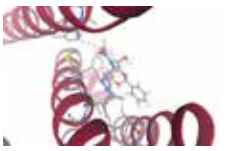
Table 3.2.5. *The top five most overlapping small molecule agonists found for GPR119 (PDB code 7XZ5) using four of the ten binding interactions identified by Pharmit, as well as the calculated RMSD value. The selected binding sites can be seen in Figure 3.2.3.*

Name	Z56781437	Z1275113833	Z4308609202	Z16191985	Z2234634547
Structure					
RMSD Value	0.013	0.014	0.017	0.018	0.019

3.3. Virtual screening of free energy of binding interactions of identified potential agonists via molecular docking using Swissdock

The molecule with the lowest AC Score was Z1275113833, suggesting that it has the greatest binding capabilities with GPR119. Its structure can be found in Figure 3.3.1. below. This was not the expected result, as the molecule with the lowest RMSD value from 3.2.2. was Z202499044. This result is limited because only one chain in GPR119 was used for this experiment. The R chain was chosen since Prankweb identified the most promising binding site to be in this chain, as Swissdock's limits on analysis size prevented the entire molecule from being studied. Swissdock is known to be accurate and it provides good supporting evidence for the efficacies of identified agonists (Bugnon et al., 2024; Röhrig et al., 2023).

Table 3.3.1. *The 3D docking structure and AC scores of the fifteen molecules identified from the previous experiment done by Swissdock to test for viability for becoming agonists of GPR119 (PDB code 7XZ5)*

Molecule Name	Docking 3D structure	AC Score
Z56781437		53.919072
Z18360185		–0.089938
Z202499044		–11.978319
Z57728534		15.633942

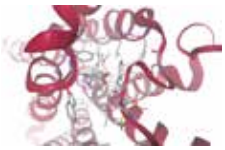
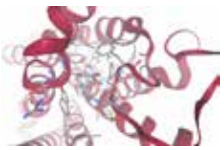
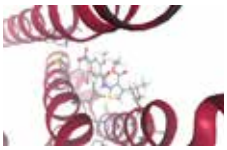
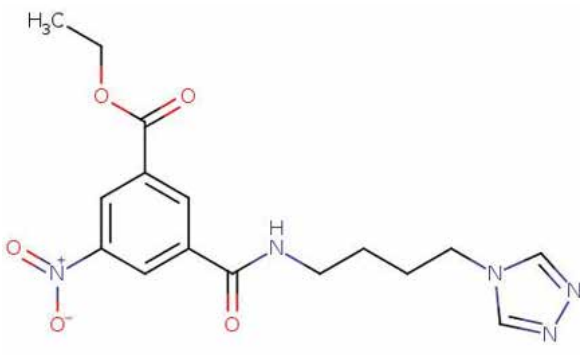
Molecule Name	Docking 3D structure	AC Score
Z1151811424		–4.828343
Z24778861		62.207398
Z18338344		–8.683106
Z31000072		85.659912
Z56781437		53.474198
Z131263998		42.842200
Z1275113833		–27.537900
Z4308609202		15.375294
Z2234634547		–19.860010
Z56891512		21.817742
Z16191985		14.015483

Figure 3.3.1. *Structure of Z1275113833, obtained from Molport (accessed at: https://www.molport.com/shop/index)*



3.4. Screening to determine ADME profile of top five molecules using SwissADME

Z1275113833 (Figure 3.3.2) was the best molecule identified according to the following criteria: 1) follows Lipinski's rules, 2) has high GI absorption, and 3) low BBB permeation. All of the molecules selected from the previous SwissDock experiment followed Lipinski's criteria. The specific parameters used for Log P and Log S were the iLOGP and Log S (ESOL) on the SwissADME site. In addition, all of them were not BBB permeants. Only Z1275113833 and Z1151811424 had high GI absorption, however, which suggests that these two would have the best chance at being effective drugs targeting GPR119 for T2DM patients. Among these two, Z1275113833 had the better score on Swissdock, making it the better potential agonist. This experiment has a few limitations, most importantly that virtual screening has the potential to be extremely accurate, however, the data found below has not been experimentally achieved and is subject to variability.

