WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 20, 235-251. Review Article ISSN 2277– 7105

COMPUTATIONAL INSIGHTS INTO SULFONYLUREA CONTAINING ANTIDIABETIC DRUGS TARGETING PPAR-γ: A COMPREHENSIVE REVIEW

Shubham N. Karle*[1] and Dr. Megha T. Salve[2]

[1,2]Department of Bachelor in Pharmacy, Shivajirao Pawar College of Pharmacy, Pachegaon, Ahmednagar-413725.

Article Received on
20 Sept. 2023,
Revised on 10 Oct. 2023,
Accepted on 31 Oct. 2023
DOI: 10. 20959/wjpr202320-30213

***Corresponding Author**
Shubham N. Karle
Department of Bachelor in Pharmacy, Shivajirao Pawar College of Pharmacy, Pachegaon, Ahmednagar-413725.

ABSTRACT

Diabetes mellitus is a global health concern characterized by impaired insulin function or production, leading to elevated blood glucose levels. SU-containing antidiabetic drugs have long been utilized in the management of type 2 diabetes mellitus. Their mechanism of action primarily involves the stimulation of insulin secretion from pancreatic β-cells. In recent years, the role of PPAR-γ in glucose and lipid metabolism has gained significant attention. This comprehensive review explores the molecular interactions between SU drugs and PPAR-γ through computational methods, shedding light on their potential significance in diabetes treatment. This comprehensive review provides a detailed exploration of Binding affinity to the receptor, Toxicity, Pharmacokinetic, Pharmacodynamic properties such as BBB permeation, HIA, P-glycoprotein substrate, cytochrome P450 isoform inhibition, Log Kp, and bioavailability ranking etc. of SU-based antidiabetic drugs and their ability to produce agonist effect on PPAR isoforms (PPAR-γ) by using various in silico evaluation software's like Molinspiration, ADMETlab 2.0, ProTox-II, 1-Click Docking, ChemSketch, SwissADME etc. A major focus of this review is the utilization of computational techniques and tools to rationalize the design of PPAR-γ agonists. Utilizing in silico techniques, potential agonistic effects on PPAR- γ have been uncovered, focusing on the examination of six commercially available anti-diabetic agents. The study pinpointed PPAR- γ a protein targets (1i7i). Further investigation is advised to explore the potential of these marketed anti-diabetic agents to evolve into a safe and scientifically substantiated multi-target drug for diabetes treatments.

KEYWORDS: Computer-aided method, Sulfonylurea-containing antidiabetic drugs, Pharmacokinetics, Peroxisome Proliferator-Activated Receptor-γ (1i7i), Toxicity Profile.

INTRODUCTION

Diabetes Mellitus is a serious chronic disease that occurs either when the pancreas is unable to produce enough insulin or a hormone that is responsible for regulating blood glucose levels. Diabetes mellitus is one of the major disorders that is growing at a faster rate second after the cancer.[1] The chronic hyperglycemia of diabetes is associated with dysfunction, long-term damage, and failure of different organs, especially organs like kidneys, nerves, heart, eyes, and blood vessels.[2] There are various categories of medications available for managing type 2 diabetes. Each class of medication works in a different way to reduce blood sugar levels.[3] Medicament used for type 2 diabetes mellitus treatment (antidiabetics) including:

Metformin: On a large scale the amount of glucose can be reduces by metformin which is produced by the body, and has been used for a long period. It's one of the best-tolerated, as well as the best-studied diabetes medication.

Sulfonylureas: It assists the body to produce more insulin. Drug like metformin, have also been in utilize for quite a while.

Glitazones: They are used to control high blood sugar in patients with type 2 diabetes. Pioglitazone belongs to the glitazone class that continues to be available on the market.

Glinides: They are responsible for the enhancement of insulin production in the body.

Gliptins (dipeptidyl peptidase-4 inhibitors): Gliptins act to provoke the production of insulin. Including drugs like saxagliptin, vildagliptin, linagliptin, and sitagliptin.

Gliflozins (SGLT2 inhibitors): Gliflozins include the drugs like dapagliflozin, empagliflozin and canagliflozin. They cause more sugar to be excreted in the urine, lowering blood sugar levels.

Amylin analogs: Amylin is a hormone that secretes insulin from the β-cells in the pancreas.[4,5]

This comprehensive review focuses on Sulfonylureas containing antidiabetic because SUs has long been the only alternative to metformin or are considered as an ideal complementary therapy in case of failure of metformin monotherapy. The International Diabetes Federation (IDF) Guidelines Task Force suggested that metformin is the preferred first choice for monotherapy, but other glucose-lowering drugs are recommended if metformin is not tolerated, preferably an SU (not glibenclamide), an alpha-glucosidase inhibitor or a DPP-4i, and similar choices are recommended for dual (second-line) therapy after metformin failure.[6,7]

Structure and Function of PPAR

The peroxisome proliferator-activated receptors (PPARs) are nuclear fatty acid receptors that have been implicated to play crucial roles in metabolic diseases such as hyperlipidemia, insulin resistance, and diabetes, comprising of the following three subtypes: PPARα, PPARγ, and PPARβ/δ, whereas activation of PPAR-γ causes insulin sensitization and enhance glucose metabolism.[8,9]

PPAR-γ is further classified into four isoforms.

1. γ1 - present in virtually all tissues, including heart, muscle, colon, kidney, pancreas, and spleen.
2. γ2 – present mainly in adipose tissue (30 amino acids longer).
3. γ3 - present in macrophages, large intestine, and white adipose tissue.
4. γ4 - present in endothelial cells.[8]

Structure- The peroxisome proliferator-activated receptors have the canonical domain structure common to other nuclear receptor family members.[10] The macrophages, colon, and adipose tissue are the primary locations where PPARG is mainly found. There are two types of isoforms of PPARG detected in the human and the mouse: PPAR-γ1 (present in nearly all tissues except muscle) and PPAR-γ2 (mostly present in adipose tissue and the intestine).[11] The following figure represents the structure of PPARs as one-dimensional shapes. It illustrates that the *N*-terminal (5’), is associated with the phosphorylation of PPAR, which contains DBD but the C-terminal (3’) contains the LBD as demonstrated in the 3-D structure of PPARs. 5’-AF-1 domains are concerned with a region that is individualistic of the A/B domain that is accountable for the phosphorylation of peroxisome proliferator-activated receptors.[12,13]

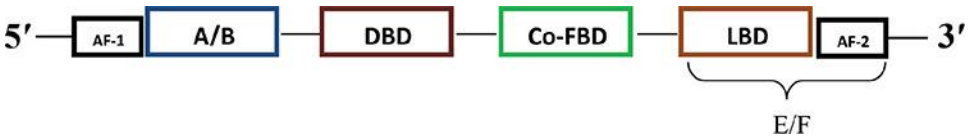


Fig. 1: One-dimensional structure of the different binding domains of PPARs.[14]

