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Thiazolidinedione Derivatives: Multifaceted Pharmacological Activities and Therapeutic Potential

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ABSTRACT
Thiazolidinediones are a class of well-established antidiabetic medications, similarly termed as glitazones. Thiazolidinedione structure has been a significant primary area of exploration, including plan and improvement of novel medications aimed at the administration of type 2 diabetes. Far reaching research has uncovered that the proposed antidiabetic movement in type II diabetes is because of their agonistic impact on peroxisome proliferator-initiated receptor (PPAR) having a place with the atomic receptor family. Glitazones have specific partiality to PPARγ. Pharmacology as well as science of thiazolidinedione as PPARγ agonists and the capability of more up to date analogs as double agonists of PPARs and other promising focuses for the treatment of type II diabetes. This audit features the thiazolidinedione which would direct the forthcoming examination in plan of new thiiazolidinedione subsidiaries for the administration of type II diabetes.

KEY WORDS: Thiazolidinediones, Oxazolidine, Pioglitazone.

I. INTRODUCTION

The thiazolidinediones also known as glitazones, are a class of medications used in the treatment of diabetes mellitus type 2. They were introduced in the late 1990s. They contain a functional group in which thiazolidine serves as a dione. These (TZDs) are a new class of antidiabetic agents and include three compounds that have come to clinical use — troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Actos) — as well as several others that have been limited to pre-clinical study[1]. 2,4-thiazolidenedione (TZD) is an attractive scaffold because of its prestigious position in medicinal chemistry as this unit is responsible for numerous pharmacological and biological activities, e.g., antidiabetic[2,3],antidiarrheal[4], anticonvulsant[5], antimicrobial[6], antihistaminic[7], anticancer[8], anti-HIV[9], 15-hydroxyprostaglandin dehydrogenase inhibitors[10], and anti-ischemic[11].

The position of these molecules seems to be most significant as they are a subset of commercially employed non-insulin-dependent diabetes mellitus and insulin-sensitizing agents (Figure 1) such as rosiglitazone, parastate, pioglitazone, AD-5061, pioglitazone, and so on.

The properties of thiazolidinediones includes: Chemical formula- C_3H_7NS, Molar mass-89.16 $g{\cdot}mol^{-1}$, Density-1.131 g/cm^3, Boiling point-72 to 75 °C (162 to 167 °F; 345 to 348 K) at 25 torr where as the Chemical formula of 2,4-Thiazolidinedione is $C_3H_3NO_2S$ and the boiling point of 2,4-Thiazolidinedione was found to be 178-179 °C (19 mmHg) and its melting point is 125-127°C

The endocrine elements of the pancreas are islets Langerhans & they contribute to 1% of total mass of pancreas. The pancreas beta-cell produces insulin and is synthesized primarily as a poly peptide precursor called preproinsulin. Preproinsulin is changed in pancreas for forming pro-insulin, by removing 4 amino acid precipitates and forms same amount of C peptide and insulin. Insulin protein consists of 51 AAs in 2 chains which are joined by 2-disulphide bonds. Inside the islets cells, insulin & C-peptide are packed into granular material.

Glucose stimulates the release of insulin. This reaction is activated by the consumption of enrichments and the liberation of hormone called gastrointestinal peptide. With the IV injections of glucose and there will be a response to the biphasic insulin. There is also a rapid reaction initially in the first two minutes, and after 5-10 minute this is

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followed by 2nd reaction which is lesser effective but is undergo over 1 hr. The first reaction indicates the releasing of the insulin which is stored and second response means the discharge of insulin that is synthesized newly. Glucose and sulphonylureas will not result in the biosynthesis of insulin but only stimulate the release of insulin. The insulin that is released from pancreas entering into the hepatic circulation. It is quickly degraded by liver and half of it reaches the circulatory system in the blood vessels. At base level, the secretion of insulin is approximately 1unit/hr. The food intake results in a push for 5 to10 times increase in its level. Over all daily insulin secretion is around 40 units. Insulin in monomer form circulates freely in the blood and it has a half-life of about 4minutes and liver and kidneys will metabolize the produced insulin in blood. In kidneys, glomeruli filters the insulin and it is degraded and reabsorbed into the body by tubules. When the patient has hepatic conditions and renal diseases, insulin clearance either increases or decreases therefore necessary dose adjustment is to be done. Insulin is also degraded by peripheral tissues like fat and muscle but it is very less significant compared to others.