Table 3.4.1. *Selected metrics for the top five molecules identified from the previous docking experiment to determine their ADME profiles, including Log P, number of hydrogen bond acceptors, number of hydrogen bond donors, Log S, GI absorption, and BBB permeation*

Molecule	Z1275113833	Z2234634547	Z202499044	Z18338344	Z1151811424
Log P	1.97	2.41	2.78	2.77	1.78
Number of Hydrogen Bond Acceptors	7	8	6	8	4
Number of Hydrogen Bond Donors	1	1	1	2	2
Molecular Weight (g/mol)	361.36	439.43	434.51	499.49	341.37
Log S	–2.36	–4.83	–4.97	–5.06	–3.39
GI Absorption	High	Low	Low	Low	High
BBB Permeant	No	No	No	No	No

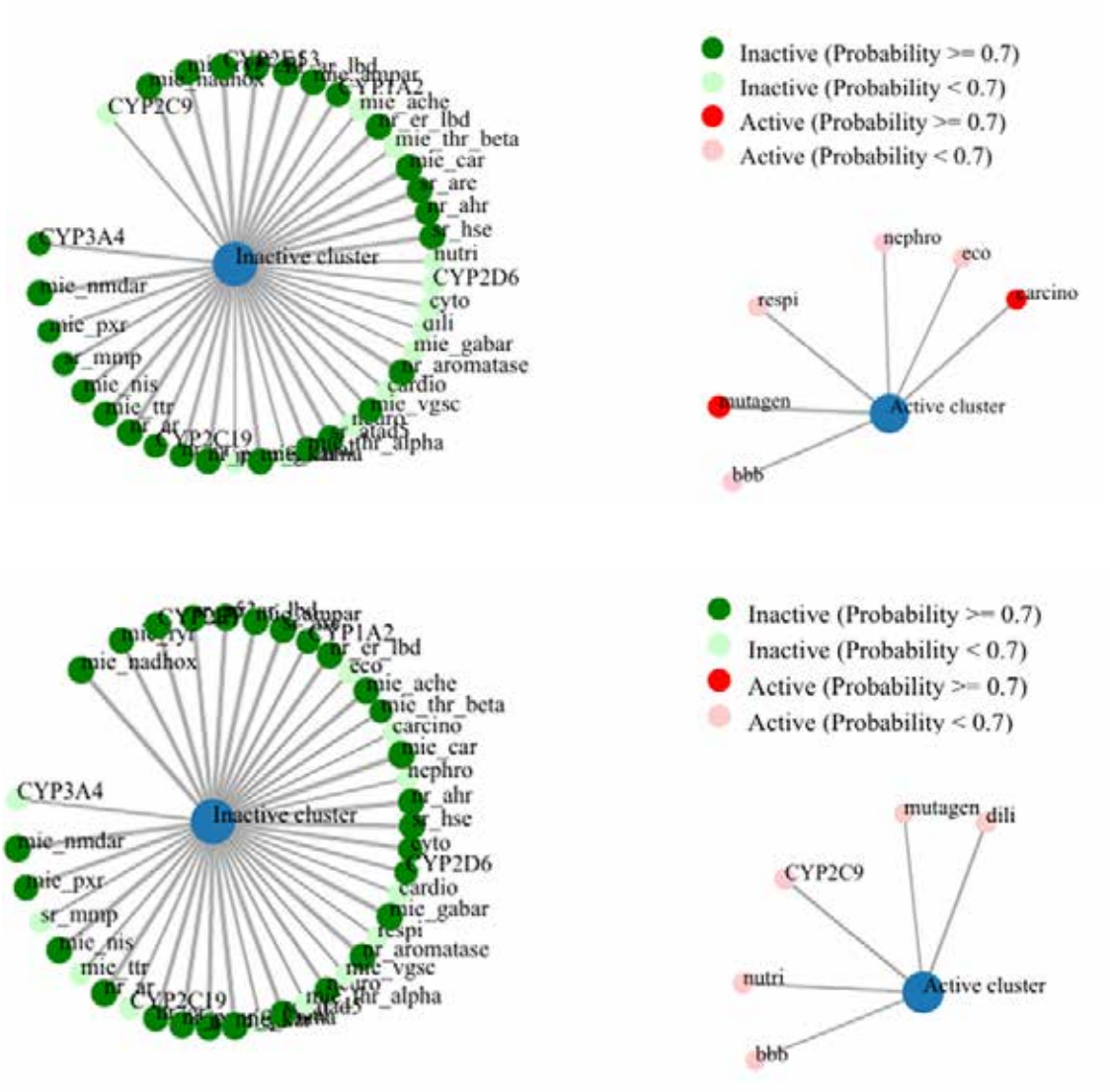
3.5. Virtual toxicological screening of top compounds using ProTox-3.0

Due to a slight concern on the mutagenic toxicity of the top compound identified by Section 3.4., the top two compounds identified earlier, Z1275113833 and Z2234634547, were tested using ProTox-3.0. While Z1275113833, the best GPR119 agonist and with the best ADME profile, was generally found to be safe, with an LD50 of 1340 mg/kg and Toxicity Class of 4.