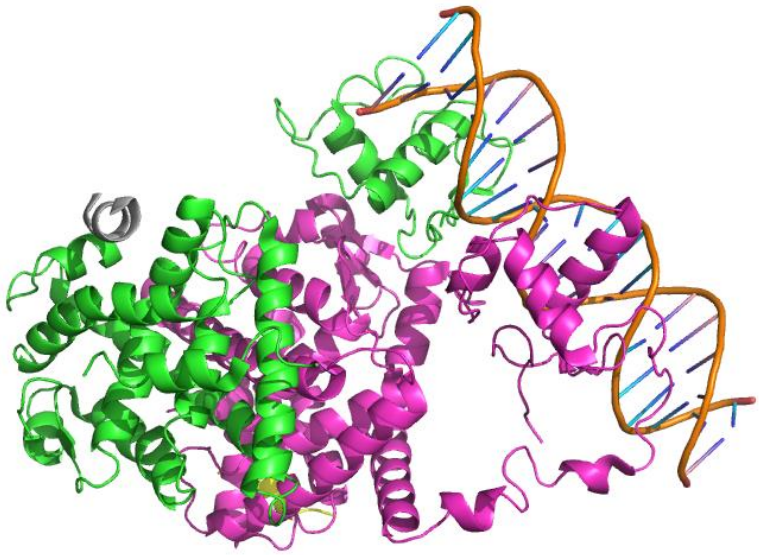


Fig. 2: 3D structure of peroxisome proliferator-activated receptors (1I7I).[15]

Function- Primarily PPARG modulates fatty acid storage and glucose metabolism. The genes activated by PPARG provoke lipid uptake and adipogenesis by fat cells. PPARG increases insulin sensitivity improves peripheral glucose disposal, which reduces the demand for insulin secretion from β-cells and hepatic glucose production by increasing the storage of fatty acids in fat cells (reducing lipotoxicity), by increasing adiponectin release from fat cells, by modulating FGF21. Primarily pancreatic β-cells and liver are targets of insulin, induce insulin sensitivity contributes to the insulin-dependent triggering of hepatic glucose metabolism and functional restoration of β-cells.[15,16]

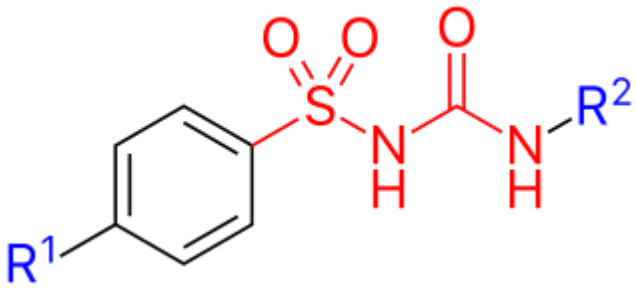
Sulfonylurea Antidiabetic Drugs

Sulfonylureas have been widely used in the treatment of type 2 diabetes since the 1950s,[17] because they stimulate insulin secretion from pancreatic β-cells by closing ATP-sensitive K-channels in the beta-cell plasma membrane,[18] and so initiate a chain of events that results in insulin release.[19]

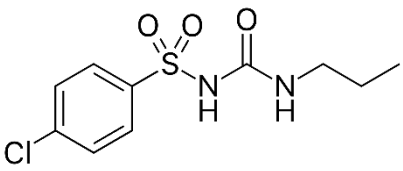
Based on the therapeutic efficiency of their antidiabetic action sulfonylureas are divided into 3 classes

- First-generation drugs- Drug like acetohexamide, tolazamide, and tolbutamide, carbutamide, chlorpropamide, glycyclamide, metahexamide.
- Second-generation drugs- Drug like glibenclamide (glyburide), glibornuride, gliclazide, glipizide, gliquidone, glisoxepide, and glyclopyramide.
- Third-generation drugs- Drug like glimepiride, sometimes it is considered a second-generation drug.[15]

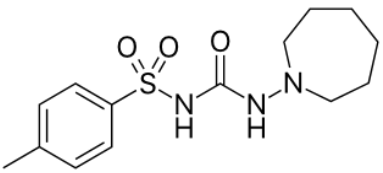
The functional group consists of a sulfonyl group (-S(=O)2) with its Sulphur atom bonded to a nitrogen atom of a ureylene group (N, N-dehydrourea, a urea derivative). The side chains R1 and R2 distinguish various sulfonylureas.[15]



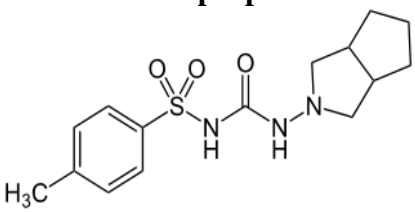
Following sulfonylurea antidiabetic drugs used for computational investigation-



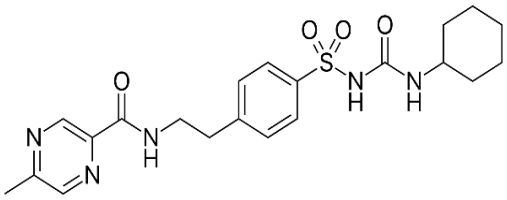
A1 Chlorpropamide



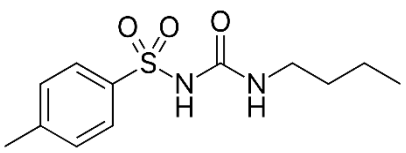
A2 Tolazamide



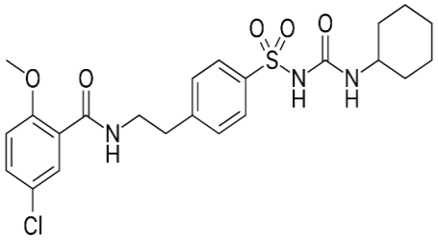
A3 Gliclazide



A4 Glipizide



A5 Tolbutamide



A6 Glibenclamide

Mechanism of action of Sulfonylurea Antidiabetic Drugs

Sulfonylureas bind to and close the ATP-sensitive potassium channels (K) on the pancreatic beta cells. Due to this potassium efflux reduce, and the beta-cell membrane depolarizes.[15] This depolarization opens voltage-gated Ca2+ channels, leading to calcium influx and increased intracellular calcium, which stimulates insulin secretion from the pancreatic beta cells. Sulfonylureas stimulate insulin secretion independently of the prevailing blood glucose levels. K is made of two proteins, Kir6.2 which forms the pore of the K channels, and a sulfonylurea receptor (SUR).