Insulin sensitive receptors are present in tissues and they cause insulin to bind reversibly to them. The response of insulin in body can be very specific and can be altered by changing the receptor affinity to bind insulin or changing the number of receptors. The receptor number changes rapidly in the following situations namely obesity & long-term exposure to excessive insulin dose. These both cause to a rapid lowering in the number of insulin receptors that is down regulation.

When insulin reacts with the receptor and binds to it, it will release a chain of messengers inside the cell there by opening the process of glucose transport, amino acids and electrolytes. When there is an acute insulin deficiency it leads to uncontrolled glycogenolysis in the liver and this causes a raise in hepatic glucose output. The hyperglycemia issues and insulin sensitive tissues will lack the insulin reuptake due to this. So, as a result of the hormonal disturbance or due to acute illness or any infection causes an elevated production of the hormones which are counterregulatory such as growth hormone, catecholamine, glucagon and cortisol. These all will raise glucose production in the liver. Simultaneously, the normally occurring restraining effect of insulin is restricted and restrained. Fatty acids which are non-esterified are liberated into the systemic flow and are pick up by the liver, it generates acetyl coenzyme A (acetyl CoA). Due to rapidrelease of increased amounts of hydroxyl-butyrate, Ketone bodies and acetoacetate intothe systemic circulation leads to the condition called DKA (diabetic ketoacidosis).

Molecular mechanism of action of thiazolidinedione as oral hypoglycemic drug:

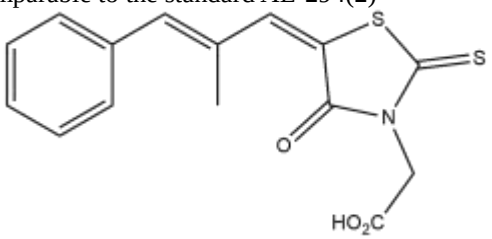
PPARϒ is a member of a family of nuclear receptors. Another member of this class, peroxisome proliferator-activated receptor alpha (PPARϒ), is predominantly expressed in the liver and is thought to mediate the triglyceride lowering actions of fibrates. PPARϒ is expressed in many tissues, including colon, skeletal muscle, liver, heart and activated macrophages, but is most abundant in adipocytes. Thiazolidinediones are selective agonists of PPARϒ. When activated by a ligand, such as a thiazolidinedione, PPARϒ binds to the 9-cis retinoic acid receptor (RXR [retinoid X receptor]) to form a heterodimer. This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism[12].

Thiazolidinediones bind to the gamma form of the peroxisome proliferator- activated receptor (PPAR). This stimulates peripheral adipocytes to increase their uptake of free fatty acids, which leads to reductions in the fat stored in muscle, liver and visceral fat deposits. The thiazolidinediones also lead to an increase in the secretion of adiponectin and a decrease in the production of resist in and tumour necrosis factor α(TNF- α). It is unknown if thiazolidinediones have direct effects on muscle or liver.

Therapeutic uses:

Anti-diabetic activity:

Sohda et al. synthesized a series of 4-(2-methyl-2-phenylpropoxy) benzyl derivatives and evaluated their hypoglycemic and hypolipidemic activities with genetically obese and diabetic mice. Among these, compound (1) was found to possess good hypoglycemic and hypolipidemic activities comparable to the standard AL-294(2) [18]