Table 3.5.1. *LD50 and Toxicity Class of selected molecules, Z1275113833 and Z2234634547, obtained from ProTox-3.0*

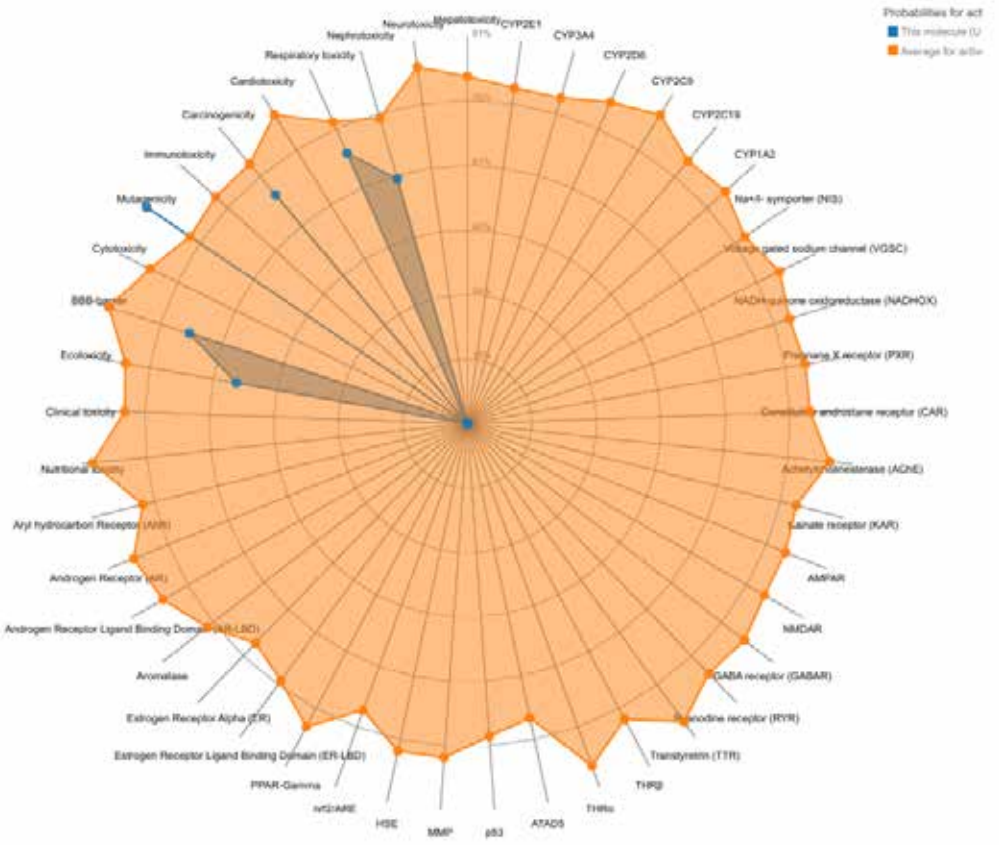
Molecule	Z1275113833	Z2234634547
LD50 (mg/kg)	1340	2500
Toxicity Class	4	5

Figure 3.5.1. *Comparison of the Network Charts of Z1275113833, shown on the left, and Z2234634547, shown on the right. The active cluster displays both the areas both compounds are considered toxic towards and the level of toxicity shown through colour*



This is considered safe under the guidelines of LD50 > 500 mg/kg and Toxicity Class > 3. It had, however, a higher than average level for mutagenicity. The second best molecule was also tested. It was found to be far safer, having an LD50 of 2500 mg/kg and a Toxicity Class of 5. In addition, all of its parameters were found to be well below the averages for each of its categories. Therefore, Z2234634547 is considered to be safer than Z1275113833.

Figure 3.5.3. *Comparison of the Toxicological Radar Charts of Z1275113833, shown on the left, and Z2234634547, shown on the right. The area shown in orange represents the toxicity of the average FDA approved drug. Blue dots outside of the orange, notably the mutagenicity of Z1275113833, show where the compound has higher toxicity*



4. Conclusion:

The aim of this study was to use virtual screening to identify small molecules capable of binding to GPR119 for potential consideration in the development of new medications for T2DM patients. A combination of virtual screening tests were used, firstly determining the amount and viability of binding sites in GPR119 through geometric, energetic, and AI based methods. Next, virtual screening of the pharmacophore map was done. The top fifteen compounds were selected to proceed. Next, a molecular docking experiment was done using the R side chain. The top compounds from the proceeding tests were then put through ADME profile tests and toxicity screens. Z1275113833 was determined by this experiment to be the most promising potential agonist of GPR119.