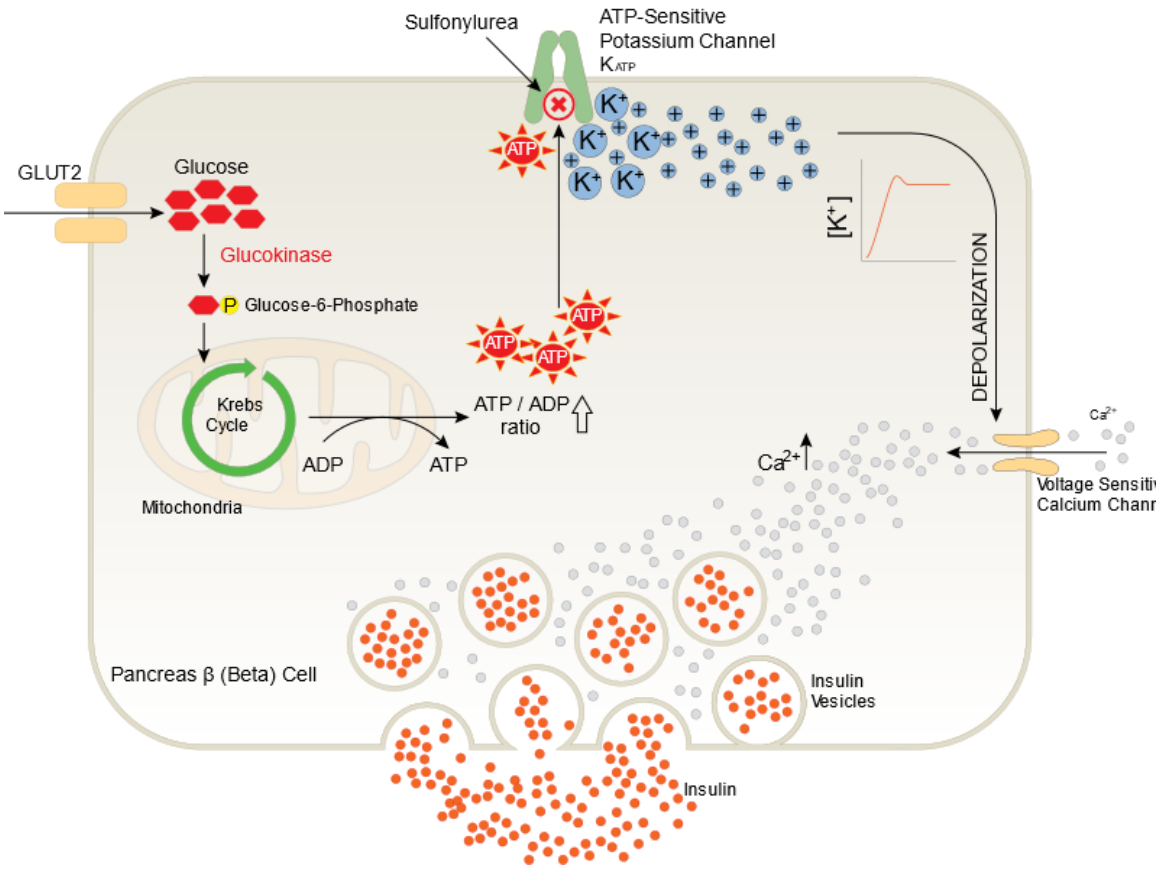


Fig. 3: Diagram of glucose reduction and insulin release in the pancreas by Sulfonylurea.[15]

SUR1 and SUR2 are subtypes of SUR. The SUR1 is primarily found in the brain and on the beta cells in the pancreas. SUR2 is found in the smooth muscle (as isoform SUR2A) and the cardiac muscle (as isoform SUR2B).[19,20] As compared to other sulfonylureas, glimepiride has a lower affinity to the cardiac muscles and is not affiliated with cardiovascular safety concerns. Sulfonylureas possess diverge in their affinity regarding to the SUR subtype receptors and their efficacy in closing the K channels. With the help of decreasing insulin

metabolism in the liver sulfonylureas also lower serum glucose levels, decreasing glucagon secretion and enhancing sensitivity to insulin in peripheral tissues.[21]

PPAR-γ (1i7i) as a potential target for Sulfonylureas

In general mechanism of sulfonylurea is the primarily enhance insulin secretion by binding to its receptor present on the pancreatic β-cells. Recent studies have suggested that sulfonylureas induce insulin sensitivity through the activation of peroxisome proliferator-activated receptor γ (1i7i), one of the nuclear receptors. In addition, glimepiride is directly bound to peroxisome proliferator-activated receptor gamma in a manner competitive to rosiglitazone, which is a proven ligand for peroxisome proliferator-activated receptor gamma. Additionally, in 3T3-L1 adipocytes, glimepiride modify mRNA levels of peroxisome proliferator-activated receptor gamma target genes including aP2, leptin, and adiponectin and promote the transcriptional activity of the gene promoter containing peroxisome proliferator-activated receptor-responsive element. Which result in induction of adipose by glimepiride differentiation in 3T3-F442A cells, which were known to differentiate into adipocytes in a peroxisome proliferator-activated receptor gamma -dependent manner.

These data strongly suggest that glimepiride and glibenclamide, both of which belong to sulfonylurea agents, should have peroxisome proliferator-activated receptor gamma agonist activity, whose potencies were 16-25% of the maximum level achieved by pioglitazone. Many studies have observed that glimepiride and glibenclamide could act not only on sulfonylurea receptor but also on peroxisome proliferator-activated receptor gamma may give an important clue to the development of novel antidiabetic drugs, which can enhance both insulin secretion from pancreatic beta-cells and peripheral insulin sensitivity.[22,23]

Consideration of the following parameter for computational investigation

Molecular Properties of the ligands- Evaluation of the drug is based on Lipinski's rule of five[24], also known as Pfizer's rule of five or simply the rule of five (RO5) is help to describe molecular properties of drug compounds required for estimation of important pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion is done by SwissADME.[25] The rule is helpful in drug design and development.

Components of the rule

- It shouldn't contain more than 5 hydrogen bond donors (the total number of N-H and O-H bonds).

- It shouldn't contain more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms).
- It should have a molecular mass less than 500 Daltons.
- It should have a calculated octanol-water partition coefficient (Clog P) that does not exceed 5.[26]

Table 1: Molecular Properties of the ligands.

