MS.ID-IJPBS-0507
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2022) 12 (4): 75-81
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Potential Activity of Synthetic Thiazolidinedione as Antidiabetic Agents

[1]Pinki, [2]Satendra Kumar and [3]Anita Singh*

[1]Research Student, Department of Pharmaceutical Sciences, Kumaun University, Bhimtal Campus, Nainital - 263136.

[2]Assistant Professor, Dev Bhoomi School of Pharmacy and Research-Top Pharmacy College in Dehradun.

[3]Associate Professor, (Head of Department), Department of Pharmaceutical Sciences, Kumaun University, Bhimtal campus, Nainital - 263136.

Received: 16 Jul 2022/ Accepted: 18 Aug 2022 / Published online: 1 Oct 2022
***Corresponding Author Email:** dranitaku@gmail.com

Abstract

One of the chronic medical disorders (Diabetes) characterized by a deficiency of insulin or inadequate insulin use. Diabetes has been one of the fastest increasing chronic diseases in recent years. Thiazolidinediones (TZDs) or Glitazones are a type of insulin sensitizer that is commonly utilized in the management of Type II diabetes mellitus (T2DM). TZDs have been discovered to have diabetes-preventing properties through antihyperglycemic, hypoglycaemic, and hypolipidemic agents. The aim of this synthetic review is to look into the anti-diabetic activity of thizazolidinedione-based drugs based on published studies along with their synthetic scheme. Several research about the compounds' biological screening against a variety of targets, including aldose reductase, -glucosidase, -amylase, PPAR-, and PTPT1B, was discovered in this study. Some compounds mentioned are also tested in vivo in living organisms.

Keywords

Thiazolidinediones, Antidiabetic activity, PPAR- γ, Amylase, Aldose reductase.

*****

INTRODUCTION:

Diabetes mellitus is some sort of disease that causes persistently elevated blood glucose. [1,2]. According to the 16th international diabetes federation (IDF) conference in 1997, diabetes could be branched into two classes: Type 1 diabetes mellitus is insulin-dependent (IDDM) in which the pancreatic islet b-cells in the human body were damaged and incapable of producing insulin or producing a small amount of insulin, this is a chronic autoimmune disorder. Type 2 diabetes mellitus is a type of non-insulin-dependent diabetes mellitus in which there is less insulin resistance and insulin deficiency developed [3,4]. Gestational DM (GDM) is defined as the glucose intolerance of any credential that starts or is recognized for the first-time during pregnancy. About 4% of pregnancies are affected by this complication. Due to the significant hormonal changes that take place during pregnancy, GDM is brought on by maternal tissue insulin resistance [5]. Diabetes Mellitus is one of the major menaces to human health worldwide and it will be the seventh leading cause of death in 2030. A report by WHO is of high concern that the number of people after teenage getting affected by diabetes has rapidly increased. NIDDM is the most prevalent form of

diabetes, affecting 90% of individuals worldwide [6]. If it is not treated on time, diabetes can cause various symptoms that are a polyurea, increased thrust, increased hunger, weight loss, hypertension, and eye, kidney, and liver injury [7]. For the treatment of type 2 diabetes, a variety of drugs such as sulfonylureas, biguanides, glinides, and glitazones are used, but all of them have unintended consequences such as hypoglycemia and obesity [6]. Due to severe side effects, biguanides are banned in western such as lactic acidosis and sulfonylurea treatment has stopped because of primary or secondary failure of efficacy [7].

Thiazolidinediones (TZDs) that serve as PPAR- γ agonists are one of the selective weapons which are orally active as antidiabetic agents [8]. TZDs are five-membered heterocyclic compounds made up of thiazole containing an atom nucleus of N, O, and S [9]. Normalization of glucose levels occurs due to activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ) (normalization of sugar levels); a member of the nuclear receptor family that enhance glucose detection capability of pancreatic β cells, it is widely required to treat type-2 diabetes mellitus. These receptors are found in diverse tissues. TZDs, also known as glitazones activate the PPAR-γ receptor and improve the transcription of genes that encode for factors involved in the intake of glucose and the metabolism of glucose and fatty acids [8]. Many drugs have been reported for the management of type-2 diabetes mellitus like pioglitazone, rosiglitazone, troglitazone, etc [10]. After the launch of the thiazolidinediones, several treatment-related toxicity reports have been published. Along with maintaining diabetes, these drugs also show other harmful effects like rosiglitazone cause hepatotoxicity and troglitazone show liver injury as well as pioglitazone causes bladder cancer [1,11]. Treatment with pioglitazone is still available in most countries like the USA and European markets, is cost-effective, and has gained renewed approval after novel advantageous indications [12,13]. To find fewer toxic derivatives of TZDs, in this article, we introduce a library of novel derivatives thiazolidinedione that have powerful activity for the management of type-2 diabetes mellitus carrying two atoms of oxygen, one of sulfur, and one of nitrogen [14].