Moving forwards, the goals of this study are to inspire biophysical screening of Z1275113833 to validate the results. Secondly, testing in mice neuronal cells would also need to be completed. A long-term goal for this study would be the completion of an animal model for diabetic mice to receive appropriate doses of the compound and test for the efficacy and safety of Z1275113833 to be used as a potential drug in humans.

This study differs from a recent study performed by Nema et al. in that in they focused specifically on pyrimidine derivatives while we screened a range of compounds.

There were a few limitations with this study. First and foremost that computational and virtual screening requires real experimental validation, which this study did not accomplish. Evidence suggests that the virtual screening methods used were all known to be extremely accurate and trustworthy, however, further experimentation is still needed. Secondly, the top candidate found during this experiment was not the safest compound, and had higher than average levels of mutagenicity when compared with other FDA approved drugs.

References

Abdel-Rahman, S. A., & Gabr, M. T. (2024). Small molecules from antibody pharmacophores (SMAbPs) as a hit identification workflow for immune checkpoints. *Science Advances*, – – 10(42). – eadq5540. URL: https://doi.org/10.1126/sciadv.adq5540

Ansarullah, Lu, Y., Holstein, M., DeRuyter, B., Rabinovitch, A., & Guo, Z. (2013). Stimulating β-Cell Regeneration by Combining a GPR119 Agonist with a DPP-IV Inhibitor. *PLoS ONE*, – 8(1). – e53345. URL: https://doi.org/10.1371/journal.pone.0053345

Apostolova, N., Iannantuoni, F., Gruevska, A., Muntane, J., Rocha, M., & Victor, V. M. (2020). Mechanisms of action of metformin in type 2 diabetes: Effects on mitochondria and leukocyte-endothelium interactions. *Redox Biology*, – 34. – 101517 p. URL: https://doi.org/10.1016/j.redox.2020.101517

Bugnon, M., Röhrig, U. F., Goullieux, M., Perez, M. A. S., Daina, A., Michielin, O., & Zoete, V. (2024). SwissDock 2024: Major enhancements for small-molecule docking with Attracting Cavities and AutoDock Vina. *Nucleic Acids Research*, – 52(W1). – W324–W332. URL: https://doi.org/10.1093/nar/gkae300

Carls, G., Huynh, J., Tuttle, E., Yee, J., & Edelman, S. V. (2017). Achievement of Glycated Hemoglobin Goals in the US Remains Unchanged Through 2014. *Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders*, – 8(4). – P. 863–873. URL: https://doi.org/10.1007/s13300–017–0280–5

Chu, Z.-L., Jones, R. M., He, H., Carroll, C., Gutierrez, V., Lucman, A., Moloney, M., Gao, H., Mondala, H., Bagnol, D., Unett, D., Liang, Y., Demarest, K., Semple, G., Behan, D. P., & Leonard, J. (2007). A Role for β-Cell-Expressed G Protein-Coupled Receptor 119 in Glycemic Control by Enhancing Glucose-Dependent Insulin Release. *Endocrinology*, – 148(6). – P. 2601–2609. URL: https://doi.org/10.1210/en.2006–1608

Drzazga, A., Sowińska, A., & Koziołkiewicz, M. (2014). Lysophosphatidylcholine and lysophosphatidylinosiol – Novel promissing signaling molecules and their possible therapeutic activity. *Acta Poloniae Pharmaceutica*, – 71(6). – P. 887–899.

Feingold, K. R. (2000). Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes. In K. R. Feingold, S. F. Ahmed, B. Anawalt, M. R. Blackman, A. Boyce, G. Chrousos, E. Corpas, W. W. de Herder, K. Dhatariya, K. Dungan, J. Hofland, S. Kalra, G. Kaltsas, N. Kapoor, C. Koch, P. Kopp, M. Korbonits, C. S. Kovacs, W. Kuohung, … D. P. Wilson (Eds.), *Endotext*. MDText.com, Inc. URL: http://www.ncbi.nlm.nih.gov/books/NBK279141