Ligands	Molecular weight	TPSA	Molar Refractivity	MlogP	Rotatable bonds	H-bond donors	H-bond acceptors
A-1	276.74	83.65	65.16	1.60	6	2	3
A-2	311.40	86.89	84.23	1.76	5	2	4
A-3	323.41	86.89	86.93	2.01	5	2	4
A-4	445.54	138.53	115.30	0.62	10	3	6
A-5	270.35	83.65	69.92	1.62	7	2	3
A-6	494.00	121.98	126.25	2.58	11	3	5

Key: TSPA= Topological polar surface area, MlogP= partition coefficient between n-octanol and water

Bioactivity Scores of the ligands- Drug score values indicate the overall potential of a compound to be a drug candidate. Molinspiration[27] is a web-based tool used to predict the bioactivity score of synthesized compounds against regular human receptors such as GPCRs, ion channels, kinases, nuclear receptors, proteases, and enzymes. Calculated drug-likeness score of each compound and compared with the specific activity of each compound, and the results were compared with standard drug. For organic molecules the probability is if the bioactivity scores (>0), then it is active, if (-5.0-0.0) then moderately active, if (<-5.0) then inactive.[24,28]

Table 2: Bioactivity Scores of the ligands.

Ligands	GPCR	ICM	KI	NRL PI EI	PI	EI
A-1	0.02	-0.06	-0.66	-0.75	0.07	0.11
A-2	0.06	-0.37	-0.24	-0.41	0.16	0.07
A-3	0.19	-0.35	-0.34	-0.37	0.17	0.01
A-4	0.31	-0.01	-0.17	-0.40	0.39	0.16
A-5	0.04	-0.12	-0.60	-0.63	0.14	0.13
A-6	0.20	-0.05	-0.27	-0.33	0.24	0.05

Key: GPCR= G-protein coupled receptor, ICM= ion channel modulators, KI=Kinase inhibitors, NRL= nuclear receptor ligands, PI=protease inhibitors, EI= enzyme inhibitors

Pharmacokinetic Profile of ligand- The SwissADME[25] Web tool was used to calculate physicochemical, pharmacokinetic, drug-like and related parameters for sulfonylureas antidiabetic drug which including Blood-brain barrier (BBB) permeation, Human Intestinal Absorption (HIA), P-glycoprotein substrate (P-gp), Cytochrome P450 isoform inhibition, Skin permeation Log Kp, and bioavailability score.[29]

Table 3: Pharmacokinetic Profile.

Ligands	HIA	BBB permeation	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Bioavailability
A-1	High	No	No	No	No	No	No	No	0.55
A-2	High	No	No	No	Yes	Yes	No	No	0.55
A-3	High	No	Yes	No	No	No	No	No	0.55
A-4	Low	No	Yes	No	No	Yes	Yes	Yes	0.55
A-5	High	No	No	No	No	No	No	No	0.55
A-6	Low	No	No	No	Yes	Yes	Yes	Yes	0.55

HIA=Human intestinal absorption, BBB=blood brain barrier, P-gp= P glycoprotein substrate CYP= cytochrome P450

Prediction of Toxicity of ligand- The ProTox-II[30] server was used to estimate different levels of toxicity such as oral toxicity, organ toxicity (hepatotoxicity), toxicological endpoints (such as mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity) and LD50. Toxic levels are typically expressed as LD50 values, measured in milligrams per kilogram of body weight.

Table 4: Toxicity Model Report.

Ligands	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
A-1	Inactive	Inactive	Inactive	Inactive	Inactive
A-2	Inactive	Inactive	Inactive	Inactive	Inactive
A-3	Inactive	Inactive	Inactive	Inactive	Inactive
A-4	Inactive	Inactive	Inactive	Inactive	Inactive
A-5	Inactive	Inactive	Inactive	Inactive	Inactive
A-6	Inactive	Inactive	Inactive	Inactive	Inactive

According to the globally harmonized system of classification of labeling of chemicals, toxicity classes are defined and LD50 values are given below (mg/kg):

- Class I: It can be fatal if swallowed ($LD50 \leq 5$)
- Class II: It can be fatal if swallowed ($5 < LD50 \leq 50$)
- Class III: It can be toxic if swallowed ($50 < LD50 \leq 300$)
- Class IV: It can be harmful if swallowed ($300 < LD50 \leq 2000$)
- Class V: It may be harmful if swallowed ($2000 < LD50 \leq 5000$)

- Class VI: No toxicity (LD50 > 5000)[31]

Table 5: Oral Toxicity Prediction Results.

Ligands	LD50 (mg/kg)	Classification
A-1	1100	IV
A-2	1000	IV
A-3	1750	IV
A-4	15000	VI
A-5	490	IV
A-6	3250	V

LD= Lethal dose

Molecular Docking Studies- Aim behind the molecular docking is to give a prediction of the ligand-receptor complex structure using computer-based methods.[32] In this comprehensive review Molecular docking was performed by using 1-Click Docking[33] online software to predict the binding orientation of SU antidiabetic drugs at the binding site of a target i.e., peroxisome proliferator-activated receptors- gamma and estimate the binding affinity. The binding affinity (free energy of binding) of a ligand-receptor complex estimate by the docking score of 1-Click Docking. More negative docking scores indicate greater affinity.[34] The binding affinities (kcal/mol) of the active amino acid residues, as well as the ligand energies (kcal/mol) for the docked molecules, are presented in Table 6. The 2D and 3D docking orientations of these molecules are also depicted below.

Table 6: The binding interactions of all the designed molecules (A1-A6) with peroxisome proliferator-activated receptor-γ (1i7i).

Ligand	Binding affinity (Kcal/mol)	Type of interaction
A-1	-6.5	Van der Waals, Alkyl, Pi-Sulfur, Pi-Alkyl
A-2	-8.2	Van der Waals, Alkyl, Carbon Hydrogen bond, Pi-Sulfur, Pi-Alkyl
A-3	-7.7	Van der Waals, Alkyl, Carbon Hydrogen bond, Pi-Sulfur, Pi-Alkyl
A-4	-9.2	Van der Waals, Conventional Hydrogen bond, Pi-Sulfur, Pi-Alkyl, Pi- Sigma, Alkyl.
A-5	-7.4	Van der Waals, Conventional Hydrogen bond, Pi-Sulfur, Pi-Alkyl, Amide Pi-Stacked, Alkyl, Pi-Pi T Shaped.
A-6	-9.8	Van der Waals, Conventional Hydrogen bond, Pi-Sulfur, Pi-Alkyl, Carbon Hydrogen Bond, Pi- Cation, Pi- Donor Hydrogen Bond, Alkyl.