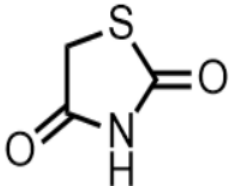
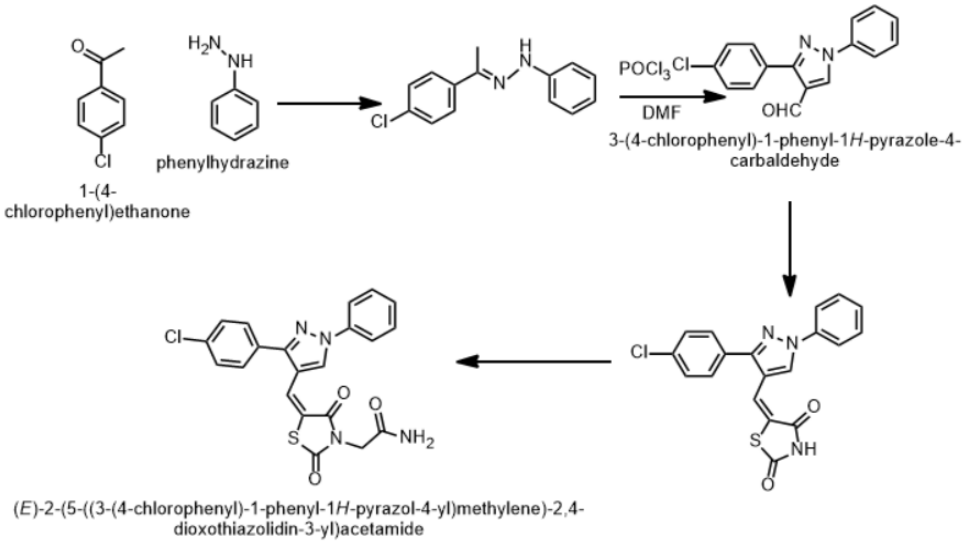


