https://doi.org/10.48047/AFJBS.6.Si3.2024.3124-3129

Design and In Silico Evaluation of Thiazolidinediones Analogues as Antidiabetic Agents

Ranjeet Kumar[1*], Prashant Kumar[2], Vishal Dubey[3], Megha Tiwari[4],Akhilesh Kumar[5]

[1*,2,3,4,5]Naraina Vidyapeeth Group of Institutions, Faculty of Pharmacy, Panki, Gangaganj, Kanpur,208020

ArticleInfo

Volume6, Issue Si3,May2024

Received: 15May2024

Accepted:22June 2024

Published:11July2024

Doi

10.48047/AFJBS.6.Si3.2024.3124-3129

ABSTRACT:

The disease is characterized by elevated thrust levels, hunger, and urination. The leading cause of developing this disease is the production of insufficient insulin by the pancreas. There are two major categories of diabetes mellitus found: one is insulin-dependent diabetes mellitus (IDDM), and another is noninsulin-dependent diabetes mellitus (NIDDM).Using AutoDock Vina v1.5.7 and the CHARMm-based docking tool CDOCKER from Discovery Studio Client v20.1.0.19295, molecular docking simulations were performed to examine the binding interactions of the synthesized compounds within the target protein 5TT0's active site. All the four compounds having the capability to bind towards the PPAR-γ receptors and showing the better ADMEt results while checking through swiss ADME

These compounds can be further synthesized in the laboratory and tested for their PPAR-γ binding activity

1. Introduction

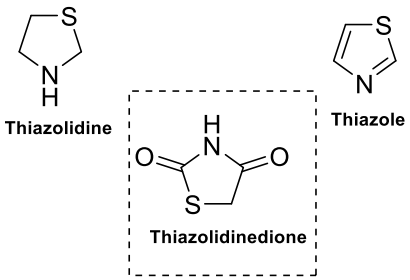
Diabetes mellitus (DM) is a disease identified by the hyped blood glucose level in a specific period. The disease is characterized by elevated thrust levels, hunger, and urination. The leading cause of developing this disease is the production of insufficient insulin by the pancreas. There are two major categories of diabetes mellitus found: one is insulin-dependent diabetes mellitus (IDDM), and another is noninsulin-dependent diabetes mellitus (NIDDM).(Shafrir & Raz, 2003) Insulin-dependent diabetes mellitus occurs when there is a destruction in the insulin production cells, while non-insulin-dependent diabetes mellitus is characterized by either resistance or irregular production of insulin. According to the report of the International Diabetes Federation (IDF), 77 million people in India currently have diabetes, and this number is increasing continuously, which may increase to upto124 million by 2045, and almost 25 million Indians are prediabetic.

The disease is also called a lifestyle disease due to improper functioning in daily life and lack of physical activities. Thiazolidinediones are the heterocyclic five-membered ring system, having nitrogen and sulfur as heteroatoms with two ketonic groups (Ali et al., 2024). They are considered the analogs of thiazolidine. These thiazolidinediones exhibit various pharmacological actions, such as antioxidant, anti-inflammatory, antiviral, antiplasmodial, and antihyperglycemics. Several thiazolidinedione derivatives are synthesized and tested for their antidiabetic activities; some clinically approved thiazolidinediones are pioglitazone and rosiglitazone, which are used to treat diabetes mellitus (Vulichi et al., 2021). Some are withdrawn from the market due to their toxicity, such as troglitazone and ciglitazone.

These thiazolidinediones are also known as glitazones and are now known as the activators of the PPAR-γ to treat NIDDM. Apart from the available glitazones for treating diabetes mellitus, the study on these thiazolidinediones continues to develop safer analogs with fewer side effects as the adverse cardiovascular effects are reported with the market available glitazones. (Gharge et al., 2024)

Thiazolidinediones

Heterocyclic nucleuses are well known for their importance in medicinal chemistry aspects and it is also known that more than 80% of medicinal agents exhibits a least one heterocyclic ring system in their structures. Thiazolidinediones can be characterized as the derivatives of thiazoles. Thiazoles are the five membered ring system exhibit **Thia** means sulfur and **azoles** means nitrogen group in a cyclic ring system, when the thiazole ring is saturated is called as thiazolidines. The structure of thiazole, thiazolidine and thiazolidinediones is illustrated in the (Long, Le Gresley, & Wren, 2021)