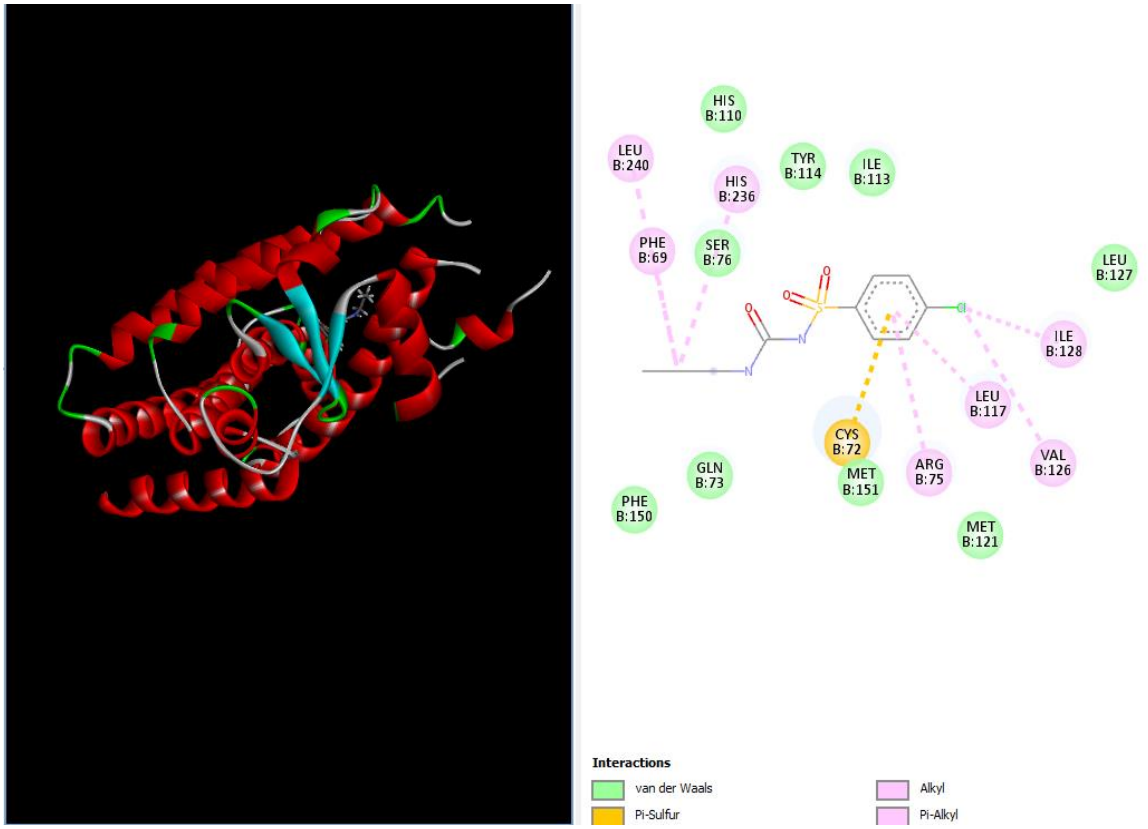


Fig. 4: 3-D & 2-D interaction diagram of compound A-1 at the binding cavity of peroxisome proliferator-activated receptor-γ (1i7i).

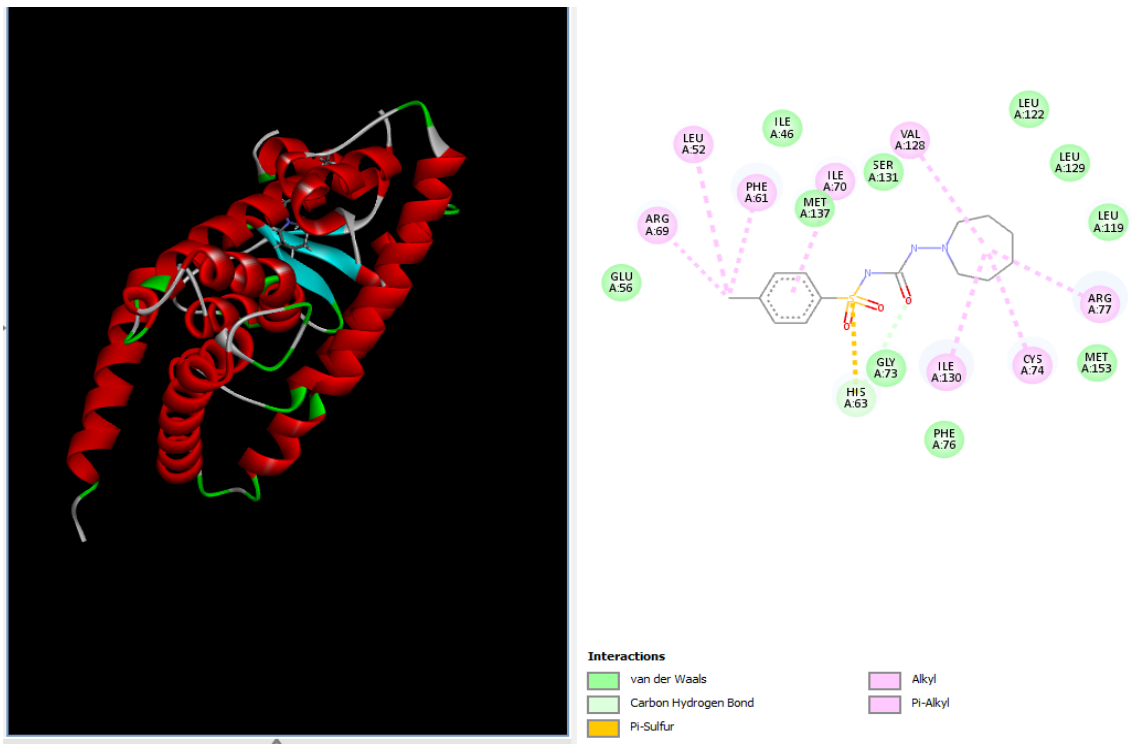


Fig. 5: 3-D & 2-D interaction diagram of compound A-2 at the binding cavity of peroxisome proliferator-activated receptor-γ (1i7i).