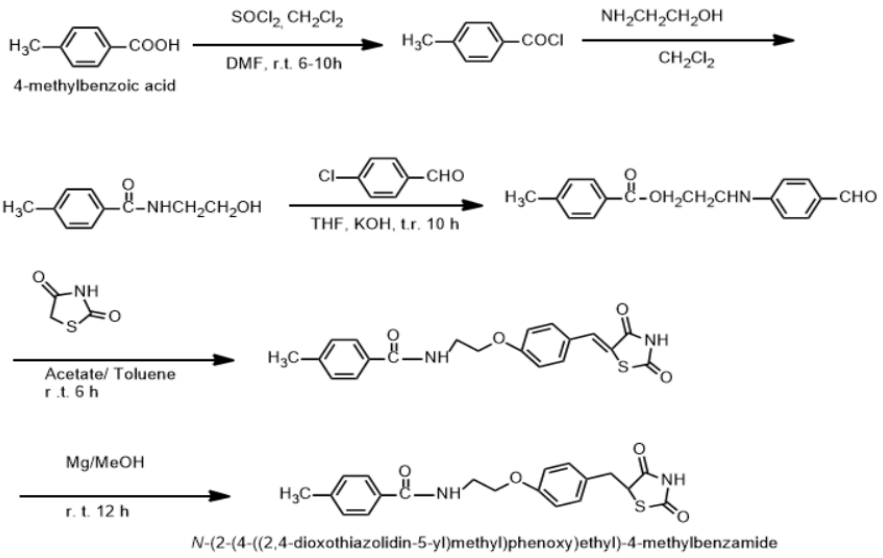
Fig 1: Thiazolidinedione

Mohd. Javed Naim et.al has reported a series of thiazolidinedione-based amide derivatives that were designed, synthesized, and docked concerning the PPAR-γ receiver target. A series was synthesized by acetophenones and phenyl hydrazine with the help of the Villsmeyer Hack reaction in the presence of DMF & POCl3 and Knoevenagel condensation. According to the data analyzed, chemicals 6c and 6m had blood glucose reducing effects of 142.4 7.45 & 145.4 5.57 compared to pioglitazone (134.8 4.85) & rosiglitazone (144.6 6.56). When compared to reference medications, compounds 6e and 6n demonstrated substantial outcomes; 6a, 6b, 6i, and 6l demonstrated moderate results; however, compounds 6g, 6k, and 6d did not provide promising results. Due to the activation of PPAR-c receptors, compound 6c demonstrated the most effective effects that were compatible with the in vitro findings. 2-(5-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4yl) methylene)-2,4-dioxothiazolidin-3-yl) acetamide which has been synthesized by scheme 1, showed a high potency antidiabetic and 2.1 increased folds in the expression of PPAR-**γ** against pioglitazone and Compound 6c with biochemical endpoints in the interval showed no evidence of hepatotoxicity without any significant weight gain [15].



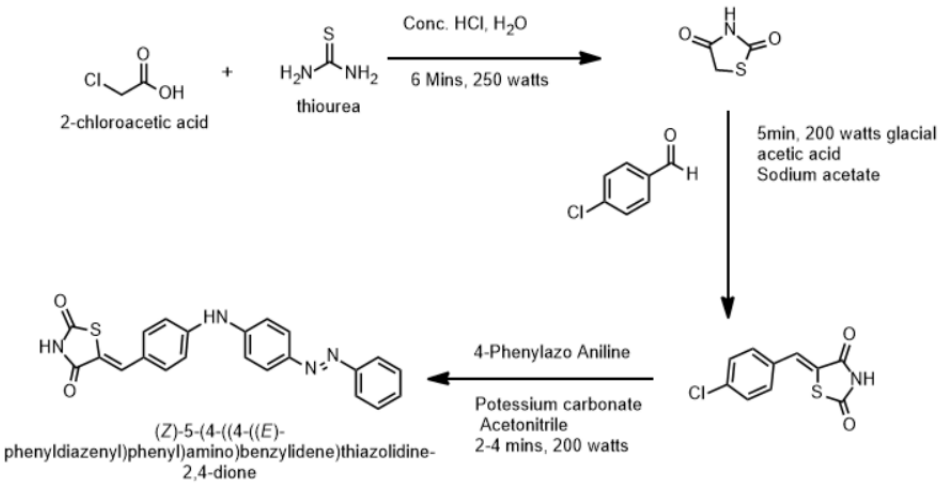
SCHEME: 1

Huiying Zou et al. Using the bioisostere principle, created novel derivatives of 2,4-thiazolidinedione. Rosiglitazone was selected as the main ingredient in this investigation. In particular, the biological activity of compounds 6a, 6e, 6f, 6g, and 6i in vitro was better, with compound 6e EC50 for PPAR-γ being 0.03 ±0.01 µmol/l. The compounds 6a, 6e, 6f, 6g, and 6i were evaluated in vivo using the in vivo activity test. The test indicators were acute toxicity, cell survival experiments, glucose tolerance tests, insulin tolerance tests, and in vivo investigations. Compound 6e N-(2-(4-((2,4-dioxothiazolidin-5-yl) methyl) phenoxy) ethyl)-4-methylbenzamide which tends to increase blood sugar had an inhibiting effect and had a significant insulin hypoglycaemic effect of enhancing and extending the exogenous. They discovered that these substances fall within the category of low toxicity substances based on the results of cytotoxicity tests and acute toxicity tests (LD50). These target compounds were created using the five steps of acyl chlorination, amidation, condensation, Knoevenagel, and addition reaction (Scheme 2). The straightforward operation, high total yield, and friendly reaction conditions of the synthetic method were its distinguishing features [3].