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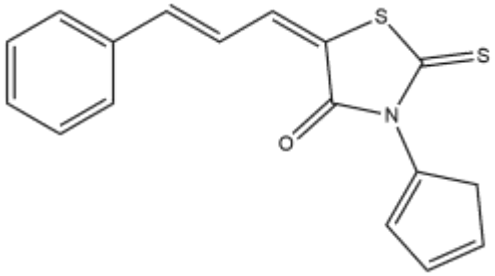
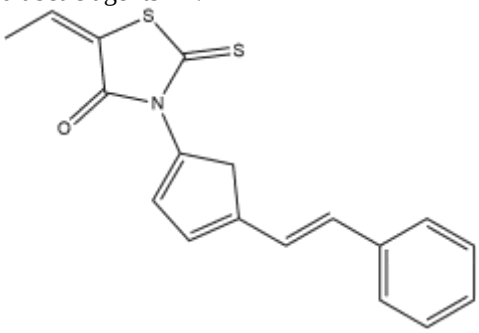
Yoshioka et al. synthesized of a novel series of chroman thiazolidine-2, 4-diones and evaluated for their hypoglycemic activity. Among these, compound (3) exhibited hypoglycemic and hypolipidemic activities and was well established as troglitazone [19]. This was later followed by pioglitazone (4) and rosiglitazone (5) which were established as potent hypoglycemic agents [20]. Replacement of the phenyl ring with a chroman ring in the C-5 position of thiazolidinedione moiety led to the synthesis of englitazone(6) [21].

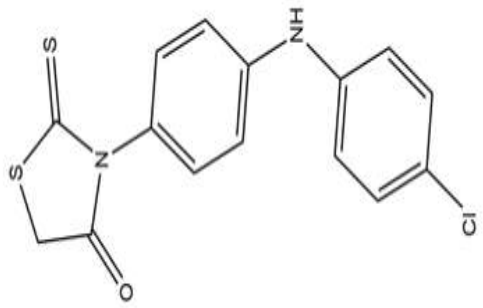


Nazreen et al. synthesized novel 1, 3, 4-oxadiazole and 2, 4-thiazolidinedione based bis-heterocycles and studied blood glucose lowering effect comparable with standard drug pioglitazone (4) and rosiglitazone (5). Compound (7) may be considered as a potential candidate for the development of new antidiabetic agents [22].

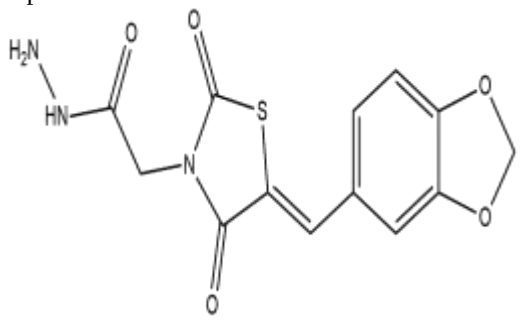


Aldose reductase inhibitory activity:

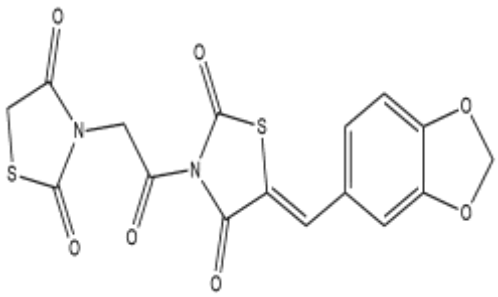
Ottana et al. synthesized 5-arylidene-4-thiazolidinediones as aldose reductase inhibitors. Compounds (8) and (9) showed interesting dual inhibitory activity against aldose reductase enzyme as well as excellent antioxidant property [23].



Bruno et al. synthesized (Z)-5-arylidene-2, 4-thiazolidinediones and evaluated as aldose reductase inhibitors. where (11) N-unsubstituted derivatives exert maximum inhibitory activity same as standard sorbinil (10) where as introduction of an acidic side chain on N-3 of thiazolidinedione moeity (12) led to a marked increase in inhibitory activity which was similar with tolrestat and methyl ester derivative (13) which devoid of any acidic functionality showed appreciable inhibitory activity similar to that of the N-unsubstituted compounds [24].



Bozdag-Dundar et al. synthesized novel flavonyl-2, 4-thiazolidinedione derivatives and evaluated aldose reductase inhibitory activity and insulinotropic activities in INS-1 cells. Compound (14) shown the highest aldose reductase inhibitory activity (86.57%)[25].