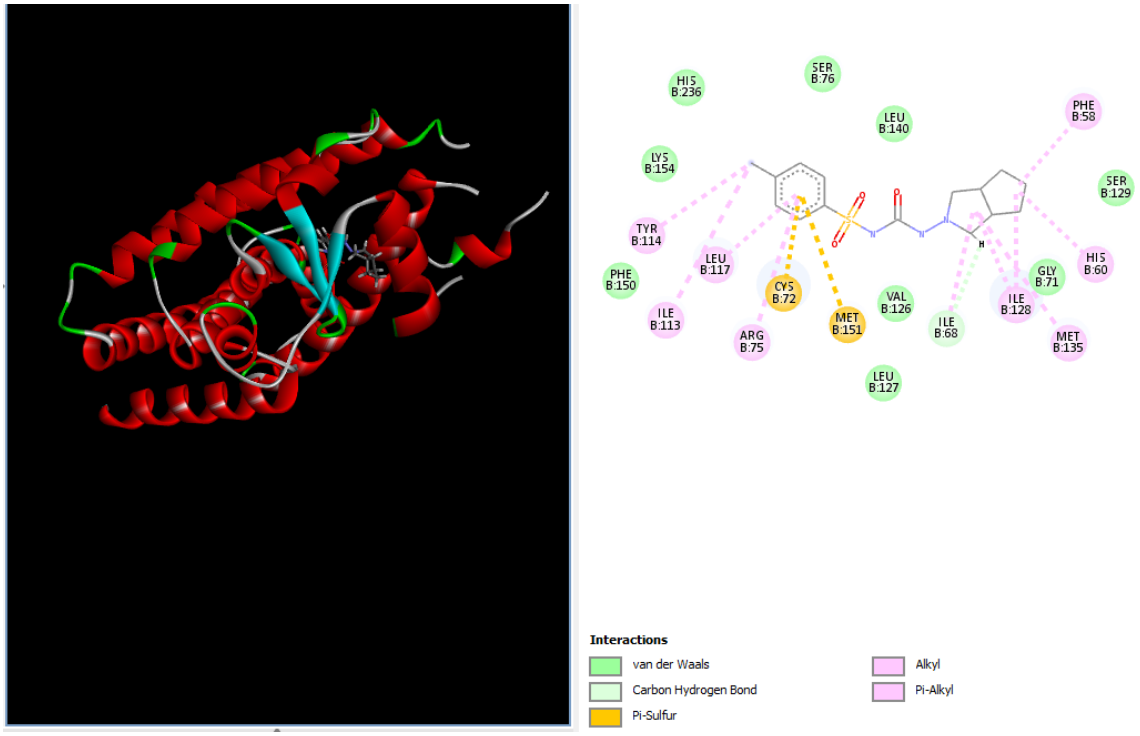


Fig. 6: 3-D & 2-D interaction diagram of compound A-3 at the binding cavity of peroxisome proliferator-activated receptor-γ (1i7i).

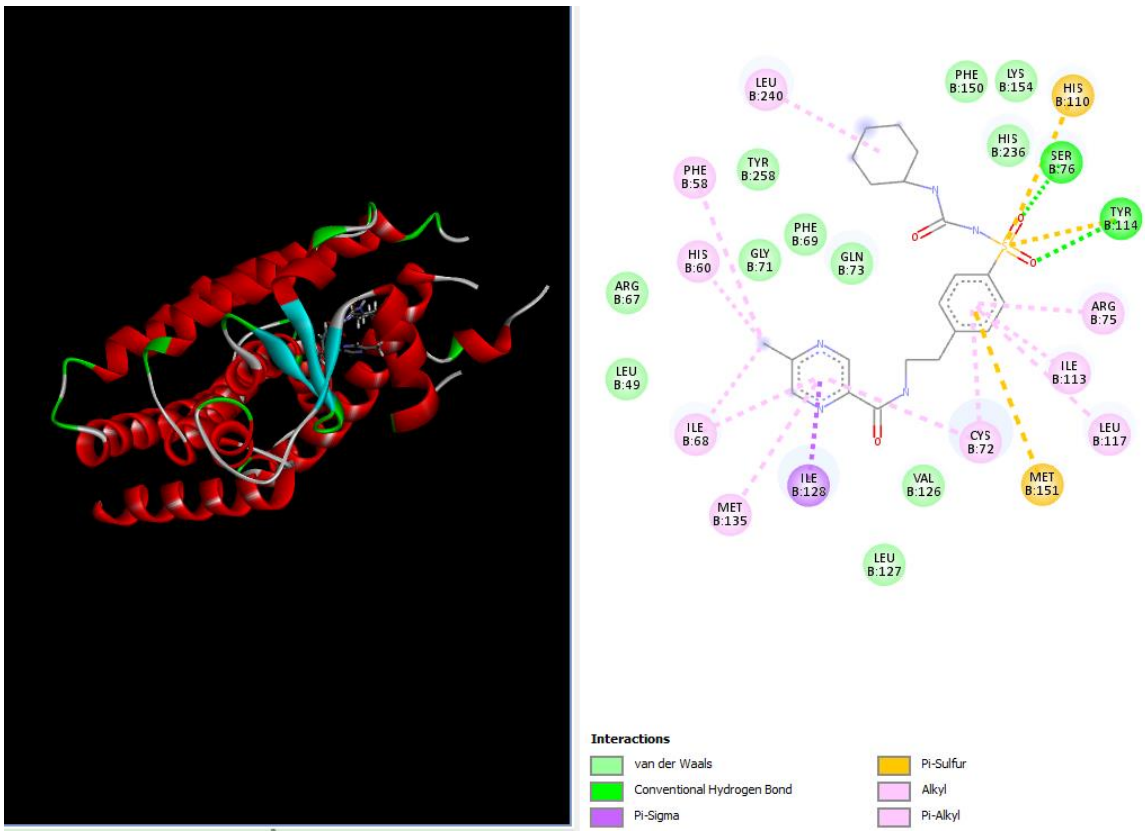


Fig. 7: 3-D & 2-D interaction diagram of compound A-4 at the binding cavity of peroxisome proliferator-activated receptor-γ (1i7i).