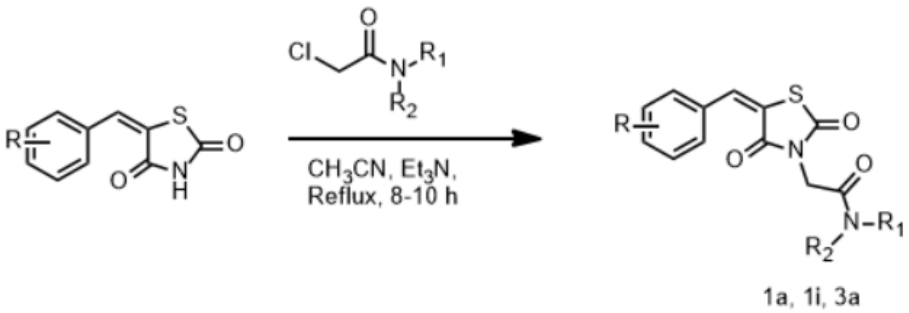
SCHEME: 2

Geetha B. et al have designed and synthesized novel derivatives of thiazolidinedione by using scheme 3 which is a microwave-assisted technique. They screened out the synthesized derivatives by Insilico methods (molecular docking, quantitative structure-activity relationship studies) for the assessment of antidiabetic activity. They employed Autodock for docking, with PPAR as the target (1ZGY). With a glide score of -9.6 Kcal/mol and involvement in binding with the amino acid residues Tyr 473, His 323, Leu 340, Arg 288, Met 364, Cys 285, Ile 341, Phe 363, and His 449, IIP3 has also demonstrated increased binding affinity to the target. Nearly 12 substances had a greater affinity for the target PPAR-γ. -10.5 Kcal/mol, docking experiments show that compound IIA8 [5-((Z)-4-((4-((E)-phenyl diazenyl) phenyl) amino)benzylidene]thiazolidine-2,4-dione] is the most efficient binding substance. It included bonding with amino acid residues Ser 342, His 266, Asp 260, Leu 330, and Ile 341, They claimed that substances with a thiazolidinedione ring and amine groups will have stronger anti-diabetic effects [16].



SCHEME: 3

Yasmin Sabina et al have proposed the synthesis and testing of a collection of brand-new 5-benzylidene-thiazolidine-2,4-dione (BTZD) derivatives comprising a substituent on nitrogen thiazolidine nucleus which have been synthesized by scheme 4. 1a, 1i, and 3a substances were identified as weak to moderate partial agonists with PPAR-gamma selectivity. Furthermore, docking studies revealed that BTZDs interact with PPAR in a novel way, primarily making hydrophobic contacts with the ligand-binding pocket (LBD) rather than directly making H-bonding connections with critical residues in H12, as is typical of full agonists. Among them all, 1i was the least cytotoxic substance, while 3a was shown to be the most effective. This study showed that PPAR selectively targeted pharmacological agents are extremely promising for further research in the treatment of type 2 diabetes mellitus, which is mentioned in table 1. According to the outcomes of in vitro investigations, therefore, 1a, 1i, and 3a are valuable in terms of their safety and effectiveness [14].

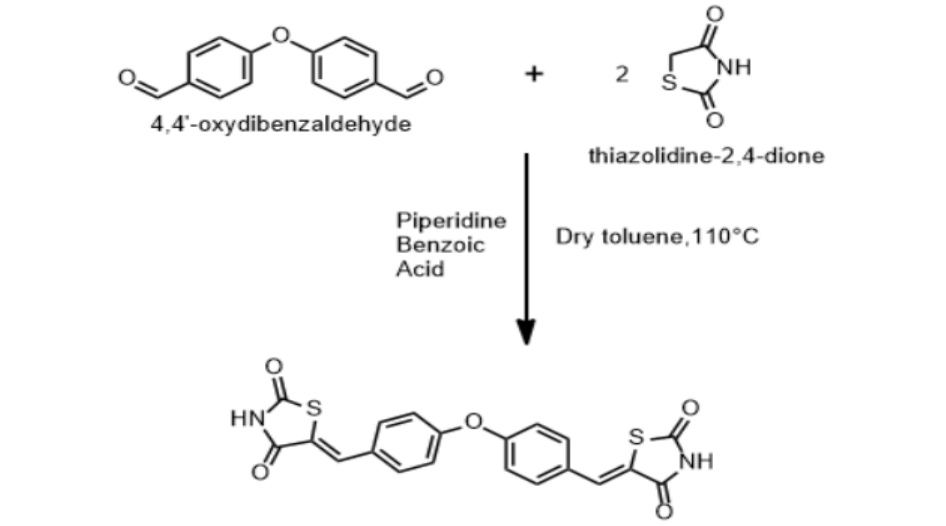


SCHEME: 4

TABLE 1:

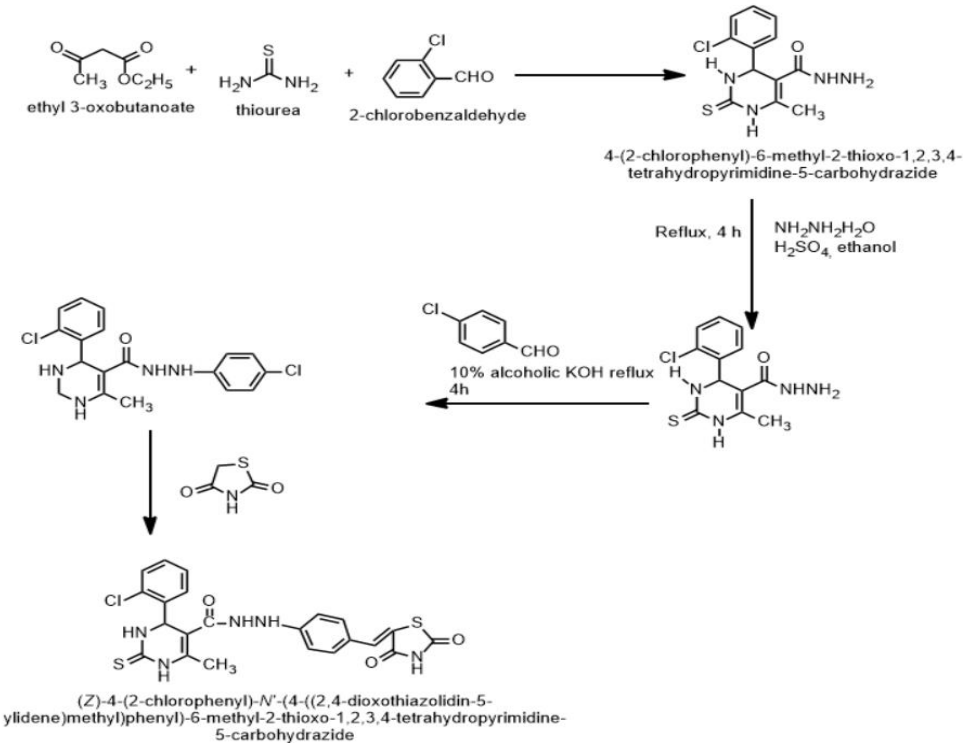
Code	R	R_1	R_2
1a	H	H	$-(CH_2)_3CH_3$
1i	H	$-C_2H_5$	$-C_2H_5$
3a	4-Cl	H	H

Álvarez-Almazán, S et al. studied the analysis of 219 new derivatives of thiazolidinedione in Silico, they selected the best one for synthesis. They had to use female rats to assess acute oral toxicity and streptozocin-induced rat models for diabetes to manage diabetes-related parameters. The animal did not exhibit any hazardous symptoms, so the dose was increased for the following rat by 3.2 progression factors (550 mg/kg), with the same results. Visual Molecular Dynamics was used to examine H-bond interactions. In type 2 diabetes animal models and also in patients, the level of sugar is normalized through the activation of the PPARs receptor. They synthesize the compound successfully by Knoevenagle condensation which has been mentioned in scheme 5. The pharmacological actions of the compound are related to pioglitazone and also reduce the other risk factors like polydipsia, polyphagia, and systemic inflammation. This research also reveals that besides diabetes, compound 1G is also an effective candidate for the treatment of arthritis, inflammation, heart disease, and cancer [8].