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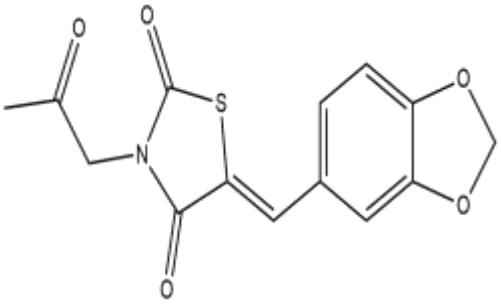
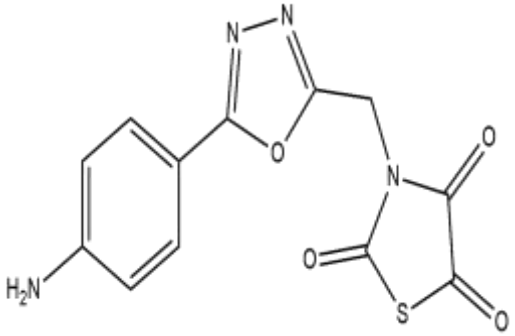
Anticancer activity:

Shibata et al. synthesized 2-[4-(2, 4-thiazoldinedione -5-ylmethyl) phenoxymethyl]-1H benzimidazoles, among which compounds (15) and (16) showed significant inhibitory activity against human large bowel cancer cell growth [26].

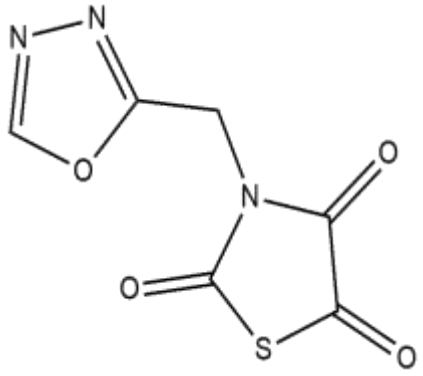
COMPOUND NUMBER	X	Y
15	O	CH or N
16	S	CH or N



Gududuru et al. synthesized a new series of 2-aryl-4-oxo-thiazolidin-3-yl amides (17) were designed and synthesized by all the synthesized compounds were evaluated against five human prostate cancer cell lines. Increase in the alkyl chain enhanced antiproliferative activity while replacement of the alkyl chain with aryl group reduced biological activity [27].



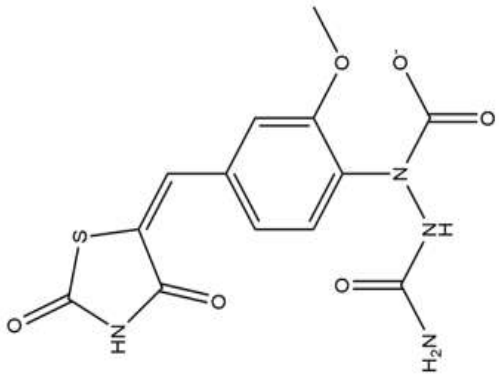
Chandrappa et al. synthesized a new series of 2-(5-((5-(4-chlorophenyl) furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3- yl)acetic acid derivatives (18) and evaluated these for their cytotoxic activity [28].



ANTIMICROBIAL:

ANTIBACTERIAL AND ANTIFUNGAL:

Aneja et al synthesized three series of compounds, namely, ethyl 2-((Z)-5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)-2, 4-dioxothiazolidin-3-yl)acetates (A), methyl 2-((Z)-5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)-2, 4-dioxothiazolidin-3-yl)acetates (B), and 2-((Z)-5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)-2, 4-dioxothiazolidin-3-yl)acetic acids (C). All the new compounds were tested for their in vitro antibacterial and antifungal activity using all the new compounds were tested for their in vitro antibacterial and antifungal activity. The antifungal and antibacterial acitvites were carried out by Sabouraud dextrose agar (SDA) is used as medium and Fluconazole is used as Standard antibiotic and agar well-diffusion method respectively. Antifungal evaluation of the compounds has shown signifincant antifungal activity against Aspergillus flavus and Aspergillus niger and the mycelia growth of inhibition(%) varies between 54.4 to 77.7 and 60.0 to 81.1.Moreover the compounds have also shown antibacterial activity against Staphylococcus aureus and Bacillus subtillis.[29]