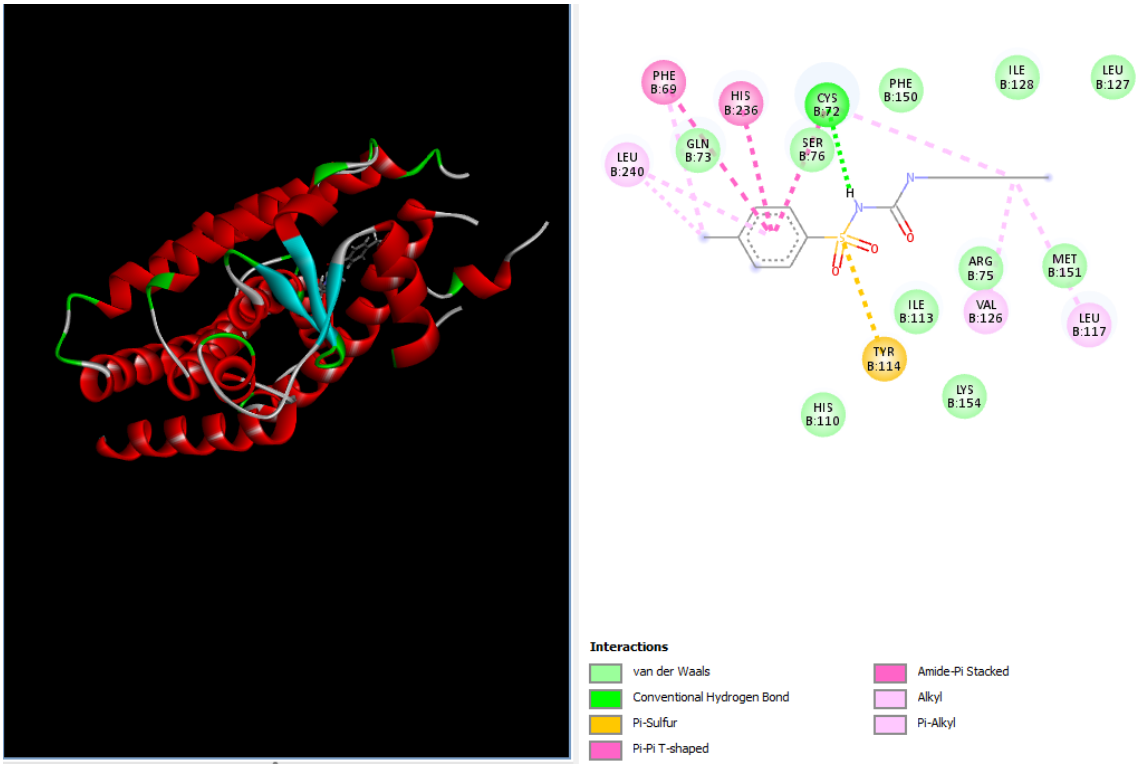


Fig. 8: 3-D & 2-D interaction diagram of compound A-5 at the binding cavity of peroxisome proliferator-activated receptor-γ (1i7i).

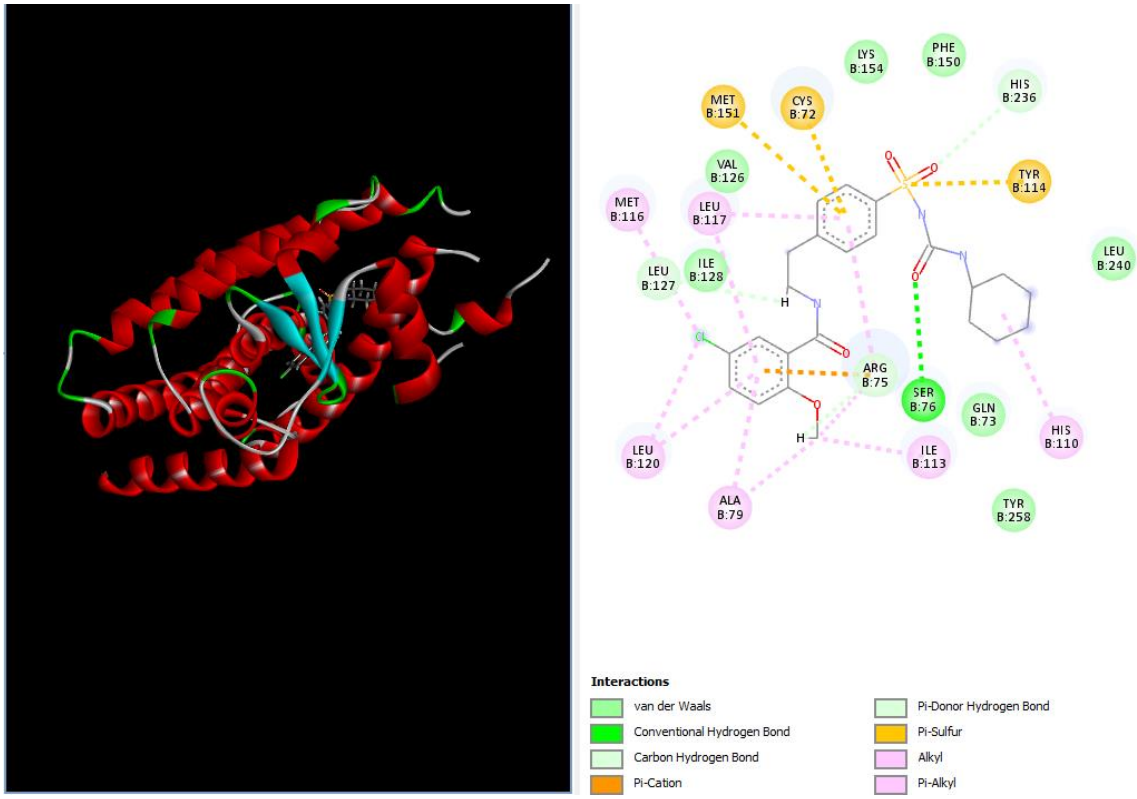


Fig. 9: 3-D & 2-D interaction diagram of compound A-6 at the binding cavity of peroxisome proliferator-activated receptor-γ (1i7i).

CONCLUSION

In conclusion, this comprehensive review underscores the significance of Computational Insights into Sulfonylurea Containing Antidiabetic Drugs Targeting PPAR-γ. There are many medications available in the market that provide antidiabetic action and exhibit high therapeutic effects against T2DM such as metformin, sulfonylurea, gliptin etc. In this review paper, we offer crucial insights into sulfonylurea a major class of antihyperglycemic drugs, highlighting the successful treatment options and shedding light on the innovative mechanisms presently under clinical development. The dynamic interplay between sulfonylureas and PPAR-γ holds promise for a brighter future in diabetes management. The knowledge of traditional pharmacology with a computational approach will help to researchers, clinicians, and pharmaceutical scientists in the development of more effective and safe medication for T2DM.

ACKNOWLEDGEMENT

The corresponding author would like to express sincere gratitude to Dr. Megha T. Salve for their aspiring guidance, valuable contributions and support throughout the preparation of this review article. Her dynamic vision, genuine sincerity, and unwavering motivation have been a profound source of inspiration for me. It was a tremendous privilege and a source of great honor to have the opportunity to learn and collaborate under their exceptional guidance.