Flock, G., Holland, D., Seino, Y., & Drucker, D. J. (2011). GPR119 Regulates Murine Glucose Homeostasis Through Incretin Receptor-Dependent and Independent Mechanisms. *Endocrinology*, – 152(2). – P. 374–383. URL: https://doi.org/10.1210/en.2010-1047

Ganesan, K., Rana, M. B. M., & Sultan, S. (2025). Oral Hypoglycemic Medications. In *StatPearls*. StatPearls Publishing. URL: http://www.ncbi.nlm.nih.gov/books/NBK482386/

Hryciw, D. H., Patten, R. K., Rodgers, R. J., Proietto, J., Hutchinson, D. S., & McAinch, A. J. (2024). GPR119 agonists for type 2 diabetes: Past failures and future hopes for preclinical and early phase candidates. *Expert Opinion on Investigational Drugs*, – 33(3). – P. 183–190. URL: https://doi.org/10.1080/13543784.2024.2321271

Hu, J., Cao, Y., Duan, L., & Peng, J. (2024). What is holding back preclinical GPR119 agonists from their potential as the therapeutics of type 2 diabetes? *Expert Opinion on Therapeutic Targets*, – 28(10). – P. 825–828. URL: https://doi.org/10.1080/14728222.2024.2421751

IDF Diabetes Atlas 11th Edition. (2025). International Diabetes Federation.

Kim, M.-K., Cheong, Y. H., Lee, S. H., Kim, T. H., Jung, I. H., Chae, Y., Lee, J.-H., Yang, E. K., Park, H., Yang, J.-S., & Hong, K. W. (2021). A novel GPR119 agonist DA-1241 preserves pancreatic function via the suppression of ER stress and increased PDX1 expression. *Biomedicine & Pharmacotherapy*, – 144, – 112324 p. URL: https://doi.org/10.1016/j.biopha.2021.112324

Lautsch, D., Boggs, R., Wang, T., Gonzalez, C., Milligan, G., Rajpathak, S., Malkani, S., McLeod, E., Carroll, J., & Higgins, V. (2022). Individualized HbA1c Goals, and Patient Awareness and Attainment of Goals in Type 2 Diabetes Mellitus: A Real-World Multinational Survey. *Advances in Therapy*, – 39(2). – P. 1016–1032. URL: https://doi.org/10.1007/s12325-021-01985-3

Leiter, L. A., Cheng, A. Y. Y., Ekoé, J.-M., Goldenberg, R. M., Harris, S. B., Hramiak, I. M., Khunti, K., Lin, P. J., Richard, J.-F., Senior, P. A., Yale, J.-F., Goldin, L., Tan, M. K., & Langer, A. (2019). Glycated Hemoglobin Level Goal Achievement in Adults With Type 2 Diabetes in Canada: Still Room for Improvement. *Canadian Journal of Diabetes*, – 43(6). – P. 384–391. URL: https://doi.org/10.1016/j.jcjd.2018.10.005

Magliano, D. J., Sacre, J. W., Harding, J. L., Gregg, E. W., Zimmet, P. Z., & Shaw, J. E. (2020). Young-onset type 2 diabetes mellitus-Implications for morbidity and mortality. *Nature Reviews. Endocrinology*, – 16(6). – P. 321–331. URL: https://doi.org/10.1038/s41574–020-0334-z

Manaithiya, A., Alam, O., Sharma, V., Javed Naim, Mohd., Mittal, S., & Khan, I. A. (2021). GPR119 agonists: Novel therapeutic agents for type 2 diabetes mellitus. *Bioorganic Chemistry*, –113, – 104998 p. URL: https://doi.org/10.1016/j.bioorg.2021.104998

Młynarska, E., Czarnik, W., Dzieża, N., Jędraszak, W., Majchrowicz, G., Prusinowski, F., Stabrawa, M., Rysz, J., & Franczyk, B. (2025). Type 2 Diabetes Mellitus: New Pathogenetic Mechanisms, Treatment and the Most Important Complications. *International Journal of Molecular Sciences*, – *26*(3). – 1094 p. URL: https://doi.org/10.3390/ijms26031094

Ngan, C.-H., Hall, D. R., Zerbe, B., Grove, L. E., Kozakov, D., & Vajda, S. (2012). FTSite: High accuracy detection of ligand binding sites on unbound protein structures. *Bioinformatics (Oxford, England)*, – 28(2). – P. 286–287. URL: https://doi.org/10.1093/bioinformatics/btr651