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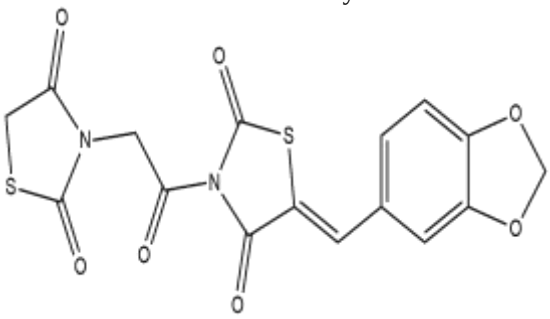
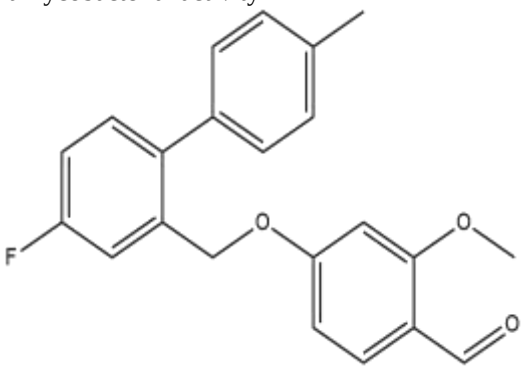
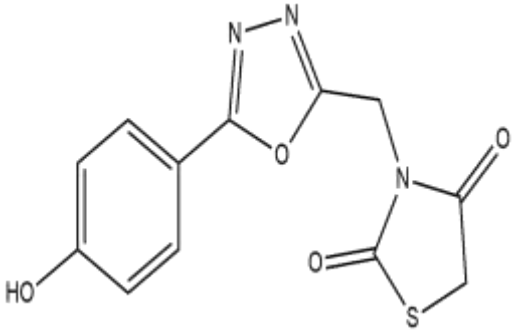
Harnden et al. synthesized a series of 2-methylaminothiazoliinones. Among all the compounds, compound (19) showed significant antiviral and antibacterial activity [30].



Mizzoni et al. synthesized a series of thiazolines (20) and thiazolidinones (21) exhibiting significant antimycobacterial activity [31].

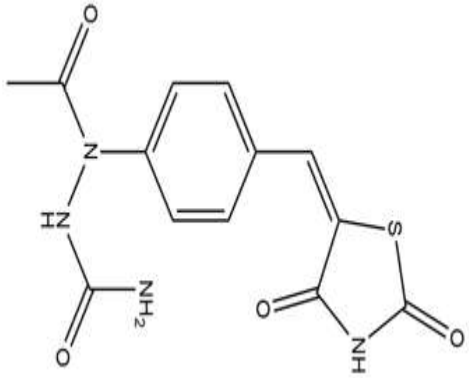


Babaoglu et al. prepared a library of 2, 3, 5-trisubstituted-4-thiazolidinones and evaluated them for antimycobacterial activity. Compound (22) showed potent activity against Mycobacterium tuberculosis in vitro [32].

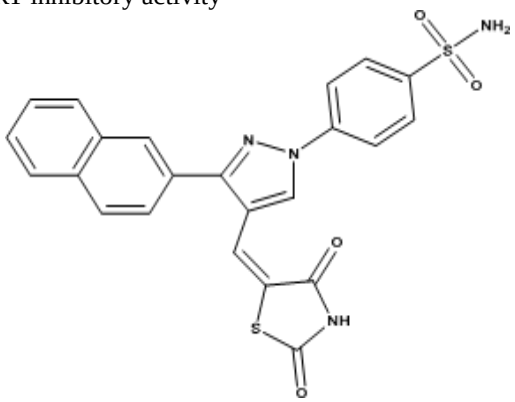


Antiviral:

Balzarini et al. studied the QSAR and suggested that molecules with higher lipophilicity improved activity. [33]. Novel thiazolidinones with 3-hydrazono-5-nitro-2-indolinone linked at the N-3 of the thiazolidinone ring were screened by against yellow fever virus and bovine viral diarrhea virus (BVDV). Among all the compounds, compound (23) showed highest activity which was attributed to the methyl group at C-5 of the thiazolidinone ring [34].



Balzarini et al. prepared 2-adamantyl-substituted thiazolidin-4-ones. Compound (24) exhibited very high inhibitory activity with an EC50 of 0.35μM, which was attributed to the presence of adamantyl moiety at C-2 position. The other derivatives lacking the adamantyl moiety were devoid of HIV-1RT inhibitory activity [35].