REFERENCE

1. The use of herbal preparation in the management of Type-II diabetes mellitus: a review article | IJPPR. (n.d.). https://ijppr.humanjournals.com/the-use-of-herbal-preparation-in-the-management-of-type-ii-diabetes-mellitus-a-review-article/
2. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2010; 33(1): S62–S69. https://doi.org/10.2337/dc10-s062
3. Institute for Quality and Efficiency in Health Care (IQWiG), October 22, 2020. Medication for type 2 diabetes. InformedHealth.org - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK279506/
4. *Diabetes treatment: Medications for type 2 diabetes*. (2022, October 29). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/in-depth/diabetes-treatment/art-20051004
5. *List of Antidiabetic agents - Generics Only*. (n.d.). Drugs.com. https://www.drugs.com/drug-class/antidiabetic-agents.html

6. Scheen, A. Sulphonylureas in the management of type 2 diabetes: To be or not to be? Diabetes Epidemiology and Management, 2021; 1: 100002. https://doi.org/10.1016/j.deman.2021.100002
7. Aschner, P. New IDF clinical practice recommendations for managing type 2 diabetes in primary care. Diabetes Research and Clinical Practice, 2017; 132: 169–170. https://doi.org/10.1016/j.diabres.2017.09.002
8. Tyagi, S., Gupta, P., Saini, A. S., Kaushal, C., & Sharma, S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. Journal of Advanced Pharmaceutical Technology & Research, 2011; 2(4): 236. https://doi.org/10.4103/2231-4040.90879
9. [PPAR and diabetes]. (2005, April 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/15828230/
10. Zoete, V., Grosdidier, A., & Michielin, O. Peroxisome proliferator-activated receptor structures: Ligand specificity, molecular switch and interactions with regulators. Biochimica Et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 2007; 1771(8): 915–925. https://doi.org/10.1016/j.bbalip.2007.01.007
11. Wikipedia contributors. (2023, September 11). *Peroxisome proliferator-activated receptor gamma*. Wikipedia. https://en.wikipedia.org/wiki/Peroxisome_proliferator-activated_receptor_gamma
12. Ahmadian, M., Suh, J. M., Hah, N., Liddle, C., Atkins, A. R., Downes, M., & Evans, R. M. PPARγ signaling and metabolism: the good, the bad and the future. Nature Medicine, 2013; 19(5): 557–566. https://doi.org/10.1038/nm.3159
13. Qaoud, M. T., Almasri, I. M., & Önkol, T. Peroxisome Proliferator-Activated Receptors as Superior Targets for Treating Diabetic Disease, Design Strategies - Review article. Turkish Journal of Pharmaceutical Sciences, 2022; 19(3): 353–370. https://doi.org/10.4274/tjps.galenos.2021.70105
14. Brown, J., & Plutzky, J. Peroxisome Proliferator–Activated receptors as transcriptional nodal points and therapeutic targets. Circulation, 2007; 115(4): 518–533. https://doi.org/10.1161/circulationaha.104.475673
15. Wikipedia contributors. (2023a, March 30). *Sulfonylurea*. Wikipedia. https://en.wikipedia.org/wiki/Sulfonylurea#cite_note-2
16. Kim, H., & Ahn, Y. Role of peroxisome Proliferator-Activated Receptor-Γ in the Glucose-Sensing apparatus of liver and B-Cells. Diabetes, 2004; 53(1): S60–S65. https://doi.org/10.2337/diabetes.53.2007.s60

17. Moini, J. Treatment of diabetes. In *Elsevier eBooks*, 2019; 163–174. https://doi.org/10.1016/b978-0-12-816864-6.00011-0
18. Ashcroft, F. M. Mechanisms of the glycaemic effects of sulfonylureas. Hormone and Metabolic Research, 1996; 28(09): 456–463. https://doi.org/10.1055/s-2007-979837
19. Sulfonylureas. (2023, January 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/30020597/
20. Proks, P., Reimann, F., Green, N., Gribble, F. M., & Ashcroft, F. M. (2002). Sulfonylurea stimulation of insulin secretion. Diabetes, 51(suppl_3), S368–S376. https://doi.org/10.2337/diabetes.51.2007.s368
21. Confederat, L., Constantin, S., Lupaşcu, F., Pânzariu, A., Hăncianu, M., & Profire, L. HYPOGLYCEMIA INDUCED BY ANTIDIABETIC SULFONYLUREAS. PubMed, 2015; 119(2): 579–584. https://pubmed.ncbi.nlm.nih.gov/26204670
22. Lee, K. W., Ku, Y. H., Kim, M., Ahn, B. Y., Chung, S. S., & Park, K. S. Effects of Sulfonylureas on Peroxisome Proliferator-Activated Receptor γ Activity and on Glucose Uptake by Thiazolidinediones. Diabetes & Metabolism Journal, 2011; 35(4): 340. https://doi.org/10.4093/dmj.2011.35.4.340
23. Fukuen, S., Iwaki, M., Yasui, A., Makishima, M., Matsuda, M., & Shimomura, I. Sulfonylurea Agents Exhibit Peroxisome Proliferator-activated Receptor γ Agonistic Activity. Journal of Biological Chemistry, 2005; 280(25): 23653–23659. https://doi.org/10.1074/jbc.m412113200
24. Khan, T., Dixit, S., Ahmad, R., Raza, S., Azad, I., Joshi, S., & Khan, A. R. Molecular docking, PASS analysis, bioactivity score prediction, synthesis, characterization and biological activity evaluation of a functionalized 2-butanone thiosemicarbazone ligand and its complexes. Journal of Chemical Biology, 2017; 10(3): 91–104. https://doi.org/10.1007/s12154-017-0167-y
25. *SwissADME*. (n.d.). http://www.swissadme.ch/
26. Wikipedia contributors. (2023b, July 23). *Lipinski's rule of five*. Wikipedia. https://en.wikipedia.org/wiki/Lipinski%27s_rule_of_five
27. *Calculation of molecular properties and bioactivity score*. (n.d.). https://www.molinspiration.com/cgi/properties
28. Koleva–PhD, Y., Georgieva–PhD, S., Student, A.P.N.A.P. and Student, I.I.P., 2019. Molecular properties and bioactivity score of newly synthesized derivatives of bexarotene.

29. Daina, A., Michielin, O., & Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, 2017; *7*(1). https://doi.org/10.1038/srep42717
30. https://tox-new.charite.de/protox_II/
31. Banerjee, P., Eckert, A., Schrey, A. K., & Preißner, R. ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Research*, 2018; *46*(W1): W257–W263. https://doi.org/10.1093/nar/gky318
32. Meng, X., Zhang, H., Mezei, M., & Cui, M. Molecular Docking: a powerful approach for Structure-Based drug discovery. *Current Computer - Aided Drug Design*, 2011; *7*(2): 146–157. https://doi.org/10.2174/157340911795677602
33. *1-Click-Docking*. (n.d.). https://mcule.com/apps/1-click-docking/
34. *dockingvina [online documentation]*. (n.d.). https://doc.mcule.com/doku.php?id=dockingvina