Ning, Y., O'Neill, K., Lan, H., Pang, L., Shan, L. X., Hawes, B. E., & Hedrick, J. A. (2008). Endogenous and synthetic agonists of GPR119 differ in signalling pathways and their effects on insulin secretion in MIN6c4 insulinoma cells. *British Journal of Pharmacology*, – 155(7). – P. 1056–1065. URL: https://doi.org/10.1038/bjp.2008.337

Overton, H. A., Fyfe, M. C. T., & Reynet, C. (2008). GPR119, a novel G protein-coupled receptor target for the treatment of type 2 diabetes and obesity. *British Journal of Pharmacology*, *153 Suppl 1*(Suppl 1). – P. 76–81. URL: https://doi.org/10.1038/sj.bjp.0707529

Panaro, B. L., Flock, G. B., Campbell, J. E., Beaudry, J. L., Cao, X., & Drucker, D. J. (2017). β-Cell Inactivation of Gpr119 Unmasks Incretin Dependence of GPR119-Mediated Glucoregulation. *Diabetes*, – 66(6). – P. 1626–1635. URL: https://doi.org/10.2337/db17-0017

Petersmann, A., Müller-Wieland, D., Müller, U. A., Landgraf, R., Nauck, M., Freckmann, G., Heinemann, L., & Schleicher, E. (2019). Definition, Classification and Diagnosis of Diabetes Mellitus. *Experimental and Clinical Endocrinology & Diabetes: Official Journal, German Society of Endocrinology [and] German Diabetes Association*, – *127*(S 01). – S1–S7. URL: https://doi.org/10.1055/a-1018-9078

Röhrig, U. F., Goullieux, M., Bugnon, M., & Zoete, V. (2023). Attracting Cavities 2.0: Improving the Flexibility and Robustness for Small-Molecule Docking. *Journal of Chemical Information and Modeling*, – 63(12). – P. 3925–3940. URL: https://doi.org/10.1021/acs.jcim.3c00054

Ruze, R., Liu, T., Zou, X., Song, J., Chen, Y., Xu, R., Yin, X., & Xu, Q. (2023). Obesity and type 2 diabetes mellitus: Connections in epidemiology, pathogenesis, and treatments. *Frontiers in Endocrinology*, – 14. – 1161521 p. URL: https://doi.org/10.3389/fendo.2023.1161521

Soga, T., Ohishi, T., Matsui, T., Saito, T., Matsumoto, M., Takasaki, J., Matsumoto, S., Kamohara, M., Hiyama, H., Yoshida, S., Momose, K., Ueda, Y., Matsushime, H., Kobori, M., & Furuichi, K. (2005). Lysophosphatidylcholine enhances glucose-dependent insulin secretion via an orphan G-protein-coupled receptor. *Biochemical and Biophysical Research Communications*, – 326(4). – P. 744–751. URL: https://doi.org/10.1016/j.bbrc.2004.11.120

Strati, M., Moustaki, M., Psaltopoulou, T., Vryonidou, A., & Paschou, S. A. (2024). Early onset type 2 diabetes mellitus: An update. *Endocrine*, – 85(3). – P. 965–978. URL: https://doi.org/10.1007/s12020-024-03772-w

Volkamer, A., Kuhn, D., Rippmann, F., & Rarey, M. (2012). DoGSiteScorer: A web server for automatic binding site prediction, analysis and druggability assessment. *Bioinformatics*, – 28(15). – P. 2074–2075. URL: https://doi.org/10.1093/bioinformatics/bts310

Yerevanian, A., & Soukas, A. A. (2019). Metformin: Mechanisms in Human Obesity and Weight Loss. *Current Obesity Reports*, – 8(2). – P. 156–164. URL: https://doi.org/10.1007/s13679-019-00335-3

Zander, M., Madsbad, S., Madsen, J. L., & Holst, J. J. (2002). Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: A parallel-group study. *The Lancet*, – 359(9309). – P. 824–830. URL: https://doi.org/10.1016/S0140-6736(02)07952-7

Zhang, N., & Li, D. (2017). *Druggability analysis of membrane proteins by DoGSiteScorer*. PeerJ Preprints. URL: https://doi.org/10.7287/peerj.preprints.2868v1

Zhao, J., Zhao, Y., Hu, Y., & Peng, J. (2021). Targeting the GPR119/incretin axis: A promising new therapy for metabolic-associated fatty liver disease. *Cellular & Molecular Biology Letters*, – 26(1). – 32 p. URL: https://doi.org/10.1186/s11658-021-00276-7

submitted 14.08.2025;
accepted for publication 24.08.2025;
published 31.10.2025

Contact: wangzalison@gmail.com