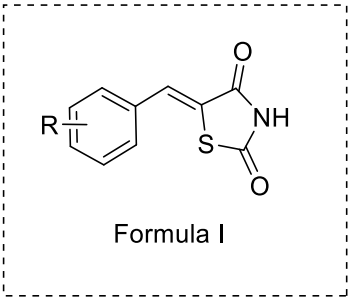
Chemical Structure of thiazole, thiazolidine and thiazolidinedione

Due to the presence of two ketonic group and alpha hydrogens this nucleus is also exist in the tautomeric form, the synthetic scheme for this nucleus was first given by Kallenberg in 1923. (Long et al., 2021) Thiazolidinediones were known for their wide range of biological activities over a long period of time as antimicrobial, antiviral, antioxidant, antiinflammatory, antimicrobial, COX inhibitors, xanthine oxidase inhibitors, anticancer agents and antihyperglycemic agents (Naim et al., 2017) Thiazolidinediones are also known as the glitazones due to its capability in treatment of diabetes mellitus from the late 1990s through the activation of peroxisomal proliferator activate receptor (PPAR) receptors. PPAR subtypes mostly PPAR γ are the nuclear receptors that regulates the synthesis of glucose and lipid metabolism.

Thorough literature search on thiazolidinediones shows that several compounds synthesized and evaluated for their antidiabetic activities. While some are approved for the treatment by FDA and others withdrawn from the market due to its side effects associated. (Stumvoll & Häring, 2002)

Aim and Objective-

1. Designing of thiazolidinedione derivatives as antidiabetic agents as per Formula 1
2. Discussing the binding affinity results of derivatives
3. Predicting the ADME of designed compounds.



Formula I

2. Methodology

General

Using AutoDock Vina v1.5.7 and the CHARMm-based docking tool CDOCKER from Discovery Studio Client v20.1.0.19295 (Dassault Systèmes Biovia Corp, 2019), molecular docking simulations were performed to examine the binding interactions of the synthesized compounds within the target protein 5TT0's active site. The compounds' structures were prepared and sketched using the PyMOL workspace (version 4.6). The target proteins' X-ray crystallographic structures were acquired from the Protein Data Bank (http://www.rcsb.org/pdb) and prepared for docking analysis in accordance with Parate et al.'s guidelines (2021). In this optimization process, hydrogen atoms were added, water molecules were removed, bond orders were completed, and hydrogen bonds were assigned. The AutoDock Vina program was then used to dock the compounds into the protein's active site. The negative values of the compounds' interaction energies were used to estimate their binding energies with the target proteins (Shih et al., 2011).

ADME studies were performed by swiss ADME free software to check the pharmacokinetics of synthesized compounds

3. Result and Discussion

To validate the pharmacological studies, molecular docking studies of compounds 1 through 4 were carried out at the active pockets of the target protein (5TT0). The docking results showed that all the compounds interacted through various bonding mechanisms with key amino acid residues at the target proteins' active sites, including hydrogen bonding, л-л interactions, Van der Waals forces, л-alkyl, л-sulfur, л-anion, and carbon-hydrogen bonding. Compound had the highest binding energy of all, measuring -7.9 Kcal mol-1 (Table 1). The 2D and 3D interaction positions of artemisinin with corresponding target proteins are shown in Figures 1-4. The amino acids of the different target proteins that artemisinin interacted with are listed.

Table 1. Docking energy & Interaction of test compounds with the active residues of target proteins

Compound	Target Protein	Interaction Energy (kcal/mol)
1	5TT0	-7.4
2	5TT0	-7.1
3	5TT0	-7.3
4	5TT0	-7.3

From the swiss ADME results it was concluded that:

1. None of the designed compound viloating the lipinski rule of five criteria
2. All of the designed compounds shows high GI absorption
3. All of the designed compounds having optimum water solubility
4. None of the compounds is showing the PAINS alerts

4. Conclusion

From the designed four compunds we can conclude that all the four compounds exhibits affinity towards the active binding site of PPAR-γ (PDB ID: 5TTO) with the binding score of -7.4,7.1,7.3 and -7.3 kcal/mol respectively.