Anti-psychotic activity:

Hrib et al. studied the structure-activity relationships of a series of novel (piperazinylbutyl) thiazolidinone related to 3-[4-[4-(6-flurobenzo[b]thien-3-yl)-1-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone maleate as antipsychotic and evaluated in vitro for dopamine D2 and serotonin 5HT2 and 5HT1A receptor affinity. The compounds were examined in vivo in animal models of male CD-1mice and male wistar rats for potential antipsychotic activity. The compounds (25) and (26) showed potential efficacy against the negative symptoms of schizophrenia [36].

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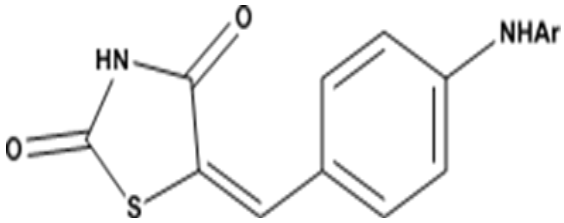
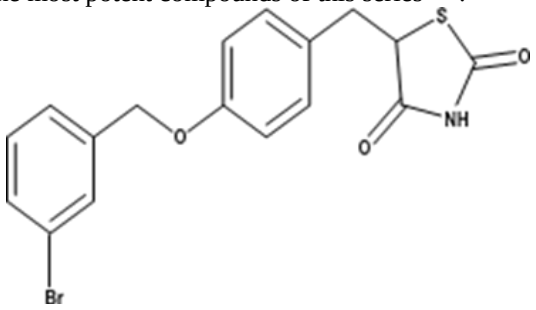
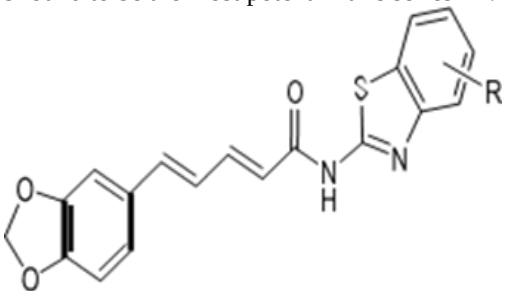


Anti arrythmic :

Jackson et al. synthesized a series of thiazolidinones and evaluated these for the treatment of arterial arrhythmias. The 3, 4-dimethyl derivatives (26) and (27) were found to be the most potent compounds of this series [37].

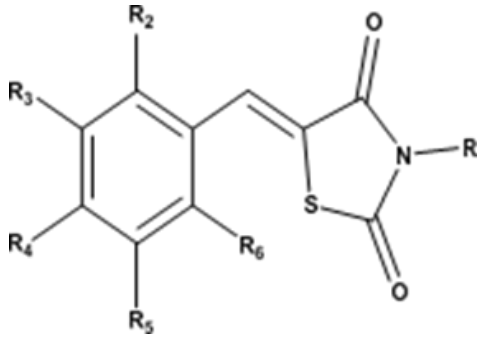


Bhandari et al. synthesized 2-(2- (4-(3-((5-substituted methylene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-2-hydroxypropylamino) benzoyl) hydrazinyl)-2-oxoethyl nitrates and evaluated them for electrocardiographic, antiarrhythmic, vasorelaxing and antihypertensive activity as well as for in-vitro nitric oxide (NO) releasing ability. Compound (28) was found to be the most potent in this series [38].

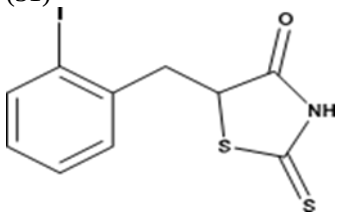


Anti-convulsant and antidepressants :

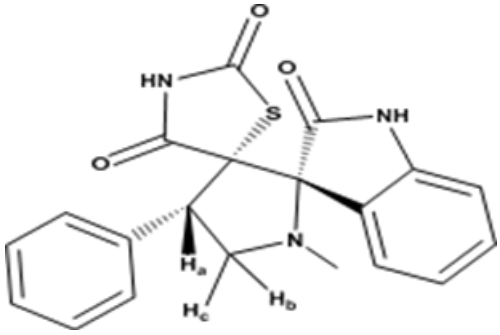
Karall et al. synthesized a series of 3-[(3-substituted-5-methyl-4-thiazolidinon-2-ylidene) hydrazono]-1H-2-indolinone derivatives and evaluated for CNS antidepressant activity. Compound (29) with para methyl phenyl group on thiazolidinone ring exhibited reasonable anticonvulsant activity. Replacement of para methyl phenyl group with an allyl group was found to increase its antidepressant activity [39].