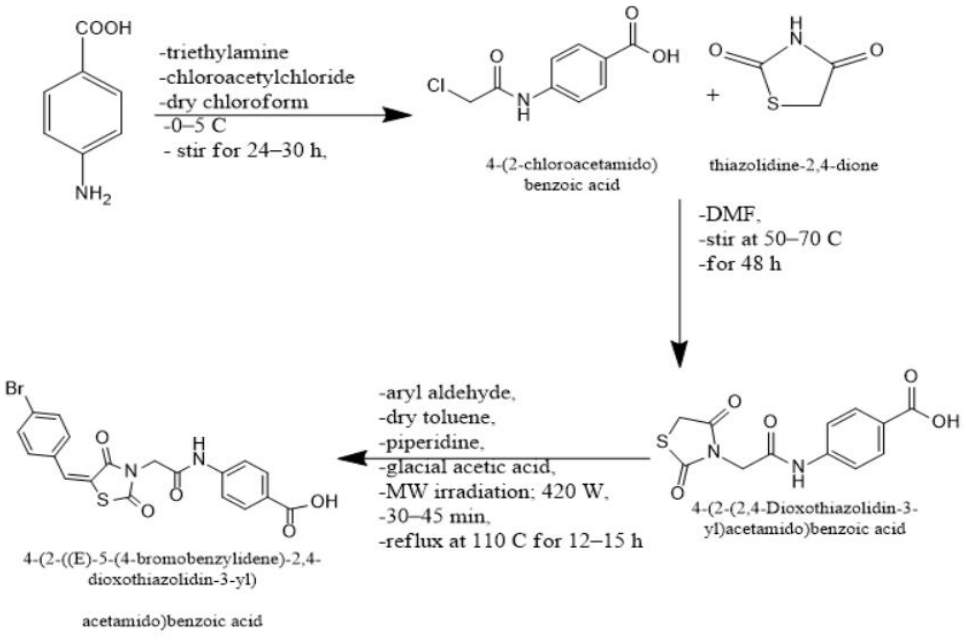
SCHEME: 5

Sawant Ramesh L.et al. created novel thiazolidine compounds and docked them with the active site of the PPAR using scheme 6. For molecular docking experiments, they were forced to use VLife MDS 4.3 software. The Hydrazide-containing compounds were chosen for synthesis after molecular docking experiments. Wistar rats were used to test the anti-diabetic efficacy of the title compounds utilizing an alloxan-induced approach. By generating hydrogen bond interactions with the amino acid residues HIS370D and ASP517D, as well as hydrophobic contacts with the amino acid residues LEU500D and SER336D, the ligand 4b attaches to the PPAR-receptor. In comparison to the usual medication, pioglitazone, molecule 4b exhibits similar hydrophobic interactions. They reported that by substituting nonpolar, electron-withdrawing substituents at positions 4 of the pyrimidine skeleton and the nitrogen of the thiazolidine with hydrogen bond acceptors, potent anti-diabetics could be developed to inhibit peroxisome proliferator-activated receptor. [7].



SCHEME: 6

Kar Koyel et al. created 12 brand-new thiazolidinediones with rhodanine, bio isostere, and oxazolidine ring architectures. For the in-vitro glucose uptake assay and determination of antidiabetic efficacy in the presence and absence of insulin, they used a rat hemidiaphragm. They stated that the compound 16[4-(2-((E)-5-(4-bromobenzylidene)-2,4-dioxothiazolidin-3-yl] acetamido] is a viable candidate for glucose-lowering action and that this research is based on the structure-activity relationship [17].



SCHEME: 7

CONCLUSION:

The only current diabetes medications that work largely by improving insulin sensitivity are thiazolidinediones (TZDs). Many compounds based on thiazolidinedione have been developed recently and tested for their increased pharmacological properties. This article's numerous schemes generated a lot of interest and inspired chemists and biologists to conduct in-depth research or engage in molecular alterations, leading to the ongoing development of a new procedure with better observation. The different thiazolidinedione derivatives schemes that have a specific contribution to diverse pharmacological domains are the major subject of this review.

REFERENCES:

1. Madhavan GR, Chakrabarti R, Vikramadithyan RK, Mamidi RN, Balraju V, Rajesh BM, Misra P, Kumar SK, Lohray BB, Lohray VB, Rajagopalan R. Synthesis and biological activity of novel pyrimidinone containing thiazolidinedione derivatives. Bioorganic & medicinal chemistry, 10(8): 2671-80, (2002 Aug 1).
2. DeFronzo RA. Pathogenesis of type 2 (non-insulin-dependent) diabetes mellitus: a balanced overview. Diabetologia, 35(4): 389-97, (1992 Apr).
3. Huiying Z, Guangying C, Shiyang Z. Design, synthesis, and biological activity evaluation of a new class of 2, 4-thiazolidinedione compounds as insulin enhancers. Journal of Enzyme Inhibition and Medicinal Chemistry, 34(1): 981-9, (2019 Jan 1).
4. Elampulakkadu A, Thankamma MP, Thirumoorthy P. In silico Design and Molecular Docking Studies of Benzimidazole Bearing thiazolidine-4-one Derivatives as PPARγ Agonists in Diabetes Mellitus Int. J. Pharm. Sci. Rev. Res., 65(1): 88-91, (November - December 2020).
5. Bánhidy F, Ács N, Puhó EH, Czeizel AE. Congenital abnormalities in the offspring of pregnant women with type 1, type 2 and gestational diabetes mellitus: A population-based case-control study. Congenital anomalies,50(2):115-21, (2010 Jun).
6. Thangavel N, Al Bratty M, Javed SA, Ahsan W, Alhazmi HA. Targeting peroxisome proliferator-activated receptors using thiazolidinediones: a strategy for the design of novel antidiabetic drugs. International Journal of medicinal chemistry. 2017: 20 Pages, (2017).
7. Sawant RL, Wadekar JB, Kharat SB, Makasare HS. Targeting PPAR-γ to design and synthesize antidiabetic thiazolidines. EXCLI journal.17:598, (2018).
8. Álvarez-Almazán S, Navarrete-Vázquez G, Padilla-Martínez II, Correa-Basurto J, Alemán-González-Duhart D, Tamay-Cach F, Mendieta-Wejebe JE. A new symmetrical thiazolidinedione derivative: in silico design, synthesis, and in vivo evaluation on a streptozotocin-induced rat model of diabetes. Processes.9(8):1294, (2021 Jul 27).
9. Napoleon AA, Nadu T. Review on recent developments and biological activities of 2, 4 thiazolidinediones. J. Pharm. Tech.9:429-43, (2016).
10. Dadasaheb K, Jain N, Vijay J, Kashid G. Design synthesis and evaluation of novel thiazolidinedione derivatives as antidiabetic agents. Pharma Innov J.6:390-8, (2017).
11. Datar PA, Aher SB. Design and synthesis of novel thiazolidine-2, 4-diones as hypoglycemic agents. Journal of Saudi Chemical Society.20: S196-201, (2016 Sep 1).
12. Nesti L, Tricò D, Mengozzi A, Natali A. Rethinking pioglitazone as a cardioprotective agent: a new perspective on an overlooked drug. Cardiovascular Diabetology.20(1):1-7, (2021 Dec).
13. Unlusoy MC, Kazak C, Bayro O, Verspohl EJ, Ertan R, Dundar OB. Synthesis and antidiabetic activity of 2, 4-thiazolidinedione, thiazolidinedione, and 2-thioxo-imidazolidine-4-one derivatives bearing 6-methyl chromonyl pharmacophore. Journal of enzyme inhibition and medicinal chemistry.28(6):1205-10, (2013 Dec 1).
14. Yasmin S, Capone F, Laghezza A, Piaz FD, Loiodice F, Vijayan V, Devadasan V, Mondal SK, Atlı Ö, Baysal M, Pattnaik AK. Novel benzylidene thiazolidinedione derivatives as partial PPARγ agonists and their antidiabetic effects on type 2 diabetes. Scientific reports.7(1):1-7 (2017 Oct 31).
15. Naim MJ, Alam MJ, Nawaz F, Naidu VG, Aaghaz S, Sahu M, Siddiqui N, Alam O. Synthesis, molecular docking and anti-diabetic evaluation of 2, 4-thiazolidinedione based amide derivatives. Bioorganic chemistry.73:24-36, (2017 Aug 1).
16. Geetha B, Swarnalatha G, Reddy GS. MICROWAVE-ASSISTED SYNTHESIS, QSAR, AND MOLECULAR DOCKING STUDIES OF 2, 4-THIAZOLIDINEDIONE DERIVATIVES. system.12(3):1063-71, (2019 Jul).
17. Kar K, Krithika U, Basu P, Kumar SS, Reji A, Kumar BP. Design, synthesis, and glucose uptake activity of some novel glitazones. Bioorganic chemistry.56:27-33, (2014 Oct 1).