All the four compounds having the capability to bind towards the PPAR-γ receptors and showing the better ADMEt results while checking through swiss ADME

These compounds can be further synthesized in the laboratory and tested for their PPAR-γ binding activity

5. References

1. Ali, I. H., Hassan, R. M., El Kerdawy, A. M., Abo-Elfadl, M. T., Abdallah, H. M., Sciandra, F., & Ghannam,A. (2024). Novel thiazolidin-4-one benzenesulfonamide hybrids as PPARγ agonists: Design, synthesis and in vivo anti-diabetic evaluation. European journal of medicinal chemistry, 269, 116279.
2. Feingold, K. R. (2022). Oral and injectable (non-insulin) pharmacological agents for the treatment of type 2 diabetes. Endotext [Internet].
3. Gharge, S., Alegaon, S. G., Ranade, S. D., Khatib, N., Kavalapure, R. S., Kumar, B. P., . . . Bavage, N. B. (2024). Design, synthesis of new 2, 4-thiazolidinediones: In-silico, in-vivo anti-diabetic and anti-inflammatory evaluation. European Journal of Medicinal Chemistry Reports, 11, 100151.
4. Kaur, P., Kumar, M., Parkash, J., & Prasad, D. (2019). Oral hypoglycemic drugs: An overview. Journal of Drug Delivery and Therapeutics, 9(3-s), 770-777.
5. Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A review on diabetes mellitus: type1 & Type2. World Journal of Pharmacy and Pharmaceutical Sciences, 9(10), 838-850.
6. Long, N., Le Gresley, A., & Wren, S. P. (2021). Thiazolidinediones: an in–depth study of their synthesis and application to medicinal chemistry in the treatment of diabetes mellitus. ChemMedChem, 16(11), 1717-1736.
7. Lorenzati, B., Zucco, C., Miglietta, S., Lamberti, F., & Bruno, G. (2010). Oral hypoglycemic drugs: pathophysiological basis of their mechanism of action. Pharmaceuticals, 3(9), 3005-3020.
8. Mane, P. B., Antre, R. V., & Oswal, R. J. (2012). Antidiabetic drugs: An overview. Int. J. Pharm. Chem. Sci, 1(1), 301-306.
9. Naim, M. J., Alam, M. J., Ahmad, S., Nawaz, F., Shrivastava, N., Sahu, M., & Alam, O. (2017). Therapeutic journey of 2, 4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship. European journal of medicinal chemistry, 129, 218-250.
10. Shafrir, E., & Raz, I. (2003). Diabetes: mellitus or lipidus? Diabetologia, 46, 433-440.
11. Sharma, A., Kumar, N., Gulati, H. K., Rana, R., Jyoti, Khanna, A., . . . Bedi, P. M. S. (2024). Antidiabetic potential of thiazolidinedione derivatives with efficient design, molecular docking, structural activity relationship, and biological activity: an update review (2021–2023). Molecular Diversity, 1-25.
12. Singh, G., Singh, R., Monga, V., & Mehan, S. (2024). 3, 5-Disubstituted-thiazolidine-2, 4-dione hybrids as antidiabetic agents: Design, synthesis, in-vitro and In vivo evaluation. European journal of medicinal chemistry, 266, 116139.
13. Stumvoll, M., & Häring, H.-U. (2002). Glitazones: clinical effects and molecular mechanisms. Annals of medicine, 34(3), 217-224.
14. Uppal, S., Italiya, K. S., Chitkara, D., & Mittal, A. (2018). Nanoparticulate-based drug delivery systems for small molecule anti-diabetic drugs: An emerging paradigm for effective therapy. Acta Biomaterialia, 81, 20-42.
15. Vulichi, S. R., Kabra, A., Kumar, R., Suman, K., Rao, C. V., & Cruz-Martins, N. (2021). Concise perspectives on some synthetic thiazolidine-2, 4-dione derivatives and their specific pharmacodynamic aspects. Life sciences, 271, 119182.
16. WHO. Retrieved from https://www.who.int/healthtopics/diabetes?gad_source=1&gclid=CjwKCAjwvvmzBhA2EiwAtHVrbyubBzA7rL5HwnSfTbCVK7vXcCZivGQpxSlBVQDJBXRn-Ok3Zv7W3hoCrdgQAvD_BwE#tab=tab_1. https://www.who.int/health-topics/diabetes?gad_source=1&gclid=CjwKCAjwvvmzBhA2EiwAtHVrbyubBzA7rL5

HwnSfTbCVK7vXcCZivGQpxSlBVQDJBXRn-
Ok3Zv7W3hoCrdgQAvD_BwE#tab=tab_1