Agrawal et al. reported a new series of thiazolidinonyl2-oxo/thiobarbituric acids. Compound (30) exhibited highest anticonvulsant activity, higher than the standard drug sodium phenytoin (31) [40].



Kaur et al. synthesized a number of substituted thiazolidinones. Among all the compounds, compound (32) exhibited potent antipsychotic as well as anticonvulsant activities [41].



Anti-inflammatory and analgesic agents :

Goel et al. synthesized new anthranilic acid derivatives of 4-thiazolidinone and evaluated for their anti-inflammatory activity against carageenan- induced oedema in albino rats by Compound (33) showed maximum antiinflammatory activity [42].

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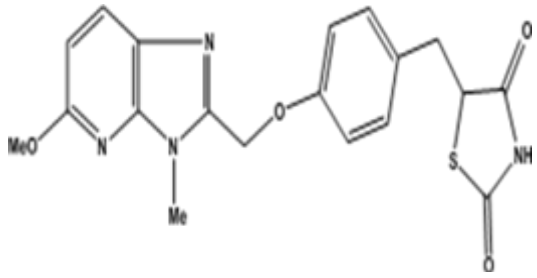
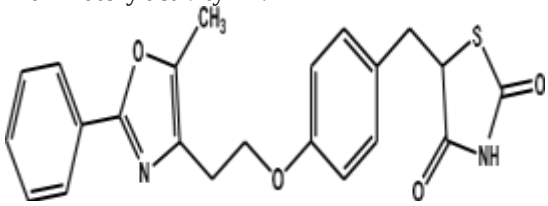
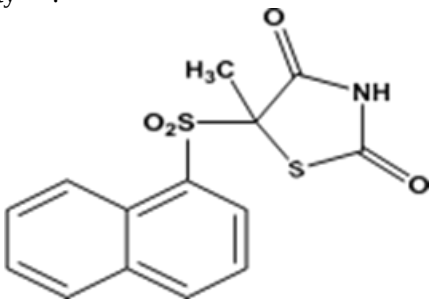


Ali et al. reported a series of thiazolidine-2, 4-diones and proved that absence of 5-arylmethylidene moiety in compound (34) enhanced its anti-inflammatory activity and decreased the analgesic activity. Bulky groups incorporated at the N position of thiazolidine-2,4-dione ring either decreased or abolished the anti-inflammatory activity [43].

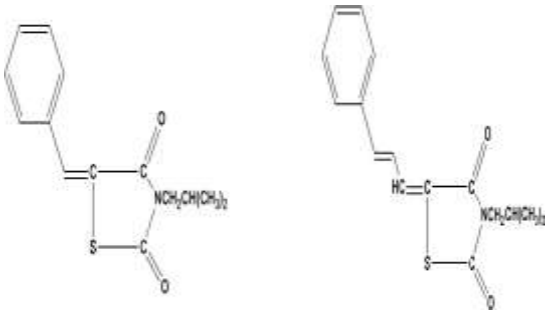


Amin et al. prepared several spiro [(2H,3H) quinazoline-2,10-cyclohexan]-4(1H)-ones which were evaluated for their antiinflammatory, ulcerogenic and analgesic activities. Compound (35) showed highest anti-inflammatory activity and considerable analgesic activity [44].

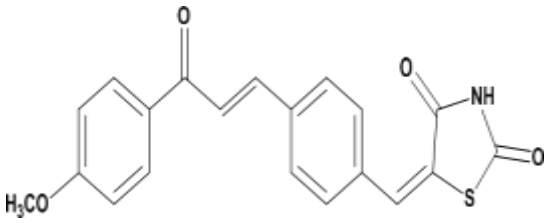


Anti hyperlipidemic :

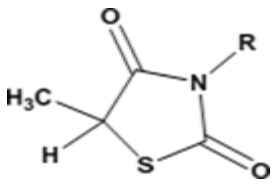
Lohray et al. synthesized indole containing thiazolidinedione derivatives as potent euglycemic and hypolipidemic agents. Compound (36) consider as a superior euglycemic and hypolipidemic agent than troglitazone (37) [45].



Lee et al. synthesized novel pyrimidine derivatives having thiazolidinedione and were evaluated for their glucose and lipid lowering activity in 3T3-L1 cells of KKAy mice. Compound (38) and (39) exhibit more potent biological activity than that of the reference compounds pioglitazone (4) and rosiglitazone (5) [46].



Leite et al. synthesized novel arylidene thiazolidinedione and compound (40), (41), (42) showed potential hypoglycemic and hypolipidemic activities [47].



Antiobesity:

Bhattaraj et al. synthesized benzylidene-2, 4-thiazolidinedione derivatives with substitutions on the phenyl ring at the ortho or para positions of the thiazolidinedione group were synthesized as PTP1B inhibitors. (43) compound bore an IC50 of 5.0μm and show potential activity [48].

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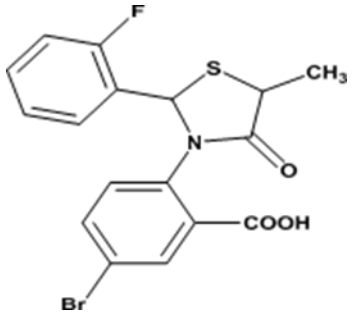
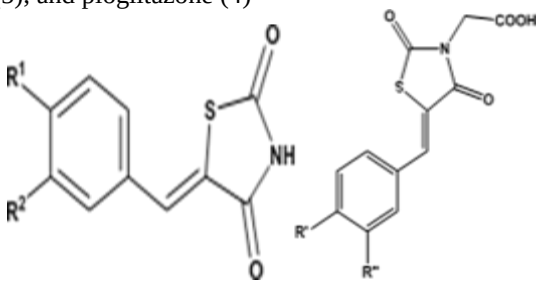
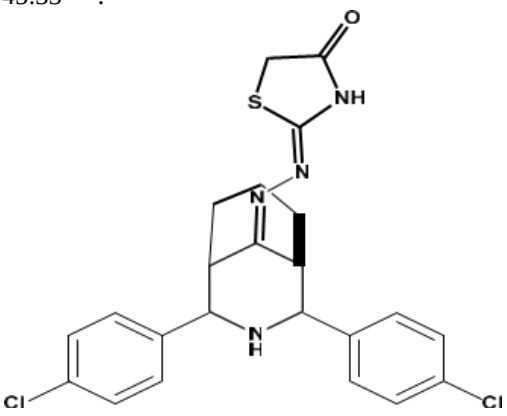


Bhattaraj et al. synthesized novel benzylidene -2, 4-thiazolidinedione derivatives as PTP1B inhibitors. Compound (44) bore an IC50 of 1.3 μm to activate the transcription of the receptor comparable with troglitazone (37), rosiglitazone (5), and pioglitazone (4) [49].



Antimalarial:

Sharma et al. synthesized a series of thiazolidinedione as plasmodium falciparum cysteine protease falcipain-2 inhibitor as well as antiparasitic. Compound (46) show modest activity due to presence of methyl substituents bore an IC50 of 45.33 [50].



II. SUMMARY AND CONCLUSION

Thiazolidinediones TZDs are a significant class of medications that demonstration by expanding the transactivation movement of PPARs, because of, their diminish hepatic glucose creation, increment fringe usage of glucose as well as lipid digestion. These activities, subsequently, diminish the preload & after load on β- cells in addition to lipid homeostasis. Thus, the impact of endogenous insulin increases to keep up with the degree of blood glucose. The TZDs were developed for clinical purpose as PPARs through which the modulations of molecular mechanisms are mediated. Based on the recent developments in computer aided drug design and better understanding of molecular targets through rationalized approaches, novel antidiabetic agents are designed. Hence thiazolidinediones are useful leads for designing compounds for treating diabetes, cancer and inflammatory diseases.

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